710 SAFETY AND SURVIVAL RESULTS FROM A PHASE 1/2 TRIAL OF INTRATUMORAL AGENT INT230–6 (CISPLATIN VINBLASTINE) INDUCES IMMUNOLOGICAL CANCER CELL DEATH ALONE OR WITH PEMBROLIZUMAB IN PATIENTS WITH REFRACTORY, METASTATIC CANCERS

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Background Study IT-01, KN-A10: INT230-6 is a new product with a unique dual anti-cancer mechanism. The drug is comprised of cisplatin and vinblastine co-formulated with a molecule that enables drug dispersion throughout an injected tumor and diffusion into cancer cells. The drug directly kills cancer and activates an immune response. Results from a neo-adjuvant breast cancer study confirms that a single injection induces necrosis in up to 95% of a tumor and recruits TILs.[1]

Methods INT230-6 intratumoral (IT) treatments are Q2W up to 5 followed by maintenance dosing Q9W. Dose is set by the tumor's longest diameter or volume. Pembrolizumab is 200mg IV Q3W in the INT230-6 comboniation arm. Biopsies from the injected tumor at pretreatment and day 28 are sent for immunohistochemistry analysis. Endpoints are safety and exploratory efficacy by overall survival.

Results Sixty-four subjects received INT230-6 alone (median 4 prior treatments). Thirty received INT230-6 + pembrolizumab (median 3 prior). There were 652 image-guided INT230-6 IT injections (378 to visceral tumors eg lung, liver, pancreas) median 5 injections, range (1,50). Doses ranged from 0.14 up to 175mL (87.5 mg of cisplatin, 17.5mg vinblastine – much higher than typical IV doses). The INT230-6 arm enrolled 19 cancer types; the PEM combination recruited primarily colon, pancreatic, TNBC or bile duct cancers. IHC results show marked reduction in DAPI of proliferating cancer cells with influx of CD4 and CD8 T-cells. Non-injected visceral tumors shrank in several INT230-6 monotherapy subjects. Due to drug absorption or immune influx RECIST is not ideal for use with INT230-6 (ASCO2022). Overall survival is preferred. The estimated median OS (mOS) was 361 days for INT230-6; the mOS for the combination has not been reached (173 days of median follow-up). Pharmacokinetics shows >95% of the active agents remain in the injected tumor at 1 hour[2] compared to IV. The most common (>20%) treatment-related adverse events (TRAEs) for INT230-6 alone/combination were localized pain (59%/50%), nausea (39%/13%), fatigue (28%/20%) and vomiting (23%/20%). The incidence of grade 3 TRAEs for the INT230-6 and combination arms were 10% and 20%. One combination patient had a grade 4 neutrophil decrease that quickly resolved. No patient discontinued therapy due to treatment toxicities.

Conclusions Intratumoral injections of large drug volumes into visceral tumors was feasible and well-tolerated. Biopsies confirmed immunological cell death. OS was compelling for this heavily pretreated population lacking standard therapeutic options. INT230-6 may offer a well-tolerated treatment for refractory patients and is entering randomized controlled trials.

Trial Registration [Intensity-IT-01, Merck-KN-A10] NCI#03058289

REFERENCES

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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 clinicaltrials.gov with registration no. NCT03058289.

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