XIX CONGRESSO NAZIONALE SIES 2026

Clinical and Biological Impact of Plasma Cytokine Levels in Newly Diagnosed Chronic Lymphocytic Leukemia

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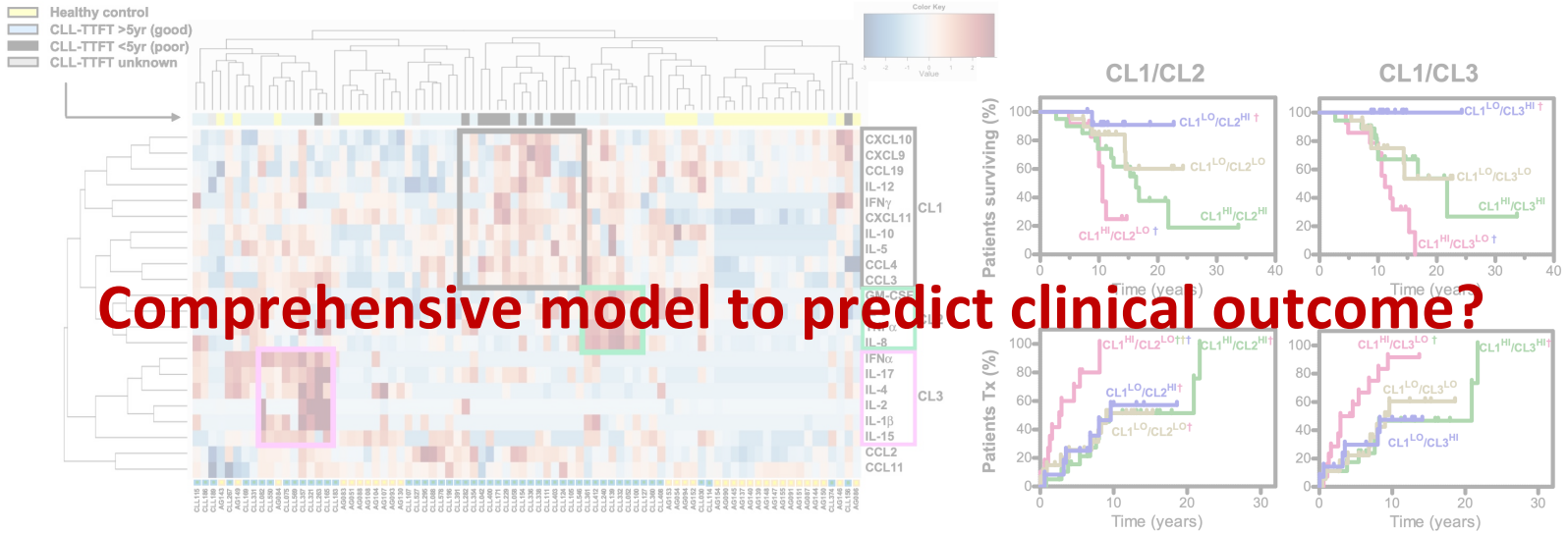
Palazzo degli Affari

Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

Serum Cytokine levels in CLL



Comprehensive model to predict clinical outcome?

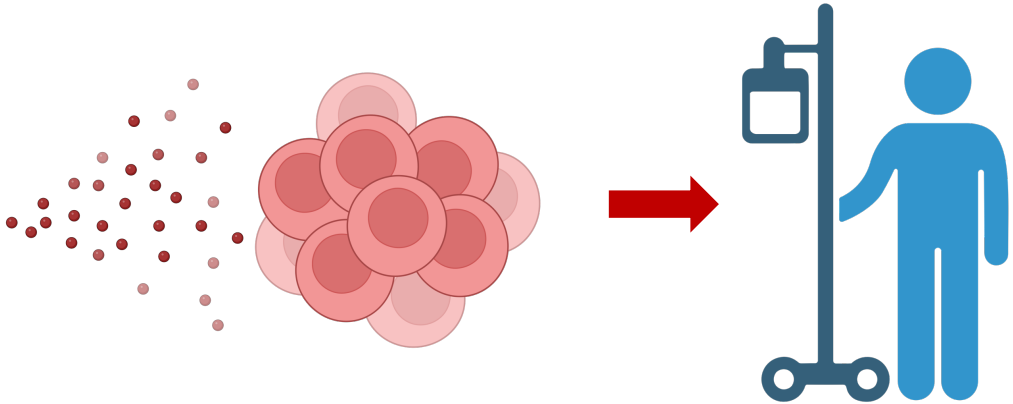
- Cytokine/chemokine serum levels may be used to predict OS and TTFT of CLL patients based on the differential concentration of cytokines divided into three groups

Yan *et al., Blood*. 2011

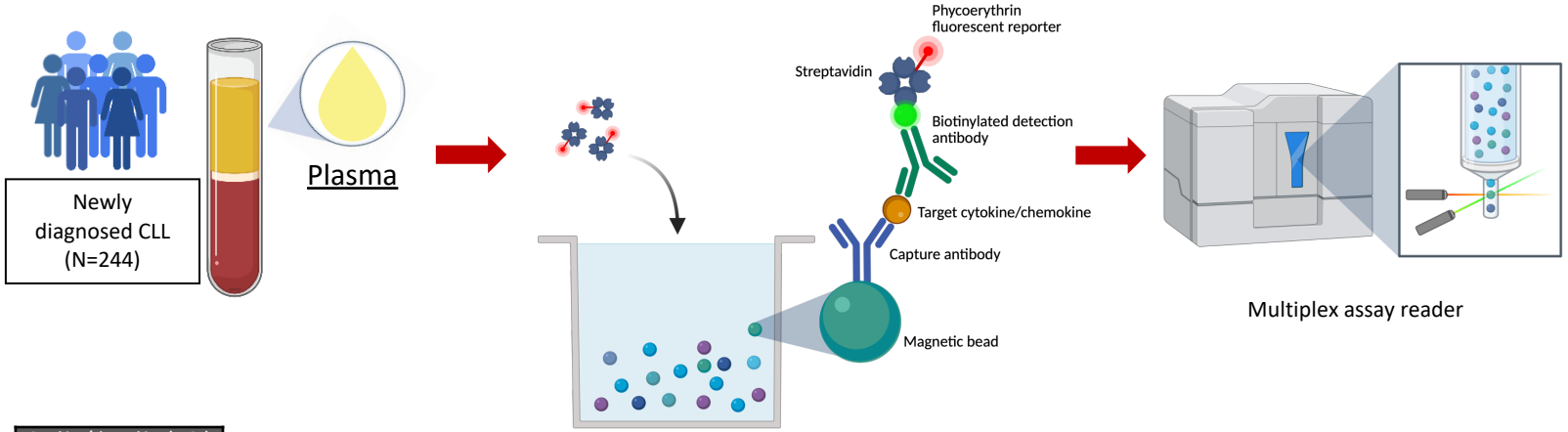
Aims of the study

- To assess the correlation between plasma cytokine/chemokine levels and baseline clinical and biological features of CLL

- To establish the relationship between baseline cytokine/chemokine profiles and clinical outcome of CLL



Experimental workflow

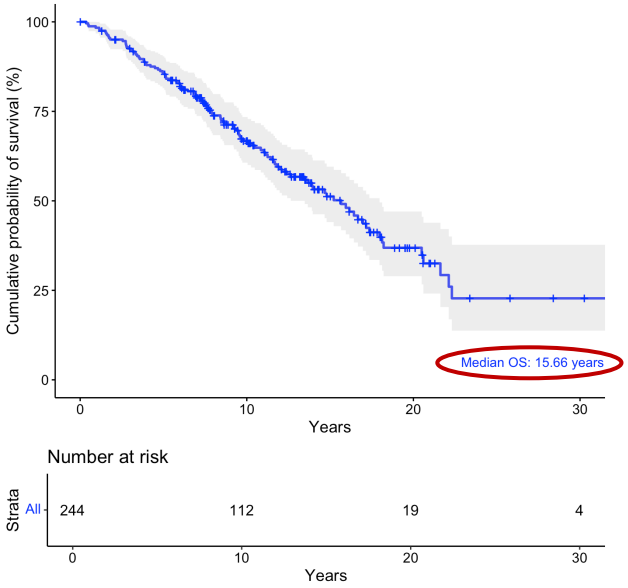


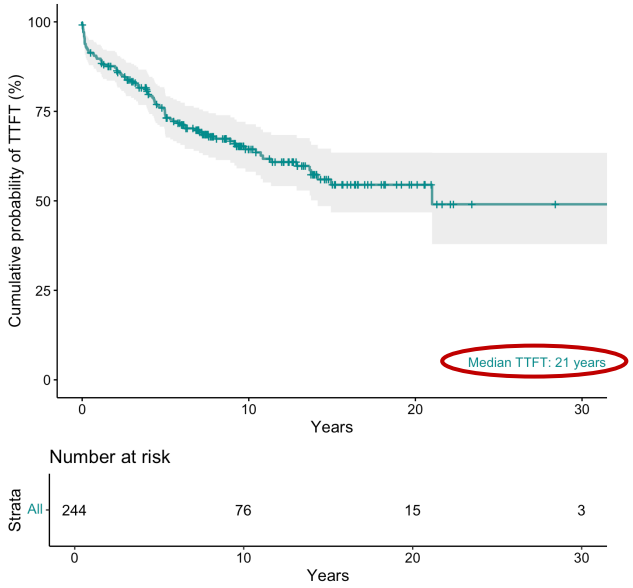
Cytokine/chemokine (n=27)	
FGF basic	IL-10
Eotaxin	IL-12 (p70)
G-CSF	IL-13
GM-CSF	IL-15
IFN-γ	IL-17A
IL-1β	IP-10
IL-1ra	MCP-1 (MCAF)
IL-2	MIP-1α
IL-4	MIP-1β
IL-5	PDGF-BB
IL-6	RANTES
IL-7	TNF-α
IL-8	VEGF
IL-9	

- Plasma was analyzed using a bead-based 27-plex sandwitch immunoassay
- Optimal cytokine/chemokine concentration cut-offs for risk analyses were defined using maximally selected rank statistics
- The machine-learning algorithms “self-organizing map” (SOM) and “K-means” were applied to divide patients into clusters based on cytokine/chemokine levels

Patient characteristics

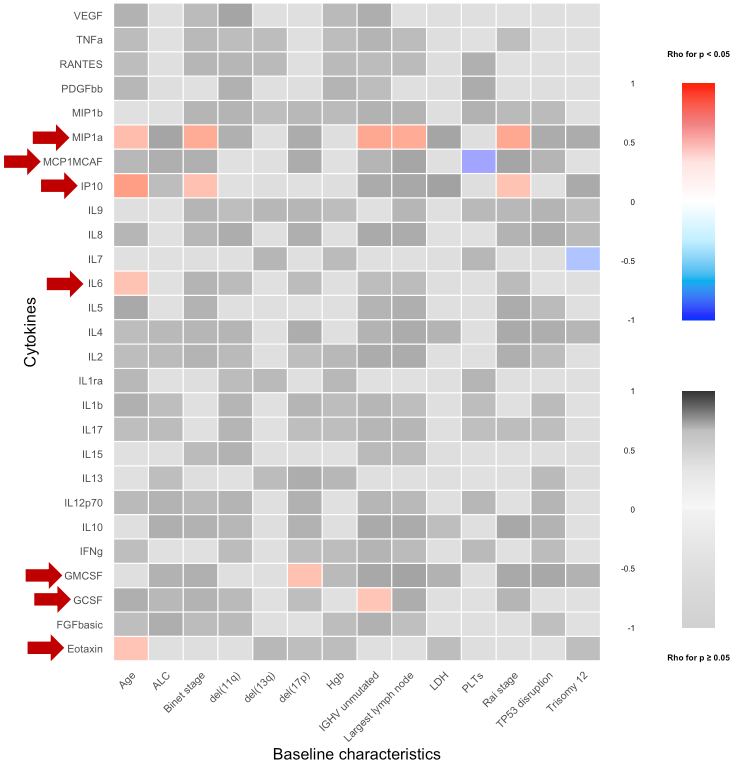
Characteristic	N (%)
Gender (n. %)	
Male	135 (55.3%)
Female	109 (44.7%)
Age (median)	68.9
Lymphocyte x10^3/µL (median)	8.4
Hb g/dL (median)	13.9
Platelet x10^3/µL (median)	210
IGHV status	
Unmutated	73 (29.9%)
Mutated	163 (66.8%)
***TP53* disrupted**	
Yes	16 (6.6%)
No	226 (92.6%)
Trisomy 12	
Present	34 (13.9%)
Absent	208 (85.2%)
Del11q	
Present	15 (6.1%)
Absent	227 (93.0%)
Del13q	
Present	124 (50.8%)
Absent	118 (48.4%)
Richter transformation	
Yes	9 (3.7%)
No	235 (96.3%)
Treated	
Yes	87 (35.7%)
No	157 (64.3%)
Type of 1st line treatment	
Chemo-immunotherapy	73 (83.9%)
BTKi or BCL2i	14 (16.1%)





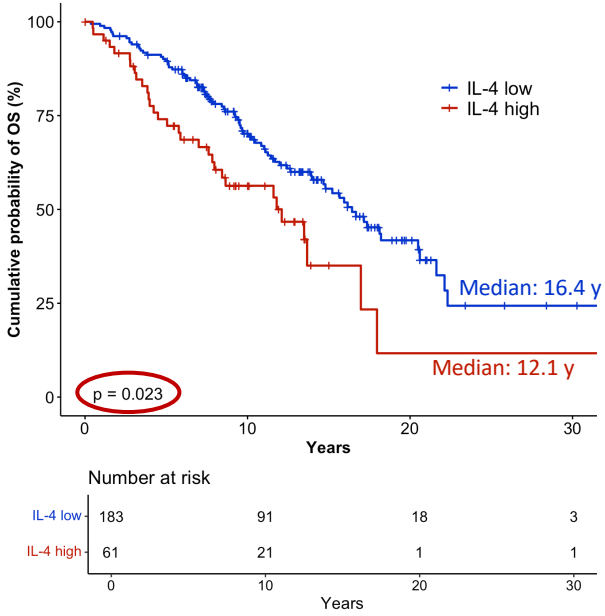
Median follow-up: 13.42 years

Cytokine/chemokine levels correlate with baseline characteristics



- High MIP-1α correlates with older age, advanced Rai/Binet stage, unmutated IGHV and large lymph node diameter
- High MCP-1 is associated with a lower platelet count
- High IP-10 associates with older age and advanced Rai/Binet stage
- High IL-6 and eotaxin are linked to older age
- High GM-CSF correlates with del(17p)
- High G-CSF is associated with unmutated IGHV

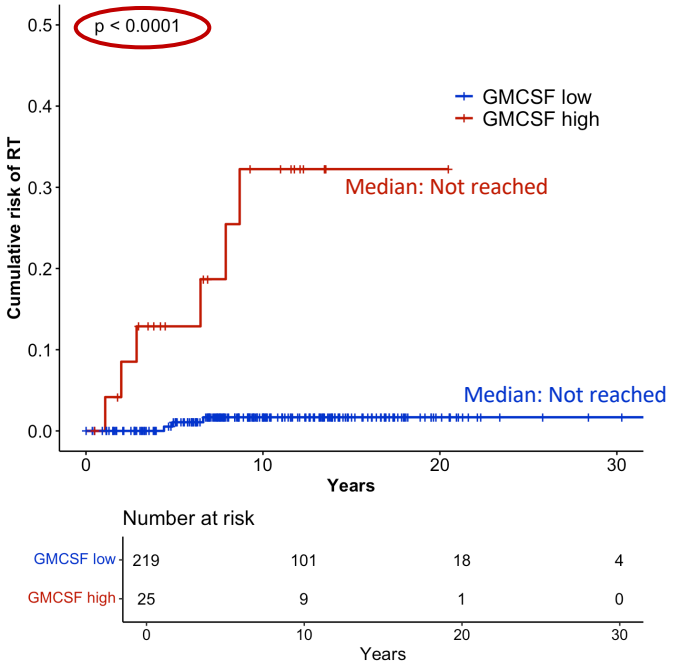
High IL-4 levels are associated with shorter OS



Variable	N	Hazard ratio	p
Age>65 years	234	5.67 (3.33, 9.66)	<0.001
TP53 Mut/Del	234	5.09 (2.60, 9.98)	<0.001
IGHV Unmutated	234	2.34 (1.52, 3.58)	<0.001
MIP1a high	234	1.12 (0.59, 2.12)	0.732
IP10 high	234	1.09 (0.71, 1.68)	0.691
GCSF high	234	1.17 (0.61, 2.26)	0.634
PDGFbb high	234	1.53 (0.93, 2.51)	0.093
IL4 high	234	2.20 (1.23, 3.94)	0.008
GMCSF high	234	1.26 (0.65, 2.45)	0.494
IL5 high	234	0.97 (0.46, 2.06)	0.938
IL6 high	234	1.30 (0.58, 2.93)	0.526
IL2 high	234	1.43 (0.85, 2.40)	0.176
IL9 high	234	0.59 (0.37, 0.92)	0.021

- High levels of **IL-4**, using a cut-off of **5.78 pg/mL**, independently associated with shorter OS

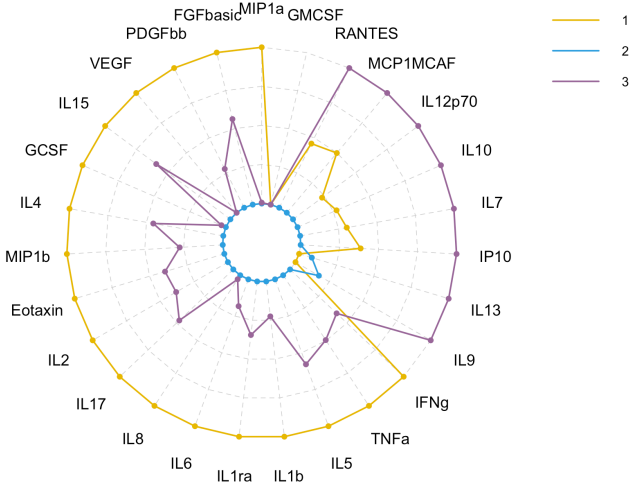
High GM-CSF levels are associated with shorter time to RT

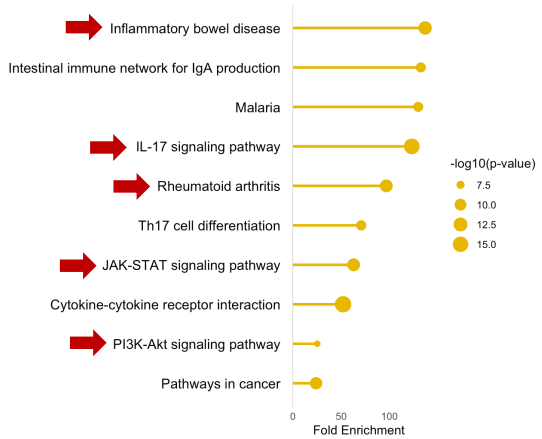


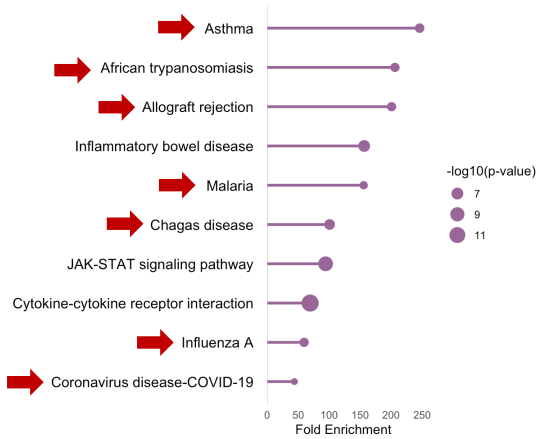
Variable	N	Hazard ratio	p
TP53 Mut/Del	242	4.39 (0.45, 42.36)	0.201
GMCSF high	242	9.32 (1.73, 50.27)	0.009
MIP1a high	242	2.44 (0.57, 10.49)	0.231
IL4 high	242	2.29 (0.32, 16.56)	0.413
IL10 high	242	1.60 (0.34, 7.59)	0.553

- **GM-CSF**, with a cutoff of **0.86 pg/mL**, independently predicted RT (HR 9.32)

Three patient clusters based on levels of 27 cytokines/chemokines

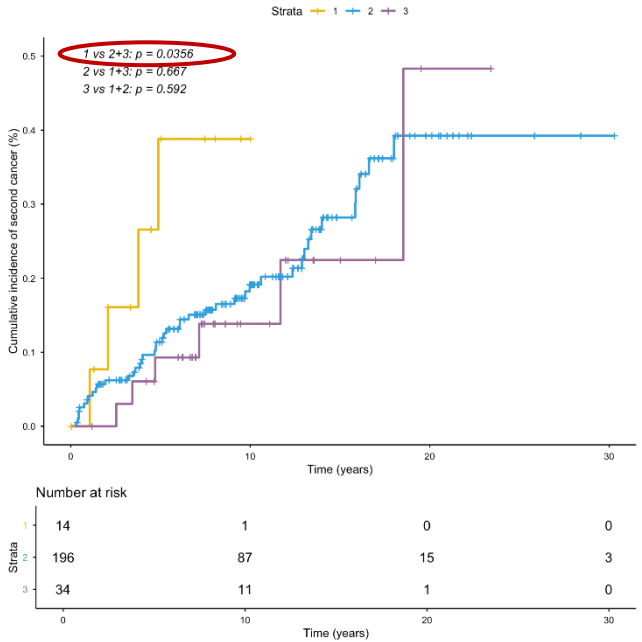






- Unsupervised clustering identified three patient groups, with distinct cytokine/chemokine profiles
- Cluster 1 displayed higher activation of inflammation-related pathways
- Cluster 3 is characterized by the activation of autoimmunity and infection response pathways

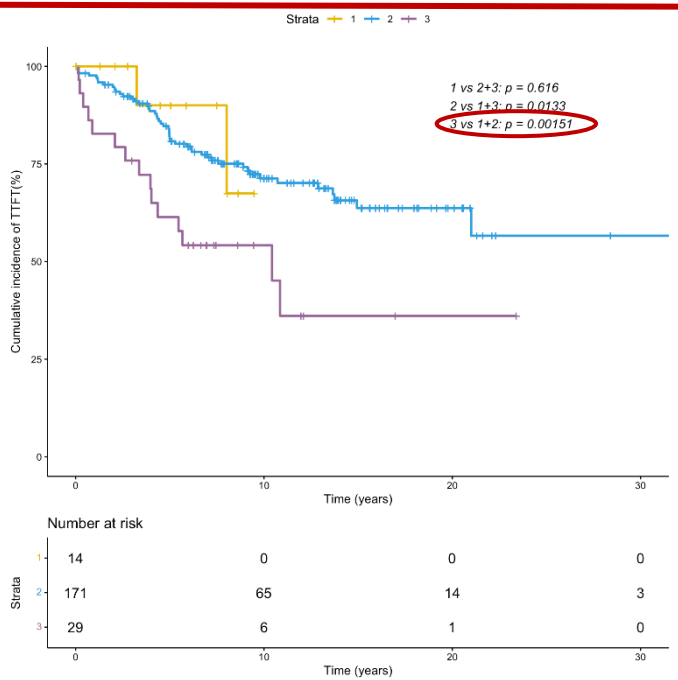
Cluster 1 predisposes to second malignancies



Variable	N	Hazard ratio	p
Exposed to CIT	244	1.60 (0.91, 2.79)	0.10
Cluster 1	244	3.30 (1.14, 9.54)	0.03
Age>65 years	244	1.12 (0.64, 1.95)	0.70

- C1 was associated with higher risk of second malignancy development (i.e. occurred after CLL diagnosis)

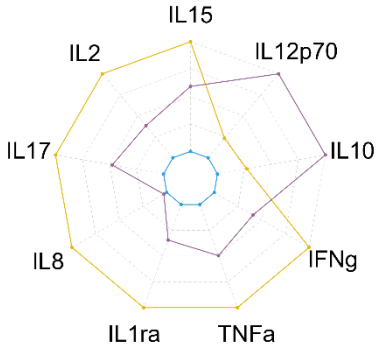
Cluster 3 predicts shorter TTFT

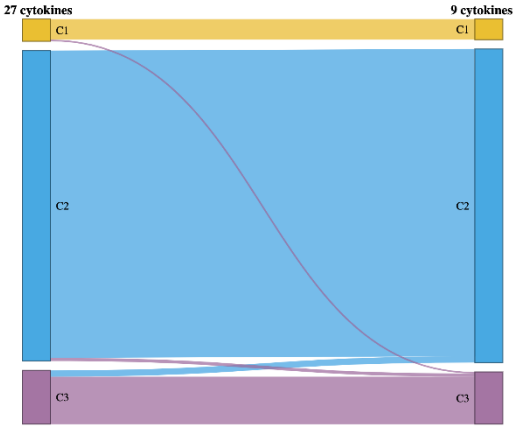


Variable	N	Hazard ratio	p
Cluster 3	206	2.10 (1.13, 3.90)	0.019
IGHV Unmutated	206	4.95 (2.94, 8.35)	<0.001
nodal involvement	206	3.44 (2.03, 5.83)	<0.001
ALC > 15x10^9	206	2.38 (1.38, 4.10)	0.002

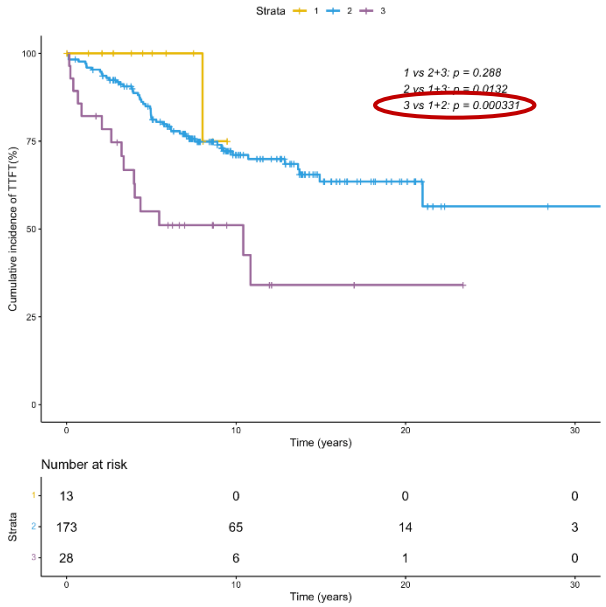
- Rai 0/1 patients in C3 experienced a shorter TTFT, indicating a higher risk of early disease progression possibly due to impaired T-cell immunity

A 9-cytokine panel preserves original clustering patterns

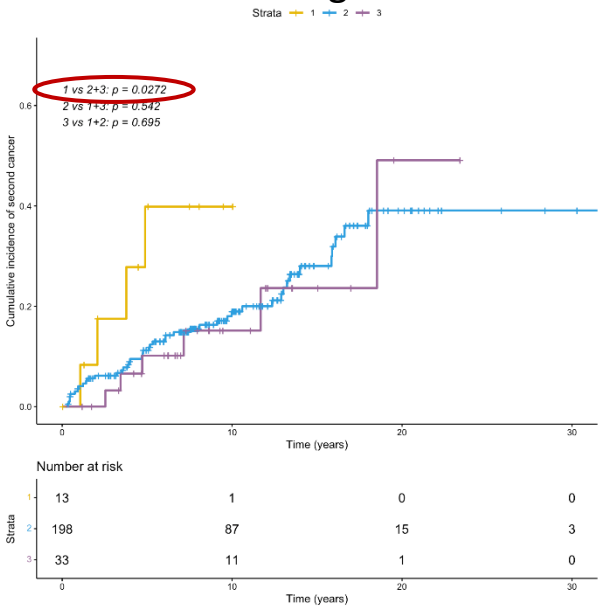




TTFT



Second malignancies



- Adjusted Rand index (ARI)= 0.893

Conclusions

- Plasma levels of immunomodulatory cytokines/chemokines are associated with unfavourable clinical and biological features at the time of CLL diagnosis
- High IL-4 levels are independently associated with shorter OS, while high GM-CSF correlates with shorter time to RT in multivariate analysis
- Differential cytokines/chemokine profiles can be used to divide patients into three distinct clusters, which predict shorter occurrence of second malignancy (cluster 1), and shorter TTFT (cluster 3)
- A simplified panel of 9 cytokines is sufficient to preserve the original cluster structure.

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Thank you!
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