7th edition) showed no statistically significant difference in OS between nivolumab and ipilimumab; however, OS events were fewer than expected. In the phase 3 EORTC 18071 trial in patients with resected stage IIIA–IIIC melanoma (AJCC, 6th edition), OS was improved with ipilimumab versus placebo. Here, we provide an update on RFS and an analysis of OS in ITCs of nivolumab and placebo using data from these 2 trials with a common comparator arm: ipilimumab 10 mg/kg.

Methods ITCs of nivolumab versus placebo were conducted using 4-year minimum follow-up data from CheckMate 238 (NCT02388906) and 5.3-year median follow-up data from EORTC 18071 (NCT00636168). Bucher ITCs were performed to estimate RFS and OS in the intention-to-treat populations. A sensitivity analysis of OS adjusting for subsequent therapy options was conducted in 2 steps: (1) after controlling for possible confounders and assuming that the only difference was the effect of different subsequent therapies, postrecurrence survival was compared between the 2 ipilimumab arms in each study, and (2) after adjusting for differences in postrecurrence survival, ITCs of nivolumab versus adjusted placebo were performed.

Results In these ITC analyses, RFS and OS results with nivolumab suggested an improvement compared with placebo. In the intention-to-treat population, nivolumab was associated with a lower risk of recurrence or death (RFS HR, 0.55; 95% CI, 0.43–0.70) and a lower risk of death (OS HR, 0.62; 95% CI, 0.44–0.88) than placebo. In the sensitivity analysis, a 63% average increase in postrecurrence survival benefit was estimated with ipilimumab in CheckMate 238 compared with ipilimumab in EORTC 18071. After adjusting for this increase in both the ipilimumab and placebo arms in EORTC 18071, nivolumab was associated with a lower risk of death than placebo (OS HR, 0.65; 95% CI, 0.45–0.91), similar to the unadjusted analysis.

Conclusions Despite the changing treatment landscape and the increased number of therapeutic options for metastatic melanoma, these ITCs suggested clinically meaningful improvement in RFS and OS with adjuvant nivolumab compared with a wait-and-watch strategy in high-risk patients with resected melanoma.

Acknowledgements Writing and editorial assistance were provided by Kakoli Parai, PhD, and Andrea Lockett of Ashfield Healthcare Communications, funded by Bristol-Myers Squibb Company.

Trial Registration NCT02388906 (CheckMate 238), NCT00636168 (EORTC 18071)

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0308

309 THE ROLE OF TUMOR-DRAINING LYMPH NODES IN THE TUNING OF SYSTEMIC T CELL IMMUNITY BY CTLA-4 BLOCKADE IS REVEALED BY LOCAL DELIVERY OF TREMELIMUMAB IN EARLY-STAGE MELANOMA: DATA FROM A PHASE-I TRIAL

[1]Jessica Notohardjo*, [1]Kim van Pul, [1]Anita Stam, [1]Dafni Chondronasiou, [1]Sinead Lougheed, [1]Petrousjka van den Tol, [2]Karin Jooss, [3]Ronald Vuylsteke, [1]Alfons van den Eertwegh, [1]Tanja de Gruijl. *[1]Amsterdam University Medical centers, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands; [2]Pfizer Inc, San Diego, CA, USA; [3]Spaarne Gasthuis, Haarlem, Netherlands*

Background The sentinel lymph node (SLN) is the first node to receive lymphatic drainage from the primary tumor and the site where naïve T cells are first primed. As such it is of great importance in initiating an effective anti-tumor immune response and an attractive target for immunomodulatory agents. Pre-clinical studies have reported that i.t. administration of anti-CTLA-4 is as effective in inducing tumor eradication as systemic delivery, without the risk of treatment related side effects. However, it remains unclear whether this is due primarily to modulation of the tumor microenvironment or of tumor-draining lymph nodes (TDLN). Here, we have evaluated the safety, tolerability and immunomodulatory effects in the SLN and peripheral blood mononuclear cells (PBMC) of anti-CTLA-4/tremelimumab, delivered locally at the tumor excision site in patients with early-stage melanoma. This unique setting (post tumor excision but prior to SLN biopsy) allowed us to clinically assess the role of TDLN in the biological efficacy of CTLA-4 blockade.

Methods In this phase I dose-escalation trial, patients with clinical stage I-II melanoma received one intradermal injection of tremelimumab at four dose levels (2, 5, 10 [n=3 each] or 20 mg [n=4]) around the primary excision site of the tumor, seven days prior to re-excision and SLN biopsy. Flow cytometry was performed to study viable cells from melanoma SLN and PBMC (prior to tremelimumab administration [day 0], and at 7 days, 3 weeks and 3 months after tremelimumab injection). Systemic melanoma antigen (MART-1/NY-ESO-1)-specific T cells responses were assessed by IFN-γ ELISPOT assay.

Results Intradermal delivery of tremelimumab was safe and well tolerated. In terms of biological efficacy it selectively induced profound and durable decreases in Treg frequencies in both SLN and PBMC, decreased systemic MDSC rates, activated migratory dendritic cell subsets in the SLN, and induced T cell activation (by HLA-DR and ICOS up-regulation), both in SLN and PBMC. Moreover, systemic anti-melanoma T cell responses were induced (n=5) or boosted (n=2), in association with T cell activation and central-memory T cell differentiation. Of note, tumor recurrences so far were only observed in two patients who did not develop a systemic anti-tumor T cell response.

Conclusions These findings indicate that i.d. administration of anti-CTLA-4 may offer a safe and promising adjuvant treatment strategy for patients with early-stage melanoma. Moreover, they demonstrate a central role for TDLN in the biological efficacy of CTLA-4 blockade and warrant the development of TDLN-targeted delivery methods for anti-CTLA-4.

Acknowledgements This study received funding from the Harry J. Lloyd Charitable Trust; tremelimumab was provided by Pfizer Inc.

Trial Registration NCT04274816

Ethics Approval The study was approved by the Medical Ethics Committee of the VU University Medical Center and Spaarne Gasthuis.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0309