



Notice of opposition to a European patent

I. Patent opposed

Patent No.	EP3464373
Application No.	EP17731359.0
Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)	27 October 2021
Title of the invention	USE OF ANTI-PD-1 ANTIBODY IN THE TREATMENT OF PATIENTS WITH COLORECTAL CANCER

II. Proprietor of the patent

first named in the patent specification	Bristol-Myers Squibb Company
Opponent's or representative's reference	BD 42383/CV

III. Opponent

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Multiple opponents (see additional sheet)	☐	

IV. Authorisation

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authorisation

☐

Authorisation(s)

is/are enclosed

☐

has/have been registered under No.

☐

V. Opposition is filed against

the patent as a whole

☒

claim(s) No(s).

VI. Grounds for opposition:

Opposition is based on the following grounds:

(a) the subject-matter of the European patent opposed is not
patentable (Art. 100(a) EPC) because:

• it is not new (Art. 52(1); Art. 54 EPC)

☒

• it does not involve an inventive step (Art. 52(1);
Art. 56 EPC)

☒

• patentability is excluded on other grounds, namely
articles

☐

(b) the patent opposed 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 (Art. 100(b) EPC; see Art.
83 EPC).

☒

(c) the subject-matter of the patent opposed extends beyond
the content of the application/of the earlier application as
filed (Art. 100(c) EPC, see Art. 123(2) EPC).

☒

VII. Facts (Rule 76(2)(c) EPC)

presented in support of the opposition are submitted herewith
on an attached document

☒

VIII. Other requests:

IX. Evidence presented

D01	Other evidence	D1 - WO2017210637A1 Application as filed original file name: D1 - WO2017210637A1 Application as filed.pdf attached as: Other-evidence-1.pdf
D02	Other evidence	D2 - Priority Document original file name: D2 - Priority Document.pdf attached as: Other-evidence-2.pdf
D03	Other evidence	D3 - ASCO Meeting Abstract original file name: D3 - ASCO Meeting Abstract.pdf attached as: Other-evidence-3.pdf
D03a	Other evidence	D3a - ASCO Meeting Abstract (Screenshot) original file name: D3a - ASCO Meeting Abstract (Screenshot).pdf attached as: Other-evidence-4.pdf
D03b	Other evidence	D3b - Confirmation of Publication Date of D3 original file name: D3b - Confirmation of Publication Date of D3.pdf attached as: Other-evidence-5.pdf
D04	Other evidence	D4 - Clinical Trials gov original file name: D4 - Clinical Trials gov.pdf attached as: Other-evidence-6.pdf
D05	Other evidence	D5 - Larkin et al original file name: D5 - Larkin et al.pdf attached as: Other-evidence-7.pdf
D06	Other evidence	D6 - Duraiswamy et al, D8 aus WO-ISA original file name: D6 - Duraiswamy et al, D8 aus WO-ISA.pdf attached as: Other-evidence-8.pdf
D07	Other evidence	D7 - Llosa et al, D6 aus WO-ISA original file name: D7 - Llosa et al, D6 aus WO-ISA.pdf attached as: Other-evidence-9.pdf
D08	Other evidence	D8 - Kroemer et al, D5 aus WO-ISA original file name: D8 - Kroemer et al, D5 aus WO-ISA.pdf attached as: Other-evidence-10.pdf
D09	Other evidence	D9 - Xiao et al 2015 original file name: D9 - Xiao et al 2015.pdf attached as: Other-evidence-11.pdf
D10	Other evidence	D10 - ASCO 2015 - No 4516 original file name: D10 - ASCO 2015 - No 4516.pdf attached as: Other-evidence-12.pdf
D11	Other evidence	D11 - ASCO 2015 - No TPS4578 original file name: D11 - ASCO 2015 - No TPS4578.pdf attached as: Other-evidence-13.pdf
D12	Other evidence	D12 - ASCO 2015 - No 7503 original file name: D12 - ASCO 2015 - No 7503.pdf

		attached as: Other-evidence-14.pdf
D13	Other evidence	D13 - Le at al, D1 aus WO-ISA original file name: D13 - Le at al, D1 aus WO-ISA.pdf attached as: Other-evidence-15.pdf
D14	Other evidence	D14 - D2 aus WO-ISA, WO2016077553A1 Pembrolizumab original file name: D14 - D2 aus WO-ISA, WO2016077553A1 Pembrolizumab.pdf attached as: Other-evidence-16.pdf
D15	Other evidence	D15 - Nivolumab Label 9-2015 original file name: D15 - Nivolumab Label 9-2015.pdf attached as: Other-evidence-17.pdf
D16	Other evidence	D16 - Pawlik et al original file name: D16 - Pawlik et al.pdf attached as: Other-evidence-18.pdf

X. Payment

Method of payment

Debit from deposit account

The European Patent Office is hereby authorised, to debit from the deposit account with the EPO any fees and costs indicated in the fees section below.

Currency:

EUR

Deposit account number:

28001644

Account holder:

Michalski Hüttermann & Partner Patentanwälte mbB

Refunds

Any refunds should be made to EPO deposit account:

28001644

Account holder:

Michalski Hüttermann & Partner Patentanwälte mbB

Fees

	Factor applied	Fee schedule	Amount to be paid
010 Opposition fee	1	840.00	840.00
Total:		EUR	840.00

A Forms

Details:

System file name:

A-1

Form for notice of opposition

ep-oppo.pdf

B Attached document files

Original file name:

System file name:

B-1

1. Facts and arguments

opposition as filed on 25 July 2022.pdf

OPPO.pdf

C Attached evidence files

Original file name:

System file name:

C-1

1. Other evidence

D1 - WO2017210637A1 Application as filed.pdf

Other-evidence-1.pdf

C-2

2. Other evidence

D2 - Priority Document.pdf

Other-evidence-2.pdf

C-3

3. Other evidence

D3 - ASCO Meeting Abstract.pdf

Other-evidence-3.pdf

C-4

4. Other evidence

D3a - ASCO Meeting Abstract (Screenshot).pdf

Other-evidence-4.pdf

C-5

5. Other evidence

D3b - Confirmation of Publication Date of D3.pdf

Other-evidence-5.pdf

C-6

6. Other evidence

D4 - Clinical Trials gov.pdf

Other-evidence-6.pdf

C-7	7. Other evidence	D5 - Larkin et al.pdf	Other-evidence-7.pdf
C-8	8. Other evidence	D6 - Duraiswamy et al, D8 aus WO-ISA.pdf	Other-evidence-8.pdf
C-9	9. Other evidence	D7 - Llosa et al, D6 aus WO-ISA.pdf	Other-evidence-9.pdf
C-10	10. Other evidence	D8 - Kroemer et al, D5 aus WO-ISA.pdf	Other-evidence-10.pdf
C-11	11. Other evidence	D9 - Xiao et al 2015.pdf	Other-evidence-11.pdf
C-12	12. Other evidence	D10 - ASCO 2015 - No 4516.pdf	Other-evidence-12.pdf
C-13	13. Other evidence	D11 - ASCO 2015 - No TPS4578.pdf	Other-evidence-13.pdf
C-14	14. Other evidence	D12 - ASCO 2015 - No 7503.pdf	Other-evidence-14.pdf
C-15	15. Other evidence	D13 - Le et al, D1 aus WO-ISA.pdf	Other-evidence-15.pdf
C-16	16. Other evidence	D14 - D2 aus WO-ISA, WO2016077553A1 Pembrolizumab.pdf	Other-evidence-16.pdf
C-17	17. Other evidence	D15 - Nivolumab Label 9-2015.pdf	Other-evidence-17.pdf
C-18	18. Other evidence	D16 - Pawlik et al.pdf	Other-evidence-18.pdf

Signature of opponent or representative

Place: Düsseldorf

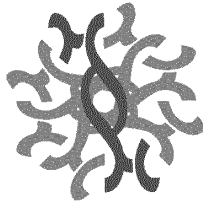
Date: 25 July 2022

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Capacity: (Representative)

**Online-Filing**

Europäisches Patentamt

80298 München

Official Number
3 464 373
Bristol-Myers Squibb

Our Ref.
BD 42383/CV

Düsseldorf,
25 July 2022

Opposed patent: EP 3 464 373 B1
Title: Use of Anti-PD-1 Antibody in the Treatment of Patients with Colorectal Cancer
Patent proprietor: Bristol-Myers Squibb Company
Opponent: Michalski Hüttermann & Partner Patentanwälte mbB

With respect to European Patent EP 3 464 373 B1 assigned to Bristol-Myers Squibb Company (in the following: "patent proprietor"),

O p p o s i t i o n

is herewith filed by

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under Art. 99 EPC. Please withdraw the opposition fee from the account No 28001644 of Michalski Hüttermann Patentanwälte in accordance with the enclosed payment form. As a precautionary measure, the EPO

ST:CV

is herewith authorized to withdraw the correct amount should the amount declared in the payment form be incorrect.

1. Requests

It is requested to revoke European Patent EP 3 464 373 B1 (in the following: "patent in dispute") in its entirety on the grounds of Art. 100 (a), Art. 100 (b) and Art. 100 (c) EPC based on the facts, evidence and arguments set forth below. In the event the opposed patent will not be revoked in its entirety in the course of the written proceedings, oral proceedings are requested according to Art. 116 EPC.

2. References on which the opposition is based

The following references are introduced into the proceedings. In the following, only the reference numbers shown in the first column will be used (**Table 1**).

No.	Publ. Date	Document
D1	07 Dec 2017	WO 2017/210637 A1 (Application as originally filed)
D2		US 201662345662 P (Priority Document)
D3	20 May 2016	Overman <i>et al.</i> (2016) Nivolumab +/- ipilimumab in treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): CheckMate-142 interim results. Meeting Abstract, 2016 ASCO Annual Meeting. <i>Journal of Clinical Oncology</i> Vol. 34 No. 15 Suppl., 3501; DOI: 10.1200/JCO.2016.34.15_suppl.3501
D3a	20 May 2016	See D3 above; Screenshot version
D3b		EMail Confirmation by Jessica Wood, Counsel of the American Society of Clinical Oncology, regarding the publication date D3, received 01 July 2022
D4	11 Feb 2014	A Study of Nivolumab and Nivolumab plus Ipilimumab in recurrent and metastatic Colon Cancer (CheckMate 142). Clinical Study NCT02060188. https://clinicaltrials.gov/ct2/history/NCT02060188?V_1=View#Study

- 3 -

		PageTop; first submitted 18 Dec 2013; [retrieved on 06 July 2022] (D3 in WO-ISA)
D5	31 May 2015	Larkin <i>et al.</i> (2015) Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. <i>New England Journal of Medicine</i> Vol. 373, p. 23-34
D6	15 June 2013	Duraiswamy <i>et al.</i> (2013) Dual blockade of PD-1 and CTLA-4 combined with tumor vaccine effectively restores T cell rejection function in tumors. <i>Cancer Research</i> Vol. 73 No. 12, p. 3591-3603
D7	01 July 2015	Llosa <i>et al.</i> (2015) The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints. <i>Cancer Discovery</i> Vol. 5 No. 1, p. 43-51
D8	July 2015	Kroemer <i>et al.</i> (2015) Colorectal cancer: the first neoplasia found to be under immunosurveillance and the last one to respond to immunotherapy? <i>Oncolmmunology</i> Vol. 4 No. 7, p. 1-3
D9	Jan 2015	Xiao and Freeman (2015) The microsatellite instable (MSI) subset of colorectal cancer is a particularly good candidate for checkpoint blockade immunotherapy. <i>Cancer Discovery</i> Vol. 5 No. 1, p. 16-18
D10	20 May 2015	Hammers <i>et al.</i> (2015) Expanded cohort results from CheckMate 016: A phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC). <i>Journal of Clinical Oncology</i> Vol. 33 No. 15 Suppl., 2015 ASCO Annual Meeting Proceedings, Abstract # 4516
D11	20 May 2015	Hammers <i>et al.</i> (2015) CheckMate 214: A phase III, randomized, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in patients with previously untreated metastatic renal cell carcinoma. <i>Journal of Clinical Oncology</i> Vol. 33 No. 15 Suppl., 2015 ASCO Annual Meeting Proceedings, Abstract # TPS4578
D12	20 May 2015	Antonia <i>et al.</i> (2015) Phase I/II study of nivolumab with or without ipilimumab for treatment of recurrent small cell lung cancer (SCLC): CA209-032. <i>Journal of Clinical Oncology</i> Vol. 33 No. 15 Suppl., 2015 ASCO Annual Meeting Proceedings, Abstract # 7503
D13	30 May 2015	Le <i>et al.</i> (2015) PD-1 blockade in tumors with mismatch-repair deficiency. <i>New England Journal of Medicine</i> Vol. 372, p. 2509-2520
D14	19 May 2016	WO 2016/077553 A1
D15	Sept 2015	Nivolumab US Prescription Label 9/2015
D16	2004	Pawlik <i>et al.</i> (2004) Colorectal carcinogenesis: MSI-H versus MSI-L. <i>Disease Markers</i> Vol. 20, p. 199-206

3. Introductory remarks

3.1. Patent in dispute

The patent in dispute issued on 27 October 2021 from European patent application no. 17731359.0, which relies on international application no. PCT/US2017/035822 (called herein “application as filed”) filed on 02 June 2017 (published as WO 2017/210637 A1), claiming priority of US 201662345662 P filed on 03 June 2016.

The patent in dispute relates to nivolumab for use in methods for treating a tumor derived from a colorectal cancer exhibiting a high degree of microsatellite instability (MSI-H) in a subject in need thereof. Nivolumab is administered in combination with ipilimumab. In some embodiments, the colorectal cancer is rectal cancer, colon cancer, or any combination thereof.

3.2. Patent claims

The independent claims (claims 1 and 10) as granted comprise the following features:

1. (a) Nivolumab
(b) for use in a method of treating a colorectal cancer tumor in a subject, wherein
(c) the tumor exhibits a high degree of microsatellite instability ("MSI-H"), wherein
(d) the subject is administered nivolumab at a dose of about 3 mg/kg body weight
(e) in combination with ipilimumab
(f) at a dose of about 1 mg/kg body weight
(g) once about every three weeks.
10. (a) A kit
(b) for use in a method of treating a colorectal cancer tumor in a subject, comprising:
(c) nivolumab; and
(d) ipilimumab
(e) wherein the method is defined as in any one claims 1 to 9.

Dependent claims are relating to the following further limitations (**Table 2**):

#	Ref to claim #	Further Limitation
2.	1	tumor is a colon cancer or a rectal cancer
3.	1, 2	tumor exhibits one or more characteristics from group consisting of: (a) germline alteration in at least two, at least three, at least four, or at least five DNA mismatch repair genes ("MMR genes"); (b) germline alteration in at least 30% of five or more MMR genes; (c) at least one protein encoded by DNA MMR genes is not detected in the tumor; and (d) any combination thereof
4.	3	DNA MMR genes comprise MSH2, MLH1, MSH6, PMS2, PMS1 or any combination thereof
5.	1 - 4	(i) progression-free survival of at least about one month... or (ii) overall survival of at least about one month... after the administration
6.	1 - 5	administration of nivolumab and ipilimumab is followed by an anti-PD-1 antibody monotherapy
7.	1 - 5	administration of nivolumab and ipilimumab comprises four doses for each
8.	1 - 7	one, two, three, four, five or more prior cancer treatments
9.	1 - 8	subject has progressed on other cancer treatments

3.3. Invalid Priority

The patent in dispute is claiming priority of US 201662345662 P filed on 03 June 2016.

However, as will be set forth below, the claims as granted comprise added matter that extends beyond the application as filed. This already renders the priority claims void.

Grounds for Opposition

4. Added matter (Art. 100 (c) and Art. 123 (2) EPC)

According to established case law by the Boards of Appeal, questions of added matter are to be examined under Art. 123 (2) EPC with utmost scrutiny. In T 383/88 the Board held that the normal standard of proof ("the balance of probability") was inappropriate for determining the allowability of an amendment under Art. 123 (2) EPC. Instead, a rigorous standard, *i.e.*, one equivalent to "beyond reasonable doubt" was considered to be the right one to apply.

In T 581/91 the Board again held that the balance of probabilities was not an appropriate criterion to be applied in a case where a correction under R. 88 EPC 1973 was at stake, and applied a standard equivalent to "beyond reasonable doubt".

In T 307/05 the Board stated that, as indicated in the decision T 64/03, it is established case law that a very rigorous standard, namely that of "beyond reasonable doubt", is to be applied when checking the allowability of amendments under Arts. 123 (2) and 123 (3) EPC. A similar rigorous standard was also expressed in decisions T 581/91 and T 113/86, in which it was stated that the "slightest doubt" that the unamended patent could be construed differently to the patent as amended would preclude the allowability of the amendment.

The patent in dispute has been amended to contain subject matter which extends beyond the content of the application as originally filed, thus violating Art. 123(2) EPC, for the following reasons.

4.1. Added matter in the main claim (*for use in a method of treating a colorectal cancer*)

The main claim of the patent in dispute recites:

“Nivolumab for use in a method of treating a colorectal cancer tumor in a subject, wherein the tumor exhibits a high degree of microsatellite instability (“MSI-H”), wherein the subject is administered nivolumab at a dose of about 3 mg/kg body weight in combination with ipilimumab at a dose of about 1 mg/kg body weight once about every three weeks.” [Emphasis added]

The feature “*for use in a method of treating a colorectal cancer tumor*” in the main claim is not disclosed anywhere in the application as originally filed (WO publication of the international application), and thus represents added matter. Albeit claim 1 of the application as filed refers to an anti-PD-1 antibody “*for use in a method of treating a subject afflicted with a tumor*”, this refers to a different matter, and is not disclosed in the context with all the other features of the main claim as granted.

4.2. Added matter in the main claim (Intermediate generalization)

According to established case law (as summarised, *e.g.*, in T 219/09 or T 1944/10), it will normally not be allowable to base an amended claim on the extraction of isolated features from a set of features originally disclosed only in combination, *e.g.*, a specific embodiment in the description. Amended subject matter that amounts to a generalisation of a particular embodiment disclosed in the original application but is still more specific than the original definition of the invention in general terms is often called an “intermediate generalisation” (see *e.g.* T 461/05, T 191/04).

The combination of features present in the main claim as granted has to be considered as representing an intermediate generalization from the particular embodiment disclosed in paragraph [0170] of the application as originally filed, which is reciting:

“In a particular embodiment, the subject afflicted with a colorectal cancer with MSI-H is treated with an initial stage (*e.g.*, an anti-PD-1 antibody monotherapy, *e.g.*, nivolumab at a dose of 3 mg/kg once every two weeks), a combination stage (*e.g.*, an anti-PD-1 antibody and an anti-CTLA-4 antibody combination, *e.g.*, nivolumab at a dose of 3 mg/kg once every three weeks and ipilimumab at a dose of 1 mg/kg once every

- 8 -

weeks), and a final stage (*e.g.*, an anti-PD-1 antibody monotherapy, *e.g.*, nivolumab at a dose of 3 mg/kg once every two weeks).

The combination of features present in the main claim as granted is an extraction of isolated features, namely the combination stage (an anti-PD-1 antibody and an anti-CTLA-4 antibody combination, *e.g.*, nivolumab at a dose of 3 mg/kg once every three weeks and ipilimumab at a dose of 1 mg/kg once every weeks), out of the overall treatment regimen of initial stage, combination stage and final stage.

Whereever the combination of features present in the main claim as granted, relating to said combination stage, is referred to in the application as filed, it is disclosed together with a nivolumab monotherapy treatment stage prior and/or following said combination stage. See for example:

“Briefly, patients included in the *monotherapy* arm were administered 3 mg/kg nivolumab once every two weeks in Stage 1 of treatment... enrollment was continued for a secondary stage of treatment. In Stage 2 of treatment, patients were administered 3 mg/kg *nivolumab* once every two weeks. Patients included a separate combination arm were administered 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab once every three weeks for four doses, followed by 3 mg/kg *nivolumab* once every two weeks in Stage 1 of treatment... enrollment was continued for a secondary stage of treatment. In Stage 2 of treatment, patients were administered 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab once every three weeks for four doses, followed by 3 mg/kg *nivolumab* once every two weeks.”

(paragraph [0194] of application as filed)

and

“The results of this study demonstrated that combination therapy with nivolumab + ipilimumab provided durable responses, sustained disease control, and encouraging survival data in pretreated patients with dMMR/MSI-H metastatic colorectal cancer.”

(paragraph [0203] of application as filed)

and Figures 1, 2, and 8.

In T 962/98 it was held that an intermediate generalization was admissible *only if* the skilled person could recognize without any doubt from the application as filed that those characteristics were *not closely related* to the other characteristics of the working example (initial stage and final stage of the treatment regimen), and that in order to be acceptable, this intermediate generalization had to be the result of *unambiguous information* that a skilled person would draw from a review of the example and the content of the application as filed. However, this is not the case with the present application as filed, because it is obvious that the initial stage and final stage have a significant impact on whether the combined features of the combination stage as claimed alone are able to achieve the technical effect as claimed in the patent in dispute.

In conclusion, the main claim as granted has no basis in the application as originally filed. Hence this also applies to all claims dependent from the main claim. Since claim 10 is semi-dependent from the main claim with regard to the method as defined in any one of claims 1 – 9, it further also applies to claim 10.

4.3. Added matter in claim 9

The combination of features present in the main claim as granted with the additional subject matter of dependent claim 9 (“*wherein the subject has progressed on other cancer treatments*”) is not disclosed anywhere in the application as originally filed. The only respective disclosure in the application as filed appears to be paragraph [0123] (“*In some embodiments, the subject has progressed on other cancer treatments*”), which disclosure, however, does not put this feature in the context of the combination of features present in the main claim.

For these reasons, all claims as granted contain subject matter which extends beyond the content of the application as originally filed, thus violating Art. 123(2) EPC.

5. Insufficiency of disclosure (Art. 100 (b) and Art. 83 EPC)

Art. 83 EPC demands that a patent application shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. The patent in dispute fails to satisfy this requirement in several aspects.

Opponent is well aware of the general principle that objecting reproducibility of a patent, *i.e.*, challenging whether the technical teaching is workable, requires provision of respective evidence. However, as set forth, *e.g.*, in T 63/06, the power of the assumption that the teaching is workable depends upon how detailed the written description actually is. In the present case, with regard to the following aspects, the level of detail the skilled person could benefit from is rather poor, as will be shown in the following.

Even though the Boards of Appeal permit a reasonable amount of trial and error when it comes to sufficiency of disclosure, the skilled person has to have at his disposal, either in the specification or on the basis of common general knowledge, adequate information leading necessarily and directly towards success through the evaluation of initial failures (T 226/85, following T 14/83, T 48/85, T 307/86 and T 326/04).

Where the skilled person can only establish by trial and error whether or not his particular choice of numerous parameters will provide a satisfactory result, this amounts to an undue burden (T 32/85), hence the claimed subject matter suffers from an insufficient disclosure in the meaning of Art. 83 EPC.

It is respectfully requested that the Opposition Division duly considers the severe insufficiency of the granted claims, as will be explained in the following.

5.1. Insufficiency of disclosure with regard to antibody dosages

The main claim of the patent in dispute recites:

“Nivolumab for use in a method of treating a colorectal cancer tumor in a subject, wherein the tumor exhibits a high degree of microsatellite instability ("MSI-H"), wherein the subject is administered nivolumab at a dose of about 3 mg/kg body weight in combination with ipilimumab at a dose of about 1 mg/kg body weight once about every three weeks.” [Emphasis added]

The term “*about*” is used three times in the main claim, which is expected to specify all essential features of the invention, and, together with the description of the application, disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. This is presently not the case.

The term “*about*” *per se* is a vague term. According to the patent in dispute’s own definition of the term “*about*” (paragraph [0052]; identical with paragraph [0112] in the application as originally filed), “*about*” for example “*can mean within 1 or more than 1 standard deviation*“, “*can mean a range of up to 20%*“, but also “*can mean up to an order of magnitude or up to 5-fold of a value*“. Hence, the patent in dispute’s own definition provides little guidance on how to construe said term. The value range opened up by the term “*about*” in the main claim by this definition ranges basically from “*more than 1 standard deviation*” to “*a range of up to 20%*” to the “*5-fold of the value*” or even 10-fold of the value (“*up to an order of magnitude*”). Thus the value range in the main claim could be intended to be construed as, for example, a nivolumab dose of 0.3 to 30 mg/kg body weight in combination with an ipilimumab dose of 0.1 to 10 mg/kg body weight. Correspondingly, “*once about every three weeks*” could be construed as a time interval ranging from a few days to more than 7 months.

Even though the person skilled in the art would certainly be aware that dosage levels of 10 or even 30 mg/kg body weight would have significant impact on toxicity, immunogenicity and thus tolerability of the antibody therapeutics in patients, which might even be fatal, and that 10-fold lower dosage levels would reduce or even eliminate therapeutic efficacy, the person skilled in the art is not provided with plausible means and data for assessing, without undue burden, whether a particular nivolumab or ipilimumab dosage lower or higher than 30 mg/kg

and 10 mg/kg, respectively, or time interval for administration of lower or higher than 3 weeks, falls within the scope of the main claim as granted.

In fact, the dosage and time interval as used in the Examples of the patent in dispute refer to “3 mg/kg body weight”, “1 mg/kg body weight”, and “every three weeks”, respectively, only. The study designs as shown in the Examples do not provide any dosage or time interval ranges. Hence, the “*about*” clauses, and in particular the combination of the three “*about*” clauses, render the main claim basically indefinite, so that the alleged invention rather represents an invitation to perform a (clinical) research program, rather than setting plausible metes and bounds.

Therefore, it is evident that the alleged invention is not sufficiently supported, at least not over the full scope of the main claim as granted.

5.2. Insufficiency of disclosure with regard to administration regimen

The main claim of the patent in dispute relates to an administration regimen of administering nivolumab at a dose of about 3 mg/kg in combination with ipilimumab at a dose of about 1 mg/kg once about every three weeks in a subject having an MSI-H colorectal cancer tumor. However, it appears that this administration scheme is not supported by any of the experimental studies shown in the Examples, and that thus the technical problem cannot be solved.

Fig. 1 shows the overall study design for patients in the MSS cohort (paragraph [0118] in patent in dispute), *i.e.*, the control group, in Example 1. Fig. 2 shows the overall study design for patients in the MSI-H cohort in Example 2 (paragraph [0119] in patent in dispute). Fig. 8 shows the overall study design for patients with MSI-H colorectal cancer tumor in Example 2 (paragraph [0134] in patent in dispute).

The study design in Fig. 1 relates to the MSS control group, hence not to the subject matter of the invention as claimed. The study design in Fig. 2 relates to a four-stage administration

scheme, composed of a monotherapy stage 1 (Nivolumab), a monotherapy stage 2 (Nivolumab), a combination therapy stage 1 (which is a combination of the (NIVO + IPI) administration scheme as claimed and a subsequent monotherapy with NIVO), and finally a combination therapy stage 2 (which again is a combination of the (NIVO + IPI) administration scheme as claimed and a subsequent monotherapy with NIVO). For the monotherapy stage 2 and the combination therapy stage 2, additional patients have been enrolled.

According to this study design, none of the MSI-H colorectal cancer tumor patients received the combination therapy (NIVO + IPI) as claimed without having received a prior monotherapy (NIVO alone). Obviously, patients treated by monotherapy with NIVO before enrolling for the combination therapy (NIVO + IPI) as claimed will show different therapeutic effects than a patient cohort *not* treated before by monotherapy, or by any prior therapy at all.

Hence, the experimental data in Example 1 do not support the subject matter as claimed in the main claim.

The study design in Fig. 8 relates to a two-stage administration scheme of a monotherapy (NIVO) arm and a two-stage administration scheme of a combination therapy arm, respectively. The two-stage administration scheme of the monotherapy arm does not relate to the subject matter of the invention as claimed. In the two-stage administration scheme of the combination therapy arm, each stage of the combination therapy arm consists again of a combination of the (NIVO + IPI) administration scheme as claimed (3 mg/kg NIVO + 3 mg/kg IPI, once every three weeks), applied 4 times, and a subsequent monotherapy with NIVO (3 mg/kg, once every two weeks).

According to this study design, all of the MSI-H colorectal cancer tumor patients who received the combination therapy (NIVO + IPI) as claimed also received then subsequently a monotherapy (NIVO alone); thus also in this case the patients will show different therapeutic effects than a patient cohort *without* subsequent monotherapy would show.

Hence, also the experimental data in Example 2 do not support the subject matter as claimed in the main claim.

Therefore, the subject matter of the alleged invention as claimed also for this reason is not supported by the application as filed.

In conclusion, the subject matter of claims as granted is not disclosed in a manner sufficiently complete for it to be carried out by a person skilled in the art over the full breadth of the claims. The claims therefore contravene Art. 83 EPC and are hence invalid.

6. Lack of novelty (Art. 100 (a), Art. 54 EPC)

6.1. Lack of novelty over D3

D3 (Overman *et al.* 2016) is a Meeting Abstract which was published online on 20 May 2016, it is a prior art document under Art. 54(2) EPC. The main claim of the patent in dispute is lacking novelty over D3. Reference **D3a** is an easier-to-read screenshot version of the same Meeting Abstract, with identical content. Reference **D3b** herewith introduced into the procedure is a copy of the email correspondence of the opponent with the Legal Counsel of the American Society of Clinical Oncology (ASCO). The ASCO is the editor of the Journal of Clinical Oncology; in the latter, as a supplement version, the ASCO on a regular basis publishes contributions of clinicians, scientists, companies and healthcare organizations to the ASCO Annual Meeting. In line with the bibliographic data of the online version of the Meeting Abstract D3, the Legal Counsel of the ASCO confirms in the email correspondence submitted as reference D3b that the Meeting Abstract was published through the Journal of Clinical Oncology on 20 May 2016, *i.e.*, about two weeks in advance prior to the 2016's ASCO Annual Meeting in June 2016, and before the priority date of 03 June 2016 of the patent in dispute.

In this respect, opponent further notes that according to the ASCO's Legal Counsel in D3b, the Abstract was even made available through an access-restricted part of the ASCO's website to ASCO members already on 18 May 2016. This means, in fact, that the actual publication date to be considered was two days earlier than 20 May 2016 in view of respective EPC Guidelines and respective case law by the Boards of Appeal.

As provided in EPC Guideline G.IV.7.5.1, "neither restricting access to a limited circle of people (e.g. by password protection) nor requiring payment for access (analogous to purchasing a book or subscribing to a journal) prevent a web page from forming part of the state of the art. It is sufficient if the web page is in principle available without any bar of confidentiality."

According to the Case Law of the BoA (Ninth edition, July 2019, I.C.3.2.3, pp. 87/88), in terms of determining the publication date, "what is required, rather, is a practical possibility of having access, *i.e.* "direct and unambiguous access" to the means of disclosure for *at least one member of the public* as set out in G 1/92 and T 952/92". If a document could (i) be found in the internet with the help of a public web search engine by using one or more keywords all related to the essence of the content of that document and (ii) remained accessible at that URL for a period of time long enough for *a member of the public, i.e.*, someone under no obligation to keep the content of the document secret, to have direct and unambiguous access to the document, then the document was made available to the public within the meaning of Art. 54(2) EPC. This applies with regard to D3.

D3 relates to the clinical phase-2 study "CheckMate-142" involving nivolumab with or without ipilimumab in treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H), and interim results thereof.

The Meeting Abstract D3 discloses that the anti-PD-1 monoclonal antibody nivolumab (= *nivolumab*) was used together with the anti-CTLA-4 monoclonal antibody ipilimumab (= *in combination with ipilimumab*) in patients with metastatic colorectal cancer having high

microsatellite instability (= *for use in a method of treating a colorectal cancer tumor in a subject, high degree of microsatellite instability*; in “Background”). D3 further discloses that patients received nivolumab at a dose of 3 mg/kg plus ipilimumab at a dose of 1 mg/kg (= *nivolumab at a dose of about 3 mg/kg body weight, ipilimumab at a dose of about 1 mg/kg body weight*), and that this was done at intervals of 3 weeks (= *once about every three weeks*; in “Methods”).

Hence, all features of the main claim of the patent in dispute are disclosed in the Meeting Abstract D3. Thus D3 represents novelty-destroying prior art with regard to the main claim.

Semi-independent claim 10 also can be considered lacking novelty in the sense of Art. 54 EPC. As phase-2 clinical studies are usually conducted in hospitals or clinical research facilities, as applications of concentrated and costly monoclonal antibody therapeutics are performed by clinical personnel under clear prescriptions, as nivolumab and ipilimumab are applied in combination, and as the term “kit” is not specifically defined in the patent in dispute any different from the common understanding of a kit being any kind of suitable containment for storing and providing the therapeutics to be applied in combination, the subject matter of claim 10 can be deemed to be at least implicitly disclosed by D3 as well.

6.2. Lack of novelty over D4

D4 (Clinical Study NCT02060188, termed CheckMate 142) was initially published (“first submitted”) on 18 December 2013 in the clinical trial database “clinical trials.gov”; it is a prior art document under Art. 54(2) EPC. The main claim of the patent in dispute is lacking novelty over D4.

ClinicalTrials.gov is a web-based resource that provides patients, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions. The Web site is maintained

by the US National Library of Medicine (NLM) at the National Institutes of Health (NIH). Information on ClinicalTrials.gov is provided and updated by the sponsor or principal investigator of the clinical study (see <https://www.clinicaltrials.gov/ct2/about-site/background>). The NIH and the Food and Drug Administration (FDA) worked together to develop the site, which was made available to the public in February 2000. In addition, there is also the ClinicalTrials.gov results database, which contains summary information on study participants and study outcomes, including adverse events. The results database was made available to the public in September 2008. Searching ClinicalTrials.gov does not require registration or personal identification.

D4 relates to the same clinical study covered by the Meeting Abstract D3, which study is entitled “*A Study of Nivolumab and Nivolumab Plus Ipilimumab in Recurrent and Metastatic Colon Cancer, CheckMate 142*“, containing further information on the trial.

D4 discloses that in an experimental study arm “nivolumab + ipilimumab“ was tested (= *nivolumab, in combination with ipilimumab*; in “Arms and Interventions“, p. 2 of D4). D4 further discloses that patients with recurrent and metastatic colon cancer who also have a specific biomarker in their tumors, and that the microsatellite instability high (MSI-High) part of the trial was non-randomized (= *for use in a method of treating a colorectal cancer tumor in a subject, high degree of microsatellite instability*; in “Study Description“, p. 2 of D4). In addition, D4 teaches that in dose level 2b, nivolumab at a dose of 3 mg/kg intravenously was combined with ipilimumab at a dose of 1 mg/kg every 3 weeks for 4 doses (= *nivolumab at a dose of about 3 mg/kg body weight, ipilimumab at a dose of about 1 mg/kg body weight, and once about every three weeks*; in “Arms and Interventions, Dose Escalation Phase“, p. 2 in D4).

Hence, all features of the main claim of the patent in dispute are readily disclosed in D4. Thus D4 represents anticipating prior art with regard to the main claim. With regard to semi-independent claim 10, the same applies as described for D3 above.

In conclusion, documents D3 and D4, respectively, disclose all features of the independent claim of the patent in dispute, and hence the latter lacks novelty in the sense of Art. 54 EPC.

7. Lack of inventive step (Art. 100 (a), Art. 56 EPC)

For selecting the closest prior art when assessing inventive step by the problem/solution approach, the following criteria should be applied (see Guidelines for Examination, G-VII, 5.1).

“The closest prior art is that which in one single reference discloses the combination of features which constitutes the most promising starting point for a development leading to the invention. In selecting the closest prior art, the first consideration is that it must be directed to a similar purpose or effect as the invention or at least belong to the same or a closely related technical field as the claimed invention. In practice, the closest prior art is generally that which corresponds to a similar use and requires the minimum of structural and functional modifications to arrive at the claimed invention.”

This was confirmed by T 606/89. Thus, in order to determine the closest prior art, the purpose or objective of the alleged invention and the technical problem that the alleged invention seeks to address must be established.

The patent in dispute does not specifically define the technical problem, but notes that “*there remains a need for therapies with an acceptable safety profile and high efficacy that enhance antitumor immune responses compared to monotherapy and other immunotherapy combinations*” (paragraph [0006] of the patent in dispute). The objective technical problem, depending upon the choice of the closest prior art to be used as a springboard, might be considered to be the identification of another suitable medical indication, *i.e.*, providing an application of the well known combination of the immune checkpoint inhibitors nivolumab and ipilimumab with a well known dosage regimen to another oncologic indication; or might be considered to be the provision of a dosage regimen for the immunotherapy combination of nivolumab and ipilimumab in a well known oncologic indication, meeting said need of acceptable safety profile and high efficacy.

7.1. Technical Background

It is important to note that at the priority date of the patent in dispute, all aspects relating to the alleged invention were known to the person skilled in the art, who could be considered to be an oncologist or a team of clinicians including an immunologist and an oncologist.

First, at the priority date of the patent in dispute, programmed death 1 (PD-1) immune checkpoint inhibitors, in particular the anti-PD-1 antibody nivolumab, and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) immune checkpoint inhibitors, in particular the anti-CTLA-4 antibody ipilimumab, were well known (see D5; Abstract). Both antibodies had regulatory approval for various indications in Europe and in US.

Second, it was further known that the dual blockade of two or more immune checkpoint inhibitors had an increased effect as compared to a single blockade; this was also shown for the anti-PD-1 antibody nivolumab in combination with the anti-CTLA-4 antibody ipilimumab, see D5, Abstract:

“Nivolumab (a programmed death 1 [PD-1] checkpoint inhibitor) and ipilimumab (a cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4] checkpoint inhibitor) have been shown to have complementary activity in metastatic melanoma.... The median progression-free survival was 11.5 months (95% confidence interval [CI], 8.9 to 16.7) with nivolumab plus ipilimumab, as compared with 2.9 months (95% CI, 2.8 to 3.4) with ipilimumab... Among previously untreated patients with metastatic melanoma, nivolumab alone or combined with ipilimumab resulted in significantly longer progression-free survival than ipilimumab alone.”

and see D6, p. 3595, regarding the synergistic effect of a combination therapy observed in a CT26 colon carcinoma mouse model:

- 20 -

“we tested whether simultaneous blockade of PD-1 and CTLA-4 could promote tumor rejection in mice. We found that treatment with anti-PD-1 or anti-PD-L1 showed CT26 tumor regression in 25% and 33% of the mice, respectively (Fig. 3A; Table 1). CTLA-4 blockade alone led to tumor regression in 50% of the mice. Further, we noticed that combination of either anti-PD-1 or anti-PD-L1 with anti-CTLA-4 induced tumor regression in 75% of mice.”

Third, it was further well known from the prior art that some colorectal cancers are associated with a high degree of microsatellite instability (MSI-H), which results from impaired DNA mismatch repair, and that MSI-H colorectal cancers are associated with a high mutational burden and are particularly susceptible to immune checkpoint inhibitor blockade. This is shown, for example, in D7:

“A subset of colorectal cancer displayed high infiltration with activated CD8+ CTL as well as activated Th1 cells... virtually all of the tumors with this active Th1/CTL microenvironment had defects in mismatch repair, as evidenced by microsatellite instability (MSI)... MSI tumors selectively demonstrated highly up-regulated expression of multiple immune checkpoints, including... PD-1, CTLA-4... currently being targeted clinically [Abstract]...

immunotherapeutic interventions involving checkpoint blockade might be selectively effective in this important subset of cancers...CRC cohorts demonstrated a very low response rate to PD-1 or PD-L1 blockade, however...we found that there was a dramatic overexpression of immune checkpoint-related proteins in the microenvironment of MSI tumors,... suggesting that immunotherapeutic interventions involving checkpoint blockade might be selectively effective in this important subset of cancers... [Results]

MSI tumors will respond to checkpoint blockade with agents such as anti-PD-1 or anti-PD-L1 antibodies, while MSS tumors will be much less responsive. [Discussion]“

and in D8:

“With the exception of a minority of lesions characterized by microsatellite instability (MSI), CRC seems to be insensitive to the blockade of immunological checkpoints with monoclonal antibodies (mAbs) specific for cytotoxic T lymphocyte-associated protein 4 (CTLA4), programmed cell death 1 (PDCD1, best known as PD-1)...“ [Abstract]

and further confirmed in D9:

“[T]he high expression of checkpoint molecules PD-1,... CTLA-4... in MSI [microsatellite instable] CRC distinguishes MSI from microsatellite stable (MSS) CRC... MSI subset of CRC is a particularly good candidate for checkpoint immunotherapy.”

[Abstract]

“[C]linical trials have been initiated to test PD-1 blockade in MSI CRC patients. Combinations with... CTLA-4 and other checkpoints will likely follow.”

[p. 18, last paragraph]

Fourth, with regard to the dosage regimen employed in the alleged invention, it is important to note that the combination of nivolumab at a dose of about 3 mg/kg body weight with ipilimumab at a dose of about 1 mg/kg body weight, once about every 3 weeks, was a well-known standard dosage regimen for this combination of antibodies that had been used already in the treatment of various cancer types, including melanoma, metastatic desmoplastic melanoma, renal cell carcinoma, and small cell lung cancer before (in addition to MSI-H colorectal cancers, see D3 and D4), as will be explained in detail below, and was therefore obvious and lacking any inventive step at all.

Hence, the skilled artisan was well aware of all these aspects at the priority date of the patent in dispute, and nothing about the putative concept of the patent required any inventive skills.

7.2. Subject matter of the claims as granted does not solve the technical problem

As readily visible from the study schematics depicted in Figures 1, 2 and 8, the subject matter of the claims as granted cannot be considered as solving any technical problem, because the subject matter relates to a combination therapy using nivolumab in combination with ipilimumab under a particular dosage regimen for use in a method of treating a colorectal cancer tumor with a high degree of microsatellite instability (MSI-H). However, all Examples and

experimental data relate to a combination using nivolumab and ipilimumab at 3 mg/kg and 1 mg/kg body weight, respectively, once about every three weeks, *in combination with a monotherapy using nivolumab at 3 mg/kg body weight once about every two weeks*. Therefore, none of the experimental data collected as described in Examples 1 and 2 can be related to actual outcome and endpoints of a combination therapy using nivolumab in combination with ipilimumab under said particular dosage regimen only.

In case outcome and endpoints of the combination therapy using nivolumab in combination with ipilimumab under said particular dosage regimen should have been collected *prior* to the second stage of monotherapy using nivolumab at 3 mg/kg body weight once about every two weeks (“*then NIVO 3 mg/kg Q2W*”) applied to the same patients enrolled in the NIVO + IPI combination therapy, the study data from the monotherapy as collected in Tables 7, 8 and 9 have to be considered obsolete and of no value, because in this case the data do not represent a comparison between the NIVO + IPI combination therapy and the NIVO monotherapy, as alleged, but a comparison between a NIVO + IPI combination therapy group with a NIVO monotherapy group having received a NIVO + IPI combination therapy earlier, which is irrelevant.

7.3. D10 as closest prior art

7.3.1. Lack of inventive step in view of D10 in combination with D7

D10 is a Meeting Abstract from the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting which is relating to the results of a phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC). D10 discloses the exact same combination of the immune checkpoint inhibitors nivolumab and ipilimumab, with the exact same dosage regimen as in claim 1 of the patent in dispute (see **Table 3** below), for use in a method of treating metastatic renal cell carcinoma. It is hence plausible to use D10 as closest prior art, as it relates to the same technical field of immuno-oncology, in particular the use of

combination of immunotherapeutic immune checkpoint-inhibiting antibodies, and to the same technical problem, which is the application of such combination therapy with high efficacy to particular suited oncologic indications.

Claim 1 as granted	D10 (Hammers <i>et al.</i> # 4516)
<i>nivolumab</i>	Nivolumab (N) (Background, line 1)
<i>nivolumab at a dose of about 3 mg/kg body weight</i>	Nivolumab N 3 mg/kg (Methods, line 6)
<i>in combination with ipilimumab</i>	N 3 + I 3 (Methods, line 6)
<i>ipilimumab at a dose of about 1 mg/kg body weight</i>	Ipilimumab I 1 mg/kg (Methods, line 6)
<i>once about every three weeks</i>	IV Q 3 W for 4 doses (Methods, line 7)

D10 further teaches that a progression-free survival for 24 weeks (6 months) was achieved in 53% of the patients treated with a combination therapy of nivolumab and ipilimumab using said dosage regimen.

Therefore, looking for a further possible oncologic indication to which said combination of agents and said successful dosage regimen could be applied to, the person skilled in the art would without any doubt consider the disclosure of pre-published document D7, as it relates to the same technical field (see above) and same technical problem as the patent in dispute (“selecting patient population most likely to benefit from the application”, second page, last paragraph in D7).

The authors of D7 found that, albeit the majority of colorectal cancers (CRC) demonstrated a very low response rate to PD-1 blockade, a subset of colorectal cancers (CRC) displaying high infiltration with activated CD8+ cytotoxic T lymphocytes (CTL) as well as activated Th1 cells, that means with a vigorous immune microenvironment, virtually all had defects in mismatch repair, as evidenced by microsatellite instability (MSI). Counterbalancing this active Th1/CTL microenvironment, MSI tumors selectively demonstrated highly up-regulated ex-

pression of multiple immune checkpoints, including PD-1 (the target of nivolumab) and CTLA-4 (the target of ipilimumab). These findings link tumor genotype with the immune microenvironment, and explain why MSI tumors are not naturally eliminated despite a hostile Th1/CTL microenvironment. These findings “*further suggest that blockade of specific checkpoints may be selectively efficacious in the MSI subset of CRC*” (Abstract of D7), and that “*immunotherapeutic interventions involving checkpoint blockade might be selectively effective in this important subset of cancers*” (D7, third page, second paragraph), motivating the person skilled in the art to apply the therapeutic combination and dosage regimen as claimed to the indication of CRC with high microsatellite instability. See **Table 4** below.

Claim 1 as granted	D7 (Llosa <i>et al.</i>)
<i>use in a method of treating a colorectal cancer tumor in a subject</i>	subset of colorectal cancer possesses a highly activated Th1- and CTL-rich microenvironment; immunotherapeutic interventions involving checkpoint blockade might be selectively effective in this important subset of cancers (Introduction, last paragraph)
<i>high degree of microsatellite instability (“MSI-H”)</i>	this subset of tumors harbored microsatellite instability (MSI), indicating that they were mismatch repair deficient (differences in the length of 2 or more markers (the standard Bethesda panel uses 5 markers) was indicative of MSI status) (Materials and Methods, second para)

Hence, it was straightforward for the person skilled in the art to apply the combination therapy from D10, employing nivolumab and ipilimumab under the dosage regimen successfully applied in renal cell carcinoma, with a high likelihood of success in view of the teaching in D7, to CRC with high microsatellite instability.

The straightforward combination of D10 with D7 is disclosing all features of the main claim of the patent in dispute. In conclusion, subject matter of claim 1 is obvious in the sense of Art. 56 EPC over D10 in combination with D7.

Of note, according to the patent in dispute (paragraph [0057]), the feature “*the tumor exhibits a high degree of microsatellite instability (MSI-H)*” is based on a publication by Pawlik *et al.* (introduced as D16 by opponent). The authors of D16 suggest that microsatellite instability (MSI)-high (MSI-H) tumors might represent a phenotype distinguishable from MSI-Low (MSI-L) tumors, in that the MSI-H tumors have “*distinct clinicopathological features characterized by an overall better long-term prognosis*” than MSI-L tumors (D16, Abstract, lines 4-5). However, it needs to be noted that the authors stress that “*although the use of the MSI-L category is widespread, there continues to be some debate as to whether a discrete MSI-L group truly exists. Rather, it has been suggested that MSI-L tumors differ quantitatively from MSS (microsatellite-stable) tumors*”. Hence, this means that a difference between MSI-H and MSI-L tumors has not necessarily been commonly acknowledged. Furthermore, with regard to inventive step assessment, this means that references disclosing colorectal tumors with microsatellite instability (MSI), as opposed to microsatellite stability (MSS), which might not use the uncommon parameters of MSI-H and MSI-L, have to be regarded as disclosing said feature of the main claim nevertheless.

Furthermore, as set forth above, D10 teaches that by use of a dosage regimen which is identical to the dosage regimen as claimed in the patent in dispute, a progression-free survival for 24 weeks (6 months) was achieved in 53% of the patients. Just assuming that such patients had been MSI-L tumor patients – which opponent denies – the progression-free survival rate could be expected to have been even higher with MSI-H patients, as they allegedly have an even better long-term prognosis according to D16. Hence, also for this reason, an assessment of a colorectal MSI tumor as a MSI-H tumor does not render the main claim inventive.

7.3.2. Lack of inventive step in view of D10 in combination with D8

With D10 as closest prior art, and looking for a further possible oncologic indication to which said combination of nivolumab and ipilimumab and said successful dosage regimen could be

- 26 -

applied to, the person skilled in the art would necessarily have considered the disclosure of pre-published document D8, because it also relates to the same technical field and same technical problem as the patent in dispute.

D8 teaches that neither the blockade of the PD-1/PD-L1 axis with nivolumab, nor the blockade of CTLA4 with ipilimumab has conferred any major clinical benefits to patients bearing mismatch repair-*proficient* colorectal cancers, however, that mismatch repair-*deficient* colorectal cancers (microsatellite instability-positive), whose etiology is very different from that of their mismatch repair-proficient (MSI negative) counterparts and which are prone to accumulate somatic mutations, significantly increasing their immunogenicity, are well amenable to immune checkpoint inhibitors (D8, second page, left column, last paragraph). Hence, in line with the teaching in D7, D8 confirms that colorectal cancer characterized by microsatellite instability are sensitive to the blockade of immunological checkpoints with monoclonal antibodies like nivolumab and ipilimumab (D8, Abstract). See **Table 5** below.

Claim 1 as granted	D8 (Kroemer <i>et al.</i>)
<i>nivolumab</i>	blockade of PD-1/PD-L1 axis with nivolumab (second page, left column)
<i>use in a method of treating a colorectal cancer tumor in a subject</i>	minority of CRC lesions characterized by microsatellite instability are sensitive to blockade of immune checkpoints with mAbs specific for PD-1 and CTLA-4 (Abstract)
<i>high degree of microsatellite instability ("MSI-H")</i>	CRC lesions characterized by microsatellite instability (Abstract)
<i>ipilimumab</i>	blockade of CTLA-4 with ipilimumab (second page, left column)

Hence, it was straightforward for the person skilled in the art to apply the combination therapy from D10, employing nivolumab and ipilimumab under the dosage regimen successfully applied in renal cell carcinoma, to CRC with high microsatellite instability, being motivated by the teaching in D8 and having a high likelihood of success in view of the same.

Subject matter of claim 1 as granted is obvious in the sense of Art. 56 EPC over D10 in combination with D8.

7.3.3. Lack of inventive step in view of D10 in combination with D13

With D10 as closest prior art, and searching for a further possible oncologic target to be treated with a combination of nivolumab and ipilimumab and said successful dosage regimen, the skilled person would also have considered pre-published document D13, because it also relates to the same technical field and same technical problem as the patent in dispute.

D13 summarizes results of a phase-2 study which shows that mismatch repair-deficient colorectal cancers, having a mean of 1782 somatic mutations per tumor, but hardly any mismatch repair-proficient colorectal cancer could successfully be treated with the PD-1 immune checkpoint inhibitor monoclonal antibody pembrolizumab (D13, Abstract; p. 2510, penultimate paragraph; Fig. 2A), which serves to blockade the PD-1/PD-L1 pathway. The mismatch repair status of the respective colorectal cancer, termed microsatellite instability, allowed to predict clinical benefit of immune checkpoint blockade with pembrolizumab (D13 p. 2509, last paragraph). See **Table 6** below.

Claim 1 as granted	D13 (Le et al.)
<i>use in a method of treating a colorectal cancer tumor in a subject</i>	Phase-2 clinical study in patients with mismatch repair-deficient colorectal cancer (Abstract, Methods)
<i>high degree of microsatellite instability ("MSI-H")</i>	accumulation of mutations in these regions of the genome is termed microsatellite instability; mismatch-repair status was assessed in tumors (p. 2512, left column, third paragraph)

Thus, it was straightforward for the person skilled in the art to apply the combination therapy from D10 to CRC with high microsatellite instability with a very high likelihood of success in view of the teaching in D13. Subject matter of claim 1 as granted is obvious in the sense of Art. 56 EPC over D10 in combination with D13.

7.3.4. Lack of inventive step in view of D10 in combination with D14

With D10 as closest prior art, and searching for a further possible oncologic target to be treated with a combination of nivolumab and ipilimumab and said successful dosage regimen, the skilled person would also have considered pre-published document D14, as it also relates to the same technical field and same technical problem as the patent in dispute.

D14 discloses a method of treating a colon cancer patient by administering to the patient an immune checkpoint inhibitory antibody, wherein the cancer patient has a microsatellite unstable cancer (MSI), and wherein the antibody is directed, for example, to PD-1 or CTLA-4 (D14, claims 1, 2, 3, and 5). The MSI cancer patient is tested to evaluate stability of one or more microsatellite markers prior to the administration of the antibody. D14 further discloses that microsatellite instability (MSI) tumors are deficient in DNA mismatch repair which leads to a high rate of spontaneous mutations and the potential for the expression of neo-antigens; furthermore, that similar to melanoma, in MSI-positive colon cancers, often prominent lymphocyte infiltration can be found, and that any tumors with MSI may be treated by immune checkpoint inhibitory antibodies (D14, paragraph [31]).

Furthermore, D14 teaches that the progression-free survival (PFS) at twenty weeks (*i.e.*, 5 months) was reached in 78% of patients with mismatch repair (MMR) gene-deficient colorectal cancers, but only in 11% of patients with mismatch repair (MMR) gene-proficient colorectal cancers (Fig. 11). See **Table 7** below.

Claim 1 as granted	D14 (WO 2016/077553)
---------------------------	-----------------------------

<i>use in a method of treating a colorectal cancer tumor in a subject</i>	method of treating a colon cancer patient by administering to the patient an immune checkpoint inhibitory antibody, e.g., pembrolizumab (Claim 2, claim 10)
<i>high degree of microsatellite instability ("MSI-H")</i>	wherein the cancer patient has a microsatellite instable cancer (MSI) (Claim 1)

Thus, it was straightforward for the person skilled in the art to apply the combination therapy from D10 to CRC with high microsatellite instability, with a very high likelihood of success in view of the teaching in D14. Subject matter of claim 1 as granted is obvious in the sense of Art. 56 EPC over D10 in combination with D14.

7.4. D11 as closest prior art

7.4.1. Lack of inventive step in view of D11 in combination with D7

D11 is also a Meeting Abstract from the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting which is relating to the results of a phase III study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC). D11 also discloses the exact same combination of the immune checkpoint inhibitors nivolumab and ipilimumab, with the exact same dosage regimen as in claim 1 of the patent in dispute (see **Table 8** below), for use in a method of treating mRCC. It is hence fully plausible to alternatively use D11 as closest prior art, as it relates to the same technical field of immuno-oncology, in particular the use of combination of immunotherapeutic immune checkpoint-inhibiting antibodies, and to the same technical problem, which is the application of such combination therapy with high efficacy to a different, suited oncologic indication.

Claim 1 as granted	D11 (Hammers <i>et al.</i> # TPS4578)
<i>nivolumab</i>	Nivolumab (N) (Background, Methods)
<i>nivolumab at a dose of about 3 mg/kg body weight</i>	Nivolumab N 3 mg/kg

- 30 -

	(Methods, line 22)
<i>in combination with ipilimumab</i>	N 3 + I 3 (Methods, line 22-23)
<i>ipilimumab at a dose of about 1 mg/kg body weight</i>	ipilimumab (I) 1 mg/kg (Methods, line 23)
<i>once about every three weeks</i>	every 3 weeks for 4 doses (Methods, line 23)

Looking for further possible oncologic indications to which said combination of agents and said successful dosage regimen could be applied to, the person skilled in the art would without any doubt consider the disclosure of pre-published document D7, as explained above (see Section 7.3.1.), because it relates to the same technical field (see above) and same technical problem as the patent in dispute (“selecting patient population most likely to benefit from the application”, second page, last paragraph in D7). For a description of the disclosure in D7, please refer to Section 7.3.1. and Table 4 therein.

Thus, it was straightforward for the person skilled in the art to apply the combination therapy and dosage regimen from D11 to CRC with high microsatellite instability, with a very high likelihood of success in view of the teaching in D7.

Subject matter of claim 1 as granted is obvious in the sense of Art. 56 EPC over D11 in combination with D7.

7.4.2. Lack of inventive step in view of D11 in combination with D8

With D11 as closest prior art, and searching for further suitable oncologic indication to which said combination of nivolumab and ipilimumab and said successful dosage regimen could be applied to, the person skilled in the art would necessarily have considered the disclosure of pre-published document D8, because it also relates to the same technical field and same technical problem as the patent in dispute.

For detailed description of the disclosure in D8, please refer to Section 7.3.2. and Table 5 therein.

It was straightforward for the person skilled in the art to apply the combination therapy disclosed in D11, employing nivolumab and ipilimumab under the dosage regimen successfully applied in metastatic renal cell carcinoma, to CRC with high microsatellite instability, being motivated by the teaching in D8 and having a high likelihood of success in view of the same.

Subject matter of claim 1 as granted is obvious in the sense of Art. 56 EPC over D11 in combination with D8.

7.4.3. Lack of inventive step in view of D11 in combination with D13

With D11 as closest prior art, and searching for further suitable oncologic indication to which said combination of nivolumab and ipilimumab and said successful dosage regimen could be applied to, the person skilled in the art would necessarily have considered the disclosure of pre-published document D13, because it also relates to the same technical field and same technical problem as the patent in dispute.

For detailed description of the disclosure in D13, please refer to Section 7.3.3. and Table 6 therein.

It was straightforward for the person skilled in the art to apply the combination therapy disclosed in D11, employing nivolumab and ipilimumab under the dosage regimen successfully applied in metastatic renal cell carcinoma, to CRC with high microsatellite instability, being motivated by the teaching in D13 and having a high likelihood of success in view of the same.

Subject matter of claim 1 as granted is obvious in the sense of Art. 56 EPC over D11 in combination with D13.

7.4.4. Lack of inventive step in view of D11 in combination with D14

With D11 as closest prior art, and searching for further suitable oncologic indication to which said combination of nivolumab and ipilimumab and said successful dosage regimen could be applied to, the person skilled in the art would necessarily have considered the disclosure of pre-published document D14, because it also relates to the same technical field and same technical problem as the patent in dispute.

For detailed description of the disclosure in D14, please refer to Section 7.3.4. and Table 7 therein.

It was straightforward for the person skilled in the art to apply the combination therapy disclosed in D11, employing nivolumab and ipilimumab under the dosage regimen successfully applied in metastatic renal cell carcinoma, to CRC with high microsatellite instability, being motivated by the teaching in D14 and having a high likelihood of success in view of the same.

Subject matter of claim 1 as granted is obvious in the sense of Art. 56 EPC over D11 in combination with D14.

7.5. D12 as closest prior art

7.5.1. Lack of inventive step in view of D12 in combination with D7

D12 is a further Meeting Abstract from the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting which is relating to the results of a phase I/II study of nivolumab in

combination with ipilimumab for treatment of recurrent small cell lung cancer (SCLC). D12 also discloses the exact same combination of the immune checkpoint inhibitors nivolumab and ipilimumab, with the exact same dosage regimen as in claim 1 of the patent in dispute (see **Table 9** below), for use in a method of treating SCLC. It is hence fully plausible to alternatively use D12 as closest prior art, as it relates to the same technical field of immuno-oncology, in particular the use of combination of immunotherapeutic immune checkpoint-inhibiting antibodies, and to the same technical problem, which is the application of such combination therapy with high efficacy to a different, suited oncologic indication.

Claim 1 as granted	D12 (Antonia <i>et al.</i> # 7503)
<i>nivolumab</i>	Nivolumab (NIVO) (Background, line 4)
<i>nivolumab at a dose of about 3 mg/kg body weight</i>	Nivolumab (NIVO) 3 mg/kg (Methods, lines 10-11)
<i>in combination with ipilimumab</i>	NIVO + IPI (Methods, line 10)
<i>ipilimumab at a dose of about 1 mg/kg body weight</i>	Ipilimumab (IPI) 1 mg/kg (Methods, line 11)
<i>once about every three weeks</i>	Q3W, every 3 weeks for 4 doses (Methods, line 11)

D12 further discloses that NIVO + IPI combination was tolerable in SCLC patients, and that overall response rates (ORR) were 15% in NIVO alone patients, but 25% in NIVO + IPI patients (D12, Conclusions), indicating a combination of efficacies of the two antibodies, possibly a synergistic effect.

In search for further oncologic indications to which said combination of agents and said successful dosage regimen could be applied to, the person skilled in the art would without any doubt consider the disclosure of pre-published document D7, as explained above (see Section 7.3.1.), because it relates to the same technical field (see above) and same technical problem as the patent in dispute (“selecting patient population most likely to benefit from the application”, second page, last paragraph in D7). For a description of the disclosure in D7, please refer to Section 7.3.1. and Table 4 therein.

Thus, it was obvious for the person skilled in the art to apply the combination therapy and dosage regimen from D12 to CRC with high microsatellite instability, with a very high likelihood of success in view of the teaching in D7. No inventive step was required in view of the combination of these two documents.

Subject matter of claim 1 as granted is obvious in the sense of Art. 56 EPC over D12 in combination with D7.

7.5.2. Lack of inventive step in view of D12 in combination with D8

With D12 as closest prior art, and searching for further suitable oncologic indication to which said combination of nivolumab and ipilimumab and said successful dosage regimen could be applied to, the person skilled in the art would necessarily have considered the disclosure of pre-published document D8, because it also relates to the same technical field and same technical problem as the patent in dispute.

For detailed description of the disclosure in D8, please refer to Section 7.3.2. and Table 5 therein.

It was straightforward for the person skilled in the art to apply the combination therapy disclosed in D12, employing nivolumab and ipilimumab under the dosage regimen successfully applied in recurrent small cell lung cancer (SCLC), to CRC with high microsatellite instability, being motivated by the teaching in D8 and having a high likelihood of success in view of the same.

Subject matter of claim 1 as granted is obvious in the sense of Art. 56 EPC over D12 in combination with D8.

7.5.3. Lack of inventive step in view of D12 in combination with D13

With D12 as closest prior art, and searching for further suitable oncologic indication to which said combination of nivolumab and ipilimumab and said successful dosage regimen could be applied to, the person skilled in the art would necessarily have considered the disclosure of pre-published document D13, because it also relates to the same technical field and same technical problem as the patent in dispute.

For detailed description of the disclosure in D13, please refer to Section 7.3.3. and Table 6 therein.

It was straightforward for the person skilled in the art to apply the combination therapy disclosed in D12, employing nivolumab and ipilimumab under the dosage regimen successfully applied in recurrent small cell lung cancer (SCLC), to CRC with high microsatellite instability, being motivated by the teaching in D13 and having a high likelihood of success in view of the same.

Subject matter of claim 1 as granted is obvious in the sense of Art. 56 EPC over D12 in combination with D13.

7.5.4. Lack of inventive step in view of D12 in combination with D14

With D12 as closest prior art, and searching for further suitable oncologic indication to which said combination of nivolumab and ipilimumab and said successful dosage regimen could be applied to, the person skilled in the art would necessarily have considered the disclosure of pre-published document D14, because it also relates to the same technical field and same technical problem as the patent in dispute.

For detailed description of the disclosure in D14, please refer to Section 7.3.4. and Table 7 therein.

It was straightforward for the person skilled in the art to apply the combination therapy disclosed in D12, employing nivolumab and ipilimumab under the dosage regimen successfully applied in small cell lung cancer (SCLC), to CRC with high microsatellite instability, being motivated by the teaching in D14 and having a high likelihood of success in view of the same.

Subject matter of claim 1 as granted is obvious in the sense of Art. 56 EPC over D12 in combination with D14.

7.6. D9 as closest prior art

7.6.1. Lack of inventive step in view of D9 in combination with D10

D9 is entitled “*The microsatellite instable (MSI) subset of colorectal cancer is a particularly good candidate for checkpoint blockade immunotherapy*” (and hence already at first glance perfectly qualifies also as second document to be combined with any of prior art documents D10, D11, and D12, respectively, discussed above).

D9 teaches that the microsatellite instable (MSI) subset of colorectal cancer (CRC) exhibits an active Th1/CTL immune microenvironment, probably due to recognition of a high number of tumor neoantigens. However, high expression of, for example, checkpoint molecules PD-1 and CTLA-4 in MSI CRC distinguishes MSI from microsatellite stable (MSS) CRC and creates an immunosuppressive microenvironment that may help MSI tumors evade immune destruction by the infiltrating immune cells. Although CRC in general does not have a good response rate to PD-1 pathway immunotherapy, these results suggest that the *MSI subset of CRC* is a particularly good candidate for checkpoint immunotherapy (D9, Summary).

- 37 -

D9 further discloses that “two clinical trials have been initiated to test PD-1 blockade in MSI CRC patients. *Combinations with...CTLA-4 and other checkpoints will likely follow.*” (D9, third page, last two sentences), providing the skilled person with motivation to employ such combinations of PD-1 and CTLA-4 inhibitors. D9 does not disclose any dosage regimen.

It is hence also plausible to alternatively use D9 as closest prior art and springboard, as it relates to the same technical field of immunooncology, in particular the use of combination of immunotherapeutic immune checkpoint-inhibiting antibodies in MSI CRC patients. See **Table 10** below.

Claim 1 as granted	D9 (Xia and Freemann, 2015)
<i>nivolumab</i>	PD-1 blocking mAb (pembrolizumab) (third page, last paragraph)
<i>use in a method of treating a colorectal cancer tumor in a subject</i>	clinical trials to test PD-1 blockade in CRC patients (third page, last paragraph)
<i>high degree of microsatellite instability (“MSI-H”)</i>	with microsatellite instability (MSI) (third page, last paragraph)
<i>in combination with ipilimumab</i>	combination with CTLA-4 blockade; ipilimumab (third page, last paragraph)

The distinguishing technical feature between claim 1 of the patent in dispute and D9 is the dosage regimen. The objective technical problem, starting from D9, hence can be defined as providing a dosage regimen for said combination therapy in MSI CRC patients yielding good tolerability and high efficacy.

Searching for a suitable dosage regimen in the prior art, the person skilled in the art would of course take document D10 into consideration and thus arrive without any inventive step at exactly the dosage regimen as claimed in the patent in dispute (3 mg/kg body weight PD-1 inhibitor, Nivolumab; 1 mg/kg body weight ipilimumab; once every three weeks; see Table 3 reproduced again below). According to D10 (penultimate sentence), said combination dosage regimen was found to be safe and showing promising antitumor activity.

Claim 1 as granted	D10 (Hammers <i>et al.</i> # 4516)
<i>nivolumab</i>	Nivolumab (N) (Background, line 1)
<i>nivolumab at a dose of about 3 mg/kg body weight</i>	Nivolumab N 3 mg/kg (Methods, line 6)
<i>ipilimumab at a dose of about 1 mg/kg body weight</i>	Ipilimumab I 1 mg/kg (Methods, line 6)
<i>once about every three weeks</i>	IV Q 3 W for 4 doses (Methods, line 7)

Hence, subject matter of claim 1 as granted is obvious in the sense of Art. 56 EPC over D9 in combination with D10.

7.6.2. Lack of inventive step in view of D9 in combination with D11

With D9 as closest prior art, and searching for a dosage regimen for said combination therapy in MSI CRC patients yielding good tolerability and high efficacy, the person skilled in the art would necessarily have considered the disclosure of pre-published document D11, because it relates to the same technical field and same technical problem as the patent in dispute.

For detailed description of the disclosure in D11, please refer to Section 7.4.1. and Table 8 therein.

It was straightforward for the person skilled in the art to apply the dosage regimen disclosed in D11, to the combination of anti-PD-1 mAb and ipilimumab used for treatment of CRC with high microsatellite instability, being highly motivated by the teaching in D11 and having a high likelihood of success in view of the same.

Subject matter of claim 1 as granted is obvious in the sense of Art. 56 EPC over D9 in combination with D11.

7.6.3. Lack of inventive step in view of D9 in combination with D12

Finally, with D9 as closest prior art, and searching for a dosage regimen for said combination therapy in MSI CRC patients yielding good tolerability and high efficacy, the person skilled in the art would also have considered the disclosure of pre-published document D12, because it relates to the same technical field and same technical problem as the patent in dispute.

For detailed description of the disclosure in D12, please refer to Section 7.5.1. and Table 9 therein.

It was straightforward for the person skilled in the art to apply the dosage regimen disclosed in D12 to the combination of anti-PD-1 mAb and ipilimumab used for treatment of CRC with high microsatellite instability, being highly motivated by the teaching in D12 and having a high likelihood of success in view of the same.

Subject matter of claim 1 as granted is obvious in the sense of Art. 56 EPC over D9 in combination with D12.

7.7. Conclusion

Hence, the subject matter of the independent claims as granted does not rely on an inventive step. The claims therefore contravene Art. 56 EPC and are thus invalid.

8. Dependent claims

The dependent claims add no further limitations that are suitable to render the independent claim novel and inventive. As shown below, the dependent claims are anticipated or obvious

- 40 -

in view of the prior art cited or even in view of the common general knowledge of the person skilled in the art at the time of filing.

Claim 2 as granted further defines that the tumor may be a colon cancer or a rectal cancer. Said further specification does neither render the claim novel nor inventive. For example, D16 teaches that colorectal carcinogenesis involves the stepwise accumulation of multiple genetic alterations that allow the growth of neoplastic cells, and relates to adenocarcinomas of the *colon* and of the *rectum* (D16, p. 199, left column, first paragraph). Also D3 and D4, respectively, disclose the use of nivolumab and ipilimumab for treatment of colorectal or colon cancer.

Claim 3 as granted relates to the tumor exhibiting one or more characteristics from the group consisting of: (a) germline alteration in at least two, at least three, at least four, or at least five DNA mismatch repair genes ("MMR genes"); (b) germline alteration in at least 30% of five or more MMR genes; (c) at least one protein encoded by DNA MMR genes is not detected in the tumor; and (d) any combination thereof. Said further specification does neither render the claim novel nor inventive. For example, D16 teaches that "*in most cases, the genetic basis for instability in MSI tumors is an inherited germline alteration in any one of the five human MMR genes*", in particular, germline mutations in MSH2 and MLH1 genes (D16, p. 200, left column, first paragraph).

Claim 4 as granted relates to DNA mismatch repair (MMR) genes MSH2, MLH1, MSH6, PMS2, and PMS1. Respective limitation does neither render the claim novel nor inventive. For example, D16 discloses that "*the five human MMR genes [are]: MSH2, MLH1, MSH6, PMS2, and PMS1*" (D16, p. 200, left column, first paragraph).

Claim 5 as granted relates to (i) a progression-free survival of at least about one month... 12 months after administration, or (ii) overall survival of at least about one month... 12 months after the administration. Respective specification does neither render the claim novel nor inventive. D3 discloses a four-months progression-free survival rate of 80% of patients having

received the “NIVO 3 mg/kg + IPI 1mg/kg, once every three weeks“ dosage regimen as claimed, and a five-months overall survival rate in 100% of patients (D3, Table). D10 discloses a six-months progression-free survival rate of 53% of patients having received the “NIVO 3 mg/kg + IPI 1mg/kg, once every three weeks“ dosage regimen as claimed in metastatic renal cell carcinoma (D10, Table, last line). Further, D5 discloses a median 14-months progression-free survival rate of melanoma patients having received a “NIVO + IPI“ dosage regimen (D5, Abstract).

Claim 6 as granted relates to administration of nivolumab and ipilimumab followed by an anti-PD-1 monotherapy. Respective specification does neither render the claim novel nor inventive. D3 discloses an administration of a combination of nivolumab and ipilimumab, with dosage and intervals exactly as claimed, followed by nivolumab, 3 mg/kg, monotherapy in MSI-H colorectal cancer patients (D3, lines 6-7). D4 discloses an administration of nivolumab 3 mg/kg i.v. combined with ipilimumab 1 mg/kg i.v. every 3 weeks for 4 doses, followed by nivolumab 3mg/kg i.v. every 2 weeks (D4, “dose level 2b“). D10 teaches an administration of a combination of nivolumab and ipilimumab, with dosage and intervals exactly as claimed, followed by nivolumab, 3 mg/kg, monotherapy in metastatic renal cell carcinoma patients (D10, lines 7-8).

Claim 7 as granted specifies that administration of nivolumab and ipilimumab comprises four doses for each. Respective specification does neither render the claim novel nor inventive. D3 teaches that four doses for each of nivolumab and ipilimumab, as combination with dosage and intervals exactly as claimed, are administered (D3, line 6). D10 discloses that four doses for each of nivolumab and ipilimumab, as combination with dosage and intervals exactly as claimed, are administered as well (D10, lines 7-8).

Claim 8 as granted specifies that the subject has received one to five or more prior cancer treatments. Respective specification is an arbitrary choice that does neither render the claim novel nor inventive. D3 teaches that patients with MSI-H colorectal cancer were enrolled for

the combination therapy as claimed in the patent in dispute who had intolerance/progression on one or more prior treatments (D3, line 5).

Claim 9 as granted specifies that the subject has progressed on other cancer treatments. Respective specification does neither render the claim novel nor inventive. As set forth above, D3 teaches that patients with MSI-H colorectal cancer were enrolled for the combination therapy as claimed in the patent in dispute who had progression on one or more prior treatments (D3, line 5). D4 discloses that there was an exclusion criteria concerning patients with prior treatment with an anti-PD-1- or CTLA-4-specific antibody or other immune checkpoint-related antibodies (D4, p. 4, Exclusion Criteria). Hence, patients enrolled for the combination therapy as claimed in the patent in dispute who had progressed on one or more prior treatments must have progressed on other cancer treatments, otherwise they would not have been enrolled.

9. Summary

According to a general principle, the extent of the monopoly conferred by a patent should correspond to and be justified by the technical contribution to the art at the filing date, or, when applicable, the priority date (see, for example, technical board decisions T 409/91 and T 435/91). In the present case, patent proprietor has, at the filing date, not contributed to the art any of the subject-matter as defined by the granted claims because

- a) Claimed subject-matter has later been added (Art. 123(2) EPC)
- b) Claimed subject-matter is not disclosed sufficiently clear and complete for it to be carried out by a person skilled in the art (Art. 83 EPC)
- c) Claimed subject-matter is not novel (Art. 54 EPC)
- d) Claimed subject-matter is obvious to the skilled person, and does not solve the technical problem of the alleged invention (Art. 56 EPC).

- 43 -

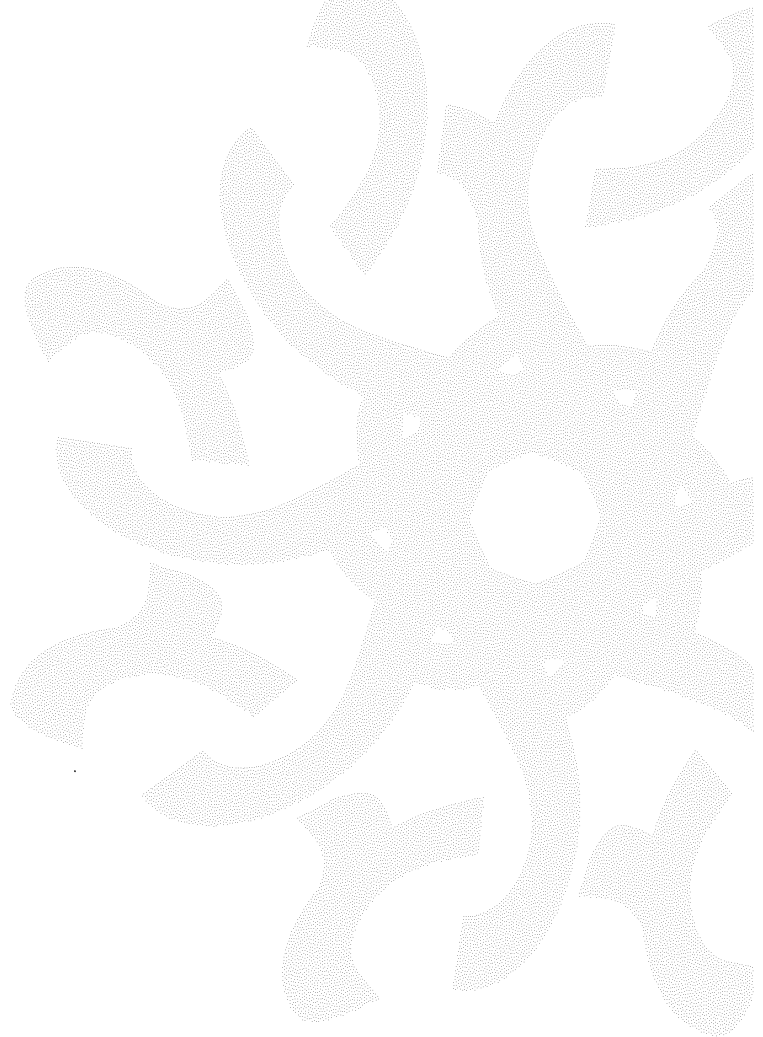
For these reasons, the patent has to be revoked in its entirety. The request set forth above is thus justified.

Michalski · Hüttermann & Partner



Dr. Christoph Volpers
Association No. 289

Encl.
Payment form
References D1 – D16
EPO form 2300



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26 July 2022
MF

Re.: European Patent No. 3 464 373
European Patent Application No. 17731359.0
Patentee: Bristol-Myers Squibb Company
Opponent: Lederer & Keller Patentanwälte Partnerschaft mbB

On behalf of

Lederer & Keller Patentanwälte Partnerschaft mbB
Unsöldstr. 2
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Germany

OPPOSITION

is lodged according to Article 99 EPC against the above-referenced patent of Bristol-Myers Squibb Company entitled

"Use of anti-PD-1 antibody in the treatment of patients with colorectal cancer".

The opposition fee amounting to EUR 840.-- is paid via online fee payment.

The opponent has appointed us as their representatives, and it is respectfully requested to send all notifications to our address.

European patent EP 3 464 373 is opposed in its full extent (claims 1 to 10).

The opposition is based on the grounds of Articles 100(a) and 100(b) EPC. In particular, it is submitted that the subject matter of the opposed patent is not sufficiently disclosed, is not novel and does not involve an inventive step.

It is requested to revoke the European patent in its entirety. Oral proceedings in accordance with Article 116 EPC are requested in the event that the Opposition Division does not reach the decision to revoke the patent on the basis of the written submissions of the opponent.

Detailed statement of the grounds for opposition

1. Bibliographic information

The opposed patent is based on European application no. 17731359.0, which is the European phase of international application PCT/US2017/035822, published as WO 2017/210637 A1. Said application was filed on 2nd June 2017, claiming priority of 3rd June 2016.

2. Cited documents

2.1 Reference will be made to the following documents:

- D1:** Overman, M.J. *et al.*, *J. Clin. Oncol.* **2016**, 34(15S), abstract 3501;
- D2:** Clinical study record NCT02060188 entitled “A Study of Nivolumab and Nivolumab Plus Ipilimumab in Recurrent and Metastatic Colon Cancer (CheckMate 142)”, version 50, 25th May **2016**;
- D3:** Llosa, N.J. *et al.*, *Cancer Discov.* **2015**, 5(1), 43-51;
- D4:** Rosenbaum, M.W. *et al.*, *Mod. Pathol.* **2016**, 29 1104-1112;
- D5:** Dudley, J.C. *et al.*, *Clin. Cancer Res.* **2016**, 22(4) 813-820;
- D6:** Boutros, C. *et al.*, *Nat. Rev. Clin. Oncol.* **2016**, 13(8), 473-86.

2.2 Documents D1 to D6 were published before the priority date of the opposed patent and are thus full prior art for all claims.

2.3 Documents D5 and D6 are review articles. These documents are thus, by definition, an account of the common general knowledge and the state of the art prior to their own publication date (see, e.g., T 777/08, r. 5.2).

3. The opposed patent

3.1 Technical field and background

3.1.1 The opposed patent relates to the treatment of colorectal cancer exhibiting a high degree of microsatellite instability (MSI-H) with nivolumab in combination with ipilimumab (opposed patent, paragraph [0001]).

3.1.2 The opposed patent explains in the background art section that colorectal cancer is the third most common type of cancer in both men and women in the United States. Some colorectal cancers are associated with a high degree of microsatellite instability (MSI-H), which results from impaired DNA mismatch repair. DNA mismatch repair-deficient/microsatellite instability-high (dMMR/MSI-H) metastatic colorectal cancer (mCRC) (~5% of patients) is associated with a high mutational burden and is known to be particularly susceptible to immune checkpoint inhibitor blockade (opposed patent, paragraph [0005]).

3.1.3 The opposed patent further explains that Nivolumab (formerly designated 5C4, BMS-936558, MDX-1106, or ONO-4538) is a fully human IgG4 (S228P) PD-1 immune checkpoint inhibitor antibody that selectively prevents interaction with PD-1 ligands (PD-L1 and PD-L2), thereby blocking the down-regulation of antitumor T-cell functions (opposed patent, paragraph [0004]). It also discloses that record NCT02060188 of clinicaltrials.gov describes a phase 2 clinical trial of nivolumab and nivolumab combinations in recurrent and metastatic microsatellite high colon cancer (opposed patent, paragraph [0006]).

3.2 The common general knowledge

3.2.1 D5 is a review article on microsatellite instability (MSI) as a biomarker for PD-1 blockade (D5, title). D5 explains that microsatellites are defined as repeats of the same base or sequence of up to 6 DNA bases. DNA polymerases are more prone to make mistakes in these regions, by either inserting or removing additional bases, leading to mismatched DNA strands. Following DNA replication, the mismatch repair (MMR) machinery slides along the

DNA and targets mismatches for correction when it encounters them (D5, page 815, left-hand column, last paragraph).

3.2.2 D5 explains that certain tumours have defects in mismatch repair, resulting in microsatellite instability (MSI), i.e., increased mutation rate. Such tumours have also significant upregulation of immune check point proteins, including PD-1 and PD-L1, enabling them to survive (D5, page 814, left-hand column, second paragraph). Therefore, MSI has proven to be useful as predictive marker for response to PD-1 blockade and thus the immune-related objective response rate (D5, page 814, right-hand column, first paragraph). Moreover, MSI status has been used to predict outcomes: MSI colorectal cancer is associated with a lower stage at diagnosis and improved stage-specific prognosis (D5, page 814, right-hand column, second-last paragraph).

3.2.3 Therefore, according to D5, *“These results have the potential to significantly improve therapeutic options. Immune checkpoint blockade inhibition is less toxic than chemotherapeutic regimens and has potential for durable responses in advanced cancer patients who would otherwise live a few months”* (D5, page 815, left-hand column, first paragraph, emphasis added).

3.2.4 Review D6 discusses the safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination (D6, tile). D6 explains that *“Inhibition of immune checkpoints using anti-programmed cell death-1 (PD-1) or anti cytotoxic-T-lymphocyte-associated antigen 4 (CTLA-4) monoclonal antibodies has revolutionized the management of patients with advanced-stage melanoma and is among the most promising treatment approaches for many other cancers”* (D6, abstract, emphasis added).

3.2.5 In particular, D6 teaches that ipilimumab is a fully humanized monoclonal antibody directed against CTLA-4 approved in 2011 in Europe and the United States for the treatment of melanoma. It also explains that nivolumab and pembrolizumab are two monoclonal IgG4 antibodies designed to block the PD-1 receptor (D6, page 474, left-hand column, second paragraph). Both of them were already approved at the relevant date in Europe and the United States for the treatment of melanoma (D6, page 474, right-hand column, first and second paragraph).

3.2.6 D6 also teaches that *“CTLA-4 and PD-1 receptors are both able to regulate T-cell activation, but have distinct mechanisms of action. Consequently, antibodies that inhibit these receptors modulate the T-cell immune response at different levels. Thus, dual blockade of*

CTLA-4 and PD-1 is a reasonable and potentially synergistic therapeutic strategy". The combination of ipilimumab and nivolumab already demonstrated promising results in patients with melanoma (D6, page 474, right-hand column, third paragraph). While patients receiving the combination therapy had a higher incidence of adverse events compared with the monotherapy groups, more serious adverse events could be managed with the use of corticosteroids (D6, page 482, right-hand column, second paragraph).

3.2.7 In conclusion, the skilled person knew that microsatellite instability was associated with better prognosis and was used as a biomarker for PD-1 blockade in colorectal cancer patients. Moreover, the combination of nivolumab and ipilimumab was known to be a reasonable and potentially synergistic therapeutic strategy which had already shown promising results in patients with melanoma.

3.3 The claims

3.3.1 The opposed patent comprises 10 claims. Claims 1 and 10 represent independent claims and claims 2 to 9 refer directly or indirectly back to claim 1.

3.3.2 Independent claim 1 relates to

1. *Nivolumab*

for use in a method of treating a colorectal cancer tumor in a subject, wherein the tumor exhibits a high degree of microsatellite instability ("MSI-H"), wherein the subject is administered nivolumab at a dose of about 3 mg/kg body weight in combination with ipilimumab at a dose of about 1 mg/kg body weight once about every three weeks.

3.3.3 Claim 2 specifies that the tumour is a colon cancer or a rectal cancer. Claim 3 specifies that the tumour exhibits one or more characteristics selected from the group consisting of: (a) the tumour comprises a germline alteration in at least two, at least three, at least four, or at least five DNA mismatch repair genes ("MMR genes"); (b) the tumour comprises a germline alteration in at least 30% of five or more MMR genes; (c) at least one protein encoded by DNA MMR genes is not detected in the tumour; and (d) any combination thereof. Claim 4 specifies that DNA MMR genes comprise MSH2, MLH1, MSH6, PMS2, PMS1, or any combination thereof.

3.3.3 Claim 5 specifies that (i) the subject exhibits a progression-free survival of at least about one month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, or at least about 12 months after the administration or (ii) the subject exhibits an overall survival of at least about one month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, or at least about 12 months after the administration.

3.3.4 Claim 6 specifies that the administration of nivolumab and ipilimumab is followed by an anti-PD-1 antibody monotherapy. Claim 7 specifies that the administration of nivolumab and ipilimumab comprises four doses for each.

3.3.5 Claim 8 specifies that the subject has received one, two, three, four, five or more prior cancer treatments. Claim 9 specifies that the subject has progressed on other cancer treatments.

3.3.6 Independent claim 10 relates to

1. A kit
for use in a method of treating a colorectal cancer tumor in a subject, comprising:
(a) nivolumab; and
(b) ipilimumab
wherein the method is defined as in any one claims 1 to 9.

3.4 The examples

The opposed patent contains 2 examples.

3.4.1 Example 1 discloses a clinical study of nivolumab and ipilimumab in the treatment of patients with metastatic colorectal cancer with and without high microsatellite instability (MSI-H). MSI-H patients were administered 3 mg/kg nivolumab once every 2 weeks in an initial monotherapy stage of treatment. MSI-H patients were then administered 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab once every 3 weeks for a total of 4 doses, followed by 3 mg/kg nivolumab once every two weeks (opposed patent, paragraph [0119] and figure 2). A different dosage protocol was followed for the microsatellite stable (MSS) cohort of patients

(opposed patent, paragraph [0118] and figure 1). The protocol of this trial had already been disclosed in prior-art document D2.¹

3.4.2 The results of the study demonstrated the encouraging activity of both nivolumab monotherapy and nivolumab and ipilimumab combination therapy in patients with MSI-H status. Moreover, both arms demonstrated tolerable safety profiles in relation to the clinical benefit and were consistent with observations in other solid tumours (opposed patent, paragraph [0132]). The interim results of this trial had already been disclosed in prior-art document D1 (see lack of novelty section).

3.4.3 Example 2 discloses that the efficacy and safety of nivolumab in combination with ipilimumab was investigated in an expanded population of patients with MSI-H metastatic colorectal cancer (opposed patent, paragraph [0133]). The results of the expansion cohort confirmed the efficacy and safety of the combination therapy (opposed patent, paragraph [0143]).

3.4.4 In conclusion, the examples show the efficacy and safety of the claimed dosage regimen in colorectal cancer patients with a high degree of microsatellite instability. However, this already belonged to the state of the art at the priority date of the opposed patent.

4. Insufficiency of disclosure

4.1 Claim 5 of the opposed patent specifies that the treated subject exhibits a progression-free survival or an overall survival of a certain length. Therefore, claim 5 attempts to define the subject-matter in terms of the result to be achieved, namely in the form of efficacy for a certain period of time.

4.2 However, the original application does not teach how to select the subjects to be treated or how the treatment should be administered so that the claimed duration of efficacy is achieved. Instead, the original application teaches that only *"In certain embodiments of the disclosure, the therapy of the present disclosure (e.g., administration of an anti-PD-1 antibody alone or in combination with an anti-CTLA-4 antibody) effectively increases the duration of survival of the subject"* (original application, paragraph [0128], emphasis added). Some

¹ The trial was registered on clinicaltrials.gov database with the number NCT02060188 and was known in the field with the acronym CheckMate-142 (D2, title).

exemplary lengths of duration of survival are then listed, without however explaining how a certain duration can be achieved.

4.3 Therefore, the original application fails to teach the technical means needed to provide the specific lengths of survival according to claim 5. This information cannot be found in the common general knowledge either. Hence, the opposed patent does not comply with Article 83 EPC.

5. Lack of novelty

5.1 Claim 1

5.1.1 Document D1 is the abstract of a presentation given at the Annual Meeting of the American Society of Clinical Oncology (ASCO) held in Chicago, Illinois, on 3rd-7th June 2016. Although the meeting started on the priority date of the opposed patent, the conference abstracts were published on the Journal of Clinical Oncology about 2 weeks before, on 20th May 2016, as it is customary for the ASCO annual meeting abstracts (see D1, page 1, middle column, *"Article Citation"*).

5.1.2 D1 discloses the interim results of the clinical trial of example 1 of the opposed patent, CheckMate-142 (D1, title). D1 explains in the background section that evidence supports use of nivolumab (N) in patients with metastatic colorectal cancer (mCRC) with high microsatellite instability (MSI-H). Moreover, nivolumab and ipilimumab (I) have shown favourable safety and efficacy in other tumours. The phase 2 study Checkmate-142 evaluates nivolumab plus $\pm$ ipilimumab in patients with mCRC, MSI-H and non-MSI-H.

5.1.3 D1 further discloses that, in one of the study arms, MSI-H patients received nivolumab 3 mg/kg every 2 weeks ("q2 wk", this regimen is abbreviated as "N3") or nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 2 weeks ("q3 wk", this regimen is abbreviated as "N3+I1") x 4 doses followed by nivolumab 3 mg/kg every 2 weeks until disease progression (PD) or other discontinuation (D1, *"Background"*). Therefore, D1 discloses the drugs, the dosage regimen, the indication and the patient population of claim 1 of the opposed patent.

5.1.4 D1 further discloses in the table on page 2 the interim efficacy results of the trial in 33 MSI-H patients dosed with nivolumab only and in 26 MSI-H patients dosed with the combination therapy. In the combination therapy arm, there were 4 cases of partial response,

17 cases of stable disease and only 2 cases of progressive disease. Neither the median progression-free survival (PFS), nor the median overall survival (OS) had been reached for this group. All patients were still alive after 5 months (5-mo OS rate = 100%).

5.1.5 D1 concludes that *"N and N+I were well tolerated in most pts and demonstrated encouraging clinical activity and survival in MSI-H mCRC"* (D1, *"Conclusions"*). Therefore, D1 discloses the safety and efficacy of the claimed treatment.

5.1.6 In conclusion, Document D1 discloses all features of granted claim 1, taking away its novelty. Hence, claim 1 does not meet the requirements of Article 54 EPC.

5.2 Claims 5-9

5.2.1 Claim 5 specifies that the subject exhibits an overall survival of at least about one month after the administration. D1 discloses the survival all subjects after 5 months.

5.2.2 Claim 6 specifies that the administration of nivolumab and ipilimumab is followed by an anti-PD-1 antibody monotherapy. D1 discloses that the combination treatment is followed by nivolumab (an anti-PD-1 antibody) 3 mg/kg every 2 weeks until disease progression (PD) or other discontinuation (D1, *"Background"*).

5.2.3 Claim 7 specifies that the administration of nivolumab and ipilimumab comprises four doses for each. This is already disclosed in the background of D1.

5.2.4 Claim 8 specifies that the subject has received one, two, three, four, five or more prior cancer treatments. D1 discloses that 92% of MSI-H patients receiving the combination therapy had 2 or more prior regimens (D1, *"Background"*).

5.2.5 Claim 9 specifies that the subject has progressed on other cancer treatments. The patients of D1 must have progressed on the previous treatments, otherwise they would not have been switched to an investigational treatment, as this would have been unethical.

5.2.6 In conclusion, also the additional features of claims 5 to 9 are disclosed in document D1. Therefore, these claims do not comply with Article 54 EPC either.

6. Lack of inventive step

6.1 Claims 1 and 5-9

As explained in the previous section, document D1 is novelty destroying for claims 1 and 5 to 9 of the opposed patent. It is therefore not possible to apply the problem and solution approach for these claims.

6.2 Claims 2-4

6.2.1 As far as claims 2 to 4 are concerned, document D1 represents the closest prior art, since it is directed to the same purpose (the treatment of colorectal cancer in patients with MSI-H) and has the most technical features in common with these claims (see lack of novelty section).

6.2.2 Claim 2 specifies that the tumour is a colon cancer or a rectal cancer. No technical effect is however associated in the opposed patent to the location of the tumour.

6.2.3 Claim 3 specifies that the tumour exhibits certain characteristics in the DNA mismatch repair genes ("MMR genes"). Claim 4 specifies that DNA MMR genes comprise MSH2, MLH1, MSH6, PMS2, PMS1, or any combination thereof. Again, no technical effect is associated with these characteristics of the tumour.

6.2.4 For claims 2 to 4, the objective technical problem to be solved over D1 is thus the provision of a treatment for an alternative type of colorectal cancer with high microsatellite instability.

6.2.5 Document D2, the protocol of the clinical trial of D1, specifically refers to colon cancer in its title.

6.2.6 Moreover, it belongs to the common general knowledge that *"MSI usually arises from either germline mutations in components of the mismatch repair (MMR) machinery (MSH2, MSH6, MLH1, PMS2) in patients with Lynch syndrome or somatic hypermethylation of the MLH1 promoter"* (D5, abstract). Documents D3 and D4 detail further known characteristics of colorectal cancer with high microsatellite instability. I should also be noted that the options recited in claims 3 and 4 encompasses most MSI-H cancers.

6.2.7 The skilled person would have thus expected that the treatment and dosage regimen of D1 were successful also in the types of cancer recited in claims 2 to 4.

6.2.8 Hence, claims 2 to 4 are obvious over D1 in the light of the common general knowledge, optionally in combination with any of D2 to D4. Therefore, claims 2 to 4 of the opposed patent do not meet the requirements of Article 56 EPC.

6.3 Claim 10

6.3.1 Claim 10 is directed to a kit for use in the method of claims 1 to 9, i.e., containing the two medicaments and, usually, instructions on how to use them in combination (opposed patent, paragraph [0113]).

6.3.2 No ingenuity is required for the skilled person to put nivolumab and ipilimumab together in a kit accompanied with instructions to apply the method of claim 1. Therefore, claim 10 is not inventive either and thus does not meet the requirements of Article 56 EPC.

7. **Conclusion**

It has been shown above that the opposed patent is not in accordance with the requirements of Articles 54, 56 and 83 EPC. Therefore, the request to revoke EP 3 464 373 in its entirety is fully justified.

Marco Fachini

Enc.

Documents D1-D6



Notice of opposition to a European patent

I. Patent opposed

Patent No.	EP3464373
Application No.	EP17731359.0
Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)	27 October 2021
Title of the invention	Use of anti-PD-1 antibody in the treatment of patients with colorectal cancer

II. Proprietor of the patent

first named in the patent specification	Bristol-Myers Squibb Company
Opponent's or representative's reference	ESP00567LED

III. Opponent

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Multiple opponents (see additional sheet)	☐	

IV. Authorisation

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Additional representative(s) on additional sheet/see
authorisation

☐

Authorisation(s)

is/are enclosed

☐

has/have been registered under No.

☐

V. Opposition is filed against

the patent as a whole

☒

claim(s) No(s).

VI. Grounds for opposition:

Opposition is based on the following grounds:

(a) the subject-matter of the European patent opposed is not
patentable (Art. 100(a) EPC) because:

• it is not new (Art. 52(1); Art. 54 EPC)

☒

• it does not involve an inventive step (Art. 52(1);
Art. 56 EPC)

☒

• patentability is excluded on other grounds, namely
articles

☐

(b) the patent opposed 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 (Art. 100(b) EPC; see Art.
83 EPC).

☒

(c) the subject-matter of the patent opposed extends beyond
the content of the application/of the earlier application as
filed (Art. 100(c) EPC, see Art. 123(2) EPC).

☐

VII. Facts (Rule 76(2)(c) EPC)

presented in support of the opposition are submitted herewith
on an attached document

☒

VIII. Other requests:

• Oral proceedings are hereby requested auxilarily.

IX. Evidence presented

D1	Other evidence	Overman, M.J. et al., J. Clin. Oncol. 2016, 34(15S), abstract 3501 original file name: D1 Overman, J. Clin. Oncol. 2016, 34(15S), abstract 3501.pdf attached as: Other-evidence-1.pdf
D2	Other evidence	Clinical study record NCT02060188 entitled "A Study of Nivolumab...", version 50, 25th May 2016 original file name: D2 NCT02060188 v. 50 25 May 2016.pdf attached as: Other-evidence-2.pdf
D3	Other evidence	Llosa, N.J. et al., Cancer Discov. 2015, 5(1), 43-51 original file name: D3 Llosa Cancer Discov 2015 5(1) 43-51 (MSI CRC, good).PDF attached as: Other-evidence-3.PDF
D4	Other evidence	Rosenbaum, M.W. et al., Mod. Pathol. 2016, 29 1104-1112 original file name: D4 Rosenbaum Mod Pathol 2016 29 1104-1112.PDF attached as: Other-evidence-4.PDF
D5	Other evidence	Dudley, J.C. et al., Clin. Cancer Res. 2016, 22(4) 813-820 original file name: D5 Dudley Clin Cancer Res 2016 22(4) 813-820.pdf attached as: Other-evidence-5.pdf
D6	Other evidence	Boutros, C. et al., Nat. Rev. Clin. Oncol. 2016, 13(8), 473-86 original file name: D6 Boutros Nat Rev Clin Oncol. 2016 13(8) 473-86.PDF attached as: Other-evidence-6.PDF

X. Payment

Method of payment

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Fees

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010 Opposition fee	1	840.00	840.00
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A Forms

Details:

System file name:

A-1

Form for notice of opposition

ep-oppo.pdf

B Attached document files

Original file name:

System file name:

B-1

1. Facts and arguments

opposition.pdf

OPPO.pdf

C Attached evidence files

Original file name:

System file name:

C-1

1. Other evidence

D1 Overman, J. Clin. Oncol. 2016, 34(15S), Other-evidence-1.pdf abstract 3501.pdf

C-2

2. Other evidence

D2 NCT02060188 v. 50 25 May 2016.pdf Other-evidence-2.pdf

C-3

3. Other evidence

D3 Llosa Cancer Discov 2015 5(1) 43-51 (MSI CRC, good).PDF Other-evidence-3.PDF

C-4

4. Other evidence

D4 Rosenbaum Mod Pathol 2016 29 1104-1112.PDF Other-evidence-4.PDF

C-5

5. Other evidence

D5 Dudley Clin Cancer Res 2016 22(4) 813-820.pdf Other-evidence-5.pdf

C-6

6. Other evidence

D6 Boutros Nat Rev Clin Oncol. 2016 13(8) Other-evidence-6.PDF
473-86.PDF

Signature of opponent or representative

Place München

Date: 26 July 2022

Signed by: Marco Fachini 46014

Association: LEDERER & KELLER PATENTANWÄLTE PARTNERSCHAFT MBB

Representative name: Marco Fachini

Capacity: (Representative)



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II. Proprietor of the patent

first named in the patent specification	Bristol-Myers Squibb Company
Opponent's or representative's reference	PAJAR.0048

III. Opponent

Name	Pajaro Limited
Address:	12 New Fetter Lane London Greater London EC4A 1JP United Kingdom
State of residence or of principal place of business	United Kingdom
Multiple opponents (see additional sheet)	☐

IV. Authorisation

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Additional representative(s) on additional sheet/see
authorisation

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Authorisation(s)

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has/have been registered under No.

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V. Opposition is filed against

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☒

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☒

VII. Facts (Rule 76(2)(c) EPC)

presented in support of the opposition are submitted herewith
on an attached document

☒

VIII. Other requests:

• Oral proceedings are hereby requested auxilially.

IX. Evidence presented

BB01	Patent document	EP3 464 373 (B1) original file name: BB01 - EP 3 464 373 B1.PDF attached as: Published-Evidence-1.PDF
BB01a	Other evidence	Feature analyses of claims 1+10 of the opposed patent original file name: BB01a - Feature analyses.PDF attached as: Other-evidence-1.PDF
BB02	Patent document	WO2017/210637 (A1) original file name: BB02 - WO 2017_210637 A1.PDF attached as: Published-Evidence-2.PDF
BB03	Patent document	US62/345,662 (A) original file name: BB03 - US 62_345,662 (prio).PDF attached as: Published-Evidence-3.PDF
BB04	Other evidence	Meeting Abstract; ASCO Annual Meeting I; Journal of Clinical Oncology, Volume 36, Issue 15 suppl; published online May 20, 2016 original file name: BB04 - Journal of Clinical Oncology.PDF attached as: Other-evidence-2.PDF
BB05	Other evidence	clinical trials NCT02060188 (published on 25 May 2016) original file name: BB05 - History of Changes for Study NCT02060188, 25 May 2016.PDF attached as: Other-evidence-3.PDF
BB06	Other evidence	List of medical abbreviations Q (excerpt of Wikipedia) original file name: BB06 - List of medical abbreviations Q - Wikipedia.PDF attached as: Other-evidence-4.PDF
BB07	Other evidence	Wolchok et al., N Engl J Med 2013, 369, 2, 122-133 original file name: BB07 - Wolchok et al., 2013.PDF attached as: Other-evidence-5.PDF
BB08	Other evidence	Wolchok, Meeting Abstract 2016 ASCO Annual Meeting I (published on 20 May 2016) original file name: BB08 - Wolchok, 2016.PDF attached as: Other-evidence-6.PDF
BB09	Other evidence	Ansell et al., N Engl J Med 2015, 372, 4, 311-319 original file name: BB09 - Ansell et al., 2015.PDF attached as: Other-evidence-7.PDF
BB10	Other evidence	Le et al., N Engl J Med 2015, 372, 26, 2509-2520 original file name: BB10 - Le et al., 2015.PDF attached as: Other-evidence-8.PDF
BB11	Patent document	WO2016/077553 (A1) original file name: BB11 - WO 2016_077553 A1.PDF attached as: Published-Evidence-4.PDF
BB12	Other evidence	Llosa et al., Cancer Discov 2015, 5(1), 43-51 original file name: BB12 - Llosa et al., 2015.PDF attached as: Other-evidence-9.PDF

BB13	Other evidence	Postow, ASCO EDUCATIONAL BOOK, 2015, 76-83 original file name: BB13 - Postow et al., 2015.PDF attached as: Other-evidence-10.PDF
BB14	Other evidence	Hamid et al., N Engl J Med 2013, 369, 2, 134-144 original file name: BB14 - Hamid et al., 2013.PDF attached as: Other-evidence-11.PDF
BB15	Other evidence	Dudley et al., Clin Cancer Res 2016, 22(4); 813-820 (published on 15 February 2016) original file name: BB15 - Dudley et al., 2016.PDF attached as: Other-evidence-12.PDF
BB16	Other evidence	Pawlik et al., Disease Markers 2004, 20, 199-206 original file name: BB16 - Pawlik et al., 2004.PDF attached as: Other-evidence-13.PDF
BB17	Other evidence	Rosenbaum et al., Modern Pathology 2016, 29, 1104-1112 (published on 20 May 2016) original file name: BB17 - Rosenbaum et al., 2016.PDF attached as: Other-evidence-14.PDF
BB18	Other evidence	Karahan et al., Int J Clin Exp Pathol 2015, 8(4), 4044-4053 original file name: BB18 - Karahan et al., 2015.PDF attached as: Other-evidence-15.PDF
BB19	Other evidence	McDermott et al., Cancer Medicine 2013, 2(5), 662-673 original file name: BB19 - McDermott et al., 2013.PDF attached as: Other-evidence-16.PDF
BB20	Other evidence	Banerjee et al., PLoS ONE, 2008, 3(7), e2740, 1-16 original file name: BB20 - Banerjee et al., 2008.PDF attached as: Other-evidence-17.PDF
BB21	Other evidence	Demetri et al., J Clin. Oncol 2009, 27(25) 4188-4196 original file name: BB21 - Demetri et al., 2009.PDF attached as: Other-evidence-18.PDF
BB22	Other evidence	Raedler et al., Am Health Drug Benefits. 2015;8(Spec Feature):180-3 original file name: BB22 - Raedler et al., 2015.PDF attached as: Other-evidence-19.PDF
BB23	Other evidence	Hammers et al., Annals of Oncology 2014, 25 (Supplement 4): iv361-iv372 original file name: BB23 - Hammers et al., 2014.PDF attached as: Other-evidence-20.PDF
BB24	Other evidence	Meeting Abstract; 2016 ASCO Annual Meeting I; Journal of Clinical Oncology, 34, No. 15 suppl; published online May 20, 2016 original file name: BB24 - Meeting abstract, 2016.PDF attached as: Other-evidence-21.PDF

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ep-oppo.pdf

B Attached document files

Original file name:

System file name:

B-1

1. Facts and arguments

220726 Pajaro - Opposition against EP 3
464 373.pdf

OPPO.pdf

C Attached evidence files

Original file name:

System file name:

C-1

1. Patent document

BB01 - EP 3 464 373 B1.PDF

Published-Evidence-1.PDF

C-2

2. Patent document

BB02 - WO 2017_210637 A1.PDF

Published-Evidence-2.PDF

C-3

3. Patent document

BB03 - US 62_345,662 (prio).PDF

Published-Evidence-3.PDF

C-4

4. Patent document

BB11 - WO 2016_077553 A1.PDF

Published-Evidence-4.PDF

C-5

1. Other evidence

BB01a - Feature analyses.PDF

Other-evidence-1.PDF

C-6

2. Other evidence

BB04 - Journal of Clinical Oncology.PDF

Other-evidence-2.PDF

C-7	3. Other evidence	BB05 - History of Changes for Study NCT02060188, 25 May 2016.PDF	Other-evidence-3.PDF
C-8	4. Other evidence	BB06 - List of medical abbreviations Q - Wikipedia.PDF	Other-evidence-4.PDF
C-9	5. Other evidence	BB07 - Wolchok et al., 2013.PDF	Other-evidence-5.PDF
C-10	6. Other evidence	BB08 - Wolchok, 2016.PDF	Other-evidence-6.PDF
C-11	7. Other evidence	BB09 - Ansell et al., 2015.PDF	Other-evidence-7.PDF
C-12	8. Other evidence	BB10 - Le et al., 2015.PDF	Other-evidence-8.PDF
C-13	9. Other evidence	BB12 - Llosa et al., 2015.PDF	Other-evidence-9.PDF
C-14	10. Other evidence	BB13 - Postow et al., 2015.PDF	Other-evidence-10.PDF
C-15	11. Other evidence	BB14 - Hamid et al., 2013.PDF	Other-evidence-11.PDF
C-16	12. Other evidence	BB15 - Dudley et al., 2016.PDF	Other-evidence-12.PDF
C-17	13. Other evidence	BB16 - Pawlik et al., 2004.PDF	Other-evidence-13.PDF
C-18	14. Other evidence	BB17 - Rosenbaum et al., 2016.PDF	Other-evidence-14.PDF
C-19	15. Other evidence	BB18 - Karahan et al., 2015.PDF	Other-evidence-15.PDF
C-20	16. Other evidence	BB19 - McDermott et al., 2013.PDF	Other-evidence-16.PDF
C-21	17. Other evidence	BB20 - Banerjee et al., 2008.PDF	Other-evidence-17.PDF
C-22	18. Other evidence	BB21 - Demetri et al., 2009.PDF	Other-evidence-18.PDF
C-23	19. Other evidence	BB22 - Raedler et al., 2015.PDF	Other-evidence-19.PDF
C-24	20. Other evidence	BB23 - Hammers et al., 2014.PDF	Other-evidence-20.PDF
C-25	21. Other evidence	BB24 - Meeting abstract, 2016.PDF	Other-evidence-21.PDF

Signature of opponent or representative

Place

Munich

Date:

26 July 2022

Signed by:

Andreas Obermeier 50235

Association: Bird & Bird LLP

Representative name: Dr. Andreas Obermeier

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Munich, 26 July 2022

Our ref. (please always state): PAJAR.0048

European patent EP 3 464 373 B1
Application No. 17 731 359.0
Patentee: Bristol-Myers Squibb Company
Opponent: Pajaro Limited

The facts and arguments (point VII) for the

OPPOSITION

filed in the name and on behalf of **Pajaro Limited**, 12 New Fetter Lane, London, EC4A 1JP, United Kingdom, against the European patent EP 3 464 373 B1 entitled “Use of anti-PD-1 antibody in the treatment of patients with colorectal cancer” (European patent application No. 17 731 359.0) of Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, NJ 08543 / US, are presented in the following.

A.

Requests

- 1) It is requested to revoke the patent in its entirety, based on the grounds that:
 - i. its subject matter is not patentable within the terms of Arts. 52 to 57 EPC (Art. 100(a) EPC), since it is neither novel nor based on an inventive step (Arts. 54 and 56 EPC);
 - ii. the European 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 (Art. 100(b) EPC, Art. 83 EPC); and
 - iii. the subject matter of the European patent extends beyond the content of the application as filed (Art. 100(c) EPC, Art. 123(2) EPC).
- 2) Oral proceedings pursuant to Art. 116 EPC are requested.

The opposition fee is to be debited from our deposit account No. 28002046 in the name of Bird & Bird LLP.

B.

Relevant References

The opposition is based on the following prior art:

- BB1** EP 3 464 373 B1 (opposed patent)
- BB1a** Feature analysis of claim 1 of the opposed patent
- BB2** WO 2017/210637 A1 (originally filed application)
- BB3** US 62/345,662 (priority application)
- BB4** Meeting Abstract; 2016 ASCO Annual Meeting I; Journal of Clinical Oncology, Volume 34, Issue 15 suppl; published online May 20, 2016 (see https://ascopubs.org/doi/10.1200/JCO.2016.34.15_suppl.3501)

- BB5** clinical trials NCT02060188 (published on 25 May 2016)
- BB6** List of medical abbreviations (excerpt of Wikipedia)
- BB7** Wolchok et al. N Engl J Med 2013, 369, 2, 122-133
- BB8** Meeting Abstract; 2016 ASCO Annual Meeting I; Journal of Clinical Oncology, Volume 34, Issue 15 suppl; published online May 20, 2016 (see https://ascopubs.org/doi/10.1200/JCO.2016.34.15_suppl.9505)
- BB9** Ansell et al. N Engl J Med 2015, 372, 4, 311-319
- BB10** Le et al. N Engl J Med 2015, 372, 26, 2509-2520
- BB11** WO 2016/077553 (published on 19 May 2016)
- BB12** Llosa et al. Cancer Discov 2015, 5(1), 43-51
- BB13** Postow ASCO EDUCATIONAL BOOK, 2015, 76-83
- BB14** Hamid et al. N Engl J Med 2013, 369, 2, 134-144
- BB15** Dudley et al. Clin Cancer Res 2016, 22(4); 813-820 (published on 15 February 2016)
- BB16** Pawlik et al. Disease Markers 2004, 20, 199-206
- BB17** Rosenbaum et al. Modern Pathology 2016, 29, 1104-1112 (published on 20 May 2016)
- BB18** Karahan et al. Int J Clin Exp Pathol 2015, 8(4), 4044-4053
- BB19** McDermott et al. Cancer Medicine 2013, 2(5), 662-673
- BB20** Banerjee et al. PLoS ONE, 2008, 3(7), e2740, 1-16
- BB21** Demetri et al. J Clin. Oncol. 2009, 27(25) 4188-4196
- BB22** Raedler et al. Am Health Drug Benefits. 2015; 8 (Spec Feature), 180-183
- BB23** Hammers et al. Annals of Oncology 2014, 25 (Supplement 4): iv361-iv372
- BB24** Meeting Abstract; 2016 ASCO Annual Meeting I; Journal of Clinical Oncology, 34, No. 15 suppl; published online May 20, 2016 (see https://ascopubs.org/doi/10.1200/JCO.2016.34.15_suppl.3001)

C.

Feature analysis and subject matter of the claims

I.

The opposed patent

1. The opposed patent EP 3 464 373 B1 (submitted as **BB1**) is entitled “Use of anti-PD-1 antibody in the treatment of patients with colorectal cancer”. The opposed patent derives from PCT application PCT/US2017/035822 (submitted as **BB2**), filed on 2 June 2017 and claims priority of United States patent application US 62/345,662 (submitted as **BB3**), filed on 3 June 2016.
2. The opposed patent relates to nivolumab for use in methods for treating a tumor derived from a colorectal cancer exhibiting a high degree of microsatellite instability (MSI-H) in a subject in need thereof. Nivolumab is administered in combination with ipilimumab (cf. para. [0001] of opposed patent).

II.

The subject matter of the claims

3. The opposed patent comprises two quasi-independent claims.
4. Independent claim 1 reads as follows:
 1. *Nivolumab*
 2. *for use in a method of treating a colorectal cancer tumor in a subject, wherein*
 - 2.1 *the tumor exhibits a high degree of microsatellite instability ("MSI-H"), wherein*
 - 2.2 *the subject is administered*
 - 2.2.1 *nivolumab at a dose of about 3 mg/kg body weight in combination with*
 - 2.2.2 *ipilimumab at a dose of about 1 mg/kg body weight once about every three weeks.*

Bird & Bird

16 July 2022
page 5

5. According to the claim wording the administration of nivolumab is only limited by its dose (see feature 2.2.1) and the administration of ipilimumab is limited by both its dose and its interval (see feature 2.2.2). The phrase "*once about every three weeks*" stated in context with ipilimumab does not apply for nivolumab as well, since it should have been stated there. We refer to [0170] of **BB2** according to which the interval is mentioned for both nivolumab and ipilimumab.
6. Independent claim 10 reads as follows:
 1. *A kit for use in a method of treating a colorectal cancer tumor in a subject, comprising:*
 2. *nivolumab; and*
 3. *ipilimumab*
 4. *wherein the method is defined as in any one claims 1 to 9.*
7. These feature analyses are enclosed as a separate document (**Exhibit BB1a**).
8. Nivolumab (formerly designated 5C4, BMS-936558, MDX-1106, or ONO-4538) is a fully human IgG4 (S228P) PD-1 immune checkpoint inhibitor antibody that selectively prevents interaction with PD-1 ligands (PD-L1 and PD-L2), thereby blocking the downregulation of antitumor T-cell functions (cf. [0004] of the opposed patent). Thus, nivolumab is an antibody that binds specifically to Programmed Death-1 receptor (PD-1) and inhibits PD-1 activity ("anti-PD-1 antibody") (cf. [0007] of the opposed patent).
9. Ipilimumab is an antibody that specifically binds to Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) and inhibits CTLA-4 activity ("anti-CTLA-4 antibody") (cf. [0007] of the opposed patent).
10. According to claim 1, the tumor exhibits a high degree of microsatellite instability ("MSI-H"). According to [0061] of the opposed patent, microsatellite instability is the condition of genetic hypermutability that results from impaired DNA mismatch repair (MMR). In certain embodiments, the subject receiving tumor treatment has a high degree of microsatellite instability (MSI-H) and has at least one mutation in genes MSH2, MLH1, MSH6, PMS2, or PMS1 ([0061] of the opposed patent).

11. In section D below, we will show that the claimed subject matter of the opposed patent is not originally disclosed. In section E below, we will demonstrate that the claimed subject matter was not novel over **BB4** and in section F, below, that the claimed subject matter is at least not inventive when starting from **BB5**.
12. In detail:

D.

Added matter (Art. 123(2) EPC)

I.

Claim 1

13. Claim 1 as granted requires that nivolumab is administered at a dose of about 3 mg/kg body weight in combination with ipilimumab at a dose of about 1 mg/kg body weight once about every three weeks.
14. Consequently, the claim requires that ipilimumab is administered once every three weeks, whereas the administration intervals of nivolumab have not been specified in the claim, even though it is required by the original disclosure (cf. [0035] and [0170] of BB2):

[0035]

“E18. The method of embodiment E17, wherein the anti-PD-1 antibody is administered at a dose of about 3 mg/kg body weight once about every 3 weeks.”

-emphasis added-

[0170]

“In other embodiments, the anti-PD-1 antibody is administered at 3 mg/kg once every 3 weeks and the anti-CTLA-4 antibody is administered at 1 mg/kg once every 3 weeks.”

-emphasis added-

15. Thus, an intermediate generalization has been claimed which is not allowable with the present disclosure.
16. Consequently, the subject matter of claim 1 as granted is not originally disclosed.

II. Claim 10

17. The kit according to claim 10 as granted is specified as being used in the method of claim 1 and by comprising nivolumab and ipilimumab. Due to the dependency from claim 1, nivolumab is to be administered in the method at a dose of about 3 mg/kg body weight in combination with ipilimumab at a dose of about 1 mg/kg body weight. Nevertheless, the dosage of nivolumab and ipilimumab comprised in the kit according to claim 10 is not limited.
18. In contrast thereto, claim 15 as originally filed reads as follows:

“A kit for treating a patient afflicted with a tumor derived from colorectal cancer, wherein the tumor exhibits a high degree of microsatellite instability (“MSI-H”), the kit comprising:

(a) a dosage ranging from 0.1 mg/kg to 10 mg/kg body weight of an anti-PD-1 antibody;

(b) a dosage ranging from 0.1 mg/kg to 10 mg/kg body weight of an anti-CTLA-4 antibody; and

(c) instructions for using the anti-PD-1 antibody and the anti-CTLA-4 antibody according to any one of claims 8-14.”
19. Consequently, the dosages of anti-PD-1 antibody and anti-CTLA-4 antibody comprised in the kit were omitted (features (a) and (b)). Additionally, the instructions (feature (c)) have been omitted in claim 10 as granted.
20. Thus, intermediate generalizations have been claimed which are not allowable with the present disclosure.
21. Consequently, the subject matter of claim 10 as granted is not originally disclosed.

E.

Lack of novelty (Art. 54 EPC, Art. 100(a) EPC)

22. The opposed patent lacks novelty (Art. 54 EPC, Art. 100(a) EPC) over Meeting Abstract; 2016 ASCO Annual Meeting I; Journal of Clinical Oncology, Volume 34, Issue 15 suppl. **(BB4)** (see also https://ascopubs.org/doi/10.1200/JCO.2016.34.15_suppl.3501).
23. **BB4** was published on 20 May 2016 and is therefore prior art under Art. 54(2) EPC, irrespectively of whether the priority (priority date: 3 June 2016) of the opposed patent is valid.

I.

Claim 1

24. **BB4** discloses interim results of the CheckMate-142 study (see title of BB4).
25. CheckMate-142 is the name of “*A Study of Nivolumab Alone or Nivolumab Combination Therapy in Colon Cancer That Has Come Back or Has Spread*”. Information on said study can be accessed at the website of ClinicalTrials.gov (see <https://clinicaltrials.gov/ct2/show/NCT02060188>). The disclosure content of the website of ClinicalTrials.gov regarding the clinical trials NCT02060188 as published on 25 May 2016 is submitted as **BB5**.
26. The title of **BB4** reads as follows:

“Nivolumab ± ipilimumab in treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): CheckMate-142 interim results.”
27. The patients received either (a) nivolumab (“N”) alone or (b) in combination with ipilimumab (“I”) (see abstract, “Methods” of BB4):

“MSI-H pts received N 3 mg/kg q2 wk (N3) or N 3 mg/kg + I 1 mg/kg q3 wk (N3+I1) x 4 doses followed by N3 until disease progression (PD) or other discontinuation.”

Bird & Bird

16 July 2022
page 9

28. The terms “q2 wk” and “q3 wk” are commonly used medical abbreviations which is evidenced by **BB6** (excerpt of Wikipedia: List of medical abbreviations: Q; 3rd entry “q2wk”), **BB20** (Banerjee et al. PLoS ONE, 2008, 3(7), e2740, 1-16; see page 2, left col, section “COP-1 Immunization”) and **BB21** (Demetri et al. J Clin. Oncol 2009 27(25) 4188-4196; see abbreviations below table 1). The term “q2 wk” stands for “once every 2 weeks” and the term “q3 wk” stands for “once every 3 weeks”.
29. Consequently, **BB4** discloses that patients with metastatic colorectal cancer (mCRC) having a high microsatellite instability (MSI-H) received – four doses each – nivolumab (N) at a dose of 3 mg/kg and ipilimumab (I) at a dose of 1 mg/kg once every three weeks (“N3+I1”). Thus, features 1, 2.2, 2.2.1 and 2.2.2 of claim 1 of the opposed patent are disclosed in **BB4**.
30. According to **BB4** the treatment was effective with all MSI-H patients (100%) in the N3 + I3 group surviving after 5 months, whereas in the N3 group the 5-months OS was 75% (see table of BB4):

	N3 (n = 33)	N3 + I1 (n = 26)
4-month PFS rate	55 %	80 %
5-month OS rate	75 %	100 %

31. In addition, the above data show that the progression-free survival (PFS) and overall survival (OS) rate of patients with high microsatellite instability (MSI-H) which received the combination of nivolumab and ipilimumab lasts longer than those of patients with MSI-H having received nivolumab alone.
32. Accordingly, the authors of **BB4** concluded (see chapter “Conclusion” of BB4):

*“N and N + I (annotation: N = nivolumab; I = ipilimumab) were well tolerated in most pts (annotation: pts = patients)” **and demonstrated encouraging clinical activity and survival in MSI-H mCRC** (annotation: MSI-H = high microsatellite instability; mCRC = metastatic colorectal cancer).”*

-annotations added-

33. Thus, features 2 and 2.1 of claim 1 of the opposed patent have also been disclosed in **BB4**. Consequently, all features of claim 1 of the opposed patent are disclosed in **BB4** and as such, the subject matter of claim 1 of the opposed patent is not novel over **BB4**.

II.

Claim 2

34. In claim 2 of the opposed patent, the tumor is specified as colon cancer or rectal cancer.
35. **BB4** discloses that the patients treated suffer from colorectal cancer (see e.g., title or section "Background" of BB4). Colorectal cancer starts in the colon or the rectum. Accordingly, these cancers can be called colon cancer or rectal cancer, depending on where they start. We refer to para. [0057] of the opposed patent.
36. Thus, the results of the CheckMate-142 study are based on patients who have colon cancer and/or rectal cancer.
37. Thus, all features of claim 2 of the opposed patent are disclosed in **BB4** and as such, the subject matter of claim 2 of the opposed patent is not novel over **BB4**.

III.

Claims 3 and 4

38. According to claim 3 of the opposed patent, the tumor exhibits one or more characteristics selected from the group consisting of:
- (a) the tumor comprises a germline alteration in at least two, at least three, at least four, or at least five DNA mismatch repair genes ("MMR genes");
 - (b) the tumor comprises a germline alteration in at least 30% of five or more MMR genes;
 - (c) at least one protein encoded by DNA MMR genes is not detected in the tumor; and
 - (d) any combination thereof.

Bird & Bird

16 July 2022
page 11

39. According to claim 4, the DNA MMR genes shall comprise MSH2, MLH1, MSH6, PMS2, PMS1, or any combination thereof.
40. A person skilled in the art knows that microsatellite instability goes along with germline mutations. The genetic basis for instability in MSI tumors is an inherited germline alteration in any one of the five human MMR genes: MSH2, MLH1, MSH6, PMS2, and PMS1. We refer to **BB15** (Dudley et al. Clin Cancer Res; 22(4); 813–820) and **BB16** (Pawlik et al. Disease Markers 20 (2004) 199–206):

See page 813, abstract of **BB15**:

MSI usually arises from either germline mutations in components of the mismatch repair (MMR) machinery (MSH2, MSH6, MLH1, PMS2) in patients with Lynch syndrome or somatic hypermethylation of the MLH1 promoter.

-emphasis added-

Abstract of **BB16**:

“Microsatellite instability (MSI) is a well-recognized phenomenon that is classically a feature of tumors in the hereditary non-polyposis colorectal syndrome. Ten to 15% of sporadic colorectal cancers, however, will have MSI.”

-emphasis added-

41. Furthermore, according to **BB18** (Karahana et al. Int J Clin Exp Pathol 2015;8(4):4044-4053) the relationship between MLH-1, MSH-2, PMS-2, MSH-6 expression and clinicopathological features in colorectal cancer was investigated (see title and abstract of BB18).
42. Thus, the subject matters of claims 3 and 4 of the opposed patent are not novel over **BB4**. In case the subject matter of these claims was considered to be novel, which opponent does not concede, it at least would not have been inventive to use the treatment regimen of **BB4** in patients having known alterations in genes related to the MSI phenotype.

IV.

Claim 5

43. According to claim 5 (i) the subject exhibits a progression-free survival of at least about one month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, or at least about 12 months after the administration **or** (ii) the subject exhibits an overall survival of at least about one month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, or at least about 12 months after the administration.
44. **BB4** discloses a progression-free survival of at least four months for 80% of the treated patients and an overall survival of five months for 100% of the treated patients.
45. Thus, the subject matter of claim 5 of the opposed patent is not novel over **BB4**.

V.

Claim 6

46. Claim 6 requires that the administration of nivolumab and ipilimumab is followed by an anti-PD-1 antibody monotherapy.
47. In **BB4** the combination therapy was followed by nivolumab treatment (see section “Methods” of BB4). Nivolumab is an anti-PD-1 antibody ([0004] and [0007] of the opposed patent).
48. Thus, the subject matter of claim 6 of the opposed patent is not novel over **BB4**.

VI.

Claim 7

49. According to claim 7, the administration of nivolumab and ipilimumab comprises four doses for each.

- 50. In **BB4** four doses of nivolumab and ipilimumab were administered (see section “Methods” of BB4).
- 51. Thus, the subject matter of claim 7 of the opposed patent is not novel over **BB4**.

VII. Claims 8 and 9

- 52. According to claim 8, the subject has received one, two, three, four, five or more prior cancer treatments.
- 53. According to claim 9 the subject has progressed on other cancer treatments.
- 54. In **BB4** the patients received one or more prior treatments and patients have been included who have progressed thereon (see section “Methods” of BB4: “*intolerance/progression on ≥ 1 tx*”).
- 55. Thus, the subject matters of claims 8 and 9 of the opposed patent are not novel over **BB4**.

VIII. Claim 10

- 56. According to claim 10, the kit comprises nivolumab and ipilimumab and is used for a method as defined in claims 1 to 9.
- 57. **BB4** teaches the use of the claimed two active ingredients nivolumab and ipilimumab for the treatment of colorectal cancer. In light of the teachings of **BB4**, they were known as a composition (“kit-of-parts”). All arguments brought forward in context with claim 1 also apply *mutatis mutandis* for claim 10.
- 58. Thus, the subject matter of claim 10 of the opposed patent is not novel over **BB4**. In case the subject matter of claim 10 was considered to be novel, which opponent does not concede, it at least would not have been inventive as all the kit parts and use were

disclosed in **BB4** and it would have been obvious to one of skill in the art to provide them in kit format in light of the teachings of **BB4**.

F.

Lack of inventive step (Art. 56 EPC, Art. 100(a) EPC)

59. Should the Opposition Division unexpectedly be of the opinion that **BB4** is not novelty destroying for claims 1 to 10 as granted (which we deny), we will show in the following that the claimed subject matter was obvious starting from **BB4** or the clinical trials NCT02060188, which are also called “Checkmate-142” (**BB5**).

I.

Starting from **BB4**

60. As explained above, **BB4** discloses every feature of claims 1 to 10 as granted. If the Opposition Division unexpectedly concludes that one or more features are missing (which we deny), then this distinguishing feature will be obvious over the common general knowledge or anyone of **BB5**, **BB7** to **BB19**, and **BB22** to **BB24**.
61. Thus, the subject-matters of claims 1 to 10 are not inventive over **BB4** in combination with the common general knowledge or anyone of **BB5**, **BB7** to **BB19**, and **BB22** to **BB24**.

II.

Starting from **BB5**

62. **BB5** was published on 25 May 2016 and is therefore prior art under Art. 54(2) EPC, irrespectively of whether the priority (priority date: 3 June 2016) of the opposed patent is valid.

(1)

Claim 1

(a)

Disclosure content

63. **BB5** discloses a study of nivolumab and nivolumab plus ipilimumab in recurrent and metastatic colon cancer (CheckMate 142) (see title of BB5).
64. The patients treated were to receive nivolumab 3mg/Kg IV combined with ipilimumab 1 mg/Kg IV every 3 weeks for 4 doses followed by nivolumab 3mg/Kg IV every 2 weeks until disease progression (see page 11, “Dose Level 2b” of BB5). Thus, features 1, 2.2, 2.2.1 and 2.2.2 of claim 1 of the opposed patent are disclosed in **BB5**.

(b)

Difference (if any)

65. The only difference, if any, between the subject matter of claim 1 and **BB5**, is that in claim 1 the claimed therapeutic efficacy is explicitly stated that one expected to achieve in the clinical study (“treating a colorectal cancer tumor”; features 2 and 2.1). If subject-matter of claim 1 of the opposed patent is found to be novel over the teachings of **BB5**, it is not inventive over **BB5** in combination with **BB4** or anyone of BB7 to BB14, BB17 to BB19, and BB22 to BB24, since the person skilled in the art had a reasonable expectation of success that the treatment regimen of **BB5** will have said therapeutic efficacy as discussed in detail below.

(c)

Technical problem

66. The technical problem is the provision of a treatment of colorectal cancer.

(d)

It was expected that the treatment of BB5 was therapeutically effective

67. The subject-matter of claim 1 of the opposed patent is not inventive over **BB5** in combination with **BB4** or anyone of BB7 to BB14, BB17 to BB19, and BB22 to BB24,

since the person skilled in the art had a reasonable expectation of success that the treatment regimen of **BB5** will have said therapeutic efficacy.

(I)

IN COMBINATION WITH **BB4**

68. In order to show the efficacy of the therapy as disclosed in **BB5** we refer to **BB4** (see marg. nos. 25 to 32, above). The authors of **BB4** concluded (see chapter “Conclusion”):

“N and N + I (annotation: N = nivolumab; I = ipilimumab) were well tolerated in most pts (annotation: pts = patients”) and demonstrated encouraging clinical activity and survival in MSI-H mCRC (annotation: MSI-H = high microsatellite instability; mCRC = metastatic colorectal cancer).”

-annotations added-

69. Thus, patients suffering from colorectal cancer with high degree of microsatellite instability have been successfully treated by a combination of nivolumab and ipilimumab. We refer to our arguments made in context with our attack based on lack of novelty over **BB4** (see chapter E, above)
70. Consequently, subject-matter of claim 1 of the opposed patent is not inventive over **BB5** in combination with **BB4**.

(II)

IN COMBINATION WITH **BB7 TO BB14, BB17 TO BB19 AND BB22 TO BB24**

71. In addition, the above additional references teach nivolumab and/or ipilimumab to be effective in treating other types of cancer. The cited references also teach colorectal cancer with microsatellite instability can be treated by a combination of PD1 and CTLA-4 inhibitors. And in light of the cited prior art references, nivolumab and ipilimumab were known as effective PD1 and CTLA-4 inhibitors, respectively, at various dosages including those presently claimed in other cancers. Furthermore, in view of the prior art teachings, the antibodies can be effectively administered in the claimed dosages.

Bird & Bird

16 July 2022
page 17

72. Thus, it was obvious to use a combination of nivolumab and ipilimumab in the dosage regime for treating colorectal cancer as claimed in claim 1 as granted.

73. In detail:

(aa)

Nivolumab and ipilimumab were known as being effective in other cancers

74. Nivolumab and ipilimumab were known as being effective in other cancers.

75. **BB7** (Wolchok et al. N Engl J Med 2013, 369, 2, 122-133) discloses the following (page 122, abstract, chapter “CONCLUSIONS” of BB7):

“Concurrent therapy with nivolumab and ipilimumab had a manageable safety profile and provided clinical activity that appears to be distinct from that in published data on monotherapy, with rapid and deep tumor regression in a substantial proportion of patients. (Funded by Bristol-Myers Squibb and Ono Pharmaceutical; ClinicalTrials.gov number, NCT01024231.)”

-emphasis added-

76. Said reference confirms the efficacy of ipilimumab and nivolumab in treating cancers (page 123, left col, 1st para. of BB7):

“Escape from immune surveillance is a recognized feature of cancer; therefore, the development of therapies to enhance tumor immunity is a rational treatment strategy. Immune checkpoint blockade is one approach that has induced regressions in several types of cancer. Ipilimumab, a fully human, IgG1 monoclonal antibody blocking cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), improved overall survival in patients with advanced melanoma. Nivolumab, a fully human IgG4 antibody blocking the programmed death 1 (PD-1) receptor, produced durable objective responses in patients with melanoma, renal-cell cancer, and non-small-cell lung cancer.”

-emphasis added-

77. Additionally, it is stated that the proteins CTLA-4 and PD-1 appear to play complementary roles in regulating adaptive immunity which make antibodies regulating their expression as effective therapeutic agents in treating cancer (see page 123, left col, 2nd para. of BB7):

Bird & Bird

16 July 2022
page 18

“CTLA-4 and PD-1 appear to play complementary roles in regulating adaptive immunity. Whereas PD-1 contributes to T-cell exhaustion in peripheral tissues, CTLA-4 inhibits at earlier points in T-cell activation. In preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity than blockade of either pathway alone.”

78. This is evidenced by **BB13** (Postow ASCO EDUCATIONAL BOOK, 2015, pages 76-83) (see page 76, overview):

“Immune checkpoint-blocking antibodies that enhance the immune system’s ability to fight cancer are becoming important components of treatment for patients with a variety of malignancies. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) was the first immune checkpoint to be clinically targeted, and ipilimumab, an inhibitor of CTLA-4, was approved by the U.S. Food and Drug Administration (FDA) for patients with advanced melanoma. The programmed cell death-1 (PD-1) receptor and one of its ligands, PD-L1, more recently have shown great promise as therapeutic targets in a variety of malignancies. Nivolumab and pembrolizumab recently have been FDA approved for patients with melanoma and additional approvals within this therapeutic class are expected.”

-emphasis added-

79. It has also been reported that based on CheckMate-067 the combination of nivolumab and ipilimumab is even better than each agent alone when treating melanoma (Meeting Abstract; 2016 ASCO Annual Meeting I; Journal of Clinical Oncology, Volume 34, Issue 15 suppl; published online May 20, 2016 (see https://ascopubs.org/doi/10.1200/JCO.2016.34.15_suppl.9505)) submitted as **BB8**:

“Conclusions: NIVO+IPI (annotation: NIVO = nivolumab; IPI = ipilimumab) and NIVO alone continue to demonstrate superior clinical activity vs IPI monotherapy. NIVO+IPI appears to have greater efficacy than either agent alone, regardless of PD-L1 expression or BRAF mutation status.”

-annotation added-

80. In **BB9** (Ansell et al. N Engl J Med 2015, 372, 4, pages 311-319) the efficacy of nivolumab has been shown in Relapsed or Refractory Hodgkin’s Lymphoma (see title of BB9). It was known that in Hodgkin’s lymphomas PD-1 is overexpressed and the PD-1 blockade is one way for treating said cancer (see page 312, left col., last para. of BB9):

Bird & Bird

16 July 2022
page 19

“The complementary mechanisms of PD-1 ligand overexpression in Hodgkin’s lymphoma suggest that this disease may have genetically determined vulnerability to PD-1 blockade.”

81. Said PD-1 blockade was effectively mediated by nivolumab (see page 316, right col., last para. of BB9):

“In this study, we found that nivolumab-mediated PD-1 blockade was a highly effective therapy in patients with Hodgkin’s lymphoma, a disease with a genetic basis for PD-1 ligand overexpression and a marked but ineffective inflammatory and immune-cell infiltrate.”

-emphasis added-

82. Accordingly, the authors concluded that nivolumab as anti-PD-1 antibody is effective in treating relapsed or refractory Hodgkin’s lymphoma (see page 311, abstract, chapter “CONCLUSION” of BB9):

“Nivolumab had substantial therapeutic activity and an acceptable safety profile in patients with previously heavily treated relapsed or refractory Hodgkin’s lymphoma. (Funded by Bristol-Myers Squibb and others; ClinicalTrials.gov number, NCT01592370.)”

83. **BB14** (Hamid et al. N Engl J Med 2013, 369, 2, pages 134-144) discloses that nivolumab was effective in various types of cancer and PD-1–PD-L1 axis can be used as a therapeutic target (see page 135, left col., penultimate para. of BB14):

“Two large, dose-escalation, phase 1 clinical trials evaluating the safety of the anti–PD-1 antibody nivolumab (formerly known as BMS936558) and the anti–PD-L1 antibody BMS936559 showed significant antitumor activity in patients with advanced melanoma, lung carcinoma, and renal-cell carcinoma, among other cancers, thus validating the PD-1–PD-L1 axis as a therapeutic target.”

84. **BB24** (Meeting Abstract; 2016 ASCO Annual Meeting I; Journal of Clinical Oncology, Vol. 34, No. 15 suppl; published online May 20, 2016 (see https://ascopubs.org/doi/10.1200/JCO.2016.34.15_suppl.3001)) discloses that the combination of nivolumab and ipilimumab is effective in treating advanced NSCLC (“CheckMate 012”) (see chapter “Conclusions”):

“1L therapy with N+I demonstrates clinical activity and a manageable safety profile.”

Bird & Bird

16 July 2022
page 20

85. Consequently, in light of the prior disclosures, nivolumab and ipilimumab were known to be effective in other cancers than colorectal cancer with high microsatellite instability.

(bb)

Other anti-pd-1 Antibodies were known as being effective in colorectal cancer

86. Other anti-PD-1 antibodies were known as being effective in colorectal cancer.
87. **BB10** (Le et al. N Engl J Med 2015, 372, 26, page 2509-2520) discloses that pembrolizumab, an anti PD-1 antibody, was used *inter alia* in treating mismatch repair-deficient colorectal cancers and mismatch repair-deficient non colorectal cancers (see page 2509, abstract, chapter “METHODS” of BB10):

“We conducted a phase 2 study to evaluate the clinical activity of pembrolizumab, an anti-programmed death 1 immune checkpoint inhibitor, in 41 patients with progressive metastatic carcinoma with or without mismatch-repair deficiency. Pembrolizumab was administered intravenously at a dose of 10 mg per kilogram of body weight every 14 days in patients with mismatch repair-deficient colorectal cancers, patients with mismatch repair-proficient colorectal cancers, and patients with mismatch repair-deficient cancers that were not colorectal.”

-emphasis added-

88. The mismatch repair-deficient cancers are also known as cancers with microsatellite instability (see e.g., page 2512, left col. 3rd para. of BB10):

“Tumors with genetic defects in mismatch-repair pathways are known to harbor hundreds to thousands of somatic mutations, especially in regions of repetitive DNA known as microsatellites. The accumulation of mutations in these regions of the genome is termed microsatellite instability.”

-emphasis added-

89. The clinical efficiency of pembrolizumab was shown for all mismatch repair-deficient cancers (see abstract chapters “RESULTS” and “CONCLUSION” of BB10):

“Patients with mismatch repair-deficient noncolorectal cancer had responses similar to those of patients with mismatch repair-deficient colorectal cancer (immune-related objective response rate, 71% [5 of 7

patients]; immune-related progression-free survival rate, 67% [4 of 6 patients]).”

“This study showed that mismatch-repair status predicted clinical benefit of immune checkpoint blockade with pembrolizumab. (Funded by Johns Hopkins University and others; ClinicalTrials.gov number, NCT01876511.)”

90. Thus, the clinical efficiency of an anti-PD-1 antibody in treating colorectal cancer with microsatellite instability was shown in **BB10**. Thus, a person skilled in the art would have expected based upon the prior art teachings that nivolumab would be effective which was also known to be an anti-PD-1 antibody.
91. This is confirmed by **BB11** (WO 2016/077553; published on 19 May 2016) (see e.g., Fig. 2A to 2D).

(cc)

PD-1 and CTLA-4 blockade is effective in colorectal cancers

92. It was known that PD-1 and CTLA-4 inhibitors can be used in treating colorectal cancer.
93. **BB12** (Llosa et al. Cancer Discov, 2015, 5(1); 43–51) discloses that in colorectal cancer with microsatellite instability (“MSI”) multiple immune checkpoints, e.g., PD-1 and CTLA-4, are highly up-regulated and shall be targeted by inhibitors in order to treat said cancer (see page 43, abstract of BB12):

“MSI tumors selectively demonstrated highly upregulated expression of multiple immune checkpoints, including five – PD-1, PD-L1, CTLA-4, LAG-3, and IDO – currently being targeted clinically with inhibitors. These findings link tumor genotype with the immune microenvironment, and explain why MSI tumors are not naturally eliminated despite a hostile Th1/CTL microenvironment. They further suggest that blockade of specific checkpoints may be selectively efficacious in the MSI subset of colorectal cancer.”

-emphasis added-

94. Based on these finding two clinical trials (using pembrolizumab, nivolumab and ipilimumab) have been initiated (see page 49, right col. end of 2nd para. of BB12):

“Regardless, a very important prediction of our findings on differential expression of immune-inhibitory ligands, receptors, and metabolic enzymes is that MSI tumors will respond to checkpoint blockade with agents such as anti-PD-1 or anti-PD-L1 antibodies, whereas MSS tumors will be much less responsive. Indeed, based on these findings, two clinical trials testing anti-PD-1 antibodies in patients selected based on MSI have been initiated (NCT01876511 and NCT02060188).”

95. Furthermore, **BB17** (Rosenbaum et al. Modern Pathology (2016) 29, 1104–1112) also discloses that microsatellite-unstable colorectal carcinoma can be treated by PD-1/PD-L1 pathway blockade (see page 1104, abstract, last two sentences of BB17):

“PD-L1 expression in colorectal carcinoma is associated with clinicopathologic and molecular features of the serrated pathway of colorectal carcinogenesis, and is associated with a worse outcome within microsatellite-unstable tumors. These findings support the role of PD-L1 expression in providing normally immunogenic colorectal carcinoma a means of immune evasion and a more aggressive biology, provide a potential mechanistic explanation for the favorable response of microsatellite-unstable colorectal carcinoma to PD-1/PD-L1 pathway blockade, and suggest potential predictive and prognostic roles of PD-L1 immunohistochemistry in colorectal carcinoma.”

-emphasis added-

96. **BB17** also emphasizes that the PD-L1 expression is a common mechanism in different types of cancer and the treatment with PD-1 inhibitors is beneficial throughout the different types of cancers (see page 1110, right col. penultimate para. of BB17):

“In addition, as in microsatellite-unstable colorectal carcinoma, lung cancers with a high mutational burden and neoantigen formation appear to be associated not only with induction of PD-L1 expression on tumor cells, but also with an improved objective response to anti-PD-1 agents with durable clinical benefit and better progression-free survival. These findings suggest a common mechanism for induction of PD-L1 expression in these tumors despite different site of origin and driver mutations.”

-emphasis added-

97. Finally, **BB19** (McDermott et al. Cancer Medicine 2013; 2(5): 662–673) states that the combination of inhibitors of PD-1 and CTLA-4 present a promising approach (see page 668, right col. 1st para. of BB19):

Bird & Bird

16 July 2022
page 23

“Preclinical data [46] suggest that the combination of inhibitors of PD-1 and CTLA-4 may present a promising approach, which is currently being explored in the clinical setting [NCT01454102, NCT01024231].”

98. Thus, the aforementioned reference demonstrate that it was already known that PD-1 and CTLA-4 inhibitors could be used to treat colorectal cancer.

(dd)

the dosages of Nivolumab and ipilimumab were known as being effective

99. **BB4** confirms that the dosages of nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) are effective (see chapter “Conclusion”):

“N and N + I (annotation: N = nivolumab; I = ipilimumab) were well tolerated in most pts (annotation: pts = patients”) and demonstrated encouraging clinical activity and survival in MSI-H mCRC (annotation: MSI-H = high microsatellite instability; mCRC = metastatic colorectal cancer).”

-annotations added-

100. **BB8** discloses the efficacy of nivolumab at a dosage of 3 mg/kg when treating advanced melanoma (see abstract, section “Methods”, “Results” and “Conclusions” of BB8).
101. The same applies to **BB9** wherein patients with relapsed or refractory Hodgkin’s lymphoma received nivolumab (at a dose of 3 mg per kilogram of body weight) (see abstract, section “METHODS”, “RESULTS” and “CONCLUSIONS” of BB9).
102. **BB22** (Raedler et al. Am Health Drug Benefits. 2015; 8 (Spec Feature), 180-183) discloses on page 181, left col., penultimate para. the following:

*“All patients’ disease had progressed after previous therapy with ipilimumab and, if the patients were positive for a BRAF V600 mutation, after treatment with a BRAF inhibitor. These patients were randomized to receive **nivolumab 3 mg/kg** (N = 268) or investigator’s choice chemotherapy (N = 102) with dacarbazine 1000 mg/m² **every 3 weeks** or with carboplatin (area under the curve, 6 mg•min/mL) plus paclitaxel 175 mg/m² every 3 weeks until disease progression or until unacceptable toxicity.”*

-emphasis added-

Bird & Bird

16 July 2022
page 24

103. **BB23** (Hammers et al. *Annals of Oncology* 2014; 25 (Supplement 4): iv361–iv372) showed that the combination of nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) every three weeks is effective in metastatic renal cell carcinoma (mRCC):

Chapter “Methods”

“Patients (pts) with mRCC were randomized to nivolumab 3 mg/kg + IPI 1 mg/kg (arm N3 + I1) or nivolumab 1 mg/kg + IPI 3 mg/kg (N1 + I3) IV every 3 wk for 4 doses then nivolumab 3 mg/kg IV every 2 wk until progression/toxicity (protocol-defined post-progression treatment allowed).”

Chapter “Conclusions”

“Nivolumab + IPI showed acceptable safety and encouraging antitumor activity in mRCC, with most responses ongoing. Studies are ongoing to explore this combination in a Phase III trial.”

104. To sum up, each of the claim elements were known in the art. In view of the common general knowledge, a person skilled in the art had a reasonable expectation of success to obtain the therapeutic efficacy of nivolumab in combination with ipilimumab when treating colorectal cancer with high degree of microsatellite instability.
105. Consequently, the subject matter of claim 1 is not inventive over **BB5** in combination with the common general knowledge, as evidenced by for instance **BB7** to **BB14**, **BB17** to **BB19**, and **BB22** to **BB24**.

II.

Claim 2

106. In claim 2 of the opposed patent the tumor is specified as colon cancer or rectal cancer.
107. **BB5** discloses that the patients treated suffer from colorectal cancer (see page 13, section “Inclusion Criteria” of **BB5**). Colorectal cancer starts in the colon or the rectum. These cancers can be termed colon cancer or rectal cancer, depending on where they start. We refer to para. [0057] of the opposed patent.

108. Thus, the CheckMate-142 study (BB5) is based on patients who have colon cancer and/or rectal cancer.
109. Thus, the subject matter of claim 2 of the opposed patent is not inventive over **BB5** in combination with the common general knowledge, as evidenced by for instance **BB4**, **BB7** to **BB14**, **BB17** to **BB19**, and **BB22** to **BB24**.

III.

Claims 3 and 4

110. According to claim 3 of the opposed patent the tumor exhibits one or more characteristics selected from the group consisting of:
- (a) the tumor comprises a germline alteration in at least two, at least three, at least four, or at least five DNA mismatch repair genes ("MMR genes");
 - (b) the tumor comprises a germline alteration in at least 30% of five or more MMR genes;
 - (c) at least one protein encoded by DNA MMR genes is not detected in the tumor; and
 - (d) any combination thereof.
111. According to claim 4 the DNA MMR genes shall comprise MSH2, MLH1, MSH6, PMS2, PMS1, or any combination thereof.
112. A person skilled in the art knows that microsatellite instability goes along with germline mutations. The genetic basis for instability in MSI tumors is an inherited germline alteration in any one of the five human MMR genes: MSH2, MLH1, MSH6, PMS2, and PMS1. We refer to **BB15** (Dudley et al. Clin Cancer Res; 22(4); 813–820) and **BB16** (Pawlik et al. Disease Markers 20 (2004) 199–206):

See page 813, abstract of **BB15**:

MSI usually arises from either germline mutations in components of the mismatch repair (MMR) machinery (MSH2, MSH6, MLH1, PMS2) in

patients with Lynch syndrome or somatic hypermethylation of the MLH1 promoter.

-emphasis added-

Abstract of **BB16**:

“Microsatellite instability (MSI) is a well-recognized phenomenon that is classically a feature of tumors in the hereditary non-polyposis colorectal syndrome. Ten to 15% of sporadic colorectal cancers, however, will have MSI.”

-emphasis added-

Page 200, left col. 1st para of **BB16**

“In most cases, the genetic basis for instability in MSI tumors is an inherited germline alteration in any one of the five human MMR genes: MSH2, MLH1, MSH6, PMS2, and PMS1.”

-emphasis added-

113. Furthermore, according to **BB18** (Karahan et al. Int J Clin Exp Pathol 2015;8(4):4044-4053) the relationship between MLH-1, MSH-2, PMS-2, MSH-6 expression and clinicopathological features in colorectal cancer was investigated (see title and abstract of BB18).
114. Thus, the subject matters of claims 3 and 4 of the opposed patent are not inventive over **BB5** in combination with the common general knowledge, as evidenced by for instance **BB4**, **BB7** to **BB19** and **BB22** to **BB24**.

IV.

Claim 5

115. According to claim 5 (i) the subject exhibits a progression-free survival of at least about one month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, or at least about 12 months after the administration or (ii) the subject exhibits an overall survival of at least about one month, at least about 2 months, at least about 3 months,

at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, or at least about 12 months after the administration.

- 116. **BB4** discloses a progression-free survival of at least four months for 80% of the treated patients and an overall survival of five month for 100% of the treated patients.
- 117. Thus, the subject matter of claim 5 of the opposed patent is not inventive over **BB5** in combination with for instance **BB4**, **BB7** to **BB14**, **BB17** to **BB19**, and **BB22** to **BB24**.

V.

Claim 6

- 118. Claim 6 requires that the administration of nivolumab and ipilimumab is followed by an anti-PD-1 antibody monotherapy.
- 119. In **BB5** the combination therapy was followed by nivolumab treatment (see page 11, section “Dose Level 2b” of BB5).
- 120. Thus, the subject matter of claim 6 of the opposed patent is not inventive over **BB5** in combination with the common general knowledge, as evidenced by for instance **BB4**, **BB7** to **BB14**, **BB17** to **BB19**, and **BB22** to **BB24**.

VI.

Claim 7

- 121. According to claim 7 the administration of nivolumab and ipilimumab comprises four doses for each.
- 122. In **BB5** four doses of nivolumab and ipilimumab were administered (see page 11, section “Dose Level 2b” of BB5).
- 123. Thus, the subject matter of claim 7 of the opposed patent is not inventive over **BB5** in combination with the common general knowledge, as evidenced by for instance **BB4**, **BB7** to **BB14**, **BB17** to **BB19**, and **BB22** to **BB24**.

VII.

Claims 8 and 9

124. According to claim 8 the subject has received one, two, three, four, five or more prior cancer treatments.
125. According to claim 9 the subject has progressed on other cancer treatments.
126. In **BB4** the patients received one or more prior treatments and patients have been included who has progressed thereon (see section “Methods” of **BB4**: “intolerance/progression on ≥ 1 tx”).
127. Thus, the subject matters of claim 8 and 9 of the opposed patent are not inventive over **BB5** in combination with **BB4** and the common general knowledge, as evidenced by for instance **BB7** to **BB14**, **BB17** to **BB19**, and **BB22** to **BB24**.

VIII.

Claim 10

128. According to claim 10 the kit comprises nivolumab and ipilimumab and is used for a method as defined in claims 1 to 9.
129. The two active ingredients nivolumab and ipilimumab had been used together for a joint effect (treatment of colorectal cancer) in **BB5**. Thus. They were known as a composition (“kit-of-parts”). All arguments brought forwards in context with claim 1 also applies mutatis mutandis for claim 10.
130. Thus, the subject matter of claim 10 of the opposed patent is not inventive over **BB5** in combination with the common general knowledge, as evidenced by for instance **BB4**, **BB7** to **BB14**, **BB17** to **BB19**, and **BB22** to **BB24**.

G.

Lack of sufficiency of disclosure (Art. 83 EPC)

131. According to claim 5 (i) the subject exhibits a certain progression-free survival after the administration **or** (ii) the subject exhibits certain overall survival of at after the administration.
132. There is no disclosure in the opposed patent regarding to which the progression-free survival or overall survival of a patient can be influenced, i.e., shortened or prolonged.
133. Thus, in light of the particular specification and state of the art at the time of filing, 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.

H.

Summary

134. It has been explained in detail that the opposed patent has severe defects in many respects. In particular, the subject matter of claim 1 and several dependent claims as granted lacks novelty over **BB4**. Additionally, the subject matter of all the claims as granted is not based on an inventive step (starting from **BB5**) and is not originally disclosed.
135. Therefore, the opposed patent is to be revoked in its entirety.

>>electronically signed<<

Dr. Andreas Obermeier
European Patent Attorney
(Association no. 748)

Enclosures:

BB1 to BB24

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Official Ref.: EP 17731359.0 / EP 3 464 373
Patentee: Bristol-Myers Squibb Company
Opponent: Maiwald Patentanwalts- und Rechtsanwaltsgesellschaft mbH

Our Ref.: 11845EPOP

We herewith file

Notice of Opposition

against

EP 3 464 373 B1
Application number: 17731359.0
Title: USE OF ANTI-PD-1 ANTIBODY IN THE
TREATMENT OF PATIENTS WITH COLORECTAL
CANCER
Proprietor: Bristol-Myers Squibb Company, Princeton,
NJ 08543 (US)

In the name and on behalf of

**Maiwald Patentanwalts- und
Rechtsanwaltsgesellschaft mbH**
Elisenhof, Eisenstrasse 3
80335 Munich, Germany

Geschäftsführer
(Board of Directors)

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Dr. Eva Dörner
Dr.-Ing. Sophie Ertl
Dr. Marco Stief, LL.M.
Dr. Ralf Kotitschke
Dr. Christian Pioch
Dr. Naho Fujimoto

HRB Nr. 111307
Amtsgericht München

The opposition fee is to be debited from our account number 28 000 741.

F:JUM:SME:kp

A. Requests

- ¹ We request that that EP 3 464 373 B1 (hereafter: the opposed patent) is revoked in its entity.
- ² Oral proceedings are requested in case the above request cannot be granted based on our written submissions.

B. Scope

- ³ The opposition is based on the following grounds:
 - Article 100(a) EPC (the subject matter of the opposed patent is not novel and does not involve an inventive step),
 - Article 100(b) EPC (the European 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), and
 - Article 100(c) EPC (the subject matter of the opposed patent extends beyond the content of the application as filed).

C. Documents

- ⁴ The following documents are cited in this opposition:

WO WO 2017/210637

P US 62/345,662

D1 Overman et al.: Nivolumab ± ipilimumab in treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): CheckMate-142 interim results.; Meeting Abstract, 2016 ASCO Annual Meeting I, Journal of Clinical Oncology 34, no. 15_supplement (May 20, 2016) 3501;

D2 Confirmation of D1's publication date from ASCO;

D3 NCT02060188 from clinicaltrials.gov, version of May 25, 2016;

D4 Marjorie Canfield Willis: Medical Terminology, The Language of Health Care; Second Edition, Lippincott, Williams & Wilkins, 2006;

- D5** A-Z Family Medical Encyclopedia, BMA, 2014;
- D6** Jaafar and Flores-Rozas: Elucidating the role of human mismatch repair factor hMLH3; Cancer Biology & Therapy 8:14, 1421-1423; 15 July 2009;
- D7** Boland: Roles of the DNA Mismatch Repair Genes in Colorectal Tumorigenesis; Int. J. Cancer (Pred. Oncol.): 69, 47-49 (1996);
- D8** Buchbinder and Desai: CTLA-4 and PD-1 Pathways – Similarities, Differences, and Implications of Their Inhibition; Am J Clin Oncol 2016;39:98-106;
- D9** NCT02231749 from clinicaltrials.gov, version of May 25, 2016;
- D10** Broderick: Nivolumab/Ipilimumab Combo More Effective than Monotherapy in mCRC; www.targetedonc.com, June 15, 2016;
- D11** Le et al.: PD-1 Blockade in Tumors with Mismatch-Repair Deficiency; N ENGL J MED 372;26, June 25, 2015;
- D12** WO 2016/077553 A1
- D13** Kroemer et al.: Colorectal cancer: the first neoplasia found to be under immunosurveillance and the last one to respond to immunotherapy?; Oncoimmunology 4:7, e1058597; July 2015;
- D14** Dudley et al.: Microsatellite Instability as a Biomarker for PD-1 Blockade; Clin Cancer Res; 22(4) February 15, 2016;
- D15** Selby et al.: Preclinical Development of Ipilimumab and Nivolumab Combination Immunotherapy: Mouse Tumor Models, In Vitro Functional Studies, and Cynomolgus Macaque Toxicology; PLOS ONE | DOI:10.1371/journal.pone.0161779 September 9, 2016.

D. The claimed subject matter

- ⁵ Claim 1 of the opposed patent relates to

"[n]ivolumab for use in a method of treating a colorectal cancer tumor in a subject, wherein the tumor exhibits a high degree of microsatellite instability ("MSI-H"), wherein the subject is administered nivolumab at a dose of about 3 mg/kg body weight

in combination with ipilimumab at a dose of about 1 mg/kg body weight [once about every three weeks]."

- ⁶ Claim 2 specifies the tumor of claim 1 to be a colon cancer or a rectal cancer.
- ⁷ Claim 3 further specifies the tumor to exhibit one or more of the characteristics selected from the group consisting of:
 - (a) the tumor comprises a germline alteration in at least two, at least three, at least four, or at least five DNA mismatch repair genes ("MMR genes");
 - (b) the tumor comprises a germline alteration in at least 30% of five or more MMR genes;
 - (c) at least one protein encoded by DNA MMR genes is not detected in the tumor; and
 - (d) any combination thereof.
- ⁸ Claim 4 further specifies the DNA MMR genes to comprise MSH2, MLH1, MSH6, PMS2, PMS1 or combinations thereof.
- ⁹ Claim 5 specifies various periods of progression free survival ranging from at least one to 12 months after administration and various overall survival periods ranging from at least one to 12 months after administration.
- ¹⁰ Claim 6 specifies that the administration of nivolumab and ipilimumab is followed by an anti-PD-1 antibody monotherapy.
- ¹¹ Claim 7 specifies that the administration of nivolumab and ipilimumab comprises four doses each.
- ¹² Claim 8 specifies that the subject has received at least one prior cancer treatment.
- ¹³ Claim 9 specifies that the subject has progressed on other cancer treatments.
- ¹⁴ Claim 10 relates to a kit comprising nivolumab and ipilimumab for use in a method as defined in the previous claims.

E. Grounds of opposition

I. Added subject matter (Article 100(c) EPC)

1. Claim 1

- ¹⁵ The subject matter of the opposed patent extends beyond the subject matter of the application as filed (**WO**).
- ¹⁶ Claim 1 of the application as filed relates to a combination of an anti-PD1 antibody for use in treating a tumor derived from colorectal cancer, wherein the tumor exhibits a high degree of microsatellite instability (MSI-H). During prosecution, claim 1 has been limited to treatment of an MSI-H colorectal cancer tumor involving a combination of the antibodies nivolumab and ipilimumab in a specific dosing regimen (see granted claim 1).
- ¹⁷ The applicant/patentee referred to original claims 1, 7 and 10 as well as paragraphs [0032], [0035], [0041], [0044] and [0170] of the application as filed as basis for these amendments (applicant/patentee's submission dated November 18, 2019, paragraph bridging pages 1 and 2).
- ¹⁸ Yet, the sections referred to by the patentee fail to directly and unambiguously disclose the subject matter of claim 1. Several of these sections disclose or are part of lists of various alternatives with regard to the antibodies and the dosing regimen (amount and interval).
- ¹⁹ Original claims 7 and 10 each disclose an additional alternative for an anti-PD1 antibody and an anti-CTLA4 antibody. The same applies to paragraphs [0032]/[0033] and paragraphs [0041]/[0042]. Hence, two selections are necessary to arrive at the claimed antibody combination.
- ²⁰ Various different dosing regimens involving different amounts of antibody and different intervals are disclosed throughout the application as filed (e.g., paragraphs [0010], [0012], [0034], [0035], [0043] – [0048]). Accordingly, the dosing regimen referred to in granted claim 1 is the result of additional selections.
- ²¹ Finally, the applicant/patentee referred to paragraph [0170] as basis for claim 1 during prosecution. However, the disclosure provided in the last sentence of this paragraph involves an additional initial stage with anti-PD1 antibody monotherapy and an additional final stage with anti-PD1

antibody monotherapy which are both absent from claim 1. Hence, this paragraph also cannot serve as basis for granted claim 1.

- ²² For the sake of completeness, it is noted that the examples of the application as filed likewise cannot serve as basis for claim 1 as granted, as they involve additional features that are not recited in claim 1. For example, Example 1 describes that the MSI-H patients selected for inclusion in the MSI-H cohort of the study had received at least 1 prior treatment for metastatic disease, at least 1 target lesion, and an ECOG performance status of 0-1. In addition, they received monotherapy with nivolumab prior to and after the combination therapy (application as filed, paragraph [0179]).
- ²³ Example 2 e.g., requires that the patients eligible for inclusion in the reported study *inter alia* received at least one prior line of therapy. In addition, they received monotherapy with nivolumab after the combination therapy (application as filed, paragraphs [0193] and [0194]).
- ²⁴ Taken together, claim 1 violates the provisions of Article 123(2) EPC.
- ²⁵ The dependent claims 2-9 violate the provisions of Article 123(2) EPC at least for the same reasons as outlined above for claim 1.

II. Invalid priority claim

- ²⁶ The claimed subject matter is not directly an unambiguously derivable from the priority document (P).
- ²⁷ The same reasons as outlined above for Article 123(2) EPC apply. Several selections from lists are necessary in order to arrive at the subject matter of claim 1 (see, e.g., P, claims 11-16, 20-25 and 28-31). In addition, it is noted that the disclosure provided in paragraph [0170] of the application as filed is not present in the priority document. Hence, the patentee cannot rely on this disclosure under Article 87 EPC.
- ²⁸ Therefore, the effective filing date for the claimed subject matter is June 2, 2017.

III. Lack of novelty (Article 54 EPC)

1. Lack of novelty in view of D1

1.1 Claim 1

²⁹ Claim 1 of the opposed patent is directed to a combination of antibodies for use in a method of treating a colorectal cancer tumor in a subject. Claim 1 requires that the tumor shows a high degree of microsatellite instability (MSI-H), that the subject is administered nivolumab at a dose of 3 mg/kg body weight in combination with ipilimumab at a dose of about 1 mg/kg body weight and that the doses are administered once about every three weeks.

³⁰ The method of claim 1 lacks novelty in view of D1.

³¹ D1 is a meeting abstract of the 2016 American Society of Clinical Oncology Annual Meeting I. D1 was published on May 20, 2016 (as confirmed by the publisher, see D2) and is thus prior art pursuant to Article 54(2) EPC irrespective of the validity of the priority claim.

³² D1 describes the interim results of the clinical study CheckMate-142. D1 discloses “[n]ivolumab ± ipilimumab in treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): CheckMate-142 interim results.” (D1, heading, emphasis added). D1 further discloses that MSI-H patients received either 3 mg/kg nivolumab every two weeks (q2 wk¹) or 3 mg/kg nivolumab and 1 mg/kg ipilimumab every three weeks (q3 wk) for four doses followed by 3 mg/kg Nivolumab monotherapy until disease progression (D1, Methods, first sentence).

³³ Hence, D1 discloses the treatment of colorectal cancer with high microsatellite instability as defined in claim 1 of the opposed patent.

³⁴ In addition, D1 discloses that the provided treatment is efficacious.

³⁵ Specifically, D1 shows a comparison of clinical results of patients treated with 3 mg/kg Nivolumab monotherapy (N3) and with a combination of 3 mg/kg Nivolumab and 1 mg/kg Ipilimumab (N3+I1) (D1, table entitled MSI-H efficacy). For the combination treatment, D1 reports that 80% of the treated patients show progression free survival after 4 months (“4-mo PFS

¹ q = every; wk = week (e.g., D4, page 93)

rate, %") and 100% of the patients showed an overall survival rate after 5 months ("5-mo OS rate, %"). For the treatment involving only nivolumab, 55% of the treated patients exhibited progression free survival after 4 months and 75% exhibited overall survival after 5 months.

- ³⁶ **D1** concludes from this data that "*N and N+I were well tolerated in most pts and demonstrated encouraging clinical activity and survival in MSI-H mCRC*" (**D1**, Conclusions, first sentence).
- ³⁷ **D1** thus discloses efficacy for treatment of patients with colorectal cancer with high microsatellite instability with nivolumab at 3 mg/kg in combination with ipilimumab at 1 mg/kg, wherein the combination is administered every three weeks.
- ³⁸ As a result, the claimed subject matter lacks novelty in view of the disclosure provided in **D1**.

1.2 Claims 5-9

- ³⁹ **D1** discloses an overall survival of 100% at 5 months after administration for patients receiving the combination treatment (**D1**, table, "5-mo OS rate %"). Hence, the subject matter of claim 5 is disclosed in **D1**.
- ⁴⁰ **D1** also discloses that the patients were treated with 3 mg/kg nivolumab (anti-PD1 antibody) until disease progression or discontinuation after the combination treatment (**D1**, "Methods"). Accordingly, the subject matter of claim 6 is disclosed in **D1**.
- ⁴¹ **D1** discloses the administration of 3 mg/kg nivolumab and 1 mg/kg ipilimumab of four doses each (**D1**, Methods, "*(N3+I1) x 4 doses*"). Therefore, **D1** discloses the subject matter of claim 7.
- ⁴² The patients of the study described in **D1** received prior cancer treatment and showed intolerance/progression to at least one treatment (**D1**, Methods, first sentence). As a result, the subject matter of claims 8 and 9 is disclosed in **D1**.
- ⁴³ Taken together, at least the subject matter of dependent claims 5-9 cannot establish novelty in view of **D1**.

2. Lack of novelty in view of D3

- ⁴⁴ **D3** is a study protocol from clinicaltrials.gov concerned with clinical trial NCT02060188 that was published on May 25, 2016 and is thus prior art pursuant to Article 54(2) EPC irrespective of the validity of the priority claim.
- ⁴⁵ NCT02060188 in **D3** is entitled “A Phase 2 Clinical Trial of Nivolumab and Nivolumab Plus Ipilimumab in Recurrent and Metastatic Microsatellite High (MSI-H) Colon Cancer” (**D3**, Official Title bridging pages 5 and 6). Colon cancer is a colorectal cancer (see, e.g., granted claim 2 of the opposed patent).
- ⁴⁶ The study reported in **D3** involves 2 arms (**D3**, page 7, Study design, number of arms) and the corresponding dosing regimens are disclosed in the table bridging pages 7 and 8 of **D3**. Dose level 2b involves administration of nivolumab at 3 mg/kg and ipilimumab at 1 mg/kg every 3 weeks.
- ⁴⁷ Hence, the dosing of claim 1 of the opposed patent is already disclosed in **D3**. Therefore, the subject matter of at least claim 1 lacks novelty in view of **D3**.
- ⁴⁸ It is noted that clinical trial NCT02060188 was apparently already considered by the examiner during search/examination of the application underlying the opposed patent (see IPRP issued by the EPO; referred as **D3**, section on novelty starting on page 6) document.
- ⁴⁹ It seems that the examiner considered the treatment involving monotherapy with nivolumab as disclosed in **D3** as novelty destroying for WO claims 1-5 and 7 relating to such monotherapy. Yet, any WO claims relating to a combination therapy involving an additional anti-CTLA4 antibody (e.g., WO claim 8) were considered novel by the examiner in view of **D3**.
- ⁵⁰ From the above discussion of NCT02060188 as disclosed in **D3**, it becomes apparent that **D3** discloses the claimed combination treatment as well as the dosing regimen recited in granted claim 1. During search/examination, the examiner did apparently not fully take the disclosure provided in this document into account and/or the examiner was referring to an earlier version of this document.
- ⁵¹ Yet, in case the full disclosure of **D3** is taken into account, novelty of at least claim 1 should be denied.

IV. Lack of inventive step (Article 56 EPC)

1. Lack of inventive step in view of D1

- ⁵² **D1** discloses all features of at least claims 1 and 5-9. Should the opposition division come to the conclusion that the subject matter of these claims is nonetheless novel in view of **D1**, it is submitted that the subject matter of these claims lacks inventive step starting from **D1** as closest prior art.
- ⁵³ On the subject of dependent claims 2-4 and claim 10, it is submitted that none of the additional features of any of these claims has been shown to establish any unexpected technical effect.
- ⁵⁴ Claim 2 specifies that the colorectal cancer is colon cancer or rectal cancer. As colorectal cancer is the umbrella term for colon cancer and rectal cancer, claim 2 does not add any feature that could establish the presence of inventive step (**D5**, page 186, left column).
- ⁵⁵ Claims 3 and 4 further define the colorectal cancer tumor to be treated by specifying that the tumor carries mutations in mismatch repair genes. Yet, from the examples provided the opposed patent, it cannot be concluded that any technical effect is associated in particular with treating tumors as defined in these claims. In other words, there is no basis to conclude that the claimed treatment is particularly efficacious in tumors as defined in these claims.
- ⁵⁶ Moreover, claim 1 specifies that the tumor exhibits a high degree of microsatellite instability (MSI-H). Yet, at the effective filing date of the opposed patent, it had long been established that MSI-H colorectal cancers exhibit defects in DNA mismatch repair (MMR) which is caused by mutations in e.g., the MSH2 and MLH1 genes (**D6**, paragraph bridging pages 1421 and 1422; **D7**, page 48, left column, second paragraph; **D14**, sentence bridging left and right column of abstract). Hence, claims 3 and 4 merely rely on the common definition of MSI-H colorectal cancer.
- ⁵⁷ Taken together the additional features of claims 3 and 4 are nothing but the established definition of colorectal cancer with MSI-H as already referred to in claim 1. In addition, these additional features have not been shown to be associated with any technical effect. Therefore, they cannot render the claimed subject matter inventive.

- ⁵⁸ Claim 10 refers to a kit comprising nivolumab and ipilimumab for carrying out the claimed medical use. Yet, merely combining the two antibodies in a kit likewise cannot render the claimed subject matter inventive.
- ⁵⁹ For these reasons, the subject matter of these claims likewise lacks inventive step starting from **D1**.

2. Lack of inventive step in view of D3

2.1 D3 is suitable as closest prior art

- ⁶⁰ The subject matter of claim 1 lacks novelty in view of **D3** for the reasons outlined above. Should the opposition division come to the conclusion that the claimed subject matter is novel vis-à-vis **D3**, it is submitted that the claimed subject matter lacks inventive step for the reasons outlined below.
- ⁶¹ Claim 1 refers to a combination therapy for a colorectal cancer tumor with MSI-H involving 3 mg/kg body weight nivolumab and 1 mg/kg body weight ipilimumab administered once about every three weeks.
- ⁶² **D3** is a study protocol of a clinical trial concerning the therapy of MSI-H colorectal cancer with a combination of nivolumab and ipilimumab. The study reported in **D3** involves 2 arms, one of which involves the dosing regimen as defined in the present claims (see section on novelty above).
- ⁶³ Accordingly, **D3** is concerned with the same purpose as the claimed subject matter. In addition, **D3** discloses all structural features of claim 1 of the opposed patent. **D3** is therefore suitable as closest prior art.

2.2 The underlying technical problem

- ⁶⁴ If anything, the only difference that can be identified between the claimed subject matter and the disclosure provided in **D3** is that the disclosure provided in **D3** does not (yet) involve data on efficacy.
- ⁶⁵ Thus, the underlying technical problem may be formulated as the provision of an efficacious treatment for colorectal cancer with MSI-H.
- ⁶⁶ The solution provided by the opposed patent in granted claim 1 is entirely obvious for the reasons outlined below.

2.3 Obviousness

- ⁶⁷ According to the established EPO case law, a course of action can be considered obvious within the meaning of Article 56 EPC if the skilled person would have carried it out in expectation of some improvement or advantage. Thus, a solution is obvious not only when the results are clearly predictable, but also when success can realistically be expected. Furthermore, for a solution to be obvious, it is sufficient to establish that the skilled person would have followed the teaching of the prior art document with a reasonable expectation of success (Case Law Book, Ninth Edition, D 7.1).
- ⁶⁸ **D3** discloses the protocol for a clinical trial concerned with the treatment of patients with colorectal cancer with MSI-H. The trial involves two treatment arms: One arm involving nivolumab monotherapy and one arm involving a combination of nivolumab and ipilimumab. The latter arm involves two dosing regimens (dose level 2a and dose level 2b) and two lower starting doses (dose level -1 and dose level 1) for the dose escalation phase (**D3**, table bridging pages 7 and 8).
- ⁶⁹ Nivolumab is an anti-PD1 antibody and ipilimumab is an anti-CTLA4 antibody. Both antibodies act on inhibitory immune checkpoints and by blocking these inhibitory immune checkpoints enhance the immune response (**D8**², e.g., Abstract, first and second sentence; and **D13**³, e.g., page 1, left column, first paragraph). Furthermore, before the effective filing date of the opposed patent, combination therapies involving nivolumab and ipilimumab had been shown to exhibit increased efficacy in the majority of cancers tested as compared to the corresponding monotherapies. Furthermore, the applicability of such combination therapies in various cancers was discussed in the field (**D8**, e.g., page 104, left column, last paragraph and right column, first paragraph).
- ⁷⁰ Accordingly, the skilled person was aware from his/her common general knowledge that a combination of nivolumab and ipilimumab results in enhanced anti-cancer activity for the majority of cancers tested.
- ⁷¹ The skilled person aiming at the provision of an efficacious treatment for colorectal cancer with MSI-H would therefore have assumed that the combination therapy involving ipilimumab and nivolumab exhibits a higher

² **D8** is a review article from the field of cancer treatment and, hence, representative of the common general knowledge at the time.

³ **D13** is a review article from the field of colorectal cancer treatment and, hence, representative of the common general knowledge at the time.

degree of efficacy. Hence, s/he would have further developed the combination therapy disclosed in **D3**.

⁷² **D3** discloses two different dosing regimens for the combination therapy: dose level 2a and dose level 2b. The latter dose level is a dosing regimen as defined in the present claims.

⁷³ First of all, it is submitted that the choice of dose level 2b cannot render the claimed subject matter non-obvious. There is no data in the opposed patent supporting that a dosing regimen according to dose level 2b is more efficacious as compared to a dosing regimen according to dose level 2a. According to established EPO case law, the presence of other options in the prior art has no bearing on the obviousness of one specific option. In case all options are equally likely, the choice of one option is a non-inventive selection (Case Law Book, Ninth Edition, I.D.9.19.10).

⁷⁴ Already for this reason, the claimed subject matter is obvious starting from **D3**.

⁷⁵ It is further submitted that the skilled person starting from **D3** also had a reasonable expectation of success for the dosing regimen according to dose level 2b to exhibit clinical efficacy.

⁷⁶ **D3** is a protocol for a clinical trial involving human cancer patients. Such trials are subject of high ethical standards in order to be approved. Specifically, such trials are only conducted in case there is substantial evidence supporting therapeutic efficacy. Hence, the mere fact that a clinical trial was planned involving a dosing regimen according to dose level 2b supports that there was a reasonable expectation of success for such dosing regimen to exhibit efficacy in treating MSI-H colorectal cancer. Otherwise, dose level 2b would not have been included in the trial in the first place.

⁷⁷ This reasoning was adopted by the Board of Appeal in charge of T 239/16. The situation underlying T 239/16 is similar to the present case. The relevant prior art document was a clinical trial protocol disclosing the treatment defined in the medical use claim is suit in one out of five study arms. Yet, the relevant prior art document did not involve any data supporting therapeutic efficacy (T 239/16, reasons 5.2 referring to document (55)). The Board reasoned under Article 56 EPC

“that the mere fact that an active agent selected from the group of bisphosphonates is being tested in a clinical study for the treatment of osteoporosis (as disclosed in document (55)) leads to an

expectation of success, due to the fact that clinical studies are based on data obtained by pre-clinical testing both in vitro and in animals and require authority approval which takes ethical considerations into account. This means in the present case that the skilled person would expect all study arms to treat osteoporosis effectively, unless he was dissuaded from this by the prior art" (T 239/16, reasons 6.5);

and

"that there remained a residual doubt that the desired treatment would be obtained, which however did not diminish the prospects of success to such an extent that the reasonable expectation turned into a mere "hope to succeed". Clinical trials in humans are planned scientific investigations. They require authority approval, which is only given after a risk/benefit evaluation. For ethical (but also economic) reasons it has to be ensured that research risks are minimised and are reasonable in relation to any potential benefits. Ethical and economical considerations require that the "benefit" will arise with reasonable certainty and will not only "be hoped for". This has to be taken into consideration as part of the technical circumstances when assessing the level of confidence of the skilled person in making rational predictions about achieving the envisaged treatment" (T 239/16, reasons 6.6).

- ⁷⁸ Hence, as there is no teaching in the prior art that would dissuade the skilled person from using a dosing regimen according to dose level 2b of **D3** in the treatment of colorectal cancer with MSI-H, the skilled person is provided with a reasonable expectation of success for this dosing regimen to exhibit therapeutic efficacy by the fact that this dosing regimen is tested in a clinical trial involving human patients.
- ⁷⁹ T 239/16 also confirms that choosing a dosing regimen from one of several study arms cannot render a claimed treatment inventive. Rather, T 239/16 confirms that *"the skilled person would expect all study arms to treat [...] effectively, unless he was dissuaded from this by the prior art"*.
- ⁸⁰ Taken together, **D3** discloses a treatment for colorectal cancer with MSI-H as defined in claim 1 of the opposed patent in dose level 2b.
- ⁸¹ For the reasons outlined above and based on the reasoning provided in T 239/16, it is submitted that the mere choice of dose level 2b cannot render the claimed subject matter inventive. In the absence of any teaching to the contrary, the skilled person would consider that all treatment arms included in a study have a high likelihood to result in

treatment efficacy. Hence, s/he was provided for a reasonable expectation success that the monotherapy as well as the two dosing regimens provided for the combination therapy result in therapeutic efficacy.

- ⁸² Irrespective thereof, the skilled person was aware from the common general knowledge that combination therapies involving nivolumab and ipilimumab give higher anti-cancer effects as compared to the corresponding monotherapies. Hence, the skilled person was provided with strong motivation to focus further developments on such combination therapies.
- ⁸³ As a result, the dosing regimen according to granted claim 1 lacks inventive step when starting from **D3**.
- ⁸⁴ The subject matter of granted claims 2-10 is likewise obvious when starting from **D3**.
- ⁸⁵ For claims 2-4 and 10, it is referred to the reasoning provided above in the context of lack of inventive step in view of **D1**.
- ⁸⁶ Claim 5 specifies time periods for progression free survival and overall survival for the therapy of claim 1. Yet, as the therapy of claim 1 is disclosed in **D3**, these time periods must likewise be met upon implementing the teaching of **D3**. Hence, the additional features of claim 5 cannot establish the presence of inventive step.
- ⁸⁷ Claim 6 specifies that the combination therapy of claim 1 is followed by monotherapy with an anti-PD1 antibody and claim 7 specifies that the combination therapy is administered for four doses. Both of these requirements are part of dose level 2b as disclosed in **D3** (**D3**, top of page 8).
- ⁸⁸ Claim 8 limits the treatment to subjects that received at least one prior cancer treatment and claim 9 requires that the subjects progressed on prior cancer treatments. As no effect is associated with these additional limitations, the additional features of the claims cannot render the claimed subject matter inventive.
- ⁸⁹ For these reasons, the subject matter of claims 1-10 is obvious starting from **D3**.

3. Lack of inventive step in view of D3 in combination with D9

⁹⁰ **D9** was published in May 25, 2016 and is prior art pursuant to Article 54(2) EPC irrespective of the validity of the opposed patent's priority claim.

⁹¹ **D9** is a clinical trial protocol aiming at the investigation of a combination therapy involving nivolumab and ipilimumab for treating renal cancer. The combination treatment is compared to sunitinib treatment (**D9**, page 4, "Study Description").

⁹² As outlined above in detail, **D3** is concerned with a cancer therapy involving the combination of nivolumab and ipilimumab. The skilled person starting from **D3** and aiming at the provision of an efficacious cancer therapy would have consulted other disclosures relating to cancer treatment involving said antibody combination. Thus, the skilled person would have consulted **D9**.

⁹³ From **D9**, the skilled person would have learned that the investigators in charge of **D9** considered the dosing regimen involving nivolumab at 3 mg/kg and ipilimumab at 1 mg/kg administered every three weeks (**D9**, page 4, second row of table) as very promising, as this is the only dosing regimen tested for the combination of the two antibodies. Accordingly, the skilled person starting from **D3** would have focused on this particular dosing regimen during their further developments as this dosing regimen is considered to have efficacy also in the treatment of other types of cancers.

⁹⁴ Therefore, the claimed subject matter lacks inventive step in view of **D3** in combination with **D9**.

4. Lack of inventive step in view of D3 in combination with D15

⁹⁵ **D15** was published in September 9, 2016 and is prior art pursuant to Article 54(2) EPC in view on the invalidity of the opposed patent's priority claim.

⁹⁶ **D15** discloses data showing that a combination of nivolumab and ipilimumab exhibits therapeutic efficacy in a murine colon cancer model (**D15**, e.g., page 5, last two paragraphs). **D15** stems from the field of cancer therapy, and it is concerned with analyzing the efficacy of a combination of nivolumab and ipilimumab in colorectal cancer treatment. Hence, the skilled person starting from **D3** would have considered this disclosure.

⁹⁷ **D3** entirely discloses the claimed treatment. In addition, based on the promising murine data provided in **D15**, the skilled person was provided with a reasonable expectation of success that such treatment is also efficacious in the treatment of colorectal cancer in human patients.

⁹⁸ For this reason, the claimed subject matter also lacks inventive step in view of **D3** in combination with **D15**.

5. Lack of inventive step in view of **D10**

⁹⁹ **D10** was published on June 15, 2016. In view of the invalid priority claim of the opposed patent, **D10** is prior art pursuant to Article 54(2) EPC.

¹⁰⁰ **D10** is a comment on the ASCO conference where Overman et al. presented results of the CheckMate-142 trial. **D1** is the abstract corresponding to this presentation.

¹⁰¹ **D10** discloses a combination therapy involving nivolumab and ipilimumab in the treatment of patients with MSI-H colorectal cancer (**D10**, page 1, first paragraph). The dosing regimen used for the combination therapy involves 3 mg/kg nivolumab and 1 mg/kg ipilimumab (**D10**, page 1, last full paragraph).

¹⁰² **D10** reports efficacy for the combination therapy (**D10**, e.g., page 2, sixth and seventh paragraph). **D10** concludes that

“[w]e believe the data presented at ASCO support our hypothesis that the combination of Opdivo [nivolumab] with Yervoy [ipilimumab] has the potential to lead to greater clinical activity than Opdivo monotherapy in patients with MSI-H metastatic colorectal cancer. We are encouraged by the preliminary results from our ongoing efforts to evaluate the full potential of this combination regimen across a range of malignancies” (**D10**, penultimate paragraph on page 3).

¹⁰³ Accordingly, **D10** discloses efficacy in the treatment of MSI-H colorectal cancer.

¹⁰⁴ **D10** serves the same purpose, i.e., treatment of MSI-H colorectal cancer, as the claimed subject matter and shares a high number of structural features, i.e., a combination of nivolumab and ipilimumab, with the claimed subject matter. **D10** is therefore suitable as closest prior art.

- ¹⁰⁵ The only difference that can be identified between the subject matter of claim 1 and the disclosure provided in **D10** is that **D10** does not indicate at which interval the combination of nivolumab and ipilimumab is administered.
- ¹⁰⁶ The underlying technical problem may thus be formulated as the provision of a full dosing regimen for a combination therapy involving nivolumab at 3 mg/kg and ipilimumab at 1 mg/kg for the treatment of MSI-H colorectal cancer.
- ¹⁰⁷ Yet, the solution provided by the claimed subject matter, i.e., the administration of such combination in a three-week interval, is obvious.
- ¹⁰⁸ As indicated above, **D10** discloses that the results discussed therein are from the CheckMate-142 trial. Hence, the skilled person aiming at using the successful treatment disclosed in **D10** would have simply searched for the dosing interval used in the CheckMate-142 trial. **D1** and **D3** are both disclosures concerned with CheckMate-142 (**D1**, title; **D3**, title). **D1** and **D3** disclose that the combination of nivolumab and ipilimumab is administered every three weeks (**D1**, Methods; **D3**, top of page 8).
- ¹⁰⁹ Hence, the claimed subject matter lacks inventive step in view of **D10** in combination with **D1** or **D3**.

6. Lack of inventive step starting from D11

- ¹¹⁰ **D11** was published on June 25, 2015 and is therefore prior art pursuant to Article 54(2) EPC, irrespective of the validity of the priority claim.
- ¹¹¹ **D11** discloses treatment of patients with mismatch repair deficient colorectal cancers⁴ with the anti-PD-1 antibody pembrolizumab (**D11**, e.g., Abstract, Methods). **D11** reports that patients with mismatch repair deficient colorectal cancers exhibit higher response rates compared to patients with mismatch repair proficient colorectal cancers (**D11**, e.g., Table 2 and Figure 2 A and B).
- ¹¹² As **D11** is concerned with treatment of MSI-H colorectal cancer and as **D11** provides a treatment that is particularly efficacious in such cancer, **D11** relates to the same purpose as the claimed subject matter. In addition, it already involves an anti-PD1 antibody and therefore also

⁴ Mismatch repair deficient colorectal cancers are MSI-H colorectal cancers (**D6**, e.g., page 1421, right column, last paragraph; **D7**, page 48, left column, second paragraph; and **D14**, sentence bridging left and right column of abstract).

shares a high structural similarity with the claimed subject matter. **D11** is therefore suitable as closest prior art.

- ¹¹³ The difference that can be identified between the claimed subject matter and **D11**, is that the claimed subject matter involves a combination of a different anti-PD1 antibody and a CTLA4 antibody that are to be administered at the dosing regimen as defined in the present claims.
- ¹¹⁴ No effect has been shown to be associated with using nivolumab instead of pembrolizumab. Hence, the choice of nivolumab as anti-PD1 antibody cannot establish the presence of inventive step.
- ¹¹⁵ The combination of an anti-CTLA-4 antibody with an anti-PD1 antibody administered in the dosing regimen as defined in claim 1 of the opposed patent has been shown to be improved over monotherapy with an anti-PD1 antibody. Accordingly, starting from **D11**, the underlying technical problem may be formulated as the provision of an improved therapy for treating MSI-H colorectal cancer.
- ¹¹⁶ The skilled person starting from **D11** would have learned that treatment of MSI-H colorectal cancer with an anti-PD1 antibody is highly beneficial as explained above. **D11** further teaches that microenvironment of tumors with DNA mismatch repair strongly expresses immune checkpoint ligands including PD-1, PD-L1 and CTLA4 (**D11**, page 2517, left column, second sentence of second paragraph). Accordingly, the skilled person was provided with motivation to additionally block other checkpoint inhibitors such as CTLA4 to enhance the anti-cancer effect. This applies all the more against the background that the skilled person was well aware from his/her common general knowledge that a combination of an anti-PD1 antibody and an anti-CTLA4 antibody exhibits an increased anti-cancer effect as compared to the respective monotherapies (**D8**, e.g., page 104, left column, last paragraph and right column, first paragraph). Hence, starting from **D11** the skilled person was motivated to provide a combination treatment involving an anti-PD1 antibody and an anti-CTLA4 antibody.
- ¹¹⁷ **D1** or **D3** already provide a combination therapy involving an anti-PD1 antibody and an anti-CTLA4 antibody for the treatment of MSI-H colorectal cancer. The skilled person aiming at the development of such combination therapy would have consulted these documents to solve this task as these documents relate to treatment of the same indication and they already provide a dosing regimen that is tested (in **D3**) or has even been successfully applied (in **D1**) to human patients. Again, **D1** and **D3**

disclose the dosing regimen for nivolumab and ipilimumab as defined in the present claims.

- ¹¹⁸ Hence, the claimed subject matter lacks inventive step starting from **D11** in combination with **D1** or **D3**.
- ¹¹⁹ It is noted that **D11** was considered to be the closest prior art during examination of the underlying application (IPRP, pages 7 and 8, document referred to as D1). The examiner appears to acknowledge in the IPRP that a combination of an anti-PD1 antibody and a CTLA4 antibody had been suggested in the prior art and such combination cannot render the claimed subject matter inventive (IPRP, page 8, third paragraph to end of page 8). The presence of inventive step is only acknowledged for a specific dosing regimen (IPRP, page 9, first paragraph).
- ¹²⁰ Opponent agrees with the examiners statements, except for the dosing regimen being non-obvious. As explained above, the examiner was apparently not aware of **D1** and, as already explained above, the disclosure provided in **D3** was not fully taken into account during examination. Yet, from these documents it becomes immediately apparent that the skilled person aiming at the provision of a combination therapy involving an anti-PD1 antibody and an anti-CTLA4 antibody as suggested by **D11** (in combination with the common general knowledge), the skilled person would have chosen a dosing regimen as disclosed in **D1/D3**.
- ¹²¹ Accordingly, upon taking **D1/D3** into account, the presence of inventive step must be denied when following the examiner's reasoning as outlined in the IPRP.

7. Lack of inventive step in view of D12

- ¹²² **D12** was published on May 19, 2016 and is thus prior art pursuant to Article 54(2) EPC irrespective of the validity of the priority claim.
- ¹²³ **D12** provides a disclosure that is very similar to the disclosure provided in **D11**. **D12** relies on the same data as shown in **D11** (see, e.g., **D11** and **D12**, Figure 2, respectively).
- ¹²⁴ **D12** discloses treatment of patients with mismatch repair deficient colorectal cancer with the anti-PD1 antibody pembrolizumab (**D12**, paragraphs [43] and [47]). **D12** discloses that patients with mismatch

repair deficient colorectal cancer particularly benefit from this treatment (D12, e.g., Figures 2A and 2B). D12 also describes upregulation of CTLA4 in the microenvironment of mismatch repair deficient tumors (D12, paragraph [37]).

- ¹²⁵ The claimed subject matter can be derived in an obvious manner when starting from D12 for the same reasons as outlined above for D11.
- ¹²⁶ For the sake of completeness, it is noted that D12 was also identified in the IPRP (referred to as D2 therein) and the comments provided in the context of the IPRP for D11 above equally apply here.

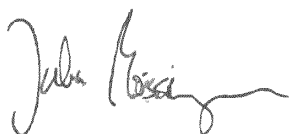
V. Insufficiency (Article 83 EPC)

- ¹²⁷ Claim 1 of the opposed patent is a second medical use claim. Accordingly, therapeutic efficacy is a functional feature of this claim and, in line with established EPO case law, the patent must disclose the suitability of the antibody combination for the claimed therapeutic application. This may be proven by any kind of evidence as long as it reflects the therapeutic effect on which the therapeutic application relies (Case Law book, Ninth Edition, II.C.7.2).
- ¹²⁸ Further, sufficiency of disclosure is only affirmed in case the claimed subject matter can be worked in the whole range claimed (Case Law Book, Ninth Edition, II.C.1).
- ¹²⁹ The opposed patent provides data from a clinical study in the examples of the opposed patent. This study involves treatment of patients selected based on specific criteria (see, e.g., paragraphs [0116], [0117] and [0133] of the opposed patent). Further, the patients are treated with a dosing regimen involving a combination therapy of nivolumab and ipilimumab administered in four doses, followed by a monotherapy with nivolumab (see, e.g., paragraphs [0119] and [0134] of the opposed patent). Hence, while the studies reported in the examples of the opposed patent are concerned with specifically selected patients and a dosing regimen that is limited to four doses of combination therapy flanked by nivolumab monotherapy, none of these features is present in claim 1.
- ¹³⁰ Hence, at least claim 1 of the opposed patent fails to establish suitability for the claimed treatment over the whole scope claimed.

F. Conclusion

- ¹³¹ To conclude, the subject-matter as granted in the opposed patent extends beyond the content of the application as filed.
- ¹³² Furthermore, the claimed subject matter is neither new, nor inventive over the cited prior art.
- ¹³³ Finally, the alleged invention as defined in the claims as granted is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.
- ¹³⁴ Therefore, the request to revoke the opposed patent in its entirety is fully justified.

Maiwald Patentanwalts- und Rechtsanwaltsgesellschaft mbH
- Association No. 174 -



Dr. Julia Mössinger
Patentanwältin | European Patent Attorney

Enclosures
P, WO, D1-D15



Notice of opposition to a European patent

I. Patent opposed

Patent No.

EP3464373

Application No.

EP17731359.0

Date of mention of the grant in the European Patent Bulletin
(Art. 97(3), Art. 99(1) EPC)

27 October 2021

Title of the invention

USE OF ANTI-PD-1 ANTIBODY IN THE TREATMENT
OF PATIENTS WITH COLORECTAL CANCER

II. Proprietor of the patent

first named in the patent specification

Bristol-Myers Squibb Company

Opponent's or representative's reference

11845EPOP/JUM

III. Opponent

Name

Maiwald Patentanwalts- und Rechtsanwaltsgesellschaft
mbH

Address:

Elisenhof, Elisenstrasse 3
80335 Munich
Germany

State of residence or of principal place of business

Germany

Multiple opponents (see additional sheet)

☐

IV. Authorisation

1. Representative

Department:

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174

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Additional representative(s) on additional sheet/see
authorisation

☐

Authorisation(s)

is/are enclosed

☐

has/have been registered under No.

☐

V. Opposition is filed against

the patent as a whole

☒

claim(s) No(s).

VI. Grounds for opposition:

Opposition is based on the following grounds:

(a) the subject-matter of the European patent opposed is not
patentable (Art. 100(a) EPC) because:

• it is not new (Art. 52(1); Art. 54 EPC)

☒

• it does not involve an inventive step (Art. 52(1);
Art. 56 EPC)

☒

• patentability is excluded on other grounds, namely
articles

☐

(b) the patent opposed 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 (Art. 100(b) EPC; see Art.
83 EPC).

☒

(c) the subject-matter of the patent opposed extends beyond
the content of the application/of the earlier application as
filed (Art. 100(c) EPC, see Art. 123(2) EPC).

☒

VII. Facts (Rule 76(2)(c) EPC)

presented in support of the opposition are submitted herewith
on an attached document

☒

VIII. Other requests:

• Oral proceedings are hereby requested auxilially.

IX. Evidence presented

D1	Non-patent literature - article	Overman, Michael J. et al., "Nivolumab ± ipilimumab in treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): CheckMate-142 interim results" Journal of Clinical Oncology, Vol. 34, No. 15, 20 May 2016 original file name: D1_Overman et al..pdf attached as: Published-Evidence-3.pdf
D10	Non-patent literature - internet	Broderick, Jason M., "Nivolumab/Ipilimumab Combo More Effective than Monotherapy in mCRC" , [cited 15.06.2016] Available from: [www.targetedonc.com] original file name: D10_Broderick_2016.pdf attached as: Published-Evidence-8.pdf
D11	Non-patent literature - article	Le et al., "PD-1 Blockade in Tumors with Mismatch-Repair Deficiency" N ENGL J MED , Vol. 372, No. 26, 25 June 2015 original file name: D11_Le et al..pdf attached as: Published-Evidence-9.pdf
D12	Patent document	WO2016/077553 (A1) , 19.05.2016 original file name: D12_WO2016077553A1.pdf attached as: Published-Evidence-10.pdf
D13	Non-patent literature - article	Kroemer, Guido et al., "Colorectal cancer: the first neoplasia found to be under immunosurveillance and the last one to respond to immunotherapy?" Oncol Immunology, Vol. 4, No. 7, July 2015 original file name: D13_Kroemer et al..pdf attached as: Published-Evidence-11.pdf
D14	Non-patent literature - article	Dudley, Jonathan C. et al., "Microsatellite Instability as a Biomarker for PD-1 Blockade" Clin Cancer Res, Vol. 22, No. 4, 15 February 2016 original file name: D14_Dudley et al..pdf attached as: Published-Evidence-12.pdf
D15	Non-patent literature - article	Selby, Mark J. et al., "Preclinical Development of Ipilimumab and Nivolumab Combination Immunotherapy: Mouse Tumor Models, In Vitro Functional Studies, and Cynomolgus Macaque Toxicology" PLOS ONE, 09 September 2016 original file name: D15_Selby et al..pdf attached as: Published-Evidence-13.pdf
D2	Other evidence	Confirmation of D1's publication date from ASCO original file name: D2_ASCO.pdf attached as: Other-evidence-1.pdf
D3	Other evidence	NCT02060188 from clinicaltrials.gov, version of May 25, 2016 original file name: D3_NCT02060188.pdf attached as: Other-evidence-2.pdf
D4	Non-patent literature - book	Canfield Willis, Marjorie, "Medical Terminology, The Language of Health Care" Lippincott, Williams & Wilkins, 2006, Ed. 2nd original file name: D4_Marjorie Canfield Willis.pdf attached as: Published-Evidence-4.pdf
D5	Other evidence	A-Z Family Medical Encyclopedia, BMA, 2014

		original file name: D5_A-Z Family Medical Encyclopedia.pdf attached as: Other-evidence-3.pdf
D6	Non-patent literature - article	Jaafar, Lahcen et al., "Elucidating the role of human mismatch repair factor hMLH3" Cancer Biology & Therapy , Vol. 8, No. 14, 15 July 2009 particular relevance: 1421-1423 original file name: D6_Jaafar et al..pdf attached as: Published-Evidence-5.pdf
D7	Non-patent literature - article	Boland, C. Richard, "Roles of the DNA Mismatch Repair Genes in Colorectal Tumorigenesis" Int. J. Cancer (Pred. Oncol.), Vol. 69, 1996 particular relevance: 47-49 original file name: D7_Boland_1996.pdf attached as: Published-Evidence-6.pdf
D8	Non-patent literature - article	Buchbinder, Elizabeth I. et al., "CTLA-4 and PD-1 Pathways - Similarities, Differences, and Implications of Their Inhibition" Am J Clin Oncol , Vol. 39, 2016 particular relevance: 98-106 original file name: D8_Buchbinder et al. .pdf attached as: Published-Evidence-7.pdf
D9	Other evidence	NCT02231749 from clinicaltrials.gov, version of May 25, 2016 original file name: D9_NCT02231749_2016.pdf attached as: Other-evidence-4.pdf
P	Patent document	US62/345,662 (Prio) , 03.06.2016 original file name: P_US201662345662.pdf attached as: Published-Evidence-2.pdf
WO	Patent document	WO2017/210637 (A1) , 07.12.2017 original file name: WO2017210637.pdf attached as: Published-Evidence-1.pdf

X. Payment

Method of payment

Debit from deposit account

The European Patent Office is hereby authorised, to debit from the deposit account with the EPO any fees and costs indicated in the fees section below.

Currency:

EUR

Deposit account number:

28000741

Account holder:

Maiwald Patentanwalts- und Rechtsanwaltsgesellschaft mbH

Refunds

Any refunds should be made to EPO deposit account:

28000741

Account holder:

Maiwald Patentanwalts- und Rechtsanwaltsgesellschaft mbH

Fees

	Factor applied	Fee schedule	Amount to be paid
010 Opposition fee	1	840.00	840.00
Total:		EUR	840.00

A Forms

Details:

System file name:

A-1 Form for notice of opposition

ep-oppo.pdf

B Attached document files

Original file name:

System file name:

B-1 1. Facts and arguments

Notice of Opposition.pdf

OPPO.pdf

C Attached evidence files

Original file name:

System file name:

C-1 1. Patent document

WO2017210637.pdf

Published-Evidence-1.pdf

C-2 2. Patent document

P_US201662345662.pdf

Published-Evidence-2.pdf

C-3 3. Patent document

D12_WO2016077553A1.pdf

Published-Evidence-10.pdf

C-4 1. Non-patent literature - article

D1_Overman et al..pdf

Published-Evidence-3.pdf

C-5 2. Non-patent literature - article

D6_Jaafar et al..pdf

Published-Evidence-5.pdf

C-6 3. Non-patent literature - article

D7_Boland_1996.pdf

Published-Evidence-6.pdf

C-7	4. Non-patent literature - article	D8_Buchbinder et al. .pdf	Published-Evidence-7.pdf
C-8	5. Non-patent literature - article	D11_Le et al..pdf	Published-Evidence-9.pdf
C-9	6. Non-patent literature - article	D13_Kroemer et al. .pdf	Published-Evidence-11.pdf
C-10	7. Non-patent literature - article	D14_Dudley et al..pdf	Published-Evidence-12.pdf
C-11	8. Non-patent literature - article	D15_Selby et al..pdf	Published-Evidence-13.pdf
C-12	9. Non-patent literature - book	D4_Marjorie Canfield Willis.pdf	Published-Evidence-4.pdf
C-13	10. Non-patent literature - internet	D10_Broderick_2016.pdf	Published-Evidence-8.pdf
C-14	1. Other evidence	D2_ASCO.pdf	Other-evidence-1.pdf
C-15	2. Other evidence	D3_NCT02060188.pdf	Other-evidence-2.pdf
C-16	3. Other evidence	D5_A-Z Family Medical Encyclopedia.pdf	Other-evidence-3.pdf
C-17	4. Other evidence	D9_NCT02231749_2016.pdf	Other-evidence-4.pdf

Signature of opponent or representative

Place: München

Date: 26 July 2022

Signed by: Julia Mössinger 50647

Association: Maiwald Patentanwalts- und Rechtsanwaltsgesellschaft mbH

Representative name: Julia Mössinger

Capacity: (Representative)



Dörries Frank-Molnia & Pohlman
Patentanwälte Rechtsanwälte PartG mbB

Patents – Trademarks – Designs

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July 26, 2022

Opposition against Patent 3 464 373
(Application No. 17 731 359.0)

Title: USE OF ANTI-PD-1 ANTIBODY IN THE
TREATMENT OF PATIENTS WITH COLORECTAL
CANCER
Proprietor: Bristol-Myers Squibb Company
Opponent: Sandra Pohlman
Our Ref.: SP26935OP

On behalf of: Sandra Pohlman
Fünf Höfe, Theatinerstraße 16
80333 Munich
Germany,

we herewith file **Opposition** pursuant to Article 99(1) EPC against:

European Patent No. EP 3 464 373 B1
(European Appl. No. 17731359.0)

Publication and mention of the grant: 27.10.2021.

Title of the patent: USE OF ANTI-PD-1 ANTIBODY IN THE TREATMENT OF
PATIENTS WITH COLORECTAL CANCER

Proprietor: Bristol-Myers Squibb Company
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1 European Patent Attorney
2 European Trademark Attorney
3 European Design Attorney
4 Patentanwalt / Patentanwältin
5 Solicitor (England & Wales)
6 U.S. Patent Attorney
7 U.S. Patent Agent
8 Rechtsanwältin / Rechtsanwalt
9 Fachanwältin für
gewerblichen Rechtsschutz

Partnerschaftsregister des AG München
PR-Nr. 1278

We request that the opposition fee in the amount of EUR 840.00 be debited from our deposit account No. 28001000 (see also the corresponding debit order on the form accompanying the online submission of the present Notice of Opposition).

I. Extent of the Opposition and Requests

1. The opposition is directed against all claims 1 to 10 of the European patent EP 3 464 373 B1 (hereinafter "the opposed patent"). It is requested that the opposed patent be revoked in its entirety pursuant to Article 101(2) EPC.
2. Oral proceedings are requested in accordance with Article 116(1) EPC in the event that the Opposition Division does not consider the above request justified on the basis of our written submissions.

II. Grounds in Support of the Opposition

3. The opposition is based on the following grounds:
 - (a) the subject matter of the opposed patent lacks novelty (Art. 100(a) in connection with Art. 54 EPC),
 - (b) the subject matter of the opposed patent is not based on an inventive step (Art. 100(a) in connection with Art. 56 EPC) and
 - (c) the subject matter of the opposed patent is insufficiently disclosed (Art. 100(b) EPC in connection with Art. 83 EPC).

III. Documents relied upon in the Present Opposition Proceedings

4. The following documents are relied upon in this notice of opposition and submitted herewith:
 - D1:** Overman, MJ et al., "*Nivolumab ± ipilimumab in treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): CheckMate-142 interim results*", May 20, 2016, J. Clin. Oncol., 34:15_suppl, 3501-3501;
 - D2:** Snapshot of the website, Cancer.net, taken on May 23, 2016 by the WayBack machine;
 - D3:** Excerpts from Alberts et al., *Essential Cell Biology*, second edition, 2004;
 - D4:** Snapshot of Meriam Webster's definition of "colorectal" taken on May 22, 2016 by the WayBack Machine;
 - D5:** Excerpt from Stedman's Medical Dictionary, 27th Ed., 2000;

- D6:** Boland CR, et al., *"A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer"*, 1998, Cancer Res. 58(22):5248-57;
 - D7:** Boland CR, Goel A., *"Microsatellite instability in colorectal cancer"*, 2010, Gastroenterology, 138(6):2073-2087;
 - D8:** Poulogiannis G et al., *"DNA mismatch repair deficiency in sporadic colorectal cancer and Lynch syndrome"*, 2010, Histopathology, 56(2):167-79;
 - D9:** Buecher B et al., *"Role of microsatellite instability in the management of colorectal cancers"*, 2013, Dig Liver Dis., 45(6):441-9;
 - D10:** Vilar E, Gruber SB. *"Microsatellite instability in colorectal cancer-the stable evidence"*, 2010, Nat Rev Clin Oncol., 7(3):153-62;
 - D11:** Bellizzi AM and Frankel WL, *"Colorectal cancer due to deficiency in DNA mismatch repair function: a review"*, 2009, Adv Anat Pathol., 16(6):405-17;
 - D12:** Jass JR., *"Towards a molecular classification of colorectal cancer"*, 1999, Int J Colorectal Dis., 14(4-5):194-200;
 - D13:** Dietmaier, W. „Mikrosatelliteninstabilität“, 2010, Pathologe, 31:268–273;
 - D14:** Weissman SM, et al., *"Genetic counseling considerations in the evaluation of families for Lynch syndrome--a review"*, 2011, J Genet Couns., 20(1):5-19;
 - D15:** Giardiello FM, et al., *"AGA technical review on hereditary colorectal cancer and genetic testing"*, 2001, Gastroenterology, 121(1):198-213;
 - D16:** Loughrey MB, et al., *"Incorporation of somatic BRAF mutation testing into an algorithm for the investigation of hereditary non-polyposis colorectal cancer"*, 2007, Fam Cancer., 6(3):301-10;
 - D17:** Gatalica Z, et al., *"High microsatellite instability (MSI-H) colorectal carcinoma: a brief review of predictive biomarkers in the era of personalized medicine"*, 2016, Fam Cancer., 15(3):405-412; and
 - D18:** Pawlik, TM et al., *"Colorectal carcinogenesis: MSI-H versus MSI-L"*, 2004, Disease markers 20(4-5):199-206.
5. None of the documents cited above were considered during prosecution of the opposed patent.

IV. Formalities and Bibliographic Data

- 6. EP 3 464 373 B1 stems from PCT application No. PCT/US2017/035822, filed on June 2, 2017 and published as WO 2017/210637 A1.

7. The opposed patent claims priority from the US provisional application, US 201662345662 P, filed on **June 3, 2016**.

V. Priority (Article 87 EPC)

8. It is noted that the priority document, US 201662345662 P, does not contain example 2 of the opposed patent. Accordingly, in the event that any of the specifics of this example become relevant, we reserve the right to file further prior art.

VI. The claimed subject matter

9. The opposed patent has been granted with 10 claims. Claim 1 is an independent, second medical use claim; claims 2-9 contain dependent features of the claimed medical use; and claim 10 relates to a kit comprising the combination of agents to be used according to claims 1-9.
10. Independent claim 1 of the opposed patent is reproduced below for convenience, with key features emphasized:

Nivolumab for use in a method of treating a **colorectal cancer** tumor in a subject, wherein the tumor exhibits a **high degree of microsatellite instability ("MSI-H")**, wherein the subject is administered **nivolumab at a dose of about 3 mg/kg** body weight **in combination** with **ipilimumab at a dose of about 1 mg/kg** body weight **once about every three weeks**.

11. Dependent **claims 2-4** further define the tumor according to claim 1, requiring that the tumor:
 - "is a colon cancer or a rectal cancer" (**claim 2**); and/or
 - "exhibits **one or more** characteristics selected from the group consisting of:
 - (a) the tumor comprises a germline alteration in at least two, at least three, at least four, or at least five DNA mismatch repair genes ("MMR genes");
 - (b) the tumor comprises a germline alteration in at least 30% of five or more MMR genes;
 - (c) **at least one** protein encoded by DNA MMR genes is not detected in the tumor; and
 - (d) any combination thereof,
 wherein the DNA MMR genes comprise MSH2, MLH1, MSH6, PMS2, PMS1, or any combination thereof" (**claims 3 and 4**).
12. Dependent **claim 5** specifies that the subject exhibit either a **PFS** or **OS** of at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months after the administration of the claimed combination therapy.

13. Dependent **claims 6 and 7** further define the administration of the claimed combination therapy. Specifically, the administration of nivolumab and ipilimumab is either “followed by an anti-PD-1 antibody monotherapy” (claim 6), or “comprises four doses for each” (claim 7).
14. Dependent **claims 8 and 9** further define the subject to be treated. Specifically, the subject has “received one, two, three, four, five or more prior cancer treatments” (claim 8) and/or “progressed on other cancer treatments” (claim 9).
15. **Claim 10** specifies “A kit for use in a method of treating a colorectal cancer tumor in a subject, comprising: (a) nivolumab; and (b) ipilimumab, wherein the method is defined as in any one claims 1 to 9”.

VII. Claim Interpretation

16. Claims 3(a) and (b) each specify that “the tumor comprises a germline alteration...”
17. It is noted that a germline alteration is commonly known as a genetic change occurring in a reproductive cell (egg or sperm) that becomes incorporated into the DNA of every cell of the offspring (c.f., **D2**, page 1, “Germline mutations”; and **D3** pages 293-249, “Generating Genetic Variation”; figure 9-2; and page G:8, entries for “germ cell” and “germ line”).
18. Since a tumor does not comprise any reproductive cells, it is not clear how a tumor may comprise a germline alteration; and the patent does not provide any guidance in that regard. There is no teaching in the description as to how a germline alteration may occur in a tumor; and the examples have not demonstrated any means of germline testing, let alone in a tumor. If claims 3(a) and (b) are indeed intended to mean that a tumor comprises a germline alteration, then these features are not sufficiently disclosed.
19. Claim 3(a) and (b) may instead be interpreted as meaning that the subject according to claims 1 or 2 comprises a germline alteration in at least two DNA MMR genes, or at least 30% of five MMR genes (i.e., that the tumor has an inherited alteration in at least two MMR genes, or at least 30% of five MMR genes). This interpretation is consistent with [0061] of the opposed patent.
20. Regarding claim 3(b), this feature requires a germline alteration in “at least 30% of five MMR genes”. In other words, claim 3(b) requires a germline alteration in 1½ MMR genes. However, a gene is a whole unit entity and cannot be defined by a fraction, i.e., a fraction of a gene is no longer a gene. Accordingly, claim 3(b) will be interpreted as requiring an alteration in at least two MMR genes, which is equivalent to the requirement of claim 3(a) and thus adds no further limitation to the claim.
21. Claims 3 and 4 can thus be interpreted as requiring that,
 - (i) the **subject** comprises a germline alteration in at least two...DNA MMR genes;

- (ii) at least one protein encoded by DNA MMR genes is not detected in the tumor; or
- (iii) any combination thereof...

wherein the DNA MMR genes comprise MSH2, MLH1, MSH6, PMS2, PMS1, or any combination thereof.

VIII. Novelty (Articles 100(a) EPC 54 EPC)

VIII.1 Claims 1-9 lack novelty in view of D1

- 22. **D1** is an abstract for the 2016 ASCO annual meeting, which discloses interim results of the CheckMate-142 trial. **D1** was published on May 20, 2016, before the priority date, and thus qualifies as full prior art under Article 54(2) EPC.

Claim 1

- 23. Claim 1 of the opposed patent is reproduced again below for convenience, with key features emphasized:

Nivolumab for use in a method of treating a **colorectal cancer** tumor in a subject, wherein the tumor exhibits a **high degree of microsatellite instability ("MSI-H")**, wherein the subject is administered **nivolumab at a dose of about 3 mg/kg** body weight **in combination** with **ipilimumab at a dose of about 1 mg/kg** body weight **once about every three weeks**.

- 24. All features of claim 1 are disclosed in **D1**, as outlined below.
- 25. **D1** relates to **"Nivolumab ± ipilimumab in treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): CheckMate-142 interim results"** (Title, emphasis added). **"CheckMate-142, a phase 2 study, evaluates N ± I [Nivolumab ± Ipilimumab] in pts with mCRC, MSI-H and non-MSI-H"** (**D1**, page 2, "Background").
- 26. **D1** thus discloses interim results of the CheckMate-142 trial, which evaluates the use of Nivolumab ("N") with or without Ipilimumab ("I") for treating a subject with a colorectal cancer tumor which exhibits a high degree of microsatellite instability (MSI-H).
- 27. According to **D1**, **"MSI-H pts received N 3 mg/kg q2 wk (N3) or N 3 mg/kg + I 1 mg/kg q3 wk (N3+I1) x 4 doses followed by N3..."** (**D1**, page 2, "Methods" section, emphasis added).
- 28. Accordingly, **D1** discloses that MSI-H subjects in the trial were administered nivolumab either as a monotherapy or as part of a combination therapy. Those patients receiving the combination therapy were administered nivolumab at a dose of 3 mg/kg body weight in combination with ipilimumab at a dose of 1 mg/kg body weight, once every three weeks.

29. Finally, **D1** discloses that Nivolumab alone and in combination with Ipilimumab offered a therapeutic benefit to MSI-H patients.
30. In particular the table bridging pages 3 and 4 of **D1** shows the therapeutic efficacy of N and N+I in MSI-H patients¹. The table is reproduced below, for the sake of convenience:

MSI-H^a efficacy.

	N3 (n = 33)	N3+I1 (n = 26)
ORR, n (%)	9 (27)	4 (15)
CR	0	0
Confirmed PR	9 (27)	4 (15)
SD	8 (24)	17 (65)
PD	11 (33)	3 (12)
Not determined/not reported	5 (15)	2 (8)
Median duration of response (95% CI), mo	NR (4.2-NE)	NR (NE-NE)
Median PFS (95% CI), mo	5.3 (1.4-NE)	NR (NE-NE)
4-mo PFS rate, ^b %	55	80
Median OS (95% CI), mo	16.3 (8.3-NE)	NR (NE-NE)
5-mo OS rate, ^c %	75	100

NR, not reached; NE, not estimable ^aBy local screen ^bPFS Kaplan-Meier plot estimate, N3 = 17/33 events, N3+I1 = 4/26 events ^cPFS Kaplan-Meier plot estimate, N3 = 11/33 events, N3+I1 = 0/26 events

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31. As may be taken from the above table, an 80% 4-mo PFS rate; and 100% 5-mo OS rate were observed for MSI-H patients receiving the combination therapy according to claim 1. **D1** thus concludes, that “*N and N+I were well tolerated in most pts and demonstrated **encouraging clinical activity and survival in MSI-H mCRC***” (Page 3, conclusions, emphasis added).
32. Accordingly, **D1** discloses that the claimed combination therapy is therapeutically effective in patients with a colorectal cancer tumor exhibiting a high degree of microsatellite instability.
33. Claim 1 thus lacks novelty in view of **D1**.

¹ As may be taken from the “methods” section on page 2 of **D1**, the annotations “N3” and “N3 +I1” used in the table refer to the monotherapy of Nivolumab 3 mg/kg Q2W; and the combination of Nivolumab 3 mg/kg + Ipilimumab 1mg/kg Q3W, respectively. In particular, the methods disclose that “*MSI-H pts received N 3 mg/kg q2 wk (**N3**) or N 3 mg/kg + I 1 mg/kg q3 wk (**N3+I1**) x 4 doses followed by N3*”.

Claim 2

34. Claim 2 requires that *“the tumor is a colon cancer or a rectal cancer”* (emphasis added).
35. Colorectal cancer is by definition a colon cancer or a rectal cancer. According to a snapshot taken of the Meriam-Webster Medical Dictionary in May 2016 (**D4**), the term “colorectal” is defined as *“relating to or affecting the **colon** and the **rectum**”* (see also the entry for “colorectal” in the medical dictionary provided in **D5**). Claim 2 is thus not limiting in view of claim 1, which requires that the patient have a colorectal cancer.
36. **D1** explicitly discloses that the patients have colorectal cancer. Accordingly, these patients will necessarily have a colon cancer or a rectal cancer.
37. Claim 2 thus lacks novelty in view of **D1** for the same reasons as claim 1.

Claims 3 and 4

38. As we have explained above, claims 3 and 4 can be interpreted as requiring that,
- (i) the **subject** comprises a germline alteration in at least two...DNA MMR genes;
 - (ii) at least one protein encoded by DNA MMR genes is not detected in the tumor; or
 - (iii) any combination thereof...
- wherein the DNA MMR genes comprise MSH2, MLH1, MSH6, PMS2, PMS1, or any combination thereof.
39. **D1** does not explicitly disclose features (i)-(iii), however an explicit disclosure is not required to deprive the claimed subject matter of novelty. In particular, it is well-established that,

*“...a prior art disclosure is novelty-destroying if the subject-matter claimed can be inferred directly and unequivocally from that disclosure, including features which for the skilled person are implicit in what is explicitly disclosed (see **T 677/91**; **T 465/92**, OJ 1996, 32; **T 511/92**; and **T 2170/13**...)”*

*“In **T 701/09** the board found that direct and unambiguous disclosure was not limited to explicit or literal statements, but equally included implicitly disclosed information which a reader skilled in the art would unequivocally gather from the overall context of a cited document.”*

(Page 116, section I.C.4.3 of the CLB, 9th Ed.).

40. We submit that the skilled person would clearly and unambiguously derive the characteristics of claims 3 and 4 from **D1** in view of the patients’ disclosed MSI-H status.

41. As will be explained below, MSI was a well-known form of genetic instability occurring in CRC tumors. This form of instability was known to be a direct consequence of a defective MMR system, and was commonly diagnosed by observing a lack of expression of one of the five known MMR proteins recited in claim 4. In other words, the skilled person knew that a tumor that had been diagnosed as “MSI” will necessarily exhibit the characteristic according to claims 3(c) and 4 (feature (ii)). It was further known that MSI tumors could be characterized as displaying a “high” MSI frequency (MSI-H), or a “low” MSI frequency (MSI-L); and that MSI tumors were classified as “MSI-H” or “MSI-L” according to a set of recognized international guidelines. Indeed, the patent followed these well-known guidelines to classify tumors as “MSI-H” in the examples. It must then be concluded that the characteristics of claims 3(a), (b) and 4 (i.e., feature (i)) are clearly derivable from a disclosure of a CRC tumor that has been classified as “MSI-H”.
42. Given that the patients in **D1** are explicitly disclosed to have MSI-H tumors, it is immediately clear to the skilled person based on his or her common general knowledge at the relevant date that these patients will necessarily exhibit one or more of the characteristics recited in claims 3 and 4. Claims 3 and 4 thus lack novelty in view of **D1** by virtue of the patients’ disclosed MSI-H status.
43. The feature recited in claims 3(c) and 4 (feature (ii)) is the broadest characteristic, being anticipated by a disclosure of a CRC tumor that has been classified as MSI (irrespective of whether the MSI displays a “high” or “low” frequency). Accordingly, this feature will be discussed first. We will then address the characteristic recited in claims 3(a), (b) and 4 (feature (i)).

Claims 3(c) and 4 are derivable from the “MSI” classification given in D1

44. Granted claims 3(c) and 4 (feature (ii)) merely recite a well-known diagnostic feature of microsatellite instability (MSI). Accordingly, any CRC tumor that has been classified as displaying MSI will necessarily lack expression of at least one protein encoded by the MSH2, MLH1, MSH6, PMS2, or PMS1 genes.
45. At the time of priority, microsatellite instability (MSI) had been defined as *“a change of any length due to either insertion or deletion of repeating units, in a microsatellite within a tumor when compared to normal tissue”* (**D6**, page 5249, right column, “Definitions”). Microsatellites are short repetitive units of DNA (typically 1–6 bases) that are distributed throughout the genome (in coding and non-coding regions). The repetitive nature of microsatellites makes them vulnerable to insertion/deletion errors during replication, which are typically repaired by the MMR system, a group of proteins comprising MSH2, MLH1, MSH6, PMS2, and PMS1 (**D7**, pages 2075-2076, “DNA MMR System”; **D8**, page 168, right column, “The molecular basis of MMR deficiency”, 1st par.). However, when the MMR system is not functioning properly (i.e., when the MMR system is defective), these errors are not repaired, leading to instability (i.e., MSI) (c.f. **D7**, page 2075 “DNA MMR System” and **D9**, page 441, section 2.1). A defective MMR system (and consequently MSI) may be attributed to a loss of function in any one of the known MMR proteins, but most commonly

occurs with MSH2, MLH1, MSH6 or PMS2 (D8, page 168, left column, penultimate par.; see also D10, abstract).

46. Accordingly, it was part of the skilled person's common general knowledge before the priority date that MSI in CRC tumors was a direct consequence of a defective MMR system. This is further supported by the following excerpts from various review articles:

*"Microsatellite instability (MSI) is a hypermutable phenotype **caused by** the loss of DNA mismatch repair activity" (D7, abstract, emphasis added).*

*"Microsatellite instability (MSI) is **the molecular fingerprint of a deficient mismatch repair system**" (D10, abstract, emphasis added).*

*"First discovered in CRC, **the MSI phenotype continues to serve as the hallmark of defective MMR...**" (D10, page 154, left column, emphasis added).*

*"DNA mismatch repair (MMR) deficiency is one of the best understood forms of genetic instability in colorectal cancer (CRC), and is **characterized by the loss of function of the MMR pathway**. Failure to repair replication-associated errors due to a defective MMR system allows persistence of mismatch mutations all over the genome, but especially in regions of repetitive DNA known as microsatellites, **giving rise to** the phenomenon of **microsatellite instability (MSI)**" (D8, abstract, emphasis added).*

*"Microsatellite instability is **the consequence** of a deficient mismatch repair system" (D9, abstract, emphasis added).*

47. This is indeed consistent with the teaching of the patent which states that, *"Microsatellite instability is the condition of genetic hypermutability that **results from** impaired DNA mismatch repair (MMR). The presence of MSI represents **phenotypic evidence** that MMR is not functioning normally"* (par. [0061]).
48. Given that a loss of function in the MMR system manifests as an MSI "phenotype", detection of a deficient MMR system became an accepted tool for diagnosing MSI. In particular, it was known that a loss of function in one of the MMR proteins could be detected (and consequently, MSI could be diagnosed) by observing a lack of expression of at least one MMR protein in an immunohistochemical assay:

*"Methods to detect MSI are **well established** and **routinely incorporated** into clinical practice. A clinical and molecular profile of MSI tumors has been described, leading to the concept of an MSI phenotype in CRC" (D10, abstract, emphasis added).*

*"**Immunohistochemical analysis of MMR proteins has become a popular alternative to detect MSI** in the clinical setting and as a complement to the genetic testing of Lynch*

syndrome. Antibodies against MLH1, MSH2, MSH6 and PMS2 provide insight into the functionality of the MMR system. Lack of expression of one or more of these proteins is diagnostic of deficient MMR, and determines which encoding gene is most likely to harbor a germline mutation or to have been inactivated by another mechanism" (D10, page 154, right column, final par., emphasis added).

*"Deficient mismatch repair (dMMR) function **manifests as** immunohistochemically detectable absence of one or more MMR proteins and microsatellite instability (MSI)"* (D11, abstract, emphasis added).

*"Immunohistochemistry is a simple, fast and inexpensive method to detect MSI. It was shown to have a...**100% predictive value of MSI phenotype** in case of abnormal pattern"* (D9, pages 442-443, section 3.3; see also Table 1, emphasis added).

*"**MSI-H cancers show loss of mismatch repair proteins** which can be demonstrated immunohistochemically"* (D12, page 197, left column, 2nd par., emphasis added).

49. In view of the above common general knowledge, it is evident that the skilled person was aware that MSI was caused by the loss of function of one or more of the MMR proteins, such as MLH1, MSH2, MSH6, PMS1 or PMS2; and that MSI could be diagnosed immunohistochemically by lack of expression of one or more of these proteins. Accordingly, the skilled person knew that any tumor that has been confirmed to display MSI (irrespective of whether the MSI exhibits a high or low frequency) will necessarily lack expression of at least one of the proteins encoded by the genes in claim 4.
50. Given that the mCRC patients in D1 are explicitly disclosed to have tumors that are classified as displaying MSI-H, it is immediately clear to the skilled person that at least one protein encoded by a DNA MMR gene according to claim 4 will not be detected in these tumors. Accordingly, the features of at least claims 3(c) and 4 are clearly and unambiguously derivable as a direct consequence of the known "MSI-H" status of the patients' tumors in D1.
51. Given that claim 3 only requires that one characteristic from the list of items (a)-(d) be displayed; and that claim 4 in combination with claim 3(c) only requires one of the specific DNA MMR genes to be disclosed, it is already apparent that claims 3 and 4 lack novelty in view of D1.

Either a patient according to claims 3(a),(b) and 4 cannot be distinguished from the MSI-H patients in D1, or they are clearly derivable from the "MSI-H" classification given in D1

52. As we have explained above, granted claims 3(a) and (b) are equivalent, each requiring that (i) the **subject** comprises a germline alteration in at least two...DNA MMR genes. According to claim 4, the DNA MMR genes comprise MSH2, MLH1, MSH6, PMS2, PMS1, or any combination thereof.

53. As will be explained below, either a patient exhibiting the feature according to claims 3(a), (b) and 4 is indistinguishable from the MSI-H patients of **D1**, or this feature must be considered derivable based on the skilled person's common general knowledge regarding the MSI-H status disclosed in **D1**.
54. In particular, CRC tumors were known to be classified as "MSI-H" according to a set of internationally recognized guidelines. Notably, patients in the examples of the patent were indeed classified as MSI-H based on these guidelines. The skilled person further knew that MSI-H was a hallmark characteristic of Lynch syndrome, a heritable form of CRC which is characterized by a germline alteration in at least one of the DNA MMR genes. Lynch syndrome patients were known to account for approximately 20% of all MSI cases and were nearly always classified as MSI-H. It is thus reasonable to assume that a non-negligible portion of the MSI-H patients in **D1** had this heritable form of disease and consequently exhibited a germline alteration in at least one MMR gene.
55. Although claims 3(a) and (b) require a germline alteration in at least two MMR genes, this feature cannot establish a discernable clinical situation in view of **D1**. In particular, irrespective of whether a patient has a germline alteration in at least one or at least two MMR genes, they will ultimately exhibit the same MSI-H tumor "phenotype" and benefit from the same therapy.
56. Accordingly, the recitation of a germline alteration in at least two MMR genes is, at best, an arbitrary feature that has no functional link to the therapeutic effect.

*"In T 233/96 the board held that if the use of a compound was known in the treatment or diagnosis of a disease of a particular group of subjects, the treatment or diagnosis of the same disease with the same compound could nevertheless represent a novel therapeutic or diagnostic application, provided that it was carried out on a new group of subjects which was **distinguished from the former by its physiological or pathological status** (T 19/86, OJ 1989, 25; T 893/90). **This did not apply, however if the group chosen overlapped with the group previously treated, or the choice of the novel group was arbitrary** which meant that no functional relationship existed between the particular physiological or pathological status of this group of subjects (here humans who were unable to exercise adequately) and the therapeutic or pharmacological effect achieved" (page 156, section I.C.7.2.4.b) of the CLB, 9th Ed., emphasis added).*

57. At any rate, given that the opposed patent did not perform any germline testing, least of all demonstrate the presence of a germline alteration in at least two MMR genes, it must be concluded that this feature can be clearly derived from classifying a tumor as MSI-H according to the well-known guidelines. If this is not the case, then the claimed medical use is not sufficiently disclosed.

58. We will outline below what was known to the skilled person at the time of priority regarding the MSI-H classification and why the skilled person would assume that the trial in **D1** included Lynch syndrome patients based on this specific classification.

An “MSI-H” classification was based on a set of well-known international guidelines

59. As explained above, MSI was a well-known form of genetic instability occurring in CRC tumors which was caused by a defective MMR system. In particular, it was known that loss of function of at least one of the MMR proteins resulted in the system's failure to repair replication-associated errors, thereby leading to a high accumulation of mutations in microsatellites (short repetitive stretches of DNA that are especially prone to replication errors) (c.f. **D8**, page 168, left column, penultimate par.; and **D9**, page 441, right column, section 2.1). Depending on the frequency of the resulting instabilities, MSI could be classified as “high” or “low”.
60. It was thus known to the skilled person that CRC tumors could be classified into one of three categories depending on their MSI status: (i) microsatellite stable (MSS); (ii) low frequency of microsatellite instability (MSI-L); or (iii) high frequency of microsatellite instability (MSI-H) (c.f., **D8**, page 168, right column, last par; and **D10**, page 154, “Detection of MSI”).
61. CRC tumors were known to be classified as MSS, MSI-L or MSI-H according to a set of guidelines that were established at an international consensus meeting held in 1997:

*“Several studies...have now shown that a subset of colorectal cancer demonstrates the phenomenon of MSI and that such tumors can be divided into several groups. The first is characterized by MSI-H (that is, the majority of markers exhibit MSI); a second group with MSI-L (i.e., only a minority of markers exhibit MSI); and a third group lacking apparent instability (none of the markers exhibit MSI; MSS) (**D6**, page 5249, right column, 3rd par).*

*“On the basis of those studies performed to date, it was clear that many markers could be used to define and distinguish MSI-H from MSI-L/MSS tumors. For the purposes of providing some uniformity in this area, however, the workshop participants agreed to identify a working “reference” panel of markers with guidelines for defining the MSI-H tumor groups (Table 1). The recommended panel validated by Ruschoff and Fishel... is composed of two mononucleotide repeats (BAT26 and A4725) and three dinucleotide repeats (D5S346, D2S123. and D17S250). Using this reference panel, MSI-H tumors are defined as having instability in two or more markers, whereas MSI-L tumors are defined as having instability in one marker... these reference markers will identify those tumors characterized by defective mismatch repair, primarily in the two major mismatch repair genes, hMSH2 and hMLH1... If more than five markers are used to identify these particular tumor phenotypes, then the participants recommended that the criteria be modified to assess the percentage of markers demonstrating instability rather than the absolute number. In this case, the **MSI-H group of tumors would be defined as***

having MSI in 30-40% of the markers tested...” (D6, page 5250, left and right columns, bridging par.).

62. The above recommendations are summarized in table 1 of D6, which is reproduced below, for convenience, with the criteria for MSI-H classification highlighted.

Table 1 International guidelines for evaluation of MSI in colorectal cancer

Reference panel			
Marker	Repeating unit	GenBank accession no.	
BAT25	Mononucleotide	9834508	
BAT26	Mononucleotide	9834505	
D5S346	Dinucleotide	181171	
D2S123	Dinucleotide	187953	
D17S250	Dinucleotide	177030	

Criteria for interpretation			
	5 loci analyzed	>5 loci analyzed	Interpretation
No. of markers	≥2	≥30–40%	MSI-H
Exhibiting instability	1	<30–40%	MSI-L
Length changes	0	0	MSS or MSI-L

Alternative loci ^a			
BAT40	D18S55	D3S1029	D5S107
BAT34C4	D18S58	D10S197	D8S87
TGF-β-RII	D18S61	D13S175	D18S69
ACTC (635/636)	D18S64	D17S588	D13S153
			D17S787
			D7S519
			D20S100

^a Marker information was contributed by J. Ruschoff, R. Fishel, S. Hamilton, R. Fodde, J. Gilbert, R. Hamelin, I. Kirsch, S. Markowitz, B. Bapat, and S. N. Thibodeau.

63. The above guidelines for classifying CRC MSI status were well-recognized and indeed formed part of the skilled person’s common general knowledge before the priority date, as evidenced by the numerous review articles submitted herewith, which reference the above information (c.f. D7 page 2083, “MSI-High and “MSI-Low”; D9, page 442, section 3.2; D10, page 154, “Detection of MSI”; D12, page 195, left column, “Testing for DNA microsatellite instability”.; D13, page 269, left column, 1st par.; D14, page 8, right column, “Microsatellite Instability”; and D15, Table 5).
64. It was thus known that CRC tumors were known to be classified as MSI-H if they displayed an instability (i.e, an alteration) in at least two out of five reference loci (or in ≥30% of reference loci, if more than five were analyzed).
65. It is noted that the patent indeed followed the above guidelines to classify tumors as “MSI-H” in the examples:

“The colorectal cancer of patients was determined to be microsatellite instability-high (MSI-H) by polymerase chain reaction (PCR) if two or more markers showed instability out of 5 loci tested or if at least 30% of the markers showed instability when 5 or more loci were tested” ([0117] of the B1 spec, emphasis added).

66. The above guidelines do not specify that all reference loci are associated with MMR genes, or that the instability is a “germline” alteration (i.e., the guidelines do not specify that the panel of markers identifies a germline alteration in at least two MMR genes). However, given that an MSI-H classification was known to be a hallmark of Lynch syndrome, a hereditary form of CRC characterized by the presence a germline mutation in at least one MMR gene, the skilled person would expect any group of MSI-H CRC patients to encompass individuals exhibiting this characteristic.

An “MSI-H” classification was known to be a hallmark of Lynch Syndrome

67. As we have explained above, MSI was a well-known form of genetic instability occurring in CRC tumors as a result of a deficient MMR system.
68. Further, MSI was known to occur in roughly 15% of all CRC tumors: 3% of MSI cases were attributed to a heredity form of disease, known as Lynch syndrome (also known as HNPCC²), which is caused by germline mutations in the MMR genes. The remaining 12% of MSI cases were associated with non-familial (“sporadic”) cancer, which is caused by silencing of the MLH1 MMR gene. MLH1 silencing in sporadic MSI cancer was known to primarily occur through hypermethylation of the MLH1 promoter, but had also been seen as a result of germline mutations in MSH2 and MLH1.

“MSI is detected in about 15% of all colorectal cancers; 3% are of these are associated with Lynch syndrome and the other 12% are caused by sporadic, acquired hypermethylation of the promoter of the MLH1 gene, which occurs in tumors with the CpG island methylator phenotype” (D7, abstract).

*“Lynch syndrome is a hereditary cancer predisposition syndrome that is inherited in an autosomal dominant manner and is **caused by germline mutations in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2**” (D14, page 6, left column, 2nd par., emphasis added).*

“The majority of MSI observed in sporadic cases seem to be caused by somatic hypermethylation of the hMLH1 promoter. It has also been observed that absent hMSH2 IHC expression is associated with germline hMSH2 mutation, and a minority of absent hMLH1 IHC expression is associated with germline hMLH1 mutation” (D15, page 205, left column, 1st par., emphasis added).

69. Accordingly, the skilled person knew that if a patient was classified as having an “MSI” CRC tumor, then they either had a heritable form of the disease (Lynch syndrome) resulting from a germline mutation in one of the main MMR genes, or sporadic MSI owing primarily to epigenetic

² Lynch syndrome is also known as hereditary nonpolyposis colorectal cancer (HNPCC), c.f. D7, page 2074, right column, last par.; D10, page 154, left column); and D14, page 6, left column, last par.

silencing of MLH1. The former case (Lynch syndrome) was nearly always classified as MSI-H, making the MSI-H classification a “hallmark” of the disease.

“Ninety five percent or more of Lynch syndrome-related CRCs are MSI-H...Thus an MSI-H tumor is suggestive...of Lynch syndrome” (D14, page 8, right column, “MSI”, 2nd par., emphasis added).

***“MSI at high frequency caused by a defective MMR system is a hallmark of the most common hereditary form of CRC, previously known as HNPCC, but which has now reverted to being called Lynch syndrome. LS sufferers inherit one germ-line mutation in an MMR gene and develop tumours from clonal expansion of those cells acquiring a second hit, mutation or loss or epigenetic inactivation, of the remaining wild-type allele resulting in no overall expression of functional proteins for that MMR gene**”* (D8, page 171, left column, 2nd par., emphasis added).

70. Given that Lynch syndrome was known to account for roughly 20% (3/15) of all MSI cases; and that MSI-H, was a “hallmark” of this disease, it is reasonable to assume that a non-negligible portion of the MSI-H patients in D1 had this heritable form of disease and consequently, a germline mutation in at least one of the five MMR genes. In support of this assumption, D1 explicitly discloses that only 25% of the MSI-H patients receiving the combination therapy tested positive for the BRAF V600E mutation, which is a specific marker known to be useful for excluding Lynch syndrome (c.f. D1, page 3, line 2; D8, page 173, left and right columns, bridging paragraph; D9, page 444, left column, 2nd par.); D11, page 411, bridging par. and table 3; and D16, page 302, left column, 1st par.; “Introduction”, last 2 paragraphs; pages 308-309, bridging par.).
71. Although claims 3(a) and (b) require a germline alteration in at least two MMR genes, this feature cannot create a distinct clinical situation in view of the known patients exhibiting a germline alteration in at least one MMR gene. In particular, both sets of patients will ultimately display the same MSI-H “phenotype” and consequently benefit from the same therapy.
72. We note that this argument applies even if the all of the MSI-H patients in D1 *arguendo* had sporadic CRC owing to a somatic mutation in an MMR gene. Irrespective of whether an MMR protein has lost its function as a result of a somatic mutation or a germline mutation, this loss of function will ultimately manifest as the same MSI-H “phenotype” and be treated with the same therapy.
73. Accordingly, a patient according to claims 3(a), (b) and 4 cannot be distinguished from the MSI-H patients disclosed in D1 in a meaningful way. Whether a patient displays the MSI-H “phenotype” as the result of a somatic mutation in an MMR gene, a germline mutation in at least one MMR gene, or a germline mutation in at least two MMR genes has no bearing on the therapeutic effect and a patient group defined accordingly must be considered arbitrary (T 233/96).

74. At any rate, given that the patent did not perform any germline assays, it must be concluded that a patient whose CRC tumor has been classified as “MSI-H” according to the well-known guidelines will inevitably exhibit a “germline alteration in at least two...DNA MMR genes”. If this is not the case, then the opposed patent has not shown a therapeutic effect in a subject according to claims 3(a) and (b), which would consequently lack sufficiency of disclosure.
75. Accordingly, either a patient according to claims 3(a), (b) and 4 cannot be distinguished from the MSI-H patients of **D1**, or the feature according to claims 3(a), (b) and 4 must be derivable from a tumor that has been classified as “MSI-H”. If the latter is not the case, then claims 3(a) and (b) are not sufficiently disclosed.

Claim 5

76. Claim 5 recites that *“(i) the subject exhibits a progression free survival of...at least about 4 months...or (ii) the subject exhibits an overall survival of...at least 5 months...”*
77. As we have explained above under claim 1, the table in **D1** shows that 80% of the subjects receiving the claimed combination therapy exhibited a PFS of 4 months; and 100% of the subjects exhibited an OS of 5 months. Accordingly, **D1** discloses a subject falling within the scope of claim 5.
78. Claim 5 thus lacks novelty in view of **D1**.

Claims 6 and 7

79. Claim 6 specifies that the combination therapy is *“followed by an anti-PD-1 antibody monotherapy”*.
80. Claim 7 requires that *“the administration of nivolumab and ipilimumab comprises four doses each”*.
81. According to the “methods” section on page 2 of **D1**, the MSI-H patients receiving the combination therapy were administered *“N 3 mg/kg + I 1 mg/kg q3 wk (N3+I1) x 4 doses followed by N3...”* As we have noted above, “N3” is denoted in **D1** as referring to the monotherapy of Nivolumab 3 mg/kg, 2QW (see footnote under claim 1). Nivolumab is an anti-PD-1 antibody (c.f. par. [0004], [0007], [0076]-[0078] of the opposed patent).
82. Accordingly, the patients in **D1** were administered 4 doses each of nivolumab and ipilimumab, followed by an anti-PD-1 antibody monotherapy.
83. Claims 6 and 7 thus lack novelty in view of **D1**.

Claim 8

84. Claim 8 specifies that *“the subject has received one, two, three, four, five or more prior cancer treatments”*.
85. According to **D1**, 92% of MSI-H patients receiving the combination therapy *“had ≥ 2 prior regimens”* (**D1**, “Results”, sentence bridging pages 2 and 3). Accordingly **D1** discloses a subject falling within the scope of claim 8.
86. Claim 8 thus lacks novelty in view of **D1**.

Claim 9

87. Claim 9 specifies that *“the subject has progressed on other cancer treatments”*.
88. According to the “methods” section on page 2 of **D1**, *“Pts had ECOG PS 0–1, and intolerance/progression on ≥ 1 tx”*. Accordingly, the subjects in **D1** had progressed on at least one previous treatment.
89. Claim 9 thus lacks novelty in view of **D1**.
90. In summary, it has been shown that claims 1-9 lack novelty in view of **D1**.

IX. Inventive Step (Articles 100(a) and 56 EPC)**IX.1 If novel, claims 1 and 2 lack an inventive step in view of D1**

91. As made clear above, claim 1 lacks novelty over **D1**. If for some reason the OD acknowledges the novelty of claim 1, the claimed subject matter is not inventive, since all features of claim 1 are disclosed in **D1**.
92. As we have explained above, claim 2 lacks novelty in view of **D1**. For completion, we submit that a limitation to “colon cancer” or “rectal cancer” would further lack an inventive step.
93. As explained above, the patients in **D1** were explicitly disclosed to have colorectal cancer and will thus have either a colon cancer or a rectal cancer. This is a direct consequence of the definition of “colorectal”.
94. Accordingly, it would be entirely obvious to treat either a colon cancer or a rectal cancer in view of **D1**. Given that the patent has not shown that either of these cancers is more responsive to the claimed therapy than the other, any limitation based on claim 2 would be an arbitrary selection from **D1** and thus lack an inventive step.

IX.2 If novel, claims 3 and 4 lack an inventive step in view of D1 in light of the common general knowledge

Claims 3(a), (b) and 4

95. If the OD does not agree that the patients in **D1** whose tumors were classified as MSI-H are indistinguishable from the patient group according to claims 3(a), (b) and 4, then this patient group must be considered obvious in view of the common general knowledge regarding CRC MSI-H tumors.
96. As we have explained above, **D1** explicitly discloses that the mCRC patients included in the Checkmate-142 study had MSI-H tumors. Based on his or her common general knowledge regarding MSI tumors, the skilled person understood that these patients either had a sporadic form of cancer, or a hereditary form the disease (Lynch syndrome). Given that Lynch syndrome was known to account for roughly 20% (3/15) of all MSI cases; and that MSI-H, was a “hallmark” of this disease, it is reasonable to assume that a non-negligible portion of the MSI-H patients in **D1** had this heritable form of disease and consequently, a germline mutation in at least one of the five MMR genes (see discussion under Novelty).
97. Claims 3(a), (b) and 4 thus allegedly differ from this well-known category of MSI-H tumors in that the patient is required to exhibit a germline mutation in at least two MMR genes.
98. There is no technical effect associated with any alleged difference of having an additional germline mutation. In particular, the patent has not even demonstrated that the therapeutic effect is related to the presence of a single germline mutation (as opposed to a somatic mutation), let alone two germline mutations.
99. The technical problem in view of **D1** is thus the selection of an alternative MSI-H patient group to treat with the combination therapy.
100. **D1** already demonstrated that the claimed combination therapy was effective in CRC tumors that were classified as MSI-H. Given that MSI-H was known as the “hallmark” of Lynch syndrome, the skilled person would have assumed that the trial disclosed in **D1** encompassed patients with this hereditary form of disease. At the very least, there would have been a strong motivation to treat this patient group based on the MSI-H status disclosed in **D1** and the common general knowledge regarding this classification.
101. Given that Lynch syndrome patients are known to have a germline mutation in at least one MMR gene, it would have been obvious to include patients with a mutation in at least two MMR genes. Ultimately, both groups of patients will exhibit the same MSI-H “phenotype” and would be expected to be equally likely to benefit from the known therapy.

102. In that regard, it was known that CRC tumors exhibiting the MSI-H “phenotype” were likely respond to therapies targeting the checkpoint inhibitor pathway because they upregulate immune inhibitory molecules including PD-1/PD-L1 and CTLA-4 (**D17**, page 409, right column, last par.). Accordingly, any CRC tumor that exhibits the MSI-H phenotype would be expected to be targeted by the same pathway (and consequently respond to the same therapies), irrespective of whether this phenotype has been caused by a somatic mutation in MMR gene(s), a germline mutation in at least one MMR gene, or a germline mutation in at least two MMR genes. If this is not the case, then the opposed patent has not sufficiently disclosed the medical use according to claims 3(a) and (b).
103. In particular, we would like to emphasize again that the opposed patent has not performed any germline testing. The efficacy data disclosed in the patent merely relates to “MSI-H” patients in general; there is no distinction between patients with sporadic cancer vs. Lynch syndrome (LS), let alone a further stratification among LS patients based on the number of MMR genes containing a germline alteration (see e.g., tables 6-8; 13 and [0141] of the patent). Thus, if a therapeutic effect in these MSI-H subgroups cannot be expected based on the efficacy results given in **D1** for MSI-H patients in general, then the opposed patent must be said to suffer the same deficiency.
104. Accordingly, either the treatment of a tumor according to claims 3(a), (b) and 4 is obvious in view of **D1** and the common general knowledge, or the medical use according to claims 3(a) and (b) is not sufficiently disclosed.

Claims 3(c) and 4

105. As we have explained above, claims 3(c) and 4 merely recite a well-known diagnostic feature of MSI tumors.
106. In particular, it was common general knowledge that MSI was caused by the loss of function of one or more of the MMR proteins, such as MLH1, MSH2, MSH6, PMS1 or PMS2; and that MSI could be diagnosed immunohistochemically by lack of expression of one or more of these proteins (see discussion under novelty).
107. Thus, to the extent that this feature is considered novel (which we deny), then it would be entirely obvious in view of **D1** to treat an MSI-H patient exhibiting this characteristic.

IX.3 Claim 10 lacks an inventive step in view of D1

108. As we have explained above **D1** discloses the claimed medical use according to claims 1-9. In particular, it had already been shown that the claimed combination of nivolumab and ipilimumab was therapeutically effective in treating a CRC tumor in a subject, wherein the tumor exhibits a high degree of microsatellite instability.

109. **D1** does not disclose “a kit” comprising (a) nivolumab and (b) ipilimumab, however it would be entirely obvious for the skilled person to provide the known therapeutically effective agents together in the form of a kit.
110. Accordingly, claim 10 lacks an inventive step in view of **D1**.

X. Sufficiency of Disclosure (Articles 100(b) EPC and 83 EPC)

X.1 Claims 3(a) and (b) are not sufficiently disclosed

111. Claims 3(a) and (b) both require that “...*the tumor comprises a germline alteration*...”
112. As we have explained above, it was well-known that a “germline alteration” is a genetic change occurring in a reproductive cell (an egg or sperm) (c.f., **D2**, page 1, “Germline mutations”; and **D3** pages 293-249, “Generating Genetic Variation”; figure 9-2; and page G:8, entries for “germ cell” and “germ line”). Since tumors do not comprise reproductive cells, the skilled person is left in doubt as to how a germline alteration may be identified within a tumor. We note, again, that the patent has not provided any guidance in that regard. For this reason already, claims 3(a) and (b) lack sufficiency of disclosure.
113. Further, and as noted above, the patent has not performed any germline testing. The examples in the patent merely implement the well-known guidelines for classifying a CRC tumor as “MSI-H” (c.f., **D6**, page 5250, table 1; and paragraph [0117] of the opposed patent). In particular, the specific reference cited in paragraph [0057] of the opposed patent regarding the definition of MSI-H (submitted herewith as **D18**) cites the same guidelines outlined above (c.f. **D18**, page 200, right column, 1st par., last sentence; and reference number 37 in **D18**).
114. If tumors exhibiting the characteristics recited in claims 3(a), (b) and 4 are indeed to be considered distinguished from the “MSI-H” tumors disclosed in **D1**, then the claimed medical use has not been sufficiently disclosed for this “sub-group” of tumors.
115. In particular, the efficacy data in the patent merely relates to “MSI-H” patients in general and makes no distinction between “MSI-H” tumor sub-groups (i.e., the efficacy data does not discern between MSI-H patients who have somatic mutations vs germline mutations, let alone further stratify patients based on the number of MMR genes containing a germline mutation) (c.f., tables 6-8; 13 and [0141] of the opposed patent). Accordingly, a therapeutic effect in the specific “sub-group” of tumors according to claims 3(a), (b) and 4 has not been demonstrated.
116. If a therapeutic effect in a tumor exhibiting a germline alteration in at least two MMR genes selected from MSH2, MLH1, MSH6, PMS2 and PMS1 can be expected based on the efficacy data given in the patent for “MSI-H” patients in general, then the same must be said of the data

in **D1**. Accordingly, if the medical use according to claims 3(a), (b) and 4 is supported by the data in the patent, then the treatment of this “sub-group” must be considered obvious in view of **D1**.

117. Accordingly, if a tumor according to claims 3(a), (b) and 4 can be distinguished from **D1** (which we deny), then the claimed medical use is either obvious, or insufficiently disclosed.

X.2 Claim 5 is not sufficiently disclosed

118. Claim 5 requires that the subject exhibits either a PFS or OS of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 months after administration of the combination therapy.
119. However, it is clear from the data in the patent that not all patients will exhibit a PFS or OS for the claimed duration. For example, table 7 shows that the 6 month PFS rate was only 66.6%; and table 8 shows that the 6 and 9 month OS rates were each only 85.1% (see also Figure 12). It is thus apparent that not all patients will exhibit the claimed PFS or OS durations. Accordingly, claim 5 does not meet the requirements of Article 83 EPC.
120. In summary, claims 3(a), (b) and 5 contravene Article 83 EPC.

XI. Summary

121. As explained above, the opposed patent should be revoked on the ground set out under Article 100(a) in connection with Articles 54 and 56 EPC, as the subject-matter of claims 1 to 10 of the opposed patent lacks novelty or an inventive step. Alternatively, the patent should be revoked under Articles 100(b) and 83 EPC for insufficiency of disclosure. Considering the above-presented facts, evidence and arguments, our request to revoke the opposed patent in its entirety is fully justified.



Sandra Pohlman
Rechtsanwältin
Legal Practitioner No. 157080

SP/DS

Enclosures
Cited documents **D1** to **D18**



Notice of opposition to a European patent

I. Patent opposed

Patent No.	EP3464373
Application No.	EP17731359.0
Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)	27 October 2021
Title of the invention	USE OF ANTI-PD-1 ANTIBODY IN THE TREATMENT OF PATIENTS WITH COLORECTAL CANCER

II. Proprietor of the patent

first named in the patent specification	Bristol-Myers Squibb Company
Opponent's or representative's reference	DFMP27181OP

III. Opponent

Name	Greiner, Dr. Elisabeth
Address:	Theatinerstraße 16 80333 München Germany
State of residence or of principal place of business	Germany
Multiple opponents (see additional sheet)	☐

IV. Authorisation

1. Representative	Greiner, Dr. Elisabeth
Address of place of business	df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Theatinerstraße 16 80333 München Germany
Telephone/Fax	004989210 296 004989210 296 33
E-mail:	info@df-mp.com

Additional representative(s) on additional sheet/see
authorisation

☐

Authorisation(s)

is/are enclosed

☐

has/have been registered under No.

☐

V. Opposition is filed against

the patent as a whole

☒

claim(s) No(s).

VI. Grounds for opposition:

Opposition is based on the following grounds:

(a) the subject-matter of the European patent opposed is not
patentable (Art. 100(a) EPC) because:

• it is not new (Art. 52(1); Art. 54 EPC)

☒

• it does not involve an inventive step (Art. 52(1);
Art. 56 EPC)

☒

• patentability is excluded on other grounds, namely
articles

☐

(b) the patent opposed 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 (Art. 100(b) EPC; see Art.
83 EPC).

☒

(c) the subject-matter of the patent opposed extends beyond
the content of the application/of the earlier application as
filed (Art. 100(c) EPC, see Art. 123(2) EPC).

☒

VII. Facts (Rule 76(2)(c) EPC)

presented in support of the opposition are submitted herewith
on an attached document

☒

VIII. Other requests:

• Oral proceedings are hereby requested auxilially.

IX. Evidence presented

D01	Other evidence	History of Changes for Study NCT02060188 2016-05-25 original file name: D01_History of Changes for Study NCT02060188 2016-05-25.PDF attached as: Other-evidence-1.pdf
D02	Other evidence	History of Changes for Study NCT02060188 2017-06-01 original file name: D02_History of Changes for Study NCT02060188 2017-06-01.PDF attached as: Other-evidence-2.pdf
D03	Other evidence	Overman et al. 2016 Journal of Clinical Oncology original file name: D03_Overman et al. 2016 Journal of Clinical Oncology.PDF attached as: Other-evidence-3.pdf
D03a	Other evidence	Overman 2016 PPT original file name: D03a_Overman 2016 PPT.PDF attached as: Other-evidence-4.pdf
D03b	Other evidence	Wayback Machine Snapshot original file name: D03b_Wayback Machine Snapshot.PDF attached as: Other-evidence-5.pdf
D04	Other evidence	Sharma 2015 original file name: D04_Sharma 2015.PDF attached as: Other-evidence-6.pdf
D05	Other evidence	Hamid Exp Op Biol Ther 2013 original file name: D05_Hamid Exp Op Biol Ther 2013.PDF attached as: Other-evidence-7.pdf
D06	Other evidence	DUDLEY CLINICAL CANCER RESEARCH 2016 original file name: D06_DUDLEY CLINICAL CANCER RESEARCH 2016.PDF attached as: Other-evidence-8.pdf
D07	Other evidence	LLOSA 2015 original file name: D07_LLOSA 2015.PDF attached as: Other-evidence-9.pdf
D08	Other evidence	Buchbinder 2016 original file name: D08_Buchbinder 2016.PDF attached as: Other-evidence-10.pdf
D09	Other evidence	Sunshine 2015 original file name: D09_Sunshine 2015.PDF attached as: Other-evidence-11.pdf
D10	Other evidence	DUNG T. LE ET AL NEJM original file name: D10_DUNG T. LE ET AL NEJM.PDF attached as: Other-evidence-12.pdf
D11	Other evidence	Boland 2010 original file name: D11_Boland 2010.PDF attached as: Other-evidence-13.pdf

D12	Other evidence	Vilar 2010 original file name: D12_Vilar 2010.PDF attached as: Other-evidence-14.pdf
D13	Other evidence	Pino 2011 original file name: D13_Pino 2011.PDF attached as: Other-evidence-15.pdf
D14	Other evidence	Antonia 2016 original file name: D14_Antonia 2016.PDF attached as: Other-evidence-16.pdf
D15	Other evidence	Wolchok 2013 original file name: D15_Wolchok 2013.PDF attached as: Other-evidence-17.pdf
D16	Other evidence	Antonia 2014 original file name: D16_Antonia 2014.PDF attached as: Other-evidence-18.pdf
D17	Other evidence	Antonia 2015 original file name: D17_Antonia 2015.PDF attached as: Other-evidence-19.pdf
D17a	Other evidence	Antonia 2015 PPT original file name: D17a_Antonia 2015 PPT.PDF attached as: Other-evidence-20.pdf
D18	Other evidence	History of Changes for Study NCT01928394 original file name: D18_History of Changes for Study NCT01928394.PDF attached as: Other-evidence-21.pdf
D19	Other evidence	Postow 2015 original file name: D19_Postow 2015.PDF attached as: Other-evidence-22.pdf
D20	Other evidence	Overman 2016 original file name: D20_Overman 2016.PDF attached as: Other-evidence-23.pdf
D21	Other evidence	Topalian 2012 original file name: D21_Topalian 2012.PDF attached as: Other-evidence-24.pdf
D22	Other evidence	Hofmann 2016 Cancer Therapy Advisor original file name: D22_Hofmann 2016 Cancer Therapy Advisor.PDF attached as: Other-evidence-25.pdf
D23	Other evidence	History of Changes for Study NCT02231749 original file name: D23_History of Changes for Study NCT02231749.PDF attached as: Other-evidence-26.pdf

X. Payment

Method of payment

Debit from deposit account

The European Patent Office is hereby authorised, to debit from the deposit account with the EPO any fees and costs indicated in the fees section below.

Currency:

EUR

Deposit account number:

28001000

Account holder:

df-mp Dörries Frank-Molnia & Pohlman

Refunds

Any refunds should be made to EPO deposit account:

28001000

Account holder:

df-mp Dörries Frank-Molnia & Pohlman

Fees

	Factor applied	Fee schedule	Amount to be paid
010 Opposition fee	1	840.00	840.00
Total:		EUR	840.00

A Forms

Details:

System file name:

A-1

Form for notice of opposition

ep-oppo.pdf

B Attached document files

Original file name:

System file name:

B-1

1. Facts and arguments

2022 07 27 Notice of Opposition.PDF

OPPO.pdf

C Attached evidence files

Original file name:

System file name:

C-1

1. Other evidence

D23_History of Changes for Study
NCT02231749.PDF

Other-evidence-26.pdf

C-2

2. Other evidence

D22_Hofmann 2016 Cancer Therapy
Advisor.PDF

Other-evidence-25.pdf

C-3

3. Other evidence

D21_Topalian 2012.PDF

Other-evidence-24.pdf

C-4

4. Other evidence

D20_Overman 2016.PDF

Other-evidence-23.pdf

C-5

5. Other evidence

D19_Postow 2015.PDF

Other-evidence-22.pdf

C-6

6. Other evidence

D18_History of Changes for Study
NCT01928394.PDF

Other-evidence-21.pdf

C-7	7. Other evidence	D17a_Antonia 2015 PPT.PDF	Other-evidence-20.pdf
C-8	8. Other evidence	D17_Antonia 2015.PDF	Other-evidence-19.pdf
C-9	9. Other evidence	D16_Antonia 2014.PDF	Other-evidence-18.pdf
C-10	10. Other evidence	D15_Wolchok 2013.PDF	Other-evidence-17.pdf
C-11	11. Other evidence	D14_Antonia 2016.PDF	Other-evidence-16.pdf
C-12	12. Other evidence	D13_Pino 2011.PDF	Other-evidence-15.pdf
C-13	13. Other evidence	D12_Vilar 2010.PDF	Other-evidence-14.pdf
C-14	14. Other evidence	D11_Boland 2010.PDF	Other-evidence-13.pdf
C-15	15. Other evidence	D10_DUNG T. LE ET AL NEJM.PDF	Other-evidence-12.pdf
C-16	16. Other evidence	D09_Sunshine 2015.PDF	Other-evidence-11.pdf
C-17	17. Other evidence	D08_Buchbinder 2016.PDF	Other-evidence-10.pdf
C-18	18. Other evidence	D07_LLOSA 2015.PDF	Other-evidence-9.pdf
C-19	19. Other evidence	D06_DUDLEY CLINICAL CANCER RESEARCH 2016.PDF	Other-evidence-8.pdf
C-20	20. Other evidence	D05_Hamid Exp Op Biol Ther 2013.PDF	Other-evidence-7.pdf
C-21	21. Other evidence	D04_Sharma 2015.PDF	Other-evidence-6.pdf
C-22	22. Other evidence	D03b_Wayback Machine Snapshot.PDF	Other-evidence-5.pdf
C-23	23. Other evidence	D03a_Overman 2016 PPT.PDF	Other-evidence-4.pdf
C-24	24. Other evidence	D03_Overman et al. 2016 Journal of Clinical Oncology.PDF	Other-evidence-3.pdf
C-25	25. Other evidence	D02_History of Changes for Study NCT02060188 2017-06-01.PDF	Other-evidence-2.pdf
C-26	26. Other evidence	D01_History of Changes for Study NCT02060188 2016-05-25.PDF	Other-evidence-1.pdf

Signature of opponent or representative

Place

Munich

Date: 27 July 2022

Signed by: Elisabeth Greiner 23990

Representative name: Elisabeth Greiner

Capacity: (Representative)



Dörries Frank-Molnia & Pohlman
Patentanwälte Rechtsanwälte PartG mbB

Patents – Trademarks – Designs

By E-Filing

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July 27, 2022

Opposition against European Patent EP 3 464 373 (Application No. 17 731 359.0)

Title: USE OF ANTI-PD-1 ANTIBODY IN THE TREATMENT OF
PATIENTS WITH COLORECTAL CANCER

Proprietor: Bristol-Myers Squibb Company

Opponent: Dr. Elisabeth Greiner

Our Ref.: DFMP27181OP

On behalf of **Dr. Elisabeth Greiner**
Theatinerstraße 16
80333 Munich
Germany

we herewith file a **Notice of Opposition** pursuant to Article 99(1) EPC against

European Patent No. EP 3 464 373 B1
(European Appl. No. 17 731 359.0)

Publication and
mention of the grant: **October 27, 2021**

Title of the patent: USE OF ANTI-PD-1 ANTIBODY IN THE TREATMENT OF
PATIENTS WITH COLORECTAL CANCER

Proprietors: **Bristol-Myers Squibb Company**
Route 206 and Province Line Road
Princeton, NJ 08543 / US

We request that the opposition fee in the amount of EUR 840.00 be debited from
our deposit account No. 28001000 (see also the corresponding debit order on the
form accompanying the online submission of the present Notice of Opposition).

Dr. H. Ulrich Dörries ^{1,2,3,4}
David Molnia ^{1,2,3,4,7}
Sandra Pohlman ^{5,6,8}
Philipp Nordmeyer ^{1,2,3,4}
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Dr. Christoph Klöckner ^{1,2,3,4}

1 European Patent Attorney
2 European Trademark Attorney
3 European Design Attorney
4 Patentanwalt / Patentanwältin
5 Solicitor (England & Wales)
6 U.S. Patent Attorney
7 U.S. Patent Agent
8 Rechtsanwältin / Rechtsanwalt
9 Fachanwältin für
gewerblichen Rechtsschutz

Partnerschaftsregister des AG München
PR-Nr. 1278

I. Extent of the Opposition and Requests

1. The opposition is directed against all claims of the European patent EP 3 464 373 B1 (hereinafter referred to as “the opposed patent”). It is requested that the opposed patent be revoked in its entirety pursuant to Article 101(2) EPC.
2. Oral proceedings are requested in accordance with Article 116(1) EPC in the event that the Opposition Division does not consider the above request justified on the basis of our written submissions.

II. Grounds in Support of the Opposition

3. The opposition is based on the following grounds:
 - i) the subject matter of the opposed patent lacks novelty (Art. 100(a) in connection with Art. 54 EPC),
 - ii) the subject matter of the opposed patent is not based on an inventive step (Art. 100(a) in connection with Art. 56 EPC),
 - iii) 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 (Art. 100(b) in connection with Art. 83 EPC), and
 - iv) the subject-matter of the opposed patent extends beyond the content of the application as filed (Art. 100(c) in connection with Art. 123(2) EPC).

III. Formalities and Bibliographic Data

4. The European Patent is based on application No. EP 17 731 359.0 filed June 2, 2017, which was published as WO 2017/210637 A1 (hereinafter **WO**) on December 7, 2017. The opposed patent claims the priority of US application No. 62/345,662 (hereinafter **P**), which was filed on June 3, 2016. EP 3 464 373 B1 (hereinafter **B1**, or “the opposed patent”) was granted on October 27, 2021.

IV. Cited Documents

5. The following documents are relied upon in this notice of opposition and filed herewith:

- P:** US 62/345,662, filed on June 3, 2016.
- WO** WO 2017/210637 A1, filed on June 2, 2017.
- D1:** History of Changes for Study NCT02060188, database entry dated **May 25, 2016**.
- D2** History of Changes for Study NCT02060188, database entry dated **June 1, 2017**.
- D3** Overman, M. J. *et al.*, *J. Clin. Oncol.* **2016**, 34(15 Suppl), 3501 (e-pub. **May 20, 2016**).
- D3a** Power Point presentation corresponding to abstract **D3**, presented at the ASCO Annual Meeting 2016 (**June 3 to June 7, 2016**).
- D3b** Snapshot of http://abstract.asco.org/176/CatAbstView_176_729_AT.html, dated May 24, 2016, retrieved from https://web.archive.org/web/20160524054000/http://abstract.asco.org/176/CatAbstView_176_729_AT.html
- D4** Sharma, P. and Allison, J. P. *Science* **2015**, 348, 56-61.
- D5** Hamid, O. and Carvajal, R. D. *Expert Opin. Biol. Ther.* **2013**, 13(6), 847-61.
- D6** Dudley, J. C. *et al.*, *Clin. Cancer Res.* **2016**, 22(4), 813-820 (**Feb. 15, 2016**).
- D7** Llosa, N. J. *et al.* *Cancer Discov.* **2015**, 5(1), 43–51.
- D8** Buchbinder, E. I and Desai, *Am. J. Clin. Oncol.* **2016**, 39(1), 98-106 (**Feb. 2016**).
- D9** Sunshine, J and Taube, J. M., *Curr. Opin. Pharmacol.* **2015**, 23, 32-38
- D10** Le, D. T. *et al.*, *N. Engl. J. Med.* **2015**, 372, 2509-20.
- D11** Boland, C. R. and Goel, A., *Gastroenterology* **2010**, 138, 2073-2087.
- D12** Vilar, E and Gruber S. B., *Nature Rev. Clin. Oncol.* **2010**, 7, 153-162.
- D13** Pino, M. S. and Chung, D. C., *Expert Rev. Gastroenterol. Hepatol.* **2011**, 5(3), 385-399.
- D14** Antonia *et al.*, *J. Clin. Oncol.* **2016**, 34(15 Suppl), 100 (e-pub. **May 20, 2016**).
- D15** Wolchok, J. D. *et al.*, *N. Engl. J. Med.* **2013**, 369, 122-33.
- D16** Antonia *et al.*, *J. Clin. Oncol.* **2014**, 32(15 Suppl), 8023.
- D17** Antonia *et al.*, *J. Clin. Oncol.* **2015**, 33(15 Suppl), 7503.
- D17a** Power Point presentation corresponding to abstract **D17a**, presented at the ASCO Annual Meeting 2015 (**May 29 to June 2, 2015**).
- D18** History of Changes for Study NCT01928394, database entry dated **May 25, 2016**.
- D19** Postow, M. A. *et al.*, *N. Engl. J. Med* **2015**, 372, 2006-17.
- D20** Overman, M. J. *et al.*, *Annals Oncol.* **2016**, 27 (Supplement 6): vi149–vi206 (**October 2016**).
- D21** Topalian, S. L. *et al.*, *N. Engl. J. Med.* **2012**, 366, 2443-54.
- D22** Hoffman, J. **2016**, Cancer Therapy Advisor, press release re. ASCO Annual Meeting 2016, published on **June 5, 2016**.
Retrieved from: <https://www.cancertherapyadvisor.com/home/news/conference->

[coverage/american-society-of-clinical-oncology-asco/asco-2016/nivolumab-%C2%B1-ipilimumab-demonstrates-encouraging-activity-survival-in-mcrc/](#)

D23 History of Changes for Study NCT02231749, database entry dated **May 25, 2016**.

D3a, D20 and **D22** represent full prior art for all claims which do not enjoy the priority date of June 3, 2016.

V. The Claimed Subject Matter

6. The opposed patent contains 10 claims, with claims 1 and 10 being independent claims.

7. Claim 1 is directed to

*“Nivolumab for use in a method of **treating a colorectal cancer tumor** in a subject, wherein the tumor exhibits a high degree of microsatellite instability (“MSI-H”), wherein the subject is administered nivolumab at a dose of about 3 mg/kg body weight in combination with ipilimumab at a dose of about 1 mg/kg body weight once about every three weeks.”* (emphasis added)

8. Notably, due to the use of the term “about”, the doses of nivolumab and ipilimumab to be administered are somewhat ambiguous. The specification of the opposed patent contains a definition of the term “about” (cf. **B1**, [0052]), but this fails to limit the term in a meaningful manner.

9. In the broadest sense, the term “about” is defined as referring to a value that is “*within an acceptable error range for the particular value or composition as determined by one of ordinary skill in the art, which will depend in part on how the value or composition is measured or determined, i.e., the limitations of the measurement system*” (ibid.). Neither the measurement system, nor the method according to which the value (here: the dose) is to be determined are specified in the claim and, as a consequence, the “*acceptable error range*” in respect of the doses recited in claim 1 remains undefined.

10. Paragraph [0052] of the patent discloses further alternative definitions of the term “about”, including “*within 1 or more than 1 standard deviation per the practice in the art*”, “*a range of up to 20%*” and “*up to an order of magnitude or up to 5-fold of a value*”.

11. It is not entirely clear which of the alternative definitions is applicable to the claimed doses. Moreover, at least the first two definitions recited above¹ are vague and do not result in a defined range of values.
12. The doses to be administered are hence defined in a vague manner, which must be considered in the context of *inter alia* the assessment of inventive step, as explained in further detail below.
13. The same applies to the timing of administrations ("*once about every three weeks*") required by claim 1. It is again unclear what extent of variation is encompassed by the term "about" in this specific context.
14. Dependent claim 2 further specifies that the tumor is "*a colon cancer or a rectal cancer*".
15. The tumor of claims 1 and 2 is further defined in claim 3 as exhibiting one or more of the characteristics selected from the group consisting of:

"(a) the tumor comprises a germline alteration in at least two, at least three, at least four, or at least five DNA mismatch repair genes ("MMR genes");
(b) the tumor comprises a germline alteration in at least 30% of five or more MMR genes;
(c) at least one protein encoded by DNA MMR genes is not detected in the tumor; and
(d) any combination thereof."
16. The DNA MMR genes (i.e., DNA mismatch repair genes) according to claim 3 are specified to comprise MSH2, MLH1, MSH6, PMS2, PMS1, or any combination thereof in dependent claim 4.
17. Dependent claim 5 refers back to any one of claims 1 to 4 and further defines the outcome of the therapeutic use as follows:

"(i) the subject exhibits a progression-free survival of at least about one month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, or at least about 12 months after the administration or
(ii) the subject exhibits an overall survival of at least about one month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, or at least about 12 months after the administration."

¹ That is "*within an acceptable error range for the particular value or composition as determined by one of ordinary skill in the art [...]*" and "*within 1 or more than 1 standard deviation per the practice in the art*".

18. Dependent claim 6 relates back to claims 1 to 5 and further specifies that *"the administration of nivolumab and ipilimumab is followed by an anti-PD-1 antibody monotherapy"*.
19. The administration of nivolumab and ipilimumab according to claims 1 to 5 is defined as comprising *"four doses for each"* in claim 7.
20. The subject to be treated according to claims 1 to 7 is specified as having received *"one, two, three, four, five or more prior cancer treatments"* in dependent claim 8 and as having *"progressed on other cancer treatments"* in claim 9.
21. Independent claim 10 relates to a *"kit for use in a method of treating a colorectal cancer tumor in a subject, comprising: (a) nivolumab; and (b) ipilimumab wherein the method is defined as in any one claims 1 to 9"*.

VI. Added Matter (Articles 100(c) and 123(2) EPC)

VI.1 Claim 1

22. During the prosecution of the application giving rise to the opposed patent, the Patentee has referred to original claims 1, 7 and 10, as well as to paragraphs [0032], [0035], [0041], [0044] and [0170] as alleged basis for the subject matter of granted claim 1 (cf. Applicant's letter dated November 18, 2019, par. bridging pp. 1 and 2).
23. For the reasons indicated hereinbelow, the application as originally filed fails to provide a direct and unambiguous basis for claim 1 (cf. Case Law of the Boards of Appeal (hereinafter CLBA), II.E.1.1), and hence contravenes Article 123(2) EPC.
24. In contrast to original claim 1, the granted claim refers to a combination treatment comprising the use of two specific antibodies, nivolumab and ipilimumab. Claim 1 as granted moreover recites specific doses to be administered in a specific administration scheme and relates to a medical condition that differs from the medical condition recited in original claim 1.
25. The concept of a direct and unambiguous disclosure as applied by the Boards of Appeal prohibits an Applicant from treating the application as filed as a reservoir, i.e., to combine features pertaining to separate embodiments in order to artificially create a particular embodiment. In the absence of any pointer to a particular combination, a combined selection of features does not, for the person skilled in the art, emerge clearly and unambiguously from the content of the application as filed (cf. CLBA, II.E.1.6.1). In particular an embodiment requiring

selections of features from two or more lists is generally considered to lack a direct and unambiguous disclosure according to the gold standard (cf. CLBA II.E.1.6.2).

26. In the present case, taking original claim 1 as a starting point for the assessment of compliance with Article 123(2) EPC, the skilled artisan would be faced with various selections in order to arrive at the claimed subject matter.
27. First of all, original claim 1 does not refer to a specific anti-PD-1 antibody. The skilled artisan would thus have to select nivolumab as the anti-PD-1 antibody. In this regard, the application as filed teaches various different alternatives including an antibody that cross-competes with nivolumab (or pembrolizumab), an antibody that binds to the same epitope as nivolumab (or pembrolizumab), an antibody that has the same CDRs as nivolumab (or pembrolizumab) or nivolumab and pembrolizumab (cf. **WO**, [0009], [0138] and [0139]). Further alternatives are disclosed in **WO**, par. [0137].
28. Original claim 7 which the Proprietor has relied on as basis for nivolumab also refers to nivolumab and pembrolizumab as equivalent alternatives. It should moreover be noted that original claim 6 further refers to an anti-PD-1 antibody that cross-competes with nivolumab and paragraphs [0032] (to which the Patentee has pointed during prosecution) and [0028], [0029] and [0033] further refer to antibodies defined by their epitope specificity, nivolumab and pembrolizumab as alternative anti-PD-1 antibodies.
29. In other words, the application as filed, including the original claims, discloses various alternative anti-PD-1 antibodies in the form of equivalent alternatives, i.e., in the form of a list, from which the skilled artisan would have to specifically select nivolumab.
30. This represents a first choice from a list in the sense of Board of Appeal case law.
31. In a second step, the person of skill in the art would have to select a combination therapy with an anti-PD-1 antibody and an anti-CTLA-4 antibody from the two alternatives of monotherapy and combination therapy. Original claims 1 to 7 relate to a therapy with an anti-PD-1 antibody and do not mention combination therapy. The alternative "combination therapy" is only introduced with original claim 8. The skilled artisan is thus again confronted with two alternatives from which he/she would have to pick one (here: combination therapy), thus representing a second choice.
32. In a further selection step, the skilled person would have to select a specific anti-CTLA-4 antibody. In this respect, the application again discloses various alternatives, including an antibody that cross-competes with ipilimumab or tremelimumab, an antibody that binds to the same epitope region of (human) CTLA-4 as ipilimumab or tremelimumab, ipilimumab and tremelimumab (cf. **WO**, [0011], [0156] to [0158]). Further alternatives are disclosed in **WO**,

[0155]. Original claim 10 and paras. [0037] to [0042] also teach several alternative anti-CTLA-4 antibodies. From these alternative embodiments, the skilled artisan would have to make a third selection, in order to select ipilimumab as the anti-CTLA-4 antibody.

33. The dosing regimen required by granted claim 1 represents yet another alternative that is disclosed alongside a large number of alternatives (cf. **WO**, [0161] to [0170]) hence requiring a further (i.e., a fourth selection step).
34. The subject matter of granted claim 1 thus requires at least four selection steps to extract the recited features from the original disclosure. A combination of features that necessitates no less than four selections from lists violates Article 123(2) EPC.
35. The Patentee has treated the original disclosure as a reservoir to generate an artificial combination of features that (as a combination) lacks a direct and unambiguous disclosure in the application documents as filed.
36. Lastly, it should be noted that claim 1 as granted refers to *"treating a colorectal cancer tumor"*, whereas original claim 1 (see also, e.g., **WO**, [0001], [0007], [0018], etc.) relate to *"treating a subject afflicted with a tumor derived from colorectal cancer"* (emphasis added).
37. This is not merely a verbal change. In the context of the original disclosure, the terms "colorectal cancer" and "tumor derived from colorectal cancer" have different technical meanings.
38. This is readily derivable from **WO**, par. [0093], which teaches:

*"Following metastasis, **the distal tumors** can be said to be "derived from" the original, pre-metastasis tumor. For example, a "tumor derived from" a colorectal cancer **refers to a tumor that is the result of a metastasized colorectal cancer**. Because the distal tumor is derived from the pre-metastasis tumor, the "derived from" tumor can also comprise the pre-metastasis tumor, e.g., a tumor derived from a colorectal cancer can comprise a colorectal cancer."* (emphasis added)
39. The phrase "tumor derived from colorectal cancer" as used in the original disclosure thus refers to a tumor that is **the result of a metastasized colorectal cancer**. While the "derived from" tumor may also comprise the colorectal cancer as such, the phrase "tumor derived from colorectal cancer" does not include the treatment of (the original) colorectal cancer only.
40. In other words, the original application discloses the treatment of a tumor that may conceptually be (i) the metastases of a colorectal cancer or (ii) the metastases of a colorectal cancer plus the original colorectal cancer (*"can also comprise the pre-metastasis tumor"*).

41. However, claim 1 as granted relates to neither of these two alternatives, but instead refers to the treatment of a colorectal cancer tumor (as such).
42. In contrast, the application as filed consistently uses the “derived from” language that is also used in original claim 1 (cf. **WO**, [0001], [0007], [0018], [0116], [0127], [0153], etc.)
43. The granted claim therefore relates to a specific embodiment, which as such lacks original disclosure.
44. This represents a further violation of Article 123(2) EPC.
45. Taken together, claim 1 as granted thus fails to comply with the requirements of Article 123(2) EPC. This also applies to claims 2-6 by virtue of their back referenced to claim 1.

VI.2 Claims 7 to 9

46. Dependent claim 7 as granted allegedly finds basis in **WO**, par. [0170] (cf. Proprietor’s letter dated November 18, 2019, p. 2, 3rd par.).
47. However, the administration of “four doses for each” is disclosed in **WO**, [0170] as part of a long list of various different administration schemes and thus requires a selection from a list. Together with the at least four selections necessary to arrive at the subject matter of granted claim 1, this represents another violation of Article 123(2) EPC.
48. This similarly applies to the subject matter of claims 8 and 9. Paragraph [0123], to which the Proprietor has referred to during prosecution teaches the recited patient characteristics side-by-side with further alternatives (e.g., *“the subject is treatment-naïve”* or *“the cancer has reoccurred”*). The alternatives recited in dependent claims 8 and 9 represent selections from this list of alternatives and in combination with the selections that are required to extract the subject matter of granted claim 1 from the original disclosure, result in violations of Article 123(2) EPC.

VI.3 Claim 10

49. As basis for claim 10, the Patentee has referred to original claim 15. Given that original claim 10 defines the disclosed treatment in a similar manner as original claim 1, claim 10 as granted suffers from the same problems under Article 123(2) EPC as granted claim 1.

VI.4 Summary

50. In summary, the granted claims violate Article 123(2) EPC.

VII. Priority (Article 87 EPC)

51. The “same invention” requirement pursuant to Article 87(1) EPC presupposes that a priority document discloses the claimed subject matter in a direct and unambiguous manner. The disclosure content is to be assessed in the same way as in the assessment of compliance with Article 123(2) EPC (cf. CLBA, II.D.3.1.2).
52. The priority document fails to disclose the claimed subject matter for essentially the same reasons laid out above in the context of Article 123(2) EPC.
53. In order to arrive at the claimed subject matter, the skilled artisan must make at least four selections within the disclosure of the priority document:
 - Nivolumab must be selected as the anti-PD-1 antibody from various alternatives, cf. **P**, [0008], [0081] to [0091], claims 11 to 16;
 - combination therapy must be selected from the alternatives of monotherapy and combination therapy, see **P**, claims 1 to 18 (which all relate to monotherapy)
 - Ipilimumab must be selected from various alternative embodiments (cf. **P**, [0010], [0092] to [0096], claims 20 to 25);
 - The claimed dosing and administration regimen must be extracted from the large number of dosing regimen taught in the priority filing (cf. **P**, [0009], [0011], [0099] to [0107]), claims 17 and 26 to 31.
54. In addition, the priority document relates to “*methods for treating a tumor derived from a colorectal cancer*” (emphasis added) instead of “*a method of treating a colorectal cancer tumor*”. The reasoning provided above applies *mutatis mutandis*.²
55. The priority document moreover fails to disclose the subject matter of granted claim 7.
56. With respect to granted claims 8 and 9, reference is made to the reasons provided above (compare **WO**, [0123] and **P**, [0070]).
57. For at least these reasons, the priority document thus fails to disclose the claimed invention. As a consequence, the granted claims are not entitled to the priority of US 62/345,662, but only to the filing date.

² See definition of “derived from” tumor in **P**, par. [0041].

VIII. Technical Background

58. The alleged invention relates to the field of immune-checkpoint inhibitor-based cancer therapy.
59. At the priority date, immune-checkpoint inhibition has been a recognized approach in cancer therapy that was widely regarded as a highly promising type of cancer treatment which had already been shown to be efficacious in different types of cancer, including melanoma (cf. **D4**, p. 56, left col.). Generally speaking, immune-checkpoint inhibition in the treatment of cancer is based on the depression of the host immune response against tumor cells, in particular in the tumor microenvironment.
60. CTLA-4 and PD-1 were known as immune-suppressive signals and with ipilimumab (anti-CTLA-4), nivolumab and pembrolizumab (both anti-PD-1), at least three antibodies targeting immune-checkpoint inhibitors had already been approved for cancer therapy by the US Food and Drug Administration (FDA), cf. **D4**, p. 56, left col., **D5**, Table 3 and **D8**, Table 1). Various further agents targeting PD-1 or CTLA-4 were known to be at different stages of clinical evaluation (**D8**, p. 102, Table 1), while applications of approved agents were expanded to further indications, including ipilimumab and pembrolizumab in phase II clinical studies for the treatment of colorectal cancer (ibid.).
61. Specifically, with regard to colon cancer, it had been commonly known that expression of PD-L1, one of the ligands binding PD-1, was associated with poorer prognosis (**D5**, Table 2), thus suggesting an involvement of PD-1/PD-L1 signaling in the growth and/or metastasis of colon cancer. The first clinical study to investigate the efficacy of nivolumab for that indication involved 39 patients with *inter alia* advanced colorectal cancer, one of which experienced a complete response (**D5**, p. 6, left col., ultimate par.).³ The patient experiencing a complete response had been suffering from a microsatellite instability-high tumor (cf. **D9**, p. 33, footnote at the bottom of Table 2 and **D10**, p. 2510, left col., 2nd par.).
62. Back then it was widely considered that colorectal tumors with a high degree of microsatellite instability (MSI-H) represent a specific subclass of colorectal cancer with unique properties, including responsiveness to therapy and an overall better prognosis (cf. review articles **D11**, abstract and pp. 2074/75 under “MSI as a Unique Mechanism in Tumor Development”, **D12**, abstract and p. 158 under “Prognostic value of MSI in CRC”, **D13**, abstract and introduction on pp. 385/86).
63. At the priority date it was further an emerging concept that cancers with a higher mutational burden (such as tumors with a high degree of microsatellite instability) are more likely to respond to immune checkpoint therapy (cf. **D4**, p. 61, left col., bottom par., **D6**, abstract and p.

³ Notably, this patient had been treated with a nivolumab dose of 3 mg/kg, cf. **D5**, p. 6, left col., ultimate par.

814, par. bridging columns with reference to **D7** and **D8**, p. 104, left col., 2nd par.). Particularly with respect to colon/colorectal cancer, this was considered to represent a potentially decisive factor determining responsiveness to anti-PD-1 treatment (**D4**, p. 61, left col., bottom par.).

64. This arises, e.g., from **D9**, a review article relating to PD-1/PD-L1 inhibitors as cancer therapeutics (**D9**, title), which teaches (with respect to nivolumab-based cancer therapy) that

“Response rates in patients with colorectal carcinoma have been meager overall, unless the patients have microsatellite-unstable tumors [8,10]. As such, efforts are now focused on studying these agents in tumors that are microsatellite instability (MSI)-high.” (**D9**, p. 34, right col., 1st par, emphasis added)

65. Applying nivolumab (in combination with ipilimumab) in the treatment of MSI-H colorectal cancer, the inventors thus clearly followed a general trend in the field at the relevant date.

66. With respect to combination therapies, it was generally considered:

“[t]hat CTLA-4 and PD-1 regulate distinct inhibitory pathways and have nonoverlapping mechanisms of action suggested that concurrent combination therapy with both might be more efficacious than either alone.” (**D4**, p. 58, left col., penultimate par.)

67. In other words, combination therapy using an anti-CTLA-4 antibody and an anti-PD-1 antibody was considered a promising approach.

68. Indeed, a substantial body of evidence was available which indicated that a combination of nivolumab and ipilimumab could be expected to possess a higher clinical efficacy as compared to nivolumab monotherapy.

69. For example, regarding the treatment of advanced melanoma, results of a first study comparing nivolumab/ipilimumab combination treatment with nivolumab only were already published in 2013 (cf. **D15**, abstract). This initial study included a cohort of patients that was treated with nivolumab at a dose of 3 mg/kg and ipilimumab at a dose of 1 mg/kg (**D15**, p. 123, right col., 3rd par.), among other combination regimens. The authors concluded that

“Although not formally compared in this study, concurrent treatment with nivolumab and ipilimumab was associated with rates of objective response that exceeded the previously reported results with either nivolumab or ipilimumab alone.^{3,5} Rapid and deep responses occurred in a substantial proportion of treated patients, with the majority of patients who had a response also having tumor regression of 80% or more at the time of the initial tumor assessment, including some patients who had had extensive and bulky tumors. Particularly striking was the observation that across the concurrent-regimen cohorts, 31% of the patients

with a response that could be evaluated had tumor regression of 80% or more by week 12.” (D15, p.131 left col., 1st par., emphasis added)

70. Results of a clinical study comparing the combination of nivolumab and ipilimumab with ipilimumab alone in treating melanoma were published in 2015 (D19) and again showed that the combination was more effective than the comparator (ipilimumab only), cf. D19, abstract under “Conclusions” and p. 2016, par. bridging columns.
71. In other words, the combination treatment was observed to result in an improved clinical response as compared to monotherapy with either nivolumab or ipilimumab alone.
72. Motivated by this encouraging data for advanced melanoma, the combination was also applied to other types of cancer, including non-small cell lung cancer (NSCLC) and interim results presented in 2014 indicated the combination treatment to be safe and effective also for this cancer, with the N3+11 Q3W dosing regimen being the most effective (cf. D16). Similar results were available for small cell lung cancer (SCLC), cf. D17 (cf. “Conclusions”) and the corresponding presentation held at the 2015 ASCO (American Society of Clinical Oncology) meeting (filed herewith as D17a, cf. in particular slides 9, 13 and 14). The results for SCLC were later confirmed by D14 shortly before the priority date, which will be discussed in more detail below.
73. A phase I/II study comparing the efficacy of nivolumab versus nivolumab in combination with ipilimumab in different administration regimens, including the claimed regimen, in various solid tumors was ongoing at the relevant date (NCT01928394, cf. database entry D18).
74. In other words, the combination of nivolumab and ipilimumab was actively investigated for the treatment of different types of cancer at the priority date and had already been reported to offer superior clinical efficacy in two different tumor types, i.e., in at least melanoma (D15) and SCLC (D14, D17/D17a).
75. Taken together, both ipilimumab and nivolumab were commonly known as active agents for the treatment of cancer; ipilimumab and an alternative anti-PD-1 antibody (pembrolizumab) were known to be in phase II studies for the treatment of colorectal cancer and microsatellite instability (or, more generally, a high mutational burden), and the latter was known to be a potential predictor of responsiveness to anti-PD-1 therapy, in particular in colorectal cancer therapy. Combination therapy using two immune checkpoint inhibitors, with a particular focus on the claimed combination of nivolumab and ipilimumab, was generally regarded to represent a highly promising approach in the treatment of cancer.
76. It should be noted in this regard that D4 to D6, D9 and D11 to D13 are review articles and thus represent the common general knowledge at the priority date (cf. CLBA, I.C.2.8.5).

IX. Lack of Novelty (Article 54 EPC)

IX.1 Lack of novelty over D3

IX.1.1 Claim 1

77. During prosecution of the application giving rise to the opposed patent, the Examining Division has cited database entries for two clinical studies as relevant prior art (D3 and D4 during prosecution). The database entries related to clinical studies NCT02060188 (i.e., CheckMate 142) and NCT01876511.
78. The most recent entries for NCT02060188 predating the priority date or the filing date of the opposed patent are filed herewith as **D1** (published May 25, 2016) and **D2** (published June 1, 2017), respectively.
79. With respect to the same clinical trial, a meeting abstract (filed herewith as **D3**) comprising preliminary results was published on May 20, 2016 and thus prior to the priority date of the opposed patent (cf. **D3**, first page right hand side).⁴ **D3** is full prior art for the granted claims irrespective of priority entitlement.
80. **D3** teaches the use of nivolumab and ipilimumab in the treatment of metastatic colorectal cancer with and without microsatellite instability (**D3**, title). Accordingly, **D3** relates to the treatment of a colorectal cancer tumor in a subject, wherein the tumor exhibits a high degree of microsatellite instability, as required by claim 1.
81. The administration scheme is described on p. 2 of **D3**, under “Methods” as follows:

“MSI-H pts received N 3 mg/kg q2 wk (N3) or N 3 mg/kg + I 1 mg/kg q3 wk (N3+I1) x 4 doses followed by N3 until disease progression (PD) or other discontinuation.”
82. MSI-H is used in **D3** (like in the opposed patent) as an abbreviation for high microsatellite instability (see title of **D3**). N and I are used as abbreviations for nivolumab and ipilimumab, respectively (cf. **D3**, p. 1 last par.), “q3wk” is a common abbreviation for an administration once every three weeks.

⁴ We refer to the publication date that is explicitly indicated in **D3** which leaves no doubt on the public accessibility of its contents. This is also confirmed by **D3b**, which represents a snapshot dated May 24, 2016, retrieved from the Internet Archive, which shows that abstract **D3** was available on the 2016 ASCO Annual Meeting home page **on this date** (cf. p. 4, 4th entry). Reference is made to the Guidelines for Examination (G-IV 7.5.4) in this context.

83. **D3** hence discloses an administration of nivolumab and ipilimumab at doses of 3 mg/kg and 1 mg/kg, respectively, every three weeks, which matches the claimed administration regimen. The administration regimen is referred to as “N3+I1” in **D3**.
84. The results are summarized in the following table from **D3**:

	N3 (n = 33)	N3+I1 (n = 26)
ORR, n (%)	9 (27)	4 (15)
CR	0	0
Confirmed PR	9 (27)	4 (15)
SD	8 (24)	17 (65)
PD	11 (33)	3 (12)
Not determined/not reported	5 (15)	2 (8)
Median duration of response (95% CI), mo	NR (4.2–NE)	NR (NE–NE)
Median PFS (95% CI), mo	5.3 (1.4–NE)	NR (NE–NE)
4-mo PFS rate, ^b %	55	80
Median OS (95% CI), mo	16.3 (8.3–NE)	NR (NE–NE)
5-mo OS rate, ^c %	75	100

NR, not reached; NE, not estimable ^aBy local screen ^bPFS Kaplan-Meier plot estimate, N3 = 17/33 events, N3+I1 = 4/26 events ^cPFS Kaplan-Meier plot estimate, N3 = 11/33 events, N3+I1 = 0/26 events

85. As reported in **D3**, the 4-month progression-free survival rate (4-mo PFS rate) was 80% for the combination treatment (N3+I1), as compared to 55% for the nivolumab monotherapy (N3). Moreover, the 5-month overall survival rate (5-mo OS rate) was 100% for the combination treatment, while 75% are reported for the nivolumab monotherapy.
86. Taken together, **D3** thus teaches the active agents provided by claim 1 (nivolumab + ipilimumab), for use in the treatment of the same medical condition (MSI-H colorectal cancer) and administered according to the same treatment regimen (3 mg/kg + 1 mg/kg Q3W). Moreover, **D3** firstly teaches this regimen to be therapeutically effective and secondly, to offer an advantage in terms of progression-free survival and overall survival over nivolumab monotherapy.
87. **D3** anticipates all features provided by claim 1 and thus deprives claim 1 of novelty.

IX.1.2 Claims 2 and 5 to 9

88. **D3** relates to the CheckMate 142 trial, i.e., to the same clinical trial as **D1** and **D2**. This trial encompassed the treatment of colon cancer. **D3** even comprises a direct link to the information

in **D1** or **D2** (cf. **D3**, p. 2, bottom par: “*Clinical trial information: NCT02060188*”)⁵ which refer to colon cancer already in the title. **D3** thus also teaches a treatment of colon cancer, as provided by claim 2.

89. **D3** further teaches a 4-month progression-free survival rate of 75% (cf. above table) and thus discloses subjects that have experienced a progression-free survival of at least four months (claim 5(i)). Similarly, a 5-month overall survival rate of 100% is taught, i.e., subjects that have experienced an overall survival of at least 5 months (claim 5(ii)). **D3** thus anticipates claim 5.
90. Patients in **D3** were treated with nivolumab plus ipilimumab for four doses, followed by nivolumab monotherapy (cf. **D3** under “Methods”: “*N 3 mg/kg + I 1 mg/kg q3 wk (N3+I1) x 4 doses followed by N3 until disease progression (PD) or other discontinuation*”, emphasis added).
91. The subject matter of granted claims 6 and 7 is thus likewise anticipated by **D3**.
92. Patient characteristics are described in **D3** as follows: “*Pts had ECOG PS 0–1, and intolerance/progression on ≥ 1 tx*”. Tx is used as an abbreviation for treatment(s) in **D3** (see title). **D3** therefore teaches the treatment of patients that had received one or more previous cancer treatments (claim 8) and have progressed on these previous treatments (claim 9). **D3** hence also anticipates claims 8 and 9.
93. In summary, **D3** thus further deprives at least dependent claims 2 and 5 to 9 of novelty.

IX.2 Lack of novelty over **D3a** or **D20**

94. Since the claimed subject matter lacks priority entitlement, **D3a**, the power point presentation corresponding to **D3**, which was presented at the 2016 ASCO Meeting held from June 3 to 7, 2016 is also full prior art to the claimed subject matter.
95. **D3a** relates to the treatment of MSI-H metastatic colorectal cancer (**D3a**, slide 1, title). With reference to **D15** and **D19** (there: cited as references 6 and 7). **D3a** suggests that the combination of nivolumab and ipilimumab has demonstrated deep and durable responses in solid tumors (**D3a**, slide 5, 4th bullet point).
96. Similar to **D3**, **D3a** discloses details about the CheckMate 142 clinical trial, including the treatment regimen for one patient cohort afflicted with MSI-H colon cancer that was treated with

⁵ The hyperlink embedded in **D3** directly links to the database entry for NCT02060188: <https://clinicaltrials.gov/ct2/show/NCT02060188>.

a combination of nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) once every three weeks, followed by nivolumab (3 mg/kg) once every two weeks (**D3a**, slide 8).

97. With respect to efficacy of the two evaluated treatments, **D3a** teaches that the combination treatment resulted in an overall response rate of 33%, as compared to 25% for the nivolumab monotherapy. Similarly, the ratio of partial responses (33% vs. 25%), stable disease (52% vs. 30%), 6-month progression-free survival (67% vs. 46%) and 9-month overall survival (85% vs. 66%) are reported to be higher for the combination treatment (cf. **D3a**, slides 13, 14 and 16).
98. The skilled artisan would thus have taken from **D3a** that the N3+I1 Q3W combination treatment to be clinically effective in MSI-H colon cancer and at least equivalent, if not superior to the tested comparator, i.e., N3 Q2W, in terms of clinical efficacy.
99. Accordingly, **D3a** teaches the treatment regimen required by claim 1 for the same disease and in the same patient group recited in claim 1.
100. **D3a** thus deprives at least granted claim 1 of novelty.
101. This also applies to **D20**, a meeting abstract published in October 2016. Similar to **D3a**, **D20** represents prior art to the granted claims in view of the invalid priority entitlement.
102. We refrain from discussing the contents of **D20** in detail for the sake of brevity. We note, however, that **D20** teaches the same clinical results that are disclosed in **D3a** (cf. **D20**, under “Methods”, “Results” and Table) and is thus novelty-destroying for the subject matter of at least claim 1 for the reasons given above with regard to **D3a**.

X. Lack of Inventive Step (Article 56 EPC)

X.1 Lack of Inventive Step over **D3 alone, or in combination with the common general knowledge (reflected e.g., by any one of **D11**, **D12** or **D13**)**

X.1.1 Claims 1, 2 and 5 to 9

103. As outlined above, claims 1, 2 and 5 to 9 lack novelty over **D3**, and therefore none of these claims relates to subject matter that is inventive in view of **D3** either.

X.1.2 Claims 3, 4 and 10

104. **D3** is also a suitable starting point for the assessment of inventive step of claims 3, 4 and 10.

105. The subject matter of claims 3 and 4 differs from the disclosure of **D3** in the specific characterization of the MSI-H tumor. The features recited in claims 3 and 4 correspond to the well-known characteristics of MSI-H colorectal cancer, as is evidenced by review articles **D11**, **D12** and **D13**⁶. Accordingly, no specific technical effect arises from the features recited in dependent claims 3 and 4.
106. As taught in **D11**, it had been known since the early 1990ies that about 15% of colorectal tumors are characterized by a high degree of microsatellite instability (**D11**, p. 2076, left col., penultimate par., **D12**, p. 153, left col. under “Introduction”, **D13**, p. 386, Fig. 1), which is caused by defects in the DNA mismatch repair (MMR) system (**D11**, p. 2075, left col., 3rd par., see also **D12**, abstract, **D13**, p. 385, left col., 1st par.).
107. The members of the MMR system were commonly known to include MLH1, MLH3, MSH2, MSH3, MSH6, PMS1 and PMS2 (cf. **D11**, p. 2079, Fig. 4, **D12**, p. 153, right col., 2nd par.). MSI-H colorectal cancer patients, including a subgroup suffering from a hereditary deficiency in DNA mismatch repair called Lynch syndrome, were known to often exhibit germline mutations in the MSH2, MLH1, PMS1, PMS2 and/or MSH6 genes (**D11**, p. 2076 to 2078, under “*MSH2 and HNPCC*” and “*MLH1, PMS2, PMS1 and MSH6*”, **D13**, p. 385, par. bridging pp. 385/86).
108. In other words, it was generally known that MSI-H colorectal tumors were often characterized by comprising germline mutations in multiple MMR genes (cf. granted dependent claim 3(a)), including the specific genes recited in granted dependent claim 4.
109. Moreover, **D11** teaches that
- “The majority of colorectal tumors with MSI have lost expression of MLH1 and PMS2 protein.”*
(**D11**, p. 2079, right col., 2nd par., see also **D13**, p. 388, par. bridging columns)
110. If the tumors lost expression of the two recited genes, this of course means that the proteins encoded by the respective DNA MMR genes (here: MLH1 and PMS2) cannot be detected in the tumor (cf. granted dependent claim 3(c)). Lack of protein expression of MLH1, MSH2, MSH6 and/or PMS2 proteins as a marker for MSI-H colorectal tumors is also disclosed in **D12** and **D13** (cf. **D12**, p. 155, Table 1, **D13**, p. 389, Table 2). Mutations leading to loss of expression in two genes (MLH1 and PMS2) also represent alterations in at least 30% of five or more MMR genes (two out of five being 40%), cf. granted claim 3(b).
111. In summary, the tumor characteristics provided by dependent claims 3 and 4 represent well-known attributes of MSI-H colorectal cancer. The features recited in these claims thus cannot

⁶ **D11**, **D12** and **D13** are review articles published in 2010 and 2011 and thus represent common general knowledge at the relevant date.

render the claimed subject matter inventive over **D3** alone, or in combination with common general knowledge, as represented by **D11**, **D12** or **D13**.

112. The subject matter of claim 10 differs from the teaching of **D3** by the requirement of nivolumab and ipilimumab to be comprised in a kit. No specific technical effect arises from this feature. Moreover, no inventive activity is required in order to combine the active agents used in **D3** into a kit.

113. Accordingly, claim 10 lacks an inventive step over **D3** alone.

X.2 Lack of inventive step over **D1** or **D2**

114. **D1** and **D2** are also suitable starting points for the evaluation of an inventive step of the claims, given that the clinical study disclosed therein relates to the treatment of the same medical condition with the same active agents and relying on the same dosing and administration scheme.

X.2.1 Claim 1 lacks inventive step vis-à-vis **D1/D2** in combination with the common general knowledge

115. **D1** and **D2** disclose the use of nivolumab and ipilimumab in the treatment of metastatic colon cancer (cf. **D1/D2** title, p. 4 under “Study Identification” and p. 5 under “Conditions”), including a study arm with MSI-H colon cancer (cf. **D1/D2**, p. 5, under “Study Description” and “Conditions”). The active agents used in the treatment were nivolumab and ipilimumab, the administration regimens included 3 mg/kg nivolumab plus 1 mg/kg ipilimumab once every 3 weeks (**D1/D2**, p. 6, under “Arms and Interventions”).

116. Both **D1** and **D2** therefore teach all features of granted claim 1.

117. While **D1** and **D2** do not include any study results, the skilled artisan would have had no doubts that nivolumab and ipilimumab could be used to successfully treat MSI-H colorectal cancer, in view of his/her common general knowledge; as discussed above, a high degree of microsatellite instability was generally considered to render colon cancer more responsive to anti-PD-1 treatment (cf. review article **D4** at p. 61, left col., bottom par.: “[...] *it appears that colon cancer with microsatellite instability, and consequently a higher overall mutational load, may be responsive to treatment with anti-PD-1 (67)*”, see also **D9**, p. 34, right col., 1st par.). The skilled artisan would thus have reasonably expected that the treatment taught in **D1** and **D2** is effective against colon/colorectal cancer.

X.2.2 Claim 1 lacks inventive step vis-à-vis D1/D2 in combination with any of D3, D14, D15, D17 or D23

118. Opponent further submits that **D3** would have alleviated any doubts regarding the efficacy of the treatment disclosed in **D1** and **D2**, and would have provided the skilled artisan with a reasonable expectation of success regarding the therapeutic efficacy of nivolumab in combination with ipilimumab for treating MSI-H colorectal cancer.
119. As explained above, **D3** teaches the combination of nivolumab and ipilimumab to result in favorable clinical outcome as compared to monotherapy with nivolumab only (cf. **D3**, Table on pp. 2/3, cf. above).
120. A further document that would have encouraged the skilled artisan to use nivolumab in combination with ipilimumab in the expectation of achieving a better response rate and/or survival rates is **D14**, a meeting abstract of the 2016 ASCO Annual Meeting, i.e., the same symposium where the authors of **D3** presented their work.
121. Similar to **D3**, **D14** was published online on May 20, 2016 and is thus full prior art to the granted claims irrespective of priority entitlement.
122. **D14** relates to the CheckMate 032 trial (NCT01928394), which was aimed at evaluating the efficacy of nivolumab alone or in combination with ipilimumab in patients afflicted with advanced tumors including small-cell lung cancer (SCLC, cf. **D14**, under “Background”). The combination of nivolumab and ipilimumab was administered in the very doses and administration regimen required by granted claim 1, i.e., nivolumab at a dose of 3 mg/kg and ipilimumab at a dose of 1 mg/kg, once every three weeks (Q3W), cf. **D14**, under “Methods”.
123. The results are summarized in the table below:

	N3 ^a n=80	N1 + I3 ^b n=47
ORR, % (n/N) ^c	13 (7/55)	31 (14/45)
Median DOR, mo	Not reached	6.90
Median OS, mo	3.55	7.75
Median PFS, mo	1.38	3.35
1yr OS rate, %	27	48

^a15 pts had <6 weeks minimum follow-up ^bMinimum follow-up = 120 days ^c25 pts in N3 and 2 pts in N1 + I3 were non-evaluable for tumor response DOR = duration of response

124. Notably, the overall response rate (ORR), the median overall survival (median OS), the median progression-free survival (median PFS) and the one-year overall survival rate (1yr OS) were

higher in patients treated with the combination of nivolumab and ipilimumab as compared to the cohort treated with nivolumab alone.

125. **D14** thus clearly indicates that the combination treatment can be expected to be more effective than treatment with nivolumab alone.
126. This is relevant for the present case given that, during prosecution of the application leading to the opposed patent, the Examiner seemed to have acknowledged an inventive step for the claimed combination treatment based on the consideration that said treatment offers a surprisingly prolonged progression-free survival as compared to nivolumab monotherapy (cf. separate sheet 5, 1st par. of the WO-ISA).
127. Yet, based on the evidence submitted herewith, this conclusion cannot be followed. To the contrary, an improved clinical response for the combination treatment was exactly what the skilled artisan would have expected at the relevant date.⁷
128. While **D14** relates to the treatment of SCLC and thus to the treatment of a condition other than colorectal cancer, it was common in the field of immune-checkpoint inhibitor-based cancer therapy to compare (and possibly transfer) efficacy data of immune-checkpoint inhibitor across cancer types. Moreover, it was well-known to the skilled artisan in the field of immune-checkpoint inhibitor-based cancer therapy that the combination of nivolumab and ipilimumab was actively investigated for the treatment of different types of cancer at the relevant date and had already been reported to offer superior clinical efficacy in different types of cancer, as explained above and demonstrated in **D15** and **D17/17a**.
129. It should further be noted in this context that initial clinical trials for the evaluation of the efficacy of nivolumab encompassed patients suffering from various different cancers, including colorectal cancer, melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC) and prostate cancer (cf. **D5**, p. 6, left col., ultimate par. and right col., 2nd par., **D9**, pp. 32 to 34, under “Early clinical development”). Nivolumab and ipilimumab were commonly known to be approved or in late-stage clinical evaluation for a wide range of cancer types (cf. **D8**, p. 102, Table 1).
130. The skilled artisan would thus have had a reasonable expectation that the results reported in **D14** may also be transferred to MSI-H colorectal cancer.

⁷ We note, for the sake of completeness, that the Patentee should not be able to rely on the data in the patent to support an allegedly surprising technical effect, since the data in the patent is firstly inconclusive (as explained further below in the context of sufficiency) and, secondly, the claims are not limited to doses of 3 mg/kg nivolumab and 1 mg/kg ipilimumab, due to the „about“ language used in claim 1.

131. Our position in this regard is confirmed by **D22**, an editorial relating to the data presented by Overman et al. at the 2016 ASCO Meeting (i.e., **D3/D3a**), that was published on June 5, 2016, i.e., two days after the priority date of the opposed patent. Reference is made to **D3** at the bottom of the article. The author notes that

"[p]revious research has supported the use of nivolumab in high microsatellite instability mCRC. Because the combination of nivolumab and ipilimumab has favorable safety and efficacy in other cancers, researchers aimed to evaluate nivolumab with or without ipilimumab in patients with high microsatellite instability mCRC and in patients without high microsatellite instability mCRC in a phase 2 study." (**D22**, p. 1, 3rd par.)

132. Accordingly, the skilled artisan would firstly have expected nivolumab and ipilimumab to be effective in the treatment of MSI-H colorectal cancer. Secondly, the person of skill in the art would have been aware that the phase 2 CheckMate 142 trial (which *inter alia* **D1** to **D3** relate to) had been initiated based on the finding that the combination of nivolumab and ipilimumab had been found to be beneficial in other types of cancer.
133. In other words, based on clinical data obtained for other types of cancer (such as **D14**), the skilled artisan would have reasonably expected the combination treatment to offer similar advantages over nivolumab therapy in MSI-H colorectal cancer.
134. Similarly, **D15** or **D17** would have encouraged the skilled artisan to use nivolumab in combination with ipilimumab in the expectation of achieving a better response rate and/or survival rates, as these documents teach the combination to be associated with higher rates of objective response as compared to monotherapy with either ipilimumab or nivolumab (cf. discussion above, **D15**, p.131 left col., 1st par., **D17**, last sentence).
135. Yet another prior art reference that would have further supported the skilled artisan's reasonable expectation regarding the clinical efficacy of the claimed combination treatment is **D23**, a database entry relating to the clinical study CheckMate 214 (NCT02231749). In this phase III study, the claimed combination treatment was compared with sunitinib monotherapy for the treatment in renal cell cancer (RCC). As repeatedly held by the Boards of Appeal, a published clinical study will generally provide the skilled artisan with a reasonable expectation of success regarding the clinical efficacy of the evaluated treatment, because clinical studies are typically preceded by *in vitro* and *in vivo* pre-clinical studies, followed by peer review and ethical approval (cf., e.g., **T 239/16**, reasons 6.6, 5th par., **T 96/20**, reasons 9, **T 2506/12**, reasons 3.10, 3.11 and 3.14). Only such treatments that may reasonably be expected to be effective will be allowed to enter the clinical stage.

136. Accordingly, starting from **D1** or **D2**, and taking either **D3**, **D14**, **D15**, **D17** or **D23** into consideration, the skilled artisan would have expected that (i) nivolumab and ipilimumab in the claimed dosing and administration regimen would be effective in the treatment of MSI-H colorectal cancer and (ii) the combination would be more effective as compared to nivolumab monotherapy.
137. Accordingly, claim 1 lacks an inventive step vis-à-vis each of **D1** and **D2**, alone or in combination with the skilled person's common general knowledge, or in combination with any one of **D3**, **D14**, **D15**, **D17** or **D23**.

X.2.3 Claims 2 and 6 to 9

138. The additional features of claims 2 and 6 to 9 are disclosed in **D1** and **D2**, respectively. The CheckMate 142 trial relates to the treatment of recurrent and metastatic colon cancer (cf. **D1** and **D2** under "Study Identification"). Claim 2 therefore lacks an inventive step for the same reason as claim 1.
139. The dosing schemes taught in **D1** and **D2** include "*Nivolumab 3mg/Kg IV combined with Ipilimumab 1 mg/Kg IV every 3 weeks for 4 doses followed by Nivolumab 3mg/Kg IV every 2 weeks until disease progression*" (cf. dose level 2b under "Arms and Interventions"). Hence the skilled person would have arrived at the claimed dosing schemes of claims 6 and 7 without inventive skill.
140. Patients were suffering from recurrent and metastatic colon cancer (cf. **D1**, under "Study Description"; in **D2** the expression "has come back" is used instead). A cancer is recurrent, if it comes back after initial treatment. In other words, patients suffering from recurrent cancer have undergone at least one previous cancer treatment and thus fulfil the requirements of granted claim 8.
141. Given that the cancer is recurrent (or "has come back"), it has apparently progressed on the previous treatment. Granted claim 9 thus also lacks inventive step over **D1** and **D2**.
142. In summary, at least granted dependent claims 2 and 6 to 9 lack an inventive step over **D1** and **D2**.

X.2.4 Claims 3, 4 and 10

143. We have explained hereinabove why the subject matter of claims 3, 4 and 10 fails to involve an inventive step over **D3** alone or in combination with common general knowledge (**D11**, **D12** or

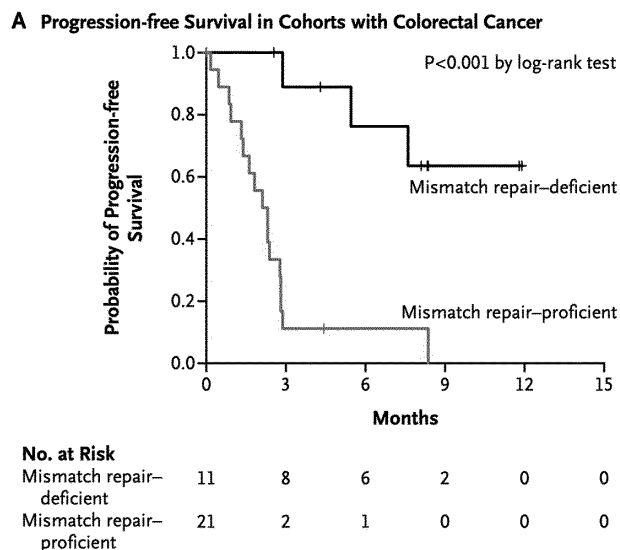
D13) and the same arguments apply *mutatis mutandis* to **D1** or **D2** as possible starting points for the assessment of inventive step.

144. Dependent claim 5 merely formulates a desired outcome (a certain degree of clinical improvement), i.e., it merely recites a result to be achieved and therefore cannot render the claimed subject matter inventive.
145. Taken together none of the granted claims satisfies the requirements of Article 56 EPC starting from **D1** or **D2** and taking common general knowledge (**D11**, **D12** or **D13**) or into consideration.

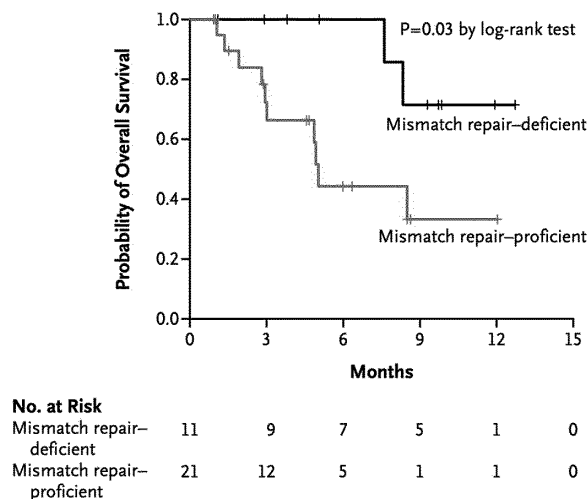
X.3 Lack of inventive step over **D10** in combination with **D1**, **D2**, **D3** or **D14** (or **D17**)

146. **D10** may also be used as an alternative closest prior art document, as it relates to the treatment of the same medical condition (MSI-H colorectal cancer) with an immune-checkpoint inhibitor, i.e., with an active agent belonging to the same functional class of active agents as nivolumab and ipilimumab.
147. The contents of **D10** have been discussed hereinabove. Briefly, **D10** relates to a phase 2 clinical study to evaluate the clinical activity of pembrolizumab, an anti-PD-1 antibody and immune checkpoint inhibitor (**D10**, abstract under “Methods” and pp. 2510 to 2512 under “Study Design”).
148. Patients enrolled in the study included a cohort afflicted with mismatch-repair deficient colorectal adenocarcinoma (cf. **D10**, p. 2510, right col., under “Patients”), i.e., patients suffering from MSI-H colorectal cancer. The rationale underlying the clinical study was that *“mismatch repair–deficient tumors are more responsive to PD-1 blockade than are mismatch repair–proficient tumors”* (**D10**, p. 2510, left col., lower half), which, as explained above, was a widely shared assumption in the field at the relevant date.
149. Pembrolizumab was administered at a dose of 10 mg/kg body weight every 14 days (**D10**, p. 2510, right col. bottom par.).
150. Clinical response was observed to be markedly better in mismatch repair deficient patients as compared to mismatch repair proficient patients (cf. **D10**, p. 2513, Table 2, p. 2514, Fig. 1 and right col., lower part, p. 2515, Fig. 2), leading to the conclusion that *“[t]he data from this small phase 2 trial of pembrolizumab for the treatment of tumors with and tumors without mismatch-repair deficiency support the hypothesis that mismatch repair–deficient tumors are more responsive to PD-1 blockade than are mismatch repair–proficient tumors”*.
151. **D10** thus teaches an effective treatment of mismatch repair-deficient colorectal cancer involving an anti-PD-1 antibody, i.e., an immune-checkpoint inhibitor.

152. The difference between the disclosure of **D10** and the subject matter of granted claim 1 is the claimed dosing and administration regimen of N3+I1 Q3W.
153. No technical effect arises from this distinguishing feature.
154. The patent does not comprise any comparative data that would allow for a proper comparison of pembrolizumab monotherapy and the claimed dosing and administration regimen.
155. Clearly, only a clinical study directly comparing the alternative treatments would allow for a proper comparison of their clinical efficacies. It is nonetheless notable that, looking at the clinical efficacy data disclosed in the patent and in **D10**, it seems as if pembrolizumab monotherapy would result in at least equivalent, if not better clinical response.
156. According to Table 7 on p. 21 of the opposed patent, the claimed N3+I1 Q3W regimen resulted in a 6-month progression-free survival rate of 66.6%. In comparison, the 6-month PFS rate observed for the pembrolizumab monotherapy in **D10** was about 75% in mismatch repair-deficient colorectal cancer patients, as is apparent from Fig. 2A of **D10**, which is reproduced below, for convenience:



157. According to Table 8 on p. 21 of the patent, the 6-month overall survival rate was 85.1% for the claimed combination treatment, while **D10** teaches a 6-month OS rate of 100%, cf. **D10**, Fig. 2B:

B Overall Survival in Cohorts with Colorectal Cancer

158. Thus, while no reliable comparison can be made in the absence of a true comparative study, pembrolizumab monotherapy as taught in **D10** would appear to be at least equivalent in terms of clinical efficacy as compared to the claimed combination treatment.
159. Starting from **D10**, the problem to be solved may thus be formulated as the provision of an alternative immune-checkpoint inhibitor-based therapy for the treatment of MSI-H colorectal cancer.
160. If the problem to be solved is defined as the provision of an alternative, any (known) variation of the subject matter disclosed in the closest prior art represents an equally obvious option for the skilled artisan. The skilled artisan would take any available modification into consideration. We direct the OD's attention to decision **T 631/06**, in which the competent Board (Board 3.3.01) stated (cf. reasons 2.3.10):

"In a case where the problem to be solved consists merely to provide an alternative, all the information contained in a document is treated equally by the person skilled in the art, notwithstanding whether it is preferred or not, or whether the implementation of some of the said information presents some difficulties. The so called "could-would" approach, applies when the technical problem to be solved relates in the provision of an improvement or in the suppression of disadvantages, not in the provision of an alternative." (**T 631/06**, reasons 2.3.10, emphasis added)

161. Similarly, in decision **T 674/08**, Board 3.3.02 stated (item 2.7 of the reasons):

"The appellant repeatedly argued that the skilled person might have attempted a combination of surfactants, but would not have contemplated the combination according to the invention.

This argumentation could not be taken into consideration, because the would-could approach is in general not meaningful when the problem is to find an alternative or further solution. If the problem is purely to find an alternative or further formulation, the skilled person would modify the existing product in any way he could by arbitrary choice". (emphasis added)

162. We further refer to the CLBA in this regard, which holds that:

"In T 892/08 the board referred to the established case law whereby, when the technical problem is simply that of providing a further composition of matter or a further method, i.e. an alternative to the prior art, any feature or combination of features already conventional for that sort of composition of matter or method represented an equally suggested or obvious solution to the posed problem. The boards have repeatedly established that the simple act of arbitrarily selecting one among equally obvious alternative variations is devoid of any inventive character (see also T 311/95)." (CLBA, I.D.9.19.8, last par.)

163. Accordingly, starting from **D10**, the skilled artisan would have considered any technically sensible alternative to pembrolizumab monotherapy as a potential substitute. This clearly includes the claimed N3+I1 Q3W regimen that is disclosed in multiple prior art references, as explained above.
164. Looking for an equivalent alternative for the treatment of MSI-H colorectal cancer, the skilled artisan would have taken any of **D1**, **D2** or **D3** into consideration, as all of these documents relate to the treatment of MSI-H colorectal cancer with immune-checkpoint inhibitors, i.e., they relate to the same purpose as **D10**.
165. Any of these documents, the teachings of which have been discussed in detail above, would have motivated the skilled artisan to consider N3+I1 Q3W as an alternative to the therapeutic regimen taught in **D10** in the expectation of arriving at an alternative therapy that provides a comparable degree of clinical efficacy.
166. It is notable in this context that the hypothesis which the study of **D10** was based on was that mismatch repair deficient tumors are "*more responsive to PD-1 blockade*" (cf. **D10**, p. 2510, left col., bottom third, p. 2516, right col., bottom par., emphasis added), i.e., the underlying rationale relied on the functional approach of PD-1 blockade and was not tied to the specific PD-1 blocking antibody being pembrolizumab. The skilled artisan would thus have considered the specific antibody used in the clinical study according to **D10** to be in principle exchangeable by an alternative anti-PD-1 antibody, which includes nivolumab, as the skilled artisan would have been aware at the relevant date.
167. Explaining their reasoning, the authors of **D10** make reference to "*reports of the effects of PD-1 blockade in human tumors*" (**D10**, p. 2510, left col., 2nd par.) citing two publications (footnotes 10

and 12) that both relate to uses of nivolumab in the treatment of cancer. The title of footnote 12, a paper by Brahmer et al., published in 2010 (cf. reference list on p. 2519 of **D10**) refers to “single-agent anti-programmed death 1 (MDX-1106)”, MDX-1106 being a synonym for nivolumab (cf. **B1**, [0004]). Similarly, footnote 10 (Topalian et al.), which is filed herewith as **D21**, relates to cancer treatment using nivolumab⁸ (cf. **D21**, abstract and p. 2444, under “Study Design”).

168. Thus, when **D10** refers to “PD-1 blockade”, a skilled person would readily understand that nivolumab can be used instead of pembrolizumab. As a consequence, the skilled artisan would have considered nivolumab as a suitable alternative to pembrolizumab. Motivated by the teaching of any one of **D1**, **D2** or **D3**, the skilled artisan would have considered the N3+I1 Q3W combination therapy taught in these documents as a suitable alternative to the regimen taught in **D10**.
169. In particular **D3** would have motivated the skilled artisan to consider N3+I1 Q3W as an alternative regimen, as it indicates that the combination treatment led to a higher 4-month progression-free survival rate as compared to nivolumab alone (cf. Table at the bottom of **D3**).
170. The combination of **D10** with any one of **D1**, **D2** or **D3** would thus have guided the skilled artisan to the subject matter of at least claim 1 (and claim 10) in an obvious manner.
171. Alternatively, **D14** (or **D17**) would have provided a motivation for the skilled artisan to consider the N3+I1 Q3W regimen as an alternative due to the reasons laid out above.
172. Accordingly, at least claims 1 and 10 lack an inventive step over **D10** in combination with **D1**, **D2**, **D3** or **D14** (or **D17**).
173. With respect to the dependent claims, reference is made to the above arguments which apply *mutatis mutandis*.

XI. Lack of Sufficient Disclosure (Article 83 EPC)

XI.1 The claims incompletely reflect the therapy and patient group assessed in the Examples

174. Claim 1 as granted relates to “[n]ivolumab for use in a method of treating a colorectal cancer tumor in a subject, wherein [...] the subject is administered nivolumab at a dose of about 3

⁸ Referred to as BMS-936558, i.e., nivolumab, cf. **B1**, [0004].

mg/kg body weight in combination with ipilimumab at a dose of about 1 mg/kg body weight once about every three weeks”.

175. Neither the number of doses, nor the preceding or subsequent treatment of the treated subjects is defined in claim 1.
176. This is notable, because the claim language thereby fails to fully reflect the treatment for which clinical data is presented in the patent.
177. The patent comprises two Examples, both of which relate to essentially the same treatment regimen (cf. **B1**, paras. [0119], [0134]). According to par. [0119] of the patent,

“Patients with 2nd MSI-H colon cancer who had received at least 1 prior treatment for metastatic disease, who had at least 1 target lesion, and who had an ECOG performance status of 0-1 were selected for inclusion in the MSI-H cohort of patients. Nineteen MSI-H patients were administered 3 mg/kg nivolumab once every 2 weeks in an initial monotherapy stage of treatment (mStage 1). Certain MSI-H patients exhibiting positive responses were then selected for inclusion in a combination therapy stage of treatment (cStage 1). Nineteen of these MSI-H patients were then administered 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab once every 3 weeks for a total of 4 doses, followed by 3 mg/kg nivolumab once every two weeks in cStage 1. A number of patients with positive responses from the cStage 1 are currently being enrolled in a second stage of combination therapy (cStage 2). In cStage 2, 48 patients (19 patients from cStage 1 plus 29 additional patients) will receive 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab once every 3 weeks for a total of 4 doses, followed by 3 mg/kg nivolumab once every two weeks. A separate group of patients exhibiting positive responses in mStage 1 were selected for inclusion in a second stage of monotherapy (mStage 2). In mStage 2, 48 patients (19 patients from mStage 1 plus 29 new patients) were administered 3 mg/kg nivolumab once every 2 weeks. Figure 2 shows the overall study design for patients in the MSI-H cohort.” (**B1**, [0119])

178. The cohort treated with the claimed combination therapy had been treated in three stages: first, patients received a 3 mg/kg nivolumab once every 2 weeks. This initial phase was followed by a combination stage in which one cohort was treated with 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab once every 3 weeks for a total of 4 doses, which was, as the third stage, followed by another round of nivolumab monotherapy (cf. **B1**, Fig. 2), 3 mg/kg Q2W.
179. Example 2 relates to the same treatment regimen (cf. **B1**, [0134]).
180. Based on the data disclosed in the patent, it is impossible to draw any sound conclusions regarding (a) clinical efficacy, or (b) any alleged advantages (or drawbacks) of the N3+I1 Q3W combination regimen as an isolated treatment.

181. None of the patients assessed according to the Examples has been treated with just the claimed regimen. In contrast, all patients received nivolumab monotherapy before and after their combination treatment.
182. Yet, granted claim 1 solely relates to the combination therapy stage of the evaluated schedule.
183. It is moreover noticeable that the patients undergoing combination therapy were preselected for being responsive to nivolumab therapy (cf. **B1**, [0119]: *“Certain MSI-H patients exhibiting positive responses were then selected for inclusion in a combination therapy stage of treatment [...]”*). In other words, the clinical data presented in the patent relates to patients that are characterized by being nivolumab responders!
184. Patients in Example 2 were selected in a similar manner (cf. **B1**, [0134]). This is obviously a highly meaningful limitation of the patient group as compared to a group of subjects that is solely characterized by the disease it is afflicted with.
185. Given that patients that have been treated with the claimed therapeutic regimen had been preselected for being responders to nivolumab therapy, i.e., for responding to one of the two claimed active agents, no scientifically reasonable conclusion can be drawn with respect to clinical efficacy in patient groups that have not undergone similar preselection.
186. In contrast, claim 1 defines the subject to be treated solely by their medical condition, i.e., MSI-H colorectal cancer and is silent with regard to nivolumab responder status.
187. Thus, the clinical efficacy of the claimed treatment regimen is not rendered plausible by the teaching of the opposed patent over the entire claim scope.
188. The data is inconclusive at least with respect to, firstly, the clinical efficacy of the claimed combination regimen, in isolation from an associated nivolumab monotherapy and, secondly, a patient group that has not been preselected for being nivolumab responders.

XI.2 The clinical data in the patent is incomplete and therefore flawed

189. Upon analysis of the clinical data in the opposed patent, a further point is immediately noticeable. Clinical outcome is only reported for some of the patients that were treated in the study.
190. According to **B1**, [0119], a total of 48 patients was treated with the claimed combination regimen (cf. **B1**, p. 18, ll. 7 and 8), but clinical results are only presented for 30 out of these 48 patients (cf. **B1**, Tables 2, 3 and 4), i.e., no clinical data is presented for over a third of the treated patients.

191. The data therefore does not provide a complete picture of the clinical response in the treated patient group. It is conceivable that only responders have been chosen for the evaluation, which would significantly skew the analysis in favor of the claimed treatment regimen.
192. In any case, the data disclosed in the patent does not allow for a reliable conclusion regarding the clinical efficacy of the claimed combination therapy, given that it is unclear how one third of the treated patients responded.
193. In the case of Example 2, it is completely unclear whether results for all subjects are reported, as the opposed patent is silent with respect to the number of patients included in the study who received the combination treatment.
194. Taken all together, the incomplete data regarding subjects treated with the claimed combination regimen represents another reason that the data in the patent is insufficient with respect to clinical efficacy of the claimed dosing and administration regimen over the entire claim range.

XI.3 The subject matter of dependent claim 5 is insufficiently disclosed

195. Claim 5 formulates a range of desired clinical outcomes, including progression-free survival for up to “at least about 12-months” or overall survival for up to “at least about 12-months”.
196. To satisfy the requirements of Article 83 EPC, the opposed patent is required to supply the skilled artisan with sufficient information to allow him/her to achieve the claimed clinical outcome, without undue burden, i.e., without having to resort to trial and error (CLBA, II.C.6.7).
197. However, the data in the patent provides reasonable doubts whether this clinical outcome can be reliably achieved. In Example 1, a 6-month progression-free survival rate of 66.6% is reported for the patients receiving the N3+I1 Q3W combination regimen (cf. **B1**, table 7). This only slightly exceeds 50%, which means that the skilled artisan would essentially be faced with trial and error when trying to put the claimed treatment into practice to achieve the clinical outcome recited in claim 5.
198. Notably, no 12-month progression-free survival rate is indicated, leaving it completely unclear whether 12-month progression-free survival is associated with a chance that exceeds (or is significantly below) 50%.
199. The same applies to overall survival as the clinical outcome (granted dependent claim 5(ii)). In this case, a higher rate is taught (as compared to 6-month PFS rates), but there is firstly no 12-month overall survival rate disclosed in the patent (cf. **B1**, Table 8) and, secondly, the rate of 85% disclosed in the context of Example 1 (6-months OS rate), still means that the skilled artisan would be faced with a substantial failure rate, when trying to achieve the claimed result.

200. Accordingly, granted dependent claim 5, which defined the claimed subject matter in the form of a *desideratum*, confronts the skilled artisan with an undue burden and thus violates Article 83 EPC.

201. The remaining claims share the same deficiencies due to their back-reference to these claims.

XII. Summary

202. As is evident from the above facts, evidence and arguments, the claimed subject matter of the opposed patent lacks novelty (Article 100(a) EPC and Article 54 EPC) and does not involve an inventive step over the cited prior art (Article 100(a) EPC and Article 56 EPC). Furthermore, the granted claims do not comply with the requirements of Article 83 EPC (Article 100(b) EPC) and Article 123(2) EPC (Article 100(c) EPC). Our request to revoke the opposed patent in its entirety is therefore fully justified.



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Enclosures
Documents **D1** to **D23**