Alemtuzumab (ALE) Improves Disability After Switch from Other Disease Modifying Therapies in a High Disability, Treatment-Refractory Relapsing MS Cohort

Consortium of Multiple Sclerosis Centers 2015 Abstract #3485

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  - BiogenIdec Consulting fees, Speaking, Research
  - Novartis Consulting Research
  - Osmotica Consulting, Research
  - Questcor Consulting, Speaking
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  - Synthon Grant/Research
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Background Alemtuzumab

- Anti-CD52, humanized monoclonal IgG
  - Labeled previously CAMPATH® and now Lemtrada® (Genzyme-Sanofi)
- US indication: Relapsing MS generally third line treatment
- Older cohort given 10-20-30 mg 1st course and 10mgX3 2nd
- Now given as 5X12mg infusions and 3X12 mg after 12 months
  - As needed retreatment 3X12 mg (relapse or MRI eligible)

Background: The problem of refractory MS

- Treatment-refractory MS (TRMS)
  - e.g. recurrent relapses and worsening disability on therapy
  - Widespread therapeutic nihilism and bias against therapy of "progressive" MS
  - Worsening gait or poor Expanded Disability Status Scale (EDSS) scores
  - Perspective may become obsolete with evidence of treatment benefit.
- Alemtuzumab (ALE)
  - an FDA-approved, humanized anti-CD52, cytotoxic monoclonal IgG,
  - selective and transient lymphocyte depletion, with subsequent immune reconstitution
  - superior EDSS and Relapse outcomes over high dose IFNbeta-1a in relapsing MS.
- An early phase I ALE study suggested stability in patients with progressive features, and our prior retrospective reports support long-term EDSS improvement in TRMS.
  - Given risk-benefit ratio of ALE
    - Possibly appropriate for higher disability, active patients
    - Differ from relapsing lower disability, short disease duration, age, experience
      - profile of phase II/III clinical trials.

Real World Cohort of Difficult MS

Global Multiple Sclerosis Severity Scores (MSSS) from 9,892 European patients

	0	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5	EDSS
1	0.67	2.44	[illegible]	5.87	7.08	7.93	8.64	9.09	9.35	9.50	9.63	9.74	9.84	9.90	9.94	9.97	9.98	9.98	9.99	
2	0.53	2.01	3.6[illegible]	5.24	6.46	7.27	7.98	8.58	[illegible]	9.18	9.38	9.59	9.79	9.88	9.93	9.97	9.99	9.99	9.99	
3	0.45	1.77	3.34	4.82	6.00	6.81	7.54	8.14	8.55	[illegible]	9.07	9.35	9.63	9.77	9.86	9.92	9.97	9.98	9.99	
4	0.35	1.45	2.87	4.[illegible]	5.41	6.24	6.98	7.65	8.12	8.42	[illegible]	9.08	9.47	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
5	0.30	1.28	2.60	3.90	4.95	5.79	6.58	7.26	7.75	8.08	8.38	[illegible]	9.32	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
6	0.25	1.13	2.33	3.54	[illegible]	5.38	6.14	6.81	7.33	7.66	7.98	8.50	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
7	0.24	1.04	2.10	3.17	4.1[illegible]	4.96	5.75	6.46	6.98	7.32	7.65	8.24	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
8	0.21	0.94	1.92	2.93	3.81	[illegible]	5.36	6.10	6.61	6.95	7.32	7.97	[illegible]	9.21	9.55	9.74	9.89	9.96	9.99	
9	0.21	0.88	1.76	2.65	3.45	4.[illegible]	4.93	5.64	6.14	6.50	6.90	7.65	[illegible]	9.09	9.47	9.70	9.87	9.95	9.99	
10	0.19	0.78	1.53	2.34	3.10	3.79	4.55	5.28	5.77	6.14	6.58	7.39	[illegible]	8.92	9.34	9.61	9.83	9.94	9.99	
11	0.17	0.71	1.40	2.13	2.82	3.46	[illegible]	4.94	5.42	5.82	6.30	7.18	[illegible]	8.79	9.24	9.52	9.78	9.92	9.98	
12	0.16	0.64	1.28	1.98	2.64	3.25	3.9[illegible]	4.63	5.13	5.54	6.03	6.92	[illegible]	8.63	9.13	9.43	9.71	9.88	9.97	
13	0.13	0.57	1.14	1.80	2.44	3.05	3.70	[illegible]	4.91	5.32	5.80	6.74	[illegible]	8.55	9.03	9.34	9.65	9.85	9.96	
14	0.11	0.49	1.03	1.70	2.33	2.91	3.55	4.[illegible]	4.82	5.23	5.70	6.56	[illegible]	8.34	8.86	9.20	9.57	9.82	9.95	
15	0.10	0.45	0.99	1.64	2.26	2.82	3.44	4.14	4.68	5.09	5.51	6.33	7.41	8.17	8.70	9.11	9.51	9.78	9.94	
16	0.09	0.38	0.85	1.42	1.99	2.56	3.17	3.86	[illegible]	4.81	5.18	6.00	7.14	7.97	8.54	9.04	9.49	9.75	9.94	
17	0.05	0.32	0.76	1.28	1.77	2.30	2.95	3.65	4.17	4.55	4.94	5.74	6.89	7.77	8.38	8.99	9.52	9.79	9.96	
18	0.04	0.26	0.66	1.12	1.57	2.09	2.70	3.37	3.89	[illegible]	4.62	5.43	6.62	7.54	8.23	8.94	9.51	9.78	9.96	
19	0.05	0.28	0.63	1.00	1.39	1.89	2.50	3.19	3.72	4.[illegible]	4.49	5.35	6.59	7.51	8.22	8.98	9.57	9.81	9.96	
20	0.05	0.26	0.59	0.94	1.29	1.71	2.29	2.99	3.51	3.93	[illegible]	5.15	6.43	7.45	8.23	8.98	9.58	9.80	9.95	
21	0.05	0.30	0.66	1.02	1.39	1.77	2.34	2.97	3.43	3.83	[illegible]	5.09	6.35	7.33	8.08	8.87	9.49	9.77	9.96	
22	0.04	0.23	0.54	0.90	1.28	1.66	2.20	2.82	3.29	3.69	[illegible]	5.04	6.35	7.35	8.10	8.84	9.42	9.73	9.95	
23	0.05	0.27	0.58	0.91	1.26	1.64	2.19	2.78	3.21	3.69	[illegible]	5.16	6.47	7.46	8.20	8.87	9.43	9.75	9.95	
24	0.05	0.24	0.52	0.86	1.25	1.63	2.15	2.71	3.09	3.52	4.01	5.03	6.36	7.38	8.15	8.81	9.39	9.74	9.96	
25	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	2.05	2.53	2.84	3.21	3.74	4.88	6.26	7.24	8.00	8.73	9.35	9.75	9.98	
26	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	2.08	2.63	2.99	3.4[illegible]	3.95	5.02	6.39	7.44	8.21	8.89	9.48	9.80	9.96	
27	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	2.03	2.56	2.91	3.[illegible]	3.86	4.93	6.33	7.38	8.14	8.91	9.56	9.85	9.98	
28	0.04	0.17	0.40	0.74	1.16	1.52	1.88	2.39	2.76	3.04	3.46	4.54	5.99	7.07	7.90	8.75	9.45	9.80	9.98	
29	0.03	0.18	0.47	0.80	1.19	1.51	1.79	2.27	2.68	3.01	3.41	4.35	5.68	6.76	7.66	8.62	9.38	9.75	9.96	
30	0.01	0.13	0.45	0.82	1.19	1.45	1.69	2.23	2.75	3.13	3.50	4.35	5.61	6.66	7.54	8.47	9.27	9.67	9.91	
Years																				

Malignant MS

Benign MS

Roxburgh, R. H.S.R. et al. Neurology 2005;64:1144-1151

=1st Decile
=2nd Decile
=3rd Decile
= 6th Decile
= 7th Decile
= 8th Decile

Background Retrospective Analysis #1

- Hunter et al 2009 AAN *n*=43, 9M 34F relapsing (*n*=23) or secondary progressive (*n*=20)
  - mean EDSS 5.5 (median 6.0, 2.5-9), disease duration median 9.0 (3-33) years,
  - MS Severity score 6.9 ± 1.9SD (range 2.6-9.8)
  - Annualized two-year relapse rate 1.3 (median 1, range 0-3).
- Results:
  - EDSS improved mean 0.4 at median 12 months,
  - 46% unchanged, 43% of patients improved mean 1.2, and 11% worsened mean 1.0.
  - EDSS at more than 12 months after first cycle improved mean 0.7 (n=13).
  - MS Severity Scores also improved (0.50).
  - Annualized relapse rate was unaltered overall (1.2, n=41), but declined 46% in those with ≥2 relapses yearly before alemtuzumab (n=12).
  - Following 15 months(n=19), annualized relapse rate still remained similar (1.4)

1 year = minor improvement

Background Retrospective Analysis #2

Hunter et al 2011 AAN

3 years = improved disability and relapses

Patients:	55 serial clients, 46 female, 9 male
Age at ALE:	Median 47 years, range 28-67 years, median ~9 years disease duration
Phenotypes in cohort:	Severe relapsing, progressive relapsing, transitional progressive, secondary progressive, and MS with marked MRI activity on therapy
Annualized Relapse Rate during prior 2 years:	1.5 median, 1.4 mean, range 0.5-3 (excludes those receiving regular corticosteroids)
EDSS at ALE:	Mean 5.5 ± 1.6, Median 6.0, range 2.5-8.5

Months at last Follow up:	33 median, 31 mean, range 6-46
ALE Courses:	3 – 30 , 2 – 19, 1 – 6
EDSS Change pretreatment to follow up:	-0.7 ± 1.2 Mean, *n* = 55 ***p*** < 0.0001, Student's paired *t* test Median -0.5, Range -4 to +1.0
Change in EDSS at last follow up:	**Improved** 30/55 (55%) by mean -1.5 EDSS, range -4 to -0.5 **Worsened** 7/55 (13%) by mean 0.6 median 0.5, range +0.5 to +1.0 **Stable** 18/55 33%
Annualized Relapse Rate **Excluding patients with baseline regular corticosteroids:** *n* = 47	**Two years pretreatment** Mean 1.36 ± 0.79 (median 1.5), range 0.5-3 **During follow up period** Decreased -43%, Mean 0.93 ± 0.71, Median 0.88, range 0-3.0 ***p*** = 0.0009, Student's paired *t* test

Background Retrospective Analysis #3

- Hunter et al AAN 2015

5 year = significant response

Treatment cohort:	Entire cohort *n* = 29	Prior Interferon-beta cohort *n* = 18	Prior Natalizumab cohort *n* = 7
Months at last Follow up (Mean ± SD):	**60 ± 22 months** **Median 63, Range 9-90**	**63 ± 20 months,** **Median 69, Range 24-90**	**47 ± 20 months** **Median 53, Range 27-78**
EDSS Baseline (Mean ± SD):	**5.1 ± 1.3** **Median 5.5, Range 2.0 - 7.5**	**4.7 ± 1.0** **Median 5.0, Range 2.0 - 7.5**	**5.7 ± 1.0** **Median 6.0, Range 4.0 - 6.5**
EDSS Change baseline to *best follow up* (Mean ± SD):	-0.8 ± 1.1 (improved) Median -1.0, Range -3.0 to +1.0	-1.0 ± 1.1 (improved) Median -1.0, Range -3.0 to +1.3	-0.6 ± 1.3 (improved) Median -1.0, Range -3.0 to +1.0
MS Severity Score (MSSS Mean ± SD)	**6.6 ± 2.1** **Median 6.9, Range 1.8-9.6**	**6.3 ± 2.1** **Median 6.7, Range 1.8-9.6**	**8.0 ± 1.9** **Median 8.6, Range 4.4-9.8**
Last Change in MS Severity *Score* (deciles Mean ± SD):	-1.8 ± 1.6 (improved) Median -2.3, Range -5.1 to +1.3	-2.3 ± 1.5 (improved) Median -2.5, Range -5.1 to +0.8	-1.6 ± 1.5, (improved) Median -1.9, Range -3.2 to +0.5
Annualized Relapse (ARR) Rate 2 yrs pre ALE Mean ± SD	**1.6 ± 0.7** **median 1.5, range 0.5-3.5**	**1.6 ± 0.8** **median 1.5, range 0.5-3.5**	**1.7 ± 0.6** **median 1.5, range 1.0-3.0**
ARR Months 1-36 post ALE Mean ± SD	-27% + 53% median -33%, *n* – 26	-39% + 52% median -47%, *n* – 17	-12% + 51% median -33%, *n* – 7

Background Retrospective Study Design

Improvement despite poor prognostic factors

- Hunter et al AAN 2015

Demographic	Best change EDSS Below Median Mean ± SD	Best change EDSS Above Median Mean ± SD
Age first ALE	<53 yo: -1.0 ± 1.2	≥53 yo: -1.0 ± 1.1
Clinical Phenotype	RR: -0.9 ± 0.9	SP: -0.7 ± 1.4 p=NS
Disease duration	<8.0 yrs: -1.0 ± 1.1	≥8.0 yrs: -0.7 ± 1.2 p=NS
Baseline EDSS	<5.5 : -0.4 ± 0.8	≥5.5: -1.1 ± 1.2 p=NS
MSSS	<6.9 : -0.5 ± 1.1	≥6.9: -1.1 ± 1.2 p=NS

Open label Refractory MS Therapy with ALE

- **Phase I retrospective and prospective:** NCT01624714: clinicaltrials.gov
  - Combination trial design
  - Retrospective data collection (EDSS/relapse/safety)
  - Prospective MSFC, EDSS, OCT, EDSS, Relapse, Safety

Benchmark Responses to ALE after other immunotherapy

  - **ALE-experienced Inclusion criteria**
    - Off-label treated, refractory, MS clinic cohort
    - MS with documented relapses
    - Prior treatment experience with approved disease modifying agents
    - ≥1 courses of prior ALE therapy
  - **ALE-naive Inclusion criteria**
    - Documented relapses on therapy prior two years
    - Prior treatment experience with disease modifying agents
    - EDSS 3-7
- **Exclusion:** pregnancy, neoplasm, infection, uncontrolled autoimmunity

Method - Interim first year analysis

Phase I prospective analysis of EDSS and MSSS change following ALE.

Inclusion criteria: prior immunotherapy failure, and relapse within two years, regardless of apparent progressive features.

60 ALE-treated TRMS subjects enrolled

- 30 ALE-naïve analyzed prospectively for a short-term cohort
- 30 ALE-experienced analyzed retrospectively and prospectively for a long-term cohort

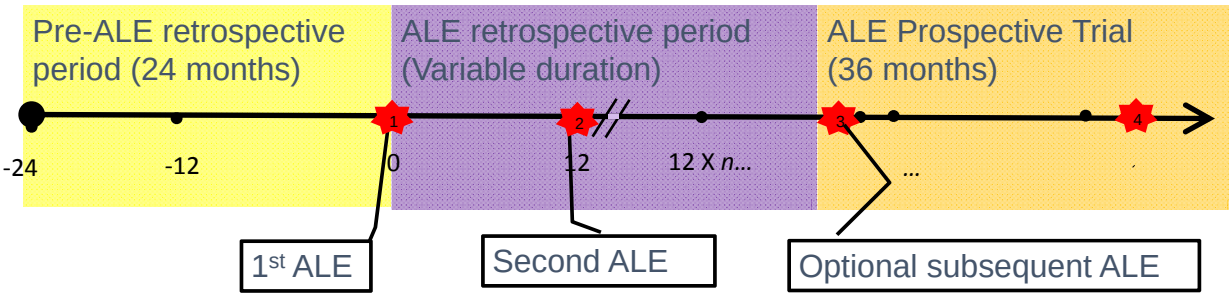
Primary outcomes: Change in EDSS and MSSS

Groups were stratified by

- (i) median lunar months follow up (MFU) duration:
  - long-term (LT) 82 MFU (27-104, *n*=30) or
  - short-term (ST) 10 MFU (6-25, *n*=30), and
- (ii) DMD immediately before and within the prior 2 year epoch before ALE:
  - interferon-beta or glatiramer acetate (IFNGA)
  - fingolimod (FTY)
  - natalizumab (NAT).

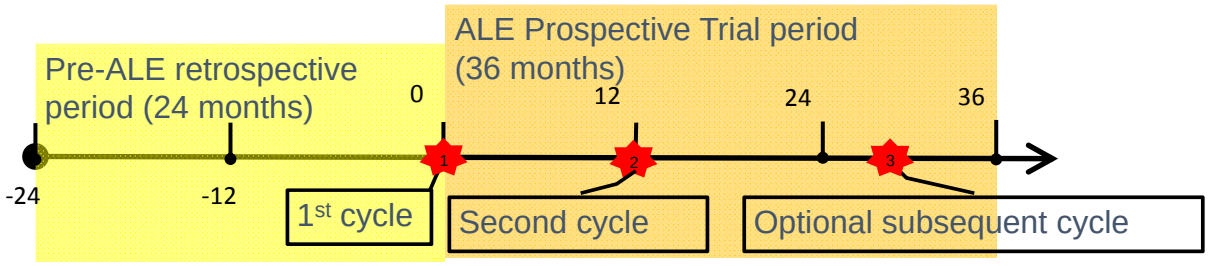
Interim Data Inspection 6 months after first ALE in prospective trial

ALE Experienced Cohort ca. 2006-2012



- Treated outside of trials with CAMPATH
- Several prior retrospective analyses, baseline data is retrospective
- Long-term, treatment responders – seek further treatment
- Prior treatment principally interferon-beta and short term natalizumab
  - combination with steroids or immunosuppressives

ALE Naïve Cohort – ca. 2012-2014



- "Modern era MS patients"
- Substantial prior fingolimod and longterm natalizumab

Prospective Outcome by Follow up Cohort

COHORT	Age At ALE	Follow up Months (range)	BASELINE EDSS Mean±SD (range)	Change EDSS Mean±SD (range)	BASELINE MSSS Mean±SD (range)	Change MSSS Mean±SD (range)
LONG TERM *n*=30	48 ± 9 (33-63)	82 (27-104)	5.5 ± 1.3 (2.0-7.5)	-1.0 ± 1.4 (-4.0 to +2.0)	6.49 ± 2.09 (1.70-9.63)	-2.34 ± 1.95 (-6.84 to +0.89)
SHORT TERM *n*=30	49 ± 10 (33-68)	10 (6-25)	5.0 ± 1.3 (2.5-7.0)	-0.4 ± 1.4 (-4.5 to +1.5)	6.09 ± 2.16 (1.28-9.90)	-0.54 ± 0.97 (-2.82 to +1.16)

Similar to First Retrospective Cohort

Prospective Outcome by Immediate prior DMD

COHORT	Follow up Months (range)	Change EDSS Mean±SD (range)	Change MSSS Mean±SD (range)
IFN-GA *n*=26	82 (12-104)	-0.9 ± 1.4 (-4.0 to +2.0)	-2.24 ± 1.97 (-6.84 to +1.02)
Fingolimod *n*=14	10 (6-25)	-0.4 ± 1.0 (-2.0 to +1.0)	-0.53 ± 1.06 (-2.82 to +1.16)
Natalizumab *n*=11	49 (6-99)	-0.5 ± 1.5 (-3 to +1.5)	-1.24 ± 2.05 (-5.0 to +0.89)

N.B. These groups are exclusive

Outcome by DMD within prior two years

COHORT	Follow up Months (range)	Change EDSS Mean±SD (range)	Change MSSS Mean±SD (range)
IFN-GA *n*=34	61 (6-103)	-0.8 ± 1.4 (-4.0 to +2.0)	-2.24 ± 1.97 (-6.84 to +1.02)
Fingolimod/FTY *n*=14	14 (6-36)	-0.4 ± 1.0 (-2.0 to +1.0)	-0.61 ± 1.06 (-2.17 to +1.16)
Natalizumab *n*=29	29 (6-99)	-0.2 ± 1.5 (-3.0 to +2.0)	-0.59 ± 1.36 (-5.0 to +1.16)
Transition from Nat. to FTY to ALE *n*=10	12	-0.4 ± 1.2 (-2.0 to +1.0)	-0.57 ± 1.07 (-2.17 to 1.16)

N.B. These groups are not exclusive.

Conclusions

- Length of follow up important in assessing ALE response
- Short term (<1 year) improvements smaller
- ALE equals immunotherapeutic rescue for most TRMS patients
  - group-wise EDSS and MSSS stability or improvement,
    - notwithstanding other recent, effective, and even aggressive, prior therapies.
- Further analysis required to ascertain effects of prior therapy
- Improvement favors treatment of high disability TRMS
- Benchmarks outcomes following ALE for TRMS after standard immunotherapy
- Possible ongoing long-term sustained disability improvement 5-8 years, regardless of prior immunotherapy

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