Molecular features of young cannabis smokers with advanced non-small cell lung cancer (aNSCLC)

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BACKGROUND

- Regular cannabis consumption has been reported at a high frequency in young patients diagnosed with NSCLC (Betser *et al*, ERJ 2021). Their genomic and clinical features may define a unique disease biology.
- **Aim:** to report molecular characteristics of a cohort of young cannabis smokers with aNSCLC.

METHODS

- **Restrospective analysis, including:**
- aNSCLC patients aged ≤ 50 years-old;
- Available molecular profile (next-generation sequencing) of tumor tissue or blood;
- Inclusion period between 2018-2021;
- Cannabis consumption, defined as >10 joints/month for ≥ 1 year.

- Clinical, molecular and radiological data were collected. The presence of actionable genomic alterations (defined as ESCAT* I and II tiers), TMB, PD-L1 expression and *STK*11/*KEAP1* mutations were interrogated.

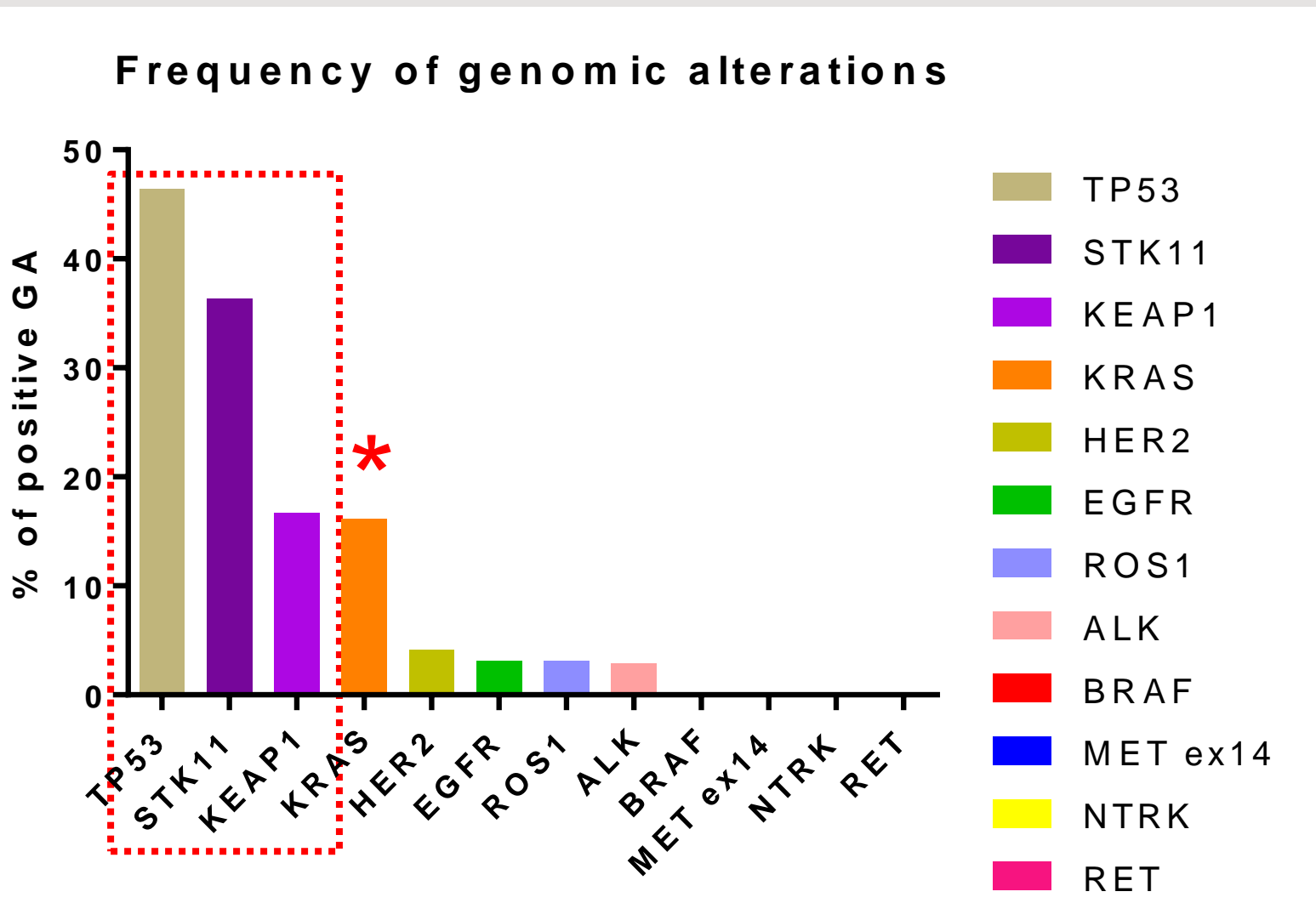- Objective response (OR) and progression-free survival (PFS) were determined.

* ESCAT - ESMO Scale for Clinical Actionability of molecular Targets

RESULTS

Out of 46 young cannabis smokers with aNSCLC, 34 patients had an available molecular profile.

The majority were male patients with heavy tobacco consumption and initial advanced disease presentation.

Baseline characteristics (N=34)

Male	82%
Age, median [range]	43 [39-48]
Tobacco smoker Pack years: median [range]	97% 25 [13.5-30]
Cannabis Joint-year Current smoker	104 [50-165] 47%
Histology Adenocarcinoma Other	68% 32%
Apical bullous emphysema	44%
At diagnosis - Stage IV Stage III	76% 24%
Number of metastatic sites Median [range]	2 [1-4]
Treatment Single agent ICB ICB+chemo Chemo Targeted therapy/trial Prior chemoradiation	23.5% 41% 26.5% 9% 15%

Frequency of genomic alterations

Legend: TP53, STK11, KEAP1, KRAS, HER2, EGFR, ROS1, ALK, BRAF, MET ex14, NTRK, RET

* 3 *KRAS* G12C

These patients harbor a high frequency of *TP53, STK11* and *KEAP1* mutations.

The frequency of targetable drivers is low, with *KRAS* G12C being the most frequent (3/7).

Half of patients have less than 1% PD-L1 expression.

Molecular characteristics

ESCAT I-II targetable genomic alterations*, N (%)	7/34 (20.5%)
* Pack Years: median [range]	20 [7-25]
PD-L1 expression, median [25-75% range]	1 [0-70]
TMB (mut/Mb), median (range)	10 [5-18.9]
STK11/KEAP1 mutations, N (%)	11/23 (48%)

Clinical outcomes

	ICB+/- chemo	Chemo	p
OR	8/21 (38%)	3/9 (30%)	1
PFS Median	5.75 [2.6-8.8]	3.55 [0.8-6.2]	0.35
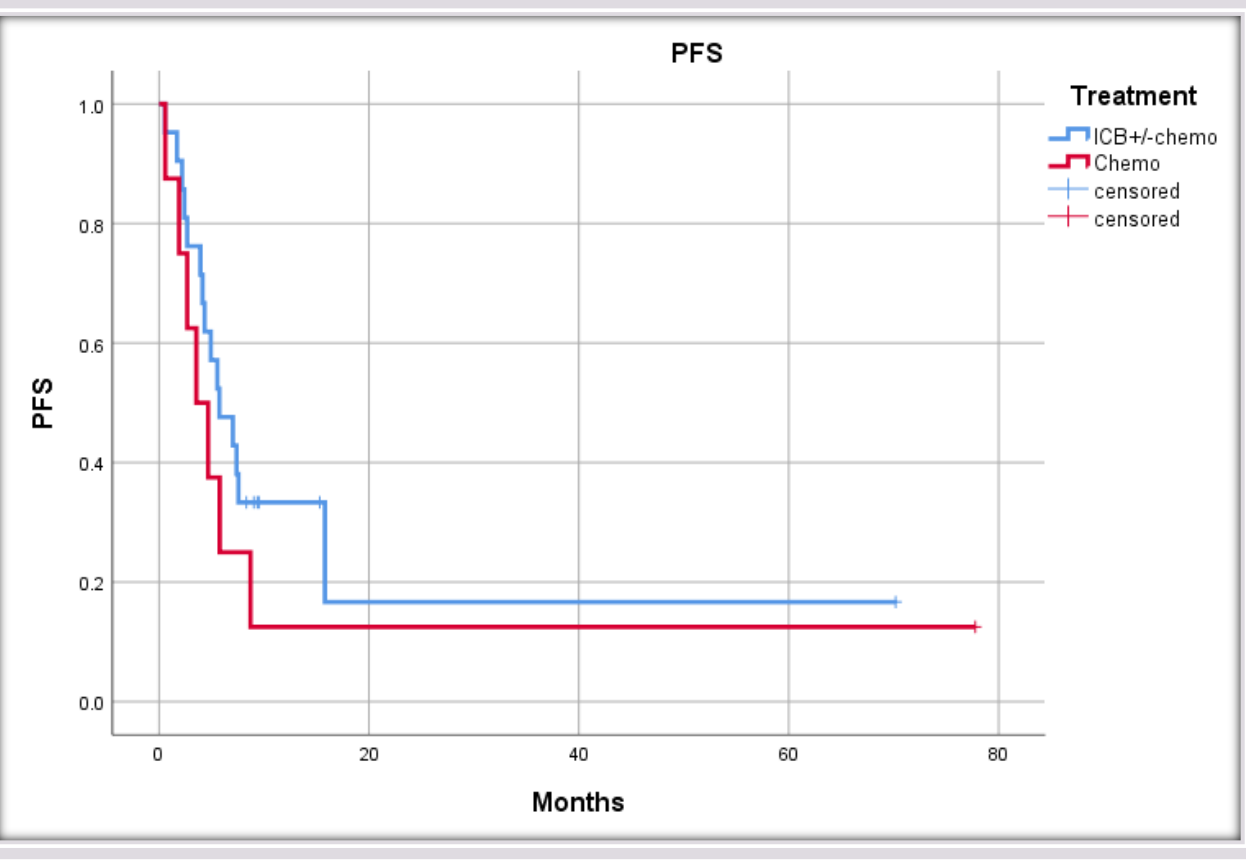
CONCLUSIONS

- Nearly 80% of young cannabis smokers with aNSCLC do not harbor an actionable driver.
- *STK11* mutations have a high prevalence in this population and PD-L1 expression is generally low.
- Despite high TMB and heavy tobacco smoking, ICB outcomes appear lower than expected in the frontline setting.

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