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P1261 ALLG LABORATORY SCIENCE STUDY LS21: MOLECULAR CORRELATES OF RESPONSE IN RELAPSED/REFRACTORY MARGINAL ZONE LYMPHOMA (RRMZL) PATIENTS TREATED WITH ZANUBRUTINIB IN THE MAGNOLIA TRIAL

Topic: 20. Lymphoma Biology & Translational Research

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Background: The MAGNOLIA trial demonstrated the safety and efficacy of zanubrutinib, a second generation BTK inhibitor (BTKi), in patients with rrMZL (ORR 68.2%, CR 26%, 15-month PFS 83%). An exploratory analysis of the ibrutinib-treated rrMZL study showed mutations in genes regulating NF-kB signalling pathway: *TNFAIP3* (*A20*) and *MYD88* predicted response, whereas *KMT2D* (*MLL2*) and *CARD11* were associated with primary resistance. The impact of acquired mutations in BTK and PLCg2 which mediate resistance to BTKi in CLL is unknown in MZL.

Aims: This Australasian Leukaemia and Lymphoma Group (ALLG) laboratory science correlative study LS21 seeks to determine if the baseline molecular profile by whole exome sequencing (WES) can predict primary resistance to zanubrutinib, and whether the emergence of resistance mutations in circulating tumour DNA (ctDNA) can herald clinical progression.

Methods: DNA was extracted from baseline FFPE tumour samples from 18 patients. Longitudinal monitoring to detect the acquisition of resistance mutations was monitored in 7 patients at multiple time points using cell-free DNA (cfDNA) isolated from plasma. NGS libraries were constructed using Agilent XTHS. Unique molecular barcoding was used to facilitate error correction. Agilent WES Ver7 was used for tumour sequencing. A bespoke bait capture of 48 genes set was used for ctDNA and buccal analysis. Sequencing was performed by NovaSeq 6000 (Illumina, SP flow cell, 2x150bp chemistry) and data processing of FASTQ files via in-house bioinformatic pipeline incorporating fgbio (for UMI de-duplexing, Fulcrumgenomics), *VarDict* for variant calling and *CNVkit* for copy number analysis. Variant calls in patient samples (identified by *VarDict*) were manually curated from a predetermined list of 48 candidate genes by inspecting BAM files in Integrative Genomics Viewer (IGV). Mutational analysis was correlated with clinical data and survival analysis calculated using the Kaplan-Meier (log-rank) method.

Results: Baseline WES identified mutations in 33/48 (69%), with a median of 5 genes affected per sample (range: 0-8). In patients treated with zanubrutinib (screen failure n=1), NFkB and NOTCH pathway genes were implicated in 13 (73%) and 10 (56%) patients respectively. *KMT2D* was most affected (n=7) followed by *NOTCH1, NOTCH2, TNFAIP3* and *MYD88* (all n=4). Patients with either *MYD88* or *TNFAIP3* mutations had improved median PFS (not reached (NR) vs 11.1 months, p: 0.009, HR: 0.09, 95% CI: 0.02-0.55); patients with *KMT2D* showed a trend to worse outcomes (PFS: 13.40 months vs NR, p: 0.06, HR 6.5, 95%CI: 1.06-38.76) [Figure 1a-c]. *NOTCH* mutations did not associate with outcome. *CARD11* mutations were not detected. *PLCy2 (*H244R, L704V) mutations were detected in 2 patients prior to BTKi commencement but neither was associated with primary resistance.

Within the ctDNA cohort, 8/14 (57%) mutations detected in tumour samples were present in ctDNA at study entry. Furthermore, ctDNA also harboured mutations not present in tumour WES in 4 patients, likely reflective of tumour

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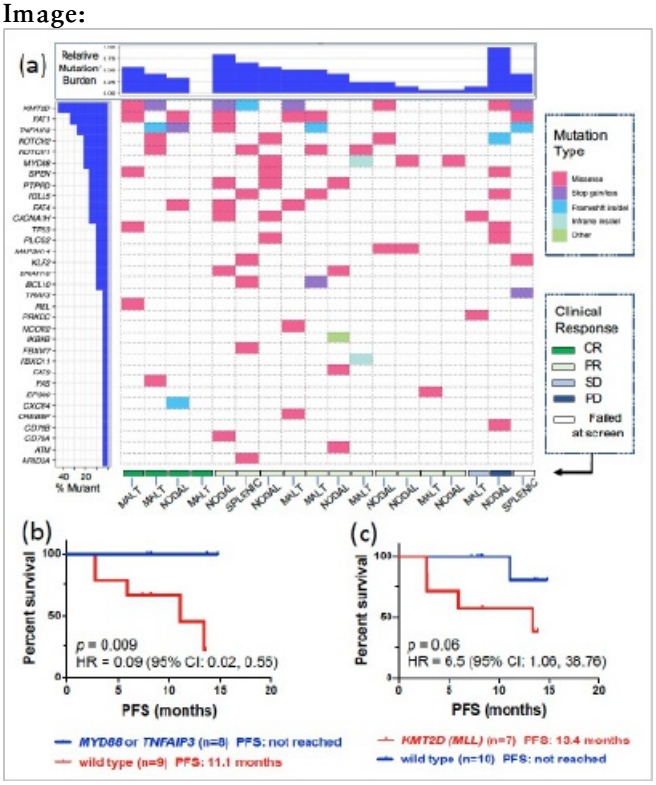
heterogeneity. Two patients had persistent *MYD88* mutations detectable in ctDNA 15 months after treatment commencement (to sensitivity of AF 0.13%). Acquired resistance mutations, *BTK* (C515Y/515F) and *PLCy2* (R665W/R742P*)* were detected in 2 patients who progressed on therapy.

Image:



Summary/Conclusion: Mutations in genes associated with the NFkB pathway present at baseline are predictive of response to zanubrutinib in rrMZL patients. Detection of acquired *BTK* and *PLCy2* mutations on therapy is feasible and may herald clinical disease progression.

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