Conclusions Both bTMB and rTMB are potentially useful biomarkers for enriching responses to D+T in previously untreated, advanced UC. Neither bTMB nor rTMB was associated with better outcomes for D monotherapy. Cuttoffs of 24 mut/Mb for bTMB and 10 mut/Mb for rTMB appear optimal associated with better outcomes for D monotherapy. Cutoffs of 24 mut/Mb for bTMB and 10 mut/Mb for rTMB appear optimal for D+T in the setting of previously untreated, advanced UC.

Methods The trial is registered with ClinicalTrials.gov, NCT02516241, and the EU Clinical Trials Register, EudraCT number 2015-001633-24.

REFERENCES

Ethics Approval The study protocol was approved by the Ethics Board at each investigator’s institution.

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PSEUDOPROGRESSION PATTERNS: ANALYSIS FROM 2 INDEPENDENT PHASE-2 STUDIES WITH IMMUNOTHERAPY FOR RECURRENT CERVICAL CANCER

Background The phenomenon of pseudoprogression (PsP) may appear with cancer immunotherapy. The underlying etiology is not fully elucidated, tumor flare is the suspected mechanism of early pseudoprogression that may resolve gradually while continuing treatment. Further, immunotherapy-induced sarcoidosis may mimic PsP. Here we present examples of 3 observed patterns of PsP in cervical cancer (CC) patients treated with balstilimab (BAL; anti-PD-1), alone or in combination with zalifrelimab (ZAL; anti-CTLA-4).

Methods The evaluated patients received either BAL 3 mg/kg every 2 weeks alone (NCT03104699) or in combination with ZAL dosed at 1 mg/kg every 6 weeks (NCT03495882). PsP was defined as radiologic disease progression per RECIST1.1 following by a significant reduction of measurable baseline lesions, disappearance of the non-measurable lesions, or no further progression for at least two tumor assessments after initial progressive disease (PD) by Independent Evaluation Review Committee (IERC). PsP was divided into 3 categories – early (before or at week 12 of treatment), delayed (after week 12) and serial (at least 2 PsP occurrences).

Results Overall, 313 patients with post-chemotherapy recurrent CC with baseline measurable disease were treated with either BAL (n=160) or in combination with ZAL (n=143). Early PsP was observed in 7 patients treated with BAL and 8 with BAL/ZAL while 5 patients experienced delayed PsP (BAL (n=1); ZAL(n=4)). Serial PsP was observed in 1 patient (BAL only) and another (n=1) BAL treated experienced showed PsP (new Medistinal lesions) present in 2 consecutive CT scan evaluations before disappearance – hence were classified as PD even by iRECIST. Immune-related sarcoidosis was confirmed histologically in 2 patients following confirmation by mediastinal lymph node biopsy. PsPs were accompanied with clear clinical benefit of disease improvement and weight stabilization, improvement in performance status, and decreased pain. PsP was observed in 7 patients treated with BAL and 8 with BAL/ZAL. PsP-confounded IERC evaluation of tumor response was seen in some CC patients treated with BAL or combination of BAL and ZAL. The differentiation of PD and PsP has important consequences for disease assessment in clinical trials and disease management and outcomes. Further efforts to elucidate the underlying mechanisms and clearly define the characteristics of PsP are crucial for better treatment management of affected patients. Standard response evaluation systems including iRECIST may need further refinement to recognize the importance of PsP.

Trial Registration NCT03104699 and NCT03495882

Ethics Approval C-700-01: The WIRB Study # is 1173375 and the site IRB approval # is 20170314. and for C-550-01: ICON Cancer Center in South Brisbane, Queensland, Australia.- IRB approval # is 2017-10-766.

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A PHASE 1 STUDY OF RETIFANLIMAB (INCMGA00012), A PD-1 INHIBITOR, IN PATIENTS WITH ADVANCED SOLID TUMORS: PRELIMINARY RESULTS IN RECURRENT MSI-HIGH OR DMMR ENDOMETRIAL CANCER (POD1UM-101)

Background The phenomenon of pseudoprogression (PsP) may appear with cancer immunotherapy. The underlying etiology is not fully elucidated, tumor flare is the suspected mechanism of early pseudoprogression that may resolve gradually while continuing treatment. Further, immunotherapy-induced sarcoidosis may mimic PsP. Here we present examples of 3 observed patterns of PsP in cervical cancer (CC) patients treated with balstilimab (BAL; anti-PD-1), alone or in combination with zalifrelimab (ZAL; anti-CTLA-4).

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Background Management of patients with recurrent endometrial cancer after failure of platinum therapy remains an important clinical challenge. Tumors characterized by abnormalities in DNA repair are associated with high numbers of neoantigens, making immunotherapy a promising approach. Retifanlimab (INCMGA00012) is an investigational humanized immunoglobulin G4 monoclonal antibody against PD-1. In the dose escalation and tumor expansion portions of the POD1UM-101 phase 1 study, retifanlimab monotherapy demonstrated acceptable tolerability and durable clinical activity in multiple advanced tumor types, including pretreated endometrial cancer. Here we present interim clinical activity and safety data from a preplanned futility assessment in patients with microsatellite instability-high (MSI-H) recurrent endometrial cancer.

Methods Patients eligible for this cohort had histologically proven, unresectable recurrent endometrial cancer that was MSI-H or deficient mismatch repair (dMMR) based on local testing (either by PCR or IHC), ECOG performance status (PS) ≤ 1, disease progression during or following ≤ 5 prior systemic treatments, measurable disease per RECIST v1.1, and no prior treatment with immune checkpoint inhibitors. The primary endpoint is safety (using CTCAE v4.03 grading). Confirmed benefit overall response rate and duration of response were evaluated by RECIST v1.1 (investigator’s assessment). Retifanlimab 500 mg Q4W was administered up to 2 years.

Results As of April 7, 2020, 44 patients who received at least 1 dose of retifanlimab were assessed for safety, including 24 patients who were fully assessable for the planned futility analysis. Median age was 63 (49–86) years, 45.5% had prior systemic therapy (n=1 each: polychemotherapy, 72.7% were treated with radiotherapy, and 90.9% underwent surgery. Median drug exposure was 1.9 (0.03–11.11) months. Eight patients (18.2%) experienced Grade (G) 3/4 AEs regardless of causality with anemia being the leading event (n=3, 6.8%). Two patients (4.5%) had immune-related AEs (n=1 each: dry mouth [G3] and myositis [G3]); both patients discontinued study treatment because of the event. No treatment-related deaths occurred. Confirmed responses (7 PR, 1 CR) versus 143 were obtained from patients enrolled in CP1108 trial (n=19, NCT01693562) were profiled by gene expression. Primary tumor biopsies (N=198) from HNSCC have been assessed by Whole Exome Sequence (WES). Expression of immune markers including CD8, Nkp46 was evaluated by immunohistochemistry (IHC) on 186 and 214 tumors biopsies, respectively. The expression of 80 immune related soluble factors was evaluated in serum derived from n=285 patients of HNSCC enrolled in EAGLE (NCT02369874), a randomized, open-label, study assessing Durvalumab and Tremelimumab vs. Standard of Care (SoC). Statistical comparison between HPV (-) vs. HPV (+) samples was conducted using R software.

Results Patients with HPV(-) vs. HPV(+) HNSCC were characterized by worse prognosis. Increased levels of immunosuppressive factors including VEGF (p=0.01), IL-8 (p=0.02), IL6 (p=0.07) and macrophages chemo attractive factor CCL4 (p=0.07) was observed in the serum of HPV(-) vs HPV(+) HNSCC patients. In the tumor microenvironment, higher mRNA expression of immune signatures associated with MDSC, Cancer Associated Fibroblast (CAF), and Metalloproteinase (MMP) was observed in HPV(-) vs. HPV (+) HNSCC patients. In contrast, HNSCC HPV(+) patients were characterized by increased mRNA expression of DC signatures and IFNγ related genes (i.e. CXCL9). No differential infiltration of T and NK cells (CD8+ and Nkp46+) were found in HPV (-) vs. HPV(+) patients. Enrichments of mutations in EGFR, and DNA repair genes (PMS1, POLK, ATM) was observed in HPV(+) patients. On the contrary, enrichments of mutations in TP53 was observed in HPV(-) patients.

Conclusions Deep evaluation of tumoral and peripheral landscape of viral- versus carcinogen-driven HNSCC might help understanding differential outcome of treatments regimens in HPV(+) vs HPV (-) HNSCC thus leading to novel therapeutic interventions.

Trial Registration NCT01693562,NCT02369874
Ethics Approval The study was approved by AstraZeneca.