Considerations of checkpoint inhibitor therapy in kidney transplant patients

Provincewide Nephrology Rounds

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Disclosure

- I am not an oncologist
- Natera Inc.

- 69M ESRD from PCKD
- LD transplant 2013 – good kidney function, no immediate complications
- Current Cr: 109 umol/L, uACR: 1.3 mg/mmol
- Baseline IS: MMF 500 mg BID, Tac, Pred 5 mg OD

- June 2019: preauricular SCC, involving periparotid lymph nodes → curative radiation

- May 2020: chest pain → CT: multiple masses in R Lung + R pleural effusion

  - Lung mass bx = poorly differentiated SCC, likely metastatic
  - Bone scan: uptake in right 4/5th ribs
  - PET: FDG activity in right preauricular region, R lung, R chest wall

- Considerations:

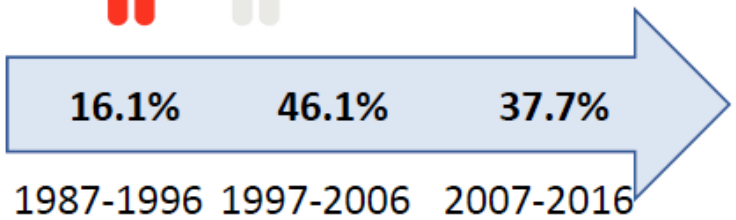
  - Goals of treatment
  - IS management
  - Cancer treatment
  - Follow-up

Oncologist would like to treat with checkpoint inhibitor – seeks approval

Changes in cancer incidence and outcomes among kidney transplant recipients in the United States over a thirty-year period.

U.S. Kidney Transplant Recipient (KTRs) Cohort

N = 101, 014



Transplant Cancer Match Study = SRTR + 18 Cancer Registries
(https://www.transplantmatch.cancer.gov)

Cancer Incidence over Time

- Overall Cancer
- Colorectum
- Lung
- Breast
- Kidney
- Melanoma
- Non-Hodgkin lymphoma (NHL)

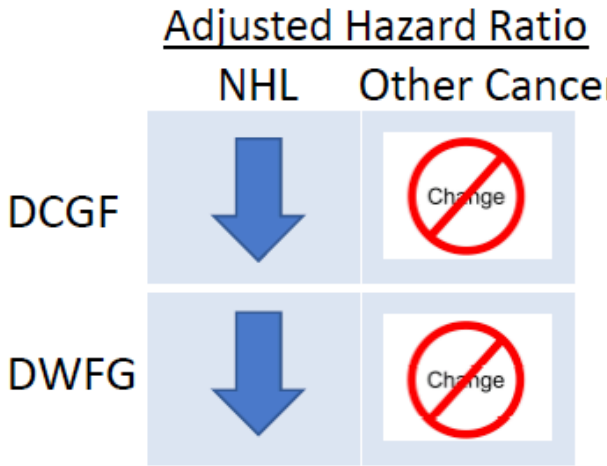
Except for a decrease in

- Prostate (p=0.014)

Cancer Outcomes over Time

- **Graft Failure (DCGF)**
- **Death (DWFG)**

Adjusted Hazard Ratio

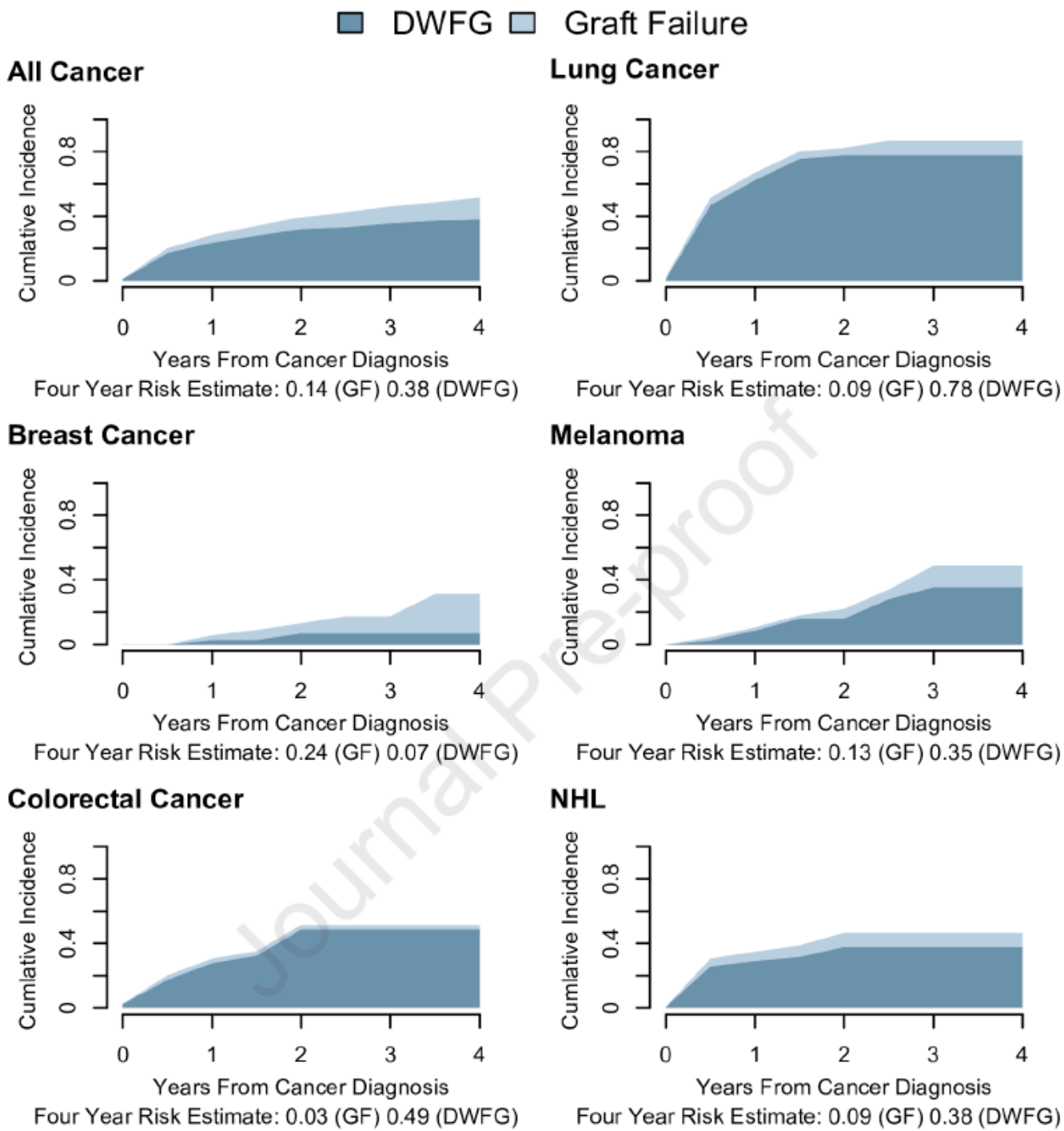


CONCLUSION:

Across a 30-year period in the U.S., there was no overall change in cancer incidence among KTRs. Despite improvements in outcomes for NHL, cancer remains a major cause of morbidity and mortality.

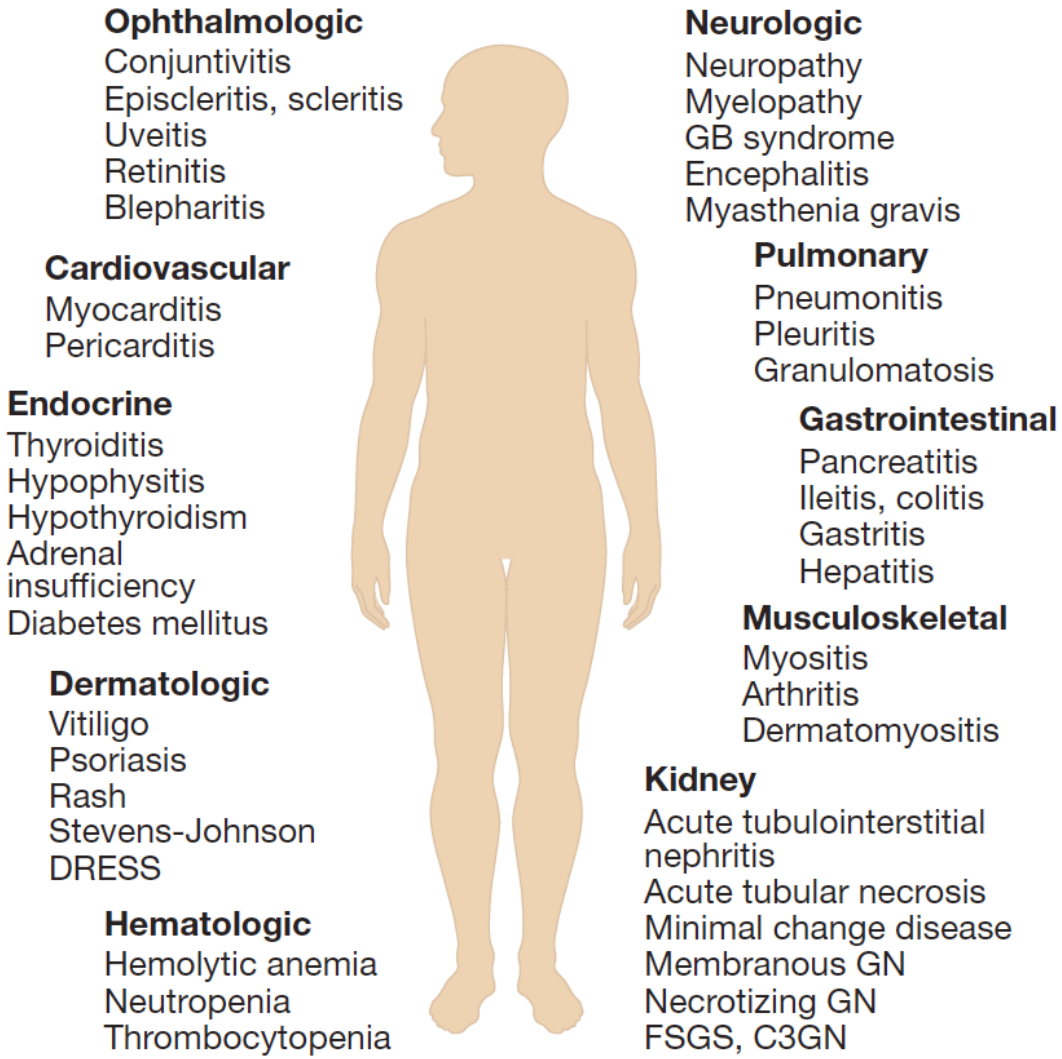
ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Blosser et al, 2020



Immune checkpoint inhibitor nephrotoxicity: what do we know and what should we do?

Mark A. Perazella[1,2] and Anushree C. Shirali[1]



Perazella, KI, 2020

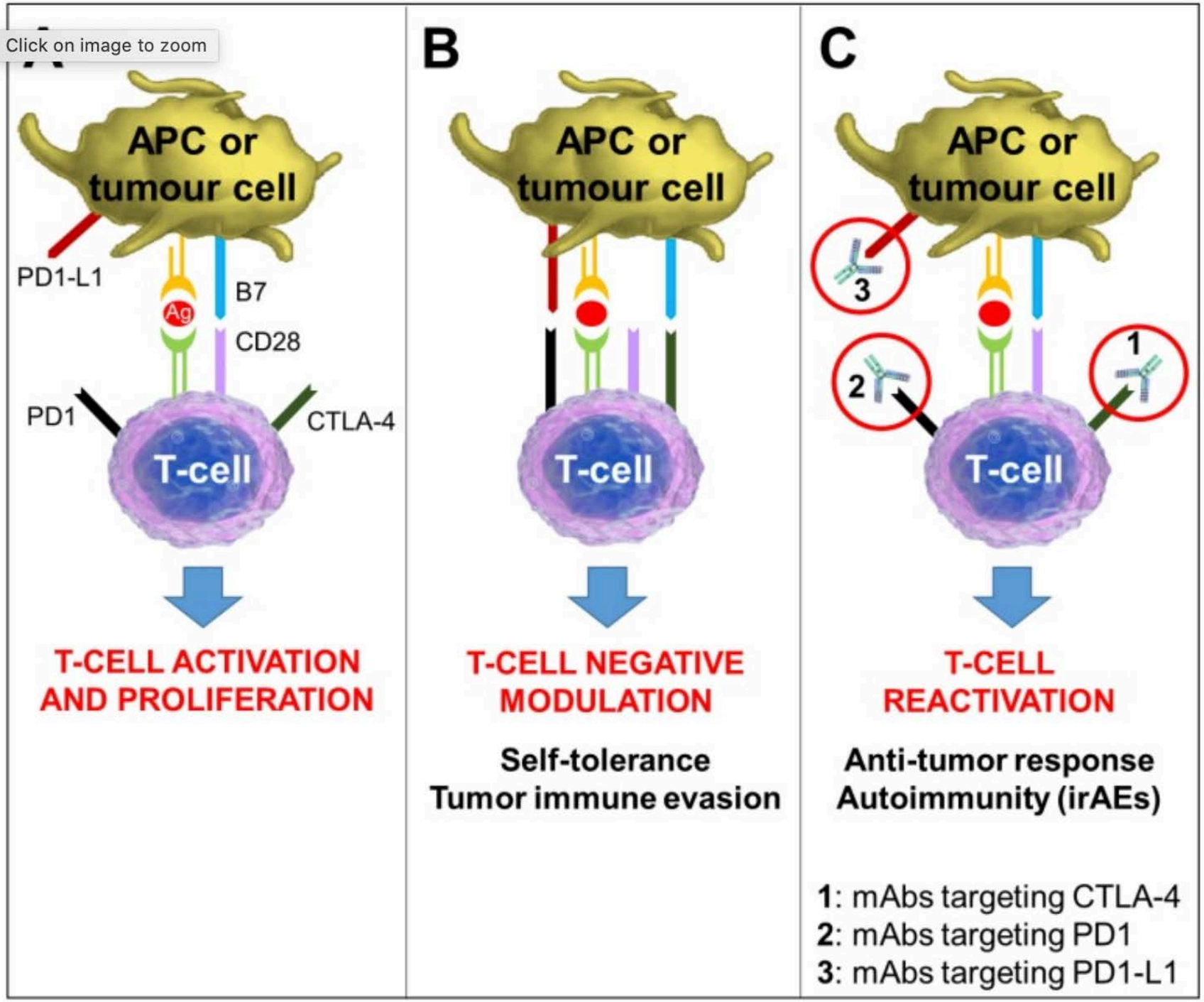
Table 1 | Pharmacology of immune checkpoint inhibitors[27–44]

Immune checkpoint inhibitor		Drug dosing (mg/kg)	Vd (l)	$t_{1/2}$ (d)	Steady state (wk)	Clearance (l/d)
Ipilimumab	(CTLA-4)	0.3–10	3.11–4.15	14.7	9	0.36 Linear
Tremelimumab	(CTLA-4)	10–15	3.97	22	ND	0.2 Linear
Nivolumab	(PD-1)	0.1–20	2.78–3.63	25	12	0.23 Linear
Pembrolizumab	(PD-1)	1–10	3.48–4.06	27.3	18	0.22 Linear
Cemiplimab	(PD-1)	350 mg	5.3	19	16	0.32 Linear
Atezolizumab	(PD-1L)	1–20	3.28–3.63	27	6–9	0.20 Linear
Durvalumab	(PD-1L)	0.1–20	3.45–3.51	21	16	0.23 Linear and nonlinear
Avelumab	(PD-1L)	1–20	1.17–2.83	6.1	4–6	0.59 Linear

ND, no data; $t_{1/2}$, half-life; Vd, volume of distribution.

Perazella, KI, 2020

Click on image to zoom



ORIGINAL ARTICLE

AJT

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

Thibaut d'Izarny-Gargas[1] | Antoine Durrbach[2,3,4] | Mohamad Zaidan[1,3]

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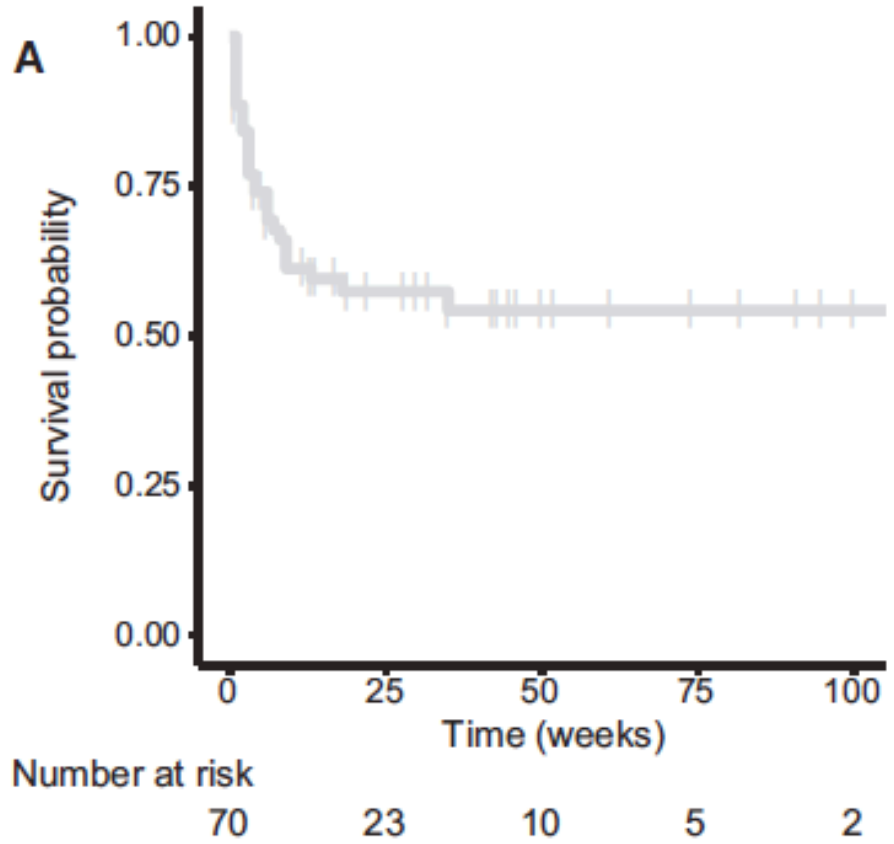
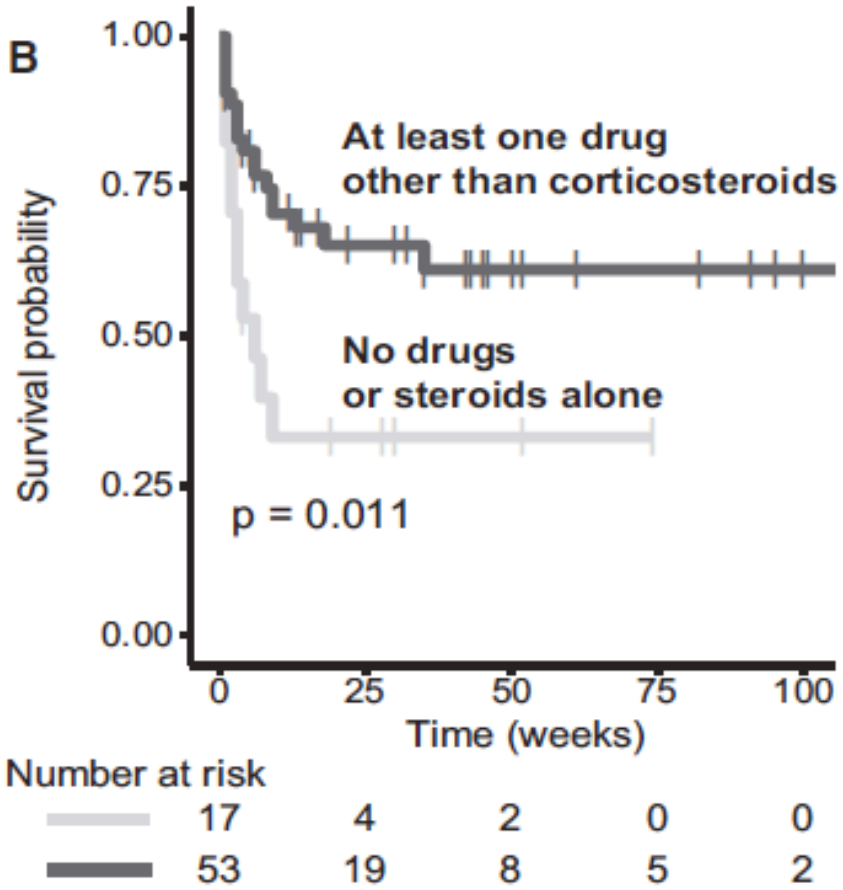
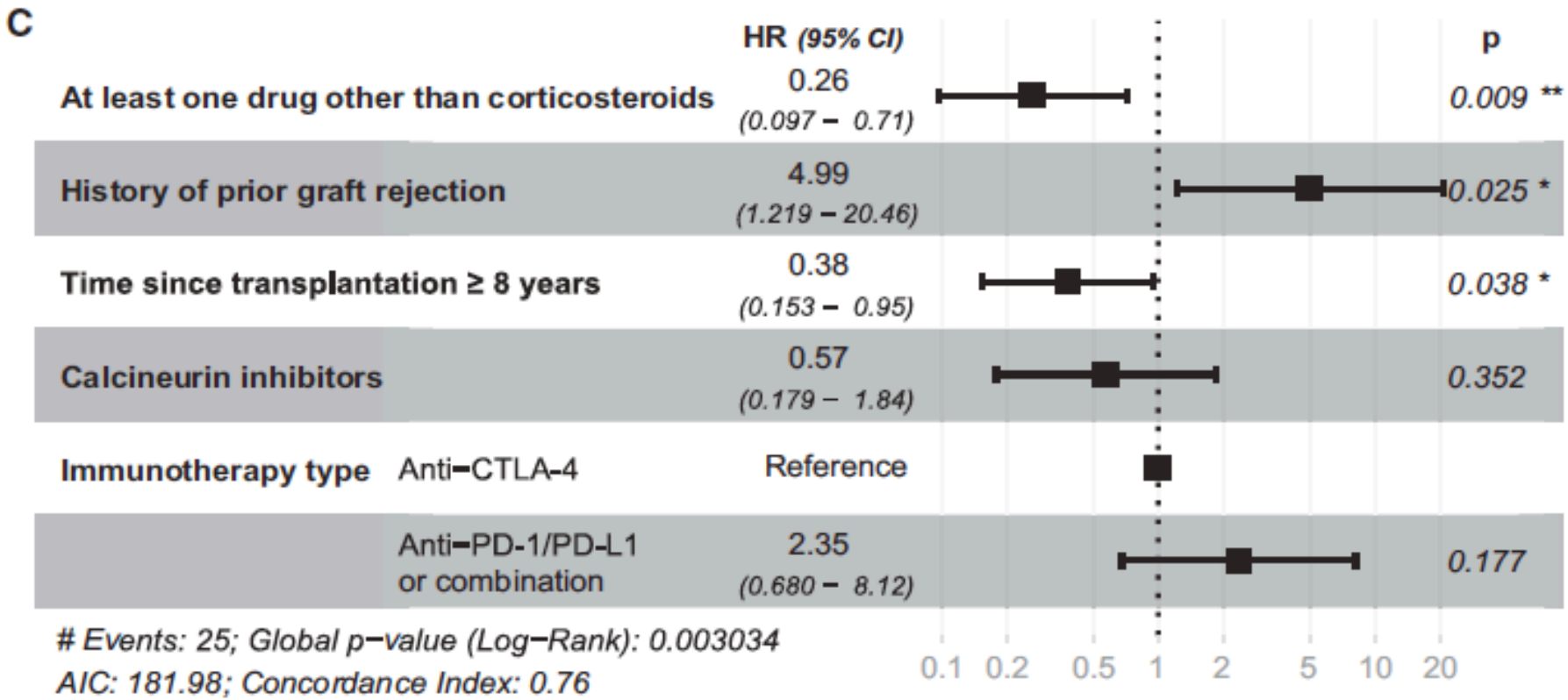
Solid organ transplant (SOT) is frequently complicated by cancers, which render immunosuppression challenging. Immune checkpoint inhibitors have emerged as treatments for many cancers. Data are lacking regarding efficacy and rejection risk in the SOT population. We conducted a systematic literature review and analyzed 83 cases of immune checkpoint inhibitor use for cancer in SOT. Two thirds of these patients received anti–programmed death ligand 1 therapy, 15.7% received anti–cytotoxic T lymphocyte–associated protein 4 therapy, and 10.8% received a combination. Allograft rejection occurred in 39.8% of patients, leading to end-stage organ failure in 71.0% of cases. Outcomes were similar across organs and immunotherapy regimens. The use of immunosuppressants other than steroids, time since transplant, and prior episodes of rejection were associated with the risk of rejection. The median overall survival of patients was 36 weeks. Most of the deaths were related to

CPI and Risk of Graft Rejection



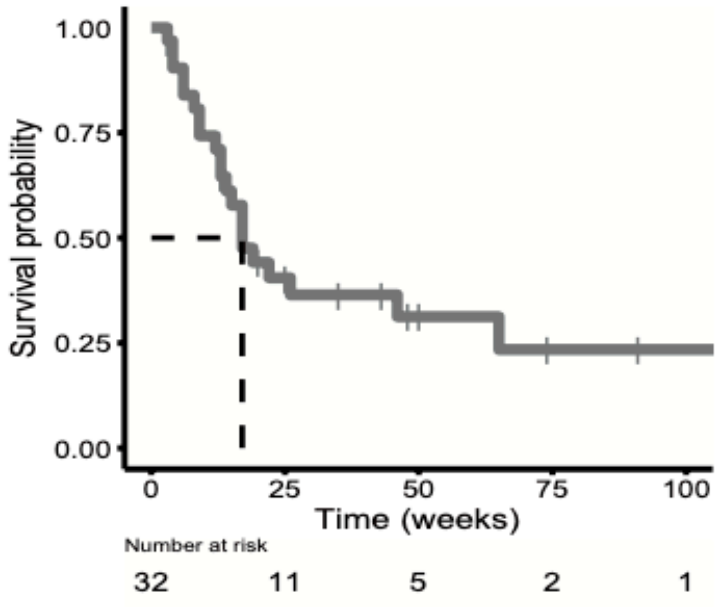


Risk and Protective Factors for Rejection on CPI

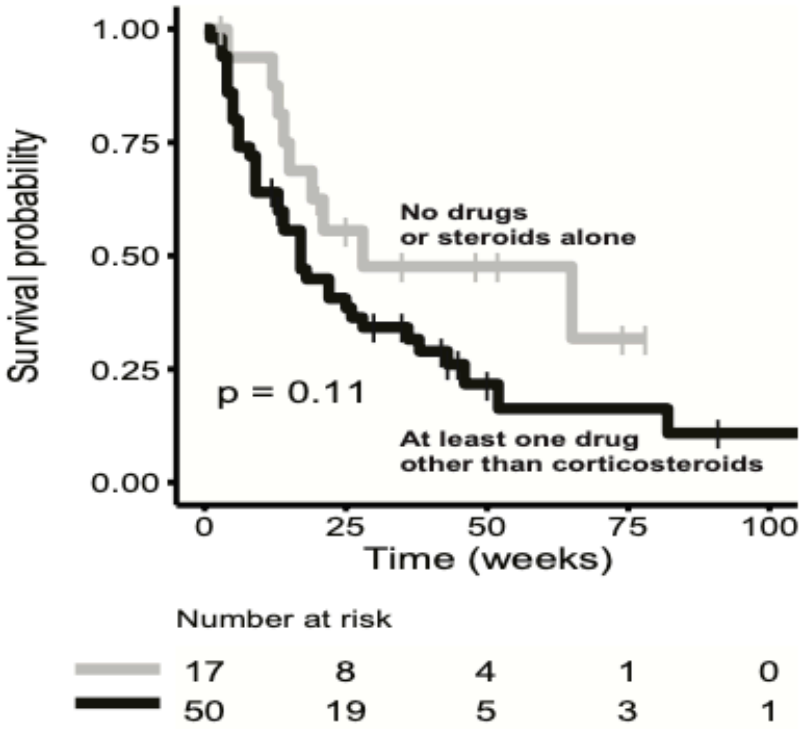


Concurrent IS and Efficacy of CPI on anti-tumor response

A - Progression-free survival in patients with melanoma



B - Progression-free survival according to immunosuppression



Summary

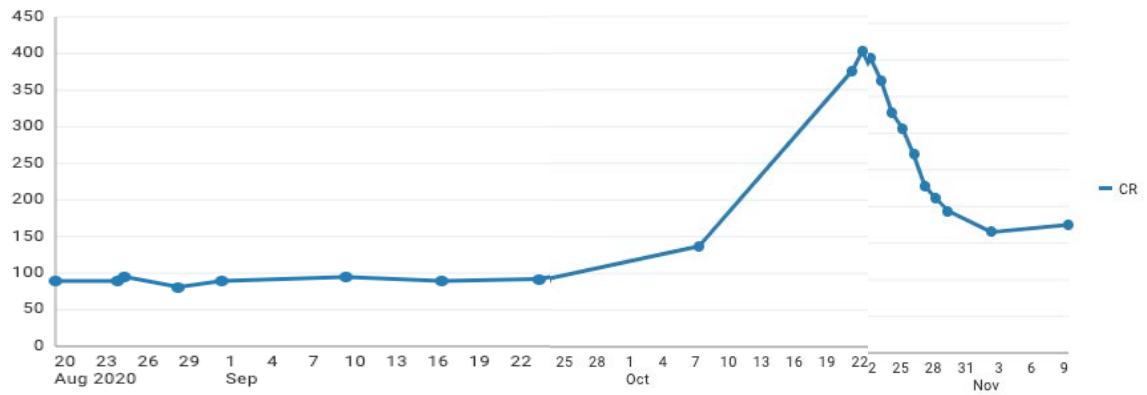
- CPI in transplant recipients is associated with 40% risk of rejection, among which 70% develop end-stage organ failure
- Rejection occurred early – median time to rejection was 5 weeks
- Protective factors for rejection: time since transplant, use of steroid + >= 1 IS agent
- No association between rejection and other immune-mediated adverse events
- No association between rejection and anti-tumor response
- Patient survival did not differ between those with vs. without rejection
- 1/3 of patients experienced stabilization/regression of tumor
- At the end of study 20% of patients were alive, free from rejection and tumor progression

- How can we better risk-stratify?
- mTOR - potential agent to reduce risk of rejection without compromising anti-tumor activity?
- How to better follow patient?

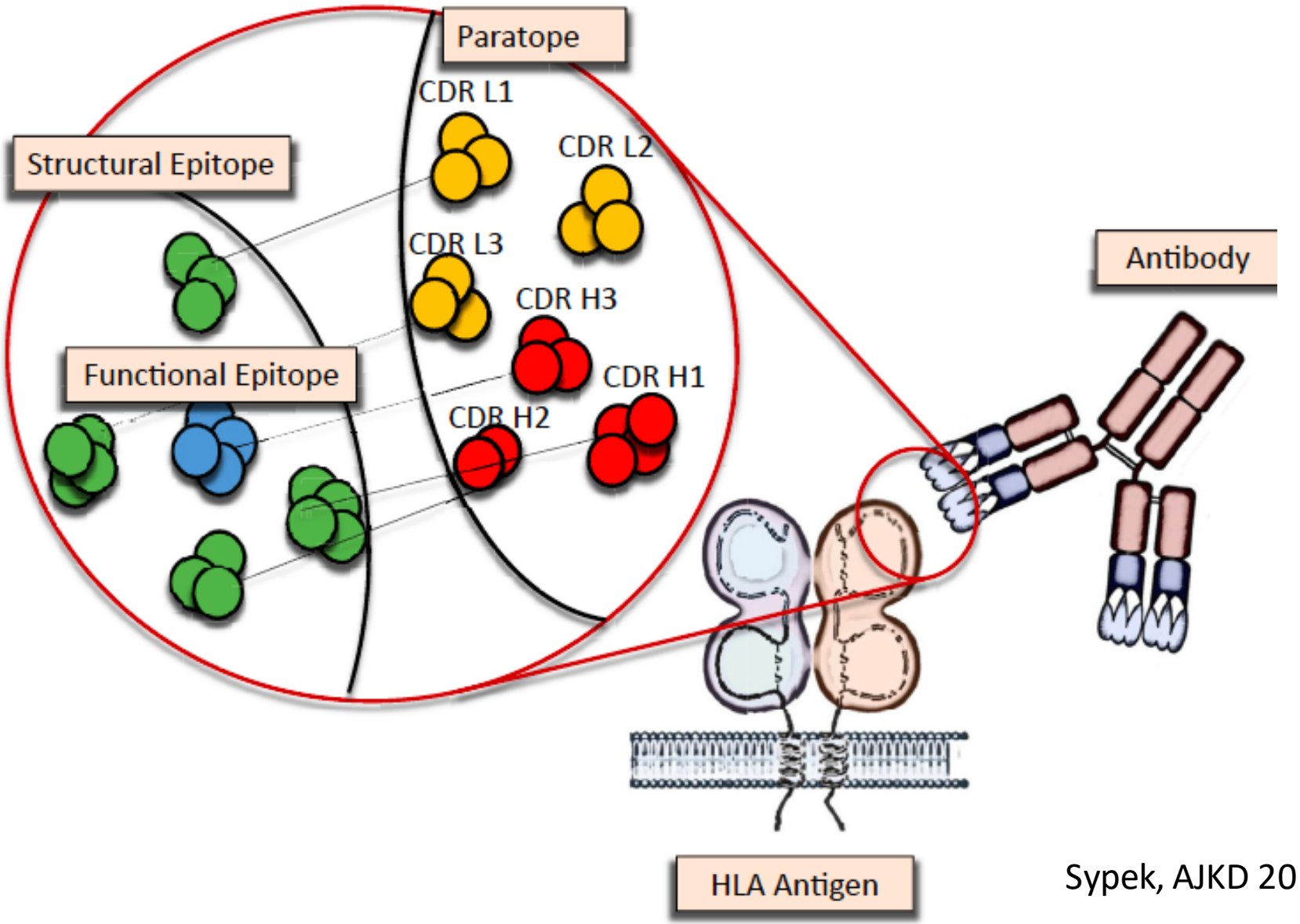
Back to our patient

- Clarified goals of care
- Immunosuppression adjustment:
  - MMF stopped at time of discovery of metastatic SCC
  - Tacrolimus switched to sirolimus before initiating CPI
- Interdisciplinary clinic follow-up q weekly

Allograft biopsy: T cell rejection (i2, t3, v1)

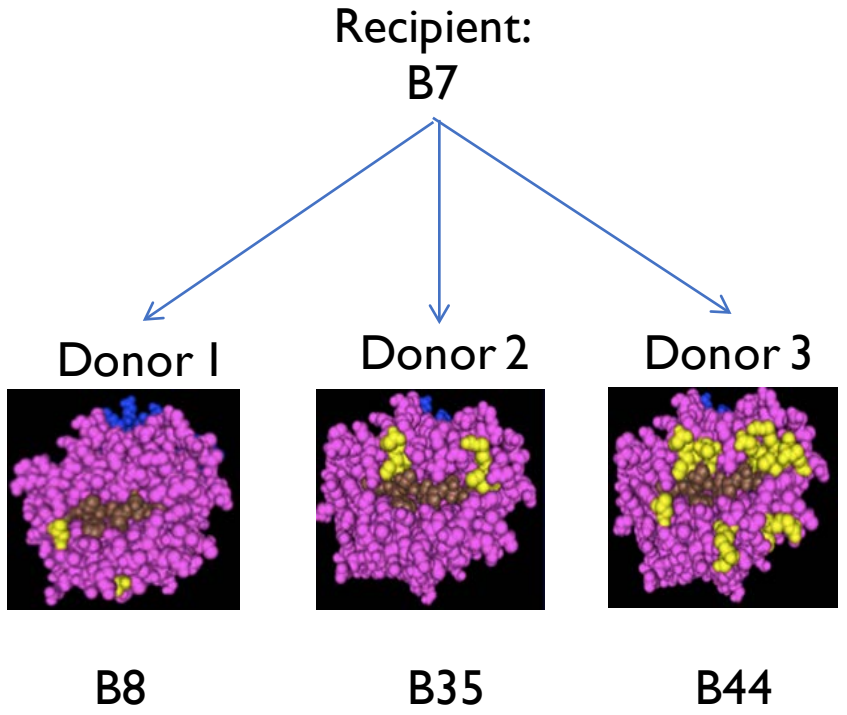


Can we improve patient risk-stratification?



Sypek, AJKD 2018

Eplet analysis: not all mismatches are created equal



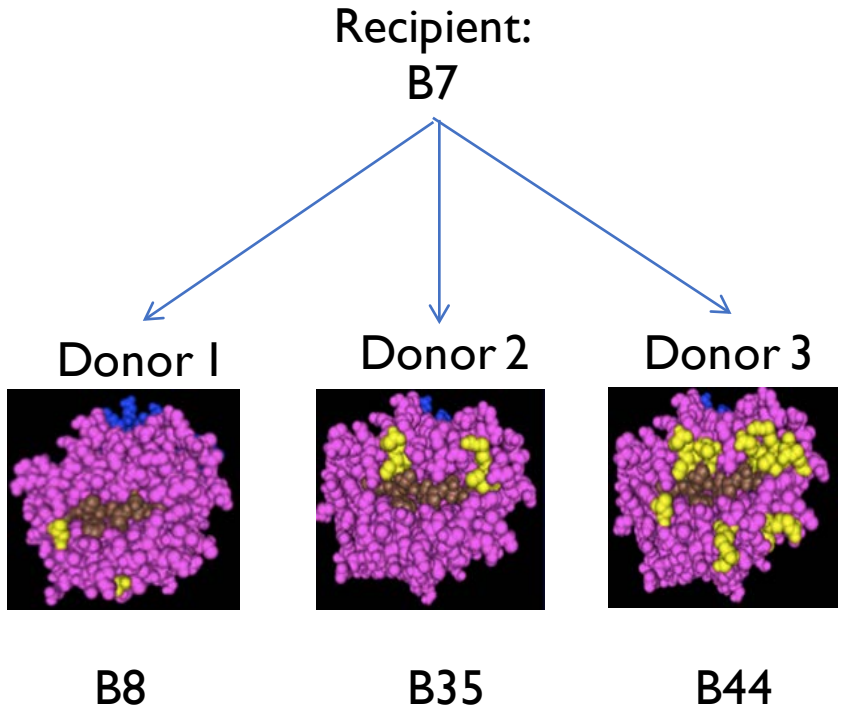
Recipient B*7

Donor 1 B*8

Donor 2 B*35

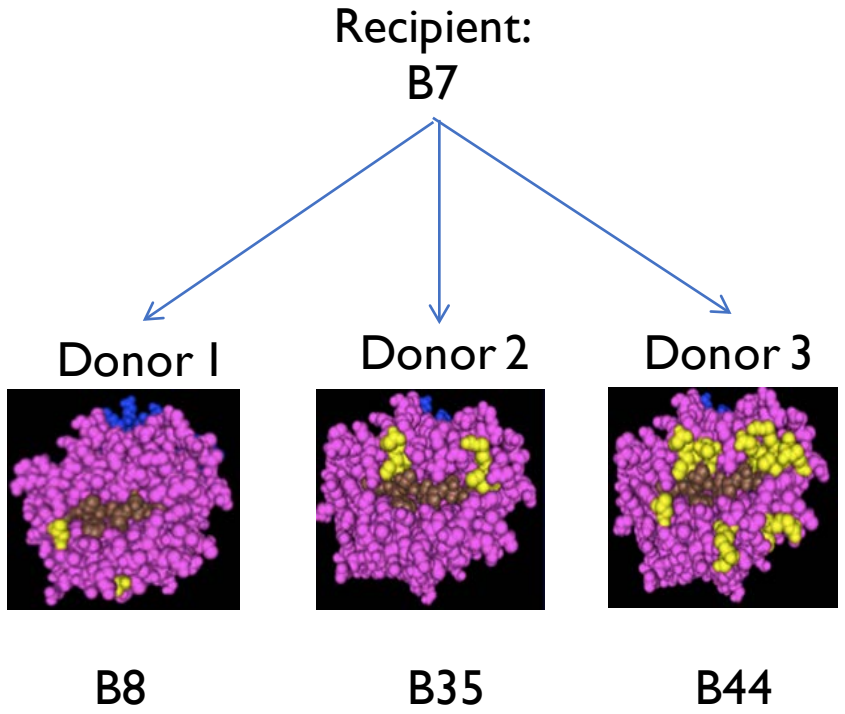
Donor 3 B*44

Eplet analysis: not all mismatches are created equal



Recipient B*7		
Donor 1	B*8	1 antigen mismatch
Donor 2	B*35	1 antigen mismatch
Donor 3	B*44	1 antigen mismatch

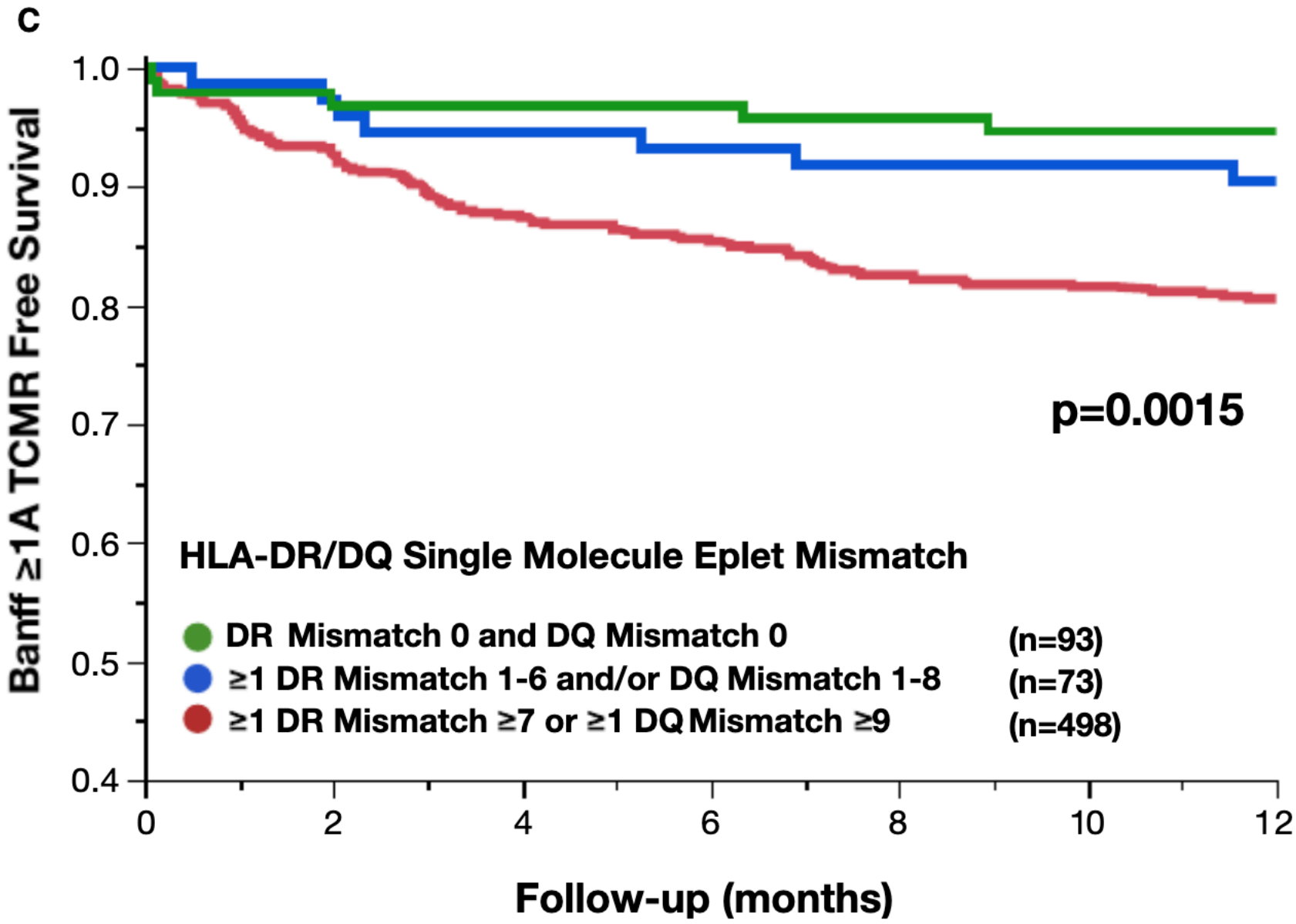
Eplet analysis: not all mismatches are created equal



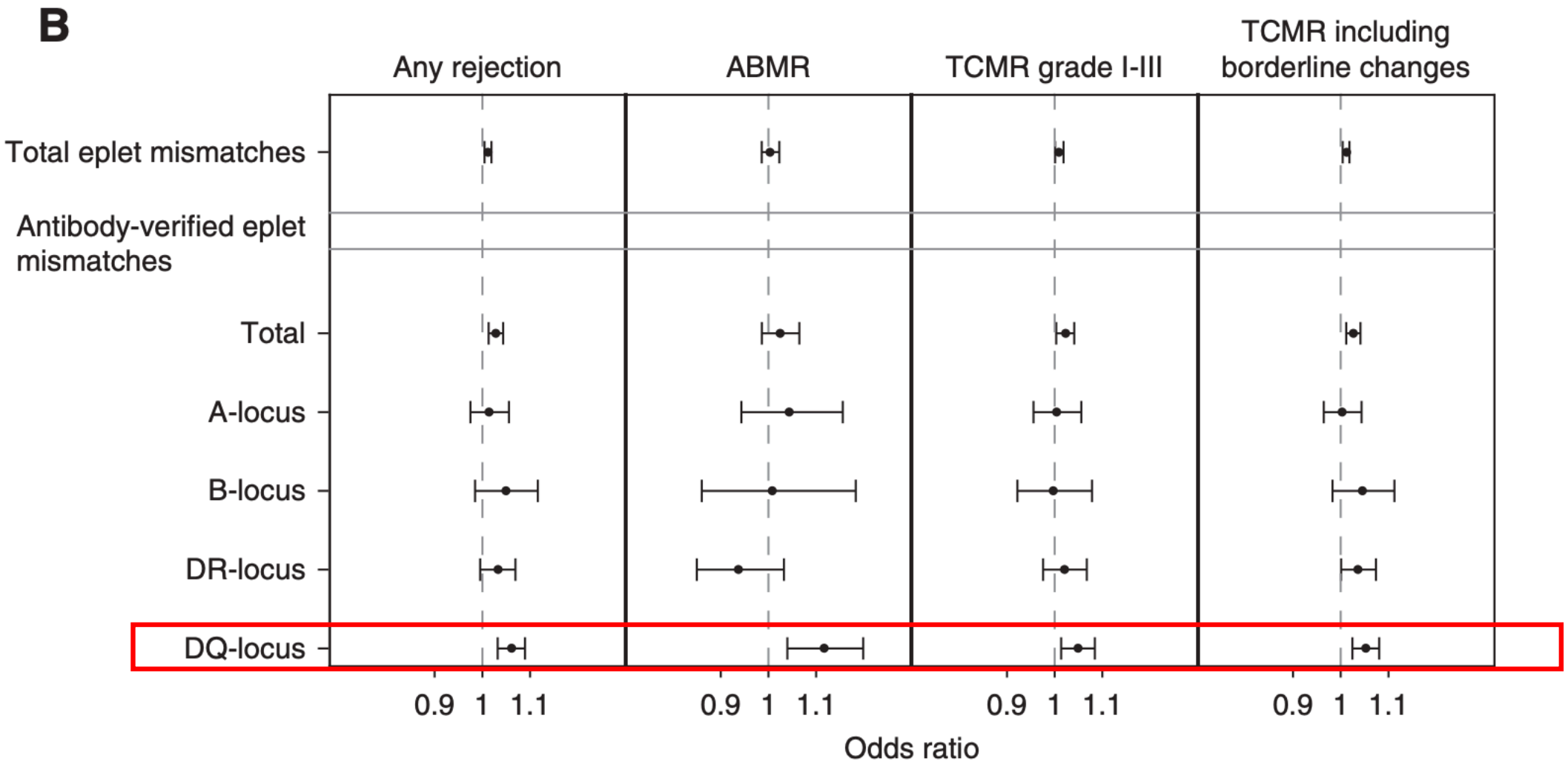
	80 90
Recipient B*7	AQTDRESLRN LRGYYNQSEA
Donor 1 B*8	T---------- ----------
Donor 2 B*35	T--Y------ ----------
Donor 3 B*44	T--Y--N--T ALR-------

HLA Antigen vs. Eplet Matching

- Antigen matching: are two HLA molecules the same (yes or no)
- Eplet matching: how similar/dissimilar are two HLA molecules

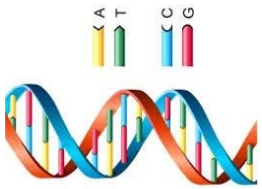


Wiebe, AJT, 2019



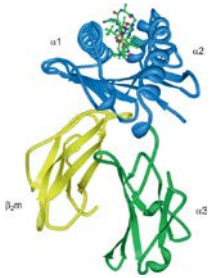
Senev, JASN 2020

Innovation in rapid HLA sequencing for molecular mismatch analysis



HLA-A*02:01

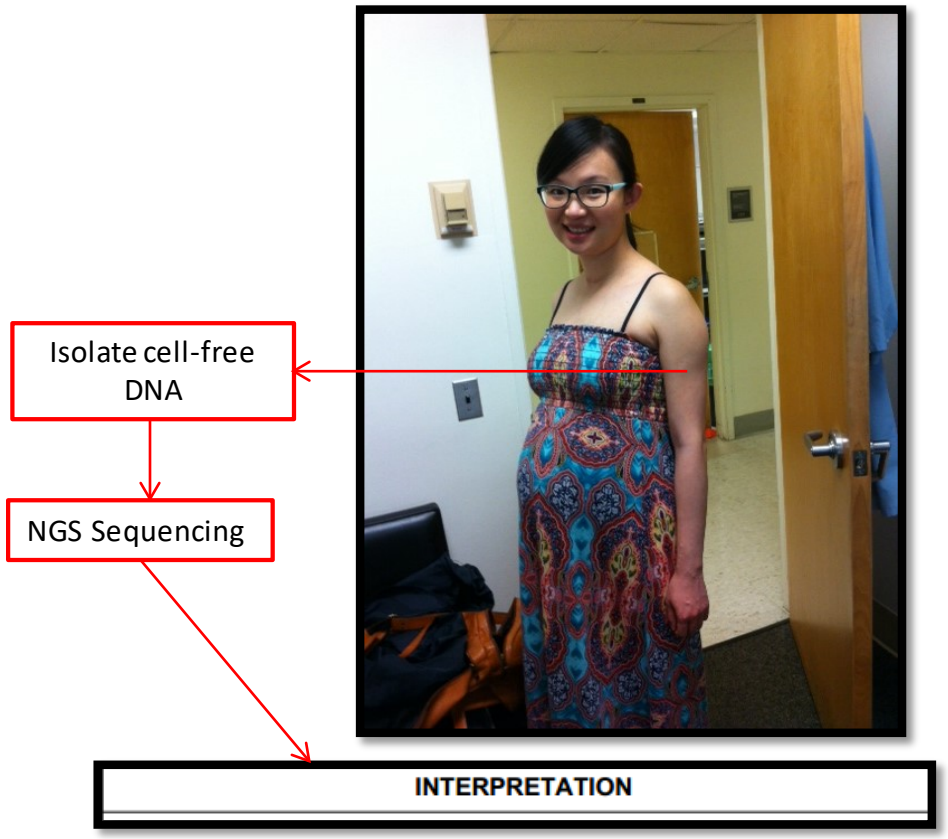
HLA matchmaker

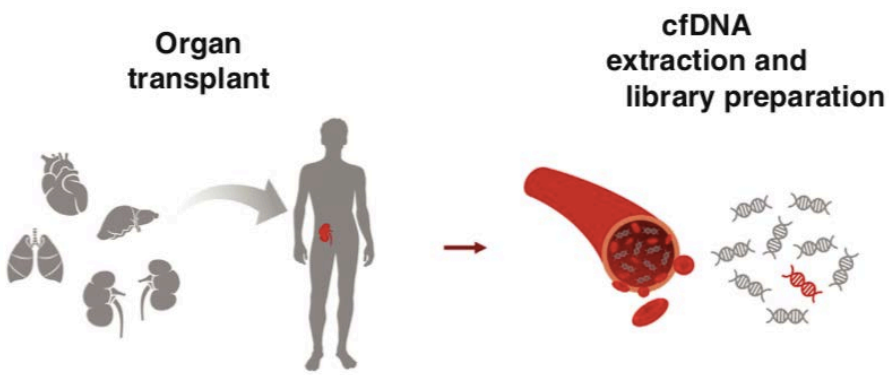


Class	Status	Gene	Eplet Mismatches
Class I	Total	ABC	17
	Antibody-verified	ABC	11
	Non-verified	ABC	6
Class II	Total	Class II	70
	Antibody-verified	Class II	26
	Non-verified	Class II	44
	Total	DRB1345	27
	Antibody-verified	DRB1345	12
	Non-verified	DRB1345	15
	Total	DQ	28
	Antibody-verified	DQ	10
	Non-verified	DQ	18
	Total	DQB1	18
	Antibody-verified	DQB1	6
	Non-verified	DQB1	12
	Total	DQA1	10
	Antibody-verified	DQA1	4
	Non-verified	DQA1	6
	Total	DP	15
	Antibody-verified	DP	4
	Non-verified	DP	11
	Total	DPB1	9
	Antibody-verified	DPB1	3
	Non-verified	DPB1	6
	Total	DPA1	6
	Antibody-verified	DPA1	1
	Non-verified	DPA1	5

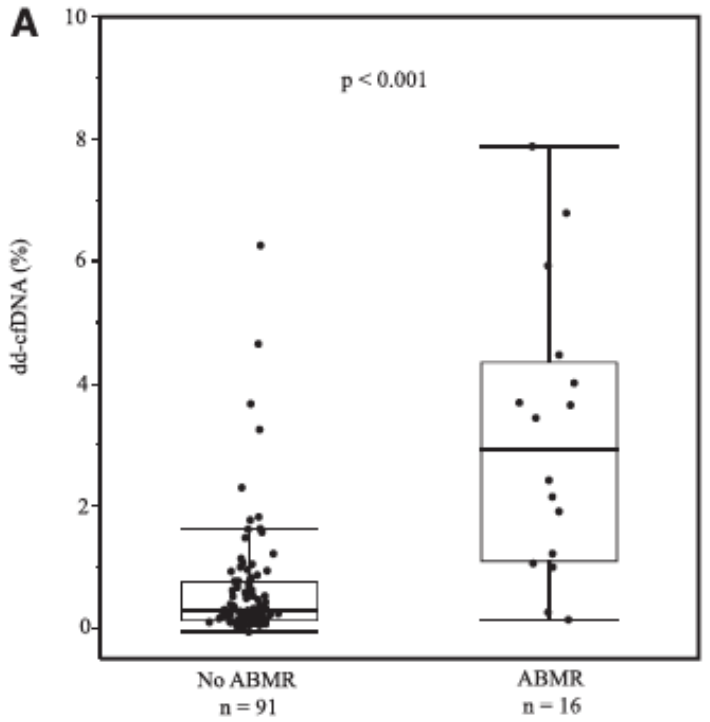
Can we monitor patients better?

Non-invasive monitoring: donor-derived cell-free DNA

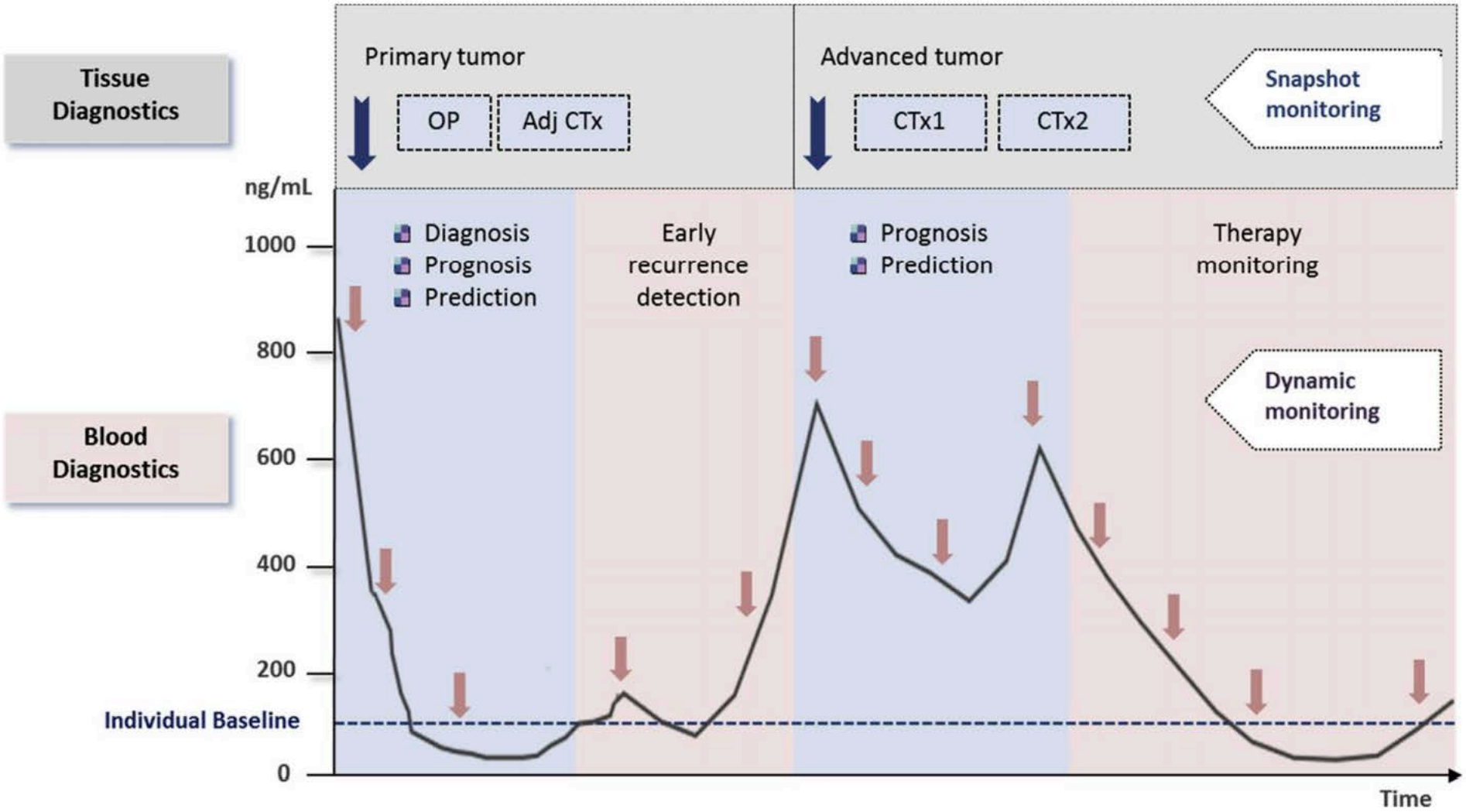




JASN 2017



Tumor-derived cell-free DNA

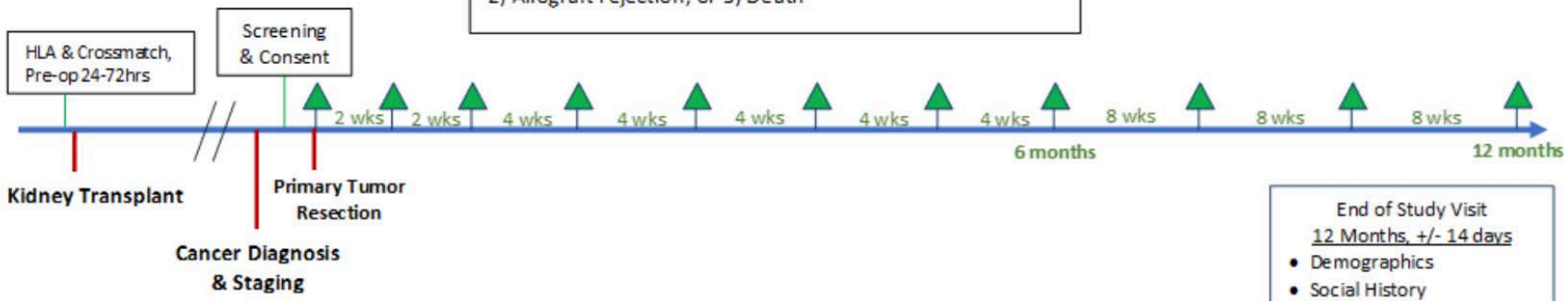


Biomolecular Detection and Quantification 2019

Taking the first step toward precision medicine

Study Flow Chart

Primary Endpoints: 1) Clinical progression of cancer, 2) Allograft rejection, or 3) Death

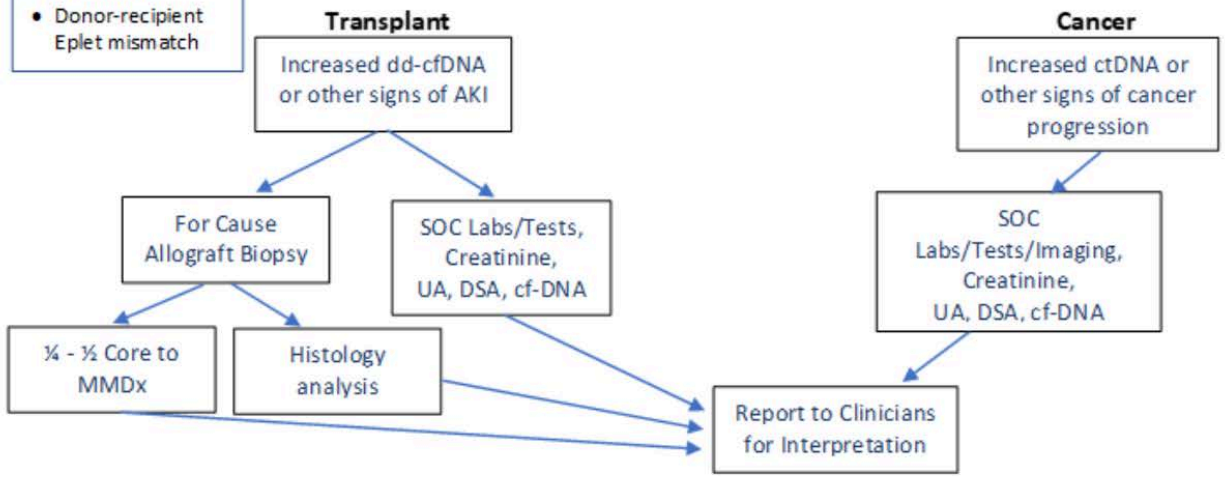


Baseline Study Visit
- Demographics
- Transplant History
- Social History
- Physical Exam
  - Vitals
  - Height & Weight
- eGFR & creatinine
- CNI trough levels (if available)
- Comorbitities
- Cancer Grade & Stage
- Baseline IS
- Donor-recipient Eplet mismatch

▲ = Prospera, Signatera (post-resection), Routine Labs. Increased dd-cfDNA or ctDNA will lead to clinical evaluation and usual care for rejection or cancer recurrence.

Inclusion Criteria
Age ≥ 18 years
Kidney Transplant Recipient
Receiving ongoing care at UW or UBC Transplant Program
Patient has capacity to provide informed consent
Solid Tumor Malignancy with indication for CPI Treatment
Exclusion Criteria
Pregnancy
Multi-organ transplant
Currently on acute or chronic dialysis

End of Study Visit
12 Months, +/- 14 days
- Demographics
- Social History
- Physical Exam
  - Vitals
  - Height & Weight
- eGFR & creatinine
- IS regimen
- CNI trough levels (if available)
- Comorbidities
- ED & Urgent Care Visits
- Hospitalizations
- Cancer Stage
- Progression of Disease (Cancer)
- IRAEs
- Allograft Rejection



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