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Clinical trials and new treatments for castration-resistant prostate cancer

Yuanhong Jiang[1], Jiazheng Yu[1], Shijie Li[1]* and Xiaonan Chen1*

Corresponding Author

Shijie Li, Department of Urology, Shengjing Hospital of China Medical University, Shenyang 110004, Liaoning, People's Republic of China .

Email : *sjli@cmu.edu.cn*

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ABSTRACT

During the 2023 American Society of Clinical Oncology-Genitourinary (ASCO- GU) Cancers Symposium, a number of new and promising treatment options as well as clinical trials addressing castration-resistant prostate cancer (CRPC) were presented. 177Lu/111In-J591 and 225Ac-J591, two notable radionuclide drug conjugates (RDC), shown improved therapeutic efficacy in the treatment of patients with CRPC. Prostate stem cell antigen (PSCA)-directed chimeric antigen receptor (CAR)-T cell immunotherapy-BPX-601, protein kinase inhibitor (AKTi)-CAPltello-280, and dual anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti-programmed death-1 (PD-1) blockade in rare tumors (DART)-Lorigerlimab were additional promising treatment approaches for CRPC. We have compiled the most recent CRPC therapy approaches that were discussed at the ASCO-GU Cancers Symposium in 2023, as well as the most recent developments in CRPC clinical trials.

Keywords : CRPC, RDC, Amphiphiles and retargeted proteins, CAR-T, AKTi

INTRODUCTION

Regarding the editor The ASCO-GU Cancers Symposium honors significant advancements and discoveries in gynecological oncology each year. We have thoroughly examined these significant developments in medications and cutting-edge treatments for colorectal cancer (CRPC), as they were presented at the 2023 ASCO-GU Cancer Symposium.

RDC in prostate cancer (PCa) RDC drugs localize radiation from the radioisotope on the target tissue for effective and precise treatment while minimizing systemic exposure and radiation-induced toxicity to other tissues [1]. They do this by using antibodies or small molecules to modify specific targets and deliver cytotoxic or imaging agents to the target location.

Radioactive 177Lu and 111In, in combination with either hydrocortisone or ketoconazole, were utilized to label the anti-prostate-specific membrane antigen (PSMA) mAb J591 (NCT00859781) in a randomized, double-blind phase II research. The majority of patients with non-metastatic CRPC (M0CRPC) treated with radiolabeled J591 and ketone/HC showed a significant reduction in PSA levels (PSA decline ratio > 50% (PSA50): 82% and 71% in the 177Lu and 111In groups, respectively; PSA decline ratio > 90% (PSA90): 50% and 35% in the 177Lu and 111In groups, respectively). The 177Lu group had a considerably higher 18-month PFS than the 111In group, with biochemical progression-free survival (bPFS) of 18.67 and 8.87 months, respectively; nevertheless, hemato-logic toxicity was more prevalent in this group [2]. These results bolster the creation of locally advanced PCa with anti-PSMA radioimmunotherapy; nevertheless, the best radionuclide and targeting agent have still to be found. In both phase I/II trials, a substantial PSA response was demonstrated by a novel triple therapy consisting of 225Ac-J591 (a PSMA-targeted radionuclide therapy), pembrolizumab, and an androgen receptor pathway inhibitor (ARPI) (NCT04946370). Thirteen percent (4/12) of the patients were still progression-free after six months of follow-up. Nevertheless, 7–14 days after starting treatment, 58% (7/12) of the patients experienced unexpected cytokine release syndrome (CRS), which is characterized by a low blood cell count, fever, and morbid rash. However, after stopping the ARPI, patients' responses usually improved in a week. Furthermore, 33% (4/12)

of the patients experienced typical immune-related adverse events (irAEs), all of which were controllable [3].

innovative PCa treatments

In a trial of 42 PSA-assessable patients with mCRPC (35 RECIST-assessable), lorigerlimab (a DART mole- cule [4] that improves CTLA-4 blocking of dual expression while preserving a maximum blockade of PD-1) was found to have an objective response rate (ORR) of 25.7% (9/35). Due to fatal adverse effects that were unrelated, only four cases were discontinued. In patients with chemorefractory mCRPC (NCT03761017), lerigerlimab showed encouraging anti-tumor activity and a manageable safety profile [5]. Preliminary findings from a phase 1 multicenter trial on BPX-601, an autologous PSCA-directed CAR-T cell immunotherapy [6] that expresses a mature-induced MyD88/CD40 costimulation switch to improve T cell potency and persistence, were presented in another multicenter trial (NCT02744287). There was a PSA50 response in 42.9% (3/7) of the 28-day patients. Based on RECIST, preliminary findings showed that the patient had a stable illness of 42.9% (3/7) and a partial response (PR) of 14.3% (1/7). Only 14.3% (1/7) of the patients experienced disease progression, while 14.3% (1/7) of the patients had stable disease (SD) for more than nine months [7].

The effectiveness of AKTi-CAPItello-280 (effective selective inhibition [8] of AKT1/2/3) in combination with docetaxel was assessed in a phase III trial, and patients with mCRPC showed improved overall survival (OS). The Phase II trial data showed that patients attained a median OS of 31.5 months, clinical PFS of 7.03 months, and PSA50 rate of 45% (NCT05348577), even if the Phase III trial is still ongoing [9].

As indicated by the data in Tables 1 and 2, the 2023 ASCO-GU Cancer Symposium showcased noteworthy progress in the treatment of colorectal cancer. The symposium brought to light a number of promising new medications and clinical trials that hold promise for developing innovative CRPC treatment approaches.

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