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posters

19TiP **A phase Ib study combining the second-generation DNA hypomethylating agent (DHA) guadecitabine (SGI-110) and ipilimumab in patients with metastatic melanoma: The NIBIT-M4 Study**

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Background: Epigenetic alterations play a pivotal role in cancer development, progression and immune escape. In vitro and in vivo experimental evidences pointed to a strong immunomodulatory activity of DHA; therefore, we hypothesized that "epigenetic drugs" could represent suitable agents to test in the clinic novel therapeutic combinations with emerging immunotherapies (Maio et al., Clin Can Res, in press). Targeting immune check-point(s) with immunomodulatory monoclonal antibodies (mAb) is a novel and rapidly evolving strategy to treat cancer, rapidly spreading to different tumor histologies. The prototype approach of this therapeutic modality relies on the inhibition of negative signals delivered by CTLA-4 expressed on activated T lymphocytes. CTLA-4 blockade has changed the therapeutic landscape of metastatic melanoma (MM), significantly improving the survival of MM patients. However, objective clinical responses are limited, and a minority of patients achieves long-term disease control, thus opening the path to combination regimens to improve its efficacy. Based on the immunomodulatory activity of the second-generation DHA guadecitabine (Covre et al., Semin Oncol, 2015), we designed the phase 1b NIBIT-M4 study sequencing guadecitabine and ipilimumab in MM patients to provide proof-of-concept to the immunologic and clinical efficacy of DHA combined with CTLA-4 blockade.

Trial design: This is a Phase 1b, dose-escalation study in treatment naïve or pretreated unresectable Stage III or MM patients, amenable to serial tumor biopsies. Primary objective will evaluate MTD and safety of guadecitabine combined with ipilimumab. Secondary objectives will include immune-related (ir) -DCR, -ORR, -PFS, median OS, and survival rate at 1 and 2-years. Immune-biologic correlates will be exploratory objectives. The dose escalation of guadecitabine will follow a 3 + 3 design. Cohorts of 3-6 patients will receive ipilimumab i.v. 3 mg/kg on W1, 4, 7 and 10 day 1 q21 and guadecitabine s.c on W0, 3, 6, 9, days 1-5 q21 at the one of following doses: Dose Level (DL) -1: 15 mg/m^2 day; DL 0: 30 mg/m^2 day; DL +1: 45 mg/m^2 day. Sample size will range from 6 to 19 patients.

Disclosure: M. Maio: Consultant, Advisor or both of Bristol Myers Squibb, Roche, Medimmune-Astra Zeneca, Merck Sharp and Dohme. P. Taverna, J. Lowder, M. Azab: Employees of Astex. All other authors have declared no conflicts of interest.