RATIONALE-304: baseline tumour genomic alterations according to programmed death-ligand 1 (PD-L1) subgroups in nonsquamous non-small cell lung cancer (nsq- NSCLC) treated with first-line tislelizumab (TIS) plus chemotherapy (CT) vs CT alone

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Background (398 characters): In the open-label, randomised, phase 3 RATIONALE-304 trial (NCT03663205), patients (pts) with locally advanced/metastatic nsq-NSCLC receiving TIS + CT experienced improved survival vs those receiving CT alone, with the magnitude of benefit being more pronounced in pts with tumour cell PD-L1 membrane expression ≥50% vs those with PD-L1 <50%, aligning with the general trend of programmed cell death protein-1 inhibitor efficacy increasing with PD-L1 expression.

Methods (471 characters): Adult pts with stage IIIB/IV nsq-NSCLC were randomised (2:1) to TIS + platinum-based CT + pemetrexed every 3 weeks or platinum-based CT + pemetrexed. The primary endpoint was progression-free survival (PFS) by independent review committee. Overall survival (OS) was a key secondary endpoint. Crossover from CT to TIS + CT was allowed upon independent review committee-confirmed disease progression. Genomic profiling and tumour mutational burden (TMB) analyses were performed on PD-L1–evaluable tumour tissue using next-generation DNA sequencing.

Results (576 characters): Overall, 159/334 pts were biomarker-evaluable (PD-L1 <1%, n=57; PD-L1 1%-49%, n=45; PD-L1 ≥50%, n=57). Tumours with PD-L1 ≥50% were enriched for *KRAS*, *PBRM1*, and *EMSY* alterations. Conversely, *FOXA1* alterations were enriched in tumours with PD-L1 <50% (*P*<.05). *ARID1A, STK11, EPCAM, GRIN2A,* and *IRF4* were enriched in PD-L1 <1% tumours (*P*<.05). Higher prevalence of *PIK3* and *NRF2* pathway alterations was observed in PD-L1 <1% tumours (*P*=.006 and .078, respectively). No difference in TMB was observed in tumours with PD-L1 tumour cell expression <1% vs 1%-49% vs ≥50% (*P*=.357). *NRF2* pathway alterations were associated with reduced PFS and OS benefit in the TIS + CT arm vs the CT arm.

Conclusion (193 characters): In nsq-NSCLC, distinct genomic profiles were observed between PD-L1 subgroups, while TMB was similar across all PD-L1 expression levels. Further validation of independent NSCLC datasets with larger sample sizes is required