JUDGMENT

DISTRICT COURT THE HAGUE

Commercial law team

case number / docket number: C/09/517753 / HA ZA 16-1056

Judgment of 21 February 2018

in the action between

CELLTRION INC., a company under foreign law,
having its registered office in Incheon (South Korea),
claimant,
attorney: previously *mr.* M.G.R. van Gardingen in Amsterdam, currently *mr.* D.F. de Lange in Amsterdam, the Netherlands,

and

BIOGEN INC., a company under foreign law,
having its registered office in Cambridge (Massachusetts, United States),
defendant,
attorney: *mr*. J.A. Dullaart in Naaldwijk, the Netherlands.

Hereinafter, the parties will be called Celltrion and Biogen.

For Celltrion, the case was argued by *mrs.* D.F. de Lange and H.J. Pot, attorneys in Amsterdam. For Biogen, *mrs*. R.M. Kleemans and M.G.A. Egeler appeared, attorneys in Amsterdam, assisted by the patent attorney Dr. M. Klok.

1. The Proceedings

1.1. The course of the proceedings is shown by:
- the decision by the preliminary relief judge of this district court of 10 May 2016, in which Celltrion was granted leave to litigate in accordance with the Accelerated Regime in Patent Cases;
- the amended decision by the preliminary relief judge of this district court of 12 May 2016, in which a manifest error in the decision of 10 May 2016 was rectified;
- the writ of summons of 13 May 2016;
- the document containing exhibits of 7 September 2016 on Celltrion's part, with the exhibits 1-33;
- the statement of defense of 16 November 2016 with the exhibits 1-18;
- the document containing additional exhibits and amendment of claim on Celltrion's part of 22 February 2017, with the exhibits 34-43;
- the document containing additional exhibits on Biogen's part of 22 February 2017, with the exhibit 19;
- the document containing responsive exhibits on Celltrion's part of 21 April 2017, with the exhibits 44-53;
- the document containing responsive exhibits on Biogen's part of 21 April 2017 with the exhibits 20-24, in which also the amendment of claim and the submission of exhibit 39 were objected to;
- the further document on Celltrion's part with exhibit 54, sent with a letter of 10 May 2017;

- the further document on Biogen's part of 12 May 2017 with exhibit 25;
- the e-mail message by *Mr.* De Lange, also on behalf of Biogen's attorneys, of 16 May 2017 with respect to an arrangement on the costs of the proceedings;
- the pleading notes submitted at the occasion of the hearing of 19 May 2017 on Celltrion's part, in which the paragraphs 42 and 49-56 have been struck through as these were not pleaded;
- the pleading notes submitted at the occasion of the hearing of 19 May 2017 on Biogen's part, in which the paragraphs 67, 81, 103 from the second sentence up to and including 105, 107 from the second sentence up to and including 110, 112-113, 115-118 and 120-121 have been struck through as these were not pleaded.

1.2. At the hearing, also taking into account the objections on Biogen's part, the district court refused Celltrion's amendment of claim and exhibit 39 (study protocol of the O'Brien study) and exhibit 54 (statement by Prof. dr. M.H.J. van Oers of 11 April 2017) on Celltrion's part due to conflict with the principles of due process. It counted heavily that Celltrion appeared to be unable, also after a request thereto, to concretize the legal basis of its amendment of claim. This makes it impossible for the opposite party and the district court to adequately follow a debate to be held for the first time at the hearing. With regard to exhibit 39, Celltrion itself opted for proceedings in accordance with the accelerated regime and thereby cut off the possibility to submit new publications (when these could already be known to it from the opposition proceedings and could thus have been submitted earlier) in the course of the proceedings. Exhibit 54 was refused as this was submitted beyond the terms mentioned in the ARPC decision. Exhibit 40 (The University of Texas M.D. Anderson Cancer Center Leukemia Insights Newsletter, vol. 3, no. 2, summer 1998) and related exhibit 41 (electronic online version of the abovementioned newsletter) and exhibit 42 (statement by Dr. Michael Andreeff) on Celltrion's part were refused ex officio by the district court as these exhibits pertain to prior art on which Celltrion bases a new inventive step attack, which is also contrary to the principles of due process.

1.3. Finally, it was further determined that judgment would be rendered today.

2. The Facts

Parties

2.1. Celltrion is a global biopharmaceutical company headquartered in South Korea. One of Celltrion's activities is the development of so-called biosimilars, alternatives to known biological medicinal products, having a similar pharmacokinetic profile. Celltrion developed a biosimilar of a chimeric monoclonal anti-CD20 antibody called "rituximab" that according to Celltrion is bio-equivalent to the medicinal product MabThera to be mentioned below. By now, Celltrion has obtained a European marketing authorization for the biosimilar in question and has stated that it plans to enter the market in the Netherlands with its biosimilar together with the pharmaceutical group Teva.

2.2. Biogen is an American (bio)pharmaceutical company. It is the proprietor of the European patent EP 2 055 313 (hereinafter: EP 313 or the patent) for a '*Treatment of hematologic malignancies associated with circulating tumor cells using chimeric anti-CD20 antibody*'. The patent was granted on 29 April 2015 further to an application for this on 9 November 1999. The patent invokes priority on the basis of the American patent application with number US 60/107,658 (hereinafter: US 658) and filing date 9 November 1998. EP 313 is in force *inter alia* in the Netherlands. F. Hoffman La Roche AG and Genentech Inc. are licensees of this Biogen patent and market a medicinal product based on

this patent, under the trademarks MabThera® - the product is marketed in the Netherlands under this trademark – and Rituxan® (in the United States).

The Patent Family and the Grant History

2.3. EP 313 is a divisional of the European patent with number EP 1 616 572 (hereinafter: EP 572) also in Biogen's name entitled '*Chimeric anti-CD2O antibody, rituxan, for use in the treatment of chronic lymphocytic leukemia*'. EP 572 was granted on 1 September 2010 further to an application for this on 9 November 1999. Also EP 572 invokes priority on the basis of US 658. EP 572 is in turn a divisional of the European patent application EP 1 131 093 (hereinafter: the parent application or EP 093), published on 18 May 2000 as the international application WO 00/27428, also invoking the priority of US 658. After Biogen had filed the divisional application for EP 572, it withdrew the parent application. The Opposition Division of the European Patent Office (EPO) revoked EP 572 on 24 September 2013. An appeal was lodged against this with the EPO's Technical Board of Appeal. This appeal was rejected on 20 September 2016. At the time of the hearing in this case, the written grounds of this decision were not available yet.

2.4. An opposition was filed to the grant of EP 313. On 9 March 2017, the Opposition Division of the EPO gave a provisional (non-binding) opinion implying that EP 313 is invalid because of added matter. The district court knows ex officio that the oral hearings at the Opposition Division of the EPO took place on 6 November 2017. The Opposition Division revoked the patent on that same day because of added matter.

2.5. The claims of EP 313 as granted are the following in the original English language:

1. Use of an anti-CD20 antibody comprising human gamma 1 constant regions in the manufacture of a medicament for treatment of chronic lymphocytic leukemia (CLL) in a human patient, wherein the medicament is for administration to the human patient at a dosage of 500 to 1500 mglm^2.
2. Use according to claim 1, wherein the medicament is for use in combination with chemotherapy.
3. Use according to claim 1 or claim 2, wherein the anti-CD20 antibody is a chimeric antibody.
4. Use according to claim 1 or claim 2, wherein the anti-CD20 antibody is a humanized antibody.
5. Use according to claim 1 or claim 2, wherein the anti-CD20 antibody is a human antibody.
6. Use according to claim 1 or claim 2, wherein the anti-CD20 antibody comprises a CD20-binding antibody fragment.
7. Use according to claim 3, wherein the anti-CD20 antibody is rituximab.
8. Use according to any one of claims 1-7, wherein the patient is refractory to a treatment previously administered for the chronic lymphocytic leukemia.
9. An anti-CD20 antibody comprising human gamma 1 constant regions for use in a method for treatment of chronic lymphocytic leukemia (CLL) in a human patient, the method comprising administering the antibody to the human patient at a dosage of 500 to 1500 mg/m^2.
10. The antibody for use according to claim 9. wherein the method comprises administering the antibody in combination with chemotherapy.
11. The antibody for use according to claim 9 or claim 10, wherein the anti-CD20 antibody is a chimeric antibody.
12. The antibody for use according to claim 9 or claim 10. wherein the anti-CD20 antibody is a humanized antibody.
13. The antibody for use according to claim 9 or claim 10, wherein the anti-CD20 antibody is a human antibody.
14. The antibody for use according to claim 9 or claim 10, wherein the anti-CD2O antibody comprises a CD20-binding antibody fragment.
15. The antibody for use according to claim II, wherein the anti-CD2O antibody is rituximab.
16. The antibody for use according to any one of claims 10 to 15, wherein the patient is refractory to a treatment previously administered for the chronic lymphocytic leukemia.

2.6. In the undisputed Dutch translation, these claims are the following:

1. Toepassing van een anti-CD20-antilichaam, omvattende menselijke gamma 1 constante regio's bij de bereiding van een geneesmiddel voor behandeling van chronische lymfocytische leukemie (CCL) bij een menselijke patiënt, waarbij het geneesmiddel dient voor toediening aan de menselijke patiënt in een dosering van 500 tot 1500 mg/m^2.
2. Toepassing volgens conclusie 1, waarbij het geneesmiddel dient voor toepassing in combinatie met chemotherapie.
3. Toepassing volgens conclusie 1 of 2, waarbij het anti-CD20-antilichaam een chimeer antilichaam is.
4. Toepassing volgens conclusie 1 of 2, waarbij het anti-CD20-antilichaam een gehumaniseerd antilichaam is.
5. Toepassing volgens conclusie 1 of2, waarbij het anti-CD20-antilichaam een menselijk antilichaam is.
6. Toepassing volgens conclusie 1 of 2, waarbij het anti-CD20-antilichaam een CD20-bindend antilichaamfragment omvat.
7. Toepassing volgens conclusie 3, waarbij het anti-CD20-antilichaam rituximab is.
8. Toepassing volgens één van de conclusies 1-7, waarbij de patiënt ongevoelig is voor een behandeling die eerder voor de chronische lymfocytische leukemie is toegediend.
9. Anti-CD20-antilichaam. omvattende menselijke gamma 1 constante regio's, voor toepassing bij een werkwijze voor behandeling van chronische lymfocytische leukemie (CLL) bij een menselijke patiënt, waarbij de werkwijze toediening van het antilichaam aan de menselijke patiënt in een dosering van 500 tot 1500 mg/m^2 omvat.
10. Antilichaam voor toepassing volgens conclusie 9, waarbij de 'werkwijze toediening van het antilichaam in combinatie met chemotherapie omvat.
11. Antilichaam voor toepassing volgens conclusie 9 of 10, waarbij het anti-CD20-antilichaam een chimeer antilichaam is.
12. Antilichaam voor toepassing volgens conclusie 9 of 10, waarbij het anti-CD20-antilichaam een gehumaniseerd antilichaam is.
13. Antilichaam voor toepassing volgens conclusie 9 of 10, waarbij het anti-CD20-antilichaam een menselijk antilichaam is.
14. Antilichaam voor toepassing volgens conclusie 9 of 10, waarbij het anti-CD20-antilichaam een CD20-bindend antilichaamfragment omvat.
15. Antilichaam voor toepassing volgens conclusie 11, waarbij het anti-CD20-antilichaam rituximab is.
16. Antilichaam voor toepassing volgens één van de conclusies 10-15, waarbij de patiënt ongevoelig is voor een behandeling die eerder voor de chronische lymfocytische leukemie is toegediend.

2.7. In these proceedings, Biogen filed an auxiliary request with respect to EP 313. The claims hereof differ from the granted claims of EP 313 as it has been specified in the auxiliary request in the claims 1 and 3 that the anti-CD20 antibody pertains to rituximab, as currently included in the granted claims 7 and 15. The claims 3-8 and 11-16 of the granted claims have been deleted in the auxiliary request and all the claims have been renumbered. The claims according to the auxiliary request are as follows, in the submitted Dutch-language version:

1. Toepassing van een anti-CD20-antilichaam, omvattende menselijke gamma 1 constante regio's bij de bereiding van een geneesmiddel voor behandeling van chronische lymfocytische leukemie (CCL) bij een menselijke patiënt, waarbij het geneesmiddel dient voor toediening aan de menselijke patiënt in een dosering van 500 tot 1500 mg/m^2, en waarbij het anti-CD20-antilichaam rituximab is.
2. Toepassing volgens conclusie 1, waarbij het geneesmiddel dient voor toepassing in combinatie met chemotherapie.
3. Anti-CD20-antilichaam, omvattende menselijke gamma 1 constante regio's, voor toepassing bij een werkwijze voor behandeling van chronische lymfocytische leukemie (CCL) bij een menselijke patiënt, waarbij de werkwijze toediening van het antilichaam aan de menselijke patiënt in een dosering van 500 tot 1500 mg/m2 omvat, en waarbij het anti-CD20-antilichaam rituximab is.
4. Antilichaam voor toepassing volgens conclusie 3, waarbij de werkwijze toediening van het antilichaam in combinatie met chemotherapie omvat.

2.8. The description of EP 313 *inter alia* comprises the following example[1]:

EXAMPLE 3

[1] Writing errors have not been corrected in this quotation.

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Phase I/II Study of RITUXAN® in CLL

[0033] RITUXAN® is a monoclonal antibody targeting CD20 that has significant activity in the treatment of low-grade lymphoma (LGL). When given at a dosage of 375 mg/m^2 weekly/four response rate in relapsed patients (PIS) was 43% (McClaughlin et al, KOO, Vol. 14, 1998). Patients with small lymphocytic lymphoma had lower response rates (13%) than patients with other subtypes of LGL and lower serum levels of RITUXAN®. Reduced response seen in SLL could be related to lower density of CD20 antigen and/or higher circulating B-cell counts. Both factors would be expected to impact (negatively) on response seen in CLL. In an attempt to maximize activities in CLL we are conducting a Phase 1/11 study. All patients receive a first dose of 375 mg/m^2 to m^2 minimize infusion-relapsed side effects.
[0034] Subsequent weekly dosages (3) remain the same but are given at an increased dose level. Sixteen patients have been treated at dosages of 500-1500 mg/m^2. Medium age was 66 years (range, 25-78). Eighty-one percent had end-stage III-IV disease. Medium white blood cell count was 40 x 10^9/L (range, 4-200), Hgb 11.6 g/dl (range, 7.7-14.7), platelets 75 x 10^9/l(range, 16-160), median β_2 immunoglobulin was 4.5 mg/L (range, 3.1-9.2). Median numbers of prior therapies was 2.5 (range 1-9). Sixty percent of patients were refractory to treatment. Two patients developed severe hypertension with the first dose (375 mgm2); another one received further therapy. Toxicity at subsequent escalated dosages has been mild although no patient at the 1500 mg/m^3 [it is meant to state: 1500 mg/m^2 skin surface, district court] dose level has been fully evaluated. Eight patients have completed therapy (4 at 500 mg/m^2, 3 at 650 mg/m^2, 1 at 825 mg/m^2). One patient treated at 560 mg/m^2 achieved full remission. One patient has progressive lymphocytosis on treatment and all other patients had reduction in peripheral blood lymphocytosis but less effect on lymph nodes. Dose escalation studies are ongoing.

The Prior Art[2]

2.9. In 1992, the article *Relationship between Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma* by A. Batata and B. Shen was published in the journal *Cancer*.[3] The summary at the beginning of this article *inter alia* comprises the following passages:

Background. Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are considered different tissue expressions of the same disease process, although they are clinically separable nosologic entities. A systematic comparison of the membrane phenotypes in the two entities needs to be investigated.
(...)
Methods. Cell suspensions from peripheral blood of 184 patients with CLL. bone marrow from 23 patients with CLL. and lymph nodes from 86 patients with SLL were analyzed to compare the membrane phenotypes.
Results. There were no significant differences between the three groups in the mean percentages of cells expressing surface immunoglobulin (SI_g). CD5, CDI9. CD20, CD2 or in the frequency of cases with weak SI_g.
(...)
Conclusions. The similarity of membrane phenotypes between CLL and SLL provided evidence that the two are different tissue expressions of the same disease.

2.10. In 1993, the article *Malignant Disorders of Small Lymphocytes — Small Lymphocytic Lymphoma, Lymphoplasmacytic Lymphoma, and Chronic Lymphocytic Leukemia: Their Clinical and Laboratory Relationship*, by G.A. Pangalis et al. was published in the *American Journal of Clinical Pathology*.[4] This article *inter alia* comprises the following passages:

IMMUNOLOGCC FINDINGS
(...)
Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia appears to be the leukemic equivalent of SLL because the immunophenotype of the two is similar. (...)
(...)

[2] In the passages quoted below, internal footnotes will be omitted, unless otherwise stated. Literature cited will always be indicated in the continuation of this judgment with exclusively the last name of the first author.
[3] Cancer, (1 August) 1993, vol. 70, no. 3: pp. 625-632
[4] American Journal of Clinical Pathology, Volume 99, Issue 4, 1 April 1993, pp. 402—408
(submitted by Biogen as exhibit 21, annex A)

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COMMENTARY

Malignant disorders of small lymphocytes, despite their morphologic and immunologic similarity, differ clinically and hematologically; therefore they require separate classification and clinical consideration. This is particularly significant because some of the modem lymphoma classifications fail to recognize them as separate entities (particularly the category of SLL). The simple fact, for example, that a patient with the lymph node histology of SLL and blood lymphocytosis has CLL and not SLL is overlooked. As a result of this approach, in a recent report of 268 cases of SLL, more than 30% of the patients had absolute blood lymphocytosis (the higher number of white blood cells in this report was 232.7 X 10^9/l), and therefore they were cases of CLL. Another significant implication of making no distinction between SLL and CLL is the fact that, if CLL cases are classified as SLL on the basis of lymph node histology alone, automatically all are going to be considered as stage IV according to the Ann Arbor staging system, because in CLL the bone marrow is always involved. Small lymphocytic lymphoma and CLL, however, have other significant differences that make their distinction necessary. SLL involves the bone marrow occasionally, and its pattern of positivity is nodular, whereas in CLL the bone marrow is always involved and four patterns have been demonstrated; SLL is rarely complicated by bone marrow failure or autoimmune cytopenias and hypogammaglobulinemia, findings that are frequent in CLL. Furthermore SLL, lymph node lymphocytes express the adhesion molecule LFA-1 (CDI11a/CD 18), which is absent from the lymph nodes or blood lymphocytes of CLL, although both SLL and CLI share a large number of common antigens. including CD5. These observations support the notion that CLL is primarily a disease of the bone marrow and SLL a disease of the lymph nodes.

2.11. In October 1994, the article *Phase 1 Clinical Trial Using Escalating Single-Dose Infusion of Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8,) in Patients With Recurrent B-cell Lymphoma*, by D.G. Maloney et al. was published in the journal *Blood*.[5] This article *inter alia* comprises the following passages:

The B-cell antigen CD20 is expressed on normal 3 cells and by nearly all 8-celi lymphomas. This nonmodulating antigen provides an excellent target for antibody-directed therapies. A chimeric anti-CD20 antibody (IDEC-C2B8), consisting of human IgGI-k constant regions and variable regions from the murine monoclonal anti-CD20 antibody IDEC-2B8. has been produced for clinical trials. It lyses $CD20^+$ cells in vitro via complement and antibody-dependent cell-mediated lysis. Preclinical studies have shown that the chimeric antibody selectively depletes 3 cells in blood and lymph nodes in macaque monkeys. In this phase 1 clinical trial, 15 patients (3 per dose level) with relapsed low-grade B-cell lymphoma were treated with a single dose (10, 50, 100, 250, or 500 mg/m^2) of antibody administered intravenously. Treatment-related symptoms correlated with the number of circulating CD20 cells and grade II events consisted of fever (5 patients). nausea (2), rigor (2), orthostatic hypotension (2), bronchospasm (1), and thrombocytopenia(1). No significant toxicities were observed during the 3 months of follow-up. Serum C3, IgG, and IgM levels, neutrophils, and T cells were largely unchanged. At the three higher dose levels. pharmacokinetics of the free antibody showed a serum half-life of 4.4 days (range, 1.6 to 10.5). Levels greater than 10 µg/mL persisted in 6 of 9 patients for more than 14 days. No quantifiable immune responses to the infused antibody have been detected. $CD20^+$ B cells were rapidly and specifically depleted in the peripheral blood at 24 to 72 hours and remained depleted for at least 2 to 3 months in most patients. Two-week postinfusion tumor biopsies showed the chimeric antibody bound to tumor cells and a decrease in the percentage of 3 cells. Tumor regressions occurred in 6 of 15 patients (2 partial and 4 minor responses). The results of this single-dose trial have been used to design a multiple-dose phase 1/11 study.

(...)

In contrast, the antigen CD20, a 32-kD nonglycosylated phosphoprotein present on the surface of nearly all 3 ceils provides a more universal target for immunotherapy. CD20 is expressed on the surface of normal 3 cells from the time of cytoplasmic µH chain expression throughout differentiation until the antibody-secreting plasma cell stage. Importantly, it is not expressed on early pre-B cells, stem cells, or antigen-presenting dendritic reticulum cells. More than 90% of B-cell NHLs express this surface protein. It is also expressed at a lower density on B-cell chronic lymphocytic leukemia. Although the function of this molecule is not completely defined, it may aggregate and function as a calcium channel. Antibodies binding to surface CD20 can induce a transmembrane signal that can cause a variety of effects from cell activation to blocking cell cycle progression and differentiation.
The CD2O protein has multiple *trans*-membrane domains and does not modulate from the cell surface in response to antibody binding and thus provides an ideal target for immunotherapeutic strategies not depending on internalization for their antitumor effect.
(...)

[5] Blood, vol. 84, no. 8 (15 October) 1994: pp. 2457-2466; hereinafter: Maloney 1994

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DISCUSSION

In this phase 1 clinical trial, patients with relapsed NHL received a single infusion of chimeric anti-CD2O MoAb IDEC-C2B8 in doses ranging from 10 to 500 mg!m2. All patients received the planned dose and no dose-limiting toxicities were identified. Symptoms were mild to moderate and easy manageable and more commonly observed in the three patients with high numbers of CD20 antigen-bearing B cells (normal or malignant) present in the peripheral blood, suggesting that the destruction or removal of these cells during the early portions of the antibody infusion may contribute to the adverse events observed.
(...)
Treatment caused a selective elimination of the peripheral CD20-expressing B cells in all but 1 patient receiving doses of 100 mg/m^2 or greater. (...)
(...)
The mechanism of the antibody-induced antitumor effect is not dear. Serum complement levels (C3) were slightly changed in only 2 patients during therapy. The chimeric antibody is capable of lysing target tumor cell lines in vitro by complement and antibody-dependent cell-mediated lysis. (...)
(...)
Based on these observations of safety and tumor responses to a single infusion of this chimeric anti-CD20 MoAb, a phase I/II trial using four weekly doses of antibody in patients with relapsed B-cell NHL has been initiated.

2.12. In September 1997, the article *IDEC-C2B8 (Rituximab) Anti-CD2O Monoclonal Antibody Therapy in Patients With Relapsed Low-Grade Non-Hodgkin's Lymphoma*, by D.G. Maloney et al. was published in the journal *Blood* in the form of a "rapid communication".[6] This article *inter alia* comprises the following passages:

IDEC-C2B8 is a chimeric monoclonal antibody (MoAb) directed against the B-cell-specific antigen CD20 expressed on non-Hodgkin's lymphomas (NHL). The MoAb mediates complement and antibody-dependent cell mediated cytotoxicity and has direct antiproliferative effects against malignant B-cell lines in vitro. Phase I trials of single doses up to 500 mg/m^2 and 4 weakly doses of 375 mg/m^2 showed clinical responses with no dose-limiting toxicity. We conducted a phase II, multicenter study evaluating four weekly infusions of 375 mg/m^2 IDEC-C2B8 in patients with relapsed low grade or follicular NHL (Working Formulation groups A-D). Patients were monitored for adverse events, antibody pharmacokinetics, and clinical response. Thirty-seven patients with a median age of 58 years (range, 29 to 81 years) were treated. All patients had relapsed after chemotherapy (median of 2 prior regimens) and 54% had failed aggressive chemotherapy. Infusional side effects (grade 1-2) consisting of mild fever, chills. respiratory symptoms. and occasionally hypotension were observed mostly with the initial antibody infusion and were rare with subsequent doses. Peripheral blood B-cell depletion occurred rapidly, with recovery beginning 6 months posttreatment. There were no significant changes in mean lgG levels and infections were not increased over what would be expected in this population. Clinical remissions were observed in 17 patients (3 complete remissions and 14 partial remissions). yielding an intent to treat response rate of 46%. The onset of these tumor responses was as soon as 1 month posttreatment and reached a maximum by 4 months posttreatment. In the 17 responders, the median time to progression was 10.2 months (5 patients exceeding 20 months). Likelihood of tumor response was associated with a follicular histology, with the ability to sustain a high serum level of antibody after the first infusion, and with a longer duration of remission to prior chemotherapy. One patient developed a detectable but not quantifiable immune response to the antibody that had no clinical significance. IDEC-C2B8 in a dose of 375 mg/m^2 weekly for 4 weeks has antitumor activity in patients with relapsed low-grade or follicular NHL. Results with this brief, outpatient treatment compare favorably with results with standard chemotherapy, and IDEC-C2B8 has a better safety profile. Further studies evaluating IDEC-C2B8 in other types of lymphoma either alone or combined with chemotherapy' are warranted.
(...)
IDEC-C238 is a chimeric anti-CD2O MoAb containing human IgGl and k constant regions with murine variable regions. It binds the CD20 antigen with high affinity (5x10^{-9} mol/L). Because of the human constant Ig regions, the chimeric antibody efficiently kills CD20 cells in virtro by augmented complement-mediated lysis and participates in antibody-dependent cell-mediated cytotoxicity (ADCC) using human complement and immune effector cells. In some NHL cell lines, the binding of the antibody inhibits proliferation and directly induces apoptosis. In patients with lymphoma, the administration of single doses up to 500 mg/m^2 was not associated with any dose limiting toxicity. Rapid binding to and depletion of CD20$^+$ normal B cells and tumor cells in the peripheral blood and bone marrow was observed, and tumor cells in lymph node biopsies obtained 2 weeks after antibody therapy showed that the chimeric MoAb bound to CD20 antigen sites. The treatment was well tolerated, causing only minimal infusion-related symptoms. (...)

[6] Blood. vol. 90. no. 6 (15 September) 1997: pp. 2188-2195; hereinafter: Maloney 1997

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2.13. In July/August 1998, the article *Rapid tumor lysis in a patient with B-cell chronic lymphocytic leukemia and lymphocytosis treated with an anti-CD2O monoclonal antibody (IDEC-C2B8, rituximab)*, by M. Jensen et a;. was published in the journal *Annals of Hematology* in the form of a "rapid communication".[7] The article is the following:

Summary In this report we present a patient with B-cell chronic lymphocytic leukemia who developed an acute tumor lysis syndrome after administration of the human anti-CD20 antibody IDEC-C2B8 (RITUXIMAB) in standard dose of 375 mg/m^2. IDEC-C2B8 has been demonstrated to have only mild and tolerable side effects in patients with follicular lymphoma. In these trials patients with lymphocytosis >5000/µl were excluded.
Physicians must be aware of this hitherto unreported phenomenon in patients with high CD20-positive blood counts.

(…)

Introduction

Clinical trials with the chimeric human monoclonal anti-CD20 antibody IDEC-C2B8 (rituximab) demonstrated remission rates up to 50% in relapsed low-grade follicular non-Hodgkin's lymphoma. Efficacy and safety in the treatment of chronic lymphocytic leukemia (CLL) and other blood-born tumors has not been investigated yet.
Here we report on a 26-year-old woman with B-CLL who experienced a rapid reduction of circulating malignant cells accompanied by severe side effects after her first rituximab infusion.

Case report

In October 1997, a 26-year-old female patient with progressive low-grade B-cell lymphoma was admitted to our hospital. She had been heavily pretreated including 12 cycles of intensive chemotherapy and high dose chemotherapy with peripheral stem cell support. She had enlarged cervical and abdominal lymph nodes, hepatosplenomegaly and bone marrow infiltration. A leukocytosis of 111.9 x 10^9/L with 97% small malignant lymphocytes was noticeable, phenotypically resembling B-cell chronic lymphocytic leukemia (CD5+, CDI0+-, CD 19+, CD23+. CD25+). The CD20 surface marker was expressed on 100% of these cells. As a result of clinical reevaluation, a treatment with the anti-CD2O antibody rituximab was initiated. After prophylactic hydration. as well as administration of 1000 mg acetaminophen and 300 mg allopurinol, treatment was begun with a predose of 50 mg antibody. The patient complained about moderate scratching sensations in her throat, chills, and a moderate rise in body temperature 90 min after this test infusion. Following pethidine, she recovered quickly, and the remaining 550 mg of the planned dose (375 mg/m^2) was given over four and one-half hours. Shortly after the infusion was completed, chills occurred again and fever up to 39.7°C developed. The pulse increased to 124/min. The patient complained about nausea and vomiting. A blood count revealed a sharp decline in leukocytes from 111.9 x 10^9/L to 24.0 x 10^9/L and a drop in platelets from 137.0 x 10^9/L to 35.0 x $10^{9/}$L. The plasma prothrombin time fell from 92% to 65%, and serum LDH activity rose from 464 U/L to 793 U/L.
During the following 24 hours, the clinical condition and laboratory parameters of the patient further deteriorated (see Figure), resembling an acute tumor lysis syndrome with disseminated intravascular coagulation. Serum LDH rose to >2000 U/L: plasma prothrombin time and platelets continued to drop to 47% and 23 x 10^9/L, respectively. The plasma D-dimers rose from 4.8 mg/L to 42.2 mg/L; serum transaminase activities were moderately increased (Figure). Importantly, complement factors were undetectable 7 hours after the beginning of the infusion. The patient was intensively treated with forced diuresis including furosemide, bicarbonate, calcium, potassium, platelet transfusion as well as ondansetron. As a result, the clinical performance status gradually improved from day two onwards. and laboratory parameters began to normalize. Three further infusions of rituximab were administered in full dose on days 8, 15, and 22 without clinical problems. The patient's leukocyte count subsequently normalized (8.8 x 10^9/L) for 3 weeks whereafter she showed signs of progressive disease, requiring salvage chemotherapy.

Discussion

Fast but transient clearance of circulating lymphoma cells without major side effects using a monoclonal antibody was reported by Nadler et al. in a patient with diffuse, poorly differentiated lymphocytic lymphoma (DPDL) and a WBC of 110.000 x 10^9/L. In patients with chronic lymphocytic leukemia elimination of malignant cells from the blood stream has been observed using another human monoclonal antibody, Campath-1H (anti-CD52). The effector mechanisms of Campath-1H include complement-mediated lysis and cellular cytotoxicity and are very similar to those employed by rituximab. Since complement factors dropped to undetectable levels in our patient within seven hours, it might be speculated that the complement-mediated cell lysis played a decisive role in triggering the acute tumor lysis observed.

[7] Ann Hematol 1998, 77: pp. 89-91

Although the major non-hematological side effects such as nausea, fever, rigor or hypotension are similar for rituximab and Campath-1H, none of 29 CLL patients treated with Campath-1H showed signs of rapid tumor lysis. One possible explanation is the different schedule used: Campath-1H was administered three times weekly at initial doses of 3 or 10 mg which were escalated to 30 mg. The recommended standard dose of375 mg/m^2 for rituximab was established in patients with follicular lymphoma and lymphocyte counts of less than 5.0 x 10^9/L. Thus, this dose might be too high for the treatment of patients with substantial peripheral tumor bad.
Alternatively, high peripheral tumor cell counts must be reduced using cytostatic drugs prior to administration of rituximab. Recently. we have treated six additional B-CLL patients and one patient with a leukemic mantle cell lymphoma with rituximab. The clinical side effects were minor in three patients with lymphocyte counts of 0.2 x 10^9/L, 6.6 x 10^9/L. and 9.4 x 10^9/L, respectively. Signs of acute tumor lysis and NCI grade III and IV toxicities occurred in patients with marked lymphocytosis who had 30.7 x 10^9/L, 60.8 x 10^9/L, 69.8 x 10^9/L, 108.5 x 10^9/L, and 294.3 x 10^9/L lymphocytes, respectively.
When treating patients with CLL and marked lymphocytosis with the monoclonal antibody rituximab, physicians need to be aware of the risk of hitherto unreported acute tumor lysis and intravascular coagulation.

2.14. In August 1998, the article *Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose treatment program*, by P. McLaughlin et al. was published in the *Journal of Clinical Oncology*.[8]

Purpose: The CD20 antigen is expressed on more than 90% of B-cell lymphomas. It is appealing for targeted therapy, because it does not shed or modulate. A chimeric monoclonal antibody more effectively mediates host effector functions and is itself less immunogenic than are murine antibodies.
Patients and Methods: This was a multiinstitutional trial of the chimeric anti-CD20 antibody, IDEC-C2B8.
Patients with relapsed low grade or follicular lymphoma received an outpatient treatment course of IDEC-C2B8 375 mg/m^2 intravenously weekly for four doses.
Results: From 31 centers, 166 patients were entered. Of this intent-to-treat group, 48% responded. With a median follow-up duration of 11.8 months, the projected median time to progression for responders is 13.0 months. Serum antibody levels were sustained longer after the fourth infusion than after the first, and were higher in responders and in patients with lower tumor burden. The majority of adverse events occurred during the first infusion and were grade 1 or 2; fever and chills were the most common events. Only 12% of patients had grade 3 and 3% grade 4 toxicities. A human antichimeric antibody was detected in only one patient.
Conclusion: The response rate of 48% with IDEC-C2B8 is comparable to results with single-agent cytotoxic chemotherapy. Toxicity was mild. Attention needs to be paid to the rate of antibody infusion, with titration according to toxicity. Further investigation of this agent is warranted, including its use in conjunction with standard chemotherapy.

Approximately 80% of malignant lymphomas are of B-cell origin. Virtually all patients with low grade or follicular histology will eventually relapse after treatment with currently available standard therapies, as will many with more aggressive histologic categories. Those who relapse need alternative therapeutic approaches. The cell-surface antigen CD20 is expressed on more than 90% of B-cell lymphomas and chronic lymphocytic leukemias. and on 50% of pre-B-cell acute lymphoblastic leukemia. It is expressed on normal B cells from the pre-B-cell stage to the activated B-cell stage, but is not expressed on stem cells, plasma cells, or cells of other lineages. It is a transmembrane protein that appears to act as a calcium channel and to play an important role in cell-cycle progression and differentiation. Monoclonal antibodies that target the CD20 antigen have been developed, both for diagnostic and therapeutic purposes. The CD20 antigen is appealing for targeted therapy, because it does not shed, modulate, or internalize.
(...)
The chimeric human-mouse anti-CD20 monoclonal antibody, Rituximab (IDEC-C2B8; IDEC Pharmaceuticals Corp, San Diego, CA), is a human immunoglobulin (Ig) Gl kappa antibody, with mouse variable regions isolated from a murine anti-CD20 monoclonal antibody, IDEC-2B8. A single-dose phase I trial demonstrated both biologic efficacy in terms of transient 3-cell depletion and a good safety profile. [*footnote 18: Maloney DG, Liles TM, Czerwinski DK et al; Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma, Blood 84:2457-2466, 1994*] Subsequently. a multiple-dose schedule was shown to be feasible and to achieve a 50% response rate in a cohort of 34 patients with relapsed low grade lymphoma. [*footnote 19: Maloney DG, Grillo-Lopez AJ, White CA, et al: IDEC-C2B8 (Rituximab) anti-CD20 antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma, Blood 90:2188-2195, 1997*]
The current report summarizes results of a multiinstitutional trial of a four-dose course of therapy with this chimeric anti-CD20 monoclonal antibody.

[8] Journal of Clinical Oncology, vol. 16, no. 8 (August) 1998: pp. 2825-2833

PATIENTS AND METHODS

Eligibility
Adult patients with relapsed low grade or follicular B-cell lymphoma, histologically confirmed and positive for CD20, were eligible. Patients with chronic lymphocytic leukemia (lymphocytes >$5x10^9$/L) were excluded.
Patients had to have either not responded to primary therapy or relapsed (...). have progressive measurable disease, and sign an institutional review board-approved informed consent. (...)

Therapy
The antibody dose was 375 mg/m^2, administered intravenously once weekly for a total of four infusions (days 1, 8, 15, and 22) on an outpatient basis. (...)

(...)

RESULTS

Patient Features
The 166 patients were enrolled at 31 centers in the United States and Canada between April 1995 and March 1996. The median age was 58 years (range. 22 to 79). There were 105 men and 61 women. There were 33 with small lymphocytic lymphoma (SL), 67 with follicular small cleaved, 53 with follicular mixed, three with other low grade lymphoma variants, and 10 with follicular large cdl. The median time since diagnosis was 4.1 years (range, 0.5 to 25).
(...)
Response
The overall response rate for the intent-to-treat group of all 166 patients was 48%, of which 6% were CRs and the remainder PRs.
(…)

DISCUSSION

The response rate was 50% with this outpatient four-dose course of therapy with IDEC-C2B8 for patients with relapsed low grade or follicular lymphoma. Most of the responses were partial (6% complete), which is typical of single-agent therapy in the setting of relapsed lymphoma. These results are comparable to some of the most encouraging recent chemotherapy results for relapsed indolent lymphoma. such as with fludarabine or 2-chlorodeoxyadenosine.
(...)
The toxicity of the current program was notably mild, particularly with respect to myelosuppressive toxicities that are typical of standard chemotherapy or RIT. Adverse events occurred mainly with the first infusion, in a constellation that typically included modest (grade 1 or 2) and brief (minutes to hours) fever, chills, and aches.
By the second and subsequent infusions. the majority of patients experienced no further infusion-related toxicities. (...)
(…)
The high response rate with this antibody was encouraging. including its efficacy in patients with adverse prognostic features (...) and in patients who often tolerate standard therapies poorly (...). Observations in patient subsets with low response rates were also informative. A rapid clearance of the antibody, which may be related, in part, to high tumor burden ("antigen sink"), correlated with a lower response rate. Conceivably, higher doses or more protracted dosing schedules might overcome this problem. The lower response rate with SL lymphoma, compared with follicular lymphoma, may relate to the lower density of CD20 antigen expression on SL cells.
However, patients with SL in this trial also typically had higher circulating B-cell counts and consequently a more rapid clearance of the agent than other patients. so the lower response rate in SL lymphoma may also be related to their lower measurable antibody levels.
(...)
Many additional issues about this agent remain to be explored. (...) On the basis of the 50% response rate in this trial, using this well-tolerated, outpatient treatment schedule that is completed in 22 days, further trials with this agent are warranted.

2.15. In September 1998, the article *Association of serum Rituximab (IDEC-C2B8,) concentration and anti-tumor response in the treatment of recurrent low-grade or follicular non-Hodgkin's lymphoma*, by N.L. Berinstein et al. was published in the journal *Annals of Oncology*.[9] This article *inter alia* comprises the following passages:

[9] Annals of Oncology 9:995-1001. 1998

C/09/517753 / HA ZA 16-1056
21 February 2018

Summary

Background: Monoclonal antibodies are being utilized for treatment of patients with low-grade non-Hodgkin's lymphoma as well as other cancers. Results from phase 1 and II clinical studies has shown that the chimeric monoclonal antibody Rituximab has minimal toxicity and significant therapeutic activity in low grade non-Hodgkin's lymphoma.
Patients and methods: We have recently reported on a multi-centre pivotal phase III clinical trial involving 166 patients with recurrent low-grade lymphoma who were treated with four infusions of Rituximab. Eighty patients (48%) achieved objective responses including 10 patients (6%) with complete responses. Overall, 126 patients (76%) had a 20% reduction in overall tumor size. The median response duration and time to progression are 11.6 and 13.2 months, respectively. The infusional and long term toxicities were limited.
Results: In this report we describe the pharmacokinetic data obtained on these patients. Measurable concentrations of Rituximab were detected in all patients after the first infusion and increased throughout the treatment course. The half-life of the monoclonal antibody increased from 76.3 hours after the first infusion to 205.8 hours after the fourth infusion and was concomitant with a four-fold decrease in the antibody clearance. At three months and six months post-treatment, the median Rituximab serum levels were 20.3 µg/ml (range 0.0 to 96.8µg/ml in 104 patients) and 1.3 ig!m1 (range 0.0-28.7 µg/ml in 13 patients), respectively. A statistically significant correlation was found between the median antibody concentration and response for multiple time points during the treatment and followup. The mean serum antibody concentration was also inversely correlated with measurements of tumor bulk and with the number of circulating 3 cells at baseline.
Conclusions: We conclude that Rituximab is therapeutically effective against 3-celI lymphoma. Pharmacokinetic data suggests that certain subsets of patients may possibly benefit from increased dosing and studies to address this are currently underway.

(...)
Discussion
(...)
The level of Rituximab used in this study (375 mg/m^2) was chosen based upon these previous studies because it was a safe. non toxic dose with demonstrable therapeutic activity. However extrapolation of these results suggest that higher doses of Rituximab may result in even higher serum levels of Rituximab and possibly greater therapeutic activity in certain patient subsets.

(…)
The association of high serum antibody concentration and response and the association of high serum antibody concentration with lower tumor bulk suggest that higher doses (or more doses) of Rituximab may be necessary to induce responses in some subsets of patients such as those with bulky disease.
(...)
Future studies will address whether anti-tumor activity can be enhanced even further by administration of larger total doses of Rituximab.

2.16. In September 1998, the article *Rituximab (Anti-CD20 Monoclonal Antibody) for the Treatment of Patients With Relapsing or Refractory Agressive Lymphoma: A Multicenter Phase II Study*, by B. Coiffier e.a. was published in the journal *Blood*.[10] The last paragraph of this article (p. 1932, right column) is:

In conclusion, the results of this study indicate that rituximab therapy has significant anti-lymphoma activity in DLCL and MCL patients without the toxicity commonly observed with combination chemotherapy regimens.
There was no marked differences in efficacy between the two dosing regimens, but the safety profile of the higher dose (500 mg/m^2) was less favorable as compared with the standard dose regimen (375 mg/m^2). This regimen should be evaluated in combination with standard chemotherapy in patients with aggressive B-cell lymphoma.

[10] Blood, vol 92, no 6(15 September) 1998: pp. 1927-1932

C/09/517753 / HA ZA 16-1056
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The Preliminary Relief Proceedings

2.17. In the judgment of 12 May 2017, the preliminary relief judge of this district court rejected Biogen's infringement claims in proceedings between *inter alia* Biogen and Celltrion because in his provisional judgment a serious, non-negligible chance exists that the patent would be nullified in proceedings on the merits or revoked in opposition because of added matter.

3. The Dispute

3.1. Celltrion claims:

1. to nullify the Dutch part of EP 572 and EP 313;
2. to order Biogen in a judgment having immediate effect to pay the reasonable and proportionate costs of these proceedings in accordance with section 1019h DCCP[11], to be paid within two business days after the date of the judgment, failing which said amount is increased by the statutory interest as referred to in article 6:119 DCC[12], from the third business day after the judgment until the day of full payment.

3.2. In its document of 22 February 2017, Celltrion supplemented its claim under 1 as follows:

- to declare that Biogen is not entitled to enforce the Dutch part of EP 313 against Celltrion.

As assessed above under 1.2, this amendment of claim was refused at the hearing.

3.3. At the hearing, Celltrion indicated to be prepared to withdraw its claim for nullification of the Dutch part of EP 572 as after the issue of the writ of summons this patent has been irrevocably revoked, with the proviso that it maintains its claim to order Biogen to pay the costs of the proceedings with respect to EP 572.

3.4. With reference to EP 313, Celltrion appealed to article 76(1) EPC (which the district court interprets as an appeal to section 75(1)(c) Dutch Patents Act 1995 with regard to the Dutch part of EP 313) and advanced that the matter of EP 313 contains added matter as compared to the original application. Furthermore, Celltrion is of the opinion that EP 313 cannot derive any priority from the invoked priority document, causing the O'Brien Abstract submitted by it as exhibit 25 to be novelty destroying prior art.. Furthermore, EP 313 lacks inventive step and is also insufficiently disclosed, according to always Celltrion.

3.5. Biogen puts up a defense.

3.6. The parties' assertions will be further discussed below, as far as relevant.

4. The Assessment

Jurisdiction

[11] Dutch Code of Civil Procedure
[12] Dutch Civil Code

4.1. The district court has international jurisdiction to hear the claims pursuant to article 24(4) Brussels I Regulation[13]. The relative competence rests on section 80(1)(a) Dutch Patents Act.

EP 572

4.2. The district court considers the claim with respect to the nullification of EP 572, in view of Celltrion's statement at the hearing, as withdrawn so that this need not be discussed anymore.

EP 313

Introduction to the Art

4.3. The following introduction to the art of the patent has been derived from undisputed parts of – *inter alia* – the writ of summons, the statement of defense, exhibits submitted by the parties and the debate at the hearing.

4.4. *Cancer*

4.4.1. Cancer is a disease in which cells proliferate abnormally. In many forms of cancer, this leads to tumors, i.e. a proliferation of mutated and (initially) locally growing cells. Cancerous cells may invade neighboring tissue or even spread through the body and form new tumors in other places (metastasis). Forms of cancer are often referred to with a name that is derived from the place in the body where (solid) tumors are found. Well-known forms of cancer are, for example, esophageal cancer, lung cancer and breast cancer.

4.4.2. Other forms of cancer, like leukemia, do not form solid tumors. Instead, in leukemia cells of particular cell types in the blood mutate and start proliferating in an uncontrollable manner. Chronic lymphocytic leukemia (hereinafter: CLL)) is the most common subtype of leukemia in America and Europe.

4.4.3. In CLL, a specific type of white blood cells (the B-cells, also referred to as B-lymphocytes; see below under 4.5.1.) mutate. These mutated B-cells are present in abnormally large numbers in blood and bone marrow (where blood cells are produced), so that the total number of white blood cells (normal and cancerous) is very high. Measurement of an abnormally high number of lymphocytes circulating in the blood is the most common way to diagnose CLL. At the priority date, the American National Cancer Institute (NCI) had two sets of guidelines, one published in 1988 and an update hereof from 1996. According to these guidelines, CLL was diagnosed by the presence in patients of more than 5×10^9/L circulating lymphocytes in the blood.

4.4.4. The lymphatic system is part of the circulatory system, which together with the blood vessels takes care of transport of all sorts of substances. The lymphatic system is an important part of the immune system. In the lymphatic system not blood but lymph is present, a clear fluid that contains lymphocytes just like blood.

4.4.5. A lymphoma is a cancer of the lymphatic system. Unlike leukemia, lymphomas are solid tumors that accumulate in the lymph nodes.

[13] Regulation (EU) No. 1215/2012 of the European Parliament and of the Council of 12 December 2012 on Jurisdiction and the Recognition and Enforcement of Judgments in Civil and Commercial Matters.

4.4.6. Small lymphocytic lymphoma (SLL) is a lymphoma. SLL is often classified as a sub-category of Non-Hodgkin lymphoma (NHL). SLL-patients in general do not have circulating tumor cells.

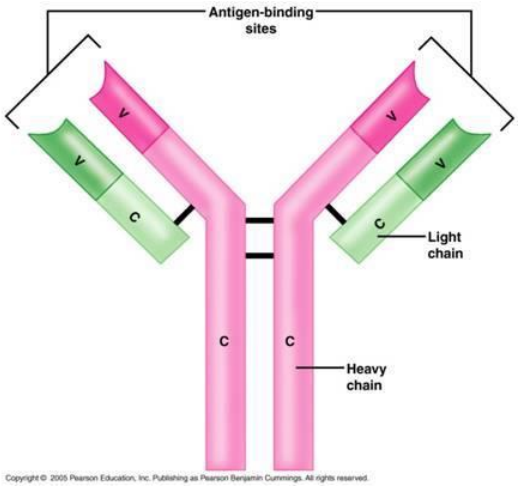
4.4.7. According to the *current* classification of the World Health Organization (WHO), CLL and SLL are viewed as different expressions of the same disease, in which CLL mainly manifests itself in the blood/bone marrow and SLL mainly in the lymph nodes.

4.4.8. The treatment of cancer is focused on the removal or killing of the cancer cells. The removal of mutated cells must take place as selectively as possible, so that healthy, normally proliferating tissue gets damaged as little as possible. In the case of solid tumors this can be accomplished surgically. Cancerous cells can also be subjected to agents that kill the cancerous cells. Well-known methods are subjecting tumors to radiation (radiotherapy) or administering medicaments (chemotherapy). In almost all cases however healthy tissue is inevitably also affected. Another form of therapy is immunotherapy, in which the immune system of the patient is used to combat cancerous cells. This case is about a medicinal product for immunotherapy.

4.5. The Immune System and Monoclonal Antibodies

4.5.1. When the body is faced with pathogens (agents that cause disease) such as bacteria or viruses, the human immune system generates antibodies to identify and neutralize these harmful agents. The immune system comprises numerous kinds of cells involved in protecting the body against pathogens, such as white blood cells. An important subcategory of white blood cells are the so-called lymphocytes, which make up around 30% of the white blood cells in a healthy individual. Lymphocytes can be further subdivided into *natural killer cells* (NK-cells), T-cells and B-cells.

4.5.2. Antibodies are relatively large, Y-shaped proteins and contain both constant regions and variable regions, which differ depending on the specific antigen to which that antibody can bind. An antigen is a molecule that is capable of triggering a response by the immune system. Pathogens contain many protruding molecule-ends that can function as antigens. An antibody binds to a unique specific part of the antigen via the variable region located at the 'tip' of the Y, as depicted below:



Light coloured regions marked with a 'c' depict **c**onstant regions; darker coloured regions marked with a 'v' depict **v**ariable regions.

There are millions of possible variations in the variable region. Therefore, the different antibodies are able to recognize and neutralize a corresponding number of different antigens.

4.5.3. Although antibodies are naturally created by the immune system, they can also be produced outside of a patient's body and then injected to fight a disease or help the immune system fight a disease. Such antibodies can be used to target antigens which do not naturally trigger a (sufficient and/or quick enough) immune response. The most used method for creating antibodies involves selecting and then cloning cell lines derived from antibody-producing cells from mice. Because all antibodies that are created via this method result from the cloning of the same cell line, such antibodies are called 'monoclonal antibodies'.

4.5.4. A well-known problem with antibodies (originally) obtained from mice (so-called '*murine antibodies*') is that the human immune system recognizes these antibodies as pathogens, and thus creates its own antibodies to fight these murine antibodies. This is known as the '*human anti-mouse antibody (HAMA) response*'. As the HAMA response neutralizes the antibodies administered to the patient, it stands in the way of efficacy. The response also results in systemic inflammatory effects. To prevent the HAMA response, the antibodies can be engineered to appear more like human antibodies. One way of doing this is by creating so-called '*chimeric antibodies*'. These antibodies are made by fusing the variable regions of the murine antibody (the antibody derived from the mouse) to constant regions of human antibodies. The antibody obtained resembles an antibody made by the human body itself more closely.

4.6. Rituxitnab

4.6.1. Rituximab (initially also called IDEC-C2B8) is a chimeric monoclonal antibody that specifically targets an antigen that is known as 'CD20'. The CD20 antigen is a protein expressed on the surface of one type of white blood cells, i.e. mature B cells. This antigen is not expressed on other cell types. As rituximab targets the CD20-antigen, rituximab is called an anti-CD20 antibody. Rituximab does not attack cells which do not express the CD20 antigen. Rituximab also does not affect the early forms of B-cells, such as stem B-cells and pro-B-cells, as these do not yet express CD20. Therefore the body can continue the creation of new B-cells; the immune system is thus not permanently affected by rituximab.

4.6.2. Rituximab is used to treat diseases which involve B-cells or abnormalities in the B-cells, such as the type of cancers described before called CLL and SLL.

4.6.3. When rituximab binds to the CD20 surface protein on a B-cell, a process is triggered which will cause the cell membrane of that cell to rupture, thereby destroying the cell. This process is called 'lysis'. The contents of the cell then enter the bloodstream. When a large number of cells are destroyed, a patient may experience a number of side effects as a result. In the fight against cancer, the more severe cases of side effects are called '*acute tumor lysis syndrome*' (TLS). As TLS is caused by cell death (which is the purpose of the treatment), the occurrence of TLS is an indication as such that therapy is working. This process is not unique for rituximab and can also take place with other medicines that kill cells. It is and was a well-known side-effect of chemotherapy.

Lack of Inventive Step

4.7. The district court sees cause to first assess whether EP 313, as Celltrion asserted, is invalid because of lack of inventive step. For this, it will focus on the claims according to the auxiliary

request. For if these are held invalid, the same also applies to the broader claims of the patent as granted.

4.8. In its inventive step attack, Celltrion departs from McLaughlin as closest prior art (see 2.14.). However, Biogen advanced that the skilled person, looking for a treatment method for CLL, would have searched for publications about the treatment of CLL. Biogen is of the opinion that Jensen (see 2.13.) forms the *most promising springboard*, as the Opposition Division also assumed.

4.9. Although it can be admitted to Biogen that McLaughlin does not pertain to the treatment of CLL - McLaughlin is about the treatment of lymphomas like SLL and patients with CLL are explicitly excluded from the study in McLaughlin (see ground 4.16 - 4.18 below) –a patent must in principle be inventive as compared to all prior art as long as a publication does form a suitable starting point.

4.10. Although the parties have a difference of opinion on the question whether SLL and CLL can be designated as the same disease, it is not in dispute that SLL and CLL are at least related pathologies[14], because both diseases share the similarity that they originate from a mutation of B-cells leading to the uncontrolled proliferation of these cells. This is supported by the statements of the party experts from both sides, Prof. D. Oscier and Prof. V.A. Boussiotis for Celitrion and Prof. S.E. Coutré for Biogen.

4.11. With reference to Batata and Shen (see 2.9.) and the publication by Pangalis (see 2.10.), of which Boussiotis was the co-author, Prof. Oscier and Prof. Boussiotis also explained in their statements that the morphology, the immunophenotype and the molecular features of tumor cells are equal in CLL and SLL (for this case, the equality of the CD20 proteins on the cell surface is particularly relevant) so that CLL, although this disease manifests itself clinically in a different way than SLL (i.e. in the blood and not in the lymphatic region) and is also classified in a different way (the 'cut of' in CLL is at more than 5.0×10^9/L circulating lymphocytes, where this is $\leq 4.0 \times 10^9$/L in SLL), can be regarded as a disease related to SLL. Biogen has not disputed this or not in a sufficiently substantiated manner.

4.12. In view of the above, it cannot be said that McLaughlin is not a realistic starting point, and for that reason the district court will assess the inventive step of (the auxiliary request of) EP 313 on the basis of this publication.

4.13. The district court assumes, as does Celltrion, that in this case the skilled person consists of a team that in any case includes a clinician who specializes in hematologic malignancies with knowledge of CLL and SLL. Whether the treating clinician is a hematologist or an oncologist is not so relevant, as also Biogen, when asked at the hearing, acknowledged that in the Netherlands (different from in the United States) at the time of the priority date which Biogen invokes and which the district court assumes (9 November 1998) no strict division existed in that sense that SLL was always treated by an oncologist and CLL by a hematologist. This is also consistent with the statement by Biogen's own expert, Prof. M.H.J. van Oers, emeritus professor hematology, that he '*prior to, as well as after, November 1998 [... "] was' treating patients having hematologic malignancies, including lymphoma and leukemia*'.[15]

[14] See the paragraphs 12, 14 and 18 pleading notes Biogen
[15] Biogen's exhibit 22, paragraph 1

4.14. McLaughlin describes a clinical trial with 166 patients with B-cell lymphoma ('*patients with relapsed low grade or follicular lymphoma*') treated with four weekly intravenous dosages of the anti-CD20 antibody rituximab (in the publication also called: 'IDEC-C2B8') of 375 mg/m^2. Under the heading 'Eligibility' it is indicated that '*Patients with chronic lymphocytic leukemia ('lymphocytes > 5 x 10^9/L) were excluded*'.

4.15. It is not in dispute between the parties that the claims 1 and 3 of the auxiliary request of EP 313 as compared to McLaughlin differ in a higher dosage of 500 – 1500 mg/m^2 rituximab.

4.16. Biogen is of the opinion that the application of rituximab for the treatment of CLL forms a second difference measure. Celltrion does not agree with this because McLaughlin, although it is stated in that publication that this is not the case, does actually include patients with CLL in the trial. In this respect, Celltrion refers to example 3 of EP 313 that mentions that the number of white blood cells of the patients participating in the trial is between 4 x 10^9/L and 200 x 10^9/L. As about 30% of the white blood cells consists of lymphocytes, the lower limit for lymphocytes in example 3 is around 1.2 x 10^9/L. As McLaughlin defines the upper limit for the number of lymphocytes in his trail on 5 x 10^9/L there is an overlap, according to still Celltrion.

4.17. Biogen contested this argument in a substantiated manner. With reference to the article by Cheson[16] it advanced that it was generally known that CLL is diagnosed by a quantity of over 5 x 10^9/L circulating lymphocytes at the moment of the diagnosis. Although after treatment the quantity of circulating lymphocytes may decrease under the value mentioned, the diagnosis of patients does not change, they remain CLL-patient. Example 3 of the patent pertains to CLL-patients who have at least been treated one time before. In view of the lower limit of the number of white blood cells mentioned in the example, this trial apparently involved patients in whom earlier treatment has taken such good effect that the quantity of lymphocytes in them has actually been reduced to under the 'cut off' 5 x 10^9/L. However, this does not mean that can be spoken of an overlap between the patient population in this example and the one of McLaughlin, according to Biogen.

4.18. At the hearing, Celltrion did not further dispute Biogen's interpretation so that Celltrion's argument to the contrary is rejected.

4.19. The distinguishing features of the claims 1 and 3 of the auxiliary request of EP 313 as compared to McLaughlin are therefore 1) the application of rituximab for the treatment of CLL and 2) the higher dosage of 500 - 1500 mg/m^2.

4.20. The technical effect of the distinguishing features is an effective treatment of CLL-patients with rituximab so that the objective technical problem may be formulated as the provision of an effective treatment for CLL.

4.21. McLaughlin first teaches the skilled person that the antigen CD20 is expressed on over 90% of the surface of B-cells in both lymphomas and chronic lymphocytic leukemia (CLL) and that it is '*appealing is for targeted therapy*'. Subsequently, McLaughlin describes the anti-CD20 antibody rituximab and the earlier phase I and II trials in which this antibody was used for the treatment of relapsed low grade NHL and follicular NHL as represented in the publications by Maloney 1994 (15 patients with a single dose rituximab of 10, 50, 100, 250 or 500 mg/m^2 - see 2.11.) and Maloney 1997

[16] B.D. Cheson e.a., *National Cancer Institute - Sponsored Working Group Guidelines for Chronic Lymphocytic Leukemia: Revised Guidelines for Diagnosis and Treatment*, in: Blood, Vol 87, No 12 (15 June) 1996, pp 4990-4997

(34 patients with a dosage rituximab of 375 mg/m^2 - see 2.12.). Then, McLaughlin discusses the own trial with 166 patients of which it is stated that '*adult patients with relapsed low grade or follicular 3-cell lymphoma, histologically confirmed and positive for CD20, were eligible'* whereas '*patients with chronic lymphocytic leukemia (lymphocytes > 5 x 10^9/L)*' were excluded. The subtype SLL is specifically included in the study, as the various passages in McLaughlin show where SLL is mentioned or discussed. McLaughlin shows an '*over all response rate*' of 48% of which the '*discussion'* paragraph indicates that '*These results are comparable to some of the most encouraging recent chemotherapy results for relapsed indolent lymphoma, such as with fludarabine or 2-chlorodeoxyadenosine*'. McLaughlin identifies that the '*toxicity of the current program was notably mild*'. Negative responses mainly occurred at the first injection whereas at the second and following injections these infusion-related toxicity problems did not show in the majority of the patients. McLaughlin subsequently establishes that:

> Observations in patients with low response rates were also informative. A rapid clearance of the antibody. which may be related, in part, to high tumor burden ("antigen sink"). correlated with a lower response rate. Conceivably, higher doses or more protracted dosing schedules might overcome this problem.

McLaughlin ends with the following conclusion:

> On the basis of the 50% response rate in this trial, using this well-tolerated, outpatient treatment schedule that is completed in 22 days, further trials with this agent are warranted.

4.22. With Celltrion, the district court is of the opinion that McLaughlin forms a sufficient incentive for the average skilled person to do research into the use of rituximab for the treatment of CLL-patients in higher dosages than weekly 375 mg/m^2.

4.23. It is not in dispute that the skilled person who reads McLaughlin would understand the mechanism of action of the anti-CD20 antibody rituximab on the antigen CD20 on malignant B-cells involved in FL (follicular lymphoma)[17] or SLL, as this was already explained in the publications by Maloney from 1994 and 1997, which are recalled in McLaughlin and to which reference is made. McLaughlin himself subsequently explains in the introduction that the antigen CD20 is not only expressed on the surface of B-cells in lymphomas, but *also* on B-cells in CLL. In this respect, it may be assumed that the skilled person would understand that the anti-CD20 antibody rituximab would equally affect the antigen CD20 on the malignant B-cells involved in CLL.

4.24. Biogen only countered this by arguing that SLL was at the priority date regarded as a different disease than CLL and that, although it was known that both diseases involve mutated B-cells, major differences existed between the diseases which also manifested themselves at different places and in different forms in the body (CLL with freely circulating cells in blood and bone marrow, NHL/SLL with tumors in the lymphatic region). Prof. Boussiotis is right to observe in her declaration though that neither Biogen nor its expert Prof. Coutré explain why this would be relevant for the treatment of CLL-patients with rituximab. In other words: Biogen has not argued in a substantiated manner that the mechanism discussed above would not work or work differently in CLL than in SLL so that the district court departs from the same mechanism of action and the presence of knowledge hereof in the skilled person on the priority date.

4.25. In view of the fact that the trial that McLaughlin reports on was in any case 'over all' very successful (McLaughlin says that the results are similar to some of the most encouraging recent chemotherapy results and Biogen's own expert Van Oers speaks - as Celltrion undisputedly argued at

[17] Follicular lymphoma is another form of NHL in which malignant B-cells are involved.

the hearing[18] - of a '*pivotal trial*' that '*generated much attention in the field because it was a ground-breaking article*') and that the toxicity appeared to be mild, the skilled person would therefore be sufficiently motivated to research this and he also had a reasonable expectation of success. This is so also in view of the following.

4.26. McLaughlin indicates that a lower response was seen in SLL compared to follicular lymphoma. The skilled person might think for a moment that the use of rituximab for CLL patients would then also be less attractive. However, McLaughlin immediately provides two explanations. The publication in general indicates that a '*rapid clearance of the antibody, which may be related, in part, to high tumor burden ("antigen sink")*' was associated with a lower '*response rate*' and that possible higher dosages or '*more protracting dosing schedules*' could counter this. With reference to SLL in particular, it is remarked that:

> The lower response rate with SL lymphoma, compared with follicular lymphoma, may relate to the lower density of CD20 antigen expression on SL cells. However, patients with SL in this trial also typically had higher circulating B-cell counts and consequently a more rapid clearance of the agent than other patients, so the lower response rate in SL lymphoma may also be related to their lower measurable antibody levels.

This explanation by McLaughlin makes it obvious for the skilled person to apply a higher dosage of rituximab in SLL. Simultaneously, as Prof. Oscier and Prof. Boussiotis have stated, the explanation by McLaughlin will induce the skilled person for the same reason to study higher dosages in the treatment of CLL. After all, the tumor cells involved in SLL and CLL are identical as regards morphology, immunophenotype and molecular features (see ground 4.11.). Compared to FL, there is a lower concentration of CD20-antigen at the surface of the B-cells involved in SLL and CLL and there is a higher number of circulating B-cells in CLL. As a result hereof, in his research into the application of rituximab in CLL-patients the skilled person would be induced to use a higher dosage than 375 mg/m^2 where necessary. In the words of Prof. Boussiotis:

> The finding of McLaughtin would prompt me to try rituximab also in the treatment of CLL. Due to the higher amount of circulating B-cells, it would be logical to try higher doses, as also suggested by McLaughlin. I would have felt comfortable to try higher doses on subsequent infusions due to the reported safety profile, which is very favourable.

Prof. Oscier has stated in a similar manner:

> I think it would have been obvious to try dose escalation for the treatment of SLL. Given that CLL cells were also known to express low levels of CD20 and that Rituximab appeared to lack most of the toxicities associated with chemotherapy, it would also have been obvious to consider the use of higher (subsequent) doses of Rituximab in CLL.

4.27. The fact that the skilled person would try a dosage of 500 mg/m^2 when increasing the dosage of rituximab in CLL is obvious as Maloney already applied the same dosage in the treatment of SLL in his publication quoted above in 2.11. and reported that there were '*no significant toxicities*'. This dosage falls within the range claimed by Biogen in EP 313. Biogen did not dispute that the specific range of 500 mg/m^2 - 1500 mg/m^2 cannot provide any inventive step because this is a usual dose escalation.

4.28. The fact that the increase of the dosage in CLL seemed an appropriate measure is furthermore implied by the publication of Berinstein mentioned above in 2.15., on which Celltrion based its

[18] Paragraph 57 pleading notes Celltrion

inventive step attack in combination with McLaughlin.[19] Berinstein (of which McLaughlin, and also Maloney for that matter, was co-author) was published in September 1998, i.e. one month after the publication by McLaughlin in August 1998, and contains the pharmacokinetic data obtained in the trial on FL/SLL-patients described in McLaughlin (see the passage quoted under '*Summary*' at '*Results*'). Berinstein hints at a number of places that an increase of the dosage can be useful, for example immediately in the '*Summary*':

> We conclude that Rituximab is therapeutically effective against B-cell lymphoma. Pharmacokinetic data suggests that certain subsets of patients may possibly benefit from increased dosing and studies to address this are currently underway.

This suggestion is furthermore made on p. 999, l.c.:

> The level of Rituximab used in this study (375 mg/m^2) was chosen based upon these previous studies because it was a safe, non toxic dose with demonstrable therapeutic activity. However extrapolation of these results suggest that higher doses of Rituximab may result in even higher serum levels of Rituximab and possibly greater therapeutic activity in certain patient subsets.

and p. 1000, l.c.:

> The association of high serum antibody concentration and response and the association of high serum antibody concentration with lower tumor bulk suggest that higher doses (or more doses) of Rituximab may be necessary to induce responses in some subsets of patients such as those with bulky disease.

and finally in the conclusion (p. 1000, r.c.):

> Future studies will address whether anti-tumor activity can be enhanced even further by administration of larger total doses of Rituximab.

4.29. This means that Berinstein is an additional incentive for the skilled person to apply higher dosages in the treatment of SLL and therefore, as explained above, also CLL. Biogen's defense that the hinting to higher dosages in Berinstein only applies to increased tumors in the lymph ('*bulky disease*') fails. In the first place because Berinstein induces the skilled person to the use of higher dosages in general in multiple places, and not exclusively in connection with '*bulky disease*'. In the second place, Biogen again fails to take account of the fact that the skilled person would understand that the operating mechanism of rituximab will be the same in SLL and CLL and would certainly apply incentives with regard to SLL in the treatment of patients with CLL.

4.30. Finally, Biogen advanced that the publication by Jensen mentioned above in 2.13., which pertains to the treatment of CLL with rituximab, would point the skilled person away from the invention because this publication would teach that the dose must be lower than 375 mg/m^2. This argument fails for two reasons.

4.31. Jensen was published in July/August 1998 as a so-called '*Rapid Communication*' and describes that a seriously ill CLL-patient of 26 years old with high CD20 antigen blood values (111.9 x 10^9/L) – in brief – suffered from side effects (TLS) after the first administration of a dosage of 375 mg/m^2 rituximab.

4.32. In the first place, in Jensen, contrary to what Biogen argues, it is not stated that the dosage must be lower than 375 mg/m^2. Jensen indicates that '*the recommended standard dose of 375 mg/m^2*

[19] Paragraph 80 of the writ of summons

for rituximab was established in patients with follicular lymphoma and lymphocyte counts of less than 5.0x10^9/L' and that this dose '*might be too high for the treatment of patients with substantial peripheral tumor load*' or that in these patients the '*high peripheral tumor cell counts must be reduced using cytostatic drugs prior to administration of rituximab*'.

4.33. In the second place, TLS is a well-known but annoying side effect of almost all cancer medicines. It *may* be life-threatening but in general it can be treated well and/or be prevented. Jensen would therefore not be an obstacle for the skilled person in his research into the use of rituximab in CLL-patients in a higher dosage. As Prof. Oscier has stated, the efficacy of the product and the side effects must be appropriately distinguished from each other. The fact that the patient described in Jensen had serious side effects seems to indicate that the treatment took effect (i.e. the malignant B-cells were destroyed with as a result the occurrence of TLS). Furthermore, the results in this specific patient cannot be extrapolated to the entire patient population, as Prof. Oscier explains in his statement. It must be borne in mind that CLL is incurable and that doctor and patient will balance the advantages and drawbacks of the treatment.

4.34. For that matter, the side effects in the patient described in Jensen did not withhold the researchers from continuing the treatment with rituximab with her (p. 90, l.c.) just as in another six patients (symptoms of TLS seemed to occur in three of them in whom also high lymphocyte values were measured). This would not have been done if the researchers would have thought that the treatment with rituximab would not be safe.

4.35. In conclusion, it can be said that the publication of Jensen would have alerted the skilled person to the occurrence of TLS in CLL-patients with high lymphocyte values, but would not have withheld him from carrying out his research into the application of rituximab with a higher dosage in CLL.

4.36. Biogen did not assert that there would be other '*pointers-away*' that would withhold the skilled person from researching the use of rituximab in CLL-patients with a higher dosage than 375 mg/m^2. To the extent that Biogen invokes the article by Coiffier in this respect, it has not made it clear why this must be regarded as such a pointer. The mere assertion that this article implies that a higher dose of rituximab in other B-cell disorders – as the district court understands, it is not about SLL or CLL but about particular types of aggressive B-cell lymphoma – does not necessarily lead to improved results and a lower dose must be used in the case of a higher toxicity (for that matter, the latter cannot be deduced from the passage quoted by Biogen on p. 1932, last paragraph (see 2.16.)), is without a further explanation insufficient to lead to that conclusion.

Conclusion

4.37. The above means that the claims 1 and 3 of the auxiliary request are invalid because of lack of inventive step. This also applies to the dependent claims 2 and 4, which Biogen did not defend separately either. This means that the auxiliary request cannot save the patent.

4.38. The conclusion is that the Dutch part of EP 313 will be nullified, as claimed. With this, the other arguments that Celltrion advanced, such as the assertion that there is added matter, need not be discussed anymore.

Costs of the Proceedings

4.39. Biogen being the unsuccessful party will be ordered to pay the costs of the proceedings.

4.40. The parties agree that Celltrion's claims must be considered as an anticipated non-infringement defense, that therefore section 1019h DCCP applies and that € 250,000 is a reasonable and proportionate compensation for the costs of the proceedings of the successful party. The parties also agree that the amount mentioned pertains both to the claim with respect to EP 572 withdrawn by now and the claim with respect to EP 313.

4.41. This means that the district court estimates the costs of the proceedings incurred by Celltrion on the amount agreed on by the parties of € 250,000. It will be declared that the order to pay costs has immediate effect as claimed and will be allowed as to be mentioned below for the remainder.

5. The Decision

The district court

5.1. nullifies the Dutch part of EP 313;

5.2. orders Biogen to pay the costs of the proceedings, on Celltrion's side currently estimated at € 250,000 to be increased by the statutory interest with effect from 14 days after the service of this judgment until the day of full payment;

5.3. declares that this judgment has immediate effect as regards the order to pay costs.

This judgment was rendered by *mr*. J.Th. van Walderveen, *mr*. A.M. Brakel and *mr*. C.T. Aalbers and pronounced in open court on 21 February 2018.