

Internal distribution code:

- (A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

**Datasheet for the decision
of 16 July 2018**

Case Number: T 1351/12 - 3.3.04
Application Number: 04785793.3
Publication Number: 1639010
IPC: C07K16/00, A61K39/395,
A61P35/00
Language of the proceedings: EN

Title of invention:

Surrogate therapeutic endpoint for anti-CTLA-4 based immunotherapy of disease

Applicant:

E. R. Squibb & Sons, L.L.C.

Headword:

Anti-CTLA-4 based immunotherapy/SQUIBB

Relevant legal provisions:

EPC Art. 83, 111(1)
RPBA Art. 11

Keyword:

Main request - sufficiency of disclosure
Substantial procedural violation - (yes)
Remittal to the department of first instance (yes)
Reimbursement of appeal fee - (yes)

Decisions cited:

Catchword:

-



Beschwerdekammern
Boards of Appeal
Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1351/12 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 16 July 2018

Appellant: E. R. Squibb & Sons, L.L.C.
(Applicant) Route 206 and Province Line Road
Princeton, NJ 08540 (US)

Representative: Reitstötter Kinzebach
Patentanwälte
Sternwartstrasse 4
81679 München (DE)

Decision under appeal: Decision of the Examining Division of the
European Patent Office posted on 30 November
2011 refusing European patent application No.
04785793.3 pursuant to Article 97(2) EPC.

Composition of the Board:

Chairwoman G. Alt
Members: B. Claes
P. de Heij

Summary of Facts and Submissions

- I. The appeal lies from the decision of the examining division dated 30 November 2011 to refuse European patent application No. 04 785 793.3, published as international patent application WO2005/003298 and entitled "*Surrogate therapeutic endpoint for anti-CTLA-4 based immunotherapy of disease*".
- II. The examining division held that certain claims of the main request lacked clarity (Article 84 EPC) and/or were for methods excluded from patentability under Article 53(c) EPC and that certain claims of auxiliary request 1 related to added subject-matter (Article 123(2) EPC). It further decided that the application did not meet the requirements of Article 83 EPC in relation to the invention defined in claim 1 of auxiliary requests 2 and 3. All auxiliary requests were filed during the oral proceedings.

Claim 1 of auxiliary request 2 read:

"1. An anti-CTLA-4 antibody for use in the treatment of cancer in a subject, which treatment comprises inducing a breakthrough event in the subject by administering the anti-CTLA-4 antibody to the subject until observing the breakthrough event wherein the breakthrough event is an autoimmune Grade 3 or 4 adverse event." (emphasis added by the board)

Claim 1 of auxiliary request 3 read:

"1. An anti-CTLA-4 antibody for use in the treatment of cancer in a subject, which treatment comprises inducing a breakthrough event in the subject by administering the anti-CTLA-4 antibody to the subject until observing

the breakthrough event wherein the breakthrough event is a Grade 3 or 4 adverse event selected from the group consisting of diarrhea, enterocolitis, dermatitis, hypophysitis, panhypopituitarism, rash, and pruritis." (emphasis added by the board)

- III. With the statement of grounds of appeal the applicant (hereinafter "appellant") re-submitted auxiliary request 3 as considered by the examining division (see section II) as its main request, submitted further experimental data (see paragraph bridging pages 6 and 7 and three first full paragraphs on page 7) and new documentary evidence (Weber *et al.* (2009), Clin. Cancer Res., Vol. 15, No. 17, pages 5591 to 5598, referred to hereinafter as "document D10"). The appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the main request. On an auxiliary basis, oral proceedings were requested.
- IV. In response to a telephone enquiry by the board the appellant withdrew its request for oral proceedings in a letter dated 25 April 2018.
- V. The appellant's arguments may be summarised as follows:

The decision under appeal - lack of reasoning

The examining division had not made a distinction between claim 1 of auxiliary request 2 and claim 1 of auxiliary request 3 pending before it and had wrongly asserted that claim 1 of the latter recited an autoimmune grade 3 or 4 adverse event. It had thus not appreciated that the breakthrough event in the latter was defined as being "a grade 3 or 4 adverse event selected from the group consisting of diarrhea,

enterocolitis, dermatitis, hypophysitis, panhypopituitarism, rash and pruritis".

The decision under appeal was to be set aside on account of this deficiency.

Sufficiency of disclosure

A grade 3 adverse event was observed in 1 out of 17 patients referred to in example 2 of the application as filed (see table 2) and this patient did not have an objective tumor response. The observed event however was not an adverse event as defined in claim 1. Also the fact that two patients had displayed a partial response but no serious adverse events could not cast doubt on the claimed teaching.

The claimed dosage regimen allowed the efficacy of cancer treatment with anti-CTLA-4 antibody to be enhanced by inducing adverse events. This however did not preclude that patients who did not experience an adverse event might still demonstrate clinical benefit with the anti-CTLA-4 antibody.

The application as filed comprised clear evidence that the antibody caused the adverse effects and the administration of the antibody alone was sufficient to induce said adverse events.

In the field of cancer treatment, the observation that not all patients benefited from a given treatment was in itself not a reason to doubt that the treatment was clinically useful. A response rate of 50% in patients with grade 3 or 4 adverse events was unexpectedly high as compared to the response rate across all patients and was not to be considered an ineffective treatment.

The statistical analyses in examples 5 and 6 clearly corroborated that administering the anti-CTLA-4 antibody until a recited serious adverse event was observed enhanced the response rate, i.e. the probability that patients would respond to the treatment.

The post-published data in document D10 demonstrated that, independently of whether anti-CTLA-4 antibody was administered with or without a further compound (here budesonide), the disease control rate was significantly higher in patients with grade 3 to 4 immune-related adverse events (irAE) than in patients with grade 0 to 2 irAEs, although many patients with grade 1 to 2 irAEs experienced clinical benefit (see abstract; page 5592, left-hand column; page 5596, right-hand column, first full paragraph; page 5597, left-hand column, first full paragraph).

Reasons for the Decision

1. The appeal is admissible.

The decision under appeal - lack of reasoning

2. The appellant correctly noted that the examining division had not appreciated that claim 1 of auxiliary request 3 before it (the present main request) was different from claim 1 of auxiliary request 2 in that it specified the breakthrough event as being selected from the group consisting of diarrhoea, enterocolitis, dermatitis, hypophysitis, panhypopituitarism, rash and pruritis. The subject-matter that was assessed in view of the requirements of Article 83 EPC in paragraph 9 of the decision was therefore only that of claim 1 of

auxiliary request 2. The reasoning of the examining division or parts of it might have been envisaged to also apply to claim 1 of auxiliary request 3. It cannot be inferred from the decision, however, whether this is the case and, if so, which arguments would apply correspondingly.

3. As a result the appealed decision, contrary to Rule 111(2) EPC, is not reasoned to the extent that it refused the application with claims according to auxiliary request 3.
4. The failure in the decision to provide adequate reasoning under Rule 111(2) EPC for the rejection of auxiliary request 3 is to be considered as a substantial procedural violation and a fundamental deficiency in the first instance proceedings in the sense of Article 11 RPBA.
5. The board therefore agrees with the appellant that the appealed decision should be set aside.
6. According to Article 11 RPBA a board shall remit a case to the department of first instance if fundamental deficiencies in the first instance proceedings are apparent "*unless special reasons present themselves for doing otherwise*".
7. The board considers such special reasons to be given in view of the duration of the proceedings. Indeed, it would be inexpedient to remit the case to the examining division without further considering the appellant's appeal because such remittal only might unnecessarily prolong the proceedings even more. Consequently, the board decided to not remit the case without considering

the further grounds raised against the decision under appeal.

Sufficiency of disclosure (Article 83 EPC)

8. The examining division decided that the patent application did not disclose the invention as defined in claim 1 of auxiliary requests 2 and 3 (the latter now being the main request; see section II) in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and accordingly failed to meet the requirements of Article 83 EPC. It based its finding on two lines of argument.

9. **In a first line of argument** the examining division held that the application as filed "*neither demonstrates nor does it make plausible that the administration of the anti-CTLA-4 antibody alone is sufficient to induce breakthrough events*".

10. In the board's view, for determining whether the application teaches the ability of the anti-CTLA-4 antibody on its own, i.e. in the absence of other co-administered compounds such as gp100 peptide vaccines, to induce breakthrough events, account needs to be taken of the common general knowledge of the skilled person on CTLA-4 and antibodies antagonising this compound, which is for example summarised in the application on page 2, line 26, to page 3, line 18. Accordingly, the board emphasises that CTLA-4 blockade was known, e.g. to enhance induced autoimmune disease (see page 2, line 33) and anti-CTLA-4 autoantibodies were known to have a pathogenic role in certain autoimmune patients (see page 3, lines 4 to 7), both facts implying that an anti-CTLA-4 antibody has the

potential of undesired influences on T-cell activation, i.e. causing undesired adverse events.

11. It is in this context that the skilled person will find confirmation for his understanding in example 1 of the application disclosing that administration of anti-CTLA-4 antibody in increasing doses (together with a steady dose of gp100/tyrosinase/MART-1 peptide vaccine) correlates to an increasing number of breakthrough events in resected stage III/IV melanoma patients, the conclusion there being that *"Anti-CTLA-4 antibody dose dependent, organ specific auto-immune-like adverse events were observed"* (see page 24, lines 13 to 14).
12. The board also refers to table 3 of document D10 submitted by the appellant upon appeal which experimentally corroborates the understanding of the skilled person that it is the administration of the anti-CTLA-4 antibody alone which results in grade 3 or 4 breakthrough events (see e.g. document D10, table 3, results for the group B patients).
13. For the above reasons the board considers that, contrary to the finding of the examining division, the application teaches the skilled person that the administration of the anti-CTLA-4 antibody alone is sufficient to induce breakthrough events.
14. **In a second line of argument** the examining division held that the application failed to establish a significant causal link between induced breakthrough events and an objective tumour response. It argued that, whereas in example 3, of the 8 patients in whom severe breakthrough events were observed, 50% (four) displayed a tumour response, the other 50% of those patients did not exhibit tumour response at all. The

examining division alleged that a 50% response rate did not support a statistically significant correlation between the appearance of grade 3 and 4 side-effects and objective tumor responses.

15. The board cannot agree with the examining division in this respect and refers to the - correct - conclusion of example 3 that the study *"demonstrated that clinical responses to anti-CTLA-4 antibody in combination with melanoma peptide vaccines strongly correlates with the occurrence of autoimmune-like adverse side-effects. Four of eight (50%) patients with autoimmune-like serious adverse effects had a clinical response. Only 2 of 28 patients (7%) had a response in the absence of any serious autoimmune-like adverse effect"* (page 34, lines 3 to 8). Accordingly, the appropriate reference for a statistical correlation in this context are those responders who did not have observed breakthrough events (i.e. 7%) and not, as would seem to be suggested by the examining division, those patients with observed breakthrough events who were non-responders (i.e. 50%).
16. For this statistical analysis the board refers to example 5 of the application as filed, which concerns a double (Chi-square test and Fisher's exact test) statistical analysis of these results and which confirms a statistically significant correlation between responders and patients that develop breakthrough events (see page 35, lines 13 to 17), and to example 6 where similar results were obtained when analysing the data of examples 2 to 4 with the same two test methods.
17. The above considerations lead the board to conclude that in the decision under appeal the examining division came to the finding that the application did

not meet the requirements of Article 83 EPC for reasons which the board considers to be insufficient to justify such finding.

18. Since the non-compliance with Article 83 EPC was the sole reason for the refusal of the application, the board accordingly sets aside the decision under appeal also for this additional reason.

*Remittal to the examining division for further prosecution
(Article 111(1) EPC)*

19. The case is remitted to the examining division for further examination as to the requirements of patentability in respect of the main request. This examination shall also involve establishing whether or not there is a causal link between an objective tumor response and the specific breakthrough events recited in claim 1 of the present main request.

Reimbursement of the appeal fee (Rule 103(1)(a) EPC)

20. In view of the substantial procedural violation (see points 4 above), the board considers it equitable to order the reimbursement of the appeal fee in accordance with Rule 103(1)(a) EPC).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the examining division for further prosecution.
3. The appeal fee is reimbursed.

The Registrar:

The Chairwoman:



P. Cremona

G. Alt

Decision electronically authenticated