Mutational and copy number analysis at diagnosis and relapse of mantle cell lymphoma

Erel Joffe,[1] Manik Uppal,[1,2] Serena Zheng,[1] Kurt S. Bantilan,[1] Connie Batlevi,[1] Zachary Epstein-Peterson,[1,2] Paola Ghione,[1,2] Paul Hamlin,[1,2] Matthew Matasar,[1] Alison Moskowitz,[1,2] Ariela Noy,[1,2] Maria L. Palomba,[1,2] Gotfried von Keudell,[1] Lorenzo Falchi,[1,2] Joachim Yahalom,[1,2] Vitaly Segodin,[3] Nikita Kotlov,[3] Evgeniy Egorov,[3] Sandrine Degryse,[3] Aleksander Bagaev,[3] Nathan Fowler,[3] Maria Arcila,[1,2] Ahmet Dogan,[1,2] Gilles Salles,[1,2] Anita Kumar[1,2#] and Andrew D. Zelenetz[1,2#]

[1]Memorial Sloan Kettering Cancer Center, Department of Medicine, New York, NY; [2]Weill Cornell College of Medicine, New York, NY and [3]BostonGene, Corporation. Waltham, MA, USA

[#]AK and ADZ contributed equally as senior authors.

Correspondence: E. Joffe
erelj@tlvmc.gov.il

A.D. Zelenetz
zeleneta@mskcc.org

Received: January 11, 2025.
Accepted: November 17, 2025.
Early view: November 27, 2025.

https://doi.org/10.3324/haematol.2024.286813

SUPPLEMENTARY MATERIALS

Figure S1: Copy Number Alteration (CNA) calling

Figure S2: Example of the effect of heterozygous loci enrichment for CNA calling

Figure S3: Consort Diagram (mutations only)

Figure S4: Genomic landscape of MCL (grouped by Ki67; mutations only)

Figure S5: Genomic landscape at frontline and at later lines of treatment comparing patients with long remission to those with earlier progression of disease

Figure S6: Genomic landscape prior to frontline treatment and at POD (sequential samples; mutations only)

See Supplementary Excel files

Table S1: Gene list - MSK-IMPACT targeted Heme panel

Table S2: CNA SNP validation: Evaluation of CNA calling compared to SNP array (n=18)

Table S3: MUT-CNA Diagnosis vs Relapse - Mutational and CNA landscape pre-treatment and at progression of disease

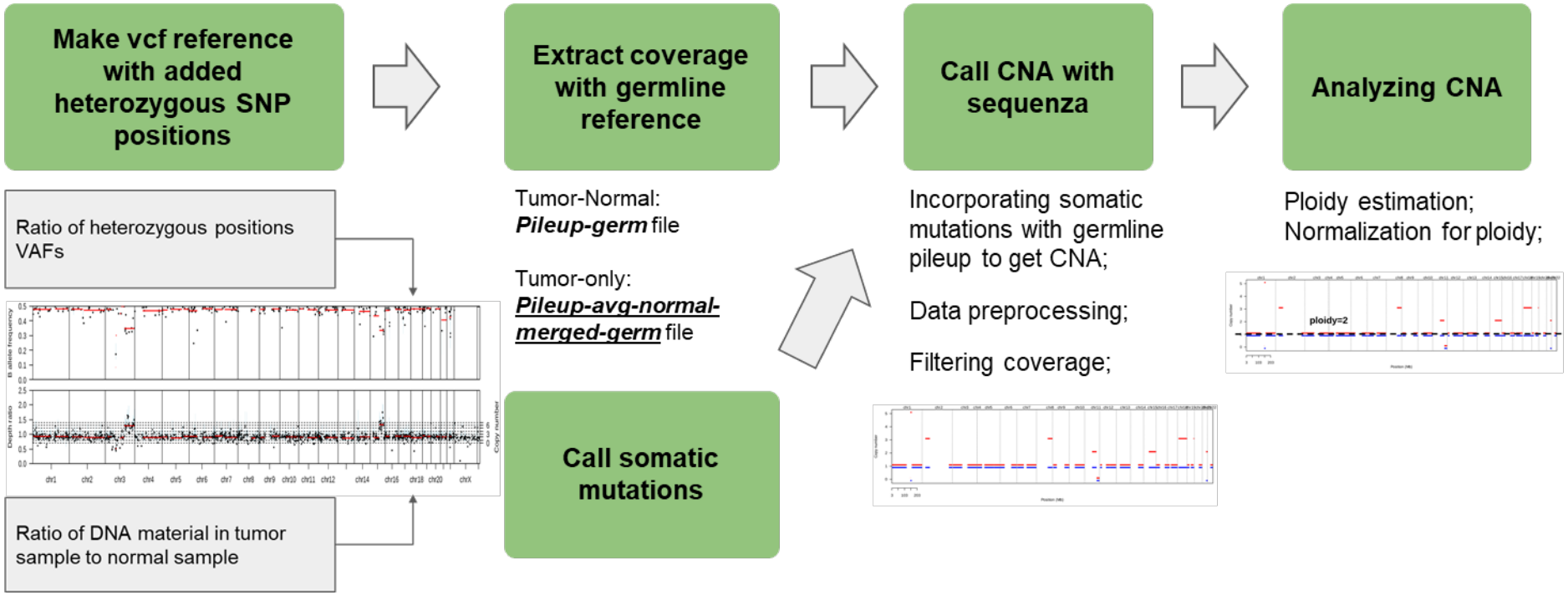
Table S4: MUT-CNA Ki67 - Mutational and CNA prevalence by Ki67

Table S5: Sequential samples - Copy Number Alteration (CNA) calling

Table S6: MUT-CNA PFS multivariable - Association of mutations and CNA with progression f ree survival - multivariable analysis

Table S7: MUT-CNA OS multivariable - Association of mutations and CNA with overall survival - multivariable analysis

Figure S1: Copy Number Alteration (CNA) calling



For CNA calling we used a modified algorithm of Sequenza v2.1.2, which was optimized for better filtration (of possible focal false-positive segments in centromere regions), as well as being introduced to the usage of FACETS v0.5.14 SNPs database for better coverage extraction and faster work. However, since all the samples were sequenced on a targeted platform, we faced the problem of lacking heterozygous positions for calling allele-specific CNAs. This issue was solved with the usage of heterozygous germline mutations called by Strelka v2.8.2. Positions of heterozygous mutations were included into individual reference vcf files for each sample, thus enriching the targeted regions and providing us with more statistical information for reliable segmentation and CNA calling.

Figure S2: Example of the effect of heterozygous loci enrichment for CNA calling

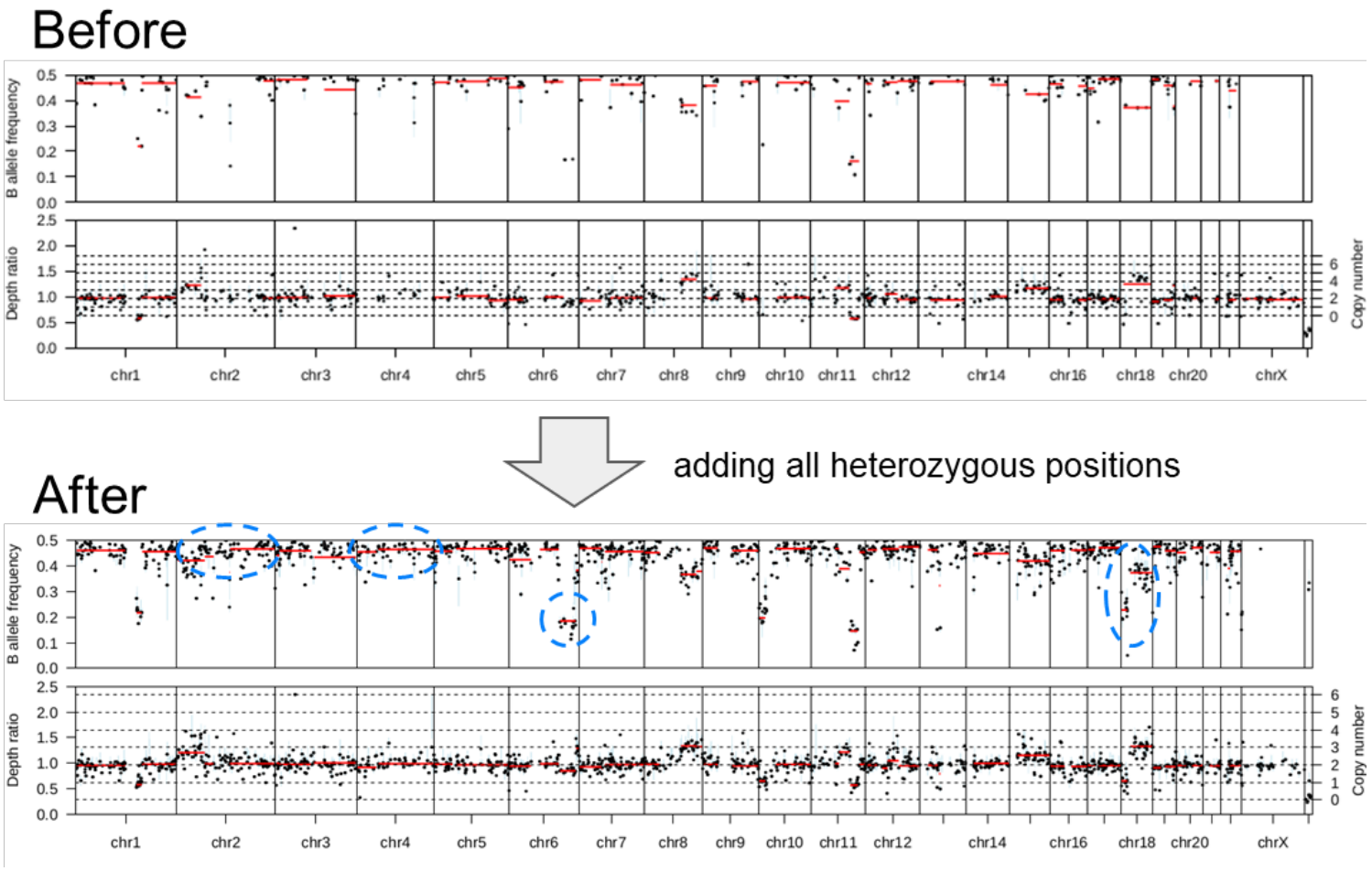


Figure S3: Consort Diagram (mutations only)

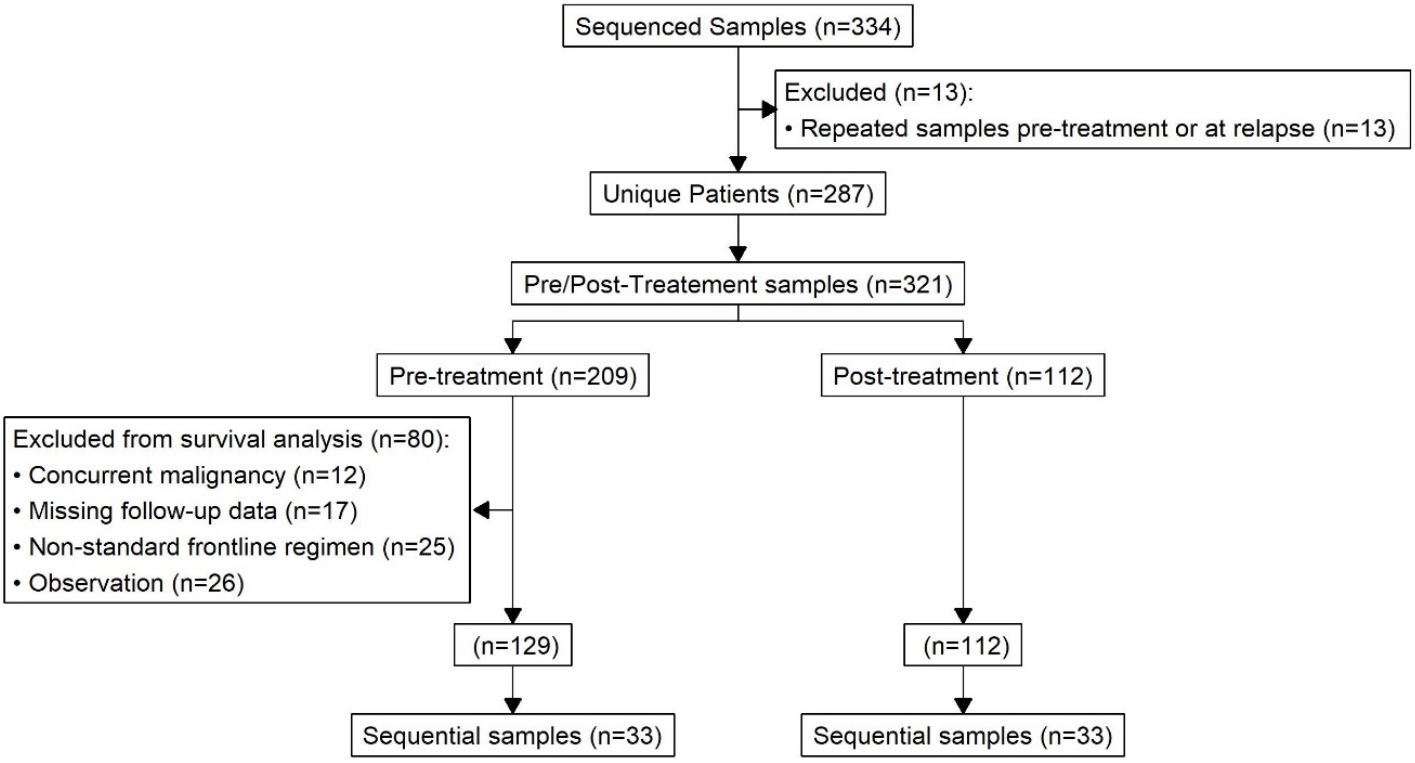
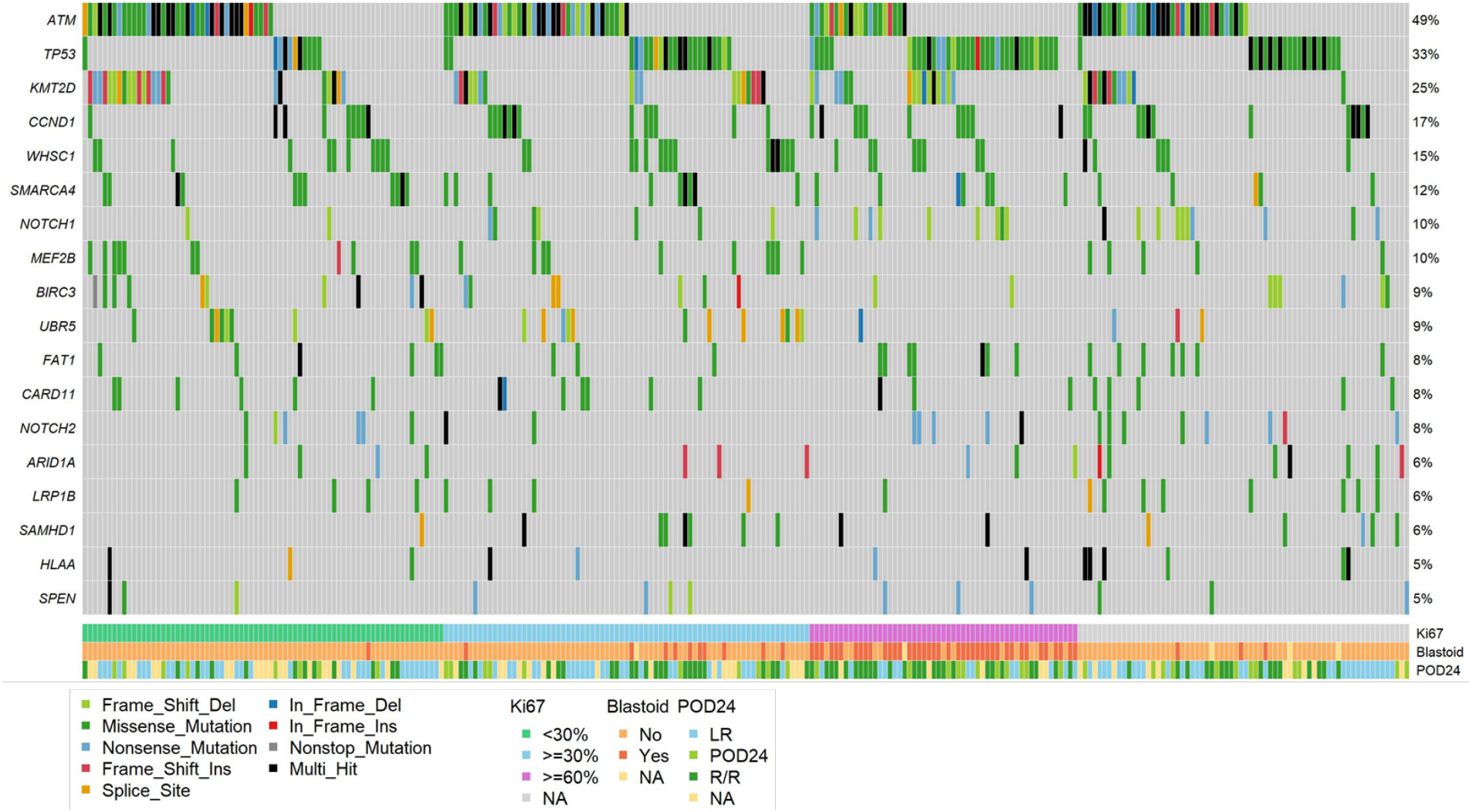
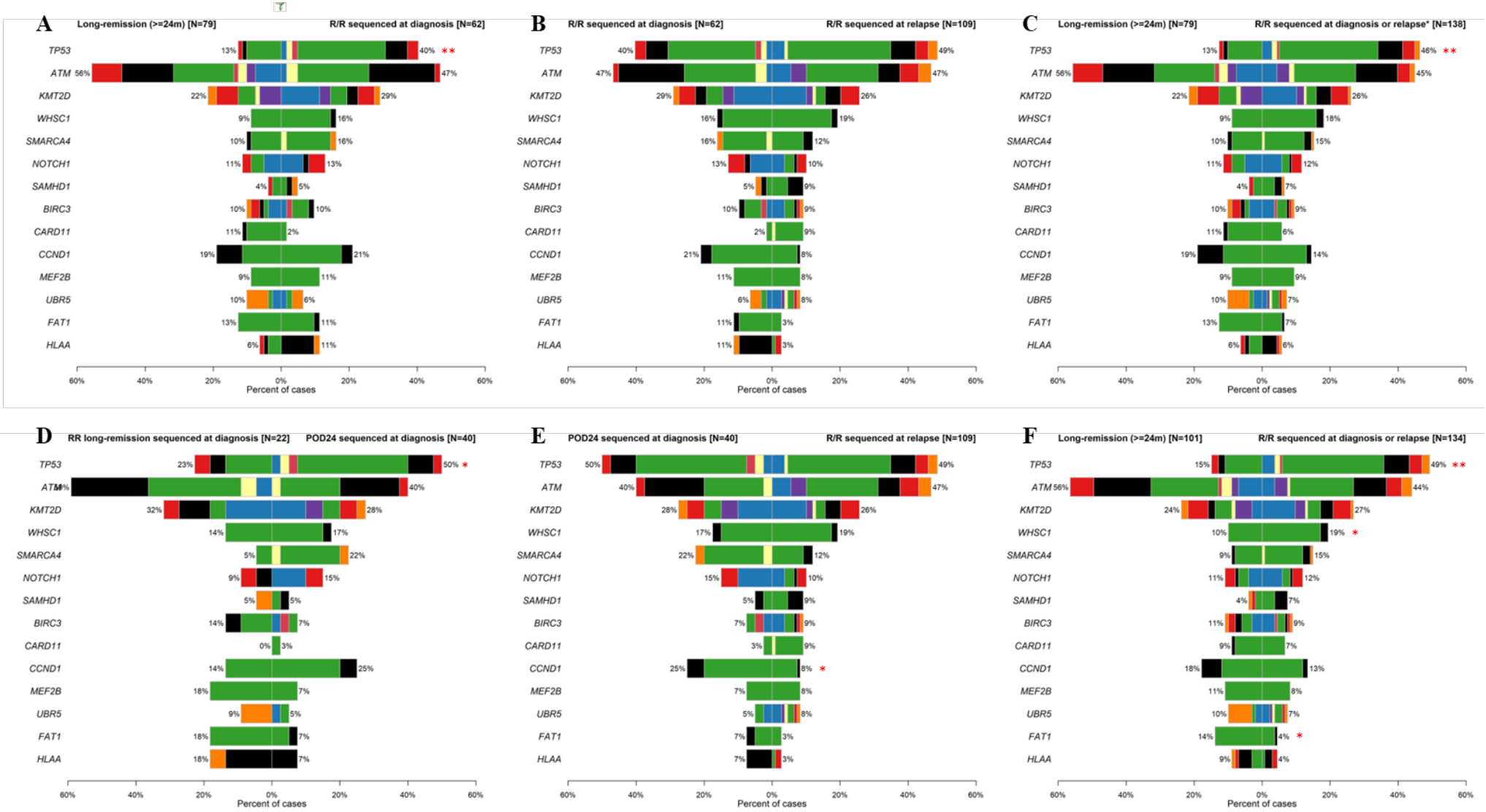


Figure S4: Genomic landscape of MCL (grouped by Ki67; mutations only)



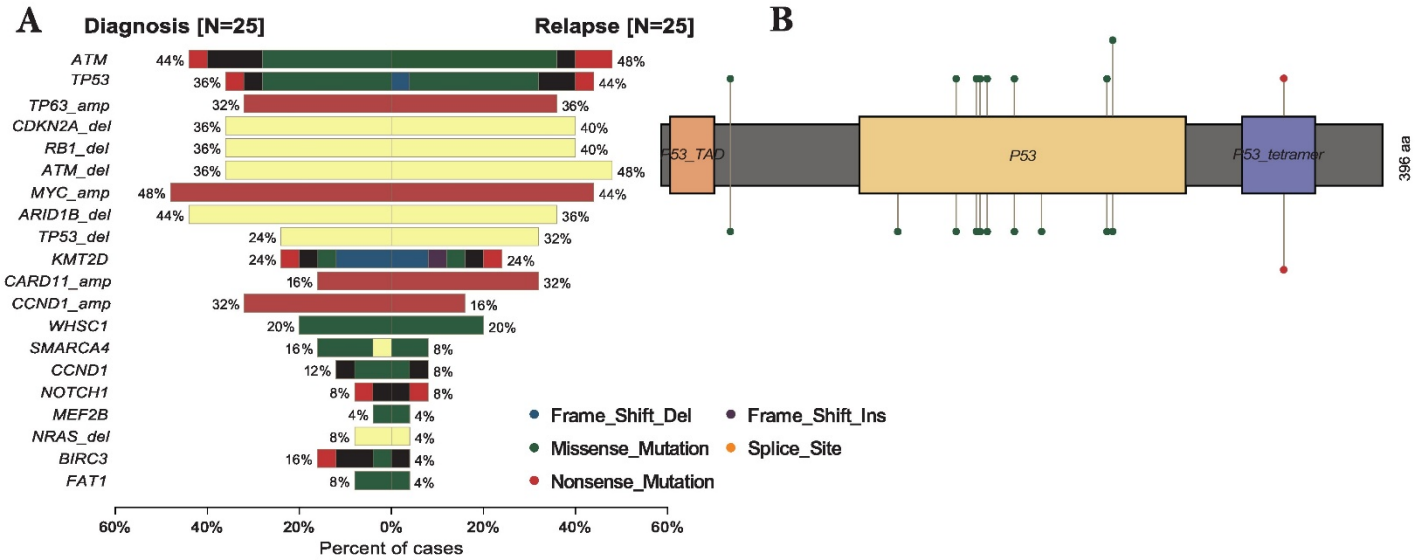
Unique cases only, excluding sequential samples from the same patient.
POD24 – cases sequenced pre-treatment who experienced a POD within ≤24m vs LR patients with a longer remission vs R/R samples sequenced at time of relapse.

Figure S5: Genomic landscape at frontline and at later lines of treatment comparing patients with long remission to those with earlier



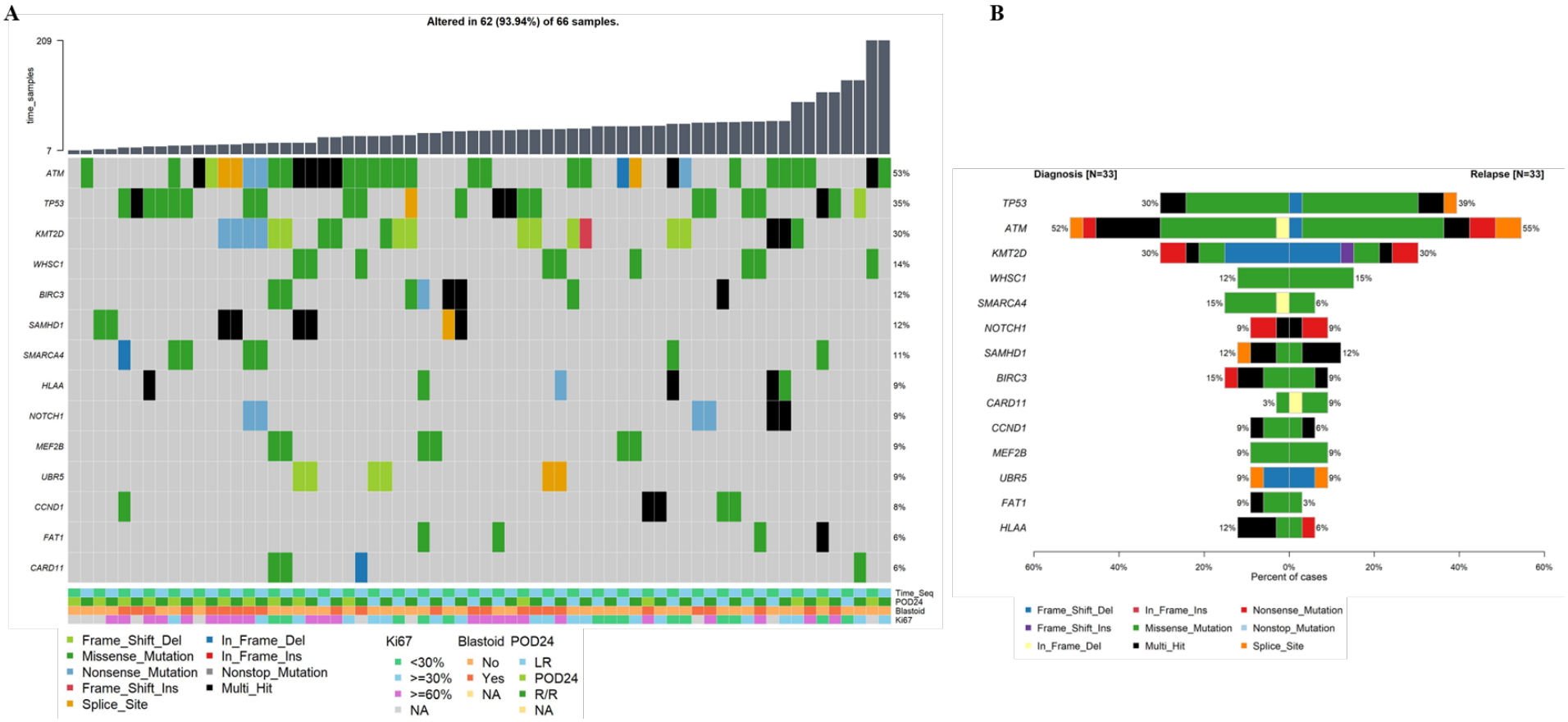
Long Remission – follow-up of at least 24m without POD; Progression – disease relapse at any time (deaths without lymphoma not considered an event); Excluded are 71 samples of patients with insufficient follow-up or not treated with chemoimmunotherapy. (A) Samples prior to frontline therapy comparing patients with a long remission (>24m) to those of patients who experienced a relapse at any time; (B) samples prior to frontline therapy from patients who later experienced a POD compared to samples sequenced at relapse; (C) Samples from patients who experienced a relapse, whether sequenced prior to frontline treatment or at a subsequent line of therapy were enriched for mutations in TP53 (** $p \leq 0.001$). (D) Samples prior to frontline treatment from patients who experienced a POD24 (N=40) had a higher rates of TP53 (* p=0.03; insignificant after correction for FDR) E) samples sequenced at frontline from patients with POD24 were very similar to those sequenced at relapse; (F) Samples from patients sequenced at frontline who later experienced a POD24 and those sequenced at relapse had higher rate of mutations in WHSC1 and lower rate of mutations in FAT1 (* $p \leq 0.05$; insignificant after correction for FDR). Note: plots C&E exclude sequential samples from the same patient.

Figure S6: Genomic landscape prior to frontline treatment and at POD (sequential samples)



A) Overall rates of genomic alterations comparing paired pre-treatment and at POD samples; C) Lollipop plots of loci of mutations in the TP53 gene in sequential cases sequenced pre-treatment and at POD.

Figure S7: Genomic landscape prior to frontline treatment and at POD (sequential samples; mutations only)



A) Sequential samples where Time_Seq (top_bottom_row) represent the timing of sequencing pre-treament (light-green) or at the time of subsequent treatment; POD24 (second_row) represents whether the first relapse occurred within 24 months (POD24 light-green) or whether the relapse occurred after a longer remission (LR light-blue). Thus, a combination of a light-blue box and a dark-green box on this line indicates a couplet of samples from before frontline treatment and after a considerable remission (the length of time between samples can be inferred from the bars at the top of the plot). Blastoid/Ki67 refers to disease status at the time of sequencing. B) Overall rates of genomic alterations comparing paired pre-treatment and at POD samples.