F3151

Lymphocyte Pharmacodynamics and Safety of Fingolimod Use in Patients Previously Treated With Alemtuzumab

Krzysztof W Selmaj,[1] Ann D Bass,[2] Keith R Edwards,[3] Per S Sørensen,[4] David H Margolin,[5] Linda Kasten,[6] Jeffrey A Cohen[7]; on behalf of the CAMMS223 and CARE-MS I and II Investigators

[1]Medical University of Łódź, Łódź, Poland; [2]Neurology Center of San Antonio, San Antonio, TX, USA; [3]MS Center of NE New York, Latham, NY, USA; [4]Danish Multiple Sclerosis Center, Rigshospitalet, Copenhagen, Denmark; [5]Genzyme, a Sanofi company, Cambridge, MA, USA; [6]PROMETRIKA, LLC, Cambridge, MA, USA; [7]Cleveland Clinic, Cleveland, OH, USA

INTRODUCTION

- Alemtuzumab is a humanized anti-CD52 monoclonal antibody approved for patients with relapsing-remitting multiple sclerosis (RRMS) in over 40 countries
- Alemtuzumab demonstrated superior efficacy over 2 years versus high-dose subcutaneous interferon beta-1a (SC IFNB-1a) in patients with active RRMS, who were treatment-naive (CAMMS223 [NCT00050778] and CARE-MS I [NCT00530348])[1,2] and in patients who have had an inadequate response, defined as at least one relapse, to a prior disease-modifying therapy (DMT; CARE-MS II [NCT00548405])[3]
  - Patients could enter an ongoing, open-label extension (NCT00930553); alemtuzumab had durable efficacy over an additional 2 years in the extension, during which most patients did not receive retreatment with alemtuzumab (71%) and 96% did not receive another DMT[4,5]
- The most frequent adverse events (AEs) with alemtuzumab were infusion-associated reactions; other AEs of interest included autoimmune AEs (eg, thyroid disorders, immune thrombocytopenia, and nephropathies)[2,3]
- Alemtuzumab depletes circulating T and B lymphocytes, after which a distinctive pattern of T- and B-cell repopulation begins within weeks[6-8]
  - B-cell counts return to baseline levels within 6 months; T-cell counts generally reach the lower limits of normal (but not baseline) by 12 months[9,10]
- Depending on the clinical needs of the individual patient, physicians may want to use DMTs such as fingolimod; however, few data exist on the safety of this practice and effects on the immune system
- Because alemtuzumab[8,10] treatment is associated with long-term effects on the immune system, and fingolimod is known to cause reductions in peripheral lymphocyte counts that persist with therapy,[11] it is important to investigate how subsequent fingolimod is tolerated in alemtuzumab-treated patients

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- To assess lymphocyte pharmacodynamics and safety of fingolimod use in RRMS patients previously treated with alemtuzumab

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- Alemtuzumab's efficacy and safety were assessed in 3 randomized, rater-blinded, active-controlled studies
  - CAMMS223: SC IFNB-1a 44 µg 3 times weekly, or up to 3 annual courses of alemtuzumab 12 mg or 24 mg[1]
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RESULTS

Fingolimod Use

- Data cut-off for this analysis was October 4, 2013
- In the pooled study population (N=1486), there were 6483 total patient-years of follow-up, with a mean (SD) follow-up of 4.4 (1.7) years per patient
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- Fingolimod use was reported in 13 patients who entered the extension study
  - 12 patients received alemtuzumab in the core studies; 1 patient received SC IFNB-1a in the CARE-MS I core study and alemtuzumab in the extension
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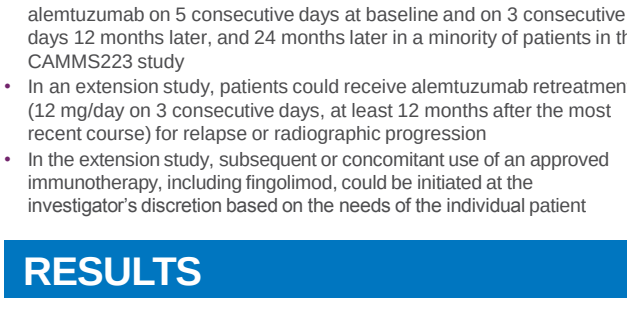

- As expected with the mechanism of action of each therapy, depletion and repopulation of CD4+ and CD8+ T-cell counts and CD19+ B-cell counts were observed after treatment with alemtuzumab; lymphocyte counts were decreased during treatment with fingolimod (**Figure 2**)

Safety

- The incidence of AEs and serious AEs was not increased in patients receiving fingolimod treatment relative to the overall study population
- No AE type predominated during fingolimod treatment
  - Of the 13 patients who received fingolimod after alemtuzumab, 11 experienced AEs, including infections (n=9), thyroid AEs (n=2), cytopenia (n=4), and malignancy (AEs of basal cell carcinoma and papillary thyroid carcinoma after fingolimod treatment; n=1; described at right)
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  - Patient 8: Vasovagal syncope (17 months after the last alemtuzumab dose and 5 months after starting fingolimod); patient recovered on the same day as the event and with no subsequent syncope episodes
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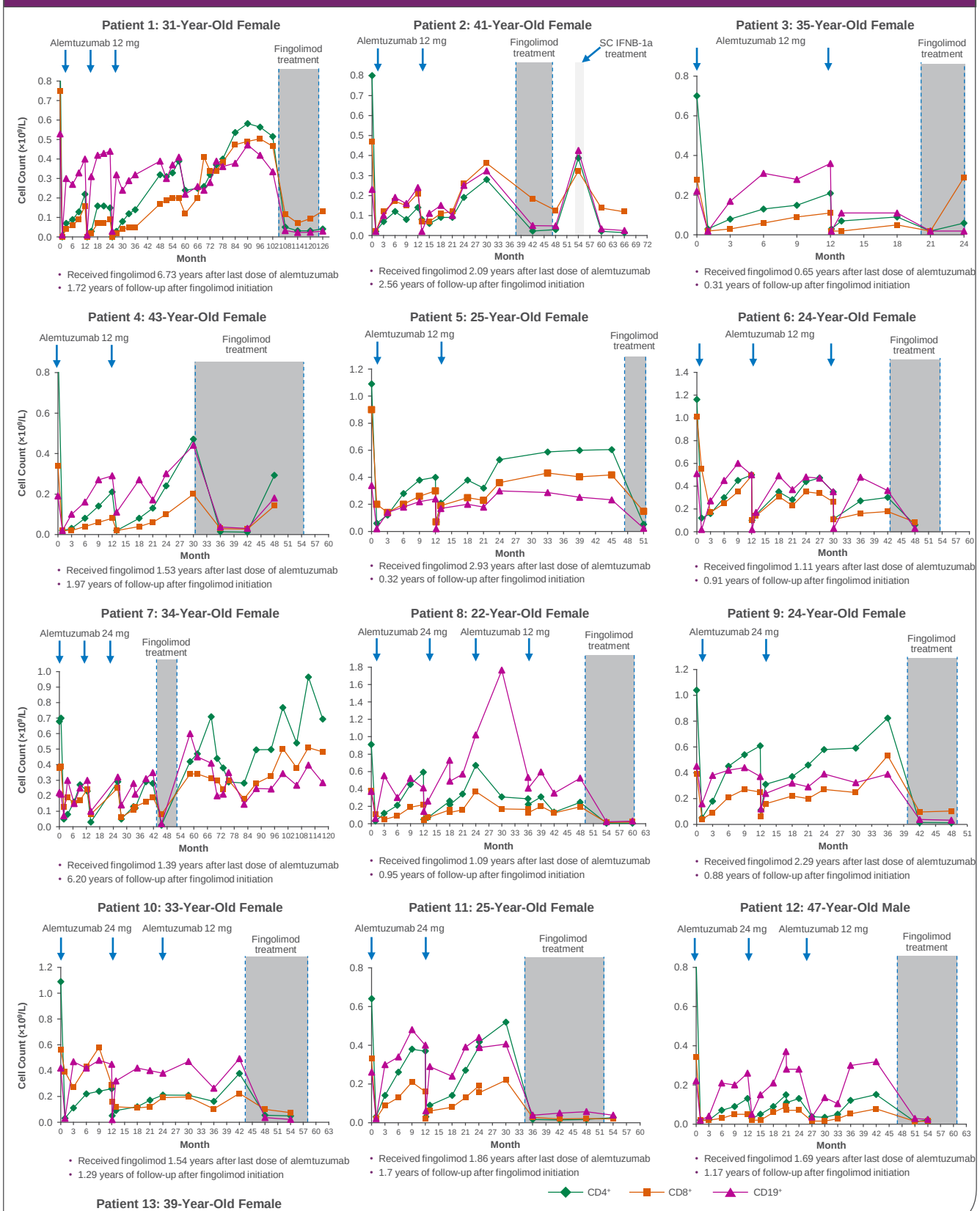

CONCLUSIONS

- Lymphocyte counts after switching from alemtuzumab to fingolimod were consistent with the known pharmacodynamic effects of fingolimod
- Overall AE profiles of fingolimod and alemtuzumab were consistent with the known safety profiles of each drug
- In this small group of patients, there were no safety findings to preclude use of fingolimod following alemtuzumab, although additional experience is needed

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CARE-MS=Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis

Rebif® is a registered trademark of Merck Serono Europe Ltd.

Alemtuzumab is approved in many countries around the world for treatment of adults with relapsing forms of multiple sclerosis (MS). In the EU, it is approved to treat patients with relapsing-remitting MS with active disease defined by clinical or imaging features. In the US, the indication provides that, because of its safety profile, the use of alemtuzumab should generally be reserved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of MS. This material may contain information that is outside of the approved labeling in some countries.

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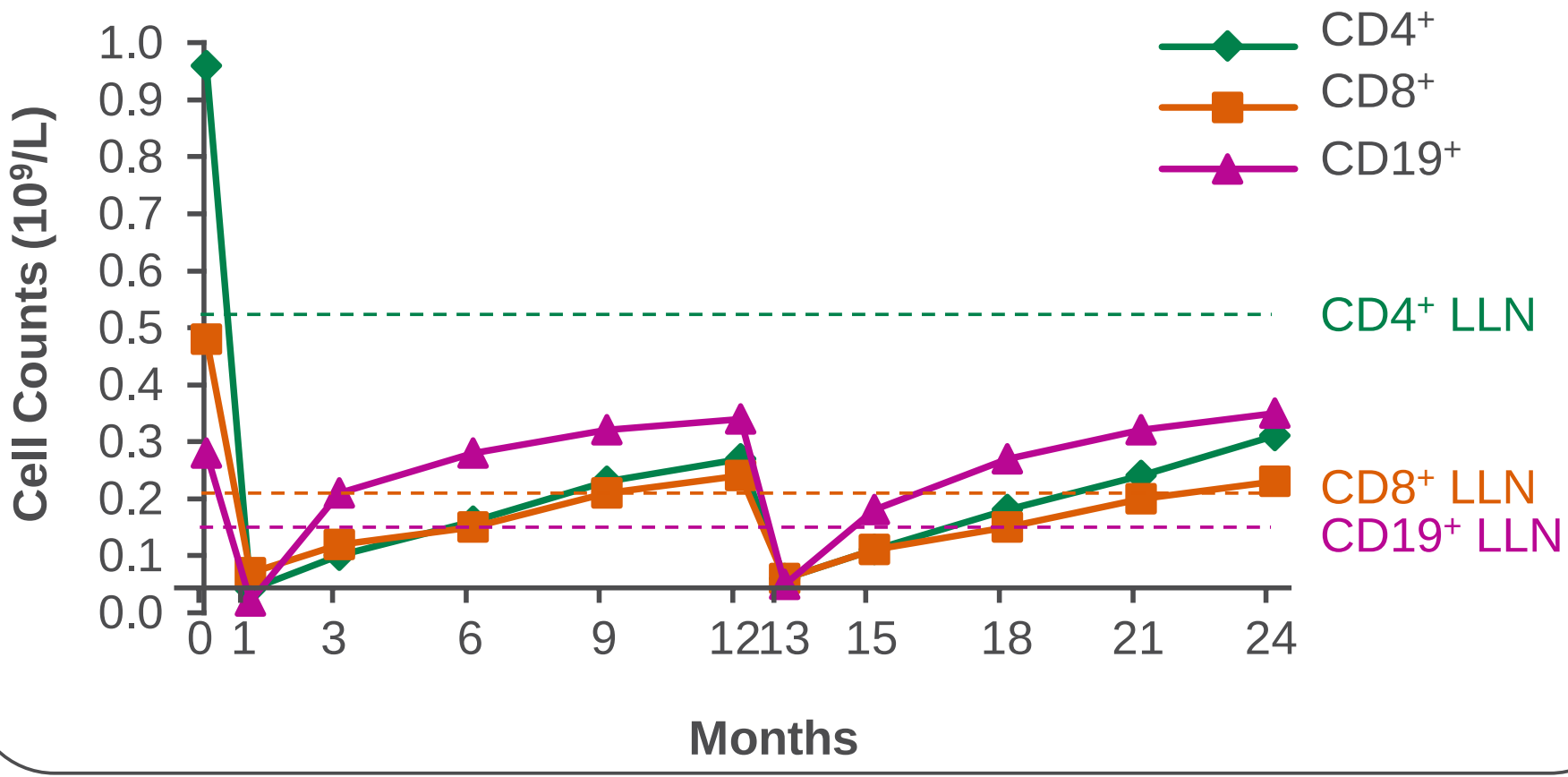

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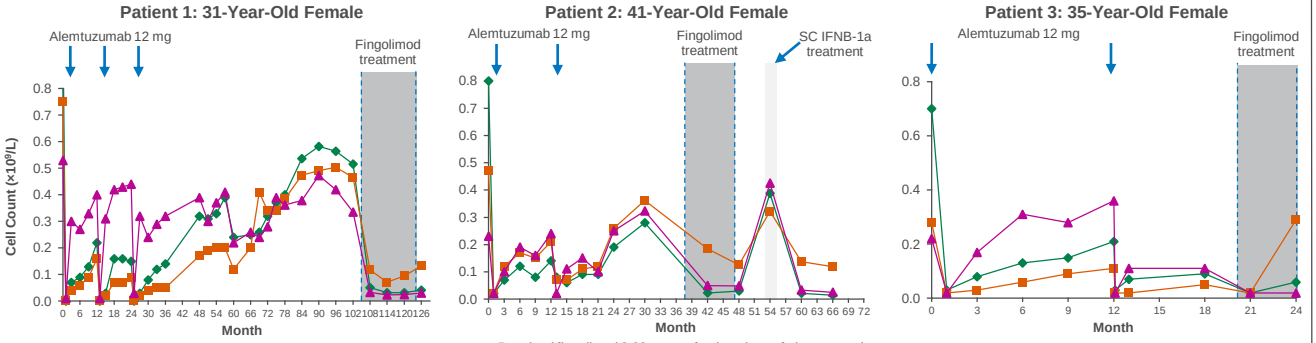
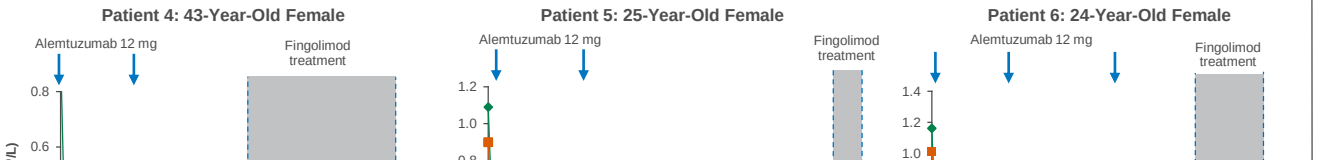


- Received fingolimod 6.73 years after last dose of alemtuzumab
- 1.72 years of follow-up after fingolimod initiation

- Received fingolimod 2.09 years after last dose of alemtuzumab
- 2.56 years of follow-up after fingolimod initiation

- Received fingolimod 0.65 years after last dose of alemtuzumab
- 0.31 years of follow-up after fingolimod initiation


Patient 4: 43-Year-Old Female
Alemtuzumab 12 mg
Fingolimod treatment
Cell Count (×10⁹/L)
0.0
0.2
0.4
0.6
0.8
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60
Month
• Received fingolimod 1.53 years after last dose of alemtuzumab
• 1.97 years of follow-up after fingolimod initiation
Patient 5: 25-Year-Old Female
Alemtuzumab 12 mg
Fingolimod treatment
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51
Month
• Received fingolimod 2.93 years after last dose of alemtuzumab
• 0.32 years of follow-up after fingolimod initiation
Patient 6: 24-Year-Old Female
Alemtuzumab 12 mg
Fingolimod treatment
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60
Month
• Received fingolimod 1.11 years after last dose of alemtuzumab
• 0.91 years of follow-up after fingolimod initiation

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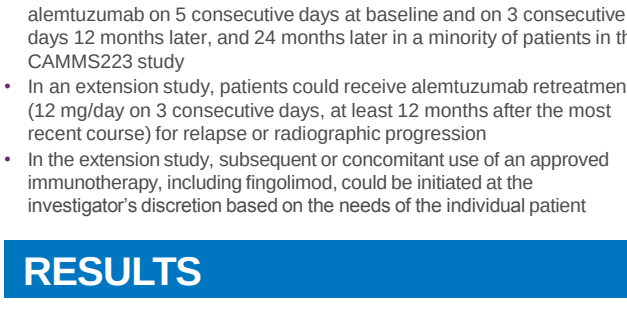

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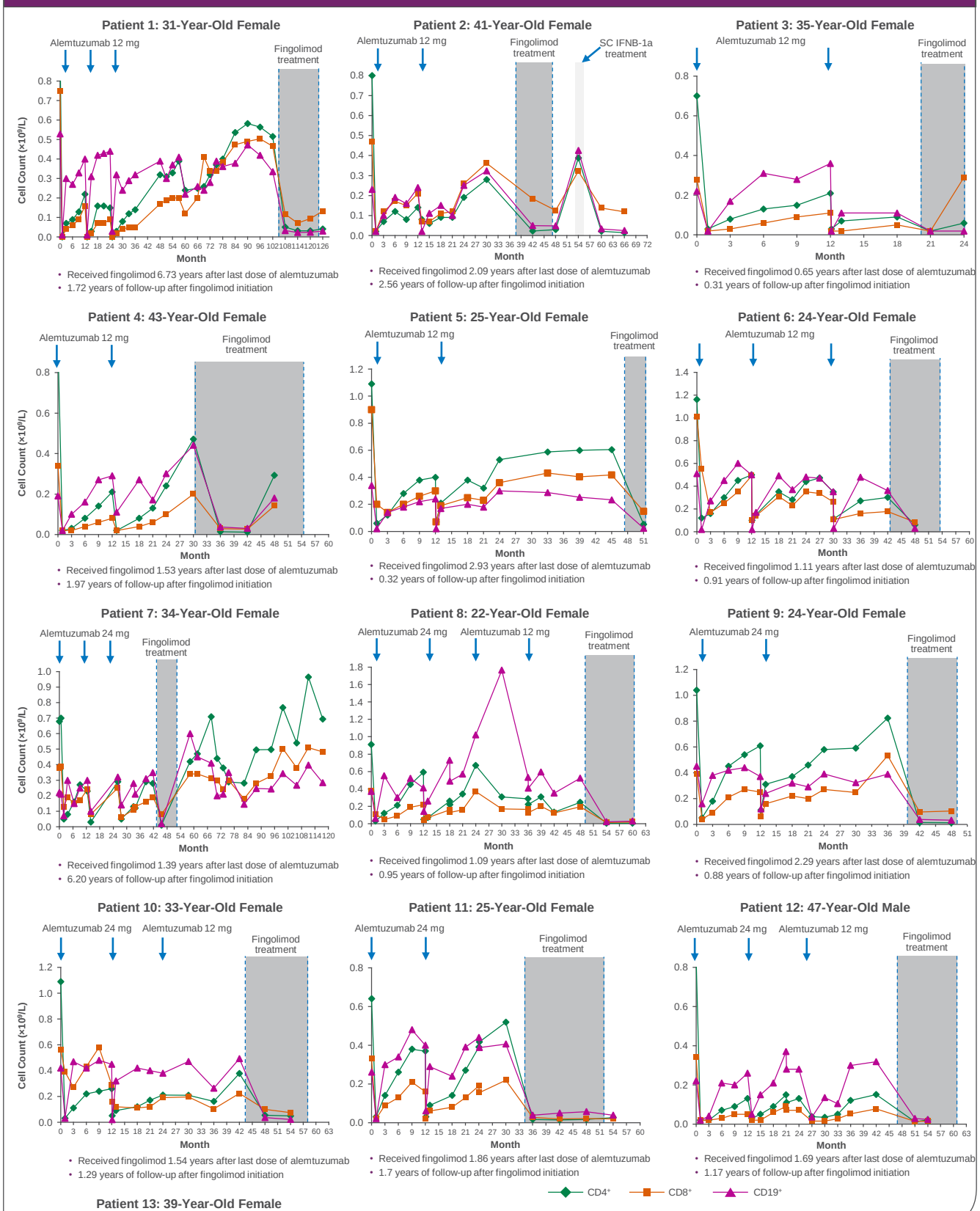

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Funding provided by Genzyme, a Sanofi company

F3151

Lymphocyte Pharmacodynamics and Safety of Fingolimod Use in Patients Previously Treated With Alemtuzumab

Krzysztof W Selmaj,[1] Ann D Bass,[2] Keith R Edwards,[3] Per S Sørensen,[4] David H Margolin,[5] Linda Kasten,[6] Jeffrey A Cohen[7]; on behalf of the CAMMS223 and CARE-MS I and II Investigators

[1]Medical University of Łódź, Łódź, Poland; [2]Neurology Center of San Antonio, San Antonio, TX, USA; [3]MS Center of NE New York, Latham, NY, USA; [4]Danish Multiple Sclerosis Center, Rigshospitalet, Copenhagen, Denmark; [5]Genzyme, a Sanofi company, Cambridge, MA, USA; [6]PROMETRIKA, LLC, Cambridge, MA, USA; [7]Cleveland Clinic, Cleveland, OH, USA

INTRODUCTION

- Alemtuzumab is a humanized anti-CD52 monoclonal antibody approved for patients with relapsing-remitting multiple sclerosis (RRMS) in over 40 countries
- Alemtuzumab demonstrated superior efficacy over 2 years versus high-dose subcutaneous interferon beta-1a (SC IFNB-1a) in patients with active RRMS, who were treatment-naive (CAMMS223 [NCT00050778] and CARE-MS I [NCT00530348])[1,2] and in patients who have had an inadequate response, defined as at least one relapse, to a prior disease-modifying therapy (DMT; CARE-MS II [NCT00548405])[3]
  - Patients could enter an ongoing, open-label extension (NCT00930553); alemtuzumab had durable efficacy over an additional 2 years in the extension, during which most patients did not receive retreatment with alemtuzumab (71%) and 96% did not receive another DMT[4,5]
- The most frequent adverse events (AEs) with alemtuzumab were infusion-associated reactions; other AEs of interest included autoimmune AEs (eg, thyroid disorders, immune thrombocytopenia, and nephropathies)[2,3]
- Alemtuzumab depletes circulating T and B lymphocytes, after which a distinctive pattern of T- and B-cell repopulation begins within weeks[6-8]
  - B-cell counts return to baseline levels within 6 months; T-cell counts generally reach the lower limits of normal (but not baseline) by 12 months[9,10]
- Depending on the clinical needs of the individual patient, physicians may want to use DMTs such as fingolimod; however, few data exist on the safety of this practice and effects on the immune system
- Because alemtuzumab[8,10] treatment is associated with long-term effects on the immune system, and fingolimod is known to cause reductions in peripheral lymphocyte counts that persist with therapy,[11] it is important to investigate how subsequent fingolimod is tolerated in alemtuzumab-treated patients

OBJECTIVE

- To assess lymphocyte pharmacodynamics and safety of fingolimod use in RRMS patients previously treated with alemtuzumab

METHODS

- Alemtuzumab's efficacy and safety were assessed in 3 randomized, rater-blinded, active-controlled studies
  - CAMMS223: SC IFNB-1a 44 µg 3 times weekly, or up to 3 annual courses of alemtuzumab 12 mg or 24 mg[1]
  - CARE-MS I and II: SC IFNB-1a 44 µg 3 times weekly, or 2 annual courses of alemtuzumab 12 mg (or 24 mg in CARE-MS II)[2,3]
- Annual courses in the core studies consisted of intravenous infusions of alemtuzumab on 5 consecutive days at baseline and on 3 consecutive days 12 months later, and 24 months later in a minority of patients in the CAMMS223 study
- In an extension study, patients could receive alemtuzumab retreatment (12 mg/day on 3 consecutive days, at least 12 months after the most recent course) for relapse or radiographic progression
- In the extension study, subsequent or concomitant use of an approved immunotherapy, including fingolimod, could be initiated at the investigator's discretion based on the needs of the individual patient

RESULTS

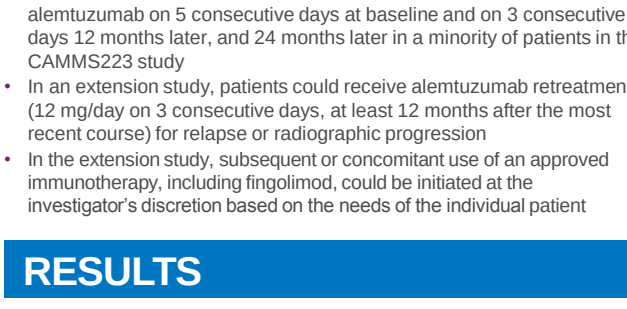
Fingolimod Use

- Data cut-off for this analysis was October 4, 2013
- In the pooled study population (N=1486), there were 6483 total patient-years of follow-up, with a mean (SD) follow-up of 4.4 (1.7) years per patient
- Overall few patients required treatment with another DMT such as fingolimod following alemtuzumab (4%)
- Fingolimod use was reported in 13 patients who entered the extension study
  - 12 patients received alemtuzumab in the core studies; 1 patient received SC IFNB-1a in the CARE-MS I core study and alemtuzumab in the extension
  - There were 22.0 total patient-years of follow-up after fingolimod initiation, with a mean (SD) follow-up of 1.7 (1.6) years per patient; mean (SD) time from most recent alemtuzumab dose to fingolimod initiation was 2.0 (1.5) years
  - Overall, treatment with fingolimod after alemtuzumab in this small cohort of patients did not appear to positively impact clinical or MRI activity (data not shown)

Lymphocyte Counts

- Lymphocyte count dynamics during core study alemtuzumab treatment in the overall study population are shown in **Figure 1**

Figure 1. Mean Lymphocyte Counts in Overall Study Population Treated With Alemtuzumab 12 mg



- As expected with the mechanism of action of each therapy, depletion and repopulation of CD4+ and CD8+ T-cell counts and CD19+ B-cell counts were observed after treatment with alemtuzumab; lymphocyte counts were decreased during treatment with fingolimod (**Figure 2**)

Safety

- The incidence of AEs and serious AEs was not increased in patients receiving fingolimod treatment relative to the overall study population
- No AE type predominated during fingolimod treatment
  - Of the 13 patients who received fingolimod after alemtuzumab, 11 experienced AEs, including infections (n=9), thyroid AEs (n=2), cytopenia (n=4), and malignancy (AEs of basal cell carcinoma and papillary thyroid carcinoma after fingolimod treatment; n=1; described at right)
- There were no serious infections, thyroid AEs, nephropathies or immune thrombocytopenia events
- Three patients experienced serious AEs after fingolimod initiation
  - Patient 8: Vasovagal syncope (17 months after the last alemtuzumab dose and 5 months after starting fingolimod); patient recovered on the same day as the event and with no subsequent syncope episodes
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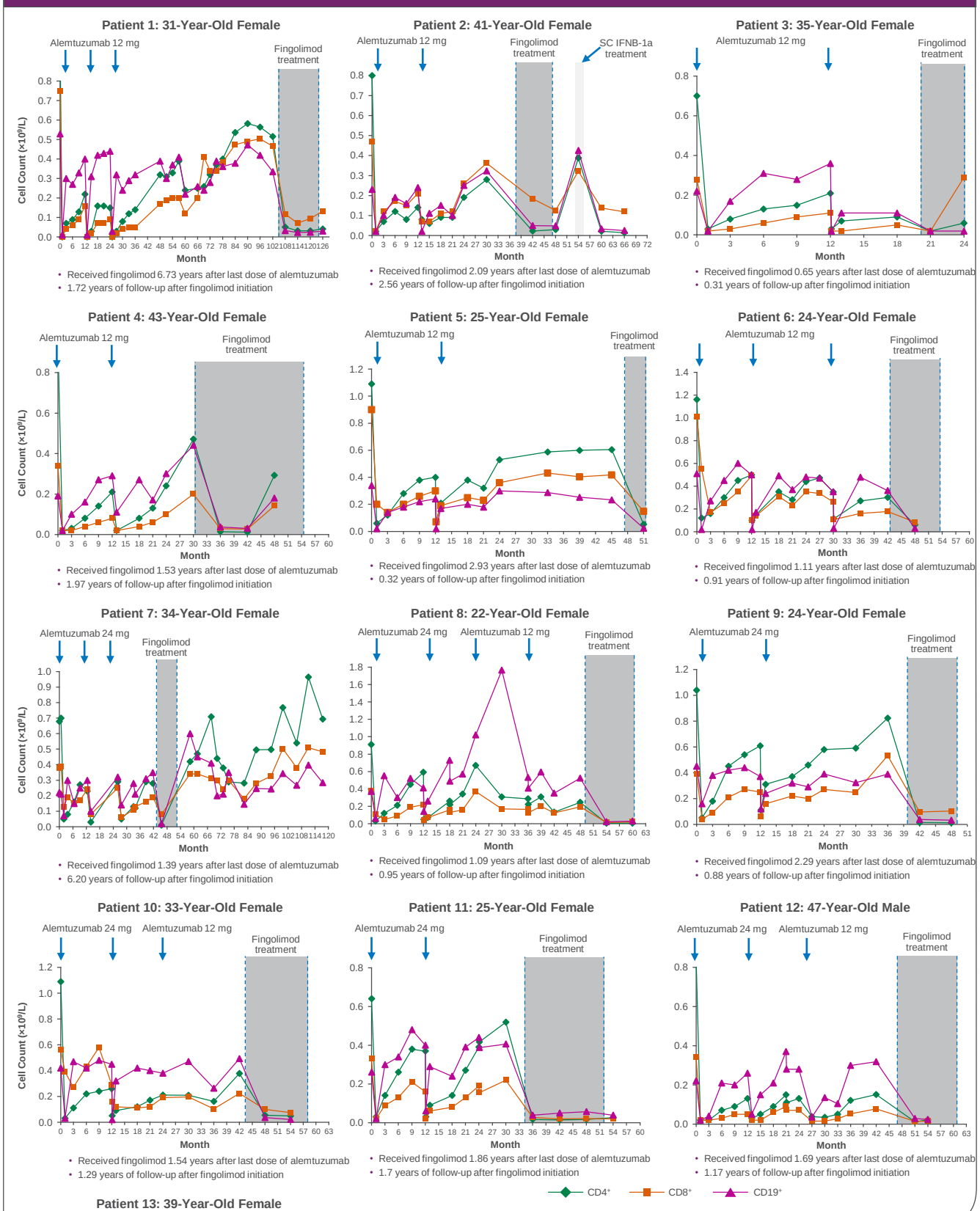

CONCLUSIONS

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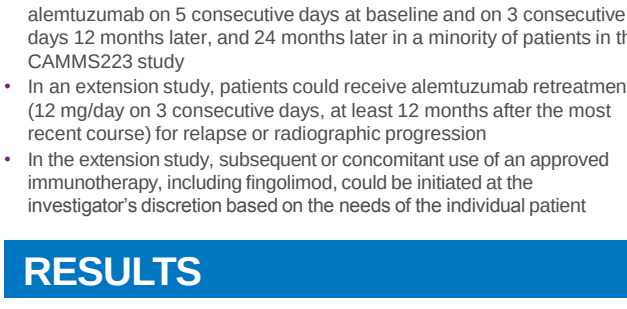

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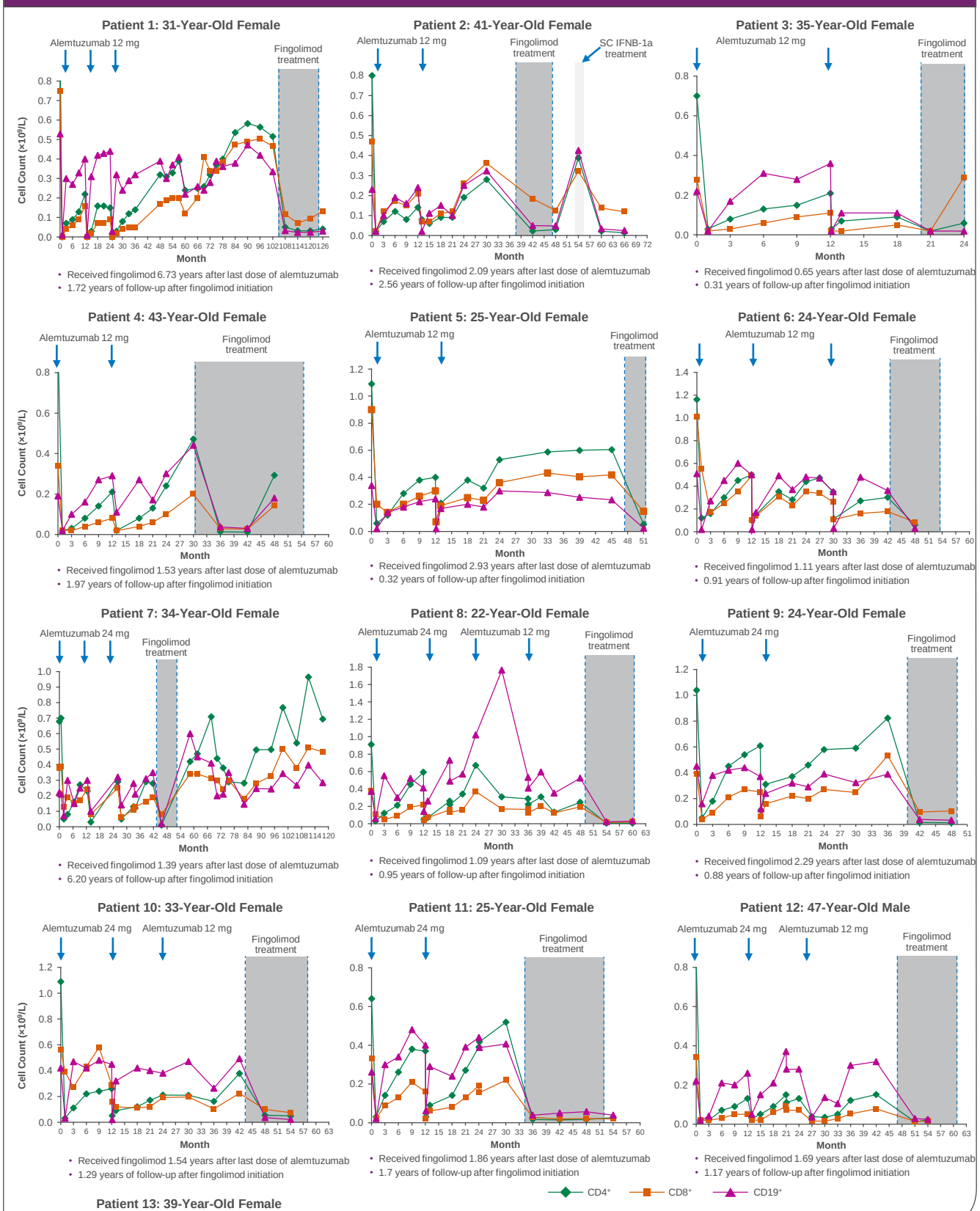

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