MELANOMA AND OTHER SKIN TUMOURS

1245PD Intratumoral (IT) Injection of the TLR9 agonist tilsotolimod (IMO-2125) in combination with ipilimumab (ipi) triggers durable responses in PD-1 inhibitor refractory metastatic melanoma (RMm):
Results from a multicenter, phase II study

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Background: Subsequent treatment with ipi offers 10-13% ORR (Bowyer 2016, Long 2016) in aPD1 refractory MM. Tilsotolimod, a synthetic TLR9 agonist oligonucleotide, acts on macrophages and dendritic cells to alter the tumor microenvironment. Local drug-induced type I interferon response results in increased antigen presentation and downstream T cell activation and proliferation in injected and non-injected lesions (Haymaker, SITC 2017).

Methods: The study will enroll up to 60 pts with RMm to receive IT (with/without IG) tilsotolimod (scheduled weeks 1, 2, 3, 5, 8, 11, 17, 23 and 29); ipi is given per product label starting at week 2. Pts with M1c disease, mucosal melanoma and BRAF mutations were included. The primary endpoint is RECIST1.1 objective response rate (ORR); other endpoints are safety and tolerability and disease control rate (DCR). Immune analyses of T-cell repertoire diversity evaluated by high-throughput CDR3 sequencing. Phase 2 accrual is ongoing.

Results: As of 9 Apr 2018, 26 pts have been treated with tilsotolimod 8mg + ipi, including 5 pts who received IG injections to deep visceral lesions or lymph nodes. Median age 65.8 (range 39-91 yrs); 11 IVM1c. 6 pts had irAEs (hypophysitis (2), hepatitis (2), adrenal insufficiency (1), Guillain-Barré syndrome (1), colitis (1), enterocolitis (1)), which responded to standard measures. Injection-related toxicities were grade 1-2 transient fever and flu-like symptoms lasting <48 hours. Major expanding T-cell clones are found to be shared in responding local and distant lesions indicating that reactivation is to a shared antigen in responding patients. As of 9 May 2018, 21 pts were assessed for response: 38% ORR and 71% DCR (2 CR, 6 PR, 7 SD). 6 of 8 responses are ongoing including 1 CR >23 mo. 10 pts had BRAF mutations (1 CR, 3 PR, and 4 SD).

Conclusions: IT tilsotolimod 8mg + ipi is well tolerated and shows substantial clinical benefit and durable responses. The ORR of 38% compares favorably to ipi in this challenging population, leading to an ongoing global randomized Phase 3 study of tilsotolimod 8mg + ipi vs. ipi in aPD1-1 MM.

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