Bladder Cancer 9 (2023) 383–385
DOI 10.3233/BLC-239012
IOS Press



Paper Alert

# A New Standard of Care for Bladder Cancer

Edward M. Messing*
*University of Rochester Medical Center, Rochester, NY, USA*

Received 8 November 2023
Accepted 12 November 2023
Pre-press 8 December 2023
Published 13 December 2023

Locally advanced and metastatic (LA/M) urothelial cancer (UC) has an ominous prognosis [1–4], and for patients with contraindications to receiving cisplatin containing chemotherapy including inadequate renal function, poor performance status, significant hearing impairment, and other comorbidities, the outlook is even less favorable [5–8]. Unfortunately, carboplatin+gemcitabine is commonly used in cisplatin ineligible patients but is still a rigorous regimen with lower response rates than cisplatin containing regimens [9–12]. Thus, it is welcome news that the combination of Enfortumab Vedotin (EV) and Pembrolizumab (Pembro), an anti PD-1 (programmed death protein -1) monoclonal antibody, showed "acceptable" tolerability and impressive efficacy in a dose escalation study in cisplatin ineligible patients with LA/M UC as first line (1 L) treatment [13].

EV is an antibody drug conjugate of a humanized monoclonal antibody to nectin-4 (which is widely expressed in urothelial cancer) linked with monomethyl auristatin E (MMAE). The MMAE is delivered to cells expressing nectin-4, resulting in a cytotoxic response by blocking tubulin polymerization and inhibiting microtubule formation, arresting cells in the M phase of the cell cycle [13]. This not only kills those cells receiving EV, but also results in the release of "damage associated molecular patterns" which are recognized by innate and adaptive immune cells [14–17]. The ensuing inflammatory response includes engulfment of tumor cells by antigen presenting T cells and presentation of tumor associated antigens to cytotoxic T cells. This T cell response is further augmented by inhibitors of immune check points PD-1 and PD-L1, enhancing the anti-tumor immune response. This is the rationale for combining EV with Pembro, especially since as single agents each alone has shown efficiency as second line (2 L) treatments following platinum containing chemotherapy [18–21].

In the current report [22], 151 patients deemed ineligible for cisplatin containing chemotherapy who had not received prior systemic treatment for UC, and who had never received EV or similarly acting agents or PD-1, PD-L1 or PD-L2 inhibitors, who were free of active central nervous system metastases or uncontrolled diabetes, were randomly assigned to EV+Pembro or EV alone. EV (1.25 mg/kg) was administered by an intravenous (IV) infusion over 30 minutes of day 1 and 8 of a 3—week cycle and 200 mg Pembro was administered IV on day 1. Baseline PD-L1 status (combined positive score $< 10$ or $\geq 10$) and nectin-4 expression in the tumor were assessed. A statistical analysis comparing toxicity or efficacy in the two groups was intentionally not performed because the purpose of the trial was to obtain safety and efficacy information on the combination and EV alone in the 1 L setting [22].

Patients were well randomized for demographics, primary tumor and metastatic site(s), and PD-L1 status. The median duration of treatment was 9.6 months in the EV+Pembro group and 5.5 months in the EV alone arm. Median following was around 15 months for both groups.

In the combination group, Grade 3 + skin reactions occurred in 21%, peripheral neuropathy in 2%,

*Correspondence to: Edward M. Messing, University of Rochester Medical Center, Rochester, NY, USA. E-mail: Edward_Messing@urmc.rochester.edu.

hyperglycemia in 6.6%, fatigue in 9.2%, and pneumonitis (from Pembro) in 5%. The EV alone group had grade 3 + cutaneous reactions in 8.2% (surprisingly low since nectin-4 is expressed in the skin), while the incidence of Grade 3 + fatigue and hyperglycemia were similar in both arms. Nearly 4% of patients in the combination group and 3% receiving EV alone died from consequences of adverse events. Dose reductions, discontinuation of treatment, and corticosteroid administration for severe rash or pneumonitis also occurred; 42% in the combined group and 19% in the EV group discontinued therapy because of treatment related adverse events (TRAEs). These TRAEs were like those reported in other studies of EV+Pembro in similar patients including those taking part in the earlier dose finding study [13].

But importantly, responses were also similar to those reported in prior studies. In the combination group, nearly 65% experienced objective responses compared with 45% in the EV alone group. Complete responses occurred in 10.5% of those in the combination group and 4.1% in the EV alone group, and median duration of response was not reached in the combination group and was 13.2 months for EV monotherapy. Importantly, the times to objective responses were rapid, 2 months for each group. PD-L1 status and nectin-4 expression (where ~80% of UCs are nectin-4 positive) did not predict response in either group. Progression free survival was 55% at 12 months and overall survival was > 80% at 12 months in the combination group; both being considerably greater than in the EV monotherapy group.

We eagerly await results from ongoing trials of EV+Pembro versus platinum containing combination chemotherapy as 1 L treatment in LA/M UC, and EV+Pembro versus cisplatin containing chemotherapy as neoadjuvant treatment before cystectomy in patients with stage cT2-T4, No-1 Mo UC. One cannot help but to be impressed with both how rapidly the studies have been rolled out and sequenced: dose finding; figuring out which component of the combination was contributing to efficacy (and toxicity); and then testing against the current "best" treatment for LA/M and muscle invasive disease. It appears very likely that a new standard of care for treating bladder cancer has been found.

## CONFLICTS OF INTEREST

The author has no conflicts of interest to report.

## REFERENCES


[1] Wong MCS, Fung FDH, Leung C, et al., The global epidemiology of bladder cancer: A joinpoint regression analysis of its incidence and mortality trends and projection. Sci. Rep. 2018;8:1129.

[2] Richters A, Aben KKH, Kiemeney L. The global burden of urinary bladder cancer: An update. World J. Urol. 2020;38:1895-1904.

[3] Ferlay J, Soerjomataram I, Dikshit R, et al., Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int. J. Cancer. 2015;136:E359-E386.

[4] Shah MV, McGovern A, Hepp Z. Targeted literature review of the burden of illness in urothelial carcinoma. Value Health. 2018;21:S32-S33.

[5] Dash A, Galsky MD, Vickers AJ, et al., Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer. 2006;107:506-513.

[6] Galsky MD, Hahn NM, Rosenberg J, et al., Treatment of patients with metastatic urothelial cancer "unfit" for cisplatin-based chemotherapy. J. Clin. Oncol. 2011;29:2432-2438.

[7] Galsky MD, Pal SK, Lin SW, et al., Real-world effectiveness of chemotherapy in elderly patients with metastatic bladder cancer in the United States. Bladder Cancer. 2018;4:227-238.

[8] Grivas P, Plimack E, Balar AV, et al., Pembrolizumab (pembro) as first-line therapy in cisplatin-ineligible advanced urothelial cancer (UC): Outcomes from KEYNOTE-052 in senior patients (pts) with poor performance status. Ann. Oncol. 2017;28:v301.

[9] De Santis M, Bellmunt J, Mead G, et al., Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J. Clin. Oncol. 2012;30:191-199.

[10] von der Maase H, Sengelov L, Roberts JT, et al., Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J. Clin. Oncol. 2005;23:4602-4608.

[11] Bukhari N, Al-Shamsi HO, Azam F. Update on the treatment of metastatic urothelial carcinoma. Scientific World Journal. 2018;2018:5682078.

[12] Kim TJ, Cho KS, Koo KC. Current status and future perspectives of immunotherapy for locally advanced or metastatic urothelial carcinoma: A comprehensive review. Cancers (Basel). 2020;12:e192.

[13] Hoimes CJ, Flaig TW, Milowsky MI, Friedlander TW, Bilen MA, Gupta S, Srinivas S, Merchan JR, McKay RR, Petrylak DP, Sasse C, Moreno BH, Yu Y, Carret AS, Rosenberg JE. Enfortumab Vedotin Plus Pembrolizumab in Previously Untreated Advanced Urothelial Cancer. J. Clin. Oncol. 2023;41(1):22-31.

[14] Challita-Eid PM, Satpayev D, Yang P, et al., Enfortumab vedotin antibody-drug conjugate targeting Nectin-4 is a highly potent therapeutic agent in multiple preclinical cancer models. Cancer. Res. 2016;76:3003-3013.

[15] Doronina SO, Senter PD. Chapter 4: Auristatin payloads for antibody-drug conjugates (ADCs), in Cytotoxic Payloads for Antibody-Drug Conjugates. Cambridge, UK, Royal Society of Chemistry 2019, pp 73-99.

[16] Doronina SO, Toki BE, Torgov MY, et al., Development of potent monoclonal antibody auristatin conjugates for cancer therapy. Nat. Biotechnol. 2003;21:778-784.
[17] Krysko DV, Garg AD, Kaczmarek A, et al., Immunogenic cell death and DAMPs in cancer therapy. Nat. Rev. Cancer. 2012;12:860-875.
[18] Powles T, Csoszi T, Ozguroglu M, et al., Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): A randomised, open-label, phase 3 trial. Lancet. Oncol. 2021;22:931-945.
[19] Rosenberg JE, O'Donnell PH, Balar AV, et al., Pivotal trial of enfortumab vedotin in urothelial carcinoma after platinum and anti-programmed death 1/programmed death ligand 1 therapy. J. Clin. Oncol. 2019;37:2592-2600.
[20] Swami U, Haaland B, Kessel A, et al., Comparative effectiveness of immune checkpoint inhibitors in patients with platinum refractory advanced urothelial carcinoma. J. Urol. 2021;205:709-717.
[21] Powles T, Rosenberg JE, Sonpavde GP, et al., Enfortumab vedotin in previously treated advanced urothelial carcinoma. N. Engl. J. Med. 2021;384:1125-1135.
[22] O'Donnell PH, Milowsky MI, Petrylak DP, et al. Enfortumab Vedotin With or Without Pembrolizumab in Cisplatin-Ineligible Patients With Previously Untreated Locally Advanced or Metastatic Urothelial Cancer. Journal of Clinical Oncology 2023;41:25, 4107-4117.