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**Datasheet for the decision of 13 March 2024**

**Case Number:**
T 1639/21 - 3.3.04

**Application Number:**
14706481.0

**Publication Number:**
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**IPC:**
C07K16/28, A61K39/00,
A61K39/395, A61K39/39

**Language of the proceedings:**
EN

**Title of invention:**
Combination of vaccination and inhibition of the PD-1 pathway

**Patent Proprietor:**
CureVac SE

**Opponents:**
Schnappauf, Georg
ModernaTX, Inc.
Strawman Limited
eTheRNA Immunotherapies NV
Merck Sharp & Dohme LLC

**Headword:**
mRNA/anti-PD-1 combination vaccine/CUREVAC

**Relevant legal provisions:**
EPC Art. 56, 112(1)(a)
**Keyword:**

Inventive step - (no)
Referral to the Enlarged Board of Appeal - (no)

**Decisions cited:**

T 1642/07, T 1814/11, T 2156/14, T 2097/15, T 0116/18,
T 1336/19

**Catchword:**

Obviousness of synergistic effect (see points 15 to 18 and 62 to 69)
Case Number: T 1639/21 – 3.3.04

DECISION
of Technical Board of Appeal 3.3.04
of 13 March 2024

Appellant I: CureVac SE
(Patent Proprietor)
Friedrich-Miescher-Straße 15
72076 Tübingen (DE)

Representative: Graf von Stosch, Andreas
Graf von Stosch
Patentanwaltsgesellschaft mbH
Prinzregentenstraße 22
80538 München (DE)

Appellant II: Schnappauf, Georg
(Opponent 1)
ZSP Patentanwälte PartG mbB
Hansastraße 32
80686 München (DE)

Appellant III: ModernaTX, Inc.
(Opponent 2)
200 Technology Square
Cambridge MA (US)

Representative: Hoffmann Eitle
Patent- und Rechtsanwälte PartmbB
Arabellastraße 30
81925 München (DE)

Appellant IV: Strawman Limited
(Opponent 3)
Orchard Lea
Horns Lane
Combe, Witney
Oxfordshire OX29 8NH (GB)

Representative: Vossius & Partner
Patentanwälte Rechtsanwälte mbB
Siebertstrasse 3
81675 München (DE)
Appellant V: eTheRNA Immunotherapies NV
(Opponent 4)
Galileilaan 19
2845 Niel (BE)

Representative: Arnold & Siedsma
Bezuidenhoutseweg 57
2594 AC The Hague (NL)

Appellant VI: Merck Sharp & Dohme LLC
(Opponent 5)
126 East Lincoln Avenue
Rahway, NJ 07065 (US)

Representative: Kilburn & Strode LLP
Lacon London
84 Theobalds Road
Holborn
London WC1X 8NL (GB)

Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted on
28 July 2021 concerning maintenance of the
European Patent No. 2 958 588 in amended form

Composition of the Board:
Chairwoman M. Pregetter
Members: B. Rutz
L. Bühler
Summary of Facts and Submissions

I. The appeals by the patent proprietor and opponents 1 to 5 lie from the decision of the opposition division that European patent No. 2 958 588 (the patent), entitled "Combination of vaccination and inhibition of the PD-1 pathway", met the requirements of the EPC in amended form according to auxiliary request 1. In this decision, the appellants are identified by their roles in the opposition.

II. The opposition proceedings were based on the grounds of Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and Article 100(b) and (c) EPC.

III. For the main request (filed with the letter of 16 April 2021), the opposition division found that its claims complied with Article 123(2) EPC and the claimed invention complied with Article 83 EPC but that the subject-matter of claim 1 lacked novelty over the disclosure of document D1 (Article 54(3) EPC).

IV. The opposition division admitted auxiliary request 1 (filed during oral proceedings) into the proceedings and found that it complied with the requirements of the EPC.

V. During the written proceedings, opponents 1 and 5 and the patent proprietor submitted a number of documents (D119 to D136). In the oral proceedings, they indicated that they would not rely on any of these documents.

VI. With its reply to the appeals by the opponents, the patent proprietor re-filed sets of claims of a main
request (first filed on 16 April 2021), auxiliary request 1 (filed during oral proceedings before the opposition division) and auxiliary request 3 (first filed as auxiliary request 1 on 16 April 2021). The patent proprietor further filed new auxiliary requests 2 and 4.

VII. The board summoned the parties to oral proceedings, as requested, and informed them of its preliminary opinion in a communication under Article 15(1) RPBA 2020.

VIII. In this communication, the board indicated that it agreed with the findings of the opposition division on the novelty of claim 1 of the main request and that it found the subject-matter of claim 1 of auxiliary requests 1 to 4 to lack an inventive step.

IX. With the letter dated 15 January 2024, opponent 4 indicated that it would neither be attending nor represented at the oral proceedings.

X. With the letter dated 7 March 2024, opponent 2 submitted document D137.

XI. Oral proceedings took place on 12 and 13 March 2024 in the absence of opponent 4 in accordance with Rule 115(2) EPC. During oral proceedings, the patent proprietor renumbered auxiliary request 1 to auxiliary request 2 and vice versa. At the end of the oral proceedings, the Chairwoman announced the board's decision.
XII. Claim 1 of the main request reads as follows:

"1. A vaccine/inhibitor combination comprising:
(i) as vaccine an RNA vaccine comprising at least one RNA, wherein the at least one RNA is an mRNA comprising at least one open reading frame (ORF) coding for at least one antigen and
(ii) as inhibitor a composition comprising a PD-1 pathway inhibitor, wherein the PD-1 pathway inhibitor is an antagonistic antibody, which is directed against PD-1, wherein the at least one RNA of the RNA vaccine is an isolated RNA."

Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that the antigen is a "tumor antigen".

Claim 1 of auxiliary request 2 differs from claim 1 of the main request in that it contains the proviso: ", and wherein the antagonistic antibody is not BMS-936558/MDX1106,".

Claim 1 of auxiliary request 3 differs from claim 1 of the main request as follows (changes highlighted):
"1. A vaccine/inhibitor combination consisting of:
(i) as vaccine an RNA vaccine comprising at least one RNA, wherein the at least one RNA is an mRNA comprising at least one open reading frame (ORF) coding for at least one antigen and
(ii) as inhibitor a composition comprising an immune checkpoint inhibitor, wherein the immune checkpoint inhibitor is a PD-1 pathway inhibitor, wherein the PD-1 pathway inhibitor is an antagonistic antibody, which is directed against PD-1, wherein the at least one RNA of the RNA vaccine is an isolated RNA."
Auxiliary request 4 differs from the main request in that claims 1 to 15 are deleted and claims 1 and 2 read as follows:

"1. A PD-1 pathway inhibitor, wherein the PD-1 pathway inhibitor is an antagonistic antibody, which is directed against PD-1, for use in therapy of a tumor or cancer disease in combination with an RNA vaccine comprising at least one RNA, wherein the at least one RNA is an mRNA comprising at least one open reading frame (ORF) coding for at least one antigen and wherein the at least one RNA of the RNA vaccine is an isolated RNA.

2. An RNA vaccine comprising at least one RNA, wherein the at least one RNA is an mRNA comprising at least one open reading frame (ORF) coding for at least one antigen and wherein the at least one RNA of the RNA vaccine is an isolated RNA, for use in therapy of a tumor or cancer disease in combination with a PD-1 pathway inhibitor, wherein the PD-1 pathway inhibitor is an antagonistic antibody, which is directed against PD-1."
XIII. The following documents are referred to in this decision:


D9 M. Mkrtichyan et al., "Anti-PD-1 synergizes with cyclophosphamide to induce potent anti-tumor vaccine effects through novel mechanisms", European Journal of Immunology 41, 2011, 2977-86

D10 Q. Zhou et al., "Blockade of Programmed Death-1 Pathway Rescues the Effector Function of Tumor-Infiltrating T Cells and Enhances the Antitumor Efficacy of Lentivector Immunization", The Journal of Immunology 185, 2010, 5082-92

D11 B. Li et al., "Anti-Programmed Death-1 Synergizes with Granulocyte Macrophage Colony-Stimulating Factor-Secreting Tumor Cell Immunotherapy Providing Therapeutic Benefit to Mice with Established Tumors", Clinical Cancer Research 15(5), 2009, 1623-34

D12 M. Y. Song et al., "Enhancement of Vaccine-induced Primary and Memory CD8+ T-cell Responses by Soluble PD-1", Journal of Immunotherapy 34, 2011, 297-306


D15  S. L. Topalian et al., "Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity", Current Opinion in Immunology 24, 2012, 207-12

D28  WO 2008/156712 A1

D29  M. A. Curran et al., "PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors", PNAS 107(9), 2010, 4275-80

D31  C. L. Slingluff, "The Present and Future of Peptide Vaccines for Cancer: Single or Multiple, Long or Short, Alone or in Combination?", Cancer Journal 17(5), 2011, 343-50


D45  R. M. Wong et al., "Programmed death-1 blockade enhances expansion and functional capacity of human melanoma antigen-
specific CTLs", International Immunology 19(10), 2007, 1223-34


D65 S. J. Ha et al., "Enhancing therapeutic vaccination by blocking PD-1-mediated inhibitory signals during chronic infection", The Journal of Experimental Medicine 205, 2008, 543-55
D68   US 8,008,449 B2
D71   J. B. Ulmer et al., "RNA-based vaccines", Vaccine 30, 2012, 4414-8
D78   Supplementary Results, dated 15 April 2020, 5 pages
D80   A. J. R. McGray et al., "Combined vaccination and immunostimulatory antibodies provides durable cure of murine melanoma and induces transcriptional changes associated with positive outcome in human melanoma patients", OncoImmunology 1(4), 2012, 419-31
D91   M. M. Berrien-Elliott et al., "Durable Adoptive Immunotherapy for Leukemia Produced by Manipulation of Multiple Regulatory Pathways of CD8+ T-Cell Tolerance" 73(2), 2012, 605-16
D95   Declaration of Dr Heidenreich, dated 16 April 2021
D99   Declaration of Dr Fotin-Mleczek, dated 16 April 2021

XIV. The patent proprietor's submissions relevant to the decision are summarised as follows.

Admission document D137

Document D137 was filed very late even though PD-L1 expression for inventive step with regard to document D13 had been discussed in the decision under appeal (see paragraph bridging pages 23 and 24). Moreover,
document D137 was post-published and therefore not relevant for the knowledge of the skilled person at the relevant date.

Main request - claim 1
Inventive step (Article 56 EPC)

Document D13 represented the most promising springboard to the invention since it also concerned improving the effectiveness of an mRNA vaccine by combining it with a checkpoint inhibitor. The difference between document D13 and the subject-matter of claim 1 was the use of an antagonistic antibody against PD-1.

The use of the claimed vaccine/inhibitor combination resulted in improved therapeutic effectiveness compared to the prior-art combination. The experimental results in the patent and the supplementary results in document D78 illustrated that the therapeutic effect obtained when using the claimed vaccine/inhibitor combination was due to a synergistic interaction between the mRNA vaccine and the antagonistic antibody directed against PD-1.

The administration of the combination of an RNA vaccine and an anti-CTLA-4 antibody as described in document D13 thus resulted in a prolongation of survival of 18.5 days compared to animals receiving buffer (see diagram and table, first submitted in reply to the oppositions of 2 January 2019 and reproduced in reply to the opponents' appeals). In contrast, administration of the vaccine/inhibitor combination according to the claims achieved a prolongation of survival of 30 days compared to buffer. These results clearly demonstrated that the claimed vaccine/inhibitor combination represented a significant improvement over the prior art.
The minor differences in the administration regime between the patent and document D13 did not hinder a direct comparison of the results (see declaration D99 by one of the authors of D13).

The objective technical problem was therefore the provision of an improved RNA vaccine combination.

The solution according to claim 1 was not obvious for several reasons. Firstly, the unexpected synergistic effect could not have been anticipated by the skilled person (see also decisions T 1814/11, T 2156/14 and T 2097/15). Secondly, the solution was not suggested by document D13, either taken alone or in combination with any prior-art document cited by the opponents.

The synergistic effect of document D13 could not merely be extrapolated to any other checkpoint inhibitor. For example, a combination of an RNA vaccine with an antagonistic anti-LAG3 antibody was not effective, as shown during opposition in a comparative experiment.

When starting from document D13, the skilled person did not have a reasonable expectation of obtaining an improved synergistic effect for several reasons.

(i) Different vaccine types were not equal and not interchangeable, as illustrated by the example of GVAX and FVAX in document D29.

(ii) Different checkpoint inhibitors were not interchangeable as illustrated by the example of the anti-LAG3 antibody in combination with an mRNA vaccine. Moreover, the inhibitory pathways targeted by an anti-CTLA-4 and an anti-PD-1 antibody, respectively, were
structurally and functionally distinct (see e.g. documents D14 and D35 and declaration D95).

Moreover, there was no motivation for the skilled person to replace the anti-CTLA4 antibody because the potential safety issue in document D13 was resolved and the antibody was FDA approved (see page 437, left-hand column, second paragraph to right-hand column, second paragraph).

The secondary documents cited by the opponents concerned vaccine types distinct from mRNA vaccines which the skilled person would not have combined with the teaching of document D13. The cited review articles provided only vague speculation as to a synergistic effect.

The skilled person would also have been dissuaded from targeting PD-1 because document D13 did not report PD-L1 expression, which was known to be required for an effect of a PD-1 inhibitor.

Auxiliary requests 1 to 4 - claim 1
Inventive step (Article 56 EPC)

The subject-matter of claim 1 of these requests was inventive for the same reasons as the main request.

Request for referral to the Enlarged Board of Appeal (Article 112 EPC)

A synergistic effect was per se not foreseeable, even if the prior art described a synergistic effect between related compounds (see Case Law of the Boards of Appeal of the EPO, 10th edition 2022, I.D.9.9.6). This general notion was also reflected in the Guidelines for
Examination (see section G.VII.), which stated that the presence of a synergistic effect characterised an actual "combination of features" (which was not to be considered as obvious) as opposed to a mere "aggregation or juxtaposition of features". Decision T 1814/11 explicitly stated that mechanistic or structural similarities did not render a synergistic effect foreseeable.

In the case at hand, the mechanisms of action of a PD-1 inhibitor and a CTLA-4 inhibitor were distinct. The skilled person was aware of the different effects of different checkpoint inhibitors and would not merely have replaced one checkpoint inhibitor in a combination (such as the anti-CTLA4 antibody in document D13) with another checkpoint inhibitor (such as the anti-PD-1 antibody according to claim 1 of the main request). The established case law acknowledged that a different mechanism of action by itself excluded any extrapolation (see e.g. T 1642/07).

Moreover, it was unpredictable if and how the individual components of the claimed combination would interact with each other. The mechanism which resulted in this interaction and thus allowed for a more than additive effect was still not understood. This was the case for both the combination in document D13 and the inventive combination according to claim 1. A more than additive effect was generally considered remarkable since the exact mechanism, by which two components interacted to generate synergy, could typically not be explained, let alone expected (see also decision T 1336/19).
To ensure uniform application of the law, the board should refer the following questions to the Enlarged Board of Appeal:

"1. When (if at all) is it appropriate for a Board of Appeal to depart from the established case law of the Boards of Appeal in which, regardless of the actual decision, there has been a uniform consistency of principle or principles?

2. In particular, if the established case law has consistently reflected a principle accepted by the scientific community (here, that a synergistic effect resulting from a new combination is unpredictable), when (if at all) is it correct for a Board of Appeal to make a decision which, as regards such a principle, is inconsistent with the established case law?"

XV. Opponent 1's to 5's submissions relevant to the decision are summarised as follows.

Admission document D137

Document D137 was filed in response to the statement of the patent proprietor that EG.7-OVA cells had no relevant PD-L1 expression. Document D137 showed that this was not correct.

Main request - claim 1
Inventive step (Article 56 EPC)

The difference between the subject-matter claimed in the opposed patent and the disclosure of document D13 was that instead of an anti-CTLA-4 antibody, an anti-PD-1 antibody was used in combination with the mRNA vaccine. In view of the known toxicity of CTLA-4 (see
e.g. documents D13, D28, D11 and D14), the technical problem could be formulated as the provision of an mRNA vaccine and inhibitor composition which had an improved safety profile in view of fewer and less severe side effects.

The prior art showed that anti-PD-1 antibodies (i) had fewer side effects compared to anti-CTLA-4 antibodies, (ii) had increased vaccine efficacy in combination with a vaccine compared to the vaccine alone and (iii) affected the immune system independently of the vaccine (see e.g. D9, D10, D11, D12, D14, D29, D31, D35, D51, D52, D55, D56, D65 and D80). This provided the motivation to the skilled person to replace the anti-CTLA-4 antibody of document D13 with an anti-PD-1 antibody with a reasonable expectation that the combination of an anti-PD-1 antibody and an mRNA vaccine would result in a synergistic immune response compared to the mRNA vaccine alone with fewer side effects. Thus, the skilled person not only could but would have modified the vaccine/inhibitor combination disclosed in document D13 by replacing the anti-CTLA-4 antibody with an anti-PD-1 antibody.

The review articles D14 and D37, each representing common general knowledge, taught blocking the PD-1 pathway as the next advance or an alternative to blocking the CTLA-4 pathway in enhancing vaccination.

Document D15 also showed that the skilled person would have expected a synergistic effect when an effective cancer vaccine (regardless of which type and, thus, including mRNA vaccines) was combined with a "PD-1 pathway blockade".
The different mechanisms of action could not play a role in predicting a synergistic effect because numerous prior-art documents showed that the use of either CTLA-4 or PD-1 inhibitors strongly enhanced the amplitude of vaccine-induced antitumour responses in many poorly immunogenic tumour models and that this effect was independent of the antigen or how it was provided to the subject.

Moreover, there was no prejudice for using anti-PD-1 antibodies in combination with an RNA vaccine as compared to anti-CTLA-4 antibodies since the immune system checkpoint blockade was known to be an effect independent of the vaccine providing the antigen.

The absence of a mention of PD-L1 expression in document D13 would not have dissuaded the skilled person from using an anti-PD-1 antibody because only a small number of "strongly activated" genes was listed, other documents showed that also PD-L1 negative tumour models could be responsive to anti-PD-1 (see e.g. D68) and the skilled person could have switched to tumour models for which PD-L1 expression or upregulation was established.

Therefore, a skilled artisan looking for an alternative vaccine/inhibitor combination would certainly have considered replacing CTLA-4 (as taught in D13) with PD-1 (as suggested in D13 and evident from e.g. D35), and they would also have expected the combination to work synergistically, as evident from any of D65, D11 and D15.

In view of the many positive indications in the prior art, the skilled person seeking an anti-PD-1/vaccine combination would also have adopted a "try and see"
approach and would have replaced the anti-CTLA4 antibody with an anti-PD-1 antibody even if a synergistic effect was not certain (Case Law of the Boards of Appeal of the EPO, 10th edition 2022, I.D. 7.2).

Accordingly, whether or not the expectation of synergy for PD-1 inhibitors was included in the assessment of inventive step, the subject-matter of claim 1 was not inventive.

_Auxiliary requests 1 to 4 - claim 1_

_Inventive step (Article 56 EPC)_

The amendments to claim 1 compared to the main request did not contribute anything beyond what was commonly known in the art, and the subject-matter was thus also not inventive in accordance with Article 56 EPC.

_Request for referral to the Enlarged Board of Appeal (Article 112 EPC)_

A decision against the proprietor on its position on synergy would not be inconsistent with the established case law, i.e. that synergism was fact specific. The skilled person's expectations depended on the circumstances of the case. There was thus no point of law of fundamental importance.

_XVI._ The patent proprietor requested that the decision under appeal be set aside and that the patent be maintained based on the set of claims of the main request or, alternatively, the set of claims of auxiliary request 1 to 4 as filed with the reply to the opponents' appeals, with the order of auxiliary requests 1 and 2 reversed. It further requested that documents D107 to D118 and
D124 to D133 be admitted and that documents D119 to D123 and D135 to D137 not be admitted into the proceedings. The patent proprietor further requested referral of a question to the Enlarged Board of Appeal (D134).

Opponents 1, 2, 3 and 5 requested that the decision under appeal be set aside and that the patent be revoked. They further requested that auxiliary requests 1 to 4 be held inadmissible and that documents D124 to D133 be not admitted into the proceedings. They also requested that the patent proprietor's request to refer a question to the Enlarged Board of Appeal (D134) be refused. Opponent 1 further requested that documents D119 to D123, D135 and D136 be admitted into the proceedings. Opponent 2 additionally requested that document D137 be admitted into the proceedings. Opponent 4 had requested in writing that the decision under appeal be set aside and that the patent be revoked.
Reasons for the Decision

Absence of a party (Rule 115(2) EPC)

1. Opponent 4 had indicated that it would neither be attending nor represented at the oral proceedings and was thus treated as relying on its written case in accordance with Article 15(3) RPBA.

Admission of documents D107 to D133 and D135 to D137

2. Documents D107 to D118 were filed during the opposition proceedings. Documents D119 to D136 were filed during the appeal proceedings. Since none of these documents were required for the decision, it was not necessary to decide on their admission.

3. Document D137 was filed a few days before the oral proceedings. Article 13(2) RPBA therefore applies. Opponent 2 has not brought forward any exceptional circumstances justifying the late filing. Document D137 was not admitted into the proceedings.

Technical background
Tumour antigens and immune checkpoints

4. Due to the accumulation of mutations and genetic aberrations, cancer cells often express cell-surface molecules not present on other cells in the body. These so-called tumour antigens are promising targets for immunotherapy because they allow targeting tumour cells while sparing healthy cells and tissues. Although the immune system often recognises tumour antigens, it usually does not efficiently attack them because of the
action of immune checkpoints. In principle, immune checkpoints prevent the overreaction of the immune system against the body's own cells and tissues through multiple pathways, including the attenuation of early activation signals, competition for positive co-stimulation and direct inhibition of antigen-presenting cells. However, tumours have been shown to employ the immune checkpoints' regulating function to prevent an efficient immune response against them and to hide behind the checkpoints' protective mechanisms. In immunotherapy for cancer treatment, the immune checkpoints, in particular CTLA-4 and PD-1, have been intensively discussed in literature. Their activity is shown in, e.g. document D14 (see below).

Figure 3 from document D14: Immune checkpoints regulate different components in the evolution of an immune response; role of checkpoint proteins CTLA4 and PD1
mRNA vaccination

5. Similar to plasmid DNA and recombinant viruses, messenger RNA (mRNA) can be used to carry exogenous genetic information inside cells. The expression of the encoded protein in cells of the body leads to the presentation of peptidic antigens of the protein to the immune system and triggers an immune response. mRNA-based vaccines provide a number of safety features: persistence, no integration into the genome and no induction of autoantibodies. Moreover, mRNA generated by in vitro transcription are easy to produce in large amounts at a very high purity. mRNA, due to its interaction with pattern recognition receptors, apart from providing an antigen, can also stimulate innate immunity (see document D6, pages 23 to 24; document D38, pages 33 to 34, "Messenger RNA-Based Vaccine"; document D71, Abstract).

Main request
Inventive step (Article 56 EPC)
Closest prior art

6. Claim 1 of the main request is a vaccine/inhibitor combination which comprises an isolated mRNA comprising an open reading frame coding for an antigen and an antagonistic antibody directed against PD-1. This subject-matter includes vaccine/inhibitor combinations in which the mRNA codes for a tumour antigen. In view of the focus of the arguments of the parties on vaccine/inhibitor combinations comprising mRNA encoding tumour antigens, the board will limit its analysis of inventive step to these vaccine/inhibitor combinations.

7. The parties agree that document D13 represents a suitable starting point for an inventive-step analysis.
It discloses the vaccination of E.G7-OVA mice with an mRNA vaccine encoding the OVA antigen in combination with a monoclonal antibody blocking the immune checkpoint protein CTLA-4. E.G7-OVA is a mouse tumour model challenged with a T-cell lymphoma cell line stably expressing *Gallus gallus* OVA protein. The vaccination resulted in a strong synergistic antitumour effect causing complete tumour rejection in some of the vaccinated mice (see Figure 6A and page 437, right-hand column, lines 4 to 8).

**Difference, effect and objective technical problem**

8. It is undisputed that the difference of the claimed subject-matter to the disclosure in document D13 consists in the different immune checkpoint target of the antagonistic antibody: PD-1 instead of CTLA-4.

9. The patent proprietor argues that the use of an anti-PD-1 antibody resulted in "improved therapeutic effectiveness" as evident from the higher median survival rate in Example 2 of the patent compared to the results in document D13. The patent proprietor, in its reply to the appeals by the opponents (see page 31), submitted as evidence a figure and a table first submitted in reply to the oppositions on 2 January 2019 and allegedly corresponding to the data of Figure 6 of document D13 (see declaration D99 by one of the authors of document D13, point 3). Supplementary post-published evidence was provided as document D78. According to the patent proprietor, the experiments in the patent and document D13 were comparable despite the minor deviations in the dosing schedules (see declaration D99).
10. The opponents, in contrast, are of the opinion that the therapeutic effectiveness of the claimed vaccine/inhibitor combination - if at all shown in the patent - was not better than in document D13, which reported three out of eight complete responders (see Figure 6 and its legend). The survival curves relied on by the patent proprietor were inconsistent with the data of D13 because they showed only 12.5% complete responders, i.e. one out of eight mice. Furthermore, the conditions under which the vaccination and challenge experiments in the patent and document D13 were performed were different and therefore could not be compared.

11. The board has not been provided with a convincing explanation for the inconsistency between the data in the patent proprietor's reply to the opponents' appeals and the data in document D13. The label of one of the curves in Figure 6B of D13 reads "complete responders after treatment with RNA and a-CTLA-4 (n=3)". The legend to Figure 6B refers to "complete responders from (A), treated previously with OVA vaccine and anti-CTLA-4 combination therapy". Experiment (A), however, was carried out on "n=8" mice, which presumably refers to eight mice per treatment arm (see the legend to Figure 6A). This cannot be reconciled with the post-published data provided by the patent proprietor, which shows only 12.5%, i.e. one complete responder, in the "OVA-RNAActive + a-CTLA4" group (see page 31 of patent proprietor's reply to the appeal dated 25 April 2022). Also, the statement in document D99 (page 2, footnote 1) that "the results obtained for that additional mice group treated by 'OVA-RNAActive + control IgG' have not been presented by our publication (document E13)" cannot resolve this inconsistency because the data label of Figure 6B in document D13 refers to "complete responders after treatment with RNA and a-CTLA-4"
(n=3)". The post-published data in the reply by the patent proprietor is therefore considered not suitable for a meaningful comparison of the experiments in the patent and those of document D13.

12. The board furthermore finds that although the same dosing of 100 µg of antibody was used in document D13 and in the patent (see Figure 6 in document D13 and Table 1 in the patent), the time points and intervals for the vaccine and antibody administration differ between document D13 and the patent. In document D13, the antibody was administered on days 4, 7, 11, 14 and 18, while the mRNA vaccine was administered on days 3, 6, 10, 13 and 17 (see Figure 6A and its legend). In the patent, the anti-PD-1 antibody and the mRNA vaccine were administered on the same day ("with a minimum of four hours between the treatments") on days 4, 7, 11, 14, 18 and 21 (see paragraph [0243] and Figure 1 in the patent). In the post-published experiments D78, presumably both the mRNA vaccine and anti-PD-1 antibody were administered on days 6, 9, 13, 16, 20 and 23 (see Figure 3). The board concludes that there are considerable differences in the dosage schedule between the experiments in document D13 and the patent or the post-published document D78. The expert declaration D99 cited by the patent proprietor cannot change this finding because it merely states that "these experiments exhibits such a high level of consistency that I do not expect any lack of comparability resulting from minor deviations of the set-up". The board considers administering the mRNA on different days than the antibody and on different days than it was administered in the patent represents more than "minor deviations". It is established case law that if comparative tests are chosen to demonstrate an inventive step on the basis of an improved effect over
a claimed area, the nature of the comparison with the close state of the art must be such that the alleged advantage or effect is convincingly shown to have its origin in the distinguishing feature of the invention compared with the closest state of the art (see Case Law of the Boards of Appeal of the EPO, 10th edition 2022, I.D.4.3.2).

13. Even assuming that the data in the patent (and in post-published experiment D78) could be compared to the data in document D13, the survival of three out of six animals in the patent (i.e. 50%, see Figure 2) or five out of nine (i.e. 55%) in the post-published experiment shown in document D78 compared to three out of eight animals (i.e. 37.5%) in document D13 is not considered significant in view of the small number of test animals.

14. In conclusion, the board agrees with the opposition division that an "improved therapeutic effectiveness" of the claimed vaccine/inhibitor combination in comparison with the vaccine/inhibitor combination disclosed in document D13 cannot be acknowledged.

15. While the board cannot acknowledge a significantly increased therapeutic effectiveness of the claimed vaccine/inhibitor combination over document D13, the patent proprietor's argument that there was a synergistic interaction between the mRNA vaccine and the PD-1 inhibitor in terms of a more than additive increase in therapeutic effectiveness needs to be addressed. As argued by the opponents, the circumstances of the case must be assessed when evaluating synergism. In the current case, the distinct mechanisms of action of the components, i.e. of the
vaccine and the checkpoint inhibitor, have to be taken into account.

16. The mRNA vaccine elicits an immune response against the tumour, i.e. a therapeutic effect. The anti-immune checkpoint antibody, however, on its own, does not have a direct effect on the tumour; it only counteracts an inhibition of the immune response, i.e. the immune system checkpoint blockade as termed in the parties' submissions. Releasing this blockade can only have a therapeutic effect in combination with an existing immune response, which can either come from the immune system itself which recognises the tumour as "non-self" or be stimulated by a vaccine. The lower part of Figure 5 of document D14 (reproduced in point 32. below) was, inter alia, referred to.

17. To illustrate the foregoing, the board finds it helpful to draw on an analogy made in document D14 and other documents cited by the parties for the mechanism of inhibiting the immune system checkpoint blockade, which is described as the release of a brake (see e.g. D14, page 262, right-hand column, first full paragraph: "the potential antitumour activity of a patent's endogenous immune system once the 'brakes' elicited by the immune system have been released"; D54, page 23, left-hand column, second paragraph: "In healthy people, CTLA-4 is a godsend because it's a natural brake on immune attacks"; D91, page 614, left-hand column, first full paragraph: "The ability of antibody blockade to 'release the brakes' on T-cell responses against cancer has been clinically successful for anti-CTLA4").

18. It goes without saying that releasing a brake alone does not move a car (speed=0) but allows a faster speed when the motor is on. The speed generated by the motor
with the brake released (speed=x) will always be more than additive compared to the speed when the brake is on (speed=x-y) because y (the reduction of speed imposed by the brake) will always be greater than zero.

19. In light of these considerations, the claimed combination and the combination disclosed in document D13 (see point 7. above) can be seen as showing a synergistic effect at least for mRNA encoding a tumour antigen. This is apparent from the data in the patent (see Example 2 and Figure 2), which show that the combined effect of an anti-PD-1 antibody and a tumour antigen mRNA vaccine is greater than the sum of the individual effects. It is also supported by the post-published evidence in document D78, which reports that vaccination of a different tumour model with an mRNA encoding a different tumour antigen in combination with an anti-PD-1 antibody results in a synergistic effect (see Figures 4 and 5).

20. The objective technical problem can thus be formulated as providing a further synergistic mRNA vaccine/immune checkpoint inhibitor combination.

21. The problem is considered to be solved at least for mRNA tumour antigen vaccine/inhibitor combinations (see point 19. above).

Obviousness

22. From its title, "Highly potent mRNA based cancer vaccines represent an attractive platform for combination therapies supporting an improved therapeutic effect", it is evident that, despite reporting new experimental results, document D13 is also a review article summarising recent findings in
immunotherapy (see indication "REVIEW ARTICLE" at the top right corner of page 428).

23. The skilled person learns from the abstract of document D13 that "by combining the mRNA vaccines with therapies in clinical use (chemotherapy or anti-CTLA-4 antibody therapy), an even more effective anti-tumor response can be elicited". The introduction of D13 states that "mRNA vaccines can be combined with other therapies to further improve their therapeutic effect", and in the "Conclusions" section, the authors envisage "that combination approaches will play central role in future clinical developments, opening the possibility for attacking tumors via complementary, synergistically-acting mechanisms" (page 437, right-hand column, last paragraph). The advantages of combination therapy are further highlighted by stating that "the chance of successfully treating cancer with a monotherapy is still very low, the vaccine should be able to be combined with other therapies (such as chemotherapy, radiation, monoclonal antibodies), providing an enhanced therapeutic effect" (see page 429, left-hand column, end of first paragraph).

24. In the introduction of document D13, a number of immunotherapy approaches are listed, including "treatment with monoclonal antibodies such as anti-CTLA-4 [2,9], anti-PD1 [10], CD40 [11] and OX40 [12]" (see page 428, last paragraph). From their common general knowledge, the skilled person knew that the targets of the listed antibodies are immune checkpoint proteins. This is underlined in the following sentence, which states that "the goal of all these approaches is the same: to stimulate the immune system and to mobilize it to use its cellular and molecular tools in the fight against cancer".
25. At the end of the "Results and Discussion" section, the skilled person furthermore learns that "[a]nother possibility for increasing the therapeutic efficacy of mRNA vaccines is to combine them with other non-antigen specific immunotherapies. One example for such approach is the recently FDA approved ipilimumab, a human anti-CTLA-4 antibody for the treatment of melanoma. This antibody increases the activation of T cells by blocking the CTLA-4 receptor, which is responsible for the attenuation of the signal cascade [50,51]" (see page 437, left-hand column, last paragraph).

26. Examples of "non-antigen specific immunotherapies" are the monoclonal antibodies against immune checkpoint proteins, including anti-CTLA-4 and anti-PD-1, listed in the introduction (see point 24. above). Reference [10] cited for "anti-PD1" (D56 in this appeal) has the title "PD-1 blockade by CT-011, anti-PD-1 antibody, enhances ex vivo T-cell responses to autologous dendritic cell/myeloma fusion vaccine". This reference title in D13 thus already points the skilled person to the enhancing effect of an anti-PD-1 antibody on T-cell response to a cellular vaccine. A further relevant reference in document D13 is reference [50] (D35 in this appeal), which follows the above cited passage on anti-CTLA-4 antibody being "one example for such approach". The title of this reference is "Immune Checkpoint Proteins: A New Therapeutic Paradigm for Cancer – Preclinical Background: CTLA-4 and PD-1 Blockade", i.e. it presents CTLA-4 and PD-1 as two promising immune checkpoint proteins.

27. Document D13 further points to possible shortcomings of blocking CTLA-4, which "is rarely associated with severe side effects as a result of the non-selective
activation of autoimmune cells [52]". These side
effects are avoided in D13 by using a lower than
previously reported dose (100 µg instead of >= 200 µg)
(see paragraph bridging both columns on page 437).

28. In conclusion, the skilled person already knew from the
disclosure of document D13 that CTLA-4 blockade has
known safety issues and that PD-1 is a further immune
checkpoint protein which enhances the effect of cancer
vaccines.

29. In trying to solve the objective technical problem, the
skilled person was aware of review articles D14, D15
and D35 (the latter cited as reference [50] in document
D13), which the parties agree represent common general
knowledge in tumour immunotherapy at the relevant date.
All three reviews focus almost exclusively on CTLA-4
and PD-1 (see D14, Abstract; D15, page 207, right-hand
column, first full paragraph: "The two checkpoint
receptors that have been most actively studied in the
context of clinical cancer immunotherapy, CTLA-4 and
PD-1"; D35, Abstract).

30. Several review articles also discuss the safety of
blocking PD-1 compared to CTLA-4. Document D14
indicates "that blockade of this pathway [PD1] would
result in less collateral immune toxicity than for
CTLA4 blockade, which seems to be the case in clinical
trials" and that "the frequency of immune-related
toxicities from anti-PD1 treatment seems to be less
than anti-CTLA4 treatment" (see page 260, left-hand
column, end of first full paragraph and last full
paragraph). The review article D31 states in the
section "Combination Immune Therapy" on page 8, middle
of page: "Clinical experience with one of these [anti-
PD-1 antibody MDX-1106] is that it induces objective
clinical responses in 30% of patients with advanced melanoma, with high durability, and a safety profile that may be better than that of CTLA-4 antibody, and with MTD [maximum tolerated dose] not reached in initial studies". The review article D54 mentions that "[e]arly data suggest medications that target a kill switch called PD-1, similar to CTLA-4, could pair well with vaccines and have fewer side effects" (page 23, middle column, last paragraph).

31. The following further passages in documents D14, D15, D35 and D37 corroborate that the skilled person aiming to replace CTLA-4 would have considered PD-1 as the first and most obvious alternative target (highlighting by the board).

32. Document D14:
Abstract: "Preliminary clinical findings with blockers of additional immune-checkpoint proteins, such as programmed cell death protein 1 (PD1), indicate broad and diverse opportunities to enhance antitumour immunity with the potential to produce durable clinical responses."
page 253, paragraph bridging both columns: "the two immune-checkpoint receptors that have been most actively studied in the context of clinical cancer immunotherapy, cytotoxic T-lymphocyte-associated antigen 4 (CTLA4; also known as CD152) and programmed cell death protein 1 (PD1; also known as CD279) – which are both inhibitory receptors – regulate immune responses at different levels and by different mechanisms. The clinical activity of antibodies that block either of these receptors implies that antitumour immunity can be enhanced at multiple levels and that combinatorial strategies can be intelligently designed,
guided by mechanistic considerations and preclinical models."

page 256, right-hand column, first paragraph:
"Similarly to CTLA4, PD1 is highly expressed on T_{Reg} cells, where it may enhance their proliferation in the presence of ligand\textsuperscript{60}. Because many tumours are highly infiltrated with T_{Reg} cells that probably further suppress effector immune responses, blockade of the PD1 pathway may also enhance antitumour immune responses by diminishing the number and/or suppressive activity of intratumoral T_{Reg} cells."

page 260, left-hand column, second full paragraph:
"Although the clinical experience with PD1 antibodies is currently much less extensive than with CTLA4 antibodies, the initial results look extremely promising."

page 262, right-hand column, last paragraph: "However, expanded efficacy might be achieved when PD1-pathway blockade is combined with a vaccine or any other therapy that induces de novo antitumour immune responses (FIG. 5)."

Lower part of Figure 5 and its legend:

"Multiple interventions, such as vaccines, that activate a de novo antitumour immune response may not induce tumour regressions because tumours respond by upregulating immune-checkpoint ligands. Therefore, combining the two approaches may induce tumour regressions in patients that would not have responded to either treatment alone."
33. Document D15:

page 208, right-hand column, end of first paragraph: "The adaptive resistance mechanism directly implies that any treatment that induces anti-tumor immunity (e.g., vaccination) will provide therapeutic synergy with PD-1 pathway blockade."

page 210, Conclusions: "Despite early successes with monotherapies blocking PD-1 pathways, preclinical models indicate that combinatorial therapies will deliver maximum clinical impact. Several clinical trials are already planned or in progress, combining anti-PD-1 mAbs with cancer vaccines (melanoma, prostate cancer, renal cell carcinoma, AML), antitumor mAbs (lymphoma), or chemotherapies (pancreatic cancer, NSCLC). These synergistic treatment strategies will provide a foundation for the next generation of clinical investigations."

34. Document D35:

Abstract: "For PD-1 blockade, murine experiments have suggested that the antibody alone and combined with adoptive cell transfer or vaccine approaches would be therapeutically beneficial, and that clear effects on T-cell proliferation and activation, as well as T-regulatory cell function would be observed in patients."

page 435, left-hand column, line 14 from bottom: "Combining PD-1 blockade with GM-CSF-secreting melanoma tumor cell immunotherapy prolonged the survival of tumor-bearing animals compared with animals treated with either therapy alone."

page 435, right-hand column, Conclusion: "both CTLA-4 and PD-1 abrogation with human antibodies are clinically promising and appear to provide clinical benefit in different tumor types."
35. Document D37:

page 6, right-hand column, last paragraph:
"A novel therapeutic approach, in patients with NSCLC, is the direct vaccination with messenger RNA (mRNA) encoding tumor antigens. Aimed to be used in combination therapies, this is a potent cancer vaccine that can facilitate the response to standard treatment. [...] Clinical data were obtained from a phase I/II trial with promising results (65) [reference corresponding to D13]."

page 7, left-hand column, first paragraph:
"Since tumor microenvironment is highly immune suppressive, it was logical to complement attempts to immune therapy of cancer with methods regulating the function of T cells."

page 7, left-hand column, third paragraph:
"Programmed cell death protein 1 (PD-1) is another T-cell inhibitory receptor important for regulation of immune responses. PD-1 blockade was shown to enhance the effect of immune therapy in pre-clinical settings (69). In recent years a fully human IgG4 anti-PD-1 blocking antibody (MDX-1106) was used in a multicentre trial to evaluate safety, antitumor activity, pharmacokinetics, and immunological correlates in patients with refractory metastatic NSCLC, renal cell carcinoma, melanoma, or prostate cancer. The antibody was well tolerated with clear antitumor activity... Within this trial maximum tolerated dose was not reached."

36. The board concludes from the cited passages in the closest prior art D13 and in review articles D14, D15, D31, D35, D37 and D54 that the skilled person starting from the disclosure of document D13 would have considered PD-1 as a promising immune checkpoint target
for an antagonistic antibody in combination with cancer vaccines.

Reasonable expectation of success

37. Thus, the question to be asked is whether the skilled person had a reasonable expectation of obtaining a similar therapeutic effect, i.e. an improvement of vaccine efficacy in a synergistic manner (see point 17. above) when replacing the anti-CTLA-4 antibody in document D13 with an anti-PD-1 antibody.

38. The patent proprietor was of the opinion that, in view of the different mechanisms through which CTLA-4 and PD-1 acted (see e.g. the expert declaration D95, points 3.1 to 3.9 and 4), the skilled person could not have expected that a similar synergistic effect would occur when using an anti-PD-1 antibody as an inhibitor.

39. The opponents counter-argued that it was known from the state of the art that anti-PD-1 antibodies enhanced, often synergistically, the effect of tumour antigen vaccines in different formats (e.g. viral, peptide and cellular vaccines in combination with an anti-PD-1 antibody). A synergistic effect was also expected when using mRNA as the vaccine platform because the effect of blocking immune checkpoint proteins was not dependent on the delivery method of the antigen. For example, it was commonly known that T cells could become exhausted upon exposure to high antigen levels by repetitive immunisations. This occurred independent of the vaccine format and could be counteracted by PD-1 blockade (see, for example, D52, second page, penultimate sentence and D45, page 1224, left column, first full paragraph).
40. To establish whether the skilled person would have reasonably expected a similar synergistic effect to occur when replacing anti-CTLA-4 with anti-PD-1, the board considers it necessary to look at both components of the claimed vaccine/inhibitor combination and what the skilled person knew about them and their interaction with each other.

mRNA vaccine

41. The mRNA vaccine in document D13 is shown to lead to the expression of a tumour antigen (OVA) in a mouse which is recognised by the immune system as foreign, resulting in an immune response which acts on the tumour in the mouse model (EG.7-OVA) carrying the same tumour antigen. With regard to known mRNA vaccine designs, document D13 states in the "Introduction" section that "[t]he two-component vaccines activated the adaptive and innate immune system to induce balanced humoral, as well as T cell mediated immunity. This balanced immune response was based on the induction of antigen specific CD4+ T helper cells and cytotoxic CD8+ T cells" (see page 429, left-hand column). Document D13 further shows that blocking checkpoint inhibition with an anti-CTLA-4 antibody leads to a synergistic effect with the mRNA tumour vaccine similar to what had been observed for combinations of anti-CTLA-4 antibodies with cellular or peptide vaccines (see review article D35 cited as reference [50] in D13, page 437, left-hand column, third paragraph). The skilled person therefore knew from document D13 that the different vaccine format (mRNA compared to cellular or peptide) did not interfere with the enhancing effect of the antibody.
Immune checkpoint mechanisms (CTLA-4 and PD-1)

42. It was undisputed that CTLA-4 and PD-1 immune checkpoint proteins reduce or block the T-cell response by different mechanisms (see point 4. above).

- CTLA-4 "downmodulates the amplitude of T cell activation" (see document D14, page 253, "At a glance" box and page 258, Figure 3). Blocking CTLA-4 therefore counteracts the dampening effect of CTLA-4 on T-cell activation, as seen in D13: "This antibody increases the activation of T cells by blocking the CTLA-4 receptor, which is responsible for the attenuation of the signal cascade" (page 437, left-hand column, second full paragraph).

- PD-1 "limit[s] T cell effector functions within tissues" and represses the immune response of antigen-experienced or more mature T cells. This is employed by tumour cells, which upregulate ligands for PD-1 and thus block antitumour immune responses in the tumour microenvironment (see document D14, page 253, "At a glance" box and Figures 3 and 4).

43. CTLA-4 can therefore be seen as a more general "brake" at the start of the immune response, while PD-1 limits the local effects of T cells in tissue, including tumours.

Interaction of mRNA vaccine and immune checkpoint inhibitor

44. The board has not been presented with any evidence that there was a direct interaction between the mRNA vaccine and the antibody targeting an immune checkpoint protein (CTLA-4 or PD-1). It is common general knowledge that mRNA vaccination leads to the expression of an antigen in the body which is recognised by the immune system
and presented on dendritic cells in an MHC complex
where it primes naive or resting T cells, leading to a
cellular immune response (see point 5. above). This
immune response is regulated by immune checkpoints at
different stages and with different mechanisms (see
Figure 3 of document D14 reproduced in point 4. above).

45. The board therefore concludes that a synergistic effect
of the components of the claimed vaccine/inhibitor
combination does not arise by a direct molecular
interaction but by an indirect interaction, namely the
release of an immune checkpoint block which allows an
effective immune response to the vaccination (see
points 15. and 17. above).

46. The question remains whether knowledge of the
mechanistic difference between CTLA-4 and PD-1 activity
would have prevented the skilled person from assuming
that an anti-PD-1 antibody would exert a similar
synergistic effect as the anti-CTLA-4 antibody in
document D13.

Vaccine enhancing or synergistic effect of anti-PD-1 antibody

47. The opponents referred to a number of documents showing
the effectiveness of anti-PD-1 antibodies in
combination with vaccines in formats other than RNA,
e.g.:
- viral vector vaccines of various types (see D10 and
  D80)
- peptide vaccines of various types (see D9, D31 and
  D65)
- cellular vaccines of various types (see D11, D29,
  D51, D52, D55 and D56)
48. Taking into account the comments by the patent proprietor on the disclosure in these documents, the board concludes that three documents explicitly disclose a synergistic effect between anti-PD-1 antibody and cancer vaccines (D29 with FVAX, and D11 and D55 with GVAX). Two further documents disclose a synergistic effect between an anti-PD-1 antibody, a further agent and cancer vaccines (D80 with anti-4-1BB antibody and an adenoviral vaccine and D9 with cyclophosphamide and a peptide vaccine). Still further documents disclose an enhancement of the vaccination effect by an anti-PD-1 antibody but do not explicitly mention synergism (D10 with a lentiviral vaccine, D51 with a transduced tumour cell vaccine, and D52 and D56 with a DC/myeloma fusion vaccine). Document D65 discloses synergism between the blockade of the PD-1 pathway through an anti-PD-L1 (the ligand of PD-1) antibody and a peptide vaccine.

49. Based on the state of the art and the common general knowledge on checkpoint inhibition (see points 15. and 17. above), the skilled person had a reasonable expectation that anti-PD-1 antibodies achieve a synergistic effect when combined with an mRNA vaccine.

50. The skilled person also had no reason to assume that this synergistic effect would not occur with an mRNA vaccine based on the disclosure of document D13, which showed this effect for an anti-CTLA-4 antibody (see point 41. above), and the common general knowledge on mRNA vaccines (see point 5. above).

Further arguments on inventive step

51. The patent proprietor considered potential safety issues to have been solved in document D13 with the use
of a lower dosage. These issues would have thus been of no concern to the skilled person, who would have had no reason to look for an alternative checkpoint protein to be targeted. Moreover, as indicated in document D13, the anti-CTLA-4 antibody ipilimumab was the only FDA-approved antibody at the priority date.

52. The board does not consider these arguments pertinent because the skilled person is always interested in finding alternatives and improving existing products and processes. The solution to potential safety issues by limitation to a low dose in document D13 is thus not a reason for the skilled person not to look for alternatives which did not have this limitation, such as anti-PD-1 antibodies (see point 30. above). Also, the fact that a CTLA-4 antibody was already approved by the FDA would not have dissuaded the skilled person from looking for other, not yet approved, alternatives.

53. The patent proprietor further argued that it was common general knowledge (see e.g. document D14, page 253, "At a glance" box) that "[r]esponses to PD1 blockade may correlate with the expression of PD1 ligands by tumour cells". Since in document D13 no expression or induction of PD-L1 was reported (see Figure 3C. and its legend), the skilled person would have assumed that the tumour model disclosed in document D13 would not be responsive to PD-1 blockade.

54. The board does not agree because the skilled person knew from several review articles that tumours respond to an increased antitumour immune response with increased PD-L1 expression (see e.g. D14, Figure 5). This is also evident from review article D15 (page 208, paragraph bridging columns): "recent findings support an alternative model, that B7-H1/PD-L1 upregulation on
tumor cells reflects their adaptation to endogenous immune responses directed at tumor antigens—a process we term adaptive resistance (J Taube et al., unpublished). In adaptive resistance, the tumor co-opts the natural physiology of the PD-1 pathway for tissue protection in the face of inflammation, to protect itself from an anti-tumor response."

55. Furthermore, document D13 does not mention PD-L1 expression or induction. It only reports 67 genes (mostly unidentified), the expression of which changed compared to the buffer control. Nineteen genes are listed as "strongly activated genes" (see Figure 3B and C and legend). The skilled person could therefore not know from the disclosure of document D13 whether PD-L1 was expressed or induced and to what level.

56. The post-published statement by one of the authors of document D13 that "the 'gene expression analysis' experiments presented in document E13 did not show any significant induction of PD-L1 expression by the mRNA vaccine in the used tumor model" (see point 1 in document D99) is not relevant because this knowledge was not available to the skilled person at the relevant date. Moreover, even in document D99 the absolute level of PD-L1 expression is not mentioned; only the absence of induction is (see point 2: "the 'gene expression analysis' presented in document E13 did not show any significant induction of PD-L1 expression by the mRNA vaccine", underlining in the original).

57. The board concludes that the skilled person would not have been dissuaded from replacing the anti-CTLA-4 antibody used in document D13 with an anti-PD-1 antibody.
58. The patent proprietor further argued that not all checkpoints were equally suited for combination with vaccines and referred to the example of anti-LAG3, which did not result in any enhancement of the vaccination effect in experiments submitted by the patent proprietor during the opposition proceedings (see patent proprietor's reply of 25 April 2022, page 35). The person skilled in the art could therefore not reasonably expect that anti-PD-1 antibodies would show a similar effect to anti-CTLA-4.

59. The board does not agree because the post-filed evidence on anti-LAG3 antibodies was not available to the skilled person at the relevant date. Moreover, it does not relate to a PD-1 pathway blocking agent and, therefore, cannot cast doubt on the statements made in the prior art that a PD-1 blockade together with an antitumour vaccine lead to a synergistic effect (see e.g. document D15, cited above). Also, the closest prior art D13 does not mention LAG3 but refers to other immunotherapeutic agents, including anti-PD-1 antibodies.

60. The patent proprietor also referred to the different results obtained with the cancer vaccines GVAX and FVAX in combination with anti-PD-1 antibodies (see document D29) as an indication that anti-PD-1 antibodies could not be reasonably expected to achieve a synergistic effect when combined with a different vaccine platform.

61. The board does not agree because document D13 already shows the effectiveness of an mRNA vaccine combined with a checkpoint inhibitor (anti-CTLA-4). Whether other vaccine formats might be less effective is therefore irrelevant for the expectation of success of the skilled person. The GVAX tested in document D29
also failed in combination with an anti-CTLA-4 antibody, thus pointing to the failure being due to the experimental set-up. Furthermore, a GVAX vaccine was shown to provide therapeutic benefit in combination with an anti-PD-1 antibody in document D11 (see title and abstract).

*Synergistic effect*

62. The patent proprietor also argued that a "synergistic effect was per se unpredictable" and would therefore warrant an inventive step as established by a number of decisions from the boards (see, for example, T 1814/11, T 2156/14, T 1642/07, T 1336/19 and T 2097/15).

63. The board disagrees because the decisions cited by the patent proprietor do not support such an "automatic inventiveness" approach.

64. In T 1814/11, the board found that the state of the art did not allow anticipating a synergistic effect when one of the compounds was structurally modified. It further found that a synergistic effect could not be predicted for classes of compounds but only for specific fungicides (see point 3.3).

65. In the case underlying decision T 2156/14, a compound with a known herbicidal activity in a combination was replaced by another compound with a known herbicidal activity but for which synergism was not predictable (see point 7.7). Also in decision T 2097/15 the board found that a synergistic effect could not be clearly expected when replacing one herbicide in a combination with another herbicide (see points 10.1 and 10.2).
66. In decision T 1642/07, the board formulated the objective technical problem as achieving an alternative potentiated effect "wherein 'potentiated' means additive until synergistic, or in other words 'at least additive'". The decision is therefore not relevant for inventive step of a composition showing a synergistic effect.

67. In decision T 1336/19, the board stated: "In principle, synergy is unpredictable. The state of the art does not hint at combining the three acids specified in claim 1 with any aldehyde, let alone with trans-2-hexenal, with the aim of obtaining a synergistic composition." Also in this case, the state of the art did not suggest combining the different components to provide a synergistic composition.

68. The board therefore agrees with decision T 116/18 (see Reasons 17.4.3) that "[a] synergistic effect, however, does not deserve a special position compared with other effects on which patent applicants or proprietors regularly rely for inventive step". Accordingly, as for any other effect, it has to be established whether, having regard to the state of the art, obtaining a synergistic effect was obvious. The answer depends on the details of the case and the state of the art.

69. In the case in hand, however, the finding that the synergistic effect could be reasonably expected to occur depended on the skilled person's fundamental understanding of the mechanistic relationship between the mRNA vaccine and the antibody targeting an immune checkpoint (see points 15. and 17. above) and not on any structural elements of the compounds under consideration.
70. The vaccine/inhibitor combination of claim 1 lacks an inventive step (Article 56 EPC).

Request for referral of questions to the Enlarged Board of Appeal (Article 112(1)(a) EPC)

71. The patent proprietor alleged that a referral of questions to the Enlarged Board of Appeal was required to ensure uniform application of the law because the board in the current case deviated from established case law on the inventive step of compositions showing a synergistic effect. It was a principle established by the case law of the boards that a synergistic effect is per se not foreseeable, this supporting the inventiveness of the claimed subject-matter.

72. The board did not agree that it was necessary to refer a question to the Enlarged Board of Appeal because neither had a point of law of fundamental importance arisen, nor was there any deviation from the established case law of the boards (see points 62. to 68. above). Rather, the relevant issue was of a substantive (factual) and not a legal nature. As outlined above, in the case in hand, due to the common knowledge on the interaction between vaccines and immune checkpoint inhibitors, a synergistic effect could reasonably be expected by the skilled person. The questions proposed by the patent proprietor (see D134 and point XIV. above) were therefore also not relevant in coming to a decision.

73. The board therefore did not allow the request.
Auxiliary requests 1 to 4 - claim 1

Inventive step (Article 56 EPC)

74. The patent proprietor did not submit arguments on inventive step for the claims of these requests.

75. The subject-matter claimed lacks an inventive step for the same reasons as outlined for the main request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated