501 SURVIVAL AND IMMUNE RESPONSE DATA FROM INTRATUMORAL INT230–6 ALONE (IT-01) AND WITH PEMBROLIZUMAB [KEYNOTE-A10] IN SUBJECTS WITH LOCALLY ADVANCED, UNRESECTABLE AND METASTATIC SOLID TUMORS

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Background Background: Study IT-01 (KEYNOTE-A10) evaluates INT230-6, a novel formulation of cisplatin (CIS) and vinblastine (VIN) with an amphiphilic cell penetration enhancer designed for intratumoral (IT) administration, as monotherapy and in combination with pembrolizumab (PEM). In preclinical studies, INT230-6 increases drug dispersion throughout the tumor, allows drug diffusion into cancer cells and recruits dendritic, CD4 and CD8 T cells. The addition of PEM improves these responses in mouse models.

Methods IT-01 is an open-label phase 1/2 study, currently enrolling adult subjects with solid tumors in phase 2. The study assesses the safety and efficacy of INT230-6 IT Q2W up to 5 doses as monotherapy or with PEM 200mg Q3W. Biopsies from injected tumor are taken pretreatment and Day 28 for immunohistochemistry (IHC) analysis.

Results Fifty-seven INT230-6, two INT230-6 then PEM combination, and thirteen INT230-6 + PEM combination subjects were enrolled having a median of 4 prior therapies (0, 10). Median age was 62. 20+ cancer types were accrued; breast cancer and sarcoma were the most frequent. Over 500 image guided INT230-6 IT injections were given (253 to deep tumors) at doses of 0.3 to 172mL (86 mg CIS, 17.2 mg VIN) in a single session (contains higher amounts than typical IV chemo doses). PK shows that 95% of INT230-6 active agents remain in the tumor.[1] The most common (>25%) related adverse events (AEs) for INT230-6 alone were localized pain (59%), nausea (37%), and fatigue (29%). Safety profile of the PEM combination was similar. There were no related grade 4 or 5 AEs in either arm. The median overall survival (mOS) estimated with removal of <2cm3 and >700cm3 tumor burdens was 433 days for monotherapy (n=51) and 513 days for PEM combination (n=12), which compares favorably to results seen in basket studies of patients having similar prognostic factors (ECOG, LDH, # of metastatic sites).[2] IHC results indicate influx of CD4 and CD8 T-cells in injected lesions. No meaningful changes were observed in circulating inflammatory cytokines. Abscopal effects in the monotherapy arm were observed in 15 visceral/deep lesions in 11 patients, primarily who received an INT230-6 dose >50% of their total tumor burden (TTB).

Conclusions INT230-6 is well tolerated when administered IT as monotherapy and combined with PEM. Data suggests that INT230-6 prolongs survival compared to published basket studies in patients with similar prognostic factors. IHC and abscopal results indicate dosing INT230-6 may also activate a T-cell mediated immune response.

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REFERENCES

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2. Abstract. Wagner M, et al. Validation of the Royal Marsden Hospital (RMH) prognostic score in 100 patients with advanced sarcoma enrolled in early phase clinical trials at a major cancer center. *JCO* 2015. https://ascopubs.org/doi/abs/10.1200/jco.2015.33.15_suppl.10558

Ethics Approval The protocol was approved by an institutional review board, independent ethics committee, or research ethics board at each institution. All subjects or their legally acceptable representative provided written informed consent before screening. The study was designed, undertaken, and reported in accordance with the Declaration of Helsinki, and is registered with clinicaltrial.gov with registration no NCT03058289.

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