B cells and tertiary lymphoid structures as biomarkers for prognosis and immunotherapy

Wolf H Fridman

INSERM U1138
Cordeliers Research Centre
Université Paris Descartes
Paris, France

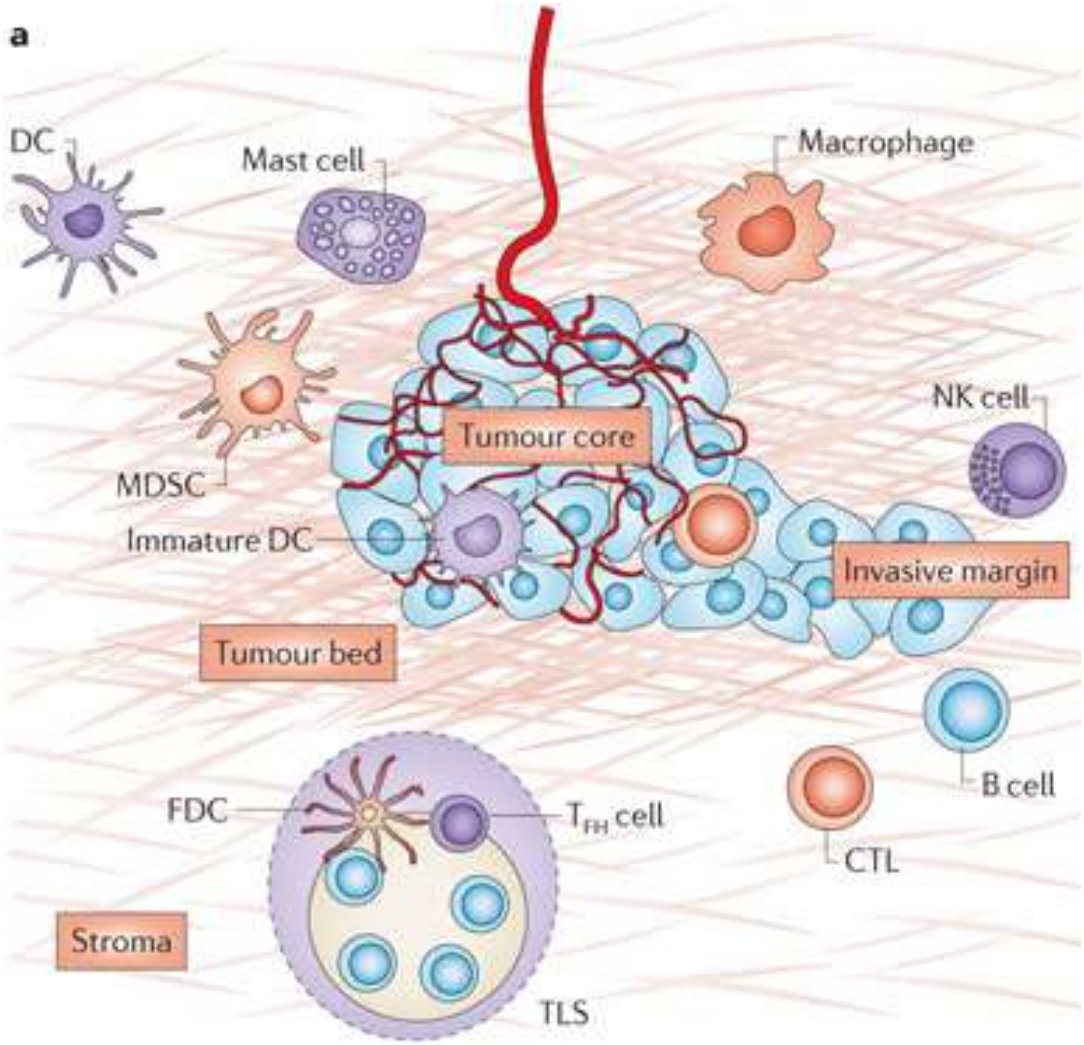
DISCLOSURE INFORMATION

I am a consultant, advisor or speaker for:

Adaptimmune, Anaveon, BMS, Catalym, IPSEN, Medimmune, Novartis, OSE Immunotherapeutics,

I receive royalties from HalioDX

The immune microenvironment



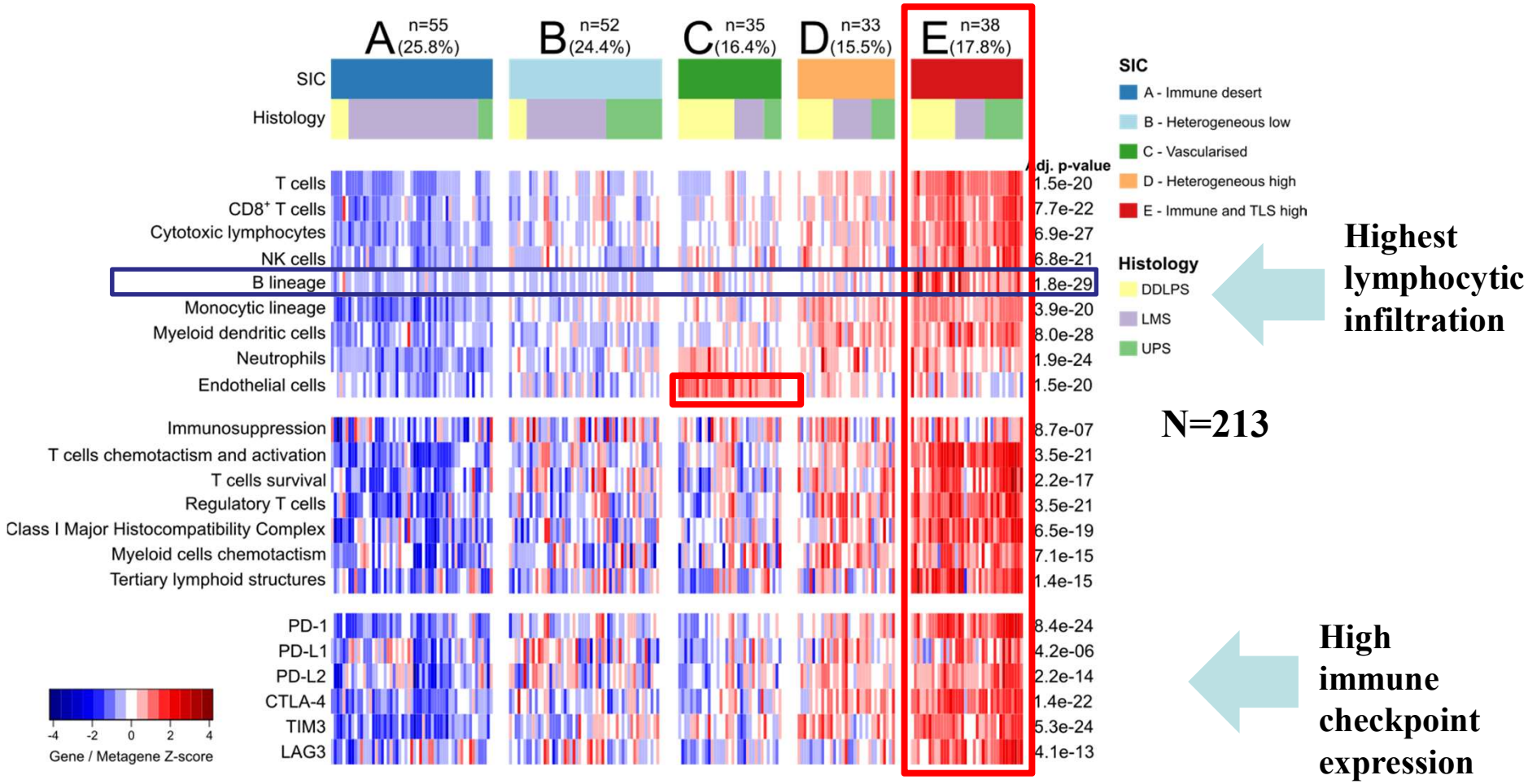
W H Fridman et al., Nature Rev. Cancer, 12, 298-306, 2012

IMMUNE CLASSIFICATION OF SOFT TISSUE SARCOMAS : TLS AS POTENTIAL PREDICTIVE BIOMARKERS

- **Soft tissue sarcoma (STS) are rare tumors : around 1% of all adult solid tumors.**
- **Sparse information about infiltration by immune cells and the response to immune check point blockade is limited : need for biomarkers of response**
- **STS can be classified in 70 different histological types. We selected the three most common histologies : leiomyosarcoma (LMS) ; dedifferentiated liposarcoma (DDLPS) and undifferentiated pleomorphic sarcoma (UPS)**
- **We classified them on the basis on the abundance of different immune and stromal cells using a transcriptomic-based deconvolution method (MCP-Counter immune cell signatures)**

Becht et al. Genome Biol (2016) 17:218; D'Angelo SP et al. Hum Pathol 2015; 46:375-65; Kim JR et al. PLoS One 2013; 8: e 82870; TCGA Cell 2017; 171:950-65;

5 STS Immune Clusters (SIC) with highly different characteristics
TCGA cohort (n:213)



Highest lymphocytic infiltration

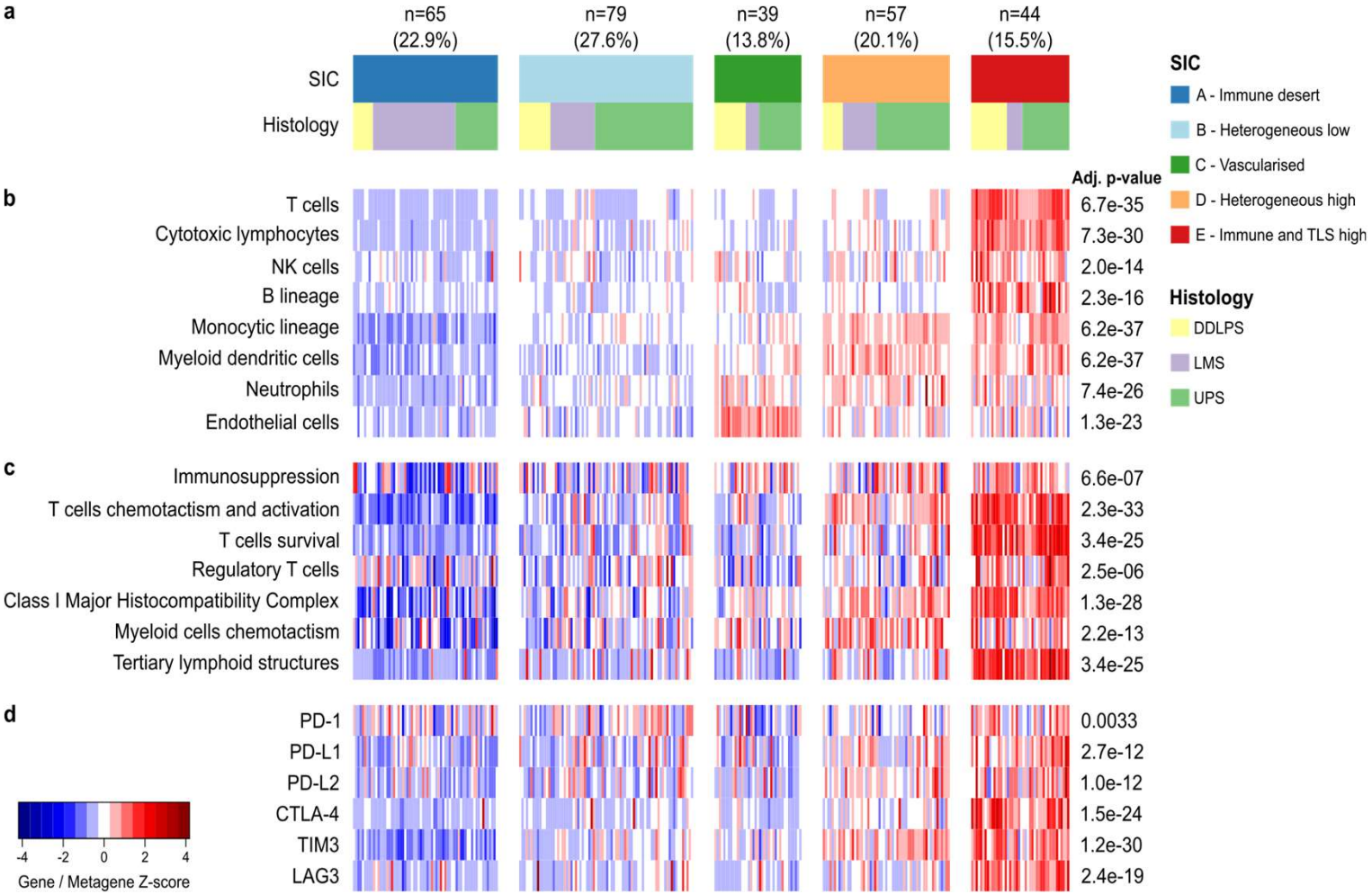
N=213

High immune checkpoint expression

Petitprez *et al.*, Nature, 577, 556-560, 2020

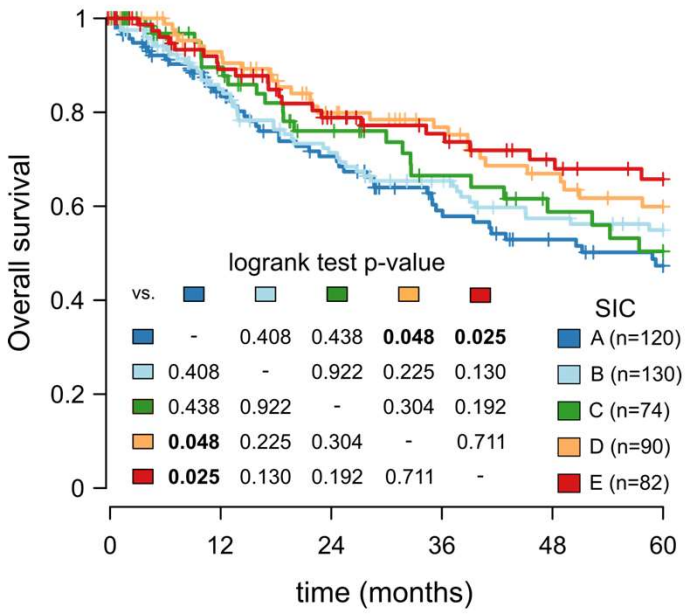
5 STS Immune Clusters (SIC) with highly different characteristics

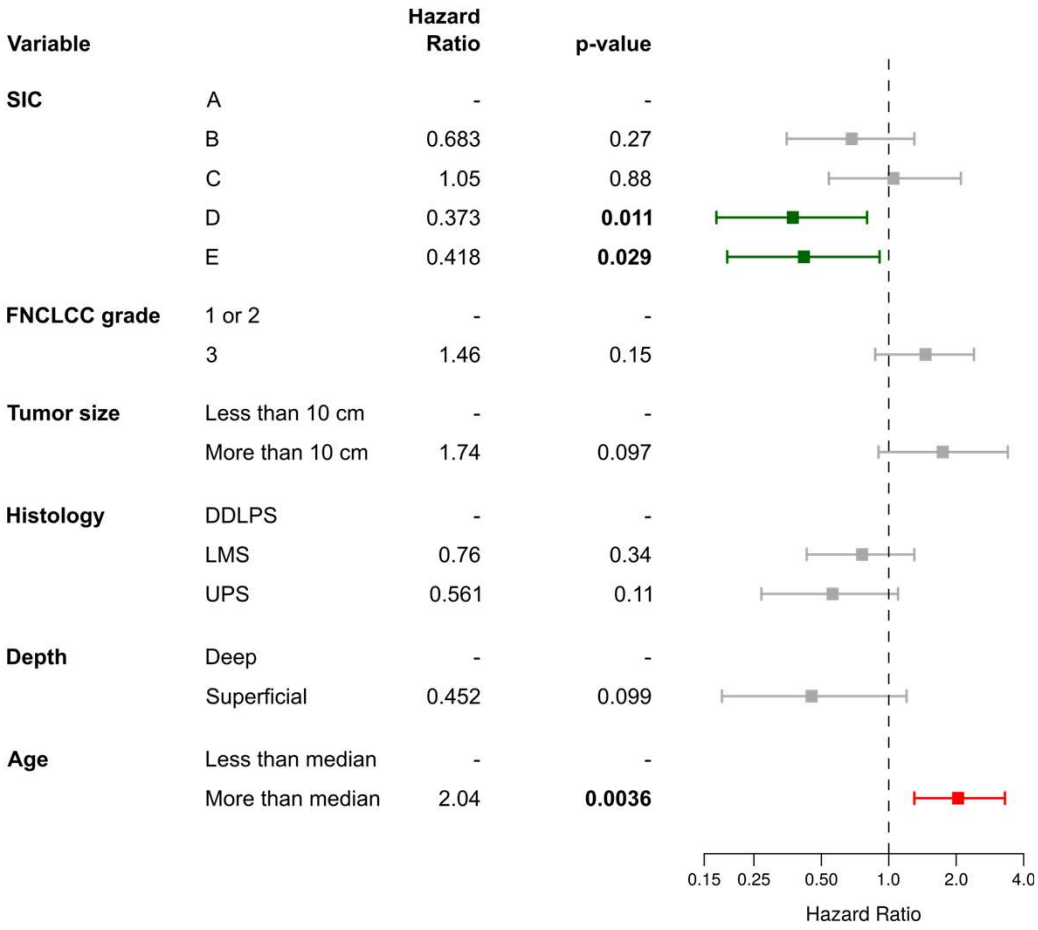
French Sarcoma Group, GSE21050 cohort (n=283)



F Petitprez et al, Nature, 577,556-560, 2020

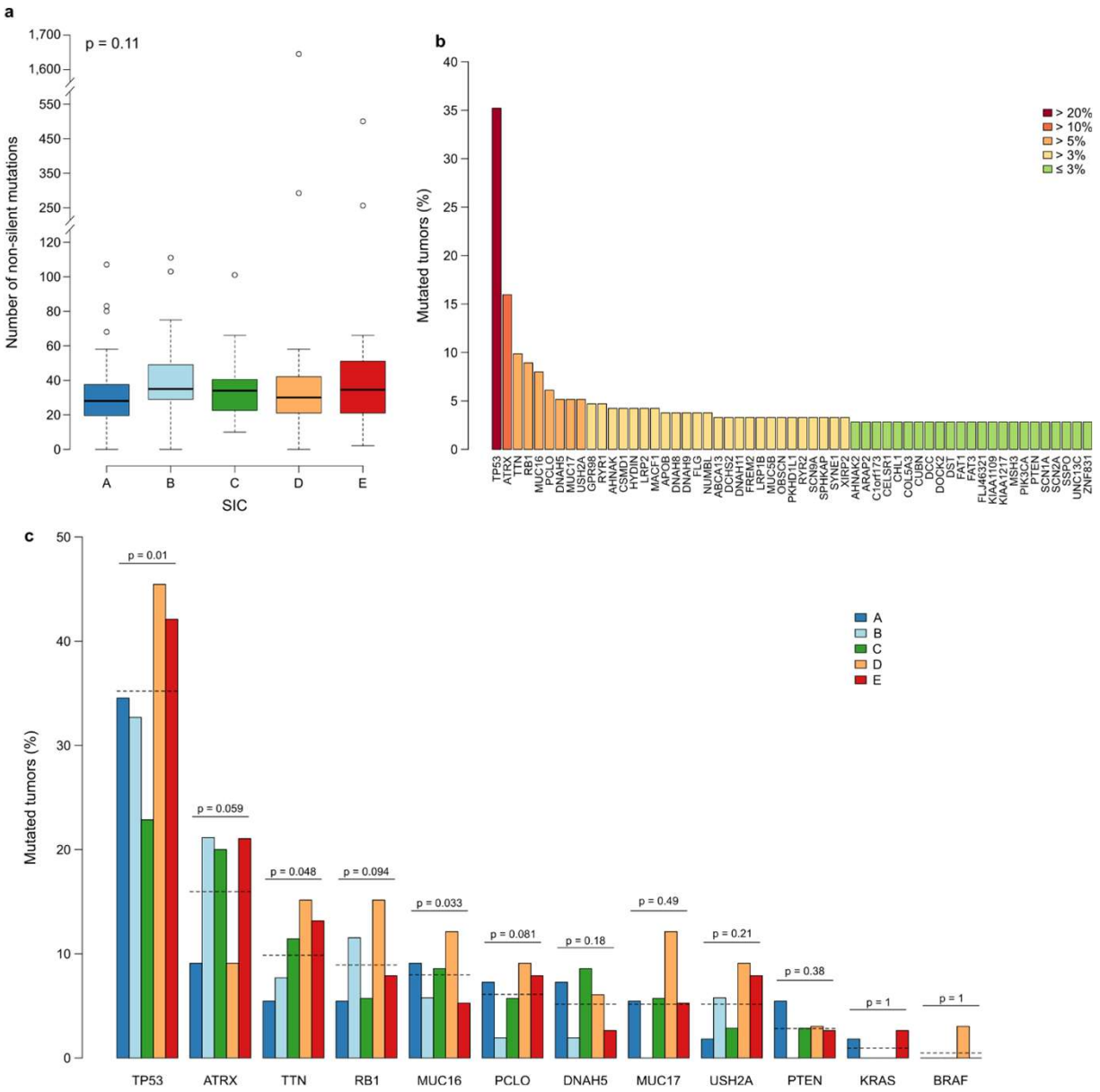
SIC correlate with Overall Survival in STS in multivariate analysis





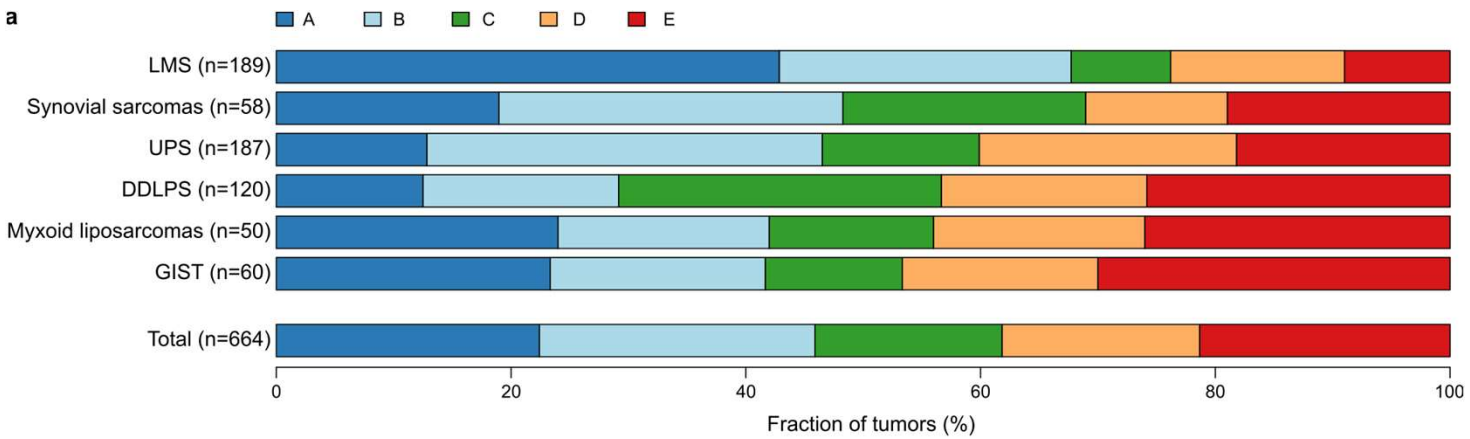
F Petitprez et al, Nature, 577, 566-560, 2020

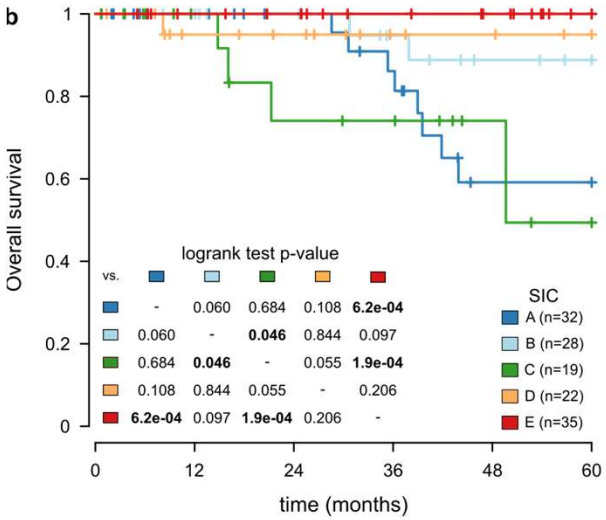
The mutational landscape of STS tumours does not vary significantly between SICs



F Petitprez et al, Nature, 577, 556-560, 2020

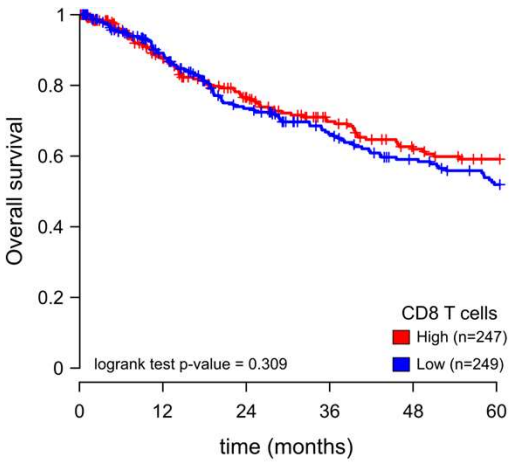
SIC classification and Overall Survival in various sarcoma histologies

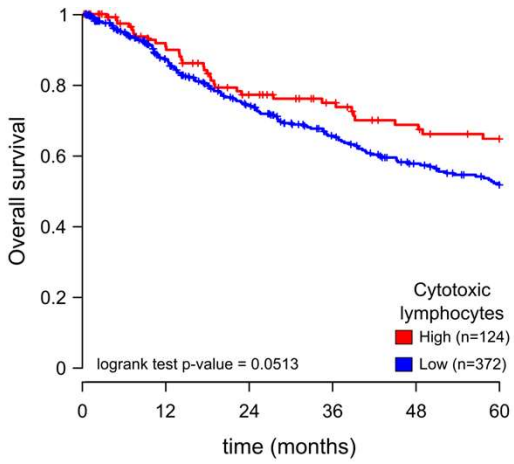


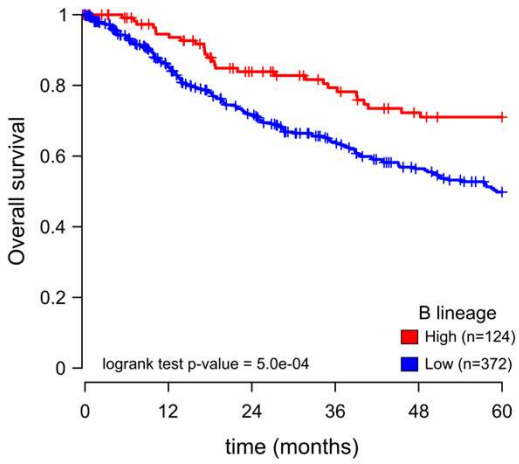


F Petitprez et al, Nature, 577, 556-560, 2020

B cell signature is a better predictor than cytotoxic signature for OS in STS



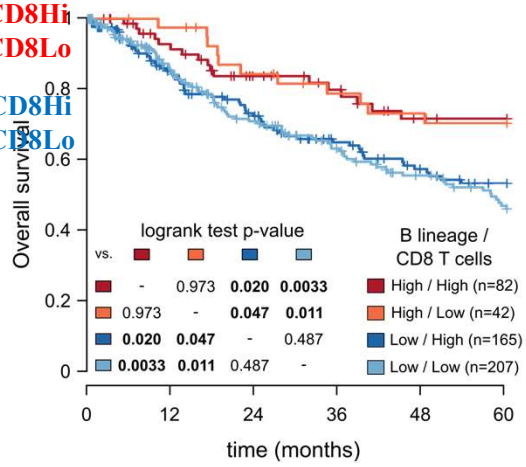




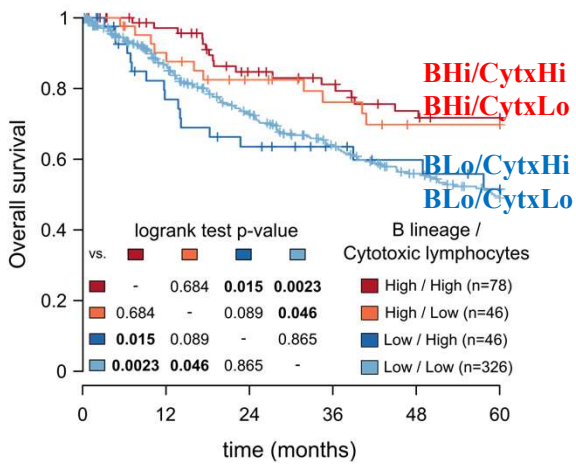
BHi

BLo

BHi/CD8Hi
BHi/CD8Lo
BLo/CD8Hi
BLo/CD8Lo



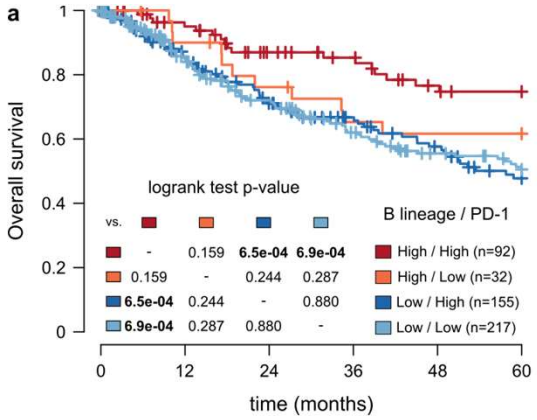
BHi/CytxHi
BHi/CytxLo
BLo/CytxHi
BLo/CytxLo



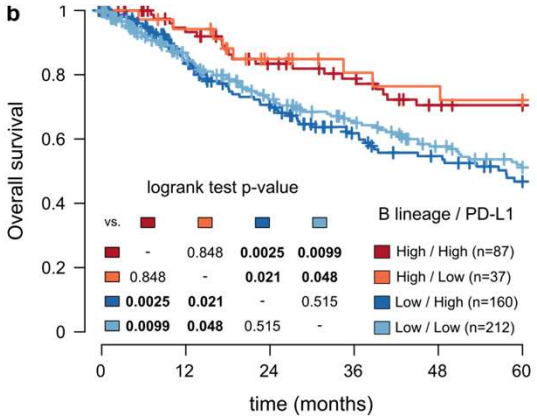
F Petitprez et al, Nature, 577, 556-560, 2020

B cell signature is a better predictor than PD-1, PD-L1 and FoxP3 for OS in STS

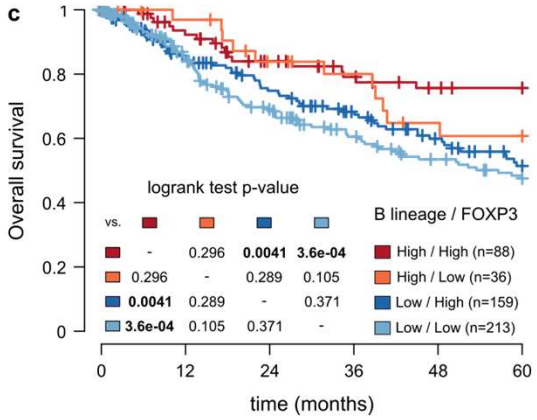
B/PD-1



B/PD-L1

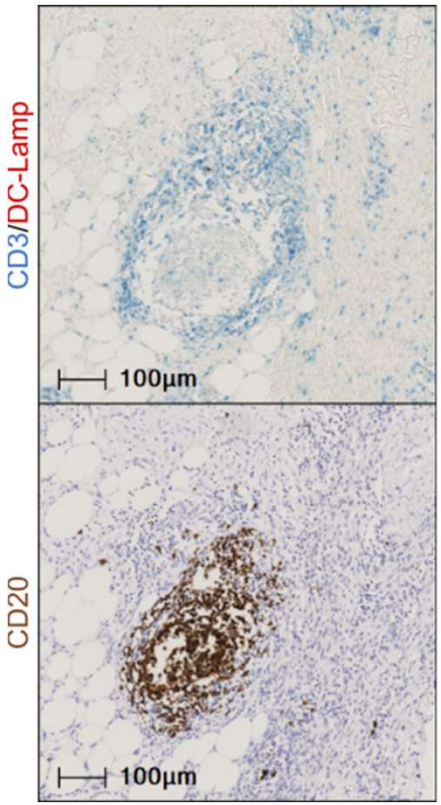


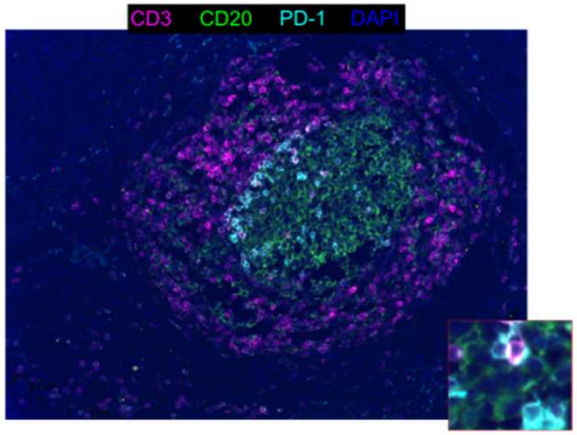
B/FoxP3

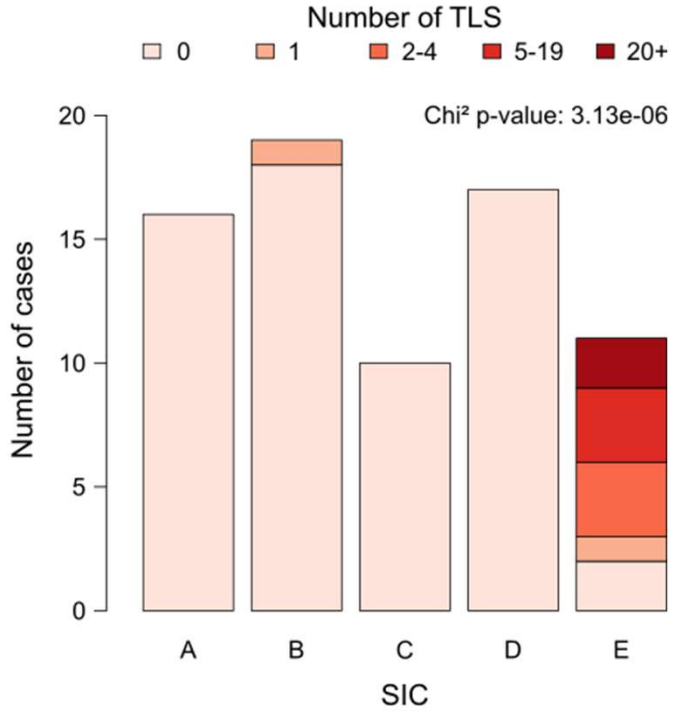


F Petitprez et al, Nature, 577, 556-560, 2020

Tumors from SIC E are characterized by the presence of TLS







Petitprez *et al.*, Nature, 577, 556-560, 2020

SIC E group demonstrates highest response rate to PD1 blockade by Pembrolizumab

Sarc028 phase 2 trial
(H Tawbi, MDACC) :

47 patients

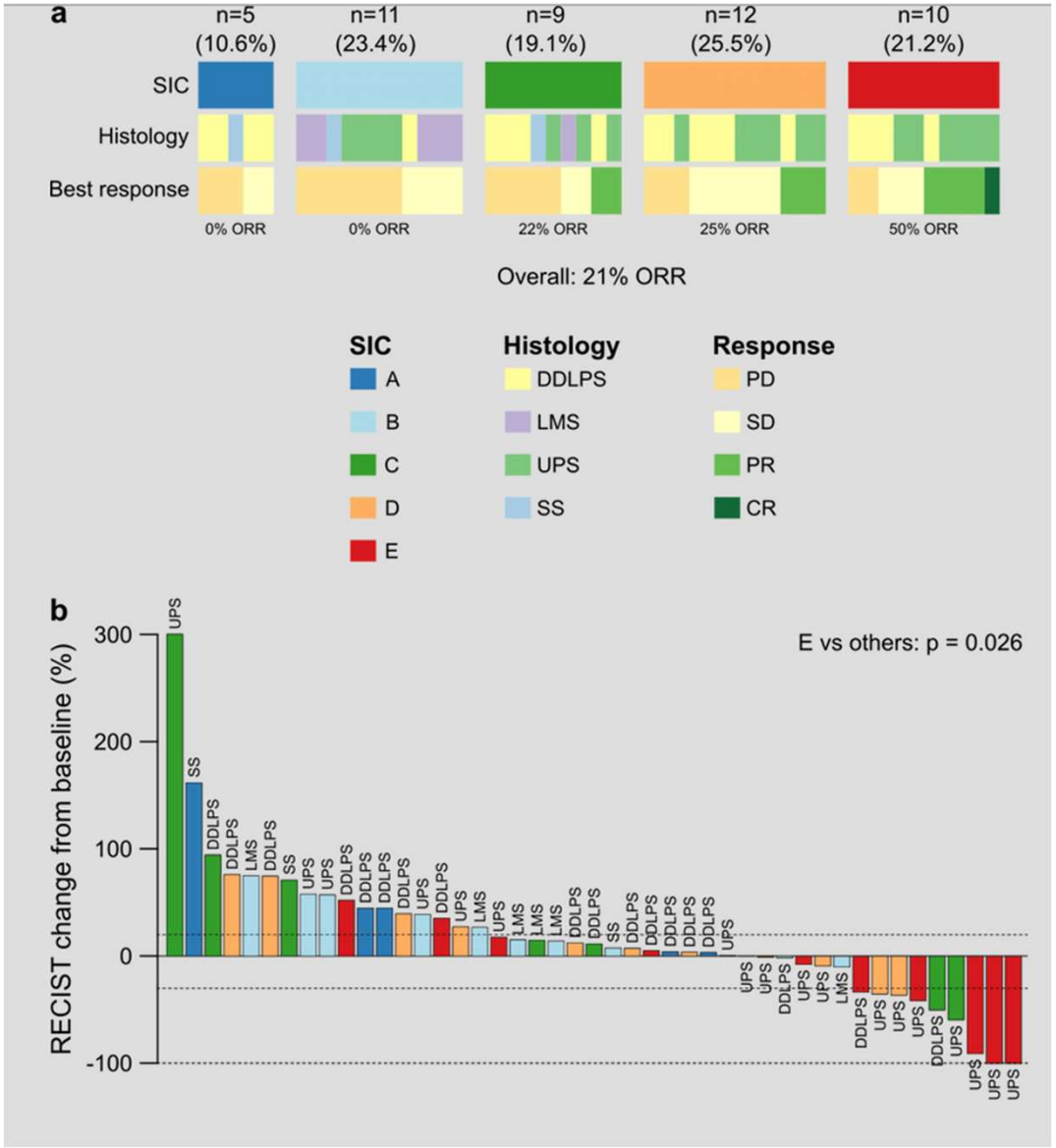
ORR :

SIC E* : 50%

SIC D : 25%
SIC C : 22%
SIC A : 0%
SIC B : 0%

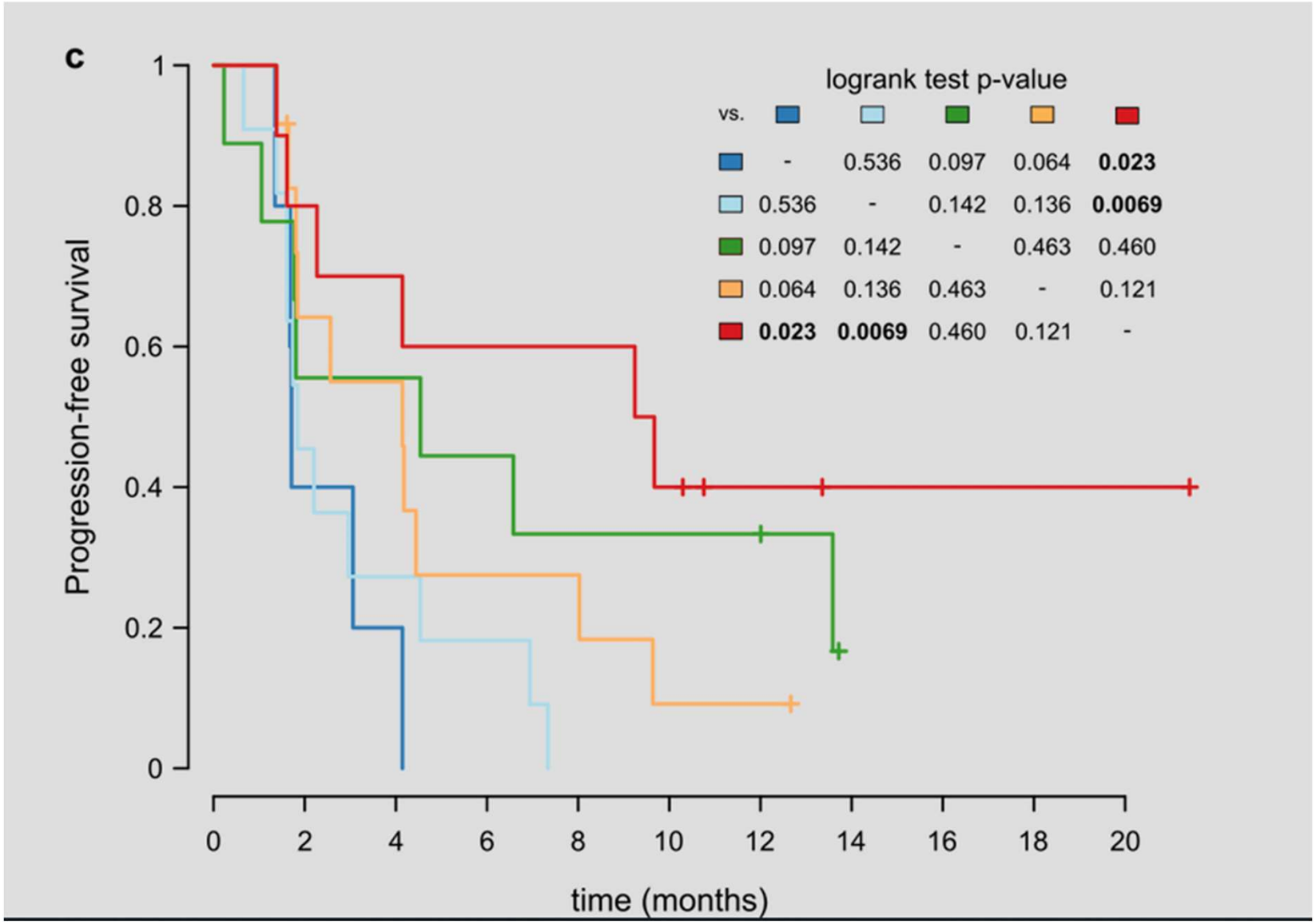
p=0.026

Complete Response
SIC E : 1



F Petitprez et al, Nature, 577, 556-560, 2020

SIC and PFS in STS patients treated with Pembrolizumab



F Petitprez et al, Nature, 557, 556-560, 2020

Conclusions

In soft tissue sarcoma :

-Identification of an immune high group of patients, SIC E, with 50% response to pembroluzimab.

-An endothelial high group of patients, SIC C, may beneficiate of a combination of anti-angiogenic and ICB therapies

-Each histology has different proportions of each SIC cluster

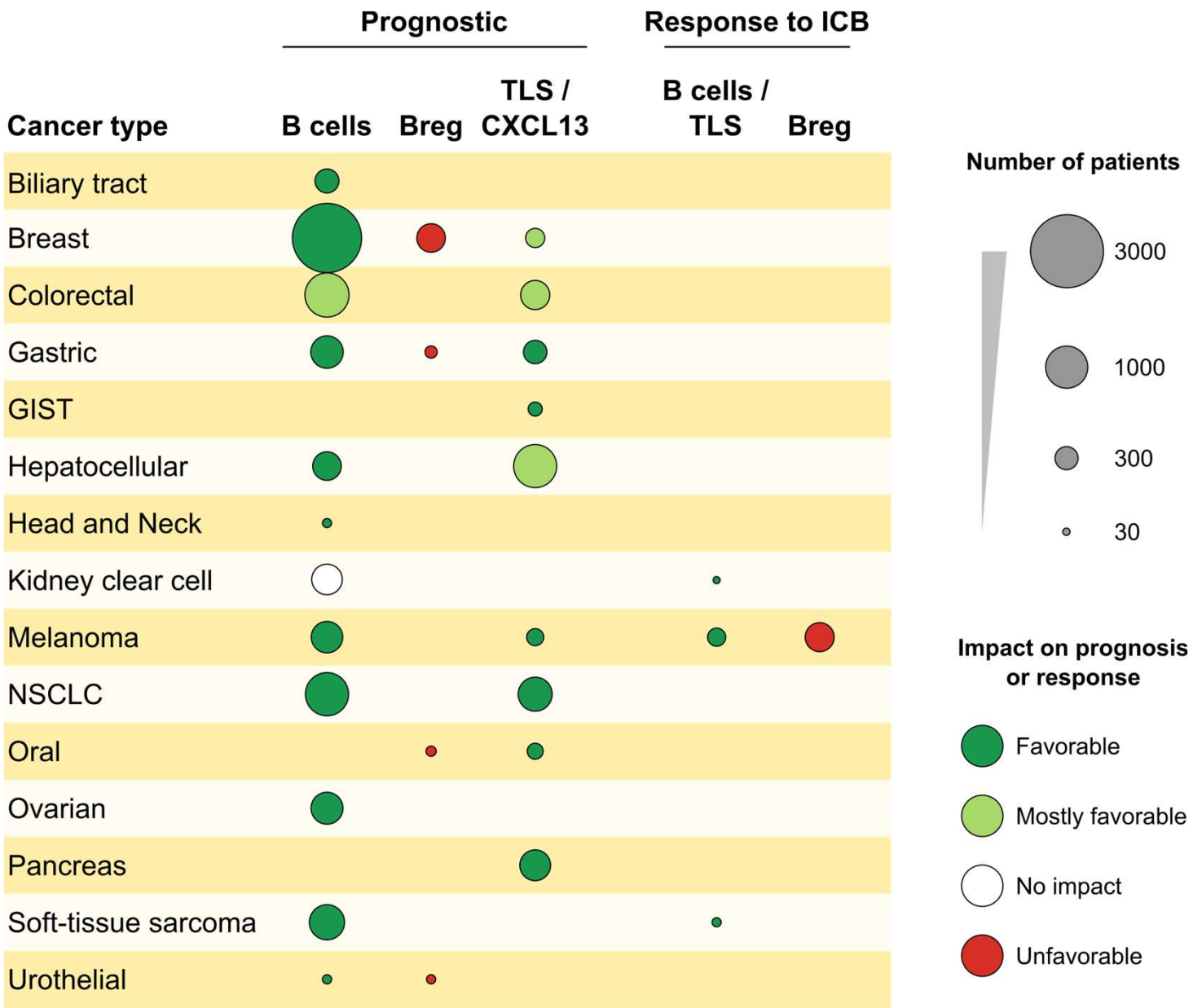
-B cells are associated with favorable prognosis

-TLS can be used as surrogate marker for SIC E group

Suggest that TLS could be used as predictive biomarkers for response to ICB in STS.

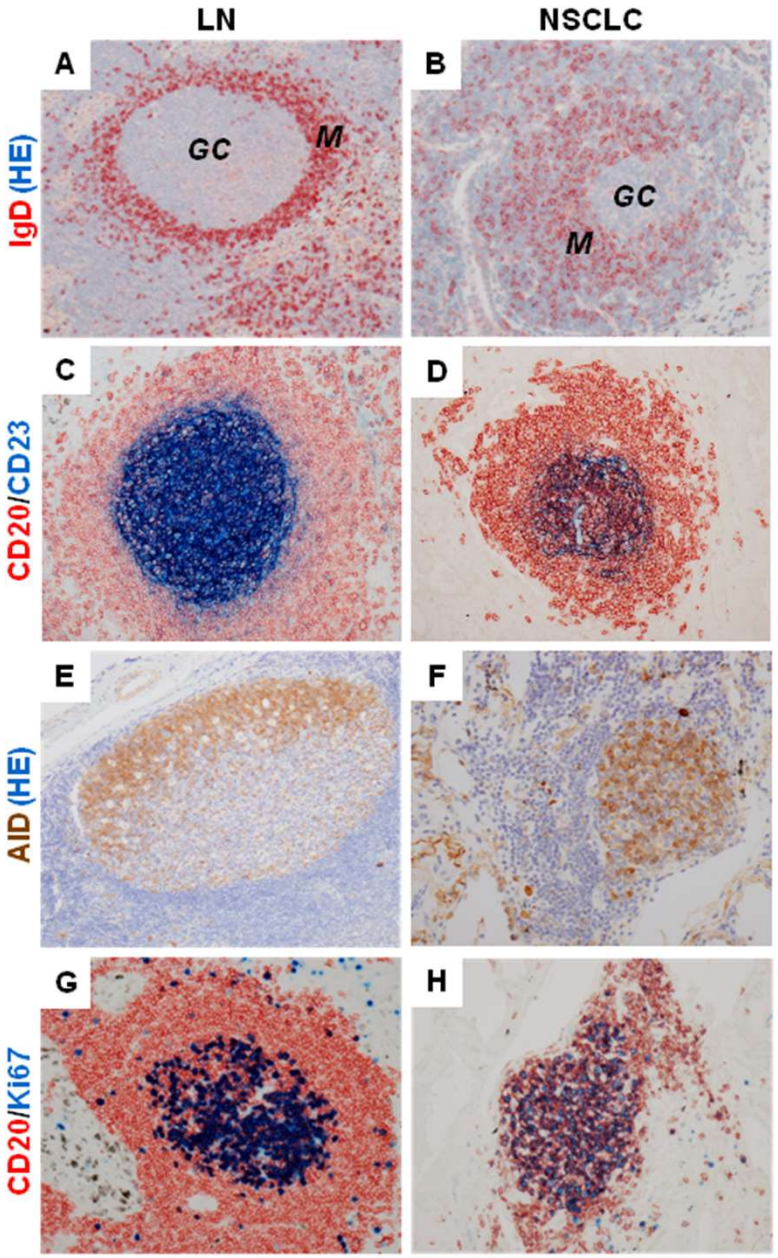
A prospective clinical trial, under the auspices of the French Sarcoma Group (PI: A. ITALIANO), with Pembroluzimab in which patients are included on the basis of the presence of TLS in their tumor, has completed its inclusions

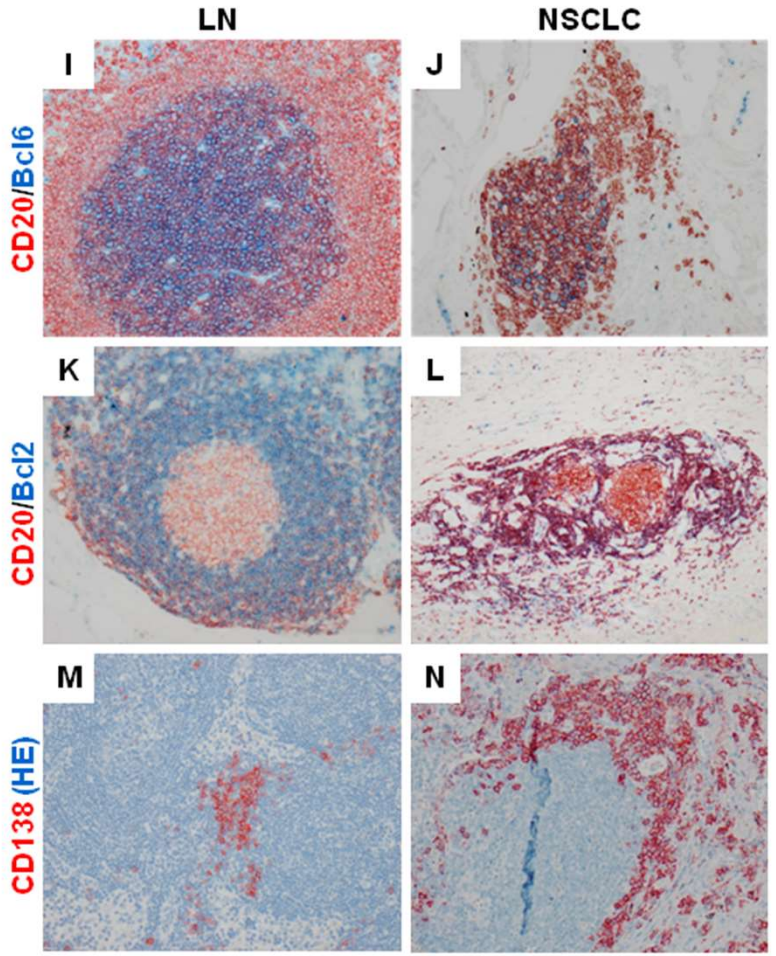
Prognostic and theranostic impact of B cells and TLS in human cancers



W H Fridman et al, J Exp Med, in press

B cells within TLS display the same organization as in secondary lymphoid organs





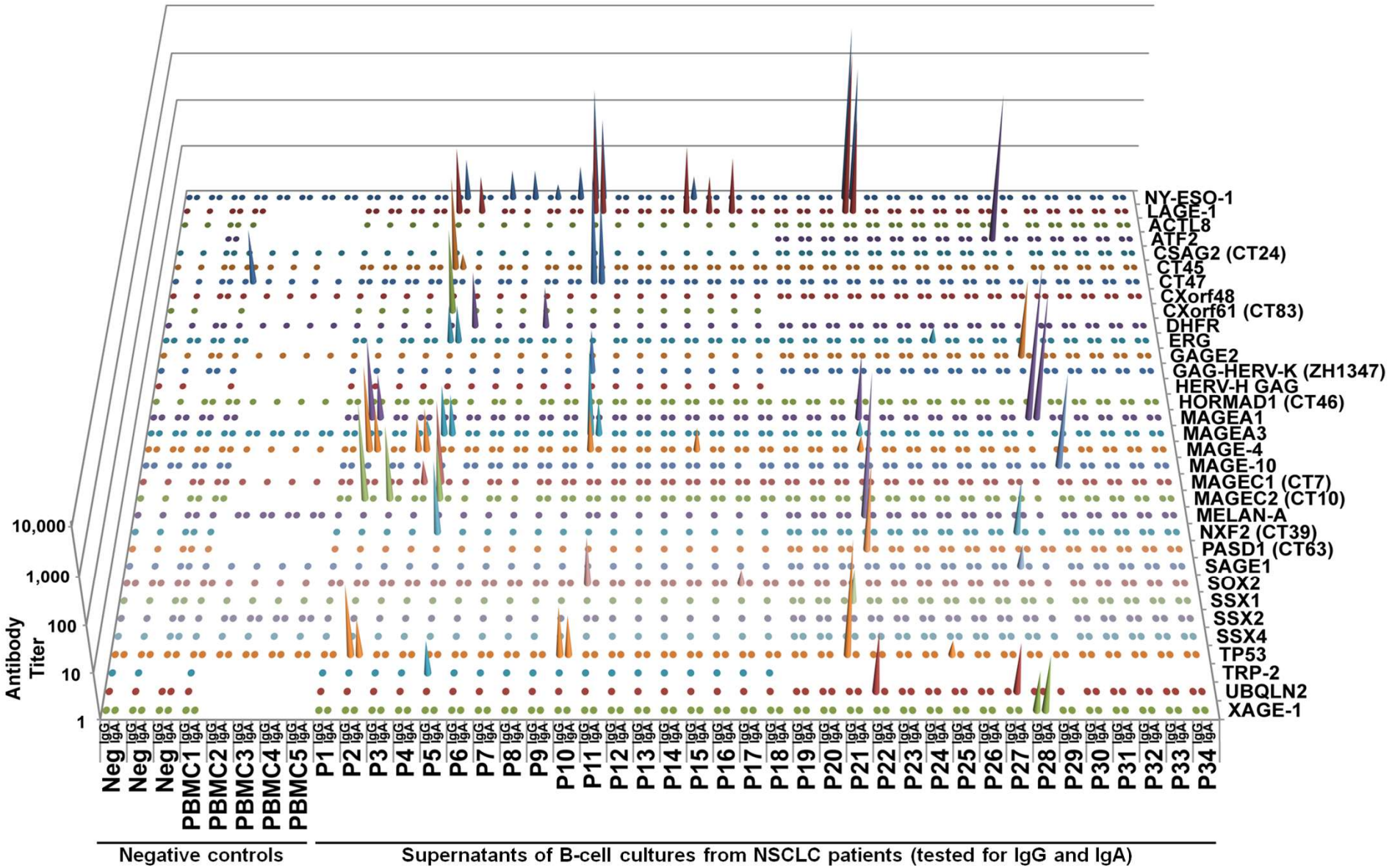
Early-activated B cells undergo active proliferation in B cell follicles.
SHM and CSR machineries are activated.

C Germain et al, Am J Respir Crit Care Med, 189, 832-844, 2014

Tumor-infiltrating B cells secrete IgG and/or IgA specific for several tumor antigens in half of the patients tested

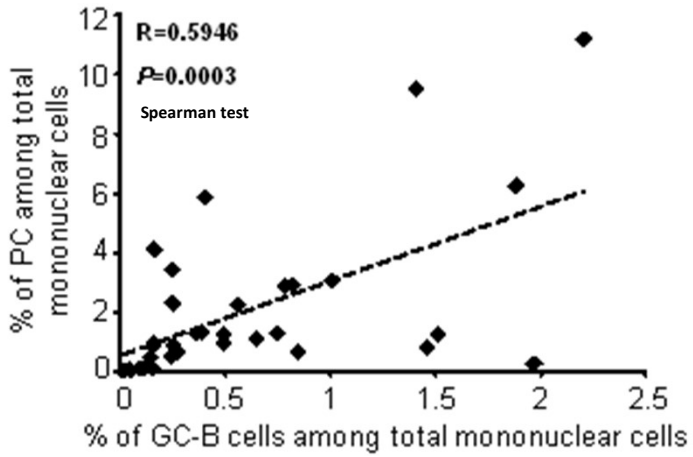
Culture of sorted tumor-infiltrating B cells in the presence of a polyclonal activator (n=34 NSCLC patients)

(n=33 tumor antigens)



Correlation between % of GC B cells and Plasma cells

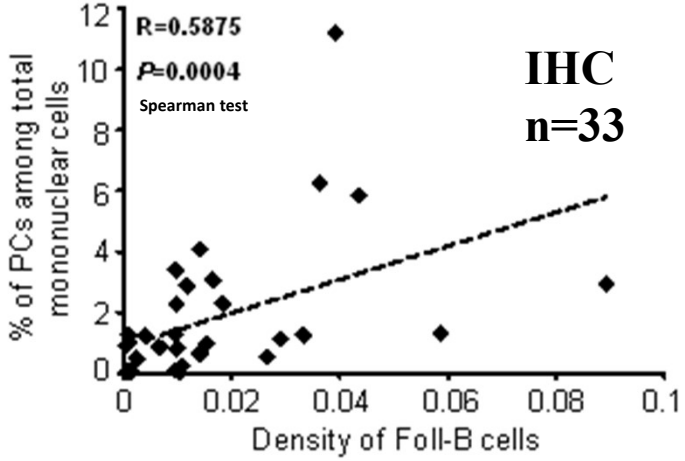
Flow cytometry
n=33



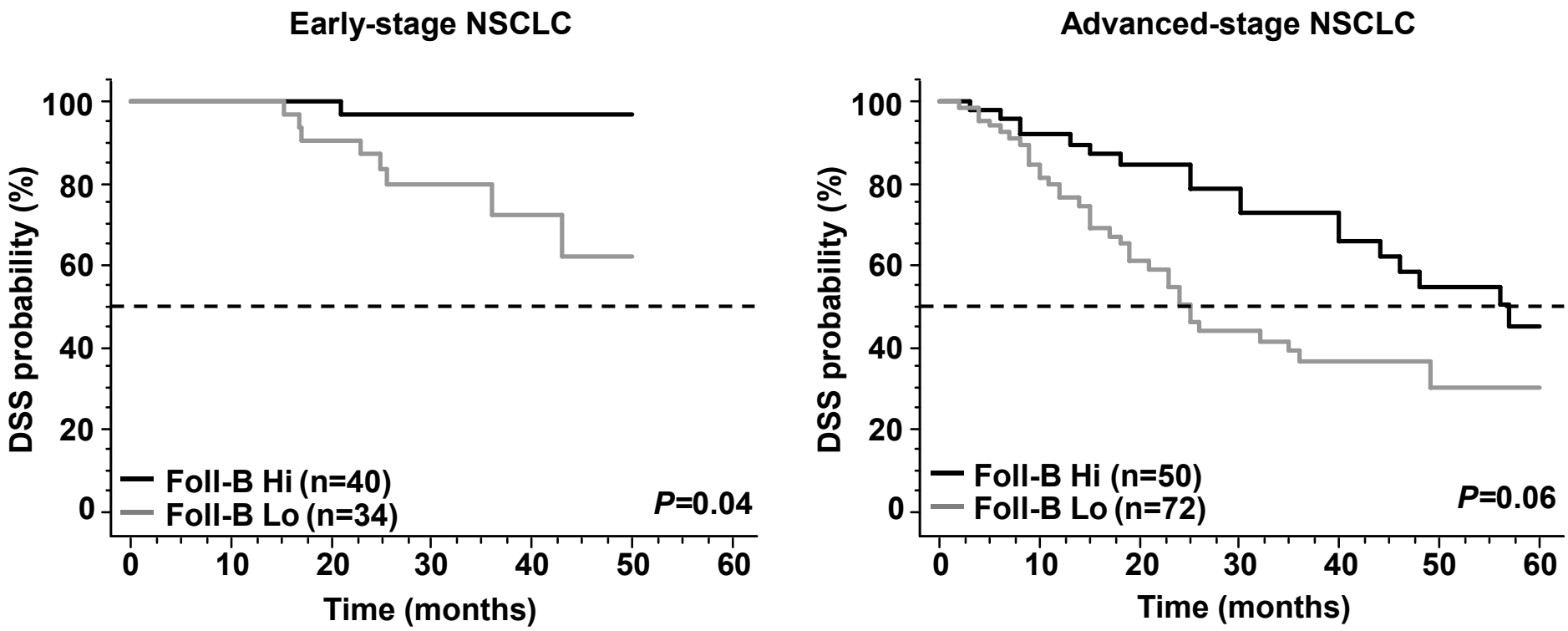
Density: total surface of CD20+ B-cell follicles (μm^2)

total surface of tumor area (μm^2)

IHC
n=33

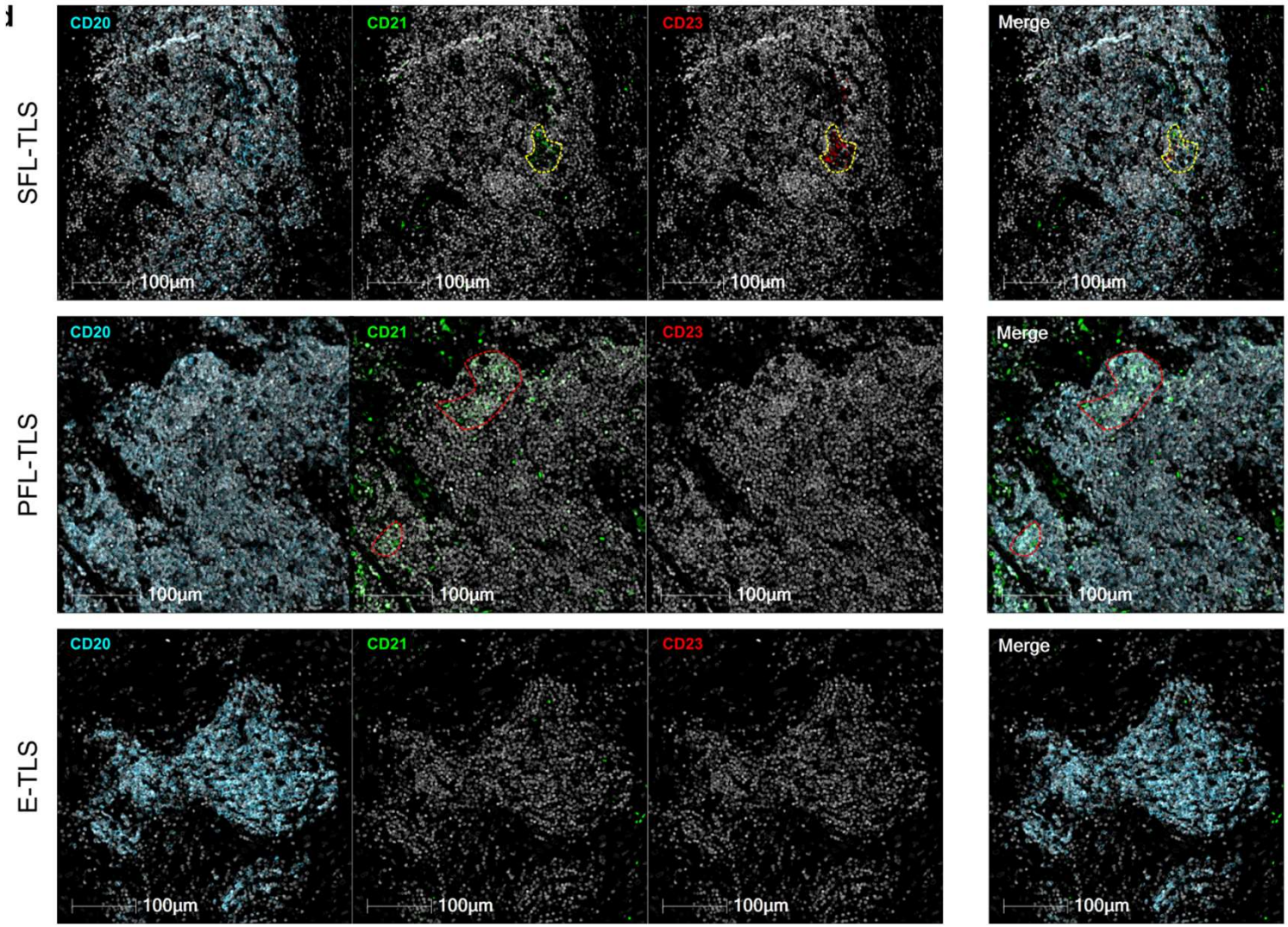


High density of follicular B cells correlates with good prognosis in NSCLC

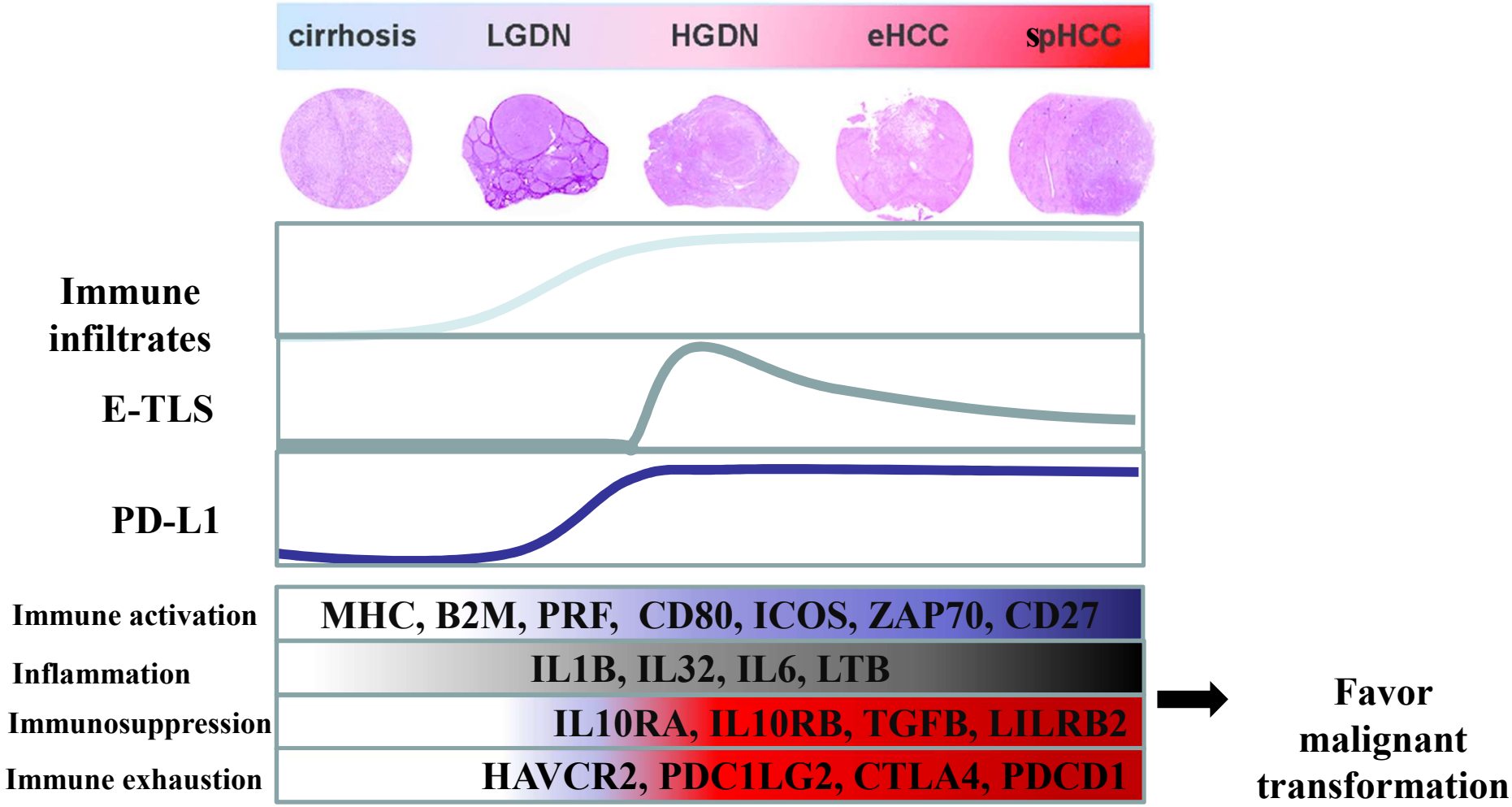


C Germain et al, Am J Respir Crit Care Med. 189, 832-844, 2014

Maturation stages of Tertiary Lymphoid Structures (TLS) from Early (E), Primary (PFL) to Secondary Follicles (SFL) (F Posch et al, OncoImmunol, 7, 2017)

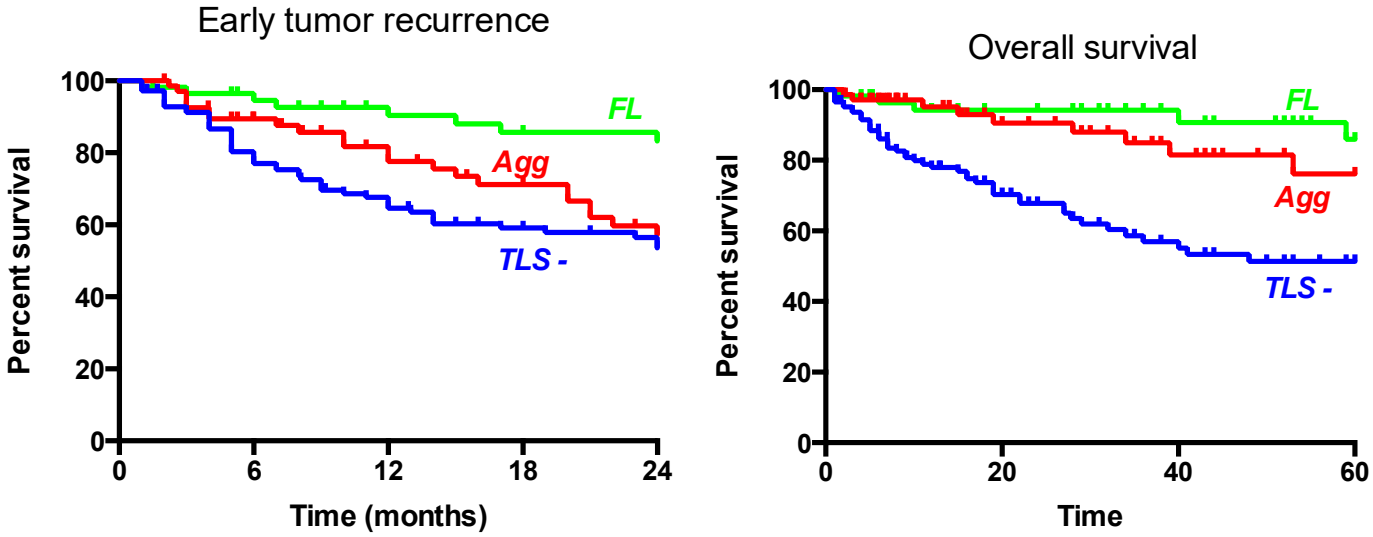


The immune changes during progression of early hepatic lesions to HCC



M Meylan et al, Clin Cancer Res, 158, 806-811, 2020

Impact of maturation of intratumoral TLS in HCC (n=273)



J Calderaro et al, J Hepatol, 2019

CONCLUSIONS

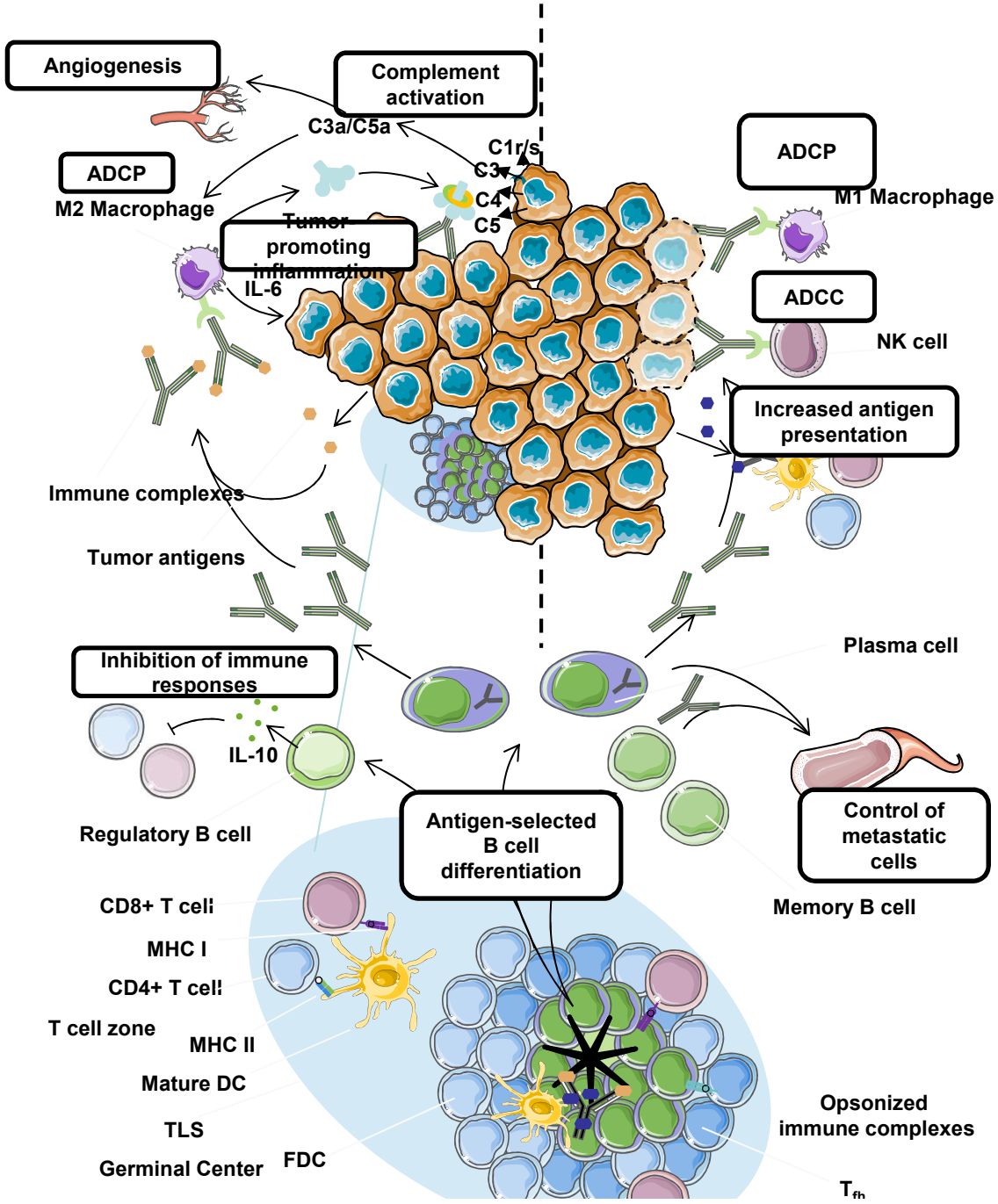
The impact of B cells in the tumor microenvironment is context dependent:

They may produce anti-tumor antibodies and/or present tumor antigens to T cells in TLS and have a favorable clinical impact, such as in Non Small Lung Cancer, melanoma, breast cancer or Soft Tissue Sarcoma

Early TLS are associated with an inflammed and immunosuppressive milieu and may favor tumor progression

B cells and antibodies: Pro-tumor effects

Anti-tumor effects



WH Fridman et al
J Exp Med, in press

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