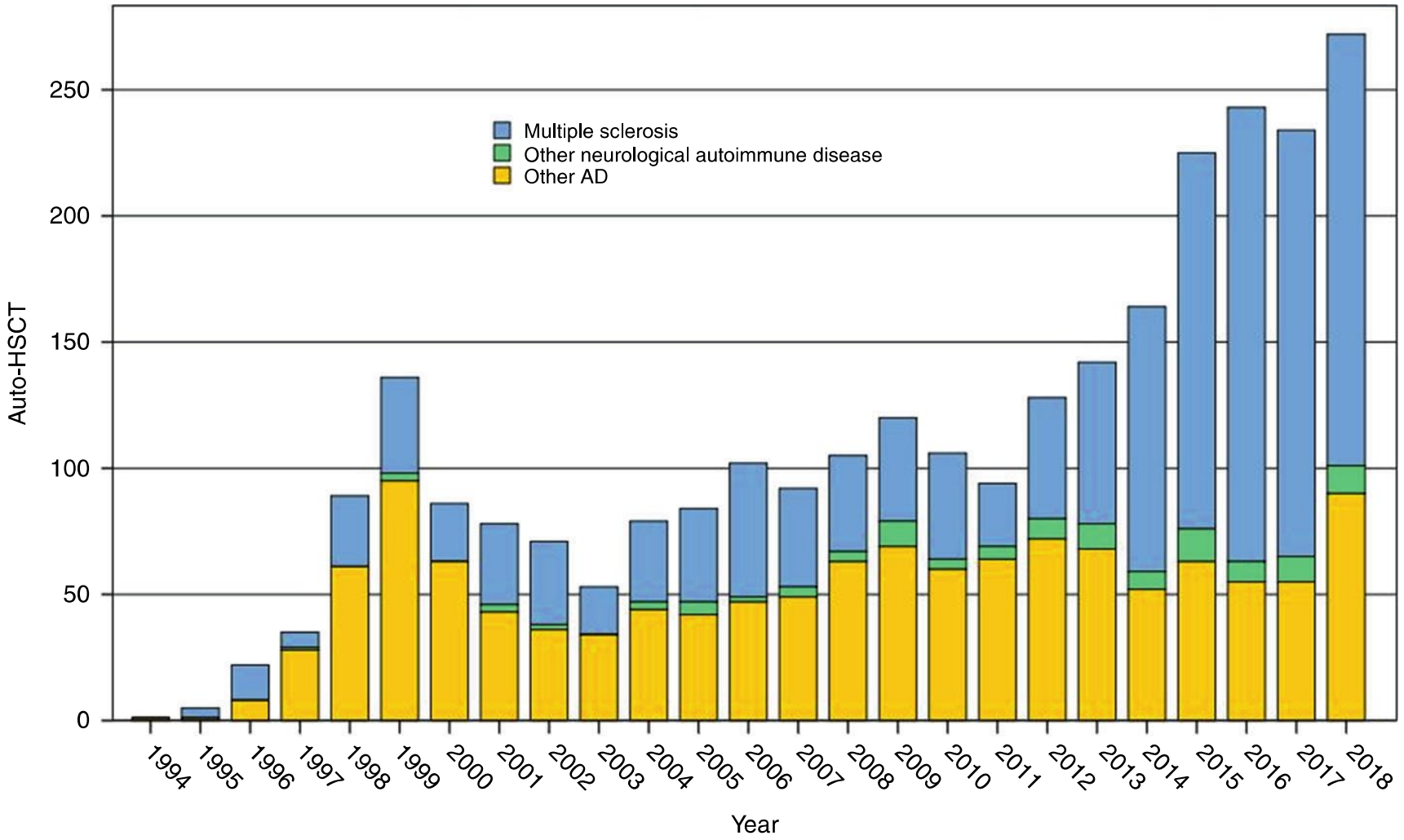
AHSCT for MS

Who, What, When, Where and Why

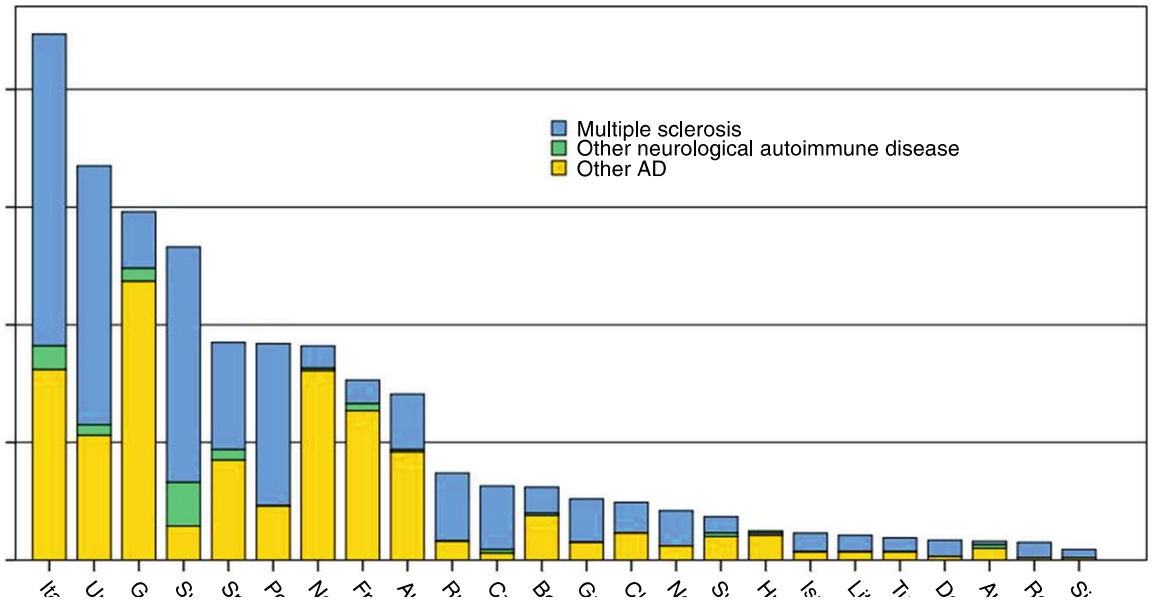
JENNIFER MASSEY

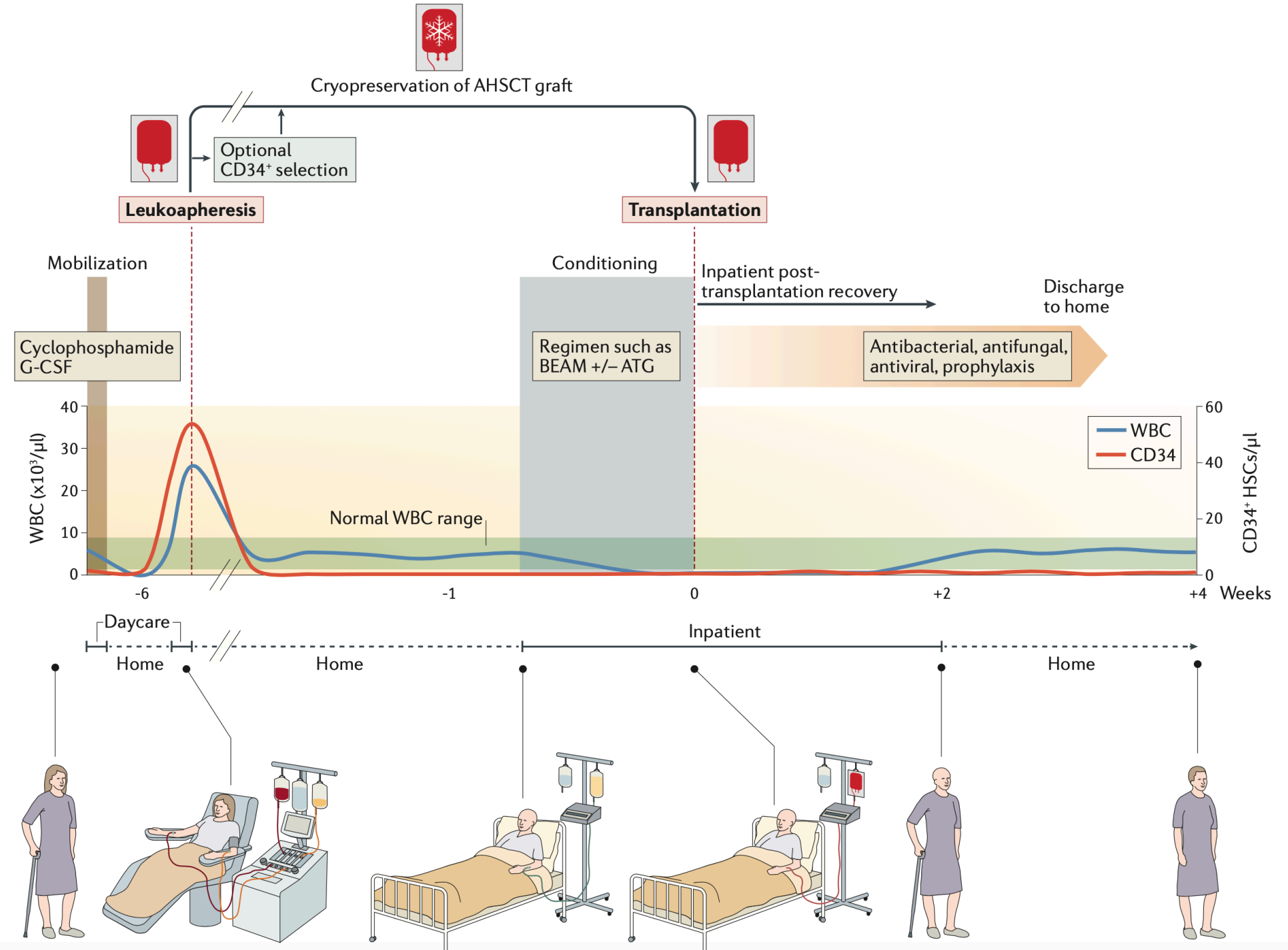
St Vincent’s Hospital, Sydney, Australia

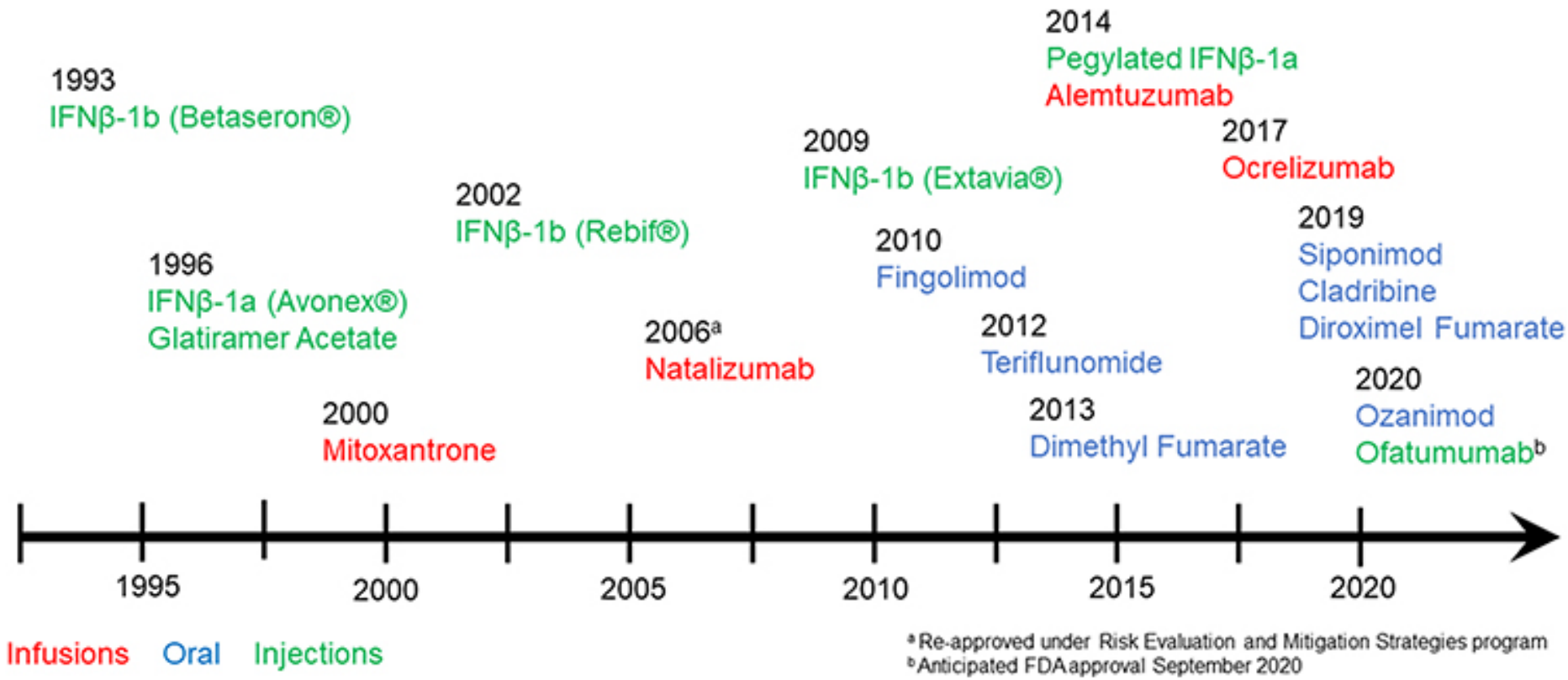
EBMT Auto-HSCT for AD: diagnosis per year 1994-July 2019 (n = 2766)



EBMT Auto-HSCT for AD: diagnosis per year 1994-July 2019 (n = 2766)

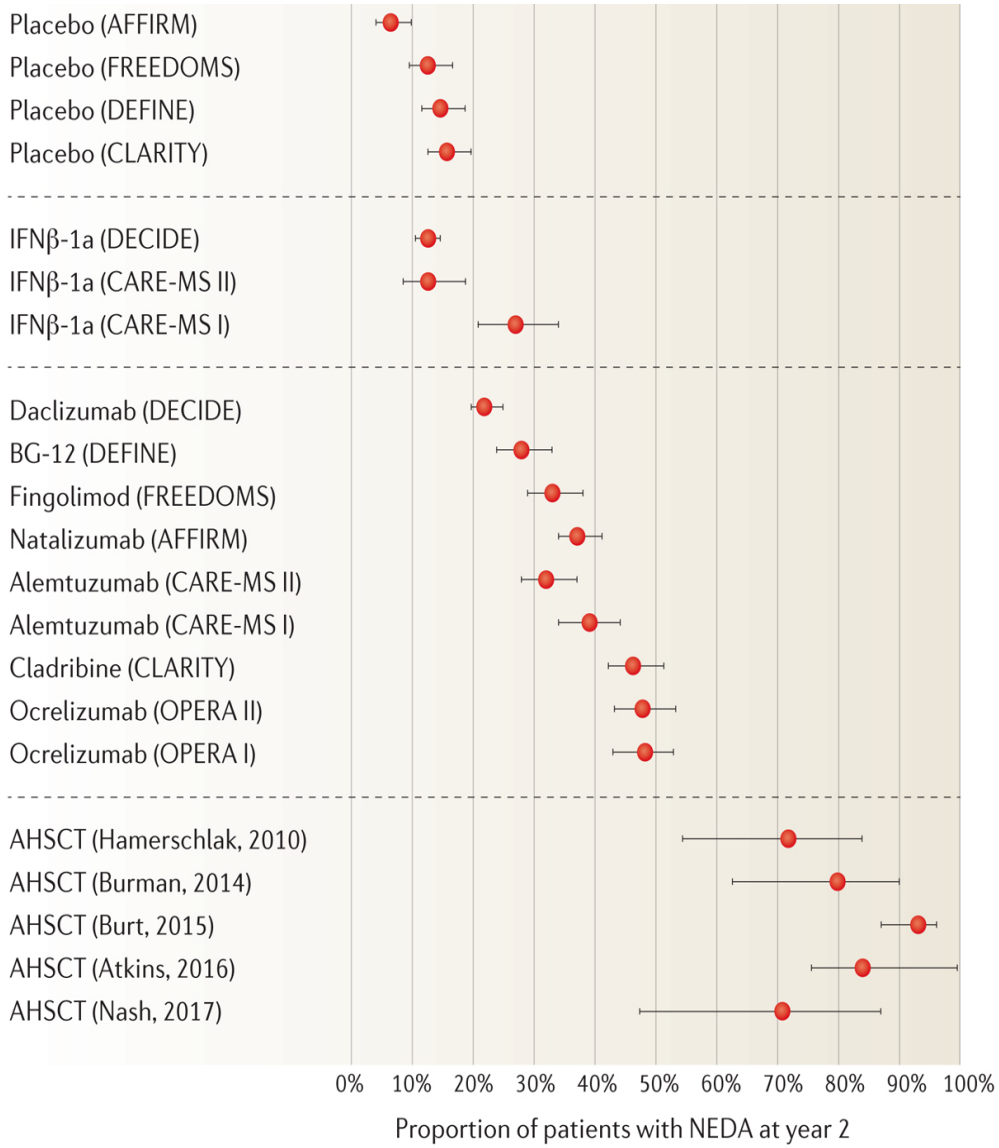



Cryopreservation of AHSCT graft
Optional CD34+ selection
Leukoapheresis
Transplantation
Mobilization
Conditioning
Inpatient post-transplantation recovery
Discharge to home
Cyclophosphamide G-CSF
Regimen such as BEAM +/– ATG
Antibacterial, antifungal, antiviral, prophylaxis
WBC (x10³/µl)
CD34+ HSCs/µl
Normal WBC range
WBC
CD34
Weeks
Daycare
Inpatient
Home
Home
Home


1993
IFNβ-1b (Betaseron®)
1996
IFNβ-1a (Avonex®)
Glatiramer Acetate
2000
Mitoxantrone
2002
IFNβ-1b (Rebif®)
2006[a]
Natalizumab
2009
IFNβ-1b (Extavia®)
2010
Fingolimod
2012
Teriflunomide
2013
Dimethyl Fumarate
2014
Pegylated IFNβ-1a
Alemtuzumab
2017
Ocrelizumab
2019
Siponimod
Cladribine
Diroximel Fumarate
2020
Ozanimod
Ofatumumab[b]
1995
2000
2005
2010
2015
2020
Infusions
Oral
Injections
[a] Re-approved under Risk Evaluation and Mitigation Strategies program
[b] Anticipated FDA approval September 2020

Why AHSCT?

NEDA at 2 years with DMD and AHSCT

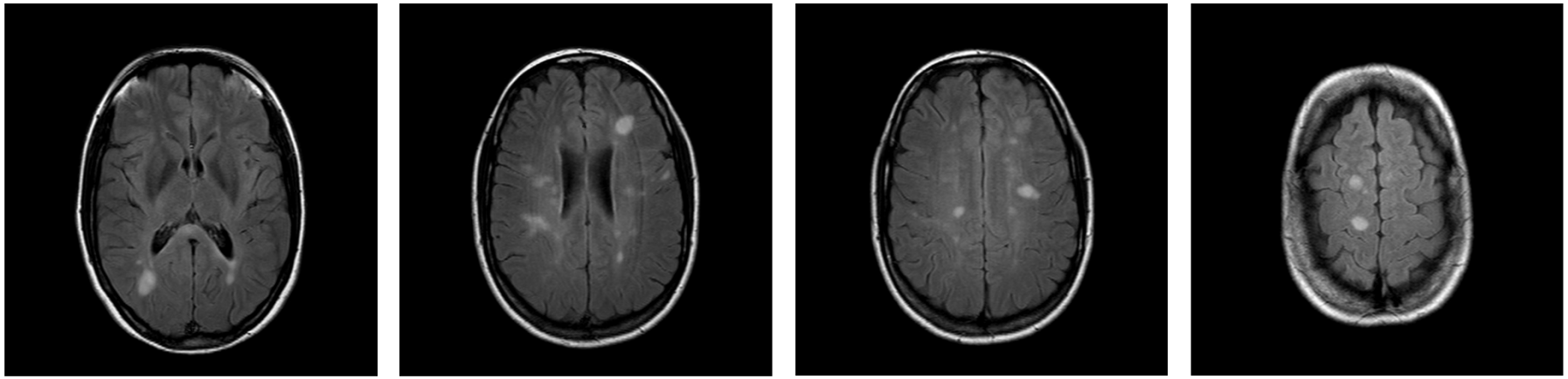


Muraro et al. Nat. Rev. Neurol, 2017

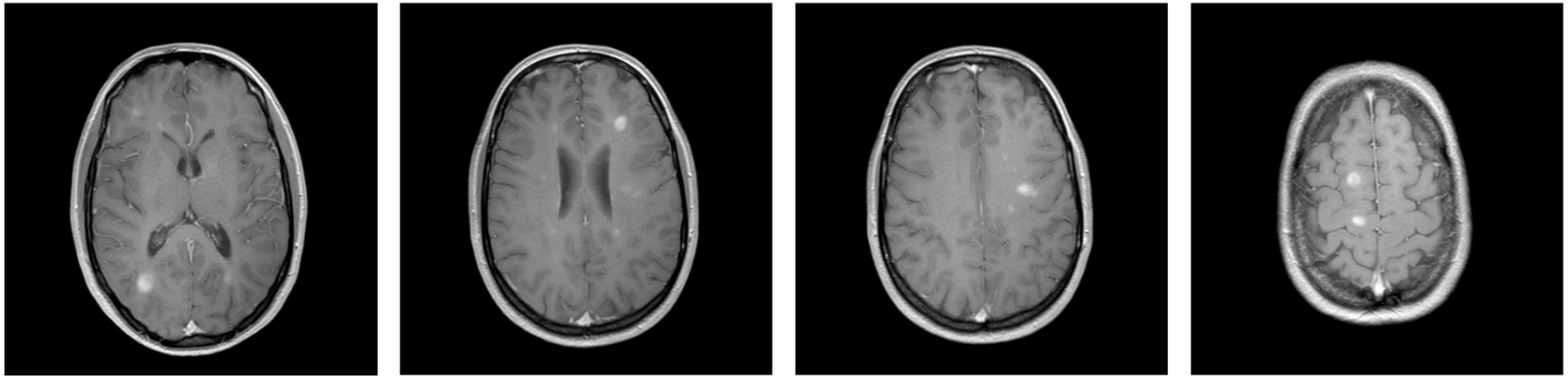
Limitations of Long Term Immune suppression

- Fertility/Pregnancy
- Opportunistic Infection (**PML**)
- Rebound syndrome after medication cessation

FLAIR



T1 Gad



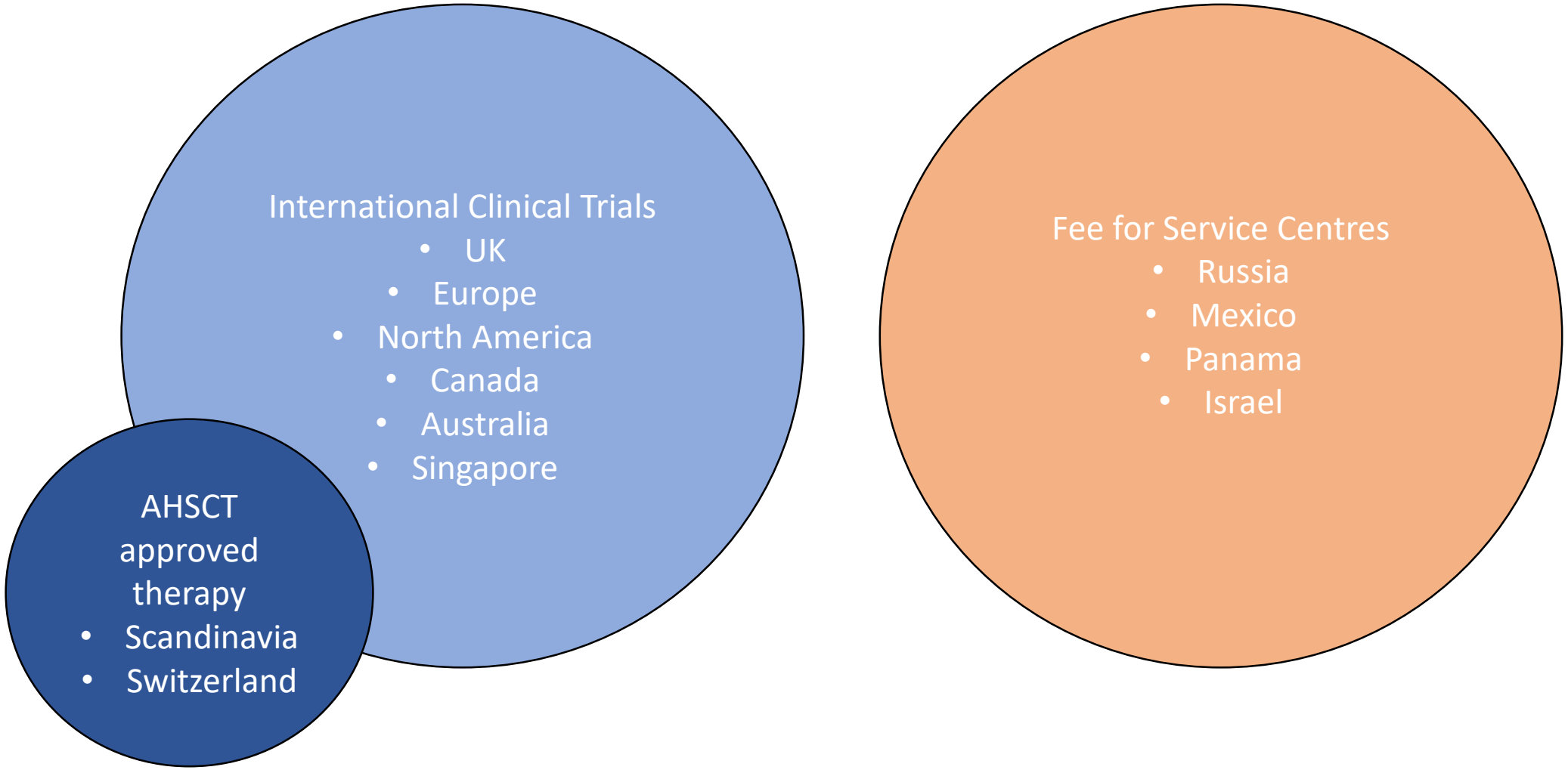
Immune reconstitution therapies

On PBS:

- Cladribine
- Alemtuzumab

- AHSCT

AHSCT for MS – Global Perspective



Australian AHSCT

- NSW
  - SVHA
    - Commenced 2010
    - 62 patients (8-10/yr)
    - 9 ‘non-MS’ neuroimmunological diseases
  - ?second centre
- Victoria
  - Alfred Hospital
  - Austin Hospital
- Tassie, Qld, SA – ad hoc
- NZ

RESEARCH PAPER

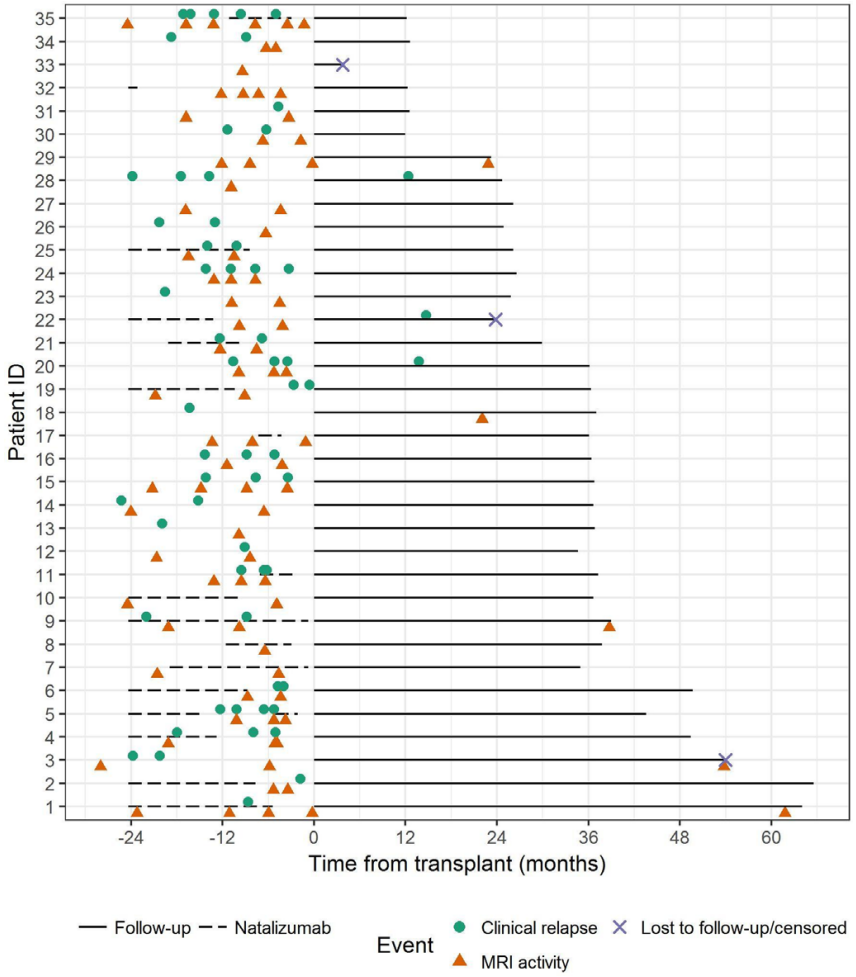
Prospective phase II clinical trial of autologous haematopoietic stem cell transplant for treatment refractory multiple sclerosis

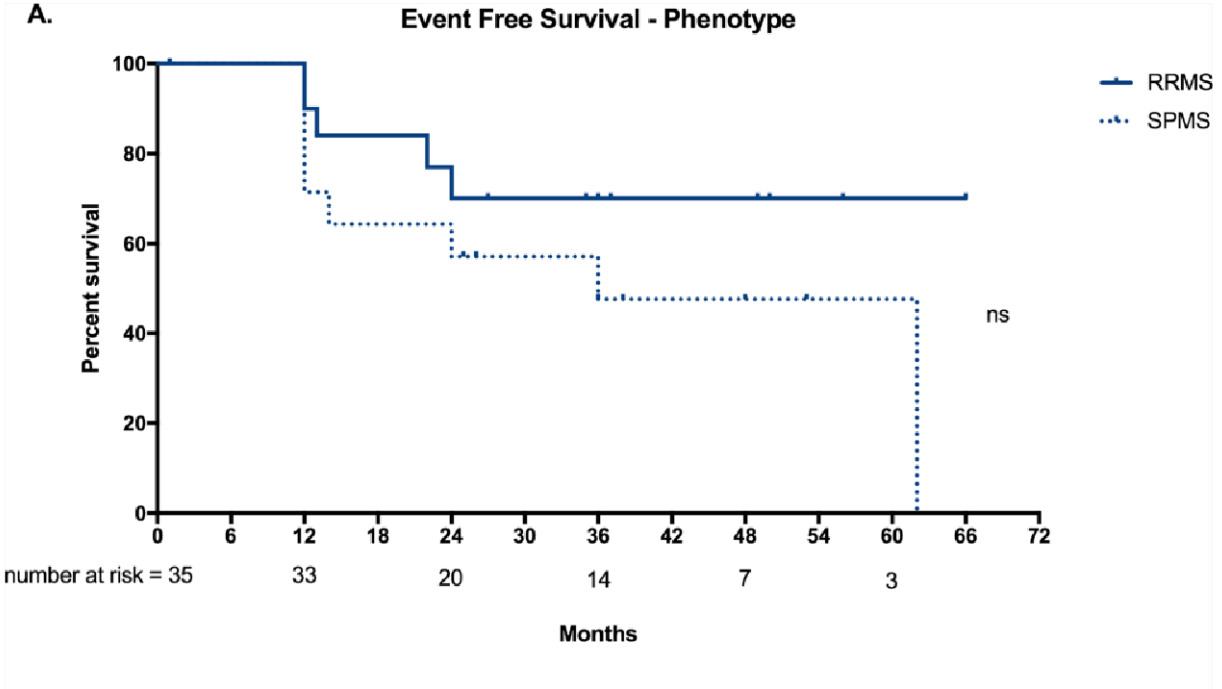
John J Moore,[1] Jennifer C Massey,[2] Carole D Ford,[3] Melissa L Khoo,[3] John J Zaunders,[4] Kevin Hendrawan,[3] Yael Barnett,[5] Michael H Barnett,[6] Kain A Kyle,[6] Robert Zivadinov,[7] Kris C Ma, Sam T Milliken,[1] Ian J Sutton,[2] David D F Ma[1]

Moore JJ, *et al*. *J Neurol Neurosurg Psychiatry* 2018;**0**:1–8. doi:10.1136/jnnp-2018-319446

35 pwMS – 20 RRMS, 15 SPMS
Median f/up 36m (12 – 66)
Median EDSS 6 (2- 7)
No TRM

- MS relapse-free survival was 90% at 3 years after AHSCT.
- No new MRI lesions were detected in 83% at 3 years.
- EDSS progression-free survival (PFS) was 73% at 3 years.





August 2021

N = 60 MS patients
54 >12m follow up

33F, 21M

31 RRMS, 23 ‘active’ SPMS

Mean age at Tx 37.9 years

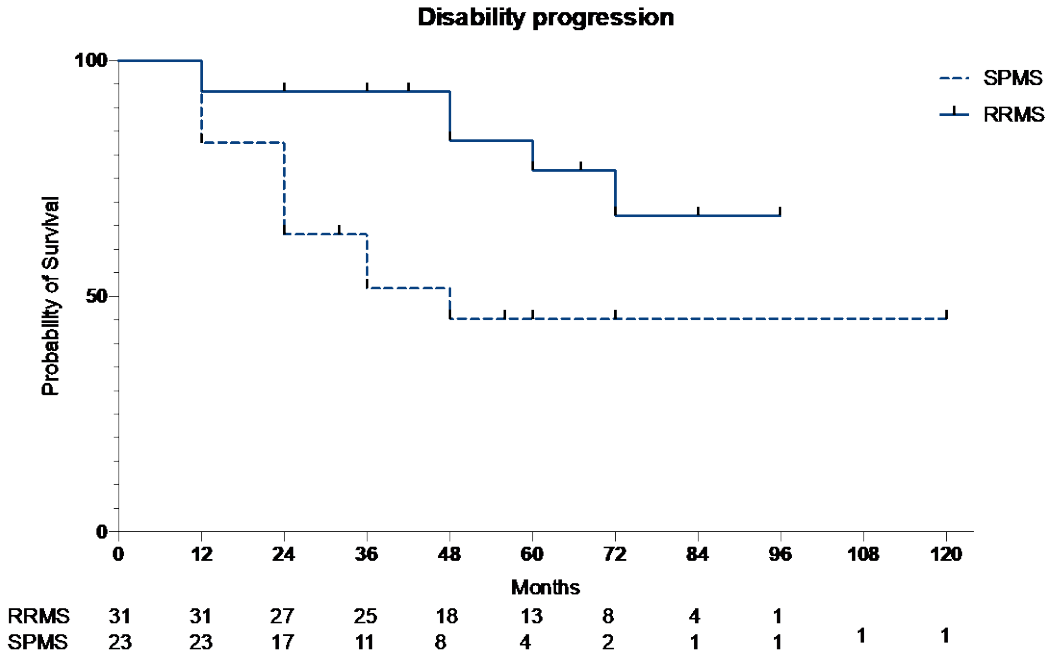
Median duration follow up = 48m

Median EDSS at baseline = 4.5 (1 – 7)

% free from disability progression

Months	SPMS	RRMS
24.000	63.171	93.548
Months	SPMS	RRMS
48.000	45.225	83.154

P value	0.0089



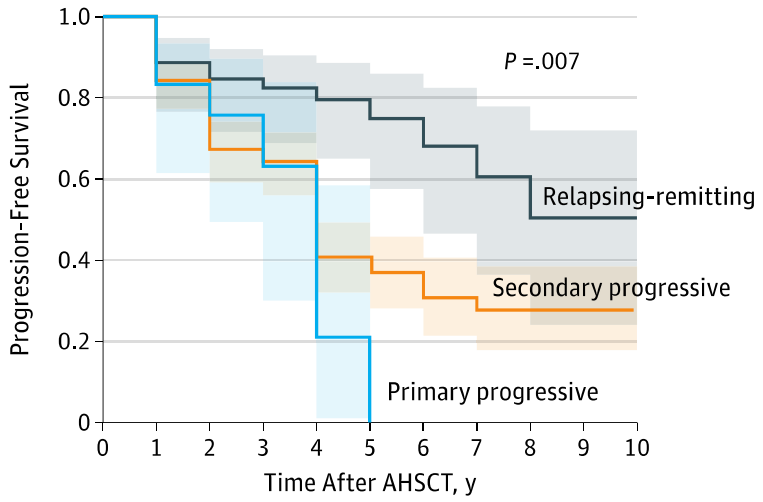
2017

Long-term Outcomes After Autologous Hematopoietic Stem Cell Transplantation for Multiple Sclerosis

Paolo A. Muraro, MD; Marcelo Pasquini, MD; Harold L. Atkins, MD; James D. Bowen, MD; Dominique Farge, MD; Athanasios Fassas, MD; Mark S. Freedman, MD; George E. Georges, MD; Francesca Gualandi, MD; Nelson Hamerschlak, MD; Eva Havrdova, MD; Vassilios K. Kimiskidis, MD; Tomas Kozak, MD; Giovanni L. Mancardi, MD; Luca Massacesi, MD; Daniela A. Moraes, MD; Richard A. Nash, MD; Steven Pavletic, MD; Jian Ouyang, MD; Montserrat Rovira, MD; Albert Saiz, MD; Belinda Simoes, MD; Marek Trněný, MD; Lin Zhu, MD; Manuela Badoglio, MSc; Xiaobo Zhong, MS; Maria Pia Sormani, PhD; Riccardo Saccardi, MD; for the Multiple Sclerosis-Autologous Hematopoietic Stem Cell Transplantation (MS-AHSCT) Long-term Outcomes Study Group

Variable	CIBMTR (n = 111)	EBMT (n = 170)	Total Cohort (N = 281)
No. of centers	8	17	25
Age, median (range), y	40 (26 to 60)	35 (15 to 65)	37 (15 to 65)
Age group, No. (%), y			
10-19	0	6 (3.5)	6 (2.1)
20-29	11 (9.9)	47 (27.6)	58 (20.6)
30-39	40 (36.0)	67 (39.4)	107 (38.1)
40-49	44 (39.6)	41 (24.1)	85 (30.2)
>50	16 (14.4)	9 (5.3)	25 (9.0)
Sex, No. (%)			
Male	48 (43.2)	69 (40.6)	117 (41.6)
Female	63 (56.8)	101 (59.4)	164 (58.4)
MS subtype at baseline, No. (%)			
Relapsing-remitting	12 (10.8)	34 (20.0)[b]	46 (16.4)
Progressive relapsing	0	17 (10.0)	17 (6.0)
Primary progressive	16 (14.4)	16 (9.4)	32 (11.4)
Secondary progressive	83 (74.8)	103 (60.6)	186 (66.2)
Conditioning Regimen, No. (%)			
High intensity	43 (38.7)	10 (5.9)	53 (18.9)
Cyclophosphamide plus TBI plus antithymocyte globulin	28 (25.2)	0	28 (10.0)
Busulfan plus cyclophosphamide plus antithymocyte globulin	15 (13.5)	0	15 (5.3)
Busulfan plus antithymocyte globulin	0	10 (5.9)	10 (3.6)
Intermediate intensity	28 (25.2)	151 (88.8)	179 (63.7)
BEAM plus antithymocyte globulin	23 (20.7)	86 (50.6)	109 (38.8)
BEAM	0	40 (23.5)	40 (14.2)
Cyclophosphamide plus thiotepa	0	7 (4.1)	7 (2.5)
TLI plus melphalan	5 (4.5)	0	5 (1.8)
Carmustine plus cyclophosphamide plus antithymocyte globulin	0	18 (10.6)	18 (6.4)
Low intensity	40 (36.0)	9 (5.3)	49 (17.4)
Cyclophosphamide plus antithymocyte globulin	37 (33.3)	9 (5.3)	46 (16.4)
Cyclophosphamide plus fludarabine phosphate	3 (2.7)	0	3 (1.1)
Antithymocyte globulin	104 (93.7)	128 (75.3)	232 (82.6)

Eight deaths (2.8%; 95% CI, 1.0%-4.9%) were reported within 100 days of transplant and were considered transplant-related mortality



No. at risk

Relapsing-remitting	53	53	44	38	29	17	11	9	6	4	1
Secondary progressive	162	162	121	90	71	32	18	10	4	2	1
Primary progressive	24	24	11	6	3	1					

Current inclusion criteria

- EDSS score 0-6.5*
- Active MS despite the use of high efficacy disease modifying therapy* for >3 months prior to the relapse. ‘Active MS’ defined as:
  - ≥1 clinical relapse in the opinion of the referring neurologist
- AND/OR
  - Evidence of radiological disease activity (T1 lesion, T2/FLAIR lesion, Gd+ lesion) and evidence that this new activity did not preclude commencement of high-efficacy DMT.

*High efficacy DMT currently includes: natalizumab, ocrelizumab, ofatumumab, alemtuzumab, fingolimod and cladribine. Future DMT’s of a similar class/mechanisms of action will also be considered high efficacy eg: future CD-20 monoclonal antibodies (mAbs) for MS

Important Questions

- ?correct decision for people with inflammatory SPMS
  - Procedure performed to prevent relapse associated disability
  - ?trajectory of progression

- Early vs. late referral for AHSCT
  - Difficult to predict long term outcomes based on limited follow up

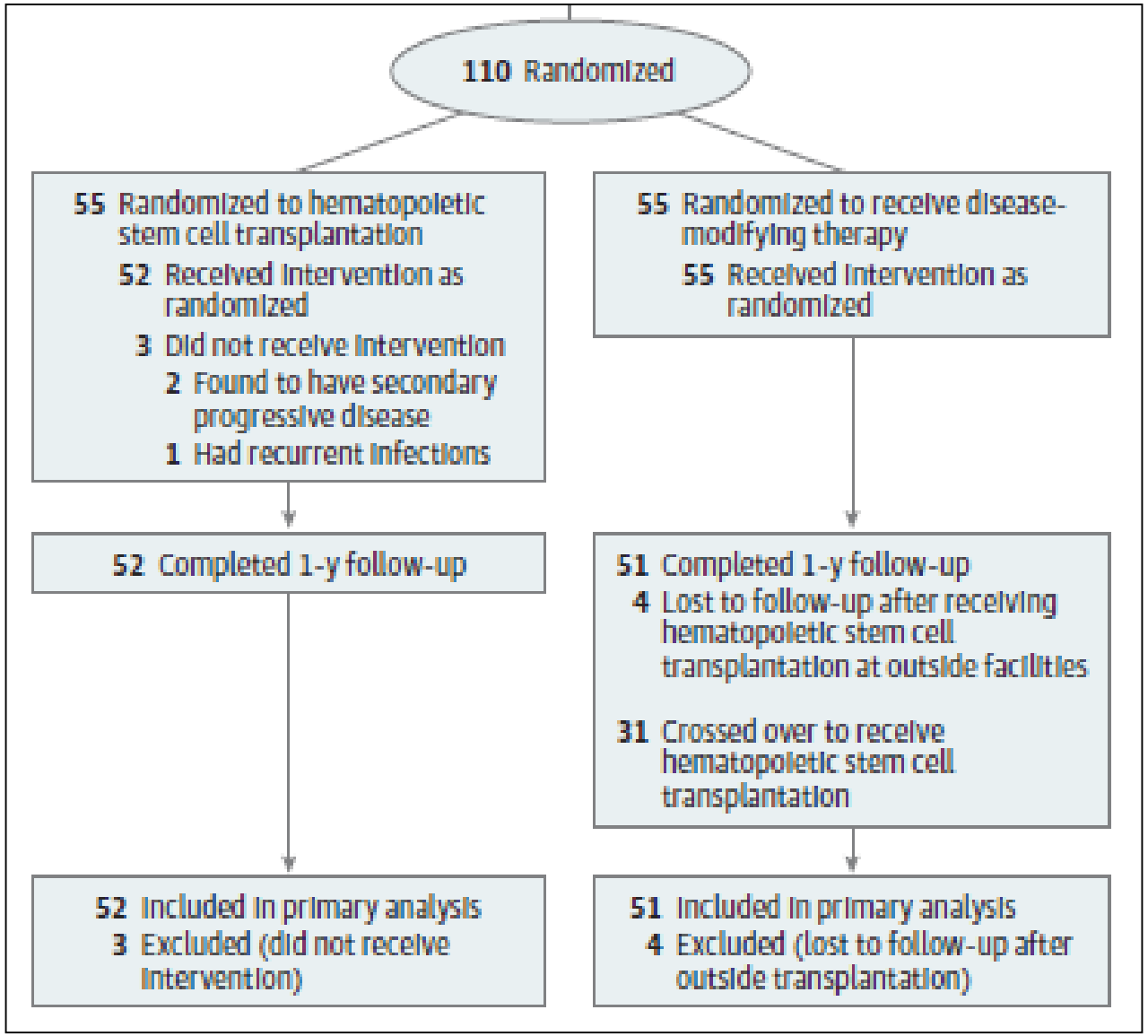
More unanswered Qs

- AHSCT vs. DMT
- Chemo regimen

Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients With Relapsing-Remitting Multiple Sclerosis

A Randomized Clinical Trial

JAMA. 2019;321(2):165-174. doi:10.1001/jama.2018.18743



- Patients randomized to the DMT group received an FDA-approved DMT of higher efficacy or a different class based on the judgment of their treating neurologist.

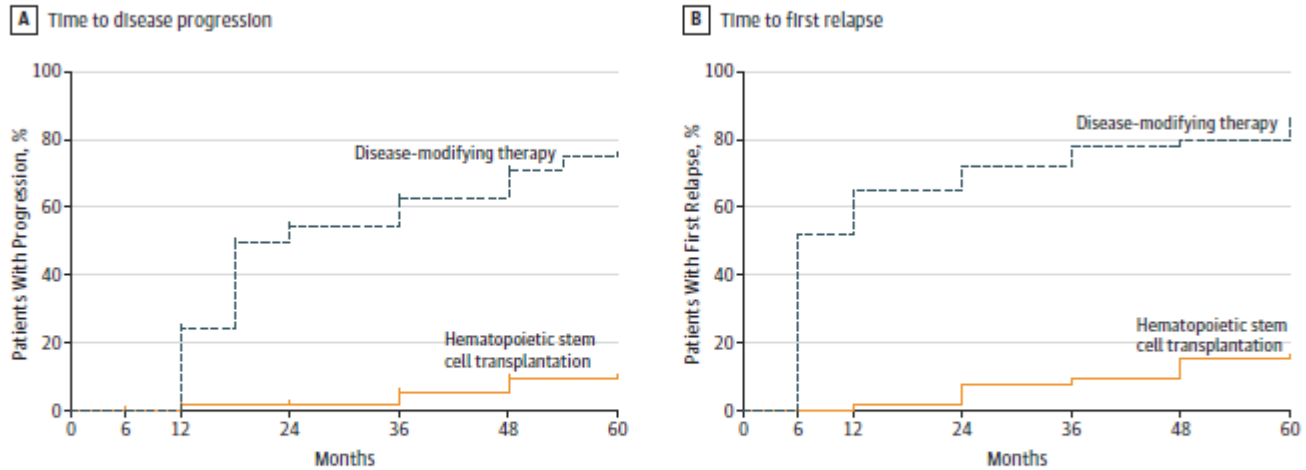
- In addition to DMT, patients could receive methylprednisolone, rituximab, intravenous immunoglobulin, or cyclophosphamide.

- Ocrelizumab was excluded as it was not FDA licensed until 2017.

- Alemtuzumab was excluded because of drug-related persistent lymphopenia and autoimmune disorders that might increase complications and risk related to HSCT in the crossover group.

21 Natalizumab
14 Dimethyl fumarate
14 Fingolimod
9 Glatiramer acetate
7 Interferonbeta-1a
6 Mitoxantrone
1 Teriflunomide.

Figure 2. Time to Disease Progression and First Relapse Among Patients Receiving Hematopoietic Stem Cell Transplantation vs Disease-Modifying Therapy



No. at risk

Hematopoietic stem cell transplantation	52	52	51	51	50	49	48	53	53	52	49	48	45	45
Disease-modifying therapy	54	54	43	30	26	24	23	55	26	18	15	12	11	9

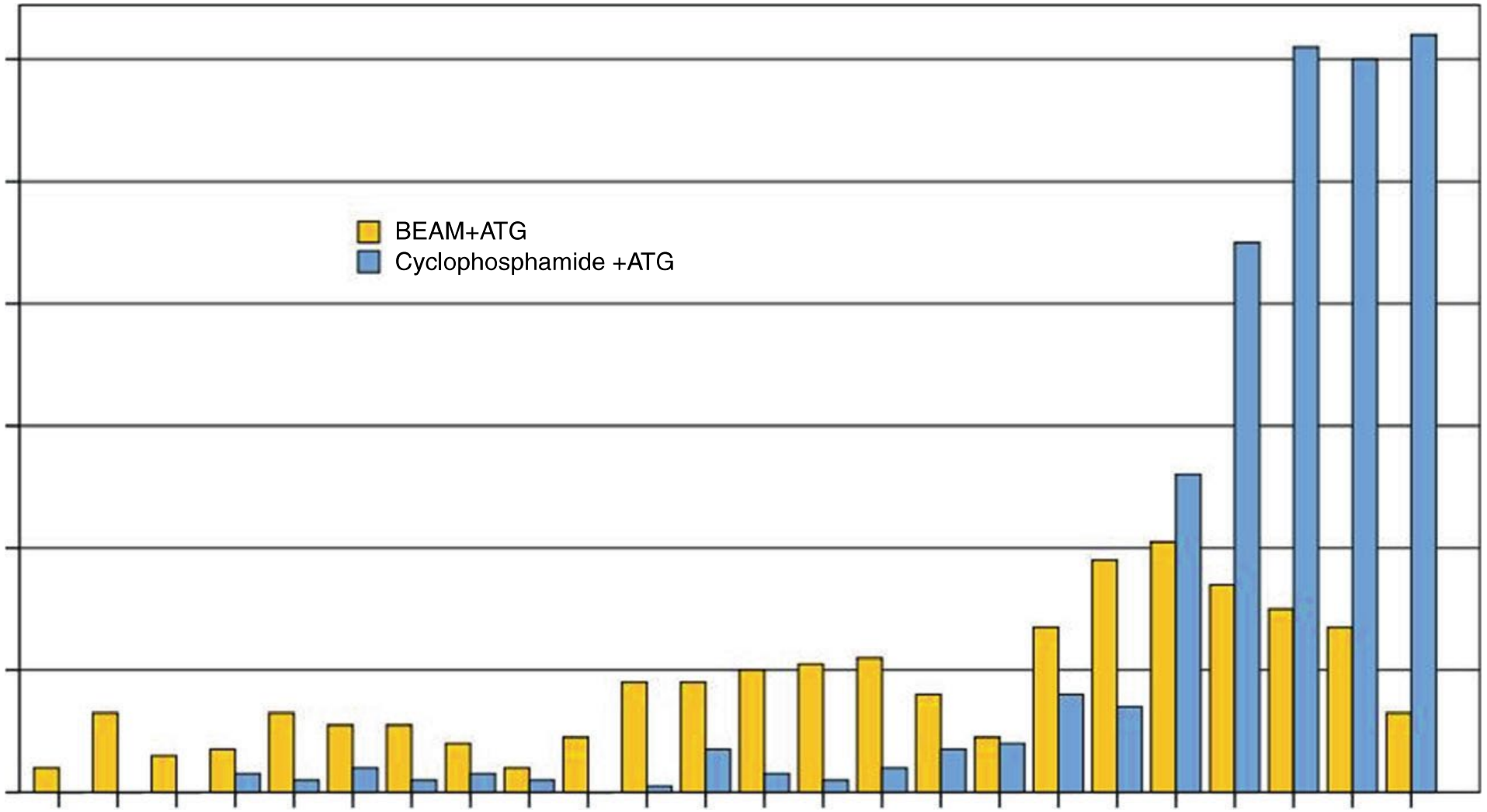
Median follow-up time was 24 months (interquartile range, 12-48 months).

- Relapse rate of 50% of the DMT group at six months and 69% at one year.

Inadequate for TGA approval of AHSCT

Future trials

Name (NCT)	Type of study	Conditioning protocol	Comparator	Primary endpoint	Sample size: recruited/goal	Age (range)	MS form	EDSS	Estimated completion	Status
RAM-MS (NCT03477500)	Phase III RCT	Cy + ATG	alemtuzumab, ocrelizumab, or cladribine	NEDA at 2 y	36/100	18-50	RR	0.0-5.5	March 2024	recruiting
BEAT-MS (NCT04047628)	Phase III RCT	BEAM + ATG	natalizumab, alemtuzumab, ocrelizumab, or rituximab	RFS at 3 y	0/ 300	18-55	R-MS (PP excluded)	2.5-5.5	November 2028	not yet recruiting
NET-MS	Phase II RCT	BEAM + ATG	natalizumab, alemtuzumab, ocrelizumab, or rituximab	NEDA at 3 y	0/90	18-50	RR; active SP	2.0-6.0	NR	not yet recruiting
COAST	Phase II RCT	Cy + ATG	alemtuzumab, ocrelizumab	NEDA at 2y	0/50	18-55	RR	0.0-6.0	NR	not yet recruiting
STAR-MS	Phase III RCT	Cy + ATG	alemtuzumab, ocrelizumab	NEDA at 2 y	0/198	16-55	RR	0.0-6.0	NR	not yet recruiting

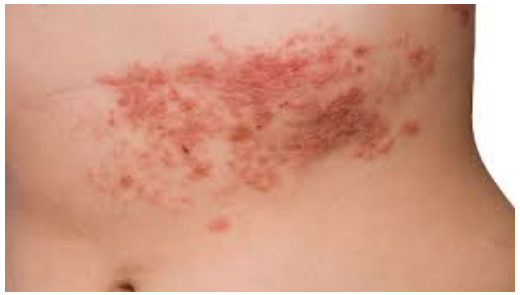


EBMT 2019

Complications

0.3 – 0.5% mortality risk – BEAM
0.1 - 0.3% mortality risk - CYC

VZV



Long-term Outcomes After Autologous Hematopoietic Stem Cell Transplantation for Multiple Sclerosis

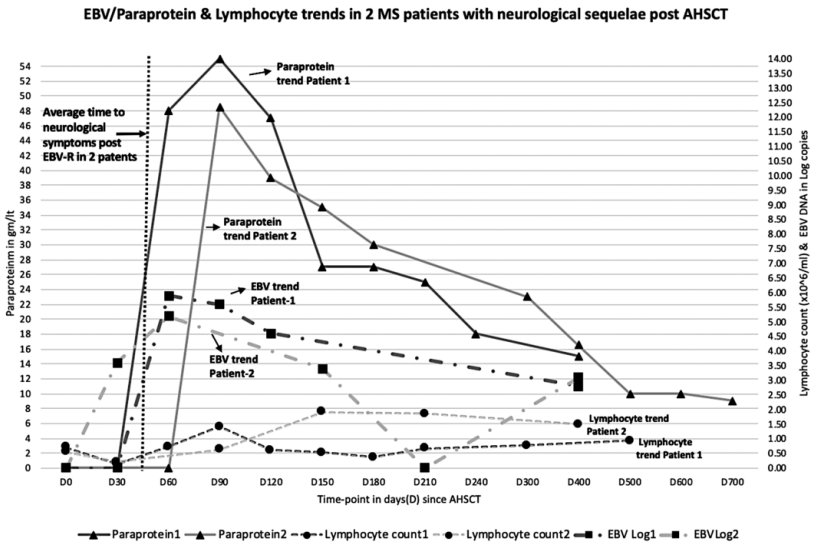
B. Causes of death after post-transplant day 100

	n	Prior MS treatments
Patients at risk	*273*	
MS progression	9	IFNb (n=7)
Infection	5	IFNb (n=3), CY, mitox
Malignancies	3	IFNb (n=2), CY (n=1), AZA (n=1)
Accident	1	IFNb1a
Diverticulitis	1	Methotrexate
Organ failure	1	Corticosteroids only
Rejection/poor graft function	1	AZA, IvIG, IFNb1a, IFNb1b, mitox
Arterial thromboembolism lower limbs	1	None reported
Interstitial pneumonia	1	IFNb, AZA

Outcome	Alemtuzumab	AHSCT	Cy/ATG[a]	BEAM/ATG[a]	Reference DMTs[b]
No.	132	139	94	45	2,486
Infection					
Varicella zoster (diagnosis)	3 (8.3)	9 (20.4)	4 (16.6)	5 (24.9)	16 (1.8)

Boffa et al. Neurology 2021

EBV



No cases of PML post AHSCT for MS to date

Muraro et al. 2017 JAMA Neurol

A. Malignancies

Myelodysplastic syndrome		3
Breast cancer		2
Squamous cell carcinoma		1
Prostate cancer		1
Cervical Carcinoma		1
Glioblastoma Multiforme		1

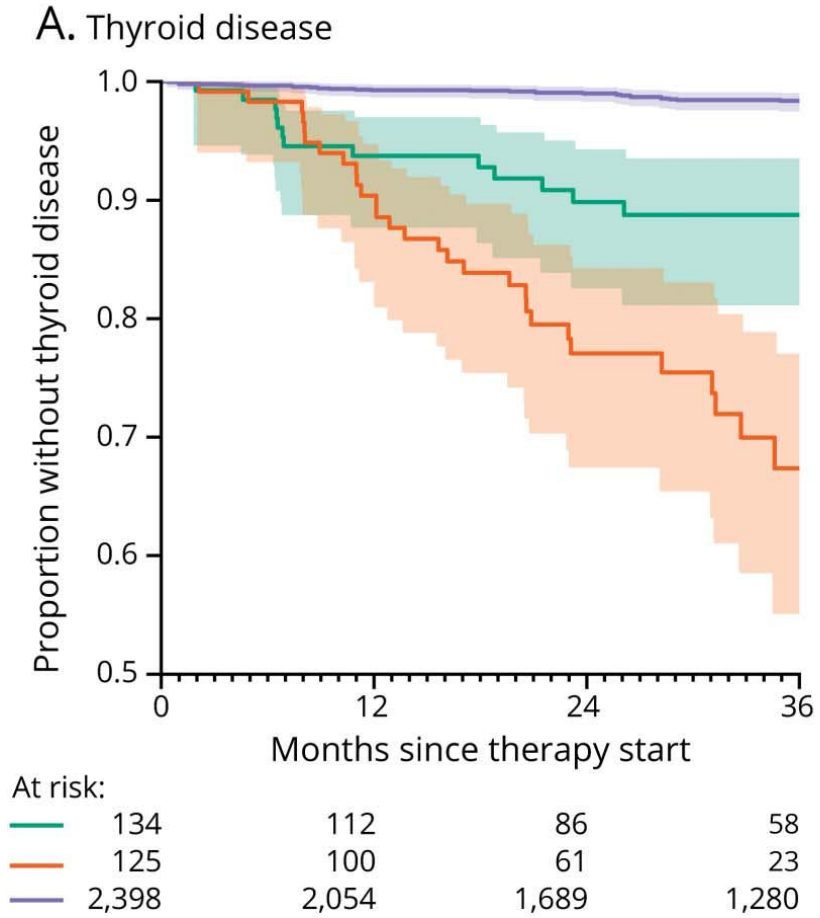
Total 9

B. New Autoimmune Disease

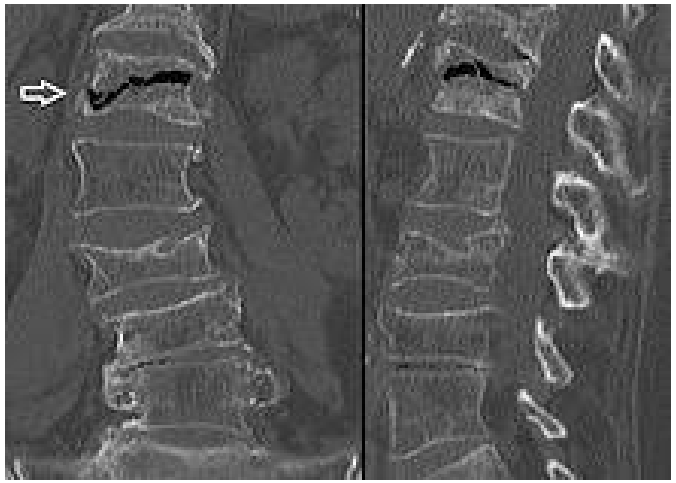
Autoimmune thyroid disease	8
Autoimmune thrombocytopenia	3
Acquired haemophilia	2
Crohn's disease	1

Total 14

Alping et al. 2021 Neurology



Ongoing management



Bone Health

Vaccinations

ORIGINAL ARTICLE

Onset and outcome of pregnancy after autologous haematopoietic SCT (AHSCT) for autoimmune diseases: a retrospective study of the EBMT autoimmune diseases working party (ADWP)

E Snarski[1,17], JA Snowden[2,17], MC Oliveira[3], B Simoes[4], M Badoglio[5], K Carlson[6], J Burman[7,8], J Moore[9], M Rovira[10], RE Clark[11], A Saiz[12], S Hadj-Khelifa[13], J Tan[9], A Crescimanno[14], M Musso[14], T Martin[15] and D Farge[16] on behalf of the Autoimmune Diseases Working Party (ADWP) of the European Group for Blood and Marrow Transplantation (EBMT) in collaboration with the University of Sao Paulo, Ribeirão Preto, Brazil

13 pregnancies in 7 women w MS

BMT 2015

EBT database 1994 - 2011

	Diagnosis	*Age at AHSCT*	*Conditioning regimen*	*Menstruation after AHSCT*	*Pregnancy number*	*Delivery and baby outcome*	*Age of the mother at delivery*	*Autoimmune disease status post pregnancy*	*Mother's status at last follow-up*
1	MS	28	BCNU+CY +ATG	No	1	Natural, alive	32	No change	Alive
					2	Natural, alive	35	No change	
2	MS	32	BEAM+ATG	Yes	1	Caesarian, alive	35	No change	Alive
					2	Natural abortion		No change	
					3	Caesarian, alive	39		
					4	Natural abortion			
3	MS	17	BEAM+ATG	Yes	1	Induced abortion		No change	Alive
4	MS	28	BEAM+ATG	Yes	1	Induced abortion		No change	Alive
					2	Natural, alive	31	No change	
					2	Natural, alive	31	No change	
5	MS	27	BEAM+ATG	Yes	1	Natural, alive	33	No change	Alive
6	MS	30	BEAM+ATG	Yes	1	Natural, alive	37	No change	Alive
7	RA	25	CY	Yes	1	Natural, alive	27	Relapse	Alive
					2	Natural, alive	29		
8	JIA	27	BEAM	No	1	Natural, alive	32	No change	Alive
9	SSc	32	CY+ATG	No	1	Caesarian, alive	36	No change	Alive
10	MS	31	BEAM+ATG	Yes	1	Natural, alive	32	No change	Alive

Pregnancy post autologous stem cell transplant with BEAM conditioning for multiple sclerosis

Sophie Chatterton, Barbara Withers, Ian J Sutton, Samuel T Milliken, David DF Ma, John J Moore and Jennifer C Massey

Multiple Sclerosis Journal
1–4
DOI: 10.1177/13524585211005660

+1 F
+3 M

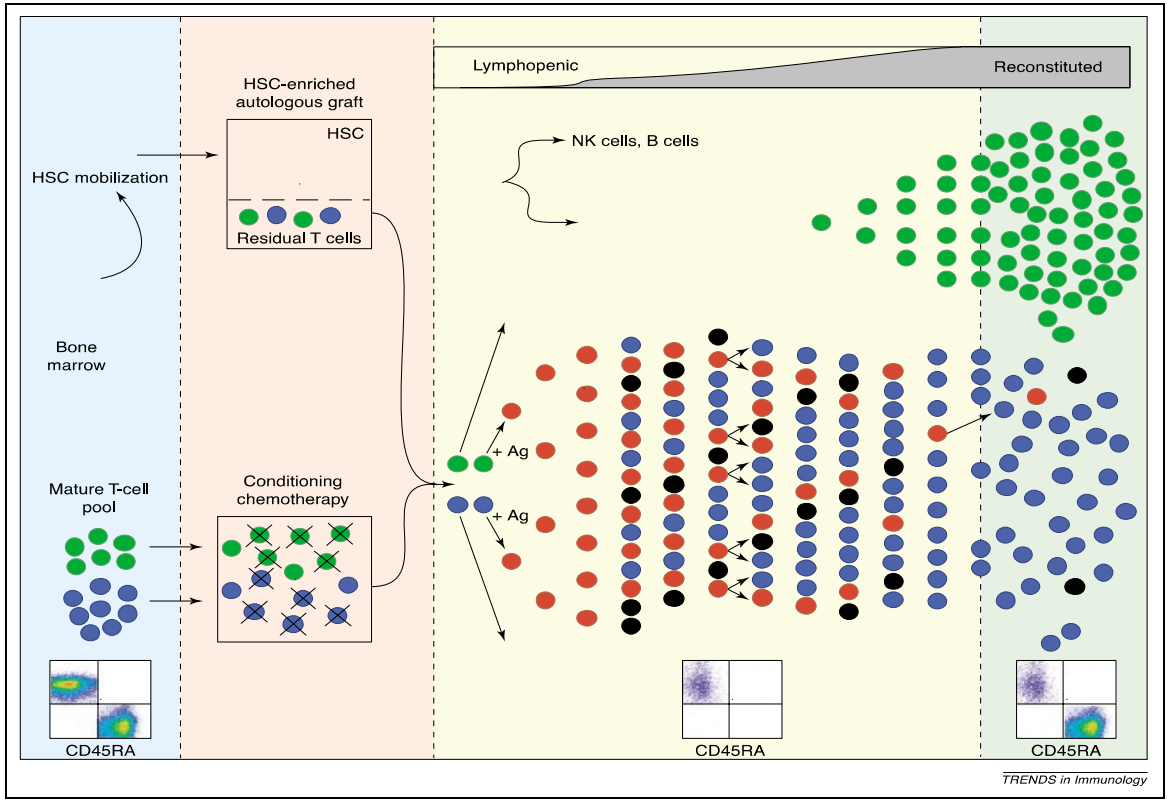
Table 1. Summary of pregnancies in our female cohort of multiple sclerosis patients post-AHSCT.

Age at transplant (years)	Age at conception (years)	Menstruation post AHSCT	Interval between AHSCT and conception (months)	Pregnancy number	Delivery and baby outcome	MS status post pregnancy	Complications
22	26	Amenorrhoea	24 and 48, respectively	2	First pregnancy unplanned, elective termination performed Full-term delivery via emergency Caesarean-section due to prolonged labour	Stable	No pregnancy or newborn complications aside from delivery
38	39	Oligomenorrhoea	11	2 (first post AHSCT)	Normal vaginal delivery, induced at 39 weeks due to advanced maternal age	Transitioned to secondary progressive MS	Nil
31	33	Normal menses	30	1	Elective termination, intrauterine device in situ	Stable	Nil

AHSCT: autologous haematopoietic stem cell transplant; MS: multiple sclerosis.

AHSCT for MS
Who, What, When and Why

1. Deletion of lymphocyte populations
2. Induction of a lymphopenic state
3. A tolerant *milieu*.
4. Thymic repopulation



Conclusion

- IRT have provided significant advances in the management of MS.
- In the correct setting, AHSCT may offer protracted periods of disease remission.
- We are always happy to have a discussion about the trial and answer questions.

Acknowledgements
SVH Haematology and Neurology Departments
9S Nursing staff
MS Australia
MS Angels
Our patients and their families