# Clinical safety of combined therapy of immune checkpoint inhibitors and Viscum album L. therapy in patients with advanced or metastatic cancer.

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**BACKGROUND:**

Despite improvement of tumour response rates in patients with progressive and metastatic cancer, immune checkpoint inhibitors (ICM) induce toxicities in cancer patients. Viscum album L. (VA, mistletoe) extracts are applied as add-on cancer therapy especially in German speaking countries and within integrative and anthroposophical concepts with the goal to improve quality of life. The primary objective of this pilot observational cohort study was to determine the rate of adverse events (AE) related to ICM therapy with and without VA in patients with advanced or metastatic cancer in a certified Cancer Center.

**METHODS:**

ICM or combined ICM/VA therapies were applied in patients with progressive or metastatic cancer. AE rates of both therapy groups were compared.

**RESULTS:**

A total of sixteen cancer patients were treated with ICM: nivolumab (75%), ipilimumab (19%) or pembrolizumab (6%). The median age of the study population was 64 years (IQR 57.8; 69.3); 44% were male. Of the sixteen patients receiving ICM, nine patients received additional VA (56%; ICM/VA group) and seven did not (44%; ICM group). No statistically significant differences were seen between groups with respect to AE-rates (67% ICM/VA versus 71% ICM). Adjusted multivariate regression analysis revealed that concomitant application of VA did not alter the AE rate in ICM treated patients. 85% of AEs were expected ICM reactions. No AEs of grade 3 or greater were documented for the total study cohort.

**CONCLUSIONS:**

This is the first study evaluating the clinical safety profile of ICM in combination with VA in patients with advanced or metastatic cancer. The overall AE rate of the study cohort is comparable to AE rates of ICM treatment in the literature. Our data indicate a first impression that concomitant VA application may not alter ICM-induced AE rates. However, the nature of this study does not allow excluding possible immunological interactions between ICM and VA. Further prospective trials in larger study cohorts should focus on the assessment of safety aspects, clinical efficacy and health related quality of life in patients with combined ICM/VA therapy.

**TRIAL REGISTRATION:**

DRKS00013335 , retrospectively registered (November 27th, 2017) at the German Clinical Trials Register ( www.drks.de ).

**KEYWORDS:**

CTLA-4; Drug interaction; Immune checkpoint inhibitors; Mistletoe; PD-1; Targeted therapy; Viscum album L.

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