

Background Pembrolizumab and Pembrolizumab-chemotherapy are two first line options for advanced, non-oncogene addicted NSCLC. Currently, PD-L1 is the only biomarker guiding physicians' choice, but it is often unsatisfying.

Methods This retrospective, multicentric study aims to assess the potential benefit from first line pembrolizumab +/- chemotherapy in pre-specified clinical (age, gender, PS ECOG, smoking history, histology, concomitant treatments, LDH-NLR stratified in three categories) radiological (number/type of metastatic sites, tumor burden), molecular (*KRAS*) subgroups of advanced NSCLC. Primary endpoint is OS. Prognostic factors were evaluated in a multivariable Cox regression model stratified per center. Interaction between treatment*features was assessed in a Cox regression model. OS and PFS were expressed through Kaplan-Meier curves, compared through log-rank test.

Results A total of 443 patients were included, 436 suitable for survival analysis (216 and 220 treated with pembrolizumab and combination, respectively).

Older age ($p=0.03$), PS ECOG ≥ 2 ($p<0.001$), *KRAS*-mutant ($p=0.02$), LDH-NLR poor ($p=0.03$), tumor burden >102 mm ($p=0.02$), treatment with corticosteroids ($p=0.02$) and proton pump inhibitors ($p=0.01$) were independent, negative prognostic factors in the overall population.

OS was significantly improved by pembrolizumab in male ($p=0.01$), <68 years old ($p=0.007$), PS ECOG 0-1 ($p=0.04$), adenocarcinoma histology ($p=0.01$), *KRAS* wild type ($p=0.03$), with an interaction treatment*feature confirmed for age ($p=0.04$), PS ECOG ($p<0.001$), histology ($p=0.007$ for squamous and $p=0.01$ for other non-adenocarcinoma histology).

Conclusions Patients younger than 68, with PS ECOG 0-1 and adenocarcinoma histology might benefit from first line pembrolizumab, avoiding the exposure to chemotherapy. NLR-LDH stratification provides a new prognostic score, irrespectively of the addition of chemotherapy to pembrolizumab.