

Durable and Treatment-Agnostic *PTK7* Expression in *EGFR* Wild-Type Lung Adenocarcinoma Supports Targeted ADC Development

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Objective

This analysis aimed to evaluate expression of protein tyrosine kinase 7 (*PTK7*) before and after standard-of-care treatment and relative to other antibody-drug conjugate (ADC) targets in epidermal growth factor receptor (*EGFR*) wild-type non-small cell lung cancer (NSCLC)

Conclusions

- » *PTK7* expression is highly stable before and after treatment across standard therapies for *EGFR* wild-type lung adenocarcinoma
- Stable *PTK7* expression is also observed in paired tumor samples
- » *PTK7* shows lower variation in pre- to post-treatment expression compared with other ADC targets, indicating low susceptibility to therapy-induced modulation
- In contrast, *CD274* (programmed death-ligand 1 [PD-L1]), *MET*, and *ITGB6* (integrin beta-6 [Iβ6]) are downregulated after treatment with single-agent immunotherapy and/or chemotherapy

» In *EGFR* wild-type lung adenocarcinoma, *PTK7* expression is largely unaffected by other actionable genomic alterations, further highlighting the stability of *PTK7* across clinically relevant subgroups

» HWK-007, a next-generation, 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)³

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Background

- » Protein tyrosine kinase 7 (PTK7) is a promising antibody-drug conjugate (ADC) target in non-small cell lung cancer (NSCLC). PTK7 is a catalytically inactive receptor tyrosine kinase associated with tumor progression, metastatic potential, and treatment resistance.^{1,2} While *PTK7* is minimally expressed in most normal adult tissues, it is overexpressed across multiple malignancies, including NSCLC.^{1,2}
- *PTK7* expression is detected in >80% of NSCLC tumors and remains consistently high irrespective of histologic subtype, disease stage, or epidermal growth factor receptor (*EGFR*) mutation status,^{1–3} supporting its potential as a broadly applicable ADC target
- » Patients with advanced *EGFR* wild-type NSCLC continue to have poor outcomes after standard-of-care therapies^{4,5}
- Median overall survival remains approximately 9–15 months in the second- or later-line setting,^{4,5} highlighting the need for effective new therapeutic approaches and targetable biomarkers

- » Paired biopsies from patients with NSCLC have shown dynamic post-treatment changes in target protein expression, including trophoblast cell-surface antigen 2 (TROP2), human epidermal growth factor receptor 2 (HER2), and MET, with higher rates of change in actionable genomic alteration (AGA)-negative versus AGA-positive tumors⁶
- It is therefore important to select the appropriate ADC or therapeutic target based on the current biomarker status of the tumor

Methods

- » Multimodal data from a real-world database (Tempus AI, Inc.) were used to examine *PTK7* mRNA expression in pre- versus post-treatment tumor samples (paired, when available, and unpaired) from patients with advanced unresectable (stage 3B or 3C)/metastatic *EGFR* wild-type lung adenocarcinoma treated with standard-of-care treatments in any line of therapy
- Pre- versus post-treatment expression of other ADC targets in development for the treatment of NSCLC was also assessed
- The programmed death-ligand 1 (PD-L1) status of tumor samples was defined according to tumor proportion score (negative, <1%; positive, 1–49%; high positive, ≥50%)
- » The prevalence of other AGAs across all tumors (pre- and post-treatment samples) and their effect on *PTK7* expression were evaluated
- The AGAs assessed were those with 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)^{7,8}
- » Median *PTK7* expression was quantified as log₂(transcripts per million [TPM]+1)
- Group differences were analyzed using the Wilcoxon test, and fold changes in pre- to post-treatment expression were calculated and converted to percentage changes

Results

EXPRESSION OF *PTK7* AND OTHER ADC TARGETS BEFORE AND AFTER STANDARD-OF-CARE TREATMENTS

- » The analysis included 7856 *EGFR* wild-type lung adenocarcinoma tumor samples
- » *PTK7* expression (log₂[TPM+1]) remained largely stable following standard-of-care therapies in advanced NSCLC, including immunotherapy (IO), chemotherapy, chemotherapy plus IO, and tyrosine kinase inhibitors (TKIs) (Table 1 and Figure 1)
- Across treatment classes, median post-treatment *PTK7* expression remained within 20% of pre-treatment levels (i.e., –18% to +2%), suggesting that *PTK7* expression remains generally stable throughout therapeutic exposure (Table 1)
- Consistent findings were observed in paired tumor samples from the same patients (data not shown). *PTK7* expression remained stable following chemotherapy (–8%; n=20) and chemotherapy plus IO (+6%; n=77); a modest decrease was observed in both the TKI (–22%; n=16) and IO monotherapy (–34%; n=18) patient groups, although sample sizes were limited for these two therapies
- When stratified by PD-L1 status, changes in median *PTK7* expression pre to post treatment with chemotherapy plus IO were –8%, –21%, and –8%, respectively, in PD-L1–negative (pre, n=608; post, n=196), PD-L1–positive (pre, n=623; post, n=242), and PD-L1–high positive (pre, n=309; post, n=105) samples (data not shown)
- In the subset of paired tumor samples, *PTK7* expression remained broadly stable after chemotherapy plus IO treatment, with percentage changes of +19%, –5%, and +28%, respectively, in PD-L1–negative (n=28), PD-L1–positive (n=25), and PD-L1–high positive (n=14) samples

- » In contrast, several other ADC targets demonstrated high treatment-associated variability (Table 1 and Figure 1)
- *CD274* (PD-L1) expression decreased following treatment with IO (–38%) or chemotherapy (–29%), while *MET* expression decreased after treatment with IO (–37%) but increased following TKI therapy (+20%); *ITGB6* (integrin beta-6 [Iβ6]) expression decreased after TKI therapy (–36%) (Table 1)
- Additional targets that exhibited high (>25% increase or decrease) treatment-dependent changes in expression were *SLC34A2* (sodium-dependent phosphate transport protein 2B [NaPi2b]), *MSLN*, and *VTCN1* (B7-H4) (Table 1)

EFFECT OF OTHER AGAs ON *PTK7* EXPRESSION

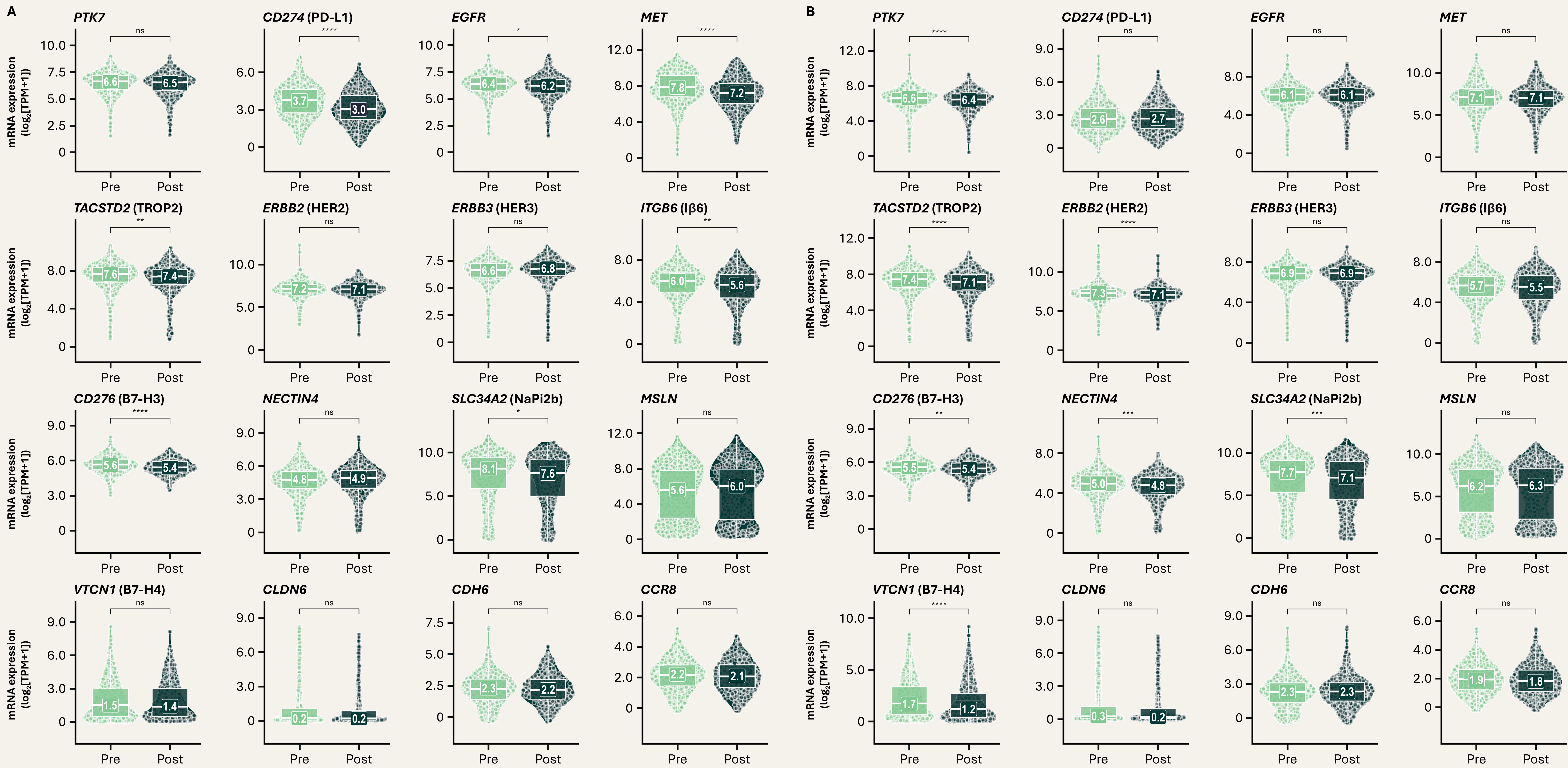
- » Across all 7856 *EGFR* wild-type lung adenocarcinoma tumor samples, the most common AGAs were *KRAS*^{G12C} (15.6%), *ALK* (5.6%), and *MET* (3.8%) (data not shown)
- » There was minimal change in median *PTK7* expression (log₂[TPM+1]) with mutated versus wild-type *KRAS*^{G12C}, *ALK*, or *MET* (*KRAS*^{G12C}: 6.6 vs 6.6 [n=1222 vs 6634]; *ALK*: 6.5 vs 6.6 [n=439 vs 7417]; *MET*: 6.6 vs 6.6 [n=296 vs 7560]) (data not shown)
- Similarly, other evaluated AGAs (i.e., *BRAF*^{V600E}; *HER2*; or any *NRG1*, *NTRK1/2/3*, *RET*, or *ROS1* fusions) demonstrated minimal impact on *PTK7* expression levels

TABLE 1. Changes in Median mRNA Expression of *PTK7* and Other ADC Targets From Pre to Post Treatment (Unpaired Analysis)

Change in median mRNA expression (pre to post treatment) ^a	Treatment							
	IO (pre: n=649; post: n=358)		Chemotherapy (pre: n=701; post: n=512)		Chemotherapy plus IO (pre: n=1951; post: n=821)		TKI ^b (pre: n=294; post: n=250)	
	Fold change	% change	Fold change	% change	Fold change	% change	Fold change	% change
<i>PTK7</i>	0.93	–7	1.02	+2	0.87	–13	0.82	–18
<i>CD274</i> (PD-L1)	0.62	–38	0.71	–29	1.03	+3	0.91	–9
<i>EGFR</i>	0.88	–12	1.02	+2	0.99	–1	1.01	+1
<i>MET</i>	0.63	–37	0.79	–21	0.95	–5	1.20	+20
<i>TACSTD2</i> (TROP2)	0.84	–16	0.95	–5	0.82	–18	1.02	+2
<i>ERBB2</i> (HER2)	0.95	–5	1.08	+8	0.88	–12	0.99	–1
<i>ERBB3</i> (HER3)	1.08	+8	1.06	+6	1.01	+1	1.01	+1
<i>ITGB6</i> (Iβ6)	0.79	–21	1.02	+2	0.91	–9	0.64	–36
<i>CD276</i> (B7-H3)	0.85	–15	1.02	+2	0.94	–6	0.91	–9
<i>NECTIN4</i>	1.13	+13	1.05	+5	0.89	–11	0.86	–14
<i>SLC34A2</i> (NaPi2b)	0.72	–28	1.05	+5	0.64	–36	0.74	–26
<i>MSLN</i>	1.36	+36	0.83	–17	1.07	+7	1.27	+27
<i>VTCN1</i> (B7-H4)	0.90	–10	0.83	–17	0.70	–30	1.16	+16
<i>CLDN6</i>	0.98	–2	0.96	–4	0.97	–3	1.00	0
<i>CDH6</i>	0.95	–5	1.11	+11	1.03	+3	1.00	0
<i>CCR8</i>	0.94	–6	0.76	–24	0.93	–7	0.93	–7

^aA one-unit change in mRNA expression (log₂[TPM+1]) corresponds to a two-fold change in transcript abundance (TPM+1); a fold change of >1.00 indicates increased expression (blue), and <1.00 indicates decreased expression (red). ^bIncludes inhibitors of ALK, ROS1, MET, EGFR, BRAF, RET, and VEGFR. ADC, antibody-drug conjugate; ALK, anaplastic lymphoma kinase; CCR8, C-C motif chemokine receptor 8; CDH6, cadherin 6; CLDN6, claudin 6; EGFR, epidermal growth factor receptor; HER2/3, human epidermal growth factor receptor 2/3; Iβ6, integrin beta-6; IO, immunotherapy; NaPi2b, sodium-dependent phosphate transport protein 2B; PD-L1, programmed death-ligand 1; PTK7, protein tyrosine kinase 7; TKI, tyrosine kinase inhibitor; TPM, transcripts per million; TROP2, trophoblast cell-surface antigen 2; VEGFR, vascular endothelial growth factor receptor.

FIGURE 1. Pre- Versus Post-Treatment mRNA Expression of *PTK7* and Other ADC Targets With (A) IO^a and (B) Chemotherapy Plus IO^b



ns=ns; *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001. ^aPre, n=649; post, n=358. ^bPre, n=701; post, n=512. ADC, antibody-drug conjugate; CCR8, C-C motif chemokine receptor 8; CDH6, cadherin 6; CLDN6, claudin 6; EGFR, epidermal growth factor receptor; HER2/3, human epidermal growth factor receptor 2/3; Iβ6, integrin beta-6; IO, immunotherapy; NaPi2b, sodium-dependent phosphate transport protein 2B; ns, not significant; PD-L1, programmed death-ligand 1; PTK7, protein tyrosine kinase 7; TPM, transcripts per million; TROP2, trophoblast cell-surface antigen 2.