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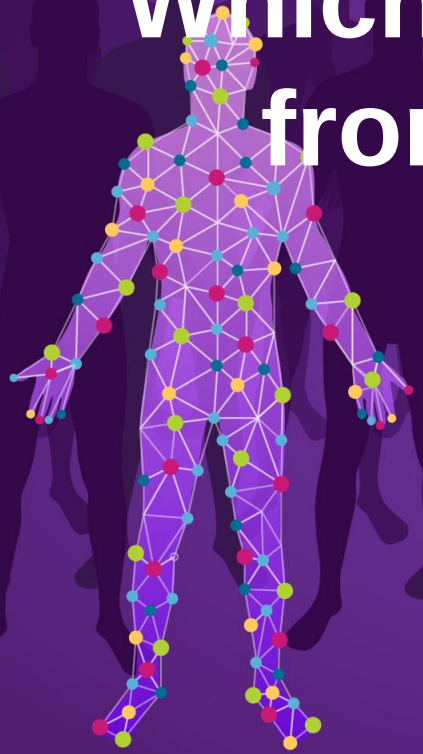
To Treat or Not to Treat: Which Patients May Benefit from Induction Therapy?



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CEOT CUTTING EDGE of TRANSPLANTATION

TRANSPLANT SUMMIT 2019

NO SIZE FITS ALL: *Uncovering the Potential of Personalized Transplantation*

FEBRUARY 21–23, 2019 • ARIZONA BILTMORE • PHOENIX, AZ

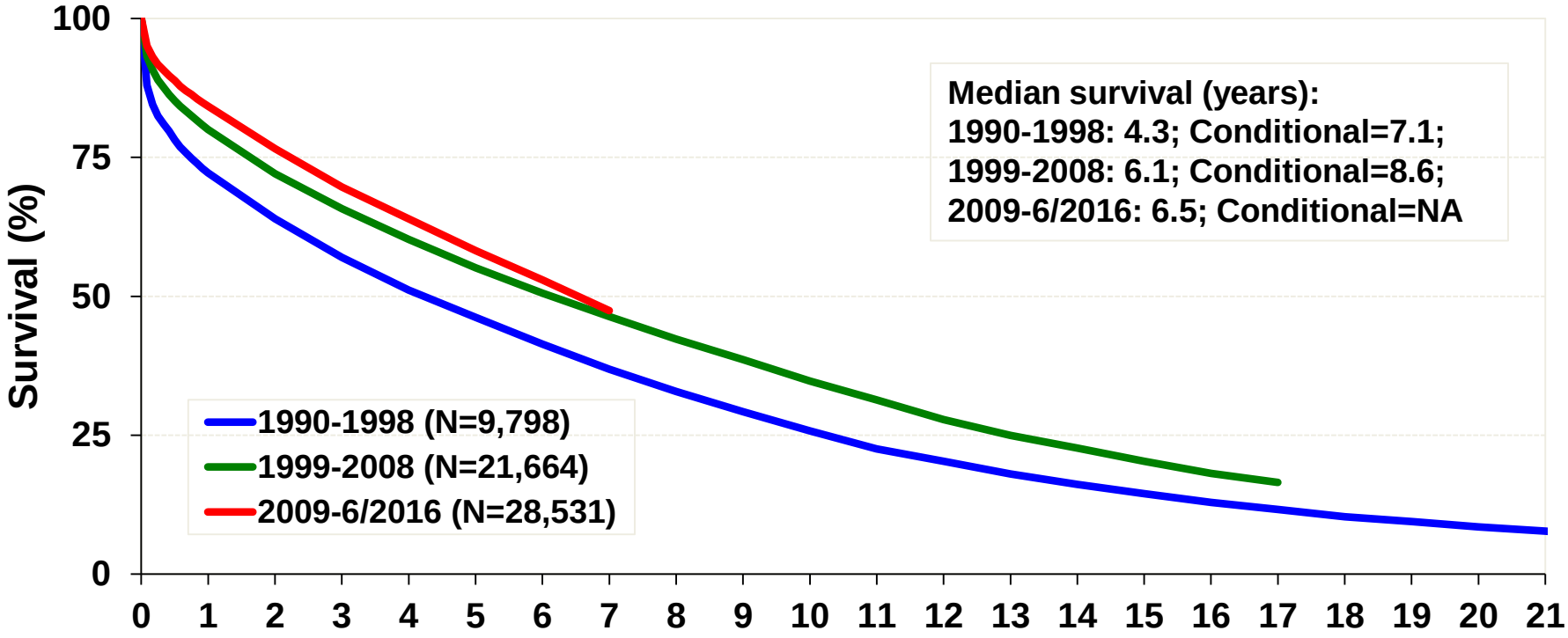
Disclosures

- Bristol Myers Squibb – grant funding
- Therakos – grant funding
- Transmedics – consultant
- Theravance Biotherapeutics – advisory board
- Vectura – advisory board
- No medication is FDA-approved for lung transplantation – all drugs/treatments discussed in this presentation are off-label

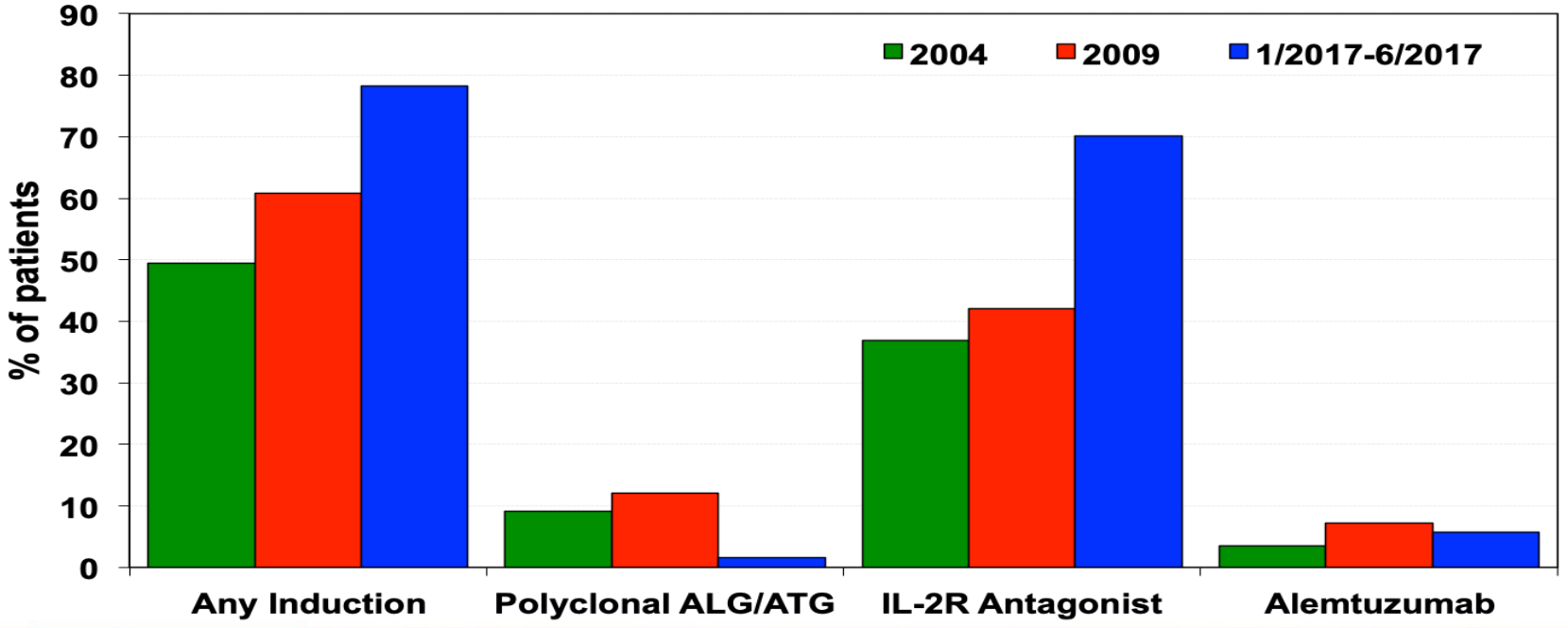
Learning Objectives

- Review literature on induction immunosuppression after lung transplantation
- Identify potential benefits & risks
- Outline potential patients who may benefit the most

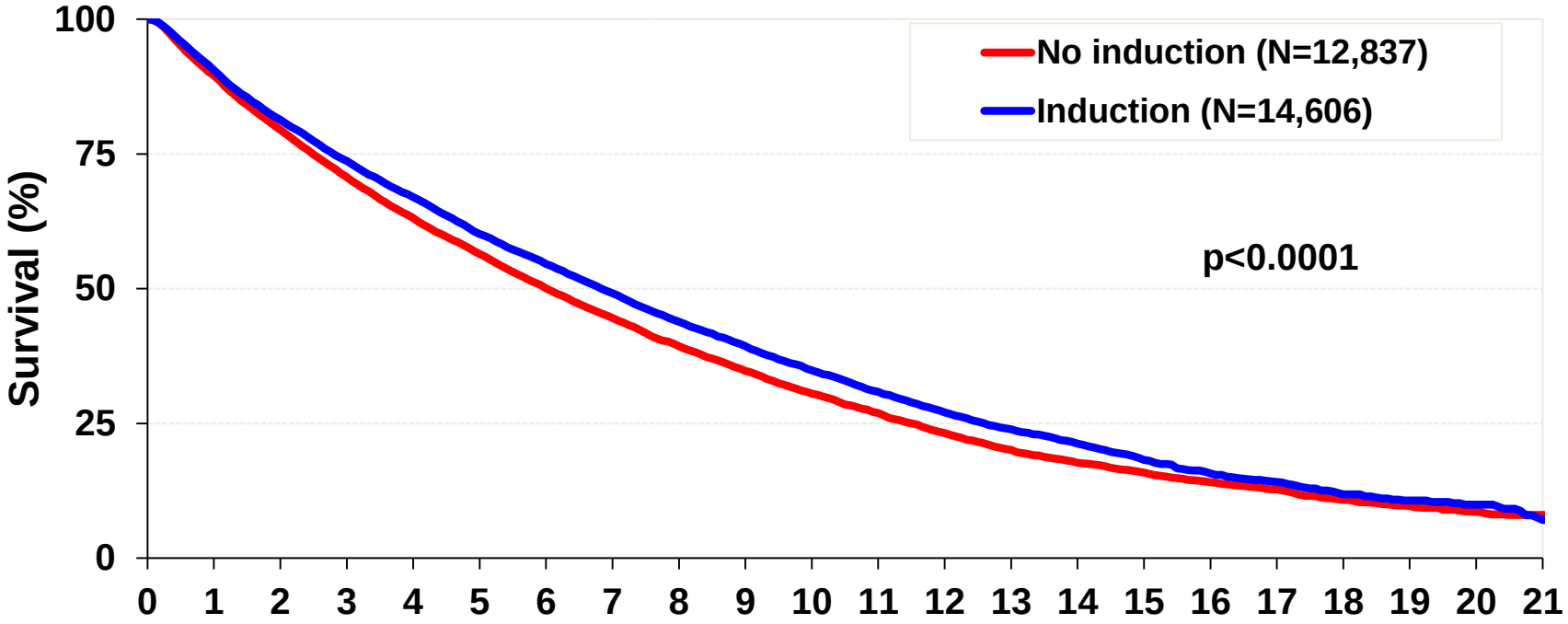
Survival – ISHLT Registry



Induction Immunosuppression



Survival & Induction Use



Limitations of Registry Data

- Unadjusted survival
  - Additional variables that might influence survival & variables that might influence decision to use induction are not accounted for
- Immunosuppression is center-specific rather than patient-specific
  - Center effect vs. induction effect

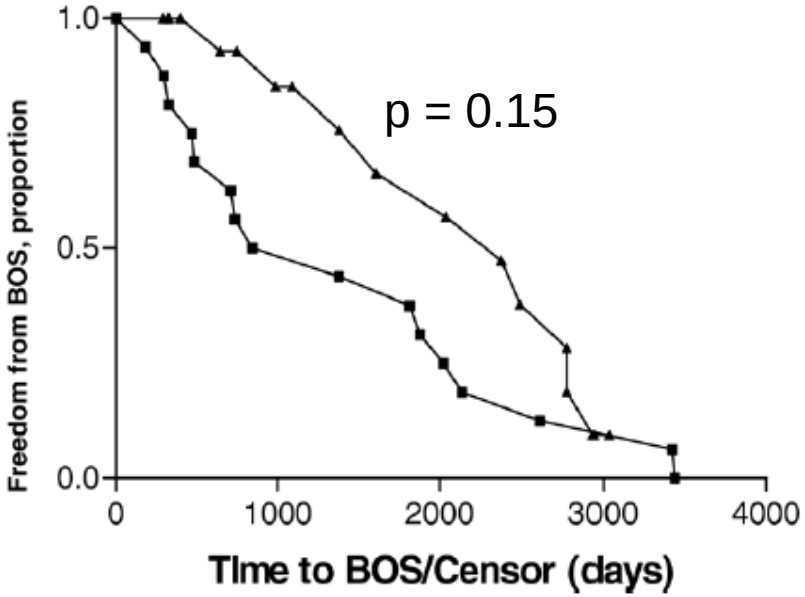
Reference	Design	Sites	N	Agents
Palmer, 1999	RCT	1	44	ATG vs. No induction
Brock, 2001	RCT	1	87	OKT3 vs. ATG vs. Daclizumab
Lischke, 2007	Non-randomized	1	25	ATG vs. Daclizumab
Hartwig, 2008	RCT	1	44	ATG vs. No induction
Jaksch, 2014	RCT	1	60	ATG vs. Alemtuzumab
Snell, 2014	RCT	Multi	223	ATG vs. Placebo

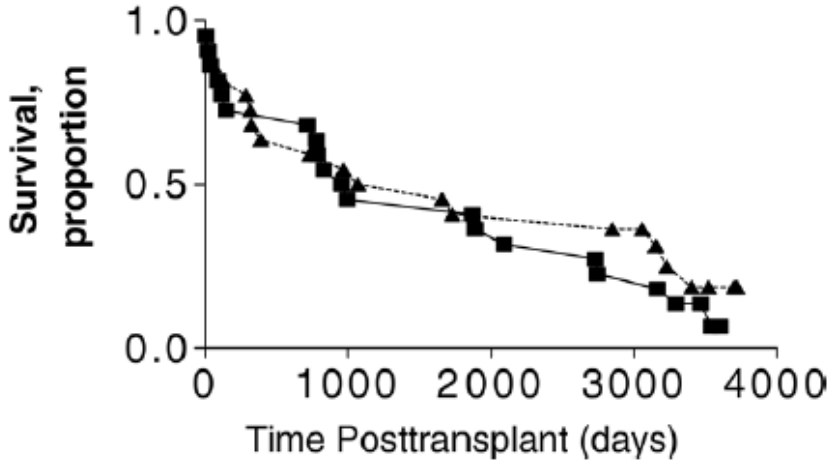
Rabbit ATG

- RCT of ATG vs. no induction, n = 44
- CSA, Azathioprine, Prednisone
- ACR ≥ A2: ATG, 23% vs. no induction, 55% (p = 0.003)
- No difference in BOS
- No difference in infection or malignancy

Chest 1999; 116: 127

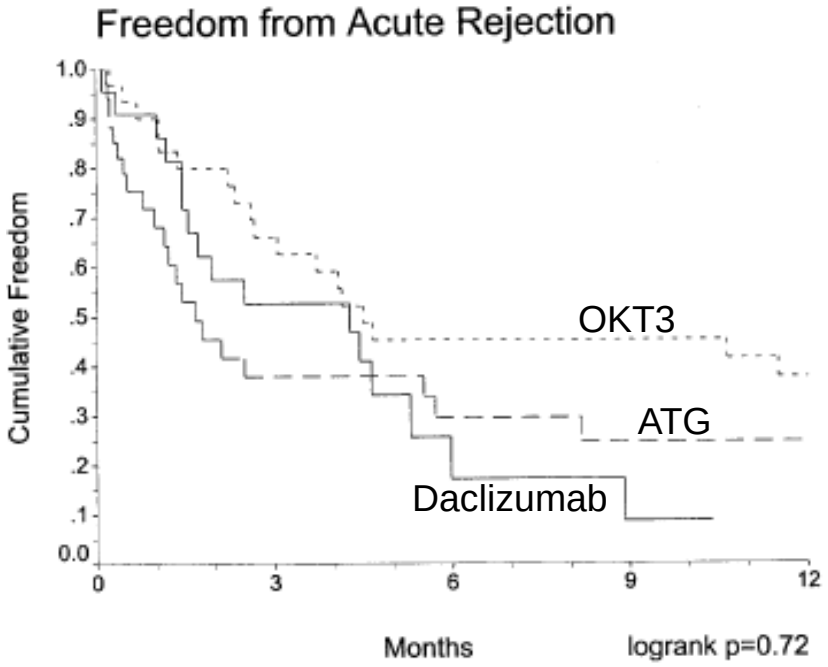
Rabbit ATG Long Term Outcomes

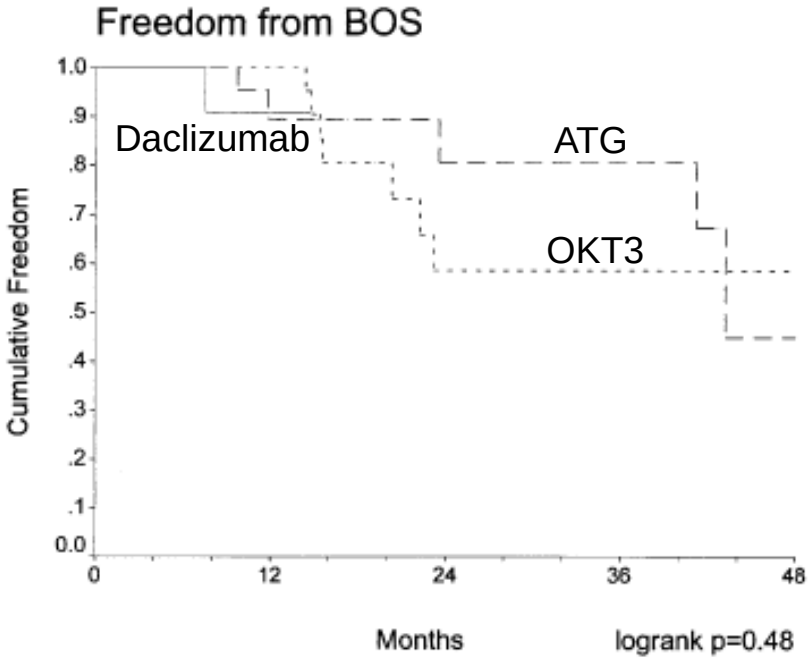




J Heart Lung Transplant 2008; 27: 547

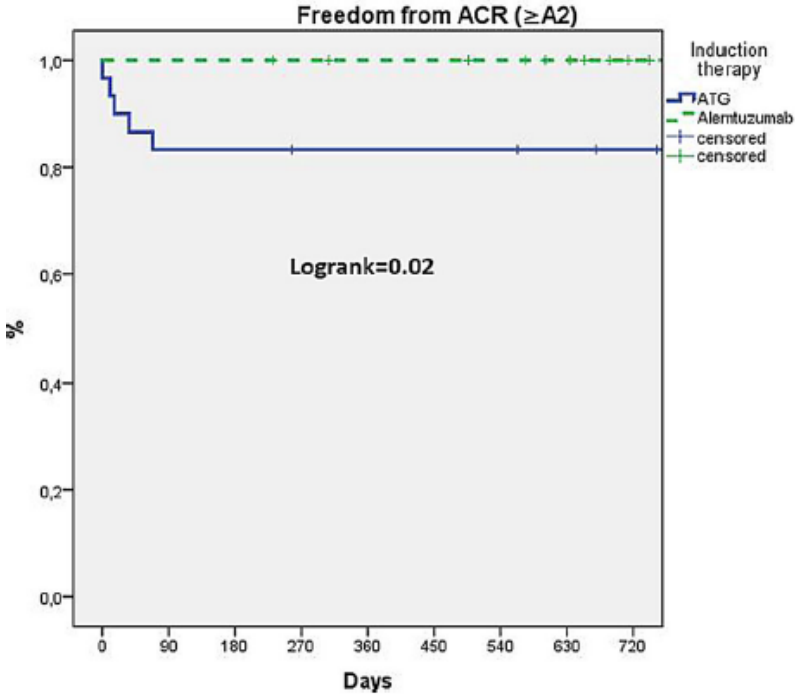
OKT3 vs. ATG vs. Daclizumab

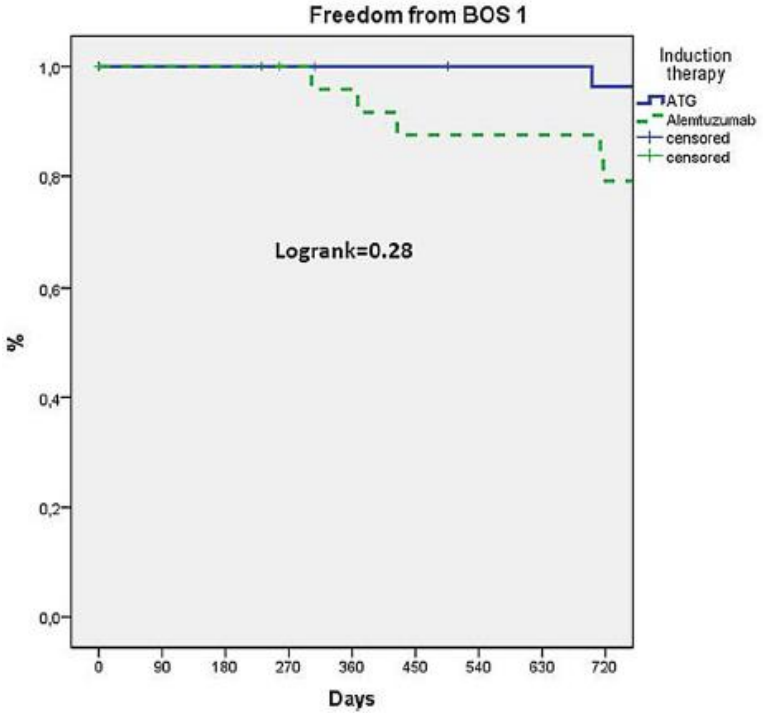




J Heart Lung Transplant 2001; 20: 1282

Alemtuzumab vs. ATG



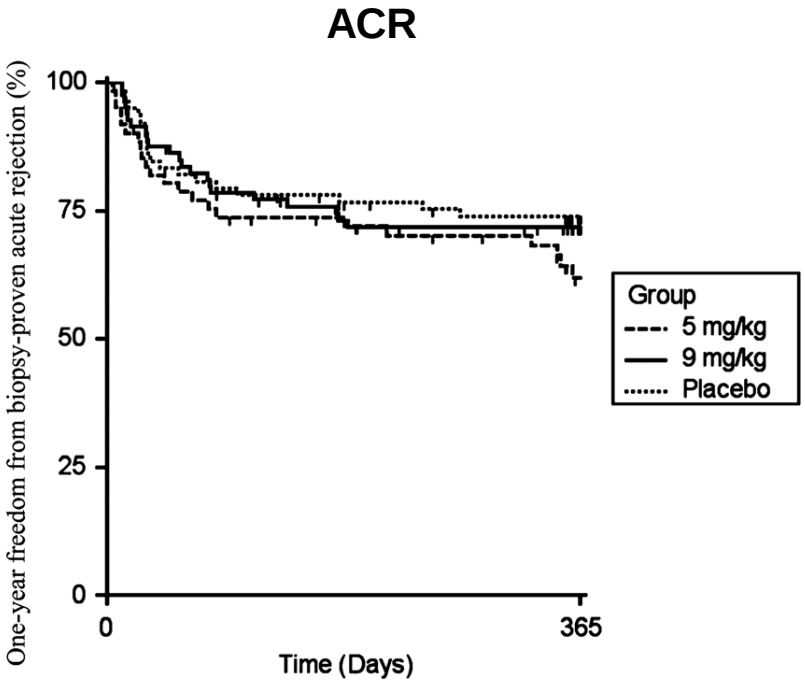


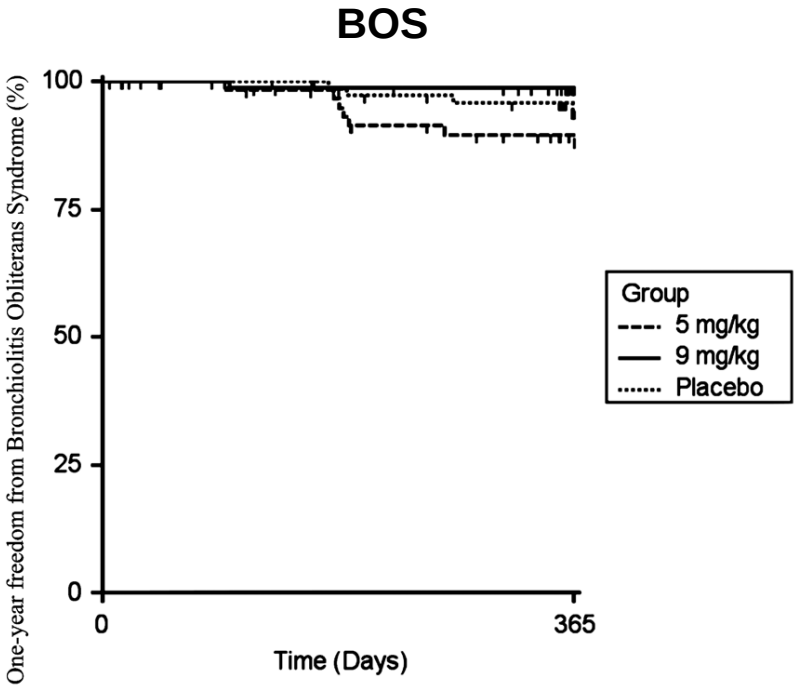
Am J Transplant 2014; 14: 1839

Fresenius ATG

- Multicenter, double blind, RCT
- Enrolled 233 patients
- 2 doses of ATG-F vs. placebo
- Interim analysis: low-dose was ineffective and impossible to enroll enough patients to show difference between high-dose & placebo

Fresenius ATG





Am J Transplant 2014; 14: 1191

Fresenius ATG

- ATG group had higher incidence of leukopenia, thrombocytopenia, CRS
- No difference in bacterial, viral, fungal infections
- Illustrates challenges of RCTs in lung transplantation

Induction Immunosuppression

- Difficult to make conclusions based on these studies
- Lack of power?
- Endpoint of ACR
- No benefit in long-term & patient-centered outcomes (CLAD, survival)
- Practice is based on institutional protocols

Potential Benefits & Risks

Benefits

- Delay initiation of CNI
- Target lower CNI levels
- Lower risk of ACR
- No data to support hypothesis that this leads to lower risk of CLAD or better survival

Risks

- Hematologic toxicity
- Cytokine release syndrome
- Serum sickness
- Infection
- Malignancy

Special Circumstances

- AKI or CKD
- Increased immunologic risk
  - Poorly defined in lung transplantation
  - Pre-transplant DSA, positive virtual XM, positive direct XM
- Not evidence-based

Conclusions

- Use of induction is increasing
- Basiliximab is the most commonly used drug
- Little data to support benefit
  - No RCT has investigated Basiliximab in lung transplant
- Some agents (Alemtuzumab) may have lower risk of ACR
- No evidence that induction improves freedom from CLAD or survival