



Phase II trial of zanolimumab (HuMax-CD4) in relapsed or refractory non-cutaneous peripheral T-cell lymphoma

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Running Head: Zanolimumab in relapsed or refractory non-cutaneous peripheral T-cell lymphoma

Phase II trial of zanolimumab (HuMax-CD4) in relapsed or refractory non-cutaneous peripheral T-cell lymphoma

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Summary

Purpose

To explore efficacy and safety of zanolimumab (HuMax-CD4) in patients with relapsed or refractory peripheral T cell lymphoma (PTCL).

Patients and Methods

Twenty-one adult patients with relapsed or refractory CD4+ PTCL of non-cutaneous type (angioimmunoblastic T-cell lymphoma (AITL) n=9, PTCL-not otherwise specified (NOS) n=7, anaplastic large cell lymphoma (ALCL) n=4 and enteropathy type T-cell lymphoma n=1) were treated in a single-arm multi-center study, with weekly intravenous infusions of zanolimumab 980 mg for 12 weeks. Median age was 69 years (range 26-85). Seventeen of the patients had advanced stage disease (Ann Arbor stages III-IV).

Results

Objective tumor responses were obtained in 24% of the patients with 2 complete responses unconfirmed (CRu) and 3 partial responses (PR). One of the CRus lasted more than 252 days. Responses were obtained in different PTCL entities: AITL (n=3), ALCL (n=1) and PTCL-NOS (n=1). In general, the trial drug was well tolerated with no major toxicity.

Conclusion

Zanolimumab at a dose of 980 mg weekly demonstrated clinical activity and an acceptable safety profile in this poor-prognosis patient population, suggesting that the potential benefit combining zanolimumab with standard chemotherapy in the treatment of PTCL should be investigated.

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Keywords: PTCL, CD4, angioimmunoblastic, anaplastic, zanolimumab

For Peer Review

Introduction

Systemic PTCL of non-cutaneous type is a heterogeneous group of mature non-Hodgkin's lymphomas with diverse histological, molecular and clinical characteristics (Armitage *et al*, 2008). In western countries, PTCL accounts for 7-10% of all non-Hodgkin lymphomas and approximately 20% of the aggressive lymphomas (Morton *et al*, 2006; Anderson *et al*, 1998; Rudiger *et al*, 2002). Within the group of aggressive lymphomas the T-cell phenotype itself is associated with a poor prognosis with a 5-year overall survival of 30-35% using standard chemotherapy (Gisselbrecht *et al*, 1998; Coiffier *et al*, 1990; Melnyk *et al*, 1997; Morabito *et al*, 2004; Lopez-Guillermo *et al*, 1998; Gallamini *et al*, 2004; Zaja *et al*, 1997). Because of these disappointing results, novel therapies are needed for PTCL.

Specific immunotherapy with an anti-CD20 antibody added to standard chemotherapy has markedly improved the prognosis for aggressive B-cell lymphomas (Coiffier *et al*, 2002; Feugier *et al*, 2005; Habermann *et al*, 2006; Pfreundschuh *et al*, 2006). A similar approach with addition of specific immunotherapy to standard therapy in T-cell lymphoma could potentially also improve the prognosis T-cell lymphomas. The CD4 molecule is expressed on the malignant cells in the majority of cases of PTCL-NOS, ALCL and AITL, and is therefore a relevant target for immunotherapy.

Zanolimumab (HuMax-CD4) is a human monoclonal antibody specific for the CD4 antigen which is expressed on a subset of T cells (Fishwild *et al*, 1996). Zanolimumab inhibits CD4⁺ T cells by combining signaling inhibition with potent induction of Fc-mediated effector functions. T-cell activation is inhibited by a fast dual mechanism in which the antibody abrogates signaling via the T-cell receptor and, in addition, down regulates T-cell activation by transmission of direct inhibitory signals. In addition zanolimumab induces killing of CD4⁺ T

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cells via antibody-dependent cellular cytotoxicity (ADCC) (Rider *et al*, 2007). A phase 2 trial exploring weekly doses of 280, 560 and 980 mg zanolimumab demonstrated good safety and efficacy in patients with relapsed or refractory cutaneous T-cell lymphoma (CTCL) (Kim *et al*, 2007). Best results were obtained at the dose level 980 mg thus; a prospective multicenter clinical trial was designed to evaluate the efficacy and safety of zanolimumab given as single agent in patients with relapsed or refractory non-cutaneous CD4⁺ PTCL.

For Peer Review

Patients and methods

Study design

This phase 2 trial was conducted as a single-arm multi-center trial in patients with refractory or relapsed CD4⁺ PTCL of non-cutaneous type. Patients were enrolled from October 2004 until January 2007 from 11 medical oncology and hematology departments in Denmark (2 sites), Sweden (3 sites), United Kingdom (1 site), Germany (3 sites) and France (2 sites). Ethical approval was obtained from the independent ethics committees and by the national clinical trial agencies. The trial was performed in accordance with the Declaration of Helsinki. ClinicalTrial.gov no. NCT00877656.

The trial period was 18 weeks including a treatment period of 12 weekly zanolimumab infusions followed by a 6 week efficacy assessment period. The trial period continued in a follow-up period up to 24 months to evaluate time to progression and safety.

All patients received the same dose level, 980 mg weekly. Zanolimumab was administered as an intravenous infusion over approximately 80 minutes for the first infusion and over approximately 60 minutes for subsequent infusions if no infusion-related reactions occurred. To minimize the risk of infusion-related AEs, patients were pretreated with acetaminophen or similar anti-pyretic agent prior to start of first treatment. The patients did not receive anti-histamines or steroids as premedication. Prophylactic antibiotics and granulocyte colony stimulating factor (G-CSF) could be given at the discretion of the treating physician.

During the trial period, the use of other anti-neoplastic therapies or systemic steroids was prohibited.

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Patient cohort

Patients (≥ 18 years) with a histological diagnosis of systemic non-cutaneous CD4⁺ PTCL relapsed after or refractory to at least one prior systemic lymphoma regimen were included in the trial. Twelve out of 21 patients received more than one prior line of treatment. The remaining patients were either allocated to experimental treatment after a dose-dense intensive first-line therapy or because the responsible physician did not consider them eligible for further treatment intensification. No patients eligible for curative treatment were enrolled. Histological diagnosis according to the WHO classification of lymphoid neoplasms was established (World Health Organization classification of tumours, 2001) and CD4 expression by immunohistochemistry was assessed on tumor specimens obtained at any time before enrollment. CT-scan should show at least two demarcated lesions with a diameter ≥ 1.5 cm or at least one lesion ≥ 2.0 cm.

Patients were excluded from the trial if they had received prior treatment with anti-CD4 monoclonal antibodies or within the last year had received alemtuzumab.

Before inclusion in the trial all patients gave written informed consent.

Study End Points

The objective of the trial was to explore efficacy and safety of zanolimumab in relapsed or refractory patients with CD4⁺ PTCL of non-cutaneous type. Overall response rate (ORR) was the primary endpoint (threshold for continuation of the study at 20%) and the secondary assessments included frequency and severity of AEs, response duration, time to response, time to progression, human anti human antibodies (HAHA) and serum concentration of zanolimumab.

Efficacy assessment

A pre-therapeutic CT scan (neck, thorax, abdomen and pelvis) was performed before start of treatment for diagnostic and staging purposes, and to ensure compliance with eligibility criteria.

Responses were assessed according to the international Workshop on NHL response criteria (Cheson *et al*, 1999).

Evaluation of objective response was based upon CT scan data assessed by the local radiologist, bone marrow biopsy (if pre-therapeutically involved), physical lymph node and organ examination assessed by the investigator and biochemistry. Evaluation of the objective response was based upon these assessments and performed by the investigator.

Response assessment was done at weeks 6, 12, 18 and subsequently every 8 weeks until progression or until the end of the follow-up period.

Safety assessment

Safety assessments included AEs, physical examination, vital signs, standard laboratory parameters (flowcytometry, hematology and clinical chemistry) and host immune response.

Occurrence of AEs were recorded throughout the trial period and also during the follow-up period if the patient was followed for low CD4 count. The AE reporting period continued until PD or until a maximum follow-up of 24 months. Serious adverse events (SAEs) were reported on an ongoing basis throughout the trial period and the post-trial follow-up period.

AEs were categorized and graded according to the National Cancer Institute Common Criteria for AEs, version 3.0 and coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 6.0.

Safety was monitored by an independent data monitoring committee.

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Host immune response to zanolimumab was evaluated by determining presence of HAHA in serum. This was done by a zanolimumab coated enzyme-linked immunosorbent assay (ELISA) performed before treatment and at the last visit in the treatment period, i.e. week 18. The serum concentration of zanolimumab was determined by ELISA (limit of quantification: 0.015 µg/mL) at each visit from week 0 until week 18. All laboratory samples including flowcytometry were analyzed by the Bio analytical research corporation (BARC), Ghent, Belgium.

Statistical methods

All patients who received study drug irrespective of their compliance to the planned course of treatment (intention-to-treat population) were included in the efficacy and safety analysis. Endpoints are presented as descriptive statistics or graphically.

Results

Patient cohort

Patient characteristics are summarized in Table 1. In addition, Table 2 shows an overview of the therapy received by each patient prior to inclusion in the study.. Twenty-one patients (11 male and 10 female) were enrolled in the trial. Median age was 69 years (range 26-85) and median time from primary diagnosis to trial-entry was 1.2 years (range 0.4-10.6). All but 4 patients, showed advanced disease (stages III-IV according to Ann Arbor staging). Nineteen out of 21 patients had previously received and failed 1-2 lines of cytoreductive treatment (see Table 2).

All patients received at least one infusion of zanolimumab. Out of 21 patients, 8 (38%) received all 12 infusions, 8 (38%) received 6-9 infusions and 5 (24%) received 1-3 infusions. Reasons for early discontinuation of treatment were: Disease progression (n=10), AEs (n=2) and administrative reasons (n=1).

Efficacy

Objective tumor responses were obtained in 5 out of 21 patients (ORR 24%; 95% CI: 8%-47%) as shown in Table 3 . Partial response (PR) was obtained by 3 patients (patient 002, 012 and 013), and 2 patients (patient 006 and 015) achieved a complete response unconfirmed (CRu). Responses were seen in localized and advanced stage disease, and throughout histological subgroups, i.e. AITL (3 patients), ALCL (1 patient) and PTCL-NOS (1 patient).

Of the objective responses, 4 were observed 6 weeks after start of treatment and 1 was observed in the follow-up period (182 days after start of treatment).

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Response duration was 43 days and 46 days in the 2 patients (patient 002 and 006 respectively) who experienced disease progression. In a third responder (patient 012 who had PR at week 6 (see figure 1) one lymph node was increased in size at week 12, while all other lesions were decreased and was therefore assessed as having disease progression and a response duration of 51 days. At the following visits, including follow-up visits no evidence of disease was detected. No relapse/progression was documented in patients 013 and 015 by the time of reporting.

Pharmacokinetics and pharmacodynamics

Zanolimumab trough concentrations showed an increase over time after weekly repeated infusions in the majority of patients (Figure 2). The highest maximum trough zanolimumab serum concentrations were obtained in the patients who received the highest number of doses. Up to week 6, 10 patients obtained trough C_{max} concentrations above 160 µg/ml, including all those who obtained an objective tumor response either at week 6 (4 patients) or later, i.e. week 26 (1 patient). A decrease in the concentration of blood CD3⁺CD4⁺ T cells was demonstrated in all patients by flow cytometry after zanolimumab administration regardless of their response. All 4 patients who obtained their response in the trial period were rapidly, profound and sustained CD3⁺CD4⁺ T cell depleted throughout this period. The relationship between the trough concentrations of zanolimumab and CD3⁺CD4⁺ T cell concentrations showed that all patients, who obtained an objective tumor response at week 6 had zanolimumab concentrations above 160 µg/ml coinciding with markedly reduced blood CD3⁺CD4⁺ T cell counts. The patient who obtained a late objective response had temporarily

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3 a zanolimumab concentration exceeding 160 µg/ml, but the CD3⁺CD4⁺ T cell concentration
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5 was not markedly suppressed at this time point.
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8 Anti-zanolimumab antibodies were not detected in any of the patients, including the five who
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10 reached visit 15 at the scheduled time point (week 18). Although not systematically analyzed
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12 in relapsed/progressing cases, the CD4-positivity of the tumors was found preserved in those
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14 cases, where biopsies were performed after zanolimumab treatment.
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18 **Safety**

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21 During the trial, 108 AEs were reported. One death (disease progression) occurred during the
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23 trial period and 7 deaths were reported during the follow-up period (until December 3rd, 2007).
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26 All deaths were evaluated as unrelated to the trial drug.
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28 Furthermore 18 SAEs in 11 patients were reported during the trial period. Among these, 4
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30 SAEs in 4 patients occurred as infusion-related events and were reported related to the trial
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32 drug by the investigator (see below).
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35 Ten AEs were reported as non-serious grade 3 AEs; 5 were related and 5 were non-related to
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37 the trial drug. The related events were decreased lymphocyte count (2 events), arthralgia
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39 (one event) and 2 infusion-related events (see below).
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42 The most frequently reported AEs were rash (5 events) and pyrexia (5 events).
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46 **Infusion-related**

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48 Four SAEs (thrombocytopenia- grade 4, hyperpyrexia with hypotension- both grade 1, face
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50 edema and pyrexia- both grade 2, and cytokine-release syndrome- grade 3) in 4 patients
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52 were infusion-related and judged as related to the trial drug by the investigator. In the patient
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54 with thrombocytopenia the platelet count was normalized 8 hours later without intervention.
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The event occurred the day after the first infusion, whereas the remaining related SAEs occurred on the first infusion day. All 4 patients recovered.

Two related non-serious grade 3 AEs (one event of bronchospasm and one event of infusion-related allergic reaction) occurred on the first infusion day. Both patients recovered.

Fifty AEs reported on 16 patients had onset on infusion days. Of these infusion-related AEs, 23 (46%) were reported on the first and 3 (6%) on the second infusion day. The most frequently related AEs on the day of first infusion were pyrexia (3 events in 3 patients), rigors (3 events in 3 patients) and hypotension (2 events in 2 patients).

Infections

During the trial, 7 infectious episodes were reported in 6 patients. Five of these 7 events were graded as SAEs. Among the latter, two episodes of viraemia occurred in the same patient and required hospitalization. During the first event the patient developed chills and fever but recovered after 3 days with intravenous antibiotics. A polymerase chain reaction (PCR)-based analysis for Epstein Barr virus (EBV) DNA was positive. A corresponding analysis for cytomegalovirus (CMV) DNA was negative. During the second event the patient had diarrhea, vomiting, abdominal pain, fever, increased C-reactive protein and again a positive EBV DNA PCR. PCR for CMV DNA was still negative. The patient recovered after one week of treatment with intravenous antibiotics, immunoglobulin and acyclovir. The patient subsequently continued zanolimumab treatment. The additional infectious SAEs were a bacterial septicaemia, a febrile neutropenia and one episode of bronchitis.

Safety laboratory parameters

A decrease in the concentration of blood CD3⁺CD4⁺ T cells was demonstrated in all patients by flowcytometry after zanolimumab administration. At the start of the follow-up period, the level of the CD3⁺CD4⁺ T cells was found to be normalized in only a few patients (Figure 3). CD3⁺CD8⁺ T cells and neutrophils were not depleted.

All other abnormal laboratory values either reflected the underlying disease and/or pre-trial chemotherapy treatments.

Discussion

Zanolimumab is a biologically active drug that targets the CD4 antigen present on a subset of T cells. Among T-cell lymphomas, CD4 expression has been demonstrated in CTCL (Ralfkiaer, 1991), PTCL-NOS (Went *et al*, 2006; Matutes *et al*, 1996), AITL (Went *et al*, 2006; Chen *et al*, 2006) and ALCL (Krenacs *et al*, 1997; Juco *et al*, 2003; Felgar *et al*, 1999).

Two phase 2 clinical trials have demonstrated the efficacy of zanolimumab monotherapy in refractory CD4⁺ CTCL (Kim *et al*, 2007). In the present open-label clinical exploratory trial, 21 patients with relapsed or refractory CD4⁺ non-cutaneous PTCL, were treated with weekly intravenous zanolimumab at a dose of 980 mg for 12 weeks. Five out of the 21 patients (24%) obtained an objective tumor response, one of them with long lasting CRu (>252 days).

Serum trough levels of zanolimumab in the majority of patients showed a gradual accumulation over time depending on the number of doses received. All patients who obtained an objective tumor response during the trial period, had serum zanolimumab concentrations above 160 µg/mL along with a marked depletion of CD3⁺CD4⁺ T cells at the time when the response was detected. The patient who first obtained response in the follow-up period also temporarily reached a zanolimumab concentration above 160 µg/mL. For this

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patient, however, the concentration of CD3⁺CD4⁺ T cells was not markedly suppressed. No objective tumor response was observed in patients that did not, at any time during the treatment or follow-up period, reach a serum trough level of at least 160 µg/mL . This observation and the fact that all patients were not completely depleted of CD3⁺CD4⁺ T cells indicates that the optimal dose of zanolimumab for patients with systemic PTCL may be higher than 980 mg weekly. Other factors may influence the optimal therapeutic level of the drug such as tumor cell burden and administration schedule.

In all patients, zanolimumab caused depletion of CD3⁺CD4⁺ T cells in the peripheral blood. The mechanisms responsible for zanolimumab-induced T-cell depletion are inhibition of T-cell receptor (TCR) signaling and ADCC. Inhibition of TCR signaling is caused by a dual mechanism leading to impaired cell proliferation and survival (Rider *et al*, 2007). Concentrations of neutrophils and CD3⁺CD8⁺ T cells were unaffected by zanolimumab treatment.

In the 5 patients who reached week 18, the HAHA test was negative and coincided with undetectable levels of zanolimumab in the patient serum. Significant concentration levels of the drug are therefore not likely to have interfered with HAHA detection. This is in accordance with the results from zanolimumab treated CTCL patients, where no development of HAHA was detected (Kim *et al*, 2007).

Overall, zanolimumab demonstrated a favorable safety profile. All infusion-related SAEs, except one case of transient grade 4 thrombocytopenia, occurred on infusion days, were mild to severe in intensity and resolved within a range of 8 hours to 4 days from the onset of the event.

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3 The most frequently reported AE was rash (either infusion related or non-infusion related)
4 which is consistent with the findings recorded in zanolimumab-treated CTCL patients (Kim *et*
5 *al*, 2007). The non-infusion related rash events may be explained by the depletion of CD4⁺ T
6 regulatory cells normally engaged in down regulating immune responses.
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10 Interestingly, despite profound depletion of CD3⁺CD4⁺ T cells, the frequency of severe
11 infections was rather low. A case of bacterial septicaemia, one of neutropenic fever and one
12 of promptly recovering bronchitis were recorded. Perhaps more interestingly, a clinically
13 significant and recidivating EBV viremia was reported in a patient with AILT pre-
14 therapeutically positive for EBV. A possible relationship between this episode and an
15 antibody-induced CD4-depletion cannot be outruled. A larger clinical experience is needed in
16 order to assess the frequency of these events, particularly if the antibody is to be used in
17 combination with other potentially immunosuppressive anti-neoplastic drugs. At the
18 investigators discretion, 6 patients (29%) received prophylactic treatment with
19 trimethoprim/sulphamethoxazole, fluconazole, aciclovir or valaciclovir alone or in combination.
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21 No cases of CMV reactivation were reported.
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25 Alemtuzumab, a humanized anti-CD52 IgG1, is effective in T-cell malignancies (i.e. T-cell
26 prolymphocytic leukemia and CTCL) (Dearden *et al*, 2002). In addition, a response rate of
27 36% in 14 patients with relapsed or refractory PTCL treated with alemtuzumab as
28 monotherapy was demonstrated in a Nordic trial (Enblad *et al*, 2004). However, despite
29 trimethoprim/sulphamethoxazole and valaciclovir prophylaxis administered to all patients, the
30 treatment resulted in a high rate of opportunistic infections with 5 patients dying of infectious
31 complications leading to a premature closure of the trial (Enblad *et al*, 2004). Even with
32 mandatory prophylaxis, alemtuzumab is associated with infectious complications also when
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used in the first-line setting (Gallamini *et al*, 2007; Kluin-Nelemans *et al*, 2008; Weisel *et al*, 2008).

Other monoclonal antibodies have been tested, primarily as monotherapy, in phase 1-2 trials. Treatment with anti-CD30 in relapsed ALCL of primary cutaneous or systemic type showed a response rate of 28% along with an acceptable safety profile (Ansell *et al*, 2007). Anti-CD25 (IL-2 receptor) antibody treatment has shown clinical effect in anecdotal cases. Other drugs targeting the CD25 receptor, such as diphtheria toxin-linked to human IL-2, have been used in the treatment of CTCL (Olsen *et al*, 2001) and in relapsed systemic PTCL, where an overall response rate of 48% in 27 patients was reported (Talpur *et al*, 2002; Dang *et al*, 2007). Anti-CD2 treatment has been used in a mixed group of T-cell malignancies where objective tumor responses were observed. However, a marked decline in CD4⁺ and CD8⁺ T-cells and in NK cells resulted in CMV reactivation and development of EBV-related B-cell lymphoproliferative disease (Morris *et al*, 2008). Within the field of lymphoma, immunotherapy with anti-CD4 antibodies, including zanolimumab, has previously only been tested in CTCL (Kim *et al*, 2007; Knox *et al* 1991; Knox *et al*, 1996). In this paper, we present the first data on systemic PTCL. We obtained a response rate of 24% with zanolimumab monotherapy in relapsed/refractory systemic PTCL. Responses were observed throughout all the common subtypes of CD4⁺ PTCL and some of them were long lasting. The safety profile of zanolimumab in this heavily pretreated patient population was favorable.

Recently, new non-antibody compounds, such as the histone-deacetylase inhibitor romidepsin (Woo *et al*, 2009) and the antifolate pralatrexate (O'Connor *et al*, 2009), have been shown to have clinical activity as monotherapy in relapsed/refractory cutaneous and systemic PTCL.

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3 In the light of the therapeutic refractoriness of systemic PTCL, even in the first line setting,
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5 this result is encouraging and supports a role for anti-CD4 immunotherapy within the well-
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7 defined limits of this indication. Additional PTCL trials with zanolimumab exploring the
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9 pharmacokinetics, efficacy and safety of higher doses of the antibody given as monotherapy
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11 and/or in combination with other PTCL-active compounds are warranted.
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20
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31 T.R., H.T., A.Ö., F.M., M.G., M.D., H.H.).
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35 Contribution: F d'Amore, in collaboration with Genmab A/S designed the trial. All the authors
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37 performed the research, collected the data, interpreted the data and contributed to the
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39 manuscript in collaboration with Dorthe Grønnegaard Hansen.
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44 **Disclosures**

45
46 This trial was sponsored by Genmab A/S, and subsequently licensed in its entirety when
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48 exclusive worldwide rights to zanolimumab were acquired by TenX Biopharma, Inc.
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51
52 B.Bang was formerly employed by Genmab A/S, whose investigational drug zanolimumab
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54 was studied in the present work. F. d'Amore: Participation in 3 advisory board meetings on
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zanolimumab. H. Hagberg: Involved in data monitoring committee work concerning Humax-
CD20. All other authors: No relevant conflicts of interest to disclose.

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Table 1. Patient Baseline Characteristics

<i>Total number of patients</i>		<i>21</i>
Male / Female		11 / 10
Age (years), median (range)		69 (26 – 85)
Weight (kg), median (range)		76 (40 – 98)
Time (years) since first diagnosis, median (range)		1.2 (0.4 – 10.6)
Diagnosis		
Angioimmunoblastic T-cell lymphoma		9
Peripheral T-cell lymphoma-NOS		7
Anaplastic large cell lymphoma		4*1
Enteropathy type T-cell lymphoma		
Clinical stage (Ann Arbor)		
Localized Disease (B symptoms):		
II		4 (1)
Disseminated Disease (B symptoms):		
III		7 (3)
IV		10 (5)
International Prognostic Index		
low/low-intermediate		6
intermediate-high/high		15

* (3 alk-negative and 1 with unknown alk-status)

Table 2. Prior Therapy Data

Pt #	Therapy	Status at study entry
01	CHOP	PD + frail pt
02	CHOP x6, BEAM+ASCT, Radiation, Cy+MTX+AraC+steroid	3 rd relapse
03	CHOP, IF-RT (nasal cavity)	1 st relapse + frail pt
04	CHOP, BEAM, Radiation	3 rd relapse
05	CHOP, Radiation	2 nd relapse
06	CHOEP, Cisplatin+AraC+steroid	PD after 2 nd line therapy
07	CHOP	PD + frail pt
08	CHOP, Ara-C, Cy+MTX+Etoposide, Radiation	3 rd relapse
09	ACVBP, IVAM, BEAM, ESHAP	3 rd relapse
10	CHOP-like	1 st relapse
11	CHOP x 6, Fludarabin, Chl, VAD, Ara-C	PD after 3 rd relapse
12	VAPAC - B x 7, ACx3	2 nd relapse
13	CHOP, vindesin+steroid, steroid	PD after 2 nd line therapy
14	ACVBP, MTX	1 st relapse + frail pt
15	Mitoxantrone + Cy, VAPAC-B	1 st relapse + frail pt
16	CHOP	1 st relapse
17	CHOEP, BEAC	2 nd relapse
18	CHOP+MTX	1 st relapse
19	CHOP, ICE	PD after 2 nd line therapy
20	CHOP	1 st relapse
21	CHOP-Bleo	1 st relapse

PD= progressive disease

Cy= cyklophosphamide ; MTX= methotrexate ; AraC= cytosine arabinoside; BLEO= bleomycin; Chl= chlorambucil; IF-RT= involved-field radiotherapy;

CHOP= cyclophosphamide+doxorubicin, vincristine, prednisone; CHOEP= CHOP+etoposide; IVAM= iphosphamide, etoposide, doxorubicin, methotrexate; BEAM/-C= BCNU, etoposide, cytosine arabinoside, melphalan/-cyclophosphamide; ESHAP= etoposide, steroid, high-dose AraC, cis-platin; VAD=vincristine, adriamycin, dexamethasone; ACVBP= doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; VAPAC= vincristine, cytosine arabinoside, prednisone, doxorubicin, cyclophosphamide; VAPAC-B= VAPAC+bleomycin

Table 3. Patient characteristics in responders

<i>Pat.</i>	<i>No. of prior treatment regimens</i>	<i>Age, years</i>	<i>Sex</i>	<i>Histo- logical Diagnosis</i>	<i>No. of infu- sions</i>	<i>Objective response</i>	<i>Response duration, days</i>	<i>Ann Arbor Stage</i>	<i>LDH at baseline</i>
002	2	26	Male	ALCL*	12	PR	43	IIB	Normal
006	1	61	Male	PTCL-NOS	12	CRu	46	IVA	Elevated
012	2	72	Female	AITL	12	PR	51**	IVB	Elevated
013	2	74	Female	AITL	12	PR	>1***	IVB	Normal
015	2	74	Female	AITL	9	CRu	>252	IVA	Normal

CRu=complete response unconfirmed; ne=data not evaluable; PD=progressive disease;

PR=partial response; PTCL = peripheral T-cell lymphoma, ALCL = anaplastic large cell lymphoma, AITL = angioimmunoblastic T-cell lymphoma, NOS=not otherwise specified

Table notes:

*ALK-protein status unknown

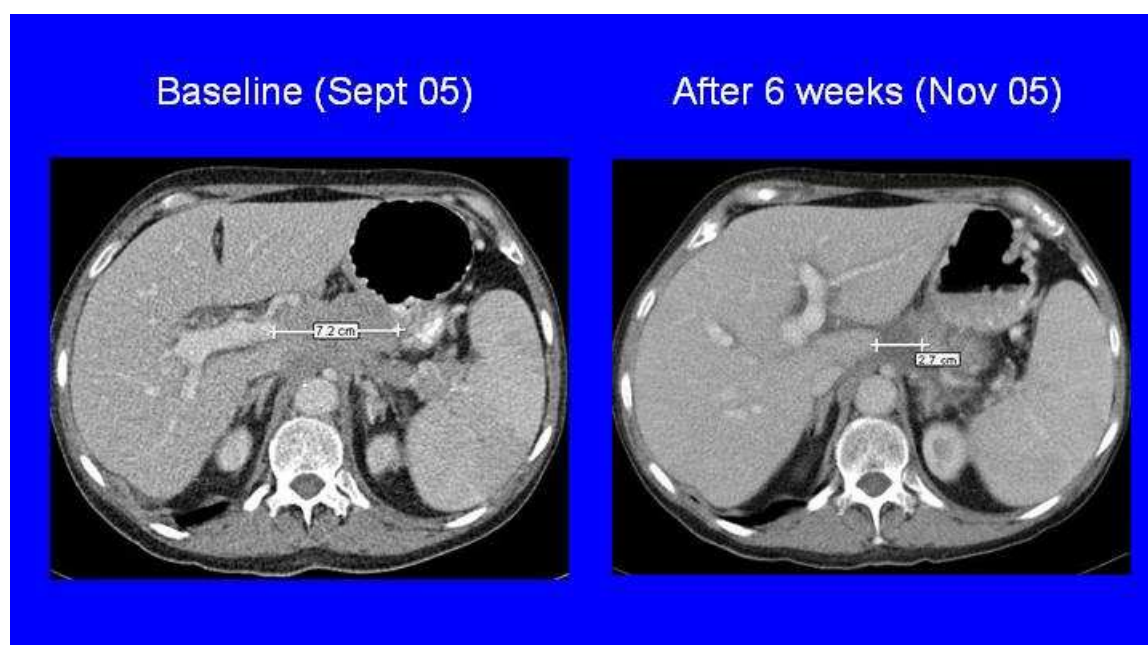
** See efficacy section for details

*** Response documented at last efficacy assessment and no relapse has been documented

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Figure 1. Abdominal CT scans from a patient with AITL showing a marked reduction in lymph node diameter (partial remission) after 6 infusions of i.v. zanolimumab 980 mg given as monotherapy



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Figure 2. Zanolimumab serum concentration from baseline to week 14 in 21 patients. The serum samples were obtained before administration of Zanolimumab (serum trough values)

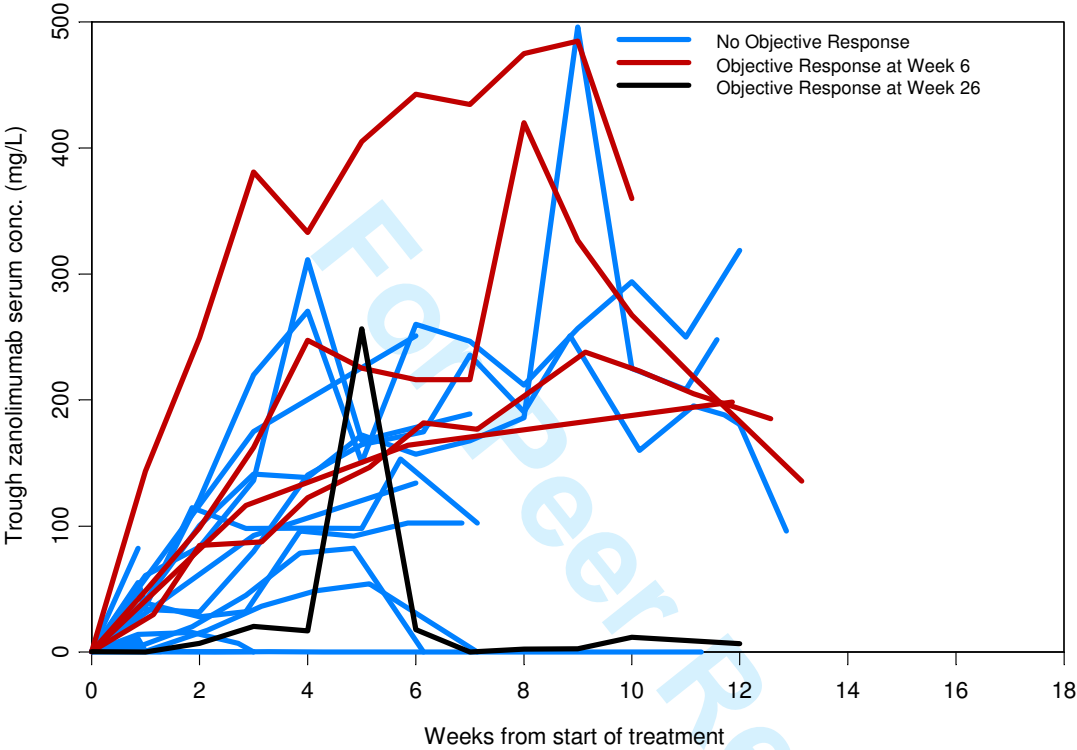
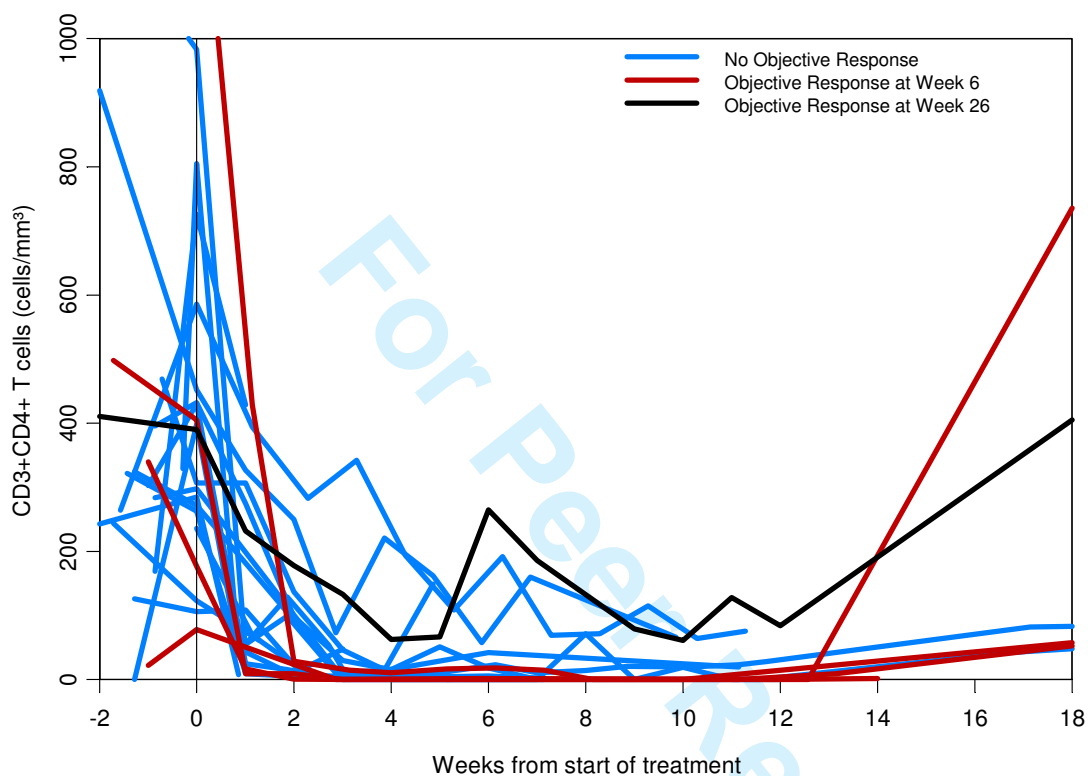


Figure 3. Concentration of CD3⁺CD4⁺ peripheral blood T cells from pre-therapeutic screening to end of follow-up (21 patients)



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