NCI Designated Comprehensive Cancer Center

VANDERBILT-INGRAM CANCER CENTER

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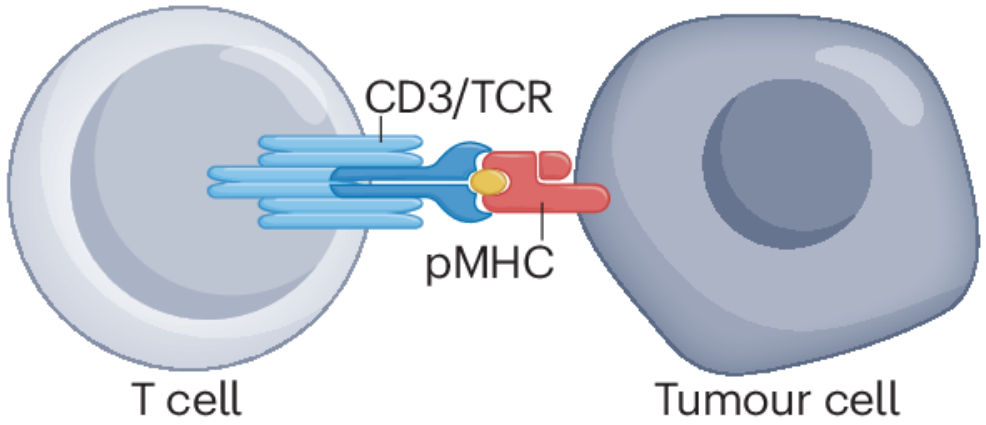
Hematology and Oncology Post Solid Organ Transplant

Outline

- Normal immune surveillance against malignancy
- Incidence of malignancies post solid organ transplant
- Pathogenesis and Treatment of post transplant lymphoproliferative disorder (PTLD)
- Future directions with post transplant VUMC database
- Pancytopenia post solid organ transplant

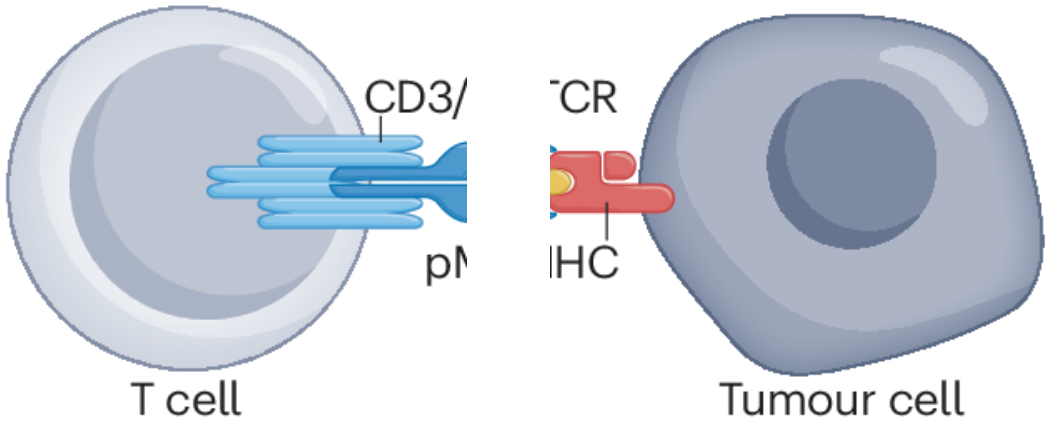
Why is there cancer after transplant?

Normal Immune Surveillance of Tumors



- T cells are designed to prevent cancer and kill cancer
- Tumor cells self identify themselves and T cells kill them

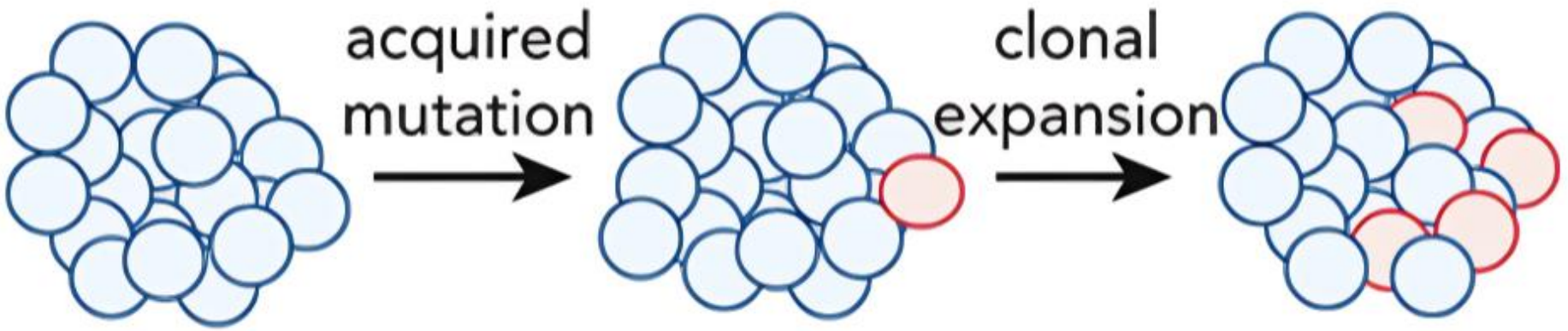
Dysregulated Immune Surveillance

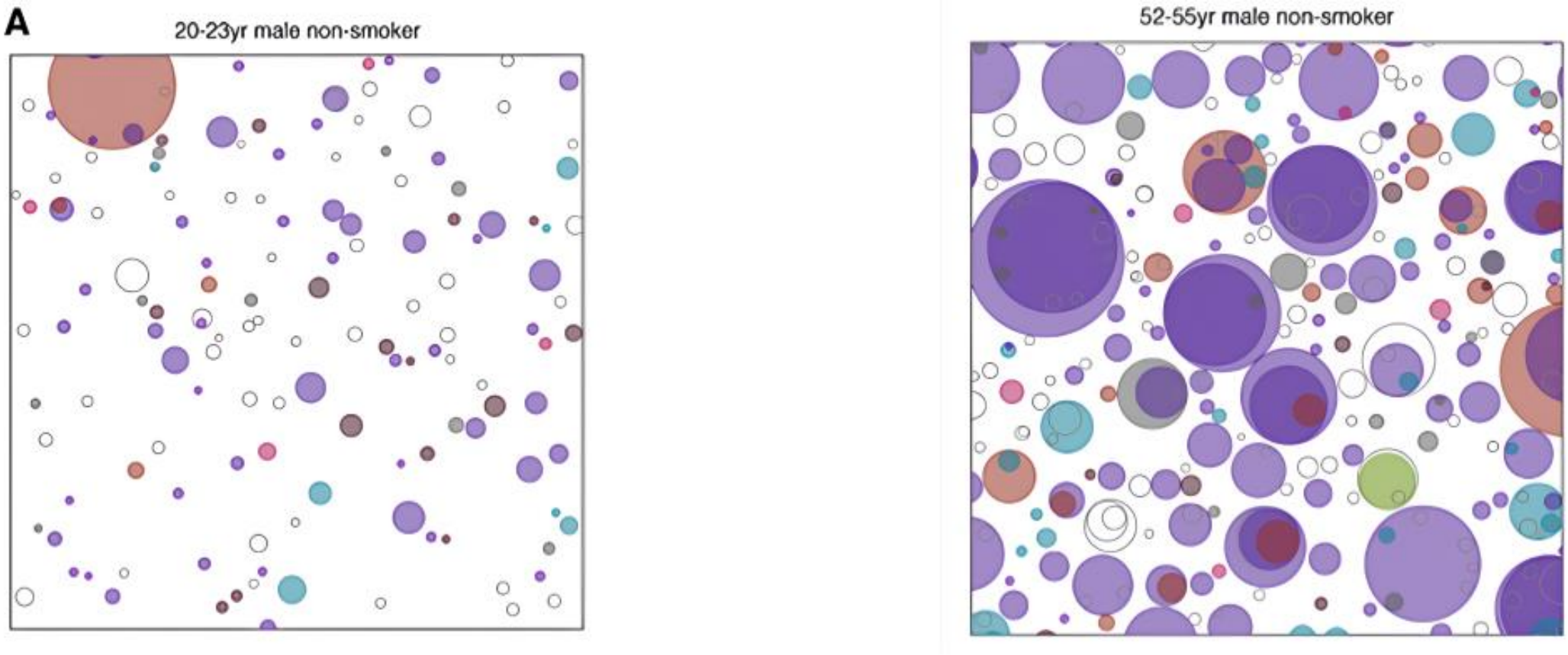


- Tacrolimus, MMF, Azathioprine make these T cells drunk
- They don’t recognize cancerous cells which are then free to grow

Wait so naturally we all get pre cancer?

1. All of our cells are dying and renewing
2. During the renewal, DNA is replicated and mutations can occur accidentally
3. If we miss the bad guy, then it will start expanding and cause cancer
4. We all have pre cancer as we age just by chance





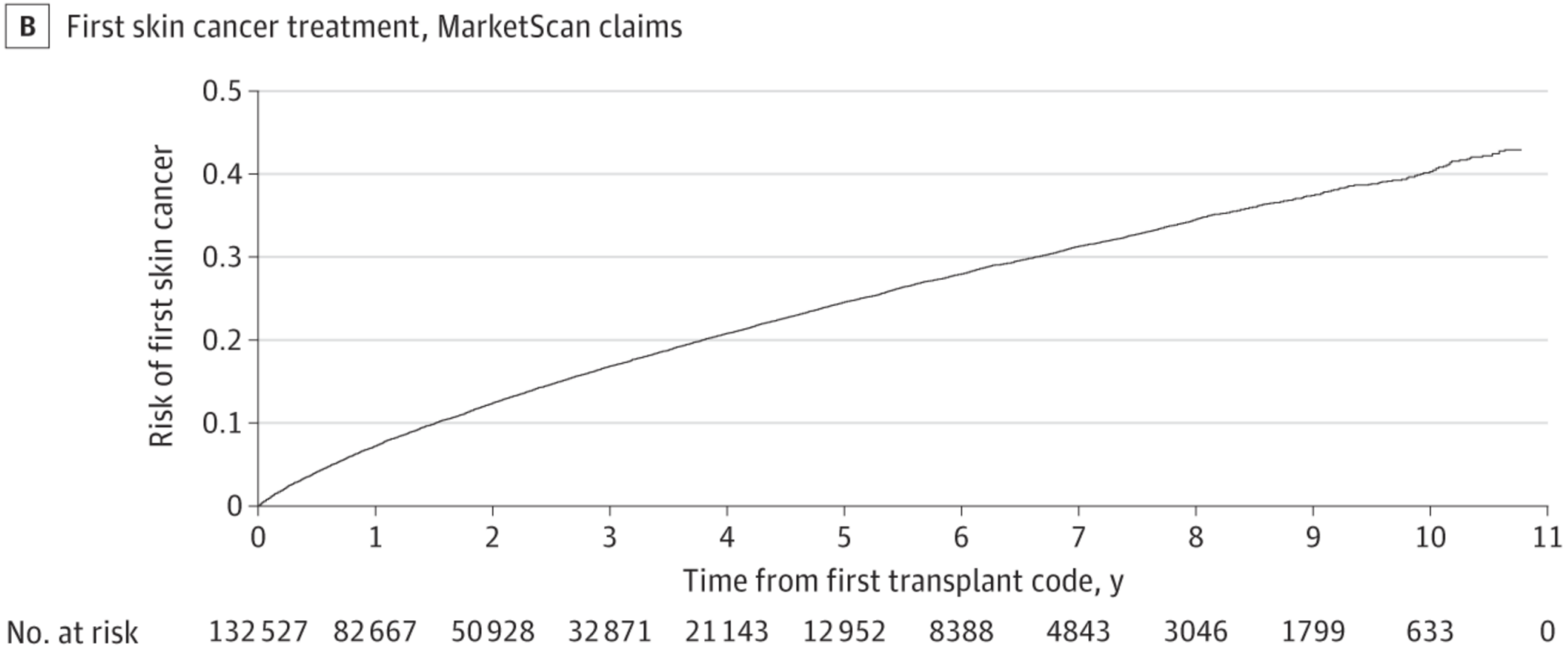
Patients had random biopsies of esophagus tissue (area 17 cm^2)

Circles represent any cells with mutations…remember not all mutations lead to cancer

As you can see, mutations can develop over time but our bodies prevent cancer through immune surveillance

Martincoerna et al, Science 2018

Non melanoma skin cancers are common

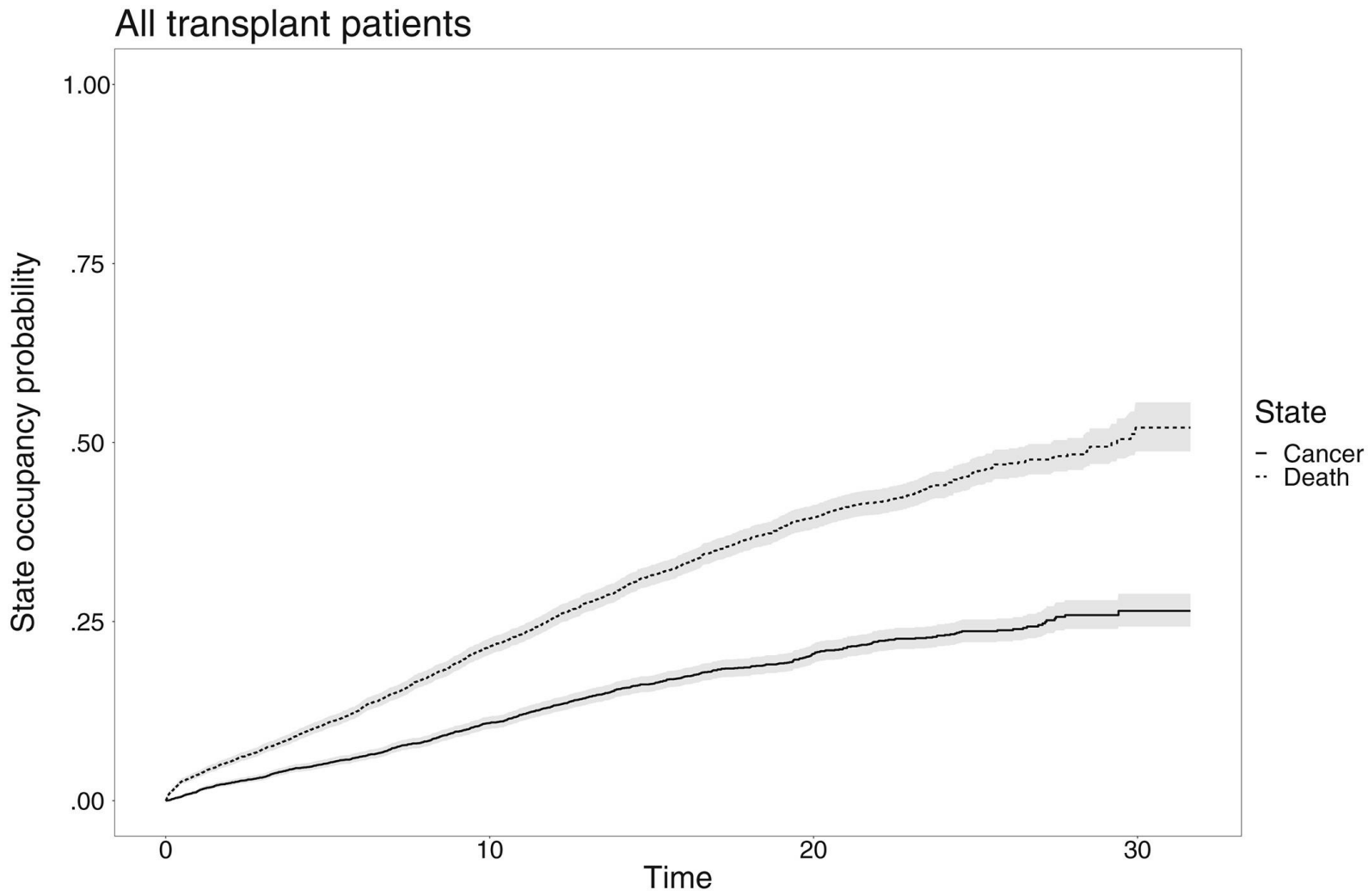


Risk of skin cancer requiring treatment approaches 40% at 10 years

Wehner et al, JAMA Dermatol 2021

What about other cancers?

- Population based cohort of 30 year follow up in Finland
- N = 6548 patients
- Excluded non melanoma skin cancers
- Roughly 25% incidence of any malignancy which is 2x higher than normal population



Friman et al, IJC 2022

What is the most common cancer?

- US registry of solid organ transplant recipients
- N = 175,732 patients
- From 1987-2008
- Lymphoma, lung, liver, and kidney most common
- Lymphoma highest risk

	Cancer Site			
	Non-Hodgkin Lymphoma	Lung Cancer	Liver Cancer	Kidney Cancer
	Standardized Incidence Ratio (95% CI)			
Sex				
Male	7.11 (6.68-7.57)	1.82 (1.71-1.95)	10.78 (10.02-11.58)	4.39 (4.03-4.77)
Female	8.54 (7.82-9.32)	2.33 (2.12-2.56)	16.06 (13.86-18.50)	5.50 (4.77-6.30)
Age at transplant, y				
0-34	45.86 (41.54-50.51)	2.62 (1.26-4.83)	27.55 (18.16-40.09)	16.63 (12.60-21.55)
35-49	8.87 (8.02-9.79)	2.74 (2.41-3.11)	12.09 (10.53-13.81)	8.39 (7.45-9.41)
≥50	4.78 (4.43-5.15)	1.85 (1.74-1.96)	11.15 (10.33-12.02)	3.28 (2.97-3.62)
Transplanted organ				
Kidney	6.05 (5.59-6.54)	1.46 (1.34-1.59)	1.08 (0.80-1.43)	6.66 (6.12-7.23)
Liver	7.77 (6.99-8.61)	1.95 (1.74-2.19)	43.83 (40.90-46.91)	1.80 (1.40-2.29)
Heart	7.79 (6.89-8.79)	2.67 (2.40-2.95)	1.02 (0.54-1.74)	2.90 (2.32-3.59)
Lung	18.73 (15.59-22.32)	6.13 (5.18-7.21)	2.04 (0.56-5.22)	1.49 (0.64-2.94)

Engels et al, JAMA 2011

Liver cancer now less common?

- This registry was done in an era with frequent hepatitis B and C infections
- The signal is for developing hepatocellular carcinoma
- We don't see this issue as much in current era

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Engels et al, JAMA 2011

What about lung and kidney?

- These are already common cancers
- Natural prevention of these cancer subtypes rely primarily on immune surveillance
- These patients get scanned more frequently so likely to have lead time bias

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Engels et al, JAMA 2011

Why are you so into lymphoma signal?

- Lymphoma is not a subtle disease
- Even if found incidentally, these patients will progress within months
- This eliminates the length time bias
- More biologic rationale

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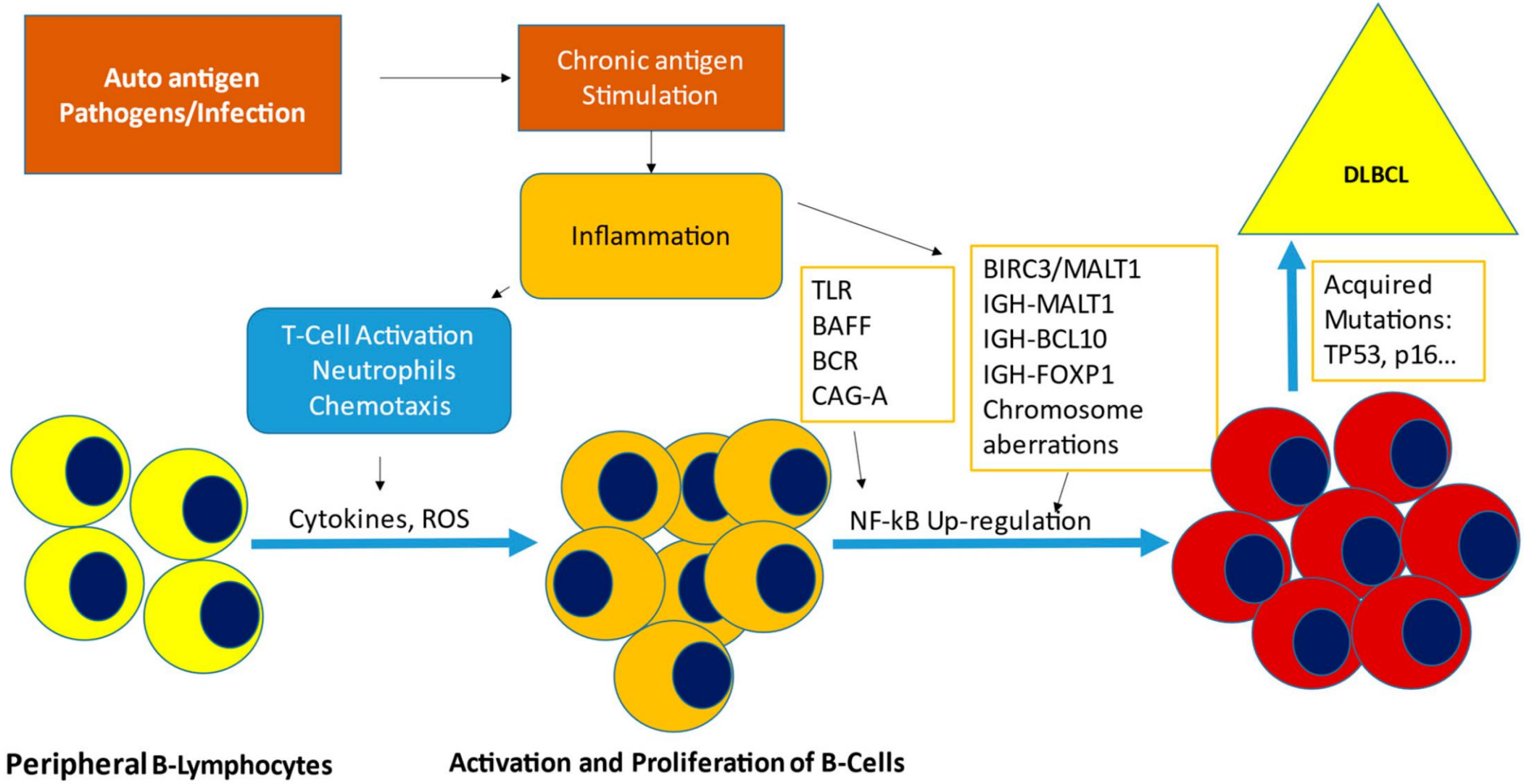
Engels et al, JAMA 2011

Why is lymphoma so common?



Rocco, et al. Cancers 2022

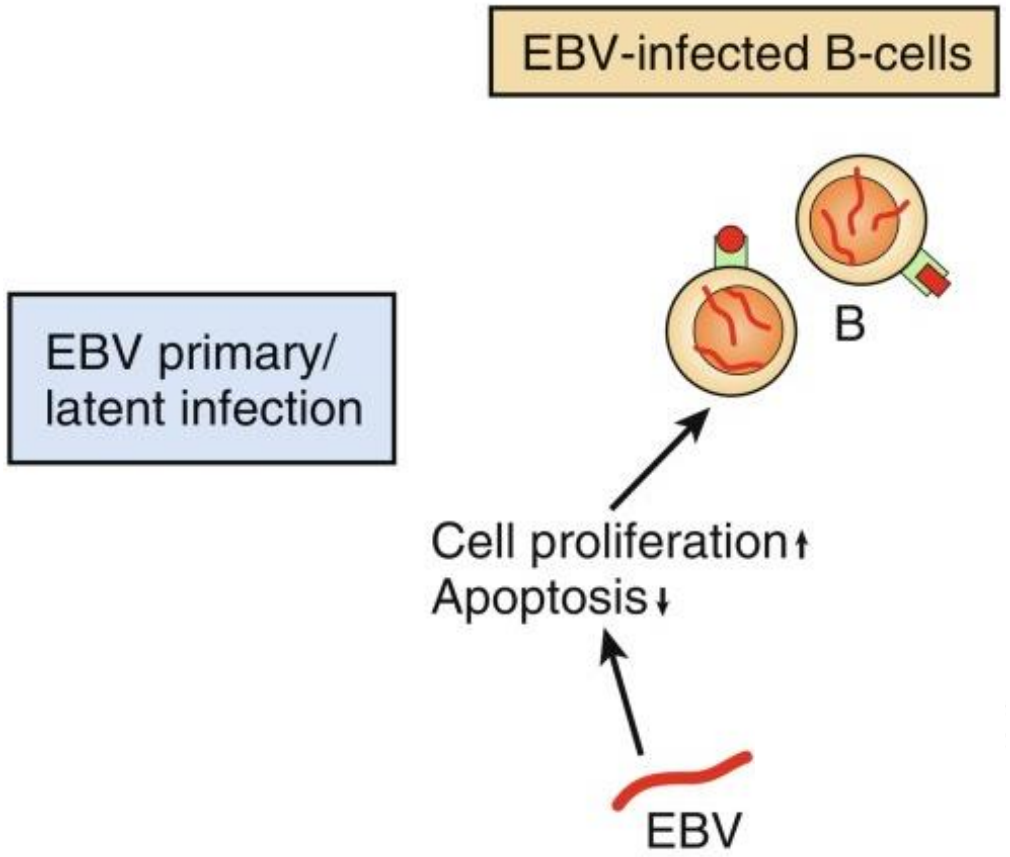

I HAVE NO IDEA
WHAT'S GOING ON!
memegenerator.net

What just happened on that last slide?

1. Patient gets a transplant…we're all celebrating
2. Patient immune suppressed so the get chronic infections whether noticeable or not (think about low viral titers)
3. B cells will expand in response to infection and have to replicate their DNA
4. Uh oh a mistake happened during replication so now it is mutated
5. Not noticed by immune surveillance and it then picks up a second mutation and then another → lymphoma

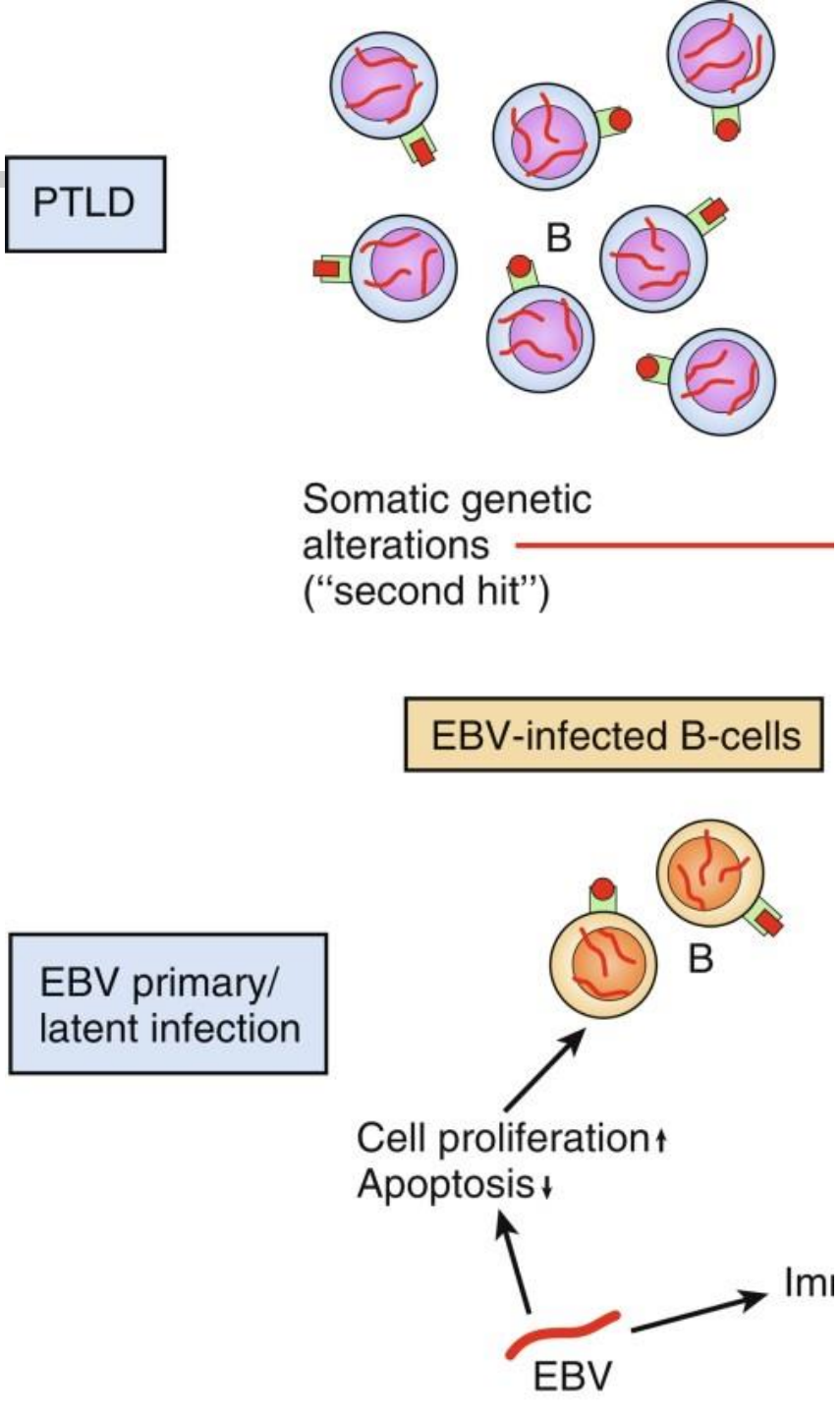
But we always check EBV…why?

- EBV is incredibly common in the normal population
- This virus will infect B cells and immortalize them
- This is done because the EBV machinery takes over the normal DNA
- Normal immune system is suppressed so these infected B cells proliferate



EBV Driven Lymphoma

- PTLD is called post transplant lymphoproliferative disorder
- This is literally means lymphoma
- With EBV, these immortalized cells are janky and a second mutation occurs during replication
- This is bad enough to lead to formation of the cancer



EBV+ vs. EBV- PTLD (i.e. lymphoma)

PTLD Type	Timing Post Transplant	Prognosis
EBV positive	< 12 months	Likely better
EBV negative	> 12 months	Same as lymphoma in a non transplant patient

Hallmark of treatment is always reduced immune suppression

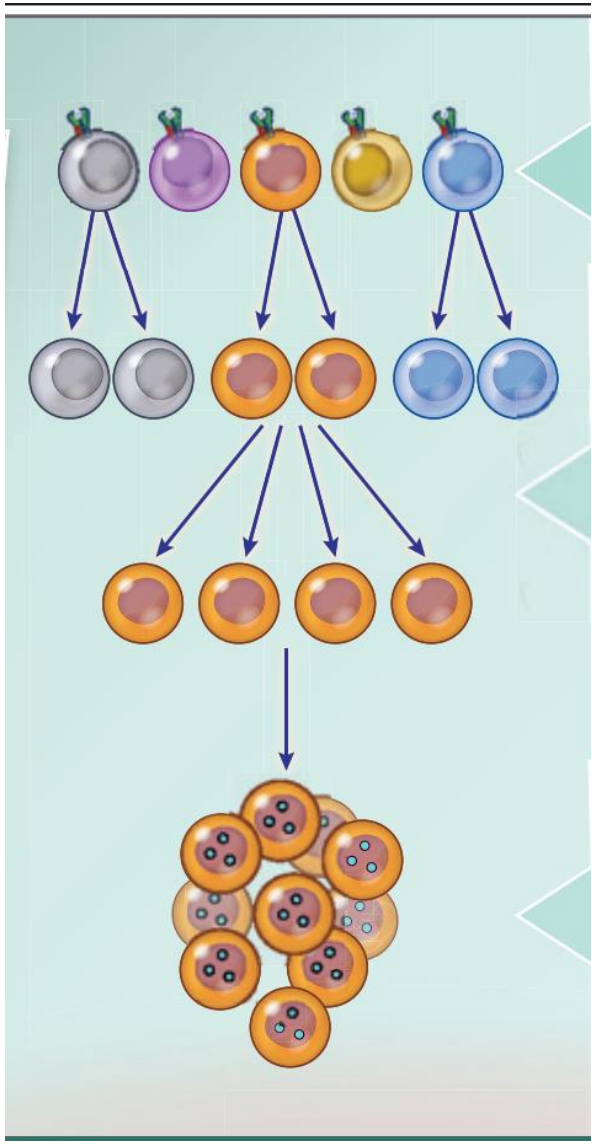
Need to reconstitute normal immune surveillance against tumors

Polymorphic and Monomorphic PTLD

PTLD Type	What???	Prognosis
Polymorphic	Mass with lots of different types of B cell clones	Better
Monomorphic	Dominant bad cancer clone takes over so all looks the same	Worse Still high cure rate

Polymorphic can be cured with reduced immune suppression

Polymorphic and Monomorphic PTLD



This is polymorphic because there are multiple different types of B cells

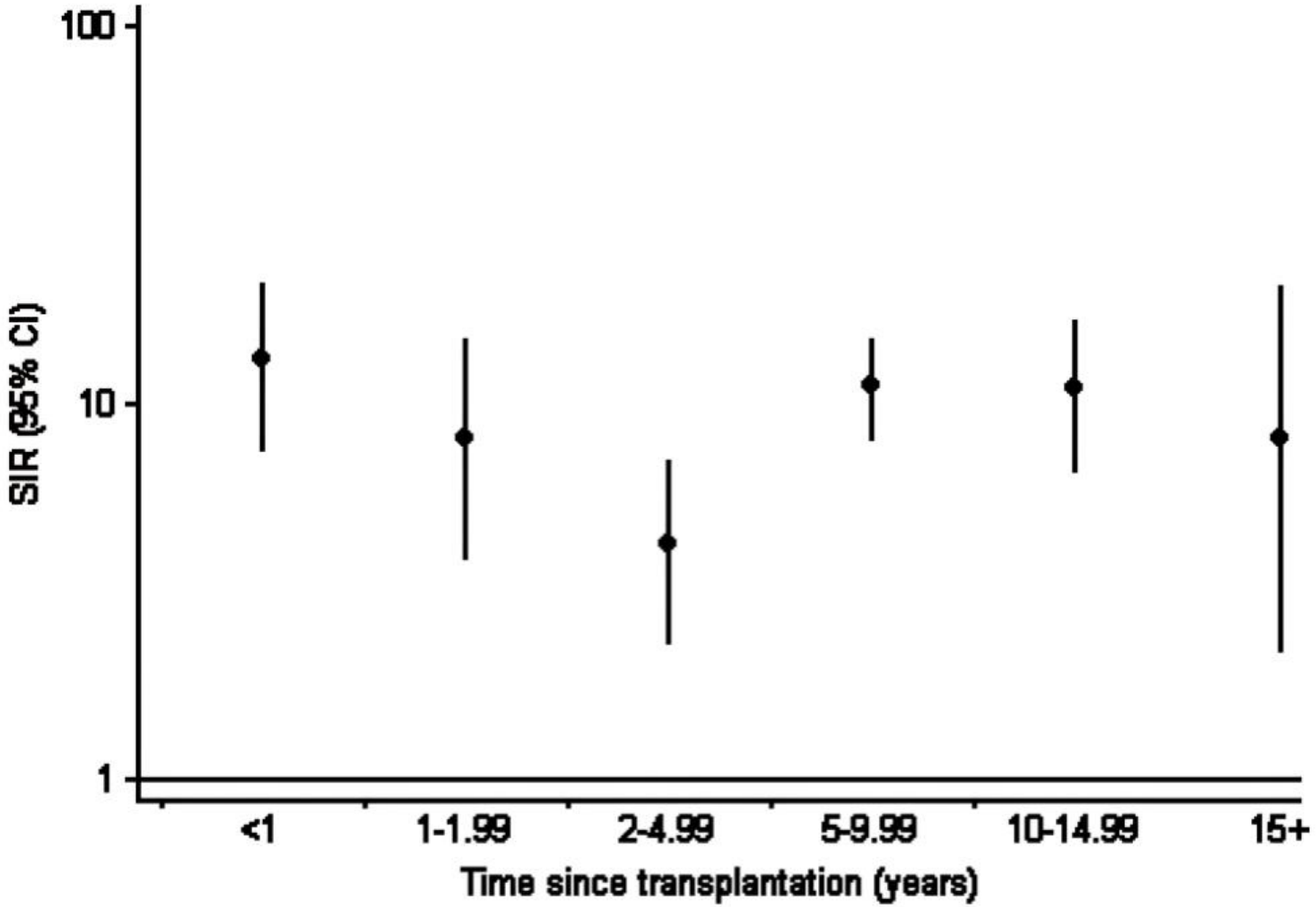
At some point one dominant “bad” clone emerges

This is monomorphic because it all looks the same and only the bad guy is left

Rossi, et al. NEJM 2022

When does this PTLD happen?

- Study looked at kidney transplant patients from Australia and New Zealand
- Included 8164 patients
- Total 133 developed PTLD
- This shows incidence ratio compared to standard population
- Elevated risk persists



Leeuwen, et al. Blood 2009

Risk Factors for PTLD

Variable	Risk after Solid-Organ Transplantation
Established risk factors	
	Type of transplanted organ, relative risk: multiorgan and intestinal, 239.5; lung, 58.6; pancreas, 34.9; liver, 29.9; heart, 27.6; kidney, 12.6
	EBV mismatch at time of transplantation (recipient EBV-negative, donor EBV-positive); relative risk, 10–75
	Intensity of induction immunosuppressive therapy and duration of maintenance therapy (including graft-rejection episodes); overall SIR, 10
Strong evidence of risk	
	Increased risk associated with ATG, OKT3, tacrolimus, azathioprine, new agents (e.g., belatacept in EBV-negative transplant recipient)
	Controversial degree of risk associated with alemtuzumab, cyclosporine, mTOR inhibitors
	No increase in risk associated with mycophenolate mofetil, basiliximab, daclizumab

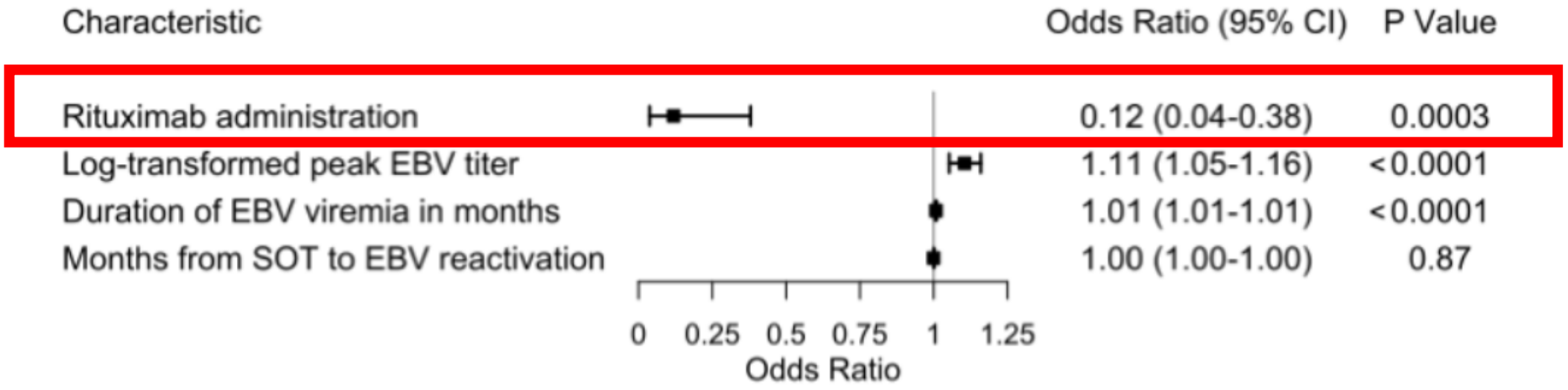
Dierickx, et al. NEJM 2018

Can we prevent PTLD by treating EBV?

We treat EBV viremia with an antibody to CD20 called rituximab

This binds and kills B cells so we kill the EBV that is living in the B cells

Still unclear when to check and at what EBV viral load to treat



Orlando, et al. ASH 2023

How do we treat PTLD?

You will always reduce the immune suppression for two reasons:

- Waking up T cells will allow for our immune system to start killing the lymphoma

- We may give chemotherapy which has a high risk for infection and hospitalization with concomitant immune suppression

Refer to hematologist and we take care of the rest

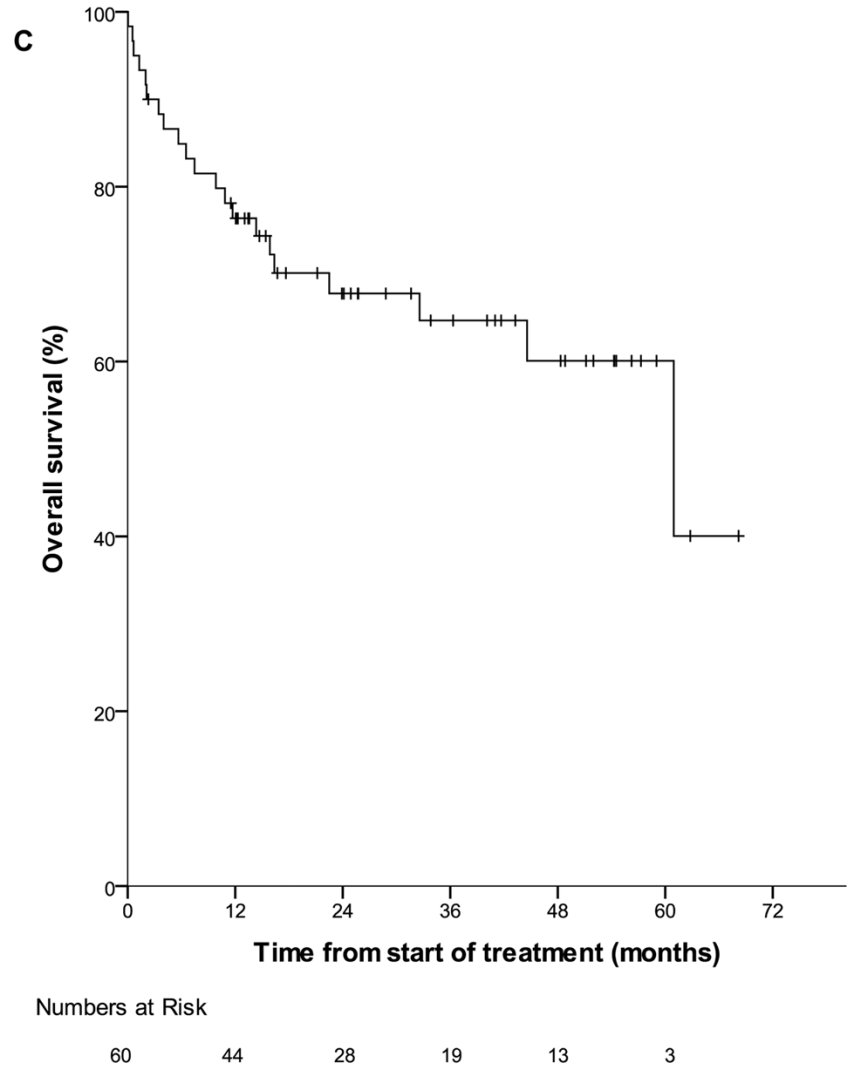
- There are lots of types of lymphomas so that could change treatment

- Some patients can get rituximab monotherapy and be good

- Most patients with late EBV negative PTLD need chemotherapy

Long Term Outcomes for PTLD

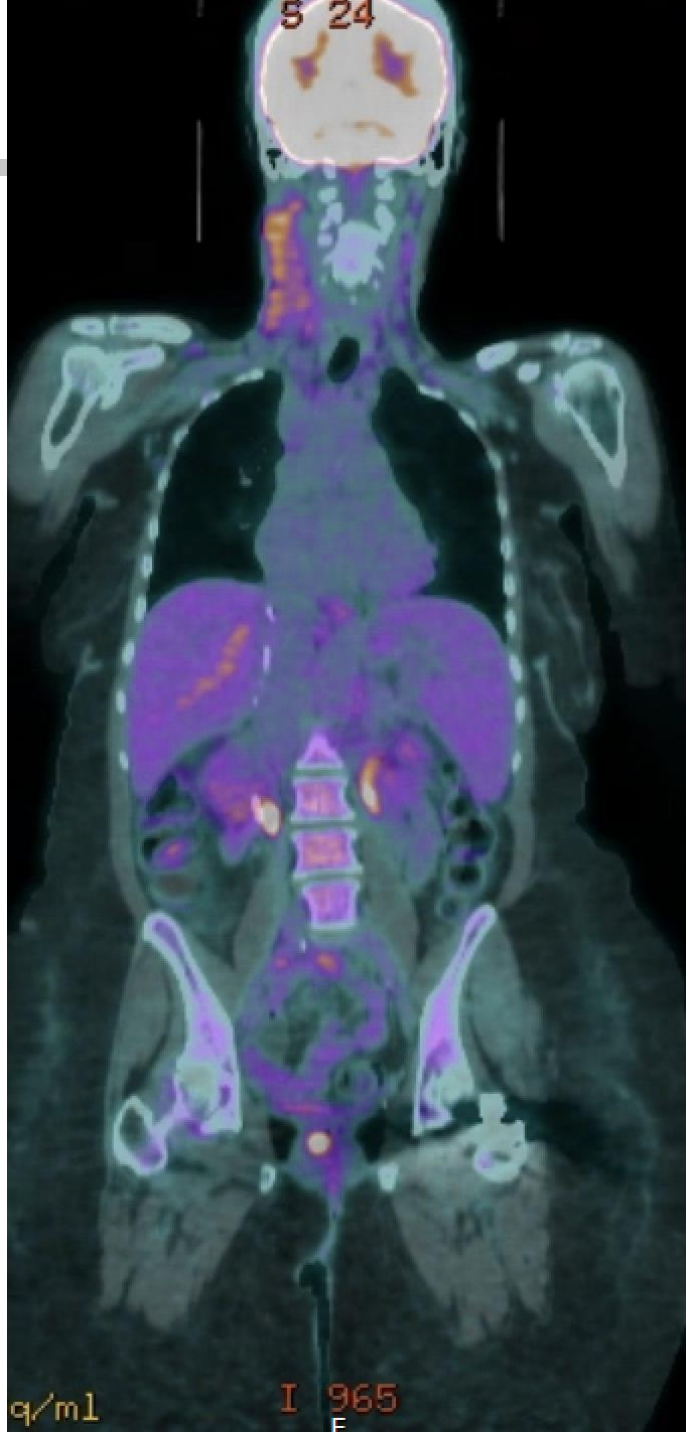
- Very little prospective evidence
- Two clinical trials
- PTLD-1 and PTLD-2
- Overall survival at 3 years is about 60% in the newer PTLD-2 trial --> these patients likely cured
- 50% get hospitalized for infection
- 10% die from treatment complications

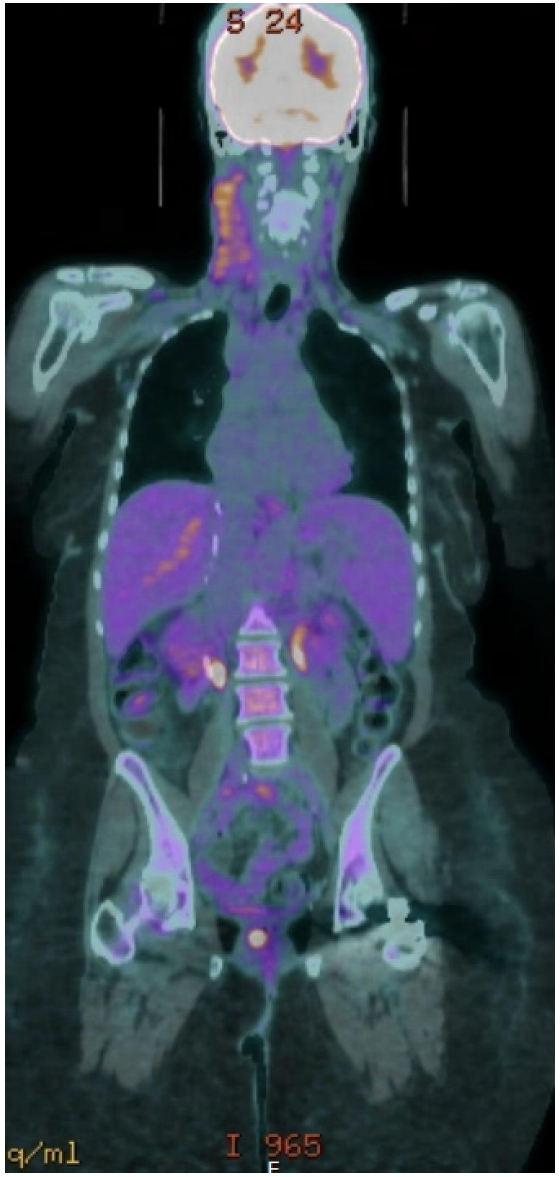


Zimermann, et al. Leukemia 2022

Patient Case #1

- 57 y/o female with PSC s/p liver transplant 6 years ago
- Presented with new asymptomatic neck mass that has rapidly enlarged
- Biopsy showed PTLD (Hodgkin Lymphoma type)
- After reduced immune suppression alone, her adenopathy had nearly resolved
- Treated with new targeted, low intensity therapy

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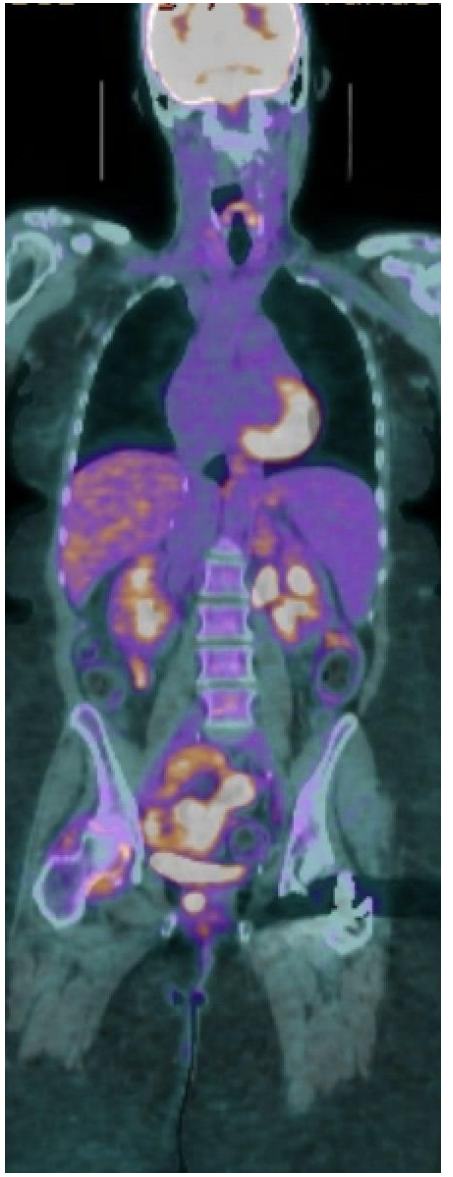

Vanderbilt Post Transplant Database

- Working with informatics to develop a database for all solid organ transplant recipients
- We will look at risk factors for developing PTLD and strategies for prevention
- We need to better understand when to monitor EBV after transplant
- We need to better understand when EBV titer actually matters → not all patients with low level EBV will develop PTLD
- We need to understand risk of graft rejection after treatment and risk factors for relapse

Pancytopenia Post Transplant

- 60 y/o female with BOLT on tacrolimus and cellcept who was admitted from clinic with new mild pancytopenia

- She has felt well otherwise and had normal counts 6 months ago
  - WBC 1.8 with ANC 900
  - Hgb 9.7
  - Plt 103

- PMH: prior ILD, HTN, HLD, depression

- Meds: tacrolimus, cellcept, losartan, atorvastatin, citalopram, valcyte, bactrim

How I Approach Pancytopenia

- Acute Leukemia or MDS is extremely rare!!!
  - Prior JAMA study we discussed showed incidence 0.5 cases per 100,000 people per year
  - Another study showed 25 cases per 100,000 people per year

- My general schema to approach pancytopenia:
  - Bone marrow environment stressed → medications!!!
  - Not enough building blocks for cells
  - Peripheral sequestration or destruction of cells
  - Infiltration of bone marrow*
  - Primary bone marrow failure*

Remember to think this

Very unlikely acute leukemia → look for report of blasts on peripheral smear

<u>Infections, medications, toxins → most common causes</u>

Nutritional issue → B12, folate, iron studies, copper

Bad kidneys → EPO made by these so deficient → anemia (need EPO and/or iron)

If not the above, heme will investigate marrow

First Pass Workup

- CBC w/ diff and peripheral smear (obtain prior baseline)
- CMP, LDH, uric acid +/- haptoglobin
- PT, PTT, Fibrinogen
- Reticulocyte count
- B12, folate, iron studies, copper level
- CMV, EBV, parvovirus, Hepatitis C, HIV reasonable

Why Reticulocyte Count?

- If low then it is less likely a peripheral issue
- If zero then makes you think parvovirus and aplastic anemia
- If elevated makes you think of peripheral destruction or blood loss
- Bottom line: not incredibly useful unless it is elevated
- Don’t get an IPF as it doesn’t add anything but get it if it makes you happy

Case #2: Lung Transplant Patient

- 60 y/o female with BOLT on tacrolimus and cellcept who was admitted from clinic with new mild pancytopenia
- CMV, EBV, parvovirus, HIV, Hepatitis C negative
- B12, folate, iron wnl
- Eventually sent copper wnl
- No evidence of splenomegaly, no concern for ticks, no new supplement (always ask)

When to give G-CSF?

- Always stop the valcyte first and monitor CMV viral load if feasible as this is the most common offender
- Would decrease or stop dose of MMF or Azathioprine if on those medications if feasible
- Always ok to give filgrastim (i.e. short acting G-CSF) x 3 doses empirically and monitor CBC weekly for ANC < 500
- If ANC still less than 500 and stopped offending medications, do another 3 doses
- If no response after 3-7 days → refer to heme for bone marrow biopsy

Any risk of G-CSF?

- Very little risk for empiric G-CSF

- There is a theoretical concern for stimulation of leukemic blasts in acute leukemia which is extremely unlikely → easily can be evaluated by seeing if ”other cells” or “blasts” are reported in the diff

- If any patient has ANC < 500 and admitted for fever, then always reasonable to give empiric G-CSF

- It’s pretty much always medications or infections and G-CSF can prevent neutropenic fever hospitalization or severe infection

Case #2: Lung Transplant Patient

- 60 y/o female with BOLT on cellcept who was admitted from clinic with new mild pancytopenia
- Changed immunosuppression and taken off cellcept
- 2 months later counts recovered
- No indication for bone marrow biopsy in most…these patients are unlikely to have a cancer in their bone marrow and PTLD does not cause pancytopenia
- Bone marrow biopsy can be done to diagnose infection infiltrating the marrow and help guide ID therapy which would be another reason

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QUESTIONS?