Circulating tumor DNA at baseline as a prognostic marker in untreated follicular lymphoma

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Circulating Tumor DNA at Baseline as a Prognostic Marker in Untreated Follicular Lymphoma

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Supplementary data

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Supplementary table 1

	Not sampled (N=786)	Sampled for ctDNA population (N=416)	Intention to Treat Population (N=1202)	weighted biomarker population* (N*=1202)
Age				
Mean (SD)	57.668 (11.980)	58.291 (11.664)	57.884 (11.870)	58.339 (11.725)
Range	23 - 88	27 -7 85	23 - 88	27 - 85
Sex				
F	407 (51.8%)	232 (55.8%)	639 (53.2%)	692 (57.6%)
M	379 (48.2%)	184 (44.2%)	563 (46.8%)	510 (42.4%)
Race				
American Indian or Alaska native	1 (0.1%)	0 (0%)	1 (0.1%)	0 (0%)
Asian	155 (19.7%)	43 (10.3%)	198 (16.5%)	124 (10.3%)
Black or African AMerican	3 (0.4%)	1 (0.2%)	4 (0.3%)	4 (0.3%)
Multiple	3 (0.4%)	0 (0%)	3 (0.2%)	0 (0%)
Native Hawaiian or other pacific islander	1 (0.1%)	0 (0%)	1 (0.1%)	0 (0%)
other	18 (2.3%)	9 (2.2%)	27 (2.2%)	24 (2.0%)
white	605 (77.0%)	363 (87.3%)	968 (80.5%)	1050 (87.4%)
Geographic region				
Asia	144 (18.3%)	41 (9.9%)	185(15.4%)	114 (9.5%)
Eastern Europe	94 (12.0%)	63 (15.1%)	157 (13.1%)	184 (15.3%)
North America	98 (12.5%)	54 (13.0%)	152 (12.6%)	165 (13.7%)
Other	88 (11.2%)	39 (9.4%)	127 (10.6%)	126 (10.5%)
Western Europe	362 (46.1%)	219 (52.6%)	581 (48.3%)	612 (50.9%)
Arm				
G-Benda	231 (29.4%)	114 (27.4%)	345 (28.7%)	345 (28.7%)
G-CHOP/CVP	167 (21.2%)	89 (21.4%)	256 (21.3%)	256 (21.3%)

R-Benda	229 (29.1%)	112 (26.9%)	341 (28.4%)	341 (28.4%)
R-CHOP/CVP	159 (20.2%)	101 (24.3%)	260 (21.6%)	260 (21.6%)
FLIPI				
HIgh	325 (41.3%)	178 (42.8%)	503 (41.8%)	503 (41.8%)
Intermediate	301 (38.3%)	147 (35.3%)	448 (37.3%)	448 (37.3%)
Low	160 (20.4 %)	91 (21.9%)	251 (20.9%)	251 (20.9%)
Ann Arbor Stage at Diagnosis				
	3 (0.4%)	4 (1.0%)	7 (0.6%)	14 (1.1%)
I	11 (1.4%)	7 (1.7%)	18 (1.5%)	19 (1.6%)
II	52 (6.6%)	33 (7.9%)	85 (7.1%)	93 (7.7%)
III	299 (38.0%)	118 (28.4%)	417 (34.7%)	342 (28.5%)
IV	421 (53.6%)	254 (61.1%)	675 (56.2%)	734 (61.1%)
PFS group				
censored < 5y	143 (18.2%)	58 (13.9%)	201 (16.7%)	201 (16.7%)
PFS <= 2y	79 (10.1%)	98 (23.6%)	177 (14.7%)	177 (14.7%)
2y <= PFS <= 5y	124 (15.8%)	62 (14.9%)	186 (15.5%)	186 (15.5%)
PFS > 5y	440 (56.0%)	198 (47.6%)	638 (53.1%)	638 (53.1%)
FLIPI 2				
	28 (3.6%)	9 (2.2%)	37 (3.1%)	27 (2.2%)
High	297 (37.8%)	178 (42.8%)	475 (39.5%)	504 (41.9%)
Intermediate	386 (49.1%)	198 (47.6%)	584 (48.6%)	576 (48.0%)
Low	75 (9.5%)	31 (7.5%)	106 (8.8%)	95 (7.9%)

*Inverse probability weighted according to FLIPI1, treatment arm and PFS group.

Supplementary Table 2

Confusion Matrices for MMPM cutoff Performance.

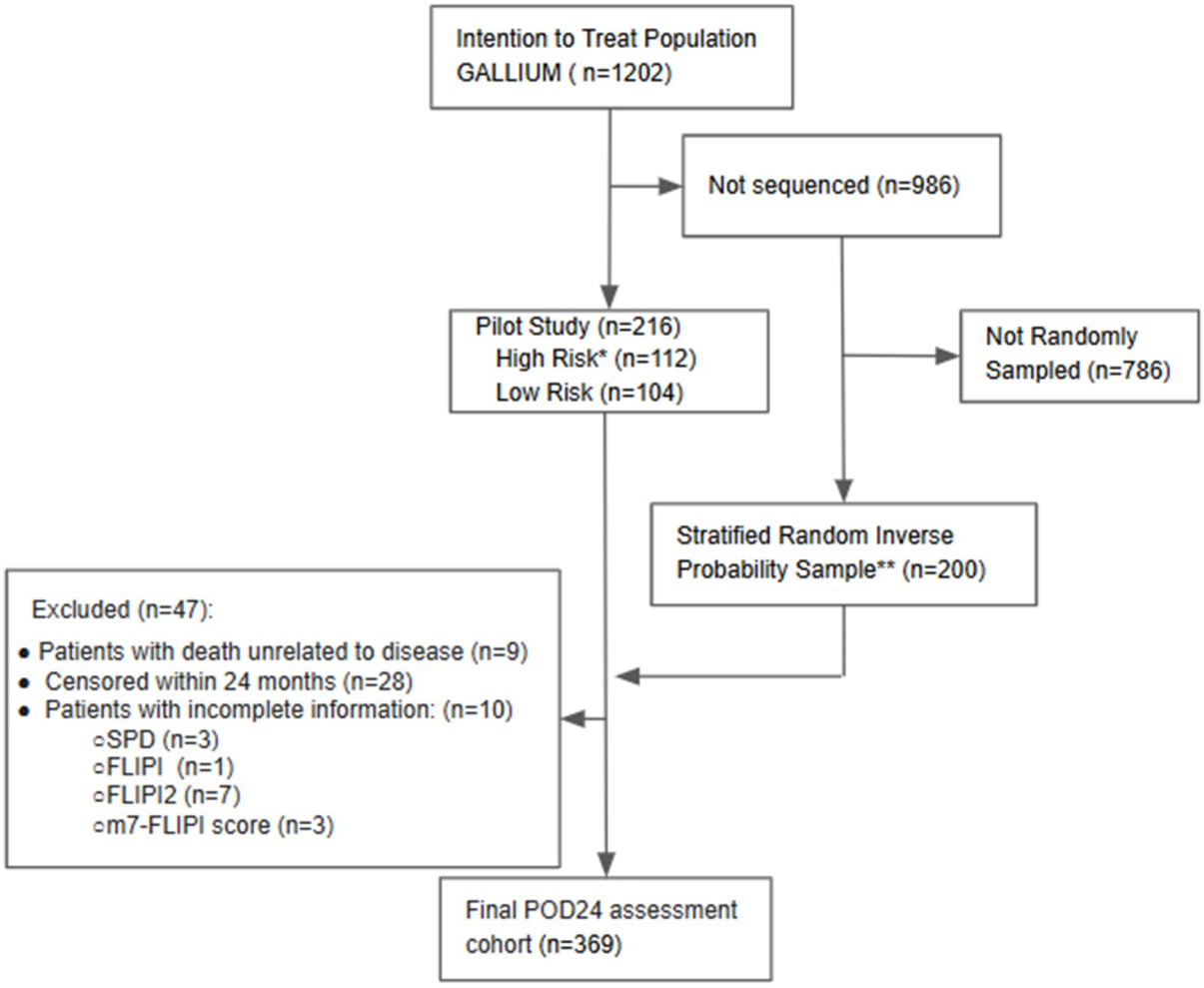
A Confusion matrix for MMPM cutoff 168.57 predicting Progression of Disease within 24 months (POD24)

Prediction POD24	Positive	Negative
High MMPM (POD24)	116.95	60.05
Low MMPM (No POD24)	291.77	639.93

B Confusion matrix for MMPM cutoff 168.57 predicting transformation to high-grade lymphoma (trFL)

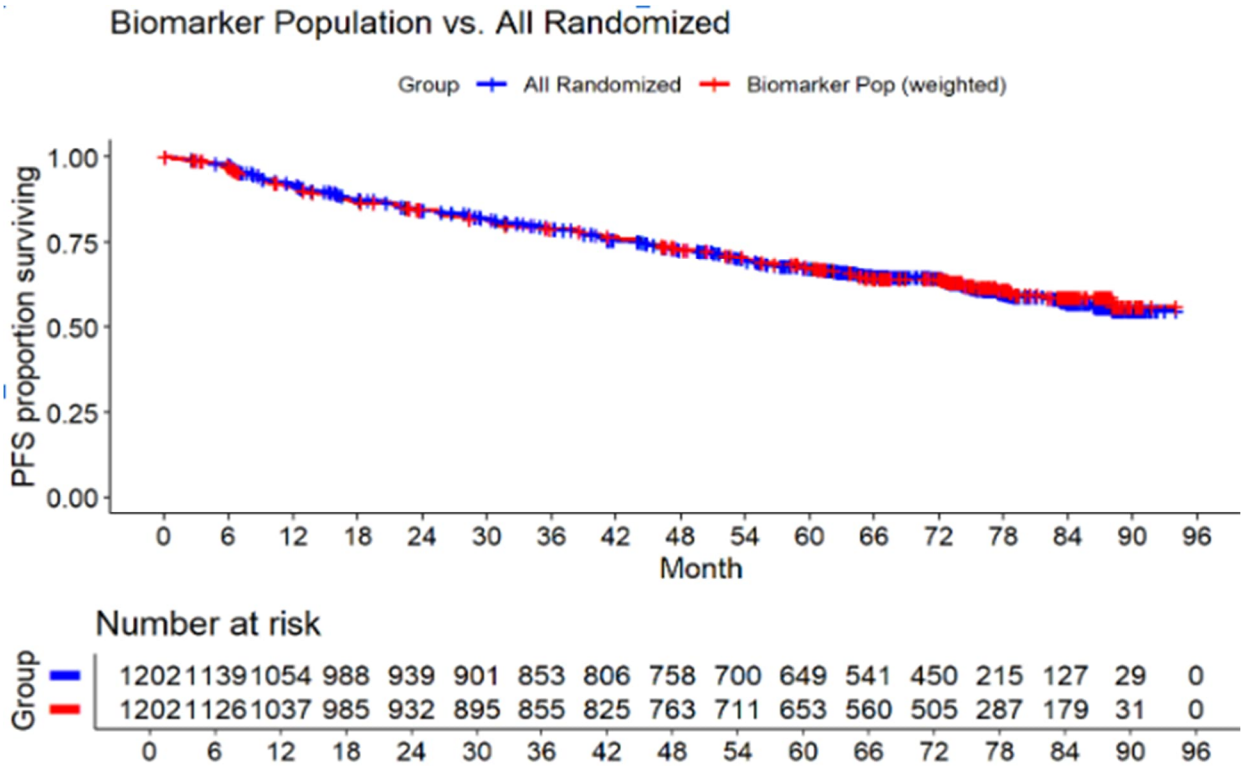
Prediction trFL	Positive	Negative
High MMPM (Transformed)	38.6	396
Low MMPM (No Transformed)	21.8	746

Supplementary Figure 1

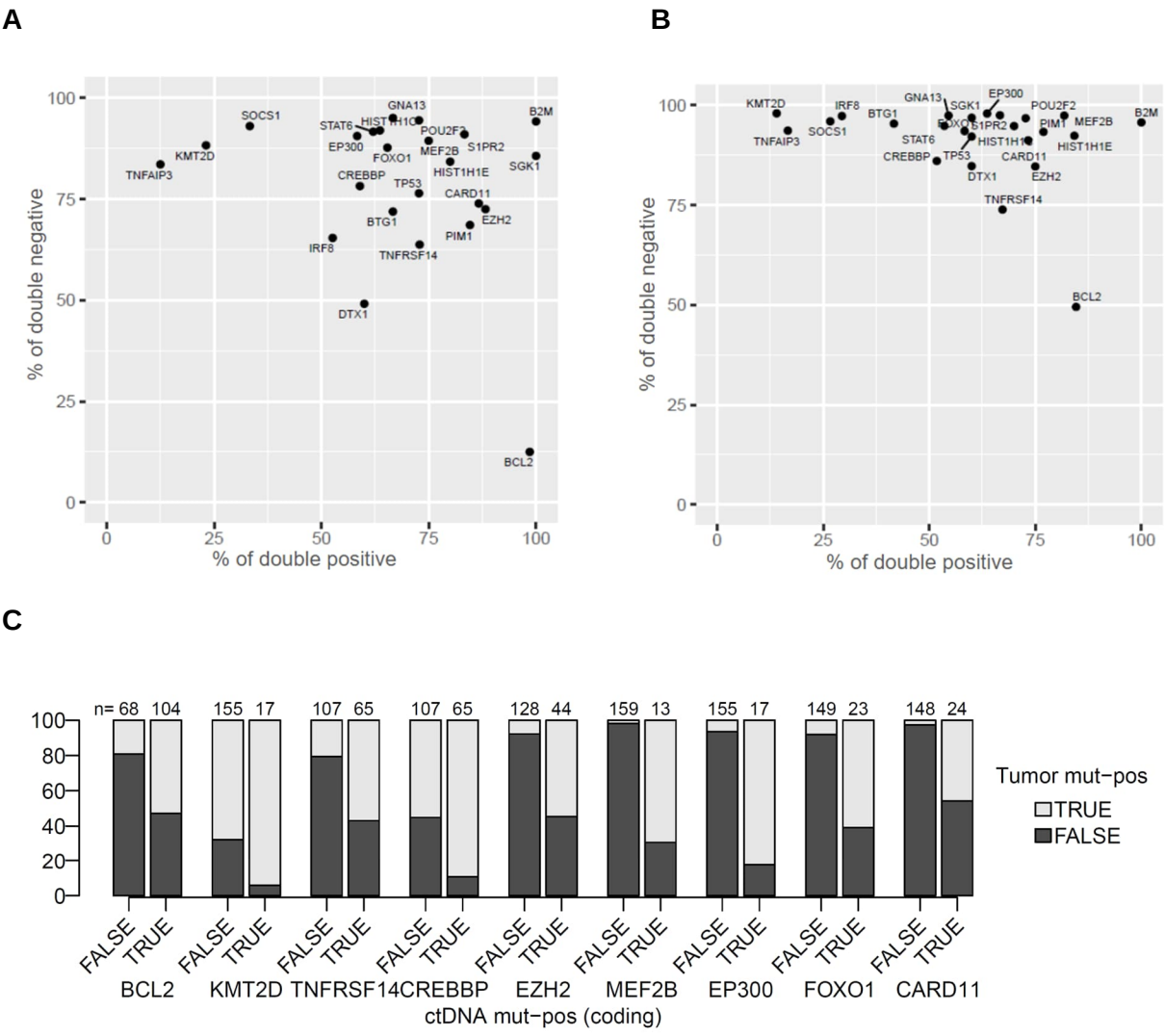


*High risk: cases with early progression or transformation to an aggressive disease
Low risk: long-term responders with progression-free survival (PFS) > 5 years
** Inverse probability stratified random sampling to achieve adequate representation across PFS, FLIPI groups, and treatment groups reflecting GALLIUM ITT population after combination with the pilot cohort.

Supplementary Figure 2



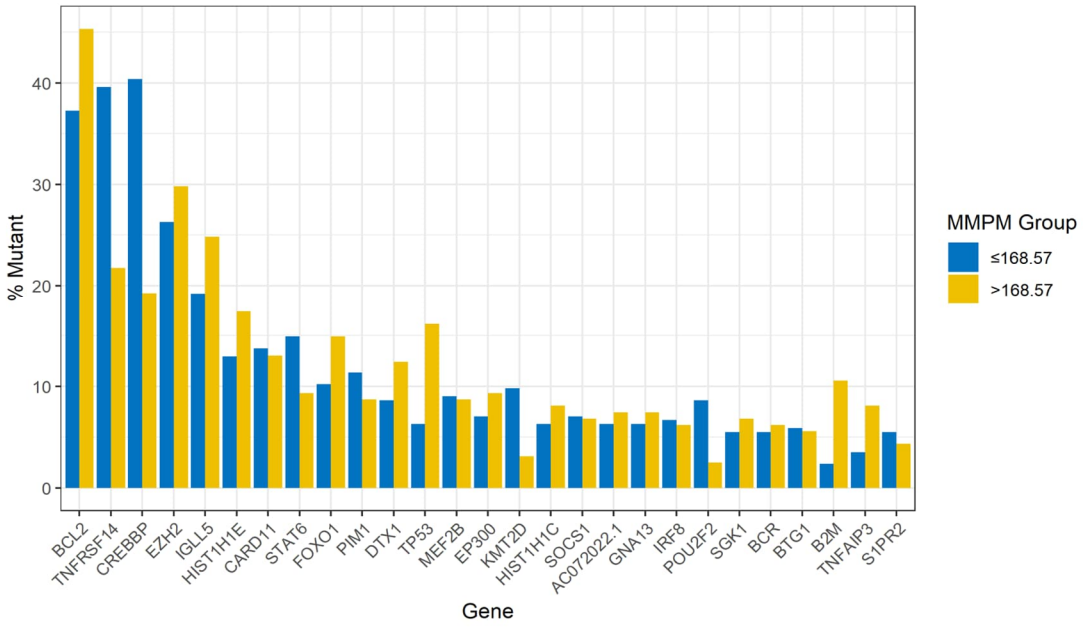
Supplementary Figure 3



Supplementary Figure 3. Concordance of Mutation Calls Between CAPP-seq in ctDNA and Targeted Exon Sequencing of Tumor Biopsies.

A) Scatter plots comparing mutation calls for 24 genes common to both the CAPP-seq in plasma and targeted sequencing panels. Targeted sequencing of tumor biopsies was used as reference for comparison. The % double positive and the % double negative are defined as the fraction of samples with an overlapping mutation stats call (mutated or unmutated) between the two assays, normalized to the total number of positive calls by targeted sequencing **B)** concordance after filtering ctDNA data for SNV in the coding region with an AF > 0.5%. **C)** Paired analysis of somatic mutation status across 10 recurrently mutated genes in lymphoma showing the concordance of mutational status (TRUE=mutated, FALSE= non mutated) between plasma-derived mutation in ctDNA by CAPPseq and tumour tissue derived mutation by targeted sequencing. Y-axis represents the percentage of patients within each category. n = number of patients

Supplementary Figure 4



Supplementary Figure 4: Molecular characterization of MMPM high vs MMPM low.

The bar graph indicates the percentage of patients with mutations in each gene respectively. This stratification is based on the MMPM cutoff.