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Platinum Priority – Urothelial Cancer

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Phase 2 Trial of Gemcitabine, Cisplatin, plus Ipilimumab in Patients with Metastatic Urothelial Cancer and Impact of DNA Damage Response Gene Mutations on Outcomes

Matthew D. Galsky[a,*], *Huan Wang*[b,c], *Noah M. Hahn*[d], *Przemyslaw Twardowski*[e], *Sumanta K. Pal*[e], *Costantine Albany*[f], *Mark T. Fleming*[g], *Alexander Starodub*[h], *Ralph J. Hauke*[i], *Menggang Yu*[j], *Qianqian Zhao*[j], *Guru Sonpavde*[k], *Michael J. Donovan*[l], *Vaibhav G. Patel*[a], *John P. Sfakianos*[m], *Josep Domingo-Domenech*[l], *William K. Oh*[a], *Nicholas Akers*[b], *Bojan Losic*[b], *Sacha Gnjatic*[a], *Eric E. Schadt*[b,c], *Rong Chen*[b,c], *Seunghee Kim-Schulze*[a], *Nina Bhardwaj*[a], *Andrew V. Uzilov*[b,c]

[a] *Division of Hematology and Medical Oncology, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA;* [b] *Icahn Institute for Genomics and Multiscale Biology and Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA;* [c] *Sema4, a Mount Sinai venture, Stamford, CT, USA;* [d] *Johns Hopkins University School of Medicine, Baltimore, MD, USA;* [e] *City of Hope Comprehensive Cancer Center, Duarte, CA, USA;* [f] *Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN, USA;* [g] *US Oncology Research, Virginia Oncology Associates, Hampton, VA, USA;* [h] *Indiana University Health Goshen Center for Cancer Care, Goshen, IN, USA;* [i] *Nebraska Cancer Specialists, Omaha, NE, USA;* [j] *Department of Biostatistics & Medical Informatics, University of Wisconsin Madison, WI, USA;* [k] *University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL, USA;* [l] *Department of Pathology, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA;* [m] *Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY, USA*

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Abstract

Background: Chemotherapy may exert immunomodulatory effects, thereby combining favorably with the immune checkpoint blockade. The pharmacodynamic effects of such combinations, and potential predictive biomarkers, remain unexplored.
Objective: To determine the safety, efficacy, and immunomodulatory effects of gemcitabine and cisplatin (GC) plus ipilimumab and explore the impact of somatic *DNA damage response* gene alterations on antitumor activity.
Design, setting, and participants: Multicenter single arm phase 2 study enrolling 36 chemotherapy-naïve patients with metastatic urothelial cancer. Peripheral blood flow cytometry was performed serially on all patients and whole exome sequencing of archival tumor tissue was performed on 28/36 patients.
Intervention: Two cycles of GC followed by four cycles of GC plus ipilimumab.
Outcome measurements and statistical analysis: *The* primary endpoint was 1-yr overall survival (OS). Secondary endpoints included safety, objective response rate, and progression-free survival.
Results and limitations: Grade $\geq$3 adverse events occurred in 81% of patients, the majority of which were hematologic. The objective response rate was 69% and 1-yr OS was 61% (lower bound 90% confidence interval: 51%). On exploratory analysis, there

* Corresponding author. Mount Sinai School of Medicine, Tisch Cancer Institute, 1 Gustave Lower Levy Place, New York, NY 10029, USA. Tel. +1 212 659 5412; Fax: +1 212 659 5599.
E-mail address: matthew.galsky@mssm.edu (M.D. Galsky).

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were no significant changes in the composition and frequency of circulating immune cells after GC alone. However, there was a significant expansion of circulating CD4 cells with the addition of ipilimumab which correlated with improved survival. The response rate was significantly higher in patients with deleterious somatic DNA damage response mutations (sensitivity = 47.6%, specificity = 100%, positive predictive value = 100%, and negative predictive value = 38.9%). Limitations are related to the sample size and single-arm design. ***Conclusions:*** GC + ipilimumab did not achieve the primary endpoint of a lower bound of the 90% confidence interval for 1-yr OS of >60%. However, within the context of a small single-arm trial, the results may inform current approaches combining chemotherapy plus immunotherapy from the standpoint of feasibility, appropriate cytotoxic *backbones*, and potential predictive biomarkers. Trial registration: ClinicalTrials.gov NCT01524991. ***Patient summary:*** Combining chemotherapy and immune checkpoint blockade in patients with metastatic urothelial cancer is feasible. Further studies are needed to refine optimal combinations and evaluate tests that might identify patients most likely to benefit.

1. Introduction

Metastatic urothelial cancer (UC) is a relatively chemotherapy-sensitive neoplasm with objective responses achieved in 50–60% of patients treated with cisplatin-based chemotherapy [1]. However, response durations are generally short and median survival is only ~14 mo [1]. Attempts to improve outcomes with additional cytotoxic agents have proven unsuccessful suggesting a therapeutic ceiling has been reached and highlighting the need for novel approaches [2].

Ipilimumab is a fully human monoclonal antibody directed against the immune checkpoint molecule cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) [3]. In a syngeneic murine bladder cancer model, CTLA-4 blockade induced tumor regression, improved survival, and increased levels of tumor-reactive T-cells [4]. A "window of opportunity" study demonstrated that ipilimumab induced immunomodulatory effects when administered prior to cystectomy in 12 patients with localized invasive UC [5]; however, the role of CTLA-4 blockade in metastatic UC has been underexplored.

Studies in model systems, and in patients, have demonstrated that cytotoxic chemotherapy may also exert immunomodulatory effects and therefore combine favorably with immune checkpoint blockade [6]. While the effects on the immune system are pleiotropic, chemotherapy can potentially augment tumor immunity via two key mechanisms: (1) by inducing immunogenic cell death (ie, the concomitant release of tumor antigens and danger associated molecular patterns such as high mobility group box 1 protein (HMGB-1), and/or (2) by direct modulation of the quantity and/or activity of immunosuppressive cellular subsets [6–10]. In syngeneic murine tumor models, combining ipilimumab with cytotoxic chemotherapy demonstrated synergistic antitumor activity accompanied by an increase in activated T-cells and a decrease in myeloid-derived suppressor cells [11].

Apart from the direct immunomodulatory effects of some cytotoxic agents, combining chemotherapy with immune checkpoint blockade could also represent an attractive strategy for patients with tumors harboring genomic alterations conferring sensitivity to both classes of therapies. The presence of somatic mutations in *DNA damage response* (*DDR*) genes has been correlated with response to cisplatin-based chemotherapy in UC [12–15]. Studies across various tumor types have demonstrated a correlation between higher tumor mutational load and response to immune checkpoint blockade [16,17]. Deleterious mutations in *DDR* genes may lead to hyper-accumulation of somatic mutations [18–20]. Therefore, tumors harboring somatic *DDR* mutations may be particularly vulnerable to the combination of cisplatin-based chemotherapy plus immune checkpoint blockade (Supplementary Fig. 1).

To better understand the potential role of combining chemotherapy plus immune checkpoint blockade, we designed a clinical-translational phase 2 study.

2. Patients and methods

2.1. Study design and treatment

Hoosier Cancer Research Network GU-148 was an investigator-initiated multi-center phase 2 trial. Both based on the hypothesis that chemotherapy administered first might induce immunogenic cell death, and to facilitate pharmacodynamic assessments, a *phased* schedule was employed (Supplementary Fig. 2). Patients received two cycles of gemcitabine (1000 mg/m^2 on days 1 and 8) plus cisplatin (70 mg/m^2 on day 1) every 21 d (GC). Patients subsequently received four cycles of GC plus ipilimumab (10 mg/kg on day 1) every 21 d. After completion of cycle 6, patients with at least stable disease could continue maintenance ipilimumab every 3 mo.

The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the local ethics committees at each participating site and informed consent was provided by all patients before enrollment.

2.2. Patients

Eligible patients were aged ≥18 yr and had metastatic UC of the bladder, urethra, ureters, or renal pelvis. Patients had received no prior systemic chemotherapy for metastatic disease; prior neoadjuvant/adjuvant therapy was permitted if completed ≥12 mo prior to registration. Patients were required to have adequate organ function and a Karnofsky performance status of at least 80%.

2.3. Study assessments

Tumor assessments were conducted using cross-sectional imaging of the chest, abdomen, and pelvis at screening, after cycle 2, after cycle 6, and every 3 mo. Response and progression were investigator assessed and were determined both by Response Evaluation Criteria in Solid Tumors