ニター、監査担当者、治験審査委員会及び規制当局による査察又は直接閲覧に応じるものとする。また、症例報告書に直接記入され、且つ原資料と解すべきデータとその内容を以下に示す。

1) 登録症例としての適格性
2) 併用療法の併用理由
3) 一般臨床検査の正異判定及び、異常変動の有無
4) 有害事象（臨床検査値異常変動を含む）のグレード、治験薬との因果関係及び重篤／非重篤の判定
5) 抗腫瘍効果の評価
6) 個々の被験者の治験薬の投与中止の理由、投与中止後の処置及びその後の経過、治験中止の理由、治験中止後の処置及びその後の経過
7) コメント

17. 治験の品質管理及び品質保証

治験の品質管理及び品質保証は、別途定める「治験実施に係る標準業務手順書」に従い行う。

18. 倫理的配慮

18-1. 遵守すべき諸規則

本治験は、「ヘルシンキ宣言」ならびに、且つ本治験実施計画書、薬事法第 14 条第 3 項及び第 80 条の 2 に規定する基準及び「医薬品の臨床試験実施の基準に関する省令（GCP）」（厚生省令第 28 号）に則り実施する。

18-2. 治験審査委員会

本治験は、実施に先立ち、各実施医療機関の治験審査委員会において、治験実施計画書、被験者の同意を得るのに使用される方法、治験薬概要書及びその他の必要な文書を審議し、本治験が倫理的及び科学的に妥当であるかどうか、その他、本治験が実施医療機関において行うのに適当であるかどうかを審査する。

継続審査

1) 治験責任医師は、治験審査委員会の継続審査を受けるために、治験の現状の概要を年に 1 回又は治験審査委員会の求めに応じてそれ以上の頻度で、実施医療機関の長に文書をもって提出する。
2) 実施医療機関の長は当該実施医療機関における治験の現況の報告、重篤で予測できない副作用等について自ら治験を実施する者から通知を受けた場合、重篤な有害事象について治験責任医師から通知を受けた場合、及び治験について継続して参加するかどうかについて被験者の意思に影響を与える情報を得た場合、当該治験の継続について治験審査委員会に意見を求めるものとする。

18-3. インフォームド・コンセント

治験責任医師等は、被験者に治験について十分に説明し、文書による同意を得る。被験者が熟読し保管できるように、治験の詳細を示した説明文書を被験者に渡す。被験者に情報を十分に考慮する時間を与え、疑問点を確認した後で、同意文書に署名及び日付を記入する。

18-4. 新たな情報の提供

自ら治験を実施する者は、被験者の安全性に悪影響を及ぼし、治験の実施に影響を与え、又は治験審査委員会の承認を変更する可能性のある情報、あるいは重篤で予測できない副作用等の情報を入手した場合は、治験審査委員会に速やかに文書で報告する。自ら治験を実施する者は同意文書及びその他の説明文書を改訂する必要があると認めた場合は、速やかに改訂する。

18-5. 被験者の機密保持・プライバシー確保

被験者の登録及び症例報告書における被験者の特定はデータ・試料管理担当者によって、被験者識別コード等で行う等連結可能匿名化を行なう。原資料の直接閲覧・取り扱い等においては被験者のプライバシー保護に十分配慮する。被験者試料等も、同様に被験者識別コード等で連結可能匿名化を行うとともに、他施設への試料の移送等に際しては、この被験者識別コード等にて識別する。

19. 必須文書の保存

19-1. 自ら治験を実施する者

自ら治験を実施する者は別途定める「記録の保存に関する手順書」に従い、本治験に関する記録を以下の 1）又は 2）のうち、いずれか遅い日までの期間適切に保存する。なお、当該記録の保存について、自ら治験を実施する者が所属する実施医療機関の長にその業務を依頼することができる。また、当該自ら治験を実施する者がその所属する実施医療機関に所属しなくなった場合については、その所属する実施医療機関の長が当該記録の保存業務を担うことができる。

また、これらの資料について治験調整委員会がこれよりも長期間の保存を必要と判断する場合には、保存期間及び保存方法について治験調整委員会とその対応について協議する。

自ら治験を実施する者は、保管の必要がなくなった場合には、その旨を実施医療機関の長又は実施医療機関の長を経由して、治験審査委員会の設置者に通知しなければならない。

1) 当該被験薬に係る製造販売承認日（GCP 省令第 26 条の 10 第 2 項及び第 3 項の規定により開発の中止若しくは治験の成績が承認申請書に添付されない旨の通知を受けた場合には開発中止が決定された若しくは申請書に添付されない旨の通知を受けた日から 3 年が経過した日）

2) 本治験の中止もしくは終了の後 3 年が経過した日

19-2. 実施医療機関

実施医療機関の長又は治験審査委員会の設置者が保存すべき必須文書は、実施医療機関の長が定めた記録保存責任者が適切に保管する。保存期間は以下の 1）又は 2）のうちいずれか遅い日ま

でとする。

1) 当該被験薬に係る製造販売承認日（GCP 省令第 26 条の 10 第 2 項及び第 3 項の規定により開発の中止若しくは治験の成績が承認申請書に添付されない旨の通知を受けた場合には開発中止が決定された若しくは申請書に添付されない旨の通知を受けた日から 3 年が経過した日）

2) 本治験の中止もしくは終了後 3 年が経過した日

19-3. 治験責任医師

治験責任医師は、治験に係る文書を実施医療機関の長の指示に従って保存する。

20. 金銭の支払い及び保険

20-1. 金銭の支払い

被験者の本治験に係る負担軽減費については、症例登録後の治験のための来院について、各実施医療機関の取り決めに従い、被験者へ支払うか否かを各実施医療機関で決定する。

20-2. 補償

本治験において何らかの健康被害を認めた場合には、速やかに適切な診断と処置を医療健康保険の範囲内で行う。しかし、本治験に起因した健康被害に対する補償金は支払われない。

21. 資金源及び起こりうる利害の衝突

Mogamulizumab（抗 CCR4 抗体）は、協和発酵キリン株式会社により無償提供される。その他の費用は公的研究費により支払われる。

22. 試験成果の帰属と結果の公表

22-1. 結果の公表

試験終了後、その成果をまとめ、しかるべき国内外の学会及び英文誌に発表する。

22-2. 総括報告書の作成

最終症例の投与開始から 1 年までのデータが固定された時点及び治験終了後に、自ら治験を実施する者は別途定める「総括報告書の作成に関する手順書」に従い、総括報告書を作成する。

22-3. データの提供

試験終了後、規制当局の指示・指導もしくは関係企業等の希望により、個人情報を除いた本試験データを有償又は無償で提供することがある。

22-4. データの二次利用

本試験で得られたデータを二次利用することが有益であると治験調整委員会が判断した場合は、

個人情報の保護に細心の注意を払い、データの二次利用をできる。

23. 参考文献

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付録 1. 皮膚障害が認められた場合に推奨する対処法

（協和発酵キリン株式会社提供、「ポテリジオの皮膚障害対策　臨床医が推奨する対処法」より）

<table>
<tr><th colspan="2">薬効分類</th><th>Grade 1</th><th>Grade 2</th><th>Grade 3</th><th>Grade 4</th></tr>
<tr><td rowspan="4">副腎皮質ステロイド剤（外用）</td><td rowspan="2">very strong（かなり強力）</td><td colspan="4">【体幹四肢】・0.05%ベタメタゾン酪酸エステルプロピオン酸エステル、
・0.1%モメタゾンフランカルボン酸エステル等　1日2回塗布</td></tr>
<tr><td colspan="4">副腎皮質ステロイド剤の内服を開始後は適宜中止可能</td></tr>
<tr><td rowspan="2">strong（強力）</td><td colspan="4">【顔面】※1・0.12%ベタメタゾン吉草酸エステル、
・0.025%ベクロメタゾンプロピオン酸エステル等　1日2回塗布</td></tr>
<tr><td colspan="4">副腎皮質ステロイド剤の内服を開始後は適宜中止可能</td></tr>
<tr><td colspan="2" rowspan="2">副腎皮質ステロイド剤（内服）※2</td><td>－</td><td>プレドニゾロン
0～60mg/日※3
（0～1mg/kg）</td><td colspan="2">プレドニゾロン
60mg/日以上
（1mg/kg以上）</td></tr>
<tr><td colspan="4">皮膚症状を観察しながら適宜漸減</td></tr>
<tr><td colspan="2" rowspan="2">抗ヒスタミン剤</td><td colspan="4">オロパタジン塩酸塩10mg/日内服等</td></tr>
<tr><td colspan="4">d-クロルフェニラミンマレイン酸塩 8mg/日内服等</td></tr>
<tr><td colspan="2">副腎皮質ステロイド剤（静注）【ステロイドパルス療法】※4</td><td>－</td><td colspan="3">メチルプレドニゾロン1,000mg/body、3日間
（・体格や全身状態を考慮して、500mg/日で投与することもある
・症状が回復しない場合はもう1クール追加することもある）</td></tr>
<tr><td colspan="2">その他の治療法</td><td>－</td><td>－</td><td>－</td><td>・血漿交換療法
・ヒト免疫グロブリン製剤静注（IVIG）療法</td></tr>
</table>

Grade は有害事象共通用語基準（CTCAE）v3.0 日本語訳 JCOG/JSCO 版に準ずる

副腎皮質ステロイド剤の全身投与が長期化する場合は、日和見感染のリスクが高まることに十分に注意する

※1：顔面への副腎皮質ステロイド剤（外用）の長期間の使用は避ける
※2：副腎ステロイド剤の内服は、漫然とした長期投与は避け、皮膚障害の状況に応じて減量を検討すること
※3：粘膜障害を伴う場合や症状が進行中の場合は 1mg/kg を投与
※4：Grade 2 では、中毒性表皮壊死融解症/Stevens-Johnson 症候群（TEN/SJS）が疑われるような粘膜障害を伴う場合に実施。ステロイドパルス療法終了後は副腎皮質ステロイド剤の内服を継続する

Ⅳ．研究成果の刊行に関する一覧表

3 研究成果の刊行に関する一覧表

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Ogura M, **Ishida T**, Hatake K, Taniwaki M, Ando K, Tobinai K, Fujimoto K, Yamamoto K, Miyamoto T, Uike N, Tanimoto M, Tsukasaki K, Ishizawa K, Suzumiya J, Inagaki H, Tamura K, Akinaga S, Tomonaga M, **Ueda R.**	Multicenter phase II study of mogamulizumab (KW-0761), a defucosylated anti-CCR4 antibody, in patients with relapsed peripheral T-cell lymphoma and cutaneous T-cell lymphoma.	J Clin Oncol.	32	1157-63	2014
Narita T, **Ishida T,** Masaki A, Suzuki S, Ito A, Mori F, Yamada T, Masaki Ri, Kusumoto S, Komatsu H, Miyazaki Y, Takatsuka Y, Utsunomiya A, Niimi A, **Iida S, Ueda R.**	HTLV-1 bZIP factor specific CD4 T cell responses in ATL patients after allogeneic hematopoietic stem cell transplantation.	J Immunol.	192	940-7	2014
Mizote Y, Wakamatsu K, Ito S, Uenaka A, Ohue Y, Kurose K, Isobe M, Ito A, Tamura Y, Honda H, Yamashita T, Nohara S, **Oka M,** Jimbow K, and **Nakayama E.**	TLR4 and NLRP3 inflammasome activation in monocytes by N-propionyl cysteaminylphenol-maleimid-dextran (NPCMD).	J Dermatol Sci,	73	209-15	2014
Mizote Y, Uenaka A, Isobe M, Wada H, **Kakimi K,** Saika T, Kita S, Koide Y, **Oka M,** and **Nakayama E.**	Production of NY-ESO-1 peptide/DRB1*08:03 tetramers and ex vivo detection of CD4 T-cell responses in vaccinated cancer patients.	Vaccine	32	957-64	2014
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Nakano N, Kusumoto S, Tanaka Y, **Ishida T,** Takeuchi S, Takatsuka Y, Akinaga S, Mizokami M, **Ueda R,** Utsunomiya A.	Utsunomiya A. Reactivation of hepatitis B virus in a patient with adult T-cell leukemia-lymphoma receiving the anti-CC chemokine receptor 4 antibody mogamulizumab.	Hepatol Res.	44	354-7	2014
Nishikawa H, Sakaguchi S	Regulatory T cells in cancer immunotherapy.	Eur J Haematol.	27	1-7	2014
Sugiyama D, **Nishikawa H**, Maeda Y, Nishioka M, Tanemura A, Katayama I, Ezoe S, Kanakura Y, Sato E, Fukumori Y, Karbach J, Jager E and Shakaguchi S	Anti-CCR4 mAb selectively depletes effector-type FoxP3+CD4+ regulatory T cells, evoking anti-tumor immune responses in humans.	Proc. Natl. Acad Sci USA.	110	17945-50	2014
Mori F, **Ishida T,** Ito A, Sato F, Masaki A, Narita T, Suzuki S, Yamada T, Takino H, Ri M, Kusumoto S, Komatsu H, Hishizawa M, Imada K, Takaori-Kondo A, Niimi A, **Ueda R,** Inagaki H, **Iida S.**	Antitumor effects of bevacizumab in a microenvironment-dependent human adult T-cell leukemia/lymphoma mouse model.	Eur J Haematol.	92	219-28	2014
Zwick C, Held G, Auth M, Bernal-Mizrachi L, Roback JD, Sunay S, **Iida S,** Kuroda Y, Sakai A, Ziepert M, **Ueda R,** Pfreundscuh M, Preuss K-D.	Over one third of African-American MGUS and multiple myeloma patients are carriers of hyperphosphorylated paratarg-7, an autosomal-dominantly inherited risk factor for MGUS/MM.	Int J Cancer		Epub ahead of print.	2014
Nishikawa S. Konno M., Hamabe A., Hasegawa S., Ogawa H., Kano Y., Fukusumi T., Ohta K., Noguchi Y, Ozaki M., Kudo T., Sakai D., Haraguchi N., Satoh T.,**Doki Y.,** Mori M. and Ishii.	Aldehyde dehydrogenasehigh gastric cancer stem cells are resistant to chemotherapy.	Int J Oncol	42	1437-42	2014
Ogino T., Nishimura J., Barman S., Kayama H., Uematsu S., Okuzaki D., Osawa H., Haraguchi N., Uemura M., Hata T., Takemasa I., Mizushima T., Yamamoto H., Takeda K., **Doki Y.,** Mori M.	Increased Th17-inducing activity of CD14+ CD163 low myeloid cells in intestinal lamina propria of patients with Crohn's disease.	Gastroenterol	145	1380-91	2014

Wada I, Matsushita H, Noji S, Mori K, Yamashita H, Nomura S, Shimizu N, Seto Y, **Kakimi K.**	Intraperitoneal injection of in vitro expanded Vγ9Vδ2 T cells together with zoledronate for the treatment of malignant ascites due to gastric cancer.	Cancer Med.	3	362-75	2014
Ichimura T, Morikawa T, Kawai T, Nakagawa T, Matsushita H, **Kakimi K,** Kume H, Ishikawa S, Homma Y, Fukayama M.	Prognostic Significance of CD204-Positive Macrophages in Upper Urinary Tract Cancer.	Ann Surg Oncol.		Epub ahead of print	2014
Xia H, Yamada S, Aoyama M, Sato F, Masaki A, Ge Y, Ri M, **Ishida T, Ueda R,** Utsunomiya A, Asai K, Inagaki H.	Prognostic impact of miR-145 down-regulation in adult T-cell leukemia/ lymphoma.	Human Pathol		in press	2014
Ishida T, Hishizawa M, Kato K, Tanosaki R, Fukuda T, Takatsuka Y, Eto T, Miyazaki Y, Hidaka M, Uike N, Miyamoto T, Tsudo M, Sakamaki H, Morishima Y, Suzuki R, Utsunomiya A.	Impact of GVHD on allogeneic hematopoietic cell transplantation for adult T-cell leukemia-lymphoma focusing on preconditioning regimens: nationwide retrospective study Biology of Blood and Marrow Transplantation.	Biol Blood Marrow Transplant.	19	1731-9	2013
Suzuki T, Kusumoto S, Yoshida T, Mori F, Ito A, Ri M, **Ishida T**, Komatsu H, Niimi A, **Iida S.**	Successful salvage therapy using lenalidomide in a patient with relapsed multiple myeloma after allogeneic hematopoietic stem cell transplantation.	Int J Hematol.	97	540-3	2013
Masaki A, **Ishida T,** Suzuki S, Ito A, Mori F, Sato F, Narita T, Yamada T, Ri M, Kusumoto S, Komatsu H, Tanaka Y, Niimi A, Inagaki H, **Iida S, Ueda R.**	Autologous Tax-specific CTL therapy in a primary ATL cell-bearing NOD/Shi-*scid*, IL-2Rγ^{null} mouse model.	J Immunol.	191	135-44	2013
Sato F ,**Ishida T**, Ito A, Mori F, Masaki A, Takino H, Narita T, Ri M, Kusumoto S, Suzuki S, Komatsu H, Niimi A, **Ueda R**, Inagaki H, **Iida S.**	Angioimmunoblastic T-cell lymphoma mice model.	Leuk Res.	37	21-27	2013

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Ⅴ．研究成果の刊行物・別冊

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ORIGINAL REPORT

Multicenter Phase II Study of Mogamulizumab (KW-0761), a Defucosylated Anti-CC Chemokine Receptor 4 Antibody, in Patients With Relapsed Peripheral T-Cell Lymphoma and Cutaneous T-Cell Lymphoma

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ABSTRACT

Purpose
CC chemokine receptor 4 (CCR4) is expressed by peripheral T-cell lymphomas (PTCLs) and is associated with poor outcomes. Mogamulizumab (KW-0761) is a defucosylated humanized anti-CCR4 antibody engineered to exert potent antibody-dependent cellular cytotoxicity. This multicenter phase II study evaluated the efficacy and safety of mogamulizumab in patients with relapsed PTCL and cutaneous T-cell lymphoma (CTCL).

Patients and Methods
Mogamulizumab (1.0 mg/kg) was administered intravenously once per week for 8 weeks to patients with relapsed CCR4-positive PTCL or CTCL. The primary end point was the overall response rate, and the secondary end points included safety, progression-free survival (PFS), and overall survival (OS).

Results
A total of 38 patients were enrolled, and 37 patients received mogamulizumab. Objective responses were noted for 13 of 37 patients (35%; 95% CI, 20% to 53%), including five patients (14%) with complete response. The median PFS was 3.0 months (95% CI, 1.6 to 4.9 months), and the median OS was not calculated. The mean maximum and trough mogamulizumab concentrations (± standard deviation) after the eighth infusion were 45.9 ± 9.3 and 29.0 ± 13.3 μg/mL, respectively. The most common adverse events were hematologic events, pyrexia, and skin disorders, all of which were reversible and manageable.

Conclusion
Mogamulizumab exhibited clinically meaningful antitumor activity in patients with relapsed PTCL and CTCL, with an acceptable toxicity profile. Further investigation of mogamulizumab for treatment of T-cell lymphoma is warranted.

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INTRODUCTION

Mature T/natural killer (NK)-cell neoplasms comprise approximately 20 subclassified heterogeneous groups of non-Hodgkin lymphomas (NHLs) that account for approximately 10% of NHLs in Western countries[1-3] and approximately 25% of NHLs in Japan.[4,5] Mature T/NK-cell neoplasms are largely subdivided into peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL), and different treatment strategies are used for each of these entities.[1,6]

According to the WHO classification, PTCL includes peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large-cell lymphoma (ALCL).[1-3] Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and CHOP-like regimens have been widely used as the standard first-line treatment for patients with PTCL.[7,8] With the exception of those patients with anaplastic lymphoma kinase-positive ALCL, the efficacy of these combination therapies is unsatisfactory because those who achieve remission eventually experience relapse and poor outcomes.[3,9] Several agents have been approved by the US Food and Drug Administration for the treatment of relapsed or refractory (Rel/Ref) PTCL: pralatrexate, romidepsin for Rel/Ref PTCL, and brentuximab vedotin for Rel/Ref ALCL. The overall response rates

(ORRs) were reported to be 29% and 25% for PTCL and 86% for ALCL, respectively.[10-12]

CTCL can be classified as mycosis fungoides (MF), Sézary syndrome, or cutaneous ALCL. The majority of cases of CTCL in Japan consist of MF.[13] The therapeutic approaches and outcomes for these conditions are primarily dependent on disease stage.[6,7,14] Patients with advanced stage CTCL who relapse after systemic chemotherapies and those with transformed MF have particularly poor outcomes.[15,16] Recently, the US Food and Drug Administration approved agents for Rel/Ref CTCL treatment, including vorinostat, denileukin diftitox, and romidepsin, with ORRs of 30%, 30%, and 34%, respectively.[17-19] However, there are few treatment options or approved agents for CTCL in Japan, partly because of its low prevalence here.[5,12,13]

CC chemokine receptor 4 (CCR4) is a marker for type 2 helper T cells or regulatory T (Treg) cells and is expressed on tumor cells in approximately 30% to 65% of patients with PTCL.[20,21] CCR4-positive patients (eg, in the PTCL-NOS subgroup) have a shorter survival time when compared with CCR4-negative patients.[21-23] Further, CCR4 expression increases with advancing disease stage in patients with MF/Sézary syndrome.[24]

Mogamulizumab (KW-0761) is a humanized anti-CCR4 monoclonal antibody with a defucosylated Fc region that enhances antibody-dependent cellular cytotoxicity.[25,26] In vitro antibody-dependent cellular cytotoxicity assay and in vivo studies in a humanized mouse model revealed that mogamulizumab exhibited potent antitumor activity against T-cell lymphoma cell lines and against primary CTCL cells from patients.[26-28]

In a phase I study of patients with relapsed adult T-cell leukemia-lymphoma (ATL) and PTCL/CTCL, mogamulizumab was well tolerated up to a dose of 1.0 mg/kg. An ORR of 31% (five of 16) was obtained, including one partial response (PR) among three patients with PTCL/CTCL.[29] Mogamulizumab yielded an ORR of 50% (13 of 26) for relapsed CCR4-positive ATL in a subsequent phase II study.[30] In the United States, a phase I/II study for patients with Rel/Ref CTCL revealed that mogamulizumab was well tolerated with an ORR of 37% (14 of 38, 8% complete response [CR], 29% PR) and a median PFS of 341 days.[31]

The present report describes the results of a multicenter phase II study in Japan that was designed to assess the efficacy and safety of mogamulizumab in patients with relapsed CCR4-positive PTCL or CTCL.

PATIENTS AND METHODS

Study Design and Treatment

This was a multicenter, single-arm phase II study conducted at 15 Japanese centers. At least 35 patients were required to detect a lower limit of the 95% CI that exceeded the 5% threshold, and the expected ORR for mogamulizumab was 25% with a statistical power of 90%.[10,29]

All patients gave written informed consent before enrollment. Patients received intravenous infusions of 1.0 mg/kg mogamulizumab once per week for 8 weeks. Dose modification of mogamulizumab was not allowed. Oral antihistamine and acetaminophen were given before each dose of mogamulizumab as premedication.[29,30] A systemic corticosteroid (hydrocortisone 100 mg intravenously) was also administered before the first dose of mogamulizumab to prevent an infusion reaction. The same dose of hydrocortisone was administered before the second and subsequent administrations at the investigators' discretion. The plasma concentrations of mogamulizumab and antimogamulizumab antibodies in plasma were determined by using enzyme-linked immunosorbent assays.[29,30] Blood samples were collected from all patients who received at least one dose of mogamulizumab at times determined by the protocol for pharmacokinetic analyses. Maximum plasma mogamulizumab concentration and trough concentration parameters were calculated from 0 to 7 days after the eight doses. T-cell subsets and NK cell distribution were also investigated by flow cytometry during and after mogamulizumab treatment. This study was conducted in accordance with the Declaration of Helsinki and in compliance with Good Clinical Practices. The protocol was approved by the institutional review board at each participating institution.

Patients

Patients who were ≥ 20 years of age and who had CCR4-positive PTCL or CTCL with relapse after their last systemic chemotherapy were eligible for participation. Patients who were refractory to their most recent therapy were not eligible for this study. Histopathological subtypes were assessed and reclassified by the Independent Pathology Review Committee according to the 2008 WHO classification.[1] CCR4 expression was determined by immunohistochemistry by using an anti-CCR4 monoclonal antibody (KM2160) and was confirmed by central review, as described previously.[29] In brief, CCR4 expression was classified according to the proportion of stained tumor cells (negative, < 10%; 1+, 10% to <25%; 2+, 25% to < 50%; 3+, ≥ 50%). Staging of nodal/extranodal and/or cutaneous lesions was performed if the lesions met the following requirements: nodal and extranodal lesions were > 1.5 cm in measurable length on cross-sectional computed tomography images, cutaneous lesions were identifiable on visual inspection, and peripheral blood abnormal lymphocyte count was ≥ 1,000/μL and comprised ≥ 5% of total leukocytes. All patients were required to have an Eastern Cooperative Oncology Group performance status of 0 to 2. Other notable eligibility criteria regarding laboratory values were as follows: neutrophil count ≥ 1,500/μL, platelet count ≥ 50,000/μL, hemoglobin level ≥ 8.0 g/dL, AST level ≤ 2.5× the upper limit of normal (ULN), ALT level ≤ 2.5× the ULN, total bilirubin level ≤ 1.5× the ULN, and serum creatinine level ≤ 1.5× the ULN. Patients were excluded if they had any severe complications, such as CNS involvement or a bulky lymphoma mass requiring emergent radiotherapy, a history of allogeneic stem-cell transplantation, active concurrent cancers, an active infection, or positivity for hepatitis B virus DNA, hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency virus antibody.

Efficacy and Safety Assessment

The primary objective was to assess the best overall response, and the secondary objectives included assessments of the best response according to disease site, progression-free survival (PFS), and overall survival (OS). Efficacy was evaluated by the Independent Efficacy Assessment Committee according to modified response criteria based on the International Working Group Criteria.[32,33] Cutaneous lesions were evaluated by using the modified Severity Weighted Assessment Tool.[34] In addition, treatment efficacy in patients with CTCL was evaluated by using a Global Response Score.[35] Responses were assessed after the fourth and eighth mogamulizumab infusions and at 2 and 4 months after the end of treatment. Treatment was discontinued if progressive disease (PD) was evident. PD and survival were monitored until at least 4 months after the completion of dosing. For safety evaluations, adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for AEs, version 4.0.

Statistical Analysis

PFS and OS were analyzed by using the Kaplan-Meier method. PFS was defined as the time from the first dose of mogamulizumab to progression, relapse, or death by any cause (whichever occurred first). OS was measured from the day of the first dose to death by any cause.

RESULTS

Patient Characteristics

Sixty-five patients were screened, and 64 biopsy specimens were histologically confirmed as PTCL or CTCL by the Independent Pathology Review Committee. In total, 50 (78%) of the 64 screened

patients were CCR4-positive. Of these, 38 eligible patients were enrolled in the study and 37 received at least one infusion of mogamulizumab. One patient withdrew because of an infectious complication before dosing. Patient characteristics, histopathology subtypes, and previous systemic therapies are shown in Table 1.

Table 1. Baseline Patient Demographic and Clinical Characteristics

Characteristic*	Patients (N = 37) No.	%	Patients With PTCL (n = 29) No.	%	Patients With CTCL (n = 8) No.	%
Age, years						
Median	64		67		50	
Range	33-80		33-80		36-70	
≥ 65	18	49	17	59	1	13
Sex						
Male	23	62	20	69	3	38
Female	14	38	9	31	5	63
ECOG performance status						
0	24	65	19	66	5	63
1	12	32	10	34	2	25
2	1	3	0	0	1	13
Elevated LDH level†	21	57	18	62	3	38
Bone marrow involvement	7	19	7	24	0	0
No. of previous systemic regimens						
Median	2		2		3	
Range	1-6		1-5		1-6	
1	14	38	13	45	1	13
2	15	41	12	41	3	38
≥ 3	8	22	4	14	4	50
Types of systemic therapy						
Chemotherapy	37	100	29	100	8	100
CHOP/CHOP-like regimen	36	97	29	100	7	88
DeVIC	6	16	4	14	2	25
CHASE	5	14	5	17	0	0
Single-agent therapy	5	14	0	0	5	63
Other	10	27	10	34	0	0
Auto-PBSCT	3	8	3	10	0	0
Radiotherapy	9	24	5	17	4	50
Intensity of CCR4 expression‡						
1+	6	16	4	14	2	25
2+	6	16	4	14	2	25
3+	25	68	21	72	4	50
Histopathology by central review						
PTCL-NOS	16	43	16	55		
AITL	12	32	12	41		
ALCL, ALK negative	1	3	1	4		
MF	7	19			7	88
c-ALCL	1	3			1	13

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; c-ALCL, cutaneous anaplastic large-cell lymphoma; CHASE, cyclophosphamide, cytosine arabinoside, etoposide, and dexamethasone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CTCL, cutaneous T-cell lymphoma; DeVIC, dexamethasone, etoposide, ifosfamide, and carboplatin; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; MF, mycosis fungoides; NOS, not otherwise specified; PBSCT, peripheral-blood stem-cell transplantation; PTCL, peripheral T-cell lymphoma.

*Of the 38 patients enrolled, 37 received at least one infusion of mogamulizumab.

†Elevated LDH level: higher LDH level than upper limit of the normal range.

‡The denominator used for the intensity of CC chemokine receptor 4 (CCR4) expression is based on subjects who were positive for CCR4 by immunohistochemistry.

Of the 37 patients who received mogamulizumab, 25 (68%) completed the planned course of eight infusions. Nine patients (24%) discontinued treatment because of PD, and three patients (8%) due to serious AEs.

Efficacy

The ORR for the 37 treated patients was 35% (13 of 37; 95% CI, 20% to 53%), and 14% of patients (five of 37) achieved a CR, of which one was unconfirmed (Table 2). Reponses (CR/PR) were observed in at least one patient with each subtype of disease, but the ORR differed between subtypes. The ORR was 34% (10 of 29; 95% CI, 18% to 54%) in patients with PTCL (three of 16 for PTCL-NOS, six of 12 for AITL, and one of one for ALCL, anaplastic lymphoma kinase-negative) and 38% (three of eight; 95% CI, 9% to 76%) in those with CTCL (two of seven for MF and one of one for cutaneous ALCL). In addition, ORR in patients with CTCL was 50% (four of eight; 95% CI, 16% to 84%) according to the Global Response Score.

Total ORR did not significantly correlate with CCR4 expression level, patient age, or the number of previous chemotherapy regimens. The response rates for lymph node and cutaneous lesions were 33% (11 of 33) and 58% (seven of 12), respectively.

The median PFS was 3.0 months (95% CI, 1.6 to 4.9 months) for the entire population and 2.0 months for patients with PTCL. Although the median OS was not reached for the entire population at the

Table 2. Best Response (N = 37)

Parameter	No. of Patients	No. of Patients With Best Response CR/CRu	PR	SD	PD	Response Rate (%)*
Overall response	37	5	8	13	11	35
Histopathology by central review						
PTCL	29	5†	5	9	10	34
PTCL-NOS	16	1	2	6	7	19
AITL	12	3	3	3	3	50
ALCL, ALK negative	1	1†	0	0	0	100
CTCL	8	0	3	4	1	38
MF	7	0	2	4	1	29
c-ALCL	1	0	1	0	0	100
Age, years						
< 65	19	1†	6	7	5	37
≥ 65	18	4	2	6	6	33
Intensity of CCR4 expression						
1+	6	1	1	3	1	33
2+	6	1	2	2	1	50
3+	25	3†	5	8	9	32
No. of previous systemic regimens						
1	14	3	3	6	2	43
2	15	1	1	6	7	13
≥ 3	8	1†	4	1	2	63

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; c-ALCL, cutaneous anaplastic large-cell lymphoma; CCR4, CC chemokine receptor 4; CR, complete response/complete remission; CRu, uncertain complete response/uncertain complete remission; CTCL, cutaneous T-cell lymphoma; MF, mycosis fungoides; NOS, not otherwise specified; PD, progressive disease; PR, partial response/partial remission; PTCL, peripheral T-cell lymphoma; SD, stable disease.

*Response rate (%): 100 × number of responders/number of subjects in each category included in the efficacy analysis set.

†Among the patients who showed CR/CRu, one showed CRu.

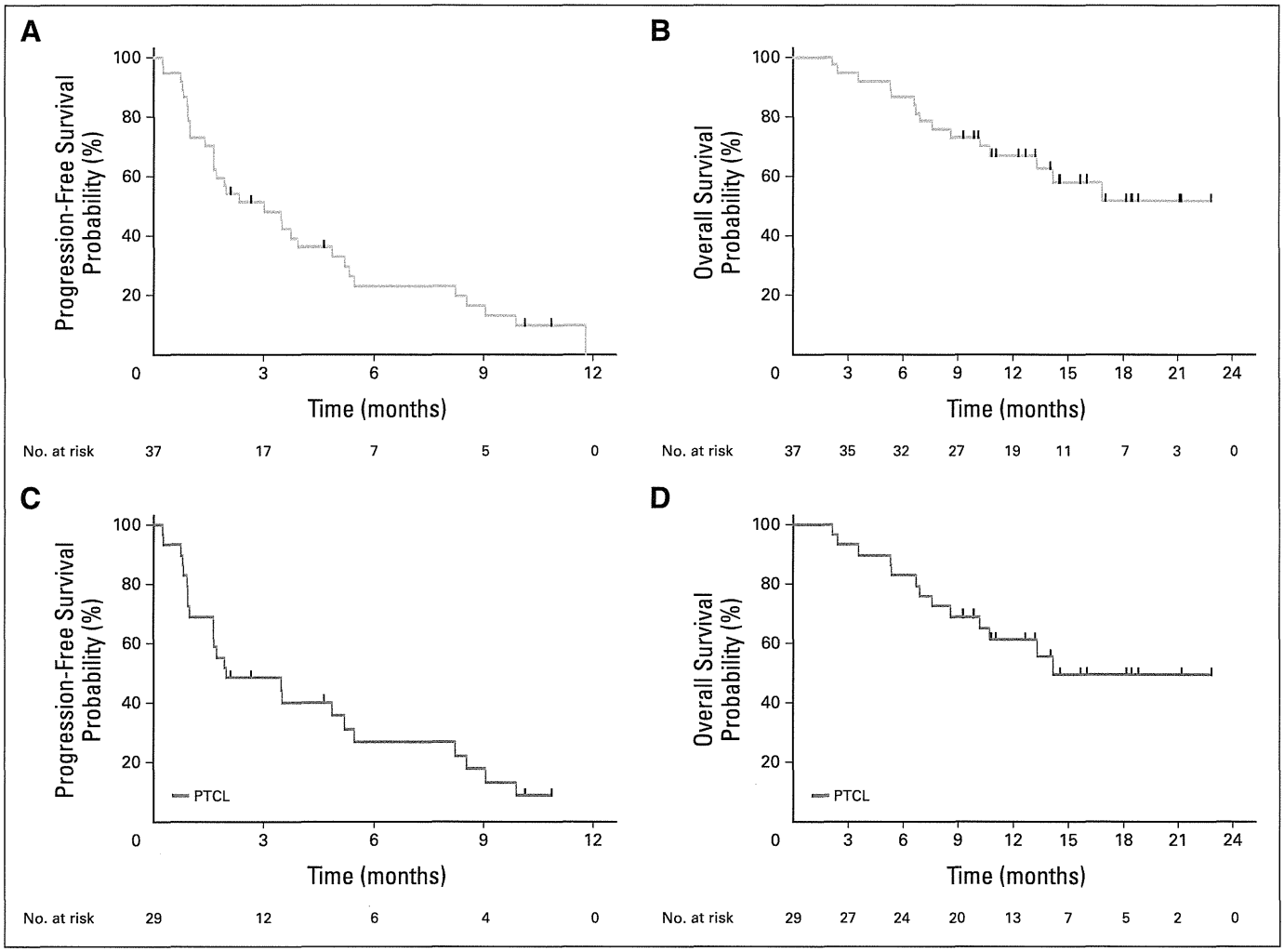

Fig 1. Kaplan-Meier curves of (A) estimated progression-free survival (median, 3.0 months), (B) overall survival (median not reached), (C) progression-free survival in patients with peripheral T-cell lymphoma (PTCL; median, 2.0 months), and (D) overall survival in patients with PTCL (median, 14.2 months).

time of this report, it was 14.2 months for patients with PTCL (Fig 1). Moreover, the median PFS of all 13 responders was 5.5 months, and for PTCL responders (n = 10), it was 8.2 months.

Safety

The most common treatment-related AEs of all grades and treatment-related AEs of grade 3/4 were lymphocytopenia (81%, 73%), neutropenia (38%, 19%), and leukocytopenia (43%, 14%), whereas the most common nonhematologic AE was pyrexia (30%; grade 2 or lower) (Table 3). Lymphocytopenia occurred in 30 patients (81%) and was noted after the first dose in 26 of these patients. For 19 of the patients, lymphocyte counts were $< 800/\mu L$ (grades 2 to 4) before the first dosing. The lymphocyte count ultimately recovered to normal or baseline levels in all patients.

Infusion reaction (24%; grade 2 or lower) occurred primarily at the first infusion, after which it became less frequent, and all patients recovered. No infusion prolongation/interruption was caused by the infusion reaction.

In addition, treatment-related skin disorders were commonly reported (all grades, 51%; grade 3/4, 11%) when grouped according to system organ class. Of the 19 patients who suffered from skin disorder complications, 15 patients experienced improvement, whereas the remaining patients discontinued treatment because of PD or switched to other post treatments. One patient who had a history of psoriasis before the study treatment developed two serious skin disorders (toxicoderma and psoriasis vulgaris) during the study period.

Fifteen serious treatment-related AEs were observed among eight patients (22%); these AEs included grade 3 polymyositis in one patient, grade 2 cytomegalovirus retinitis in two patients, and grade 4 second primary malignancy in one patient with AITL. All patients improved over time, and there were no deaths related to AEs.

Pharmacokinetics and Pharmacodynamics

The mean maximum mogamulizumab concentration and trough mogamulizumab concentration ($\pm$ standard deviation) in plasma after the eighth infusion were 45.9 $\pm$ 9.3 and 29.0 $\pm$ 13.3 μg/mL, respectively. Antimogamulizumab antibodies were not detected after dosing in any patients. These results were consistent with the findings of a previous study of patients with ATL.[30] As an exploratory study, we assessed the effect of mogamulizumab on the number of CD4+/CD25+/Foxp3+ cells (the Treg cell subset) and CD45+/CD16+/CD56+ cells (the NK cell subset). Patients given

