Chemotherapy, Targeted Therapy, Immunotherapy, Oh My! Oncology Implications in Solid Organ Transplant Pharmacology

Heidi Brink, PharmD, BCPS, BCCP
Department of Pharmacy

University of Nebraska Medical Center

Disclosures

Heidi Brink has served on an advisory board for Merck.

Objectives

Compare the incidence of cancer in the solid organ transplant and general population.

Review treatment modalities of the most common cancers in solid organ transplant.

Assess the implication of chemotherapy/immunotherapy agents in the immunosuppressed population.

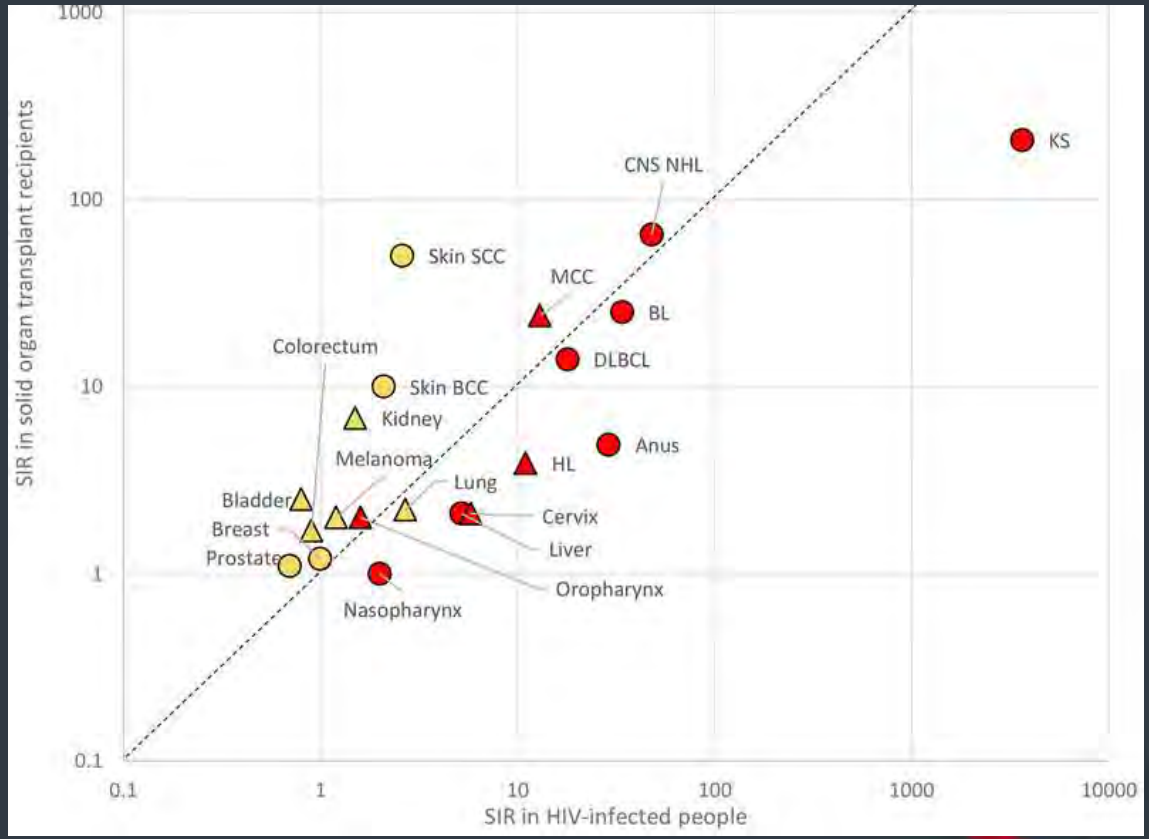
Top 10 Cancer Types – New Cases in 2024

Prostate	299,010	29%
Lung & bronchus	116,310	11%
Colon & rectum	81,540	8%
Urinary bladder	63,070	6%
Melanoma (skin)	59,170	6%
Kidney & renal pelvis	52,380	5%
Non-Hodgkin lymphoma	44,590	4%
Oral cavity & pharynx	41,510	4%
Leukemia	36,450	4%
Pancreas	34,530	3%

Breast	310,720	32%
Lung & Bronchus	118, 270	12%
Colon & rectum	71,270	7%
Uterine corpus	64,880	7%
Melanoma (skin)	41,470	4%
Non-Hodgkin lymphoma	41,470	4%
Pancreas	31,910	3%
Thyroid	31,520	3%
Kidney & renal pelvis	29,230	3%
Leukemia	26,320	3%

Standardized Incidence Ration (SIR) in SOT

- Virus-related cancers
- Virus-unrelated cancers
- Cancers for which checkpoint inhibitor therapy has been approved

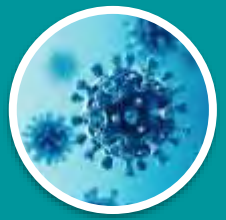


Engles. AJT 2019; 19:3223-3232

Cancer Risk

Patient

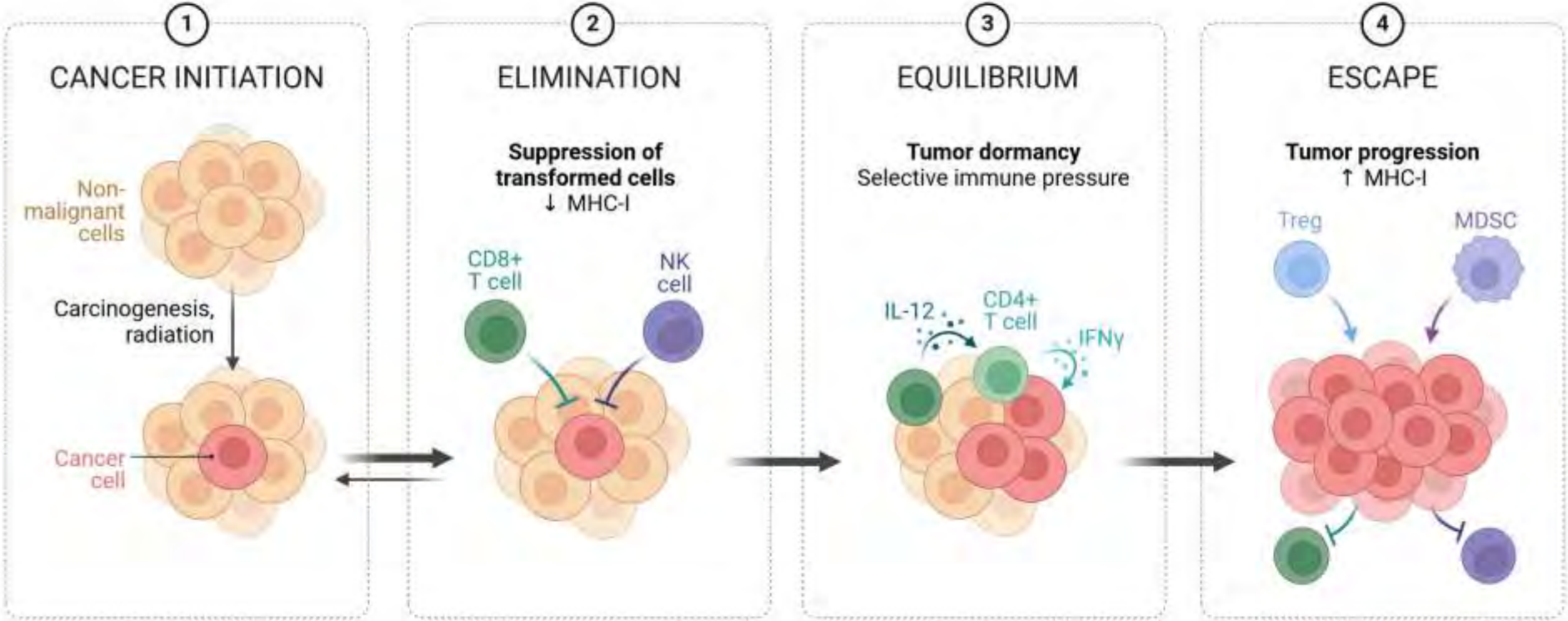
Organ



Oncologic Viruses

Immunosuppression

CANCER IMMUNOEDITING



Drug	Impact on immune cells	Oncologic Risk
Polyclonal lymphocyte depleting agent	• Interferes with T-cells, B-cells, NK, and DC functions	• Increased risk of PTLD

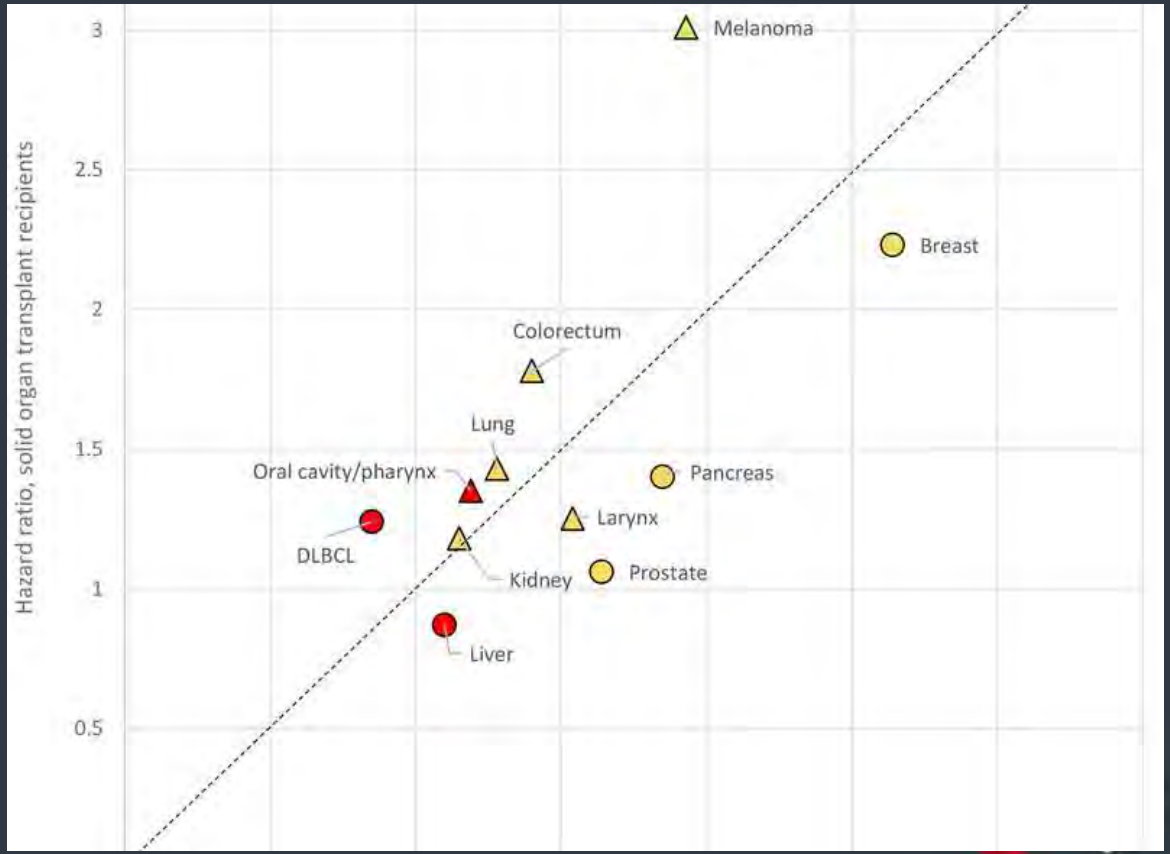
Alemtuzumab	• Significantly depletes B and T cells	• Increased risk for:
		  • NHL (2.5-fold)
		  • Colorectal (2.5-fold)
		  • Thyroid (3-fold)
		• Mixed results with PTLD

Azathioprine	• Interfere with T-cells stimulation and proliferation • Selectively depletes memory T-cells (CD4+) • Photosensitizes skin	• Linked to late SCC and myelodysplastic syndrome
Mycophenolate Mofetil	• Antiproliferative and antioncogenic potential • Significant reduction of CD107 expression in NK cells • Significant reduction in INF-γ production by NK cells • Down-regulation of co-stimulatory and adhesion molecules human monocyte-derived DC	• Protective. • Reduces risk of PTLD
Cyclosporine A / Tacrolimus	• **Downregulate T-bet dependent immunosurveillance** • Inhibits antigen presentation by DC • Prevents naïve T cell differentiation • Impairs elimination of oncogenic viruses • Upregulates growth-promoting and pro-angiogenetic cytokines (TGF-β, IL-10, VEGF)	• Suppress immune response against melanoma
mTOR inhibitors	• Reduces ability of B cells to undergo EBV lytic cycle replication • Promotion of CD8+ central memory T cells • Antioncogenic and antiproliferative role	• Protective.

Cangemi, et al. Front. Onncol. 2019; 9.

Prognosis of Cancers Post-Transplant

- Virus-related cancers
- Virus-unrelated cancers
- Cancers for which checkpoint inhibitor therapy has been approved



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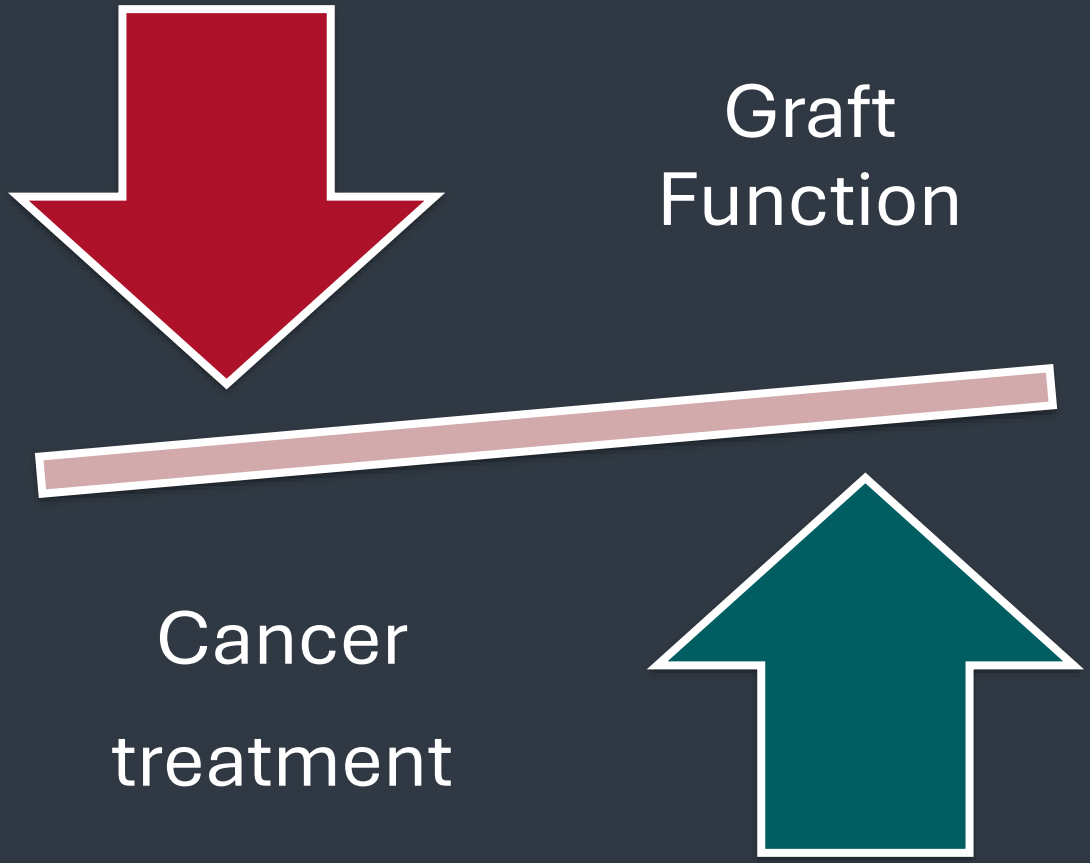

Graft
Function
Cancer
treatment

Patient Case

Linda

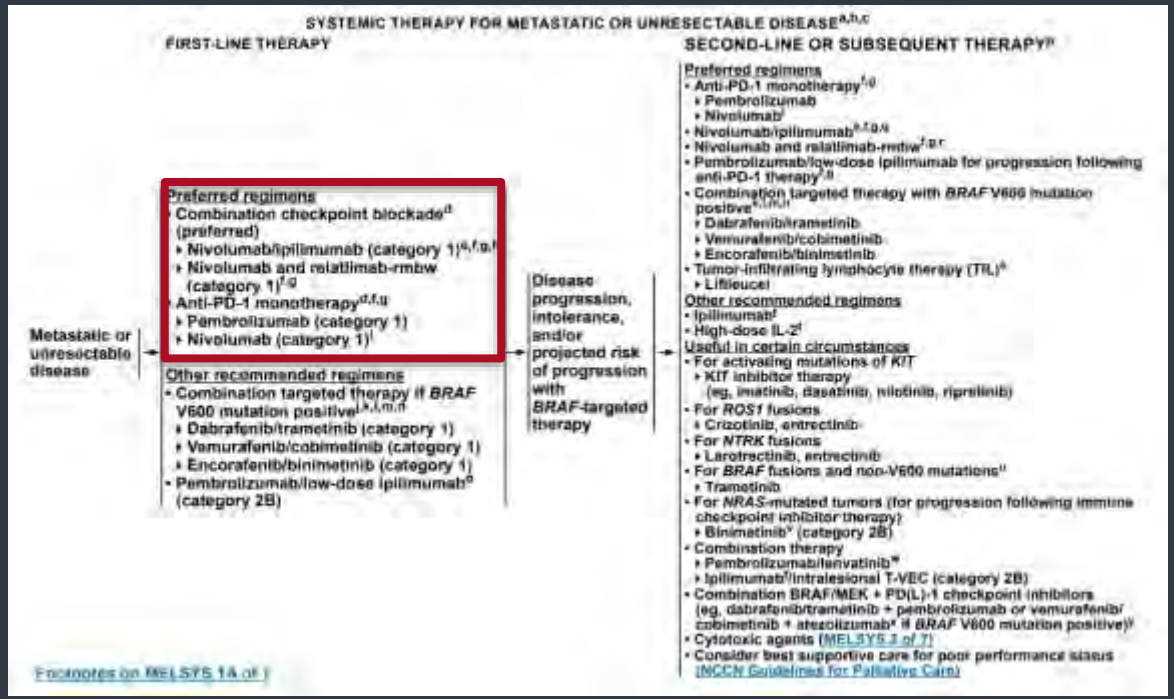
- BOLT 2019
- CLAD Stage 3
- New Diagnosis: Stage 4 Melanoma

<u>Pertinent Medications:</u>

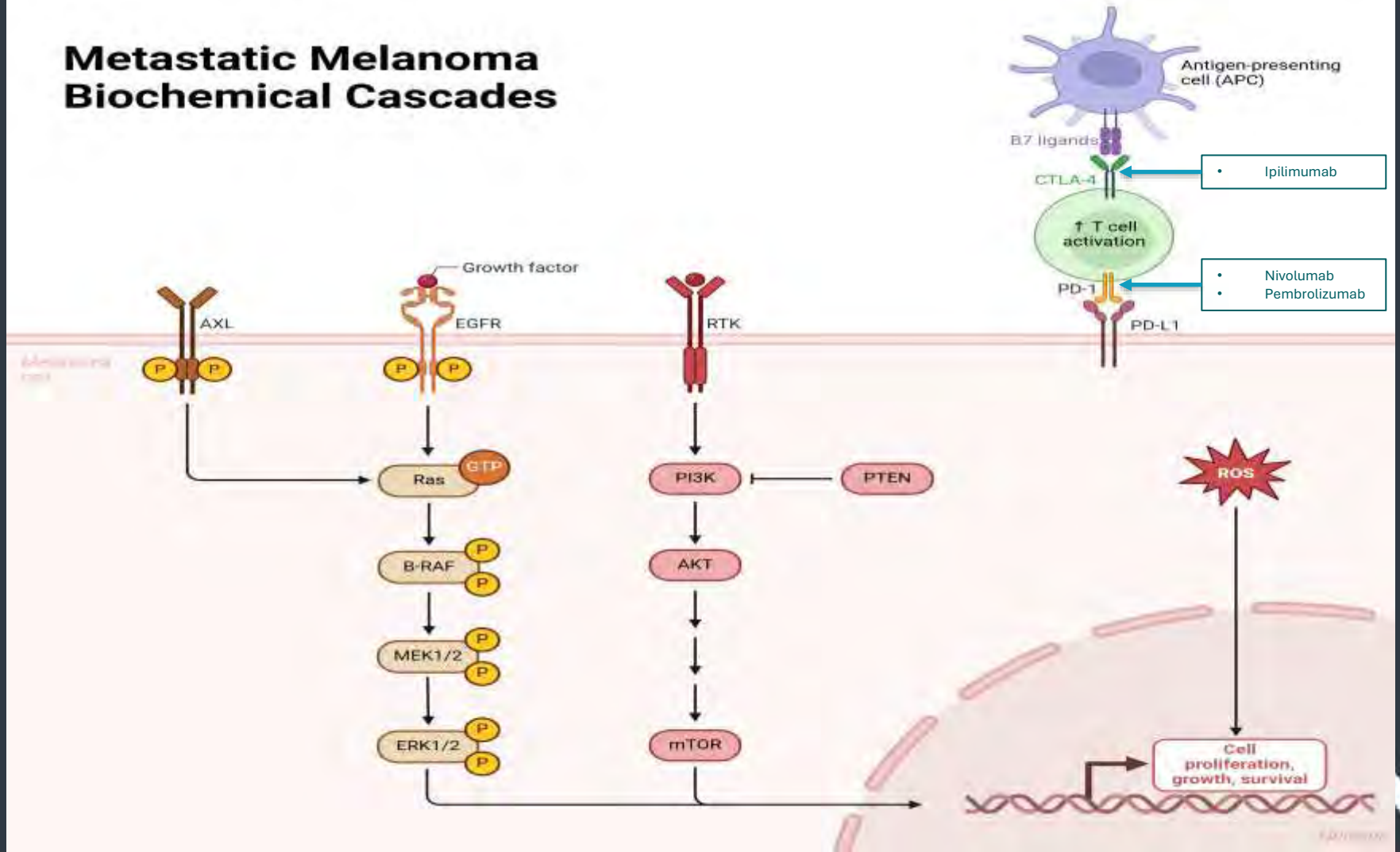
- Tacrolimus (FK goal 6-8)
- MMF 1000mg BID
- Prednisone 5mg

NCCN – Guidelines for Melanoma (2025)

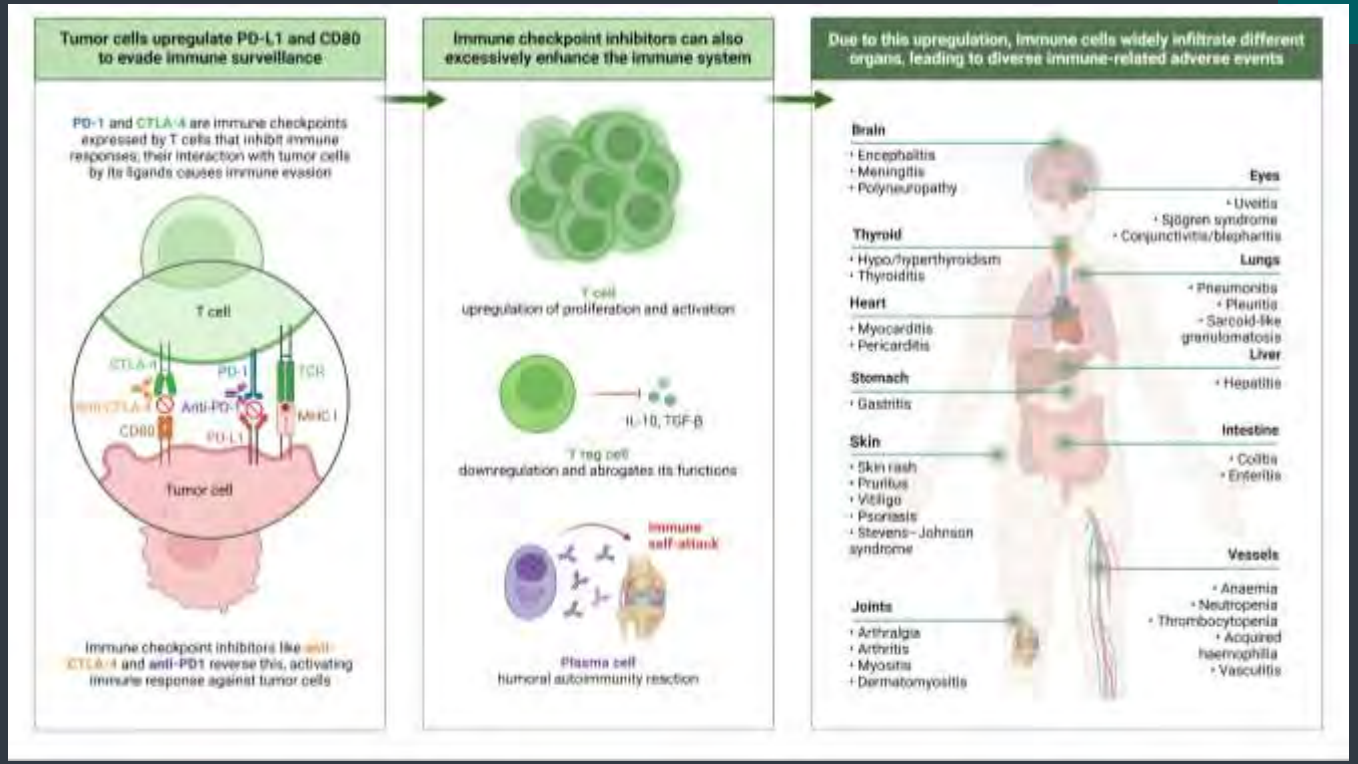
Systemic therapy for metastatic or unresectable disease



Metastatic Melanoma Biochemical Cascades



Checkpoint Inhibitors



Checkpoint Inhibitors in SOT

Efficacy and tolerance of immune checkpoint inhibitors in transplant patients with cancer: A systemic review

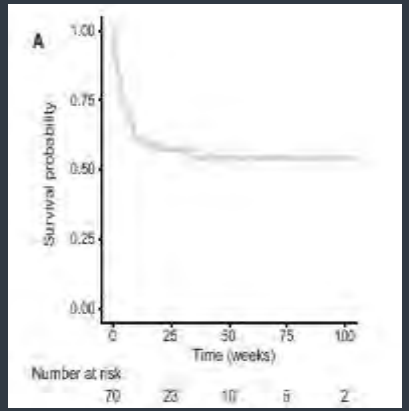
D'Izarny-Gargas. Am J Transplant. 2020

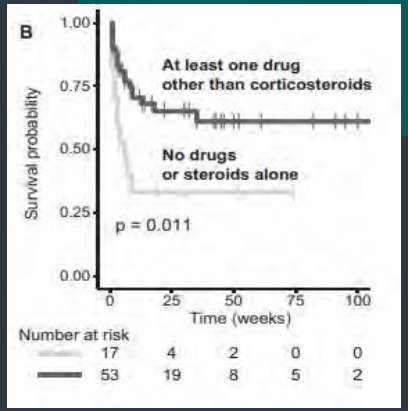
- 48 Original Articles
- SOT:
  - Kidney (53 cases)
  - Liver (24 cases)
  - Heart (6 cases)
- Cancers:
  - Melanoma (46 cases)
  - Hepatocellular carcinoma (12 cases)
  - Squamous cell carcinoma (10 cases)
- Treatment:
  - 73%: PD-1/PD-L1 therapy
    - 31 cases: Nivolumab
    - 29 cases: Pembrolizumab
  - 15.7%: CTLA-4 antibody (ipilimumab)
  - 10.8%: Combination therapy
- Mean time from transplant
  - 9.3 years

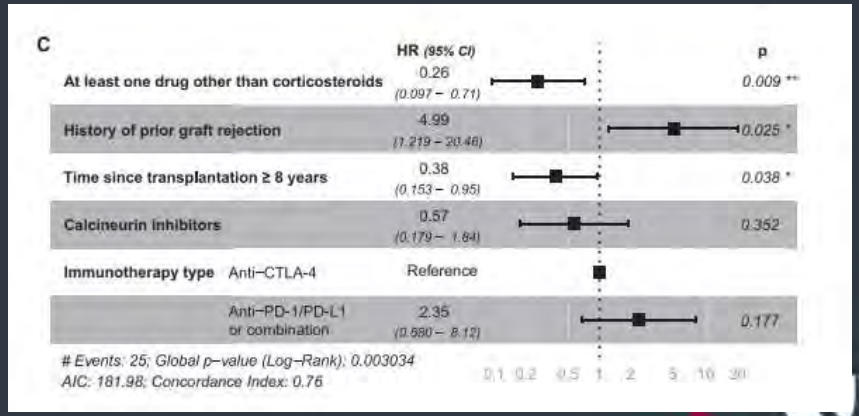
D'Izarny-Gargas. Am J Transplant. 2020;20:2457-2465

Checkpoint Inhibitors in SOT

	Kidney	Liver	Heart
Allograft rejection	43.4% (23/53)	37.5% (9/24)	16.7% (1/6)
Mortality	52.8% (28/53)	66.7% (16/27)	66.7% (4/6)







D'Izarny-Gargas. Am J Transplant. 2020;20:2457-2465

Immune Checkpoint inhibitors in kidney transplant patients: a multi-center study

Retrospective cohort study (2010-2020)

International muti-center (23 institutions)

Kidney transplant recipients (n=69)

ICI therapy for advanced cancer (aPD-1, aPD-L1, aCTLA-4)

Efficacy

- Tumor response to ICI therapy (Complete response + partial response)
  - SCC (n=24): 36%
  - Melanoma (n=22): 40%

Safety

- Acute Rejection: 42%
- Time to rejection: 24 days
- Graft loss: 65% of rejection

Conclusion

- ICI are associated with high acute rejection rates
- ICI result in reasonable tumor response

Murakami et al. Kidney Int. 2021 July;100(1):196-205

Checkpoint Inhibitors in SOT

	Findings	Consideration
IS Reduction	• Higher number of immunosuppression agents used at the time of ICI initiation is associated with lower risk of acute rejection • Cancer outcomes did not differ when stratified to the number of immunosuppression agents	• Suggests IS reduction may not be beneficial in the setting of ICI therapy
Steroids	• Peri-infusion prednisone mini-pulses followed by maintenance prednisone has been reported to be effective in the prevention of acute rejection	• Prednisone may offer potential IS modifications • Prednisone 40mg daily x 3 days (starting day 1), 20mg for 3 days, then 10mg for the rest of the cycle
mTORi	• Rejection-free graft survival and overall graft survival were longer with mTORi-treated patients	• Consider mTORi conversion to reduce rejection and help control cancer

Kawashima, et al. Korean J Transplant. 2022;36(2):82-98

Patient Case

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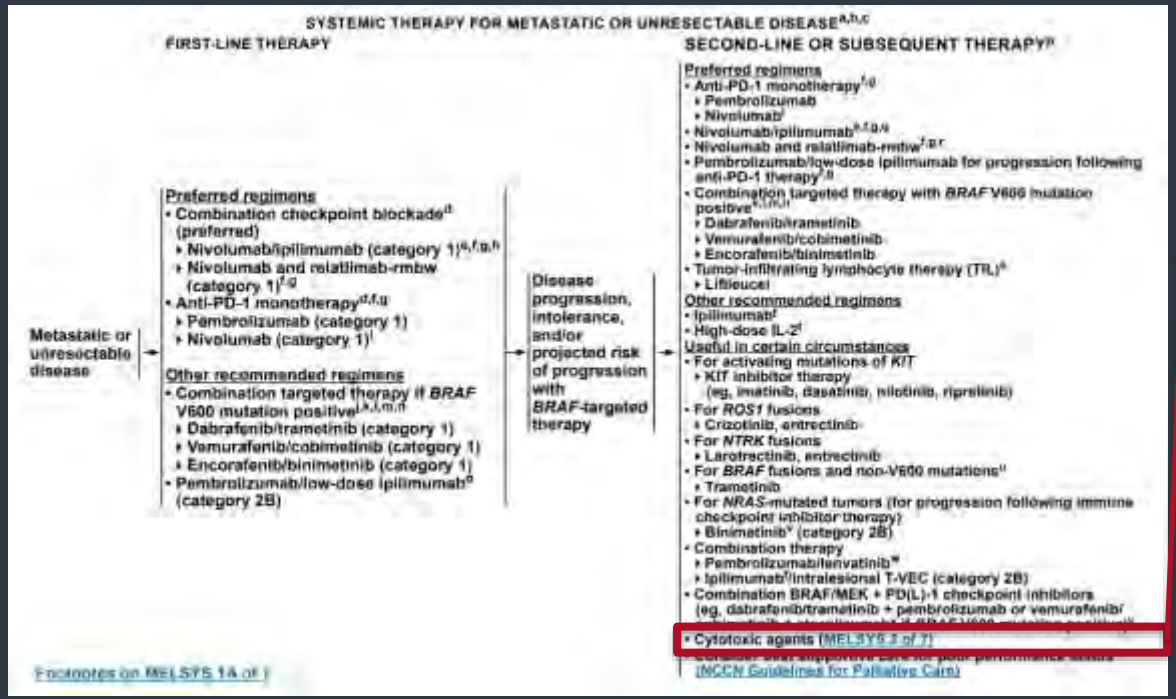
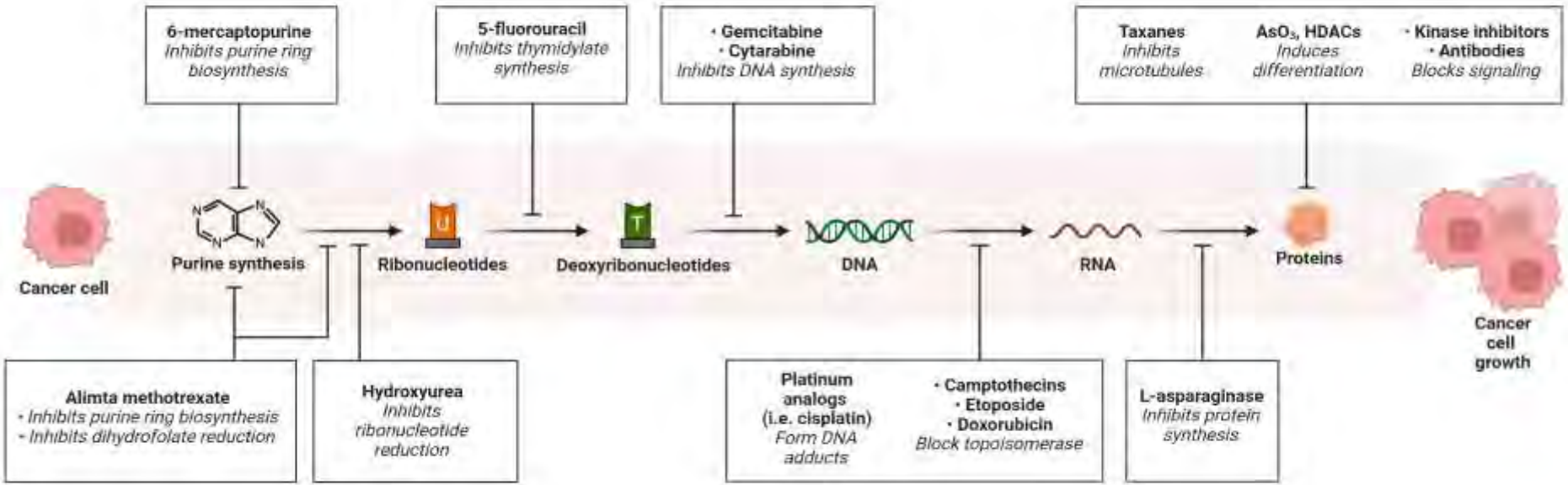


- Dacarbazine
- Temozolomide
- Paclitaxel
- Albumin-bound paclitaxel
- Paclitaxel/carboplatin
- Cisplatin/vinblastine/ dacarbazine (CVD)

Basic Methods of Chemotherapy



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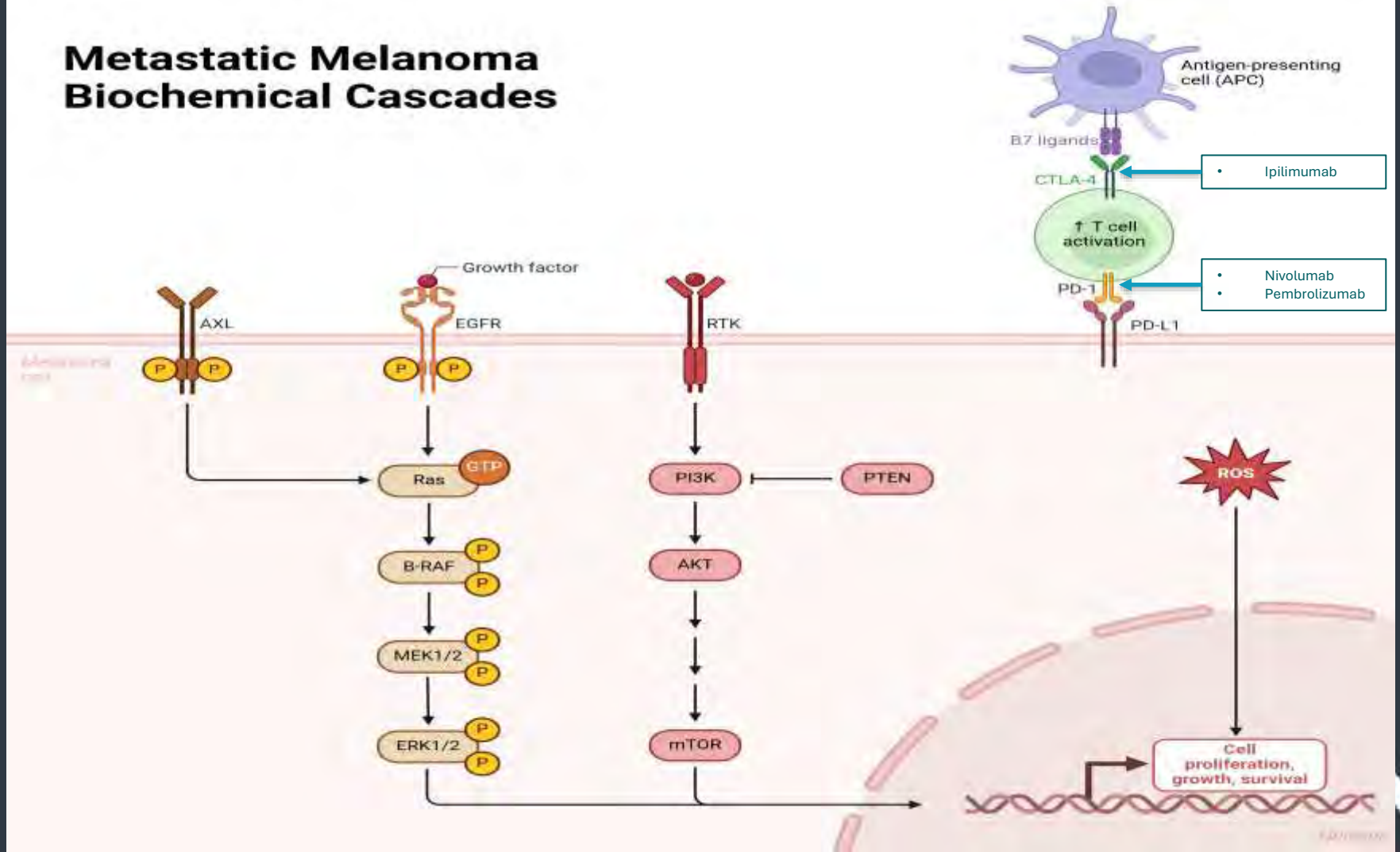


Cytotoxic Therapy

Graft toxicity

Drug-Drug Interactions

Pharmacodynamics

Graft Toxicity

Renal

- Cellular Toxicity:
  - Anthracyclines
    - Doxorubicin
  - Taxane

Cardiac

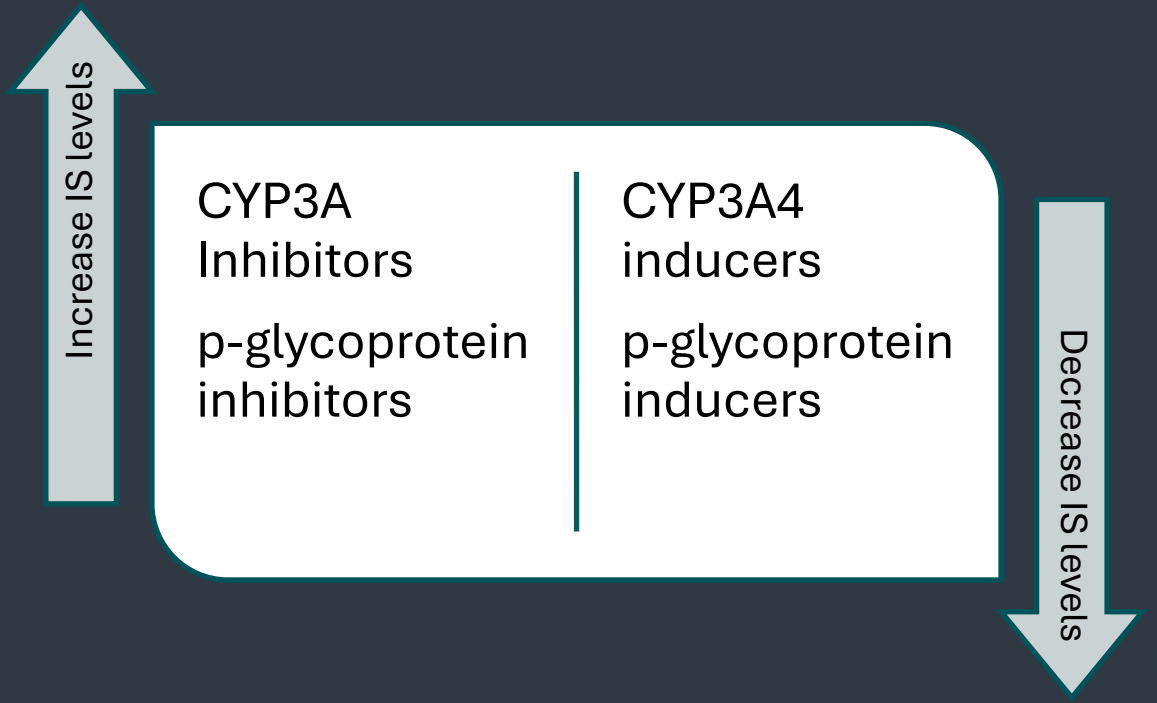
- Cardiotoxic effects
  - Anthracyclines
  - EGFR inhibitors
  - Vinca Alkaloids
  - BRAF-MEK inhibitors

Hepatic

- Highest hepatotoxic potential
  - BRAF-MEK inhibitors
  - ALK inhibitors
  - EGFR inhibitors

Maggiore, et al. Transplant International 2021; 34: 2442-2458

Drug-Drug Interactions



Modifications to Immunosuppression

Guideline Recommendations

Guidelines	Recommendation	Class / Level
KDIGO	We suggest consideration be given to reducing IS medications for KTRs with cancer	2C
	For patients with Kaposi sarcoma, we suggest using mTORi along with a reduction in overall IS	2C
ISHLT	There is ***no evidence*** to support a reduction in immunosuppression in patients with solid tumors unrelated to the lymphoid system. Maintenance immunosuppression should be continued unless there are specific reasons to reduce certain drugs, such as reduction of bone marrow suppressive agents if leucopenia occurs.	1C
AASLD	N/A	N/A

Management of immunosuppression in kidney transplant recipients who develop malignancy

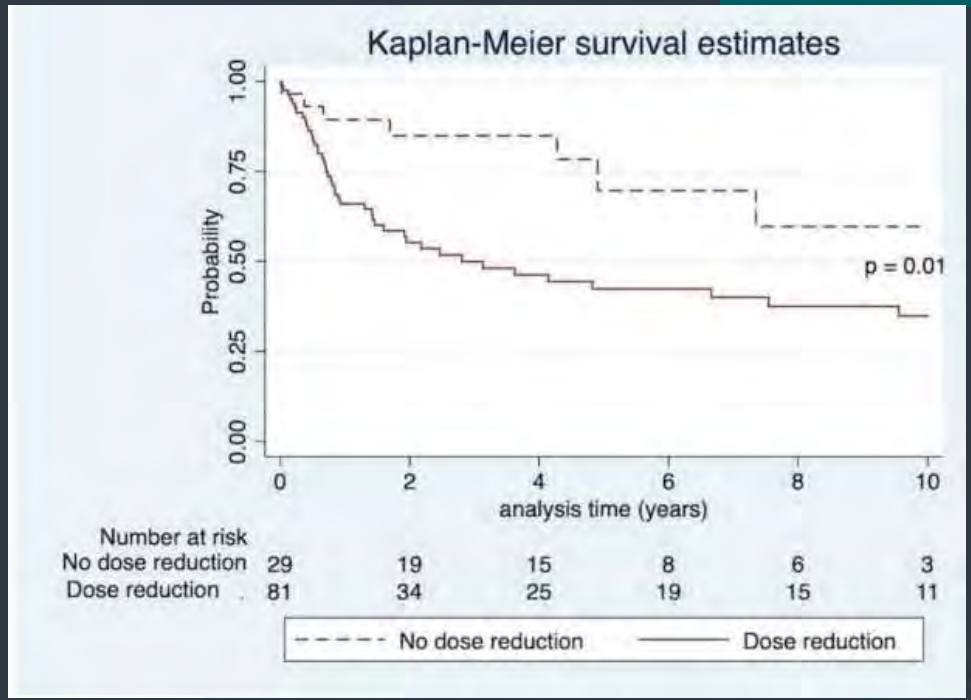
Retrospective cohort study (1990-2018)

Single Center

Kidney transplant recipients (n=110)

IS Dose reduction: 81 pts

No IS dose reduction: 29 pts



Yang, et al. J Clin Med. 2019 Dec 11;8(12):2189

Modifications to immunosuppression

mTORi conversion

- Associated with significantly lower risk of de novo malignancies and PTLD
- High discontinuation rate (15%)
- Higher rates of ACR

CNI reduction/discontinuation

- Data is mixed
- May consider reduction in susceptible cancers

Important Considerations

Cancer Diagnosis	Stage of Cancer at Diagnosis
	Will the malignancy be exacerbated by IS?
	Available therapies
	Does IS interfere/impact the ability to administer standard chemotherapy?
	What is the intent of therapy?

Strategies for Management

Management		
	Appropriate screening and patient education	
	Multidisciplinary team-work	
	Close monitoring of immunosuppression and oncologic therapies	TDM
		Graft function
	Appropriate dose adjustments when required	
	Alternative Chemo Options (if able)	
	Pharmacogenomic testing	

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