

# A NEW PARADIGM IN UROTHELIAL CANCER

## THE CONVERGENCE OF IMMUNO-ONCOLOGY AND UROLOGY

- Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemotherapy in stage III non–small-cell lung cancer. *New Engl J Med*. 2017;377(20):1919–1929.
- Apolo AB, Ellerton J, Infante JR, et al. Avelumab treatment of metastatic urothelial carcinoma (mUC) in the phase 1b JAVELIN solid tumor study: updated analysis with  $\geq 6$  months of follow-up. Abstract 856P. Presented at: ESMO 2017 Congress; September 10, 2017; Madrid, Spain.
- Apolo AB, Infante JR, Balmanoukian A, et al. Avelumab, an anti-programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: results from a multicenter, phase 1b study. *J Clin Oncol*. 2017;35(19):2117–2124.
- Bajorin DF, De Wit R, Vaughn DJ, et al. Planned survival analysis from KEYNOTE-045: phase 3, open-label study of pembrolizumab (pembro) versus paclitaxel, docetaxel, or vinflunine in recurrent, advanced urothelial carcinoma (UC). Abstract 4501. Presented at: ASCO Annual Meeting; June 2–6, 2017; Chicago, Illinois.
- Balar AV, Castellano D, O’Donnell PH, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2017;18(11):1483–1492.
- Balar AV, Dreicer R, Loriot Y, et al. Atezolizumab (atezo) in first-line cisplatin-ineligible or platinum-treated locally advanced or metastatic urothelial carcinoma (mUC): Long-term efficacy from phase II study IMvigor210. Abstract 4523. Presented at: American Society of Clinical Oncology Annual Meeting; June 2, 2018; Chicago, Illinois.
- Balar AV, Galsky MD, Rosenberg JE, et al; IMvigor210 Study Group. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *Lancet*. 2017;389(10064):67–76.
- Bellmunt J, de Wit R, Vaughn DJ, et al. Two-year follow-up from the phase 3 KEYNOTE-045 trial of pembrolizumab (pembro) vs. investigator’s choice (paclitaxel, docetaxel, or vinflunine) in recurrent, advanced urothelial cancer (UC). Abstract 410. Presented at: ASCO Genitourinary Cancers Symposium; February 8–10, 2018; San Francisco, California.
- Bellmunt J, de Wit R, Vaughn DJ, et al; KEYNOTE-045 Investigators. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med*. 2017;376(11):1015–1026.
- Bellmunt J, Powles T, Vogelzang NJ. A review on the evolution of PD-1/PD-L1 immunotherapy for bladder cancer: the future is now. *Cancer Treat Rev*. 2017;54:58–67.
- Bellmunt J, Théodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol*. 2009;27(27):4454–4461.
- Bellmunt J, von der Maase H, Mead GM, et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC intergroup study 30987. *J Clin Oncol*. 2012;30(10):1107–1113.
- Bohle A, Brandau S. Immune mechanisms in bacillus Calmette-Guérin immunotherapy for superficial bladder cancer. *J Urol*. 2003;170(3):964–969.
- Chamie K, Saigal CS, Lai J, et al; Urologic Diseases in America Project. Quality of care in patients with bladder cancer: a case report? *Cancer*. 2012;118(5):1412–1421.
- Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity*. 2013;39(1):1–10.
- de Reijke TM, De Boer EC, Kurth KH, Schamhart DH. Urinary interleukin-2 monitoring during prolonged bacillus Calmette-Guérin treatment: can it predict the optimal number of instillations? *J Urol*. 1999;161(1):67–71.
- 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(2):191–199.

- 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 “unfit” for cisplatin-based chemotherapy: phase II—results of EORTC study 30986. *J Clin Oncol*. 2009;27(33):5634–5639.
- de Wit R, Kamat AM, Bellmunt J, et al. Pembrolizumab in patients with bacillus Calmette-Guérin (BCG)-unresponsive, high-risk, non-muscle-invasive bladder cancer (NMIBC): phase 2 KEYNOTE-057 study. *Ann Oncol*. 2016;27(Suppl 6):vi266–vi295.
- Dinney CP, Greenberg RE, Steinberg GD. Intravesical valrubicin in patients with bladder carcinoma in situ and contraindication to or failure after bacillus Calmette-Guérin. *Urol Oncol*. 2013;31(8):1635–1642.
- Dreicer R, Hoffman-Censits JH, Flaig TW, et al. Updated efficacy and >1-y follow up from IMvigor 210: atezolizumab (atezo) in platinum (plat) treated locally advanced/metastatic urothelial carcinoma (mUC). Abstract 4515. Presented at: ASCO Annual Meeting; June 3–7, 2016; Chicago, Illinois.
- FDA Approved Drug: Atezolizumab. U.S. Food and Drug Administration. October 2016.  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2016/761041Orig1s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/761041Orig1s000lbl.pdf). Accessed April 2018.
- FDA Approved Drug: Avelumab. U.S. Food and Drug Administration. March 2017.  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/761049s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761049s000lbl.pdf). Accessed April 2018.
- FDA Approved Drug: Durvalumab. U.S. Food and Drug Administration. April 2017.  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/761069s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761069s000lbl.pdf). Accessed April 2018.
- FDA Approved Drug: Infliximab. U.S. Food and Drug Administration. November 2013.  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/103772s5359lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103772s5359lbl.pdf). Accessed April 2018.
- FDA Approved Drug: Nivolumab. U.S. Food and Drug Administration. December 2017.  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/125554s055lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125554s055lbl.pdf). Accessed April 2018.
- FDA Approved Drug: Pembrolizumab. U.S. Food and Drug Administration. May 2017.  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/125514s014lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s014lbl.pdf). Accessed April 2018.
- FDA News Release. FDA approves new, targeted treatment for bladder cancer. May 18, 2016.  
<https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm501762.htm>. Accessed April 2018.
- Funt SA, Rosenberg JE. Systemic, perioperative management of muscle-invasive bladder cancer and future horizons. *Nat Rev Clin Oncol*. 2017;14(4):221–234.
- Hayden EC. Antibody alarm call rouses immune response to cancer. *Nature*. 2012;486(7401):16.
- Hinotsu S, Akaza H, Naito S, et al. Maintenance therapy with bacillus Calmette-Guérin Connaught strain clearly prolongs recurrence-free survival following transurethral resection of bladder tumour for non-muscle-invasive bladder cancer. *BJU Int*. 2011;108(2):187–195.
- Hurst CD, Knowles MA. Bladder cancer: multi-omic profiling refines the molecular view. *Nat Rev Clin Oncol*. 2018;15(4):203–204.
- Kamat AM, Bellmunt J, Galsky MD, et al. Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of bladder carcinoma. *J Immunother Cancer*. 2017;5(1):68.
- Kamat AM, Hahn NM, Efstathiou JA, et al. Bladder cancer. *Lancet*. 2016;388(10061):2796–2810.
- Kamat AM, Porten S. Myths and mysteries surrounding bacillus Calmette-Guérin therapy for bladder cancer. *Eur Urol*. 2014;65(2):267–269.
- Kamat AM, Sylvester RJ, Böhle A, et al. Definitions, end points, and clinical trial designs for non-muscle-invasive bladder cancer: recommendations from the International Bladder Cancer Group. *J Clin Oncol*. 2016;34(16):1935–1944.
- Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette Guérin immunotherapy for recurrent TA, T1, and carcinoma in situ transitional cell carcinoma of the bladder: a randomized southwest oncology group study. *J Urol*. 2000;163(4):1124–1129.
- Lawrence MS, Stojanov P, Polak P, et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. *Nature*. 2013;499(7457):214–218.
- Lerner SP, et al. The Cancer Genome Atlas Project in muscle-invasive bladder cancer: insights into biology and clinical applications. Presented at: ASCO Genitourinary Cancers Symposium; February 9, 2018; San Francisco, California. (<https://meetinglibrary.asco.org/record/154348/slide>)
- Lerner SP, Bajorin DF, Dinney CP, et al. Summary and recommendations from the National Cancer Institute’s clinical trials planning meeting on novel therapeutics for non-muscle invasive bladder cancer. *Bladder Cancer*. 2016;2(2):165–202.
- Li R, Amrhein J, Cohen Z, et al. Efficacy of mycobacterium phlei cell wall-nucleic acid complex (MCNA) in BCG-unresponsive patients. *Bladder Cancer*. 2017;3(1):65–71.
- Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol*. 2018;71(16):1755–1764.

- Massard C, Gordon MS, Sharma S, et al. Safety and efficacy of durvalumab (MEDI4736), an anti-programmed cell death ligand-1 immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer. *J Clin Oncol*. 2016;34(26):3119–3125.
- Massari F, Di Nunno V, Cubelli M, et al. Immune checkpoint inhibitors for metastatic bladder cancer. *Cancer Treat Rev*. 2018;64:11–20.
- McCaffrey JA, Hilton S, Mazumdar M. Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. *J Clin Oncol*. 1997;15(5):1853–1857.
- Melero I, Hervas-Stubbs S, Glennie M, et al. Immunostimulatory monoclonal antibodies for cancer therapy. *Nat Rev Cancer*. 2007;7(2):95–106.
- Meluch AA, Greco FA, Burris HA, et al. Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: a phase II trial of the Minnie pearl cancer research network. *J Clin Oncol*. 2001;19(12):3018–3024.
- Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. *Eur J Cancer*. 2016;54:139–148.
- Morales A, Eidinger D, Bruce AW. Intracavitary bacillus Calmette-Guérin in the treatment of superficial bladder tumors. *J Urol*. 1976;116(2):180–183.
- Mukherjee N, Svatek RS, Mansour AM. Role of immunotherapy in bacillus Calmette-Guérin-unresponsive non-muscle-invasive bladder cancer. *Urol Oncol*. 2018;36(3):103–108.
- Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol*. 2016;27(7):1362.
- Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol*. 2015;26(12):2375–2391.
- Necchi A, Joseph RW, Loriot Y, et al. Atezolizumab in platinum-treated locally advanced or metastatic urothelial carcinoma: post-progression outcomes from the phase II IMvigor210 study. *Ann Oncol*. 2017;28(12):3044–3050.
- Oddens J, Brausi M, Sylvester R, et al. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guérin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. *Eur Urol*. 2013;63(3):462–472.
- O'Donnell PH, Grivas P, Balar, AV, et al. Biomarker findings and mature clinical results from KEYNOTE-052: first-line pembrolizumab in cisplatin-ineligible advanced urothelial cancer. Abstract 4502. Presented at: ASCO Annual Meeting; June 2–6, 2017; Chicago, Illinois.
- Packiam VT, Lamm DL, Barocas DA, et al. An open label, single-arm, phase II multicenter study of the safety and efficacy of CG0070 oncolytic vector regimen in patients with BCG-unresponsive non-muscle-invasive bladder cancer: interim results. *Urol Oncol*. 2017;S1078-1439(17):30350–30352.
- Plimack Oral Abstract Discussion: 2016 ASCO Annual Meeting. Escudier BJ, Motzer RJ, Sharma Padmanee, et al. Treatment beyond progression with nivolumab (nivo) in patients (pts) with advanced renal cell carcinoma (aRCC) in the phase III CheckMate 025 study. Abstract 4509. Presented at: ASCO; June 6, 2016; Chicago, Illinois.
- Powles T, Duran I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomized controlled trial. *Lancet*. 2018;391(10122):748–757.
- Powles T, Eder JP, Fine GD, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. *Nature*. 2014;515(7528):558–562.
- Powles T, O'Donnell PH, Massard C, et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. *JAMA Oncol*. 2017;3(9):e172411.
- Puzanov I, Diab A, Abdallah K, et al; Society for Immunotherapy of Cancer Toxicity Management Working Group. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer*. 2017;5(1):95.
- Roberson AG, Kim J, Al-Ahmadie H, et al. Comprehensive molecular characterization of muscle-invasive bladder cancer. *Cell*. 2017;171(3):540–556.
- Roberts SA, Lawrence MS, Klimczak LJ, et al. An APOBEC cytidine deaminase mutagenesis pattern is widespread in human cancers. *Nat Genet*. 2013;45(9):970–976.
- Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicenter, phase 2 trial. *Lancet*. 2016;387(10031):1909–1920.

- Rosenberg JE, Petrylak DP, Van Der Heijden MS, et al. PD-L1 expression, Cancer Genome Atlas (TCGA) subtype, and mutational load as independent predictors of response to atezolizumab (atezo) in metastatic urothelial carcinoma (mUC; IMvigor 210). Abstract 104. Presented at: ASCO Annual Meeting; June 3–7, 2016; Chicago, Illinois.
- Roth BJ, Dreicer R, Einhorn LH. Significant activity of paclitaxel in advanced transitional-cell carcinoma of the urothelium: a phase II trial of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 1994;12(11):2264–2270.
- Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. *Science*. 2015;348(6230):69–74.
- Shah JB, Kamat AM. Strategies for optimizing bacillus Calmette-Guérin. *Urol Clin North Am*. 2013;40(2):211–218.
- Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2017;18(3):312–322.
- Shore ND, Boorjian SA, Canter DJ, et al. Intravesical rAd-IFN $\alpha$ /Syn3 for patients with high-grade, bacillus Calmette-Guérin-refractory or relapsed non-muscle-invasive bladder cancer: a phase II randomized study. *J Clin Oncol*. 2017;35(30):3410–3416.
- Sonpavde G, Galsky MD, Latini D, et al. Cisplatin-ineligible and chemotherapy-ineligible patients should be the focus of new drug development in patients with advanced bladder cancer. *Clin Genitourin Cancer*. 2014;12(2):71–73.
- Sternberg CN, de Mulder PH, Schornagel JH, et al. European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. *J Clin Oncol*. 2001;19(10):2638–2646.
- Sternberg CN, Yagoda A, Scher HI, et al. Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. *Cancer*. 1989;64(12):2448–2458.
- Steinberg G, Bahnsen R, Brosman S, et al. Efficacy and safety of valrubicin for the treatment of bacillus Calmette Guérin refractory carcinoma in situ of the bladder. The Valrubicin Study Group. *J Urol*. 2000;163(3):761–767.
- Sylvester RJ, Brausi MA, Kirkels WJ, et al; EORTC Genito-Urinary Tract Cancer Group. Long-term efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, bacillus Calmette-Guérin, and bacillus Calmette-Guérin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. *Eur Urol*. 2010;57(5):766–773.
- Sylvester RJ, van der Meijden AP, Lamm DL. Intravesical bacillus Calmette-Guérin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. *J Urol*. 2002;168(5):1964–1970.
- Teply BA, Lipson EJ. Identification and management of toxicities from immune checkpoint-blocking drugs. *Oncology* (Williston Park). 2014;28(Suppl 3):30–38.
- Voena C, Chiarle R. Advances in cancer immunology and cancer immunotherapy. *Discov Med*. 2016;21(114):125–133.
- Von der Maase H, Hansen SW, Roberts JT. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol*. 2000;18(17):3068–3077.
- Vuky J, Balar AV, Castellano DE, et al. Updated efficacy and safety of KEYNOTE-052: A single-arm phase II study investigating first-line pembrolizumab (pembro) in cisplatin-ineligible advanced urothelial carcinoma (UC). Abstract 4524. Presented at: American Society of Clinical Oncology Annual Meeting; June 2, 2018; Chicago, Illinois.
- Winer A, Bodor JN, Borghaei H. Identifying and managing the adverse effects of immune checkpoint blockade. *J Thorac Dis*. 2018;10(suppl 3):S480–S489.
- Witjes JA, Palou J, Soloway M, et al. Current clinical practice gaps in the treatment of intermediate- and high-risk non-muscle-invasive bladder cancer (NMIBC) with emphasis on the use of bacillus Calmette-Guérin (BCG): results of an international individual patient data survey (IPDS). *BJU Int*. 2013;112(6):742–750.
- Witjes JA, vd Meijden AP, Debruyne FM, et al. Use of intravesical bacillus Calmette-Guérin in the treatment of superficial transitional cell carcinoma of the bladder: an overview. *Urol Int*. 1990;45(3):129–136.