Background We report the results from the advanced malignant mesothelioma (aMM) expansion cohort of the PEMBIB Phase Ib trial (NCT02856425) evaluating the safety, efficacy & biomarkers of an antiangiogenic tyrosine kinase inhibitor (nintedanib) with an anti-PD1 immunotherapy (pembrolizumab).

Methods Patients with aMM relapsing after at least one line of platinum doublet chemotherapy and not previously pre-exposed to IO were treated with a combination of oral nintedanib (150mg BID) & IV pembrolizumab (200mg Q3W) with a 7 days nintedanib lead-in preceding pembrolizumab initiation. Baseline and on-treatment (cycle D2, day 1 [C2D1]) fresh tumor & blood samples were prospectively phenotyped by flow cytometry (FC). RNAseq was run on tumor samples. Immune factors were titrated on tumor secretome and plasma.

Results 30 aMM patients were treated and 29 evaluable for response. Median age was 68 years old (38–85) and 86% of aMM were epithelioid. The most frequent adverse events (AE) (grades 1–3) related to the combination were liver enzymes increase, fatigue, nausea, and diarrhea. 4 (13.3%) patients developed grade 3–5 immune-related AE. Patients died of cancer progression (n=14, 46.7%), myocarditis with thromboembolic event (n=1, 3.3%) and COVID-19 (n=1, 3.3%). Median follow-up was 14.8 months (95%CI [9.70–18.2]). Best Overall Response Rates (BORR) per RECISTv1.1 were Partial Response (PR, n=7/29; 24.1%), Stable Disease (SD, n=17/29; 58.6%) and Progressive Disease (n=5/29; 17.2%). Disease Control Rate (DCR) (defined as PR + SD) was 46.6% at 6 months. Patients with DCR at 6 months had significantly higher percentage of PDL1 expression on tumor cells (by Immuno-Histo-Chemistry, antibody clone SP263) and higher CD8+ T cells infiltrate in tumor biopsies (by FC) at screening. Upon treatment, soluble plasma rate of CXCL9 and CXCL13 increased in all patients, as well as tumor immune infiltrates estimated by deconvolution of tumor biopsies RNA-seq. But deconvoluted estimates of NK cells, T cells and myeloid dendritic cells infiltrates on baseline tumors and C2D1 biopsies were higher in patients with DCR at 6 months. Pre & on-treatment IL6 and IL8 rates in tumor secretome & plasma were higher in patients without DCR. Gene Set Enrichment Analyses on RNA-seq from screening biopsies highlighted an enrichment in E2F, MYC and KRAS gene pathways and lower expression of type 1 interferon signature in patients without DCR than those with DCR at 6 months.

Conclusions With a BORR of 24% and a DCR of 47% at 6 months, pembrolizumab and nintedanib combination provided valuable therapeutic benefits for patients with aMM.


References

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