# Traitements innovants du lupus systémique


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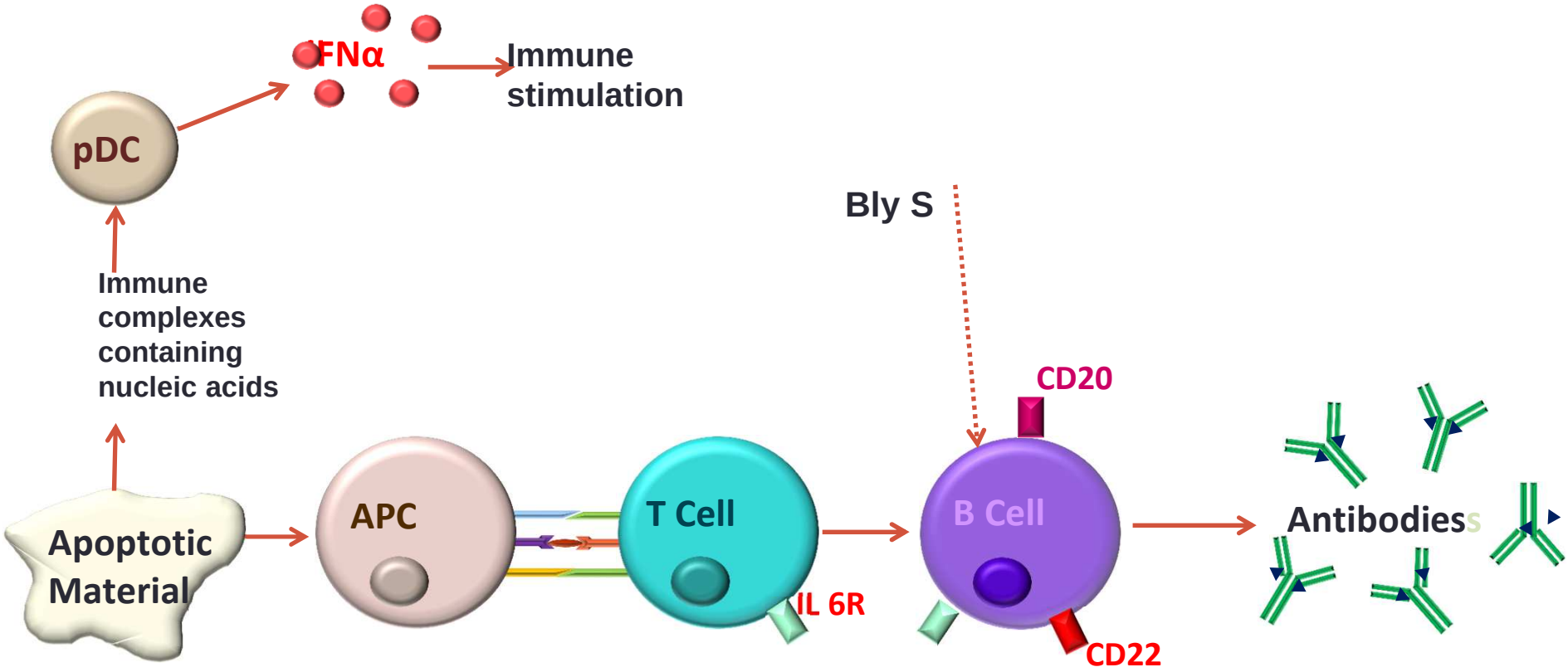
# Biologics in rheumatic diseases

| RA | PA | AS | SLE |
|---|---|---|---|
| infliximab | infliximab | infliximab | |
| etanercept | etanercept | etanercept | |
| adalimumab | adalimumab | adalimumab | |
| certolizumab | certolizumab | certolizumab | |
| golimumab | golimumab | golimumab | |
| abatacept | ustekinumab | secukinumab | |
| tocilizumab | | | |
| kineret | | | |
| tofacitinib | | | |
| | | | belimumab |

# Cibles thérapeutiques au cours du lupus



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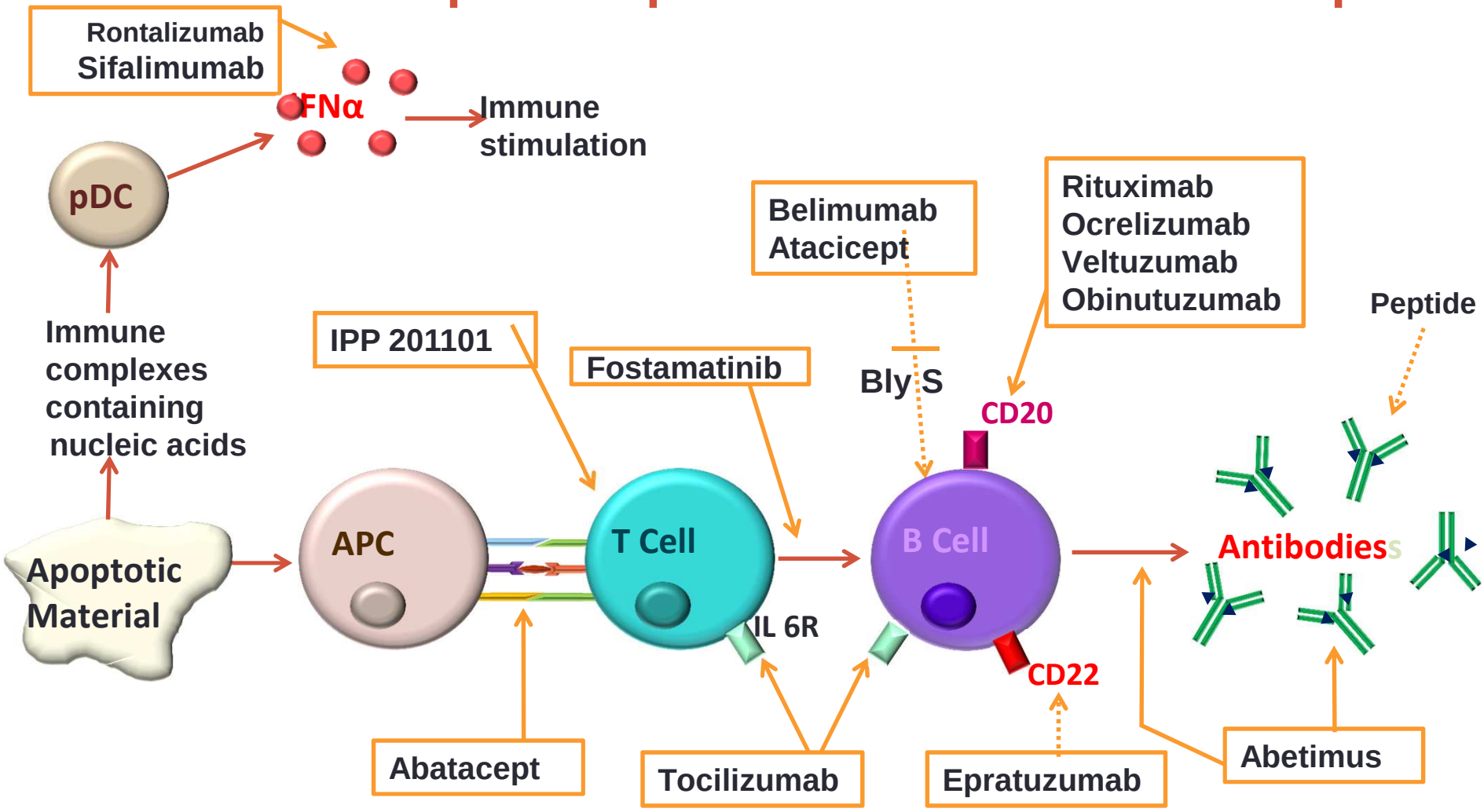


# B-cell-depletion therapy in SLE--what are the current prospects for its acceptance?

**Favas C, Isenberg DA.**

**Nat Rev Rheumatol. 2009 Dec;5(12):711-6.**

- The failure of rituximab, a monoclonal antibody that induces B-cell depletion, to meet its primary and secondary end points in trials of nonrenal SLE (EXPLORER) and renal (LUNAR) lupus nephritis has been disappointing given the success reported in many open-label studies. Concluding that B-cell-depletion therapy is not effective in SLE seems rather extreme.
- Further analysis of the as-yet unpublished results and their comparison with data from published studies might provide insight into whether B-cell depletion will eventually be accepted as a useful approach for the treatment of SLE.

# Reasons for failure – Poor design

- Superiority design required by medical agencies
- Statistical power defined on a too ambitious effet
- Too much GC/immunosuppressants
- Too short trial and/or exposure to SD
- Underestimation of the role of ethnicity
- Wrong definition of the primary outcome measure

Courtesy F Houssiau

# RTX in lupus: bad in controlled trials but good in real life ? Registry data

| | AIR | GRAD | BIOGEAS |
|---|---|---|---|
| Country | France | Germany | UK/Spain |
| Number | 136 | 85 | 164 |
| Renal | 31% | 37% | 100% |
| Previous MMF | 42% | 42% | 60% |
| Previous CYC | 34% | 33% | 80% |
| CR | 45-77%* | 47% | 30% |
| PR | 15-29%* | 34% | 37% |

*: according to organ involvement

Terrier *et al.* A&R 2010; 62; 2458
Witt *et al*. Lupus 2013; 22: 1142
Diaz-Lagares *et al*. Autoimmun Rev 2012; 11: 357

# RTX use in expert European rheumatology centers

| Country | Numbers SLE on RTX | % SLE on RTX |
|---|---|---|
| Belgium | 52 | 1.0 |
| Denmark | 10 | 1.0 |
| France | 350 | 1.6 |
| Germany | 150 | 0.5-3.0 |
| Greece | 80-100 | 1.0-3.5 |
| Hungary | 15 | 0.3-0.5 |
| Italy | 70-150 | 0.2-2.7 |
| Spain | 150-450 | 0.4-3.0 |
| Sweden | 80-135 | 2.0-4.5 |
| The Netherlands | 16-120 | 0.4-4.0 |
| Turkey | 40 | 1.3 |
| United Kingdom | 150-300 | 0.6-1.2 |
| **Total** | **1163-1872** | **0.7-2.0** |

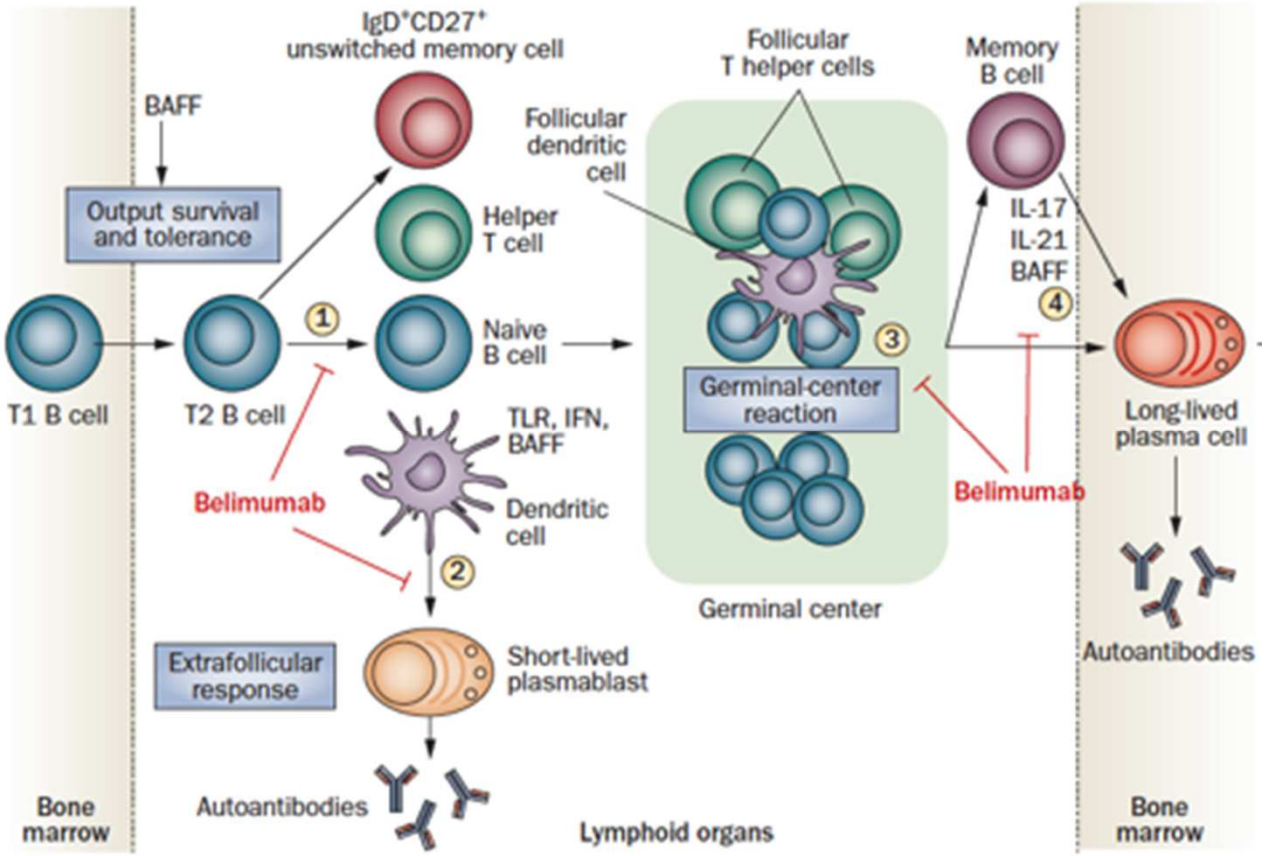
Ryden Aulin M *et al*., unpublished data

# RTX is not lupus' panacea

- Does not work in all patients, despite efficacious BCD
- Beware of PML
- Beware of HBV reactivation !
- Does not deplete long-lived plasma cells
- May even promote the development of auto-immune long-lived plasma cells

# Reasons for failure – Wrong target

Where is lupus




Lupus is there

Sanz I. Nat Rev Rheumatol 2011; 7: 255

# The last rituximab believers

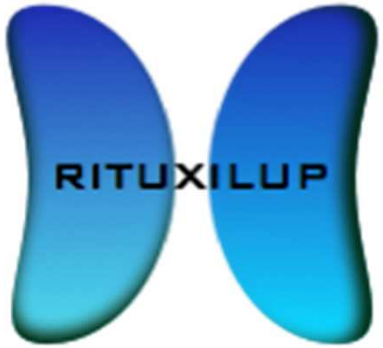
RITUXILUP trial – L. Ligthstone

CALIBRATE trial – B. Diamond

RING trial – F. Houssiau

Lupus Nephritis Trials Network

# The RITUXILUP controlled study




IV MP + MMF + Rituximab

*vs*

IV MP + MMF + Oral steroids

Lupus Nephritis Trials Network

- Non-inferiority trial
- If the RTX arm is inferior to the oral steroids arm, is it because RTX is a bad drug for LN or because LN requires some oral steroids ?

# Reconstitution of the B-cell repertoire

## CALIBRATE

Lupus Nephritis Trials Network

B cell depletion (RTX) followed by BAFF inhibition (BLM)

Prospective, randomized, open label safety study (N=40)

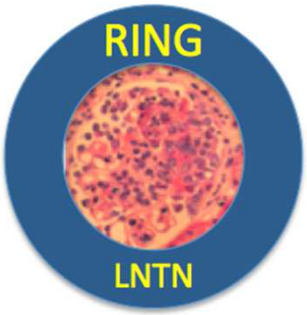
2 arms

- Rituximab/Cyclophosphamide/Steroids
- Rituximab/Cyclophosphamide/Steroids/Belimumab

Primary endpoint – Grade 3 or higher infectious AEs

# RING – RItuximab for lupus Nephritis with remission as a Goal

Lupus Nephritis Trials Network




ELCY (3M) + AZA/MMF (3M)

NIH CY (6M) + AZA/MMF (3M)

AZA > 6M

MMF > 6M

ISN/RPS III/IV/V

-8w -2w 0

S R — Proteinuria ≥1g/d confirmed

Proteinuria ≥1g/d
On max 10 mg/d prednisolone
On ACEI/ARB at screening

CRR

0 6 12 18 24

AZA or MMF – Pred ≤10mg/d

RTX or placebo

CRR: uP/C ratio (measured in a 24-h collection) < 0.5 (mg/mg) **AND** eGFR >60ml/min, or, if <60ml/min at screening, not fallen by >20% compared *to* screening **AND** no need to increase GC (except *per* protocol) or introduce another IS

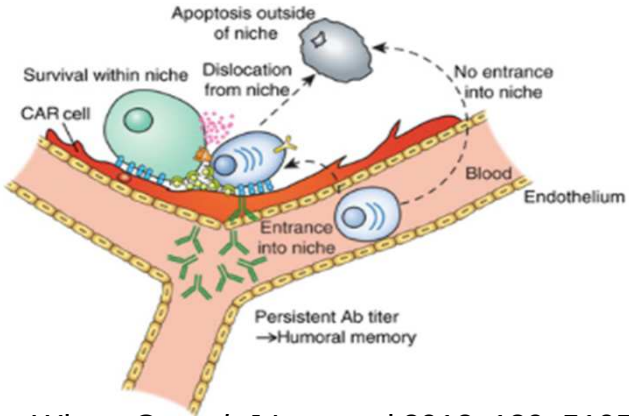
# Reasons for failure – Wrong target

Current therapies do not tackle the real bad boys

RTX, BEL, EPR are anti-B cell therapies

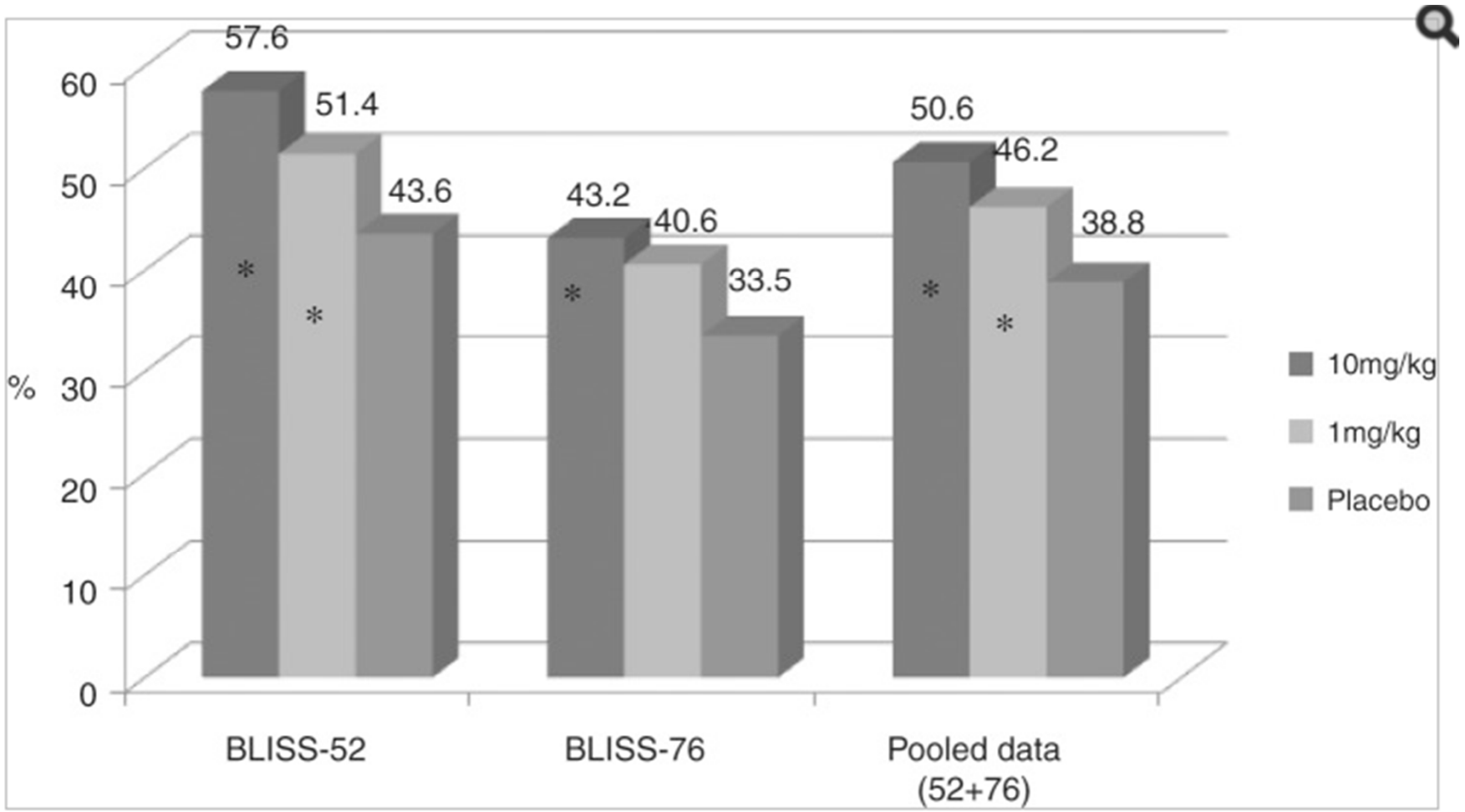
Yet, RTX, BEL, EPR do not (partially) target

- Germinal center B cells
- Memory B cells
- Plasma cells
- Long-lived plasma cells




Winter O *et al*. J Immunol 2012; 189: 5105

# Belimumab: the two pivotal Phase III trials



# Belimumab: the BLISS-SC Phase III trial

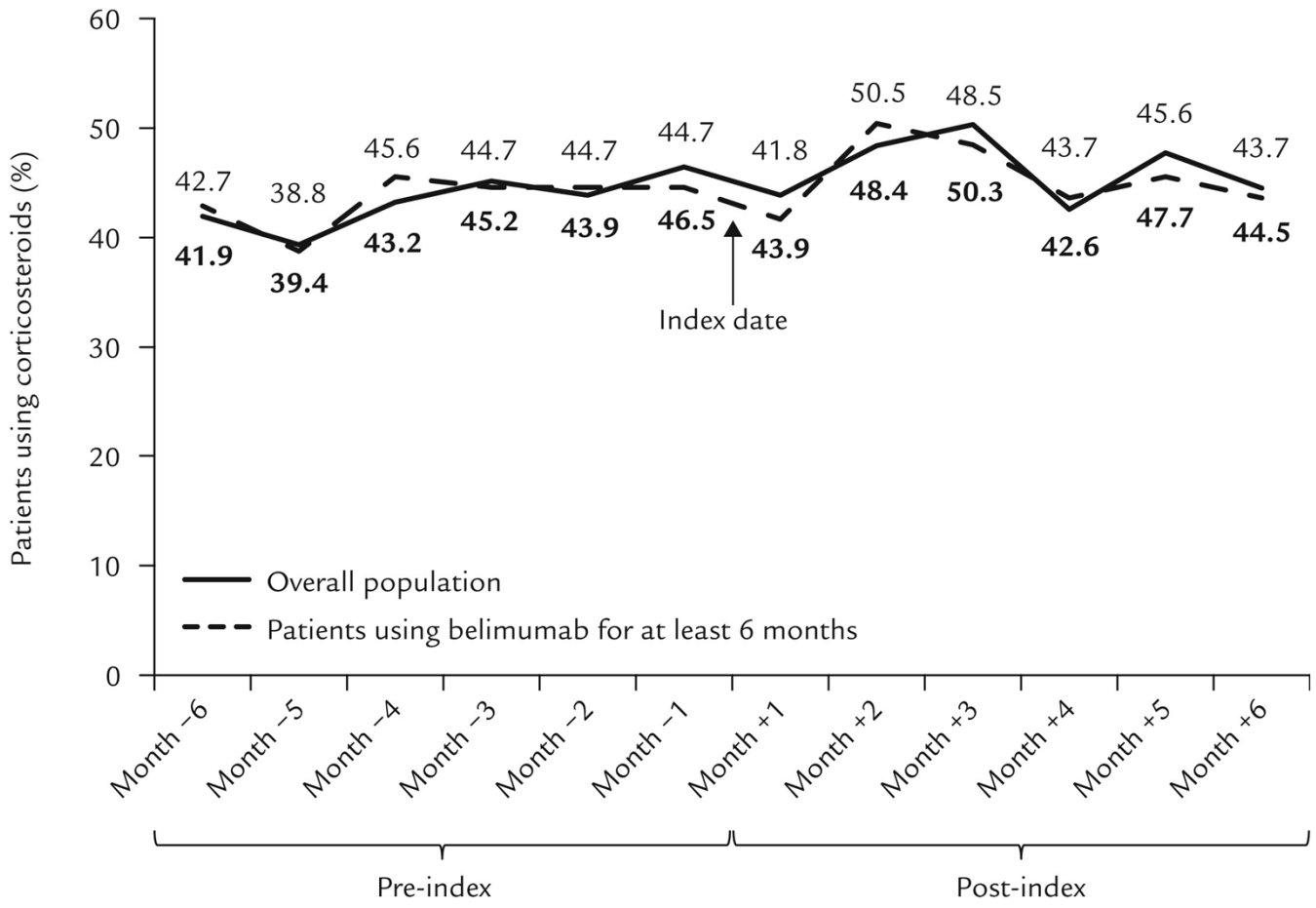
*GSK announces positive results from phase III BLISS-SC study of Benlysta® (belimumab) administered subcutaneously in patients with systemic lupus erythematosus* – Nov 7, 2015

- 836 patients: 556 BEL and 280 PBO
- SRI-4 responders at week 52: 48.5% PBO *vs* 60.8% BEL (*p*=0.0011)
- Time to first flare: 116 days PBO *vs* 170 days BEL (*p*=0.0003)
- Pred ≤7.5mg/d (in those ≥7.5 at baseline): 18.2% PBO *vs* 11.9% BEL (*p*=0.07)

# Belimumab: pros and cons

| Pros | Cons |
| --- | --- |
| Rationale | Not a major effect (10-15%) |
| 1st SLE targeted therapy | Very expensive Plaquenil ! |
| Effect despite SOC | BLISS 76 less impressive |
| Three concordant trials | Not a prompt effect |
| Above the noise! | Mainly mild MS/MC cases |
| Benefit in severe patients | Very active patients excluded |
| Steroid-sparing | ? Active in afroamericans |
| Effect on QOL | ? Active in LN |
| No major toxicity signal | |

# Belimumab data from the real-world




Ke X *et a*l., Clin Ther 2015; 37: 2852

# Belimumab data from the real-world

*Table 3*. Adverse events and reasons for discontinuation of belimumab.

| Reasons for Discontinuation | No. Patients |
|---|---|
| Development/worsening neuropsychiatric SLE | 6 |
| Severe disease flares | 4 (renal, arthritis) |
| Myocardial infarction | 1 |
| Loss of insurance | 2 |
| Infection | 7 (most severe: pneumonia, Group A streptococcal bacteremia, axillary MRSA) |
| Infusion reaction | 3 |
| Elective surgery | 1 |
| Patient choice | 2 |
| No clinical response | 6 |
| Total (out of 195) | 32 (16%) |

SLE: systemic lupus erythematosus; MRSA: methicillin-resistant *Staphylococcus aureus*.

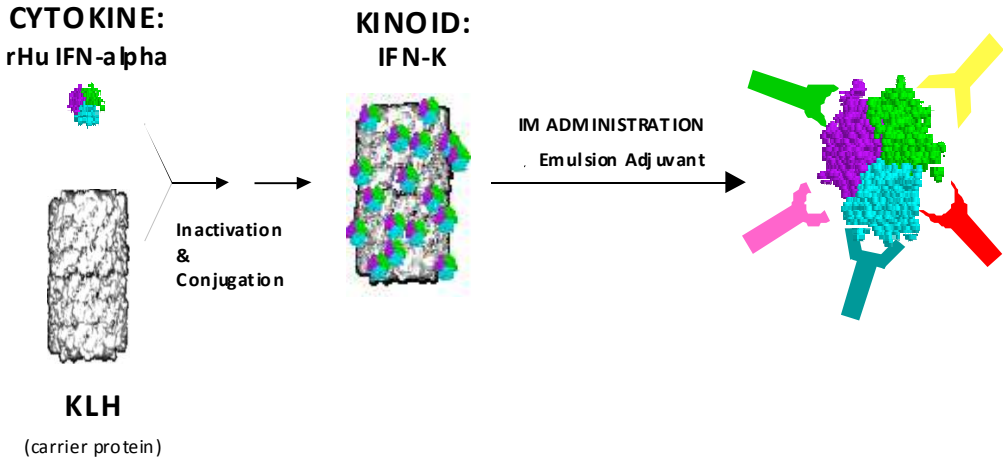
Hui-Yuen JS *et a*l., J Rheumatol 2015; 42: 2288

# The future may be bright...

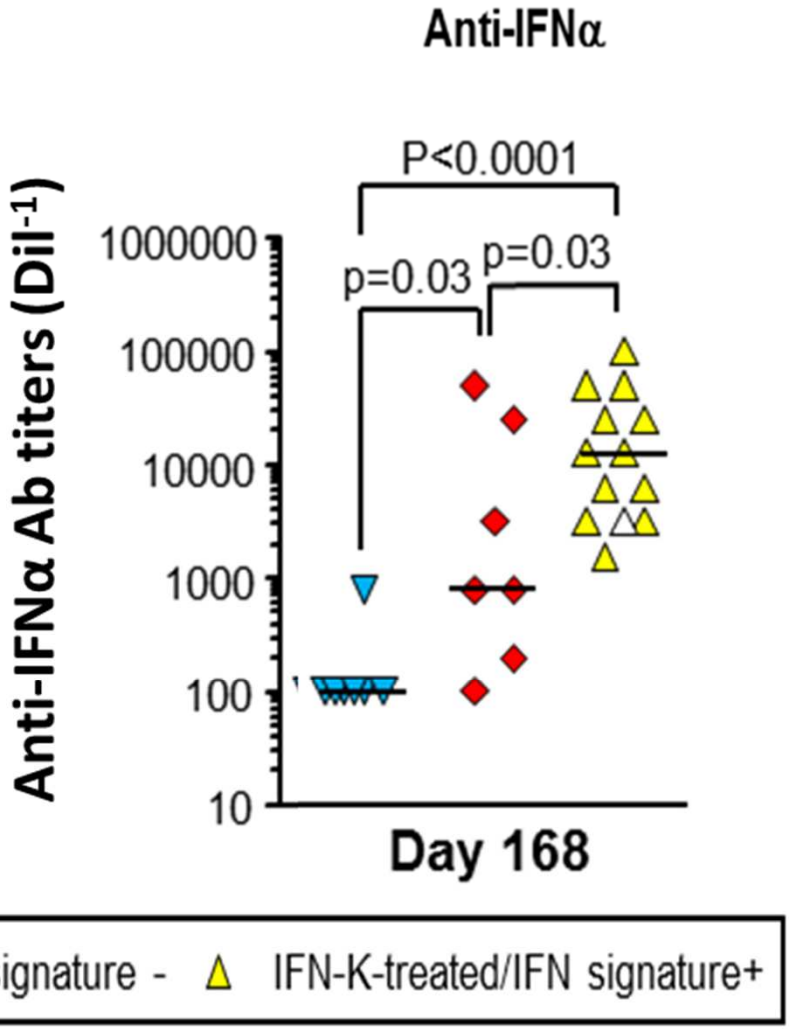
| | | | |
|---|---|---|---|
| Anifrolumab | anti-IFNAR | L III<br>LN II | Astra-Zeneca<br>Medimmune |
| Belimumab | anti-BAFF | LN III | HGS/GSK |
| Abatacept | CTLA4Ig | LN III | BMS |
| Rigerimod | 21-mer peptide | L III | ImmuPharma |
| ALX-0061 nanobody | anti-IL6R | L II | Ablynx |

« First-in-class » drug

# IFNα Kinoid – Personalized medicine




Self polyclonal anti-IFNα antibodies




Lauwerys B *et al*. Arthritis Rheum 2013; 65: 447

# Anifrolumab antagoniste des IFN R de type 1

- 305 patients ont été traités pendant 48 semaines pour recevoir de l'anifrolumab intraveineux à la dose de 300 mg ou 1000 mg ou un placebo en sus du traitement standard

- randomisation était stratifiée selon le score SLEDAI 2K ≤ 10, en fonction des doses de corticoïdes (< 10 ou ≥ 10 mg/j) et selon la signature interféron (élevée ou basse) sur la base de l'analyse de l'expression de 4 gènes

EULAR 2016; **OP0291** – **R. Furie** L

# Anifrolumab et lupus systémique : anti-IFN

| | | Placebo | Anifrolumab 300mg | | | Anifrolumab 1000mg | | |
|---|---|---|---|---|---|---|---|---|
| | | N (%) | N (%) | Odds ratio (90% CI) | *P*-value | N (%) | Odds ratio (90% CI) | *P*-value |
| **Primary endpoints** | | | | | | | | |
| **SRI + CS <10mg at Day 169** | **305** | **18 (17.6)** | **34 (34.3)** | **2.38 (1.33, 4.26)** | **0.014** | **30 (28.8)** | **1.94 (1.08, 3.49)** | **0.063** |
| | | | | | | | | |
| **IFNGS high** | 229 | 10 (13.2) | 27 (36.0) | 3.55 (1.72, 7.32) | 0·004 | 22 (28.2) | 2.65 (1.27, 5.53) | 0.029 |
| IFNGS low | 76 | 8 (30.8) | 7 (29.2) | 0.96 (0.34, 2.74) | 0·946 | 8 (30.8) | 1.04 (0.37, 2.88) | 0.953 |
| | | | | | | | | |
| **Secondary endpoints** | | | | | | | | |
| SRI + CS <10mg at Day 365 | 305 | 26 (25.5) | 51 (51.5) | 3.08 (1.86, 5.09) | <0.001 | 40 (38.5) | 1.84 (1.11, 3.04) | 0.048 |
| CS≤7,5mg/d at Day 365 | 182 | 17 (26.6) | 31 (56.4) | 3.59 (1.87, 6.89) | 0.001 | 20 (31.7) | 1.23 (0.64, 2.37) | 0.595 |

- Furie J et al. Abstract #OP0291 THU0295 Clinical science session. EULAR 2016.

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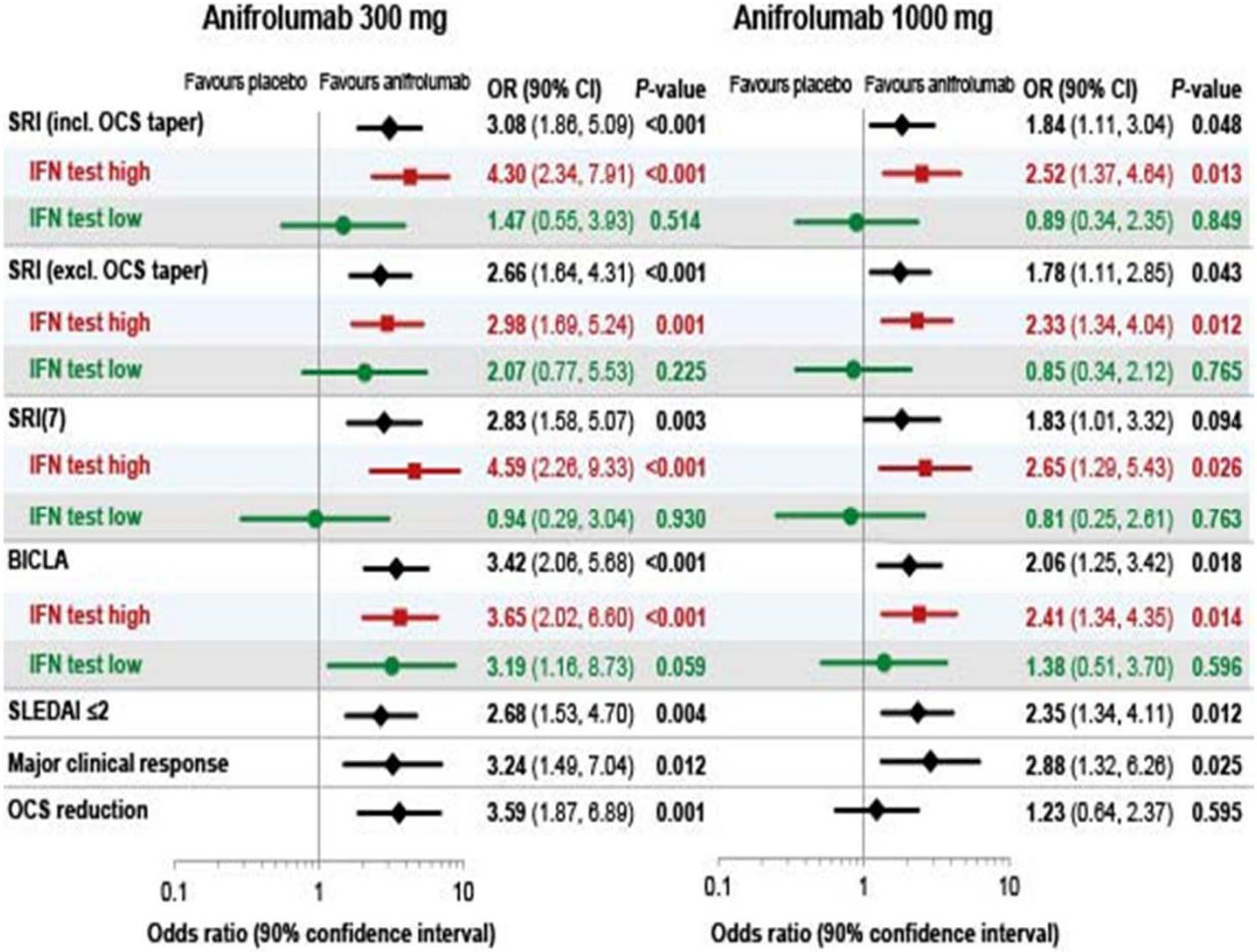
# Anifrolumab antagoniste des IFN R de type 1




BICLA, BILAG-based Combined Lupus Assessment; CI, confidence interval; IFN, interferon; OCS, oral corticosteroids; OR, odds ratio; SLEDAI-2K, SLE Disease Activity Index 2000; SRI, SLE responder index

EULAR 2016; **OP0291** – **R. Furie** L

# Anifrolumab et lupus systémique : anti-IFN

- **Tolérance**
- **Fréquence similaire des effets indésirables graves**
  - 18,8% des patients sous placebo vs 16,7% des patients sous anifrolumab
- **Plus grande fréquence**
  - **des épisodes de grippe**
    - 1% dans le groupe placebo
    - 6,1% dans le groupe 300 mg
    - 7,6% dans le groupe 1000 mg
  - **d'infections à HSV**
    - 2% dans le groupe placebo
    - 5,1% dans le groupe 300 mg
    - 9,5% dans le groupe 1000 mg


- Furie J et al. Abstract #OP0291 THU0295 Clinical science session. EULAR 2016.

# Anifrolumab et lupus systémique : anti-IFN

- Cet essai démontre l'**intérêt de l'anifrolumab dans le lupus systémique**.
  - En particulier en cas de signature interféron élevée
  - Sur la plupart des atteintes d'organes
- **Effet similaire des 2 doses testées**
  - Possiblement liée à effet d'inhibition similaire de la voie interféron
    - Comme en témoigne signature des gènes interférons de type 1
- Profil de tolérance acceptable
  - Avec une **augmentation de la fréquence des infections virales**


- Furie J et al. Abstract #OP0291 THU0295
  Clinical science session. EULAR 2016.

# Targeted therapy in lupus in 2026…
## Towards personalised medicine