

Via CMS

European Patent Office 80298 MUNICH GERMANY

Gif-sur-Yvette, 2 July 2019

Opposition against European patent n°3214091 (Application number 17153799.6) In the name of The Trustees of The University of Pennsylvania For « USE OF CHIMERIC ANTIGEN RECEPTOR-MODIFIED T CELLS TO TREAT CANCER » Opponent: Public Eye

O. Ref.: C000227-PE

Dear Madam/Sir,

We hereby file an opposition pursuant to Article 99 EPC against European patent n°3214091 (hereafter "the patent" or "the opposed patent") entitled "USE OF CHIMERIC ANTIGEN RECEPTOR-MODIFIED T CELLS TO TREAT CANCER" granted to The Trustees of The University of Pennsylvania on 3 October 2018 (see attached notice of opposition).

The opposition is filed against all claims of the patent on the grounds of Articles 100(a), 100(b) and 100(c) of the EPC.

Revocation of the patent in its entirety is hereby requested.

Oral proceeding pursuant to Article 116(1) EPC are requested should the opposition division consider not granting our request.

Yours faithfully,

Lionel Vial

Cabinet Lionel Vial 2 rue Jean Rostand 91400 Orsay (Bureaux) - 6 rue de Vaugondran 91190 Gif-sur-Yvette (Siège) Téléphone : +33 1 85 08 34 80 - Télécopie : +33 1 85 41 01 62 Courriel : contact@vial-ip.com - Site web : http://www.vial-ip.com SAS au capital de 1000 euros - RCS Evry 801 054 271 - APE 6910Z Nos conditions générales de services se trouvent sur notre site web.

Statement of facts and arguments

I. The opposed patent

The patent application from which the opposed European patent EP3214091 results, was filed as a divisional application of European patent application No. 11846757.0 (EP2649086) itself resulting from International application PCT/US2011/064191 (WO2012/079000) filed on 9 December 2011 and claiming the priority dates of US provisional applications Nos. 61/421,470 filed on 9 December 2010 and 61/502,649 filed on 29 June 2011.

The opposed patent was granted on 3 October 2018 and relates to the field of CAR Tcell therapy. The opposed patent thus claims *inter alia* a T cell genetically modified to express a chimeric antigen receptor (*i.e.* a CAR) wherein the CAR comprises (a) an antigen binding domain that is an anti-CD19 scFv (b) a costimulatory 4-1BB signalling region, and (c) a CD3 zeta signalling domain for use in a method for treating cancer in a human, wherein the human is resistant to at least one chemotherapeutic agent.

A schematic view of the so-called second generation CAR harboured by the claimed CAR T-cell for use in a method for treating cancer is presented below:





As we will see the opposed patent appears to be an attempt at evergreening patent protection of CAR T-cells harboring such CARs for use in the treatment of cancers, probably fueled by the desire to offer a renewed protection to the drug Kymriah® which has recently been authorised. Indeed, the corresponding CAR T-cells, explicitly developed for treating drug-resistant B-lineage acute lymphoblastic leukemia (ALL) had been described, and patented, at least 6 years before the priority date of the opposed patent.

Documents filed in support of the opposition

Reference	Document	Publication date
D1	US provisional application No. 60/421,470	N.A.
D2	US provisional application No. 60/502,649	N.A.
D3	Porter et al. (2011) Journal of Cancer 2 :331	01/06/2011
D4	Kalos et al. (2011) Science Translational Medicine 3 : 95ra73	10/08/2011
D5	Porter et al. (2011) The New England Journal of Medicine 365 :725	25/08/2011
D6	Milone et al. (2009) Journal of the American Society of Gene Therapy 17 :1453	21/04/2009
D7	Imai et al. (2004) Leukemia 18 :676–684	12/02/2004
D8	Nicholson et al. (1997) Mol. Immunol. 34:1157–1165	1997
D9	US 2005/0113564	26/05/2005
D10	NM_000734	09/10/2003
D11	NP_000725	02/06/2019
D12	P20963	10/10/2003
D13	US 2004/043401	04/03/2004
D14	Kochenderfer et al. (2010) Blood 116 :4099	28/07/2010
D15	Davila et al. (2010) Blood 116 :3268	06/12/2010 ¹

¹ As indicated by the patentee in the information disclosure statement (IDS) filed by the applicant at the USPTO on 15/01/2016 in a corresponding examination procedure

<u>I. The subject-matter of the European patent extend beyond the content of the earlier</u> <u>application as filed (Art. 100(c) EPC)</u>

The opposed patent has been filed as a divisional application of the European patent application EP2649086 itself resulting from the international application WO2012079000.

• The closest support for claim 1 of the opposed patent appears to be the combination of the following paragraphs (see page 4, lines 5 to 11 of the international application as filed):

"The invention also provides a method of treating a human with chronic lymphocytic leukemia. In one embodiment, the method comprises administering to a human a T cell genetically engineered to express a CAR wherein the CAR comprises an antigen binding domain, a costimulatory signalling region, and a CD3 zeta signalling domain comprising the amino acid sequence of SEQ ID NO: 24."

In one embodiment, the human is resistant to at least one chemotherapeutic agent." (underlining added).

However, it is not specified that the antigen binding domain is an anti-CD19 scFv, in particular of sequence SEQ ID NO: 20, and that the costimulatory signalling region is 4-1BB.

Thus, the subject-matter of claim 1 results from the selection within at least **2** lists of features:

- Selection of the antigen binding domain; and
- Selection of the costimulatory signalling region.

According to the Guidelines for Examination in the EPO (November 2018 edition, Part G, Chapter VI, paragraph 8), if a selection from two or more lists of a certain length has to be made in order to arrive at a specific combination of features then the resulting combination of features, not specifically disclosed in the prior art, confers novelty.

In other words, the subject-matter of claim 1 cannot be considered as deriving directly and unambiguously from the generic description of the international application WO2012079000 as it results from the selection of specific characteristics from two or more lists.

In addition, even if the above selection in at least two lists could be considered allowable, the subject-matter resulting from the selection would relate only to the treatment of chronic lymphocytic leukemia and not to any cancer as is provided in claim 1. Therefore, the mention of the term "cancer" in claim 1 also extends beyond the content of the earlier application as filed.

In addition, the provision that the human is resistant to at least one chemotherapeutic agent is only associated to the feature according to which the human is afflicted with chronic lymphocytic leukemia.

Accordingly, providing that the human resistant to at least one chemotherapeutic agent is afflicted with a cancer, in general, also extends beyond the content of the earlier application as filed.

Consequently, the subject-matter of claim 1 extends beyond the content of the earlier application as filed.

Since the specification of the international application is similar to the specification of the application as filed, the same reasoning applies mutatis mutandis to the application as filed.

As such, the subject-matter of claim 1 extends beyond the content of the application as filed.

• The subject-matter of claims 2 to 6 and 15 to 18, which depend from claim 1, therefore also extend beyond the content of the earlier application as filed and beyond the content of the application as filed.

• The closest support for the subject-matter of claim 7 of the opposed patent appears to be the following paragraph (see page 4, lines 14 to 21 of the earlier application as filed):

"The invention also includes a method of generating a persisting population of genetically engineered T cells in a human diagnosed with cancer. In one embodiment, the method comprises administering to a human a T cell genetically engineered to express a CAR wherein the CAR comprises an antigen binding domain, a costimulatory signalling region, and a CD3 zeta signalling domain comprising the amino acid sequence of SEQ ID NO: 24, wherein the persisting population of genetically engineered T cells persists in the human for at least one month after administration."

However, it is not specified that the antigen binding domain is an anti-CD19 scFv, in particular comprising the amino acid sequence of SEQ ID NO: 20, and that the costimulatory signalling region is 4-1BB.

Thus, the subject-matter of claim 7 results from the selection within at least **2** lists of features:

- Selection of the antigen binding domain; and
- Selection of the costimulatory signalling region.

Thus, for the same reason as given above, claim 7 cannot be considered as deriving directly and unambiguously from the generic description of the international application WO2012079000 as it results from the selection of specific characteristic from two or more lists (see the Guidelines for Examination in the EPO, November 2018 edition, Part G, Chapter VI, paragraph 8).

In addition, even if the above selection in at least two lists could be considered allowable, the subject-matter resulting from the selection would be limited to a CD3 zeta signalling domain comprising the amino acid sequence of SEQ ID NO: 24 and not to a CD3 zeta signalling domain comprising another amino acid sequence as provided in claim 7.

Therefore, making the amino acid sequence of SEQ ID NO: 24 of the CD3 zeta signalling domain optional with the adding of the term "or" also extends beyond the content of the earlier application as filed.

Furthermore, the method of generating a population of genetically engineered T cells that persists in the human is not associated with a human which is resistant to at least one chemotherapeutic agent in the earlier application as filed.

Accordingly, the provision that the generation of a persisting population of genetically engineered T cells in a human applies to a human resistant to at least one chemotherapeutic agent also extends beyond the content of the earlier application as filed.

Consequently, the subject-matter of claim 7 extends beyond the content of the earlier application as filed.

Since the specification of the international application is similar to the specification of the application as filed, the same reasoning applies mutatis mutandis to the application as filed.

Thus, the subject-matter of claim 7 also extends beyond the content of the application as filed.

• The subject-matter of claims 8, 9 and 13 to 18, which depend from claim 7, therefore also extend beyond the content of the earlier application as filed and beyond the content of the application as filed.

• The closest support for claim 10 of the opposed patent appears to be the following paragraph (see page 5 lines 1 to 7 of the international application as filed).

"The invention also provides a method of expanding a population of genetically engineered T cells in a human diagnosed with cancer. In one embodiment, the method comprises administering to a human a T cell



The arguments relating to claim 7 apply to the subject matter of claim 10.

In particular, this paragraph, does not specified that the antigen binding domain is an anti-CD19 scFv, in particular having the amino acid sequence of SEQ ID NO:20, and that the costimulatory signalling region is 4-1BB.

Thus, as for claim 1 and 7, the subject-matter of claim 10 results from the selection within at least **2** lists of features:

- Selection of the antigen binding domain; and
- Selection of the costimulatory signalling region.

Accordingly, claim 10 cannot be considered as deriving directly and unambiguously from the generic description of the international application WO2012079000 as it results from the selection of specific characteristic from two or more lists (see the Guidelines for Examination in the EPO, November 2018 edition, Part G, Chapter VI, paragraph 8).

In addition, even if the above selection in at least two lists could be considered allowable, the subject-matter resulting from the selection would be limited to a CD3 zeta signalling domain comprising the amino acid sequence of SEQ ID NO: 24.

Therefore, the alternative between an anti-CD19 scFv comprising the amino acid sequence of SEQ ID NO:20 **or** a CD3 zeta signalling domain comprising the amino acid sequence of SEQ ID NO:24 in claim 10 extends beyond the content of the earlier application as filed.

Furthermore, the provision that the human is resistant to at least one chemotherapeutic agent is not associated with the method of expanding a population of genetically engineered T cells that persists in the human.

Accordingly, providing that the expansion of a persisting population of genetically engineered T cells in a human applies to a human resistant to at least one chemotherapeutic agent also extends beyond the content of the earlier application as filed.

Consequently, the subject-matter of claim 10 extends beyond the content of the earlier application as filed.

Since the specification of the international application is similar to the specification of the application as filed, the same reasoning applies mutatis mutandis to the application as filed.

Thus, the subject-matter of claim 10 also extends beyond the content of the application as filed.

• The subject-matter of claims 11 to 18, which depend from claim 10, therefore also extend beyond the content of the earlier application as filed and beyond the content of the application as filed.

II. The opposed patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 100(b) EPC)

Independent claims 1, 7 and 10 of the opposed patent all relate to the treatment of cancer, *in general*, in a human who is resistant to at least one chemotherapeutic agent.

However, as is recalled in the Case Law of the Boards of Appeal of the EPO, Eighth Edition (July 2016), Part II, Chapter C, Paragraph 6.2., under Art. 83 EPC [which provisions are similar to that Art. 100(b) EPC], unless this is already known to the skilled person at the priority date, the application must disclose the suitability of the product to be manufactured for the claimed therapeutic application.

While the patent presents data obtained in 3 individuals affected with chronic lymphocytic leukemia (CLL) of B cell type, <u>no other data are presented which would disclose the suitability of the claimed CAR T cells for treating other types of cancers in a human</u>. In particular, no data are presented with regards to other specific cancers which treatment is claimed, such as acute lymphocytic leukemia (ALL), mantle cell lymphoma, diffuse large B-cell lymphoma, non-Hodgkin's lymphoma, multiple myeloma or Hodgkin's disease.

In this regard, it should be recalled that according to the Patentee, "achievement of a "remission" in a human cancer patient, and the durable CAR T cell persistence and expansion in vivo associated therewith, could not have been predicted or reasonably expected based on the teaching" of the prior art (see page 7 of letter of the Patentee dated 14 October 2016 filed during the examination of the parent patent EP2649086)

In other words, the Patentee considers that at the priority date of the opposed patent it was not credible that CAR T cells could achieve remission in a human cancer patient.

Besides, as similar reasoning applies to subject-matter according to which the claimed CAR T-cells would persist in the human for at least eight months (claim 7) since the opposed patent does not show a persistence over six months after infusion (see paragraph [0287] of the opposed patent).

☞ As such, the requirement of sufficiency of disclosure is not fulfilled for the claimed invention, inasmuch as the latter relates to treating <u>any</u> type of cancer different from CLL in a human who is resistant to at least one chemotherapeutic agent (*i.e.* the subject-matter of claims 1 to 5, 7-12, 15-18) or to a persistence of the engineered T cells for at least eight months (*i.e.* the subject-matter of claims 7-9).

III. The subject-matter of the opposed patent is not patentable under Article 52 to 57 EPC (Article 100(a) EPC)

III.1. The priority right is not validly claimed

The opposed patent was filed on 9 December 2011 and claims the benefit of:

- the priority date of 9 December 2010 from US provisional application No. 60/421,470 (D1);
- the priority date of 29 June 2011 from US provisional application No. 60/502,649 (D2).

However, the patent is not entitled to the priority dates for the following reasons.

III.1.1. Formal reasons

US provisional applications Nos. 60/421,470 and 60/502,649 were filed in the name of inventors/applicants **Carl JUNE**.

In contrast, the International application from which the opposed patent derives was filed in the name of **The Trustees of the University of Pennsylvania**.

Article 87 EPC provides that any person who has duly filed, in or for any State party to the Paris Convention for the Protection of Industrial Property or any Member of the World Trade Organization, an application for a patent, a utility model or a utility certificate, <u>or his successor in title</u>, shall enjoy, for the purpose of filing a European patent application in respect of the same invention, a right of priority during a period of twelve months from the date of filing of the first application.

In the present case The Trustees of the University of Pennsylvania cannot be considered the successor in title of the inventor Carl JUNE since the transfer of the priority right has not been established in the course of the examination procedure.

As such, none of the claims are entitled to priority and the effective date of the patent is 9 December 2011.

III.1.2. <u>Substantive reasons</u>

In the event that The Trustees of the University of Pennsylvania would be considered the successor in title of the applicants of the priority application, then we submit that the subject-matter of the claims of the opposed does not derive directly and unambiguously from US provisional applications Nos. 60/421,470 and 60/502,649.

Indeed, among other features or combination of features, all three independent claims 1, 7 and 10 recite specific sequences, respectively SEQ ID NO 20 and SEQ ID NO: 24 for the anti-CD19 scFv and the CD3 zeta signalling domain. However, neither US provisional application No. 60/421,470 nor US provisional application No. 60/502,649 disclose any specific sequences for the anti-CD19 scFv and the CD3 zeta signalling domain.

Besides, while both US provisional applications Nos. 60/421,470 and 60/502,649 are restricted to the treatment of CLL, all three independent claims 1, 7 and 10 relate to the treatment of cancer, *in general*, in a human who is resistant to at least one chemotherapeutic agent.

As such, none of the claims are entitled to priority and the effective date of the patent is 9 December 2011.

III.2. The claimed subject-matter lacks novelty (Art. 54 EPC)

III.2.1. In view of the foregoing, the effective date of the opposed patent is 9 December 2011. As such, all three articles:

- Porter et al. (2011) Journal of Cancer 2:331 (D3) published on 1 June 2011;
- Kalos *et al.* (2011) Science Translational Medicine **3**: 95ra73 (**D4**) published on 10 August 2011; and
- Porter et al. (2011) The New England Journal of Medicine **365**:725 (**D5**) published on 25 August 2011;

are prior art pursuant to Article 54(2) EPC.

The subject-matter of the claims lacks novelty in view of any of D3, D4 and D5.

Only D3 is discussed below, however similar conclusions as regards the lack of novelty can be drawn from any of D3, D4 and D5 as all are based on results from the same clinical trial.

D3 discloses that "CART-19 cells expressing the 4-1BB signalling domain can have unprecedented and massive <u>in-vivo expansion</u>, traffic to tumor sites, <u>persist long term</u> <u>in vivo</u>, and induce rapid and <u>potent anti-tumor activity</u> <u>in chemotherapy refractory</u> <u>CLL patients</u>" (see page 332, left column of D3). It is also mentioned that the infused T cells could be observed 6 months after their infusion.

The CART-19, which CAR combines a CD19 antigen recognition domain of a specific antibody with an intracellular domain of the CD3-zeta chain and the 4-1BB signalling domain, are more specifically described by reference to reference 7, Milone *et al.* (2009) Journal of the American Society of Gene Therapy **17**:1453 (**D6**):

"Our group has tested a CAR directed against CD19 linked to the CD137 (4-1BB) co-stimulatory molecule signalling domain to enhance activation and signalling after recognition of CD19. By inclusion of the 4-1BB signalling domain, in vitro tumor cell killing, and in-vivo anti-tumor activity and persistence of CART-19 cells in a murine xenograft model of human ALL is greatly enhanced ⁷.

Given these preliminary findings, we have initiated a clinical trial to test the feasibility and safety of CART-19 cells in patients with CD19+ lymphoid malignancies." (see from page 331, right column, last paragraph of D3).

Figure 1a of D6 represents a schematic diagram showing the CD19-specific CAR used in this study:



The CAR in the middle (aCD19-BB- ζ) is that of the CART-19 of D3.

Further details concerning aCD19-BB- ζ are given in reference 11 of D6:

"All CARs contain an single-chain variable fragment that recognizes the human CD19 antigen. The cDNA for the CARs that contain a truncated form of the TCR- ζ intracellular domain (aCD19- $\Delta\zeta$), a full-length TCR- ζ domain (aCD19- ζ) or a TCR- ζ domain in cis with the intracellular domain of the 4-1BB receptor (aCD19-BB- ζ) were generated at St Jude's Childrens Research Hospital.¹¹" (see page 1462, right column of D6).

Reference 11 of D6 is Imai *et al.* (2004) *Leukemia* **18**:676–684 (**D7**)². D7 shows that Lymphocytes expressing anti-CD19-BB- ζ receptors exerted powerful and specific cytotoxicity against ALL cells, which was superior to that of lymphocytes with receptors lacking 4-1BB (abstract). D7 further discloses that:

"The plasmid encoding anti-CD19 scFv was previously reported.⁴³" (see page 677, left column of D7).

Reference 43 of D7 is Nicholson *et al.* (1997) *Mol. Immunol.* 34:1157–1165 (**D8**) which relates to the construction and characterisation of a functional CD19 specific single chain Fv fragment for immunotherapy of B lineage leukaemia and lymphoma.

Figure 1 of D8 discloses the sequences of the variable parts of the heavy (V_H) and light (V_L) chains constituents of an anti-CD19 antibody:

² It is to be noted that D7 is the scientific disclosure of the invention forming the subject-matter of US application US 2005/0113564 (**D9**) which could therefore also be used instead of D7 (see paragraph [0047] of D9

GAG GTG AAA CTG CAG GAG TCA GGA CCT GGC CTG GTG GCG CCC TCA CAG AGC CTG TCC GTC Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val> * ACA TGC ACT GTC TCA GGG GTC TCA TTA CCC GAC TAT GGT GTA AGC TGG ATT CGC CAG CCT Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro> CCA CGA ANG GGT CTG GAG TGG CTG GGA GTA ATA TGG GGT AGT GAA ACC ACA TAC TAT AAT Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn> TCA GCT CTC AAA TCC AGA CTG ACC ATC ATC AAG GAC AAC TCC AAG AGC CAA GTT TTC TTA Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu> AAA ATG AAC AGT CTG CAA ACT GAT GAC ACA GCC ATT TAC TAC TGT GCC AAA CAT TAT TAC Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr> TAC GGT GGT AGC TAT GCT ATG GAC TAC TGG GGT CAA GGA ACC TCA GTC ACC GTC TCC TCA Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser>

CHRI-19Fv1 H chain

GAC ATC CAG ATG ACA CAG ACT ACA TCC TCC CTG TCT GCC TCT CTG GGA GAC AGA GTC ACC Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val Thr> ATC AGT TGC AGG GCA AGT CAG GAC ATT AGT AAA TAT TTA AAT TGG TAT CAG CAG AAA CCA Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro> GAT GGA ACT GTT ANA CTC CTG ATC TAC CAT ACA TCA AGA TTA CAC TCA GGA GTC CCA TCA Asp Gly Thr Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser> AGG TTC AGT GGC AGT GGG TCT GGA ACA GAT TAT TCT CTC ACC ATT AGC AAC CTG GAG CAA Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln> GAA GAT ATT GCC ACT TAC TTT TGC CAA CAG GGT AAT ACG CTT CCG TAC ACG TTC GGA GGG Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gly> GGG ACT AAG TTG GAA ATA ACA CGG GCT GAT GCT GCA CCA ACT GTA TCC ATC TTC CCA CCA Gly Thr Lys Leu Glu Ile Thr Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro> TCC AGT AAT Ser Ser Asn>

CHRI-19Fv1 L chain

Fig. 1. DNA sequence of $FMC63V_H$ and $FMC63V_L$. Sequences have been submitted to EMBL Nucleotide Sequence Database.

The two chains are assembled according to the protocol described on page 1158 right column which introduces a $(Gly_4Ser)_3$ linker between them (after nucleotide 321 in the L chain and before the first nucleotide in the H chain), to yield a scFv having a sequence identical to SEQ ID NO:20.

Thus by specifically incorporating by reference the teachings of D6, D7 and D8 relating to the CAR, D3 discloses a T cell genetically modified to express a CAR wherein the CAR comprises (a) an antigen binding domain that is an anti-CD19 scFv (b) a costimulatory 4-1BB signalling region, and (c) a CD3 zeta signalling domain for use in a method for treating cancer in a human (specifically CLL), wherein the anti-CD19 scFv comprises the amino acid sequence of SEQ ID NO:20 and wherein the human is resistant to at least one chemotherapeutic agent, i.e. the subject-matter of claim 1.

D3 further discloses the subject-matter of claims 2, 3, 4 and 6.

D3 also discloses a T cell genetically engineered to express a CAR, wherein the CAR comprises (a) an antigen binding domain that is an anti-CD19 scFv, (b) a 4-1BB costimulatory signaling region, and (c) a CD3 zeta signaling domain, for use in a method for treating cancer that comprises administering said T cell to a human diagnosed with cancer, wherein the anti-CD19 scFv comprises the amino acid sequence of SEQ ID NO:20 or the CD3 zeta signaling domain comprises the amino acid sequence of SEQ ID NO:24, and wherein said method expands a population of genetically engineered T cells in the human, and wherein the human is resistant to at least one chemotherapeutic agent, i.e. the subject-matter of claim 10.

D3 further discloses the subject-matter of claim 12, 13, 14, 15, 17 (with a body weight of the treated patient anywhere between 5 and 1000 kg) and 18 (taking into account that the conditions (i) to (vi) are not cumulative but alternative as is evidenced by the "or" between conditions (v) and (vi)).

D3 also discloses that persisting population of genetically engineered T cells comprises at least one cell selected from the group consisting of a T cell that was administered to the human, a progeny of a T cell that was administered to the human, and a combination thereof (which covers all the possibilities for the origin of the persisting engineered T cells).

Accordingly, the claimed subject-matter lacks novelty

It should be noted that D4 discloses the presence of memory T cells within the persisting population genetically engineered T cells (claims 9 and 11) (see abstract) and the previous treatment with Rituxan (claim 16) (see page 9, right column of D4).

III.2.2. Should the claimed subject-matter of the opposed patent be considered to be in conformity with the requirements of Art. 100(b) EPC, it is submitted that the subject-matter of at least claims 1 to 6 of the opposed patent also lacks novelty in view of D9,



in particular in view of the subject-matter of claims 17-21, as applied to the individuals understood from paragraph [0066] as those likely to benefit the most from the claimed invention, with the preferred CAR described in paragraph [0047] with reference to the anti-scFv described in D8.

III.3. The claimed subject-matter lacks an inventive step (Art. 56 EPC)

III.3.1. In the unlikely case novelty would be recognized in view of D3, D4, D5 or D9, we submit that it is clear the claimed subject-matter (all claims) lacks an inventive step in view of these same documents as closest prior art.

In particular, the subject-matter of claims 5 and 7-9 is obvious in view of these documents.

III.3.2. Besides, if the claims were restricted to a T cell genetically modified to express a CAR wherein the CAR comprises the CD3 zeta signalling domain comprising the amino acid sequence of SEQ ID NO: 24 as an obligatory feature, then the following should be noted.

The amino acid sequence of the CD3 zeta signalling domain was known in the art at the effective date of the opposed patent.

By way of example, the entry NM_000734 (**D10**) in the GenBank database, which was available from 9 October 2003 to 31 January 2008, *i.e.* at the effective date of the opposed patent, and to which D9 refers in paragraph [0047], discloses an amino acid sequence of CD3 zeta which comprise a sequence identical to SEQ ID NO: 24 except for a single conservative substitution of the Gln (Q) in position 65 of NM_000734 by a Lys (K) in SEQ ID NO: 24 (corresponding to the underlined part below) as was noted by the Examiner in the written opinion established for the parent patent:

MKWKALFTAAILQAQLPITEAQSFGLLDPKLCYLLDGILFIYGVILTALFL<u>RVKFSRSADAPAYQQGQNQLYNEL</u> K NLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKD

TYDALHMQALPPR

It was well known at that time that the signalling domain of CD3 zeta corresponds to the cytoplasmic part thereof which starts at amino acid 52 of the full length protein as is evidenced by entry NP_000725 of GenPept (**D11**) or P20963 of UniProtKB/Swiss-Prot (**D12**).

Similarly, US 2004/043401 (**D13**) (cited as D1 in the examination procedure of the parent patent) discloses in SEQ ID NO: 14 which is identical to SEQ ID NO: 24 except for a single conservative substitution of the Gln (Q) in position 65 of NM_000734 by a Lys (K) in SEQ ID NO: 24 (corresponding to the underlined part below) as was noted by the Examiner in the written opinion established for the parent patent.

As was rightly pointed by the Examiner in the written opinion established for the parent patent the technical effect of this substitution has not been established. As such, SEQ ID NO: 24 is merely the result of an <u>arbitrary selection</u> among all the available variants of the CD3 zeta signalling domain, which cannot involve an inventive step.

III.3.3. In addition, we submit the following subsidiary inventive step attack based on D7 (which forms the scientific disclosure of D9) as the closest prior art.

As seen above and referring to the arguments set forth by the Patentee during the examination procedure of the parent patent, the feature of claims 1 to 5 of the opposed which could be considered not be disclosed in D7 would be the treatment of a human resistant to at least one therapeutic agent.

With this difference, the objective technical problem would be to provide a treatment for human resistant to at least one therapeutic agent affected by cancer.

However, D7 provides a clear and strong incitation to use the CAR T cells it describes in such individuals as is evidenced by the beginning of the abstract which explicitly refers to **drug-resistant** B-lineage acute lymphoblastic leukemia (ALL).

Moreover, contrary to what was argued by the Patentee, several publications had established at the effective date of the opposed patent that anti-CD19 CAR T-cell therapy could be effective in human resistant to at least one therapeutic agent (see the description of the patient on page 4099 of Kochenderfer et al. (2010) Blood **116**:4099 (**D14**) or Davila et al. (2010) Blood **116**:3268 (**D15**)).

Accordingly, in view of D7 and D14 or D15 one of skill in the art wishing to solve the objective technical problem would have been incited to test the CAR T-cells of D7 in a human resistant to at least one therapeutic agent, rendering the claimed subject-matter obvious.