

Macrophage-derived CXCL9 and CXCL11 production, CD8 T-cell skin recruitment and long-term disease control in mogamulizumab-treated CTCL patients

<u>Adèle de Masson</u>^{*1,2,3}, Delphine Darbord^{*4}, Gabor Dobos^{1,2,3}, Marie Boisson⁷, Marie Roelens^{2,5}, Caroline Ram-Wolff¹, Charles Cassius^{1,2,3}, Hélène Le Buanec^{2,3}, Pierre de la Grange⁶, Fanélie Jouenne^{2,3,7}, Baptiste Louveau^{2,3,7}, Aurélie Sadoux^{3,7}, Jean-David Bouaziz^{1,2,3}, Anne Marie-Cardine^{2,3}, Martine Bagot^{*1,2,3}, Hélène Moins-Teisserenc^{2,5}, Samia Mourah^{2,3,7}, **Maxime Battistella**^{2,3,4}







Conflict of interest

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Background



Mogamulizumab = humanized, defucosylated anti-CCR4 antibody

Antibody-dependent cell cytotoxicity

MAVORIC phase III clinical trial

European Market Authorization in Mycosis Fungoides and Sezary syndrome

Rashes have been reported with mogamulizumab treatment

Our objective was to describe the clinical and molecular characteristics of these rashes and correlation with outcome.

Characteristics of the patients

	All Patients	Patients with	Patients without	р
	(11=44)	(n=14)	(n=30)	
Age (years)	65.8 [33-87]	67.8 [33-83]	65 [33-87]	0.33
Sex				
Male	23 (52%)	6 (43%)	17 (57%)	
Female	21 (48%)	8 (57%)	13 (43%)	0.52
ECOG performance status				
0	28 (64%)	12 (86%)	16 (53%)	
1	10 (23%)	0 (0%)	10 (33%)	
2	2 (4%)	0 (0%)	2 (7%)	
3	1 (2%)	0 (0%)	1 (3%)	
NA	3 (7%)	2 (14%)	1 (3%)	0.06
Disease type				
Mycosis fungoides	9 (20%)	0 (0%)	9 (30%)	
Sézary syndrome	35 (80%)	14 (100%)	21 (70%)	0.04
mSWAT	85 [0-200]	74 [13.5-174]	90 [0-200]	0.52
LDH (UI/L)	372 [181-603]	384.5 [253-589]	365 [181-603]	0.50
Number of previous treatment lines	5.2 [1-11]	4 [1-10]	5.8 [1-11]	0.19
Number of previous systemic	4 [1-9]	3 [1-6]	4 [1-9]	0.04
treatment lines				
Time from diagnosis (days)	<u>1393 [142-41632]</u>	762 [238-41423]	<u>1904 [142-41632]</u>	<u>0.02</u>
Latest treatment before				
mogamulizumab				
Bexarotene	15 (34%)	7 (50%)	8 (27%)	
Interferon	2 (4%)	0 (0%)	2 (7%)	
Methotrexate	1 (2%)	1 (7%)	0 (0%)	
HDAC inhibitor	11 (25%)	3 (21%)	8 (27%)	
Conventional chemotherapy	11 (25%)	3 (21%)	8 (27%)	
Brentuximab vedotin	2 (4%)	0 (0%)	2 (7%)	
Lacutamab (anti-KIR3DL2)	2 (4%)	0 (0%)	2 (7%)	0.35

RAM: Rash Associated with Mogamulizumab

Gradual elimination of the tumor clone in patients with rash

Before treatment



Rash





Complete remission without treatment 18 months after





Gradual elimination of the tumor clone in patients with rash

All patients



Rash histology: macrophage and CD8 T cell infiltration











Gene expression in skin at rash: interferon alpha response

Immune System Cytokine Signaling in Immune system Interferon Signaling Interferon gamma signaling Innate Immune System Adaptive Immune System Chemokine receptors bind chemokines Extracellular matrix organization Antigen processing-Cross presentation Signaling by Interleukins / interactions between a Lymphoid and a non-Lymphoid cell Degradation of the extracellular matrix Interleukin-10 signaling Class I MHC mediated antigen processing & presentation Assembly of collagen fibrils and other multimeric structures Initial triggering of complement Syndecan interactions Neutrophil degranulation Collagen formation Extracellular matrix Activation of C3 and C5 Immune system 1.5 2.0 2.5 12 0 2 8 10 -log10(adjPV)

REACTOME pathways

GSEA

interferon alpha response interferon gamma response complement cascade allograft rejection IL6 STAT3 signaling during acute phase response inflammation blood vessel formation programmed cell death; caspase pathway blood coagulation cascade epithelial mesenchymal transition TNFA signaling via NF_B cell cycle progression: E2F targets KRAS signaling, upregulated genes cell cycle progression: G2/M checkpoint androgen response UV response: upregulated genes response to hypoxia; HIF1A targets mTORC1 signaling

0.0

0.5

1.0

NES

Gene expression in skin at rash: overexpression of CXCL9 and 11



CXCL9 and 11 are produced by macrophages in CTCL skin



Recruitment of new T cell clones in skin at the time of rash



Increased number of exhausted PD1+ and TIGIT+ reactive T cells in blood at baseline in patients with rash



Blood



Rash: hallmark of antitumor immune response ?

- Increased number of exhausted PD1+ and TIGIT+ reactive T cells in blood at baseline in patients with rash
- Recruitment of CXCL9- and CXCL11-producing macrophages in skin
- Expression of the receptor CXCR3 by T cells in CTCL skin
- Recruitment of new reactive T cell clones
- Diminution/disappearance of the tumor T cell clone
- Long term disease control





Thank you !



	Rash associated with
	mogamulizumab
Number of rash episodes/patient (n=14 patients)	
1	10 (71%)
2	4 (29%)
Time to skin rash, days (n=14 patients)	221 4 [15-1734]
Rash CTCAE grade (n=18 rashes)	
	1 (22%)
2	(22.70)
2	2 (11%)
NA	1 (6%)
Clinical presentation (n=18 rashes)	
Papules or plaques	13 (72%)
Macules without papules or plaques	5 (28%)
Facial edema	5 (28%)
Mucosal involvement	3 (17%)
Entbroderma	2(11%)
Scaling of the scale	2 (11%)
Pustules	1 (6%)
Histonathological patterns (n-18 rashes)	1 (0 /0)
Granulomatous	10 (56%)
Lichenoid	Q (50%)
Psoriasiform/spongiotic	13 (72%)
Immunohistochemical analysis (n=18 rashes)	10 (12,0)
Intraenidermic CD8+ T-cells	13 (72%)
CD4+/CD8+T-cell ratio	3 5 [0 25-10]
PD1+ cells (% lymphoid cells)	28 9 [0-80]
	20.0 [0 00]
Associated findings (n=14 patients)	
Pruritus	6 (43%)
Fever	2 (14%)
Elevated serum creatinin	1 (7%)
Auto-immune disease (vitiligo alopecia areata	5 (36%)
auto-immune hepatitis auto-immune thyroiditis)	
Management (n=18 rashes)	
Hospital admission	1 (6%)
Class III topical steroids	12 (67%)
Class IV topical steroids	4 (22%)
Antihistamines	2 (11%)
No specific treatment	1 (6%)
Discontinuation of mogamulizumab (n=18 rashes)	
	8 (44%)
Ves temporarily	6 (33%)
Yes permanently	4 (22%)
Recurrence after rechallenge (n=6 rechallenges)	4 (66%)