(PD39-03) Hypoxia-Inducible Factor (HIF) Pathway Genes Predict Overall Survival for Metastatic Clear Cell Renal Cell Carcinoma

Introduction

- Prognosis for metastatic renal cell carcinoma (RCC) is variable
- Aberrant HIF signaling is associated with progression of RCC

![Diagram showing the regulation of HIF-α and its target gene induction](image)
Objective

- Assess HIF pathway genes as predictors of overall survival in metastatic RCC using primary tumor tissue from CALGB 90206

Rini et al., JCO, 28:2137
Methods | Design, Setting, Participants

- Gene expression was determined from 324 archival pretreatment nephrectomy specimens available from a phase III trial of 732 patients treated with interferon alpha vs. interferon alpha plus bevacizumab.
• TaqMan RT-qPCR was performed on the OpenArray platform using RNA extracted from tumor tissue macrodissected based on review of H&E staining by a GU pathologist
Methods | Statistical Methods

- Normalized gene expressions were centered and scaled across samples with means set at 0 and standard deviations set at 1 (z-score)
- HIF pathway genes were assessed in univariable and multivariable cox proportional hazard models as predictors of OS
- TCGA RCC dataset was used for validation of the multivariable prognostic model
Results | Univariable Analysis

- 17 HIF pathway genes were assessed in univariable analysis
- 5 of these genes were associated with OS
  - VHL (p=0.006)
  - HIF2a (p=0.044)
  - VEGF-D (p=0.026)
  - TGFA (p=0.014)
  - CCND1 (p=0.039)
Kaplan-Meier curves for overall survival for risk groups determined based on mean gene expression score

**Individual Gene Models**

**VEGFD**
- High vs. Low groups
  - P=0.026
  - HR=0.77 [0.61-0.97]
- Overall survival rate
- Time to death (months)

**TGFA**
- High vs. Low groups
  - P=0.014
  - HR=0.75 [0.60-0.94]
- Overall survival rate
- Time to death (months)

**VHL**
- High vs. Low groups
  - P=0.038
  - HR=1.27 [1.01-1.60]
- Overall survival rate
- Time to death (months)

**HIF2A**
- High vs. Low groups
  - P=0.045
  - HR=0.78 [0.62-0.99]
- Overall survival rate
- Time to death (months)

**CCND1**
- High vs. Low groups
  - P=0.039
  - HR=0.79 [0.63-0.99]
- Overall survival rate
- Time to death (months)
• In multivariable analysis, VEGF-D, TGFA and VHL were significant predictors of overall survival
Cohorts were stratified at 75-percentile value of 3-gene model risk scores
Kaplan-Meier curve for overall survival based on multi-gene + MSKCC risk score model applied to CALGB cohort

Cohorts were stratified at 75-percentile value of 3-gene model risk scores

**3-gene plus MSKCC risk score model**

- **Low group**
- **High group**

**High vs. Low groups**
- P = 1.65e-5
- HR = 1.77 [1.36-2.29]
Kaplan-Meier curve for overall survival based on multi-gene model applied to TCGA cohort

Cohorts were stratified at 75-percentile value of 3-gene model risk scores

3-gene model

High vs. Low groups
P=0.022
HR=1.48 [1.06-2.06]
Conclusion

• The HIF pathway genes associated with OS include CCND1, VEGF-D, HIF2a, TGFA, and VHL

• In a multivariable model, VEGF-D, TGFA and VHL were independent predictors of OS

• Pathway directed analysis → elucidate information on biological drivers of mRCC to provide future targets
Future Directions

• Future studies should consider HIF pathway genes and multivariable models based on these genes as predictors of response to treatments targeting the hypoxia pathway and angiogenesis.
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