Thursdays Webinars

EuroBloodNet

Title: Innovative Treatments of Cutaneous T Cell Lymphomas

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

Co-funded by
the Health Programme
of the European Union

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

Conflicts of interest

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

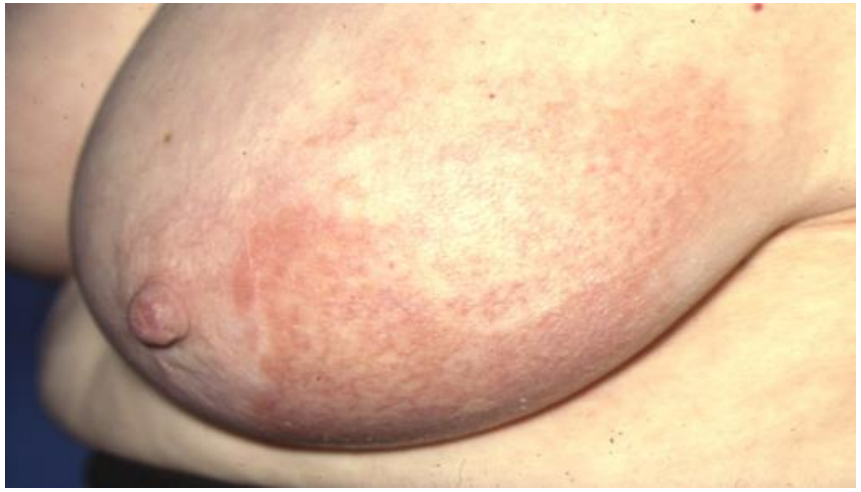
Practical issues before starting

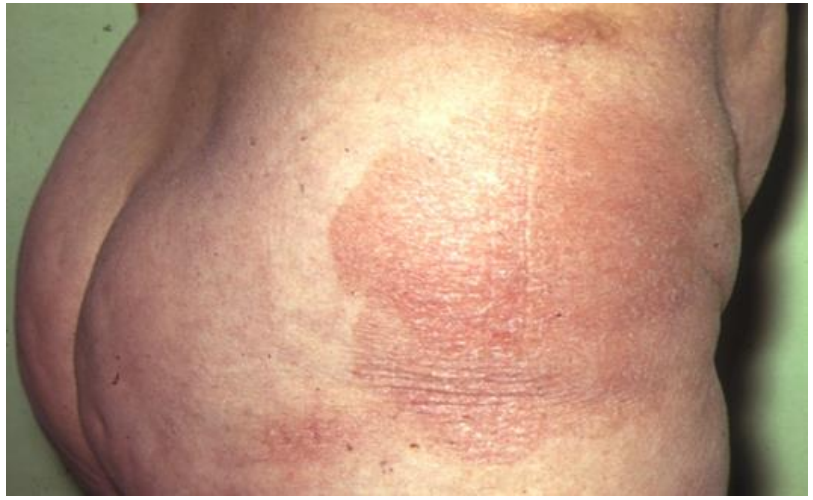
- ✓ **30-35min presentation (30 slides max) + 15 min Q&A session**
- ✓ **Microphones will be muted by host to avoid back noise**
- ✓ **Please, stop your video to improve internet conexion**
- ✓ **Send your questions during the presentation through the chat, they will be gathered and answered after the presentations.**

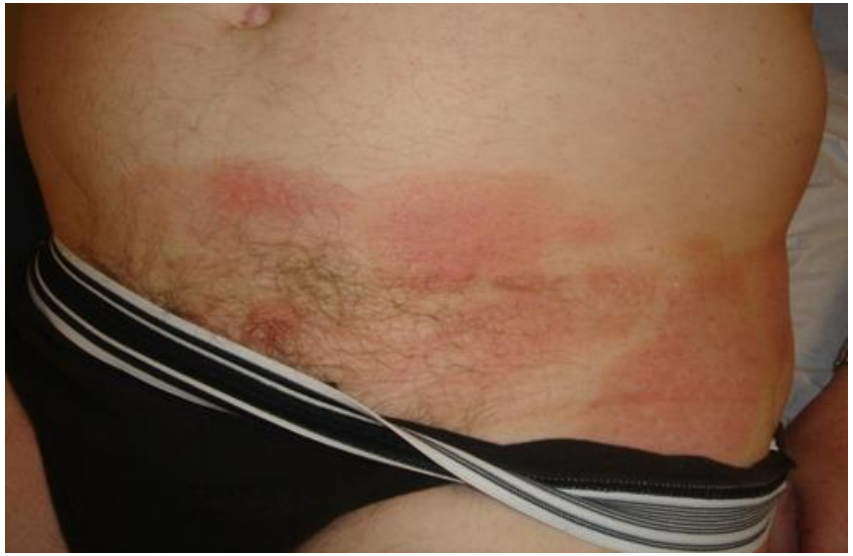
Learning objectives of the webinar

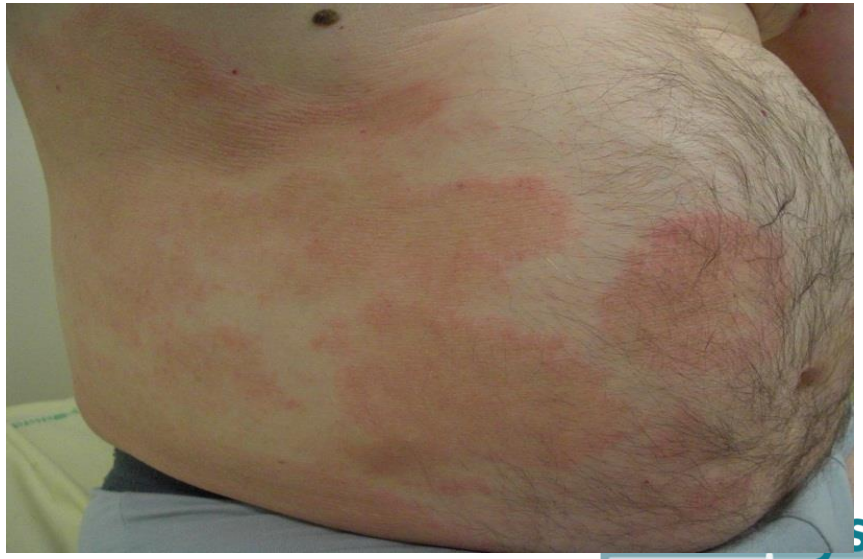
1. To understand the needs for innovative treatment of cutaneous lymphomas
2. To know the new monoclonal antibodies approved for the treatment of cutaneous lymphomas
3. To know the monoclonal antibody with a possible future approval for the treatment of cutaneous lymphomas

Early stage Mycosis Fungoides

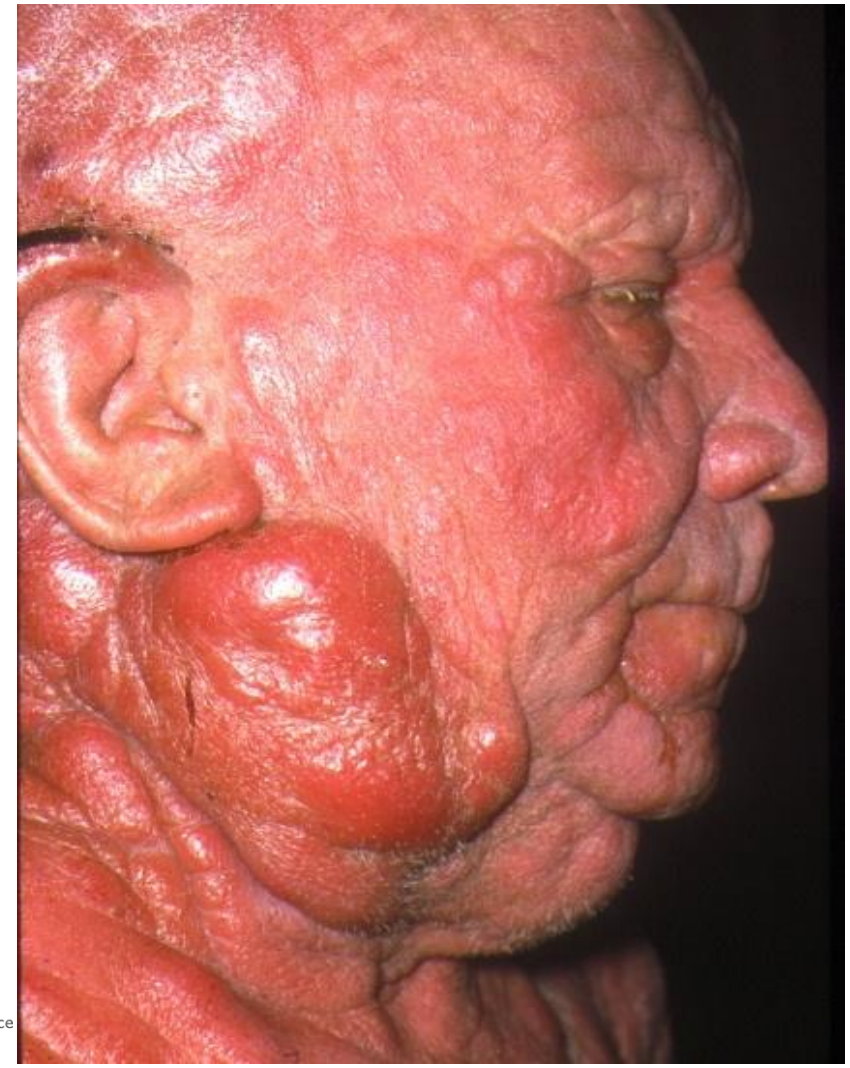


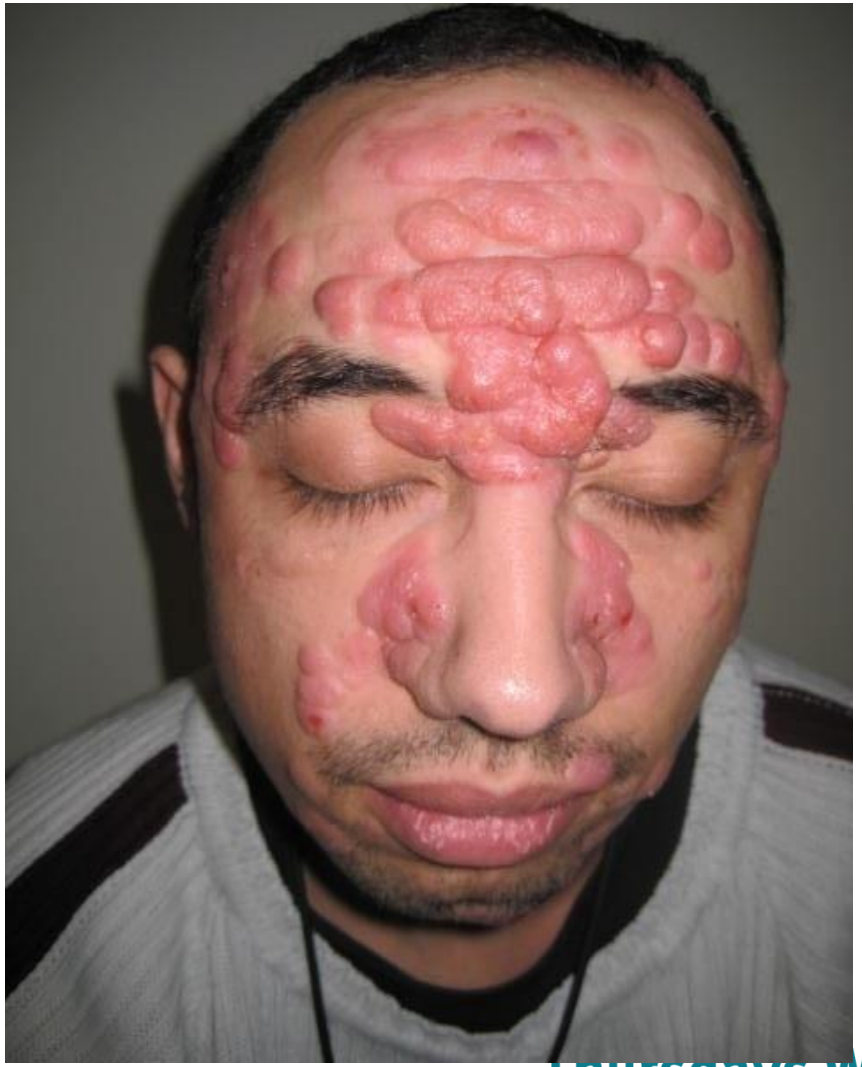




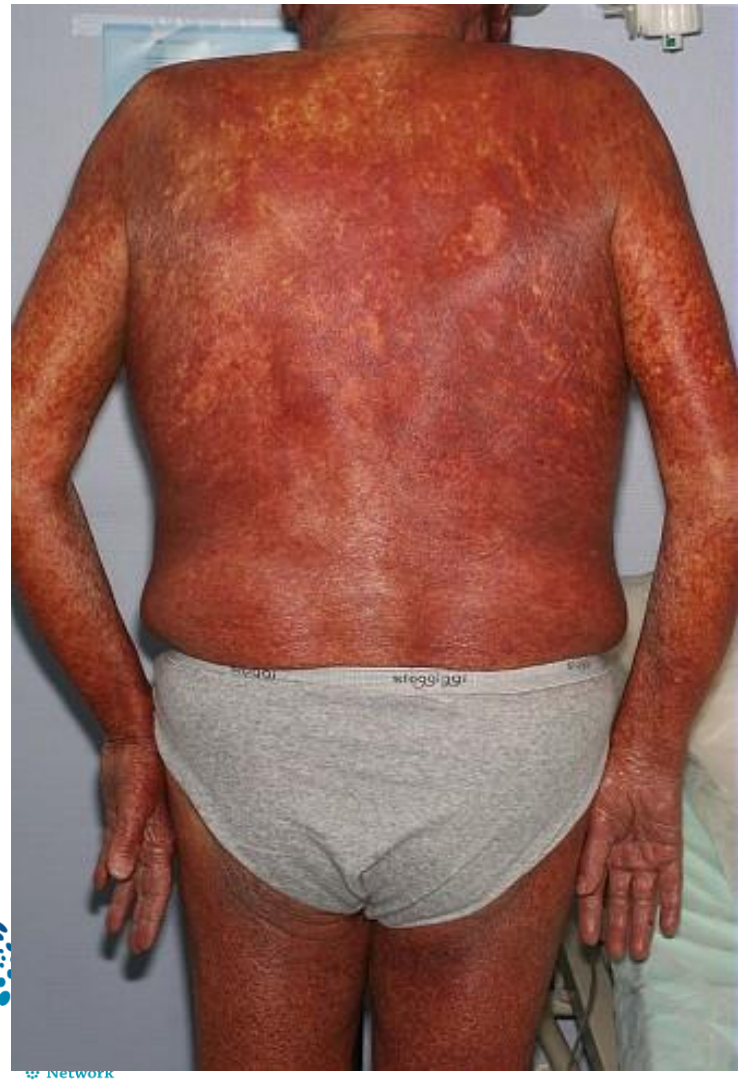


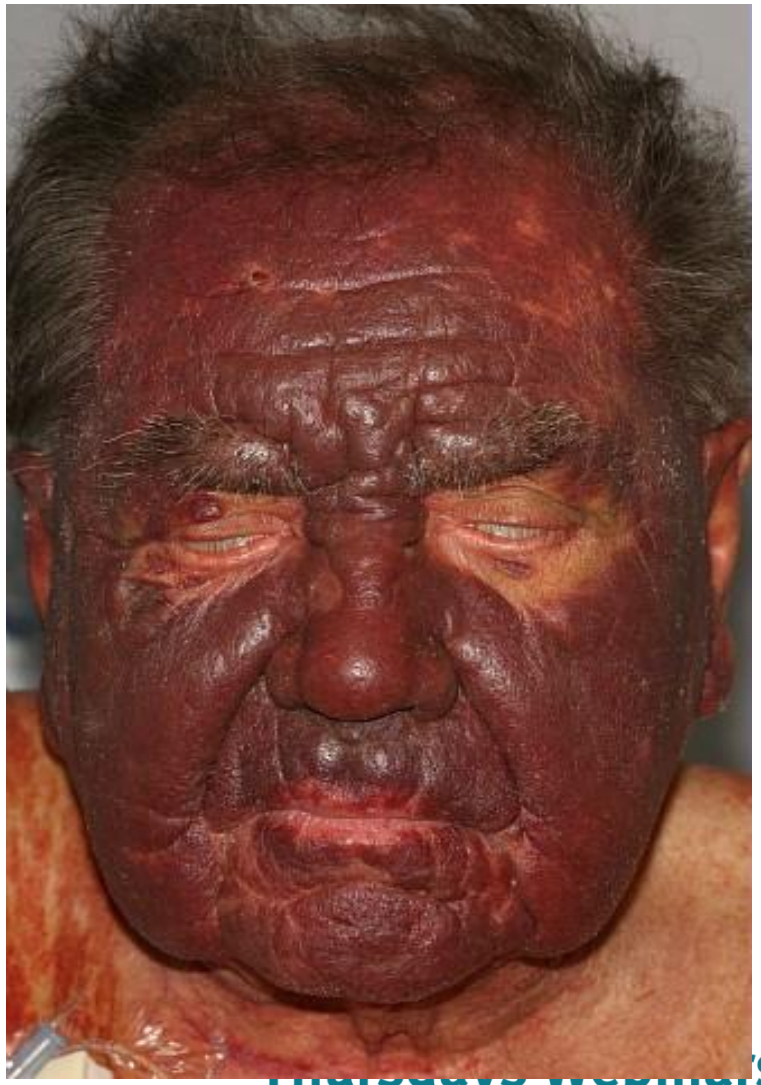
Tumor stage Mycosis Fungoides



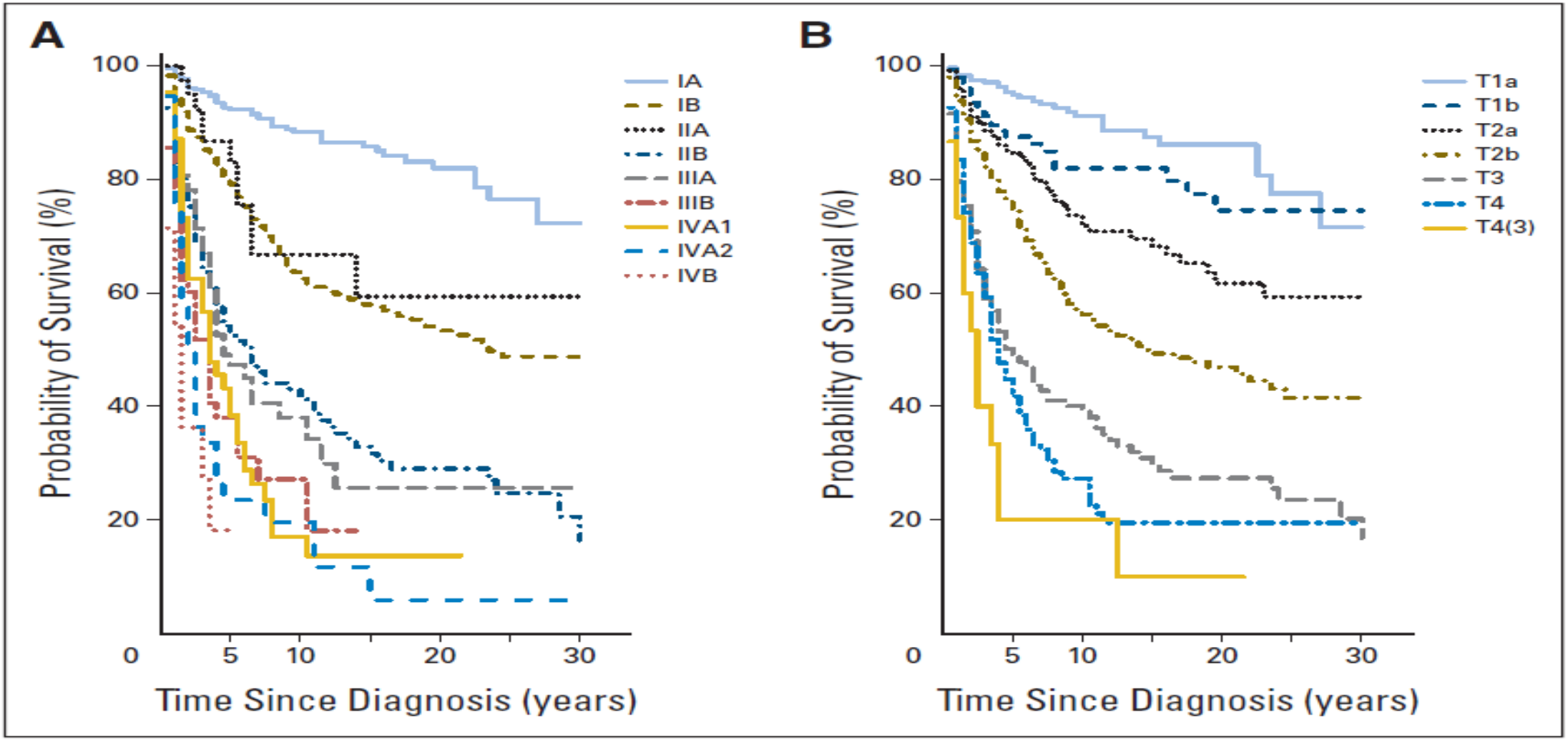


Sézary Syndrome





MF/SS Survival curves



Classical treatments for advanced CTCL

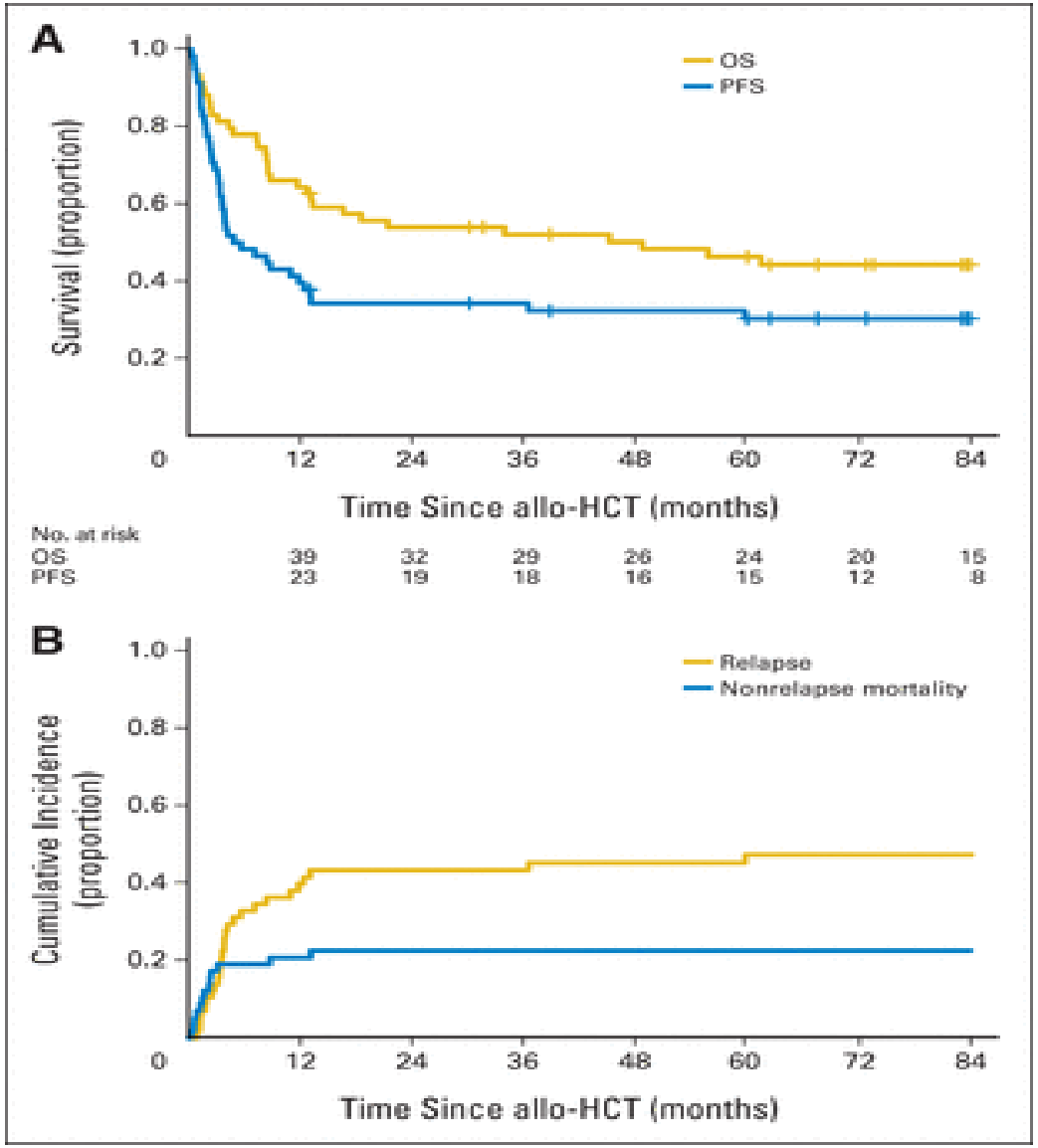
- Systemic Immunomodulatory agents
  - Retinoids (bexarotene)
  - Interferon
  - Methotrexate

- Local treatments
  - Chlormethin gel
  - Radiotherapy : Total skin electronbeam therapy, localized radiotherapy

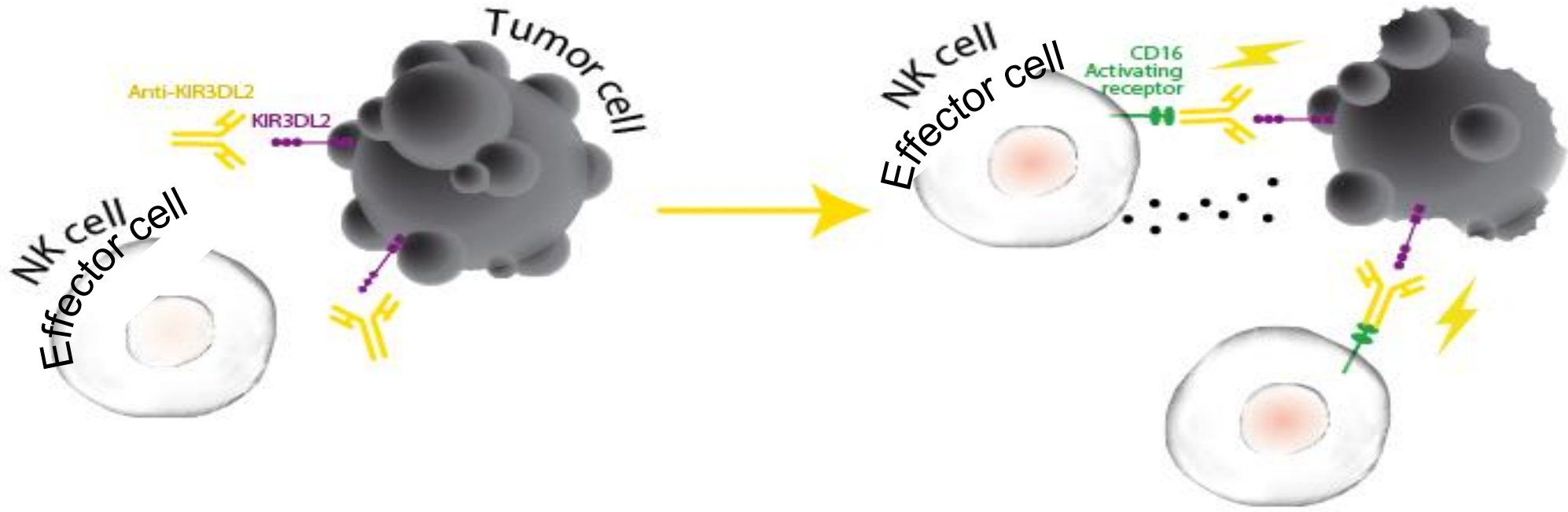
Classical treatments for advanced CTCL

- Photopheresis
- Histone Deacetylase inhibitors
  - Vorinostat, Romidepsine
  - Not approved in Europe
- Monochemotherapy
  - Gemcitabine, Pegylated liposomal doxorubicin
- Polychemotherapy
- Allogeneic stem cell transplantation: selected patients, CR or almost CR

Allogeneic SCT for CTCL. *Duarte et al, JCO 2014*



Targeted mAbs: a new hope for CTCL treatment



mAb binds to target on tumor cells

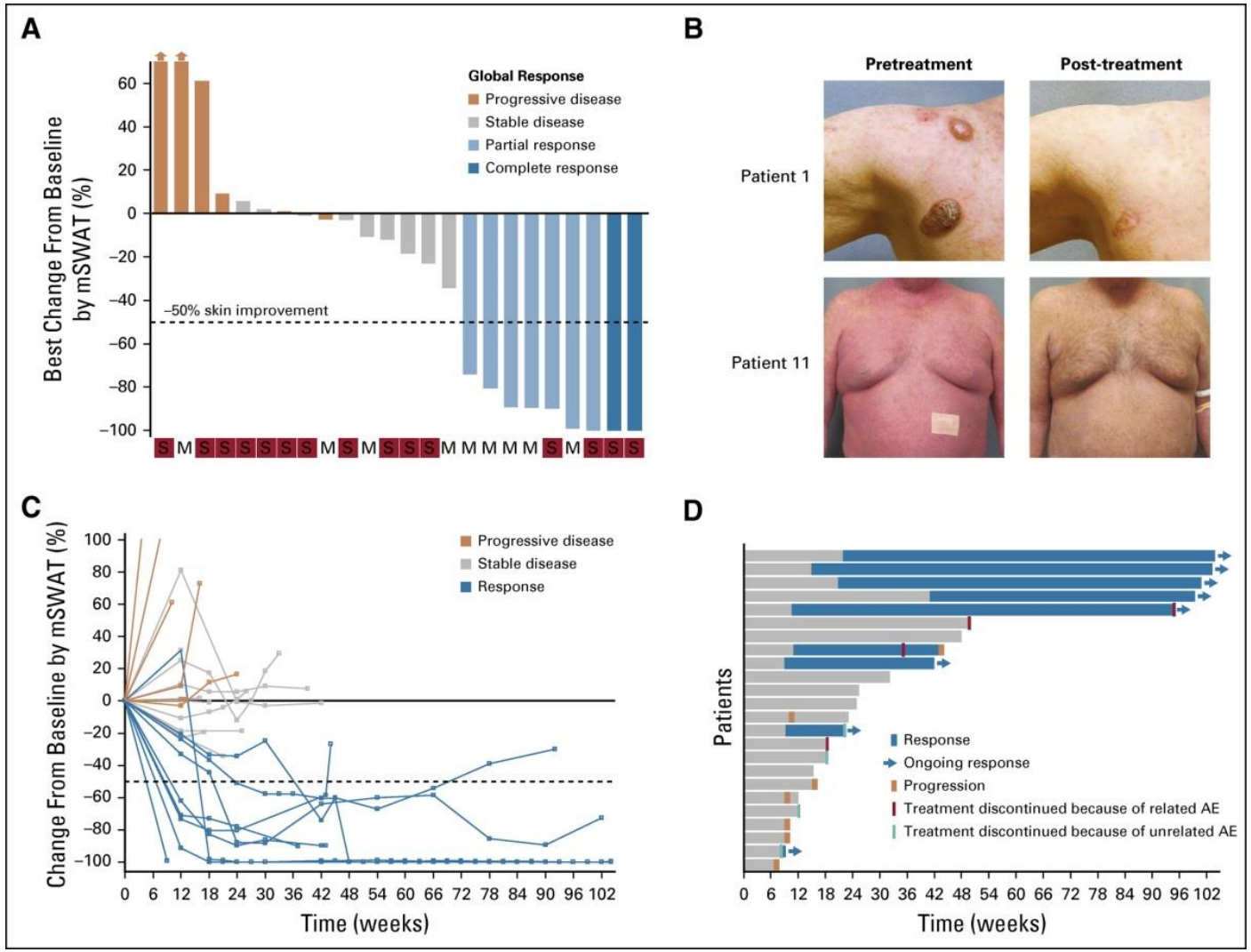
Recruitment of effector cells and depletion of tumor cells

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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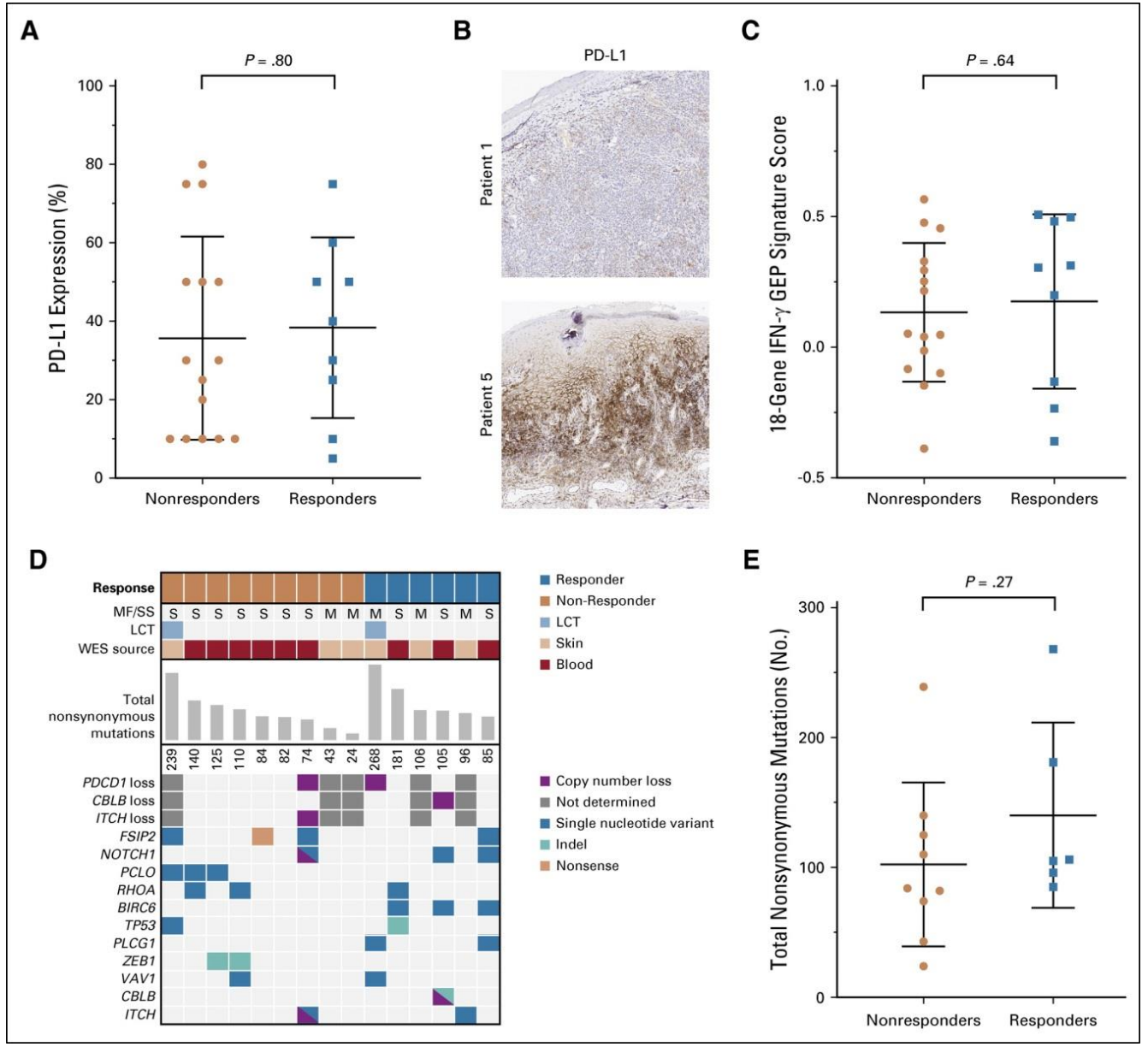
- Transient worsening of erythroderma and pruritus occurred in 53% of patients with SS.
- This cutaneous flare reaction did not result in treatment discontinuation for any patient.
- The flare reaction
  - correlated with high PD-1 expression on Sézary cells
  - but did not associate with subsequent clinical responses or lack of response.
- Treatment responses did not correlate with expression of PD-L1, total mutation burden, or an interferon-gamma gene expression signature.



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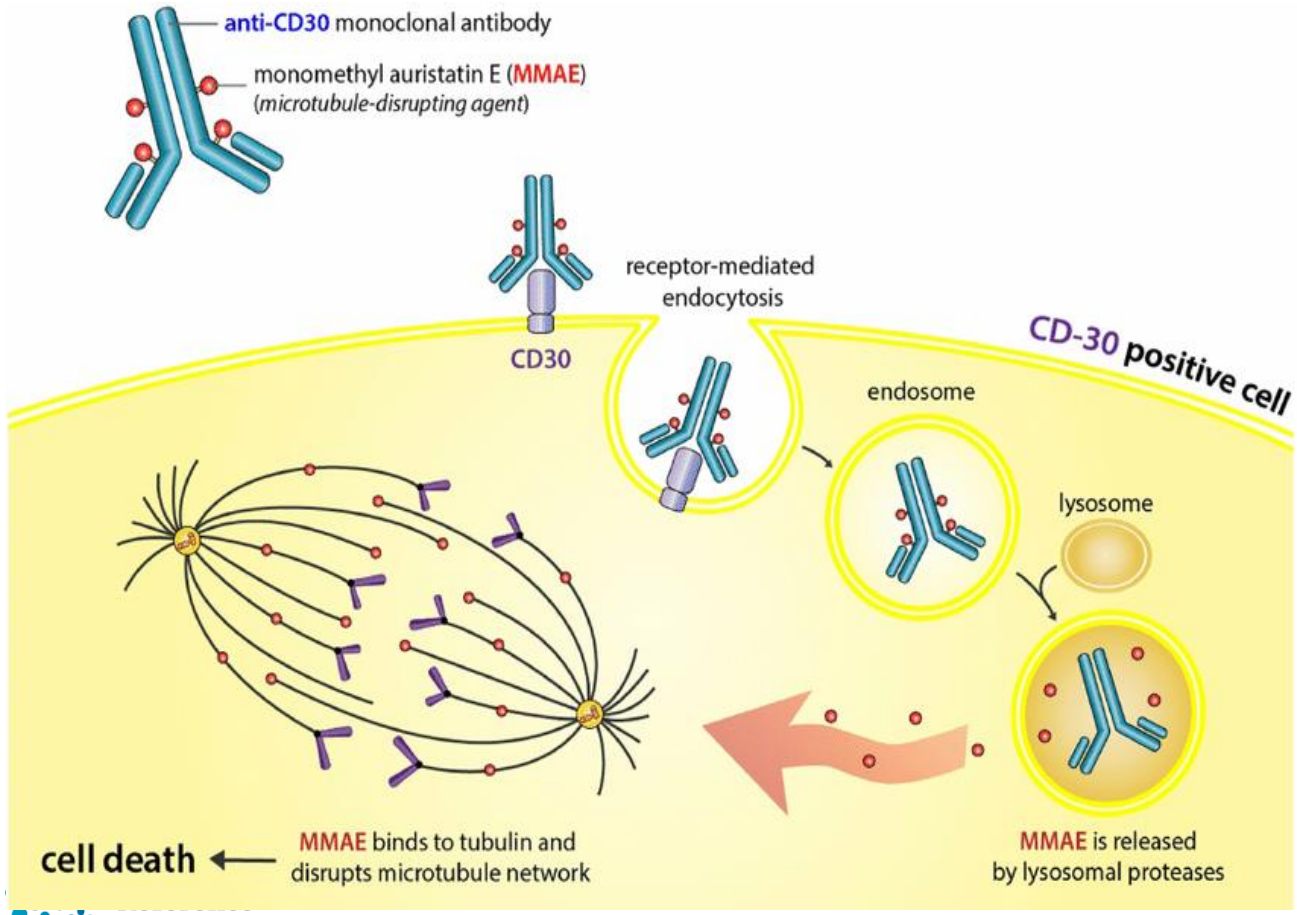
Brentuximab vedotin

an anti-CD30 antibody–drug conjugate



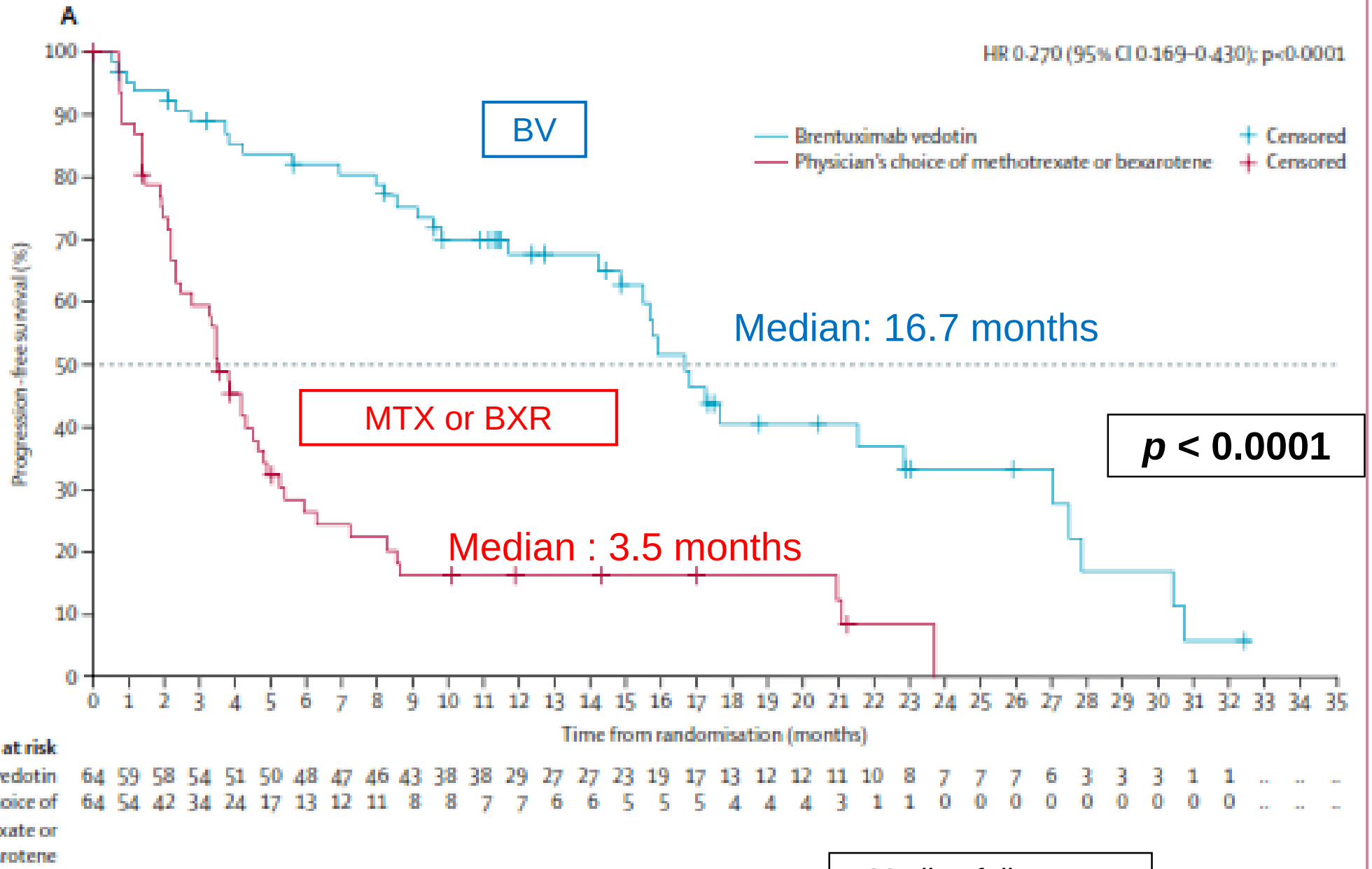
- Brentuximab vedotin (SGN-35) is a chimeric anti-CD30 mAb conjugated to monomethyl auristatin E (MMAE), a cytotoxic anti-tubulin agent

- BV has been approved by FDA and EMA for patients with primary cutaneous ALCL or CD30-expressing MF after at least one prior systemic therapy

Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial

H Miles Prince, Youn H Kim*, Steven M Horwitz, Reinhard Dummer, Julia Scarisbrick, Pietro Quaglino, Pier Luigi Zinzani, Pascal Wolter, Jose A Sanches, Pablo L Ortiz-Romero, Oleg E Akilov, Larisa Geskin, Judith Trotman, Kerry Taylor, Stephane Dalle, Michael Weichenthal, Jan Walewski, David Fisher, Brigitte Dréno, Rudolf Stadler, Tatyana Feldman, Timothy M Kuzel, Yinghui Wang, Maria Corinna Palanca-Wessels, Erin Zagadailov, William L Trepicchio, Wenwen Zhang, Hui-Min Lin, Yi Liu, Dirk Huebner, Meredith Little, Sean Whittaker†, Madeleine Duvic†, on behalf of the ALCANZA study group‡*

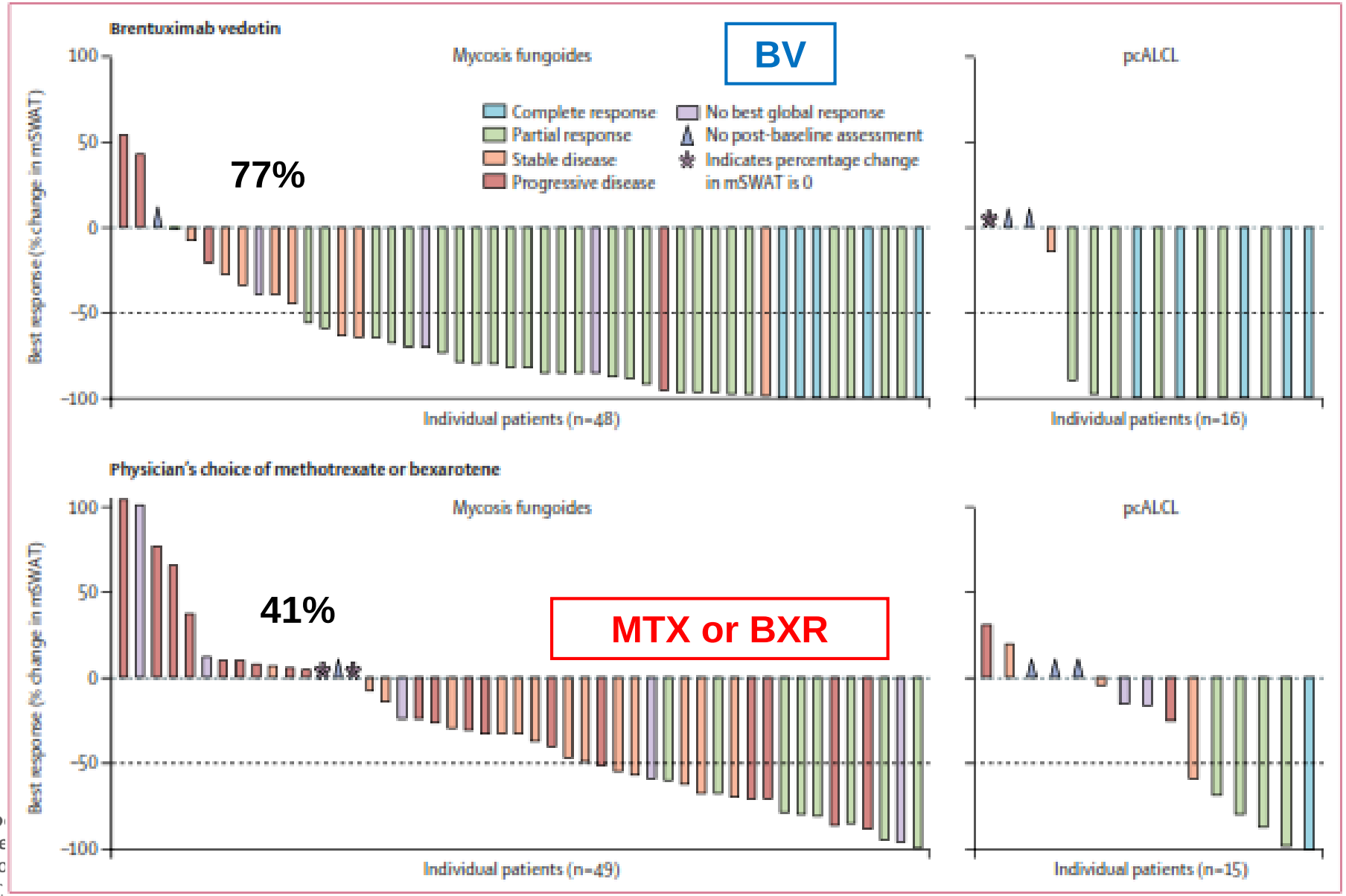
Lancet, 2017;390:555-566



67% of patients develop neuropathies

Median follow-up : 23 months

% mSWAT change



Skindex-29 : - 27 pts

Skindex-29 : - 8.6 pts

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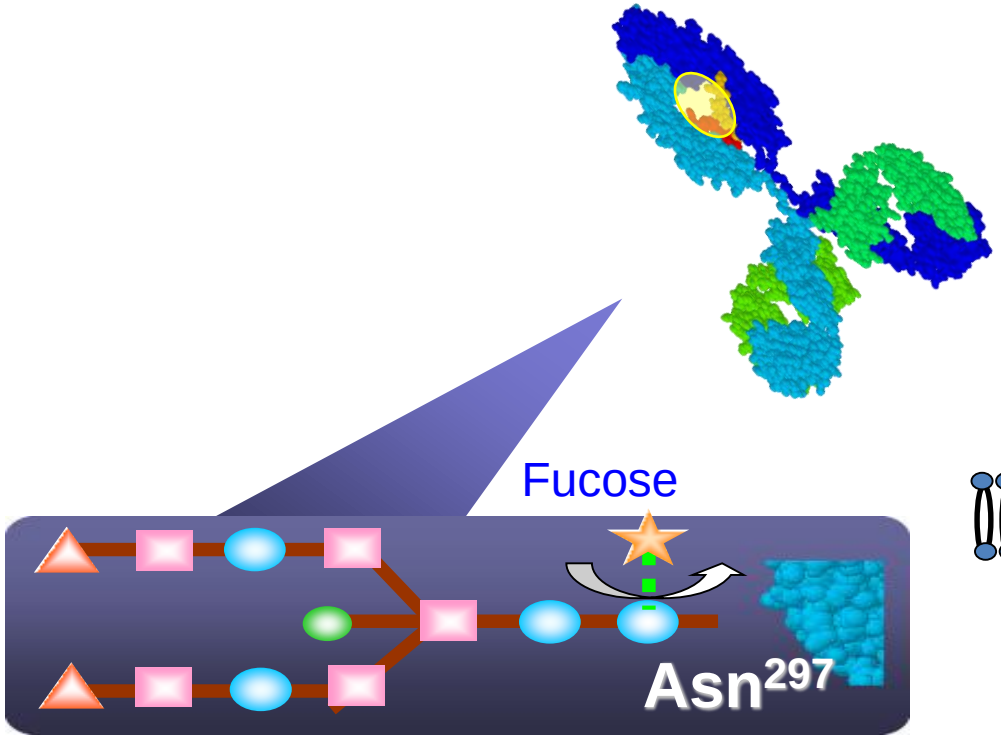
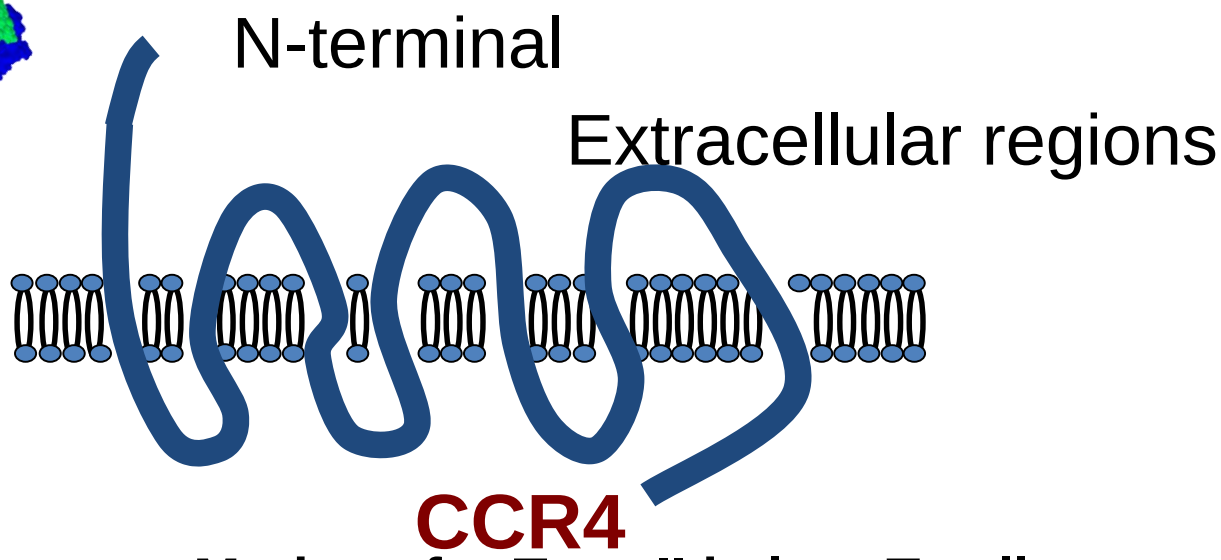
Mogamulizumab: a humanized anti-CCR4 antibody with a defucosylated Fc region



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

Inclusion:
- Stage IB – IVB histologically confirmed MF or SS (B2)
- At least one prior course of systemic therapy

Exclusion:
- Patients with large cell transformation

1:1 Randomization

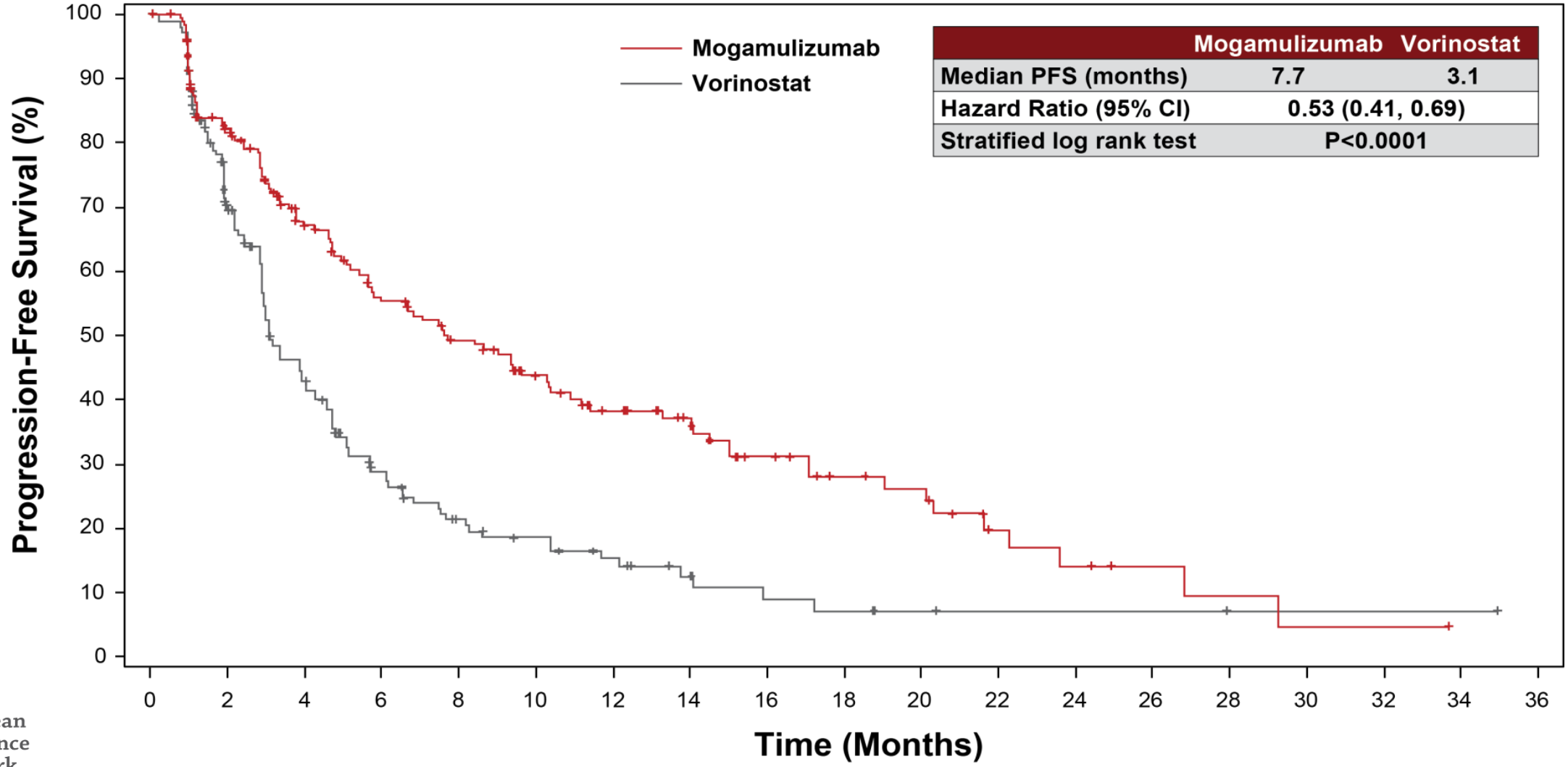
Mogamulizumab
1.0 mg/kg IV
Weekly for first 28-day cycle; days 1 and 15 of subsequent cycles

Vorinostat
400 mg PO daily

One-way crossover after PD or intolerable toxicity

- 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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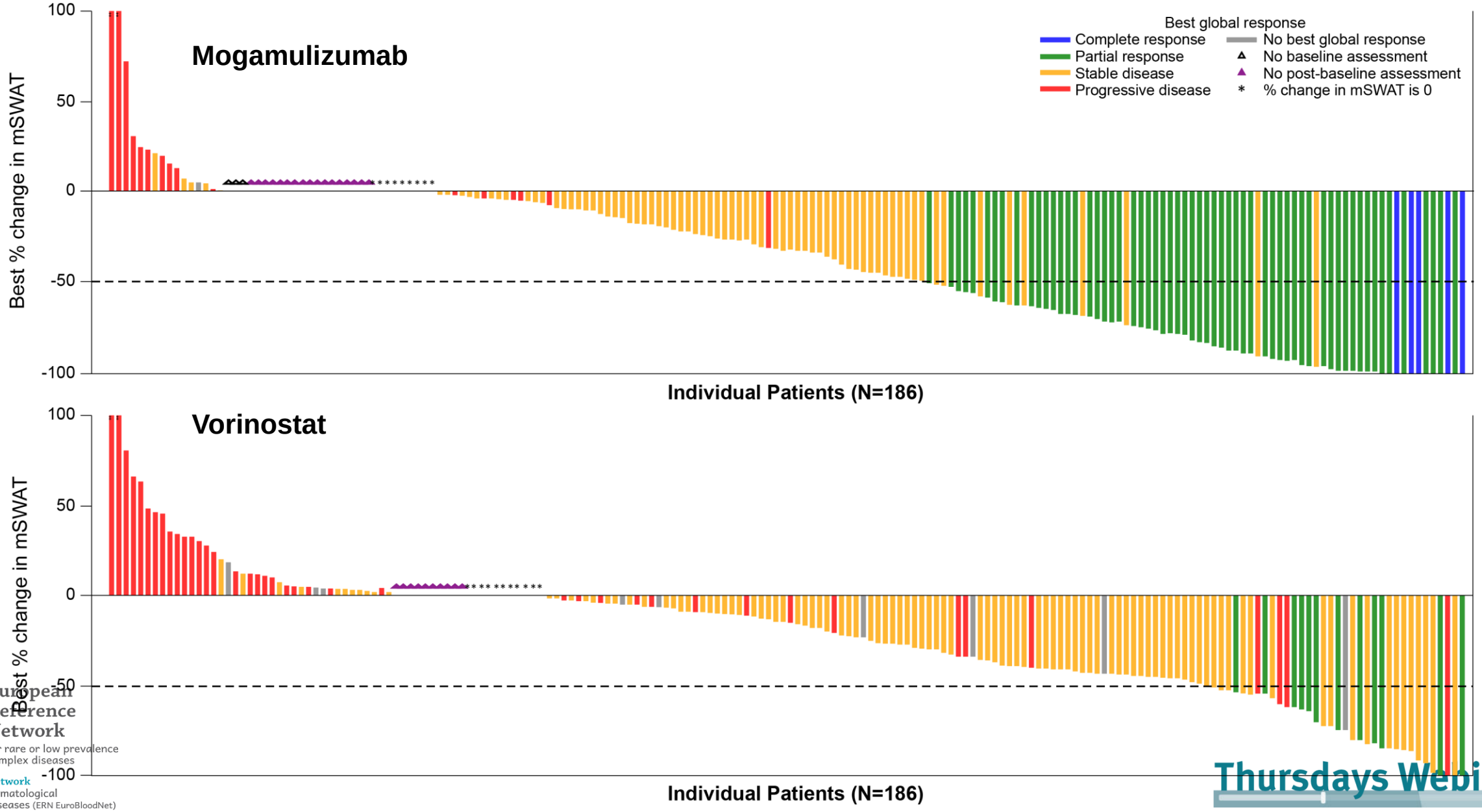
Mogamulizumab with Greater Reduction in mSWAT Score and Superior Best Global Response



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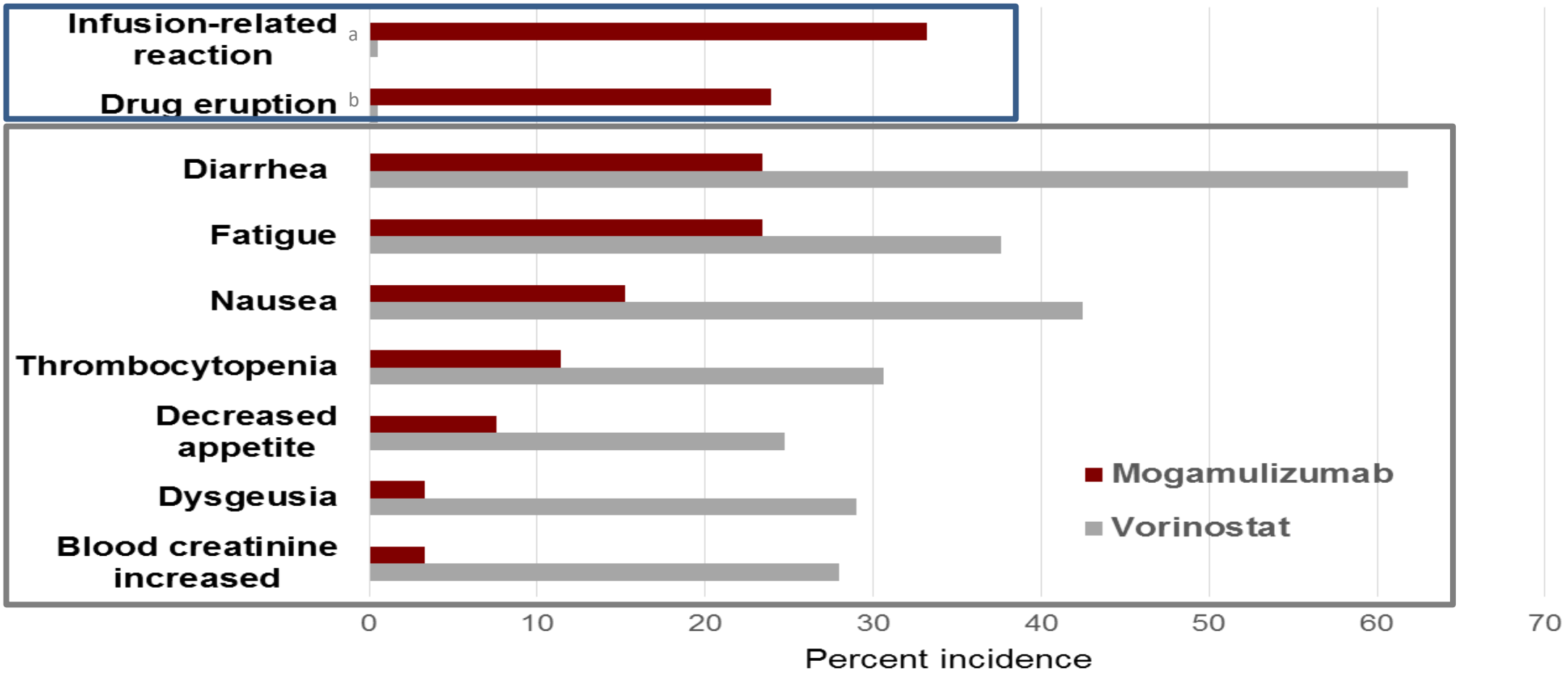
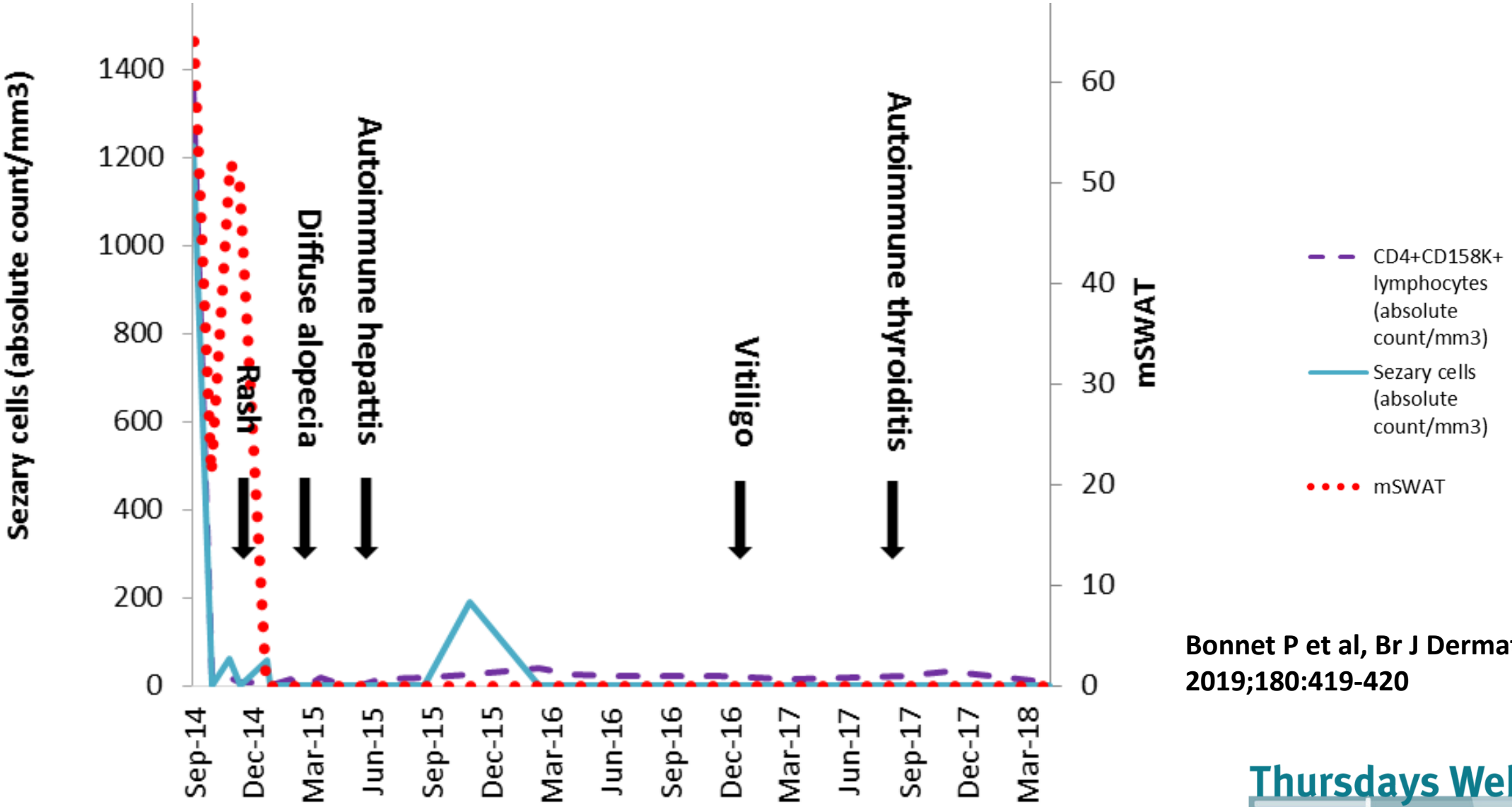
Mogamulizumab was approved in the USA and Europe in 2018 for relapsed or refractory Mycosis Fungoides or Sezary Syndrome after ≥1 prior systemic therapy based on the MAVORIC trial

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

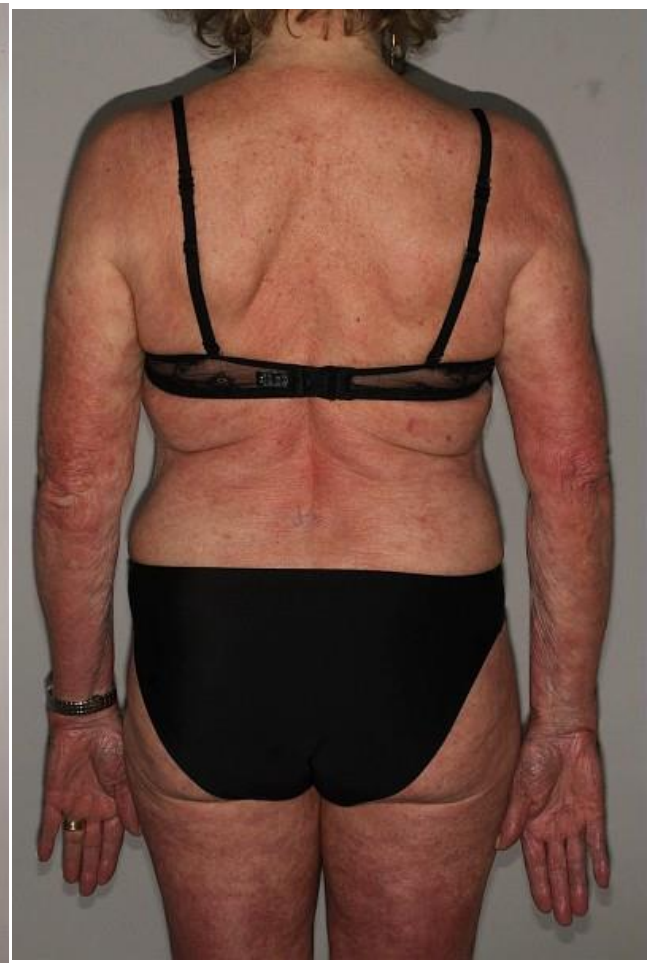


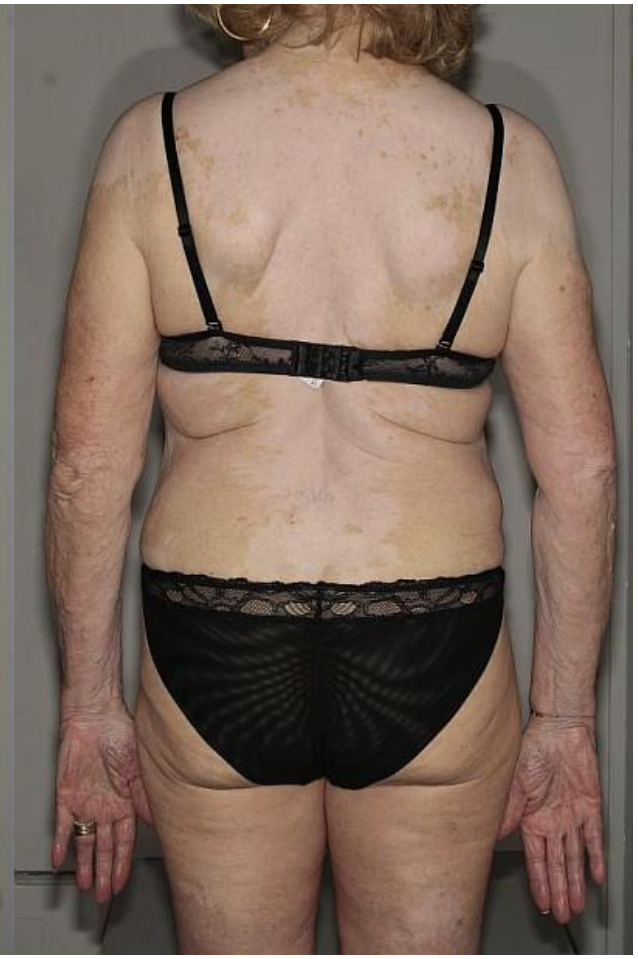
- Mogamulizumab group: ≥ 3 Grade AEs ranged from 0%-4.3% of patients
- Vorinostat group: ≥ 3 Grade AEs ranged from 0%-5.9% of patients

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



- 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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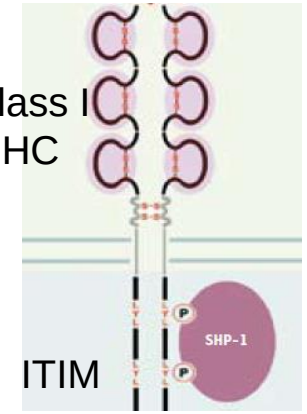
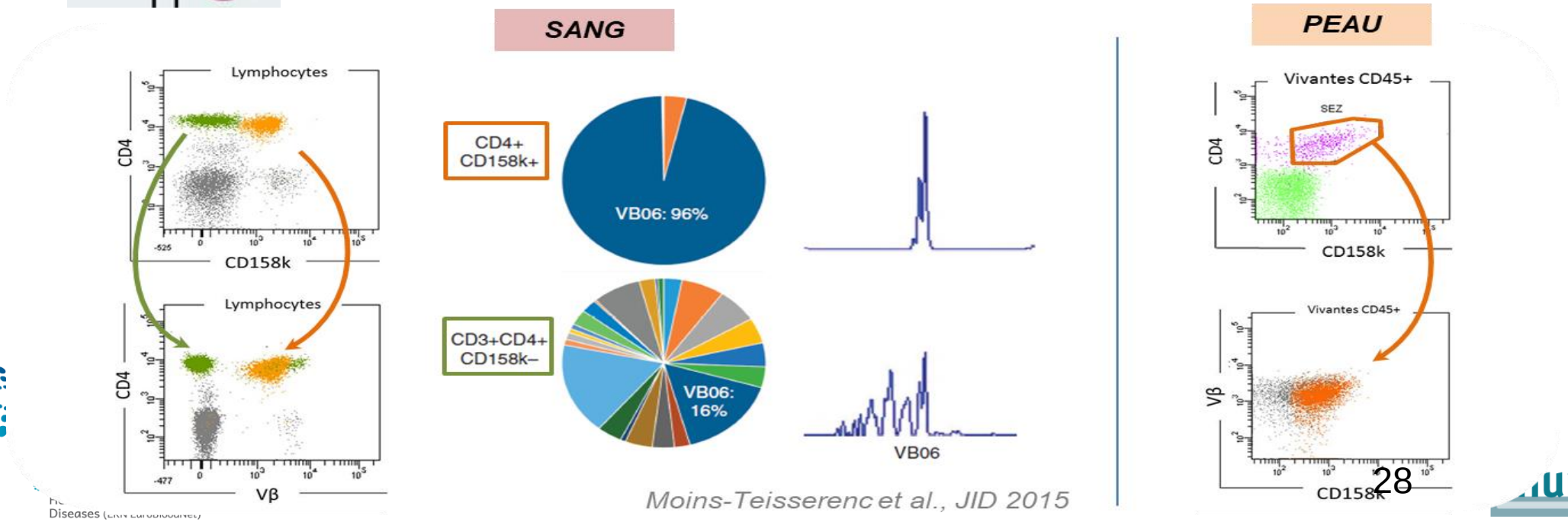
KIR3DL2, a specific marker for Sezary cells

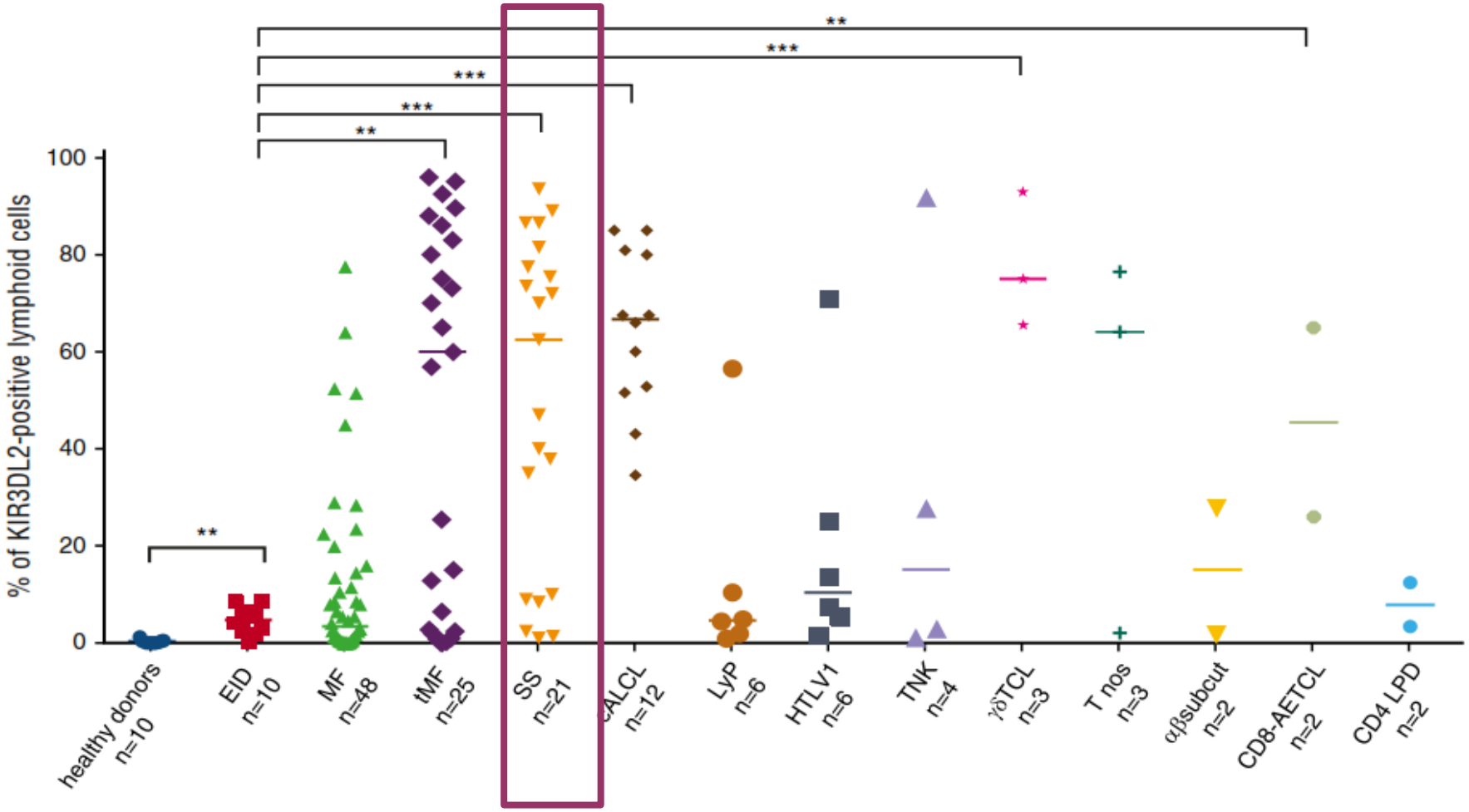
KIR3DL2 (CD158k)



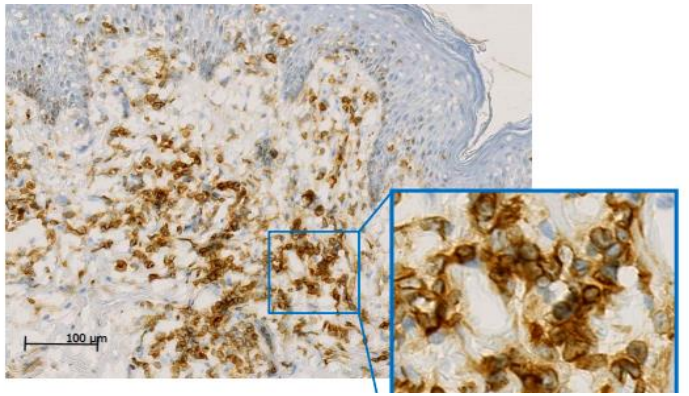
- KIR3DL2 / CD158k is expressed by Sezary cells *(Bagot et al., Blood 2001; Poszepczynska-Guigné et al., JID 2004 ; Ortonne et al., JID 2008)*
- Currently used for diagnostic and follow-up *(Moins-Teisserenc et al., JID 2015)*



KIR3DL2 is expressed by CTCL especially Sézary Syndrome



Expression of KIR3DL2 in a SS patient

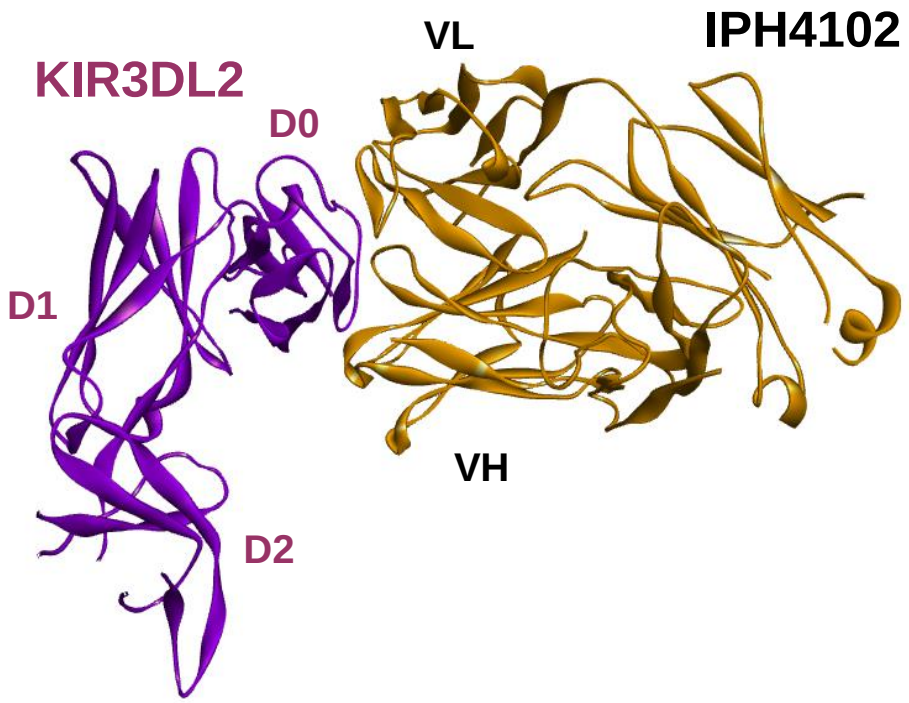


Bagot M et al; Blood 2001

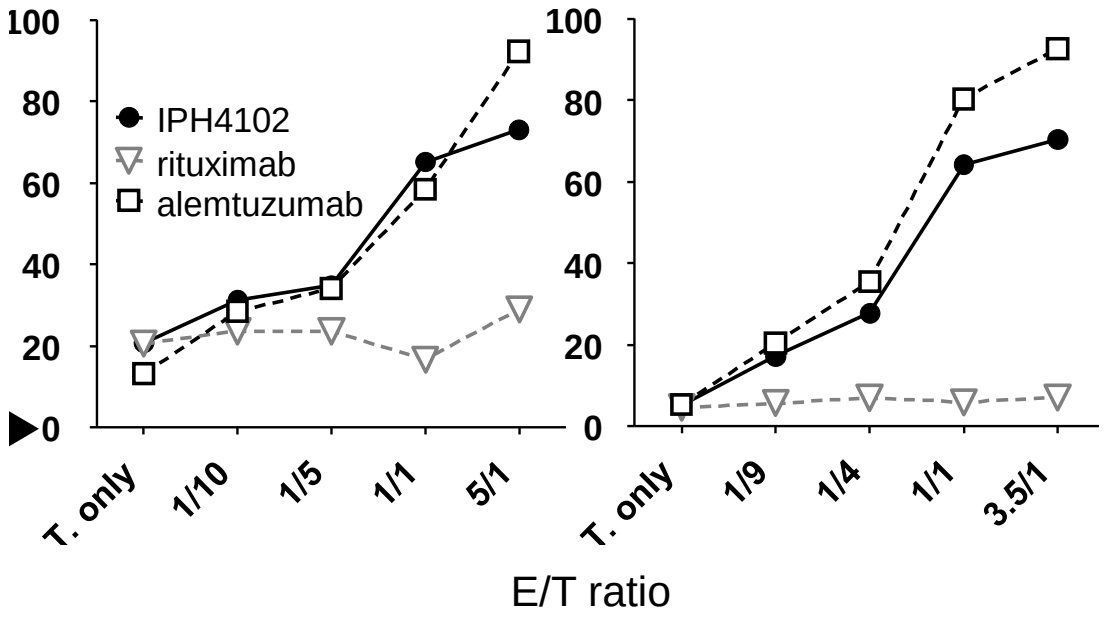
Battistella M et al; Blood 2017

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

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

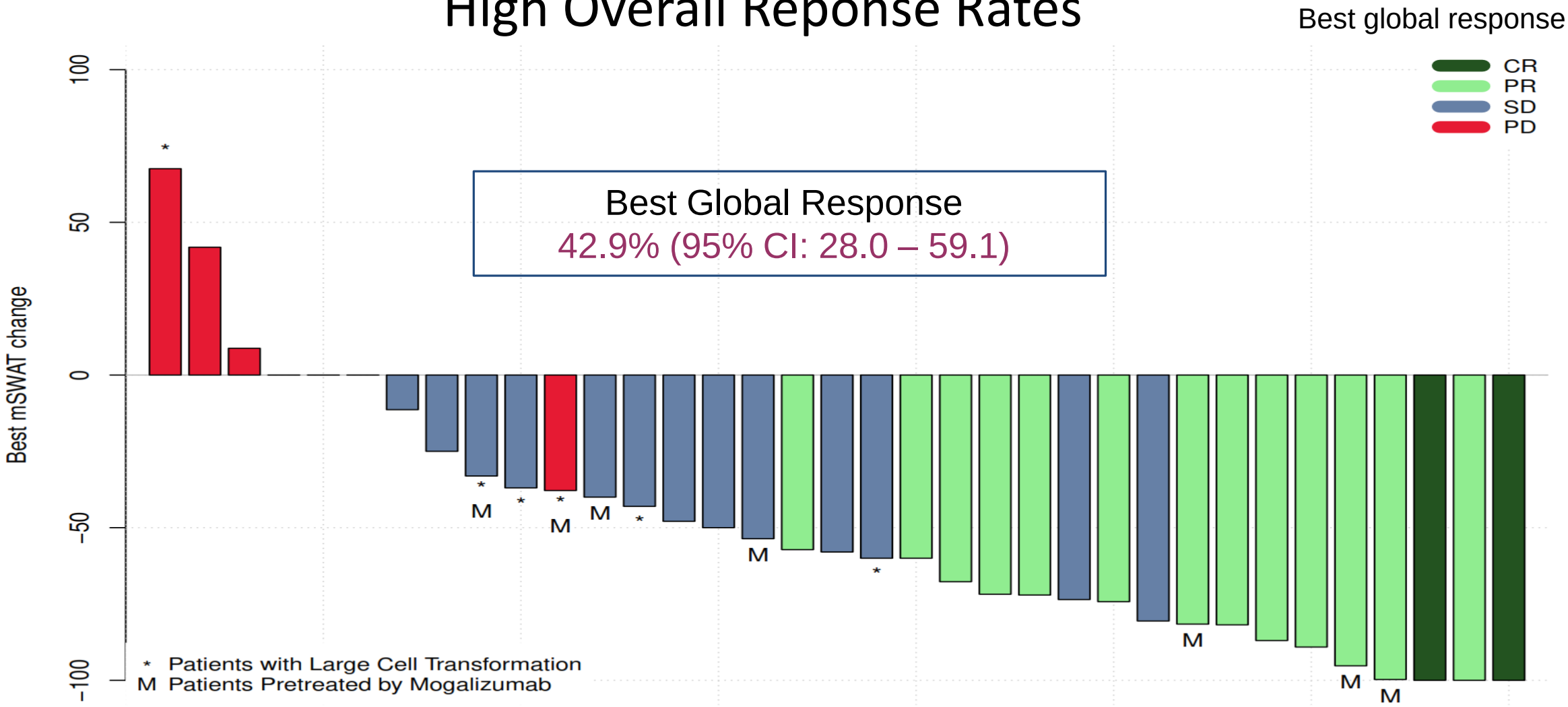


NK cells kill Sezary cells in autologous ADCC mediated by IPH4102

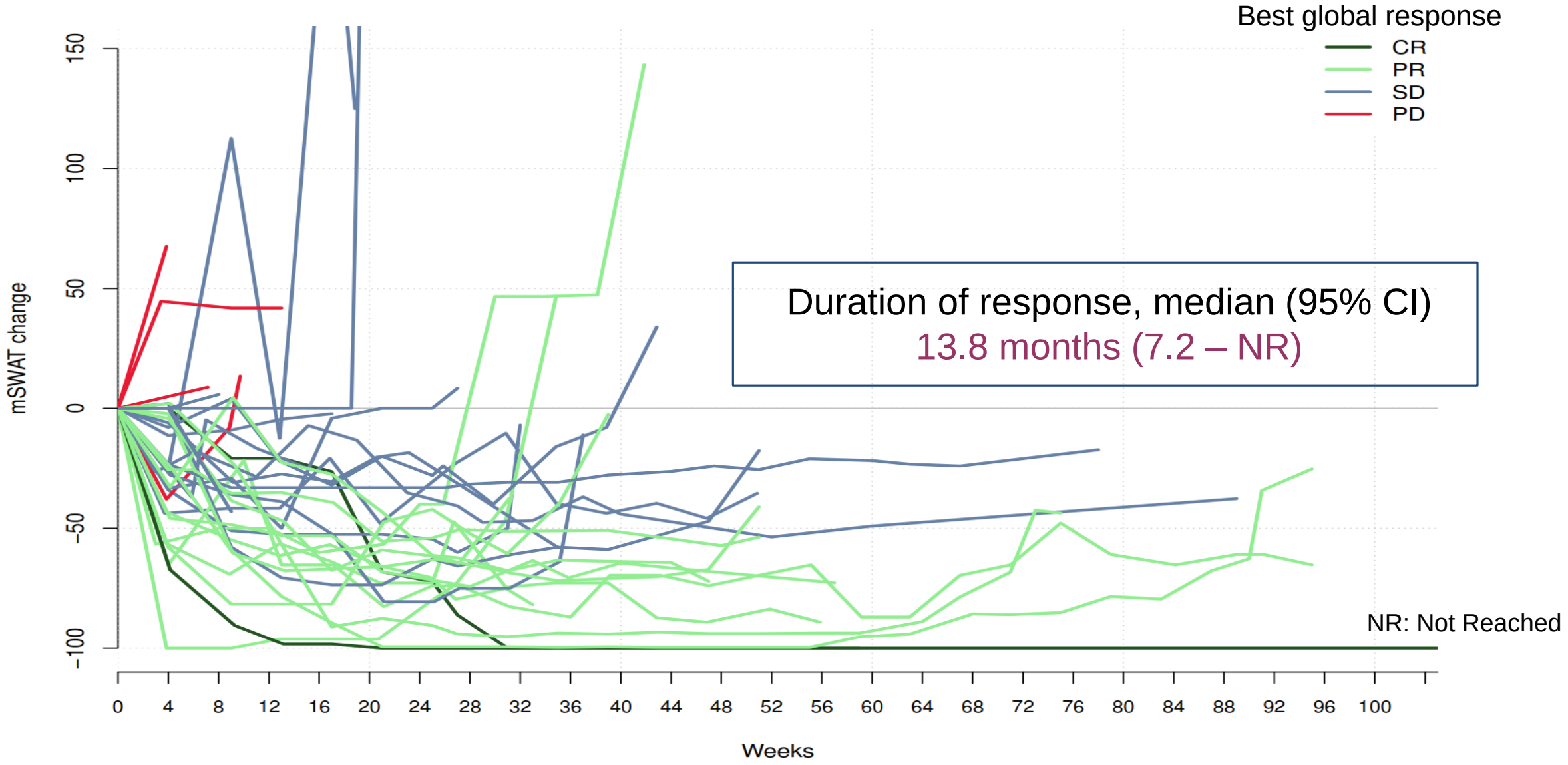


Marie-Cardine A et al, Cancer Res 2014

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

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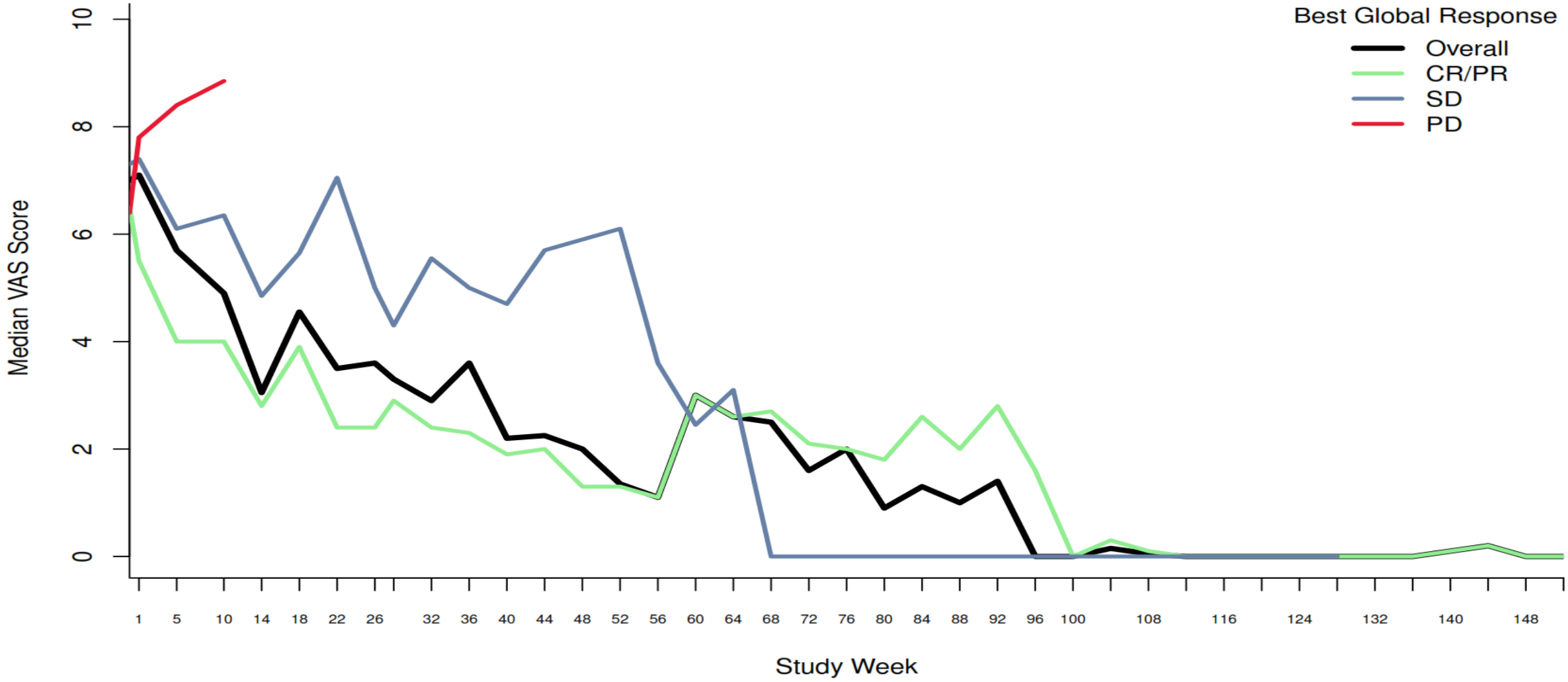
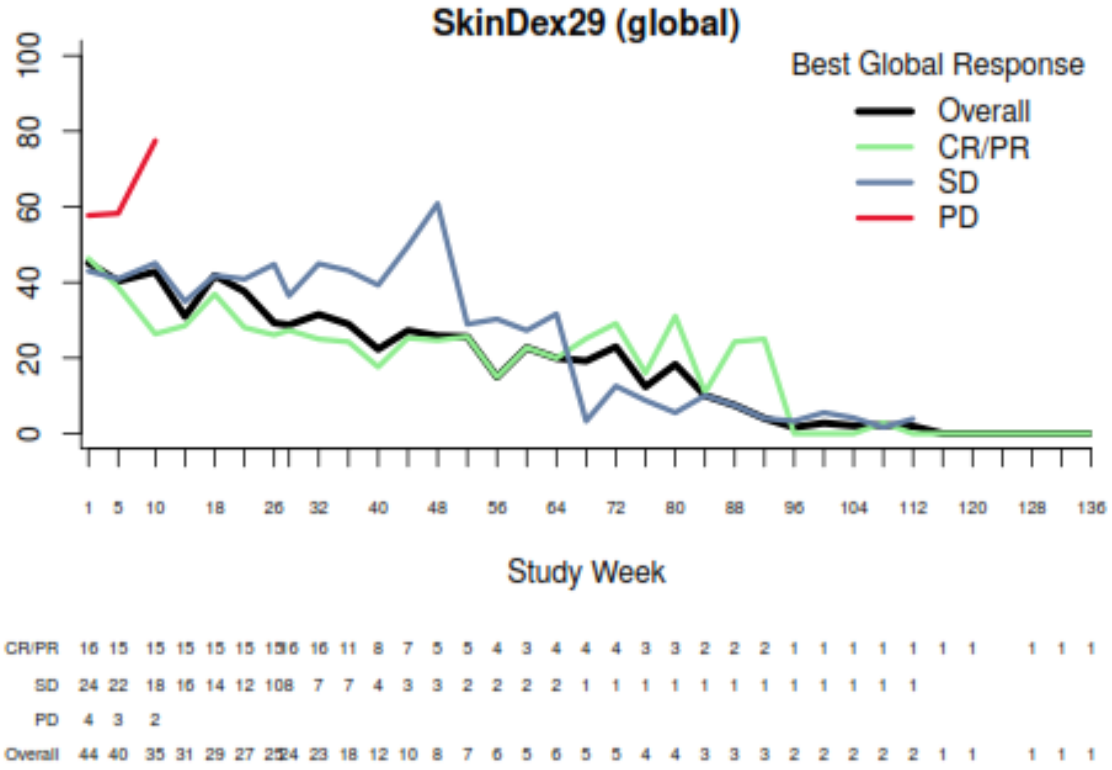
Quality of Life

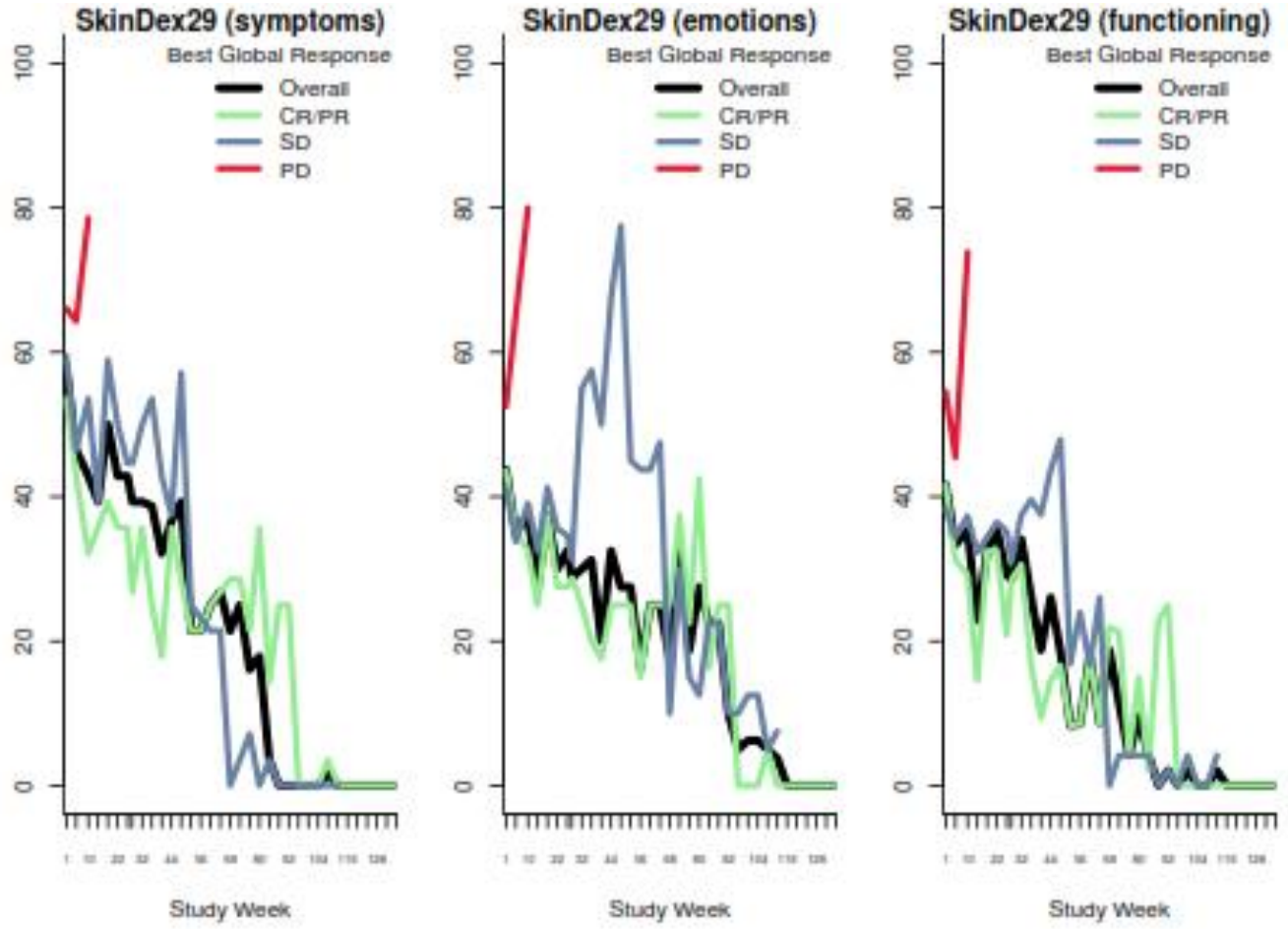
Pruritus Visual Analogue Scale Score (n = 35)



Improvement of Quality of Life

Measured by Skindex29





IPH4102 improves Skindex29 global, symptoms, emotional and functional scores over time, including in patients in global SD

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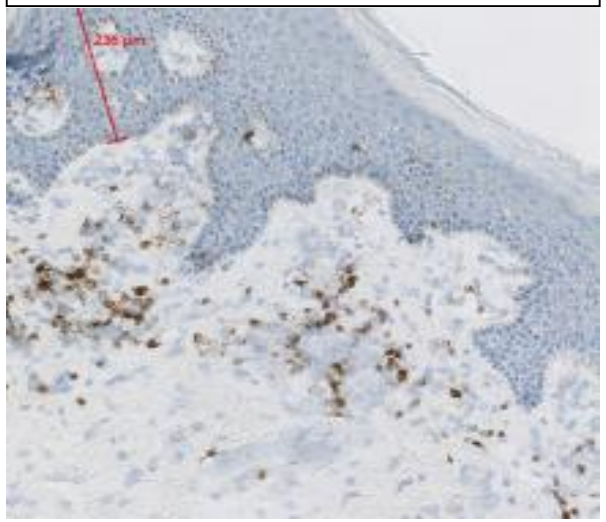
Exploratory Biomarkers

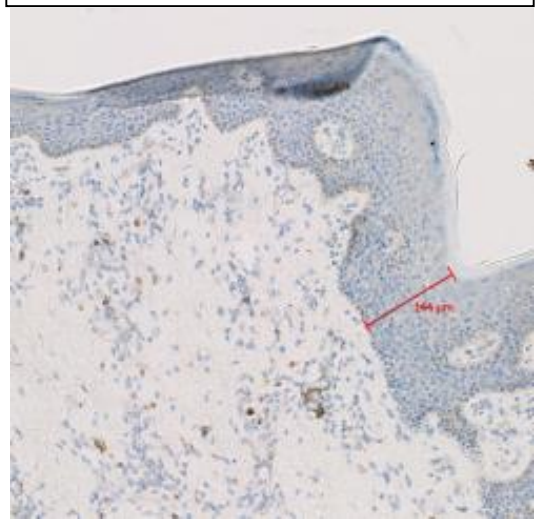
Changes in KIR3DL2 expressing cells in skin

Patient 11-005, global partial response lasting 1 year and 8 months

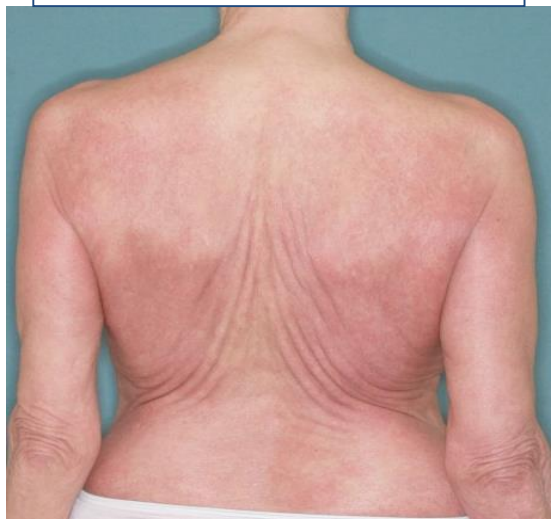
Baseline
KIR3DL2: 52%



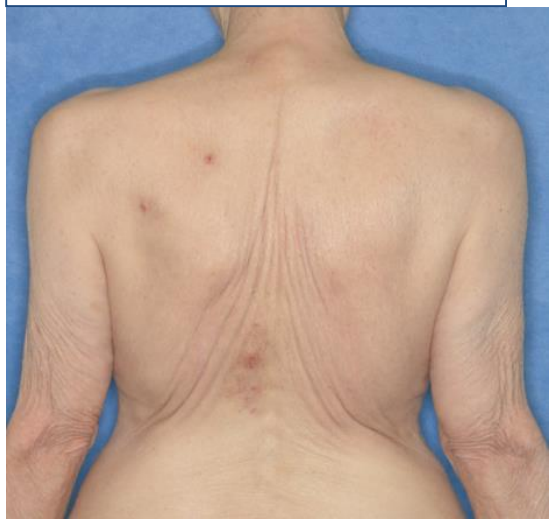
Week 5
KIR3DL2: 4.4%



Baseline
mSWAT: 80.5/1/0



Week 64
mSWAT = 5.2/0/0

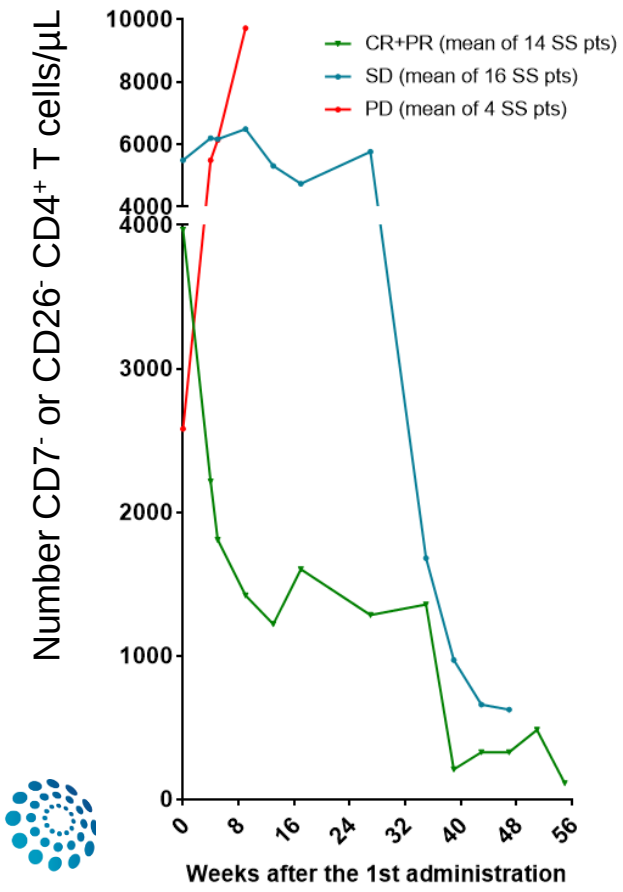


77 y old woman, received 6 prior lines of systemic therapies including Bex, IFN, HDAC and Mogamulizumab
Global PR since week 10 (starting dose : 0.05 mg/kg)

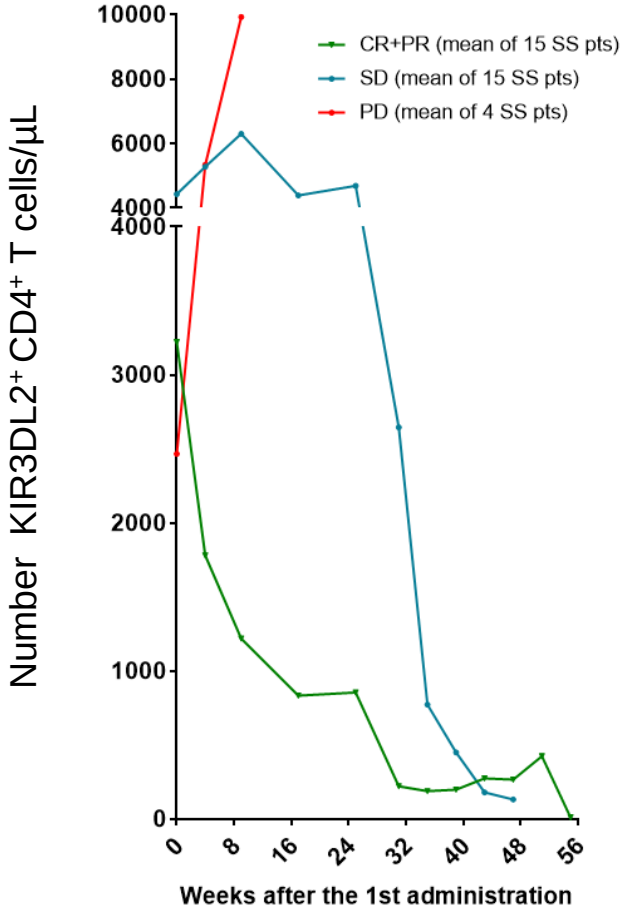
Exploratory Biomarkers

Changes of tumor cells and KIR3DL2 cells in blood

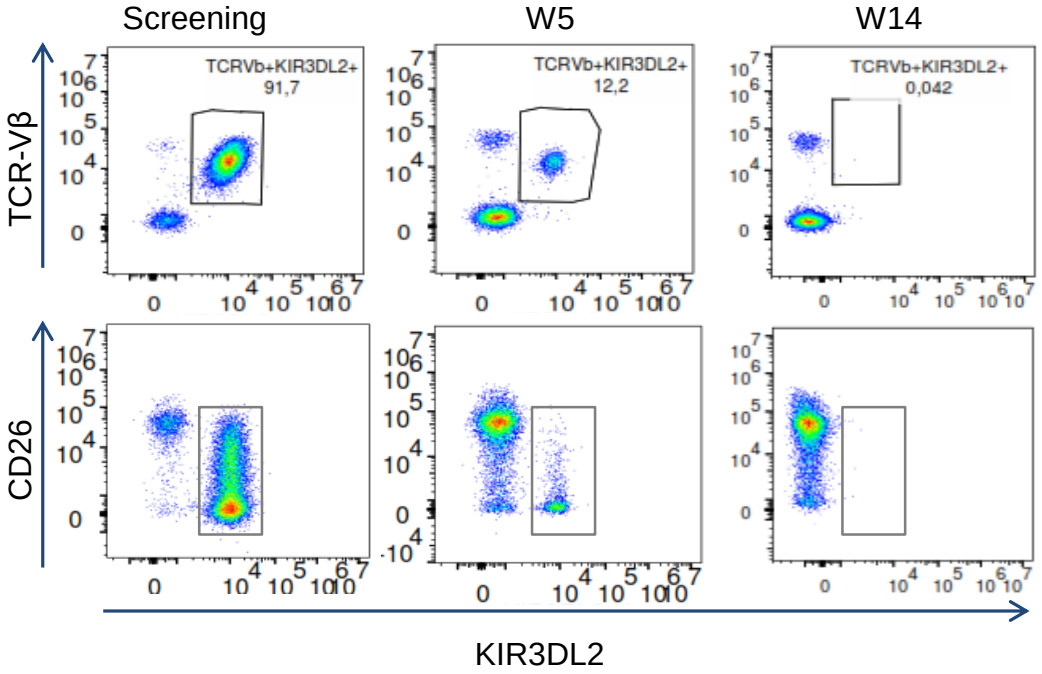
Aberrant cells



KIR3DL2+ CD4+ T cells



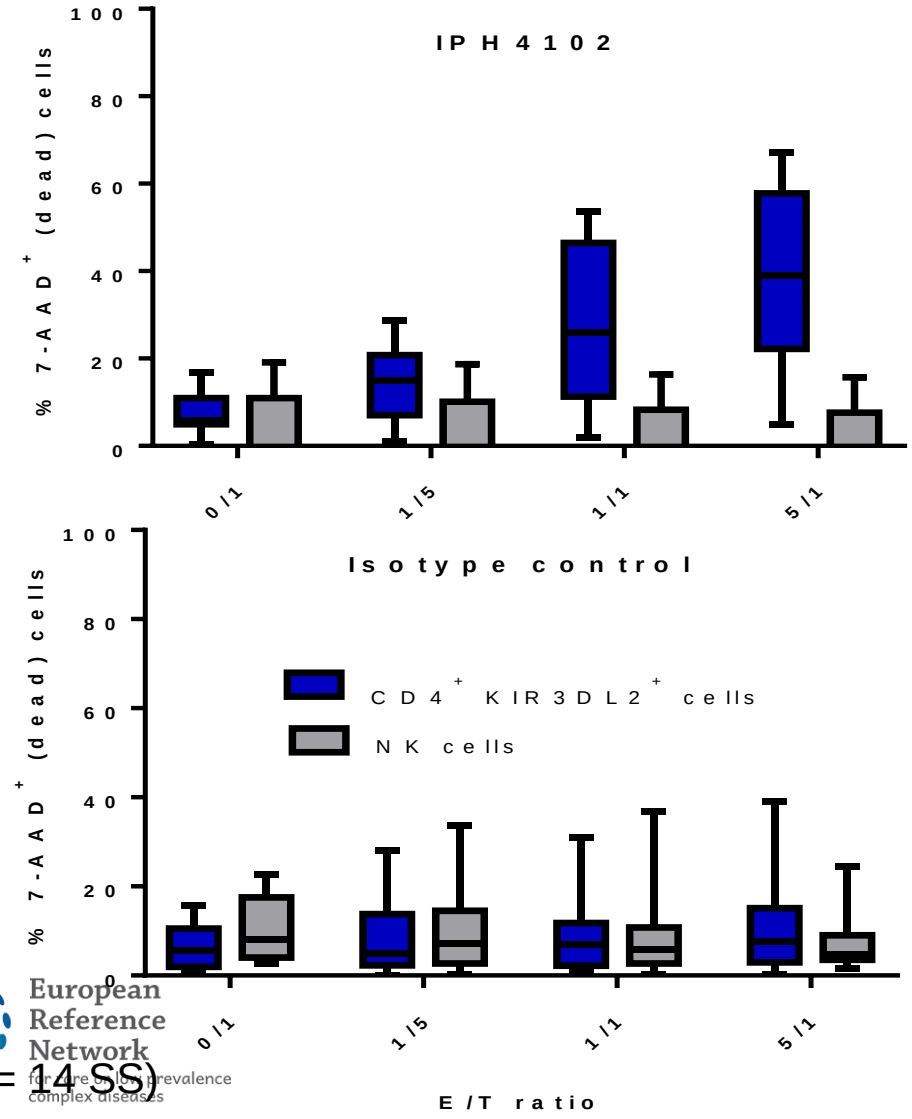
Patient 01-036, ongoing complete response > 1 year



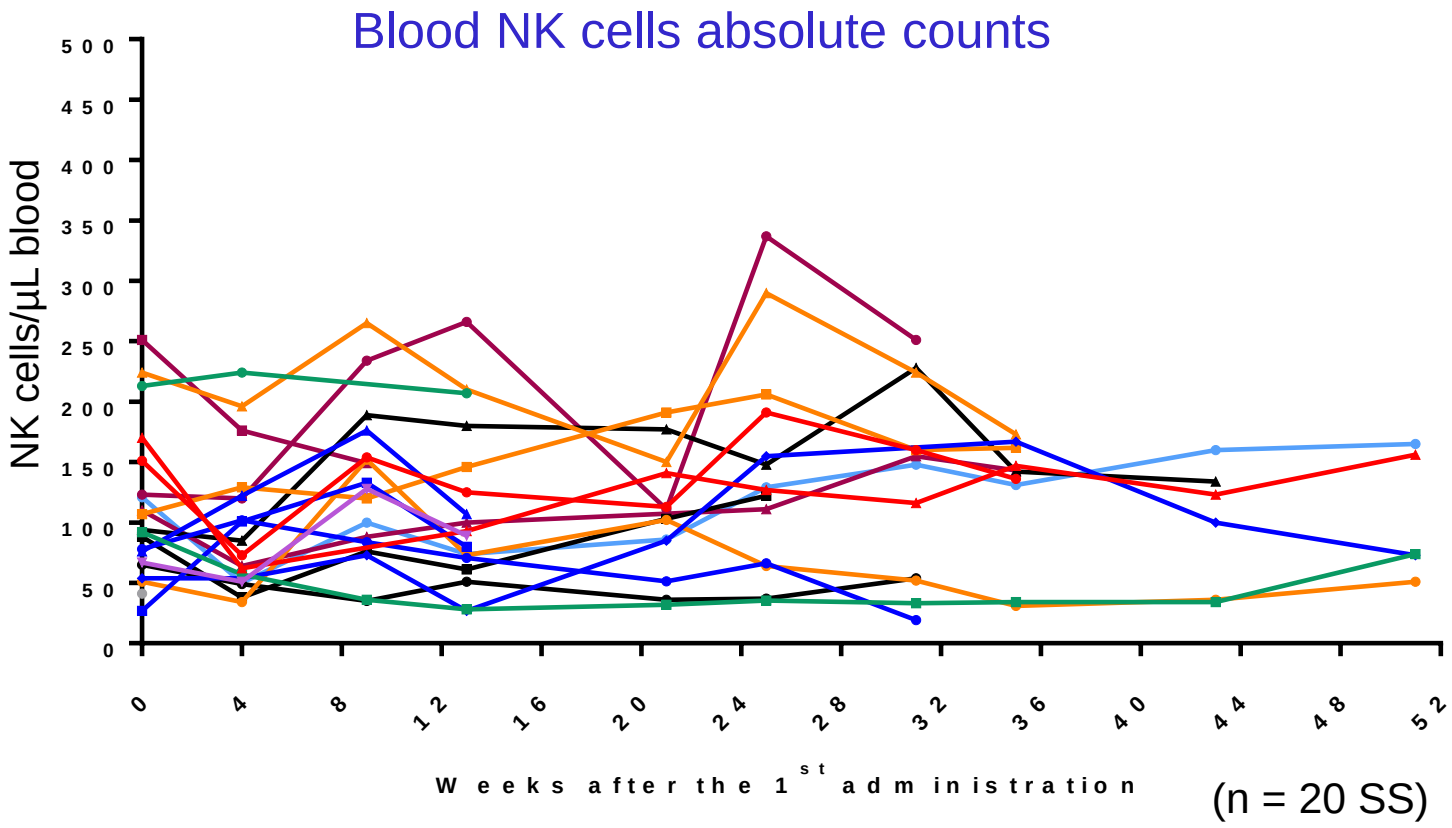
Network Hematological Diseases (ERN EuroBloodNet)

Thursdays Webinars

SS patients NK cells are functional *ex vivo* at baseline and not depleted in blood during treatment



(n = 14 SS)



(n = 20 SS)

European Reference Network for rare, low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

Thursdays Webinars

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

PHASE 2 STUDY (N≈250)
TELLOMAK : T-CELL LYMPHOMA ANTI-KIR3DL2 THERAPY

TELLOMAK

Sézary Syndrome
≥ 2 prior systemic therapies that must include mogamulizumab

Mycosis Fungoides
≥ 2 prior systemic therapies including biological agents

IPH4102
single agent

Peripheral T Cell Lymphoma
≥ 1 prior systemic therapy including anthracycline-based chemo

IPH4102
+
GEMOX

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

Thursdays Webinars