PROFILING OF RELAPSED OR REFRACTORY LARGE B-CELL LYMPHOMA AND ITS ASSOCIATION WITH PROGRESSION-FREE SURVIVAL FOLLOWING FIRST-LINE THERAPY

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INTRODUCTION

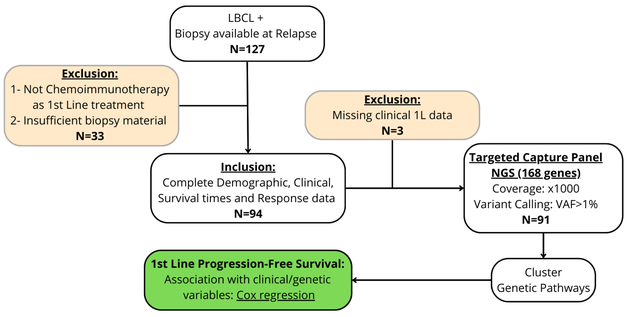
Definitive cure rates after first line treatment with chemoimmunotherapy for Large B-cell Lymphoma (LBCL) are found to be approximately 60%, with 15% of patients being primary refractory to this line, and a further 15% of them relapsing within the first 12 months after end of treatment.

The molecular alterations that drive poor response to front-line chemoimmunotherapy treatment in LBCL are currently unknown.

AIM

This study aims to describe which LBCL **molecular alterations detected at relapse** are associated with shorter first-line PFS and identify them as potential resistance drivers.

METHODS



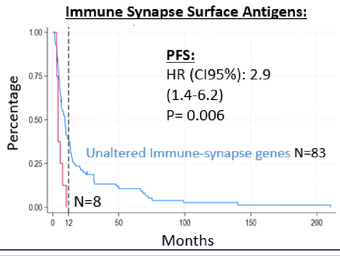
RESULTS

Variables	Total (N=91)
Sex, Male	59% (N=54)
Median Age [IQR]	62.2 Years [52-74]
1st Line Treatment	R-CHOP: 80% (N=73)
	R-DA-EPOCH: 2% (N=2)
	Platinum-based: 12% (N=11)
	Other: 6% (N=5)
1st Line Relapse Latency	Primary Refractory: 41% (N=37)
	Early Relapse <12 months EOT: 41% (N=37)
	Late Relapse >12 months EOT: 18% (N=17)
Histology	DLBCL: 85% (N=77)
	HGBCL: 14% (N=13)
	THRBCL: 1% (N=1)
Cell Of Origin (Hans)	GCB: 75% (N=68)
	Non-GCB: 23% (N=21)
	NA: 2% (N=2)
International Prognostic Index	0-2: 44% (N=40)
	3-5: 56% (N=51)
Relapse-Free Survival [IQR]	7.3 months [4-15]

Functional B-cell genes regulating T-cell immunity:

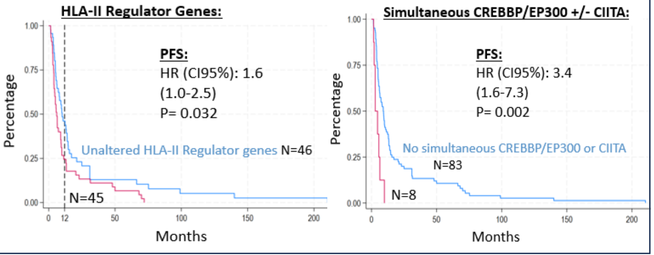
Immune Synapse Surface Antigens: N=8

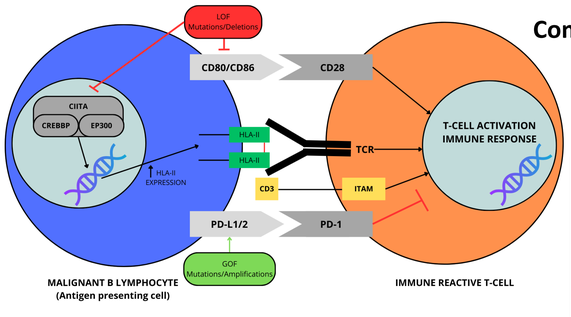
CD80 **LOF Mutations/Deletions** N=6, HR (CI95%): 3.7 (1.6-8.8), p= 0.003
CD86 **LOF Mutations/ Deletions** N=4 HR (CI95%): 2.8 (1.0-7.9), p= 0.048
PD-L1 **GOF Mutations/Gains** N=2 HR (CI95%): 4.2 (0.99-18.1), p= 0.051
PD-L2 **GOF Mutations/Gains** N=3 HR (CI95%): 2.1 (0.7-6.7), p= 0.21



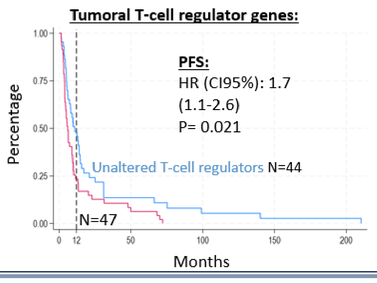
HLA-II Regulator Genes: N=45

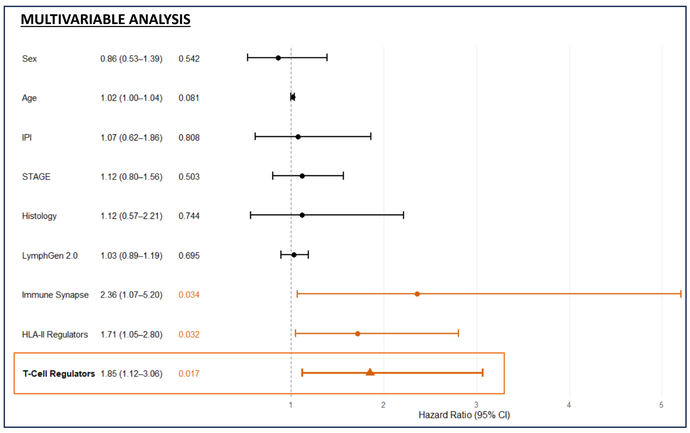
CIITA **LOF Mutations/Deletions** N=3, HR (CI95%): 4.0 (1.2-13.1), p= 0.021
CREBBP **LOF Mutations/ Deletions** N=41 HR (CI95%): 1.8 (1.2-2.8), p= 0.008
EP300 **LOF Mutations/ Deletions** N=10 HR (CI95%): 1.4 (0.7-2.7), p= 0.3
Simultaneous *CREBBP/EP300* LOF N=7 HR (CI95%): 3.8 (1.7-8.5), p< 0.001





Combined alterations of B-cell genes controlling T-cell Responses: HLA-II Regulators + Immune Synapse





CONCLUSIONS

Shorter progression free survival times following first line chemoimmunotherapy in Large B-cell Lymphoma are significantly associated with genetic alterations in tumoral B-cell genes that mediate T-cell activation and anti-tumoral response, as detected at relapse. Whether these alterations are present at diagnosis and drive primary treatment resistance, or arise during the course of disease progression, remains to be elucidated.

Sequencing of paired biopsies at initial diagnosis is currently underway to determine clonal selection at relapse.

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