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POSTER ABSTRACTS

636.MYELODYSPLASTIC SYNDROMES-BASIC AND TRANSLATIONAL

Prognostic and Therapeutic Implications of *TP53* expression in Chronic Myelomonocytic Leukaemia: Results of a Multicentre Study

Yu-Hung Wang, MD MSc[1,2], Chien-Chin Lin, MD PhD[3,2], Kristian Gurashi, PhD[1], Fabio Amaral, PhD[4], Chi-Yuan Yao, MD[2,3], Joanna Storer, PhD[1], Luciano Nicosia, PhDMS,BS[4], Bettina Wingelhofer, PhD[4], Hsin-An Hou, MD PhD[5], Andres Jerez, MD PhD[6], Wen-Chien Chou, MD PhD[3,5], Kiran Batta, PhD[7], Hwei-Fang Tien, MD PhD[8,2], Daniel H Wiseman, MBBChir,FRCPath,MRCP,PhD[9]

[1] The University of Manchester, Manchester, United Kingdom
[2] Division of Hematology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
[3] Department of Laboratory Medicine, National Taiwan University Hospital, Taipei, Taiwan
[4] Cancer Research UK Manchester Institute, Manchester, United Kingdom
[5] Division of Hematology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
[6] Hematology Department, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain
[7] Division of Cancer Sciences, The University of Manchester, Manchester, United Kingdom
[8] Department of Internal Medicine, Far-Eastern Memorial Hospital, New Taipei, Taiwan
[9] Division of Cancer Sciences, University of Manchester, Manchester, United Kingdom

Thetumor suppressor *TP53* is among the most mutated genes in cancer, including many hematological malignancies in which it usually imparts more aggressive, chemo-refractory, and poor prognosis diseases. *TP53* mutations are, though, remarkably rare in chronic myelomonocytic leukemia (CMML): affecting 2.4% of cases in a recent study (*Gurney et al, Leukemia 2023*). We found pathogenic *TP53* mutations (*TP53* ^{MT}) in only 1.1% of 640 genotyped UK CMML patients. As expected, *TP53* ^{MT} conferred worse leukemia-free (LFS: median 23 v 28 mo, p=0.031) and overall (OS: 26 v 29 mo, p=0.015) survival compared with *TP53* ^{WT}cases.

The clinical relevance in CMML of *TP53* expression, however, remains unexplored. To address this we studied 92 *TP53* ^{WT} CMML patients (discovery cohort) from the National Taiwan University Hospital (Taipei, Taiwan) with available RNA-seq on presentation bone marrow (BM), each with extensive longitudinal clinical, laboratory and outcome data. Validation cohorts comprised 33 RNA-sequenced patients from The Christie (Manchester, UK) and 24 from Hospital Morales Meseguer (Murcia, Spain). For all cohorts, RNA-seq data from healthy controls (HCs) were available.

Patients in the discovery cohort were divided into low and high *TP53* expression groups, determined by the maximally selected rank statistics. *TP53* ^{low} patients (n=15) displayed significantly lower expression than HCs, while *TP53* ^{high} (n=77) had expression levels comparable to HCs. Thus, although most CMML patients are *TP53* ^{WT}, a subset has down-regulated *TP53* expression and potential for altered p53 (and downstream) functions. *TP53* ^{low} and *TP53* ^{high} patients did not differ in clinical features or concurrent genetic alterations, although in all cohorts *TP53* ^{low} patients showed a trend towards poorer response to hypomethylating agents (HMA).

TP53 ^{low} patients displayed significantly worse outcomes than *TP53* ^{high} patients (LFS 7 v 19 mo, p=0.002; OS 11 v 26 mo, p=0.001). Moreover, *TP*53 expression further stratified prognosis within different CMML-specific prognostic scoring system (CPSS)-molecular risk groups (Fig 1) . Time-dependent ROC analysis indicated *TP53* expression as complementary to current risk stratification systems. In multivariable analysis, low *TP53* expression remained prognostically detrimental. Survival analyses were consistent in both validation cohorts.

GSEA and IPA analyses revealed that compared with HCs or *TP53* ^{high}, *TP53* ^{low} cells exhibited depleted expression of p53-dependent pathways, including MYC targets, E2F targets, G2/M checkpoints, and DNA repair. Interestingly, these are all among the most upregulated pathways in *TP53* ^{MT} (v *TP53* ^{WT}) samples across multiple cancers in TCGA data (*Donehower et al, Cell Rep 2019*), indicating distinct roles for p53 in regulating these pathways in a *TP53* ^{WT} context, and that the driving biology of *TP53* ^{low} CMML is distinct from (and not functionally equivalent to) that of oncogenic *TP53* mutations. *TP53* ^{low} patients demonstrated significantly enhanced TNF-alpha and inflammatory response signals, highlighting other distinctive pathobi-

ology of the *TP53* ^{low} subgroup. In line with our clinical observation, single-sample GSEA showed significant enrichment of HMA resistance signatures in *TP53* ^{low} patients, potentially contributing to the dismal prognosis in this group.

We next investigated whether this could be exploited therapeutically. We treated primary CMML BM cells *ex vivo* with azacitidine and NSC-207895, an MDMX inhibitor with p53 activating properties, observing clear and substantial synergy for combination therapy in samples from 10 of 11 patients. There was a trend towards inverse correlation between *TP53* expression and empirical synergy scores (r=-0.35), suggesting potential for p53 activation to enhance HMA sensitivity in CMML, with broad efficacy, perhaps preferentially in adverse risk *TP53* ^{low} cases.

In summary, we have identified and validated, across three cohorts from three countries, that a subgroup of CMML patients display aberrantly low *TP53* expression, associated with HMA resistance and worse survival. Transcriptomic analyses revealed distinctive biology driving this novel *TP53* ^{low} subgroup (Fig 2), mandating further mechanistic study. Importantly we report consistent and substantial synergy for combining pharmacological p53 activation with HMA, presenting a novel targeted approach to improve HMA response for this unmet clinical need.

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Figure 1

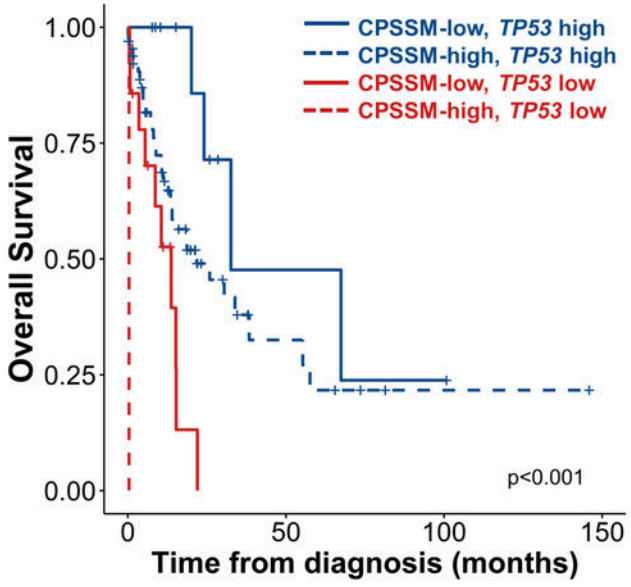

Figure 2

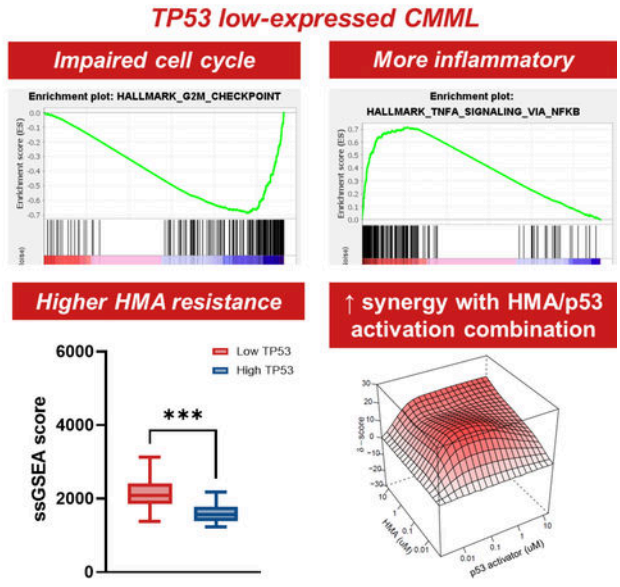

Figure 1

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