IRMA 2

IRbesartan MicroAlbuminuria in Type 2 Diabetic Subjects

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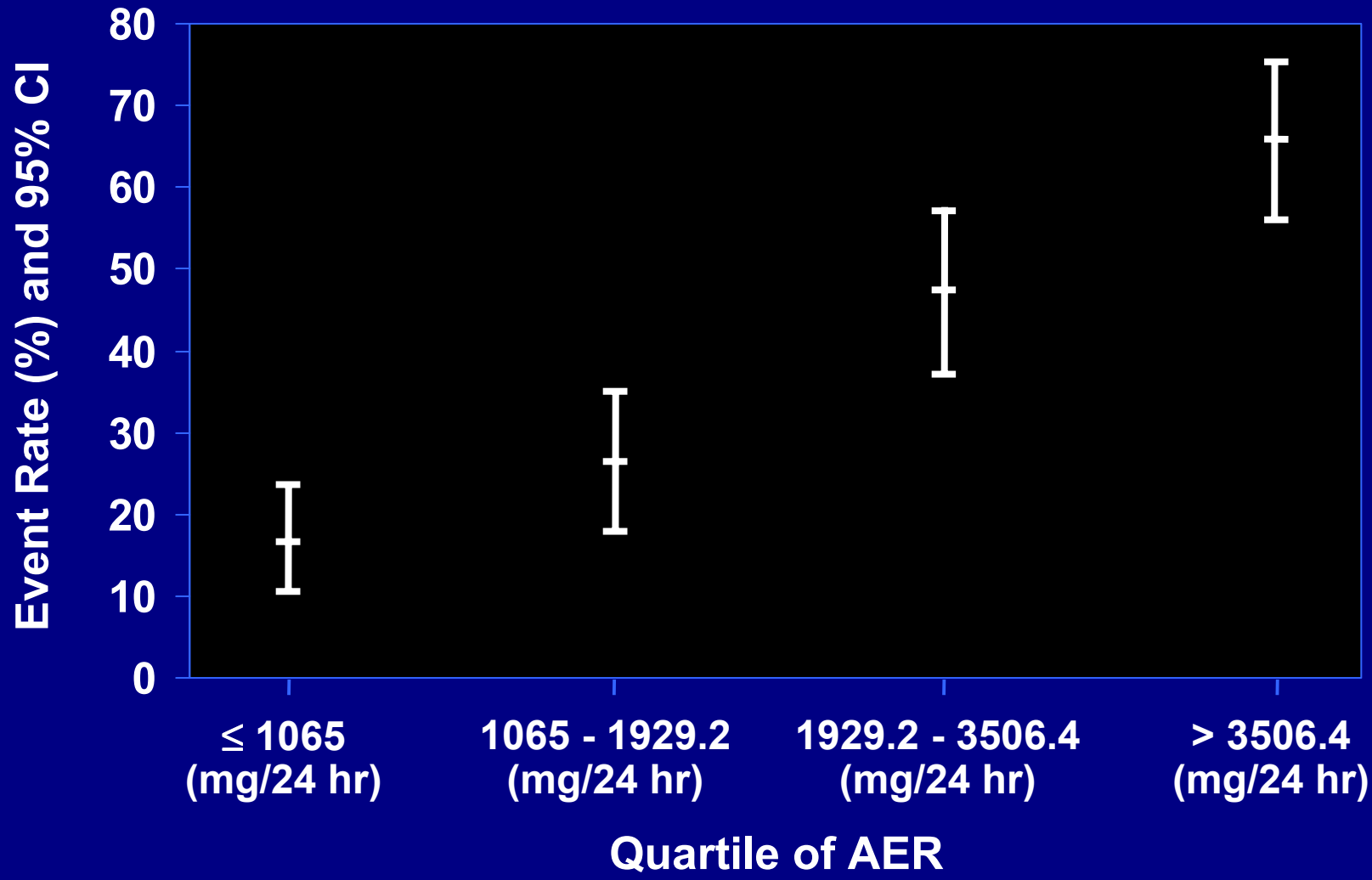
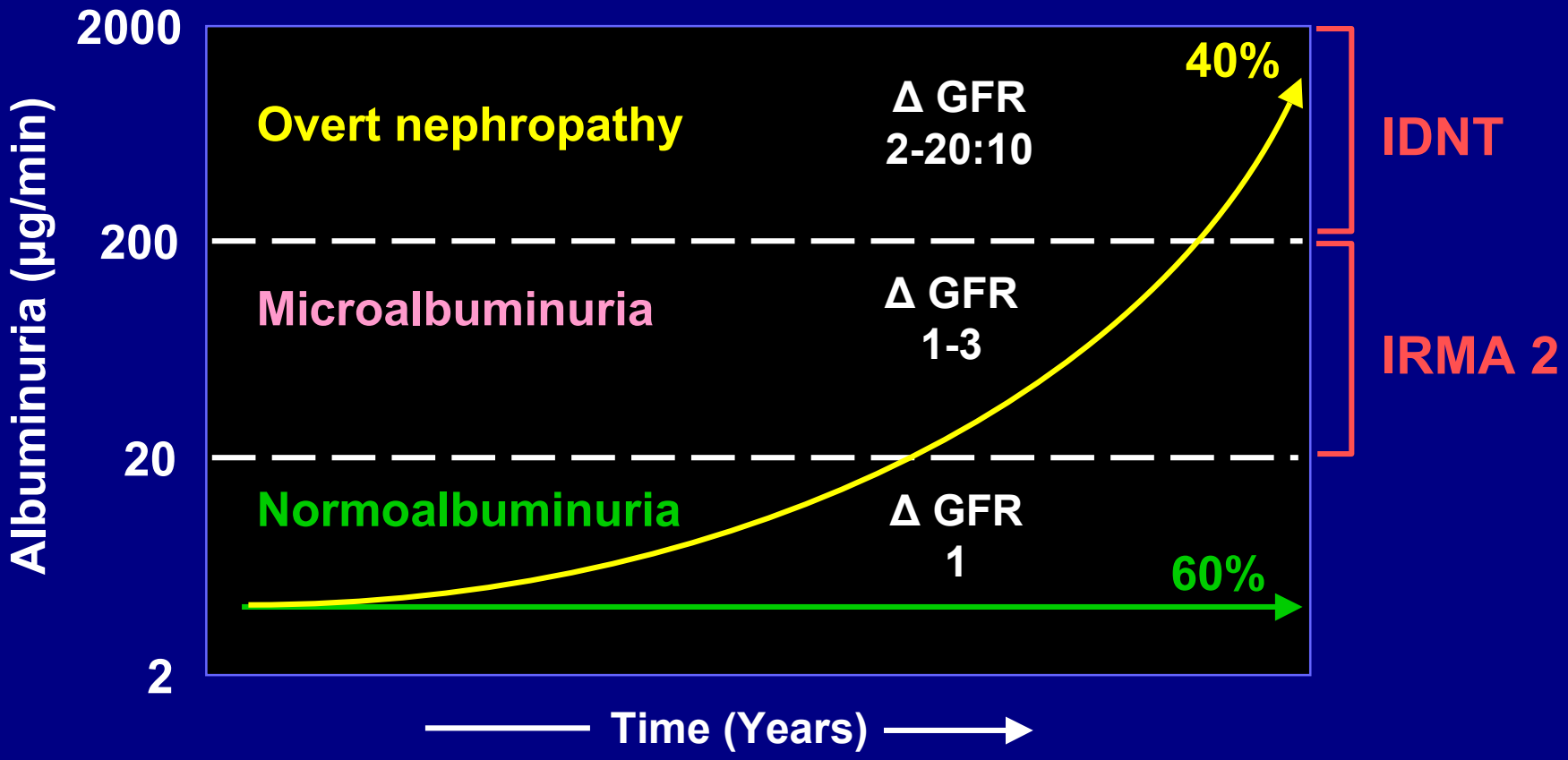
IDNT: Kaplan-Meier Estimates (3 Years) for Primary Composite Endpoint for Quartile of Baseline AER all Placebo Subjects with Measurement of AER



Progression of Diabetic Renal Disease in Patients with Type 2 Diabetes



Microalbuminuria – Type 2 Diabetes

- Marker of early diabetic kidney disease (structural / biochemical evidence)
- Progression to overt nephropathy: 5 - 10% per year
- Decline in GFR: 1 - 3 ml/min/year
- Recommendations from the American Diabetes Association and International Diabetes Federation advocate early screening and treatment of microalbuminuria in patients with diabetes

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Hypothesis

Irbesartan has beneficial effects above and beyond blood pressure control alone on the progression to overt diabetic nephropathy as compared with conventional antihypertensive therapy in hypertensive patients with type 2 diabetes and microalbuminuria

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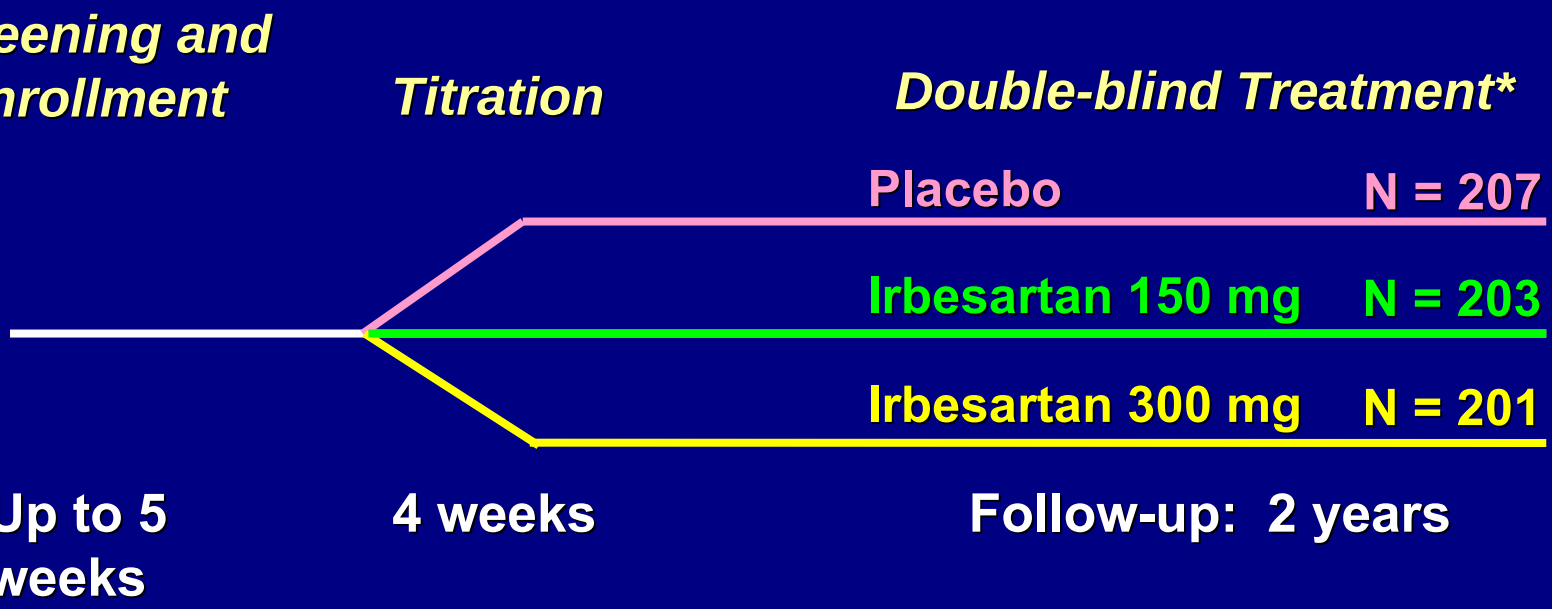
Study Design



*Subjects received various classes of open label antihypertensive medication except inhibitors of the RAS (ACE-I or ARBs) or dihydropyridine calcium channel antagonists to lower blood pressure to a target of ≤ 135/85 mmHg.

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Outcome Measures

Primary End Point

Time to first occurrence of an urinary albumin excretion rate (AER) > 200 µg/min and an increase of at least 30% from baseline at 2 successive evaluations

Secondary End Points

- Change from baseline in overnight urinary AER
- Change from baseline in estimated creatinine clearance (Cockcroft and Gault formula)

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Baseline Characteristics of all Randomized Subjects*

	Placebo	Irbesartan 150 mg	Irbesartan 300 mg
N	207	203	201
Age (yr)	58.4	58.3	57.3
Male (%)	69	66	70
Race – White (%)	98.1	97.5	96.5
BMI (kg/m^2)	30.3	29.8	30.0
Known Diabetes (yr)	10.5	9.7	9.5
HbA_{1c} (%)	7.2	7.3	7.0
Urinary AER (μg/min)†	56.4	58.6	52.8
Serum Creatinine (mg/dL)	1.1	1.0	1.1
Creatinine Clearance (mL/min $1.73m^2$)†	108.9	109.4	107.7
Blood Pressure (mmHg)	153/90	153/90	153/91

*Mean values
†Geometric mean

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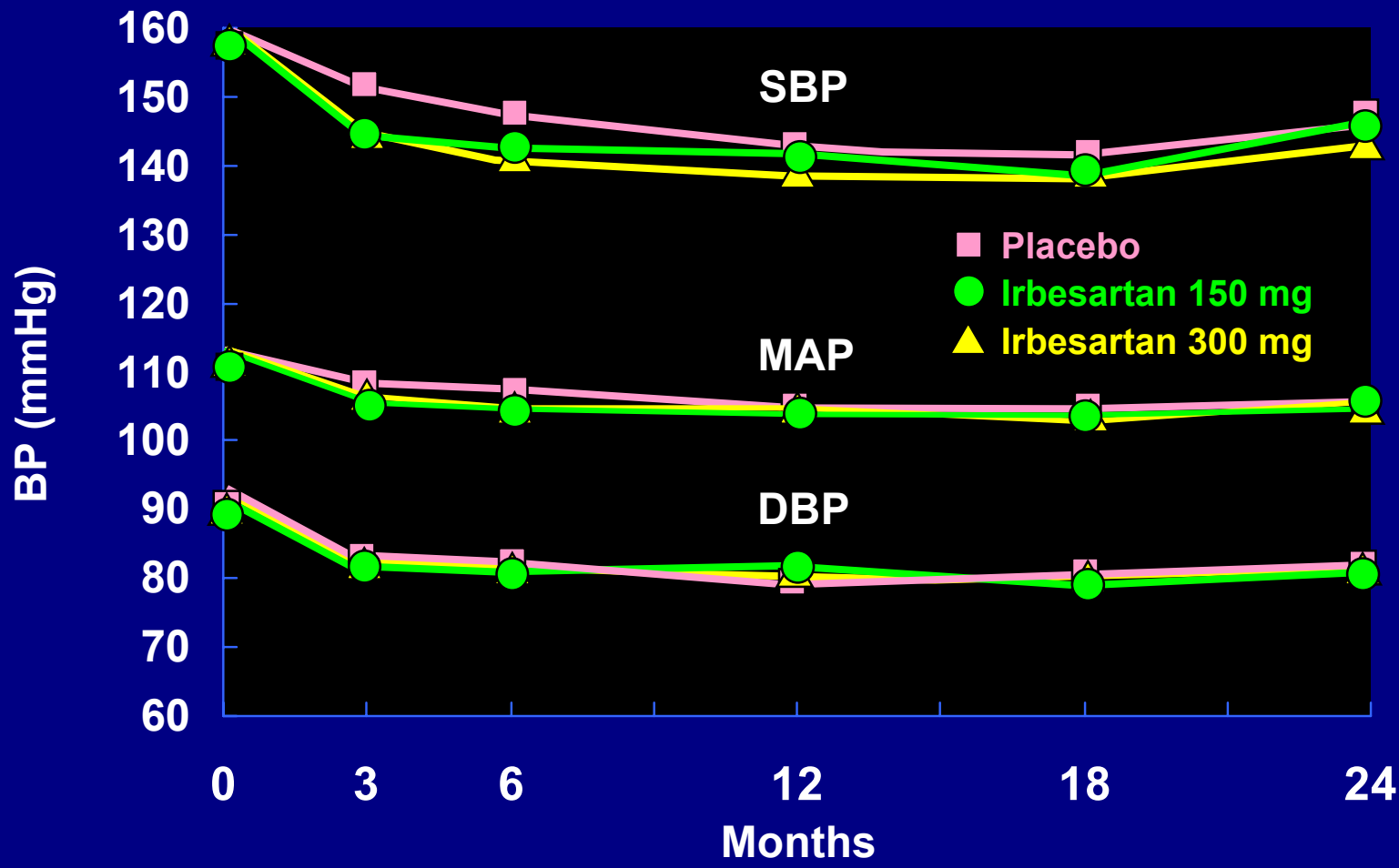
Mean Systolic (SBP), Diastolic (DBP) and Mean Arterial Blood Pressure (MAP) Throughout the Study



Concomitant antihypertensive agents received by 56% of patients in the control group, 45% in the irbesartan 150 mg group, and 43% in the irbesartan 300 mg group.

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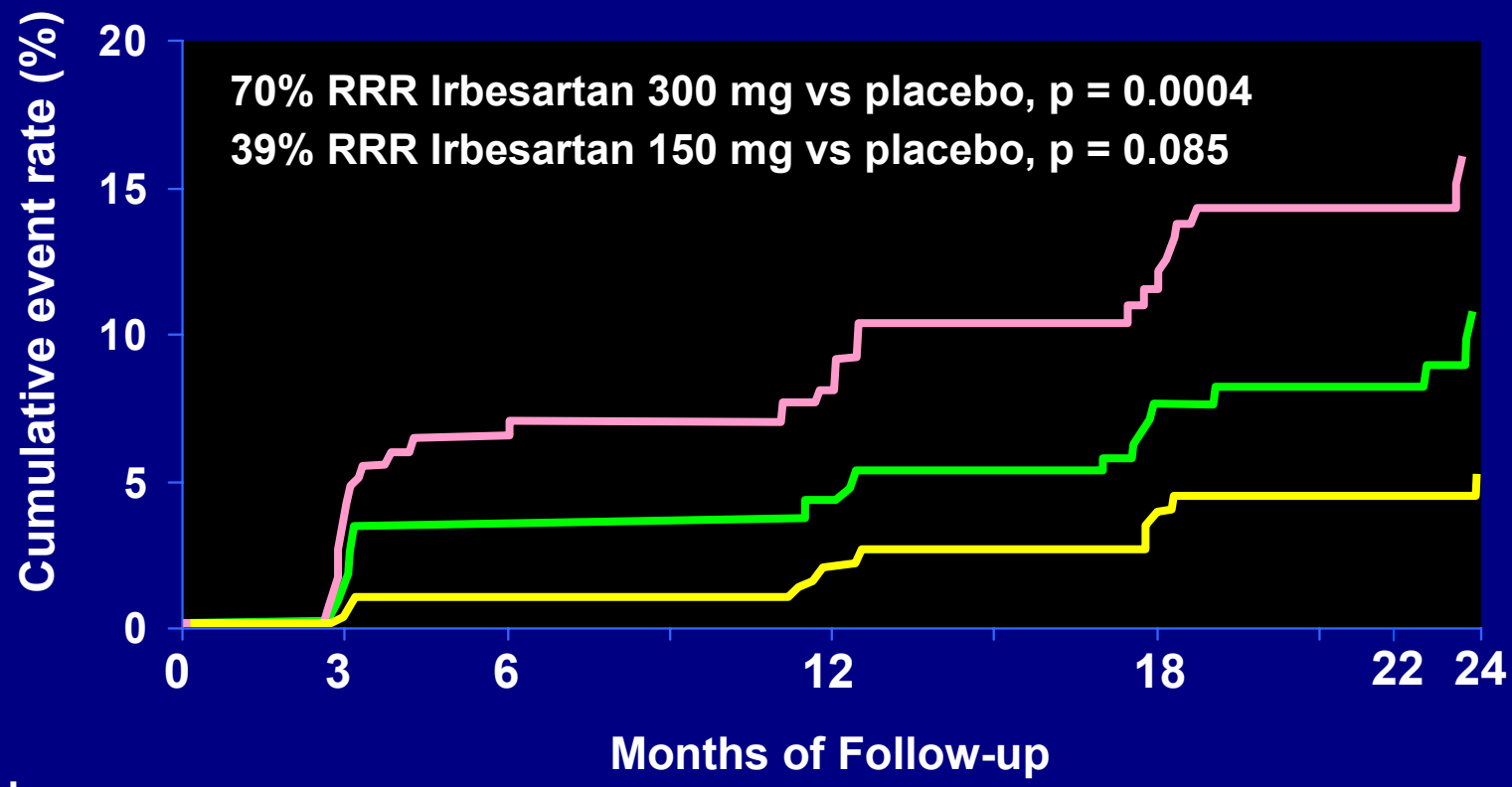
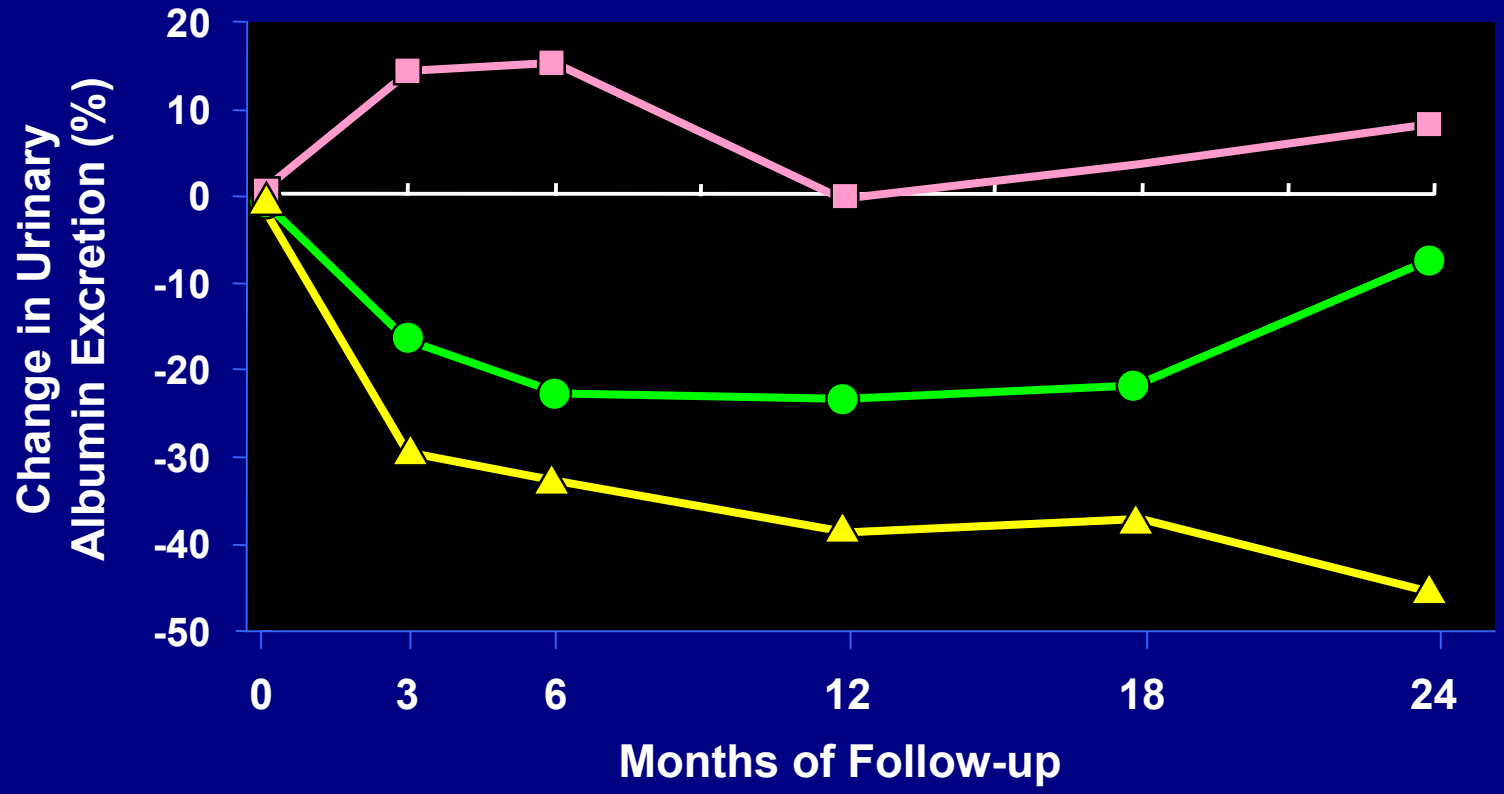
Primary End Point: Time to Development of Overt Nephropathy



No. at Risk

Placebo	201	201	164	154	139	129	36
Irbesartan 150 mg	195	195	167	161	148	142	45
Irbesartan 300 mg	194	194	180	172	159	150	49

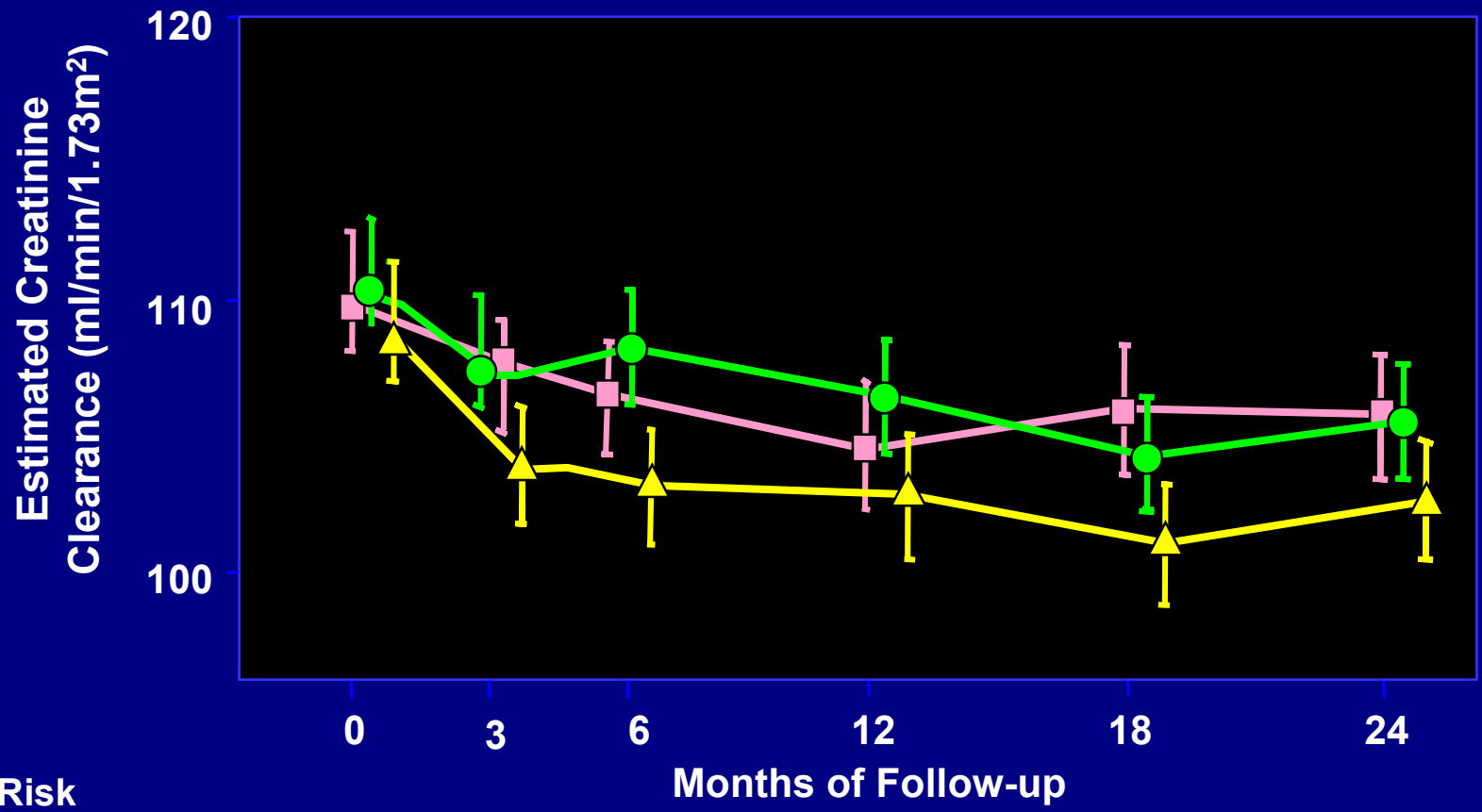
IRMA 2: Change From Baseline in Urinary Albumin Excretion Rate



Placebo	201	192	179	158	146	140
Irbesartan 150 mg	195	185	170	166	156	151
Irbesartan 300 mg	194	187	183	170	162	157

IRMA 2: Estimated Creatinine Clearance*

New BB Figure 6.6.2.3



No. at Risk

Placebo	200	193	180	156	148	159
Irbesartan 150 mg	194	187	177	166	158	167
Irbesartan 300 mg	194	188	183	175	169	169

Dataset: ITT analysis

*Based upon Cockcroft and Gault formula

IRMA 2: Safety Profile

	Number (%) of Subjects		
	Placebo (N = 206)	Irbesartan 150 mg (N = 202)	Irbesartan 300 mg (N = 200)
Adverse Events (AEs)	141 (68.4)	129 (63.9)	149 (74.5)
Serious Adverse Events SAEs	47 (22.8)	32 (15.8)	30 (15.0)
Discontinuations due to an AE	19 (9.2)	18 (8.9)	11 (5.5)
Deaths	5 (2.4)	3 (1.5)	8 (4.0)

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Summary

- 70% reduction in the risk of progression from microalbuminuria to overt nephropathy with irbesartan 300 mg once daily
- Observed relative risk reduction was dose dependent
- Benefits of irbesartan were in addition to blood pressure reduction alone
- Irbesartan was safe and well tolerated in this population