Age-associated differences in transcriptional expression and tumor immune microenvironment composition among older patients with cancer

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Background

- Older patients (pts) with cancer are underrepresented in registrational clinical trials for immune checkpoint inhibitor (ICI) therapies.
- Are there any relevant differences in the makeup of the tumor microenvironment (TME) and in genomic signatures of cancer in older pts?

Methods

- Next-generation sequencing (CLIA-certified laboratory; Caris Life Sciences, Phoenix, AZ)
  - DNA (592 gene panel, NextSeq or whole-exome sequencing, NovaSeq) - CLIA-certified laboratory
  - RNA (whole transcriptome sequencing, NovaSeq)
- PD-L1 expression assessment by immunohistochemistry (IHC), and high tumor mutational burden (TMB-H) was defined as ≥10 mut/Mb.
- Pt samples: non-small cell lung carcinoma (NSCLC; n = 19,891), melanoma (MEL n = 2,899), and renal cell carcinoma (RCC; n = 1,333)
  - Age subgroup stratification: ≥80 and < 80 years (yr)
  - Comparison of DNA damage response (DDR) gene alterations, gene expression profiling, and TME analysis (MCP-counter; Becht, 2016).

Table 1 – Baseline characteristics

Pts ≥80 yr accounted for 16.0%, 19.9% and 5.3% of NSCLC, MEL and RCC pts, respectively.

Tumor Type >	NSCLC		MEL		RCC	
Age groups (years)>	≥ 80	< 80	≥ 80	< 80	≥ 80	< 80
Total Count (N;%)	2739 (16.0)	17152 (84.0)	482 (19.9)	2417 (80.9)	67 (5.3)	1266 (94.7)
Median Age	83.0	67.0	84.0	65.0	81.0	63.0
Male (%)	50.6 (1387/2739)	50.3 (8630/17152)	67.6 (326/482)	60.9 (1471/2417)	77.6 (52/67)	70.9 (898/1266)
Female (%)	49.4 (1352/2739)	49.7 (8522/17152)	32.4 (156/482)	39.1 (946/2417)	22.4 (15/67)	29.1 (368/1266)

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Results

Figure 1. Mutation landscape

Compared to pts < 80 yr, NSCLC and MEL pts ≥80 yr had similar DDR gene mutation rates, while BRCA1 mutations were more common in MEL pts ≥80 yr (2.1 vs. 0.8%; exploratory-p < 0.05).

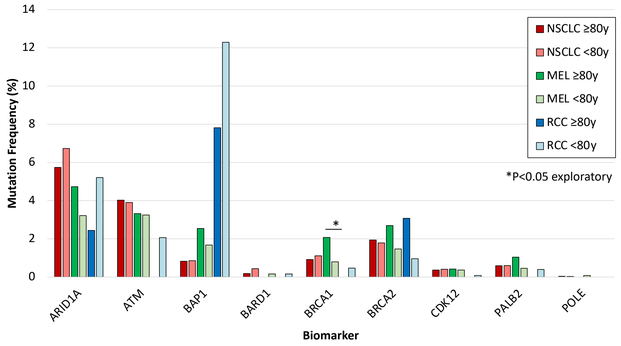


Figure 2 – IO-related biomarkers

TMB-H was less common in NSCLC (29.7 vs. 36.5%, p < 0.001) and more common in MEL pts ≥80 yr (65.7 vs. 49.0%, p < 0.01), and PD-L1 (IHC-SP142, ≥2+|5%) expression was less frequent in RCC pts ≥80 yr (9.1 vs. 19.4%, exploratory p < 0.05).

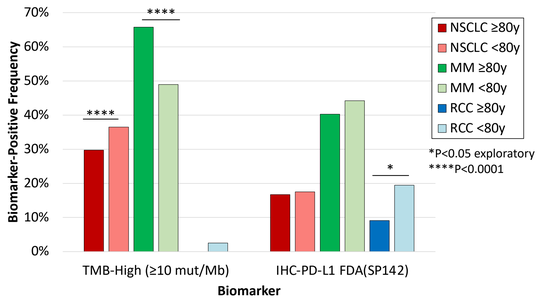


Figure 3 – TME

NSCLC ≥80 yr TMEs had increased abundance of fibroblasts (1.09-fold, p < 0.01), dendritic cells (1.07-fold, p < 0.01) and macrophages (1.04-fold, p < 0.01), and MEL≥80 yr TMEs had fewer infiltrating T-lymphocytes (0.87-fold, p = 0.02).

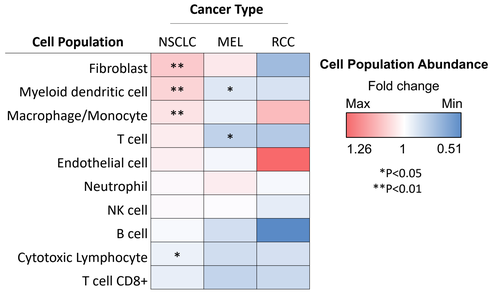


Figure 4 – Immune checkpoint genes

Increased expression of immune checkpoint (IC) genes PDCDL1G2 (PD-L2; 1.11-fold), HAVCR2 (TIM-3; 1.11-fold), and CD80/86 (1.07/1.08-fold, p < 0.05) was seen in NSCLC pts ≥80 yr, while IL-6 expression was decreased (0.88-fold; p < 0.05).

The largest change in IC gene expression was for IL-6 (1.24-fold, p = 0.78) in MEL, and GZMB (0.56-fold; p = 0.17) in RCC

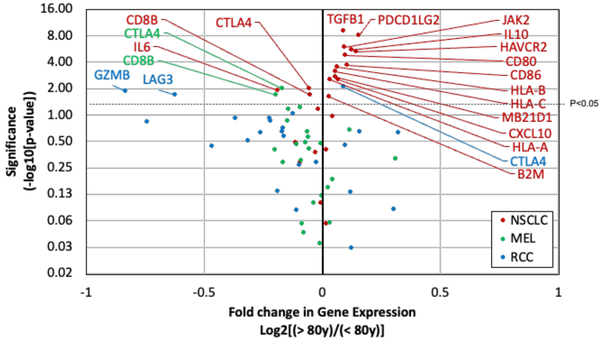
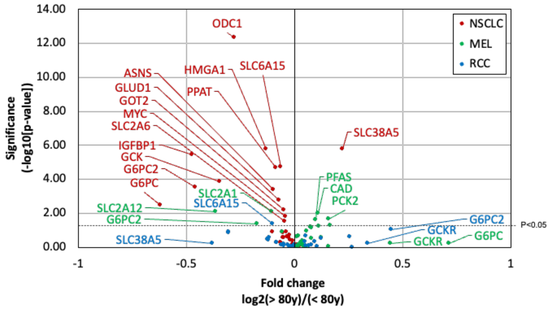


Figure 5 – glutamine and glucose metabolism

Profiling of glutamine and glucose metabolism-related genes revealed increased SLC38A5 (1.17-fold; p < 0.0001) and decreased G6PC (0.65-fold, p < 0.01) expression in NSCLC ≥80 yr.

While not statistically significant, MEL and RCC pts ≥80 yr had opposite trends for SLC38A5 and G6PC expression



Conclusions

- Our analysis provides new insights to immune landscape of NSCLC, MEL, and RCC pts ≥80 yr.
- Differential gene expression and TME composition changes in this population suggest unique, cancer-specific therapeutic opportunities, and a potential to explore biomarkers of response to ICIs

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