



Lymphomes et Sjögren: nouveautés physiopathologiques et dans la prise en charge

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Sjögren and lymphoma

- Risk of lymphoma: x 10-15
- 5% of patients with SS will develop lymphoma
- Marginal zone histology and high rate of mucosal localizations
 - → MALT histology
 - Possibility of DLBCL (transformation of marginal zone lymphomas ?)
- Most frequently in salivary glands: the targets of autoimmunity
- Escape of autoimmune B cells

Moving to Scolyss – NECESSITY Project

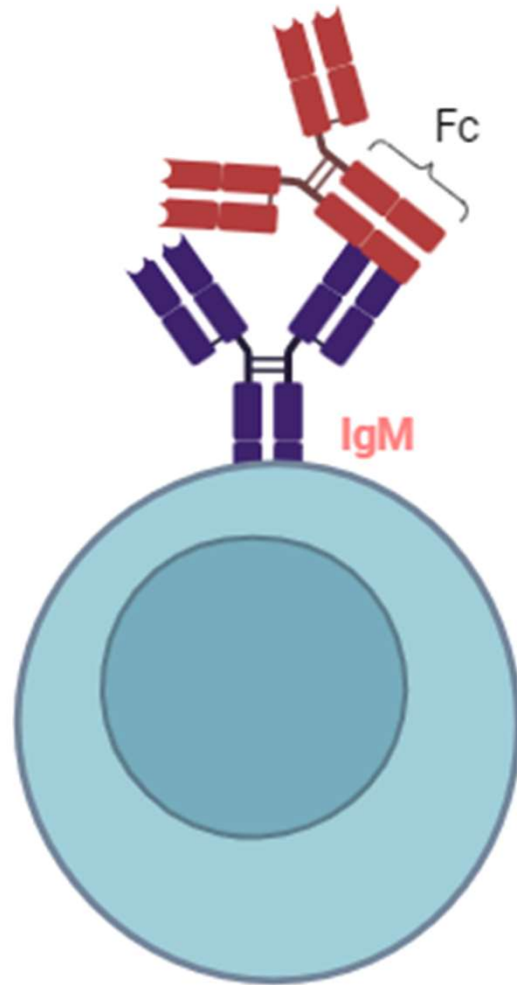
Score of Lymphoma risk in Sjogren disease

- Parotid swelling
- Splenomegaly or adenopathy
- Purpura
- Lymphopenia < 1000 (or 500)
- Monoclonal component component in the blood or urine
- Low C4 level
- Rheumatoid factor
- To define thresholds of risk
- To describe the evolution of this score over time according to treatments received by the patients

Chronic stimulation of autoimmune B cells: Why ?

- The role of immune complexes
- The role of BAFF
- The role of abnormalities of TNFAIP3/A20 or other genes controlling NF- κ B activation

Le personnage central de l'intrigue



RF and lymphoma in pSS

- RF activity of membrane Ig in 2 cases of lymphoma complicating Sjögren's syndrome
- Homology of BCR from salivary MALT lymphoma with RF

MALT localization	n	t (11, 14)	n	Homology CDR3-RF
Salivary glands	114	2 (2%)	32	13 (41%)
Stomach	209	50 (24%)	45	8 (18%)
Lung	113	47 (42%)	19	0
Others	ND	ND	4	0



OPEN ACCESS

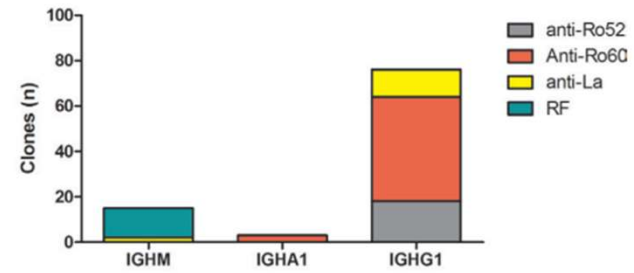
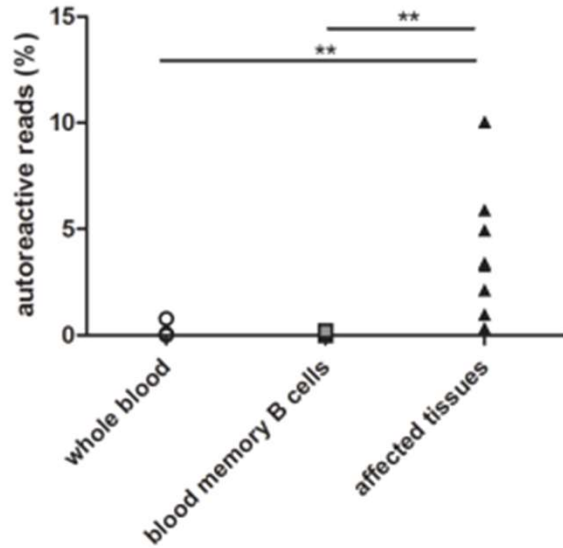
TRANSLATIONAL SCIENCE

Proteogenomic analysis of the autoreactive B cell repertoire in blood and tissues of patients with Sjögren's syndrome

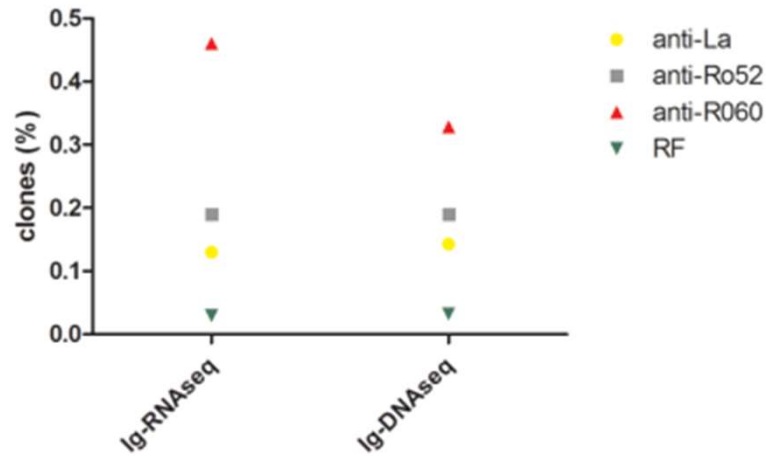
Mathijs G A Broeren,^{1,2} Jing J Wang,³ Giulia Balzaretto,⁴ Patricia J T A Groenen,⁵ Barbera D C van Schaik,⁶ Tim Chataway,⁷ Charlotte Kaffa,⁸ Sander Bervoets,⁸ Konnie M Hebeda,⁵ Gergana Bounova,⁹ Ger J M Pruijn,² Thomas P Gordon,¹⁰ Niek De Vries,⁴ Rogier M Thurlings ¹

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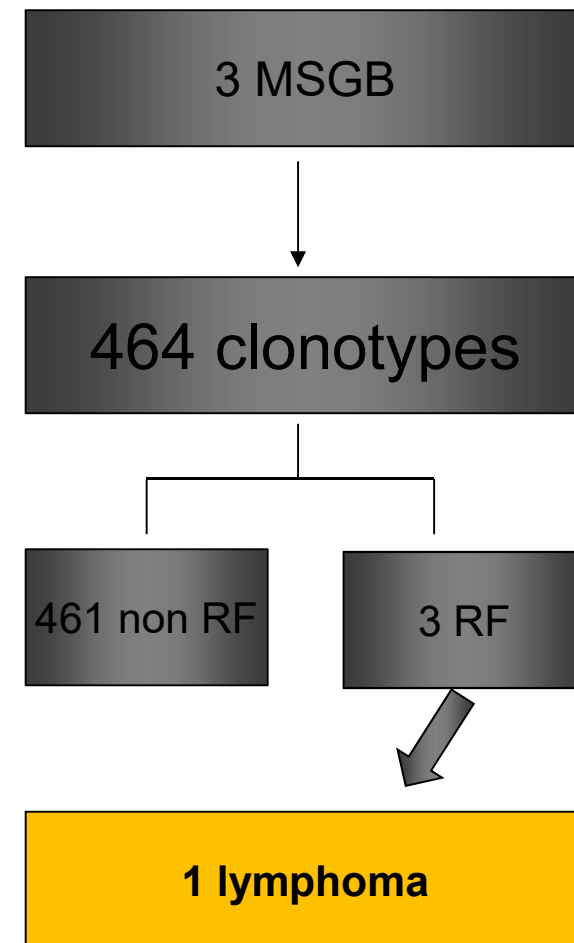


Stereotypic Rheumatoid Factors That Are Frequently Expressed in Mucosa-Associated Lymphoid Tissue–Type Lymphomas Are Rare in the Labial Salivary Glands of Patients With Sjögren’s Syndrome

Richard J. Bende, Linda M. Slot, Robbert Hoogeboom, Thera A. M. Wormhoudt, Akanbi O. Adeoye, Jeroen E. J. Guikema, and Carel J. M. van Noesel

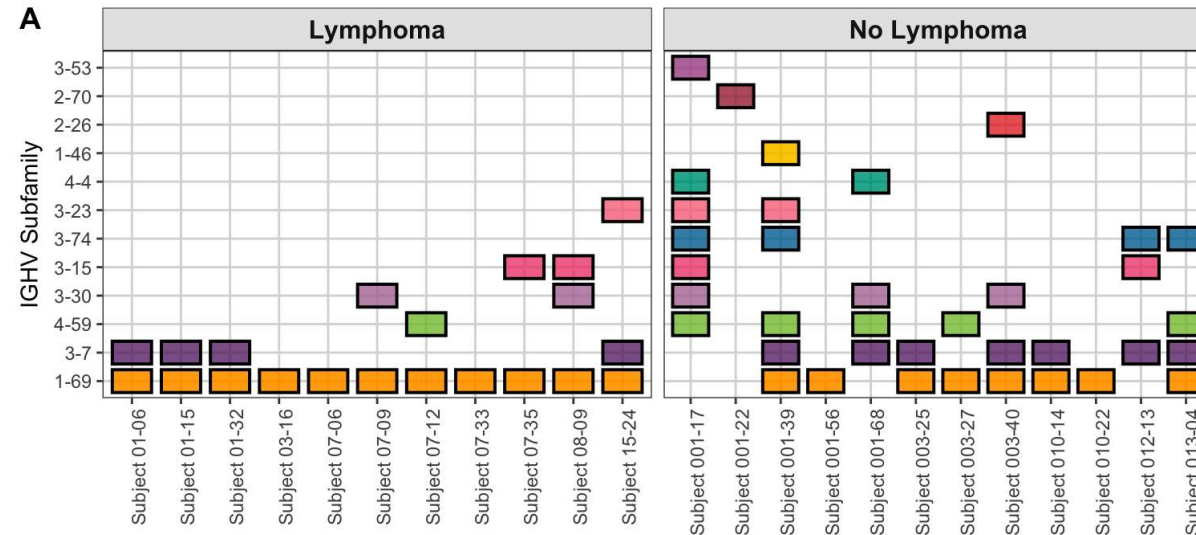
- Extensive analyses of the B cell Ig VH region repertoire on microdissected labial salivary glands from 3 patients with SS
- Among the identified 464 distinct Ig clonotypes, only 3 stereotypic RF–expressing clones
- One patient developed lymphoma 2 years later: The lymphoma B-cell clone was one of the 3 RF clones.
- → RF clones are rare among the salivary infiltrate but are more prone to transform into lymphoma
- → strong selection advantage of RF–expressing B cells

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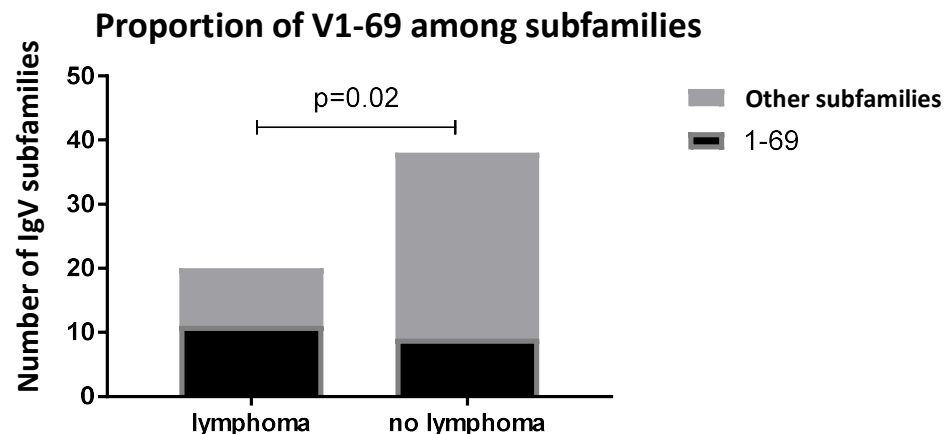
Rôle de certains sous types de RF?

- Collaboration with the group of T Gordon
 - Molecular profiling of secreted RF
 - 11 cases and 12 controls



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BTK Overexpression Is Associated with the Risk of Lymphoma in Primary Sjögren's Syndrome: Data from ASSESS

Bruton's Tyrosine Kinase (BTK) Gene Overexpression is Associated With Risk of Lymphoma in Primary Sjögren's Syndrome

1 Objective

To analyze whole blood gene expression and investigate the role of B cell genes in primary Sjögren's syndrome-related lymphoma (pSS-NHL)

Study Design

The prospective ASSESS cohort: n=395 pSS patients with a 10-year follow-up

Transcriptomic analysis

Primary analysis (solid red arrows)
Sensitivity analyses (dashed red arrows)

3 Conclusion

Antigen-induced chronic B-cell activation

BCR

BTK

NF-κB

APRIL

BCR Downstream Signaling

In the peripheral blood of pSS patients with incident lymphoma,

- **BTK**, a pivotal B cell receptor transducer,
- **APRIL**, a cytokine involved in B cell activation and growth,

→ overexpressed prior to lymphoma

2 Results

Primary analysis

Sensitivity analysis

BTK overexpression was confirmed by real-time quantitative RT-PCR

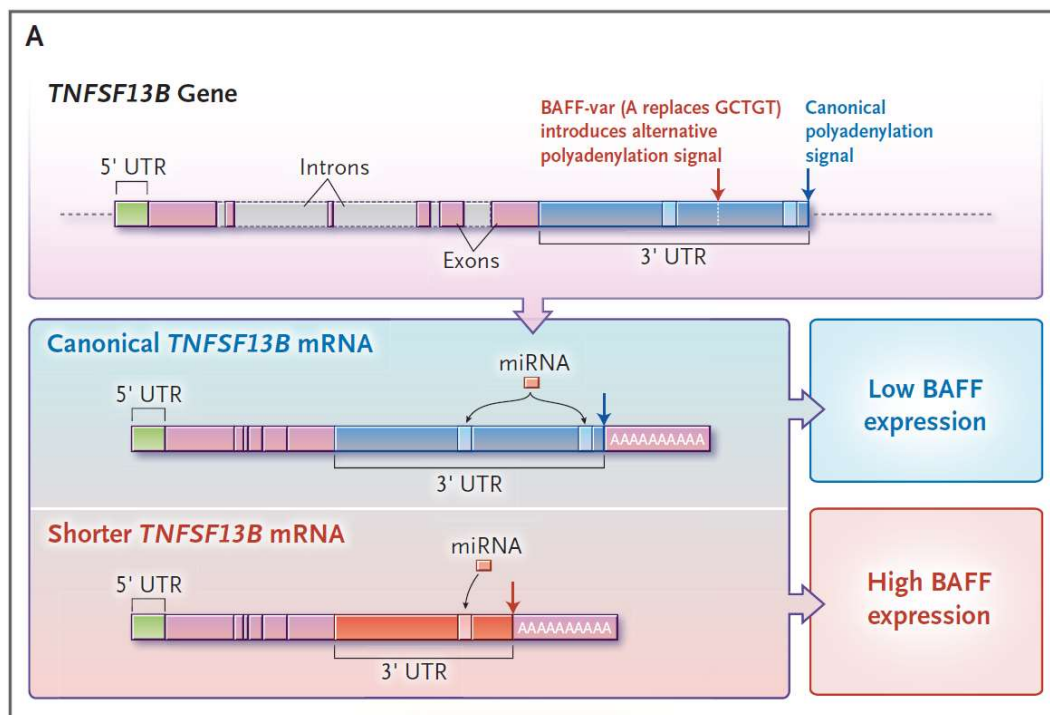
BTK
BAFF (TNFSF13B)
BCMA (TNFRSF17)
TRAIL (TNFSF10)
APRIL (TNFSF13)
CXCL13
MYD88
CD180

Duret PM, Schleiss C, Kawka L, et al. Bruton's tyrosine kinase (BTK) gene overexpression is associated with risk of lymphoma in primary Sjögren's syndrome. *Arthritis Rheumatol* 2023. *Arthritis & Rheumatology* AMERICAN COLLEGE of RHEUMATOLOGY Empowering Rheumatology Professionals

Chronic stimulation of autoimmune B cells: Why ?

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BAFF-var



pSS Paris Saclay cohort	Controls EFS	p
37/408 (9%)	20/399 (5%)	P=0.02

	BAFF-VAR (n= 37)	BAFF-WT (n= 185)	p
Demographic data			
Afro-Caribbean ethnicity	2/37 (5.4%)	37/185 (20%)	0.0334
Paraclinical features			
BAFF serum level (pg/ml)	1845 [1393 ; 1965] n= 33	1335 [1069 ; 1962] n= 171	0.0137
Activity and complications			
Lymphadenopathy	10/37 (27%)	25/185 (14%)	0.0490
Low activity: ESSDAI < 5	13/37 (35%)	99/185 (54%)	0.0482
Moderate-High activity: ESSDAI ≥ 5	24/37 (65%)	86/185 (46%)	
Marginal Zone lymphoma	6/37 (16.2%)	10/185 (5.4%)	0.0321

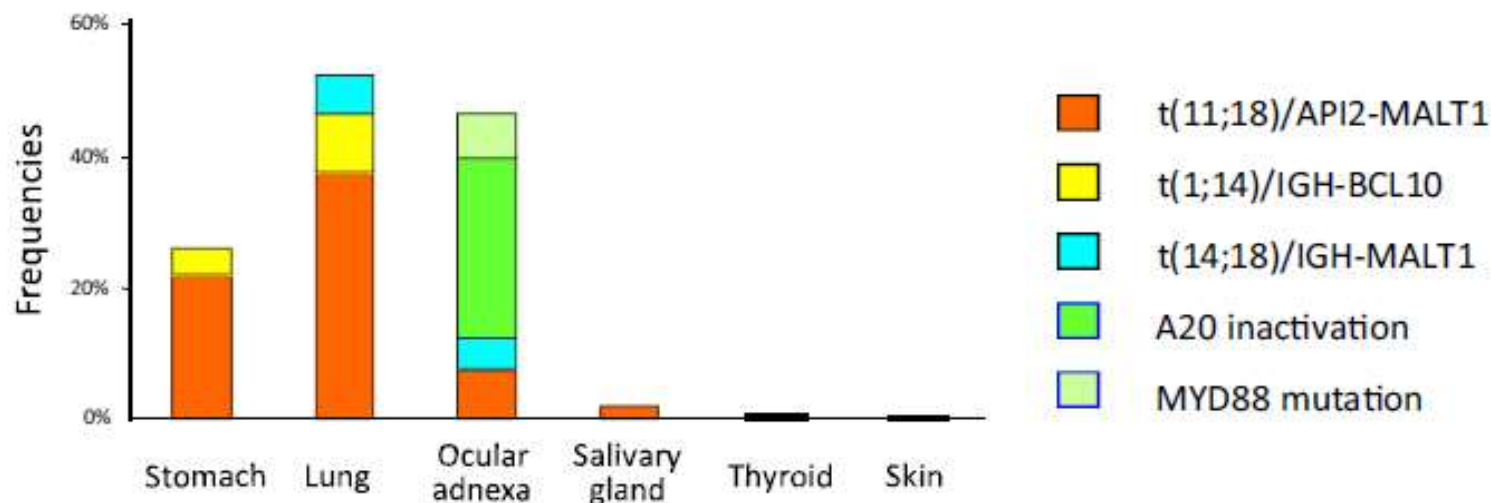
Steri et al. NEJM 2017
Steri et al., ACR meeting 2022

Chronic stimulation of autoimmune B cells: Why ?

- **The role of immune complexes**
- **The role of BAFF**
- **The role of abnormalities of TNFAIP3/A20 or other genes controlling NF- κ B activation**

The role of genetic change in MALT

- Somatic mutations are infrequent in salivary gland MALT lymphoma



- Could the genes somatically impaired in MALT lymphoma be enriched in germinal variants in pSS patients?

Activation de la voie NF-KB

□ Data WES

- 41 pSS + lymphoma patients
- 46 pSS without lymphoma patients

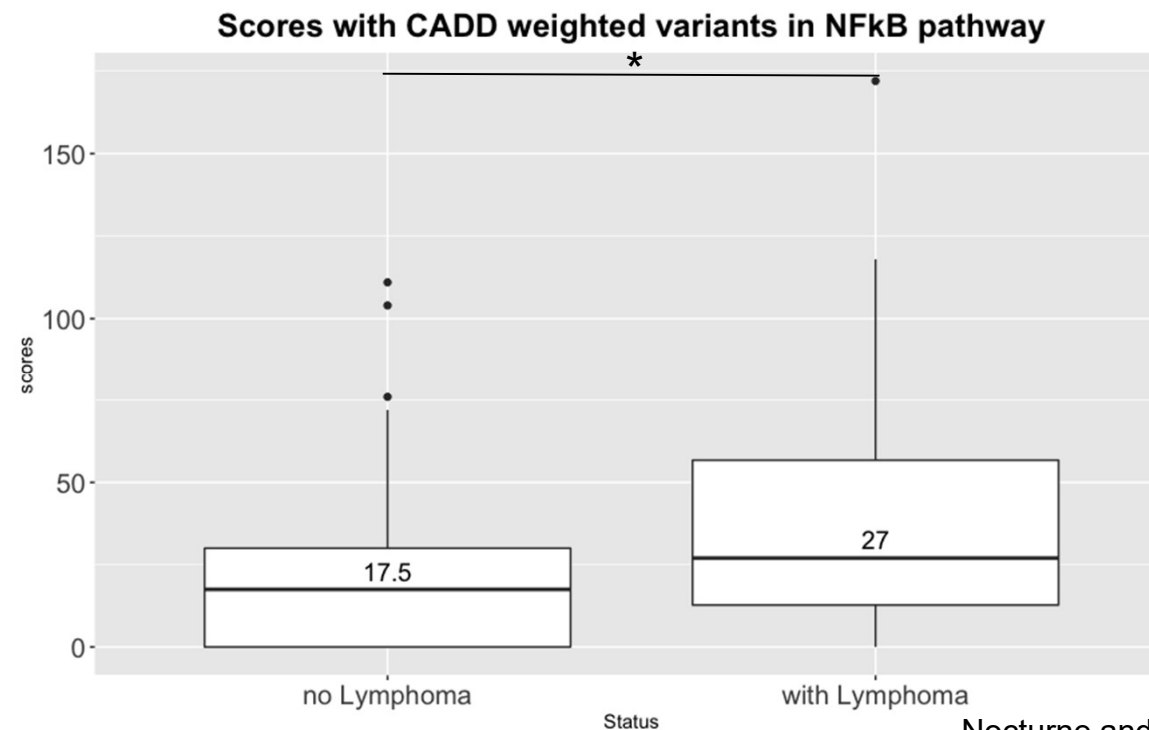
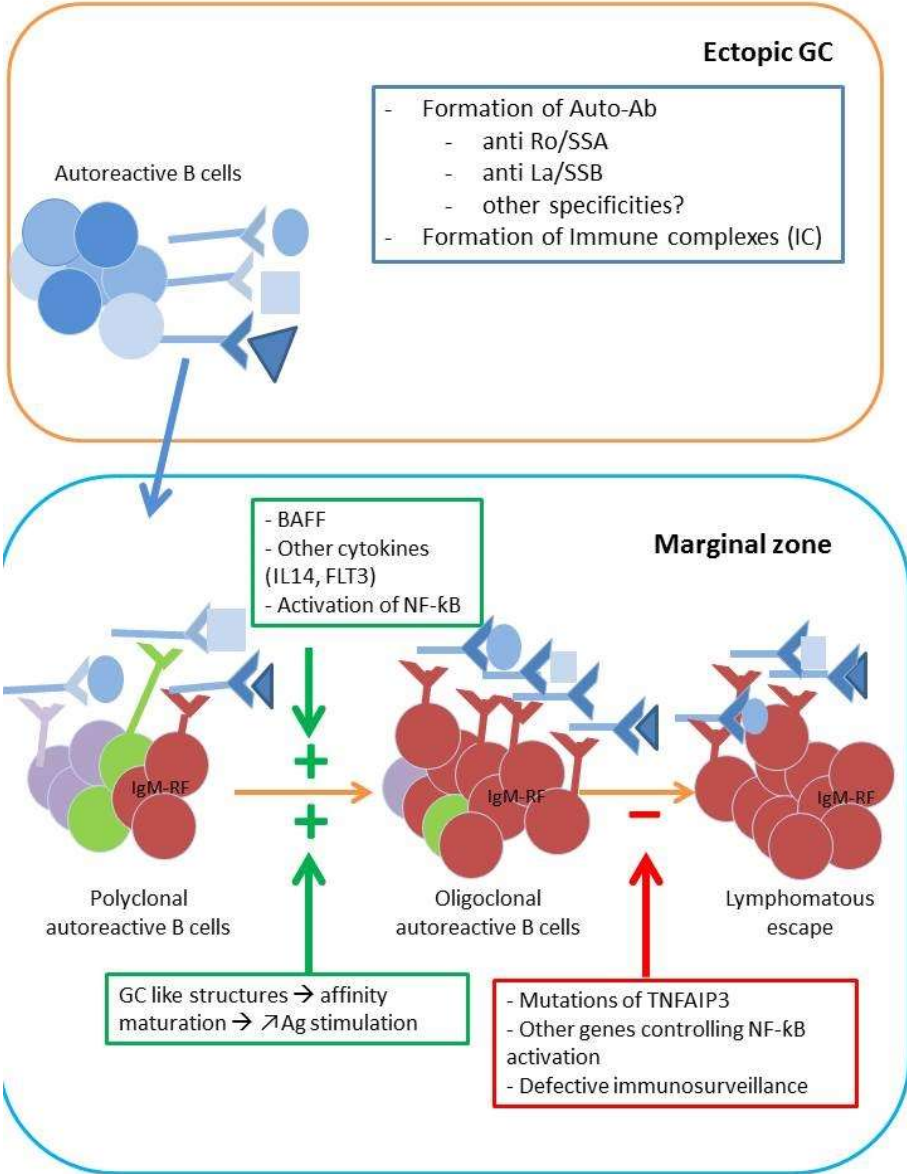


Figure 2



In clinical practice?

- Warning:
 - Fixed parotidomegaly
 - Cryo/RF
 - monoclonal gammopathy/hypogamma
- Explorations:
 - MSGB
 - PET-TDM

Contribution of MSGB to diagnosing pSS associated lymphoma

- 21 pSS patients + lymphoma and available MSGB at time of lymphoma diagnosis
 - 13 (54.2%) histology of lymphoma on MSGB
 - MSGB: only site enabling NHL diagnosis in 10/13 (76.9%) patients
- Interest of obtaining MSGB at pSS diagnosis and during the follow-up when NHL is suspected ++

Traitement?

- Quatre options
 - Simple surveillance
 - Traitement local (chirurgie, radiothérapie)

Involved-site radiotherapy, with a recommended dose of 24 Gy, is also the preferred option for localized, nongastric extranodal MZLs, leading to long-term local control in about 90% of patients.⁸⁴⁻⁸⁶ Possible long-term complications include xerostomia after parotid irradiation, hypo-

- Rituximab seul
- Chimiothérapie: alkylant +/- R

Symptomatic, advanced-stage MZLs are best treated with rituximab-based approaches. Rituximab in combination with chlorambucil has superior efficacy, as compared with either chlorambucil or rituximab monotherapy. The rate of long-term disease control is 50% with rituximab alone and 68% with the chlorambucil-rituximab combination; however, overall survival curves associated with the two regimens are superimposable.⁸⁹

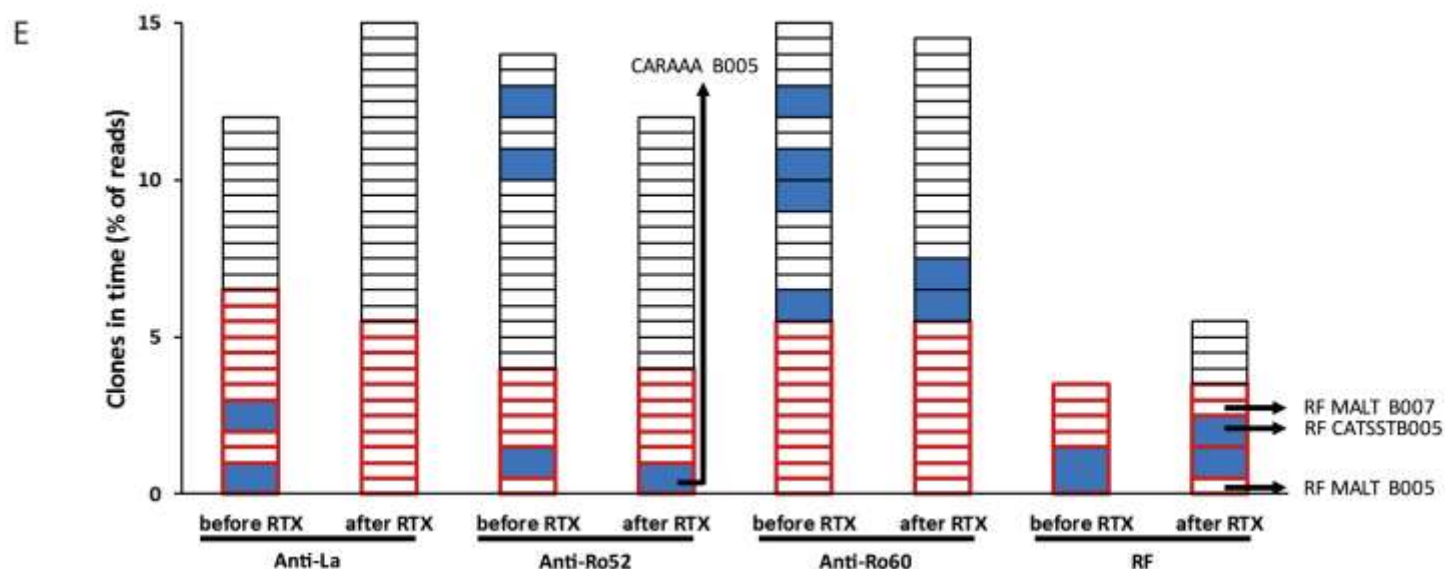
Rituximab seul ?

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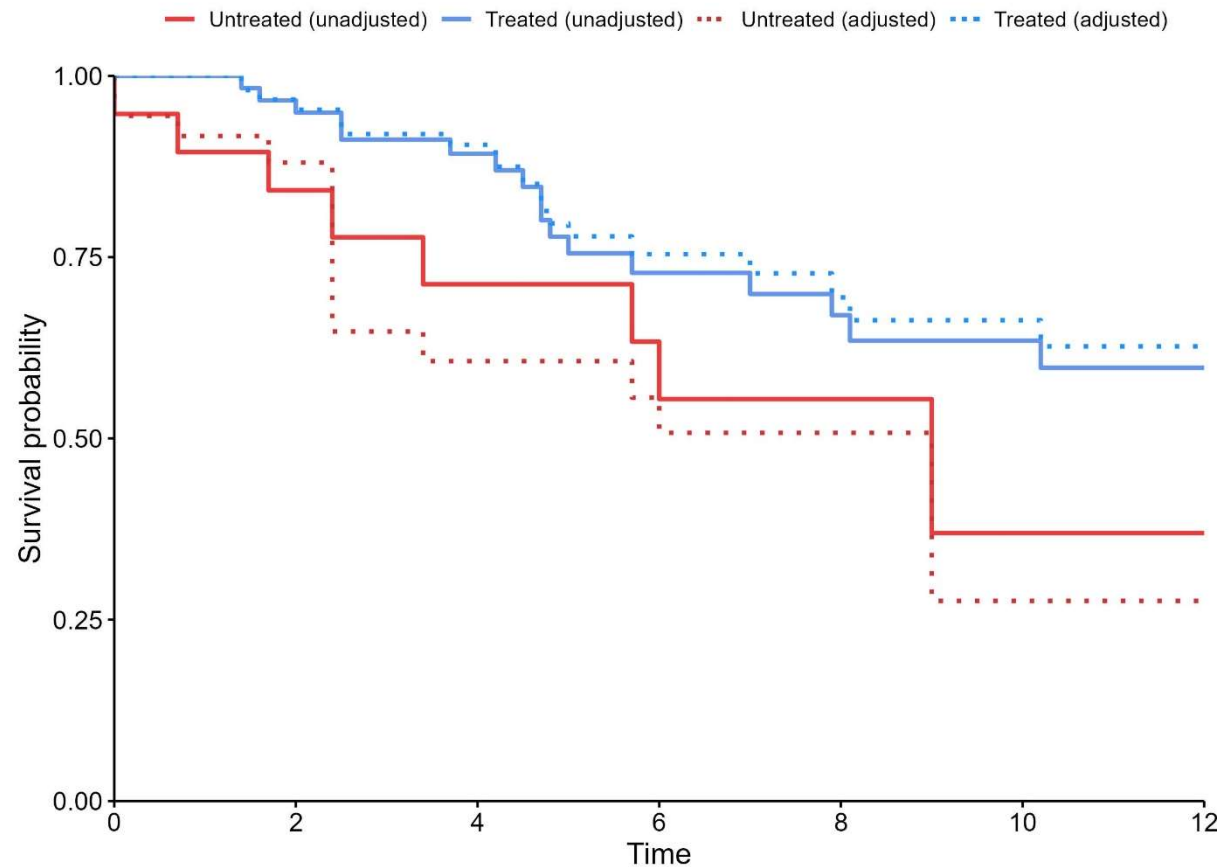


Impact of lymphoma treatment strategy on hematologic response and autoimmune disease activity in Sjogren patients developing lymphoma

- 106 pSS patients with lymphoma
 - 82 MZ → 68 MALT
- ESSDAI at lymphoma diagnosis:
 - 22 and 10 when excluding lymphoma
- Treatment strategy
 - Wait and see in 23%
 - Local therapy in 17%
 - Systemic therapy in 60%
- Treating or not:
 - No impact on OS and lymphoma PFS

Probability of Sjögren relapse or death according to initial treatment status , before and after propensity score adjustment

Protective for pSS relapse: HR 0.4
[0.17-0.95], p = 0.038



En résumé

- Lymphome: partie immergée de l'iceberg de l'hyperactivation au cours du pSS
- Recherche translationnelle:
 - Comprendre le continuum entre auto-immunité et lymphome
- Recherche clinique
 - Workflow
 - Définir la stratégie thérapeutique

Remerciements

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 - Société Française de Rhumatologie
 - Arthritis foundation
 - Fondation pour la Recherche Médicale
 - FAI2R

