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Datasheet for the decision of 17 December 2025

Case Number: T 1909/23 - 3.3.04

Application Number: 18199105.0

Publication Number: 3473267

IPC: A61K39/00, C12Q1/68, A61P35/00, G01N33/50

Language of the proceedings: EN

Title of invention:
Individualized vaccines for cancer

Patent Proprietors:
BioNTech SE
TRON - Translationale Onkologie an der Universitätsmedizin der Johannes Gutenberg-Universität Mainz gemeinnützige GmbH

Opponent:
Withers & Rogers LLP

Headword:
RNA cancer vaccines II/BIONTECH

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

This datasheet is not part of the Decision
It can be changed at any time and without notice

Keyword:
Grounds for opposition - lack of patentability (no) - insufficiency of disclosure (no) - extension of subject-matter (no)

Decisions cited:
T 2084/11, T 1270/20, T 2168/21

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Case Number: T 1909/23 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 17 December 2025

Appellant: (Opponent)	Withers & Rogers LLP 2 London Bridge London SE1 9RA (GB)
Representative:	Tombling, Adrian George Withers & Rogers LLP 2 London Bridge London SE1 9RA (GB)
Respondent I: (Patent Proprietor 1)	BioNTech SE An der Goldgrube 12 55131 Mainz (DE)
Respondent II: (Patent Proprietor 2)	TRON - Translationale Onkologie an der Universitätsmedizin der Johannes Gutenberg-Universität Mainz gemeinnützige GmbH Freiligrathstraße 12 55131 Mainz (DE)
Representative:	Schnappauf, Georg ZSP Patentanwälte PartG mbB Hansastraße 32 80686 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 26 September 2023 rejecting the opposition filed against European patent No. 3 473 267 pursuant to Article 101(2) EPC**

Composition of the Board:

Chairwoman	A. Bacchin
Members:	B. Rutz
	D. Luis Alves

Summary of Facts and Submissions

I. The appeal by the opponent (appellant) lies from the decision of the opposition division to reject the opposition against European Patent No. EP 3 473 267 (the patent). The patent has been granted on European Patent application 18 199 105.0 (the application) which is a divisional application of European Patent application 12 723 117.3 which was published under the PCT as international application WO 2012/159754 (the parent application).

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

III. Claim 1 of the patent reads as follows:

"1. An individualized cancer vaccine for use in a method of treating a cancer patient, said method comprising the steps:
(A) providing the individualized cancer vaccine by a method comprising the steps:
(a) identifying cancer specific somatic mutations in a tumor specimen of the cancer patient to provide a cancer mutation signature of the cancer patient, comprising
(aa) obtaining nucleic acid sequence information by sequencing genomic DNA and/or RNA of the tumor specimen of the cancer patient,
(bb) obtaining reference nucleic acid sequence information by sequencing DNA or

RNA of normal non-cancerous cells obtained from the cancer patient, and

(cc) comparing the nucleic acid sequence information from the tumor specimen obtained in step (aa) with the reference nucleic acid sequence information obtained in step (bb); and

(b) providing an RNA vaccine featuring the cancer mutation signature obtained in step (a), wherein the RNA vaccine comprises RNA encoding a recombinant polyepitopic polypeptide comprising mutation based neo-epitopes; and

(B) administering the individualized cancer vaccine to the cancer patient."

IV. With its statement of grounds of appeal the appellant filed documents D24 to D27.

V. With their reply to the appeal the patent proprietors (respondents) filed auxiliary requests 1 to 12.

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

D1 H. G. Rammensee et al., "*Cancer Vaccines: Some Basic Considerations*", Genomic and Personalized Medicine Volumes I and II, 2009, Chapter 50, 573-89

D2 H. G. Rammensee, "*Some considerations on the use of peptides and mRNA for therapeutic vaccination against cancer*", Immunology and Cell Biology 84, 2006, 290-4

D3 A. Suhrbier, "*Multi-epitope DNA vaccines*", Immunology and Cell Biology 75, 1997, 402-8

D4 A. Suhrbier, "*Polytope vaccines for the codelivery of multiple CD8 T-cell epitopes*", Expert Review Vaccines 1(2), 2002, 207-13

D5 J. H. Kessler and C. J. M. Melief, "*Identification of T-cell epitopes for cancer immunotherapy*", Leukemia 21, 2007, 1859-74

D6 J. P. Carralot et al., "*Production and characterization of amplified tumor-derived cRNA libraries to be used as vaccines against metastatic melanomas*", Genetic Vaccines and Therapy 3(6), 2005, 1-10

D7 S. Kreiter et al., "*Tumor vaccination using messenger RNA: prospects of a future therapy*" Current Opinion in Immunology 23, 2011, 399-406

D8 WO 2005/028505 A2

D13 Experimental Data, 2 pages

D14 Anonymous (Editorial), "*The problem with neoantigen prediction*", Nature Biotechnology 35(2), 2017, 97

D15 M. Günder, "*Charakterisierung des HLA-Ligandoms und des Exoms von Hepato- und Cholangiozellularen Karzinomen im Hinblick auf eine patientenindividualisierte Peptidvakzinierung*", Doctoral thesis, 2012, 1-216

D16 U. Sahin and Ö. Tureci, "*Personalized vaccines for cancer immunotherapy*", Science 359 (6382), 2018, 1355-60

D17 U. Sahin et al., 2017, "*Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer*", Nature 547, 2017, 222-6, Supplementary Information (14 pages)

D18 J. C. Castle et al., "*Exploiting the Mutanome for Tumor Vaccination*", Cancer Research 72(5), 2012, 1081-91

D24 EP 2100620 A1

D25 WO 02/098443 A2

D26 US 2006/0204523 A1

D27 US 2006/0188490 A1

VII. The board summoned the parties to oral proceedings and issued a communication under Article 15(1) RPBA highlighting in particular the similarities of the case to earlier case T 2168/21 which dealt with the patent granted from the parent application.

VIII. In its preliminary opinion the board *inter alia* expressed the view that the subject-matter of the patent as granted did not extend beyond the content of the parent application as filed, that the subject-matter of granted claim 1, as well as of the dependent claims 2 to 13, was novel over document D1, that the invention to which the claims of the patent as granted relate was sufficiently disclosed and that the claimed subject-matter was inventive.

IX. With the letter dated 21 August 2025 the appellant indicated that it would not attend the oral proceedings.

X. In view of the fact that the respondents had requested oral proceedings only "*in the event a decision not to maintain the Patent as granted is contemplated*" the board cancelled the oral proceedings.

XI. The appellant's submissions are summarised as follows.

Claim interpretation

Feature 1.5.2 in claim 1 ("*wherein the RNA vaccine comprises RNA encoding a recombinant polyepitopic polypeptide comprising mutation based neo-epitopes*") did not define the nature of "RNA", i.e. whether it represented a single type RNA (molecule) or an ensemble ("collection") of distinct type RNA molecules. Thus, both embodiments fell under the scope of claim 1 and

might encode "a recombinant polyepitopic peptide". It was well established that the undefined article "a" covered "one or more polypeptides". That understanding was in line with the provision of either a "single type RNA molecule" or an "ensemble of distinct type RNA molecules". Accordingly, feature 1.5.2 did not exclusively define one single type RNA coding for one single polyepitopic polypeptide. Rather, its nature remained undefined by claim 1. By the language of feature 1.5.2 (including the embodiment with more than one encoded polypeptide) embodiments with distinct RNA molecules encoding distinct polypeptides were encompassed by claim 1, wherein each polypeptide might comprise one single (or more) "mutation-based epitopes".

Dependent claim 13 of the opposed patent defined the vaccine as a "collection of MHC presented epitopes incorporating sequence changes" which was synonymous to "neo-epitopes" (see paragraph [0029] of the opposed patent). The term "collection" was defined by paragraph [0029] of the opposed patent by exemplary embodiments, e.g. "2 or more" neo-epitopes. Thus, "2 or more neo-epitopes" was not a mandatory feature of claim 1, but a preferred embodiment, as evidenced by the claim set itself and by the opposed patent's specification.

Added subject-matter (Article 100(c) EPC)

Paragraph [0038] of the opposed patent defined that "*... the invention may provide one or more neo-epitopes (including known neo-epitopes and neo-epitopes identified according to the invention) as well as one or more epitopes not containing cancer-specific somatic mutations...*".

In other words, "known neo-epitopes" were not identified according to the invention, whereas other neo-epitopes were those identified according to the invention. "Neo-epitopes identified according to the invention" corresponded to the subject-matter of original claim 1, which formed the basis for claim 1 as granted.

While the "cancer mutation-based signature" referred to the specific set of "neo-epitopes identified according to the invention" (meaning according to the subject-matter of original claim 1), the opposed patent defined a set of "known" neo-epitopes, which were – as a matter of fact – not identified according to the invention (thus did not correspond to the subject-matter of original claim 12). That set of "known neo-epitopes" was, however, encompassed by the scope of claim 1 of the opposed patent as well. The language of claim 1 of the opposed patent was not restricted to "neo-epitopes" of the "cancer signature according to the invention" (which meant according to the method of original claim 1), thereby going beyond the original disclosure.

Page 9 (lines 9-12) explicitly referred to "neo-epitopes identified according to the invention". Also page 11, ultimate paragraph, referred to a "vaccine obtainable by the method according to the invention" and linked the neo-epitopes to cancer specific mutations in a tumor specimen of the patient.

Thus, the citations by the original disclosure all exclusively referred to "*neo-epitopes identified according to the invention*" (i.e. according to original claim 1) and not to "*known neo-epitopes*" (as defined by paragraph [0038] of the opposed patent). Yet, claim 1

of the opposed patent was not restricted to "neo-epitopes identified according to the invention", but covered any "neo-epitope" (including other "known epitopes"). Any "neo-epitope" meant that it might be a "cancer neo-epitope" of the "cancer mutation signature" as identified according to the method of the invention or another "(known) neo-epitope" (which was not identified by the method of the invention and/or not identified for the patient to be treated).

For that reason alone, the subject-matter of claim 1 of the opposed patent went beyond the original disclosure.

The term "cancer mutation signature" as such also did not match with "neo-epitopes" or "neo-epitopes as identified according to the invention" (see patent, paragraph [0029], reflecting common general knowledge). A "cancer-specific mutation" was a necessary, but not a sufficient prerequisite for rendering a peptide having a cancer mutation a "neo-epitope".

Novelty (Articles 100(a) and 54 EPC)

The subject-matter of claim 1 lacked novelty over the disclosure of document D1.

Feature 1.2 ("providing the individualized cancer vaccine") and 1.6 ("administering the individualized cancer vaccine") were redundant and did not further limit the claimed "use in a method of treating a cancer patient". They might thus be disregarded when assessing novelty.

All of the (genuine) features of claim 1 were anticipated by document D1 (see Figure 50.1 and its legend).

Feature 1.5.2 was anticipated by Figure 50.1 as well ("all tumor-associated/specific structures", i.e. all of the "tumor-specific mutations" identified by the step represented by the box). Such "tumor specific mutations" were even defined as a highly relevant factor on page 576, right-hand column, first full paragraph when referring to Figure 50.1. This underlined the understanding that an "ideal vaccine" should contain "*all tumor structures distinguishing the tumor from normal cells, including the mutations, the apparent gene expression and the post-translational modifications*".

Thus, the "ideal vaccine" of D1 contained all such tumor-specific mutations as a key element for realizing its "ideal character".

Even if document D1 were interpreted such that it exclusively taught "*multi-epitope vaccines*" based on a multitude of RNA molecules each encoding one single neo-epitope only, such an embodiment would still fall under the scope of claim 1 due to its broad language.

Thereby, all of the (genuine) features of claim 1 were anticipated by document D1.

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

The scope of claim 1 was essentially limited only by process-like features characterizing the individualised approach. It was readily understood that these process-like features were generically defined as well. It was further noted that just one single embodiment of a claimed RNA vaccine encoding a poly-neo-epitopic polypeptide (i.e. as described at paragraphs [0347],

[0348] and [0349]) and used by the Examples of the opposed patent fell under the scope of claim 1. While under specific conditions one single embodiment might be sufficient to establish "sufficiency of disclosure", in view of the breadth of claim 1 and the complexity of the technology required to arrive at functional individualised cancer vaccines (which factors must be weighed in), the opposed patent's one single embodiment could not establish "sufficiency of disclosure over the entire scope" of claim 1 as a product-for-use claim.

Documents D14 to D18 were cited as evidence that the invention as claimed was not sufficiently disclosed.

Inventive step (Articles 100(a) and 56 EPC)
Document D1 as starting point

Even if document D1 were not considered as novelty-challenging, its teaching clearly suggested mRNA as the preferred compound class for designing an individualised cancer vaccine based on the patient's characteristic tumor mutation pattern (see e.g. D1's Figure 50.1).
Even by ignoring D1's pointers to multi-epitope vaccines, poly-epitopic anti-cancer (peptide and nucleic acid) vaccines were well known in the art as an attractive option for designing an individualised vaccine for the treatment of malignant disorders, as e.g. evidenced by the review publications D3/D4/D5.
Thus, for an individualised approach in view of D1, the skilled person was prompted to use mRNA coding for a recombinant polyepitopic polypeptide comprising mutation-based neo-epitopes as a cancer vaccine by his common general knowledge.

In particular, there was no inventive merit, as it was common general knowledge
1. to pursue a personalised approach for designing and synthesizing a personalised mRNA-based vaccine containing all tumour associated or specific structures (cf. D1);
2. to successfully use mRNA for tumour vaccination (cf. D2, D7); and
3. to successfully employ poly(neo)epitopic constructs for cancer therapy (cf. D3, D4, D5).

Alternatively, D1 textbook knowledge in combination with documents D8, D24, D25, D26 or D27 suggested the claimed subject-matter as well.

The opposed patent did not support any unexpected or superior effects. If at all, it taught that mRNA encoding a poly-neo-epitopic fusion polypeptide elicited an anti-tumor response (as corresponding peptide-based vaccines do). The patent proprietor did not provide any evidence for an improvement by the mRNA-based vaccine vs. a peptide-based vaccine. Moreover, document D13 provided experimental evidence that the claimed embodiment (combining various mutation-based neo-epitopes on one single polypeptide (encoded by one single RNA)) was not superior, in terms of an immune response, to a vaccine comprising the same neo-epitopes encoded by distinct mRNAs.

As the opposed patent did not provide any data comparing the effects of the claimed subject-matter to prior art approaches, prior art documents D6, D8 or D3 might serve as alternative starting points leading the skilled person to the claimed subject-matter by applying his common general knowledge only.

Documents D3, D6 or D8 as starting points

The object underlying the opposed patent resided in the identification of an alternative for prior art vaccines, such as e.g. peptide-based cancer vaccines, based on an individualised approach involving mutant peptides representing the patient's tumour-specific mutations.

Prior art documents D6 (which presented experimental evidence for the efficacy of an anti-cancer (melanoma) vaccine based on mRNA), D8 (which taught multiepitopic polypeptides for use in cancer therapy), and D3 (which taught DNA cancer vaccines encoding a multiepitope polypeptide based on altered self-antigens), might serve as alternative and appropriate starting points for the skilled person's considerations. In the absence of any superior results for the claimed subject-matter over approaches as exemplified by any one of D6, D8 or D3, the claimed subject-matter was an obvious alternative to any one of the approaches taught therein.

XII. The respondents' submissions are summarised as follows.

Claim interpretation

Independent claim 1 was a purpose-limited product claim, in particular a claim directed to an individualised cancer vaccine for use in treating cancer in a patient, which RNA encoded a recombinant polyepitopic polypeptide comprising tumor-specific neo-epitopes determined from cancer tissue of the patient, which neo-epitopes were at least a portion of the cancer mutations present in one or more cancer cells of

the patient and were not present in a normal cell of the patient.

The plain wording of item (b) of claim 1 required that the recombinant polypeptide encoded by the RNA comprised "mutation based neo-epitopes", i.e. more than just a single neo-epitope.

The subject-matter of claim 1 encompassed RNA vaccines featuring the cancer mutation signature of the patient, which were cancer specific somatic mutations of the patient (identified according to the invention). Thus, at a minimum, the RNA of the vaccine had to encode neo-epitopes that were a part of the cancer mutation signature of the patient. However, other epitopes could be included in the polyepitopic polypeptide in addition to the neo-epitopes identified according to the invention, as explained on page 11, bottom paragraph of the application as originally filed and in originally filed claim 11. Thus, the vaccine might contain other epitopes "not identified according to the invention", but the vaccine had to always contain neo-epitopes "identified according to the invention".

Added subject-matter (Article 100(c) EPC)

All the features of claim 1 were disclosed in combination in claims 1, 9, and 21 and in the description as originally filed. With regard to steps (aa), (bb) and (cc) of claim 1 support was found in the description as originally filed on page 7, fourth paragraph. Further support could be found on page 11, last paragraph ("recombinant"), page 9, third paragraph ("polyepitopic") and the paragraph bridging pages 10 and 11 ("polyepitopic polypeptide").

Novelty (Articles 100(a) and 54 EPC)

The disclosure of document D1 was not an enabling disclosure of the individualised RNA cancer vaccine as claimed. The alleged "disclosure" of a method of providing an individualised cancer vaccine was purely speculative and not supported by any facts, let alone experimental data. This was highlighted by the fact that Fig. 50.1 and the paragraph bridging the columns on page 578 of document D1 referred to by the opponent/ appellant related to an "*ideal cancer vaccin*e", which, according to the authors of document D1 themselves, had not been achieved yet, and, in fact, "*can never be achieved*" (see page 576, right column, 2nd to 4th paragraph).

Additionally, the subject-matter of claim 1 was not the same since it was directed to the use of an individualised RNA cancer vaccine, which vaccine featured the mutation signature of a patient comprising an RNA encoding a recombinant polyepitopic polypeptide comprising mutation based neo-epitopes. D1 did not disclose a polyepitopic polypeptide, much less an RNA encoding such a polyepitopic polypeptide and its use as a vaccine to treat a cancer patient (see paragraph bridging the left- and right-hand columns on page 578).

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

The patent provided detailed information on how to put the invention into practice, including how to determine cancer-specific mutation based neo-epitopes, and showed that an RNA vaccine encoding such mutation based neo-epitopes was able to treat cancer in the patient. The opponent/appellant had not provided substantial

submissions as to why the claimed invention could not be carried out.

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

The closest prior art, i.e. D1, failed to disclose polyepitopic polypeptides comprising mutation-based neo-epitopes, let alone evidence in the form of experimental data, that the administration of an RNA molecule encoding a recombinant polyepitopic polypeptide comprising cancer specific somatic mutation based neo-epitopes identified in a cancer patient had an anti-tumor effect in said cancer patient.

The objective technical problem was to provide a personalised cancer vaccine with therapeutic efficacy.

Neither common general knowledge nor prior art documents D2, D3, D4, D5, D8, D24, D25, D26 and D27 could compensate for the lack of enabling disclosure in D1.

Even if D1 were to be considered as an enabling prior art document for achieving a therapeutic effect, D1 still could not render obvious the claimed subject-matter. In addition, the teaching of D1 was generally not combinable with most of the secondary references cited by the opponent/appellant. The teaching of D1 aimed at achieving a therapeutic effect by providing the broadest possible number, kind and variety of epitopes found in cancer cells (see also Figure 50.1 of D1). It was evident that the "ideal" cancer vaccine of D1 was therefore based on the concept of providing a broad spectrum of epitopes of the cancer cells of a patient to ensure that an effective immune response could be launched against the cancer of the patient.

The skilled person would not have considered delivering the epitopes of this concept of D1 by making use of the DNA of D3, D4, D5 or D8 which encoded a polyepitopic polypeptide designed to provide a limited number of epitopes only. Taking into account that this combination would have significantly reduced the number of epitopes of the "ideal" vaccine of D1, the skilled person would not have had the required reasonable expectation that the concept of D1 would still work when delivering only a few of the epitopes of the "ideal" vaccine of D1 with the DNA-encoded polyepitopic polypeptide of D3, D4, D5 or D8.

Document D6 relied on the use of the entire transcriptome of a tumour, which was not the same as the identification of cancer specific somatic mutations determined from a tumour specimen of a patient, but rather all antigens expressed in the tumour cell. It was not apparent how a skilled person, based on D6 could have envisaged administering an RNA which comprised all epitopes of the RNA library. It was not even clear whether this would be feasible without restricting the coding sequence of the RNA to a limited number of promising epitopes (e.g. cancer specific somatic mutations or neo-epitopes).

There was no suggestion in D6 that only cancer specific somatic mutations should be used for immunotherapy of a cancer patient. Most of the transcripts identified in Table 2 of D6 encoded products of normal housekeeping genes essential for the survival of all healthy cells and tissues. D6 did not mention that any of these proteins comprised a single mutation based neo-epitope, let alone two or more neo-epitopes as required by claim 1. The opponent/appellant failed to explain why the skilled person should have linked the coding

sequence for two or more mutation based neo-epitopes of the RNA library of D6 to generate a polyepitopic polypeptide comprising mutation based neo-epitopes when this document did not even mention neo-epitopes or polyepitopic polypeptides.

Even if documents D3, D4 and D5 were considered common general knowledge, in order to find the claimed subject-matter obvious, without the use of hindsight, there still needed to be a pointer to combine the teachings in the prior art.

Documents D3 and D8 did not aim at providing an individualised cancer therapy, or at least a vaccine suitable for an individualised cancer therapy. Thus, these documents were not suitable as closest prior art.

XIII. The appellant requested that the decision under appeal be set aside and the patent be revoked.

The respondents requested that the appeal be dismissed, i.e. the opposition be rejected and the patent be maintained as granted.

Reasons for the Decision

Admittance of documents D24 to D27 (Article 12(4) and (6) RPBA)

1. Documents D24 to D27 have been filed for the first time in appeal proceedings. They concern polyepitopic nucleic acid constructs in the field of vaccines. The board does not admit these documents in application of Article 12(4) and (6) RPBA because they address issues which were already discussed in the context of inventive step in opposition proceedings and thus could and should have been filed earlier.

Technical background

2. Cancers may arise from the accumulation of genomic mutations and epigenetic changes, of which only a fraction may have a causative role. **Tumour-specific antigens (TSAs)** are present only on tumour cells and not on any other cell, while **tumour-associated antigens (TAAs)** are present on some tumour cells and also on some normal cells. TSAs are particularly interesting targets for immunotherapy because they allow targeting the tumour without damaging normal cells. Human cancers carry on average 100 to 120 non-synonymous mutations, i.e. DNA-level mutations which lead to a change in the encoded protein. More than 95% of tumour mutations are unique and patient specific (see patent, paragraph [0005]). Non-synonymous point mutations resulting in amino acid changes that will be presented by the patient's **major histocompatibility complex** (**MHC**) molecules provide **novel epitopes** (**neo-epitopes**) which are specific to the patient's cancer and not found in normal cells of the patient (see patent, paragraph [0010]).

3. Vaccination can be carried out in a variety of formats, such as inactivated or attenuated pathogens, recombinant proteins, peptides, viral vectors, DNA and RNA.

4. The advantages of using RNA as "a *kind of reversible gene therapy*" for vaccination include transient expression and a non-transforming character. "*RNA does not need to enter the nucleus in order to be expressed and moreover cannot integrate into the host genome, thereby eliminating the risk of oncogenesis. Transfection rates attainable with RNA are relatively*

high. Furthermore, the amounts of protein achieved correspond to those in physiological expression" (patent, paragraph [0012]). mRNA "*has an intrinsic adjuvant effect by triggering mechanisms of innate immunity through pattern recognition receptors (PRRs) expressed by antigen-presenting cells (APCs) such as dendritic cells (DCs)*" (document D7, page 399, left-hand column).

Main request - patent as granted
Patent family and decision T 2168/21 concerning European patent No. 2 714 071

5. This board in a different composition decided in case T 2168/21 about European patent No. 2 714 071 which was granted from the parent application of the present application.

6. Claim 1 of EP 2 714 071 reads as follows:

"1. An individualized cancer vaccine for use in a method of treating a cancer patient, said method comprising the steps:
(a) providing said individualized cancer vaccine by a method comprising the steps:
(aa) identifying cancer specific somatic mutations in a tumor specimen of the cancer patient to provide a cancer mutation signature of the patient; and
(ab) providing an RNA vaccine featuring the cancer mutation signature obtained in step (aa), wherein the RNA vaccine featuring the mutation signature of the patient comprises RNA encoding a recombinant polyepitopic polypeptide comprising mutation based neo-epitopes; and

(b) administering said individualized cancer vaccine to the patient."

7. Claim 1 of the present patent reads as follows (differences to claim 1 of EP 2 714 071 highlighted by the board):

"1. An individualized cancer vaccine for use in a method of treating a cancer patient, said method comprising the steps:
(A) providing ~~said~~the individualized cancer vaccine by a method comprising the steps:
(a) identifying cancer specific somatic mutations in a tumor specimen of the cancer patient to provide a cancer mutation signature of the cancer patient, comprising
(aa) obtaining nucleic acid sequence information by sequencing genomic DNA and/or RNA of the tumor specimen of the cancer patient,
(bb) obtaining reference nucleic acid sequence information by sequencing DNA or RNA of normal non-cancerous cells obtained from the cancer patient, and
(cc) comparing the nucleic acid sequence information from the tumor specimen obtained in step (aa) with the reference nucleic acid sequence information obtained in step (bb);
and
(b) providing an RNA vaccine featuring the cancer mutation signature obtained in step (a), wherein the RNA vaccine ~~featuring the mutation signature of the patient~~comprises RNA encoding a recombinant polyepitopic polypeptide comprising mutation based neo-epitopes; and

(B) administering ~~said~~the individualized cancer vaccine to the cancer patient."

8. Claim 1 of the present patent thus essentially differs from claim 1 of EP 2 714 071, dealt with in decision T 2168/21, in the addition of steps (aa), (bb) and (cc) and in the absence of the further characterisation of the RNA vaccine as "*featuring the mutation signature of the patient*".

9. The decision in case T 2168/21 is formally not binding on the present board due to the independency of the proceedings between parent and divisional application(s). Neither has it an effect of *res iudicata* for the present proceedings due to the lack of identity of facts and claimed subject-matter (cf. e.g. T 1270/20, Reasons 3.8.2; T 2084/11, Reasons 1.3; see also Benkard, EPÜ (4th edition), Art. 76, Rn 10). However, in view of the very similar wording of claim 1 of both patents, the conclusions drawn in the present case and the reasoning of this decision are similar to those of T 2168/21.

Claim interpretation

10. The claim relates to a purpose-limited product in the sense of Article 54(5) EPC. Both method steps (A) and (B), including the sub-steps (a) and (b), constitute characterising and limiting features of the claimed subject-matter because they form an integral part of the method of treating a patient, which is a method referred to in Article 53(c) EPC. Without these steps, the claimed "*individualized cancer vaccine*" cannot be implemented and would not be defined.

11. With regard to sub-steps (aa), (bb) and (cc) it might be argued that the exact process of identifying the "*cancer mutation signature of the cancer patient*" is only limiting on the claim as far as it confers distinguishing features on the product, i.e. the RNA vaccine. For example, a method to identify a "*cancer mutation signature of the cancer patient*" employing peptide sequencing instead of nucleic acid sequencing or identifying the cancer specific somatic mutations with other methods than sequencing, still would result in the same RNA vaccine for a given patient.

12. The board, however, considers this aspect of claim interpretation not relevant in the present case because no state of the art has been cited for which steps (aa), (bb) and (cc) would represent the relevant difference to the claimed subject-matter.

13. The claim wording also makes clear that there is a direct, specific and treatment-related link between the "*individualized cancer vaccine*", its features and the administration to the patient within the method for treating cancer. Indeed, the individualised cancer vaccine of steps (A) and (B), which is the same as that of the preamble of the claim, is provided in step (b) as "*an RNA vaccine featuring the cancer mutation signature obtained in step (a)*" and is "*administer[ed] ... to the cancer patient*" in step (B).

14. Step (a) further prescribes that "*a cancer mutation signature of the cancer patient*" is provided by "*identifying cancer specific somatic mutations in a tumor specimen of the cancer patient*". The patient to which an individualised cancer vaccine is administered is therefore the same patient from which a tumour specimen for the identification of cancer-specific

mutations originated giving rise to a cancer mutation signature of this very patient. Since these steps are mandatory to obtain the individualised cancer vaccine under consideration, the legal fiction of a purpose-limited product in accordance with Article 54(5) EPC applies at least to step (A), including the sub-steps (a) and (b), and step (B) of the method, which are thus limiting on the claim.

15. The wording in claim 1 "*RNA encoding a recombinant polyepitopic polypeptide comprising mutation based neo-epitopes*" requires the RNA in the vaccine to encode a polypeptide which contains several ("poly") epitopes, among which are more than one mutation-based neo-epitopes. The board does not agree with the appellant that the wording also includes an ensemble of RNA encoding individual epitopes because the peptide products from such RNA ensemble would not be understood by the skilled person as "a recombinant polyepitopic polypeptide". The claim wording does not distinguish between known neo-epitopes and neo-epitopes identified according to the invention/teaching (see also paragraph [0038] of the patent and page 11 of the parent application).

Added subject-matter (Article 100(c) EPC)

16. The board agrees with the decision under appeal that the subject-matter of the patent as granted does not extend beyond the content of the (parent) application as filed.

17. The parent application and the application as filed appear to be identical except that the wording of claims 1 to 45 of the parent application as filed is present in paragraph [0406] of the application as filed

after the statement: "*The invention provides, in particular, the following:*". The application as filed further contains new claims 1 to 17. In the following reference is therefore made to the parent application as filed.

18. The board considers that the subject-matter of claim 1 is disclosed in claims 1, 6, 9, 16 and 21 of the parent application as filed in combination with the disclosure on page 7, paragraph 3 and 4, page 9, paragraph 3, page 10, last paragraph, and page 36, last paragraph, of the parent application as filed.

Claim 21 of the parent application as filed reads:
"*21. A method of treating a cancer patient comprising the steps:*
(a) providing an individualized cancer vaccine by the method according to any one of claims 1 to 17; and
(b) administering said vaccine to the patient."

Claim 1 of the parent application as filed reads:
"*1. A method for providing an individualized cancer vaccine comprising the steps:*
(a) identifying cancer specific somatic mutations in a tumor specimen of a cancer patient to provide a cancer mutation signature of the patient; and
(b) providing a vaccine featuring the cancer mutation signature obtained in step (a)."

Claim 6 of the parent application as filed reads:
"*6. The method according to any one of claims 1 to 5, wherein the step of identifying cancer specific somatic mutations comprises sequencing genomic DNA and/or RNA of the tumor specimen.*"

Claim 9 of the parent application as filed reads:

"*9. The method according to any one of claims 1 to 8, wherein the vaccine featuring the mutation signature of the patient comprises a polypeptide comprising mutation based neo-epitopes, or a nucleic acid encoding said polypeptide.*"

Claim 16 of the parent application as filed reads: "*16. The method according to any one of claims 1 to 15, wherein the vaccine is an RNA vaccine.*"

19. By way of their dependencies the subject-matter of claims 21, 16, 9, 6 and 1 of the parent application as filed is also disclosed in combination.

20. Polyepitopic RNA is a particularly preferred embodiment (see description page 9, third paragraph and page 10 last paragraph of the parent application as filed) so that the combination of this feature with the subject-matter of claims 1, 6, 9, 16 and 21 of the parent application as filed is also disclosed.

21. The respondents pointed to page 7 of the parent application as filed as basis for steps (aa) "*sequencing genomic DNA and/or RNA of the tumor specimen*" (third paragraph), (bb) "*obtaining reference nucleic acid sequence information*" (fourth paragraph) and (cc) "*comparing [...] with the reference nucleic acid sequence information*" (fourth paragraph). The board agrees that these passages disclose the relevant features and notes further relevant passages on page 32, penultimate paragraph; paragraph bridging pages 33 and 34 and paragraph bridging pages 36 and 37 which support the disclosure on page 7.

22. The board considers the argument of the appellant with regard to "known neo-epitopes" versus "neo-epitopes

according to the invention/teaching" (see points 1.2 to 1.6 of the statement of grounds of appeal) not pertinent because the wording of claim 1 does not make that distinction (see point 15. above). Moreover, claim 9 of the parent application, which is dependent on claims 1 to 8, discloses a "*vaccine featuring the mutation signature of the patient* [which] *comprises a polypeptide comprising mutation based neo-epitopes*", i.e. it also does not distinguish between different types of neo-epitopes.

23. No objections were raised against the subject-matter of dependent claims 2 to 13 for added subject-matter.

Novelty (Article 100(a) and Article 54 EPC)

24. The board agrees with the decision under appeal that the subject-matter of the granted claims is novel.

25. The appellant considered document D1 to disclose the subject-matter of claim 1. In light of the claim interpretation in points 10. to 15. above, the board agrees with the decision under appeal that the subject-matter of the claims is novel. Document D1 does not disclose all features of the claim, in particular "*providing an RNA vaccine featuring the cancer mutation signature obtained in step (a), wherein the RNA vaccine comprises RNA encoding a recombinant polyepitopic polypeptide comprising mutation based neo-epitopes*". The cited state of the art furthermore does not disclose achieving a therapeutic effect, this being a functional feature of the claim.

26. The same applies to dependent claims 2 to 13, which share all features of claim 1. The claimed subject-matter is novel (Article 54 EPC).

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

Therapeutic effect

27. The experiments with polyepitopic RNA in mice reported in the patent (see Example 8) render achieving a therapeutic effect in tumours credible because the underlying principle, i.e. vaccination with tumour-specific antigens not present in normal tissue, applies to all cancer types. Those antigens are used to design polyepitopic mRNA vaccines which achieve an anti-tumoural effect in a mouse melanoma model (see Figure 21). The board has also not been presented with any evidence why the principle of using mRNA as a vaccine should not be applicable to all cancer types. Achieving the therapeutic effect is therefore credible from the disclosure of the patent.

28. The post-published evidence in document D17 confirms that anti-cancer mRNA vaccination is applicable to human melanoma patients and shows (i) the development of T-cell responses against multiple neo-epitopes encoded by the RNA vaccine, (ii) vaccine-induced T-cell infiltration and neo-epitope-specific killing of autologous tumour cells and (iii) a reduction of the cumulative rate of metastatic events, resulting in a sustained progression-free survival.

29. The board therefore concludes that attaining the therapeutic effect is sufficiently disclosed.

Mutation prioritisation

30. The appellant questioned whether the prioritisation of individual cancer mutations which involved further

steps based on specific computer tools was sufficiently disclosed. The appellant referred in this regard to an editorial in the journal Nature Biotechnology (D14) which considered still in 2017: "*The truth is then that current neoepitope prediction algorithms return a vast number of candidates, of which only a tiny handful are ever found to trigger bona fide antitumor responses in patients. Despite the profundity of cancer cell mutations, immunogenic neoantigens are the exception rather than the rule. This means there is a great deal more research to do before neoepitope prediction and validation becomes routine and personalized immunotherapy a clinical reality.*" Also, a doctoral thesis (D15) on identifying mutated peptides on the surface of human tumour cells and published in 2012, i.e. shortly after the filing date, failed to detect any tumour-specific neoantigens (see page 89). Of the, on average, 582 somatic mutations per tumour detected (see page 92, first paragraph and Table 3.1), no TSAs could be confirmed at the level of ligands (see page 98, last paragraph).

31. The board finds that the patent provides a complete workflow for the identification of neo-epitopes (see Examples 1 and 9), including several known computer algorithms for mutation prioritisation. The statement in the post-published editorial D14 provides a retrospective view on the developments after the filing date, but does not establish the skilled person's knowledge at the time of filing. Moreover, becoming a "*clinical reality*" cannot be equated with the requirement of sufficient disclosure for the person skilled in the art of cancer vaccines. With regard to the failed attempts to identify tumour-specific neoantigens in document D15, the board accepts the argument by the respondents that the techniques used

(e.g. "*experimental mass spectrometry-based HLA-ligandome analysis*") differ from those employed in the patent and that an individual failed attempt would not have raised serious doubts for the skilled person. Moreover, document D15 also states that "*we are* [...] *on the right path to identify TSAs in the near future*" (see page 98, last paragraph, translation by the board). This hope was confirmed by the experiments disclosed in the patent.

32. The appellant has not provided evidence that applying the methods disclosed in the patent to identify and prioritise somatic cancer mutations would have put an undue burden on the skilled person. Applying this workflow led to a list of 50 validated mutations in the mouse model (see Table 1), several of which were confirmed to be effective in an mRNA vaccine (see Table 8; Figures 13 and 21).

In vivo tests for immunogenicity

33. The appellant further considered that the results obtained in mice could not be transferred to humans without undue burden. The post-published review article D16 stated: "*Clinical translation from syngeneic mice to humans who have 'one-of-a-kind' cancers is more complex because it requires personalization of the process, including identification of mutations, prediction of potential neoepitopes and design and manufacture of the vaccine (Fig. 1). This was recently accomplished by three first-in-human studies in malignant melanoma patients (20-22)*" (page 1, right-hand column, last paragraph). The in-human studies cited in document D16 were published in 2015 and 2017, i.e. after the relevant date of the patent.

34. The appellant also referred to document D18 in which among 962 identified non-synonymous mutations, 50 mutations were selected, in particular based on the predicted immunogenicity (see page 1084, left-hand column, ultimate paragraph). Even among these prediction-based panel of mutations, only about 30% (16 out of 50) were found to elicit immune responses in immunised mice (see page 1084, right-hand column, fourth paragraph).

35. The board finds that although immunogenicity was tested *in vivo* in the patent (see Example 2), the patent also discloses alternative *in vitro* methods to test immunogenicity (see paragraph [0030]), e.g. with an enzyme-linked immunospot assay (ELISpot) using dendritic cells (see paragraph [0336]).

36. The board therefore considers that in the present case *in vivo* testing of immunogenicity is not necessary to establish the claimed therapeutic method in human beings. Moreover, the patent shows that some of the peptide epitopes included in the polyepitopic polypeptide encoded by the mRNA of Example 8 (see Table 8) showed no immune response when tested individually in a peptide immunogenicity assay *in vivo* (see Table 7). Still, the same peptide epitopes in the format of a polyepitopic RNA induced an immune response against various epitopes (MUT08, MUT27 and MUT33) and strongly improved survival of tumour mice (see Figures 13 and 21; paragraphs [0351], [0356] and [0357]). This indicates that the polyepitopic RNA format allows for the induction of an immune response.

Linkers in polyepitopic RNA

37. The appellant objected that linkers of a particular type (Gly-Ser) and length for separating multiple epitopes in a polyepitopic mRNA were not defined in the claims even though they were considered "*critically important for the creation of bad* [sic] *MHC binding epitopes*" (see paragraph [0312]). Such non-immunogenic glycine/serine linkers were also used in the post-published study D17.

38. However, the appellant failed to provide verifiable facts to show that the lack of a linker or the use of the wrong linker in the polypeptide resulted in the neo-epitopes not being presented to T cells or the RNA vaccine not being effective. The board therefore has no reason to doubt that the skilled person with the teaching of the patent in hand and applying common general knowledge could design the polyepitopic mRNA referred to in the claims.

39. The claimed invention is sufficiently disclosed (Article 100(b) EPC).

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

40. The claimed subject-matter is inventive essentially for the same reasons as outlined in decision T 2168/21.

41. In particular, the claimed subject-matter is not obvious over the disclosure of document D1 (D5 in T 2168/21) alone or in combination with other prior art documents, i.e. D2 (Rammensee, D20 in T 2168/21), D3 (Suhrbier, D24 in T 2168/21), D4 (Suhrbier, D25 in T 2168/21), D5 (Kessler and Melief, D26 in T 2168/21), D6 (Carralot et al., D27 in T 2168/21), D7 (Kreiter et

al., D35 in T 2168/21) or D8 (WO 2005/028505, D38 in T 2168/21).

Document D1 starting point

42. Document D1 is a review article summarising steps on the way to "*THE IDEAL THERAPEUTIC CANCER VACCINE*" (see title on page 576, left-hand column). Figure 50.1 discloses a potential approach for "[d]*esigning antigen composition of the ideal tumor vaccine*" (see figure legend). The figure shows three inputs for the "[d]*esign and synthesis of molecularly defined, personalized vaccine consisting of peptides and mRNA/ DNA containing all tumor associated/specific structures*":
- "*Differential analysis-list of overexpressed genes*"
- "*Differential analysis-list of tumor-specific mutations*"
- "*Differential analysis-list of tumor-associated peptides*"

Differences, effects and objective technical problem

43. According to the claim interpretation in points 10. to 15. above, claim 1 relates to an individualised cancer vaccine generated in two steps:
"*(a) identifying cancer specific somatic mutations in a tumor specimen of the cancer patient to provide a cancer mutation signature of the cancer patient* [...]*; and*
(b) providing an RNA vaccine featuring the cancer mutation signature obtained in step (a), wherein the RNA vaccine comprises RNA encoding a recombinant polyepitopic polypeptide comprising mutation based neo-epitopes".

44. Step (a) is disclosed in a conceptual manner in document D1 as part of Figure 50.1 ("*Differential list of tumor-specific mutations*"). The first part of step (b) as reproduced above is equally disclosed in Figure 50.1 ("*synthesis of molecularly defined, personalized vaccine consisting of peptides and mRNA/DNA containing all tumor associated/specific structures*"). The respondents questioned whether the wording "*peptides and mRNA/DNA*" disclosed an mRNA vaccine. The board, however, finds that claim 1 of the patent does not exclude the presence of additional molecules of different types. Moreover, document D1 contains a dedicated section on messenger RNA-based anti-tumour vaccines (see page 581, right-hand column) so that the skilled person would consider an mRNA vaccine to be a preferred option.

45. The second part of step (b): "*wherein the RNA vaccine comprises RNA encoding a recombinant polyepitopic polypeptide*" is not disclosed in document D1. The relevant statements on page 584, right-hand column that "*RNA or DNA-based vaccines, not dependent on HLA typing, similarly have the potential to be used for multi-epitope vaccines in the near future, again, if immunogenicity can be improved*" and that "[s]*ince tumors are genetically unstable, and tend to lose their antigens and MHC molecules, especially if under immune attack, successful vaccines will contain multiple antigens*" merely predict possible future developments. These passages cannot be seen as an enabling disclosure of a medical use of such vaccines. Moreover, they do not specify the form in which the multi-epitopes are encoded in the RNA vaccine, i.e. on separate molecules or on a single molecule.

46. The third part of step (b), "*comprising mutation based neo-epitopes*", is also not disclosed in document D1. Figure 50.1 of document D1 refers to "*mRNA/DNA containing all tumor associated/specific structures*". This includes overexpressed proteins, proteins comprising tumour-specific mutations and post-translational modifications (see page 576, right-hand column, second to fourth full paragraphs). But it does not specify neo-epitopes, i.e. a subset of tumour-specific mutations/structures that will be presented by the patient's MHC molecules (see patent, paragraph [0010]). Neo-epitopes are indirectly disclosed in document D1 by referring to the importance of MHC specificity in peptide vaccines (see page 576, paragraph bridging both columns). However, this passage does not apply these considerations to RNA vaccines. Rather, document D1 suggests that RNA or DNA-based multi-epitope vaccines, in contrast to the previously discussed peptide vaccines, are not dependent on HLA typing (see page 584, right-hand column, penultimate paragraph). This assumption seems to be based on the concept of tumour-derived (differential) RNA libraries encoding entire proteins (see page 577, left-hand column, first paragraph).

47. The board agrees with the appellant that mRNA libraries are likely to also encode neo-epitopes. However, based on the rarity of non-synonymous mutations in human cancers (100 to 120 mutations per cancer, see point 2. above), it would be mere speculation whether any polypeptide encoded by an RNA in such a library would necessarily carry more than one neo-epitope.

48. The board therefore finds that the claimed subject-matter differs from the disclosure of document D1 in

the RNA encoding a polyepitopic polypeptide comprising more than one neo-epitope.

49. Document D1 does not contain any experimental data but refers to a number of studies on several aspects of the envisaged "*ideal therapeutic cancer vaccine*". A reference to data for a personalised vaccine relates to "*a RNA (Carralot et al., 2005)* [document D6 in this appeal] *or DNA library from fresh autologous tumor tissue*" (see page 577, left-hand column, first paragraph). In document D6, amplified tumour-derived cRNA libraries are used as vaccines against metastatic melanomas. These libraries contain TAAs (see page 5) and might also allow targeting tumour-specific mutations (see page 6, left-hand column). They, however, also contain antigens present on healthy cells. The further step envisaged in document D1 in this regard, i.e. "*depleted by the genes expressed in normal tissue*", is not supported by the provided reference D6.

50. The board therefore concludes that a therapeutic effect of a hypothetical "*personalized vaccine*" based on mRNA encoding epitopes from a "[d]*ifferential analysis-list of tumor-specific mutations*" has not been credibly achieved in document D1 and represents a further difference compared to the claimed invention.

51. The respondents argued that these differences resulted in an improved personalised cancer vaccine. While the board agrees that achieving a therapeutic effect is an "improvement" over a merely speculative vaccine, no comparative evidence has been provided to show an improvement over known cancer vaccines, e.g. in other formats (DNA, peptide or viral) or with multiple epitopes present on separate RNA molecules (RNA

libraries). The board therefore concludes that no improved therapeutic effect has been shown to result from the differences.

52. The objective technical problem can be formulated as providing a personalised RNA cancer vaccine with therapeutic efficacy.

Obviousness

53. Document D1 does not provide an incentive to the skilled person to use RNA or DNA vaccines for multi-epitope vaccines (see page 584, right-hand column). Rather, to arrive at the claimed invention, the skilled person starting from the disclosure in document D1 had to make several selections, each of which brought uncertainties with it, and possibly modify the teaching of document D1. The first choice required having to select, from the "multi-epitope vaccines" suggested in document D1, which include libraries of epitopes on separate molecules, a nucleic acid encoding a polyepitopic polypeptide. However, document D1, with regard to nucleic acid vaccines, focuses on total RNA libraries from tumours which contain multiple epitopes on separate molecules (see page 577, left-hand column, first paragraph: "[...] *to get closer to our ideal for a cancer vaccine by using a RNA (Carralot et 2005) or DNA library from fresh autologous tumor tissue of the patient depleted by the genes expressed in normal tissue, in an individualized setting*"). This is also apparent from the section on "*Messenger RNA-Based Anti-Tumor Vaccines*", which refers to total RNA isolated from tumours or to RNA encoding individual TAAs, e.g. PSA. A further choice required selecting RNA over other formats disclosed in document D1, e.g. DNA, viral or peptide. A final modification, not suggested in

document D1 (see point 46. above), had to be made to provide several neo-epitopes in polyepitopic format.

54. The appellant referred to page 576, right-hand column, first full paragraph, which highlighted the importance of tumour-specific mutations which elicit T cells and are expected to have higher affinity than those against overexpressed antigens due to constraints of self-tolerance. However, this passage does not contain any suggestion to identify neo-epitopes among the tumour-specific mutations and to provide them as a vaccine in the form of polyepitopic polypeptides encoded by RNA.

55. The additional documents cited by the appellant (D2, D3 to D8) also do not allow the skilled person to arrive, from the disclosure in document D1, in an obvious manner at the claimed invention.

55.1 Document D2, which is a review article "*on the use of peptides and mRNA for therapeutic vaccination*", proposes using somatic cancer mutations from a patient's tumour. However, it does not teach to select neo-epitopes and present them in a polyepitopic mRNA format.

55.2 Document D3 discloses DNA cancer vaccines against melanoma ("*Summary*" on page 402, last line or, e.g. page 404). They encode a multi-epitope polypeptide which might contain, *inter alia*, "*altered self-antigens*" (page 404, right-hand column, line 32). However, D3 cautions that "*the relative therapeutic benefit of generating responses directed at each of these group of epitopes remains to be established*". From D3, it is also not apparent whether the polyepitopic concept could be transferred to RNA.

55.3 Document D4 is a review which discloses conjoining T-lymphocyte epitopes, derived from several antigens into a single artificial construct (see Abstract) in the form of DNA, viral vectors, recombinant protein or KUN replicons (i.e. RNA) or peptide vaccines (see Tables 1 and 2). It fails to disclose neo-epitopes for cancer vaccination.

55.4 Document D5 refers to the multi-epitope approach for "*enhanc*[ing] *the barrier against escape of antigen loss variants of the tumor*" (page 1869, left-hand column, first paragraph), mentions personalised immunotherapy, but also foresees "*tremendous technical and logistic difficulties*" with this approach (page 1862, left-hand column) and would thus provide no reasonable expectation of success for the skilled person.

55.5 Document D6 relates to a vaccine comprising amplified coding regions of a tumour comprised in an mRNA library and suggests: "*this method might also allow the targeting of tumor-specific mutations. These features makes* [sic] *of the amplification of tumor mRNA the method of choice to easily obtain unlimited amounts of RNA coding for patient's specific TAAs that can be applied as anti-tumor immunotherapy*" (see page 6, left-hand column). Document D6 fails to disclose an RNA encoding a polyepitopic polypeptide comprising neo-epitopes (see discussion on neo-epitopes in RNA libraries in point 47. above). Document D6 would thus provide the skilled person with no reason to change the mRNA library, which is also referred to in the closest prior art D1, to a polyepitopic format.

55.6 Document D7 has the title "*Tumor vaccination using messenger RNA: prospects of a future therapy*" and indicates that "[a]*ntigen-encoding mRNA is in principle*

capable of eliciting polyepitopic humoral and cellular immune responses" (see page 401, left-hand column, third full paragraph) but only discloses immunotherapy by autologous total tumour mRNA or previously known tumour antigens (see Table 1 on pages 402 to 403). It therefore also does not suggest the use of neo-epitopes in a polyepitopic RNA.

55.7 Document D8 relates to multi-epitope polypeptides for use in cancer therapy. It discloses in claims 1 and 3: "*A recombinant nucleic acid sequence encoding a multiepitope polypeptide (MEP), which* [...] *encodes a T cell epitope derived from a tumor associated antigen (TAA)* [...] *wherein said nucleic acid is any one of DNA, RNA and any combination thereof*". Although RNA is mentioned as an expression vector encoding such polypeptides (see e.g. claim 48 or page 32, lines 1 to 2), an RNA vaccine is not disclosed in D8. D8 also does not disclose neo-epitopes as part of the encoded polypeptide and does not disclose an individualised approach.

56. The documents invoked by the appellant thus do not mention the missing features in a context that would have led the skilled person towards the claimed technical features. Furthermore, none of the cited documents contains experimental evidence for the effectiveness of a vaccine based on polyepitopic mRNA encoding neo-epitopes from a patient's tumour. Even if the skilled person had combined the disclosure of a polyepitopic RNA vaccine with the use of neo-epitopes, they would have had no reasonable expectation of achieving a therapeutic effect with this approach. The board concludes that none of the cited documents suggests modifying the hypothetical vaccines proposed

in document D1 by the use of RNA encoding a polyepitopic polypeptide comprising neo-epitopes.

57. The same applies to dependent claims 2 to 13, which share all features of claim 1. The claimed subject-matter involves an inventive step when assessing inventive step starting from D1 (Article 56 EPC).

Documents D3, D6 or D8 as starting points

58. Documents D3, D6 and D8 were cited by the appellant as alternative starting points for assessing inventive step. The disclosure of these documents has been discussed above and is briefly summarised again highlighting the differences to the claimed subject-matter.

59. Document D3 discloses DNA vaccines encoding multiepitope polypeptides based on "*altered self-antigens*". It does not disclose (i) an RNA-based vaccine and (ii) an individualised approach, i.e. the selection of neo-antigens from the patient to be treated.

60. Document D6 discloses the preparation of an "*individualized*" vaccine comprising "*autologous*" (patient-own) amplified tumour (melanoma) mRNA (see Abstract). The tumour-specific mRNAs contain aberrantly overexpressed antigens and mutated antigens. The decision under appeal noted that "[n]*o neo-epitopes are disclosed*". The board agrees with this conclusion because while neo-epitopes are likely to have been present in the libraries used for vaccination they were not identified. Furthermore, document D6 does not disclose RNA encoding a recombinant polyepitopic polypeptide comprising mutation based neo-epitopes,

i.e. one RNA molecule encoding at least two neo-epitopes. A phase I/II clinical study in patients with metastatic melanoma is reported without providing results (see page 2, left-hand column, first full paragraph).

61. Document D8 discloses a transdermal drug delivery system (LTB) and uses a peptide multiepitopic vaccine (MEP). RNA encoding the fusion protein in a composition for inducing an immune response is mentioned, but not used in any of the examples (see e.g. claims 48 and 62 and Examples). The vaccine is (i) not individualised and (ii) neo-epitopes are not mentioned.

62. The board fails to see why any of documents D3, D6 or D8 would provide a more promising starting point than document D1 which shares a similar purpose with the claimed subject-matter and discloses more features in common with the claimed method. Moreover, combining the disclosure of any of documents D3, D6 or D8 with the disclosure of document D1 or with each other would equally not lead to the claimed invention in an obvious manner (see discussion of inventive step in points 53. to 56. above). In particular, none of the cited combinations of disclosures would have provided a reasonable expectation of a therapeutic effect for an individualised RNA vaccine as claimed.

63. The subject-matter of the claims is thus also not obvious when assessing inventive step starting from D3, D6 or D8.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

A. Wille A. Bacchin

Decision electronically authenticated