Background: Tremelimumab plus durvalumab and chemotherapy (T+D+CT), for first-line treatment of metastatic NSCLC, has been evaluated vs CT in a randomized phase III trial, POSEIDON (NCT03164616). In the absence of head-to-head studies, indirect treatment comparisons (ITCs) can be used to compare the efficacy of T+D+CT vs other currently approved agents including pembrolizumab plus CT (P+CT) and nivolumab plus ipilimumab plus CT (N+I+CT). However, given the potential differences in baseline characteristics between patient populations across studies, a standard ITC may be subject to bias and is therefore not necessarily the most appropriate method to derive comparative efficacy estimates. An anchored matching-adjusted indirect comparison (MAIC) is an alternative ITC method which attempts to adjust for cross-trial heterogeneity in patient populations using CT as the common comparator or anchor.

Methods: Patient-level data from POSEIDON was weighted to match the baseline covariate distribution from the CheckMate 9LA trial, for both intention-to-treat (mixed histology) and non-squamous histology (NSQ) cohorts, and matched to the KEYNOTE-189 trial for the NSQ cohort. Overall survival (OS) was compared. Patient baseline characteristics and endpoints in POSEIDON were statistically tested to identify potential treatment effect modifiers (TEMs) which were subsequently clinically validated. Reweighting for POSEIDON was conducted in a pairwise manner against each comparator trial in turn using a propensity score weighting approach for the covariates that were identified as TEMs and were imbalanced across the trials. Hazard ratios (HRs) for OS were then re-estimated for POSEIDON using weighted Cox regression models and indirectly compared with those of CheckMate 9LA and KEYNOTE-189 using an ITC approach.

Results: Covariates identified as TEMs through a series of interaction tests with treatment were race, histology and smoking status. For the mixed histology cohort, the estimated OS HR (95% CI) of T+D+CT vs N+I+CT after weighting was 0.89 (0.68, 1.16). For the NSQ cohort, the estimated OS HRs (95% CI) of T+D+CT vs P+CT and vs N+I+CT were 0.96 (0.69, 1.35) and 0.76 (0.55, 1.07), respectively.

Conclusions: The MAIC approach provides a method to generate comparative effectiveness estimates by accounting for heterogeneity in the baseline distribution of TEMs across trials. After adjusting for these differences between the considered trials, the OS HR point estimates were numerically in favour of treatment with T+D+CT vs N+I+CT in the mixed histology and NSQ populations and indicated similar OS with T+D+CT and P+CT in the NSQ population. This comparison supports T+D+CT as a potential new first-line treatment option for metastatic NSCLC.

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Trial Registration: Clinicaltrials.gov: NCT03164616; NCT03215706; NCT02578680

Ethics Approval: All studies were performed in accordance with applicable local regulations with approval from independent ethics committees or institutional review boards. These were large international, multicenter trials and there are too many ethics approvals to feasibly list these details for each site. All patients provided written informed consent for participation.