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European Patent Office  
80298 Munich

Opposition against: EP 2 161 336 (09013687.0)  
Proprietor: ONO Pharmaceutical Co., Ltd. et al.  
Opponent: 4-Antibody AG  
Our Ref.: 103539OPPOEPT1

In the name and on behalf of 4-Antibody AG, Hochbergerstrasse 60C, 4057 Basel, Switzerland

### NOTICE OF OPPOSITION

is submitted herewith to European patent EP 2 161 336 B1 entitled "Human monoclonal antibodies to programmed death 1 (PD-1) and methods for treating cancer using anti-PD-1 antibodies alone or in combination with other immunotherapeutics" (hereinafter "Opposed Patent") of ONO Pharmaceutical Co., Ltd. and Medarex, Inc.

The opposition fee is to be deducted from our account No. 28 001 197.

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## 1. REQUESTS

It is requested that the Opposed Patent be revoked in its entirety based on the grounds that

- according to Article 100(a) EPC, the subject-matter of the Opposed Patent is not patentable in the sense of Articles 52 to 57 EPC;
- according to Article 100(b) EPC, the Opposed Patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art in the sense of Article 83 EPC, and
- according to Article 100(c) EPC, the subject-matter of the European patent extends beyond the content of the instant application as well as the parent application as filed, in the sense of Articles 123(2) and 76(1) EPC, respectively.

Should the Opposition Division mind to maintain the Opposed Patent, oral proceedings according to Article 116 EPC are requested.

The Opposed Patent is to be revoked on the basis of the following facts and evidence.

## 2. EVIDENCE

- D1:** WO 2006/121168 A1 by ONO Pharmaceutical Co., Ltd. et al.
- D2:** EP 09013687.0, published as EP 2161336 A1 by ONO Pharmaceutical Co., Ltd. et al.
- D3:** US 679466 P (filed on May 9, 2005)
- D4:** US 738434 P (filed on November 21, 2005)
- D5:** US 748919 P (filed on December 8, 2005)
- D6:** WO 2004/056875 A1 by Wyeth et al., published on August 7, 2004

- D7:** Bennett et al., J. Immunol. (2003) 170: 711-718
- D8:** Iwai et al., Immunol. Letters (2002) 83: 215-220
- D9:** EP 1537878 A1 by ONO Pharmaceutical Co., Ltd. et al., published as WO 2004/004771 A1 on January 15, 2004.
- D10:** Exhibit 1 “Human anti-PD-1 antibodies: binding to PD-1, cross-competition with 5C4 and affinity to PD-1”
- D11:** Agata et al., Int. Immunol. (1996) 8(5): 765-772
- D12:** EP 1445264 A1 by ONO Pharmaceutical Co., Ltd. et al., published as WO 03/011911 A1 on February 13, 2003
- D13:** Hirano et al., Cancer Res (2005) 65(3): 1089-1096
- D14:** Iwai et al., PNAS (2002) 99(19): 12293-12297
- D15:** EP 1591527 A1 by ONO Pharmaceutical Co., Ltd. et al., published as WO 2004/072286 A1 on August 26, 2004
- D16:** Iwai et al., J Exp. Med. (2003) 198(1): 39-50
- D17:** Carter & Carreno, Immunologic Research (2003) 28 (1): 49-59
- D18:** Blank et al., Cancer Immunol Immunother (2005) 54: 307-314
- D19:** WO 02/078731 A1 by Wyeth, published on October 10, 2002

### 3. OPPOSED PATENT

#### 3.1 Bibliography

The Opposed Patent was granted on the basis of European patent application **D2: EP 09013687.0**, which is a divisional application of European patent application 06746353.9 (EP 1 530 465), presently abandoned, which was filed on May 2, 2006 claiming priority from **D3: US 679466 P** (filed on May 9, 2005), **D4: US 738434 P** (filed on November 21, 2005) and **D5: US 748919 P** (filed on December 8, 2005) and

published as **D1: WO 2006/121168 A1**. The date of publication of the mention of the grant of the Opposed Patent in the EP Patent Bulletin was July 31, 2013.

The application underlying the Opposed Patent gave rise to three presently pending divisional applications, EP 11178187.8 (EP 2 418 278), EP 11178188.6 (EP 2 439 272) and EP 11178191.6 (EP 2 439 273).

### **3.2 Subject matter of the Opposed Patent**

- 3.2.1 The Opposed Patent generally pertains to monoclonal antibodies that specifically bind to human Programmed Death 1 (PD-1) protein, antibodies that cross-compete for binding to PD-1 with said anti-PD-1 antibodies as well as medicinal uses thereof.
- 3.2.2 Claim 1 of the Opposed Patent as granted relates to an isolated monoclonal anti-human PD-1 antibody, or antigen binding portion thereof, as defined by six CDRs. According to claim 2, the antibody is defined by the two variable (light and heavy) chains. The CDR and variable chain sequences recited in claims 1 and 2 are derived from the human monoclonal antibody termed **5C4**.
- 3.2.3 Independent claim 3 is directed to a monoclonal antibody, or antigen binding portion thereof, that cross-competes for binding to PD-1 with the antibodies defined in claims 1 and 2.
- 3.2.4 Dependent claims 4 to 10 recite further features of the antibodies defined in claims 1 to 3. Claims 4, 5, 9 and 10 specify the antibody affinity, specificity, isotype and ADCC/CDC activity, respectively. Claims 6 to 8 recite the effects of the antibodies on the immune system or certain lymphocytes. According to the established EPO practice, such characterization of a product by the result to be achieved is generally not allowed, cf. Guidelines F-IV-4.10. Therefore, the features of these claims can only be

viewed as an explicit recitation of the intrinsic properties of the antibodies defined in technical (claims 1 and 2) and functional (claim 3) terms. In other words, these features cannot be considered as further limitations of the claimed antibodies as defined in claims 1 to 5.

- 3.2.5 Independent claim 12 relates to the claimed antibodies for use in a method of *modulating an immune response*. The claim is drafted in the purpose-limited product format reserved for claims directed to substances for use in a method of treatment in the sense of Article 53(c) EPC, cf. T 241/95, T 4/98, T 1020/03, G 2/08 and Guidelines F-IV-4.22 and G-VI-7.1. Because “modulating an immune response” does not amount to a method of treatment of a disease or medical condition, claim 12 is to be viewed as a “normal” product claim specifying an intended product use. In this regard reference is made to the preliminary opinion of the Board of Appeal, dated September 22, 2008 in the decision T 1790/06. In analogy to the instant situation, the second medical use claim then under examination failed to include any disease indication and was considered by the Board as a conventional use claim.

According to the established EPO practice, a claim directed to a product *for* use is to be interpreted as a product *suitable for* said use, cf. Guidelines F-IV-4.13. For examination of compliance with the criteria of novelty/inventive step, such products are considered solely with respect to the technical features, disregarding the method for which they are thought to be applicable, cf. Guidelines F-IV-4.13.

Therefore, the subject matter of claim 12 corresponds to the subject matter of the product (antibody) claims it references.

- 3.2.6 Independent claims 13 and 16 relate to the claimed antibodies for use in a method of inhibiting the growth of tumor cells and treating an infectious disease, respectively. Dependent claims 14, 15 and 17 provide laundry lists of tumors, viruses and bacteria.

It is noted that the group of viruses recited in claim 17 erroneously includes numerous bacterial species.

- 3.2.7 Independent claim 18 relates to an immunoconjugate of the claimed antibody to a therapeutic agent which is further defined in dependent claims 20 and 22.
- 3.2.8 Independent claim 24 relates to a bispecific molecule comprising the claimed antibody linked to a functional moiety having a different binding specificity than said antibody.
- 3.2.9 Independent claims 11, 19, 21, 23 and 25 are directed to compositions comprising a pharmaceutically acceptable carrier and the claimed antibody, immunoconjugate or bispecific molecule.

### **3.3 Experimental evidence in the Opposed Patent**

- 3.3.1 The Opposed Patent provides data on the generation and structural characterization of seven human monoclonal antibodies to human PD-1 which are designated in the patent as **17D8**, **2D3**, **4H1**, **5C4**, **4A11**, **7D3** and **5F4** (Examples 1 and 2). Binding affinity and specificity to PD-1 and other CD28 family members was measured (Example 3).
- 3.3.2 Some antibodies (**5C4**, **4H1**, **17D8** and **2D3**) were shown to promote T cell proliferation and IFN- $\gamma$  and IL-2 production in a Mixed Lymphocyte Reaction to varying degrees (Example 5). **5C4** and **4H1** blocked ligand binding to PD-1 (Example 6). **5C4** was found insufficient to reduce T-cell apoptosis (Example 8). In line with the established knowledge that anti-PD-1 antibodies do not stimulate resting T cells, no stimulation of human blood cells to release cytokine was observed for **5C4** and **4H1** (Example 7). The **5C4** antibody was demonstrated to partially release inhibition imposed by regulatory T cells on proliferation and IFN- $\gamma$  secretion of CD4<sup>+</sup> CD25<sup>-</sup> T cells (Example 21) and to enhance T cell proliferation and IFN- $\gamma$  production (Example 22).

Dependency of antibody-dependent cellular cytotoxicity, ADCC, on the Fc region (Example 23) and absence of complement-dependent cytotoxicity, CDC (Example 24), was shown on activated CD4 T cells for **5C4**.

- 3.3.3 A rat anti-mouse PD-1 antibody was observed to increase antibody titers in mice challenged with T1-antigen (Example 10). In mice implanted with fibrosarcoma cells, a chimeric rat anti-mouse antibody (**4H2**) extended the mean time to reaching the tumor end point volume from about 25 days to about 40 days (Example 11).

#### 4. **ADDED SUBJECT MATTER (Articles 123(2) and 76(1) EPC)**

- 4.1 The subject matter of the Opposed Patent extends beyond the content of the instant and parent applications as filed, in breach of the requirements of Articles 123(2) and 76(1) EPC, respectively. As the disclosures of the parent and instant applications are identical, for the purpose of further discussion reference will be made to the publication of the parent application, **D1: WO 2006/121168 A1** (hereinafter “original application”).
- 4.2 Claim 3 of the Opposed Patent is directed to a monoclonal antibody which cross-competes for binding to PD-1 with an antibody that is defined by the six CDRs of **5C4** (claim 1). Such an antibody cannot be derived from the disclosure of the original application. The original application refers to antibodies that cross-compete for binding to PD-1 with an antibody defined by the heavy chain variable region comprising SEQ ID NO: 4 and light chain variable region comprising SEQ ID NO: 11, i.e., the **5C4** antibody (page 3, last paragraph and claim 12). However, it is silent about an antibody cross-competing for binding with an antibody defined by the six CDRs of **5C4**.

- 4.3 Claim 4 of the Opposed Patent is directed to an antibody defined by either the six CDRs of **5C4**, the two variable chains of **5C4** or cross-competition with those which in addition binds to human PD-1 with a  $K_D$  of  $5 \times 10^{-9}$  or less and binds to neither human ICOS, CTLA-4 nor CD28. This combination of features cannot be derived from the original application. The original application discloses an antibody defined by the heavy chain variable region having at least 80% homology to either of SEQ ID NOs: 1, 2, 3, 4, 5, 6, and 7; and the light chain variable region having at least 80% homology to either of SEQ ID NOs: 8, 9, 10, 11, 12, 13, and 14; which in addition binds to human PD-1 with a  $K_D$  of  $1 \times 10^{-7}$  M or less and does not bind to any of human ICOS, CTLA-4 or CD28 (middle of page 5, original claim 25). A  $K_D$  of  $5 \times 10^{-9}$  or less is disclosed in the original application in the context of a different antibody, namely an antibody characterized by a combination of five features recited in claim 1 of the original application (claim 6 of original application, paragraph spanning pages 2 and 3). An antibody characterized by the two variable chains,  $K_D$  and binding to ICOS, CTLA-4 or CD28 (granted claim 4 combined with claim 2) may be considered as a selection from the generic disclosure of original claim 25, additionally combined with the  $K_D$  of original claim 6. According to the established EPO practice, selecting and combining individual features from different contexts constitutes added matter. Moreover, there is no disclosure of an antibody characterized by the six CDRs of **5C4** or cross-competition with **5C4** (granted claim 4 in combination with claim 1 or 3) in the context of the above referenced disclosure of  $K_D$  and ICOS, CTLA-4 or CD28 binding.
- 4.4 Claim 6 of the Opposed Patent is directed to an antibody as defined in claims 1 to 5 which in addition inhibits the suppression of CD4<sup>+</sup> CD25<sup>-</sup> T cells by regulatory T cells. The latter feature is disclosed in the original application only within the very specific context of Example 21 relating exclusively to the **5C4** antibody. There is no disclosure of said feature in the generic sense applicable to the generically defined antibodies as defined in granted claims 1 to 5.

- 4.5 Claim 7 of the Opposed Patent is directed to an antibody as defined in claims 1 to 5 which in addition enhances the antigen specific memory response to a tumor or a pathogen. This feature is disclosed nowhere in the original application.
- 4.6 Claim 8 of the Opposed Patent is directed to an antibody as defined in claims 1 to 5 which in addition confers a persistent immunity to tumor relapse. The only disclosure of the latter feature can be found in the original application in Example 19 (page 97, end of 1<sup>st</sup> paragraph) in the specific context of combination therapy of colorectal cancer cells with a rat anti-mouse PD-1 antibody **4H2** and an anti-CTLA-4 antibody **9D9**. There is no disclosure of said feature in the generic sense applicable to the generically defined antibodies as defined in granted claims 1 to 5.
- 4.7 Claim 10 of the Opposed Patent is directed to an antibody as defined in claims 1 to 5 which in addition has neither ADCC nor CDC activity. The only disclosure of the latter feature can be found in the original application in Examples 23 and 24 (pages 98-99) in the specific context of the **5C4** antibody. Specific mutations in the Fc region leading to the reduction of the CDC or ADCC activity are disclosed in the penultimate paragraph at page 35 and 1<sup>st</sup> paragraph at page 36, respectively. However, there is no disclosure of the claimed feature in the generic sense applicable to the generically defined antibodies as defined in granted claims 1 to 5.
- 4.8 Claims 11-25 refer to claims 1 to 10 and hence suffer from the same deficiencies as the latter.
- 4.9 Taken together, the subject matter of the Opposed Patent contravenes the requirements of Articles 123(2) and 76(1) EPC.

## 5. PRIORITY (Article 87 EPC)

5.1 According to the requirements of Article 87 EPC, a valid claim to priority of an earlier application must satisfy *inter alia* the following conditions:

- (i) the earlier application must have been filed by the applicant of the European application or his predecessor in title; and
- (ii) the previous application must have been the first application filed in respect of the same invention as the one to which the European application relates.

5.2 As to the first criterion, the following is herewith observed:

5.2.1 The first priority application **D3: US 679466 P** of May 9, 2005 does not list any applicants.

5.2.2 The second priority application **D4: US 738434 P** of November 21, 2005 lists  
Alan J. Korman  
Mark J. Selby  
Josephine M. Cardarelli  
Bing Chen  
Tseng-Hui Timothy Chen  
Changyu Wang  
Haichun Huang  
as inventors and hence applicants.

5.2.3 The third priority application **D5: US 748919 P** of December 8, 2005 lists the same inventors/applicants as the second priority application.

5.2.4 The applicants for the Opposed Patent are ONO Pharmaceutical Co., Ltd. and Medarex, Inc.

- 5.2.5 There is no evidence on file that the priority right has been properly transferred from the applicants of the priority applications to the applicants for the Opposed Patent prior to the filing of the PCT application, from which the application underlying the Opposed Patent originated. Therefore, unless the opposite is proven, the first criterion for a valid priority claim is not fulfilled.
- 5.3 As concerns the second criterion, the expression “same invention” in the sense of Article 87(1) EPC means that the subject matter of a claim in a European application may enjoy the priority of an earlier application only if the skilled person can derive the subject matter of the claim directly and unambiguously, using common general knowledge, from said earlier application, **G 2/98**. The test for determining whether this criterion is satisfied is the same as the test for determining added matter in the sense of Article 123(2) EPC, cf. Guidelines F-VI-2.2. As will be demonstrated below, the subject matter of the Opposed Patent extends beyond the content of the priority applications, in breach of the respective requirement of Article 87(1) EPC.
- 5.3.1 Claims 1 and 2 of the Opposed Patent are directed to an isolated monoclonal anti-PD-1 antibody defined by the six CDRs (SEQ ID NOS: 18, 25, 32, 39, 46 and 53) or the two variable chains (SEQ ID NOS: 4 and 11) of the human antibody **5C4**, respectively. None of the priority documents discloses an antibody defined by said specific combinations of sequences. In fact, none of the priority applications contains a sequence listing. Therefore, the skilled person would not be able to allocate a particular sequence to the sequence numbers mentioned in the priority applications. Accordingly, the sequence combinations claimed in the Opposed Patent cannot be derived from any of the priority applications, let alone directly and unambiguously.
- 5.3.2 Claim 3 of the Opposed Patent is directed to a monoclonal antibody which cross-competes for binding to PD-1 with an antibody of claims 1 or 2. Such an antibody cannot

be derived from the disclosure of any of the priority applications. The first priority application **D3: US 679466 P** refers to antibodies that cross-compete for binding to PD-1 with an antibody defined by a permutation of five different light and heavy chain sequences (middle of page 3, and claim 8). However, as indicated above, the priority application does not disclose any correspondence between sequences and sequence numbers. Moreover, the priority application is silent about an antibody cross-competing for binding with an antibody defined by its CDRs and hence fails to disclose the same, for the reasons analogous to the reasons provided in Section 4.2 *supra*.

- 5.3.3 Claim 4 of the Opposed Patent is directed to an antibody defined by either the six CDRs of **5C4**, the two variable chains of **5C4** or cross-competition with those which in addition binds to human PD-1 with a  $K_D$  of  $5 \times 10^{-9}$  or less and does not bind to either of human ICOS, CTLA-4 or CD28. This combination of features cannot be derived from any priority application. The first priority application **D3: US 679466 P** discloses an antibody defined by the heavy chain variable region having 80% homology to either of SEQ ID NOs 1, 2, 3, 4, and 5; and the light chain variable region having at least 80% homology to either of SEQ ID NOs: 6, 7, 8, 9, and 10; which in addition binds to human PD-1 with a  $K_D$  of  $1 \times 10^{-7}$  or less and does not bind to either of human ICOS, CTLA-4 or CD28 (paragraph spanning pages 5 and 6, claim 23). Apart from the fact that the first priority application **D3: US 679466 P** does not contain any sequence listing, selecting and combining individual features from different contexts is deemed to lack proper basis, in accordance with the EPO's practice, cf. reasoning provided in Section 4.3 *supra*.
- 5.3.4 Claim 6 of the Opposed Patent is directed to an antibody as defined in claims 1 to 5 which in addition inhibits the suppression of CD4+ CD25- T cells by regulatory T cells. The latter feature is not disclosed in any of the priority applications.

- 5.3.5 Claim 7 of the Opposed Patent is directed to an antibody as defined in claims 1 to 5 which in addition enhances the antigen specific memory response to a tumor or a pathogen. This feature is not disclosed in any of the priority applications.
- 5.3.6 Claim 8 of the Opposed Patent is directed to an antibody as defined in claims 1 to 5 which in addition confers a persistent immunity to tumor relapse. The only disclosure of this feature can be found in the third priority application **D5: US 748919 P** in Example 8 (page 46, end of last paragraph) in the specific context of a combination therapy of colorectal cancer cells with a chimeric rat anti-mouse PD-1 antibody **4H2** and an anti-CTLA-4 antibody **9D9**. There is no disclosure of said feature in the generic sense applicable to the generically defined antibodies as defined in granted claims 1 to 5. In fact, the third priority application is concerned with a combination therapy by anti-PD-1 and anti-CTLA-4 antibodies, and not with the immunotherapy by an anti-PD-1 antibody, subject of the Opposed Patent.
- 5.3.7 Claim 10 of the Opposed Patent is directed to an antibody as defined in claims 1 to 5 which in addition has neither ADCC nor CDC activity. The only disclosure of this feature can be found in the first priority application **D3: US 679466 P** in connection with specific mutations in the Fc region leading to the reduction of the CDC or ADCC activity (page 38, 3<sup>rd</sup> and 5<sup>th</sup> paragraphs). The second priority application **D4: US 738434 P** discloses ADCC in the context of Fc modification of the chimeric rat anti-mouse PD-1 antibody **4H2** (page 42, 2<sup>nd</sup> paragraph). However, in neither of the priority documents can one find a disclosure of the claimed feature in connection with the generically defined antibodies as defined in granted claims 1 to 5.
- 5.4 Taken together, the subject matter of the Opposed Patent is not entitled to the benefit of the filing dates of any of the priority applications. Accordingly, the relevant date for the assessment of novelty and inventive step of the subject matter of the Opposed Patent is the filing date of the parent PCT application, **May 2, 2006**.

## 6. NOVELTY (Article 54 EPC)

### 6.1 D6: WO 2004/056875 A1 by Wyeth et al.

6.1.1 **D6: WO 2004/056875 A1** generally relates to modulation of immune responses regulated by PD-1 receptor (paragraph [001]). More specifically, **D6: WO 2004/056875 A1** provides anti-PD-1 antibodies that specifically bind to PD-1, including human PD-1, and block PD-1 interaction with its natural ligands (paragraph [010]). Specific binding to PD-1 implies that the antibodies do not bind to related, but different molecules such as CD28, ICOS or CTLA-4.. The anti-PD-1 antibodies may be of the isotype subclasses IgG1 and IgG4 (claim 8, paragraph [043]). The antibodies are intended for modulating immune response, in particular increasing or decreasing the T cell response mediated by T cell receptor and CD28 (paragraph [012], [083]). As explained in paragraph [084], antagonistic PD-1 antibodies would enhance T-T cell responses by inhibiting or reducing the down-regulatory activity associated with PD-1. Blockage of PD-1/PD-L interaction with such antagonizing anti-PD-1 antibodies was demonstrated to lead to enhanced T cell proliferative responses and increased IL-2 production (paragraph [084], Example 6 and 9). The disorders susceptible to treatment with the anti-PD-1 antibodies of **D6: WO 2004/056875 A1** include infectious diseases and cancer (claim 13, paragraphs [012], [083], [0129] and [0130]), more specifically melanoma and prostate cancer (paragraphs [083] and [0136]). Compositions comprising the antibodies and a carrier are disclosed in paragraphs [0101] and [0102].

6.1.2 Four specific human antibodies to human PD-1, **PD1-17**, **PD1-28**, **PD1-33** and **PD1-35** and an anti-mouse PD-1 antibody (PD1-F2), are provided and characterized by their heavy and light variable chain sequences and respective CDRs (Tables 1 to 3 at pages 11 and 12). The PD-1 binding scFv's of these antibodies were selected from a human scFv phagemid library described by Vaughan et al., Nature Biotech (1996) 14:

309-314 (Example 1). Their specificity to PD-1 (Example 2), ability to inhibit PD-1 binding to PD-L1 (Example 6) and enhance T cell responses (Example 9) was demonstrated. The scFvs were converted to IgGs (Example 5) and their binding to a distinct site on PD-1 was demonstrated. The site was found to be different from the site of binding of two known anti-human PD1 antibodies **J110** and **J116** (Example 7, Figure 4).

6.1.3 The **PD1-28**, **PD1-33** and **PD1-35** antibodies of **D6: WO 2004/056875 A1** cross-compete for binding to human PD-1 with the **5C4** antibody of the Opposed Patent as evidenced by the cross-competition studies conducted by the Opponent and submitted herewith as **D10: Exhibit 1**. In the experiments reflected in **D10: Exhibit 1**, **PD1-28**, **PD1-33** and **PD1-35** antibodies were synthesized based on the sequence information from **D6: WO 2004/056875 A1**. Anti-PD-1 antibodies **5C4**, **5F4** and **4H1** disclosed in the Opposed Patent were used as positive controls and an indication of comparative-ness of the Opponent's data with the data submitted by the Patentee during prosecution of the application underlying the Opposed Patent. Negative controls included  $\alpha$ -human IgG and  $\alpha$ -mouse IgG. It can be taken from the experimental data of **D10: Exhibit 1** that the Wyeth antibodies **PD1-28**, **PD1-33**, and **PD1-35** (i) bind to human PD-1 on the surface of PD-1 expressing Jurkat cells, (ii) cross-compete with **5C4** for PD-1 binding and (iii) have a  $K_D$  of  $3.23 \times 10^{-9}$ ,  $6.29 \times 10^{-9}$  and  $4.71 \times 10^{-9}$  M, respectively. Similar results were obtained for **5C4** (self-competition) as well as **5F4** and **4H1**. No PD-1 binding was observed for the control antibodies.

6.1.4 In view of the above, the subject matter of claims 3, 4, 5, 6, 9, 11, 12, 13, 14, 15 and 16 lacks novelty over the disclosure of **D6: WO 2004/056875 A1**.

## 6.2 **D7: Bennett et al., 2003**

- 6.2.1 **D7: Bennett et al., 2003**, co-authored by researchers from Wyeth Research, is concerned with the elucidation of the effect of PD-1 engagement upon TCR activation on T cell co-stimulation and cytokine-driven proliferation. In the subsection “Abs and fusion proteins” of the Materials and Methods section it is described that human antibodies to human PD-1 were produced by screening a human scFv phagemid library described by Vaughan et al., *Nature Biotech* (1996) 14: 309-314. The antibodies were available upon request from Wyeth Research, Cambridge, MA. Human antibodies **PD1-17** and **PD1-35** were characterized for their ability to inhibit PD-1 binding to its ligands using ELISA and FACS assays. FACS assays were performed using a human PD-1 expressing Jurkat cell line. **PD1-17** and **PD1-35** were found to neutralize PD-1/PD-L interaction (page 713, left col., 2<sup>nd</sup> paragraph). It was further observed that incubation of PD-1 expressing CD4<sup>+</sup> T cells with soluble anti-human PD-1 antibodies (**PD1-17** and **PD1-35**) resulted in up to 4-fold increase in proliferative responses (page 713, right col., 2<sup>nd</sup> paragraph). Similarly, increase in IFN- $\gamma$  levels was also measured in these cultures. It is suggested in **D7: Bennett et al., 2003** that PD-1/PD-L interactions play a role in regulation of T-T cell interaction and that anti-PD-1 antibodies can act as antagonists to modulate this response (page 713, right col., 2<sup>nd</sup> paragraph).
- 6.2.2 The **PD1-35** antibody disclosed in **D7: Bennett et al., 2003** cross-competes for binding to PD-1 with **5C4**, as discussed in Section 6.1.2 *supra* with reference to **D10: Exhibit 1**.
- 6.2.3 In view of the above, the subject matter of claims 3, 4, 5, 6 and 12 lacks novelty over the disclosure of **D7: Bennett et al., 2003**.
- 6.3 **D8: Iwai et al., 2002**
- 6.3.1 **D8: Iwai et al., 2002** relates to the characterization of PD-1 distribution in human tonsils. The authors describe the generation of monoclonal antibodies to human PD-1 by immunization of BALB/c mice with a fusion protein of the extracellular domain of hPD-1 and

the constant region of human  $\gamma 1$  heavy chain, and fusing the spleen cells with mouse myeloma cells, resulting in hybridomas, which were screened for PD-1 binding. Five clones, **J105**, **J108**, **J110**, **J116** and **J121**, were isolated and characterized (page 216, under Item 2.2)<sup>1</sup>. The specific binding of these antibodies to human PD-1 was confirmed by flow cytometry (page 218, under Item 3.1; Figure 1a).

- 6.3.2 The **J105** antibody of **D8: Iwai et al., 2002** cross-competes for binding to human PD-1 with the 5C4 antibody as evidenced by the cross-competition studies reflected in **D10: Exhibit 1**. Similar to the Wyeth **PD1-28**, **PD1-33** and **PD1-35** antibodies, **J105** specifically binds to PD-1 and cross-competes with **5C4** for PD-1 binding.
- 6.3.3 In view of the above, the subject matter of claims 3 and 5 lacks novelty over the disclosure of **D8: Iwai et al., 2002**.

## 7. INVENTIVE STEP (Article 56 EPC)

### 7.1 Introduction

- 7.1.1 The subject matter of the Opposed Patent relates to anti-PD-1 antibodies and their use in modulating immune response, more specifically adaptive T cell immune response. T cell regulation has been intensively studied prior to the relevant date. T cell activation is a multi-step process requiring a number of signaling events between the T cell and antigen-presenting cell. On the one hand, a signal delivered to the antigen-specific T cell receptor on a resting T cell confers specificity to the immune response. On the other hand, a co-stimulatory signal delivered through accessory receptors on the T cell regulates the magnitude of the response. A primary co-stimulatory signal is delivered to the activating

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<sup>1</sup> There is a typo under Item 2.2 at page 216 of **D8: Iwai et al., 2002**, designating the **J105** antibody as **J106**; however, it is clear from the content of the entire publication that **J105** was meant.

CD28 receptor upon engagement of its ligands B7-1 and B7-2. The same ligands binding to the inhibitory CTLA-4 receptor antagonizes co-stimulation mediated by CD28. The development of an effective immune response is ensured by the regulation of CD28 and CTLA-4 expression and hence a balance between activating and inhibitory signals.

- 7.1.2 Like CTLA-4, PD-1 is an inhibitory receptor (reviewed in **D17: Carter & Carreno, 2003** and **D18: Blank et al., 2005**). PD-1 is a member of the Ig superfamily, expressed on T and B cells activated through the antigen receptor, or activated macrophages. PD-1 ligands are PD-L1 (B7-H1) and PD-L2 (B7-DC) whose expression is upregulated upon activation of antigen-presenting cells, including dendritic cells, monocytes, and B cells. Experimental data implicates the interaction of PD-1 with its ligands in down-regulation of central and peripheral immune responses. Specifically, PD-L1 and PD-L2 stimulation suppresses the activation (cellular proliferation and various cytokine production) of PD-1 expressing T lymphocytes. In addition, PD-L1 expression was found to be abundant on numerous murine and human cancers of various origin. This observation has led to the hypothesis that tumors might escape from the host immune system by negative attenuation of tumor-specific T-cell responses via PD-1/PD-L1 interaction. The established role of PD-1 as an important negative regulator of the immune system rendered the PD-1 pathway an attractive target for therapeutic intervention. *“Agonists of this pathway may inhibit unwanted immune responses and provide therapies for autoimmune diseases and transplantation, while antagonists may enhance immune responses and provide useful therapies in oncology and vaccine setting”* (**D16: Carter & Carreno, 2003**, page 56, right col., paragraph 3).
- 7.1.3 At the priority date of the Opposed Patent, numerous anti-PD-1 antibodies of various origins were available for studying the role of PD-1 in the regulation of the immune system.

7.1.3.1 The generation of a hamster monoclonal antibody to mouse PD-1, **J43**, and its specificity to the PD-1 antigen is described in **D11: Agata et al., 1996** (cf. page 766, under Section Antibodies; page 767, right col., 2<sup>nd</sup> and 3<sup>rd</sup> paragraphs). The **J43** producing hybridoma identified by International Trust Number PERM BP-8118 was deposited as Trust Number PERM P-18356 with the National Institute of Advanced Industrial Science and Technology, International Patent Organism Depository in Central 6, 1-1-1 Higashi, Tsukuba, Ibaraki, Japan (ZIP code 305-8566) on May 30, 2001, and was transferred to International Deposit on July 16, 2002. The **J43** antibody sequence is provided in **D12: EP 1445264 A1** by ONO Pharmaceutical Co. On the example of **J43**, it was demonstrated in **D9: EP 1537878 A1** that anti-PD-1 antibodies significantly reinforced activity of PD-1 expressing cytotoxic T lymphocytes (CTL) (Example 12, paragraph [0127] and Figure 17) and suppressed metastasis of carcinoma cells to liver in a mouse model of melanoma (paragraph [0044], Example 13). **J43** was used to construct bispecific antibodies to PD-1 and TCR/BCR in **D12: EP 1445264 A1** by ONO Pharmaceutical Co.

7.1.3.2 Another hamster anti mouse PD-1 monoclonal antibody, **G4**, is described in **D13: Hirano et al., 2005**. **G4** is specific to mouse PD-1 and does not bind to mouse CTLA-4, CD28 or ICOS (page 1090, left col., 2<sup>nd</sup> paragraph). The **G4** antibody is capable of blocking the binding of B7-H1 to PD-1. It abrogates the inhibition of CTL lysis in B7-H1 expressing mastocytoma cell cultures (P815) and completely suppresses the outgrowth of tumors in the presence of P1A CTLs in adoptive transfer experiments *in vivo* (page 1093, right col., 2<sup>nd</sup> paragraph, Figure 5). These results suggest that blockade of PD-1 by a monoclonal antibody could eliminate tumor resistance and enhance tumor immunity (page 1093, right col., 2<sup>nd</sup> paragraph, last sentence).

7.1.3.3 A rat anti-mouse PD-1 monoclonal antibody is described in **D14: Iwai et al., PNAS, 2002** (page 12293, right col., penultimate paragraph). Similar to **D13: Hirano et al., 2005**, this publication relates to the elucidation of the role of PD-1 and its ligands in

tumor cell escape from the host immune system. The findings that growth of the myeloma cells in normal syngeneic mice was significantly inhibited by the administration of an anti-PD-L1 Ab *in vivo* and was suppressed completely in the syngeneic PD-1-deficient mice suggest that the expression of PD-L1 can serve as a potent mechanism for potentially immunogenic tumors to escape from host immune responses and that blockade of interaction between PD-1 and its ligand may provide a promising strategy for specific tumor immunotherapy (Abstract).

7.1.3.4 As discussed in Section 6.3 *supra*, **D8: Iwai et al., 2002** describes five mouse anti-human PD-1 monoclonal antibodies, **J105**, **J108**, **J110**, **J116** and **J121**. The **J110** producing hybridoma identified by International Trust Number PERM BP-8392 was deposited as Trust Number PERM P-19162 with the National Institute of Advanced Industrial Science and Technology, International Patent Organism Depository in Central 6, 1-1-1 Higashi, Tsukuba, Ibaraki, Japan (ZIP code 305-8566) on Dec. 19, 2002, and was transferred to International Deposit on June 5, 2003. The **J110** monoclonal antibody was commercially available from eBioscience (San Diego, CA) (cf. **D7: Bennett et al., 2003**, page 711, right col., last paragraph). **J110** is the subject of **D9: EP 1537878 A1** directed to the use of anti-PD-1 antibodies for the treatment of cancer and infections by inhibiting immunosuppressive signal induced by PD-1 and its interaction with PD-L1 and PD-L2 (cf. discussion in Section 7.2 *infra*). **J110** was used to produce a PD-1/CD3 bispecific antibody in **D15: EP 1591527 A1** by ONO Pharmaceutical Co.

7.1.3.5 As discussed in more detail in Section 6.1 and 6.2 *supra*, **D6: WO 2004/056875 A1** and **D7: Bennett et al, 2003** describe human antibodies to human PD-1, **PD1-17**, **PD1-28**, **PD1-33** and **PD1-35**, which were sequenced and available upon request from Wyeth Research, Cambridge, MA (**D7: Bennett et al., 2003**, page 712, left col, end of 1<sup>st</sup> paragraph). Soluble anti-PD-1 antibodies **PD1-17** and **PD1-35** were demonstrated in **D7: Bennett et al., 2003** to block PD-1/PD-L interaction and to act as antagonists of the PD-1 pathway to increase proliferative T cell responses and IFN- $\gamma$  secretion.

7.1.4 It is evident from the above discussion that the state of knowledge about PD-1 and its role in the regulation of the immune system was far advanced at the priority date. Numerous anti-PD-1 antibodies were available and actively used for studying the involvement of PD-1 in immunological disorders and its utility in the treatment of those. More specifically, anti-PD-1 antibodies were shown to exert anti-tumor activities *in vivo*. It was also demonstrated that by a similar mechanism, anti-PD-1 antibodies activated T cell immunity in infections by pathogens.

**7.2 D9: EP 1537878 A1** by ONO Pharmaceutical Co., Ltd. et al.

7.2.1 **D9: EP 1537878 A1** can be taken as the closest prior art. This patent application is generally directed to compositions for activating immunity by down-regulating the inhibitory signals induced by PD-1 and its ligands. The compositions are intended for the treatment of infectious diseases, cancers and cancer metastasis (paragraph [0010], claims 15 and 16). More specifically, **D9: EP 1537878 A1** teaches anti-PD-1 antibodies and in particular the mouse anti-human PD-1 antibody deposited under International Trust Number FERM BP-8392, i.e, **J110**, as active ingredient of said compositions (paragraph [0012], item 8 and 9; claims 8 and 9). Methods of producing human antibodies in mice and by phage display methods are discussed [0030]. Immunotherapy is suggested as an alternative to chemo- and radiation therapy which are notoriously accompanied by severe side-effects (paragraph [0049]). Various cancer types susceptible to treatment by the compositions are listed in paragraph [0047].

7.2.2 It is explained in **D9: EP 1537878 A1** that the rationale behind the use of anti-PD-1 antibodies for cancer treatment is in reinforcing the cytotoxic activity of the host cytotoxic T lymphocytes that have been compromised by presenting PD-L1 to PD-1 expressed by these cells (paragraph [0043]). In PD-1 deficient mice, it was demonstrated that the inhibition of PD-1 function completely abrogated proliferation of transplanted tumor cells in

mice (paragraph [0043], Example 5 and Figure 3). In culture of PD-L1 expressing mastocytoma cells P815, anti-PD-1 antibody (**J43**, deposited under International Trust Number FERM BP-8118) was shown to significantly reinforce CTL activity (Example 12, Figure 17) and suppress metastasis in mice bearing B16 melanoma cells (Example 13).

- 7.2.3 Similarly, it is taught in **D9: EP 1537878 A1** that blocking PD-1 could prevent viruses from escaping the host immune system by using conjugate suppressive factors such as PD-1 on T lymphocytes (paragraph [0054]). Data from PD-1 deficient mice infected with adenovirus suggests that PD-1 could inhibit T cell proliferation in inflammatory tissue (Example 10). Accordingly, compositions comprising anti-PD-1 antibodies are suggested for the treatment of a variety of viral diseases (paragraph [0055]).
- 7.2.4 Taken together, **D9: EP 1537878 A1** teaches anti-PD-1 antibodies and their use in the regulation of the immune system and the treatment of cancer, metastasis and infection. Specific antibodies (**J110** and **J43**) to human and mouse PD-1 are disclosed.

### 7.3 Problem-Solution-Approach

- 7.3.1 The *difference* between **D9: EP 1537878 A1** and the subject matter of claims 1 to 3 of the Opposed Patent is in the definition of an anti-PD-1 antibody either by sequences derived from a human anti-human PD-1 antibody **5C4** or by cross-competition with same.
- 7.3.2 Accordingly, the *objective technical problem* of the Opposed Patent is to provide an *alternative* antibody to the antibodies taught in **D9: EP 1537878 A1**. The problem is solved by the antibodies as defined in claims 1 and 3.
- 7.3.3 The solution is, however, obvious in view of the ample teaching of numerous anti-PD-1 antibodies and their proven medical utility in **D9: EP 1537878 A1** as well as other prior

art documents, cf. Section 7.1 *supra*. Therefore, the subject matter of claims 1 to 3 does not involve an inventive step.

#### 7.4 Obviousness of claims 4 to 25

- 7.4.1 The  $K_D$  value of  $5 \times 10^{-9}$  or less specified in claim 4 of the Opposed Patent is an arbitrary value, very close to the  $K_D$  values of known anti-PD-1 antibodies, cf. **D10: Exhibit 1 for PD1-28, PD1-33 and PD1-35**. Similarly, the lack of binding to related molecules such as ICOS, CTLA-4 and CD28 is the feature of all PD-1 specific antibodies disclosed in **D9: EP 1537878 A1** or elsewhere in the documents discussed in Section 7.1 *supra* (cf., e.g., **D13: Hirano et al., 2005** and **D8: Iwai et al., 2002**).
- 7.4.2 The fact that the anti-PD-1 antibodies bind to human PD-1 expressed on cell surface is equally obvious from the teaching of known anti-PD-1 antibodies binding to PD-1 expressing cells, cf., e.g., **D6: WO 2004/056878 A1** and **D7: Bennett et al., 2003**.
- 7.4.3 As indicated in Section 3.2.4 *supra*, claims 6 to 8 purposefully defining the antibodies by the effect-to-be achieved, are to be interpreted as reciting intrinsic features of the antibodies defined by structural/functional features of claims 1 to 5. Therefore, every antibody fulfilling the requirements of claims 1 to 5 would automatically have the features of claims 6 to 8. Should the Patentee argue otherwise, this would amount to a lack of sufficient disclosure and sufficient definition in the sense of essential features of the antibodies of the Opposed Patent.
- 7.4.4 Different antibody isotypes, including IgG<sub>4</sub> recited in claim 9, are commonly known in the art, cf., e.g., **D6: WO 2004/056875 A1**. It is also known that it is the Fc region of the antibody that is responsible for the antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) recited in claim 10. Methods of altering C1q binding and hence abolishment of CDC are known, e.g., from U.S. Patent No. 6,194,551

referenced in paragraph [0087] of the Opposed Patent. Similarly, antibody modifications which alter antibody affinity for an Fc receptor and thus ADCC are known from the literature referenced in paragraph [0089] of the Opposed Patent.

- 7.4.5 The subject matter of claims 12 to 17 directed to the use of anti-PD-1 antibodies for modulating immune response and the treatment of cancer and infectious diseases is obvious in view of **D9: EP 1537878 A1** explicitly teaching these properties of anti-PD-1 antibodies. Inhibition of viral infection by anti-PD-1 antibodies is further taught in **D16: Iwai et al., 2003**, concerned with studying of the regulatory function of PD-1 at the effector phase of immune responses. The authors of **D16: Iwai et al., 2003** showed that adenovirus infection of PD-1 deficient mice and the resulting inflammation were significantly suppressed compared to infection of wild type mice (page 44 of Results, Figure 7). These data established that inhibition of the immunosuppressive signal of PD-1 augments anti-viral immunity and is effective in treating viral infection (cf. also Abstract). Medical utility of anti-PD-1 antibodies for the treatment of cancer is further taught in **D13: Hirano et al., 2005** and **D14: Iwai et al., PNAS, 2002**, discussed in Section 7.1.3.2. and 7.1.3.3 *supra*.
- 7.4.6 The subject matter of claims 18 to 23 directed to a conjugate of an anti-PD-1 antibody and a therapeutic agent is obvious in view of common general knowledge of antibody conjugates, including immunotoxins, and specifically immunoconjugates of anti-PD-1 antibodies, cf. **D19: WO 02/078731 A1** by Wyeth (page 80, line 27 through page 81, line 23).
- 7.4.7 The subject matter of claims 24 and 25 directed to a bispecific molecule is obvious in view of **D15: EP 1591527 A1** which discloses the development of bispecific antibodies that recognize human PD-1 as well as part of the TCR/BCR complex such as CD3 (paragraph [010]). More specifically, the anti-PD-1 part of the bispecific antibody was derived from **J110** (EP'527, Examples 1 to 3). The bispecific anti-PD-1/CD3 antibodies were

suggested for therapeutic use (paragraph [0072]). Similar disclosure of a divalent antibody to PD-1 and CD3 or BCR can be found in **D12: EP 1445264 A1**, whereby the PD-1 binding part was derived from the **J43** anti-PD-1 antibody (cf. paragraph [010], Examples 1 and 4, respectively).

- 7.4.8 Taken together, the subject matter of the Opposed Patent is obvious in view of **D9: EP 1537878 A1** alone or in combination with other prior art documents.

## 8. INSUFFICIENT DISCLOSURE (Article 83 EPC)

- 8.1 As indicated in one of the cornerstone decisions on the issue of sufficiency of patent disclosure, **T 694/92**, “Article 83 EPC requires an invention to be disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. As made clear in **T 409/91** (OJ EPO 1994, 653, see in particular points 3.3 to 3.5 of the Reasons), the extent to which an invention is sufficiently disclosed is highly relevant when considering the issue of support within the meaning of Article 84 EPC, because both these requirements reflect the same general principle, namely that the scope of a granted patent should correspond to its technical contribution to the state of the art” (**T 694/92**, reason 5; emphasis added).
- 8.2 As demonstrated in Sections 6 and 7 *supra*, anti-PD-1 antibodies, including those that cross-compete for PD-1 binding with **5C4**, were available in the art and their medical utility was described. The identification of a further anti-PD-1 antibody cannot amount to an inventive contribution to the art. On the other hand, the subject matter claimed in claims 1 to 3 encompasses antibodies defined only by their CDRs as well as antibodies that cross-compete with these antibodies for PD-1 binding. Given the importance of the framework regions and the positioning of CDRs, as well as the very broad definition of cross-competition, it becomes evident that the scope of the Opposed Patent is

not commensurate with its contribution to the art, so that the requirements of Article 83 EPC are not met.

- 8.3 Moreover, even if the Patentee would take the position that the specific **5C4** antibody were an advance over the art, the Opposed Patent does not provide any proof that the properties of a particular (reference) antibody would be translated into any other antibody by virtue of its cross-competition therewith. Rather, the opposite appears true from the experimental evidence in the Opposed Patent. For example, significant differences in IFN- $\gamma$  and IL-2 secretion were observed between antibodies **2D3** and **5C4**, cf. Example 5 and Figure 16, albeit their common genetic background, high similarity in CDRs and cross-competition between the two antibodies, as indicated by the Patentee during the prosecution of the application underlying the Opposed Patent. This confirms the well known fact that even minor alterations in the amino acid sequence may result in significant functional differences. Thus, also in this event sufficiency over the entire scope claimed would not be given.
- 8.4 According to the well-established principles under the EPC, where a therapeutic application is claimed in the form of a use of a substance for a defined therapeutic application, attaining the claimed therapeutic effect is a functional feature of the claim. As a consequence, under Article 83 EPC the application must disclose the suitability of the product for the claimed therapeutic application (see **G 2/88** and **G 6/88**, Headnote III, and reason 9; **T 609/02**, reason 2). In this regard it is noted that the Opposed Patent does not provide any evidence for a therapeutic effect of any antibody that cross-competes with **5C4** or an antibody having merely the CDRs of **5C4**, as required by claims 12 to 17. Thus, also from this perspective the requirements of Article 83 EPC are not fulfilled.

8.5 Taken together, the Opposed Patent is insufficiently disclosed in the sense of Article 83 EPC.

In view of the foregoing, revocation of the Opposed Patent *in toto* is justified.

A handwritten signature in black ink, appearing to read 'O. Bezzubova', with a long horizontal flourish extending to the right.

Dr. Olga Bezzubova  
European Patent Attorney  
Association No. 215

**Enclosures**  
**D1 to D19**  
**EPO Form 1010**