STATE OF THE ART -

AN UPDATE ON THE ASSESSMENT AND TREATMENT OF LUPUS

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DISCLOSURES

Professor Isenberg has consulted for the companies:-

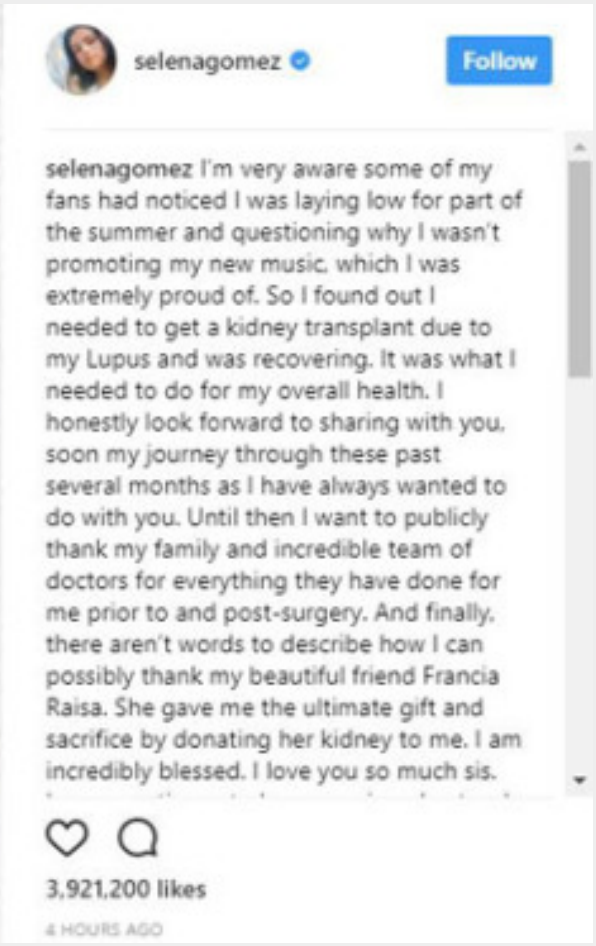
Merck Serono, Pfizer, Glaxo Smith Kline,

ImmuPharma, UCB, GSK, Celgene and Eli Lilly.

The honoraria offered are passed onto a local arthritis charity.

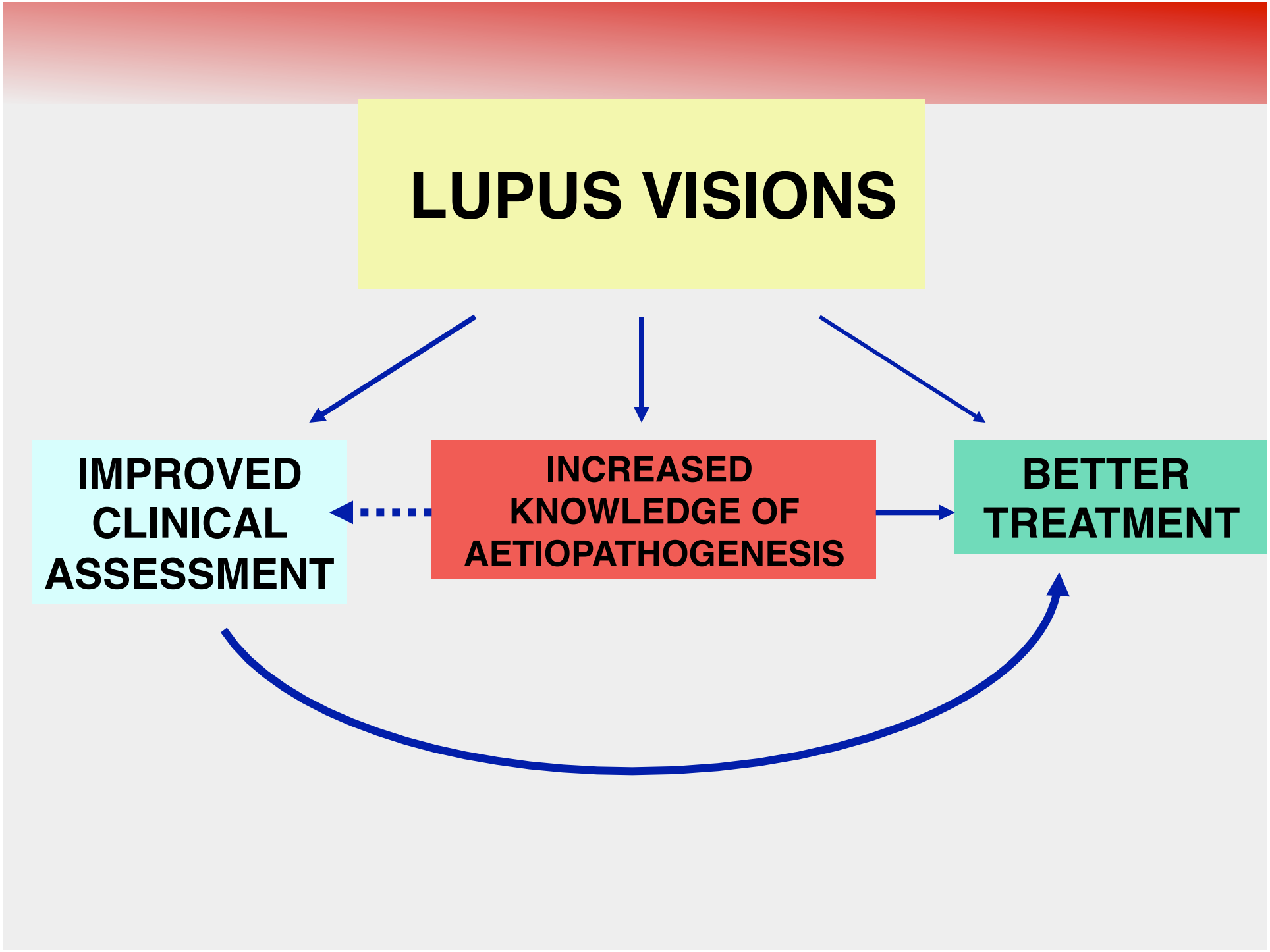
LUPUS STREET

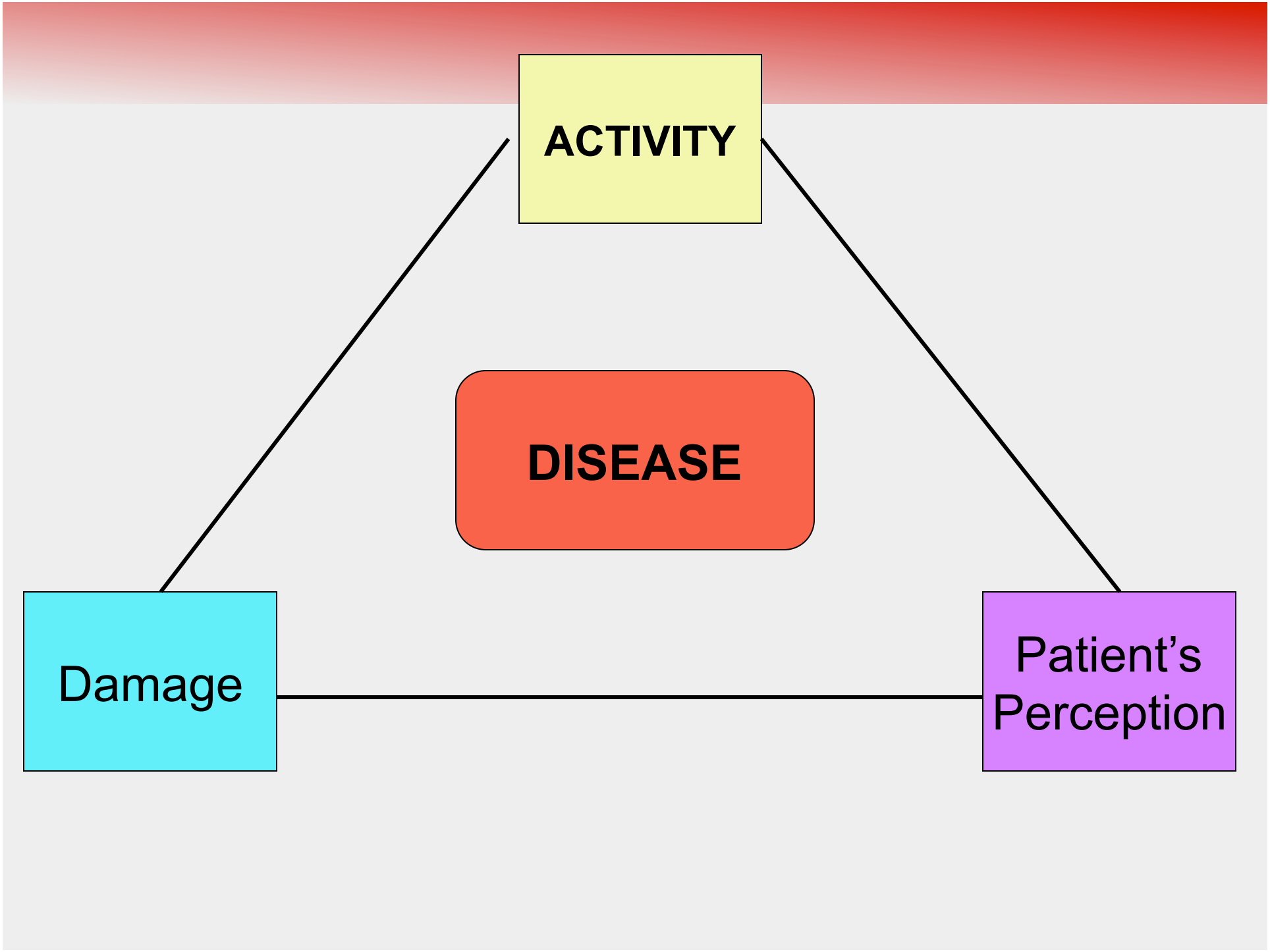
SELENA GOMEZ HAS A KIDNEY TRANSPLANT BECAUSE OF LUPUS NEPHRITIS



LUPUS – IT'S EVERYWHERE!

History of Lupus


LUPUS VISIONS
IMPROVED CLINICAL ASSESSMENT
INCREASED KNOWLEDGE OF AETIOPATHOGENESIS
BETTER TREATMENT


ACTIVITY
DISEASE
Damage
Patient's Perception

AGE MATTERS –
DEMOGRAPHIC DATA OF THE UCL (+) LUPUS COHORT

Characteristic	All JSLE	Childhood	Adolescent	All Adult	Adult	Mature
Numbers	413	136	277	511	467	44
Female: Male	6:1	5:1	7:1	13:1	13:1	11:1
Median age	13	10	14	31	30	54
Ethnicity (%)						
White	50	45	53	60	58	84
Asian	25	31	28	10	14	4
Black	25	21	17	25	26	9

Ambrose et al. Lupus 2016: 25; 1542

AGE MATTERS – GENERAL CHARACTERISTICS OF THE UCL (+) LUPUS COHORT

Characteristic	All JSLE	Childhood	Adolescent	All Adult	Adult	Mature	Significance (P)
Rash	60	70	70	67	68	52	0.362
Photosensitivity	34	33	35	41	42	30	0.057
Alopecia	47	48	46	23	24	18	< 0.001
Oral ulcers	39	35	41	26	26	32	< 0.001
Joint	72	66	75	93	93	98	< 0.001
Serositis	23	18	26	41	43	27	< 0.001

All JSLE = < 18 years: Childhood = < 12 years; Adolescent = 12 – 17 years; All Adult = 18 – 48 years; Mature = 50 years or older. Significance (P) = comparison of All JSLE to All Adult SLE patients.

RENAL DISEASE – AGE DIFFERENCES

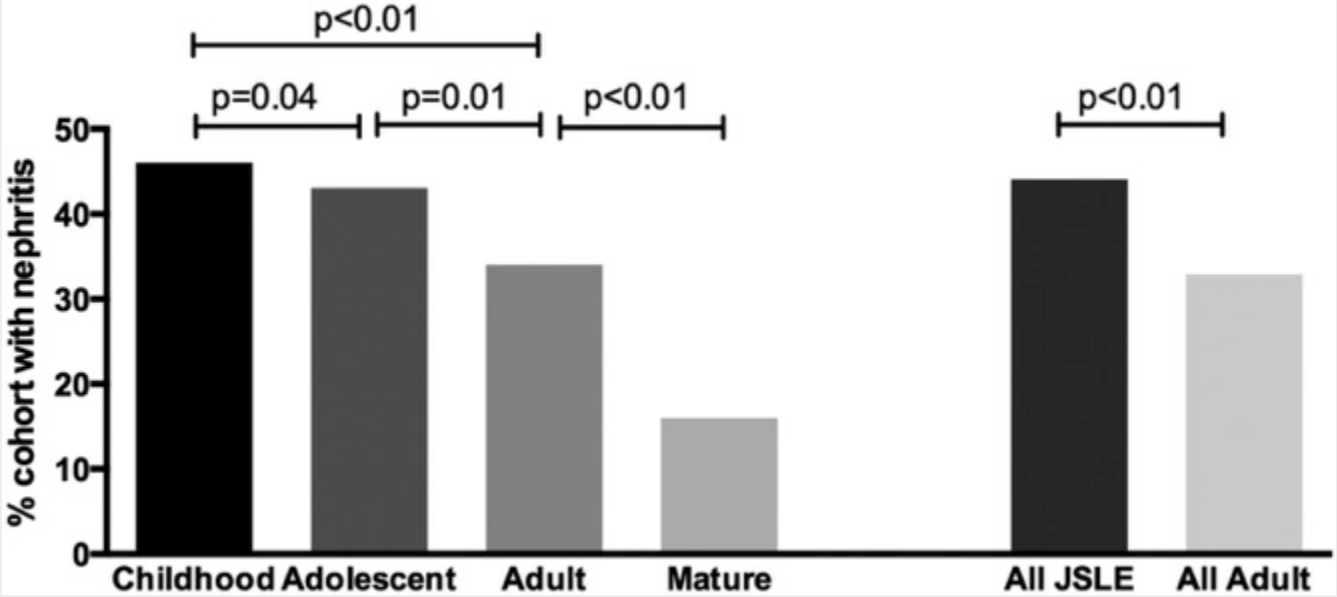


Figure 1 Breakdown of renal involvement by age. The left-hand bars show the breakdown by age as divided into four groups. The right-hand bars summarize key differences between JSLE and adult SLE groups. JSLE: juvenile systemic lupus erythematosus; SLE: systemic lupus erythematosus.

DOI: (10.1177/0961203316644333)

CNS DISEASE – AGE DIFFERENCES

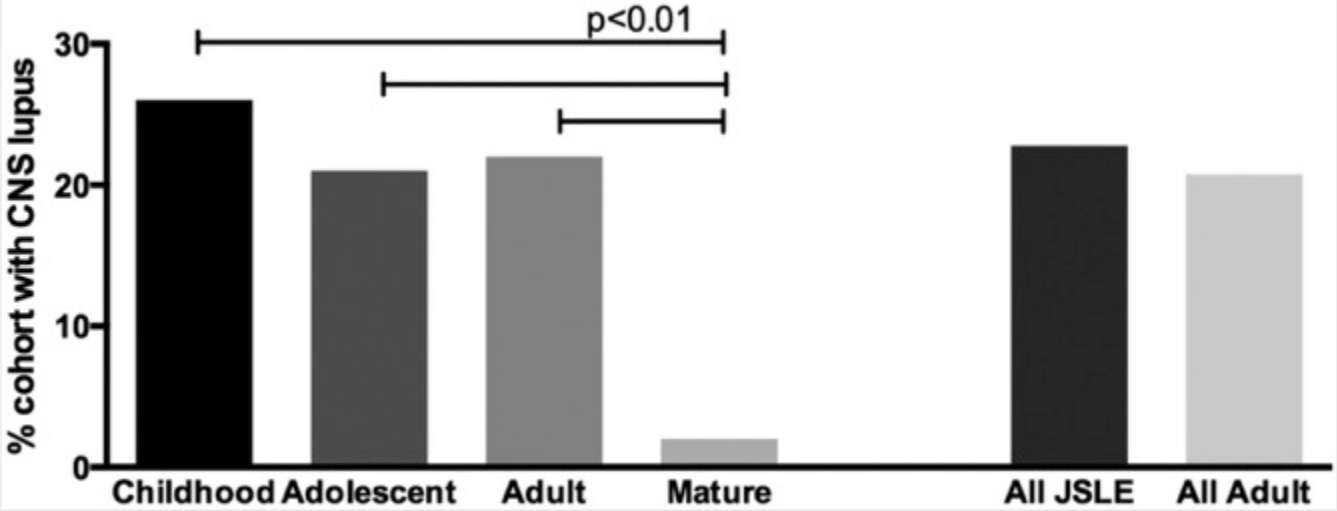


Figure 2 Breakdown of CNS lupus by age. The left-hand bars show the breakdown by age as divided into four groups. The right-hand bars summarize key differences between JSLE and all-adult SLE groups. CNS: central nervous system; JSLE: juvenile systemic lupus erythematosus; SLE: systemic lupus erythematosus.

DOI: (10.1177/0961203316644333)

AGE MATTERS – HAEMATOLOGICAL AND IMMUNOLOGICAL INVOLVEMENT OF THE UCL (+) LUPUS COHORT (1)

	All JSLE	Childhood	Adolescent	All Adult	Adult	Mature	Significance (P)
HAEMATOLOGICAL							
Lymphopenia	62	51	68	76	75	84	< 0.001
Leucopenia	32	29	34	30	31	26	0.590
Thrombocytopaenia	21	19	22	15	15	16	0.011
Haemolytic anaemia	20	24	19	3	3	0	< 0.001
Coombs positive	24	24	23	21	21	16	0.350

AGE MATTERS – HAEMATOLOGICAL AND IMMUNOLOGICAL INVOLVEMENT OF THE UCL (+) SLE COHORT (2)

	All JSLE	Childhood	Adolescent	All Adult	Adult	Mature	Significance (P)
IMMUNOLOGICAL							
ANA	97	98	97	94	94	95	0.061
dsDNA	71	75	69	63	63	57	0.009
Low C3	62	57	65	46	48	23	< 0.001
Sm	22	19	23	16	17	7	0.021
RNP	36	33	37	29	30	18	0.038
Ro	35	30	37	38	40	23	0.335
La	17	13	18	15	15	14	0.450

A FEW WORDS ABOUT MONITORING (1)

- See SLE patients regularly
  - active disease – every 1-3 mn
  - inactive disease – every 6-12 mn

- Close monitoring of drugs is necessary especially:
  - Immunosuppression and steroids
  - HCQ [eye checks but? how often]

A FEW WORDS ABOUT MONITORING (2)

- **Serological awareness**
  - **anti Ro/La – photosensitivity/heart block**
  - **anti-phospholipid abs – clots/miscarriage**
  - **↑ dsDNA – renal disease**

- **Watch for co-morbidities**
  - **Atherosclerosis**
  - **Osteoporosis/avascular necrosis**
  - **Infection**
  - **Cancer**

SLE – TREATMENT STRATEGIES (1)

	MILD DISEASE [BILAG C Scores/single B/SLEDAI <6]
FEATURES	Fatigue, malar rash, diffuse alopecia, myalgia, platelets 50 – 149 x 10^9/L
TYPICAL DRUGS & TARGET DOSE	Prednisolone topical or < 20mg/day for 1 – 2 weeks/IM or IA Methylprednisolone + HCQ $\leq$ 6.5mg/kg/day +/- NSAIDs maybe Methotrexate
MAINTENANCE DOSE	Prednisolone $\leq$ 7.5mg/day + HCQ 200mg/day +/- Methotrexate 10mg/week

Gordon et al. Rheumatology 2018; 57: 14-18 (BSR Guidelines)

SLE – TREATMENT STRATEGIES (2)

	MODERATE DISEASE 2 OR MORE BILAG Bs/SLEDAI 6-12
FEATURES	Fever, rash (< 2/9 body surface area), cutaneous vasculitis, renal, pleurisy, pericarditis, platelets 25 – 49 x 10^9/L
TYPICAL DRUGS & TARGET DOSE	Prednisolone ≤ 0.5mg/day or IV or IA Methylprednisolone + AZA 2mg/kg/day or MTX 10-25mg/week or MMF 2-3g/day
MAINTENANCE DOSE	Prednisolone ≤ 7.5mg/day + AZA 50-100mg/day or MTX 10mg/week or MMF 1g/day + HCQ 200mg/day

SLE – TREATMENT STRATEGIES (3)

	SEVERE DISEASE 1 OR MORE BILAG A/SLEDAI > 12
FEATURES	Rash > 2/9 body surface area, severe pleurisy/pericarditis, psychosis, renal/myositis/ platelets < 25 x 10^9/L
TYPICAL DRUGS & TARGET DOSE	Prednisolone ≤ 0.5mg/day and/or IV Methylprednisolone (500mg IV x 3) + AZA 2-3mg/kg/day or MMF 2-3g/day or IV Cyclo 750 + HCQ 200mg/day
MAINTENANCE DOSE	Prednisolone ≤ 7.5mg + AZA 50-100mg/day or MMF 1g/day or MTX 10mg/week + HCQ 200mg/day

TREAT TO TARGET (1)

1.The treatment target of SLE should be remission of systemic symptoms and organ manifestations/lowest possible disease activity – measured by a validated activity index and/or organ-specific markers.

2.Prevention of flares (especially severe flares) is a realistic target and should be a therapeutic goal.

[Van Vollenhoven et al. Ann Rheum Dis 2014; 73: 958]

TREAT TO TARGET (2)

3. It is not recommended that the treatment in clinically asymptomatic patients be escalated based solely on stable/persistent serological activity.

4. Since damage predicts subsequent damage and death, prevention of damage accrual should be a major therapeutic goal in SLE.

TREAT TO TARGET (3)

5.Factors negatively influencing health-related quality of life [HRQOL] eg fatigue or pain, should be addressed in addition to control of disease activity and damage prevention.

6.Early recognition and treatment of renal involvement in lupus is strongly recommended.

TREAT TO TARGET (4)

7.For lupus nephritis following induction therapy at least 3 years of immunosuppressive maintenance therapy is recommended.

8.Lupus maintenance treatment should aim for the lowest glucocorticoid dosage needed to control disease (and if possible withdrawn completely).

TREAT TO TARGET (5)

9. Prevention and treatment of APS related morbidity should be a therapeutic goal.

10. Irrespective of other treatments consideration should be given to using anti-malarials.

11. Relevant therapies adjunctive to any immunomodulation should be considered to control co-morbidity in SLE.

WHAT WERE THESE BRITISH RHEUMATOLOGISTS DOING IN 2014?

A 30 YEAR CELEBRATION

BILAG at 30

FLARE RATES USING BILAG 2004 INDEX

During Jan 2014 – Dec 2014
323 patients were seen on at least 3 occasions

135 patients had a flare

Severe	Moderate	Mild	No Flares
1 ‘A’ at least	2 ‘B’s	1 ‘B’ or 3 ‘C’s	
8.4%	9.3%	35%	47%

Ciang, Isenberg. Rheumatology 2016; 55: S169

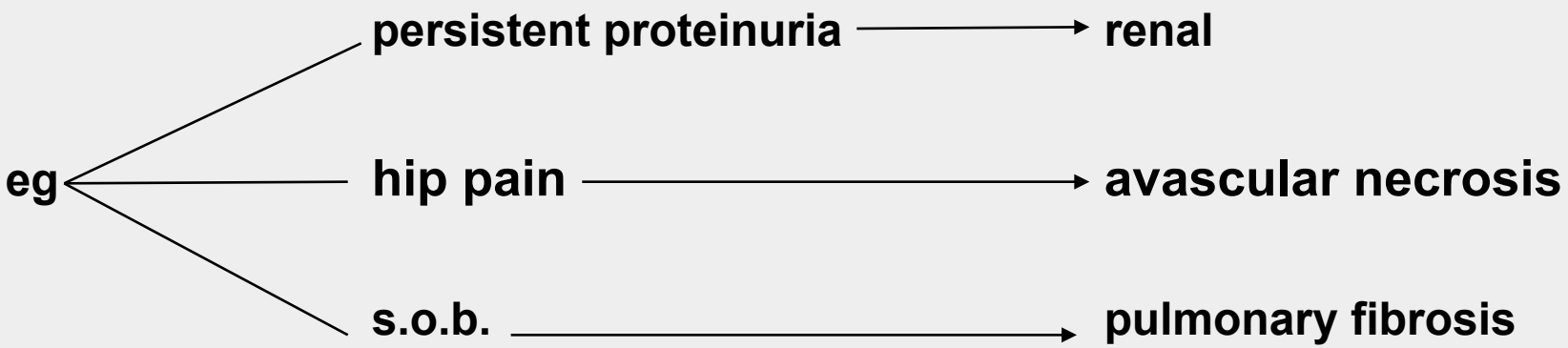
A FEW WORDS ABOUT ALTERNATIVE EXPLANATIONS FOR CLINICAL FEATURES IN LUPUS (1)

A)

CONCOMITANT DISEASE IN UCL COHORT (1978 – 2018) (n = 700)	
Hypothyroid	8%
Sjögren's	7%
Antiphospholipid antibody syndrome	7%
Myositis	4%
Diabetes	3%

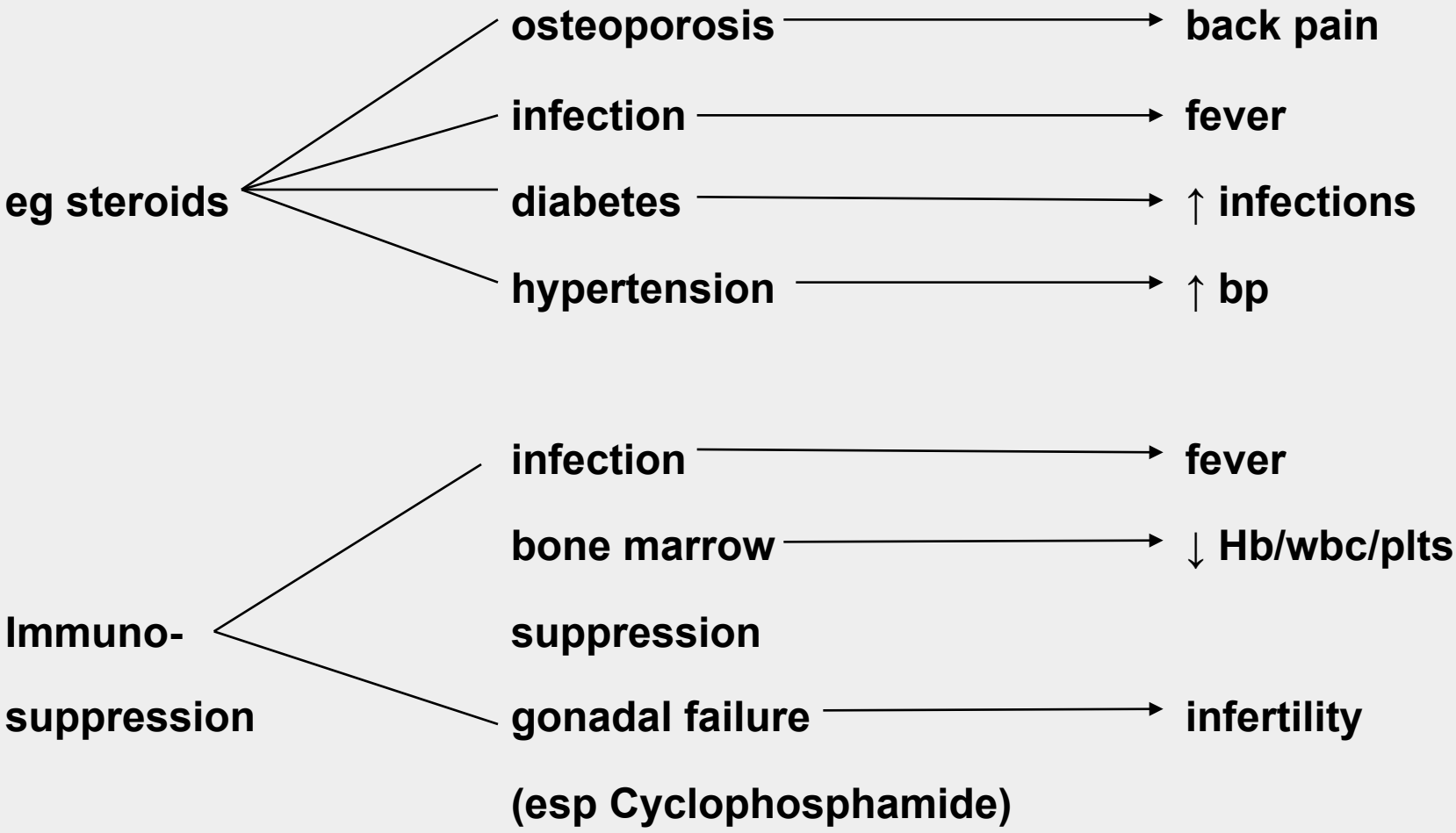
A FEW WORDS ABOUT ALTERNATIVE EXPLANATIONS FOR CLINICAL FEATURES IN LUPUS (2)

B) CONCOMITANT DAMAGE



A FEW WORDS ABOUT ALTERNATIVE EXPLANATIONS FOR CLINICAL FEATURES IN LUPUS (3)

C) CONCOMITANT DRUGS



TREATMENT ALGORITHMS IN SLE (1)

STUDY INVOLVED

- 69 SLE experts approached (54% responded)

- Each respondent sent 16 scenarios to suggest how to treat

- Algorithms constructed and agreement determined ($\geq$ 50% respondents indicating $\geq$ 70% agreement)

Muangchan et al. Arthritis Care Res 2016; 67: 1232

TREATMENT ALGORITHMS IN SLE (2)

EXAMPLES

	1
	Constitutional symptoms
1st Line	**HCQ/CS/ Immunomodulation**
2nd Line	**MMF**
3rd Line	**Rituximab/ Belimumab**

TREATMENT ALGORITHMS IN SLE (2)

EXAMPLES

	1	2
	Constitutional symptoms	Widespread DLE
1st Line	HCQ/CS/ Immunomodulation	HCQ ± CS
2nd Line	MMF	ADD AZA
3rd Line	Rituximab/ Belimumab	AZA → MMF or MTX

TREATMENT ALGORITHMS IN SLE (2)

EXAMPLES

	1	2	3
	Constitutional symptoms	Widespread DLE	Polyarthritis
1st Line	HCQ/CS/ Immunomodulation	HCQ ± CS	HCQ + CS
2nd Line	MMF	ADD AZA	ADD MTX
3rd Line	Rituximab/ Belimumab	AZA → MMF or MTX	Rituximab

TREATMENT ALGORITHMS IN SLE (2)

EXAMPLES

	1	2	3	4
	Constitutional symptoms	Widespread DLE	Polyarthritis	Thrombo-cytopenia
1st Line	HCQ/CS/ Immunomodulation	HCQ ± CS	HCQ + CS	CS ± HCQ
2nd Line	MMF	ADD AZA	ADD MTX	AZA/MMF
3rd Line	Rituximab/ Belimumab	AZA → MMF or MTX	Rituximab	Rituximab/ IV Cyclo/ Ivlg

TREATMENT ALGORITHMS IN SLE (3)

EXAMPLE

	5
	Lupus APS arterial thrombolysis
1st Line	Warfarin/ LMW Hep IHCU
2nd Line/ Induction	Add aspirin/ Dipyriadamole/ Platelet agg inhib
3rd Line	/

TREATMENT ALGORITHMS IN SLE (3)

EXAMPLE

	5	6
	Lupus APS arterial thrombolysis	**Mononeuritis Multiplex**
1st Line	**Warfarin/ LMW Hep IHCU**	**CS + IV Cyclo**
2nd Line/ Induction	**Add aspirin/ Dipyriadamole/ Platelet agg inhib**	**Add Rituximab or IVIG/PE**
3rd Line	/	/

TREATMENT ALGORITHMS IN SLE (3)

EXAMPLE

	5	6	7
	Lupus APS arterial thrombolysis	**Mononeuritis Multiplex**	**Nephritis III/IV**
1st Line	Warfarin/ LMW Hep IHCU	CS + IV Cyclo	CS + MMF
2nd Line/ Induction	Add aspirin/ Dipyriadamole/ Platelet agg inhib	Add Rituximab or IVIG/PE	IV Cyclo
3rd Line	/	/	Add Rituximab

TREATMENT ALGORITHMS IN SLE (3)

EXAMPLE

	5	6	7	8
	Lupus APS arterial thrombolysis	Mononeuritis Multiplex	Nephritis III/IV	Nephritis V
1st Line	Warfarin/ LMW Hep IHCU	CS + IV Cyclo	CS + MMF	CS + MMF
2nd Line/ Induction	Add aspirin/ Dipyriadamole/ Platelet agg inhib	Add Rituximab or IVIG/PE	IV Cyclo	→ AZA/IV Cyclo or Rituximab
3rd Line	/	/	Add Rituximab	/

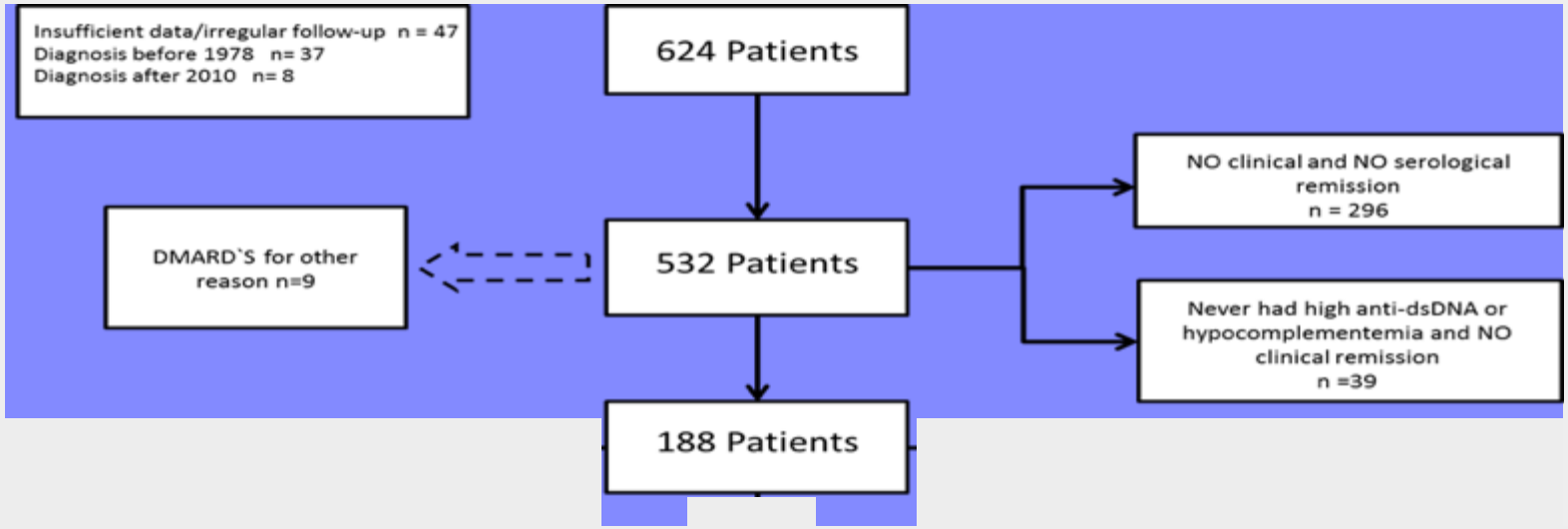
DEFINING REMISSION (1)

- No clinical features

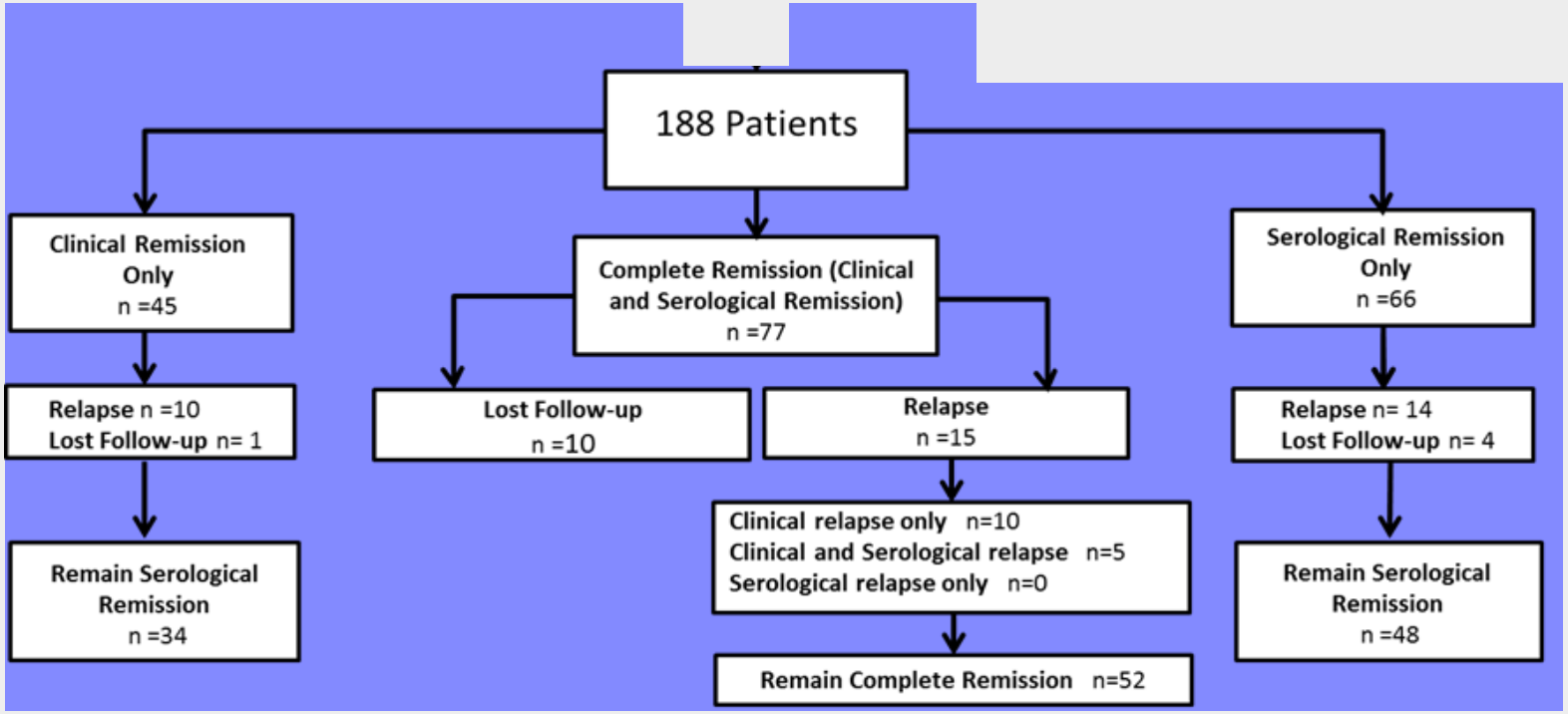
- No abnormal serologies

- No requirement for steroids/immunosuppression

COMPLETE REMISSION IN THE UCL COHORT (1)



COMPLETE REMISSION IN THE UCL COHORT (2)



DEFINING REMISSION (2)

BUT:

- **Should complete remission be considered at 1yr/3yrs/ 5yrs etc.**

- **Is 'no clinical features/abnormal serologies' sufficient?**

  After all many SLE patients are kept on low-dose

  Prednisolone as a 'just in time' strategy.

- **What of serologically active clinically quiescent patients?**

SO GETTING TO FULL REMISSION IS HARD …… WHAT THEN?! (1)

Definition/Validation of a Lupus Low Disease Activity State [LLDAS]

-used Delphi and nominal group techniques [6-11 experts]

-criterion validity determined by measuring LLDAS attainment in a single SLE cohort to predict non-accrual of irreversible organ damage [SLICC/ACR index]

-Validation study (n = 191) followed for a mean of 3.9 years

Franklyn et al. Ann Rheum Dis 2016; 75: 1615

SO GETTING TO FULL REMISSION IS HARD …… WHAT THEN?! (2)

	LLADS definition	
	Domain – items	**Mean Agreement** **1 – strongly disagree → 5 – strongly agree**
1.	SLEDAI-2K ≤ 4 with no activity in major organ systems	5
2.	No new features of lupus activity compared to previous assessment	4.2
3.	SELENA-SELENA PGA (0→3) = ≤ 1	4.8
4.	Current steroid dose ≤ 7.5mg/ day	4.5
5.	Well tolerated standard maintenance doses of immunosuppressives/biologics	4.5

SO GETTING TO FULL REMISSION IS HARD …… WHAT THEN?! (3)

KEY MESSAGE

Patients who spent > 50% of their observed time in LLDAs had:-

1.Significantly reduced organ damage accrued compared to those <50% of their time in LLDAs [p = 0.0007]

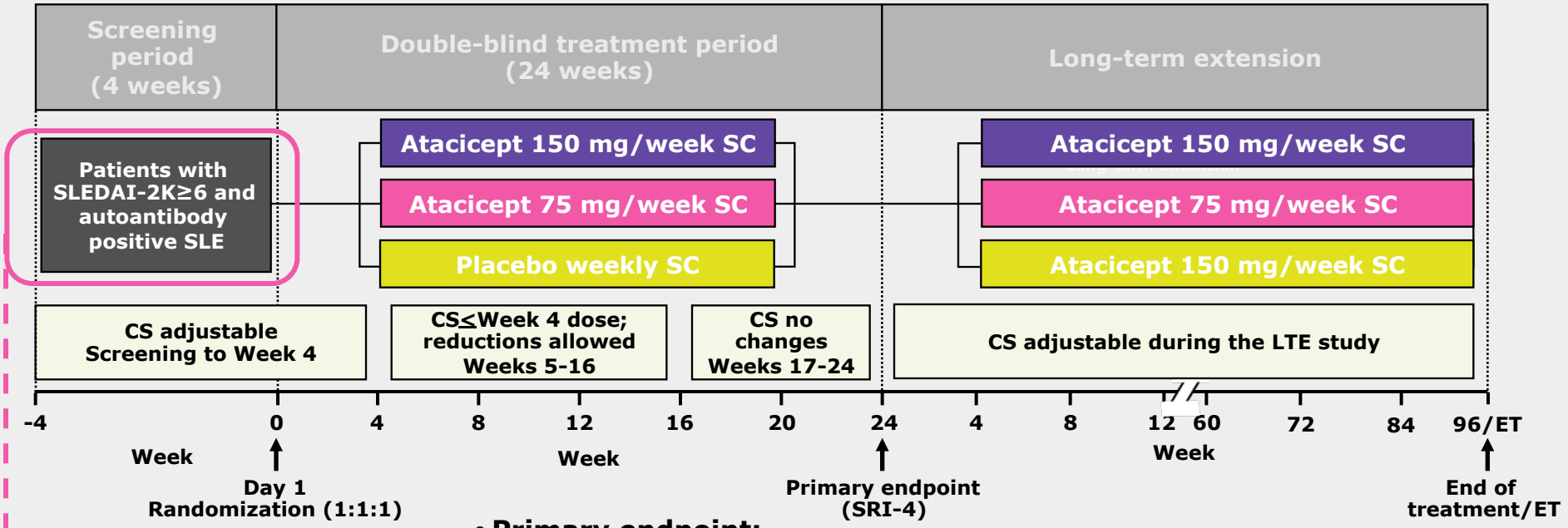
and

1.Were significantly less likely to have an increase in their SLICC/ACR damage index ≥

(relative risk 0.47, 95% C1 0.28 to 0.79 ~ p = 0.005)

Tsang-A-Sjoe MW et al. Rheumatology 2017; 65: 12

ATACICEPT IN ACTIVE LUPUS STUDY DESIGN



HDA (SLEDAI-2K≥10 at Screening):
- **Atacicept 150 mg: 51/104**
- **Atacicept 75 mg: 55/102**
- **Placebo: 52/100**

- **Primary endpoint:**
  SRI-4 response at Week 24
- **Other select endpoints:**
  SRI-6 attainment in patients with HDA at Screening at Week 24

CS, corticosteroids; **SC,** subcutaneous; **SRI,** SLE responder index

LOW DISEASE ACTIVITY AND REMISSION DEFINITIONS USED IN THIS POST-HOC ANALYSIS*

Criteria	LDA	LLDAS	Remission
SLEDAI-2K ≤2	✓		
SLEDAI-2K ≤4 without major organ activity		✓	
Clinical SLEDAI-2K=0			✓
Prednisone-equivalent ≤7.5 mg/day		✓	
Prednisone-equivalent ≤5 mg/day			✓
Physician's Global Assessment ≤1		✓	
Physician's Global Assessment ≤0.5			✓
Stable maintenance doses of immunosuppressants		✓	
No new features of lupus disease activity compared with previous assessment		✓	

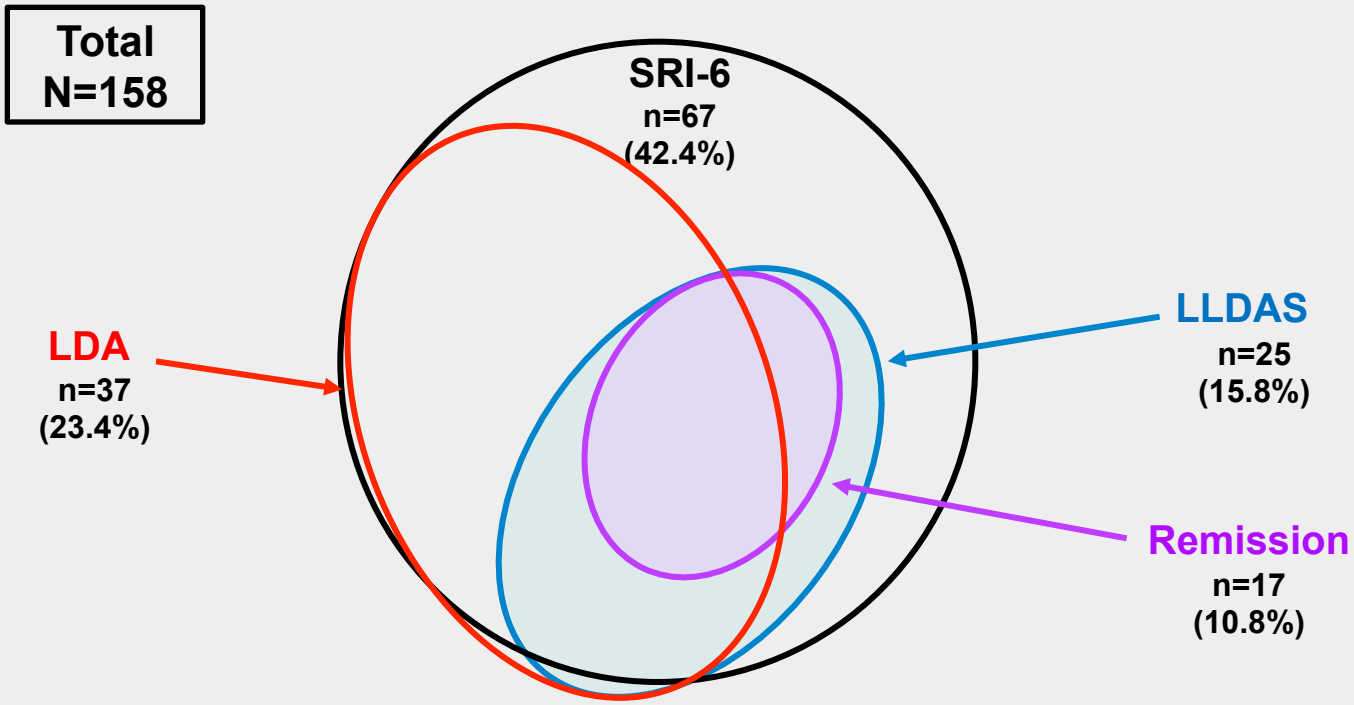
LDA = Low Disease Activity

LLDAS = Lupus Low Disease Activity State

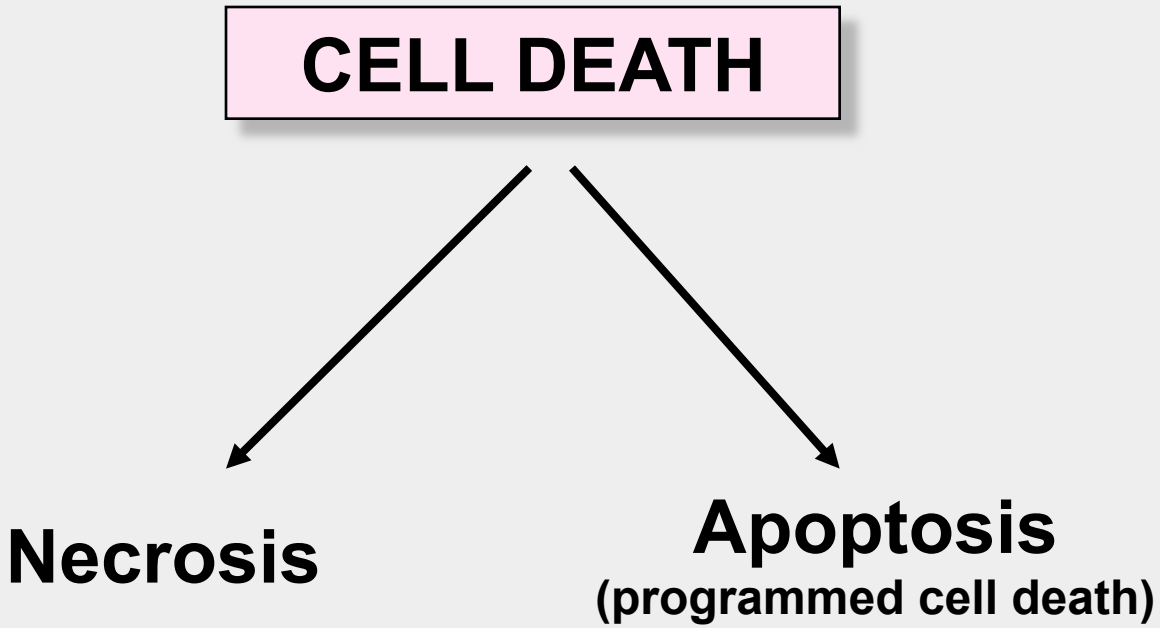
*Assessed at each study visit

Courtesy of Dr Eric Morand and Dr Amy Kao

ENDPOINT STRINGENCY OF LDA, LLDAS AND REMISSION VERSUS SRI-6 ACROSS TREATMENT ARMS AT WEEK 24 IN HDA PATIENTS



CELL DEATH

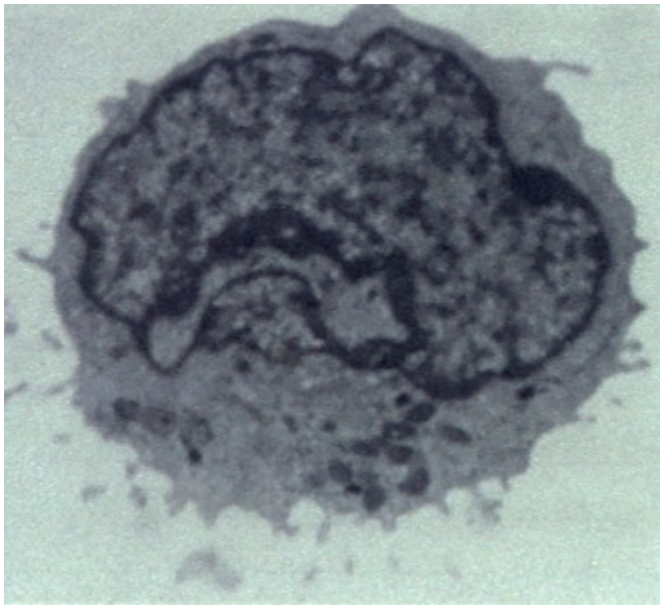


APOPTOSIS - HISTORY

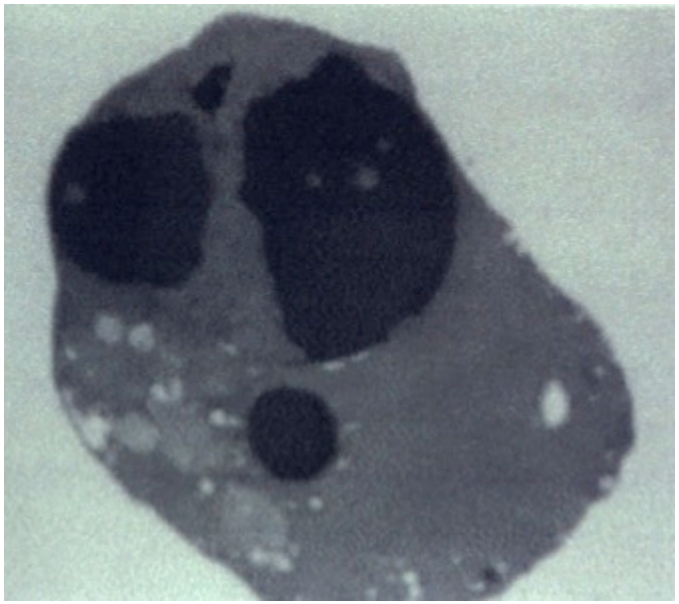
- First observed histochemically by Kerr (Australia) in 1965
- Was referred to as ‘shrinking necrosis’ in 1971
- ‘Apoptosis’ first used in 1972
- Now thought to be the major mechanism of normal cell death in complex organs
- Characterised by an orderly sequence of well-defined biochemical events

MORPHOLOGY OF APOPTOSIS

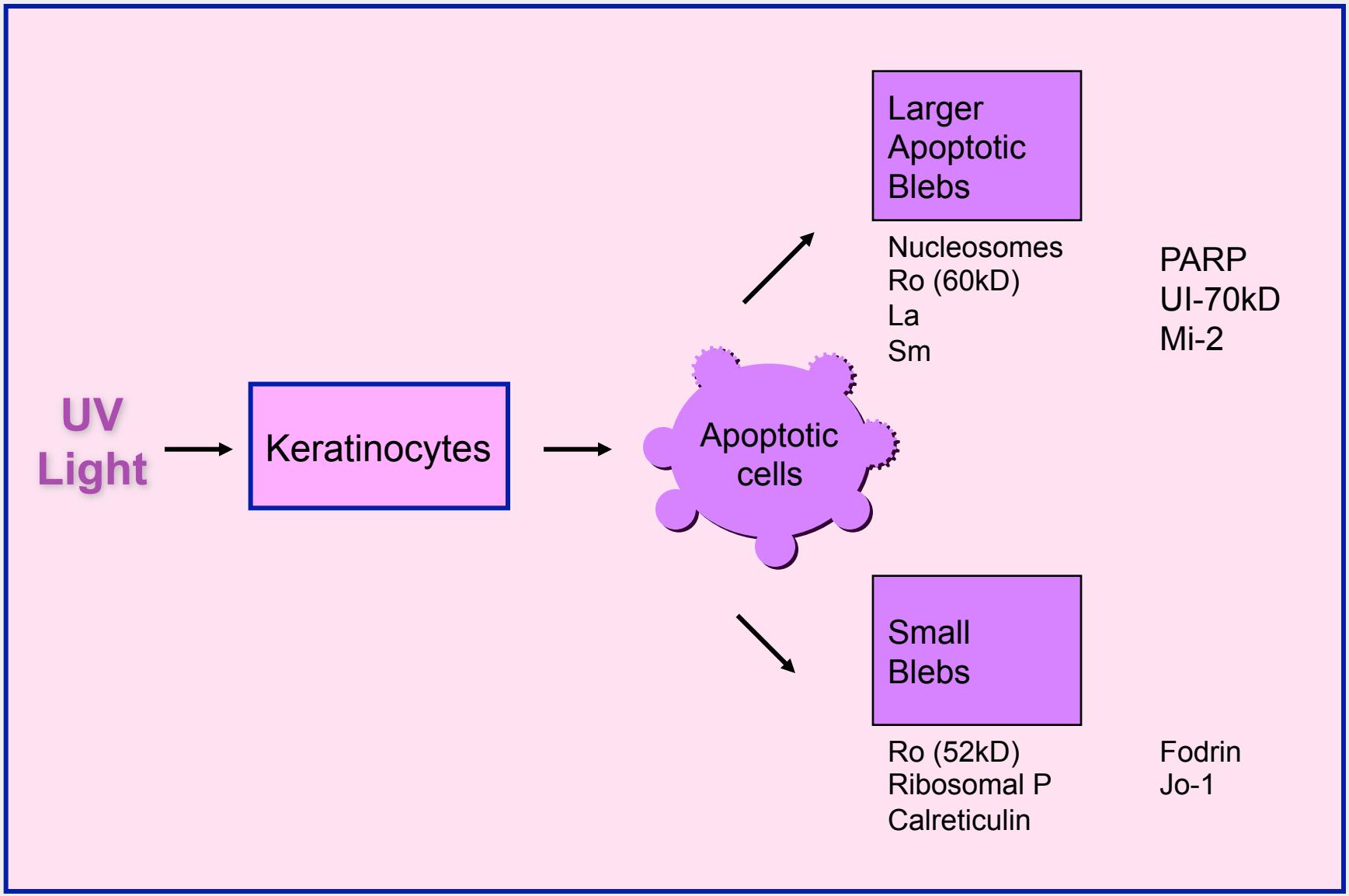
Viable cell



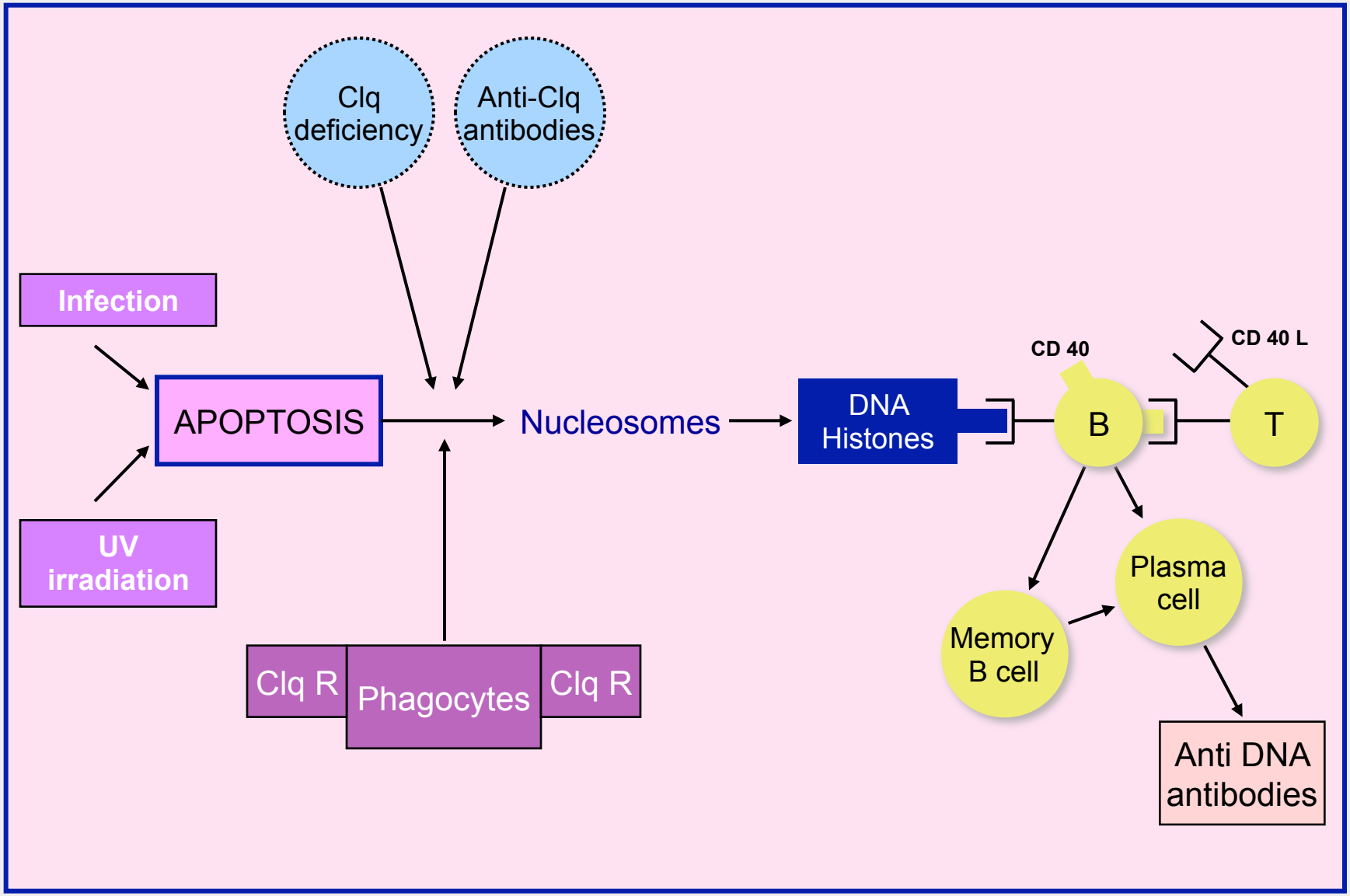
Apoptosis



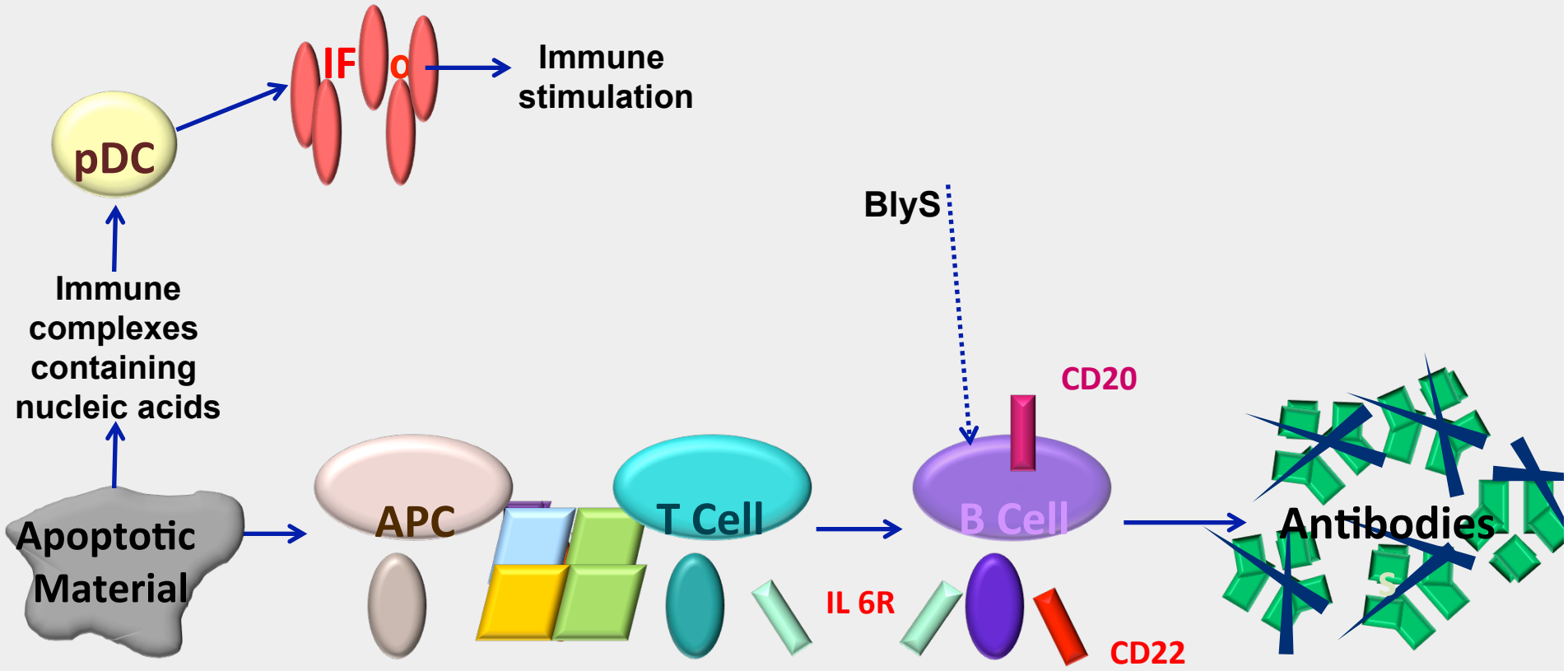
CELL DEATH


UV Light
Keratinocytes
Apoptotic cells
Larger Apoptotic Blebs
Nucleosomes
Ro (60kD)
La
Sm
PARP
UI-70kD
Mi-2
Small Blebs
Ro (52kD)
Ribosomal P
Calreticulin
Fodrin
Jo-1

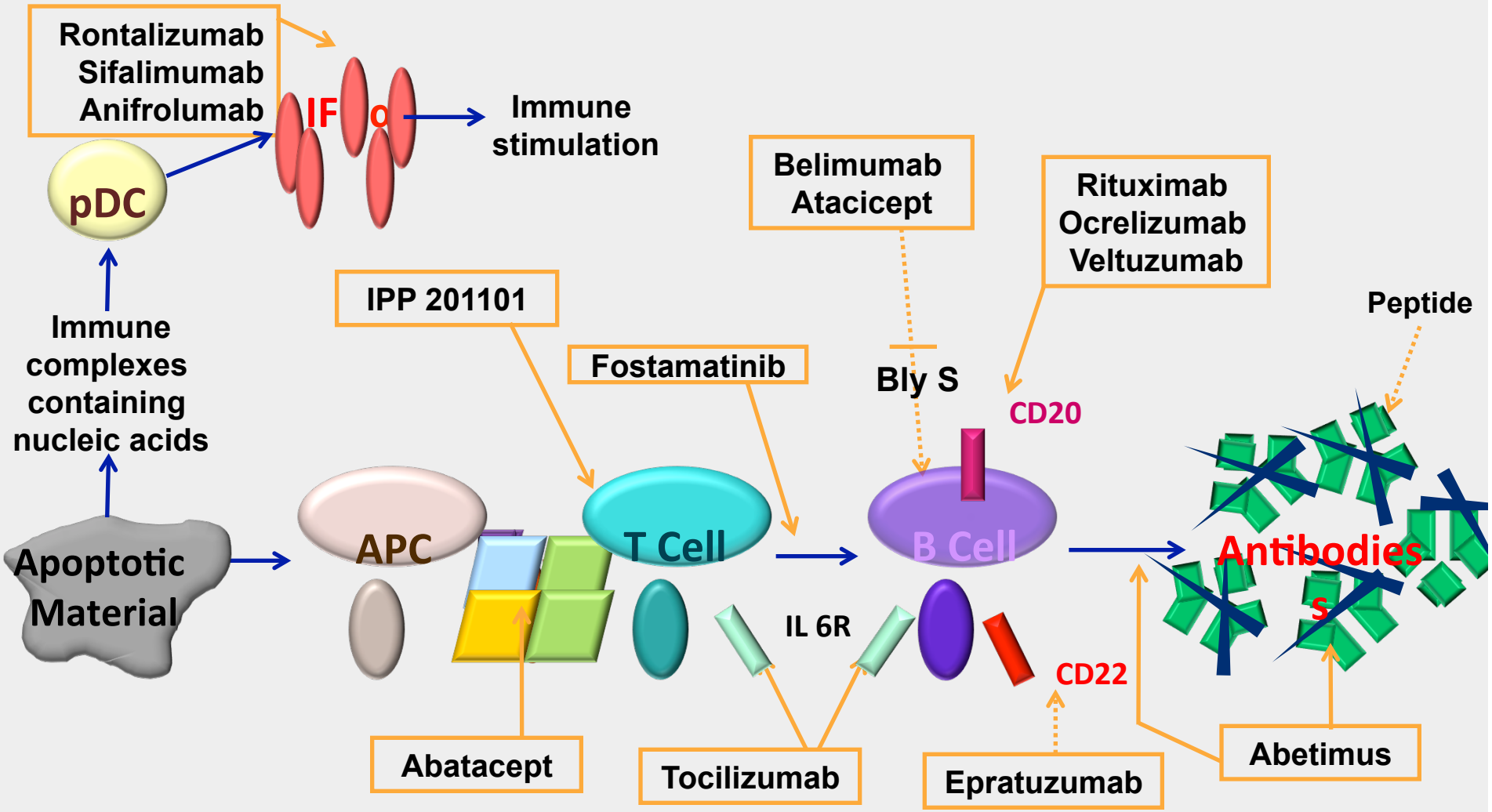
CELL DEATH


Clq deficiency
Anti-Clq antibodies
Infection
UV irradiation
APOPTOSIS
Nucleosomes
DNA Histones
CD 40
CD 40 L
B
T
Plasma cell
Memory B cell
Anti DNA antibodies
Clq R
Phagocytes
Clq R

TARGET PATHWAY FOR SLE THERAPIES



SOME TARGETED THERAPIES FOR SLE



OVERVIEW – BIOLOGIC TREATMENT IN LUPUS -1-

BIOLOGIC	TRIAL RESULTS	CURRENT 'REAL-WORLD USE'
B-CELL BLOCKING Rituximab (anti-CD20)	EXPLORER - FAILED (non-renal) LUNAR - FAILED (renal) (some clinical and serological benefits noted in post-hoc analyses)	Widely-used, most physicians have found this drug to be of benefit.
Epratuzumab (anti-CD22)	EMBODY 1 – FAILED EMBODY 2 – FAILED	UCB are most unlikely to proceed to further studies.
APC – T-CELL BLOCKING Abatacept	MMF+ Abatacept – FAILED ACCESS - FAILED (Cyclophos + Abatacept)	Another trial of Abatacept and MMF is underway

RCA
ELVIS
HEARTBREAK
HOTEL
I WAS THE ONE
COLLECTORS'
SERIES
LIMITED EDITION

Heartbreak HOTEL

HEARTBREAK HOTEL – ELVIS PRESLEY

Well, since my baby left me

Well, I found a new place to dwell

Well, it's down at the end of Lonely Street

At Heartbreak Hotel

Where I'll be—where I get so lonely, baby

Well, I'm so lonely

I get so lonely, I could die

Well, those lupus trials failed

Another one bites the dust

The wolves of hell are waiting for me

In the Heartbreak Hotel

Where I'll be…in good company

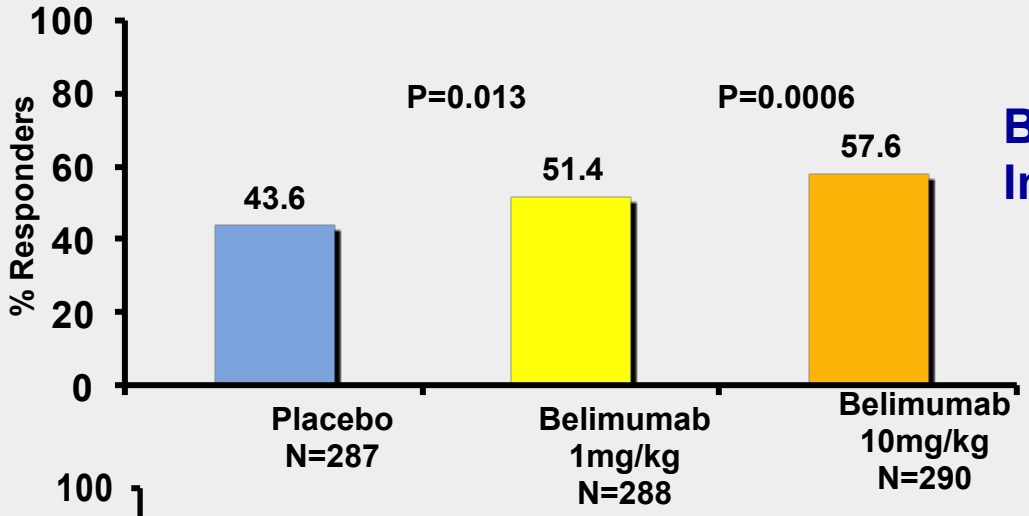
Yes in good company

And so depressed cos my patients could die

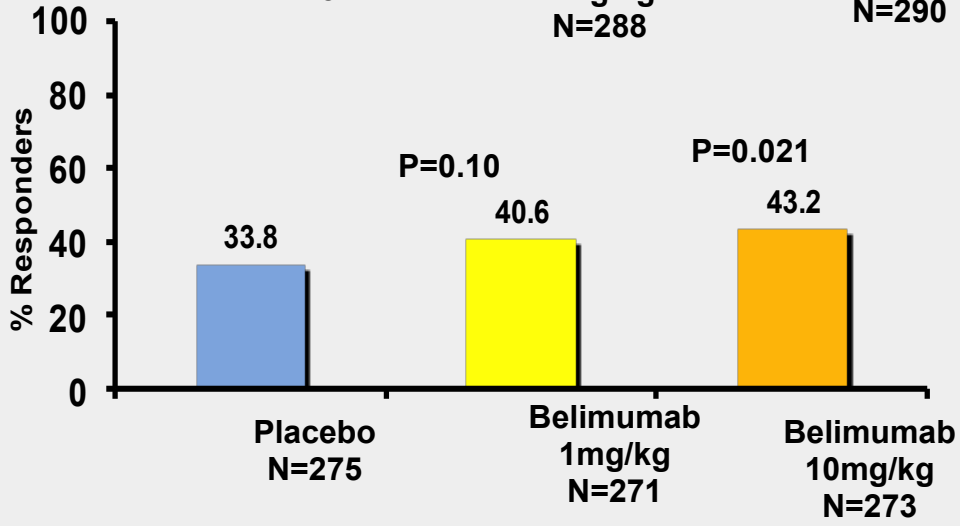
OVERVIEW – BIOLOGIC TREATMENT IN LUPUS -2-

BIOLOGIC	TRIAL RESULTS	CURRENT TRIALS & 'REAL-WORLD USE'
BLOCKING B-CELL ACTIVATING FACTORS Belimumab (anti BAFF/BLyS)	BLISS-52 met its primary endpoint with both doses. BLISS-76 met its primary endpoint with higher dose.	Increasingly used in USA and Europe, but not UK where NICE have not approved it.
Tabalimumab (anti-BAFF)	ILLUMINATE 1 – FAILED ILLUMINATE 2 – Met its primary endpoint	Eli-Lilly have decided not to proceed to any further studies.
Blisibimod (anti-BAFF)	In PEARL-SC (phase II) post-doc analysis of SR1-8 and high disease activity the drug -200mg wk - showed benefit.	Phase III trial (CHABLIS) – FAILED.
Atacicept (anti-BAFF and APRIL)	APRIL-SLE safety committee prematurely and incorrectly terminated the higher dose arm; but ITT showed this dose reduced the numbers of flares and time to first flare.	Phase III trial (ADDRESS) of patients with active lupus – SUCCESSFUL.

UPDATE ON BENLYSTA (1)



BLISS-52:SLE Responder Index*: % Response at Week 52



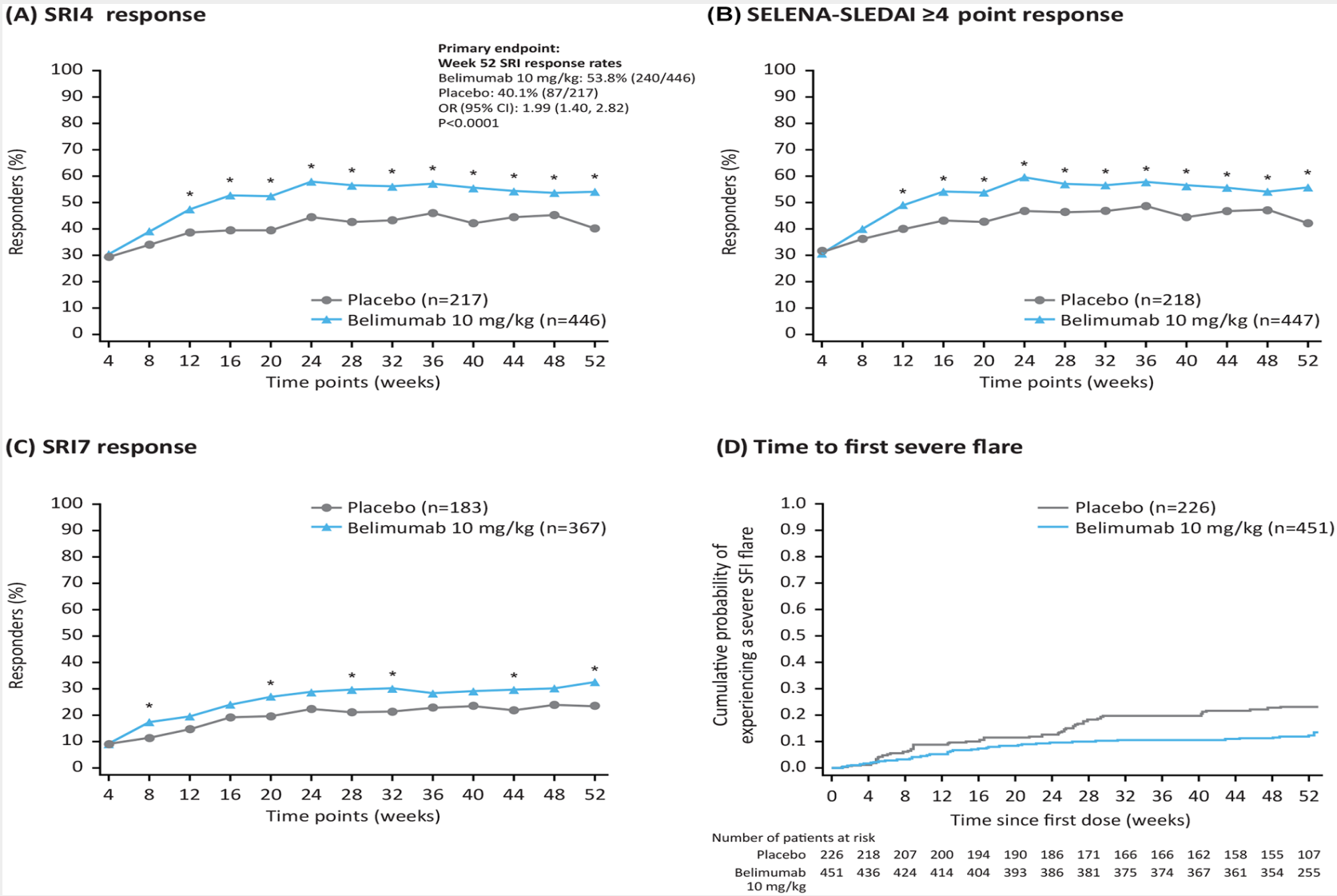
BLISS-76: SLE Responder Index: % Response at Week 52

Week 76 response rates of Belimumab groups were not significantly different from placebo - the secondary endpoint was not met

The responder index used in the BLISS studies was built around SLEDAI

Belimumab was generally well-tolerated in both studies

UPDATE ON BENLYSTA (2)



Zhang F et al. Ann Rheum Dis 2018; 77: 355-363

UPDATE ON BENLYSTA (3)

1. Approved by the FDA (2011) for use in SLE patients with skin and joint disease.

2. Approved by NICE (2016) under stringent conditions with a pending review after 300 patients are treated.

3. Long-term studies confirm this is a safe drug with benefit in approximately 2/3 of patients.

OVERVIEW – BIOLOGIC TREATMENT IN LUPUS -3-

BIOLOGIC	TRIAL RESULTS	CURRENT 'REAL WORLD USE'
BLOCKING INTERFERON α Sifalimumab	Primary endpoint (SR1-4 at 1 year) was achieved in a phase III study.	No further studies.
Anifrolumab	Primary endpoint (SR1-4 at 1 year) was achieved in a phase III study.	Further studies ongoing .
Rontalizumab	ROSE - FAILED (Some improvement in disease activity and ↓ steroid use in those with low interferon signature gene expression).	Genentech will not undertake any further studies.

UPDATE ON RITUXIMAB USE IN SLE (1)

1) Recommended in the ACR and EULAR guidelines for the treatment of lupus nephritis

2) Approved in the UK by NHS England

3) Widely used for many aspects of lupus

4) No help in approximately 10% of patients

5) Be aware of hypogammaglobinaemia and allergic responses

UPDATE ON RITUXIMAB USE IN SLE (2)

SPEED OF ONSET:-

1)Anaemic/thrombocytopenia	-	within 2 weeks
2)Arthritis	-	1 – 2mn
3)Pleurisy/pericarditis	-	1 – 2mn
4)Skin	-	variable
5)Renal	-	maybe several months

RITUXIMAB (RTX) IN SLE – UCL EXPERIENCE (UPDATE) – 3 -

	1st RTX cycle	All RTX cycles
	%	%
% pts ↓ dsDNA ≥ 50% or normalisation	38.2	37.7
% pts with ↑ in C3 ≥ 25% or normalisation	36.5	31.8
% loss of all BILAG As and Bs	43	42
% loss of some but not all BILAG As and Bs	29	27
% with no response	28	30
% successful $CD19^+$ lymphocyte depletion	94	92

RITUXIMAB (RTX) IN SLE (n = 115) – UCL EXPERIENCE (UPDATE) – 4 -

Adverse Event	1ST RTX cycle	All RTX cycles
Severe infections	8	13
Hypersensitivity reactions	3	13
Hypogammaglobulinaemia	27	53

Nb: During the follow-up period [up to 15 years] 5 patients had at least 1 CVS event and 11 have died.

Aguiar, Araujo, Papoila, Alves, Isenberg. Arthritis Care Res 2017; 69: 257-62

Severe Sub-acute Cutaneous Lupus - Before B cell Depletion

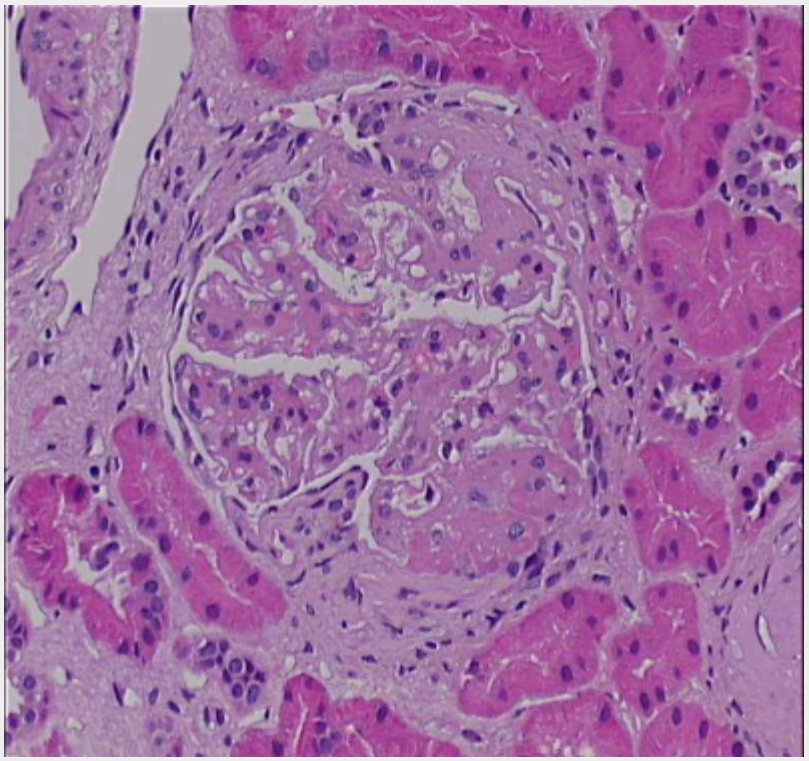
Severe Sub-acute cutaneous Lupus Treated with B cell Depletion - Before and 1 Month Afterwards

B-CELL DEPLETION USING RITUXIMAB IN CUTANEOUS LUPUS

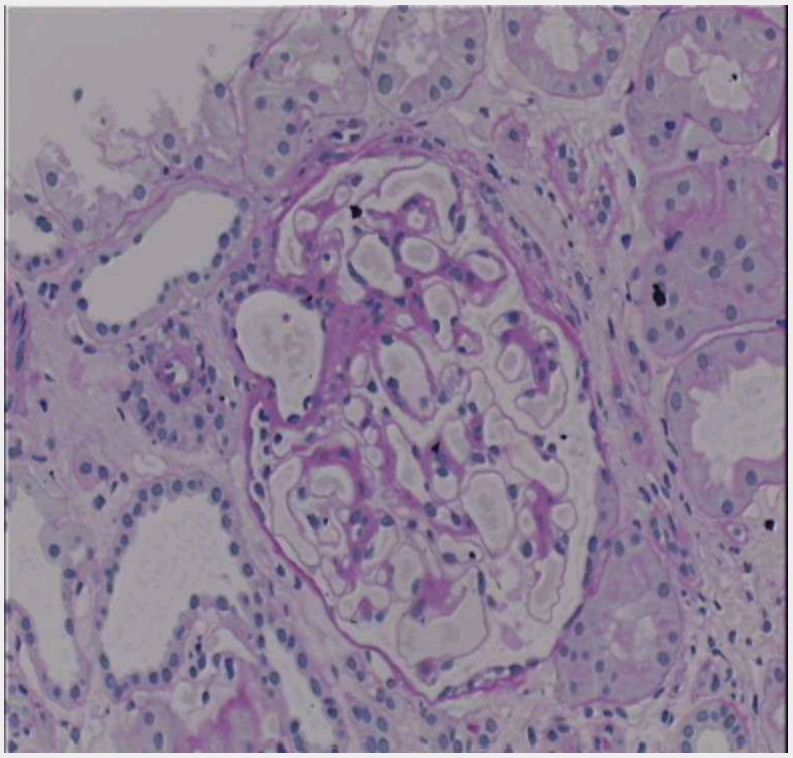
COMPLETE RESPONDER [LOST BILAG A/B STATUS]			
	n =	6/12	1 yr
Acute cutaneous lupus (ACLE)	23	35%	57%
Subacute cutaneous lupus (SCLE)	6	33%	33%
Chronic cutaneous lupus (CCLE)	12	42%	46%
Non-specific lupus (NSLE)	11	46%	60%

Costa, Aguirre-Alastuey, Isenberg, Saracino JAMA-Dermatology. In press

Renal biopsy appearance



Before

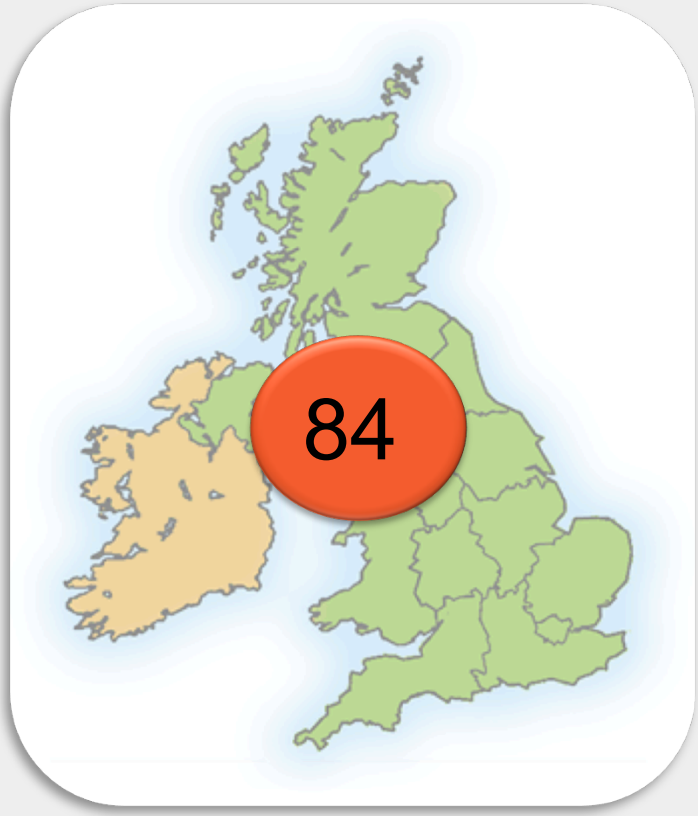


After

With thanks to Professor Ronald Van Vollenhoven

Objective: the UK-BIOGEAS Registry

Patients with lupus nephropathy treated with rituximab



Díaz-Lagaresa, C *et al*. *Autoimmunity Reviews* In Press. 10.1016/j.autrev.2011.10.009

Methods: inclusion criteria

1. Fulfilment of SLE classification criteria
2. Age >14 years
3. Biopsy-proven lupus nephropathy
4. Homogeneous definition of therapeutic response at 6 and/or 12 months

Complete response (CR):

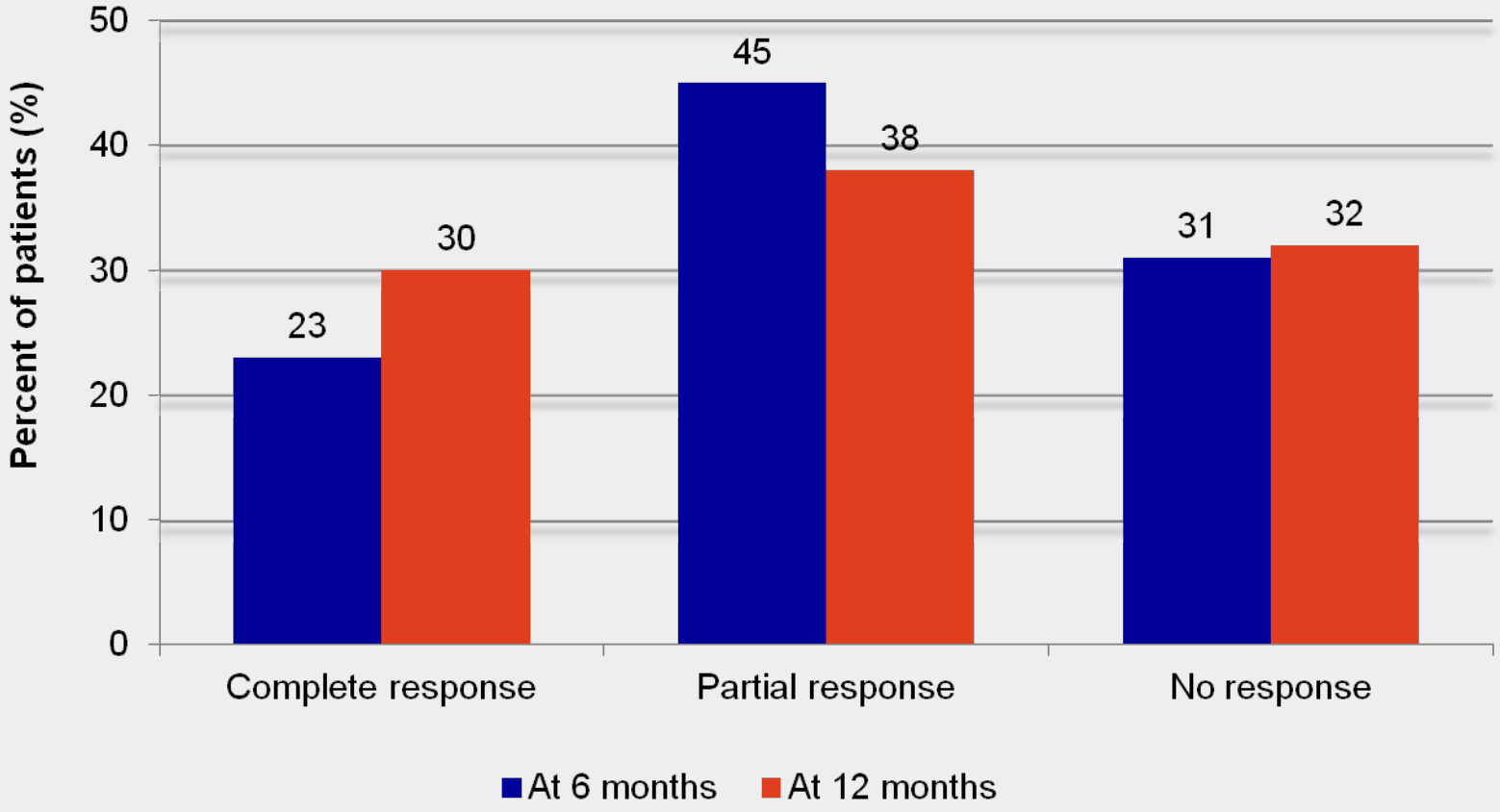
- normal serum creatinine
- normal serum albumin levels
- inactive urinary sediment
- 24-hour urinary albumin <0.5 g

Partial response (PR):

- >50% improvement in all renal parameters that were abnormal at baseline, with no deterioration in any parameter

Díaz-Lagaresa, C *et al*. *Autoimmunity Reviews* In Press. 10.1016/j.autrev.2011.10.009

Results: response to rituximab at 6 & 12 months



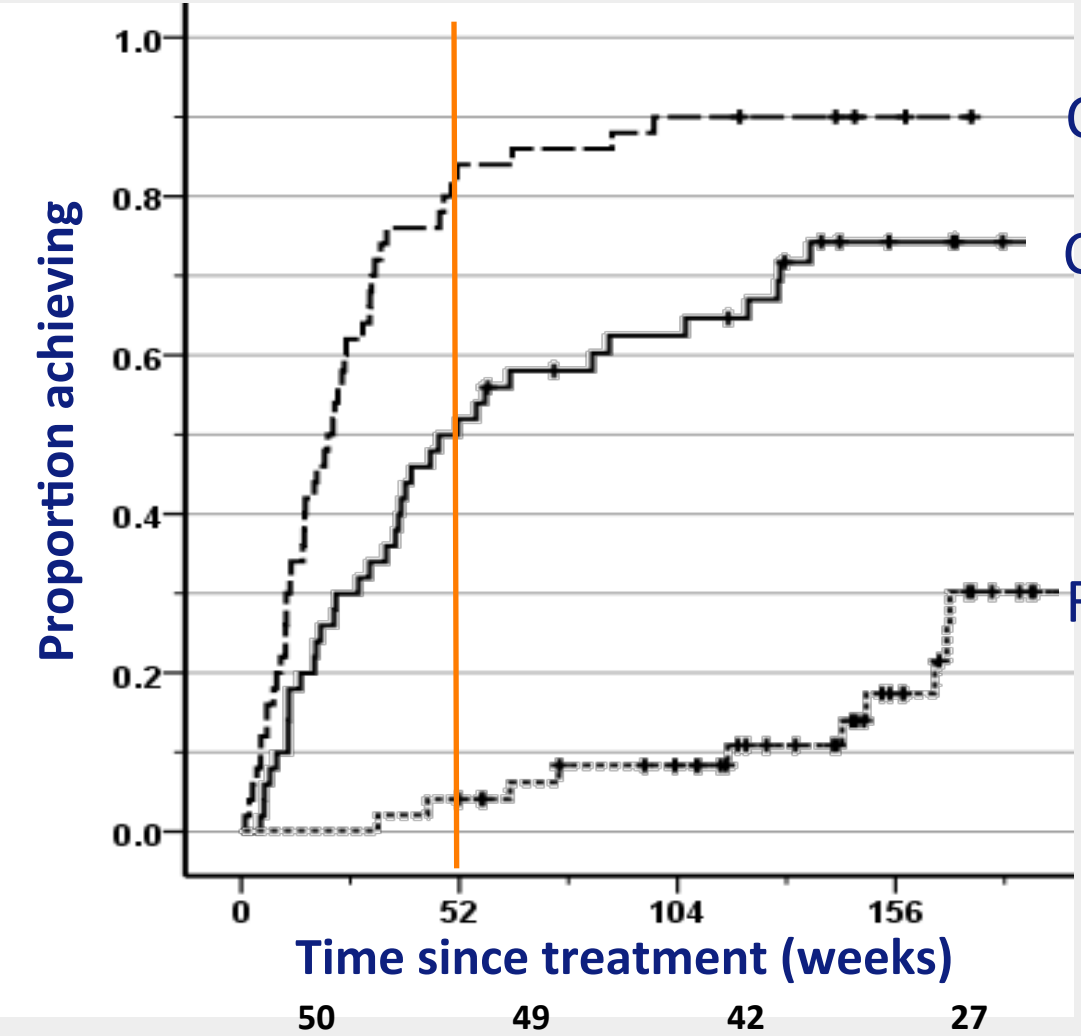
Díaz-Lagaresa, C *et al. Autoimmunity Rev* 2012; 11: 357-64

Treatment regime - Rituxilup

- Steroid avoiding regime
- Used in all new and relapsing lupus who are not already on steroids and who do not have cerebral lupus
- Very low toxicity
- Established as our first line treatment protocol

Condon et al. Annals Rheum Dis. 2013. 72:1280-6

Time to remission and relapse



In CR:

- 12 wks 9 (18%)
- 26 wks 16 (32%)
- 52 wks 26 (52%)

Condon et al Ann Rheum Dis. 2013; 72: 1280-6.

Early B-cell Depletion – Long-Term Follow-Up – 1-

- **16 SLE patients treated at diagnosis in UCLH since 2008**

- **Each matched with 3 other patients treated conventionally from the cohort for:**

ethnicity

sex

age

clinical features

disease duration

Gracia-Tello et al. Lupus Sci Med 2017; 4: e000182

Early B-cell Depletion – Long-Term Follow-Up – 3-

Follow-Up:-

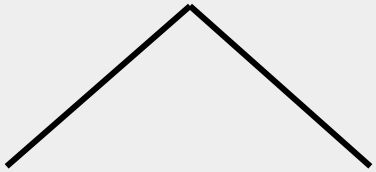
- **Outpatient appointments approximately every 2 months**
- **Disease activity [BILAG]**
- **Steroid requirement**

Over a period of 1 – 6.5 years carefully observed and compared to the conventionally treated patients

Early B-cell Depletion – Long-Term Follow-Up – 4-

Results:-

- All Rituximab treated patients achieved B-cell depletion
- Clinical Flares [new BILAG A or B]



BCDT Conventional Treatment

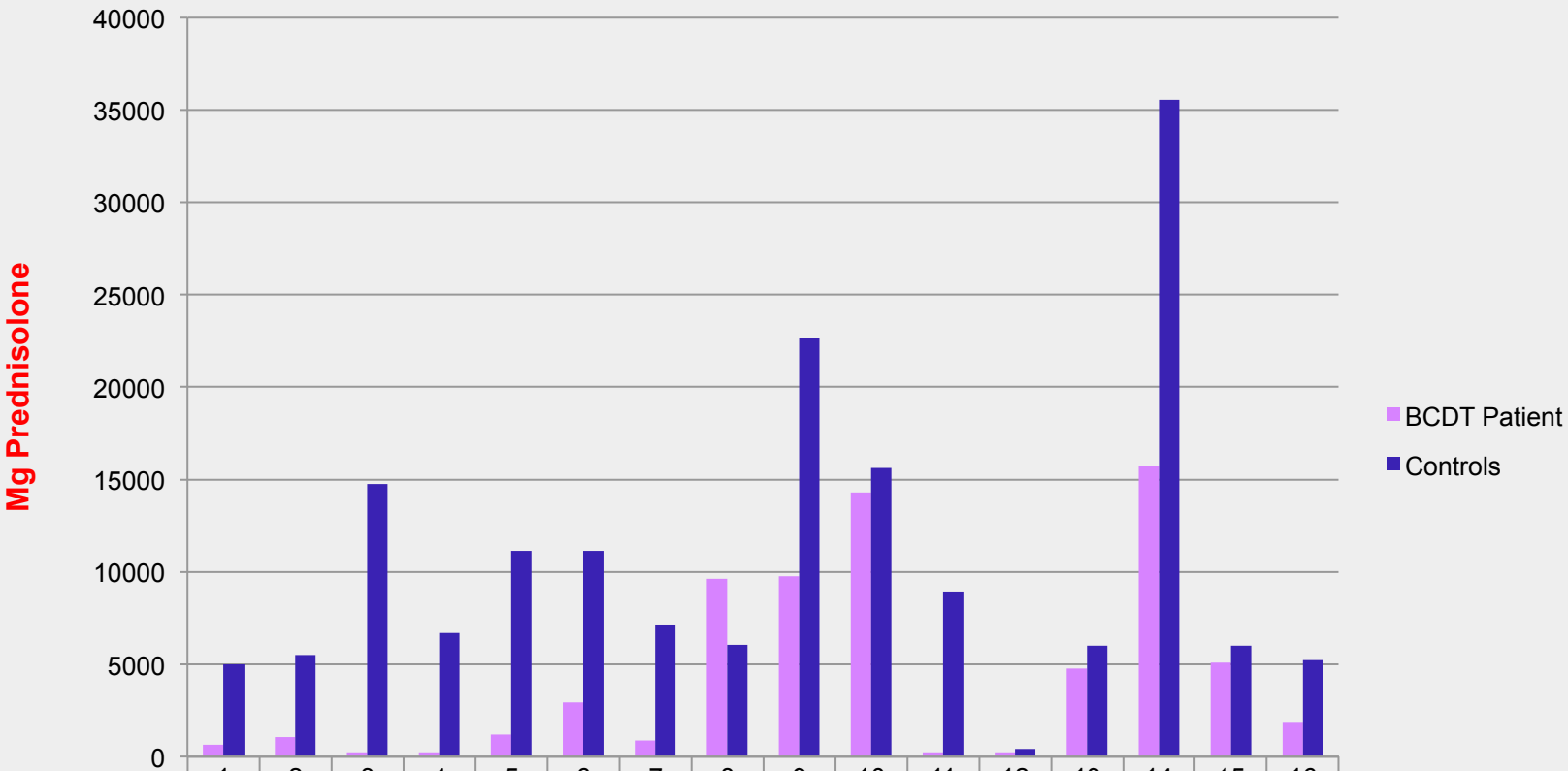
Overall	50%	70%
Numbers of flares	3.75 (SD = 4.0)	4.27 (SD = 4.0)

Early B-cell Depletion – Long-Term Follow-Up – 5-

Results:-

	BCD group (n = 16)
Mean dsDNA antibody (n = <50 U/ml)	1113.87 [SD 1699.3] → 194 [SD = 346]
ESR	↓ by > 70% at 6 months
C3	Normalized in 7 patients

Steroid burden in newly-diagnosed SLE patients



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
BCDT Patient	659	1071	250	250	1186	2924	884	9640	9773	14281	250	250	4758	15695	5088	1897
Controls	4981	5501	14746	6679	11134	11134	7155	6064	22610	15644	8960	399	5994	35555	5999	5217

CHARACTERISTICS OF TYPE I AND II ANTI-CD20 MONOCLONAL ANTIBODIES

	Type I	Type II
Established mAb	Rituximab Ofatumumab Ocrelizumab Velutuzumab	Obinutuzumab Tositumomab
Redistributes CD20	Yes	No
Internalisation of anti-CD20-mAb complexes	Yes, but highly variable	To a small extent and significantly less than rituximab
Complement-dependent-cellular cytotoxicity	Potent	Weak
Antibody-dependent cellular cytotoxicity	Yes	Yes
Antibody-dependent cell phagocytosis	Yes	Yes
Direct cell death	Apoptosis	Non-apoptotic lysosome mediated cell death

ROLE OF INTERFERON-α IN SLE

Genetic susceptibility

Antigen presentation
HLA-DR2, -3

TLR and IFN signaling
IRAK1, IRF5, SPP1 , STAT4, TREX1, ATG5

T cell signaling
TNFSF4, PDCD1, PTPN22, STAT4 , OX40L

B cell signaling
BANK1, BLK, LYN, FCGR2B

Immune complex clearance
FCGR2A, FCGR3A, ITGAM, CRP, C4A, C4B, C2, C1Q

Others PXK, …

Immune pathogenesis of SLE

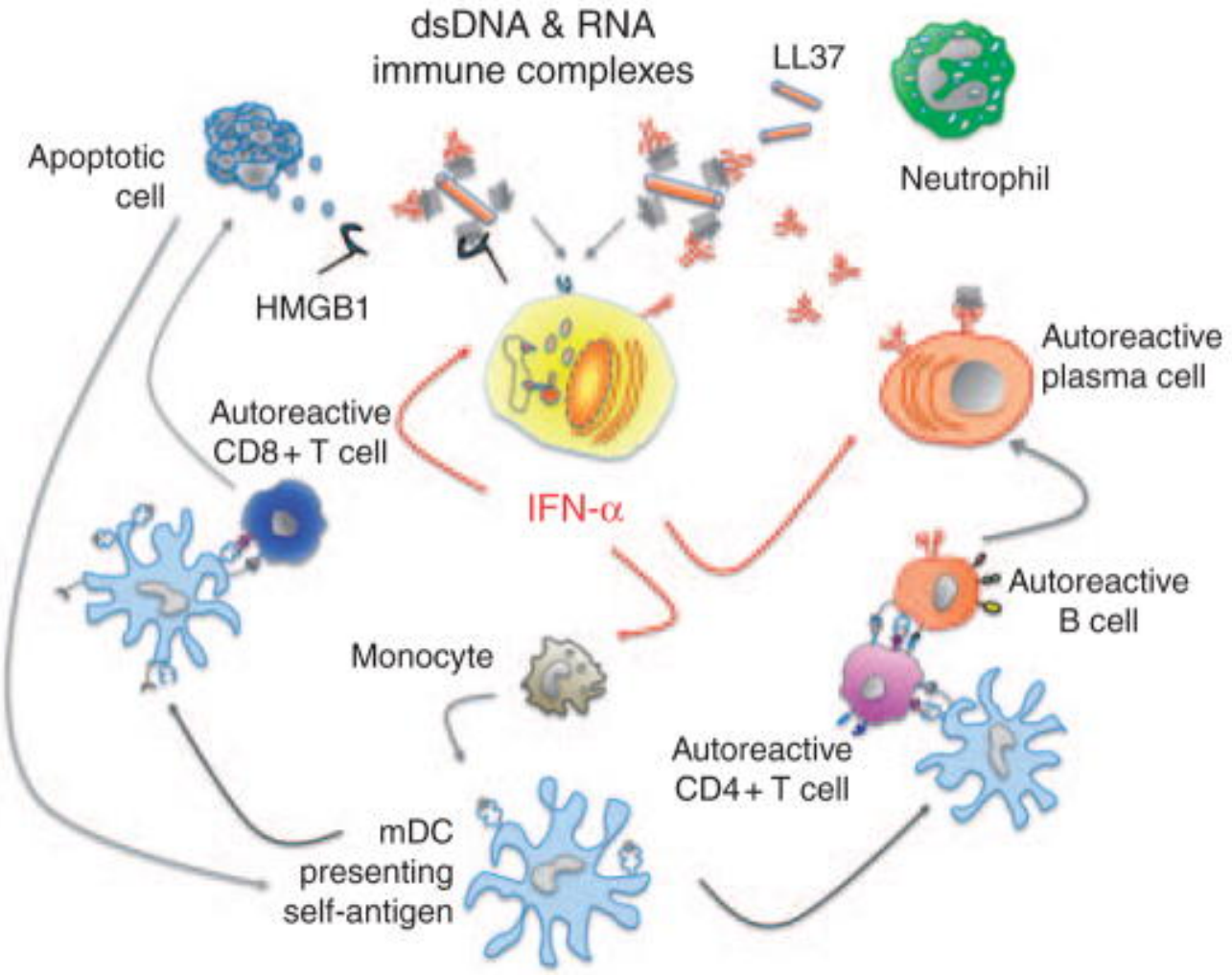
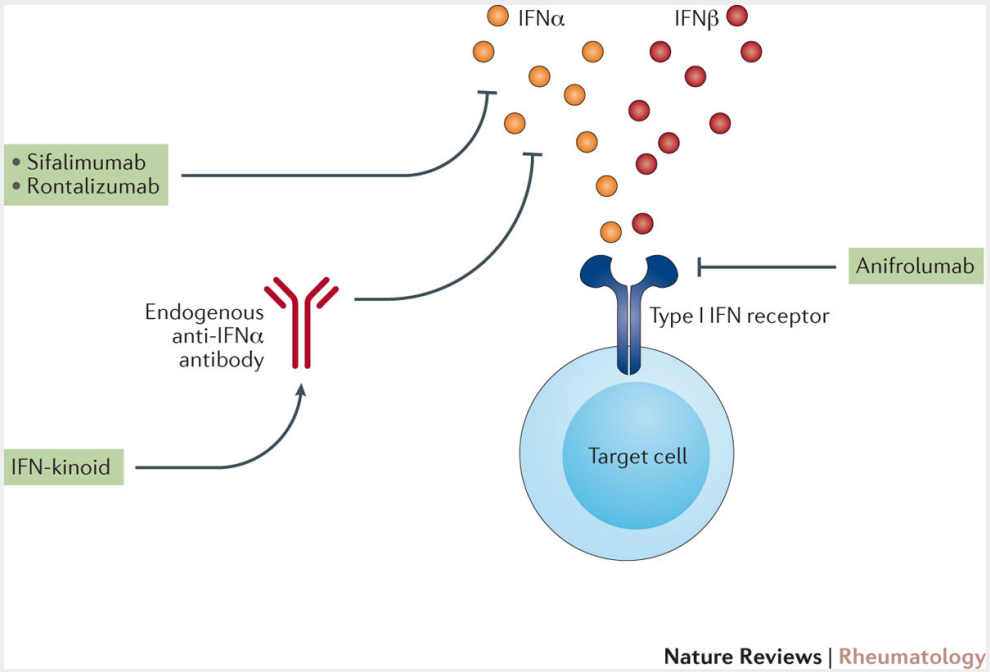


Figure 1 The mechanism of action of anti-IFN therapies currently in development for SLE



Niewold, T. B. *et. al.* (2016) Targeting type I interferon in systemic lupus erythematosus *Nat. Rev. Rheumatol.* doi:10.1038/nrrheum.2016.83

SLE RESPONDER INDEX (SRI)

[eg SRI 4]

A composite index

a)Improvement of 4 points or more using SELENA-SLEDAI

b)No new BILAG A; only 1 new BILAG

c)No increase in Physicians Global Assessment of > 0.3cm

Primary end point: BILAG-based Combined Lupus Assessment (BICLA) response at Week 12

BILAG improvement:

- All BILAG A scores at study entry improved to B/C/D, and
- All BILAG B scores at study entry improved to C/D, and
- No BILAG worsening in other body systems = no new BILAG A or ≥2 new BILAG B scores

SLE Disease Activity Index (SLEDAI):

- No worsening in SLEDAI total score compared with study entry

Physician's global disease activity assessment:

- No worsening (defined as <10% worsening) compared to study entry
  on 100 mm visual analogue scale (VAS)

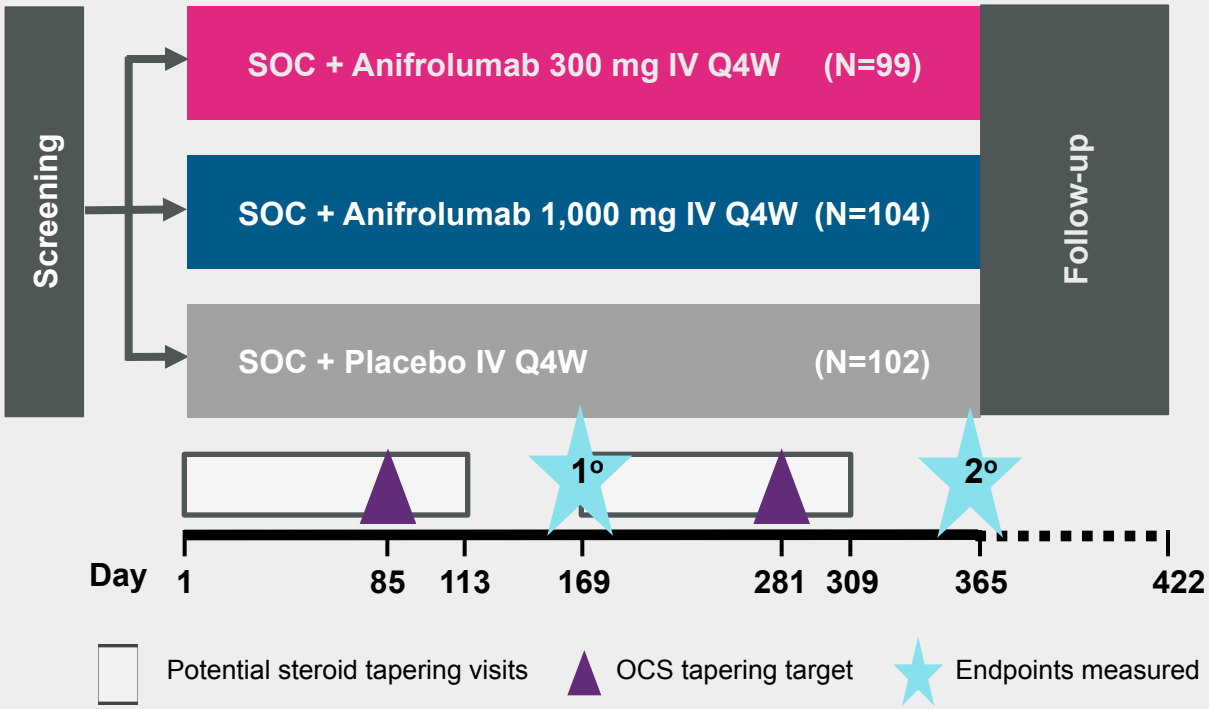
Treatment failure:

Defined as added or increased immunosuppressants or anti-malarials, or corticosteroid increase above baseline or tapering level at any point following randomization

All criteria must be achieved to meet 'responder' classification

Wallace et al; ARD 2014 Jan;73(1):183-90

STUDY DESIGN – ANIFROLUMAB TRIAL



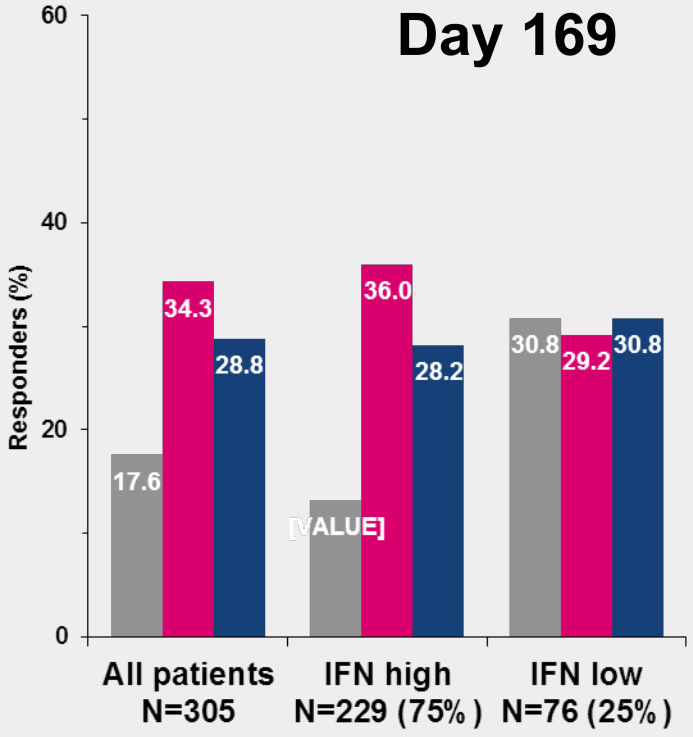
Primary efficacy measure

- **SRI(4) at Day 169 with a sustained reduction of oral corticosteroid to <10 mg/day prednisone and ≤Day 1 dose, from Day 85 through Day 169**

Q4W=every 4 weeks; SOC=standard of care; SRI=SLE responder index.

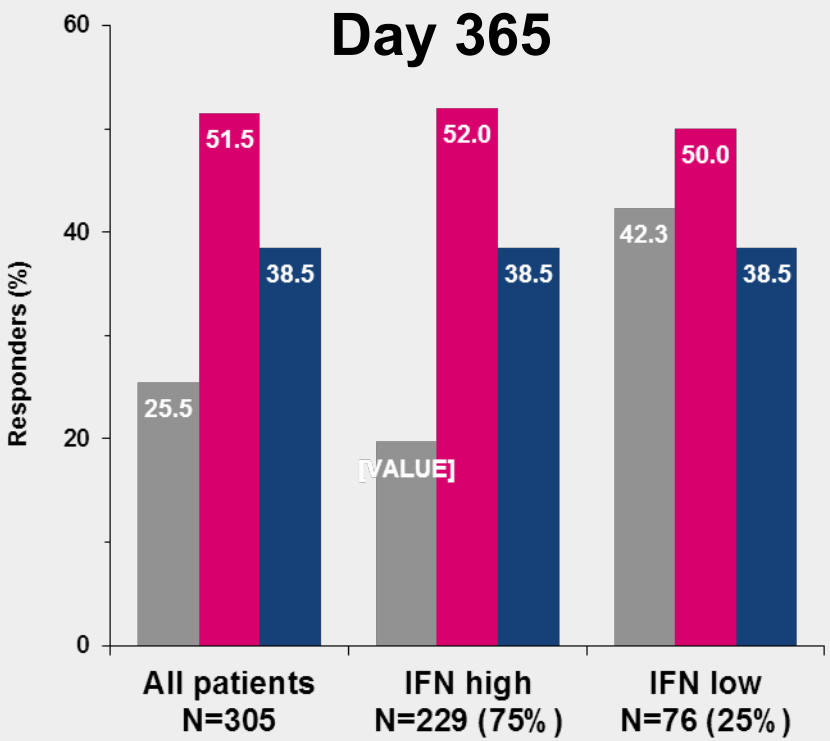
SRI(4) INCLUDING OCS TAPER

Primary endpoint Day 169



	300 mg	1,000 mg	300 mg	1,000 mg	300 mg	1,000 mg
Delta:	16.7%	11.2%	22.8%	15.0%	-1.6%	0.0%
OR:	2.38	1.94	3.55	2.65	0.96	1.04
90% CI:	(1.33, 4.26)	(1.08, 3.49)	(1.72, 7.32)	(1.27, 5.53)	(0.34, 2.74)	(0.37, 2.88)
P:	0.014	0.063	0.004	0.029	0.946	0.953

Secondary endpoint Day 365



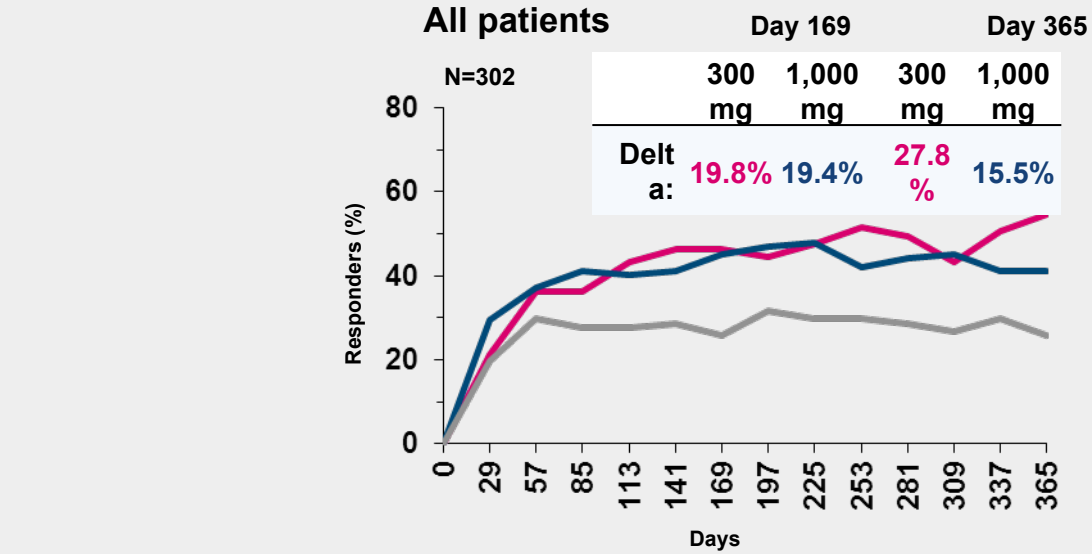
300 mg	1,000 mg	300 mg	1,000 mg	300 mg	1,000 mg
26.0%	13.0%	32.3%	18.8%	7.7%	-3.8%
3.08	1.84	4.30	2.52	1.47	0.89
(1.86, 5.09)	(1.11, 3.04)	(2.34, 7.91)	(1.37, 4.64)	(0.55, 3.93)	(0.34, 2.35)
<0.001	0.048	<0.001	0.013	0.514	0.849

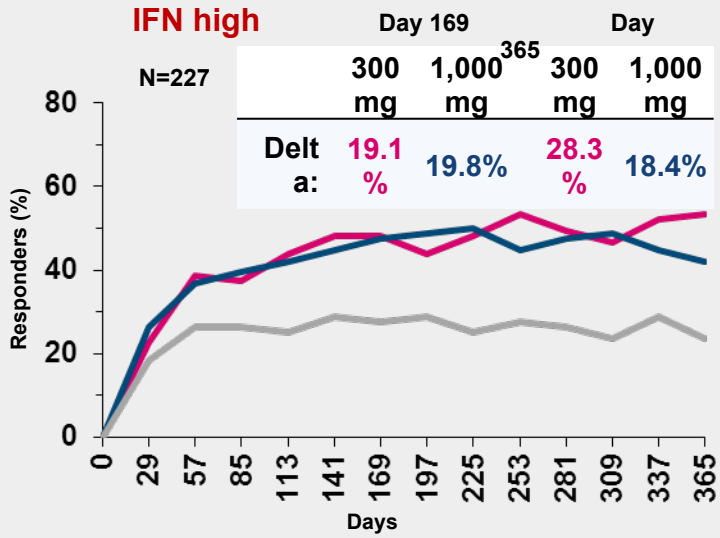
Placebo Anifrolumab 300 mg Q4W Anifrolumab 1,000 mg Q4W

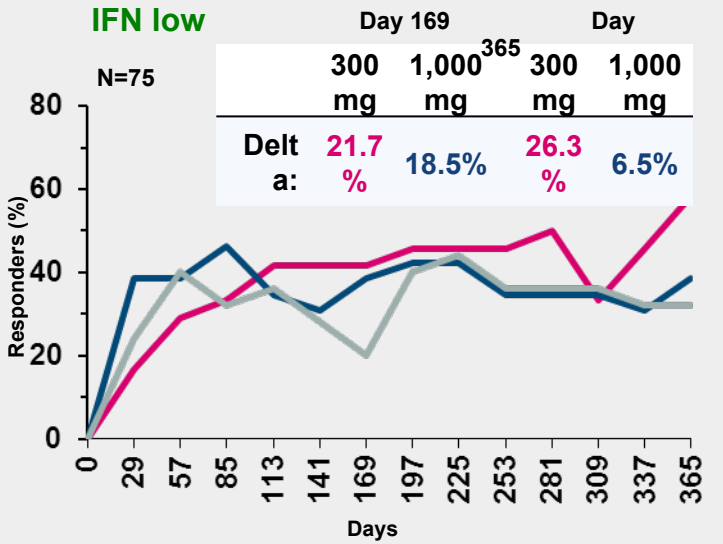
Dropouts and patients whose medication use exceeded protocol threshold were imputed as failures.

Delta=dosage vs. placebo .

BICLA RESPONSE







Placebo

Anifrolumab 300 mg Q4W

Anifrolumab 1,000 mg Q4W

*$P \leq 0.05$ compared with placebo

Delta=dosage vs. placebo.

BUT SADLY….

- **On 31 August AstraZeneca/MedImmune announced:**

"The phase III TULIP 1 trial (a randomized double-blind 52-week placebo-controlled multi-centre trial of Anifrolumab in adult patients with moderate-to-severe SLE) did not meet the primary end point as measured by the SRI4 index."

We await results of the TULIP 2 trial later this year.

AND AFTER BENLYSTA/RITUXIMAB/? ANIFROLUMAB

Possibilities being investigated:-

1. Fully humanised anti-CD20 monoclonals
2. Blocking BAFF and APRIL (Atacicept)
3. Anti-CD40 L (Dapirolizumab)
4. Antibodies to FcγIIB (SM 101)
5. BTK covalent small molecule inhibitor (Ibrutinib)
6. P140 peptide (Lupuzor) blocks auto reactive T cells

NOT ONLY ….BUT ALSO….

1. Anti-Il-3R (CD23)
2. JAK-STAT inhibition (Baricitinib)
3. Anti-Bcl 2 antagonist (Venetoclax)
4. Small peptide influencing T-cell function based on the 16/6/ DNA antibody idiotype
5. Low-dose Interleukin-2 (He et al. Nature Med 2016; 22: 991
6. Selective inhibition of the immunoproteasome (Kzr-616)

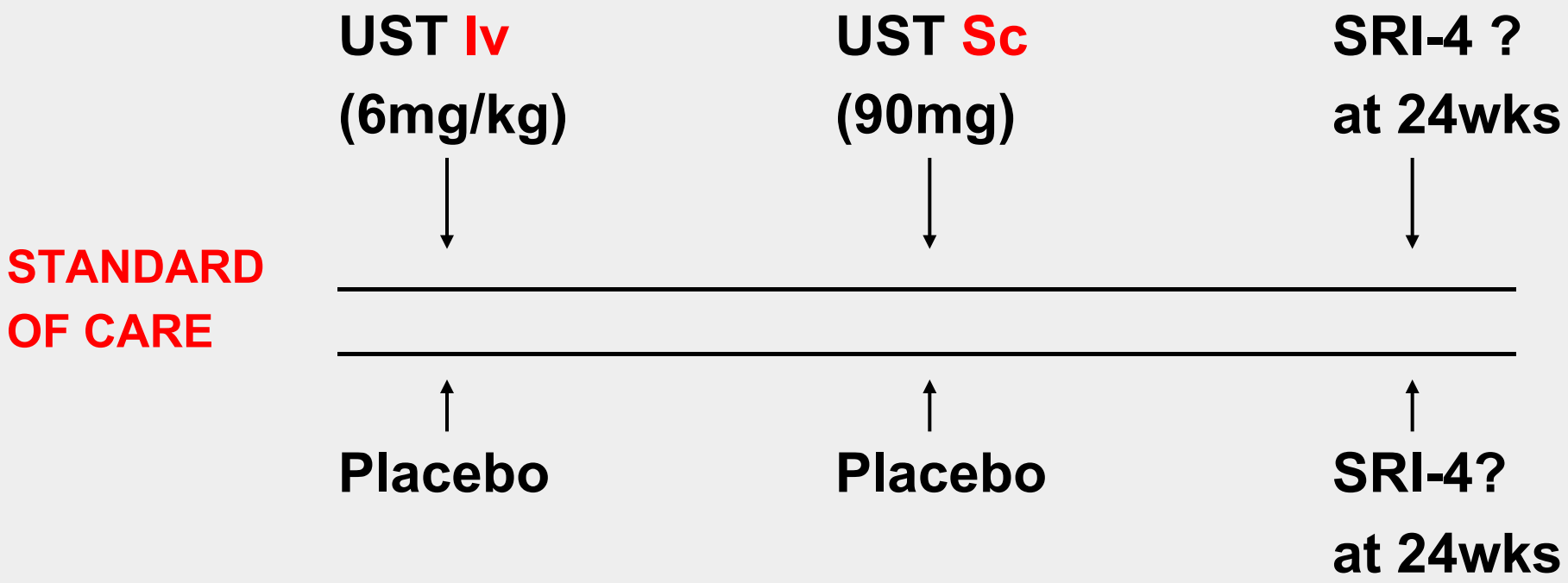
USE OF USTEKINUMAB [anti-Il12/23] - 1 -

- Known to be useful in the treatment of psoriasis, psoriatic arthritis and Crohn's disease.

- Has now been assessed in a phase II placebo controlled study of adult seropositive SLE patients [n = 102].

- Patients met SLICC criteria, with a SLEDAI $\geq$ 6 and $\geq$ 1 BILAG 'A' and/or $\geq$ BILAG.

USTEKINUMAB TRIAL – 1 -



USTEKINUMAB TRIAL – 2 -

	Placebo	Ustekinumab	p value
Patient n =	42	60	-
SRI-4 at 24 weeks	13 (31%)	36 (60%)	0.0046
Change from baseline SLEDAI 2k median (range)	- 2 (- 20; 10)	- 6 (- 10; 3)	0.0265
Patients with 50% improvement from baseline joint disease activity % (95% CI)	63.2 (61.7 – 64.6)	87.7 (86.8 – 88.6)	0.02
Patients with 50% improvement from baseline CLASI % (95% CI)	25.2 (23.1 – 27.4)	58.7 (57.4 – 60.1)	0.04

USTEKINUMAB TRIAL – 3 -

No safety signals

BUT

No improvement in:-

a)Change in baseline PGA
b)BICLA response
c)dsDNA antibody level
d)C3 level

THE ELEPHANT IN THE ROOM

THE ISSUE OF COMPLIANCE!

COMPLIANCE ISSUES – HYDROXYCHLOROQUINE LEVELS IN SLE PATIENTS (1)

CENTRE	Patient Number	Visit Date	Hydroxychloroquine measurements ng/ml
013	013-001-S-R	29/04/2013	319
013	013-002-C-P	03/06/2013	1747
013	013-003-I-P	03/06/2013	0
013	013-004-E-M	03/06/2013	370
013	013-005-A-O	05/06/2013	107
013	013-006-A-C	10/06/2013	792
013	013-007-O-A	17/06/2013	186
013	013-008-S-S	17/06/2013	146
013	013-009-H-J	04/07/2013	1721
013	013-010-P-R	15/07/2013	595
013	013-011-C-R	22/07/2013	1770
013	013-012-G-B	19/08/2013	1151
013	013-013-S-N	02/09/2013	1227
013	013-014-G-C	16/09/2013	1262
013	013-015-T-R	23/09/2013	30
013	013-016-B-J	23/09/2013	1457
013	013-017-B-C	25/11/2013	58
013	013-018-B-C	16/12/2013	1699
013	013-019-L-N	06/01/2014	1032
013	013-020-O-C	13/01/2014	987
013	013-021-F-I	20/01/2014	874
013	013-022-Y-T	03/02/2014	423
013	013-023-D-A	24/02/2014	0
013	013-024-N-D	10/03/2014	732
013	013-025-W-C	17/03/2014	723
013	013-026-M-C	24/03/2014	820
013	013-027-J-D	31/03/2014	0

Courtesy of Prof Nathalie Costedoat-Chalumeau

COMPLIANCE ISSUES – HYDROXYCHLOROQUINE LEVELS IN SLE PATIENTS (2)

013	013-028-R-R	07/04/2014	469
013	013-029-F-M	28/04/2014	951
013	013-030-A-M	19/05/2014	0
013	013-031-E-A	16/06/2014	1331
013	013-032-P-V	16/06/2014	905
013	013-033-L-E	16/06/2014	1279
013	013-034-R-J	23/06/2014	525
013	013-035-C-D	14/07/2014	1969
013	013-036-C-J	04/08/2014	2019
013	013-037-V-C	11/08/2014	2790
013	013-038-K-R	11/08/2014	175
013	013-039-P-D	08/09/2014	235
013	013-040-P-L	06/10/2014	725
013	013-041-G-G	13/10/2014	1060
013	013-042-P-A	20/10/2014	172
013	013-043-K-N	03/11/2014	130
013	013-044-P-S	24/11/2014	1928
013	013-045-D-A	26/01/2015	0
013	013-047-H-M	09/02/2015	1351
013	013-048-T-A	09/02/2015	1497
013	013-049-T-R	16/02/2015	0
013	013-050-W-G	23/02/2015	549
013	013-051-A-M	30/03/2015	0
013	013-052-C-R	13/04/2015	116
013	013-053-J-A	20/04/2015	1548
013	013-054-A-S	01/06/2015	265
013	013-055-K-W	08/06/2015	1339
013	013-056-J-V	15/06/2015	127

CONCLUSIONS (1)

1. The mortality from SLE has improved significantly in the past 50 years.
2. We are moving from an era of “serendipity to sense” introducing new therapies on a far more rational basis.
3. Unfortunately the successful use of biologic drugs in SLE lags behind that for RA and psoriatic arthritis (by about a decade!)
4. Early open-label success with Rituximab was not followed by clinical trials which met their endpoints with either this drug or several others (although it is widely acknowledged that Rituximab does work for many patients).

CONCLUSIONS (2)

5. Benlysta (anti-BAFF) met its clinical trial endpoints and is approved by the FDA and (belatedly) NICE.

6. Very encouraging results are now emerging with the use of Atacicept (anti-BAFF and APRIL) and blocking interferon-alpha (especially in those with high signature)

7. We await more, successful trials of biological therapies for SLE.

8. More careful thought needs to be given to the design of clinical trials.

9. The first use of combinations of biologics in SLE is underway.

10. The use of biological therapy in lupus patients at diagnosis needs to be formally tested.

UPDATE ON SLE TREATMENT – THE DENOUEMENT!

PAST IMPERFECT

FUTURE TENSE

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LUPUS STREET

LUPUS HOTEL

LUPUS HOTEL

Evening Standard

LONDON, TUESDAY, 21 FEBRUARY, 1989

20p

Murder hunt after man is stabbed at his flat

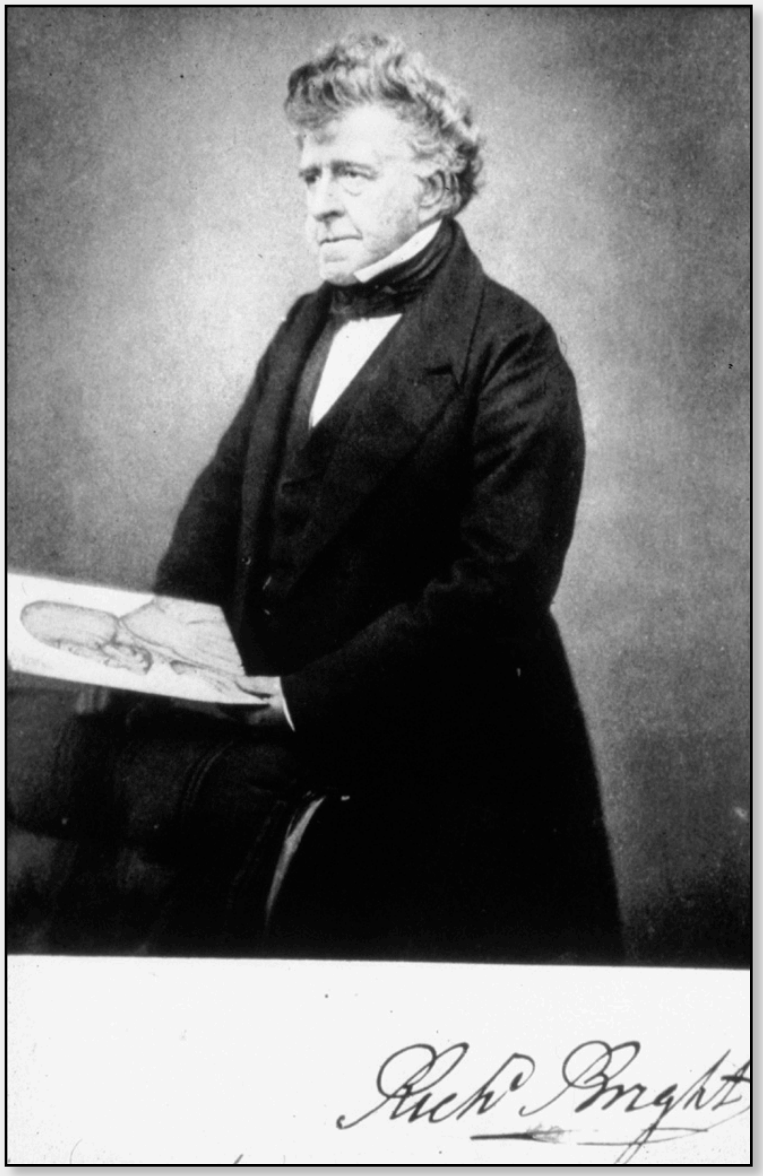
A MURDER hunt was under way today after a hotel owner was found stabbed to death in his flat.

Henry Bright's body was found at his rooms in the Lupus Hotel, Lupus Street, Pimlico. A post-mortem showed that Mr Bright, 56, died from stab wounds. His body was discovered yesterday when a hotel resident checked Mr Bright's apartment after he failed to appear downstairs at reception.

A Scotland Yard spokesman said: "A murder inquiry has been launched.

"We are appealing for witnesses who might have seen anything unusual in the area yesterday morning."

The victim was described as white, 5ft 8in tall with dark greying hair.

He was stockily built and overweight.

RICHARD BRIGHT