Young Adults (YA) with Non-Small Cell Lung Cancer (NSCLC): Snapshot of the Oncogeninc Drivers and Immune Landscapes

Markey Cancer Center
An NCI Comprehensive Cancer Center

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CARIS PRECISION ONCOLOGY ALLIANCE

Background

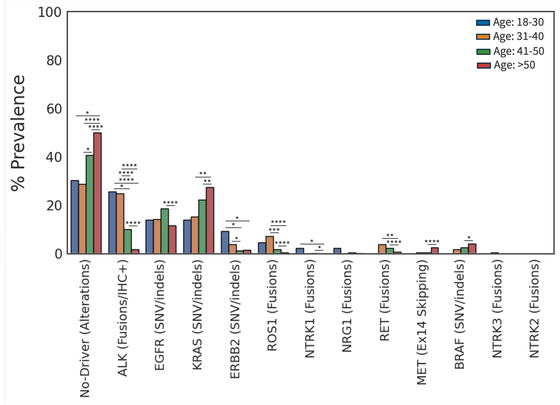
- Approximately 5% of NSCLC occurs in patients 50 years or younger (median age:71) representing distinct clinicopathological features.
- Reports characterizing genomic alterations are scarce and limited by cost/availability of NGS.
- Using a large real-world (RW) dataset, we characterize oncogenic drivers, and immune landscapes to better understand YA with NSCLC

Methods

- 42,326 NSCLC specimens were analyzed using next-generation sequencing of DNA (DNA-592 panel or whole exome) or RNA (whole transcriptome) at Caris Life Sciences (Phoenix, AZ).
- YA (≤50 years) were categorized into three groups (years): 18-30 (A1, n=61), 31-40 (A2, n=277) & 41-50 (A3, n=1,549); vs >50 (A4, n=40,437). Composition of tumor microenvironment (TME) was estimated from bulk RNA sequencing using QuanTIseq method.
- RW survival on Osimertinib (Osi-OS) was obtained from insurance claims and calculated from initiation of Osi treatment to last contact and was compared between ages 18-50 and >50 years. Osi-TOT was similarly calculated from the initiation to termination of Osi treatment. Hazard ratio (HR) was calculated using the Cox proportional hazards model.
- Statistical significance was determined using Chi-square, Fisher's Exact, Mann-Whitney U and log-rank tests and corrected for multiple comparisons where applicable (q<0.05)

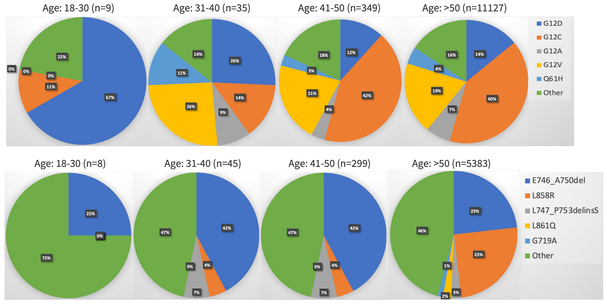
Results

Figure 1.Distribution of driver mutations by age



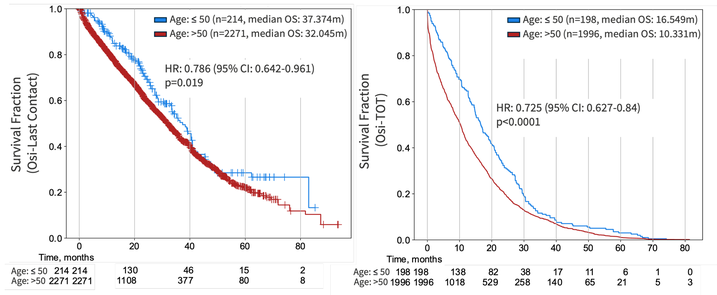
Among driver alterations, *ALK* (IHC+), *ROS1*, *RET* and *NTRK1* fusion were enriched and *KRAS* mutations were reduced in YA. Notably, there was an increase in prevalence of tumors with no known driver alterations among A vs YA.

Figure 2.Distribution of *KRAS* and *EGFR* mutations by age



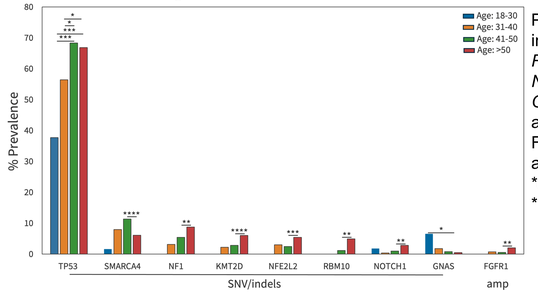
The distribution of *KRAS* and *EGFR* mutations differed with age. While the prevalence of $KRAS^{G12D}$ from transition (non-smoker related) and $EGFR^{E746\_A750}$ decreased with age, $KRAS^{G12C}$ from transversion increased with age in YA

Figure 3. Osi-OS and Osi-TOT associated with age



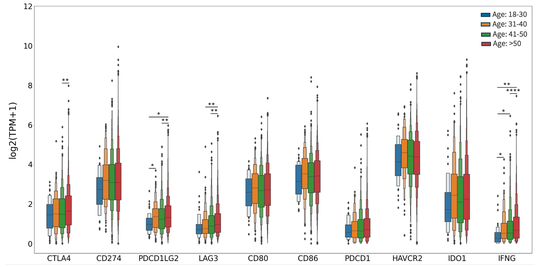
YA had an improved survival on Osimertinib (37.374m vs 32.045m in A, p=0.019) and an improved time on Osimertinib treatment (16.549m vs 10.331m in A, p<0.0001).

Figure 4. Molecular Alterations associated with age



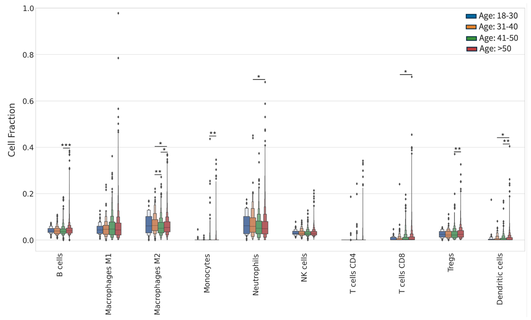
Prevalence of mutations in *TP53*, *KMT2D*, *NF1*, *RBM10*, *NFE2L2* and *NOTCH1* increased while *GNAS* decreased with age. An increase in FGFR1 amplification was also seen with age. *q<0.05, ** q<0.01, ***q<0.001, **** q<0.0001

Figure 5. Association of immune checkpoint gene expression with age



PDCD1LG2 (A1/A4: 0.63, A3/A4: 0.89), *LAG3* (A2/A4: 0.73, A3/A4: 0.89) and *IFNG* (A1/A4: 0.32, A3/A4: 0.75) were reduced. *q<0.05, ** q<0.01, ***q<0.001, **** q<0.0001

Figure 6. Association TME infiltrates with age



Median fold change of M2 macrophages (A2/A4: 1.2) and neutrophils (A2/A4: 1.2) were increased in YA (all q<0.05). *q<0.05, ** q<0.01, ***q<0.001, **** q<0.0001

Conclusions

- We report an increased prevalence of *RET* and *NTRK1* fusions in YA and key differences in distributions of frequent *KRAS* and *EGFR* mutations in YA (vs A4)
- We further observe decreased expression of immune related genes and cells comprising the tumor microenvironment in YA.
- The implications are under active investigation.

Contact Information

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