**Background**

ICBs revolutionized the treatment of advanced NSCLC patients but only a fraction of them obtain a response and clinical benefit from these treatments is often difficult to predict. Viral infections, either acute, chronic or latent, have an impact on the immune system but their effect on ICBs efficacy is unknown. The aim of our study is to unveil the potential implications of antibody response versus previous viral infections in predicting the response to ICBs in NSCLC patients.

**Methods**

Sera from patients enrolled in the prospective PREMIS (NCT 03984318) and MSN (NCT02105168) were analyzed with VirScan (CDI Labs, US), a high-throughput method that comprehensively analyzes epitope-level antiviral IgG antibodies via programmable phage display and immunoprecipitation sequencing (Phip-Seq). The library contains ~100,000 clones displayed as 56-residue peptides, with 28-residue overlap, that together span the reference protein sequences of all viruses with known human tropism in the UniProt database collapsed to 95% sequence similarity.

**Results**

3 L2-penalized logistic regression models were trained with a 10x10-fold cross-validation to predict 6-month PFS to ICBs from (I) known predictive clinical variables, (II) VirScan peptides, and (III) a combination of both. Statistical significances were computed with the corrected resampled t-test to accommodate for training set dependencies in cross-validation.

- **129 patients treated with ICBs alone (45 1st line, 70 2nd line, 14 3rd or later), 66 with ICB in combination with chemotherapy and 61 with chemotherapy alone were included.**

A signature based on the positive peptides only showed an AUC of 0.657 in predicting PFS > 6 months vs 0.708 for a model including only clinical variables (sex, age, ECOG PS, site of metastasis, histology, derived neutrophil/lymphocytes ratio, LDH) and 0.752 combining clinical data and Virscan results (all p < 0.05).

The viral signature did not show predictive value in chemo-immunotherapy (AUC 0.437) and chemotherapy (AUC 0.529).

**Conclusion**

- Previous viral infections as assessed by VirScan may have a role in predicting the response to ICBs in NSCLC patients.

- Further analysis are ongoing to validate these findings.