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POSTER ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Predicted Functional Consequences of *TP53* Alterations and Prognosis in *TP53*-Mutated Mantle Cell Lymphoma

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Background: Mantle cell lymphoma (MCL) cases with *TP53* mutations (*TP53mut*) are associated with poor responses to chemoimmunotherapy (Eskelund *Blood* 2017). Across myeloid and solid tumors, predicted functional consequences and pathogenicity of specific *TP53* mutations have been linked to differential patient outcomes (Pollock *Breast Cancer Res Treat* 2022, Yabe *Cancers* 2021). We aimed to characterize the impact of these features and associated molecular alterations on treatment outcome in *TP53mut* MCL patients treated with standard frontline regimens and on the ongoing phase 2 BOVEN trial. The BOVEN trial aims to assess the efficacy of frontline treatment with zanubrutinib, obinutuzumab, and venetoclax in *TP53mut* MCL (Kumar *Blood* 2021).

Methods: The BOVEN trial enrolled 25 patients with *TP53mut* MCL. Retrospective chart review was performed for 22 patients with *TP53mut* MCL treated at frontline with standard chemoimmunotherapy regimens (Joffe *Blood* 2019). Tumor histology and FISH were obtained for each case. Mutational profiling (SNV/indels, CNA) was obtained prior to therapy with various CLIA-certified targeted sequencing platforms (Cheng *J Mol Diagn* 2015, Dias-Santagata *EMBO Mol Med* 2010). Mutations in *TP53* were annotated using predicted phenotypes and pathogenicity from the *TP53* Database (de Andrade *Cell Death Differ* 2022) and from phenotypic annotation of *TP53* mutations (Giacomelli *Nat Genet* 2018). The primary outcome measures were overall and progression-free survival (OS/PFS).

Results: Each patient included in the BOVEN cohort featured variants in *TP53* with 26 SNV/indels across all 25 patients. There were 25 SNV/indels across all 22 patients treated with standard regimens. Within the trial cohort 14/25 cases had evidence of biallelic inactivation of *TP53* with co-occurring SNV/indels in the gene and 17p loss by FISH or *TP53* copy losses by SNParray; the comparator cohort featured 11/22 cases with biallelic losses. Across cohorts, most mutations were missense (>80% in both), with the majority occurring in the DNA binding domain of the p53 protein (76% and 91%, respectively), and with >30% at known hotspot codons in both cohorts. Most mutations (>70% in both cohorts) were predicted to adversely impact WT p53 function, including nonfunctional transactivation activity and dominant negative effect on the WT allele. The majority were also predicted to be highly pathogenic by bioinformatic methods (AGVGD, SIFT, PolyPhen2, PHANTM, REVEL, BayesDel). However, none of these features correlated with outcome. In the BOVEN cohort the variant allele frequency (VAF) of the *TP53* SNV/indels approached significant association with poor PFS (HR 33.2, p=0.05) but not OS (HR 28.6, p=0.09). In contrast, in the comparator cohort *TP53* VAF appeared to have an opposite effect direction, though this was not significant for PFS (HR 0.98, p=0.2) or OS (HR 0.97, p=0.06).

We next investigated the impact of co-occurring molecular alterations on outcome. Besides *TP53*, the most frequently mutated genes in the trial cohort were *KMT2D* (24%), *ATM* (16%), *NOTCH2* (12%), and *CCND1* (12%). Alterations in these genes did not correlate with outcome. Within the comparator cohort the recurrently mutated genes were *SMARCA4* (23%), *ARID1A* (18%), *ARID1B* (14%), *ATM* (14%), and *CCND1* (14%). As described previously in this cohort (Joffe *Blood* 2019), alterations in *SMARCA4* were associated with worse PFS (HR 4.2, p=0.02) but not OS (HR 2.2, p=0.27). Mutational burden (SNV and CNA load) was not prognostic in either 12/25 BOVEN samples sequenced with the same panel or the comparator cohort. There was no significant difference in outcome between patients with single mutations in *TP53* vs. those with biallelic losses in *TP53* in either cohort.

Conclusion: Across patients with *TP53mut* MCL treated either with standard frontline chemoimmunotherapy or on the BOVEN trial, predictions of intrinsic pathogenicity and functional consequences of the *TP53* alterations were not prognostic. The

impact of *TP53* mutation VAF remains unclear, with seemingly opposite effect directions between the two cohorts, though neither finding was significant. As previously described in the comparator cohort, alterations in *SMARCA4* are associated with worse PFS in *TP53mut* MCL, though this was not observed in the BOVEN cohort. There were no significant differences in outcome among patients with biallelic inactivations in *TP53* or with higher burdens of somatic alterations.

Disclosures Joffe: *Beigene:* Honoraria; *Abbvie:* Honoraria. **Salles:** *AbbVie:* Consultancy, Honoraria; *BeiGene:* Consultancy; *EPIZYME:* Consultancy; *Nurix:* Consultancy; *Kite/Gilead:* Consultancy; *Debiopharm:* Consultancy; *Novartis:* Consultancy; *Merck:* Consultancy, Honoraria; *Nordic Nanovector:* Consultancy; *Loxo/Lilly:* Consultancy; *Ipsen:* Consultancy, Research Funding; *Genentech, Inc./F. Hoffmann-La Roche Ltd:* Consultancy, Research Funding; *ATB Therapeutics:* Consultancy; *BMS/Celgene:* Consultancy; *Janssen:* Consultancy, Research Funding; *Genmab:* Consultancy; *Incyte:* Consultancy; *Owkin:* Current holder of *stock options* in a privately-held company; *Orna:* Consultancy; *Molecular Partners:* Consultancy. **Soumerai:** *AstraZeneca, Beigene, Biogen, Bristol Myers Squibb, Roche, Seattle Genetics:* Consultancy; *Adaptive Biotechnologies, Beigene, BostonGene, Genentech/Roche, GlaxoSmithKline, Moderna, Takeda, TG Therapeutics:* Research Funding. **Zelenetz:** *Pharmacyclics:* Consultancy, Honoraria; *Lymphoma Research Foundation:* Membership on an entity's Board of Directors or advisory committees; *F. Hoffmann-La Roche Ltd:* Consultancy, Honoraria, Research Funding; *Janssen Pharmaceuticals:* Consultancy, Honoraria; *BMS:* Consultancy, Honoraria; *Gilead:* Consultancy, Honoraria; *BeiGene:* Consultancy, Honoraria, Research Funding; *MEI Pharma Inc:* Consultancy, Honoraria, Research Funding; *None other than mutual funds (401K):* Current equity holder in publicly-traded company; *SAB:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Research Funding; *AstraZeneca:* Consultancy, Honoraria. **Kumar:** *Seattle Genetics:* Research Funding; *Pharmacyclics:* Research Funding; *Astra Zeneca:* Consultancy, Research Funding; *Loxo/Lily Oncology:* Consultancy, Research Funding; *Adaptive Biotechnologies:* Research Funding; *Beigene:* Research Funding; *Genentech:* Consultancy, Research Funding; *Janssen:* Consultancy; *Kite Pharma:* Consultancy; *BridgeBio:* Current equity holder in publicly-traded company; *Abbvie Pharmaceuticals:* Research Funding; *Celgene:* Research Funding.

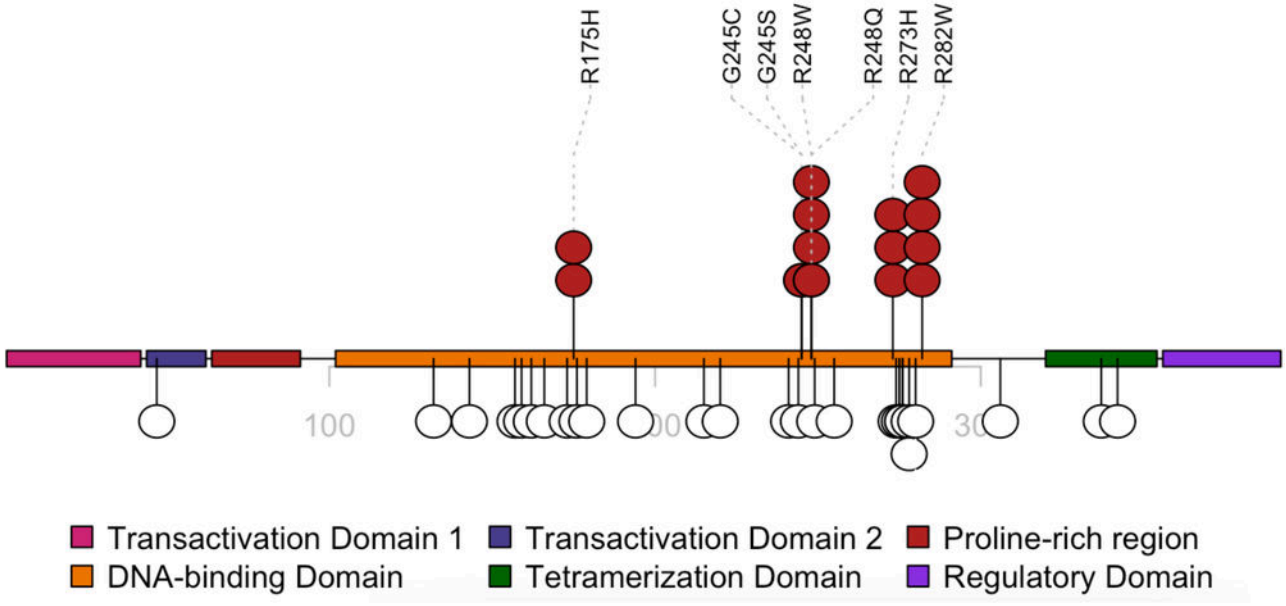

Figure 1

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