

OPPOSITION AGAINST EP 2 161 336

IN THE NAME OF ONO PHARMACEUTICAL CO., LTD. & MEDAREX, INC.

BY JANSSEN BIOTECH, INC.

09013687.0 | O006244EP

1 INTRODUCTION AND REQUESTS

1.1. European patent 2 161 336, which was granted from application 09013687.0, in the name of ONO Pharmaceutical Co., Ltd. and Medarex, Inc. is opposed by Janssen Biotech, Inc. under Article 99 EPC and Rule 76 EPC.

1.2. Opposition is made to the extent of all claims for all designated states.

GROUND OFS OF OPPOSITION

1.3. Opposition is made under Article 100(a) EPC because the invention is not patentable within the terms of Articles 52 to 57 EPC, more particularly because the claims lack novelty and inventive step.

1.4. Opposition is made under Article 100(b) EPC because the 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.

1.5. Opposition is made under Article 100(c) EPC because the patent extends beyond the content of its parent application (EP 06746353.9) as originally filed.

1.6. Briefly, the main deficiencies in the patent are:

- Claim 3 lacks novelty over D5, which discloses a monoclonal antibody that cross-competes for binding to PD-1 with the antibody of claim 1 or claim 2.
- If claim 3 is novel then it must lack an inventive step. The wide range of antibodies encompassed by this claim would not all share the properties of the exemplified 5C4 antibody and thus no technical problem is solved across the scope of this claim.
- All the claims lack an inventive step starting from D5. D5 discloses anti-PD-1 antibodies that modulate immune responses, while the claimed antibodies provide the same technical effect. Providing an alternative antibody with this effect is a routine task and would not involve an inventive step.
- Claim 3 is insufficient because the skilled person cannot ascertain whether any given antibody has the required functional properties and falls within the scope of this claim.
- Claim 3 adds matter under Article 76(1) EPC because there is no disclosure in the parent application of an antibody that cross-competes with an antibody defined by the CDRs listed in claim 1.
- Claims 6-8 and 10 also add matter because they contain intermediate generalisations from specific embodiments and thereby introduce new technical teaching that was not derivable from the parent application as filed.

REQUESTS

- 1.7. The Opponent requests revocation of the patent in accordance with Article 101(2) EPC.
- 1.8. If the Opposition Division cannot grant the request for revocation on the basis of the written proceedings, oral proceedings are requested under Article 116 EPC.

CITED DOCUMENTS

- 1.9. The documents relied upon in the opposition are listed in section 6. Documents D1-D4 were cited during examination. D5-D20 are newly cited.

THE CLAIMS

- 1.10. The patent contains 25 claims. Claims 1 and 3 are independent claims.
- 1.11. Claim 1 relates to an isolated monoclonal antibody, or antigen binding portion thereof, which specifically binds human Programmed Death 1 (PD-1) protein, and which comprises six particular complementarity determining regions (CDRs). The six CDRs correspond to those of the antibody referred to as 5C4 in the patent (see page 11, paragraph [0056]).
- 1.12. Claim 3 relates to a monoclonal antibody, or antigen binding portion thereof, that cross-competes for binding to PD-1 with the antibody of claim 1 (defined by the CDR regions of the 5C4 antibody) or claim 2 (defined by the variable regions of the 5C4 antibody; see page 11, paragraph [0055]).
- 1.13. Claims 4-10 are dependent claims that further define characteristics of the antibodies of claims 1-3.
- 1.14. Claim 11 relates to a composition comprising the antibody (or antigen-binding portion thereof) of any of claims 1-10.
- 1.15. Claims 12-17 relate to medical uses of the claimed antibodies and antigen-binding portions thereof.
- 1.16. Claims 18-25 relate to immunoconjugates, bispecific molecules and compositions comprising such molecules, which comprise the antibody (or antigen-binding portion thereof) of any of claims 1-10.

2 NOVELTY

Various claims lack novelty over D5

- 2.1. D5 was published on 8th July 2004, before the filing date of the patent.
The “cross-competes” feature in claim 3 must be interpreted broadly
- 2.2. Claim 3 relates to a monoclonal antibody, or antigen binding portion thereof, which cross-competes for binding to PD-1 with an antibody defined by the CDR regions or the complete variable regions of the 5C4 antibody.
- 2.3. As set out in detail below¹, D5 discloses several antibodies which fall within the scope of claim 3, as they would inevitably cross-compete for binding with the 5C4 antibody. The antibodies

¹ Paragraphs 2.16-2.23

disclosed in D5 were not tested for cross-competition to the 5C4 antibody in that document, because the 5C4 antibody was disclosed after the filing date of D5. However, the fact that the particular parameter of cross-competition with 5C4 is not mentioned in the prior art is of no relevance: this parameter cannot confer novelty on claim 3, as is made clear by the Guidelines for Examination, Part G-VI-6:

In the case of a prior document, the lack of novelty... may be implicit in the sense that, in carrying out the teaching of the prior document, the skilled person would inevitably arrive at a result falling within the terms of the claim... Situations of this kind may also occur when the claims define the invention... by parameters (see F-IV, 4.11)... It may happen that in the relevant prior art a different parameter, or no parameter at all, is mentioned. If the known and the claimed products are identical in all other respects... then in the first place an objection of lack of novelty arises. The burden of proof for an alleged distinguishing feature lies with the applicant. No benefit of doubt can be accorded if the applicant does not provide evidence in support of the allegations (see T 1764/06)².

- 2.4. The term “cross-competes” in claim 3 is a parameter that is not mentioned in the prior art. Furthermore, the antibody of claim 3 is identical to the known antibodies of D5 in all other respects, as the only further requirements in claim 3 are that the antibody should be a) monoclonal and b) bind to PD-1. Furthermore, the term “cross-competes” is precisely the kind of “unusual parameter” referred to in the Guidelines at F-IV-4.11, where “no meaningful comparison with the prior art can be made” and which may “disguise lack of novelty”. The Guidelines at G-VI-6 emphasise that where the claimed products are identical, except (potentially) for the features defined only by parameters, a lack of novelty objection must arise, and that the burden of proof for dispelling this novelty objection lies with the applicant (in this case the Proprietors).
- 2.5. The present case is in this situation: not only is “cross-competition” with a specific antibody an unusual parameter to use as the sole defining feature of an antibody; it is also a parameter that could not have been referred to in any document published prior to the disclosure of the 5C4 antibody sequence. In such a situation, it is clear that for novelty of claim 3 to be acknowledged, the Proprietors must provide convincing evidence (T 1920/09) that the antibodies of D5 (at least) do not “cross-compete” with an antibody as defined in claim 1 or claim 2.
- 2.6. As explained in more detail below, D5 provides compelling evidence that at least some of the antibodies disclosed in that document would indeed compete with the 5C4 antibody. In this situation, the Proprietors’ burden of proof cannot be discharged without evidence that none of these antibodies cross-competes with an antibody as defined in claim 1 or claim 2.
- 2.7. Before considering the disclosure of D5’s anti-PD-1 antibodies in detail, it is important to consider what is meant in the patent by the term “cross-competes”. This interpretation is essential in order to determine whether any evidence subsequently adduced by the Proprietors would be sufficient to establish novelty for the antibodies of claim 3. It is the

² T 1764/06 explained that where the only expressed distinction between the definition of a claimed product and the prior art product relies on a parameter feature that is not usual for the skilled person, the presumption that the claimed product is not novel must be displaced by evidence. The onus of proof lies with the applicants and no benefit of the doubt can be accorded. See also T 1920/09, in which the Board reiterated these requirements and stated that in the absence of convincing evidence, novelty cannot be acknowledged.

opponent's view, based on the information in D5, that antibodies disclosed in that document would necessarily cross-compete with the 5C4 antibody, particularly in view of the broad definition of this term in the patent.

2.8. It is a well-established principle that a non-specific definition in a claim should be given its broadest technically sensible meaning when assessing novelty of a claim (T 79/96, T 596/96 etc.). The definition of “*cross-compete*” in claim 3 must therefore be interpreted as broadly as is technically sensible in these proceedings, taking into account the definition of this term in the patent.

2.9. The definition of the term “*cross-compete*” is found in paragraph [0070], pages 13-14 of the patent under the heading “*Antibodies that bind to the same epitope as anti-PD-1 antibodies of the invention*”. The first requirement for an antibody that cross-competes with an antibody of claim 1 or claim 2 is that it binds to the same epitope on human PD-1 as an antibody defined by the CDRs or variable regions of the 5C4 antibody, as set out in paragraph [0070]:

“...the invention provides antibodies that bind to the same epitope on human PD-1 as any of the PD-1 monoclonal antibodies of the invention (i.e., antibodies that have the ability to cross-compete for binding to PD-1 with any of the monoclonal antibodies of the invention).” (emphasis added)

2.10. The patent does not define what is meant by binding to the “*same epitope*” as an antibody of the invention. For example, the patent does not state whether or not this feature requires binding to each and every amino acid that forms part of the epitope, or whether binding to some of the same residues is enough. There is no information in the patent regarding whether binding to an overlapping epitope of human PD-1 would be considered binding to the “*same epitope*”. Furthermore, there is no information regarding how the actual epitope(s) bound by the antibodies of the invention should be determined, nor is the epitope bound by the 5C4 antibody disclosed anywhere in the patent. Accordingly, the statement that a cross-competing antibody should “*bind to the same epitope*” as an antibody of claim 1 or 2 does not provide any useful technical information to the skilled person as to how the term “*cross-compete*” should be interpreted.

2.11. Paragraph [0070] goes on to discuss ways in which cross-competing antibodies could be identified via binding assays:

“Such cross-competing antibodies can be identified based on their ability to cross-compete with 5C4 in standard PD-1 binding assays. For example, BIAcore analysis, ELISA assays or flow cytometry may be used to demonstrate cross-competition with the antibodies of the current invention. The ability of a test antibody to inhibit the binding of, for example, 5C4 to human PD-1 demonstrates that the test antibody can compete with 5C4 for binding to human PD-1 and thus binds to the same epitope on human PD-1 as 5C4.” (emphasis added)

2.12. In the above passage, binding to the same epitope is equated with inhibition of binding of an antibody of the invention to human PD-1, as determined by standard binding assays. It is thus clear from the patent that cross-competition is to be determined by inhibition of binding in standard assays, with BIAcore analysis, ELISA assays and flow cytometry mentioned specifically.

2.13. However, nowhere in paragraph [0070], nor indeed at any other place in the patent, is there any mention of the degree to which binding must be inhibited in order for an antibody to be classed as a cross-competing antibody. Thus, in accordance with the requirement that terms in the claim be given their broadest technically sensible meaning when considering novelty, the above passage must be interpreted as meaning that an antibody cross-competes with 5C4 if, when tested in standard binding assays, it results in **any** inhibition of binding of 5C4 to PD-1. Neither claim 3, nor the description of the term “*cross-compete*” in the patent, puts any lower limit on the degree of inhibition required. Accordingly, the term “*cross-compete*” must be interpreted broadly for the assessment of novelty; there is no support in the patent for a narrower definition.

2.14. Furthermore, the common general knowledge provides no support for a narrow definition of this term. It is clear from D6 (a textbook chapter representative of the skilled person’s common general knowledge) that an epitope contains different antigenic determinants, and inhibition of binding can occur whether all or only some of the same antigenic determinants are recognised by two different antibodies:

“Inhibition of the binding of individual labeled antibodies by other unlabeled antibodies is then determined. This permits designation of unique and shared antigenic determinants recognized by these antibodies.” (D6, page 172, emphasis added)

The protocol for epitope mapping by competitive inhibition ELISA outlined on pages 176-177 of D6 further demonstrates that inhibition can be complete or partial, as inhibition is a continuum and is defined as a percentage³.

2.15. The common general knowledge thus supports the broad definition of the term “*cross-competes*” in the patent. As explained below, the antibodies of D5 would certainly cross-compete to some degree with the 5C4 antibody, in particular when the broad definition in the patent of “*cross-competes*” is taken into account.

The antibodies disclosed in D5 fall within the scope of claim 3

2.16. Claim 3 requires that the antibody or antigen-binding portion thereof cross-competes for binding to PD-1 with the antibody of claim 1 or claim 2. As outlined above, the 5C4 antibody in the patent falls within the scope of claim 1 and claim 2, and this is the only such antibody disclosed in the patent. As explained below, the binding characteristics and functional properties of the 5C4 antibody described in the patent are essentially identical to those of a group of antibodies disclosed in D5.

2.17. The characteristics of the 5C4 antibody include specific binding to PD-1 on the surface of cells (Examples 3 and 4, pages 40-41 of the patent), promotion of T-cell proliferation and cytokine (including IL-2) secretion (Example 5, page 41) and blocking of ligand binding to PD-1 (Example 6, page 41). The fact that the 5C4 antibody binds specifically to cell-surface PD-1 demonstrates that it must bind to the extracellular domain of PD-1. Moreover, the fact that ligand binding is blocked suggests that the 5C4 antibody binds within the ligand-binding domain of PD-1.

³ Percentage inhibition is calculated according to the following formula: $1 - [(\text{OD with inhibitor MAb present}) / (\text{OD with inhibitor MAb absent})] \times 100$

- 2.18. D5 discloses a group of antibodies referred to as PD1-17, PD1-28, PD1-33, PD1-35, and PD1-F2, whose CDR and variable region sequences are summarised in Table 1, page 11 of D5. Specific binding to human PD-1 is demonstrated in Example 2, pages 35-36 and Figures 1A and 1B. Further information regarding the binding specificity of the antibodies disclosed in D5 is found in paragraph [046], page 13 (emphasis added):

“In certain embodiments, the antibodies specifically bind an epitope within the extracellular domain of human PD-1. The predicted extracellular domain consists of a sequence from about amino acid 21 to about amino acid 170 of SEQ ID NO:41 (Swissport Accession No. Q15116)... In further embodiments, antibodies of the invention bind to the PD-L-binding domain of PD-1.”

- 2.19. The Examples of D5 show that the PD1-17, PD1-28, PD1-33, PD1-35, and PD1-F2 antibodies both bind the extracellular domain of human PD-1, and that they specifically bind within the PD-L-binding domain of PD-1. The ELISA assay described in Example 6, pages 39-40 and Figure 3 of D5 demonstrates that the PD1-17, PD1-28, PD1-33, PD1-35, and PD1-F2 inhibit binding of PD-L1 to PD-1. It is concluded that these antibodies “*block PD-1/PD-L1 interaction*”, in contrast to anti-PD-1 antibodies J110⁴ and PD1-30.

- 2.20. Cross-blocking results from the inhibition assays described in Example 7, pages 39-40 and Figure 4 demonstrate that the PD1-17, PD1-28, PD1-33 and PD1-35 antibodies bind to a distinct site on human PD-1 from the J110 antibody (which, as shown in Example 6, does not block PD-L1 binding to PD-1). Paragraph [0122], page 40 concludes as follows:

“This suggests that the tested anti-PD-1 antibodies bind to at least two distinct epitopes: one recognized by J110 and J116, and the other one recognized by PD1-17, PD1-28, PD1-33, and PD1-35.” (emphasis added)

- 2.21. The clear implication is that the PD1-17, PD1-28, PD1-33 and PD1-35 must bind to the ligand binding domain of PD-1 as described in paragraph [046]; otherwise, these antibodies would be unlikely to all share the property of preventing PD-L1 binding to PD-1. As explained above, the same is true of the 5C4 antibody described in the patent. It is therefore clear that these antibodies (at least) will cross-compete with the 5C4 antibody, as they bind to the same ligand-binding domain of PD-1.

- 2.22. Further functional characteristics of the PD1-17, PD1-28, PD1-33, PD1-35, and PD1-F2 antibodies demonstrate properties that are shared with the 5C4 antibody, and strongly suggest that these antibodies all bind to human PD-1 at a similar location and with similar properties. Example 9, pages 41-42 and Figure 6 show that PD1-17 enhances T cell proliferation, and PD1-35 is said to have the same effect. In contrast, the J110 antibody did not have this effect, showing that the effect of enhanced T cell proliferation is linked to prevention of ligand binding to PD-1. Paragraph [0128], page 42 further shows that prevention of ligand binding enhances both proliferation and IL-2 production:

“Selected anti-PD1 antibodies, as exemplified by PD1-17 and PD-35, inhibit the interaction of PD-1 with its natural ligands and thereby block delivery of a negative

⁴ Further details of antibody J110 are disclosed in D15.

signal. The blockade of the negative signal also results in enhanced proliferation and IL-2 production."

- 2.23. Again, these properties parallel those of the 5C4 antibody⁵. In light of these results, it would be scientifically untenable to suggest that the PD1-17 and PD1-35 antibodies at least (and likely also the PD1-28 and PD1-33 antibodies) would not compete for binding with an antibody according to claim 1 or claim 2 of the patent. There is, accordingly, a strong presumption that the antibody of claim 3 lacks novelty (as in T 1764/06), and as outlined above this presumption may be displaced only by compelling evidence to the contrary adduced by the Proprietors. However, given the extent of the properties shared between the antibodies of D5 described above and the 5C4 antibody of the patent, any comparison between these antibodies would most likely confirm the lack of novelty of claim 3 rather than dispel the strong presumption of lack of novelty. Claim 3 therefore lacks novelty over D5.

At least claims 5, 9, 11-14, 16 and 17 lack novelty over D5, insofar as they refer to claim 3

- 2.24. Claim 5 differs from claim 3 in that it is directed to an antibody which binds to human PD-1 expressed on a cell surface. Example 9, pages 41-42 of D5 demonstrates that at least the PD1-17 and PD1-35 antibodies are able to bind human PD-1 expressed on the surface of CD4+ T cells. The effects of enhanced T cell proliferation (see Figure 6) and IL-2 production can be attributed only to the presence of the antibody, and the effects of this antibody are clearly the result of its binding to PD-1, which is present in this assay only on the surface of CD4+ T cells. This is confirmed in paragraph [0128], page 42 of D5, which explains that the observed effects of these antibodies are attributable to the binding of these antibodies to PD-1, which blocks ligand binding:

"Selected anti-PD1 antibodies, as exemplified by PD1-17 and PD-35, inhibit the interaction of PD-1 with its natural ligands and thereby block delivery of a negative signal."

Claim 5 therefore lacks novelty over D5.

- 2.25. Claim 9 refers to an antibody of IgG4 isotype. In view of paragraph 103, page 19 of the patent, it appears this must refer to a human IgG4 isotype. D5 discloses PD1-17, PD1-28, PD1-33, and PD1-35 antibodies of IgG4 isotype in paragraph [043], page 12. Claim 9 therefore lacks novelty over D5.
- 2.26. Claim 11 encompasses a composition comprising the antibody (or antigen binding portion thereof) of claim 3, together with a pharmaceutically acceptable carrier. Compositions comprising the antibodies of D5 are disclosed, *inter alia*, in claim 11 and on page 3, paragraph [012] and page 29, paragraph [095] of D5. Although paragraph [095] of D5 refers to a "pharmaceutically acceptable excipient" rather than a "carrier", the definition of the excipient at paragraph [095] is essentially identical to the definition of a "carrier" in the patent (paragraph [0154], pages 25-26). Accordingly, claim 11 also lacks novelty over D5.
- 2.27. Claim 12 covers the use of an antibody of claim 3 in a method of modulating an immune response. Since D5 also discloses that antibodies which fall within the scope of claim 3 of the patent can be used to modulate an immune response (see claim 25 of D5), claim 12 also lacks novelty.

⁵ See paragraph 2.17

- 2.28. Claim 13 covers the use of an antibody of claim 3 in a method of inhibiting the growth of tumour cells, and claim 14 refers to specific cancers. D5 discloses the use of antibodies which fall within the scope of claim 3 in treating cancer, and specifically refers to melanoma and prostate cancer (see paragraphs [012] and [083] of D5), both of which are listed in claim 13 of the patent. Although D5 does not specifically state that the treatment of cancer is due to the inhibition of growth of tumour cells, this is implicit in the disclosure of treating cancer. The mere difference in the wording of the mechanism used to treat cancer is insufficient to establish novelty (see T 114/86). Accordingly, claims 13 and 14 also lack novelty over D5.
- 2.29. Claim 16 covers the use of an antibody of claim 3 in a method of treating an infectious disease, while claim 17 lists specific diseases. D5 discloses the use of antibodies which fall within the scope of claim 3 in treating infectious diseases, including diseases such as influenza that are specifically listed in claim 17 of the patent (see paragraphs [012] and [083] of D5). Thus claims 16 and 17 also lack novelty over D5.
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3 INVENTIVE STEP

The claims lack inventive step over D5

- 3.1. As mentioned above, many of the claims lack novelty over D5. However, if D5 is considered not to disclose all of the features of the claims, then the claims still lack inventive step over this document.

D5 is the closest prior art

- 3.2. D5 is an appropriate choice of closest prior art because it relates to the same purpose and effect as the claimed invention, namely the identification of antibodies against human PD-1 which modulate immune responses (see paragraph [010], page 3 of D5). As discussed above⁶, D5 discloses antibodies which bind to human PD-1 and block ligand binding, thereby modulating immune responses by promoting T-cell proliferation and cytokine secretion.

Claim 3 lacks inventive step over D5 because no technical problem is solved across the scope of the claim

- 3.3. As explained above, the antibodies of D5 would inevitably cross-compete with an antibody according to claim 1 or claim 2 of the patent, and claim 3 therefore lacks novelty over D5. However, in the unlikely event that the Proprietors should adduce evidence suggesting that the antibodies of D5 do not cross-compete with an antibody according to claim 1 or claim 2, claim 3 in any event lacks inventive step over D5.
- 3.4. The broad definition of the term “cross-compete” in the patent⁷ results in claim 3 covering a variety of antibodies with a wide range of binding properties, including antibodies which cross-compete for binding with the 5C4 antibody only to a very limited degree, e.g. because they have low affinity for PD-1. It is implausible that all such antibodies would share the effects of the 5C4 antibody. Accordingly, even if one of the effects of the 5C4 antibody described in the patent were considered to provide a technical effect that was not expected from the prior art,

⁶ Paragraphs 2.18-2.21

⁷ See paragraphs 2.2-2.15

this technical effect would not be provided by all antibodies falling within the scope of claim 3. Accordingly, any technical problem based on this effect would not be solved across the whole scope of claim 3 (T 939/92). In any event, as explained below, none of the effects of the claimed antibodies is unexpected in view of the prior art.

The “cross-compete” feature in claim 3 does not provide a technical effect

- 3.5. The only feature that potentially distinguishes the antibodies of claim 3 from the antibodies of D5 is that they “cross-compete” with an antibody according to claim 1 or 2. However, the patent does not disclose any technical effect associated with this difference. The effects relied upon by the Proprietors during prosecution (outlined in paragraphs 3.6-3.14 below) are limited to the exemplified 5C4 antibody and it is implausible that all antibodies according to claim 3 would share these features. Furthermore, the effects of the 5C4 antibody are in any event predictable from the prior art.
- 3.6. In their response of 17th August 2011, the Proprietors relied upon several alleged “*unexpectedly advantageous properties*” of the 5C4 antibody as evidence of an inventive step. The Proprietors argued that the *in vitro* (“pre-clinical”) data in the application as filed was predictive of “*superior therapeutic activity*” said to be demonstrated after the filing date in clinical trials. However, none of the properties relied upon in this discussion was unexpected; nor can these properties simply be extrapolated to any cross-competing antibody according to claim 3.
- 3.7. First, the applicants referred to the “*high specificity of the antibody in binding to PD-1 but not to any of the related human receptors ICOS, CD28 or CTLA-4 (Example 3)*” (as claimed in claim 4(b) of the patent). However, the antibodies of D5 bind specifically to PD-1, as stated in paragraph [010], page 3 of D5. While the antibodies of D5 were not tested experimentally for a lack of cross-reactivity to ICOS, CD28 and CTLA-4 specifically, Example 2 (pages 35-36) and Figures 1A and 1B show specific binding to PD-1 and not to control proteins. Furthermore, it is clear from paragraph [005], page 2 that the whole disclosure of D5 relates to antibodies which bind to PD-1 and not to CD28, CTLA-4 or ICOS (emphasis added):

“Molecular homologues of CD28 and CTLA-4 and their B-7 like ligands have been recently identified. ICOS is a CD28-like costimulatory receptor. PD-1 (Programmed Death 1) is an inhibitory receptor and a counterpart of CTLA-4. This disclosure relates to modulation of immune responses mediated by the PD-1 receptor.”

It is thus clear that D5 does not relate to modulation of immune response mediated by ICOS, CD28 or CTLA-4. An antibody cross-reactive with any of these proteins therefore does not form part of the disclosure of D5.

- 3.8. In addition to this, it is clear from the binding properties of the antibodies disclosed in D5 that they would not cross-react with ICOS, CD28 or CTLA-4. As discussed above⁸, the PD1-17, PD1-28, PD1-33, and PD1-35 antibodies of D5 bind to an epitope distinct from that bound by other prior art PD-1 antibodies, and this epitope must fall within the PD-L-binding domain of PD-1 (given that the antibodies block ligand binding). Accordingly, this shared epitope present in the ligand-binding domain of PD-1 would have to be present in ICOS, CD28 and

⁸ Paragraphs 2.18-2.23

CTLA-4 for the antibodies of D5 to be cross-reactive with these proteins. This is the case for several reasons. First, the fact that these proteins bind different ligands from PD-1⁹ makes it highly unlikely that shared epitopes will be present in the ligand-binding domain. Second, the sequence of the ligand binding domain of PD-1 is not conserved in any of CD28, CTLA-4 or ICOS¹⁰. This is demonstrated graphically in D9, which provides sequence alignments between the protein sequences of PD-1 and each of CD28, CTLA-4 and ICOS. In the extracellular domain (amino acids 21-170; see D5, paragraph [046], page 13), there are no conserved stretches of amino acids which could form cross-reactive epitopes. In view of the lack of sequence identity, it is very unlikely that an antibody specific for PD-1 would bind to CD28, CTLA-4 or ICOS. Far from being unexpected, therefore, a lack of binding to CD28, CTLA-4 and ICOS would be a property predictable for any antibody specific for PD-1.

- 3.9. Of all the antibodies which might be expected to cross-react with CD28, CTLA-4 or ICOS, the most likely candidates would be antibodies which cross-compete only to a limited degree with an antibody according to claim 1 or claim 2 (which, as explained above, are encompassed within the scope of claim 3). Accordingly, if the Proprietors seek to rely on a technical effect of lack of cross-reactivity with other CD28 family members, it is not plausible that this technical effect would be shared by all antibodies according to claim 3, and the technical problem would therefore not be solved across the scope of this claim.
- 3.10. The Proprietors also referred to the “*effect of the antibody in releasing the inhibition imposed by T regulatory cells on proliferation and IFN-gamma secretion of CD4+ CD25- T cells (Examples 21 and 22)*”. However, the same effect would be expected with the PD-1 antibodies disclosed in the prior art (such as those of D5) which block ligand binding and stimulate cytokine secretion. In particular, increased IFN-γ secretion has been observed *in vivo* in response to treatment with an anti-PD-1 antibody (see the paragraph spanning pages 66-67 in D10), *i.e.* in a physiologically-relevant situation where T regulatory cells would be present. Therefore, this is not a surprising property of an anti-PD-1 antibody that blocks ligand binding¹¹.
- 3.11. Moreover, the effects on proliferation and cytokine secretion provided by the 5C4 antibody in the patent and by the antibodies in D5 (which also block ligand binding) would not be provided by all antibodies falling within the scope of claim 3. An antibody which shows a low degree of cross-competition with an antibody according to claim 1 or 2 is unlikely to provide enough inhibition of ligand binding to stimulate proliferation and cytokine secretion to a significant degree. Therefore, if the Proprietors seek to rely again on this effect, the technical problem would not be solved across the scope of claim 3.
- 3.12. A further feature that the Proprietors tried to rely upon was the “*absence of ADCC and CDC activity in the antibody (Examples 23 and 24)*”. However, this feature depends not on the CDR and variable region sequences of the claimed antibody, but rather on the constant

⁹ As explained on page 1, lines 30-35 of the application as filed, there are two ligands which bind to the PD-1 receptor (PD-L1 and PD-L2), and neither of these ligands bind to other CD28 family members. See also D7, page 309, right-hand column under the heading “Immunological functions of PD-1”, which confirms that there is no overlap between the ligands bound by PD-1 and those which bind to the other CD28 family members.

¹⁰ D8, page 337, left-hand column, sets the sequence identity between PD-1 and CD28, CTLA-4 or ICOS at ~20%.

¹¹ For the avoidance of doubt, the anti-PD-1 antibody used in D10 (J43) also blocks binding of both PD-L1 and PD-L2 to PD-1 (see legend to Figure 1 on page 64)

regions. Figure 9.19 on page 389 of D13 shows that it was a well-known fact that IgG1 is a good mediator of ADCC (“sensitization for killing by NK cells”) and CDC (“activates complement system”), whereas IgG4 has little or no ADCC or CDC activity. Indeed, it is acknowledged in Example 23 (page 98, lines 29-32) of the application as filed that ADCC activity is a property of the constant region and not the variable region:

“Results showed that 5C4-IgG4 did not mediate ADCC on activated CD4 T cells, while 5C4-IgG1 did mediate ADCC on activated CD4 T cells (Figure 53), indicating that ADCC activity is related to its Fc region of the anti-PD-1 antibody.” (emphasis added)

Accordingly, the absence of ADCC is not a property of the 5C4 antibody variable region in general; it requires an IgG4 constant region. There is no inventive step involved in selecting an IgG4 constant region, since the inability of this constant region to mediate ADCC would form part of the skilled person’s common general knowledge. Furthermore, claim 3 is not limited to an IgG4 constant region and so this technical effect would in any event not be provided by all antibodies falling within the scope of this claim.

- 3.13. CDC activity of antibodies is also usually related to the constant region rather than the variable region, with IgG1 typically able to activate complement relatively efficiently in comparison to IgG4, which cannot (see D13). This is acknowledged in the application as filed on page 35, lines 33-36, which states that amino acids 329, 331 and 332 of an antibody Fc region can be replaced to reduce or abolish CDC activity. The inability of both 5C4-IgG1 and 5C4-IgG4 to mediate CDC in Example 24 (pages 98-99), therefore, is not a surprising property attributable to the variable region of the 5C4 antibody; indeed, it is most likely that this phenomenon is related to antigen density. It is well known that two IgG molecules must engage distinct antigenic epitopes within 30-40 nm of each other in order to adequately engage C1q and initiate complement (see D13, page 396, first paragraph), and that antigen density is a major factor affecting complement activation. Thus the lack of CDC activity is likely related to low density of the PD-1 antigen, whereas the ability of the anti-HLA-ABC antibody (whose isotype is not mentioned) to mediate CDC is most likely related to higher antigen density. In any event, the application as filed certainly does not provide any suggestion, let alone evidence, that the 5C4 antibody’s inability to fix complement in the assay carried out in Example 24 depends on any of the properties of the variable region of this antibody.
- 3.14. The Proprietors also suggested that “entry of the claimed antibody into the clinic” provided evidence for the alleged superior therapeutic efficacy, referring to Phase I and II clinical trials of the MDX-1106 antibody¹². However, even if these post-filing data were relevant for the assessment of inventive step (which is denied; see paragraph 3.23 below), they would be irrelevant to claim 3 which does not encompass only the MDX-1106 antibody, but also any cross-competing antibodies. It is implausible that many cross-competing antibodies would share the clinical effects of MDX-1106.

¹² The MDX-1106 antibody comprises the same CDR and variable region sequences as the 5C4 antibody. This antibody is also referred to in the literature as ONO-4538 and BMS-936558.

- 3.15. Furthermore, there are various other anti-PD-1 antibodies currently in clinical trials, including pidilizumab (CT-011, humanised BAT-1¹³) and pembrolizumab/lambrolizumab (MK-3475). Indeed, a Phase I clinical trial with CT-011 was already underway before the filing date (and first priority date) of the Patent (see D18¹⁴; D19, page 3046, left-hand column under “Results”). Accordingly, the report of a Phase I clinical trial with the MDX-1106 antibody in 2010 is not, as alleged by the Proprietors, evidence of “*superior therapeutic efficacy*” compared to other prior art antibodies.
- 3.16. Leaving aside the technical effects relied upon by the Proprietors in prosecution, the patent does not disclose or suggest any further technical effects that could support an inventive step. The properties of specific binding to PD-1 on the surface of cells, promotion of T-cell proliferation and IL-2 secretion, and blocking of ligand binding to PD-1 are all shared by the antibodies of D5¹⁵. Furthermore, as explained in paragraph 3.11, these properties would not be shared by all antibodies falling within the scope of claim 3.
- 3.17. The other data provided in the patent relating to the 5C4 antibody do not demonstrate any effect that is surprising in view of the prior art. In Example 5, IFN-γ production (in addition to IL-2 production) is demonstrated in a mixed lymphocyte reaction (MLR), and further assays in Examples 9 and 22 confirm increased IFN-γ secretion in other assays. However, there is nothing surprising about the fact that IFN-γ production is stimulated in addition to IL-2 production. Although IFN-γ production was not analysed in D5, various other studies of PD-1 or PD-1 ligand blockade consistently show increased IFN-γ secretion¹⁶. Indeed, the fact that PD-1 engagement is known to suppress the production of various cytokines, including IFN-γ, (see D7, page 309, right-hand column) makes it predictable that any antibody that blocks ligand binding will enhance production of these same cytokines.
- 3.18. Accordingly, there is no technical effect that can be said to be provided by substantially all antibodies falling within the scope of claim 3, and even the technical effects that might be possessed by specific antibodies (e.g. the exemplified 5C4 antibody) are not surprising. The technical problem starting from D5 is therefore the provision of an alternative antibody to PD-1, and the solution is the antibodies of claim 3. This solution is obvious because the skilled person would have been motivated to make these antibodies¹⁷, and would have faced no technical difficulties in doing so given that the techniques required would have been well

¹³ Details of humanised BAT-1 antibodies were made available in D17.

¹⁴ This report of the CT-011 clinical trial was published after the first priority date. However, D18 forms part of the state of the art because the Patent is not entitled to any of the three priority dates (see D20, which shows that the assignments from the inventors to Medarex were executed after the filing date of the patent).

¹⁵ See paragraphs 2.16-2.23

¹⁶ D1 (see abstract) demonstrates increased IFN-γ secretion using PD-L1 and PD-L2 blocking antibodies; D7 (page 311, left-hand column, end of second paragraph) cites several studies showing that neutralising antibodies against PD-L1 augment IFN-γ production from tumour-specific CTLs; D10 (paragraph spanning pages 66-67) shows increased frequency of IFN-γ producing cells in mice treated with anti-PD-1 or anti-PD-L1 antibodies.

¹⁷ For example in view of pages 14-15 (paragraphs [050]-[051]) of D5, which refer to methods for obtaining other antibodies specific for PD-1, including variants, derivatives and analogues of the antibodies of the invention. Furthermore, it is clear from documents such as D7, D11, D12 and D14 (discussed in paragraph 3.26 below) that anti-PD-1 antibodies which block ligand binding were generally understood in the art to be very promising candidates for cancer immunotherapy at least, and it would therefore be desirable to generate further antibodies.

known from the skilled person's common general knowledge, and guidance is furthermore provided in the description and examples of D5¹⁸.

- 3.19. Claim 3 therefore lacks inventive step over D5.

Claim 1 lacks inventive step over D5

- 3.20. The only difference between the antibodies of D5 and the antibodies of claim 1 are the specific CDR sequences corresponding to those of the 5C4 antibody. As explained above for claim 3, the technical effects of the 5C4 antibody are the same as those of the antibodies of D5, and no further technical effect is provided by the antibodies of the invention as compared with the technical effects of the anti-PD-1 antibodies disclosed in D5¹⁹. The objective technical problem therefore remains to provide an alternative antibody to PD-1 that modulates immune responses. Providing an alternative antibody mediating the same effects as the antibodies of D5 is a routine task that could be carried out by a person skilled in the art without requiring inventive skill, based on techniques well known from the skilled person's common general knowledge, and following the guidance outlined in the description and examples of D5¹⁷. Accordingly, the provision of antibodies according to claim 1 would have been obvious starting from D5.

- 3.21. Therefore, claim 1 lacks an inventive step in view of D5.

Claim 2 lacks inventive step over D5

- 3.22. The only difference between the antibodies of D5 and the antibodies of claim 2 are the specific variable region sequences corresponding to those of the 5C4 antibody. However, as stated above, the technical effects of the 5C4 antibody are the same as those of the anti-PD-1 antibodies of D5, and the objective technical problem is merely to provide an alternative antibody to PD-1. As discussed for claim 1 above, providing an alternative antibody is routine and would not have required an inventive step.
- 3.23. The Proprietors' suggestion that the Phase I and II clinical trials of MDX-1106 support an inventive step is also wrong for the antibody of claim 2. In this instance, following the guidance in T 1329/04, post-filing data cannot be taken into account for the assessment of inventive step, because the disclosure in the application does not make it plausible that its teaching solves the problem it purports to solve. The invention cannot therefore be acknowledged as a contribution to the art (*i.e.* solving a technical problem rather than merely putting one forward). The application as filed contains no information to suggest, let alone make it plausible, that the 5C4 antibody will have superior therapeutic efficacy, or indeed any technical effect not already provided by prior art anti-PD-1 antibodies. As explained above, each of the effects demonstrated in the application as filed with the 5C4 antibody was already known or entirely predictable from the prior art to be a property of antibodies against PD-1.
- 3.24. No *in vivo* experiments were conducted with the 5C4 antibody in the application as filed; all the experiments in mouse models (*e.g.* Examples 11 and 18) were conducted with the chimeric anti-mouse-PD-1 antibody referred to as 4H2 (described on page 86, lines 15-22).

¹⁸ See *e.g.* paragraph [035], page 8 and Example 1, pages 33-35 of D5, which discuss the generation of antibodies. The remaining Examples explain how to test for the properties of the antibodies disclosed in D5.

¹⁹ Discussed in paragraphs 2.16-2.23 and 3.5-3.16

No sequence information is disclosed for this antibody, and there is no indication that it shares the CDR sequences of the 5C4 antibody, as required by claim 1. Even if the 4H2 antibody were to cross-compete with the antibody of claim 1, and thus fall within the scope of claim 3, the results obtained with it would be no more applicable to the antibodies of claim 2 than they are to prior art anti-PD-1 antibodies such as those of D5.

- 3.25. Moreover, beneficial effects of anti-PD-1 antibodies in *in vivo* mouse tumour models had already been demonstrated in the prior art. For example, D11 provides evidence that injection with an anti-PD-1 monoclonal antibody inhibits tumour growth in mice injected with melanoma or colon cancer cells (page 140, right-hand column, final two paragraphs); and D12 shows that an anti-PD-1 antibody which blocks PD-L1 binding prevents tumour resistance to CTL lysis and completely abrogates tumour outgrowth (page 1093, right-hand column, first full paragraph)²⁰. Accordingly, at the filing date, the beneficial effects of anti-PD-1 antibodies in anti-tumour therapy were already known. The application as filed does not go any further than the prior art in terms of experimental support for a therapeutic effect; and certainly not for the 5C4 antibody, which was not even tested *in vivo*.
- 3.26. D7, D11, D12 and D14 also clearly contradict the allegation in the Proprietors' response of 17th August 2011 that *"an agent that disrupts the interaction between PD-1 and PD-L1, such an anti-PD-1 antibody as claimed, would have no beneficial anti-tumor effect in vivo"*. This statement was based on a single study published in 2001; clearly, this view had been superseded in the literature closer to the filing date of the patent; by that time, it was well known that interfering with this interaction showed great promise for cancer immunotherapy, as concluded by the authors of the review article D7 (page 312, final paragraph, emphasis added):

"Interfering with the interaction of PD-L1... with its receptor PD-1 on T cells... might potentiate antitumor T-cell effector function in vivo. Translating these ideas to therapy approaches for human cancer patients should be a high priority in future studies."

The likely beneficial effect of anti-PD-1 antibodies in cancer treatment was therefore predictable from the bulk of the literature in this field at the filing date.

- 3.27. It should also be noted that the simple fact of entry of an antibody into clinical trials in no way demonstrates superior efficacy or an inventive step; the reasons why a particular antibody is advanced into clinical trials while another is not include various considerations that have nothing to do with antibody efficacy (for example financial considerations). There is nothing to suggest that an antibody with the variable region sequences of the 5C4 antibody would perform any better in the clinic than prior art antibodies against PD-1 which block ligand binding, including those of D5.
- 3.28. Accordingly, claim 2 also lacks an inventive step in view of D5.
- The dependent claims also lack an inventive step over D5
- 3.29. None of the additional features provided in dependent claims 4-10 render the claims inventive, because none of these features provide an unexpected technical effect over the prior art. The

²⁰ See also D14, Example 13, column 31, paragraphs [0128]-[0129], which shows that anti-PD-1 antibody inhibits cancer metastasis.

features referred to in claims 5, 9, 11-14 and 16-17 are all specifically mentioned in D5²¹ and thus cannot support an inventive step. The features of claims 4(b), 6 and 10 have already been discussed above²².

- 3.30. The K_D of 5×10^{-9} [M] or less referred to in claim 4(a) is not shown to provide any technical effect in the application as filed. Examples 5 and 6 (pages 81-82) and Figures 16 and 17 show that there is no correlation between antibody affinity and effects on T cell proliferation, cytokine secretion and blocking of ligand binding. Indeed, although not all of the antibodies were compared in all the assays, Figure 16A shows that antibody 4H1 (which has the lowest affinity of any of the antibodies tested and falls outside the range recited in claim 4(a), at 5.46×10^{-9} M) stimulated T cell proliferation to a greater extent than the 5C4 antibody, despite having ~7.5-fold lower affinity for PD-1²³. In any event, it would be routine to generate antibodies with an affinity of 5×10^{-9} M; this is certainly not a surprisingly high affinity²⁴.
- 3.31. The features of claim 7 (enhancement of the antigen specific-memory response to a tumor or a pathogen) and claim 8 (persistent immunity to tumour relapse) are simply not demonstrated at all in the application as filed, let alone for the 5C4 antibody. Similarly, the provision of immunoconjugates, bispecific molecules and compositions comprising immunoconjugates and bispecific molecules (claims 18-25) are not demonstrated in the application as filed (and the generation of such compounds would in any case be routine). Accordingly, a technical effect cannot be derived from these features, since the application as filed would not show that the technical problem had been solved.

4 INSUFFICIENCY

Claim 3 is insufficient because the skilled person cannot identify when s/he has obtained an antibody with the claimed properties

- 4.1. Claim 3 is insufficient under Article 83 EPC because the 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. This is because the patent provides insufficient information to allow the skilled person to ascertain whether any given antibody falls within the scope of this claim.
- 4.2. The only structural feature in claim 3 is the requirement for the claimed molecule to be an antibody or antigen binding portion thereof. In all other respects, the molecule is functionally defined. The use of such functional features in claims is only allowable when the skilled person can identify when the features are present. If this is not the case, then the claims contravene Article 83 EPC²⁵.

²¹ See paragraphs 2.24-2.29

²² Paragraphs 3.7-3.13

²³ Antibody affinities are given in Table 2, page 80 of the application as filed.

²⁴ For example, the K_D of the PD1-F2 antibody of D5 is 6.7×10^{-9} M (paragraph [0117], page 38), which is not substantially different from 5×10^{-9} M.

²⁵ See page 327 of the 7th Edition of the Case Law of the Boards of Appeal of the European Patent Office (English version): *In T 464/05, the board held that the patent in suit did not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Art. 83 EPC 1973). This finding essentially corresponded to the requirement that the skilled person had to know "when he is working within the forbidden area of the claims" (see e.g. decisions T 256/87 and decisions T 387/01, T 611/02 and T 252/02 of board 3.2.06). In the board's view, although this requirement in its broad reading was*

- 4.3. It is impossible to determine the limits of the scope of protection provided by claim 3 because the conditions under which the cross-competition parameter are to be measured have not been defined. This leads to problems under Article 83 EPC because the skilled person cannot determine whether a given antibody meets the functional requirements of the claim.
- 4.4. Cross-competition as defined in the patent cannot be reliably measured. The patent at paragraph [0070] refers to three different binding assays that may be used to determine whether an antibody “cross-competes” with an antibody according to claim 1 or 2 and therefore falls within the scope of claim 3: ELISA assays, BIAcore analysis or flow cytometry. As explained in D6, inhibition of binding measured by ELISA is a continuum, with the degree of inhibition expressed as a percentage²⁶. The same will be true for both BIAcore analysis and flow cytometry. However, the different experimental setup and sensitivity of each of these assays means that the results will not correlate completely. How is the skilled to know whether or not s/he is working within the scope of claim 3 if an ELISA assay sets the level of cross-competition at, say, 10%, whereas in a flow cytometry assay it is negligible?
- 4.5. D16 illustrates the problem: in an analysis of epitope specificity of antibodies binding to cell surface epitopes, the flow cytometry results in some cases contradicted those obtained by ELISA (abstract, lines 15-16 and page 867, right-hand column). One suggested reason for this discrepancy is the better accessibility of cell surface epitopes when cells are maintained in suspension (flow cytometry) rather than coated on microtitre plates (ELISA; see page 867, right-hand column, final sentence). Similar inconsistencies would therefore be expected between competitive binding ELISA and flow cytometry results for the cell-surface antigen PD-1.
- 4.6. The fact that no parameters are mentioned for any of the assays makes the problem all the more acute. First, variation of the assay conditions could affect whether or not cross-competition was detectable. Moreover, the lack of a minimum cut-off value for defining an antibody as “cross-competing” means that there will always be uncertainty for the skilled person as to whether s/he is operating in the forbidden area of the claims or not. For example, would an antibody that results in 1% inhibition of binding of an antibody according to claim 1 or 2 fall within the scope of claim 3? What about 5%, or 10%? No guidance in this regard can be found in the patent or the prior art.
- 4.7. Although for novelty purposes each claim feature must be given its broadest technically sensible meaning, this is not the case for the purposes of sufficiency of disclosure²⁷. Indeed, the Guidelines for Examination at G-VI-6 (continuing from the passage cited in paragraph 2.3 above):

If, on the other hand, the applicant is able to show, e.g. by appropriate comparison tests, that differences do exist with respect to the parameters, it is questionable whether the application discloses all the features essential to manufacture products having the parameters specified in the claims (Art. 83).

certainly related to Art. 84 EPC 1973 (see e.g. decision T 943/00), it was in fact related to Art. 83 EPC 1973 in its restricted reading, implying that the skilled person had to be able to determine whether a particular object fell within the forbidden area of the claims intended as the area including those embodiments that effectively solved the technical problem underlying the patent in suit.

²⁶ See paragraph 2.14

²⁷ T 79/96: “when assessing novelty of the claimed subject-matter, an expression in a claim should be given its broadest technically sensible meaning.”

Thus, even in the unlikely event that claim 3 was found to be novel in view of any comparative tests conducted by the Proprietors, the patent would inevitably be insufficient as the conditions and parameters used for comparison would not be disclosed in the patent or the prior art.

- 4.8. Accordingly, claim 3 is insufficient.
 - 4.9. For the reasons outlined above, claims 4-25 are also insufficient, as they are dependent on claim 3, and in some cases contain further functional definitions that are not defined in the patent.
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5 ADDED MATTER

Claim 3's reference to claim 1 adds matter

- 5.1. Granted claim 3 refers to both claim 1, which relates to an antibody comprising only the CDRs of the 5C4 antibody, and claim 2, which relates to an antibody comprising the variable regions of the 5C4 antibody. However, the description and claims of the parent application as originally filed referred only to antibodies which cross-compete with an antibody comprising the full variable regions of the 5C4 antibody. There is no disclosure in the parent application of an antibody that cross-competes with an antibody defined only by its CDRs. Accordingly, claim 3 adds matter compared to the parent application and does not meet the requirements of Article 76(1) EPC.
- 5.2. For example, claims 8 to 15 of the parent application relate to antibodies which cross-compete with an antibody according to the invention, defined according to the full sequences of the heavy chain and light chain variable regions. Claim 8 as filed reads as follows (emphasis added):

"An isolated human monoclonal antibody, or an antigen-binding portion thereof, wherein the antibody cross-competes for binding to PD-1 with a reference antibody comprising:

- a) a human heavy chain variable region [that] comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 2, 3, 4, 5, 6 and 7; and*
- b) a human light chain variable region [that] comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 9, 10, 11, 12, 13 and 14."*

SEQ ID NOs: 4 and 11 relate to the variable region sequences of the heavy and light chains, respectively, of the 5C4 antibody. Claim 12 as filed recites the specific combination of SEQ ID NOs: 4 and 11. None of the claims relating to cross-competing antibodies refers to an antibody that cross-competes with an antibody defined only by its CDR sequences.

- 5.3. The description of the parent application as filed also does not provide any basis for the dependency of claim 3 of the patent on claim 1. The description first refers to cross-competing antibodies at page 3, lines 12-18. This passage uses the same wording as claim 8 of the parent application as filed (cited above). The description continues on pages 3-4 to refer explicitly to the specific combinations of heavy and light chain variable regions which correspond to each of the antibodies disclosed in the application as filed; lines 32-35 relate to the 5C4 antibody. The next reference to a cross-competing antibody occurs at page 29, line

25 to page 6, line 9, which again refers to the antibodies of the invention, including 5C4, in terms of their complete variable regions (emphasis added):

“In another embodiment, the invention provides antibodies that bind to the same epitope on human PD-1 as any of the PD-1 monoclonal antibodies of the invention (i.e., antibodies that have the ability to cross-compete for binding to PD-1 with any of the monoclonal antibodies of the invention). In preferred embodiments, the reference antibody for cross-competition studies can be the monoclonal antibody ... 5C4 (having VH and VL sequences as shown in SEQ ID NOs: 4 and 11, respectively)...”

The remainder of this paragraph, on page 30 of the parent application as filed, refers to the antibodies only by name (e.g. “5C4”). There is no mention of an antibody defined solely by CDR sequences. This information was added in the claim set filed with divisional application 09013687.0 on 29th October 2009, thus adding matter over the parent application as filed.

- 5.4. As explained above for inventive step (paragraph 3.19), the CDR sequences of an antibody alone are not sufficient to define its binding characteristics. Clearly, claim 1 covers a much greater range of antibodies with a greater variety of binding characteristics than claim 2. Therefore, by making claim 3 dependent on claim 1 as well as claim 2, the Proprietors have increased the range of cross-competing antibodies encompassed by this claim. This is contrary to the principle that that “an applicant is not allowed to improve his position by adding subject-matter not disclosed in the application as filed, which would give him an unwarranted advantage and could be damaging to the legal security of third parties relying on the content of the original application...” (Guidelines for Examination, Part H-IV-2.2). As outlined above, there is no disclosure in the parent application, explicit or implicit, that would be understood by the skilled person as referring to an antibody that cross-competes with any antibody defined by CDRs alone, let alone the CDRs of the 5C4 antibody in particular. Claim 3 as granted therefore presents the skilled person with information that is not directly and unambiguously derivable from the parent application as originally filed. Accordingly, claim 3, insofar as it refers to claim 1, comprises an unallowable extension of subject-matter and does not meet the requirements of Article 76(1) EPC.

Claim 6 adds matter over the parent application as filed

- 5.5. Claim 6 refers to an antibody according to any one of claims 1-4, wherein the antibody inhibits the suppression of CD4+ CD25- T cells by regulatory T cells. However, the only reference to T regulatory (Treg) cells anywhere in the earlier application as filed is in Example 21, page 97. Only the 5C4 antibody was tested in this example, and there is no basis for extrapolating the results to any antibody as defined in claims 1-4. As outlined above, claims 1-4 comprise a wide variety of antibodies which may differ significantly from 5C4 in terms of their binding properties, particularly in claim 3 which covers antibodies that cross-compete with an antibody such as 5C4 even to a very limited extent.
- 5.6. Furthermore, the 5C4 antibody in Example 21 was tested under specific reaction conditions (e.g. at a concentration of 10 µg/ml). Thus there is no general disclosure of inhibiting the suppression of CD4+ CD25- T cells by Treg cells; this phenomenon is referred to only as an observation in the context of the specific antibody used and the reaction conditions described in Example 21. Furthermore, page 98, lines 1-2 of the application as filed states that “addition of anti-PD-1 human monoclonal antibody 5C4 partially released inhibition imposed by Treg cells...” (see also Figure 51B), suggesting that the reaction conditions used in Example 21

result in only a modest reduction of Treg inhibition. This partial inhibition would not be understood by the skilled person to be more widely applicable to all the antibodies and reaction conditions covered by claims 1-4 of the patent.

- 5.7. The Boards of Appeal have repeatedly confirmed that an intermediate generalisation of this kind, where certain characteristics are isolated from a working example, is allowable only if *“the skilled person could recognise without any doubt from the application as filed that those characteristics were not closely related to the other characteristics of the working example and applied directly and unambiguously to the more general context”* (Case Law of the Boards of Appeal, 7th Edition, page 373, summarising T 962/98). The same principle was followed in T 714/08 and T 477/09; the Boards explained that generalisations from examples that related to a very specific combination of technical features did not provide basis for a generalised amendment. As explained above, the extrapolation of Example 21 to cover a wide variety of different antibodies and reaction conditions is precisely such an impermissible generalisation.
- 5.8. This extension of subject-matter introduces new technical teaching contrary to G 1/93, as the technical effect of inhibition of Treg suppression of CD4⁺ CD25⁻ T cells is extended to antibodies and reaction conditions which are not suggested or demonstrated to have this effect. Accordingly, claim 6 extends beyond the content of the parent application as originally filed.

Claim 7 adds matter over the parent application as filed

- 5.9. Claim 7 relates to an antibody of claims 1-5 which *“enhances the antigen-specific memory response to a tumor or a pathogen”*. The effect of stimulating antigen-specific memory responses is not mentioned at all in the claims of the parent application as filed. Furthermore, no basis for this wording can be found in the description of the parent application, as none of the references in the application as filed to enhancing or stimulating antigen-specific memory responses (page 3 line 3; page 16 line 9; page 21 line 27; page 27 line 9; page 28 line 32; and page 38 line 37) refer specifically to enhancement of a response to a tumour or pathogen. There is no reference at all in the parent application as filed to enhancing a memory response to any specific antigen, let alone to a tumour antigen or pathogen. Accordingly, claim 7 adds matter over the parent application as originally filed.

Claim 8 adds matter over the parent application as filed

- 5.10. Claim 8 relates to an antibody of claims 1-5 which *“confers a persistent immunity to tumor relapse”*. Again, there was no reference to this technical effect in the claims of the parent application as originally filed, and the description provides no basis for applying this technical effect to anti-PD1 antibodies according to claims 1-5.
- 5.11. The only reference to “persistent immunity to tumor relapse” in the parent application as filed is in the description of Figure 49 in Example 19 (page 97, line 3):

“Figure 49 shows the mean tumor volume for the naïve and re-challenged mice. These data indicate that, similar to the antibody monotherapy, the combination antibody therapy resulting in PD-1 and CTLA-4 blockade produces a persistent immunity to tumor relapse.”

However, the “antibody monotherapy” referred to in the above passage did not involve an antibody according to claims 1-5 of the patent. Page 96, line 26 states that the only anti-PD-1 antibody used in this example was “*anti-PD-1 monoclonal antibody 4H2*”. As stated above²⁸, this is a chimeric antibody against mouse PD-1 whose CDR and variable region sequences were not disclosed in the application as filed, and which is not suggested to bear any similarity to the 5C4 antibody in terms of either sequence or binding specificity. The results presented in Figure 49 cannot be interpreted as applying to any PD-1 antibody, and there is no basis for taking an isolated statement relating to the effect of the 4H2 antibody and applying this to the antibodies of claims 1-5 (see T 962/98, T 714/08 and T 477/09). Again, this introduces new technical teaching, contrary to G 1/93. Accordingly, claim 8 adds matter over the parent application as originally filed.

Claim 10 adds matter over the parent application as filed

- 5.12. Claim 10 relates to an antibody of claim 9 (*i.e.* of IgG4 isotype) which has neither ADCC activity nor CDC activity. ADCC and CDC activity are, again, technical effects that were not mentioned in the claims of the parent application as filed. Moreover, the general disclosure in the parent application as filed refers to ADCC only in the context of increasing its activity, and at no point is an antibody lacking ADCC or CDC activity mentioned. For example, page 36, lines 1-2 states that:

“...the Fc region is modified to increase the ability of the antibody to mediate antibody dependent cellular cytotoxicity (ADCC)...” (emphasis added)

The description continues on pages 36-37 to discuss methods of increasing the ADCC activity of antibodies. Similarly, page 49 discusses ADCC as a desirable property of bispecific molecules of the invention.

- 5.13. Reducing ADCC activity is mentioned only in Example 12, page 87 and Example 23, page 98 of the application as filed. However, the rationale for reducing ADCC activity in Example 12 is simply to prevent ADCC against the foreign Fc region of the 4H2 antibody to allow its used in the experimental mouse model used in this Example, as explained on page 87, lines 23-27:

*“For use in the mouse tumor models, the 4H2 rat anti-mPD-1 needed to be modified so the mouse immune system would not neutralize the immunotherapeutic antibody (*i.e.*, so the antibody would have better pharmacokinetics) and to avoid antibody-dependent cellular cytotoxicity (ADCC) by reducing Fc receptor interactions (*i.e.*, so blockade by anti-PD-1 could be evaluated with being compromised by ADCC effects).”*

Thus the requirement for reduced ADCC activity is mentioned here only with reference to the 4H2 antibody and the specific experimental setup of Example 12. This Example does not relate to an antibody with the CDR sequences of the 5C4 antibody, and the above reference to reducing ADCC activity therefore provides no basis for claim 10.

- 5.14. Example 23 relates to the assessment of ADCC activity of 5C4. Both IgG1 and IgG4 isotypes were tested, and the conclusion reached is that ADCC activity is related to the Fc region of the antibody (page 98, lines 29-32):

²⁸ Paragraph 3.24

“Results showed that 5C4-IgG4 did not mediate ADCC on activated CD4 T cells, while 5C4-IgG1 did mediate ADCC on activated CD4 T cells (Figure 53), indicating that ADCC activity is related to its Fc region of the anti-PD-1 antibody.”

At no point does Example 23 comment that reduced or absent ADCC activity is a desirable property of the 5C4 antibody, and such inferences cannot be drawn from this example in view of the general teaching on pages 36-37 which clearly indicates the opposite. Accordingly, claim 10 presents the skilled person with new technical teaching that is not derivable from the parent application as originally filed.

- 5.15. CDC is discussed on page 35, lines 33-36, with reference only to a specific example in which amino acids 329, 331 and 332 of an antibody Fc region can be replaced to reduce or abolish CDC activity. Thus a reduction of CDC activity is contemplated only with reference to these specific mutations, which are not present in the antibody of claim 10. CDC activity is tested in Example 24 (pages 98-99 of the application as filed), but this disclosure is limited to the 5C4 antibody.
- 5.16. Claim 10 is not limited to the 5C4 antibody, but encompasses antibodies with different variable region framework sequences and even antibodies with different CDR sequences that show a low degree of cross-competition with 5C4. Therefore, even if the results in Examples 23 and 24 show that 5C4-IgG4 does not mediate ADCC or CDC, the same is not necessarily true of other antibodies falling within the scope of claim 10, and the parent application as filed does not disclose absence of ADCC and CDC as general properties of the claimed antibodies. Accordingly, claim 10 adds matter over the parent application as originally filed and contravenes Article 76(1) EPC.

6 CITATIONS

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