Survival and Mutational Differences based on *ESR1* and *ESR2* expression in Non-Small Cell Lung Cancer (NSCLC)

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Background

- Estrogen receptor (ER) can activate MAPK signaling but the contribution of the two classical receptors, ER-alpha (*ESR1*) and ER-beta (*ESR2*), is unclear.
- Past trials targeting ER and EGFR in NSCLC lacked efficacy.
- We evaluated the association of *ESR1&2* expression with the genomic landscape and overall survival (OS) in NSCLC.

Methods

- NSCLC tumors (N = 21603) were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing of DNA (592-gene or whole exome) and RNA (whole transcriptome).
- Mutation prevalence (-Mt) was calculated for pathogenic SNVs/indels.
- Subgroups stratified by *ESR1&2* expression quartiles (transcripts per million, top (-H) and bottom (-L) quartiles were compared).
- A transcriptomic signature associated with MAPK activation (MPAS) was applied (Wagel 2018.)
- The χ^2 and Mann Whitney U tests were applied as appropriate, p-value was adjusted for multiple comparisons ($p < 0.05$).
- Real-world OS was obtained from insurance claims and Kaplan-Meier estimates were calculated.

Results

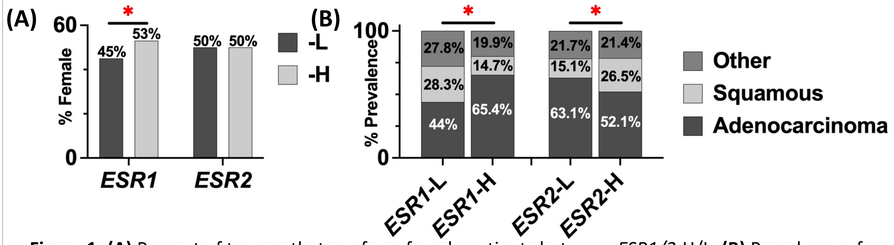

Figure 1: **(A)** Percent of tumors that are from female patients between *ESR1/2*-H/L. **(B)** Prevalence of different histology's between *ESR1/2*-H/L. Red asterisk indicate statistical significance ($p < 0.05$).

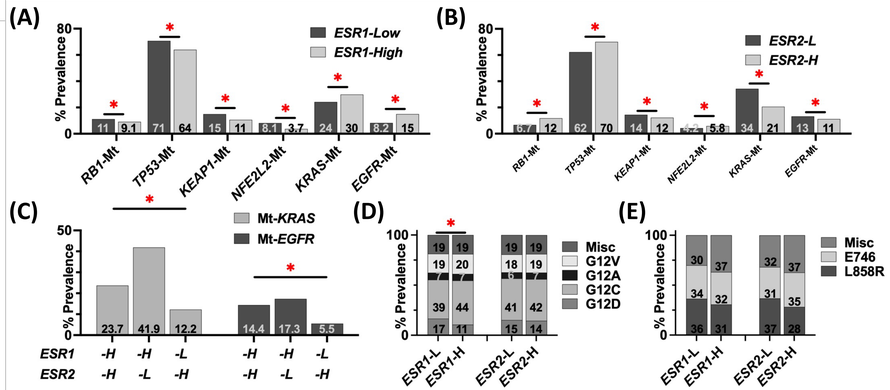

Figure 2: **(A, B)** Genomic landscape of NSCLC segmented by *ESR1/2*-H/L tumors. **(C)** Distribution of *EGFR* and *KRAS* mutations between *ESR1/2*-H/L. **(D,E)** Prevalence of different *EGFR* and *KRAS-Mt* across different *ESR1/2* tumors. Red asterisk indicates statistical significance ($p < 0.05$).

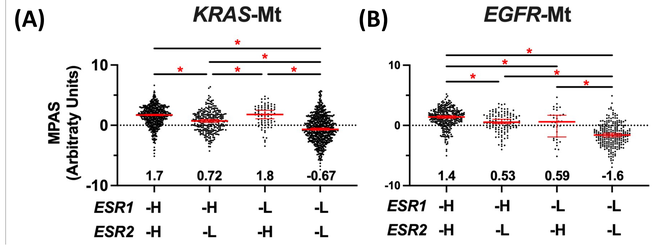

Figure 3 MPAS between *ESR1/2*-H/L tumors that have either **(A)** *KRAS* or **(B)** *EGFR* pathogenic mutations. Red asterisk indicate statistical significance ($p < 0.05$).

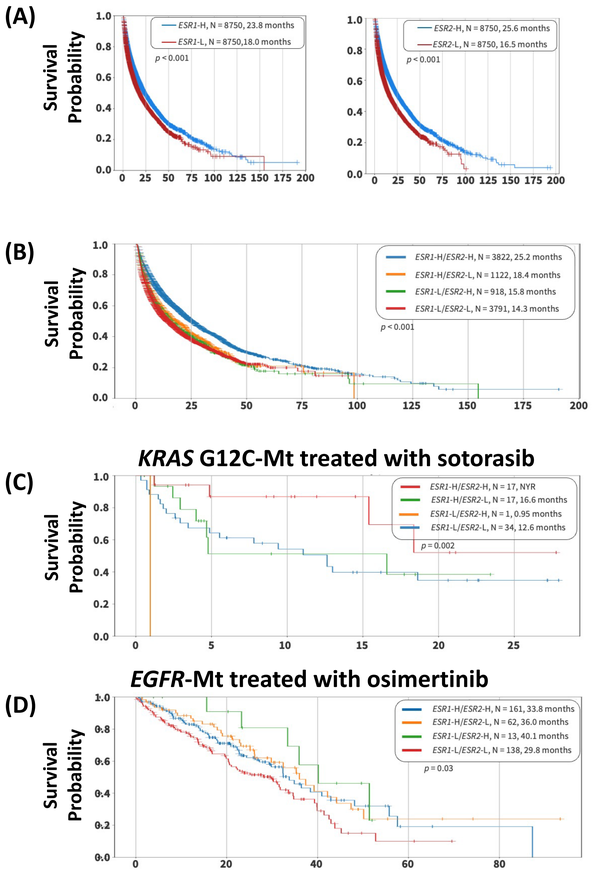

Figure 4: **(A)** OS (collection->last contact) between *ESR1/2*-H/L tumors. **(B)** OS between different *ESR1/2* tumors**. (C)** Survival since start of sotorasib between different *ESR1/2* tumors that are KRAS G12C-Mt. **(D)** Survival since start of osimertinib between different *ESR1/2* tumors that are *EGFR*-Mt.

Study Highlights

- *ESR1*-H had a greater proportion of females (53% vs. 45%) and adenocarcinoma histology (65% vs. 44%) vs. *ESR1*-L (p<0.05)
- *ESR2*-H had no sex differences (50% vs. 50%) and a greater proportion of squamous cell carcinoma cases (27% vs. 15%) vs. *ESR2*-L
- *ESR1*-H had greater prevalence of *EGFR* (15.0% vs. 8.2%) and *KRAS*-Mt (29.9% vs. 24.2%) vs -L (p<0.05)
- *ESR2*-H had lower prevalence of *EGFR* (11.2% vs. 13.2%) and *KRAS*-Mt (20.6% vs. 34.0%) vs -L (p<0.05)
- *ESR1*-H/*ESR2*-H tumors had the highest MPAS (1.4 AU) vs. ESR1-H/ESR2-L (.52), ESR1-L/ESR2-H (.59) or ESR1-L/ESR2-L (-1.6) (p<0.05)
- *ESR1*-H had a longer OS (23.8 months vs. 18.0 months) than *ESR1*-L (p<0.001) as well as *ESR2*-H (25.6 months) vs. *ESR2*-L (16.5 months) (p<0.001)
- *ESR1*-H/*ESR2*-H tumors had the longest OS (25 months) compared *ESR1*-H/*ESR2*-L (18 months), *ESR1*-L/*ESR2*-H (16 months) and *ESR1*-L/*ESR2*-L (14 months) (p < .001)
- In patients treated with osimertinib, *ESR1-L*/*ESR2*-H had the longest median OS (40.1 months) (p=0.03)

Conclusions

- There are sex differences seen in high vs. low *ESR1* expression not seen in high vs. low *ESR2*
- Higher *ESR1* expression is enriched in *EGFR* and *KRAS* mutations contrary to high *ESR2* expression
- Longer survival seen in both high *ESR1* and *ESR2* expressors
- *ESR1&2* may play key roles in activating the MAPK pathway and future trials could consider targeted therapy combined with ER inhibition based on *ESR1&2* expression

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