Unlocking therapeutic potential: IL-1β as a target in non-small cell lung cancer with oncogenic mutations – prognostic and predictive insights

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Abstract 8030

Background:

- Heterogeneity in interleukin-1β (IL-1β) expression in non-small cell lung cancer (NSCLC) samples has been observed
- Despite the incidental finding of improved lung cancer incidence and mortality with the IL-1β inhibitor canakinumab, clinical trials such as CANOPY 1 and 2 failed to show improved outcomes with chemo/immunotherapy
- The clinical implications and interplay of oncogenic driver mutations and IL-1β in the setting of varying treatment modalities including immune-checkpoint inhibitors (ICIs) have not been previously explored
- The aim of this study is to evaluate the prognostic and predictive role of IL-1β in NSCLC with respect to driver mutations such as *KRAS, EGFR, ERBB2, BRAF, STK11*, and *ALK* fusion

Methods:

- Next-generation DNA and RNA sequencing of 34,960 NSCLC tumor samples were performed at Caris Life Sciences
- Tumor samples were stratified by quartiles based on IL-1β expression - Quartile 1 (Q1): lowest IL-1β expression [Cohort 1] and Quartile 4 (Q4): highest IL-1β expression [Cohort 2]
- The presence or absence of oncogenic driver mutations based on quartiles of IL-1β expression were analyzed
- Primary endpoints included overall survival (OS), defined as time of tissue collection to last contact, and time on treatment (TOT)
- Significance was calculated using chi-square, Fisher's exact, and Mann-Whitney U test

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IL-1β expression is closely linked to key oncogenic driver mutations and has prognostic value, especially for patients with *EGFR* mutant, *KRAS* mutant or *ALK* fusion NSCLC. Our findings suggest IL-1β expression may have interplay with PD-L1 and encourage studies involving IL-1β expression and ICIs. In addition, our results point to the potential benefit of targeting IL-1β in high IL-1β expressing NSCLC with oncogenic driver mutations. Overall, low IL-1β expression in NSCLC is associated with improved OS across NSCLC subtypes.

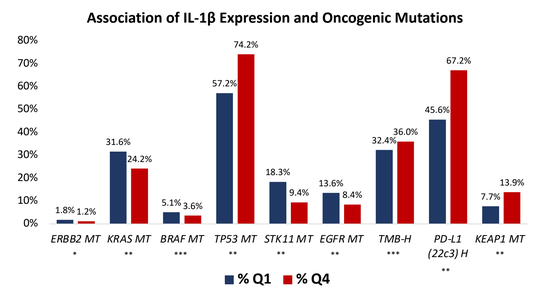

Figure 1 High IL-1β expression (Q4) was positively associated with *TP-53* and *KEAP1* mutations, high TMB, and high PD-L1 expression compared to low IL-1β expression (Q1). On the other hand, low IL-1β expression (Q1) was positively associated with *ERBB2, KRAS, BRAF, STK11,* and *EGFR* mutations compared to high IL-1β expression (Q4). **Legend** MT: mutant; H: high; *: $p < 0.05$; **: $p < 0.001$; ***: $p < 0.005$

Results:

- In the entire cohort, low IL-1β expression was associated with improved OS compared to high IL-1β expression
- IL-1β expression demonstrated significant associations with key oncogenic driver mutations (*TP-53, KEAP1, KRAS, EGFR, ERBB2, BRAF*, and *STK1*), tumor mutational burden (TMB) and PD-L1 expression (Figure 1)
- Superior OS was seen with low IL-1β expressors with *EGFR* mutant NSCLC, with augmented OS benefit in the adenocarcinoma subgroup (Figure 2A); similar improved OS was seen with low IL-1β expressors with *ALK* fusion NSCLC (Figure 2B)
- In patients with *ALK* fusion / *TP53* mutant NSCLC, superior OS was demonstrated by low IL-1β expressors compared to high IL-1β expressors (median OS: not reached vs 16.25 months, HR 0.418, 95% CI 0.178-0.982, p = 0.039)
- On the other hand, in *KRAS*-mutant adenocarcinoma, high IL-1β expressors showed improved TOT on pembrolizumab (Figure 2C)
- For NSCLC without driver mutations, IL-1β expression did not correlate with OS difference

Figure 2

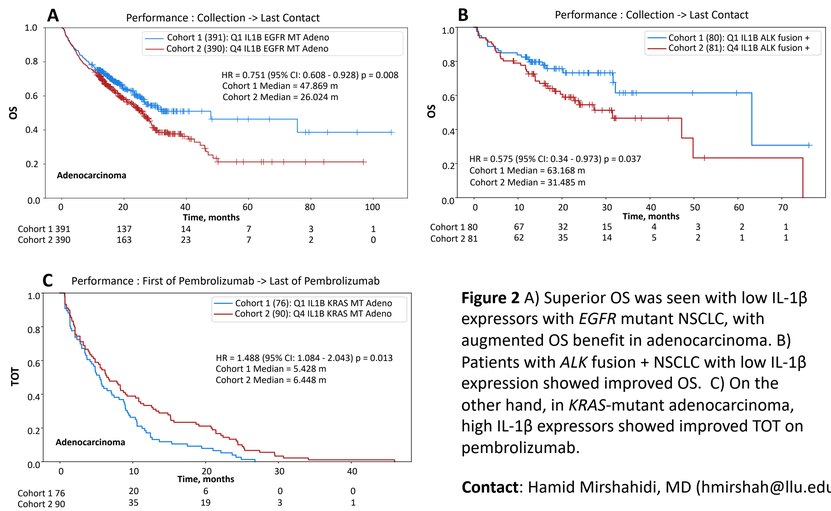

Figure 2 A) Superior OS was seen with low IL-1β expressors with *EGFR* mutant NSCLC, with augmented OS benefit in adenocarcinoma. B) Patients with *ALK* fusion + NSCLC with low IL-1β expression showed improved OS. C) On the other hand, in *KRAS*-mutant adenocarcinoma, high IL-1β expressors showed improved TOT on pembrolizumab.

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