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**Datasheet for the decision of 25 April 2023**

**Case Number:** T 2354/18 - 3.3.08

**Application Number:** 11824247.8

**Publication Number:** 2614369

**IPC:** G01N33/50, G01N33/68, G01N33/53, A61K38/17, C07D473/34, A61P35/00, G01N33/574

**Language of the proceedings:** EN

**Title of invention:**
Method for determining the suitability of inhibitors of human EZH2 in treatment

**Patent Proprietor:**
Epizyme, Inc.

**Opponent:**
GlaxoSmithKline Intellectual Property (No.2) Limited

**Headword:**
EZH2 inhibitor/EPIZYME

**Relevant legal provisions:**
EPC Art. 56, 83, 100(c)
RPBA Art. 12(4)

**Keyword:**
Grounds for opposition - subject-matter extends beyond content of earlier application (yes)
Inventive step - (yes)
Sufficiency of disclosure - (yes)

**Decisions cited:**
G 0001/03

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**Case Number: T 2354/18 - 3.3.08**

# D E C I S I O N
# of Technical Board of Appeal 3.3.08
# of 25 April 2023

| | |
|---|---|
| **Appellant:** (Opponent) | GlaxoSmithKline Intellectual Property (No.2) Limited<br>980 Great West Road<br>Brentford Middlesex TW8 9GS (GB) |
| **Representative:** | Billson, Siân Catherine<br>GlaxoSmithKline<br>Global Patents (CN925.1)<br>980 Great West Road<br>Brentford, Middlesex TW8 9GS (GB) |
| **Respondent:** (Patent Proprietor) | Epizyme, Inc.<br>400 Technology Square, 4th Floor<br>Cambridge, MA 02139 (US) |
| **Representative:** | Russell, Tim<br>Venner Shipley LLP<br>200 Aldersgate<br>London EC1A 4HD (GB) |
| **Decision under appeal:** | **Decision of the Opposition Division of the European Patent Office posted on 16 July 2018 rejecting the opposition filed against European patent No. 2614369 pursuant to Article 101(2) EPC** |

**Composition of the Board:**

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| **Chair** | T. Sommerfeld |
| **Members:** | A. Schmitt |
| | L. Bühler |

## Summary of Facts and Submissions

I. The appeal lodged by the opponent (appellant) lies from the opposition division's decision to reject the opposition filed against European patent No. 2 614 369 (hereinafter "the patent").

Claims 1, 3, 5 and 6 of the patent as granted read as follows:

"1. A method for determining whether a subject who has or is suspected to have cancer selected from lymphoma and melanoma is a candidate for treatment with an inhibitor of EZH2, comprising;
detecting a Y641 mutant of an EZH2 polypeptide, if present, in a sample obtained from the subject;
wherein the presence of the Y641 mutant indicates the subject is a candidate for treatment with an inhibitor of EZH2.

3. A method according to any one of the preceding claims wherein the cancer is follicular lymphoma or diffuse large B cell lymphoma (DLBCL).

5. The method of claim 4, wherein the target region resequencing comprises amplifying at least a portion of the nucleic acid with at least one PCR primer.

6. A method according to any one of claims 1 to 5 wherein the inhibitor of EZH2
a. inhibits trimethylation of H3-K27, or
b. inhibits histone methyltransferase activity of the Y641 mutant of EZH2, optionally wherein the inhibition is selective inhibition."

II. The patent, entitled "*Method for determining the suitability of inhibitors of human EZH2 in treatment*", was granted on European patent application No. 11 824 247.8, which had been filed as an international application published as WO 2012/034132 (hereinafter "the application").

III. The opposition proceedings were based on the grounds for opposition in Article 100(a) EPC, in relation to inventive step (Article 56 EPC), and in Article 100(b) and (c) EPC.

IV. With the statement of grounds of appeal, the appellant submitted two documents, D20 and D21, which were identical to documents D18 and D19, respectively, submitted in opposition.

V. With the reply to the appeal the patent proprietor (respondent) submitted two documents, D22 and D23, and sets of claims of auxiliary requests 1 to 28.

Claim 1 of auxiliary request 1 differs from claim 1 as granted (see section I.) in that the expression "or is suspected to have" has been deleted. Moreover, claim 5 as granted as well as the alternative "or diffuse large B cell lymphoma (DLBCL)" in claim 3 as granted have been deleted.

VI. The board summoned the parties to oral proceedings in accordance with their requests and, in a communication pursuant to Article 15(1) RPBA, expressed its preliminary opinion, *inter alia*, that it was minded to set aside the decision and to remit the case to the opposition division since part of the decision relating to the admittance of documents and sufficiency of disclosure appeared not to be sufficiently reasoned.

The board invited the parties to comment on its intention to remit the case to the opposition division.

VII. In response to the board's communication, the respondent requested that the case be remitted to the opposition division and that the oral proceedings be cancelled only if all the parties and the board were in agreement that the complete case could be remitted to the opposition division without holding the oral proceedings.

VIII. In response to the board's communication, the appellant indicated that it would not attend the oral proceedings scheduled for 25 April 2023 and that it was relying upon its previous written submissions. No further requests were formulated.

IX. Oral proceedings were held in the absence of the appellant. At the end of the oral proceedings, the Chair announced the board's decision.

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

D1 R. D. Morin et al., Nature Genetics 42(2), 2010, 181-187

D7 T. J. Wigle et al., FEBS Letters 585, 2011, 3011-3014

D8 C. J. Sneeringer et al., Proc Natl Acad Sci 107(49), 2010, 20980-20985

D9 D. B. Yap et al., Blood 117(8), 2011, 2451-2459

D15 I. Velichutina et al., Blood 116(24), 2010, 5247-5255, doi:10.1182/blood/2010-04-280149, published online on 24 August 2010

D16 W. Hong et al., PLoS One 5(1), 2010, e8570, 1-10

D17 T. Ernst et al., Nature Genetics 42(8), 2010, 722-727

D18/D20 Declaration by Mr Martin Brandt dated 15 March 2018

D19/D21 Sanger Institute, "Cosmic sample ID COSS1451273"

D22 S. W. Park et al. Leukemia Research 35, 2011, e6-7

D23 D. R. Bentley, Curr Opin Genet Dev. 16, 2006, 545-52

XI. The appellant's arguments, insofar as they are relevant to the decision, are summarised as follows.

*Main request (patent as granted)*
*Amendments (Article 100(c) EPC) - claim 1*

The application did not disclose practising the method of claim 1 on a subject who was "suspected" to have cancer. The passage in the application that used the word "suspected" (see line 5 of the first full paragraph on page 31) referred to cells that were suspected to have a Y641 mutation. This was different from a subject who was suspected to have cancer and was therefore not a basis for this feature.

*Sufficiency of disclosure (Article 100(b) EPC)*

The claimed method was not able to correctly identify patients that were candidates for treatment with an EZH2 inhibitor where the EZH2 Y641 mutation was not a gain-of-function mutation, where this mutation was homozygous, and where the patient had cancer that did not rely on an EZH2 gain-of-function mutation; however,

the invention as defined in claim 1 of the patent encompassed each of these options. The fact that each of these options existed was clear from common general knowledge, Table 1 of the patent, page 3013, lines 4 to 16 of the right-hand column of document D7, page 2451, right-hand column, lines 12 to 16 of document D9, document D20, and document D21.

The patent did not support the fact that EZH2 inhibition was suitable for treating lymphomas other than follicular lymphoma and diffuse large B cell lymphoma (DLBCL). Document D17 disclosed that frameshift and truncation mutations of EZH2 were observed in myeloid malignancies (see page 724, right-hand column, lines 15 to 20) and therefore demonstrated that cancers may result from an EZH2 loss-of-function mutation.

The invention as defined in claims 1 and 6 as granted was not sufficiently disclosed in the patent insofar as it covered mutant-specific EZH2 inhibitors other than those known in the art at the time of the invention.

*Inventive step (Articles 100(a) and 56 EPC)*

Document D1 was the closest prior art and the objective technical problem was to identify a treatment for subjects having a Y641 EZH2 mutation. Document D1 already suggested that the EZH2 Y641 mutations were likely to be gain-of-function mutations. This was evident from the paragraph bridging the left-hand and right-hand columns on page 184, which discussed that the EZH2 Y651 mutations were either loss-of-function mutations or mutations in which the substrate specificity had been changed, as known for the so-called phenylalanine-tyrosine switch site in other SET

domain-containing proteins. In the latter case, they would be gain-of-function mutations.

Document D16 supported the view that EZH2 Y641 mutations were gain-of-function mutations as it disclosed that the corresponding mutation in the SET domain-containing protein G9a increased trimethylation activity at the expense of mono- and dimethylation (see Figure 3 of document D16). As SET domains were highly conserved, it was likely that the corresponding mutation in EZH2 had the same effect.

Document D15 also supported the fact that EZH2 Y641 mutations were gain-of-function mutations. Document D15 discussed that the data in document D1 were not incompatible with an overall gain-of-function effect of the EZH2 Y641 mutations and that targeting EZH2 might have anti-lymphoma effects (see page 5254, right-hand column, lines 27 to 33 of document D15).

A further indication that the EZH2 Y641 mutations were gain-of-function mutations was the fact that all the EZH2 mutations detected in document D1 affected a single site and were heterozygous, as discussed in document D17 (see page 724, right-hand column, first full paragraph).

The teaching in document D1 in combination with the teaching in either document D16 or document D15 therefore suggested to the skilled person that the EZH2 Y641 mutations disclosed in document D1 were gain-of-function mutations. If doubt remained on the function of these mutations, the skilled person would have tested the mutated enzymes in a routine assay with the expectation of finding gain-of-function activity. Since there were only two possibilities (gain-of-function or

loss-of-function mutations), which could both be envisaged in advance, there was no element of surprise. It was evident that the skilled person would have tested the mutated enzymes from the fact that this had actually happened (see post-published documents D8 and D9).

Moreover, the claimed subject-matter covered areas in which the problem was not solved for the same reasons as the reasons why the invention defined in the claim was not sufficiently disclosed in the application.

XII. The respondent's arguments, insofar as they are relevant to the decision, are summarised as follows.

*Main request (patent as granted)*
*Amendments (Article 100(c) EPC) - claim 1*

The appellant argued for the first time on appeal that the feature "subject who ... is suspected to have" (cancer selected from lymphoma and melanoma) in claim 1 did not have a basis in the application as filed, but did not justify why this objection was raised only then.

The basis for this feature was found in the application in the second paragraph on page 6, which referred to a subject in general, in the first full paragraph on page 31, in which there was a literal basis for the term "suspected to", and in the second paragraph on page 54, in which the term "subject" was defined as including any human subject who had been diagnosed with, had symptoms of, or was at risk of developing a disorder, i.e. subjects suspected of having cancer. Since diagnosis was never 100% accurate, a subject that

had been diagnosed with cancer was also a subject suspected of having cancer.

*Sufficiency of disclosure (Article 100(b) EPC)*

The skilled person only had to detect the presence of an EZH2 Y641 mutation to carry out the claimed method. This detection step was described in the patent and was therefore sufficiently disclosed.

The appellant had not provided any evidence that EZH2 Y641 mutations that were not gain-of-function mutations existed in lymphoma or melanoma patients. Loss-of-function mutations known for other residues in an active site of an SET domain could not support the existence of EZH2-inactivating mutations at the Y641 site. As the patent disclosed that all the EZH2 Y641 mutants were deficient in catalysing the first H3K27 methylation step but were superior to the unmutated enzyme in catalysing di- and trimethylation of mono- and dimethylated H3K27 peptides, minor differences in the kinetic parameters of the mutant enzymes evident from Table 1 of the patent and document D7 were irrelevant and could not support the allegation that EZH2 Y641 mutations other than gain-of-function mutations existed in cancer patients.

Document D20 concerned an artificial EZH2 Y641 mutation. There was no evidence that this mutation would occur in cancer patients. The burden of demonstrating or explaining how this artificial mutation could arise in cancer lay with the appellant. Document D1 disclosed that five of the eight possible non-synonymous variants of the EZH2 Y641 codon "TAC" were found in cancer patients (see Figure 1C of document D1). All of these had the same gain-of-

function effect, as demonstrated in the patent and document D7. If an EZH2 Y641 mutation existed that was not a gain-of-function mutation, a subject having said mutation would not be a subject with lymphoma or melanoma as required in the claim.

The appellant's allegation that homozygous EZH2 Y641 mutations existed was incorrect, as was evident from document D22 (see legend of Figure 1). The appellant's objection in this respect was therefore not substantiated and the appellant had not met its burden of proof.

Claim 1 was not concerned with the treatment of all lymphomas and melanomas, but with the selection of patients suitable for the treatment with an EZH2 inhibitor based on the presence of an EZH2 Y641 mutation. It was therefore irrelevant for the claimed method that not all lymphomas and melanomas resulted from an EZH2 gain-of-function mutation.

As two selective EZH2 inhibitors were exemplified in the patent, it was justified that claim 6 generally referred to selective EZH2 inhibition.

*Inventive step (Articles 100(a) and 56 EPC)*

The closest prior-art document, D1, described mutations at the Y641 position of EZH2 in certain B-cell lymphomas and disclosed that EZH2 proteins harbouring a mutation at this site had reduced enzymatic activity *in vitro*. Document D1 neither mentioned cancer treatment in general nor was concerned with treatment options for patients harbouring the described EZH2 mutations.

The objective technical problem was to provide a method that allowed improved treatment of lymphoma and melanoma patients. The skilled person would not have expected from the teaching in document D1 that detection of an EZH2 Y641 mutation could indicate that a patient was a candidate for treatment with an EZH2 inhibitor. Document D1 suggested that the enzymatic activity of EZH2 was greatly reduced in the mutant forms, as was evident from Figure 2 of document D1, and hence provided teaching leading away from the claimed method.

Document D15 was not primarily concerned with EZH2 mutations. It mentioned the EZH2 Y641 mutation only by reference to document D1 as an observation contradictory to the teaching of document D15 on the functional roles of EZH2 in normal and malignant germinal centre B-cells (see the full paragraph in the right-hand column of page 5254). In the same paragraph, document D15 stated that the *in vivo* function of the Y641 mutation was not known; the other comments on this mutation in this paragraph were mere speculation. The conclusion drawn in document D15 that therapeutic targeting of EZH2 might have anti-lymphoma effects had to be understood in the context of treating DLBCL primary tumours other than those harbouring an EZH2 Y641 mutation, which were the least likely patients to respond to this treatment.

The skilled person would not have considered that the teaching in document D16 on a different methyltransferase and another substrate was relevant to EZH2. The appellant's arguments presented in this respect were based on hindsight.

The same was true for the appellant's argument that the skilled person would have tested whether the EZH2 mutant forms had gain-of-function activity, contrary to the disclosure in document D1. The reference in document D1 to the so-called phenylalanine-tyrosine switch site in SET domain-containing proteins on page 184 (first paragraph of right-hand column) had no bearing on this assessment since, as also acknowledged in document D1 (*ibid.*), the EHZH2 Y641 residue was distinct from this site. Document D1 did not refer to the last stages of the trimethylation activity of EZH2 when discussing a possibly altered product or target specificity of EZH2 Y641 mutant forms (*ibid.*).

XIII. The parties' requests, insofar as they are relevant to the decision, were as follows.

The appellant requested that the decision under appeal be set aside, that the patent be revoked, and that documents D16, D17, D18/D20 and D19/D21 be admitted into the appeal proceedings.

The respondent requested that the appeal be dismissed or, alternatively, that the patent be maintained based on the claims of one of auxiliary requests 1 to 28, all filed with the reply to the appeal, that documents D18/D20 and D19/D21 not be admitted, and that documents D22 and D23 be admitted into the appeal proceedings.

## Reasons for the Decision

1. The appellant was not represented at the oral proceedings as announced previously (see section VIII. above). In accordance with Rule 115(2) EPC and Article 15(3) RPBA 2020, the proceedings were continued

in the absence of the appellant, which was considered to be relying only on its written case.

*Admittance of documents and a line of argument on added matter (Article 12(4) RPBA 2007)*

2. Under Article 25(2) of the Rules of Procedure of the Boards of Appeal (RPBA), the new Article 12(4) to (6) RPBA does not apply to appeals in which the statement of grounds of appeal was filed before 1 January 2020 and any reply to it was filed in due time. Instead, Article 12(4) RPBA 2007 continues to apply. This is the case for this appeal. According to Article 12(4) RPBA 2007, the board has the power to hold inadmissible facts, evidence or requests which could have been presented in the opposition proceedings.

3. With respect to claim 1 of the main request, on appeal the appellant submitted that the feature that a subject was only "suspected" to have cancer did not have a basis in the application as filed. The respondent remarked that this objection was presented for the first time on appeal and that the appellant did not justify why it had been raised only then; however, Article 12(4) RPBA 2007 does not require a party to submit such a justification. This argument is therefore not a sufficient reason in itself for holding the objection inadmissible.

4. Moreover, an objection that the expression "for determining whether a subject who has or is suspected to have cancer selected from lymphoma and melanoma" in claim 1 had no basis in the application had already been raised in the opposition proceedings (see point 8 of the notice of opposition), albeit with a different

argument. The objection to the feature "is suspected to have cancer" raised by the appellant on appeal is directed to a part of that expression and is considered *prima facie* relevant. Hence, the board decided to exercise its discretion under Article 12(4) RPBA 2007 to consider this objection on appeal.

5. The board decided to consider documents D16 and D17, as well as documents D18 and D19 submitted as documents D20 and D21 with the grounds of appeal (Article 12(4) RPBA 2007). In view of the outcome of this case, it is not necessary to provide reasons for this part of the decision.

6. Document D22 was submitted by the respondent in response to an objection based on document D21. As the board decided to admit document D21, it decided to also consider document D22 under Article 12(4) RPBA 2007 for reasons of equal treatment.

7. It was not required to decide on the admittance of document D23 as this document was cited in the context of an objection which is not relevant for the present decision (see point 14. below).

*Main request - patent as granted*
*Amendments (Article 100(c) EPC) - claim 1*

8. Claim 1 is directed to a method for determining whether a subject who has or is suspected to have cancer selected from lymphoma and melanoma is a candidate for a given treatment (for the complete wording, see section I.). As a basis for "a subject who (...) is suspected to have cancer", the appellant referred to the second paragraph on page 6, the first full

paragraph on page 31, and the second paragraph on page 54 of the application.

9. The second paragraph on page 6 discloses that an aspect of the invention is "*a method of identifying a subject as a candidate for treatment with an inhibitor of EZH2*" and that the method "*comprises the steps of performing an assay to detect a Y641 mutant of EZH2 in a sample from a subject; and identifying a subject expressing a Y641 mutant of EZH2 as a candidate for treatment with an inhibitor of EZH2, wherein the inhibitor inhibits histone methyl-transferase activity of EZH2*".

10. Hence, this section of the application refers to "subjects" in general without defining them any further and therefore, as such, does not provide a basis for a subject who is suspected to have cancer.

11. The term "subject" is defined in the application as including any human subject "*who has been diagnosed with, has symptoms of, or is at risk of developing a disorder*" (see second paragraph on page 54). This passage hence does not refer to a subject who is suspected to have cancer, either. The appellant argued that there was no fundamental difference between patients who were suspected to have cancer and patients who had been diagnosed with cancer because a diagnosis was never 100% accurate; however, this argument cannot be followed because it contradicts the common meaning of a medical diagnosis, which is the identification of the nature and cause of a patient's symptoms. A subject diagnosed with cancer is a subject who has cancer. A subject suspected to have cancer has not yet been diagnosed.

12. The only passage in the application that uses the expression "suspected of" is the first full paragraph on page 31, which discloses that, in one embodiment, a sample from a subject "*includes cells suspected to express Y641 mutant of EZH2, e.g., cancer cells*". This expression does not concern a subject who is suspected to have cancer and hence does not disclose this feature, either.

13. Consequently, the application as filed does not disclose the method in claim 1 insofar as it relates to determining whether a subject who is "suspected" to have lymphoma and melanoma is a candidate for treatment with an EZH2 inhibitor. Claim 1 of the patent as granted hence contains subject-matter that extends beyond the content of the application as filed and Article 100(c) EPC prejudices the maintenance of the patent as granted.

14. The appellant had also raised an objection under Article 100(c) EPC against claim 5 as granted and the respondent had relied on document D23 in its argument against this objection; however, in view of the conclusions concerning claim 1 and the fact that claim 5 as granted is no longer found in auxiliary request 1 (see section V.), there is no need for the board to decide on this issue.

*Auxiliary request 1*

15. The appellant did not provide any arguments in response to the respondent's reply to the appeal, and thus has not raised any objections against auxiliary request 1. In view of the deletions made in auxiliary request 1 (see section V.), only the objections raised by the appellant against the main request concerning

sufficiency of disclosure and inventive step starting from D1 as the closest prior art are relevant.

*Sufficiency of disclosure (Article 83 EPC)*

16. The appellant essentially argued that the claims as granted related to subject-matter which was not sufficiently disclosed because i) the method of claim 1 was not capable of accurately identifying patients that were candidates for treatment with an EZH2 inhibitor, and ii) the method of claim 6 (and ultimately claim 1) covered mutant specific EZH2 inhibitors for which there was no enabling teaching in the patent.

17. The patent discloses that enzymatic coupling between unmutated (wild-type) EZH2 and Y641 mutant EZH2 leads to increased trimethylation of lysine 27 of histone H3 (H3K27) compared with cells comprising only wild-type EZH2 and that this results in the malignant phenotype of cells heterozygous for EZH2 Y641 mutants (see Example 6 of the patent). This effect was calculated for Y641F, Y641H, Y641N and Y641S EZH2 mutants based on steady-state kinetic parameters and demonstrated for various cell lines harbouring Y641N or Y641F mutant EZH2 forms (see Figures 3A and 3B of the patent). The presence of any of these EZH2 Y641 mutations in a cancer patient's sample therefore indicates that this patient is a candidate for treatment with an EZH2 inhibitor. This was not contested by the appellant.

18. However, the appellant argued that other EZH2 Y641 mutations existed that were not gain-of-function mutations for the trimethylating activity of EZH2 and that the detection of such a mutation in a subject's sample would not indicate that the subject was a candidate for treatment with an EZH2 inhibitor. The

same was true for subjects homozygous for an EZH2 Y641 mutation. In either case, the claimed method could not be carried out.

19. However, the appellant did not convincingly demonstrate that mutations at the EZH2 Y641 residue other than the five point mutations described in the patent and document D1 would indeed occur in lymphoma or melanoma. Loss-of-function mutations could in principle occur when mutating residues in the active site of an enzyme and loss-of-function mutations were also found in the asparagine-histidine-serine motif in methyltransferases (see document D9, page 2451, lines 12 to 16 of the right-hand column); however, these observations on other amino-acid residues are not sufficient for the skilled person to reasonably expect that loss-of-function mutations would also occur at the EZH2 Y641 residue in lymphoma or melanoma.

20. Document D20 discloses that an artificially created EZH2 Y641W mutant enzyme lost its enzymatic activity; however, this does not prove that an EZH2 Y641W mutation would also occur in lymphoma or melanoma. It is noteworthy that an EZH2 Y641W mutation (codon "TGG") could not arise from a single point mutation in the EZH2 Y641 codon "TAC"; however, all five EZH2 Y641 mutations that were found in lymphoma samples arose from such a single point mutation, as is evident from Figure 1C of document D1. The legend of Figure 1C of document D1 explains that "[w]*ith one exception, all EZH2 mutations found in FL* [follicular lymphoma] *and DLBCL* [diffuse large B-cell lymphoma] *alter this amino acid* [Y641]" and goes on to explain that "*[t]he mutants identified comprised five of the eight possible nonsynonymous variants of this codon*". This observation supports the fact that it was not likely that the

artificially created EZH2 Y641W mutation would indeed be found in lymphoma samples.

21. The appellant also pointed to the fact that the five EZH2 Y641 mutations that were found in lymphoma samples varied in their kinetic parameters and substrate specificity; however, since all these EZH2 Y641 mutant forms have increased trimethylation activity compared with the wild-type EZH2 enzyme (see Table 1 of the patent; Figure 1 and page 3013, lines 4 to 16 of the right-hand column of document D7), the variations in kinetic parameters and substrate specificity observed for them cannot serve as proof, either, that EZH2 Y641 loss-of-function mutations would exist in lymphoma or melanoma. This argument by the appellant is therefore not persuasive either.

22. The appellant also did not convincingly demonstrate that lymphoma patients homozygous for a somatic EZH2 Y641 mutation existed. Document D21, a data overview for a particular lymphoid tumour sample harbouring a somatic EZH2 mutation, alleges that this mutation was homozygous (see page 3 of document D21); however, the publication associated with the data described in document D21 discloses that this lymphoma sample was in fact heterozygous (see Figure 1 of document D22). This thus raises doubts on the data in document D21. Consequently, the appellant did not submit any persuasive evidence that homozygous EZH2 Y641 mutations would occur in lymphoma or melanoma.

23. As regards the appellant's argument that an appropriate treatment would not be selected when the patient had a cancer that did not rely on EZH2 gain of function, the board notes that, in the context of the claimed method, it is not relevant that not all lymphomas and melanomas

result from an EZH2 gain-of-function mutation. This is the case because the method is based on the detection of an EZH2 Y641 mutant form and thus, if no mutant form is detected, the subject is not a candidate for the treatment with an EZH2 inhibitor, irrespective of the lymphoma type. Therefore, the fact that EZH2 Y641 gain-of-function mutations were only detected in follicular lymphoma or germinal centre B-cell like (GCB) diffuse large B-cell lymphoma (DLBCL) (see Table 3 of document D1) and that other cancer forms even resulted from EZH2 loss of function (see document D17, page 724, right-hand column, lines 15 to 20) do not prevent the skilled person from being able to carry out the claimed method.

24. Finally, the appellant's argument that the invention as defined in claims 1 and 6 as granted (claims 1 and 5 in auxiliary request 1) was not sufficiently disclosed in the patent insofar as it covered mutant-selective EZH2 inhibitors other than the two selective EZH2 inhibitors disclosed in the patent is not persuasive, either. The claimed method identifies subjects in which the H3L27 trimethylation activity of EZH2 is increased as candidates for the treatment with a (mutant-selective) EZH2 inhibitor. This method can be carried out by the skilled person, irrespective of whether or not the EZH2 inhibitor is disclosed in the patent or known in the art.

25. In view of the above considerations, neither of the appellant's arguments for why the invention defined in the claims was not sufficiently disclosed in the application is persuasive. The requirements of Article 83 EPC are therefore met.

*Inventive step (Article 56 EPC)*

26. In the decision under appeal, document D1 was seen as the most suitable starting point for the assessment of inventive step. In the statement of grounds of appeal, the appellant agreed with this finding (see point (42) of the statement of grounds of appeal). The board sees no reason to differ from this assessment. Document D1 describes somatic mutations at residue Y641 of EZH2 in biopsies taken from follicular lymphoma and DLBCL of germinal-centre origin (see title, page 182, right-hand column, Tables 2 and 3, Figure 1 of document D1). It discloses that EZH2 Y641 mutant forms have reduced enzymatic activity to trimethylate an unmethylated peptide substrate *in vitro* (see last sentence of the abstract, sentence bridging the left-hand and right-hand columns on page 184, Figure 2 of document D1).

27. Document D1 is neither concerned with the selection of a treatment for patients afflicted with these cancer types nor compares any treatment options for these patients. Therefore, the objective technical problem cannot be formulated as that of providing an improved treatment for lymphoma and melanoma patients, as suggested by the respondent. The board therefore decided to assess inventive step based on the objective technical problem as formulated by the appellant, which was that of identifying a treatment for subjects having the EZH2 Y641 mutations disclosed in document D1.

28. Document D1 discloses that EZH2 Y641 mutant forms have reduced enzymatic activity *in vitro* and states that "*Tyr641-altering mutations of EZH2, and possibly a reduction in H3K27 trimethylation, are involved in the pathogenesis of GBC lymphomas*" (see the sentence bridging the left-hand and right-hand columns on

page 184 of document D1). From this disclosure, the skilled person would not have considered that patients harbouring an EZH2 Y641 mutation were suitable for the treatment with an EZH2 inhibitor. The claimed subject-matter was therefore not obvious to the skilled person from the experimental data disclosed in document D1.

29. The appellant argued that the skilled person would have understood that the EZH2 Y641 mutant forms disclosed in document D1 were likely to be gain-of-function mutations, despite the experimental evidence in document D1. The board is not persuaded by these arguments for the following reasons.

30. It is true that document D1 discusses that its experimental data do not rule out the possibility that the EZH2 Y641 mutations "*may alter the product (or target) specificity of EZH2*", as known for the so-called phenylalanine-tyrosine switch site in other SET domain-containing proteins (see lines 2 to 14 in the right-hand column on page 184 of document D1); however, in the same passage, document D1 also discloses that the Y641 residue is distinct from the phenylalanine-tyrosine switch site. Moreover, an altered product or target specificity encompasses options other than an overall gain-of-function activity due to increased H3K27 trimethylation. The skilled person therefore would not have realised from this disclosure in document D1 that the EZH2 Y641 mutations must be either gain-of-function or loss-of-function mutations.

31. Document D15 is a scientific article published as a printed version in the journal "Blood" on 9 December 2010, and, according to the footer on the first page of this article (page 5247 of the journal), it was pre-published online as Blood First Edition

paper on 24 August 2010. The respondent's doubts as to whether document D15 belonged to the prior art were thus unfounded. Furthermore, the respondent did not file any evidence in support of its allegation that the online version of document D15 was different from document D15 as submitted in opposition. Document D15 was therefore held to be part of the prior art under Article 54(2) EPC.

32. Document D15 discusses the role of EZH2 in GBC cells and lymphomagenesis. It mentions that the EZH2 Y641 mutations described in document D1 are heterozygous, which "*is not incompatible with an overall gain-of-function effect of the mutation*" (see page 5254, right-hand column, last paragraph). A similar statement can be found in document D17, which considers that the fact that no EZH2 mutations other than at residue Y641 were detected and that all the Y641 mutations seemed to be heterozygous suggested "*a very specific mode of action that may involve a gain of function*" (see page 724, right-hand column, first full paragraph of D17).

33. However, these comments in document D15 and D17 are just theoretical speculations. Neither of these documents discloses any data on EZH2 Y641 mutant forms. Document D15 also states in the same paragraph that the EZH2 Y641 mutant forms reduced H3K27 methylation *in vitro* and that the *in vivo* impact of these mutations was not known (see page 5254, right-hand column, last paragraph). The conclusion in document D15 that therapeutic targeting of EZH2 might have significant anti-lymphoma effects (*ibid.*) therefore cannot be understood in the context of EZH2 Y641 mutant forms of which the *in vivo* impact is decidedly unclear. Instead, it must be seen in the context of the experimental data in document D15 itself, which show that siRNA-mediated

downregulation of EZH2 in DLBCL cells results in cell cycle arrest and upregulation of tumour suppressor genes (see page 5254, left-hand column, first paragraph).

34. Consequently, documents D15 and D17 do not contain any teaching that would have necessarily caused the skilled person to question the experimental data on the enzymatic activity of the EZH2 Y641 mutant forms as disclosed in document D1.

35. Document D16 discloses that a Y to F mutation in the catalytic domain of the histone methyltransferase G9a increased trimethylation activity of the mutant enzyme on an H3K9 peptide (see Figure 3 of document D16). This document therefore concerns a different enzyme (G9a) which methylates another substrate (lysine 9 in histone H3). The argument that the skilled person would immediately transfer the teaching on G9a to EZH2 is based on hindsight, which must be avoided. The board is therefore not persuaded that the teaching of document D16 was sufficient to cast serious doubts on the disclosure in document D1 that the Y641 EZH2 mutant protein had reduced enzymatic activity.

36. The appellant's argument that the skilled person, in view of their doubts on the *in vivo* function of the mutated enzyme, would have tested it in a routine assay with the expectation of finding gain of function, as evident from post-published documents D8 and D9, is also based on hindsight. As discussed above in the context of documents D1 and D15, the *in vivo* function of the EZH2 Y641 mutant forms was not known on the priority date of the application and there were not just two possibilities (gain of function or loss of function) for how the Y641 mutations might have altered

the *in vivo* function of the enzyme (see points 30. and 33. above). Therefore, even if the skilled person felt the need to further investigate the function of the mutated enzyme, they could not have known in advance which functional tests on which substrates were necessary to elucidate the *in vivo* function of the enzyme and which outcome was to be expected.

37. Consequently, neither the comments in document D1 on the phenylalanine-tyrosine switch site in SET domain-containing proteins nor the disclosure in any of documents D15, D16 and D17 was sufficient for the skilled person to seriously consider that the EZH2 Y641 mutant forms were gain-of-function mutants, despite the teaching in document D1 pointing to the contrary. The claimed subject-matter was therefore not obvious to the skilled person in view of the teaching in document D1 combined with that in either document D15, D16 or D17.

38. The appellant also argued that the technical problem was not solved over the entire scope of the claim where the EZH2 Y641 mutation was not a gain-of-function mutation, where the mutation was homozygous and where the patient had a cancer that did not rely on an EZH2 gain-of-function mutation; however, since the purpose, i.e. the effect, of the claimed method is expressed in the claim, the appropriate legal provision for dealing with these arguments is sufficiency of disclosure (see the Enlarged Board of Appeal's decision G 1/03 (OJ EPO 2004, 413), point 2.5.2 of the Reasons). These arguments were therefore considered under Article 83 EPC (see points 17. to 23. above).

39. In view of the above considerations, the appellant's arguments on inventive step were not persuasive. The

claimed subject-matter involves an inventive step in the sense of Article 56 EPC.

## Order

**For these reasons it is decided that:**

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to to maintain the patent in amended form with the following claims and a description and drawings possibly to be adapted thereto:

   Claims 1 to 5 of auxiliary request 1 filed with the reply to the appeal.

The Registrar: The Chair:

C. Rodríguez Rodríguez T. Sommerfeld

Decision electronically authenticated