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Datasheet for the decision of 13 May 2025

Case Number: T 1411/23 - 3.3.07

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Language of the proceedings: EN

Title of invention:
DOSE AND REGIMEN FOR HDM2-P53 INTERACTION INHIBITORS

Patent Proprietor:
Novartis AG

Opponents:
STRAWMAN LIMITED
BOEHRINGER INGELHEIM INTERNATIONAL GMBH

Relevant legal provisions:
RPBA 2020 Art. 12(4), 12(6), 13(1), 13(2)
EPC Art. 56

Keyword:
Late-filed evidence - admittance of documents filed in appeal proceedings
Inventive step - main request and auxiliary requests 1 to 7 (no)

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Case Number: T 1411/23 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 13 May 2025

Appellant: (Patent Proprietor)	Novartis AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Bardehle Pagenberg S.L. Avenida Diagonal 598, 3°, 1ª 08021 Barcelona (ES)
Respondent: (Opponent 1)	STRAWMAN LIMITED Orchard Lea Horns Lane Combe Witney, Oxfordshire OX29 8NH (GB)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstraße 3 81675 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 31 May 2023 revoking European patent No. 3541387 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	M. Steendijk
Members:	J. Lécaillon
	S. Ruhwinkel

Summary of Facts and Submissions

I. European patent 3 541 387 (hereinafter "the patent") concerned an HDM2-p53 interaction inhibitor for use in the treatment of cancer and was granted on the basis of 18 claims.

II. Two oppositions were filed against the patent on the grounds that its subject-matter lacked novelty and inventive step, it was not sufficiently disclosed and it extended beyond the content of the application as originally filed.

III. With the letter dated 2 November 2023, opponent 2 withdrew its opposition and is no longer party to the proceedings.

IV. The opposition division took the decision to revoke the patent. The decision was based on an amended main request and seven auxiliary requests.

V. The decision of the opposition division, posted on 31 May 2023, cited *inter alia* the following documents:

D1: Hyman *et al.*, "Dose- and Regimen-finding Phase I Study of NVP-HDM201 in Patients with TP53 Wild-type Advanced Tumors" Poster presented at EORTC-NCIIACCR, 29. November - 2 December 2016
D3: WO 2015/198266 A1
D6: WO 03/043632 A2
D7: WO 02/064214 A2
D31: LoRusso *et al.*, J. Clin. Oncol., 39, 15_suppl, 2021, Abstract 3016

VI. The opposition division decided in particular as follows:

(a) The main request did not meet the requirement of Article 83 EPC.

(b) The subject-matter of the main request was novel.

(c) The main request did not meet the requirement of Article 56 EPC. The claimed subject-matter differed from the one of the closest prior art D3 in the specific dosage schedule. The alleged technical effect of lowering levels of thrombocytopenia had not been appropriately substantiated, let alone over the entire claimed scope. The objective technical problem resided thus in the provision of an alternative treatment of TP53 wild-type tumors with a HDM2-p53 interaction inhibitor. The skilled person would have been motivated to turn to an already existing dosage schedule such as disclosed in D6 or D7. Furthermore there was no direct and unambiguous teaching away from the administration at day 8 in D3.

(d) Auxiliary requests 1 to 7 all suffered from the same deficiencies under Articles 83 and 56 EPC as the main request.

VII. The patent proprietor (appellant) lodged an appeal against the above decision of the opposition division.

VIII. With its statement setting out the grounds of appeal the appellant defended its case on the basis of the amended main request filed during the opposition proceedings on 17 February 2023, and on the basis of auxiliary requests 1-7 filed during the opposition

proceedings on 17 February 2023 (auxiliary request 1, 3 and 5) and 13 June 2022 (auxiliary requests 2, 4, 6 and 7).

The content of the claims upon which the present decision is based is represented as follows:

Claim 1 of the main request read as follows:

"1. An HDM2-p53 interaction inhibitor for use in the treatment of a TP53 wild-type tumor,

wherein the drug is administered on two different administration days within a treatment cycle,

wherein the first administration day and second administration day are interrupted by a short administration-free period, and the second administration day of the first or earlier treatment cycle and the first administration of the following cycle are interrupted by a long administration-free period,

wherein the short administration-free period is composed of 6 days, and the long administration-free period is composed of 20 days, and

wherein the treatment is composed of at least 2 treatment cycles."

Claim 1 of auxiliary request 1 was identical to claim 1 of the main request.

Claim 1 of auxiliary request 2 corresponded to claim 1 of the main request wherein the following feature was added at the end of the claim:

"and wherein the TP53 wild-type tumor is a solid tumor."

Claim 1 of auxiliary request 3 corresponded to claim 1 of the main request wherein the following feature was added at the end of the claim:

"and wherein the treatment reduces the risk of hematological toxicities".

Claim 1 of auxiliary request 4 was identical to claim 1 of auxiliary request 2.

Claim 1 of auxiliary request 5 was identical to claim 1 of auxiliary request 3.

Claim 1 of auxiliary request 6 corresponded to claim 1 of the main request wherein the following features were added at the end of the claim:

"wherein the treatment reduces the risk of hematological toxicities, and wherein the TP53 wild-type tumor is a solid tumor."

Claim 1 of auxiliary request 7 was identical to claim 1 of auxiliary request 6.

IX. The following items of evidence were filed by the parties during the appeal proceedings:

(a) Documents filed by the appellant with its statement setting out the grounds of appeal:

D47: Excerpt of clinical trial protocol for study CHDM201X2101
D48: LoRusso *et al.*, Cancer Discov., 13, Aug. 4 2023, 1802-1813

(b) Documents filed by the respondent with its reply to the statement setting out the grounds of appeal (D49-D51) and with letter of 12 May 2025 (D52):

D49: ClinicalTrials.gov, NCT05512377, Brightline-2
D50: ClinicalTrials.gov, NCT06058793, Brightline-4
D51: ClinicalTrials.gov, NCT05218499, Brightline-1
D52: Jacob Plieth, "Another false dawn for p53", published on the website "ApexOnco - Oncology Pipeline" on 11 April 2025, https://www.oncologypipeline.com/apexonco/another-false-dawnp53

X. Oral proceedings were held before the Board on 13 May 2025.

XI. The appellant requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request filed during the opposition proceedings on 17 February 2023 (main request), or on the basis of one of the auxiliary requests 1 to 7 filed during the opposition proceedings on 17 February 2023 (auxiliary requests 1, 3 and 5) and 13 June 2022 (auxiliary requests 2, 4, 6 and 7). They further requested that document D52 not be admitted into the appeal proceedings

XII. The respondent (opponent 1) requested that the appeal be dismissed. They further requested that documents D47 and D48 not be admitted into the appeal proceedings and that documents D49 to D52 be admitted.

XIII. The arguments of the appellant, as far as relevant for the present decision, can be summarised as follows:

(a) Admittance of items of evidence

D47 was to be admitted into the appeal proceedings because it was submitted in direct response to the issue of inventive step based on the dose limiting toxicities (DLTs) raised for the first time in the impugned decision.

D48 was to be admitted because it was highly relevant for the discussion on inventive step. D48 demonstrated the same advantageous effect for BI907828 (Brigimadlin), a further HDM2-p53 interaction inhibitor, as shown for HDM201 in the patent.

No objection was raised against the admittance of D49 to D51.

D52 should not be admitted into the appeal proceedings because it was very late filed (filed on the day preceding the oral proceedings) and not *prima facie* relevant, so that its submission went against the principle of procedural economy.

(b) Main request

The subject-matter of claim 1 of the main request differed from the one of the closest prior art D3, in the administration schedule (d1d8q4w in the main request and q3w in the examples of D3). The claimed administration schedule resulted in a reduction of the occurrence of severe grades of thrombocytopenia while maintaining a similar efficacy. The reduction of the occurrence of severe grades of thrombocytopenia had been substantiated in the patent as well as in D31 and D48. Furthermore D1 confirmed this finding. The objective technical problem resided therefore in the provision of a treatment schedule of an HDM2-p53

interaction inhibitor having a reduced incidence of serious thrombocytopenia while maintaining efficacy. None of the cited prior art documents suggested the present administration schedule as a solution to this problem.

Even if the problem would be considered less ambitious, *i.e.* as the provision of an alternative treatment of TP53 wild-type tumors, the skilled person would not have considered the administration schedule of D6 or D7 because the results of examples 2, 3 and 6 of D3 taught away from a second administration on day 8.

Hence, the main request met the requirement of Article 56 EPC.

(c) Auxiliary requests

Auxiliary requests 1 to 7 fulfilled the requirement of Article 56 EPC for the same reasons as the main request.

XIV. The arguments of the respondent, as far as relevant for the present decision, can be summarised as follows:

(a) Admittance of items of evidence

D47 was not to be admitted into the appeal proceedings because it should have already been filed in the opposition proceedings.

D48 should not be admitted because it was not *prima facie* relevant for the discussion on inventive step.

D49 to D51 were to be admitted into the appeal proceedings because they were filed in direct response to D48 and were *prima facie* relevant.

D52 should be admitted into the appeal proceedings because the publication of the document on 11 April 2025 constituted exceptional circumstances justifying its late filing. Furthermore it was highly relevant as it substantiated that MDM2 inhibitors were not efficient in the claimed treatment of TP53 wild-type tumors.

(b) Main request

The subject-matter of claim 1 of the main request differed from the one of the closest prior art D3, in the administration schedule (d1d8q4w in the main request and q3w in the examples of D3). The alleged technical effect of reduction of the incidence of severe grades of thrombocytopenia had not been credibly substantiated compared to the administration schedule of the closest prior art. The objective technical problem resided therefore in the provision of an alternative use of HDM2-p53 interaction inhibitors in the treatment of TP53 wild-type tumors. D3 itself suggested an intermittent administration schedule encompassing a first administration on day 1 and a second one on *e.g.* day 8 of a 28 days cycle. The skilled person having knowledge of D6 or D7 which disclosed the present intermittent administration schedule for further anti-cancer agents, would have applied said schedule to the treatment of D3 to solve the mentioned objective technical problem. Contrary to the opinion of the appellant, D3 did not teach away from such an administration schedule with a second administration on day 8.

Hence, the main request did not meet the requirement of Article 56 EPC.

(c) Auxiliary requests

Auxiliary requests 1 to 7 did not fulfil the requirement of Article 56 EPC for the same reasons as the main request.

Reasons for the Decision

1. Admittance of new items of evidence

1.1 D47

1.1.1 The respondent requested not to admit D47 in the appeal proceedings. This document was filed by the appellant together with the statement setting out the grounds of appeal.

1.1.2 According to the appellant, D47 was submitted in direct response to the impugned decision which placed for the first time in the proceedings the emphasis on the dose limiting toxicities in table 4 of the patent in the discussion of inventive step. The respondent argued that this issue had already been raised in the opponent's written submissions in the opposition proceedings (see submission of opponent 2 of 8 September 2022, page 12 and submission of opponent 1 of 14 February 2023 page 20 last paragraph to page 21 4th paragraph).

1.1.3 The Board observes that:

- on page 12 of its submission of 8 September 2022 as well as on page 8 of its submission of 16 February

2023, in the context of the discussion on achievement of the alleged effect of the invention over the prior art for inventive step, opponent 2 pointed to the lack of data in table 4 of the patent for patients treated with 200 mg in regimen 1B as well as to the issues related to the use of different dose levels in each regimen (1A and 1B),

- the results regarding occurrence of hematological toxicities in the treatment of hematological tumors reported in table 4 in paragraph [0102] of the patent were discussed in the context of inventive step, in particular of achievement of a particular effect, by opponent 2 in the submission of 8 September 2022 (see page 13) and opponent 1 in the submission of 14 February 2023 (see page 20 last paragraph to page 21 4th paragraph), and
- while no details regarding the specific data to be discussed was provided, the preliminary opinion of the opposition division identified the issue of "whether the patent in suit credibly shows that a technical effect has been obtained" would have to be discussed during oral proceedings (see top of page 7 of the annex to the summons to oral proceedings of 25 October 2022).

1.1.4 It follows that the issue and underlying reasoning regarding the achievement of a technical effect over the prior art, in particular based on the data regarding toxicity (including the DLTs of table 4 of the patent), had indeed already been raised in the written proceedings and identified as a discussion point for oral proceedings in the opposition proceedings. The appellant even shortly addressed this point in its submission of 17 February 2023 (see page 6, 3rd paragraph). Hence, contrary to the opinion of the appellant, the reasoning regarding DLTs was not put

forward for the first time during oral proceedings and in the impugned decision. D47, which according to the appellant corresponds to part of the protocol of the phase 1 study underlying the discussed results, should therefore have already been submitted during the opposition proceedings in support of the appellant's reply to this argument in their submission of 17 February 2023.

1.1.5 Accordingly, the Board does not to admit D47 into the appeal proceedings (Article 12(6), 2nd sentence RPBA).

1.2 D48

1.2.1 The respondent requested not to admit D48 in the appeal proceedings. This document was filed by the appellant together with the statement setting out the grounds of appeal.

1.2.2 According to the appellant, D48 was submitted for the discussion of inventive step to demonstrate that the same advantageous effect of the claimed administration regimen was observed for the HDM2-p53 interaction inhibitor BI907828 (Brigimadlin) as for HDM201 used in the patent. The respondent disputed that D48 would actually substantiate such an advantageous effect over the prior art administration regimen.

1.2.3 The Board observes that D48 concerns the results of a phase Ia study of a further HDM2-p53 interaction inhibitor in the treatment of solid tumors. It does therefore appear suitable to address the issue of achievement of the alleged technical effect over the whole scope of the claim in the context of inventive step. In the present case, the question of whether D48 actually convincingly supports the argument of the

appellant requires a deeper analysis of the document and goes beyond the affirmation of the question of suitability to address the issues which led to the decision under appeal as defined in Article 12(4) RPBA. Furthermore, it was undisputed that the document could not have been submitted earlier, so that its submission with the statement of grounds of appeal is not against procedural economy.

1.2.4 As a result, D48 is admitted into the appeal proceedings (Article 12(4) RPBA).

1.3 D49 to D51

D49 to D51, submitted with the reply to the statement of the grounds of appeal, concern studies evaluating BI 907828 (Brigimadlin) in the treatment of cancer and relate therefore to the same compound as studied in D48. As brought forward by the respondent, these documents were filed in direct response to D48 and the argument of the appellant that the effect reported in the patent for one particular highly potent HDM2-p53 inhibitor may be extrapolated to further HDM2-p53 inhibitors. The Board further notes that no objection against the admittance of these documents was raised.

Hence, D49 to D51 are admitted into the appeal proceedings (Article 12(4) RPBA).

1.4 D52

1.4.1 The appellant requested that D52 not be admitted into the appeal proceedings. D52 was filed on 12 May 2025, *i.e.* one day before the oral proceedings. Its admittance is to be decided on the basis of Articles 13(1) and 13(2) RPBA.

1.4.2 The respondent argued that the publication of the document on 11 April 2025 constituted exceptional circumstances justifying its late filing.

1.4.3 Independently of whether there are exceptional circumstances justifying the late filing of D52 in the present case (Article 13(2) RPBA), the requirements of Article 13(1) RPBA, which also apply at the third level of the convergence approach under Article 13(2) RPBA (see Case Law of the Boards of Appeal, 10th edition, V.A.4.5.1), are not fulfilled.

1.4.4 D52 is an article published on the Website "ApexOnco - Oncology Pipeline" which discusses the decision of Boehringer Ingelheim to discontinue its project on the MDM2 inhibitor brigimadlin. However, as argued by the appellant, there is no disclosure in the article that brigimadlin was not efficient at all. The article mentions the discontinuation of several other MDM2 inhibitors from other pharmaceutical companies without specifying the reasons therefor. Hence, contrary to the respondent's opinion, D52 does not show that MDM2 inhibitors are not efficient in the claimed treatment of TP53 wild-type tumors. There might indeed by several reasons justifying the discontinuation of a project on a given drug or even several drugs of the same class. This does not mean that all the industry stopped the development of the present class of compounds as stated by the respondent during oral proceedings. On the contrary, the article mentions several still on going projects.

It follows that D52 is not suitable to resolve the issues on file relating to the efficacy of the claimed treatment (Article 13(1) RPBA).

1.4.5 Furthermore, the Board agrees with the respondent that submitting D52 with their earlier submission of 10 April 2025 was not possible (D52 having been published on 11 April 2025). However, submitting this document on 12 May 2025 *i.e.* more than one month after its publication and one day before the oral proceedings prevented the appellant from providing a proper reply.

As a consequence, the submission of D52 at this stage of the proceedings is detrimental to procedural economy (Article 13(1) RPBA).

1.4.6 Accordingly, D52 is not admitted into the appeal proceedings (Article 13(1) RPBA).

Main request

2. Inventive step

2.1 Closest prior art

2.1.1 The main request relates to HDM2-p53 interaction inhibitors for use in treating TP53 wild-type tumors with a specific intermittent administration regimen (administration on day 1 and day 8 of a 28 days cycle; minimum of 2 cycles).

2.1.2 In accordance with the submissions by both parties, D3 is considered to represent a suitable closest prior art. It discloses MDM2 inhibitors for use in the treatment of cancer. In particular, D3 describes the use of HDM201 (compound A in D3) in intermittent dosage regimens (see page 9 lines 8 to 10), and provides *in vivo* efficacy data as well as data regarding

hematologic side effects (decrease WBCs, neutrophils and platelets).

2.2 Distinguishing feature and technical effect

2.2.1 It was undisputed that the distinguishing feature compared to D3 resides in the specific administration schedule (one administration every 3 weeks in D3, d1q3w *versus* administration on days 1 and 8 of a 28 days cycle in the main request, d1d8q4w).

2.2.2 The appellant argued that, compared to the closest prior art, the claimed administration schedule would lead to a reduction of the incidence of severe grades of thrombocytopenia while maintaining a similar efficacy. As evidence of the reduction of the occurrence of severe grades of thrombocytopenia they referred to the results provided in the patent (see in particular Table 3, Table 4 on page 23 and paragraph [0076] including Table 8) as well as in D31 and D48. They also indicated that D1 would confirm this finding.

2.2.3 The data as presented in Table 3 of the patent appear at first glance to indicate a reduction of thrombocytopenia grades 3/4 in patients with solid tumors with HDM201 administered according to regimen 1B compared to regimen 1A while the thrombocytopenia of all grades are comparable.

However, as pointed out by the respondent, the administered doses are different between the administration regimen 1A and 1B (see Table 1, page 10 of the patent). The appellant explained in response that the frequency of administration was also different, so that there appeared to be at least some overlap in the overall dose administered. While the

Board agrees that this argument might be relevant when assessing overall efficacy of the treatment, the situation is different when it comes to the occurrence of severe thrombocytopenia. It was undisputed that, as shown by D3 (see *e.g.* Example 6 on page 24), thrombocytopenia is dose dependent. It follows that, if less patients receive single high doses, it can be expected that less severe thrombocytopenia will be observed.

In the present case, in regimen 1A a total of 11 patients received doses of 250 or 350 mg and a total of 15 patients received doses of 200 mg or less, while the highest administered dose in regimen 1B was 200 mg (total of 20 patients receiving 120, 150 or 200 mg doses). The fact that, as argued by the appellant, some patients in regimen 1A are administered much lower doses than in regimen 1B does not undermine the fact that 11 patients of regimen 1A received a dose higher than the highest dose of regimen 1B. Since severe thrombocytopenia is known to occur at higher doses, this cannot be expected to be somehow balanced by patients receiving lower doses than in regimen 1B. It follows that, in view of the different individual doses administered between regimen 1A (according to D3) and regimen 1B (according to the present claims), it cannot be concluded that the reduction of thrombocytopenia grades 3/4 observed in Table 3 is indeed directly linked to the administration schedule (frequency of administration) and not the dose administered.

2.2.4 Furthermore, the respondent mentioned the lack of data on hematologic dose limiting toxicities (DLT) in the second cycle for the patients receiving the 200 mg dose in regimen 1B (see Table 4 on page 13 of the patent). The Board agrees with the appellant that hematologic

DLTs encompass further side effects and are not indicative of specifically thrombocytopenia, let alone of grades 3/4. Nevertheless, the lack of data for cycle 2 at the dose of 200 mg for regimen 1B because the data were "not available at the clinical cutoff" raise doubts as to the collection of data provided in Table 3 (extracted from the same study).

2.2.5 D48 provides results of a phase Ia study of the MDM2-p53 inhibitor brigimadlin in patients with advanced or metastatic solid tumors. The content of D48 is similar to the one of D31 but contains more data. The present observations therefore apply *mutatis mutandis* to D31.

The same situation as with the data provided for HDM201 in the patent is found in D48. The data in tables 2 and 4 appear at first sight to indicate a maintained efficacy and a reduced severe thrombocytopenia for the regimen according to the claims (D1D8q4w) compared to the one of D3 (D1q3w). However, the doses administered in regimen D1D8q4w are lower than those administered in regimen D1q3w. For the same reasons as detailed for the results on HDM201 in the patent, it cannot be concluded that the observed reduction of occurrence of severe thrombocytopenia is directly attributable to the administration frequency and not the administered doses.

Furthermore, as argued by the respondent, the authors of D48 do not conclude to the presence of any added benefit (see page 1804, right column, end of first paragraph).

2.2.6 The appellant referred to paragraph [0079] of the patent including Table 8 and which concludes to an "overall better tolerability at therapeutically

relevant doses". This argument is however not convincing for the following reasons:

(a) This paragraph does not relate specifically to thrombocytopenia, let alone of grades 3/4.

(b) No detail is provided on the origin of the data presented in Table 8. The appellant indicated during the oral proceedings that the data presented in Table 8 were "based on the preceding data". However, for the reasons detailed above, the preceding data are not conclusive with respect to the technical effect relied upon by the appellant. Hence this paragraph constitutes merely the presentation of information already detailed before and found not conclusive.

2.2.7 Regarding the lack of improvement in the occurrence of severe thrombocytopenia between regimen 1A and regimen 1B for patients with hematologic tumors reported in the patent (see Table 4 on page 23 of the patent), the appellant explained that it was due to the low number of patients in regimen 1B. During oral proceedings, the appellant argued that the data obtained on patients with solid tumors (Table 3, page 13 of the patent) and on patients with hematologic tumors (Table 4, page 23 of the patent) could however be pooled. By doing so, an overall reduction of severe thrombocytopenia was observed in case of regimen 1B compared to regimen 1A.

The Board disagrees. Even if the low number of patients with hematologic tumors receiving the treatment regimen 1B indeed prevented any significant comparison between both regimen, this cannot justify the pooling of results from different clinical studies. Moreover the issue regarding the difference in the administered

doses would still apply. It follows, that there is no data substantiating a reduction of thrombocytopenia in patients with hematologic tumors treated with the regimen 1B compared to regimen 1A.

2.2.8 During oral proceedings, the appellant stated that D1 confirmed that the alleged effect was obtained with the claimed administration schedule. Independently of the issue of whether D1 can at all be taken into consideration, the provided experimental results appear to be the same as in the patent, so that in particular the same issue with the difference in the administered doses applies.

2.2.9 The Board therefore concludes that the evidence provided by the appellant does not convincingly support that HDM201 or brigimadlin, let alone every HDM2-p53 interaction inhibitor, administered according to the claimed administration schedule leads to a reduction of the occurrence of severe grades of thrombocytopenia when used in the treatment of any TP53 wild-type tumor.

2.3 Objective technical problem and obviousness

2.3.1 It follows that the objective technical problem resided, as formulated by the respondent, in the provision of an alternative use of HDM2-p53 interaction inhibitors in the treatment of TP53 wild-type tumors.

2.3.2 As brought forward in the impugned decision and by the respondent, D3 suggests further types of intermittent administration schedule including the administration of the second dose 1 to 14 days, *i.e.* including 7 days, after the first dose has been administered (see claim 8 of D3). Furthermore, the administration of anti-cancer agents according to an intermittent dosage on days 1

and 8 of a 28 days cycle had been conventionally applied in cancer therapy with gemcitabine or paclitaxel (see D6 or D7). The skilled person seeking to provide an alternative administration schedule to the one of D3 would therefore have turned to known intermittent administration schemes generally encompassed by D3. Hence, the skilled person would have been motivated to apply the intermittent administration schedule known from either D6 (see *e.g.* page 8 lines 5 to 7, page 9 lines 10 to 12 and Table 2B) or D7 (see *e.g.* page 5 lines 22 to 24) to the treatment with HDM201 disclosed in D3.

2.3.3 The appellant considered that D3 actually taught away from an administration of the second dose at day 8 of the cycle, so that the skilled person would not have used such an administration schedule. They referred to example 2 of D3 which showed that following the intravenous administration of a single high dose of HDM201 to rats (20 mg/kg), 92% tumor regression was obtained after 14 days while a lower white blood cell count (WBCC) was observed one week after administration of HDM201 before (partial) recovery after 21 days (see Figure 7). According to the appellant, the same effect would be reported in example 3 for white blood cells as well as for platelets (see Figure 9). Furthermore, example 6 (see page 24 lines 11 to 14 and Figure 15) would substantiate the importance of platelets recovery before the second administration. The skilled person would therefore not have applied a second dose a week after the first.

2.3.4 This argument is not convincing. As brought forward by the respondent, examples 2, 3 and 6 of D3 were performed on rats to determine the therapeutic range. The dose of 20 mg/kg used therein is very high. An

equivalent dose for a human of 75 kg would require the administration of 1500 mg of anti-cancer agent, *i.e.* 7.5 and 4.3 times more than the highest dose administered according to regimen 1B and 1A in the examples of the patent. The skilled person being aware thereof would have understood that the white blood cells and platelets levels reported in examples 2, 3 and 6 of D3 are not representative of a treatment on humans. Accordingly, there is no direct and unambiguous teaching away in D3 from applying the administration schedule of D6 or D7.

2.4 As a result, the subject-matter of claim 1 of the main request does not comply with Article 56 EPC.

Auxiliary request 1

3. Inventive step

3.1 The subject-matter of claim 1 of auxiliary request 1 is identical to the one of claim 1 of the main request, so that the same reasoning applies.

3.2 Hence, auxiliary request 1 does not meet the requirement of Article 56 EPC.

Auxiliary requests 2 and 4

4. Inventive step

4.1 In claim 1 of auxiliary request 2 the TP53 wild-type tumor has been limited to a solid tumor. D3 already describes the treatment of solid tumors (see examples) and no particular effect has been substantiated for solid tumors, so that this feature does not represent a distinguishing feature compared to D3 and the same

reasoning as developed for the main request applies *mutatis mutandis* to claim 1 of auxiliary request 2.

4.2 The subject-matter of claim 1 of auxiliary request 4 is identical to the one of claim 1 of auxiliary request 2, so that the same reasoning applies.

4.3 Accordingly, auxiliary requests 2 and 4 do not fulfil the requirement of Article 56 EPC.

Auxiliary requests 3 and 5

5. Inventive step

5.1 Claim 1 of auxiliary request 3 has been amended compared to claim 1 of the main request by adding the feature that "the treatment reduces the risk of hematological toxicities".

5.2 The Board observes that this feature has not been shown to represent a distinguishing feature compared to the closest prior art D3. It follows that, in the absence of further arguments specific to present claim 1 of auxiliary request 3, the same conclusion under Article 56 EPC applies as for the main request.

5.3 The subject-matter of claim 1 of auxiliary request 5 is identical to the one of claim 1 of auxiliary request 3, so that the same reasoning applies.

5.4 Therefore, auxiliary requests 3 and 5 do not meet the requirement of Article 56 EPC.

Auxiliary requests 6 and 7

6. Inventive step

6.1 Claim 1 of auxiliary request 6 contains the additional features of auxiliary requests 2 and 3. It was undisputed that these two features were not interrelated and could hence be evaluated for inventive step independently. It follows that the subject-matter of claim 1 of auxiliary request 6 is not inventive for the same reasons as provided for auxiliary requests 2 and 3.

6.2 The subject-matter of claim 1 of auxiliary request 7 is identical to the one of claim 1 of auxiliary request 6, so that the same reasoning applies.

6.3 As a consequence, auxiliary requests 6 and 7 do not fulfil the requirement of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos M. Steendijk

Decision electronically authenticated