ICBs become the backbone of non-oncogene addicted NSCLC, both alone and in combination with chemotherapy (CT-ICB). To date, PD-L1 is the only predictive factor for ICBs benefit. Tumor burden is a new emerging additional biomarker to select those pts who may derive a benefit from a chemotherapy (CT) combination approach compared to single agent ICBs. The biological correlates of tumor burden is largely unknown.

This is a multicentric retrospective study involving 12 centers. 18F FDG PET scans were performed within 42 days from 1st line treatment initiation (CT, ICBs or CT-ICB). Total Metabolic tumor volume (MTV) was calculated with a threshold of 42% of SUV max. Progression Free Survival (PFS) and Overall Survival (OS) were analyzed with Kaplan Meyer method and log rank test. On a subset of patients included in prospective MATCH-R study, with available PET scan performed within 30 days from biopsy, transcriptomic data on fresh frozen tissue were correlated with PET parameters of the biopsied lesion. Data were analyzed with R version 4.1.1 and Cibersort.

493 patients were enrolled at 12 centers across 4 countries, 163 treated with ICBs alone, 236 with CT-ICB and 94 with CT.

Median iMTV in the whole cohort was 100.1 cm3. There was no difference in terms of MTV distribution among treatment groups (p = 0.4264).

PD-L1 was always ≥ 50% for patients treated with ICBs alone. 22.5% of patients in CT-ICB group had PD-L1 ≥ 50% while most of the control group had no PD-L1 available.

Median PFS for patients with iMTV > median was 3.26 months vs 14.70 for those with iMTV < median (p = 0.0005).

Patients with iMTV > median had a median OS of 11.4 months vs 33.1 months for those with iMTV < median, p = 0.00067.

A trend towards better PFS was seen in Chemo-Io (p = 0.059) but no difference in OS (p = 0.12).

No difference in PFS (p = 0.16) and a difference in OS (7.04 vs 10.75 months, p = 0.022) was seen for chemotherapy cohort.

Among patients with iMTV > median, PFS was better for CT-ICBs vs ICBs (11.94 vs 3.26, p = 0.043) and OS was numerically better too, albeit it did not reach significance at 0.05 level (20 vs 11.4, p = 0.11).

Locally, higher MTV was negatively correlated to Regulation of immune response (NES -2.33, p adj 0.0047), immune effector process (NES -2.31, p adj 0.047) and borderline with inflammatory response (-2.12, p adj 0.09) GOBP pathways. Moreover, it was negatively correlated with the sum of immune cells absolute scores as quantification of the immune infiltrate measured by cibersort (r = 0.36, p = 0.016). On the other side, higher iMTV was correlated with higher LDH, neutrophils, WBC (p = 0.0001), CRP (p = 0.0008), with lower CD8+ T cells count (p = 0.0252) and borderline with higher dNLR (p = 0.0560).

Patients with high iMTV derived limited benefit from ICBs alone, with high rate of early progression and death.

High iMTV is correlated with higher systemic degree of inflammation and with a reduction of immune infiltrate and immune response in the tumor.

Patients with high iMTV have better outcome if treated with combination of CT-ICBs.