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

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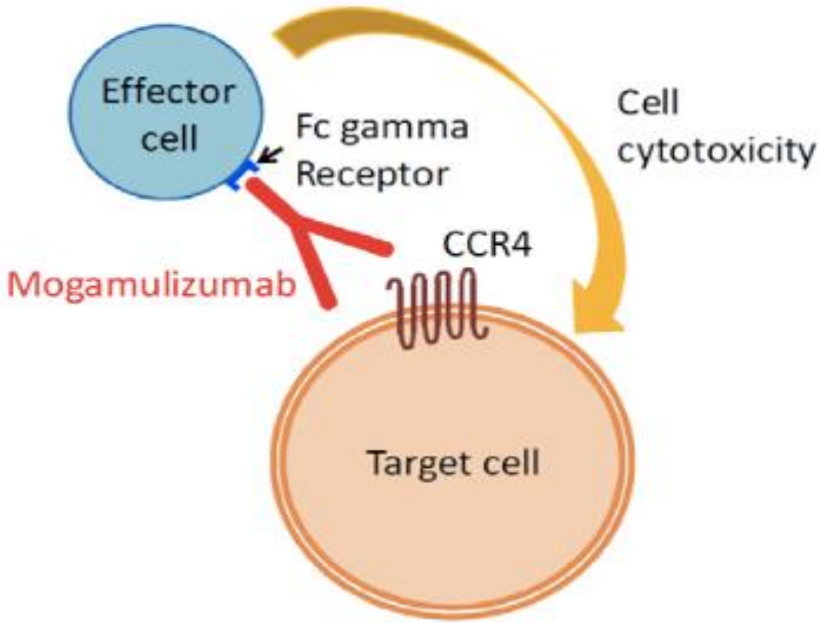
Conflict of interest

This study has been partially supported by a grant from Kyowa Kirin.

The sponsor had no influence on the study design and interpretation of data presented here.

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.

Kim, Bagot et al, Lancet Oncol 2018

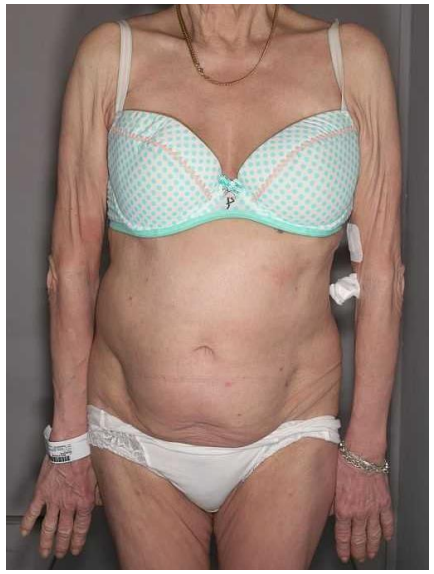
Characteristics of the patients

	All Patients (n=44)	Patients with RAM (n=14)	Patients without RAM (n=30)	p
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 treatment lines	4 [1-9]	3 [1-6]	4 [1-9]	0.04
Time from diagnosis (days)	1393 [142-41632]	762 [238-41423]	1904 [142-41632]	0.02
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

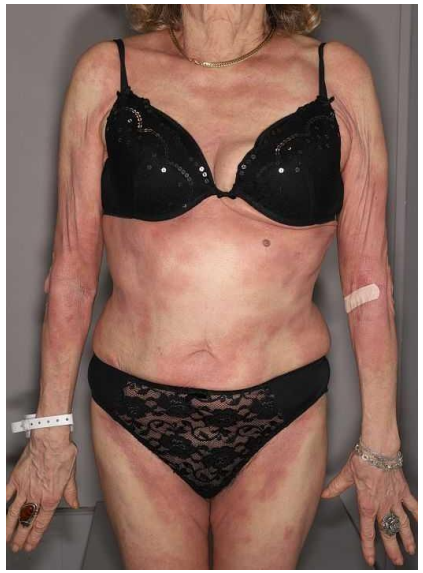
RAM: Rash Associated with Mogamulizumab

Gradual elimination of the tumor clone in patients with rash

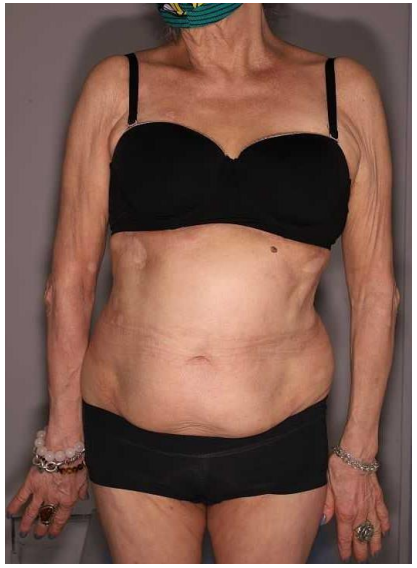
Before treatment

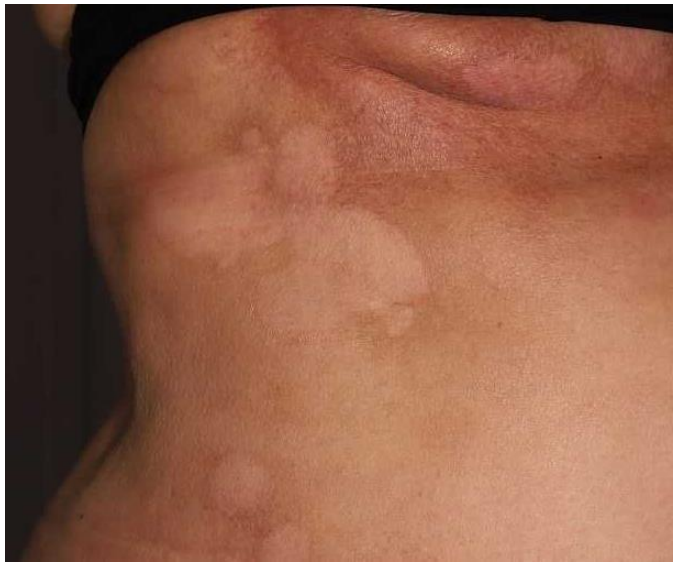


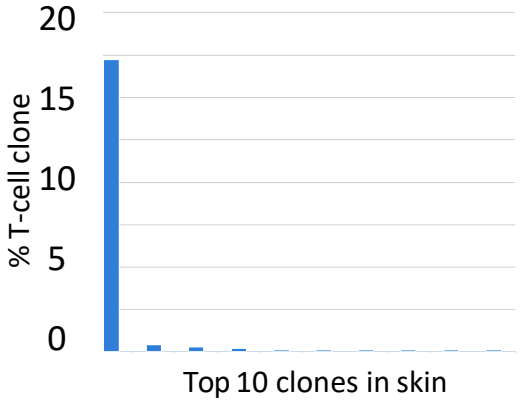
Rash

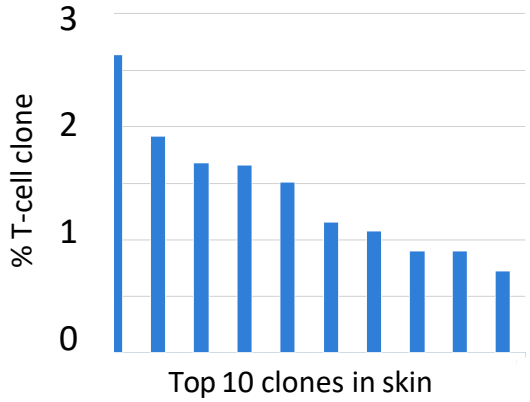


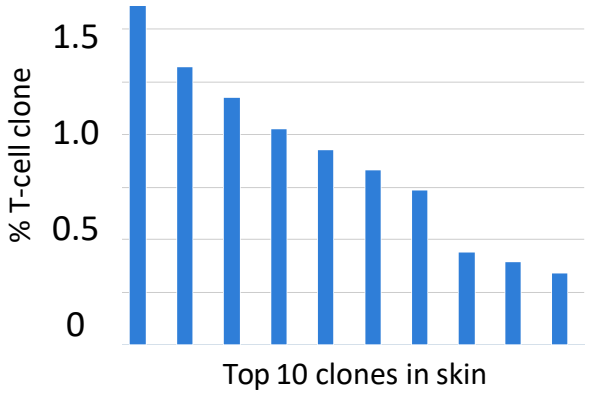
Complete remission without treatment 18 months after

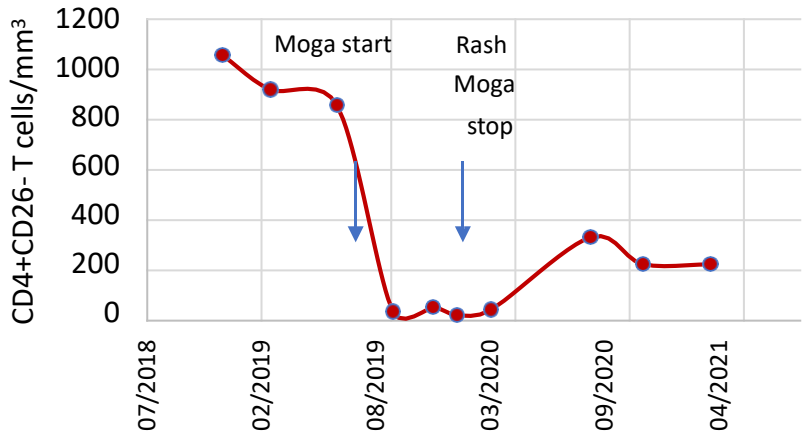




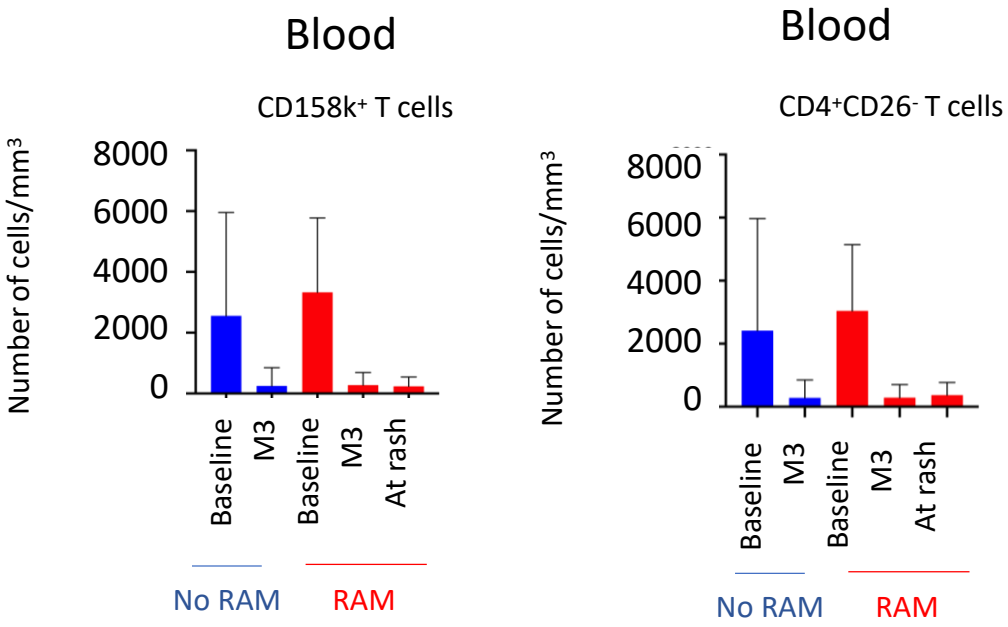


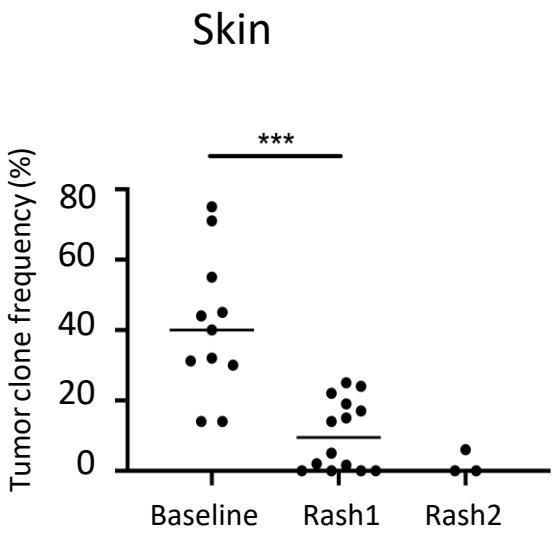




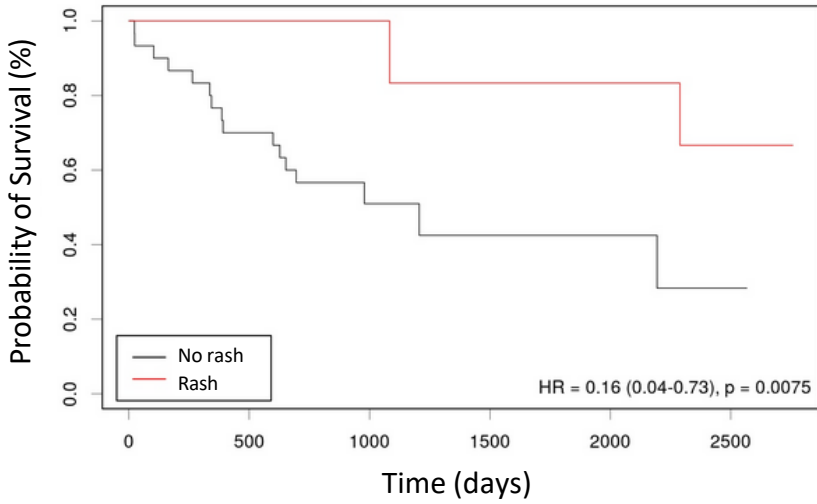


Gradual elimination of the tumor clone in patients with rash

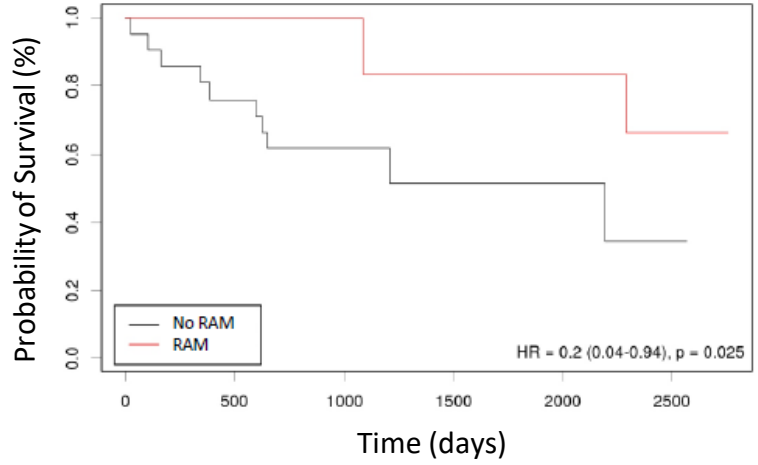




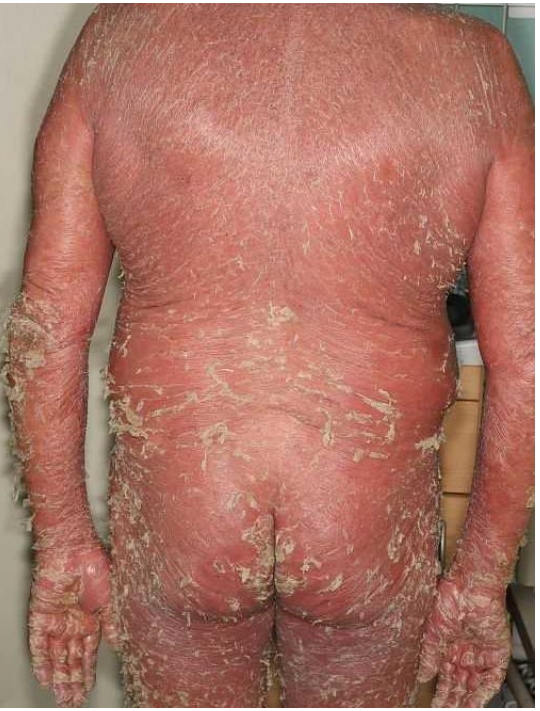
All patients

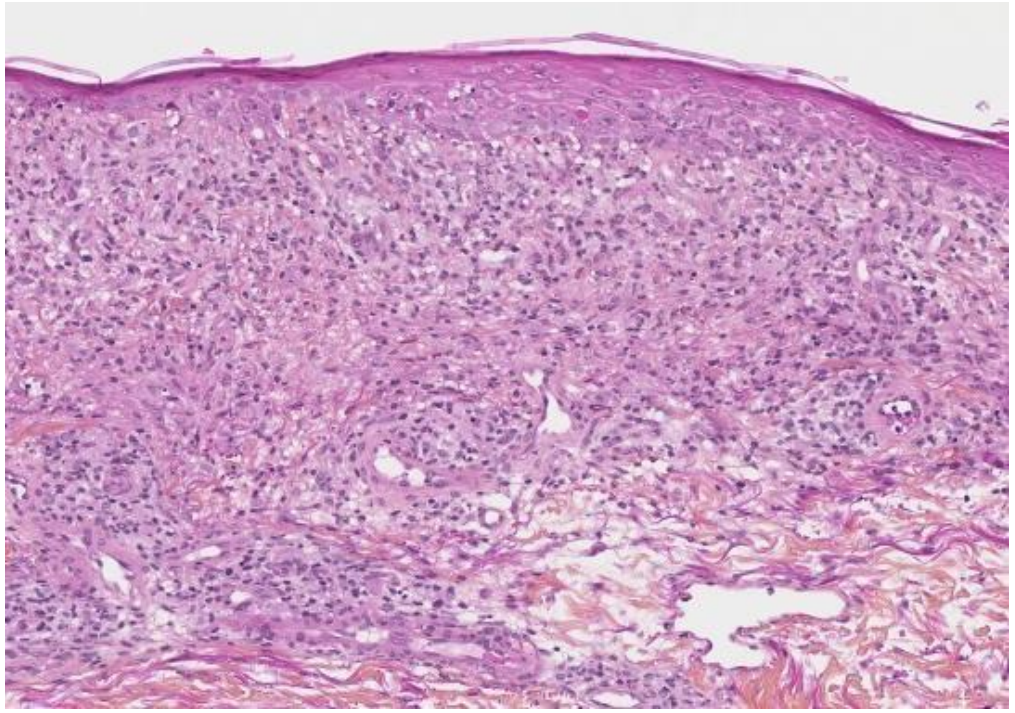


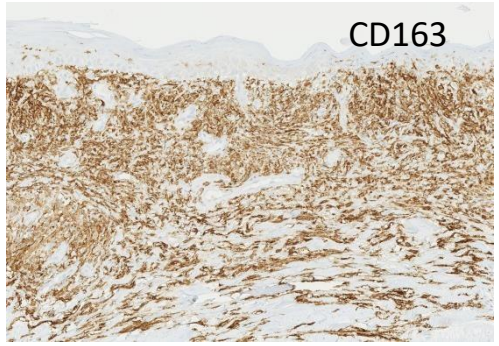
Sezary patients

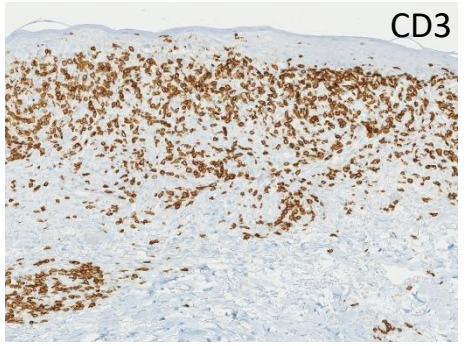


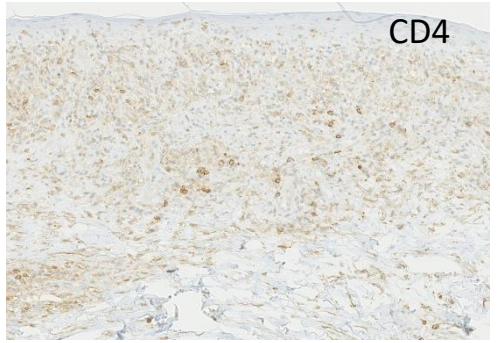
Rash histology: macrophage and CD8 T cell infiltration

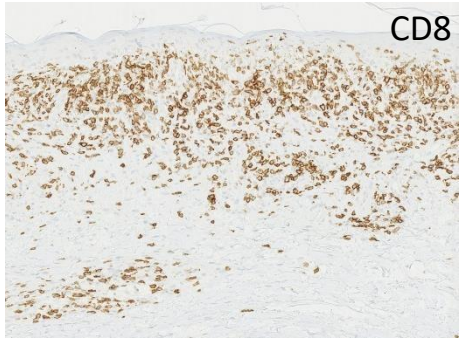


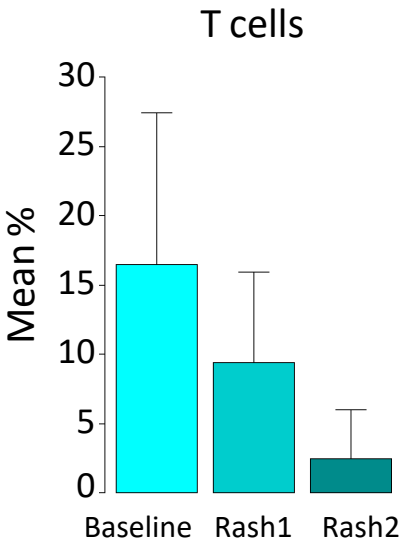


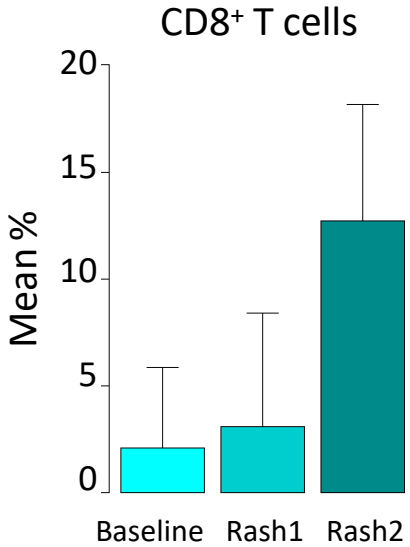


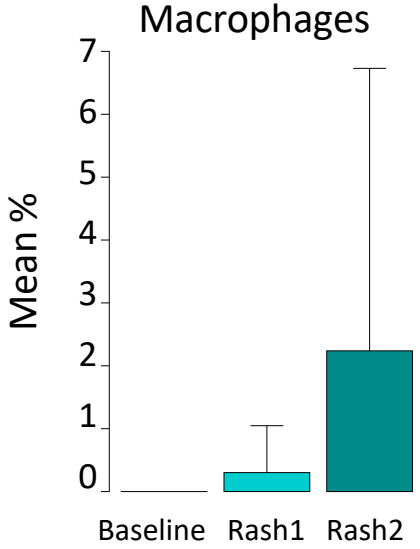


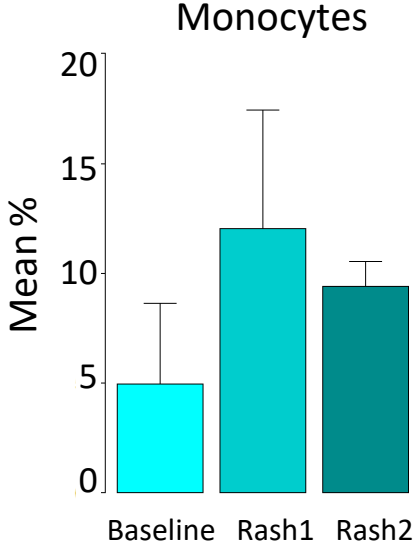




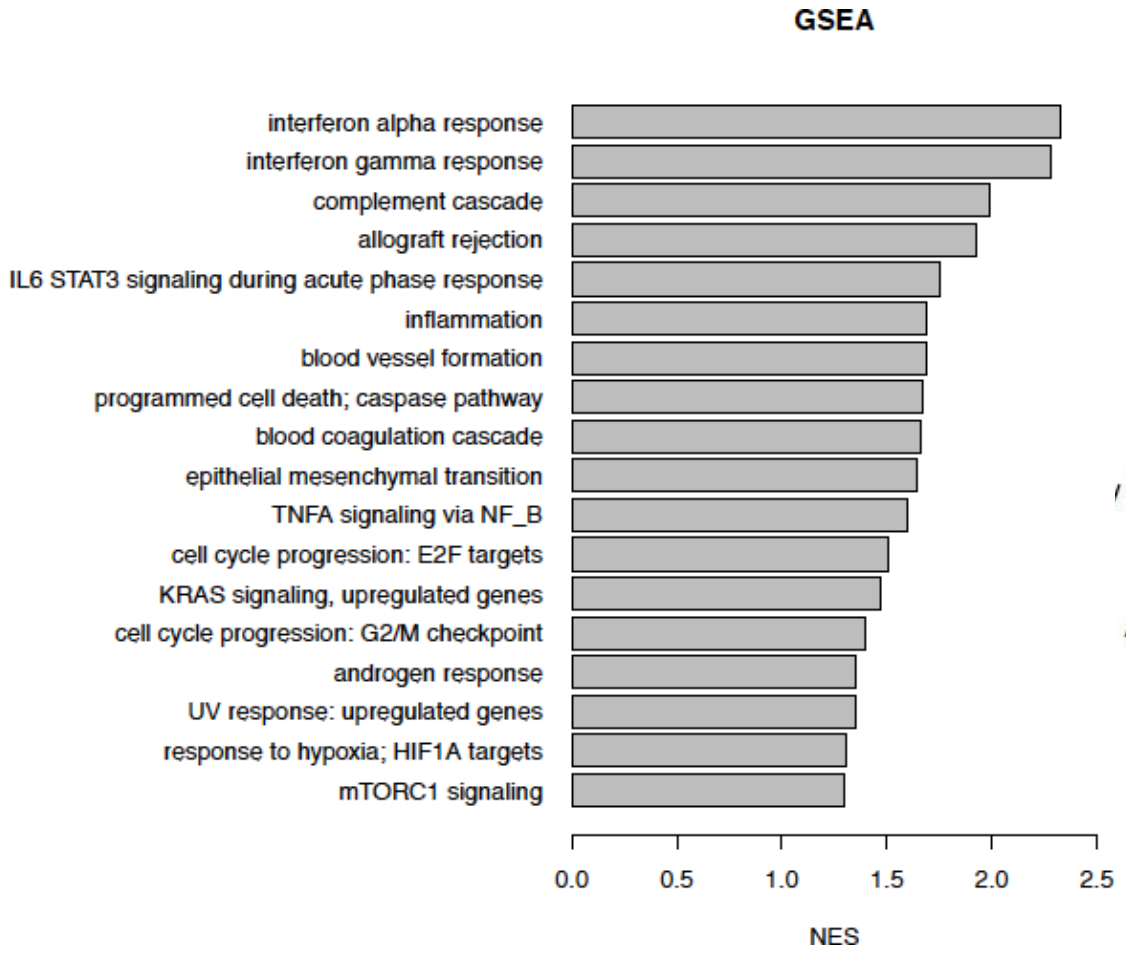


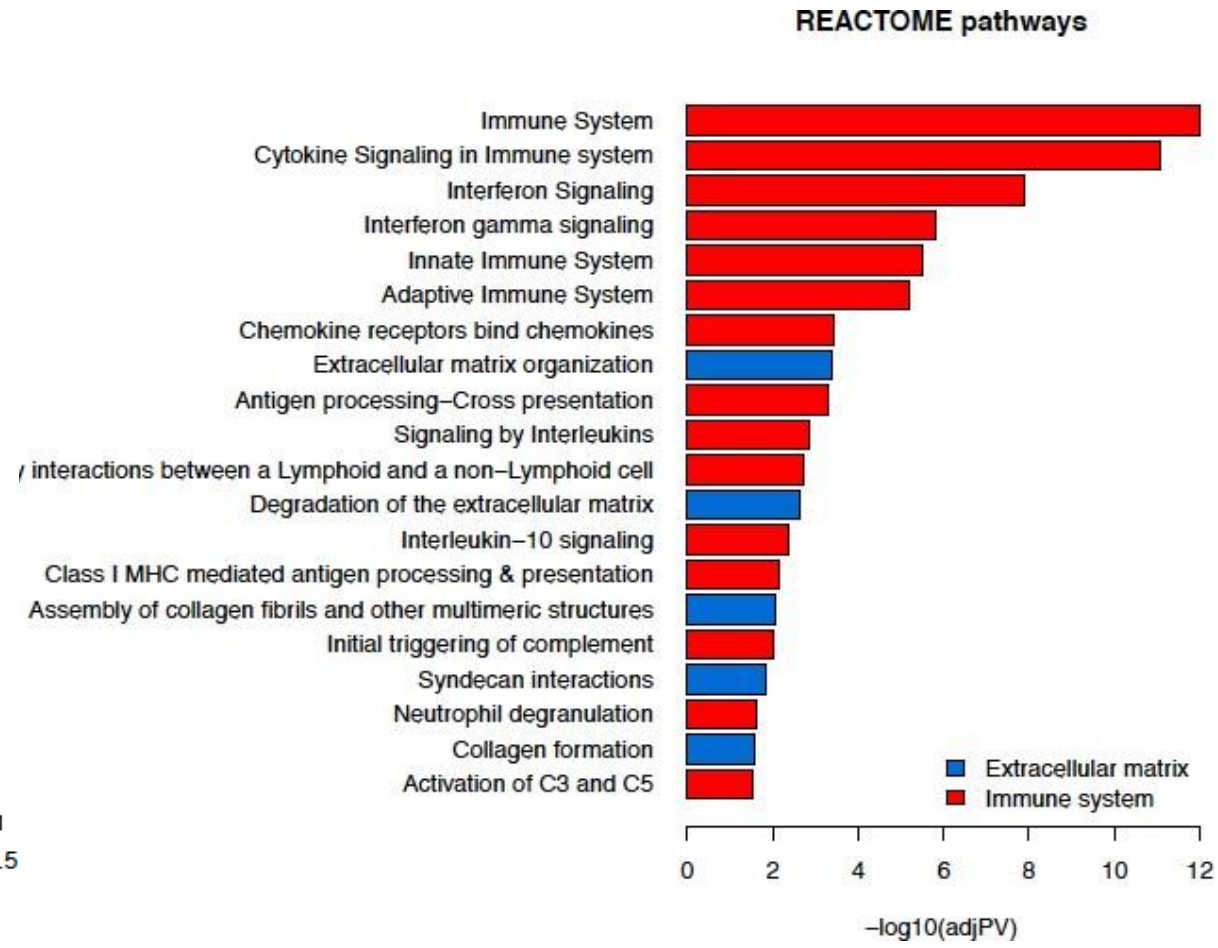




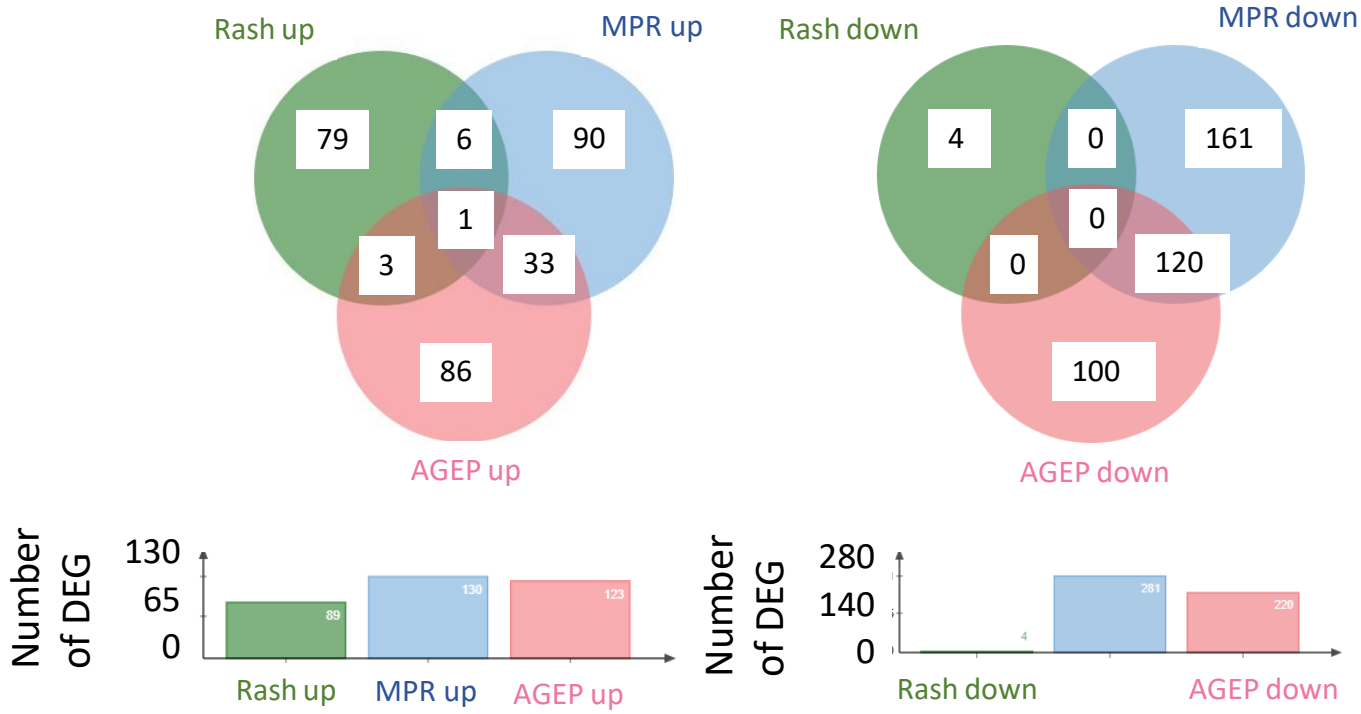


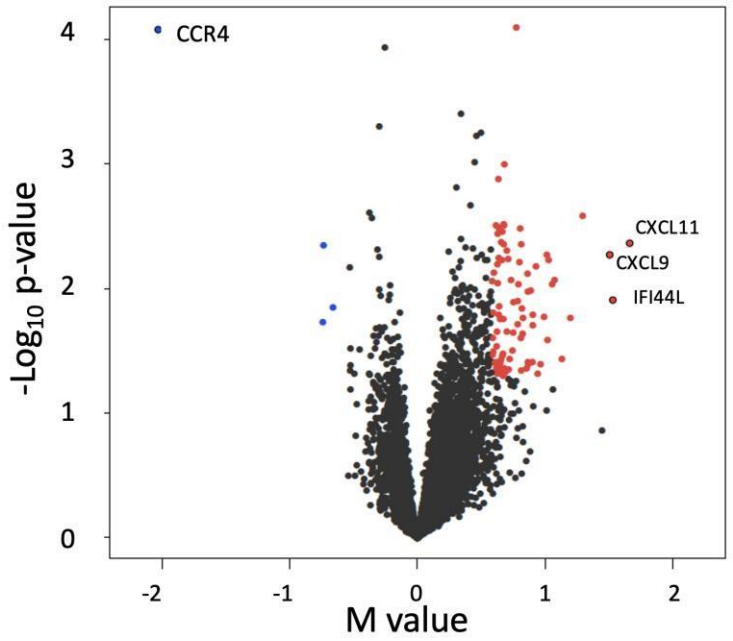
Gene expression in skin at rash: interferon alpha response



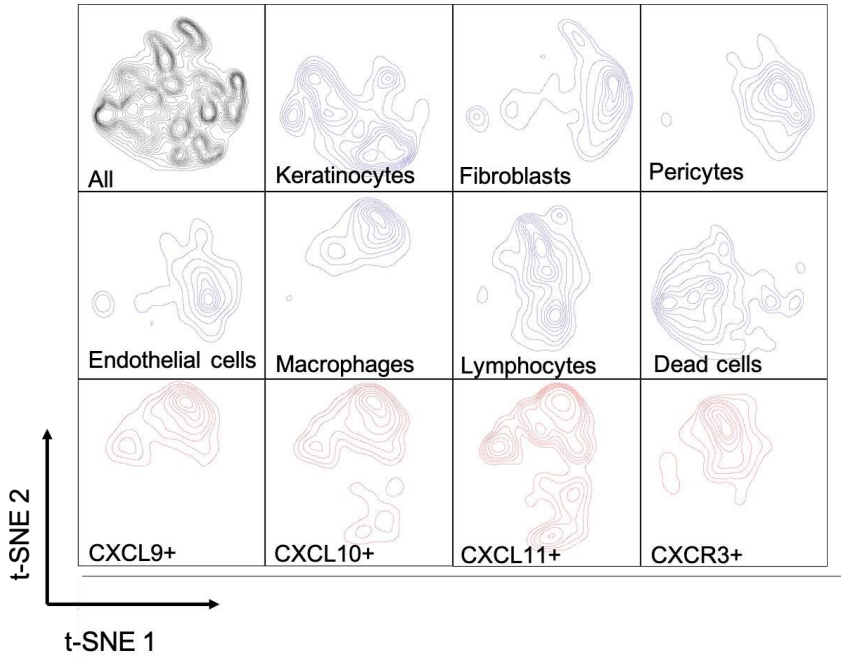


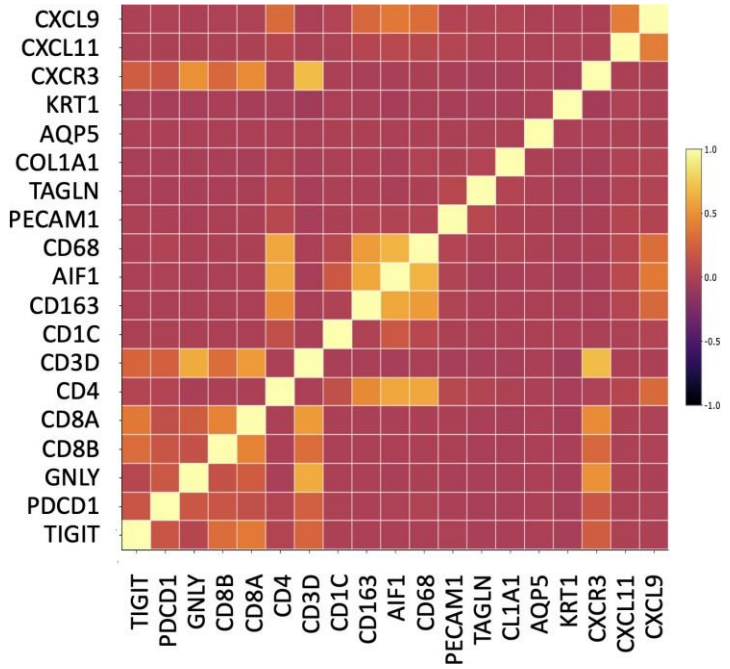
Gene expression in skin at rash: overexpression of CXCL9 and 11

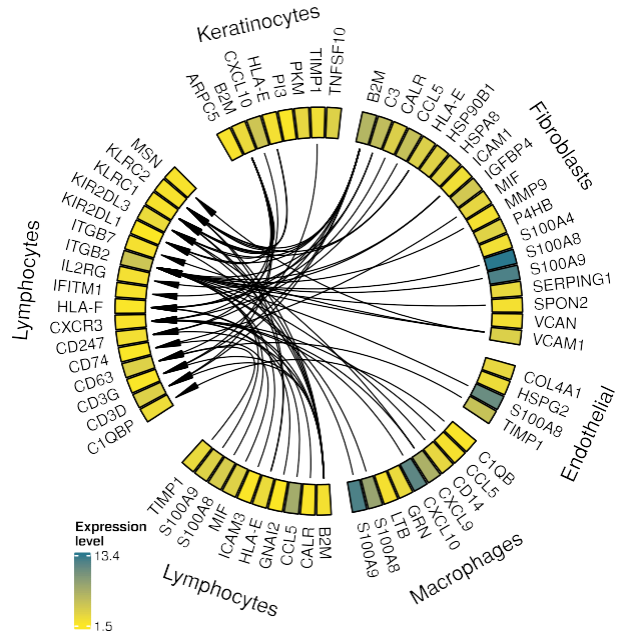


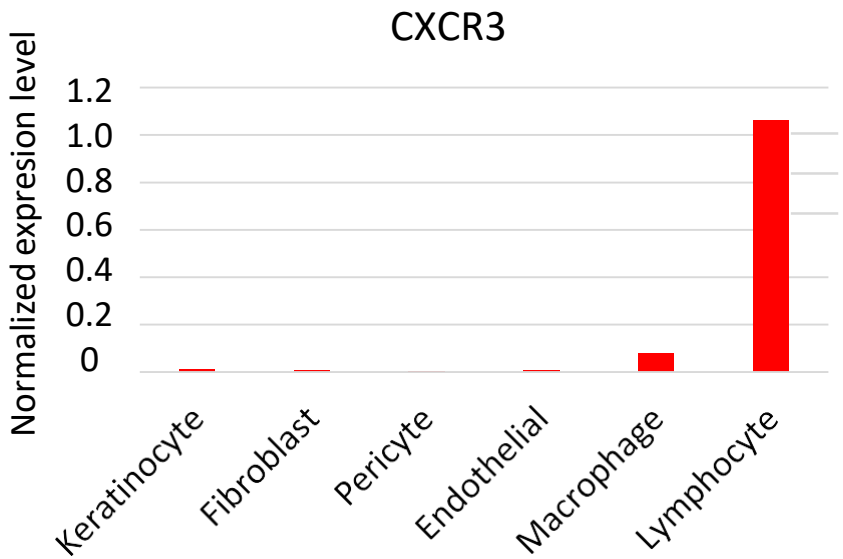


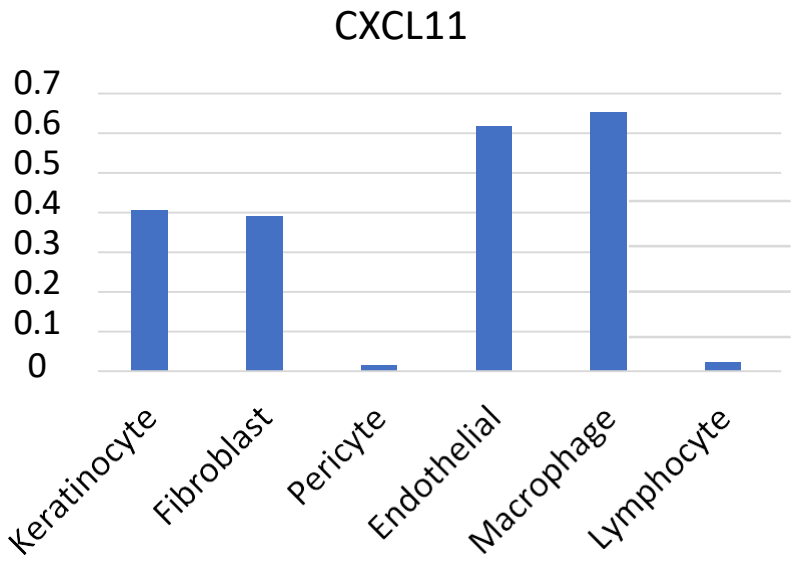
CXCL9 and 11 are produced by macrophages in CTCL skin

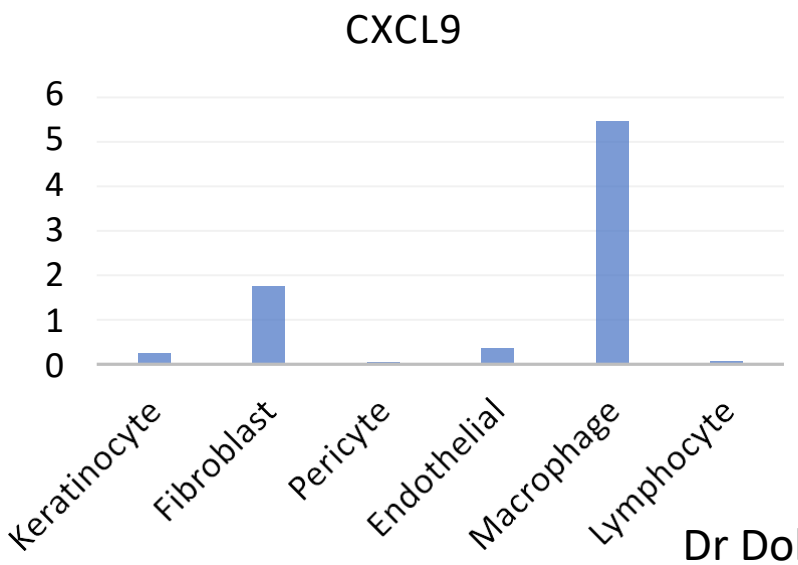






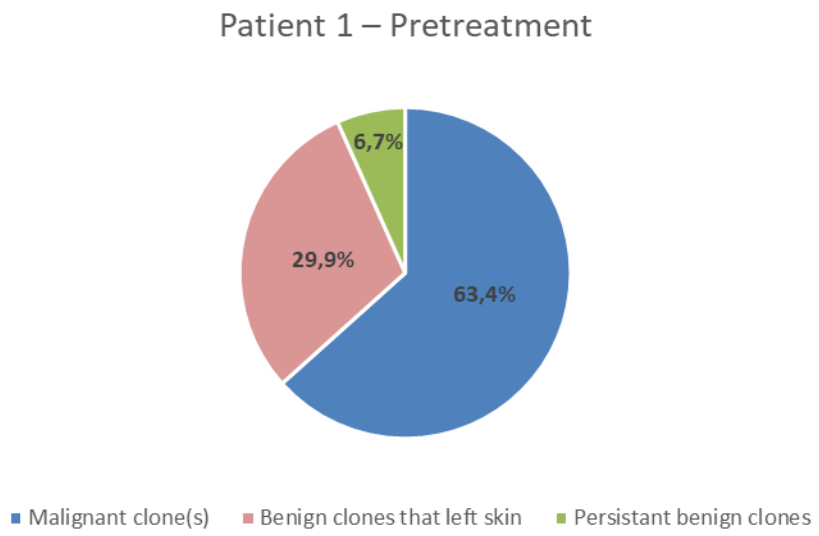


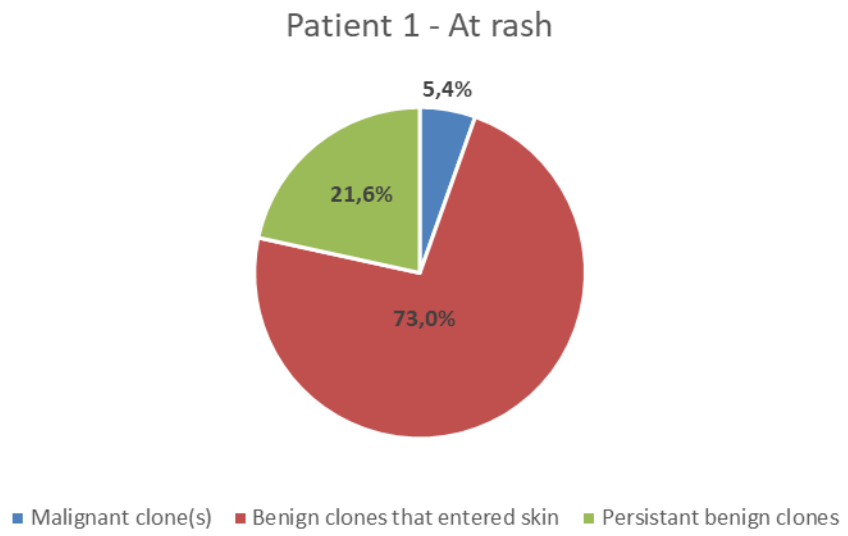


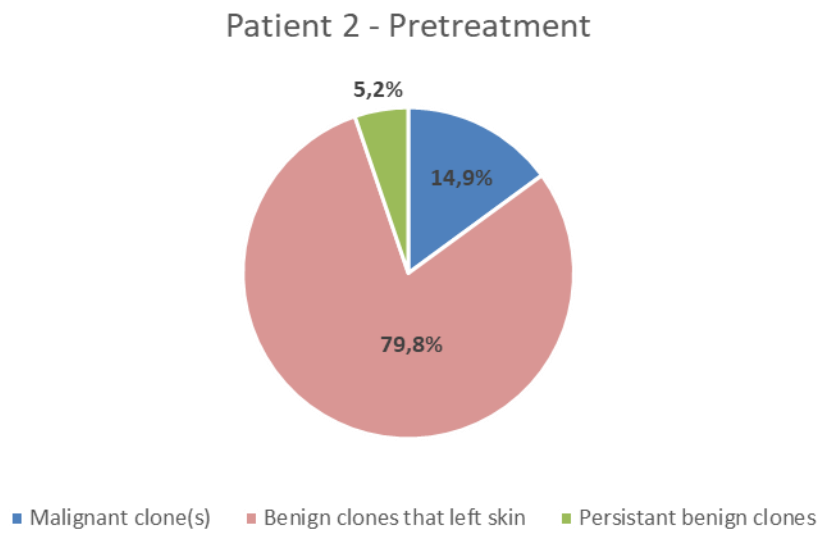


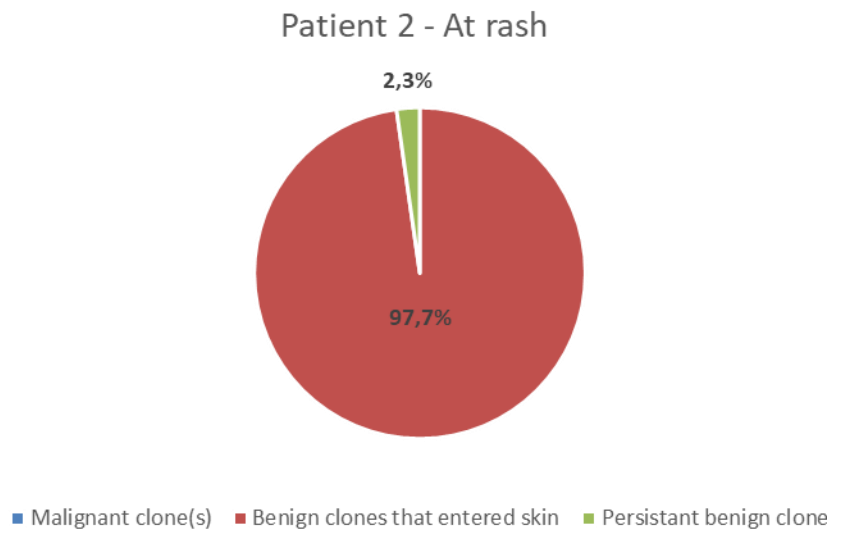
Dr Dobos

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

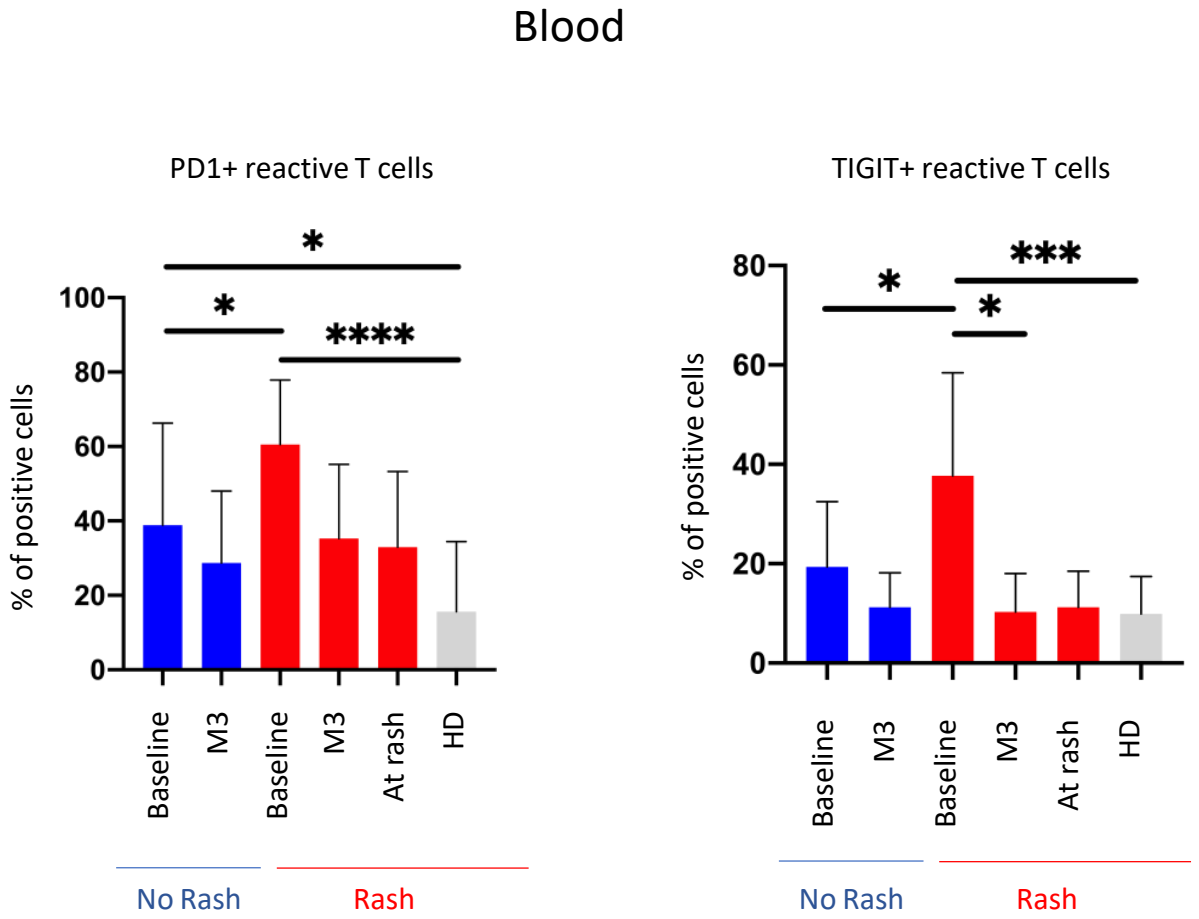








Increased number of exhausted PD1+ and TIGIT+ reactive T cells in blood at baseline in patients with rash



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	4 (22%)
2	11 (61%)
3	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%)
Erythroderma	2 (11%)
Scaling of the scalp	2 (11%)
Pustules	1 (6%)
Histopathological patterns (n=18 rashes)	
Granulomatous	10 (56%)
Lichenoid	9 (50%)
Psoriasiform/spongiotic	13 (72%)
Immunohistochemical analysis (n=18 rashes)	
Intraepidermic CD8+ T-cells	13 (72%)
CD4+/CD8+ T-cell ratio	3.5 [0.25-10]
PD1+ cells (% lymphoid cells)	28.9 [0-80]
Associated findings (n=14 patients)	
Pruritus	6 (43%)
Fever	2 (14%)
Elevated serum creatinin	1 (7%)
Auto-immune disease (vitiligo, alopecia areata, auto-immune hepatitis, auto-immune thyroiditis)	5 (36%)
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)	
No	8 (44%)
Yes, temporarily	6 (33%)
Yes, permanently	4 (22%)
Recurrence after rechallenge (n=6 rechallenges)	4 (66%)