A RANDOMIZED, OPEN-LABEL STUDY TO COMPARE TWO DIFFERENT SIROLIMUS (SRL) REGIMENS WITH TACROLIMUS (TAC) AND MYCOPHENOLATE MOFETIL (MMF) IN *DE NOVO* RENAL ALLOGRAFT RECIPIENTS: The ORION Study

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Optimizing
Renal Transplant
Immunosuppression to
Overcome
Nephrotoxicity

Disclosure

This study was sponsored by
Wyeth Pharmaceuticals, Collegeville, PA
Study no. 0468H1-101497
NCT# 00266123

COMMON KNOWLEDGE OF THE ORION TRIAL

ORION =

Food and Drug Administration Clinical Trials

Phase IV: also known as Post Marketing Surveillance Trial.

Phase IV trials involve the safety surveillance (pharmaco-vigilance) and ongoing technical support of a drug after it receives permission to be sold. Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I-III clinical trials.

PURPOSE

- Calcineurin-inhibitor sparing and avoidance strategies are being developed primarily to improve renal allograft function.
- To compare the 2-year results from an open-label, randomized, multinational trial of 2 sirolimus (SRL) regimens versus tacrolimus (TAC) + mycophenolate mofetil (MMF) regimen.

SRL-MMF-Cs CNI-free IS and Acute Rejection

Study	Induction	N	6 Months (%)	12 Months (%)
Morales et al 2002 Srl-AzA/MMF/Cs	None	81		36
Kreis et al 2004 SRL/Cs	None	194		28
		N = 275		**Average = 33%**
Flechner et al 2004	IL2R	31	6.8	6.8
Dean et al 2004	TMG	44	9.0	
Lo et al 2004	IL2R	29	6.9	6.9
Flechner et al 2005	IL2R/TMG	260	13	13.5
Hamdy et al 2005	IL2R	67		13.2
Glotz et al 2005	TMG	71	14.2	
Larson et al 2006	TMG	81		13.0
Martinez-Mier et al 2006	IL2R	21		5.2
Shaffer et al 2006	TMG	41		12.2
Figueiro et al 2007	IL2R	293		8.5
Buchler et al 2007	TMG	71		14.6
Hoim et al 2008	IL2R	220		6.3
		N = 1,228	**Average = 9.9%**	**Average = 10.02%**

STUDY DESIGN

- Open-label, randomized, comparative, multinational study in de novo renal allograft recipients. 76 centers entered trial; 65 centers actually enrolled; 58 centers < 5 and 7 ≥ 5 patients.
- Patients were enrolled between March 2004 and May 2005
- 469 patients enrolled; 19 untransplanted. 443 patients were randomly assigned (1:1:1) into 1 of 3 groups, stratified by race (black versus nonblack)
- All patients received daclizumab induction and corticosteroids

Group 1: SRL + TAC (elimination at 3 mos) + CCS	n = 152
Group 2: SRL + MMF + CCS	n = 152
Group 3: TAC + MMF + CCS (CONTROL)	n = 139

ORION Study

Group 1: SRL + TAC Elim + CCS

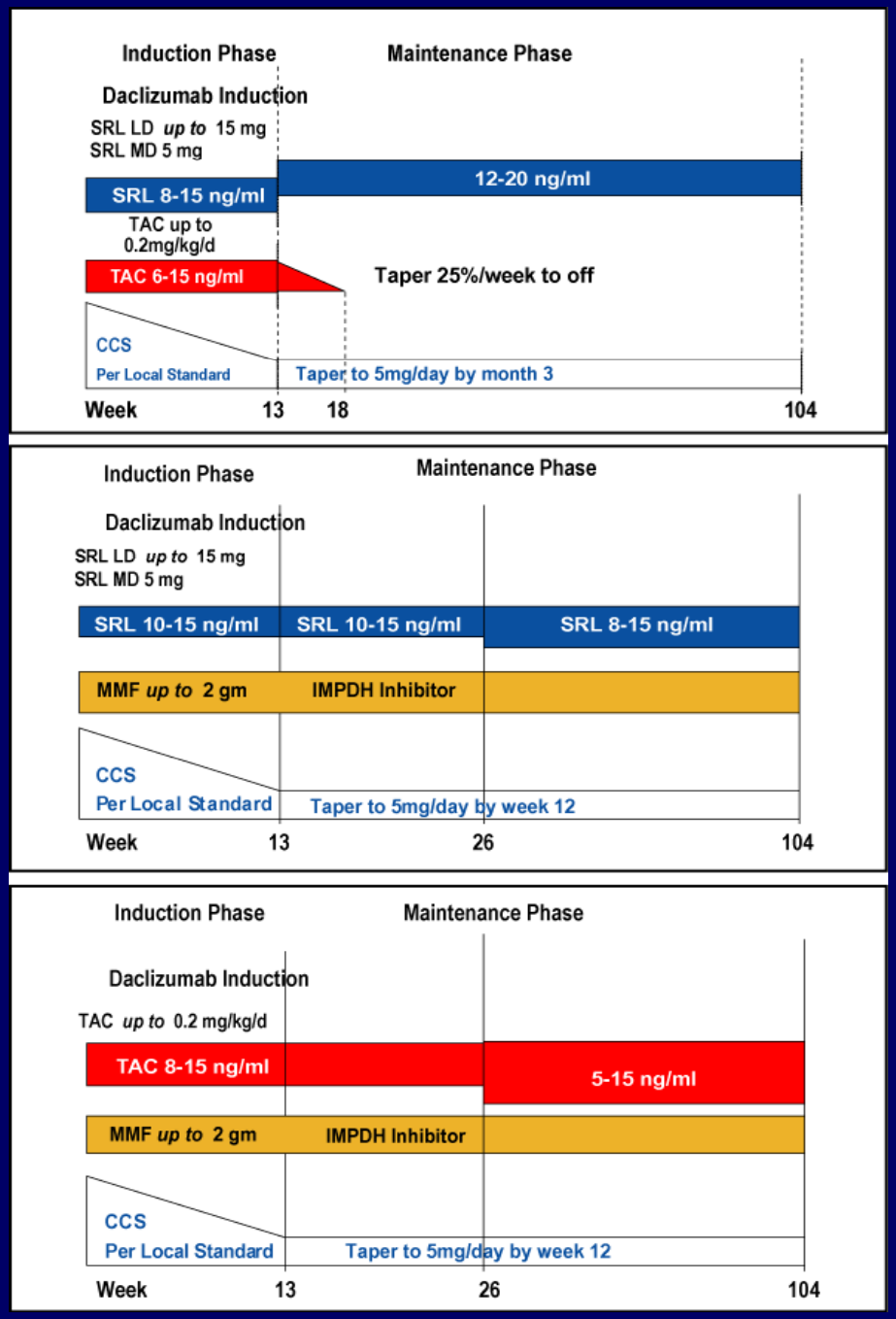
N=152

Group 2: SRL + MMF + CCS

N=152

Group 3: TAC + MMF + CCS

N=139



INCLUSION & EXCLUSION CRITERIA

INCLUSION CRITERIA

- 18 years of age or older
- End-stage renal disease and scheduled for renal allograft
- First or second kidney-only transplant; negative crossmatch

EXCLUSION CRITERIA

- Evidence of active systemic or localized major infection at screening
- History of multiple organ transplants
- At high risk for acute rejection (in the opinion of the investigator), or with cold ischemia time of donor kidney > 30 hours
- History of malignancy within 5 years (excluding adequately treated basal cell or squamous cell skin cancer)
- Body Mass Index > 32 kg/m^2
- White cell count $\leq$ 3,000/mm^3
- Platelet count $\leq$ 100,000 mm^3
- Fasting triglycerides $\geq$ 400 mg/dL ($\geq$ 4.6 mmol/L)
- Fasting total cholesterol $\geq$ 300 mg/dL ($\geq$ 7.8 mmol/L)

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STUDY AMENDMENT

- In June 2006, Group 2 patients were discontinued from assigned therapy (after all patients were accrued) because of higher than anticipated acute rejection rates.
- Mean length of follow-up in on-therapy Group 2 patients was 322 days.
- This decision was made by the Study Sponsor; excluding the study site investigators; there was no data safety monitoring board. Termed "Sponsor Terminated"

METHODOLOGY

Primary Efficacy Endpoint:

eGFR (Nankivell) at 12 months after transplantation

Secondary Efficacy Endpoints:

eGFR (Nankivell) up to 2 years after transplantation
Serum creatinine
Patient and Graft survival,
Incidence and severity of biopsy-confirmed acute rejection
Time to first biopsy-confirmed acute rejection
Incidence of antibody treatment for acute rejection

Safety Endpoints

Incidence of anemia, wound healing complications, hyperlipidemia, malignancy, delayed graft function, and urine protein-creatinine ratio

METHODOLOGY

- Analysis was performed on a modified ITT population, which included patients who had a transplant and also received at least one dose of TAC or SRL.
- With 140 subjects per group, and assuming a standard deviation of 18 mL/min, there was a 90% power to detect differences of 8 mL/min in calculated creatinine clearance between the treatment groups (α=0.025, 2-sided).

Patient Demographics

Characteristic		SRL+TAC Elim n = 152	SRL+MMF n = 152	TAC+MMF n = 139	Total n = 443
Age ± SD (years)		47.9 ± 13.3	50.4 ± 12.9	48.4 ± 13.2	48.9 ± 13.2
Gender n (%) male		109 (71.7)	110 (72.4)	81 (58.3)[1]	300 (67.7)
Race n (%)	White	114 (75.0)	117 (77.0)	102 (73.4)	333 (75.2)
	Black	14 (9.2)	17 (11.2)	15 (10.8)	46 (10.4)
	Asian	6 (4.0)	4 (2.6)	5 (3.6)	15 (3.4)
	Other	18 (11.8)	14 (9.2)	17 (12.2)	49 (11.1)
HLA Mismatches		3.38	3.36	3.32	3.35
PRA ± SD (%)		6.2 ± 17.3	13.3 ± 62.5	6.7 ± 18.3	8.8 ± 39.4
Retransplants (%)		11 (7.2)	13 (8.6)	11 (7.9)	35 (8.0)
Donors	Deceased	92 (60.5)	96 (63.2)	89 (64.0)	277 (62.5)
	Living Related	36 (23.7)	39 (25.7)	31 (22.03)	106 (23.9)
	Living Unrelated	24 (15.8)	17 (11.2)	19 (13.7)	60 (13.5)
Age ± SD (years)		43.2 ± 13.6	45.5 ± 14.9	44.4 ± 13.9	44.4 ± 14.2

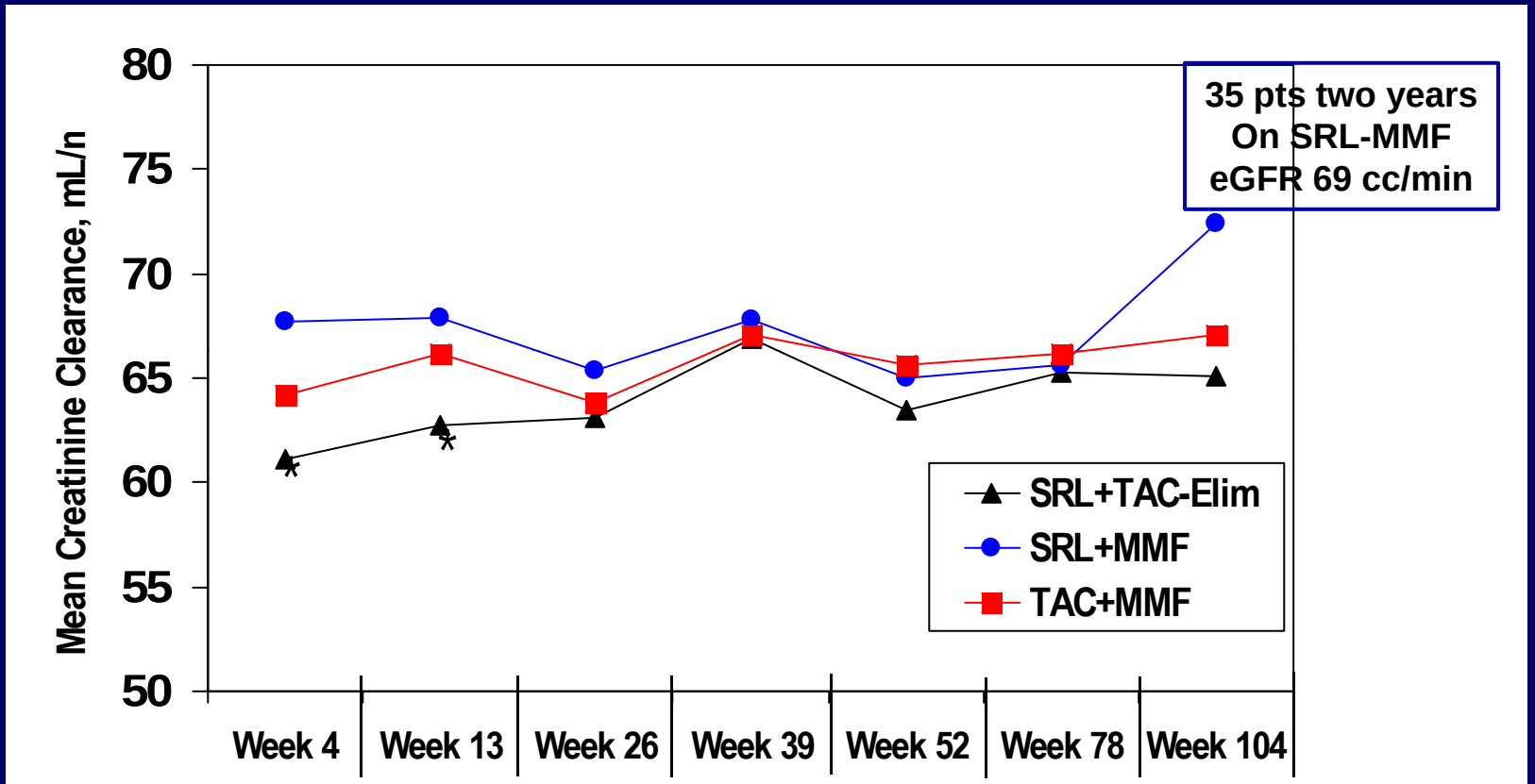
[1]p<0.05 TAC+MMF compared to other groups. Otherwise NS among groups.

Summary of Subject Disposition

Conclusion Status	Overall P-Value	SRL+TAC Elim n = 152	SRL+MMF n = 152	TAC+MMF n = 139	Total n = 443
Discontinued	<0.001***	48 (31.58)	150 (98.68)	28 (20.14)	226 (51.02)
Lost to Follow-up	0.793	6 (3.95)	5 (3.29)	7 (5.04)	18 (4.06)
Self withdrew	0.876	6 (3.95)	6 (3.95)	7 (5.04)	19 (4.29)
Deceased	0.506	8 (5.26)	8 (5.26)	5 (3.56)	21 (4.71)
Dropped Subject	0.764	1 (0.66)	0	1 (0.72)	2 (0.45)
Other	<0.001***	27 (17.76)	131 (86.18)	9 (6.47)	167 (37.70)

***Total discontinued is the sum of individual reasons because they are mutually exclusive by subject.
Overall p-value: Fisher's exact test p-value (2-tail).

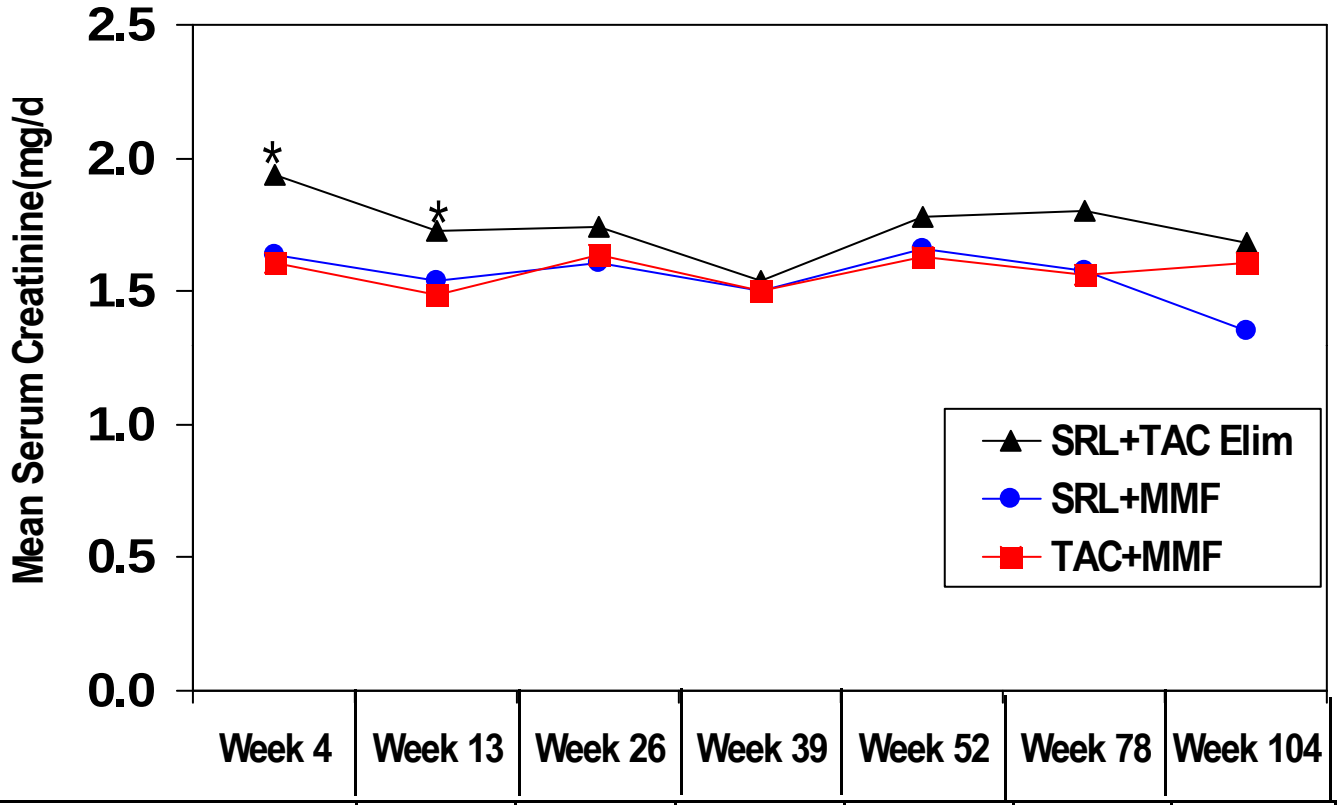
Primary Efficacy Endpoint: Mean Calculated Creatinine Clearance (ITT)



SRL+TAC-Elim, n=132	111	131	77	127	118	116
SRL+MMF, n=132	109	136	85	132	86	10
TAC+MMF, n=127	119	119	102	116	112	109

Note: * $p<0.05$, SRL+TAC-Elim vs TAC+MMF; Otherwise NS among/between groups.

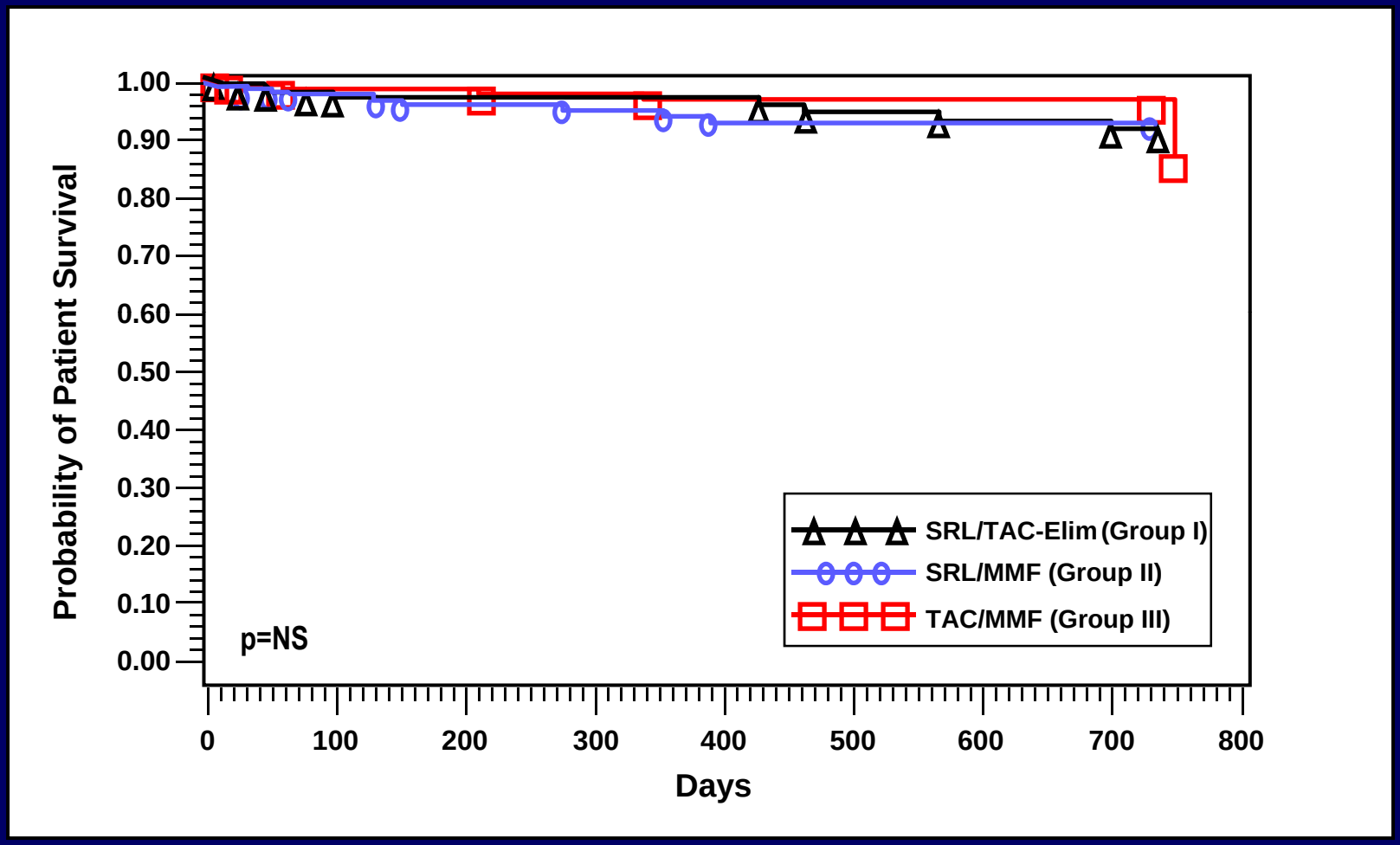
Mean Serum Creatinine (ITT)



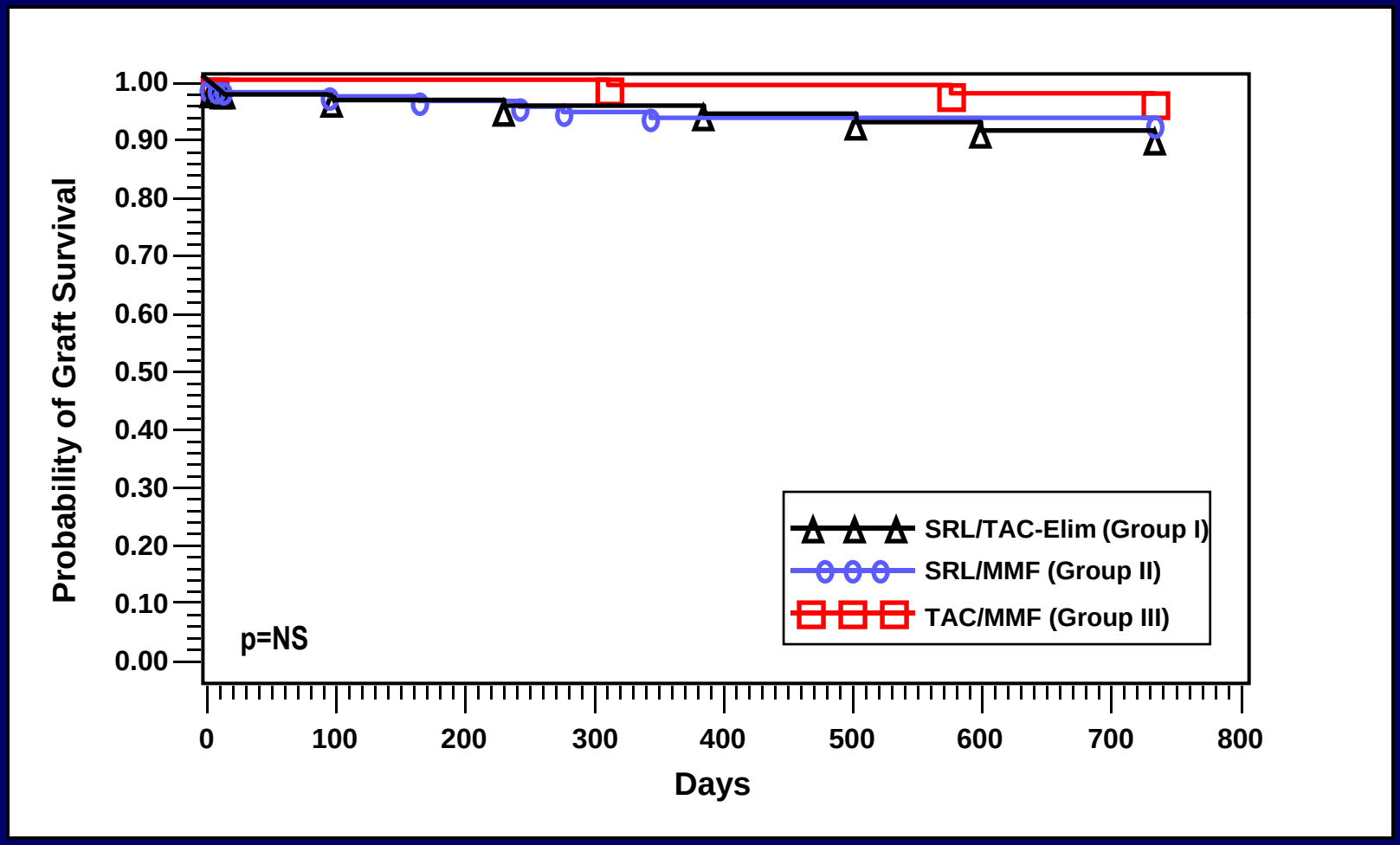
SRL+TAC Elim, n=133	113	136	80	132	122	121
SRL+MMF, n=132	113	138	85	134	87	10
TAC+MMF, n=130	121	126	105	121	116	112

Note: * $p<0.05$, SRL+TAC-Elim vs TAC+MMF; Otherwise NS among/between groups.

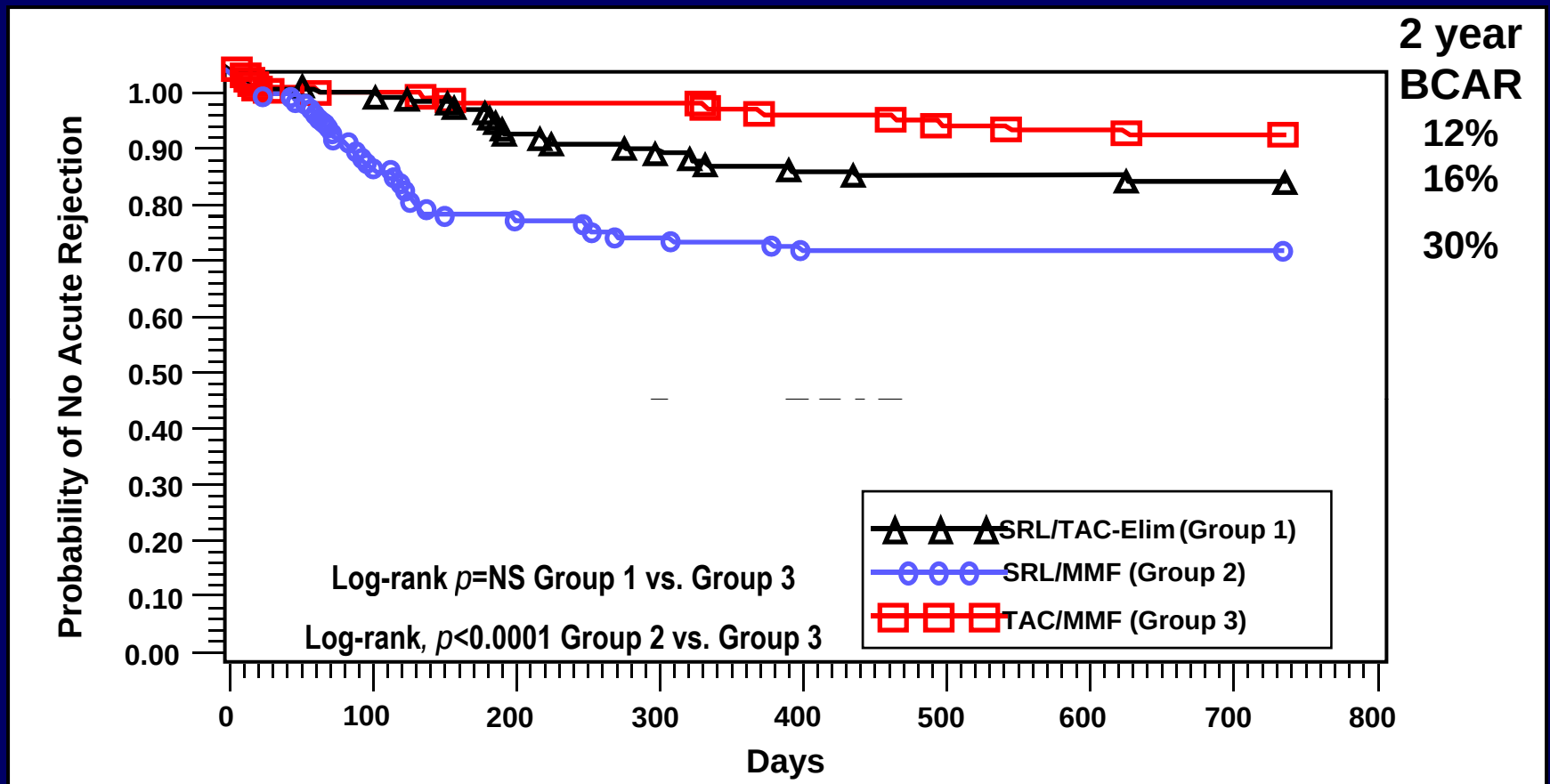
Patient Survival: ITT Population



Graft Survival: ITT Population



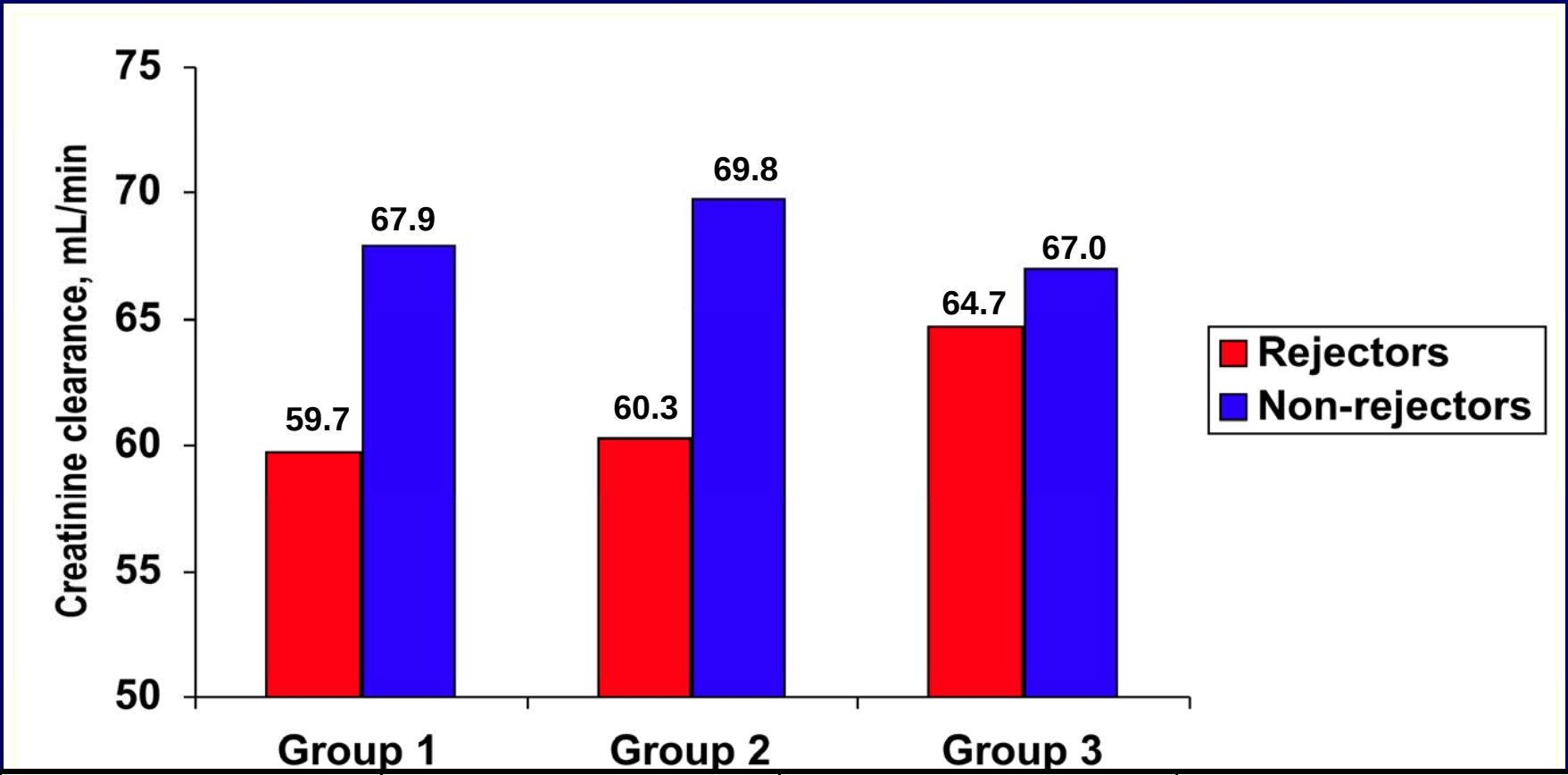
Biopsy-Confirmed Acute Rejection: mITT*



Acute Rejection by Severity (on-therapy):	Group	Grade I	Grade II	Grade III
	SRL+TAC-Elim	75% (15/20)	25% (5/20)	0
	SRL+MMF	76.7% (33/43)	23.3% (10/43)	0
	TAC+MMF	53.8% (7/13)	46.2% (6/13)	0

*Group 2 censored at treatment group termination.

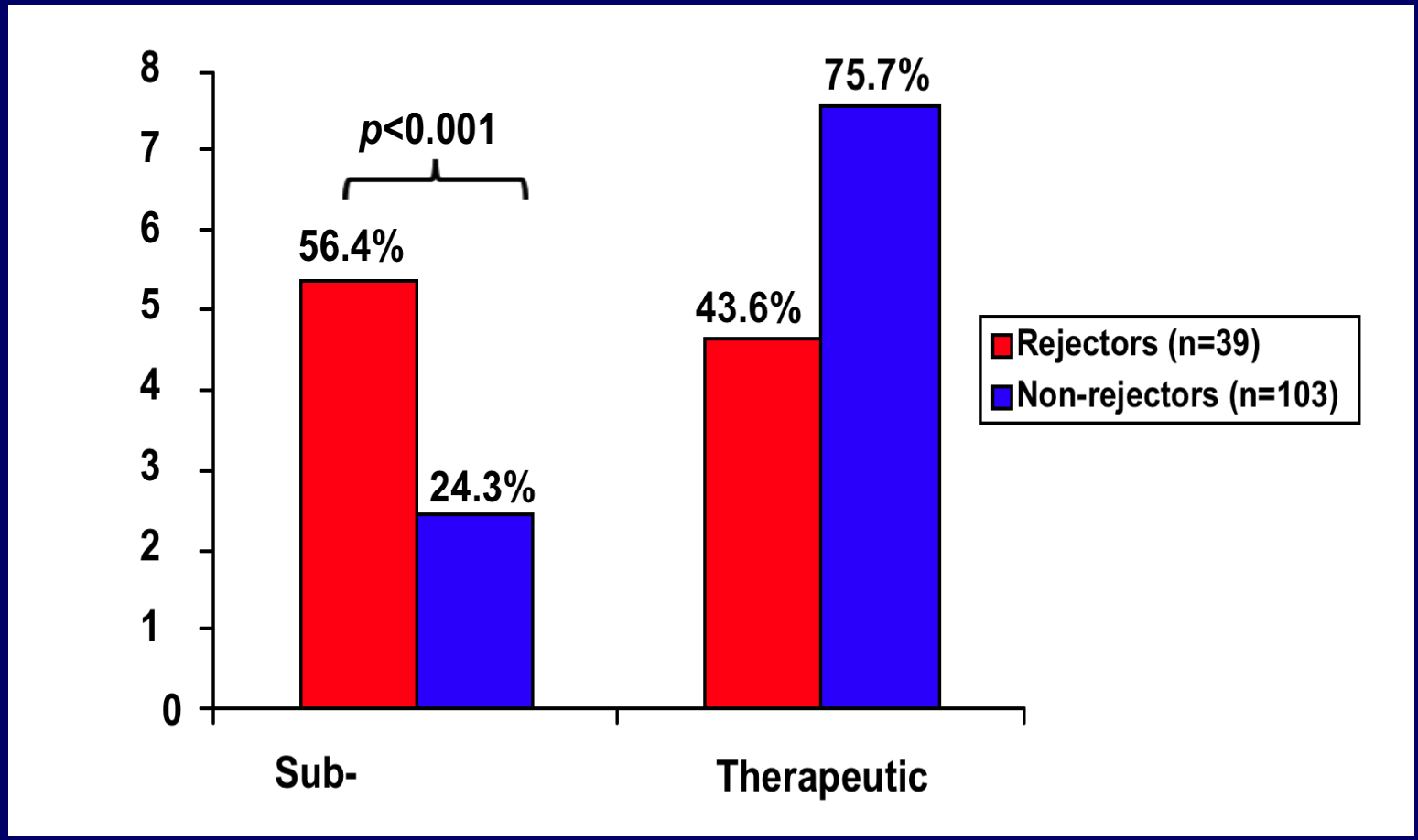
One Year Mean Calculated Creatinine Clearance (On-Therapy)



Group	1: SRL+TAC-Elim	2: SRL+MMF	3: SRL+TAC
Rejectors, n	6	13	9
Non-rejectors, n	69	64	92

p=NS rejectors vs. non-rejectors

Frequency of Low SRL Blood Levels in Group II Patients:



- **Therapeutic** defined as SRL C_0 levels 10-15 ng/ml at week 1 and months 1,3,6
- **Sub-therapeutic** defined as 2 or more SRL C_0 levels <10ng/ml or 1 level <10ngml within a week of BCAR

ORION and 318 Patients Transplanted at CCF

Patient	Source	Week 1	Week 2	Week 3	Week 4	Month 2	Month 3	Month 4	Month 5	Month 6
Patient 1	(no transplant)	X	X	X	X	X	X	X	X	X
Patient 2	LR	9.8	11.2	10	23.9	12.6	11.2	12.1	8.1	11.3
Patient 3	DD	5	16.6	19.7	15.2	14.4	12.7	9.2	10.5	14.4
Patient 4	LUR	11.8	11.4	13.5	12.1	13.5	14.8	9.5	11.4	10.1
Patient 5	LUR	13	21.1	9.8	11.5	14.6	17.2	22.3	16.5	16.3
Patient 6	DD	10.3	17.7	21.4	11.6	12.3	6.9	ND	7.7	7.4
Patient 7	DD	3.5	7.8	37.8	24.2	11.8	12.2	10	7.7	10.6
318- 1	LR	11.3	15.9	14	20.2	12.2	12.6	13.7	17.1	12.6
318- 2	DD	15.5	16.8	10.6	12.7	9.7	8.7	10.7	11.6	12
318- 3	LUR	23.4	21.8	12	12.9	7.3	14.5	9.9		
	Average	**11.51**	**15.59**	**16.53**	**16.03**	**12.04**	**12.31**	**12.18**	**11.33**	**11.84**
	SD	5.82	4.66	8.98	5.28	2.31	3.14	4.36	3.73	2.72
	Median	**11.3**	**16.6**	**13.5**	**12.9**	**12.3**	**12.6**	**10.4**	**10.9**	**11.6**

No cases of Acute Rejection the first 6 months

Treatment-Emergent Noninfectious Adverse Events, n (%)

Adverse Event	SRL+TAC Elim n = 152	SRL+MMF n = 152	TAC+MMF n = 139	Total n = 443
Anemia	62 (40.3)	74 (47.4)[XX]	51 (36.4)	187 (41.6)
Thrombocytopenia*	20 (13.2)	25 (16.4)	4 (2.9)	49 (11.1)
Hyperkalemia*	36 (23.4)	19 (12.2)	24 (17.1)	79 (17.6)
Hypophosphatemia	34 (22.1)	38 (24.4)	34 (24.3)	106 (23.6)
Hyperlipidemia**	52 (33.8)	66 (42.3)	30 (21.4)	148 (32.9)
Nausea/vomiting	40 (26.0)	41 (26.3)	43 (30.7)	124 (27.6)
Abdominal pain	32 (20.8)	29 (18.6)	34 (24.3)	95 (21.1)
Diarrhea*	45 (29.2)	64 (41.0)	58 (41.4)	167 (37.1)
Hyperglycemia	38 (24.7)	33 (21.2)	30 (21.4)	101 (22.4)
NODAT*[1]	27/120 (22.5)	7/117 (6.0)	12/110 (11.9)	46/347 (13.3)
Tremor**	34 (22.1)	12 (7.7)	34 (24.3)	80 (17.8)
Hypertension	63 (40.9)	54 (34.6)	48 (34.3)	165 (36.7)
Peripheral edema*	77 (50.0)	77 (49.4)	51 (36.4)	205 (45.6)

*Overall $p < 0.05$ among groups. **Overall $p < 0.01$ among groups [XX]ESA use 2 vs 3 42 vs. 27% $p < 0.05$

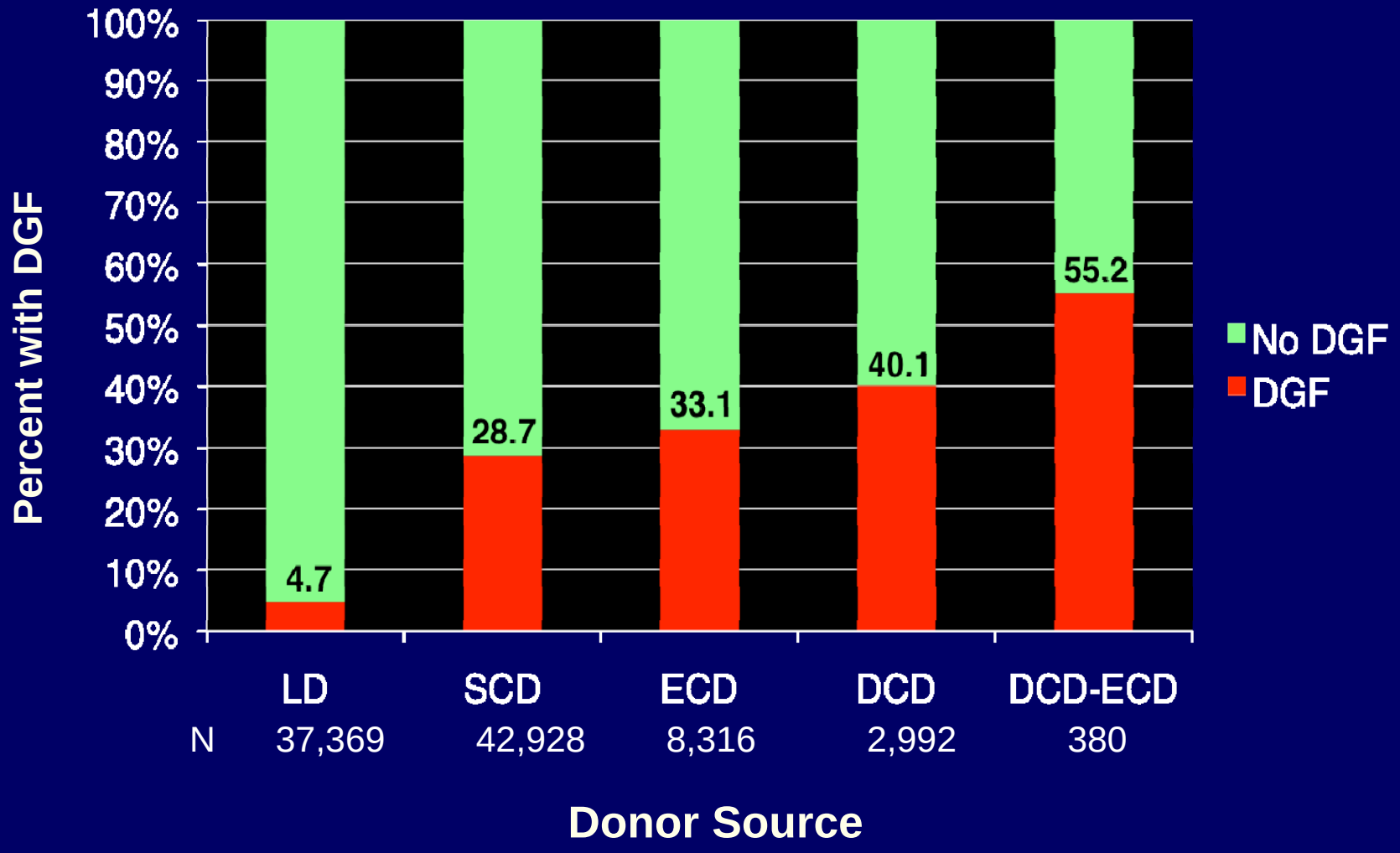
[1]Defined: ≥30 days on oral hypoglycemic agents, insulin, or their combination

Adverse Events of Interest with mTORi n (%)

Adverse Event	SRL+TAC Elim n = 152	SRL+MMF n = 152	TAC+MMF n =139	Total n = 443
Delayed Wound Healing	25 (16.4)*	35 (23.0)*	8 (5.8)	68 (15.3)
Lymphoceles	25 (16.4)*	28 (18.4)*	12 (8.6)	65 (14.7)
All Cancers	7 (4.6)	5 (3.3)	5 (3.6)	17 (3.8)
Skin	6	4	1	11
Solid	1	1	4	6
Proteinuria median p/c ratio	0.21**	0.14	0.13	

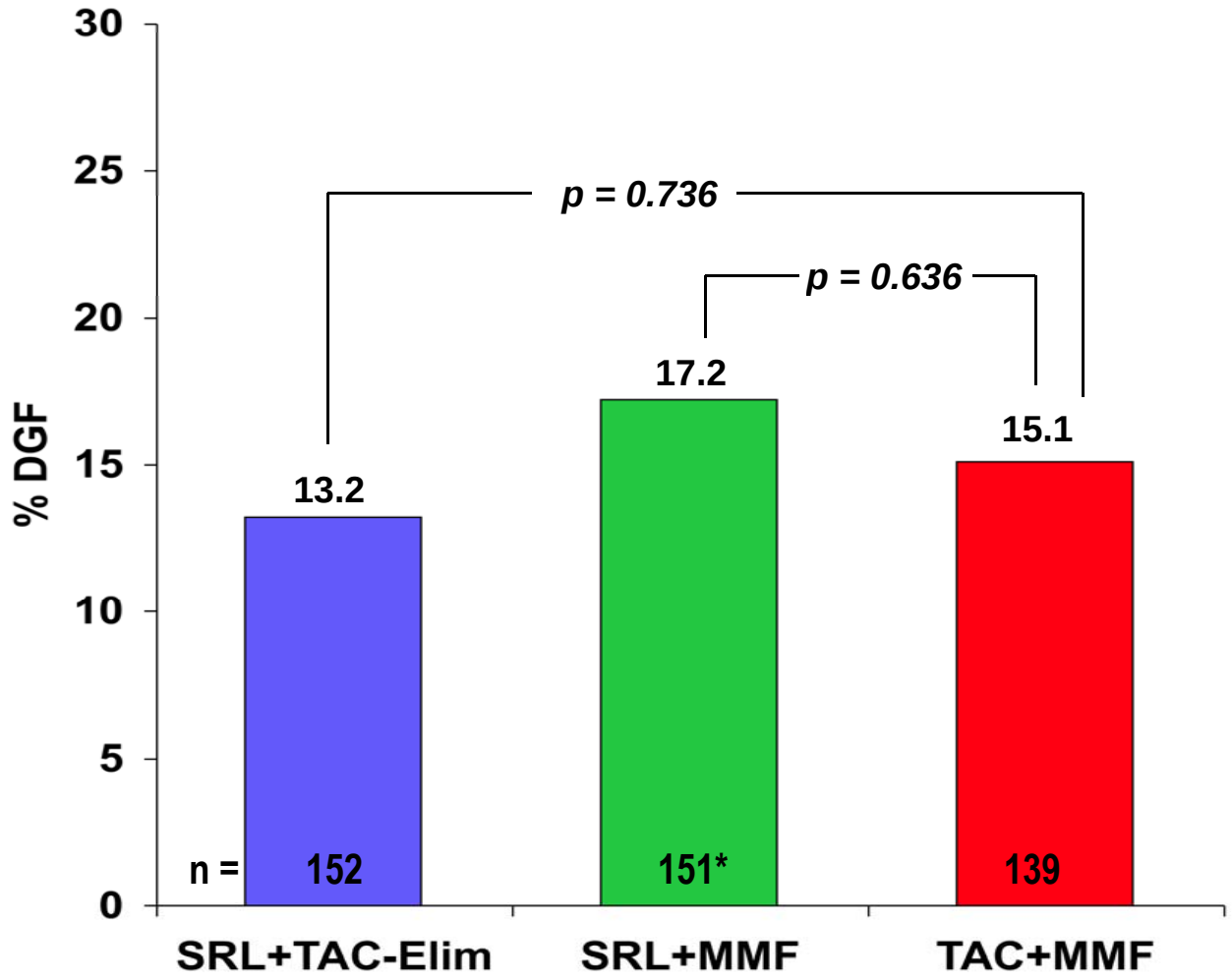
*Overall p < 0.05 among groups

Rate of Delayed Graft Function (1st week dialysis) by Donor Source: 2000-2006



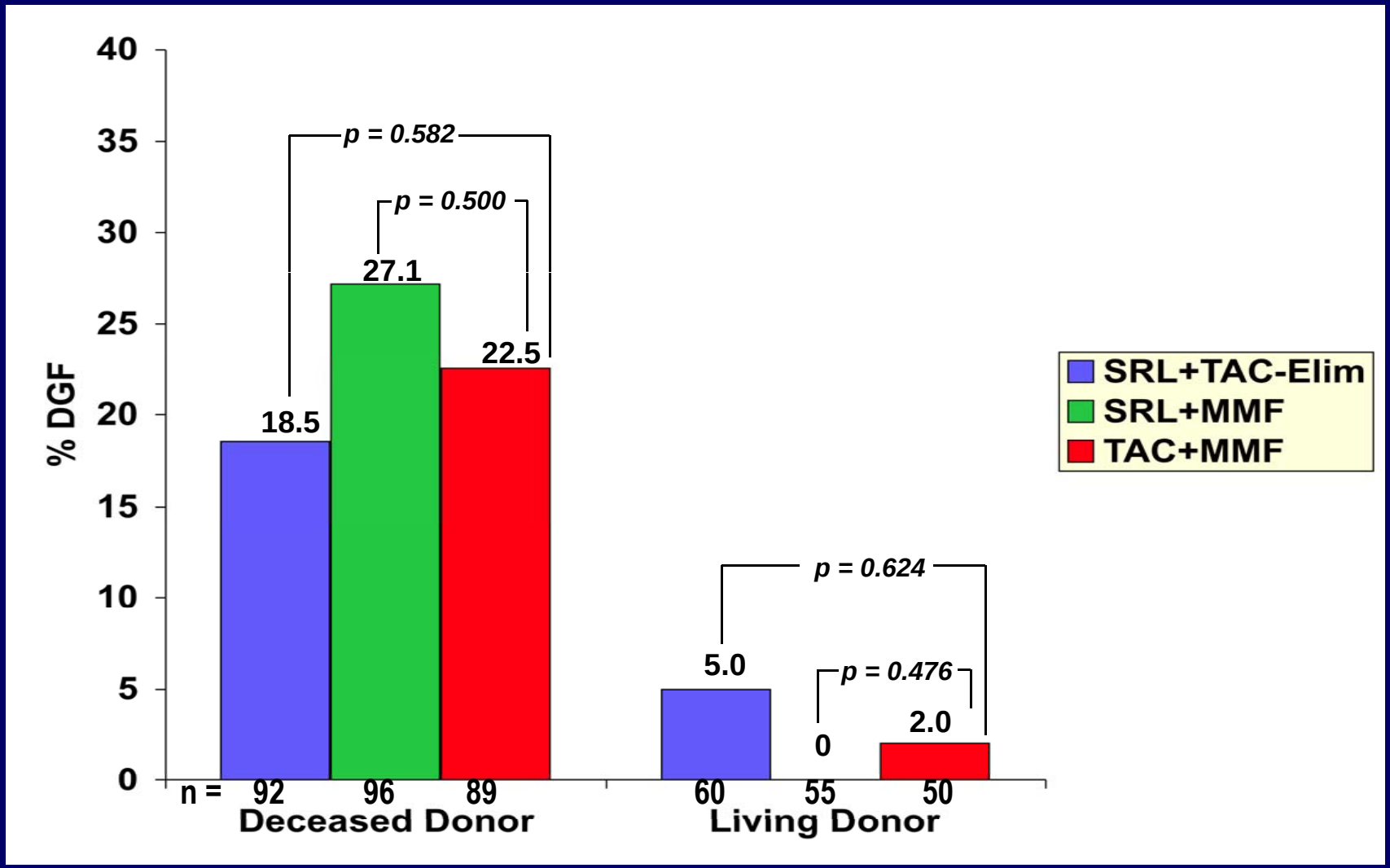
OPTN/SRTR 2007 Annual Report

Incidence of DGF: Deceased Plus Live Donor Transplants

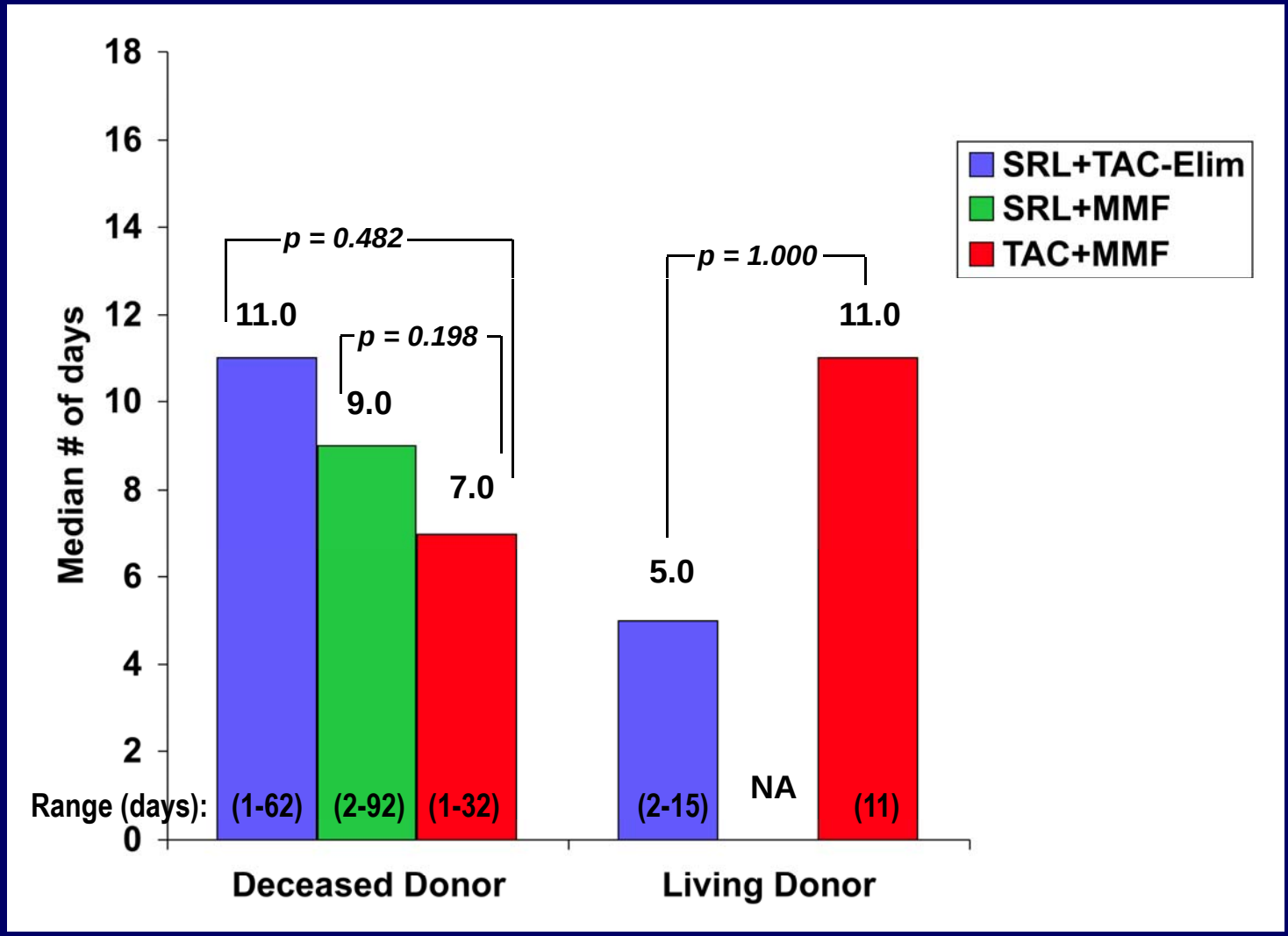


*1 patient excluded from analysis due to withdrawal from study on day 7.

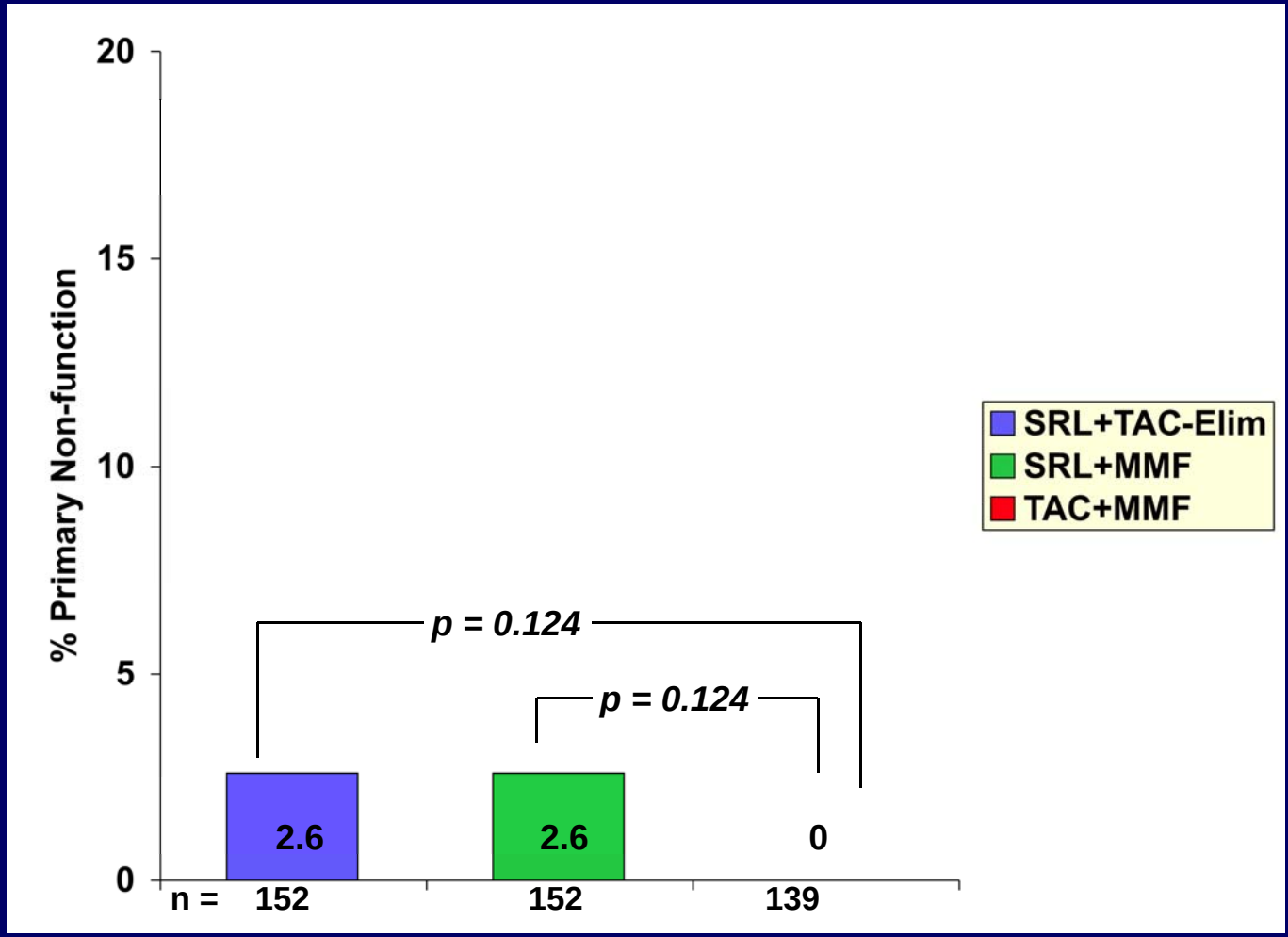
Incidence of DGF: Donor Source



Median Duration of DGF: Donor Source



Primary Non-Function



SRL+TAC-Elim: 2 patients with RVT day 1, day 4

SRL+MMF: 1 patient with thrombosed kidney day 1, 1 patient with ATN/cortical necrosis day 1

Conclusions from the ORION Study Efficacy

At 2 years: using the mITT population

- Excellent patient and graft survival was observed in all groups with no significant differences.
- Higher rates of BCAR observed for SRL-MMF especially when levels <10ng/ml first 6 months.
- Similar renal function among treatment groups, despite higher AR rates in SRL+MMF group.
- Early adequate exposure to sirolimus is mandatory to achieve desired (low BCAR) rates.

Conclusions from the ORION Study SAFETY

At 2 years: using the mITT population

- Hyperlipidemia, delayed wound healing, and edema were more frequent in patients receiving SRL+MMF.
- Tremor, hyperkalemia, and NODAT was more frequent in patients receiving TAC+MMF.
- Diarrhea was least in patients receiving SRL-Tac Elim.
- Proteinuria, although significantly greater in SRL+TAC-Elim group, was minimal in all groups and not different between de novo SRL+MMF and TAC+MMF groups.
- No significant differences in DGF between groups.

Delayed Introduction of Sirolimus in patients at risk for TORi complications