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Optimizing immunotherapy in locoregional and metastatic urothelial cancer

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General introduction and thesis outline

GENERAL INTRODUCTION

Urothelial cancer (UC) involves cancers emerging from the urinary bladder, ureters, and renal pelvis. Overall, most cases of UC originate and evolve from the bladder (90-95%). With 429,793 new diagnoses worldwide in 2012, bladder cancer is the seventh most common cancer in men and nineteenth most common in women, resulting in 123,051 and 42,033 deaths in 2012, respectively (1). While UC is generally non-invasive at diagnosis, UC can progress to muscle-invasive disease. Approximately 30-40% of patients present with more advanced disease that invades the detrusor muscle of the bladder (2, 3). For patients with locally advanced or metastatic UC, platinum-based chemotherapy is the mainstay of treatment. Initial response rates to chemotherapy are high (4), but long-term remissions are found in only a small subset of patients with metastatic disease (5, 6). Over time, virtually all patients with metastasized disease and a substantial proportion of patients with locally advanced UC will eventually present with platinum-refractory disease. At this stage, benefit from standard therapeutic treatment lines is at best limited. Several chemotherapeutic agents have been tested in the platinum-refractory setting, demonstrating marginal response rates at the cost of substantial toxicity (7). However, the abysmal outlook of patients with more advanced disease stages has changed with the introduction of therapies targeting the immune system to fight tumors.

PD-1/PD-L1 and CTLA-4 immune checkpoints

An immune response directed against tumor cells is one of the body's natural defenses against the growth and progression of cancer. However, over time and under pressure from immune elimination, cancer cells evolve and develop strategies to evade immune-mediated killing (8), allowing them to develop and invade healthy tissues without interference. One such mechanism which cancer cells use involves upregulation of specific proteins (immune checkpoints) that deliver inhibitory signals to cytotoxic T cells. For example, programmed cell death ligand 1 (PD-L1) is upregulated broadly across cancers and is highly common within patient populations. PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation (9). PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized and exploited by tumors to evade detection and elimination by the host anti-tumor immune response (9). In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell (9, 10). This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting tumors from immune elimination (11). Similarly, cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), an activation-induced T-

cell surface molecule, is a member of the CD28:B7 immunoglobulin superfamily that competes with CD28 for B7 (12). CTLA-4 mediated signals are inhibitory and dampen T cell-dependent immune responses by interference of the interaction of CTLA-4 with B7 molecules on antigen presenting cells, primarily occurring in lymph nodes (12).

Targeting the PD-1/PD-L1-axis in UC

The first sign that PD-L1 inhibition could have potent activity in advanced bladder cancer patients originated from an expansion cohort of a phase 1 study testing atezolizumab (MPDL3280A) (13). In this study, durable responses were found in patients heavily pre-treated with chemotherapy. Responses were associated with PD-L1 positivity on immune cells based on immunohistochemistry (IHC), though responses were seen in all PD-L1 subgroups, including tumors displaying limited to no PD-L1. Results from the expansion cohorts were confirmed in a large Phase 2 trial. Here, 315 patients with advanced bladder cancer that progressed on or after platinum-based chemotherapy were treated with atezolizumab until loss of clinical benefit. In the overall study population, 15% responded and ongoing responses were found in 84% of patients after a median follow-up of 11.7 months (14). In a phase 3 trial with pembrolizumab as second-line therapy for advanced urothelial carcinoma, durable responses were seen in heavily pre-treated patients. Here, 542 patients with advanced urothelial cancer that recurred or progressed after platinum-based chemotherapy were randomly assigned to receive pembrolizumab 200 mg every 3 weeks or the investigator's choice of chemotherapy with paclitaxel, docetaxel, or vinflunine. Pembrolizumab was associated with significantly longer overall survival (by approximately 3 months) and with a lower rate of treatment-related adverse events when compared to chemotherapy (15). Nivolumab monotherapy has shown to be effective in patients with recurrent metastatic bladder cancer as well. In the CheckMate 032 study, 86 patients with metastatic urothelial carcinoma were enrolled in the nivolumab monotherapy group of which 78 received at least one dose of treatment. A confirmed investigator-assessed tumor objective response rate (ORR) was achieved in 19 of 78 patients (24% ORR) (16). Another study with nivolumab (CheckMate 275) in 270 patients progressing on or after platinum-based chemotherapy showed a response in 19.6% of patients (17). In the phase I/II Study 1108, durvalumab monotherapy was tested in patients with locally advanced or metastatic urothelial cancer. A response rate of 20.4% was found in all evaluable patients (n=103) and 29.5% in patients whose tumors expressed PD-L1 (n=61) (18). While various immune checkpoint inhibitors (ICIs) have shown clinical activity in bladder cancer, pembrolizumab is the only compound showing significant survival benefit in a randomized phase III trial. The clinical activity to ICIs appears to increase when these therapies are given to first-line patients. In patients who are ineligible to receive cisplatin-based therapy, a generally more fragile patient population, the response rate to atezolizumab was 23% (+8% compared to second line

treatment (19). Similarly, a response rate of 24% was found in a trial testing pembrolizumab as first-line treatment in 370 cisplatin-ineligible UC patients (+8% compared to second line treatment) (20). Ongoing studies are also testing whether cisplatin-eligible patients may benefit from first-line ICIs when compared to cisplatin-based chemotherapy.

Although promising activity to anti-PD-L1/anti-PD-1 antibodies has been observed in patients with metastasized urothelial cancer, the majority of patients do not respond. Reasons for failure to respond to these agents could include insufficient priming of the immune system by cancer antigens and/or negative regulation of other steps in the "cancer immunity cycle" (21). The addition of anti-CTLA-4 treatment could prevent negative regulation of T-cell priming and thereby broaden and intensify the immune response to cancer antigens.

Targeting CTLA-4 signaling in UC

Ipilimumab, a monoclonal antibody targeting CTLA-4, showed prolonged OS in two randomized trials in patients with advanced melanoma (22, 23). While PD-1 blockade induces higher response rates than CTLA-4 blockade in melanoma patients (24, 25), the depth of clinical responses (percentage of tumor load reduction) could be further enhanced by the combination of nivolumab and ipilimumab (26, 27). The response rate and progression-free survival was superior to ipilimumab or nivolumab monotherapy in a randomized phase 3 trial (28), and superior to ipilimumab in another randomized phase 2 trial (29). The combination of CTLA-4 plus PD-(L)1 blockade has also been tested in patients with platinum-refractory UC. In the Checkmate 032 trial, two schedules of ipilimumab and nivolumab were tested: 4 courses of either ipilimumab 1 mg/kg plus nivolumab 3 mg/kg (n=104) or ipilimumab 3 mg/kg plus nivolumab 1 mg/kg (n=92), followed by nivolumab monotherapy 3 mg/kg every 2 weeks. Response rates were 26% and 38.5%, respectively (30). Similar to melanoma, combination immunotherapy could potentially change the therapeutic landscape for UC patients. Metastatic UC patients with lymph node only disease, treated with frontline immunotherapy, appear to benefit most (20). Since responses to immunotherapy often appear to be durable, preoperative immunotherapy treatment strategies may be an attractive neo-adjuvant treatment strategy and could potentially improve prognosis.

Preoperative immunotherapy in UC

Although muscle-invasive UC can be cured by surgery, recurrence rates are high. The 5-year OS is only 45-55% for patients with pT3N0 tumors, and even worse for patients having pT4aN0 (35-45%) or pTxN+ (10-35%) tumors. Neo-adjuvant cisplatin-based chemotherapy induces impressive tumor responses, including a pathological complete

response (pCR) rate of 22-40% (31). However, the absolute benefit in terms of OS is only 5% (32), at the cost of substantial toxicity. Given the high rate of distant recurrences, improvement of systemic treatment strategies is warranted in order to change the abysmal prognosis of operable UC, particularly for tumors having high-risk of recurrence (T3-4N0M0 or T1-4N1-3M0).

A single-arm study (PURE-01 trial) testing pre-operative pembrolizumab in a cohort of cT2-4aN0 UC patients showed a pCR rate of 37% (33). In addition, a trial (ABACUS) testing neo-adjuvant atezolizumab in a similar cohort of UC demonstrated a pCR rate of 31% (34), providing further confidence that pre-operative immunotherapy may be a viable treatment option. However, pathologic complete responses were primarily found in less advanced (cT2N0) tumors (34), whereas patients with more extensive disease (cT3-4N0) showed only limited pCR to anti-PD1 or anti-PD-L1. As patients with more extensive disease or local lymph node involvement have poor prognosis (20-50% OS) and are less likely to respond, a more intensive systemic treatment regimen can more easily be justified. Thus, combinations including anti-PD-1/anti-PD-L1 plus anti-CTLA might be an attractive treatment approach for high-risk resectable UC, as has been shown for UC and melanoma in the metastatic setting.

Immunotherapy biomarkers in UC

Although the introduction of immunotherapy has changed the treatment landscape of UC, many patients do not experience clinical benefit to anti-PD-(L)1 alone or combined with anti-CTLA-4. Thus, there is an unmet need for biomarkers predicting response and survival. Potential biomarkers that have been investigated in UC are tumor mutation burden (TMB), tumor molecular subtypes and PD-L1 expression on tumor and immune cells (35). However, these markers have not been validated yet and the exact relation with tumor response rate and clinical outcome is still unclear. In addition, comparison of biomarker findings across trials is complicated by variability in biomarker assays (i.e. PD-L1 assessment) and heterogeneity in tumor tissue used to assess biomarkers. Heterogeneity in prior therapies and use of archival tissue (diagnostic tumor tissue vs metastasized tumor tissue) for biomarker development further cloud interpretation. Despite recent efforts, more knowledge on the tumor immune contexture is warranted to better understand the immunotherapy response in UC.

This thesis focuses on the outcome to immunotherapy in locoregional and metastatic urothelial cancer and biomarkers in the tumor-immune microenvironment that may inform outcome, ultimately enhancing cancer immunotherapy. Firstly, we discuss the outcome of urothelial cancer patients treated with checkpoint immunotherapy in the metastatic **(Part I)** and preoperative setting **(Part II)**. Next, we focus on the UC tumor-

immune microenvironment **(Part III)**, as this may facilitate the discovery and development of novel cancer immunotherapy as well as predictive biomarkers for immunotherapy response in UC. A comprehensive framework based on tumor- and host-specific parameters to better understand immunotherapy response in UC is also provided **(Part III)**. An outline of this thesis and the corresponding parts is described below.

THESIS OUTLINE

In **Part I: chapter 2 and 3**, the outcome of metastatic urothelial cancer patients treated with checkpoint immunotherapy is explored, as well as the efficacy of subsequent systemic therapy. In **chapter 2**, we retrospectively studied whether chemotherapy is still effective after progression to ICIs in metastatic UC. We first explore the response rates of chemotherapy in metastatic UC patients who progress after checkpoint inhibition. A subgroup comparison of the response rates of patients who received third-line treatment (following chemo- and ICI) and second-line treatment (after ICI only) was also performed. In **chapter 3**, we assessed the survival outcome and efficacy of subsequent systemic treatment (SST) after discontinuation of anti–PD-1/PD-L1 treatment in first-line and second-line UC using patient data from various patient (study)cohorts. First, we assessed the OS outcome of patients having SST or no SST after progressing to checkpoint inhibitors. We also explored objective radiological response and progression-free survival to subsequent therapies after previous exposure to checkpoint inhibitors.

In **Part II: chapter 4 and 5**, the feasibility, efficacy and outcome to preoperative combination immunotherapy is explored, including a retrospective outcome comparison to preoperative chemotherapy. In **chapter 4**, we elaborate on a phase Ib single-arm trial that explored whether the addition of anti-CTLA-4 to PD-1 blockade is feasible as preoperative treatment in locoregionally advanced (stage III) UC. This is a patient population with more extensive disease, which showed limited response to anti-PD-1 or anti-PD-L1 alone in previous studies, thus, justifying a more intensive treatment schedule with a higher toxicity profile. Furthermore, we performed exploratory analysis to study whether this combination treatment could broaden efficacy to tumors with only limited baseline $CD8^+$ T cell immunity. Additionally, we assessed pretreatment B cell abundance and TLS dynamics, given the recently published studies correlating B cell and TLS presence to response. In **chapter 5**, we retrospectively compared the efficacy of anti-CTLA-4 plus anti-PD-1 to neoadjuvant/induction platinum-based combination chemotherapy in cohorts of locoregionally-advanced UC patients. For this assessment, the NABUCCO-patient cohort (anti-PD-1 + anti-CTLA-4) was compared to a cohort of stage-matched patients treated with preoperative platinum-based combination che-

motherapy. Patients in both cohorts attended the Antoni van Leeuwenhoek bladder cancer clinic during the same time period.

In **Part III: chapter 6 and 7**, we explore potential biomarkers in the UC tumor-immune contexture, and provide a comprehensive framework based on tumor- and host-specific parameters to better understand immunotherapy response in UC. In **chapter 6**, we describe the tumor immune landscape in UC slides by using (immunofluorescence) staining and subsequent computational image analysis to better understand the complex interplay between immune cells and tertiary lymphoid structures (TLS), given the importance for biomarker discovery. Firstly, we provide an overview of the UC immune landscape, followed by detailed assessment of the immune composition of tertiary lymphoid structures in untreated and immunotherapy-treated tumors. In **chapter 7**, a novel framework is proposed for UC (UC immunogram), based on accessible translational and clinical data. The UC immunogram describes various tumor and host-specific parameters that are needed for immunotherapy treatment to be successful. These seven parameters include tumor foreignness, immune cell infiltration, absence of inhibitory checkpoints, general performance and immune status, absence of soluble inhibitors, absence of inhibitory tumor metabolism, and tumor sensitivity to immune effectors. The UC immunogram can be used to better understand the complexity of the anti-tumor immune response in UC and to help prioritize biomarkers that should be prospectively tested in clinical studies. This might eventually lead to a multifactorial model that can better predict clinical responses to immunotherapy in UC.

In **chapter 8**, we provide a discussion on the most important findings and future directions.

REFERENCES

1. Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A. Epidemiology of Bladder Cancer. Med Sci (Basel). 2020;8(1).
2. Sternberg CN, de Mulder PH, Schornagel JH, Theodore C, Fossa SD, van Oosterom AT, et al. 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. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2001;19(10):2638-46.
3. von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, et al. 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. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2000;18(17):3068-77.
4. Yeshchina O, Badalato GM, Wosnitzer MS, Hruby G, RoyChoudhury A, Benson MC, et al. Relative efficacy of perioperative gemcitabine and cisplatin versus methotrexate, vinblastine, adriamycin, and cisplatin in the management of locally advanced urothelial carcinoma of the bladder. Urology. 2012;79(2):384-90.
5. Roberts JT, von der Maase H, Sengelov L, Conte PF, Dogliotti L, Oliver T, et al. Long-term survival results of a randomized trial comparing gemcitabine/cisplatin and methotrexate/vinblastine/doxorubicin/cisplatin in patients with locally advanced and metastatic bladder cancer. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2006;17 Suppl 5:v118-22.
6. Sternberg CN, de Mulder P, Schornagel JH, Theodore C, Fossa SD, van Oosterom AT, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. Eur J Cancer. 2006;42(1):50-4.
7. Di Lorenzo G, Buonerba C, Bellelli T, Romano C, Montanaro V, Ferro M, et al. Third-Line Chemotherapy for Metastatic Urothelial Cancer: A Retrospective Observational Study. Medicine (Baltimore). 2015;94(51):e2297.
8. Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. Nature. 2017;541(7637):321-30.
9. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol. 2008;26:677-704.
10. Park JJ, Omiya R, Matsumura Y, Sakoda Y, Kuramasu A, Augustine MM, et al. B7-H1/CD80 interaction is required for the induction and maintenance of peripheral T-cell tolerance. Blood. 2010;116(8):1291-8.
11. Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol. 2008;8(6):467-77.
12. Postow MA, Harding J, Wolchok JD. Targeting immune checkpoints: releasing the restraints on anti-tumor immunity for patients with melanoma. Cancer journal. 2012;18(2):153-9.
13. Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature. 2014;515(7528):558-62.
14. Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016.
15. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carci-

noma. The New England journal of medicine. 2017.
16. Antonia SJ, Lopez-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. The Lancet Oncology. 2016;17(7):883-95.
17. Sharma P, Retz M, Siefker-Radtke A, Baron A, Necchi A, Bedke J, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. The Lancet Oncology. 2017;18(3):312-22.
18. Massard C, Gordon MS, Sharma S, Rafii S, Wainberg ZA, Luke J, 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. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2016;34(26):3119-25.
19. Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, et al. 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.
20. Balar AV, Castellano D, O'Donnell PH, Grivas P, Vuky J, Powles T, 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. The Lancet Oncology. 2017;18(11):1483-92.
21. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013;39(1):1-10.
22. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. The New England journal of medicine. 2010;363(8):711-23.
23. Robert C, Thomas L, Bondarenko I, O'Day S, M DJ, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. The New England journal of medicine. 2011;364(26):2517-26.
24. Ribas A, Hodi FS, Kefford R, Hamid O, Daud A, Wolchok JD, et al. Efficacy and safety of the anti-PD-1 monoclonal antibody MK-3475 in 411 patients (pts) with melanoma (MEL). J Clin Oncol 2014;32:5s, suppl; abstr LBA9000^.
25. Hodi FS, Sznol M, Kluger HM, McDermott DF, Carvajal RD, Lawrence DP, et al. Long-term survival of ipilimumab-naive patients (pts) with advanced melanoma (MEL) treated with nivolumab (anti-PD-1, BMS-936558, ONO-4538) in a phase I trial. J Clin Oncol 2014;32:5s, (suppl; abstr 9002).
26. Wolchok JD, Kluger HM, Callahan MK, Postow MA, Gordon RA, Segal NH, et al. Safety and clinical activity of nivolumab (anti-PD-1, BMS-936558, ONO-4538) in combination with ipilimumab in patients (pts) with advanced melanoma (MEL). J Clin Oncol 2013;31(suppl; abstr 9012^).
27. Sznol M, Kluger HM, Callahan MK, Postow MA, Gordon RA, Segal NH, et al. Survival, response duration, and activity by BRAF mutation (MT) status of nivolumab (NIVO, anti-PD-1, BMS-936558, ONO-4538) and ipilimumab (IPI) concurrent therapy in advanced melanoma (MEL). J Clin Oncol 2014;32:5s, suppl; abstr LBA9003^.
28. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. The New England journal of medicine. 2015.
29. Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, et al. Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma. The New England journal of medicine. 2015.
30. Sharma P, Siefker-Radtke A, Braud Fd, Basso U, Calvo E, Bono P, et al. Nivolumab Alone and With Ipilimumab in Previously Treated Metastatic Urothelial Carcinoma: CheckMate 032

Nivolumab 1 mg/kg Plus Ipilimumab 3 mg/kg Expansion Cohort Results. 2019;37(19):1608-16.
31. Zargar H, Espiritu PN, Fairey AS, Mertens LS, Dinney CP, Mir MC, et al. Multicenter Assessment of Neoadjuvant Chemotherapy for Muscle-invasive Bladder Cancer. European urology. 2014.
32. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. European urology. 2005;48(2):202-5; discussion 5-6.
33. Necchi A, Raggi D, Gallina A, Madison R, Colecchia M, Luciano R, et al. Updated Results of PURE-01 with Preliminary Activity of Neoadjuvant Pembrolizumab in Patients with Muscle-invasive Bladder Carcinoma with Variant Histologies. European urology. 2020;77(4):439-46.
34. Powles T, Kockx M, Rodriguez-Vida A, Duran I, Crabb SJ, Van Der Heijden MS, et al. Clinical efficacy and biomarker analysis of neoadjuvant atezolizumab in operable urothelial carcinoma in the ABACUS trial. Nat Med. 2019;25(11):1706-14.
35. Blank CU, Haanen JB, Ribas A, Schumacher TN. CANCER IMMUNOLOGY. The "cancer immunogram". Science. 2016;352(6286):658-60.