

INTRODUCTION

- Multiple myeloma (MM) is a hematological malignancy associated with a malignant proliferation of plasma cells.
- Despite responsiveness to initial therapies, MM remains incurable with inevitable relapse.**
- ISS/R-ISS scoring systems have progression-free survival concordance index (c-index) below 60%, leaving much to be desired.
- WEE1 is a tyrosine kinase involved in multiple aspects of the cell cycle process including the G1-S stage, S stage, and G2M stage.
- 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.

AIM

To show WEE1 expression's importance for prognostication independent of standard biomarkers and explore the associated genomic dysregulation.

DATA & METHODS

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

- CoMMpass dataset 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:

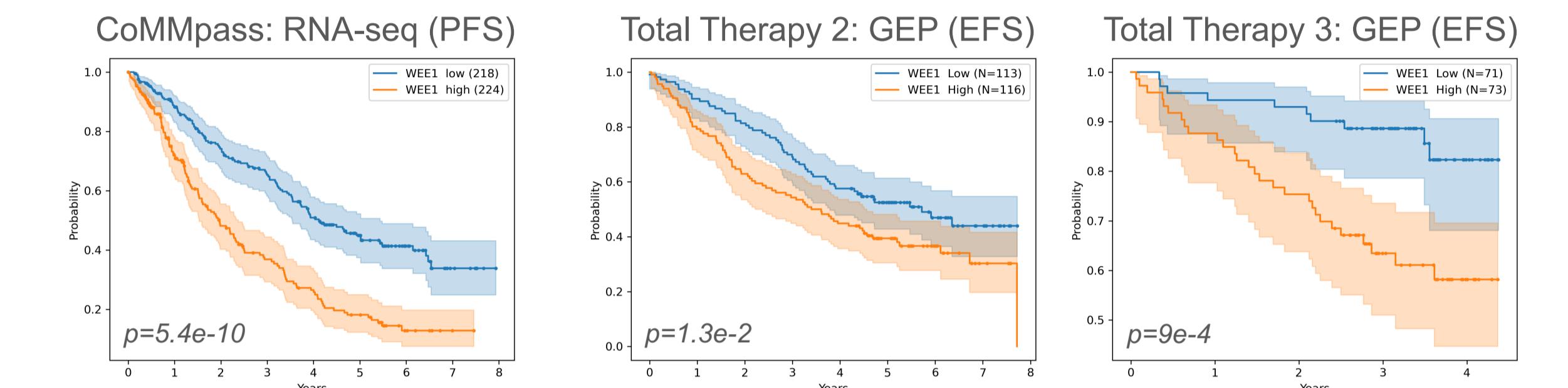
- High-risk (HR):** top-third of WEE1 expression of a given cohort.
- Low-risk (LR):** bottom-third of WEE1 expression of a given cohort.

Methods:

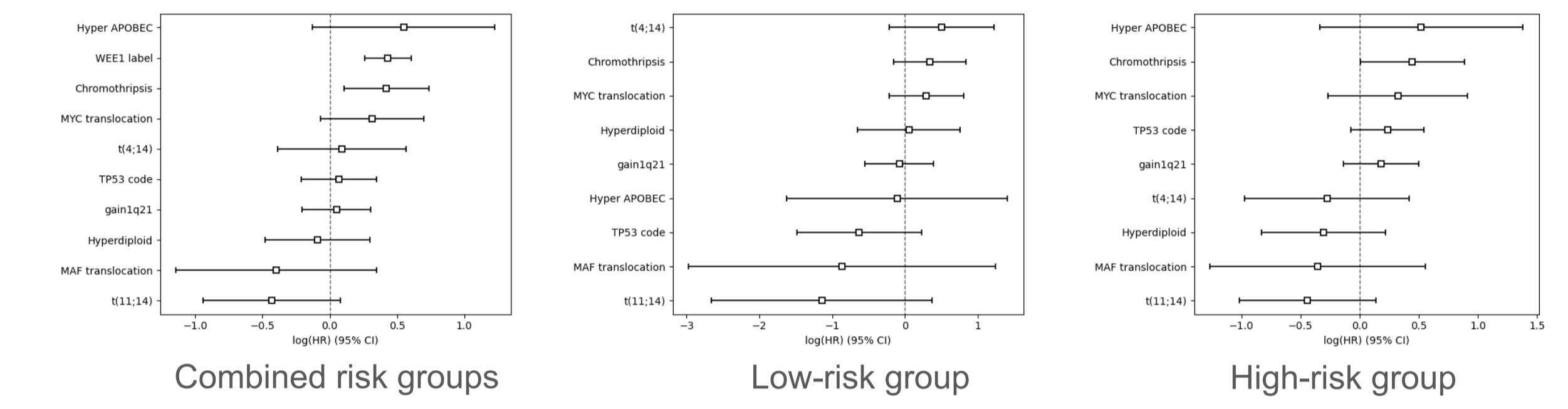
- Network information was extracted from the STRING database.
- Multivariate modeling was performed using Cox proportional hazards (CPH) models, predicting progression-free survival (PFS) using WEE1 risk-group membership and known biomarkers of MM.
- Random forests (RF) were used to predict WEE1 expression using WEE1 gene neighborhood values.
- Random survival forests (RSF) were used to compute the concordance index (c-index). Models were trained on the listed set of input variables and predict PFS.

RESULTS

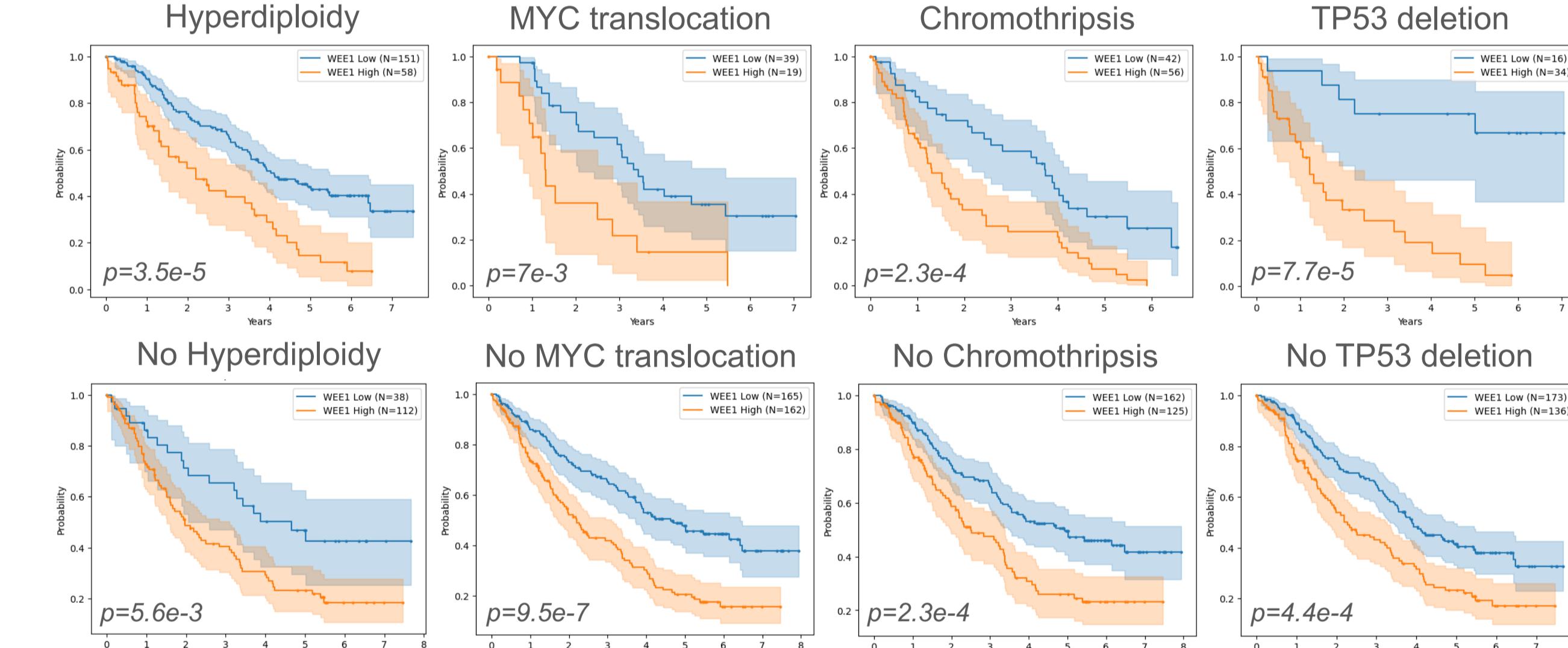
WEE1 is prognostic for outcomes in RNA-seq and GEP data



Multivariate Cox proportional hazards modeling shows WEE1 is prognostic when accounting for known MM markers



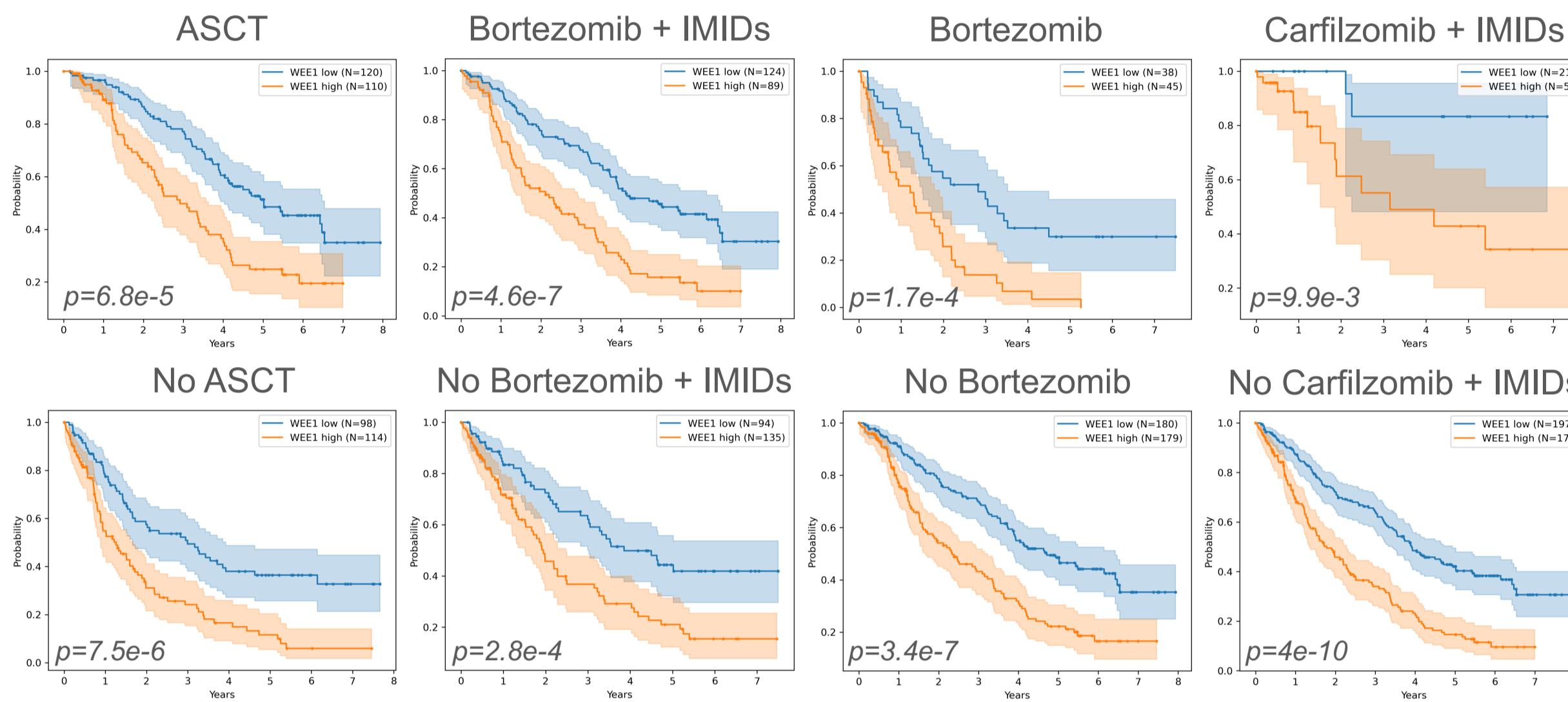
WEE1 is prognostic independent of known MM biomarkers (CoMMpass RNA-seq)



METHODS

- To determine if an increase of WEE1 correlates with changes in its neighboring genes, we computed the anti-correlation:
 - Anti-correlation = (high-risk correlations) – (low-risk correlations)
- Differential gene expression analysis between the HR and LR cohorts conducted using DESEQ2 from Bioconductor. Significance defined as corrected $p < 0.05$ and absolute log-fold change > 2 .
- Gene set enrichment analysis (GSEA) was conducted to compute hallmark pathway membership.
- Random forests (RF) were used to predict WEE1 expression using WEE1 gene neighborhood values.
- Random survival forests (RSF) were used to compute the concordance index (c-index). Models were trained on the listed set of input variables and predict PFS.

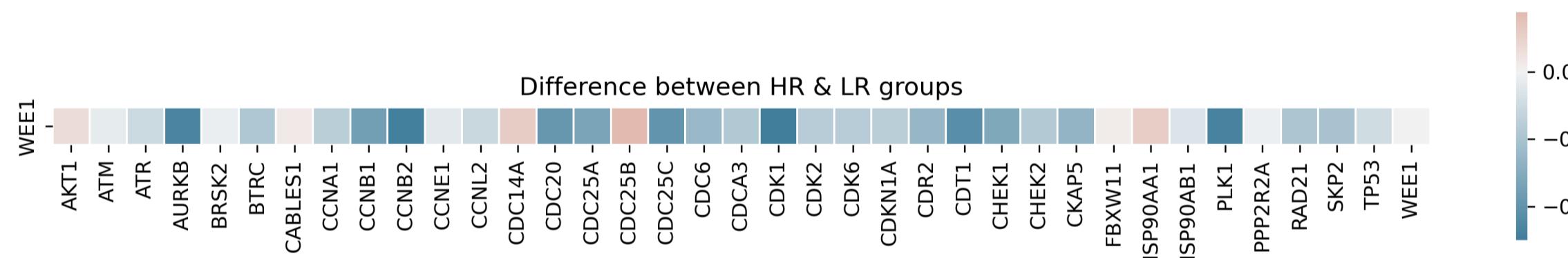
WEE1 is prognostic independent of certain treatments (CoMMpass RNA-seq)



WEE1 differentiates outcomes an average of two years for known biomarkers

Feature name	Positive (years)	Negative (years)
Hyperdiploidy	1.838	2.685
t(4;14)	1.115	2.436
t(11;14)	ND	1.956
MAF translocation	ND	1.921
MYC translocation	2.121	2.436
Chromothripsis	2.427	2.427
Hyper APOBEC	2.378	1.942
TP53 deletion	ND	1.608

WEE1 expression growth uncorrelated with neighboring genes



When comparing correlation between the high-risk and low-risk groups, the rise in WEE1 expression is not correlated with an equivalent rise or fall in cell cycle genes including AURKB, CCNB1, CDK1, & PLK1.

Patient Table

	Low WEE1 (N=218)	High WEE1 (N=224)	p-value
Age	63.4312	61.1027	0.0212
Sex	M: 114; F: 104	M: 139; F: 85	0.0435
ISS	(I): 75; (II): 88; (III): 48	(I): 79; (2): 73; (3): 69	0.0804
HRD	(0): 38; (1): 151	(0): 112; (1): 58	7.94E-19
t(4;14)	(0): 182; (1): 22	(0): 161; (1): 20	1.00E+00
t(11;14)	(0): 193; (1): 11	(0): 112; (1): 69	7.16E-16
MAF translocation	(0): 200; (1): 4	(0): 159; (1): 22	6.16E-05
MYC translocation	(0): 165; (1): 39	(0): 162; (1): 19	2.20E-02
Chromothripsis	(0): 162; (1): 42	(0): 125; (1): 56	2.57E-02
Hyper APOBEC	(0): 198; (1): 6	(0): 154; (1): 25	1.02E-04
Gain 1q21	(0): 141; (1): 47; (2): 1	(0): 105; (1): 46; (2): 19	3.48E-05
TP53 mutation	(0): 157; (1): 15; (2): 0	(0): 114; (1): 22; (2): 13	5.55E-05

Table 1 — Difference in CoMMpass data patient characteristics between high-risk and low-risk groups. The 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 mutation, 0 = diploid, 1 = either deletion or mutation, 2 = biallelic loss. Data not available for all subjects.

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. Determining the causes of abnormal WEE1 expression may uncover therapeutic targets.

ACKNOWLEDGEMENT

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