



## Cancer Screening and Cancer Treatment in Kidney Transplant Recipients

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### Abstract

As the population ages and post-transplant survival improves, pretransplant and post-transplant malignancy are becoming increasingly common. In addition, rapid advances in cancer therapies and improving outcomes prompt us to rethink pretransplant cancer-free wait time and screening strategies. Although kidney transplant recipients (KTRs) are at higher risk of developing cancer, epidemiological data on how to best screen and treat cancers in KTRs are incomplete. Thus, current recommendations are still largely on the basis of studies in the general population, and their validity in KTRs is uncertain. Kidney transplant candidates without prior cancer should be evaluated for latent malignancies even in the absence of symptoms. Conversely, individuals with a history of malignancy require thorough monitoring to detect potential recurrences or *de novo* malignancies. When treating KTRs with cancer, reducing immunosuppression can enhance antitumor immunity, yet this also increases the risk of graft rejection. Optimal treatment and immunosuppression management remains undefined. As the emergence of novel cancer therapies adds complexity to this challenge, individualized risk-benefit assessment is crucial. In this review, we discuss up-to-date data on pretransplant screening and cancer-free wait time, as well as post-transplant cancer screening, prevention strategies, and treatment, including novel therapies such as immune checkpoint inhibitors and chimeric antigen receptor T-cell therapies.

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### Introduction

Cancer is a leading cause of morbidity and mortality in kidney transplant recipients (KTRs) and patients with ESKD. These patients present a two- to four-fold increased risk of malignancy compared with the age-matched and sex-matched population.<sup>1–3</sup> The increase in risk is cancer specific, being higher for Kaposi sarcoma (incidence up to 500 times more frequent) and nonmelanoma skin cancer (NMSC, up to 40 times), as well as for virus-related cancers, such as post-transplant lymphoproliferative disorder (PTLD).<sup>1,4</sup> In KTRs, their prognosis is worse than in the general population in all cancer types and management is challenging. The disease course is frequently more aggressive, and therapeutic options are limited because of patients presenting multiple comorbidities and the risk of rejection and graft loss after reduction in immunosuppression.<sup>5,6</sup> Preventive measures are paramount. Screening allows early detection of malignancy and might increase the chance of curative treatment in some types of cancer, reducing morbidity and mortality.<sup>7</sup> Here, we review available screening guidelines for

transplant candidates and KTR, cancer general management, and new therapies aimed at improving outcomes in KTRs.

### Cancer Screening and Cancer-Free Wait Time for Transplant Candidates

Although CKD increases malignancy risk, screening uptake is lower than in patients without CKD.<sup>8</sup> Candidates without a history of malignancy should be evaluated for asymptomatic malignancies. Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend that kidney transplant candidates undergo routine cancer screening, as per local guidelines for the general population.<sup>9</sup> Cancers of the urinary tract system are associated with ESKD. KDIGO recommends ultrasonography in candidates at increased risk for renal cell carcinoma (RCC) and suggests cystoscopy in candidates at increased risk of bladder carcinoma.<sup>9</sup> Screening for hepatocellular carcinoma in candidates with cirrhosis before transplantation is also recommended.<sup>9</sup>

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As the ESKD population ages and cancer treatments improve, more patients with a history of cancer are evaluated for solid organ transplantation (SOT).<sup>10,11</sup> Active malignancy (excluding NMSC) constitutes an absolute contraindication to kidney transplantation. The likelihood of recurrence varies depending on tumor type. The benefits of transplantation should be weighed up against the risk of tumor recurrence because immunosuppression dose and regimen increase the risk of cancer recurrence and potentially affect post-transplant survival.<sup>12</sup> The timing of SOT in patients with a history of malignancy hinges on various factors, including stage at diagnosis, time from treatment, treatment response, required organ, and level of immunosuppression. Historically, most clinical guidelines recommended a recurrence-free waiting period of 2–5 years before candidate listing. However, this interval should be individualized as recent population-based studies show lower cancer recurrence rates than initially reported.<sup>13</sup> Despite risks, overall patient survival with transplantation may exceed expectations, with therapy advancements potentially improving recurrence outcomes. The American Society of Transplantation (AST) and the International Transplant Skin Cancer Collaborative published a thorough consensus expert opinion statement with waiting period recommendations for various cutaneous, hematological, and solid organ malignancies.<sup>10,12,13</sup> In Table 1, we outline recommended wait time for SOT candidates with a history of the main cancer types.

### Cancer Screening Post-Kidney Transplant

Because KTRs live longer, they develop *de novo*, recurrent, or donor-derived cancers more frequently. Screening recommendations follow those for the general population. Because there is little evidence available, the decision to screen is based on the judgment of the treating physician.<sup>7</sup> Although there is some evidence regarding skin and cervical cancers, there is no consensus among international guidelines about screening modality and frequency.<sup>14</sup>

The decision should be tailored, depending on patient comorbidities, life expectancy, cancer risk, and preferences.<sup>7,15</sup> In Table 2, we present current evidence and a summary of clinical practice guidelines for cancer screening in KTRs.

#### Skin and Lip

KDIGO and the United Kingdom Kidney Association (UKKA) recommend KTRs to be informed about their high-risk skin cancer status, especially patients with fair skin tones, who reside in areas with high ultraviolet exposures, have occupations requiring sun exposure, and have a history of skin cancer.<sup>22,23</sup> All patients should minimize life-long sun exposure and use appropriate ultraviolet sunscreen and hats.<sup>22,24,25</sup> Self-examination and annual clinical skin examination are recommended, whether by a primary care physician or a dermatologist.<sup>22,25–28</sup> A tailored surveillance program is recommended on the basis of risk stratification.<sup>15</sup> A Delphi survey advised screening within 2 (high-risk

patients) to 5 years (low-risk patients) of transplant, without specifying ongoing screening intervals.<sup>29</sup>

#### Cervical

KDIGO and the UKKA recommend Papanicolaou cytology with pelvic examination every 3 years in patients between ages 21 and 65 years, according to general population recommendations.<sup>22,23</sup> However, the optimal frequency for KTRs remains undetermined. Canadian Society of Transplantation and the Canadian Society of Nephrology (CST/CSN), the Kidney Health Australia–Caring for Australasians with Renal Impairment (KHA-CARI), AST, and European Best Practice Guidelines (EBPG) guidelines recommend more frequent screening with annual pelvic examination and Pap smear.<sup>24,25,27,28</sup> In addition, a visual inspection of the anal and vulvar area should be included.<sup>30</sup> The AST Infectious Diseases Community of Practice suggested that transplant recipients should be screened with the same periodicity as patients with HIV because of their immunodeficient status.<sup>31</sup>

Some guidelines advocate the use of human papillomavirus (HPV) DNA testing alongside cytological screening for women aged older than 30 years in the general population.<sup>7</sup> However, there is limited evidence supporting its application in KTRs. Some physicians use HPV testing at 1 year, and, if positive, screening continues every 6 months.<sup>6,31</sup> Studies demonstrating the benefits of HPV vaccines in transplant cohorts remain limited.<sup>32</sup> According to the Pediatric Transplantation Association, vaccination in the SOT should differ from the general population.<sup>33</sup> SOT recipients should receive three doses of HPV vaccine, regardless of age. Vaccination can be considered in adult SOT recipients between age 26 and 45 years.<sup>33</sup> Vaccination is more effective before transplantation, and if administered post-transplant, it should be administered 3–6 months post-transplant to enhance immune response.<sup>34</sup>

#### Colorectal

AST, CST/CSN, KDIGO, and UKKA recommend screening colorectal cancer (CRC) in KTRs similarly to the general population, and EBPG advocates only fecal occult blood tests without specification for frequency.<sup>14,22,24,25,28</sup> Guidelines for the general population at average risk for CRC recommend initiating screening at age 50 years. However, the increasing incidence of CRC in the younger population has prompted the American Cancer Society to lower the starting age to 45 years. Screening involves annual high-sensitivity guaiac fecal occult blood test or fecal immunochemical test, stool DNA-fecal immunochemical test testing every 1–3 years, a flexible sigmoidoscopy every 5 years, or colonoscopy every 10 years.<sup>6,35</sup> It is reasonable to consider adjusting the intervals of colonoscopy between 5 and 10 years for post-transplant patients, tailored to individual factors for CRC.<sup>36</sup> High-risk patients or patients exposed to high-intensity immunosuppression may benefit from screening at earlier age or with shorter intervals.<sup>36</sup> The choice of CRC screening modalities are most frequently at the discretion of patient-clinician discussions, and no consensus guidelines are available from transplant organizations.

**Table 1. Recommended wait time for solid organ transplantation candidates with a history of breast, lung, colon, rectal, gynecological, renal cell carcinoma, bladder, prostate, or skin cancer**

| Cancer | Risk/Stage/Type                                                                   | 5-yr Disease-Specific Survival | Time Interval to Transplant                              | Additional Considerations                                                                                                                                                                   |
|--------|-----------------------------------------------------------------------------------|--------------------------------|----------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Breast | Low risk <ul style="list-style-type: none"><li>• DCIS</li><li>• Stage 1</li></ul> | 97%–99%                        | No wait time necessary <sup>a</sup>                      | Hormone receptor negative disease may have a slightly higher risk of recurrence in the first 2–3 yr                                                                                         |
|        | Intermediate risk <ul style="list-style-type: none"><li>• Stage 2</li></ul>       | 90%–99%                        | 1–2 yr NED <sup>a</sup>                                  | Hormone receptor negative disease may have a slightly higher risk of recurrence in the first 2–3 yr                                                                                         |
|        | High risk <ul style="list-style-type: none"><li>• Stage 3</li></ul>               | 66%–97%                        | 3–5 yr NED <sup>a</sup>                                  | Hormone receptor negative disease may have a slightly higher risk of recurrence in the first 2–3 yr<br>Inflammatory breast cancer likely has a higher risk of recurrence and worse survival |
|        | Prohibitive risk <ul style="list-style-type: none"><li>• Stage 4</li></ul>        | 32%–38%                        | Not a SOT candidate                                      |                                                                                                                                                                                             |
| Lung   | 1                                                                                 |                                |                                                          |                                                                                                                                                                                             |
|        | T1aN0                                                                             | 92%                            | ≥3 yr<br>PET-CT; consider biopsy post-SBRT <sup>b</sup>  | 5-yr recurrence-free survival is safest                                                                                                                                                     |
|        | T1bN0                                                                             | 83%                            | ≥3 yr<br>PET-CT; consider biopsy post-SBRT <sup>b</sup>  |                                                                                                                                                                                             |
|        | T1cN0                                                                             | 77%                            | 3–5 yr<br>PET-CT; consider biopsy post-SBRT <sup>b</sup> |                                                                                                                                                                                             |
|        | 1B                                                                                |                                |                                                          |                                                                                                                                                                                             |
|        | T2aN0                                                                             | 68%                            | 5 yr<br>PET-CT <sup>b</sup>                              |                                                                                                                                                                                             |
|        | 2A                                                                                |                                |                                                          |                                                                                                                                                                                             |
|        | T2bN0                                                                             | 60%                            | 5 yr<br>PET-CT <sup>b</sup>                              |                                                                                                                                                                                             |
|        | 2B                                                                                |                                |                                                          |                                                                                                                                                                                             |
|        | T3N0                                                                              | 53%                            | 5 yr<br>PET-CT <sup>b</sup>                              |                                                                                                                                                                                             |
|        | 3A                                                                                | 36                             | 5 yr<br>PET-CT <sup>b</sup>                              | Special caution with N2 disease                                                                                                                                                             |
|        | 3B                                                                                | 26                             | N/A                                                      | Not an SOT candidate                                                                                                                                                                        |
|        | 3C                                                                                | 13                             | N/A                                                      | Not an SOT candidate                                                                                                                                                                        |
|        | 4A                                                                                | 10                             | N/A                                                      | Not an SOT candidate                                                                                                                                                                        |
|        | 4B                                                                                | 0                              | N/A                                                      | Not an SOT candidate                                                                                                                                                                        |

Table 1. (Continued)

| Cancer | Risk/Stage/Type                                                                     | 5-yr Disease-Specific Survival | Time Interval to Transplant                         | Additional Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|--------|-------------------------------------------------------------------------------------|--------------------------------|-----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Colon  | Low risk<br>• Stage 1 (T1 or T2, N0, M0)                                            | 91%                            | 1 year                                              | Low-risk features<br>MSI without BRAF mutation<br>High-risk features<br>LVI or PNI<br>Mucinous or Signet Histology<br>Poorly differentiated histology<br>Bowel obstruction<br>Tumor perforation<br><12 lymph nodes examined<br>*Tumor deposits considered as N+ disease *Consider chemotherapy before transplantation for high-risk stage 2 disease<br>*Patients with stage 3 disease should complete chemotherapy                                                                                                                                                                                                                                                                                       |
|        | Low intermediate risk<br>• Stage 2 (T3, N0, M0)                                     | 72%                            | 2 yr, consider longer if high-risk features present |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|        | High intermediate risk<br>• Stage 2 (T4, N0, M0)<br>• Stage 3 (any T, N+, M0)       |                                | 3 yr, 5 yr if high-risk features present            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|        | High risk<br>• Stage 4 (any T, any N, M+)                                           | 13%                            | 5 yr NED                                            | SOT not recommended before 5 yr; see special consideration regarding resectable CRC metastasis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Rectal | Low risk<br>• Stage 1 (T1 or T2, N0, M0)<br>• Full oncologic resection              | 85%–88%                        | 1 yr, consider 2 yr if high-risk features present   | Low-risk features<br>MSI without BRAF mutation<br>Upper 1/3 rectum or rectosigmoid<br>High-risk features<br>LVI or PNI<br>Mucinous or Signet Histology<br>Poorly differentiated histology<br>Bowel obstruction<br>Tumor perforation<br><12 lymph nodes examined<br>Lower 1/3 of rectum<br>Incomplete mesorectal excision<br>*Tumor deposits considered as N+ disease<br>*Patients with stages 2 and 3 disease should complete trimodality treatment (chemoradiotherapy, surgery, and chemotherapy) unless elimination of one of these is deemed appropriate after multidisciplinary discussion<br>*For patients who have undergone preoperative radiotherapy, response to treatment is highly prognostic |
|        | Low intermediate risk<br>• Stage 1 (T1, N0, M0)<br>• Local excision                 | 78%–88%                        | 2 yr                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|        | High intermediate risk<br>• Stage 2 (T3 or T4, N0, M0)<br>• Stage 3 (any T, N+, M0) | 70%                            | 3 yr, 5 yr if high-risk features present            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|        | High risk<br>• Stage 4 (any T, any N, M+)                                           | 14%                            | 5 yr NED                                            | SOT not recommended before 5 yr; see special consideration regarding resectable CRC metastasis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|        |                                                                                     |                                |                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

Table 1. (Continued)

| Cancer               | Risk/Stage/Type                                                                                                                                                                                                                                                                                                                                                         | 5-yr Disease-Specific Survival                           | Time Interval to Transplant                                                            | Additional Considerations |
|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------------------------------------|---------------------------|
| Gynecological cancer | Low risk <ul style="list-style-type: none"><li>• Stage 1A/1B, grade 1–2 endometrial cancer without lymph-vascular space invasion</li><li>• Stage 1A/1B/1C grade 1–2 epithelial ovarian cancer</li><li>• Stage 1A1, 1A2 squamous/adenocarcinoma of the cervix</li></ul>                                                                                                  | <5% risk of recurrence                                   | No waiting period after completion of primary treatment                                |                           |
|                      | Intermediate risk <ul style="list-style-type: none"><li>• Stages 1/2 endometrial cancer+risk factors<sup>c</sup></li><li>• Stage 1B squamous/adenocarcinoma of the cervix</li></ul>                                                                                                                                                                                     | 5%–15% risk of recurrence                                | 2–3 yr after completion of treatment                                                   |                           |
|                      | High risk <ul style="list-style-type: none"><li>• Serous, clear cell, or carcinosarcoma of uterus (all stages)</li><li>• Stage 3 grade 1–3 endometrioid cancer of the uterus</li><li>• Stage 2/3 epithelial ovarian cancer</li><li>• Stage 2/3 squamous cell/adenocarcinoma cervical cancer</li></ul>                                                                   | >30% risk of recurrence                                  | 5 yr after completion of treatment                                                     |                           |
|                      | Very high risk <ul style="list-style-type: none"><li>• Stage 4 endometrial cancer (all grades)</li><li>• Recurrent or metastatic endometrial cancer</li><li>• Stage 4 epithelial ovarian cancer (any grade)</li><li>• Recurrent ovarian cancer</li><li>• Stage 4 squamous cell/adenocarcinoma of the cervix</li><li>• Metastatic or recurrent cervical cancer</li></ul> | >80% chance of recurrence                                | Not a SOT candidate                                                                    |                           |
| RCC                  | T1a ( $\leq 4$ cm), N0, M0                                                                                                                                                                                                                                                                                                                                              | 95%–98%                                                  | No wait time                                                                           |                           |
|                      | T1b ( $>4$ cm $\leq 7$ cm), N0, M0                                                                                                                                                                                                                                                                                                                                      | 91% for FG $\frac{1}{2}$<br>80%–82% for FG $\frac{3}{4}$ | FG 1–2: no wait time<br>FG 3–4: 1–2 yr                                                 |                           |
|                      | T2 (7–10 cm), N0, M0                                                                                                                                                                                                                                                                                                                                                    | 80%                                                      | 2 yr                                                                                   |                           |
|                      | T3, N0, M0                                                                                                                                                                                                                                                                                                                                                              | 43%–80%                                                  | Minimum of 2 yr, then reassess                                                         |                           |
|                      | T4, N0, M0                                                                                                                                                                                                                                                                                                                                                              | 28%–55%                                                  | Minimum of 2 yr, then reassess                                                         |                           |
|                      | Any T, node positive, metastatic disease                                                                                                                                                                                                                                                                                                                                | 0%–32%                                                   | Not a candidate (if solitary metastasis resected, tumor board discussion on candidacy) |                           |
|                      | Any T with sarcomatoid and/or rhabdoid histologic features                                                                                                                                                                                                                                                                                                              | 15%–27%                                                  | Not a SOT candidate                                                                    |                           |
|                      | Collecting duct or medullary RCC                                                                                                                                                                                                                                                                                                                                        | <10%                                                     | Not a SOT candidate                                                                    |                           |

Table 1. (Continued)

| Cancer   | Risk/Stage/Type                                                                                                                                                                                                                                                                                                                                                           | 2-yr Local Recurrence from Baseline Trans Urethral Resection of Bladder Tumor | Time Interval to Transplant                                                                                                                 |                                                                            |
|----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Bladder  | Nonmuscle invasive bladder cancer low risk—solitary, ≤3 cm, low grade, Ta tumor, absence of CIS                                                                                                                                                                                                                                                                           | 19%                                                                           | 6 mo                                                                                                                                        |                                                                            |
|          | Intermediate risk—solitary tumor >3 cm, recurrence within 12 mo with low-grade Ta tumor, multifocal low-grade Ta tumor, low-grade T1 tumor, or high-grade tumor <3 cm                                                                                                                                                                                                     | 39%                                                                           | 6 mo                                                                                                                                        |                                                                            |
|          | High risk—any CIS, high-grade Ta tumor >3 cm, high-grade T1 tumor, multifocal high-grade Ta tumor, any recurrent high-grade Ta tumor, CIS, variant histology, LVI, high-grade prostatic urethral involvement, recurrence after BCG intravesical therapy. Although 2-yr recurrence rate is lower than intermediate risk, the progression rate to muscle invasion is higher | 38%                                                                           | 2 yr                                                                                                                                        |                                                                            |
|          | Muscle invasive bladder cancer, postradical cystectomy<br>Muscle invasive bladder cancer, postchemoradiation                                                                                                                                                                                                                                                              | 25%–37%<br>25%–30% (10 yr)                                                    | 2 yr<br>Not a SOT candidate                                                                                                                 |                                                                            |
| Cancer   | Risk/Stage/Type                                                                                                                                                                                                                                                                                                                                                           | Survival                                                                      | Time Interval to Transplant                                                                                                                 | Additional Considerations                                                  |
| Prostate | Very low risk <ul style="list-style-type: none"><li>• PSA &lt;10 ng/ml</li><li>• Three or fewer cores of Gleason 6 (grade group 1); no &gt; 50% of individual core</li><li>• T1c–T2a</li></ul>                                                                                                                                                                            | <1% risk of mets/death over 15 yr                                             | None                                                                                                                                        | Surveillance is strongly recommended                                       |
|          | Low risk <ul style="list-style-type: none"><li>• PSA &lt;10 ng/ml</li><li>• Gleason 6 (not meeting very low-risk criteria)</li><li>• T1c–T2a</li></ul>                                                                                                                                                                                                                    | Approximately 2%–3% risk of mets/death over 15 years                          | None                                                                                                                                        | Extenuating circumstances may require treatment                            |
|          | Low-volume intermediate risk <ul style="list-style-type: none"><li>• One of the following criteria: PSA &gt;10 ng/ml, gleason 7 (grade group 2 or 3), T2b</li></ul>                                                                                                                                                                                                       | <5% risk of mets/death over 15 yr                                             | If surveillance, no wait time<br>If treatment initiated, and nomogram predicts cancer-specific death over the next 15 yr <10%, no wait time | Surveillance is strongly recommended                                       |
|          | High-volume intermediate risk, high-risk, or very high-risk <ul style="list-style-type: none"><li>• PSA &gt;20 ng/ml or high-volume Gleason 7 or any Gleason 8–10, T3</li></ul>                                                                                                                                                                                           | 20%–70% risk of mets/death over 15 yr                                         | If treatment initiated, and nomogram predicts cancer-specific death over the next 15 yr <10%, no wait time                                  | Extenuating circumstances may require treatment                            |
|          | Metastatic castration-sensitive                                                                                                                                                                                                                                                                                                                                           | Median survival approximately 5–6 years                                       | If stable disease for 2 yr with prolonged estimated life expectancy, may consider transplant                                                | Surveillance or treatment, depending on patient and cancer characteristics |
|          | Mestastatic castration-resistant                                                                                                                                                                                                                                                                                                                                          | Median survival 2–3 yr                                                        | Not a SOT candidate                                                                                                                         | Treatment                                                                  |
|          |                                                                                                                                                                                                                                                                                                                                                                           |                                                                               |                                                                                                                                             | Best systemic therapy±local treatment                                      |
|          |                                                                                                                                                                                                                                                                                                                                                                           |                                                                               |                                                                                                                                             | Best systemic therapy                                                      |

| Cancer | Risk/Stage/Type |                                                                                                           | 5-yr Disease-Specific Survival | Time Interval to Transplant      | Additional Considerations                                                                  | Appropriate Treatment Pretransplantation                                                                     |
|--------|-----------------|-----------------------------------------------------------------------------------------------------------|--------------------------------|----------------------------------|--------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| Skin   | CSCC            | No history of SCC but at risk for development of SCC                                                      |                                | No delay necessary               | Treatment of field disease                                                                 |                                                                                                              |
|        |                 | Low risk                                                                                                  |                                | No delay necessary               | Surgical excision with clear margins or Mohs micrographic surgery                          |                                                                                                              |
|        |                 | High-risk SCC (not including PNI)                                                                         |                                | 2 yr                             | Surgical excision with clear margins or Mohs micrographic surgery                          |                                                                                                              |
|        |                 | High-risk SCC with <ul style="list-style-type: none"> <li>• PNI or</li> <li>• Two risk factors</li> </ul> |                                | 2–3 yr                           | Surgical excision with clear margins or Mohs micrographic surgery ART                      |                                                                                                              |
|        |                 | High risk with local nodal metastatic disease                                                             |                                | 5 yr                             | Surgical excision with appropriate lymph node dissection plus ART                          |                                                                                                              |
|        |                 | Distant metastasis                                                                                        |                                | Not eligible for transplantation | Refer for oncology opinion                                                                 |                                                                                                              |
|        | MCC             | Local with negative SLNB biopsy                                                                           |                                | 2 yr                             | Wide local excision ART                                                                    |                                                                                                              |
|        |                 | Local with nodal metastasis                                                                               |                                | 3–5 yr                           | Wide local excision, lymph node dissection, ART                                            |                                                                                                              |
|        |                 | Distant metastasis                                                                                        |                                | Not eligible for transplantation | Refer for oncology opinion                                                                 |                                                                                                              |
|        | MM              | <i>In situ</i>                                                                                            | 99%                            | No wait time necessary           | Follow-up 3 mo post-SOT                                                                    | Wide local excision                                                                                          |
|        |                 | Stage 1A (T1a)                                                                                            | 99%                            | 1 yr                             |                                                                                            | Wide local excision                                                                                          |
|        |                 | Stage 1B (T1b or T2a)                                                                                     | 97%                            | year                             | If positive SLNB at time of diagnosis, imaging as for stage 2A disease                     | Wide local excision plus SLNB                                                                                |
|        |                 | Stage 2A (T2b or T3a)                                                                                     | 94%                            | 1 yr                             | Imaging of the brain, CAP<br>Imaging of the neck for those with head/neck melanoma primary | Wide local excision plus SLNB                                                                                |
|        |                 | Stage 2B (T3b or T4a)                                                                                     | 87%                            | 2–4 yr                           | Imaging as above                                                                           | Wide local excision plus SLNB                                                                                |
|        |                 | Stage 2C (T4b)                                                                                            | 82%                            | 2–4 yr                           | Imaging as above                                                                           | Wide local excision plus SLNB                                                                                |
|        |                 | Stage 3A (T1-2a, N1a or 2a)                                                                               | 93%                            | 1–2 yr                           | Imaging as above oncology referral                                                         | Wide excision plus SLNB plus lymph node dissection                                                           |
|        |                 | Stage 3B (T0-3a and N1a/b/c, N2a/b)                                                                       | 83%                            | 2–4 yr                           | Imaging as above oncology referral                                                         | Wide excision plus SLNB plus lymph node dissection                                                           |
|        |                 | Stage 3C (T3b-4b and N2b/c-N3b/c)                                                                         | 69%                            | At least 5 yr                    | Imaging as above oncology referral (no consensus was possible for this group)              | Adjuvant therapy with CKI<br>Wide excision plus SLNB plus lymph node dissection                              |
|        |                 | Stage 3D (T4b and N3a–3c)                                                                                 | 32%                            | At least 5 yr                    | Imaging as above oncology referral (no consensus was possible for this group)              | Adjuvant therapy with CKI<br>Wide excision plus SLNB plus lymph node dissection                              |
|        |                 | Stage 4                                                                                                   | 15%–20%                        | At least 5 yr                    | Imaging as above oncology referral (no consensus was possible for this group)              | Adjuvant therapy with CKI<br>Wide excision plus SLNB plus lymph node dissection<br>Adjuvant therapy with CKI |

<sup>a</sup>After completion of all standard treatments. Endocrine therapy does not need to be completed before transplant, as this is an oral medication that is fairly well tolerated with few serious side effects and often continues for 5–10 years.

<sup>c</sup>Risk factors: older age, lymph-vascular space invasion, grade 2 or 3 endometrioid, deeply invasive tumor.



**Table 2. Recommendations for cancer screening in kidney transplant recipients**

| Cancer                                             | Screening                                              | Frequency                                                                                                                                      | Guidelines                                  |
|----------------------------------------------------|--------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| Skin and lip                                       | Self-examination                                       | Monthly<br>Not specified                                                                                                                       | AST, KDIGO<br>CST/CSN, KHA-CARI, UKKA       |
|                                                    | Examination by primary care physician or dermatologist | Annually <sup>a</sup>                                                                                                                          | AST, CST/CSN, KDIGO, KHA-CARI, UKKA         |
| Cervical                                           | Pelvic examination <sup>b</sup>                        | Every 3 yr<br>Annually                                                                                                                         | KDIGO, UKKA<br>AST, CST/CSN, EBPG           |
|                                                    | Pap smear <sup>b</sup>                                 | Not specified                                                                                                                                  | KHA-CARI                                    |
|                                                    |                                                        | Every 3 yr                                                                                                                                     | KDIGO, UKKA                                 |
|                                                    |                                                        | Annually                                                                                                                                       | AST, CST/CSN, EBPG                          |
| Colorectal                                         | FOBT <sup>c</sup>                                      | Not specified                                                                                                                                  | KHA-CARI                                    |
|                                                    | Sigmoidoscopy <sup>c</sup>                             | Follow general population guidelines (annually)                                                                                                | AST, CST/CSN, KDIGO, UKKA, EBPG, KHA-CARI   |
|                                                    | Colonoscopy <sup>c</sup>                               | Follow general population guidelines (every 5 yr)                                                                                              | AST, CST/CSN, KDIGO                         |
| RCC                                                | Not recommended                                        | Follow general population guidelines (every 10 yr)                                                                                             | AST, CST/CSN, EBPG, KDIGO, UKKA             |
|                                                    | Ultrasound <sup>d</sup>                                | Annually                                                                                                                                       | AST, CST/CSN, KDIGO, UKKA, KHA-CARI         |
| Prostate                                           | Digital rectal examination <sup>e</sup>                | Not specified                                                                                                                                  | EAU                                         |
|                                                    |                                                        | Annually                                                                                                                                       | EBPG                                        |
|                                                    | PSA <sup>e</sup>                                       | Follow general population guidelines <sup>f</sup>                                                                                              | AST, EBPG<br>CST/CSN, KDIGO, KHA-CARI, UKKA |
| Breast                                             | Mammography <sup>g</sup>                               | Annually                                                                                                                                       | AST, EBPG                                   |
|                                                    |                                                        | Follow general population guidelines                                                                                                           | CST/CSN, KDIGO, KHA-CARI, UKKA              |
| Post-transplantation lymphoproliferative disorders | Physical examination                                   | 1–2 yr                                                                                                                                         | AST                                         |
|                                                    | EBV viremia <sup>h</sup>                               | Follow general population guidelines                                                                                                           | CST/CSN, KDIGO, RA, EBPG, KHA-CARI          |
| Hepatocellular carcinoma                           | $\alpha$ -fetoprotein <sup>i</sup>                     | Every 3 mo in the first year, then annually                                                                                                    | AST                                         |
|                                                    |                                                        | Once in the first week after transplantation, monthly for the first 3–6 mo and then every 3 mo until the end of the first post-transplant year | KDIGO, UKKA                                 |
|                                                    |                                                        | Annually                                                                                                                                       | CST/CSN, KDIGO, UKKA                        |
| Lung                                               | Abdominal ultrasound <sup>i</sup>                      | Every 6–12 mo                                                                                                                                  | AST                                         |
|                                                    |                                                        | Annually                                                                                                                                       | CST/CSN, KDIGO, UKKA                        |
|                                                    |                                                        | Every 6–12 mo                                                                                                                                  | AST                                         |
|                                                    |                                                        | Not recommended                                                                                                                                | AST, CST/CSN, EBPG, KDIGO, KHA-CARI, UKKA   |

AST, American Society of Transplantation; CST/CSN, Canadian Society of Transplantation and the Canadian Society of Nephrology; EAU, European Association of Urologists; EBPG, European Best Practice Guidelines; EBV, Epstein-Barr virus; FOBT, fecal occult blood test; KDIGO, Kidney Disease Improving Global Outcomes; KHA-CARI, Kidney Health Australia–Caring for Australasians with Renal Impairment; Pap, Papanicolaou; PSA, prostate-specific antigen; RCC, renal cell carcinoma; UKKA, United Kingdom Kidney Association.

<sup>a</sup>The United Kingdom Kidney Association recommends at least biannual review by a specialist up to 5 years post-transplant and annual review from 5 years onward.

<sup>b</sup>Screening age is variable among guidelines. Kidney Disease Improving Global Outcomes recommends initiation of screening for women within 3 years of onset of sexual activity or age 21 until age 65 years (if previous examinations have no abnormality); American Society of Transplantation recommends for women older than 18 years. The United Kingdom Kidney Association recommends screening every 3 years between age 25 and 49 years and every 5 years between age 50 and 64 years.

<sup>c</sup>American Society of Transplantation and Kidney Disease Improving Global Outcomes recommend annual fecal occult blood test in adults older than 45 years; the United Kingdom Kidney Association recommends every 2 years in adults aged 60–74 years; European Best Practice Guidelines advocates using fecal occult blood test with no specific frequency in adults older than 50 years. High-risk patients might benefit from earlier and more frequent screening.

<sup>d</sup>European Association of Urologists recommends annual screening and the European Best Practice Guidelines recommends native renal cell carcinoma screening using ultrasonography, with variable frequency between 1 and 3 years based on expected growth rate of tumors.

<sup>e</sup>Screening in adults 50 years and older with at least 10-year expected life span.

<sup>f</sup>In Australia and the United Kingdom, there is no national screening program for prostate cancer. The US Preventive Services Task Force recommends screening between age 50 and 68 and the Canadian Urological Association advocates screening in age 50 for most men and age 45 in men at increased risk of prostate cancer.<sup>16,17</sup>

<sup>g</sup>American Society of Transplantation recommends mammography screening at age 50–60; the US Preventive Services Task Force, Australian and Canadian national guidelines recommend mammography every 2 years in women aged 50–74 years, the National Health Service (United Kingdom) recommends screening every 3 years for women aged 50–70 years.<sup>18–21</sup>

<sup>h</sup>Only for high-risk patients (donor seropositive/recipient seronegative).

<sup>i</sup>Only for patients with liver disease.



## RCC

KTRs are at elevated risk of RCC in native kidneys. Current screening recommendations are not consensual. AST and KDIGO guidelines do not recommend screening for RCC.<sup>22,25,37</sup> The European Association of Urologists recommends annual evaluation, and the EBPG recommends native RCC regular screening using ultrasonography, with no specification about frequency.<sup>24,37,38</sup>

RCC screening should be individualized and focus on high-risk subgroups, such as those with a family history of renal cancer, acquired cystic disease, or familial syndrome.<sup>24,37–39</sup>

The optimal screening modality for RCC is yet to be determined. Despite being less expensive and widely available, ultrasound is operator dependent, may not detect early lesions, and its quality is limited by patient-related factors such as obesity. Contrast-enhanced computed tomography (CT) is the gold standard to detect renal mass and might be particularly effective in acquired kidney disease. However, it presents higher cost and risk of radiation exposure and contrast nephropathy.<sup>40</sup>

## Prostate

CST/CSN, KDIGO, KHA-CARI, and UKKA follow general population guidelines.<sup>14,22,27,28</sup> AST and EBPG recommend annual digital rectal examination and prostate-specific antigen testing for male patients older than 50 years and older with at least 10-year expected life span.<sup>24,25</sup> The AST guidelines add that screening at an earlier age might be reasonable for men with individual risk factors such as a family history of prostate cancer.<sup>25</sup>

## Breast

CST/CSN, KDIGO, KHA-CARI, EBPG, and UKKA recommend KTRs to follow general population guidelines.<sup>14,22,28</sup> AST recommends average-risk women to begin screening at age 50 years with mammography every 1–2 years. Screening between 40 and 49 years should be based on individual risk and coexisting comorbidities.<sup>25,41</sup>

## PTLDs

AST recommends history and physical examination for constitutional symptoms and lymphadenopathy/organomegaly every 3 months in the first post-transplant year and annually thereafter.<sup>25</sup> Most transplant programs test for viremia in Epstein-Barr virus (EBV) mismatched KTRs (donor seropositive/recipient seronegative). If rising EBV load is identified in seronegative KTRs, immunosuppression should be reduced to prevent EBV-related diseases and PTLT.<sup>22,25,30,42</sup> Evidence is currently insufficient to support the use of preemptive rituximab or antiviral agents.<sup>43</sup>

EBV viremia should also be evaluated after acute rejection treatment.<sup>22</sup>

## Hepatocellular Carcinoma

AST, CST/CSN, EBPG, and KDIGO recommend that high-risk individuals, including those with cirrhosis, liver disease, or chronic viral infection (such as hepatitis B or hepatitis C viruses), undergo screening using  $\alpha$ -fetoprotein and ultrasound every 6–12 months.<sup>22,23,25,28</sup> CT improves

the ability to characterize small hepatic lesions and diagnose early stage hepatocellular cancer, although to our knowledge, there are no studies evaluating the test performance of CT or magnetic resonance imaging for screening KTRs.<sup>25</sup>

## Lung

Previous trials conducted in the general population, using x ray alone or in combination with sputum cytology, failed to demonstrate any mortality benefits in the screened population.<sup>44</sup> Therefore, AST, CST/CSN, KDIGO, KHA-CARI, and UKKA do not currently recommend lung cancer screening in KTRs.<sup>22,25,27,28</sup> However, more recent evidence suggests that high-risk general population individuals benefit from annual screening.<sup>45</sup> The American Cancer Society and the US Preventive Services Task Force advocate annual screening with low-dose CT in individuals aged 50–80 years with a  $\geq 20$  pack-year history of smoking or current smokers.<sup>46,47</sup> The effectiveness of low-dose CT in high-risk KTRs remains unclear.<sup>25</sup>

## Cancer Treatment

### General Approach of Cancer Treatment in KTRs

In KTRs diagnosed with cancer, treatment options encompass conventional multimodal therapies, including radiotherapy and chemotherapy, combined with alterations in immunosuppressants. Cumulative immunosuppression is the primary factor to determine the risk of cancer in KTRs, and reduction in immunosuppression is considered as the first step to promote antitumor immune response. Nevertheless, there is no consensus regarding the optimal approach for reducing immunosuppressants during cancer treatment in KTRs. The permissible degree and effectiveness of immunosuppressant dose reduction vary depending on the type and stage of the underlying cancer. In addition, this approach needs to be carefully weighed up against the risk of graft rejection. Collaboration among transplant nephrologists and oncologists is imperative to ensure optimal patient care.

Alterations in immunosuppressants could affect the risk of cancer in KTRs. Calcineurin inhibitors (CNIs) can promote cancer progression through several mechanisms, including the production of TGF- $\beta$ ,<sup>48</sup> vascular endothelial growth factor,<sup>49</sup> and activation of the rat sarcoma-rapidly accelerated fibrosarcoma pathway.<sup>50</sup> Several studies have indicated that switching to mammalian target of rapamycin (mTOR) inhibitors reduces the risk of cancer in KTRs, as discussed in the following section. In KTRs, the use of IL-2 receptor antagonists (e.g., basiliximab)<sup>51</sup> is associated with a lower risk of cancer, compared with depleting induction therapies such as antithymoglobulin and muromonab-CD3.<sup>52</sup> Azathioprine use is associated with the increased risk of cancer, especially cutaneous squamous cell carcinoma (CSCC) in KTRs.<sup>53</sup> On the other hand, mycophenolate mofetil may be associated with a lower risk of cancer in KTRs compared with azathioprine.<sup>54</sup> Belatacept, a costimulatory blockade agent, has been routinely used as immunosuppression post-transplant. Initial trials indicated clearly elevated risk of PTLT in patients seronegative for EBV, which led to a black box warning by US Food and Drug Administration.<sup>55,56</sup> However, studies suggested conflicting data on the effect of belatacept on the incidence of post-transplant malignancy. Cochrane review,<sup>57</sup> based on the pooled data from Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial

and BENEFIT-EXTended criteria donors studies, indicated the effect of belatacept on post-transplant malignancy was inconclusive, except for PTLT. For CSCC, an initial single-center study<sup>58</sup> suggested a lower incidence of CSCC in patients treated with belatacept compared with CNIs, but recent studies showed<sup>59,60</sup> an equivocal incidence of CSCC for patients on belatacept compared with others.

The choice and dosing of chemotherapeutic agents should be carefully determined according to allograft function and potential interactions between drugs. Several chemotherapeutic agents have been reported to increase allograft rejection rate. High-dose IL-2 therapy, which has been used to treat metastatic RCC, could increase rejection rate in KTRs through robust effector T-cell activation.<sup>61</sup> Immunomodulatory drugs, such as lenalidomide and pomalidomide used against multiple myeloma, are associated with increased rejection rate because of direct activation of costimulatory signaling (CD28) of T cells.<sup>62,63</sup> Anti-vascular endothelial growth factor therapy can induce thrombotic microangiopathy in the allograft and in native kidneys.<sup>64</sup> The efficacy and tolerability of newer anticancer treatments, exemplified by immune checkpoint inhibitors (ICIs) and cell therapies (notably chimeric antigen receptor T [CAR-T]-cell therapy), have also been investigated in KTRs, and we will discuss these novel treatments in the subsequent sections by reviewing updates in two clinical contexts that highlight cancer management in KTRs: skin cancer and PTLT.

### Skin Cancer in KTRs

Compared with the general population, KTRs are at higher risk of developing skin cancer, especially CSCC and basal cell carcinoma (BCC).<sup>65</sup> The standardized incidence ratio (SIR) of skin cancer in KTRs is approximately 65–250 (CSCC), 10–16 (BCC), 0–8 (melanoma), and 84–500 (Kaposi sarcoma) compared with the age-matched and sex-matched general population.<sup>42</sup> CSCC is the most common type of skin cancer in KTRs followed by BCCs, while this ratio is reversed in the general population. The mortality in KTRs by CSCC and BCC is over 20 times higher than that in the general population.<sup>66</sup> While melanoma is less common than CSCC and BCC, the risk of melanoma remains higher in KTRs than in the general population.<sup>67</sup> Recurrent or multiple site skin cancer is common in KTRs, with a cumulative incidence of secondary skin cancer reaching 59% in 3 years after the first skin cancer.<sup>68</sup>

Choice of immunosuppressants affects the incidence of skin cancer in KTRs. Regimens including mTOR inhibitors such as sirolimus and everolimus rather than CNIs reduce the risk of NMSC and delay the onset in KTRs.<sup>69</sup> In a meta-analysis including 39,039 KTRs, sirolimus use was associated with the reduction in the incidence of NMSC with incidence rate ratio of 0.49 (95% confidence interval [CI], 0.32 to 0.76).<sup>70</sup> This was partly attributable to the withdrawal of cyclosporine because the protective effect of sirolimus was most notable in studies comparing sirolimus against cyclosporine (incidence rate ratio, 0.19; 95% CI, 0.04 to 0.84). Indeed, in a mouse model of ultraviolet-induced skin cancer, larger tumors developed in mice treated with cyclosporine or tacrolimus than in those treated with sirolimus.<sup>71</sup> mTOR inhibitors are effective in secondary prevention of skin cancer in KTRs because conversion from

CNIs to sirolimus decreased the risk of secondary skin cancer in KTRs with previous CSCC.<sup>72</sup> Another study, however, showed a higher mortality rate in patients receiving mTOR inhibitors, which was attributable to increased cardiovascular and infection-related deaths (hazard ratio, 1.43; 95% CI, 1.21 to 1.71).<sup>73</sup> Therefore, switching to mTOR inhibitors should be carefully determined considering risks of cardiovascular events and benefits of cancer prevention. Although evidence is limited, mycophenolate mofetil is also reported to be associated with a lower incidence of skin cancer in SOT recipients compared with azathioprine.<sup>74</sup> Another option to prevent skin cancer in KTRs is the use of chemoprotective agents such as acitretin and nicotinamide, but evidence is scarce.

ICIs have demonstrated favorable outcomes as a novel treatment for various types of malignancies. ICI might improve outcomes in KTRs with skin cancer whereas it could increase the risk of graft rejection. In a multicenter retrospective study of KTRs receiving ICI, 42% of the patients developed acute rejection, a rate significantly higher than that of the non-ICI-treated cohort (5.4%).<sup>75</sup> Despite high rejection rate, patients with CSCC treated with ICI exhibited a significantly longer overall survival (median overall survival of 19.8 versus 10.6 months), suggesting that ICI might be useful in specific subpopulations of KTRs. The optimal immunosuppressant regimen to prevent rejection under ICI use has not yet been confirmed; however, a recent study has shown a promising regimen (Table 3).<sup>76–79</sup> In a phase 1 clinical trial testing cemiplimab in KTRs with advanced CSCC, a combination of mTOR inhibitors and corticosteroids completely avoided graft rejection or loss, with durable antitumor responses.<sup>78</sup> Future study is needed to solidify the data on favorable approaches of immunosuppression under ICI treatment.

### Post-Transplant Lymphoproliferative Disease in KTRs

PTLD is one of the life-threatening complications after transplantation characterized by abnormal lymphoproliferation. Sprangers *et al.* provided a comprehensive summary of PTLT in KTRs in their review article.<sup>80</sup> The lifetime risk of lymphoproliferative disease is 30-fold higher in childhood recipients (SIR, 29.5; 95% CI, 21.9 to 38.8) and eight-fold higher in adult recipients (SIR, 8.4; 95% CI, 7.7 to 9.2) than the age-matched general population.<sup>81</sup> In a retrospective cohort study including pediatric recipients of SOT, the risk of cancer after transplantation, among which PTLT was the most common, was highest in the first year post-transplant (adjusted hazard ratio, 176; 95% CI, 117 to 264) and remained elevated beyond 10 years (adjusted hazard ratio, 10.8; 95% CI, 6.3 to 18.6).<sup>82</sup> PTLT has bimodal presentation peaks—early presentation within 1 year post-transplant (commonly EBV positive) and late presentation later than 10 years post-transplantation (commonly EBV negative; 38%–48%). EBV-associated transformation of B cells plays key roles on the pathogenesis of PTLT, by expression of EBV-related proteins, including membrane proteins (latent membrane protein 1/2A) and nuclear EBV proteins (epstein-barr virus nuclear antigen-2 and EBNA-leader protein), which induce abnormal B-cell growth and proliferation. CNIs and depleting induction therapy (*e.g.*, antithymoglobulin) are associated with increased risk of PTLT.<sup>83,84</sup>

**Table 3. Summary of clinical trials on the optimal immunosuppressant regimen to prevent rejection using immune checkpoint inhibitors**

| Cancer Type           | Any Cancers (Incurable, Metastatic Tumors) | Skin Cancers (Melanoma, CSCC, BCC, MCC)  | CSCC                                     |
|-----------------------|--------------------------------------------|------------------------------------------|------------------------------------------|
| Transplant ICI        | Kidney<br>Nivolumab                        | Kidney<br>Nivolumab ± ipilimumab         | Kidney<br>Cemiplimab                     |
| Immunosuppression     | Keep the same dose                         | Tac (2–5 ng/ml) + Pred 5 mg/d            | mTOR inhibitors + dynamic Pred           |
| No. of patients       | 17                                         | 8                                        | 12                                       |
| Rejection             | 2 (11.7%)                                  | 2 (25%)                                  | 0 (0%)                                   |
| Overall response rate | 53%                                        | 33%                                      | 45%                                      |
| Registry              | ANZCTR<br>CA209-9931SR                     | NCT03816332                              | NCT04339062                              |
| Country               | Australia                                  | US                                       | US                                       |
| Reference             | <i>Lancet Oncol</i> (2022) <sup>76</sup>   | <i>J Clin Oncol</i> (2024) <sup>77</sup> | <i>J Clin Oncol</i> (2024) <sup>78</sup> |

Adapted from Van Meerhaeghe *et al.*<sup>79</sup> Immune checkpoint inhibitor use improves outcomes of kidney transplant recipients with cancer; however, it may increase the risk of graft rejection. Recent clinical trials have shown that optimizing immunosuppressant therapy can mitigate the risk of rejection during immune checkpoint inhibitor use. Combination of mammalian target of rapamycin inhibitors with pulsed-dose corticosteroids prevented rejection in kidney transplant recipients with advanced cutaneous squamous cell carcinoma that were treated with cemiplimab. ANZCTR, Australian New Zealand Clinical Trials Registry; BCC, basal cell carcinoma; BRAF, v-Raf murine sarcoma viral oncogene homolog B1; CSCC, cutaneous squamous cell carcinoma; ICI, immune checkpoint inhibitors; KTR, kidney transplant recipients; MCC, Merkel cell carcinoma; mTOR, mammalian target of rapamycin; Pred, prednisolone; Tac, tacrolimus.

Clinical presentation of PTLD is highly variable, most commonly affecting lymph nodes, gastrointestinal tract, and central nervous system and allograft.<sup>80,85</sup> According to the 2017 World Health Organization criteria, PTLD is categorized into four subtypes: early lesions (plasmacytic hyperplasia and infectious mononucleosis-like lesions), polymorphic PTLD, monomorphic PTLD, and classical Hodgkin lymphoma-like PTLD.<sup>86</sup> In a recently updated version (the fifth edition of the World Health Organization classification), PTLD is classified within a more comprehensive category of immunodeficiency-associated lymphoproliferative disorders, which arise in various contexts of immune dysfunction, rather than being solely based on morphological classification.<sup>80,85,87</sup> The mainstay of treatment for PTLD is reduction in immunosuppression,<sup>88</sup> but a combination with systemic chemotherapy/targeted therapy, radiation or surgery is sometimes necessary. In patients with CD20-positive PTLD, rituximab has become a standard treatment option. In KTRs, rituximab combined with cyclophosphamide, doxorubicin, vincristine, prednisolone chemotherapy reduced the risk of renal graft impairment.<sup>89</sup> The effectiveness of single-agent rituximab has also been reported.<sup>90</sup>

Recently, CAR-T therapy, which has shown substantial efficacy in patients with relapsed/refractory diffuse large B-cell lymphoma,<sup>91,92</sup> has been used in patients with refractory PTLD. In the earlier case series, however, the outcome was unfavorable: Most of the patients failed to show response to CAR-T therapy and developed complications, including cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome.<sup>93,94</sup> Conversely, more recent studies have reported promising results, showing good response to CAR-T therapy while maintaining low rejection rate.<sup>95,96</sup> It seems that an induction therapy with cyclophosphamide before CAR-T therapy following minimum dose of immunosuppression (e.g., prednisone 5–10 mg/d) reduces the risk of rejection while sustaining efficacy of CAR-T therapy. In a multicenter, retrospective analysis of patients with relapsed/refractory PTLD treated by CAR-T therapy, the 2-year progression-free survival, and

overall survival rates were 35% and 58%, respectively, which is similar to the previously reported result of CAR-T therapy on patients with diffuse large B-cell lymphoma.<sup>97</sup> Future studies are necessary to better understand the effectiveness and tolerability of CAR-T therapy in patients with PTLD.

### Future Directions

In the era of precision medicine, pretransplant and post-transplant cancer screening using noninvasive and sensitive molecular diagnostics will become increasingly important. For example, circulating tumor DNA testings have been integrated in clinics to detect molecular residual disease of solid tumors, such as lung cancer,<sup>98,99</sup> and CRC.<sup>100–102</sup> Similarly, minimal/measurable residual disease testing is a next-generation sequence-based diagnostic test to detect a very small number of cancer cells in hematological malignancy, such as multiple myeloma,<sup>103–105</sup> leukemia,<sup>106</sup> and lymphoma.<sup>107</sup> These molecular diagnostics can be useful to ensure a stringent cancer-free condition pretransplant and can be used to monitor post-transplant cancer recurrence. Furthermore, the long-term outcomes of premalignant conditions such as pancreatic neuroendocrine tumor, gastrointestinal stromal tumor, smoldering myeloma/monoclonal gammopathy of undetermined significance and clonal hematopoiesis of indeterminate potential, especially under long-term chronic immunosuppression, will need to be further studied in the future to tailor immunosuppression regimens on the basis of individuals' cancer risks.<sup>108</sup>

### Conclusion

Pretransplant malignancy is increasingly common in kidney transplant candidates and can affect post-transplant outcomes. Although cancer management after transplantation is challenging and relies on a fine balance of immunosuppression reduction, novel therapies and improved outcomes give us some hope. Because KTRs are generally



excluded from cancer-related clinical trials, prospective data from patients with malignancies before and after transplantation, as historically done in the Israel Penn International Transplant Tumor Registry, should ideally be collected, shared, and analyzed to allow the development of standardized screening guideline.<sup>109</sup> We call for further research to evaluate how cancer screening, risk factor prevention, modalities of immunosuppression reduction, and novel cancer therapies affect outcomes.

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