TPS8669 **Poster Session**

A biomarker-directed, multi-center phase II/III study of ctDNA molecular response adaptive immuno-chemotherapy in patients with non-small cell lung cancer (BR.36).

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Background: Minimally invasive analyses of circulating cell-free tumor DNA (ctDNA) have shown clinical value as an early endpoint of immunotherapy response, allowing patients with primary resistance to be rapidly and accurately identified. In the first of two independent stages, the BR.36 trial demonstrated a sensitivity of ctDNA response for radiographic RECIST response of 82% and a specificity of 75%, with a median time to ctDNA response of 2.1 months. **Methods:** BR.36 is a multi-center, open-label, biomarker-directed, phase II/III clinical trial of ctDNA molecular response adaptive immuno-chemotherapy in patients with treatment-naïve metastatic NSCLC. The main objective is to evaluate if adding chemotherapy to pembrolizumab for patients who have persistent ctDNA on liquid biopsy after 6 weeks of pembrolizumab, will result in better PFS and OS compared to patients who remain on pembrolizumab until radiographic clinical progression. Key eligibility criteria include: age ≥18 years, ECOG performance status 0-2, metastatic NSCLC, EGFR and ALK mutation negative and PD-L1 Tumor Proportion Score (TPS) ≥ 50%, at least and not more than 2 cycles of the 200 mg or 2 mg/kg IV Q3W dose/schedule of pembrolizumab as first line systemic immunotherapy at the time of screening and RECIST non-PD or clinically stable PD documented prior to enrolment that can continue on immunotherapy if randomized to that arm. The phase II primary endpoint is PFS and has secondary endpoints of feasibility, overall response rate and safety/tolerability. Sex, RECIST response and ECOG status represent stratification criteria. With 110 randomized patients evaluable for progression (55 patients per arm and 71 PFS events observed in this phase of the clinical trial), we would be able to detect a hazard ratio difference of 0.67 with a 1-sided alpha of 0.2 and power of 0.80 using a phase II screening design. The trial will not stop accrual for the phase II analysis of PFS if feasibility endpoints are achieved. In the phase III portion, a total of 210 randomized patients recruited over 3 years and followed for an additional 24 months are required to detect an OS hazard ratio difference of 0.67 with 1-sided alpha of 0.05 and power of 0.8. The total number of events for the final analysis is expected to be 156, and assuming 10% of patients are lost to follow-up, we are targeting 230 patients to be included overall. The primary endpoint of the phase III portion is overall survival, with secondary endpoints of best overall response, response duration, progression-free survival and safety/tolerability. Exploratory endpoints include longitudinal ctDNA analyses by targeted next-generation sequencing and whole genome sequencing approaches. The BR.36 clinical trial is open to enrollment and to date 2 patients have been registered (ClinicalTrials.gov ID: NCT04093167). Clinical trial information: NCT04093167. Research Sponsor: Cancer Research Institute; The Mark Foundation for Cancer Research; LabCorp.