Mogamulizumab *versus* investigator's choice of chemotherapy regimen in relapsed/refractory adult T-cell leukemia/lymphoma

Adrienne A. Phillips,[1] Paul A. Fields,[2] Olivier Hermine,[3] Juan C. Ramos,[4] Brady E. Beltran,[5] Juliana Pereira,[6] Farooq Wandroo,[7] Tatyana Feldman,[8] Graham P. Taylor,[9] Ahmed Sawas,[10] Jeffrey Humphrey,[11] Michael Kurman,[11] Junji Moriya,[11] Karen Dwyer,[11] Mollie Leoni,[11] Kevin Conlon,[12] Lucy Cook,[13] Jason Gonsky[14] and Steven M. Horwitz;[15] on behalf of the 0761-009 Study Group

[1]Division of Hematology and Medical Oncology, Weill Cornell Medical College, New York Presbyterian Hospital, New York, NY, USA; [2]Department of Haematology Guy's and St Thomas' Hospitals NHS Trust Hospital, London, UK; [3]Department of Hematology, Necker University Hospital, Paris, France; [4]Division of Hematology/Oncology, University of Miami Miller School of Medicine, Sylvester Comprehensive Cancer Center, FL, USA; [5]Hospital Nacional Edgardo Rebagliati Martins and Centro de Investigación de Medicina de Precision, Universidad de San Martin de Porres, Lima, Peru; [6]Department of Hematology, University of São Paulo, Brazil; [7]Sandwell and West Birmingham Hospitals NHS Trust, West Bromwich, and University of Birmingham, UK; [8]John Theurer Cancer Center, Hackensack UMC, NJ, USA; [9]National Centre for Human Retrovirology, St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK; [10]Center for Lymphoid Malignancies, Columbia University Irving Medical Center, New York, NY, USA; [11]Kyowa Kirin, Princeton, NJ, USA; [12]Warren Grant Magnuson Clinical Center, National Cancer Institute, Bethesda, MD, USA; [13]Department of Haematology and National Centre for Human Retrovirology, Imperial College Healthcare NHS Trust, London, UK; [14]Division of Hematology/Oncology, Department of Medicine, New York City Health + Hospitals/Kings County and SUNY Downstate Medical Center, Brooklyn, NY, USA and [15]Hematology/ Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

 doi:10.3324/haematol.2018.205096

Received: August 22, 2018.

Accepted: December 18, 2018.

Pre-published: December 20 2018.

Correspondence: ADRIENNE A. PHILLIPS adp9002@med.cornell.edu

Table S1. Patient demographic and clinical characteristics before and after major protocol amendment

	Before major protocol amendment		After major protocol amendment	
Baseline characteristic or response	**Mogamulizumab (n = 22)**	**Investigator choice (n = 12)**	**Mogamulizumab (n = 25)**	**Investigator choice (n = 12)**
BASELINE CHARACTERISTICS				
Age (y)				
Median (range)	52.5 (22-73)	50.5 (36-65)	55.0 (36-82)	46.0 (24-80)
>65 years, n (%)	3 (14)	0	8 (32)	1 (8)
<40 years, n (%)	4 (18.)	2 (17)	2 (8)	5 (42)
Sex, n (%)				
Male	12 (55)	4 (33)	12 (48)	6 (50)
Female	10 (46)	8 (67)	13 (52)	6 (50)
Race, n (%)				
Black	17 (77)	8 (67)	15 (60)	7 (58)
White	1 (5)	2 (17)	5 (20)	3 (25)
Asian	1 (5)	1 (8)	1 (4)	0
Other	0	0	1 (4.0)	0
Unknown*	3 (14)	1 (8)	3 (12)	2 (17)
Geographic region, n (%)				
North America	15 (68)	9 (75.0	10 (40)	5 (42)
Europe	5 (23)	3 (25)	9 (36)	4 (33)
South America and Caribbean	2 (9)	0	6 (24)	3 (25)
ECOG performance status, n (%)				
0	6 (27)	4 (33)	6 (24)	7 (58)
1	7 (32)	4 (33)	9 (36)	2 (17)
2	9 (41)	4 (33)	10 (40)	3 (25)
ATL subtype at study entry, n (%)				
Acute	11 (50)	6 (50)	10 (40)	6 (50)
Lymphoma	10 (46)	5 (42)	9 (36)	4 (33)
Chronic	1 (5)	1 (8)	6 (24)	2 (17)
Disease site, n (%)				
Lymph nodes	18 (82)	11 (92)	23 (92)	9 (75)
Peripheral blood	18 (82)	10 (83)	19 (76)	7 (58)
Bone marrow	14 (64)	6 (50)	13 (52)	2 (16.7)
Skin	6 (27)	4 (33)	7 (28)	5 (42)
Extranodal masses	8 (36)	2 (17)	4 (16)	6 (50)
Spleen	6 (27)	3 (25)	4 (16)	1 (8)
Liver	2 (9)	3 (25)	0	0
Other	0	0	1 (4)†	0
Not reported	0	0	0	1 (8)
CCR4 expression status, n (%)				
Positive	19 (86)	10 (83)	24 (96)	12 (100)
Negative	1 (5)	1 (8)	1 (4)	0
Not done	2	1	0	0
Prior ATL regimens, n (%)				
AZT	8 (36)	3 (25)	11 (44)	6 (50)
CHOP	10 (46)	4 (33)	11 (44)	1 (8)
Interferon	7 (32)	3 (25)	8 (32)	6 (50)
EPOCH	3 (14)	4 (33)	6 (24)	2 (17)
hyperCVAD	4 (18)	1 (8)	1 (4)	0
ICE	2 (9)	2 (17)	1 (4)	1 (8)
Pralatrexate	2 (9)	0	2 (8)	0
Autologous SCT	0	0	1 (4)	1 (8)
Other	14 (64)	8 (67)	20 (80)	8 (67)
Best response to immediate prior ATL therapy, n (%)				
CR	2 (9)	3 (25)	1 (4)	2 (17)
PR	3 (14)	3 (25)	6 (24)	3 (25)
SD	5 (23)	2 (17)	7 (28)	1 (8)
PD	9 (41)	3 (25)	10 (40)	6 (50)
Unknown	3 (14)	1 (8)	1 (4)	0

ATL, adult T-cell leukemia/lymphoma; AZT, zidovudine; CCR4, C-C chemokine receptor 4; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; CVAD, cyclophosphamide, vincristine, cyclophosphamide, and doxorubicin; ECOG, Eastern Cooperative Oncology Group; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; ICE, ifosfamide, carboplatin, and etoposide; PD, progressive disease; PR, partial response; SCT, stem cell transplantation; SD, stable disease.

*Not reported for those countries that do not allow race/ethnicity data to be collected.

†This patient met eligibility criteria with disease in blood and not in lymph nodes according to the investigator but showed lymph node and no blood involvement on independent review.

Table S2. Best response by disease compartment for patients receiving ≥2 cycles of mogamulizumab.

Patient no.	Disease compartment best response					
	Blood	Skin	Lymph nodes	Extranodal masses	Liver/spleen	Bone marrow
1	NI	PD	NI	PD	NI	NR
2	CR	NI	?PD*	NI	NI	CR
3	CR	PR	NI	uCR	NI	NR
4	CR	NI	PR	NI	NI	ND
5	CR	NI	SD	NI	NI	NI
6	CR	PR	SD	NI	NI	NR
7	CR	PR	SD	NI	NI	NI
8	CR	CR	SD	NI	NI	NR
9	SD	PR	SD	NI	NI	NR
10	CR	NI	uCR	NI	NI	NR
11	CR	CR	SD	NI	NI	CR
12	CR	PR	SD	NI	PD-spleen	SD
13	NI	NI	SD	NI	NI	NI
14	CR	SD	SD	NI	SD	NR
15	CR	NI	SD	NI	NI	SD
16	CR	NI	PR	NI	NI	NI
17	CR	NI	PR	NI	NI	NI
18	CR	NI	SD	NI	NI	NR
19	CR	CR	ND	ND	ND	NI
20	SD	SD	SD	NI	NI	SD
21	CR	CR	SD	NI	NI	NI
22	CR	NI	SD	NI	NI	NI
23	CR	NI	PR	NI	NI	NR
24	NI	PR	PD	SD	NI	NI

CR, complete response; ND, not done; NI, no disease involvement; NR, not reassessed after baseline; PD, progresssive disease; PR, partial response; SD, stable disease; uCR, uncertified complete response.

*Biopsy showed reactive node.

Table S3. Additional disease compartment response according to investigator assessment during randomization and after crossover to mogamulizumab (ITT population)

Best response overall and by disease compartment	Randomized			After crossover
	Mogamulizumab	Investigator choice		Mogamulizumab
Bone marrow	**n = 27**	**n = 8**		**n = 6**
CR	2 (7)	0		0
CRu	0	0		0
PR	0	0		0
SD	3 (11)	2 (25)		1 (17)
PD	0	0		0
Not assessable*	22 (82)	6 (75)		5 (83)
Spleen/liver	**n = 14**	**n = 5**		**n = 4**
CR	0	0		0
CRu	0	0		0
PR	0	0		0
SD	4 (29)	3 (60)		1 (25)
PD	2 (14)	0		0
Not assessable*	8 (57)	2 (40)		3 (75)
Extranodal masses	**n = 19**	**n = 10**		**n = 9**
CR	0	0		0
CRu	1 (5)	0		0
PR	1 (5)	0		0
SD	2 (11)	4 (40)		2 (22)
PD	9 (47)	5 (50)		3 (33)
Not assessable*	6 (32)	1 (10)		4 (44)

NOTE: Data are given as n (%) unless otherwise stated.

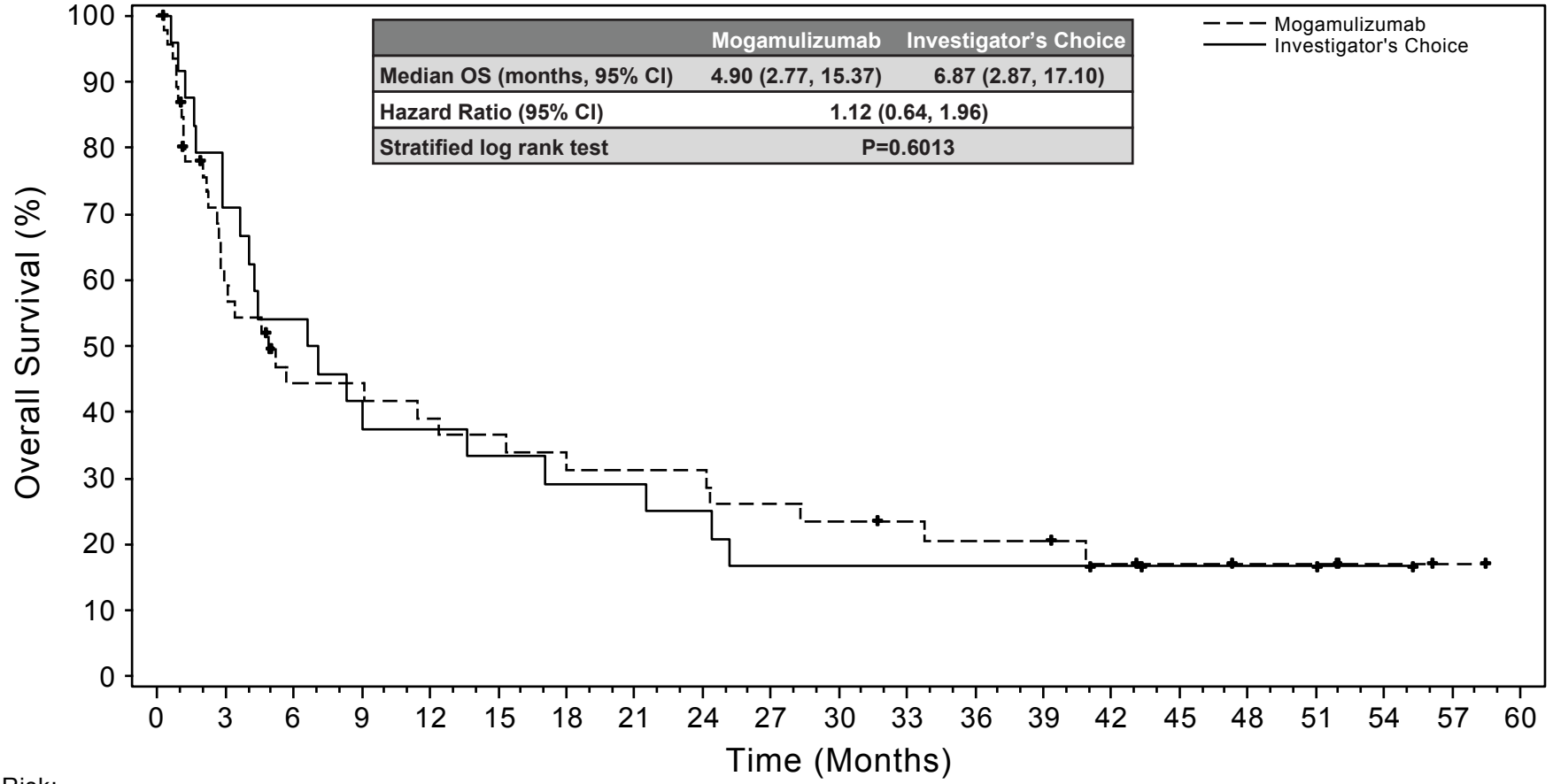
CR, complete response; CRu, uncertified CR; ITT, intent-to-treat; PD, progressive disease; PR, partial response; SD, stable disease.

†All but one patient considered not evaluable for overall response received ≤1 cycle of treatment and did not have assessments for response . Of these, on the mogamulizumab arm, reasons for treament discontinuation from mogamulizumab were; adverse event (7), PD (6), death (2), withdrawal of consent (1), other (1); On the IC arm, PD (4), adverse event (2) withdrawal of consent (1)}. All were counted as non-responders for ORR in the ITT analysis. The patient on the IC arm who completed >1 treatment cycle, met eligibility criteria with disease in blood on local flow and not in lymph nodes according to the investigator but showed lymph node and no blood involvement on independent review and so was considered not evaluable for response by investigator assessment.

One subject in crossover received 7 infusions of mogamulizumab and was discontinued from treatment due to an adverse event. Although this patient had a CR in blood and CR in skin, CT scan was not performed and so was not evaluable for overall response (See patient 19 in Figure 4).

*If there was no post-baseline tumor assessment for response assessment or there was no disease in that compartment, the response was designated not assessable.

FIGURE S1. KAPLAN-MEIER ANALYSIS OF OVERALL SURVIVAL (ITT POPULATION)



	Mogamulizumab	Investigator's Choice
Median OS (months, 95% CI)	4.90 (2.77, 15.37)	6.87 (2.87, 17.10)
Hazard Ratio (95% CI)	1.12 (0.64, 1.96)	
Stratified log rank test	P=0.6013	

No. at Risk:

Mogamulizamab:	47	25	17	17	15	14	12	12	12	10	9	8	7	7	5	4	3	3	2	1	0
IC:	24	17	13	10	9	8	7	7	6	4	4	4	4	4	3	2	2	2	1	0	0

Note: + = censored.
Survival analysis was confounded by the one-way crossover design. Eighteen of the 24 patients (75%) from the investigator choice arm crossed over to receive mogamulizumab.