Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 30 January 2025

Case Number: T 0781/23 - 3.3.04

Application Number: 17702315.7

Publication Number: 3405495

IPC: C07K16/28, A61K39/395, A61P35/00

Language of the proceedings: EN

Title of invention:
Neutralization of inhibitory pathways in lymphocytes

Patent Proprietor:
Innate Pharma

Opponent:
Høiberg P/S

Headword:
NKG2A inhibition/Innate

Relevant legal provisions:
EPC Art. 100(a), 100(b), 54, 56, 87

Keyword:
Patent as granted: Priority - (yes) - presumption of validity
Novelty - (yes)
Inventive step - (yes)
Sufficiency of disclosure - (yes)

Decisions cited:
G 0001/21, T 0609/02, T 0895/13, T 2605/18, T 2623/18, J 0014/19, T 0019/20, T 0247/20, T 0499/20, T 0907/20, T 1132/22

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0

Case Number: T 0781/23 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 30 January 2025

Appellant: (Opponent)	Høiberg P/S Adelgade 12 1304 Copenhagen K (DK)
Representative:	Zwicker, Jörk ZSP Patentanwälte PartG mbB Hansastraße 32 80686 München (DE)
Respondent: (Patent Proprietor)	Innate Pharma 117, Avenue de Luminy 13009 Marseille (FR)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 20 February 2023 rejecting the opposition filed against European patent No. 3405495 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	D. Luis Alves
	A. Bacchin

Summary of Facts and Submissions

I. European patent No. 3 405 495, entitled "*Neutralization of inhibitory pathways in lymphocytes*", was granted on the basis of European patent application No. 17 702 315.7, filed as an international application published as WO 2017/125532 claiming priority from patent application US 62/281,217 filed on 21 January 2016.

The patent was granted with 13 claims. Claims 1, 12 and 13 read:

"1. An antibody that neutralizes the inhibitory activity of human NKG2A for use in treating cancer in a human individual who experiences progressive disease upon (during or following) treatment with an antibody that neutralizes the inhibitory activity of human PD-1."

"12. An invitro [sic] method for identifying an individual having a cancer who is a poor responder to treatment with an antibody that neutralizes the inhibitory activity of human PD-1, the method comprising:

a) determining levels of NKG2A expression on NK and/or CD8 T cells and/or numbers of NKG2A-expressing NK and/or CD8 T cells in an individual who has been treated with an antibody that neutralizes the inhibitory activity of human PD-1; and

b) upon a determination that the individual has increased levels of NKG2A expression on NK and/or CD8 T

cells and/or increased numbers of NKG2A-expressing NK and/or CD8 T cells, identifying the individual as a poor responder to treatment with an antibody that neutralizes the inhibitory activity of human PD-1."

"13. An antibody that neutralizes the inhibitory activity of NKG2A, for use in the treatment or prevention of a cancer in an individual who is being treated with an antibody that neutralizes the inhibitory activity of PD-1, the treatment comprising

a) determining levels of NKG2A expression on NK and/or CD8 T cells and/or numbers of NKG2A-expressing NK and/or CD8 T cells in the individual; and

b) upon a determination that the individual has increased levels of NKG2A expression on NK and/or CD8 T cells and/or increased numbers of NKG2A-expressing NK and/or CD8 T cells, administering to the individual an antibody that neutralizes the inhibitory activity of a human NKG2A polypeptide."

Claims 2 to 11 are dependent on claim 1.

II. An opposition was filed invoking grounds for opposition under Article 100(a) EPC in combination with Article 54 EPC (lack of novelty) and Article 56 EPC (lack of inventive step) as well as grounds for opposition under Article 100(b) and (c) EPC.

The opposition division decided to reject the opposition. The opposition division held, *inter alia*, that the ground for opposition in Article 100(c) EPC had not been substantiated and, therefore, the objection under this ground for opposition was not admitted. Further, it dismissed objections under

Article 100(b) EPC, and under Article 100(a) EPC for lack of novelty and lack of inventive step. Further, it held that the patent was entitled to the claimed priority. Document D17 was not admitted into the opposition proceedings.

III. The opponent (appellant) appealed this decision.

In its statement setting out the grounds of appeal, it contested the reasoning of the opposition division on sufficiency of disclosure, priority, novelty and inventive step. The decision was not contested in respect of the ground for opposition under Article 100(c) EPC. Documents D25 and D26 were filed.

IV. With the reply to the appeal, the patent proprietor (respondent) submitted arguments and claim sets of auxiliary requests 1 to 19.

V. The board summoned the parties to oral proceedings. In a communication pursuant to Article 15(1) RPBA, it informed them of its preliminary opinion on some of the substantive and legal matters concerning the appeal.

VI. Oral proceedings were held as scheduled. At the end of the oral proceedings, the chair announced the board's decision.

VII. The following documents are referred to in the present decision.

D2: Perez-Gracia *et al.*, Current Opinion in Immunology 27, 2014, pages 89-97

D6: Press release Innate Pharma "*Fourth clinical trial opened with Monalizumab (IPH2201)*", 2015, 4 pages

D7: Press release AstraZeneca "*AstraZeneca and Innate Pharma announce global co-development and commercialisation collaboration for IPH2201 in immuno-oncology*", 2015, 6 pages

D9: Innate Pharma Company Presentation at Jefferies Healthcare Conference June 2015, pages 1-19

D11: Pezo, RC and Bedard, PL, *ESMO Handbook of Translational Research*", 2015 Chapter 1, pages 1-11

D12: Press release Innate Pharma "*New data presented at AACR support for the rationale for combination treatment with monalizumab and durvalumab*", April 2016, 4 pages

D13: Innate Pharma Poster, Sola, C *et al.*, "*NKG2A immune checkpoint blockade enhances the anti-tumor efficacy of PD-1/PD-L1 inhibitors in a preclinical model*", 2016

D14: Bernardo, M *et al.*, Oncoimmunology 10(1) e1881268, 2021, pages 1-10

D16: Legal opinion of Michel Abello, dated 11 April 2022 and Exhibits 1 to 23

D18: Legal opinion of François Pochart, dated 17 November 2022

D19: Assignments for application US 16/071,499

D20 Decision 21/18398 of the Paris Court of Appeals

D21: English translation of D20

D23: Legal opinion of Michel Abello, dated 15 January 2023

D23a: Proprieté Industrielle Bulletin Documentaire 1971, No67 III 278

D23b: Proprieté Industrielle Bulletin Documentaire 1974, No125 I 159

D24: Legal opinion of François Pochart, dated 20 January 2023

D25: Segal *et al.*, Journal of Clinical Oncology 33(15), Supplement 3011, Meeting Abstracts 2015 ASCO Meeting, 2015

D26: Li, Y and Manuzza, RA, Frontiers in Immunology 5(123), 2014, pages 1-20

VIII. The appellant's arguments, where relevant to this decision, may be summarised as follows.

Main request (patent as granted)

Claim interpretation

Claim 1 related to treatment of two different patient groups and not to two different treatments. This was confirmed in dependent claim 4, which further specified that the treatment could be with a combination of antibodies for PD-1 and NKG2A blockade. This reading of claim 1 was further confirmed in the description of the patent (see paragraphs [0012], [0117] and [0119]).

Disclosure of the invention (Article 100(b) EPC)

Admittance of lines of argument into the appeal proceedings

Claims 12 and 13 had been objected to in the notice of opposition and therefore lines of argument relating to them should be admitted into the appeal proceedings. While the arguments relating to the tissue sample required for determining NKG2A and to a correlation of poor response to PD-1 inhibitor treatment with NKG2A levels or frequency of NKG2A-expressing cells had not been put forward in such detail in opposition

proceedings, they nevertheless built on the objections raised previously.

The patent did not disclose how to provide an antibody "*that neutralizes the inhibitory activity of human NKG2A*". The patent taught that any antibody binding to the extracellular domain of NKG2A would fulfil this requirement in the claims. However, this was not the case, as could be seen from document D26, which showed where NKG2A interacted with its ligand HLA-E. Insufficiency of disclosure of the antibody had been raised in the notice of opposition (see page 21, third paragraph and page 35, third paragraph), and therefore these lines of argument should be admitted into the appeal proceedings.

In general, the arguments put forward in the appeal proceedings built upon those presented during the opposition proceedings. This was admissible (see T 247/20). Moreover, the reference to assess whether a party's case had been amended was the decision under appeal. Points 2.6 to 2.16 of that decision, in particular points 2.10, 2.11 and 2.16, dealt with the examples in the patent and the conclusions that could be drawn from them. Therefore, arguments addressing the examples in the patent should be admitted into the appeal proceedings.

Examples 7 and 8 of the patent were contradictory and showed that treatment with an NKG2A inhibitor antibody only (monotherapy) did not have a therapeutic effect. Arguments regarding monotherapy had been submitted prior to the oral proceedings before the board, namely with the statement of grounds of appeal (see page 44, third paragraph and page 42, point 2.1.3, second

paragraph), but no direct comparison between Examples 7 and 8 had been made.

Admittance of document D26 into the appeal proceedings

This document represented common general knowledge. It concerned the interaction between NKG2A and its ligand, HLA-E. It was filed to support the argument that attaining antibodies that neutralise NKG2A as defined in the claims was an undue burden. Its filing was a response to the opposition division's decision, which had taken the appellant by surprise in considering the antibody to be sufficiently disclosed. So filing of document D26 did not constitute an amendment, rather, it built upon arguments on the lack of disclosure of the antibody filed with the statement of grounds of appeal.

Claim 1

The experimental results in the patent had not been obtained in a relevant animal model. Examples 5 to 8 did not show models of tumours that were resistant to PD-1-inhibitor therapy. In Example 6, 33% of the animals reacted to therapy with an antibody to PD-1. Examples 5, 7 and 8 did not show models of tumours resistant to a PD-1 inhibitor. Therefore, these examples did not allow conclusions to be drawn regarding a therapeutic effect of NKG2A inhibitor antibodies on poor responders to PD-1 inhibitor treatment.

A cell line resistant to anti-PD-1 antibody treatment would result in a resistant tumour in every animal. However, this was not the case in the examples in the patent. Example 6 characterised cell line A20 as being

particularly resistant to PD-1 inhibitor treatment, yet Figure 6 showed that a significant proportion of animals experienced complete tumour regression. Therefore, even if the tumour had acquired resistance, the cell line itself was not resistant and could not be considered a model of a resistant tumour. Such a model was developed later (see document D14, page 2, left-hand column, second paragraph and Figure 1). Moreover, to draw conclusions, the tumour should be homogeneous, that is, every tumour cell should be resistant. The same cell line was used in Examples 7 and 8 as in Example 6. As regards Example 5, no mention of resistance was made. Moreover, while it was not disputed that some of the animals develop resistant tumours, many did not, and it was not possible to determine whether those responding to NKG2A blockade were resistant to PD-1 blockade.

The patent did not show that NKG2A expression was responsible for resistance to PD-1 blockade. The NKG2A expression observed in Example 6 did not result from PD-1 blockade but from the establishment of the tumour. Furthermore, the observations in Example 4 could not be extrapolated to A20 models, which were used in Examples 5, 7 and 8.

Furthermore, Example 6 used only animals experiencing a moderate reduction in tumour with PD-1 treatment, and there was no comparison with the effect on tumours that had not been treated with PD-1 blockade (see page 52 of the patent application). It was indicated only that 10% of the CD8+ T cells in the tumour expressed NKG2A.

Additionally, the claim encompassed treatment with an antibody to NKG2A, following treatment with an antibody to PD-1 (monotherapy). However, the patent did not show

a therapeutic effect for monotherapy since Examples 5 to 8 related to combination therapy, i.e. therapy with both an anti-NKG2A antibody and an anti-PD1 antibody. Further, Examples 7 and 8 contradicted each other and showed that there was no benefit to monotherapy.

Example 4 had several deficiencies in demonstrating a correlation between resistance to anti-PD-1 treatment and the frequency of NKG2A NK/T cells among tumour infiltrating lymphocytes (TILs): (a) it did not compare NKG2A expression in responders versus non-responders; (b) it showed a low number of $NKG2A^+$ NK/T cells, calling into question the relevance of NKG2A inhibition for therapy; (c) that number was inconsistent with the number in Example 3; (d) NKG2A expression in TILs was only of relevance to tumours expressing the NKG2A ligand, HLA-E (see document D9). Moreover, despite its title referring to resistance, it did not include any evidence that the animals were resistant.

Example 3 contradicted the assertion that cells expressed NKG2A as a result of PD-1 blockade: for the same cell line (MC38) used in Example 4, 43% of the CD8+ T cells were double positive without PD-1 treatment. The results in Example 3 did not make credible that NKG2A increased with PD-1 blockade since the expression levels were high in the untreated animals.
The high variability between Examples 3 and 4 implied that no conclusions could be drawn on a correlation between NKG2A expression and PD-1 treatment. The model was not suitable for drawing this conclusion.

Even if Examples 5 to 8 were relevant to the suitability of anti-NKG2A therapy, despite the animal models used, this would only apply to one embodiment in

claim 1, namely that relating to individuals who experience disease progression following treatment and not to those experiencing disease progression "*during*" treatment.

Claims 12 and 13

In addition to the lines of argument applicable to claim 1, the invention defined in these claims lacked disclosure as regards the sample on which the determination of step a) was to be carried out.

Priority

The patent was not entitled to the priority date claimed because the applicants were not the successors in title of the applicants for the priority document from which priority was claimed.

The filing of the priority application in the United States in the name of the inventors as applicants was not a requirement but a choice. Consequently, to validly claim priority, a transfer of rights prior to filing the European patent application was required. Furthermore, there was no basis in the EPC for considering that the US provisional application had been filed by the inventor-applicants on behalf of their employer, the applicant of the patent in suit. The right to claim priority was distinct from the right to file a patent application, and the right to claim priority therefore belonged to the applicants of the priority application, i.e. the inventors (see document D18). Since there was no evidence that a transfer of this right had occurred, the priority was not validly claimed by the applicant. Moreover, the evidence filed by the respondent with document D16, in particular

Exhibits 15, 16 and 17, was not relevant under the applicable law, namely French law. The submitted email exchanges involving some of the inventors was not sufficient evidence of a transfer of rights.

Novelty (Articles 100(a) and 54 EPC)

Claim 1 was not novel in view of the disclosure in each of documents D6, D12 and D13. Claims 12 and 13 were not novel in view of the disclosure in each of documents D12 and D13.

Documents D12 and D13 were to be taken into account for the assessment of novelty because the patent was not entitled to the claimed priority date. These documents disclosed in combination all features of claims 1, 12 and 13.

Claim 1 was also not novel in view of document D6. It disclosed cancer patients who did not respond to treatment with anti-PD-L1 antibody (see page 3, second paragraph). It further disclosed a planned clinical trial for treatment of solid tumours with the combination of an anti-PD-L1 antibody (durvalumab) and an anti-NKG2A antibody (monalizumab) (see page 3, fifth and sixth paragraphs). Therefore, this document disclosed the combination therapy for poor responders to PD-1-inhibitor treatment.

Inventive step (Articles 100(a) and 56 EPC)

The closest prior art was represented by document D6, disclosing poor responders to PD-1 blockade, the patient group in claim 1 (see page 3, first to third paragraphs). Claim 1 differed therefrom in the treatment with NKG2A blockade.

The patent did not make credible that the problem of providing a therapy for patients as defined in claim 1 had been solved. Examples 4 and 6 of the patent did not show any treatment; Example 8 did not show a treatment response to monotherapy and did not use a model for patients as defined in claim 1. Therefore, the problem should be formulated as the provision of an alternative medicament for administration to the patient as defined in claim 1.

The solution in claim 1 was obvious from document D6 taken alone. It disclosed that therapy with the PD-L1 inhibitor durvalumab resulted in a very low response rate and that other checkpoint inhibitors had been tested and had shown some therapeutic effect. New treatment options were needed (see page 3, paragraphs 2 to 3). From this disclosure, the skilled person would have considered other checkpoint inhibitors a solution to the above-mentioned problem. On the same page, the checkpoint inhibitor monalizumab, which targets NKG2A, was disclosed (see paragraphs 5 and 6), as well as a planned clinical trial for the combination of durvalumab and monalizumab (see sixth paragraph, second sentence). Therefore, the claimed solution was obvious.

The solution was also obvious in view of the disclosure in any of documents D7 or D9.

Document D7 disclosed the planned clinical trial with a combination of the PD-1 inhibitor durvalumab and the NKG2A inhibitor monalizumab (see page 3, second paragraph). The skilled person knew from this document that solid tumours overexpressed HLA-E, and, therefore, these tumours were a target for treatment with monalizumab. The skilled person also knew from

document D6 that squamous cell cancer of the head and neck (SCCHN) expressed HLA-E and would understand that HLA-E was a suitable target for further treatment with monalizumab. Therefore, the solution in claim 1 was obvious from document D6 in view of document D7.

Also, document D9 disclosed that many solid tumours expressed HLA-E. This made them a target for monalizumab. Therefore, the solution was also obvious from document D6 in view of document D9.

Claim 12 did not involve an inventive step either. It was common general knowledge that cancer treatments were first initiated after verification that the target protein of interest was actually expressed at a significant or increased level in the tumour tissue (see document D11), and document D9 disclosed that HLA-E was overexpressed in many tumour types, this implying to the skilled person that the tumour would be particularly resistant to NK and CD8 T cells expressing NKG2A. As treating patients as defined in claim 1 with antibodies inhibiting NKG2A was obvious in view of documents D6 in combination with D7 or D9, as discussed for claim 1, claim 12 also lacked an inventive step over document D6 taken alone or further in view of any of documents D7 or D9 since the method of determining the patient group benefiting from treatment with antibodies inhibiting NKG2A activity merely amounted to routine procedure in the art.

Claim 13 lacked inventive step over document D6 taken alone and in view of document D7, D9 or D11. Document D6 disclosed that therapy with durvalumab resulted in a low response rate and that a clinical trial of the combination of durvalumab and monalizumab was planned. Claim 13 differed therefrom in that the therapy

comprised a step of determining whether the patient had increased levels of NKG2A expression on NK and/or CD8 T cells and/or increased numbers of NKG2A-expressing NK and/or CD8 T cells. There was no technical effect that could be taken into account since the claim was not limited to combined therapy with a PD-1 inhibitor and an NKG2A inhibitor. The objective technical problem was the provision of a therapy to treat the tumour of an individual that had been treated with an antibody that neutralises the inhibitory activity of human PD-1 and which had been shown to have increased expression and/or increased frequency of NKG2A in NK and/or CD8 cells. The solution to this problem was obvious from document D6 taken alone. D6 disclosed that clinical studies with other checkpoint inhibitors were ongoing and that HLA-E was present on many tumour cells. Therefore, the skilled person would have considered using an antibody that neutralises the inhibitory activity of NKG2A. Moreover, document D6 disclosed that a phase II combination therapy using monalizumab and durvalumab in solid tumours was planned. It was common general knowledge that cancer treatments were first initiated after verification that the target protein of interest was expressed (see document D11). Thus, the subject-matter of claim 13 did not involve an inventive step in view of documents D6 and D11.
Furthermore, the skilled person starting from the planned clinical trial for the combined therapy would also have considered combining different checkpoint inhibitors (see document D2). In this way, the skilled person would have arrived at the combined therapy. Moreover, the skilled person seeking to solve the posed problem would have considered the disclosure in each of documents D7 and D9 and would have used an antibody that neutralises the inhibitory activity of NKG2A to treat an individual that has been treated with an

antibody that neutralises the inhibitory activity of human PD-1 and which has been shown to have increased expression and/or increased frequency of NKG2A in NK and/or CD8 cells.

IX. The respondent's arguments, where relevant to this decision, may be summarised as follows.

Main request (patent as granted)

Claim interpretation

Claim 1 related to two patient groups defined by the severity of the cancer.

Resistance to treatment by PD-1 blockade did not mean complete resistance. On the contrary, according to the patent, "*poorly responsive*" meant that the cancer was not fully responsive, had progressed or had regressed (see paragraph [0009]).

Disclosure of the invention (Article 100(b) EPC)

Admittance of lines of argument into the appeal proceedings

During the opposition proceedings, it was only argued that the animal models in the examples of the patent did not represent the patient group defined in claim 1. The fact that PD-1 inhibitor treatment caused an increase in NKG2A expression was never questioned. This constituted an amendment to the appellant's case.

Likewise, attaining the NKG2A inhibitor antibody as defined in the claims was not questioned during

opposition proceedings. The passage on page 21 of the notice of opposition concerned the suitability of the antibody for attaining the therapeutic effect in the claim, rather than any undue burden in attaining the antibody itself.

Many of the appellant's arguments were new in appeal, including: challenging the correlation between an increase in NKG2A and a poor response to PD1 blockade; questioning the relevance of targeting NKG2A for tumour cells not expressing the ligand HLA-E; questioning aspects of the measurement of NKG2A, including which sample should be used; objecting to claims 12 and 13, in particular step (a); and questioning, based on document D26, the relevance of where the antibody binds on NKG2A. The alleged contradiction between Examples 7 and 8 also constituted an amendment to the appellant's case. Even if those examples were mentioned in the decision under appeal, submitting new arguments based on them was not justified by the decision and constituted an amendment of the appellant's case. The same applied to the arguments on lack of a therapeutic effect with monotherapy.

Admittance of document D26 into the appeal proceedings

Even if document D26 represented common general knowledge, it should not be admitted into the proceedings as the reasons for its filing were not properly given.
It should not be admitted into the appeal proceedings since it was filed in support of an argument that was never made in the first-instance proceedings and should therefore not be admitted into the appeal proceedings. As reasons for its admittance had not been provided with its filing, the applicable provision for reasons

provided at oral proceedings before the board was Article 13(1) RPBA.

Claim 1

The animal models in the examples in the patent showed the therapeutic effect in animals resistant to treatment with an anti-PD-1 antibody. The title of Example 4 confirmed this. It resulted from a conclusion drawn by the inventors and could not be discarded unless there were serious doubts. The appellant argued that the tumour cell line did not represent a resistant tumour. However, the cell line used was the same as in document D14. Also, Figure 1B of this document showed disease regression, while it referred to a PD-1 resistant animal model. Indeed, this document confirmed that the cell line increased resistance with PD-1 inhibitor treatment, this being consistent with what was observed in the patent. Therefore, the model based on this cell line was suitable for making the therapy in the PD-1 resistant patient group defined in claim 1 credible.

The appellant argued that in a model of resistant tumours, all tumour cells would be resistant. However, tumours evolved, regardless of the cell line in question. A homogeneous tumour would not reflect the reality in a human patient.

Example 4 showed a mechanism by which tumours escape PD-1 blockade. It provided for a comparison between treated and untreated animals. There was not much variability within the experimental results (see Figure 4 and statistical analysis). The NKG2A expression necessarily referred to mice in which the

tumour was resistant to anti-PD-1 treatment as the mice with complete tumour regression did not have a tumour.

The fact that in Example 3 the cell line MC38 expressed NKG2A even in the absence of PD-1 treatment confirmed that it was resistant.

Examples 3 and 4 were not directly comparable – see tumour sizes. Therefore, any variability between these examples did not cast doubts on the conclusions drawn from them.

Also Example 6 referred to PD-1 resistance in its title. The cell line was Qa1-, as could be seen from Example 1. Example 6 demonstrated that the cell line began to express Qa1 when treated with a PD-1 inhibitor antibody. The results necessarily related to animals with tumour rather than to a mixed population since the animals that responded to treatment with an anti-PD-1 antibody exhibited complete regression, which meant that there was no tumour, and these were therefore not included in these results (see Figure 6).

Figure 7 showed that in most animals there was no tumour regression with PD-1 blockade. Examples 5, 7 and 8 showed that it was possible to achieve tumour regression with treatment with an anti-NKG2A antibody. In Example 5, it was shown that the immune cells responded to treatment (see Figure 1B, compare NKG2A in RMAS vs A20).

Priority

In accordance with decisions G 1/22 and G 2/22, there was a rebuttable presumption that the applicant claiming priority is entitled to priority. Therefore,

it was the appellant's burden to demonstrate the facts that supported serious doubts about the applicant's entitlement to priority (see point 110 of the reasons). The rebuttable presumption was subject to the autonomous law of the EPC only, so national laws did not apply. Therefore, the patent was entitled to the priority date claimed.

Novelty (Articles 100(a) and 54 EPC)

Documents D12 and D13 were published after the priority date validly claimed by the patent and therefore did not form part of the state of the art according to Article 54 EPC.

Document D6 disclosed the results of a study with durvalumab. Out of 62 patients, 55 did not respond to treatment. It also disclosed separate clinical studies involving other checkpoint inhibitors. It, however, did not disclose that any of the patients in the study with durvalumab were subsequently treated with an NKG2A inhibitor antibody. The passage announcing a planned clinical trial involving the combination of durvalumab with monalizumab appeared in a separate passage under a different heading. Therefore, claim 1 was novel.

Inventive step (Articles 100(a) and 56 EPC)

Claim 1 differed from the disclosure in document D6 in that it provided a treatment for patients who experienced disease progression upon treatment with a PD-1 inhibitor, i.e. by the administration of an antibody that neutralises the inhibitory activity of human NKG2A.

Tumours evade therapy targeting the PD-1/PD-L1 axis by relying on the inhibitory activity of NKG2A. This technical concept was made credible in the patent.

Thus, the objective technical problem was the provision of an effective therapy for the treatment of cancer in humans experiencing progressive disease upon treatment with an antibody neutralising the inhibitory activity of human PD-1.

The claimed solution was not obvious from document D6 because the fact that a clinical trial was planned involving durvalumab and monalizumab would not make it obvious that monalizumab could be used to treat those patients who did not respond to durvalumab. The mechanism through which these cancers became resistant to treatment was unknown, and the link between NKG2A inhibition and resistance to anti-PD-1/anti-PD-L1 could not be derived from the prior art.
The disclosure in documents D7 and D9 did not go substantially beyond that in document D6. Therefore, the subject-matter of claim 1 was not obvious in view of these documents either.

The same applied to claim 12 for the following reasons. Document D6 only disclosed that poor responders to durvalumab monotherapy existed. It did not disclose a method for identifying a cancer patient who is a poor responder to such a therapy. Thus, the objective technical problem was the provision of a method for assessing what patients respond poorly to treatment with an antibody that neutralises the inhibitory activity of human PD-1. None of the documents D7, D9 and D11 suggested that NKG2A would be a good predictive marker. Therefore, the subject-matter of claim 12 was not obvious.

As regards claim 13, the same objective problem could be formulated as for claim 1. It was not obvious for the same reasons presented for claims 1 and 12.

X. The appellant requested that the decision under appeal be set aside and that the patent be revoked; that documents D18 to D21, D25 and D26 be admitted into the appeal proceedings; that documents D22, D23, D23a and D23b not be admitted into the appeal proceedings; that, if the board were to admit documents D23, D23a and D23b into the appeal proceedings, also document D24 be admitted; that all arguments submitted with the statement of grounds of appeal be admitted into the proceedings; that auxiliary requests 5 to 19 not be admitted into the appeal proceedings.

The respondent requested that the appeal be dismissed and that the patent be maintained as granted; alternatively, that the patent be maintained in amended form on the basis of one of the auxiliary requests 1 to 19 filed with the reply to the statement setting out the grounds of appeal; that documents D17 to D21 and D24 to D26 not be admitted into the appeal proceedings; that document D22 be admitted into the appeal proceedings; that documents D23, D23a and D23b be admitted into the appeal proceedings if any of D18 to D21 were admitted; that several of the arguments of the appellant not be admitted into the appeal proceedings.

Reasons for the Decision

Main request (patent as granted)

Claim interpretation

1. Claim 1 is drafted in the form of a purpose-limited product claim, pursuant to Article 54(5) EPC, and is directed to "*an antibody that neutralizes the inhibitory activity of human NKG2A*" for use in the treatment of cancer "*in a human individual who experiences progressive disease upon (during or following) treatment with an antibody that neutralizes the inhibitory activity of human PD-1*".

2. In the following, the board in some instances uses "NKG2A blockade" to mean treatment with an antibody that neutralises the inhibitory activity of human NKG2A and to "NKG2A inhibitor" to refer to that antibody. Likewise, "PD-1 blockade" is used to mean treatment with an antibody that neutralises the inhibitory activity of human PD-1 and "PD-1 inhibitor" to refer to that antibody.

3. In the appellant's view, the claim defines two patient groups: those who experience disease progression while on treatment with PD-1 blockade and those who experience disease progression following treatment with PD-1 blockade. The wording "*during or following*" thus relates to the time frame of disease progression in relation to the treatment with a PD-1 inhibitor rather than to the timing of administration of the NKG2A inhibitor. The board agrees with this claim interpretation.

4. The parties were in dispute as to whether the definition of the two patient groups also relates to different cancer severity between those groups. This, however, did not play a role in the board's decision.

Disclosure of the invention (Article 100(b) EPC) - Claims 1, 12 and 13

5. The opposition division dismissed objections to claims 1, 12 and 13. It considered the following lines of argument: in the patent, the effect of treatment with an anti-NKG2A antibody was not measured in animal populations resistant to treatment with a PD-1 inhibitor antibody, so there were doubts as to whether the therapeutic effect could be obtained; and there were doubts as to whether the therapeutic effect could be obtained with any antibody as functionally defined in the claim, i.e. including antibodies binding to a target other than NKG2A.

6. With the statement of grounds of appeal, the appellant (i) questioned, in several lines of argument, the experimental results in the patent, namely the relevance of the animal models for drawing conclusions on the therapeutic use, i.e. on the suitability for the patient group set out in the claim, and the correlation between NKG2A expression and resistance to PD-1 inhibitor treatment; (ii) questioned in several lines of argument, whether every antibody defined in the claim was attainable by the skilled person without undue burden - i.e. antibodies characterised only by the ability to neutralise the inhibitory activity of NKG2A; and (iii) raised specific objections against claims 12 and 13.

7. Admittance of lines of argument into the appeal proceedings

7.1 The respondent requested that any lines of argument newly brought forward in appeal proceedings not be admitted. According to the respondent, the arguments put forward during opposition proceedings only questioned the appropriateness of the animal models to show the suitability of the compound for treating the specific patient groups in the claim and the suitability of the functionally defined antibody for treating those patient groups, given that all examples related to one antibody but that the claim encompassed antibodies that could bind to targets other than NKG2A.

7.2 The primary object of the appeal proceedings is to review the decision under appeal in a judicial manner (Article 12(2) RPBA). In view of this primary object, Article 12(2) RPBA provides that a party's appeal case has to be directed to the facts, objections, evidence and requests on which the decision under appeal was based.

The point of reference for assessing whether any part of the appeal case has to be regarded as an amendment within the meaning of Article 12(4) RPBA is the decision under appeal and any part of the appeal case the party demonstrates was admissibly raised and maintained in the first-instance proceedings. On the other hand, the point of reference for assessing whether a case has been amended within the meaning of Article 13(1) or (2) RPBA is the statement of grounds of appeal or the reply (see J14/19, Reasons 1.2).

It follows that an amendment to a party's appeal case under Article 13 RPBA is, by analogy with Article 12(4) RPBA (with reference to Article 12(2) RPBA), a submission not directed to the requests, facts, objections, arguments and evidence relied on by the party in its statement of grounds of appeal or its reply. In other words, it goes beyond the framework established therein (see e.g. T 247/20 Reasons 1.3 endorsed e.g. in T 907/20, T 19/20 and T 499/20).

Thus, while parties must be allowed to refine their arguments, even to build on them, provided they stay within the framework of the appealed decision and the arguments and the evidence submitted in a timely fashion in the written proceedings in appeal (see T 247/20, confirmed in T 2605/18, T 2623/18 and T 1132/22), late-filed submissions containing factual elements could be disregarded (Article 114(2) EPC and Articles 12 and 13 RPBA).

This implies that in appeal it is possible to take into account, for instance, a precision of a previously pleaded line of argument, a refined illustration of what a party had already argued, or a further illustration or refinement of an objection within boundaries of the discussion which can reasonably be expected. Further elaborations which change the factual and legal framework of the appeal without any justification must not be considered.

For the reasons given in detail in the following, the submissions presented by the appellant under Article 100(b) EPC extend beyond the framework established by the appealed decision or by the statement of grounds of appeal and the reply because they contain factual elements which, far from constituting a mere refinement

of arguments, give rise to new issues for discussion. Since no justification is apparent for their filing only at the appeal stage, or at a late stage of the appeal proceedings, none of them is admitted into the appeal proceedings.

7.3 Claims 12 and 13

7.3.1 With the statement of grounds of appeal, the appellant argued that since these claims did not specify the sample to be used for determining levels of NKG2A expression and/or numbers of NKG2A-expressing cells, they lacked sufficient disclosure because it was not credible that poor-responding patients could be identified by NKG2A expression in tissue samples other than tumour tissue.

7.3.2 The appellant failed to indicate where it had presented this line of argument during opposition proceedings. Instead, it argued that claims 12 and 13 had been objected to in opposition proceedings, and despite not having been raised in as much detail, these arguments merely built on the objections raised in the notice of opposition.

7.3.3 However, the notice of opposition only challenged aspects present in claim 1. There was no mention of claims 12 and 13. These claims include a step a) of "*determining levels of NKG2A expression on NK and/or CD8 T cells and/or numbers of NKG2A-expressing NK and/or CD8 T cells*", which is not present in claim 1. Thus, it is apparent that the lines of argument presented in the notice of opposition could not have addressed this aspect specific to claims 12 and 13.

7.3.4 In agreement with the principles set out above (see point 7.2), particularly the fact that the new line of argument is not directed to facts and objections on which the decision under appeal was based, the board decided to not admit this line of argument into the appeal proceedings.

7.4 *Attaining the functionally defined antibody*

7.4.1 With the statement of grounds of appeal, the appellant brought forward the following lines of argument to question that every antibody as defined in the claim was attainable by the skilled person without undue burden.

(a) The antibodies claimed for use in treatment were merely defined by their function. For the skilled person, the identification of substantially all antibodies that neutralise the inhibitory activity of NKG2A represented an undue burden. The case law on claims directed to substances applied here because claim 1 was directed to a substance, even if for use in therapy.

(b) Not only did the patent not teach a suitable fragment of NKG2A to raise antibodies, it taught that any antibody that bound to the extracellular domain of NKG2A would fulfil the functional requirement in the claim. This was, however, not the case - see document D26 illustrating the interaction between NKG2A and its ligand HLA-E.

c) The claim was not restricted to antibodies that bind to NKG2A and included antibodies that would indirectly neutralise the inhibitory activity of NKG2A, such as an antibody to any antigen that has a function upstream or downstream of NKG2A or that binds to its ligand, HLA-E.

However, there was no teaching on how to obtain these antibodies.

7.4.2 As regards where in opposition proceedings objections concerning the antibody were raised, the appellant referred to the notice of opposition, page 21, third paragraph and page 35, third paragraph.

7.4.3 The first of these passages does refer to claim 1 as a reach-through claim, as argued by the appellant. However, from this passage, which concerns inventive step, it is clear that the argument is that a therapeutic effect has not been shown for every antibody as defined in the claim, i.e. an antibody "*that neutralizes the inhibitory activity of human NKG2A*", since the definition encompasses antibodies that bind to targets other than NKG2A. Thus, the attaining of the therapeutic effect was being questioned, not whether antibodies according to the definition in the claim could be provided. The same applies to the second passage cited.

7.4.4 The board concludes that obtaining the antibodies as functionally defined in claim 1 was never questioned during opposition proceedings. Applying the principles in point 7.2 above, particularly the fact that the new line of argument is not directed to facts and objections on which the decision under appeal was based, the board decided to not admit the line of argument into the appeal proceedings.

7.5 Suitability of an antibody to NKG2A, as a monotherapy, for treating patients as defined in claim 1 and contradiction between Examples 7 and 8

7.5.1 With the statement of grounds of appeal, the appellant submitted the following lines of argument relating to the examples in the patent.
(i) The examples do not show models of tumours resistant to PD-1/PD-L1-inhibitor therapy as several mice showed complete tumour regression.
(ii) Examples 5 to 8 relate to combination therapy (i.e. therapy with both an anti-PD-1 antibody and an anti-NKG2A antibody). They do not demonstrate an effect of monotherapy with an anti-NKG2A antibody (i.e. treatment with an anti-NKG2A antibody following treatment with an anti-PD-1 antibody), which is an embodiment also encompassed by the claims.
(iii) Example 4 has several deficiencies in demonstrating a correlation between resistance to anti-PD-1 treatment and the frequency of NKG2A+ NK/$CD8^+$ T cells among tumour-infiltrating lymphocytes (TILs).
(iv) Even if Examples 5 to 8 were relevant to the suitability of anti-NKG2A therapy, this would only apply to one embodiment in claim 1, namely that relating to individuals who experience disease progression following treatment and not those experiencing disease progression "*during*" treatment.
At the oral proceedings before the board, the appellant further argued that Examples 7 and 8 were contradictory and showed there was no benefit to monotherapy.

7.5.2 In opposition proceedings, Examples 5 to 8 were discussed merely in the context of the suitability of the animal models for representing the patient group defined in claim 1. It was not argued that they were evidence that the claimed antibody was not suitable for

treating cancer in that patient group. There was in particular no objection to the "*monotherapy*" embodiment, i.e. treatment with an NKG2A inhibitor following treatment with a PD-1 inhibitor. No distinction was made between the therapeutic effect in patients who experience disease progression following treatment versus during treatment. In other words, lines of argument (ii) and (iv) in point 7.5.1 above where not brought forward in opposition proceedings.

7.5.3 These lines of argument attack embodiments of the claims not questioned in opposition proceedings. During opposition proceedings, the focus was on a therapeutic effect of targeting the NKG2A checkpoint in patients who were poor responders to PD-1 blockade, regardless of the point in time of that poor response and whether they were still receiving PD-1 treatment. In that context, it was argued that the animal groups did not model a poor response to PD-1 blockade. A contradiction between Examples 7 and 8 of the patent was not argued until the oral proceedings before the board.

7.5.4 The appellant argued that the decision under appeal was the starting point for assessing whether there was an amendment to a party's case. The arguments in appeal that related to the examples in the patent addressed points 2.10, 2.11 and 2.16 of the decision under appeal. Therefore, the appellant argued, they should be admitted into the appeal proceedings.

7.5.5 However, upon proper consideration of these sections of the appealed decision, it is difficult to agree that the contested lines of argument address them. It instead appears that they introduce new issues for discussion beyond the framework established by the appealed decision. As regards a contradiction between

Examples 7 and 8, this line of argument, as stated above, was stated for the first time at the oral proceedings before the board.

Point 2.10 of the decision under appeal concerns determination of NKG2A expression in samples and its correlation to a poor response to PD-1 blockade. Point 2.11 concerns Example 6 and states that the A20 cell line was resistant to treatment with the anti-PD-1 antibody. Finally, point 2.16 relates to Figures 5, 7 and 8 to demonstrate an increased potency of the combination treatment with PD-1 and NKG2A blockade. It is thus apparent that the arguments questioning a therapeutic effect of monotherapy, including those based on a comparison of Examples 7 and 8, go beyond a mere response to points 2.10, 2.11 and 2.16 of the decision under appeal.

7.5.6 In view of the principles set out in point 7.2 above, the board decided to not admit these lines of argument into the appeal proceedings.

7.6 Further lines of argument of the appellant

7.6.1 The respondent requested that further lines of argument not be admitted into the appeal proceedings whereas the appellant submitted that these arguments merely refined and built upon those presented in opposition proceedings or addressed reasons in the decision under appeal.

7.6.2 In view of the conclusions reached below on the substance (see below point 11.), the board will not give reasons on the admittance of these lines of argument of the appellant.

8. Admittance of document D26 into the appeal proceedings

8.1 This document was filed by the appellant, with its statement setting out the grounds of appeal, in support of the line of argument summarised in point 7.4.1 above. In view of the decision of the board not to admit that line of argument into the appeal proceedings, there was no reason to admit the document.

9. Claim 1

9.1 In the case law of the Boards of Appeal, where a therapeutic application is claimed in the form according to Article 54(5) EPC, attaining the claimed therapeutic effect is a functional technical feature of the claim. As a consequence, to fulfil the requirements of sufficiency of disclosure, the suitability of the composition for the claimed therapeutic application must be derivable from the application, unless this is already known to the skilled person at the priority date (see T 609/02, point 9 of the Reasons and T 895/13 of 21 May 2015, points 3 to 5 of the Reasons). Once this suitability is derivable from the application, calling it into question presupposes serious doubts substantiated by verifiable facts.

9.2 Claim 1 relates to the treatment of patients who experience disease progression despite PD-1 blockade. It defines, for these patients, a treatment with NKG2A blockade. Thus, in the case in hand, the suitability of the antibody as defined in the claim for treating cancer in a patient as defined in the claim must be assessed.

9.2.1 The patent discloses as state of the art that the binding between PD-1 ligand on tumour cells and PD-1 on T cells results in a decrease in TILs and immune evasion by the tumour cells. This could be reversed by inhibiting the interaction of PD-1 with its ligand(s). This PD-1 blockade resulted in impressive anti-tumour responses, but in some cancers not all patients responded to treatment and some patients had cancers that relapsed after treatment (see page 2, lines 36 to 42). It was also state of the art that antibodies inhibiting NKG2A signalling could increase cytokine release and cytolytic activity of lymphocytes towards HLA-E-expressing tumour cells, and their use could induce control of tumour growth (see page 2, lines 24 to 30).

9.2.2 Example 4 of the patent demonstrates that the treatment of a tumour cell line with an anti-PD-1 antibody resulted in an increase in frequency of TILs expressing NKG2A.

This example is entitled "*Increased NKG2A expressing tumor infiltrating CD8 T cells in mice resistant to PD-1 treatment*". It thus relates to a model for resistance to PD-1 blockade. Mice bearing MC38 tumours were treated either with an anti-PD-1 antibody or with a control. NKG2A expression was measured in various tissue samples in both mice groups. The results show more than a 50% increase in NKG2A-expressing tumour infiltrating CD8 T cells for the PD-1 treated group versus control. The inventors concluded that NKG2A may "*have an increased contribution to the inhibition of the CD8 T cell response towards tumours in poor responders to anti-PD-1*".

9.2.3 Example 6 confirms this for cell line A20. This example is entitled "*An in vivo model of PD-1/-L1 resistant cancer*". It thus relates to a model for resistance to PD-1 blockade.

The cell line A20 expresses PD-L1 but not Qa-1^b, which is the HLA-E homologue in mice (see Example 6, first sentence). The animals were treated with anti-PD-1 or anti-PD-L1 antibodies or with a control. The inventors conclude that none of the antibodies resulted in a "*substantial anti-tumour effect*". However, Qa-1^b expression was induced on the surface of tumour cells, and more than 50% of tumour infiltrating NK cells and about 10% of CD8 T cells expressed NKG2A.

9.2.4 The board concludes from Examples 4 and 6 that in tumours (partially) resistant to treatment with PD-1 or PD-L1 inhibitors, NKG2A expression in TILs was involved in the tumour escaping the immune system. In view of the prior-art knowledge that inhibitors of NKG2A could increase the activity of lymphocytes towards tumour cells and be used to control tumour growth, it is credible that a patient who has increased levels of NKG2A expression or increased numbers of NKG2A-expressing NK and/or CD8 T cells following treatment with an antibody that neutralises the inhibitory activity of PD-1 would benefit from a treatment involving an antibody that neutralises the inhibitory activity of NKG2A.

9.3 As summarised above, Example 4 shows levels of NKG2A expression in anti-PD-1-antibody treated versus non-treated animals. The appellant argued that a comparison of responder versus non-responder animals was also necessary to draw conclusions. However, in the board's view, the objective of Example 4 was to demonstrate the

effect of anti-PD-1 treatment on NKG2A, and therefore the relevant comparison is with non-treated animals.

9.4 The appellant further disputed that the increased numbers of NKG2A-expressing cells in Example 4 referred to non-responder animals. It referred to the passage of the application on page 50, lines 29 to 32, which states that "[t]*he results suggest that in non responding mice there is a significant increase of CD8 T cells expressing NKG2A in comparison to mice treated with isotopic control mAb*". The appellant argued that the term "*suggests*" in this sentence was consistent with its assertion that Example 4 did not distinguish between mice that responded to PD-1 blockade and those that did not. Furthermore, it called into question that such a distinction would have been possible within the time frame of the experiment. Therefore, the conclusions were speculative. However, the board disagrees with this analysis of the term "*suggests*". In the board's view, it is inconsistent with the title of Examples 4 and 6 and with the concept underlying the therapeutic effect as stated in the patent in paragraph [0007].

9.5 The appellant also questioned the relevance of targeting NKG2A for treating tumours, pointing out that the number of NK- and T-cells expressing NKG2A was low. However, the appellant did not provide evidence of a relevant threshold or evidence of a treatment with an NKG2A inhibitor antibody which did not have a therapeutic effect.

9.6 The appellant noted a discrepancy in the number of NKG2A-expressing immune cells between Examples 3 and 4. In Example 3, the frequency of NKG2A-expressing TILs for non-treated mice was higher than for PD-1 treated

mice in Example 4, despite the tumour cell line being the same. This contradicted the assertion in the patent that NKG2A expression resulted from PD-1 blockade, which was based on Example 4. Therefore, it could not be concluded from these examples that there was a correlation between NKG2A expression and PD-1 blockade. The board considers that the results in Example 3 do not invalidate those in Example 4, which were obtained with a different experimental set-up. Consequently, it cannot be assumed that the results in Example 3 contradict those in Example 4. The appellant did not argue that Example 3 itself showed a decrease in NKG2A expression with PD-1 blockade.

9.7 According to the appellant, Example 4 did not show increased expression of the HLA-E homologue in mice, Qa-1^b, in the tumour. However, this was not determined in this example. Example 4 does not show an absence of expression either. Example 6, however, did show results for Qa-1^b, as set out above (see point 9.2.3). Document D9, cited by the appellant, confirms that many tumours overexpress the NKG2A ligand (see page 15), so document D9 does not support the appellant's argument. The appellant further argued that an increased frequency of NKG2A+ CD8+ T cells is a symptom of resistance to PD-1 blockade rather than the cause of resistance. However, this interpretation does not call into question that increased frequency of NKG2A-expressing TILs correlated with poor response to PD-1 blockade. This correlation is the rationale for targeting NKG2A in these patients. Therefore, neutralising the activity of NKG2A in these patients is the mechanism underlying the therapeutic effect, regardless of whether increased NKG2A expression is the cause or the consequence of poor response to PD-1 blockade.

9.8 The appellant also challenged the conclusions drawn from Example 6 on the basis that there was no comparison with expression levels in untreated tumour. However, Example 6 states that there was no expression of the ligand for NKG2A in the untreated tumour (see Example 6, first sentence). Consequently, this argument overlooks part of the information in the example and cannot be convincing.

9.9 The appellant disputed that the tumours in these animal models represented treatment-resistant tumours. However, the board notes that Examples 4 and 6 both refer to PD-1 resistance in their titles. To support its argument, the appellant referred to some animals that experienced total tumour regression. However, as the results in these examples are based on measurements of tumour cells and tumour infiltrating NK and T cells, they necessarily refer to animals that exhibited tumours, i.e. did not experience total tumour regression.

9.10 The parties disagreed on whether tumour resistance to PD-1 blockade is acquired, and whether, in view of this, a relevant animal model could be provided with a cell line that does not result in a resistant tumour in every animal. The appellant was of the view that to draw conclusions, the tumour should be homogenous and result for every animal in tumours resistant to anti-PD-1 treatment. The respondent was of the view that the tumours in the animals develop, leading to acquired resistance and to increased NKG2A expression.

9.11 Since the therapeutic effect in claim 1 relies on the causal link between PD-1 blockade and increased NKG2A

expression in TILs, these differences do not need to be addressed.

9.12 In conclusion, the appellant's lines of argument that the invention as defined in claim 1 is not sufficiently disclosed are not convincing.

10. Claims 12 and 13

10.1 The reasons set out above for claim 1 apply also to claims 12 and 13.

10.1.1 Claim 12 is directed to an *in vitro* method for identifying cancer patients who are poor responders to treatment with an antibody that neutralises the inhibitory activity of PD-1. At the basis of this identification are the numbers of NKG2A-expressing NK and/or CD8+ T cells or the levels of NKG2A expression in those cells. As set out above (see 9.2.4), a correlation between poor response to anti-PD-1 treatment and NKG2A levels is demonstrated in the patent. Therefore, the appellant's arguments are not successful.

10.1.2 Claim 13 is drafted in the form of a purpose-limited product claim, pursuant to Article 54(5) EPC, and is directed to an "*antibody that neutralizes the inhibitory activity of human NKG2A*" for use in the treatment or prevention of cancer "*in an individual who is being treated with an antibody that neutralizes the inhibitory activity of human PD-1*". It thus differs from claim 1 in the definition of the patient group. While claim 1 refers to "*an individual who experiences progressive disease upon (during or following) treatment*" with PD-1 blockade, claim 13 is limited to patients undergoing treatment. These patients are

further defined in step b) by increased NKG2A levels. As with claim 1, the therapeutic effect relies on the link between NKG2A expression and resistance to PD-1 treatment, and therefore the therapeutic effect of the anti-NKG2A antibody is credible for this patient group for the same reasons as for claim 1.

10.1.3 Further arguments by the appellant which concerned step (a) of determination were not admitted into the appeal proceedings (see point 7.3.4) and are not discussed further.

Conclusion

11. The ground for opposition under Article 100(b) EPC does not prejudice the maintenance of the patent.

Priority (Article 87(1) EPC)

12. The opposition division held that the patent was entitled to claim priority from the priority document, a US provisional patent application filed in the name of the inventors, with the consequence that documents D12 and D13 did not belong to the state of the art according to Article 54 EPC.

The opposition division considered two requirements for entitlement to priority: whether the applicant for the patent in suit was the successor in title of the applicants for the priority document (priority applicants) and whether the priority document was the first filing for the subject-matter being claimed. It considered that both were met.
Only the first aspect was contested by the appellant.

13. In accordance with decision G 1/22 of the Enlarged Board of Appeal, under the autonomous law of the EPC there is a rebuttable presumption that the applicant claiming priority is entitled to claim priority (see Headnote I).

The presumption of priority entitlement applies to any case in which the subsequent applicant is not identical to the priority applicant but receives the support of the priority applicant required under Article 88(1) EPC (see points 105 to 107 of the Reasons). Thus, the presumption applies in the current case.

The existence of a presumption of validity implies that it is the burden of the party challenging the applicant's entitlement to priority to prove that this entitlement is lacking (see point 110 of the Reasons). Thus, the appellant's argument that it is on the proprietor to demonstrate that it had the right to claim priority must fail.

The presumption is rebuttable, for instance, in cases of bad faith behaviour of the subsequent applicant or as a result of other proceedings such as litigation before national courts about the title to the subsequent application (see point 108 of the Reasons).

The presumption of entitlement exists on the date on which the priority is claimed, and the rebuttal of the presumption must also relate to this date (see point 109 of the Reasons).

14. In the case at hand, the appellant has not provided any such evidence to rebut the presumption of priority entitlement.

Document D19 is an assignment by the inventors to the applicant of the patent in suit and cannot rebut this presumption.
The further evidence provided relies on requirements of national law, such as the distinction under French law between the right to the invention and the right to the priority claim (see documents D18, D20 and D21).
Following the presumption of priority entitlement existing under the autonomous law of the EPC, considerations based on national law become irrelevant.

15. In light of the foregoing, the board comes to the conclusion that the patent is entitled to the priority claimed.

Documents D18 to D21 and D24

16. There were conflicting requests from the parties concerning admittance of these documents, all cited regarding entitlement of the patent in suit to priority. These documents were filed during opposition proceedings, but the opposition division did not take a decision on their admittance. The appellant requested admittance of documents D18 to D21. These documents were taken into account in point 14. above.
Nevertheless, the board came to the conclusion that the patent is entitled to the priority claimed. As regards document D24, its admittance was requested if documents D23, D23a and D23b were admitted into the proceedings. Since the board arrived at its decision without the need to consider them, the conditions for the appellant's request are not fulfilled, and the request to admit document D24 is moot.

Novelty (Articles 100(a) and 54 EPC)

17. The appellant raised objections against claims 1, 12 and 13.

17.1 With respect to claims 12 and 13, it relied on the disclosure in each of documents D12 and D13.

17.2 With respect to claim 1, the appellant relied on the disclosure in each of documents D6, D12 and D13.

Novelty in view of the disclosure in documents D12 and D13 (claims 1, 12 and 13)

18. Documents D12 and D13 were only made available to the public after the date of priority claimed by the patent in suit. In view of the conclusion on entitlement of the patent to priority (see point 15. above), these documents are not to be taken into account for the assessment of novelty. No other document has been cited against novelty of the subject-matter of claims 12 and 13, which therefore comply with the requirements of Article 54 EPC.

Novelty in view of the disclosure in document D6 (claim 1)

19. Document D6 is a press release by the patent proprietor announcing a fourth clinical trial with the antibody monalizumab, which is an antibody to NKG2A. This trial consists of a phase Ib/II clinical trial for the combination of monalizumab with cetuximab for treatment of patients with relapsed or metastatic squamous cell cancer of the head and neck (SCCHN). Monalizumab functions as an NKG2A checkpoint inhibitor, while cetuximab functions as an EGFR inhibitor. The document provides an overview of clinical trials for treating

the same cancer with different therapies, or for treating other cancers with monalizumab or cetuximab.

As regards previous therapies for SCCHN, cetuximab is the only approved therapy, however, with a low response rate and response duration (page 1, third paragraph).

As regards clinical trials with the antibody monalizumab, it discloses that four phase I/II clinical trials were ongoing at the time - as a monotherapy, for treating SCCHN and ovarian cancer, and, as a combination therapy with cetuximab (an EGFR inhibitor) or ibrutinib (a tyrosine kinase inhibitor). Further trials were being planned for treating solid tumours with a combination therapy of monalizumab with durvalumab (a PD-1 checkpoint inhibitor) (see page 1, last paragraph).

This overview of clinical trials is followed by a description of the clinical trial announced in the document, including the patients to be enrolled, the dosage regimen and the endpoints. The rationale for the trial is explained by the mechanism of action for each of the components of the combination. For monalizumab, this is that HLA-E, which is a ligand for NKG2A expressed on NK cells and intratumoral CD8+ T cells, is expressed on tumour cells in the majority of patients with SCCHN (see page 2, heading "*About study I PH2201-203*"). The interaction between the checkpoint NKG2A on T cells and NK cells, and HLA-E on cancer cells, results in the inhibition of T- and NK cells. Monalizumab prevents this inhibition by the cancer cells (see page 1, second paragraph).

This is followed by sections entitled "*About head and neck cancer*", "*About monalizumab*" and "*About Innate*

Pharma". The first of these sections presents the results available at the time from studies for treatment of SCCHN with cetuximab in combination with either radiation therapy or platinum-based chemotherapy, or still further as a monotherapy following chemotherapy. Studies with checkpoint inhibitors for SCCHN therapy included the concluded study with the PD-L1 inhibitor durvalumab and ongoing studies with other checkpoint inhibitors (see page 3, second paragraph). The objection of the appellant is based on this paragraph.

20. However, the clinical trial for the treatment of SCCHN with durvalumab is only presented in document D6 as part of the overview of clinical trials for SCCHN treatment. It is not mentioned in the section describing the clinical trial which is the subject of the document. Also, document D6 is concerned with a clinical trial for the combination of an NKG2A inhibitor and an EGFR inhibitor. It is not concerned with the combination of an NKG2A inhibitor and a PD-L1 inhibitor. Although document D6 describes characteristics of the patients to be enrolled in this announced clinical trial, it makes no mention of their prior treatments, let alone prior treatment with PD-L1 inhibitors. Therefore, the document does not disclose treating SCCHN patients previously treated with durvalumab, whether experiencing disease progression while on treatment or following treatment with a PD-L1 inhibitor.

21. The section entitled "*About monalizumab*" further elaborates the mechanism of action of monalizumab and the planned clinical trials involving it, mentioned on page 1 of the document, as summarised above. The appellant's objection further relies on this section,

specifically the mention of the clinical trial for the combination therapy monalizumab and durvalumab in solid tumours (see page 3, sixth paragraph).

22. However, the disclosure of a prior clinical trial with PD-1 inhibitors (on page 3, second paragraph) is in no way linked to the further clinical trials announced in the document. Indeed, document D6 does not contain an unambiguous disclosure that the patients involved in the trial for combined PD-1-inhibitor and NKG2A-inhibitor therapy had previously been treated with PD-1 inhibitors. Therefore, the appellant's argument is not convincing.

23. The appellant's arguments for not following decision T 2506/12 in the current case need not be discussed because this decision did not play a role in the board's decision in the case at hand. Indeed, claim 1 of the patent in suit is novel because document D6 does not disclose an NKG2A-inhibitor therapy for the same patient group. Decision T 2506/12, in contrast, was discussed by the parties for novelty when the prior art disclosed the same patient group.

24. In this context, the appellant submitted document D25 as evidence that durvalumab was safe as a monotherapy. Since the document was filed to address a point made in relation to decision T 2506/12, it is not of relevance, as follows from the reasons above.

Conclusion

25. The board concludes that none of documents D12 and D13 belonged to the state of the art according to Article 54 EPC. Claims 12 and 13 are thus novel over the cited prior art. Claim 1 is novel over the

disclosure in document D6. The ground for opposition under Article 100(a) in combination with Article 54 EPC does not prejudice the maintenance of the patent.

Inventive step (Articles 100(a) and 56 EPC)

26. Claim 1

26.1 Closest prior art

26.1.1 The appellant relied on the disclosure in document D6 as the closest prior art and selected the embodiment on page 3, second and third paragraphs, discussed above in the context of novelty, as the starting point for the assessment of inventive step. These paragraphs concern a previous clinical trial with a PD-L1 inhibitor for the treatment of SCCHN. The outcome was a very poor response to treatment. Thus, the starting point is the disclosure of a patient group encompassed by claim 1.

26.1.2 As set out above in the context of novelty, this poor response to monotherapy with PD-1 inhibitors is not disclosed in combination with any of the further clinical trials mentioned in the document (see point 22.). There is therefore no disclosure of a treatment for this patient group that had a poor response to treatment with the PD-L1 inhibitor durvalumab. Therefore, claim 1 differs from this prior art in that it provides a therapy for patients who had a poor response to a PD-L1 inhibitor, i.e. the patients disclosed in document D6.

26.2 Objective technical problem

26.2.1 In the current case, the technical effect is also that a therapy for the patient group defined in claim 1 is provided. In view of this technical effect, the objective technical problem may be formulated as the provision of a therapy for patients as defined in claim 1.

26.2.2 The appellant submitted that the problem was to be formulated as the provision of an alternative therapy for the patients as defined in claim 1. In the board's view, the problem could only be formulated in this way if the starting point in document D6 disclosed a therapy for patients who had a poor response to a PD-L1 inhibitor, which, as reasoned above, is not the case.

26.2.3 The appellant further submitted that it was not credible that this problem had been solved. However, an assessment of whether the therapeutic effect in claim 1 is credible was made under sufficiency of disclosure. What is to be determined in the current case for the purposes of Article 56 EPC is whether the claimed therapy with an NKG2A inhibitor was obvious for the skilled person faced with the problem of providing a therapy for the patients defined in claim 1.

26.3 Obviousness

26.3.1 The board is not persuaded by the appellant's arguments that the antibody for use in therapy as defined in claim 1 was an obvious solution to the objective technical problem, whether in view of the disclosure in document D6 on its own or in combination with document D7 or D9. Firstly, none of these documents addresses the treatment of non-responders to PD-1 inhibitors.

Secondly, as pointed out by the opposition division, without the knowledge that anti-PD-1 treatment leads to an increased number of cells of the immune system expressing NKG2A, the blockade of NKG2A was not an obvious therapy for this patient group.

26.3.2 The board agrees with the appellant that claim 1 covers treatment with an NKG2A inhibitor as a monotherapy as well as a combination therapy with PD-1 inhibitors. However, the fact that none of documents D6 to D9 addresses the treatment of poor responders to PD-1 inhibitor therapy or discloses that anti-PD-1 treatment leads to an increased number of cells of the immune system expressing NKG2A applies to both alternatives.

26.3.3 In a further line of argument, the appellant submitted that the solution was obvious from document D6 on its own, in particular its disclosure of clinical trials with checkpoint inhibitors other than NKG2A inhibitors and the disclosure of a planned clinical trial for the combination of durvalumab (a PD-L1 checkpoint inhibitor) and monalizumab (an NKG2A checkpoint inhibitor).

26.3.4 In the board's view, the mention of several clinical trials with checkpoint inhibitors does not make obvious a solution to the problem as formulated because these checkpoint inhibitors are not mentioned for patients who did not respond or no longer respond to PD-1 inhibitors. The same applies to the disclosure of a planned clinical trial with the combination of a PD-L1 inhibitor and an NKG2A inhibitor on page 3, sixth paragraph, of document D6. The board notes that this disclosure is in no way linked to the patient group identified in the second paragraph of the same page, which is suffering from SCCHN cancer, whereas the

disclosure of the combination clinical trial is directed to the treatment of solid tumours not further specified. Furthermore, a poor response was observed even for the patients who were PD-L1 positive (see page 3, second paragraph). In the board's view, this knowledge did not point the skilled person toward a solution with another checkpoint inhibitor. In the absence of a specific motivation to do so, the therapy with an NKG2A checkpoint inhibitor was not an obvious solution to the provision of a treatment.

26.3.5 The appellant further pointed to the disclosure in each of documents D7 and D9. Document D7 disclosed the combined treatment with a PD-1 inhibitor and an NKG2A inhibitor. The solution in claim 1 was obvious from this document for the same reasons as for document D6.

26.3.6 Document D7 is a press release concerning the collaboration between the companies AstraZeneca and MedImmune on the development of therapeutic applications of the anti-NKG2A antibody IPH2201 (which is an alternative designation for monalizumab). The appellant referred to page 3, first paragraph of this document, which discloses planned phase II clinical trials for the combination of monalizumab with a PD-1 inhibitor, the antibody MEDI4736 (also designated durvalumab), in the treatment of solid tumours. Therefore, the board concludes that the information in this passage does not go beyond the information on page 3, sixth paragraph of document D6. Accordingly, the above conclusion that the subject-matter of claim 1 is not obvious from document D6 applies to document D7 too. The appellant further referred to the statement on page 3, last paragraph, that "*IPH2201 may re-establish a broad anti-tumour response mediated by NK and T cells*". According to the appellant, this statement

implies that the anti-tumour response was lost before it could be re-established, and this was a pointer to use the antibody in the patient group of document D6. The board is not persuaded by this argument. Firstly, document D7 does not mention patients who did not respond or no longer responded to PD-1 inhibitors. In fact, the appellant did not point to any passage in the document mentioning such patients. Secondly, the board is of the view that the statement at issue merely conveys the understanding at the time that the interaction of HLA-E, on cancer cells, with the checkpoint NKG2A, on the surface of cells of the immune system, leads to a loss of antitumour response mediated by the latter. The statement thus refers to the re-establishment of this immune response by NK and T cells and not to a re-establishment by reference to patients who previously were responding or not responding to any given cancer treatment.

26.3.7 The appellant further argued that the skilled person knew from document D6 as well as from document D9 that solid tumours, and specifically SCCHN cancer, expressed HLA-E. For the skilled person, this meant that these tumours were suitable targets for therapy with the NKG2A inhibitor monalizumab.

(a) Document D9 is a company presentation by Innate Pharma on several products, including the antibody IPH2201 (monalizumab). It mentions phase II clinical trials for the combination of monalizumab with durvalumab, for the treatment of solid tumours (see slide 4, second line and slide 16, last line). It discloses the target for the antibody monalizumab and the mechanism by which blockade of NKG2A can result in NK- and T cell-activation (see slide 14) and that many tumours overexpress the

NKG2A ligand, which suggests a major mechanism of immune evasion (slide 15). Thus, the information in this document does not go beyond the information in document D6.

(b) The board is of the view that expression of HLA-E alone, without a further pointer, would not motivate the skilled person to treat the patient group at issue with an NKG2A inhibitor. Indeed, the starting point in document D6 is a group of patients suffering from SCCHN who did not respond or no longer responded to a PD-1 inhibitor. However, the skilled person also knew from document D6 that these patients did not respond to a PD-1 inhibitor, despite the fact that they were PD-L1 positive (see page 3, second paragraph). Therefore, in the board's view, the skilled person would not have had any motivation to treat these patients with another checkpoint inhibitor.

27. Claim 12

27.1 Claim 12 is directed to an *in vitro* method of identifying a cancer patient who is a poor responder to treatment with an antibody that neutralises the inhibitory activity of PD-1. The method relies on determining the individual's number of NKG2A-expressing NK or CD8+ T cells or level of NKG2A expressed on NK or CD8+ T cells.

Closest prior art

27.2 Document D6 discloses individuals who are poor responders based on the observed response rate to treatment, which is reported to be 11 or 18%, depending

on the patient being negative or positive for PD-L1 (page 3, second paragraph).

Objective technical problem

27.3 The method in claim 12 is an *in vitro* method based on the determination of NKG2A levels. The effect associated with this difference is that an *in vitro* method is provided. In view of this technical effect, the objective technical problem may be formulated as the provision of an alternative method of identifying cancer patients who are poor responders to treatment with PD-1 inhibitors.

Obviousness

27.4 As reasoned above for claim 1, there is no disclosure in any of the cited documents of a link between poor response to PD-1 inhibitor treatment and NKG2A levels. Therefore, claim 12 is not obvious from the cited documents for the same reasons as applicable to claim 1.

28. Claim 13

28.1 Claim 13 relates to a therapeutic application of an antibody, defined as in claim 1, in the treatment of an individual with cancer, where the antibody is administered if the individual has increased levels of NKG2A. In essence, the claim relates to the treatment with an NKG2A inhibitor of a patient suffering from cancer once the patient has been identified to have increased NKG2A levels. The patient is further characterised as "*an individual who is being treated*

with an antibody that neutralizes the inhibitory activity of PD-1".

28.2 As submitted by the appellant, claim 13 does not require that the patients be non-responders to PD-1 inhibitor therapy. Nevertheless, it requires that the patients be treated ("*being treated*") with a PD-1 inhibitory antibody and have increased NKG2A expression on NK or $CD8^+$ T cells or increased numbers of NKG2A-expressing NK or CD8+ T cells. Therefore, the question arises as to which embodiment in document D6 may be taken as the starting point for the assessment of inventive step. A possible starting point is the disclosure of anti-PD-L1 therapy of SCCHN, on page 3, second paragraph. The subject-matter of claim 13 differs therefrom in the combination therapy with an anti-PD-L1 antibody and an anti-NKG2A antibody. It further differs therefrom in the characterisation of the patients by increased NKG2A levels.

28.3 The technical effect of these differences is the provision of a therapy for the patient group defined in claim 13. The solution is not obvious from the cited documents, which identify neither this patient group nor a link between PD1 blockade and increased NKG2A levels.

28.4 The appellant identified as an alternative starting point in document D6 the disclosure of a planned clinical trial for the combination of monalizumab with durvalumab in solid tumours which are not further specified. According to the appellant, the method defined in claim 13 differs therefrom in that it requires a step of determining whether a patient who has been treated with the PD-1 inhibitor antibody has increased NKG2A levels. No technical effect of the

difference could be taken into account since it did not apply to the monotherapy embodiment also encompassed by claim 1. However, an assessment of whether the therapeutic effect is credible was made under sufficiency of disclosure (see points 10.1.2 and 11.). Therefore, the board does not agree with this argument and formulates the problem as for claim 1. The solution is not obvious for the same reasons as for claim 1.

28.5 The appellant's argument that claim 13 does not require that the patients be non-responders to PD-1 inhibitor treatment does not change this conclusion because the claim nevertheless requires that the patients be treated ("being treated") with a PD-1 inhibitor and have increased levels of NKG2A expression on NK or CD8 T cell or increased numbers of NKG2A-expressing NK or CD8 T cells.

28.6 Regarding claim 13, the appellant additionally cited documents D11 and D2. However, also in view of the disclosure in these documents, the method defined in claim 13 is not obvious for the following reasons.

28.7 Document D11 is cited for disclosing that cancer treatment would only be initiated after verifying that the protein targeted by the treatment was actually expressed at increased levels in the tumour. However, this argument does not address the point that none of documents D6 and D11 disclose NKG2A as a target protein for the patient group being treated with an antibody that neutralises the inhibitory activity of PD-1.

28.8 Document D2 was cited for disclosing therapies combining more than one checkpoint inhibitor. The same applied therefore as for document D11.

Admittance of an attack based on document D6 in combination with document D8

29. At oral proceedings, the appellant confirmed that it brought forward this line of attack for the first time in appeal proceedings. The respondent requested that it not be admitted into the appeal proceedings.

30. The board decided to not admit it since it constitutes an amendment to the appellant's case because it is a new combination of documents which, even if part of the proceedings, involves new factual circumstances.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

A. Wille M. Pregetter

Decision electronically authenticated