Actualités thérapeutiques du Syndrome de Gougerot Sjögren

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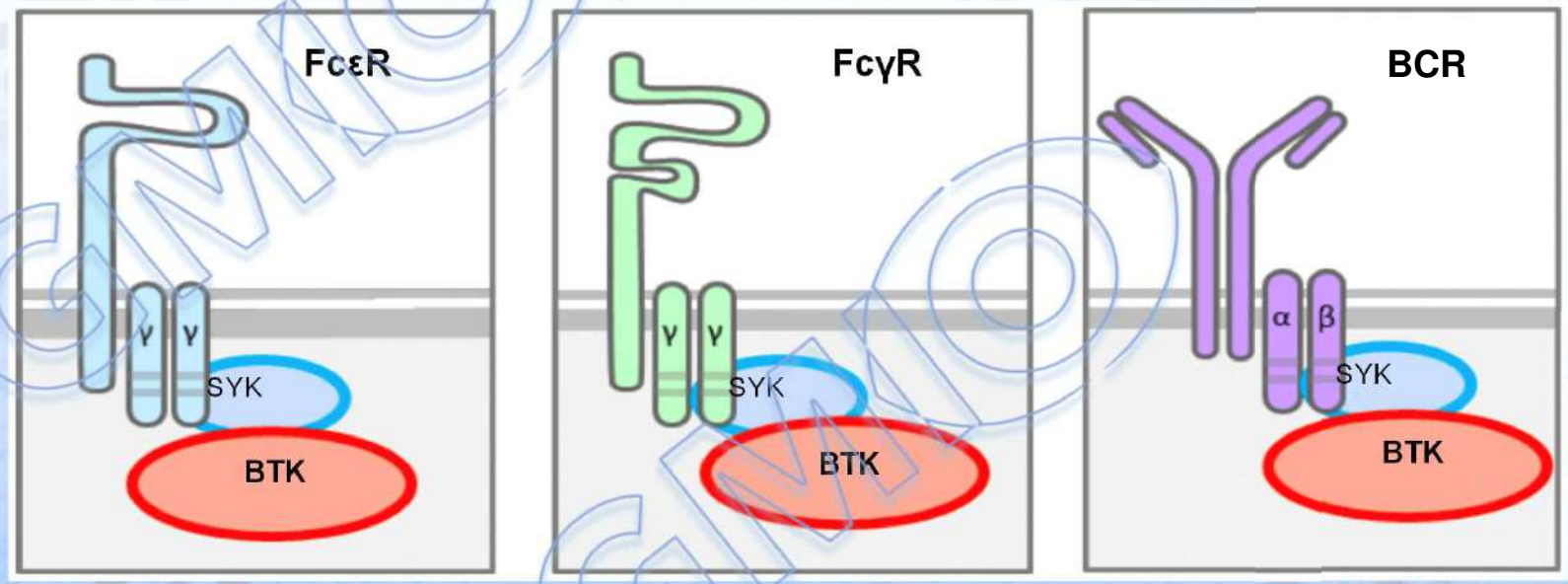
De nouvelles cibles thérapeutiques prometteuses

- Bruton tyrosine kinase
- BAFF

Bruton tyrosine kinase

BTK : la Bruton tyrosine kinase



Mastocytes
Basophiles

Macrophages

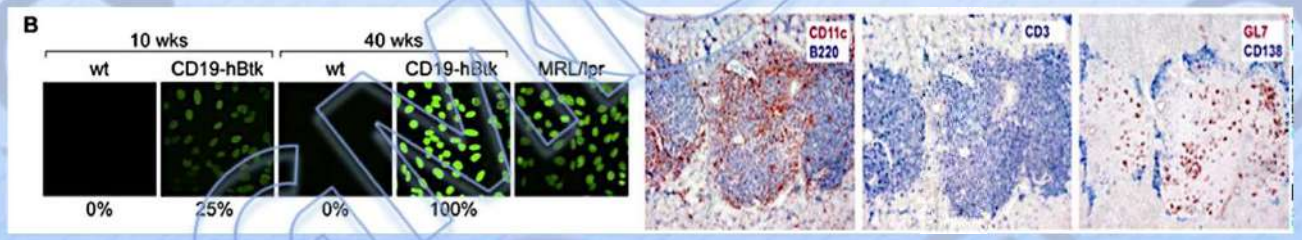
Lymphocytes B

Déficit = agammaglobulinémie

Hyperactivation = auto-immunité ….lymphome

BTK: nouvelle cible thérapeutique du SS ?

- BTK promeut la survie des LB auto-réactifs dans divers modèles animaux de SS
- Souris transgénique avec hyper-expression de BTK (h-CD19-BTK):
  - Production d'anticorps antinucléaires (ANA)
  - Néogénèse de structures lymphoïdes ectopiques au sein des glandes salivaires



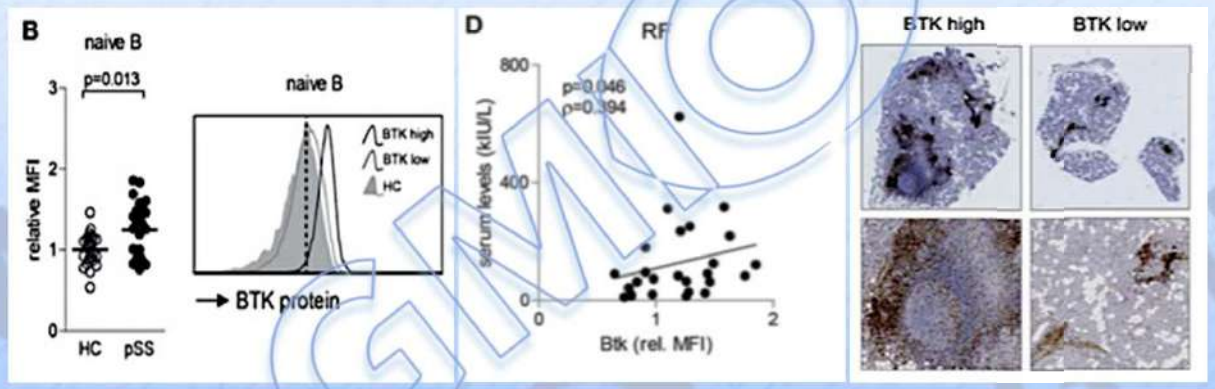
- *Kil et al. BTK levels set the treshold for B-cell activation and negative selection of autoreactive B-cells in mice. Blood 2012*
- *Rankin et al. Selective BTK inhibition prevent murine lupus. J. Immunol. 2013*

- Données précliniques d'efficacité de BTKi dans le modèle NZB/NZW F1 (modèle murin de LES/SS)

- *Mina-Osoria et al. Suppression of glomerulonephritis in lupus prone NZBxNZW mice by RN486 , a selective inhibitor of Bruton's Tyrosine Kinase. Arthritis & Rheum. 2013*

BTK: nouvelle cible thérapeutique du SS ?

- BTK est surexprimé (ARNm et protéine), dans les LB circulants de patients avec SS, en comparaison aux sujets sains



Corneth et al. Enhanced Bruton's Tyrosine Kinase activity in peripheral blood B-lymphocytes from patients with auto-immune disease. Arthritis & Rheumatology . 2017

Elévation de BTK : un facteur de risque de lymphome ?

Caractéristiques de la cohorte ASSESS

Median age (years)	58 (51-67)
Female/male	93.6/6.4%)
Disease duration (years)	5 (2-9)
Focus score ≥ 1	318/352 (87.8%)
Anti-SSA +	59.2%
Anti-SSB +	33.5%
RF +	153/372 (41.1%)
ESSDAI	2.0 (0-7.0)
ESSPRI	5.7 (4.0-7.0)
Systemic involvement at enrollment	30.9%

395 patients : prélevés à l'inclusion (ADN, sérum, transcriptome sanguin)
Suivi > 15 years

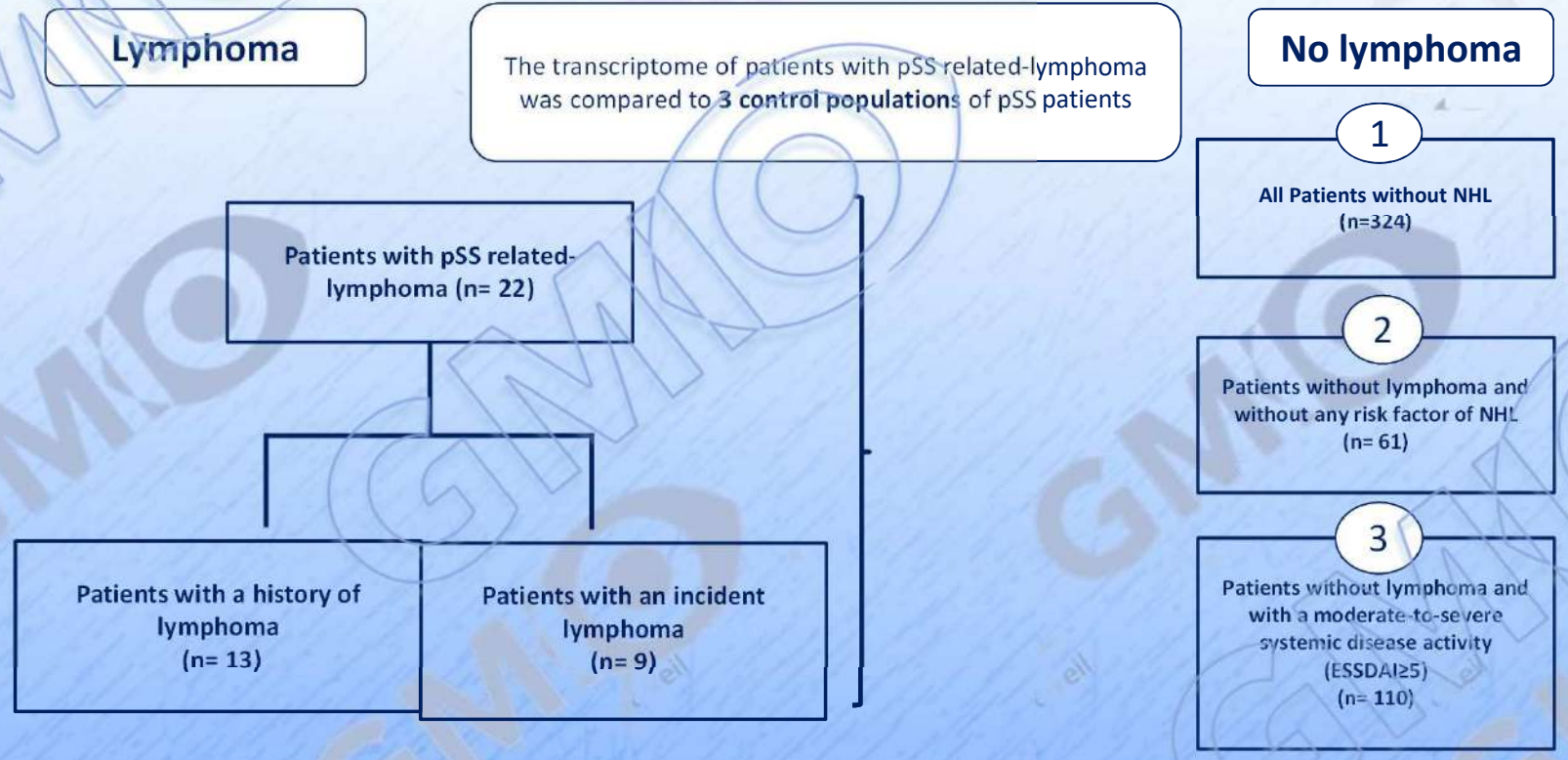
Gottenberg JE et al. Plos One 2013

Facteurs de risque de lymphome

- Clinique
  - Parotidomégalie
  - Adénopathie / Splénomegalie
  - Purpura
  - Activité systémique élevéé: ESSDAI score ≥ 5
- Examens complémentaires
  - Facteurs rhumatoides
  - Crryoglobulinémie
  - C4 bas
  - Pic monoclonal
  - Infiltrat salivaire marqué (focus score >3)
  - Lymphopénie (<1000/mm^3)
  - CD4/CD8 Ratio ≤ 0.8

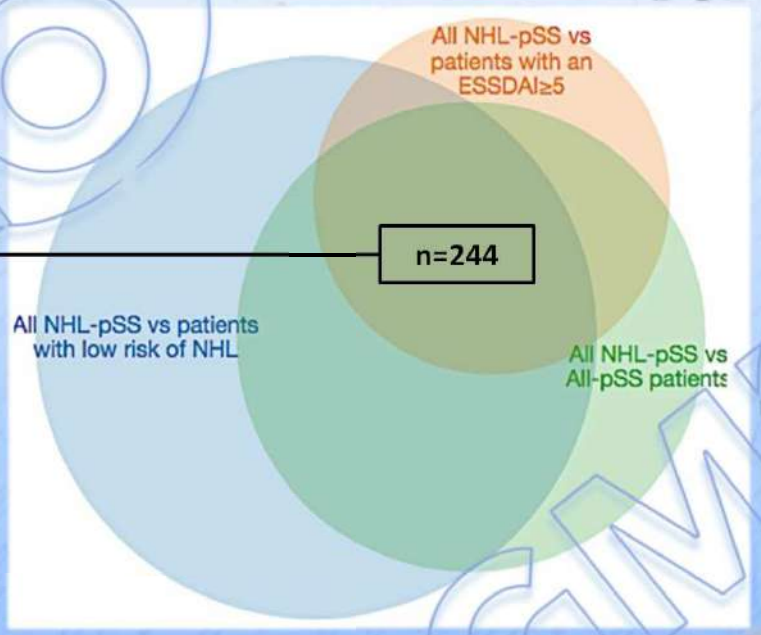
Nocturne G et al. Rheumatol. (Oxford) 2019

Analyse du transcriptome sanguin à l'inclusion dans la cohorte ASSESS



C7orf71 B4GALT1 LRRC36 SATL1 MARCH10 KRTAP4-3 ANO5 PIGS SERPINB11 TBCB OR51B5 KRT25 SNTB2 CLRN1 UCP3 MTRNR2L10 CCDC12 PLPPR4 RAB9A EMC7 OTUB1 NAALAD2 SIL1 PDGFC HIST1H2BB BARX2 MTFR1L CUEDC2 ANGPTL5 ARHGAP20 PAGE1 PPP1R32 EPDR1 TFIP11 IL6 ADH4 NSDHL LIF TUSC3 CCNB3 TXN2 MFSD13A MFSD14C CTNNAL1 CPXM1 ACOT2 NABP2 FSCN2 TNNT1 COQ8B CHCHD5 BRINP1 CDHR1 GNAT3 TRIM36 APH1A INSL6 GUSB ATG9A TMCO5A H1FOO NRM CCDC157 STK11IP FAM187B AADAC MIEN1 STPG4 STX5 TRAPPC3 VPS25 DNASE1L2 SIRT6 MYO1G THEM6 COPE GLTP CYBA FBXW5 PRSS56 KCNK5 RNF41 NUGGC ACAA1 HIST1H3E PRSS38 RASL10A GBP7 GALNT2 FAM183A ADCY7 COX8A C18orf65 MPZ COX5B CLIC1 DNASE1L1 SDHAF4 TTK IL12RB1 MANEAL HIST1H4I PI4K2A AP4M1 COLCA1 DESI1 MMP17 SIGLEC12 RPS6KA4 BTBD10 PGK1 SYNGR2 PDGFRB CCNB1 PGLS ZNF467 RAP2B ALPK2 SDHAF1 PAX2 TM9SF1 FAM90A1 COX17 HIST2H2AB SMIM14 PLA2G4D PDXK C5orf30 TMEM155 SMG8 CARS2 CMTM3 ALYREF WDR63 ALDOB WASF1 TADA3 RDH10 CDC25C PSME1 FAM160A2 NRN1 SRGAP1 AVPR1B CITED1 AGPAT4-IT1 NAPRT KCNE5 CDK5 PRR16 MIXL1 FAM241A ATP1B1 WSB2 SLC2A6 NDUFB3 FSCN1 HIST1H2BG ALDH4A1 TTC38 CORIN TMEM205 ZNF366 UQCRC1 KIAA0930 XPNPEP2 CD63 HLA-DMB TMEM170B EIF4EBP1 GPER1 KCNMB1 GCNT1 LIMK1 ADAP1 OSM SELENOT HIST1H2BI MRPL28 WDSUB1 TRPS1 SYCP3 CEBPD SPG11 ANXA4 POMP BAK1 CTSH RETN GZMB APOBEC3G SLC30A1 NAT1 SUSD1 TMEM165 SAP30 FMO5 HGF CALHM6 S100A6 GYG1 SLC7A7 SLAMF7 IDH1 GSTO1 FCN1 CPM RCAN2 **BTK** MPDU1 AGPAT4 CD300C S100A4 HIST1H3B DUSP3 MTHFD2 ERI1 MSC CLEC6A FGD2 CCR5 SMARCD3 WDR41 SGMS2 LILRA5 MVB12B SLC46A2 LGALS2 PATL2 CD300E CD86 LGALS1 HIST1H1B HK3 CD177 MS4A14 MS4A4A KYNU FLVCR2 IL18RAP ZNF683 LOXHD1 MS4A7 PLA2G7

A total of **244 genes were over-expressed** in the comparisons of pSS **patients with lymphoma** to the **three control populations** (Low-risk of NHL; ESSDAI≥5; All patients without NHL)



Elévation de BTK avant la survenue de lymphome

Table S5. Bruton's tyrosine kinase (BTK) gene expression by real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR) in peripheral blood of patients with lymphoma (pSS-NHL; n=21), patients with incident lymphoma (i-pSS-NHL ; n=9) and patients with history of lymphoma at enrolment (h-pSS-NHL; n=12) versus patients without lymphoma and with no risk factor of lymphoma (low-risk pSS; n=21) and with moderate-to-severe systemic disease activity (ESSDAI ≥ 5; n=21).

	pSS-NHL vs low-risk pSS		i-pSS-NHL vs low-risk pSS		h-pSS-NHL vs low-risk pSS		pSS-NHL vs ESSDAI ≥ 5		i-pSS-NHL vs ESSDAI ≥ 5		h-pSS-NHL vs ESSDAI ≥ 5	
Official gene symbol	**Fold change**	**P value**	**Fold change**	**P value**	**Fold change**	**P value**	**Fold change**	**P value**	**Fold change**	**P value**	**Fold change**	**P value**
BTK	1.5	0.0003	1.3	0.005	1.7	0.002	1.5	0.003	1.3	0.04	1.7	0.008

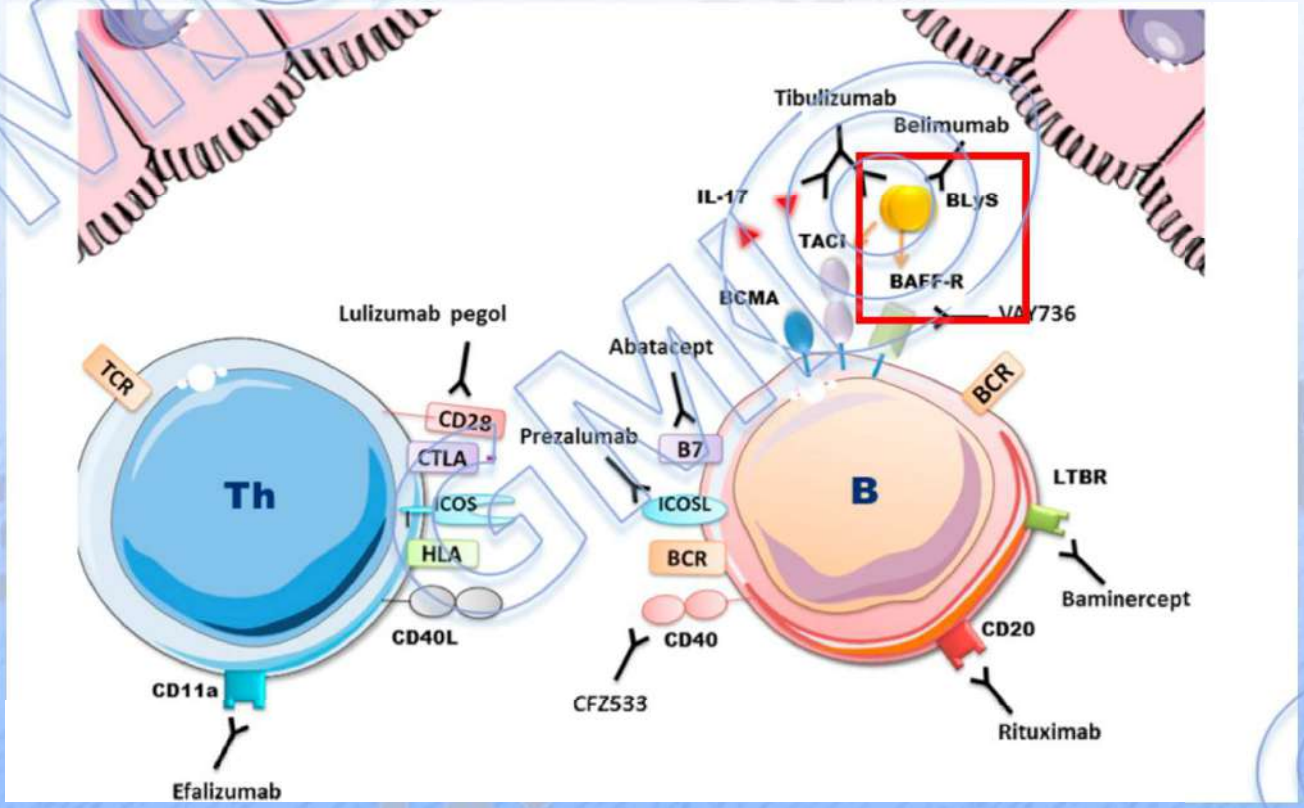
Validation data of BTK gene expression obtained by qRT-PCR were compared between groups using the Mann-Whitney test (P values ≤ 0.05 were considered statistically significant). BTK: Bruton's tyrosine kinase; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; NHL: non-Hodgkin's lymphoma ; h-NHL: a history of lymphoma at enrolment; i-NHL: incident lymphoma occuring during follow-up ; pSS: primary Sjögren's syndrome.

Facteurs de risque de lymphome

Characteristic	OR[1]	95% CI[1]	p-value
BTK (1/10)	1.3576	1.1433, 1.6430	**<0.001**
CD4/CD8<=8	10.6221	2.4948, 44.1518	**0.001**
Low C4	4.1555	1.4346, 13.8788	**0.012**
BAFF	1.0007	1.0003, 1.0012	**0.001**

[1] OR = Odds Ratio, CI = Confidence Interval

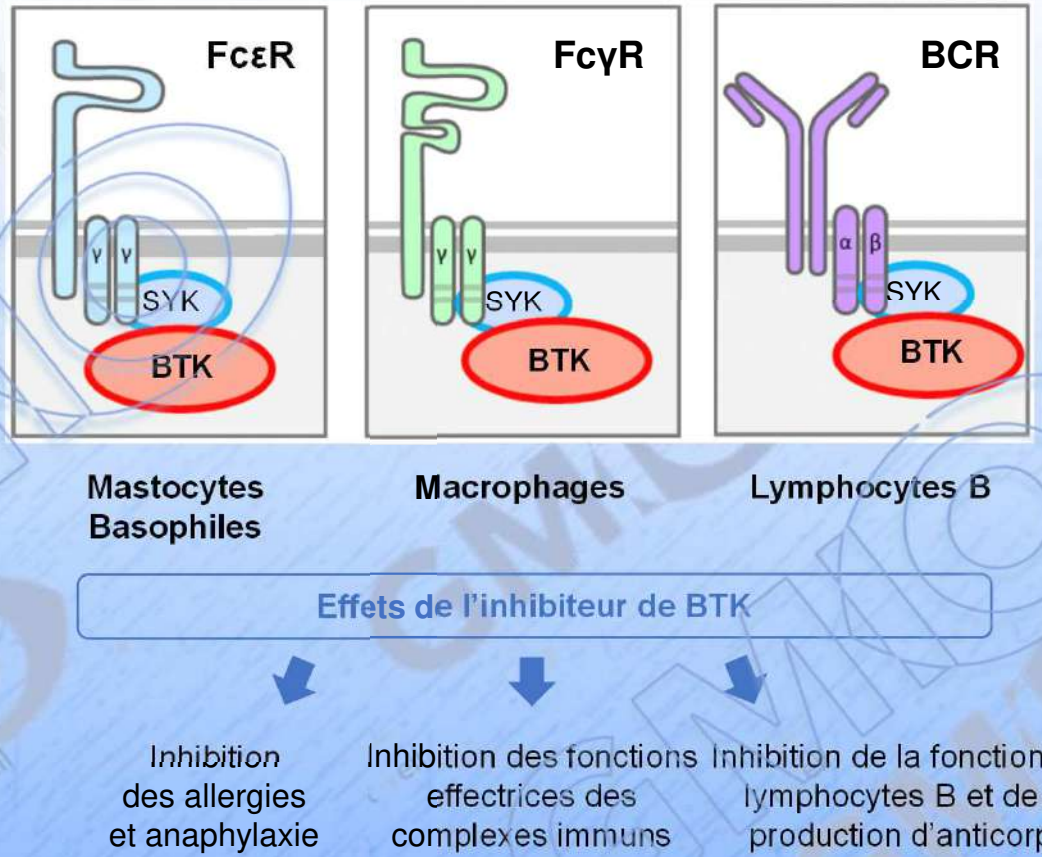
Duret PM, et al. SFR 2022, manuscrit en révision



Felten R, et al. Autoimmune Rev 2019

Le rémibrutinib, un inhibiteur de BTK, dans le syndrome de Sjögren *(1)*

- La *Bruton's tyrosine kinase* (BTK) joue un rôle crucial dans la signalisation du BCR et du FcγR
- Rémibrutinib : inhibiteur de BTK, responsable d'une diminution de la réponse cellulaire B et de la production d'anticorps

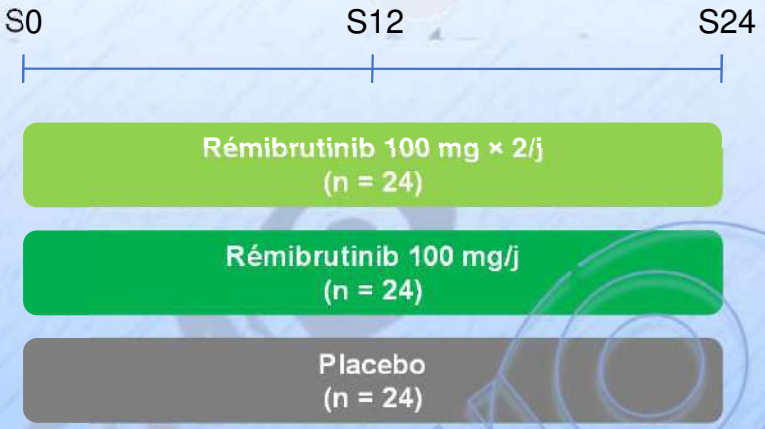


ACR 2022 - D'après Dörner T et al., abstr. 1113, actualisé

Le rémibrutinib, un inhibiteur de BTK, dans le syndrome de Sjögren (2)

Étude LOUiSSe : étude de phase II évaluant le rémibrutinib

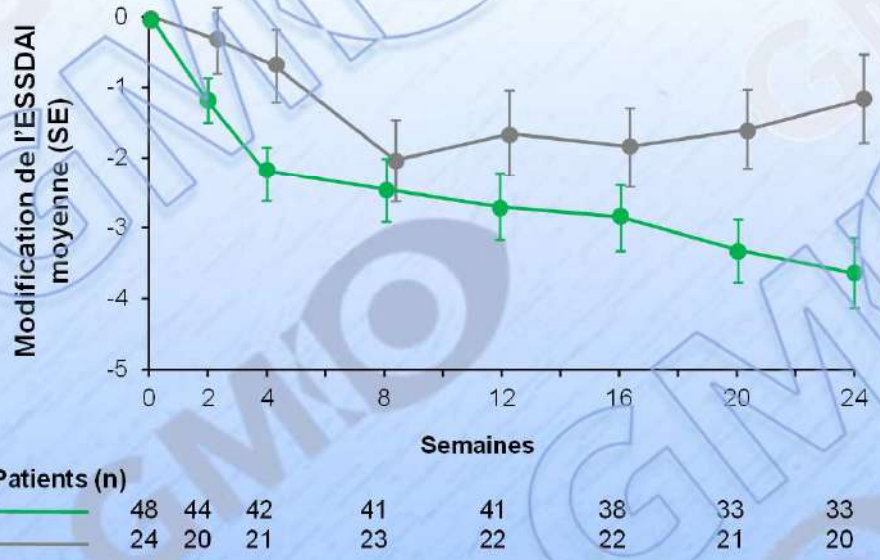
- Rémibrutinib : inhibiteur de *Bruton's tyrosine kinase* (BTK) ➔ diminution de la réponse cellulaire B et de la production d'Ac
- Critères d'inclusion
  - Âge entre 18 et 75 ans
  - Critères ACR-EULAR 2016
  - ESSDAI ≥ 5 ; ESSPRI ≥ 5
  - Présence d'anti-SSA dans les 3 mois précédant l'inclusion
  - Flux salivaire > 0 mL/min
- Critère de jugement principal : réponse ESSDAI à S24
- Critères secondaires
  - Réponse ESSPRI à S24
  - Réponse ESSPRI, FACIT-F, EQ-5D, et EVA du médecin au cours du temps
- Caractéristiques de la population
  - Rémibrutinib : âge (moy.) = 52,2 ans, durée de la maladie (moy.) = 9,5 ans ; ESSDAI (moy.) = 9 ; ESSPRI (moy.) = 6,7 ; flux salivaire = 0,08 mL/min
  - Placebo : âge (moy.) = 51 ans, durée de la maladie (moy.) = 9,9 ans ; ESSDAI (moy.) = 10 ; ESSPRI (moy.) = 6,3 ; flux salivaire = 0,07 mL/min



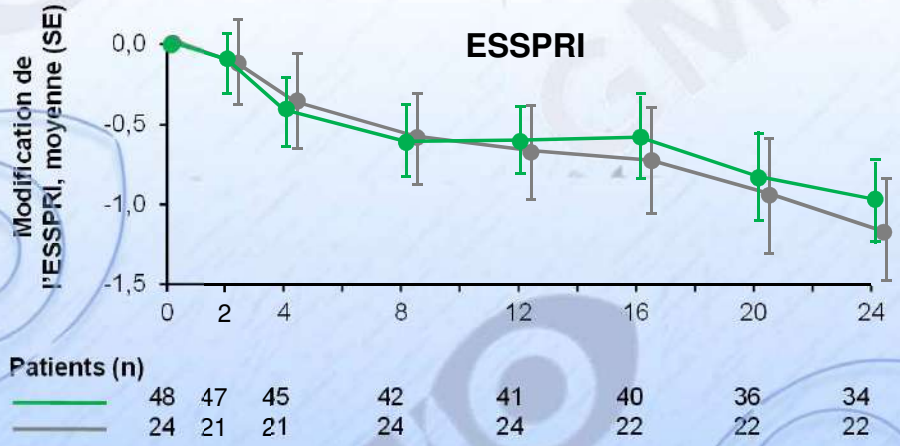
ACR 2022 - D'après Dörner T et al., abstr. 1113, actualisé

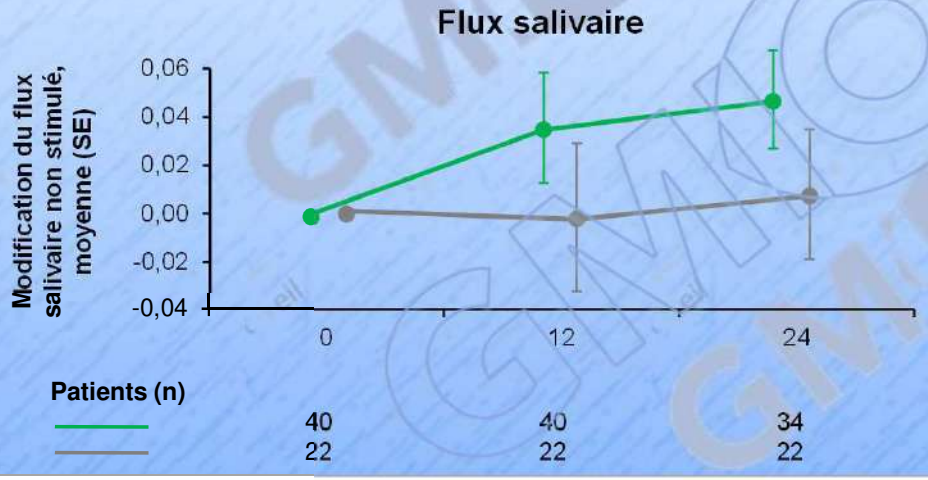
Le rémibrutinib, un inhibiteur de BTK, dans le syndrome de Sjögren *(3)*

Critère principal



Critères secondaires





- ▶ **Amélioration de l'ESSDAI**
- ⚠ **Pas de différence pour l'ESSPRI**
- ▶ **Tendance à l'amélioration du flux salivaire**

ACR 2022 - D'après Dörner T et al., abstr. 1113, actualisé

BAFF

Essai anti-BAFFR (ianalumab)

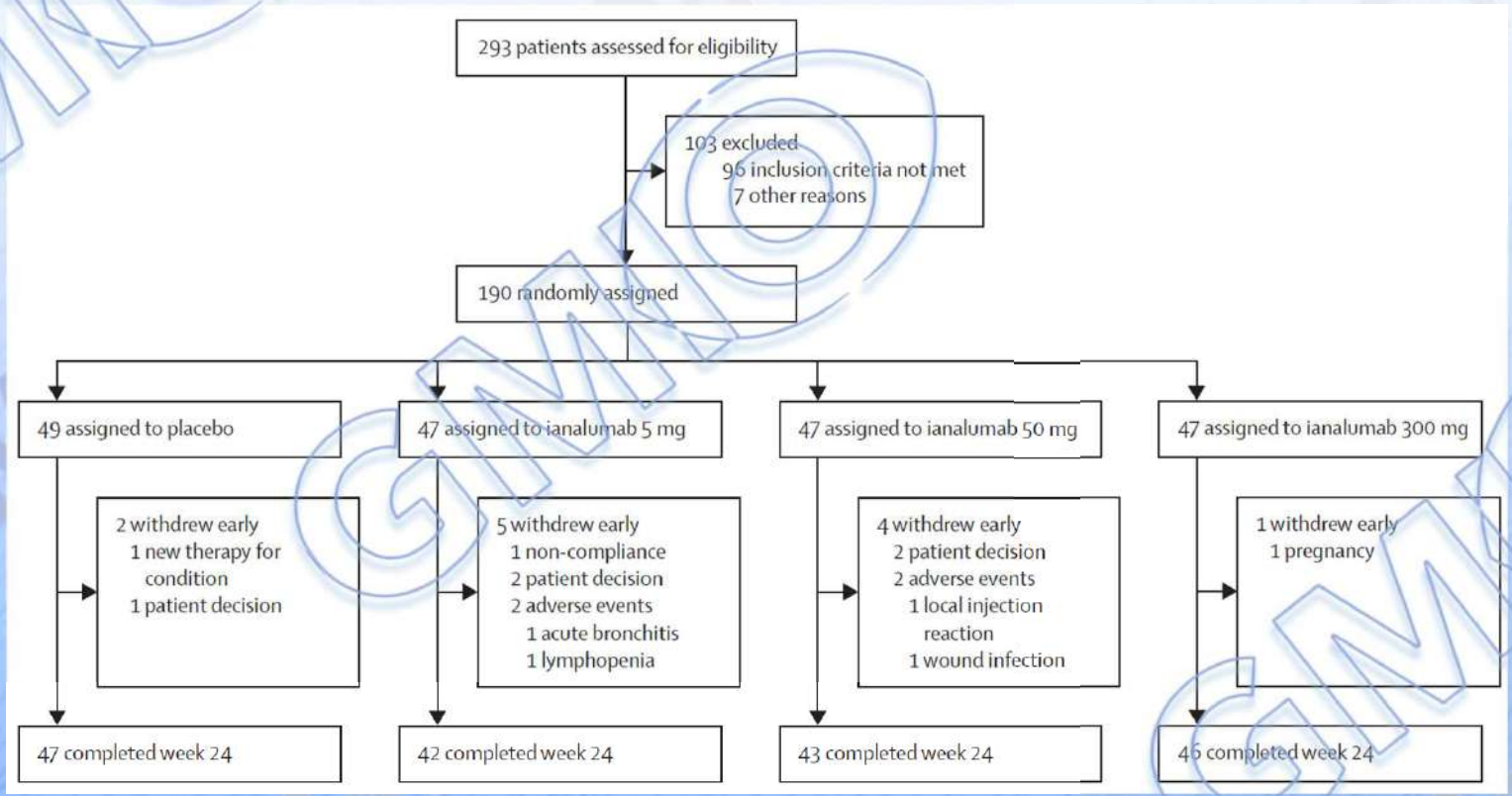


Figure 1: **Trial profile**

Lancet 2022; 399: 161–71

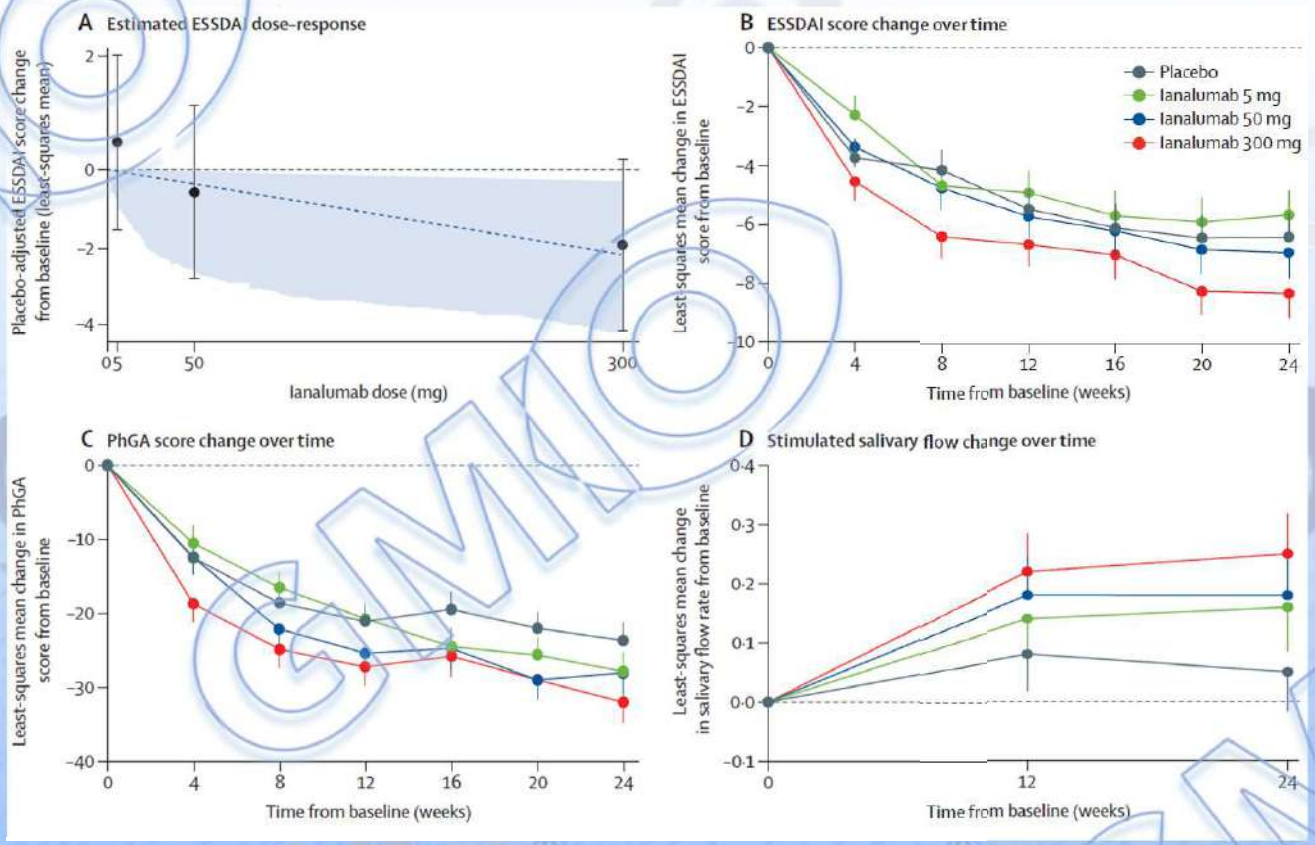
Tolérance

	Placebo (n=49)	Ianalumab 5 mg (n=47)	Ianalumab 50 mg (n=47)	Ianalumab 300 mg (n=47)
Patients with any adverse events	41 (84%)	40 (85%)	39 (83%)	44 (94%)
Patients with any serious adverse events	4 (8%)	0	1 (2%)	2 (4%)
Patients discontinued for any adverse events	0	2 (4%)	2 (4%)	0
Common adverse events of special interest by system organ class and preferred term				
General disorders and administration site conditions	9 (18%)	7 (15%)	13 (28%)	29 (62%)
Local injection site reaction	2 (4%)	4 (9%)	9 (19%)	25 (53%)
Injury, poisoning, and procedural complications	8 (16%)	8 (17%)	7 (15%)	8 (17%)
Systemic injection related reaction	2 (4%)	6 (13%)	5 (11%)	4 (9%)
Blood and lymphatic disorders	5 (10%)	5 (11%)	6 (13%)	7 (15%)
Lymphopenia	3 (6%)	2 (4%)	4 (9%)	1 (2%)
Leukopenia	2 (4%)	3 (6%)	2 (4%)	6 (13%)
Neutropenia	1 (2%)	3 (6%)	1 (2%)	4 (9%)
Infections and infestations	28 (57%)	25 (53%)	22 (47%)	23 (49%)
Nasopharyngitis	5 (10%)	4 (9%)	2 (4%)	7 (15%)
Upper respiratory tract infection	4 (8%)	3 (6%)	3 (6%)	2 (4%)
Urinary tract infection	4 (8%)	4 (9%)	2 (4%)	0
Sinusitis	4 (8%)	3 (6%)	2 (4%)	0
Pneumonia	3 (6%)	0	0	1 (2%)
Conjunctivitis	3 (6%)	3 (6%)	2 (4%)	2 (4%)
Bronchitis	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Oral herpes	1 (2%)	3 (6%)	1 (2%)	0
Tracheobronchitis	0	0	0	3 (6%)
Other common adverse events by preferred term				
Headache	7 (14%)	4 (9%)	4 (9%)	4 (9%)
Diarrhoea	4 (8%)	3 (6%)	2 (4%)	3 (6%)
Rash	3 (6%)	3 (6%)	2 (4%)	1 (2%)
Arthralgia	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Back pain	3 (6%)	0	4 (9%)	2 (4%)
Gastro-oesophageal reflux disease	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Lymphocyte count decreased	0	3 (6%)	0	1 (2%)
Dizziness	0	1 (2%)	0	3 (6%)

Adverse events are shown by preferred term and system organ class in the MedDRA22.0 dictionary. Common adverse events are defined as those in 5% or more patients in any treatment group. Data are numbers of patients, rather than numbers of events, some patients might have had more than one event.

Lancet 2022; 399: 161–71

Critère principal : essai ianalumab (anti-BAFFR)



(A) Placebo-adjusted ESSDAI score changes from baseline by dose (dots are least-squares mean and error bars are 95% CIs) at week 24, and the fitted dose-response curve (dotted line); shaded area is the 95% confidence band. (B) ESSDAI score changes from baseline over time by treatment group. (C) PhGA score changes from baseline over time by treatment group. (D) Stimulated salivary flow changes from baseline over time by treatment group.

Lancet 2022; 399: 161–71

Critères secondaires : essai ianalumab (anti-BAFFR)

	Baseline		Week 24		Mean placebo adjusted difference, least-squares mean (95% CI)	p value
	Placebo	Ianalumab 300 mg	Placebo	Ianalumab 300 mg		
ESSDAI score	13·0 (7·1)	13·1 (6·7)	7·0 (5·1)	4·9 (3·9)	−1·92 (−4·15 to 0·32)	0·092
ESSPRI score	7·3 (1·1)	6·9 (1·7)	5·5 (1·8)	5·1 (2·3)	−0·06 (−0·86 to 0·74)	0·89
FACIT-F score	24·0 (9·7)	26·7 (11·2)	33·0 (10·6)	35·3 (10·6)	0·31 (−3·58 to 4·20)	0·87
SF-36 physical component summary score	38·8 (7·2)	39·9 (7·1)	42·5 (8·8)	45·1 (7·6)	1·8 (−0·8 to 4·5)	0·17
SF-36 mental component summary score	40·0 (9·7)	42·1 (12·0)	45·0 (10·4)	47·3 (10·4)	1·00 (−2·5 to 4·5)	0·57
PhGA, mm	51·6 (16·7)	53·4 (14·7)	30·0 (17·3)	23·8 (16·6)	−8·4 (−15·5 to −1·2)	0·022
PaGA, mm	61·0 (18·2)	62·0 (21·7)	45·7 (23·2)	41·0 (23·5)	−4·77 (−14·2 to 4·7)	0·32
Stimulated salivary flow, mL/min	0·41 (0·51)	0·77 (0·88)	0·57 (0·64)	1·01 (0·98)	0·20 (0·01 to 0·38)	0·037
Unstimulated salivary flow, mL/min	0·11 (0·18)	0·22 (0·47)	0·12 (0·20)	0·17 (0·19)	−0·01 (−0·10 to 0·07)	0·73
Tear flow right, mm	6·4 (6·7)	6·8 (8·6)	7·7 (9·1)	8·7 (8·6)	0·3 (−2·3 to 2·9)	0·83
Tear flow left, mm	7·5 (8·8)	8·5 (9·8)	7·8 (9·3)	10·1 (9·4)	1·4 (−1·3 to 4·1)	0·30
IgG, g/dL	17·4 (7·1)	17·7 (7·5)	17·1 (6·7)	15·1 (5·6)	−2·0 (−2·8 to −1·2)	<0·0001
Rheumatoid factor, kIU/L	92 (136)	57 (104)	101 (180)	43 (92)	−15·8 (−38·1 to 6·5)	0·16
BAFF, pg/mL	1159 (475)	1169 (411)	1160 (374)	4098 (1710)	2907 (2507 to 3307)	<0·0001

Data are mean (SD) except where otherwise stated. p values had no adjustment for multiplicity. BAFF=B-cell activating factor. ESSDAI=EULAR Sjögren's Syndrome Disease Activity Index. ESSPRI=EULAR Sjögren's Syndrome Patient Reported Index. EULAR=European Alliance of Associations for Rheumatology (formerly European League Against Rheumatism). FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue. PaGA=Patient's Global Assessment; PhGA=Physician's Global Assessment. SF-36=Short Form (36) Health Survey.

Lancet 2022; 399: 161–71

Progrès dans l'évaluation de la réponse aux traitements

Progrès dans l'évaluation de la réponse aux traitements

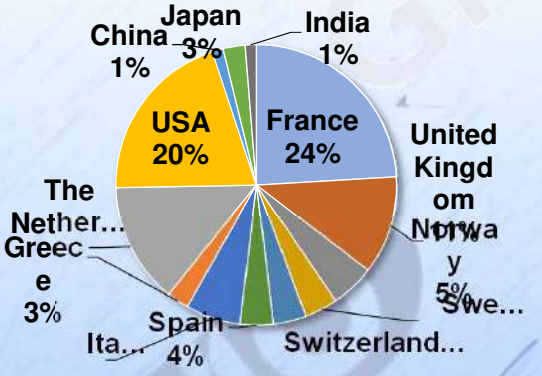
Novel clinical endpoint:
the Sjögren's Tool for Assessing Response to treatment (STAR)

Methodology:

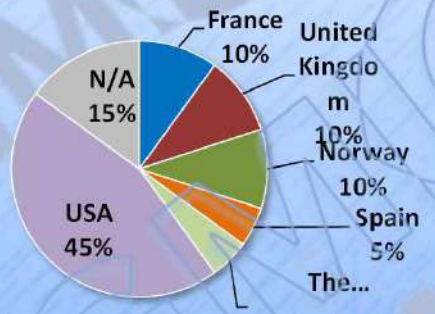
- **Data, patient, and expert driven**
  - Analysis on dataset from **9 clinical trials**
  - Consensual building through a **Delphi process**

Trial	Arms	N patients	ESSDAI	ESSPRI
TEARS	RTX/Placebo	120 (1:1)	✓	✓
TRACTISS	RTX/Placebo	133 (1:1)	✓	✓
ETAP	Toci/placebo	110 (1:1)	✓	✓
JOQUER	HCQ/Placebo	120 (1:1)	✓	✓
ASAP-III	ABA/Placebo	88 (1:1)	✓	✓
Baminercept	Baminercept/Placebo	52 (2:1)	✓	✓
Anti-CD40 PoC Novartis	Anti-CD40/PBO Cohort 1 and 2	69 (2:1)	✓	✓
Anti-BAFFR PoC Novartis	Anti-BAFFR/PBO Cohort 1 and 2	25 (1:1)	✓	✓
RepurpSS-I	HCQ+LEF/PBO	29 (2:1)	✓	✓

EXPERTS
N = 79
Mean years of experience = 18,9

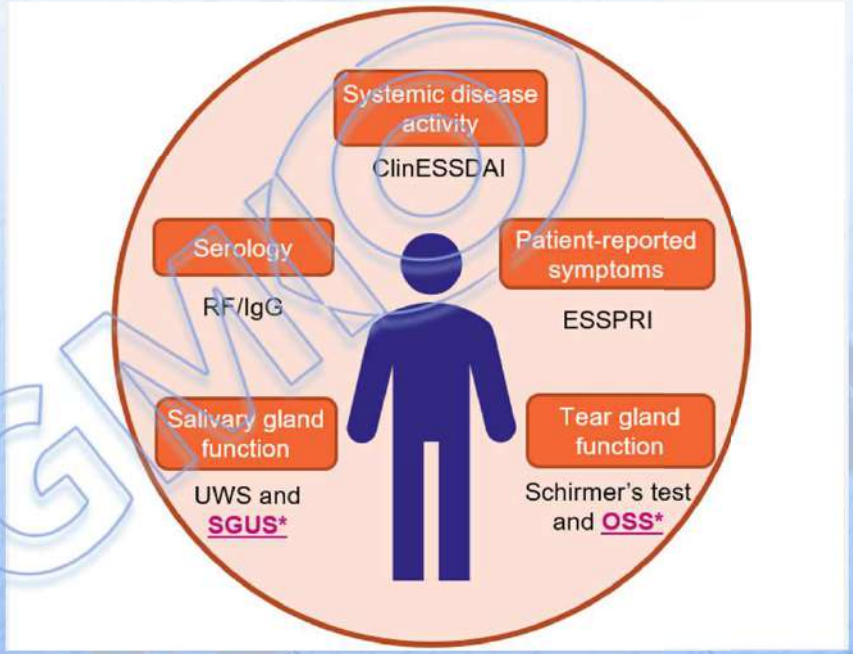


PATIENTS
N = 20
Mean age (years) = 58,3



Prise en compte de l'atteinte ophtalmologique !

The Sjögren's Tool for Assessing Response to treatment (STAR)



R. Seror ARD 2022

The Sjögren's Tool for Assessing Response to treatment (STAR)

Domain	Point	Definition of response
Systemic activity	3	Decrease of clinESSDAI ≥ 3
Patient reported outcome	3	Decrease of ESSPRI ≥ 1 point or ≥ 15%
Lachrymal gland function	1	Schirmer: If abnormal score at baseline: increase ≥ 5 mm from baseline If normal score at baseline: no change to abnormal or Ocular Staining Score: If abnormal score at baseline: decrease ≥ 2 points from baseline If normal score at baseline: no change to abnormal
Salivary gland function	1	Unstimulated Whole Salivary Flow: If score > 0 at baseline: increase ≥ 25% from baseline If score is 0 at baseline: any increase in UWSF from baseline or Ultrasound: Decrease ≥ 25% in total Hocevar score from baseline
Biological	1	IgG: decrease ≥ 10% or Rheumatoid factor: decrease ≥ 25%
Preliminary STAR responder		≥ 5 points

R. Seror ARD 2022

Conclusions

- Progrès thérapeutiques attendus : 4 essais positifs en 2 ans !

- Ces progrès concernent surtout actuellement les complications systémiques