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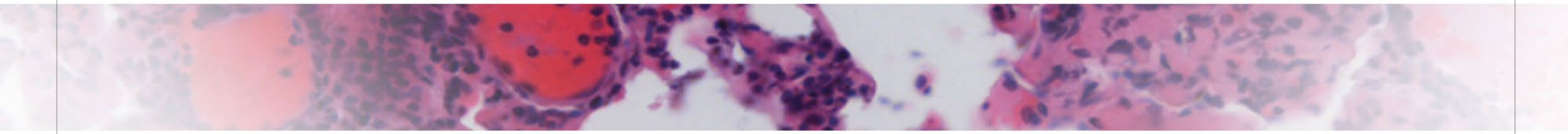

TP53 Abnormalities Correlate with Immune Infiltration and Associate with Response to Flotetuzumab Immunotherapy in Acute Myeloid Leukemia

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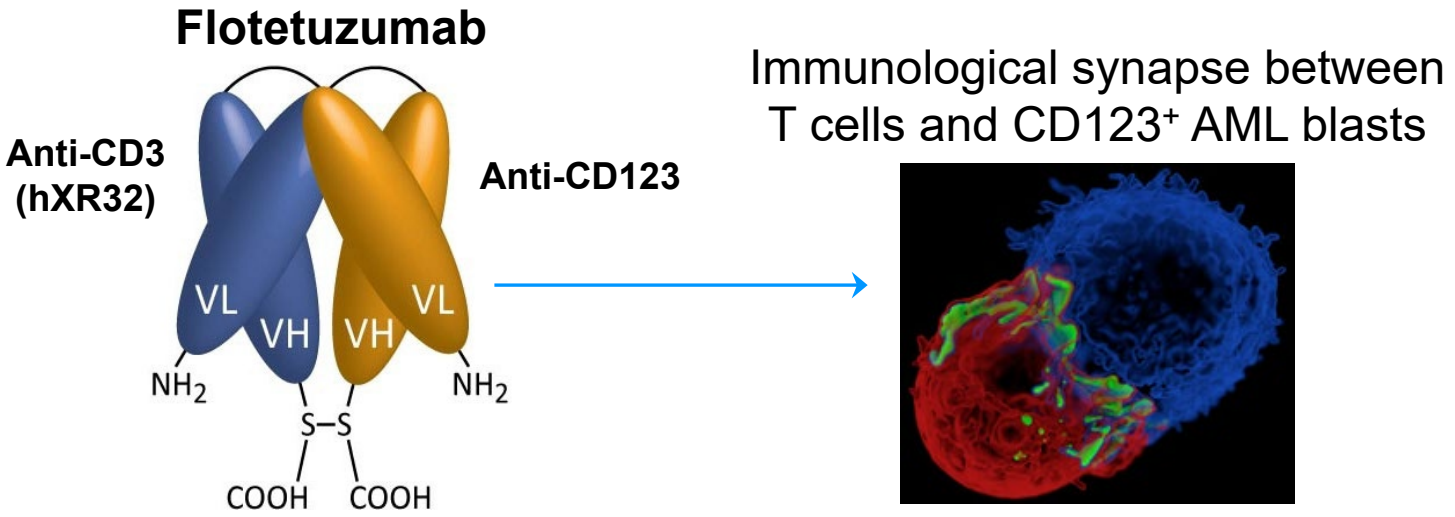
Background

- Somatic *TP53* mutations and deletions of 17p, to which *TP53* is mapped, occur in 8-10% of *de novo* AML and are associated with chemotherapy resistance, high risk of relapse and dismal prognosis even after hematopoietic stem cell transplantation
- A recent analysis of The Cancer Genome Atlas (TCGA) transcriptomic data from 10,000 non-hematologic tumors has indicated that *TP53* mutations correlate with higher proportions of PD-L1-expressing $CD8^+$ T cells, and with increased expression of T-cell effector genes and interferon (IFN)-γ–related genes
- We have recently identified bone marrow (BM) IFN-γ-related transcriptional profiles that stratify patients with AML into an immune-infiltrated and an immune-depleted subtype, and that enrich in patients with chemotherapy-refractory disease (Vadakekolathu J, *et al*. *Sci. Transl. Med.* 2020; 12: eaaz0463)

Questions and Study Aims

- Do *TP53* abnormalities correlate with the composition and functional orientation of the immunological tumor microenvironment (TME) in AML?
- Are patients with *TP53*-mutated, relapsed/refractory AML responsive to treatment with flotetuzumab, an investigational CD123 × CD3 bispecific DART® molecule?

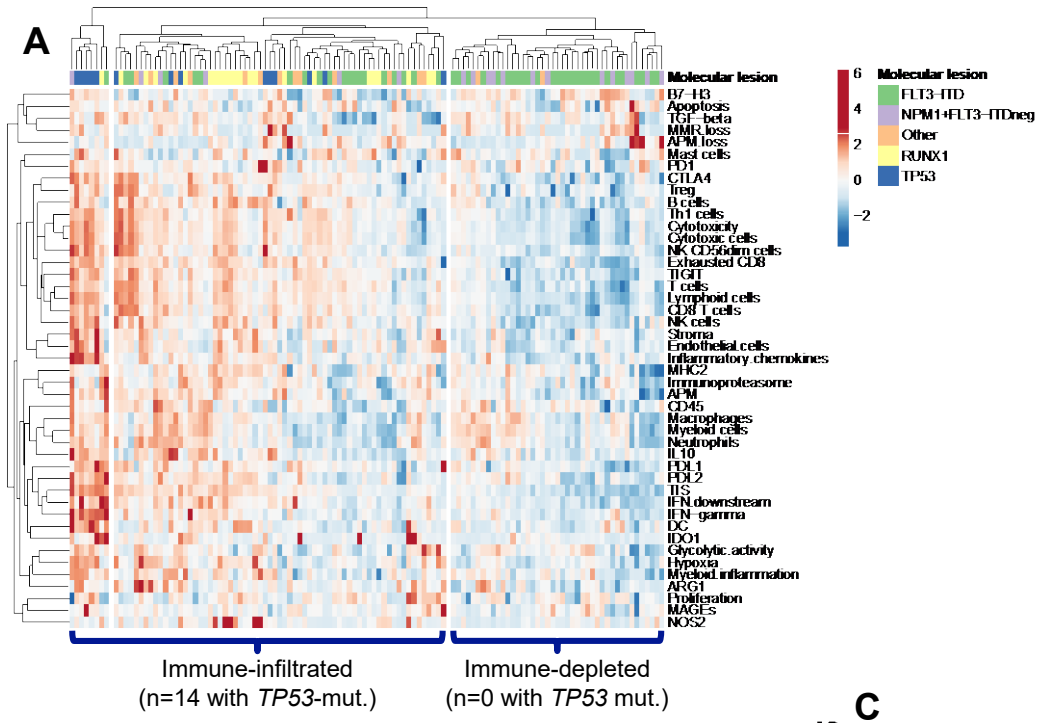


Patients and Methods

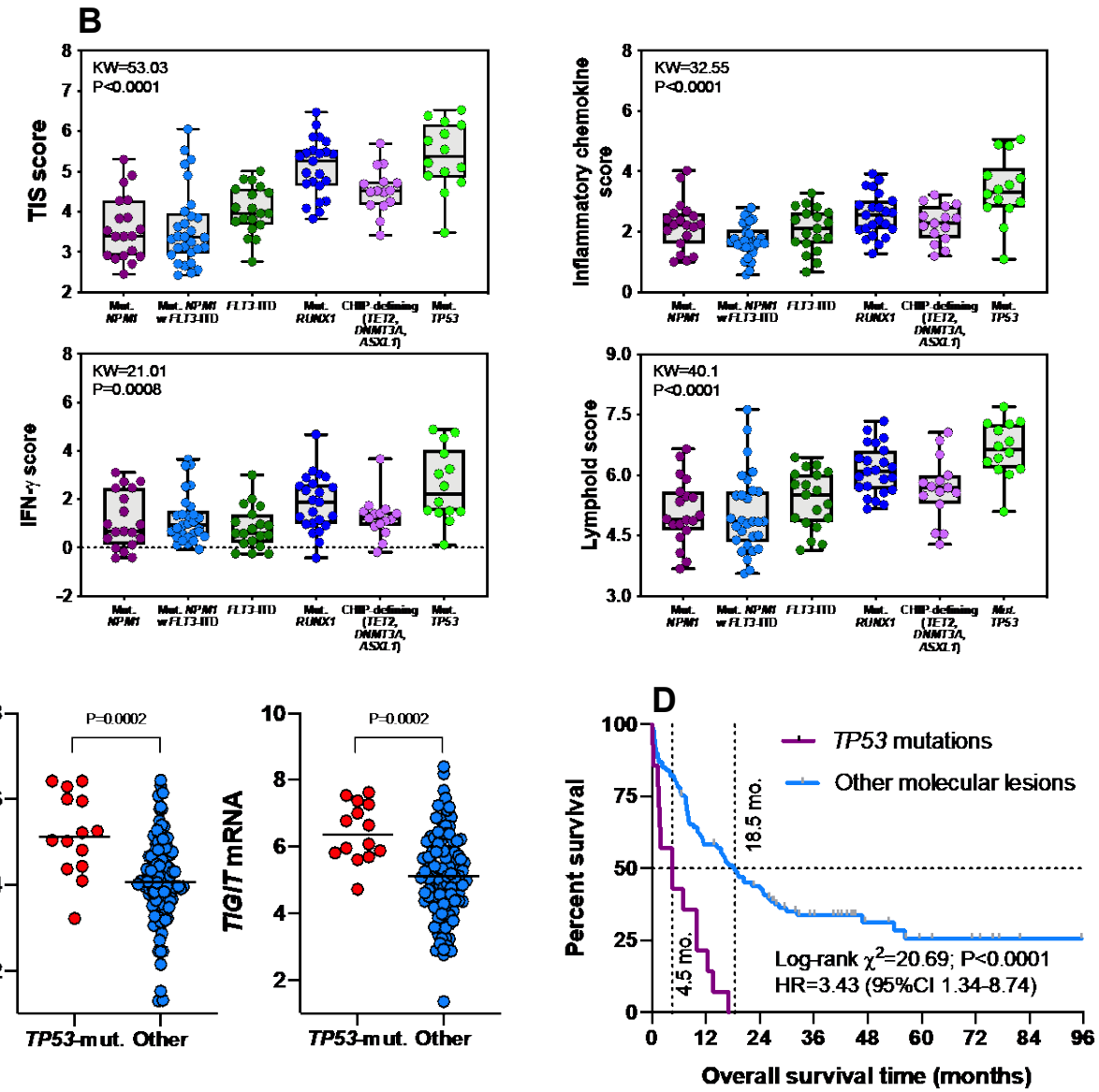
	All patients (n=45)	Patients with *TP53* mutations and/or 17p abnormalities (n=15^)
Age (years, median and range)	61 (27-81)	61 (27-81)
Males/Females, n/n	24/21	8/7
AML risk stratification (2017 ELN; n)		
Favorable	3 (6.7%)	0 (0%)
Intermediate	8 (17.8%)	0 (0%)
Adverse	34 (75.6%)	15 (100%)
Secondary AML (n)	15 (33.3%)	7 (46.7%)
Number of prior lines of therapy (median and range)	2 (1-9)	2 (1-4)

- ^BM samples from 13/15 patients were available for immune gene expression profiling. All 15 patients with *TP53* mutations/17p abnormalities were treated on the study and included in clinical analyses.
- Microenvironmental RNAs were profiled using the PanCancer IO 360™ gene expression panel on the nCounter® platform.
- Disease status was assessed by modified International Working Group (IWG) criteria. Specifically, overall response rate (ORR), collectively complete response, was defined as <5% bone marrow (BM) blasts (CR, CRh, CRi or morphologic leukemia-free state [MLFS]). Partial response (PR) was defined as >50% decrease or decrease to 5-25% BM blasts.

TP53 Mutations Associate with High Immune Infiltration in TCGA-AML

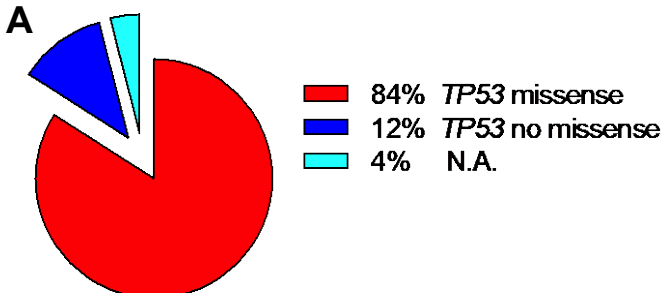


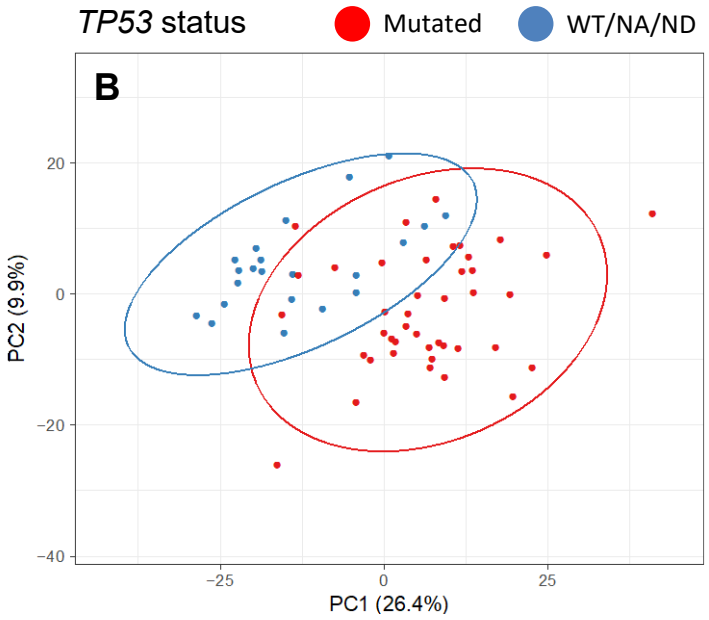
N=118 cases with available information on prognostic molecular lesions, including *TP53* mutations (n=14)

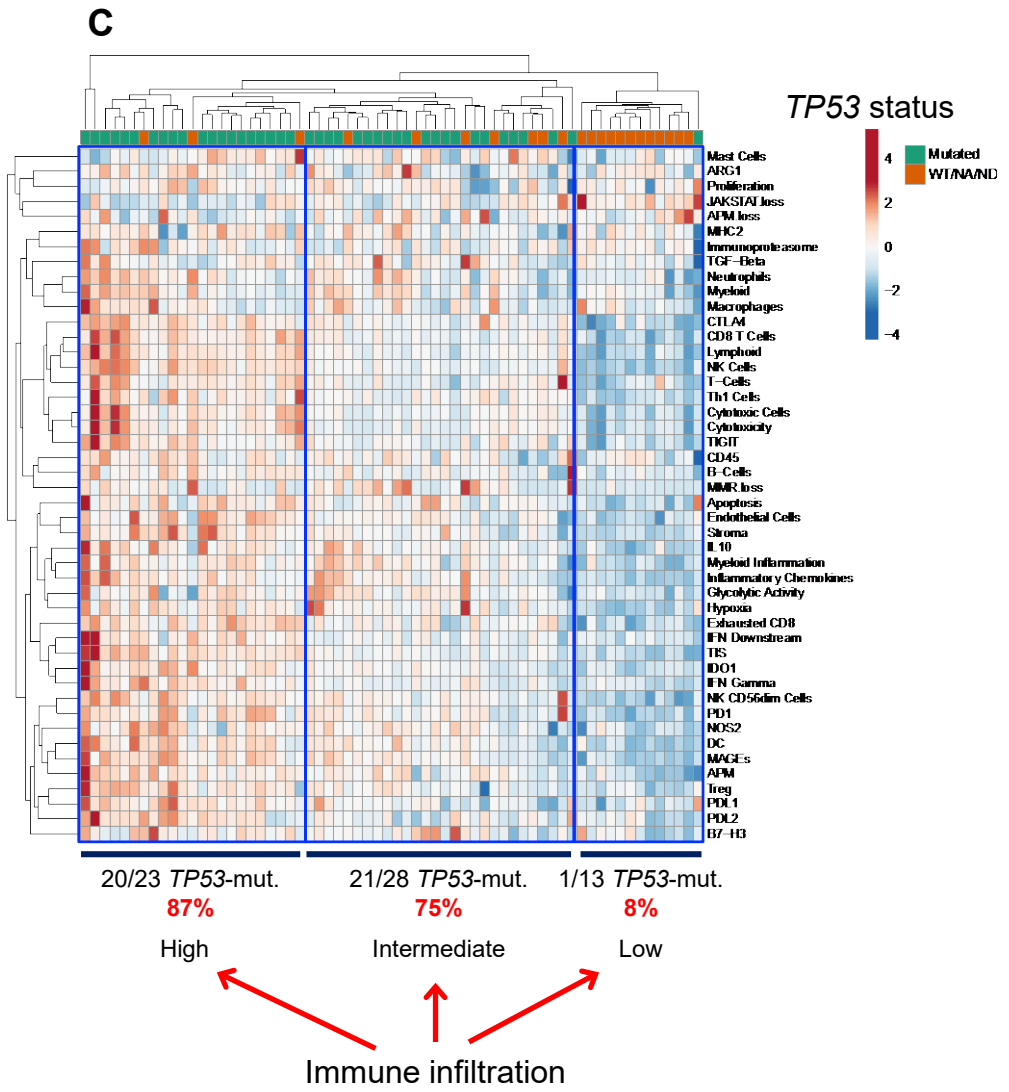


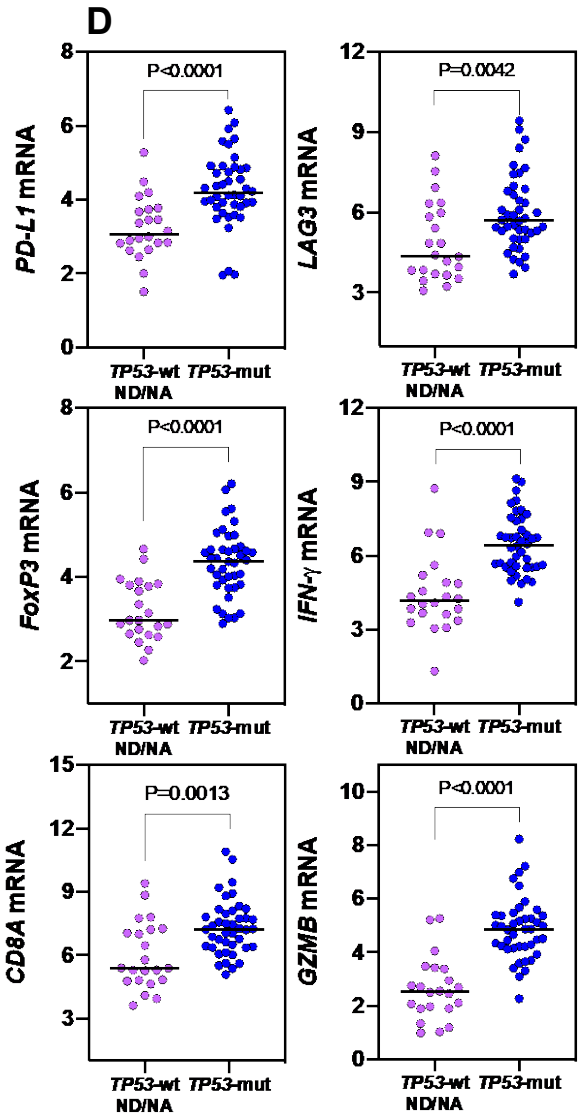
Vadakekolathu J, et al. Blood Advances 2020; 4 (20): 5011–24.

TP53 Mutations Associate with High Immune Infiltration in Primary AML Samples – SAL Cohort





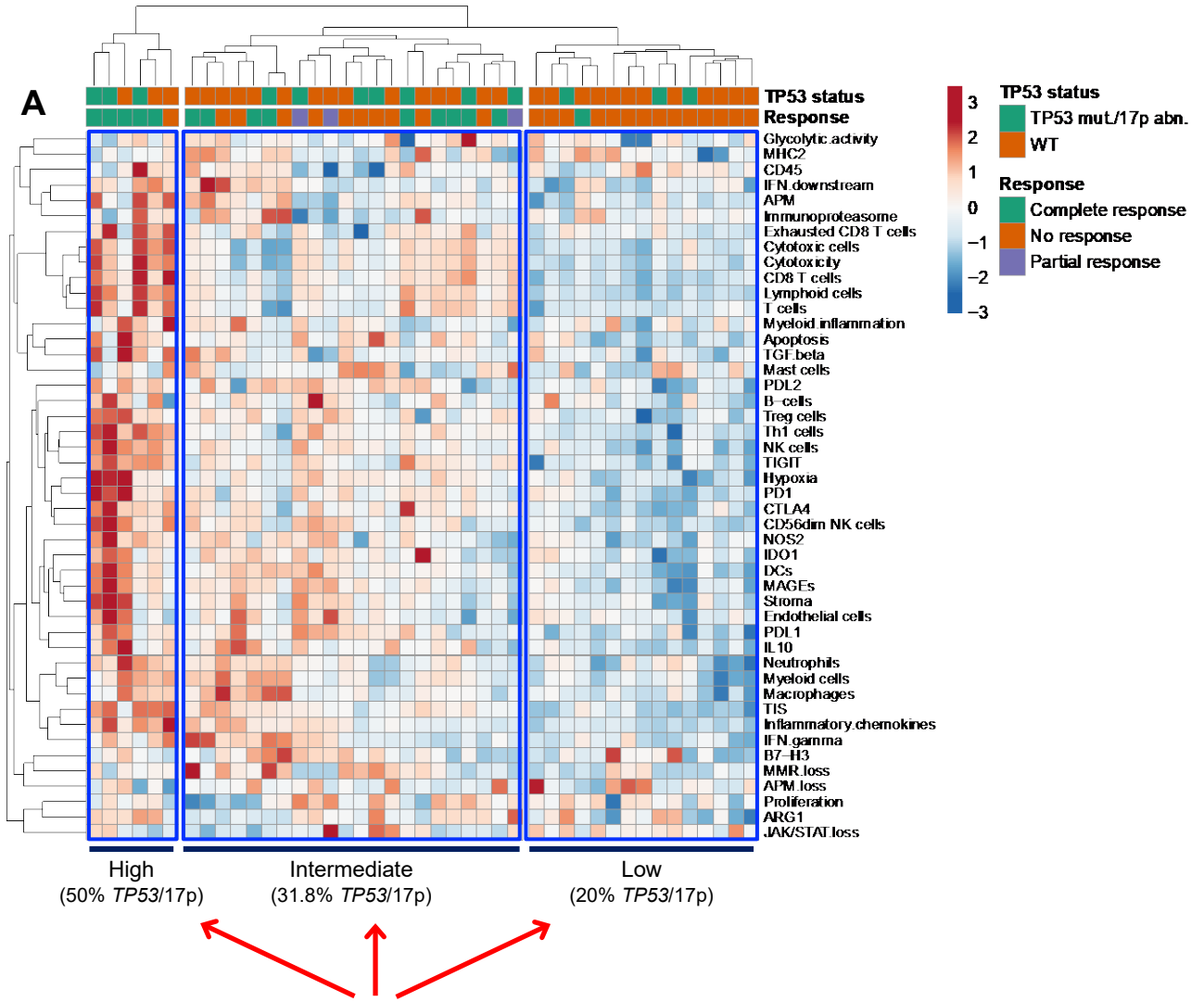




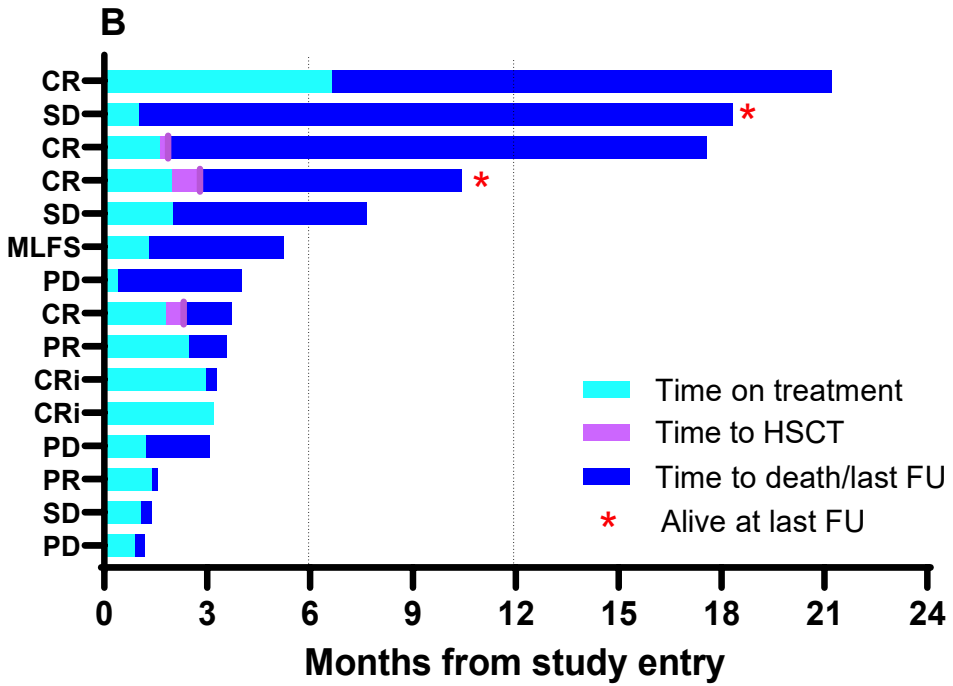
In collaboration with Martin Bornhäuser, Technische Universität Dresden, Germany

Vadakekolathu J, et al. Blood Advances 2020; 4 (20): 5011–24.

TP53 Mutations Associate with Immune Infiltration and with Response to Flotetuzumab



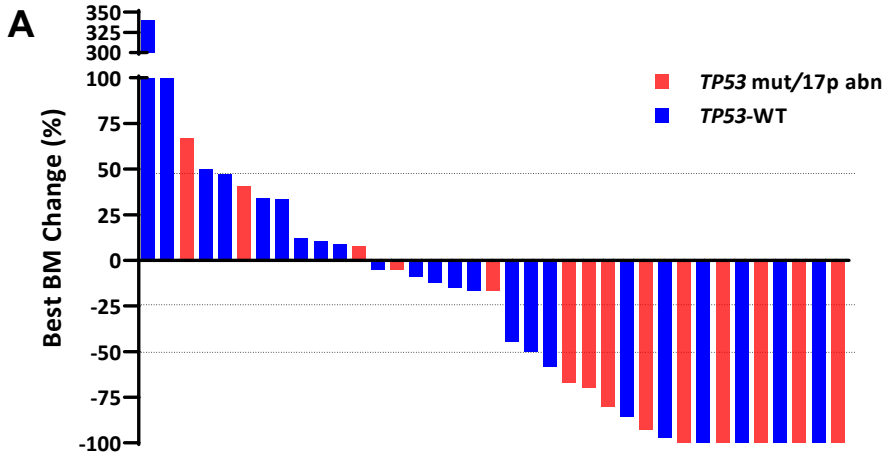
Immune infiltration int.-to-high in 10/13 (77%) patients with mutated *TP53*

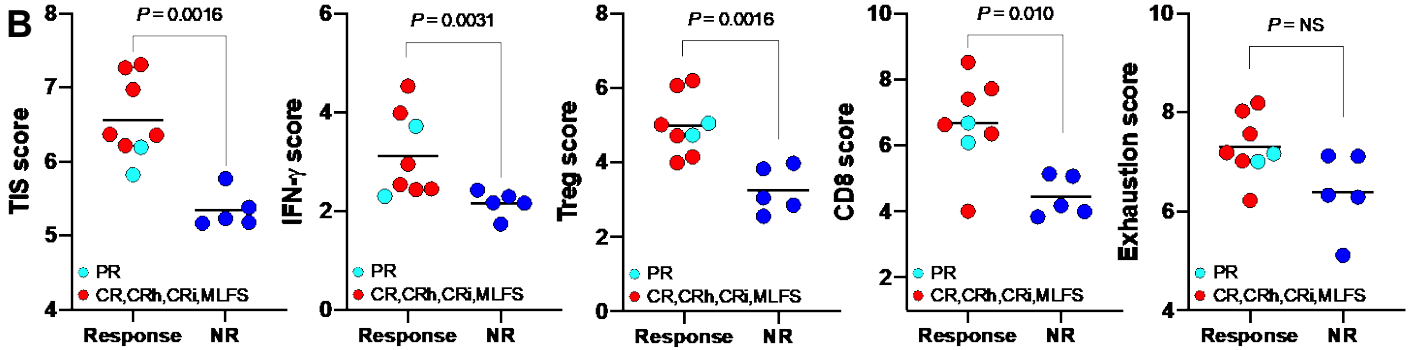


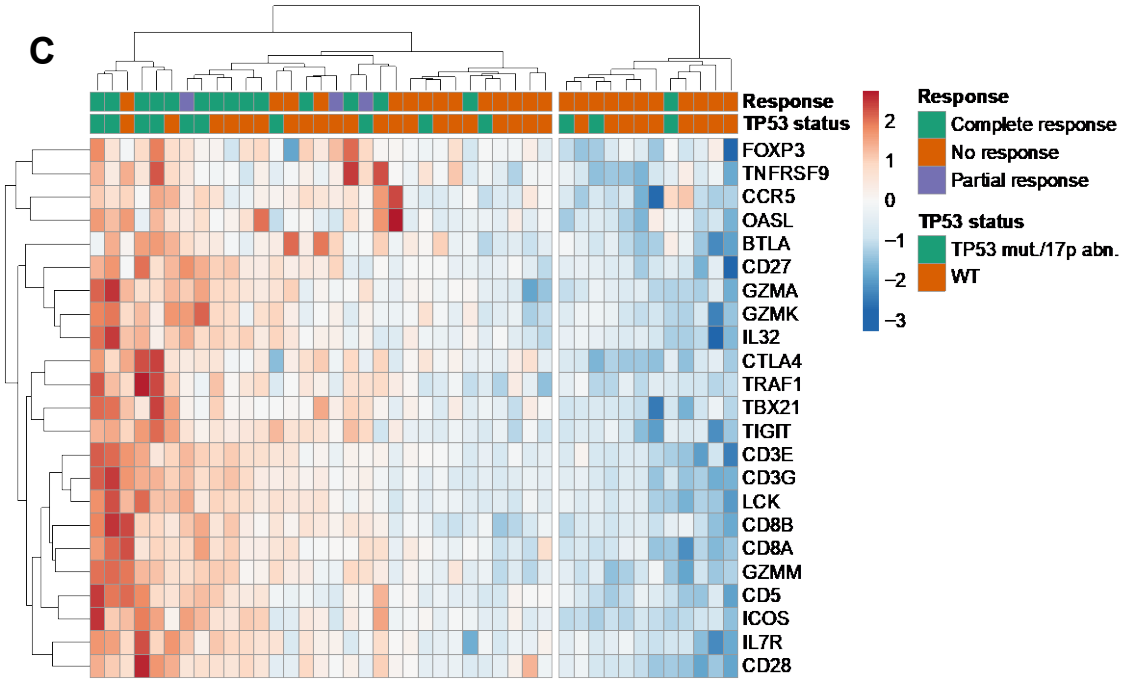
Overall response rate in evaluable patients with *TP53* mutations and/or 17p abnormalities was 60% (9/15), with 47% (7/15) achieving complete response (<5% BM blasts on study)

In responders with *TP53* mutations, median OS was 10.3 months (range 3.3-21.3)

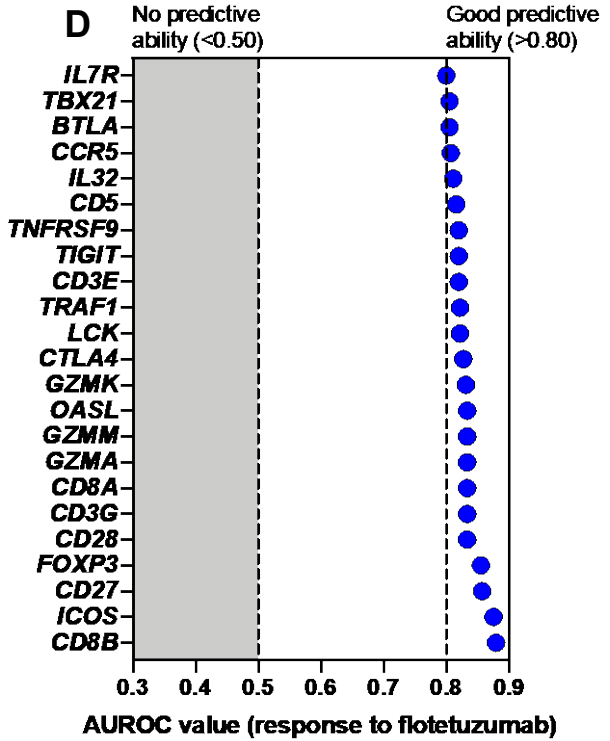
TP53 Mutations Associate with Immune Infiltration and with Response to Flotetuzumab



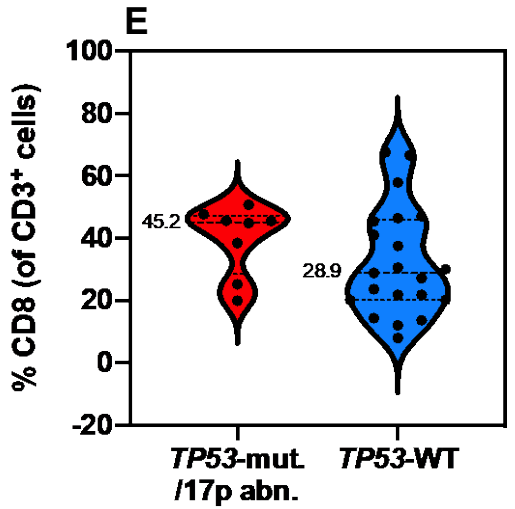




Top-ranking genes associated with response



AUROC (*CD8B*) = 0.879



Mike Rettig, WashU

Conclusions

- *TP53* mutations in AML are associated with higher T cell infiltration, expression of immune checkpoints and IFN-γ-driven transcriptional programs
- The above gene expression profiles, which have previously been shown to enrich in patients with chemotherapy resistance, correlate with disease control in response to flotetuzumab (51.2% reduction of BM blasts; 60% [9/15] overall response rate; 47% [7/15] complete response rate)
- These results encourage further study of flotetuzumab immunotherapy in patients with *TP53*-mutated AML

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