The HIV Integrase Inhibitor GS-9137 Has Potent Antiretroviral Activity in Treatment-Experienced Patients

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Background on GS-9137

- Dihydroquinoline carboxylic acid strand transfer inhibitor of HIV integrase
- Serum-free IC_{50} = 0.2 nM; EC_{90} = 1.2 nM in PBMCs
- Active against NRTI-, NNRTI-, and PI-resistant isolates tested
- No dose-limiting chronic animal toxicity
- Generic name is elvitegravir (el-vye-teg′-ra-vir)

Phase 1 Clinical Data

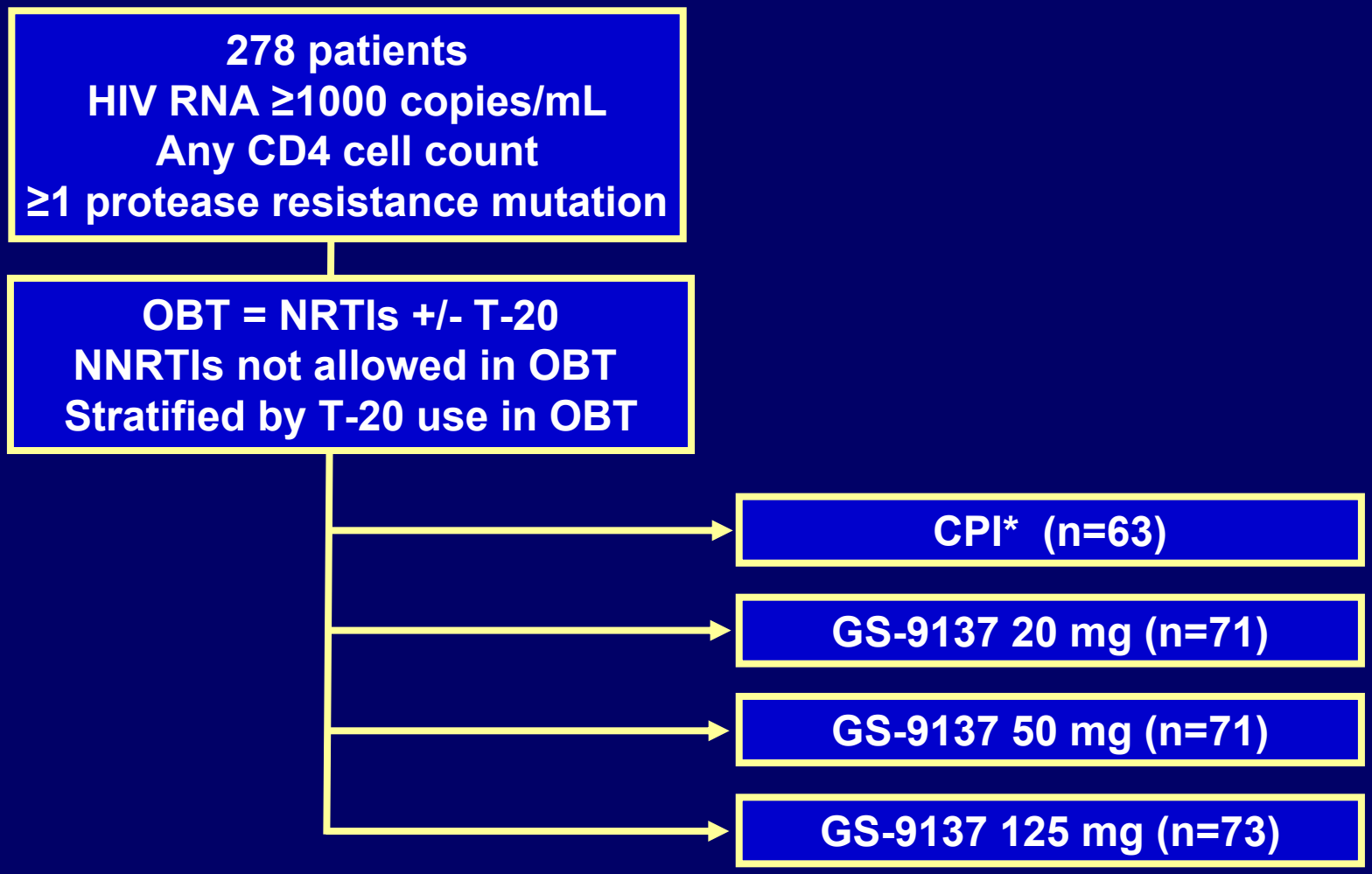
- Boosted with 100 mg qd ritonavir
  - Half-life of 9-11 hours
  - 20-fold higher systemic exposure
- 6/6 patients treated with GS-9137 50 mg/ ritonavir 100 mg qd for 10 days had >1.5 $\log_{10}$ copies/mL reductions in HIV RNA
- Well-tolerated without discontinuations of study drug

DeJesus E, Berger D, Markowitz M, Cohen C, Hawkins T, Ruane P, et al. J Acquir Immune Defic Syndr 2006;43 (1):1-5.

Phase 2 Study Design

- Randomized, active-control, partially-blinded (dose of GS-9137), dose-finding study
- Initially designed as non-inferiority study of GS-9137 (boosted with 100 mg ritonavir) and boosted PIs in treatment-experienced patients
- Optimized Background Therapy (OBT) consisted of nucleos(t)ide reverse transcriptase inhibitors
  - T-20 use was at investigator's discretion
  - PI use in GS-9137 arms was initially prohibited
- Primary endpoint was time-weighted average change from baseline in HIV RNA through 24 weeks ($DAVG_{24}$)

Phase 2 Study Schema



*CPI included 49% darunavir, 27% tipranavir

Baseline Characteristics

	CPI N = 63	GS-9137 20 mg N = 71	GS-9137 50 mg N = 71	GS-9137 125 mg N = 73
Age, median years	44	44	44	44
Male	54 (86%)	70 (99%)	63 (89%)	62 (85%)
Caucasian	54 (86%)	48 (68%)	47 (66%)	53 (73%)
HIV RNA, mean (±SD) $\log_{10}$ copies/mL	4.54 (±0.80)	4.66 (±0.79)	4.47 (±1.07)	4.71 (±0.81)
CD4 cells, mean (±SD) cells per mm^3	158 (±150)	180 (±196)	243 (±223)	157 (±158)
Genotypic Sensitivity Score (GSS) = 0 for all NRTIs in OBT	32 (51%)	35 (49%)	34 (49%)	35 (48%)
IAS Protease Resistance Mutations, median #	11	11	10	11
First use of T-20	12 (19%)	12 (17%)	17 (24%)	19 (26%)
Median # ARVs in OBT including T-20	3	3	3	3

Disposition of Patients Through Week 24

	CPI	GS-9137 20 mg	GS-9137 50 mg	GS-9137 125 mg
Randomized	73	75	75	74
Received at Least One Dose	63	71	71	73
Discontinued Study	8 (13%)	9 (13%)	8 (11%)	9 (12%)
Safety, Tolerability, Efficacy	2 (3%)	3 (4%)	3 (4%)	4 (5%)
Withdrew Consent	2 (3%)	3 (4%)	1 (1%)	0
Investigator's Discretion	2 (3%)	2 (3%)	3 (4%)	3 (4%)
Lost to Follow-up	1 (2%)	1 (1%)	1 (1%)	2 (3%)
Protocol Violation	1 (2%)	0	0	0

Week 8 DSMB Recommendations

- Close GS-9137 20 mg arm due to high rate of virologic failure; patients were offered open-label GS-9137 125 mg
- Due to new data indicating lack of drug-drug interactions, permit addition of darunavir or tipranavir to ongoing GS-9137 arms
  - Prior to Week 24, 15% of GS-9137 50 and 125 mg patients added a PI
  - Only 4 patients added a PI before Week 16: used as latest time for comparison of GS-9137 vs. PI

Primary Endpoint: Time-Weighted Average Change from Baseline in HIV RNA (DAVG)

ITT	CPI n = 63	GS-9137 50 mg n = 71	GS-9137 125 mg n = 73
$DAVG_{16}$ Mean, log_{10} copies/mL (p-value*)	-1.2	-1.5 (0.09)	-1.7 (0.01)
$DAVG_{24}$ Mean, log_{10} copies/mL (p-value*)	-1.2	-1.4 (0.27)	-1.7 (0.02)

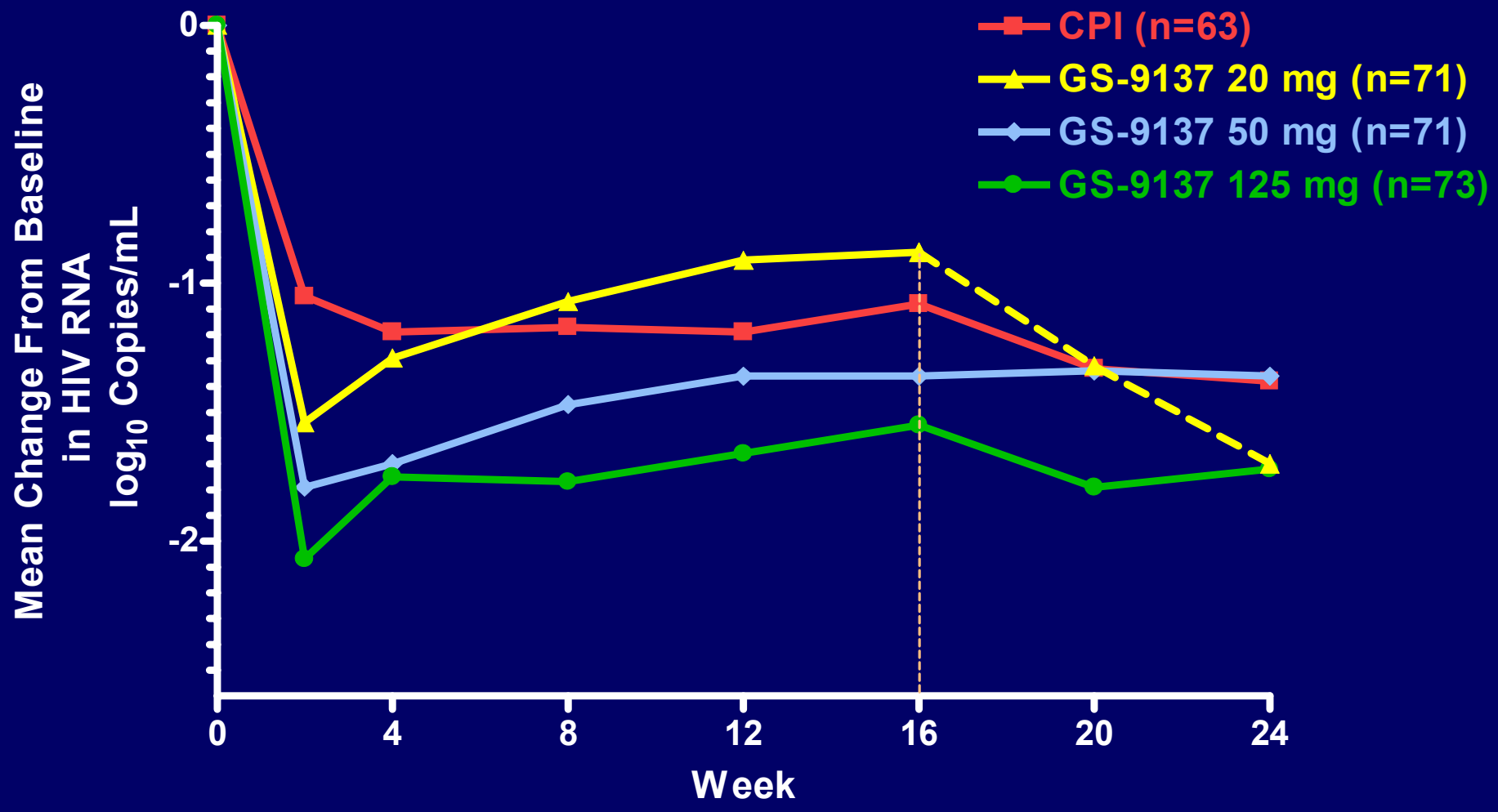
*Pairwise p-value vs. CPI/r

Viral Load Reductions: Analysis of Per Protocol Sets*

	CPI	GS-9137 50 mg	GS-9137 125 mg
Ever achieved ≥ 1 $\log_{10}$ copies/mL reduction by Week 24	61%	91%	92%
Pairwise p-value vs. CPI		$p<0.0001$	$p<0.0001$
Ever achieved ≥ 2 $\log_{10}$ copies/mL reduction by Week 24	51%	69%	76%
Pairwise p-value vs. CPI		$p=0.06$	$p=0.005$

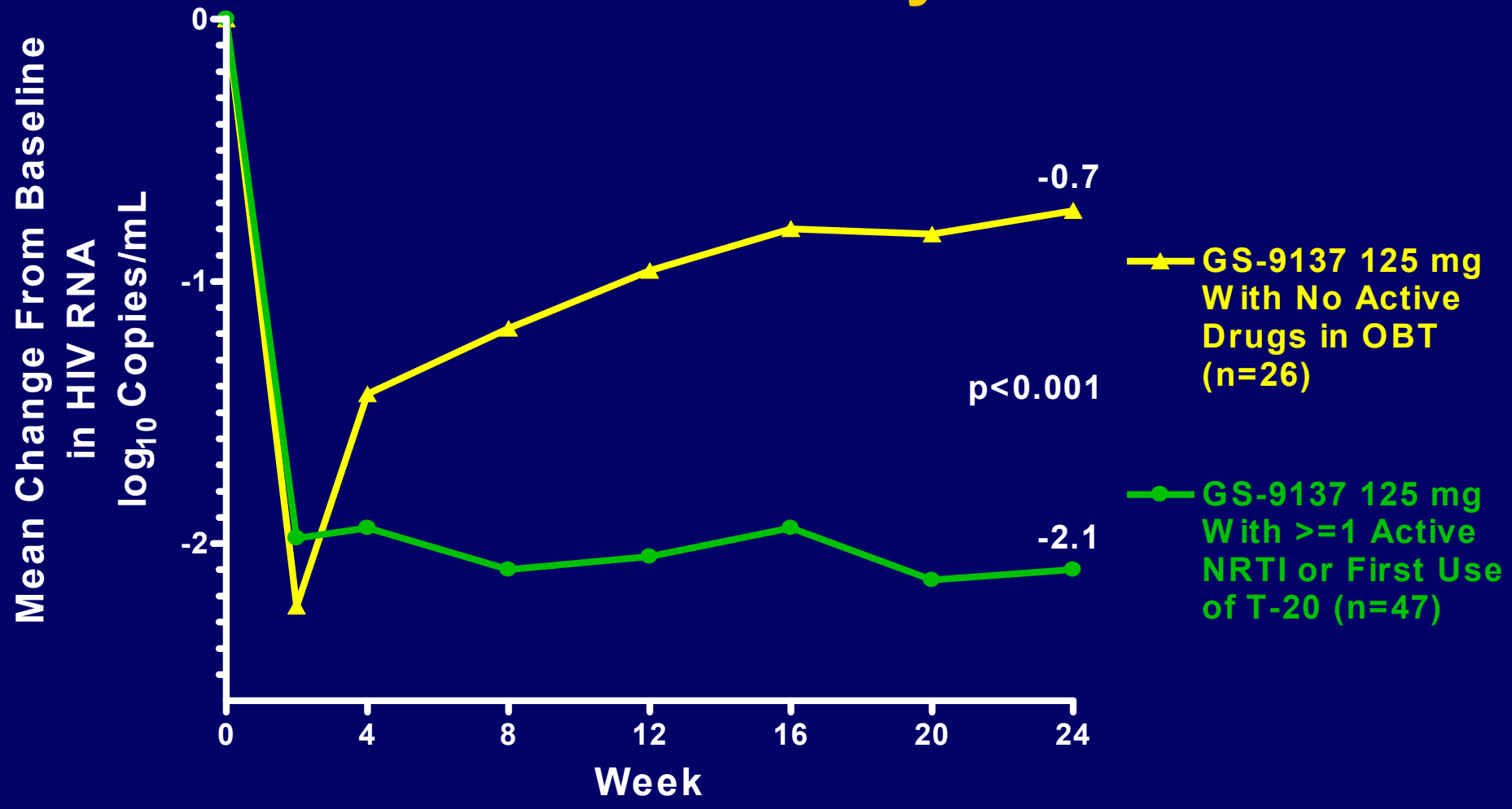
*Data from patients were excluded after switching from CPI to GS-9137 or adding a PI

Change from Baseline in HIV RNA: ITT Sets



37% of CPI patients switched to GS-9137 beginning at Week 16
GS-9137 20 mg patients switched to open-label GS-9137 125 mg beginning at Week 16 (dashed line)

Change from Baseline in HIV RNA With GS-9137 125 mg: Influence of Activity of OBT*



*Data from GS-9137 125 mg patients after addition of a PI were excluded

HIV RNA % < 50 Copies/mL (ITT, M=F)

	CPI n = 63	GS-9137 50 mg n = 71	GS-9137 125 mg n = 73
Week 16	30%	38%	40%

Mean Increase in CD4 Cell Counts (ITT, M=F)

	CPI n = 63	GS-9137 50 mg n = 71	GS-9137 125 mg n = 73
Week 16	28 (+/-69)	52 (+/-90)	61 (+/-97)

Summary of Adverse Events and Laboratory Abnormalities

Week 24	CPI N = 63	GS-9137 20 mg N = 71	GS-9137 50 mg N = 71	GS-9137 125 mg N = 73
Adverse events leading to study drug discontinuation	2 (3%)	1 (1%)	2 (3%)	1 (1%)
Grade 3 and 4 adverse events	9 (14%)	13 (18%)	9 (13%)	10 (14%)
Grade 3 and 4 laboratory abnormalities	20 (32%)	21 (30%)	15 (21%)	15 (21%)

Conclusions

- GS-9137 50 mg and 125 mg arms met primary endpoint of non-inferiority for $DAVG_{24}$
  - GS-9137 125 mg group was statistically superior to CPI group for both $DAVG_{16}$ and $DAVG_{24}$
- GS-9137 125 mg showed potency within two weeks (>2 log_{10} decrease) that was durable when combined with an active OBT
- No difference in incidence or severity of adverse events between CPI and the GS-9137 arms
- No dose relationship in Grade 3 or 4 adverse events, laboratory abnormalities, or study drug discontinuation for the GS 9137 arms

Acknowledgments

Judith Aberg, MD
Ben Barnett, MD
George Beatty, MD
Nicholaos Bellos, MD
Constance Benson, MD
Daniel Berger, MD
Gary Blick, MD
Jeffrey Burack, MD
Larry Bush, MD
Rafael Campo, MD
Calvin Cohen, MD
Ann Collier, MD
Gordon Crofoot, MD
Frederick Cruickshank, MD
Eric Daar, MD
Edwin DeJesus, MD
Leslie Diaz, MD
Robin Dretler, MD
Richard Elion, MD
Charles Farthing, MD
Todd Fralich, MD
Joel Gallant, MD
Joseph Gathe, MD
Joide Guest, MD
Roy Gulick, MD
Trevor Hawkins, MD
Thomas Jefferson, MD
Michael Karagiozis, MD
Clifford Kinder, MD
Harry Lampiris, MD
Robert Larsen, MD
Angelike Liappis, MD
Ralph Liporace, MD
Roberta Luskin-Hawk, MD
Martin Markowitz, MD
Cynthia Mayer, MD
Joseph McGowan, MD
Karam Mounzer, MD
Michael Mullen, MD
Ronald Nahass, MD
David Parks, MD
Andrew Petroll, MD
Gerald Pierone, MD
Kristin Razzeca, MD
Gary Richmond, MD
Gregory Robbins, MD
Stockton Roberts, MD
Jorge Rodriguez, MD
Peter Ruane, MD
Sonia Saavedra, MD
Jorge Santana-Bagur, MD
Lizette Santiago, MD
Stefan Schneider, MD
Shannon Schrader, MD
Lawrence Schwartz, MD
Michael Sension, MD
David Shamblaw, MD
Daniel Skiest, MD
Jeffrey Stephens, MD
William Towner, MD
Roger Trinh, MD
Vilma Vega, MD
Charles Walworth, MD
Douglas Ward, MD
David Wheeler, MD
Todd Wills, MD
Michael Wohlfeiler, MD
Bienvenido Yangco, MD
Benjamin Young, MD
Andrew Zolopa, MD
John Zurlo, MD
All Patients in Study 0105