Deckblatt Übersetzung

Daten der Übersetzung:

Court/Gericht:	Bundesgerichtshof
Date of Decision / Datum der Entscheidung:	2020-07-07
Docket Number / Aktenzeichen:	X ZR 150/18
Name of Decision / Name der Entscheidung:	Pemetrexed II

FEDERAL COURT OF JUSTICE

IN THE NAME OF THE PEOPLE

JUDGMENT

X ZR 150/18

Pronounced on:
07 July 2020
Zöller
Judicial Secretary
as Clerk of the
Court Registry

in the patent nullity proceedings

Pemetrexed II

Patent Act Sec. 81 ff., Sec. 99(1); Code of Civil Procedure Sec. 66

In patent nullity proceedings, intervening on the side of the plaintiff in the appeal instance is not inadmissible because the intervening party is challenging the patent with another nullity action on which the Patent Court has not yet ruled.

EPC Art. 56; Patent Act Sec. 4

Whether there is a reasonable expectation of success for pursuing a solution path must be determined on a case-by-case basis, taking into account the subject matter at issue, the magnitude of the incentive for the skilled person, the effort required to pursue and follow a particular approach, and the alternatives that may be considered, as well as their respective advantages and disadvantages (confirmation of Federal Court of Justice, judgment of 16 April 2019 – X ZR 59/17, GRUR 2019, 1032 – Fulvestrant).

Federal Court of Justice, judgment of 07 July 2020 – X ZR 150/18 – Federal Patent Court

ECLI:DE:BGH:2020:070720UXZR150.18.0

The X. Civil Senate of the Federal Court of Justice, following the oral hearing on 7 July 2020, attended by the presiding judge Dr. Bacher, the judges Dr. Grabinski, Hoffmann and Dr. Deichfuß as well as the judge Dr. Rombach

ruled that:

The subsidiary intervention is admitted.

On appeal by the defendant, the judgment of the 3rd Senate (Nullity Senate) of the Federal Patent Court of 17 July 2018, is amended.

The actions are dismissed.

The costs of the legal dispute at first instance shall be borne by the applicants in equal parts. The costs of the interlocutory proceedings shall be borne by the defendant. The further costs of the appeal proceedings shall be borne by the plaintiffs and the intervener, 1/3 each.

By operation of law

Facts of the case:

1 The defendant is the owner of European patent 1 313 508 (patent in suit), which was granted with effect for the Federal Republic of Germany, was filed on 15 June 2001, claiming U.S. priorities of 30 June 2000, 27 September 2000, and 18 April 2001, and relates to the use of pemetrexed disodium in combination with vitamin B12 to inhibit the growth of tumors. Patent claim 1, to which ten other patent claims, and patent claim 12, to which two other patent claims relate back, read in the language of the proceeding:

> "1. Use of pemetrexed disodium in the manufacture of a medicament for use in combination therapy for inhibiting tumor growth in mammals wherein said medicament is to be administered in combination with vitamin B12 or a pharmaceutical derivative thereof, said pharmaceutical derivative of vitamin B12 being hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin per-chlorate, azidocobalamin, chlorocobalamin or cobalamin.
>
> 12. A product containing pemetrexed disodium, vitamin B12 or a pharmaceutical derivative thereof said pharmaceutical derivative of vitamin B12 being hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin or cobalamin, and, optionally, a folic binding protein binding agent selected from the group consisting of folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid and (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid, or a physiologically available salt or ester thereof, as a combined preparation for the simultanous, separate or sequential use in inhibiting tumor growth."

2 The applicants argued that the subject matter of the patent in suit was not patentable. The defendant defended the patent in suit as granted and, in the alternative, in nine amended versions.

3 The Patent Court declared the patent in suit to be invalid. This is the subject of the defendant's appeal, which continues to defend the patent in suit with its first-instance requests. The plaintiffs and the intervener, who declared her intervention in the course of the appeal proceedings, oppose the appeal.

Grounds of the decision:

4 The admissible appeal is successful.

5 A. The intervention of the intervenor, which the Senate can also decide on in the final judgment (see Federal Court of Justice, judgment of 21 June 2005 - X ZR 151/01 under II; judgment of 11 February 1982 - III ZR 184/80, NJW 1982, 2070), is still admissible in the appeal instance (see Federal Court of Justice, judgment of 17 January 2006 - X ZR 236/01, BGHZ 166, 18 marginal no. 5 - Carvedilol I) and is also admissible in other respects.

6 1. Pursuant to Sec. 66 of the Code of Civil Procedure, an intervening party may join a party for the purpose of assisting it in any situation of the legal

dispute if it has a legal interest in that party prevailing in a legal dispute pending between other persons. For the establishment of a legal interest in this sense, it is sufficient if the intervening party is affected by the formative effect of a judgment.

7 A final decision in patent nullity proceedings has such a formative effect if it declares the patent null and void or rejects the appeal against a judgment of the Patent Court pronouncing this legal consequence. In any case, all companies which may be adversely affected by the patent in suit in their business activities as competitors are affected by the structuring effect of such a nullity judgment. This is sufficient for the admissibility of the intervening party (BGHZ 166, 18 marginal no. 7 - Carvedilol I).

8 2. Accordingly, the intervenor in the dispute has a legal interest in the plaintiffs' success.

9 An application for a preliminary injunction for infringement of the patent in suit was filed against the intervenor at the Regional Court of Munich. It follows from this that the intervening party can in principle be impaired in its business activities by the patent in suit. The fact that the application was unsuccessful does not lead to a different assessment in this respect.

10 3. Contrary to the view of the defendant, which is also partially represented in the literature (Hall/Nobbe in Benkard, Patent Act, 11th ed., Sec. 81 marginal no. 15 a.E.), a legal interest is not to be denied because the intervening party - as in this case - has filed its own nullity action against the patent in suit. This applies in any case if - as here - the Patent Court has not yet decided on the action of the intervening party and the proceedings to which the intervening party declares its intervention are already pending in the appellate instance.

11 a) In the aforementioned constellation, the intervening party's own nullity action does not represent a more efficient legal protection option compared to intervening in the appeal proceedings (see BGHZ 166, 18 marginal no. 10 - Carvedilol I). In the usual course of events, an earlier decision on the validity of the patent can be expected in the appeal proceedings.

12 b) Aspects of procedural economy also do not stand in the way of intervening. Interventions can lead to a faster decision on the basis of a comprehensive investigation of the facts (BGHZ 166, 18 marginal no. 10 - Carvedilol I). The judgment also has the effect of res judicata vis-à-vis an intervenor of the plaintiff in the event that the action is dismissed (Federal Court of Justice, judgment of 16 October 2007 - X ZR 226/02, GRUR 2008, 60 marginal no. 44 - Sammelhefter).

13 c) Contrary to the view of the defendant, the intervention cannot be considered abusive with regard to possible cost consequences.

14 The additional intervention by the party already bringing its own nullity action may lead to considerable additional costs for the patent proprietor if it is unsuccessful. However, there is also a corresponding risk for the intervener. This is because, in the event that he is unsuccessful, he must bear not only the costs of his action but also, pursuant to Sec.101(2) of the Code of Civil Procedure in conjunction with Sec.100(1) of the Code of Civil Procedure, part of the costs of the other legal action (Federal Court of Justice, judgment of 10 September 2009 - Xa ZR 130/07, GRUR 2010, 123 marginal no. 85 - Escitalopram). This higher cost risk for both sides is offset by the prospect of a faster clarification of the legal situation, which may also prove advantageous for both sides. In view of this, it is generally not to be regarded as an abuse of rights if a party in the initial situation in question makes use of the option of intervening by way of a subsidiary action provided for by law.

15 B. The Patent Court wrongly declared the patent in suit invalid.

16 I. The patent in suit relates to the use of pemetrexedisodium in combination with vitamin B12 to inhibit the growth of tumors in mammals.

17 1. The patent in suit states that antifolates are among the best studied classes of antineoplastic agents.

18 Antifolates resulted in inhibition of one or more key enzymes for the biosynthesis of thymidine and purine, specifically thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycine amide ribonucleotide formyl transferase (GARFT), by competing with reduced folate for binding of these

enzymes. Examples of such antifolates include 5-fluorouracil, Tomudex®, Methotrexate®, Lometrexol, and pemetrexedisodium (Alimta®). Pemetrexedisodium (also referred to as MTA [multitarget antifolate] LY231514 in other publications) had shown inhibition of all three enzymes mentioned (para. 2).

19 Significant toxicity to some patients is cited as a limiting factor for the development of such drugs (para. 3). Folic acid and retinoid compounds such as vitamin A had been used as agents to reduce toxicities associated with inhibition of GARFT. The role of folic acid in modulating the toxicity and efficacy of LY231514 was discussed in a publication by Worzalla et al (Role of Folic Acid in Modulating the Toxicity and Efficacy of the Multitargeted Antifolate, LY231514, Anticancer Research 1998, 3235, NIK3). Effects of dietary supplementation with vitamin B12, folate, and vitamin B6 in elderly subjects with normal serum vitamin concentrations and homocysteine levels have been shown to be indicative of expected cytotoxic events. Nevertheless, cytotoxic activity continues to be a serious concern in drug development of antifolates.

20 2. Against the background described, the invention concerns the technical problem of reducing the adverse toxic effects caused by the administration of pemetrexed disodium without compromising therapeutic efficacy (see Federal Court of Justice, judgment of 14 June 2016 - X ZR 29/15, BGHZ 211, 1 marginal no. 10 et seq. - Pemetrexed).

21 3. To solve this problem, the patent-in-suit proposes a use in claim 1 and a product in claim 12, the features of which can be divided as follows:

22 a) Patent claim 1:

A. Pemetrexed disodium is used for the manufacture of a medicament.

B. The drug is for use in combination therapy to inhibit tumor growth in mammals.

C. The drug is to be administered in combination with vitamin B12 or a pharmaceutical derivative thereof.

D. The pharmaceutical derivative of vitamin B12 is hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin

perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin, or cobalamin.

23 b) Patent claim 12:

A. A product comprising pemetrexed disodium, vitamin B12 or a pharmaceutical derivative thereof,

B. wherein the pharmaceutical derivative of vitamin B12 is hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin or cobalamin,

C. and optionally containing a folic acid binding protein agent selected from the group consisting of folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid or (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid or a physiologically available salt or ester thereof,

D. as a combination preparation for simultaneous, separate or sequential use in the inhibition of tumor growth.

24 4. According to the description in the patent specification in dispute, the use of vitamin B12 is based on the surprising finding that certain toxic effects of antifolates, such as mortality and non-hematological events, skin rashes and fatigue, can be significantly reduced by a methylmalonic acid reducing agent such as vitamin B12.

25 II. The Patent Court gave the following main reasons for its decision:

26 The subject matter of the patent in suit was not patentable because the use according to claim 1 was in any case not based on inventive step. The provision of the claimed use proved to be inappropriate in view of the publication by Shih and Thornton (Preclinical Pharmacology Studies and the Clinical Development of a Novel Multitargeted Antifolate, MTA [LY231514], in Jackman, Antifolate Drugs in Cancer Therapy, 1999, NIK15 pp. 183 ff.) in conjunction with two publications by Niyikiza et al. (MTA [LY231514]: Relationship of vitamin metabolite profile, drug exposure, and other patient characteristics to toxicity, in Annals of Oncology, Vol. 9, 1998, Supplement 4, pp. 126 f., NIK8; LY231514 (MTA): Relationship of vitamin metabolite profile to toxicity, in Proceedings of ASCO 1998, Vol. 17, Abstract No.*2139, NIK16) and the expertise represented, for example, by the contribution of Scott (Folate and vitamin B12, in Proceedings of the Nutrition Society, 1999, Vol. 58, p. 441 ff., NIK22).

27 The skilled person takes from NIK15 the positive influence of folic acid supplementation in antitumor treatment with pemetrexed. This would give the pharmacologist in the skilled person team reason to take a closer look at the biochemical reactions in which folic acid is involved. From the folate balance shown in Figure 1 of NIK22, the skilled person would see that the DNA cycle is linked to the methylation cycle via the tetrahydrofolate and its precursor 5-methyltetrahydrofolate. The conversion of 5-methyltetrahydrofolate into tetrahydrofolate is regulated by the vitamin B12-dependent enzyme methionine synthase. Thus, it was known to the skilled person that during pemetrexed administration not only the DNA cycle but also the methylation cycle was blocked by blocking the three key enzymes TS, DHFR and GARFT.

28 The skilled person would find this biochemical correlation confirmed by the correlation described in NIK8 and NIK16 between the homocysteine level before the start of treatment and the toxicities observed with pemetrexed treatment. Homocysteine was said to be a substrate in the methylation cycle. It was further known to the skilled person that the enzyme methionine synthase, and thus homocysteine levels, were regulated by both folic acid and vitamin B12. The administration of one or both of these vitamins increases the activity of methionine synthase, which leads to a reduction in the homocysteine level. Because of the known correlation between the homocysteine level and the side effects of pemetrexed, the skilled person, aware of the physiological correlations of folate balance, would be motivated to turn to vitamin B12 in addition to folic acid, which had already tested positive.

29 The state of the art shows a tendency that a combined administration of pemetrexed and folic acid is promising for efficacy in humans. The study reports of Hammond et al (A phase I and pharmacokinetic [PK] study of the multitargeted antifol [MTA] LY231514 with folic acid, ASCO Annual Meeting 1998, Abstract No. 866, HLNK3; Annals of Oncology 1998, Vol. 9, Suppl. 4, Abstract No. 620P, p. 129, HLNK4) indicated that folic acid administration allowed an increase in the dose of pemetrexed. The fact that no phase II studies had been published at the priority date did not prevent the skilled person from looking further into folic acid. This was supported by the phase II studies according to NIK8 and NIK16.

30 This assessment is also supported by experience with other antifolates. For example, the administration of folic acid to attenuate the side effects of methotrexate was described as early as 1990 (Morgan et al., The Effect of Folic Acid Supplementation on the Toxicity of low-dose Methotrexate in Patients with Rheumatoid Arthritis, in Arthritis and Rheumatism, Vol. 33, 1990, p. 9, Abstract sentence 2, NIK42). It is irrelevant that the therapeutic purpose of methotrexate was rheumatoid arthritis. Furthermore, for the antifolate lometrexol, daily administration of folic acid is described as appropriate for weekly treatment with the agent (Roberts et al, Weekly Lometrexol with daily oral folic acid is appropriate for phase II evaluation, in Cancer Chemotherapy Pharmacol 2000, 103, NIK41). Likewise, in the chapter concerning Lometrexol in the work edited by Jackman (Mendelsohn et al., Preclinical and Clinical Evaluation of the Glycinamide Ribonucleotide Formyltransferase Inhibitors Lometrexol and LY309887, NIK15, p. 261 ff.), folic acid supplementation is explicitly shown for the purpose mentioned.

31 An alleged tumor-promoting effect of vitamin B12 had not prevented the skilled person from using it to solve the task according to the invention. Publications in this regard (ViDAL®, The Dictionary, 1999, HLNK8) revealed a contraindication of the vitamin which was not related to tumor treatment of antifolates. The international patent application WO 96/08515 (HLNK9) and the publication by McLean et al. (Antibodies to Transcobalamin II Block In Vitro Proliferation of Leukemic Cells, in Blood, Vol. 89, No. 1, 1997, p. 235 ff, HLNK33) dealt with the blockade of DNA synthesis by vitamin B12 deprivation and thus with a different task.

32 The defendant's alternatively defended, self-contained version according to auxiliary claims 1 to 9 likewise did not prove to be inventive due to lack of inventive step.

33 III. This assessment does not stand up to review in the appeal proceedings.

34 Contrary to the opinion of the Patent Court, the subject-matter of patent claim 1 and thus also the subject-matter of patent claim 12 are patentable as granted.

35 1. Neither the subject-matter of patent claim 1 nor the subject-matter of patent claim 12 are fully disclosed in NIK3.

36 a) NIK3 reports a study in mice on the role of folic acid in modulating the toxicity and efficacy of pemetrexedisodium (multitarget antifolate LY231514, NIK3 p. 3235 Abstract).

37 In the study, one group of mice had been fed standard laboratory rodent chow (Purina Chow #5001) and another group had been fed low folate chow (Purina Chow #5831C-2) (NIK3, p. 3236). Both groups had been administered pemetrexed disodium from the same day after tumor transplantation (NIK3 p. 3236 l. sp., last paragraph).

38 b) Thus, there is no disclosure of features C and D according to patent claim 1.

39 It can be assumed in favor of the applicants that the standard laboratory feed administered to the mice contained a particularly high proportion of vitamin B12. For, in any case, there is no disclosure that this substance was administered in combination with pemetrexed disodium to achieve a specific therapeutic effect.

40 Patent claim 1 is directed to purpose-bound substance protection for the combination of the two active substances mentioned. A complete disclosure of this subject matter requires that the protected substances are used purposefully with the protected purpose.

41 Whether this requirement is fulfilled in the case in dispute with regard to folates, because NIK3 was concerned with their influence on the effect of pemetrexed disodium, can be left open. With regard to vitamin B12, such an objective is not disclosed in NIK3. Even if the purpose protected by the patent in suit had been achieved with the administration of vitamin B12, there was in any case no purpose-oriented use of this substance.

42 c) Nothing else applies to the subject-matter of claim 12, feature D of which requires a purpose-oriented use of the combination preparation for inhibiting tumor growth.

43 The appeal successfully challenges the assumption of the Patent Court that the provision of the use claimed by claim 1 is obvious to the skilled person from the citations NIK16 and NIK8 in connection with the technical knowledge represented, for example, in NIK22.

44 a) Correctly and not objected to by the parties, the Patent Court considered as the competent skilled person a team consisting of a pharmacologist specialized in the field of mechanisms of action of antifolates in the treatment of cancer and a medical doctor specialized in the field of oncology and having many years of experience in the chemotherapeutic treatment of cancer patients with anticancer agents such as antifolates (see BGHZ 211, 1 marginal no. 22 - Pemetrexed).

45 Whether the team also includes a biochemist and a chemist, as the intervener claims, is irrelevant for the decision of the dispute. Even if this were to be affirmed, it does not follow that a pharmacologist does not belong to the team.

46 In order to solve the technical problem underlying the patent in suit, it is necessary to consider the interaction between substances and living beings. This is the subject of pharmacology.

47 b) Based on the problem underlying the patent in suit, the skilled person had reason to deal with the publications NIK16 and NIK8.

48 These publications report on the statistical analysis of data from various studies on the use of pemetrexedisodium (MTA [LY231514]) in clinical phase II, namely with regard to the relationship between vitamin metabolite profile and toxicity. Thus, the publications address a problem comparable to that of the patent in suit.

49 c) As a reason for the investigations, NIK16 and NIK8 cite previous studies that suggested that the nutritional status of the patient might be of importance for the likelihood of suffering severe toxicities.

50 Therefore, levels of the vitamin metabolites homocysteine, cystathionine, and methylmalonic acid had been determined before treatment initiation and

then once after each treatment cycle. A strong correlation between the initial homocysteine level and the development of toxicities was found.

51 As a conclusion, NIK8 states that toxicities resulting from treatment with MTA seem to be predictable on the basis of the homocysteine concentration before treatment. An elevated baseline homocysteine level (≥ 10 µm) correlated strongly with severe hematologic and nonhematologic toxicities after treatment with MTA (NIK8 p. 127).

52 The previously published NIK16 comes to a corresponding conclusion. There is also the indication that the maximum homocysteine level does not seem to have changed during treatment with MTA compared to the baseline value (NIK16 p. 558a Abstract No. *2139).

53 The vitamin metabolite methylmalonic acid (MMA), which was also investigated, is not explicitly mentioned in NIK8 and NIK16 when presenting the results of the investigation. However, NIK16 contains the general remark that no correlation between toxicity and the other predefined predictors could be seen.

54 d) The strong correlation observed between the homocysteine level at baseline and the development of toxicities prompted the skilled person to focus on the processes and substances involved in the homocysteine level.

55 In view of the strong correlation between these two parameters, there was much to suggest that the elevated homocysteine level, or at least a relevant cause thereof, was also responsible for the occurrence of the side effects.

56 e) Based on this, the skilled person had reason to draw on general expert knowledge about factors that are decisive for the homocysteine level, as represented in NIK22.

57 The fact that NIK22 generally deals with folic acid and vitamin B12 does not speak against the consideration of this expert knowledge. Rather, the decisive factor is that NIK22 highlights the folate balance, an endogenous mechanism that influences homocysteine levels and in which folates play a significant role.

58 f) However, from the expertise documented in NIK22, there was no suggestion for the skilled person to combine pemetrexedisodium with vitamin B12.

59 aa) The endogenous metabolic pathways for folates are shown in NIK22 as a simplified scheme in Figure 1 reproduced below.

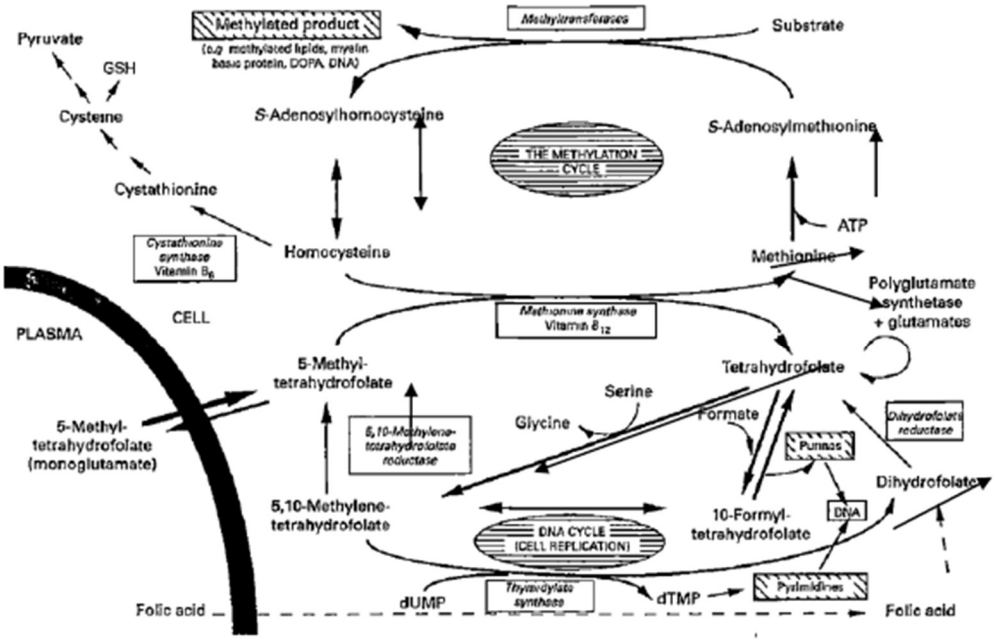

Fig. 1. The biochemical pathways involving the folates and vitamin B_{12}. DOPA, 3,4-dihydroxyphenylalanine

60 (1) The scheme distinguishes a DNA cycle (cell replication) and a methylation cycle (the methylation cycle), which are connected at a central point.

61 (2) According to NIK22, folate in the reduced form tetrahydrofolate is essential for cell replication.

62 According to this, folates obtain their C1 groups in the DNA cycle either from serine (serines) or from formate (formates). These C1-substituted forms are obviously important, since they are needed twice as 10-formyltetrahydrofolate during the de novo biosynthesis of the purine ring.

63 Similarly, the conversion of the uracil-like base found in RNA is caused by the enzyme thymidylate synthase (TS), which uses the folate cofactor 5,10-methylenetetrahydrofolate as a C1 donor.

64 Alternatively, the 5,10-methylenetetrahydrofolate form used for thymidylate synthase could be channeled to the methylation cycle. This cycle performs two functions. It ensures that the cell is always sufficiently supplied with S-adenosylmethionine. This is an activated form of methionine that acts as a methyl donor for a whole spectrum of methyltransferases. These enzymes methylated a variety of substrates, including lipids, hormones, DNA and proteins. When the methylation cycle is disrupted, as is the case with vitamin B12 deficiency, one of the clinical consequences is demyelination of the nerves (NIK22 p. 442 sp. 2 - p. 443).

65 (3) The DNA and methylation cycles both regenerated tetrahydrofolate, so the vitamin was not depleted. However, there is a considerable amount of catabolism (breakdown) of folate, as well as loss of folate due to low urinary excretion.

66 Therefore, there is a need to replenish the body's folate levels through dietary intake. If too little dietary folate is supplied to meet the requirement, this leads to a reduction in both the DNA cycle and the methylation cycle. A reduction in the former, he said, in turn reduces DNA biosynthesis and thus cell division. There is also a reduction in the methylation cycle. The most obvious expression of this reduction is an increase in plasma homocysteine, which presumably results from a reduction in the activity of the methylation cycle due to an inadequate supply of new methyl groups necessary for remethylation of plasma homocysteine. Previously, the prevailing opinion had been that an increase in plasma homocysteine was merely a good surrogate biochemical marker for possible folate deficiency (NIK22 p. 443 re. sp. para. 3 f.).

67 (4) According to the explanations in NK22, the two cycles are fed on the one hand by uptake of 5-methyltetrahydrofolate from the plasma (lower left corner of the picture), and on the other hand - to a lesser extent - by uptake of folic acid, which is converted into dihydrofolate in the cell (dashed arrows at the lower edge of the picture and in the lower right corner of the picture).

68 In the methylation cycle, homocysteine is converted to methionine by reaction with 5-methyltetrahydrofolate. This conversion is catalyzed by the enzyme methionine synthase, for which vitamin B12 is a cofactor that activates

the enzyme. Tetrahydrofolate is also formed during this conversion. This reacts to form 5,10-methylenetetrahydrofolate. This, in turn, is converted to dihydrofolate by the enzyme TS and again to tetrahydrofolate via the enzyme DHFR in a pathway referred to by the defendant as the replenishment pathway. In another pathway, referred to by the defendant as the second alternative pathway, 5,10-methylenetetrahydrofolate is converted back to 5-methyltetrahyrofolate by means of the enzyme 5,10-methylenetetrahydrofolate reductase.

69 bb) Contrary to the opinion of the Patent Court, this did not provide the skilled person with sufficient indications for the assumption that, in the case of pemetrexed administration, not only this cycle but also the methylation cycle is blocked by blocking the key enzymes TS, DHFR and GARFT in the DNA cycle.

70 (1) However, the fact that the tetrahydrofolate co-generated during methonine synthesis is converted both in the replenishment pathway, which is primarily relevant for tumor growth, and in the alternative pathway, which is also relevant for the methylation cycle, suggests that impairments in one pathway may simultaneously lead to impairments in the other pathway because sufficient tetrahydrofolate is no longer available. However, the fact that the 5,10-methylenetetrahydrofolate formed from tetrahydrofolate can also be converted to the 5-methyltetrahydrofolate required for the methylation cycle independently of the replenishment pathway also leaves open the possibility that a sufficient level of tetrahydrofolate for the methylation cycle is also available via this pathway.

71 Against this background, the skilled person would at most have had reason to look for measures to support methonine synthesis if the assumption of an influence on the methylation cycle had been confirmed by additional indications.

72 (2) Contrary to the opinion of the Patent Court, such evidence did not result from the correlation described in NIK8 and NIK16.

73 A blocking of the methylation cycle by pemetrexedisodium would lead to the expectation that the homocysteine level would increase as a result of

treatment with this active substance. However, according to the explanations in NIK8 and NIK16, such an effect could not be determined. As has already been explained, it is rather reported there that the maximum homocysteine level does not appear to have changed during treatment with MTA compared with the baseline value (NIK16 p. 558a, NIK8 p. 127).

74 While this observation does not disprove the hypothesis of an influence on the methylation cycle. Thus, the doubling of the maximum cystathionine level compared to baseline reported in NIK16 as a consequence of MTA administration could suggest that excess homocysteine was converted to cystathionine. However, the data reported in NIK16 did not provide sufficient evidence for this either. The fact that cystathionine levels after NIK16 did not correlate with hematologic toxicity or mucositis, but only showed a moderate correlation with fatigue, could point in this direction. However, it forms at best a weak indication and therefore did not give the skilled person sufficient reason to pursue the hypothesis of an influence on the methylation cycle.

75 Independently of this, an elevated level of cystathionine did not readily indicate a deficiency of vitamin B12. Cystathionine is known to be a specific marker for vitamin B6, as the second plaintiff pointed out in connection with NIK16, whereas methylmalonic acid is the only specific marker for vitamin B12 (cf. NIK22 p. 445 le. sp. para. 2). A significant increase of homocysteine, but not of cysteine, is a typical finding in folate and vitamin B12 deficiency (Brattström et al., Homocysteine and cysteine: determinants of plasma levels in middle-aged and elderly subjects, Journal of Internal Medicine 1994, pp. 633, 634, li. sp. last sentence, NIK11).

76 (3) Specific evidence of a correlation between pemetrexedisodium administration and methylmalonic acid levels cannot be inferred from NIK8 and NIK16.

77 The vitamin metabolite methylmalonic acid (MMA), whose increase according to the explanations in NIK22 indicates a deficiency of vitamin B12 (NIK22 p. 445 left column below), is indeed one of the three substances whose level was measured according to the explanations in NIK8 and NIK16. However, only homocysteine and cystathionine are mentioned in the presentation of the

test result. In addition, in NIK16 it is stated that a correlation between the toxicity and the other predefined predictors was not seen.

78 In view of this, the skilled person had no reason to believe that there could be a correlation between the administration of pemetrexedisodium and MMA levels.

79 It can be left open whether the remarks on the correlation of other predefined predictors in NIK16 refer only to those predictors that were included in the statistical analysis described in NIK16 (creatinine clearance, albumin level, liver enzyme level, and vita-min metabolites) and whether - as there is much to suggest - methylmalonic acid is one of the vitamin metabolites mentioned in this context. Even if the latter were to be negated, this would at best have the consequence that neither a positive nor a negative statement on a correlation between toxicity and methylmalonic acid can be taken from NIK16. Even with this starting position, the skilled person would have had no reason to consider the combination of pemetrexedisodium and vitamin B12.

80 (4) Contrary to the opinion of the Patent Court, no further suggestions resulted from considerations regarding the so-called methyl trap.

81 (a) In connection with vitamin B12, it is stated in NIK22 that pernicious anemia (PA) not only causes malabsorption of vitamin B12 from food, but also leads to the inability to reabsorb those amounts of vitamin B12 which are secreted daily in the bile (NIK22 p. 444 re. sp. para. 3).

82 At first glance, it was surprising that an impairment of the methylation cycle should cause a deficiency in DNA biosynthesis and anemia. It was assumed that this impairment could be explained by the methyl trap hypothesis. This states that after the formation of the folate cofactor 5-methyltetrahydrofolate, the enzyme 5,10-methylenetetrahydrofolate reductase, which forms the cofactor, cannot use it in the reverse reaction in vivo. Therefore, the only way this folate cofactor could become tetrahydrofolate again and thus participate in DNA biosynthesis and enable cell division was via the vitamin B12-dependent enzyme methionine synthase. When the activity of this enzyme is impaired, as is the case with PA, the cellular folates are progressively trapped

as 5-methyltetrahydrofolate. As a result, the cell suffers a kind of pseudo-folate deficiency. It has sufficient folate, but it is trapped in a form that cannot be used for DNA biosynthesis. The result is an anemia identical to that observed in true folate deficiency (NIK22 p. 445 r. sp. para. 2).

83 Vitamin B12 treatment, when administered intramuscularly, reactivated methionine synthase, thereby allowing myelination to resume. The entrapped folate was also released, allowing DNA synthesis and erythrocyte generation and acting against anemia (NIK22 p. 445 re. sp. para. 2).

84 (b) The methyl trap hypothesis put forward in NIK22 may have provided evidence that both the DNA and methylation cycles rely not only on an adequate supply of folate, but also on an adequate supply of vitamin B12. However, this did not give the skilled person concerned with the technical problem of the patent in suit sufficient reason to take further steps in this direction.

85 That it could come to the effect called methyl trap was not certain on the basis of NIK22. The citation speaks in this respect of a hypothesis. This is indeed presented in NIK22 as plausible and promising. However, the skilled person could not derive from this the concrete expectation that it would prove to be true.

86 The hypothesis presented in NIK22 may have indicated that an adequate supply of vitamin B12 is necessary for folates present in the body or additionally administered to the body to exert their intended effect. It could possibly at the same time provide an explanation for the observations revealed in NIK16 and NIK8, because a high homocysteine level could indicate that the patients concerned already suffered from vitamin B12 deficiency prior to the administration of pemetrexedisodium, and that for this reason the homocysteine level, which was high anyway, could no longer increase significantly in the course of treatment.

87 However, in view of the complex interrelationships that already result from the simplified representation of folate balance in NIK22, the prospects that this very effect relationship could prove to be decisive were rather vague. In this

initial situation, there was no sufficient reason for the skilled person to consider the combination of pemetrexed disodium and vitamin B12.

88 (c) Further indications did not result from the textbook by Baynes et al. (Medical Biochemistry, 1999, NIK48).

89 The statement contained therein that it is impossible to consider the function of vitamin B12 in isolation from folic acid (NIK48 p. 118) merely describes general interrelationships which, although they can also be reconciled with the teaching of the patent in suit, did not provide sufficient reason to investigate these interrelationships in depth without knowledge of this teaching.

90 3. based on the publication by Shih and Thornton (NIK15 ch. 8), there was no reasonable expectation of success with respect to vitamin B12.

91 a) However, based on NIK16 and NIK8, the skilled person had reason to consider this publication.

92 The stated goal of the article is to present a comprehensive overview of the unique biochemical and pharmacological modes of action, as well as the recent clinical results of the phase I and II studies of the multitarget antifolate MTA (LY231514) - i.e., pemetrexed disodium. Section 2.6 of the publication specifically addresses the impact of folic acid on toxicity. The homocysteine level highlighted as possibly relevant in NIK16 and NIK8 was already known as a specific marker for folate deficiency at the priority date (Cripps et al, Phase II study of first-line LY231514 [...] in patients with locally advanced or metastatic colorectal cancer: An NCIC Clinical Trials Group study, in Annals of Oncology 1999, NIK23 pp. 1175, 1179 li. sp. para. 2). These correlations gave sufficient reason to look for possible causes of high homocysteine levels in the publication.

93 b) The publication gave rise to the suggestion for the skilled person to use folic acid to reduce the toxicity of pemetrexed.

94 MTA is presented in the publication as a structurally novel antifolate discovered in structure-activity relationship studies of the novel antipurine-folic acid antagonist-lometrexol series after elimination of the C5 methylene of

lometrexol and conversion of the sp3 center at C6 to sp2 geometry. This modification resulted in a very potent cytotoxic agent against human CCRF-CEM leukemia cells in culture. This end-product reversal pattern of the new antifolate was completely different from the GARFT inhibitor lometrexol, he said. The replacement of the tetrahydropyridine ring of lometrexol with a pyrrole moiety caused a greater loss of effect in inhibiting purine biosynthesis and shifted the site of action to inhibition of pyrimidine biosynthesis (thymidylate cycle, NIK15 p. 184).

95 Section 2.6 of the publication describes the study according to NIK3. According to this, to evaluate the importance of dietary folate in modulating the toxicity of MTA, LD50 values had been determined in mice fed either a standard diet (SD) or a special low-folate diet (LFD). MTA was administered i.p. daily for 10 days. It was estimated that mice on the low-folate diet had an average folic acid intake of about 0.003 mg/kg/day, compared with 0.75-1.5 mg/kg/day for mice on the standard diet. MTA had been more toxic to several different strains of mice maintained on a low-folate diet, with LD50 values 30 to 250 times lower than in mice maintained on a standard diet. A similar effect had also been observed for antipurine antifolates such as lometrexol. The maximum tolerated dose (MTD) of lometrexol on a low folate diet was 1000- to 5000-fold lower than in mice maintained on a standard diet. DHFR inhibitors such as methotrexate would have a similar effect, but to a lesser extent (50- to 100-fold).

96 The therapeutic index of MTA against the L5178Y/TK-/HX tumor was greatly reduced when mice were switched to a folate-deficient diet without folic acid supplementation. Good antitumor activity had been observed at doses of 0.3 mg/kg and 1.0 mg/kg (i.p. daily x 10), and significant toxicity at higher doses. When daily folic acid supplementation (15 mg/day/mouse, p.o.) was co-administered with MTA, an excellent antitumor activity range (10 mg/kg to 1000 mg/kg, with antitumor activity in the range of 80% to 100%) without lethality was observed. This range of antitumor activity (with folic acid supplementation) was identical to the range of activity observed for MTA in standard diet-fed mice. These data indicated that folic acid supplementation not only modulated toxicity but also slightly enhanced the antitumor response of MTA (NIK15 pp. 190-191).

97 c) Contrary to the opinion of the defendant, the fact that the study only refers to preclinical tests on mice does not speak against the consideration of these statements.

98 Even if the studies on pemetrexed disodium had already reached the clinical phases, there was in any case reason to fall back on findings from earlier phases if unexpected problems or new findings arose. In the present context, such findings resulted from NIK8 and NIK16, which pointed to the possible relevance of high homocysteine levels.

99 d) The fact that according to both NIK3 (p. 3238) and NIK15 ch. 8 (Figure 4), the MTA dose must be increased considerably when folic acid is administered as a supplement does not necessarily speak against a detailed consideration of the influence of folic acid.

100 As shown in Figure 4 from NIK15 Ch. 8 reproduced below, 100 % enzyme inhibition could already be achieved with MTA at a dose of 0.3 mg/kg. In combination with folic acid, the dose had to be increased to 30 mg/kg, i.e. a hundredfold.

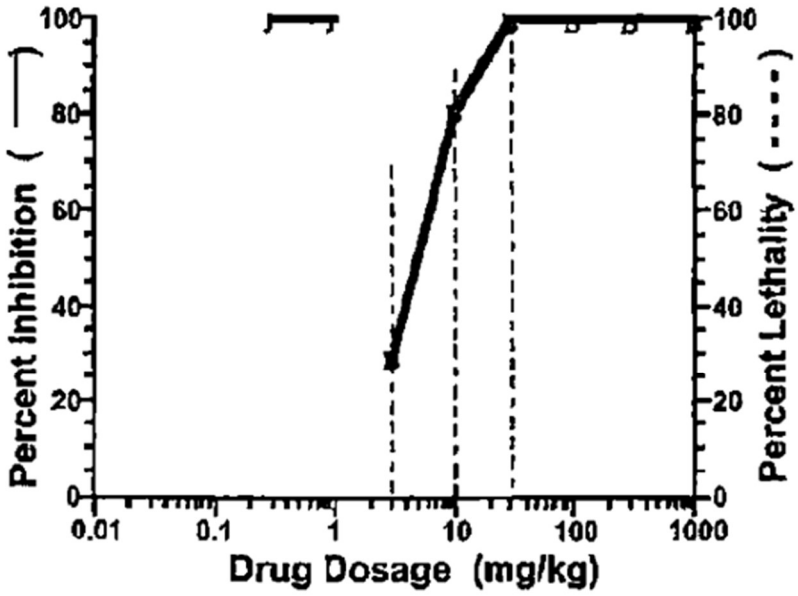

Fig. 4. Antitumor activity of MTA against L5178Y/TK⁻/HX⁻ lymphoma for mice on low folate diet (LFD) with no folate supplementation (J) and for mice on low folate diet that received 15 mg/kg/d daily folate supplementation (B); vertical dashed lines represent percent lethality in mice on low folate diet with no folate supplementation.

101 However, this circumstance did not necessarily speak against a combination of MTA and folic acid, because the latter at the same time leads to a strong reduction of toxicity. Both NIK15 ch. 8 and NIK3 state that despite the higher doses, toxicity can be reduced and the antitumor effect maintained at the same level (NIK3 p. 3238 r. sp. para. 2) or even slightly increased (NIK15 p. 191).

102 A corresponding conjecture is found in NIK23, where it is reported that there is preliminary work suggesting that toxicity is increased in patients with high homocysteine levels, and it is possible that combined administration of MTA with folic acid eliminates toxicity without reducing efficacy (NIK23 p. 1175, 1179 r. sp. para. 2).

103 e) This resulted in a suggestion for the skilled person for clinical studies on the effect of the administration of folic acid on toxicity and efficacy of pemetrexed, but not for the supplementary administration of vitamin B12.

104 aa) However, the skilled person was aware that in some patients only the combination of folic acid and vitamin B12 ensures the full homocysteine-lowering effect.

105 Thus, in the abstract of NIK9 (Brattström, Colloquium: Homocyst[e]ine, Vitamins and Arterial Occlusive Diseases, Vitamins as Homocysteine-Lowering Agents, in American Institute of Nutrition 1996, pp. 1276S, 1278S), it is stated that a combination of folic acid and cyanocobalamin (vitamin B12) ensures the best possible ("full") homocysteine-lowering effect. Furthermore, the occurrence of a vitamin B12 deficiency is prevented in this way. This is expressed more cautiously in the section "Discussion and recommendations", according to which vitamin B12 probably ensures the aforementioned effect.

106 The fact that the subject of the article is the lowering of homocysteine levels for the purpose of reducing the risk of cardiovascular disease does not prevent the article from being used. The suggestion following from NIK8, NIK16, and NIK15 to use folic acid to reduce homocysteine levels and thereby reduce the toxicity of pemetrexed without disadvantages for therapeutic efficacy gave the skilled person reason to look more deeply into the

homocysteine-reducing effect of folic acid. He therefore had reason to also deal with this citation in more detail.

107 bb) However, taking this approach was not obvious to the skilled person in view of the size of the incentive, the effort required, the results to be expected and the alternatives that could be considered.

108 (1) According to the case law of the Senate, the requirements for an appropriate expectation of success, which gives the skilled person reason to follow a possible solution despite the fact that the results cannot be predicted with certainty, cannot be formulated in a generally valid manner. Rather, they must be determined on a case-by-case basis, taking into account the field of expertise at issue, the size of the incentive for the skilled person, the effort required to take and pursue a particular approach and the alternatives that may be considered, as well as their respective advantages and disadvantages (Federal Court of Justice, judgment of 16 April 2019 - X ZR 59/17, GRUR 2019, 1032 marginal no. 31 - Fulvestrant).

109 (2) In the case in dispute, the skilled person could not immediately test the vitamin B12 supplementation in a clinical study, since - in contrast to folic acid supplementation - it had not already been used in such a study. Rather, he was required to test in animal experiments with an experimental set-up corresponding to NIK3 whether the administration of vitamin B12 in combination with folic acid is suitable to reduce the toxicity of pemetrexed without disadvantages with regard to therapeutic efficacy.

110 The effort required for this was not excessive and, in view of the trial duration of two weeks specified in NIK3, initial findings could be expected relatively quickly. However, it was unlikely that these findings could be readily applied to the clinical trials already underway.

111 In order to obtain reliable findings, subsequent pilot studies in humans would have been required, involving time-consuming analysis of methylmalonic acid before and during administration of the study drug. As can be seen from the expert opinion of Dr. H. submitted by the plaintiffs (NIK39 p. 7), the reference method for the analysis of methylmalonic acid in

plasma/urine on the priority date was more complicated compared to that of the homocysteine level, and a significant statement was more difficult to make; it was not until 2006 that a method was subsequently described that enabled a rapid, reliable and, above all, reproducible determination of this biomarker.

112 (3) Against this background, the incentive to follow this path was not sufficiently high.

113 According to the case law of the Senate, however, a high level of expenditure for subsequent investigation phases does not necessarily preclude the assumption of a sufficient expectation of success with regard to a solution path that initially requires the performance of animal experiments. In particular, if the skilled person must assume that he will not be able to avoid animal testing anyway, the requirements for the reasonable expectation of success must in principle be based on the effort required for this (Federal Court of Justice, GRUR 2019, 1032 marginal no. 32 - Fulvestrant).

114 In the case in dispute, however, the approach of reducing the toxicity of pemetrexedisodium by administering folic acid had already been pursued in a clinical trial reported in HLNK3 and HLNK4. Thus, the incentive to return to animal studies was significantly reduced.

115 (a) HLNK3 and HLNK4 report a study in which patients were given 5 mg of folic acid (FA) over a five-day period, beginning two days before treatment with MTA, to determine whether this provided a significant dose increase. Here, vitamin metabolites had been measured to determine their utility as potential prognostic markers with this combination.

116 As a result, HLNK3 reported, in patients with severe toxicities, homocysteine levels were significantly elevated. In HLNK4, it is stated that the addition of folic acid may reduce the utility of vitamin metabolites as an indicator of toxicity, however. Both publications end with the conclusion that the addition of folic acid appears to allow an increase in MTA dose by reducing toxicity.

117 (b) Given this starting point, there was little incentive for the skilled person to go back behind the stage of clinical trials already reached in HLNK3

and HLNK4 and to explore the use of folic acid together with vitamin B12 again in animal experiments.

118 In this context, it can be left open whether the positive assessment expressed in HLNK3 and HLNK4 was justified from the skilled person's point of view or whether the results revealed therein were rather sobering, as the defendant suggests. If the optimism expressed proved to be justified, there was no reason to abandon the path taken and return once again to the stage of animal testing. If the success to be expected with the use of folic acid turned out to be rather modest, it was obvious to abandon this approach completely. It is true that the results reported in HLNK3 and HLNK4 left open the possibility that an additional administration of vitamin B12 might help to achieve a decisive breakthrough. However, in view of the level of knowledge achieved, there was insufficient evidence to suggest that this hope might prove to be justified.

119 f) No further suggestions result from other citations.

120 aa) The publication by Adjei (A review of the pharmacology and clinical activity of new chemotherapy agents for the treatment of colorectal cancer, in Clin Pharmacol 1999, 265-277, NK40) reports that the dose of MTA has been successfully increased with folic acid supplementation up to 1000 mg/m2 every three weeks, which may not adversely affect the tumor-inhibiting effect of pemetrexed (NK40 p. 270 li sp., penultimate sentence).

121 This does not give rise to any further suggestions with regard to vitamin B12.

122 bb) The publication by Calvert (An Overview of Folate Metabolism: Features Relevant to the Action and Toxicities of Antifolate Anticancer Agents in Seminars in Oncology, 1999, 3-10, NIK2) states that the clinical toxicity of many antifolates is influenced by the patient's folate status prior to treatment, which is not surprising.

123 For GARFT inhibitors, the effect of folate status was particularly pronounced, with the maximum tolerated dose in patients who had received folate supplementation being at least 10-fold higher than in patients who had

not (NIK2 p. 7 re. sp. para. 2). Furthermore, folic acid is also involved in methylation processes within the cells due to its importance for methionine synthesis. The methionine synthase involved in this process is dependent on vitamin B12, but also uses 5-methyltetrahydrofolate as a cosubstrate. Therefore, any deficiency of vitamin B12 or folate leads to a reduction of the flow through methionine synthase and thus to an increase in the plasma level of homocysteine (NIK2 p. 8 r. sp. above). The measurement of homocysteine levels prior to treatment has been shown to be a suitable way to predict the toxicity of MTA (NIK2 p. 9 r. sp. above).

124 This, as well as NIK8, NIK16, and NIK15 in conjunction with NIK9, do provide evidence that vitamin B12 affects homocysteine levels. However, this does not justify an appropriate expectation of success for necessary animal experiments.

125 4. The appeal also successfully challenges the assumption of the Patent Court that the publication of Mendelsohn et al. (NIK15 ch. 12) motivated the skilled person to consider vitamin B12 on the basis of the combined use of pemetrexed with folic acid.

126 a) The publication addresses the preclinical and clinical evaluation of the GARFT inhibitors lometrexol and LY309877.

127 Section 8 describes the effect of low folic acid diet on the efficacy and toxicity of these antifolates. In mice fed a low-folic acid diet for two weeks, the toxicity of the two antifolates had increased 300- to 1000-fold. Antitumor activity could not be evaluated because of the lethality of the agents. Oral addition of folic acid (0.6-600 mg/kg) restored the sensitivity to antitumor activity of both GARFT inhibitors. High doses of folic acid (> 600 mg/kg) eliminated both toxicity and antitumor activity. The therapeutic indices (LD10AD90) of LY309887 and lometrexol had been determined over a range of added folic acid doses in two antitumor models, human GC3 colon xenograft and C3H mouse mammary tumor (Table 6). The data showed that increasing folic acid supplement doses from 0.0 to 6-15 mg/kg per day resulted in an improved therapeutic index. Furthermore, the ability to delay GC3 tumor regrowth over a wide dose range was observed only with the

higher doses of folate supplementation. A small but moderate increase in the therapeutic index of lometrexol to 2-5 had also been observed. Higher doses of folic acid supplements would have resulted in a less robust increase in therapeutic index.

128 Section 9 addresses human folate status. The folate status of cancer patients has not been systematically evaluated to date. However, early studies reported decreased serum folic acid activity in patients with metastatic cancer. Other investigators would have demonstrated decreased urinary clearance of a folic acid load. Saleh et al. had shown that patients with metastatic disease absorbed more folic acid into their reduced folate pools and had decreased folate depletion and faster clearance of folate in serum than control groups, even when serum 5-CH3-THF concentrations were maintained. The authors had concluded that the patients were folate deficient and that there was an increased folate requirement in patients with malignant disease. In these patients, the variability in metabolism, pharmacokinetics, and toxicity of classical antifolates compared with people with normal folate status would not be surprising. Furthermore, folic acid supplementation could "normalize" the dose response to achieve antitumor activity and reduce toxicity to normal tissues by restoring folate pools in tissues with low folate requirements without meeting the high folate requirements of rapidly dividing tumor cells. The biochemical pathways that utilized folate cofactors also required adequate levels of vitamins B12 and B6. Therefore, the status of all three vitamins in patients could significantly influence the severity of toxicity observed during chemotherapy, he said. R. Allen and colleagues had found that measuring specific amino acid metabolites, particularly homocysteine, N-methylglycine, and others, from these metabolic pathways allowed a more sensitive and reliable assessment of patients' vitamin status. These surrogate indicators of functional folate status provided a better indication of deficiencies and were more sensitive to nutritional supplementation (NIK15 p. 270).

129 b) It is true from these comments that vitamin B12 status can significantly affect the severity of toxicity of lometrexol and LY309877. However, it could not be inferred from this that the administration of vitamin

B12 would remain without significant effects on the therapeutic efficacy of these antifolates.

130 With regard to folic acid, NIK15 states that it was accepted that effects on efficacy could only be assessed in a phase II setting (NIK15 p. 274 para. 2). Thus, it was all the more open which consequences the administration of vitamin B12 would have on therapeutic efficacy.

131 Even if NIK15 could at least be taken as a hope for a positive result in this respect, it was uncertain whether the findings obtained and the hope based on them could be transferred to pemetrexed disodium. In particular, the statements in NIK15 chap. 8, according to which MTA, despite a similar structure, has a mode of action that differs in essential aspects from that of lometrexol, argued against this. In view of all these uncertainties, there was also no sufficient expectation of success from this starting point for further trials with folic acid and vitamin B12.

132 5. A sufficient prospect that the administration of folic acid and vitamin B12 would not significantly impair the efficacy of pemetrexed also did not arise for the skilled person from the consideration that tumor cells have a higher growth rate than healthy cells and accordingly a higher folate requirement.

133 a) It can be assumed in favor of the applicants that this - as suggested by section 9 of the NIK15 - corresponded to the scientific knowledge on the priority date. In any case, this knowledge also did not justify the prospect that the administration of growth-promoting agents would have the hoped-for effect irrespective of the active ingredient used and irrespective of the particular agent. In view of the complexity of the processes on which the result depends, this rather abstract consideration did not justify an appropriate expectation of success from the point of view of the skilled person.

134 b) Without success, the applicants claim that corresponding considerations are based on the high-dose therapy of methotrexate and leucovorin known at the priority date, which is a pure, biologically active form of folic acid (see Physicians' Desk Reference 2000, HLNK14, p. 1426 r. sp.).

135 Just like studies on lometrexol, findings relating to methotrexate cannot be readily transferred to pemetrexed. Regardless of this, there is again a lack of suggestion to use vitamin B12 to reduce side effects.

136 c) Nothing else applies to the publication NIK42.

137 In NIK42, the administration of folic acid is described to reduce the side effects of a use of methotrexate for the treatment of rheumatoid arthritis without affecting the efficacy (NIK42, abstract sentence 2). Again, no firm conclusions can be drawn from this regarding a combination of pemetrexedisodium and vitamin B12.

138 IV. The decision on costs is based on Sec. 121(2) Patent Act in conjunction with Sec. 91(1), Sec. 101(1) and (2) and Sec. 96 Code of Civil Procedure. Pursuant to Sec. 101(2) Code of Civil Procedure, the intervener is to be treated as a party (Federal Court of Justice, judgment of 10 September 2009 - Xa ZR 130/07, GRUR 2010, 123 marginal no. 85 - Escitalopram).

Judge at the Federal Court of Justice Hoffman cannot sign due to absence on vacation

Bacher Grabinski Bacher

Deichfuß Rombach

Previous instance:
Federal Patent Court, judgment of 17 July 2018 – 3 Ni 23/16 (EP) -