Biologic Therapy in SLE: Real Clinical Practice

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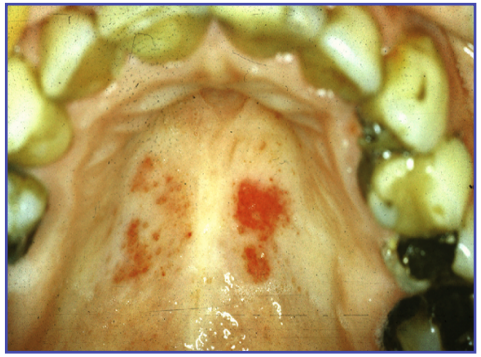
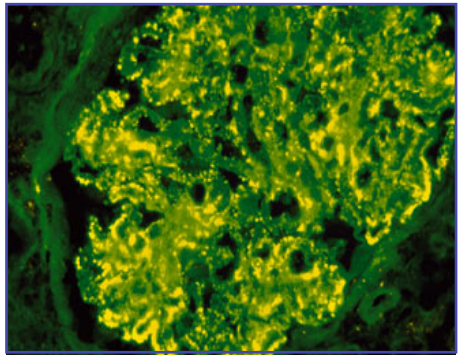
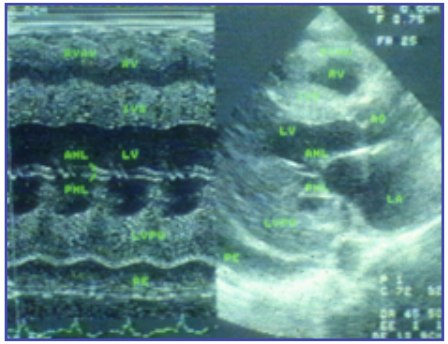
Systemic Lupus erythematosus



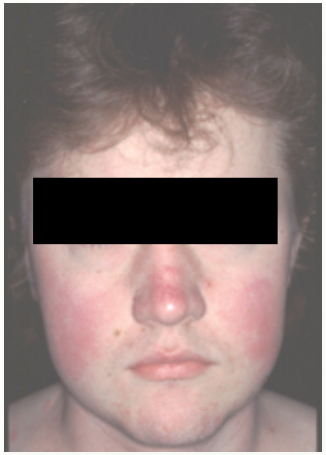
Oral Ulcer



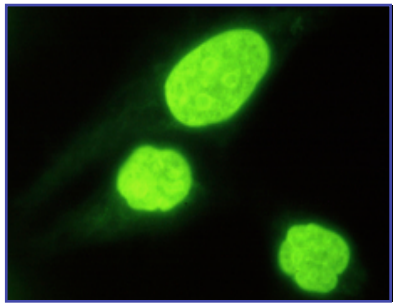
Nephritis



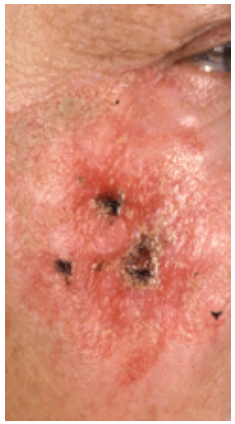
Serositis



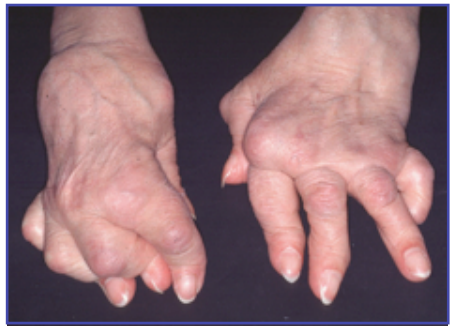
Butterfly rash



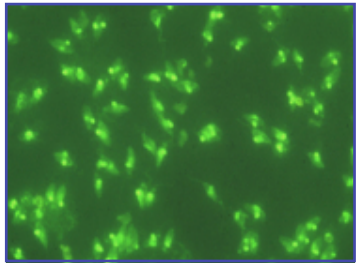
ANA



Discoid lesions



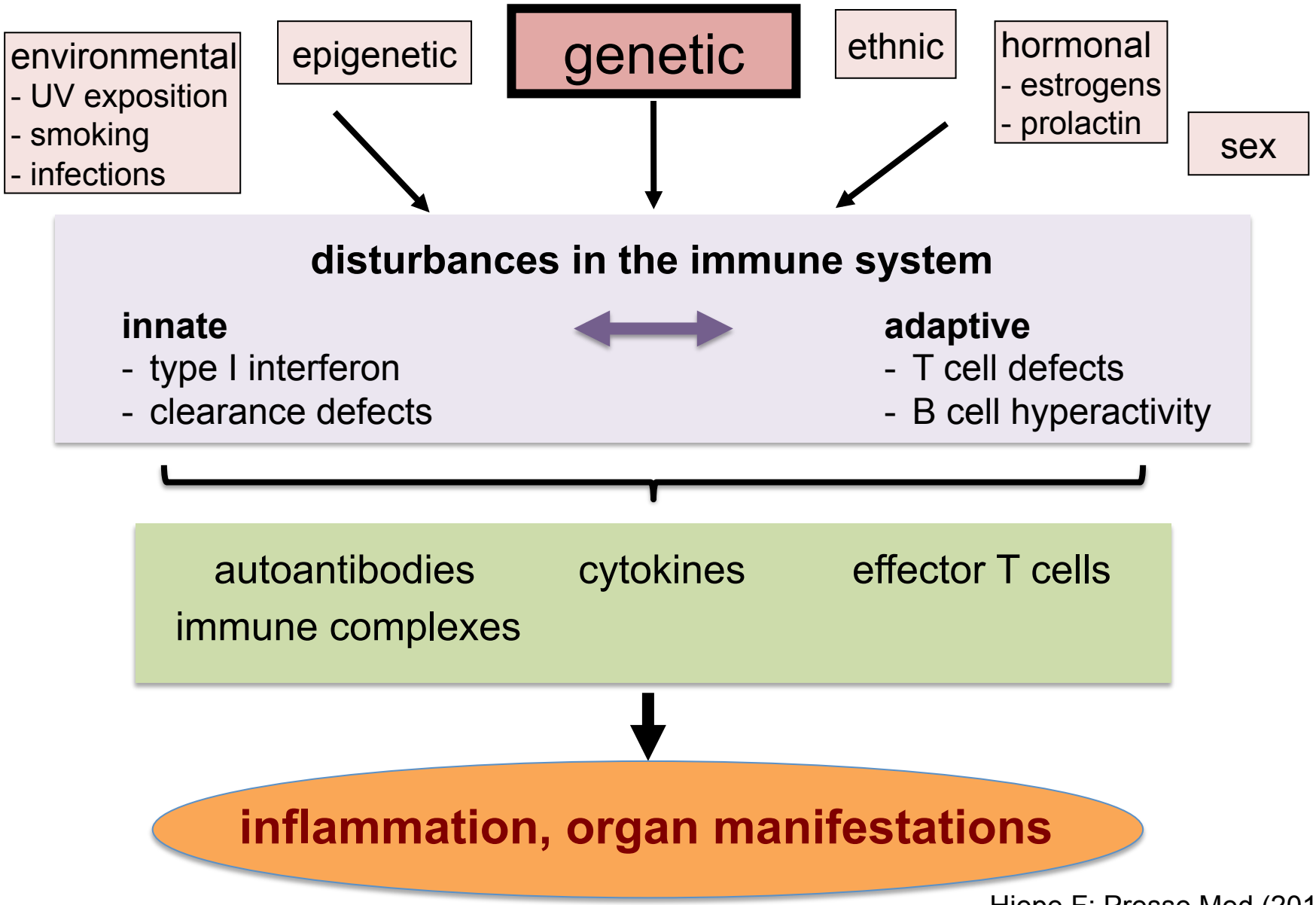
Arthritis



Anti-dsDNA
Anti-Sm

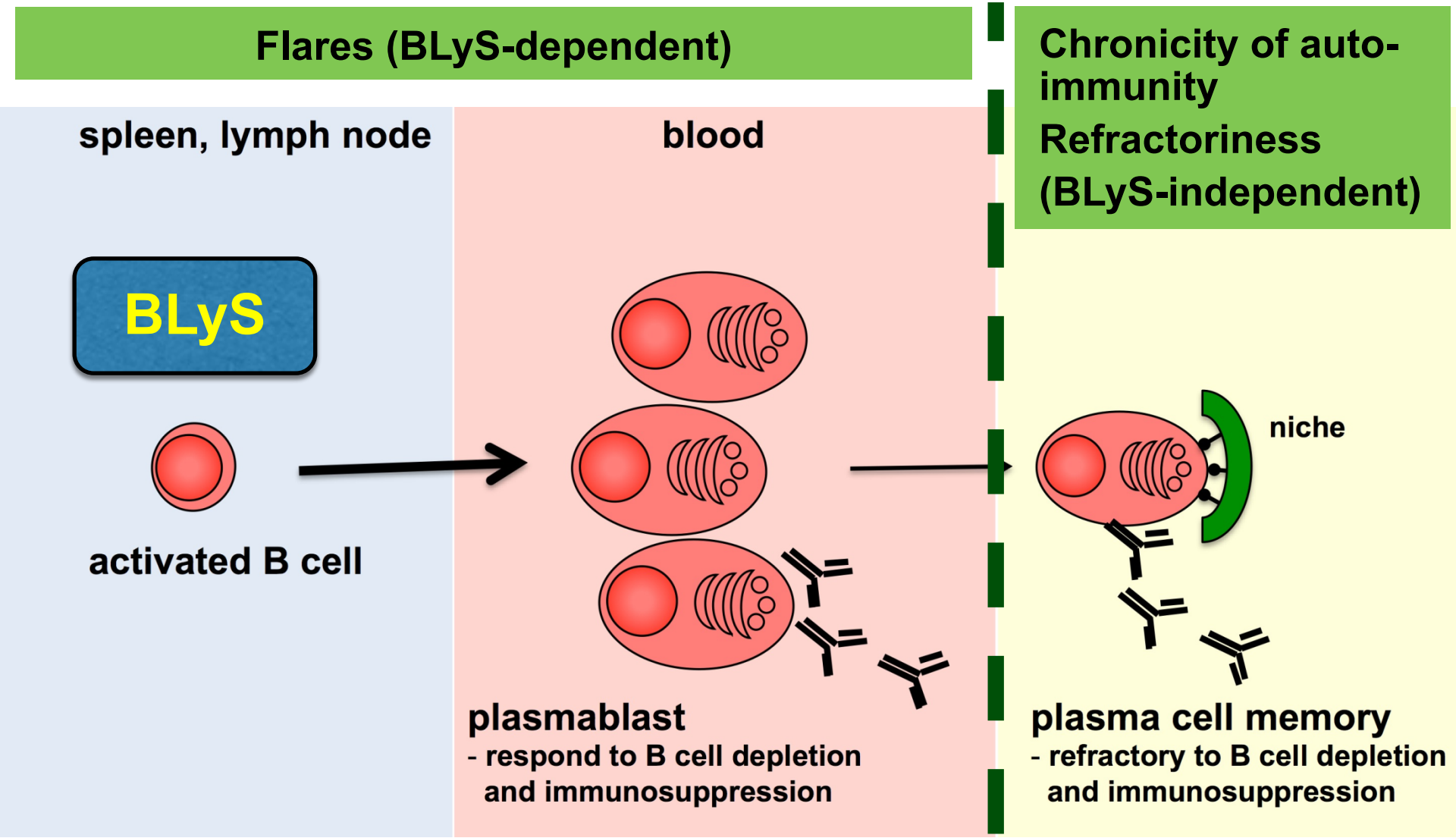
Photosensitivity
Haematologic disorders
Neuropsychiatric lupus

Factors contributing to the pathogenesis of SLE



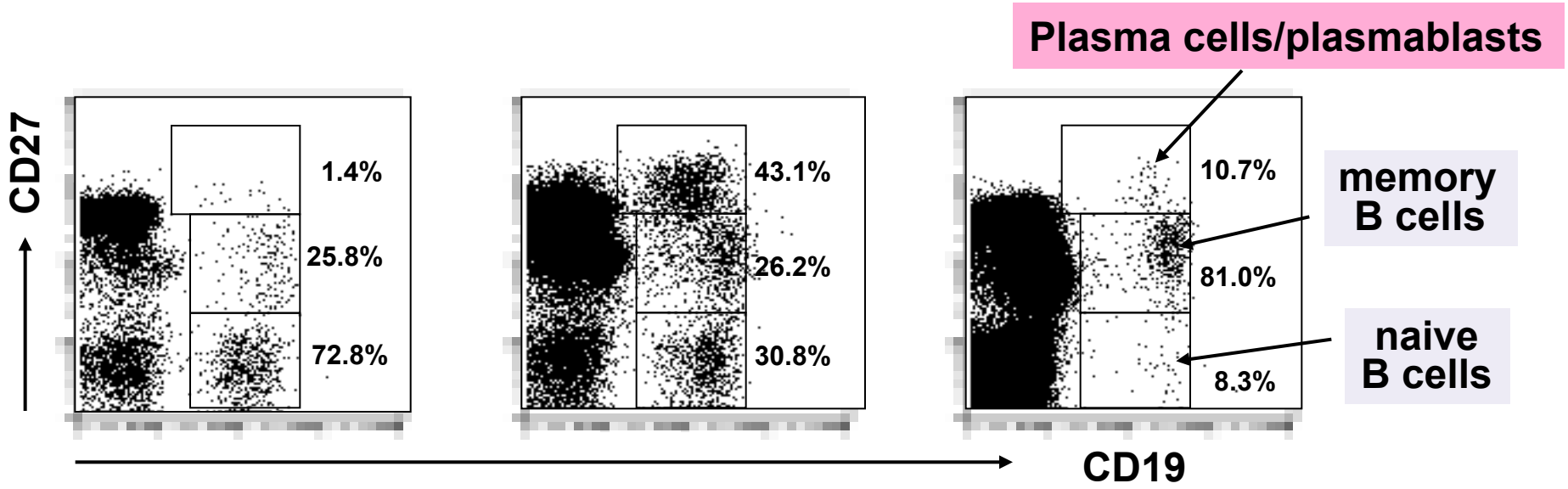
Hiepe F: Presse Med (2014)

BLyS drives proliferation of autoreactive B cells to autoreactive plasmablasts/plasma cells



modified according toHiepe et al.: Nat Rev Rheum 7:170-178 (2011)

Expansion of circulating plasma cells in active SLE



Odendahl et al., J. Immunol. (2000) 165, 5970-5979

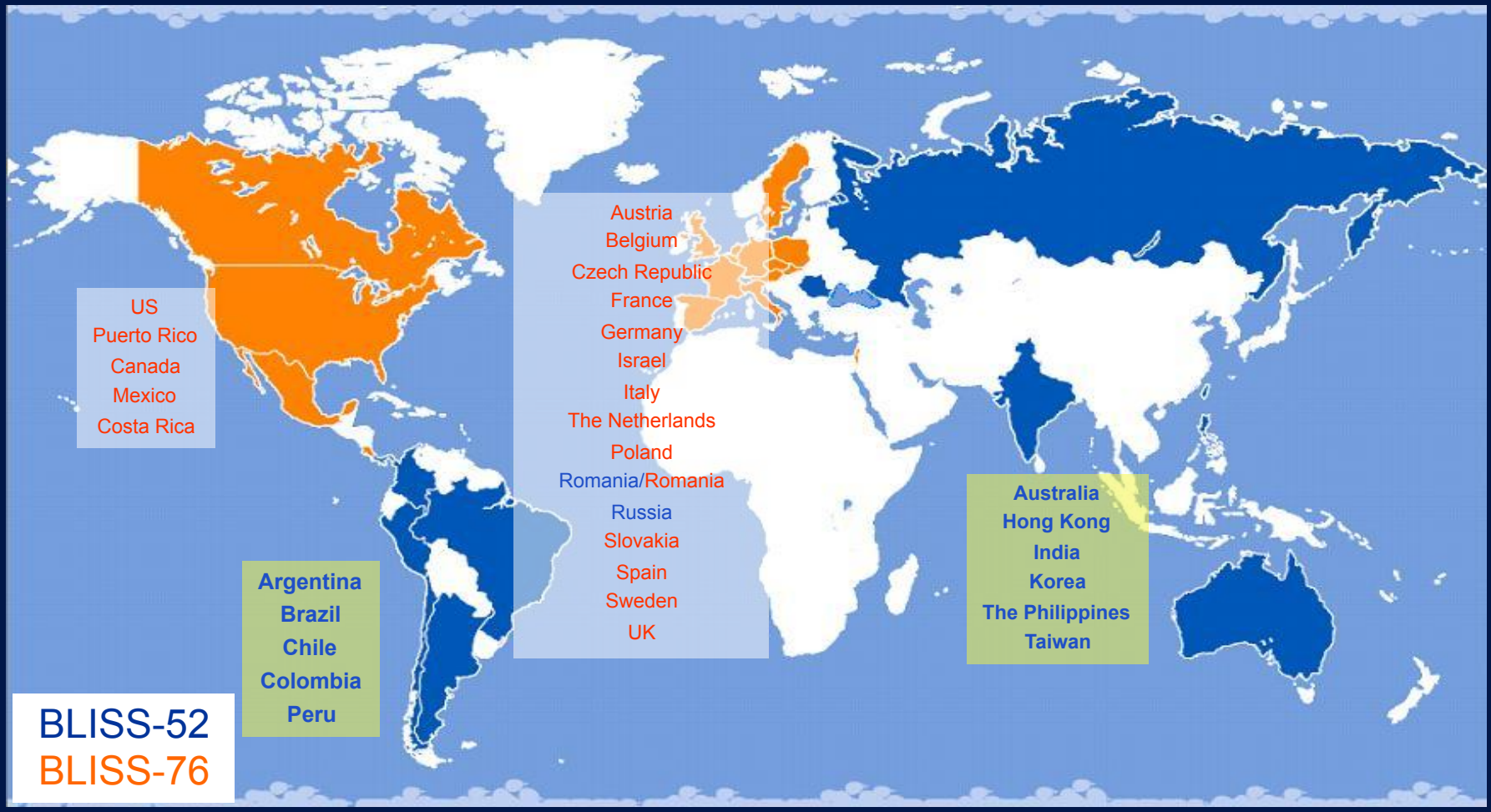
HLA-DRhigh plasmablasts reflect disease activity in patients with SLE more precisely than the entire CD27++CD20-CD19dim cell subset

		$CD27^{++}CD20^{-}$ $CD19^{dim}$ cells		$HLA\text{-}DR^{high}$ plasmablasts		$HLA\text{-}DR^{low}$ plasma cells		$CD27^{-}$ $CD20^{+}CD19^{+}$ B cells		$CD27^{+}$ $CD20^{+}CD19^{+}$ B cells	
		% of B cells	abs. number	% of B cells	abs. number	% of B cells	abs. number	% of B cells	abs. number	% of B cells	abs. number
SLEDAI	r_S	0.35	**0.54**	**0.42**	**0.55**	0.03	-0.01	0.03	-0.01	-0.2	-0.09
	p	0.08	**0.005**	**0.04**	**0.004**	0.9	0.9	0.9	0.9	0.4	0.7
anti-dsDNA	r_S	**0.45**	0.38	**0.49**	**0.44**	0.1	-0.2	-0.02	-0.2	-0.2	-0.2
	p	**0.03**	0.06	**0.01**	**0.03**	0.6	0.4	0.9	0.3	0.2	0.3

Spearman, bold numbers represent significant results

Jacobi et al., Ann Rheum Dis 69:305-308 (2010)

The BLISS phase III clinical trial programme



1,693 patients from 223 centres in 31 countries
865 (BLISS-52) and 819 (BLISS-76) patients

Belimumab in Clinical Trials (BLISS)

- **For the first time** efficacy and safety of a drug in SLE have been proven in positive clinical trials ➔ approval

- **Significant reduction in disease activity:**

  - reduced flares
  - reduced CS
  - significant improvement of skin, musculoskeletal, and vascular involvement
  - improvement in patients with renal manifestation
  - improved HRQoL

Furie RA et al. Arthritis Rheum. 2011;63:3918–3930; Navarra SV et al. Lancet 2011; 377: 721–31; van Vollenhoven RF et al. Ann Rheum Dis 2012;71:1343–9; Dooley MA et al. Lupus 2014; 22: 63-72.

Belimumab in Clinical Trials (BLISS)

- **Best clinical response** for patients with:
  - high serologic disease activity
  - high clinical disease activity

- **Overall** the clinical efficacy seems to be modest

Furie RA et al. Arthritis Rheum. 2011;63:3918–3930; Navarra SV et al. Lancet 2011; 377: 721–31; van Vollenhoven RF et al. Ann Rheum Dis 2012;71:1343–9

Baseline predictors of SLE flares

Patients who were receiving standard SLE therapy and had at baseline

- renal, neurologic, or vasculitic involvement
- elevated anti-dsDNA antibody levels or
- elevated BLyS levels, or
- low C3 level

had increased risk of clinically meaningful flare over 1 year.

Petri M. et al.: Arthritis Rheumatol 65:2143-2153 (2013)

Belimumab in Clinical Trials

OPEN QUESTION:

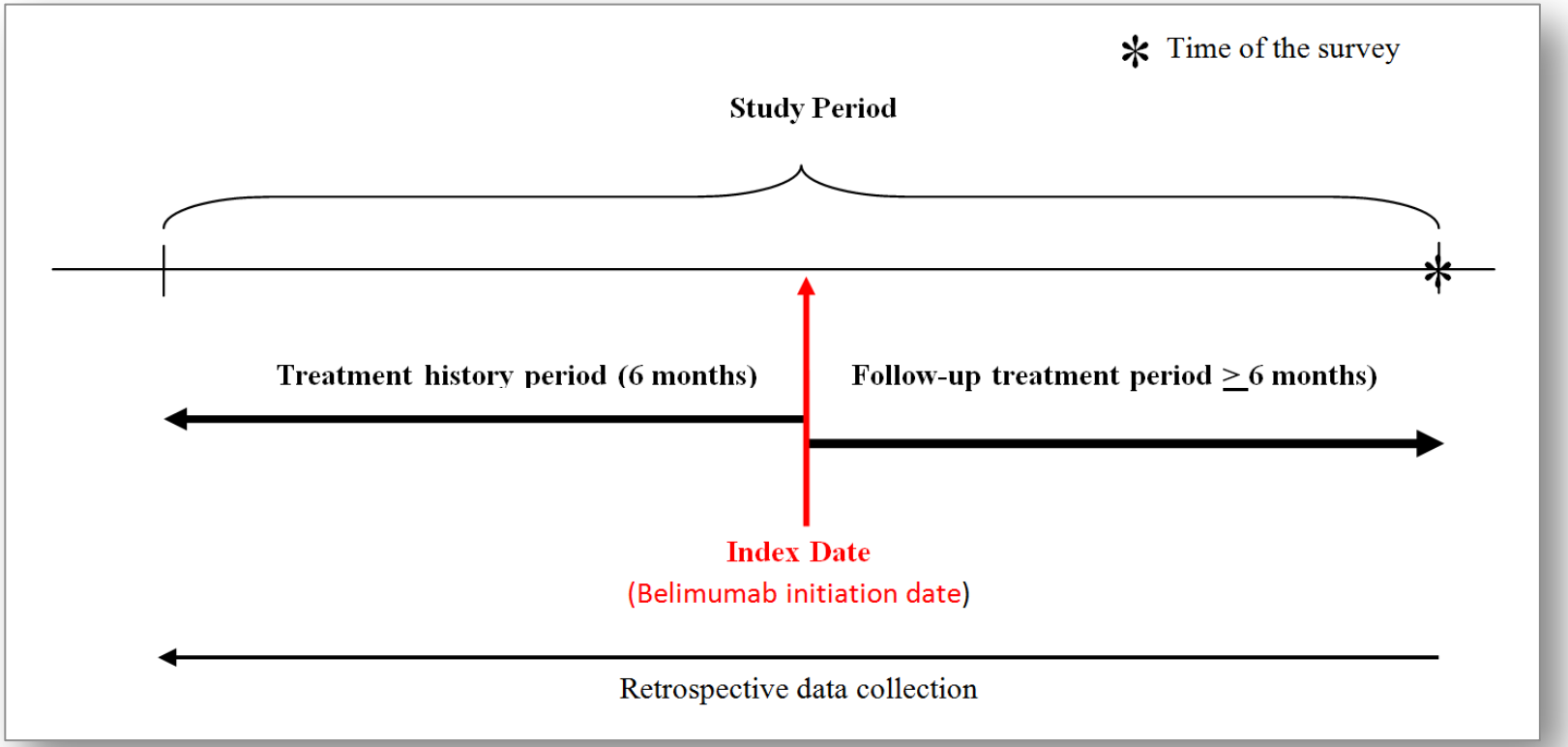
How do these data translate into clinical reality?

OBSErve studies

(US, Germany, Spain, Switzerland, …)

OBSErve Germany - Study Design: Data Collection

- **Multi-center** observational cohort study, based on review of medical patient charts
- **Retrospective** data collection for three time points: at belimumab initiation, as well as 6 months before, 6 months after



OBSErve Germany - Study Design: Endpoints

- Overall clinical response to six months of belimumab treatment (PGA-like scale)
- Clinical response for specific SLE manifestations to six months of belimumab treatment (PGA-like scale)

OBSErve Germany - Study Design: Endpoints

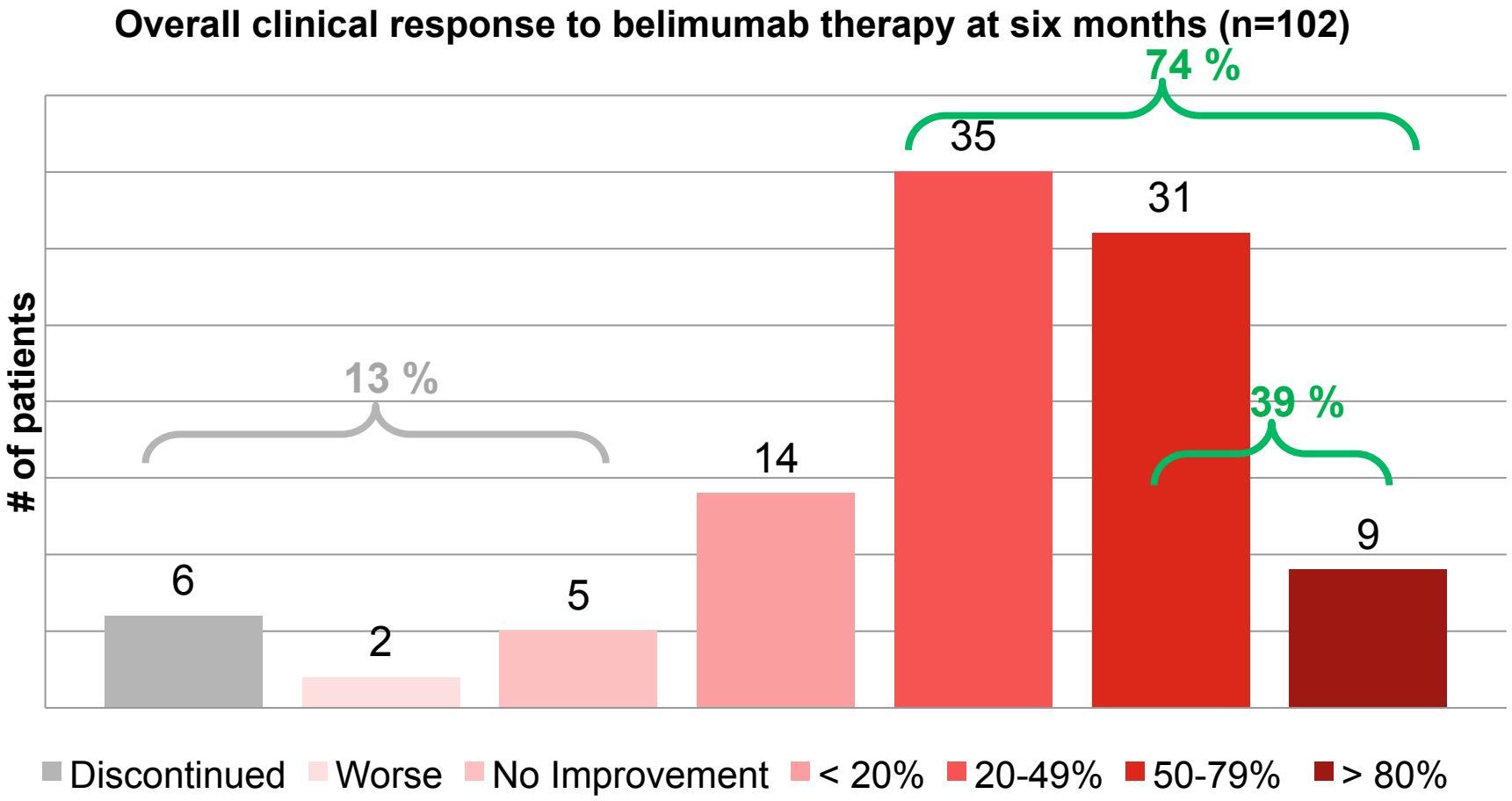
- Rate of discontinuation of belimumab within the first six months of therapy
- Treatment patterns with concomitant medication particularly with steroids in the course of the therapy: reduction of steroid dose and switch from high dose (≥7.5 mg/day) to low dose group (<7.5 mg/day).
- Routinely used disease activity tools, in particular the change of scores from belimumab initiation to six months after

OBSErve Germany - Results: Patients OBSErved

- 21 participating sites
- 102 documented patients
- 91% female, ∅ 42.5 years
- Almost 2/3 of patients diagnosed with SLE for more than 10 years

Full analysis set		n = 102	(100%)
SLE severity at belimumab therapy start:	▪ Mild ▪ Moderate ▪ Severe ▪ Don‘t know	8 61 26 7	(8%) (60%) (25%) (7%)
Number of SLE clinical manifestations at start:	▪ ≤ 2 ▪ 3 ▪ 4 ▪ ≥ 5	21 20 24 37	(21%) (20%) (24%) (36%)
Number of other SLE medications prior to belimumab:	▪ 1-3 ▪ 4-5 ▪ > 5	20 31 51	(20%) (30%) (50%)
Reasons for start of belimumab therapy:	▪ Previous treatment not effective ▪ Patient condition worsening ▪ Decrease use of steroids ▪ Previous treatment not well tolerated ▪ Previous treatment regimen inconvenient	90 62 41 27 3	(88%) (61%) (40%) (26%) (3%)

OBSErve Germany - Results: Primary Endpoint – Overall Clinical Response



OBSErve Germany - Results: Improvement of SLE Manifestations

The most common clinical signs and symptoms of SLE improved considerably after six months of belimumab therapy.

Improvement of clinical manifestations after six months of belimumab therapy (n = 96)	**# of patients presenting manifestation**		**≥ 50% improvement from baseline**	
Arthritis	66	(69%)	37	(56%)
Increased anti-dsDNA antibody levels	52	(54%)	11	(21%)
Low complement levels (C3, C4, or CH50)	44	(46%)	10	(23%)
Fatigue	40	(42%)	10	(25%)
Rash	39	(41%)	20	(51%)

OBSErve Germany - Results: Improvement of SLE Manifestations

Positive clinical assessment is supported by disease activity tools:

- For almost 80% of patients disease activity assessment tools have been documented
- For almost all assessment tools a reduction in disease activity was observed
- The SELENA-SLEDAI score decreased from 10.6 to 5.6 (n=65) during the first six months of therapy

OBSErve Germany - Results: Comedication – Steroid Sparing Effect

Change of oral steroid use during belimumab therapy by initial dosage group	**Total (n=91)**	**High dose (≥7.5 mg) (n=63)**
Dosage 6 months before belimumab start [mg/day]	11.7	12.6
Dosage at belimumab start [mg/day]	13.7	17.5
Dosage 6 months after belimumab start [mg/day]	7.6	8.6
Change of dosage from belimumab start to 6 months after [mg/day]	- 6.1	-8.9

OBSErve Germany - Results: Early Treatment Discontinuation

- 6 patients discontinued within the first 6 months of treatment:
  - 1: after 16 days – Disease progression and ineffective medication
  - 2: after 28 days – Adverse event: allergic reaction (suspected causal relationship)
  - 3: after 35 days – Disease progression
  - 4: after 68 days – Disease progression and ineffective medication; adverse event: lupus myelopathy (no causal relationship suspected)
  - 5: after 87 days – Patient request and lack of patient compliance
  - 6: after 156 days – Severe adverse event: death due to an undiagnosed cardiomyopathy / heart failure after hospitalization (no causal relationship suspected)

- Low rate (6%) of early discontinuation

➔ indicator for both efficacy and tolerability of belimumab

OBSErve Germany - Results: Strengths and Limitations

Strengths

- First evaluation of belimumab treatment in routine care in Germany → real world results
- All belimumab patients documented for participating sites

Limitations

- Physician assessment scale not validated (reflects individual judgement)
- No control group → conclusions about efficacy cannot be made
- No source of data verification
- Patients treated by participating physicians may vary from those of non-participating physicians
- Comprehensive Safety assessment was not focus of the study

OBSErve Germany - Summary: Results at 6 months belimumab therapy

- Improvement of a least 20% in 74% of patients.
- Although safety was not assessed, belimumab appeared to be well-tolerated with only 6 of 102 patients (6%) discontinuing treatment within the first six months.
- Clinically relevant steroid sparing effects were observed in the majority of study patients after the first six months.

OBSErve Germany - Summary: Results at 6 months belimumab therapy

- Improvement in disease assessment tools is coherent with positive physician assessment

➔ **Treatment with belimumab in real-life setting seems to be effective after six months and well-tolerated**

Summary:
Conclusions Using All Evidence on Belimumab

- **Efficacy and safety** of belimumab in SLE proven in the largest clinical development program ever conducted (NNT 5)[1]
- **Evidence** from OBSErve suggests even greater improvements and low discontinuation rate in clinical practice
- **Chance for significant therapeutic success**[1]:
  - Reduction in symptoms
  - Prevention or delay of flares
  - Steroid sparing effects
  - Improvement in quality of life
- **Responding** patients may be identified by six months of treatment

1: van Vollenhoven RF et al. Ann Rheum Dis 2012;71:1343–9

History female patient CS, born 1986

2000 diagnosis of UCTD: ANA+, Raynaud's phenomenon and arthritis – MTX 15 mg/week

03/2006 severe interstitial pneumonia

04/2006 MMF 2g/d + RTX 4x0,5g + Pred 10mg/d

09/2006 pancreatitis + cholecystitis, MMF>, 4 weeks on intensive care unit, transfer of the patient to our clinic

10/2006 nephritis class IV, pericarditis, panzytopenia, C3 and C4=0, anti-dsDNA +++, therapy: glucocorticoids, plasmapheresis, IVIG, IVCY

2/2007 pancreatitis, azathioprine

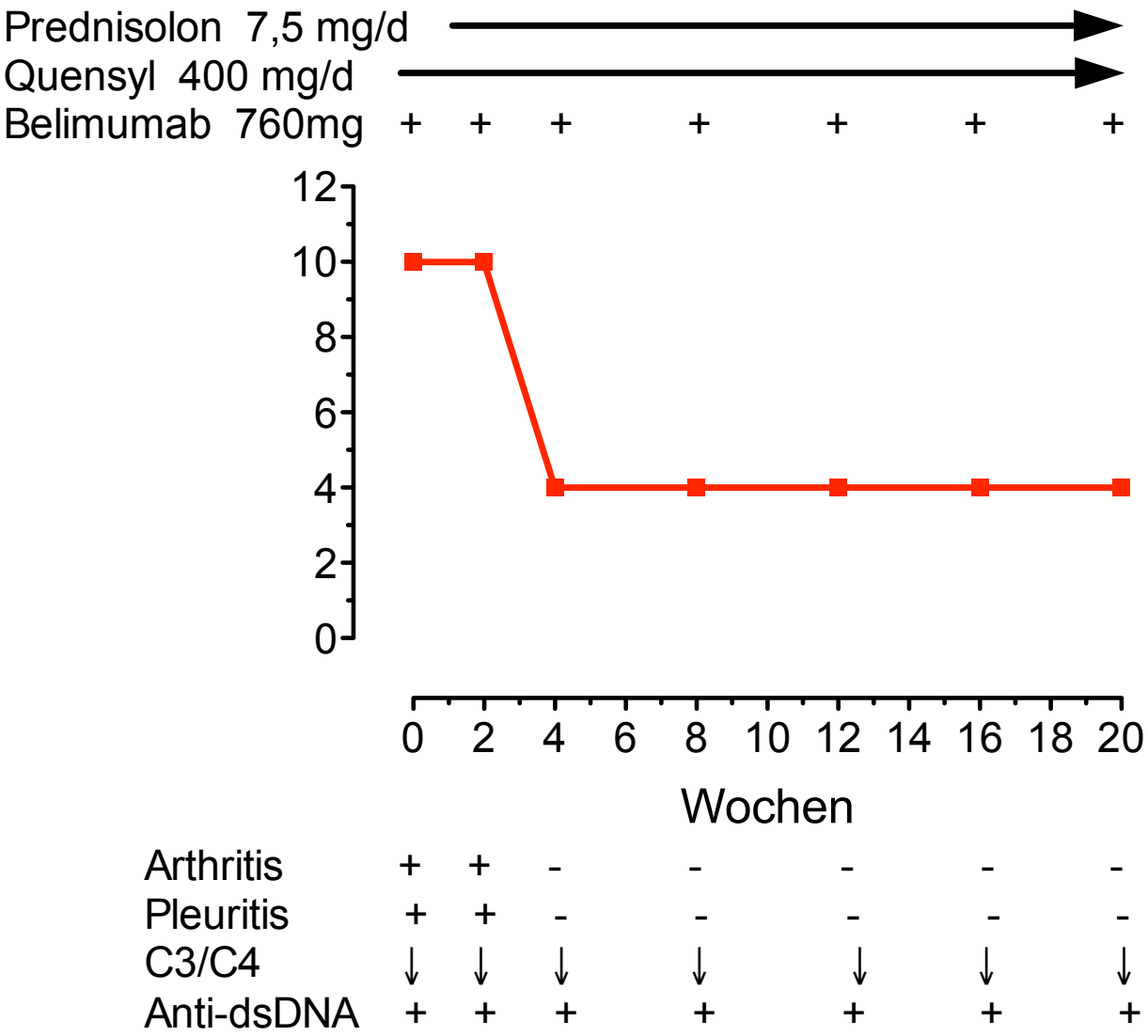
4/2007 surgical abdomen: necrotizing pancreatitis, multilocular perforation of the gut, peritonitis, left hemicolectomy, 14x laparatomy, „critical illness polyneuropathy"

03/2008 anaphylactic reaction on rituximab

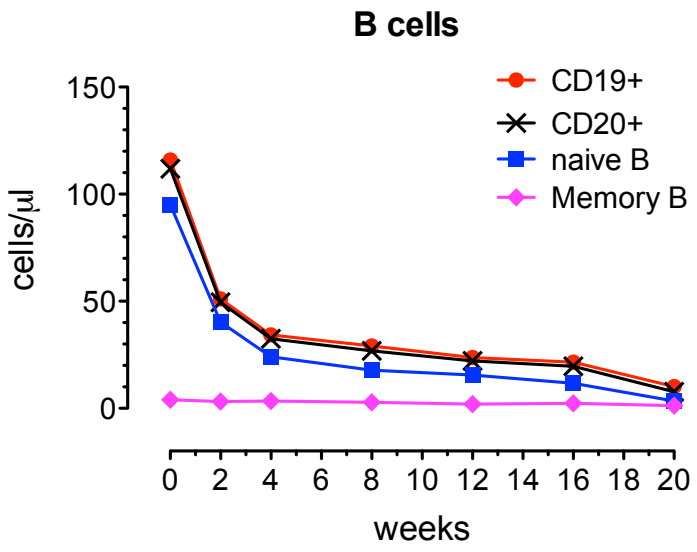
Since 1/2009 Endoxan 500mg iv every 6-8 weeks, hydroxychloroquine 200 mg/d, prednisolone 7,5 mg/d

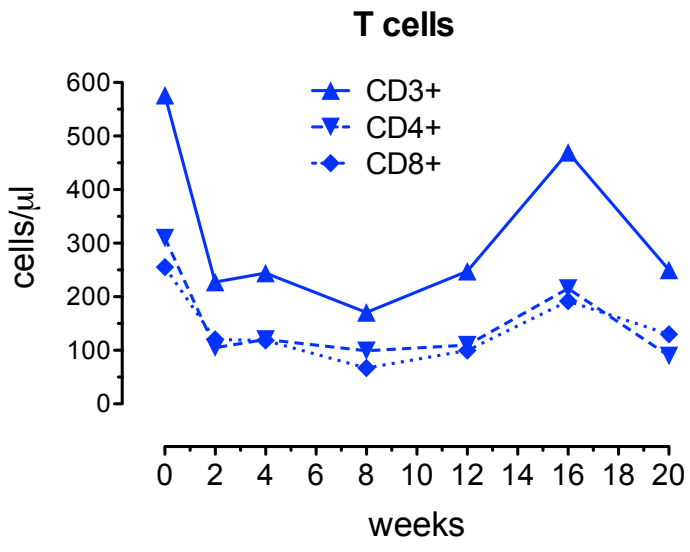
11/2011 myalgia, arthralgia, arthritis, pleuritis with continuously increasing anti-dsDNA antibodies and decreasing complement since 1/2012

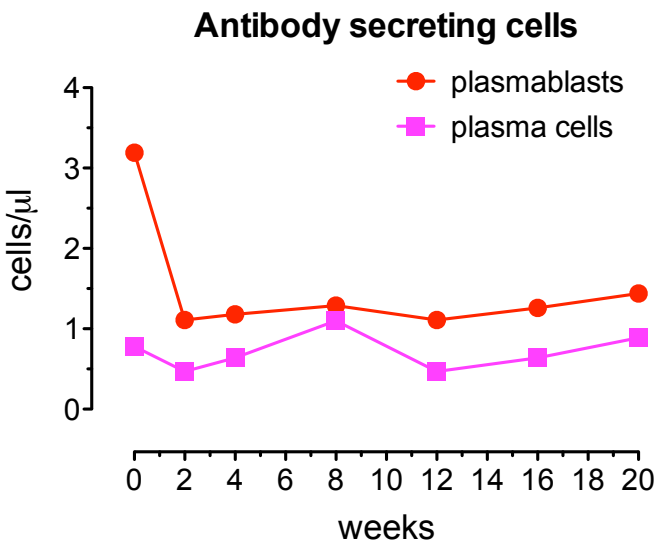
Belimumab in SLE: female patient C.S.

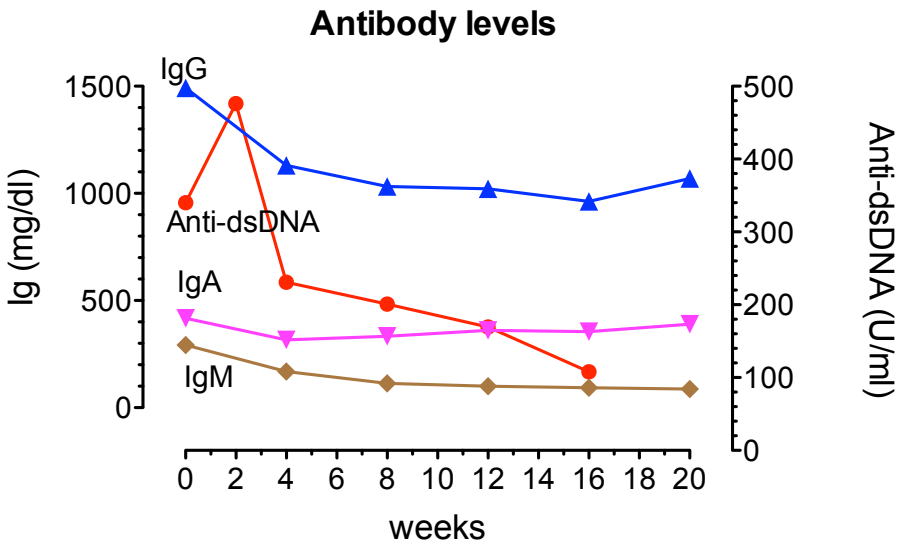


Belimumab in SLE: female patient C.S.









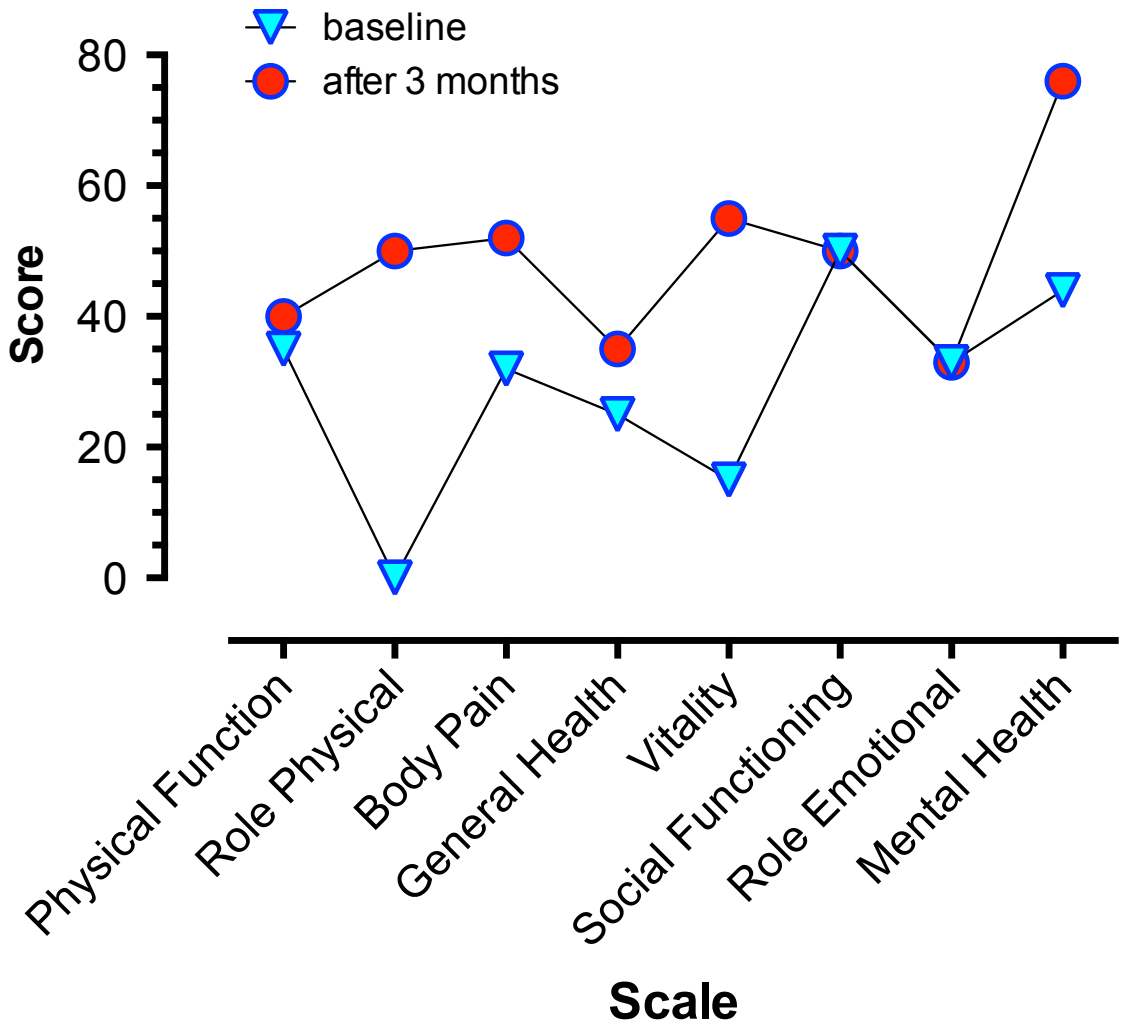
patient C.S. after belimumab

month	0	3	6	12	18
Prednisolone (mg/d)	7.5	7.5	7.5	5	5
Anti-dsDNA	**340**	**169**	**134**	**149**	**68**
C3 (mg/l)	**710**	**700**	**740**	**770**	970
C4 (mg/l)	**50**	**70**	**70**	**80**	150
Arthritis	yes	no	no	no	no
Pleuritis	yes	no	no	no	no
SLEDAI	10	4	4	4	2
PGA	84	75	67	45	35

Patient K.T., 42 years old

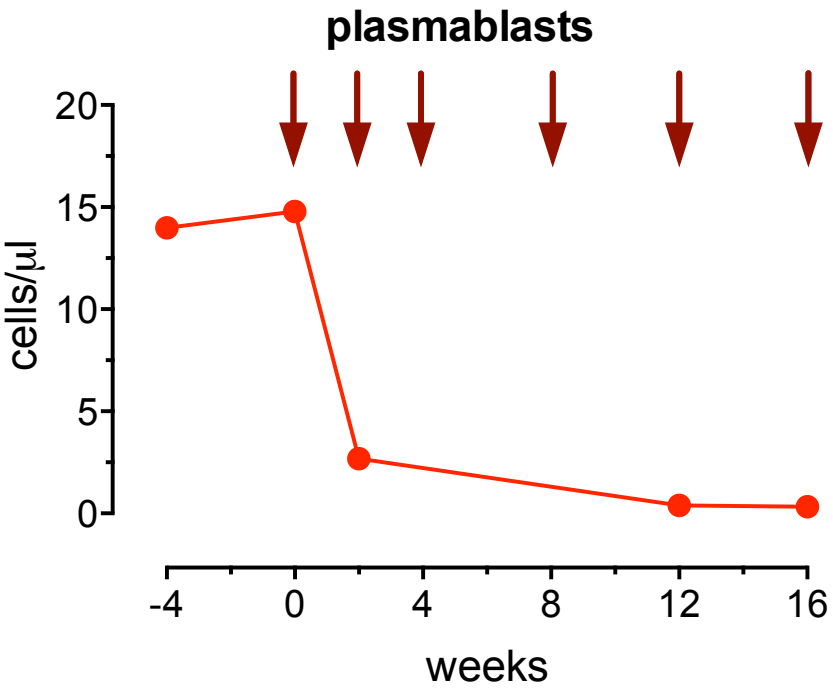
- SLE with cutaneous and musculoskeletal involvement
- ANA 1:320 positive
- Anti-Ro/SSA antibodies positive
- Anti-dsDNA antibodies negative
- Main problem: fatigue despite glucocorticoids (prednisolone 10 mg/d), antimalarials und azathioprine

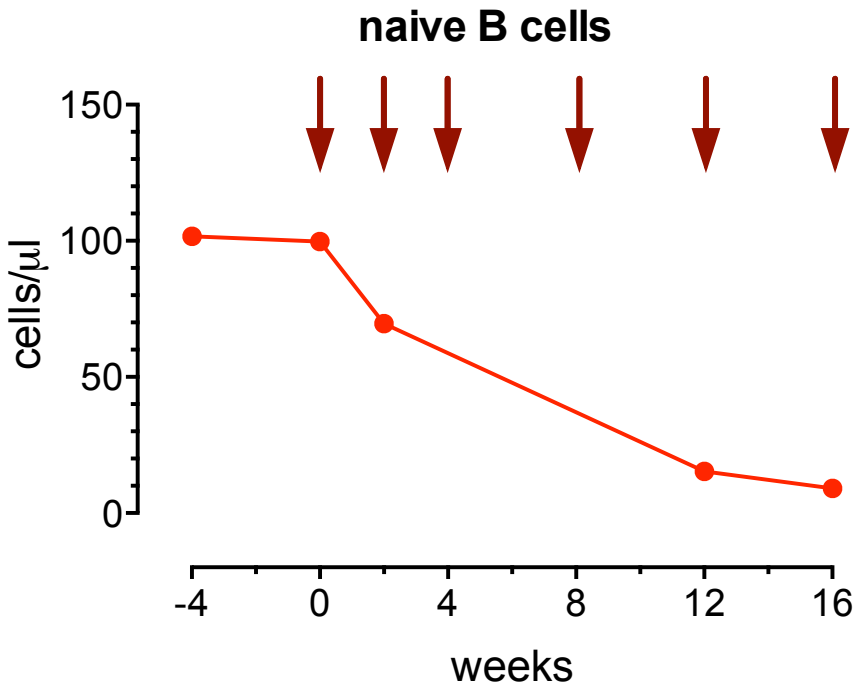
Patient K.T.: Tremendous improvement of fatigue
SF36: Quality of life

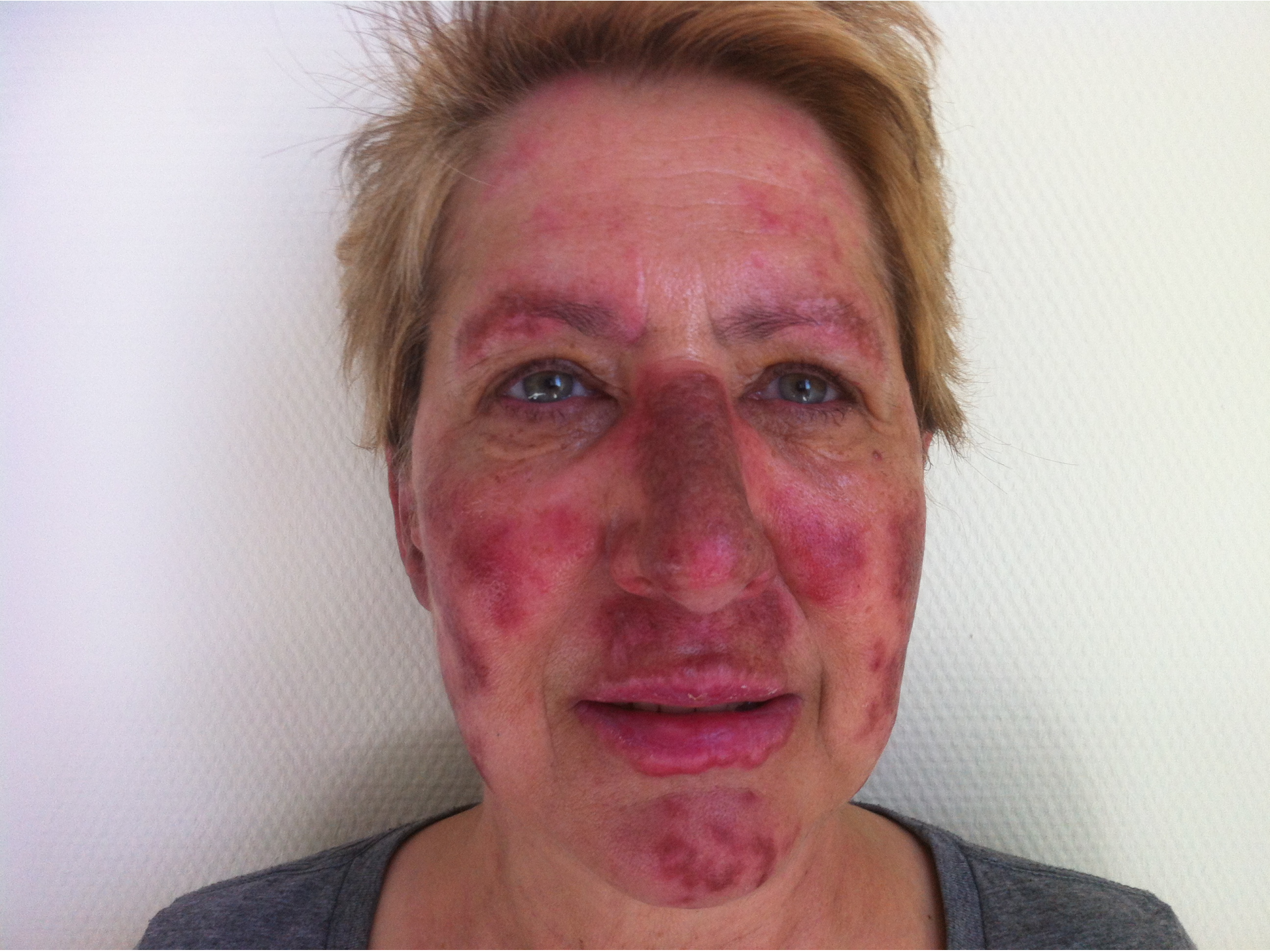


Tapering of prednisolone dose from 10 mg/d to 5 mg/d at month 3

Patient K.T., 42 years old



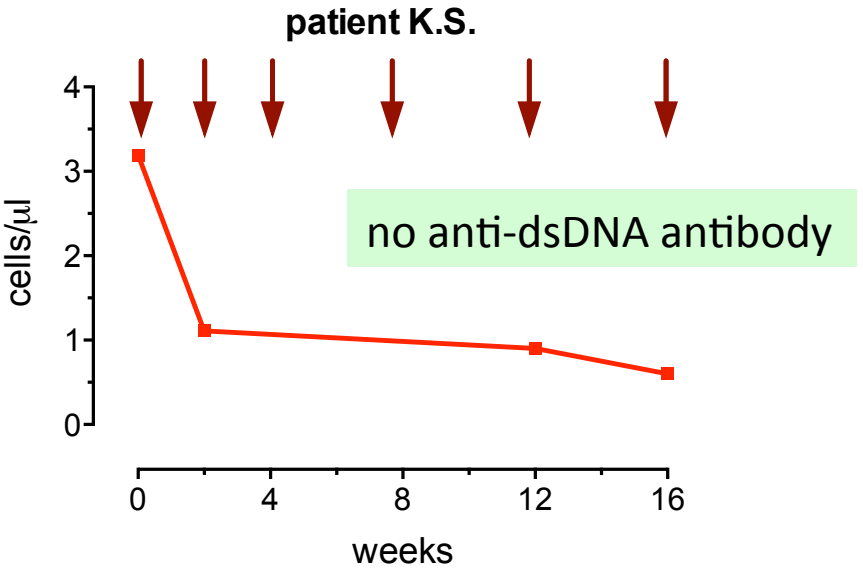


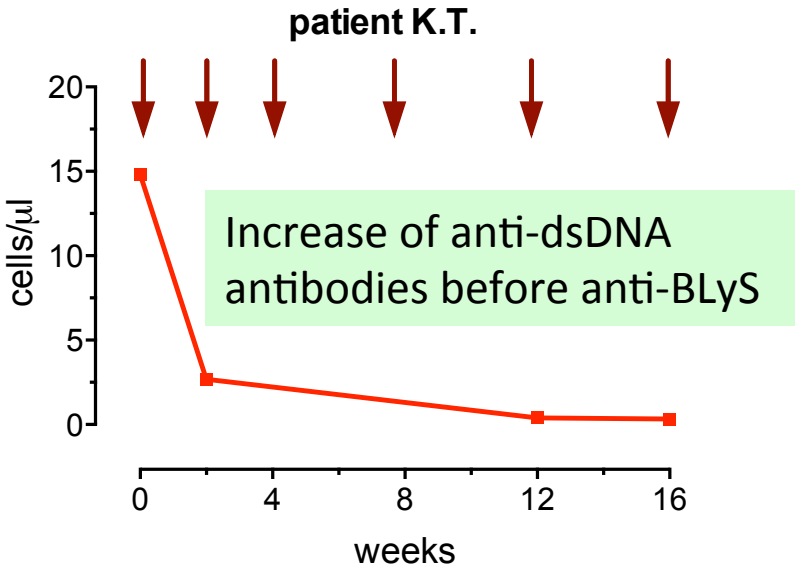


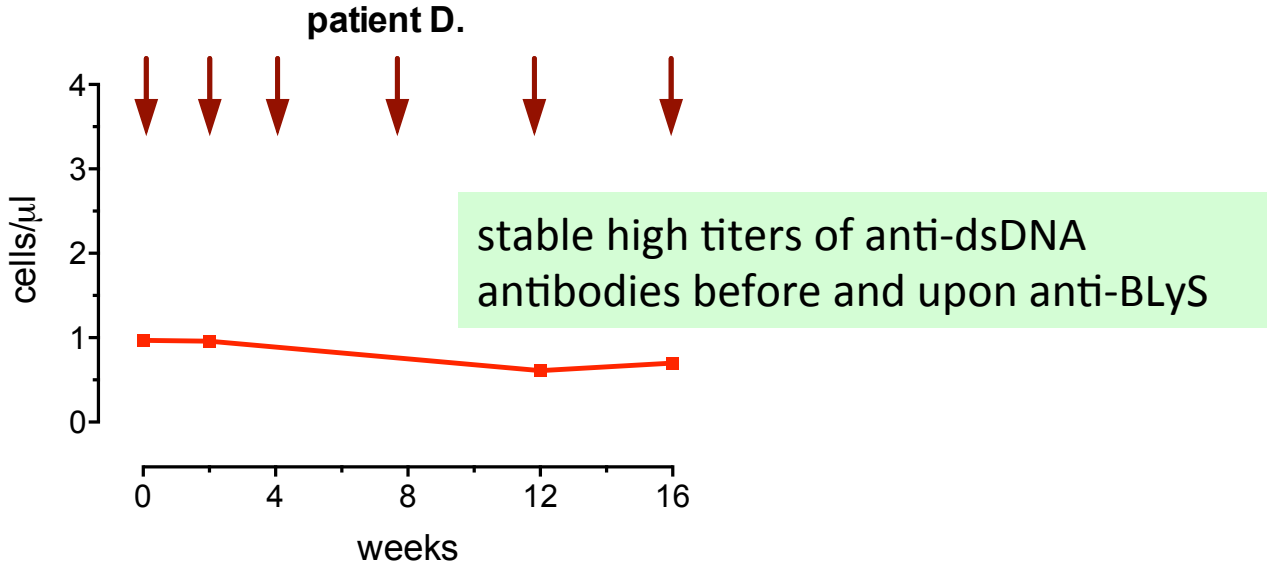
Benlysta in patient D.

	0	14 d	1 month	2 months	3 months	6 months
Pred. mg/d	20	10	10	10	10	10
SLEDAI	**12**	**10**	**6**	**8**	**8**	**8**
Joints	**4**	**4**	**0**	**0**	**0**	**0**
Alopecia	**2**	**2**	**2**	**2**	**2**	**2**
Erythema	**2**	**2**	**2**	**2**	**2**	**2**
Complement	**2**	**0**	**0**	**2**	**2**	**2**
anti-dsDNA	**2**	**2**	**2**	**2**	**2**	**2**
PGA	**85**	**82**	**80**	**85**	**85**	**88**
Anti-dsDNA	**230**	**229,6**	**327**	**318**	**315**	**320**
C3	**790**	920	930	**760**	**320**	**720**
C4	**80**	120	140	110	100	100
Plasmablasts /µl	0,97	0,96	0,69	1,00	0,61	0,28

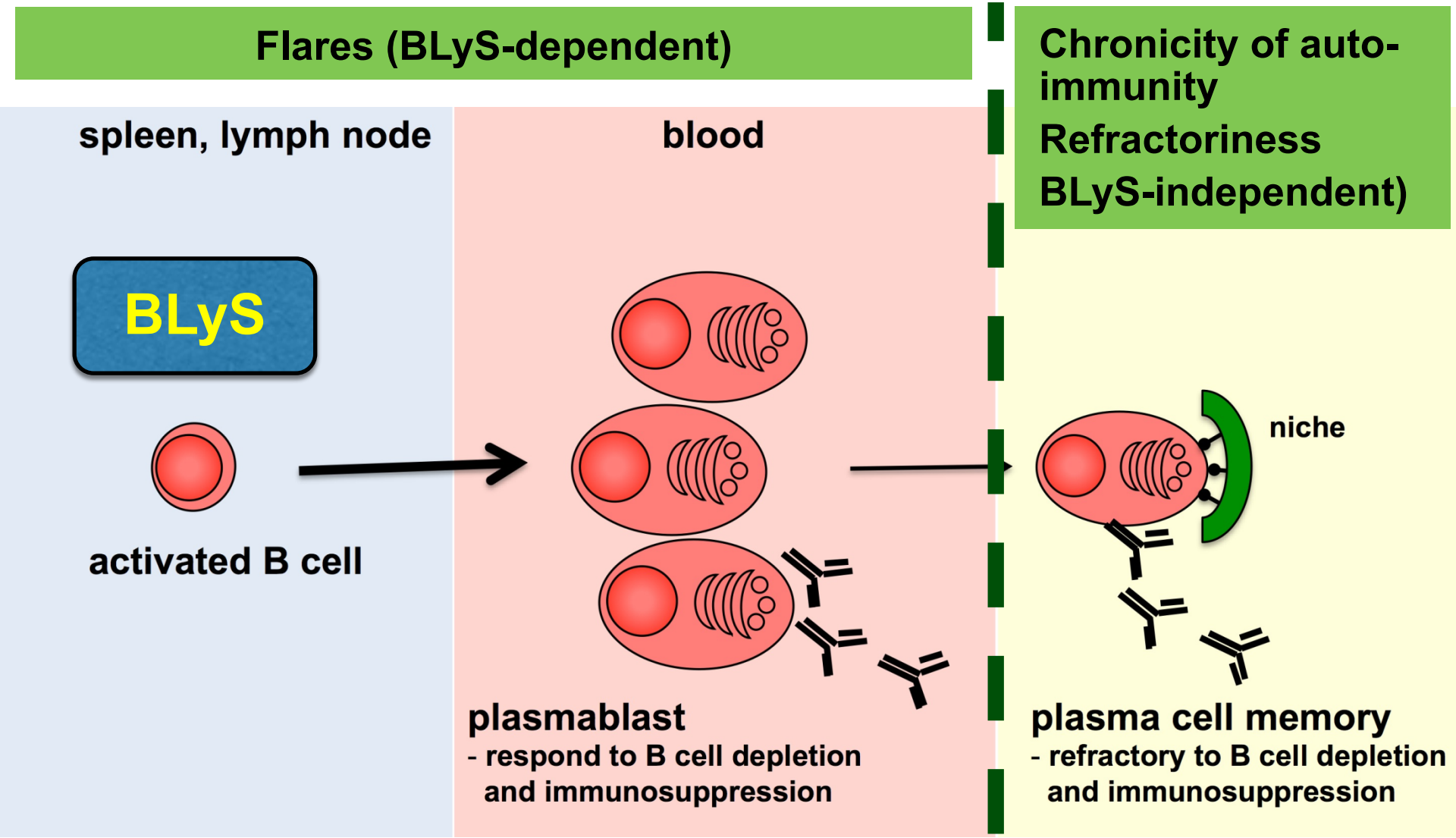
Circulating plasmablasts: predictor of response to belimumab ?







BLyS drives proliferation of autoreactive B cells to autoreactive plasmablasts/plasma cells

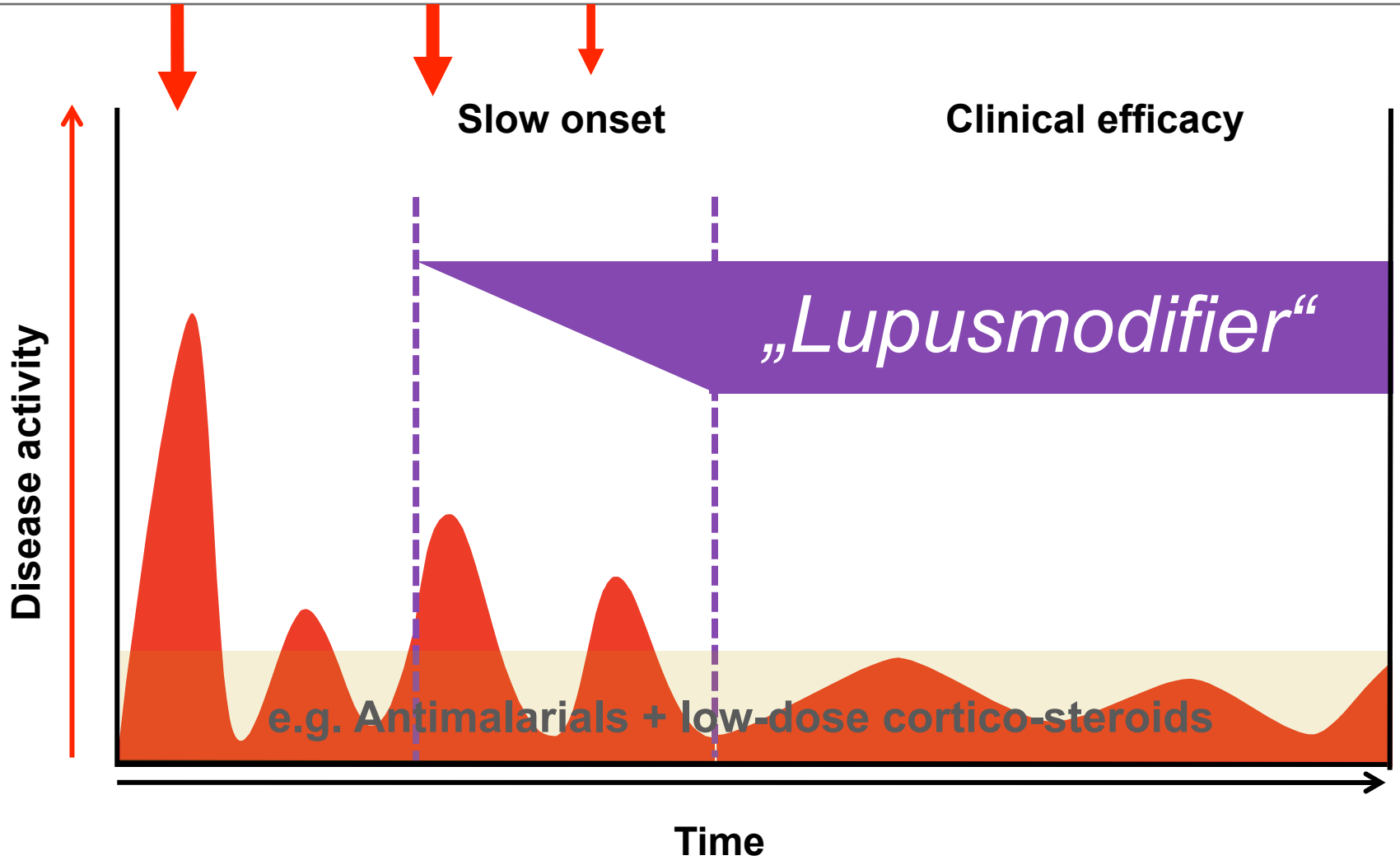


modified according toHiepe et al.: Nat Rev Rheum 7:170-178 (2011)

Who is the appropriate patient for Benlysta

- clinically active patient despite standard therapy (no chance to taper steroids)
- increased numbers of circulating plasmablasts
- elevated anti-dsDNA antibody levels (especially increase)
- low complement levels

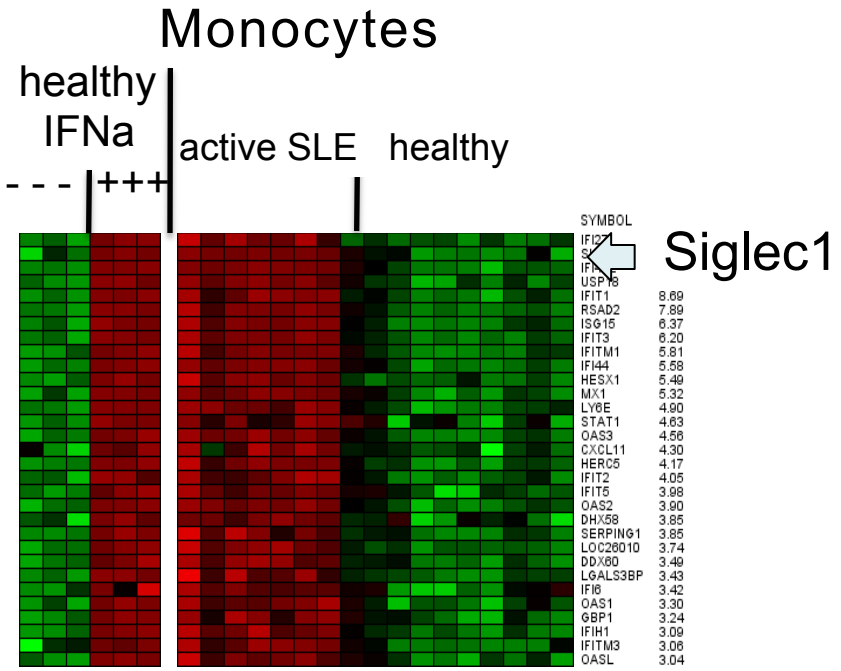
The Concept of Long-term Stabilisation of SLE

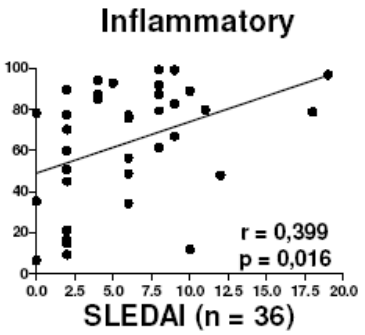


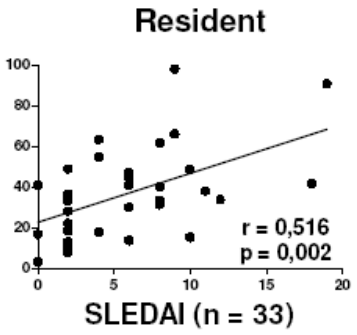

BETONDEMONTAGETE
LOVE & PEACE
IN
WEST & EAST
Test
West

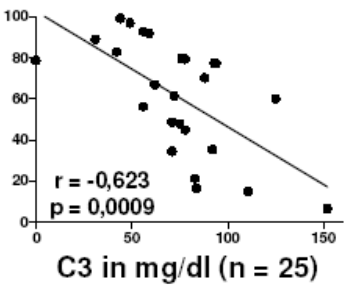
Thank you very much for your attention !

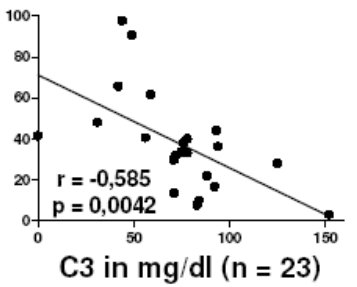
Type I interferon signature in active SLE

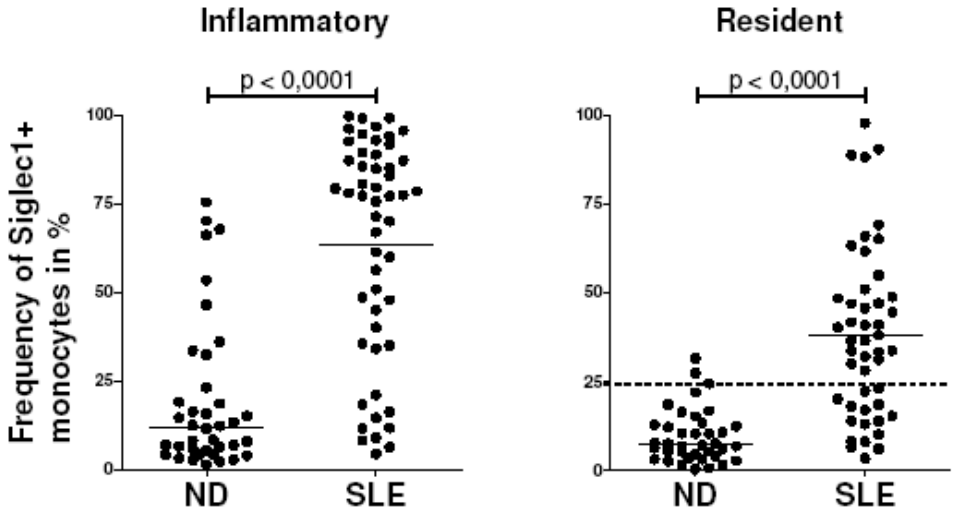


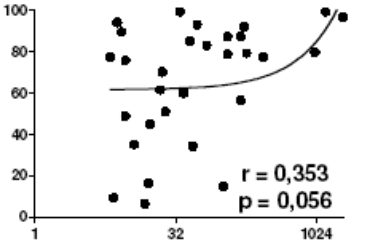


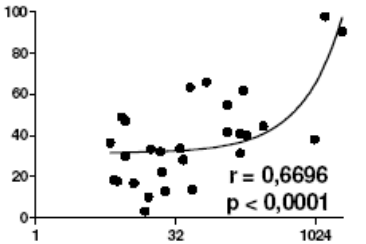






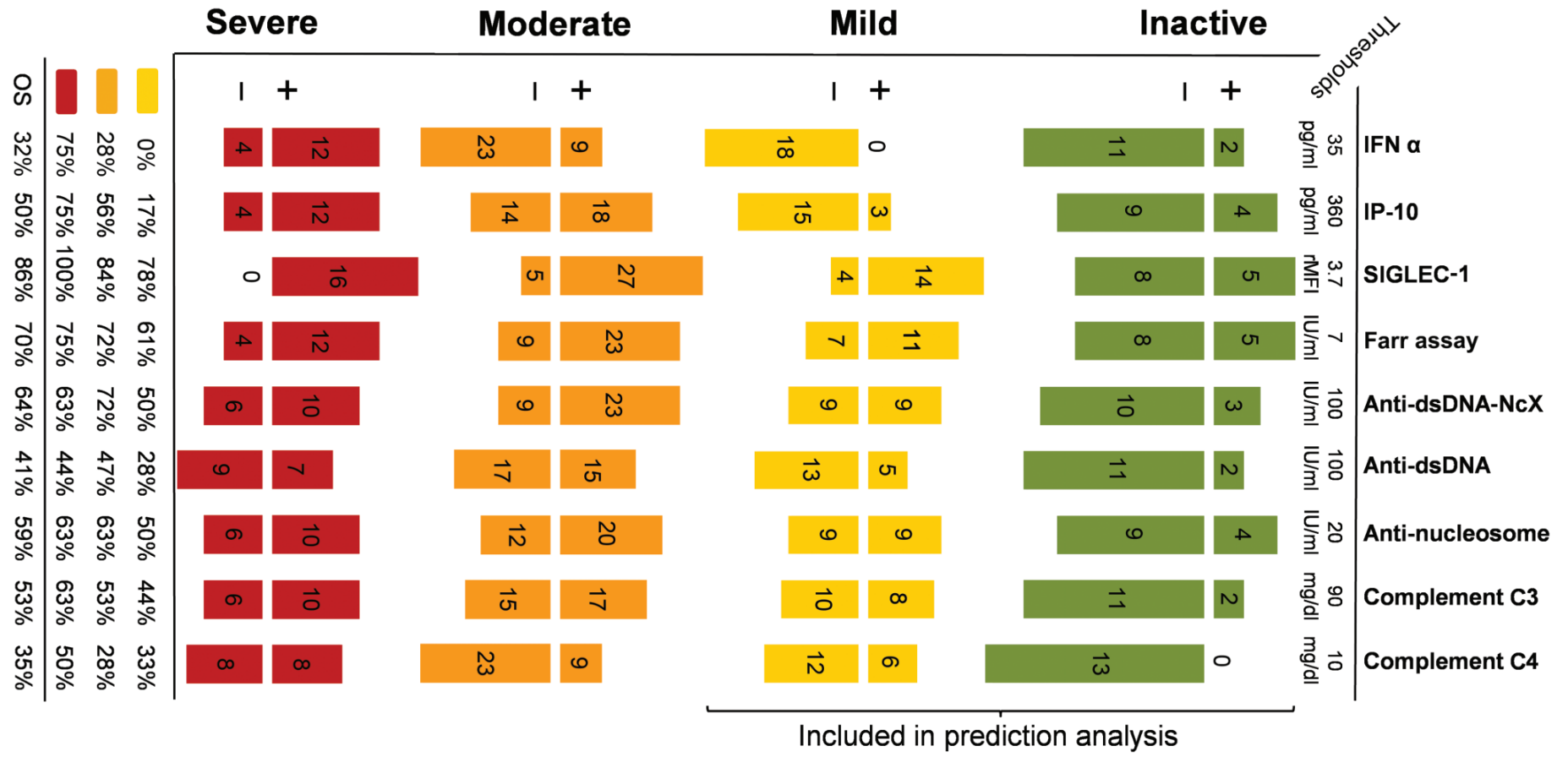






Biesen et al. Arthritis Rheum. (2008)
Rose et al. Ann.Rheum.Dis. (2013)

Interferon Type I Signature in active SLE



Rose et al. : Ann. Rheum. Dis. (2013)

Immunoablation followed by autologous stem cell transplantation might cure lupus

- The long-term, treatment-free clinical remissions observed after complete immunoablation and ASCT is accompanied by a loss of immunological memory and a fundamental resetting of the adaptive immune system
- Depletion of autoreactive memory and reactivation of thymic education are presumably the basis for regeneration of self-tolerance and clinical remission

First diagnosis: 1993
ASCT: 02/2001 due to class IV LN, CNS involvement and APS

	before	after (5 y)
ANA	1:20480	negative
anti-dsDNA	1:64	negative
anti-PL	+++	negative

Alexander T, *et al. Blood*. 2009;113(1):214-23