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**Datasheet for the decision
of 14 November 2025**

Case Number: T 1555/23 - 3.3.04

Application Number: 13817210.1

Publication Number: 2872171

IPC: A61K39/00

Language of the proceedings: EN

Title of invention:

Toxicity management for anti-tumor activity of CARs

Patent Proprietor:

The Trustees of The University of Pennsylvania
The Children's Hospital of Philadelphia

Opponents:

Strawman Limited
Boult Wade Tennant LLP
Secerna LLP
Gedeon Richter Pharma GmbH

Headword:

CAR T cell toxicity management/TRUSTEES OF THE UNIVERSITY OF
PENNSYLVANIA

Relevant legal provisions:

EPC Art. 54, 56, 83, 87, 123(2)

RPBA 2020 Art. 12(4), 12(6), 13(1)

Keyword:

Amendments - added subject-matter (no)

Priority - validity of priority date (yes)

Sufficiency of disclosure - (yes)

Novelty - (yes)

Inventive step - (yes)

Late-filed documents - admitted (no)

Decisions cited:

G 0002/98, G 0001/03, G 0001/24, T 0609/02, T 0843/03,

T 1779/21, T 0979/23, T 1465/23, T 1999/23



Beschwerdekammern

Boards of Appeal

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Case Number: T 1555/23 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 14 November 2025

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Decision under appeal: **Interlocutory decision of the Opposition
Division of the European Patent Office posted on
26 June 2023 concerning maintenance of the
European Patent No. 2 872 171 in amended form**

Composition of the Board:

Chairwoman M. Pregetter
Members: B. Rutz
A. Bacchin

Summary of Facts and Submissions

- I. The appeals by opponents 1, 2 and 4 (appellants I, II and III) lie from the opposition division's decision that European patent No. 2 872 171 (the patent), entitled "*Toxicity management for anti-tumor activity of CARs*", in amended form according to auxiliary request 45, met the requirements of the EPC. The patent has been granted from European application 13817210.1 published under the PCT as international application WO 2014/011984 (the application).
- II. The patent had been opposed on the grounds of Article 100(a) EPC, in relation to exception to patentability (Article 53(c) EPC), novelty (Article 54 EPC) and inventive step (Article 56 EPC), and Article 100(b) and (c) EPC.
- III. In the decision under appeal, the opposition division decided, *inter alia*, that the subject-matter of the claims of auxiliary request 45 was inventive when starting from the disclosure of document D23 as the closest prior art.
- IV. The opposition filed by opponent 3 was withdrawn on 7 November 2023. Accordingly, opponent 3 is no longer a party to the appeal proceedings.
- V. With its statement of grounds of appeal, appellant I filed documents D101 and D102 (renumbered as D102 and D104 by the board). Document D101 was also filed by appellants II and III as document D102.
- VI. With its statement of grounds of appeal, appellant II filed documents D36a, D36b, D101a, D102, D103a, D104 to

D106, D106a and D107 to D114 and provided links to video recordings on the internet as D101 and D103.

- VII. With its statement of grounds of appeal, appellant III filed document D102 and documents D101, D103 and D104 (renumbered by the board as D115, D116 and D104a, respectively).
- VIII. With the reply to the appeals, the respondents filed a set of claims of the main request (auxiliary request 45 held allowable by the opposition division) and sets of claims of auxiliary requests 1 to 23. Further, they filed documents D117 and D118.
- IX. Appellants II and III submitted further arguments in the letters dated 20 October 2024 and 5 February 2025, respectively.
- X. The respondents submitted further arguments in the letter dated 30 June 2025.
- XI. The board summoned the parties to oral proceedings, as requested, from 4 to 5 November 2025, and informed them of its preliminary opinion in a communication under Article 15(1) RPBA 2020.
- XII. In this communication, the board indicated that it preliminarily agreed with the findings of the opposition division with regard to added subject-matter and novelty in view of documents D23 and D24. It preliminarily found the subject-matter of claim 1 not to extend beyond what was disclosed in document P1 and highlighted several issues to be discussed with regard to enablement of the priority disclosure and the sufficiency of the patent.

XIII. Appellant III submitted further arguments in the letter dated 24 September 2025.

XIV. In the letter dated 8 October 2025, appellant I indicated that it would not attend the oral proceedings.

XV. By phone and in the letter dated 2 November 2025, appellant II requested postponement of the oral proceedings.

XVI. With the agreement of all parties, the oral proceedings were postponed to 13 to 14 November 2025 and arranged as a videoconference.

XVII. Claim 1 of the main request reads as follows:

"A T cell genetically modified to express a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen binding domain, a transmembrane domain, and an intracellular signaling domain comprising a 4-1BB signaling domain, for use in a method of treating a disease, disorder or condition associated with an elevated expression of a tumor antigen, the method comprising administering a first-line therapy and a second-line therapy to a patient in need thereof,

wherein the first-line therapy comprises administering to the patient an effective amount of said genetically modified T cell,

wherein following the administration of the first-line therapy, cytokine levels in the patient are monitored to determine the appropriate type of second-line therapy to be administered to the patient,

wherein the appropriate second-line therapy is a cytokine inhibitory therapy which comprises administering to the patient an effective amount of a cytokine inhibitory compound in order to manage the toxicity resulting from administration of the genetically modified T cell to the patient, wherein the cytokine is IL-6, further wherein said monitoring indicates an increase in the level of said cytokine, and

wherein the disease, disorder or condition is a cancer."

Claim 5 of the main request reads as follows:

"The genetically modified T cell for use according to any one of claims 1 to 4, wherein the second-line therapy is tocilizumab."

XVIII. At the end of the oral proceedings, the Chairwoman announced the board's decision.

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

- D1 J.N. Kochenderfer et al., Blood 119(12), 2012, 2709-2720
- D2a G. Lipowska-Bhalla et al., Cancer Immunol Immunother 61(7), 2012, 953-962
- D5 R.A. Morgan et al., Molecular Therapy 18(4), 2010, 843-851
- D10 C.A. Ramos et al., Expert Opin Biol Ther 11(7), 2011, 855-873
- D17 S.A. Jones et al., J Clin Invest 121(9), 2011, 3375-3383
- D23 WO 2012/079000 A1

- D24 M. Kalos et al., *Sci Transl Med* 3(95), 2011, research article 73
- D24a Supplementary materials for D24
- D25 D.L. Porter et al., *N Engl J Med* 365(8), 2011, 725-733
- D26 S.A. Grupp et al., *Blood* 120(21), 2012, abstract 2604
- D35 D.L. Porter et al., *Blood* 120(21), 2012, abstract 717
- D36 S.A. Grupp et al., *N Engl J Med* 368(16), 2013, 1509-1518
- D36a Supplementary materials for D36
- D36b ICMJE Forms for Disclosure of Potential Conflicts of Interest for each of the authors of D36
- D38 J. Wei et al., *Signal Transduction and Targeted Therapy* 5, 2020, article 134
- D39 J. Gust et al., *Cancer Discov* 7(12), 2017, 1404-1419
- D40 A. Nellan et al., *Blood* 132(6), 2018, 662-666
- D41 J.N. Kochenderfer et al., *J Clin Oncol* 33(6), 2015, 540-549
- D48 L. Yanez et al., *HemaSphere* 3(2), 2019, article e186
- D52 F.R. Brennan et al., *mAbs* 2(3), 2010, 233-255
- D53 M. Kalos et al., *Blood* 120(21), 2012, abstract 756
- D57 WO 2011/066371 A2
- D58 T.T. Hansel et al., *Nat Rev Drug Discov* 9, 2010, 325-338
- D59 S. Liu et al., *Blood Cancer Journal* 10, 2020, article 15
- D60 RoActemra (tocilizumab), Union Register of medicinal products - Public Health - European Commission (<https://ec.europa.eu/health/documents/communityregister/html/h492.htm>, retrieval date 01.06.2022)

- D66 Proposed INN, WHO Drug Information 22(4), 2008, 311, 312, 340 and 341
- D67 R.M. Myers et al., Biol Blood Marrow Transplant 26, 2020, S39
- D68 P.F. Caimi et al., 62nd ASH Annual Meeting and Exposition, 2020, abstract 738
- D71 EMA Overview of Kymriah, 2018
- D72 EMA Overview of Yescarta, 2018
- D73 EMA Overview of Tecartus, 2020
- D74 EMA Overview of Breyanzi, 2022
- D75 EMA Overview of Abecma, 2021
- D80 B. Shah et al., Blood 128(22), 2016, abstract 2803
- D90 First declaration of Prof Robert Negrin dated 22 February 2023 and curriculum vitae
- D91 O. Molostova et al., Blood 134(Supplement 1), 2019, abstract 2625
- D93 Second declaration of Prof Robert Negrin dated 22 February 2023 and curriculum vitae
- D94 S. Vadhan-Raj et al., Blood 114(22), 2009, abstract 105
- D95 C.H. Shen et al., Anesthesia and Analgesia 112(2), 2011, 454-459
- D96 EMA information for Kymriah retrieved on 24 February 2023 (https://www.ema.europa.eu/en/documents/productinformation/kymriahepar-product-information_en.pdf)
- D97 U. Anurathapan et al., Cytotherapy 16, 2014, 713-733
- D98 M.L. Davila et al., Int J Hematol. 99, 2014, 361-367
- D101 YouTube recording of Dr Carl June entitled "*Carl H. June, MD - Celebration of Science*", 6 Nov 2012, Prostate Cancer Foundation
- D101a Screenshots and transcript of D101 from 14:49 to 18:01

- D102 Tom Whitehead (as told to Jo Cavallo), "*Against all Odds*", The ASCO Post, 25 January 2018
- D103 YouTube recording of Dr Carl June presentation entitled "*Gene and Cell-Based Immunotherapy for Cancer*", 20 June 2012
- D103a Screenshot and transcript of D103 from 3:35 to 4:53
- D104 Clinical trial NCT01626495 retrieved from ClinicalTrials.gov, National Library of Medicine, 2020
- D105 Study Protocol and Statistical Analysis Plan for D104
- D106 Centre Daily Times newspaper published on 31 May 2012, front page and pages A7 and A9
- D106a New England Journal of Medicine, list of articles published in August 2011
- D107 F. Meier et al., *Immunotherapy* 5(9), 2013, 955-974
- D108 Declaration of Dr John Maher dated 1 November 2023 and curriculum vitae
- D109 H. Dominguez et al., *J Vasc Res* 42, 2005, 517-525
- D110 S. Madhusudan, *Clin Cancer Res* 10, 2004, 6528-6534
- D111 I. Nesterov et al., *Br J Clin Pharmacol* 62(4), 2006, 435-445
- D112 T.L. Whiteside, *Clin Diagn Lab Immunol* 1(3), 1994, 257-260
- D113 M. Kalos, *J Transl Med* 9, 2011, article 138
- D114 J. Kanellis et al., *Hypertension* 41, 2003, 1287-1293
- D115 Declaration of Prof Olaf Penack dated 21 September 2023
- D116 Tom, Kari and Emily Whitehead, "*Praying for Emily*", first edition, New York, Hachette Book Group, 2020, 187-194
- D117 Declaration of Dr Stephan Grupp dated 7 March 2024

D118 P.J. Stambrook et al., Mol Cancer Res 15(6), 2017,
635-650

XX. The parties' relevant submissions in writing and during oral proceedings are dealt with in the Reasons for the Decision below. In brief, the parties argued as follows.

Appellant I argued with regard to the main request that:

- the subject-matter of claim 1 (and of dependent claims 2 to 5) extended beyond the content of the application as filed
- the subject-matter of the claims was not entitled to the priority of the first priority document P1
- the invention to which the claims related was not sufficiently disclosed
- the subject-matter of the claims lacked novelty over the public prior use documented by D102
- if priority was not valid, the subject-matter of the claims lacked novelty over document D26
- the subject-matter of the claims lacked an inventive step over the disclosure of document D23 alone or in combination with document D1

Appellant II argued with regard to the main request that:

- the subject-matter of claims 1 and 5 extended beyond the content of the application as filed
- the subject-matter of the claims was neither entitled to the priority of the first priority document P1 nor to the priority of the second priority document P2
- the invention to which the claims related was not sufficiently disclosed

- the subject-matter of claims 1 to 4 lacked novelty over the disclosure of documents D23, D24 and D25
- the subject-matter of the claims lacked novelty over the public prior use documented by D102
- if priority from P1 was not valid, the subject-matter of the claims lacked novelty over documents D26 and D35
- if priority from P2 was not valid, the subject-matter of the claims lacked novelty over document D36
- the subject-matter of the claims lacked an inventive step over the disclosure of document D23 or D24 alone or in combination with document D106 or over D106 in combination with D106a and D25

Appellant III argued with regard to the main request that:

- the subject-matter of claim 1 (and of dependent claims 2 to 5) extended beyond the content of the application as filed
- the subject-matter of claim 1 lacked clarity
- the subject-matter of the claims was not entitled to the priority of the first priority document P1
- the invention to which the claims related was not sufficiently disclosed
- if priority was not valid, the subject-matter of the claims lacked novelty over each of documents D26, D53 and D35
- the subject-matter of the claims lacked novelty over the public prior use documented by D102, D104 and D116
- the subject-matter of the claims lacked an inventive step over the disclosure of each of documents D23, D24 and D25 alone or in combination with the common general knowledge evidenced in

documents D52 and D57 and the expert declaration D90

The respondents argued that the opposition division was correct in finding that, taking into consideration the amendments according to auxiliary request 45, the patent and the invention to which it related met the requirements of the EPC.

XXI. The appellants (opponents 1, 2 and 4) requested that the decision under appeal be set aside and that the patent be revoked.

Appellant I further requested that all documents filed in opposition proceedings and documents D102 and D104, filed as D101 and D102, respectively, in appeal, be admitted into the appeal proceedings.

Appellant II further requested that documents D91, D117 and D118 not be admitted into the appeal proceedings and that documents D36a, D36b, D101, D101a, D106, D106a and D107 to D114 be admitted into the proceedings.

Appellant II further requested that documents D96, D97 and D98 filed in opposition proceedings be admitted. It clarified that it no longer requested that documents D95, D102, D103, D103a, D104a (filed as D104) and D105 be admitted.

Appellant III further requested that document D115, filed as document D101 in appeal, be admitted. It no longer requested admittance of documents D102, D104a and 116, filed as documents D102, D104 and D103, respectively. Were the board not to admit these documents, documents D117 and D118 should also be not admitted into the appeal proceedings.

XXII. The respondents (patent proprietors) requested that the appeals be dismissed and that the patent be maintained in the form held allowable by the opposition division (main request).

Alternatively, they requested that:

- the patent be maintained in amended form on the basis of the sets of claims of one of auxiliary requests 1 to 23 filed with the reply to the appeals
- none of the documents filed by the appellants in appeal proceedings be admitted into the appeal proceedings
- none of the objections and arguments newly filed by the appellants in the appeal proceedings be admitted into the appeal proceedings
- documents D97 and D98 filed in opposition proceedings be not admitted into the appeal proceedings
- document D91, filed in opposition proceedings, be admitted into the appeal proceedings, and documents D117 and D118, filed in appeal proceedings, be admitted into the appeal proceedings if documents D108 and D115 were admitted

Reasons for the Decision

CAR T cell therapy for cancer, associated toxicity and its management

1. Immunotherapy of cancer makes use of the body's immune system to target antigens expressed preferentially on cancer cells to destroy them. This can be achieved by harvesting T cells from a patient, genetically modifying them *ex vivo* to express the selected antigen

and returning them into the patient. Chimeric antigen receptor-modified T cells (CAR T cells) are one approach to achieve this. Due to its stimulation of the immune system, CAR T cell therapy is often associated with drastic side effects, such as cytokine release syndrome (CRS), also known as cytokine storm, and tumour lysis syndrome (TLS).

Common general knowledge at the priority date

2. The parties agreed that the following was common general knowledge at the time of priority:
 - CRS or cytokine storm and its symptoms
 - CRS is a toxicity of CAR T cell therapy
 - IL-6 is a hallmark cytokine of CRS
 - tocilizumab is an anti-IL-6 receptor antibody and IL-6 inhibitor (previously known as MRA) approved in the US and Europe for clinical use in patients with rheumatoid arthritis (RA)

*Admission of documents D36a, D36b, D96 to D98, D101, D101a, D102, D104, D106, D106a, D107 to D115, D117 and D118
(Article 12(4) and (6) RPBA)*

3. Document D96 is cited once in the decision under appeal (see sheet 16, last three lines), although the opposition division stated that it was not referred to (see point 9.8 on sheet 5). Appellant II, during the oral proceedings in appeal, requested its admittance (see page 2 of the minutes). However, none of the parties in appeal referred to D96, either in writing or at the oral proceedings.
4. The board therefore did not decide on the admittance of D96.

5. Documents D97 to D98 had been filed during the opposition proceedings before the time limit set with the communication under Rule 116(1) EPC, in response to the filing of document D88 by the respondents, but were not discussed in the decision under appeal (see sheet 5, point 9.8). The board considers them as supplemental evidence to support the lack of sufficiency of disclosure for the administration of tocilizumab alone, which have therefore been admissibly raised and maintained during the opposition proceedings (Article 12(6) RPBA).
6. Documents D97 and D98 were admitted into the appeal proceedings.
7. Documents D102 and D104 were filed by appellant I, as D101 and D103, respectively, with its statements of grounds of appeal. Appellant I did not provide any reasons for filing these documents only in appeal. For this reason alone, the board saw no reason to admit D102 and D104 into the appeal proceedings (Article 12(4) RPBA). Since appellants II and III had withdrawn their requests to admit these documents, their admittance was not discussed during oral proceedings. The board furthermore notes that the new objections made on the basis of these documents, i.e. novelty and inventive step of claim 1, would have already applied to the claims as granted. The documents could and should therefore have been filed in opposition proceedings (Article 12(6) RPBA). Furthermore, they relate essentially to an objection of prior use which the board considered highly complex (Article 12(4) RPBA).
8. Documents D102 and D104 were not admitted into the appeal proceedings.

9. Documents D36a, D36b, D101a, D106, D106a and D107 to D114 were filed by appellant II with its statements of grounds of appeal. D101 represents a YouTube video for which appellant II submitted a URL but not the video itself. These documents and the item of evidence represent amendments to the appellant's appeal case and may be admitted into the proceedings only at the discretion of the board (Article 12(4) RPBA).

10. With regard to documents D36a, D36b, D101a and D109 to D112 and the item of evidence D101, appellant II argued that they constituted a legitimate reaction because, for the first time in oral proceedings before the opposition division, documents D26, D35 and D53 were held not to form part of the state of the art. This was a departure from the preliminary opinion of the opposition division and justified the filing of new documents.

11. The board did not accept this argument because a party has to be prepared that a preliminary opinion is indeed preliminary and might change in oral proceedings, particularly on account of arguments which are on file since the reply to the notice of opposition. In any case the board cannot see a clear discrepancy on the question of sufficiency of disclosure addressed in the preliminary opinion (in which point 12. essentially settled the framework for the discussion at the oral proceedings without giving an opinion on it) and the conclusion drawn in the written decision (point 18.). Finally, the issues which appellant II attempted to address with the filing of these documents, i.e. validity of the priority and sufficiency of disclosure, had already been relevant for the claims as granted, meaning that the documents could and should have been

filed during the opposition proceedings
(Article 12(6) RPBA).

12. Documents D36a, D36b, D101a and D109 to D112 and the item of evidence D101 were not admitted into the appeal proceedings.
13. With regard to D108, appellant II argued that it had been submitted in response to the filing of document D93 by the patent proprietor, D93's admittance into opposition proceedings and the subsequent reversal of the opposition division's preliminary opinion that administration of etanercept to the patient(s) was required to achieve an effect on toxicity.
14. The board notes that although D93 was admitted into the opposition proceedings and referred to by the patent proprietor (see sheet 16, last four lines), it was not used by the opposition division in its reasoning (see sheet 17 and 18). The validity of the priority had been a subject of the opposition proceedings, and the filing of a further expert declaration on appeal appears therefore neither timely nor appropriate (Article 12(6) RPBA).
15. Document D108 was not admitted into the appeal proceedings.
16. With regard to documents D106, D106a, D107 and D113, appellant II argued that they addressed a new development which had only become apparent during oral proceedings before the opposition division, namely that a further distinguishing feature with regard to the disclosure of documents D23 and D24 had been identified by the patent proprietor: "real-time monitoring" (see minutes, sheet 17; decision under appeal, point 21.2

bridging sheets 22 and 23). This point had not been addressed in the preliminary opinion by the opposition division, which listed only the compounds as a difference. The documents provided evidence that the inventors of D23 and D24 had indeed used real-time monitoring.

17. Documents D106, D106a and D107 represent articles from newspapers and scientific journals. They cannot provide straightforward evidence for common general knowledge at the time of filing and thus also do not constitute proof of an implicit disclosure of "real-time monitoring" in document D23 or D24.
18. Documents D106, D106a, D107 and D113 were not admitted into the appeal proceedings. The conditional request for admittance of documents D117 and D118 was therefore also moot.
19. With regard to document D114, appellant II argued that it addressed the finding of the opposition division that rasburicase in document D23 was not an IL-6 inhibitor, while corticosteroids were.
20. The board agrees with the respondents that document D114 does not mention rasburicase or IL-6 and therefore appears to be irrelevant for these aspects. Moreover, the document could and should have been filed during opposition proceedings.
21. Document D114 was not admitted into the appeal proceedings.
22. Document D115 was filed by appellant III with its statements of grounds of appeal.

23. It was argued by appellant III that the opposition division had reversed its opinion on the use of a single cytokine inhibitor (tocilizumab) for managing toxicity. However, as indicated above for D108, the validity of the priority had been a subject of the opposition proceedings. The filing of a further expert declaration upon appeal appears, therefore, neither timely nor appropriate (Article 12(6) RPBA).
24. Document D115 was not admitted into the appeal proceedings.

Main request

Admission of clarity objection (Article 13(1) RPBA)

25. In its letter dated 5 February 2025 (Section C.I at pages 3 to 6), appellant III raised for the first time a lack of clarity objection against claim 1. Further elaborations were filed with the submissions of 24 September 2025 (Section D., pages 5 and 6). Appellant III argued that the objection was caused by a new interpretation of claim 1 by the respondents in their reply to the appeals. Appellant III was of the opinion that the respondents' interpretation of claim 1, which required the monitoring of only a single cytokine, was in contradiction with the further wording of the claim that the "*appropriate type*" of second-line therapy had to be determined.
26. The board considers the objection by appellant III to represent an amendment of its appeal case which falls under the provisions of Article 13(1) RPBA. The wording of claim 1 as upheld by the opposition division has not changed in appeal. If the claim was considered unclear, in whatever possible interpretation, this could and should have been addressed in the statement of grounds

of appeal. An interpretation of the claim by the respondents which is different from the one preferred by appellant III can be addressed by arguments but does not justify a new clarity objection.

27. The board did not admit the objection into the appeal proceedings. As regards the arguments by appellant III addressing the respondents' claim interpretation, these are addressed in the following section.

Claim interpretation - claim 1

General

28. The claim is directed to a CAR T cell for use in a method for treating a disease (i.e cancer), the method comprising administering a first line therapy and a second line therapy, further requiring the monitoring of cytokine levels in the patient following the administration of the first-line therapy and where the appropriate second line therapy is a cytokine inhibitory therapy (see point XVII. above for the exact wording).
29. The parties differed in their interpretation of the claim with regard to the cytokine levels to be monitored and the cytokine inhibitory compound used in the second-line therapy.
30. The claim mentions cytokine five times: "*cytokine levels*" to be monitored, "*a cytokine inhibitory therapy*" as a second-line therapy, "*a cytokine inhibitory compound*" to be administered, "*wherein the cytokine is IL-6*" and "*said monitoring indicates an increase in the level of said cytokine*". It is common practice in claim drafting that a term preceded by "a" can be further defined by a later reference to the same

term preceded by "the". The board therefore considers that "*wherein the cytokine is IL-6*" defines the preceding undefined instances of the term "cytokine". Moreover, the phrase "*wherein the cytokine is IL-6*" follows closely after the term "*a cytokine inhibitory compound*". Based on this proximity and the articles "the" and "a", the skilled person would recognise that IL-6 is the cytokine targeted by an inhibitory compound which is comprised in a cytokine inhibitory therapy. A further link is present between IL-6 and the monitoring of "*said cytokine*". However, since "*cytokine levels*" (plural) are monitored, IL-6 need not be the only monitored cytokine. Further, the description makes clear that IL-6 inhibitors are a preferred embodiment of cytokine inhibitors or antagonists (see patent, paragraphs [0020], [0021], [0110], [0151]; Examples). Monitoring IL-6 equally represents a preferred embodiment (see patent, paragraph [107]; Examples).

31. Understanding the claim in a reasonable and technically sensible manner in the context of the description and taking into account the common general knowledge at the relevant date thus leads to the following transcription (rearrangement and abbreviation of the claim by the board highlighted):

*"A T cell genetically modified [...] for use in a method of treating **a cancer** associated with an elevated expression of a tumour antigen,*

the method comprising administering a first-line therapy and a second-line therapy to a patient in need thereof,

wherein the first-line therapy comprises administering to the patient an effective amount of said genetically modified T cell,

*wherein following the administration of the first-line therapy, cytokine (**including IL-6**) levels in the patient are monitored to determine the appropriate type of second-line therapy to be administered to the patient,*

*wherein said monitoring indicates an increase in the level of **IL-6**,*

*wherein the appropriate second-line therapy is a cytokine inhibitory therapy which comprises administering to the patient an effective amount of an **IL-6** inhibitory compound in order to manage the toxicity resulting from administration of the genetically modified T cell to the patient."*

32. In reaching this understanding of claim 1, following the teaching of decision G 1/24, the board however did not need to take position on the jurisprudence cited by appellant II, e.g. T 1465/23 (reasons 2.4) and T 1999/23 (reasons 5.6), which in implementing G 1/24 found that limiting features disclosed in the description cannot be read into the claims. As explained in the following, limiting features found only in the description are not crucial for the assessment of the current appeals, so that the cited jurisprudence does not become relevant.

Cytokine inhibitory compound

33. The parties further differed on whether an IL-6 inhibitory compound would include general inhibitors of

the immune system, such as corticosteroids, or indirect inhibitors. The appellants referred to the following definition in paragraph [0058] of the patent:

"'Inhibitors' or 'antagonists' of a soluble factor are used herein to refer to molecules of [sic] agents capable of inhibiting, inactivating or reducing the levels of the soluble factor. Inhibitors are compounds that, e.g., bind to, partially or totally block activity, decrease, prevent, delay activation, inactivate, desensitize, or down regulate the activity or expression of soluble factor, e.g., antagonists."

34. The appellants referred to IL-1 inhibitors (see paragraph [0154] of the patent); TNF- α inhibitors, such as etanercept (or Enbrel, see document D6, page 20, right-hand column, end of first paragraph); and rasburicase, a uric acid reducing agent (see document D23, page 70, lines 6 to 8, and D94, page 2, end of first paragraph).
35. Therefore, in the view of the appellants, any factor which had a general or indirect effect on IL-6 had to be considered an IL-6 inhibitor.
36. The board does not agree. The phrase *"cytokine inhibitory compound [...], wherein the cytokine is IL-6"* in the claim would be read by the skilled person in the way that a specific cytokine, namely IL-6, is targeted by the inhibitory compound and not a plethora of cytokines, among which IL-6 can be found. The description of the patent confirms this interpretation by listing a number of different cytokines individually to which a *"cytokine inhibitory compound"* could be directed, thus emphasising the specific nature of the respective inhibition (see e.g. paragraph [0081]). The

patent also classifies steroids as immunosuppressive or immunoablative agents (see paragraph [0145]) and distinguishes them from cytokine inhibitory compounds (see paragraph [0151]: "*In another embodiment, the second-line of therapy comprises administering one of [sic] more of a steroid and an inhibitor of IL-6.*").

37. The statement in paragraph [0154] of the patent that "*it is believed that anakinra and other reagents that block IL-1 may also be useful in this regard*", which was cited by the appellants, relates to the management of toxicity in general and proposes an alternative approach to the inhibition of IL-6, namely inhibiting IL-1. The skilled person would therefore not consider this passage to be classifying an IL-1 inhibitor as an IL-6 inhibitor.
38. The reference to etanercept as an IL-6 inhibitor in the sense of the claim can also not be agreed with because etanercept is a specific TNF- α inhibitor. The fact that etanercept, like most immunomodulatory agents, can have indirect effects on other cytokines does not change this.
39. Similarly, the board does not see how an enzyme which reduces uric acid levels could be considered an IL-6 inhibitor merely because some scientific reports (e.g. D94) report a correlation between rasburicase administration and reduced IL-6 levels. Following this reasoning, as also indicated by the respondents, would mean that most compounds with a specific target in the body would have to be considered "inhibitors" of a plethora of other targets because of the intricate network of biochemical and molecular interactions within the body which leads to indirect effects.

40. The board concludes that the term "*cytokine inhibitory compound* [...] *wherein the cytokine is IL-6*" refers to a molecule or agent which inhibits, inactivates or reduces the levels of IL6 or the IL6 receptor or binds to, blocks activity, decreases, prevents, delays activation, inactivates, desensitises, or down regulates the activity or expression of IL6 or its receptor (see paragraph [0058] in the patent), all in an IL6-specific manner.

Managing toxicity

41. The appellants were of the opinion that "*administering to the patient an effective amount of a cytokine inhibitory compound in order to manage the toxicity resulting from administration of the genetically modified T cell to the patient*" required that the second-line therapy reduced or abrogated any toxicity arising from CAR T cell therapy.
42. The board considers that this is not a sensible reading of a claim which aims to reduce the side effects of a known therapy. It is common general knowledge that CAR T cell therapy can have a multitude of toxicities as it interferes profoundly with the immune system. CRS is the most prominent one (see e.g. the patent, paragraph [0147]; D5; D59, page 1, left-hand column, first paragraph), but others, such as TLS, were known at the priority date (see paragraph [0003] of the patent) and could be treated prophylactically (see paragraph [0179]). To require a second-line therapy to deal with all possible toxicities of a complex therapy such as CAR T is not how the skilled person would understand the claim. Rather, the claim has to be interpreted as requiring that the second-line therapy manages, i.e. reduces, rather than totally eliminates, at least one/

some type/s of toxicity resulting from CAR T cell administration, thus allowing for the treatment of cancer while retaining some efficacy in the treatment of cancer. In view of the varying sensitivity of individual patients to toxicities, this might not be possible in all patients.

Sequence of steps

43. The appellants also questioned whether the sequence of steps of the medical use was defined in claim 1. The board concludes from its claim interpretation that this is the case (see point 31. above).

44. From the claim wording alone, the board further notes that "*following the administration of the first-line therapy*" means that the monitoring of cytokine levels (including IL-6) has to take place after the first-line therapy, i.e. after administration of the CAR T cells. Equally, an increase in the level of IL-6 based on the monitoring has to be detected after the first-line therapy. Finally, the wording "*monitored to determine*" means that the appropriate type of second-line therapy is determined based on whether an increased level of IL-6 was detected when monitoring.

45. The claim wording thus requires the following sequence of steps:
 - (a) administering CAR T cells as a first-line therapy
 - (b) monitoring of cytokine levels (including IL-6)
 - (c) establishing an increase in IL-6 levels
 - (d) administering a cytokine inhibitory therapy comprising an IL-6 inhibitory compound as a second-line therapy

46. This interpretation is also supported by the disclosure in the claims as originally filed (i.e. claims 1 to 4), in the description as filed (see page 2, lines 9 to 19; page 18, lines 1 to 6) and in the examples, which contain all the steps listed above in the same order, see e.g. page 34, lines 10 to 16:

- (a) CAR T cells as a first-line therapy
- (b) and (c) elevated levels of cytokines (including IL-6)
- (d) tocilizumab (anti-IL6) as a second-line therapy

and

page 35, lines 13 to 24:

- (a) CART19 cells as a first-line therapy
- (b) and (c) high levels of TNF- α and IL-6 (988 fold) on day nine
- (d) TNF- α and IL-6 antagonists as a second-line therapy

Link between monitoring and appropriate type of second-line therapy

47. The appellants were of the opinion that claim 1 did not require a causal relationship between measuring cytokine levels and determining the appropriate second-line therapy.

48. The board is unable to accept this interpretation. As set out above, following the administration of CAR T cells, cytokine levels (including IL-6) have to be monitored. This monitoring has to indicate an increase in the level of IL-6, thereby determining the second-line therapy which involves an IL-6 inhibitory compound.

Priority (Article 87 EPC)

49. Assessing the requirement of the "same invention" within the meaning of Article 87 EPC is based on the determination whether the subject-matter claimed can be derived by the skilled person directly and unambiguously, explicitly or implicitly, using common general knowledge, from the previous application as a whole (see decision of the Enlarged Board of Appeal, G 2/98, Reasons 9).
50. For the subject-matter of further medical use claims this entails assessing whether the priority (or previous) application at the date of its filing rendered it credible that the known therapeutic agent was suitable for the claimed therapeutic application (see also Case Law of the Boards of Appeal of the EPO, 11th edn. 2025, II.D.4.6, and e.g. T 843/03 Reasons 3). This is consistent with the general teaching in G 1/03 (Reasons 2.5.3) that the process of making the invention has to be completed when an application for a patent is filed.

Directly and unambiguously derivable from the first priority document

Claim 1

51. Appellants II and III argued that the subject-matter of claim 1 was not directly and unambiguously derivable from the first priority document (P1). Their reasoning was essentially based on an interpretation of current claim 1 in which no causal link between the monitoring step and the second-line therapy existed. Such a method without a causal link was not disclosed in P1.

52. Appellant II further argued that P1 did not disclose the general use of a single cytokine inhibitory therapy for managing toxicity resulting from CAR T cell infusion.
53. The board does not agree. Claim 1 does not refer to the general use of a (or any) single cytokine inhibitory therapy but, as outlined in points 31. and 40. above, refers to IL-6 as the cytokine to be monitored and inhibited when its level is increased. Claim 1 also includes a causal link between the result of the monitoring, i.e. increased IL-6 levels, and the administration of an IL-6 inhibitor as a second-line therapy (see points 29. to 31., 47. and 48. above).
54. As also pointed out by the respondents and acknowledged by the opposition division, a basis for IL-6 as the cytokine to be monitored and inhibited when its level is elevated can be found in several passages in P1 (see e.g. page 25, lines 11 to 17; page 26, lines 11 to 23, and page 44, lines 11 to 12: "*tocilizumab (anti-IL6) can ameliorate the toxicity of CARs*"). A further basis for this subject-matter can be found in claims 1 to 4 of P1.
55. On page 7, lines 16 to 19, P1 further discloses: "*(CAR) in combination with **toxicity management**, where a profile of soluble factors from a post T cell infusion patient is generated and a therapy directed against **the elevated soluble factor** is carried out in order to treat the cancer*" (highlighting added by the board) and on page 18, lines 21 to 26: "*second-line of therapy appropriate to treat the patient as a consequence of the first-line of therapy*".

56. The subject-matter of claim 1 is thus directly and unambiguously derivable from the disclosure of P1.

Claim 5

57. Claim 5 requires the second-line therapy to be tocilizumab. Appellants II and III were of the opinion that this subject-matter was not directly and unambiguously derivable from the disclosure in P1.

58. P1 mentions tocilizumab three times: on page 6, in the legend of Figure 9: "*The patient was critically ill on days 5 to 7, and only began to improve following tocilizumab administration*"; in the example on page 44, lines 11 to 12: "*It was observed that tocilizumab (anti-IL6) can ameliorate the toxicity of CARs and seemingly preserve antitumor effects in 2 of 2 patients (Figure 9)*" and in Figure 9 itself, which reads "*enbrel, tocilizumab*" above two arrows pointing down at about day 7 and day 7.5.

59. P1 discloses a therapeutic method comprising a first- and a second-line therapy (see claim 1 of P1). Cytokine levels are monitored following the CAR T cell first-line therapy (claim 2), and an increase in the level of a cytokine identifies a type of cytokine inhibitory therapy (claim 3). The cytokine is selected from a group comprising IL-6 (claim 4). The cytokine inhibitory therapy is selected from a group comprising antibodies (claim 5).

60. P1 contains two examples in which a patient receives a first- and second-line therapy. The first is a patient (UPN 02) who receives corticosteroid therapy after showing serious side effects of the CART19 cell therapy (see page 39, lines 21 to 28). However, although

cytokine levels were monitored for this patient (see Figure 8B), no cytokine inhibitory therapy was administered. The other two patients for which a first- and second-line therapy is reported received tocilizumab (anti-IL-6) after cytokine levels were monitored and elevated levels of IL-6 were detected (see page 44, lines 9 to 12, and Figures 8 and 9). In Figure 9, steroids and enbrel (etanercept, a TNF- α inhibitor) are also mentioned, but these compounds are not mentioned in the text on page 44 or in the figure legend on page 6, which further details that "[t]he patient was critically ill on days 5 to 7, and only began to improve following tocilizumab administration".

61. IL-6 is the only cytokine for which a detailed description is provided in P1 (see page 25, lines 11 to 17, and page 26, lines 11 to 23). The only cytokine inhibitory compound mentioned in the examples is the anti-IL-6 receptor antibody tocilizumab (see above). The cytokine IL-1 and inhibitors of it are also mentioned but only in a hypothetical manner without providing experimental or clinical data (see page 44, lines 13 to 19). The skilled person would thus have derived directly and unambiguously that the IL-6 inhibitory compound tocilizumab was a preferred embodiment of the cytokine inhibitory therapy disclosed in claims 1 to 5 of P1, i.e. the same invention as in current claim 5.

Enablement of disclosure of P1

62. The appellants argued that the invention as claimed was not enabled in P1 over its whole breadth. The objections in this regard related to:

- a CAR T cell therapy for a cancer

- a single agent in a second-line therapy
- a cytokine inhibitory compound
- a link between monitoring and IL-6 inhibitory therapy

CAR T cell therapy for a cancer

63. Appellant I objected that the CAR T cells defined in claim 1 were not limited in their antigen specificity and would thus not be capable of treating cancers which did not express the antigen targeted by the CAR T cells. Moreover, the claim was not limited to the types of cancer for which examples had been provided in P1, e.g. acute lymphoblastic leukaemia (ALL) and chronic lymphocytic leukaemia (CLL).
64. The board finds that the skilled person at the priority date was aware of the therapeutic mechanism of CAR T cells and would be able to choose the specificity of the cells, i.e. the CAR introduced into the T cell, in a way that it matched the tumour to be treated, which as the claim required was "*associated with an elevated expression of a tumor antigen*" (see for example the reviews in D2/D2a, D10 and D70).
65. The board moreover recalls that in accordance with established case law, in particular for life threatening diseases (see Case Law of the Boards of Appeal of the EPO, 11th edn. 2025, I.B.4.5.1), a therapeutic effect is not to be equated with a complete remission or cure but also includes prolonging life expectancy and alleviating symptoms associated with the disease.
66. The respondents provided evidence of CAR T cell therapy being applicable to a variety of cancers, including

solid cancers (see D70, page 4, final paragraph, and page 7, section "5. *Clinical Studies Based on CAR-Modified T Cells*", and D10, Table 2).

67. The board has not seen evidence which provided serious doubts substantiated by verifiable facts that the treatment of cancer with CAR T cells was not enabled over the whole claimed breadth.

Single agent in second-line therapy

68. The appellants argued that P1 did not disclose that a single agent, i.e. an IL-6 inhibitory compound, was capable of managing the toxicity arising from CAR T cell treatment. They argued that the document only contained assertions to this effect, while the experimental evidence in Figure 9 was not conclusive.
69. Thus, in this context, the relevant question is whether P1 makes it credible that tocilizumab is effective in managing toxicity of CAR T cells.
70. The board agrees that the labelling of Figure 9 leaves open whether enbrel and tocilizumab were given twice together as could be deduced from the comma in the wording "*enbrel, tocilizumab*" or whether enbrel and tocilizumab were given sequentially at two different time points, i.e. on day 7 and day 7.5, respectively.
71. It is undisputed that the patient in Figure 9 was treated with three therapeutic compounds in the course of several days: steroids on day 5; enbrel and/or tocilizumab on days 7 and 7.5. The other three arrows at the bottom of Figure 9 appear to represent the split CAR T cell administration, as indicated on page 42, lines 8 to 9, of P1: "*the present study was designed to*

mitigate this possibility by deliberate infusion of CAR T19 over a period of three days". Figure 9 displays the fold change from baseline of serum cytokines. Cytokine levels drop after day 5 or 6, except for TNF- α . From the data in Figure 9 alone, it cannot be deduced whether the disease state of the patient improved. It can also not be deduced whether the compounds in combination or any single agent managed the toxicity associated with the CAR T cell treatment.

72. This additional information is provided in the legend to Figure 9, which states that "[t]he patient was critically ill on days 5 to 7, and only began to improve following tocilizumab administration". From this statement, tocilizumab must have been provided as the last agent, i.e. on day 7.5 after enbrel had been given on day 7. Otherwise the inventors could not have observed the patient's condition "*following tocilizumab administration*". Moreover, this statement shows that the inventors considered tocilizumab, the IL-6 inhibitory compound, to be the critical agent. They do not speculate about contributions from the other agents, which they apparently disregarded for their respective effect(s). The same holds true for the description of the example, on page 44, which equally only refers to "*tocilizumab (anti-IL6) [which] can ameliorate the toxicity of CARs and seemingly preserve anti-tumor effects*".

73. From these passages and Figure 9, the board understands that at least one patient began to improve **only** after tocilizumab had been administered. Even if the document does not detail the complete treatment history of the patient(s) receiving tocilizumab, the board takes these statements as observations by the treating physician, which, in the absence of evidence to the contrary, have

to be taken at face value. The board therefore also does not agree with the appellants' argument that these were mere assertions which, in accordance with decision T 609/02, might not represent sufficient evidence for a therapeutic effect (see Reasons 9.). In the current case, a clinical trial, albeit with only two (or even only one) patients, was carried out, and the inventors drew conclusions from this. The board therefore considers the teaching of P1 sufficient to make it credible that the toxicity of CAR T cell therapy can be managed with a single agent.

74. Post-published evidence was also filed by the respondents. Documents D71 to D75 show the requirement by the European Medicines Agency to have tocilizumab available as an emergency medicament when undertaking CAR T cell treatment. The board, however, considers this evidence not necessary to decide on the enablement of the disclosure in P1.
75. The appellants cited post-published document D36 (published between the filing of the second priority document P2 and the filing date), which showed that the inventors themselves and other researchers in the field considered a combination treatment of etanercept and tocilizumab to be required. Other researchers had relied on this in review articles, for example in D97 (page 717, right-hand column, lines 3 to 6) and D98 (page 366, left-hand column, first full paragraph).
76. The board cannot see how a later publication by the inventors which was not available at the priority date could affect what the skilled person would take as the disclosure of the priority document. Moreover, while being more cautious, as is often the case for scientific publications, the disclosure of document D36

does not raise doubts that tocilizumab alone could also manage toxicities associated with CAR T cell treatment. This is apparent, for example, from the statement on page 1517, right-hand column, end of the first full paragraph: "*tocilizumab (anti-interleukin-6 receptor monoclonal antibody) holds promise for glucocorticoid-resistant GVHD,²²⁻²⁴ and our results are consistent with these data*". Moreover, in Table 2 it is indicated for patient 1, which according to the respondents is the same patient as in Figure 9 in P1, "*[f]ebrile neutropenia, Grade 3, Peak temperature of 40.7°C; event resolved on day 7 (within hours after administration of tocilizumab)*". The fact that document D36 also mentions etanercept as part of the anti-cytokine therapy (see Summary and page 1514, right-hand column) does not divert from the fact that also the authors of D36 considered tocilizumab the crucial agent. It is also consistent with the detailed time line of the treatment given in the legend to Figure 1 in D36. This shows that etanercept was given on the morning of day 7, while tocilizumab was only given at 6 p.m. on day 7. Complete resolution of fevers occurred only after the administration of cytokine therapy, i.e. after administering tocilizumab. This is consistent with the disclosure of P1 (see legend to Figure 9). Documents D97 and D98 do not add any further information as they merely refer to the scientific publication D36.

77. The appellants also referred to decisions T 1779/21 and T 979/23 (Dravet syndrome I and II), which found the claimed monotherapy with fenfluramine not sufficiently disclosed based on experiments with a combination therapy, in which fenfluramine was administered concomitantly and long-term with valproate, the standard of care, over a period of time. The board considers the case at hand to be different because a

patient was treated with tocilizumab in a consecutive manner, this allowing the treating physician to draw a credible conclusion on tocilizumab as a monotherapy. In contrast, in the cases of decisions T 1779/21 and T 979/23, no such consecutive treatment data of a single agent were available, and no observations which allowed the conclusion that a monotherapy would be effective were reported. Therefore the conclusions drawn in those cases are not directly applicable.

Cytokine inhibitory compound

78. A further objection related to the nature of the cytokine inhibitory compound. As outlined under the claim interpretation above, the board considers the claim to relate to specific IL-6 inhibitory compounds for second-line therapy. Appellants I and III, the latter only referring to sufficiency of disclosure, considered those compounds not enabled over the whole breadth of the claim, including all types of IL-6 inhibitors, i.e. not only antibodies binding to the IL-6 receptor, such as tocilizumab, but also antibodies binding to IL-6 itself, nucleic acids, small molecules, etc. Testing a single antibody, tocilizumab, did not make the effect plausible for these different kinds of molecules.

Antibody inhibitors

79. Appellant I furthermore argued that anti-IL-6 antibodies were not suitable, as was apparent from the review article D17, page 3379, left-hand column, last paragraph):

"However, antibody treatment led to massive systemic elevations (approaching mg quantities) in IL-6. Subsequent pharmacokinetic experiments

revealed that antibody-associated IL-6 was not cleared from the circulation, leading to a reservoir of free IL-6 as concentrations reached the K_D of the antibody (116). To overcome such difficulties, targeting strategies were redirected toward blockade of IL-6R. This led to development of tocilizumab."

80. The board notes that document D17 does not relate to a second-line therapy for cancer following CAR T cell therapy but to neutralising anti-IL-6 antibodies as (first-line) anti-tumour agents. The medical use is therefore different, and the results cannot be directly transferred.
81. The respondents have provided post-filed evidence that antibodies targeting IL-6 (siltuximab, see D38, Table 2; D80, "Results" section) can manage the toxicity of CAR T cell therapy and that the anti-IL-6 antibody siltuximab was known before the priority date (D17, Table 1; WHO publication in D66).

Other inhibitors

82. The respondents have provided post-filed evidence that anti-IL-6 nucleic acid inhibitors can manage the toxicity of CAR T cell therapy (D81). The board considers it also plausible from the disclosure in P1 that IL-6 inhibition with means other than antibodies would manage the toxicity of CAR T cell therapy. The appellants did not provide evidence to show that the design of other types of inhibitors of IL-6 would have posed an undue burden on the skilled person.

Link between monitoring and IL-6 inhibitory therapy

83. Appellant I argued that the examples in P1 showed that monitoring cytokine levels was not sufficient for determining the appropriate second-line therapy. It based its argument on the fact that patients UPN 02 and UPN 03, who had developed toxicities and showed elevated levels of cytokines, were not reported to have required anti-cytokine therapy (see page 44, lines 8 to 11, referencing Figure 8).
84. The board cannot accept this argument. It is not uncommon that a patent application contains examples which do not fall under the claims. This is even more so when the claims have been amended. The board can see no reason why individual patients for which the decision was taken, for unknown reasons, not to treat them with anti-cytokine therapy should raise doubts as to the enablement of the disclosure of P1.
85. In summary, the board finds that the invention to which claims 1 and 5 relate is disclosed in an enabling manner in document P1.
86. The claims enjoy priority from the first priority document P1. Documents D26, D35, D36 and D53 therefore do not form part of the state of the art under Article 54(2) EPC.

Sufficiency of disclosure (Article 83 EPC)

87. In view of the board's finding on priority and the fact that most of the disclosure of P1 is also found in the application as filed, only the appellants' arguments which are specific to the application as filed (and the patent as granted) and which were not also brought

forward with regard to the disclosure of the priority document P1 will be discussed in the following.

Managing the toxicity of CAR T cell therapy

88. The application as filed discloses in Example 1 that the treatment with tocilizumab, an anti-IL-6 receptor antibody, reduced toxicities after CAR T cell treatment while preserving anti-tumour effects in two out of two patients (see page 34, lines 10 to 16). This finding is further supported for one of the patients with "r/r ALL" (relapsed/refractory ALL) in the legend to Figure 2 on page 3, which states that "[t]he patient was critically ill on days 5 to 7, and only began to improve following tocilizumab administration". Example 2 supports this finding by reporting that "3 CLL patients have also been treated with tocilizumab], also with prompt and striking resolution of high fevers, hypotension and hypoxia".
89. The board finds this credible evidence that an IL-6 inhibitor can manage the toxicities associated with CAR T cell treatment. As outlined above under the claim interpretation, the claim does not require that each and every toxicity be managed (see points 41. and 42. above).
90. Appellant II argued that when treating B-cell non-Hodgkin lymphoma (B-NHL) with CAR T cells, local cytokine release syndrome (L-CRS) could arise which was not reduced by anti-IL-6 treatment but could even be aggravated by it (see D38, page 6, right-hand column, first paragraph).
91. However, the board agrees with the respondents that, as also reported in D38, not all B-NHL show L-CRS (see

page 5, right-hand column, first paragraph), and even if L-CRS occurs, it is in parallel with systemic CRS (S-CRS). Tocilizumab is "*cautiously recommended for S-CRS management*", even though "*anti-TNF- α therapy might be a better choice*" (D38, page 6, right-hand column, first paragraph and Table 2). The board therefore concludes that the disclosure of D38 does not raise serious doubts that tocilizumab manages S-CRS also in B-NHL patients.

92. Appellant II further referred to neurotoxicity as a side effect of CAR T cell therapy which could not be managed with IL-6R inhibitors (see post-published documents D39, page 11, third paragraph; D40, page 1; D41, page 547, right-hand column).
93. The respondents counter argued that in D39 it was also stated on page 9, third paragraph, that "*[n]eurotoxicity was almost invariably associated with CRS*", the latter being amenable to IL-6 inhibitor treatment, and that tocilizumab might have less effect on neurotoxicities (page 4, second paragraph), but early administration was still recommended (page 8, final paragraph). D40 suggested that an IL-6 inhibitor could manage neurotoxicity when delivered directly into the cerebrospinal fluid space (page 3, final paragraph).
94. Appellant III referred to the patent, which showed that acute infusional toxicity could arise with CAR T cell treatment (see paragraphs [0158], [0175] and [0176]). As this toxicity occurred early, immediately after infusion, there was no data showing that cytokine inhibitors could manage it. As also shown in the patent (see paragraph [0160]), early treatment with

tocilizumab had resulted in no response to CAR T treatment and was thus not suitable.

95. The respondents counter argued that appellant III had not provided evidence that acute infusional toxicity was accompanied by an increase in IL-6 levels as required by claim 1. Furthermore, as shown in post-published documents D67 and D68, also early or even preventive treatment with IL-6 inhibitors was possible (see also point 98. below).
96. In view of its claim interpretation that managing a toxicity meant that not all possible toxicities had to be managed by the second-line therapy (see points 41. and 42. above), the board considers the evidence not sufficient to raise doubts that toxicity management could be achieved.

Timing of the administration of an IL-6 inhibitory compound

97. Appellants II and III argued that the application as filed (and the patent) showed that the timing of the administration of tocilizumab was crucial. However the patent did not provide a teaching as to how to determine the appropriate time of administration. If tocilizumab was given too early, it had a negative effect on *in vivo* proliferation of CART19 cells and thus on tumour treatment, as seen in the third CLL patient (see paragraph [0160] of the patent). The negative effect was confirmed in a mouse model where cytokine blockade with tocilizumab and/or etanercept prior to T cell infusion abrogated disease control with less *in vivo* proliferation of infused CART19 cells.
98. The respondents replied that the relevance of the timing was a hypothesis ("*may interfere*", see paragraph

[0162] of the patent) which was later disproved (see documents D67 and D68). The patent also indicated that one third of all patients did not respond to CAR T cell treatment (see paragraph [0158]: "*6/9 evaluable patients had a complete recovery (CR) or partial recovery (PR), including 4 sustained CRs*"). It was therefore not surprising that one in three patients showed no response to the CAR T cell treatment. The mouse model was not suitable for adequately reflecting the situation in humans because it contained no endogenous human IL-6 receptors, meaning that all tocilizumab was targeted to IL-6 receptors on CAR T cells or xenograft cancer cells (see also paragraph 8 of D90).

99. The board considers that the disclosure of an isolated failure of the CAR T cell therapy which cannot clearly be linked to the administration of an IL-6 inhibitor does not raise serious doubts that the effect claimed, i.e. managing toxicities and maintaining therapeutic efficacy, can be achieved. In the context of cancer, therapeutic efficacy may be acknowledged even with low percentages of responders. A case by case assessment is necessary.
100. The board concurs with the respondent's explanations concerning the mouse model and its limitations.
101. Furthermore, the skilled person would consider the disclosure of paragraphs [0160] to [0162] (or the respective passages of the application as filed) a cautionary statement that early blockade of an IL-6 inhibitor "*prior to initiation of significant CART19 proliferation [...] may interfere with proliferation and effector function*". Taking a cautious approach, the skilled person might therefore have considered awaiting

CAR T cell proliferation before administering the IL-6 inhibitor. This, however, forms part of the disclosure of the application as filed (see page 36, lines 18 to 24), which is not limited to the claim wording and does not mean that the effect cannot be achieved. The respondents also submitted evidence that early administration of an IL-6 inhibitor and even administration before CAR T cell therapy is effective (see documents D67, D68 and D91). Post-published evidence thus supports the credible disclosure of the application as filed.

102. The patent thus provides also sufficient information as to the timing of administration of tocilizumab.

Link between IL-6 levels and IL-6 inhibitory therapy

103. Appellant II pointed to patient CHOP-101, who had increased IL-6 levels after CAR T cell therapy but did not receive IL-6 inhibitory treatment, while the toxicities resolved spontaneously (see paragraph [0176] in the patent). This showed that there was no link between increased IL-6 levels and a successful second-line therapy with an IL-6 inhibitory compound. The appellant was further of the opinion that the limited number of patients without suitable controls did not allow concluding that the results were significant.
104. The board disagrees. In the case at hand, a rather new and complex personalised treatment (CAR T cells) is applied to a small number of severely ill patients. A fraction of those patients develops severe toxicities which are not amenable to treatment with corticosteroids. It is therefore not surprising that no large numbers of patients are available for trials of a second-line therapy of CAR T cells in cancer.

105. The fact that in one patient (CHOP-101) the toxicities resolved spontaneously does not allow any conclusion to be drawn about the effect of an IL-6 inhibitor in another patient (CHOP-100). This is because the first patient had not received any such inhibitor and apparently also did not need it, probably because the toxicities were less severe (paragraph [0176]: "*no cardiopulmonary toxicities*"). In view of the small number of patients, it is also important to consider the individual treatment history. In patient CHOP-100, who developed severe toxicities which could not be managed with corticosteroids (see paragraph [0180]), anti-cytokine therapy consisting of etanercept and tocilizumab had a profound effect: "*within hours she defervesced, was weaned off vasoactive medications and ventilatory support as her clinical and radiologic ARDS resolved*", ultimately resulting in clinical and molecular remission of the cancer (see paragraph [0178]). The legends to Figures 2 and 4 provide further details of the treatment of patient CHOP-100:

Figure 2: "*The patient was critically ill on days 5 to 7, and only began to improve following tocilizumab administration.*"

Figure 4: "*CHOP-100 was given methylprednisolone starting on day 5 at 2mg/kg/day, tapered to off by day 12. On the morning of day 7, etanercept was given 0.8 mg/kg x 1. At 6pm in the evening of day 7, tocilizumab 8 mg/kg x 1 was administered. A transient improvement in pyrexia occurred with administration of corticosteroids on day 5 in CHOP-100, with complete resolution of fevers occurring after administration of cytokine-directed therapy consisting of etanercept and tocilizumab on day 8.*"

106. From this time line of treatment, it is apparent that the resolution of side effects occurred only after the administration of tocilizumab. The board concludes that although no direct comparison of the effect of an IL-6 inhibitory compound against placebo was possible due to the small number of patients, the treatment history of patient CHOP-100 makes it credible that toxicities can be managed while maintaining a therapeutic effect.
107. In conclusion, for the reasons outlined in points 62. to 86. and 88. to 106. above the claimed invention is sufficiently disclosed.

Added subject-matter (Article 123(2) EPC)

108. In view of the finding that the subject-matter claimed related to the same invention as disclosed in the first priority document P1 (see above) and the fact that most of the disclosure of P1 is also found in the application as filed, only the appellants' arguments which are specific to the application as filed and which have not already been dealt with under priority will be discussed in the following.
109. The appellants argued that the application as filed disclosed that administration of a cytokine inhibitory agent required that an increase in the level of a cytokine had to be detected first. However, current claim 1 did not require that the person performing the treatment be aware of the increase in cytokine levels when choosing the second-line therapy, i.e. there was no causal decision-making based on the result of the monitoring step.

110. As outlined in the claim interpretation (see points 43. to 48. above), the claim requires that "*said monitoring*", i.e. the monitoring to determine the appropriate type of second-line therapy, "[indicate] an *increase in the level of said cytokine*", i.e. IL-6. This results in the determination of the second-line therapy which is a cytokine inhibitory therapy comprising a cytokine inhibitory compound, where the cytokine is IL-6, i.e. an IL-6 inhibitory compound.
111. This is what is disclosed in the application as filed, for example in claims 1 to 4 and on pages 2, 3, 7 and 19.
112. Appellant II argued that claims 1 to 4 as filed did not mention toxicity management and could thus not provide a basis. The board does not agree because the whole application as filed is concerned with toxicity management, particularly monitoring the profile of soluble factors in the patient post T cell infusion in order to treat cancer (see e.g. page 1, last paragraph; paragraph bridging pages 6 to 7; page 7, second full paragraph; page 18, lines 7 to 16).
113. Appellant II further argued that the application as filed required a "*choice*" from a list of cytokine inhibitory therapies which was no longer required in the claim. The board considers that the selection of IL-6 from the list of cytokines in claim 4 does not add subject-matter because IL-6 is a preferred targeted cytokine for managing toxicities in the application as filed (see the examples in which the only cytokine inhibitor used is tocilizumab, which is an IL-6 inhibitor; page 24, lines 9 to 15 and page 25, lines 8 to 20; legend to Figure 1 on page 3).

114. Appellant II also argued that the claims as filed did not refer to a "*cytokine inhibitory compound*" but only to "*cytokine inhibitory therapy*". The board considers it implicit in the disclosure of the application as filed that a cytokine inhibitory therapy has to involve a compound. No other ways of inhibiting cytokines are mentioned in the application as filed. Moreover, claim 5 as filed refers to a number of compounds for the cytokine inhibitory therapy. Although this claim is dependent on claim 3 and not on claim 4, it is directly and unambiguously derivable from the application as filed to which cytokines, including IL-6 as a preferred target, the cytokine inhibitory compounds listed in claim 5 as filed are directed.

115. Appellant II also raised objections of added subject-matter of claim 5. The respective arguments were already addressed in relation to the validity of the priority (see points 57. to 61. above). In view of the disclosure of the application as filed, which includes additional references to tocilizumab as a preferred cytokine inhibitory compound (see e.g. page 33, lines 23 to 27; page 34, heading of Example 2), the board finds that the subject-matter of claim 5 does not extend beyond the content of the application as filed.

116. In conclusion, for the reasons outlined in points points 51. to 61. and 109. to 115. above the claims do not add subject-matter.

Novelty (Article 54 EPC)

Documents D23, D24 and D25

117. Appellants I and II did not raise any novelty objections based on these documents.

118. In view of the claim interpretation (see points 33. to 40. above), corticosteroids and rasburicase are not "*cytokine inhibitory compounds [...] wherein the cytokine is IL-6*" as required by the claim. The claimed subject-matter therefore already differs in this regard from the disclosure of documents D23 or D24 and is novel (Article 54 EPC).
119. It was disputed by the parties whether the step of monitoring increased levels of IL-6 to determine the appropriate second-line treatment represented a further difference. This will be discussed below under inventive step.
120. Since no separate arguments were provided for document D25 in writing or at the oral proceedings, the same conclusion applies.

Inventive step (Article 56 EPC)

Document D23 as the closest prior art

121. The opposition division considered document D23 to represent the closest prior art. The parties agreed with this choice and also used D23 as the starting point for assessing inventive step in appeal. The board agrees that D23 represents a realistic starting point. The appellants have not provided a separate reasoning starting from documents D24 or D25, having considered them equivalent to D23 for assessing inventive step.
122. Document D23 discloses a treatment of cancer patients with CAR T cells as defined in claim 1. It further discloses the monitoring of cytokine levels including IL-6 (see Figure 3 B, C and D). At least in some patients, IL-6 levels are increased post CAR T cell infusion. This was undisputed between the parties.

Differences and effects

123. The board has identified the following differences between the subject-matter of claim 1 and the disclosure of D23:
- (i) monitoring of cytokine (including IL-6) levels to determine an appropriate second-line therapy
 - (ii) IL-6 inhibitory compound as a second-line therapy
124. With regard to difference (ii), the board refers to its claim interpretation, which excludes corticosteroids and rasburicase from being IL-6 inhibitory compounds (see points 33. to 40. above).
125. With regard to difference (i), appellant II argued that document D23 disclosed the "*real-time*" monitoring of elevated IL-6 levels during the treatment of patient UPN02 and that the toxicity was subsequently managed using steroids.
126. The board is unable to derive from the disclosure of D23 at which point in time during the treatment the levels of cytokines had been determined, i.e. immediately after the samples had been taken or at some later time. The respondents pointed to the fact that the samples had been frozen and batch analysed (see D23, paragraph bridging pages 62 to 63; page 72, lines 7 to 10; page 81, lines 3 to 6), a fact that would indicate a later analysis. Appellant II referred to the expression "*to assess potential toxicities*" on page 72, lines 7 to 10, which in its view pointed to "*real-time*" monitoring. The board disagrees because potential toxicities can also be assessed *ex post facto* to gain a

better understanding of the disease and to inform future research. The decision to manage the toxicities of patient UPN 02 with corticosteroids is furthermore likely to have been taken on the basis of the clinical symptoms of the patient and not on the basis of elevated cytokine levels, as appears from D23, page 75, last paragraph:

"The patient developed fevers to 40°C, rigors and dyspnea requiring a 24 hour hospitalization on day 11 after the first infusion and on the day of the second CART19 cell boost. Fevers and constitutional symptoms persisted and on day 15, the patient had transient cardiac dysfunction; all symptoms resolved after corticosteroid therapy was initiated on day 18."

127. In conclusion, the board finds that document D23 discloses that cytokine levels, including IL-6, were monitored and found to be increased, but not whether this monitoring occurred in time to determine a second-line therapy. D23 thus also does not disclose whether the decision to manage toxicities with a second-line treatment such as corticosteroids or rasburicase was based on the monitored cytokines.
128. The effect achieved by these differences is twofold. First, choosing the second-line therapy based on a biomarker, IL-6, which is measured following CAR T cell administration and not only based on clinical symptoms allows for a more precise treatment decision. Second, administering an IL-6 inhibitor manages toxicities of CAR T cells while maintaining the therapeutic effect of those cells.

Over the whole breadth of the claims

129. Appellant I pointed to paragraph [0160] of the patent, which disclosed that a patient who had received tocilizumab at an early time point (day 3) for early fevers had no CART19 proliferation and no response. The patent further showed that increased IL-6 levels did not necessarily require IL-6 inhibitory treatment (see paragraph [0176] of the patent). This meant that the effect of managing toxicities while maintaining a therapeutic effect of the CAR T cells was not achieved over the whole breadth of claim 1.
130. It is established case law of the Boards of Appeal that for a further medical use claim, achieving the claimed therapeutic effect is a functional feature of the claim (see decision T 609/02). Consequently, the questions posed by appellant I have been dealt with under sufficiency of disclosure (see points 97. to 106. above).
131. Appellant II argued that no improvement over the toxicity management in D23 in which corticosteroids and rasburicase were administered had been established in the patent. An improvement could thus not form part of the objective technical problem.
132. A direct comparison between an IL-6 inhibitor, e.g. tocilizumab, and corticosteroid or rasburicase was, indeed, not made in the patent and was also not possible due to the small number of patients and the severity of the condition. An improvement over the treatment with corticosteroid can, however, be seen in patient CHOP100, who had been first treated with corticosteroid and "*only began to improve following tocilizumab administration*" (see paragraph [0022],

legend to Figure 2; paragraphs [0154], [0175] and [0180]).

133. A direct comparison with rasburicase is also not required because unlike an IL-6 inhibitor, it does not manage CRS but TLS, which leads to elevated levels of uric acid (see D2a, page 958, left-hand column, first paragraph; D10, page 866, right-hand column, section 7.3; D58, page 327, left margin; D94, first paragraph; D23, page 70, lines 4 to 8; D25, page 3, second paragraph). D59 identifies CRS as "*the most prominent toxicity of CAR-T cell therapy*" (page 1, left-hand column, first paragraph) and D48 explains that "*TLS after CAR T cell therapy is uncommon even in high risk situations*" (page 6, left-hand column, second paragraph). The IL-6 inhibitory compound therefore manages a different and, in CAR T cell therapy, more common toxicity than rasburicase.
134. Appellant III argued that the effect of maintaining CAR T cell efficacy in the treatment of cancer was not achieved over the entire scope of the claims and referred to Example 2 in the patent in which it was shown that the timing of the administration of a cytokine inhibitor was crucial for maintaining CAR T cell efficacy.
135. The board disagrees for the reasons outlined under sufficiency of disclosure above (see points 97. to 101.).
136. The objective technical problem can thus be formulated as the provision of an improved CAR T cell therapy of cancer.

Obviousness

D23

137. The appellants argued that the solution as claimed was obvious over the disclosure of D23. The board disagrees because neither the determination of a second-line therapy based on increased IL-6 levels nor the use of an IL-6 inhibitor is disclosed or suggested in D23.

D23 and D1

138. Appellant I argued that the skilled person starting from the disclosure in D23 would find a solution to the objective technical problem in document D1. D1 disclosed that subsequent to CAR T cell infusion, patients developed significant toxicities which were correlated with elevated cytokine levels. The authors hypothesised "*that much of the toxicity that occurred in our patients was because of elevations in inflammatory cytokines such as IFN γ and TNF*" (see page 2715, left-hand column, lines 3 to 13 and right-hand column, lines 5 to 7). D1 stated:

"We have shown that toxicity correlates with serum inflammatory cytokine levels after CAR-transduced T-cell infusion, so reducing inflammatory cytokine levels in patients receiving infusions of CAR transduced T cells is a promising approach to decreasing toxicity. [...] An additional strategy for reducing toxicity is to administer anti-TNF agents such as etanercept during episodes of severe toxicity." (page 2718, right-hand column, second paragraph)

139. Appellant I concluded that D1 proposed a practical strategy to reduce inflammatory cytokine levels by inhibiting a cytokine that was most highly elevated (in

this case, TNF) and thereby rendered the claimed subject-matter obvious.

140. The board disagrees because D1 does not disclose increased levels of IL-6 and does not suggest the use of an IL-6 inhibitor but focuses on "*serum IFN γ and TNF levels*" (see abstract) and proposes using inhibitors targeting TNF, such as etanercept.
141. Moreover, in document D23, IL-6 is only one of a number of cytokines showing an increased level (see Figures 3A to 3D and 13A to 13D). Neither D23 nor D1 therefore specifically suggests monitoring IL-6 to determine a second-line therapy. Even if the skilled person had taken from document D1 that inhibiting cytokines could be a promising second-line therapy, there was no experimental evidence that this approach would be successful for any cytokine, let alone for IL-6, which is not even mentioned in D1.

D23 with D52, D57 and D90

142. Appellant III cited in addition documents D52, D57 and D90 to be combined with the disclosure of D23.
143. Document D52 discloses that during CRS, which can be caused by monoclonal antibodies and Fc-fusion proteins "*[t]hough multiple cytokines may be present, the classic signature of CRS consists of the pro-inflammatory cytokines TNF α , IFN γ and IL-6*" and further that "*[a]nalysis of serum cytokines in humans provides a primary means of monitoring the development and resolution of this syndrome*" (page 242, paragraph bridging columns). Tocilizumab is disclosed in Table 1, but not as a treatment of CRS but of rheumatoid arthritis (RA). The board does not see how the claimed

solution can be rendered obvious by this additional disclosure, which does not suggest a treatment option.

144. Document D57 relates to anti-IL-6 therapy and discloses IL-6R antagonists in the treatment of diseases and disorders associated with elevated IL-6, e.g. tocilizumab (see paragraphs [00198] and [00300] of D57). In paragraph [00602], D57 states that these inhibitors are "*useful for ameliorating or reducing the symptoms of diseases or disorders associated with cytokine storm*". Cytokine storm is also recited in claim 35 of D57.
145. The board, however, finds that the disclosure of D57 amounts to nothing more than an assertion without any experimental evidence. D57 does not mention CAR T cell therapy. It would have been entirely uncertain for the skilled person whether inhibiting IL-6 could manage toxicities, such as CRS, associated with CAR T cell therapy. There is also no indication in D57 that monitoring IL-6 levels could guide the second-line therapy.
146. Appellants II and III also cited document D90, which is a declaration by Prof. Negri filed by the respondents. The board is unable to see how a post-published declaration could be state of the art. The relevant documents cited in this declaration are D5, D6 and D58.
147. D5 is a case report of a serious adverse event after CAR T cell therapy accompanied by a marked increase of several cytokines, including IL-6. D5 suggests conducting "*a more restricted dose-escalation trial starting at low doses that are unlikely to cause serious toxicity*" (page 849, left-hand column, penultimate paragraph).

148. D6 is a review article on cytokine storm and observes that "*IL-6 concentrations in peripheral blood have been used to assess the intensity of systemic cytokine responses in patients with sepsis, because IL-6 production is stimulated by TNF and IL-1 β , providing an integrated signal of these two early-response cytokines*" (page 20, right-hand column, first paragraph). It does not refer to CAR T cell therapy or how to manage associated toxicities.
149. D58 is a review article on the safety and side effects of monoclonal antibodies, including cytokine storm, which involves the release of pro-inflammatory cytokines, such as IL-6.
150. Appellant II further cited document D17, which is a review article on therapeutic strategies for the clinical blockade of IL-6/gp130 signalling. It lists a large number of diseases in which IL-6 has been targeted. There is, however, no mention of cytokine storms or toxicities associated with CAR T cell therapy.
151. None of the cited documents which allegedly could supplement the disclosure of D23 discloses IL-6 inhibition as a strategy for managing toxicities associated with CAR T cell therapy.
152. In conclusion, the claimed invention is not obvious over the state of the art (Article 56 EPC).

Conclusion

153. Taking into consideration the amendments made by the proprietor of the European patent during the opposition

proceedings (auxiliary request 45, main request in appeal), the patent and the invention to which it relates meet the requirements of the EPC.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar:

The Chairwoman:



I. Aperribay

M. Pregetter

Decision electronically authenticated