Early CNI-Free Strategies: Balancing Safety and Efficacy

Cynthia Gries, MD MSc
Lung Transplant Medical Director

I have nothing to disclose.

AdventHealth

Overview of Today's Talk

Review of Current Immunosuppression strategies

Review of Immunology

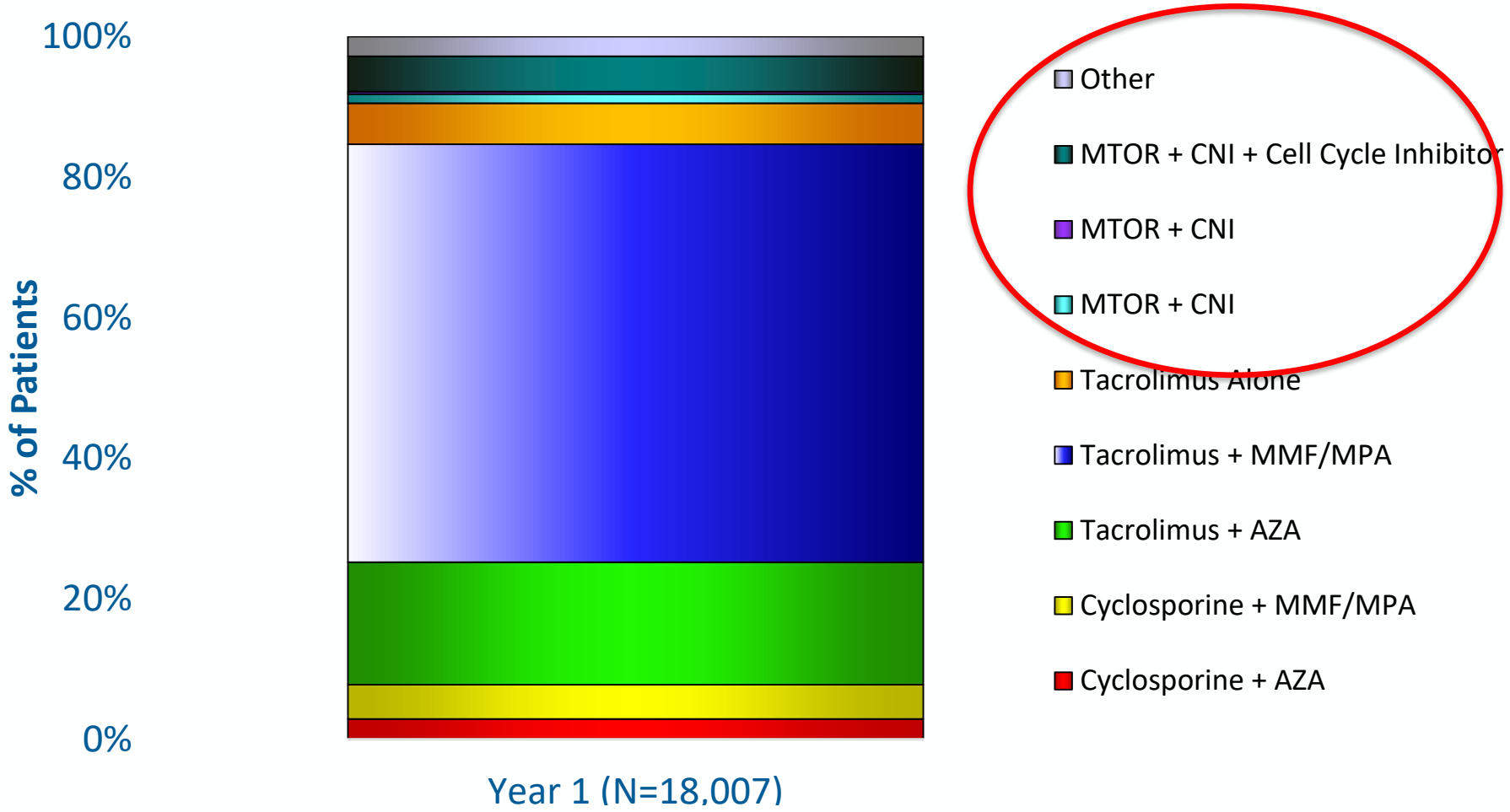
Review of Pharmacology

Safety and Efficacy of CNI-Free Regimens

AdventHealth

Maintenance Immunosuppression Drugs at 1 Year Follow up

(January 2004 – June 2017)

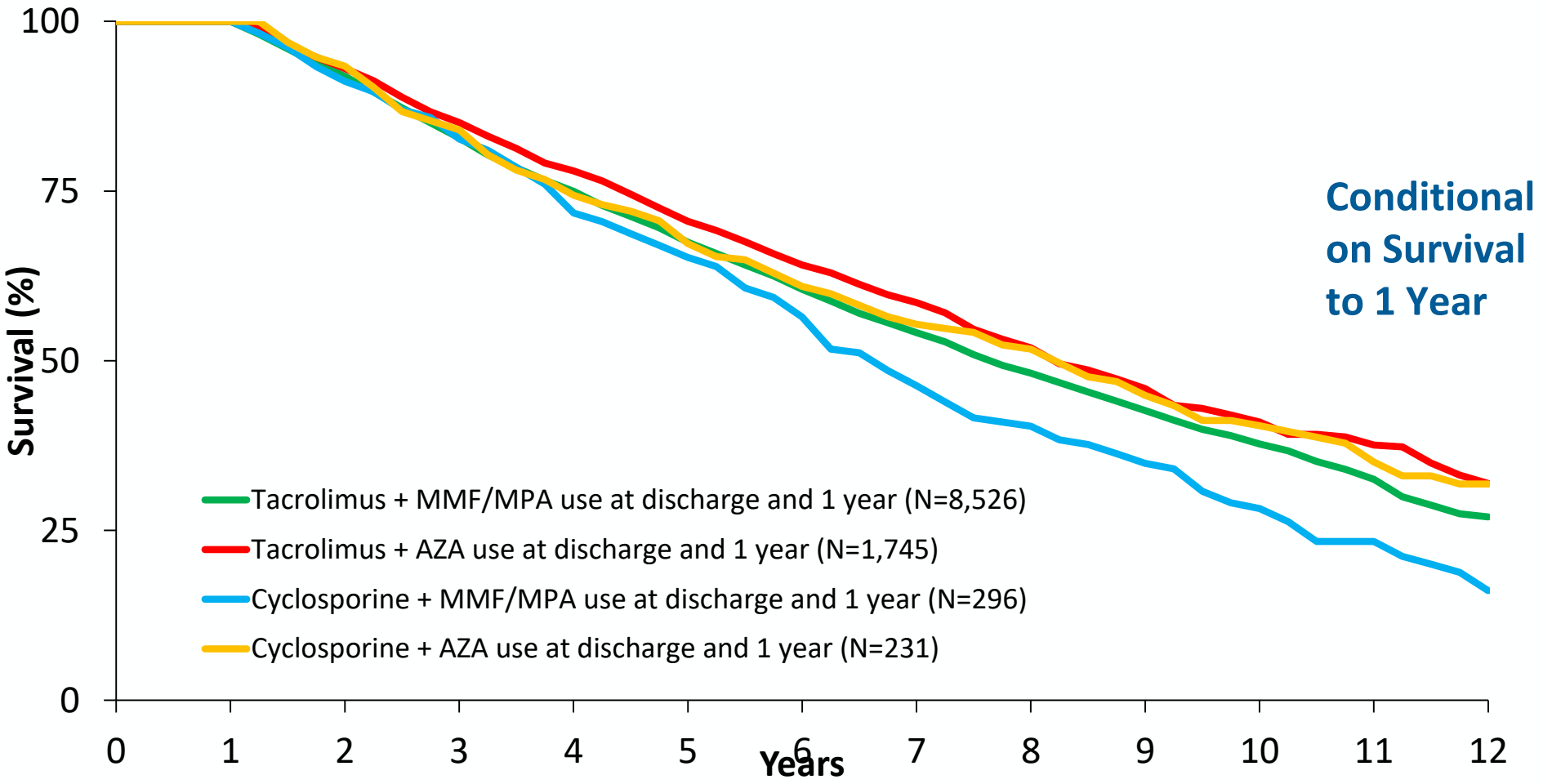


ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

AdventHealth

Survival in Lung Transplant patients by Immunosuppression

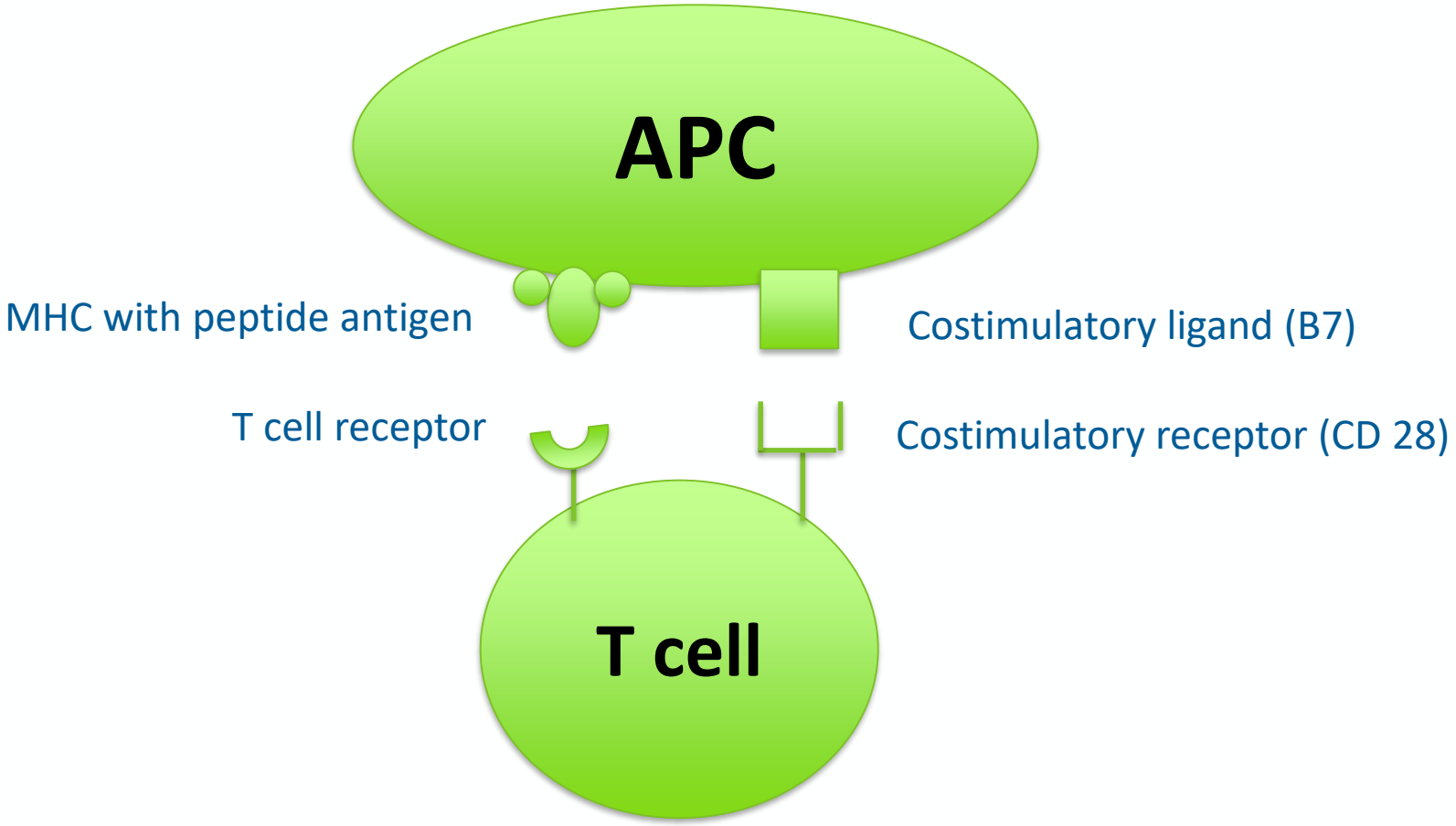
January 2004 – June 2016



ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

AdventHealth

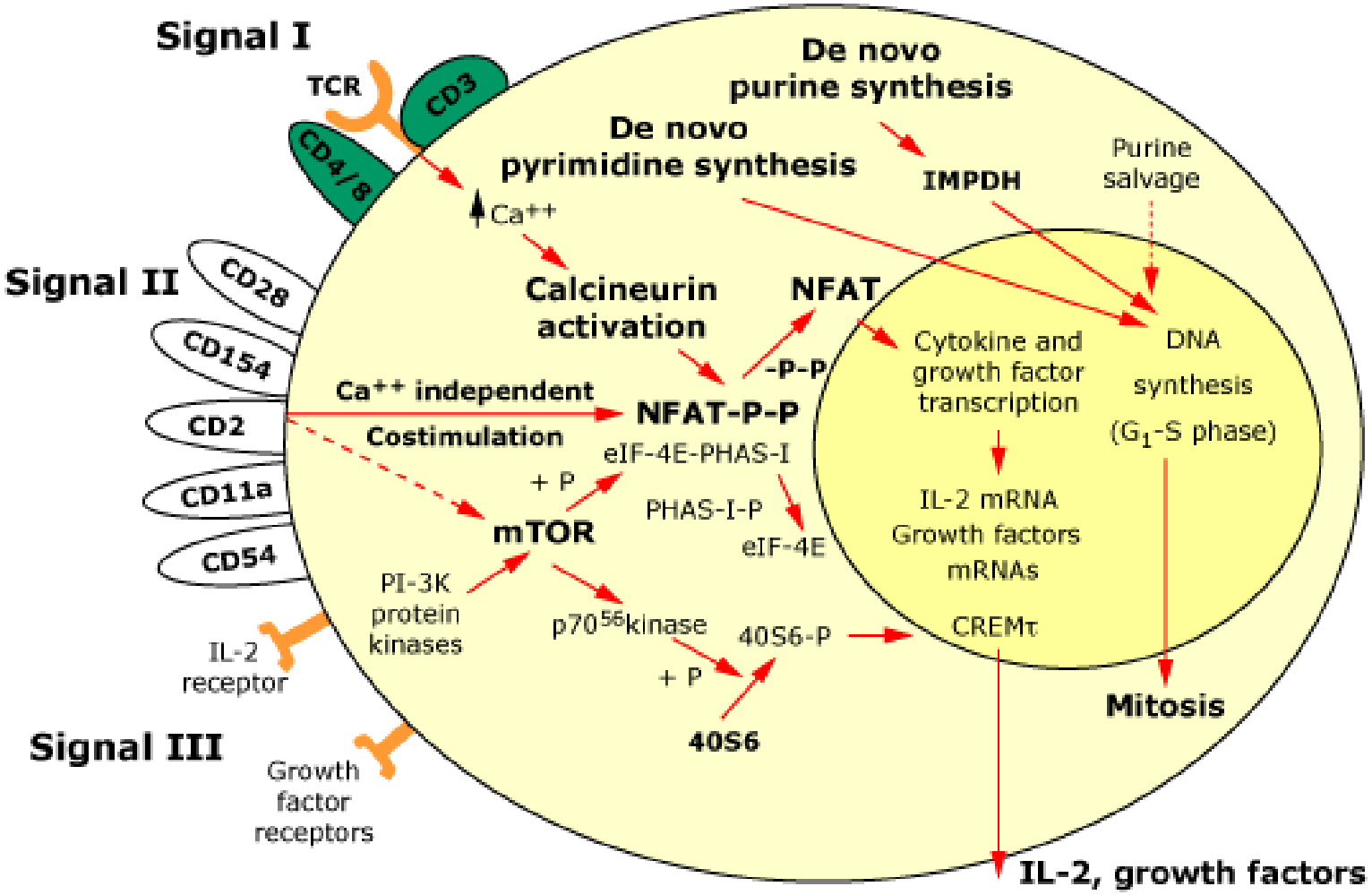
Two signal T cell activation



APC: Antigen Presenting Cell which include: macrophages, B cells and dendritic cells

AdventHealth

Basics of immune therapy



Signal I: APC presents antigen to TCR

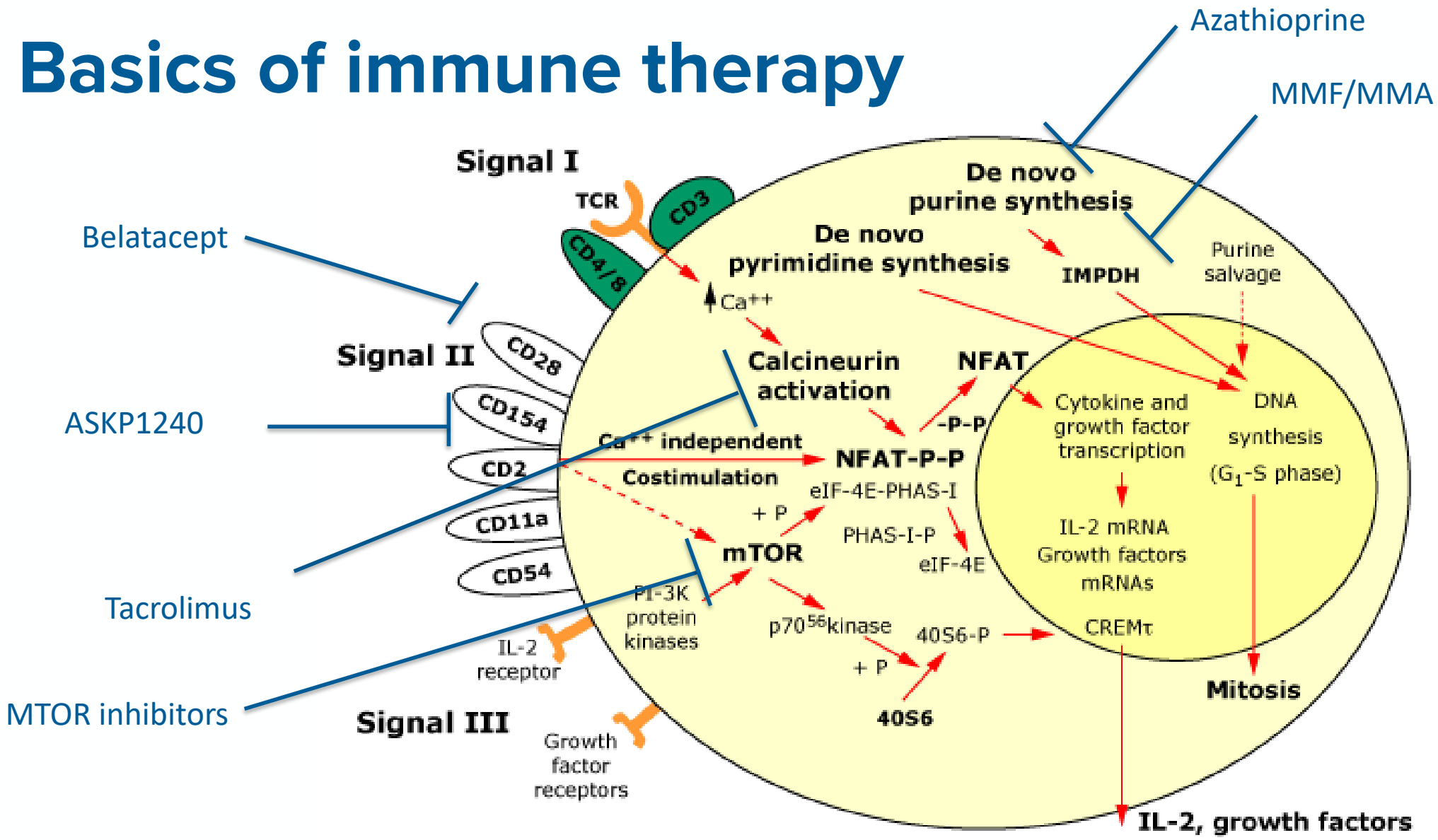
Signal II: APC binds to costimulatory receptors

Signal III: Newly synthesized IL2 and GF cause clonal expansion of newly activated T cells.

Vierling, JM. Clinical Use of Immunosuppressive Drugs to Control the Immune Response

AdventHealth

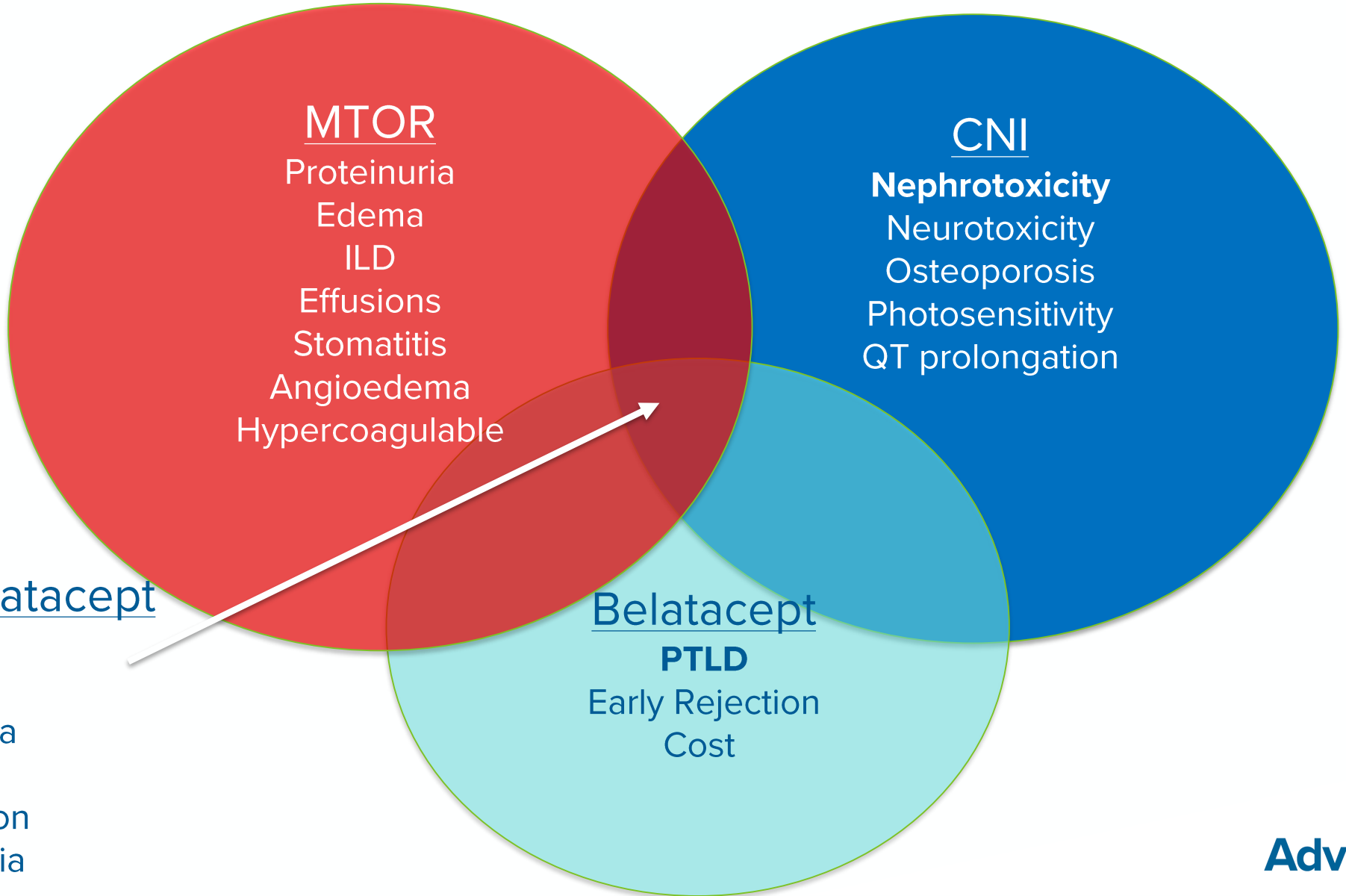
Basics of immune therapy



Vierling, JM. Clinical Use of Immunosuppressive Drugs to Control the Immune Response

AdventHealth

Adverse Reactions



MTOR/CNI/Belatacept

Cancers
Infection
Leukopenia
Diabetes
Hypertension
Dyslipidemia

AdventHealth

Cumulative Morbidity Rates at 1 and 5 Years

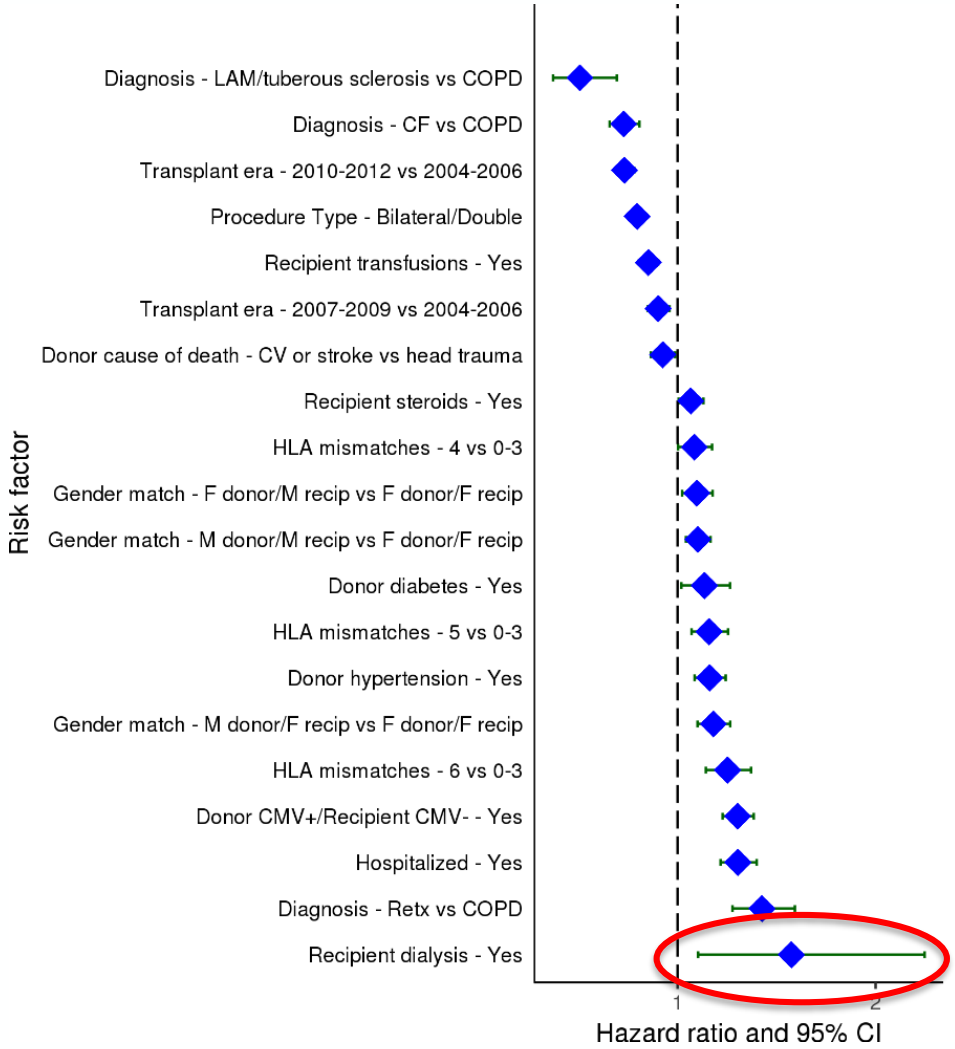
Outcome	Within 1 Year	Total number	Within 5 Years	Total number
Severe Renal Dysfunction*	5.7%	(N = 24,364)	16.3%	(N = 10,159)
Creatinine > 2.5 mg/dl (221 µmol/L)	*4.4%*		*12.9%*	
Chronic Dialysis	*1.3%*		*2.8%*	
Renal Transplant	*0.0%*		*0.6%*	

* Severe renal dysfunction = Creatinine > 2.5 mg/dl (221 µmol/L), dialysis or renal transplant

ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

AdventHealth

Risk Factors For 5 Year Mortality



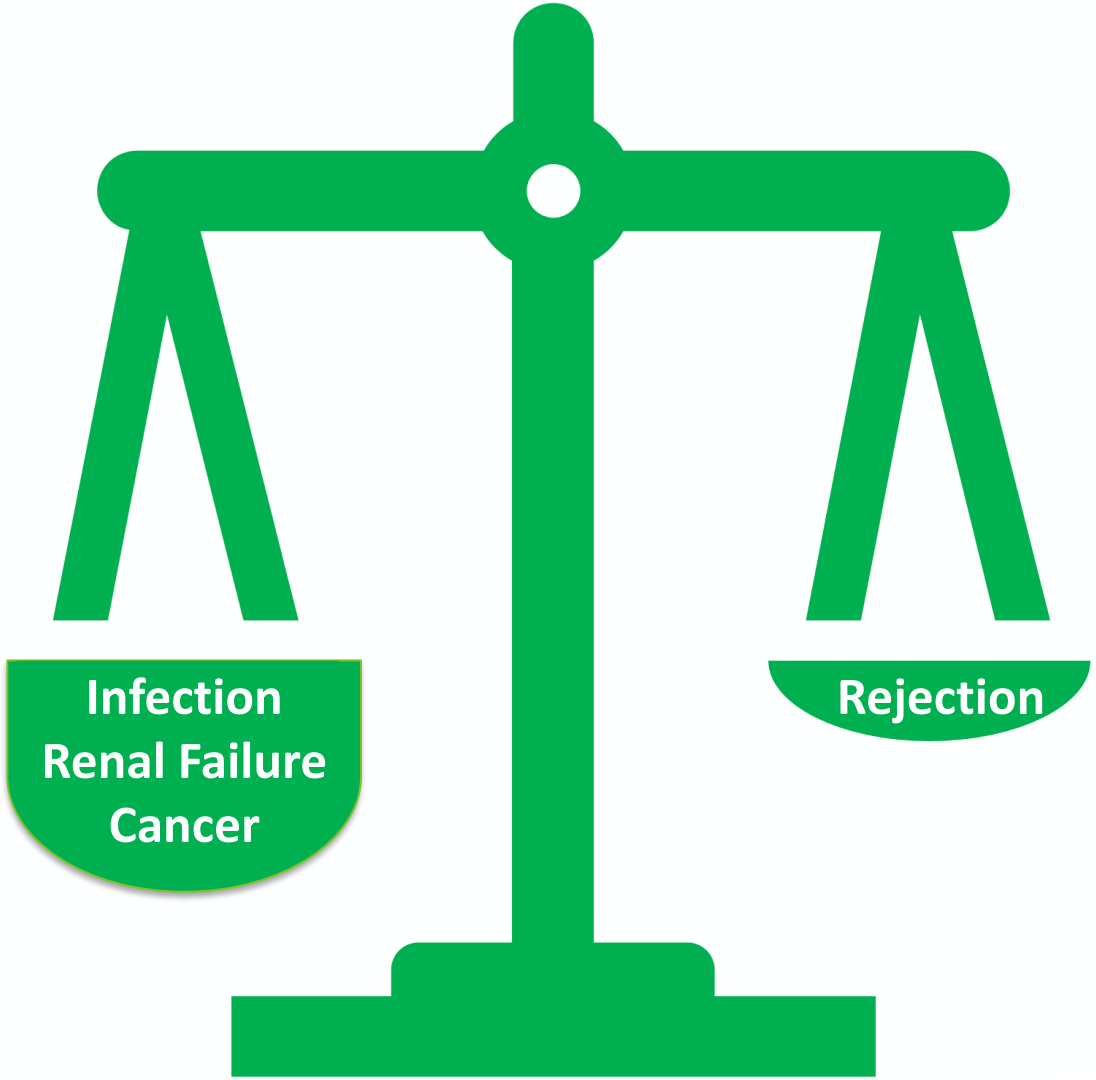
HR	LCL	UCL	pvalue	N
0.506	0.371	0.692	<0.01	319
0.728	0.657	0.807	<0.01	5442
0.731	0.685	0.780	<0.01	9396
0.795	0.756	0.836	<0.01	23121
0.852	0.805	0.900	<0.01	26054
0.902	0.848	0.959	<0.01	7540
0.924	0.865	0.987	0.02	8874
1.066	1.005	1.130	0.03	8528
1.085	1.002	1.174	0.05	5330
1.097	1.022	1.177	0.01	4981
1.102	1.042	1.166	<0.01	14497
1.135	1.019	1.265	0.02	1198
1.159	1.071	1.254	<0.01	7028
1.161	1.086	1.242	<0.01	4370
1.180	1.100	1.266	<0.01	4886
1.252	1.143	1.371	<0.01	4081
1.303	1.227	1.384	<0.01	4418
1.305	1.217	1.399	<0.01	3107
1.426	1.277	1.592	<0.01	1254
1.575	1.104	2.248	0.01	79

(N = 34,370)

ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

AdventHealth

What is the most effective regimen with the lowest side effect profile?



AdventHealth

mTOR Inhibitors

- Proliferation signal inhibitor
- Renal-sparing
- Act synergistically with CNI to allow minimization
- Everolimus vs. MMF[1] in Lung Transplant Patients
  - Lower incidence of BOS (p=0.041)
  - Lower incidence of AR (0.005)
  - Lower incidence of CMV antigenemia (0.005)
  - Lower respiratory tract infection (0.003)

- [1] Strueber AJT 2016

AdventHealth

mTOR Inhibitors: Triple vs. Quadruple Therapy

- Prospective, randomized open label study of 130 lung transplant patients
- All received cell cycle inhibitor and prednisone
- Arms:
  - Quadruple Therapy
    - Everolimus (3-5ng/mL)
    - Tacrolimus (3-5ng/mL) or Cyclosporine (25-75ng/mL)
  - Triple Therapy
    - Tacrolimus (>5ng/mL) or Cyclosporine (>100 ng/mL)

Gottlieb AJT 2019)

AdventHealth

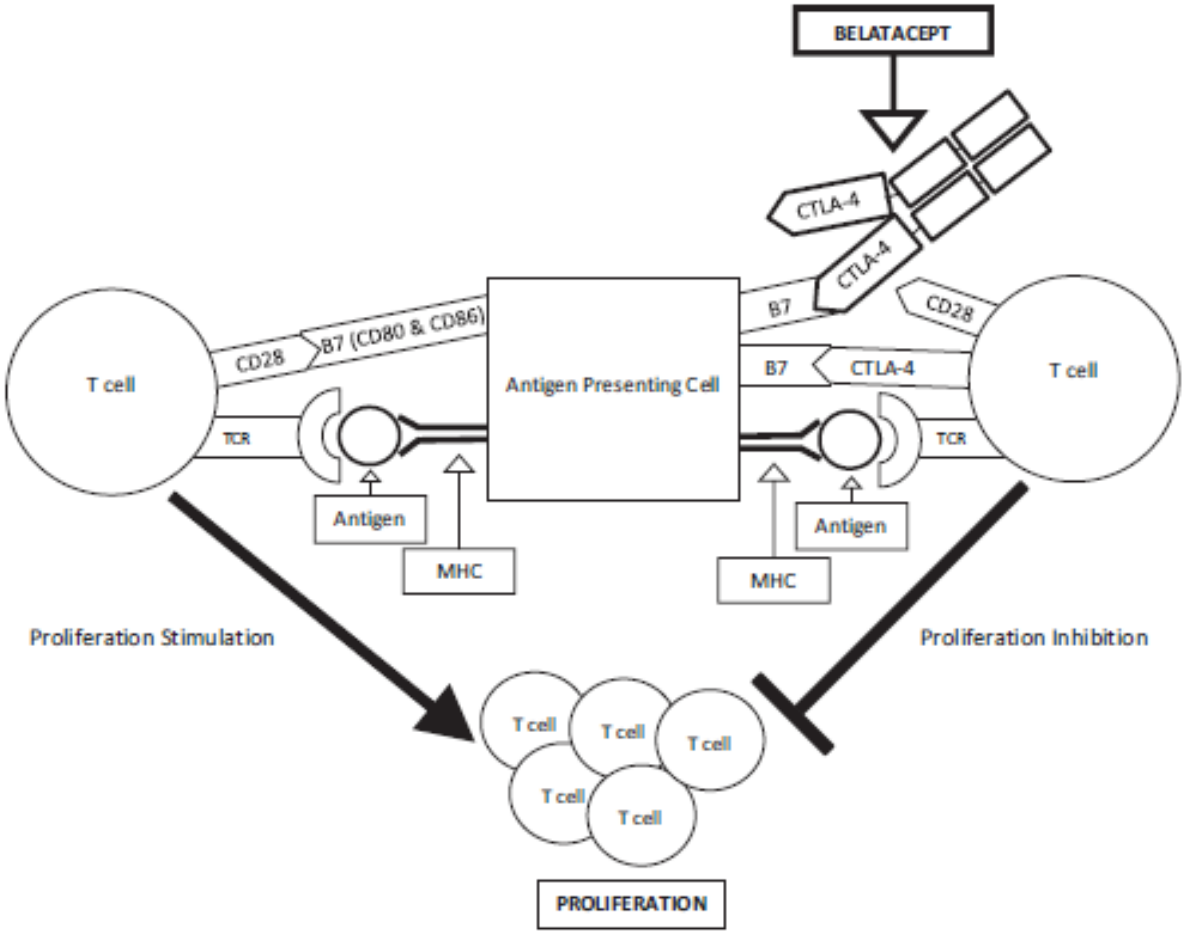
mTOR Inhibitors: Triple vs. Quadruple Therapy

- GFR better in quadruple therapy: 65(59, 70) vs. 55 (50, 60)
- Quadruple Therapy
  - More adverse events leading to drug discontinuation (0.001)
  - More edema (0.027)
  - No increased risk of infection

Gottlieb AJT 2019

AdventHealth

Belatacept



- Fusion protein that inhibits signaling thru the CD28 receptor by binding to CD80(B7-1) and CD86 (B7-2) on the APC
- Monthly infusions
- No drug levels
- Low side effect profile
- May reduce de novo DSA by blocking B7:CD28 on plasma cells

AdventHealth

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

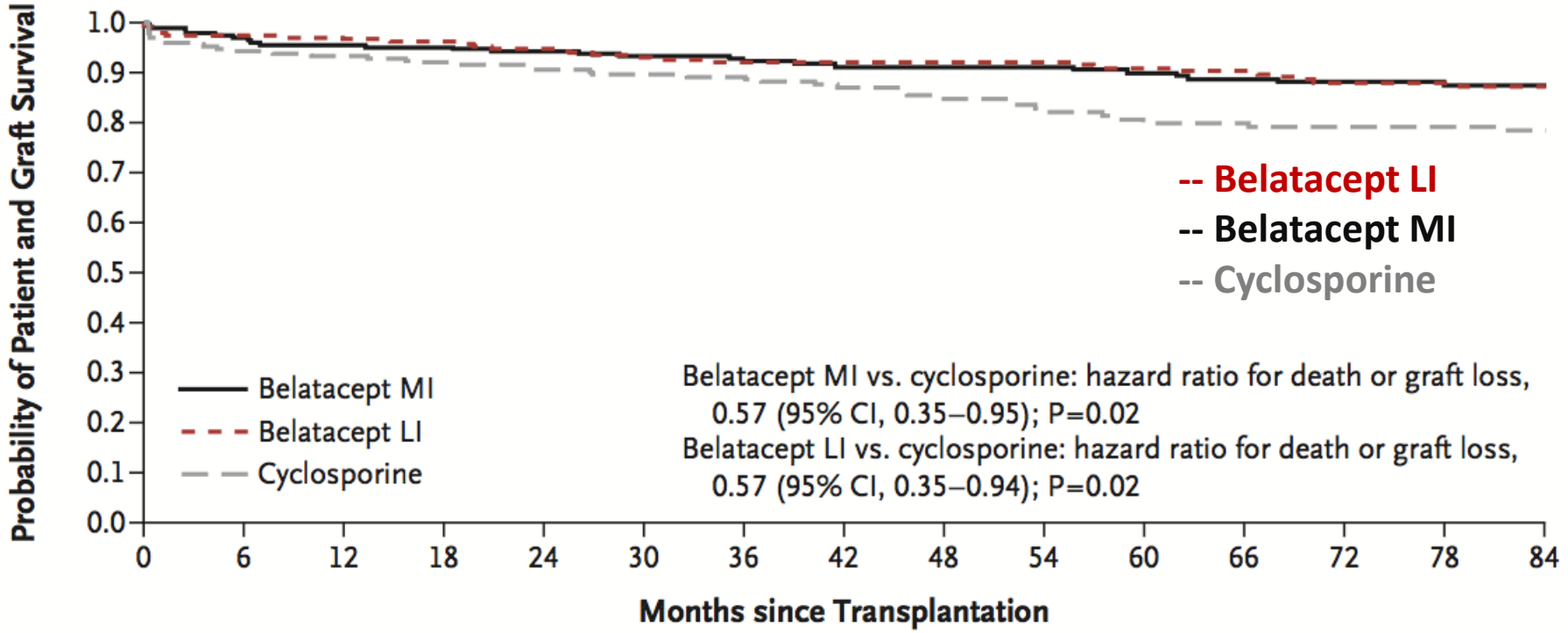
Belatacept and Long-Term Outcomes in Kidney Transplantation

Flavio Vincenti, M.D., Lionel Rostaing, M.D., Ph.D., Joseph Grinyo, M.D., Ph.D., Kim Rice, M.D., Steven Steinberg, M.D., Luis Gaite, M.D., Marie-Christine Moal, M.D., Guillermo A. Mondragon-Ramirez, M.D., Jatin Kothari, M.D., Martin S. Polinsky, M.D., Herwig-Ulf Meier-Kriesche, M.D., Stephane Munier, M.Sc., and Christian P. Larsen, M.D., Ph.D.

AdventHealth

Patient and Graft Survival by Immunosuppression Regimen

A



No. at Risk

Belatacept MI	219	212	208	206	204	202	199	153	151	149	146	142	135	131	128
Belatacept LI	226	220	218	216	213	209	204	165	161	159	152	151	142	139	137
Cyclosporine	221	208	206	202	199	197	186	137	123	117	112	107	102	100	92

AdventHealth

Acute Rejection compared to CSA

Immunosuppression Regimen	P-value	HR (95% CI)
Belatacept MI	0.0001	2.649 (1.596, 4.397)
Belatacept LI	0.0302	1.905 (1.124, 3.232)

AdventHealth

Role of Belatacept on Regulatory T Cells (Tregs)

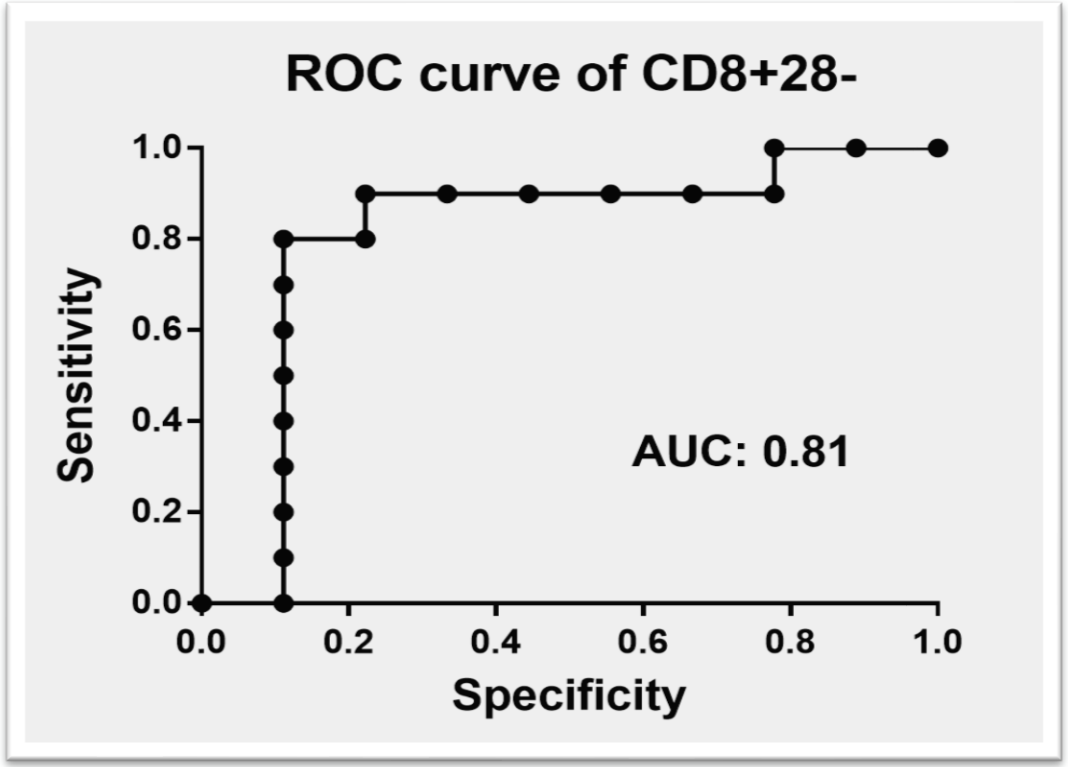
- Tregs important for immune tolerance
- C28 signaling important for survival of Tregs
- CTLA4-Ig reduced the number of Treg by half in mice.[1]
- May tip the scale to effector T cells and cause rejection

1 Riella AJT 2012

AdventHealth

Can we predict who will reject with Belatacept?

- Belatacept will not be effective on CD28- T cells
- Recipients with more than 50% $CD8^{+}CD28^{-}$ T cells pre-transplant were 19 times more likely to have rejection. (p=0.02)



Espinosa AJT 2016

AdventHealth

Belatacept with MTOR inhibitors

- Recipients with pre-existing memory cells (CD4+CD57+ cells) are resistant to costimulatory blockade
- Could be a benefit of depleting CD4+ with ATG/Alemtuzumab induction or use of MTOR

	Induction	AR	GFR (SD) ml/min per 1.73m2	Graft failure
Benefit				
Belatacept+ MMF	Basiliximab	22%	66 +/- 27	8%
CSA + MMF	Basiliximab	14%	44 +/- 24	11%
Phase II				
Bela + MMF	Thymo	15%	64 +/- 27	9%
Bela + siro	Thymo	4%	62 +/- 31	8%
Tacro + MMF	Thymo	3%	54 +/- 15	0%

AdventHealth

Era of precision medicine

Precision medicine: treatments targeted to an individual on the basis of genetics, biomarkers or phenotypic characteristics that maximize efficacy and minimizes toxicities.

AdventHealth

(*Transplantation* 2018;102: 171–177)

Original Clinical Science—General

Maintenance Belatacept-Based Immunosuppression in Lung Transplantation Recipients Who Failed Calcineurin Inhibitors

Carlo J. Iasella, PharmD,[1] Ryan J. Winstead, PharmD,[2] Cody A. Moore, PharmD,[1] Bruce A. Johnson, MD,[3] Ayelet T. Feinberg, RN,[3] Matthew R. Morrell, MD,[3] J. W. Awori Hayanga, MD,[4] Elizabeth A. Lendermon, MD,[3] Adriana Zeevi, PhD,[5] John F. McDyer, MD,[3] and Christopher R. Ensor, PharmD[1,3]

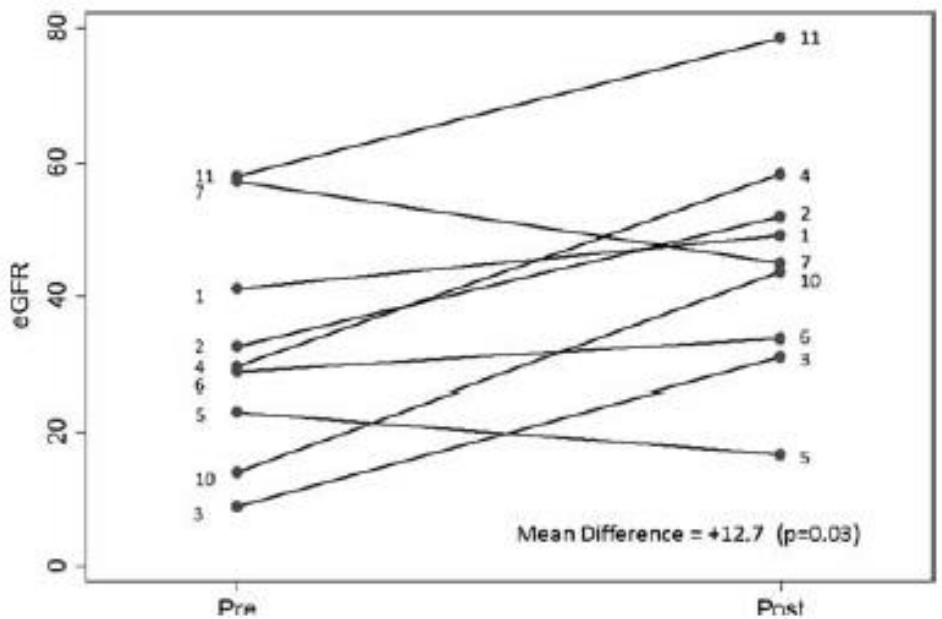
AdventHealth

TABLE 3.

Primary and secondary outcomes

Variables	Prebelatacept (mean ± SD)	Postbelatacept (mean ± SD)	*P*
CRSS	1.25 ± 1.31	1.18 ± 1.16	0.75[a]
Infection incidence, %	24.4 ± 22.5	16.0 ± 34.7	0.55[a]
eGFR, mL/min	32.53 ± 17.10	45.26 ± 17.64	0.03[b]
MAP, mm Hg	97.5 ± 8.01	92.1 ± 7.57	0.38[a]

[a] Data normally distributed by Shapiro-Wilk test. Paired *t* test reported. Due to small sample size, Wilcoxon Sign-Rank test also performed with no difference in findings.
[b] Data normally distributed by Shapiro-Wilk test. Paired t test reported. Wilcoxon sign-rank, $P = 0.05$.



AdventHealth

Transplant International

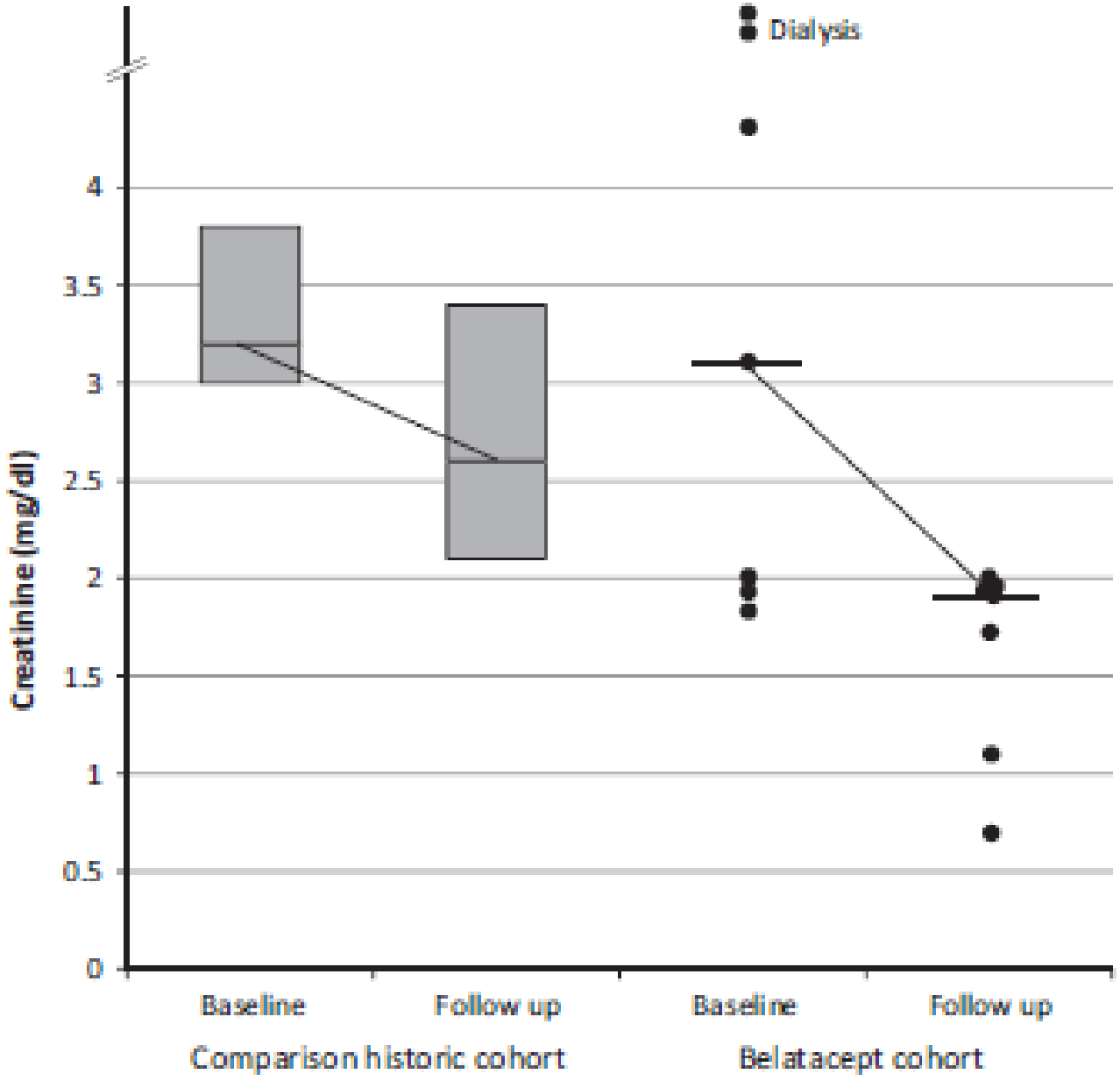
Transplant International 2016; 29: 453–463

ORIGINAL ARTICLE

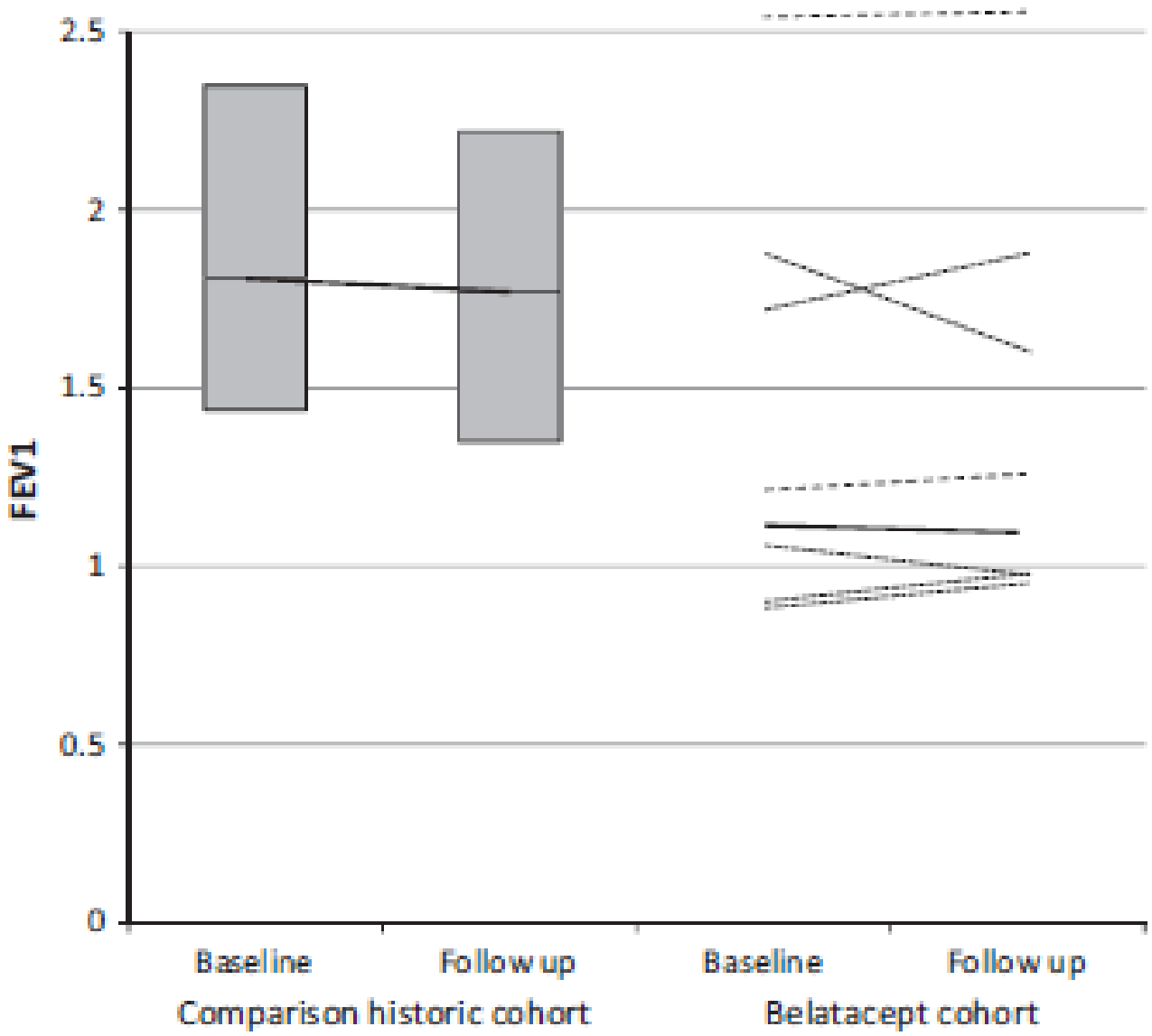
Belatacept for renal rescue in lung transplant patients

Irina Timofte[1], Michael Terrin[2], Erik Barr[2], Pablo Sanchez[3], June Kim[1], Robert Reed[4], Edward Britt[1], Bharath Ravichandran[5], Keshava Rajagopal[6], Bartley Griffith[3], Si Pham[3], Richard N. Pierson III[7] & Aldo Iacono[8]

AdventHealth



AdventHealth



AdventHealth

Other drugs in the works

- Tofacitinib:
  - JAK3 inhibitor
  - Used in RA
  - Phase IIa showed effective against rejection, but high risk of infection
- ASKP1240: Blocks CD-154 and CD-40.
  - Not effective by self
  - Murine models suggest effectiveness when combined with belatacept
- FR104 and BMS-931699
  - Antibody to CD28
  - Less adverse effect on T-regs

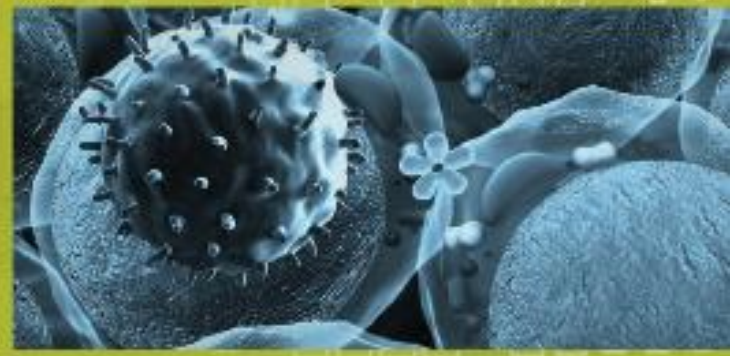
Conclusions

- Immunosuppression regimens are being investigated to improve survival and reduce side effects
- mTOR inhibitors may reduce rejection, CMV infection and renal dysfunction but have a high side effect profile
- Belatacept may help preserve renal function, but future studies are needed to determine who is at risk of rejection
- Future therapies are on their way including CD28 antibodies and targets of other co-stimulatory pathways.

AdventHealth

SAVE THE DATE

3rd Biennial Desensitization and Transplant Antibodies Course (DATA)



October 31 and
November 1, 2019

Loews Royal Pacific Resort
at Universal Orlando
Orlando, Florida

SPONSORED BY: AdventHealth

Formerly Florida Hospital Transplant Institute

Register Today at: DATAMedCourse.com