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**Datasheet for the decision
of 3 June 2015**

Case Number: T 1577/11 - 3.3.01
Application Number: 02783305.2
Publication Number: 1455781
IPC: A61K31/4196, A61P35/00
Language of the proceedings: EN

Title of invention:

USE OF ANASTROZOLE FOR THE TREATMENT OF POST-MENOPAUSAL WOMEN
HAVING EARLY BREAST CANCER

Patent Proprietor:

AstraZeneca AB

Opponents:

Hexal AG
Alfred E. Tiefenbacher GmbH & Co. KG
STADA Arzneimittel AG
Helm AG
Teva Pharmaceutical Industries Ltd.

Headword:

Estrogen synthesis inhibitor anastrozole in early breast
cancer/ASTRAZENECA

Relevant legal provisions:

EPC Art. 56
RPBA Art. 13

Keyword:

Inventive step - reasonable expectation of success (yes)
Late-filed auxiliary request - admitted (no)

Decisions cited:

G 0002/08, T 0918/01

Catchword:



**Beschwerdekammern
Boards of Appeal
Chambres de recours**

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Case Number: T 1577/11 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 3 June 2015

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Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted on 12 May 2011
revoking European patent No. 1455781 pursuant to
Article 101(3) (b) EPC.**

Composition of the Board:

Chairman A. Lindner
Members: G. Seufert
L. Bühler

Summary of Facts and Submissions

- I. The patent proprietor (appellant) lodged an appeal against the decision of the opposition division revoking European patent No. 1 455 781.
- II. The present decision refers to the following documents:
- (3) AU Budzar, *British Journal of Cancer*, Vol. 85 (Supplement 2), 2001, pages 6 to 10
 - (4) M. Baum, *Endocrine-Related Cancer*, Vol. 6, 1999, pages 231 to 234
 - (6) J. Bonneterre *et al.*, *Cancer*, Vol. 92, No. 9, 2001, pages 2247 to 2258
 - (7) Early Breast Cancer Trialists' Collaborative Group, *The Lancet*, Vol. 351, 1998, pages 1451 to 1467
 - (25) Declaration by M. Baum, dated 19 May 2009, filed by opponent 5 with notice of opposition, four pages
 - (26) Declaration of R. Ben Yosef, dated 24 May 2009, filed by opponent 5 with notice of opposition, five pages
 - (28) M. Baum, *Breast Cancer Research*, Vol. 4, No. 6, 2002, pages 213 to 217
 - (30) Statutory Declaration by J. Lindemann, dated 4 February 2011, filed by the patent proprietor with letter dated 4 February 2011, three pages
 - (32) E. Van Cutsem *et al.*, *Journal of Clinical Oncology*, Vol. 29, No. 1, 2011, pages 1 to 4
 - (33) Sanofi-aventis Press Release of 27 January 2011, two pages
 - (35) Statutory Declaration by A. Bhatnagar dated 26 January 2011, filed by opponent 1 with letter dated 28 January 2011, three pages
 - (38) A. Goldhirsch *et al.*, *Journal of Clinical*

Oncology, Vol. 19, No. 18, 2001, pages 3817
to 3827

- III. Notices of opposition were filed by opponents 1 to 5 (respondents 1 to 5) requesting revocation of the patent in its entirety on the grounds of lack of novelty and inventive step, and of insufficiency of disclosure (Article 100(a) and (b) EPC). In addition, opponent 5 requested revocation of the patent on the grounds that the claimed subject-matter was not patentable under Article 100(a) in combination with Article 53(c) EPC.
- IV. The opposition division held that the claimed invention was sufficiently disclosed and patentable under the provisions of Article 53(c) EPC in accordance with decision G 2/08. The subject-matter of the main request and sole auxiliary request was considered to be novel, but to lack inventive step starting from document (4) as the closest state of the art. In particular, the division considered that the skilled person had a reasonable expectation that the use of anastrozole would be more efficacious than tamoxifen in the treatment of early breast cancer.
- V. With the statement of grounds of appeal, the appellant resubmitted the main request underlying the decision under appeal and filed auxiliary requests 1 to 3, which were subsequently renumbered as auxiliary requests 2 to 4 (see point VI below).

Independent claims 1 and 2 of the main request read as follows:

"1. The use of anastrozole, or a pharmaceutically acceptable salt thereof, in the preparation of a

medicament for the reduction of the rate of recurrence of cancer in a post-menopausal woman having early breast cancer wherein the anastrozole is provided in the absence of tamoxifen."

"2. The use of anastrozole, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the reduction of the rate of a new contralateral primary tumour in a post-menopausal woman having early breast cancer wherein the anastrozole is provided in the absence of tamoxifen."

In auxiliary request 2 the feature "**and wherein the woman having said early breast cancer is oestrogen receptor positive and/or progesterone receptor positive**" has been introduced into the independent claims 1 and 2.

Auxiliary request 3 differs from the main request in that independent claim 1 has been deleted.

Auxiliary request 4 differs from auxiliary request 2 in that independent claim 1 has been deleted.

VI. At the oral proceedings before the board, the appellant filed a new auxiliary request 1. The previous auxiliary requests 1 to 3 were maintained as auxiliary requests 2 to 4 (see point V above).

Independent claims 1 and 2 of auxiliary request 1 differ from the main request in that the expression "**versus tamoxifen**" has been introduced between the "rate of recurrence of cancer" (claim 1) or "rate of a new contralateral primary tumour" (claim 2) and the expression "in a post-menopausal woman".

VII. The arguments provided by the appellant as far as they are relevant for the decision can be summarised as follows:

- Inventive step

The choice of the closest state of the art and the formulation of the problem to be solved by the opposition division were accepted. The data provided in the patent in suit showed that this problem was solved by using the drug anastrozole. This solution was not obvious, because the skilled person had no reasonable expectation that anastrozole would be more efficacious than tamoxifen, which at the time the invention was made was the gold standard in endocrine treatment of early breast cancer. The ATAC trial, which was set up to compare anastrozole alone, or in combination with tamoxifen, with tamoxifen alone was evidence for a certain hope to succeed, which however was not to be confused with a reasonable expectation of success.

The anastrozole arm of the ATAC trial was set up as a "non-inferiority trial" (see document (25)) designed to demonstrate that the test product was not worse, in terms of efficacy, than the comparator. This was a clear indication that superior efficacy of anastrozole was not expected.

The ATAC trial was the first of its kind. Thus, the skilled person could not rely on any studies to make presumptions on the outcome of the ATAC trial. The statements in documents (3) and (4) had to be evaluated in the light of this fact. As far as the outcome of the trial was concerned, a high degree of uncertainty and unpredictability existed (see document (30)). This was

also apparent from the surprising findings referred to in document (28).

The superior efficacy of anastrozole with respect to time-to-progression and tolerability in advanced breast cancer was neither proof nor a reliable indication that the same superiority was to be expected in the treatment of early breast cancer. Advanced and early breast cancer were different diseases requiring completely different clinical settings (see document (30)). The former could not be removed by surgery and the aim of the endocrine treatment was to alleviate symptoms, to prolong survival by disease remission or stabilisation, or to improve quality of life. In early breast cancer the tumour could be removed and the aim of endocrine treatment was to eradicate occult metastases and to prevent new primary contralateral tumours. Furthermore, the two diseases had a completely different time frame and showed a different pattern of resistance. As a consequence of the fundamental differences between advanced and early breast cancer, extrapolation of the results of the treatment of one disease to the other was impossible. This was confirmed by document (32), which showed that, contrary to expectation, the drug bevacizumab failed in clinical trials to prolong disease free survival in patients with early stage cancer. Another failure of a phase III trial was reported in document (33)

Furthermore, in view of the long-term treatment required in early breast cancer, the safety and tolerability of anastrozole was still a concern. Adverse effects on bone mineral density and the cardiovascular system might occur, as indicated in documents (3) and (4).

The statements in documents (3) and (4) were far too general. No conclusion as to an improvement in the reduction of the rate of recurrence and reduction of the rate of new contralateral primary tumours compared with the gold standard tamoxifen was possible. On the contrary, in view of the different modes of action of anastrozole, which inhibited the synthesis of estrogen, and tamoxifen, which was an estrogen receptor inhibitor, expectation of success only existed for the combination of anastrozole and tamoxifen. For these reasons the combination arm of the ATAC trial was set up as a superiority trial. Surprisingly, the combination arm did not show the expected superior efficacy, which was confirmed by document (28). This was a clear indication that it was impossible to make safe predictions as to the efficacy of anastrozole in the treatment of early breast cancer compared to tamoxifen.

The ipsilateral recurrence of the cancer and the occurrence of new contralateral breast primaries were different types of early breast cancer. Documents (3) or (4) were silent on the formation of contralateral tumours. Thus, no expectation with respect to the reduction of these tumours existed. Moreover, as shown in document (28), it came as a complete surprise even for the experts in the field that the use of anastrozole reduced the formation of contralateral breast primaries so efficiently.

The additional feature in auxiliary request 2 had no influence on the assessment of inventive step.

- Admission of new auxiliary request 1

Auxiliary request 1 should be admitted. It was filed in response to the preceding discussion, in particular in response to a new argument by respondents 2 and 3, and did not change the subject-matter which was discussed previously.

VIII. The arguments provided by the respondents, as far as they are relevant for the decision, can be summarised as follows:

- Inventive step

Starting from document (4) as the closest state of the art, the problem to be solved was the provision of an improved treatment, in terms of efficacy, tolerability and/or quality of life, of early breast cancer in post-menopausal women. The use of anastrozole was obvious for the skilled person. Based on the known superior efficacy of anastrozole in advanced breast cancer treatment, the same was expected in the treatment of early breast cancer. This was already clearly apparent from document (4) and confirmed by document (3).

Advanced and early breast cancer were different stages of the same disease and the underlying mechanism for the progression of this disease was the same, as confirmed by documents (25), (26) and (35). Proliferation of the tumour cells was stimulated by estrogen. Removal of this stimulus suppressed proliferation. This was the reason why the use of tamoxifen was successful in the treatment of both advanced and early breast cancer. For the same reason it was expected that anastrozole, an estrogen synthesis inhibitor with superior efficacy in the treatment of advanced breast cancer, would also be superior in early

breast cancer. Document (32) was irrelevant in this context, since it was concerned with a different type of cancer. Furthermore, it was filed in January 2011 and could not be used as evidence of what the skilled person would have thought in the year 2001.

The set-up of the anastrozole arm of the ATAC trial as a non-inferiority trial did not represent evidence that the skilled person merely expected anastrozole to be equivalent to tamoxifen. In view of its better tolerability it was sufficient to show that anastrozole was at least as efficacious as tamoxifen. Moreover, since, according to document (3), it was the purpose of the ATAC trial to determine whether the known superiority of anastrozole in advanced breast cancer would also translate into the early disease, it followed that the results of this trial could also show superior efficacy irrespective of how it was set up.

In the assessment of inventive step certainty of success was not required and actual clinical data were not necessary in order to show that a reasonable expectation of success existed (T 918/01). The fact that in the end the combination of anastrozole and tamoxifen turned out to be no better than anastrozole alone was no proof for the absence of an expectation of superiority for anastrozole alone, in particular since these results were not available to the skilled person until after the priority date.

In addition, the problem as defined by the appellant was not solved over the whole scope of the claims, since estrogen and/or progesterone receptor negative patients would not profit from endocrine treatment. Furthermore, the results in the patent only reflected first line treatment. No results were available with

regard to subsequential treatment, although such treatments were also covered by the claims (see patent in suit, paragraph [0019]).

Independent claim 2 was directed neither to the treatment of a different disease nor to a different group of patients, since it was impossible to separate patients who would experience ipsilateral recurrence of the cancer from those that would experience formation of contralateral primary tumours. The purpose of endocrine treatment was to prevent the cancer coming back, irrespective of where it came back. The formation of contralateral tumours was just a different end point, as could be seen from document (7). Furthermore, as was apparent from document (4), the ATAC trial also considered the formation of new breast primaries. The fact that the efficacy with respect to the reduction of the rate of contralateral primary tumours was higher than expected was a mere bonus effect.

The additional feature in auxiliary request 2 did not change the arguments. Patients with hormone-sensitive breast cancer were the obvious target group for endocrine treatment.

- Admission of new auxiliary request 1

Auxiliary request 1 should not be admitted into the proceedings. It was filed at a very late stage of the proceedings and addressed an issue, namely the understanding of claims 1 and 2, which had already been raised in the first instance proceedings. Moreover it raised potential new issues under Article 123(2) and (3) and Articles 84 and 83 EPC. The new argument, which had allegedly been advanced by respondents 2 and 3 at the oral proceedings before the board, could

already be found in their reply to the statement of grounds of appeal.

- IX. The appellant requested that the contested decision be set aside and that the patent be maintained on the basis of the claims of the main request filed with the statement of grounds of appeal, or, alternatively, of auxiliary request 1, filed during the oral proceedings of 3 June 2015, or, alternatively, of one of auxiliary requests 2 to 4, filed as auxiliary requests 1 to 3 with the statement of grounds of appeal.
- X. Respondents 1 to 5 requested that the appeal be dismissed.
- XI. At the end of the oral proceedings the decision of the board was announced.

Reasons for the Decision

- 1. The appeal is admissible
- 2. Novelty and sufficiency of disclosure (Articles 54 and 83 EPC)
 - 2.1 In the decision under appeal, it was acknowledged that the invention was sufficiently disclosed, that the priority was validly claimed and that the subject-matter was novel over the prior art. These findings were challenged by the respondents.
 - 2.2 Given the negative outcome concerning inventive step (see points 3 and 4 below), starting with document (4), which had not been considered novelty-destroying, a decision on these issues is not necessary.

Main request

3. Inventive step (Article 56 EPC)

3.1 Claims 1 and 2 of the main request are in the form of a "Swiss-type" claim and relate to the use of anastrozole for the reduction of the rate of recurrence of cancer or for the reduction of the rate of a new contralateral primary tumour in post-menopausal women with early breast cancer. The treatment is further characterised in that anastrozole is provided in the absence of tamoxifen.

3.2 The board, in accordance with the opposition division and the parties, considers document (4) as a suitable starting point for the assessment of inventive step.

This document discloses in its introductory part the use of the antiestrogen tamoxifen in endocrine treatment of advanced and early breast cancer in post-menopausal women (see abstract; page 231, left column, first paragraph). In early breast cancer treatment, tamoxifen reduces the recurrence rate and mortality in women with estrogen receptor positive and estrogen receptor unknown tumours.

3.3 The board also agrees with the opposition division and the appellant that, in view of the closest state of the art, the problem to be solved is the provision of means for reducing the rate of recurrence of cancer and the rate of formation of a new contralateral primary tumour in post-menopausal women with early breast cancer in a more efficacious way.

3.4 The proposed solution is the use of anastrozole.

Having regard to the experimental results reported in the patent in suit (see paragraphs [0048] to [0050] and the respective Figures 1 to 4 and Tables 1 to 3 of the patent in suit), and in the absence of evidence to the contrary, the board is satisfied that the aforementioned problem is plausibly solved.

The board notes that endocrine treatment is more likely to provide benefits to patients who are estrogen and/or progesterone receptor positive. However, this does not mean that patients who are receptor negative could not also benefit from such treatment, albeit to a much lesser extent (cf. document (7), section entitled "Hormone receptors" on pages 1463 and 1464). Concerning the alleged lack of superior efficacy of anastrozole in second or third line treatment advanced by respondent 5, the board notes that this allegation is speculative and not substantiated by any facts.

- 3.5 It remains to be decided whether the proposed solution is obvious to the skilled person in the light of the prior art.
- 3.5.1 Document (4) not only discloses the use of tamoxifen in early and advanced breast cancer, but also describes the use of aromatase inhibitors, such as anastrozole, in endocrine treatment of advanced breast cancer in post-menopausal women. Anastrozole has shown tolerability and efficacy advantages over standard treatment (see document (4), abstract). Furthermore, it lacks the partial estrogen agonistic activity of tamoxifen, with the consequence that effects on the endometrium and tumour stimulation seen with tamoxifen would not be expected (see document (4), abstract). Moreover, document (4) also discloses that anastrozole

is being investigated in a clinical trial (ATAC) with several thousand patients with early breast cancer. The trial is designed to compare the efficacy (time to recurrence, time to distant recurrence, incidence of new breast primaries and survival) and safety of tamoxifen with anastrozole and with the combination of tamoxifen and anastrozole (see page 232, right-hand column, penultimate paragraph). Finally, on page 233, right-hand column, last four lines of the penultimate paragraph, it is stated that "This rapid recruitment reflects both the need for improvement in breast cancer treatment and the **expectation** that the new generation aromatase inhibitors will **improve efficacy,** tolerability and/or quality of life (emphasis added by the board)."

3.5.2 The teaching of document (4) is confirmed by document (3), which discloses the superiority of anastrozole over tamoxifen in terms of time to disease progression in the treatment of patients with advanced breast cancer (page 8, left-hand column, last paragraph to page 9, left hand-hand column, first complete paragraph). Moreover, on page 9, left-hand column, last paragraph, it is stated "Given anastrozole's superior efficacy compared with tamoxifen in advanced disease, it was postulated that anastrozole would be superior in the treatment of the early disease. Tolerability assumes greater importance in the adjuvant setting when the duration of therapy extends to 5 years. Anastrozole's improved side-effect profile compared with tamoxifen particularly in term of thromboembolic events and vaginal bleeding, makes it an attractive candidate for such use."

3.5.3 In summary, at the time the invention was made, the use of tamoxifen in the treatment of advanced and early

breast cancer was well known in the art. The skilled person was also aware of the superiority of anastrozole over tamoxifen in the endocrine treatment of advanced breast cancer, and the expectation attached thereto for the treatment of early breast cancer. In other words, the skilled person would have had a reasonable expectation that anastrozole would be more efficacious than tamoxifen in the endocrine treatment of early breast cancer.

3.5.4 According to the appellant, the skilled person had no such expectation. One of the main reasons was that advanced and early breast cancer were two different diseases, which required different clinical management (see point VII above). Thus, extrapolation of results from advanced to early breast cancer treatment was not possible. In support of its arguments, the appellant relied on document (25), point 6, and on document (32), page 1, left-hand column, lines 1 to 16).

3.5.5 The board is of the opinion that advanced and early breast cancer are not different diseases, but different stages or phases of progression of the same disease, namely breast cancer. It is not contested that these different stages require different clinical management. However, at the time the invention was made it was commonly believed that the mechanism underlying the progression of advanced breast cancer and the mechanism underlying the recurrence of early breast cancer was the same. In both stages/phases proliferation of the tumour cells - in early breast cancer of undetectable micrometastatic (occult) tumour cells - is stimulated by estrogen. By removing this stimulus either by reducing the synthesis of estrogen (for example with aromatase inhibitors such as anastrozole) or by blocking the estrogen receptor (for example with

tamoxifen) this proliferation is suppressed or delayed. This was believed to be the reason for the efficacy of the antiestrogen tamoxifen in the treatment of both advanced and early breast cancer. By analogy, the estrogen synthesis inhibitor anastrozole, which has been shown to exhibit superior efficacy in advanced breast cancer compared with tamoxifen, was expected to exhibit similar advantages in the treatment of early breast cancer (see document (25), points 6 and 7); document (26), point 7; document (35), points 8 to 10).

In point 6 of document (25), on which the appellant relied as evidence of the difference between advanced and early breast cancer, Professor Baum expressed his personal belief that the mechanism by which advanced breast cancer progressed and early breast cancer relapsed were biologically dissimilar. However, he also emphasised that this was not the prevailing opinion at the time the invention was made. On the contrary, according to Professor Baum, the most predominant thought in the scientific community of breast cancer oncologists was that the mechanism was the same and that, accordingly, the mechanism used by anastrozole for reducing or slowing down cancer cell growth is the same, whether in the treatment of advanced or early breast cancer (see document (25), points 6 and 7). The appellant's argument that the experts were divided in their opinion as to the underlying mechanism cannot therefore be accepted.

Document (32) was published almost ten years after the priority date of the present invention and concerns a different type of cancer, namely colon cancer. Its results cannot be used to establish what the skilled person would have thought with respect to advanced and early breast cancer at the time the invention was made.

The same applies with respect of document (33), which was published in the same year as document (32).

- 3.5.6 In this context, the appellant also argued that the skilled person would have been very reluctant to use anastrozole, because it might exhibit serious side-effects in the long term treatment which is required for early breast cancer. In support of its argument, the appellant relied on document (3), page 9, right-hand column, third paragraph and document (4), page 233, right-hand column, line 3 ff.
- 3.5.7 Documents (3) and (4) indeed mention potential adverse effects of aromatase inhibitors, for example on bone mineral density or the cardiovascular system. However, such potential side-effects are not a deterrent which would have prevented the skilled person from replacing tamoxifen with anastrozole in the treatment of early breast cancer. In fact, it is the same potent estrogen synthesis inhibiting activity that provides the beneficial effects and the aforementioned side-effects and, as with any drug, it will be the task of the clinician/oncologist to assess whether the benefits of using anastrozole outweigh the risks of using it.

Furthermore, in the present case, the partial estrogen agonistic activity of tamoxifen is known to contribute to endometrial cell proliferation and breast tumour stimulation. Anastrozole, which lacks this activity, would therefore present itself to be more suitable than tamoxifen for the prolonged treatment required for early breast cancer (see document (4), abstract; document (3), last paragraph of the section entitled "Introduction").

- 3.5.8 According to the appellant, a further clear indication that a person skilled in the art had no reasonable expectation of success was the fact that the ATAC trial was set up as a "non-inferiority" trial (see point VII above).
- 3.5.9 However, such a set-up is not conclusive evidence for the absence of a reasonable expectation of the superiority of anastrozole over tamoxifen. An equally satisfactory explanation is that a "superiority" trial was simply not necessary, because showing that anastrozole is at least as efficacious as tamoxifen would already have been a positive result, given the known favourable toxicity profile of anastrozole compared with tamoxifen (see document (25), point 12). Furthermore, document (3) states in the last paragraph on page 10 that the favourable profile, together with its superiority over tamoxifen in advanced breast cancer, makes anastrozole a suitable agent for the assessment of its effectiveness in the treatment of early breast cancer. The results of the ATAC trial will determine if its superiority over tamoxifen in advanced breast cancer will also translate into early breast cancer. Thus, irrespective of the set-up, evaluation of the results of the ATAC trial could apparently also establish the superiority of anastrozole over tamoxifen.
- 3.5.10 Furthermore, the appellant argued that the ATAC trial was the first of its kind (see document (28), page 214, left-hand column, fourth paragraph; document (30), page 3) and that it was not possible to predict the actual outcome, in particular whether or not an aromatase inhibitor, such as anastrozole, might be able to replace tamoxifen, which had been the gold standard in the treatment of early breast cancer for many years.

As was apparent from document (28) (see page 215, left-hand column, first complete paragraph and right-hand column, first complete paragraph; page 216, left-hand column, first complete paragraph and left-hand paragraph, "Conclusion") and document (30) (last paragraph), the treatment of early breast cancer was not a field where safe predictions could have been made. Moreover, specialists in breast cancer emphasised shortly before the priority date of the patent in suit that the use of anastrozole was not indicated outside the framework of clinical trials (see document (38), page 3823, right-hand column, lines 7 to 18).

3.5.11 However, according to the established jurisprudence of the boards of appeal, which clearly distinguishes between reasonable expectation of success and certainty of success (see T 918/01 of 6 October 2004, point 9.1 of the reasons), certainty of success is not required. In order to render a solution obvious, it is sufficient to establish that a skilled person would have followed the teaching of the prior art with a reasonable expectation of success. In the present case, based on the disclosure of documents (3) and (4) and the generally accepted belief in a common mechanism by which advanced and early breast cancer progressed (see points 3.5.1, 3.5.2 and 3.5.5 above) and by which the cancer could therefore be treated, reasonable expectation was given, in spite of the understandable uncertainties which are always present in the field of biological research. The advice in document (38) reflects the cautious approach of oncologists in the absence of actual clinical data. It does not constitute evidence that there was no reasonable expectation of success.

3.5.12 In this context, the appellant also pointed out that the failure of the ATAC trial to show the expected improvement for the combination of anastrozole and tamoxifen was a further clear indication that safe predictions as to the superior efficacy of anastrozole was impossible (see document (28), page 215, right-hand column, first three lines of the second complete paragraph).

3.5.13 As explained in point 3.5.11 above, absolute certainty of success is not required. There is always the possibility that not each and every test carried out in order to demonstrate a certain effect, will yield the desired result. However, this does not mean that at the time the invention was made such a reasonable expectation did not exist.

3.5.14 For the aforementioned reasons, the board concludes that it was obvious for a person skilled in the art to replace tamoxifen with anastrozole with a reasonable expectation of more efficiently reducing the recurrence of breast cancer.

3.5.15 Concerning the subject-matter of claim 2 of the main request (see points V and 3.1. above), the board notes that it is the aim of endocrine treatment of early breast cancer to extend as much as possible the time before the cancer comes back (i.e. disease recurrence), irrespective of where it comes back (i.e. ipsilateral or contralateral). Thus, claim 2 is not directed to a different use or disease. Nor does it concern the treatment of a different group of patients, since it is not possible to distinguish between patients with early breast cancer that will experience ipsilateral recurrence of cancer and those that will experience the formation of a new contralateral primary tumour.

Ipsilateral recurrence and formation of contralateral primary tumours merely reflect different statistical end points marking the recurrence of the disease (see also patent in suit, paragraphs [0041] and [0042]).

3.5.16 Hence, the subject-matter of claim 2 is obvious for the same reasons as set out in points 3.5.1 to 3.5.14 above.

3.5.17 According to the appellant, the skilled person had no expectation of success for reducing the rate of occurrence of a new contralateral primary tumour, since documents (3) and (4) did not mention contralateral tumours. Furthermore, it was apparent from document (28) that this effect was genuinely surprising, even for the experts (see page 215, left-hand column, lines 10 to 13, page 216, lines 8 to 11 and 20 to 22).

3.5.18 Although document (4) does not explicitly mention contralateral tumours, it discloses the reduction of the recurrence rate of breast cancer with tamoxifen, which encompasses contralateral tumour occurrence (see point 3.5.15 above). This is also confirmed by document (7) (see page 1461, section entitled "Contralateral breast cancer incidence"). Incidentally, document (7) is the document on which the introductory part of document (4) is based. Furthermore, document (4) states that the ATAC trial is designed to compare the efficacy, i.e. time to recurrence, time to distant recurrence, **incidence of new breast primaries** and survival (emphasis added by the board), of tamoxifen with that of anastrozole (see page 232, right-hand column, penultimate paragraph, line 5 to 8). Hence, improved efficacy in the reduction of the rate of occurrence of primary tumours with anastrozole was

not something completely unexpected for the skilled person, although the order of magnitude may well have been surprising.

Furthermore, as explained in points 3.5.1 to 3.5.3 above, there was a reasonable expectation that, due to its superior efficacy in advanced breast cancer compared with tamoxifen, anastrozole would also improve the treatment of early breast cancer compared with tamoxifen. The skilled person therefore had a clear incentive to replace tamoxifen with anastrozole in the treatment of early breast cancer. The fact that he will later discover that the results with respect to one of the possible end points marking the recurrence of the disease may be better than expected can only be regarded as a quantitative bonus effect, which in itself cannot establish an inventive step.

3.5.19 For the aforementioned reasons, the board concludes that the subject-matter of claims 1 and 2 of the main request does not involve an inventive step, contrary to the requirement of Article 56 EPC. Accordingly, the main request must be refused.

Auxiliary request 1 filed at the oral proceedings

4. Admission into the proceedings

4.1 New auxiliary request 1 was filed at the oral proceedings before the board, after the discussion of inventive step for all the requests filed with the statement of grounds of appeal. Its subject-matter is distinguished from the main request in that the reduction of the rate of recurrence and of a new

contralateral primary tumour was defined "**versus tamoxifen**" (see point VI above).

The respondents objected to the admissibility of this request (see point VIII above).

4.2 According to the Rules of Procedure of the Boards of Appeal (RPBA), appeal proceedings in *inter partes* cases are based on the statement of grounds of appeal and the reply/replies of the other party/parties (Rule 12(1) RPBA). New submissions (requests, facts or evidence) are not entirely precluded; their admission, however, is at the discretion of the boards (Article 114(2) EPC and Article 13(1) RPBA). This discretion has to be exercised appropriately, requiring the boards to consider all relevant factors, taking into account the specific circumstances of the case. Examples of criteria to be taken into consideration by the boards when exercising their discretion are **inter alia** the complexity of the new subject-matter submitted, the current state of the proceedings and the need for procedural economy. These criteria are not exhaustive, and the boards have also considered aspects such as the reasons for the new submission or the extent of the amendments.

4.3 The appellant justified the late filing of auxiliary request 1 as being a direct reaction to the discussion that took place during oral proceedings, in particular, as an attempt to address a new argument advanced by respondents 2 and 3, namely that the reduction of the rate of recurrence/reduction of the rate of a new contralateral primary tumour in the claim sets filed with the statement of grounds of appeal had to be understood as a reduction compared with untreated patients.

4.4 However, the question as to how claims 1 and 2 of the main request are to be understood had already been an issue in the proceedings before the first instance (see minutes of the oral proceedings, page 5, first paragraph and decision, paragraph bridging pages 9 and 10 and subsequent paragraph). Furthermore, the allegedly new argument had already been advanced by respondents 2 and 3 in the context of an inventive step analysis in their reply to the statement of grounds of appeal (see, for example, respondent 3's letter of 10 April 2012, last paragraph on page 8 and first paragraph on page 9). No additional arguments were advanced in this respect during the oral proceedings. Hence, the board fails to see - and the appellant did not provide - any convincing reasons why auxiliary request 1 could not have been filed at an earlier stage during the appeal proceedings, in particular with the appellant's last submission filed one month before the oral proceedings took place. Accordingly, the board sees no justification for the late filing of auxiliary request 1.

4.5 Furthermore, taking into account the fact that the preceding discussion of inventive step was mainly focused on the question of whether or not the superior efficacy of anastrozole over tamoxifen was a reasonably expected result, with the consequence that the claimed subject-matter did not involve an inventive step, it was not immediately apparent, how the addition of the expression "versus tamoxifen" could successfully address this issue.

4.6 For the aforementioned reasons, the board did not admit auxiliary request 1 into the appeal proceedings (Article 114(2) EPC and Article 13 RPBA).

Auxiliary requests 2 to 4 (filed as auxiliary requests 1 to 3 with the statement of grounds of appeal)

5. Inventive step (Article 56 EPC)

5.1 Auxiliary request 2 differs from the main request in that the feature "wherein the woman having said early breast cancer is oestrogen receptor positive and/or progesterone receptor positive" has been added to the independent claims 1 and 2.

5.2 Estrogen receptor positive and/or progesterone receptor positive women are the obvious target group. With their tumours being responsive to estrogen stimulation, they will benefit the most from endocrine treatment designed to suppress this stimulation. Hence, the addition of this feature does not change the observations and conclusion set out in point 3 above. Indeed, the appellant conceded at the oral proceedings before the board that this feature was added to overcome an alleged objection of insufficiency of disclosure.

5.3 Hence, the board concludes that the subject-matter of claims 1 and 2 of auxiliary request 2 and claim 1 of auxiliary request 4, which is identical to claim 2 of auxiliary request 2, does not involve an inventive step (Article 56 EPC). Accordingly, these requests must also be refused.

5.4 Claim 1 of auxiliary request 3 is identical to claim 2 of the main request. Hence, the same reasoning as developed in point 3 above applies, with the consequence that this request must also be refused for lack of inventive step of the subject-matter of claim 1.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:



M. Schalow

A. Lindner

Decision electronically authenticated