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**D E C I S I O N**  
**of 16 January 2002**

**Case Number:** T 0457/99 - 3.3.2

**Application Number:** 94904249.3

**Publication Number:** 0679086

**IPC:** A61K 31/70

**Language of the proceedings:** EN

**Title of invention:**

Potentialiation of temozolomide in human tumour cells

**Patentee:**

CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED

**Opponent:**

-

**Headword:**

Potentialiation of Temozolomide /CANCER RESEARCH CAMPAIGN

**Relevant legal provisions:**

EPC Art. 56

**Keyword:**

"Main, first and second auxiliary requests - inventive step:  
no - incentive to try."

**Decisions cited:**

-

**Catchword:**

-



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Boards of Appeal

Chambres de recours

**Case Number:** T 0457/99 - 3.3.2

**D E C I S I O N**  
**of the Technical Board of Appeal 3.3.2**  
**of 16 January 2002**

**Appellant:** CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED  
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**Representative:** Ritter, Stephen David  
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**Decision under appeal:** Decision of the Examining Division of the  
European Patent Office posted 10 December 1998  
refusing European patent application  
No. 94 904 249.3 pursuant to Article 97(1) EPC.

**Composition of the Board:**

**Chairman:** P. A. M Lançon  
**Members:** J. Riolo  
C. Rennie-Smith

## Summary of Facts and Submissions

I. European patent application No. 94 904 249.3 concerning the potentiation of temozolomide in human tumour cells was refused by a decision of the Examining Division dated 19 October 1998 on the grounds of lack of inventive step.

II. The following documents, cited during the proceedings before the Examining Division and the Board of appeal, remain relevant for the present decision:

(1) Anti-cancer Drugs, **3(4)**, 401-405 (1992)

(5) Br. J. Cancer, **65**, 287-291 (1992)

III. The decision was based on claims 1 to 26 of the main request, claims 1 to 26 of the first auxiliary request and claims 1 to 26 of the second auxiliary request all filed during the oral proceedings before the Examining Division.

Independent claims 1, 2 and 3 of the main request read as follows:

"1. The use of an ATase inhibitor in the manufacture of a pharmaceutical composition for use in treating human cancer cells by a combination therapy comprising first administering said ATase inhibitor and subsequently administering temozolomide.

2. A use of temozolomide in the manufacture of a pharmaceutical composition for use in treating human cancer cells by a combination therapy comprising first

administering an ATase inhibitor and subsequently administering temozolomide.

3. The use of an ATase inhibitor and temozolomide for the manufacture of a medicament for the treatment of human cancer cells in a patient in need of such treatment."

Independent claims 1, 2 and 3 of the first auxiliary request read as follows:

"1. The use of an ATase inhibitor in the manufacture of a pharmaceutical composition for use in treating human cancer cells by a combination therapy comprising first administering said ATase inhibitor and subsequently administering temozolomide, **characterised in that administration of the ATase inhibitor and temozolomide is repeated over a period of several or multiple days.**

2. A use of temozolomide in the manufacture of a pharmaceutical composition for use in treating human cancer cells by a combination therapy comprising first administering an ATase inhibitor and subsequently administering temozolomide, **characterised in that administration of the ATase inhibitor is repeated over a period of several or multiple days.**

3. The use of an ATase inhibitor and temozolomide for the manufacture of a medicament for the treatment of human cancer cells in a patient in need of such treatment, **characterised in that administration of the ATase inhibitor is repeated over a period of several or multiple days.**"

Independent claims 1, 2 and 3 of the second auxiliary request read as follows:

"1. The use of an ATase inhibitor in the manufacture of a pharmaceutical composition for use in treating human cancer cells **selected from breast cancer tumour cells, astrocytoma tumour cells, colorectal tumour cells, melanoma tumour cells, mycosis fungoides tumour cells or glioma tumour cells** by a combination therapy comprising first administering said ATase inhibitor and subsequently administering temozolomide, **characterised in that administration of the ATase inhibitor is repeated over a period of several or multiple days.**

2. A use of temozolomide in the manufacture of a pharmaceutical composition for use in treating human cancer cells **selected from breast cancer tumour cells, astrocytoma tumour cells, colorectal tumour cells, melanoma tumour cells, mycosis fungoides tumour cells or glioma tumour cells** by a combination therapy comprising first administering said ATase inhibitor and subsequently administering temozolomide, **characterised in that administration of the ATase inhibitor is repeated over a period of several or multiple days".**

3. The use of an ATase inhibitor and temozolomide for the manufacture of a medicament for the treatment of human cancer cells **selected from breast cancer tumour cells, astrocytoma tumour cells, colorectal tumour cells, melanoma tumour cells, mycosis fungoides tumour cells or glioma tumour cells** by a combination therapy comprising first administering said ATase inhibitor and subsequently administering temozolomide, **characterised in that administration of the ATase inhibitor is**

**repeated over a period of several or multiple days".**

IV. The arguments in the decision may be summarized as follows:

The problem to be solved by the application in suit concerned the improvement of temozolomide cytotoxicity against human tumour cells.

Having regard to the disclosure in document (1) (Anti-cancer Drugs, 3(4), 401-405 (1992)), which reported that the cytotoxicity of temozolomide could be potentiated by an O<sup>6</sup>-alkylguanine DNA alkyltransferase (ATase) inhibitor in cancer cells which are resistant to alkylating agents in a mouse leukemia model, the Examining Division concluded that it was obvious for the skilled person to try to apply a similar approach in the treatment of human cancer cells, especially because document (1) explicitly recognized the possible significance of the reported findings for the treatment of human cancer cells.

It was additionally of the opinion that both the regimen involving repeated administration and the type of tumour cells to be treated were also obvious to the person skilled in the art.

V. The appellant (applicant) lodged an appeal against the said decision.

VI. In a communication dated 15 March 1999 the rapporteur drew the attention of the appellant to, among other things, the fact that the disclosures in document (1) and document (5) (the latter cited in the description of the application) apparently rendered the claimed

subject-matter obvious.

- VII. Oral proceedings were held before the Board on 16 January 2002. During the oral proceedings, the appellant filed new main and first and second auxiliary requests. These requests correspond to the requests filed during the oral proceedings before the Examining Division without the first medical use claims. In the first auxiliary request, the word "temozolomide" is moreover absent in the characterising part of claim 1.
- VIII. The appellant's submissions both in the written procedure and at the oral proceedings can essentially be summarised as follows:

As regards document (1), the appellant pointed out that this focused primarily on the treatment of cancer cells in mice and did not contemplate the use of temozolomide together with an ATase inhibitor in the treatment of human cells and, in particular, the human cancer cells of the application in suit.

Moreover, the appellant disputed the Examining Division's assumption that the skilled person would try to apply an approach similar to the one discussed in document (1) to the treatment of human cancer cells. In fact, in the appellant's opinion, due to the absence of data in document (1) concerning the level of ATase activity in human cancer cells, it should not have taken the disclosure of document (1) into account.

It further contended that the regimen involving repeated administration of the active agents was also novel and inventive as no prior art was presented against it.

IX The appellant requested that the decision under appeal be set aside and that the patent be granted on the basis of the main or alternatively the first or second auxiliary requests filed during the oral proceedings.

## Reasons for the Decision

1. The appeal is admissible.

2. *Inventive step*

2.1 Main request

2.1.1 The Board agrees with the appellant that in the present case, document (5), which discloses the use of temozolomide for treating human cancers such as malignant melanoma, mycosis fungoides and high grade gliomas, can be considered as the closest state of the art (page 290, right column, lines 15 and 16).

In the application it is stated that the temozolomide toxicity in human cancer cells can be potentiated by using inhibitors of O<sup>6</sup>-alkylguanine DNA alkyltransferase (ATase)(page 3, first paragraph).

Therefore, starting from (5), the technical problem to be solved is that of improving the toxicity of temozolomide in human cancer cells.

The proposed solution is the subject-matter of, among others, independent claim 3, which involves the use of an ATase inhibitor and temozolomide for the manufacture of a medicament.



From the examples reported in the description, the Board is satisfied that the problem is solved.

The question to be answered is thus whether the proposed solution, ie the use of an ATase inhibitor, is obvious to the skilled person faced with the problem defined above in the light of the available prior art documents (1) and (5).

Document (1), a scientific paper, shows that an ATase inhibitor ( $O^6mGua$ ) enhances the cytotoxicity of temozolomide in mouse leukemia subline cells (L210/BCNU) which are resistant to temozolomide (page 404, Figure 1).

According to this document, the high level of ATase in these cells is the reason for the resistance to the alkylating agent temozolomide and the inhibition of the repair action of ATase is the reason for the potentiation of the cytotoxicity of temozolomide (page 401, right column, lines 26 to 36 and page 404, right column, lines 1 to 23).

Moreover, this document recognises in its final paragraph the possible significance of the reported findings for the treatment of other cancer cells.

Having regard, on the one hand, to the disclosure in (5) that temozolomide shows clinical activity in various human cancers and, on the other hand, to document (1), which shows that recent studies suggest that an ATase inhibitor potentiates the cytotoxicity of temozolomide in cells by inhibiting the repair action of their alkyl transferase, the skilled person is unambiguously taught that ATase inhibitor could enhance

the cytotoxicity of temozolomide.

Accordingly, the skilled person, faced with the problem as defined above, would consider the use of an ATase inhibitor in combination with temozolomide as a promising solution.

- 2.1.2 The appellant stressed all the differences between the claimed subject-matter and the disclosure in document (1).

In that respect however, the Board points out that, when assessing inventive step using the problem-solution approach, it is as a rule the technical features distinguishing the claimed subject-matter from the closest prior art document, ie document (5) in the present case, are the relevant ones to be determined.

In the present case the only difference between the application and document (1) lies in the presence of an ATase inhibitor. Accordingly, the only point at issue is whether the use of an ATase inhibitor in order to potentiate the cytotoxicity of temozolomide was obvious to the skilled person in the light of the available prior art, namely document (1).

In reply to a question from the Board during the oral proceedings, the appellant admitted that there is no technical prejudice against the use of an ATase inhibitor for treating human being.

It was nevertheless of the opinion that the skilled person would need both motivation and a reasonable expectation of success before trying an ATase inhibitor to potentiate the cytotoxicity of temozolomide.

In its opinion, the information contained in document (1) was not sufficient as it concerned merely *in vitro* studies, which were moreover only carried out with two particular mouse cancer cells. It also noted that this document was silent about the amount of ATase present in the human cancer cells.

It therefore concluded that document (1) did not suggest using the same approach with human cancer cells and that, in any case, the skilled person would doubt whether potentiation would occur also with human cancer cells.

The Board does not disagree with that conclusion of the patentee. It is however convinced that, as explained under 2.1.1, the clear hint contained in document (1) would be sufficient to prompt the skilled person at least to attempt *in vitro* experiments with human cancer cells as shown in the application in suit; all the more so because of the need for efficient therapies in the field of cancer.

For these reasons the Board concludes that the subject-matter of the main request lacks an inventive step as required by Article 56 EPC.

## 2.2 First auxiliary request

The introduction of the best administration regimen in the claims of this request, which is, as a rule, merely the result of routine optimisation measures, required no more than ordinary technical skill, without involving an inventive step in the meaning of Article 56 EPC.

Accordingly, the conclusions under 2.1.2 also hold good for this request.

### 2.3 Second auxiliary request

Nor can the mention of the particular human cancer types in this last request provide an inventive step as these cancers are in part the same as those disclosed in the closest prior art document (5), which means that this request offers no additional distinguishing feature to be assessed.

## **Order**

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

The appeal is dismissed.

The Registrar

The Chairman

A. Townend

P. Lançon