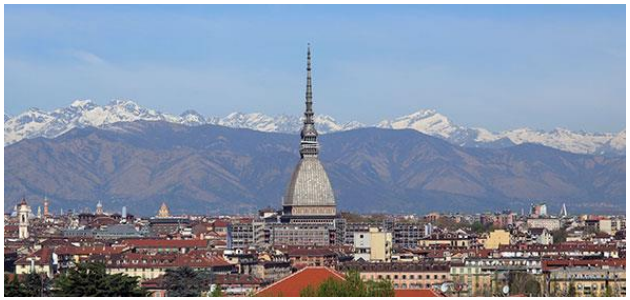


Sclerosi multipla:
Il punto sui farmaci sistemici

Alice Laroni

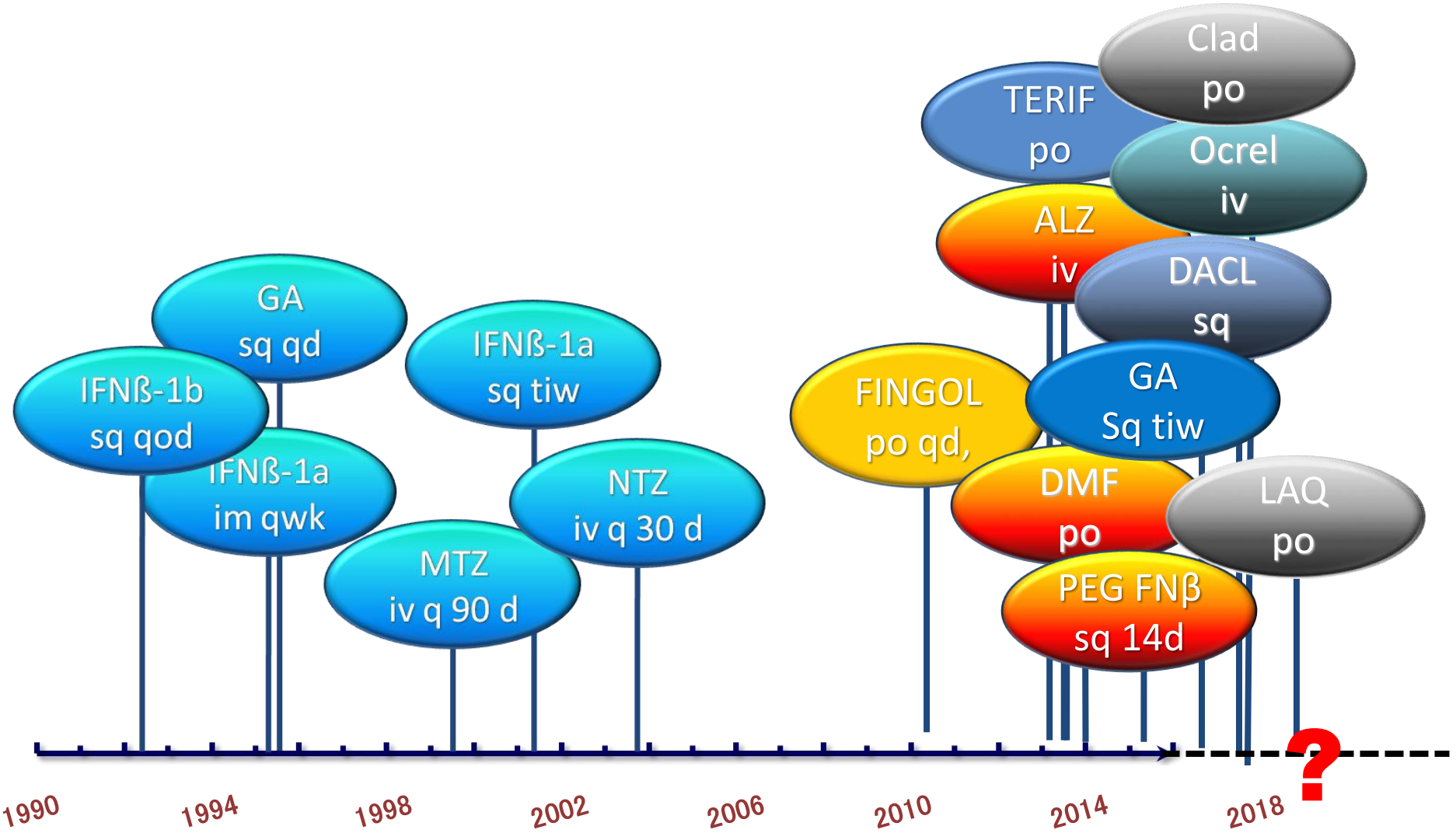
Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia,
Genetica e Scienze Materno-Infantili

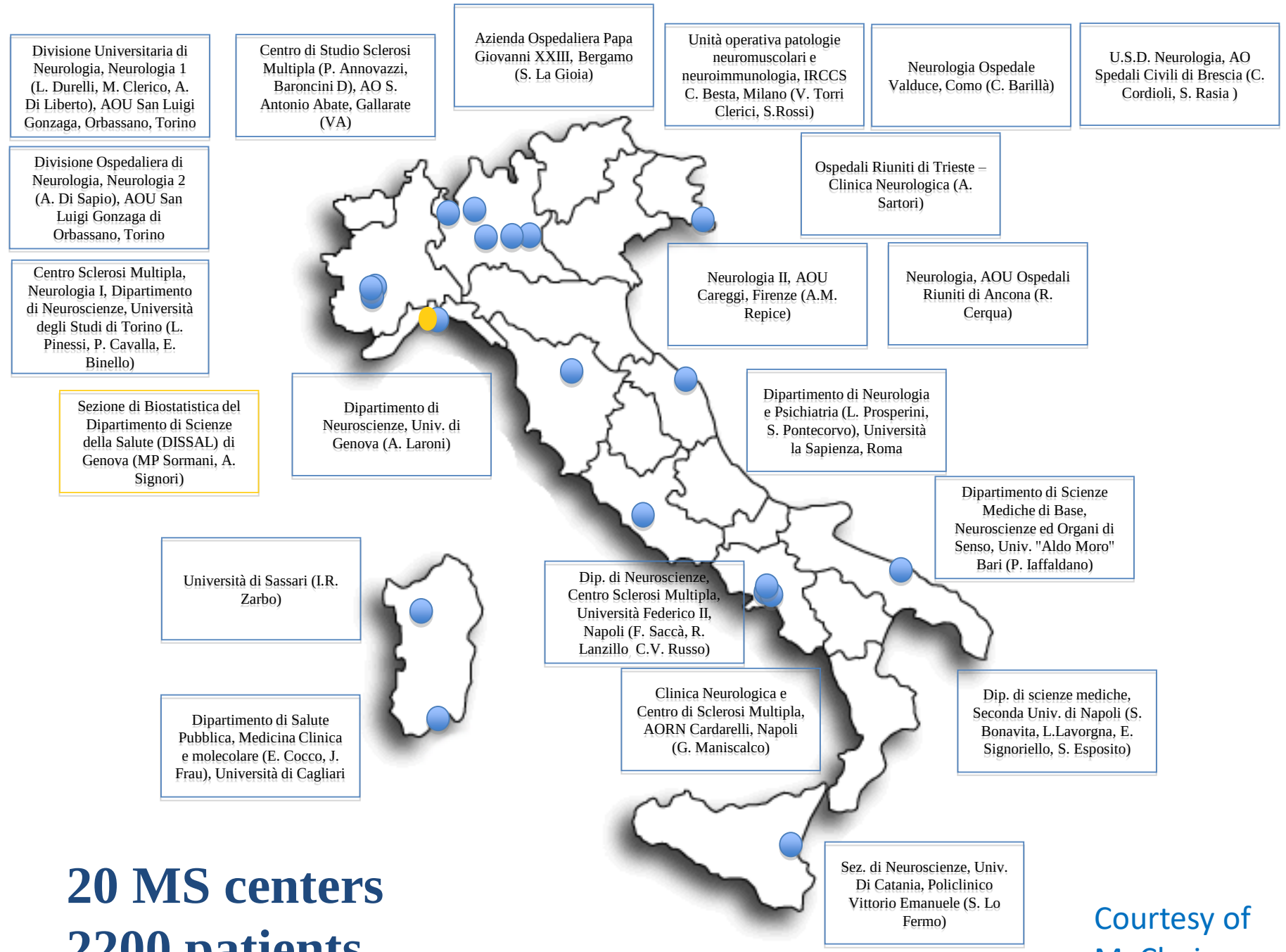
Università di Genova

Torino, 7 ottobre 2016

Quale spazio per le terapie iniettive per la SM?

Present and "near future" Disease Modifying Drugs for RRMS

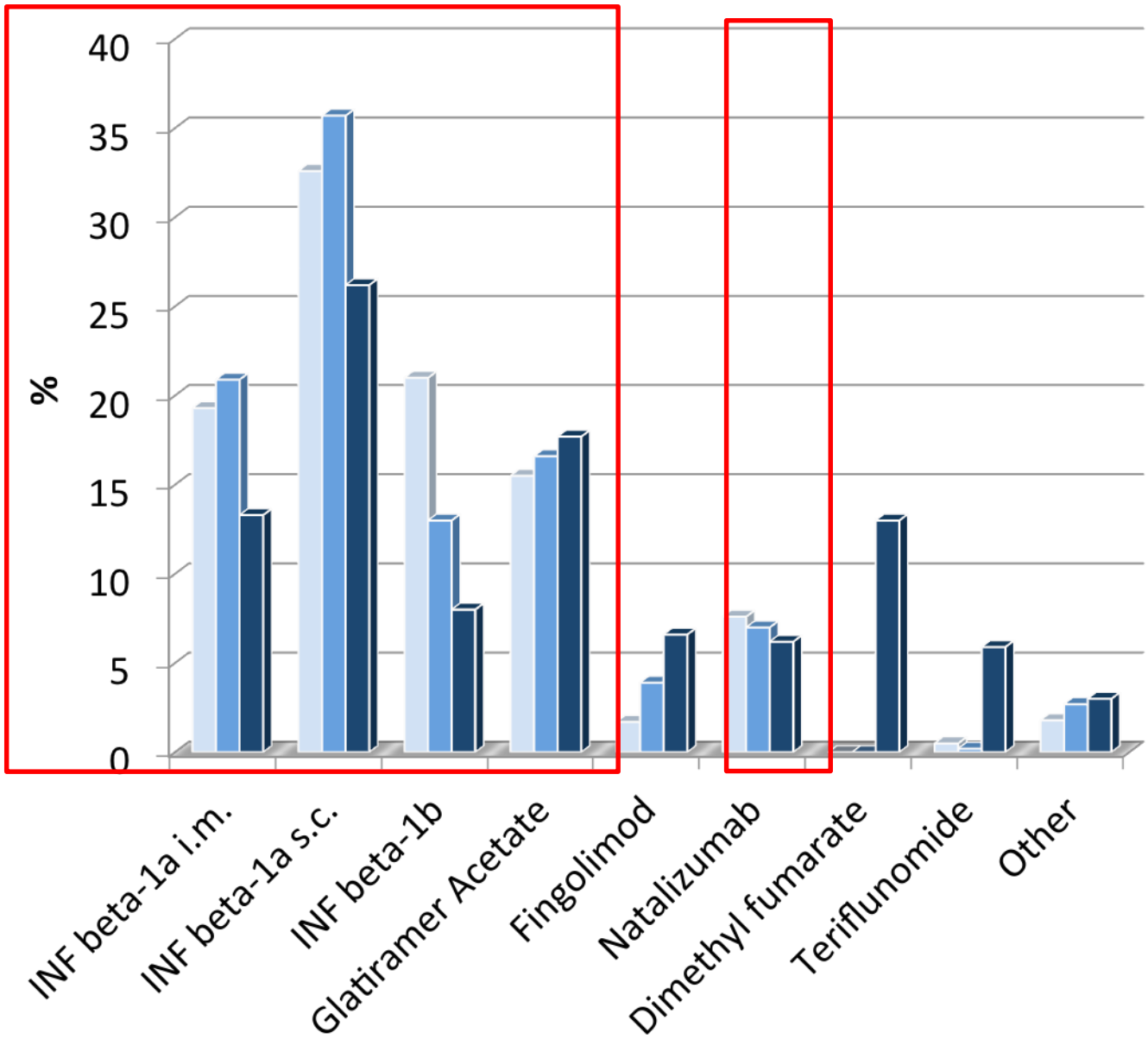




20 MS centers
2200 patients

Courtesy of M. Clerico

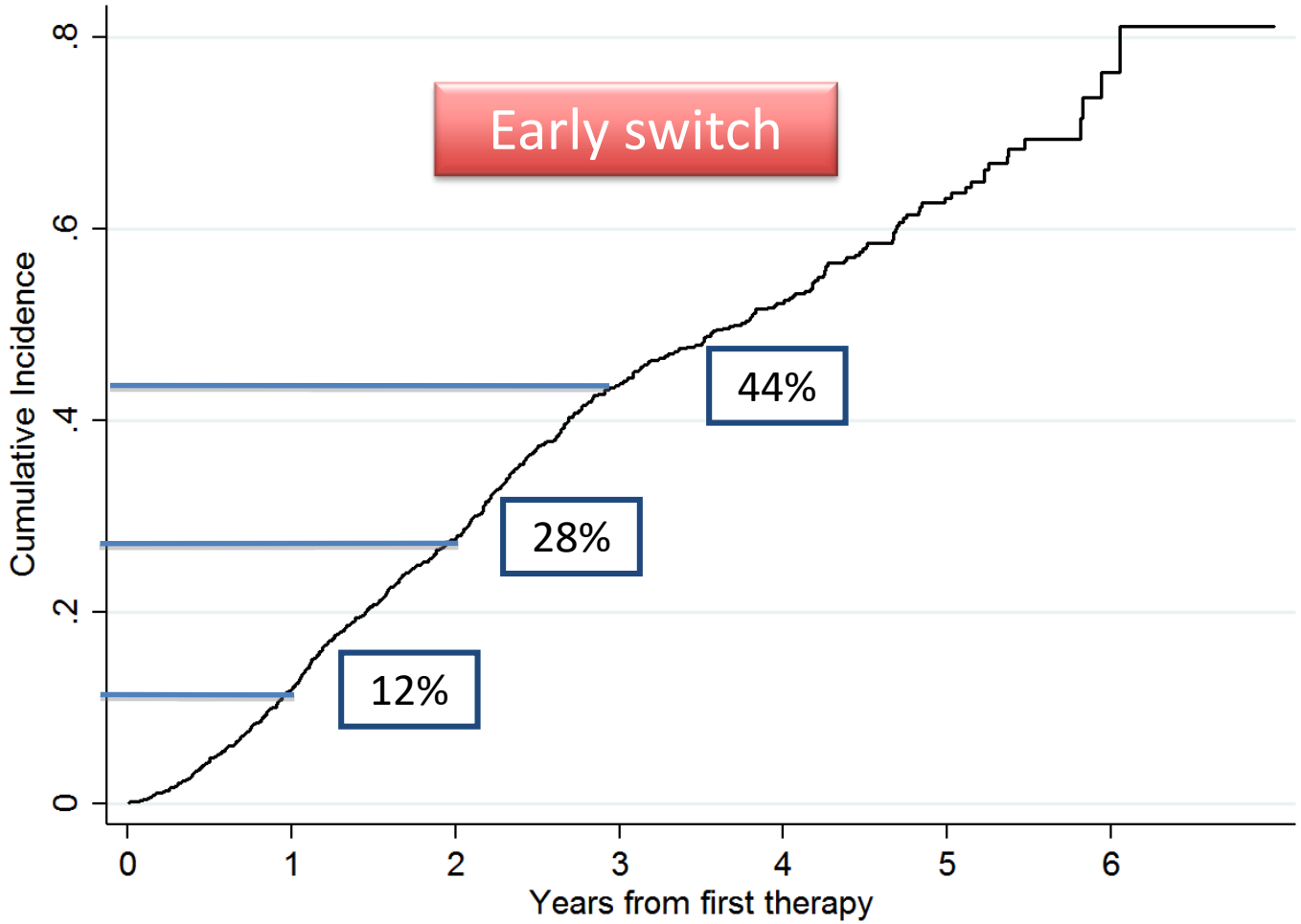
First therapy 2010-2016



Abt 75→ 65% are injectables

Courtesy of M. Clerico

Time to switch

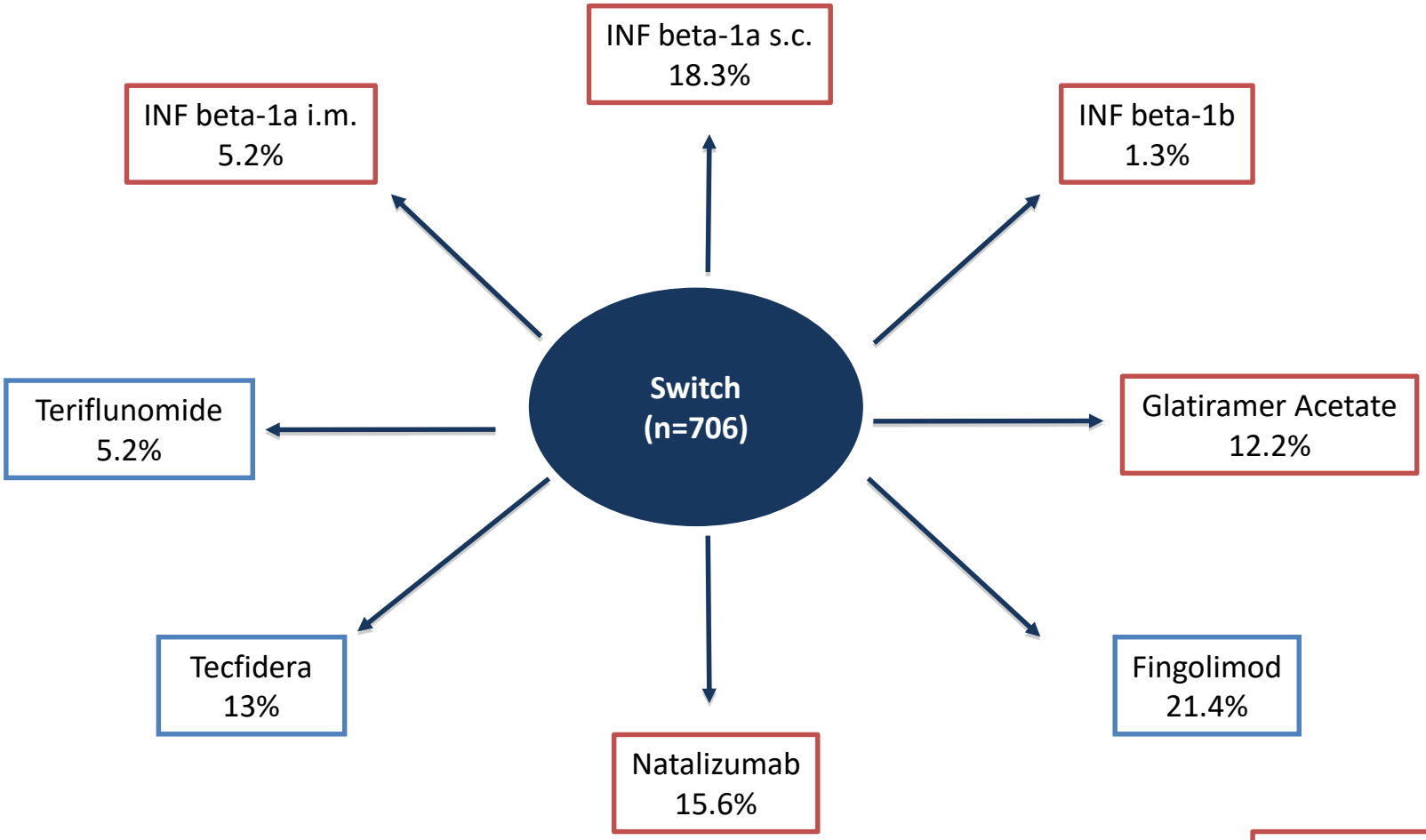


Number at risk

2034	**1389**	**843**	**474**	**234**	**74**	**8**

Courtesy of M. Clerico

Second Therapy



Other: 7.8%

Courtesy of M. Clerico

Abt 65 % are injectables

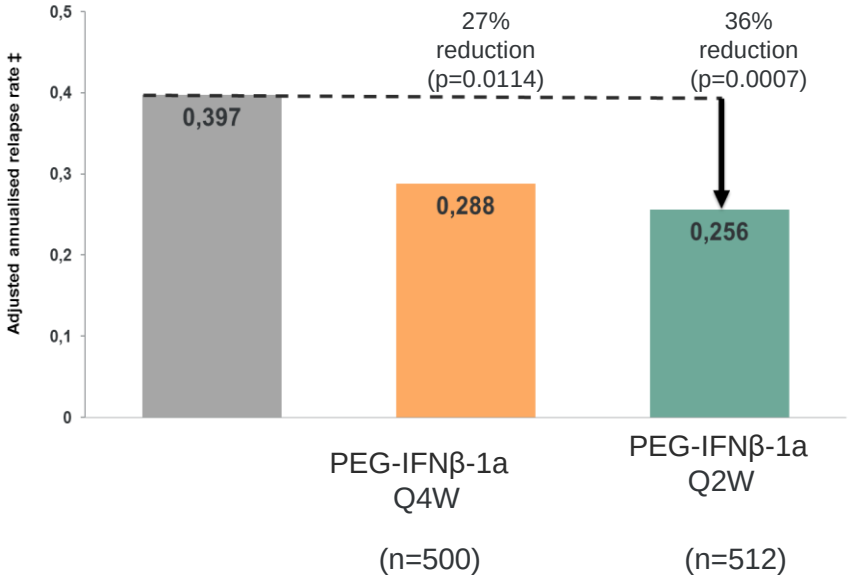
Agenda

- PEG interferone
- Copaxone 40 mg
- Natalizumab
- Alemtuzumab
- Daclizumab
- *Rituximab, Ocrelizumab e Ofatumumab*

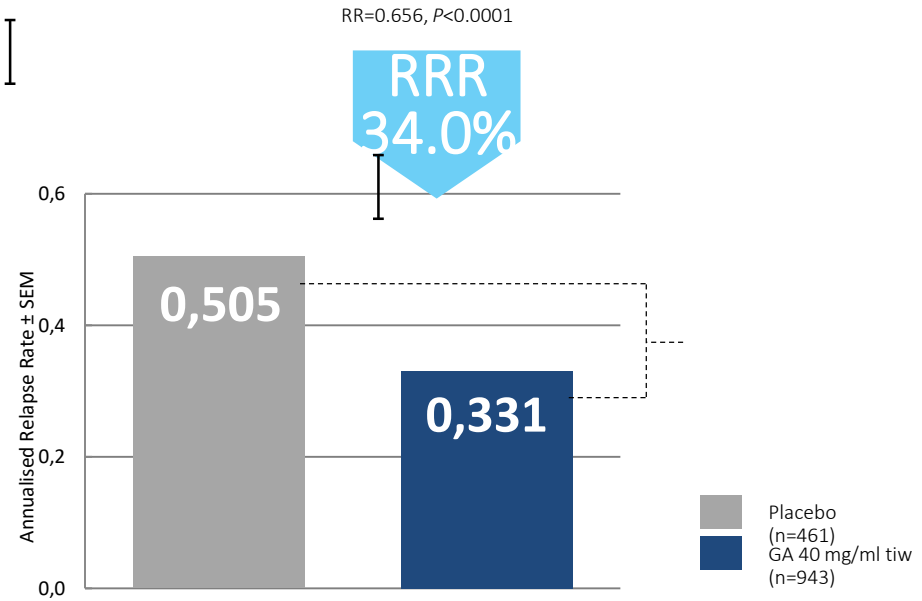
IFN Beta-1a pegilato
e Copaxone 40

Nuova formulazione/nuovo dosaggio di farmaci consolidati

Riduzione significativa dell'ARR



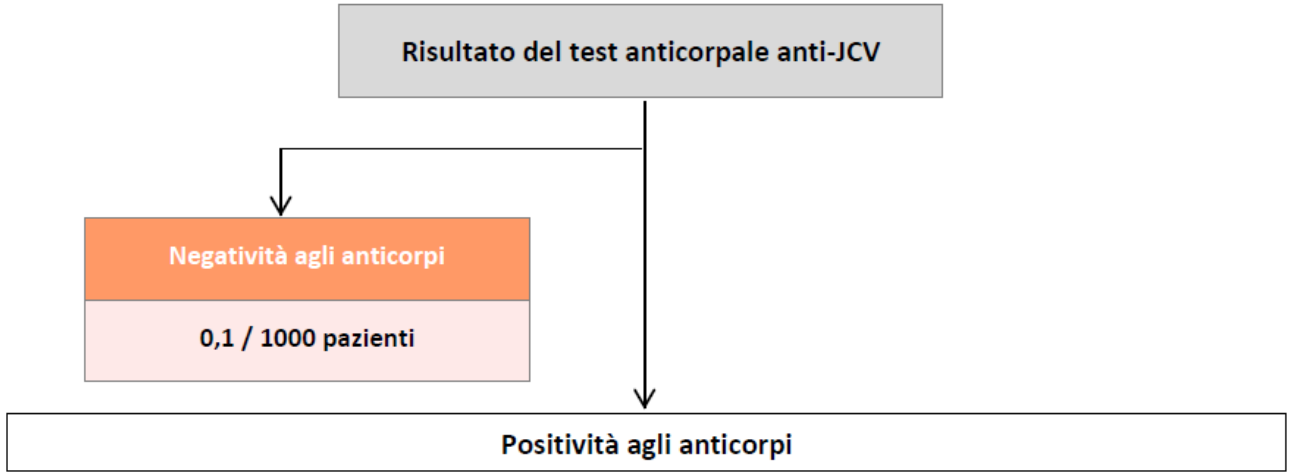
PEGinterferone è efficace rispetto a placebo



Copaxone 40 è efficace rispetto a placebo

Natalizumab

Nuove informazioni di sicurezza

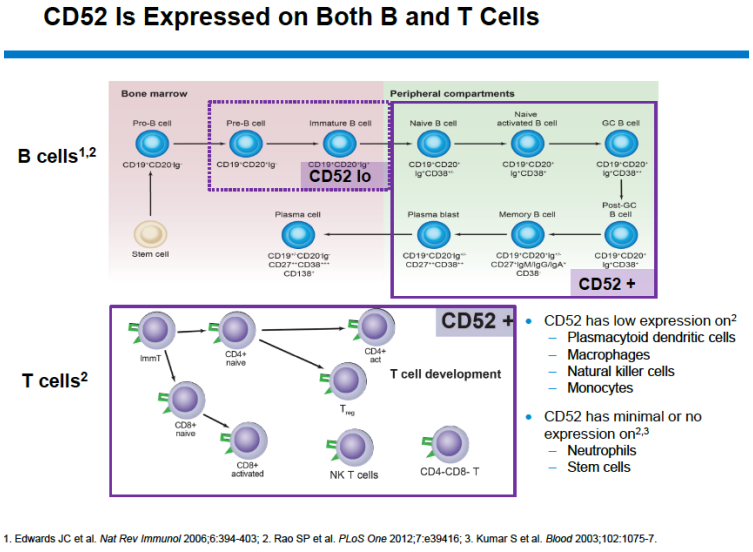


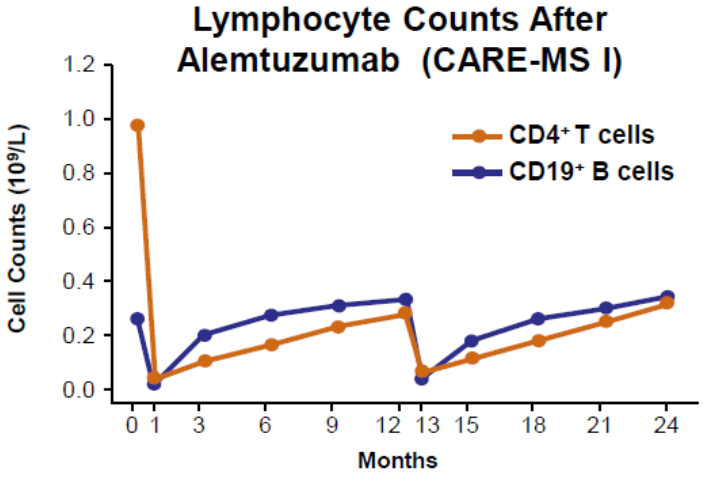
Durata del Trattamento con natalizumab	Valori stimati del rischio di PML su 1.000 pazienti				
	Pazienti senza precedente uso di immunosoppressori				Pazienti con precedente uso di immunosoppressori
	Nessun valore di Index	Index anticorpale ≤ 0,9	Index anticorpale >0,9 ≤ 1,5	Index anticorpale >1,5	
1-12 mesi	0,1	0,1	0,1	0,2	0,3
13-24 mesi	0,6	0,1	0,3	0,9	0,4
25-36 mesi	2	0,2	0,8	3	4
37-48 mesi	4	0,4	2	7	8
49-60 mesi	5	0,5	2	8	8
61-72 mesi	6	0,6	3	10	6

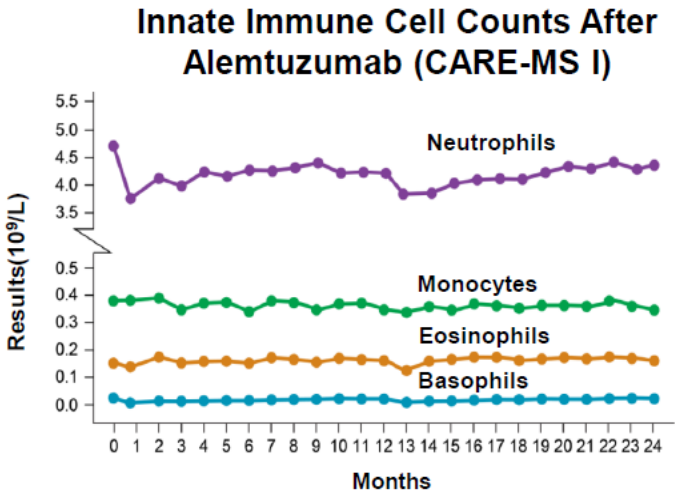
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Alemtuzumab

Anti-CD52 monoclonal antibody
IV administration
- 5 doses first year
- 3 doses second year





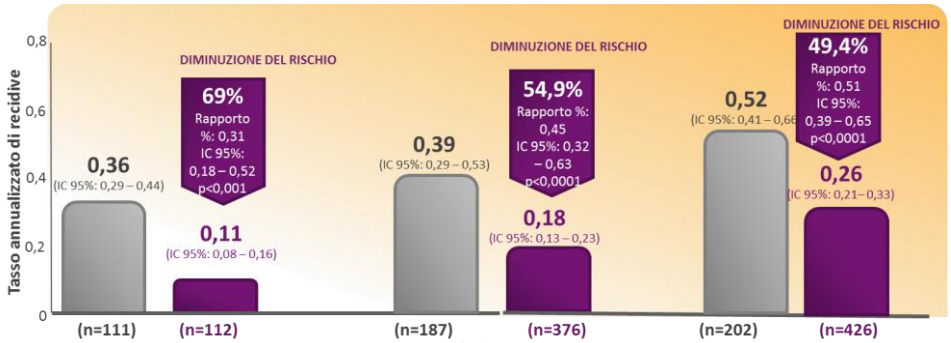


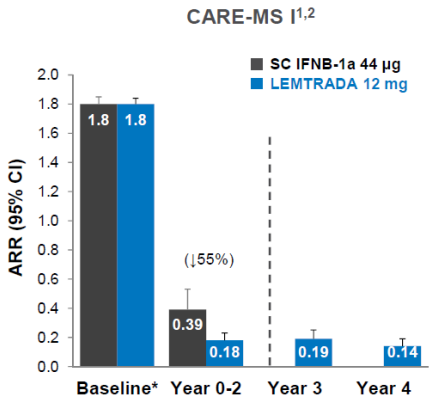
Tre Studi clinici randomizzati dimostrano che alemtuzumab è superiore a IFN beta

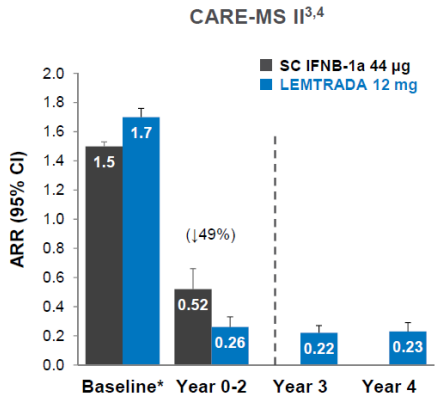
Phase 2

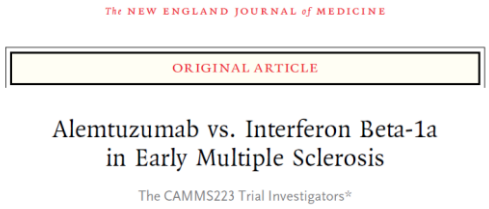
Phase 3 Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis

CAMMS223[1]	CARE-MS I	CARE-MS II
Treatment-naive 12/24 mg/day Alemtuzumab vs Rebif 44	Treatment-naive	Breakthrough disease under treatment








The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Alemtuzumab vs. Interferon Beta-1a in Early Multiple Sclerosis

The CAMMS223 Trial Investigators*


Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial


Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial

Alemutuzumab: safety

- Infusion-associated reactions (IARs)
- Infections
- Malignancy
- Autoimmune adverse events:
  - Thyroid disorders
  - Nephropathy
  - Immune thrombocytopenia

30 %

L’esperienza del centro di Genova

- N pts= 14
- F/M: 12/2
- Mean EDSS: 3.4 (SD 1.8)
- ARR last year: 2.2 (2.1)
- Disease duration: 8.1 (SD 3.2)

- Follow up: primo anno = 12, secondo anno = 2
- Ricadute durante il primo anno= 3
- Eventi avversi: 1 ipotiroidismo auto-risolto

Daclizumab

Daclizumab è un anticorpo monoclonale anti-CD25

- Subunità alfa del recettore per IL-2 ad alta affinità
- 150 mg sc ogni 4 settimane
- DECIDE Trial fase IV: vs IFN-beta, 2-3 anni

The NEW ENGLAND JOURNAL of MEDICINE

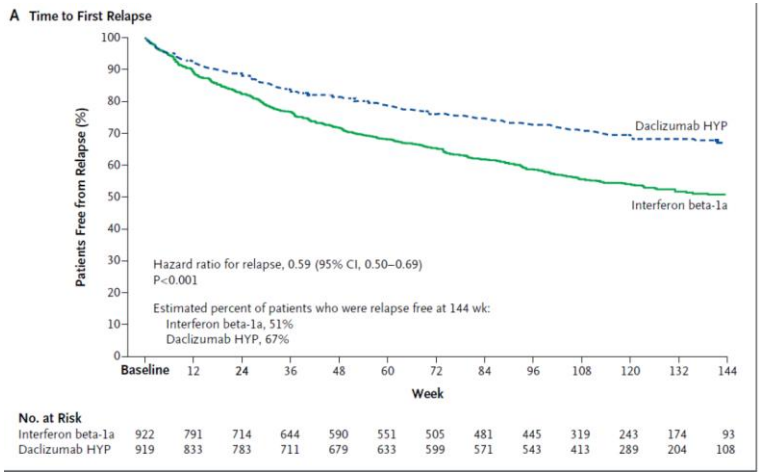
ORIGINAL ARTICLE

Daclizumab HYP versus Interferon Beta-1a in Relapsing Multiple Sclerosis

L. Kappos, H. Wiendl, K. Selmaj, D.L. Arnold, E. Havrdova, A. Boyko, M. Kaufman, J. Rose, S. Greenberg, M. Sweetser, K. Riester, G. O'Neill, and J. Elkins

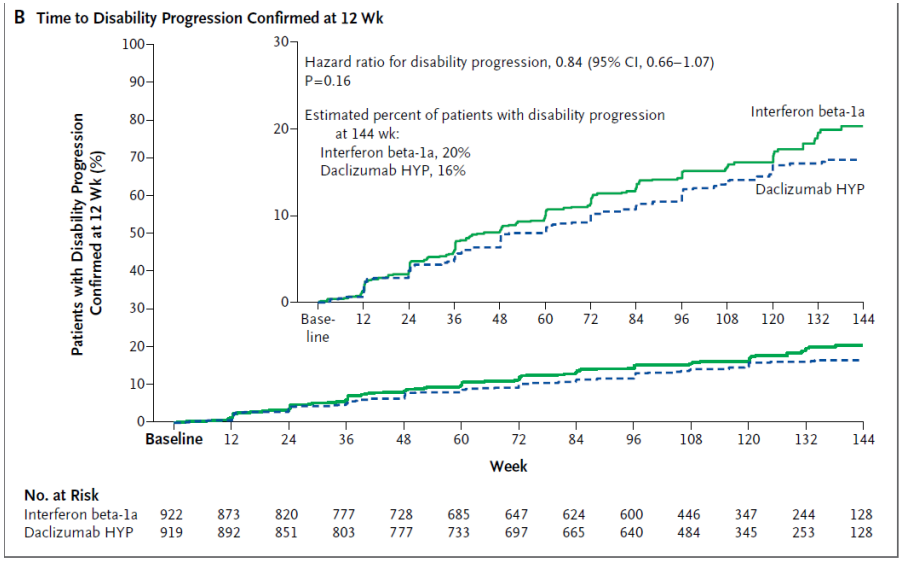
	Interferon Beta-1a (N=922)	Daclizumab HYP (N=919)
	number (percent)	
Adverse events in ≥10% of either treatment group, excluding multiple sclerosis relapse		
Nasopharyngitis	197 (21)	226 (25)
Headache	175 (19)	159 (17)
Upper respiratory tract infection	124 (13)	149 (16)
Pyrexia	134 (15)	104 (11)
Injection-site pain	102 (11)	96 (10)
Urinary tract infection	98 (11)	96 (10)
Influenza-like illness	346 (38)	88 (10)
Adverse events of special interest		
Infection†	523 (57)	595 (65)
Serious infection	15 (2)	40 (4)
Cutaneous event†	176 (19)	344 (37)
Serious cutaneous event	1 (<1)	14 (2)
Hepatobiliary disorder†	16 (2)	26 (3)
Serious hepatobiliary disorder	4 (<1)	7 (1)
Hepatic event‡	130 (14)	144 (16)
Serious hepatic event‡	4 (<1)	6 (1)

Daclizumab diminuisce significativamente il rischio di ricadute



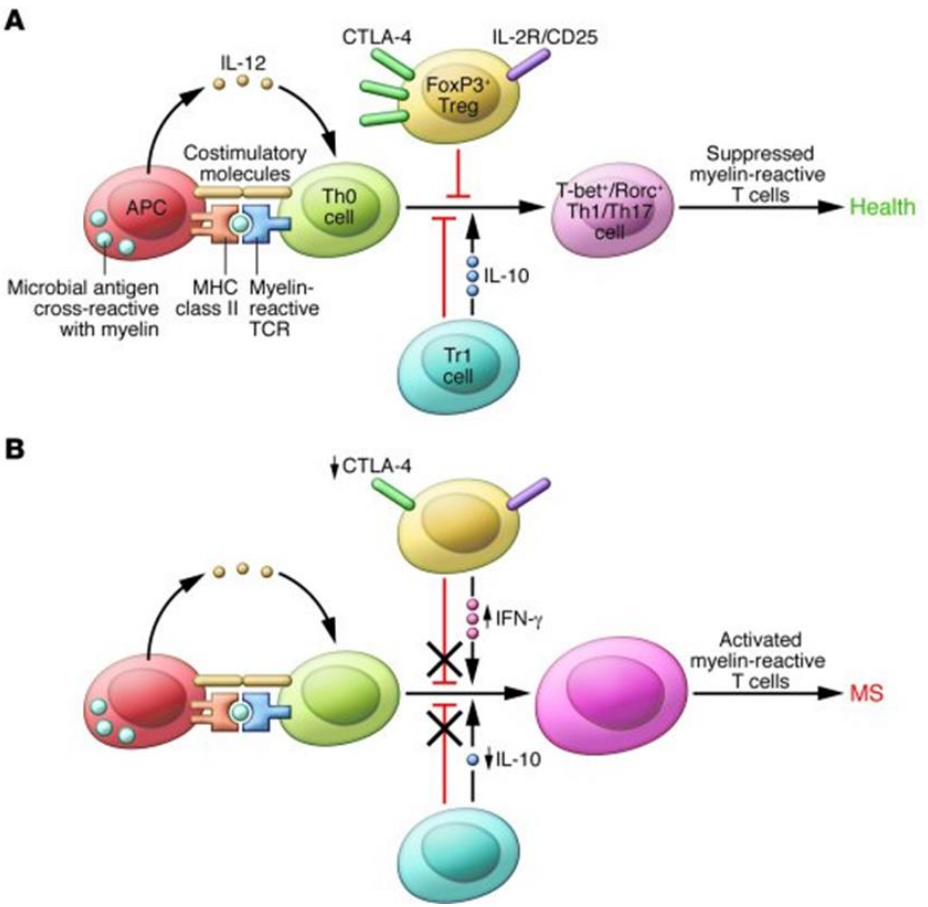
↓45 %

P= 0.16

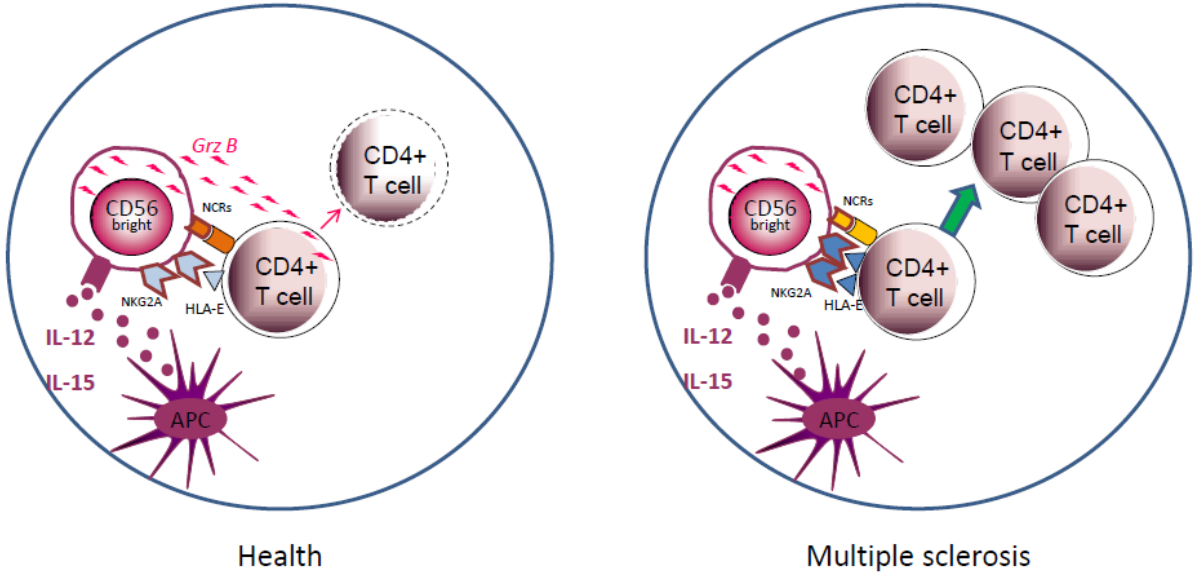


Il meccanismo d'azione di daclizumab è innovativo

Espansione di cellule immunitari e regolatorie



CD56bright NK cells –T cell interactions are impaired in MS



Health

Multiple sclerosis

Journal of Autoimmunity xxx (2016) xxx-xxx

Contents lists available at ScienceDirect

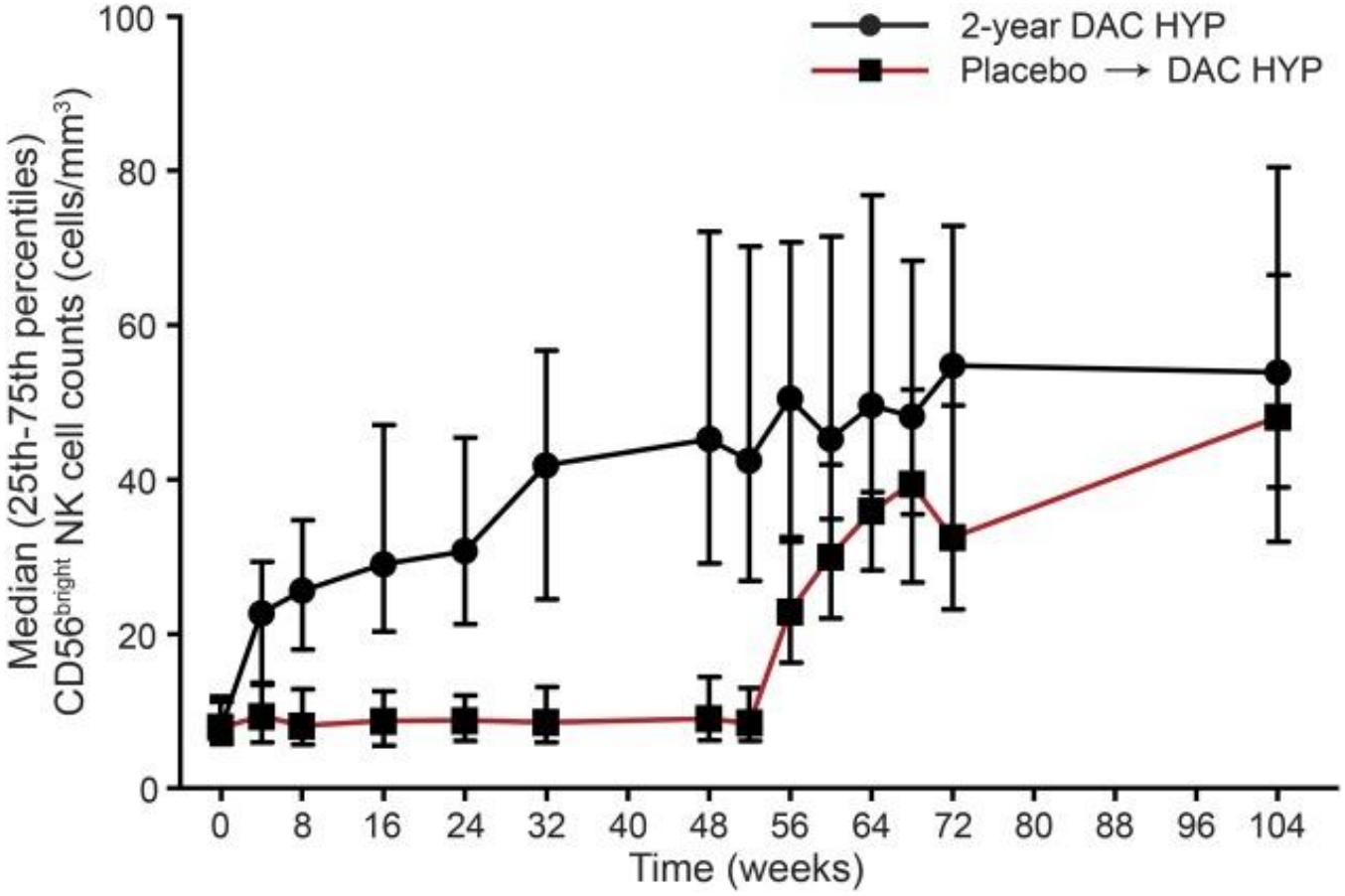
Journal of Autoimmunity

journal homepage: www.elsevier.com

Dysregulation of regulatory CD56^{bright} NK cells/T cells interactions in multiple sclerosis

Alice Laroni,[a, b, 1] Eric Armentani,[a, 1] Nicole Kerlero de Rosbo,[a] Federico Ivaldi,[a] Emanuela Marcenaro,[b, c] Simona Sivori,[b, c] Roopali Gandhi,[d] Howard L. Weiner,[d, e, f] Alessandro Moretta,[b, c] Giovanni L. Mancardi,[a, b] Antonio Uccelli [a, b, *]

Increased number of CD56bright NK cells upon daclizumab treatment



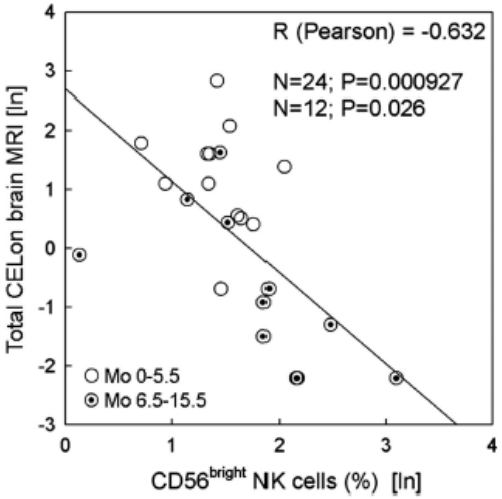
Elkins 2015

Daclizumab increases circulating CD56^{bright} NK cells that kill activated CD4+ T cells

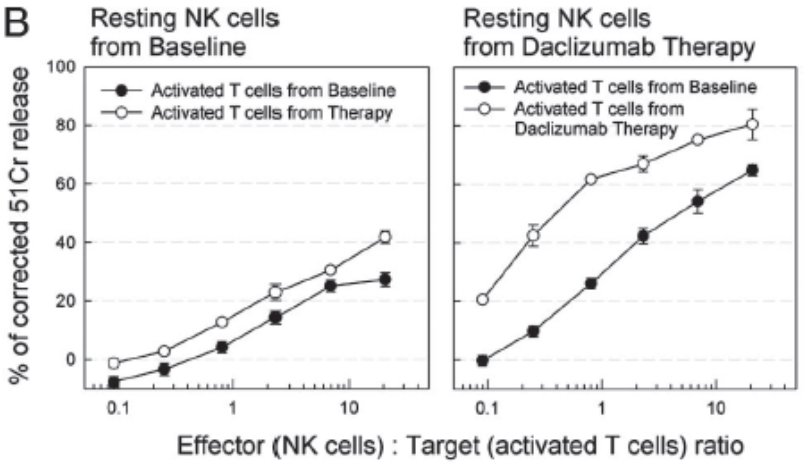
PNAS

Regulatory CD56^{bright} natural killer cells mediate immunomodulatory effects of IL-2Rα-targeted therapy (daclizumab) in multiple sclerosis

Bibiana Bielekova*†‡, Marta Catalfamo§¶, Susan Reichert-Scrivner*¶, Amy Packer*, Magdalena Cerna*, Thomas A. Waldmann‖**, Henry McFarland*, Pierre A. Henkart§, and Roland Martin*††



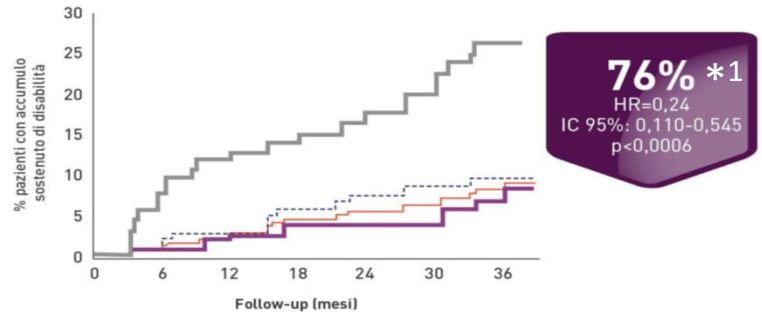
Markers examined by flow cytometry	Baseline IFN-β, mean	IFN-β therapy + dacliz., mean	% change	*P* value
NK cells and γ/δ-T cells ($n = 12$)				
CD56^{dim} NK cells, %	24.07	24.32	+1.00	NS
CD56^{bright} NK cells %	3.30	8.78	+166.10	<0.001
Absolute no.	23	68	+197.11	<0.001



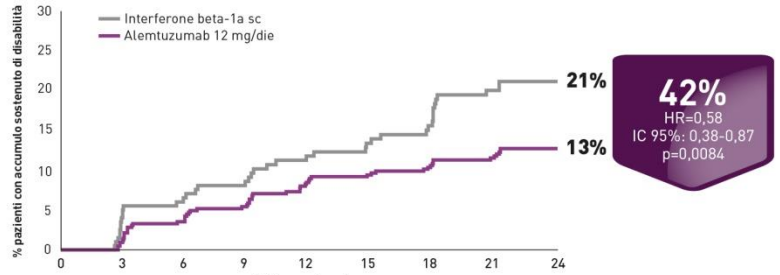
PROSPETTIVE

- Gli iniettabili rimangono un pilastro della terapia per la SM, in prima e seconda linea
- Prima linea: diradamento delle somministrazioni
- Seconda linea: anticorpi monoclonali con meccanismi d’azione avanzate
- Terapia diretta contro le cellule B

Alemtuzumab riduce l'accumulo sostenuto di disabilità rispetto a IFN beta 44 ug (studi CAMMS e Care-MS 2)

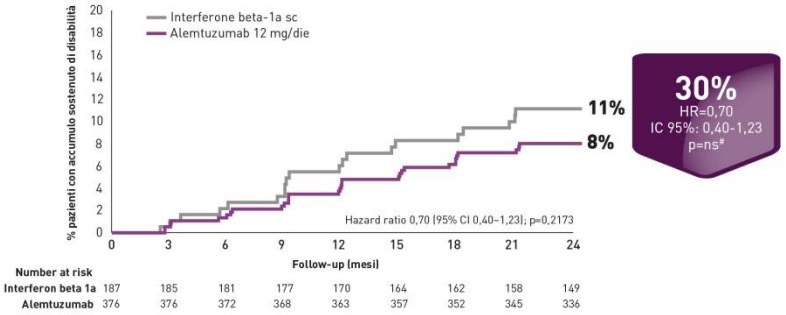


No. at Risk							
Interferon beta-1a	111	91	83	76	68	65	56
Alemtuzumab, 12 mg/day	112	106	101	98	97	94	88
Alemtuzumab, 24 mg/day	110	106	102	99	96	93	89



Number at risk									
Interferon beta 1a	202	200	184	175	167	162	155	145	131
Alemtuzumab 12 mg	426	426	412	404	392	384	380	375	154

Stima di Kaplan–Meier dell'accumulo sostenuto di disabilità, confermato a 6 mesi e valutato tramite scala EDSS.

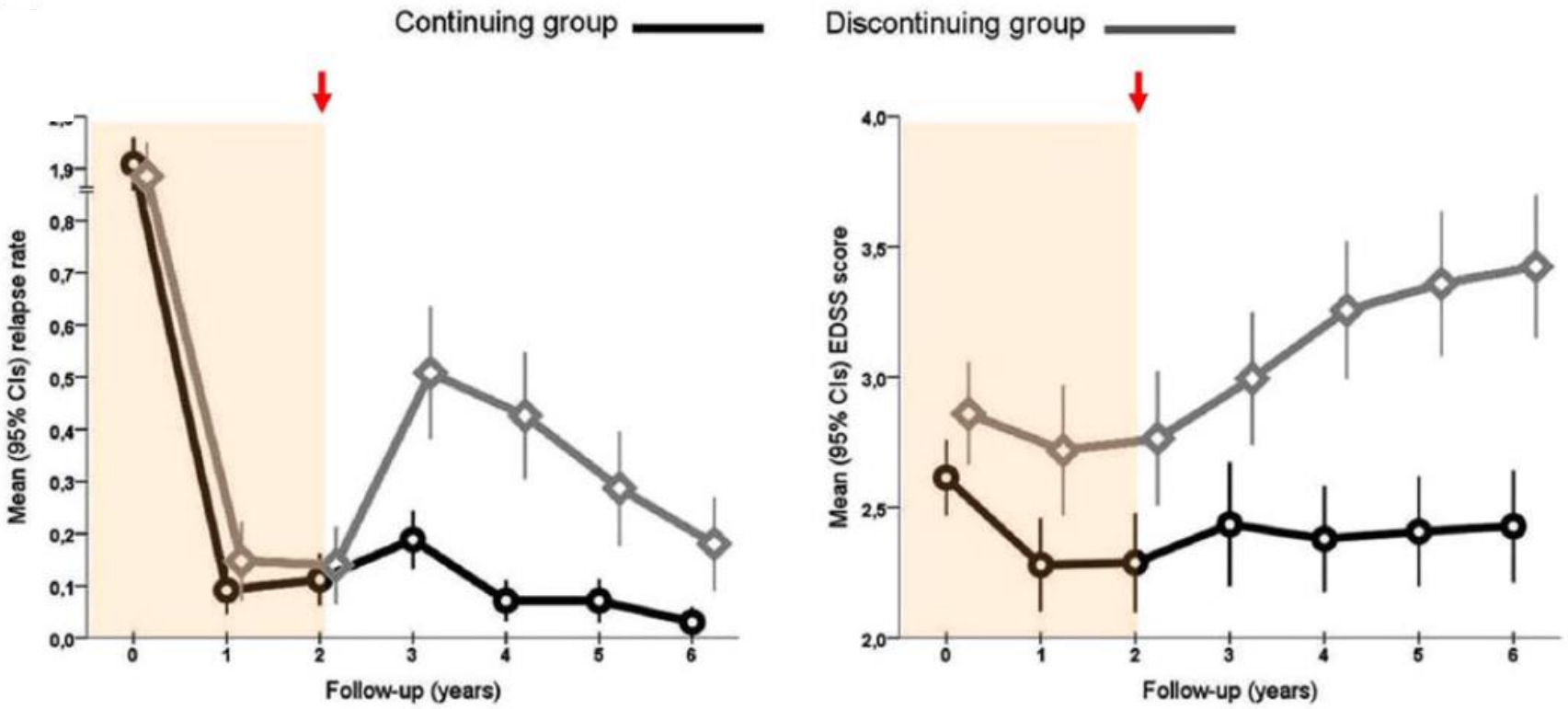


Number at risk									
Interferon beta 1a	187	185	181	177	170	164	162	158	149
Alemtuzumab	376	376	372	368	363	357	352	345	336

Stima di Kaplan–Meier dell'accumulo sostenuto di disabilità, confermato a 6 mesi e valutato tramite scala EDSS.
#un numero ridotto di pazienti nel gruppo trattato con interferone beta-1a SC (20 di 187, 11%) soddisfa in maniera inaspettata questo endpoint, il quale è stato sostanzialmente più basso rispetto al 20% osservato a 2 anni nello studio di fase 2 usato per il calcolo della potenza statistica.

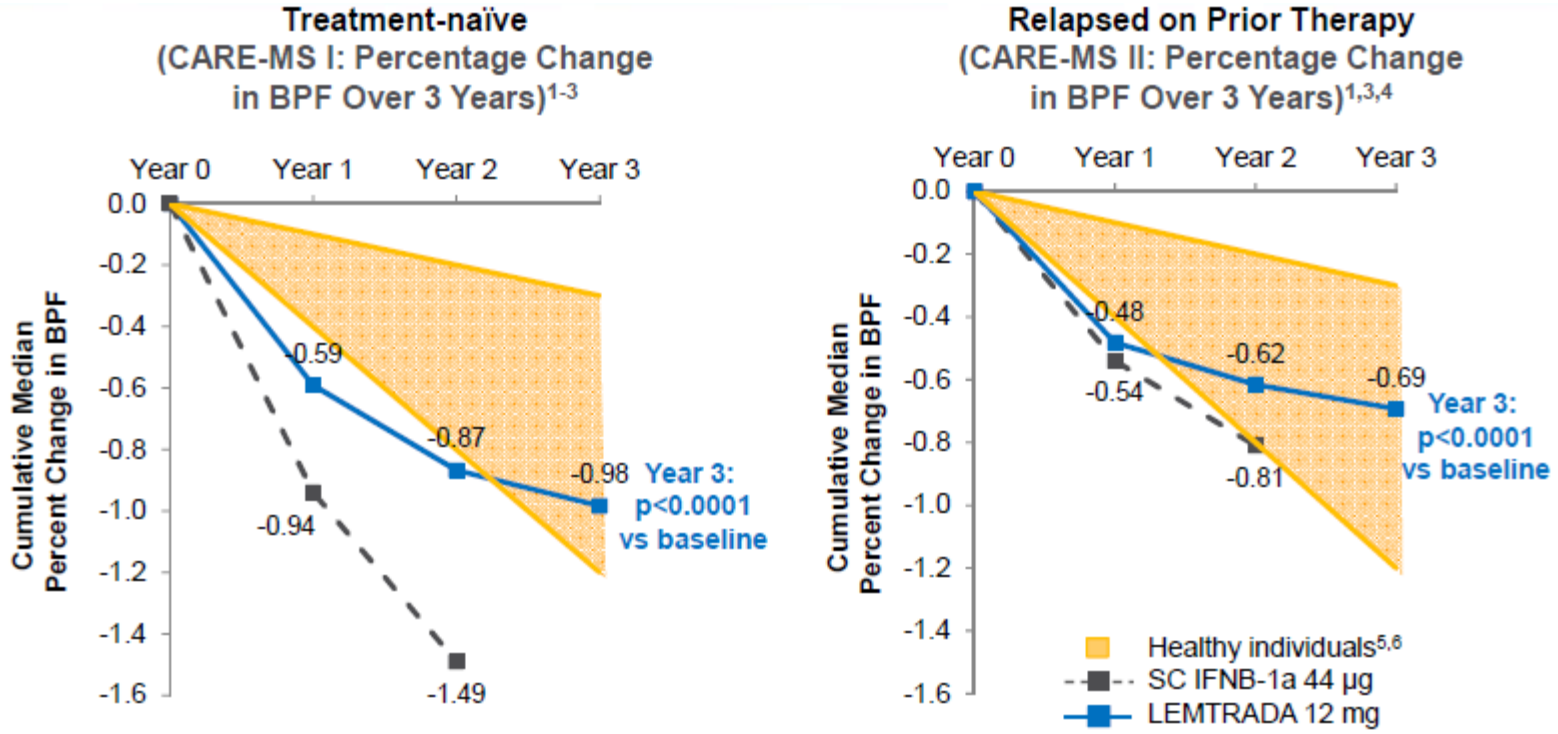
Six-month SAD defined as EDSS score increase ≥1.0 point for ≥6 months (or ≥1.5 points when baseline EDSS = 0)

Natalizumab withdrawal significantly increases the risk of new relapses and disability progression



Prosperini L, et al. Mult Scler 2015

Care-MS extension: brain volume loss



- LEMTRADA slowed the yearly rate of brain volume loss over 3 years in both treatment-naive patients and those who relapsed on prior therapy[1-4]
  - The mean annual rate of brain volume loss in healthy individuals is 0.1-0.4%[5,6]

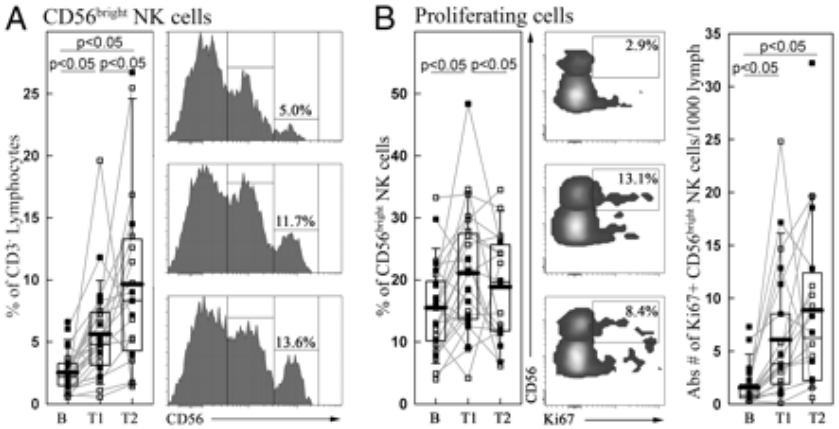
BPF=brain parenchymal fraction.

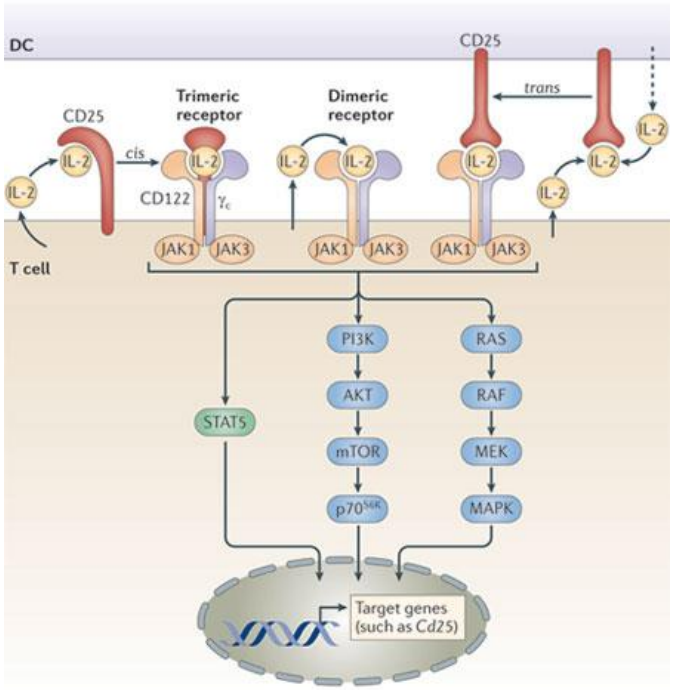
1. Data on file; 2. Arnold DL et al. Presented at AAN 2012:Platform; 3. Arnold DL et al. AAN 2014:P008; 4. Arnold DL et al. Presented at ECTRIMS 2012:P877; 5. Fotenos AF et al. *Arch Neurol* 2008; 65:113-20; 6. Miller DH *Brain* 2002;125:1676-95.

Treatment with anti-CD25 antibody enhances the proliferation of CD56bright NK cells due to increased availability of IL-2

An IL-2 Paradox: Blocking CD25 on T Cells Induces IL-2–Driven Activation of CD56^{bright} NK Cells

Jayne F. Martin, Justin S. A. Perry, Neha R. Jakhete, Xiang Wang, and Bibiana Bielekova





IL-2R:

- high affinity: CD25, CD122, CD132
- Intermediate affinity: CD122, CD132

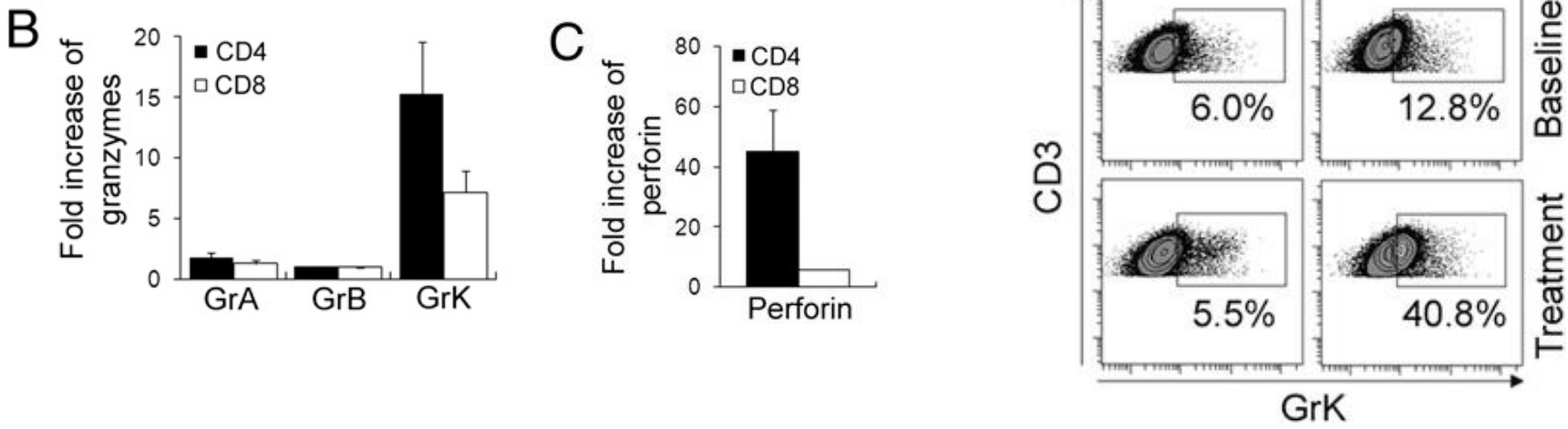
Daclizumab induces transfer of Granzyme K and perforin from CD56^{bright} NK cells to target T cells

THE JOURNAL OF IMMUNOLOGY

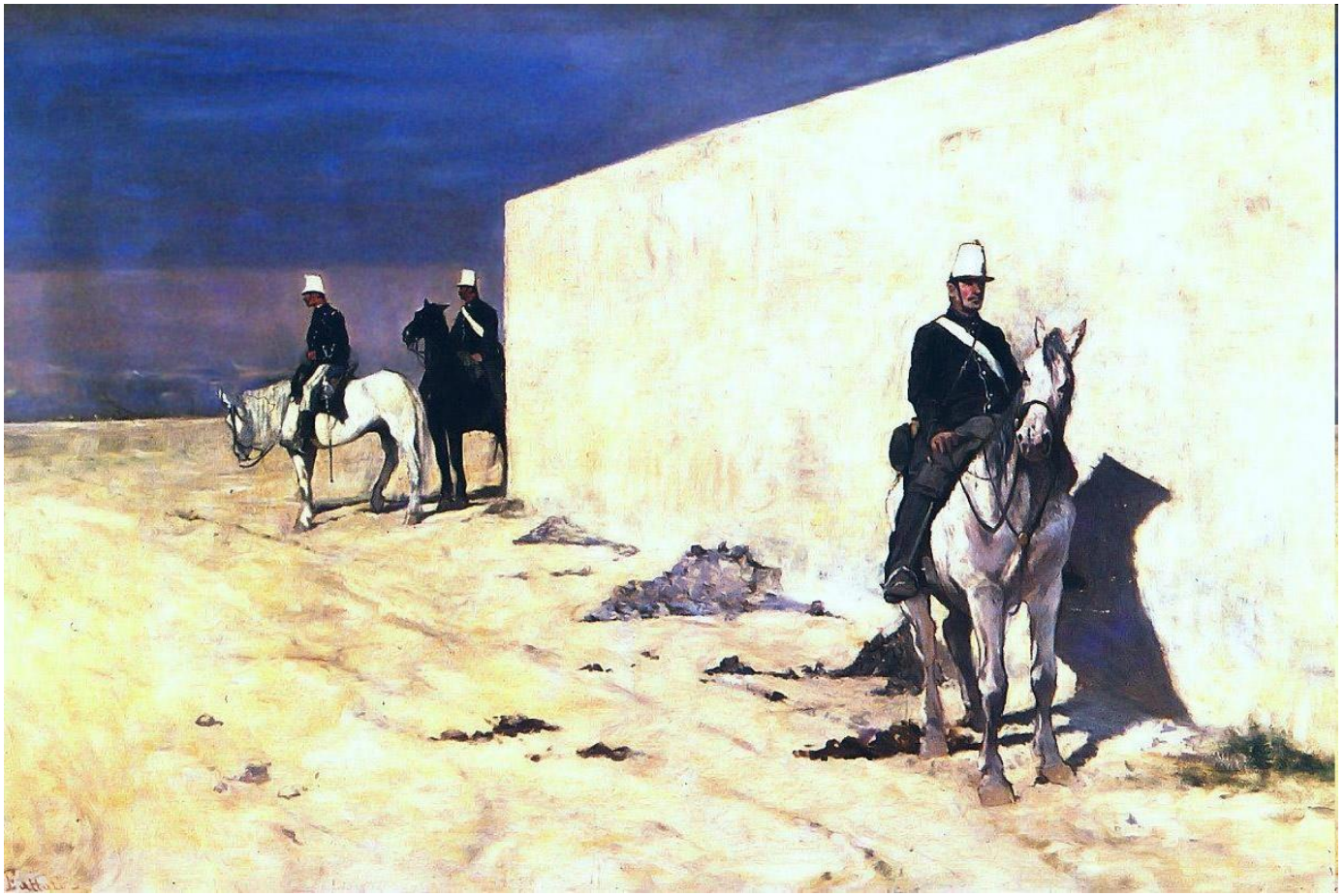
Unexpected Role for Granzyme K in CD56 bright NK Cell-Mediated Immunoregulation of Multiple Sclerosis

Wenzheng Jiang, Noo Ri Chai, Dragan Maric and Bibiana Bielekova

J Immunol 2011; 187:781-790; Prepublished online 10 June 2011;
doi: 10.4049/jimmunol.1100789
http://www.jimmunol.org/content/187/2/781



The innate immune system: soldiers and sentinels



G. Fattori “In vedetta” 1872