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Datasheet for the decision of 22 November 2023

Case Number: T 1255/21 - 3.3.04

Application Number: 15720986.7

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Language of the proceedings: EN

Title of invention:
Peptide vaccine comprising mutant RAS peptide and chemotherapeutic agent

Patent Proprietor:
Targovax Solutions AS

Opponent:
Strawman Limited

Headword:
RAS peptide vaccine/TARGOVAX

Relevant legal provisions:
EPC Art. 56, 111(2)
RPBA 2020 Art. 13(2)

Keyword:
Inventive step - (no)
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Decisions cited:
G 0002/21, T 1110/03

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Case Number: T 1255/21 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 22 November 2023

Appellant: (Opponent)	Strawman Limited Orchard Lea, Horns Lane, Combe, Whitney, Oxfordshire OX29 8NH (GB)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Respondent: (Patent Proprietor)	Targovax Solutions AS Vollsveien 19 1366 Lysaker (NO)
Representative:	Marks & Clerk LLP 15 Fetter Lane London EC4A 1BW (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 28 May 2021 rejecting the opposition filed against European patent No. 3140320 pursuant to Article 101(2) EPC**

Composition of the Board:

Chairman	L. Bühler
Members:	B. Rutz
	A. Chakravarty

Summary of Facts and Submissions

I. An appeal was lodged by the opponent (appellant) against the decision of the opposition division to reject the opposition against European patent No. 3 140 320. The patent is entitled "*Peptide vaccine comprising mutant ras peptide and chemotherapeutic agent*". The patent is based on European application No. 15 720 986.7.

II. The patent was opposed on the grounds in Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and in Article 100(b) and (c) EPC.

III. With its reply to the appeal, the respondent defended the patent as granted as its main request, re-filed sets of claims of auxiliary requests 1 to 16 and 18 to 23, identical to auxiliary requests 1 to 22 filed during the opposition proceedings, and filed new auxiliary requests 17 and 24. The respondent in its reply also indicated that it had auxiliary requests 25 to 47, which corresponded to the combination of auxiliary request 24 with each of auxiliary request 1 to 23. However, it did not file these in writing.

IV. Independent claim 1 of the patent as granted reads:

"1. At least one peptide, suitable for eliciting an immune response, wherein the or each peptide corresponds to a fragment of a wild-type RAS protein but has one amino acid substitution thereof, for use in the treatment of cancer by simultaneous or sequential administration with pyrimidine analogue or a pharmaceutically acceptable salt thereof, wherein the

or each peptide comprises a region of at least 8 amino acids which includes position 12 or 13 of the RAS protein, and wherein the amino acid substitution of the or each peptide is at said position 12 or 13, respectively, and is selected from a G13A, G13C, G13D, G13R, G13S, G13V, G12A, G12C, G12D, G12R, G12S or a G12V substitution."

Independent claim 1 of auxiliary request 10 reads:

"1. At least a first peptide and a second peptide, each suitable for eliciting an immune response, wherein each peptide corresponds to a fragment of a wild-type RAS protein but has one amino acid substitution thereof, for use in the treatment of cancer by simultaneous or sequential administration with a pyrimidine analogue or a pharmaceutically acceptable salt thereof, wherein each of the first and the second peptide comprises a region of at least 8 amino acids which includes position 13 of the RAS protein, and wherein the amino acid substitution each peptide is at said position 13, and is selected from a G13A, G13C, G13D, G13R, G13S or a G13V substitution, and wherein the amino acid substitution in the first peptide is different from the amino acid substitution in the second peptide."

V. The following documents are referred to in this decision:

D5 M. K. Gjertsen et al., "*Intradermal ras peptide vaccination with granulocyte-macrophage colony-stimulating factor as adjuvant: clinical and immunological responses in patients with pancreatic adenocarcinoma*", Int. J. of Cancer 92, 2001, 441-450.

D6 S. Wedén et al., "*Long-term follow-up of patients with resected pancreatic cancer following vaccination against mutant K-ras*", Int. J. Cancer 128, 2011, 1120-1128.

D7 S. Nishida et al., "*Wilms Tumor Gene (WT1) peptide-based cancer vaccine combined with gemcitabine for patients with advanced pancreatic cancer*", J. Immunother. 37(2), 2014, 105-114.

D8 N. Suzuki et al., "*A phase I clinical trial of vaccination with KIF20A-derived peptide in combination with gemcitabine for patients with advanced pancreatic cancer*", J. Immunother. 37(1), 2014, 36-42.

D10 J. Hou et al., "*Combination of Low-Dose Gemcitabine and* Recombinant Quail Vascular Endothelial Growth Factor Receptor-2 as a Vaccine Induces *Synergistic Antitumor Activities*", Oncology 69, 2005, 81-87.

D15 H. H. Yoon et al., "*KRAS codon 12 and 13 mutations in relation to disease-free survival in BRAF-Wild-Type stage III colon cancers from an adjuvant chemotherapy trial (N0147 Alliance)*", Clinical Cancer Research 20(11), 2014, 3033-3043.

D16 S. Shahda and B. O'Neil, "*GI-4000 in KRAS mutant cancers*", Expert opinion on investigational drugs 23(2), 2014, 273-278.

D19 L. Rettig et al., "*Gemcitabine depletes regulatory T-cells in human and mice and enhances triggering of vaccine-specific cytotoxic T-cells*", Int. J. Cancer 129, 2011, 832-838.

D23 D. A. Richards, et al., Poster and Abstract entitled "*A Phase 2 adjuvant trial of GI-4000 plus Gem vs. Gem alone in ras mutation+ resected pancreas cancer: R1 subgroup and proteomic analysis*" presented at ESMO-GI June 2012

D25 International Clinical Trials Registry Platform, A Phase I/II Trial of TG01 and Gemcitabine as adjuvant therapy for treating patients with pancreatic cancer, EUCTR2012-002400-40-NO, accessed via the following link: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR20

D26 D. H. Palmer et al., "*TG01/GM-CSF and adjuvant gemcitabine in patients with resected RAS-mutant adenocarcinoma of the pancreas (CT TG01-01): a single-arm, phase 1/2 trial*", British Journal of Cancer, 2020, 1-7.

D31 J. N. Uram and D. T. Le, "*Current advances in immunotherapy for pancreatic cancer*", Curr Probl Cancer 37(5), 2013, 273-279.

D32 G. W. Middleton et al., "*A phase III randomized trial of chemoimmunotherapy comprising gemcitabine and capecitabine with or without telomerase vaccine GV1001 in patients with locally advanced or metastatic pancreatic cancer*", Journal of Clinical Oncology 31(18) suppl, 2013.

D33 S. L. Bernhardt et al., "*Telomerase peptide vaccination of patients with non-resectable pancreatic cancer: a dose escalating phase I/ II study*", British Journal of Cancer 95(11), 2006, 1474-1482.

D37 Annex A: Declaration by V. Levitsky, dated 22 February 2021

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

VII. Oral proceedings before the board took place in the form of a videoconference on 22 November 2023. During the oral proceedings the respondent withdrew auxiliary requests 1 to 9 and 11 to 47. At the end of the oral proceedings, the Chairman announced the board's decision.

VIII. The appellant's arguments, relevant to the decision, are summarised as follows.

Main request - claim 1
Inventive step (Article 100(a) EPC and Article 56 EPC)

Document D25 described a proposal for a phase I/II clinical trial for a peptide mixture that fell under the definition of claim 1 together with gemcitabine. The difference may be seen in that document D25 did not yet provide data on whether the tested combination was effective in cancer treatment while, in contrast, the opposed patent provided corresponding data.

At the relevant date of the patent, a person skilled in the art would have had no doubt about the structure of "TG01" mentioned in document D25 because this information was disclosed in document D6. The skilled person would have realised that the designations for the components of "TG01" used in document D25 were exactly the same as those used in document D6. The respondent had previously even acknowledged that document D25 disclosed the same peptide mixture as

disclosed in document D6 (see item 5.11.1 of respondent's observations filed on February 21, 2020).

Thus, the problem to be solved might be seen as putting into practice the treatment trial proposed in document D25 to see whether the proposed treatment was effective.

The data in document D6 showed that TG01/GM-CSF monotherapy resulted in 100% positive responses in the DTH skin test (see Table 1, "*CTN-98010, seven peptide vaccination*", and page 1124, right-hand column, second paragraph) indicating that no improvement was associated with the addition of gemcitabine.

It would have been obvious that the combination described in document D25 would provide an effective treatment for cancer because for both components, the Ras-derived peptides and gemcitabine were known agents for cancer therapy. Document D19 highlighted that the combination of a peptide vaccine and gemcitabine enhanced the effect of anti-tumor vaccination (see e.g. the last paragraph of document D19).

In the present case, the skilled person would have had a reasonable expectation that the claimed combination could be used to successfully solve the technical problem and would certainly have been motivated to put the combination therapy proposed in document D25 into practice.

Auxiliary request 10 - claim 1
Admission of line of arguments with regard to inventive step submitted during oral proceedings

An objection of lack of inventive step starting from document D25 had been raised already in opposition proceedings and was maintained in appeal. In its reply to the appeal the respondent only referred to the reasons provided for the main request, but did not substantiate how the amendments in claim 1 of auxiliary request 10 would overcome the objection. During oral proceedings before the board the respondent had presented new arguments, including a new objective technical problem. This was a change of the appeal case which should not be admitted because no exceptional circumstances had been present.

IX. The respondent's arguments, relevant to the decision, are summarised as follows.

Main request - claim 1
Inventive step (Article 100(a) EPC and Article 56 EPC)

Document D25 could not be used as an alternative starting point for assessing the inventive step of the present invention because it did not provide a disclosure of the compound represented by the term "TG01". This meant that it was not possible for the skilled person to establish, directly and unambiguously, what treatment was being studied in the proposed clinical trial of document D25. In addition, document D25 did not disclose any results of the proposed clinical trial. Thus, it did not provide a direct and unambiguous disclosure of any treatment of cancer, whether improved or otherwise. Moreover, the clinical trial proposed in document D25 aimed at

assessing the potential for gemcitabine to interfere with the immune response induced by TG01. This was a different purpose to that of the present invention. Thus, document D25 was not the closest prior art to the present invention as it was not a plausible starting point for the assessment of inventive step.

In any case, the claimed invention was not obvious to the skilled person starting from the disclosure in document D25. The difference between the disclosure of document D25 and the present invention was that document D25 did not disclose whether administration of a mutated peptide of the RAS protein, simultaneously or sequentially with a pyrimidine analogue, had a therapeutic effect on cancer. The technical effect of this difference was that the combination treatment provided an improved survival benefit over peptide vaccine monotherapy due to an improved immune response as compared to treatment with a peptide vaccine alone.

Consequently, the problem to be solved was the provision of a cancer treatment with an improved therapeutic effect compared to peptide vaccine monotherapy. There was nothing in documents D25 or D6 which suggested that this problem could be solved by combining a pyrimidine analogue with a RAS peptide vaccine. In particular, at the priority date of the patent, the person skilled in the art would have considered it counter-intuitive to administer a peptide vaccine and a pyrimidine analogue in combination to treat cancer because they knew that at least one clinical trial of a peptide vaccine and gemcitabine in combination had been halted due to a lack of improvement in patient survival (see document D31). Thus, the person skilled in the art would not have

adopted a "try and see" approach to solving the problem starting from document D25.

The data in the patent, in particular, figures 1 and 2, showed an improvement of the therapeutic effect compared to a monotherapy with RAS peptides as reported e.g. in document D6. Specifically, example 1 of the patent showed that in week 8, all 9 patients (100%) in the "*TG01 + Gemcitabine*" group had a positive DTH skin reaction (see figure 1) compared to about 65% of the 11 patients in the "*TG01 alone*" group (see figure 2).

Document D26 included evidence that supported the above mentioned technical effect. On the question of whether this could be taken into account in the assessment of inventive step, reference was made to the order in the Enlarged Board of Appeal's decision G 2/21. In the case at hand, the skilled person, having common general knowledge in mind, and based on the application as originally filed, would have derived the effect of improved therapy as being encompassed by the technical teaching and embodied by the originally disclosed invention. This was evident from the disclosure in the application as filed on page 5, lines 11 to 14 (corresponding to paragraph [0023] in the patent) which stated that: "*the administration of a RAS peptide vaccine in combination with an anti-metabolite chemotherapeutic agent (gemcitabine) significantly improved the immune response of patients as compared to the administration of the RAS peptide vaccine alone*".

Auxiliary request 10 - claim 1
Admission of line of arguments with regard to inventive step submitted during oral proceedings

The line of argument presented during oral proceedings only further elaborated the reasoning presented in the reply to the appeal in point 19.6.2. It was also based on paragraph [0090] of the patent which highlighted the purpose of the invention as an improved T cell immune response.

X. The appellant (opponent) requested that the decision under appeal be set aside and that the European patent No. 3 140 320 be revoked. Furthermore, auxiliary request 10 should be not admitted into the proceedings. The respondent's request to remit the case (see below) should not be admitted into the proceedings. The respondent's submissions on inventive step of the subject-matter of claim 1 of auxiliary request 10 that inventive step should be acknowledged due to the technical effect of a broader protective coverage of patients due to the two different peptides defined in the claim should not be admitted under Article 13(2) RPBA.

The respondent (patent proprietor) requested that the appeal be dismissed, i.e. that the patent be maintained as granted, or, alternatively that the patent be maintained in amended form based on the set of claims of auxiliary request 10. Furthermore, in case the board were to reach the conclusion that the subject-matter of the main request lacked an inventive step when considered starting from document D25 as closest prior art, then, instead of taking a decision on inventive step, the case should be remitted to the opposition division for further prosecution.

Reasons for the Decision

Main request – claim 1
Inventive step (Article 100(a) EPC and Article 56 EPC)

Choice of a suitable starting point

1. In its decision, the opposition division considered document D23 represented the closest prior art. Starting its analysis of inventive step from this document it came to the conclusion that the subject-matter of the claims as granted was not obvious. Although the opposition division in point 17 of the decision under appeal had recognised that the opponent had raised "*several inventive step attacks starting from D1, D7 to D9, D12, D14, D23 or D25*", it only assessed inventive step starting from document D23 (referring to the Guidelines for Examination in the EPO, November 2019, G-VII, 5.1).

2. However, according to the established case law of the boards, the assessment of inventive step should be done from all documents that could represent alternative workable routes to the invention (see Case Law of the Boards of Appeal, 10th edition 2022, I.D.3.1). Moreover, if a piece of prior art is "too remote" from an invention, it should be possible to show that the invention would not have been obvious to a skilled person starting from this piece of prior art (*ibid.*).

3. According to the decision under appeal "*D25 discloses a proposal for a phase I/II trial of a peptide mixture, referred to as 'TG01', and gemcitabine. D25 does not disclose the sequences of the peptides and no results for the trial are shown, and, thus, D25 is not*

considered to be a promising springboard for the invention." (see point 17.6). The board disagrees because, as also acknowledged in the decision under appeal (see above), the composition disclosed in document D25, even at first glance shares at least several features with the composition of the claim and is intended for the same purpose, namely "*treating patients with pancreatic cancer*" (see "Public title").

4. Document D25 must therefore be taken into account in the assessment of inventive step.

Disclosure of document D25

5. Document D25 is a print-out from the website "*International Clinical Trials Registry Platform*" maintained by the WHO. It refers to a clinical trial with the title "*A Phase I/II Trial of TG01 and Gemcitabine as adjuvant therapy for treating patients with pancreatic cancer*" registered with EUCTR, the EU Clinical Trials Register. The proposed trial aims to "*assess the potential for interference of Gemcitabine on immune responses to TG01* [...] *in patients receiving TG01 and GM-CSF after primary resection of pancreatic adenocarcinoma*", to "*assess the safety of Gemcitabine given concomitantly with TG01/GM-CSF vaccination*" and to "*assess the efficacy of TG01 and GM-CSF in patients with resected pancreatic cancer*" (see under "*Primary Outcome(s)*"). The exploratory objective is to "*assess the relationship between KRAS status and recurrence*".

6. Under the heading "*Intervention(s)*" three compounds are listed: TG01, GM-CSF (Amoytop) and Gemcitabine. GM-CSF is a commonly known protein and commercially available in lyophilised form. Gemcitabine is a pyrimidine analogue and chemotherapeutic agent which is

commercially available ("GEMZAR 1000"). The product code "TG01" is not commonly known. It is followed by a list of seven components, each of which has a "*Current sponsor code*" ("12A", "12C" etc.), an "*Other descriptive name*" (e.g. "12-A-p21 RAS(5-21)","12-C-p21 RAS(5-21)"), a "*Concentration unit*" ("mg milligram(s)") and a "*Concentration number*" ("0.1-").

7. From this list the skilled person would understand that the product "TG01" consists of seven components having the same concentration (0.1 mg) and whose descriptive names differ only in one letter ("A", "C" etc.). They would further understand that the product "TG01" relates to the oncoprotein "p21 RAS" because this is part of each of the seven other descriptive names and also appears as "*KRAS status and recurrence*" in the context of the exploratory objectives. p21 RAS is well known in the field of oncology as an oncoprotein (see e.g. document D16, which is a review article).

8. It was disputed between the parties whether the skilled person would have been able to determine what the composition identified as "TG01" actually consisted of, in particular, whether they would have known that it referred to a peptide vaccine with a specific composition. The appellant was of the view that the disclosure on page 2 under "*Primary Outcome(s)*": "*TG01/ GM-CSF vaccination*" of a combined vaccination of TG01 with the protein GM-CSF would have indicated to the skilled person that "TG01" consisted of peptides or proteins rather than nucleic acids or whole cells. The appellant further noted that this view was reinforced by the reference to the "*TG01 specific DTH skin test reaction*" proposed in document D25 to determine the immune response to "TG01", because DTH skin tests were known to be commonly used to test peptide vaccines.

9. The respondent questioned this and was of the opinion that vaccinations could also be carried out with other modalities such as yeast vehicles, DNA or RNA which could also be used in DTH skin tests (referring to document D37, points 5 and 6).

10. While the board agrees with the respondent that other vaccine formats were in principle known to the skilled person, the envisaged "*TG01 specific DTH skin test reaction*" and the concomitant vaccination with GM-CSF would have led the skilled person to conclude that "TG01" consisted of peptides or proteins because a specific DTH skin test reaction requires the antigens to be available to the immune system in the skin, and therefore they could not be encoded by RNA or DNA or hidden in a cell. This is also apparent from points 5 and 6 in document D37 referred to by the respondent which state that "*DTH responses are in vivo cell mediated immune responses initiated by the detection of an antigen*", i.e. the antigen has to be accessible. Moreover, both the patent and the references provided in D37, point 7, disclose DTH skin tests only for peptide vaccines.

11. Document D25 contains further indications that "TG01" refers to a peptide composition. Firstly, no reference is made to genetic material or gene therapy. Such a reference would have been required if such material was going to be used in the proposed clinical trial, because of the safety and regulatory requirements within the EU for genetic material (e.g. RNA or DNA). Secondly, the codes A, C, D, R, S, V, D in the seven descriptive names of the components of "TG01" were well known as one-letter amino acid codes and were (with the exception of A and C) not used for individual nucleic

acids. The board therefore agrees with the finding in the decision under appeal that the skilled person would have recognised that "TG01" denotes a peptide composition (see point 16.3, first sentence, of the decision under appeal).

12. In a fast-moving field such as medical research, and in particular the field of oncology, review articles can be considered to reflect the skilled person's common general knowledge (see e.g. decision T 1110/03, point 2.3 of the Reasons). Document D15 is such a review article and it discloses that the seven most common KRAS mutations in codons 12 and 13 were "p.G12D","p.G12V", "p.G12C", "p.G12A", "p.G12S", "p.G12R", "p.G13D" (see document D15, Abstract and Figure 2). In the light of their common general knowledge, the skilled person at the relevant date of the patent would therefore have recognised that the seven one-letter-code amino acid designations in the descriptive names and in the sponsor codes of the p21 Ras peptide components of TG01 used in document D25 corresponded exactly to the seven most common KRAS mutations in positions 12 and 13. The skilled person would also have recognised that the designations "12" (six times) and "13" (once) in the descriptive names and in the sponsor codes corresponded to the positions of the mutations in the RAS peptide ("12-A-p21 RAS(5-21)", "13-D-p21 RAS(5-21)" etc.).

13. The skilled person was further aware of clinical trials of cancer vaccines involving "*synthetic RAS peptides encompassing residues 5 - 21 of p21 RAS*" (see review article D16, page 274, right-hand column). The length and residues of these peptides matches the nomenclature used in document D25 for the components of TG01 ("...p21 RAS(5-21)").

14. In conclusion the skilled person having common general knowledge in mind would have recognised that the "TG01" composition referred to in document D25 contained seven peptides consisting of residues 5 to 21 of the p21 RAS oncoprotein and carrying each one of the seven most frequent mutations at positions 12 and 13.

15. The review article D16 further cites documents D5 and D6 (see paragraph bridging pages 274 and 275, references 15 and 16). Document D5 discloses vaccination of pancreatic cancer patients with synthetic ras peptides encompassing residues 5-21 of p21 ras and carrying substitutions of glycine (Gly or G) at position 12 with aspartate (Asp or D), cysteine (Cys or C), valine (Val or V) or arginine (Arg or R) (see page 442, paragraph bridging both columns). Document D6 discloses vaccination against mutant K-ras of patients with pancreatic cancer using "*synthetic peptides encompassing residues 5-21 of p21 ras*". The mixture CTN-98010 disclosed on page 1123, first full paragraph, contains seven peptides comprising substitutions A, C, D, R, S and V at position 12 and substitution D at position 13 ("*12ACDRSV13D/HCL*", wherein "*HCL*" denotes that the peptides are in the form of salts) and is administered with GM-CSF as adjuvant (see page 128, left-hand column, 4th full paragraph). The full sequence of the 17 amino acid long peptides is disclosed on lines 1 to 3, left-hand column of page 1123 of document D6. Because of the reference to "*K-ras 5-21*" and the identical amino acid abbreviations at positions 12 and 13, the skilled person would understand that the peptides disclosed in document D6 are identical to the seven components of TG01 in D25 named "*12-A-p21 RAS(5-21)*", "*12-C-p21 RAS(5-21)*", "*12-D-p21 RAS(5-21)*", "*12-R-p21 RAS(5-21)*", "*12-S-p21*

RAS(5-21)", "*12-V-p21 RAS(5-21)*" and "*13-D-p21 RAS(5-21)*". The skilled person would equally understand that the peptides disclosed in document D5 are identical to the four components of TG01 in D25 having substitutions with Asp, Cys, Val or Arg at position 12, i.e. "*12-D-p21 RAS(5-21)*", "*12-C-p21 RAS(5-21)*", "*12-V-p21 RAS(5-21)*", "*12-R-p21 RAS(5-21)*".

16. In conclusion, the use of the code-name "TG01" in document D25 does not affect the status of this document as a realistic starting point for assessing inventive step because the skilled person would have been able to determine what the composition identified as "TG01" consisted of.

Difference and technical effect

17. Document D25 discloses a proposal for a clinical trial for "*TG01 and Gemcitabine as adjuvant therapy for treating patients with pancreatic cancer*" (see "*Public title*"), i.e. of a composition falling under the definition in the claim. The only difference between the disclosure in the patent and the disclosure in document D25 is that the former discloses that the therapeutic effect which the trial is set up to test, is actually obtained. The evidence in the patent that said effect is obtained comes from the results of the DTH skin tests disclosed in the examples. It is common ground that this test is a suitable indicator for the existence of the relevant therapeutic effect.

18. The respondent argued that an improvement of the therapeutic effect could not be expected from the disclosure of document D25 thus rendering the combination treatment inventive. The board does not agree because document D25 already proposes the

treatment of cancer patients with a combination of RAS peptides and the pyrimidine analogue, gemcitabine. Putting this proposal into practice would inevitably have resulted in an improved therapeutic effect, if such effect was indeed achievable (see point 19. below). Such improvement therefore represents a bonus effect, which according to established case law does not contribute to an inventive step (see Case Law of the Boards of Appeal of the European Patent Office 10th edition, 2022, I.D.10.8). Notwithstanding this finding, the board will nevertheless address the arguments of the parties in relation to the alleged improvement.

19. Even if the evidence in document D26 were taken into account, it does not provide evidence for an improved treatment compared to the disclosure in document D6. This is because it does not disclose any data for a comparison with a treatment with TG01/GM-CSF alone, but only compared to gemcitabine alone (see Tables 3 and 4). In view of the already successful treatment of patients with TG01/GM-CSF alone reported in document D6, an improvement over gemcitabine alone as reported in document D26 is irrelevant. Moreover, the statement in D26 that "*these findings may suggest synergism between TG01/GM-CSF and chemotherapy*" is rather cautious (see page 5, right-hand column, penultimate paragraph). As pointed out by the appellant, the median overall survival of 33.3 months reported in document D26 is similar to the overall survival for patients receiving TG01/GM-CSF monotherapy reported in document D6 (see Table 1).

20. The effect of improved treatment compared to the vaccination with TG01/GM-CSF alone can therefore not be taken into account for the formulation of the objective technical problem.

Objective technical problem

21. In view of the differences between the claimed subject-matter and the closest prior art, the objective technical problem can be seen as providing an effective treatment for (pancreatic) cancer.

Obviousness

22. The question to be answered in assessing the obviousness of the claimed subject matter is whether or not the skilled person starting from the disclosure of the clinical trial proposal in document D25 would have reasonably expected that putting it into practice would result in an effective treatment for pancreatic cancer patients.

23. It is common ground that TG01/GM-CSF had a therapeutic effect in pancreatic adenocarcinoma patients, as evidenced by their DTH response and their prolonged overall survival (see e.g. document D6, Table 1 and page 1124, right-hand column, last paragraph). It is also undisputed that gemcitabine was a standard treatment of pancreatic cancer at the relevant date of the patent (see e.g. document document D7, page 105, right-hand column, first full paragraph: "*Gemcitabine has been the standard first-line treatment for patients with advanced pancreatic cancer, ...*"; document D8, page 36, right-hand column, lines 7 to 10: "*Gemcitabine (GEM) is currently one of the standard therapies for advanced pancreatic cancer, ...*"; document D19, page 837, left-hand column, lines 14 to 17: "*Gemcitabine is usually given at day 1 [...] as a single-agent therapy for pancreatic and cholangiocarcinoma.*"; document D23, page 2, right-hand column, "*Background: Patients with*

resected pancreas cancer treated with standard of care gemcitabine ..."; document D33, page 1480, right-hand column, lines 1 to 2: "*Gemcitabine treatment, which is the standard treatment* [for non-resectable pancreatic cancer] *in many countries, ...*"). The skilled person therefore knew that each of the two components to be tested in the clinical trial proposal set out in document D25 could separately achieve a therapeutic effect at least in patients with pancreatic cancer.

24. The respondent argued that the skilled person would not have had a reasonable expectation that the clinical trial proposed in document D25 would yield positive results. It suggested that the skilled person would in fact have been dissuaded from implementing said clinical trial proposal because of a possible interference of gemcitabine with TG01/GM-CSF vaccination. This view was said to be supported by the disclosure in document D25 itself because the main objective was given as assessing "*the potential for interference of Gemcitabine on immune response to TG01*". The respondent further referred to documents D31 and D32 which reported that clinical trials of a peptide vaccination combined with gemcitabine had been stopped because of a lack of improvement in patient survival. The respondent also referred to paragraph [0023] of the patent as giving a rationale for why gemcitabine might interfere with peptide vaccination: "*it had previously been believed that administering an anti-metabolite chemotherapeutic agent, such as gemcitabine, to a patient causes cell death of proliferating immune cells, including proliferating T cells, which would thereby reduce the activity of the patient's immune system and thus lower the immune response of the patient to a peptide vaccine that is administered simultaneously or sequentially*".

25. However, the board is not convinced that the above mentioned considerations would have dissuaded the skilled person from putting the clinical trial proposal set out in document D25 into practice. The skilled person would have understood the reference to interference in document D25 as a standard indication for any combination therapy, and as such it would not impart to the skilled person any particular prejudice against the proposed clinical trial. The clinical trials reported in documents D31 and D32 relate to a particular peptide (GV1001 from human telomerase), the effect of which together with gemcitabine was compared to gemcitabine alone. Therefore the finding of no therapeutic improvement for the combination tested was not due to interference of the peptide with gemcitabine, but rather was a result of a lack of effect of the particular peptide vaccine. Finally, the passage on interference in the patent itself was not available to the skilled person at the relevant date and appears to reflect general theoretical observations which are not backed up by any specific evidence. In contrast, the appellant has referred to a number of documents published before the relevant date of the patent which report successful therapy using peptide or protein vaccines in combination with gemcitabine (see e.g. document D7, Summary and page 113, left-hand column, first full paragraph: "*Despite its cytotoxicity, gemcitabine reportedly has immune-modulating functions, such as increase in antigen cross-presentation, and inhibition of B-cells, myeloid-derived suppressive cells and regulatory T cells, resulting in enhancement of the antigen-specific CTL function*"; document D8, Summary: "*IFN-γ-producing cells were induced by the KIF20A-derived peptide vaccine at a high rate, even in combination with GEM.*"; document

D10, page 81, right-hand column: "... *low-dose gemcitabine did not suppress the host's immune response, but potentiated the antitumor activity of the qVEGFR vaccine.*"). Also document D19 which investigates the effect of gemcitabine on regulatory T-cells and vaccine-specific cytotoxic T-cells in the context of DNA or mRNA vaccination concludes that "... *chemotherapy* [gemcitabine] *transiently lowers regulatory T-cell frequency and boosts subsequent antitumor vaccination.*" (see page 837, last paragraph).

26. In view of these positive reports of gemcitabine in combination with peptide or nucleic acid vaccines, the board cannot conclude that there was any prejudice or teaching away from combining peptide vaccines with gemcitabine in the art, which would have dissuaded the skilled person to put the clinical trial proposal of document D25 into practice. Rather, based on the teaching in the prior art and their common general knowledge, the skilled person is judged to have had a reasonable expectation of success when putting the proposal of document D25 into practice.

27. In view of the above considerations, it is concluded that the subject-matter of claim 1 lacks an inventive step (Article 56 EPC).

Request for remittal (Article 111(2) EPC)

28. During oral proceedings, the respondent requested that in case the board were to reach the conclusion that the subject-matter of the main request lacked an inventive step when considered starting from document D25 as closest prior art, then, instead of taking a decision on inventive step, the case should be remitted to the opposition division for further prosecution.

29. This request was made for the first time at the oral proceedings before the board. It represents a change of the respondent's appeal case since it deviates from the respondent's initial request asking the board to decide on the merits of the appeal. The respondent argued that the appellant had raised several objections of lack of inventive step starting from different documents. The opposition division, in line with the Guidelines for Examination, had considered a single document as closest prior art document, namely D23. This had not been contested by the appellant. The appellant's objection of lack of inventive step starting from document D25 had not been discussed and decided upon by the opposition division. While the appellant had maintained this objection in its statement of grounds of appeal, the discussion on appeal was superficial. The respondent would hence be deprived of a second instance if the board took a decision on the merits of this attack.

30. These circumstances are not exceptional and cannot justify the late change of the respondent's case. First, according to established case law, if there is more than one suitable starting point, inventive step has to be assessed with regard to each of these documents (see Case Law of the Boards of Appeal, 10th edition 2022, I.D.3.4.1). In view of this case law and the appellant's objections in the statement of grounds of appeal, the respondent could and should have formulated a request for remittal in its reply to the appeal. The board agrees in this regard with the appellant that the late submission of this request was surprising. Second, since the request for remittal is conditional upon a conclusion by the board which is adverse to the respondent, the request is not in line

with procedural economy and fairness. Indeed, remittal would lead to an unnecessary delay, since the decision by the opposition division on this issue (which would, in fact, amount to a review by the opposition division of the board's conclusions) could be appealed by the party negatively affected by this decision. Thus, the same issue would have to be assessed twice by the board.

31. According to Article 13(2) RPBA and in the absence of any exceptional circumstances the request was not admitted.

Auxiliary request 10
Admission (Article 12(4) RPBA)

32. In view of the negative finding with regard to inventive step (see below) the board does not deem it necessary to provide reasons for the admission of this request.

Admission of line of arguments with regard to inventive step submitted during oral proceedings (Article 13(2) RPBA)

33. On the issue of inventive step of the subject-matter of auxiliary request 10 starting from document D25 as closest prior art, the respondent in its reply to the statement of grounds of appeal, stated that the difference of the claimed subject-matter to the disclosure in document D25 was "*a second peptide of the RAS protein having an amino acid substitution at position 13 of the RAS protein which is different from the position 13 substitution of the first peptide*". The technical effect of this difference and the resulting problem were the same as set out with regard to the main request.

34. However, the general line of arguments given for the main request does not take the particular difference between the subject-matter of claim 1 of auxiliary request 10 and the disclosure in document D25 into account or explain its relevance for the assessment of inventive step of the subject-matter of claim 1 of auxiliary request 10.

35. During the oral proceedings, the respondent relied on paragraph [0090] of the patent as a basis for its inventive step defence according to which : "*the at least one peptide used according to the present invention is a peptide which corresponds to the protein fragments which result from the intracellular proteolytic degradation of RAS proteins, which can then be displayed on HLA molecules, and to which individuals generally have a reactive T cell in their T cell repertoire*".

36. However, there is no direct connection between the subject-matter of claim 1 of auxiliary request 10, a composition comprising at least two peptides having different substitutions in position 13, and the general disclosure in paragraph [0090] with regard to HLA presentation of RAS protein fragments because this passage does not detail that different patient groups might have different RAS mutations which could be covered by at least two peptides. The skilled person when reading paragraph [0090] would not understand that the presence of at least two peptides was associated with an improved therapeutic effect of the composition. The board therefore found this passage in the patent was not equivalent to the line of argument put forward by the respondent which was therefore presented for the first time during oral proceedings.

37. In view of the above, the new line of arguments on inventive step presented for the first time at the oral proceedings was not admitted because it represented a change of the appeal case and no exceptional circumstances which justified its admittance were presented (Article 13(2) RPBA).

Inventive step (Article 56 EPC)

38. When disregarding the line of arguments with regard to inventive step submitted during oral proceedings and considering the case presented in the reply to the statement of grounds of appeal, the subject-matter of claim 1 lacks an inventive step for the same reasons as given for the main request.

39. In view of the above considerations, no claim request is allowable and the patent must be revoked.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

I. Aperribay L. Bühler

Decision electronically authenticated