

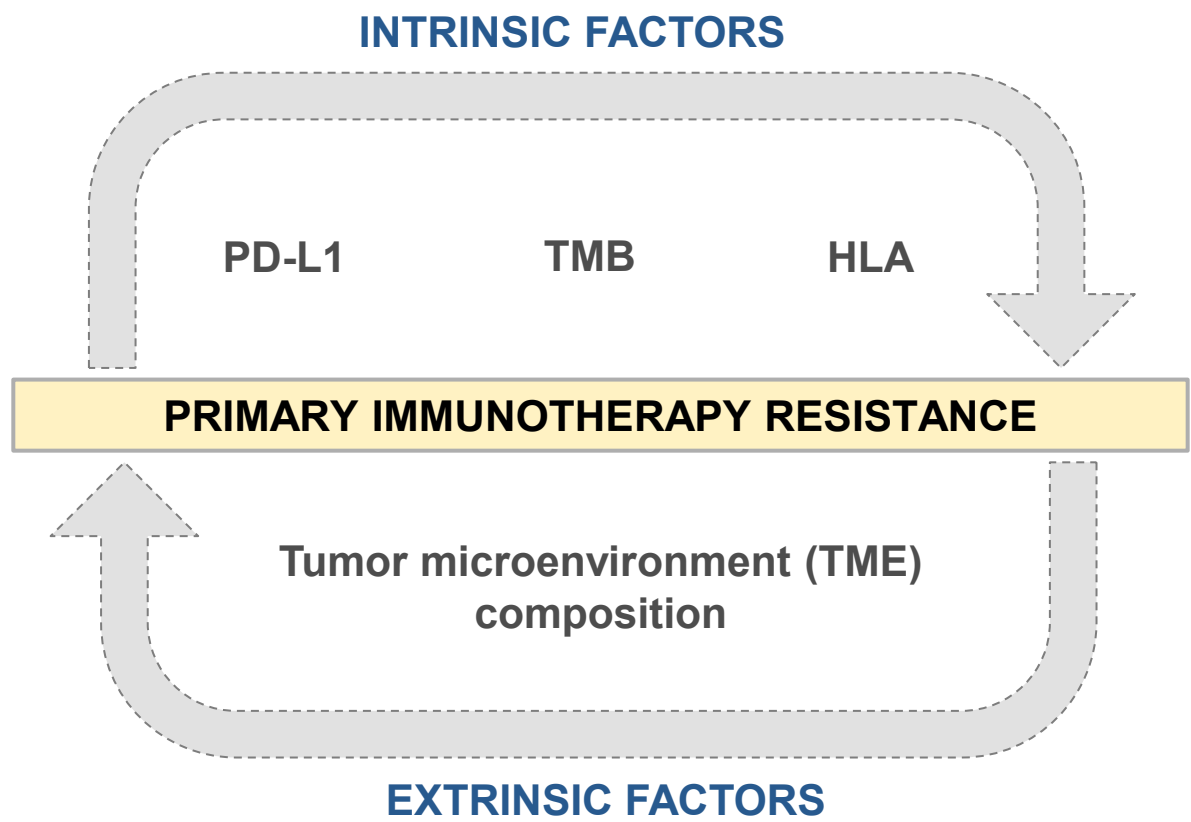
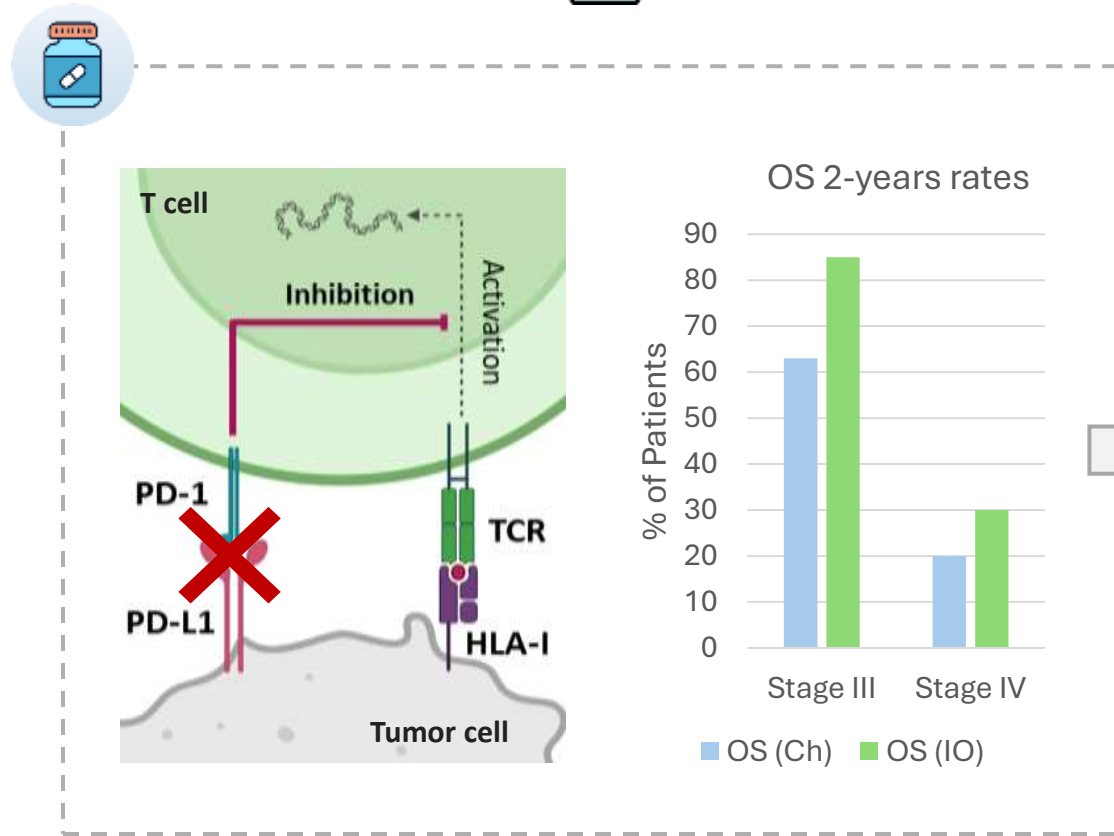
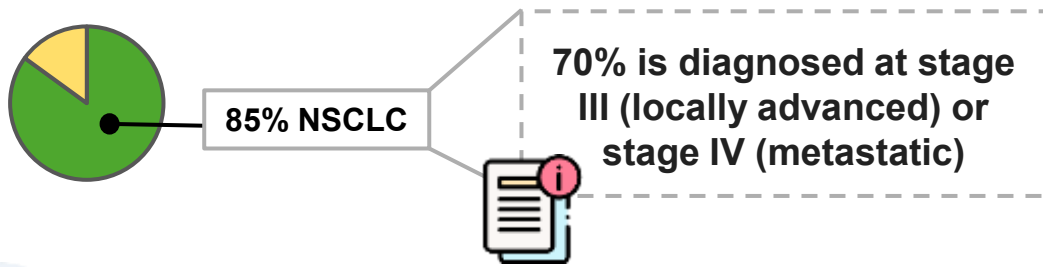
16th
CONGRESS
Lung **ON**
CANCER

BARCELONA
27 / 28
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Plasmatic CXCL13 as a biomarker of primary resistance to immunotherapy in non-small cell lung cancer

Marta Molina Alejandre

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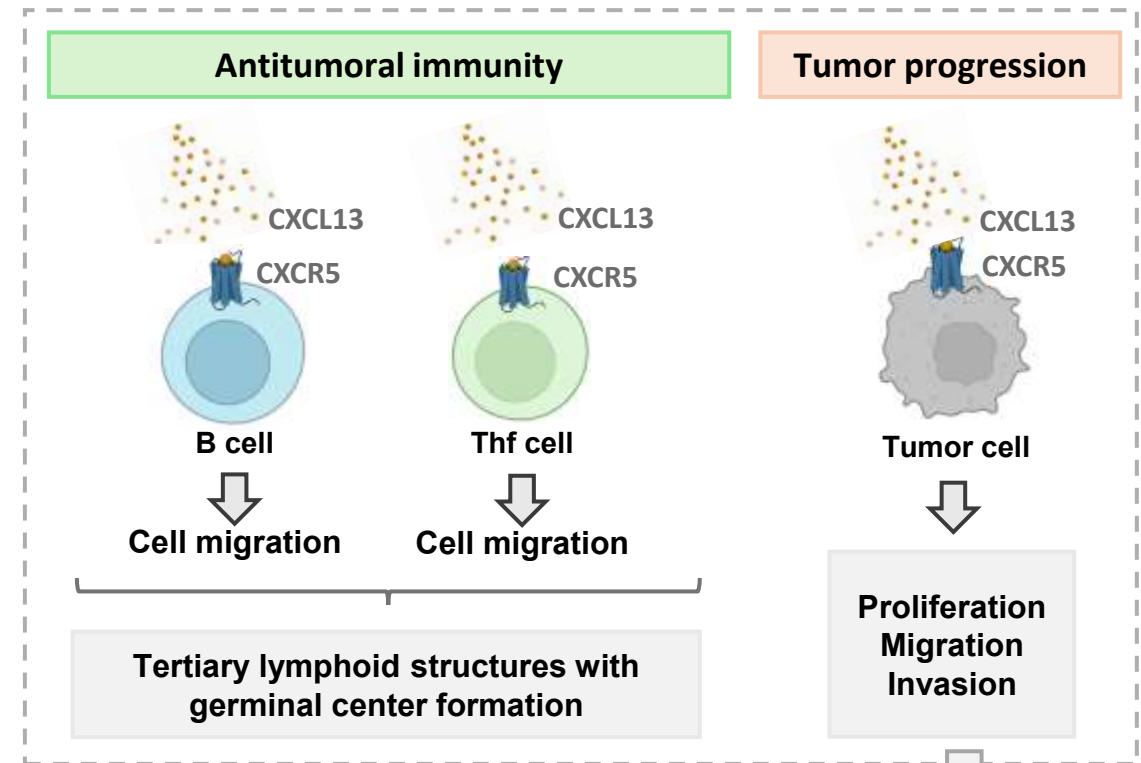




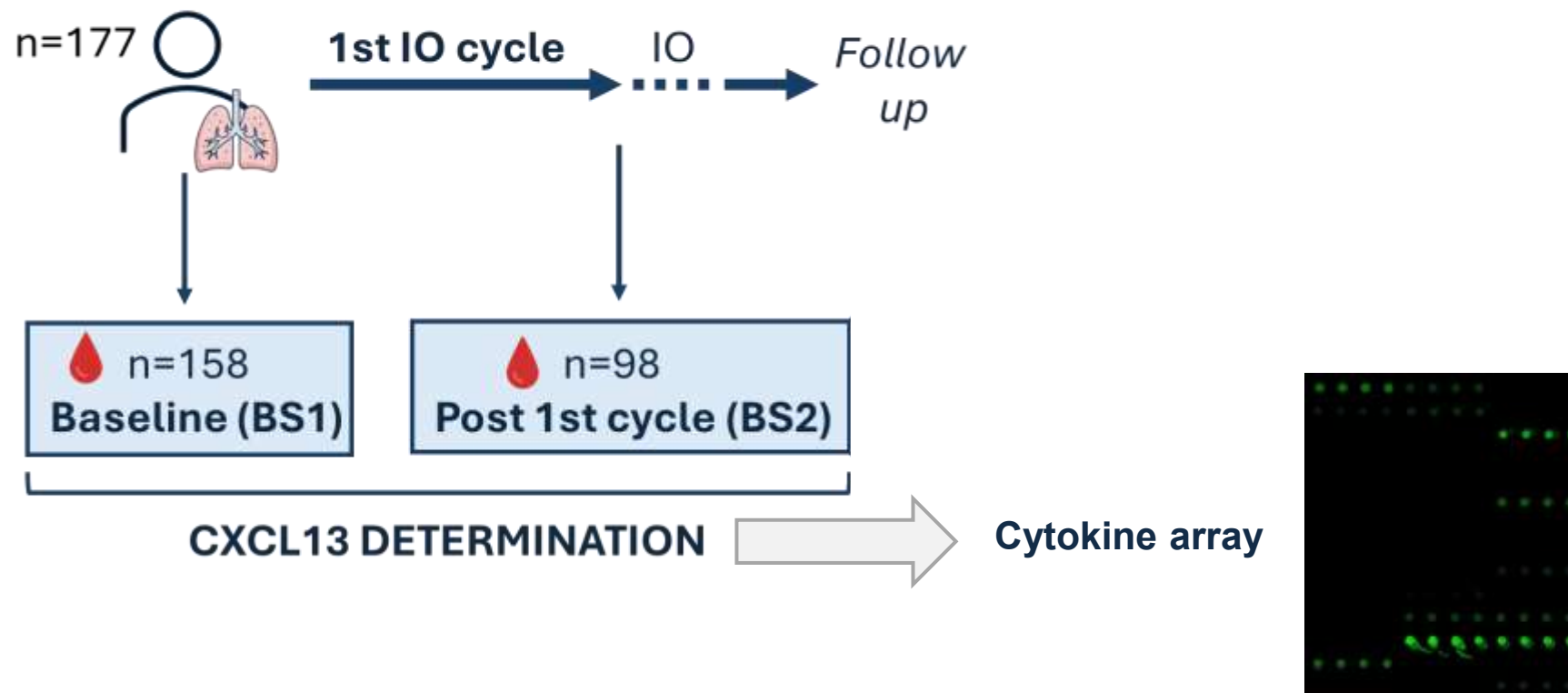
CXCL13/CXCR5 axis is key in tumor-immune processes



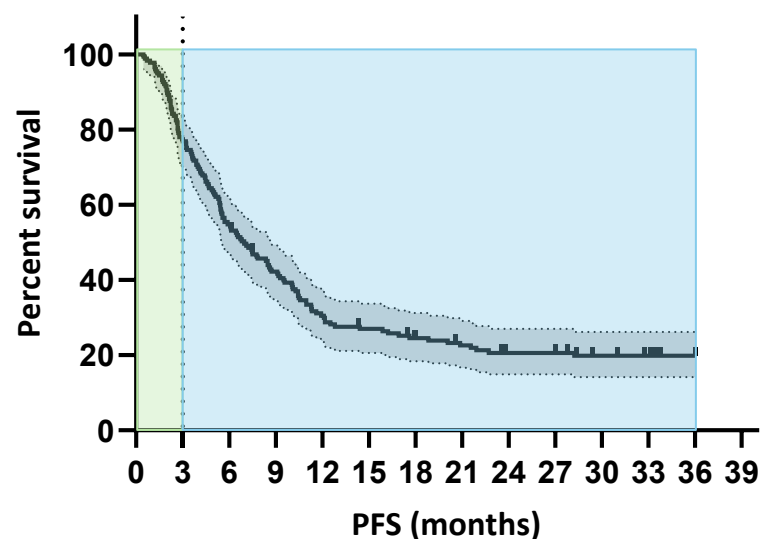
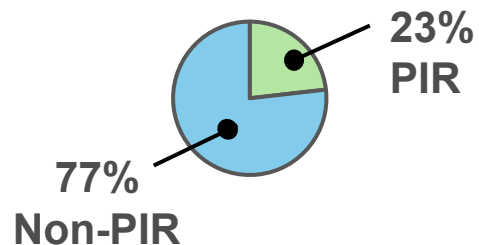
Plasma levels of **CXCL13** may be associated with **primary resistance to immunotherapy** and could potentially serve as a **non-invasive biomarker** of clinical outcomes.



Elevated systemic levels of CXCL13 have been associated with metastatic progression, poor prognosis, and resistance to immunotherapeutic approaches.

METASTATIC NSCLC (BLI-O COHORT)*PIR = Disease progression within the first 3 months of IO*

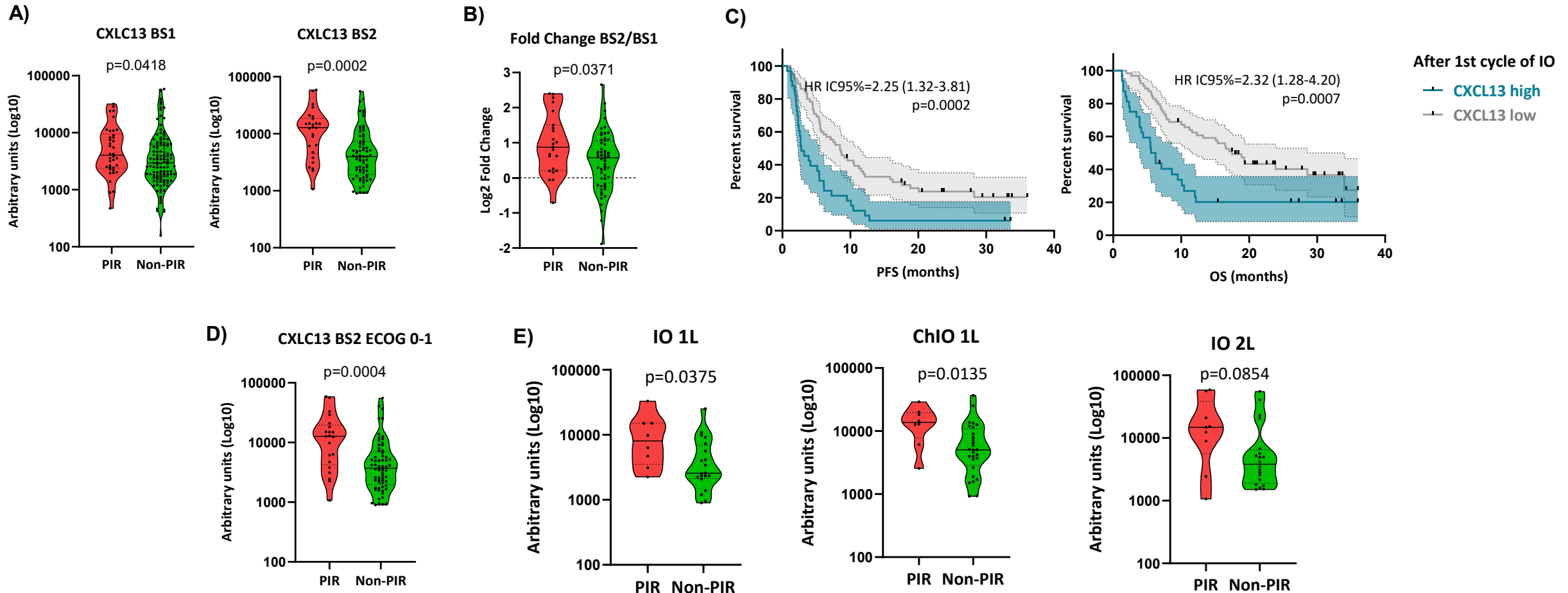
PRIMARY IMMUNOTHERAPY RESISTANCE



3-month PFS = 76.8% (95%CI = 82.4-69.6)
24-month PFS = 20.6% (95%CI = 27.0-14.9)

Characteristic	All patients (177, 100%)	PIR patients (41, 23.2%)	Non-PIR patients (136, 76.8%)	P value
Age, mean (SD)	66.0 (9.0)	67.2 (9.2)	65.6 (8.9)	0.7348
Sex (n, %)				0.1882
Female	44 (24.9)	7 (17.1)	37 (27.2)	
Male	133 (75.1)	34 (82.9)	99 (72.8)	
Smoking History (n, %)				0.0714
Never	12 (6.8)	5 (12.2)	7 (5.1)	
Former	94 (53.1)	25 (61.0)	69 (50.7)	
Smoker	71 (40.1)	11 (26.8)	60 (44.1)	
ECOG (n, %)				0.1460
0	50 (28.2)	11 (26.8)	39 (28.7)	
1	104 (58.8)	21 (51.2)	83 (61.0)	
2	23 (13.0)	9 (22.0)	14 (10.3)	
Histologic characteristics (n, %)				0.4940
Adenocarcinoma	111 (62.7)	22 (53.7)	89 (65.4)	
Squamous carcinoma	44 (24.9)	13 (31.7)	31 (22.8)	
Adenosquamous carcinoma	2 (1.1)	0 (0)	2 (1.5)	
Large cell carcinoma	3 (1.7)	1 (2.4)	2 (1.5)	
Other	2 (1.1)	0 (0)	2 (1.5)	
NOS or undifferentiated	13 (7.3)	5 (12.2)	8 (5.9)	
Unknown	2 (1.1)	0 (0)	2 (1.5)	
Cancer stage (n, %)				NE
IV	177 (100)	41 (100)	136 (100)	
Treatment (n, %)				0.2689
Immunotherapy 1st line	57 (32.2)	10 (24.4)	47 (34.6)	
Chemoimmunotherapy 1st line	53 (29.9)	11 (26.8)	42 (30.9)	
Immunotherapy 2nd line	60 (33.9)	19 (46.3)	41 (30.1)	
Unknown	7 (4)	1 (2.4)	6 (4.4)	

High levels of CXCL13 after IO are associated with PIR and poor prognosis in metastatic NSCLC...



...independently of ECOG, type of treatment, and treatment line

Klein, S. et al. Sex differences in immune responses. *Nat Rev Immunol* (2016)

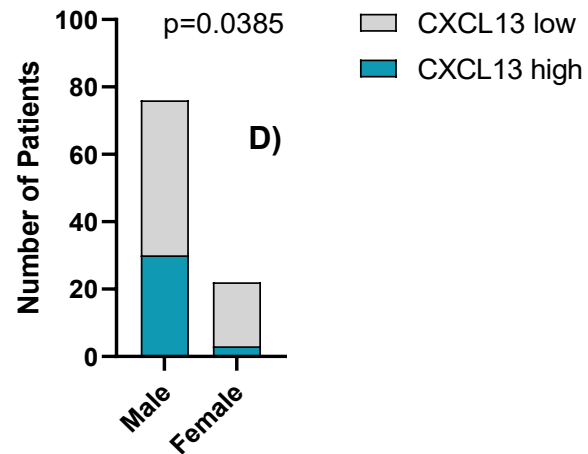
Sex differences in immune responses

Sabra L. Klein¹ and Katie L. Flanagan²

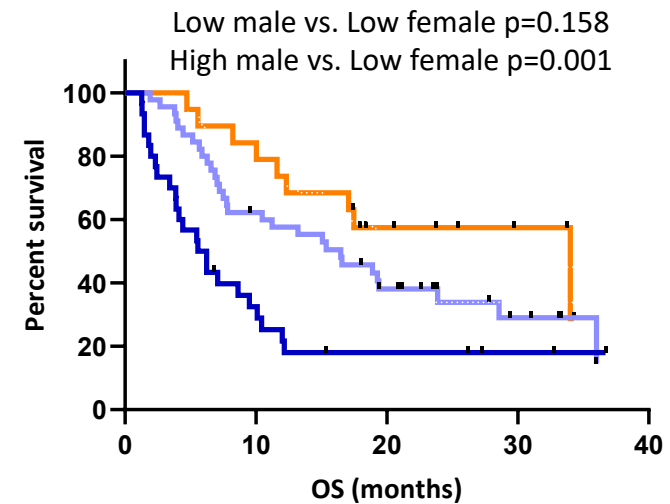
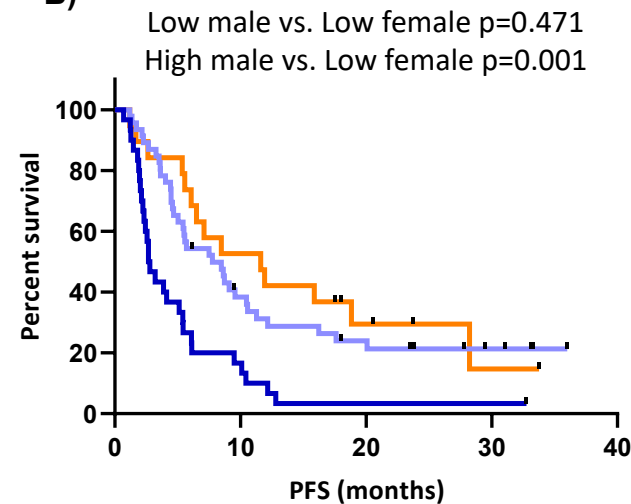
Abstract Males and females differ in their immunological responses to foreign and self-antigens and show distinctions in innate and adaptive immune responses. Certain immunological sex differences are present throughout life, whereas others are only apparent after puberty and before reproductive senescence, suggesting that both genes and hormones are involved. Furthermore, early environmental exposures influence the microbiome and have sex-dependent effects on immune function. Importantly, these sex-based immunological differences contribute to variations in the incidence of autoimmune diseases and malignancies, susceptibility to infectious diseases and responses to vaccines in males and females. Here, we discuss these differences and emphasize that sex is a biological variable that should be considered in immunological studies.

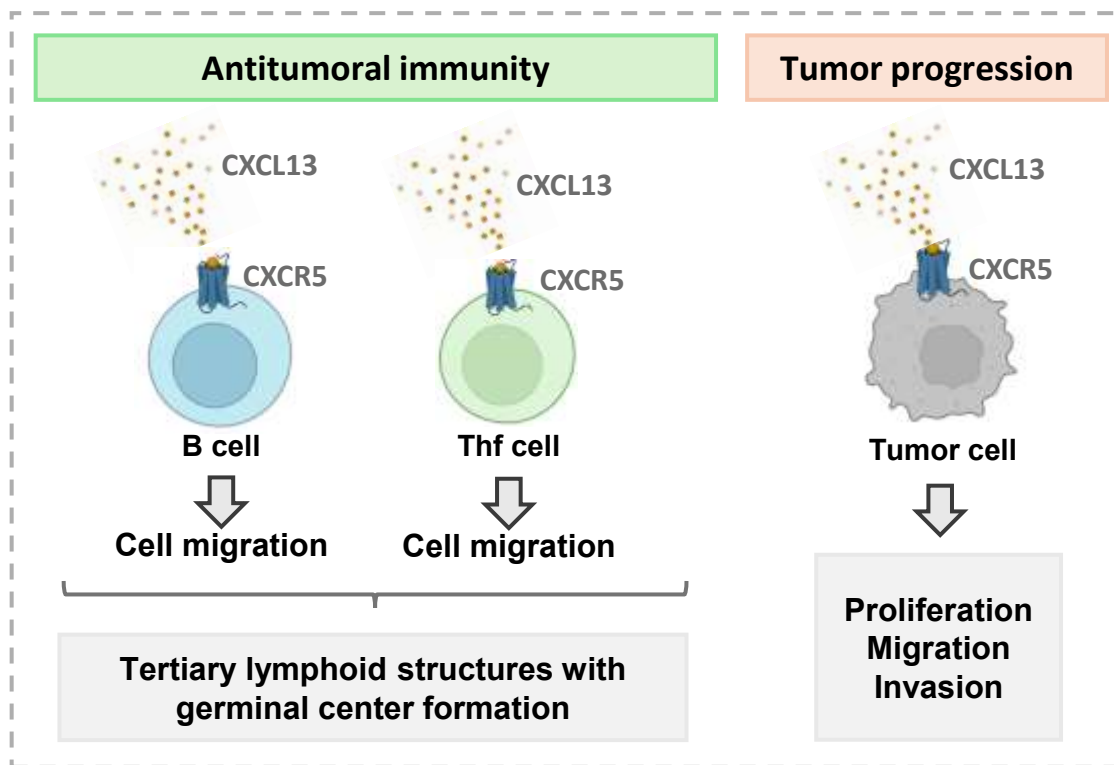
Female are mainly BS2 CXCL13 low patients, with survival rates were similar to low BS2 CXCL13 male

A)



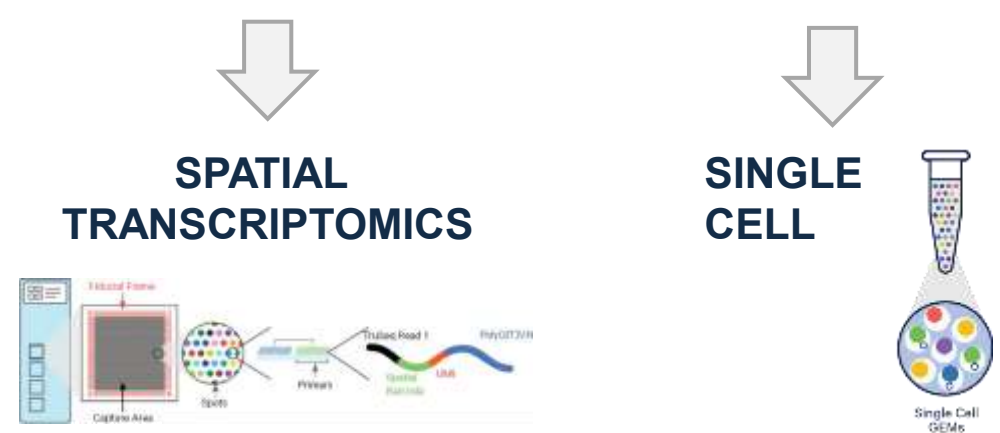
B)



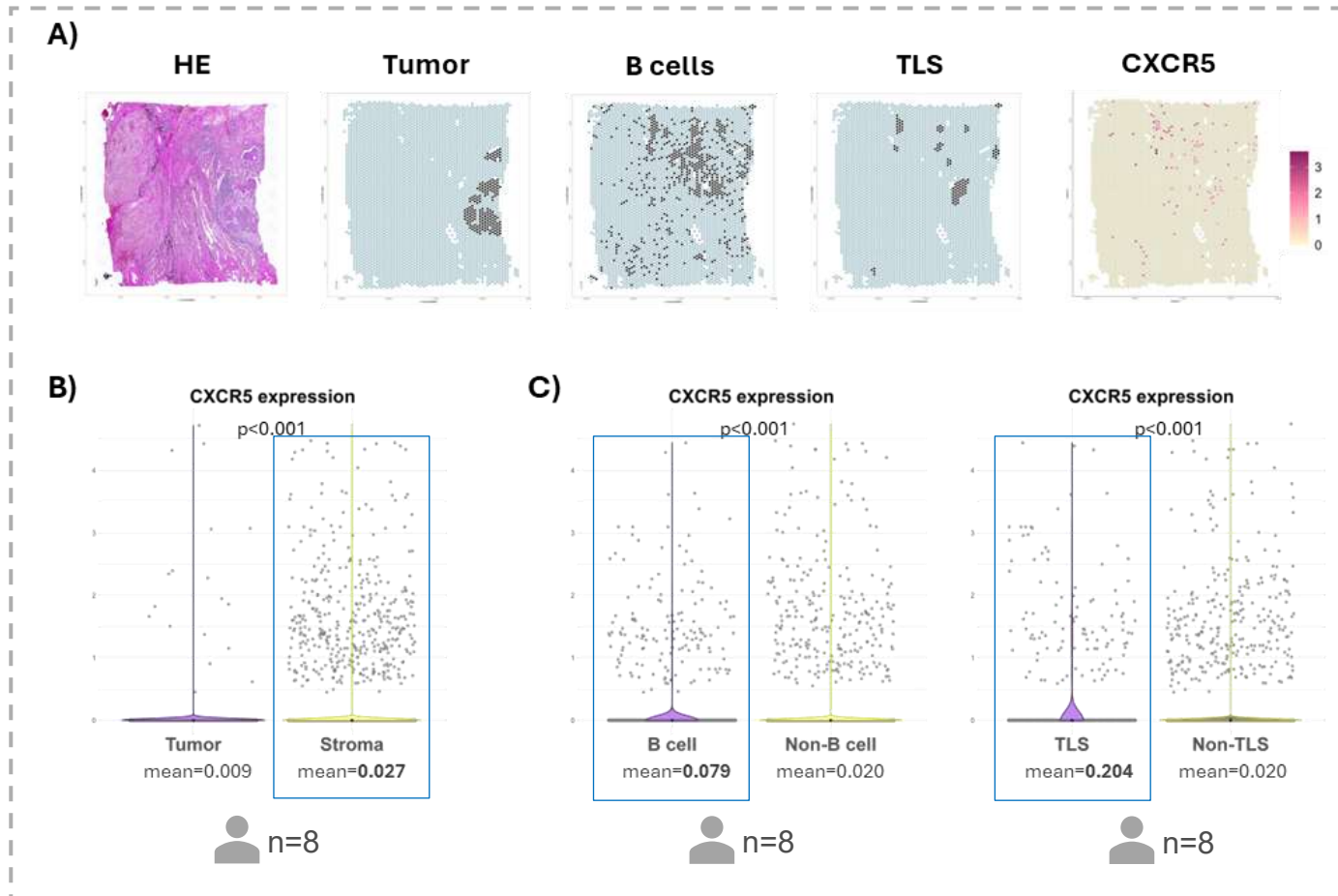


Is CXCR5 expressed by NSCLC tumor cells?

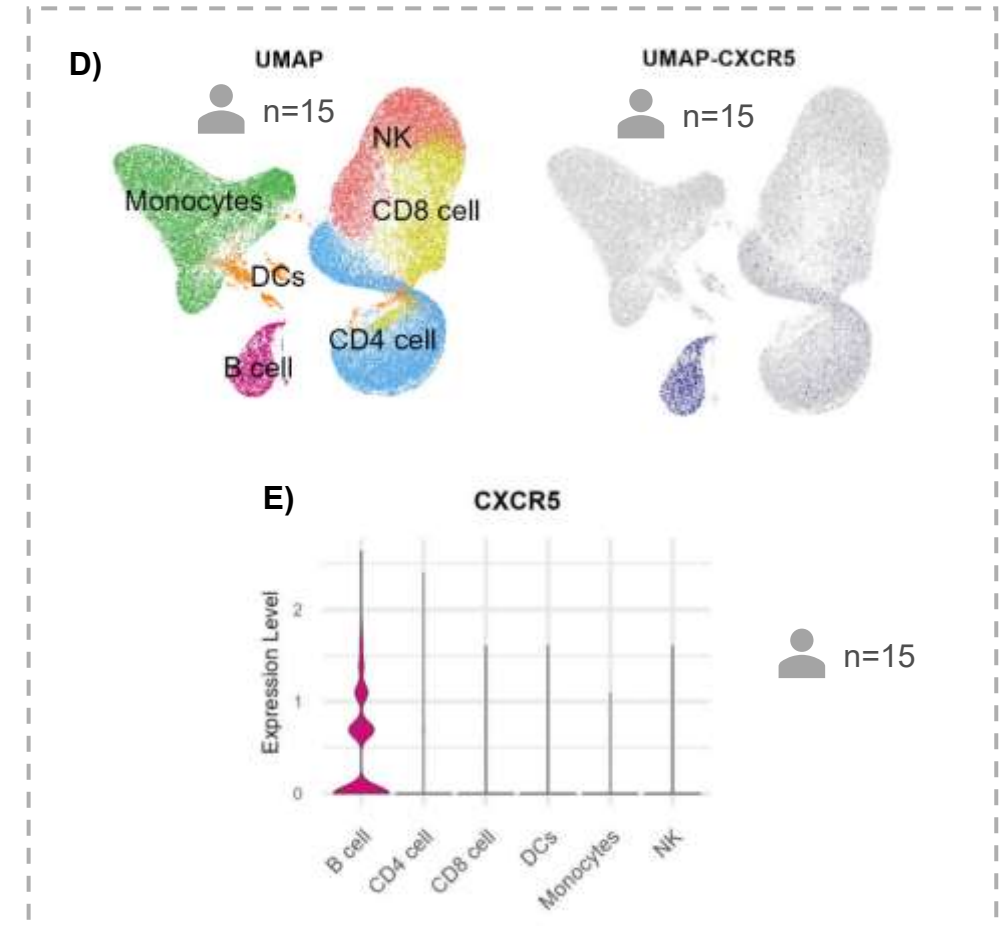
Which immune cells express CXCR5?



Is CXCR5 expressed by NSCLC tumor cells?

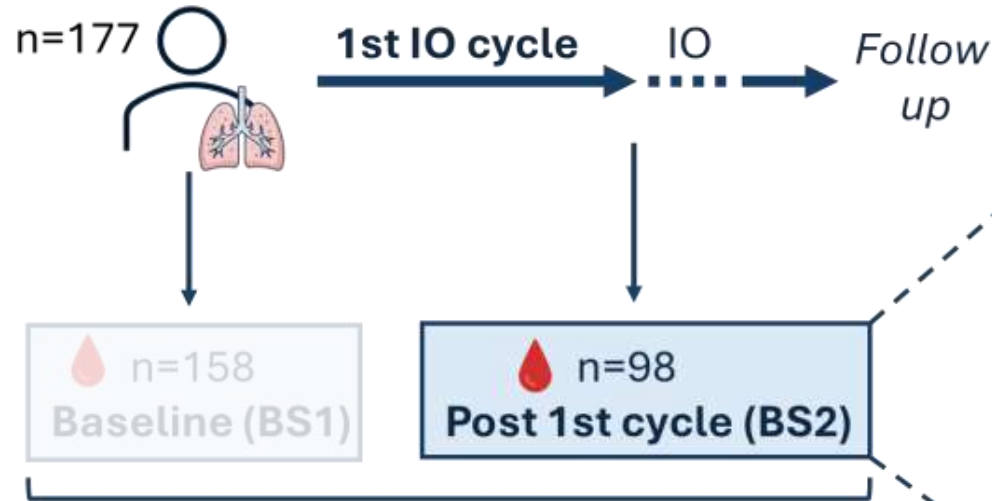


Which immune cells express CXCR5?



CXCR5 is absent in tumor cells and predominantly expressed in B cells (both in tissue and blood)

METASTATIC NSCLC (BLI-O COHORT) *PIR = Disease progression within the first 3 months of IO*



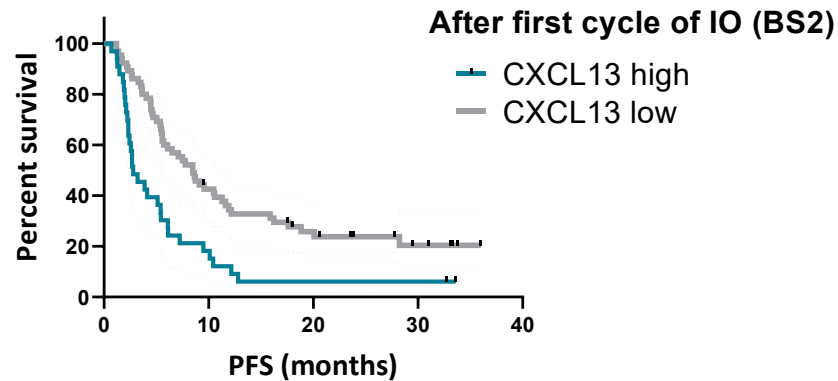
High levels of CXCL13 after IO are associated with PIR

BS2 PERIPHERAL IMMUNE STATUS BASED ON CXCL13 LEVELS

n=30	n=83	n=98
Immune phenotype of B and T cells		Cytokine determination

Flow cytometry

Cytokine array



MADURATION STATUS



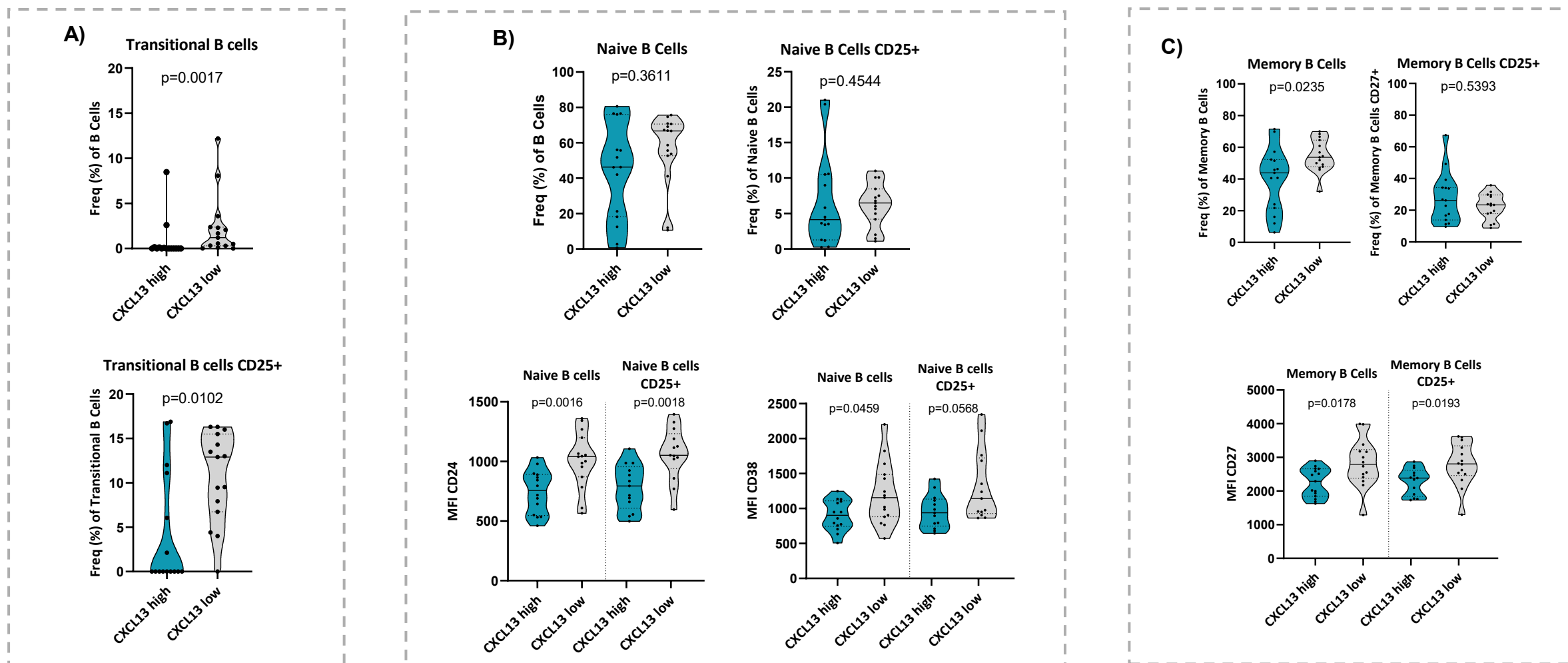
Transitional B cells



Naïve B cells

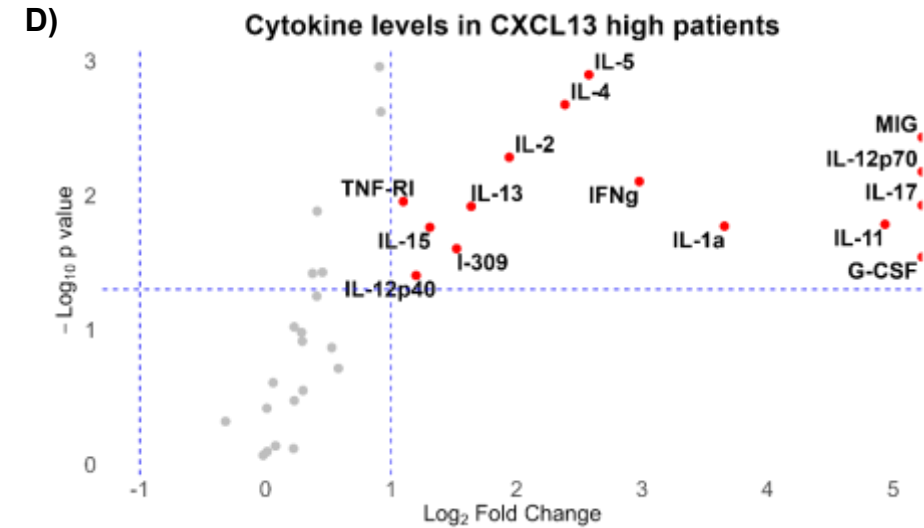
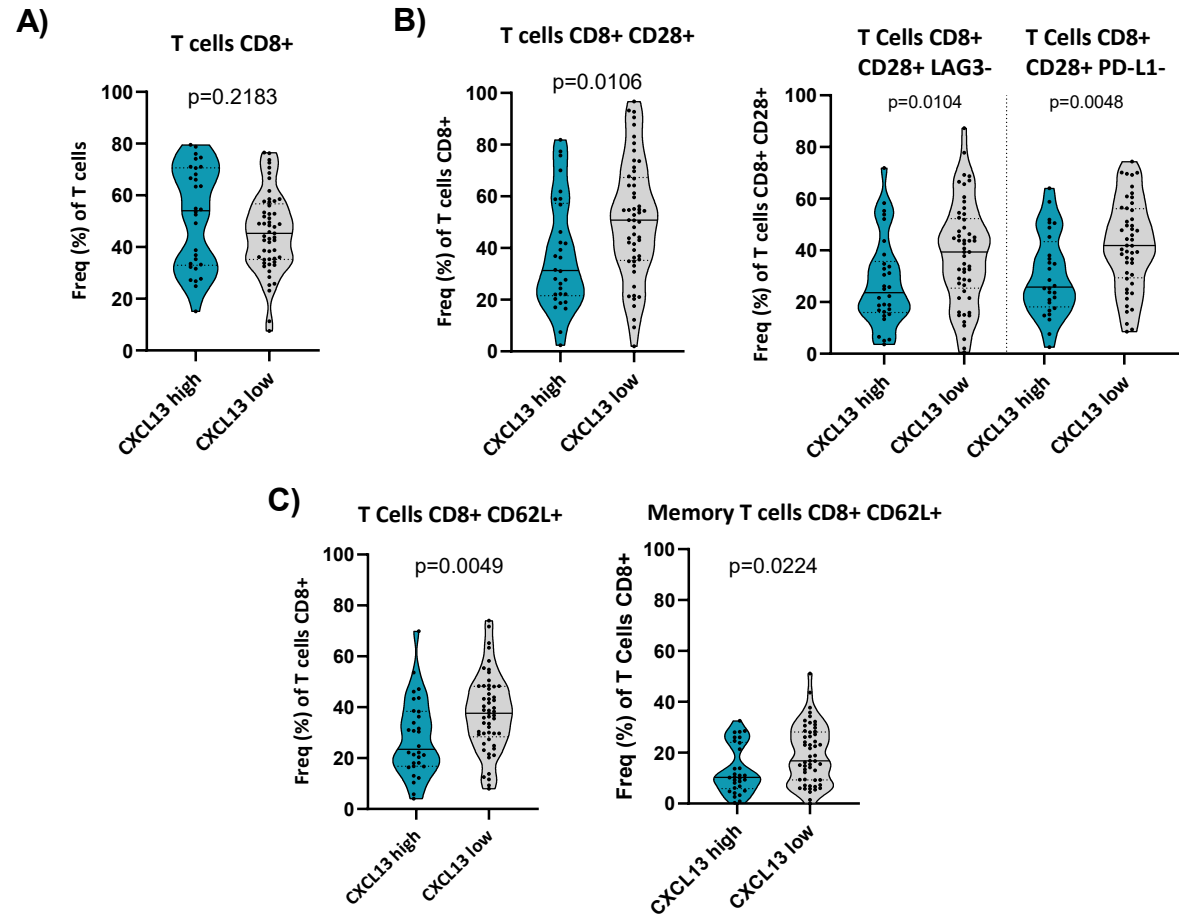


Memory B cells

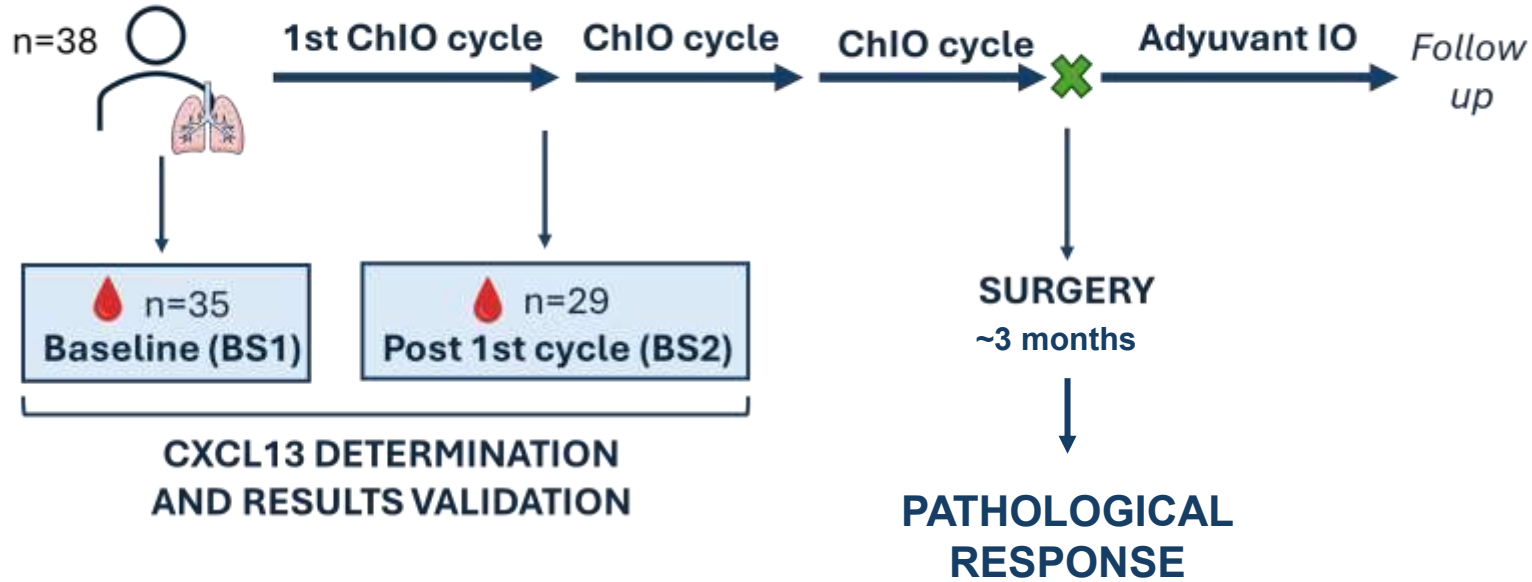


Elevated BS2 plasma levels of CXCL13 are associated with an altered peripheral B cell immunophenotype

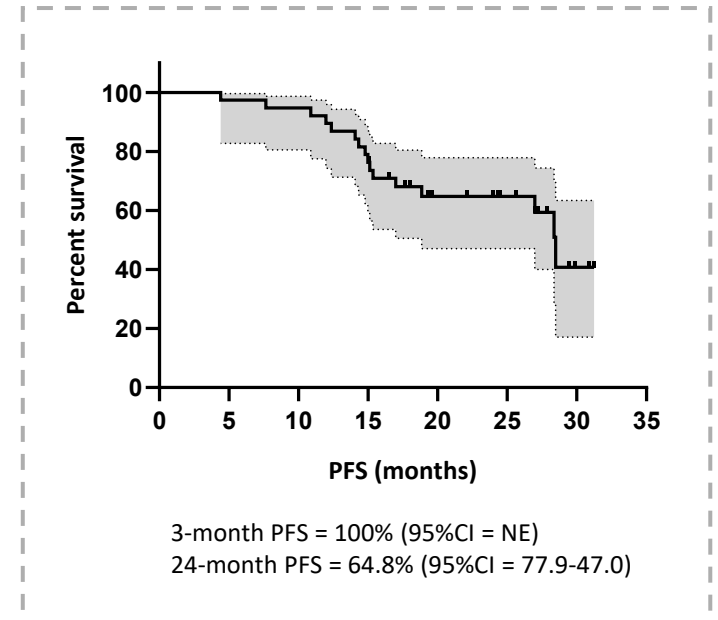
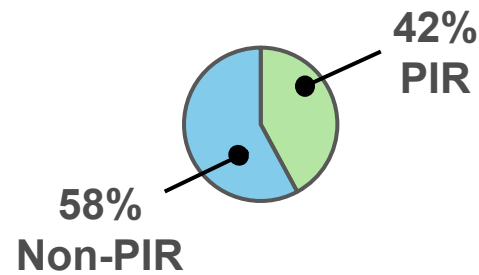
Elevated levels of CXCL13 are associated with T cell dysregulation and increased inflammatory cytokine profile



LOCALLY ADVANCED NSCLC (NADIM II COHORT) *PIR = Incomplete pathological response*

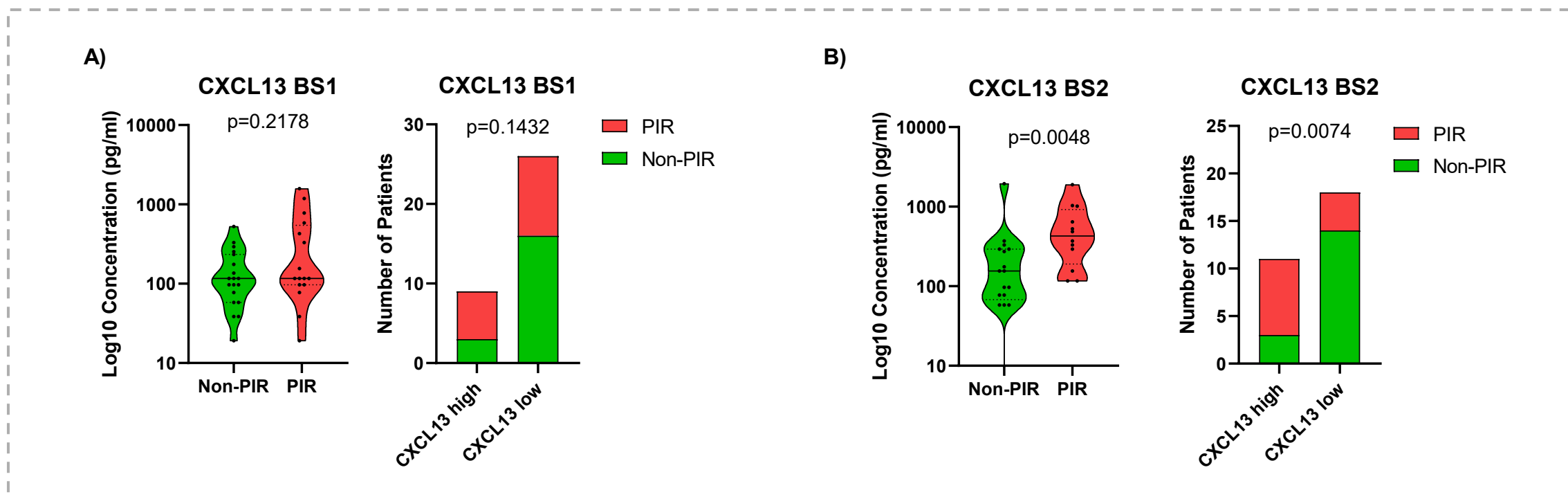


CPR (0%)	MPR (<10%)	IPR (>10%)
Non-PIR		PIR

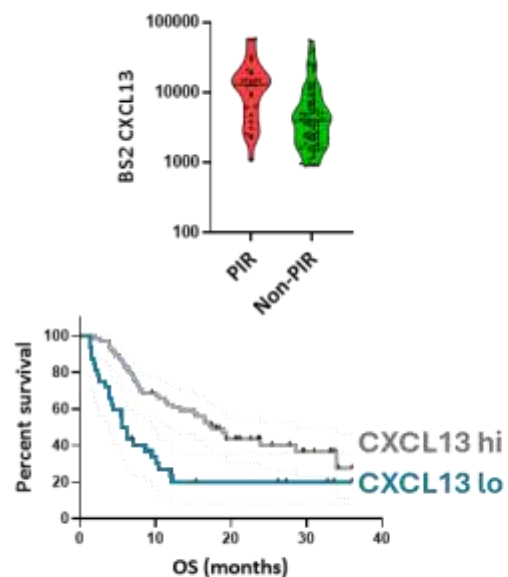


VALIDATION OF CXCL13 AS A PROGNOSTIC BIOMARKER

High CXCL13 plasma levels after first cycle of IO are a PIR biomarker in locally advanced NSCLC



CLINICAL OUTCOMES






High BS2 CXCL13 is associated with PIR

PERIPHERAL IMMUNITY IN CXCL13 HIGH PATIENTS AFTER IO

Blood

B cell compartment

-  ↓ Transitional B cells
-  ↓ CD24 and CD38 MFI in naive B cells
-  ↓ Memory B cells (with low MFI of CD27)

T cell compartment

-  ↓ Activated CD8+ T cells
-  ↓ CD62L+ CD8+ T cells
-  ↓ Memory CD62L+ CD8+ T cells

Cytokine profile



↑ IFN- γ , IL-11, IL-13, IL-1a, IL-17, IL-15, MIG, I-309, TNF-RI

Systemic inflammation with altered peripheral B and T cell phenotype, and elevated inflammatory cytokines

Elevated plasma levels of CXCL13 after the first cycle of IO are associated with primary IO resistance (PIR) in NSCLC patients, as well as increased systemic inflammation characterized by an immature and exhausted immune system, highlighting its promising role as an early biomarker for predicting PIR.

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THANK YOU