Webinars

Cutaneous Lymphoma

EuroBloodNet Topic on Focus

Title Sézary Syndrome

Speaker: M Bagot
Role: Head of Dermatology Department
Institution: Hopital Saint Louis
ERN-EuroBloodNet subnetwork: Cutaneous Lymphoma
City Paris – Country France
6 July 2020

European Reference Network

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the Health Programme
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Conflicts of interest

Clinical Trials and Scientific Boards:
Innate Pharma, Kyowa Kirin, Takeda, Helsinn/Recordati, Galderma

Biological criteria for the diagnosis of Sézary Syndrome

Sézary cells ≥ 1000 μL^{-1} (cytomorphology)

and

Identical T cell clone in blood and skin

CD4/CD8 ratio ≥ 10

or

CD4+CD7- ≥ 40 %

or

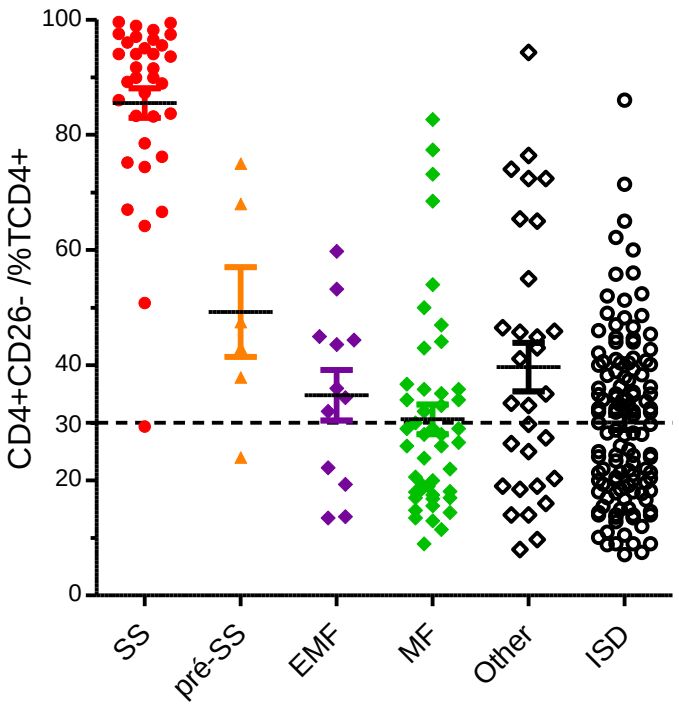
CD4+CD26- ≥ 30 %

and

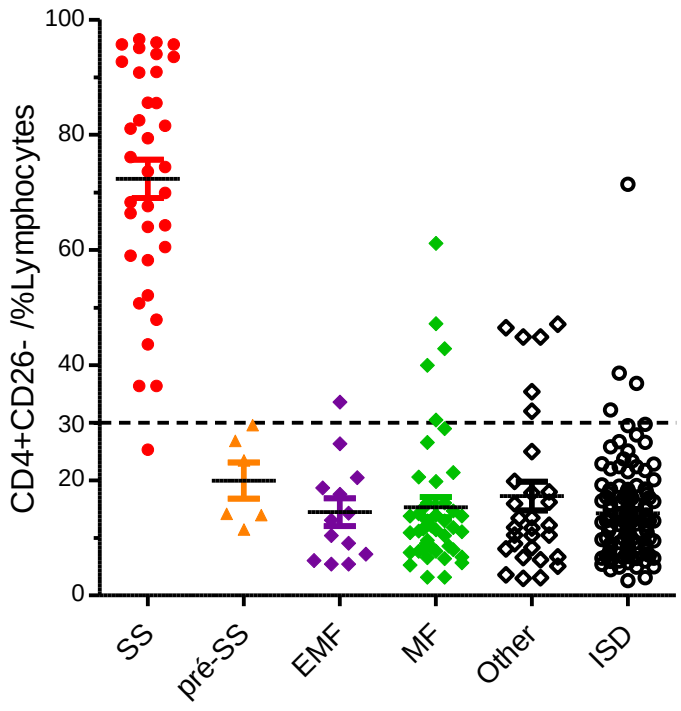
Identical T cell clone in blood and skin

Flow Cytometry

% CD4+ lymphocytes

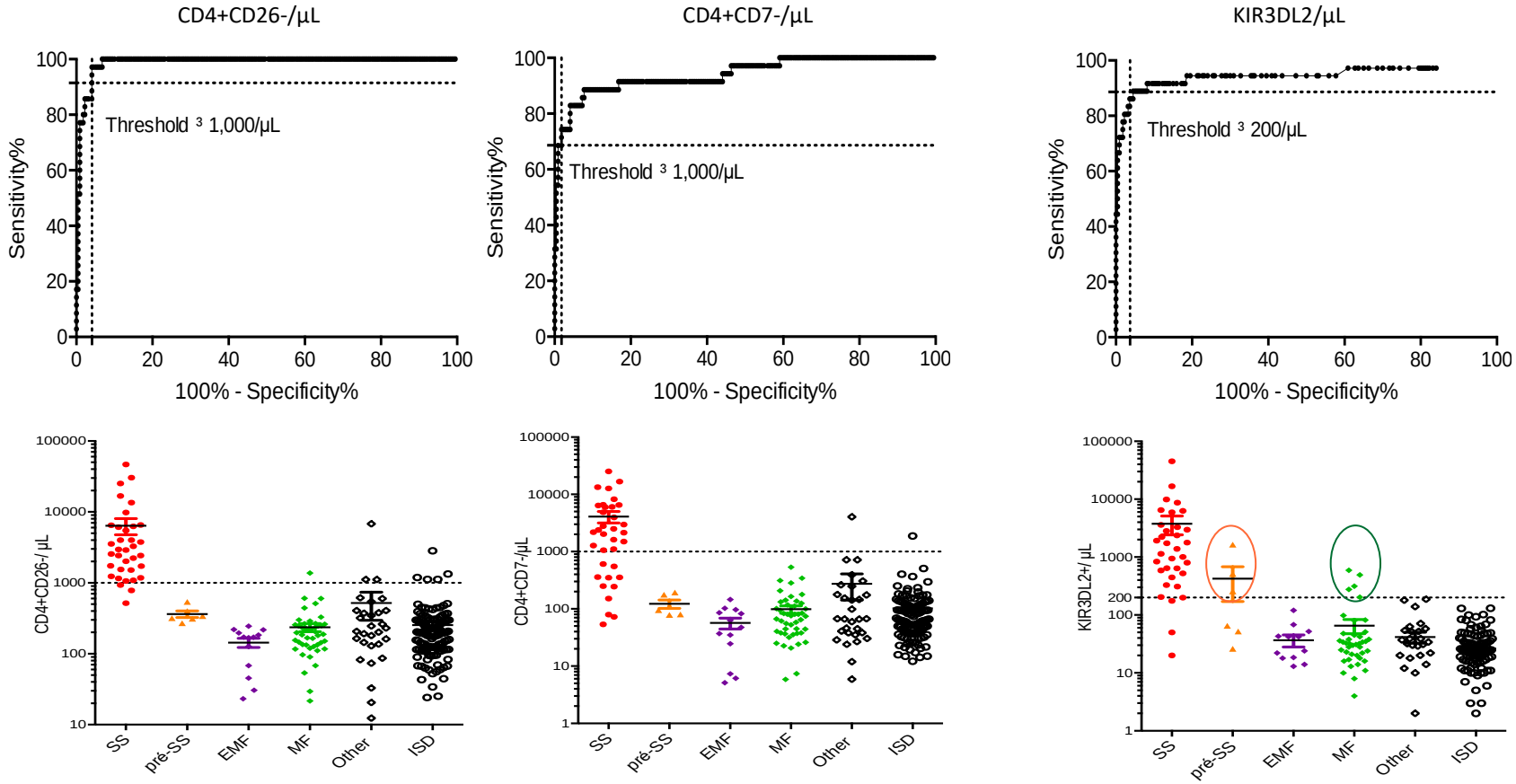


% Total lymphocytes



Flow Cytometry

254 patients at initial diagnosis



Roelens M. et al BJD 2019

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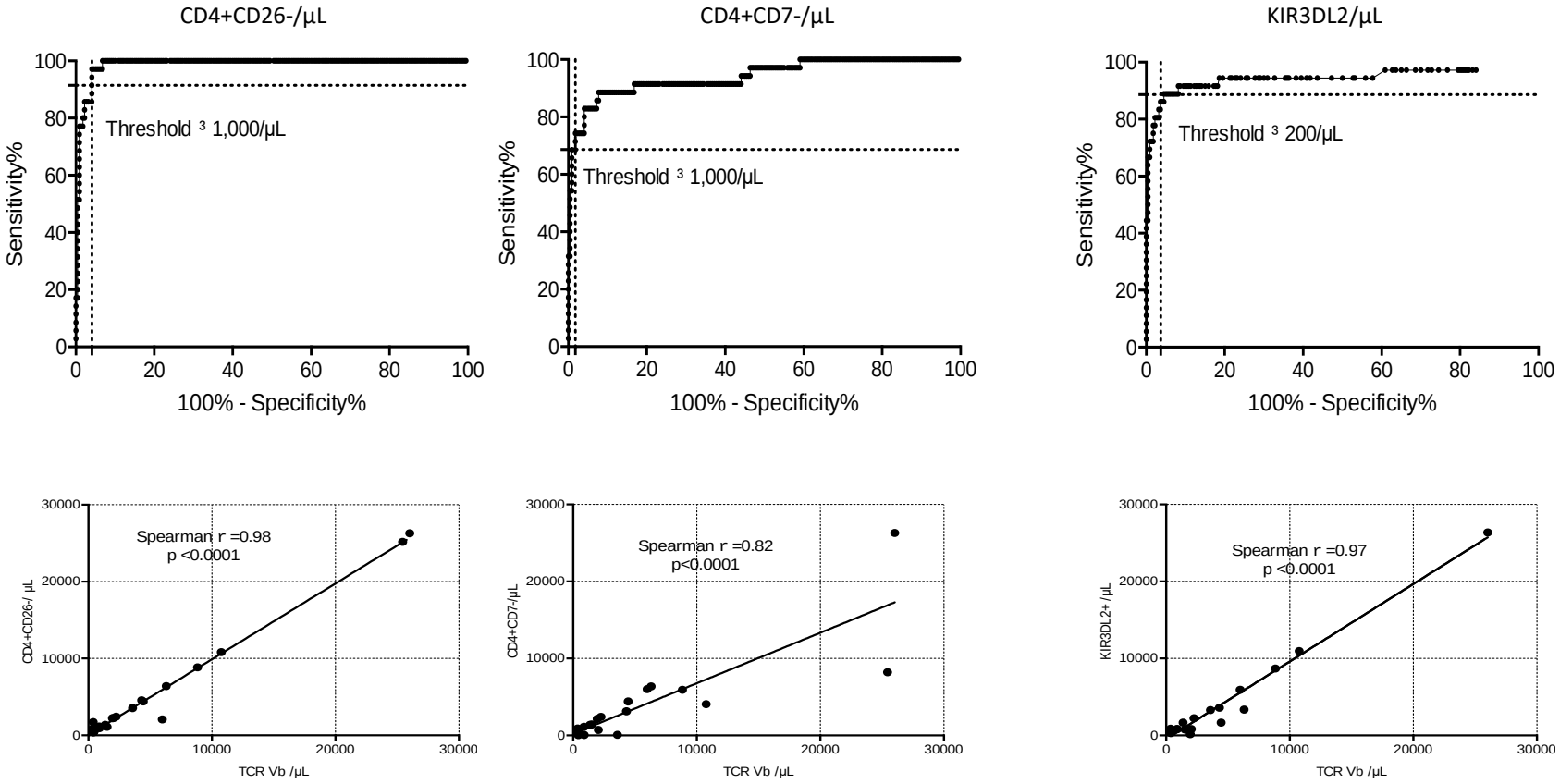
Flow Cytometry

254 patients at initial diagnosis



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New Biological criteria for the diagnosis of Sézary Syndrome

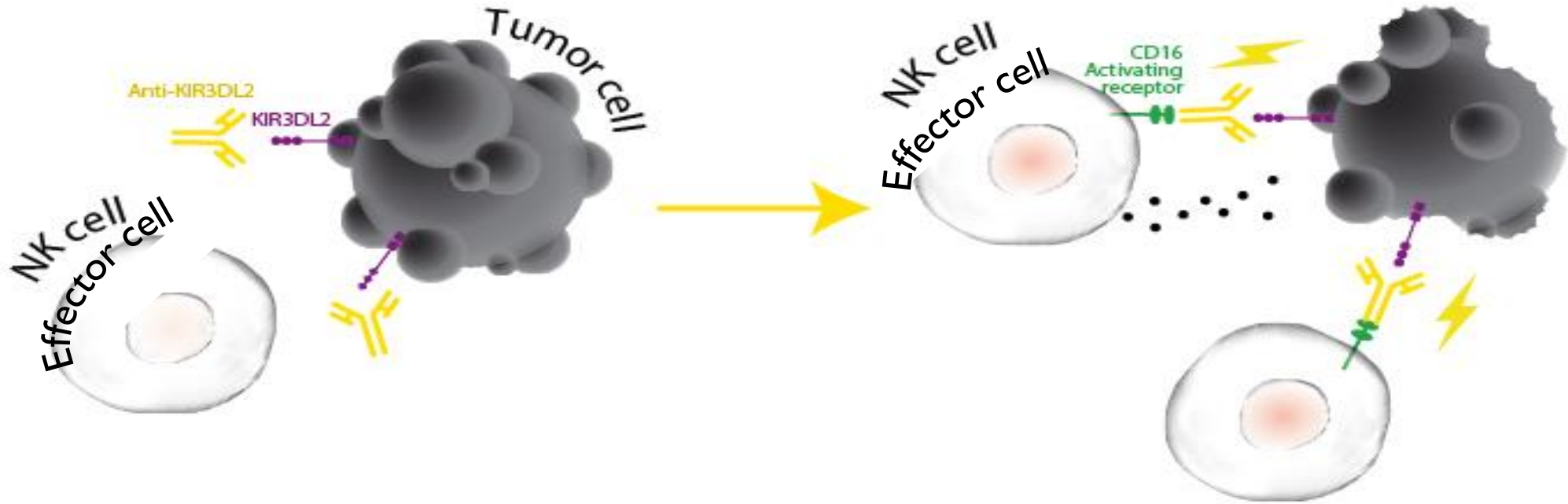
- **B0: Erythrodermic MF. Stage IIIA**
  - Sézary cells ≤ 5%
  - CD4+CD7- and CD4+CD26- < 250 μL^{-1}
- **B1: Pre-Sezary. Stage IIIB**
  - Sézary cells > 5% and < 1000 μL^{-1}
  - CD4+CD7- or CD4+CD26- ≥ 250 μL^{-1} and < 1000 μL^{-1}
- **B2: Sézary Syndrome. Stage IV**
  - Sézary cells ≥ 1000 μL^{-1}
  - Increased CD4 population with a ratio T CD4/CD8 ≥10
  - Increased TCD4 with an abnormal phenotype
    - CD4+CD7- ≥ 40 %
    - CD4+CD7- ≥ 1000 μL^{-1}
    - CD4+CD26- ≥ 30 %
    - CD4+CD26- ≥ 1000 μL^{-1}

Table 7. ISCL/EORTC revision to the staging of mycosis fungoides and Sézary syndrome

	T	N	M	B
IA	1	0	0	0,1
IB	2	0	0	0,1
II	1,2	1,2	0	0,1
IIB	3	0-2	0	0,1
III	4	0-2	0	0,1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA_1	1-4	0-2	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

Scarisbrick, EJC 2018

Targeted mAbs: a new hope for Sézary treatment



mAb binds to target on tumor cells

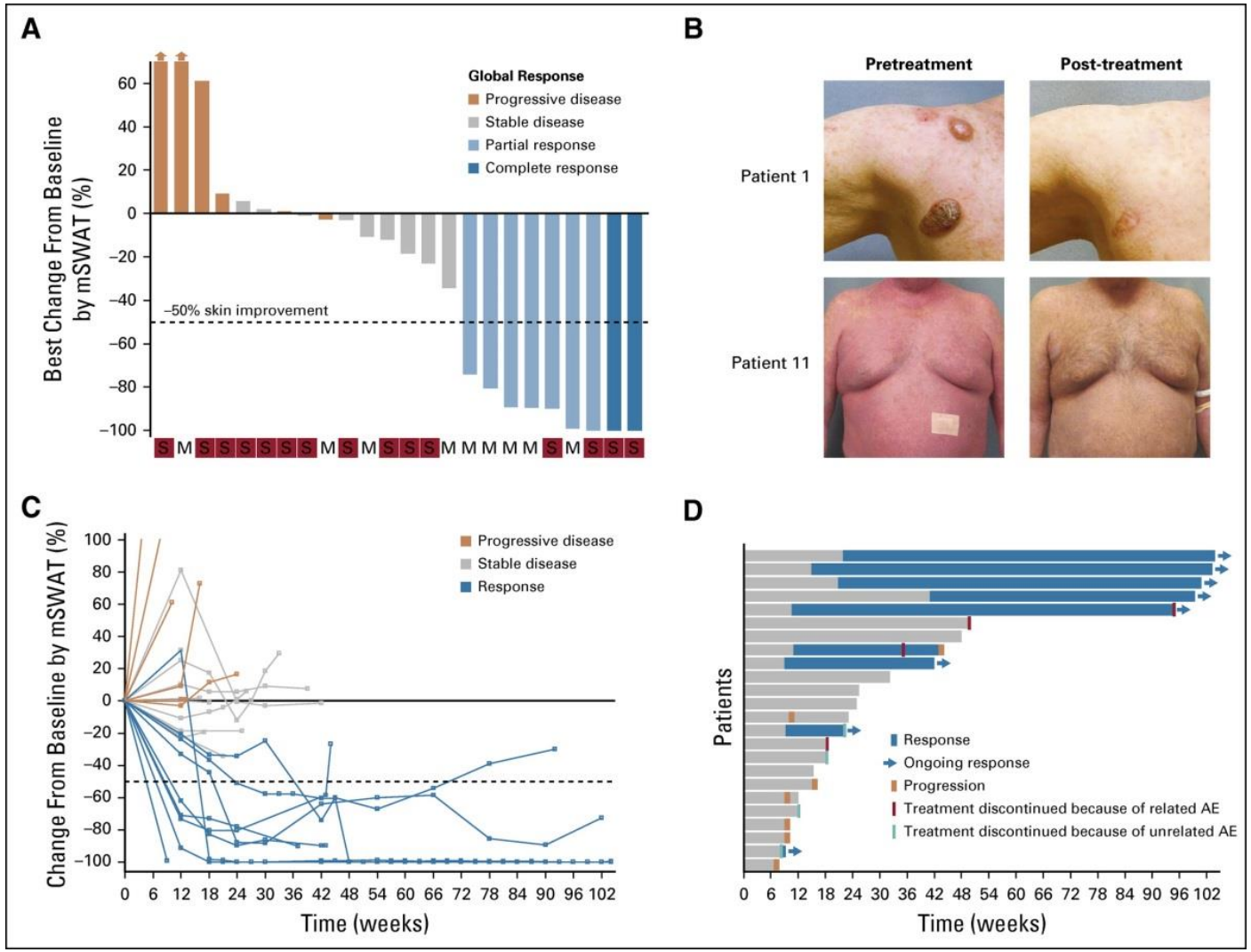
Recruitment of effector cells and depletion of tumor cells

original reports

Pembrolizumab in Relapsed and Refractory Mycosis Fungoides and Sézary Syndrome: A Multicenter Phase II Study

Michael S. Khodadoust, MD, PhD[1]; Alain H. Rook, MD[2]; Pierluigi Porcu, MD[3]; Francine Foss, MD[4]; Alison J. Moskowitz, MD[5]; Andrei Shustov, MD[6]; Satish Shanbhag, MBBS, MPH[7]; Lubomir Sokol, MD, PhD[8]; Steven P. Fling, PhD[9]; Nirasha Ramchurren, PhD[9]; Robert Pierce, MD[9]; Asa Davis, PhD[9]; Richard Shine, PharmD, BCPS[9]; Shufeng Li, MS[1]; Sophia Fong[1]; Jinah Kim, MD, PhD[1]; Yi Yang, MS[9]; Wendy M. Blumenschein[10]; Jennifer H. Yearley, DVM, PhD, DACVP[10]; Biswajit Das, PhD[11]; Rajesh Patidar, MS[11]; Vivekananda Datta, MD, PhD[11]; Erin Cantu[11]; Justine N. McCutcheon[11]; Chris Karlovich, PhD[11]; P. Mickey Williams, PhD[11]; Priyanka B. Subrahmanyam, PhD[1]; Holden T. Maecker, PhD[1]; Steven M. Horwitz, MD[5]; Elad Sharon, MD, MPH[12]; Holbrook E. Kohrt, MD, PhD[1]†; Martin A. Cheever, MD[9]; and Youn H. Kim, MD[1]

- 24 advanced MF or SS
- Previous treatments: median 4
- Pembrolizumab 2mg/kg every 3 weeks
- ORR: 38% (2 CR, 7 PR)
- Median response follow-up time: 58 weeks



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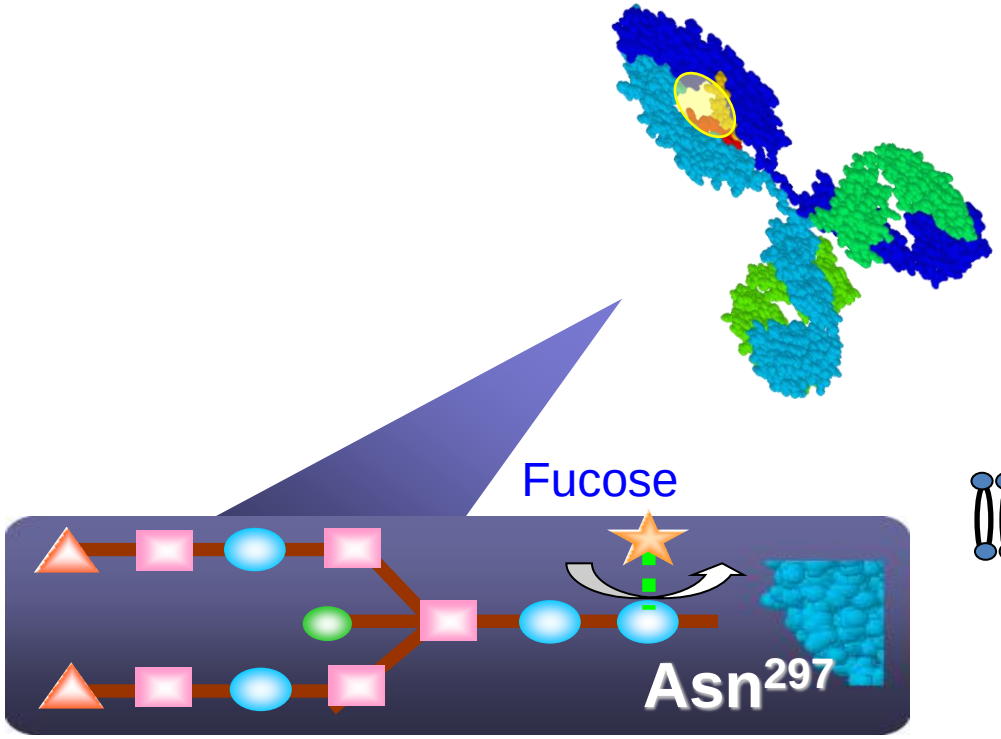
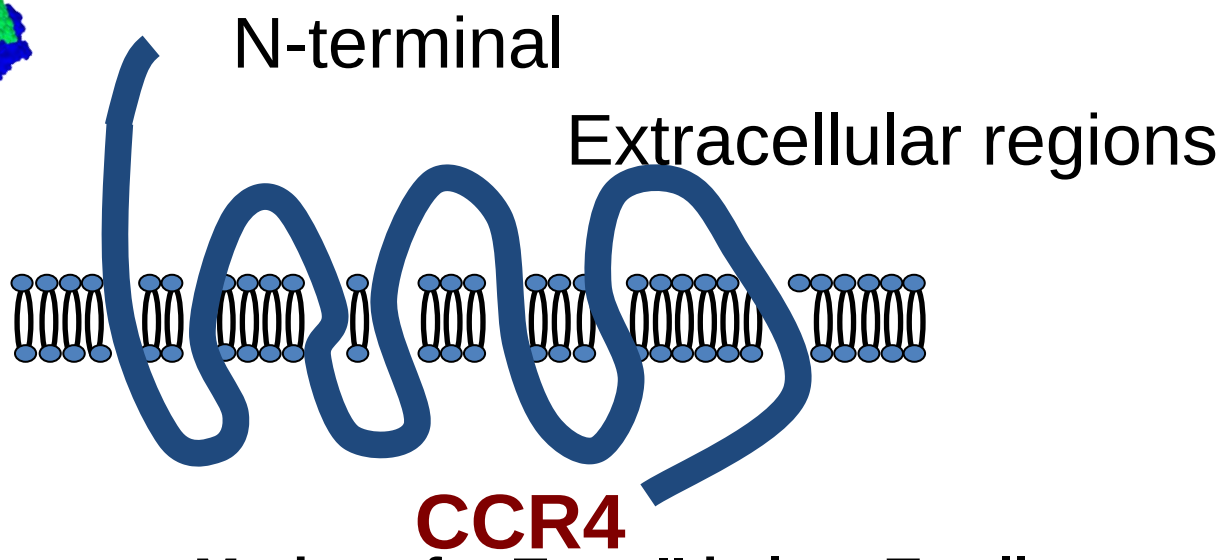
Mogamulizumab: a humanized anti-CCR4 antibody with a defucosylated Fc region



Higher ADCC due to a defucosylated Fc region by POTELLIGENT®[1-3]



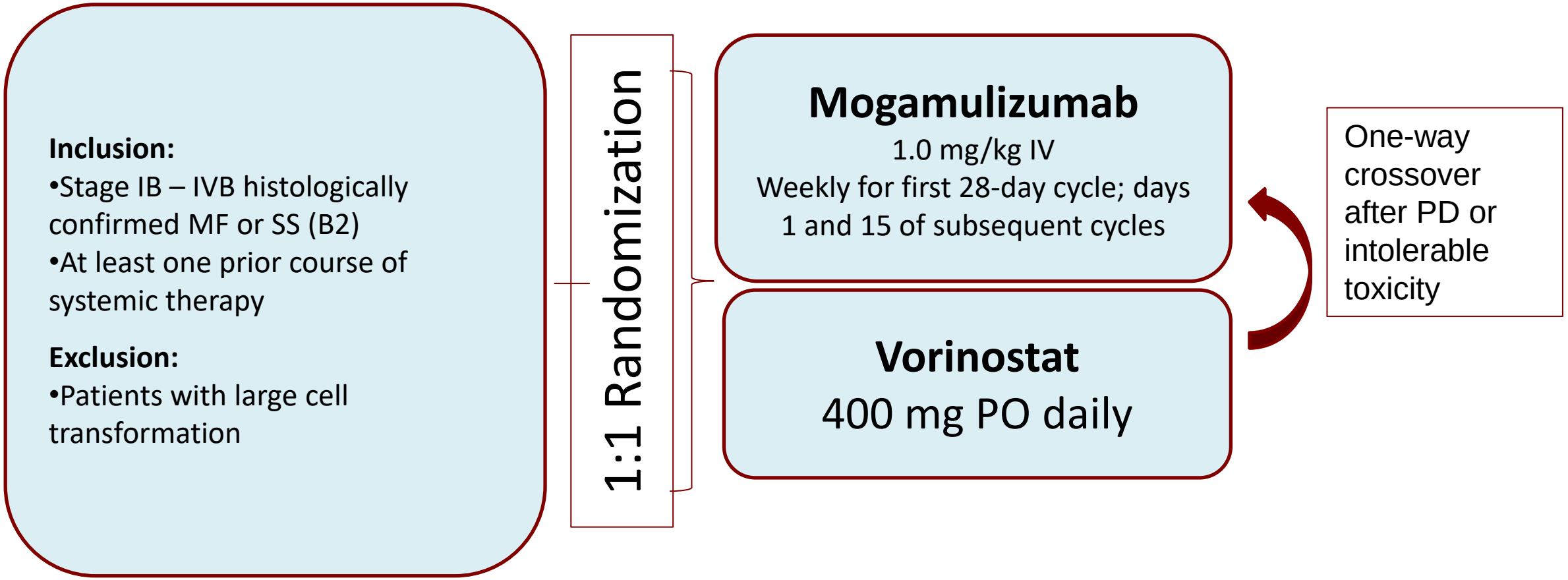
Markers for Type II helper T cells and regulatory T cells (FoxP3+)
Involved in lymphocyte trafficking to skin
Over-expressed in ATL, PTCL, and CTCL

Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial

*Youn H Kim, Martine Bagot, Lauren Pinter-Brown, Alain H Rook, Pierluigi Porcu, Steven M Horwitz, Sean Whittaker, Yoshiki Tokura, Maarten Vermeer, Pier Luigi Zinzani, Lubomir Sokol, Stephen Morris, Ellen J Kim, Pablo L Ortiz-Romero, Herbert Eradat, Julia Scarisbrick, Athanasios Tsianakas, Craig Elmets, Stephane Dalle, David C Fisher, Ahmad Halwani, Brian Poligone, John Greer, Maria Teresa Fierro, Amit Khot, Alison J Moskowitz, Amy Musiek, Andrei Shustov, Barbara Pro, Larisa J Geskin, Karen Dwyer, Junji Moriya, Mollie Leoni, Jeffrey S Humphrey, Stacie Hudgens, Dmitri O Grebennik, Kensei Tobinai, Madeleine Duvic, for the MAVORIC Investigators**

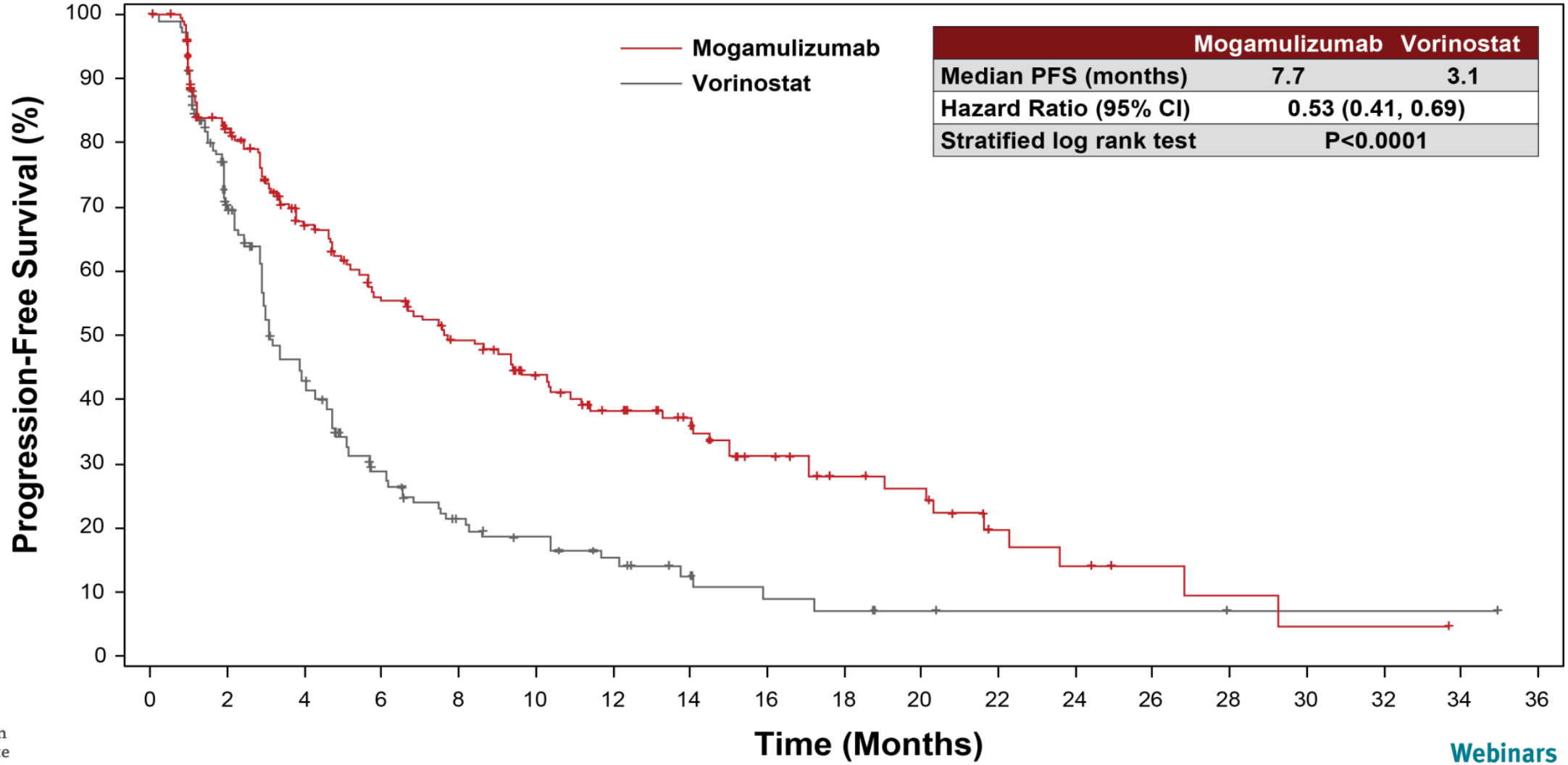
Lancet Oncology, 2018;19:1192-1204

MAVORIC Study Design



- 372 patients were randomized at 59 centers across 11 countries
- Treatment was administered on an outpatient basis
- Vorinostat was administered in accordance with US prescribing information
- Patients could remain in the treatment phase up until progression or intolerable toxicity
- CCR4 expression level was not an eligibility criterion

Primary Endpoint: Progression-Free Survival



	Mogamulizumab	Vorinostat
Median PFS (months)	7.7	3.1
Hazard Ratio (95% CI)	0.53 (0.41, 0.69)	
Stratified log rank test	P<0.0001	

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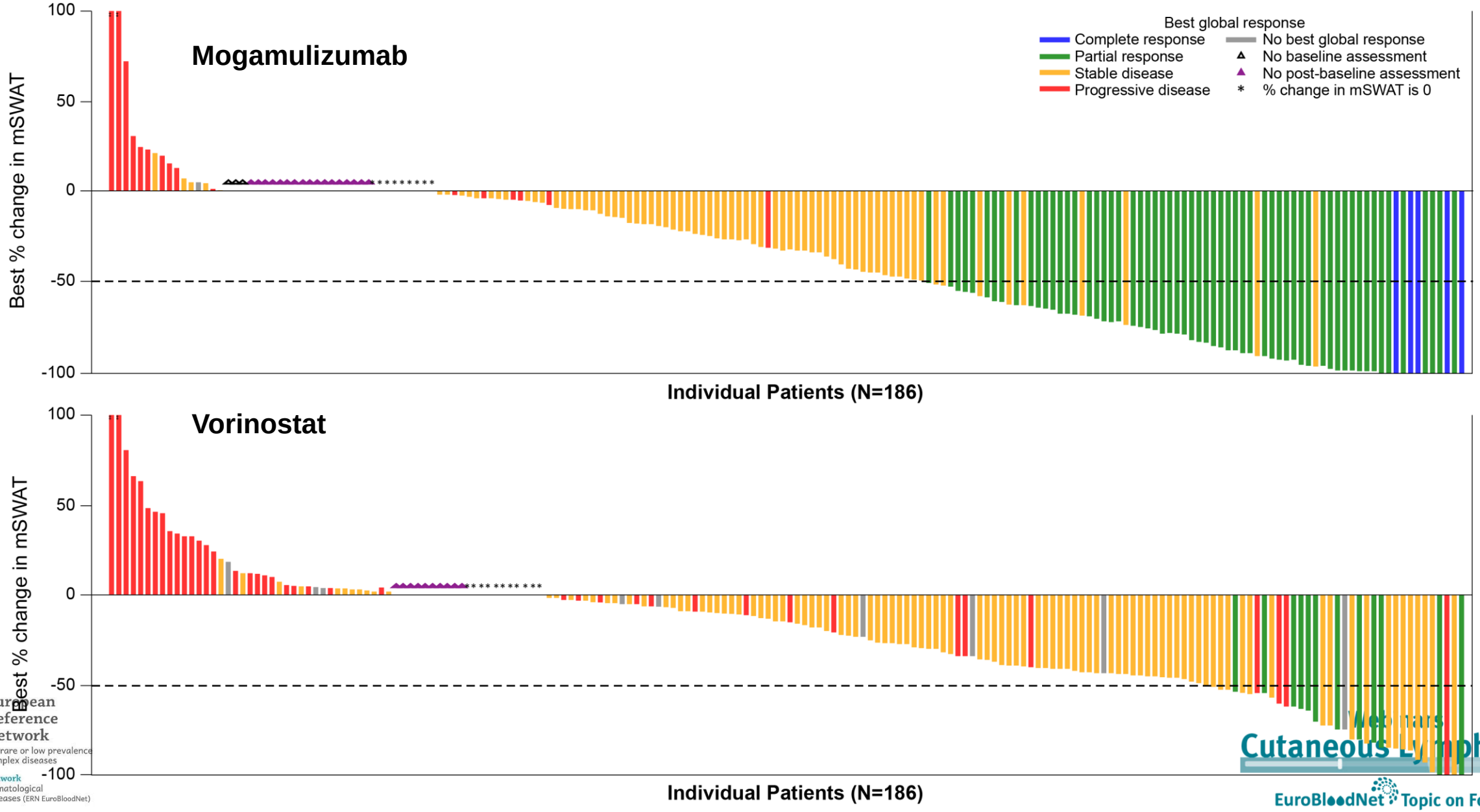
Mogamulizumab induced Greater Reduction in mSWAT Score and Superior Best Global Response



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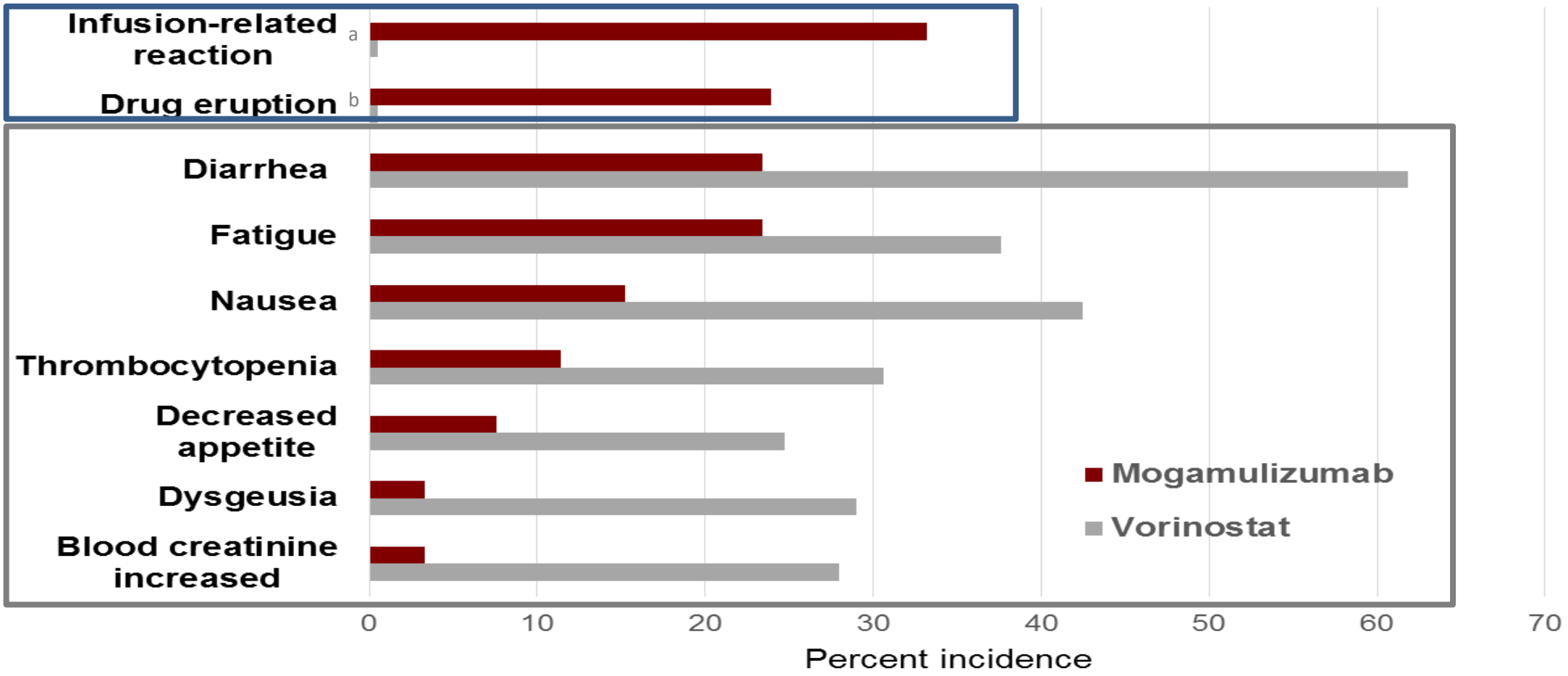
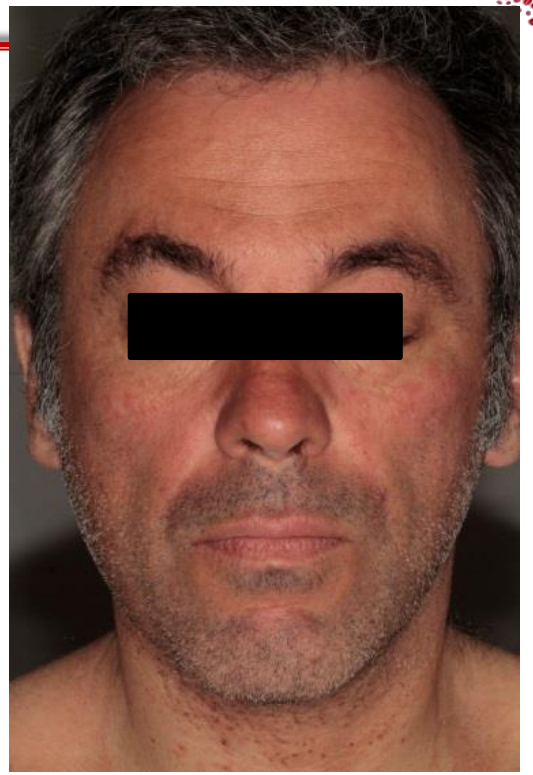
Mogamulizumab was approved in the USA and Europe in 2018 for relapsed or refractory Mycosis Fungoides or Sezary Syndrome after ≥1 prior systemic therapy based on the MAVORIC trial

Commonly Reported Treatment-Emergent Adverse Events (≥ 20% of patients)



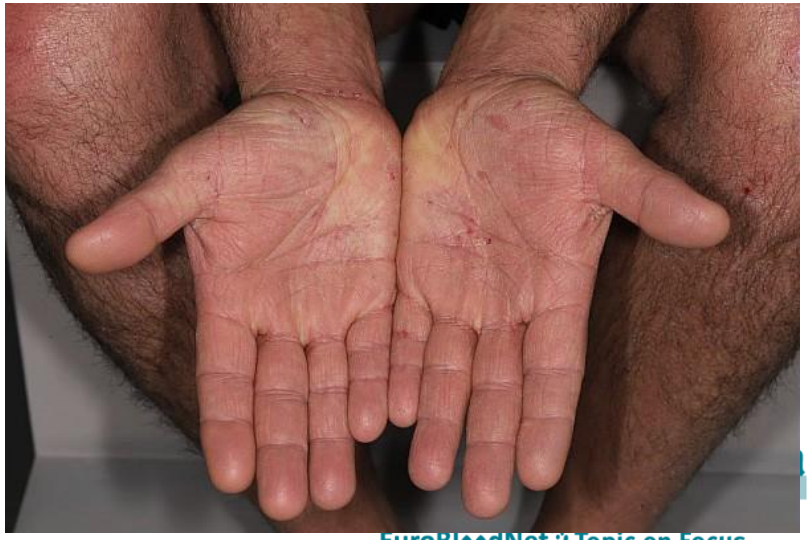
- Mogamulizumab group: ≥ 3 Grade AEs ranged from 0%-4.3% of patients
- Vorinostat group: ≥ 3 Grade AEs ranged from 0%-5.9% of patients

Mr M.B., 53 y

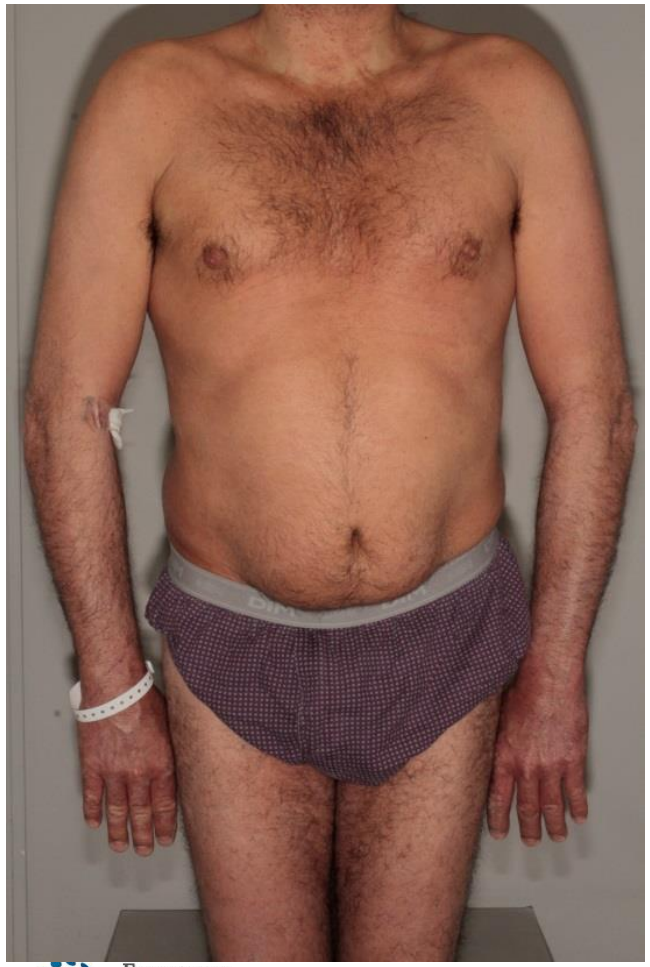


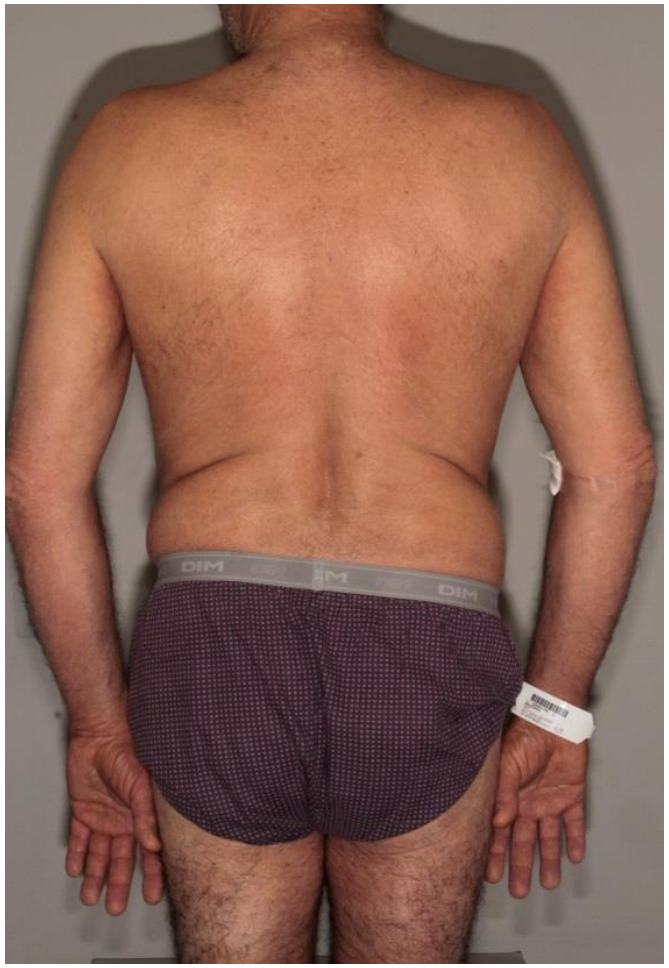
- 2010
  - Pruriginous erythematous lesions
  - Dg: atopic dermatitis
  - Tt: corticosteroids

- June 2017
  - Erythroderma, PPK, asthenia
    - Biopsy: Sézary syndrome
  - Hypereosinophilia: 750/mm3
  - LDH: 1.5 x N
  - Identical T cell clone in skin and blood
  - CT scan: axillar and inguinal adenopathies
  - Nodal biopsy: N3

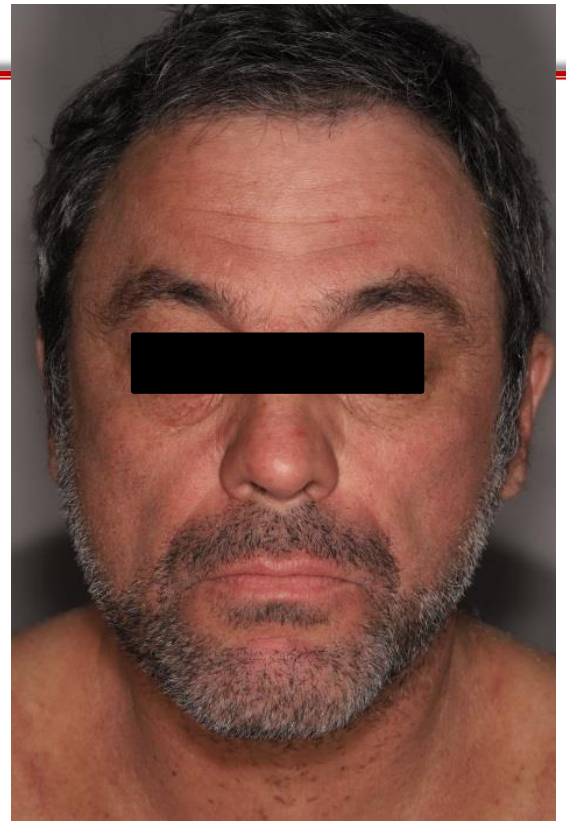


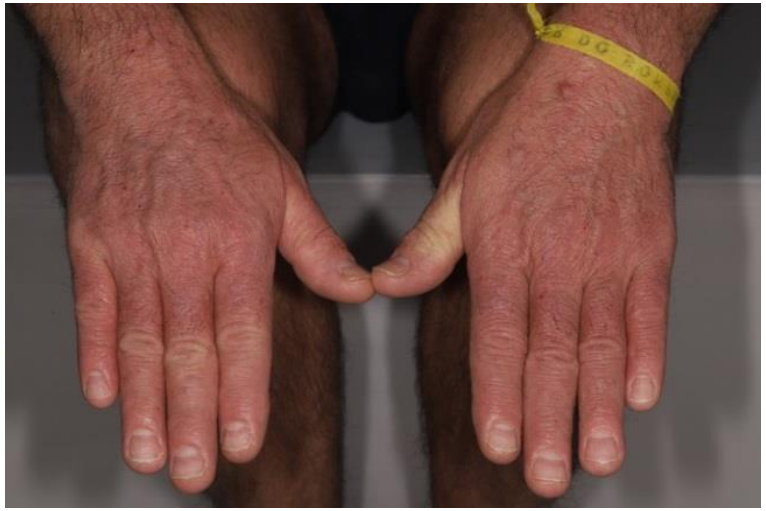
Mr M.B., 53 y



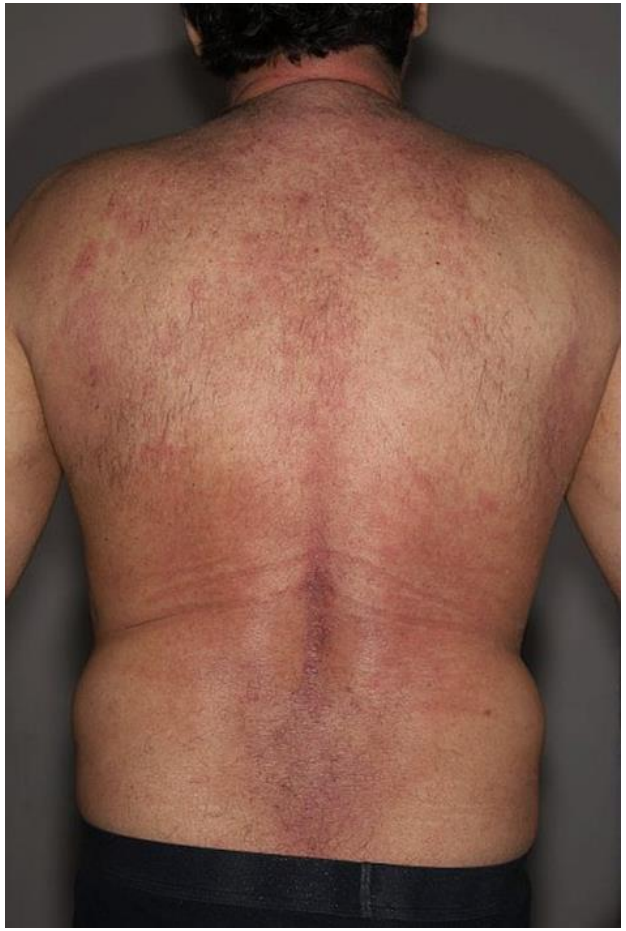


- Flow cytometry
  - CD4+CD26-: 89% (3,591/mm3)
  - CD4+KIR3DL2+: 59% (2,381/mm3)
  - CD4/CD8: 13.5
- Sezary syndrome
  - T4N3M0B2
- Treatments
  - Bexarotene + ECP
  - Interferon + ECP
  - PR





Mr M.B., 53 y

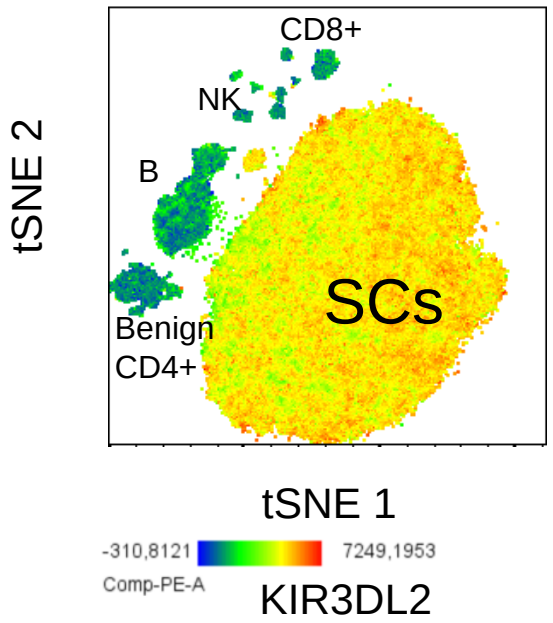


- Oct 2018
  - Progression
  - Erythroderma
  - Polyadenopathies
  - Flow cyometry
    - CD4+CD26- : 97.7% (13,440/mm3)
    - CD4+KIR3DL2+ : 70% (9,699/mm3)
    - CD4/CD8: 18.2
- Tt with Mogamulizumab

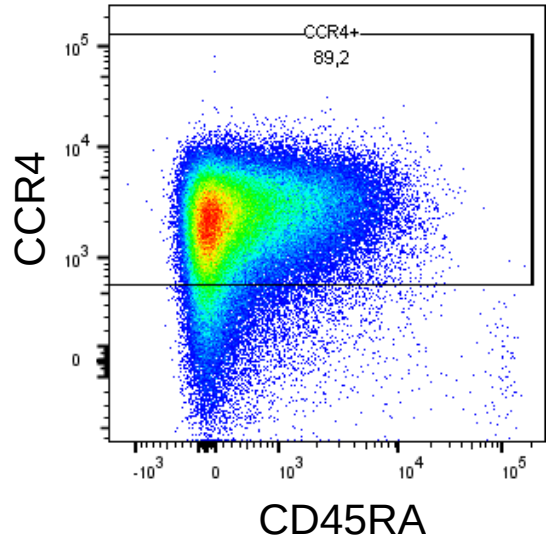
Flow cytometry

M0

Lymphocytes
(6883/µl)

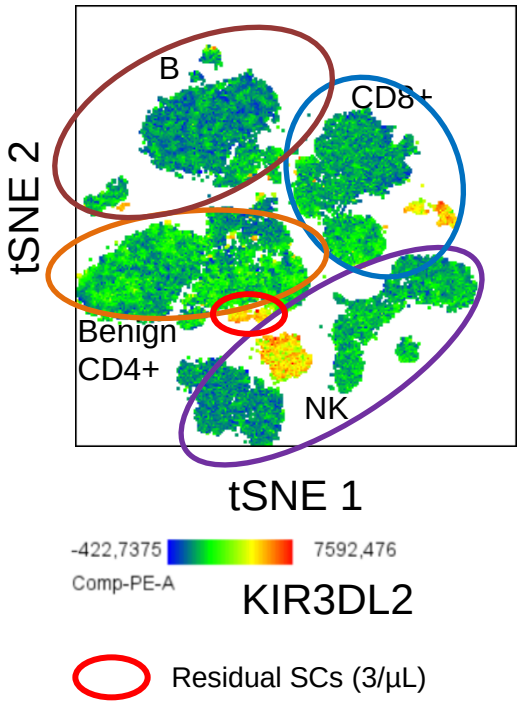


KIR3DL2+ Sézary cells
(5782/µL)

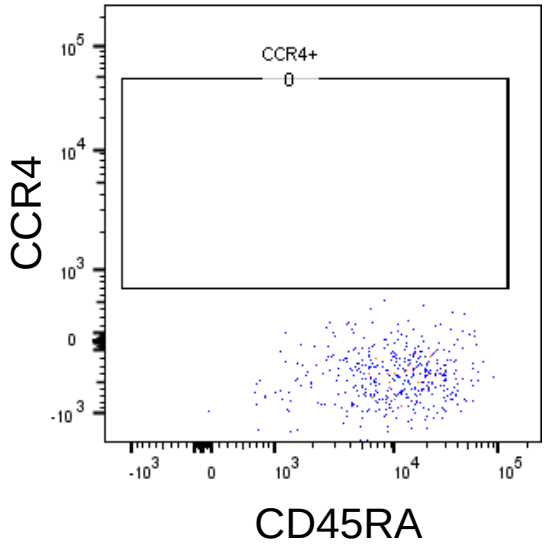


M9

Lymphocytes
(448/µL)



KIR3DL2+ Sézary cells
(3/µL)

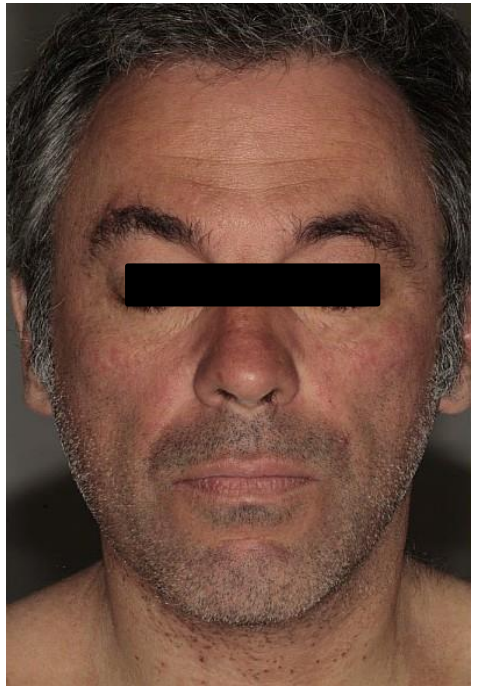


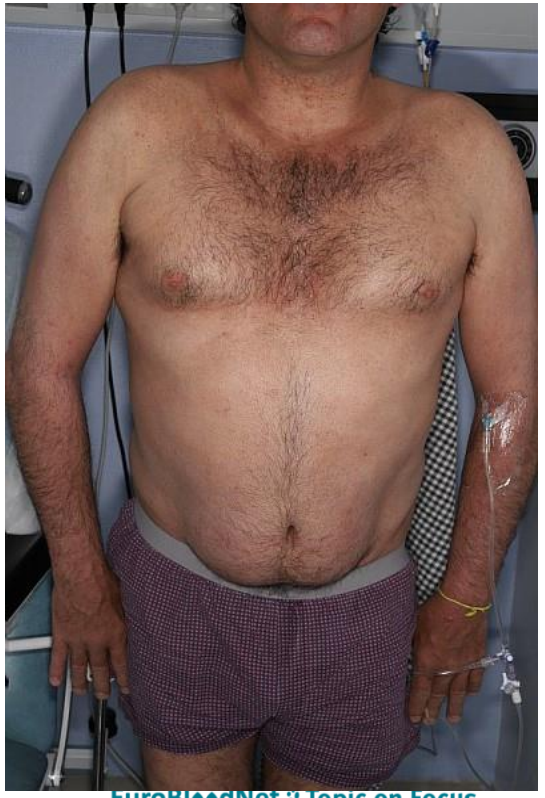
Residual SCs (3/µL)

tSNE algorithm computed from flow cytometry data for: KIR3DL2, CD26, CD4, CD3, CD16/CD56, CD8, CD25, CD127, CCR4, CD45RA, CCR7, CD27, CD95 expressions

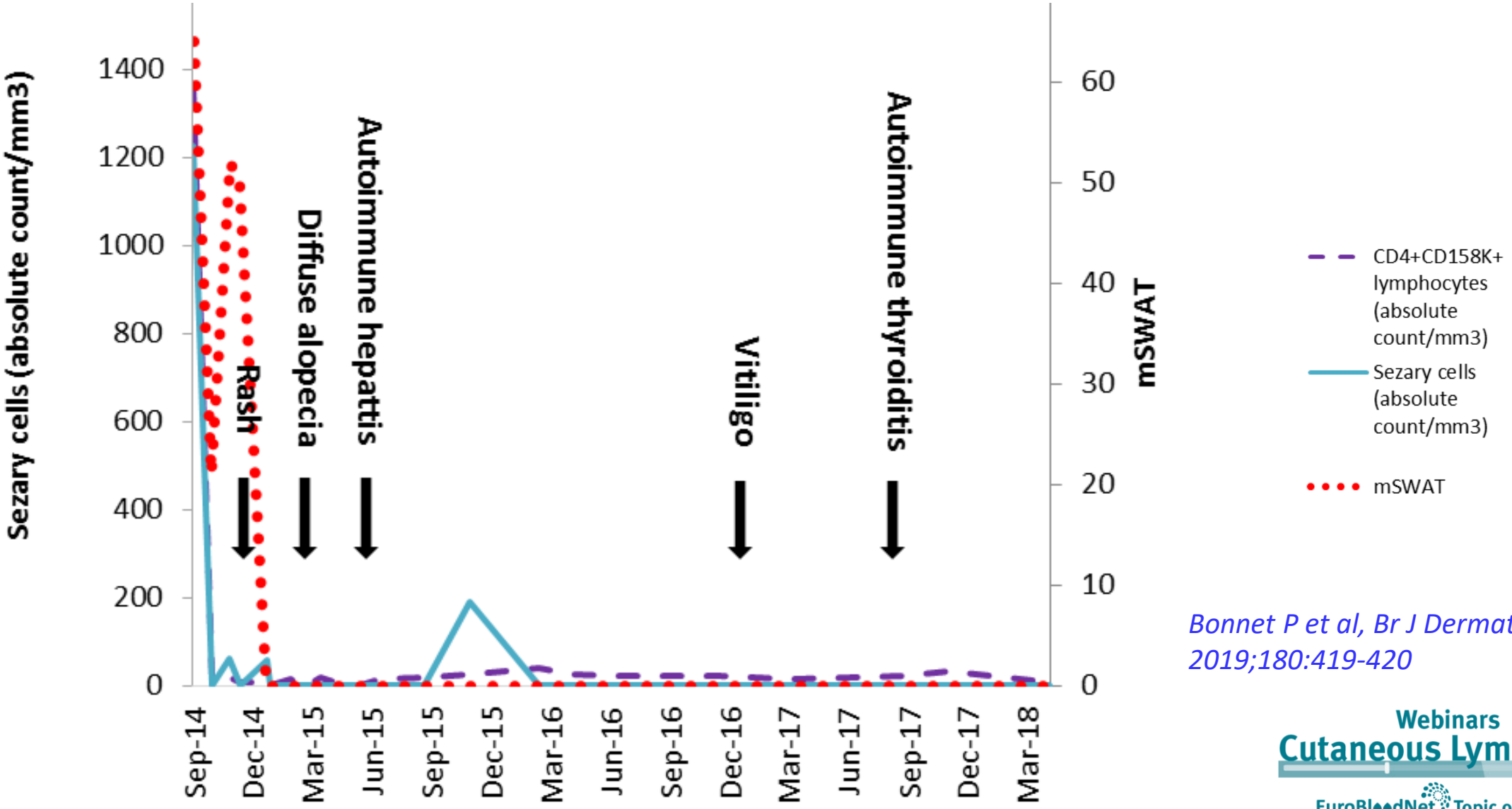
Mr M.B., 53 y

- Jan 2019 (M3)
  - CR in blood
    - Lymphopenia : 471
    - CD4+CD26- : 29.2% (70/mm3)
    - CD4/CD8: 2
- April 2019 (M6)
  - CR in skin
- July 2020 (M21)
  - Persistant CR in skin, blood and nodes





F-61y - Sézary syndrome relapsing after 8 prior lines of treatment including 3 cycles of Alemtuzumab



Bonnet P et al, Br J Dermatol. 2019;180:419-420

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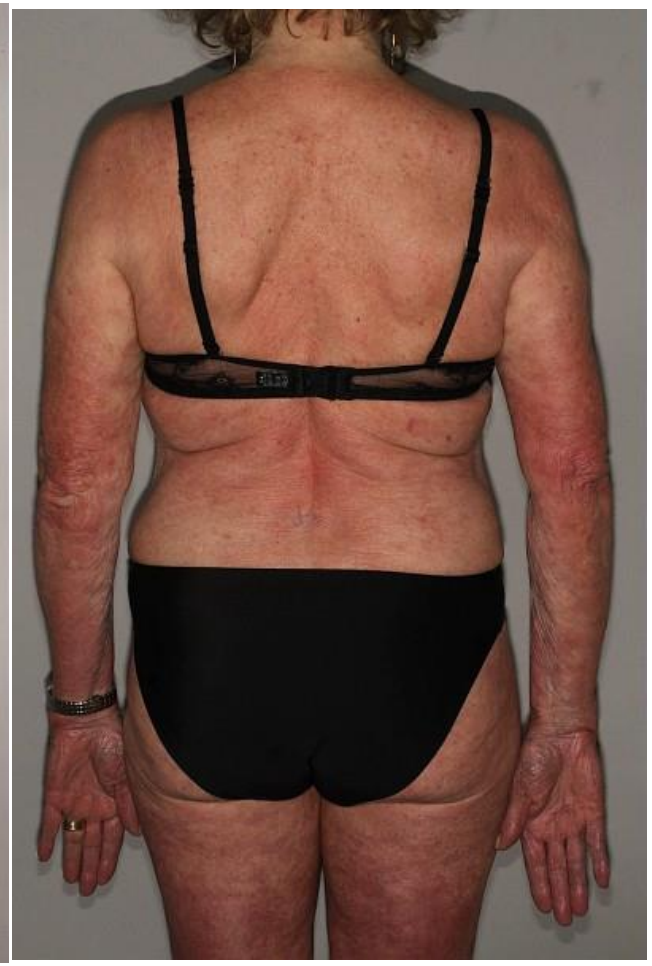

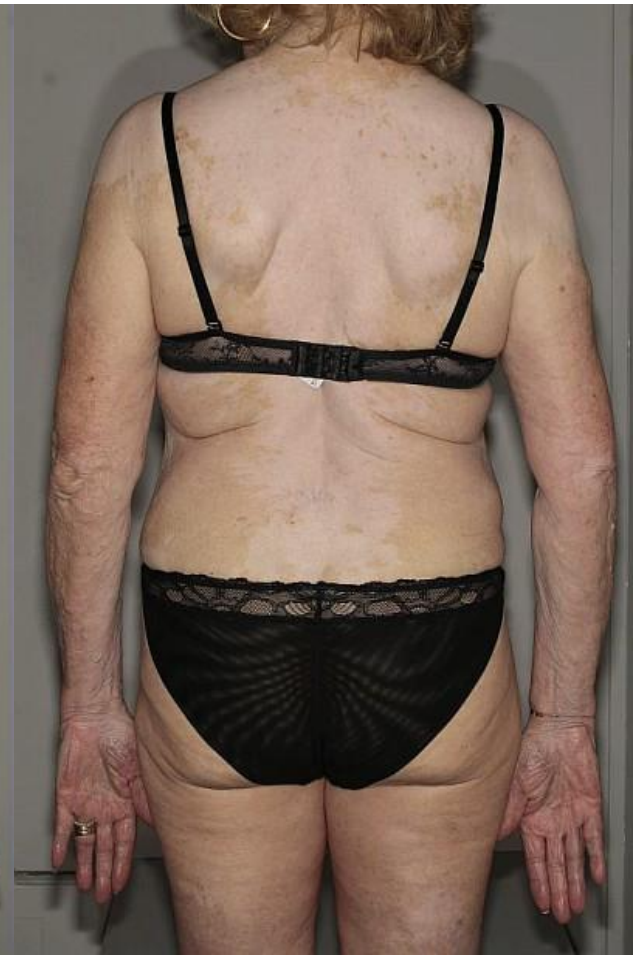

- The patient has been in CR without treatment for more than five years
- A depletion in CCR4-expressing Tregs could activate cytotoxic T lymphocytes and explain durable responses

Bonnet P, Br J Dermatol. 2019;180:419-420

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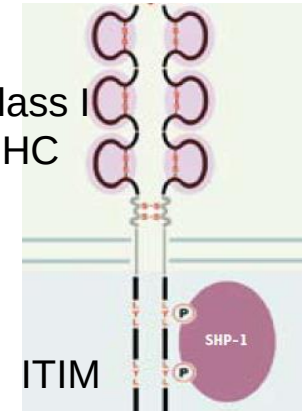
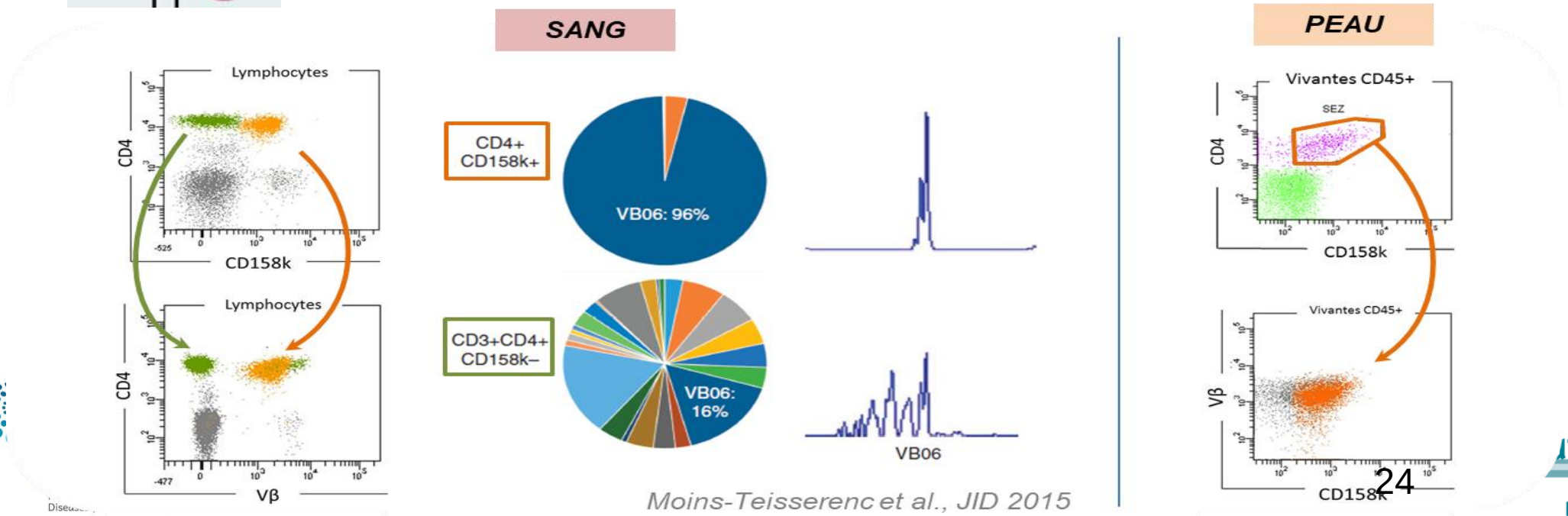
KIR3DL2, a specific marker for Sezary cells

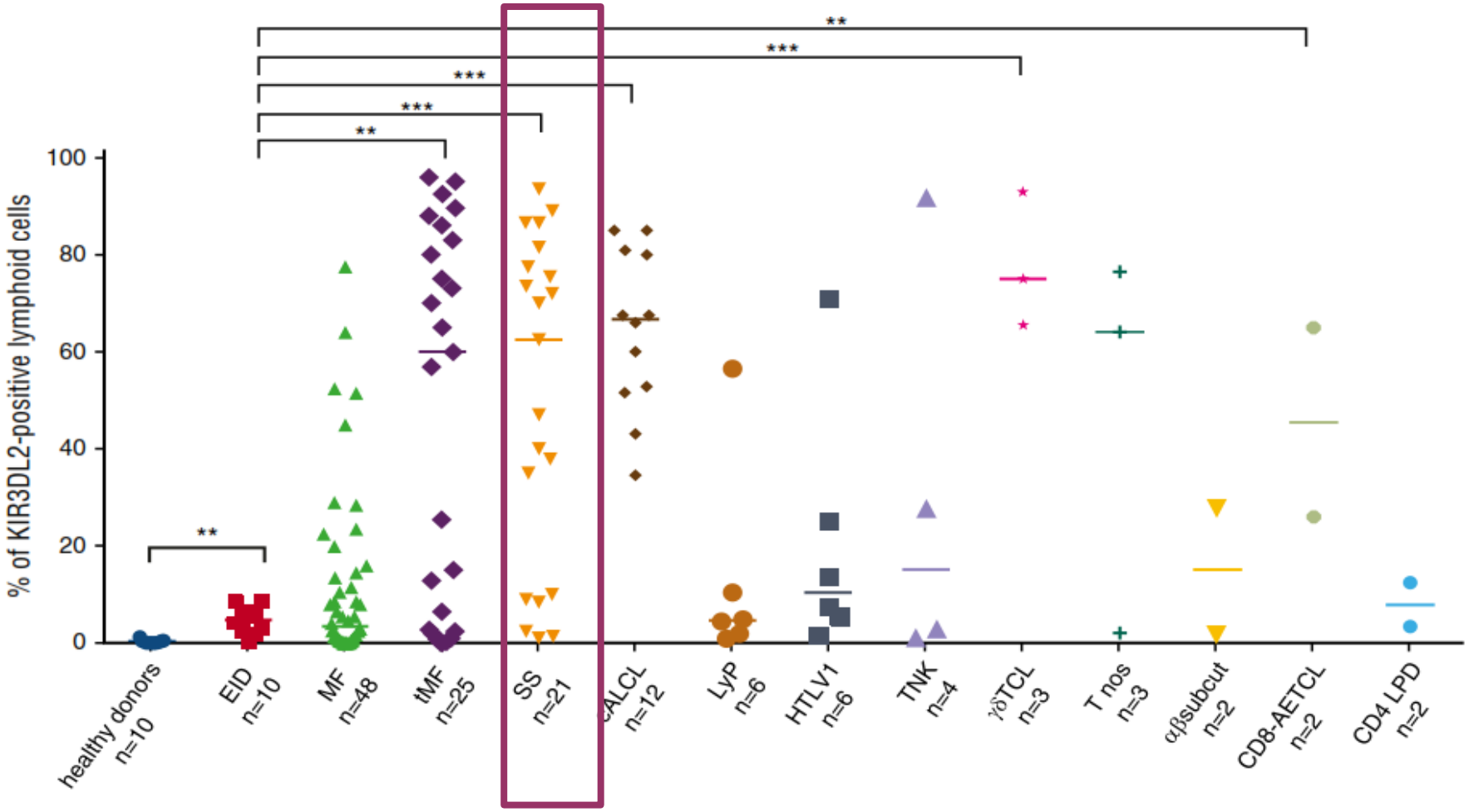
KIR3DL2 (CD158k)



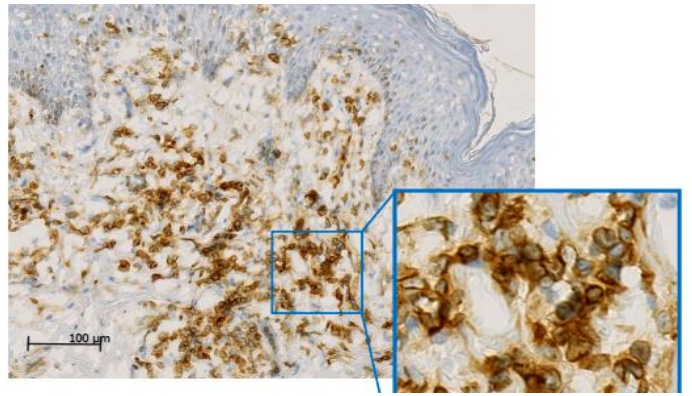
- KIR3DL2 / CD158k is expressed by Sezary cells *(Bagot et al., Blood 2001; Poszepczynska-Guigné et al., JID 2004 ; Ortonne et al., JID 2008)*
- Currently used for diagnostic and follow-up *(Moins-Teisserenc et al., JID 2015)*



KIR3DL2 is expressed by CTCL especially Sézary Syndrome



Expression of KIR3DL2 in a SS patient



Bagot M et al; Blood 2001

Battistella M et al; Blood 2017

EID: erythrodermic inflammatory disease, MF: mycosis fungoides, SS: Sézary syndrome, cALCL: cutaneous anaplastic large cell lymphoma, LyP: lymphoid papylosis, HTLV1 Adult T-cell lymphoma, TNKL nasal-type lymphoma, γ δ T-cell lymphoma, T-nos: T cutaneous peripheral T-cell lymphoma non otherwise specified, αβ T celll lymphoma, CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma, LPD: lymphoproliferative disorder

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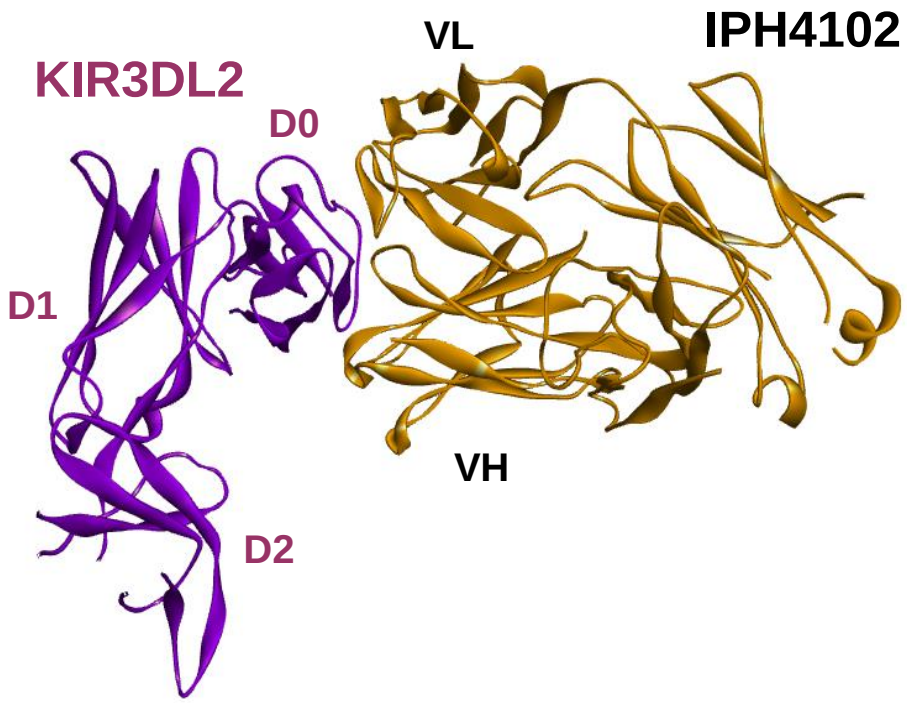
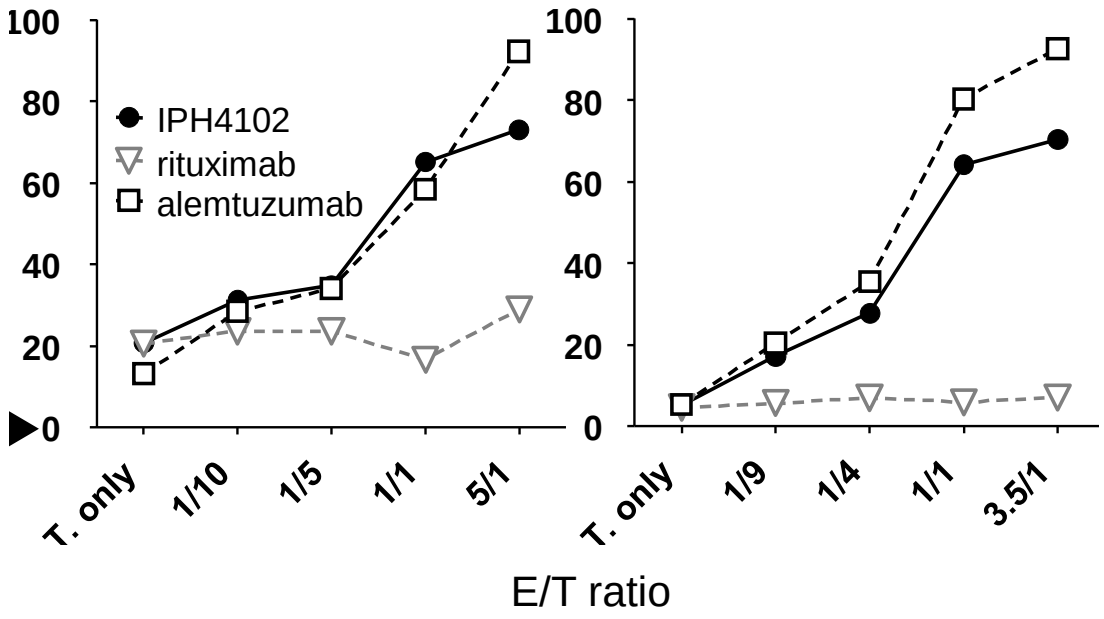
IPH4102 (Lacutamab): a first in class mAb directed against KIR3DL2



NK cells kill Sezary cells in autologous ADCC mediated by IPH4102



Marie-Cardine A et al, Cancer Res 2014

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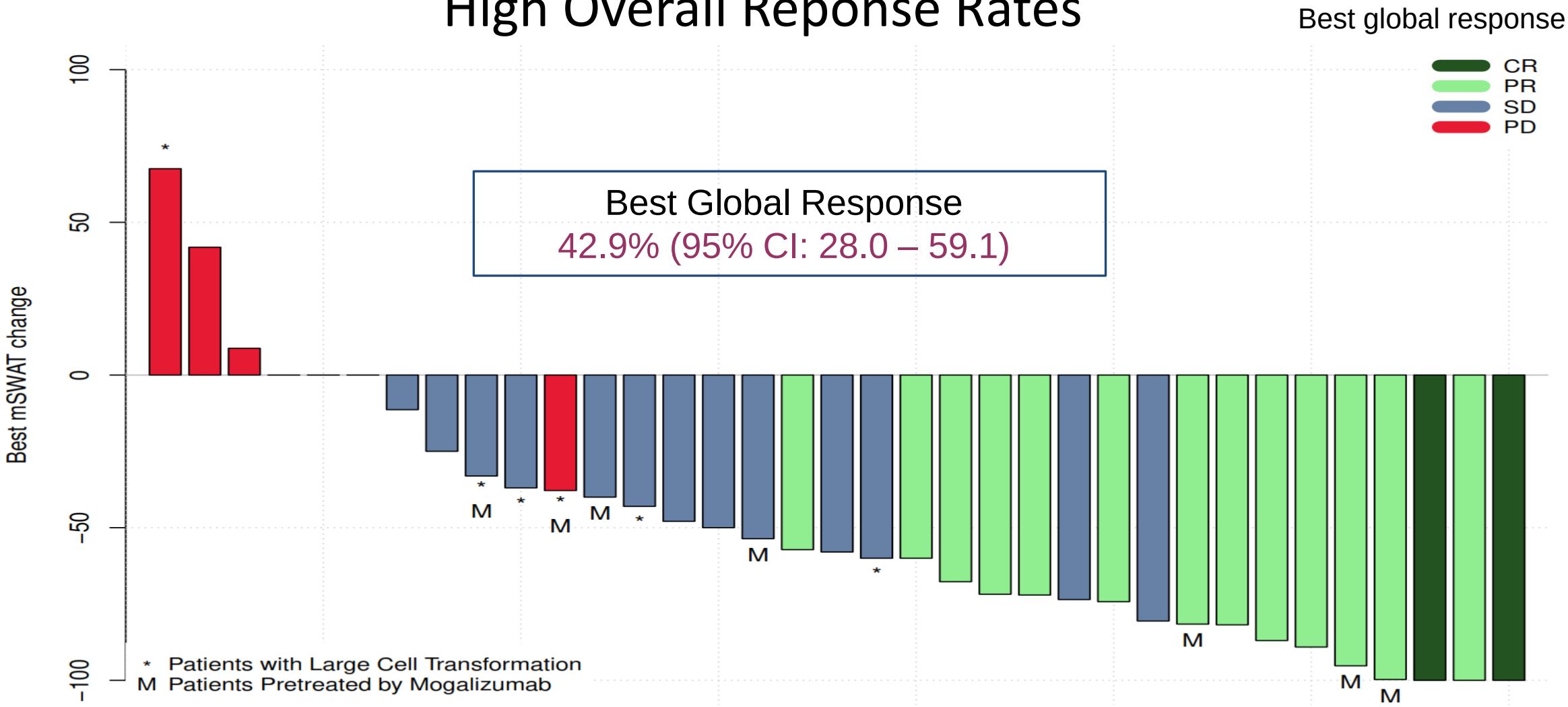
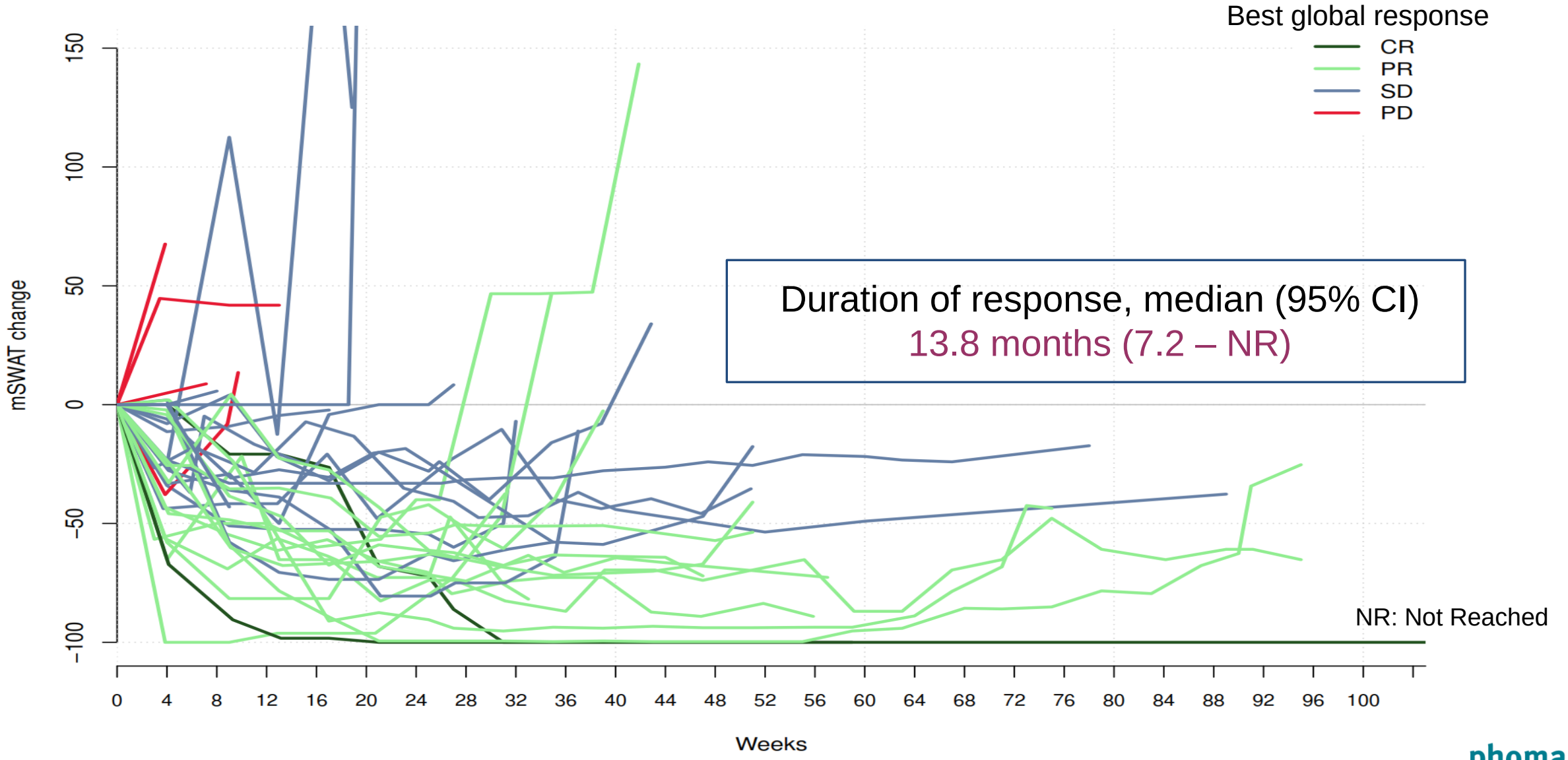
Clinical Efficacy Results: High Overall Reponse Rates



Clinical Efficacy Results : Durable Responses

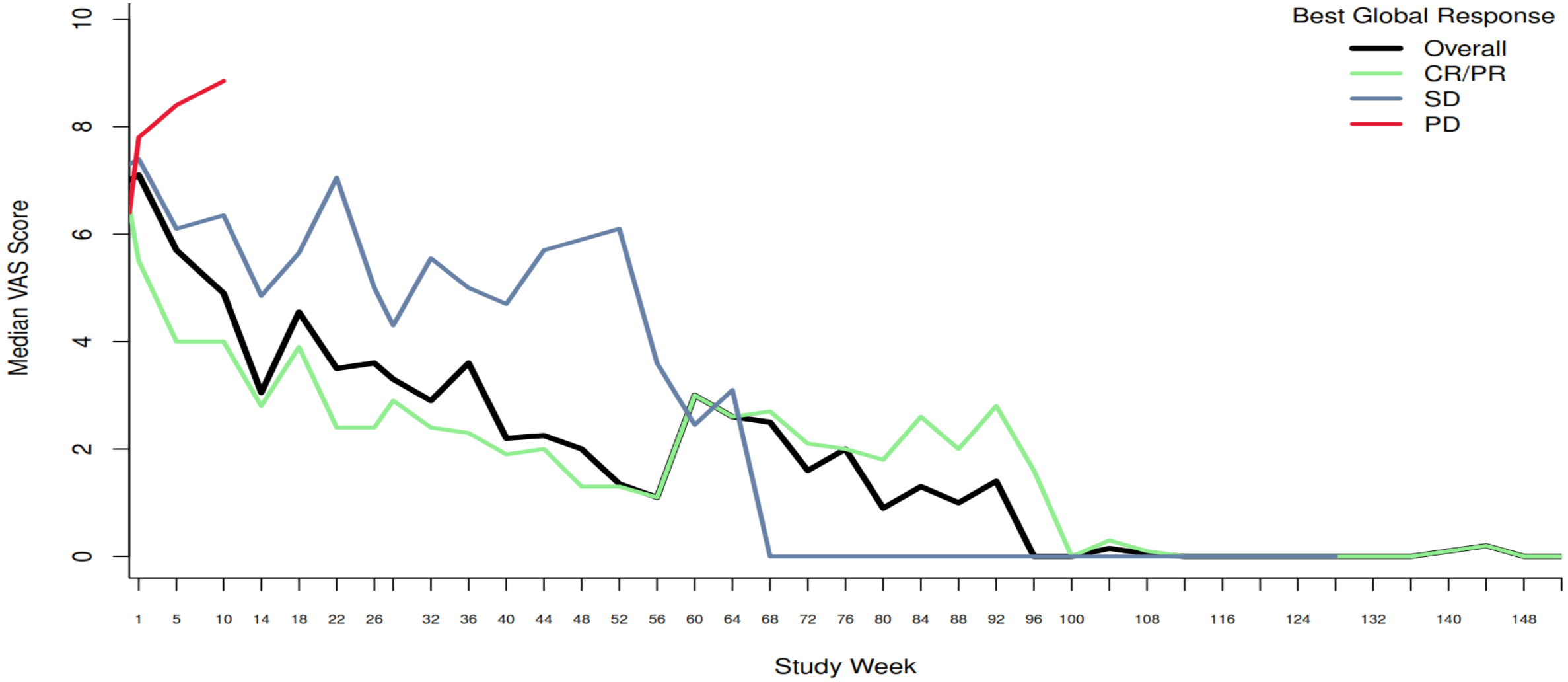


Duration of response, median (95% CI)
13.8 months (7.2 – NR)

NR: Not Reached

Quality of Life

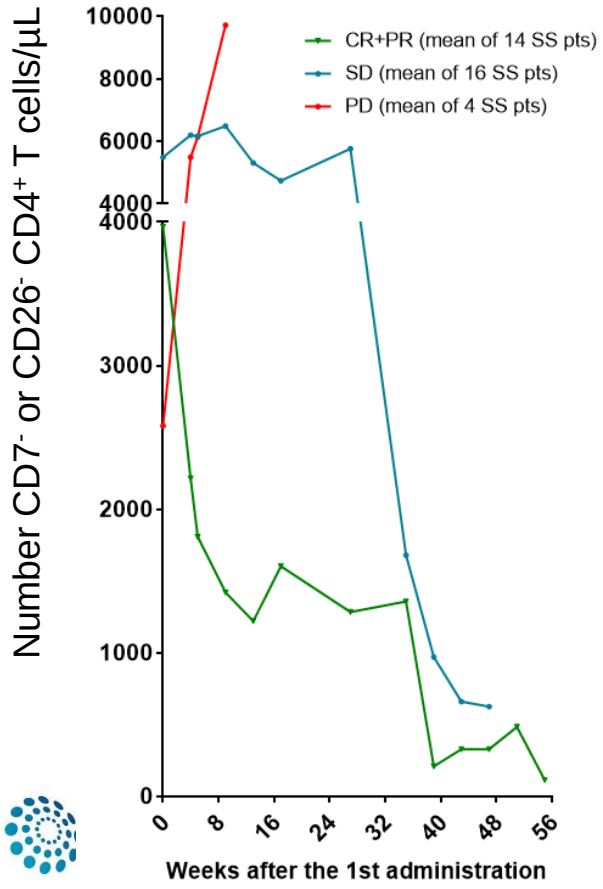
Pruritus Visual Analogue Scale Score (n = 35)



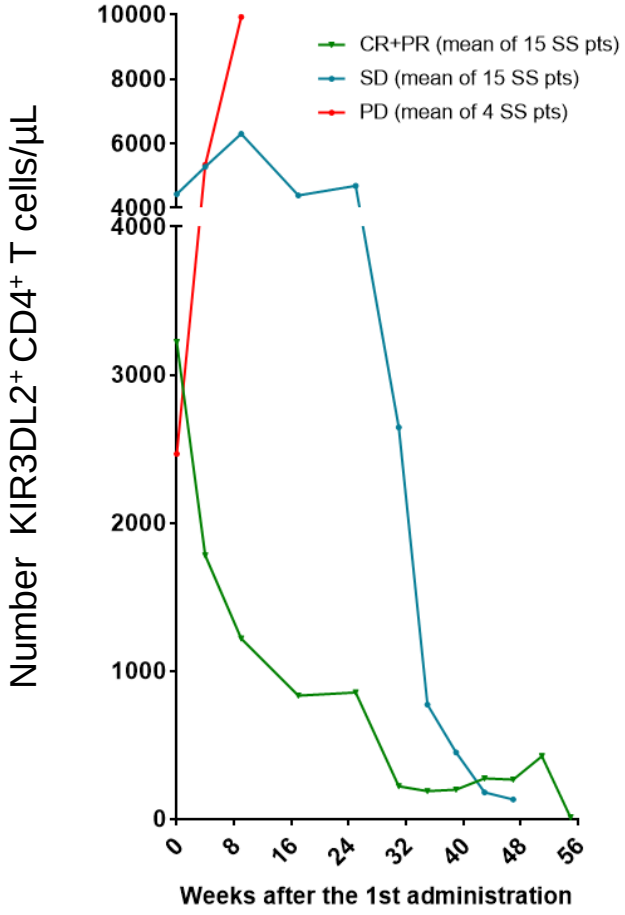
Exploratory Biomarkers

Changes of tumor cells and KIR3DL2 cells in blood

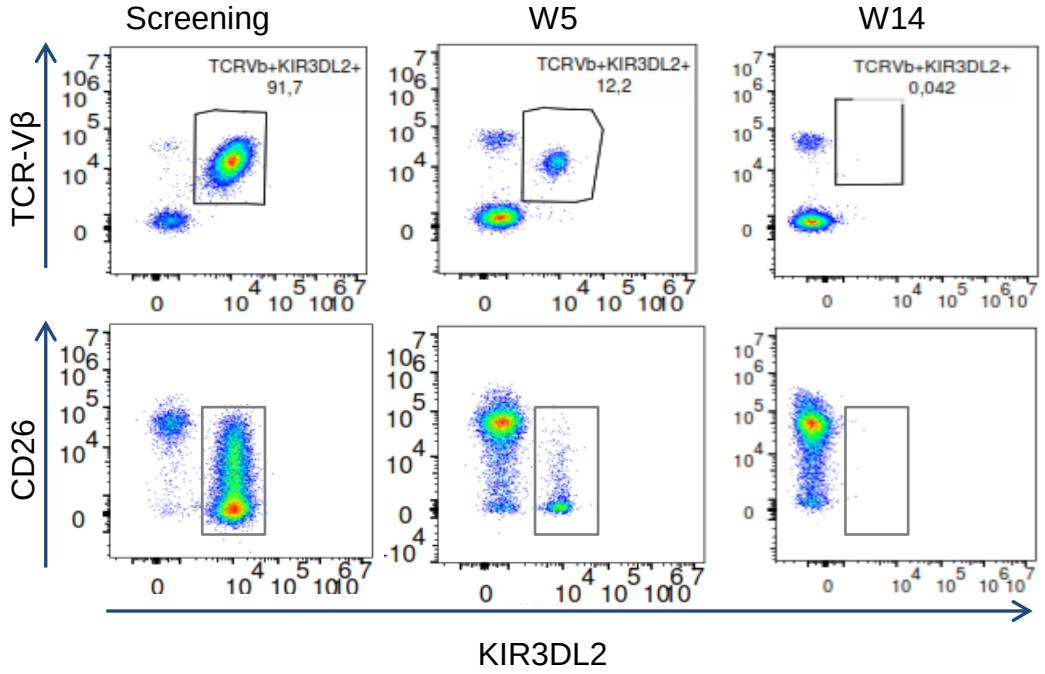
Aberrant cells



KIR3DL2+ CD4+ T cells



Patient 01-036, ongoing complete response > 1 year



Network Hematological Diseases (ERN EuroBloodNet)

Webinars Cutaneous Lymphoma

EuroBloodNet Topic on Focus

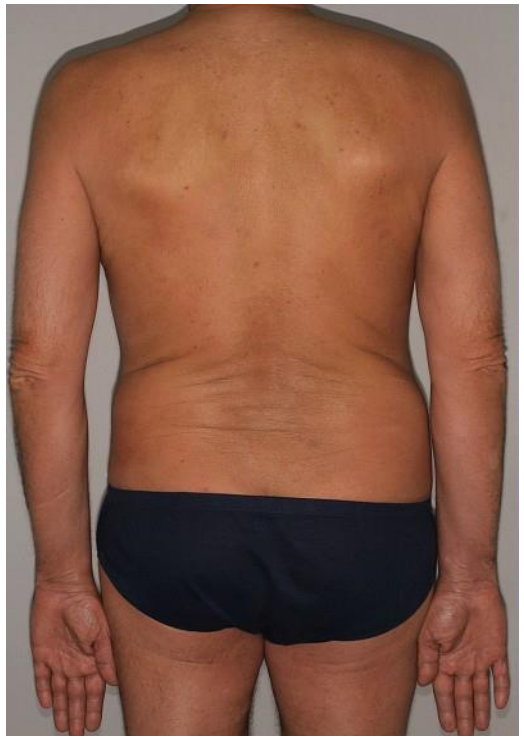
IPH4102, a first-in-class anti-KIR3DL2 monoclonal antibody, in patients with relapsed or refractory cutaneous T-cell lymphoma: an international, first-in-human, open-label, phase 1 trial

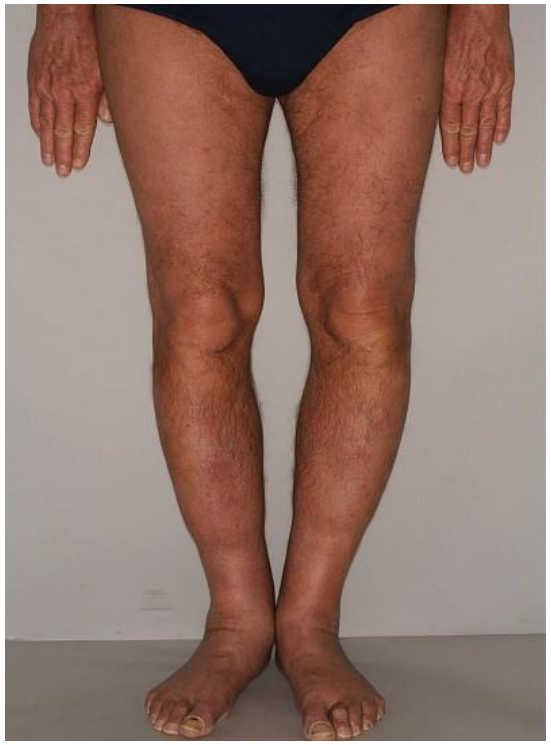
Martine Bagot, Pierluigi Porcu, Anne Marie-Cardine, Maxime Battistella, Basem M William, Maarten Vermeer, Sean Whittaker, Federico Rotolo, Caroline Ram-Wolff, Michael S Khodadoust, Armand Bensussan, Carine Paturel, Cecile Bonnafous, Helene Sicard, Hatem A Azim Jr, Youn H Kim

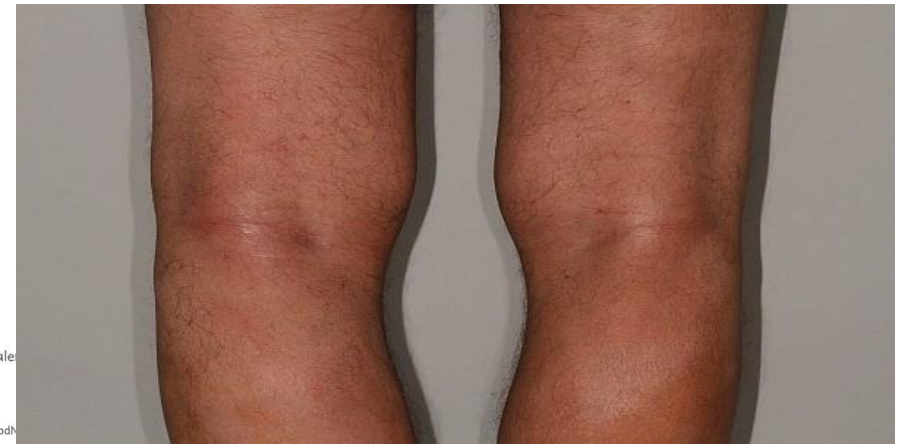
Lancet Oncology, 2019;20:1160-1170

- This study shows a favourable safety profile and very encouraging clinical activity of Lacutamab given as single agent in patients with relapsed/refractory Sézary Syndrome

- Based on these results, the FDA has granted on January 17, 2019 Fast Track designation for IPH4101 in managing relapsed/refractory Sézary Syndrome





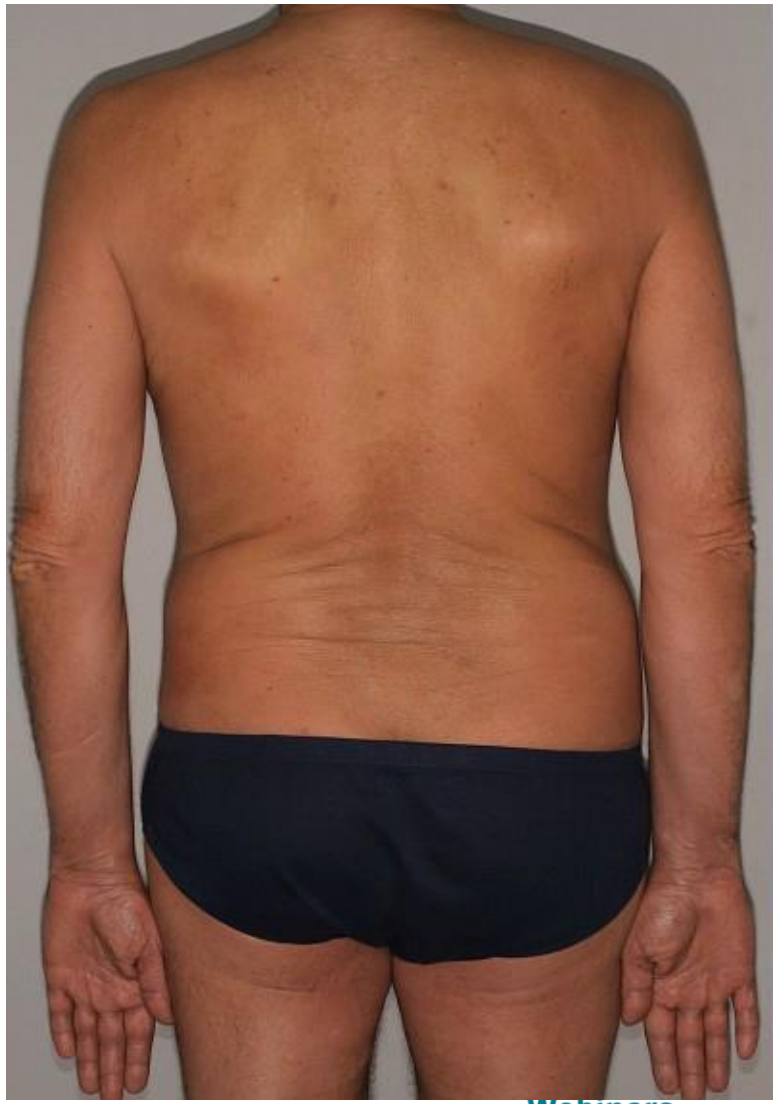


Mr S.X., 62 y

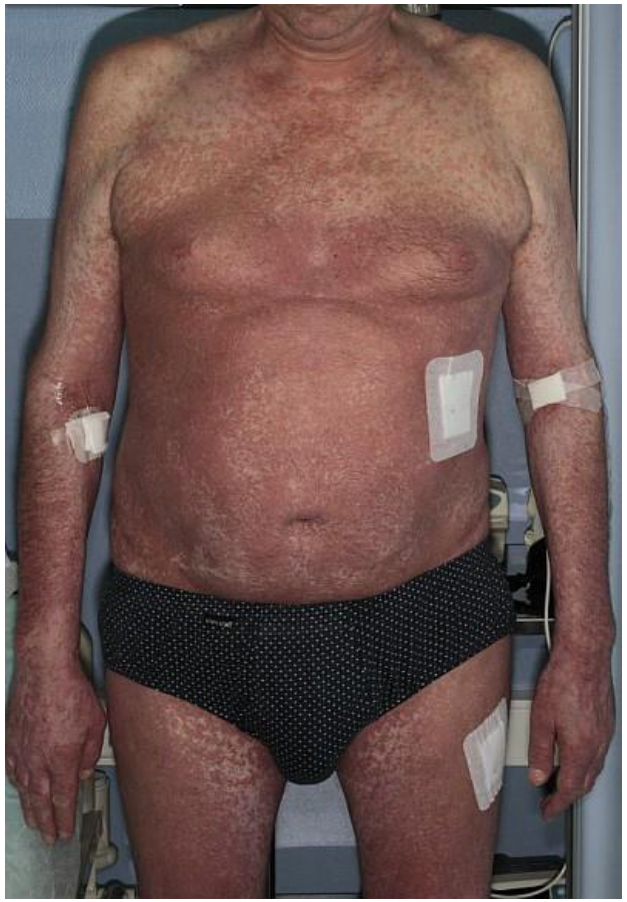
- Since 2014: pigmented pruriginous erythroderma
- Mai 2015: Diagnostic of Sézary syndrome
- Cutaneous histology : T cell lymphoma
- Flow cytometry:
  - CD4+CD26- : 86%
  - CD158k lymphocytes : 68%. 2,233/mm3
  - CD4/CD8 ratio : 15
- TAP scan : normal

Mr S.X., 62 y

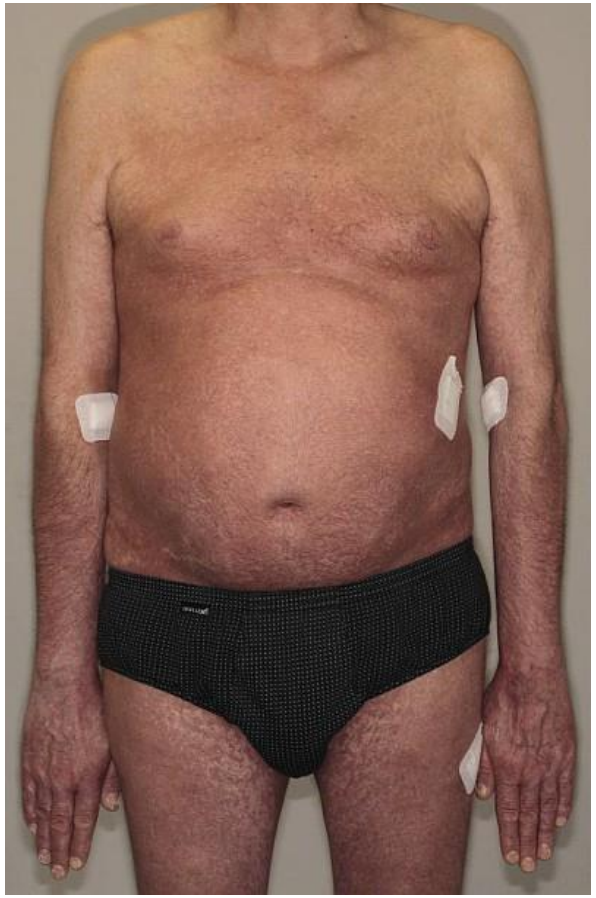
- 2015-2017: Failure of several treatment lines
  - Bexarotene
  - Bexarotène + ECP
  - Interferon
- Juin 2017: Progression
  - Ly CD4+CD26- : 73%
  - Ly CD158k : 66% = 2,450/mm3
  - CD4/CD8 ratio : 19
- Tt with Lacutamab



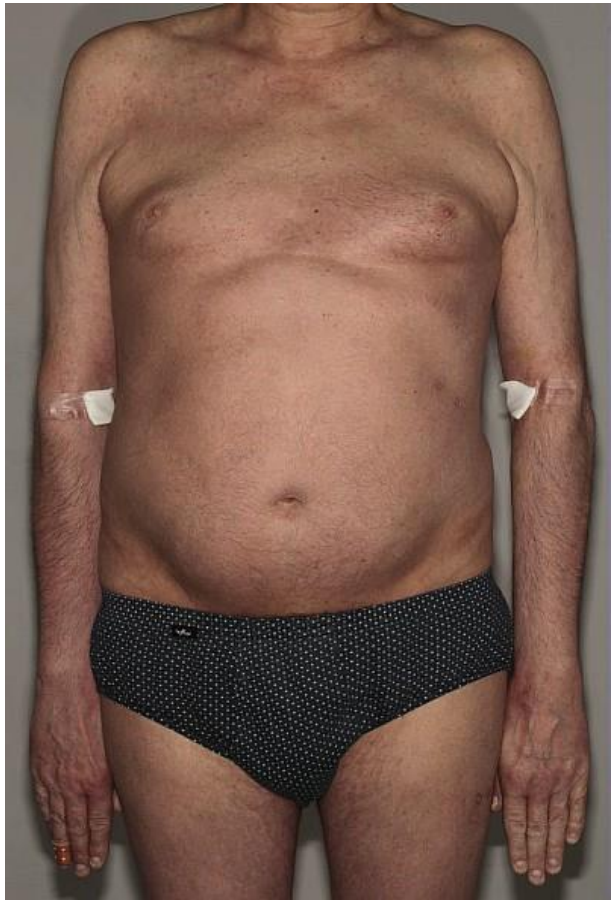
Treatment with Lacutamab



Week 1



Week 5



Week 10

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Webinars Cutaneous Lymphoma
EuroBloodNet Topic on Focus

Mr S.X., 62 y

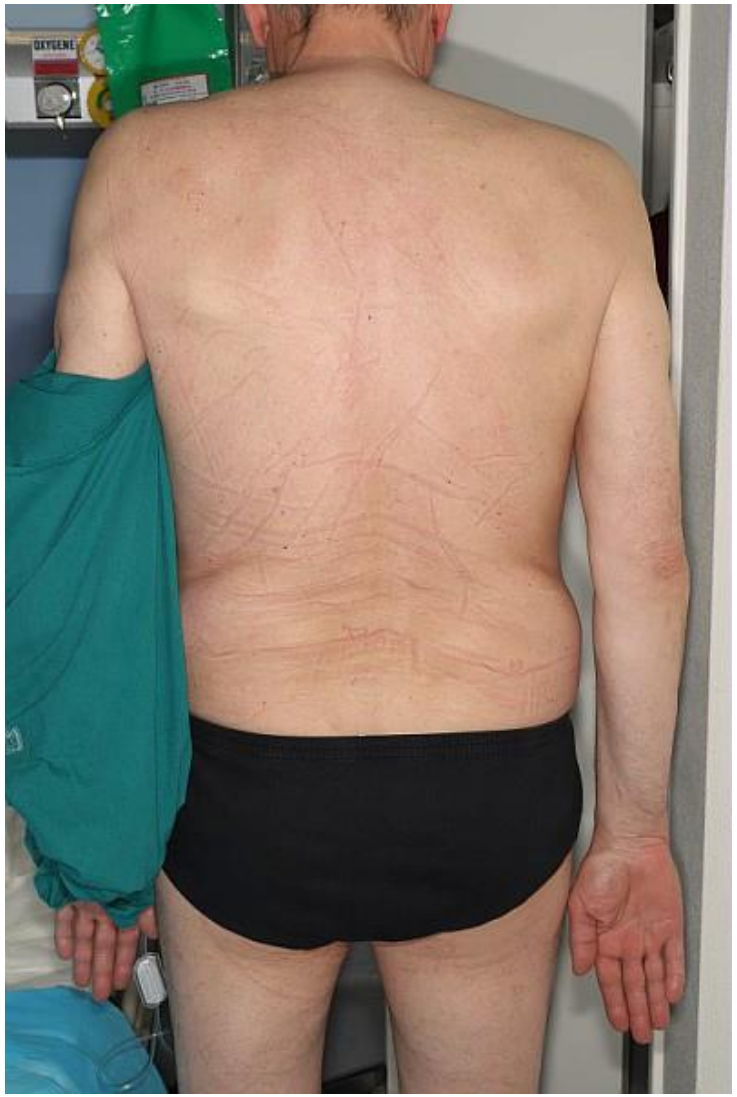
- November 2017: Week 10
  - Peau: Almost CR. mSWAT: 11
  - Sang: CR: B0

    Lymphocytes CD158k : 1.3% = 11/mm3

    CD4/CD8 ratio: 3.3

- Excellent tolerance
- Injection 1 fois/month

- July 2020: After 2 y 8 months
  - Persistant CR in skin and blood



Take home messages

1. Flow cytometry is very important for diagnostic and staging of Sézary syndrome patients

2. Mogamulizumab is a new efficient treatment of Sézary syndrome

3. Lacutamab is a potentially new treatment for Sézary syndrome