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**Datasheet for the decision
of 19 April 2017**

Case Number: T 0790/11 - 3.3.01

Application Number: 02786842.1

Publication Number: 1450799

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A61P35/00

Language of the proceedings: EN

Title of invention:

ARYL UREA COMPOUNDS IN COMBINATION WITH OTHER CYTOSTATIC OR
CYTOTOXIC AGENTS FOR TREATING HUMAN CANCERS

Patent Proprietor:

Bayer HealthCare LLC

Opponent:

Merck Patent GmbH

Headword:

Sorafenib combination therapy/BAYER

Relevant legal provisions:

EPC Art. 54, 56

Keyword:

Novelty - (yes)

Inventive step - (yes) - reasonable expectation of success (no)

Decisions cited:

T 0939/92

Catchword:



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Case Number: T 0790/11 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 19 April 2017

Appellant 1: Bayer HealthCare LLC
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Appellant 2: Merck Patent GmbH
(Opponent) Frankfurter Strasse 250
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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted on
7 February 2011 concerning maintenance of the
European Patent No. 1450799 in amended form.

Composition of the Board:

Chairman A. Lindner
Members: G. Seufert
M. Blasi

Summary of Facts and Submissions

- I. The patent proprietor (appellant 1) and the opponent (appellant 2) lodged an appeal against the interlocutory decision of the opposition division on the amended form in which the European patent No. 1 450 799 could be maintained.
- II. The present decision refers to the following documents
- (1) WO 00/42012
 - (7) *Cancer: Principles & Practice of Oncology, Fifth Edition, Editor V. T. DeVita, Jr. et al., Lippincott-Raven Publishers, Philadelphia, 1997, Chapter 17, pages 333 to 347*
 - (14) WO 00/41698
 - (15) Wikipedia, catchword "Sorafenib", pages 1 to 5
 - (16) Test Report, submitted by appellant 2 with the statement of grounds of appeal, 1 page
 - (17) *Clinical Cancer Research, Vol. 7, November 2001 (Supplement), D. Strumberg et al., abstract #285,*
 - (18) *S. J. Hotte, H. W. Hirte, Current Pharmaceutical Design, Vol. 8, 2002, pages 2249 to 2253*
 - (19) *J. F. Lyons et al., Endocrine-Related Cancer, Vol. 8, 2001, pages 219 to 225*
 - (20) *Riedl et al., abstract #4956*
 - (21) *Riedl et al., abstract #4954*
 - (22) Dissolution experiments, submitted by appellant 1 with letter of 18 October 2011, 1 page
 - (23) *R. J. Bastin et al., Organic Process Research & Development, Vol. 4, 2000, pages 427 to 435*
 - (24) *S. M. Berge et al., Journal of Pharmaceutical Sciences, Vol. 66, Nr. 1, 1977, pages 1 to 19*
 - (25) "Drug release of sorafenib tablets", experimental evidence submitted by appellant 1 with letter dated 14 February 2017

III. Notice of opposition was filed by appellant 2 requesting revocation of the patent in suit in its entirety on the grounds of lack of novelty and inventive step, insufficiency of disclosure and added subject-matter (Article 100(a), (b) and (c) EPC.

In the decision under appeal, the opposition division held *inter alia* that the subject-matter of claim 2 of the main request was anticipated by document (1). The subject-matter of claim 1 of auxiliary request 1 was novel, but lacked inventive step. The subject-matter of auxiliary request 2 was held to comply with the requirements of the EPC.

Claim 1 of auxiliary request 2 reads as follows:

"1. A composition comprising an aryl urea compound which is a raf kinase inhibitor and (a) a cytotoxic agent or (b) a cytostatic agent (c) or a pharmaceutically acceptable salt of (a) or (b) wherein said aryl urea compound is a tosylate salt of N-(4-chloro-3-(trifluoromethyl)phenyl-N'-(4-(2-(N-methyl-carbamoyl)-4-pyridyloxy)phenyl)urea." (hereinafter sorafenib tosylate)

Independent claims 12, 25 and 26 are directed to the use of the claimed composition for the manufacture of a medicament for the treatment of cancer.

IV. With the statement of grounds of appeal, appellant 1 submitted a main request and auxiliary requests 1 and 2. The main request and auxiliary request 1 were subsequently withdrawn (see point IX below). Auxiliary

request 2 is identical to auxiliary request 2 underlying the decision under appeal.

- V. With the statement of grounds of appeal, appellant 2 submitted documents (14) to (21).
- VI. In reply to appellant 2's statement of grounds of appeal, appellant 1 submitted document (22).
- VII. In a communication accompanying the summons to oral proceedings, the board expressed its preliminary opinion. In particular, it drew attention to certain issues that would have to be discussed with regard to novelty and inventive step. Documents (23) and (24) were introduced into the proceedings, in support of the skilled person's common general knowledge.
- VIII. With letter dated 14 February 2017, appellant 1 filed an auxiliary request 3
- IX. At the beginning of the oral proceedings before the board, appellant 1 withdrew the main request and auxiliary request 1 (see point III above). Auxiliary request 2 (see point III above) was its new main request, and auxiliary request 3 (see point VIII above) was the sole auxiliary request. That the version as considered allowable by the opposition division had become appellant 1's new main request amounted to a withdrawal of appellant 1's appeal and to a change of its main procedural request into the dismissal of appellant 2's appeal (for practical reasons, the designation of the parties as appellant 1 and 2 was maintained).

- X. Appellant 1's arguments, as far as they relate to the decisive issues of the present decision, can be summarised as follows:

Admission of documents (14) to (21)

These documents should not be admitted pursuant to Article 12(4) RPBA. They were late-filed and not more relevant than those already on file. The present main request had already been filed as auxiliary request 2 before the oral proceedings before the opposition division took place. The claimed subject-matter had not been changed during these proceedings.

Novelty

The subject-matter of the main request was novel over document (1). Sorafenib tosylate was not disclosed therein. A selection from two lists was required to arrive at this compound (see list of aryl ureas on page 76 to 88 and list of addition salts on page 6, lines 11 to 25 or claim 54). Moreover, document (1) did not disclose combinations of sorafenib tosylate with a cytostatic or cytotoxic agent. Even if the skilled person understood the passage on page 10, lines 13 to 14 as disclosure for potential combinations of different (cytotoxic/cytostatic) aryl ureas, such combinations would require a further selection. The "active ingredients" also mentioned on page 10, lines 13 to 14 could not be equated with "cytotoxic or cytostatic ingredients". Document (14) was not novelty destroying for essentially the same reasons.

Inventive step

Document (1) was a suitable starting point for the assessment of inventive step. The claimed subject-matter differed from the disclosure of document (1) in that sorafenib tosylate was used and that it was combined with a further cytotoxic/cytostatic agent. These distinguishing features resulted in two different effects. The use of sorafenib tosylate improved the solubility and consequently the bioavailability of sorafenib, as was apparent from documents (22) and (25). In particular, document (25) provided evidence that not every salt improved the dissolution rate compared to sorafenib free base. The second effect was the improved efficacy of the claimed combination (i.e. at least additive effects on tumour growth suppression and improvements on tumour regression) while at the same time being well-tolerated. In cancer therapy, striking a good balance between efficacy and tolerability was of particular importance. The second effect was supported by the results provided in the examples and the figures of the patent in suit. Example 2 did not show a clearly additive effect on tumour growth suppression. However, it demonstrated clear improvements in tumour regression compared to each component alone.

The problem to be solved by the present invention could therefore be defined as the provision of a composition having improved activity and bioavailability while being well-tolerated.

As shown in the examples, this problem was solved. No evidence to the contrary was provided by appellant 2.

Document (1) did not provide any pharmacological data. Furthermore, the good balance between efficacy and tolerability was not foreseeable for the skilled person

bearing in mind that improvements in efficacy was generally accompanied by increased side effects as apparent from document (7) (see in particular, page 336, left-hand column, line 24 to 31). The guidelines provided in this document were of a very general nature and not helpful in finding combinations which were at the same time highly effective (i.e. additive effects) and well-tolerated. Furthermore, an additive effect already exceeded all expectations.

Document (17) and (19) were also not helpful in this respect. They did not disclose sorafenib, let alone sorafenib tosylate, or mention combination therapy. Rather, they referred to a compound BAY 43-9006 and its usefulness in cancer treatment. Document (20), allegedly cited in document (19) and relied on by appellant 2 as evidence that BAY 43-9006 was sorafenib, had no publication date. However, even if document (20) was pre-published, it merely showed that BAY 43-9006 was sorafenib free base. The arguments provided with regard to document (1) as the closest prior art also applied, if the assessment of inventive step started from document (19) as the closest prior art. Document (18) was post-published and document (21) was undated like document (20). They were therefore not relevant for the assessment of inventive step.

XI. Appellant 2's arguments, as far as they relate to the decisive issues of the present decision, can be summarised as follows:

Admission of document (14) to (21)

These documents should be admitted into the proceedings. They were filed in response to the decision under appeal and were particularly relevant

for the assessment of inventive step, as they provided evidence for the known pharmaceutical properties of sorafenib.

Novelty

The subject-matter of the main request lacked novelty over document (1). It disclosed sorafenib as an individual compound (see page 81, entry 42; claims 61 and 67). Sorafenib was also a cytostatic compound (see document (15)). According to claims 50 and 54 of document (1), the urea compounds could be in the form of a salt, including tosylate. Hence, only one selection from a single list of suitable salts was required. Sorafenib tosylate was therefore clearly and unambiguously disclosed. Furthermore, combinations of urea compounds and combinations with other active (i.e. antitumor) ingredients were disclosed on page 10 of document (1). A similar teaching could be found in document (14), which in addition disclosed the protonated form of sorafenib (see page 111, lines 1 to 15). To arrive at the claimed subject-matter only one selection (i.e. a different counter-ion) was required.

Inventive step

Document (1) was a suitable starting point for the assessment of inventive step. It disclosed sorafenib and suitable salts thereof, including tosylate. It also disclosed combinations of urea compounds or combinations of urea compounds with active ingredients. The protonated form of sorafenib, which circulated in the blood, irrespective of the way in which sorafenib was administered, was responsible for the activity as antitumor agent, as was apparent from document (16). The tosylate ion, which distinguished the claimed

subject-matter from document (1), did not contribute to this activity. Nor could it reduce any adverse effects, as it should not have any efficacy on its own. Hence, the distinguishing feature could not support an inventive step.

The examples and figures of the patent in suit did not demonstrate any improvements compared to the closest prior art (i.e. document (1)). In order to demonstrate a technical effect, which had its origin in the distinguishing feature of the claimed invention compared to the closest prior art (i.e. tosylate), sorafenib free base or any other salt in combination with one of the cytotoxic or cytostatic agents of examples 1 to 5 should have been compared with sorafenib tosylate in combination with the same cytotoxic or cytostatic agent. Such a comparison had not been provided. The examples and figures of the patent in suit also did not demonstrate any improvements for the specifically disclosed compositions. No synergistic effects were observed and not all examples showed an additive effect. A merely additive effect could not support an inventive step. In addition, an increase in weight loss was observed in examples 4 and 5. Moreover, it had not been shown that any improvements or surprising effects, if at all present, were achieved over the whole scope of the claims (see T 939/92).

The problem to be solved was therefore the provision of alternative compositions in the treatment of cancer.

The use of a salt of sorafenib, in particular tosylate, was obvious from document (1). The treatment with two different antitumor agents was equally obvious, as combination therapy was common practice in the field of

oncology to block different pathways of cell proliferation. It was common general knowledge that tumour cells were not homogenous and reacted differently to cytostatic agents. Therefore, the probability of a therapeutic success increased, if two or more active agents were used.

Furthermore, the efficacy of sorafenib was already known from clinical studies, as was apparent from document (17) published before the priority date of the patent in suit. It disclosed efficacy and tolerability of orally administered sorafenib in patients with advanced stage cancer. In 33% of the patients stabilisation was achieved. No critical adverse effects were observed. A summary of the results could be found in post-published document (18). Oral administration meant that sorafenib was protonated *in situ* and circulated in the body in protonated form. Selecting a suitable counter ion did not require inventive skills. Document (19) confirmed the inhibitory activity of sorafenib on tumour growth (Figure 4 on page 224). With regard to the structure of sorafenib or BAY 43-9006 reference was made to document (20), which was cited in document (19). A further report on the antitumor activity of orally administered sorafenib could be found in document (21), which was a poster contribution for the 92nd annual AACR conference. This conference took place between 24 and 28 March 2001 in New Orleans, Louisiana. Starting from each of the documents (17), (19) or (21) as the closest prior art, the use of sorafenib tosylate was obvious. With regard to the combination therapy the same arguments as before applied.

XII. Appellant 1 requested as a main request that appellant 2's appeal be dismissed, or alternatively,

whilst setting aside the decision under appeal, that the patent be maintained in amended form on the basis of the claims of the auxiliary request filed as auxiliary request 3 with letter dated 14 February 2017.

XIII. Appellant 2 requested that the decision under appeal be set aside and that the patent be revoked.

XIV. At the end of the oral proceedings, the decision of the board was announced.

Reasons for the Decision

1. The appeal is admissible.

2. Admission of documents (14) to (21) -
Article 12(4) RPBA

2.1 Appellant 1 objected to the admission of these documents in its reply to appellant 2's statement of grounds of appeal, without however providing any reasons for its objection, except that the documents were late-filed. Further substantiation was for the first time provided at the oral proceedings before the board, which arguments were nevertheless taken into account by the board since they did not raise any new or complex issues.

2.2 Documents (14) to (21) were filed by appellant 2 with the statement of grounds of appeal. Appellant 2 challenged the opposition division's findings on novelty and inventive step and filed these documents in an attempt to address certain aspects which were discussed in the decision under appeal. In particular, they were filed to support appellant 2's position on

novelty and to demonstrate that the antitumor efficacy and the tolerability of sorafenib were already known in the art and had been demonstrated in clinical studies. The lack of evidence for *in vivo* properties of sorafenib was apparently considered to be relevant by the opposition division (see page 14, point 4.5 of the decision under appeal). This aspect was not addressed in the opposition division's preliminary opinion, which only indicated that the presence of a synergistic effect might be crucial. In these circumstances, the board is of the opinion that the submission of documents (14) to (21) is an appropriate and legitimate attempt by appellant 2 to further support its position with respect to novelty and inventive step.

- 2.3 Hence, the board decided to admit documents (14) to (21) into the proceedings pursuant to Article 12(4) RPBA.

Main request

3. Amendments and sufficiency of disclosure

In the decision under appeal, the opposition division held that the subject-matter of auxiliary request 2, which is identical to the present main request, complied with Article 123(2), (3) and Article 83 EPC. The board has no reason to deviate from the opposition division's findings. They were also not contested by appellant 2.

4. Novelty (Article 54 EPC)

- 4.1 In the decision under appeal, the opposition division decided that the subject-matter of auxiliary request 2

was novel over document (1). This finding was challenged by appellant 2.

- 4.2 Claim 1 of the main request is directed to a composition comprising a tosylate salt of sorafenib and a cytotoxic or cytostatic agent or pharmaceutically acceptable salts thereof. The claimed compositions are useful in the manufacture of medicaments for the treatment of cancer (see claims 12, 25 and 26).

Appellant 2's reading of claim 1 as being directed to a composition comprising sorafenib tosylate, which is a raf-kinase and a cytostatic/cytotoxic agent is not accepted. Even if the linguistic structure of claim 1 were to be considered ambiguous, which in the board's opinion is not the case, the description of the patent in suit makes it unmistakably clear that the invention relates to combinations of raf-kinase inhibitors (i.e. aryl ureas such as sorafenib) with a (further) cytotoxic/cytostatic agent (see for example paragraph [0002] "field of invention" or paragraph [0005] "Summary of the invention").

- 4.3 Document (1) discloses urea compounds of the general formula $A-NH-C(O)-NH-L-(M-L^1)_q$ (formula I) and pharmaceutical salts thereof (see claims 1, 38 and 39). A list of more than one hundred individual compounds falling within general formula I is disclosed on pages 76 to 88. This list summarises the compounds that have been synthesised and includes sorafenib free base (see entry 42 on page 81). A limited list of more than twenty compounds, including sorafenib free base, is provided in claims 61 and 67.

On page 6, lines 11 to 25, document (1) discloses a list of thirty suitable pharmaceutically acceptable

salts of the urea compounds of formula I, including p-toluenesulfonic acid (tosylate). An almost identical list is present in claims 50 and 54, which refer back to urea compound of general formula I according to claims 1 or 39, respectively.

Furthermore, compositions with one or more (aryl urea) compounds in association with one or more non-toxic pharmaceutically acceptable carriers and, if desired, other active ingredients are referred to on page 10, lines 13 to 14.

4.4 However, the specific composition of a tosylate salt of sorafenib in combination with a cytotoxic or cytostatic agent as presently claimed is not directly and unambiguously disclosed in document (1). The board also notes that according to established jurisprudence of the boards of appeal subject-matter, which is the result of a specific combination requiring the selection of elements from several lists is normally regarded as novel. Applying this principle in the present case, the board concurs with the opposition division's finding that to arrive at the claimed subject-matter a triple selection is required:

- (a) selection of sorafenib from the list of compounds on page 76 to 88 or claims 61 and 67
- (b) selection of tosylate salt from the list of salts provided on page 6 or claims 51 and 54
- (c) selection of a combination as disclosed on page 10, lines 13 to 14

The subject-matter of claim 1 is therefore novel over document (1).

4.5 Appellant 2's argument that sorafenib tosylate is the result of only one selection is not accepted as it disregards that sorafenib free base is one individual member of a list of equal individual alternative members. Thus, to arrive at sorafenib tosylate a selection from two lists is required. Document (1) does not contain any specific disclosure leading the skilled person directly and unambiguously to that particular selection of salt and urea compound. Neither sorafenib nor tosylate is indicated as preferred.

For the aforementioned reason alone, the composition of claim 1 is not anticipated by the disclosure of document (1).

4.6 In its statement of grounds of appeal, appellant 2 also raised an objection of lack of novelty based on document (14). At the oral proceedings before the board, appellant 2 stated that this document was not more relevant than document (1). The board agrees. Similar to document (1), document (14) discloses a list of aryl ureas, including sorafenib free base (entry 42 on page 101, claim 12) and a list of pharmaceutically acceptable salts, including a tosylate (page 12, line 15 to page 13, line 2). It also refers to combinations with one or more (aryl urea) compounds or active ingredients (page 17, last line to page 18, line 2). Sorafenib tosylate, let alone sorafenib tosylate in combination with a cytostatic or cytotoxic agent is not directly and unambiguously disclosed for the same reasons as set out in points 4.4 and 4.5 above. Even if the biological assays on page 111 implicitly disclosed a protonated form of the urea compounds, as asserted by appellant 2 (for which however no evidence has been provided), a triple selection would still be required to arrive at the claimed compositions: selection of

protonated sorafenib, selection of a different counter ion (i.e. tosylate) and selection of a combination with cytostatic/cytotoxic agents.

4.7 The board therefore concludes that the subject-matter of independent claim 1, and for the same token that of independent claims 12, 25 and 26, is novel within the meaning of Article 54 EPC.

5. Inventive step (Article 56 EPC)

5.1 The board, in agreement with the parties, considers document (1) as a suitable starting point for the assessment of inventive step. As explained in point 4.3 above, it discloses urea compounds of general formula I or pharmaceutically acceptable salts thereof. The compounds are raf-kinase inhibitors and are suitable in the treatment of tumours and cancerous cell growth mediated by raf-kinase (see page 2, lines 10 to 20). Sorafenib free base is disclosed as one of many urea compounds. The use of compositions with one or more urea compounds or active, but otherwise undefined ingredients is suggested, but not specifically disclosed and no (*in vitro* or *in vivo*) data as to their performance, for example tolerability, efficacy, toxicity, etc. are provided.

5.2 At the oral proceedings before the board, appellant 1 defined the problem to be solved as the provision of a composition for the treatment of cancer with improved solubility, and consequently bioavailability, and improved efficacy, while at the same time being well-tolerated.

The solution proposed relates to sorafenib in the form of its tosylate salt in combination with a cytotoxic

and cytostatic agent. In order to demonstrate that the problem as defined has been solved, appellant 1 relied on the examples and the figures of the patent in suit and documents (22) and (25).

Appellant 2 defined the problem to be solved as the provision of alternative compositions.

5.3 Document (22) consists of two figures A and B, which graphically depict the result of dissolution experiments with sorafenib and sorafenib tosylate. It is clearly apparent from this document that the dissolution behaviour of sorafenib tosylate is improved compared to its free base. Furthermore, document (25), which graphically illustrates the drug release of tablets formulated with different sorafenib salts or the free base (see also appellant 1's letter dated 14 February 2017, page 6, table 1), shows that some salts, including tosylate, provide higher drug release than the free base, while the release rate of other salts is negligible and far below that of the free base.

5.4 The examples of the patent in suit describe *in vivo* studies in mice with tumour xenografts from various tumour lines (human colon carcinoma, human pancreatic carcinoma, human mammary tumour, and human non-small cell lung carcinoma), in which compound A, that is sorafenib tosylate (see paragraph [0072] of the patent in suit), has been administered in combination with different cytotoxic or cytostatic agents (irinotecan, gemcitabine, vinorelbine, doxorubicin and gefitinib) (see patent in suit examples 1 to 5).

From the results provided in the examples an additive effect on tumour growth suppression is apparent for the

combination products in examples 1 and 3 to 5. In example 2, the effect is not additive, but still considerably improved compared to the administration of each of the active agents alone. Furthermore, at least additive effects in partial or complete tumour regression are observed in examples 1, 2 and 5.

The flatter form of the curve for the combination products in figures 1 to 4 also shows that the increase in tumour mass over time is slower than for each of the active components alone, i.e. tumour growth is delayed.

At the same time, no or at least no unacceptable weight loss was observed and no lethalties were registered for the combination products, except in example 5 where one non-specific death occurred.

5.5 Appellant 2 disputed the presence of an additive effect, since the observed tumour growth suppression of the combination product in examples 2, 3 and 5 was less than the sum of the tumour growth suppression for each of the components alone.

However, the board notes that in examples 3 and 5, these values are practically identical (cf. example 3: 136% (sum) vs 133% (combination); example 5: 319% (sum) vs 314% (combination)). In example 2, the tumour growth suppression value of the combination is indeed lower than the sum of suppression values for each component alone (cf. 222% (combination) vs 266% (sum)). However, the combination is associated with an improvement in tumour regression, not observed in the administration of each of the components alone. The board therefore concurs with appellant 1 that all examples show improved antitumor efficacy.

In this context, the board also notes that by focusing on efficacy alone, appellant 2 neglects that the compositions are not only highly effective, but at the same time also sufficiently well-tolerated, as is apparent from the data regarding weight loss and lethality.

5.6 Appellant 2's argument that the additive effect was not shown over the whole breadth of the claims (see T 939/92) and could therefore not be taken into account for the formulation of the problem to be solved is not accepted in view of a) the results provided in the examples of the patent in suit which demonstrate improved efficacy and acceptable tolerability of sorafenib with a variety of different cytostatic or cytotoxic compounds in a number of different types of cancer and b) the complete absence of any evidence or convincing arguments in support of appellant 2's contention. The board notes that the test report filed by appellant 2 (document (16)) is not relevant in this context, as it merely shows efficacy and tolerability of sorafenib free base at higher doses than those used for sorafenib tosylate in examples 1 to 5 of the patent in suit.

5.7 Appellant 2 also disputed the significance of the data provided by appellant 1. In particular, it criticised that no comparison had been made with the closest state of the art (see point XI above).

However, the board considers that, in the present case, the data provided by appellant 1 fairly reflect the effects related to the features, which distinguish the claimed subject-matter from the disclosure of document (1). Documents (22) and (25) show improved solubility of sorafenib tosylate compared to sorafenib

free base disclosed in document (1) and the examples of the patent in suit demonstrate a good balance of efficacy and tolerability of sorafenib tosylate in combination with cytotoxic/cytostatic agents.

- 5.8 For the above reasons, the board agrees with appellant 1's definition of the technical problem as formulated in point 5.2 above. Based on the study results reported in examples 1 to 5 of the patent in suit and the evidence provided in documents (22) or (25), the board is also satisfied that this problem has been solved.
- 5.9 It then remains to be decided whether or not the proposed solution is obvious in view of the prior art.
- 5.9.1 As set out above, document (1) does not put any emphasis on a particular compound, salt or combination. Moreover, it does not contain any experimental data whatsoever concerning efficacy, toxicity, tolerability, compatibility, etc., of any of the urea compounds disclosed therein, let alone any information as to their potential behaviour in combination. Hence, the skilled person cannot find any information in that document from which it can be inferred that sorafenib tosylate in combination with cytotoxic/cytostatic agents would be a highly effective and at the same time well-tolerated. Hence, document (1) on its own cannot render the claimed subject-matter obvious.
- 5.9.2 According to appellant 2, the use of two or more cytostatic/cytotoxic agents was common practice in cancer treatment. Improvements were expected, particularly if antitumor agents which were involved in different biological pathways were used.

5.9.3 The board agrees with appellant 2 insofar as combination therapy is known in cancer treatment, as can be seen from document (7) (see page 335, right hand column, last paragraph to page 337, right hand-column, line 15). This document also provides some general guidelines for the selection of drugs in the most effective drug combinations, which however requires knowledge of a drug's properties, such as efficacy and toxicity. Moreover, document (7) indicates that improvement in efficacy is often compromised by a wider range of side-effects (see page 336, left-hand column, second complete paragraph). Optimal dose and schedule of the drugs are also relevant. In the board's judgment, document (7) provides some useful guidelines for combining drugs which are already well-established in cancer treatment. However, even for those drugs it does not provide the skilled person with sufficient guidelines how to obtain in a targeted manner a drug combination which is highly effective and at the same time well-tolerated.

5.9.4 With regard to appellant 2's argument that the efficacy and tolerability of sorafenib were already known in the art, as was apparent from documents (17) and (19), the board notes the following:

These documents report on results of *in vitro* and *in vivo* assays and preliminary results of an ongoing phase I clinical pharmacokinetic and pharmacodynamic study of a raf-kinase inhibitor, designed to find dose limiting toxicities, determine the maximum tolerated dose, characterise the pharmacokinetic profile and provide some preliminary evidence as to the efficacy of a compound identified as BAY 43-9006. This compound is described as a potent raf-kinase and, based on first preliminary results, so far appears to be effective and

well-tolerated. However, neither document (17) nor document (19) discloses the chemical name or structure of BAY 43-9006. Document (20), which according to appellant 2 provided the missing information, identifies BAY 43-9006 as N-3-trifluoromethyl-4-chlorophenyl)-N'-(4-(2-methylcarbamoyl-pyridin-4yl)oxyphenyl)urea, which is sorafenib free base. However, this document has no publication date. Appellant 2 argued that document (20) reflected a poster that had been shown on the 92nd AACR Meeting, which took place in March 2001. However, in the absence of any evidence as to whether the poster that had been shown at this meeting is in fact identical to the content of document (20), the appellant's contention that the structure of BAY 43-9006 was known in the art cannot be accepted.

However, irrespective of whether the structure of BAY 43-9006 was known to be sorafenib free base, in the board's judgement, based on the limited preliminary results of a still ongoing clinical study, no conclusion can be drawn as to the potential behaviour of this compound or any of its salts in combination therapy. Based on the available information, the skilled person could not have reasonably expected that sorafenib tosylate in combination with cytostatic/cytotoxic agents would exhibit such a good balance between efficacy and tolerability. Accordingly, the solution to the above technical problem as claimed in claim 1 of the main request is not obvious for the person skilled in the art. This finding also applies, if any of documents (17) or document (19) were used as a starting point for the assessment of inventive step.

Appellant 2's argument that a sorafenib salt was implicitly disclosed in documents (17) or (19), because

sorafenib would circulate in the blood in protonated form if administered to the body, is not accepted in the absence of any evidence in this respect.

- 5.9.5 With regard to documents (18) and (21), the board concurs with appellant 1 that these documents are not relevant in the assessment of inventive step. Document (18) is post-published and document (21) has no publication date.
- 5.10 In view of the finding in point 5.9.4 above, it is not necessary to discuss whether or not the formation of a tosylate salt, which increases the solubility, and consequently the bioavailability, of sorafenib was an obvious measure for the skilled person.
- 5.11 For the aforementioned reasons, the board concludes that the subject-matter of claim 1 of the main request, and for the same token that of claims 12, 25 and 26, involves an inventive step pursuant to Article 56 EPC.
- 5.12 Having come to the conclusion that the present main request complies with the requirements of the EPC, it is not necessary to decide on the sole auxiliary request.

Order

For these reasons it is decided that:

Appellant 2's appeal is dismissed.

The Registrar:

The Chairman:



M. Schalow

A. Lindner

Decision electronically authenticated