

Increased WEE1 expression is predictive of short progression-free survival, independent of standard prognostic factors in multiple myeloma

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INTRODUCTION

- WEE1 is a tyrosine kinase involved in multiple aspects of the cell cycle.
- In the G2M stage of the cell division process, WEE1 regulates Cyclin-dependent kinase 1 (CDK1), with high WEE1 expression suppressing CDK1 expression and keeping the cell in the DNA repair state.
- High WEE1 expression has recently been shown to associate with disease aggressiveness in some solid tumors including breast cancer, ovarian cancer, and melanoma.

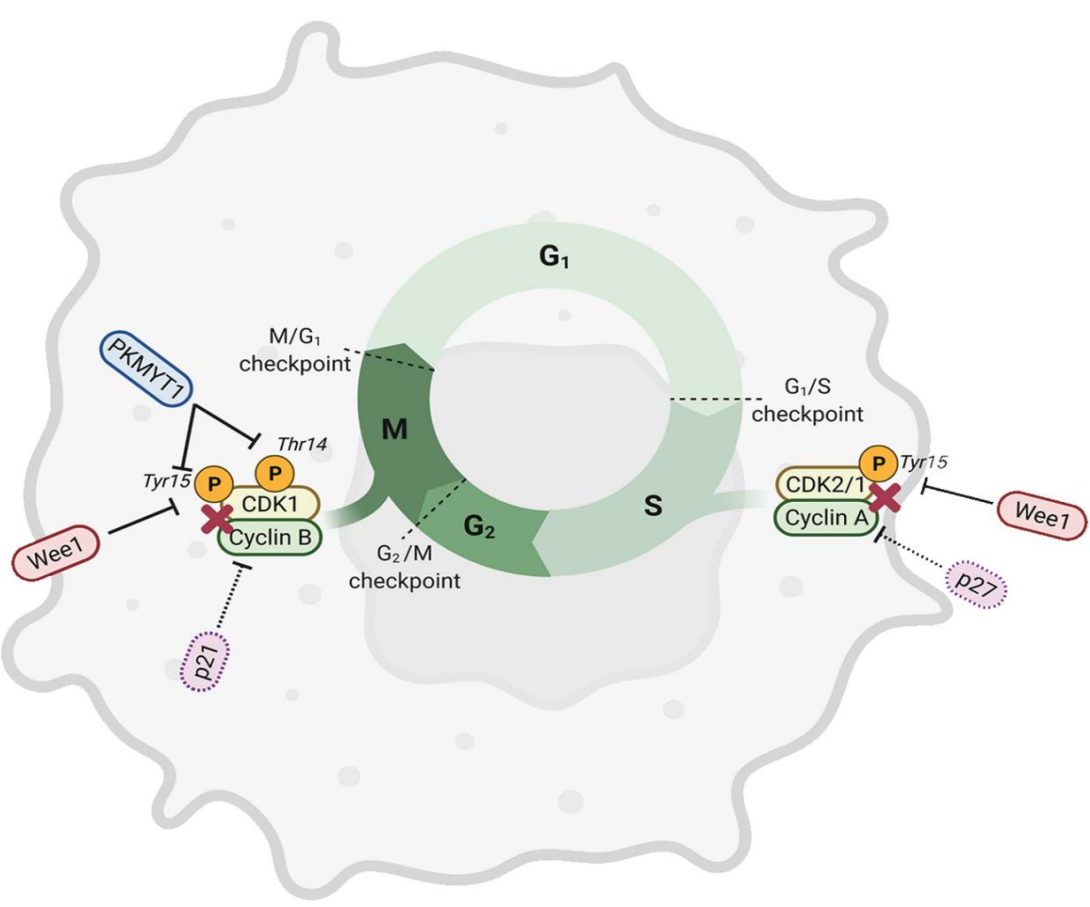


Figure 1. The Role of WEE1 and CDKs in the cell cycle. WEE1 regulates the cell cycle by phosphorylation of CDKs. Figure from Bukhari 2022.

DATA

Main data cohort: MMRF CoMMpass RNA-Seq (N=659).

- CoMMpass dataset (IA19) included clinical and treatment information. Certain genomic features such as chromothripsis were computed in an earlier study.

Validation cohorts:

- Microarray gene expression profiling (GEP) data from Total Therapy 2 (N=341) and 3 (N=214) trials.

Risk definitions:

- WEE1-high:** top-third of WEE1 expression of a given cohort.
- WEE1-low:** bottom-third of WEE1 expression of a given cohort.

	WEE1-low (N=218)	WEE1-high (N=224)	FDR p-value
Age	63.4	61.1	3.31E-02
Sex	M: 114; F: 104	M: 139; F: 85	5.22E-02
ISS	(I): 75; (II): 88; (III): 48	(I): 79; (II): 73; (III): 69	8.77E-02
Treatment	combined BTZ/IMiDs-based: 124; BTZ-based: 38; combined IMiDs/CFZ-based: 21; IMiDs-based: 14; CFZ-based: 11; combined BTZ/IMiDs/CFZ-based: 9; combined BTZ/CFZ-based: 1	combined BTZ/IMiDs-based: 89; combined IMiDs/CFZ-based: 50; BTZ-based: 45; CFZ-based: 20; IMiDs-based: 11; combined BTZ/IMiDs/CFZ-based: 9	-
Hyperdiploidy	151/189	58/170	9.53E-18
t(4;14)	22/204	20/181	1.00E+00
t(11;14)	11/204	69/181	4.30E-15
MAF translocation	4/204	22/181	1.48E-04
MYC translocation	39/204	19/181	3.31E-02
Chromothripsis	42/204	56/181	2.57E-02
Hyper APOBEC	6/204	25/179	2.04E-04
Gain 1q21	(0): 141; (1): 47; (2): 1	(0): 105; (1): 46; (2): 19	1.39E-04
TP53 aberration	(0): 157; (1): 15; (2): 0	(0): 114; (1): 22; (2): 13	1.48E-04

Table 1 — Difference in CoMMpass data patient characteristics between WEE1-high and WEE1-low cohorts. Majority of MM markers differ significantly between the two groups; however, ISS does not. Key: for gain 1q21, 0 = diploid, 1 = gain (3 copies), 2 = amplification (4 or more copies). For TP53 aberration, 0 = diploid, 1 = either deletion or mutation, 2 = biallelic loss. Certain markers not available for all subjects. BTZ: Bortezomib, CFZ: Carfilzomib.

RESULTS

WEE1 is prognostic for outcomes in RNA-seq and GEP datasets

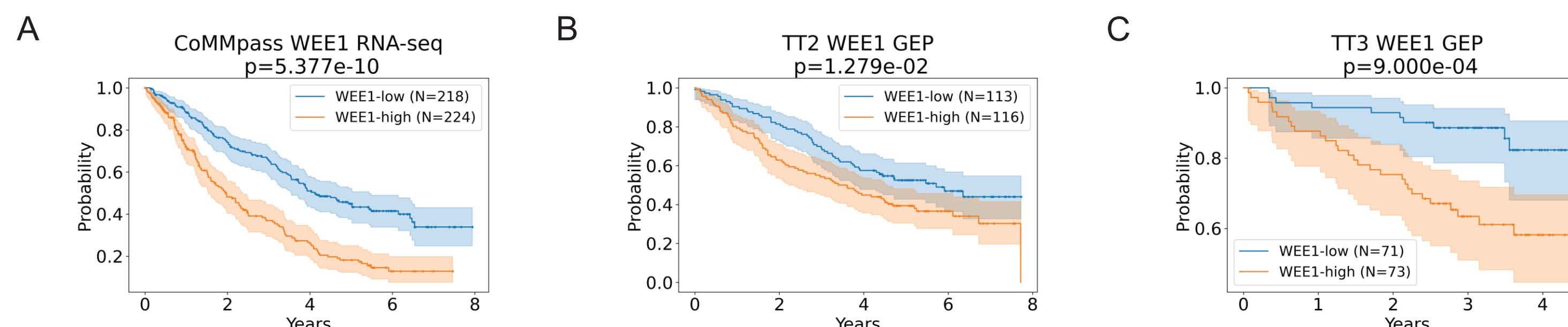


Figure 2. Prognostic value of WEE1 expression from RNA-seq and GEP data. A) Progression free survival (PFS) based on CoMMpass RNA-seq data showing the two-year difference in median PFS with a p-value of less than 1e-9. B & C) Event free survival of the Total Therapy 2 and Total Therapy 3 cohorts gene expression profiling (GEP) data, respectively, showing diverging outcomes with a P<0.05.

Multivariate modeling shows that WEE1 is an independent prognostic factor in MM

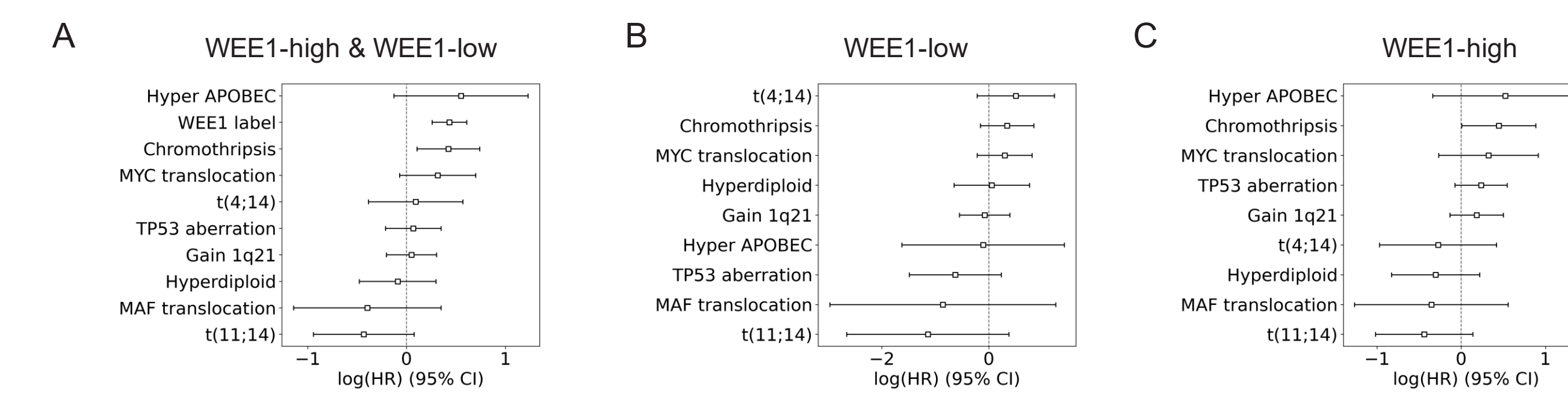


Figure 3. Cox proportional hazards (CPH) modeling of MM markers and WEE1 expression. A) Coefficients of the multivariate CPH model show WEE1 to be the most significant prognosticator. B & C) Within the WEE1-high and WEE1-low cohorts, none of the markers are significant for PFS after FDR-BH correction.

WEE1 is prognostic for outcomes independent of known biomarkers and treatment types

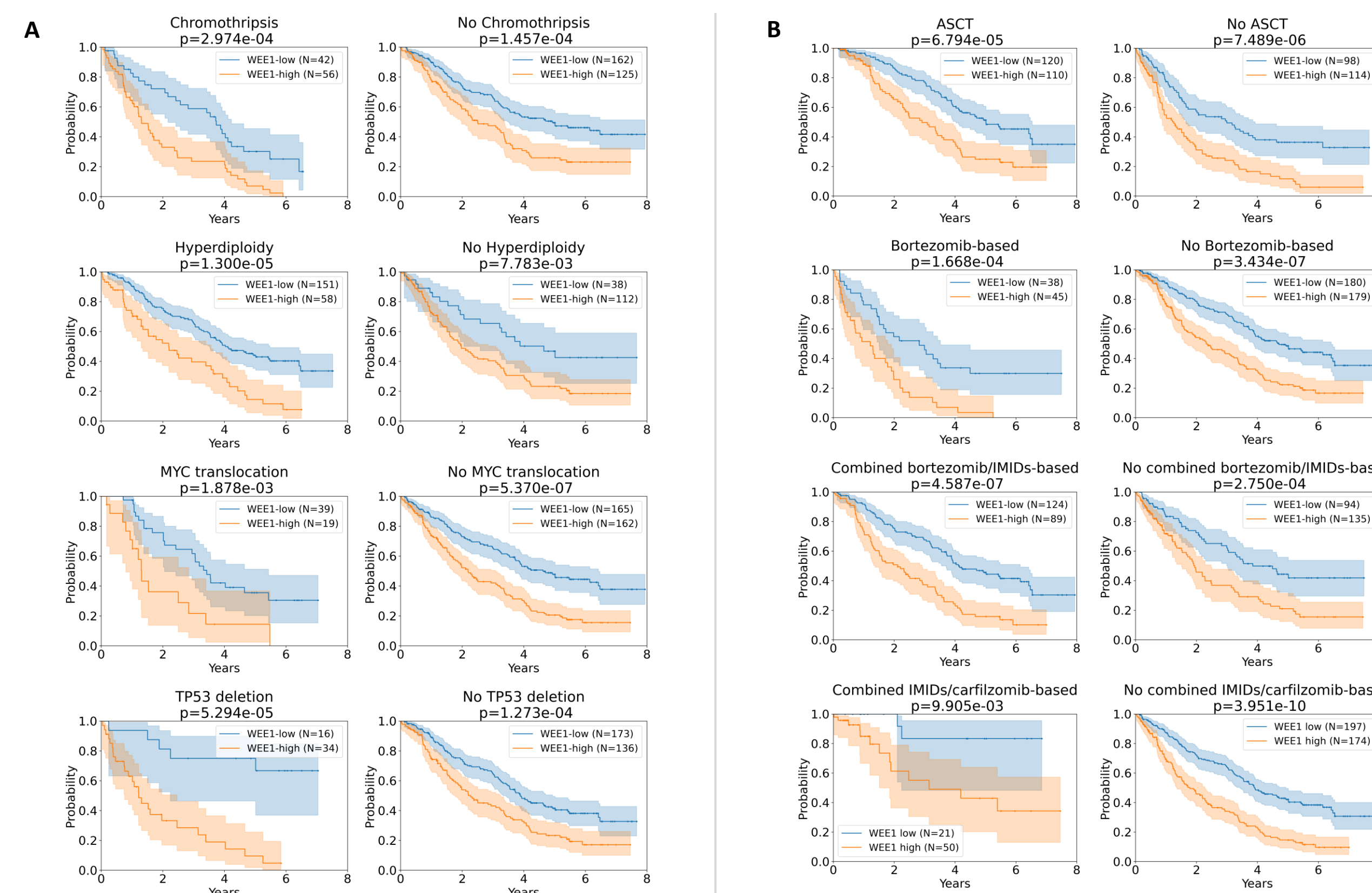


Figure 4. Kaplan-Meier curves stratified by (A) MM markers and (B) treatment type show the prognostic signal in WEE1 expression.

In the WEE1-high group, WEE1 expression is no longer predicted by CDK1 & CHEK1

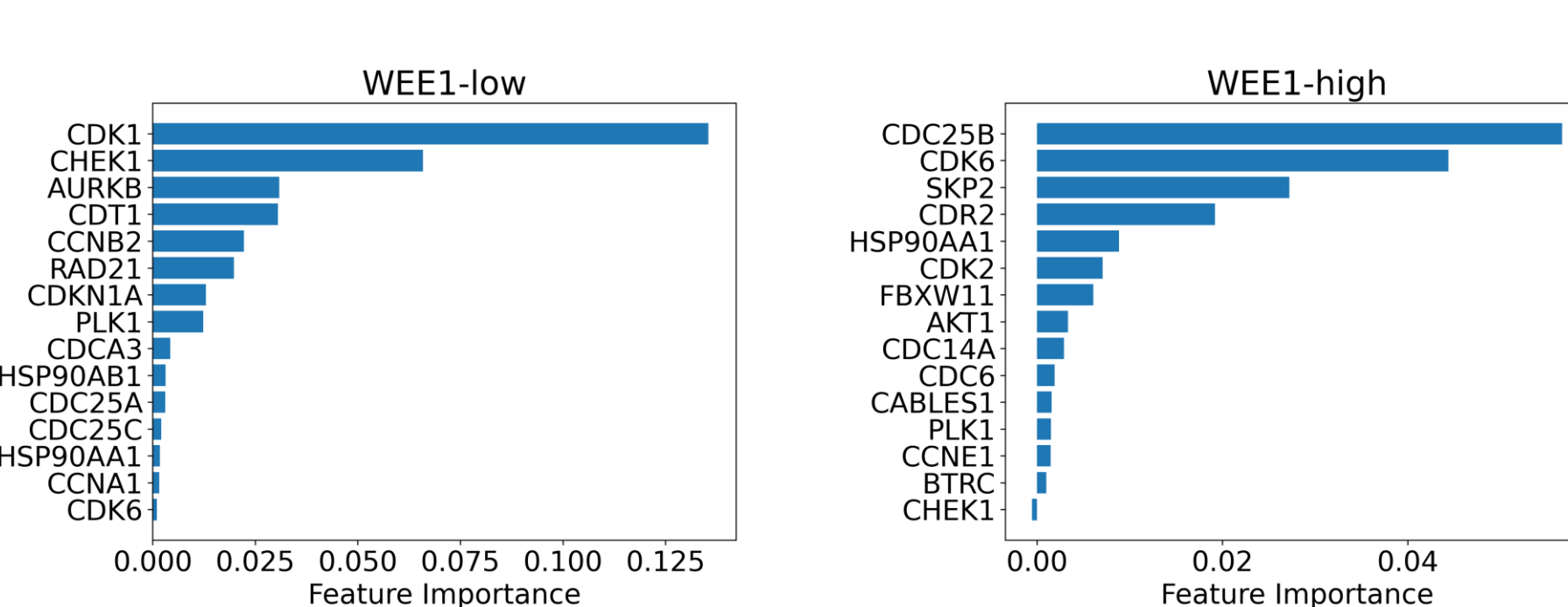


Figure 5. Random forest feature importance plots. RF modeling of WEE1 expression in the WEE1-high cohort is 3.2x more inaccurate than WEE1 expression modeling in the WEE1-low cohort.

WEE1 expression has comparable predictive value as the International Staging System (ISS)

Training features	C-index
WEE1	0.58 ± 0.04
WEE1 & interacting genes	0.63 ± 0.04
WEE1, interacting genes, & ISS	0.64 ± 0.03
ISS	0.61 ± 0.03
ISS + WEE1	0.63 ± 0.03

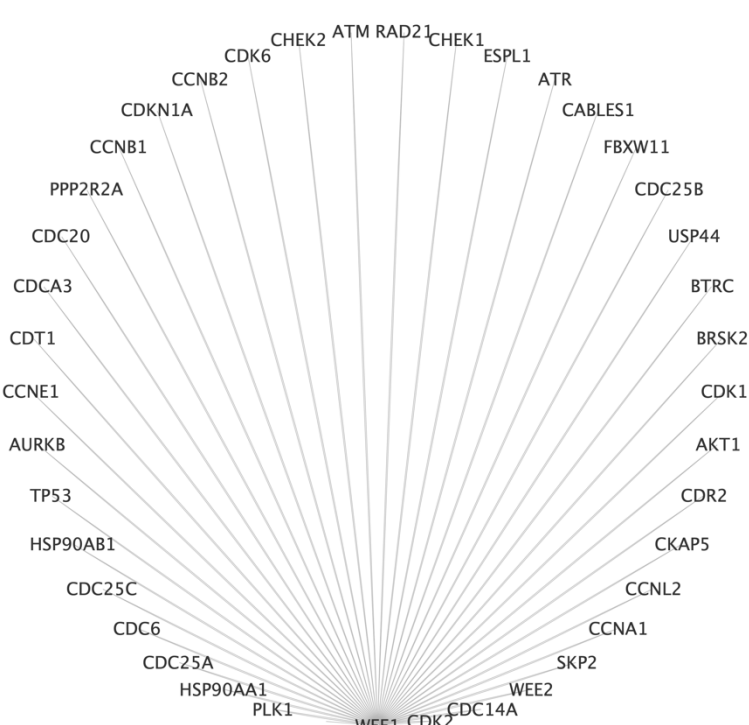
Table 2. Random forest feature importance plots. A) Feature importance plot showing the informative features for predicting WEE1 RNA-seq in the WEE1-low group.

P53 pathway-related genes are differentially expressed between WEE1-high & WEE1-low cohorts.

Hallmark gene set name	# Genes in Overlap (k)	FDR q-value
P53 pathway	7	3.10E-04
UV response DN	5	3.57E-03
Mitotic spindle	5	8.09E-03
Estrogen response early	5	8.09E-03
Adipogenesis	4	2.10E-02
Apical junction	4	2.10E-02
Epithelial mesenchymal transition	4	2.10E-02
Inflammatory response	4	2.10E-02
KRAS signaling up	4	2.10E-02
MTORC1 signaling	4	2.10E-02

Table 3. Hallmark pathways overexpressed in the WEE1-high cohort relative to the WEE1-low cohort.

Figure 6. Known interacting genes with WEE1 based on the STRING database.



CONCLUSIONS

WEE1 is

- Prognostic independent of known biomarkers,
- Differentiates outcomes associated with known markers,
- Upregulated independently of its interacting neighbors,
- Dysregulates P53 and proliferation pathways.

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