Abstract No. 5024

Overall Survival with Sunitinib versus Interferon-alfa (IFN-α) as First-line Treatment of Metastatic Renal Cell Carcinoma (mRCC)

Supported by Pfizer Inc.

Disclosure

- Advisory Role: Pfizer, Wyeth, Novartis, Keryx
- Honoraria: Pfizer, Wyeth
- Research Funding: Pfizer, Novartis, Wyeth, Keryx, Amgen, Argos

Background

- Sunitinib (SUTENT®) is a multitargeted receptor tyrosine kinase inhibitor of VEGFR and PDGFR
- Randomized phase 3 trial in mRCC showed statistically significant improvement in PFS and ORR of sunitinib compared to IFN-α[1]
  - Median PFS: 11 mo vs. 5 mo (HR: 0.415; p <0.000001)
- Results of final survival analysis are reported

[1]*Motzer et al. NEJM 2007;356:115-124*

Study Endpoints

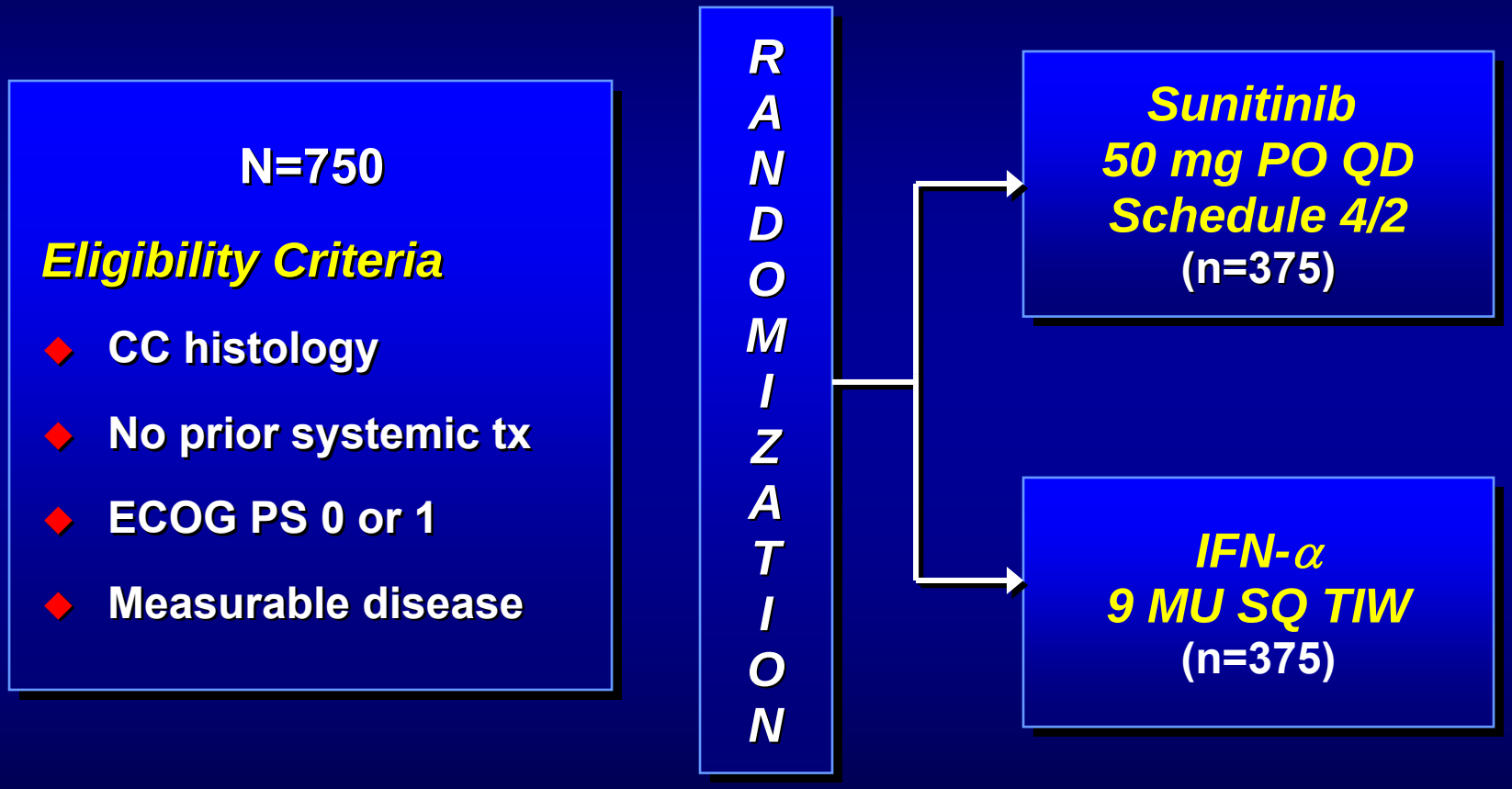
Primary Endpoint

- **Progression-free survival**
  - 90% power to detect a 35% improvement
  - Primary endpoint (EP) met at the pre-planned Interim Analysis 2

Secondary Endpoints

- **Overall survival**
  - 85% power to detect a 35.7% improvement
  - 390 events required for the final analysis
- Response rate, Safety, Patient-reported outcomes

Study Design



*Results from Interim Analysis 2 → 1°EP of PFS met → IFN-α pts allowed to crossover to sunitinib upon documented disease progression (Feb 2006)

Sunitinib Study Summary

- Randomized, phase 3 study: Sunitinib vs. IFN-α (1:1)
- Accrual: Aug 2004 to Oct 2005
- Nov 2005: Data cut-off for Interim Analysis 2
  - 1° EP of PFS met
  - 2° EP of OS analysis performed → medians not reached
- Feb 2006: Protocol amended to allow IFN-α pts to crossover to sunitinib upon documented disease progression
- Final survival analysis: 390 events required for a 2-sided, unstratified log-rank test with 85% power and significance level of 0.05

Statistical Methods

- Pre-specified survival analysis performed using unstratified / stratified log-rank and Wilcoxon tests, and the Cox model
- Stratified analyses based on three pre-specified stratification factors: ECOG PS, LDH, nephrectomy
- **Log-rank test***: more suitable test when the ratio of death rates between two treatment groups is constant over time
- **Wilcoxon test***: more appropriate test when the ratio of death rates between two treatment groups is not constant over time in situations where survival data may be confounded by crossover or post-study treatments

** Collett D. Modelling Survival Data in Medical Research. Chapman & Hall 1994*

Patient Characteristics

Characteristics	Sunitinib (n=375)	IFN-α (n=375)
Median age, yrs (range)	62 (27-87)	59 (34-85)
ECOG PS 0/1 (%)	62/38	61/39
Prior nephrectomy (%)	90	89
Sites of disease involvement (%)		
Lung	78	79
Liver	26	24
Bone	30	30
Number of metastatic sites (%)		
1	19	24
≥2	81	76
MSKCC risk factors* (%)		
0 (favorable)	38	34
1-2 (intermediate)	56	59
≥3 (poor)	6	7

** Motzer et al. JCO 2002; Excludes 17 pts from IFN-α with missing data*

Treatment Administered & Patient Disposition

	Sunitinib (n=375)	*IFN-α (n=375)*
Median treatment duration, mo (range)	11 (<1–41+)	4 (<1–40+)
Ongoing on assigned treatment, n (%)	52 (14)	6 (2)
Reason for discontinuation, n (%)		
Progressive disease	226 (60)	243 (65)*
Adverse event	70 (19)	86 (23)*
Consent withdrawn	21 (6)	38 (10)**
Protocol violation / Other	6 (2)	2 (1)

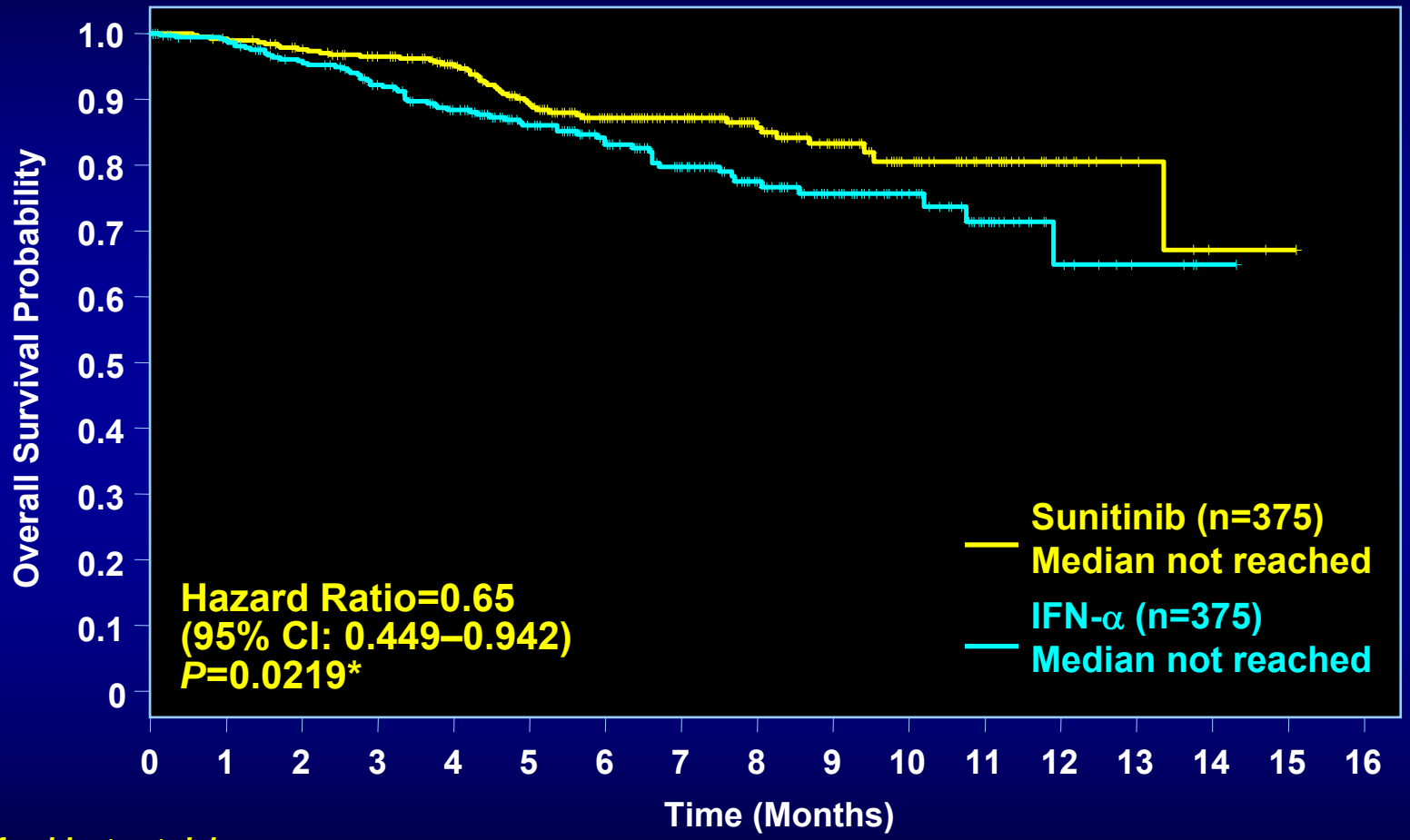
**25 pts from the IFN-α group crossed over to sunitinib on study; **15 pts (4%) randomized to IFN-α withdrew prior to starting treatment*

Updated Efficacy Results

	Sunitinib (n=375)	*IFN-α (n=375)*
Median Progression-free Survival*, mos (95% CI)		
Independent Review	11 (11-13)	5 (4-6)
Investigator	11 (11-13)	5 (4-6)
Objective response*, % (95% CI)		
Independent Review	39 (34-44)	8 (6-12)
Investigator	47 (42-52)	12 (9-16)

***Sunitinib vs IFN-α: P <0.000001**

Overall Survival: Interim Analysis 2 (data cut-off Nov 2005)

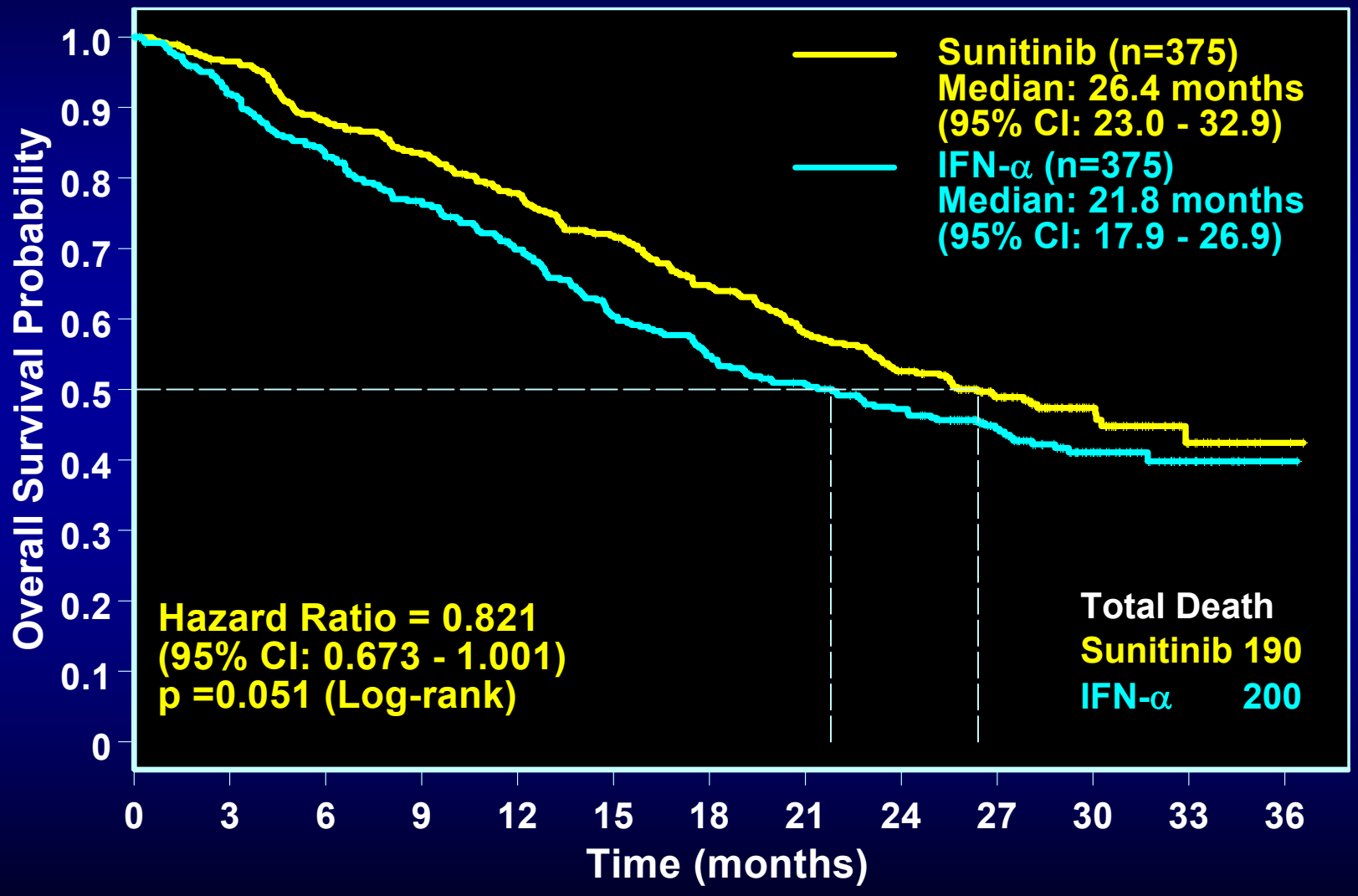


No. of subjects at risk						
Sunitinib:	375	341	190	84	15	1
IFN-α:	375	296	162	66	10	0

**The observed p-value did not meet the pre-specified level of significance for this interim analysis*

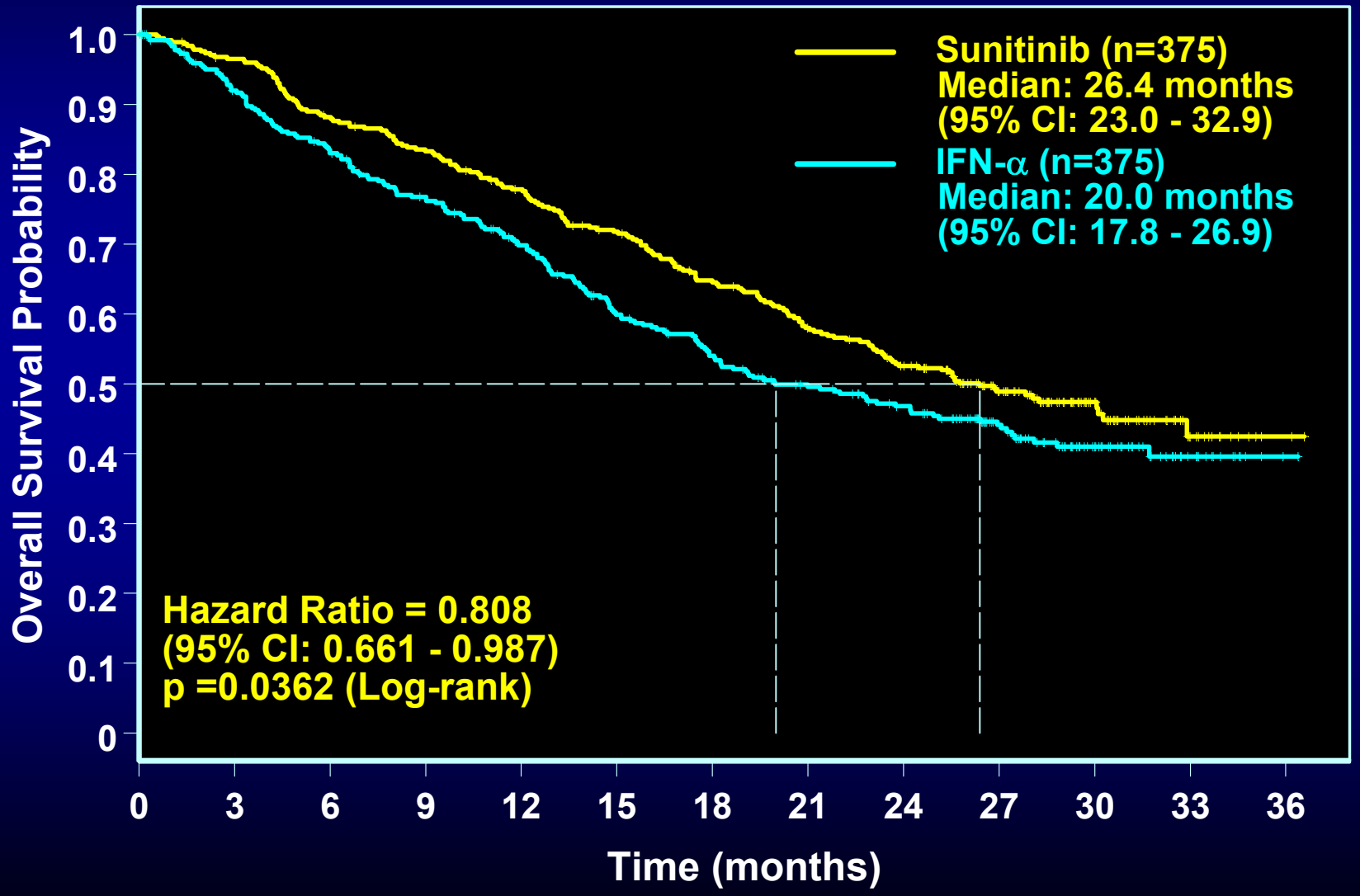
Motzer et al. ASCO 2006

Final Overall Survival



nDeath/nRisk Sunit	375	44 / 326	38 / 283	48 / 229	42 / 180	14 / 61	4 / 2
nDeath/nRisk IFN-α	375	61 / 295	46 / 242	52 / 187	25 / 149	15 / 53	1 / 1

Overall Survival: Crossover patients censored (n=25)



Overall Survival Analyses

	Pre-specified Analyses		Exploratory Analyses
	Unstratified	Stratified	Crossover pts censored
Median OS (mos)	26.4 vs. 21.8	26.4 vs. 21.8	26.4 vs. 20.0
HR (95% CI)	0.821 (0.673, 1.001)	0.818 (0.669, 0.999)	0.808 (0.661, 0.987)
P-value (Log-rank)	0.0510	0.0491	0.0362
P-value (Wilcoxon)	0.0128	0.0132	0.0081

**Stratification factors: ECOG PS, LDH, and nephrectomy*

Post-Study Treatments*

	Sunitinib, n (%) (n=323)	IFN-α, n (%) (n=359)
Any post-study treatment	182 (56)	213 (59)
Sunitinib	36 (11)	117 (33)
Other VEGF Inhibitors	106 (33)	115 (32)
Cytokines	63 (20)	47 (13)
mTOR Inhibitors	28 (9)	16 (4)
Chemotherapy	21 (6)	20 (6)

*Treatments received after discontinuation from the study

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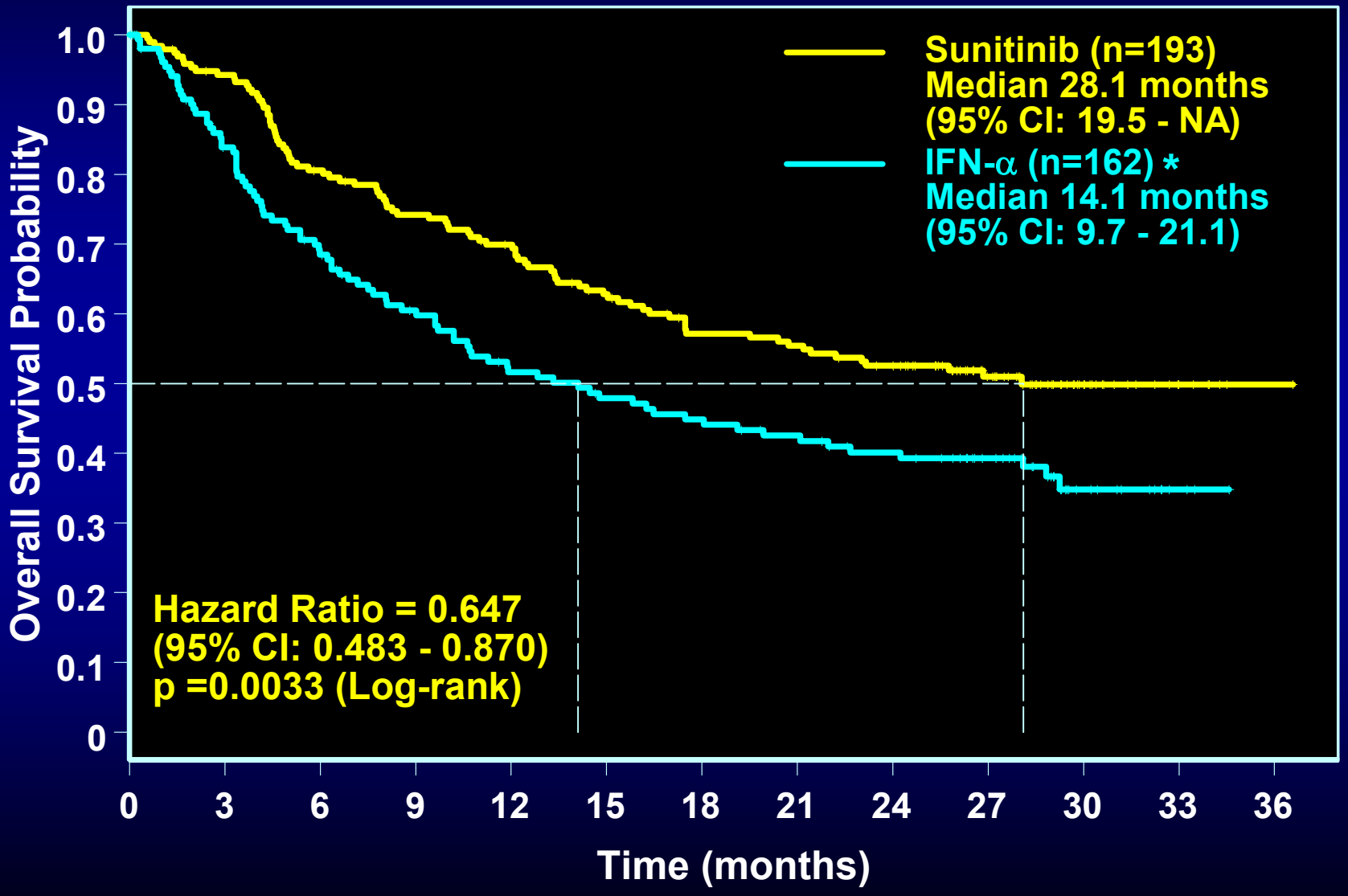
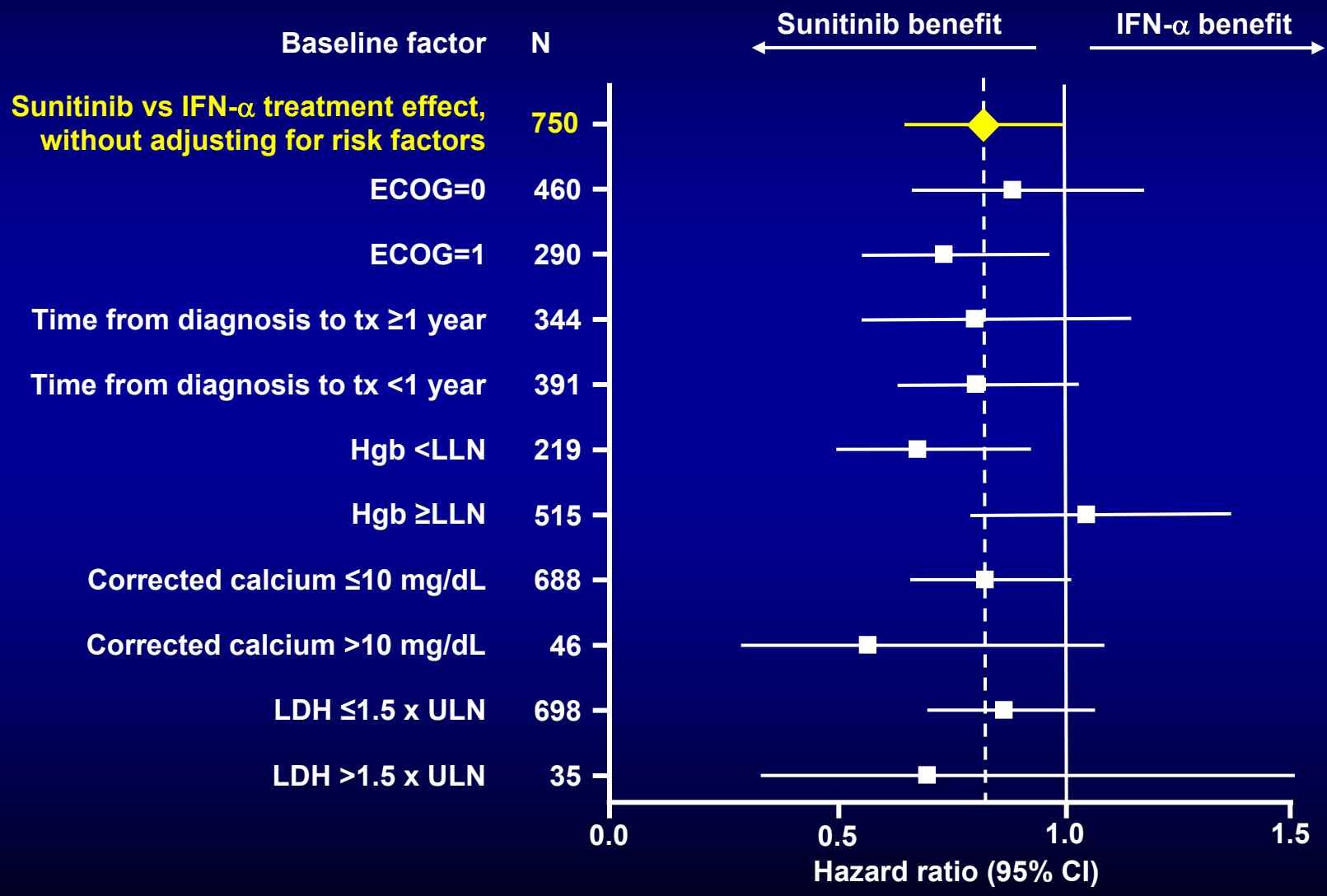
**P<0.0001*

OS in patients who did not receive any post-study treatment



*Includes 20 patients who crossed over to sunitinib on study

OS in Subgroups According to Individual Baseline Factors*



*Comparisons by individual baseline factors one at a time by Cox model

Overall Survival Multivariate Analysis*

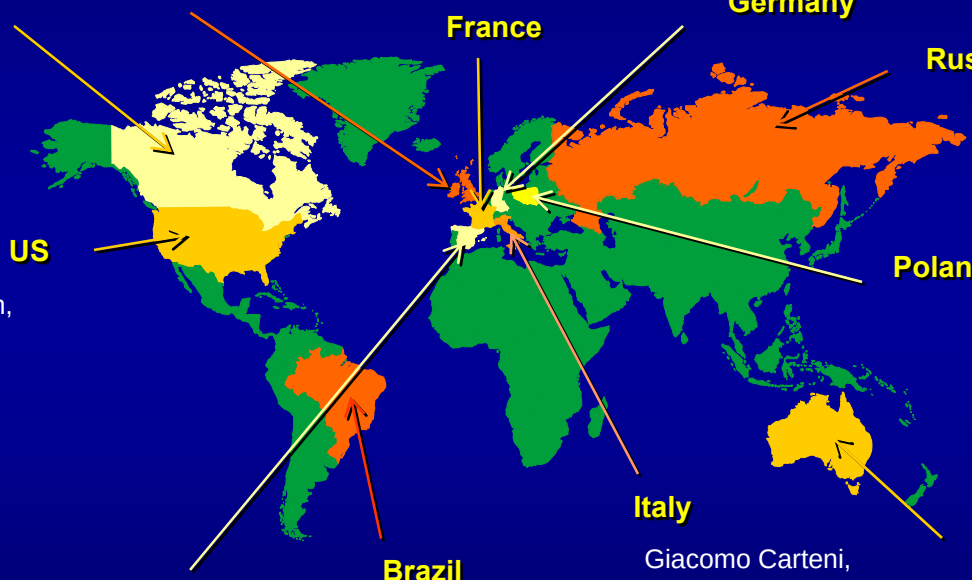
	OS		
	HR	95% CI	P-value
ECOG PS (0 vs. 1)	0.515	0.417 – 0.636	<0.0001
Hemoglobin (≥LLN vs. <LLN)	0.504	0.401 – 0.634	<0.0001
Time from diagnosis to tx (≥1 yr vs. <1 yr)	0.574	0.461 – 0.715	<0.0001
Corrected calcium (≤10 vs. >10 mg/dL)	0.466	0.327 – 0.664	<0.0001
Alkaline phosphatase (≤ULN vs. >ULN)	0.676	0.542 – 0.844	0.0005
LDH (≤1.5 vs. >1.5 x ULN)	0.500	0.337 – 0.742	0.0006
No. of metastatic sites (1 vs. ≥2)	0.664	0.503 – 0.876	0.0037
Treatment (sunitinib vs. IFN-α)	**0.764**	**0.623 – 0.936**	**0.0096**

**Treatment comparisons controlling for baseline factors simultaneously from Cox model*

Conclusions

- Sunitinib has demonstrated a survival advantage compared to IFN-α
- Sunitinib has consistently demonstrated improvements in PFS and ORR compared to IFN-α
- Sunitinib is the reference standard for the first-line treatment of mRCC

Acknowledgements



Georg Bjarnason, Scott Ernst, Christian Kollmannsberger, Andre Lavoie, Heidi Martins, Dean Ruether, Fred Saad, Judy Sutherland, Ian Tannock, Peter Venner

James Barber, Tim Eisen, Peter Harper, Robert Hawkins, Paul Nathan

Lionel Geoffrois, Brigitte Laguerre, Sylvie Negrier, Stephane Oudard, Olivier Rixe, Frederic Rolland

Wilfried Eberhardt, Viktor Gruenwald, Gerhard Jakse, Mark Ringhoffer

Oleg Gladkov, Andrey Kaprin, Petr Karlov, Oleg Karyakin, Mikhail Lichinitser, Vladimir Moiseyenko, Igor Rusakov, Elena Slonimskaya

Robert Amato, J Christian Barrett, Robert Belt, Pasquale Benedetto, Ronald Bukowski, Joseph Clark, Matthew Cooney, Thomas Cosgriff, Christopher Croot, Harry Drabkin, Arkadiusz Dudek, Janice Dutcher, Marc Ernstoff, Robert Figlin, Mayer Fishman, Gary Hudes, Ralph Hauke, Tom Hutson, Kasra Karamlou, Paul Kaywin, Alan Keller, Timothy Kuzel, Jill Lacy, Dror Michaelson, Fred Millard, David Minor, Mark Monte, Robert Motzer, Roberto Pili, Louis Puneky, Donald Richards, Christopher Ryan, Wolfram Samlowski, Lee Schwartzberg, Jeffrey Sosman, John Thompson, Ulka Vaishampayan, Jacqueline Vuky, George Wilding

Tomasz Demkow, Jerzy Lorenz, Maria Mazurkiewicz, Anna Pluzanska, Janusz Rolski, Ewa Solska, Cezary Szczylik, Piotr Tomczak

Giacomo Carteni, Pierfranco Conte, Gianpietro Gasparini, Camillo Porta, Enzo Ruggeri, Cora Sternberg

Carlos Barrios, Daniel Herchenhorn, Manuela Zereu

Daniel Castellano, Xavier Garcia del Muro, Jose Luis Gonzalez-Larriba, Jose Perez-Gracia Andres Moreno-Nogueira, Jose Luis

Adam Boyce, Ian Davis, Paul Mainwaring, Nick Pavlakis, Kenneth Pittman, Guy Toner, Simon Troon

The patients and their families