NOTTINGHAM TRENT UNIVERSITY

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TP53 abnormalities correlate with immune infiltration and are associated with response to flotetuzumab, an investigational immunotherapy, in acute myeloid leukemia

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Background

- Chemotherapy remains the standard of care for most patients with AML, despite recent approvals of novel drugs
- We have identified immune subgroups of AML ('immune-infiltrated' and 'immune-depleted') that predict chemotherapy resistance but also response to flotetuzumab immunotherapy (Vadakekolathu J, *et al*. Under revision)
    - The genetic drivers of immune infiltration in AML are presently unknown
- *TP53* mutations occur in 8-10% of *de novo* AML cases and are associated with chemotherapy resistance, high risk of relapse and dismal prognosis even after hematopoietic stem cell transplantation
- The functional consequences of *TP53* mutation/inactivation on host immune regulation have been largely overlooked in AML
    - The *TP53* mutants studied thus far in AML do not show any evidence of gain-of-function mechanisms (Boettcher S, et al. *Science* 2019)

NTU

Objectives

- To determine whether *TP53* abnormalities correlate with the composition and functional orientation of the tumor immunological microenvironment (TME) in AML
- To determine whether *TP53* abnormalities identify a subgroup of patients with AML that may benefit from immunotherapy with flotetuzumab, a CD123×CD3 bispecific DART® molecule for redirecting host T cells to AML (Chichili GR, et al. *Science Translational Medicine* 2015) in the CP-MGD006-01 clinical trial (NCT#02152956)

Graphical ‘cohorts and methods’

A ***In silico* analyses (TCGA-AML)**

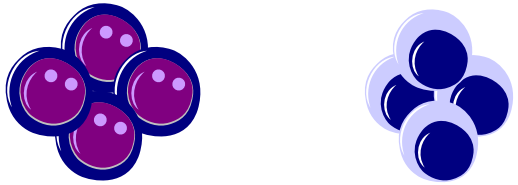
147 non-promyelocytic AMLs
(14 with *TP53* mutations)

Immune cell type and biological activity gene signatures (computed as in Danaher P, *et al*. JITC 2017 and 2018)

Correlation with prognostic molecular lesions (*TP53* mutational status, *NPM1* mutational status, *FLT3*-ITD status, CHIP-defining mutations) and clinical outcomes (Cox PH)

B **Primary AML blasts**

TP53-mutated (n=42) *TP53*-wt (n=22)



RNA extraction

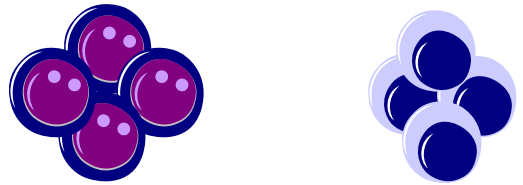
Targeted Immune GEP
(PanCancer IO 360™ Panel) - RUO

DE genes
GO ontologies (METASCAPE)
Network analysis

C **Flotetuzumab cohort (n=35)**

TP53-mutated and/or 17p abnormalities with genomic loss of *TP53* (n=11)

TP53-wt (n=24)

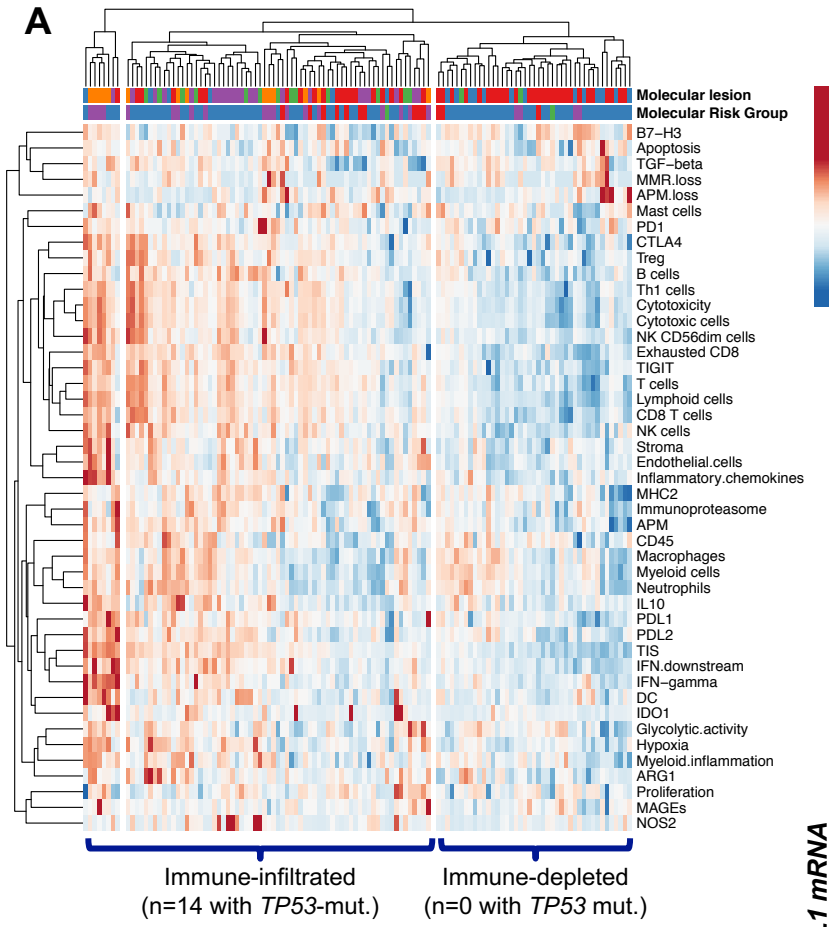


RNA extraction

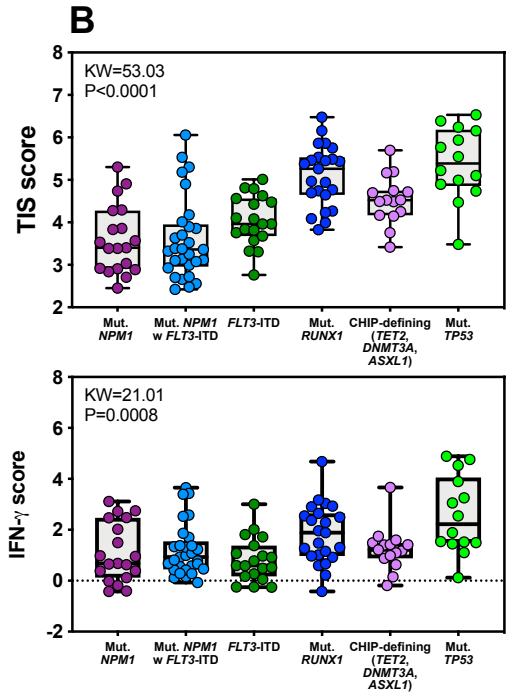
Targeted Immune GEP
(PanCancer IO 360™ Panel) - RUO

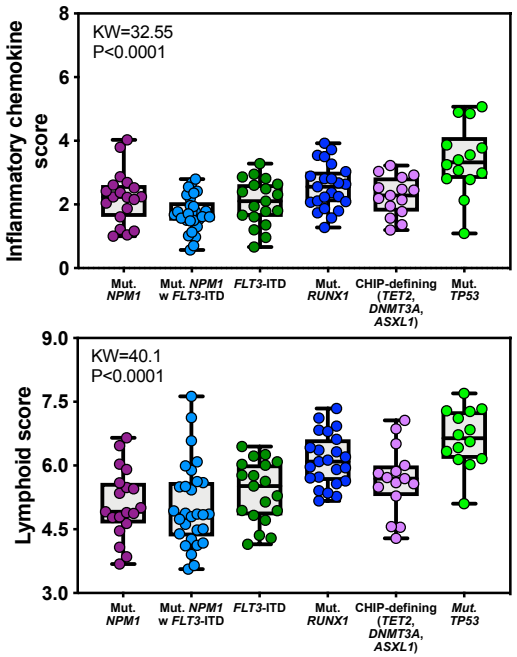
Predictors of response

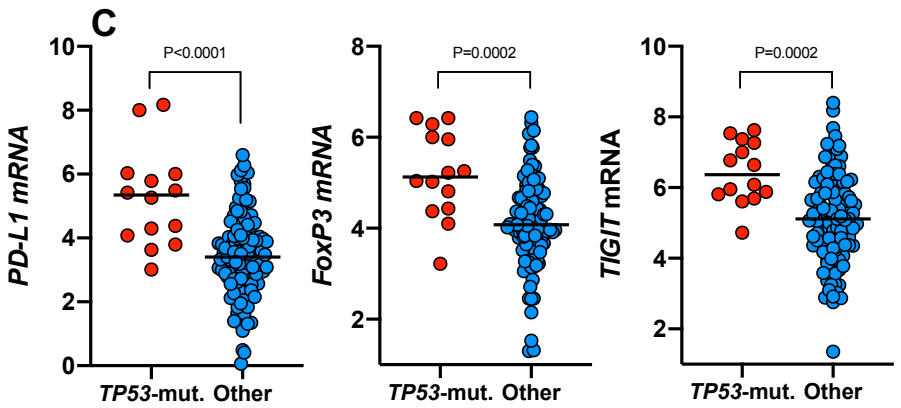
TP53 mutations associate with an immune-infiltrated TME in TCGA-AML

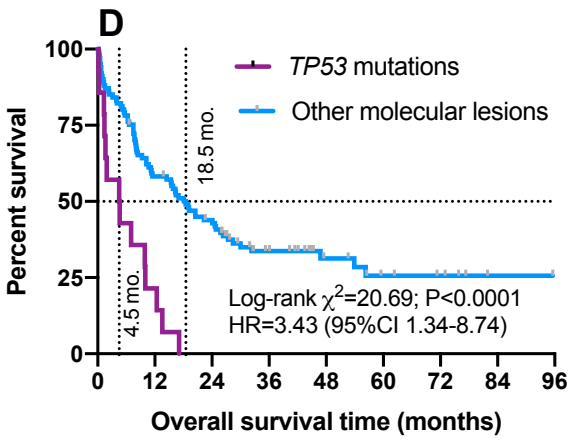


N=118 cases with available information on prognostic molecular lesions, including *TP53* mutations (n=14)

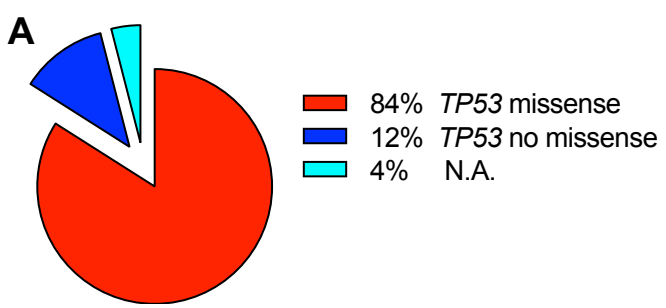


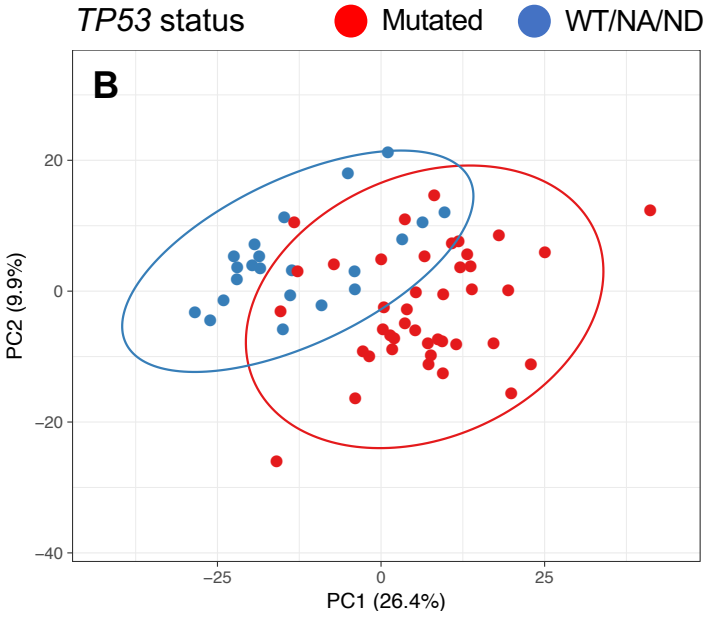


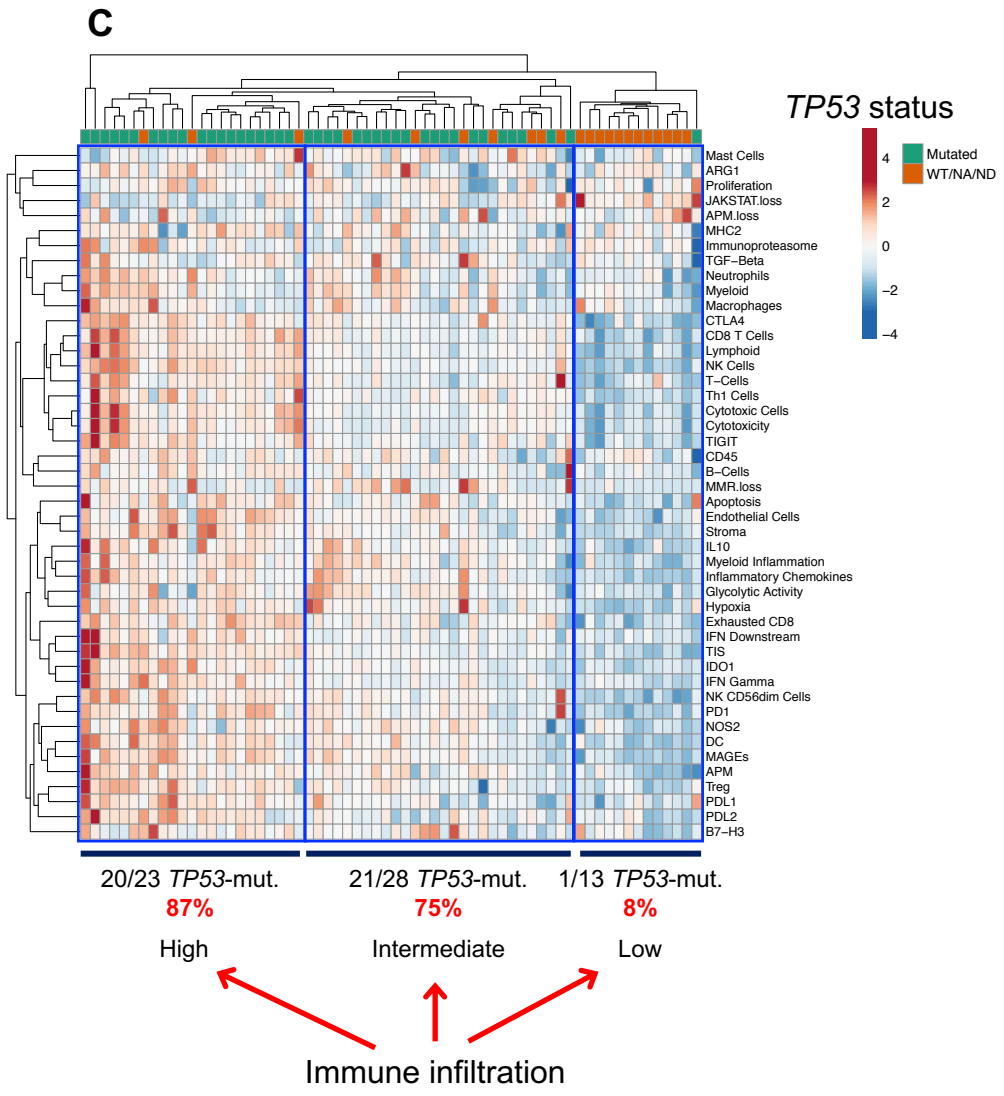


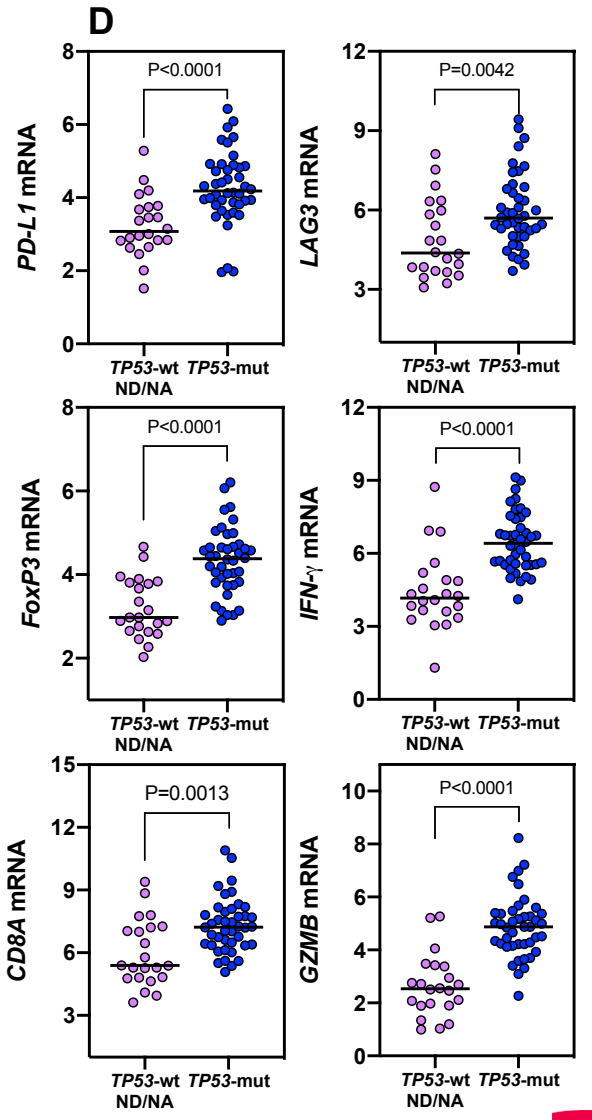


TP53–related immune profiles in primary BMs

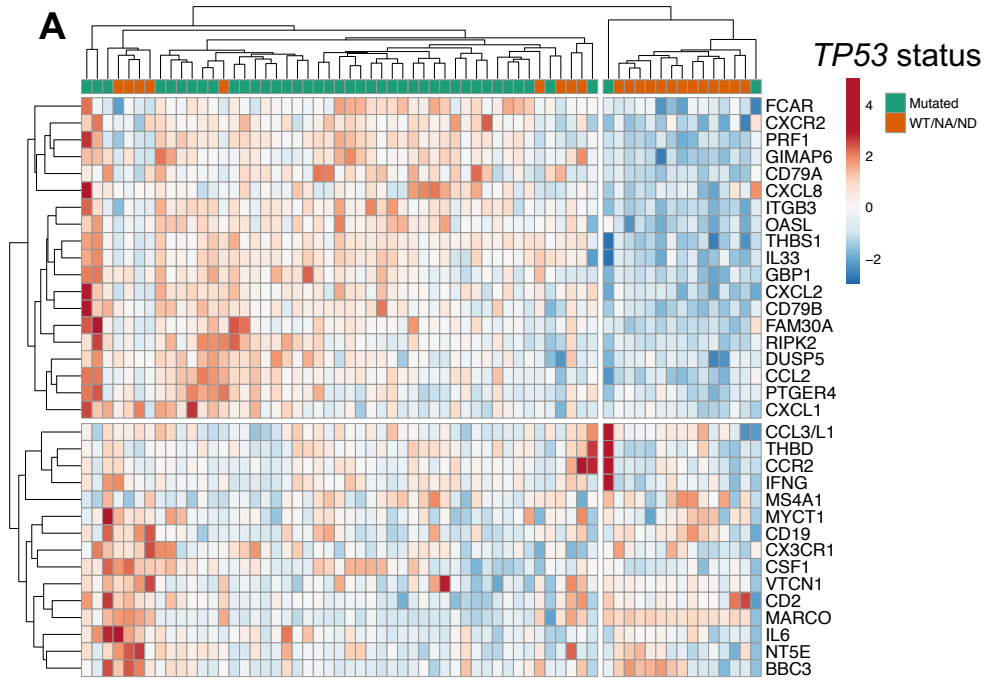


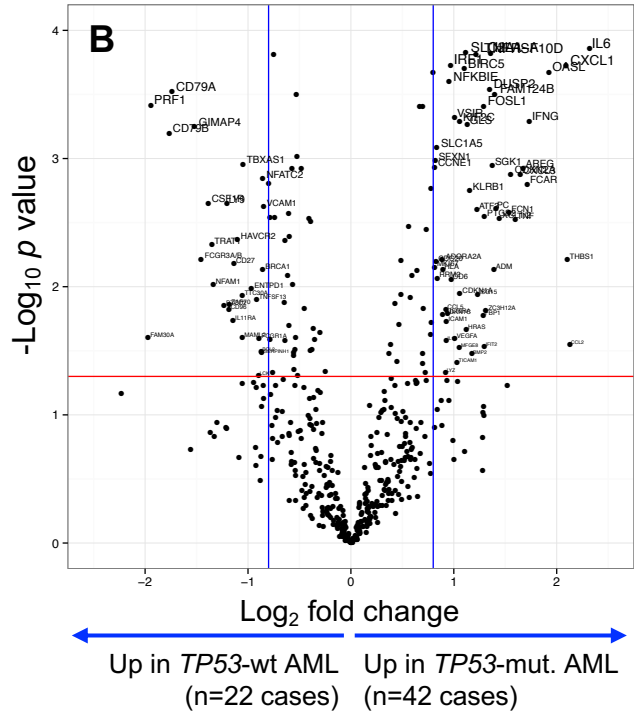






A unique immune *TP53* classifier

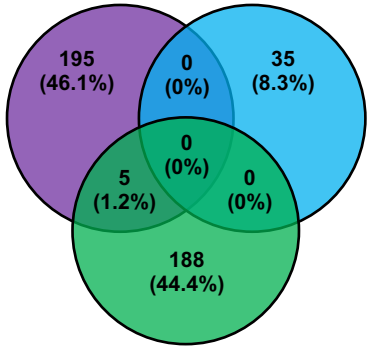




C

Hallmark *TP53* pathway genes
(M5939 MSigDB; n=200)

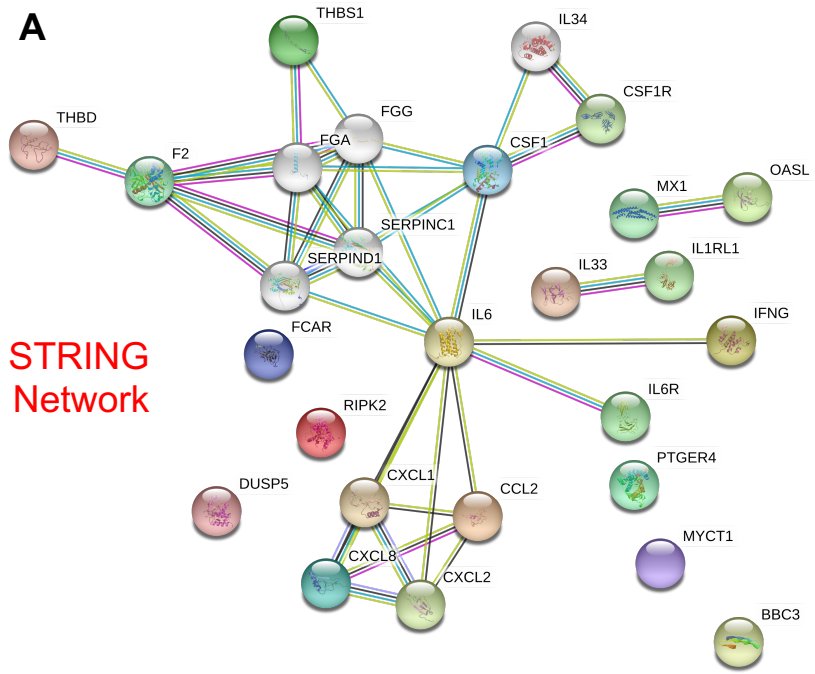
DE immune genes between
TP53 mutated and
TP53 wild t AML



TP53 pathway genes in NCI-60 cell lines
(M2698 MSigDB; n=193)

TP53–related immune genes stratify survival

A



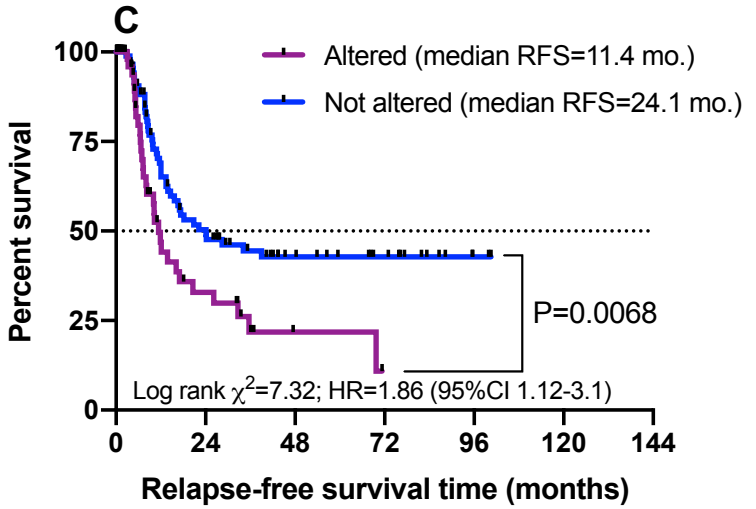
STRING
Interaction Network

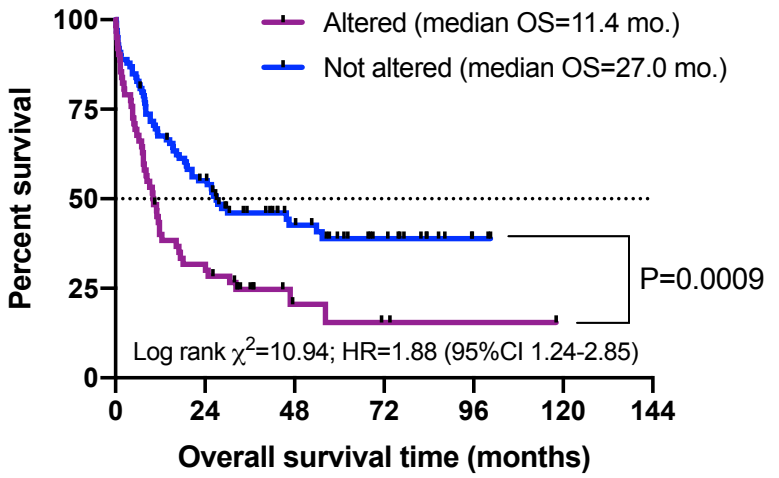
B

KEGG Pathway	Description	Count in gene set	FDR
hsa04060	Cytokine-cytokine receptor interaction	9 of 263	5.56×10^{-9}
hsa05323	Rheumatoid arthritis	6 of 84	6.37×10^{-8}
hsa04657	IL-17 signaling pathway	6 of 92	8.02×10^{-8}
hsa04621	NOD-like receptor signaling pathway	6 of 166	1.56×10^{-6}
hsa04668	TNF signaling pathway	5 of 108	4.16×10^{-6}

***In silico* prognostic power in TCGA-AML cases (18 upregulated genes in *TP53* mutated AML)**

C

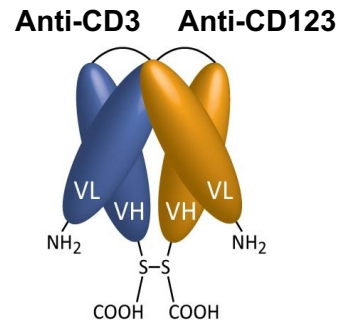




"Altered":
mRNA up-regulation
amplification
deep deletion
mis-sense mutations

Flotetuzumab immunotherapy cohort

Characteristic	NCT#02152956		Patients (n=35)*
Age (median and range)			54 years (27-74)
Gender	Male		16 (46%)
	Female		19 (54%)
Disease status at study entry	Late relapse (CR with initial duration >6 months)		7 (20%)
	Refractory to HMA		2 (5.7%)
	Refractory	Primary induction failure (PIF; ≥2 induction attempts)	**20 (57.1%)**
		Early relapse (CR with initial duration <6 months)	6 (17.2%)
2017 ELN risk stratification	Favorable		3 (8.6%)
	Intermediate		8 (22.9%)
	Adverse		**24 (68.6%)**
Secondary AML			11 (31.4%)
Number of prior lines of therapy (median and range)			3 (1-9)



Flotetuzumab

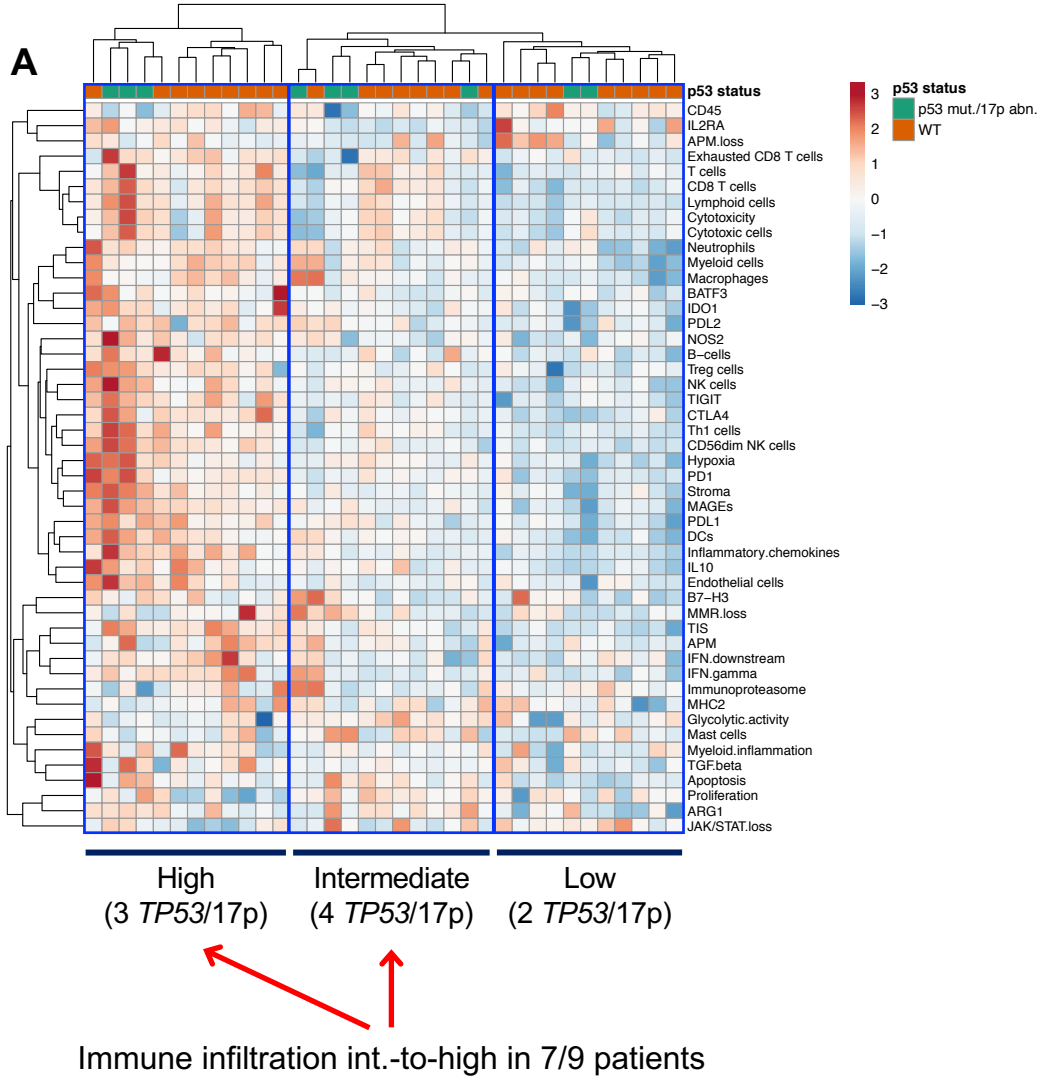
*Subgroup of 35/50 patients treated at the RP2D for whom BM samples were available

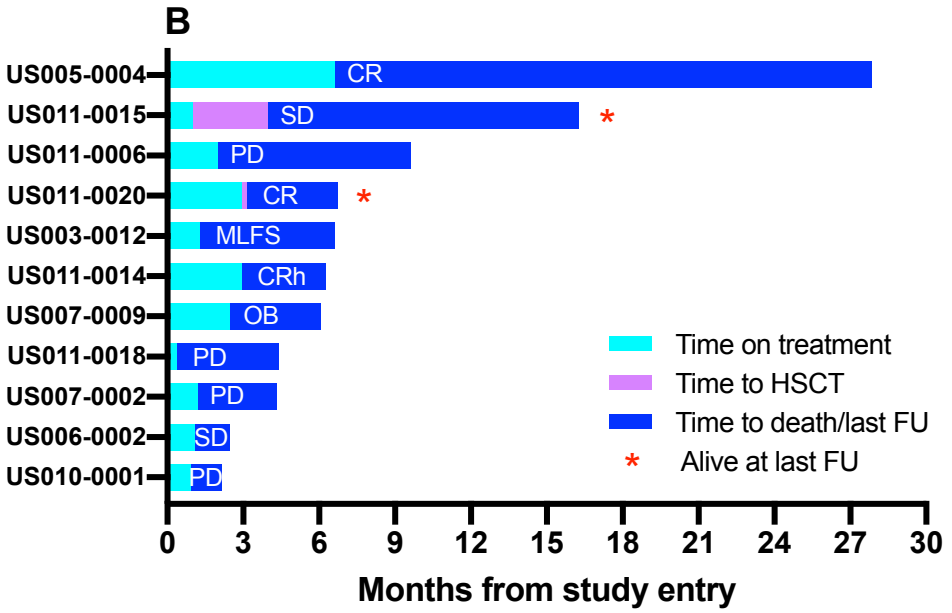
Response assessment criteria employed in analysis:

Anti-leukemic activity (ALA): CR/CRh, PR, “other benefit” (>30% decrease in BM blasts compared to baseline)

Non-responders (NR): treatment failure, stable disease, progressive disease

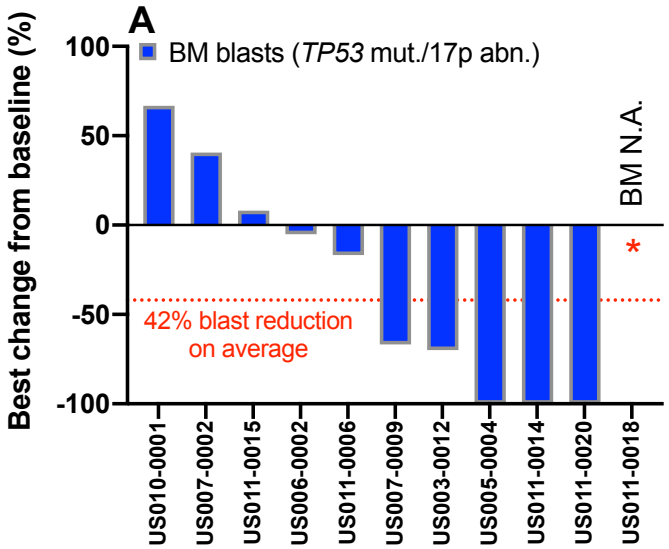
Flotetuzumab cohort – *TP53* mutations associate with an immune-infiltrated TME

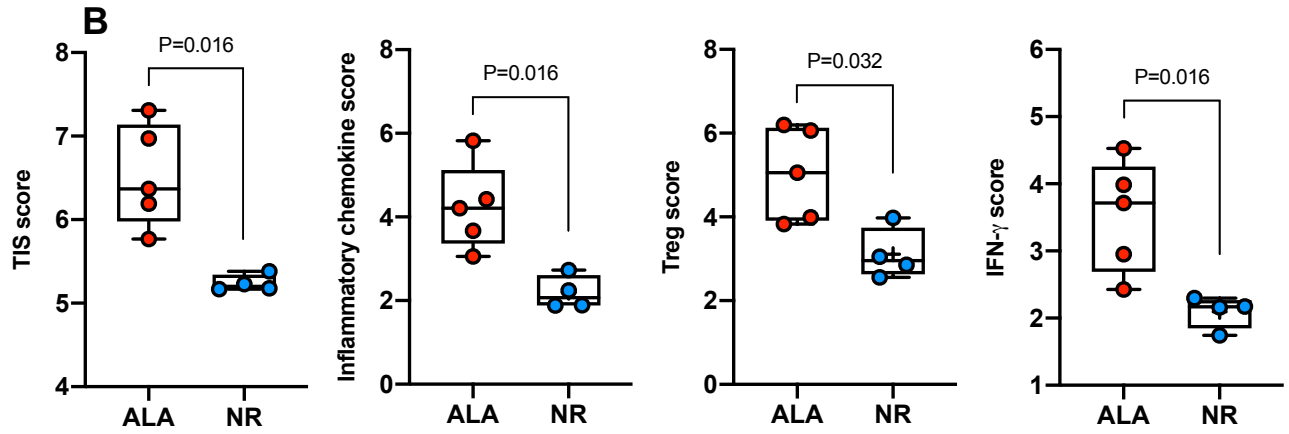


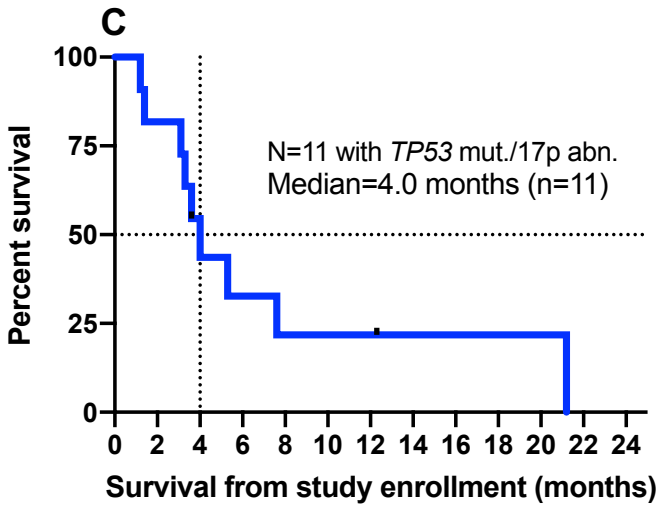


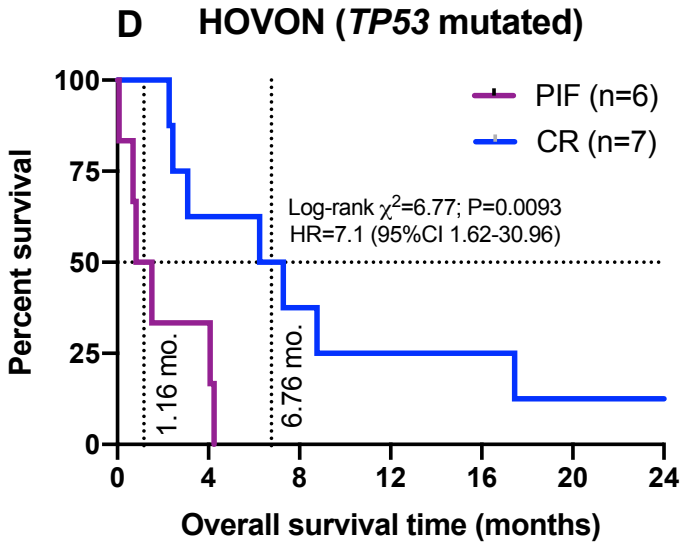
ALA in 45.5% (5/11) evaluable patients with *TP53* mutations and/or 17p abnormalities
(2 CR, 1 CRh, 1 morphologic leukemia-free state [MLFS], and 1 OB)

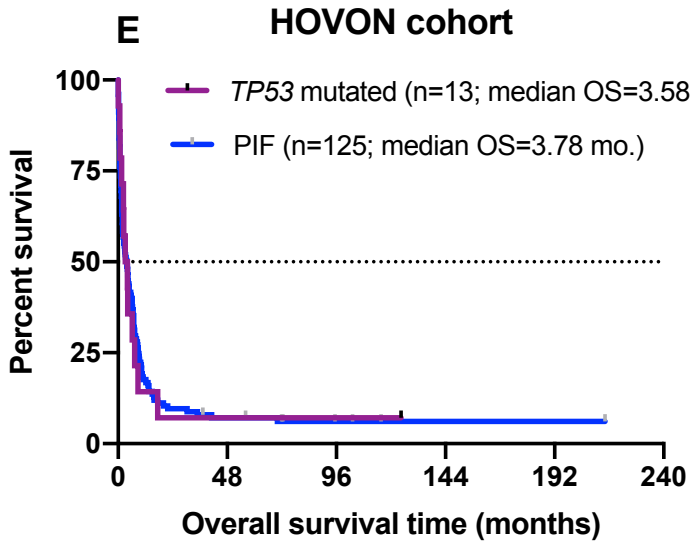
Response to flotetuzumab in *TP53* mutated patients











Conclusions

- Immune transcriptomic analyses of *in silico* and wet-lab cohorts of *TP53* mutated AML suggest the presence of high T-cell infiltration and high expression of immune checkpoints and IFN-γ signaling molecules compared with AML subgroups with other risk-defining molecular lesions
- Immunotherapy with flotetuzumab may be efficacious in individuals with altered *TP53* status, with an overall reduction of BM blasts averaging 42% and with evidence of ALA in 45.5% (5/11) of the patients
- The overall response rate observed in *TP53*-mutated patients treated with flotetuzumab encourages further study of this immunotherapeutic approach

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