

To
The Controller of Patents,
The Patent Office at Delhi

Re. Opposition under Section 25(1) against

Patent Application No. 201617025251 dated 22/07/2016

Applicant: 1. PFIZER INC; 2. MERCK SHARP & DOHME CORP.

Opponent: Dr. Priyank Purohit

Dear Sir,

This letter is in reference to submission of 'Pre-Grant Opposition' under section 25(1) of the Indian Patent Act 1970 concerning patentability of invention on the issue of 'Inventive Step' of the claims among other grounds against Patent Application No. 201617025251 dated 22/07/2016 titled: "Combination of a PD-1 antagonist and a VEGFR inhibitor for treating cancer" of whose the Applicant is 1. PFIZER INC; 2. MERCK SHARP & DOHME CORP.

In view of the above, Pre-Grant Opposition along with the relevant form and documents is being enclosed for your kind consideration.

Thanking you.

Dated: 14th September 2021

Yours faithfully,



Mr. Tarun Khurana

IN/PA/1325

Of Khurana and Khurana Advocates and IP Attorneys

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BEFORE THE CONTROLLER OF PATENTS

DELHI

**REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT UNDER
SECTION 25(1) OF THE PATENTS ACT, 1970 AGAINST PATENT APPLICATION
NO. 201617025251 DATED 22 July 2016**

Dr. Priyank Purohit, of Sachidanand Nagar, Teachers Colony, Near GIC., Rudraprayag-
246171, Uttarakhand, India

.....Opponent

-VS-

PFIZER INC. of 235 East 42nd Street New York, New York 10017, United States of America;
and MERCK SHARP & DOHME CORP. of 126 East Lincoln Avenue Rahway, New Jersey
07065, United States of America

.....Applicant

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BEFORE THE CONTROLLER OF PATENTS

DELHI

In the matter of Section 25(1) of The Patents Act, 1970 as amended by The Patents (Amendment) Act 2005;

And

In the matter of The Patents (Second Amendment) Rules 2006

And

IN THE MATTER of Indian Patent Application No. 201617025251 dated 22/07/2016 in the name of PFIZER INC. of 235 East 42nd Street New York, New York 10017, United States of America; and MERCK SHARP & DOHME CORP. of 126 East Lincoln Avenue Rahway, New Jersey 07065, United States of America

.....Applicant

And

IN THE MATTER of representation by way of opposition to grant of patent thereto by DR. PRIYANK PUROHIT, of Sachidanand Nagar, Teachers Colony, Near GIC., Rudraprayag- 246171, Uttarakhand, India

.....Opponent

**STATEMENT OF CASE FOR REPRESENTATION UNDER SECTION 25(1) OF
THE PATENTS ACT 1970**

I. THE OPPONENT

1. The Opponent herein is Dr. Priyank Purohit of Sachidanand Nagar, Teachers Colony, Near GIC., Rudraprayag- 246171, Uttarakhand, India. The Opponent is an individual with a Doctoral degree in Medicinal and Pharmaceutical Chemistry and a Master of Science degree in Medicinal Chemistry and has over 8 years of academic, research and industry experience in the field of life sciences and pharmaceuticals.

II. THE INDIAN PATENT APPLICATION NO. 201617025251

2. The Patent Application No. 201617025251 (hereinafter referred to as “the impugned application”) entitled “Combination of a PD-1 antagonist and a VEGFR inhibitor for treating cancer” was filed in India on July 22, 2016 from the PCT International Application No. PCT/US2015/014212 dated Feb. 03, 2015 which in turn claimed priority of Feb. 04, 2014. The impugned application was published in the official journal of the Indian Patent Office on Aug. 31, 2016.
3. The impugned application was filed in India with 20 claims broadly covering a combination therapy which comprises an antagonist of a Programmed Death 1 protein (PD-1) and an inhibitor of the vascular endothelial growth factor receptor (VEGFR) pathway. The complete specification of the impugned application as obtained from the IPAIRS (Indian Patent Application Information Retrieval System) database made available by the Indian Patent Office on its official website is attached herein as **Annexure I**.
4. The Indian Patent Office issued First Examination Report (F.E.R.) on Feb. 15, 2021 citing objections including, *inter alia*, lack of inventive step and non-patentability under sections 3(e), 3(n) and 3(i). The Applicant submitted its response to the F.E.R. on Aug. 02, 2021

along with an amended set of 1-14 claims. This set of amended claims 1-14 (latest/current), attached herein as **Annexure II**, is being challenged by way of this pre-grant opposition.

5. According to the Patent Office website the impugned application is not yet granted. The current status of the impugned application is “Application in Amended Examination”.

II.1 CLAIMS (LATEST/CURRENT) OF THE IMPUGNED APPLICATION

6. The claims below represent the amended set of 1-14 claims filed by the Applicant on Aug. 02, 2021 in respect of the impugned application in response to the FER.
 1. A medicament comprising an antagonist of a Programmed Death 1 protein (PD-1) for use in combination with a vascular endothelial growth factor receptor (VEGFR) inhibitor for treating a cancer in an individual, wherein the PD-1 antagonist is an anti-PD-1 monoclonal antibody which comprises a heavy chain and a light chain, wherein the heavy and light chains comprise SEQ ID NO:21 and SEQ ID NO:22, respectively, and further wherein the VEGFR inhibitor is N-methyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylsulfanyl]-benzamide or a pharmaceutically acceptable salt thereof.
 2. A medicament comprising a vascular endothelial growth factor receptor (VEGFR) inhibitor for use in combination with an antagonist of a Programmed Death 1 protein (PD-1) for treating a cancer in an individual, wherein the VEGFR inhibitor is N-methyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylsulfanyl]-benzamide or a pharmaceutically acceptable salt thereof, and further wherein the PD-1 antagonist is an anti-PD-1 monoclonal antibody which comprises a heavy chain and a light chain, wherein the heavy and light chains comprise SEQ ID NO:21 and SEQ ID NO:22.
 3. The medicament as claimed in claim 1 or 2, wherein the individual is a human.
 4. The medicament as claimed in any one of claims 1 to 3, wherein the cancer is a solid tumor that tests positive for Programmed Death-Ligand 1 (PD-L1) expression by an immunohistochemical (IHC) assay.

5. The medicament of any as claimed in claims 1 to 3, wherein the cancer is renal cell carcinoma.
6. The medicament as claimed in any one of claims 1 to 5, wherein the PD-1 antagonist is pembrolizumab and the VEGFR inhibitor is axitinib.
7. The medicament as claimed in claim 6, wherein the pembrolizumab is formulated as a liquid medicament which comprises 25 mg/ml pembrolizumab, 7% (w/v) sucrose, 0.02% (w/v) polysorbate 80 in 10 mM histidine buffer pH 5.5 and axitinib is formulated as a 1 mg tablet or a 5 mg tablet.
8. A kit which comprises a first container, a second container and a package insert, wherein the first container comprises at least one dose of a medicament comprising an antagonist of a Programmed Death 1 protein (PD-1), the second container comprises at least one dose of a medicament comprising a vascular endothelial growth factor receptor (VEGFR) inhibitor, and the package insert comprises instructions for treating an individual for cancer using the medicaments, wherein the PD-1 antagonist is an anti-PD-1 monoclonal antibody which comprises a heavy chain and a light chain, wherein the heavy and light chains comprise SEQ ID NO:21 and SEQ ID NO:22, respectively, and further wherein the VEGFR inhibitor is N-methyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylsulfanyl]-benzamide or a pharmaceutically acceptable salt thereof.
9. The kit as claimed in claim 8, wherein the instructions state that the medicaments are intended for use in treating an individual having a cancer that tests positive for Programmed Death-Ligand 1 (PD-L1) expression by an immunohistochemical (IHC) assay.
10. The kit as claimed in claim 8 or 9, wherein the individual is a human.
11. The kit as claimed in any one of claims 8 to 10, wherein the PD-1 antagonist is pembrolizumab formulated as a liquid medicament and the VEGFR inhibitor is axitinib formulated as a 1 mg tablet or a 5 mg tablet.

12. The use or kit as claimed in any one of claims 1-4 or 6-10, wherein the cancer is bladder cancer, breast cancer, clear cell kidney cancer, head/neck squamous cell carcinoma, lung squamous cell carcinoma, malignant melanoma, non-small-cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, prostate cancer, renal cell cancer, small-cell lung cancer (SCLC), triple negative breast cancer, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, Hodgkin's lymphoma (HL), mantle cell lymphoma (MCL), multiple myeloma (MM), myeloid cell leukemia-1 protein (Mcl-1), myelodysplastic syndrome (MDS), non-Hodgkin's lymphoma (NHL), or small lymphocytic lymphoma (SLL).
13. The use or kit as claimed in any one of the above claims, wherein the cancer is advanced renal cell carcinoma.
14. A medicament comprising:
- a) pembrolizumab for use in combination with axitinib for treating a cancer in a human individual by a method comprising administering to the individual (i) axitinib formulated as a 1 mg tablet or a 5 mg tablet and pembrolizumab formulated as a liquid medicament which comprises 25 mg/ml pembrolizumab or (ii) axitinib formulated as a 1 mg tablet or a 5 mg tablet and pembrolizumab formulated as a liquid medicament which comprises 25 mg/ml pembrolizumab; or
 - b) axitinib for use in combination with pembrolizumab for treating a cancer in a human individual by a method comprising administering to the individual (i) axitinib formulated as a 1 mg tablet or a 5 mg tablet and pembrolizumab formulated as a liquid medicament which comprises 25 mg/ml pembrolizumab or (ii) axitinib formulated as a 1 mg tablet or a 5 mg tablet and pembrolizumab formulated as a liquid medicament which comprises 25 mg/ml pembrolizumab.

III. GROUNDS OF OPPOSITION

7. The Opponent submits that the impugned application of the applicant is invalid and therefore grant of patent ought to be refused. The opponent relies upon the following grounds in the instant pre-grant opposition:

- i. **Section 25(1)(e)**– that the subject-matter claimed in the impugned application is obvious and clearly does not involve any inventive step.
- ii. **Section 25(1)(f)**– that the subject of any claim of the complete specification, is not an invention within the meaning of this act or is not patentable under this act.
- iii. **Section 25(1)(g)**– that the complete specification of the impugned application does not sufficiently and clearly describe the invention or the method by which it is to be performed.

IV. PRIOR ART RELIED UPON

Document	Patent No. / Article	Publication Date/Year
D1	Clinical Trials.gov: “ NCT02014636 A phase I/II study to assess the safety and efficacy of pazopanib and MK 3475 in subjects with advanced renal cell carcinoma”. The document was first posted online in December 2013. Retrieved from Clinical Trials.gov archive. Annexed herein as Annexure III	December 2013
D2	McDermott et al. , “PD-1 as a potential target in cancer therapy. Cancer Medicine.” Cancer Medicine published by John Wiley & Sons Ltd. 2013. Pages 662-673. Annexed herein as Annexure IV	21 July 2013

D3	Robert et al. “Drug of the year: programmed death-1 receptor/programmed death-1 ligand-1 receptor monoclonal antibodies”. Eur. J. Cancer. Vol. 49(14): pages 2968-71. Annexed herein as Annexure V	29 July 2013
D4	Tang and Heng. “Programmed Death 1 Pathway Inhibition in Metastatic Renal Cell Cancer and Prostate Cancer”. Current Oncology Reports. Vol. 15(2): pages 98-104. Annexed herein as Annexure VI	22 Dec. 2012
D5	van Geel et al., "Concise drug review: Pazopanib and axitinib". Oncologist, Vol. 17: pages 1081-1089. Annexed herein as Annexure VII	June 25, 2012
D6	Approval label of Axitinib by the FDA from January, 2012. Annexed herein as Annexure VIII	January, 2012
D7	Stehle et al., "Reduced immunosuppressive properties of axitinib in comparison with other tyrosine kinase inhibitors", J Biol Chem, Vol. 288(23): pages 16334-16347. Annexed herein as Annexure IX	June 2013
D8	Pal et al., "Novel therapies for metastatic renal cell carcinoma: Efforts to expand beyond the VEGF/mTOR signaling paradigm", Mol. Cancer Ther., Vol. 11: pp. 526-537. Annexed herein as Annexure X	March 2012
D9	Yasuda et al., "Simultaneous blockade of programmed death 1 and vascular endothelial growth factor receptor 2 (VEGFR2) induces synergistic anti-tumour effect in vivo", Clin. Exp. Immunol., Vol. 172(3): pp. 500-506. Annexed herein as Annexure XI	April 18, 2013
D10	Dorff et al., "Novel tyrosine kinase inhibitors for renal cell carcinoma", J. Exp. Rev. Clin. Pharmacol., Vol. 7(1): pp. 67-73. Annexed herein as Annexure XII	December 2, 2013

D11	Bailey et al. , "Immune Checkpoint Inhibitors as Novel Targets for Renal Cell Carcinoma Therapeutics", The Cancer Journal, Vol. 19(4): pp. 348-352. Annexed herein as Annexure XIII	July/August 2013
D12	Clinical Trials.gov: NCT01472081 Nivolumab (BMS-936558; MD-1106) in combination with sunitinib, pazopanib, or ipilimumab in subjects with metastatic renal cell carcinoma (RCC). The document was first posted online November, 2011 (see D12a) and updated <i>inter alia</i> in January, 2014 (see D12b) and thus is prior art. Annexed herein as Annexure XIV	November, 2011
D13	WO 2013/181452 A1. Annexed herein as Annexure XV	Dec. 05, 2013
D14	WO 2012/135408 A1. Annexed herein as Annexure XVI	Oct. 04, 2012

V. THE PERSON SKILLED IN THE ART

8. To begin with, it is helpful to point out that, in light of the current subject matter, the person skilled in the art would include a trained clinician highly familiar with designing and performing clinical studies on a regular basis, and in particular clinical studies with focus on the use of various antibodies and combination therapies to treat cancers.

VI. OBVIOUSNESS / LACK OF INVENTIVE STEP [Section 25(1)(e)]

9. The Opponent states that the subject-matter of all the claims 1 to 14 of the impugned application lacks inventive merit and is obvious to a person skilled in the art in view of the prior art documents annexed in the instant pre-grant opposition.

VI.1 The alleged invention

10. The alleged invention described in the impugned application relates to a combination therapy which comprises an antagonist of a Programmed Death 1 protein (PD-1) and an

inhibitor of the vascular endothelial growth factor receptor (VEGFR) pathway for the treatment of cancer.

11. In the claims which are discussed in further detail below, the **PD-1 antagonist** used in the combination therapy for the treatment of cancer is limited to the **anti-PD-1 antibody MK-3475** (also known as **pembrolizumab**, lambrolizumab or Keytruda) (defined in the claim by its amino acid sequence, see impugned application [0026] and [0086], confirming that sequences SEQ ID NO: 21 and 22, which are also shown in Fig. 6, define MK-3475). The **VEGFR inhibitor** is limited to the small molecule **axitinib** (defined in the claim by its chemical name) or a pharmaceutical acceptable salt thereof.

MK-3475 (Pembrolizumab or lambrolizumab or Keytruda)

12. The combination therapies of the claims incorporate an anti-PD-1 monoclonal antibody having a heavy chain and a light chain comprising SEQ ID NOs: 21 and 22, respectively.
13. The impugned application makes clear that the heavy and light chain sequences presented as SEQ ID NOs: 21 and 22 are the heavy and light chain sequences of the anti-human PD-1 antibody "MK-3475" (also known as **pembrolizumab**, lambrolizumab or Keytruda), a humanized IgG4 mAb - see paragraphs [0026], [0086] and Figure 6 of the impugned application.
14. MK-3475 (also known as Pembrolizumab or lambrolizumab or Keytruda) was widely reported as an effective anti-cancer monoclonal antibody in 2013, as reviewed in **D2** (McDermott et al., page 663, left column middle, Table 1 at page 663, and pages 666-667), **D3** (Robert et al., page 2969, left-column, penultimate paragraph) and **D4** (Tang and Heng, see, abstract) cited in the instant opposition.

Axitinib

15. The combination therapies of the claims incorporate, as a second agent, a VEGFR inhibitor that is N-methyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H -indazol-6-ylsulfanyl]-benzamide or a pharmaceutically acceptable salt thereof.

16. As explained in the impugned application (see paragraphs [00110] and [00111]), the compound CNc1ccc(cc1)/C=C/c2ccn(c2)S(=O)(=O)c3ccccc3 N-methyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylsulfanyl]-benzamide is known as "**Axitinib**" or "AG- 013736" and is a potent and selective inhibitor of VEGF receptors 1, 2 and 3. Before the priority date of the impugned application, axitinib was well-known as an anti-cancer agent for renal cell cancer, see for example, **D5** (van Geel et al., abstract). Moreover, as noted in paragraph [00111] of the impugned application, this drug was already approved in the US, Europe, Japan and other jurisdictions for the treatment of renal cell carcinoma. This fact is also reflected in the approved label of axitinib (cited here as **D6**), which shows that axitinib was approved by the FDA in 2012 for the treatment of advanced renal cell cancer (RCC).
17. It follows from the above, that the claims of the impugned application are directed to combination therapies comprising two agents that were well-established as anti-cancer agents prior to the impugned application.
18. The impugned application fails to provide any evidence of therapeutic efficacy for these two agents used in combination; indeed, the impugned application contains no experimental data whatsoever. The impugned application comprises a single Example 1, which describes the design of a study protocol for the treatment of patients with renal cell carcinoma (RCC) with a combination of axitinib and MK-3475 (pembrolizumab). The used wording shows that **Example 1 is a "paper example"**, i.e. the described study has not been performed yet (see impugned application, [00159]-[00161], emphasis added):

*"This study **will evaluate** the efficacy of a combination of axitinib and MK-3475 in human patients with RCC. Patients **will be treated** with axitinib at 5mg or 3mg BID and with MK-3475 at 1mg/kg or 2mg/kg every three weeks by intravenous infusion for a period of 18 months.*

Table 3 provided exemplary dosing information for the combination of axitinib and MK-3475.

***It is expected** that the combination of axitinib and MK-3475 will be more efficacious than either treatment alone ... "*

19. In line with the fact that Example 1 of the impugned application describes nothing more than a study design on paper, no experimental results are provided in the impugned application, i.e., no *in vitro* data, no animal model data, and no clinical data that would support the therapeutic efficacy of the claimed combination therapy. In the absence of any experimental data in the impugned application indicating unexpected efficacy for the claimed combination, the impugned application does not provide anything more than the cited art in terms of understanding the efficacy of the claimed combination.

LACK OF INVENTIVE STEP OF THE INDEPENDENT CLAIMS

VI.2 Claims 1, 2, 8 and 14 lack inventive step over the disclosure of D1 in combination with one or more of D2-D12

20. Inventive step of the subject-matter of independent claims 1, 2, 8 and 14 is to be denied starting from **D1** as closest prior art. We will first show that claim 1 lacks inventive step and will then explain why the subject-matter of the further independent claims is not inventive either.
21. **D1** discloses a clinical study wherein the anti-PD-1 antibody MK-3475 (pembrolizumab) is used in combination with the VEGFR inhibitor pazopanib for the treatment of advanced renal cell carcinoma.
22. The difference between claim 1 and **D1** is that pazopanib is replaced by the approved VEGFR-tyrosine kinase inhibitor (TKI) axitinib. As noted above, the impugned application discloses no experimental data for the claimed combination therapy but merely describes the design of a study that will be performed in the future (see hypothetical Example 1 of the impugned application).
23. The objective problem vis-à-vis **D1** can thus be defined as providing a further combination therapy with MK-3475 (pembrolizumab) and a VEGFR-TKI.
24. The solution, to replace pazopanib by axitinib in the combination therapy with MK-3475 (pembrolizumab) is rendered obvious by the prior art:

25. As outlined before, the skilled person knew as part of his common general knowledge that the VEGFR-TKI axitinib was approved in 2012 for the treatment of advanced renal cell cancer (RCC) (see, document **D6**). Axitinib was widely described and thus well-known to be well-tolerated, more potent and more selective compared to other VEGFR-TKIs, including pazopanib, and moreover, well-suited to be combined with immunotherapy. This knowledge is in particular reflected in the following documents:

- The review **D5** (van Geel et al.) provides a side-by-side comparison of the second-generation potent inhibitors pazopanib and axitinib for the treatment of renal cell cancer (RCC). Therefore, the skilled person knows that both VEGFR-TKIs can be used in the alternative for the treatment of RCC. **D5** moreover highlights important advantages that axitinib achieves compared to pazopanib in that axitinib is more selective and more potent than pazopanib. Additionally, **D5** teaches that the high selectivity of axitinib might contribute to less off-target adverse effects and a better therapeutic window (see, **D5**, page 1083, left column, penultimate paragraph under "Mechanism of Action"). These advantageous properties of axitinib over pazopanib provide a strong incentive to replace pazopanib by the more advantageous axitinib.
- Furthermore, **D7** (Stehle et al.) teaches that because of its advantageous profile, axitinib is better suited for combination therapy compared to other VEGFR-inhibitors, in particular for combination with immunotherapy. Axitinib is referred to as the "**leading candidate**" to be combined with other therapy strategies, in particular immunotherapy:

*"In conclusion, our results showed for the first time a number of **unique features of the TKI axitinib when compared with its competitors sunitinib and sorafenib.... Thus, axitinib might be better suited to be combined with other therapy strategies, in particular with immunotherapy.....**" see **D7**, page 16346, left column, second paragraph, emphasis added*

"Based on the results provided, axitinib might be the leading candidate to further explore combinatorial treatment regimens at least in combination with immunotherapy." see **D7**, page 16346, left column, last paragraph, emphasis added

This teaching that axitinib is the leading candidate for combination with immunotherapy would have further supported the already existing motivation to replace pazopanib by the more advantageous axitinib, because PD-1 inhibition by an anti-PD-1 antibody (such as MK-3475 (i.e., pembrolizumab)) is an immunotherapy.

26. In view of these known advantages of axitinib, there was a strong incentive to use axitinib as a combination partner for the anti-PD-1 antibody MK-3475 (pembrolizumab) and no inventive skills were thus required to replace pazopanib of **D1** with the more advantageous axitinib, thereby arriving at the claimed combination therapy with MK-3475 + axitinib for the treatment of cancer. It is moreover self-explanatory and also follows from **D1**, **D5** and **D7** that the therapeutic agents are comprised in a "medicament" for therapy.
27. Combining the anti-PD-1 antibody MK-3475 (pembrolizumab) with axitinib was furthermore fully in line with the general recommendation to combine anti-PD1 antibodies with approved VEGF-TKIs. The combined use of agents targeting the PD-1/PD-L1 pathway (in particular anti-PD-1 antibodies) and the VEGF/VEGFR pathway (in particular VEGFR-TKIs) for the treatment of cancer was a well-recognized therapeutic concept at the priority date of the impugned application. These facts are shown in the following documents, which also include numerous review articles:
 - According to review by Pal et al., 2012 (**D8**) VEGFR-TKIs may reach a ceiling effect at some point, necessitating exploration of novel signal axes such as anti-PD-1 antibodies (see, **D8**, page 526, right column, last paragraph and page 530 right column). It furthermore teaches that further development of anti-PD-1 antibodies (such as nivolumab, synonym MD-1106) may also include exploration of relevant therapeutic combinations, such as the anti-PD-1 antibody in combination with currently approved VEGF-TKIs:

*"Further development of the drug may also include exploration of relevant therapeutic combinations, such as MD-1106 in combination with currently approved VEGF-TKIs or mTOR inhibitors." See, **D8**, page 531, left column, first paragraph, emphasis added*

This review thus also demonstrates the acceptance of such combination therapy and explains in the context of PD-1 inhibition with an anti-PD-1 antibody (MD-1106; nivolumab) that a combination with approved VEGF-TKIs is the next (further) development.

- Yasuda et al., 2013 (**D9**) combined PD-1 blockage with VEGFR-2 inhibition for anticancer therapy in mice (using two antibodies). In the introduction, **D11** teaches that a *"number of previous studies have shown that the PD-1/PD-L1 pathway has clinical importance in several human malignancies and its blockade has a significant anti-tumour effect in rodent models [8-10]. Furthermore, recent Phase I clinical trials have shown that antihuman PD-1 or PO-L1 antibodies were tolerable for clinical use and might hold great promise as a new anti-cancer treatment for several advanced human malignancies [11,12]"* (see, **D9**, page 500, right column, emphasis added). It is concluded that their data shows a synergistic in-vivo anti-tumour effect that is induced successfully by combining PD-1 and VEGFR2 blockade and that this *"unique strategy may have clinical relevance and should have the potential to be evaluated in future clinical trials"* (see, **D9**, page 505, right column, third paragraph and abstract, last sentence).
- The review **D2** (McDermott et al.) highlights PD-1 as target in cancer therapy and teaches as noted above that anti-PD-1 antibodies such as nivolumab and MK-3475 (pembrolizumab) have shown therapeutic efficacy in the treatment of various cancers, including renal cell cancer and melanoma (see **D2**, p. 663, left column middle and p. 666-667). This review furthermore discusses that anti-PD-1 antibodies offer opportunities for combination therapy that are important to explore (see, **D2**, page 668, right column, bottom to page 669, top). As specific combination therapy, the combination with VEGFR tyrosine kinase inhibitors (TKI) is highlighted (see, page 669, right column, last paragraph). The review teaches that

combinations involving VEGFR TKIs with PD-1/PD-L pathway blockade may be better tolerated, and that in view of the interest in combining anti-PD-1 antibodies with VEGFR-TKIs, an ongoing clinical trial uses such combination therapy by combining an anti-PD-1 antibody (nivolumab) with the longer approved VEGFR-TKIs sunitinib or pazopanib (see, **D2**, page 669, right column, last paragraph to page 670, top).

- As already discussed above, **D7** (Stehle et al.) teaches that axitinib is the primary agent to explore combinatorial treatment regimes, such as in combination with immunotherapy (see, page 16346, left column, last paragraph).
- The review **D10** (Dorff et al.) discusses novel TKIs, thereunder axitinib (see, page 67, left column penultimate sentence) for the treatment of renal cell carcinoma. It furthermore teaches that immune therapy such as PD-1 pathway blockade plays an increasing role in cancer therapy (particularly metastatic renal cell cancer). It is further disclosed that *"newer agents hold potential for combinations with TKIs"* (see, **D10**, page 71, right column last paragraph). In the conclusion this review teaches that combining TKIs with anti-PD-1 antibodies is a promising strategy:

"Among the most promising targets in development for RCC [renal cell carcinoma] are immune checkpoint inhibitors, such as the programmed death ligand pathway. Several agents are in advanced stages of testing, such as nivolumab (BMS 936558), which is being tested in a multi-arm Phase I combination study, paired with either sunitinib, pazopanib or ipilimumab" (paragraph spanning from pages 71 to 72, emphasis added).

- The review **D11** (Bailey et al.) discusses the use of immune checkpoint inhibition, in particular anti-PD-1 antibodies such as MK-3475 (pembrolizumab) for treatment of renal cell carcinoma (see, page 350, left column, third paragraph and page 351, left column first paragraph). Furthermore, this review teaches that a combination therapy that combines an anti-PD-1 antibody with VEGF inhibition, e.g., by using VEGFR-TKIs, may improve the therapeutic benefit:

"Several preclinical studies have shown that increased levels of VEGF may have immunosuppressive effects. VEGF receptor tyrosine kinase inhibitors such as pazopanib or sunitinib may reduce the numbers of myeloid-derived suppressor cells and limit the negative effect of VEGF, thereby reversing tumor-induced immunosuppression. Thus, combining anti-VEGF therapy with immune therapies has a theoretical chance of augmenting benefit." See, **D11**, page 350, left column, second paragraph, emphasis added.

28. Hence, combining drug agents to target both biochemical pathways, PD-1/PD-L1 and VEGF/VEGFR, was **a common strategy** that was widely described for the treatment of cancer. There was a wide acceptance in this field that such combination therapy with a PD-1 antagonist (e.g., anti-PD1 antibody) and a VEGFR inhibitor (e.g., an approved VEGFR-TKI) is in general useful for cancer therapy, in particular for the treatment of renal cell cancer. This combination therapy concept thus belonged to the **common general knowledge** of the skilled person.
29. As a result of this established concept that a combination therapy with a PD-1 antagonist and a VEGFR inhibitor is highly useful in the treatment of cancer, multiple clinical studies were published before the priority date that applied such combination therapy for the treatment of cancer, in particular renal cell cancer. Various PD-1 antagonists, usually anti-PD-1 antibodies, were combined in these studies with various VEGFR inhibitors, usually approved VEGFR-TKIs. Regularly, approval of an agent addressing the VEGF/VEGFR pathway was followed by a combined treatment with an agent addressing the PD-1/PD-L1 pathway. These facts are reflected by the following studies that were published before the priority date of the impugned application:
 - In the study of NCT01472081 (**D12**) an anti-PD-1 antibody (nivolumab) was combined with a VEGFR-TKI (sunitinib or pazopanib) for the treatment of metastatic (i.e. advanced) renal cell cancer (the VEGFR-TKIs sunitinib and pazopanib were approved for renal cell cancer in 2006 and 2009, respectively).

- In the study NCT02014636 (**D1**) an anti-PD-1 antibody (MK-3475 - Pembrolizumab) was combined with the VEGFR-TKI pazopanib for the treatment of advanced renal cell cancer. Also here the approval of pazopanib in 2009 was followed by a clinical trial in a combination therapy with an anti-PD-1 antibody in 2013.
30. These studies further demonstrate and corroborate that a combination therapy of an agent targeting the PD-1/PD-L1 pathway, in particular anti-PD-1 antibodies, and an agent targeting the VEGF/VEGFR pathway, in particular approved VEGFR-TKIs, was well-established to be useful and therefore widely used for the treatment of cancer because of expected therapeutic benefits.
 31. Therefore, combining the anti-PD-1 antibody MK-3475 (pembrolizumab) with axitinib was furthermore fully in line with the general recommendation to combine anti-PD1 antibodies with approved VEGF-TKIs. Axitinib which was approved in 2012 (and was moreover known to be more potent, more selective and well-suited for combination therapy) was the obvious next combination partner for such combination therapy. In view of the consistent teachings in the prior art that a therapy that combines an anti-PD1 antibody with an approved VEGFR-TKI is advantageous and highly promising for cancer therapy, the skilled person also had more than reasonable expectations of success that a combination therapy with the two effective drugs MK-3475 (pembrolizumab) and axitinib will be effective and therefore, would have used this combination therapy for the treatment of cancer.
 32. Therefore, the subject-matter of claim 1 does not involve an inventive step when starting from **D1** as closest prior art and combining this with one or more of **D2** to **D12**.

The Applicant cannot rely on post-published data to establish inventive step

33. During prosecution, the Applicant argued in support of inventive step on the basis of post-published data. In particular, the Applicant sought to rely on the post-published documents Atkins et. al. 2016, Rothermundt et. al. 2016 and Rini et. al. 2019 for evidence of a technical effect. However, a technical effect based exclusively on post-published data cannot be taken into account in the assessment of inventive step. The Applicant submitted

these post-published data to remedy the deficiencies in the as-filed specification, which is not permissible under the Act. It is important to take notice of the fact that a Patentee or an Applicant is required to show workability of an invention at the time of filing of the complete specification. Having failed to provide such disclosure/information raises serious doubts on whether or not the Applicant actually possessed the invention at the time of filing the complete specification. It is established case law that post-filed data cannot be used in order to establish plausibility of claimed therapeutic effect. Instead, post-published data can only be used to back-up and confirm a therapeutic effect that is already plausibly disclosed in the application as filed. In the instant case, there are absolutely no data in the impugned application demonstrating therapeutic efficacy for the claimed combination. There is nothing in the impugned application itself to render it plausible that a surprising or unexpected therapeutic effect can be achieved with the claimed combination. The only example (Example 1) included in the impugned application is a study protocol for the testing of a combination of MK-3475 (pembrolizumab) and axitinib in renal cell carcinoma patients. No results are presented. Therefore, such insufficiency of the impugned application could not be cured by filing post-published evidence/clinical data. Therefore, the Applicant should not be allowed to rely on the post-published data to establish inventive step.

VI.3 Claim 2 lacks inventive step over the disclosure of D1 in combination with one or more of D2-D12

34. As explained above, a combination therapy with MK-3475 (pembrolizumab) and axitinib for the treatment of cancer is rendered obvious starting from **D1** as closest prior art. For the same reasons, the subject-matter of claim 2 is obvious as well, because claim 2 defines the same combination therapy, merely coming from the medicament comprising axitinib.
35. Thus, also the subject-matter of claim 2 lacks an inventive step.

VI.4 Claim 8 lacks inventive step over the disclosure of D1 in combination with one or more of D2-D13

36. A kit is nothing more than a set of reagents, here the medicaments comprising pembrolizumab (MK-3475) and axitinib provided in a first and second container. A container is mandatorily required to hold/receive the medicament and therefore, does not contribute patentable subject-matter. The single agents (pembrolizumab and axitinib) disclosed in the prior art were certainly also provided in containers. According kit concepts were moreover well-known (see e.g., **D13**, paragraphs [0014] and [153]). It is also common to provide a kit with a package insert comprising instructions for use.
37. Thus, also the subject-matter of claim 8 lacks an inventive step.

VI.5 Claim 14 lacks inventive step over the disclosure of D1 in combination with one or more of D2-D12

38. The independent claim 14 is not inventive when starting from **D1** as closest prior art. As explained above, the combination therapy with MK-3475 (pembrolizumab) and axitinib for the treatment of cancer is rendered obvious by the discussed prior art and the defined dosages and formulations do not contribute any patentable subject-matter either:

- Axitinib formulated as a 1 mg tablet or 5 mg tablet was well-known in the art and therefore, cannot contribute anything inventive. E.g., **D5** (van Geel et al.) teaches that axitinib is provided in form of an oral 1mg or 5mg tablet (see, **D5**, page 1083, left column, second paragraph, emphasis added):

"Axitinib is available as 1 mg and 5 mg oral tablets, and the recommended starting dose is 5 mg twice daily (BID) on a continuous dosing schedule."

This fact is also reflected in the approved label of axitinib (see **D6**, page 1, left column, "Dosage forms and strength"). Hence, this teaching was well-known in the art and thus an obvious choice for axitinib.

- **D1** discloses that MK-3475 (pembrolizumab) is an intravenously administered 100 mg/4mL solution (i.e., a liquid formulation comprising 25 mg/mL pembrolizumab)

(see, **D1**, page 5). Formulating pembrolizumab as a liquid medicament comprising 25 mg/mL pembrolizumab was therefore obvious.

39. Thus, also the subject-matter of claim 14 lacks an inventive step.
40. Thus, the independent claims 1, 2, 8 and 14 are obvious and do not involve any inventive step when starting from **D1** as closest prior art and combining this with one or more of **D2** to **D12**.

LACK OF INVENTIVE STEP OF THE DEPENDENT CLAIMS

VI.6 Lack of inventive step of the subject-matter of Claim 3

41. Claim 3 defines that the individual is a human. This teaching does not define any patentable subject-matter, considering that the documents discussed above administer the disclosed combination therapies to human patients.

VI.7 Lack of inventive step of the subject-matter of Claim 4

42. Claim 4 further specifies that the cancer is a solid tumor that tests positive for PD-L1 expression by an immunohistochemical (IHC) assay. This teaching does not define any patentable subject-matter, because it is essentially inherent for solid tumors that can be treated with a PD-1 antibody.

VI.8 Lack of inventive step of the subject-matter of Claim 5

43. Claim 5 defines that the cancer is renal cell carcinoma. This teaching does not define patentable subject-matter because it was in any case obvious to use a combination therapy with axitinib and MK-3475 (pembrolizumab) for the treatment of renal cell carcinoma (RCC), including advanced forms of renal cell carcinoma (aRCC). This is because the individual agents axitinib and MK-3475 (pembrolizumab), as well as combination therapies that are based on the use of an anti-PD-1 antibody in combination with a

VEGFR-TKI, were well known and described to be useful for the treatment of renal cell carcinoma, including advanced renal cell carcinoma.

- Axitinib was a next generation VEGFR-TKI, which was approved in 2012 for the treatment of advanced renal cell carcinoma (see, **D6**).
- The use of anti-PD-1 antibodies, including MK-3475, for the treatment of renal cell cancer, including advanced renal cell cancer, was widely described in the prior art, also in form of combination therapies with various VEGFR-TKIs:
 - As noted above, the review **D2** (McDermott et al.) teaches that anti-PD-1 antibodies such as nivolumab and MK-3475 (pembrolizumab) have shown therapeutic efficacy in the treatment of various cancers, including renal cell cancer and melanoma (see, **D2**, page 663, middle of left column).
 - The fact that anti-PD-1 antibodies, including MK-3475 (pembrolizumab), are useful for the treatment of renal cell cancer is further confirmed by the numerous clinical trials published before the priority date of the impugned application. Therein, different anti-PD-1 antibodies, including MK-3475, were combined with different VEGF receptor antagonists for treatment of renal cell carcinoma. This confirms that it was widely accepted that anti-PD-1 antibodies, including MK-3475, are useful for the treatment of renal cell carcinoma, including advanced renal cell carcinoma:
 - In study NCT02014636 (**D1**) **MK-3475** was combined with the **VEGF receptor antagonist** pazopanib for the treatment of **advanced renal cell carcinoma**.
 - In study of NCT01472081 (**D12**) the **anti-PD-1 antibody nivolumab** (also referred to as BMS-936558 or MD-1106) is used in combination with the **VEGFR-TKIs** sunitinib or pazopanib for treatment of **metastatic (i.e. advanced) renal cell carcinoma**. Sunitinib and pazopanib are VEGF receptor antagonists that were approved for renal cell cancer.

44. Therefore, the treatment of renal cell carcinoma, including advanced renal cell carcinoma, with a combination of an anti-PD-1 antibody (here: MK-3475, i.e., pembrolizumab) and VEGF receptor antagonist (here: axitinib) was entirely obvious in view of these established teachings and does not define patentable subject-matter.

VI.9 Lack of inventive step of the subject-matter of Claim 6

45. Claim 6 defines that the PD-1 antagonist is pembrolizumab and the VEGFR inhibitor is axitinib. This teaching does not define patentable subject-matter for the reasons discussed above in conjunction with claims 1 and 2.

VI.10 Lack of inventive step of the subject-matter of Claim 7

46. Claim 7 defines that the PD-1 antagonist (i.e., pembrolizumab) is formulated as a liquid medicament which comprises 25 mg/ml pembrolizumab, 7% (w/v) sucrose, 0.02% (w/v) polysorbate 80 in 10 mM histidine buffer pH 5.5, and that axitinib is formulated as a 1 mg tablet or a 5 mg tablet.
47. Claim 7 does not define any patentable subject-matter because (1) the formulation for pembrolizumab as well as (2) the tablet defined for axitinib were well-known in the prior art. Thus, the further features of claim 7 are obvious in view of the prior art as will be explained in the following.

The defined formulation for pembrolizumab was well-known and described as advantageous in the art

48. The formulation of claim 7 was described in **D14** (WO2012/135408) to be suitable for anti-PD1 antibodies in general and MK-3475 (pembrolizumab) specifically.
49. **D14** discloses stable formulations of anti-PD-1 antibodies (see e.g., abstract) and discloses in paragraphs [00119] and [145] the following liquid formulation:

“liquid formulation comprising 10 mM histidine pH 5.5, 7 % sucrose, 0.02 % polysorbate 80, and 25 mg/ml h409A11”

50. Thus, the liquid formulation for the anti-PD-1 antibody disclosed in **D14** is identical to the one defined in instant claim 7, and **D14** furthermore teaches that h409A11 corresponds to MK-3475 (pembrolizumab) - it identifies the same antibody. That h409A11 corresponds to MK-3475 (pembrolizumab) is e.g. evident from Example 3 of **D14** (see, e.g. paras. [161] and [163] and notably the heading of Table 5 at para. [163]).
51. Therefore, the formulation defined in instant claim 7 was known to be useful and advantageous to provide stable formulations for anti-PD-1 antibodies in general and also MK-3475 (pembrolizumab) specifically. Therefore, the skilled person had every incentive to use this formulation for pembrolizumab. Therefore, no inventive skills were required to arrive at this teaching.

Axitinib formulated as a 1mg or 5mg tablet was well-known in the art

52. Axitinib formulated as a 1 mg tablet or 5 mg tablet was well-known in the art and therefore, cannot contribute anything inventive. E.g., **D5** (van Geel et al.) teaches that axitinib is provided in form of an oral 1mg or 5mg tablet (see, **D5**, page 1083, left column, second paragraph, emphasis added):

"Axitinib is available as 1 mg and 5 mg oral tablets, and the recommended starting dose is 5 mg twice daily (BID) on a continuous dosing schedule."

53. This fact is also reflected in the approved label of axitinib (see **D6**, page 1, left column, "Dosage forms and strength"). Hence, this teaching was well-known in the art and thus an obvious choice for axitinib.
54. Therefore, the subject-matter of claim 7 lacks inventive step.

VI.11 Lack of inventive step of the subject-matter of Claim 9

55. Claim 9 defines that the instructions state that the medicaments are intended for use in treating an individual having a cancer that tests positive for PD-L1 expression by an immunohistochemical (IHC) assay.
56. As noted above, "instructions" do not represent a technical feature that limit the claim scope. Therefore, they do not define any further distinguishing feature.
57. Moreover, the indicated information was moreover obvious for the reasons discussed in conjunction with claim 4.
58. Therefore, claim 9 does not define any patentable subject-matter.

VI.12 Lack of inventive step of the subject-matter of Claim 10

59. Claim 10 further defines that the individual is a human. It is referred to our discussion of claim 3. This feature does not define patentable subject-matter.

VI.13 Lack of inventive step of the subject-matter of Claim 11

60. Claim 11 defines that the PD-1 antagonist is pembrolizumab formulated as a liquid medicament and the VEGFR inhibitor is axitinib formulated as a 1 mg tablet or a 5 mg tablet.
61. It is referred to our discussion of claim 7 where we have explained that such liquid and tablet formulations were well-known and thus obvious in view of the prior art.

VI.14 Lack of inventive step of the subject-matter of Claims 12 and 13

62. Claim 12 recites that the cancer is selected from particular types of cancer. Claim 12 *inter alia* refers to renal cell cancer. Claim 13 defines that the cancer is advanced renal cell carcinoma.

63. Claims 12 and 13 are obvious in view of the cited prior art for the same reasons as discussed in detail in conjunction with claim 5. As discussed in detail supra, it was well-established and obvious to use the claimed combination therapy for renal cancer, including advanced forms of renal cell carcinoma.
64. Thus, also claims 12 and 13 do not define any patentable subject-matter.
65. For the reasons set forth above, it is therefore respectfully submitted that the subject-matter of all the claims 1 to 14 of the impugned application is obvious and does not meet the requirements with regard to inventive step, and as such is not patentable under the provisions of Section 25(1)(e) read with Section 2(1)(ja) of the Patents Act.

VII. NOT AN INVENTION/ NOT PATENTABLE [Section 25(1)(f)]

66. Section 25(1)(f) of the Patents Act, 1970 governs the case where the subject of any claim of the complete specification is not an invention within the meaning of this act, or is not patentable under this act.

Not an Invention / Not Patentable u/s 3(e)

67. The subject-matter of claims 1-14 of the impugned application is squarely covered by Section 3(e) in light of the submissions below.

Section 3(e) of the Indian Patent Act bars patentability of a subject-matter wherein the subject-matter is "*a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance*".

68. As explained above, the claims of the impugned application are directed to combination therapies comprising two known therapeutic agents, pembrolizumab (MK-3475) and axitinib, that were well-established as anti-cancer agents prior to the impugned application. Further, as previously indicated in paragraphs 20 to 32 supra, combination therapies that are based on the use of an anti-PD-1 antibody in combination with a VEGFR

inhibitor, were well known and described to be useful for the treatment of renal cell carcinoma, including advanced renal cell carcinoma.

69. The impugned application contains no experimental data to evidence any special technical effect associated with the combined use of pembrolizumab (MK-3475) and axitinib. The only example included in the impugned application is a study protocol for the testing of a combination of MK-3475 and axitinib in renal cell carcinoma patients. No results are presented. There is nothing in the impugned application to render it plausible that the claimed combination achieves any "surprising or unexpected therapeutic efficacy".
70. The impugned application comprises a single Example 1, which describes the design of a study protocol for the treatment of patients with renal cell carcinoma (RCC) with a combination of axitinib and MK-3475. The used wording shows that **Example 1 is a "paper example"**, i.e. the described study has not been performed yet (see impugned application, [00159]-[00161], emphasis added):

*"This study **will evaluate** the efficacy of a combination of axitinib and MK-3475 in human patients with RCC. Patients **will be treated** with axitinib at 5mg or 3mg BID and with MK-3475 at 1mg/kg or 2mg/kg every three weeks by intravenous infusion for a period of 18 months.*

Table 3 provided exemplary dosing information for the combination of axitinib and MK-3475.

***It is expected** that the combination of axitinib and MK-3475 will be more efficacious than either treatment alone ... "*

71. In line with the fact that Example 1 of the impugned application describes nothing more than a study design on paper, no experimental results are provided in the impugned application, i.e., no *in vitro* data, no animal model data, and no clinical data that would support therapeutic efficacy of the claimed combination therapy. The claimed combination therapy is thus exclusively based on the well-known facts that pembrolizumab (MK-3475) is an effective anti-PD-1 antibody and axitinib is an effective VEGFR inhibitor. In the absence of any evidence for synergistic or unexpected therapeutic efficacy which has no basis in the specification of the impugned application, the therapeutic combination

according to claims 1-14 is merely an admixture resulting only in the aggregation of the properties of the components thereof. Accordingly, the claimed combination therapy squarely falls within the mischief of section 3(e) and thus ought to be rejected on this basis alone.

72. During prosecution, the Applicant sought to rely on post-published data for evidence of a technical effect. The Applicant submitted this post-published data to remedy the deficiencies in the as-filed specification, which is not permissible under the Act. It is important to take notice of the fact that a Patentee or an Applicant is required to show workability of an invention at the time of filing of the complete specification. Having failed to provide such disclosure/information raises serious doubts on whether or not the Applicant actually possessed the invention at the time of filing the complete specification. It is established case law that post-filed data cannot be used in order to establish plausibility of claimed therapeutic effect. Instead, post-published data can only be used to back-up and confirm a therapeutic effect that is already plausibly disclosed in the application as filed. In the instant case, there are absolutely no data in the impugned application demonstrating therapeutic efficacy for the claimed combination. There is nothing in the impugned application itself to render it plausible that a surprising or unexpected therapeutic effect can be achieved with the claimed combination. The only example (Example 1) included in the impugned application is a study protocol for the testing of a combination of MK-3475 (pembrolizumab) and axitinib in renal cell carcinoma patients. No results are presented. Therefore, such insufficiency of the impugned application could not be cured by filing post-published evidence/clinical data.
73. The Opponent therefore humbly implores that the impugned application be rejected under this ground alone.

VIII. INSUFFICIENT DISCLOSURE [Section 25(1)(g)]

74. **Lack of sufficiency of disclosure in relation to Claims 1-14:** The claims of the impugned application are directed to combination therapies comprising two agents, pembrolizumab (MK-3475) and axitinib, that were known as anti-cancer agents prior to the impugned

application. As noted above, the impugned application does not contain any data to demonstrate efficacy of the claimed combination in any experimental setting and certainly not in the treatment of human cancer. The impugned application comprises a single Example 1, which merely describes the design of a study protocol for the treatment of patients with renal cell carcinoma (RCC) with a combination of axitinib and MK-3475. Example 1 of the impugned application describes nothing more than a study design on paper. It follows that the claims must be found insufficient.

75. During prosecution, the Applicant sought to rely on post-published data for evidence of a technical effect. The Applicant submitted this post-published data to remedy the deficiencies in the as-filed specification, which is not permissible under the Act. It is important to take notice of the fact that a Patentee or an Applicant is required to show workability of an invention at the time of filing of the complete specification. Having failed to provide such disclosure/information raises serious doubts on whether or not the Applicant actually possessed the invention at the time of filing the complete specification. It is established case law that post-filed data cannot be used in order to establish plausibility of claimed therapeutic effect. Instead, post-published data can only be used to back-up and confirm a therapeutic effect that is already plausibly disclosed in the application as filed. In the instant case, there are absolutely no data in the impugned application demonstrating therapeutic efficacy for the claimed combination. The only example (Example 1) included in the impugned application is a study protocol for the testing of a combination of MK-3475 and axitinib in renal cell carcinoma patients. No results are presented. Therefore, such insufficiency of the impugned application could not be cured by filing post-published evidence/clinical data.
76. Hence, the claimed subject-matter is not sufficiently disclosed by the specification of the impugned application, which is a defect that cannot be fixed by post-published evidence.
77. **Claims 1, 2, 8, 12 and 14 are not enabled:** The independent claims 1, 2, 8 and 14 extend to the treatment of all cancers. As evidenced by dependent claim 12, treatment extends to a variety of solid tumors. Claim 12 provides a long list of various, very different cancers. Accordingly, to sufficiently disclose the therapeutic effect in the treatment of all these specific, very different cancers, it would need to be plausible for the skilled person that

the claimed combination therapy achieves a therapeutic effect in the treatment of **all** of these specific cancers. However, there is no evidence in the impugned application to render it credible that a therapeutic efficacy will be achieved in any cancer type. As noted above, there are absolutely **no data** in the impugned application demonstrating therapeutic efficacy for the claimed combination in any cancer type. As discussed extensively above, the examples of the impugned application include nothing more than a study protocol. It is thus not plausible that any cancer can be treated with the claimed combination therapy. Therefore, the subject-matter of claims 1, 2, 8, 12 and 14 is insufficiently disclosed, which is a defect that, as already noted above, cannot be fixed by post-published evidence.

78. It is respectfully submitted that upon detailed and careful analysis of the impugned application, several lacunae, infirmities, defects, insufficiencies and ambiguities are borne out. It is for this reason that the opponent has established various grounds of opposition under section 25(1) and the impugned application is therefore ought not to be granted.

IX. RELIEF SOUGHT

79. The Opponent states that it has established and made out a case on each of the aforesaid grounds of opposition and pray to the Learned Controller for the following relief(s):

- (a) Take on records the present representation
- (b) Leave to file further evidence
- (c) Opportunity to be heard
- (d) Refusal of the 201617025251 application *in toto*
- (e) Such other relief(s) as the Learned Controller may deem appropriate.

80. The opponent requests for a Personal Hearing before the Controller of Patents, before a decision adverse to the Opponent is taken in this matter.

Dated this 14th day of September 2021



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To
The Controller of Patents,
Patent Office,
Delhi