

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 (Princeton, NJ, USA)	Mewburn Ellis (T. Wolter, E. Couchman)
Opponent 1	Dr. H.U. Dörries (München, DE)	<i>pro se</i> (H.U. Dörries)
Opponent 2	Lederer & Keller (München, DE)	<i>pro se</i> (M. Fachini)
Opponent 3	Pajaro Ltd (London, UK)	Bird & Bird (M. Alt, A. Obermeier)
Opponent 4	Dr. E. Greiner (München, DE)	<i>pro se</i> (E. Greiner, S. Geiger)
Opponent 5	Dr. S. Pohlmann (München, DE)	<i>pro se</i> (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	Notice of Opposition 1 <u>Request:</u> Revocation in toto <u>Grounds:</u> Art. 100(a), 54, 56; Art. 100(b), 83;; Art. 100(c), 123(2) EPC. <u>Evidence:</u> D1-D11
08.12.2021	Notice of Opposition 2 <u>Request:</u> Revocation in toto <u>Grounds:</u> Art. 100(a), 53(c), 56; Art. 100(c), 123(2) EPC. <u>Evidence:</u> D1-D12, renumbered as per Annex 1
09.12.2021	Notice of Opposition 3 <u>Request:</u> Revocation in toto <u>Grounds:</u> Art. 100(a), 54, 56; Art. 100(b), 83;; Art. 100(c), 123(2) EPC. <u>Evidence:</u> BB1-BB21, renumbered as per Annex 1
10.03.2021	Notice of Opposition 4 <u>Request:</u> Revocation in toto <u>Grounds:</u> Art. 100(a), 56; Art. 100(b), 83;; Art. 100(c), 123(2) EPC. <u>Evidence:</u> D1-D21, , renumbered as per Annex 1

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 withdrawn.)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 withdrawn.)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

04.03.2024	Oral proceedings held by videoconference 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_{min} is 0.3 ug/ml, the C_{max} after nine doses is 3.7 ug/ml. For the highest dose, the one dose C_{min} is 56.5 and the C_{max} 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 EC₅₀ 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.