

European Patent Office  
D-80298 Munich  
Germany

**mewburn.com**  
mail@mewburn.com

15 July 2024

**By Online Filing**

Dear Board of Appeal

**Appeal T0715/24-3.3.04**

**In the opposition against European Patent No: 3288980 (application no. 16724512.5)**

**Proprietor: Bristol-Myers Squibb Company**

**Opposed by: Dorries, H. Ulrich *et al.***

**Mewburn Ref: 008168494**

1. We write further to our Notice of Appeal filed on 13 May 2024 against the Decision of the Opposition Division (OD), taken at oral proceedings on 4 March 2024 and notified in the written decision dated 13 March 2024, to revoke the above patent. We hereby provide the Proprietor's Grounds of Appeal.
2. Enclosed herewith are clean and marked up copies of the Main Request and all Auxiliary Requests. The marked up copies show the amendments relative to the claims as granted.
3. In the Grounds of Appeal below we refer to various D-documents. The numbering used for those documents filed during the course of the proceedings before the OD (i.e. D1-D77) is that from the consolidated document list annexed to the OD's written Decision. These documents are not filed again herewith, but can be provided at the Board's request. Documents D78 and D79 are newly filed herewith, as detailed below.

## Contents

|                                                                                             |    |
|---------------------------------------------------------------------------------------------|----|
| Requests .....                                                                              | 5  |
| New Documents .....                                                                         | 5  |
| Summary of the Patent and Grounds of Appeal .....                                           | 6  |
| Overview .....                                                                              | 7  |
| Claim Requests .....                                                                        | 7  |
| The First Instance Proceedings .....                                                        | 7  |
| The Proprietor's Initial Position .....                                                     | 8  |
| The Opponents' Initial Position .....                                                       | 8  |
| The OD's Position .....                                                                     | 8  |
| Claim Interpretation in EPO Proceedings .....                                               | 9  |
| Main Request .....                                                                          | 11 |
| Interpretation .....                                                                        | 11 |
| Our Interpretation of Claim 1 .....                                                         | 11 |
| The OD's Claim Interpretation .....                                                         | 16 |
| Rule 80 EPC .....                                                                           | 23 |
| Clarity (Art. 84 EPC) / Extension of Scope (Art. 123(3) EPC) .....                          | 24 |
| No Added Matter (Art. 123(2) EPC) .....                                                     | 24 |
| No Extension of Scope .....                                                                 | 24 |
| Basis for Disclaiming the Nivolumab + Anti-CTLA-4 Combination .....                         | 25 |
| No Need for Basis for Combination of Claimed Regimen with Pembrolizumab .....               | 26 |
| Other Objections .....                                                                      | 27 |
| Auxiliary Request 1 .....                                                                   | 31 |
| Admissibility .....                                                                         | 31 |
| No reason to file AR1 during the Proceedings Before the OD .....                            | 32 |
| Admission of the Request not Inconsistent with the Objectives of Art. 12(6) RPBA 2020 ..... | 35 |
| Other Reasons for Admission .....                                                           | 36 |
| Rule 80 EPC .....                                                                           | 37 |
| Clarity (Art. 84 EPC) / Extension of Scope (Art. 123(3) EPC) .....                          | 37 |
| No Added Matter (Art. 123(2) EPC) .....                                                     | 37 |
| Auxiliary Request 2 .....                                                                   | 39 |
| Admissibility .....                                                                         | 39 |
| No Reason to file AR2 Earlier in Proceedings .....                                          | 39 |
| Reasons for Admission of AR2 .....                                                          | 40 |
| Rule 80 EPC .....                                                                           | 41 |
| Clarity (Art. 84 EPC) / Extension of Scope (Art. 123(3) EPC) .....                          | 41 |
| No Added Matter (Art. 123(2) EPC) .....                                                     | 41 |

|                                                                    |    |
|--------------------------------------------------------------------|----|
| Auxiliary Requests 3-5 .....                                       | 43 |
| Admissibility .....                                                | 43 |
| Rule 80 EPC .....                                                  | 44 |
| Clarity (Art. 84 EPC) / Extension of Scope (Art. 123(3) EPC) ..... | 44 |
| No Added Matter (Art. 123(2) EPC) .....                            | 45 |
| Remittal .....                                                     | 46 |
| Undecided Issues .....                                             | 46 |
| Obiter Dicta .....                                                 | 47 |
| Deficiencies in Conduct of Oral Proceedings by the OD .....        | 49 |
| Other Grounds of Opposition .....                                  | 51 |
| Sufficiency (Art. 83 EPC) .....                                    | 51 |
| Efficacy of Claimed Regimen .....                                  | 51 |
| Identification of PD-L1+ Melanoma .....                            | 55 |
| Measuring PD-L1 Expression in Claim 2 .....                        | 55 |
| Reliability of PD-L1 Status as Marker .....                        | 56 |
| Excluded Subject Matter (Art. 53(c) EPC) .....                     | 56 |
| Novelty .....                                                      | 57 |
| Novelty over D1 – Main Request .....                               | 57 |
| Novelty over D1 – AR2 .....                                        | 61 |
| Novelty over D1 – AR3 to AR5 .....                                 | 62 |
| Novelty over D25a .....                                            | 62 |
| Inventive Step .....                                               | 63 |
| Common General Knowledge .....                                     | 63 |
| Closest Prior Art .....                                            | 64 |
| Other Cited Documents .....                                        | 67 |
| Technical Difference between D14 and the Claimed Invention .....   | 68 |
| Technical Effect of the Claimed Invention .....                    | 68 |
| Objective Technical Problem Solved by Invention .....              | 69 |
| Non-Obviousness .....                                              | 71 |
| D12 as Alternative Closest Prior Art .....                         | 81 |
| Auxiliary Requests 6-11 .....                                      | 83 |
| Admissibility .....                                                | 83 |
| Rule 80 EPC .....                                                  | 84 |
| Clarity (Art. 84 EPC) / Extension of Scope (Art. 123(3) EPC) ..... | 84 |
| No Added Matter (Art. 123(2) EPC) .....                            | 84 |
| Sufficiency (Art. 83 EPC) .....                                    | 85 |
| Patentable Subject Matter, Novelty and Inventive Step .....        | 85 |
| Auxiliary Requests 12-17 .....                                     | 86 |

|                                                                    |    |
|--------------------------------------------------------------------|----|
| Admissibility .....                                                | 86 |
| Rule 80 EPC .....                                                  | 87 |
| Clarity (Art. 84 EPC) / Extension of Scope (Art. 123(3) EPC) ..... | 87 |
| All Grounds of Opposition .....                                    | 87 |
| Auxiliary Requests 18-29 .....                                     | 87 |
| Admissibility .....                                                | 87 |
| Rule 80 EPC .....                                                  | 88 |
| Clarity (Art. 84 EPC) / Extension of Scope (Art. 123(3) EPC) ..... | 88 |
| Excluded Subject Matter (Art. 53(c) EPC) .....                     | 88 |
| Sufficiency (Art. 83 EPC) .....                                    | 89 |
| Novelty (Art. 54 EPC) .....                                        | 89 |
| Inventive Step (Art. 56 EPC) .....                                 | 89 |
| Admission of Documents D78 and D79 .....                           | 90 |
| Admission of Documents D13b and D76 .....                          | 92 |
| D13b – Supplementary Data to D13a .....                            | 92 |
| D76 – Declaration of Professor Dr Peter Langguth .....             | 93 |
| Summary .....                                                      | 95 |

### Requests

4. We request that the Decision of the OD be set aside, and that the patent be maintained in amended form on the basis of the enclosed Main Request, which is identical to Auxiliary Request (AR) 20 considered by the OD at the oral proceedings, and a description adapted thereto.
5. In the event that the board intends to refuse the Proprietor's Main Request, we request that the Decision of the OD be set aside, and that the patent be maintained in amended form on the basis of one of ARs 1-29 filed herewith, and a description adapted thereto.
6. We request admission into proceedings of documents D78 and D79, and ARs 1-29, all of which are newly filed herewith.
7. Should the Board of Appeal set aside the Decision of the OD, we request remittal of the case to the OD for consideration of the objections raised under Articles 83, 53, 54 and 56 EPC, which have not yet been decided upon during these proceedings.
8. Should the Board decide to consider objections raised under grounds not decided upon by the OD, we request that documents D76 (filed by Opponent 3 (O3) on 2 January 2024) and D13b (filed by O4 on 4 January 2024) not be admitted into proceedings.
9. In the event that the Board is minded to refuse our Main Request, Oral Proceedings are requested. Should oral proceedings be appointed, we will speak in English and will require simultaneous translation into English if any other language is used.

### New Documents

10. The following new facts and evidence are filed herewith:
 

**D78** – Declaration of Dr Ian Waxman

**D79** – Bristol-Myers Squibb press release of 1 October 2015
11. As the Board will note, **D78** refers to 5 annexes, which are prior art documents referred to by Dr Waxman within his declaration. Annexes A-D are documents already on file in the proceedings (specifically, Annex A corresponds to **D53**, Annex B corresponds to **D19**, Annex C corresponds to **D7** and Annex D corresponds to **D40**). Annex E is **D79**, which as noted above is newly filed now.

### Summary of the Patent and Grounds of Appeal

12. The present patent relates to the treatment of melanoma with the anti-PD-1 antibody nivolumab. The patent is based on the discovery that in the subset of the melanoma population with PD-L1+ tumours, therapy with nivolumab alone is as effective as therapy with nivolumab in combination with the anti-CTLA-4 antibody ipilimumab. By contrast, across the melanoma population as a whole, nivolumab/ipilimumab combination therapy is more effective than therapy with either antibody alone.
13. Based on this discovery the present patent provides for treatment of PD-L1+ melanoma patients with nivolumab but without an anti-CTLA-4 antibody (such as ipilimumab). This provides the included patients with an effective therapeutic regimen with reduced toxicity compared to regimens including an anti-CTLA-4 antibody as well. This explanation of the invention is set out at paragraph [0055] of the patent.
14. The claimed therapeutic regimen is referred to in claim 1 as a nivolumab “*monotherapy*”. Claim 1 of the Main Request (MR) defines the dosage regimen as follows:

*the patient is to be administered a flat dose of 480 mg of nivolumab as monotherapy once every four weeks, wherein the patient is not administered a combination of nivolumab and an anti-CTLA-4 antibody or an antigen-binding portion thereof that specifically binds to a human CTLA-4.*
15. The OD revoked the patent for added matter. Both claim 1 as granted and claim 1 of the present Main Request were found to contravene Art. 123(2) EPC.
16. The OD’s decision was wrong. In respect of the present Main Request, the OD’s decision was based (at least in part) on an erroneous and unexplained interpretation of the claims. The OD considered the claims to encompass nivolumab/anti-CTLA-4 combination therapies, despite these being explicitly disclaimed. This led to an incorrect finding that the scope of the claim had been extended relative to the claims as filed. In fact claim 1 of the present Main Request is narrower than claim 1 as filed, and all limitations made to the claim have basis in the application as filed. The decision was further based on an alleged lack of basis for a combination of features which is not even claimed, and is therefore no ground for an objection.
17. In view of the clear errors in the OD’s decision, we request that it be set aside. Given that objections relating to other grounds of opposition under Articles 83, 53, 54 and 56 EPC were not considered during the first instance proceedings, we further request that the patent be remitted to the OD for further prosecution, based on the present Main Request.

## Overview

### **Claim Requests**

18. The present Main Request corresponds to AR20 considered by the OD at the first instance hearing. All auxiliary requests are newly filed now.
19. AR1 replaces the disclaimer in claim 1 of the Main Request with the wording that:
 

*the patient is not administered a combination of an anti-PD-1 antibody or an antigen-binding portion thereof that specifically binds to a human PD-1 and an anti-CTLA-4 antibody or an antigen-binding portion thereof that specifically binds to a human CTLA-4.*
20. AR2 replaces the disclaimer in claim 1 of the Main Request with the wording that:
 

*the monotherapy comprises administering the patient nivolumab without another anti-cancer agent.*
21. ARs 3-5 correspond to the Main Request and ARs 1-2, but refer in their preambles to:
 

*A composition comprising nivolumab, and no other antibody, for use in treating a melanoma in a patient*
22. ARs 6-11 correspond to the MR and ARs 1-5, respectively, with claim 2 amended to delete the wording “*the test tissue sample comprising tumor cells and/or tumor-infiltrating inflammatory cells*”.
23. ARs 12-17 correspond to the MR and ARs 1-5, respectively, with all dependent claims deleted.
24. ARs 18-23 correspond to the MR and ARs 1-5, respectively, with the subject matter of claims 2 and 3 as granted introduced into claim 1.
25. ARs 24-29 correspond to the MR and ARs 1-5, respectively, with the subject matter of claims 2 and 3 as amended in ARs 6-11 introduced into claim 1.

### **The First Instance Proceedings**

26. Throughout the first instance proceedings, the proprietor defended claim 1 as granted, which read:
 

*A composition comprising nivolumab for use in treating a melanoma in a patient:*

(i) wherein the patient is identified as having a PD-L1 positive melanoma tumor by measuring a PD-L1 expression on the melanoma tumor; and

(ii) wherein the patient is to be administered a flat dose of 480 mg of nivolumab as monotherapy once every four weeks, wherein the patient is not administered a combination of nivolumab and ipilimumab.

27. During the written proceedings, there was disagreement between the parties as to the proper interpretation of claim 1, specifically in relation to the meaning of the term “monotherapy”.

#### The Proprietor’s Initial Position

28. The proprietor’s position was that the claim could reasonably be interpreted as being directed to a true monotherapy, in which nivolumab is administered alone (i.e. not in combination with any other drug for treating melanoma), as set out for example in our submissions of 4 January 2024 at points 44-47.

#### The Opponents’ Initial Position

29. By contrast, the opponents argued that the term “monotherapy” was defined by the disclaimer of the combination of nivolumab and ipilimumab in claim 1, see e.g. O4, Notice of Opposition (NoO), points 13-16; and submissions of 4 January 2024, points 9-11; and O5, NoO, points 25-30.
30. That is to say, the opponents argued that in claim 1 as granted, “nivolumab monotherapy” meant that nivolumab was not co-administered with ipilimumab, but co-administration with any other drug (including other anti-CTLA-4 antibodies) was encompassed.
31. By analogy, in claim 1 of the current Main Request, this interpretation would mean that nivolumab is not co-administered with an anti-CTLA-4 antibody, but co-administration with any other drug is encompassed.
32. In support of their arguments in this respect, the opponents pointed to the definition of “anti-PD-1 monotherapy” provided in the description of the patent (at paragraph [0040]) as “therapy of an anti-PD-1 antibody without an anti-CTLA-4 antibody”.

#### The OD’s Position

33. The OD’s interpretation of the claims was not made clear in their Preliminary Opinion of 27 February 2023. While the OD noted in paragraph 9.6 of their Preliminary Opinion that:

*Monotherapy is understood by the skilled person as “alone, not in combination with another therapeutic for the same disease”*

it appeared that they leant towards a definition of nivolumab monotherapy in line with that set out in the description, excluding only co-administration of nivolumab with an anti-CTLA-4 antibody:

*[43] of the original application defines [monotherapy] as "not in combination with an anti-CTLA4 antibody".*

Preliminary Opinion, paragraph 9.6

and particularly

*The Proprietor also contended that there is a further difference between the opposed claims and the teachings of D1: that according to the claims nivolumab must be a monotherapy, whereas D1 concerns nivolumab in combination therapies. The Division must put a caveat on this assertion: the claims do require monotherapy, but at [43] this "monotherapy" is defined as the use of nivolumab only excluding all CTLA-4 antibodies, but not necessarily excluding all other immunotherapeutics. Since D1 foresees combinations of nivolumab with e.g. anti-CD137 etc., it is arguable that D1 discloses a "monotherapy" as defined at [43] of the patent.*

Preliminary Opinion, paragraph 12.1.

### **Claim Interpretation in EPO Proceedings**

34. This divergence in interpreting the claims as granted is mirrored by a general divergence in the approach to claim interpretation among the EPO's Technical Boards of Appeal, both on whether the description can be used to interpret *prima facie* clear claim language and on the broader question of whether the description as a whole can be used to construe the claims in view of Article 69 EPC and/or Article 84 EPC. Two distinct lines of case law have emerged, as exemplified by decisions **T 1473/19** and **T 169/20**, and questions on how the description should be used in the context of claim interpretation have recently been referred to the Enlarged Board of Appeal by Board 3.2.01 in **G 1/24**. This reflects that claim interpretation is an unsettled matter at the EPO and explains the uncertainty that accompanied the first instance proceedings in this case.
35. In view of the opponents' arguments regarding the proper interpretation of claim 1 as granted and the existence of divergent approaches to claim interpretation in the EPO, and in an attempt to streamline a potentially lengthy proceedings (the OD oral proceedings were initially scheduled for 5 days), at the beginning of the oral proceedings the proprietor submitted that it was a reasonable position to interpret claim 1 at face value. Thus the proprietor followed the opponents' approach to interpreting claim 1 as granted, whereby

the term “*monotherapy*” is defined by the disclaimer, in accordance with the definition of the term in the description.

36. That is to say, to quote O5 (NoO, point 26), we submitted that claim 1 as granted “*only excludes co-administration of one specific anti-CTLA-4 antibody (ipilimumab)*” with nivolumab.
37. At the oral proceedings, the OD refused the then Main Request for added matter. The then AR2 was refused for lack of clarity, after which the present Main Request was filed and admitted into proceedings, as AR20. The then AR20 was found to overcome the clarity issue but also refused for added matter, and the patent was revoked.
38. It was not until the written reasons for the Decision were issued that it became apparent that the OD adopted an interpretation of claim 1 (in respect of both claim 1 as granted and claim 1 of the present Main Request) which was at odds with any interpretation previously put forward during the proceedings, including both possible interpretations suggested by the OD in their Preliminary Opinion. This interpretation led to their finding that the present Main Request adds matter. And as previously mentioned, this interpretation is completely and fundamentally wrong.
39. Compounding the error of their new claim interpretation, the OD declined to explain the interpretation they had adopted to the parties, even when explicitly requested to. This meant the proprietor only learned of the claim interpretation adopted by the OD, and the reasons for the revocation of the patent, on reading the Decision. As the OD would not explain their claim interpretation during the proceedings, and never raised the resulting objection of added matter, the proprietor was denied an opportunity to comment on it.
40. The OD also found the present Main Request to add matter for a second, quite baffling reason. Specifically, the OD found a lack of basis for a combination of features which is not recited anywhere in the claims. An alleged lack of basis for a combination which is not actually claimed cannot possibly be a ground to revoke a patent. Again, this objection was not one which had been raised by any party to the proceedings, and came as a surprise to the proprietor in the written decision.
41. We explain below why the OD’s decision to revoke the patent was incorrect.

## **Main Request**

42. Claim 1 of the Main Request reads as follows:

*A composition comprising nivolumab for use in treating a melanoma in a patient:*

- (i) wherein the patient is identified as having a PD-L1 positive melanoma tumor by measuring a PD-L1 cell surface expression on the melanoma tumor; and*
- (ii) wherein the patient is to be administered a flat dose of 480 mg of nivolumab as monotherapy once every four weeks, wherein the patient is not administered a combination of nivolumab and an anti-CTLA-4 antibody or an antigen-binding portion thereof that specifically binds to a human CTLA-4.*

43. The present Main Request was filed during the oral proceedings before the OD (as AR20) and was admitted.

## **Interpretation**

44. Claim 1 of the Main Request is directed to a nivolumab composition for treatment of a patient with PD-L1+ melanoma, wherein the patient is administered 480 mg nivolumab every 4 weeks (480 mg q4w nivolumab). The claim specifies that the patient is administered nivolumab as a monotherapy, wherein the patient is not administered a combination of nivolumab and an anti-CTLA-4 antibody.

45. As set out above, the question of the correct interpretation of the claims, and in particular the meaning of the term “*monotherapy*”, played an important role in the OD’s decision to refuse the present Main Request at first instance.

46. The Board will appreciate that most of the discussion regarding claim interpretation at first instance related to claim 1 as granted (and indeed in their Decision, the OD give their interpretation of claim 1 of the present Main Request “*by analogy*” to their interpretation of claim 1 as granted, see point 14.2). Therefore, some of the consideration of the proper interpretation of the present Main Request will by necessity refer back to arguments in relation to claim 1 as granted. However, taking the same approach as the OD, these arguments can easily be applied to the present Main Request by analogy.

## **Our Interpretation of Claim 1**

47. In line with our submissions at the first instance Oral Proceedings, we submit that the meaning of claim 1 is simple. It is directed to:

*a nivolumab composition for use in the treatment of PD-L1+ melanoma in a patient, wherein the treatment comprises administering 480 mg q4w nivolumab and does not comprise co-administration of an anti-CTLA-4 antibody.*

48. This is the claim interpretation argued for by the opponents at first instance. For example, O4 argued in their submissions of 4 January 2024 (in relation to claim 1 as granted):

*claim 1 requires that the patient be “administered a flat dose of 480 mg of nivolumab as monotherapy”. This monotherapy is then **further defined** by the feature “wherein the patient is not administered a combination of nivolumab and ipilimumab”. Claim 1 thus requires that the patient is administered nivolumab as monotherapy, wherein “monotherapy” as used in claim 1 excludes combined administration of nivolumab with ipilimumab*

O4, Submissions of 4 January 2024, point 11 (emphasis original)

49. Similarly, O5 argued in their NoO (in relation to claim 1 as granted) that:

*the presently claimed nivolumab monotherapy is defined in such a way that it only excludes co-administration of one specific anti-CTLA-4 antibody (ipilimumab)*

O5, NoO, page 9, point 26

50. At the first instance oral proceedings, this interpretation became common ground. The Proprietor acknowledged that claim 1 as granted defines the nivolumab monotherapy as administering nivolumab without ipilimumab (Minutes, point 2.4).
51. The opponents argue that there are two reasons for interpreting “*monotherapy*” in this way, rather than assigning the term its standard meaning (i.e. alone, without another active agent):
52. Firstly, claim 1 itself defines the term “*monotherapy*” in its disclaimer. Interpreting “*monotherapy*” as having its standard meaning would render the disclaimer entirely superfluous (see e.g. O4, submissions of 4 January 2024, point 19). The skilled person would not interpret the claim in such a manner. Moreover, if “*monotherapy*” were intended to be interpreted as having its standard meaning, why include the disclaimer at all? Its very presence in claim 1 points the skilled person to give monotherapy a non-standard meaning, and the only alternative meaning provided in claim 1 is that set out in the disclaimer (see e.g. O5, submissions of 3 January 2024, point 6).
53. Secondly, this is how “*monotherapy*” is defined in the description of the patent, as set out at paragraph [0040]:

*The term “anti-PD-1 antibody monotherapy” as used herein includes a therapy of an anti-PD-1 antibody without an anti-CTLA-4 antibody therapy ... In one*

*embodiment, the anti-PD-1 antibody monotherapy comprises administering one or more doses of nivolumab to a patient in need thereof, but does not include administering an anti-CTLA-4 antibody.*

54. Given that the description explicitly directs the skilled person to use an alternative, special definition of “*monotherapy*”, they would do so. Importantly, the definition of “*monotherapy*” in the description is the same as the disclaimer in claim 1 of the present Main Request, providing further evidence that the disclaimer defines the term “*monotherapy*”.
55. So based on the plain wording of claim 1, and in line with the definition of “*monotherapy*” in the description, the skilled person would understand administration of “*nivolumab as monotherapy*” in claim 1 to mean administration of nivolumab without an anti-CTLA-4 antibody. Following this interpretation, claim 1 of the present Main Request excludes any concomitant administration of nivolumab and an anti-CTLA-4 antibody.
56. This interpretation is in line with the understanding of the opponents of claim 1 as granted, as set out at first instance, as excluding any concomitant administration of nivolumab and ipilimumab:

*[claim 1 as granted] excludes co-administration of ... ipilimumab*

O5, NoO, point 26

*Claim 1 of the opposed patent further defines that the patient is not administered a combination of nivolumab and ipilimumab*

O1, NoO, point 11

*granted claim 1 ... provides that the patient does not receive ipilimumab concomitantly with nivolumab*

O4, NoO, point 14

*Claim 1 thus requires that the patient is administered nivolumab as monotherapy, wherein “monotherapy” as used in claim 1 excludes combined administration of nivolumab with ipilimumab*

O4, Submissions of 4 January 2024, point 11

57. There was no change to the opponents’ position on claim interpretation at the first instance oral proceedings.

#### *Use of the Description in Interpreting the Claims*

58. As set out above, one of the reasons that “*monotherapy*” in claim 1 should be interpreted as meaning administering nivolumab without an anti-CTLA-4 antibody is that the definition of the term “*monotherapy*” in the description corroborates such an interpretation.

59. As noted by the OD at point 8.2.3 of the Decision, the Boards of Appeal have adopted differing approaches to claim interpretation, whereby depending on the context claims have been interpreted either based on their plain wording or in light of the description.
60. In the present case, the opponents and OD have all interpreted the claims in light of the description. See, for example: O4, NoO, point 15, which refers to their claim construction being in accordance with the general teaching of the description; O4, Submissions of 4 January 2024, point 14, which refers to the definition of “*monotherapy*” in the description; O5, NoO, point 27, which does the same; the Minutes, points 2.1, 2.2 and 2.3, showing each of O3-O5 (i.e. all of the opponents present at the oral proceedings) turning to the description for interpretation of the claims; and point 8.2.3 of the Decision.
61. Despite the OD’s statement that it was common ground between the parties at oral proceedings that the claims should be interpreted in light of the description (Decision, point 8.2.3), we did not actually argue for such an approach. In fact, we argued that by the plain wording of claim 1, the disclaimer defines the term “*monotherapy*”. This is correctly captured in the Minutes (point 2.4).
62. However, in the circumstances, we are in agreement with the other parties that it is appropriate to use the description to interpret the term “*monotherapy*”. While claim 1 as granted explicitly excluded the combination of nivolumab with the specific anti-CTLA-4 antibody ipilimumab only, the fact that claim 1 additionally requires that nivolumab be administered as monotherapy can be considered as a reason for the skilled reader to consult the description in order to either confirm the plain meaning of the term monotherapy in the context of the claim or to qualify it further in line with the overall context of the claims and the description.
63. The CLBA states that “*According to the established case law, the patent document may be its own dictionary*” and notes that the Boards have frequently held that “*terms used in patent documents should be given their normal meaning in the relevant art, unless the description gives them a special meaning*” (10<sup>th</sup> Edition, II-A-6.3.3; page 342).
64. As set out in T 1646/12:

*die Ansprüche eines Patents [sind] Texte, deren Auslegung den allgemeinen Grundsätzen zur Auslegung von Texten unterliegt. Zu diesen Grundsätzen gehört auch, dass ein Begriff bzw. ein Textbestandteil nur im Kontext ausgelegt werden kann. Auf Patente angewandt bedeutet dies, dass Begriffe eines Anspruchs bzw. der Anspruchswortlaut als solcher kontextuell, d.h. im Gesamtzusammenhang des Anspruchssatzes bzw. der Beschreibung auszulegen sind. Sie können daher in der Regel nicht völlig losgelöst von der Beschreibung betrachtet werden.*

*In diesem Zusammenhang gilt es zwei Extreme zu meiden. Zum einen ist es nicht zulässig, die Ansprüche und die Beschreibung gewissermaßen als kommunizierende Gefäße zu betrachten, zum Beispiel, indem man einschränkende Merkmale, die zwar in der Beschreibung beschrieben sind, aber nicht in den Ansprüchen, in letztere hineinliest ... Zum anderen kann man den Anspruch auch nicht als von der Beschreibung völlig getrennt betrachten. Der Fachmann, der einen Anspruch auslegt, muss sich zumindest vergewissern, ob die Ausdrücke des Anspruchs ihrem üblichen Wortsinn nach zu verstehen sind oder ob die Beschreibung für diese Ausdrücke eine besondere Bedeutung definiert ... Es ist also innerhalb gewisser Grenzen zulässig, und unter Umständen sogar notwendig, die Beschreibung bei der Auslegung der Ansprüche heranzuziehen.*

T 1646/12, Reasons 2.1

In English:

*the claims of a patent are texts whose interpretation is subject to the general principles for the interpretation of texts. These principles also include the fact that a term or a part of a text can only be interpreted in context. Applied to patents, this means that the terms of a claim or the wording of a claim as such must be interpreted contextually, i.e. in the overall context of the set of claims or the description. They therefore cannot generally be considered in complete isolation from the description.*

*In this context, two extremes must be avoided. Firstly, it is not permissible to regard the claims and the description as communicating vessels, for example by reading into the claims limiting features that are described in the description but not in the claims ... Secondly, the claims cannot be considered to be completely separate from the description. The skilled person interpreting a claim must at least ascertain whether the terms of the claim are to be understood in their usual literal sense or whether the description defines a special meaning for these terms ... It is therefore permissible within certain limits, and in some circumstances even necessary, to refer to the description when interpreting the claims.*

65. In the present case, the term “anti-PD-1 antibody monotherapy” is given a special meaning in the description. The usual meaning in the art of the term monotherapy is set out by the OD as “the use of a single drug to treat a particular disorder or disease” (Decision, page 6, point 8.2.1). But the description defines “anti-PD-1 antibody monotherapy” as meaning “therapy of an anti-PD-1 antibody without an anti-CTLA-4 antibody” (paragraph [0040]), not necessarily the use of an anti-PD-1 antibody alone.

66. Thus the definition of “*monotherapy*” in the patent is broader than the normal meaning, as it encompasses co-therapy of an anti-PD-1 antibody with other therapeutics, just not an anti-CTLA-4 antibody. Since the term “*monotherapy*” is given a special meaning by the description, the weight of the case law is that this meaning should be adopted when interpreting the claims.
67. Moreover, according to both the opponents (see above) and the OD (see Preliminary Opinion of the OD of 27 February 2023, page 6, point 9.6), the reference to nivolumab monotherapy in conjunction with the disclaimer of a particular combination therapy causes a degree of ambiguity in claim 1.
68. It has previously been held by the Boards that it is the “*established case law of the Boards of Appeal [that] the description can be used as the patent’s “dictionary” to assess the correct meaning of ambiguous terms used in claims*” (T 2221/10, Reasons 33; see also CLBA 10<sup>th</sup> Edition, II-A-6.3.1, pages 340-341).
69. In the present context, if the skilled person were to find the wording of claim 1 in any way ambiguous, as suggested by the opponents and the OD, they would turn to the description for guidance, and use the definition of “*monotherapy*” provided therein.

#### The OD’s Claim Interpretation

70. The OD’s interpretation of the claims is set out under points 8.2 and 14.3 of the Decision. As set out further below, the OD appear to have chosen to understand the disclaimer as entirely separate to the specified nivolumab regimen. In other words, the OD seem to take the view that the patient is not administered 480 mg q4w nivolumab and a “separate” nivolumab/anti-CTLA-4 combination regimen.
71. This interpretation is so torturous that despite the straightforward statement in claim 1 that the patient is not administered a combination of nivolumab and an anti-CTLA-4 antibody, the OD have concluded that the claim means exactly the opposite.
72. The OD have concluded that the claim does encompass co-administration of nivolumab in combination with an anti-CTLA-4 antibody, such as ipilimumab or tremelimumab (Decision, page 12, point 14.3.1). We submit that only a mind “*desirous of misunderstanding*” (c.f. CLBA 10<sup>th</sup> edition, II-A-6.1) could have alighted on such a perverse interpretation of the claim.
73. As we explain below, the OD’s interpretation of the claims is confused, inconsistent and technically non-sensical. It runs counter to the interpretation put forward by the opponents during the first instance proceedings, as endorsed by us at the oral proceedings. It is also contradictory to both possible interpretations of the claim the OD suggested in their

preliminary opinion. Yet at no point is the OD's interpretation of the claim explained. No reasoning is given for why it was adopted, or why the claim interpretation we endorsed at oral proceedings rejected. Instead, the OD have simply asserted that their interpretation is the correct one.

74. The OD's interpretation also disregards the definition of "*monotherapy*" in paragraph [0040] of the description, despite the explicit statement of the OD that they have interpreted the term "*monotherapy*" based on the description.

#### *Approach of the OD*

75. It is not clear how the OD have reached their interpretation of claim 1. Initially, the OD state that "*the term 'monotherapy' is interpreted in the light of the description*" (Decision, point 8.2.3). According to the OD's summary of the relevant teaching, the broadest definition of "*anti-PD-1 antibody monotherapy*" is that an anti-PD-1 antibody is administered without an anti-CTLA-4 antibody, though concomitant administration of an antibody targeting another protein is permitted (Decision, point 8.2.2, referring to paragraph [0040] of the patent, paragraph [0043] in the application as filed).
76. This definition of "*monotherapy*" is in line with our interpretation of claim 1 set out above. And throughout the Decision, the OD repeatedly refer back to the definition of "*monotherapy*" set out in the description (see e.g. points 8.3.2, 8.3.3 and 14.3.2). This could give the impression that the OD are indeed basing their claim interpretation on the description. Unfortunately however, this impression is false.
77. Although it is never acknowledged, and no explanation is provided for their deviation from their stated approach, the OD have not read the definition of "*monotherapy*" provided in the description into the claims. In fact, they have disregarded it completely. As set out by the OD themselves at point 8.2.2 of the Decision, at its broadest, the definition of "*monotherapy*" provided at paragraph [0040] of the description requires that:  
  
*the anti-PD1 antibody of choice ("an anti-PD1 antibody") is to be administered without any anti-CTLA4 antibody (of any kind)*
78. Given that claim 1 is directed to a nivolumab monotherapy, and in light of this definition of "*monotherapy*", it is apparent that claim 1 must be interpreted in a manner which excludes co-administration of nivolumab and an anti-CTLA-4 antibody.
79. And indeed, in their Preliminary Opinion, this is exactly how the OD indicated that the claim would be understood if "*monotherapy*" were interpreted based on the definition in the description. As set out there, in respect of claim 1 as granted:

*Does the claim now imply that nivolumab should not be combined with ipilimumab, but a combination with any other CTLA-4 antibody is permitted? If that were the case, the Division would indeed probably have to find that there is added matter. The Division is however not persuaded that this is the case: claim 1 specifies that nivolumab must be administered as monotherapy. Monotherapy is understood by the skilled person as "alone, not in combination with another therapeutic for the same disease"; [43] of the original application defines it as "not in combination with an anti-CTLA4 antibody". Therefore, "monotherapy" does in any event not cover nivo with any other CTLA4 antibody other than ipi.*

Preliminary Opinion of OD, page 6, point 9.6 (emphasis original)

80. In other words, in their Preliminary Opinion the OD considered that if "*monotherapy*" is interpreted as having the meaning ascribed to it in the description, it does not cover administering nivolumab with any anti-CTLA4 antibody and so there is no added matter.
81. Yet in their Decision, the OD has adopted a claim interpretation which encompasses co-administration of nivolumab ("the anti-PD-1 antibody of choice") with any anti-CTLA-4 antibody (see e.g. Decision, page 12, point 14.3.1). This is completely incompatible with the definition of "*monotherapy*" which they themselves have set out (and contrary to their comments in the Preliminary Opinion set out above).
82. By adopting a claim interpretation which is wholly inconsistent with the approach they say that they have taken, with their analysis of the meaning of the term "*monotherapy*" set out in the patent, and indeed with their comments in their Preliminary Opinion, it is impossible for the proprietor to understand why the OD have adopted the interpretation they have, and how it was reached.
83. As set out above, it appears that the OD have chosen to understand the disclaimer in claim 1 as entirely separate to the specified nivolumab regimen. In other words, the OD interpret claim 1 to mean that the patient is not administered the specified nivolumab regimen *in addition* to a "separate" (but concomitant) nivolumab/anti-CTLA-4 combination therapy regimen (see Decision, point 14.3.1).
84. On this basis, the OD consider that claim 1 of the present Main Request allows the claimed 480 mg q4w nivolumab regimen to be co-administered with absolutely any other drug at all. The claimed nivolumab regimen can even be administered with an anti-CTLA-4 antibody, so long as the anti-CTLA-4 antibody is not being administered with an additional nivolumab regimen.
85. Thus the OD have interpreted claim 1 of the present Main Request to encompass, for example, co-administration of nivolumab with pembrolizumab and ipilimumab (Decision, point 14.3.1). Although not stated anywhere, it is assumed that the OD also interpret

claim 1 as encompassing co-administration of nivolumab with ipilimumab alone (without pembrolizumab).

86. The OD is therefore taking the quite bizarre position that in claim 1, administration of nivolumab as “*monotherapy*” only excludes certain combinations of nivolumab with itself.
87. We submit that the OD’s approach to the claims, and their resulting interpretation, is plainly wrong, as set out below. The proprietor also wishes to emphasise that the interpretation of the claims adopted by the OD was never once put forward during the first instance proceedings. The term “*top(ping) up*”, which appears key to the OD’s approach to the claims, and appears at least 10 times in the Decision, was not mentioned once by the OD, or any party, at the hearing, as shown by its total absence from the Minutes.

*The OD’s Approach is Inconsistent with the Overall Disclosure of the Patent*

88. The overarching approach to claim interpretation at the EPO is set out in the CLBA:

*According to the established case law, the skilled person should try, with synthetical propensity, i.e. building up rather than tearing down, to arrive at an interpretation of the claim which is technically sensible and takes into account the whole disclosure of the patent. The patent must be construed by a mind willing to understand, not a mind desirous of misunderstanding*

CLBA 10<sup>th</sup> Edition, II-A-6.1, page 337

89. We submit that in their present Decision, the OD has taken a diametrically opposite approach to that laid down by the Boards. The OD has disregarded the disclosure of the patent and paid no heed to the technical sense (or lack thereof) of their chosen claim interpretation.
90. The present patent is directed to treatment of PD-L1+ melanoma. As set out above at points 12-13, and explained during the oral proceedings before the OD (see Minutes, point 2.4.1), the present invention is based on the finding that in the PD-L1+ melanoma sub-population, progression-free survival for nivolumab monotherapy is “*substantially the same*” as for combination therapy with nivolumab and ipilimumab. This contrasts with the population as a whole, for whom nivolumab/ipilimumab combination therapy provides superior outcomes than monotherapy with either antibody.
91. For the PD-L1+ population of melanoma patients, nivolumab monotherapy is therefore a better option than nivolumab/ipilimumab combination therapy, as it provides the same efficacy with lower toxicity (paragraph [0055], Fig. 2B).
92. This is explained throughout the patent, for example:

*The present invention relates to identifying an optimal strategy for treating a PD-L1-positive melanoma. In particular, the present invention shows that for a PD-L1-positive melanoma, a monotherapy administered as a flat dose of 480 mg of nivolumab once every four weeks is a better option than a combination therapy of nivolumab and ipilimumab.*

Paragraph [0015]

*in patients having a PD-L1-positive tumor, a monotherapy of an anti-PD-1 antibody can be as effective as a combination therapy. In order to reduce the toxicity of the combination therapy in the patient, the present invention provides identifying a patient having a PD-L1-positive tumor and provides a monotherapy of nivolumab for the initial treatment option.*

Paragraph [0055]

93. Thus it is unambiguous that the premise of the claimed invention is that PD-L1+ melanoma patients can be effectively treated using nivolumab alone, without ipilimumab. And moreover, that this is desirable, because using ipilimumab as well increases the toxicity of the treatment, without improving efficacy.
94. The skilled person would appreciate that this premise extends to using nivolumab without any anti-CTLA-4 antibody: like ipilimumab, alternative anti-CTLA-4 antibodies act by blocking signalling through CTLA-4, and the results in the patent show this additional therapeutic pathway to be unnecessary in the treatment of PD-L1+ melanoma.
95. Reflecting this teaching of the “*whole disclosure of the patent*”, the claims specify that “*the patient is not administered a combination of nivolumab and an anti-CTLA-4 antibody or an antigen-binding portion thereof that specifically binds to a human CTLA-4*”.
96. The skilled person reading the claims, taking into account the whole disclosure of the patent, would immediately understand that the claims relate to the treatment of PD-L1+ melanoma using nivolumab without an anti-CTLA-4 antibody.
97. The skilled person would under no circumstances understand the claims as encompassing treatment of PD-L1+ melanoma with a combination therapy comprising nivolumab and an anti-CTLA-4 antibody (such as ipilimumab). By adopting an interpretation that encompasses such combinations, the OD’s interpretation disregards completely the purpose of the patent and the description and its technical teaching.
98. The OD appear to be firmly of the view that the disclaimer in claim 1 only excludes “*topping up ... double blockades*” (Decision, point 8.3.1, final paragraph). The OD provides no basis or explanation for this interpretation of claim 1. It is simply referred to as “*a reasonable reading*” (Decision, point 8.3.1, paragraph 2). We disagree. There is no

mention anywhere in the patent of topping up (or not) of “*double blockades*”. There is no hint or suggestion that this is the focus of the patent, or at all relevant.

*The OD’s Approach is Inconsistent with the Description*

99. As set out above (see points 58 to 69), the skilled person reading claim 1 would turn to the description to look for a definition of the term “*monotherapy*”. At paragraph [0040], as the OD have acknowledged, the skilled person would find the term defined as therapy using an anti-PD-1 antibody without an anti-CTLA-4 antibody. The skilled person would therefore interpret monotherapy as having this meaning (and understand the disclaimer, which includes this same definition, to define the term “*monotherapy*” in the claim).
100. For this reason, the skilled person would not have interpreted claim 1 to encompass co-administration of nivolumab with an anti-CTLA-4 antibody, showing that the OD’s claim interpretation is wrong.
101. Importantly, while the OD focus on the exclusion of “*double blockades*”, there is no mention of these in paragraph [0040], which simply states that an anti-PD-1 monotherapy “*does not include administering an anti-CTLA-4 antibody*”. There is no caveat to this, and no suggestion that it only applies in the context of the OD’s “*double blockades*”.
102. Indeed, in their summary of this paragraph at point 8.2.2 of the Decision, the OD make no suggestion that only co-administration with a “*double blockade*” is excluded. Rather, they acknowledge that paragraph [0040] (paragraph [0043] of the application as filed) requires the anti-PD-1 antibody “*to be administered without any anti-CTLA4 antibody*”.
103. However, by the very next page of the Decision, the OD’s reading of paragraph [0040] appears to have changed. No longer is the paragraph taken at face value, but instead the OD appear to consider it to relate to exclusion of “*double blockades*”. In point 8.3.2 of the Decision, the OD appear to state (with respect to claim 1 as granted) that if the definition of “*monotherapy*” from paragraph [0040] were imported into the claim, it would have the same scope as the present Main Request, and would only exclude co-administration of the claimed nivolumab regimen with a “*nivolumab + CTLA4*” double blockade.
104. No reason for this change in interpretation of paragraph [0040] is provided. Indeed, it is not even acknowledged. But it goes to the heart of the OD’s failings, because the result is that the OD’s claim interpretation is completely contradictory to the description.

*The OD’s Approach does not make Technical Sense*

105. The OD assert that the disclaimer in claim 1 only excludes administering the claimed 480 mg q4w nivolumab regimen in combination with a separate nivolumab/anti-CTLA-4

regimen. In other words, the disclaimer only excludes administering the claimed nivolumab regimen in combination with nivolumab itself.

106. However, the reference in claim 1 to administering to the patient 480 mg nivolumab every 4 weeks would be understood by the skilled person as defining the only nivolumab administered to the patient. The skilled person would not understand the claim to allow for additional doses of nivolumab to be administered to the patient, because in that case the patient would not be receiving 480 mg every 4 weeks – they would be receiving an unspecified, larger dose, which would not fall within the claims.
107. Moreover, even if the skilled person were to take the view that a 480 mg q4w nivolumab regimen could, technically, be combined with an additional nivolumab regimen and still exist as claimed, the skilled person would never have made such a combination. It is a wholly unrealistic suggestion. On the other hand, combination therapies of nivolumab and an anti-CTLA-4 antibody (specifically ipilimumab) are demonstrated in the patent. The skilled person would certainly, therefore, consider a simple combination of nivolumab and an anti-CTLA-4 antibody as a possibility for treating melanoma.
108. Faced with claim 1, which specifies that the patient “*is not administered a combination of nivolumab and an anti-CTLA-4 antibody...*”, the skilled person would immediately have understood this to mean that the patient is not co-administered the specified 480 mg q4w nivolumab regimen with an anti-CTLA-4 antibody. This is because the skilled person would have considered co-administration of nivolumab and an anti-CTLA-4 antibody a possible therapeutic option, which the disclaimer is telling them not to use.
109. The skilled person would not have understood claim 1 as meaning that the patient is not administered the specified 480 mg q4w nivolumab regimen in combination with a separate nivolumab/anti-CTLA-4 combination regimen, because the skilled person would never have considered “topping up” a nivolumab/anti-CTLA-4 combination regimen with a separate nivolumab regimen in the first place.
110. This is confirmed by the declaration of Dr Ian Waxman, set out in document **D78** filed herewith. Dr Waxman is a clinical oncologist with expertise in the use of checkpoint inhibitors, which is the field of the present patent. As he explains, the concept of “topping up” a particular combination regimen with extra doses of one of the drugs used within it would go against accepted clinical practice, according to which combination regimens use defined doses of each of their components (see **D78**, point 19). He also explains that when a particular dosage regimen for a drug is defined, it is understood that the specified dosage is the full amount of the drug administered during that course of therapy (**D78**, point 21). The skilled person would therefore have never interpreted the present claims in a manner which related to administering more than the specified 480 mg q4w nivolumab to the patient.

111. In view of these facts, Dr Waxman is in agreement with us that the OD's claim interpretation would never have occurred to the skilled person (**D78**, point 28), and that they would simply have understood the claims as instructing the skilled person not to administer the claimed 480 mg q4w nivolumab regimen in combination with an anti-CTLA-4 antibody (**D78**, point 29).
112. It is a well-established principle of the EPO that "*the wording of claims should typically be given its broadest technically sensible meaning*" (CLBA 10<sup>th</sup> Edition II-A-6.1; page 337). This has been repeatedly reaffirmed by the Boards, e.g. recently in T 2764/19 (Reasons 3.1.1). The presence of those two words "*technically sensible*" is important. They are there because the Boards recognise that claims should not necessarily be given their broadest possible interpretation, because in some instances the broadest possible interpretation is so obscure, bizarre or non-sensical, that it would not even be considered by the skilled person when reading the claims.
113. In the present instance it seems that the OD has gone to great lengths to find the broadest possible interpretation of claim 1, but the interpretation which they have landed on would never have been considered by the skilled person, because it requires the disclaimer to be understood as excluding, at best, treatment regimens so obscure that the skilled person would never have considered them and so never have thought that the disclaimer was referring to them. Dr Waxman's declaration confirms this.
114. In summary, the OD's interpretation of claim 1 is fundamentally wrong. We submit that the definition we have proposed above at point 47 is the correct interpretation of claim 1 of the present Main Request, i.e. that claim 1 relates to administration of 480 mg q4w nivolumab without an anti-CTLA-4 antibody.
115. The effect of this interpretation is that combination therapies asserted by the OD to fall within the claim, i.e. nivolumab + pembrolizumab + ipilimumab and nivolumab + pembrolizumab + tremelimumab (see Decision, point 14.3.1) are in fact excluded from the claim, because both combinations require co-administration of nivolumab with an anti-CTLA-4 antibody.

#### Rule 80 EPC

116. No objections under Rule 80 EPC were raised against the present Main Request at the oral proceedings before the OD. Moreover, all amendments in the present Main Request were present in former AR2. No objections under Rule 80 were made against former AR2 during the first instance proceedings. As such there are no objections under Rule 80 on file which apply to the present Main Request.
117. The amendments to claim 1 were all made to address objections of added subject matter under Art. 123(2) EPC. Claim 7 was also deleted to address an added subject matter

objection. The amendments to claim 6 were made to address an objection under Art. 83 EPC. As such all amendments to the claims were made to address objections raised under grounds for opposition, and so comply with Rule 80.

#### **Clarity (Art. 84 EPC) / Extension of Scope (Art. 123(3) EPC)**

118. No objections under Art. 84 or 123(3) EPC were raised against the present Main Request at the oral proceedings before the OD. Moreover, during the first instance written proceedings, only O3 raised objections against former AR2 under Art. 84 and 123(3) EPC (see O3 submissions of 2 January 2024, pages 24-26, points 121-131). These objections related to the term “*single antibody composition*” in former AR2, which is absent from the present Main Request. As such there is not a single objection under Art. 84 or 123(3) EPC on file which applies to the present Main Request.
119. The proprietor submits that the present amendments are clear and comply with Art. 123(3) EPC. If new objections to the request are made under these grounds by any of the opponents, the proprietor reserves the right to respond.

#### **No Added Matter (Art. 123(2) EPC)**

120. Claim 1 of the Main Request has basis in claims 1, 15 and 26 as filed, in combination with paragraph [0117] of the description as filed. Specifically, claim 1 as filed provides an anti-PD-1 antibody for the treatment of PD-L1+ melanoma, wherein the patient is administered the anti-PD-1 antibody as a monotherapy, which is defined as being wherein the patient is not administered a combination of an anti-PD-1 antibody and an anti-CTL-4 antibody. Claim 26 as filed specifies that the anti-PD-1 antibody is nivolumab, and paragraph [0117] as filed provides the 480 mg q4w dosage regimen. Claim 15 as filed specifies that the identifying comprises measuring PD-L1 expression on the melanoma tumour (part (i) of claim 1 of the Main Request). Accordingly, claim 1 of the Main Request has basis in the application as filed and complies with Art. 123(2) EPC.
121. The OD found the present Main Request to lack compliance with Art. 123(2) for two reasons: an alleged extension of its scope compared to claim 1 as granted, for which the OD found no basis in the application, and an alleged lack of basis for administering a patient the claimed nivolumab regimen in combination with pembrolizumab.

#### **No Extension of Scope**

122. The OD is wrong in their conclusion (set out at point 14.3.1 of the Decision) that claim 1 of the present Main Request is broader in scope than claim 1 as filed. This conclusion is based on the OD’s erroneous interpretation of claim 1, but when the proper interpretation is applied, it becomes clear that claim 1 of the present Main Request is in fact narrower in scope than claim 1 as filed.

123. As set out above, claim 1 of the present Main Request is directed to the treatment of PD-L1+ melanoma with a nivolumab monotherapy, by which is meant that the patient is administered nivolumab without an anti-CTLA-4 antibody.
124. Claim 1 as filed was directed to the treatment of PD-L1+ melanoma with an anti-PD-1 antibody monotherapy. Just as in present claim 1, the monotherapy was defined as administering the patient an anti-PD-1 antibody without an anti-CTLA-4 antibody.
125. Thus both claim 1 as filed and present claim 1 are directed to the administration of an anti-PD-1 antibody without an anti-CTLA-4 antibody. The key differences are that claim 1 as filed encompasses use of any anti-PD-1 antibody, whereas present claim 1 only encompasses use of nivolumab; and present claim 1 is limited to a specific dosage regimen, whereas claim 1 as filed encompassed any dosage regimen.
126. As explained at the oral proceedings before the OD, no combinations including use of an anti-CTLA-4 antibody are encompassed by the present claims (Minutes, point 5.4), and so no embodiments are encompassed by present claim 1 which were not encompassed by claim 1 as filed: any combination of nivolumab with an anti-CTLA-4 antibody is explicitly disclaimed (including combinations with additional anti-PD-1 antibodies); combination of only a different anti-PD-1 antibody (e.g. pembrolizumab) with an anti-CTLA-4 antibody does not fall within claim 1, as claim 1 requires the use of nivolumab.
127. The OD's conclusion that claim 1 of the present Main Request encompasses therapeutic regimens not encompassed by claim 1 as filed is therefore erroneous.

#### Basis for Disclaiming the Nivolumab + Anti-CTLA-4 Combination

128. At first instance, a number of the opponents objected to the wording of the disclaimer of the present Main Request, alleging that there was no basis for disclaiming the combination of an anti-CTLA-4 antibody with nivolumab, specifically (O3, submissions of 2 January 2024, point 136). Rather, it was argued that the application as filed discloses nivolumab as an antibody to be used in the claimed therapies (O3, submissions of 2 January 2024, points 28-29). See also points 5.2 and 5.3 of the Minutes.
129. However, these objections are completely baseless, and illogical given the interpretation of the disclaimer applied by the opponents themselves.
130. The claims are directed to a nivolumab monotherapy. As the opponents themselves argued (see points 48-56 above), the disclaimer defines the monotherapy. In other words, the disclaimer says "a nivolumab monotherapy means administering nivolumab without an anti-CTLA-4 antibody".

131. As the disclaimer defines the monotherapy, the basis for specifying that the monotherapy uses nivolumab also provides basis for referring to nivolumab in the disclaimer. Thus the present disclaimer has basis in the application as filed.

No Need for Basis for Combination of Claimed Regimen with Pembrolizumab

132. The OD found the present Main Request to further lack compliance with Art. 123(2) EPC due to a lack of basis for administering the specified 480 mg q4w nivolumab regimen in combination with pembrolizumab (Decision, point 14.3.3).
133. The proprietor cannot comprehend this objection. The objected to combination does not feature in the claims! Pembrolizumab is not mentioned anywhere in the claim set. The OD is objecting to a combination of features which is simply not made. No such objection was made by any of the parties at any point during the first instance proceedings and we are shocked to see such a baseless objection appear in the Decision.
134. As set out above, present claim 1 is directed to the use of the specified nivolumab regimen to treat PD-L1+ melanoma, without an anti-CTLA-4 antibody. As previously acknowledged, other combinations are encompassed by the claims, as is apparent from e.g. paragraph [0040] of the description.
135. The combination of the specified nivolumab regimen with pembrolizumab is, therefore, encompassed by claim 1 (though it seems unlikely to the proprietor that this combination would ever be made). Other combinations, with other drugs, are also encompassed. None are explicitly claimed.
136. According to the case law, a claim directed to a combination of features “*lying somewhere between an originally broad disclosure and a more limited specific disclosure*” may be considered an intermediate generalisation, and generally basis in the application as filed is required in order to recite that combination of features in a claim (CLBA 10<sup>th</sup> Edition, II-E-1.9.1, beginning at page 546).
137. However, the Boards have never held that explicit basis is required for all embodiments of an invention falling within a claim, even those not mentioned anywhere in the claim set. Such a requirement would place an impossible burden on a patent applicant or proprietor. The OD’s objection is therefore entirely unjustified and unjustifiable.
138. There is therefore no need for basis for this therapeutic combination in the application as filed. Whether such basis is present or not is irrelevant for the assessment of compliance with Art. 123(2) EPC.

### Other Objections

139. Various other objections were raised by the opponents under Art. 123(2) EPC, which were either rejected by the OD or not decided on. We submit that none of the objections raised under Art. 123(2) EPC have merit.

### *PD-L1 Cell Surface Expression*

140. O3 objected to claim 1 as granted on the grounds that it referred simply to measuring PD-L1 expression on the melanoma tumour, whereas the description taught that PD-L1 expression must be measured on the surface of the tumour cells (O3, NoO, point 14).
141. The OD correctly rejected this objection (Decision, point 8.5.1), but it is in any event moot because claim 1 of the present Main Request specifies that PD-L1 cell surface expression is measured.

### *Selections Required for Claim 1*

142. The opponents objected that claim 1 required multiple selections from lists to obtain the dosing schedule and the specific antibody recited in the claim. This objection was not decided on by the OD, though they indicate in their *Obiter Dicta* that they were inclined to reject it (Decision, points 15-15.3).
143. We submit that there is basis in the application as filed for the claimed 480 mg q4w nivolumab regimen.
144. Relative to claim 1 as filed, claim 1 as granted contains two selections: the selection of nivolumab as the anti-PD-1 antibody, which has basis at claim 26 as filed; and the selection of 480 mg q4w as the dosage regimen, which has basis at paragraph [0117] as filed.
145. The opponents have argued that the claimed dosage regimen itself requires multiple selections, e.g. of a flat dose, of the 480 mg amount and of the 4-weekly administration regimen (see e.g. O3, NoO, points 9-11). This is incorrect. Paragraph [0117] explicitly discloses a dosing regimen in which “480mg of the anti-PD-1 antibody or antigen binding fragment is administered once every 4 weeks”. This regimen is inherently flat (i.e. it uses the same dose, 480 mg, for all patients, rather than a weight-based dose), and so the single selection of this regimen includes the flat nature of the dose, the amount administered and its frequency.
146. According to the CLBA, a selection of features can be made where there is a pointer to making that particular selection (CLBA 10<sup>th</sup> Edition, II-E-1.6.1(a); pages 517-518).

147. In the present case there is a clear pointer to selecting nivolumab as the anti-PD-1 antibody.
148. Claim 1 as filed is directed to treating PD-L1+ melanoma with an anti-PD-1 monotherapy (i.e. using an anti-PD-1 antibody without an anti-CTLA-4 antibody). As set out above, and explained in the application as filed at paragraph [0058], this entire invention is based on the finding that for treatment of, specifically, PD-L1+ melanoma, treatment with nivolumab alone is as effective as treatment with nivolumab in combination with ipilimumab.
149. The results underlying this finding are set out in the Examples, in particular at paragraph [0148] as filed, which states that for PD-L1+ melanoma patients, median progression-free survival was 14 months for treatment with either nivolumab alone or nivolumab in combination with ipilimumab.
150. The use of nivolumab in the Examples is a clear pointer to the skilled person to select nivolumab as the anti-PD-1 antibody for use in the claimed therapies. The entire invention is based on data obtained with nivolumab. The only anti-PD-1 monotherapy demonstrated in the application as filed uses nivolumab, and indeed the application contains no data relating to any other anti-PD-1 antibody.
151. This unpredictable nature of the field of cancer therapy should also be taken into account here. In view of the lack of clinical evidence that the same results in PD-L1+ melanoma can be achieved by any other anti-PD-1 antibody monotherapy, the skilled person would consider the data in the Examples a very strong pointer to selecting nivolumab as the antibody with which to implement the claimed anti-PD-1 monotherapies. That is to say, the data is a pointer to use nivolumab in any and all of the anti-PD-1 monotherapies disclosed in the application as filed.
152. In this light, claim 1 requires at most a single selection from a list, i.e. the claimed dosage regimen. A single selection from a list is compliant with Art. 123(2) EPC. Accordingly, there is basis in the application as filed for administering 480 mg q4w nivolumab as monotherapy.

*Claim 7 as Granted*

153. Various opponents objected to claim 7 as granted. This objection is moot as claim 7 has been deleted (see Decision, point 8.5.2).

*Limitation of Claim 6 to Antibody 28-8*

154. O4 objected that the amendment of claim 6 to specify that the IHC assay to measure PD-L1 expression is performed with the anti-PD-1 antibody 28-8 results in a violation of

Art. 123(2) EPC (see O4, submissions of 4 January 2024, points 107-112). This objection was correctly rejected by the OD (Decision, point 8.5.3).

155. O4 objected that in claim 6 as amended, antibody 28-8 is selected from a list of anti-PD-L1 antibodies, and that this selection from a list, in combination with the selections in claim 1 (discussed above) was not disclosed in the application as filed.
156. The other antibodies were deleted from claim 6 in response to an objection of lack of sufficient disclosure under Art. 83 EPC. This was because antibodies 28-1, 28-12, 29-8 and 5H1, mentioned in claim 6 as granted, are referred to in the patent only by their clonal designations. Sequence information is provided only for 28-8.
157. As noted above, according to the CLBA selections from lists may be made where there is a clear pointer to the selection made. In the present case there are two clear pointers to selecting antibody 28-8 from the list in claim 6 as granted.
158. Firstly, paragraph [0103] of the application as filed clearly singles out antibody 28-8 of those listed. The paragraph states:

*In some embodiments, an anti-PD-L1 antibody useful for the present methods includes mAb 28-8 set forth in SEQ ID NOs. 1 and 2, respectively. The sequences of the heavy and light chain CDR domains of mAb 28-8, as delineated using the Kabat system, are set forth in SEQ ID NOs. 3-8. In other embodiments, an anti-PD-L1 antibody useful for the invention comprises mAbs 28-1, 28-12, 29-8 and 20-12...*

159. Thus paragraph [0103] teaches that the skilled person can use antibody 28-8, and goes into some detail about the antibody. Or they can use one of 4 other antibodies which are mentioned by name but otherwise not described. This singling out of antibody 28-8 is a clear pointer that it is preferred and should be selected.
160. Secondly, as noted by the opponents, only antibody 28-8 is disclosed in an enabling manner. It is hard to imagine a clearer pointer to selecting antibody 28-8, than it being impossible for the skilled person to actually make any of the other selections. Indeed, we would agree with the OD that “*there is no true additional selection when the ‘selected item’, antibody 28-8, is actually the only one actually disclosed among the antibodies recited in granted claim 6*” (Decision, point 8.5.3).
161. Accordingly, claim 6 as amended complies with Art. 123(2) EPC.

*Basis for “Composition”*

162. O1 objected that there is no basis in the application as filed for referring to a “*composition comprising nivolumab*” in claim 1 (O1, NoO, page 4, points 8-10). This is incorrect. As correctly noted by the OD in their *Obiter Dicta*:

*there is no added matter solely because the claim 1 now mentions a composition rather than an antibody as such ... An antibody, to be administered to a patient, must be in a form suitable for administration, which is nothing other than a composition: the antibody is not administered in thin air.*

Decision, point 15.2

163. In other words, it does not matter if there is explicit basis in the application as filed for referring to a composition comprising nivolumab. There is no other way in which nivolumab can be administered and, so it is implicit that references to administering nivolumab (in e.g. PCT claim 1) relate to administering a composition comprising nivolumab.
164. In summary, the claims of the Main Request comply with Art. 123(2) EPC.

### Auxiliary Request 1

165. AR1 is filed now for the first time, and we request its admission into proceedings. In line with Art. 12(6) RPBA 2020, we submit that this is not a request that should have been submitted during the first instance proceedings, and even if the Board disagrees with this, we submit that the circumstances of the appeal case justify the admission of the request. We further submit the considerations under Art. 12(4) RPBA 2020 of the complexity of the amendment, its suitability to address the issues which led to the Decision under appeal and the need for procedural economy support its admission.

### **Admissibility**

166. Claim 1 of AR1 has the following wording:

*A composition comprising nivolumab for use in treating a melanoma in a patient:*

- (i) wherein the patient is identified as having a PD-L1 positive melanoma tumor by measuring a PD-L1 cell surface expression on the melanoma tumor; and*
- (ii) wherein the patient is to be administered a flat dose of 480 mg of nivolumab as monotherapy once every four weeks, wherein the patient is not administered a combination of an anti-PD-1 antibody or an antigen-binding portion thereof that specifically binds to a human PD-1 and an anti-CTLA-4 antibody or an antigen-binding portion thereof that specifically binds to a human CTLA-4.*

167. AR1 is filed in the event that the Board concurs with the claim interpretation adopted by the OD and their finding that the disclaimer in claim 1 of the Main Request is narrower than that of claim 1 as filed, resulting in an unsupported extension of claim scope. As shown above, in AR1, the wording of the disclaimer of claim 1 is returned to the exact wording used in claim 1 as filed, thereby addressing the alleged added matter set out in point 14.3.1 of the Decision.
168. Present AR1 corresponds to AR3 as filed with our submissions of 4 January 2024, with the exception that the words “*single antibody*” have been removed from the preamble. As set out below, these words were introduced into former AR3 to address an added matter objection. Their removal has the effect of restoring the claim preamble to its wording as granted. The same amendment was made in the present Main Request relative to AR2 as filed on 4 January 2024.

No reason to file AR1 during the Proceedings Before the OD

169. Between the 5 opponents, multiple objections of added matter were raised against the claims as granted in the Notices of Opposition. Our response to the Notices of Opposition included Auxiliary Requests containing amendments to address all the added matter issues raised. However, as set out below, and explained at the Oral Proceedings before the OD, in view of the large number of added matter objections raised by the opponents, filing every possible permutation of the amendments made would have resulted in an excessive proliferation of requests. To avoid this, certain amendments were combined in the Auxiliary Requests (Minutes, page 7, point 4.4). The specific combination of amendments in present AR1 was not one of these. We submit that the proprietor had no reason to submit present AR1 with its specific combination of amendments to claim 1 during the first instance proceedings.
170. Going into more detail, the proprietor's response to the Notices of Opposition (13 July 2022) included 19 Auxiliary Requests. One of the amendments included, made in then AR1 and most of the lower-ranked Auxiliary Requests, was to introduce reference to a "*single antibody composition*" in the preamble to claim 1.
171. This amendment was made to address the objection from O1 that the reference in claim 1 to a "*composition*", without specifying "*single antibody composition*" resulted in an undisclosed intermediate generalisation, contrary to Art. 123(2) EPC.
172. AR1 also included an amendment specifying measurement of "*cell surface*" PD-L1 expression, to address the objection made by O3 that the absence of this term also resulted in an intermediate generalisation. In initial AR2 and AR3, the amendments of initial AR1 were combined with amendments to the disclaimer of claim 1.
173. If the proprietor had filed separate requests containing each of these three amendments, and all possible permutations thereof, then present AR1 would have been filed at first instance. However, this would also have resulted in the overall number of requests increasing 4-fold, from 20 to 80. This would have unnecessarily resulted in proliferation of paper during the first instance proceedings.
174. The proprietor's approach of combining amendments to address unrelated added matter objections in a single auxiliary request was therefore a legitimate attempt to set out the amendments proposed while avoiding a proliferation of claim requests.
175. In their Preliminary Opinion, the OD provided minimal comment on the Auxiliary Requests filed (see point 14 of the Preliminary Opinion of 27 February 2023). Notably, the OD provided no comments on the clarity of any amendment, including the introduction of the term "*single antibody composition*".

176. The proprietor therefore had no indication before the Oral Proceedings that the OD had any concerns about the clarity of this term, and no reason to file new claim requests with the offending term removed, such as present AR1.

177. However, at Oral Proceedings the OD found this amendment to lack clarity in the context of former AR2 (Decision, point 10). The OD found that “*the term, in plain English, is ambiguous*”. This was because:

*It is unclear whether it means “a composition comprising a single antibody”, or “a single composition which can comprise more than one antibody against the same target” as for instance set out at [42] of the original application.*

Decision, point 10

178. The objection that the term “*single antibody composition*” was inherently ambiguous was only raised for the first time by O3 in their written submissions of 26 February 2024 (see points 33-37). These submissions were forwarded to the proprietor on 27 February 2024, less than 1 week before the oral proceedings before the OD, which took place on 4 March 2024, giving the proprietor insufficient time to react before the oral proceedings. It is therefore submitted that AR1 is not a claim request which should have been filed during the written proceedings at first instance, as there was no reason to file a request containing the specific combination of amendments of AR1 at that point.

179. It is also submitted that present AR1 is not a request which should have been submitted at the first instance Oral Proceedings.

180. At the Oral Proceedings, following the refusal of the present Main Request, the proprietor asked the reasons for its refusal (Minutes, point 5.5). This was because we were surprised by the decision and did not know why the OD had reached it. The OD replied that the alleged inclusion of only part of the disclaimer of claim 1 as filed was one reason, but that there was a second reason relating to the alternatives allowed by the definition of “*monotherapy*” in paragraph [0043] of the application as filed (Minutes, point 5.5).

181. The Board, however, will note that no objection had been raised throughout the proceedings in relation to the alternative definitions of “*monotherapy*” in paragraph [0043]. Therefore the proprietor was left in the dark as to the full reasons for the OD’s decision, but understood the decision to include reasons which had not been discussed and which we were not aware of.

182. This understanding was subsequently proven correct. On reading the written Decision, the proprietor discovered that the minimal and vague statement by the OD about “*alternatives*” referred to the alleged lack of basis for combining the claimed 480 mg q4w nivolumab regimen with pembrolizumab administration, set out at point 14.3.3 of the Decision. As noted above, this objection was previously unknown to the proprietor.

183. In this regard, it should be emphasised that the opponents had adopted the interpretation of “*monotherapy*” set out in the description from the beginning of proceedings. On this reading, the combination of the claimed 480 mg q4w nivolumab regimen with pembrolizumab is encompassed by the claims as granted, the claims of the present Main Request and indeed the claims of every Auxiliary Request filed during the first instance proceedings, as acknowledged by the proprietor at Oral Proceedings before the OD.
184. Despite this, none of the opponents had ever raised this objection throughout the proceedings, and indeed the OD had indicated in their Preliminary Opinion that even if the term “*monotherapy*” was interpreted as defined in the description, there was no issue of added matter (Preliminary Opinion, point 9.6).
185. Moreover, while the opponents had objected that the combined selections of “nivolumab” as the anti-PD-1 antibody and “480 mg q4w” as the dosage regimen added matter, in their Preliminary Opinion the OD had found this combination to comply with Art. 123(2) EPC (Preliminary Opinion, point 9.5). When issuing the decision in respect of claim 1 as granted, the OD found a lack of basis for the disclaimer, but stated that their “*position regarding multiple selections had not changed*” (Minutes, point 2.5).
186. It was therefore impossible for the proprietor to predict or expect that the OD would find an issue of added matter in the present Main Request relating to the claimed 480 mg q4w nivolumab regimen, as the OD raised at point 14.3.3 of the Decision.
187. Since the OD declined to fully explain their decision to the proprietor at the oral proceedings, and the objection which the OD ultimately set out in the Decision was so unexpected and inconsistent with their previous remarks, both in writing and at the hearing itself, we simply did not and could not know all the reasons for the OD’s decision for refusing the present Main Request.
188. When deciding whether to use their discretion to admit late-filed requests into proceedings, the Boards have previously directed that an OD should consider factors including *prima facie* allowability (in view of the objection under discussion), as set out in the CLBA (10<sup>th</sup> Edition, IV-C-5.1.4(d); pages 1244-1246).
189. In order to substantiate the filing of a new claim request at the Oral Proceedings before the OD following the refusal of the present Main Request, it would therefore have been necessary for us to explain why it overcame the objections under the current ground of discussion (i.e. Art. 123(2) EPC) which led to the present Main Request being refused.
190. This is in any event a high bar to meet, but in view of the OD’s refusal to explain to the proprietor the reasoning for their Decision on the present Main Request, it was impossible to know what amendment might overcome the objections, and whether present AR1

would be suitable. We could not possibly argue to the OD that present AR1 *prima facie* overcame the issue of added matter, when fundamentally we did not understand what the issue was. Therefore, AR1 is not a claim request which should have been filed at the Oral Proceedings before the OD.

191. On this point, while the Boards have previously affirmed that a party's right to be heard does not include the right to have decisions explained to them at oral proceedings, the Boards have also held that under Art. 113(1) EPC a decision "*may only be based on grounds or evidence on which the parties concerned have had an opportunity to present their comments ... a party may not be taken by surprise by the reasons of a decision referring to unknown grounds*" (CLBA 10<sup>th</sup> Edition, V-B-4.3.8(a); page 1595). In the present case, the deficiencies in the conduct of the Oral Proceedings by the OD mean that their decision is based on grounds on which the proprietor did not have an opportunity to comment, and which came as a surprise to the proprietor on reading the written decision.
192. These deficiencies directly resulted in the proprietor losing their opportunity to file further claim requests at the time of the Oral Proceedings before the OD. As set out above, the OD provided sufficient verbal reasoning for their decision that we knew it was based on a ground which had not been discussed, but not enough reasoning that we could understand what that ground was and how it might be addressed by amendment. In the circumstances we submit that it would be inequitable for the Board not to admit new claim requests into proceedings which seek to overcome the OD's objections.

#### Admission of the Request not Inconsistent with the Objectives of Art. 12(6) RPBA 2020

193. We would also submit that the proprietor's conduct in these proceedings has been in accordance with the spirit and intentions of the RPBA and that this should be taken account of by the Board in considering the admission of AR1.
194. Art. 12(2) RPBA 2020 states:  
  
*In view of the primary object of the appeal proceedings to review the decision under appeal in a judicial manner, a party's appeal case shall be directed to the requests, facts, objections, arguments and evidence on which the decision under appeal was based.*
195. And as set out in T 34/90, "*appeal proceedings are definitely not and were never intended to be the mere continuation of first instance proceedings*".
196. In other words, the restrictions on the filing of new claim amendments on appeal (set out in Art. 12(6) RPBA) is because the general purpose of the appeal proceedings is to

review the correctness of the first instance decision, not to continue examining new claim requests for the first time.

197. In the present case, AR1 is a new claim request, in the sense that no identical claim request was filed at first instance. However, it contains no new amendments. As noted above, it simply returns the preamble of former AR3 to its wording as granted, while amendments to parts (i) and (ii) of the claim are retained.
198. As set out above, claim 1 of former AR3 contained three amendments, to address three separate and unrelated objections raised by the opponents under Art. 123(2) EPC. Had we filed separate requests containing each of these three amendments, and all possible permutations thereof, the present claim request would have been filed at first instance, but this would have resulted in a 4-fold increase in the number claim requests on file and the associated negative impacts on the simplicity and efficiency of the proceedings.
199. It is submitted that it is not, and never has been, the purpose of the Rules of Procedure of the Boards of Appeal to undermine the procedural economy and simplicity of first instance proceedings, as could be the case if patent proprietors were required to file vast proliferations of claim requests so that all combinations of possible amendments were on file, to address any combination of objections which might be considered relevant by the department of first instance.
200. Therefore we submit that there is no reason for the Board to refuse to admit AR1 into proceedings.

#### Other Reasons for Admission

201. Art. 12(4) RPBA 2020 states that reasons including the complexity of the amendment, its suitability to address the issues which led to the decision under appeal and the need for procedural economy may be considered by the Board when deciding whether to admit a new claim request.
202. The present amendment is extremely simple. It does nothing more than remove an amendment from previous AR3. It raises no new issues. Indeed, as noted above, present AR1 contains the same amendment relative to previous AR3, as the present Main Request contains relative to previous AR2. At the Oral Proceedings before the OD, when the proprietor filed the present Main Request the opponents were offered a recess to study the claim set, and all declined (Minutes, point 3.5), as they needed no time to familiarise themselves with the amendment relative to former AR2. This demonstrates the entirely minimal and straightforward nature of the amendment being made.
203. In the event that the Board adopts the OD's claim interpretation, we submit that AR1 addresses the issue of added matter and is compliant with Art. 123(2), as set out below.

204. We also submit that the filing of AR1 is beneficial to procedural economy. In filing present AR1, rather than former AR3 which contains the same amendment to the disclaimer, various issues relating to the term “*single antibody composition*” are avoided, including the lack of clarity found by the OD and other issues previously raised by the opponents, for example an objection under Art. 123(3) EPC. Present AR1 also raises no new issues which were not present in the first instance proceedings.
205. Taking into account all the reasons set out above, we request that the Board use its discretion to admit AR1 into proceedings.

#### **Rule 80 EPC**

206. The amendments to AR1 relative to the claims as granted address objections raised by the opponents and the OD under grounds for opposition. No objection to these amendments was raised under Rule 80 EPC at first instance.

#### **Clarity (Art. 84 EPC) / Extension of Scope (Art. 123(3) EPC)**

207. Both the amendments to claim 1 have been on file in the context of former AR3 since the filing of our initial opposition response on 13 July 2022. No objection under Art. 84 or 123(3) EPC was made to them by any of the opponents.
208. We submit that the amendments to claim 1 are clear. The words have their plain meaning. The amendments to the dependent claims are simply deletions and therefore not open to clarity examination in the present proceedings. The requirements of Art. 84 EPC are met.
209. In the proprietor’s view, the amendment to claim 1, part (i) does not affect the scope of the claim relative to claim 1 as granted, whereas the amendment to the disclaimer expands the disclaimer, and therefore narrows the scope of the claim, relative to claim 1 as granted. The amendments to the dependent claims cannot affect overall claim scope, and so the requirements of Art. 123(3) EPC are met.

#### **No Added Matter (Art. 123(2) EPC)**

210. The basis for the claims of AR1 is the same as for the Main Request. The amended disclaimer has basis in claim 1 as filed.
211. In the proprietor’s view, the scope of AR1 is the same as that of the Main Request, i.e. AR1 is also directed to:

*a nivolumab composition for use in the treatment of PD-L1+ melanoma in a patient, wherein the treatment comprises administering 480 mg q4w nivolumab and does not comprise co-administration of an anti-CTLA-4 antibody.*

212. But in the event that the Board concurs with the OD's interpretation of the disclaimer, and is of the view that the wording of the disclaimer in the Main Request lacks basis in the application as filed, this is addressed by AR1. The disclaimer has the exact same wording as claim 1 as filed, and so complies with Art. 123(2) EPC.
213. As set out above in respect of the Main Request, the objection raised by the OD in point 14.3.3 of the Decision, in relation to basis for combining nivolumab with pembrolizumab, is incorrect. The same reasoning applies in respect of AR1.

## **Auxiliary Request 2**

214. AR2 is filed now for the first time, and we request its admission into proceedings.

### **Admissibility**

215. Claim 1 of AR2 has the following wording:

*A composition comprising nivolumab for use in treating a melanoma in a patient:*

*(i) wherein the patient is identified as having a PD-L1 positive melanoma tumor by measuring a PD-L1 cell surface expression on the melanoma tumor; and*

*(ii) wherein the patient is to be administered a flat dose of 480 mg of nivolumab as monotherapy once every four weeks, wherein the monotherapy comprises administering the patient nivolumab without another anti-cancer agent.*

216. Thus AR2 differs to the present Main Request in that its disclaimer is much broader: the term “*monotherapy*” is defined as administering nivolumab to a PD-L1+ melanoma patient without another anti-cancer agent, i.e. as a true monotherapy.

217. As detailed below, AR2 is filed to address the OD’s objection set out in point 14.3.3 of the Decision that there is no basis for combining the claimed nivolumab dosage regimen with pembrolizumab. There was no reason to file this claim request during the first instance proceedings, because the underlying objection was raised by the OD for the first time in the written Decision itself. It is therefore submitted that the request should be admitted into proceedings, in line with Art. 12(6) EPC. We further submit the considerations under Art. 12(4) RPBA 2020 of the complexity of the amendment, its suitability to address the issues which led to the Decision under appeal and the need for procedural economy support its admission.

### **No Reason to file AR2 Earlier in Proceedings**

218. As set out above, throughout the first instance proceedings the opponents argued that the term “*monotherapy*” in claim 1 is defined by the disclaimer, in line with the definition of the term in the description. On this interpretation, the claims as granted, and the claims of all Auxiliary Requests filed at first instance, encompass a therapeutic regimen including the claimed 480 mg q4w nivolumab regimen in combination with pembrolizumab.

219. At no point was this argued to be problematic under Art. 123(2) EPC. No objection was raised to the fact this combination was encompassed by the claims of all requests.

220. While the opponents objected to the fact that the disclaimer of claim 1 as granted allowed combination of nivolumab with anti-CTLA-4 antibodies other than ipilimumab, no objections were raised about any other potential combinations encompassed.
221. Indeed, both O4 and O5 appeared to tacitly acknowledge in their final written submissions that the disclaimer of the present Main Request, as it appeared in former AR2, addressed their objection of an extension of claim scope (see O4, submissions of 4 January 2024, points 99-100; and O5, submissions of 3 January 2024, points 80-81).
222. The OD also indicated that if the term “*monotherapy*” was interpreted in line with the description, such that it excluded only combinations of nivolumab with an anti-CTLA-4 antibody, there were no added matter issues with claim 1 (Preliminary Opinion, point 9.6).
223. Thus it is apparent that no party had raised an objection prior to the Oral Proceedings in relation to the fact that the claims encompass co-administration of the specified nivolumab regimen with pembrolizumab. It is also apparent from the Minutes that this objection was not raised by any of the opponents during the Oral Proceedings, or made clear by the OD at that time. Indeed, as noted above (see point 185), the OD explicitly indicated with respect to claim 1 as granted that they saw no issue with the alleged multiple selections required. It was therefore entirely unexpected to read in the written Decision that the OD had resiled from this position without informing us.
224. Therefore, the proprietor had no reason to file the present claim request, which excludes co-administration of pembrolizumab, at any point during the first instance proceedings. AR2 is not, therefore, a claim request which should have been filed during the first instance proceedings.

#### Reasons for Admission of AR2

225. AR2 is now filed in direct reaction to the objection of added matter first detailed by the OD in point 14.3.3 of the Decision. The proprietor’s need to file this objection for the first time now is a direct result of the deficiencies in the conduct of the first instance Oral Proceedings by the OD, and their failure to detail this objection at that time. Indeed, the proprietor considers the conduct of the OD to have been actively misleading: they stated in respect of claim 1 as granted that they did not see any issue with the selections required to obtain the claimed dosage regimen, only to change their mind and refuse the patent on (*inter alia*) these grounds, without ever making clear to the proprietor that their position had changed.
226. As a result, the proprietor was left guessing as to why the OD had refused the present Main Request, and in the absence of an explanation from the OD, there was no way the proprietor could reasonably have been expected to work out the OD’s reasoning. This is

particularly so given that the objection is so far removed from the normal practice of the EPO on added matter.

227. Since the claim request is filed for the first time now only because of the deficiencies in the conduct of the first instance Oral Proceedings by the OD, in the event that the Board agree with the OD's objection as set out at point 14.3.3 of their Decision, it is submitted that AR2 should be admitted into proceedings.
228. AR2 clearly overcomes the objections raised by the OD in their Decision. It is submitted that the amendment is straightforward and provides a clear definition of the term "*monotherapy*" in claim 1. We submit that it raises no new issues and as such should be admitted.

#### **Rule 80 EPC**

229. The amendments to AR2 relative to the claims as granted address objections raised by the opponents and the OD under grounds for opposition. Specifically, the amendments to claim 1 and the deletion of claim 7 as granted all address objections raised under Art. 123(2) EPC, while the amendment of claim 6 addresses an objection raised under Art. 83 EPC.

#### **Clarity (Art. 84 EPC) / Extension of Scope (Art. 123(3) EPC)**

230. The amendment to the claim specifies that the monotherapy comprises administering the patient nivolumab without another anti-cancer agent. It is clear whether a treatment regimen does or does not include administering another anti-cancer agent along with nivolumab, and as such there is no lack of clarity as to whether any given treatment regimen falls inside the claim. As such, AR2 complies with the requirements of Art. 84 EPC.
231. The amendment also does not extend the scope of the claims relative to the claims as granted. As set out above, while the claims as granted excluded only combining nivolumab with ipilimumab, the present claims exclude combining nivolumab with any other anti-cancer agent. As the "exclusion zone" is much greater than in claim 1 as granted, the overall claim scope is narrower.

#### **No Added Matter (Art. 123(2) EPC)**

232. The claims of AR2 have the same basis as those of the Main Request, with the exception of the amended disclaimer/definition of the term "*monotherapy*". The amended disclaimer has basis at paragraph [0043] as filed, which states that:

*In other embodiments, the anti-PD-1 antibody monotherapy comprises administering one or more doses of an anti-PD-1 antibody to a patient in need thereof, but does not include administering another anti-cancer agent.*

233. The skilled person would directly and unambiguously understand that in the context of a nivolumab monotherapy (i.e. where nivolumab is selected as the anti-PD-1 antibody), this means that nivolumab is administered without another anti-cancer agent.
234. It is submitted that the selection of this definition of “*monotherapy*” from paragraph [0043], in the present context, does not add matter. The Examples, upon which the invention is based, demonstrate a true nivolumab monotherapy, in which nivolumab is administered to patients without any additional anti-cancer agent: paragraph [0136] refers to patients being treated with “*nivolumab alone*”.
235. As set out above, the use of nivolumab in the Examples provides a clear pointer for the skilled person to use nivolumab for implementation of the invention (see points 146-152). That the Examples use a true nivolumab monotherapy, rather than an alternative combination, provides a clear pointer to selecting a true monotherapy for implementation of the invention.
236. Notably, the Examples do not demonstrate any possible or suitable therapeutic agents which could be administered with nivolumab in accordance with the broader definition of “*monotherapy*” in claim 1 as filed and granted. Nor are any such additional therapeutic agents suggested anywhere in the application as filed. This absence provides the skilled person with a clear pointer towards implementing the invention in this manner.
237. Therefore, as for the Main Request, the only selection that has to be made from the application as filed to reach the claimed subject matter is the nivolumab dosage regimen. As noted above, a selection from a single list is permitted.
238. The OD objected in point 14.3.1 of the Decision that the present Main Request encompasses combination therapies which were not encompassed by the application as filed (including claim 1 as filed). Claim 1 of present AR2 excludes any combination therapies and so overcomes this objection.
239. The OD also objected in point 14.3.3 of the Decision that there was no basis for the treatment regimen of 480 mg q4w nivolumab with pembrolizumab. Pembrolizumab is an anti-cancer agent and so this combination is explicitly excluded from AR2, overcoming this objection also.
240. Accordingly, AR2 meets the requirements of Art. 123(2) EPC.

### Auxiliary Requests 3-5

241. ARs 3-5 are filed now for the first time. We request their admission into proceedings.

#### **Admissibility**

242. ARs 3-5 correspond to the present Main Request, AR1 and AR2, respectively, with the additional amendment relative to the claims as granted that the preamble of claim 1 specifies that the composition comprises "*nivolumab, and no other antibody*".

243. These claim requests are filed in the event that the Board agrees with O1 that the simple reference to "*a composition*" in the Main Request is an intermediate generalisation of the discussion in paragraph [0042] as filed of "*single antibody compositions*".

244. As set out above, the proprietor previously looked to address this objection by referring explicitly to a "*single antibody composition*" in claim 1. However, this term was found to lack clarity by the OD (Decision, point 10).

245. ARs 3-5 address the objection of O1 in an alternative way which, it is submitted, is clear.

246. There was no reason for the proprietor to file these claim requests during the first instance proceedings. (For ARs 4 and 5, this is in addition to the lack of reasons for filing AR1 and AR2 at first instance.)

247. As noted above, in our initial opposition response, the proprietor addressed O1's objection by amending claim 1 to refer to a "*single antibody composition*". In their Preliminary Opinion, the OD rightly found that the reference in claim 1 to a "*composition*" complied with Art. 123(2) EPC (Preliminary Opinion, point 9.4). They made no comment on the clarity or otherwise of the term "*single antibody composition*".

248. As further noted above, the objection raised by O3, and sustained by the OD, that the term "*single antibody composition*" is fundamentally unclear, was raised for the first time by O3 only a week before the Oral Proceedings. This left the proprietor with no time to react before the hearing.

249. At the Oral Proceedings, the objection initially raised by O1 was not pursued by any party. After the OD found former AR2 to lack clarity, the proprietor responded by filing the present Main Request, in which "*single antibody*" is deleted from claim 1, returning its preamble to its wording as filed. No objections along the lines of O1's original objection were made in response. Accordingly, the proprietor had no reason to file any of ARs 3-5 at first instance, and it cannot be said that they should have been filed at first instance.

250. Moreover, the amendment overcomes O1's objection, addresses the clarity issues with the term "*single antibody composition*" and is clear and straightforward in itself, raising no new issues.

251. Accordingly, the Board is requested to use its discretion to admit ARs 3-5.

#### **Rule 80 EPC**

252. The amendments to ARs 3-5 relative to the claims as granted address objections raised by the opponents and the OD under grounds for opposition. The amendments to claim 1 and the deletion of claim 7 as granted all address objections raised under Art. 123(2) EPC, while the amendment of claim 6 addresses an objection raised under Art. 83 EPC.

#### **Clarity (Art. 84 EPC) / Extension of Scope (Art. 123(3) EPC)**

253. In addition to the amendments in the Main Request and ARs 1 and 2, the amendment that the composition comprises "*no other antibody*" is clear and straightforward. It simply means what it says. ARs 3-5 thus comply with the requirements of Art. 84 EPC, for this reason and the reasons set out above for the Main Request and ARs 1 and 2, respectively.

254. It should be noted, contrary to arguments previously made by O3 and O5 in relation to the term "*single antibody composition*" that there is no inconsistency in the definition of the term "*monotherapy*" in AR1 and AR2 as encompassing co-administration of additional active agents, and specifying that nivolumab is administered in a composition comprising no other antibody. (See O3, submissions of 2 January 2024, points 123-125; and O5, submissions of 3 January 2024, point 79).

255. Even if nivolumab is administered in a composition without any other antibody in it, this does not, for instance, exclude the composition comprising a second, non-antibody agent, nor the co-administration of nivolumab and a second antibody in a separate composition. It is just the co-administration of nivolumab and another antibody in the same composition which is excluded. There is no unclarity.

256. In addition to the amendments in the Main Request and ARs 1 and 2, the amendment that the composition comprises "*no other antibody*" narrows the scope of claim 1. Whereas claim 1 of the Main Request allows the composition to include other antibodies (except anti-CTLA-4 antibodies), claim 1 of these ARs does not allow the nivolumab composition to include any other antibody. Arguably, the amendment in AR5 is redundant, given that the claim already specifies that the patient is administered nivolumab without any other anti-cancer agent, but in case of argument on this point, AR5 is filed now.

**No Added Matter (Art. 123(2) EPC)**

257. With the exception of the amendment to specify that the composition comprises nivolumab “*and no other antibody*”, ARs 3-5 have basis in the application as filed at the same locations as the Main Request and ARs 1 and 2, respectively, as set out above.
258. Basis for specifying that the composition comprises nivolumab “*and no other antibody*” can be found at paragraphs [0042] and [0059] of the application as filed. Paragraph [0059] teaches that the patient may be administered “*a single antibody composition comprising an anti-PD-1 antibody*”. Paragraph [0042] teaches that a “*single antibody composition can include only one specific antibody[y], e.g. nivolumab alone*”. Thus the paragraphs together disclose the administration of a composition comprising nivolumab and no other antibody.
259. Basis for selecting from paragraph [0042] a composition comprising only nivolumab, rather than a mixture of antibodies against PD-1, can be found in the Examples. The Examples demonstrate an anti-PD-1 monotherapy in which nivolumab is administered alone (see paragraph [0136]), i.e. without any other antibody. This provides a clear pointer to the use of a composition comprising nivolumab without any other antibody in the therapies of the invention.
260. In the event that the Board is in agreement with O1 that the reference in claim 1 as granted (and in the present Main Request) to, simply, “*a composition*”, is an intermediate generalisation of the reference to a single antibody composition in paragraph [0059], this objection is addressed on ARs 3-5. Although the term “*single antibody composition*” is not used, the composition for use of these requests is a single antibody composition as defined in paragraph [0042] of the application as filed.
261. The composition according to these requests therefore finds explicit basis in paragraph [0059] of the application as filed.

## Remittal

262. As set out above, in the event that the Board sets aside the decision of the OD in respect of compliance with Art. 123(2) EPC, we request remittal of the case to the OD for examination of the other grounds of opposition.
263. We submit that there are at least two reasons for remittal of the case for further prosecution: (i) aside from added matter, no issues were decided upon during the first instance proceedings; and (ii) the fundamental deficiencies in the conduct of the oral proceedings by the OD.

## **Undecided Issues**

264. As set out above, the primary object of appeal proceedings is to review the decision under appeal (see Art. 12(2) RPBA 2020).
265. In view of this primary object, the Boards have generally considered that where essential issues of patentability have not yet been decided upon, cases should be remitted to the department of first instance. This is particularly the case where a first instance decision is based on a single ground and other objections have not been considered:

*Since the main purpose of appeal proceedings is to give a losing party an opportunity to challenge a decision on its merits, remittal in accordance with Art. 111(1) EPC has generally been considered by the boards where essential questions regarding the patentability of the claimed subject-matter have not yet been examined and decided on by the department of first instance. This applies to both ex parte and inter partes proceedings.*

*In particular, remittal is considered by the boards where a first-instance department has issued a decision against a party based solely on one particular issue which was decisive for the case and left open those that were not or on which comments would have been obiter dicta.*

CLBA 10<sup>th</sup> Edition, V-A-9.3.2(a); pages 1509-1510

266. This principle was clearly set out by the Board in **T 3218/19**:

*As set out in Article 12(2) RPBA 2020, the primary object of the appeal proceedings is to review the decision under appeal in a judicial manner. This principle would not be respected if the board were to conduct a complete examination of issues which were not dealt with by the opposition division. Thus, special reasons present themselves for remitting the case (Article 11 RPBA 2020 and decisions T 1966/16 and T 731/17).*

T 3218/19, Reasons, 3.2

267. The principle that it is not the proper function of the Boards of Appeal “*to conduct a complete examination of the application or patent*” has been repeatedly affirmed (CLBA 10<sup>th</sup> Edition, V-A-9.3.2(a); page 15010), as set out in e.g. **T 1966/16** (Reasons, 2.2), **T 275/15** (Reasons, 4.3-4.4), **T 2519/17** (Reasons, 5), **T 1077/17** (Reasons, 5) and **T 1508/17** (Reasons, 3.4).
268. In the present case the Decision relates only to compliance with Art. 123(2) EPC. Objections raised under Arts. 53(c), 83, 54 and 56 EPC were not discussed at Oral Proceedings or decided upon by the OD. In the event that the Decision of the OD relating to Art. 123(2) EPC is set aside, it is therefore submitted that the Board should remit the case to the OD for further prosecution of the other issues.
269. Indeed, we note that certain objections, notably a question by O5 as to the fundamental suitability of PD-L1 as a marker for patient selection at all (O5, submissions of 3 January 2024, point 75), were raised by the opponents for the first time in their final written submissions. As such we have not previously had a chance to respond to these objections. We would submit that an appeal is not a suitable forum for considering certain issues for the very first time.
270. Moreover, if the Board is not persuaded that the case should be remitted as a matter of principle, it is submitted that examination of the issues of patentability for the first time would be an undue burden (see CLBA 10<sup>th</sup> Edition V-A-9.3.2(c), pages 1511-1512). For example, at first instance at least 9 documents/document clusters were maintained by the opponents as possible starting points for assessment of inventive step in their final written submissions (see Decision, point 19.3.11). It is submitted that it would be an undue burden for the Board to have to examine each of these documents from scratch.

#### Obiter Dicta

271. The OD has included with their Decision non-binding *obiter dicta* in relation to the issues not decided upon at first instance. It appears to the proprietor that the OD is aiming to avoid remittal in the event that the Board overturns their Decision under Art. 123(2) EPC.
272. We submit that such an approach is unhelpful in the present context. The objections under the other grounds of appeal are not related to the grounds for the revocation of the patent and there is clearly no link at all between them and the decision under appeal. As correctly held by the Boards of Appeal in decision **T 615/95** in *ex parte* proceedings, which is nonetheless entirely applicable to the present *inter partes* proceedings:

*annexes to appealable decisions listing objections having no relation to the reasons for the decision concerned and having no legal effect, would seem to be of no help to anybody, be it the Appellant, the public, the Examining Division, or*

*the Board, [...]. Moreover, it does not seem to be advisable that an Examining Division indicates in a decision, which can and has to be delivered only on the facts and requests which are on file at the very point in time when the decision is taken, what steps it may take in response to possible future submissions of an applicant. The further evolution of a case can be hardly foreseen and the potential issues which may have a bearing on the outcome of the further examination proceedings cannot reliably be predicted. Furthermore, such indications, in spite of their legal insignificance, may cause unnecessary confusion by providing for example the wrong picture of a hopeless situation or, on the contrary, give rise to unjustified expectations on the part of the applicant.*

*For these reasons, an Examining Division's decision should not be supplemented normally by annexes dealing with issues having no relation to the issues dealt with in the reasons for this decision.*

T 615/95, Reasons, 14

273. The proprietor strongly endorses this reasoning. For example, in the present case, the OD initially did not consider the question of inventive step clear cut, and declined to give an opinion on it in their Preliminary Opinion, as shown below:

13.4 Is the solution inventive?

**The Division is sitting on the fence, and needs more input from the parties.**

274. In their *obiter dicta*, having considered the further written submissions of the parties, the OD held the patent to lack inventive step. But having initially found the matter to be on a knife-edge, the proprietor submits that the OD cannot reasonably suggest that there are no circumstances under which they would have come to a different conclusion. As such it is deeply unhelpful for the OD to have included this *obiter dicta* based on incomplete arguments on the grounds for opposition.

275. But in any event, as set out in the case law quoted above:

*In particular, remittal is considered by the boards where a first-instance department has issued a decision against a party based solely on one particular issue which was decisive for the case and left open those that were not **or on which comments would have been obiter dicta.***

CLBA 10<sup>th</sup> Edition, V-A-9.3.2(a), emphasis added

276. In other words, whether *obiter dicta* comments have been provided on issues not considered at first instance should have no bearing on whether the case is remitted to the department of first instance.

## Deficiencies in Conduct of Oral Proceedings by the OD

277. As set out above, the oral proceedings before the OD were marred by deficiencies in the conduct of the proceedings by the OD.
278. The present Main Request was refused under Art. 123(2) EPC for two reasons, as set out in the Decision at points 14.3.1 and 14.3.3. As explained above, the OD's conduct of the Oral Proceedings, and the way these objections were raised (or more pertinently, not raised) resulted in deficiencies in the first instance proceedings.
279. Taking first the objection set out at point 14.3.1 of the Decision, as noted above this objection arose directly from a brand new claim interpretation set out by the OD for the first time in the written Decision. The OD's new claim interpretation, and the resulting objection of added matter, were not raised by any party or the OD at any point during the first instance proceedings, whether in writing or at the Oral Proceedings.
280. While the proprietor acknowledges that its position on claim interpretation changed at the Oral Proceedings compared to the written proceedings, this was simply to allow the case to proceed based on the interpretation argued for by the opponents. There was nothing in the proprietor's actions which could have justified the OD adopting an entirely new claim interpretation, raising a new added matter objection on that basis, and then not telling the parties about it.
281. As noted above, by failing to elucidate the objection set out at point 14.3.1 of the Decision during the Oral Proceedings, the proprietor was denied an opportunity to comment on it, and taken by surprise by it, contrary to the requirements of Art. 113(1) EPC (CLBA 10<sup>th</sup> Edition, III-B-2.3.1; page 657).
282. The deficiencies in respect of the objection raised in point 14.3.3 are, if anything, even more severe. As noted above, this objection was similarly not raised by any party during the first instance proceedings. It is notable that the objection was applicable to the claims as granted under the interpretation put forward by the opponents during the written proceeding, yet none of the opponents raised it.
283. Following discussion of the Main Request, the OD stated that their position regarding the alleged multiple selections was unchanged from their preliminary opinion (Minutes, point 2.5), meaning that they remained of the view that the claimed combination of the specific anti-PD-1 antibody and dosage regimen were not problematic under Art. 123(2) EPC.
284. Subsequently, during discussion of the present Main Request, the Chairman of the OD explicitly instructed the parties that the OD had already heard and considered the question of multiple selections and provided their view on it, and did not wish to hear this point reargued (a request to correct the Minutes of the Oral Proceedings to include this

instruction from the Chairman is being filed concurrently with these Grounds of Appeal). On receipt of the written Decision, however, it transpired that the OD had raised an objection precisely along these lines (point 14.3.3). The proprietor is astonished that the OD could see fit to refuse a claim request based on an objection which not only had not been raised by any party, but which related to a topic on which the OD themselves had instructed us not to comment.

285. And while the OD at least indicated during the Oral Proceedings that the objection set out in point 14.3.1 of the Description could have been addressed by introducing the full wording of the disclaimer from claim 1 as filed into the claims (even if they didn't tell us what the objection was), no guidance was given as to the second reason for refusal, set out in point 14.3.3 of the Decision. Essentially, the second reason was kept a secret for us to discover on receipt of the written decision. In this way, we were denied any opportunity to address the objection at the hearing itself.
286. It is thus apparent that the conduct of the Oral Proceedings by the OD suffered from fundamental deficiencies. Should the Board find in favour of the proprietor on the question of compliance with Art. 123(2), this provides another reason that the case should be remitted to the OD for prosecution of the grounds not yet considered, in line with Art. 11 RPBA 2020.

### Other Grounds of Opposition

287. It is our understanding that while requiring that an appellant sets out its complete appeal case in their Grounds of Appeal (which means the Grounds should set out clearly and concisely the reasons why it is requested that the decision under appeal be reversed, and should specify expressly all the requests, facts, objections, arguments and evidence relied on, Article 12(3) RPBA 2020), an appellant is not required to address aspects or issues that have not been discussed in the impugned decision (see also, e.g., **T 1038/18**, Reasons, 5.2.2; and **T 919/17**, Reasons, 1).
288. Nonetheless, for the record and as a matter of utmost precaution, we strongly disagree with the OD's observations under Art. 56 EPC set out in the *obiter dicta*, and explain this in detail below, along with our comments on the other issues discussed in the *obiter dicta*.
289. The proprietor emphasises that this is not, and should not be understood or suggested to be, any kind of acquiescence to the consideration of the topics covered by the OD's *obiter dicta* during the present appeal proceedings. It remains the proprietor's position that the inclusion of the *obiter dicta* was unnecessary and unhelpful, that the case should be remitted to the OD if the Board sets aside their decision under Art. 123(2) EPC, and that the inclusion of the *obiter dicta* should play no part in the Board's consideration of whether to remit the case.

### **Sufficiency (Art. 83 EPC)**

290. The proprietor agrees with the OD's opinion that the claims of the present Main Request meet the requirements of Art. 83 EPC. The claims of each of AR1 to AR5 also meet the requirements of Art. 83 EPC, for the same reasons as the Main Request, as set out below.

### Efficacy of Claimed Regimen

291. According to the OD, O3, O4 and O5 all objected that the patent does not make it plausible that the claimed dosing regimen provides a technical effect (Decision, point 16.1). However, this is something of a misrepresentation of the arguments of at least O4 and O5. Both of these opponents argued that the skilled person would indeed have expected the claimed regimen to be effective, but raised purely conditional arguments of insufficiency in case of certain arguments being made by the proprietor (see e.g. O4, NoO, points 208-209; and O5, NoO, points 152-153).
292. Indeed, O5 went so far as to state:

*To be clear, we basically agree that there was a reasonable expectation of success that the claimed dosage regimen would be suitable for treating PD-L1+ melanoma*

O5, submissions of 3 January 2024, point 69

293. In reality, only O3 actually alleged that it was not credible from the application as filed and/or the common general knowledge that the claimed dosage regimen would be effective. This position put them explicitly at odds even with their co-opponents.
294. O3's position on sufficiency is moreover completely inconsistent with their arguments in respect of inventive step. On the one hand, in relation to sufficiency of disclosure, O3 has argued that in the absence of explicit demonstration of the claimed nivolumab regimen:

*The patent therefore does not make it plausible that the claimed dosing regimen would provide any technical effect*

O3, NoO, point 61

295. On the other hand, in respect of inventive step, O3 has argued that:

*In the present case, the claimed dosage regimen of 480 mg Q4W for nivolumab was known in the prior art (D12a for NSCLC patients) and had already been implemented in clinical phase III studies. Thus, said dosage regimen was considered safe and efficacious for treating cancer patients and a person skilled in the art would have found said dosage regimen for treating melanoma based on routine skill*

O3, Submissions of 2 January 2024, point 79

*a person skilled in the art had reasonable expectation to find the dosage regimen of 480 mg Q4W for treating melanoma as it had already been used for NSCLC*

O3, Submissions of 2 January 2024, point 111

*a person skilled in the art would have been motivated to administer the dosage regimen of 480 mg Q4W to treat melanoma as already done for NSCLC*

O3, Submissions of 2 January 2024, point 115

296. And indeed in their written submissions of 26 February 2024, O3 set out 6 detailed reasons as to why the skilled person would have expected the claimed dosage regimen to be safe and effective, based on the known pharmacokinetic parameters of nivolumab (point 21).
297. Both these positions cannot simultaneously be true. O3 cannot credibly argue that based on the data in the patent, it was not plausible that the claimed dosage regimen would be effective, but that also the skilled person would have been motivated to use it and

expected it to be effective. O3's arguments should therefore be dismissed out of hand for their inconsistency.

298. But if the Board wishes to consider the arguments in more detail, we should firstly recall that in opposition proceedings the burden of proof lies with the opposing party, to substantiate any allegation of insufficient disclosure (CLBA 10<sup>th</sup> Edition, III-G-5.1.2(c); page 869). In the present case, the opponents have provided no “*verifiable facts*” to substantiate any alleged doubts that the skilled person would have been able to carry out the claimed invention.
299. Rather, we agree with the OD that the skilled person would have considered it plausible based on the data in the application as filed and their common general knowledge that the claimed nivolumab regimen would be effective (see Decision, point 16.1), and endorse their reasoning in this respect.
300. The claims of the present patent are medical use claims directed to treating a melanoma in a patient. The requirement of sufficiency of disclosure is considered as being fulfilled with respect to a medical use claim if the patent discloses the suitability of the product for the claimed use by providing some information rendering it technically plausible for the skilled person that the intended therapeutic effect can be achieved:

*because the subject-matter of second medical use claims is commonly limited to a known therapeutic agent for use in a new therapeutic application, it is usually only necessary that the patent renders it plausible that the known therapeutic agent (i.e. the product) is suitable for the claimed therapeutic application*

CLBA, 10<sup>th</sup> Edition, II-C-7.2.1; page 419

301. It is further established case law of the EPO's Boards of Appeal that the disclosure of experimental data is not necessarily required to establish sufficiency, particularly if a patent discloses a plausible technical concept and if there are no substantiated doubts that the claimed concept can be put into practice (see, e.g., T 1616/09, T 950/13). Moreover, if the patent discloses a plausible technical concept, post-filed evidence can be taken into account to support the patent's disclosure:

*For the acceptance of sufficient disclosure of a therapeutic application, **it is not always necessary for results of clinical trials to be provided at the relevant date**, but the patent/patent application must provide some information showing that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease. **Once this evidence is available from the patent/patent application, post-published evidence may be taken into account to support the disclosure in the patent application (T 433/05).***

CLBA, 10<sup>th</sup> Edition, II-C-7.2.2; page 425 (emphasis added)

302. O3's sole argument for insufficiency of the claimed regimen is that it is not demonstrated to be effective in the examples, via a clinical trial. But the case law is explicit that clinical trial data is not generally required to meet the requirements of Art. 83 EPC. Therefore O3's objections in this respect fall at the first hurdle.
303. Turning to the data in the patent, the examples demonstrate that a nivolumab monotherapy regimen is effective in treating PD-L1+ melanoma (see paragraph [0145]). This would make it plausible to the skilled person that nivolumab monotherapies, in general, are suitable for this purpose, including the regimen claimed. The opponents have provided no reasoning as to why the skilled person would not have considered it plausible that the claimed regimen would be effective, despite the demonstrated efficacy of the 3 mg/kg q2w regimen. To the contrary, the opponents' expert testimony makes the exact opposite argument, that the skilled person would have expected the claimed regimen to be safe and effective based on the data in the patent (see **D65a**). O3, O4 and O5 all endorsed this position (O3, submissions of 26 February 2024, points 21-23; O4, submissions of 4 January 2024, point 90; O5, submissions of 3 January 2024, point 36).
304. In summary, the skilled person would have considered it plausible, based on the data in the patent, that the claimed nivolumab regimen would be effective.
305. In view of this suitability demonstrated in the patent, post-published evidence may be taken into account to confirm this. The efficacy of the claimed regimen is demonstrated by, for example, the post-published documents **D27** and **D75**. **D27** was cited during prosecution of this patent, and states:
- The time-averaged steady-state exposure and safety profile of nivolumab 480 mg Q4W are consistent with that of 3 mg/kg Q2W across multiple tumor types*  
D27, Abstract, Conclusions
306. **D75** provides an analysis of the efficacy of the 480 mg q4w nivolumab regimen compared to other regimens including 3 mg/kg q2w in the treatment of metastatic melanoma (Methods). The Results section states that:
- Our data suggests that nivo 480 mg (Q4W) correlates with a better OS [overall survival] compared with other regimens*
307. Regardless of whether **D75** can be interpreted as demonstrating superiority of the claimed regimen compared to the 3 mg/kg q2w regimen demonstrated in the patent (a point of contention at first instance), we submit that it unarguably shows that the claimed regimen is at least effective.
308. Thus the requirements of Art. 83 EPC are met in respect of claim 1 and the credibility of the claimed dosage regimen.

Identification of PD-L1+ Melanoma

309. O4 raised another “conditional” objection of insufficiency, in relation to the ability of the skilled person to determine the PD-L1 expression status of a tumour (NoO, points 210-216).

310. O4 stated that this objection was raised purely in case the proprietor were to argue that the skilled person would not have been able to determine PD-L1 status of a tumour sample based on their common general knowledge (O4, NoO, point 216).

311. O4 explicitly stated that, in fact:

*PD-L1 was a well-known potential biomarker in the context of anti-PD-1 antibody treatment and the skilled artisan would have had no difficulties to reliably determine PD-L1 status of a tumor sample, based on his/her common general knowledge*

O4, NoO, point 215

312. We have never argued that the skilled person would be unable to determine tumour PD-L1 expression status based on their common general knowledge. As such, we submit that O4’s argument in this respect should be treated as having never been made. But in any event, we wholeheartedly agree with O4’s position that determining whether a melanoma tumour is PD-L1+, as required by the present claims, would have been routine based on their common general knowledge.

313. We agree with the OD on this matter (Decision, point 16.2) and endorse their reasoning.

Measuring PD-L1 Expression in Claim 2

314. O1 objected that claim 2 lacks sufficiency of disclosure because it encompasses measuring PD-L1 expression in a test tissue sample comprising tumour-infiltrating inflammatory (TII) cells (O1, NoO, points 110-113).

315. We agree wholly with the OD on this point (Decision, point 16.3). The opponents’ objection is based on the fact that claim 2 refers to a test tissue sample comprising tumour cells “and/or” TII cells. The opponents allege that this means the claim covers the use of a tissue sample comprising only TII cells, whereas claim 1 requires the measurement of PD-L1 expression on the tumour.

316. However, as noted by the OD, a biopsy will always contain tumour tissue. It would not even be possible to obtain such a sample containing only TII cells and no tumour cells. Therefore the skilled person would not read claim 2 as referring to the use of such a sample. Rather, the skilled person would understand the claim to be referring to a sample which contains tumour cells and possibly TII cells as well.

317. Moreover, claim 1 specifies that PD-L1 expression is measured on the tumour, i.e. on tumour cells. Claim 2 therefore requires the measurement of PD-L1 expression on tumour cells, and so tumour cells must be present in the sample. When read with a mind willing to understand, it is therefore clear that the sample of claim 2 must contain tumour cells, and that the interpretation of the claim set out in the paragraph above is correct. When read correctly, there is no insufficiency in this claim.

#### Reliability of PD-L1 Status as Marker

318. O5 raised an objection in their final written submissions (which the Board will note we have not previously had a chance to respond to) that PD-L1 expression is a fundamentally unsuitable marker for patient selection (O5, submissions of 3 January 2024, point 75).
319. We agree entirely with the OD (Decision, point 16.4) that O5 is confused as to the way PD-L1 is used as a biomarker in the present patent. O5 correctly notes that **D44**, **D50** and **D67** suggest that it is not appropriate to use PD-L1 expression as a marker to exclude patients from receiving anti-PD-1 therapy. But the present patent is not using PD-L1 expression in this way. Rather, PD-L1 expression is being used to select patients for treatment with anti-PD-1 monotherapy. Of course it is not specified in the claims, but the implication is that other patients should receive anti-PD1/anti-CTLA-4 combination therapy (see paragraph [0055]).
320. The present patent shows that PD-L1 expression reliably indicates which patients will receive benefit from anti-PD-L1 monotherapy, and which require anti-PD-L1/anti-CTLA-4 combination therapy (paragraph [0145]). Thus there is no issue with sufficiency of disclosure under Art. 83 EPC.

#### **Excluded Subject Matter (Art. 53(c) EPC)**

321. O2 objected that the claims relate to subject matter excluded from patentability under Art. 53(c), as the so-called “diagnostic step” of claim 1 encompasses diagnostic methods performed directly on the human body (O2, NoO, section 5).
322. We agree with the OD that the subject matter of the Main Request is not excluded from patentability under Art. 53(c) EPC (Decision, point 17), and endorse their reasoning in this respect. The subject matter of each of AR1 to AR5 also is not excluded from patentability for the same reasons.
323. However we would argue that, more fundamentally, the present claims cannot fall under the exclusions of Art. 53(c) EPC, because they do not relate to methods.

324. The present claims are directed to a product (specifically a composition comprising nivolumab) for use in a specific method of treatment, in accordance with Art. 54(5) EPC. Art. 53 EPC reads as follows:

*European patents shall not be granted in respect of:*

...

*(c) methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body; this provision shall not apply to products, in particular substances or compositions, for use in any of these methods.*

325. In other words, Art. 53(c) only excludes methods from patentability. As stated in the Guidelines:

*only method claims may fall under the exception of Art. 53(c).*

Guidelines for Examination, March 2024, G-II-4.2.1

326. And as stated in the CLBA:

*whilst a method claim falls under the prohibition on patenting methods for treatment by therapy or surgery if it comprises or encompasses at least one feature defining a physical activity or action that constitutes a method step for treatment of a human or animal body by surgery or therapy...*

CLBA 10<sup>th</sup> Edition, I-B-4.2, emphasis added

327. Art. 53(c) EPC explicitly states that it does not apply to products, including substances or compositions for use in the methods set out therein. Thus the article makes it explicit that it does not apply to compositions for use in methods of treatment, which are the focus of the present claims. Accordingly, the present claims do not fall under the ambit of Art. 53(c) EPC.

328. As noted by the OD, the discussion of measurement of PD-L1 expression on the melanoma tumour merely defines the patient to be treated using the claimed nivolumab composition. It does not encompass an active measurement step.

## Novelty

### Novelty over D1 – Main Request

329. O1 and O3 alleged a lack of novelty over D1 (WO 2016/168716), which is prior art to the present patent under Art. 54(3) EPC. We agree with the OD that the opponents are incorrect, and that the subject matter of the present Main Request is novel over D1 (Decision, point 18.1). To an extent, we agree with the OD's reasoning in this respect, as

set out below. In particular, we agree with the OD that to obtain the claimed invention from **D1** would require multiple selections from lists. An additional reason for the novelty of the Main Request over **D1** is the lack of any teaching in **D1** of a patient selection step based on tumour PD-L1 expression. The subject matter of AR1 is novel over **D1** for the same reasons as the Main Request.

330. As noted by the OD, **D1** relates to compositions comprising two antibodies. The first antibody is an anti-PD-1 antibody, and the second antibody is not defined (paragraph [0006]). The composition may be for use in treating a disease, such as cancer (paragraphs [0039-0040]). However, unlike the present claims which require a patient selection step based on PD-L1 expression by the tumour, **D1** does not teach any patient selection step.
331. Paragraphs [0037-0039] of **D1** describe administering to a patient a composition as defined therein. These paragraphs refer simply to “a *patient*”. There is no limitation based on the expression of any particular protein by cells of interest in the patient. The same is true of the corresponding claims (claims 88-90).
332. None of the other claims specify treatment of patients based on expression of a particular protein by cells of interest. Nor is there any such disclosure in the general description, nor in the Examples (none of which disclose medical methods in any case). Quite simply, nowhere in **D1** is there any teaching of performing a patient selection step.
333. And indeed, O1 was not able to point to any disclosure in **D1** of a patient selection step, but nonetheless argued that the cancers referred to in **D1** “*are clearly PD-L1 positive*” (O1, NoO, point 50). This is based on the teaching that “*inhibition of the PD-1/PD-L1 interaction mediates potent antitumour activity*” (paragraph [0106] of **D1**). But this simply teaches a mechanism by which anti-PD-1 antibodies such as nivolumab have a therapeutic effect. It does not direct the skilled person to carry out a selection step for patients with cancers expressing PD-L1.
334. The OD note that paragraph [0106] teaches that PD-1 interacts with both PD-L1 and PD-L2, and takes the view that a cancer to be treated according to **D1** must express at least one of PD-L1 and PD-L2 to be effectively treated with a PD-1 blocker. On this basis, the OD appear to take the view that a patient selection step based on tumour expression of PD-L1 or PD-L2 is implicitly disclosed.
335. We disagree with the OD that any such selection step is implicit.
336. According to the Boards,

*an alleged disclosure can only be considered "implicit" if it is immediately apparent to the skilled person that nothing other than the alleged implicit feature forms part of the subject-matter disclosed.*

...

*In this context "implicit disclosure" means disclosure which any person skilled in the art would objectively consider as necessarily implied in the explicit content, e.g. in view of general scientific laws.*

CLBA 10<sup>th</sup> Edition, I-C-4.3; page 124 (emphasis added)

337. In other words, demonstrating that a disclosure is implicit is a high bar to meet. In the present case it would mean that it must be immediately apparent to the skilled person that a patient selection step based on PD-L1 or PD-L2 must take place, as it would be technically impossible to perform therapy with an anti-PD-1 antibody without performing a selection step. But this quite plainly is not the case.
338. Importantly, there is a difference between an implicit disclosure, and a feature which is not disclosed in a document but which might be considered obvious to add to its disclosure:

*In T 572/88 and T 763/89 the boards warned against using the concept of "implicit prior description" in such a way that considerations relevant to the evaluation of inventive step were transferred to the assessment of novelty. A fair assessment of an invention's patentability called for a clear distinction between novelty and inventive step. In decision T 763/89, for example, the opponent could not claim "implicit prior description" for a material with exactly three layers, as claimed in the disputed patent, on the grounds that a skilled person, aware of the considerable outlay required for further sub-layers and the limited improvement in the quality of the image they bring, would have understood the wording of the claim, which set no upper limit for the number of layers, to be virtually synonymous with "two or three layers". To do so would be to adduce a typical criterion for the evaluation of inventive step.*

*Likewise in T 71/93 the board held that an "implicit prior description" of a feature could not be based on the grounds that a person skilled in the art would have been aware of some disadvantages and of the lack of other forms of improvement related to a feature, since this was a criterion for the evaluation of inventive step.*

CLBA 10<sup>th</sup> Edition, I-C-4.3; pages 126-127

339. In the present case, the OD has provided no justification for their conclusion that a patient selection step based on PD-L1 or PD-L2 expression is implicitly disclosed in **D1**. We

submit that it is based on both an incorrect application of the law on novelty, and an incorrect understanding of the technical field.

340. Fundamentally, just because **D1** teaches that PD-1 binds to PD-L1 and PD-L2 (paragraph [0094]), this does not directly and unambiguously teach the skilled person that cancer patients treated according to **D1** must be selected for expression of one of these proteins by their cancer.
341. Firstly, it would quite plainly be possible to administer an anti-PD-1 antibody such as nivolumab to a cancer patient without first testing their cancer for PD-L1 or PD-L2 expression. It appears to be the view of the OD that doing so would be foolish, and so the skilled person would include a patient selection step in the implementation of **D1**, as (according to the OD) it would be so obvious to do so. But as noted above, whether the addition of an undisclosed feature is obvious is a matter of inventive step, not novelty. The OD may take the view that the skilled person wouldn't administer an anti-PD-1 antibody without first performing a patient selection step, but that is hardly the same as suggesting that doing so would contravene a law of nature.
342. Secondly, the skilled person would also not consider that a patient selection step must have been intended in **D1**. This is at least because nivolumab treatment regimens lacking any patient selection step were part of the general knowledge of the skilled person at the filing date. This is evidenced by, e.g., **D6**. For example, **D6**, section 4.1.2 (bridging pages 4-5 of the document) discloses nivolumab treatment of melanoma patients irrespective of PD-L1 expression status, and teaches that nivolumab treatment was more effective than chemotherapy against PD-L1-positive and PD-L1-negative cancers. PD-L2 expression status was not even considered.
343. Even more relevantly, section 4.2 of **D6** (bridging pages 5-6 of the document) discloses nivolumab combination regimens with ipilimumab comprising treatment of melanoma patients irrespective of PD-L1 expression status. Combination therapy of nivolumab with ipilimumab was particularly effective in patients with PD-L1-negative cancers, with such patients displaying median PFS of 11.2 months, versus just 5.3 months for patients treated with nivolumab monotherapy (**D1** page 6, right-hand column, top paragraph). **D1** is explicitly focussed on nivolumab combination therapies, including with ipilimumab (see e.g. claim 12). It formed part of the skilled person's general knowledge that for nivolumab combination therapies in particular, as disclosed in **D1**, no patient selection step was necessary, and so there is no reason that the skilled person would consider such a step to be implicit in the disclosure of **D1**.
344. In summary, **D1** does not disclose nivolumab treatment of cancer patients selected for PD-L1 expression by their cancers. Accordingly, **D1** does not disclose part (i) of claim 1, which is therefore novel over **D1**.

345. But even if the Board disagrees on the question of an implied PD-1 ligand expression selection step in **D1**, to obtain the claimed subject matter would require selections from multiple lists in **D1** (specifically of the cancer to be treated and the nivolumab dosage regimen), as correctly noted by the OD.
346. As correctly identified by the OD, multiple nivolumab dosage regimens are disclosed in **D1**: but not only 360 mg q3w and 480 mg q4w (as referred to by the OD at point 18.1) but also 240 mg q2w (paragraph [0169]) and a whole host of other dosages, including both flat and weight-based dosages, as listed in paragraphs [0210-0211]. Further weight-based dosages are also disclosed in claims 99-101. There is no pointer to the 480 mg q4w regimen claimed.
347. Treatment of melanoma is also selected from a lengthy list of possible diseases (see e.g. paragraph [0040]), which are not even limited to cancers, and contains no pointer to melanoma. Thus as correctly identified by the OD, treatment of melanoma is another selection from a list.
348. We agree with the OD (point 18.1.1(e) of the Decision) that O3's arguments regarding the selection of melanoma are highly misleading (the OD's reference to O1 is mistaken).
349. Finally, as noted by the OD, even if a patient selection step based on PD-1 ligand expression is considered implicit, **D1** discloses that both PD-L1 and PD-L2 interact with PD-1 to down-regulate T cell activity (**D1**, paragraph [0106]). And so as correctly noted by the OD, a further selection would be required, of a patient selection step based on PD-L1 expression or PD-L2 expression.
350. In summary, even if a patient selection step based on PD-1 ligand expression is considered implicit in **D1**, this still leaves three selections from lists required to obtain the claimed subject matter from **D1**. As such, the claimed subject matter is novel over **D1**.
351. As an aside, we note that the OD have included at point 18.1.1(a) their comments from the preliminary opinion as to whether **D1** discloses a nivolumab monotherapy. These comments are moot in view of the interpretation of "*monotherapy*" set out above, and were presumably included by the OD by mistake.

#### Novelty over D1 – AR2

352. As set out above, AR2 specifies that the claimed nivolumab monotherapy comprises administering the patient nivolumab without another anti-cancer agent.
353. AR2 is novel over **D1** for the same reasons as the Main Request and AR1. AR2 is further novel over **D1** because **D1** does not disclose cancer treatment using nivolumab without another anti-cancer agent.

354. As set out above, **D1** discloses compositions comprising nivolumab and a second antibody, including for treatment of melanoma. All the suggested second antibodies are cancer therapeutics (see paragraphs [0009-0014] of **D1**). There is no disclosure of any second antibody which is for treatment of a disease other than cancer, and thus there is no disclosure of administering a patient nivolumab without another anti-cancer agent.

Novelty over D1 – AR3 to AR5

355. AR3 to AR5 refer specifically to a composition comprising nivolumab and no other antibody.
356. AR3 to AR5 are novel over **D1** for the same reasons as the Main Request and AR1. Additionally, AR5 is novel over **D1** for the same reasons as AR2.
357. AR3 to AR5 are further novel over **D1** because they relate to the medical use of a composition comprising nivolumab and no other antibody. That is to say, the compositions for use according to present AR3 to AR5 contain only a single antibody, nivolumab. Compositions comprising multiple (i.e. two or more) antibodies are excluded from the claims.
358. **D1** does not disclose any compositions comprising only nivolumab. All the compositions of **D1** comprise at least two antibodies. Accordingly, AR3 to AR5 are novel over **D1** for this reason.

Novelty over D25a

359. O3 alleged a lack of novelty over **D25a**. O3 alleged that **D25a** disclosed a clinical trial in which nivolumab at 480 mg q4w was used for treatment of melanoma (O3, NoO, points 21-30).
360. However, the OD has correctly identified that **D25a** is not prior art to the present patent. While clinical trial NCT01721772, to which **D25a** relates, commenced prior to the filing date of the present patent, **D25a** as submitted by O3 relates to the trial protocol in place at the time O3 filed their opposition, which was published on 4 August 2021 (see “*Last Update Posted*” date at top of first page).
361. As can be seen from **D25d**, the final update to the protocol for clinical trial NCT01721772 prior to the filing of the present patent was made on 27 January 2016. As is evident from **D25d**, this update did not mention the 480 mg q4w nivolumab regimen. Thus the objection under Art. 54 EPC based on **D25a** is incorrect. All claim requests are novel over the **D25** clinical trial protocol.

## Inventive Step

362. In their *obiter dicta*, the OD considered the closest prior art to be **D14**, and the cluster of related documents which specifically disclose the efficacy of nivolumab monotherapy at 3 mg/kg q2w in treating PD-L1+ melanoma (Decision, point 19). As noted by the OD, we consider this cluster of documents to consist of **D14**, **D6** and **D69-D73**. The OD considers that **D5** could also be included in this cluster (Decision, point 19.1). We disagree, but the point seems inconsequential.
363. The OD were of the opinion that the patent lacks inventive step over these documents (Decision, point 19.4.6). We strongly disagree, for the reasons set out below.
364. The objection based on **D12**, cited by O5 as closest prior art, was left open by the OD. We submit that **D12** is not suitable to be considered the closest prior art, as set out below, and agree with the OD's reasoning for treating this document with caution (Decision, point 19.2). We agree with the OD that all other documents cited by the opponents are less suitable to be considered closest prior art (Decision, point 19.3). These are each considered briefly below. As noted by the OD, O4 and O5 collectively also explicitly maintained objections based on **D2**, **D11**, **D40**, **D43**, **D44**, **D55** and **D60** as closest prior art (Decision, point 19.3.11). We set out below why the opponents are wrong to suggest that these documents could be considered the closest prior art.

## Common General Knowledge

365. It is the established case law of the Boards of Appeal that prior art disclosures should be considered in light of the skilled person's common general knowledge (CLBA 10<sup>th</sup> Edition, I-D-8.3; pages 231-233). According to this section of the case law:
- [The skilled person's] knowledge formed, as it were, the technical background for any activities they performed and fed into all their decisions.*
366. Before assessing the specific objections to the claims raised by the OD and the opponents, we should therefore consider what the common general knowledge was in the art at the filing date of the patent. Because some of the opponents' objections entirely disregard this.
367. The opponents have cited several academic review articles, which according to the EPO Guidelines constitute common general knowledge (Guidelines G-VII-3.1).
368. Amongst these articles are **D3**, **D6** and **D40**. Their general disclosures, if not every single detail within them, can be considered common general knowledge at the filing date of the patent.

369. **D40** teaches that multiple phase 1 dose-finding studies of nivolumab had been completed. Doses ranging from 0.1 to 10 mg/kg q2w had been found to be tolerable and to show anti-tumour activity (**D40**, section bridging pages 40-41). This has been confirmed by the opponents (see e.g. O5, NoO, points 97-99).
370. However, it also formed common general knowledge that not all the tested dosages were equally promising. Rather, the 3 mg/kg q2w regimen had demonstrated the best results of all those tested at phase 1. This is explained in **D3**:

*Based on the improved efficacy of the 3 mg/kg dose and the lack of a definitive relationship between nivolumab dose and toxicity, the 3 mg/kg dose has been selected for further investigation in late stage trials.*

D3, p. 3113, right-hand column, base of main paragraph

371. In more detail, the main paragraph of **D3**, p3113, right-hand column, teaches that the 3 mg/kg q2w regimen showed the highest overall response rate and longest progression free survival, duration of response and overall survival of the tested dosage regimens.
372. And indeed, by the current filing date, it was common general knowledge that the 3 mg/kg q2w nivolumab regimen had been approved in the USA, EU and Japan for treatment of unresectable or metastatic melanoma (**D6**, page 9, right-hand column, section entitled “6 Dosage and Administration of Nivolumab”).
373. Importantly, this means that the skilled person knew that the selection, trialling and ultimate approval of the 3 mg/kg q2w nivolumab regimen was not arbitrary. It had been selected for development by the current proprietor because it had shown the greatest therapeutic effect in phase 1 trials. Since the approved dose was not randomly selected, the skilled person also would not have randomly deviated from it.

#### Closest Prior Art

374. Having set the scene, in terms of what the skilled person knew at the filing date, we need to establish the closest prior art.
375. As noted by the OD, the opponents collectively cited 24 different documents as alleged closest prior art (see Decision, point 19). O5 alone cited 15 separate documents as alleged closest prior art (see O5, NoO, point 36).
376. The Boards of Appeal have consistently defined the closest prior art as the single reference which constitutes the most promising starting point for a development leading to the claimed invention (CLBA, 10<sup>th</sup> Edition, I-D-3.4.1; page 195).

377. While the Boards have recognised that there may in some cases be more than one equally valid starting point for the assessment of inventive step, multiple documents may only be cited as closest prior art if each is an equally valid springboard to the invention. It has been emphasised that in opposition proceedings:

*la structure de l'approche problème-solution ne consiste pas en un forum où le requérant peut à volonté développer diverses attaques en partant de divers documents de l'état de la technique dans l'espoir qu'une d'entre elles aurait une chance de réussir*

T 320/15, Reasons 1.1.2

In English

*the structure of the problem-solution approach is not that of a forum where the opponent can freely develop as many inventive step attacks as desired in the hope that one of said attacks has the chance of succeeding*

See also CLBA, 10<sup>th</sup> Edition, I-D-2; page 189.

378. It cannot reasonably be argued that 24 different documents each constitute an equally promising starting point for the development of the invention. In particular, it is plainly improper for O5 to individually cite 15 different documents as closest prior art. This is not a serious attempt to deploy the problem-solution approach to the claims at hand, but rather a scattergun approach in which O5 has simply thrown as many arguably relevant documents as they could find at the claims, in the hope that something sticks.

379. The Boards of Appeal have consistently held that:

*the closest prior art for assessing inventive step is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common*

CLBA, 10<sup>th</sup> Edition, I-D-3.1; page 190

380. The present invention relates to the treatment of PD-L1+ melanoma with a nivolumab monotherapy. The closest prior art can therefore be considered a document which also relates to the treatment of PD-L1+ melanoma.
381. Documents which relate to the treatment of cancers other than melanoma, such as lung cancer, are not directed to the same purpose. Therefore we would submit that such documents are not suitable to be considered the closest prior art.
382. Moreover, documents which relate to the treatment of PD-L1+ melanoma specifically constitute better starting points for assessing inventive step than documents which

consider treatment of melanoma generally. This is because the data in the patent shows that melanoma is not a single, homogenous disease. At least in the context of treatment with immune checkpoint inhibitors, the treatment regimen required to attain the best possible outcome differs (e.g. between monotherapy or combination therapy) depending on whether the cancer is PD-L1+ or PD-L1-. As explained at points 90-93 above, paragraph [0055] of the patent explains that it is based on the finding that nivolumab/ipilimumab combination therapy is more effective than nivolumab monotherapy for treating PD-L1- melanoma, whereas nivolumab monotherapy is equally as effective as combination therapy for treating PD-L1+ melanoma, and preferred in this population due to reduced adverse events.

383. Thus the closest prior art to the claimed invention should be a document which also relates to treatment of PD-L1+ melanoma.
384. The closest prior art should also be a document which describes a therapy which is known to be effective, and not a document which simply proposes or suggests a particular therapy.
385. The first reason for this is that the skilled person would naturally consider a therapeutic regimen shown to be effective to be a more promising springboard to find another effective regimen, than a therapeutic regimen under investigation which may or may not be effective.
386. The second reason for this is that in the context of medical use claims, attaining the claimed therapeutic effect is regarded as a functional technical feature of the claim (CLBA 10<sup>th</sup> Edition, II-C-7.2.1; pages 418-419). Therefore a therapeutic regimen shown to be effective has an additional feature in common with the claimed invention, compared to a therapeutic regimen which is proposed but not shown to be effective.
387. This means that a prior art document describing the results of a successful phase 3 clinical trial is a more promising springboard to the invention than a prior art document describing a phase 1 clinical trial. This is because a successful phase 3 trial shows a regimen to be effective, whereas even a completed phase 1 trial (let alone the disclosure of a planned or ongoing phase 1 trial) does not.
388. Of the cited documents, the only ones which describe a successful phase 3 clinical trial of a nivolumab regimen for treating PD-L1+ melanoma are **D14** and its related cluster of documents. **D14** describes the successful completion of a phase 3 trial of the 3 mg/kg q2w nivolumab regimen for melanoma treatment, both alone (monotherapy) and in combination with ipilimumab. The document includes a breakdown of results based on tumour PD-L1 expression status. The related cluster of documents (**D6** and **D69-D73**) all refer back to the results initially described in **D14**.

389. We would therefore agree with the OD that **D14** and the related cluster of documents form the closest prior art. Of these documents, **D14a** is henceforth taken as the representative member.

#### Other Cited Documents

390. We agree with the OD's reasoning for dismissing the relevance of the other documents cited by the opponents as possible closest prior art (Decision, points 19.3.1-19.3.11).
391. As noted by the OD, **D18**, **D32**, **D59b**, **D62** and **D63** all disclose planned or ongoing clinical trials, but do not disclose any results and whether the tested regimens were effective. As such these documents are less promising springboards than **D14**, which discloses a nivolumab regimen shown to be effective in a phase 3 clinical trial. **D12** can also be included in this group, as it also relates to a planned/ongoing clinical trial.
392. Indeed, **D12** and **D62** do not even relate to melanoma treatment, but to treatment of lung cancer. This is yet another reason that these documents are less promising springboards than **D14**.
393. **D33**, **D40**, **D44**, **D55** and **D66** disclose the results of preliminary, phase 1 clinical trials. While the documents may report promising results, they do not confirm the efficacy of any nivolumab regimen in the way that the phase 3 trial of **D14** does. Therefore, none of these documents are such promising starting points for the development of an effective nivolumab regimen as **D14**. Moreover, while O5 has alleged that **D55** discloses a "q4w" dosage regimen, such as that claimed (O5, submissions of 3 January 2024, points 53-54), this is highly misleading. Claim 1 of the Main Request specifies that the patient is administered nivolumab "*once every 4 weeks*". **D55** discloses a regimen comprising a 16-week cycle in which the patient is administered nivolumab with alternating 4 and 12 week gaps between doses (**D55**, page 3168, right-hand column, "*Study Design and Procedures*"). This is entirely different to the "*once every 4 weeks*" regimen claimed, and does not provide a good springboard to reach it.
394. As noted above, **D12** and **D62** do not relate to melanoma treatment at all. The same applies to **D11**. As such they are not such promising springboards as **D14**, which provides an effective nivolumab regimen for treating melanoma.
395. **D2**, **D9**, **D43**, **D44** and **D54a** all relate to melanoma treatment with nivolumab, but not to treatment of PD-L1+ melanoma specifically. **D2** does not mention PD-L1+ melanoma at all; **D9**, **D43** and **D54a** both teach against the use of PD-L1 expression as a biomarker in relation to nivolumab therapy (see **D9**, first paragraph of page 23; **D43**, page 6, left-hand column, paragraph 2; and **D54a**, page 36, bottom paragraph); **D44** teaches that nivolumab was more effective than chemotherapy in both PD-L1+ and PD-L1- melanoma

patients (page 5, right-hand column, paragraph 1) and so provides no indication that distinctive regimens would be required for treating each sub-type.

396. Additionally, as noted by the OD at point 19.3.7 of the Decision, **D44** fails to describe suitable nivolumab dosages for melanoma treatment. It refers to dosages “up to 10 mg/kg” q2w (page 5, left-hand column, paragraph 2), but does not disclose what any of the lower doses were. The 3 mg/kg q2w regimen is not mentioned at all, despite being the only regimen shown to be effective in phase 3 trials.
397. Overall, it is clear that the most promising starting point to reach the claimed invention is the **D14** document cluster, which discloses the 3 mg/kg q2w nivolumab monotherapy for PD-L1+ melanoma, as concluded by the OD (Decision, point 19.1). Therefore, it is appropriate to assess inventive step of the claimed invention using the problem-solution approach, starting from **D14**.

#### Technical Difference between D14 and the Claimed Invention

398. The technical difference between **D14** and the present invention is the nivolumab dosage regimen used: 3 mg/kg q2w in **D14**, 480 mg q4w in the patent. This was correctly noted by the OD at point 19.4.2 of the Decision.

#### Technical Effect of the Claimed Invention

399. As discussed under sufficiency, the efficacy of the claimed regimen is plausible from the application as filed (see points 291-308 above). This is also confirmed by the post-filing data in **D27**, **D75** and **D77**. For example, **D27** states that:

*The time-averaged steady-state exposure and safety profile of nivolumab 480 mg Q4W are consistent with that of 3 mg/kg Q2W across multiple tumor types.*

D27, Abstract, Conclusions

400. **D75** states that a “correlation” was found between the claimed nivolumab 480 mg q4w regimen and improved overall survival, compared to other nivolumab regimens including the 3 mg/kg q2w regimens.
401. Even if the data in **D75** is not considered by the opponents to be sufficiently robust to conclusively demonstrate that the 480 mg q4w regimen yields superior outcomes to the 3 mg/kg q2w regimen of **D14**, we would submit that it is surely enough to demonstrate that the 480 mg q4w regimen is non-inferior to the 3 mg/kg q2w regimen.
402. **D77** provides an analysis of outcomes of melanoma patients treated with nivolumab at either 3 mg/kg q2w, 240 mg q2w or 480 mg q4w (see page 2, right-hand column, first

paragraph). No difference in outcomes based on the different dosage regimens was identified (see page 6, left-hand column, first paragraph).

- 403. Thus the present invention provides an effective, non-inferior nivolumab regimen for treating PD-L1+ melanoma. This is essentially in agreement with the OD's consideration of the effect of the invention at point 19.4.3 of the Decision.
- 404. The flat nature of the claimed nivolumab regimen also results in a lower risk of errors and ease of manufacture compared to the body-weight dependent dose of **D14**, and reduced inconvenience to the patient in view of the reduced dosing frequency (every 4 weeks instead of every 2 weeks).

#### Objective Technical Problem Solved by Invention

- 405. The OD considered the technical problem to be the provision of a dosage regimen which is more convenient and less prone to error (Decision, point 19.4.4).
- 406. We do not entirely agree with the OD's formulation of the technical problem. As noted in our submissions of 4 January 2024 (point 60), and by the opponents (see e.g. O3, submissions of 2 January 2024, point 59; and O5, submissions of 3 January 2024, point 24), the increased convenience and less error prone nature of the claimed regimen compared to the 3 mg/kg q2w regimen are not unexpected. Rather, these are inherent features of converting a body weight-dependent dose to a flat dose, and reducing the frequency of dosing.
- 407. Indeed, as implied by O5 (submissions of 3 January 2024, point 24), if these features are included in the objective technical problem, this would point towards the claimed invention. Setting the skilled person, starting from a body weight-dependent dose, the problem of providing a new dosage regimen less prone to error would point the skilled person towards a flat dose. And setting the skilled person the problem of providing a new dosage regimen which causes less inconvenience to the patient would point the skilled person to reducing the dosing frequency. But according to the established case law of the Boards of Appeal:

*the technical problem addressed by an invention has to be formulated in such a way that it does not contain pointers to the solution or partially anticipate the solution, since including part of a solution offered by an invention in the statement of the problem necessarily results in an ex post facto view being taken of inventive step when the state of the art was assessed in terms of that problem*

CLBA 10<sup>th</sup> Edition, I-D-4.2.1; page 204

- 408. Therefore we would submit that the OD's formulation of the objective technical is not correct.

409. So we suggest a different objective technical problem. The objective technical problem should be objective, in the sense that it does not contain a pointer to the solution (unlike the problem as posed by the OD). It should be realistic, in the sense that it is a problem that the skilled person, having no knowledge of the invention, would have recognised as existing when reading the closest prior art. And it should be solved by the claimed invention.
410. On this basis, we submit that the objective technical problem should be the provision of an alternative, non-inferior nivolumab regimen for treating PD-L1+ melanoma.
411. The inclusion of the term “*non-inferior*” is important. O1 argued in their Notice of Opposition that the present claims do not require any minimum level of efficacy for the claimed regimen, and that the relevant question for assessing inventive step was whether the skilled person would have expected the claimed regimen to have any effect at all on PD-L1+ melanoma, even if less than the prior art regimen (O1, NoO, points 74-76). We submit that this cannot be the correct approach. Rather, the objective technical problem must be the provision of a non-inferior dosage regimen.
412. The reason for this is that the skilled person, starting from the closest prior art, would have recognised the provision of alternative, non-inferior dosage regimens as a real problem to solve. At minimum, the provision of alternative, non-inferior regimens would be advantageous, as it would provide additional treatment options and flexibility to clinicians, to the benefit of their patients.
413. On the other hand, the skilled person would have seen no purpose in providing an alternative dosage regimen that was less effective than those known in the art. Such alternative regimens would have no practical, clinical use. And so providing such a regimen would have been seen as pointless by the skilled person. Posing the objective technical problem in a way whereby the provision of inferior dosage regimens is encompassed is therefore wholly artificial, in that it is not a problem the skilled person would, in reality, ever have tried to solve. According to established case law, the formulation of artificial technical problems is to be avoided (CLBA 10<sup>th</sup> Edition, I-D-4.1.1).
414. The provision of an alternative, non-inferior nivolumab regimen for treating PD-L1+ melanoma is thus a realistic technical problem. It is objective, in that it provides no pointer to the claimed solution. And it is solved, in that the claimed solution is non-inferior to the prior art 3 mg/kg q2w regimen.
415. Thus, as set out above, the objective technical problem is the provision of an alternative, non-inferior nivolumab regimen for treating PD-L1+ melanoma.

### Non-Obviousness

416. We submit that the claimed nivolumab dosage regimen would not have been obvious to the skilled person at the filing date, starting from the closest prior art.
417. The OD took the view that the skilled person, starting from **D14** and faced with the objective technical problem, would have turned to the 480 mg q4w regimen disclosed in **D12** in the context of a clinical trial for treatment of non-small cell lung cancer (NSCLC). The OD is of the view that the skilled person would have adopted this regimen because it is more convenient and less prone to error than the 3 mg/kg q2w regimen. The OD is also of the view that the skilled person would have had a reasonable expectation that the **D12** regimen would have been effective (Decision, point 19.4.6).
418. However, we submit that the OD, in reaching this conclusion, has got ahead of itself.

### *Could-Would Approach*

419. As the OD itself noted in its Preliminary Opinion (page 13, point 13.4), in assessing inventive step the Boards apply the “*could-would approach*”. As set out in the CLBA:

*This means asking not whether the skilled person **could** have carried out the invention, but whether he **would have done** so in the expectation of solving the underlying technical problem or in the expectation of some improvement or advantage*

CLBA 10<sup>th</sup> Edition, I-D-5; page 217 (emphasis original)

420. The opponents have argued that the could-would approach should not apply in the present case, on the grounds that the claimed regimen is an arbitrary choice (see e.g. O5, submissions of 3 January 2024, points 37-38). It is not clear whether the OD agreed with these arguments. Regardless, we submit that they are mistaken.
421. According to the case law cited by O5, an arbitrary choice is one made from a group of “*equally obvious alternatives*” (CLBA 10<sup>th</sup> Edition, I-D-9.21.9(a); page 290). And indeed, according to the cited section of the CLBA, the case law holds that in this case, the “could-would” approach does not apply. Or arguably, in this case the skilled person simply needs no incentive to make any particular choice. Rather, they would be motivated to select any of the choices possible.
422. But the important point here is that a choice is only considered arbitrary if it is one of several “*equally obvious alternatives*”. That is to say, this approach only applies if the claimed solution to a problem is one of multiple equally obvious ways in which the closest prior art could have been changed to address the technical problem.

423. In the present case, this means that the claimed regimen would be an arbitrary solution if it was one of many equally obvious alternative regimens to the 3 mg/kg q2w regimen of **D14**.
424. It is therefore apparent that if the various alternative regimens that the skilled person could have selected are not all equally promising ways of solving the objective technical problem, the claimed regimen is not an arbitrary selection. This is particularly true if some alternatives are more promising than the regimen claimed.
425. In the present case, not all possible alternatives to the prior art 3 mg/kg q2w regimen would have been considered equally suitable by the skilled person.
426. According to O5, any nivolumab dosage ranging from 0.1-10 mg/kg q2w could be expected to be safe and to maintain efficacy for at least 57 days (O5, submissions of 3 January 2024, point 26). O5 basically argues that the overall efficacy of nivolumab for melanoma would be expected to be essentially the same across this whole dosage range, and that the selection of any dosage within it is arbitrary.
427. We submit that this is not, in practice, realistic. The cited range extends across two orders of magnitude. If, in reality, a dose of 0.1 mg/kg q2w was sufficient for efficacy in treating melanoma, how could a dose 100 times as high be justified? This alone would suggest that not all dosages across this range would have been considered equally obvious to the skilled person.
428. Most importantly, as set out above (see points 370-371), it formed part of the skilled person's common general knowledge that the 3 mg/kg q2w regimen had not been an arbitrary selection from this range. Rather, it was selected because it showed the most promise of the doses tested during phase 1 trials. Knowing that the closest prior art 3 mg/kg q2w regimen had been specifically selected for this reason, the skilled person would not consider any alternative dose in the range 0.1-10 mg/kg q2w an "*equally suitable*" alternative. Particularly not when the objective technical problem is to provide a "non-inferior" dosage regimen.
429. The apparent superiority of the 3 mg/kg q2w regimen to the others in the tested range would have provided a pointer to the skilled person to work in this vicinity of dose, rather than arbitrarily selecting any other dose within or similar to the 0.1-10 mg/kg q2w dose range tested.
430. Moreover, while O5 has argued that the selection of any dose in the range 0.1-10 mg/kg q2w would constitute an arbitrary selection, in view of the testing of these doses in phase 1 trials, the claimed dosage does not fall directly in this range. Not only is the claimed dosage administered every 4 weeks (instead of every 2 weeks), but it is a flat dosage as

opposed to a body-weight dependent dose. No flat dose of nivolumab had been successfully tested at the filing date of the application, and so the claimed dosage regimen is distinctly different to all prior art dosage regimens. It cannot therefore be considered one of several equally obvious alternatives.

431. Since the claimed nivolumab regimen is not an arbitrary selection, the could-would approach does apply to assessment of its inventive step.

*Inventiveness over D14 in Combination with D12*

432. In line with the general principle of the could-would approach, the Boards have previously held that:

*the disclosure of two prior documents ... could only be combined so as to result in a finding of lack of inventive step if such combination would have been obvious to a skilled person seeking to solve the problem underlying the claimed invention*

CLBA 10<sup>th</sup> Edition, I-D-9.8; page 274

433. In other words, an invention is not obvious just because it could have been reached by a combination of two particular documents. Rather, the combination of documents must be one that the skilled person would have made.
434. The OD has set out in their *obiter dicta* why they consider the combination of D14 with D12 to render the claimed invention obvious. But they have not set out any reasoning as to why the skilled person would have made this combination of documents in the first place. We submit that they would not have done so.
435. In the present case, the invention relates to the treatment of PD-L1+ melanoma with nivolumab, as does the closest prior art. There are several other documents on file which also relate to melanoma treatment with nivolumab. For example, **D2**, **D59** and **D63**.
436. We would submit that faced with the objective technical problem, the skilled person would have turned to a document such as one of these, which actually relates to treating melanoma. When there is an abundance of documents available to the skilled person providing teaching relating to the treatment of the disease of interest, why would the skilled person have turned to a document relating to the treatment of a different disease? We submit that they would not have done so. They would not have turned to a document such as **D12**, which relates to treatment of a different cancer.
437. We submit that it is pure hindsight to suggest that the skilled person, faced with a technical problem of providing a treatment for melanoma, would have disregarded the extensive art relating directly to this problem, and instead turned to a document relating to lung cancer treatment.

438. In particular, the skilled person faced with the objective technical problem would have selected a nivolumab dosage regimen which had, or was expected to have, an acceptable benefit:risk ratio in melanoma patients. The study disclosed in **D12** would have provided information on the benefit:risk ratio in NSCLC, but the skilled person would not have been able to determine merely from the publication of the study protocol whether the claimed regimen would have been expected to have an acceptable benefit:risk ratio in melanoma patients. For this, the skilled person would have been motivated to turn to documents concerning melanoma treatment, as set out above.
439. The purpose of the problem-solution approach is to assess what the skilled person, faced with the technical problem solved by the invention, would have done, and therefore whether the claimed solution is obvious. The approach is designed to avoid inadmissible ex post facto analysis which draws on knowledge of the invention (CLBA 10<sup>th</sup> Edition, I-D-6; page 219).
440. By contrast, the OD appear to have taken the approach of beginning at the invention and finding a way there from the prior art. Rather than considering reasonably what the skilled person, faced with the objective technical problem, would have done, and what documents they would have turned to, the OD has immediately alighted on the one prior art document which discloses the nivolumab regimen specified in the claims, and decided to combine it with the closest prior art, without any justification. This approach is not correct.
441. Since the skilled person, starting at **D14** and faced with the objective technical problem, would not have combined **D14** with **D12**, the OD's conclusion on inventive step is incorrect. The present claims are inventive over this "combination" of documents.
442. As noted above, the skilled person beginning at **D14** and faced with the objective technical problem would have turned to another document relating to melanoma treatment. However, none of these documents, such as **D2**, **D59** or **D63**, disclose the claimed 480 mg q4w regimen. And so there is no combination of the cited documents which the skilled person would have made which would have led them to the claimed invention.

*Inventiveness over D14 alone and in Other Combinations*

443. The opponents have argued that the claimed nivolumab regimen is obvious over **D14** alone, or in combination with various other documents which supposedly point to the arbitrariness of the 480 mg q4w nivolumab regimen. For example, O5 has cited **D54a** and **D55** in this respect (O5, submissions of 3 January 2024, point 26).

444. But as set out above, the claimed regimen is not an arbitrary selection. And as set out below, the skilled person, starting at **D14**, would not have alighted on the claimed regimen without specific direction.
445. The skilled person is considered to be naturally conservative in attitude (CLBA 10<sup>th</sup> Edition, I-D-8.1.3; page 227). He/she is disinclined to take risks. They are not imaginative, or creative (CLBA 10<sup>th</sup> Edition, I-D-8.1.1; page 225). In the present matter, the skilled person is looking for a new dosage regimen to provide a non-inferior alternative to one that is already known to be effective. In this context, the skilled person would plainly look to make a “safe” decision.
446. Notably, the Boards have previously indicated that the level of risk that the skilled person would be willing to take is dependent on the potential benefit. As set out in **T 455/91** (as quoted in the CLBA):
- within the normal design procedures, he would readily seek appropriate, manifest changes, modifications or adjustments involving little trouble or work and no or only calculable risks, especially to obtain a handier or more convenient product or simplify a procedure*
- CLBA I-D-8.1.3; page 228
447. In the present case, the skilled person is not seeking a superior dosage regimen. They are not trying to provide a better treatment which might justify taking a risk. They are simply trying to provide a non-inferior alternative to the 3 mg/kg qw2 regimen, and so would be commensurately cautious with how they would change the existing, effective regimen.
448. Since the skilled person knew that the 3 mg/kg q2w regimen was the most effective from the range of doses tested in phase 1, they would have been concerned that the further removed a potential regimen was from that prior art dose, the greater the risk it would be less effective. The skilled person would therefore have been motivated to make minimal adjustment to the existing dosage regimen.
449. From this starting point, the skilled person might have considered switching the dosage regimen to a flat regimen, rather than a weight-based one. As noted by the opponents, **D15** and **D16** show that body mass-based dosing and flat dosing are both options that can be considered for therapeutic antibodies, with the most suitable dosing type depending on the antibody. Neither document considers nivolumab specifically though, and there is no evidence on file that nivolumab had been shown to be suitable for flat dosing at the filing date, so this is debatable.
450. As the opponents have repeatedly noted, based on a person of an average weight of about 80 kg, conversion of the 3 mg/kg q2w regimen to a flat dosage would yield a

regimen of 240 mg q2w. To reach the claimed regimen from that still requires doubling the dosage and the dosing interval. However, there is no evidence that simply multiplying dosages and administration intervals can invariably be expected to successfully provide alternative, simpler dosage regimens. Doing so would not have been obvious to the skilled person.

451. And even if the skilled person had decided to try reducing the dosing frequency by multiplying the dosage and administration intervals, the opponents have not shown any reason why the skilled person would have decided to simply double them, rather than e.g. tripling or quadrupling them.
452. According to O5's arguments that any dose between 0.1-10 mg/kg would have been expected to maintain efficacy for up to 57 days, this would suggest that the prior art 3 mg/kg q2w regimen could at least be trebled, to 9 mg q6w (i.e. every 42 days) without compromising safety and efficacy. If the skilled person's motivation had been to maximise patient convenience, why would they not have done this? The opponents have provided no reasoning as to why the skilled person would have selected a 4-weekly regimen specifically.
453. Moreover, if the skilled person had decided to try the effect of reducing dosing frequency by multiplying the dosage and administration intervals (so that overall the patient was administered the same amount of nivolumab), we would submit that due to their conservative nature they would have made this change alone, not in combination with another fundamental change to the dosage regimen, such as switching to a flat regimen.
454. In other words, even if the skilled person had decided to trial a flat dosing regimen of nivolumab, or multiplying the dosage and administration intervals, due to their conservative nature the skilled person would not have made both changes at the same time. Making two untested changes to a known dosage regimen at the same time would have increased the unpredictability of the effect of the changes, and therefore the risk of making them. As set out above, the skilled person would have wished to minimise the risk associated with the changes to the 3 mg/kg q2w prior art regimen.
455. Importantly, this does not mean that the skilled person would have expected the claimed regimen not to work. As argued above under sufficiency, the skilled person would have considered it plausible, based on the data in the patent and their common general knowledge, that the claimed regimen would be effective.
456. But according to case law, just because the skilled reader considers a particular therapeutic option that is disclosed in a patent application as not implausible or even as plausible, it is not inherently obvious to select that option if there is a reason that the

skilled person would not have done so, or if seemingly better options present themselves (T 108/09).

457. T 108/09 related to a patent directed to fulvestrant for use as a third line treatment of breast cancer previously treated with tamoxifen and an aromatase inhibitor (T 108/09, Summary, I). There was no data in the application as filed demonstrating the use of the drug as a third line treatment (Reasons, 2.2.2). But fulvestrant was known as a second line treatment for breast cancer, after tamoxifen, and on this basis it was considered plausible that it would work as a third line treatment as well (Reasons, 2.4.5).
458. But for mechanistic reasons, and because the prior art disclosed alternative treatments as more promising third line options, the board considered it was not obvious to select fulvestrant for this purpose (Reasons, 2.4.6).
459. The same applies in the present case. The skilled person would have considered it plausible that changing the known 3 mg/kg q2w regimen to a flat dose, and doubling the amount and administration intervals, thereby yielding the claimed regimen, would have yielded an effective regimen. But even if they had decided to test one or other of these alterations of the D14 regimen, the skilled person would have considered it less risky, and therefore more promising, to make only one of them, rather than both in one go. Only once they had established that one of the changes was tolerated in the context of melanoma treatment, might they have considered combining the two of them.
460. The OD rejected this argument, suggesting that the skilled person would have implemented the 480 mg q4w regimen based on its disclosure in D12. However, as noted above, the skilled person starting from D14 would not have turned to D12, and so this suggestion is incorrect.

#### *The Expert Declarations*

461. Both O3 and O5 submitted expert declarations in support of their arguments that it would have been obvious for the skilled person to change the 3 mg/kg q2w regimen of D14 to the claimed 480 mg q4w regimen, based on the prior art knowledge of nivolumab pharmacokinetics. As set out above, we request that O3's declaration, D76, not be admitted into proceedings, but in case the board decides to admit it, it is addressed below as well as D65, submitted by O5.
462. Considering first D65, this is a declaration by Professor Robert Charles Frederick Leonard. We submit that it is not a particularly helpful document in assessing what the skilled person would have done, starting from the closest prior art and faced with the objective technical problem, at the filing date of the patent.

463. Professor Leonard is very eminent retired academic and clinical oncologist. He was the director of cancer services and chief of medical oncology at Imperial College NHS Trust, one of the largest hospital trusts in the UK (D65a, point 1). He's authored over 300 peer-reviewed papers (D65a, point 2) and has 25 years of experience as an expert witness (D65a, point 3).
464. The Boards of Appeal have defined the person skilled in the art as "*an experienced practitioner who has average knowledge and abilities*" (CLBA 10<sup>th</sup> Edition, I-D-8.1.1; page 224). It is clear that Prof. Leonard was not "average", and he is not representative of the notional skilled person.
465. But as noted by the OD in their Preliminary Opinion, his declaration is missing any consideration of the characteristics of the person skilled in the art, and what that means in terms of their competences or approach (see Preliminary Opinion, point 13.5.2). Rather, he appears to wrongly equate himself with the skilled person. Having set out his credentials he states that:
- consequently [he is] qualified to provide an opinion as to what a person of ordinary skill in the art would have known and concluded as of the [relevant] date*
- D65a, point 4
466. Given his own level of ability, this results in him treating the skilled person as being rather more imaginative and creative than the case law permits.
467. The OD have not considered D65 in the context of inventive step in their *obiter dicta*, but in their Preliminary Opinion they highlighted that according to Prof. Leonard, the claimed dosage regimen is obvious if one takes into account at least pharmacokinetics, pharmacodynamics, exposure-response relationships, the maximum tolerable dose, width of therapeutic window, amplitude variations of fluctuations at steady state (Preliminary Opinion, point 13.5.2). We submit that such a large and complex analysis, taking into account so many variables, would have been beyond the capabilities of a person of average skill in the art.
468. Another important flaw in the Professor's declaration is that it exaggerates the common general knowledge in the art at the filing date. For example, he appears to treat D16 as common general knowledge (see D65a, point 8), but D16 is an original research article (it is headed as such). Such articles generally do not constitute common general knowledge and no reason for treating it as such has been provided. He also refers to the 240 mg q2w nivolumab regimen as "*known*" (see D65a, e.g. point 50), seemingly based on D59a/b (see D65a, point 13). But these documents are clinical trial protocols, which again would not generally be classed as common general knowledge. This means that the 240

mg q2w regimen was not generally known at the filing date, and it was certainly not known to be effective, as the clinical trials testing it were still ongoing.

469. Indeed, in his declaration Prof. Leonard refers to over 10 documents which do not constitute CGK (including **D12b**, **D16**, **D18b**, **D25b**, **D55**, **D56**, **D57**, **D58**, **D59a**, **D59b**, **D62** and **D63**). Even if some of these are redundant, this is an excessive number, particularly given that according to the Guidelines, the need to combine more than two documents to obtain a claimed invention can be an indication of an inventive step (Guidelines G-VII-6).
470. Another fundamental failing in **D65** is that Prof. Leonard approaches his assessment of the claimed invention with hindsight and obvious bias. He states that he was asked to comment on whether the claimed dosing regimen would have been considered by the person skilled in the art at the filing date (**D65a**, point 7).
471. In other words, he was asked to start at the claimed regimen and comment on how the skilled person might have reached it. This is precisely the opposite of the proper problem-solution approach, where one should start at the closest prior art and assess what would have been obvious to the skilled person based upon it.
472. **D76** suffers from the same deficiencies. Its author, Professor Langguth, does not even mention the skilled person at any point. The entire declaration appears to be made from his own personal perspective – he states that his conclusions are made based on his own knowledge and experience (**D76a**, page 3, part III), and makes clear that he is simply providing his own opinions (see e.g. the top of page 5: “*for me the answer is yes*”).
473. But like Prof. Leonard, Prof. Langguth is not a person of average skill in the art. He’s been dean of his university faculty, has over 300 publication with an H-index of 48 and has won numerous awards (see **D76b**). He’s even been named as inventor on 13 issued patents (**D76b**, page 5). By definition, as a successful inventor his creativity and imagination far exceed those of the notional skilled person.
474. Like Prof. Leonard, Prof. Langguth also fails to make any distinction between what was and was not common general knowledge at the filing date. For example, at page 4, section 2 of his declaration he cites 12 documents, of which only 3 (**D3**, **D53** and **D54a**) might generally be considered common general knowledge. Yet he treats all their disclosures identically, as “*known*”. This is not in line with the problem-solution approach, and more generally we submit that if it is necessary to combine 9 primary documents to reach the claimed invention, this is in fact an indication of the presence of an inventive step.

475. In summary, both expert declarations are highly defective and not particularly helpful in assessing what the notional skilled person would have done, at the filing date, starting from the closest prior art and faced with the objective technical problem.

*Not a Result of Routine Dose Finding*

476. The opponents have also argued that the Boards have commonly held the identification of suitable doses of a drug to be a routine task that does not require inventive activity (see e.g. O4, NoO, section VIII.4 beginning on page 18; O3 submissions of 2 January 2024, section III(2)(c)(i), beginning on page 15). However, we submit that the cited case law is not relevant to the present situation.
477. O3 and O4 have both quoted **T 2506/12** and **T 237/15**, which held that the identification of a suitable dosage, or even optimum dosage, for a known pharmaceutical was routine (citing **T 2506/12**, Reasons, 5.4; and **T 237/15**, Reasons, 4.6.1).
478. However, what the opponents overlook is that in the present case, routine dose-finding trials had already been performed. Their results are described in several of the cited documents, e.g. **D55** and **D66**, which disclose testing of nivolumab at dosages of 0.1-10 mg/kg q2w (see **D55**, Abstract, Patients and Methods; and **D66**, Methods). The claimed dosage regimen had not been identified, so it simply cannot be argued that this regimen would have been identified in a routine dose-finding trial: the evidence is unambiguous that it was not identified in this context.
479. Rather, a different optimal dosage regimen had been identified: 3 mg/kg q2w. As set out in **D3**:

*Based on the improved efficacy of the 3 mg/kg dose and the lack of a definitive relationship between nivolumab dose and toxicity, the 3 mg/kg dose has been selected for further investigation in late stage trials.*

D3, p. 3113, right-hand column, base of main paragraph

480. Importantly, this is a fundamental difference compared to the cases cited by the opponents. In these cases, optimal dosage regimens had not been found in the prior art. **T 2506/12** related to a patent for a new combination of known drugs (Reasons, 1.1). A suitable regimen for the combination therapy had to be found. **T 237/15** related to a dose for oral administration of a drug previously known for intravenous administration (Reasons, 4-4.2). A new dosage regimen had to be found for the new administration route.
481. And so in these cases, as the relevant Boards identified, routine dose finding trials had to be performed to identify suitable regimens. The Boards held that in so doing, the regimens claimed in those cases would have been found. Indeed, in **T 2506/12**, this was

exactly how the claimed dosage regimen had been found (Reasons, 5.4), giving credence to the Board's conclusion that identification of the claimed regimen had been routine.

482. While it can therefore reasonably be concluded that where a dosage of a drug or combination therapy needs to be identified for the first time, a suitable dosage will be identified in a routine dose-finding trial, such a conclusion cannot be made here. Routine dose-finding studies had already been completed, a suitable dosage regimen identified, taken through further trials and approved. In this context, the skilled person would have had no reason to undertake routine dose-finding studies for nivolumab, and would not have done so.
483. Therefore it cannot be argued that the claimed dosage regimen would have been found in such routine dose-finding studies.

#### D12 as Alternative Closest Prior Art

484. **D12** discloses the existence of a clinical trial of the claimed 480 mg q4w nivolumab dosage regimen for treating NSCLC. O5 argued at length in their submissions of 3 January 2024 that **D12** is a suitable alternative starting point for assessing inventive step of the present claims, in line with the approach taken by the Board in **T 2443/18** (see section I.2.3 of O5's submissions, starting on page 12).
485. We agree with the OD that the *ratio decidendi* of **T 2443/18** do not apply to the present situation, and their reasoning in this respect (see Decision, point 19.2). We submit that **D12** is not an appropriate starting point for assessment of inventive step.
486. As the Board will be aware, **T 2443/18** related to a patent for tapentadol for the treatment of IBS (**T 2443/18**, Summary, I). Tapentadol is an analgesic known to be effective in treating visceral pain (**T 2443/18**, Reasons, 2.10). Visceral pain was known to be a characteristic symptom of IBS (**T 2443/18**, Reasons 2.19.1).
487. In **T 2443/18** there was a dispute over the appropriate closest prior art document for assessment of inventive step. The proprietor held it was a document relating to the same purpose, i.e. treatment of IBS with different drugs, that was the most promising starting point. The opponent held it was the document disclosing the efficacy of tapentadol in treating visceral pain (**T 2443/18**, Summary, VIII-IX).
488. The Board held that the approach taken to drug discovery, and therefore the most suitable starting point for assessing inventive step, varies depending on the stage of development:

*After the initial stage of drug discovery, the suitability of the drug for different therapeutic uses may conceivably be explored*

489. Since it was established that tapentadol was effective against visceral pain, the Board held that the “*logical next step*” for the skilled person was to determine the medical indications in which the drug was useful. Therefore the Board considered that a prior art document demonstrating the effect of tapentadol against visceral pain was a suitable starting point for assessment of inventive step, rather than a document relating to treatment of IBS (Reasons, 2.15.2).
490. Since tapentadol was effective in treating visceral pain, and visceral pain is a symptom of IBS, the Board found it to have been obvious to use tapentadol to treat IBS (Reasons, 2.19.1).
491. However, as noted by the OD, there are important distinctions between the situation underlying **T 2443/18** and the present case.
492. Firstly, In **T 2443/18**, tapentadol was known to be effective in treating visceral pain. **D12** discloses that the 480 mg q4w nivolumab regimen was under investigation for treating NSCLC, but does not demonstrate that it was effective for this purpose. **T 2443/18** itself notes that the approach the skilled person would take is dependent on the stage of drug discovery. Once a drug (or in this case, dosage regimen) is known to be effective for a particular purpose, it may then be logical to explore how else it can be used. But this reasoning does not apply where there is no evidence that a particular drug/dosage regimen is effective, as in the present case.
493. Secondly, in **T 2443/18** the known efficacy of tapentadol was against a symptom of IBS (visceral pain), so it would have been logical to use tapentadol to relieve this symptom of the condition. In the present case, **D12** discloses the claimed dosage regimen to be under investigation for treating NSCLC, whereas the claims relate to treatment of PD-L1+ melanoma. NSCLC is not a symptom (or “*typical manifestation*”, to use the language of **T 2443/18**, Reasons, 2.10) of melanoma. Rather, as noted by the OD, the two diseases are completely different cancers.
494. Therefore in the present case **D12** is not suitable to be considered the closest prior art. The skilled person would not have started from it, because they would not have considered an investigational dosage regimen for one cancer the most promising starting point for a new effective regimen for a different cancer.

### **Auxiliary Requests 6-11**

495. ARs 6-11 are filed now for the first time. We request their admission into proceedings.

### **Admissibility**

496. ARs 6-11 correspond to the present Main Request and ARs 1-5, respectively, with the additional amendment relative to the claims as granted that the wording “*the test tissue sample comprising tumor cells and/or tumor-infiltrating inflammatory cells*” has been deleted from claim 2.
497. This amendment was present in former ARs 4-7 filed with the proprietor’s submissions of 4 January 2024. Indeed, present ARs 6 and 7 correspond to former ARs 6 and 7 with the term “*single antibody*” removed from claim 1.
498. The amendment to claim 2 was made to address an objection of insufficiency initially raised by O1, that PD-L1 expression on the tumour cannot be measured (as required by claim 1) on a tissue sample containing just tumour-infiltrating inflammatory (TII) cells (see O1, NoO, points 110-113; and our opposition response, points 225-227).
499. ARs 6-11 are filed now in case the Board decides to consider sufficiency of disclosure in the current proceedings, and agrees with O1’s objection to claim 2.
500. As mentioned, ARs 6-11 correspond to the Main Request and ARs 1-5, respectively, with the additional amendment to claim 2.
501. The Main Request was filed for the first time, and admitted, at the first instance oral proceedings. However there was no reason to file present AR6 at the first instance oral proceedings, as sufficiency was not considered during the hearing.
502. As set out above, if the Board find in our favour in respect of compliance with Art. 123(2) EPC, we submit that the case should be remitted to the OD for consideration of issues which were not decided upon at first instance. However, if the OD decides not to remit the case, we submit that admissibility of AR6 should be considered based on the criteria for admission of a late-filed request by a first instance department. This is because the more stringent criteria for admission of new requests on appeal are based on the expectation that an applicant/proprietor will have had the opportunity to file claim requests addressing the relevant issues at first instance. It would be inequitable for the proprietor to be denied, based on the RPBA, the opportunity to file a claim request to overcome an issue which is being considered for the first time in proceedings.
503. The amendment in ARs 6-11 *prima facie* overcomes the objection of insufficiency of disclosure raised against claim 2 by deleting the offending wording relating to TII cells, as

tacitly acknowledged by O5 (submissions of 3 January 2024, point 86). The amendment is straightforward and raises no new issues.

504. ARs 7-11 should further be admitted for the reasons set out above in respect of ARs 1-5, respectively.

#### **Rule 80 EPC**

505. The amendment complies with Rule 80 EPC, as it is made to address an objection raised under Art. 83 EPC, which is a ground for opposition. The other amendments comply with Rule 80 for the same reasons as the corresponding ones in the Main Request and ARs 1-5, respectively.
506. O5 alleged that the amendment to claim 2 offends Rule 80 EPC, because it deletes more than is required to address the objection under Art. 83 EPC (submissions of 3 January 2024, point 86).
507. O5 has not disputed that the amendment made addresses a ground for opposition. Their objection is simply that a different amendment could have been made for this purpose. However, according to the CLBA:

*Rule 80 EPC did not place any restriction on the form of amendments a patent proprietor may (seek to) make to address objections raised ... On the contrary, a patent applicant or proprietor was free to draft proposed amendments to the specification in any manner considered appropriate.*

CLBA, 10<sup>th</sup> Edition, IV-C-5.1.2(a); page 1237 (emphasis added)

508. O5's objection is therefore groundless. The proprietor has the right to make any amendment suitable to address the objection under consideration.

#### **Clarity (Art. 84 EPC) / Extension of Scope (Art. 123(3) EPC)**

509. As noted above, the amendment in ARs 6-11 was included in AR4 and others at first instance. No objection under Art. 84 EPC was made to this amendment, and no objection under Art. 123(3) EPC can be made, as the amendment is to a dependent claim. As noted above, the amendments already present in the Main Request and ARs 1-5 also comply with Art. 123(3) EPC. Thus ARs 6-11 also comply with these requirements.

#### **No Added Matter (Art. 123(2) EPC)**

510. O3 objected that the amendment to claim 2 adds matter, because claim 2 no longer requires the sample to contain tumour cells, whereas the application as filed teaches that

the presence of tumour cells in the sample is necessary for assessing PD-L1 expression (O3, submissions of 26 February 2024, points 56-59).

511. O3 is incorrect. Claim 2 is dependent on claim 1, and claim 1 requires that the patient is identified by measuring PD-L1 expression on the melanoma tumour. Claim 2 specifies that the measuring comprises a test tissue sample from the patient. Reading the claim with a mind willing to understand, the skilled person would consider it unambiguous that the sample is for PD-L1 measurement (i.e. that PD-L1 expression is to be measured on the sample).
512. Since claim 1 specifies that PD-L1 expression is measured on the melanoma tumour, the skilled person would understand that it remains implicit in claim 2 that the sample comprises tumour cells. O3's objection is therefore based on a misreading of the claim, and so is erroneous.
513. All other aspects of ARs 6-11 comply with Art. 123(2) EPC for the same reasons as the Main Request and ARs 1-5, respectively.

#### **Sufficiency (Art. 83 EPC)**

514. In the event that the Board agrees that claim 2 lacks sufficiency of disclosure, insofar as it relates TII cells, these have now been deleted from the claim, addressing the objection.
515. All other aspects of the claims comply with Art. 83 EPC, for the same reasons as set out above for the Main Request and ARs 1-5, respectively.

#### **Patentable Subject Matter, Novelty and Inventive Step**

516. ARs 6-11 comply with Arts. 53, 54 and 56 EPC for the same reason as the Main Request and ARs 1-5, respectively.

### Auxiliary Requests 12-17

517. ARs 12-17 are filed now for the first time. We request their admission into proceedings.

#### **Admissibility**

518. ARs 12-17 correspond to the present Main Request and ARs 1-5, respectively, except that all dependent claims have been deleted.

519. This amendment (deletion of all dependent claims) was present in ARs 8-11 filed by the proprietor in their submissions of 4 January 2024. Indeed, present ARs 12 and 13 correspond to former ARs 10 and 11 with the term “*single antibody*” removed from the preamble.

520. This amendment addresses all objections to the dependent claims, e.g. that claim 2 lacks sufficiency and that its amended version in the earlier ARs lacks basis in the application as filed, and the objection that claim 6 of the previous ARs lacks basis in the application as filed.

521. These ARs are filed now in case the Board find against the proprietor in respect of any objection to the dependent claims, which is not specifically addressed elsewhere.

522. Since AR12 corresponds to the Main Request, which was admitted at first instance, with dependent claims deleted, it is submitted that it is, in effect, not a new request within the meaning of the RPBA 2020, by analogy to the previous finding by multiple Boards of Appeal that deletion of a claim during appeal proceedings does not constitute an amendment to a party’s case:

*The deletion of a claim category, of dependent claims or of alternatives within claims were held not to be amendments to the appeal case within the meaning of Art. 13 RPBA 2020 in the circumstances at issue in T 1480/16, T 2638/16, T 884/18, T 914/18, T 995/18, T 1151/18 and T 1857/19*

CLBA 10<sup>th</sup> Edition, V-A-4.2.2(d); page 1377

523. Therefore it is submitted that AR12 can be admitted without further debate.

524. In the event that AR12 is considered a new request, it is submitted that it should be admitted for the same reasons as AR6, discussed above. In particular, AR12 *prima facie* addresses all objections relating to dependent claims.

525. ARs 13-17 should be admitted for the same reasons as ARs 1-5, respectively, with the additional reason that deletion of the dependent claims simplifies proceedings.

## Rule 80 EPC

526. The amendment addresses the objection under Art. 83 EPC to claim 2, which also directly or indirectly impacts claims 3-6 of the Main Request via their dependency. It also addresses the objection under Art. 123(2) EPC to claim 6 of the Main Request. Thus the amendment to ARs 12-17 complies with Rule 80 EPC. All amendments to claim 1 comply with Rule 80 EPC for the reasons set out in respect of the Main Request and ARs 1-5, respectively.

## Clarity (Art. 84 EPC) / Extension of Scope (Art. 123(3) EPC)

527. As simple deletions of dependent claims the amendments of these requests cannot infringe Art. 84 or 123(3) EPC. All amendments to claim 1 comply with these requirements for the reasons set out in respect of the Main Request and ARs 1-5, respectively.

## All Grounds of Opposition

528. ARs 12-17 comply with the requirements of the EPC for the same reasons as the Main Request and ARs 1-5, respectively.

## Auxiliary Requests 18-29

529. ARs 18-29 are filed now for the first time. We request their admission into proceedings.

## Admissibility

530. ARs 18-23 correspond to the Main Request and ARs 1-5, respectively, with the subject matter of claims 2 and 3 as granted introduced into claim 1. ARs 24-29 correspond to the Main Request and ARs 1-5, respectively, with the subject matter of claim 2 of AR6 and claim 3 as granted introduced into claim 1. Indeed ARs 18, 19, 24 and 25 correspond to ARs 14, 15, 18 and 19, respectively, as filed with our submissions of 4 January 2024, with the term "*single antibody*" removed.
531. ARs 18-23 address the objection under Art. 53(c) EPC that the claims are directed to statutorily non-patentable subject matter, and further address the novelty objection based on D1. ARs 24-29 address these objections, and further address the objection to claim 2 as granted under Art. 83 EPC.
532. These ARs are filed now in case the Board finds against the proprietor on any of the points above.

533. By specifying in claim 1, part (i), that the measuring of PD-L1 expression comprises “*providing a test tissue sample obtained from the patient*”, the claim makes it explicit that the “diagnostic step” is performed on a sample which has already been obtained from the patient. This makes it *prima facie* clear that the claim complies with Art. 53(c) EPC.
534. Additionally, **D1** does not disclose any such measuring of PD-L1 expression. This amendment therefore *prima facie* addresses the objection that claim 1 as granted lacks novelty over **D1**.
535. Thus ARs 18-29 *prima facie* address the objections raised under Art. 53(c) and Art. 54 EPC. ARs 24-29 also *prima facie* address the objection under Art. 83 EPC to claim 2 as granted, as set out above in relation to ARs 6-11.
536. The amendments simply introduce the subject matter of dependent claims into claim 1, and so do not introduce any new issues into proceedings.
537. It is thus submitted that ARs 18 and 24 should be admitted into proceedings for the same reasons as AR6 (the arguments set out at points 501-502 apply to both AR18 and AR24).
538. It is submitted that ARs 19-23 and 25-29 should be admitted into proceedings for the same reasons as ARs 1-5, respectively. ARs 25-29 should also be admitted into proceedings for the same reasons as ARs 7-11.

#### **Rule 80 EPC**

539. The amendments of ARs 18-29 are responsive to objections raised under Art. 53(c) EPC and thus comply with Rule 80 EPC. All amendments also existing in earlier claim requests comply with Art. 80 EPC for the same reasons as the earlier requests.

#### **Clarity (Art. 84 EPC) / Extension of Scope (Art. 123(3) EPC)**

540. As the mere introduction of the subject matter of dependent claims into claim 1, clarity objections are not permitted according to **G 3/14**, and no objection under Art. 123(3) EPC is possible. The other amendments to claim 1 comply with Arts. 84 and 123(3) EPC for the same reasons as set out above in respect of the Main Request and earlier ARs.

#### **Excluded Subject Matter (Art. 53(c) EPC)**

541. O2 objected that claim 1 encompasses excluded subject matter in relation to so-called “diagnostic step” (i) of claim 1. O2 objected that in order to carry out the diagnostic step, the skilled person would have to either take a tumour sample from the body of the patient by surgery, or perform a diagnostic method on the patient (O2, NoO, point 5.3).

542. Claim 1, part (i) of ARs 18-29 refers to “*providing a test tissue sample obtained from the patient*”. It is thus explicit that the “diagnostic step” is performed on a sample which has already been obtained from the patient, i.e. the step of obtaining it is explicitly omitted from the claim. As set out above and by the OD in their *obiter dicta*, according to the Guidelines at G-II-4.2.1.1, omission of a surgical step from a claim is sufficient to comply with the requirements of Art. 53(c) EPC. Moreover, since the step is performed on a sample *ex vivo*, the claim does not relate to a diagnostic method performed on the body.

543. Accordingly, ARs 18-29 comply with the requirements of Art. 53(c) EPC.

#### **Sufficiency (Art. 83 EPC)**

544. ARs 18-23 comply with the requirements of Art. 83 EPC for the same reasons as the Main Request. ARs 24-29 additionally comply with the requirements of Art. 83 EPC for the same reasons as ARs 6-11.

#### **Novelty (Art. 54 EPC)**

545. As set out above, O1 and O3 alleged a lack of novelty over **D1**. **D1** does not disclose the provision of a tissue sample from a patient and measurement of PD-L1 expression on cells in the sample. Accordingly, ARs 18-29 are novel over D1.

#### **Inventive Step (Art. 56 EPC)**

546. ARs 18-29 all comply with Art. 56 EPC for the same reasons as the Main Request.

### Admission of Documents D78 and D79

547. We request that documents **D78** and **D79**, filed herewith, be admitted into the proceedings.
548. Document **D78** is the declaration of Dr Ian Waxman, a clinical oncologist with expertise in the use of checkpoint inhibitors. Dr Waxman's declaration relates to the proper interpretation of claim 1. The declaration explains, from the perspective of a clinician with expertise in the field of the patent, why a skilled person working in the field would not have followed, or even thought of, the interpretation of claim 1 adopted by the OD.
549. As explained above, the OD's interpretation of claim 1 has led directly to one of their findings of added matter, and this claim interpretation was not suggested by the OD, or any party to proceedings prior to, or even at, the oral proceedings before the OD. Rather, the OD's claim interpretation was only set out for the first time in their written decision.
550. As such, **D78** is filed in direct response to the OD's written decision, and could not have been filed beforehand. It is therefore submitted that **D78** is not late filed, in line with the established case law of the Boards of Appeal:

*According to the established case law of the boards of appeal on Art. 114(2) EPC, filing new facts, documents and evidence would be considered to be in due time, if the filing was occasioned by an argument or a point raised by another party or in the appealed decision and could not have been filed before under the circumstances of the case.*

CLBA, 10<sup>th</sup> Edition, V-A-5.13.1(a); page 1491 (emphasis added)

551. Although the above-cited case law is derived from proceedings held under the previous iteration of the RPBA, it is submitted that the changes made under the RPBA 2020 do not impact on a party's fundamental right to file new facts and evidence in response to points made for the very first time in the written decision under appeal.
552. Indeed, as a document filed in direct response to a point raised by the OD for the very first time in their written decision, **D78** could not have been submitted earlier in proceedings (or at least there would have been no reason to submit it earlier in proceedings). Therefore there is no reason under Art. 12(6) RPBA 2020 for the Board not to admit **D78** into proceedings.
553. Moreover, the point **D78** addresses is of fundamental importance to these proceedings. The OD's interpretation of claim 1 directly resulted in their finding that its scope is broader than the disclosure of the application as filed, contrary to Art. 123(2) EPC. **D78** provides an insight into the mindset of the skilled person, and explains why the skilled person would not have understood the claims in the same way as the OD.

554. Therefore, we submit that **D78** should be admitted into proceedings.
555. Document **D79** is a press release issued by the proprietor on 1 October 2015. As such it is prior art to the opposed patent. **D79** publicises the approval by the FDA of a nivolumab/ipilimumab combination therapy for metastatic melanoma. As noted in the first line of **D79**, this combination was the first combination of two immune-oncology agents to be approved by the FDA. **D79** is discussed by Dr Waxman in his declaration of **D78**, where it is explained that this approval was an important development in the field of oncology and so would have formed part of the skilled person's common general knowledge at the filing date of the present patent (**D78**, point 14).
556. As noted above, **D78** is being filed in direct response to the interpretation of claim 1 adopted by the OD, described for the first time in their written decision. As **D79** is a reference relied upon by Dr Waxman in his declaration, it can be seen that **D79** is being filed for the same reason as **D78**, i.e. it forms part of the proprietor's direct rebuttal of the OD's claim interpretation and resulting objection of added matter raised for the first time in their decision.
557. As such, we submit that **D79** should be admitted into proceedings for the same reasons as **D78**.

### Admission of Documents D13b and D76

558. **D13b** and **D76** were submitted by O4 and O3, respectively, with their submissions under Rule 116 EPC in relation to the inventive step of the claimed invention. As set out above, in the event that the Board chooses to consider the issue of inventive step in these proceedings, we request that these documents not be admitted into proceedings.

559. According to the EPO Guidelines, an opposition is, “*in principle ... to be examined to the extent and on the grounds submitted during the period for opposition*” (E-VI-2.1). The Boards have confirmed that:

*evidence first submitted by an opponent after expiry of the nine-month period under Art. 99(1) EPC was generally to be regarded as late for the purposes of Art. 114(2) EPC, and that R. 116(1), fourth sentence, EPC was not to be understood to mean that a fresh period during which new evidence could be filed without being treated as late was triggered on issue of the summons to oral proceedings*

CLBA, 10<sup>th</sup> Edition, IV-C-4.3.2; page 1224

560. Since these documents were not submitted during the 9-month opposition period, they can be considered late-filed. As set out below, we submit that there is no justification for this late-filing and so these documents should not be admitted into proceedings.

### **D13b – Supplementary Data to D13a**

561. **D13b** was filed by O4 with their submissions of 4 January 2024 under Rule 116 EPC. According to O4, **D13b** was filed to address the OD’s scepticism in their Preliminary Opinion that the average cancer patient weighs 80 kg (O4, submissions of 4 January 2024, footnote to page 12; see also Preliminary Opinion, point 13.4.1(b)).

562. O4 touched on the question of the average weight of a cancer patient in their Notice of Opposition, and indeed their arguments on inventive step explicitly relied on this being about 80 kg, as they used this as the conversion factor for converting the body weight-dependent prior art 3 mg/kg q2w dosage into a flat regimen (O4, NoO, point 107). Oddly, O4 failed to cite any evidence at that point to justify their use of 80 kg as the conversion factor.

563. The Boards have previously held that the expression of a particular Preliminary Opinion by an OD:

*did not necessarily justify the filing of new evidence, unless this was in **reaction to new aspects** raised in the communication.*

CLBA, 10<sup>th</sup> Edition, IV-C-4.3.2; page 1224 (emphasis original)

564. In the present case, O4 were aware when filing their Notice of Opposition that the question of the average weight of a cancer patient was important to their inventive step arguments. Therefore this cannot be considered to have been a new aspect of the case raised by the OD in their Preliminary Opinion, and **D13b** must be considered late filed. If O4 considered **D13b** relevant to the question of the average weight of a cancer patient, they should have filed it with their Notice of Opposition. Particularly given that O4 cited **D13a** in their Notice of Opposition, they cannot have been unaware of **D13b** at that time.
565. In fact, it is unsurprising that O4 did not cite **D13b** with their Notice of Opposition, because it is *prima facie* irrelevant to the patentability of the claimed invention.
566. Firstly, contrary to O4's implication that **D13b** is somehow informative as to the average weight of a cancer patient, the document provides no information on this point whatsoever.
567. Secondly, and more fundamentally, the question of the average weight of a cancer patient relates to the question of whether it would have been obvious to the skilled person to modify the prior art 3 mg/kg q2w regimen into the flat regimen claimed. A patent can only be obvious in light of the prior art. **D13** (including **D13a** and **D13b**), on the other hand, is post-published, as acknowledged by O4 (see O4, submissions of 4 January 2024, point 24). It therefore cannot be considered relevant to the inventive step of the present claims.
568. Since **D13b** is late filed and *prima facie* irrelevant to the patentability of the claimed invention, it should not be admitted.

#### **D76 – Declaration of Professor Dr Peter Langguth**

569. **D76** was filed by O3 with their submissions of 2 January 2024 under Rule 116 EPC. No justification or explanation for its filing at that point was provided, nor any reasons as to why it should be admitted into proceedings.
570. The only statement even approaching a justification for the late-filing of **D76** is in the document itself, where Prof. Langguth states that “*during the opposition proceedings another opponent submitted an expert declaration*” (**D76**, page 2, paragraph 2).
571. The suggestion is that **D76** was somehow filed as a reply to, or possibly as a supporting document to, **D65** (or maybe was simply inspired by **D65**). None of these possibilities correspond to any established reason for filing a document after the 9-month opposition period.
572. According to case law, a document filed after the 9-month opposition period can nonetheless be considered timely filed:

*if their filing was occasioned by an argument or a point raised by another party so that, under the circumstances of the case, they could not have been filed earlier*

CLBA, 10<sup>th</sup> Edition, IV-C-4.3.1; page 1223

573. Examples of such circumstances have been held to include unforeseeable claim amendments, new experimental data, etc. (CLBA, 10<sup>th</sup> Edition, IV-C-4.3.1; page 1223). The existing case law does not provide any examples of situations where the filing of a document after the 9-month opposition period could be justified based on the submissions of a co-opponent. Such a situation could conceivably arise in the event that co-opponents submitted incompatible arguments or data, but that is not the case here. In the absence of any justification for the filing of **D76** after the 9-month opposition period had expired, it must be considered late filed.
574. According to the case law, late-filed facts and evidence should only be admitted into proceedings if “*prima facie, there are reasons to suspect that such late-filed documents prejudice the maintenance of the European patent in suit*” (CLBA, 10<sup>th</sup> Edition, IV-C-4.5.1; page 1226). There are no such reasons in the present case.
575. We would submit that **D76** cannot be considered *prima facie* relevant to the validity of the opposed patent, because it contains no new facts. It is simply an opinion of a scientist, based on facts which are all already on file and available to the Board for consideration.
576. Indeed, the Boards of repeatedly found that documents which contain no more information than those filed on time can be disregarded, and indeed that this enhances procedural efficiency (CLBA 10<sup>th</sup> Edition, IV-C-4.5.3(b); page 1229). That is certainly the case here.
577. Moreover, while **D76** contains no new facts, Prof. Langguth doesn’t even provide new opinions. He simply states that he agrees with Prof. Leonard’s opinions set out in **D65** (**D76a**, page 4, paragraph 1) and then repeatedly refers back to Prof. Leonard’s opinions (see page 5, paragraph 3; page 6, paragraphs 1 and 5; and page 7, paragraph 4). Rather than constituting new evidence, **D76** is actually little more than a commentary on the earlier declaration of **D65**. It adds nothing to proceedings and should not be admitted.

**Summary**

578. The Main Request meets the requirements of Art. 123(2) EPC. The Decision of the OD to revoke the patent should be set aside and the case remitted to the OD for further prosecution based on the Main Request. In the event that the Board decides to examine the other grounds for opposition as well, we submit that the Main Request meets the requirements of the EPC and should be maintained.

Yours faithfully

*/ Edward Couchman /*

Dr Edward Couchman  
Authorised Representative  
for and on behalf of Mewburn Ellis LLP  
(Association No. 929)  
[edward.couchman@mewburn.com](mailto:edward.couchman@mewburn.com)

*/ Thomas Wolter /*

Dr Thomas Wolter  
Authorised Representative  
for and on behalf of Mewburn Ellis LLP  
(Association No. 929)  
[thomas.wolter@mewburn.com](mailto:thomas.wolter@mewburn.com)

Enc: Main Request (clean and marked up relative to the claims as granted)  
Auxiliary Requests (clean and marked up relative to the claims as granted)  
D78 – Declaration of Dr Ian Waxman  
D79 – Bristol-Myers Squibb press release of 1 October 2015

ECC/TXW/hfh

## FACTS AND SUBMISSIONS

### 1 Patent

EP3288980      *"Treatment of PD-L1-positive melanoma using an anti-PD-1 antibody"*

### 2 Parties

|            | Party                                        | Representative                               |
|------------|----------------------------------------------|----------------------------------------------|
| Proprietor | Bristol Myers Squibb<br>(Princeton, NJ, USA) | Mewburn Ellis<br>(T. Wolter, E. Couchman)    |
| Opponent 1 | Dr. H.U. Dörries<br>(München, DE)            | <i>pro se</i><br>(H.U. Dörries)              |
| Opponent 2 | Lederer & Keller<br>(München, DE)            | <i>pro se</i><br>(M. Fachini)                |
| Opponent 3 | Pajaro Ltd<br>(London, UK)                   | Bird & Bird<br>(M. Alt, A. Obermeier)        |
| Opponent 4 | Dr. E. Greiner<br>(München, DE)              | <i>pro se</i><br>(E. Greiner, S. Geiger)     |
| Opponent 5 | Dr. S. Pohlmann<br>(München, DE)             | <i>pro se</i><br>(S. Pohlmann, T. Schwarzer) |

3

### Chronology

|            |                                                                                                                                                                                                                |
|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 28.04.2015 | Filing of priority document US 62/153,954                                                                                                                                                                      |
| 28.04.2016 | Filing of PCT application PCT/US2016/029878                                                                                                                                                                    |
| 03.11.2016 | Publication of PCT application as WO2016/176504                                                                                                                                                                |
| 26.10.2017 | Entry in the European phase as application EP16724512                                                                                                                                                          |
| 10.03.2021 | Grant of patent EP3288980 announced in bulletin 21/10                                                                                                                                                          |
| 07.12.2021 | <b>Notice of Opposition 1</b><br><u>Request:</u> Revocation in toto<br><u>Grounds:</u> Art. 100(a), 54, 56; Art. 100(b), 83;; Art. 100(c), 123(2) EPC.<br><u>Evidence:</u> D1-D11                              |
| 08.12.2021 | <b>Notice of Opposition 2</b><br><u>Request:</u> Revocation in toto<br><u>Grounds:</u> Art. 100(a), 53(c), 56; Art. 100(c), 123(2) EPC.<br><u>Evidence:</u> D1-D12, renumbered as per Annex 1                  |
| 09.12.2021 | <b>Notice of Opposition 3</b><br><u>Request:</u> Revocation in toto<br><u>Grounds:</u> Art. 100(a), 54, 56; Art. 100(b), 83;; Art. 100(c), 123(2) EPC.<br><u>Evidence:</u> BB1-BB21, renumbered as per Annex 1 |
| 10.03.2021 | <b>Notice of Opposition 4</b><br><u>Request:</u> Revocation in toto<br><u>Grounds:</u> Art. 100(a), 56; Art. 100(b), 83;; Art. 100(c), 123(2) EPC.<br><u>Evidence:</u> D1-D21, , renumbered as per Annex 1     |

|            |                                                                                                                                                                                                                                                                                                                                                |
|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 10.03.2021 | <p><b>Notice of Opposition 4</b></p> <p><u>Request:</u> Revocation in toto</p> <p><u>Grounds:</u> Art. 100(a), 56; Art. 100(b), 83;; Art. 100(c), 123(2) EPC.</p> <p><u>Evidence:</u> D1, D2, D2a, D3-D19, D19a, D20-D24, D24a, D25-D31, renumbered as per Annex 1</p>                                                                         |
| 13.07.2022 | <p><b>Proprietor's Reply</b></p> <p><u>Request:</u> Rejection of the Oppositions and maintenance of the patent as granted (Main Request); subsidiarily, maintenance of the patent in amended form based on any one of Auxiliary Requests 1-19.</p> <p><u>Evidence:</u> D25c, D25d, D30a, D31a, D34a, D24a, D36a, D36b, D75, as per Annex 1</p> |
| 27.02.2023 | <p><b>Summons to oral proceedings</b>, scheduled for 4-8 March 2024. Division's preliminary opinion.</p>                                                                                                                                                                                                                                       |
| 05.12.2023 | <p><b>Opponent 2</b> announced that they would not attend the hearing. (The Opposition is <u>not</u> withdrawn.)</p>                                                                                                                                                                                                                           |
| 02.01.2024 | <p><b>Submission by Opponent 3</b></p> <p><u>Additional evidence:</u> D76 (=BB22, Expert opinion of Prf. Dr. Langguth)</p>                                                                                                                                                                                                                     |
| 03.01.2024 | <p><b>Submission by Opponent 5</b></p>                                                                                                                                                                                                                                                                                                         |
| 04.01.2024 | <p><b>Submission by Opponent 4</b></p> <p>Additional evidence: D13b (suppl. data) and D77</p>                                                                                                                                                                                                                                                  |
| 04.01.2024 | <p><b>Opponent 1</b> announced that they would not attend the hearing. (The Opposition is <u>not</u> withdrawn.)</p>                                                                                                                                                                                                                           |
| 04.01.2024 | <p><b>Submission by the Proprietor</b></p> <p><u>Requests:</u> New Main Request (MR), new Auxiliary Requests 1-19 (AR1-AR19)</p>                                                                                                                                                                                                               |
| 26.02.2024 | <p>Further submission by Opponent 3</p>                                                                                                                                                                                                                                                                                                        |

|            |                                                                                                                                                                                                              |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 04.03.2024 | <b>Oral proceedings held by videoconference</b><br><br>All parties present except for Opponent 1 and Opponent 2 (as announced). In the course of the hearing, the Proprietor filed a further request (AR20). |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

**4 Documents cited**

See the consolidated list in Annex 1.

**5 Admissibility issues**

The notices of opposition have been filed in compliance with Articles 99(1) and 100 EPC, as well as Rules 3(1), 76(1) & (2) EPC.

Insofar as discussed, not objections under Rule 80 were raised in respect of the main and auxiliary requests submitted.

**6 Priority**

*The effective date of filing is 28.04.2016*

All Opponents have argued that the patent in suit is not entitled to the priority rights, at least because P1 (US 62/153,954) does not teach the flat dose of 480 mg nivolumab for the claimed medical purpose. The Proprietor has not disputed this point.

## MAIN REQUEST

### 7 Features of independent claim 1

|    |                                                                                                                                        |
|----|----------------------------------------------------------------------------------------------------------------------------------------|
| F1 | A composition comprising nivolumab                                                                                                     |
| F2 | for use in treating a melanoma in a patient                                                                                            |
| F3 | wherein the patient is identified as having a PD-L1 positive melanoma tumor by measuring a PD-L1 expression on the melanoma tumor; and |
| F4 | wherein the patient is to be administered a flat dose of 480 mg nivolumab as monotherapy once every four weeks,                        |
| F5 | wherein the patient is not administered a combination of nivolumab and ipilimumab.                                                     |

*NB: nivolumab is an anti-PD1 antibody; ipilimumab is an anti-CTLA-4 antibody*

### 8 Art. 123(2) EPC

*The Division finds that the MR does not meet the requirements of Art. 123(2)*

All of the **Opponents** raised objections of added matter in respect of the granted claims. With the exception of one objection, rendered moot by amendment, the objections apply directly too the claims 1-6 of the Main Request. Specific objections were raised also in respect of the claims of the MR now on file.

#### 8.1 Main objections

It was objected that:

- (a) There is illicit patchworking and selections from multiple lists in respect of the therapeutic antibody for monotherapy and of the regimen chosen.
- (b) There is added matter in the definition of which therapy the patients should NOT receive - because such definition requires further selections, and/or because the scope of the excluded combinations is narrower than foreseen in the original application.

Essentially, it was argued that the choice of nivolumab among other possible PD1 blockers represents a first selection. The choice of regimen involves further choice(s). In respect of F5, it was alleged that there is no basis for the specific exclusion of nivolumab+ipilimumab. It was alleged that [105], [106], [109], for instance, speak of ipilimumab as a choice of CTLA+4 antibodies to be *used* in combination therapy -- not to be *excluded*. The basis for the notion that

the patient should not be administered a combination of nivolumab and ipilimumab was similarly questioned; in particular, the focus on ipilimumab represents a further selection. It was further alleged that there is added matter by changing the wording of claim 1 to refer to a composition whereas PCT claim 1 concerned an antibody as such.

## 8.2 Construction of claim 1

### 8.2.1 -- usual meaning --

One possibility is to interpret claim 1 in the light of the common meaning of the word monotherapy, which the Mirriam-Webster Medical Dictionary defines as *"the use of a single drug to treat a particular disorder or disease"*.

This interpretation was favoured by the proprietor during the written procedure and tentatively endorsed by the OD in its preliminary opinion. Indeed, up to the oral proceedings, the the Division followed the Proprietor's own statements during the written phase, starting with §213 and §218 of the reply of 13.07.2022 to the effect that *"single antibody composition has a clear meaning especially in the context of a claim that refers to administration of nivolumab as a monotherapy", and that "words have their plain meaning"*. This position was affirmed at §47 and §50 of the Rule 116 submission by the Proprietor, who stated verbatim that *"monotherapy should be given its standard meaning in the art, regardless of its definition in the description", and "nowhere in the patent is there any express teaching that an anti-PD-1 antibody monotherapy can include a second agent in addition to the antibody"*.

**However:**

### 8.2.2 -- patent as own dictionary --

In the Oral Proceedings, **the Proprietor changed their position**. It became **common ground between all Parties** that the term "monotherapy" in the context of the patent has a wider meaning. The Proprietor explicitly stated that the therapy only excludes the co-administration of nivolumab and ipilimumab. It was not meant to exclude co-administration of other compounds, and reference was made to PCT claim 49, which covers the "monotherapy" in combination with any other anti-cancer agent, and to the definition of "monotherapy" found at [43] of the original application (WO2016/176504), which reads:

*The term "anti-PD-1 antibody monotherapy" as used herein includes a therapy of an anti-PD-1 antibody without an anti-CTLA-4 antibody therapy. The anti-PD-1 antibody monotherapy comprises, consists essentially of, or consists of administering one or more doses of an anti-PD-1 antibody to a patient in need thereof, but does not include administering an anti-CTLA-4 antibody. In one embodiment, the anti-PD-1 antibody monotherapy comprises administering one or more doses of nivolumab to a patient in need thereof, but does not include administering an anti-CTLA-4 antibody. In another embodiment, the anti-PD-1 antibody monotherapy comprises administering one or more doses of nivolumab to a patient in need thereof, but does not include administering an*

*antibody specifically targeting a protein other than PD-1. In other embodiments, the anti-PD-1 antibody monotherapy comprises administering one or more doses of nivolumab to a patient in need thereof, but does not include administering another anti-cancer agent.*

Thus, [43] provides a gradient of progressively more restricted scenarios of what is meant by "monotherapy". In scenario 1 the anti-PD1 antibody of choice ("an anti-PD1 antibody") is to be administered without any anti-CTLA4 antibody (of any kind); however it permits the concomitant administration of an antibody that targets another protein (other than CTLA4). In scenario 2, the anti-PD1 antibody is to be administered without any antibody that targets a protein other than PD1; however it permits the co-administration with another drug such as a chemotherapeutic (say, platinum). In scenario 3, the anti-PD1 antibody is to be administered without any other anticancer drug (including chemotherapeutics).

### 8.2.3 -- consequence --

Both the "usual meaning" approach and the "patent as its own dictionary" approach have been endorsed by the BoA depending on the specific circumstances of the case at hand (see CLB section ii.a.6.3.3). In the present case, the OD does not see sufficient reasons to hold, *motu proprio*, the "usual meaning" position against the express position of all parties. Hence, following to the common grounds between the Opponents and the Proprietor, the term "monotherapy" is interpreted in the light of the description, using the "patent as its own dictionary" approach.

That being the case, claim 1 MR must be given the widest possible, technically sensible meaning, which in the assessment of the Division is:

*A composition for use in treating melanoma, wherein the melanoma is PD-L1+ (as determined by measuring PD-L1 expression on the tumor), wherein nivolumab is administered at 480 mg q4w to a patient who is NOT administered a combination of nivolumab and ipilimumab, but may be administered another anti-cancer agent.*

### 8.3 Added matter

Such subject-matter cannot be derived directly and unambiguously from the original application.

#### 8.3.1 -- the exclusion zone (F5) --

The original PCT claim 1, concerned the administration of "an anti-PD1 antibody" of choice to a patient who is not administered a combination of "an anti-PD1 antibody" and "an anti-CTLA4 antibody".

On a reasonable reading of PCT claim 1, this means that if we choose the anti-PD1 antibody for treatment (here: nivolumab), the patient should not receive a combination of any other PD1 antibody and any CTLA4. Claim 1 MR, interpreted as indicated above, only requires that the patient does not receive a combination of nivolumab+ipilimumab; the "exclusion zone" is smaller, so the scope is wider than originally foreseen.

To give a practical illustration of the effect of the widening of the exclusion zone: claim 1 MR seems to permit the administration of nivolumab (480 mg q4w) to a patient that is also receiving a combination of nivolumab+tremelimumab, or a combination of pembrolizumab+ipilimumab, or a combination of pembrolizumab+tremelimumab. Such would have been excluded by PCT claim 1 in the construction outlined above.

Or to put it in even simpler terms: PCT claim 1 forbade "topping up" with nivolumab **any** (possibly ongoing) combination therapy of PD1 x CTLA4 double blockade. Claim 1 MR only forbids topping up a combination therapy of nivolumab x ipilimumab, but allows topping up the remaining double blockades (e.g., pembrolizumab+tremelimumab); and this is not found in the original application.

#### 8.3.2 -- *additional considerations* --

The Division explored whether alternative readings might exist which would lead to a different conclusion. One could, for instance, import into the definition of monotherapy the widest requirement found at [43], to the effect that any CTLA4 antibody is excluded - not only ipilimumab (i.e., scenario 1 discussed above). That would leave us with the net result that the exclusion zone is now "nivolumab+CTLA4", but this is still less stringent than the original exclusion zone of PCT claim 1. (On this, see also section 14.3 below.)

#### 8.3.3 -- *conclusions* --

Thus, alternative readings of PCT claim 1 might *perhaps* exist depending on the interpretation of certain terms of the claim, and on the weight given to certain definitions and terms in PCT claim 1 and [43]. But none was presented to the Division leading directly to a legitimate exclusion zone of "only nivolumab + ipilimumab". And even if such reading did exist, it would not be the only valid reading in view of the foregoing discussion. This is the very definition of subject-matter which cannot be derived directly and unambiguously from the original application, as required by the Golden Rule. The burden of proving a direct and unambiguous basis for the features of the claims rests with the Proprietor; the standard of proof is beyond reasonable doubt. The Proprietor did not discharge such burden of proof.

#### 8.4 Patchworking

With regard to the allegation of illicit patchworking in respect of the choice of nivolumab over other PD-1 antibodies; the choice of the 480 mg q4w regimen v other options; and the alleged added matter in the composition: It is unnecessary to assess these matters in this context. Also, the assessment will depend on the interpretation of the claims. See on this section 14.3.2 and 16 below.

## 8.5 Unsuccessful objections

The following objections were found without merit.

### 8.5.1 -- *PD-L1 on cell surface* --

It was alleged that the feature F3 represents an intermediate generalisation because, in contrast to [73], it is not specified that the PD-L1 is expressed at the cell surface.

This objection fails directly because there is a verbatim basis for feature F3 in PCT claim 15. Moreover, measuring the expression "on" the melanoma tumour, in plain English implies that the expression is at the surface. The claim says "on", not "in".

### 8.5.2 -- *Percentage of cells in IHC test* --

It was alleged that the subject matter of claim 7 as granted involved a further selection from the percentage of cells required to bind to the PD-L1 antibody in the IHC test. This objection is  moot  because this claim is no longer present in the main request now on file.

### 8.5.3 -- *Deletion of non-disclosed antibodies from claim 6* --

It was further alleged that the revised claim 6 MR violates Art. 123(2) because, in addition to the selection in claim 1, now there is also a further selection in respect of the 28-8 antibody, excluding other antibodies that were claimed (PCT claim 21) but not disclosed (in breach of Art. 83). Opponent 3 also suggested that leaving out the sequences of 28-2 might be added matter, by reference to [103].

The Division considers that there is no true additional selection when the "selected item", antibody 28-8, is actually the only one actually disclosed among the antibodies recited in granted claim 6. Deleting from a claim those items that fail the Art. 83 test does not impart new technical information. The antibody was mentioned in PCT claim 21 by name only, not with sequences, so there is no added matter in that respect, either.

## AUXILIARY REQUEST 1

## 9 **Art. 123(2) EPC**

Claim 1 of the AR1 still comprises the offending negative feature F5, and automatically fails on the same grounds as the MR.

## AUXILIARY REQUEST 2

### 10 Art. 84 EPC

*The Division finds that AR2 does not meet the requirements of Art. 84*

Claim 1 AR2 was additionally amended to specify that the measurement of the PD-L1+ was on the surface of the cell. Prima facie, this amendment does not appear problematic in terms of clarity.

Claim 1 AR2 was also amended to read "a single antibody composition comprising nivolumab" etc etc. This amendment lacks clarity. It is unclear whether it means "a composition comprising a single antibody", or "a single composition which can comprise more than one antibody against the same target" as for instance set out at [42] of the original application.

The Proprietor argued that the term is clear in itself therefore one should not consult the description. This argument fails on two grounds:

(a) The term, in plain English, is ambiguous. There is a difference between single-antibody composition and single antibody-composition. Both readings are semantically possible. The term is not immediately clear. And given the importance of the true scope of the claim for ascertaining compliance with Art. 123(2), this is not a trivial matter.

(b) The Proprietor has explicitly argued that "nivolumab as monotherapy" in the context of claim 1 MR was not limited to true monotherapy in the sense commonly understood in the art; it should be interpreted more broadly in accordance with the teachings of the patent. Then, it is not open to the Proprietor to argue that another term should be assessed without taking into account the teachings of the patent. The Division must apply a consistent approach: either we take into account only the ordinary meaning of the words for each word of the claims; or we take into account the content of the patent (application) as "its own dictionary" - and this too for each term of the claims. The Division cannot countenance a hybrid approach, taking ordinary meaning when it suits the Proprietor, and taking internal definition when it does not.

## AUXILIARY REQUESTS 3-19

### 11 Art 84 EPC

All of the requests 3, 5-11, 13-15, 17-19 contain the offending term "single antibody composition". Accordingly, they fail the test of clarity in the same way as AR2.

12 **Art. 123(2) EPC**

It is further noted that AR4, AR12, AR16 comprise the same negative feature F5 as in the MR, which is found to violate Art. 123(2) as discussed above.

**AUXILIARY REQUESTS 20**

13 **Admissibility**

AR20 was filed in the course of the oral proceedings. It is identical to AR2 except that the offending term "single antibody composition" has been removed. This request is late-filed.

The Opponents argued against its admission as being late-filed and not prima-facie allowable.

The Proprietor noted that the term was incorporated in auxiliary requests as early as in July 2022; it was not highlighted as an issue in the Division's preliminary opinion, and only now it was found unclear. Moreover, the deletion of this term does not complicate the proceedings, and in fact it renders moot some of the objections, notably the alleged violation of Art. 123(3), raised by the Opponents in their Rule 116 submissions.

The Division exercised its discretion and allowed the filing of AR20 because, indeed, it does not unduly complicate the proceedings vis à vis AR2 and also renders moot certain concerns.

14 **Art. 123(2) EPC**

*Auxiliary request 20 does not meet the requirements of Art. 123(2)*

14.1 Amedments

AR20, as compared to AR2, defines the negative feature F5 to the effect that the patient should not be administered a combination of nivolumab and any CTLA4 antibody.

14.2 Construction of claim 1

By analogy to **8.2.3** above, claim 1 AR20 has to be interpreted as concerning:

*A composition for use in treating melanoma, wherein the melanoma is PD-L1+ (as determined by measuring PD-L1 expression on the tumor), wherein nivolumab is administered at 480 mg q4w to a patient who is NOT administered a combination of nivolumab and a CTLA-4 antibody, but may be administered another anti-cancer agent.*

### 14.3 Added matter

And by analogy to **8.3** above:

#### 14.3.1 -- *the exclusion zone F5* --

The original PCT claim 1, concerned the administration of "an anti-PD1 antibody" of choice to a patient who is not administered a combination of "an anti-PD1 antibody" and "an anti-CTLA4 antibody". Thus, PCT claim 1 forbade "topping up" with nivolumab **any** (ongoing) combination therapy of PD1xCTLA4 double blockade. Claim 1 AR20 only forbids "topping up" a combination therapy of nivolumab x CTLA4. It still permits topping up a combination therapy of, for instance, pembrolizumab+ipilimumab, or pembrolizumab+tremelimumab, which cannot be derived directly and unambiguously from the original application. Therefore, the problems outlined at 8.3.1-8.3.3 apply also to AR20.

#### 14.3.2 -- *additional considerations* --

Here too the Division explored whether alternative readings might exist which would lead to a different conclusion.

For instance, one could consider that [43] defines monotherapy by reference to "an anti-PD1 antibody", which could taken to refer to the use of a single type of anti-PD1 antibody (here, nivolumab). The wording "an" can be read to exclude the co-administration of *any other* PD1 antibody. In this case, nivolumab could be used to "top up" a therapy of an unrelated (non-PD1) cancer agent, or to "top up" a combination therapy of unrelated (non-PD1) cancer agents. Also, in this case, the incomplete exclusion zone "nivolumab + CTLA4" would be *de facto* of no consequence.

Yet also this interpretation is not the only one possible; actually, the Proprietor emphasized repeatedly that the claims should not be construed as excluding more than is stated at [43] or in PCT claim1, for instance to exclude the co-administration of nivolumab and pembrolizumab (which would be a result of the above interpretation).

#### 14.3.3 -- *A further problem* --

The Proprietor's latter assertion is not without its own problems. Is there really a basis for administering nivolumab 480 mg q4w to a patient that is receiving pembrolizumab?

It may be arguable that PCT claim 1 forbids using nivolumab to "top up" certain combination therapies, including pembrolizumab x CTLA4. It is however not excluded that it can be used to top up pembrolizumab alone; a view supported by the existence of PCT claim 49 (the method of [claim ] further comprising administering an anti-cancer agent). This appears conceptually not inconsistent with the teachings of [42] of the original application which reads:

*The term "single antibody composition" as used herein refers to a composition comprising antibodies that specifically bind to a single target, e.g., PD-1. As used herein, the single antibody composition can include a mixture of antibodies if the antibodies specifically bind*

*to the same target, e.g., nivolumab and pembrolizumab. In other embodiments, a single antibody composition can include only one specific antibodies [sic], e.g., nivolumab alone or pembrolizumab alone, but not a mixture thereof.*

However, it is far from certain that, ergo, the original application provides for using nivolumab at 480 mg q4w to treat a patient that is (already or also) receiving generic pembrolizumab treatment.

If the nivolumab and pembrolizumab are in the same composition as per [42], where is the basis for assigning the regimen of 480 mg q4w to nivolumab instead of pembrolizumab or both? (Note that [117] proposes 480 mg q4w for any of the available PD1 antibodies. And if it were argued that this is a known regimen adapted for nivolumab, then the Proprietor's inventive step argument would fall apart.)

If the nivolumab and pembrolizumab are to be administered apart, as per PCT claim 49 - then where is the basis for the specific choice of nivolumab 480 mg q4w and the specific choice of pembrolizumab as further agent? In such case there is a double selection.

#### 14.3.4 -- Conclusions --

In sum, here too, the subject-matter cannot be derived directly and unambiguously from the original application, as required by the Golden Rule - also (but not exclusively) because several interpretations can coexist which lead to different outcomes. The burden of proving a direct and unambiguous basis for the features of the claims rests with the Proprietor; the standard of proof is beyond reasonable doubt. The Proprietor did not discharge such burden of proof.

### OBITER DICTA

*In view of the turns of events in the Oral Proceedings, the other objections were not discussed. In order to assist all parties, the Division will now provide, **strictly obiter**, a reassessment of the position after taking into consideration all of the submissions received in writing prior to the oral proceedings.*

*For the sake of simplicity, the following discussion is based on the assumption that the claims concern true monotherapy - i.e., only nivolumab and nothing else. But the same considerations may apply mutatis mutandis also to the less clear scenarios discussed above.*

#### 15 Art. 123(2) EPC

Tagging on from sections 8.2.1 and 8.4 above:

Had the initial assumption been maintained, namely that the claim concerns a therapy involving the administration of **only nivolumab**, then the Division would have likely ignored the negative feature F5 as being no more than a historical relic of no import: the claim would *de facto* be

directed to the use of nivolumab - and only nivolumab - for treating PD-L1+ melanoma. There is ample basis for this in PCT claim 3+26, with a strong pointer from the examples, which use exclusively nivolumab and no other PD1 blocker.

- 15.1 The only remaining question to address would have been the choice of the specific regimen of 480 mg q4w, which finds a basis at [117]. In the assessment of the Division, if the claim were limited to nivolumab alone, this regimen represents a single selection from a long list of possible regimens that span per-weight and flat doses.

The Opponents had argued that this choice involves a double selection: going from a weight-based dose to a flat dose, then a selection of the flat dose regimen as such. The Division is not persuaded this is the correct approach; flat and per-kg regimens are presented as both valid in the original application, and therefore the skilled person would choose among the specific regimens - of whichever kind - discloses with sufficient clarity. For the per-weight regimen, 3 mg/kg q2w is presented as the classical nivolumab regimen; for the flat doses, 240 mg q2w and 480 mg q4w are the only two precise regimens (concrete in the sense of a precise dose with a corresponding precise frequency of administration) provided.

- 15.2 When giving the term "monotherapy" its normal meaning, a "composition comprising nivolumab" for use as monotherapy must be construed as a composition comprising only nivolumab and some carrier. With this regard, the Division maintains that there is no added matter solely because the claim 1 now mentions a composition rather than an antibody as such (which was one of the objections raised by Opponents). An antibody, to be administered to a patient, must be in a form suitable for administration, which is nothing other than a composition: the antibody is not administered in thin air.

- 15.3 Thus, if the strict construction of claim 1 had prevailed, as outlined in section 8.2.1 the Division would have in all likelihood concluded that there is no added matter.

## 16 Art. 83 EPC

*The claims reflect subject-matter for which there is sufficient disclosure*

A number of objections of lack of sufficient disclosure were raised in respect of the granted claims. They apply also to the claims of the requests now on file

### 16.1 No data showing an effect for 480 mg q4w

Opponent 3, Opponent 4 and Opponent 5 objected that the patent does not make it plausible that the claimed dosing regimen provides any technical effect, let alone an improved effect over the prior art.

The Division considers that at issue is whether the new dosage regimen is suitable for the stated purpose, i.e. whether it is plausible, taking the content of the patent and the prior art into account, that the selected dosage regime is able to achieve the desired therapeutic purpose. It

is known that PD-L1 (on the tumor) interacts with T1-lymphocytes, especially Tregs, by binding to PD1, which reduces the immune response to the tumor. It is also well known that inhibitors of this interaction restore the immune response, leading to enhanced anti-cancer activity.

Nivolumab is a known inhibitor of the interaction between PD-1 and PD-L1, therefore the effect (regardless of the regimen) is plausible. Effective dosages and regimen are known. There are no verifiable facts on file to sustain serious doubts that the new dosage regimen does not work. Whether or not there is no improved effect over the prior art is a question for inventive step, not sufficiency of disclosure.

Opponent 5 cited **T1592/12** in this respect. That case recalled that in medical use claims, it is not sufficient to show that the skilled person can obtain the compound and administer it, but also that it is suitable for achieving the technical effect. In the case underlying T1592/12, the regimen claimed was such that, in view of the half life of the product, it was unlikely that a sufficient drug level could be achieved; in such a case, it is incumbent on the applicant to show that it works nonetheless. In the view of the Division, this is nothing but a straightforward application of the "serious doubts" doctrine: the Board found that it being undisputed what the therapeutic levels of herceptin were (AUC), and being undisputed what the half life of herceptin was, there were *ipso facto* serious doubts. This is not the case in the present patent. There is no evidence to show that 480 mg q4w has *prima facie* a problem.

On the contrary, the examples show some positive results with 3 mg/kg q2w; taking the case of an average person of 80 kg, that is 240 mg q2w. Doubling the dose and interval to 480 mg q4w is not implausible, given that the elimination half life of nivolumab is 27 days (D19). No evidence has been presented with the notice of opposition to the effect that the level of nivolumab drops dramatically in week three, leaving the patient "drug free" for another 10 days or so, until the next 480 mg administration, *and* that this causes the overall treatment to fail. To the contrary, there is evidence that it does work: D27 (and also D75 insofar as admissible in evidence). And since from the results of the patent and the properties of nivolumab listed in D19 a monthly "stiff dose" regimen was made plausible, such post-published information is admissible as confirmation.

The submissions of the Opponents in this respect are also incompatible with the extensive assessment provided by Prof. Leonard in D65. The Professor discussed the wide therapeutic window of nivolumab, its long half life, and its pharmacokinetic properties as disclosed in D54a and D55 and concluded that a flat dosage of 240 mg q2w or of 480 mg q4w will sustain therapeutic serum levels and PD1 occupation rates. Therefore, they are to be presumed as equivalent alternatives. With such an authoritative view, it is difficult to follow Opponents' allegations of insufficiency, which are not accompanied by any verifiable fact.

Rather, the question is whether Prof. Leonards' opinion highlights the presence of a squeeze: if the claims are enabled in view of such considerations, they are probably not inventive. This will be discussed more in detail in **section 19.4.6 below**.

## 16.2 PD-L1 positivity

Opponent 4 further objected that the disclosure of the patent is misleading in respect of the identification of PD-L1 positive melanoma tumours, in that the description at [42] (B1 specification) indicates that as little as 0.01% of PD-L1 expressing cells is enough to qualify as a PD-L1+, whereas common general knowledge (D41, D50) put the cut-off level for positivity at 1%, 5% or even 10%, 5% being recommended.

The Division observes that the claim 1 does not define the percentage required; the skilled person would give the term "PD-L1 positivity" a normally accepted meaning. Since D41 and D50 are common general knowledge, the skilled person would know that it typically means 5%, and certainly not less than 1%, and would immediately recognize that 0.01% at [42] is nothing but "fluff" to be ignored as meaningless. In actual fact, the patent at [138] more aptly defines PD-L1 positivity as "at least 5% of tumor cells showing cell surface PD-L1 staining" etc., which is wholly consistent with the common general knowledge. Therefore, the patent does provide an actual example with a meaningful percentage. The "fluff" at [42] should have been amended in examination for the sake of consistency, but this a matter which is governed by Art. 84 and is not a ground for opposition.

## 16.3 Measuring PD-L1 in claim 2

Opponent 1 argued that measuring a PD-L1 expression in a sample comprising TI-inflammatory cells (note the "and/or" in claim 2) does not allow the measurement of PD-L1 expression on the melanoma tumor as required by claim 1, so claim 2 is not enabled.

Opponent 5 intervened in this matter alleging that there is lack of guidance on how to identify a PD-L1 positive melanoma tumour in the patent. On the one hand, certain passages of the description of the patent teach the the term "PD-L1 positive tumor" refers to a test tissue sample comprising both tumor cells and TI-inflammatory cells, and that at least 0.01% of the total number of cells (i.e., of tumour cells and TI-infiltrating cells) express PD-L1 [42]. On the other hand, [69] and [70] explain that PD-L1 positive tumours are expressing PD-L1 on the surface of melanoma tumour cells or TI-inflammatory cells. Likewise, [82] teaches alternative means for quantifying PD-L1 expression in a test tissues sample using an inflammatory score (AI), which is a measure of TI-infiltration inflammatory cells only. This is contrary to the general assumption that the tumour expresses PD-L1 and the TI-inflammatory cells express PD1.

The Division is not persuaded.

(a) Claim 2, which depends on claim 1, only requires the measurement of PD-L1 on the tumour cells. Contrary to Opponent 5's assumption, the claims do not imply that expression of that marker on TI-inflammatory cells can be used instead to determine PD-L1 positivity of the tumour.

(b) Claim 2 simply says that the measuring step in the medical use claim 1 is to be based on a tissue sample obtained from the patient. A biopsy will *always* contain tumour tissue. More often than not, the tumour is infiltrated by inflammatory cells. If there are lots of infiltrates, there is a good chance that the biopsy will contain not only tumour cells but also some infiltrating cells. However, it is physically impossible to get a biopsy containing *only* infiltrates. The skilled person would not read claim 2 as implying that in one alternative, the sample contains only TI-inflammatory cells. This makes no technical sense. Thus, the "and/or" used in claim 2 cannot be read literally as setting out three scenarios: biopsy containing tumour cells alone; tumour cells + infiltrates; infiltrates alone. The third scenario is absurd. Therefore, the skilled person would understand claim 2 as referring to a biopsy with tumour cells and *possibly* infiltrates.

(c) Moreover, assuming *arguendo* that we may obtain a biopsy which contains only TI-cells and no tumor cells (quod non): such a sample is useless, as it does not permit to measure PD-L1 levels on the tumour cells as required by claim 1. Therefore, the notional second alternative in claim 2 even falls outside the scope of the claims. There is no requirement in the EPC to enable subject-matter that falls outside the claims.

(c) With this regard, whether or not the description discloses also the measurement of the same marker on TI-cells is irrelevant to the enablement of the claim 2. Aside from this, there is no contradiction in terms to suggest *in the disclosure* that PD-L1 expression can be measured also on TI-cells. This is because, while conspicuously present on tumour cells, it is sometimes present also on TI-lymphocytes. It is actually for this reason that, nowadays, some researchers in some cases prefer the combined positive score (% tumour+TI-cells over total cells) to the classical positive score (% staining tumour cells over total cells).

(d) The argument based on the general disclosure at [42][69][70] is weak, because it overlooks the teachings at [138], which clearly defines PD-L1 positivity as "at least 5% of tumor cells showing cell surface PD-L1 staining". In view of this, in the assessment of the Division, it cannot be seriously alleged that the patent gives no guidance on how to identify a PD-L1 positive melanoma.

#### 16.4 Reliability of PD-L1 status as a marker

Opponent 5 alleged that some review articles (D44, D50, D67) question the suitability of PD-L1 as a predictive marker of a response to PD-1 pathway blocking agents, and posit that this marker is not appropriate for excluding patients from receiving therapy since there is clinical benefit in patients with PD-L1- tumors.

The Division is not persuaded. The point of the patent, and of determining the PD-L1 status, is not to exclude patients, but rather to check which patients can be treated with nivolumab monotherapy instead of needing a combination. There is ample basis for this relationship in D14, so the theoretical concerns raised by the Opponent 5 plainly do not apply to the reality of the present case.

16.5 Antibodies in claim 6

Opponent 4 has also objected that granted claim 6 is not enabled because only antibody 28-8 is characterized by sequences, but the other antibodies are not characterized. Antibody 5H1 is mentioned in D51, but no sequence is provided. Thus, claim 6 is only partly enabled, namely only for 28-8. This objection is moot because all of the requests now on file restrict claim 6 to clone 28-8.

For the avoidance of doubt, the Division considers that acronyms and internal names have no accepted meaning, but this is a matter falling within the ambit of Art. 84. Since 28-8 is disclosed, there is no issue of enablement in this respect.

17 **Art. 100(a), 53c EPC**

*The claims do not contain subject-matter excluded from patentability.*

Opponent 2 has objected that claim 1 infringes Art. 53c because the diagnostic step involves measuring the PD-L1 expression on the melanoma tumour - which the Opponent construes as taking place either on a tissue specimen or directly on the human body. As specified in [71], the sample can only be obtained with surgery (biopsy). Moreover, the same paragraph indicates that assessment of PD-L1 expression can be achieved without obtaining a test tissue sample, but no such non-surgical option is disclosed in the patent or in the literature cited therein (provided in these proceedings as D21-D23).

The Division refers to Guideline G-II 4.2.1, paragraph 2. Diagnostic methods applied on body tissues after they have been removed from the human or animal body, are not excluded from patentability. A method claim is not allowable under Art 53(c) only if it includes at least one feature defining a physical activity or action that constitutes a method step for treatment of the human or animal body by surgery or therapy. This method must be *actively* mentioned in the claim, thereby defining the step as part of the subject-matter protected, which is inconsistent with the freedom of the physician to operate (which freedom is what Art. 53c is safeguarding).

Here, the "*patient is identified as having...by measuring PD-L1 expression on the melanoma tumor*". Firstly, as pointed out by the Opponent, it is certainly not a routine procedure to measure PD-L1 expression in vivo. The skilled person, therefore, would in any event not interpret claim 1 as incorporating an active "in vivo step" in this limb: de facto, it is carried out in vitro. Second, this limb only *defines* the patient to be treated; even if a theoretical "in vivo step" were implied, it is passive (not active), and does not seem to impinge on the physician's freedom to act in the best interest of the patient without having to worry about patent rights, which is the purpose of Art. 53c. Moreover, GL G-II 4.2.1.1 states that the exclusion under Art. 53c applies to multi-step methods that comprise or encompass a surgical step, and this defect

can be cured by omitting the surgical step from the wording of the claims. In other words, only when a surgical step is expressly listed in the claim there is a problem. Here, there is no such wording.

18 **Art. 100(a), 54 EPC**

*The claims are novel over the state of the art.*

Lack of novelty was alleged on the basis of D1 and D25a (formerly BB3)

18.1 Teachings of D1

D1 is to be assessed under Art. 54(3) EPC. The Division observes:

- (a) [63] anticipates compositions of an anti-PD-1 antibody *and a second antibody* in a fixed dose formulation. This paragraph does not mention the target disease.
- (b) [106] anticipates a composition comprising a first and a second antibody, wherein the first antibody is anti-PD1 or anti-PD-L1. [106] mentions that inhibition of the PD-1/PD-L1 interaction mediates potent antitumor activity. This paragraph does not mention fixed dosages or the target cancer.
- (c) [007] seems to single out nivolumab and pembrolizumab as a preferred choice of PD-1 antibody, a view supported by the examples, where only nivolumab was used.
- (d) The formulation is for use in treating diseases which include but are not limited to cancer. Claim 91 says that the antibody can be used to treat infectious diseases, claim 92 says it can be used to treat cancer. Claim 93 as well as [40], [203], [204] provide a long list of possible target cancers, including but certainly not limited to melanoma.
- (e) It is unclear whether the cancer itself has to be necessarily PD-L1 positive; as explained in [94], [106], [108], PD-1 is bound and activated by two ligands: PD-L1 and PD-L2. [106] says that inhibition of the PD-L1/PD1 interaction is particularly potent (this is prior art knowledge).
- (f) [210]-[213] list suitable regimens, including per weight and flat doses. [213] mentions 360 mg q3w and 480 mg q4w as options for flat doses.

In the assessment of the **Division**, to arrive at the subject-matter of claim 1, at least three selections must be made:

- (i) which PD-L the cancer must be positive for (PD-L1, PD-L2),
- (ii) which regimen to apply (360 mg q3w, 480 mg q4w), and
- (iii) which disease to treat (melanoma out of a host of possibilities).

The subject-matter of opposed claim 1, therefore, cannot be directly and unambiguously derived from the teachings of D1.

Moreover, there is no direct and unambiguous disclosure of a PD-L1 measuring step, nor an indication in D1 that nivolumab should NOT be administered in combination with ipilimumab. On the contrary, all of the examples concern combinations of nivolumab+ipilimumab, which is explicitly excluded from opposed claim 1.

#### 18.1.1 -- Notes --

(a) The Proprietor contended that there is a *further* difference between the opposed claims and the teachings of D1: that according to the claims nivolumab must be a monotherapy, whereas D1 concerns nivolumab in combination therapies. The Division must put a caveat on this assertion: the claims do require monotherapy, but as discussed above "monotherapy" is defined as the use of nivolumab only excluding all CTLA-4 antibodies, but not necessarily excluding all other immunotherapeutics. Since D1 foresees combinations of nivolumab with e.g., anti-CD137 etc., it is at least arguable that D1 discloses a "monotherapy" as defined at [43] of the patent. Still, in view of what precedes, this point is not determinative, because there are other differences.

(b) Opponent 1 argued that there is no selection of a PD-L1 for (i) in view of [106]. The Division disagrees. Just because PD-L1 is mentioned as the most prominent of the PD1 ligands does not exclude that a PD-L2 cancer may be treated as well.

(c) Opponent 1 argued (§45 of submission of December 2023) that "nivolumab is characterized as anti-PD-L1 antibody ([118] of D1). The Division finds this manifestly mistaken. Nivolumab is characterized at [117] as an anti-PD1 antibody.

(d) Opponent 1 also argued that [209] provides an indication that the cancer must be PD-L1 positive. The Division sees no such indication. That the cancer must be PD-L1 positive is certain only if one chooses to use a PD-L1 antibody. But the same requirement is not present if one chooses to use nivolumab (a PD1 antibody), for nivolumab can be used to block the interaction PD1:PD-L1 or PD1:PD-L2. Again, just because the former is the more famous, or the more notorious, does not imply that the latter is non-existent.

(e) Opponent 1 argued that [203] says "in yet other embodiments, the cancer is lung cancer, metastatic melanoma, glioblastoma, or renal cell carcinoma", thereby restricting the list in such way that the two regimen of 360 q3w and 480 mg q4w must be applied to this short list to reveal a modest array of individualized embodiments. The Division disagrees. The "in yet other embodiments" is preceded by, followed by, and embedded in a very, very long list of cancers equally labelled as "embodiments". There is no pointer to melanoma being preferred. Nor is the administration foreseen in D1 limited to fixed doses. They are not presented as preferred.

#### 18.2 Evidential value of D25a

**Opponent 3** argued that D25a sets out a clinical trial for nivolumab 3 mg/kg q2w in melanoma, wherein *"eligible participants may switch to nivolumab at 480 mg every 4 weeks"*. It also discloses stratification by PD-L1 expression measured by IHC.

D25a, however, is a printout of the clinical trial webpage in 2021. The **Proprietor**, comparing D25b, c, and d, has shown that up to the date of filing of the patent, the clinical trials entries were silent as to the 480 mg q4w regimen.

In the assessment of the **Division**, there is no clear and convincing evidence of a publication concerning clinical trial NCT01721772 which precedes the date of filing of the patent and which anticipates, even theoretically, the use of nivolumab 480 mg q4w in as claimed in the opposed patent. Accordingly D25a cannot be considered prior art.

## 19 **Art. 100(a), 56 EPC**

The **Opponents** collectively cited D2, D5, D6, D9, D11, D12b, D14a, D14b, D18b, D32, D33, D40, D43, D44, D54a, D55, D59b, D62, D63, D66, D69a, D70, D71, D72, D73 as potential closest prior art.

The Proprietor's own choice of closest prior art is the cluster of documents teaching nivolumab for use in melanoma at 3 mg/kg q2w, showing particularly a beneficial effect in PD-L1+ melanoma patients. This cluster of documents consists of **D14, D6, D69, D71, D71, D72, D73**.

### 19.1 The orthodox closest prior art: The D14 cluster.

According to the Proprietor, the cluster consists of **D14, D6, D69, D71, D71, D72, D73**.

The Division concurs with the Proprietor in the assessment of the said cluster, but also remarks that, equally, **D5** could be deemed part of it. It is true that it concerns a different clinical context, but such context is not defined in the opposed claims.

Moreover, following Opponent 5's submissions to the effect that Prof. Leonard's considerations are based on **D54a**, this document can be added to this cluster, because it provides for the treatment of melanoma with nivolumab 3 mg/kg q2w. (This even though, to be precise, D54a at page 3/28 suggests that "PD-L1 expression did not have clinically meaningful effects on the exposure of nivolumab", thereby placing itself slightly behind D14 in the suitability ranking.)

D14 can be taken as the prime representative document, because it provides a therapeutic regimen (3 mg/kg q2w) for PD-L1+ melanoma, and compares it with ipilimumab, with a combination with ipilimumab, and their respective action also in respect of PD-L1- melanoma. It is, simply put, the most solid study from which the skilled person would start looking for improvements or alternatives.

### 19.2 The "unorthodox" alternative: D12

Opponent 5 submitted that it should be possible also to start from D12 as closest prior art, because D12a (and D12b) disclose the set up of a dose frequency optimisation for the treatment of NSCLC, comparing nivolumab 240 mg q2w to nivolumab 480 mg q4w. In this case, the

opposed claims differ from this disclosure only in one feature: the target disease (PD-L1+ melanoma instead of NSCLC). Opponent 5 drew the Division's attention to **T2443/18**; which allegedly shows that it is sometimes possible to start from a document disclosing the medical use of a compound as springboard for assessing the use of the same compound in a different disease.

The Division must take a cautious approach. T2443/18 remains an isolated decision and limited to facts germane to it. In that case, the claims concerned tapentadol for treating IBS. The "classical" closest prior art D3 was a document disclosing loperamide for treating IBS. The Board considered that it was possible to start *also* from D4, which concerned tapentadol for visceral pain. The Board observed that *"while D4 does not specifically refer to IBS, visceral pain is a typical manifestation of IBS, the therapeutic indication named in claim 1 of the patent in suit. In view of this considerable overlap in technical features and purpose... D4 cannot be ruled out as a suitable starting point for the assessment of inventive step" (reason 2.10)*. The Board further noted that *"the subject-matter of claim 1 of the patent in suit differs from the disclosure of document D4 only by giving a more specific medical indication, namely IBS instead of visceral pain" (reason 2.12)*.

The present case does not fall under the same *ratio decidendi*, because melanoma is not a more specific medical indication of lung cancer; nor is one a typical manifestation of the other. There is, of course, a common mechanism of action (PD1 axis blockade), but the actual efficacy of a cancer depends on the cancer: it is well known that some cancer respond to certain checkpoint inhibitors, others do not. There are other factors that influence efficacy, such as the balance between growth rate of the tumour and immunological attack, type and extent of blood supply to the cancer, etc - all of which was not a concern in T2443/18.

Moreover, the alternative document D4 in T2443/18 provided evidence that tapentadol was effective in models of visceral pain. In contrast, D12 sets out a regimen to be tested, but does not provide results. Against this background, it is not certain that the *ratio decidendi* of T2443/18 applies to the present situation. In the following considerations, it will be **assumed for the sake of argument** that it does.

### 19.3 Less suitable or unsuitable springboards

All other documents are either unsuitable or less suitable than the D14 cluster. If we were, *arguendo*, to accept D12 as a valid alternative for an inventive step attack, some documents are also less suitable than D12. That being the case, D14 and, if applicable D12 remain to pole-position candidates for the most promising springboards, and all other they cannot be accepted as equivalent starting points.

#### 19.3.1 **D2** relates to the treatment of solid tumors, including but not limited to melanoma using an anti-LAG-3 antibody and nivolumab. It further teaches on page 64, first paragraph, that the expression of inter alia PD-L1 of the tumor tissue can be measured using an IHC assay and

formalin-fixed paraffin-embedded (FFPE). It indicates nivolumab in this context can be administered at a dose of 80 or 240 mg (claim 1). This document is conceptually more remote from the invention, at least insofar as the examples are concerned. Moreover, to arrive at the opposed claims, this documents requires more modifications tha

- 19.3.2 **D9** is the EMA monograph for nivolumab. It does not specifically focus on PD-L1+ melanoma, nor does it disclose flat doses. It is a general document that is far less informative in respect of the opposed invention than D14. Moreover, D9 seems to suggest that nivolumab's efficacy did not appear to be related to PD-L1 expression (§2.3.4), or at least the role of this marker was still uncertain. See also Table 16, OS seems to be better in PD-L1- than in PD-L1+ subjects. With this regard, is not even a particularly promising springboard at all.
- 19.3.3 **D11** concerns the treatment of NSCLC with PD-1 blockers, including nivolumab or pembrolizumab. Nivolumab can be administered through per-kg regimens [93]-[95], or through flat doses [96] including 240 mg q2w [178]. It does not specifically concern PD-L1+ melanoma, and it is not specifically geared towards monotherapy. It is less relevant than D14 or D12 (which at least mentions 480 mg!).
- 19.3.4 **D18** is the protocol of the clinical trial reported in D14. Similarly, **D32** reports that clinical trials were ongoing, but does not provide results - and moreover seems to promote combination therapies, not monotherapies with nivolumab. Since D18 and D32 do not provide results, whereas D14 does, they are by definition *less promising* springboards than D14.
- 19.3.5 **D33, D40, D66** concern phase I trials of nivolumab in solid tumors; they are not specifically geared towards PD-L1+ melanoma, comparing per-kg doses q2w. They are less relevant than the D14 cluster or even D12, so these documents are to be relegated to the class of (far) *less suitable* springboards.
- 19.3.6 **D43** is an overview of checkpoint therapies. It does not specifically concern nivolumab for treating PD-L1+ melanoma, and does not mention any regimen. It is *not a suitable* springboard at all.
- 19.3.7 **D44** reports and comments on clinical trials of nivolumab in patients with melanoma, mentioning interesting results in particular in PD-L1+ patients. It mentions treatment by administration of nivolumab q2w, but the dosage is unclear ("up to 10 mg/kg"); it can be assumed that 10 mg/kg was tested q2w. It is *less suitable* a springboard than D14.
- 19.3.8 **D55** concern a phase I trial of nivolumab in solid tumors; they are not specifically geared towards PD-L1+ melanoma. They mention per-kg doses of nivolumab. It mentions at page 3168R that some patients received two more doses at 12 and 16 weeks - 4 weeks apart, but in respect of per-weight doses, not flat doses (much less 480 mg); this has nothing to do with a flat regimen of 480 mg q4w. It is less relevant of D14 or even D12, so D55 is to be relegated to the class of (far) *less suitable* springboards.

19.3.9 **D59b** and **D63** concern phase I trials for nivolumab in combination with other antibodies. In the combination arm, nivolumab is given at 80 and 240 mg (flat) q2w in generic solid tumors. They do not concern specifically PD-L1+ melanoma. They are *less suitable* springboards than D14 or D12 (which at least mentions 480 mg!)

19.3.10 **D62** concerns the treatment of lung cancer with an induction phase involving the combination of nivolumab 1mg/kg + ipilimumab 3 mg/kg q3w x 4; followed by a maintenance phase with nivolumab 240 mg IV q2w. It is *less suitable* a springboard than D14 or D12 (which at least mentions 480 mg!)

19.3.11 -- Note --

Opponent 4 has explicitly maintained their attacks bases on D2, D11, D40, D43, D44 (submission of 04.01.2024 section VI.1). Opponent 5 has explicitly maintained their attacks bases on D55, D66, D40 as closest prior art (submission of 04.01.2024 section I.21), which in their view the Division has "wrongly dismissed as unsuitable starting points".

The Division would have to firmly reject this approach. The applicable rules are clear. A multiple problem-solution approach is allowable only if it is shown that the documents are truly equivalent. Even in T2443/18 this principle was not questioned. It is not enough that a given document be somewhat reasonable as a springboard: it must be as reasonable as the other closest prior art. The Division has explained why the aforementioned documents are unsuitable or less suitable than the D14 cluster -- or even less suitable than the "unorthodox alternative" D12. No cogent explanation other than assertions that they are "excellent springboards" has been put forward to show that they are actually as good as D14, or in the alternative as good as D12 if that approach is taken.

Therefore, D2, D11, D40, D43, D44, D55, D66 would have to remain excluded from the pool of potential "closest prior art".

#### 19.4 Problem-solution approach starting from D14 cluster

19.4.1 The assessment can start from D14, a specimen of the cluster of closest prior art.

D14 discloses the treatment of melanoma with nivolumab alone, with ipilimumab alone, and with a combination of nivolumab+ipilimumab. Samples from the patients treated were assessed for PD-L1 expression on their surface by IHC (using antibody 28-8, see page 25L). Of the patients treated with nivolumab alone, 25.3% had PD-L1 positive tumours (Table 1). PFS in patients with PD-L1 positive tumours was similar with nivolumab or nivolumab+ipilimumab, and better than ipilimumab alone (Fig 1B). *The nivolumab-only regimen was 3 mg/kg q2w* (page 24R).

19.4.2 The difference between the teachings of D14 and the subject-matter of the opposed claims lies in the nivolumab *regimen*.

19.4.3 The effect of the difference is (i) presumed reasonable anti-cancer efficacy -- as well as (ii) lower risk of errors and ease of manufacture (flat dose) and (iii) less inconvenience to the patient (going to the hospital only once a month instead of once a fortnight).

The effect (i) "reasonable efficacy" is plausible and achieved. The regimen of 3 mg/kg q2w was shown to be effective for treating melanoma in the examples. It can be translated (taking an average weight of 80 kg) as a flat dose of 240 mg q2w. Given that the elimination half-life of nivolumab is 26.7 days (see inter alia D19, page 23, pharmacokinetics; or D54a), it is plausible that a double dose with double interval will work, too. This is confirmed by later publications, see D27 and D75. Since the effect is made plausible, D27 and D75 are admissible as confirmation that indeed this dosage-regimen works as predicted.

In the reply to the notices of opposition, the Proprietor argued that the regimen of 480 mg q4w can be associated with *improved overall survival* compared to the 3 mg/kg q2w of D14. The Division sees no evidence in the opposed patent supporting this view. Support is found only in D75, a later document. But then, "improved OS" is not an effect encompassed by the technical teachings of the original application in the sense of G2/21, so D75 cannot be taken into account for this particular purpose, as per T258/21.

The effects (ii) and (iii) are self-evident.

19.4.4 It follows that the objective problem to be solved is the provision of a dosage regime which is more convenient to the patient and less prone to error.

19.4.5 The solution is to administer it as a flat dose of 480 mg q4w.

19.4.6 The solution is not inventive, for the following reasons.

A person skilled in the art will always try to solve the objective technical problem as formulated above and does not need any motivation or suggestion to find alternative solution in the prior art. It is the normal task of the skilled person to be constantly occupied with the elimination of deficiencies, the overcoming of drawbacks and the achievement of improvements of known devices and/or products (see T15/81, T195/84).

In the assessment of the Division, the skilled person would self-evidently choose the most convenient mode of administration that remains effective. It is obvious that a flat-dose injection once a month meets the requirements of convenience, and such have been proposed (albeit for other cancers) in D12. Indeed, D12 proposes 480 mg q4w for treating lung cancer, so conceptually this regimen is not new as such.

The question is whether the skilled person would have had a reasonable expectation of success, given that D12 proposes the said flat-dose regimen but does not actually provide any data. Would the obviously more convenient regimen remain effective?

This is the case - **also because, if it were not so, the patent would be insufficiently disclosed. This is because the distinguishing feature, i.e. the 480 mg q4w regime, is merely a selection from among a long list of possibilities which have not been tested by the inventors, but only recited as fallback positions in the original application.**

It is within the normal tasks of the person skilled in the art to verify whether a proposed regimen stands a chance of working. The skilled person would have knowledge of the basic phase I and pharmacokinetic data. They would know that:

(a) Not all antibodies are suitable for flat dose administration, but those with a reasonably wide therapeutic window are good candidate for flat dose administration (D16). D16 does not disclose that nivolumab is among the antibodies known to be suitable for flat-doses, but the skilled person would suspect it might be because nivolumab is known to have an unusually large therapeutic window.

(b) D54a Table 4 reveals that the therapeutic window of nivolumab is quite large, with 0.1-10 ug/kg q2w being safe and effective - albeit with an optimum at 3 mg/kg (which thus became the standard dosage, used in D14 and in the examples of the opposed patent). Tables 6-7 provide pharmacokinetic data for the doses 0.1, 0.3, 1, 3 and 10 mg/kg. For the lowest dose, the one-dose C<sub>min</sub> is 0.3 ug/ml, the C<sub>max</sub> after nine doses is 3.7 ug/ml. For the highest dose, the one dose C<sub>min</sub> is 56.5 and the C<sub>max</sub> after nine doses is 475 ug/ml.

(c) Thus, even one dose of 0.1 mg/kg leads to a serum level of 0.3 ug/ml. This means that it is sufficient to reach a clinical effect, since the EC<sub>50</sub> of nivolumab is 0.1 ug/ml (D54a, page 31).

(d) Nivolumab has a rather long half-life in the blood. D54a further reveals that nivolumab has a mean half-life of 26.7 days in patients receiving 0.1-20 mg/kg. D55 at page 3171R reports that the serum concentrations of nivolumab (aka MDX-1106) have a serum half life of 12 days (0.3-3 mg/kg dosage) to 20 days (10 mg/kg). PD1 occupancy appeared dose independent, with a mean peak of 85% and a mean plateau occupancy of 72% lasting even 57 days.

(d) The dosages considered in D54a and D55 (0.1-10 mg/kg q2w ) can be translated to 8 mg to 800 "flat dose" q2w for the notional patient of 80 kg.

D12 represents a "dose frequency optimisation". It takes patients who already received 4 months of nivolumab at 3 mg/kg q2w or the corresponding flat dose of 240 mg q2w, and sets out to check what is the optimal long-term maintenance: 240 mg q2w or 480 mg q4w. Given the pharmacokinetic properties listed above, there no reasonable doubt that either regimen will be able to sustain therapeutic serum levels and therapeutic PD1 occupancy rates. Therefore, they are to be presumed as equivalent alternatives, of which 480 mg q4w is obviously the more convenient, unless it is shown that unexpectedly 480 mg q4w turns out to be inferior. Indeed D12a Brief Summary reads: "*The primary objective of this study is to show that PFS*

*(progression-free survival) rate at 6 months and at 1 year after randomization, of nivolumab 480 mg every 4 weeks is non-inferior to nivolumab 240 mg every 2 weeks in subjects with advanced/metastatic (Stage IIIb/IV) NSCLC (non-Sq and Sq)". (emphasis added)*

The Proprietor has argued that the skilled person is conservative; starting from 3 mg/kg q2w (the established regimen), they would in a first instance turn to the equivalent 240 mg q2w and not go "in one go" to 480 mg q4w. On the specific facts before the Division, this argument fails to persuade because D12 already sets out 480 mg q4w as a credible alternative to 240 mg. Choosing one or the other of the two valid alternatives is arbitrary (so no pointer is needed) and in any even the skilled person would choose the obviously more convenient equivalent alternative: why have the patient come to the hospital every two weeks when they can come once a month?

#### 19.5 Problem-solution approach starting from D12

*Arguendo:* Taken as an alternative closest prior art in accordance with T2443/18, D12a (and D12b) disclose the set up of a dose frequency optimisation for the treatment of NSCLC, comparing nivolumab 240 mg q2w to nivolumab 480 mg q4w.

The difference between the teachings of D12 and what is claimed in the opposed patent lies in the disease targeted.

In terms of effect, there is no more and no less than in D12. Neither D12 nor the patent show that 480 mg q4w is non-inferior to other options. This can only be set as a postulate.

The problem is to provide a further use for the regimen "nivolumab 480 mg q4w".

The solution is to use it in the treatment of PD-L1+ melanoma.

This solution is obvious because this cancer is known to respond to nivolumab (see D14 cluster). Indeed the choice of any cancer known to respond to nivolumab would be an arbitrary selection from a pool of equally likely candidates.

The Division realises that it is the normal job of a pharmaceutical company to find new applications for their products, so the above approach, while perhaps unorthodox according to the guidelines and classical case law of the EPO Boards of Appeal, is not entirely without merit.

However, the Division wishes to note that this approach can reasonably apply only to cases where the level of disclosure of the prior art and of the patent is the same. It should NOT be considered a panacea to refuse applications or revoke patents on the sole ground that they reflect similar approaches in other diseases. As always, inventive step (and sufficiency) depend on the specific facts of the case.