Mogamulizumab: targeting CCR4 in CTCL

Youn H Kim

Multidisciplinary Cutaneous Lymphoma Group
Stanford Cancer Institute
Stanford University School of Medicine

Disclosure statement

Youn H Kim, MD

- **Advisory Board or Steering committee**
  - Corvus, Galderma, Innate, Kyowa Kirin, Takeda
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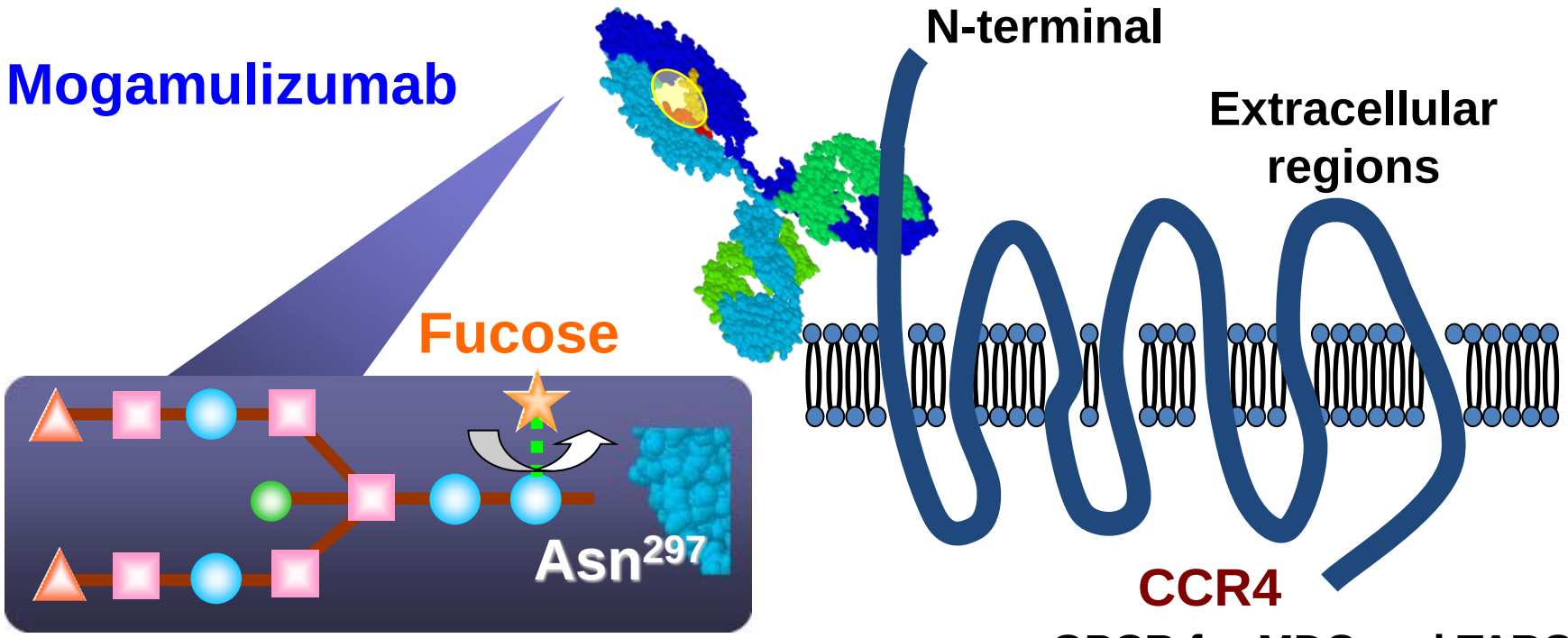
  - Corvus, CRISPR, Eisai, Elorac, Innate, Kyowa Kirin, Soligenix, Trillium

Mogamulizumab: *defucosylated humanized IgG1 anti-CCR4 mAb*



Higher ADCC due to a defucosylated Fc region by POTELLIGENT®

GPCR for MDC and TARC
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

Dual effect

Shinkawa et al. J Biol Chem 2003
Ishii et al. Clin Cancer Res 2010
Niwa et al. Cancer Res 2004

Ishida et al. Clin Cancer Res 2004
Ishida et al. Cancer Res 2006
Campbell et al. Nature 1999
Ni et al. Clin Cancer Res 2015

Official indication, regulatory status of mogamulizumab (Moga)

FDA approval 8/2018 based on MAVORIC trial

- PFS 7.7 mo Moga vs 3.1 mo vorinostat
- “For treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy”

EMA approval 11/2018

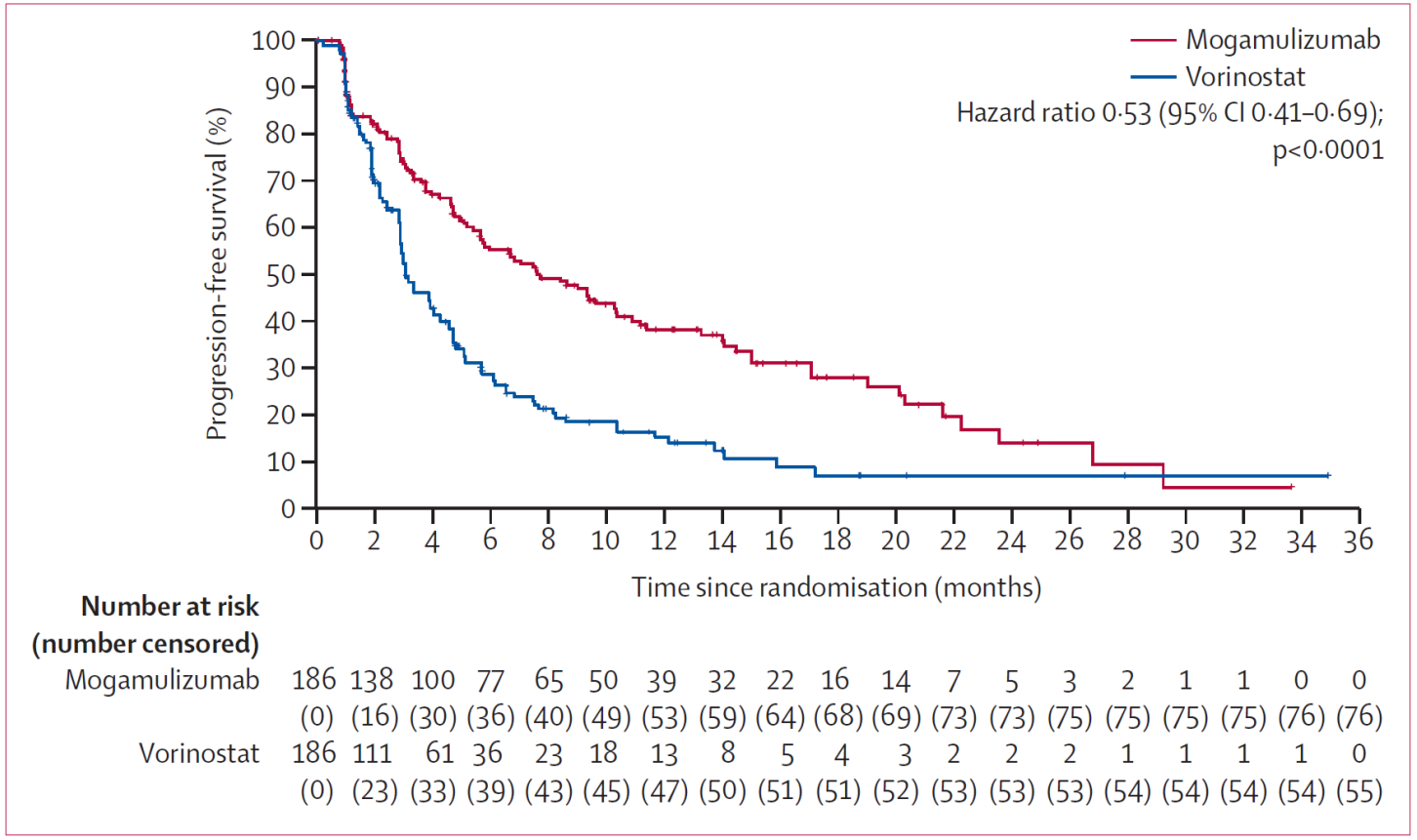
Dosage and Administration, as approved

- C1 weekly (D1, D8, D15, D22); 1 mg/kg
- C2+ D1, D15; 1 mg/kg

Currently, less freq dosing regimen under investigation (NCT04745234)

- C1 weekly (D1, D8, D15, D22); 1 mg/kg
- C2+ q 4 weeks, 2 mg/kg

Primary endpoint, PFS of moga superior over vorinostat



MAVORIC trial
Lancet Oncol 2018

Who would most likely benefit with mogamulizumab (Moga)?

Large cell transformation excluded in MAVORIC	Mogamulizumab (n=186)
Proportion of patients with an overall response by global assessment*†	52/186 (28%)
Overall responses in patient subgroups	
Mycosis fungoides	22/105 (21%)
Sézary syndrome	30/81 (37%)
Stage IB or IIA	7/36 (19%)
Stage IIB	5/32 (16%)
Stage III	5/22 (23%)
Stage IV	35/96 (36%)
Duration of response, months	14·1 (8·4–19·2)
Mycosis fungoides	13·1 (4·7–18·0)
Sézary syndrome	17·3 (9·4–19·9)
Compartment response*‡	
Skin	78/186 (42%)
Blood	83/122 (68%)
Lymph nodes	21/124 (17%)
Viscera	0/3 (0%)

Response rate is higher in Sézary syndrome

Likelihood of response was <u>not</u> associated with

- **Number of prior tx**
- **Type of immediate prior tx**
  (e.g. immune-stimulatory, neutral, inhibitory, HDAC-i)

- **Most effective in blood compartment**
- **TTR blood 1 mo,** skin 3 mo, LN 3 mo
- **DOR blood 26 mo,** skin 21 mo, LN 16 mo

ORR12
(proportion of pts with global responses lasting at least 12 mo):

- **Global/composite 11% (20/186)**

More likely in:

- Sézary syndrome *(P = 0.016)*
- Stage IVA_1 *(P < 0.001)*
- Any blood involvement *(P = 0.03)*

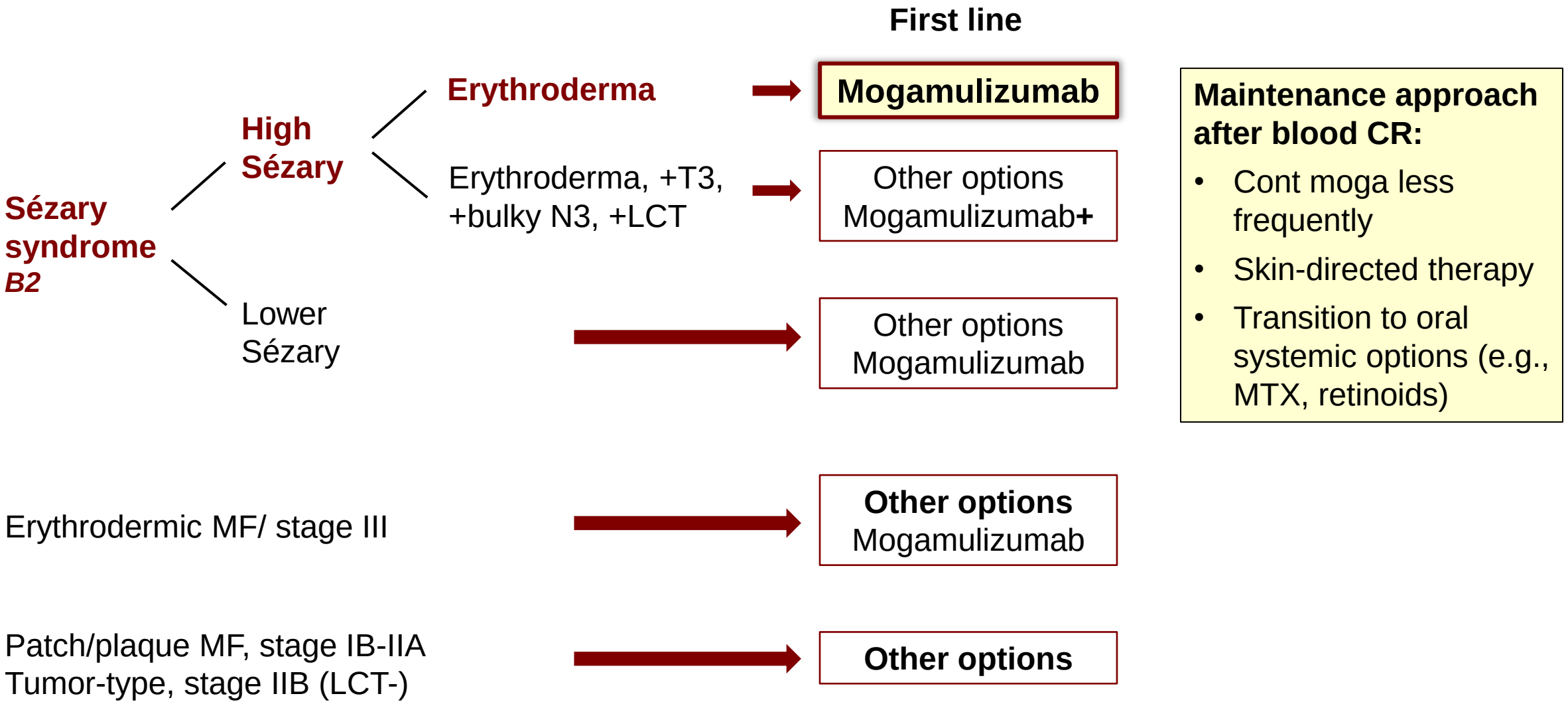
TTNT, median

- All pts 11.0 mo
- MF 8.8 mo; SS 12.9 mo

MAVORIC trial
Kim et al. Lancet Oncol 2018
Kim et al ASH 2020
Kim et al. ICML 2019
Horwitz et al. Leuk Lymphoma 2021

Where is mogamulizumab in the treatment landscape/algorithm?

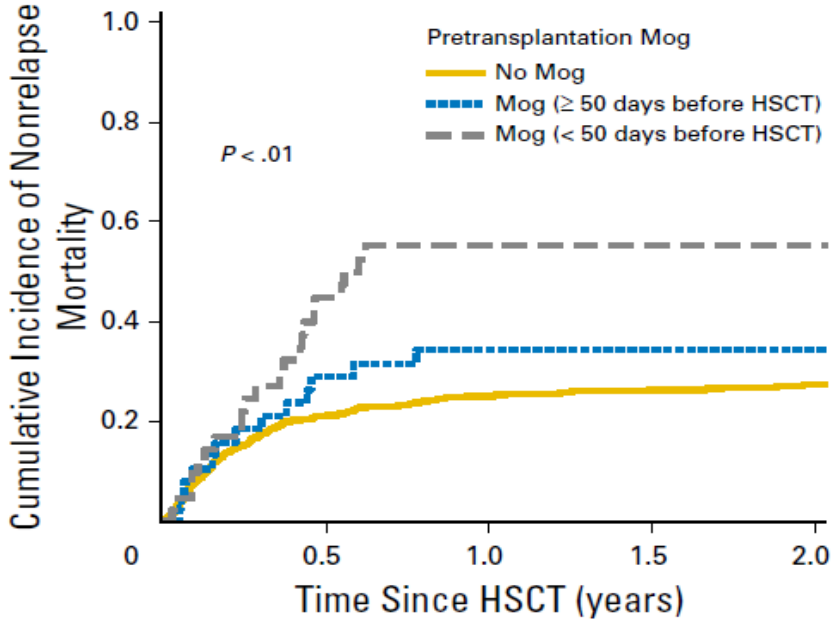
Prioritize in those with high-burden blood disease – less preferred in T3/N3/LCT



Safety/toxicity Issues with mogamulizumab therapy

- **Infusion-related reaction (IRR), 32%**
  - Usually limited to first dose, easily manageable
  - First dose, premed w/ diphenhydramine, acetaminophen; follow local IRR protocols (rarely need systemic steroids)
- **Moga associated rash (MAR)**
  **key treatment limiting toxicity
- Other immune-mediated toxicities, very rare
  - Hepatitis, polymyositis, colitis, myocarditis
- Pharmacologic ↓ALC/lymphopenia
  - ACV or valacyclovir prophylaxis if h/o recurrent HSV, recent VZV/zoster
- **Potential increased risk of severe GVHD and NRM**
  - Reports in ATLL, if moga given as bridge to allo HSCT
  - Studies needed in CTCL (safe if > 6 mo off Moga)

ATLL, ↑ severe GVHD



No. at risk					
No Mog	914	442	340	294	272
Mog (≥ 50 days before HSCT)	38	18	11	7	4
Mog (< 50 days before HSCT)	42	13	3	2	2

Fuji et al. JCO 2016

Kim et al. Lancet Oncol 2018
Bagot et al. Dermatol Therapy 2022
Ishitsuka et al. Int J Hematol 2015
Kwan JACC Case Rep 2021; Ogura et al. JCO 2014
Dai et al. JAMA Derm 2018, Fuji et al. JCO 2016

Mogamulizumab associated rash (MAR), a spectrum of presentations

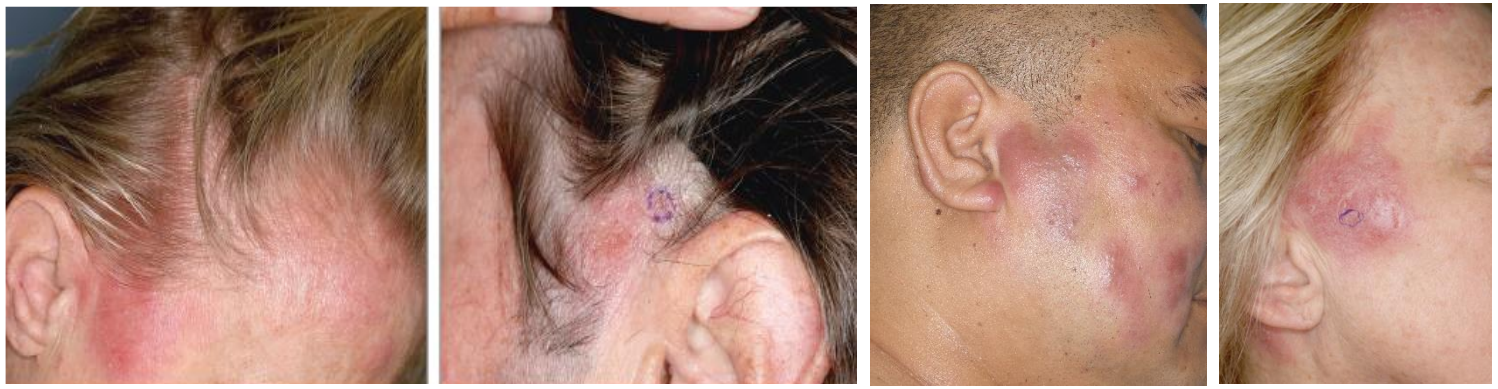
- 24% in MAVORIC – **real world >30%**
- Clinical suspicion is key (median time to MAR, 3-4 cycles/105 days)
- **Variable clinical and path features**
- **Biopsy is essential for distinguishing MAR from pt's CTCL**
  - ✓ Characterize pre-moga path/molecular

MAR clues

  - ❑ ↑granulomatous/histiocytic infiltrate
  - ❑ IHC (e.g., ↑CD8+ T-cells,)
  - ❑ TCR clonality /NGS preferred (diverse/polyclonal TCR)

- **Management based on MAR severity**
  Optimize benefit vs risk/QOL impact
  - **Mild/limited,** ok to cont Moga, topicals
  - **Mod/severe,** hold/stop Moga, systemic steroids +/- ECP, MTX
  - Photo-protection
- Retreatment in pts w/ prior mod/severe MAR
  - Minimally necessary length of Moga
  - Moga + ECP (ongoing trials) or MTX

****FMF-like plaques or nodules of the H/N region, often a/w alopecia**



Papules/plaques: psoriasiform, lichenoid, granulomatous features

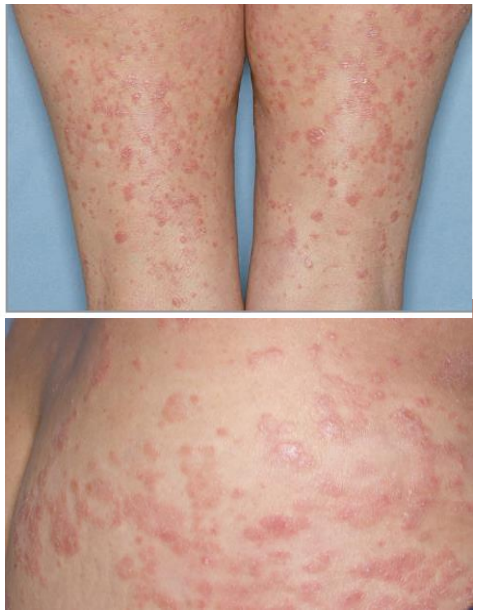
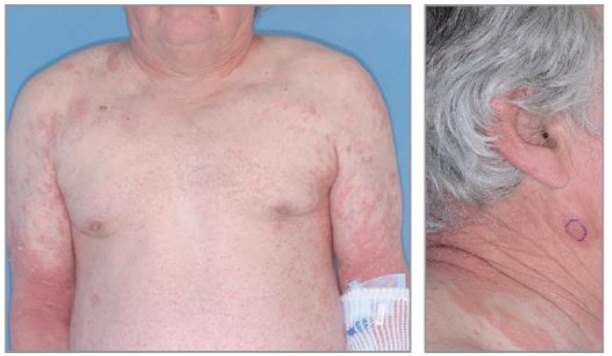
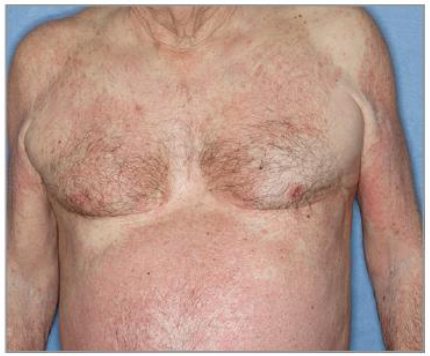


Photo-accentuated rash



Morbilliform rash



MAR more likely in SS,
not a/w prior CTCL therapy

% response in MAR+ vs MAR-
- SS, 56% v 30%, *P=0.02*
- MF, 32% v 19%, *P=0.21*

MAVORIC study, Musiek et al. ASH 2020

Kim et al. Lancet Oncol 2018
Chen et al. JAMA Dermatol 2019
Hirotsu et al. JAMA Dermatol 2021
Wang et al. Am J Surg Pathol 2020
Trum et al. Br J Dermatol 2022
de Masson et al. Blood 2022

How to maximize efficacy, optimizing combination or sequential approaches

How to maximize efficacy w/ acceptable toxicities

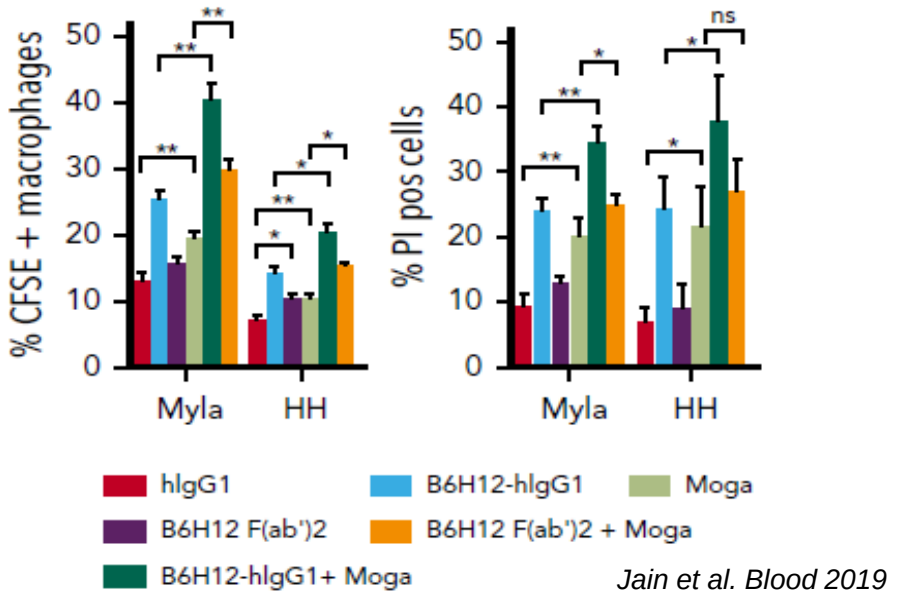
Address active compartments or profile (e.g., LCT, N3) not well treated by Moga monotherapy

- Low-dose TSEBT + Moga (NCT04256018, Stanford; EU trial NCT04128072)
- Combination or sequential strategies w/ brentuximab (NCT05414500) or other

Potential for immune augmentation, clinical synergy

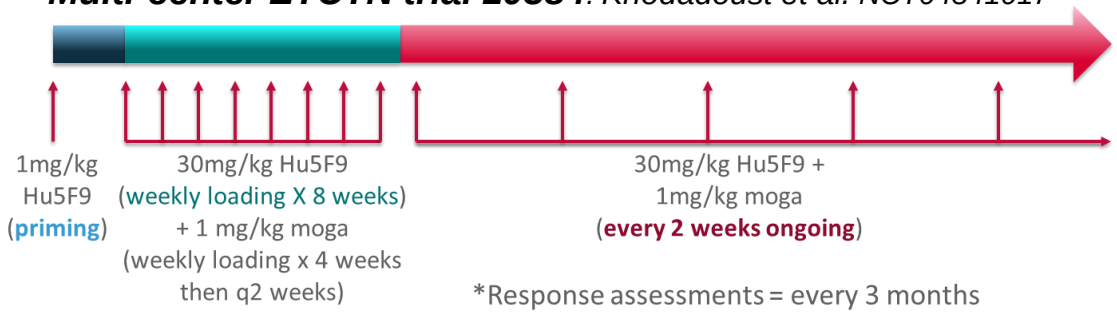
- Magrolimab + Moga trial (ETCTN, NCT04541017)
- Third-party NK cells (LD w/ flu/Cy) + Moga (NCT04848064)
- rhIL-15 + Moga (NIH NCT04185220)
- Moga + ECP (NCT04930653, NCT04676087), ? lower MAR

Synergistic activity of anti-CD47 + moga, enhancing phagocytosis and ADCC



Jain et al. Blood 2019

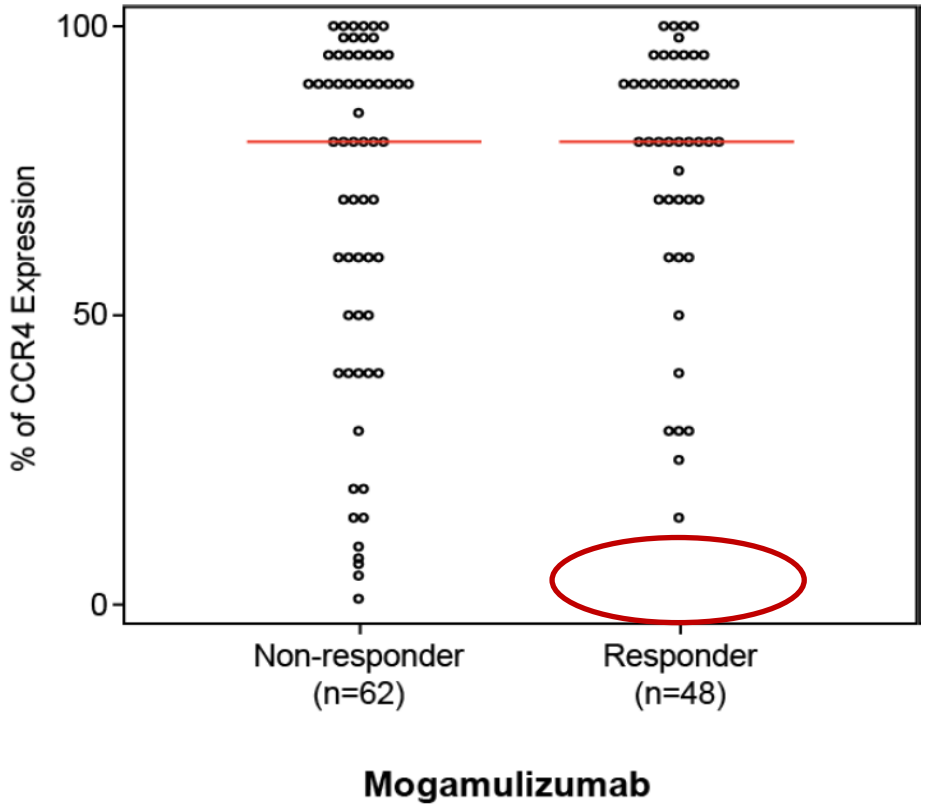
***Multi-center ETCTN trial 10384**. Khodadoust et al. NCT04541017*



Understanding predictors of response and mechanism of resistance

Relevance of pre-treatment CCR4 expression

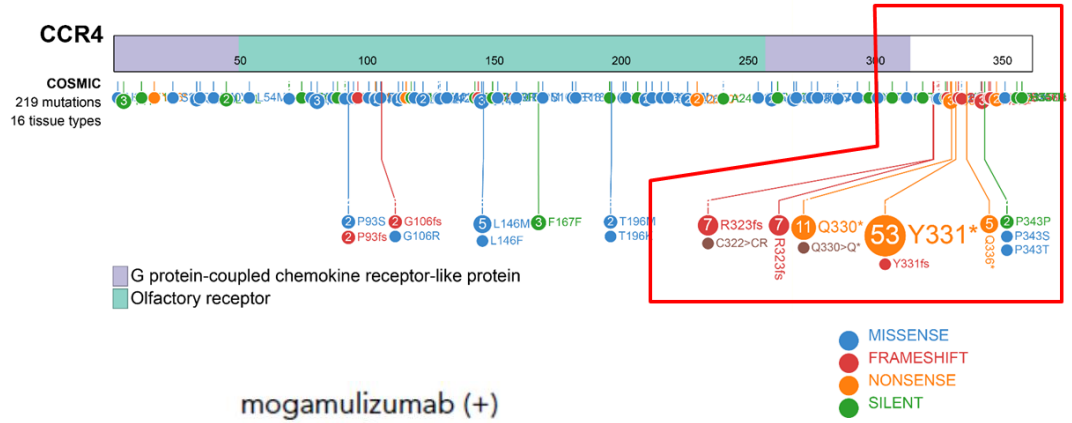
- In MAVORIC, 97% of patients had positive CCR4 expression (skin bx, >10% infiltrating lymphoid cells)
- Overall, no correlation seen between CCR4 level and clinical response
- However, a subset with CCR4 <10% lacked response

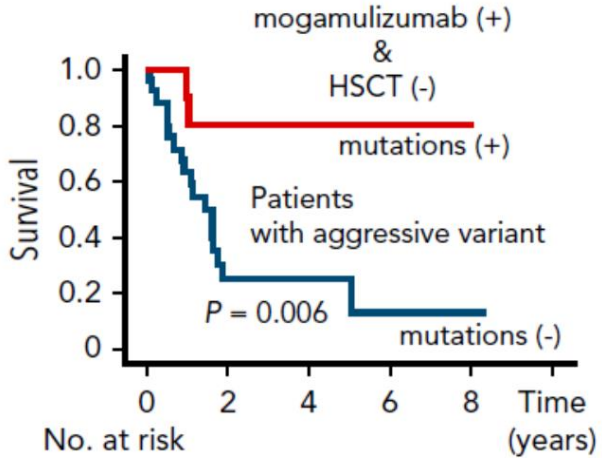


Kim et al. Lancet Oncol 2018
Appendix p.30

CCR4 gain-of-function mutations

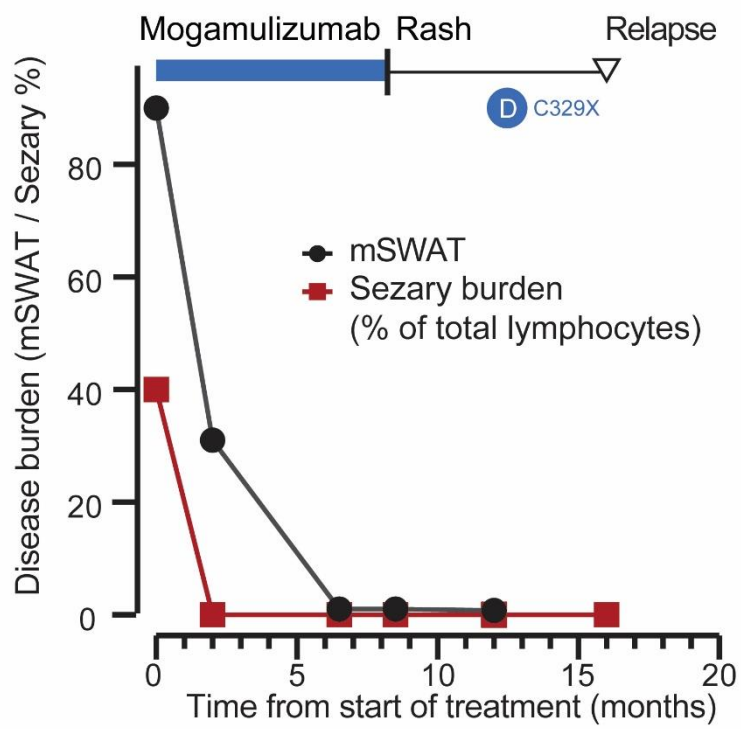
- C-terminal gain-of-function mutations in ~1/3 of ATLL
- Increases CCR4 surface expression
- Predicts durable response to mogamulizumab





Sakamoto et al Blood 2018.

Sézary syndrome



CCR4 Gain-of-Function mutations rare in CTCL

Excellent durable response to moga in a Sézary patient with CCR4 GoF mutation

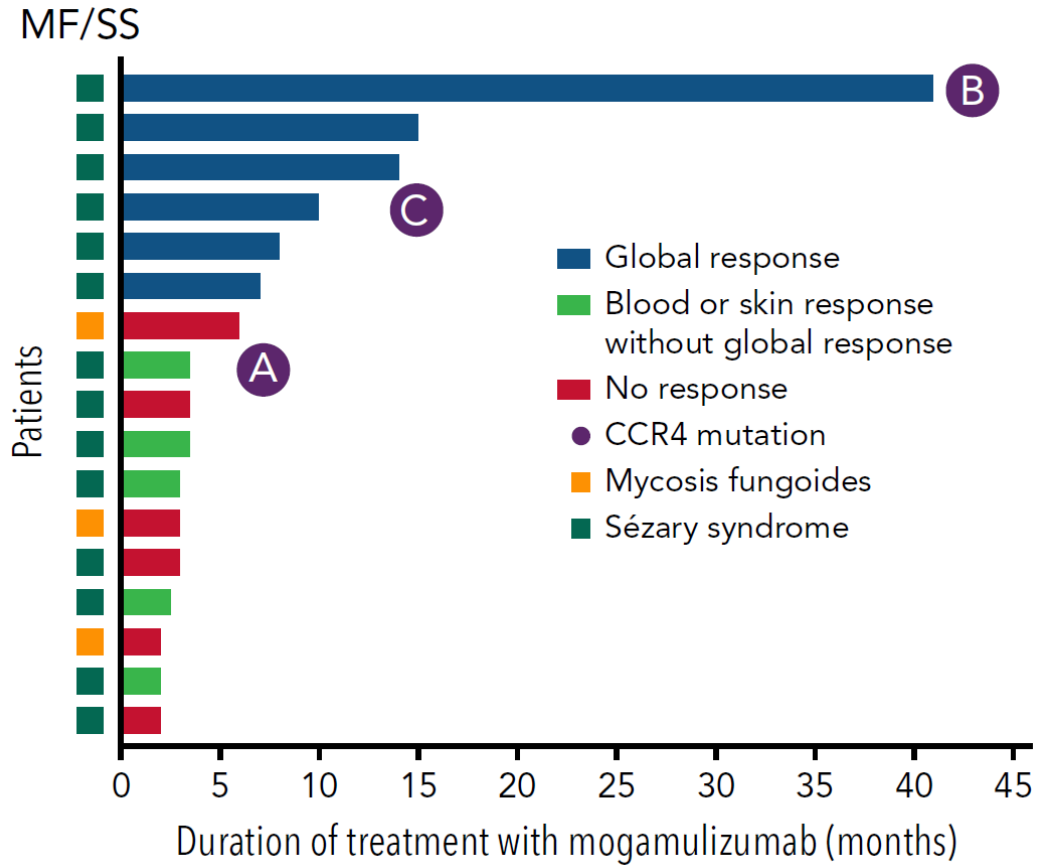
Complete lack of response in 2 others with mycosis fungoides and large cell transformation

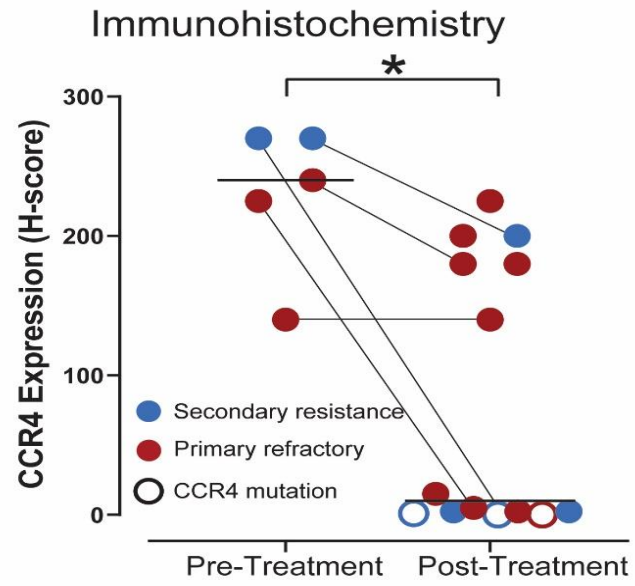
Beygi and Duran et al, Blood 2022

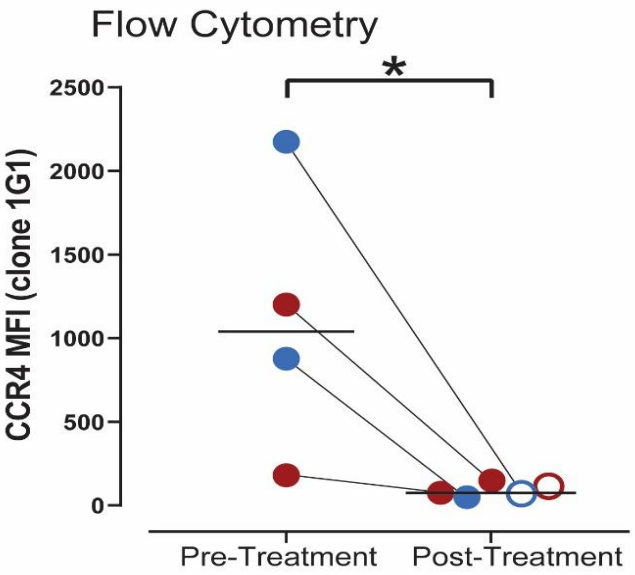
Mechanisms of resistance to mogamulizumab

Stanford experience

17 patients with primary or secondary resistance to mogamulizumab



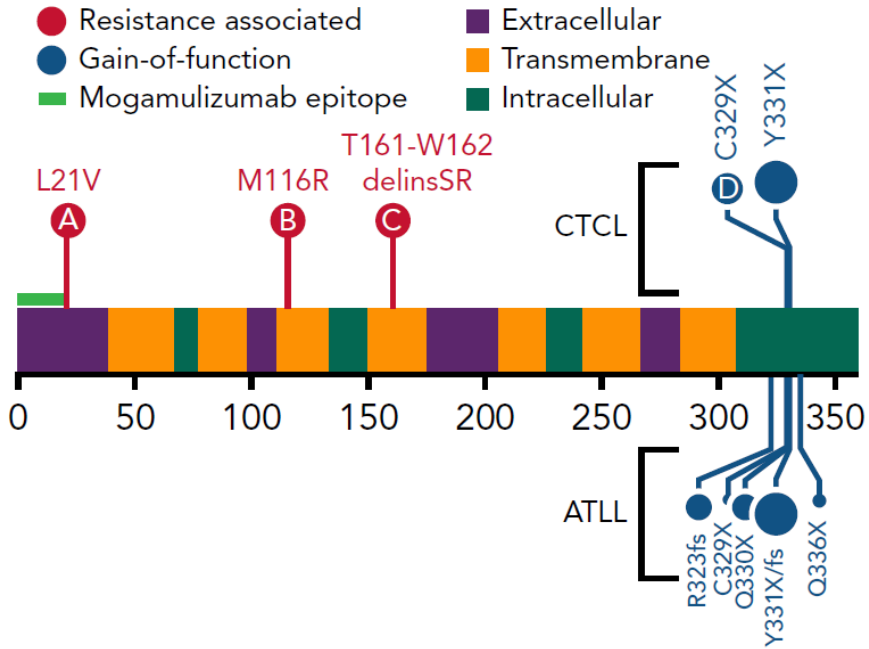


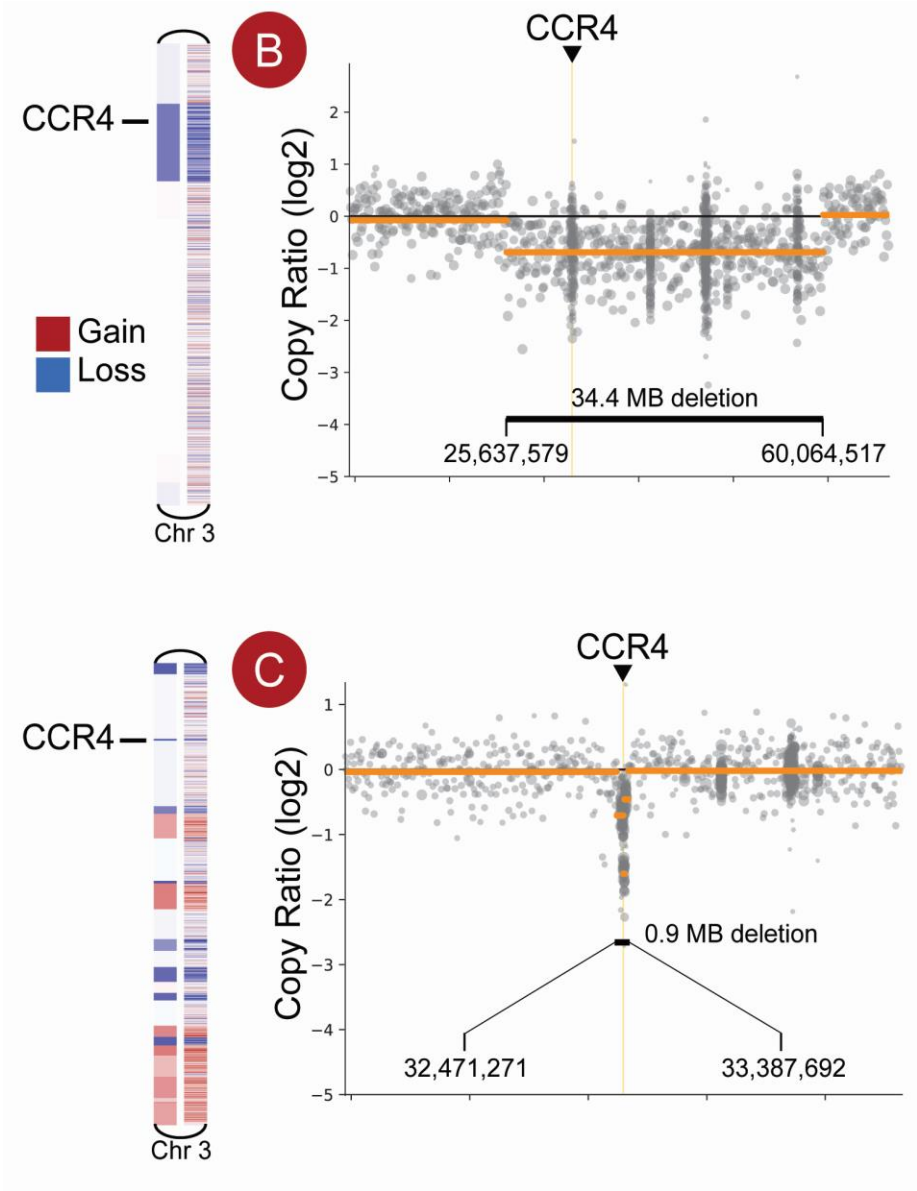


Beygi and Duran et al, Blood 2022

Resistance-associated mutations and copy loss of CCR4

- Three patients with emerging mutations in CCR4
- Two of these patients had additional deletions of CCR4
- All 3 with CCR4 genomic alterations with loss of CCR4 expression

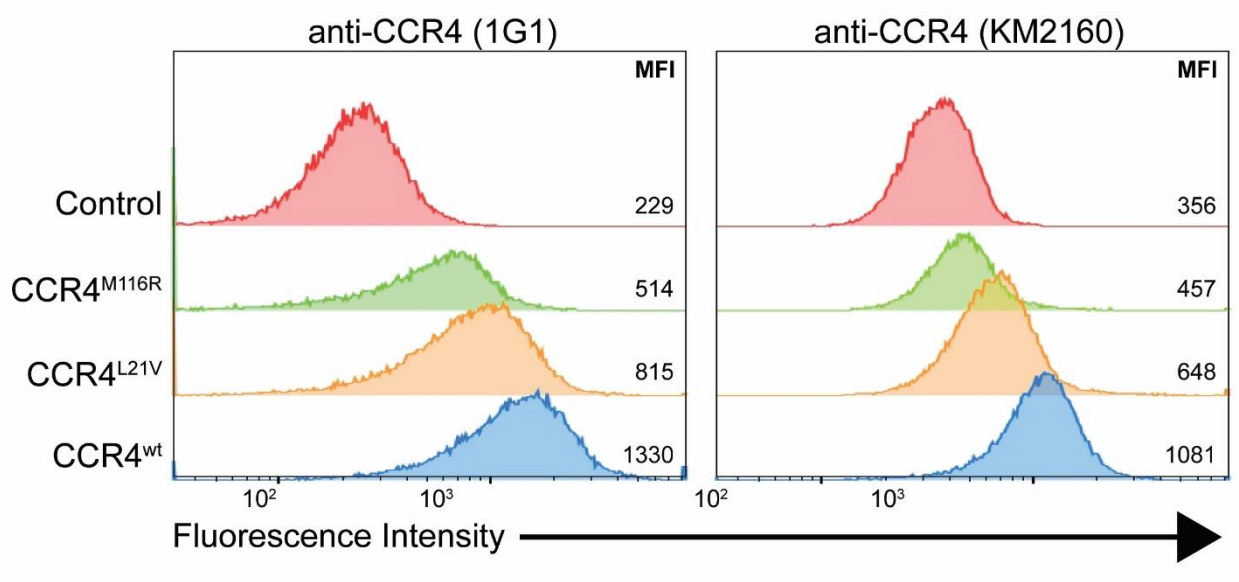




Beygi and Duran et al, Blood 2022

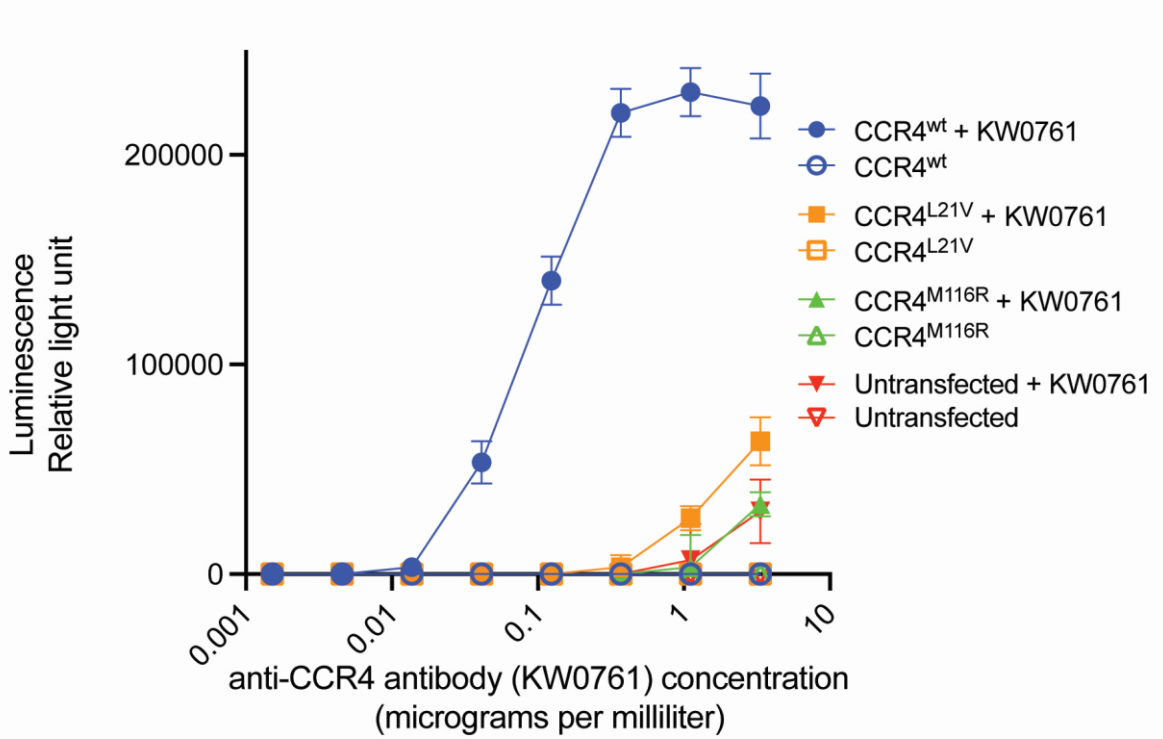
Mutations inhibit binding and ADCC by mogamulizumab

Flow cytometry anti-CCR4



Transfection of mutated L21V and M116R into Jurkat cells resulted in decreased CCR4 expression as compared with wild-type

Antibody-dependent cellular cytotoxicity



Beygi and Duran et al, Blood 2022

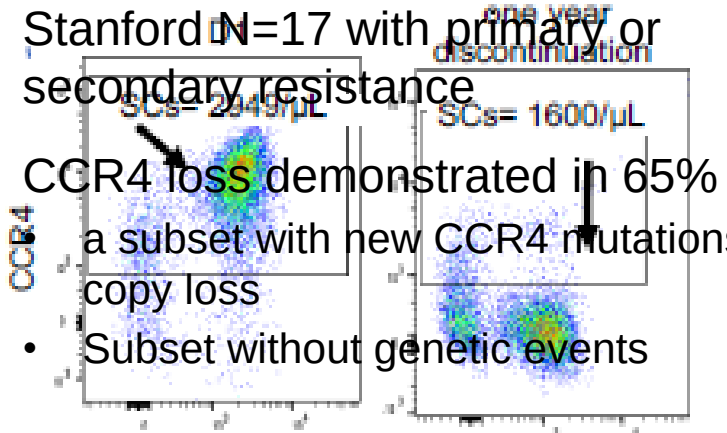
CCR4 loss as a mechanism of resistance to mogamulizumab

Stanford: N=17 with primary or secondary resistance

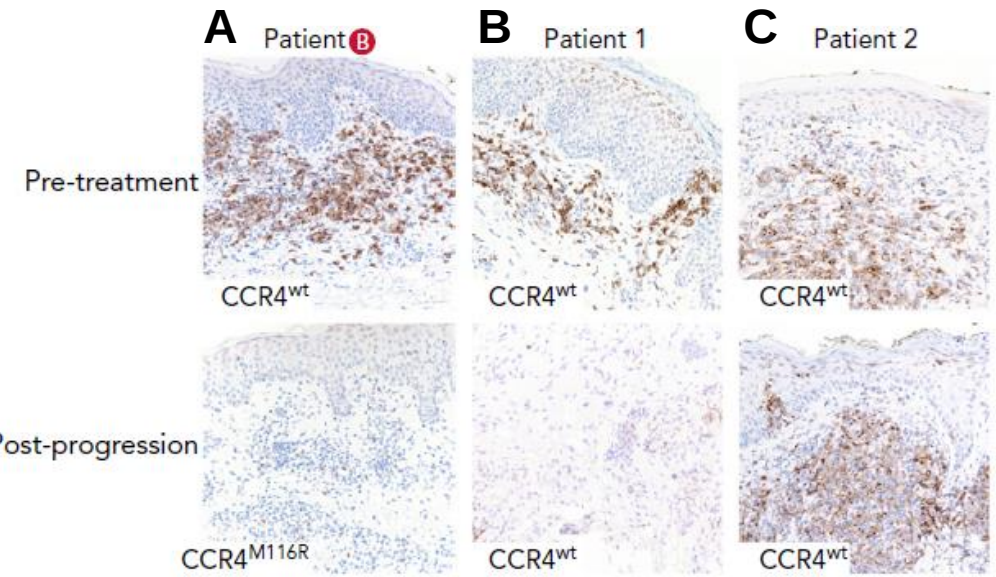
CCR4 loss demonstrated in 65%

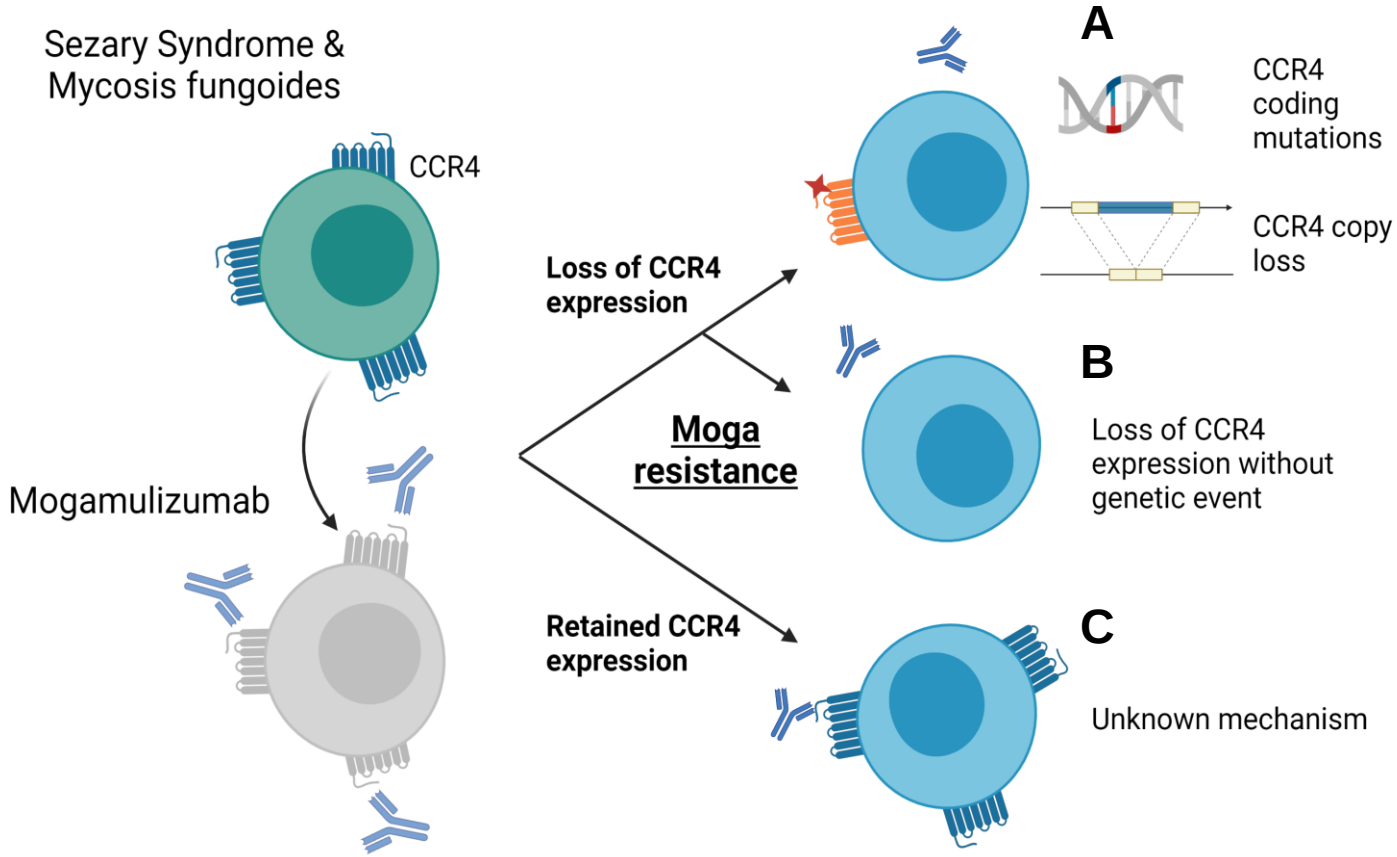
- a subset with new CCR4 mutations or copy loss
- Subset without genetic events

Others retained CCR4, unclear mechanism of resistance



Ramos et al, Br J Dermatol 2022





Beygi and Duran et al, Blood 2022

Take home summary: mogamulizumab in MF/SS-CTCL

- **Who is most likely to benefit from mogamulizumab?**
  - Great activity in Sézary syndrome patients / blood involvement
  - Not ideal in addressing skin tumors, LCT, LN/N3, or visceral disease as monotherapy
  - Pts on moga with loss of CCR4 expression may signal resistance
- **Recognition and management of potential toxicities a/w mogamulizumab**
  - Mogamulizumab-associated rash (MAR, >30%), variable features but can often mimic CTCL
    - Biopsy and high index of suspicion needed to determine progression of CTCL from MAR
    - Management depends on MAR severity & clinical benefit of Moga
    - Studies in progress to better understand the mechanism and relevance of MAR
  - Safety of Moga as bridge to allogeneic HSCT needs further study
- **Studies are ongoing to optimize risk/benefit in those treated with mogamulizumab**
  - Combination or sequentical partners that can address weaknesses of Moga needs to be explored
  - Strategies to address MAR w/o sacrificing efficacy is desired

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