Safety and Efficacy Profile of Mogamulizumab (Poteligeo) in the Treatment of Cancers: An Update Evidence From 14 Studies

Ting Zhang

Sichuan University West China Hospital

Jing Sun

Qingdao central hospital, Qingdao University

Jinying Li

Qingdao central hospital, Qingdao university

Yunuo Zhao

Sichuan University West China Hospital

Tao Zhang

Sichuan University West China Hospital

Ruoning Yang

Sichuan University West China Hospital

Xuelei Ma (✉ drmaxuelei@gmail.com)

West China Hospital, Sichuan University <https://orcid.org/0000-0002-9148-5001>

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Abstract

Background: CC chemokine receptor 4 (CCR4) is the receptor for CCL22 and CCL17, which is expressed on the surface of tumor cells from patients with adult T-cell leukemia/lymphoma (ATL), peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL). Mogamulizumab is a humanized, IgG1 kappa monoclonal antibody that is directed against CCR4. By reducing the number of CCR4 positive Treg cells, the mogamulizumab can boost antitumor immunity and achieve anti-tumor effects.

Methods: We examined the PubMed and ClinicalTrials.gov without any language restrictions until 1 February 2020. Considering variability in different studies, the overall survival (OS), progression-free survival (PFS), objective responses rate (ORR) and Hazard Ratio (HR) were selected to evaluate the efficacy. Besides, adverse events (AEs) were calculated to assess the safety.

Results: When patients were treated with mogamulizumab monotherapy, the most common all-grade AEs were lymphopenia, infusion reaction, fever, rash and chills while lymphopenia, neutropenia and rash were the top 3 grade ≥ 3 AEs. In combination therapies, the top 3 all-grade AEs were neutropenia, anaemia, and lymphopenia, and lymphopenia is the most common grade ≥ 3 AE. Besides, the overall ORR is 0.430 (95% CI: 0.393-0.469) and the pooled mean PFS is 1.060 months (95% CI: 1.043-1.077) in mogamulizumab monotherapy. In combination therapies, the overall ORR is 0.203 (95% CI: 0.022-0.746) while the overall PFS and OS were 2.093 months (95% CI: 1.602-2.584) and 6.591 months (95% CI: 6.014-7.167), respectively.

Conclusions: On the basis of present evidence, we believed that mogamulizumab had clinically meaningful antitumor activity with acceptable toxicity which had a considerable potential in treating patients with cancers.

Background

CC chemokine receptor 4 (CCR4) is the receptor for two CC chemokine ligands (CCLs)- CCL22 (also called macrophage-derived chemokine) and CCL17 (thymus activation-regulated chemokine)[1]. By binding with its ligands, CCR4 is implicated in lymphocyte trafficking to the skin and sites of skin inflammation[2, 3]. CCR4 is a novel target for immunotherapy, as it is expressed on surface of tumor cells of most patients with adult T-cell leukemia/lymphoma (ATL) and is selectively expressed in approximately 40% of patients with other subtypes of peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL)[4–9]. Mogamulizumab (also named as KW-0761, poteligeo) is a humanized, IgG1 kappa monoclonal antibody that is directed against CCR4[9–11]. Previous studies have demonstrated that mogamulizumab can highly enhance antibody-dependent cellular cytotoxicity (ADCC) activity in vitro and antitumor effects against CCR4-expressing leukemic cells in vivo[1]. So far, a series of phase I/II/III trials on mogamulizumab for CCR4-expressing T-cell lymphoma, like PTCL and CTCL have been completed. From these trials, we supposed that mogamulizumab is a potential therapy for CCR4-positive T-cell lymphoma. Besides, we also focus on the safety of mogamulizumab or mogamulizumab-related therapies. However, there is no evidence-based systematic review on the safety and efficacy of mogamulizumab in treating patients with cancer. It is urgent and important to summarize those results, offering evidence-based references to direct clinical decisions. This meta-analysis we conducted focused on the safety and efficacy of mogamulizumab in the treatment of various advanced or metastatic T-cell lymphoma based on selected clinical trials.

Methods

Literature search and selection

We followed the guidelines of PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) to complete the meta-analysis. The trials were identified through PubMed and ClinicalTrials.gov without any language restrictions until 1 February 2020. The keywords we used include: “KW-0761”, “mogamulizumab” or “poteligeo”. The title and abstract of the papers after duplicates eliminated were analyzed independently by two reviewers. Refer to the opinions of the third reviewer when there are disagreements. Full texts of selective trials were downloaded and assessed in strict accordance with the following criteria for eligibility. Besides, we screened the references of selected trials for potentially relevant trials.

Inclusion and excluded Criteria

All eligible studies have to satisfy the following criteria: (i) the study must be a clinical study containing the efficacy or safety data of mogamulizumab in cancer patients; (ii) the study must report any of the following information: overall survival (OS), progression-free survival (PFS), objective responses rate (ORR), Hazard Ratio(HR) and adverse events (AE); (iii) the study must use mogamulizumab as a single drug or in combination with other drugs. The exclusion criteria were: (i) the studies were not clinical trials; (ii) the studies are retrospective studies, editorials, expert opinions, cases; (iii) the studies lacked available data or the full texts were inaccessible.

Data extraction

Data extraction was performed independently by two reviewers and disagreements were adjudicated by a third reviewer. The basic information extracted include: first author's name, clinical trial registration number, year, study phase, total number of patients, gender, age, treatment regime, tumor type and assessment. The data needed to assess the efficacy or safety of mogamulizumab includes OS, PFS, ORR, HR and AE (all grades and grades ≥ 3). For efficacy endpoints, the OS and PFS were collected directly in each included study while the ORR was collected directly or calculated based on the data in the study. The HR and 95% CI for PFS were extracted following this method[12]. For safety endpoints, the data we extracted from the trials were grade ≥ 3 and all-grade AEs according to Common Terminology Criteria for Adverse Events (CTCAE).

Results

Study selection

Through a comprehensive search, we found 213 articles in PubMed and 7 trials in ClinicalTrials.gov. After duplicate, there are 73 articles and 1 trial left. By screening the title and abstract, we excluded 44 articles on the basis of exclusion criteria. Then we view the full texts of remained studies, and finally, 13 articles and 1 trial are involved according to the inclusion and exclusion criteria[13-26]. The overall filter procedures and results are shown in **Figure 1**.

Study characteristics

The basic information of eligible studies was listed on **Table 1**. The trials were conducted from 2010 to 2019, including 5 phase II trials, 1 phase III trial, 6 phase I trials, 1 II trial and 1 unknown trial. Among them, patients in 2 phase II trials administered mogamulizumab intravenously at a dose of 0.01, 0.1, 0.5, 1.0 mg/kg[17, 21] and 3 phase II trials and 2 phase I trials received mogamulizumab in combination with other drugs[15, 23-26], while the rest received mogamulizumab at a dose of 1.0mg/kg as a single drug or in comparison of other drugs administered alone[13-16, 18-20, 22]. There were total 1290 patients assessed in these studies, including patients with ATL, PTCL, CTCL, ect.

Overall adverse events analysis

The safety data, grade ≥ 3 or all-grade AE we extracted, were used to calculate the AEs rate to assess the safety of mogamulizumab. The details of the results were presented in **Table 2, 3**. In all eligible trials administered mogamulizumab as a single drug, we divided these trials into low dose group (mogamulizumab ≤ 0.1 mg/kg), medium dose group (0.5 mg/kg) and high dose group (1.0 mg/kg) in accordance with the dose. In low dose group, the most common all-grade AE is lymphopenia (0.700, 95% CI: 0.375-0.900) and lymphopenia (0.401, 95% CI: 0.158-0.705) is the only grade ≥ 3 AE. In medium dose group, the most common all-grade AEs are leukopenia (0.875, 95% CI: 0.463-0.983) and lymphopenia (0.875, 95% CI: 0.463-0.983) while leukopenia (0.767, 95% CI: 0.337-0.955) is the only grade ≥ 3 AE. In high dose group, the top 5 most common all-grade AEs are lymphopenia (0.805, 95% CI: 0.432-0.957), infusion reaction (0.607, 95% CI: 0.062-0.973), fever (0.472, 95% CI: 0.116-0.859), rash (0.407, 95% CI: 0.210-0.639) and chills (0.401, 95% CI: 0.129-0.751). And lymphopenia (0.648, 95% CI: 0.482-0.787) is the most common grade ≥ 3 AE. In the trials administered mogamulizumab in combination with other drugs, the top 3 all-grade AEs were neutropenia (0.812, 95% CI: 0.035-0.998), anaemia (0.687, 95% CI: 0.017-0.996), and lymphopenia (0.619, 95% CI: 0.007-0.997). The lymphopenia (0.568, 95% CI: 0.004-0.998) is the most common grade ≥ 3 AE and other grade ≥ 3 AEs were relatively rare.

Overall efficacy analysis

The overall ORR rate, mean OS and mean PFS were used to measure the efficacy of mogamulizumab in treating cancers. For monotherapy, nine trials[13-16, 18-22] were included in the ORR analysis, and 4 articles[16, 19, 20, 22] were incorporated in the mean PFS analysis. According to our analysis, the overall ORR rate is 0.430 (95% CI: 0.393-0.469) (**Fig. 3 A**). The median PFS varied from 0.93 to 7.7 months and the pooled mean PFS is 1.060 months (95% CI: 1.043-1.077 $Z=125.452$, $p=0.000$) (**Fig. 4**). Besides, we performed further analyses to evaluate the efficacy between mogamulizumab and other chemotherapeutics. In controlled trials, the HRs for PFS in 2 control trials is 0.53 and 0.71 with a total HR of 0.56 (95% CI: 0.45-0.71, $I^2=0.0\%$, $p=0.348$) (**Fig. 2**), indicating a longer PFS in mogamulizumab group. For mogamulizumab in combination with other therapies, the overall ORR rate is 0.203 (95% CI: 0.022-0.746) (**Fig. 3 B**). Then we performed subgroup analysis to identify the overall PFS and OS of patients with non-small cell lung cancer in combination therapies. The overall PFS and OS are 2.435 months (95% CI: 1.752-3.119, $Z=6.982$, $p=0.000$) and 6.519 months (95% CI: 5.523-7.514, $Z=12.836$, $p=0.000$), respectively (**Tab. 4**).

Assessment of study quality and publication bias

We use Review Manager 5.3 (Copenhagen, Sweden) to measure quality assessment of involved studies. **Figure 5** indicates the risk of bias graph and risk of bias summary of all those eligible trials. Overall, the quality of the studies was satisfactory.

Discussion

Although various advanced or metastatic malignancies remain incurable, the application of mogamulizumab does benefit patients. We selected 14 prospective trials with 1290 patients in this meta-analysis and systematically assess the safety and efficiency of mogamulizumab. The integrated results of the data analysis confirm the role of mogamulizumab in cancer patients. It is the first time to evaluated the safety and effectiveness of mogamulizumab independently and systematically. This meta-analysis reveals the potential in treating patients with cancers, offering greater evidence for clinical decision.

With regard to the safety, we analyzed the AEs of patients administered mogamulizumab by intravenous infusion. According to our analysis, top common all-grade adverse events included rash in low dose, neutropenia in medium dose and fever in high dose. Besides, lymphopenia was the most common grade ≥ 3 adverse event which happened in nearly half of the participants. For combination therapies, neutropenia is the most common AE which happened in more than 80% patients. As with low dose studies, lymphoma is the most common grade ≥ 3 adverse events which happened in nearly half of the participants. Most of the AEs associated with mogamulizumab were mild and reversible. The mogamulizumab, having a defucosylated Fc region, has increased binding affinity to the Fc γ receptor on effector cells such as NK cells which can enhance ADCC. By strongly activating NK cells, mogamulizumab can induce NK cells to release cytokines and related cytotoxic molecules which might be the mechanism of infusion reaction[14, 27, 28]. Besides, the mogamulizumab can reduce the number of CCR4-expressing cells, resulting in an alteration of the immune balance which may cause different infections[29]. What's more, because CCR4 can also contribute to lymphocyte skin-specific homing, the skin disorders were frequently observed[30, 31].

With regard to the efficiency, we analyzed the ORR, PFS, OS and HR data of included trials. Approximately 43% of participants reached complete response or partial response in monotherapy. This is a particularly promising result since the response rate of patients with ATL, PTCL, CTCL ect, to conventional chemotherapy with a single agent is reportedly extremely low. It is acknowledged that Treg cells can be activated and recruited through CCR4 and CCL22. The mogamulizumab is a humanized, IgG1 kappa monoclonal antibody that is directed against CCR4 which prevents the binding of CCR4 and CCL22 to reduce

the number of Treg cells[32]. So the mechanism of antitumor activity is that the mogamulizumab can boost antitumor immunity by reducing the number of CCR4 positive Treg cells and influence tumor microenvironment to reduce tumor escape[33]. Patients administered mogamulizumab stabilized the disease more than 1 month and the overall patient survival time ranged from 4.9 months to 17.6 months which are longer than existing standard therapies. The analysis of HR in eligible trials also indicated that mogamulizumab can prolong the PFS of cancer patients compared to other chemotherapeutics. These results above demonstrated that mogamulizumab had a considerable potential in treating patients with cancers.

However, there are several limitations to this study. Firstly, the data of this meta-analysis is limited and some included studies even miss data. More experiments with larger sample size and more comparisons with other drugs are required. Second, the deficiencies in the experimental design of the selective studies cannot be eliminated from our analysis. Third, some patients received different prior systemic chemotherapy regimens, which could affect the results of the present study. Besides, there are diversities in the study design of different experiments such as experiment duration. Finally, the cancer types of patients are different, so the heterogeneity of the enrolled patients might have affected the results.

Conclusions

Based on the current evidence, this meta-analysis elucidates that mogamulizumab had clinically meaningful antitumor activity in patients with an acceptable toxicity profile which had a considerable potential in treating patients with cancers.

Abbreviations

CCR4: CC chemokine receptor 4; ATL: adult T-cell leukemia/lymphoma; PTCL: peripheral T-cell lymphoma; CTCL: cutaneous T-cell lymphoma; OS: Overall survival; PFS: Progression-free survival; ORR: objective responses rate; HR: Hazard Ratio; AEs: Adverse events; CI: Confidence interval; ADCC: antibody-dependent cellular cytotoxicity; PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses; CTCAE: Common Terminology Criteria for Adverse Events; RCT: Randomized controlled trial

Declarations

Ethics approval and consent to participate

This research is a pooled meta-analysis of published data and does not include any studies with human participants or animals performed by any of the authors. Hence, the ethics approval and consent are not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data are available in this manuscript.

Competing interests

The authors declare that they have no competing interests.

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There was no funding for this study.

Authors' contributions

TZ (Ting Zhang) and XLM conceived of the idea. TZ and JS designed the study, defined the search strategy and selection criteria, and were the major contributors in writing the manuscript. JY and YNZ performed the literature search and the analyses. TZ (Tao Zhang) and RNY performed the tables and diagrams. All the authors contributed to the writing and editing of the manuscript. All authors approved the final manuscript, and ensured that this is the case.

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Tables

Table 1: Basic characteristics of the included trials

First author	Clinical trial registration number	Year	Phase	Sample size	Gender		Age	Treatment	Disease	Assessment (Response)	Assessment (AE)
					Male	Female					
Yamamoto, K.	NCT00355472	2010	II	16	8	8	62 (46-69)	mogamulizumab	relapsed CCR4 ⁺ ATL or PTCL	RECIL	CTCAE
Ishida, T.	NCT00920790	2012	II	27	12	15	64 (49-83)	mogamulizumab	relapsed CCR4 ⁺ ATL	RECIL	CTCAE
Ogura, M.	NCT01192984	2014	II	37	23	14	64 (33-80)	mogamulizumab	relapsed CCR4 ⁺ PTCL or CTCL	RECIL	CTCAE
Duvic, M.	NCT00888927	2015	III-IV	41	24	17	66 (35-85)	mogamulizumab	CTCL or PTCL	RECIL	CTCAE
Ishida, T.	NCT01173887	2015	II	53	28	25	---	mLSG15 + mogamulizumab or mLSG15	aggressive ATL	RECIL	CTCAE
Kurose, K.	NCT01929486	2015	II	10	---	---	---	mogamulizumab	LC or EC	RECIST	CTCAE
Zinzani, P. L.	NCT01611142	2016	II	38	23	15	58.5 (19-87)	mogamulizumab	PTCL	RECIL	CTCAE
Ishitsuka, K.	UMIN000025368	2017	II	484	258	226	---	mogamulizumab or mogamulizumab with other drugs	ATL and others	RECIL	CTCAE
Kim, Y. H.	NCT01728805	2018	II	372	216	156	64.5 (54-73)	mogamulizumab or vorinostat	CTCL	RECIL	CTCAE
Nakashima, J.	---	2018	---	45	27	18	69 (43-89)	mogamulizumab	relapsed or refractory ATL	RECIL	CTCAE
Phillips, A. A.	NCT01626664	2018	II	34	37	71	53 (22-82)	mogamulizumab, pralatrexate, gemcitabine plus oxaliplatin or DHAP	ATL	RECIL	CTCAE
---	NCT02358473	2018	II	13	5	8	---	mogamulizumab +docetaxel	NSCLC	RECIST	CTCAE
Doi, T.	NCT02476123	2019	II	96	72	24	63 (56-68)	mogamulizumab +nivolumab	NSCLC, SCLC, GC, EC, HCC, PA	RECIST	CTCAE
Cohen, E. E. W.	NCT02444793	2019	II	24	19	5	63.9 (53-75)	mogamulizumab +utomilumab	CRC, NSCLC, OC, SCCHN	RECIST	CTCAE

Abbreviations: ATL: adult T-cell leukemia-lymphoma; PTCL: peripheral T-cell lymphoma; CTCL: cutaneous T-cell lymphoma; LC: lung cancer; EC: esophageal cancer; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; GC: gastric cancer; HCC: hepatocellular carcinoma; PA: pancreatic adenocarcinoma; CRC: colorectal cancer; OC: ovarian cancer; SCCHN: squamous cell cancer of head and neck; mLSG15: modified LSG15 regimen (VCAP-AMP-VECP: vincristine, cyclophosphamide, doxorubicin and prednisolone; doxorubicin, ranimustine and prednisolone; vindesine, etoposide, carboplatin and prednisolone); AE: adverse events; RECIL: Response Evaluation Criteria in Lymphoma; RECIST: Response Evaluation Criteria in Solid Tumors; CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events

Table 2
Summary results of the all-grade and grade ≥ 3 adverse events (AEs) in mogamulizumab monotherapy

adverse events	All-grade			Grade ≥ 3							
	No. of Studies	No. of Patients	model	Event rate with 95% CI	Z value	p value	No. of Studies	No. of Patients	model	Event rate with 95% CI	Z value
KW-0761 ≤ 0.1 mg/kg											
Hematologic											
Lymphopenia	2	10	Fixed	0.700(0.375–0.900)	1.224	0.221	2	10	Fixed	0.401(0.158–0.705)	-0.619
Nonhematologic											
Fever	2	10	Fixed	0.212(0.052–0.569)	-1.618	0.106					
Rash	2	10	Random	0.351(0.045–0.860)	-0.497	0.619					
KW-0761 = 0.5 mg/kg											
Hematologic											
Leukopenia	2	6	Fixed	0.875(0.463–0.983)	1.820	0.069	2	6	Fixed	0.767(0.337–0.955)	1.250
Lymphopenia	2	6	Fixed	0.875(0.463–0.983)	1.820	0.069					
Neutropenia	2	6	Fixed	0.587(0.181–0.902)	0.370	0.711					
KW-0761 = 1.0 mg/kg											
Hematologic											
Anaemia	5	3160	Random	0.097(0.040–0.216)	-4.626	0.000	3	122	Fixed	0.056(0.025–0.119)	-6.720
Leukopenia	5	127	Random	0.310(0.125–0.586)	-1.368	0.171					
Lymphopenia	4	80	Random	0.805(0.432–0.957)	1.643	0.100	3	43	Random	0.648(0.482–0.787)	1.757
Neutropenia	6	165	Random	0.228(0.104–0.431)	-2.543	0.011	5	155	Fixed	0.139(0.087–0.213)	-6.915
Thrombocytopenia	4	149	Random	0.273(0.131–0.483)	-2.108	0.035	4	149	Fixed	0.117(0.071–0.185)	-7.311
Gastrointestinal disorders											
Diarrhea	3	90	Fixed	0.158(0.096–0.249)	-5.743	0.000					
Vomiting	2	80	Fixed	0.128(0.107–0.154)	-5.617	0.000					
Nausea	4	154	Random	0.147(0.064–0.304)	-3.716	0.000	2	80	Fixed	0.039(0.013–0.114)	-5.436
General disorders											
Chills	2	69	Random	0.401(0.129–0.751)	-0.522	0.602					
Fatigue	2	89	Random	0.096(0.024–0.312)	-3.022	0.003					
Fever	3	43	Random	0.472(0.116–0.859)	-0.116	0.907					
Pyrexia	5	348	Random	0.139(0.062–0.283)	-4.002	0.000					
Headache	3	127	Random	0.115(0.046–0.259)	-4.048	0.000					
(continued)											

adverse events	All-grade						Grade ≥ 3					
	No. of Studies	No. of Patients	model	Event rate with 95% CI	Z value	p value	No. of Studies	No. of Patients	model	Event rate with 95% CI	Z value	
Infections and infestations												
Infection	2	84	Random	0.081(0.015–0.335)	-2.730	0.006	2	84	Fixed	0.084(0.038–0.175)	-5.571	
Injury, poisoning and procedural complications												
Infusion reaction	2	64	Random	0.607(0.062–0.973)	0.272	0.786						
Infusion-related reaction	4	311	Random	0.135(0.032–0.420)	-2.370	0.018						
Metabolism and nutrition disorders /investigations												
ALT	4	121	Random	0.172(0.063–0.391)	-2.731	0.006	3	111	Fixed	0.042(0.016–0.107)	-6.107	
AST	3	84	Random	0.167(0.040–0.494)	-1.990	0.047	2	74	Fixed	0.049(0.016–0.140)	-5.007	
Decreased appetite	2	231	Random	0.017(0.002–0.119)	-3.885	0.000						
CRP	2	16	Fixed	0.128(0.032–0.395)	-2.521	0.012						
Hypercalcemia	2	37	Fixed	0.108(0.041–0.255)	-3.983	0.000						
Hypertension	2	33	Fixed	0.277(0.150–0.453)	-2.443	0.015						
Hyperuricemia	2	37	Fixed	0.137(0.058–0.289)	-3.825	0.000						
Hypokalemia	2	64	Fixed	0.083(0.035–0.184)	-5.133	0.000	2	64	Fixed	0.053(0.017–0.151)	-4.857	
Hypophosphatemia	2	64	Fixed	0.156(0.086–0.267)	-4.895	0.000						
Hypotension	2	65	Fixed	0.139(0.074–0.246)	-5.084	0.000						
Weight change	2	74	Random	0.077(0.008–0.447)	-2.143	0.032						
Musculoskeletal and connective tissue disorders												
Polymyositis	2	221	Fixed	0.012(0.003–0.047)	-6.179	0.000						
Arthralgia	2	222	Random	0.036(0.004–0.278)	-2.767	0.006						
Respiratory, thoracic and mediastinal disorders												
Hypoxemia	2	33	Fixed	0.182(0.084–0.350)	-3.330	0.001						
Pneumonia	2	221	Fixed	0.023(0.009–0.053)	-8.316	0.000	2	75	Fixed	0.042(0.014–0.123)	-5.293	
Skin and subcutaneous tissue disorders												
Pruritus	4	113	Fixed	0.153(0.097–0.232)	-6.497	0.000						
Rash	4	88	Random	0.407(0.210–0.639)	-0.782	0.434	3	48	Fixed	0.135(0.074–0.234)	-5.423	
Rash maculopapular	2	47	Fixed	0.101(0.038–0.243)	-4.085	0.000						
Drug eruption	3	269	Random	0.111(0.022–0.412)	-2.365	0.018						

Table 3
Summary results of the all-grade and grade ≥ 3 adverse events (AEs) in combination therapies.

adverse events	All-grade			Grade ≥ 3							
	No. of Studies	No. of Patients	model	Event rate with 95% CI	Z value	p value	No. of Studies	No. of Patients	model	Event rate with 95% CI	Z value
Hematologic											
Anaemia	2	53	Random	0.687(0.017–0.996)	0.319	0.750					
Lymphopenia	2	119	Random	0.619(0.007–0.997)	0.176	0.861	2	119	Random	0.568(0.004–0.998)	0.092
Thrombocytopenia	3	143	Random	0.248(0.006–0.951)	-0.534	0.593					
Neutropenia	2	42	Random	0.812(0.035–0.998)	0.600	0.549					
Gastrointestinal disorders											
Gastrointestinal disorder	2	53	Random	0.599(0.001–0.999)	0.112	0.911					
Nausea	3	127	Random	0.159(0.046–0.425)	-2.393	0.017					
Vomiting	3	127	Random	0.093(0.032–0.242)	-3.945	0.000					
Diarrhea	2	103	Fixed	0.148(0.091–0.231)	-6.240	0.000					
Stomatitis	3	143	Random	0.185(0.035–0.585)	-1.592	0.111	2	119	Random	0.046(0.004–0.393)	-2.290
General disorders											
Fatigue	3	127	Random	0.278(0.072–0.659)	-1.159	0.246					
Pyrexia	3	143	Random	0.234(0.017–0.844)	-0.810	0.418					
Chills	2	37	Fixed	0.110(0.042–0.260)	-3.930	0.000					
Oedema peripheral	2	37	Fixed	0.056(0.014–0.200)	-3.863	0.000					
Injury, poisoning and procedural complications											
Infusion related reaction	2	37	Fixed	0.110(0.042–0.260)	-3.930	0.000					
Metabolism and nutrition disorders /investigations											
AST increased	2	119	Random	0.163(0.036–0.501)	-1.956	0.050	2	119	Fixed	0.059(0.028–0.119)	-7.103
ALT increased	2	119	Random	0.197(0.030–0.663)	-1.325	0.185	2	119	Fixed	0.044(0.019–0.102)	-6.696
Hyponatraemia	2	119	Random	0.060(0.009–0.301)	-2.825	0.005	2	119	Random	0.032(0.005–0.170)	-3.659
Hyperuricaemia	2	37	Fixed	0.056(0.014–0.200)	-3.863	0.000					
Hypomagnesaemia	2	37	Fixed	0.056(0.014–0.200)	-3.863	0.000					
Hypophosphataemia	2	53	Fixed	0.116(0.053–0.236)	-4.663	0.000					
Weight decreased	2	37	Fixed	0.113(0.043–0.265)	-3.878	0.000					
(continued)											
Platelet count decreased	2	103	Fixed	0.050(0.021–0.114)	-6.436	0.000					

adverse events	All-grade						Grade $\geq$ 3				
	No. of Studies	No. of Patients	model	Event rate with 95% CI	Z value	p value	No. of Studies	No. of Patients	model	Event rate with 95% CI	Z value
Decreased appetite	3	143	Random	0.275(0.031–0.817)	-0.769	0.442					
Dehydration	2	37	Fixed	0.204(0.099–0.373)	-3.166	0.002					
Hypotension	2	114	Fixed	0.021(0.005–0.082)	-5.334	0.000					
Musculoskeletal and connective tissue disorders											
Arthralgia	2	37	Fixed	0.113(0.043–0.265)	-3.878	0.000					
Musculoskeletal chest pain	2	37	Fixed	0.056(0.014–0.200)	-3.863	0.000					
Myalgia	3	127	Fixed	0.041(0.017–0.095)	-6.889	0.000					
Abdominal pain	2	37	Fixed	0.081(0.026–0.223)	-4.029	0.000					
Neck pain	2	37	Fixed	0.081(0.026–0.223)	-4.029	0.000					
Back pain	2	37	Fixed	0.056(0.014–0.200)	-3.863	0.000					
Chest pain	2	37	Fixed	0.056(0.014–0.200)	-3.863	0.000					
Skin and subcutaneous tissue disorders											
Rash	2	114	Fixed	0.370(0.286–0.462)	-2.741	0.006					
Rash maculo-papular	2	114	Fixed	0.182(0.121–0.266)	-6.046	0.000					
Skin exfoliation	2	114	Fixed	0.035(0.013–0.090)	-6.501	0.000					
Dry skin	2	114	Fixed	0.070(0.036–0.135)	-7.033	0.000					
Infections and infestations											
Sepsis	2	37	Random	0.139(0.017–0.607)	-1.584	0.113					
Pneumonia	2	53	Fixed	0.116(0.053–0.236)	-4.663	0.000					
Pneumonitis	2	114	Fixed	0.021(0.005–0.082)	-5.334	0.000					
Urinary tract infection	2	37	Fixed	0.056(0.014–0.200)	-3.863	0.000					
Nervous system and psychiatric disorders											
Dysgeusia	2	114	Fixed	0.044(0.018–0.101)	-6.738	0.000					
Headache	2	37	Fixed	0.142(0.060–0.300)	-3.712	0.000					
Insomnia	2	37	Fixed	0.110(0.042–0.260)	-3.930	0.000					
Malaise	2	114	Fixed	0.048(0.020–0.110)	-6.509	0.000					

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Table 4
Subgroup analysis of PFS and OS in non-small cell lung cancer patients with multiple therapies.

Table 1: Basic characteristics of the included trials											
First author	Clinical trial registration number	Year	Phase	Sample size	Gender		Age	Treatment	Disease	Assessment (Response)	Assessment (AE)
					Male	Female					
Yamamoto, K.	NCT00355472	2010	I	16	8	8	62 (46–69)	mogamulizumab	relapsed CCR4+ ATL or PTCL	RECIL	CTCAE
Ishida, T.	NCT00920790	2012	I	27	12	15	64 (49–83)	mogamulizumab	relapsed CCR4+ ATL	RECIL	CTCAE
Ogura, M.	NCT01192984	2014	I	37	23	14	64 (33–80)	mogamulizumab	relapsed CCR4+ PTCL or CTCL	RECIL	CTCAE
Duvic, M.	NCT00888927	2015	II–III	41	24	17	66 (35–85)	mogamulizumab	CTCL or PTCL	RECIL	CTCAE
Ishida, T.	NCT01173887	2015	I	53	28	25	—	mLSG15 + mogamulizumab or mLSG15	aggressive ATL	RECIL	CTCAE
Kurose, K.	NCT01929486	2015	I	10	—	—	—	mogamulizumab	LC or EC	RECIST	CTCAE
Zinzani, P. L.	NCT01611142	2016	I	38	23	15	58.5 (19–87)	mogamulizumab	PTCL	RECIL	CTCAE
Ishitsuka, K.	UMIN000025368	2017	I	484	258	226	—	mogamulizumab or mogamulizumab with other drugs	ATL and others	RECIL	CTCAE
Kim, Y. H.	NCT01728805	2018	I	372	216	156	64.5 (54–73)	mogamulizumab or vorinostat	CTCL	RECIL	CTCAE
Nakashima, J.	—	2018	—	45	27	18	69 (43–89)	mogamulizumab	relapsed or refractory ATL	RECIL	CTCAE
Phillips, A. A.	NCT01626664	2018	I	34	37	71	53 (22–82)	mogamulizumab, pralatrexate, gemcitabine plus oxaliplatin or DHAP	ATL	RECIL	CTCAE
—	NCT02358473	2018	I	13	5	8	—	mogamulizumab + docetaxel	NSCLC	RECIST	CTCAE
Doi, T.	NCT02476123	2019	I	96	72	24	63 (56–68)	mogamulizumab + nivolumab	NSCLC, SCLC, GC, EC, HCC, PA	RECIST	CTCAE
Cohen, E. E. W.	NCT02444793	2019	I	24	19	5	63.9 (53–75)	mogamulizumab + utomilumab	CRC, NSCLC, OC, SCCHN	RECIST	CTCAE
Abbreviations: ATL: adult T-cell leukemia-lymphoma;PTCL: peripheral T-cell lymphoma;CTCL: cutaneous T-cell lymphoma;LC: lung cancer;EC: esophageal cancer ; NSCLC: non-small cell lung cancer ; SCLC: small cell lung cancer; GC: gastric cancer; HCC: hepatocellular carcinoma; PA: pancreatic adenocarcinoma; CRC: colorectal cancer; OC: ovarian cancer; SCCHN: squamous cell cancer of head and neck; mLSG15: modified LSG15 regimen (VCAP-AMP-VECP: vincristine, cyclophosphamide, doxorubicin and prednisolone; doxorubicin, ranimustine and prednisolone; vindesine, etoposide, carboplatin and prednisolone); AE: adverse events; RECIL: Response Evaluation Criteria in Lymphoma;RECIST: Response Evaluation Criteria in Solid Tumors; CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events											

Table 5
Subgroup analysis of PFS and OS in non-small cell lung cancer patients with multiple therapies.

Study name	Year	Treatment	Cancer type	Media PFS (months)	Z-Value	P-Value	Media PFS (months)	Z-Value	P-Value
NCT02358473	2018	mogamulizumab + docetaxel	NSCLC	2.243 (95% CI:1.235–3.250)	4.364	0.000	7.335 (95% CI:5.657–9.013)	8.570	0.000
Doi, T	2019	mogamulizumab + nivolumab	NSCLC	2.600 (95% CI:1.669–3.531)	5.473	0.000	6.075 (95% CI:4.838–7.312)	9.629	0.000
Overall				2.435 (95% CI:1.752–3.119)	6.982	0.000	6.519 (95% CI:5.523–7.514)	12.836	0.000

Abbreviation: NSCLC (non-small cell lung cancer)

Figures

Figure 1

Flow diagram of literature selection for systemic reviews and meta-analyses (PRISMA).

Figure 2

The HRs and 95% CI for PFS in control-arm trials.

A

B

Figure 3

Analysis of the ORR of the studies in monotherapy and multiple therapies. (A) monotherapy; (B) multiple therapies.

Figure 4

Overall analysis of the PFS of the studies in monotherapy.

Figure 5

The risk of bias graph and the risk of bias summary.