



## The 65th ASH Annual Meeting Abstracts

## 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<sup>1,2</sup>, Chien-Chin Lin, MD PhD<sup>3,2</sup>, Kristian Gurashi, PhD<sup>1</sup>, Fabio Amaral, PhD<sup>4</sup>, Chi-Yuan Yao, MD<sup>2,3</sup>, Joanna Storer, PhD<sup>1</sup>, Luciano Nicosia, PhD<sup>4</sup>, Bettina Winkelhofer, PhD<sup>4</sup>, Hsin-An Hou, MD PhD<sup>5</sup>, Andres Jerez, MD PhD<sup>6</sup>, Wen-Chien Chou, MD PhD<sup>3,5</sup>, Kiran Batta, PhD<sup>7</sup>, Hwei-Fang Tien, MD PhD<sup>8,2</sup>, Daniel H Wiseman, MBBChir, FRCPath, MRCP, PhD<sup>9</sup>

<sup>1</sup>The University of Manchester, Manchester, United Kingdom

<sup>2</sup>Division of Hematology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

<sup>3</sup>Department of Laboratory Medicine, National Taiwan University Hospital, Taipei, Taiwan

<sup>4</sup>Cancer Research UK Manchester Institute, Manchester, United Kingdom

<sup>5</sup>Division of Hematology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

<sup>6</sup>Hematology Department, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

<sup>7</sup>Division of Cancer Sciences, The University of Manchester, Manchester, United Kingdom

<sup>8</sup>Department of Internal Medicine, Far-Eastern Memorial Hospital, New Taipei, Taiwan

<sup>9</sup>Division of Cancer Sciences, University of Manchester, Manchester, United Kingdom

The tumor 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*<sup>MT</sup>) in only 1.1% of 640 genotyped UK CMML patients. As expected, *TP53*<sup>MT</sup> 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*<sup>WT</sup> cases.

The clinical relevance in CMML of *TP53* expression, however, remains unexplored. To address this we studied 92 *TP53*<sup>WT</sup> 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*<sup>low</sup> patients (*n*=15) displayed significantly lower expression than HCs, while *TP53*<sup>high</sup> (*n*=77) had expression levels comparable to HCs. Thus, although most CMML patients are *TP53*<sup>WT</sup>, a subset has down-regulated *TP53* expression and potential for altered p53 (and downstream) functions. *TP53*<sup>low</sup> and *TP53*<sup>high</sup> patients did not differ in clinical features or concurrent genetic alterations, although in all cohorts *TP53*<sup>low</sup> patients showed a trend towards poorer response to hypomethylating agents (HMA).

*TP53*<sup>low</sup> patients displayed significantly worse outcomes than *TP53*<sup>high</sup> patients (LFS 7 v 19 mo, *p*=0.002; OS 11 v 26 mo, *p*=0.001). Moreover, *TP53* 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*<sup>high</sup>, *TP53*<sup>low</sup> 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*<sup>MT</sup> (v *TP53*<sup>WT</sup>) 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*<sup>WT</sup> context, and that the driving biology of *TP53*<sup>low</sup> CMML is distinct from (and not functionally equivalent to) that of oncogenic *TP53* mutations. *TP53*<sup>low</sup> patients demonstrated significantly enhanced TNF-alpha and inflammatory response signals, highlighting other distinctive pathobi-

ology of the *TP53*<sup>low</sup> subgroup. In line with our clinical observation, single-sample GSEA showed significant enrichment of HMA resistance signatures in *TP53*<sup>low</sup> 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*<sup>low</sup> 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*<sup>low</sup> 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

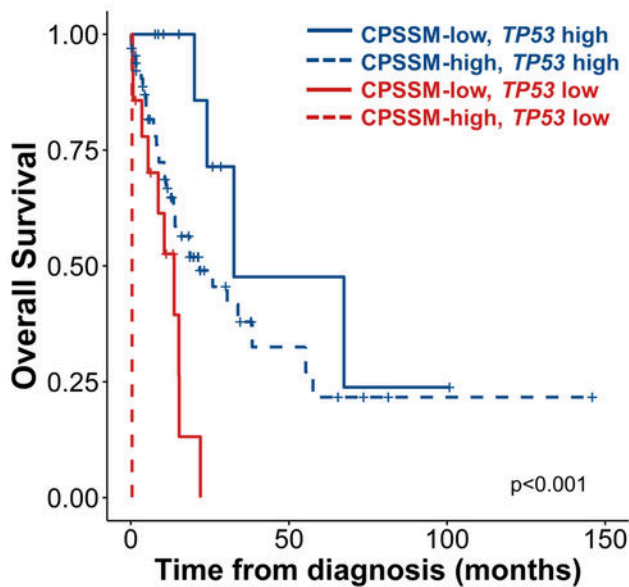


Figure 2

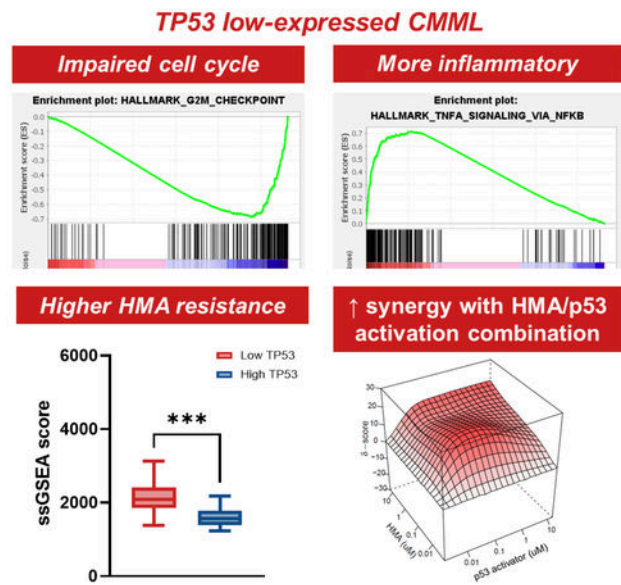


Figure 1

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