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Association Between *PTK7* Expression and Real-World Survival in Pretreated Patients With *EGFR* Wild-Type Lung Adenocarcinoma

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Objective

The aim of this analysis was to assess the prognostic associations between protein tyrosine kinase 7 (*PTK7*) expression and real-world progression-free survival (rwPFS) and real-world overall survival (rwOS) in patients with pretreated epidermal growth factor receptor (*EGFR*) wild-type lung adenocarcinoma

Conclusions

- » Among patients with *EGFR* wild-type advanced lung adenocarcinoma prior to the start of second- or later-line (2L+) therapy, medium/high *PTK7* expression was not a prognostic factor for rwOS or rwPFS despite trends toward improvement versus low *PTK7* expressors
- In multivariate analyses, Eastern Cooperative Oncology Group performance status and extent of prior therapy emerged as significant prognostic factors for rwOS, and extent of prior therapy was an independent prognostic factor for rwPFS
- *PTK7*-low tumors demonstrated enrichment of *KEAP1*- and *STK11*-associated mutations, suggesting that differences in underlying biology may contribute to the trend toward poorer survival outcomes observed in these subgroups
- Notably, in the subgroup of patients previously treated with chemoimmunotherapy, medium/high *PTK7* expression was significantly associated with longer rwPFS; in the multivariate analysis, this remained a significant predictor of rwPFS, as did line of therapy
- These data suggest that the prognostic value of *PTK7* expression in rwPFS may be dependent on prior therapeutic exposure

- » Consistent with results from clinical trials in patients with advanced *EGFR* wild-type non-small cell lung cancer (NSCLC) receiving treatment in the 2L+ setting,^{5,6} rwOS was approximately 12 months, highlighting an unmet need for new treatments in this patient population and setting
- » Results from this analysis support PTK7 as a target-engagement biomarker for antibody-drug conjugate (ADC) payload delivery, independent of prognosis in NSCLC

- » HWK-007, a novel PTK7-directed ADC, is currently being evaluated in a phase 1 clinical trial in patients with solid tumors, including non-squamous *EGFR* wild-type NSCLC (NCT07444814)¹³

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For disclosures of co-authors, please refer to the abstract.

Background

- » Non-small cell lung cancer (NSCLC) accounts for approximately 87% of all lung cancers in the US¹ and has a 5-year survival rate of around 26%²
- » Treatment for advanced NSCLC is determined by histologic subtype (e.g., adenocarcinoma) and the presence of actionable genomic alterations (AGAs) for which targeted therapies are available, most commonly epidermal growth factor receptor (*EGFR*) mutations^{3–4}
 - For patients with advanced *EGFR* wild-type NSCLC, standard-of-care treatment in the second- or later-line (2L+) setting is chemotherapy and/or immunotherapy³; for patients with tumors of non-squamous histology, this results in median progression-free survival of 2.3–4.2 months and median overall survival of 9.4–15.6 months,^{5,6} highlighting the unmet need in this population
- » Protein tyrosine kinase 7 (*PTK7*) is a catalytically inactive receptor tyrosine kinase that is downregulated in adult tissues but overexpressed in various tumor types^{7,8}
 - In many tumors (e.g., lung, ovarian, cervical, and colon cancers), *PTK7* overexpression is associated with metastasis and chemoresistance^{7,8}
 - Relatively low expression of *PTK7* in normal tissues⁸ makes it an ideal antibody-drug conjugate (ADC) target across oncology indications

- » HWK-007 is a next-generation, PTK7-targeting ADC comprising a high-affinity, anti-PTK7 monoclonal IgG1 antibody with attenuated Fc activity conjugated to the novel topoisomerase I inhibitor payload CPT116⁹
- » Research has shown high *PTK7* expression in >80% of NSCLC cases, with expression remaining high across histologic subtypes and disease stages, and irrespective of *EGFR* mutation status^{7,8,10}
 - These data support PTK7 as a promising therapeutic target in lung cancer

Methods

- » Multimodal data from a real-world database (Tempus AI, Inc.) were used to analyze real-world progression-free survival (rwPFS) and real-world overall survival (rwOS) by *PTK7* expression in tumor samples from patients with *EGFR* wild-type lung adenocarcinoma prior to the start of 2L+ therapy
 - *PTK7* expression was quantified as log₂(transcripts per million [TPM]+1), and expression was stratified into tertiles to compare outcomes by low versus medium/high *PTK7* expression
- » The associations between *PTK7* expression and rwPFS and rwOS were analyzed using a Cox proportional hazards model, adjusted for prognostic factors using multivariable regression
 - Prognostic variables included in the model were age; sex; tumor purity (i.e., the proportion of tumor vs non-tumor cells in tissue samples); tumor biopsy site; line of therapy; Eastern Cooperative Oncology Group performance status (ECOG PS); smoking status; presence of AGAs that have US Food and Drug Administration-approved therapies available, as defined per OncoKB[™] (i.e., *BRAF*^{V600E}; *EGFR*; *HER2*, *KRAS*^{G12C}; any *ALK*, *NRG1*, *NTRK1/2/3*, *RET* or *ROS1* fusions; *MET* exon 14 skipping mutations; and *MET* copy number ≥8 amplifications)^{11,12}; programmed death-ligand 1 (PD-L1) status; serine/threonine kinase 11 (*STK11*) status; and Kelch-like ECH-associated protein 1 (*KEAP1*) status
 - Hazard ratios (HRs), 95% confidence intervals (CIs), and *P*-values were calculated

Results

- » *PTK7* expression (log₂[TPM+1]) among tumor samples from 427 patients with *EGFR* wild-type NSCLC prior to the 2L+ setting was stratified into tertiles defined as low (<6.33; n=195), medium (≥6.33; n=148), and high (≥7.12; n=84) *PTK7* expression
 - The medium and high *PTK7* expression groups were combined to enable robust sample sizes for statistical analyses
 - *KEAP1* and *STK11* mutations were more common in low versus medium/high *PTK7* expressors (*KEAP1*: 12% vs 4%; *STK11*: 19% vs 8%)
- » ASSOCIATION BETWEEN *PTK7* EXPRESSION AND rwPFS
 - » Median rwPFS was numerically longer in patients with medium/high (≥6.33; n=190) versus those with low (<6.33; n=156) *PTK7* expression (6.5 vs 5.3 months; *P*=0.0915) (Figure 1A)
 - » In a multivariate analysis adjusting for age, sex, tumor purity, tumor biopsy site, line of therapy, ECOG PS, smoking status, AGAs, PD-L1 status, *STK11* status, and *KEAP1* status, *PTK7* expression was not prognostically associated with rwPFS (HR 0.75 [95% CI 0.56–1.00]; *P*=0.0529) (Figure 1B)
 - Later line of therapy was independently associated with worse rwPFS outcomes (third line [3L] vs second line [2L]: HR 1.81 [95% CI 1.29–2.55]; *P*=0.000589)
 - There was no significant prognostic association between rwPFS and sex, tumor biopsy site, ECOG PS, smoking status, PD-L1 status, *STK11* status, or *KEAP1* status
- » In subgroups of patients previously treated with chemoimmunotherapy prior to the 2L+ setting, median rwPFS was significantly longer in those with medium/high (≥6.33; n=113) versus those with low (<6.33; n=91) *PTK7* expression (6.8 vs 5.1 months; *P*=0.0115) (data not shown)
 - In the multivariate analysis, medium/high *PTK7* expression remained significantly associated with reduced risk of progression (HR 0.57 [95% CI 0.38–0.85]; *P*=0.00549) relative to low *PTK7* expressors
 - Similar to the overall *EGFR* wild-type 2L+ population, later line of therapy was independently associated with worse rwPFS outcomes (3L vs 2L: HR 2.36 [95% CI 1.47–3.78]; *P*=0.000364); there was no significant prognostic association between rwPFS and sex, tumor biopsy site, smoking status, PD-L1 status, *STK11* status, or *KEAP1* status

ASSOCIATION BETWEEN *PTK7* EXPRESSION AND rwOS

- » Median rwOS was numerically longer in patients with medium/high (≥6.33; n=232) versus those with low (<6.33; n=195) *PTK7* expression (14.8 vs 11.7 months; *P*=0.114) (Figure 2A)
- » In a multivariate analysis adjusting for age, sex, tumor purity, tumor biopsy site, line of therapy, ECOG PS, smoking status, AGAs, PD-L1 status, *STK11* status, and *KEAP1* status, *PTK7* expression was not prognostically associated with rwOS (HR 0.93 [95% CI 0.71–1.21]; *P*=0.571) (Figure 2B)
- Variables that were independently associated with worse rwOS outcomes were later line of therapy (3L vs 2L: HR 1.43 [95% CI 1.04–1.96]; *P*=0.0266) and ECOG PS (2+ vs 0: HR 2.27 [95% CI 1.28–4.02]; *P*=0.00497)
- There was no significant prognostic association between rwOS and sex, tumor biopsy site, smoking status, PD-L1 status, *STK11* status, or *KEAP1* status
- » In subgroups of patients with *EGFR* wild-type NSCLC previously treated with chemoimmunotherapy prior to the 2L+ setting (n=238), longer median rwOS was demonstrated in those with medium/high (≥6.33; n=130) versus those with low (<6.33; n=108) *PTK7* expression (14.8 vs 10.9 months; *P*=0.00433) (data not shown)
 - Similar to the overall *EGFR* wild-type 2L+ cohort, in the multivariate analysis, *PTK7* expression was not prognostically associated with rwOS (HR 0.73 [95% CI 0.49–1.07]; *P*=0.108); there was also no significant association between rwOS and sex, tumor biopsy site, smoking status, PD-L1 status, *STK11* status, or *KEAP1* status
 - As with the overall *EGFR* wild-type 2L+ population, variables that were independently associated with worse rwOS outcomes were later line of therapy (3L vs 2L: HR 2.11 [95% CI 1.37–3.25]; *P*=0.0007) and ECOG PS (2+ vs 0: HR 2.57 [95% CI 1.19–5.52]; *P*=0.0157)

FIGURE 1. (A) Kaplan–Meier Plot and (B) Forest Plot of rwPFS by *PTK7* Expression (n=346)

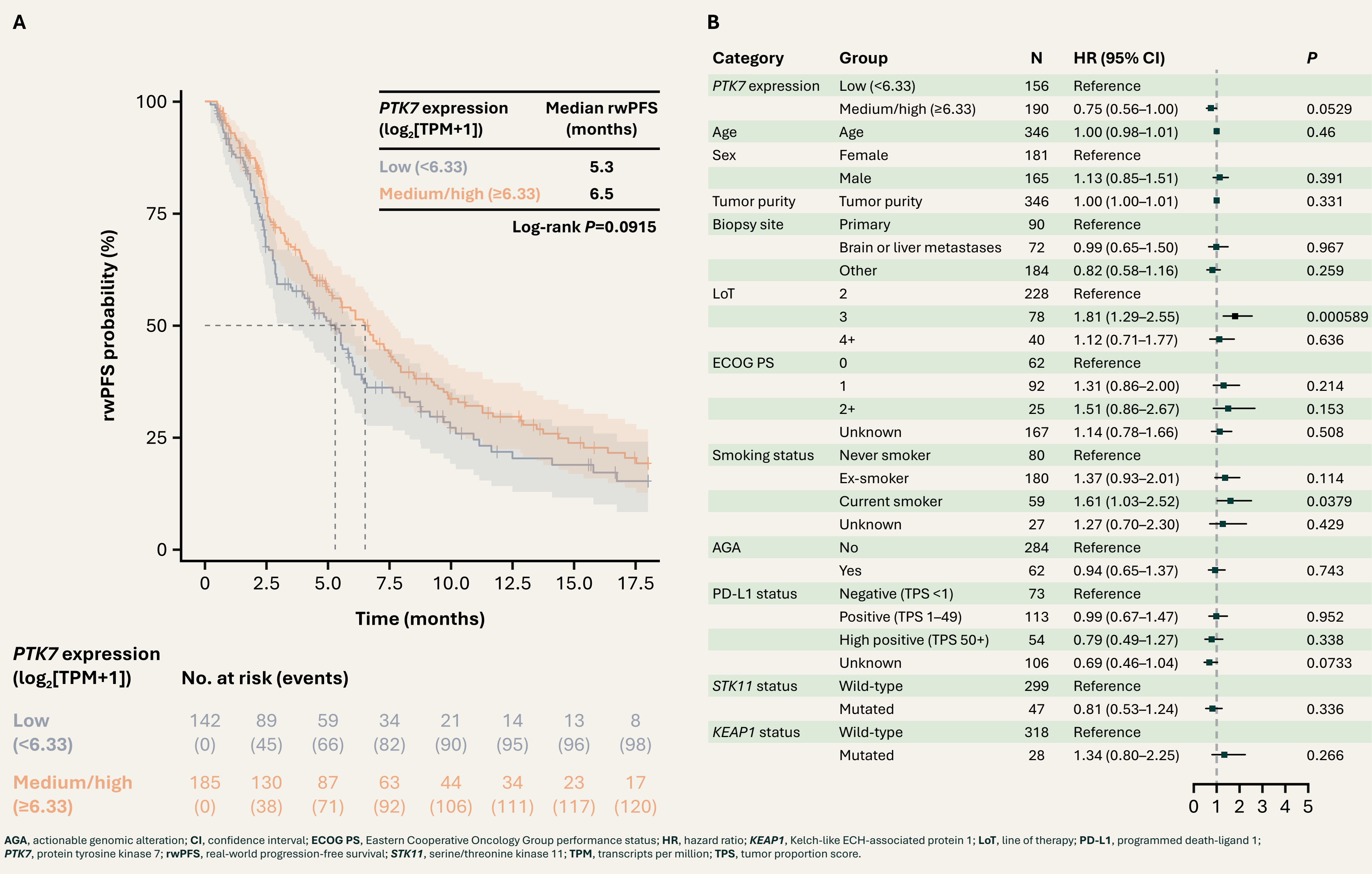


FIGURE 2. (A) Kaplan–Meier Plot and (B) Forest Plot of rwOS by *PTK7* Expression (n=427)

