

Prevention and Management of Malignancy in Solid Organ Transplant Patients

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Disclosures

- Consultant, Veloxis Pharmaceuticals (ended October 2020)

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Learning Objectives

- 1 Demonstrate the common pathogenesis of and risk factors for types of malignancy after solid organ transplant.
- 2 Distinguish between the types of malignancy that are of increased risk before and after solid organ transplant.
- 3 Assess preventative strategies for malignancy after transplantation.
- 4 Diagram an overview of immunosuppression management in the setting of malignancy.
- 5 Compare common treatment approaches to common malignancies after transplantation, including non-melanoma skin cancer, post-transplant lymphoproliferative disorder, and Kaposi's sarcoma.

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Abbreviations in this Chapter

- The United Network of Organ Sharing (UNOS)
- Organ Procurement and Transplantation Network (OPTN)
- Hepatocellular carcinoma (HCC)
- Epstein-Barr Virus (EBV)
- Post-transplant lymphoproliferative disorder (PTLD)
- Vascular endothelial growth factor (VEGF)
- Mechanistic target of Rapamycin (mTor) Inhibitor
- Calcineurin inhibitors (CNIs)
- Computed tomography (CT) scan
- Magnetic resonance imaging (MRI)
- Positron emission tomography (PET)
- Lactate dehydrogenase (LDH)
- Complete blood count (CBC)
- Immune globulin (IgG)
- Cytomegalovirus (CMV)
- Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)
- Doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVBP)
- Mechlorethamine, doxorubicin, cyclophosphamide, etoposide, vincristine, prednisone, procarbazine, methotrexate, cytarabine, bleomycin (ProMACE CytoBOM)
- Sun protection factor (SPF)
- Central Nervous System (CNS)

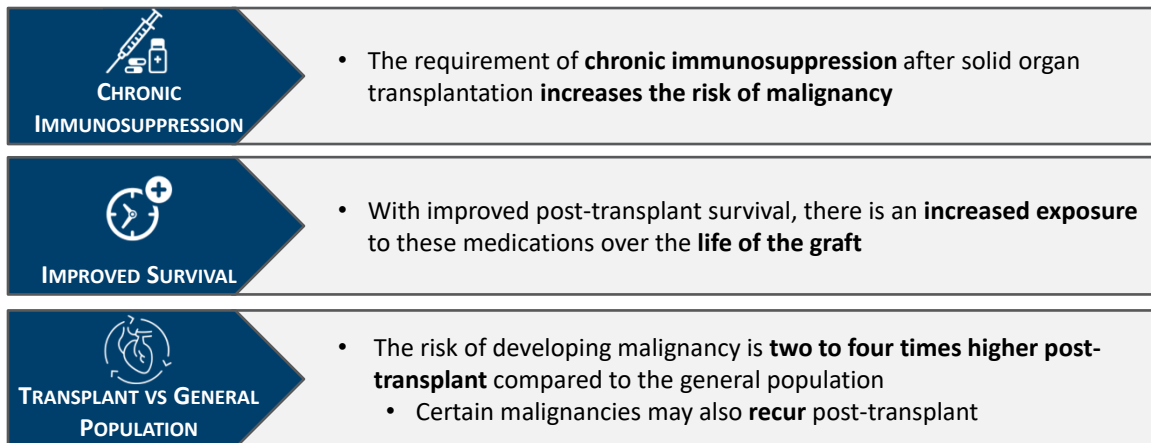
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Background, Pathogenesis, and Risk Factors



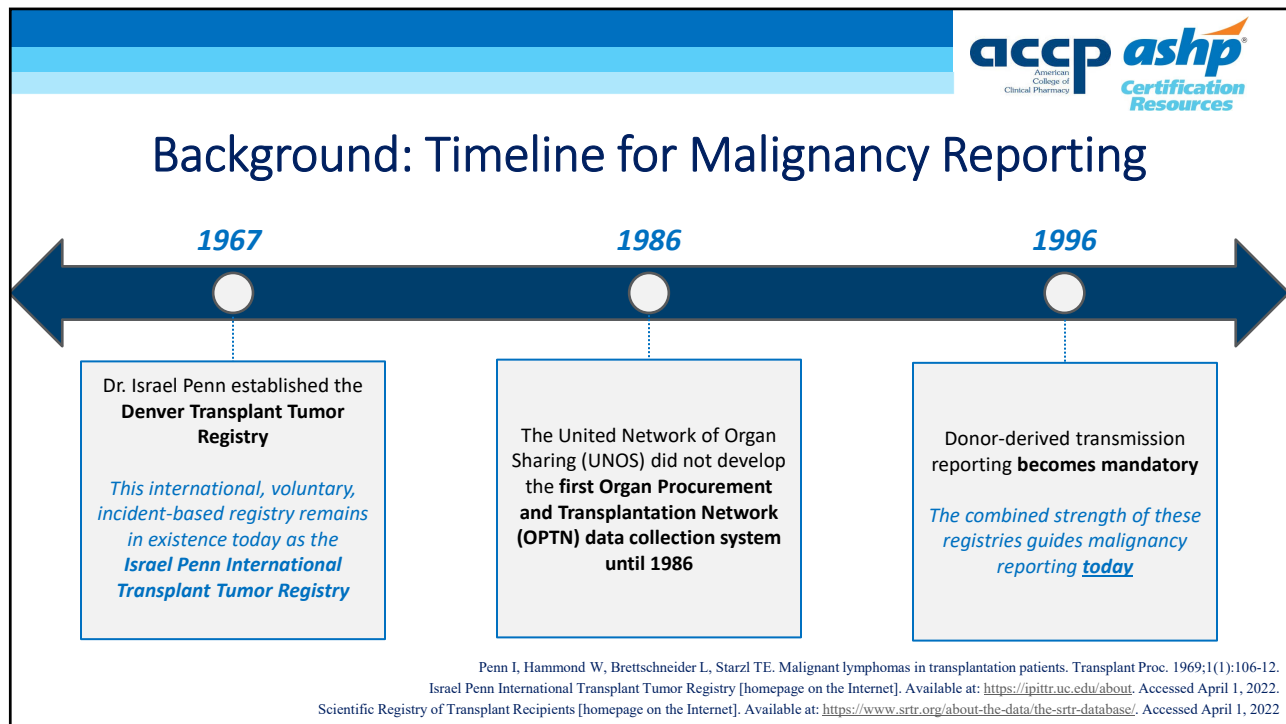
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Background: Malignancy in Solid Organ Transplant

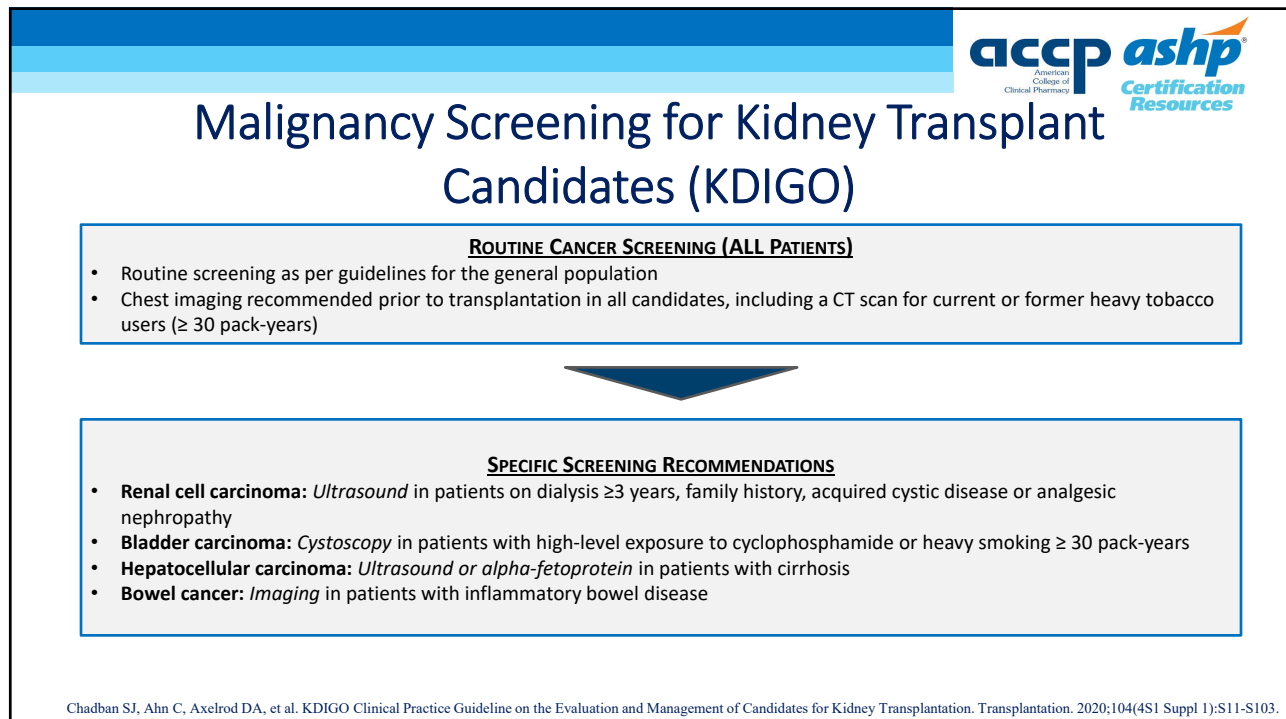


Buell JF, Gross TG, Woodle ES. Malignancy after transplantation. Transplantation. 2005;80(2 Suppl):S254-64.
Engels EA, Pfeiffer RM, Fraumeni JF Jr, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA. 2011;306(17):1891-1901.


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Malignancy Screening for Liver Transplant Candidates (AASLD)

ROUTINE CANCER SCREENING (ALL PATIENTS)

- Age- and sex-appropriate screening per guidelines for the general population




SPECIFIC SCREENING RECOMMENDATIONS

- **Colorectal cancer:** *Colonoscopy* annually in patients with primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD) both before and after transplantation

Martin P, DiMartini A, Feng S, Brown R Jr, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology*. 2014;59(3):1144-1165.


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Malignancy Screening for Heart and Lung Transplant Candidates (ISHLT)

ROUTINE CANCER SCREENING (ALL PATIENTS)

- Age- and sex-appropriate screening per American Cancer Society guidelines



SPECIFIC SCREENING RECOMMENDATIONS

- **Colorectal cancer:** Colonoscopy beginning at age 40 years and continued re-screening every 5 years in lung transplant candidates with cystic fibrosis

Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates--2006. *J Heart Lung Transplant*. 2006;25(9):1024-1042.
 Leard LE, Holm AM, Valapour M, et al. Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2021;40(11):1349-1379.

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Pre-existing Malignancy and Transplant

ACTIVE MALIGNANCY DIAGNOSED

- Patients should generally not be considered active candidates for transplant
- Notable exceptions: indolent/low-grade cancers such as prostate cancer (Gleason score ≤ 6), superficial non-melanoma skin cancer, and incidentally detected renal tumors (≤ 1 cm in diameter)

POSTPONE TRANSPLANT UNTIL SUCCESSFUL TREATMENT AND DISEASE-FREE INTERVAL

- A minimum of 2 years of wait time previously recommended for most cancers, regardless of stage and prognosis
- Time to transplant interval varies based on malignancy and should be patient- and disease-specific (especially if patients receive curative surgery)

MALIGNANCIES WITH A HIGH RATE OF RECURRENCE POST-TRANSPLANT INCLUDE:

- Melanoma
- Invasive urothelial carcinoma
- Multiple myeloma
- Sarcoma
- Malignancies of the transplanted organ

Acuna SA, Huang JW, Scott AL, et al. Cancer Screening Recommendations for Solid Organ Transplant Recipients: A Systematic Review of Clinical Practice Guidelines. Am J Transplant. 2017;17(1):103-114.
 Chadban SJ, Ahn C, Axelrod DA, et al. KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation. Transplantation. 2020;104(4S1 Suppl 1):S11-S103.

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Pre-existing Melanoma and Hematologic Malignancy and Timing of Transplant

Malignancy	Time interval to transplant (with appropriate treatment pretransplantation)
Malignant melanoma <i>In situ</i> Stage 1A-IIIB Stage IIIC, IIID, IV	No wait time, consider 3-month follow-up post-transplant 1-4 years At least 5 years
Lymphoproliferative disease	2-3 years
Multiple myeloma	Stringent complete response for 6-12 months
Amyloidosis	Hematologic response minimum of >6 months
Myelodysplastic syndrome	Discussion between transplant team and hematologist

Al-Adra DP, Hammel L, Roberts J, et al. Preexisting melanoma and hematological malignancies, prognosis, and timing to solid organ transplantation: A consensus expert opinion statement. Am J Transplant. 2021;21(2):475-483.

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Pre-existing Solid Organ Malignancy and Timing of Transplant

Malignancy	Time interval to transplant (with appropriate treatment pretransplantation)
Breast	No wait time for low risk ductal carcinoma in situ and Stage I up to 3-5 years for Stage III
Colorectal	1-2 years for Stage I up to 5 years for Stage IV <i>Possible benefit of liver transplantation in select cases for unresectable colorectal liver metastases in the absence of extrahepatic involvement</i>
Prostate	No wait time for very low risk or if predicted cancer-specific death over 15 years <10%
Renal cell	No wait time for Stage T1a up to 2 years for Stage T2-T4
Bladder	6 months for low-intermediate risk up to 2 years for high risk
Gynecologic	No wait time for low risk up to 5 years for high risk
Lung	3-5 years for Stage I up to 5 years for Stage II-IIIa

Al-Adra DP, Hammel L, Roberts J, et al. Pretransplant solid organ malignancy and organ transplant candidacy: A consensus expert opinion statement. Am J Transplant. 2021;21(2):460-474.

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Donor-derived Malignancy

- Generally, **donors with active malignancy are not accepted** given high risk of transmission
 - Exceptions exist, including:
 - Uterine cancer in situ
 - Low grade non-melanoma skin cancer
 - Select resected renal cell carcinoma
- Transmission is noted to be **0.012%**
 - Donor-transmitted malignancy usually involves the transplanted graft
 - Higher risk in organs with more lymphoid tissue (heart, lung, liver)

Myron Kauffman H, McBride MA, Cherikh WS, Spain PC, Marks WH, Roza AM. Transplant tumor registry: donor related malignancies. Transplantation. 2002;74(3):358-362.
 Green M, Covington S, Taranto S, et al. Donor-derived transmission events in 2013: a report of the Organ Procurement Transplant Network Ad Hoc Disease Transmission Advisory Committee. Transplantation. 2015;99(2):282-287.
 Nalesnik MA, Woodle ES, Dimaio JM, et al. Donor-transmitted malignancies in organ transplantation: assessment of clinical risk. Am J Transplant. 2011;11(6):1140-1147.

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Malignancy After Transplant

Higher Risk Post-transplant	<u>NOT</u> at higher risk*
Skin Cancer	Breast Cancer
Post-transplant Lymphoproliferative Disorder (PTLD)	Lung Cancer
Kaposi's Sarcoma	Prostate Cancer
Renal Carcinoma	
In Situ Carcinoma of the Uterine Cervix	
Hepatobiliary Carcinoma	
Anogenital Carcinoma	

* While not higher risk of development, disease may be more aggressive

- **Colorectal cancer risk data post-transplant is unclear and not classified above**

Engels EA, Pfeiffer RM, Fraumeni JF Jr, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA. 2011;306(17):1891-1901.
 Stallone G, Infante B, Grandaliano G. Management and prevention of post-transplant malignancies in kidney transplant recipients. Clin Kidney J. 2015;8(5):637-644.

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Common Malignancies After Transplant

- The average age at diagnosis of malignancy is **40 years**, and the average latency is **3 to 5 years** after transplantation
 - Compared to non-transplant patients, the standardized incidence ratio is **2.1** for all malignancies
- The most common malignancies after transplant are:

Malignancy Type	Standardized Incidence Ratio	Average time to presentation
Non-melanoma skin cancer	13.9	69 months
Lymphoma	11.1	32 months (highest in the first year)
Kaposi's Sarcoma	61	13-21 months
Malignancy of the Transplanted Organ	Variable	Variable

Engels EA, Pfeiffer RM, Fraumeni JF Jr, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA. 2011;306(17):1891-1901.
 Pedotti P, Cardillo M, Rossini G, et al. Incidence of cancer after kidney transplant: results from the North Italy transplant program. Transplantation. 2003;76(10):1448-1451.

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Risk Factors for Malignancy

QUANTITY AND EXPOSURE TO IMMUNOSUPPRESSION



- **Increased Risk of PTLD**
 - Anti-thymocyte globulin
 - Calcineurin-inhibitors (**dose-dependent**)
- **Not associated with increased risk:**
 - B-cell depleting therapies
 - Mechanistic target of Rapamycin (mTOR) inhibitors
 - Mycophenolate products

EPISODES OF GRAFT REJECTION



- Especially **early episodes** in the first year
 - Likely secondary to the need for **increased immunosuppression** to resolve episode, including **rescue treatment** and **increased maintenance**

VIRAL REPLICATION



- *Hepatitis C virus (HCV)* is associated with **hepatocellular carcinoma (HCC)**
- *Human papillomavirus (HPV)* is associated with **cervical, anogenital, and oropharyngeal cancers**
- *Human herpesvirus-8* is associated with **Kaposi's Sarcoma**
- *Epstein-Barr virus (EBV)* is associated with **PTLD**

Buell JF, Gross TG, Woodle ES. Malignancy after transplantation. *Transplantation*. 2005;80(2 Suppl):S254-64.

Engels EA, Pfeiffer RM, Fraumeni JF Jr, et al. Spectrum of cancer risk among US solid organ transplant recipients. *JAMA*. 2011;306(17):1891-1901.

Krisl JC, Doan VP. Chemotherapy and Transplantation: The Role of Immunosuppression in Malignancy and a Review of Antineoplastic Agents in Solid Organ Transplant Recipients. *Am J Transplant*. 2017;17(8):1974-1991.

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Non-Melanoma Skin Cancer



- About **10%** of transplant recipients have **at least one episode of non-melanoma skin cancer**
 - **70%** have recurrent episodes



- **Exposure to harmful ultraviolet light** is the underlying, preventable etiology of non-melanoma skin cancer
 - **Immunosuppression can increase photosensitivity and skin cancer risk**



- Diagnosed on a **localized tissue biopsy** that is read and evaluated by a pathologist
 - **Basal cell** and **squamous cell carcinoma** are the most common

Coghill AE, Johnson LG, Berg D, Resler AJ, Leca N, Madeleine MM. Immunosuppressive Medications and Squamous Cell Skin Carcinoma: Nested Case-Control Study Within the Skin Cancer after Organ Transplant (SCOT) Cohort. *Am J Transplant*. 2016;16(2):565-573.

Garrett GL, Blanc PD, Boscardin J, et al. Incidence of and Risk Factors for Skin Cancer in Organ Transplant Recipients in the United States. *JAMA Dermatol*. 2017;153(3):296-303.

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Kaposi's Sarcoma

- Nearly **100 times more likely** to occur in transplant recipients versus the general population
- Most common presentation is **limited to the skin**
 - Presents as lesions on legs or mucocutaneous lesions elsewhere
 - Visceral Kaposi's sarcoma has been reported
- Tumor is composed of endothelium-lined vascular spaces and spindle-shaped cell
- Often related to **human herpesvirus-8**
 - Virus upregulates vascular endothelial growth factor (VEGF), a likely growth factor for Kaposi's Sarcoma cells



Kaposi's Sarcoma lesions are most often limited to the skin

Jensen P, Hansen S, Møller B, et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. *J Am Acad Dermatol.* 1999;40(2 Pt 1):177-186.
 Stallone G, Infante B, Grandaliano G. Management and prevention of post-transplant malignancies in kidney transplant recipients. *Clin Kidney J.* 2015;8(5):637-644.

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Post-transplant Lymphoproliferative Disorder (PTLD)

- The EBV genome is found in over 90% of PTLD occurrences in the first-year post-transplant
 - Second peak at **7-10 years post-transplant**, but only half are EBV-related
- Disease presentation can be **variable**:
 - **Nodal** or **extra-nodal**
 - **Localized (often in the allograft)** or **widely disseminated**
 - Akin to **self-limited infection** or **indistinguishable from non-Hodgkin lymphoma**
- Lesions may be localized and progress slowly or may be a fulminant multisystem sepsis-like syndrome
 - Lesions characterized by 2017 World Health Organization Classification

Allen UD, Preiksaitis JK; AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant.* 2019;33(9):e13652.

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PTLD: Pathogenesis







- The pathogenesis of these disorders is complex and most often related to **two unique characteristics of EBV**:
 - **Transforming B lymphocytes**, resulting in proliferation sometimes causing secondary mutations
 - **Protective effect against apoptosis** in cells normally destined for this fate
- Cellular genetic changes are **more complex in EBV-negative PTLD**, and not well understood
- Transmission in transplant recipients can occur through:
 - Transmission from donor (EBV mismatch)
 - Receiving non-leukoreduced blood products

Allen UD, Preiksaitis JK; AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13652.

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Risk Factors for PTLD

Transplant type has a significant impact on PTLD rates:

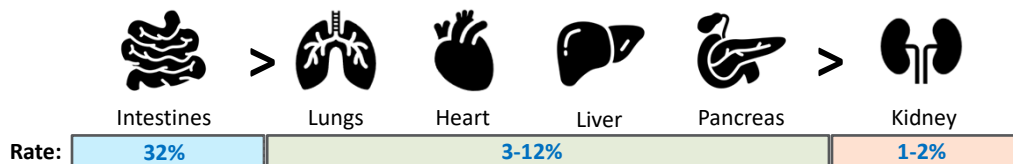
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Intestines		Lungs		Heart		Liver		Pancreas		Kidney
Early PTLD					Late PTLD					
Primary EBV infection					Duration of immunosuppression					
Younger recipient age (pediatrics)					Older recipient age (adults)					
Lymphocyte depleting therapy										

Allen UD, Preiksaitis JK; AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13652.

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Risk of PTLD by Organ and Location

PTLD risk differs by transplant type, likely driven by the amount of lymphoid tissue:



- Early PTLD often manifests in the transplanted organ, especially in the first year
- Late PTLD is often CNS or gastrointestinal

Caillard S, Lelong C, Pessione F, Moulin B; French PTLD Working Group. Post-transplant lymphoproliferative disorders occurring after renal transplantation in adults: report of 230 cases from the French Registry. *Am J Transplant*. 2006;6(11):2735-2742.

Allen UD, Preiksaitis JK; AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019;33(9):e13652.

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Question 1: Among the following organ transplant types, which has the highest risk of developing post-transplant lymphoproliferative disease?

- Answer Choice #1: Liver Transplant
- Answer Choice #2: Pancreas Transplant
- Answer Choice #3: Kidney Transplant
- Answer Choice #4: Lung Transplant
- Learning Objective 1

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 - Answer Choice #2: Pancreas Transplant
 - Answer Choice #3: Kidney Transplant
 - **Answer Choice #4: Lung Transplant**
- Learning Objective 1

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Question 2: Which of the following types of malignancy is more likely to occur after kidney transplantation?

- Answer Choice #1: Breast Cancer
 - Answer Choice #2: Prostate Cancer
 - Answer Choice #3: Non-melanoma skin cancer
 - Answer Choice #4: Lung Cancer
- Learning Objective 2

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Question 2: Which of the following types of malignancy is more likely to occur after kidney transplantation?

- Answer Choice #1: Breast Cancer
 - Answer Choice #2: Prostate Cancer
 - **Answer Choice #3: Non-melanoma skin cancer**
 - Answer Choice #4: Lung Cancer
-
- Learning Objective 2

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Diagnosis, Prevention, and Screening for Malignancy After Transplant

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Screening for Malignancy Post-transplant

Cancer	Recommendation
Breast	<ul style="list-style-type: none"> • Women 40-49 years – Screening per clinician and patient (benefit unclear) • Women 50-69– Annual screening with or without clinical breast exam • Women > 70 – Annual if life expectancy ~ 8 years
Liver	<ul style="list-style-type: none"> • If chronic hepatitis B or C and cirrhosis, serum alpha-fetal protein and liver ultrasound every 6-12 months
PTLD	<ul style="list-style-type: none"> • Complete history and exam every 3 months, especially in 1st transplant year
Anogenital	<ul style="list-style-type: none"> • Annual exam, including pelvic exam and cytologic studies in women
Cervical	<ul style="list-style-type: none"> • Annual pelvic exam for all women > 18 years of age and girls <18 that are sexually active
Skin	<ul style="list-style-type: none"> • Annual Exam (skin, conjunctivae, and oropharyngeal mucosa); patients at higher risk may require more frequent screening (ethnicity, herpes virus, certain geographic areas)

Acuna SA, Huang JW, Scott AL, et al. Cancer Screening Recommendations for Solid Organ Transplant Recipients: A Systematic Review of Clinical Practice Guidelines. Am J Transplant. 2017;17(1):103-114.

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Diagnosis of Malignancy (PTLD)

- Diagnosis (when symptoms are positive)
 - ✓ **Complete blood count (CBC) with differential** (look for bone marrow suppression and lymphopenia)
 - ✓ **Uric acid**
 - ✓ **Lactate dehydrogenase (LDH)**
 - ✓ Immune markers, including **Immune globulin (IgG)**
 - ✓ **EBV serology and replication of virus**
 - ✓ Serum may be helpful, but detecting in tissue helps to confirm EBV positive disease
 - ✓ Reporting of EBV DNA may vary by institution and is more useful within an institution
 - ✓ Studies looking at sensitivity and specificity of higher viral load with likelihood of PTLD are limited
 - ✓ **Imaging**
 - ✓ Computed tomography (CT) scan
 - ✓ Magnetic resonance imaging (MRI)
 - ✓ Positron emission tomography (PET)

Allen UD, Preiksaitis JK; AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13652.

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PTLD: Signs and Symptoms

System	Signs and Symptoms
General	<ul style="list-style-type: none"> • Lymphadenopathy • Fever or night sweats • Malaise and lethargy • Nausea, vomiting, and anorexia (weight loss)
Upper Gastrointestinal	<ul style="list-style-type: none"> • Tonsillar enlargement and inflammation • Bleeding and ulceration
Lower Gastrointestinal	<ul style="list-style-type: none"> • Abdominal pain • Bleeding and ulceration • Bowel perforation • Hepatosplenomegaly
Central Nervous System	<ul style="list-style-type: none"> • Focal neurologic signs (weakness and paralysis) • Mental status changes (confusion, ataxia, aphasia) • Headaches

Allen UD, Preiksaitis JK; AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines for diagnosis and management. *Transplantation*. 2019;103(10):2019-2030. doi:10.1093/txso/tjz055

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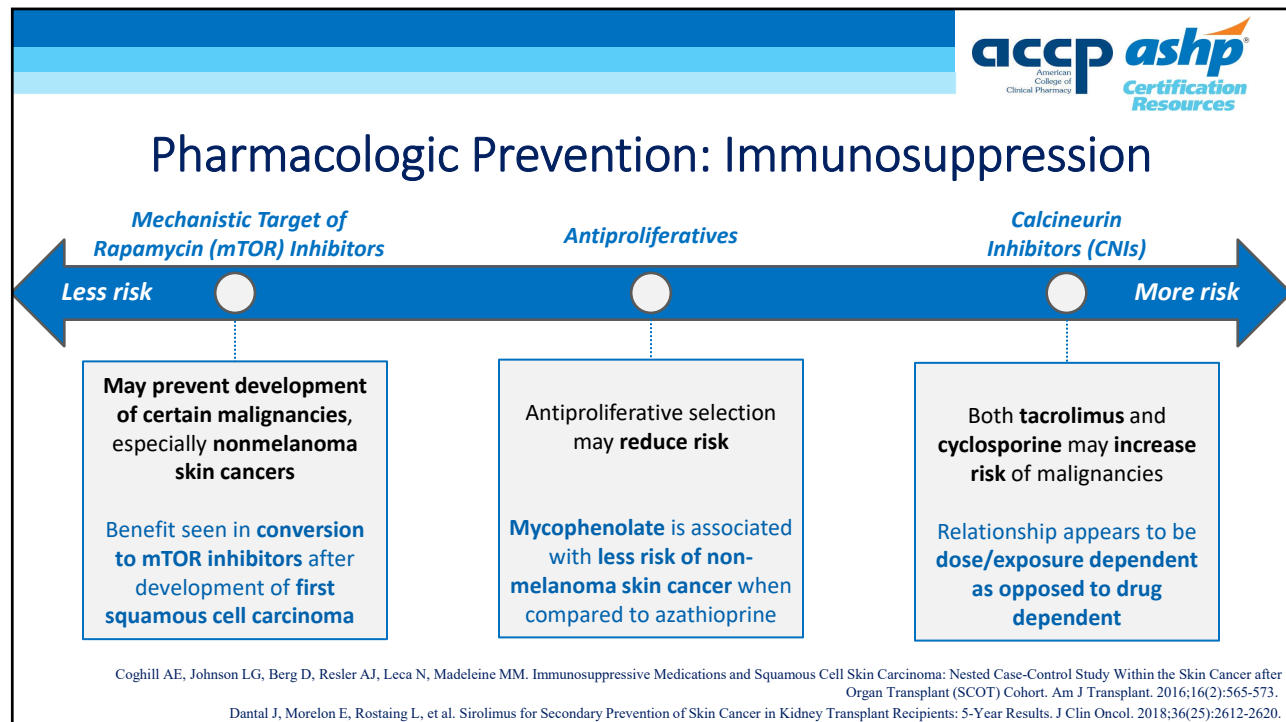
Nonpharmacologic Prevention

- Sun protection is essential to preventing skin cancer
 - Using **daily sunscreen** and wearing **protective clothing**
 - Broad spectrum, waterproof sun protection **factor (SPF) 30+**
 - **Vitamin D supplementation** is an important intervention to maintain bone mineral density after transplant when adhering to sun avoidance
- Avoid environmental exposures
- Avoid sick contacts
 - **Viral exposures may lead to certain types of malignancy**

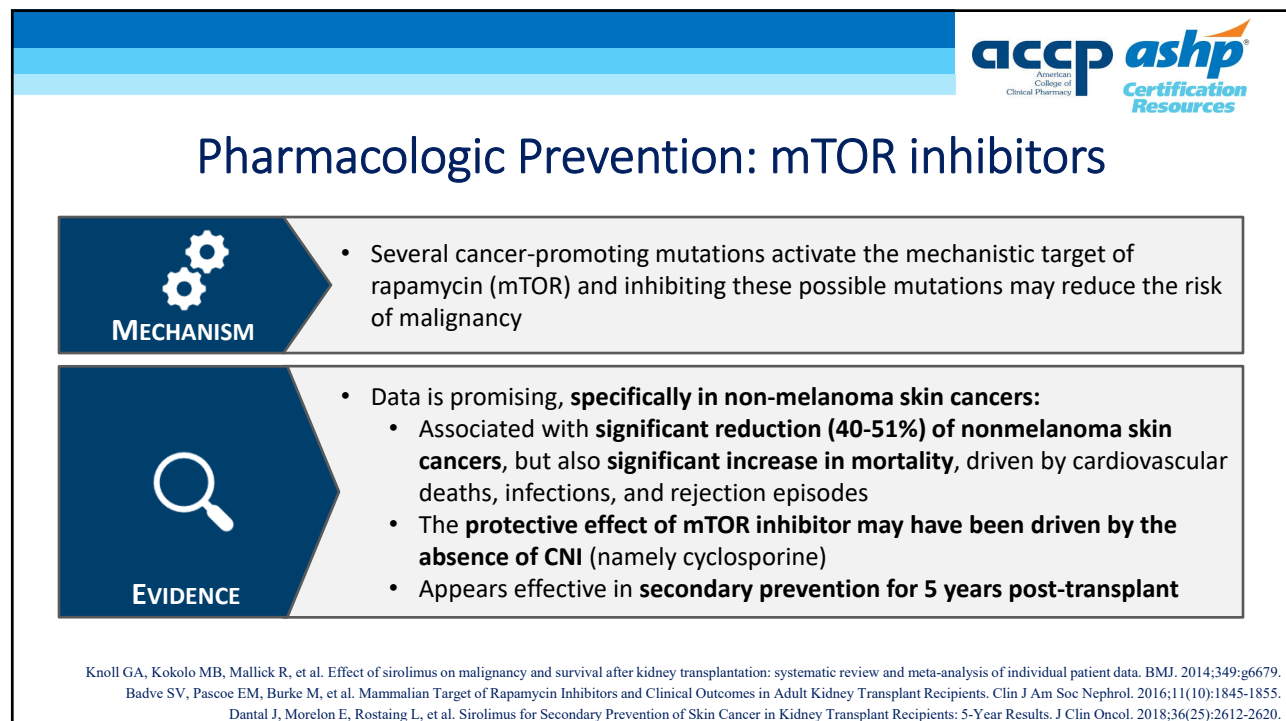


Ulrich C, Degen A, Patel MJ, Stockfleth E. Sunscreens in organ transplant patients. *Nephrol Dial Transplant*. 2008;23(6):1805-8.

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Pharmacologic Prevention: CNI Reduction

MECHANISM

- CNIs may promote the development and progression of malignancy by suppressing anti-tumor immune responses, transforming growth factor β 1 production

EVIDENCE

- **No difference in development of solid tumors between tacrolimus and cyclosporine**
 - Risk of PTLD is **slightly higher with tacrolimus** in the **absence of depleting induction**; risk of **skin cancer higher with cyclosporine**
- CNIs do not appear to increase the risk of skin cancer
- In sirolimus studies, the **protective effect of mTOR inhibitor may have been driven by the absence of CNI**

Stallone G, Infante B, Grandaliano G. Management and prevention of post-transplant malignancies in kidney transplant recipients. Clin Kidney J. 2015;8(5):637-644.
 Badve SV, Pascoe EM, Burke M, et al. Mammalian Target of Rapamycin Inhibitors and Clinical Outcomes in Adult Kidney Transplant Recipients. Clin J Am Soc Nephrol. 2016;11(10):1845-1855.
 Coghill AE, Johnson LG, Berg D, Resler AJ, Leca N, Madeleine MM. Immunosuppressive Medications and Squamous Cell Skin Carcinoma: Nested Case-Control Study Within the Skin Cancer after Organ Transplant (SCOT) Cohort. Am J Transplant. 2016;16(2):565-573.

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Pharmacologic Prevention: Antiproliferative

MECHANISM

- Mechanism: purine analog that that interrupts cell division, reducing synthesis of immune cells, potentially increasing the risk of malignancy

EVIDENCE

- **Nitroimidazole**, a metabolite of azathioprine, can cause **significant photosensitivity**, and is associated with skin cancer
 - Also associated with **metastatic disease** and **high mortality rates**
- Mycophenolate does not carry an increased risk of skin cancers, and often is associated with **lower rates of other malignancies**
 - Newer studies have shown that there might be less risk of skin cancer in regimens with tacrolimus and mycophenolate (allowing **less CNI exposure**)

Stallone G, Infante B, Grandaliano G. Management and prevention of post-transplant malignancies in kidney transplant recipients. Clin Kidney J. 2015;8(5):637-644.
 Coghill AE, Johnson LG, Berg D, Resler AJ, Leca N, Madeleine MM. Immunosuppressive Medications and Squamous Cell Skin Carcinoma: Nested Case-Control Study Within the Skin Cancer after Organ Transplant (SCOT) Cohort. Am J Transplant. 2016;16(2):565-573.

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Pharmacologic Prevention: Other Strategies (PTLD)

1

CHEMOPROPHYLAXIS AGAINST EPSTEIN-BARR VIRUS (EBV)

- Many centers use **acyclovir** or **ganciclovir** in **EBV mismatch** patients despite a **lack of evidence**
- **Universal cytomegalovirus (CMV)** prophylaxis provides some coverage during the **time of donor transmission**
- Treating EBV + living donors has also been studied, but this strategy relies on pre-donation rituximab and two weeks of valganciclovir in the donor

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IMMUNOTHERAPY

- While immunotherapies directly targeting EBV are not available, intravenous immune globulin has been used as a potential therapy at some centers
 - However, **intravenous immune globulin has not shown benefit**; vaccines remain in development

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PRE-EMPTIVE THERAPY

- Some centers monitor the **EBV viral load weekly or biweekly** to consider treatment with acyclovir or ganciclovir
 - No standard for **timing of evaluation** of EBV viral load or **quantitative target** for initiating treatment

Allen UD, Preiksaitis JK; AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13652.

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Question 3: A 57-year-old kidney transplant recipient has a significant family history of colon cancer and is very concerned about developing a malignancy after transplant. Of note, she is one-month post-transplant on a regimen of tacrolimus, mycophenolate, and prednisone. Which of the following strategies would reduce her risk of malignancy?

- Answer Choice #1: Change her mycophenolate to azathioprine immediately
- Answer Choice #2: Change her tacrolimus to cyclosporine at her three-month visit
- Answer Choice #3: Continue indefinite valganciclovir for prevention of EBV
- Answer Choice #4: Continue her current immunosuppression regimen at this time
- Objective 3

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Question 3: A 57-year-old kidney transplant recipient has a significant family history of colon cancer and is very concerned about developing a malignancy after transplant. Of note, she is one-month post-transplant on a regimen of tacrolimus, mycophenolate, and prednisone. Which of the following strategies would reduce her risk of malignancy?

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-
- Objective 3

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Treatment of Common Malignancies

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Treatment: Non-melanoma Skin Cancers

- Treatment of non-melanoma skin cancers
 - Cryotherapy for superficial lesions
 - Deeper lesions require **excisions with clean margins**
 - Typically treatment of choice for low-risk primary tumors
 - Mohs **micrographic surgery** recommended for **high-risk basal cell carcinoma**
 - **Topical 5-fluorouracil, topical imiquimod, photodynamic therapy, or radiation therapy** are other options for **basal cell carcinoma**
 - These are **not effective for squamous cell carcinoma** (surgery preferred)

Work Group; Invited Reviewers, Kim JYS, et al. Guidelines of care for the management of cutaneous squamous cell carcinoma. J Am Acad Dermatol. 2018;78(3):560-578.

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Treatment: Kaposi's Sarcoma

- **Reduction of immunosuppression**
 - Highlighted in the PTLD section as strategies are similar
- **Localized therapies:**
 - Radiation, surgical excision, cryotherapy
 - Topical treatment with **imiquimod 5% cream** or **alitretinoin gel 0.1%**
 - Intralesional chemotherapies
- **Systemic therapy**
 - Limited data to guide preferred systemic therapy for post-transplant Kaposi's sarcoma
 - **Doxorubicin** is considered **treatment of choice** in **acquired immunodeficiency syndrome-associated Kaposi's sarcoma**
 - Limited by **cardiotoxicity**, especially of concern in patients with **pre-existing heart failure** or **heart transplant**
 - Alternatives: **paclitaxel** or combination of **vincristine**, **etoposide**, and **bleomycin**
 - **Pomalidomide**
 - Increased risk of **acute rejection** through immune activation

Lebbe C, Garbe C, Stratigos AJ, et al. Diagnosis and treatment of Kaposi's sarcoma: European consensus-based interdisciplinary guideline (EDF/EADO/EORTC). Eur J Cancer. 2019;114:117-127.
 Chatterjee K, Zhang J, Honbo N, Karliner JS. Doxorubicin cardiomyopathy. Cardiology. 2010;115(2):155-162.

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Treatment of PTLD: Reduction of Immunosuppression

- Variable efficacy; rejection rates **30-40%** after reduction
- AST Guidelines:
 - **Insufficient data** to protocolize reduction or recommend for or against switching to a **mTOR inhibitor**
- British Transplantation Guidelines:
 - **Stop** mycophenolate or azathioprine if possible
 - **Reduce** CNI to lowest tolerated levels (usually by **25-50%** of baseline)
- With any change, allow **2-4 weeks** to look for a response; in studies, it may take up to **6 weeks** to **show improvement**

Allen UD, Preiksaitis JK; AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13652.
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Treatment of PTLD: Surgery and Irradiation

- Used **adjunctively** with **reduction of immunosuppression**
- Long term remission without additional therapy has been observed
 - **Radioimmunotherapy** has shown good response rates but is not widely available



*Early surgery (when possible)
can often contribute to a
positive outcome*



*Targeted radiation and
radiotherapy are likely to
become more prevalent*

Allen UD, Preiksaitis JK; AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13652.

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Treatment of PTLD: Antiviral Agents

- **Not typically effective therapy**
- **Acyclovir versus ganciclovir**
 - **Ganciclovir is 10 times more active against EBV in vitro than acyclovir**
 - **Unclear if there is benefit; should not be used alone, but can be an adjunct +/- intravenous immune globulin**

Allen UD, Preiksaitis JK; AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13652.

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Treatment of PTLD: Rituximab

 EVIDENCE	<ul style="list-style-type: none"> • Not usually effective monotherapy for lymphoma in immunocompetent patients • After reduction of immunosuppression, 4 weekly doses have shown a response rate of 50-60%, <ul style="list-style-type: none"> • Relapse rate of 25% in the first year • An additional 4 doses may increase response rates • About 25% of patients will respond to rituximab alone without additional chemotherapy
 ADVERSE EVENTS	<ul style="list-style-type: none"> • Tumor lysis syndrome • Viral reactivation • Bone marrow suppression • Infusion-related reactions

Allen UD, Preiksaitis JK; AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13652.

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Treatment of PTLD: Chemotherapy

- Consider if CD20+, B cell PTLD after reduction of IS and rituximab alone have failed **OR** for CD20- PTLD
 - All have **high infection** and **mortality rates**; **not 1st line therapy**
- The following have remission rates between **42-92%**
 - **CHOP** (cyclophosphamide, doxorubicin, vincristine, and prednisone)
 - **ACVBP** (doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone)
 - **ProMACE CytoBOM** (mechlorethamine, doxorubicin, etoposide, cyclophosphamide, vincristine, prednisone, procarbazine, methotrexate, cytarabine, bleomycin)

Allen UD, Preiksaitis JK; AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13652.

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Treatment of PTLD: Adoptive Immunotherapy

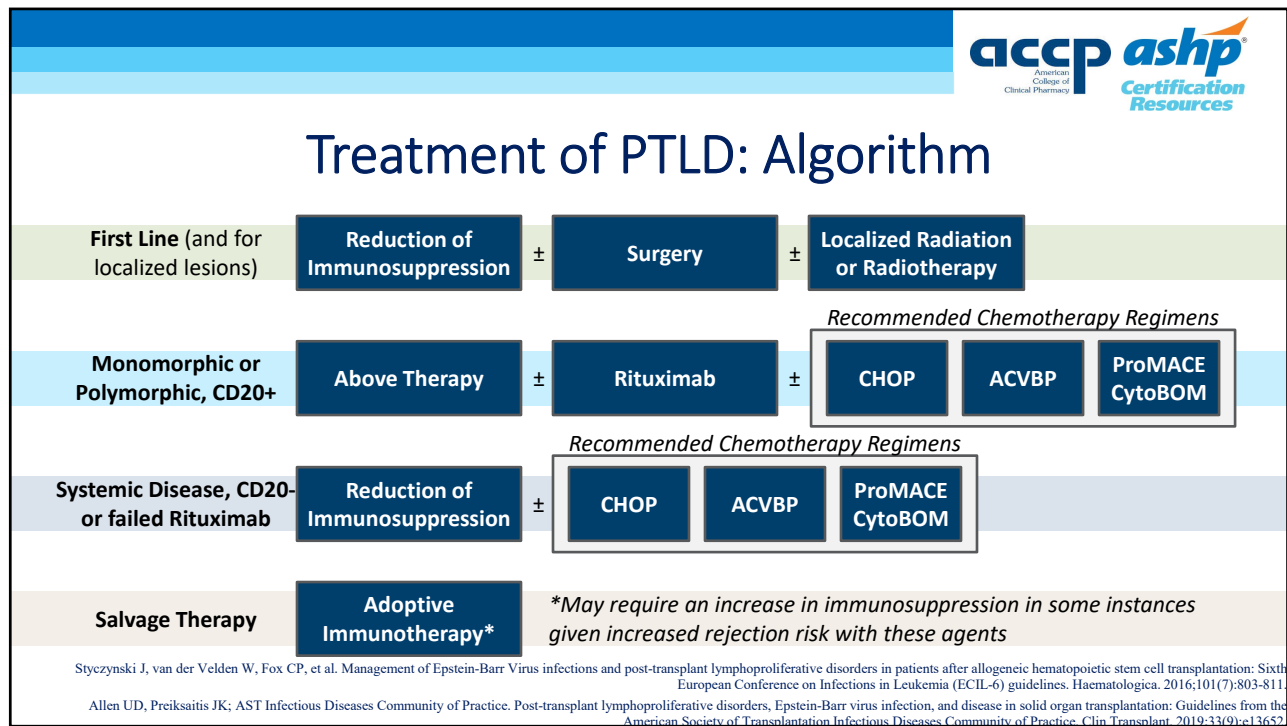
- Chimeric antigen receptor T-cell (CAR-T) therapy is CD19-directed genetically modified autologous or banked third-party, HLA-matched allogeneic T-cell immunotherapy
- Multiple CAR-T therapies are approved for various hematologic malignancies, but most reports of treatment of PTLD in solid organ transplant include **axicabtagene ciloleucel** and **tisagenlecleucel**
- Reserved as **salvage therapy** for patients who failed immunosuppression reduction, rituximab, and chemotherapy
 - **Cost and availability are barriers**
- More data is available in the hematopoietic stem cell transplant population, but a small trial in solid organ transplant showed promising response rates of 52% at 6 months
 - **Better overall remission rate of 80% and 86% five-year survival in a retrospective pediatric study**
- Benefits must be weighed against possible risks of immune activation including **cytokine release syndrome, autoimmune disease progression, and increased risk of rejection**

Styczynski J, van der Velden W, Fox CP, et al. Management of Epstein-Barr Virus infections and post-transplant lymphoproliferative disorders in patients after allogeneic hematopoietic stem cell transplantation: Sixth European Conference on Infections in Leukemia (ECIL-6) guidelines. Haematologica. 2016;101(7):803-811.

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Question 4: Which of the following could be an appropriate adjustment to therapy in a patient several years post-transplant recently diagnosed with PTLD without any history of rejection?

- Answer Choice #1: Change mycophenolate to azathioprine
- Answer Choice #2: Stop mycophenolate immediately
- Answer Choice #3: Change tacrolimus to belatacept
- Answer Choice #4: Add prednisone to the regimen
- Objective 4

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Question 4: Which of the following could be an appropriate adjustment to therapy in a patient several years post-transplant recently diagnosed with PTLD without any history of rejection?

- Answer Choice #1: Change mycophenolate to azathioprine
 - **Answer Choice #2: Stop mycophenolate immediately**
 - Answer Choice #3: Change tacrolimus to belatacept
 - Answer Choice #4: Add prednisone to the regimen
-
- Objective 4

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Question 5: Which of the following is true of CAR-T therapy for PTLD?

- Answer Choice #1: Response rates are often poor, around only 40% of patients achieving remission
 - Answer Choice #2: Since the therapy is HLA matched, rejection episodes are incredibly unlikely with this therapy
 - Answer Choice #3: It is generally avoided because it may increase the risk of rejection or autoimmune disease progression
 - Answer Choice #4: It is often used as a concomitant therapy with reduction of immunosuppression for PTLD
-
- Objective 5

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Question 5: Which of the following is true of CAR-T therapy for PTLD?

- Answer Choice #1: Response rates are often poor, around only 40% of patients achieving remission
- Answer Choice #2: Since the therapy is HLA matched, rejection episodes are incredibly unlikely with this therapy
- **Answer Choice #3: It is generally avoided because it may increase the risk of rejection or autoimmune disease progression**
- Answer Choice #4: It is often used as a concomitant therapy with reduction of immunosuppression for PTLD
- Objective 5

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Challenges in Managing Malignancy Before and After Transplant

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Treatment of PTLD: CNS Management

- **Highest treatment failure** rate (compared to other locations)
 - Multimodal approach with **antiviral** therapy, **immunotherapy**, **radiation** therapy, and **chemotherapy** often used
- Role for **high dose methotrexate** and **cytarabine** with **thiotepa** and **rituximab** (extrapolated from immunocompetent patients)
 - Methotrexate has excellent CNS penetration
 - Significant **renal** and **hepatic toxicity**



Allen UD, Preiksaitis JK; AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13652

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Malignancy and Retransplantation

- PTLD and retransplantation
 - Recommend **complete remission** for a “**significant interval**” (no specific time noted in the guidelines)
 - Relisting should only be done after **consultation with an oncologist**
- Other malignancies and retransplantation
 - Retransplantation is typically an option after **2-5 years of remission**, though earlier for certain malignancies (**consultation with oncologist**)
- Avoid **lymphocyte-depleting** induction
 - **Basiliximab** or **steroid-only** induction preferred

Allen UD, Preiksaitis JK; AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13652.

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PTLD Treatment: Pediatrics

- **Less potent regimens** may be **more effective** in pediatrics
 - Rituximab is commonly used early in the treatment algorithm
 - Less toxic regimens, especially **cyclophosphamide + prednisone**, are often used if rituximab fails
 - Remission rate ~ **70%**

Allen UD, Preiksaitis JK; AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13652.

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Other Immunotherapy

- Cancer cells can **evade normal immune surveillance** and result in tumor growth
- **Immunotherapy** targets these escaped pathways to activate and proliferate T-cells and cause anti-tumor immune responses
 - **Immune checkpoint inhibitors:**
 - Ipilimumab, pembrolizumab, nivolumab, cemiplimab, atezolizumab, avelumab, durvalumab, relatlimab
 - Approved for treatment of 19 different cancers
 - **Immunomodulatory drugs:**
 - Thalidomide, lenalidomide, pomalidomide
 - Approved for treatment of multiple myeloma and Kaposi's sarcoma

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 Holstein SA, McCarthy PL. Immunomodulatory Drugs in Multiple Myeloma: Mechanisms of Action and Clinical Experience. Drugs. 2017;77(5):505-520.

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Immunotherapy and Risk of Rejection

- The anti-tumor immune response of immunotherapy can activate T-cells targeting the **transplanted organ** resulting in **acute cellular rejection**
- The safety of these agents before and after solid organ transplant is limited, with case reports of **severe rejection** in kidney, liver, and heart transplant patients
- Patients may also present for evaluation for transplant on immunotherapy, particularly for history of multiple myeloma or hepatocellular carcinoma
 - The optimal time off immunotherapy prior to transplant is not established to minimize rejection risk
- Any anti-tumor benefit must be **carefully** weighed against risk of rejection

Huskey JL, Heilman RL, Khamash H, et al. Kidney Transplant in the Era of Modern Therapy for Multiple Myeloma. *Transplantation*. 2018;102(12):1994-2001.
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Key Takeaways

- The **need for immunosuppression** after solid organ transplant increases the **risk of several malignancies**, especially:
 - Non-melanoma skin cancer
 - Post-transplant lymphoproliferative disorder (PTLD)
 - Kaposi's sarcoma
 - Cancers of the transplant organ
- First-line treatment includes strategies that **reduce immunosuppression**:
 - Reducing CNJ exposure
 - Stopping antiproliferatives
 - Introducing mTOR inhibitors
- Chemotherapy is often a **salvage option** for transplant recipients that fail other therapies (including rituximab) as it is poorly tolerated
- **Immunotherapy** may increase the risk of rejection and should be used with caution in solid organ transplant patients

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Prevention and Management of Malignancy in Solid Organ Transplant Patients

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