Abstract No. 1155O

Updated Overall Survival Analysis from a Phase III Study of Sunitinib vs Placebo in Patients with Advanced, Unresectable Pancreatic Neuroendocrine Tumor

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Disclosure

- **Honoraria: Pfizer and Novartis**
- **Research funding: Pfizer and Novartis**

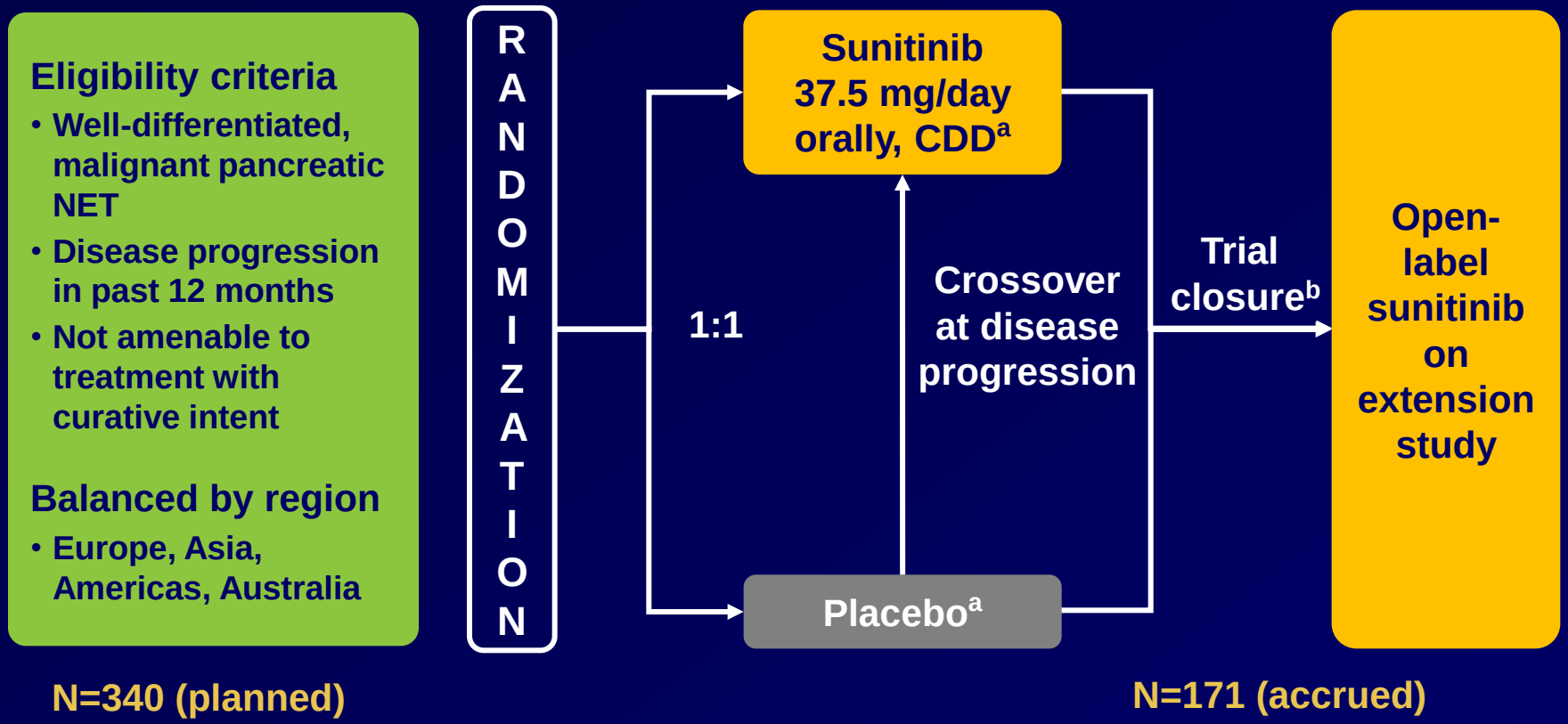
Background

- Sunitinib was approved by the EMA and US FDA for patients with advanced pancreatic NET based on a randomized, phase III, double-blind study showing an improved PFS vs placebo (primary endpoint) 11.4 vs 5.5 months (HR: 0.42; 95% CI: 0.26–0.66; P<0.001)[1]
- At trial closure, there was an advantage for sunitinib over placebo in OS (secondary endpoint)
- 69% of patients randomized to placebo crossed over to sunitinib upon disease progression or trial closure, potentially confounding OS analysis
- We now present OS data 2 years after study closure and updated OS analyses after adjusting for crossover

NET, neuroendocrine tumor

[1]Raymond E, et al. *N Engl J Med* 2011;364:501−513

Study Design



- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, time to tumor response, duration of response, safety, PROs

CDD, continuous daily dosing; PROs, patient-reported outcomes
[a]With best supportive care; somatostatin analogs permitted
[b]Early trial closure occurred due to differences in deaths, serious AEs, and PFS

Raymond E, et al
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Demographic and Baseline Characteristics

- A total of 171 patients were enrolled between June 2007 and April 2009

	Sunitinib (n=86)	Placebo (n=85)
Median (range) age, years	56 (25–84)	57 (26–78)
Male/female, n (%)	42/44 (49/51)	40/45 (47/53)
ECOG performance status, n (%)		
0	53 (62)	41 (48)
1	33 (38)	43 (51)
2	0	1 (1)[a]
Involved disease sites, n (%)[b]		
Pancreas	35 (41)	31 (36)
Lymph node	29 (34)	41 (48)
Liver	79 (92)	78 (92)
Other	30 (35)	44 (52)

[a]Protocol violation
[b]Includes both target and non-target sites; sites with multiple lesions counted once

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Tumor Functionality and Prior Therapy

	n (%)	
	Sunitinib (n=86)	Placebo (n=85)
Tumor functionality at baseline		
Non-functioning	42 (49)	44 (52)
Functioning	25 (29)	21 (25)
Unknown/missing	19 (22)	20 (24)
Prior surgery	76 (88)	77 (91)
Prior systemic therapy[a]	45 (52)	50 (59)
Anthracyclines	27 (31)	35 (41)
Streptozocin	24 (28)	28 (33)
Fluoropyrimidines	20 (23)	25 (29)
Number of prior systemic regimens[a]		
1	20 (23)	25 (29)
2	15 (17)	13 (15)
≥3	10 (12)	12 (14)
Concomitant somatostatin analog	23 (27)	25 (29)

[a]Excluding chemoembolization and regimens with somatostatin analog only

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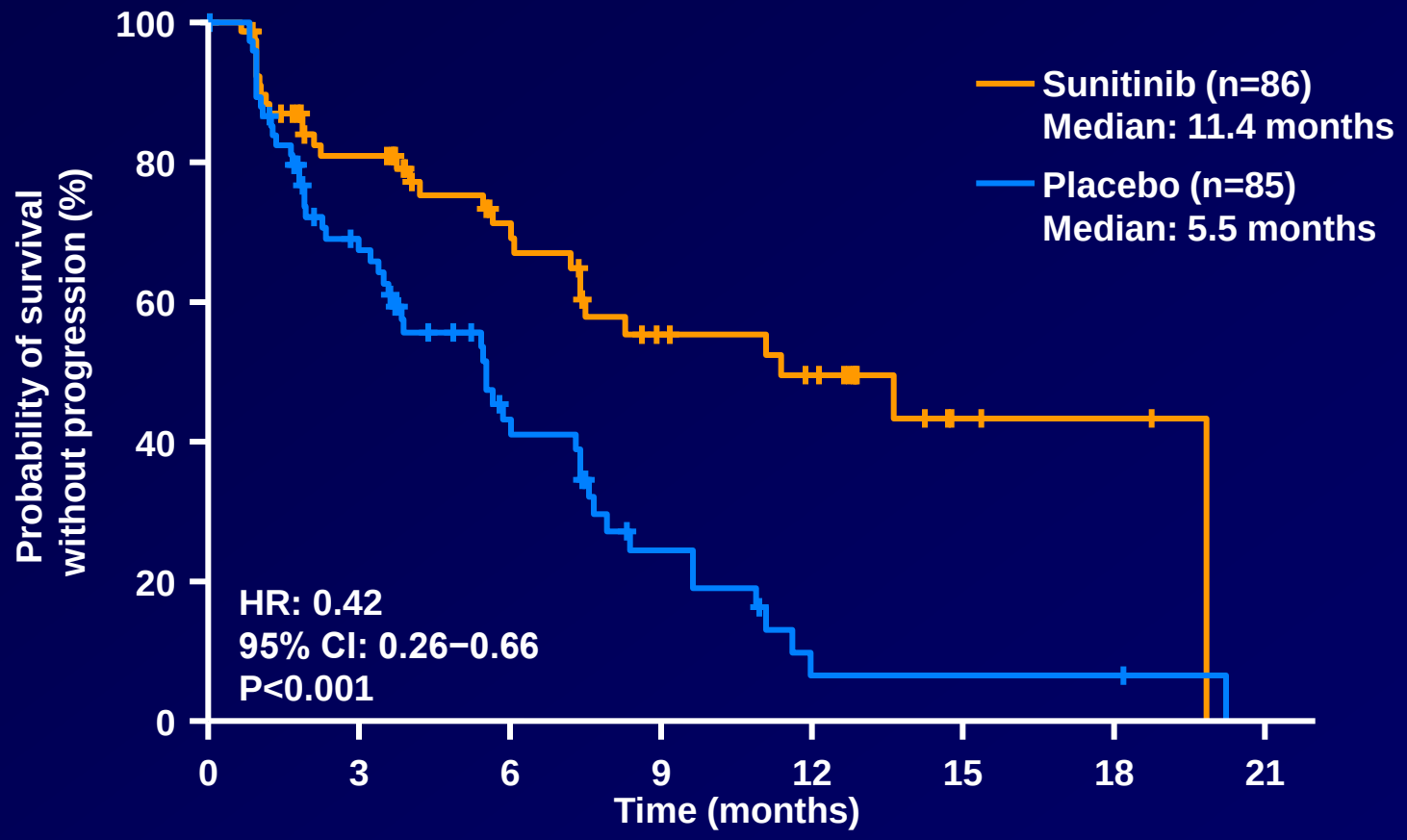
PFS (Primary Endpoint)



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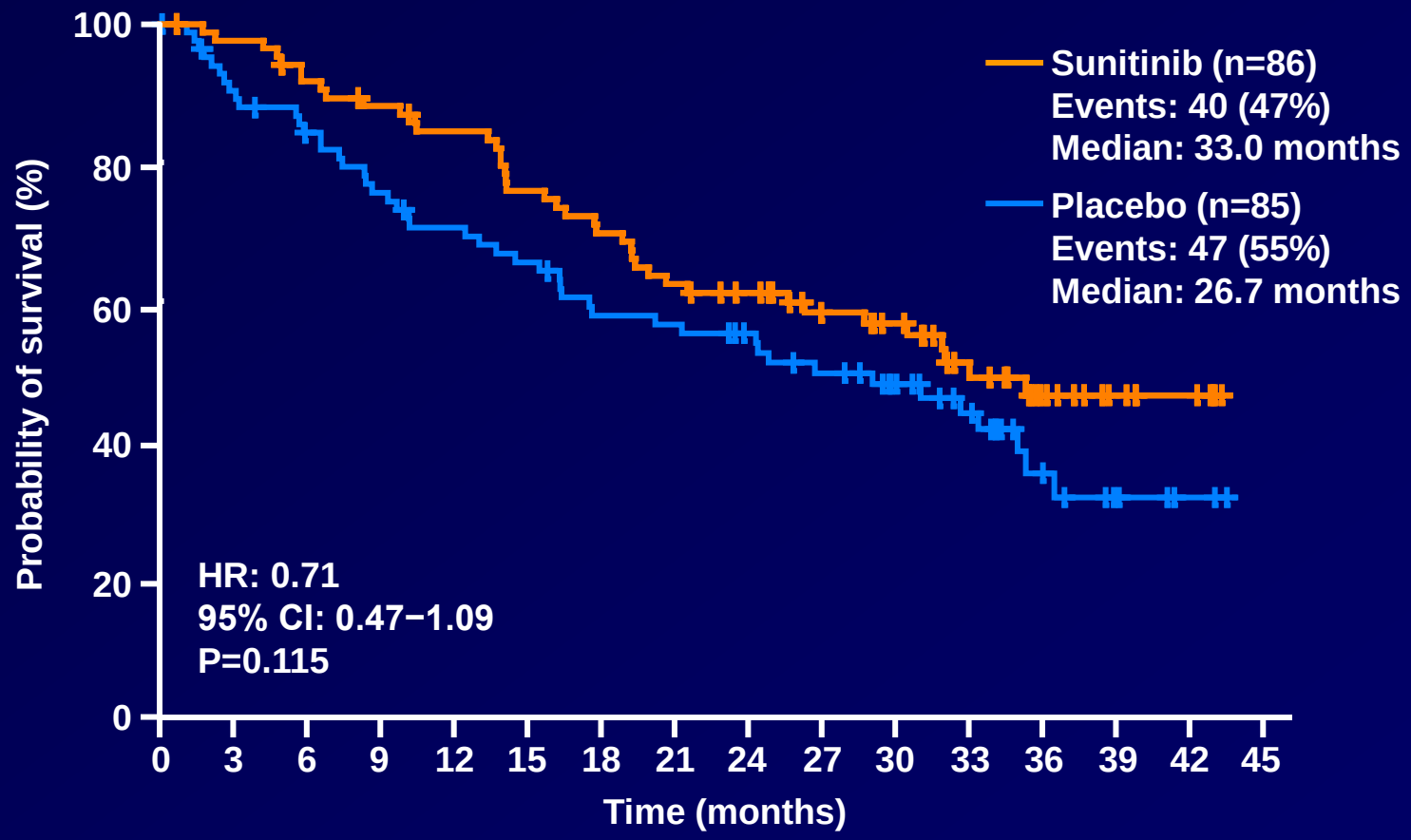
OS at 2 Years After Trial Closure: ITT Analysis

- Median duration of follow-up: 34.1 months



Vinik A, et al. ASCO 2012 Annual Meeting, poster (Abstract 4118)

Impact of Crossover

- **Crossover: often necessary for ethical reasons**
  - **Can lead to underestimation of true clinical gain in OS with standard statistical analysis (e.g., ITT analysis) if experimental drug has benefit over control**

Ishak J, et al. ENETS 2011 Annual Meeting, poster (Abstract C-50)

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- Crossover causes bias in two ways
  - Mixing of treatment effects: outcomes in control arm reflect benefit of experimental drug among patients who cross over
  - Selection bias: patients who cross over are usually those most likely to benefit from experimental drug and are not comparable to initially randomized population

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  - Mixing of treatment effects: outcomes in control arm reflect benefit of experimental drug among patients who cross over
  - Selection bias: patients who cross over are usually those most likely to benefit from experimental drug and are not comparable to initially randomized population
- Since crossover usually occurs after progression, endpoints occurring after progression, such as OS, are affected

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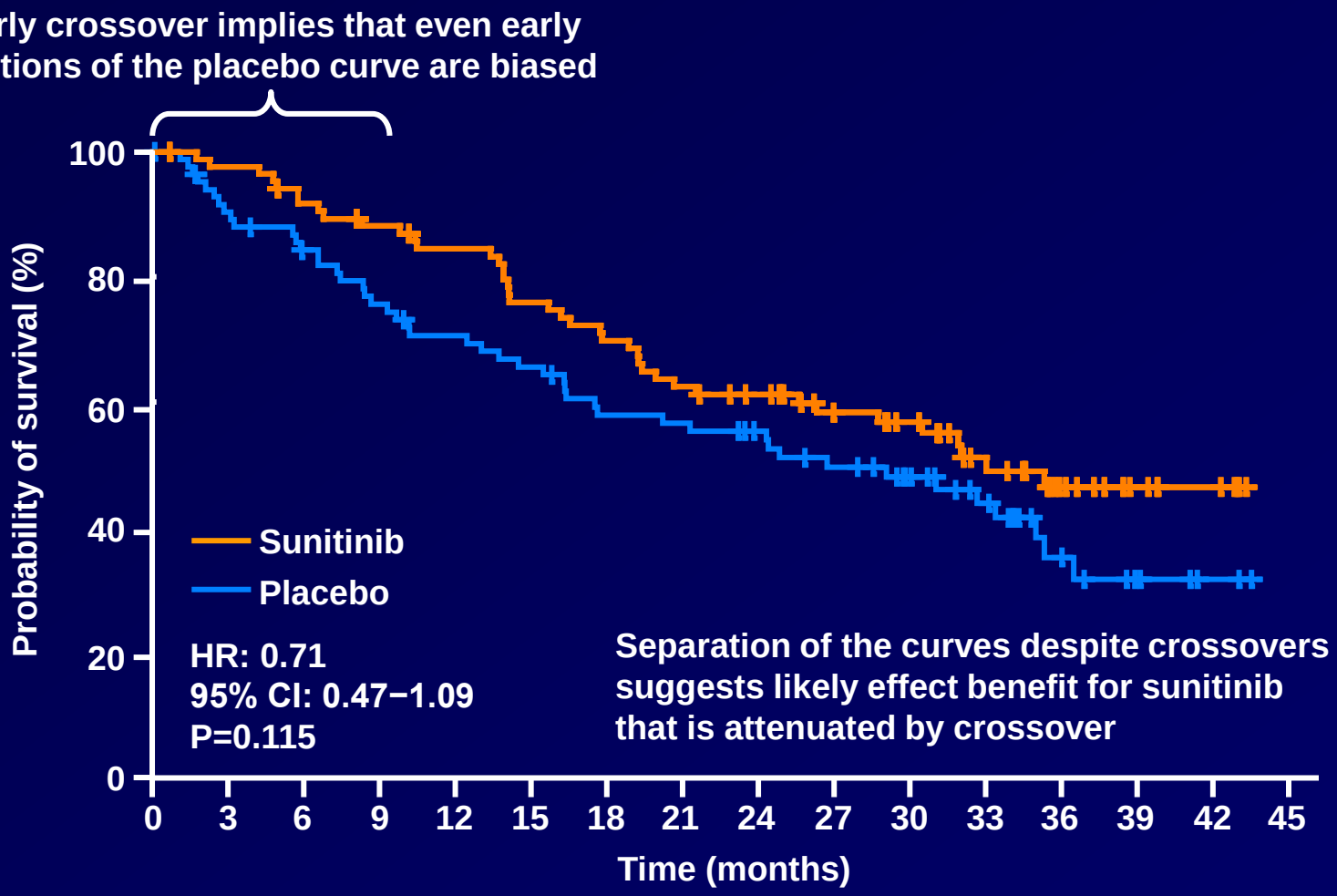
Impact of Crossover (cont'd)

- The timing of crossover can vary; early crossover may influence endpoints at early stages



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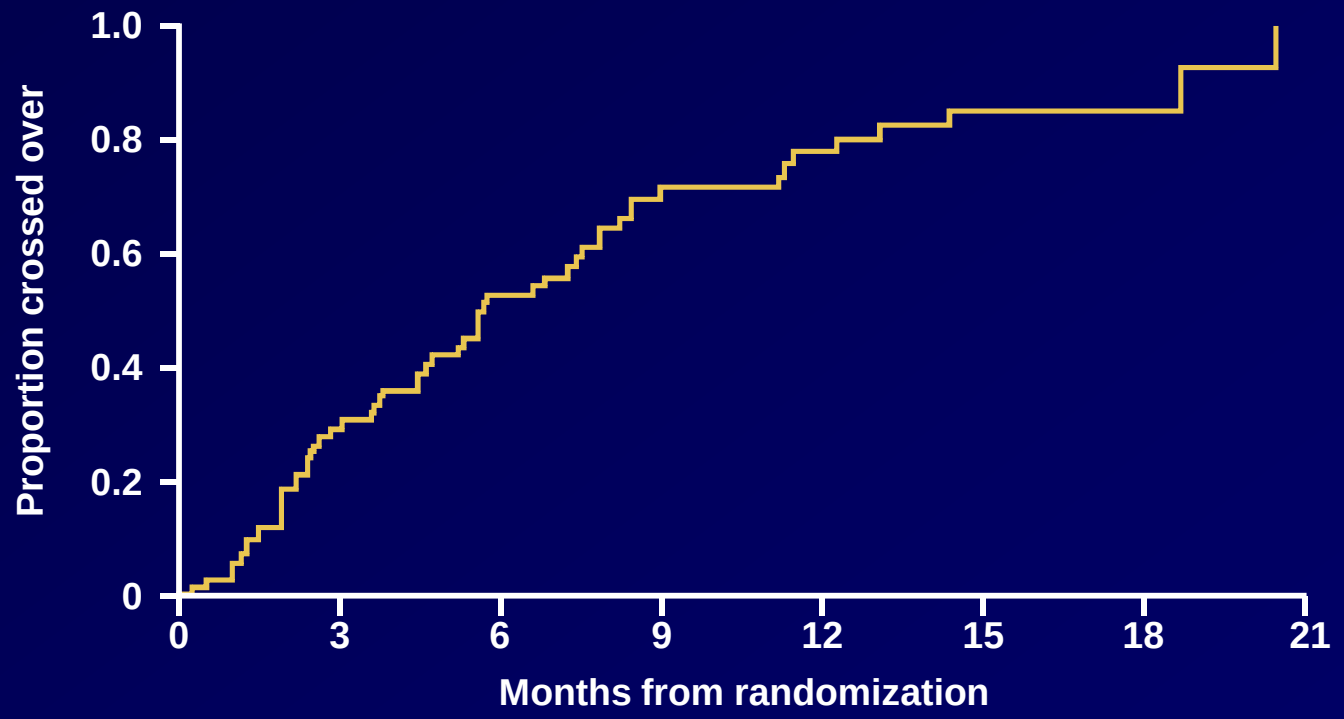
Crossover in Placebo Arm

- Of patients in the placebo arm:
  - with PD, 38 (79%) crossed over to sunitinib treatment
  - without PD, 21 (58%) crossed over on trial closure
- Crossover occurred early
  - ~30% of patients crossed over by 3 months
  - ~50% of patients crossed over by 6 months



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Adjusting for Crossover: Four Methods Used

1. **Censoring placebo-arm data at crossover**
   - **Associated with selection bias**
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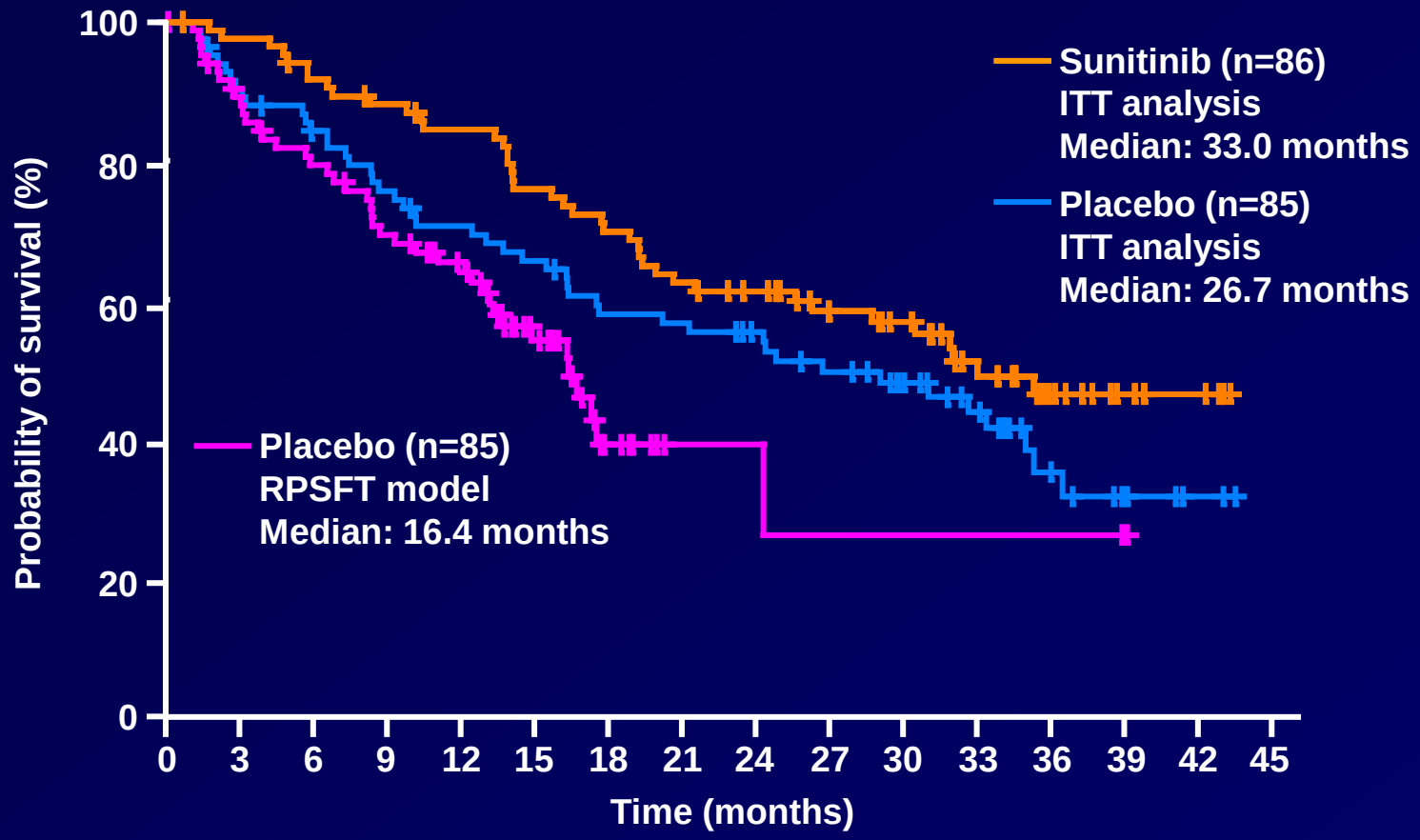
   - Times on treatment after crossover adjusted to reflect what would have happened if patients had stayed on control treatment
4. Extended RPSFT analysis
   - Assumes active treatment likely to change over time, with less effect the longer crossover is delayed (e.g., by 30% if crossover occurred 3 months after start of control treatment)

Analysis of OS with Adjustment for Crossover

OS analysis/treatment group	Deaths	Median (months)	HR[a]	95% CI	P
ITT − no adjustment for crossover					
Sunitinib (n=86)	40	33.0			
Placebo (n=85)	47	26.7	0.71	0.47–1.09	0.115
Adjustment for crossover (placebo; n=85)					
Censoring at crossover	20	16.3	0.43	0.24–0.77	0.004
Time-dependent Cox model	47	26.7	0.49	0.28–0.85	0.010
RPSFT model	41[b]	16.4	0.43	0.17–1.20[c]	0.115[d]
Extended RPSFT model adjusted for crossover time[e]	40[b]	19.1	0.57	0.18–1.09[c]	0.115[d]

[a]Sunitinib vs. placebo
[b]After recensoring
[c]From 20,000 bootstrap samples
[d]The RPSFT method does not alter the P value obtained using the ITT method
[e]Assuming active treatment effect reduced progressively based on length of crossover delay (eg, by 30% if crossover occurred 3 months after start of control treatment)

OS with and without Adjustment for Crossover



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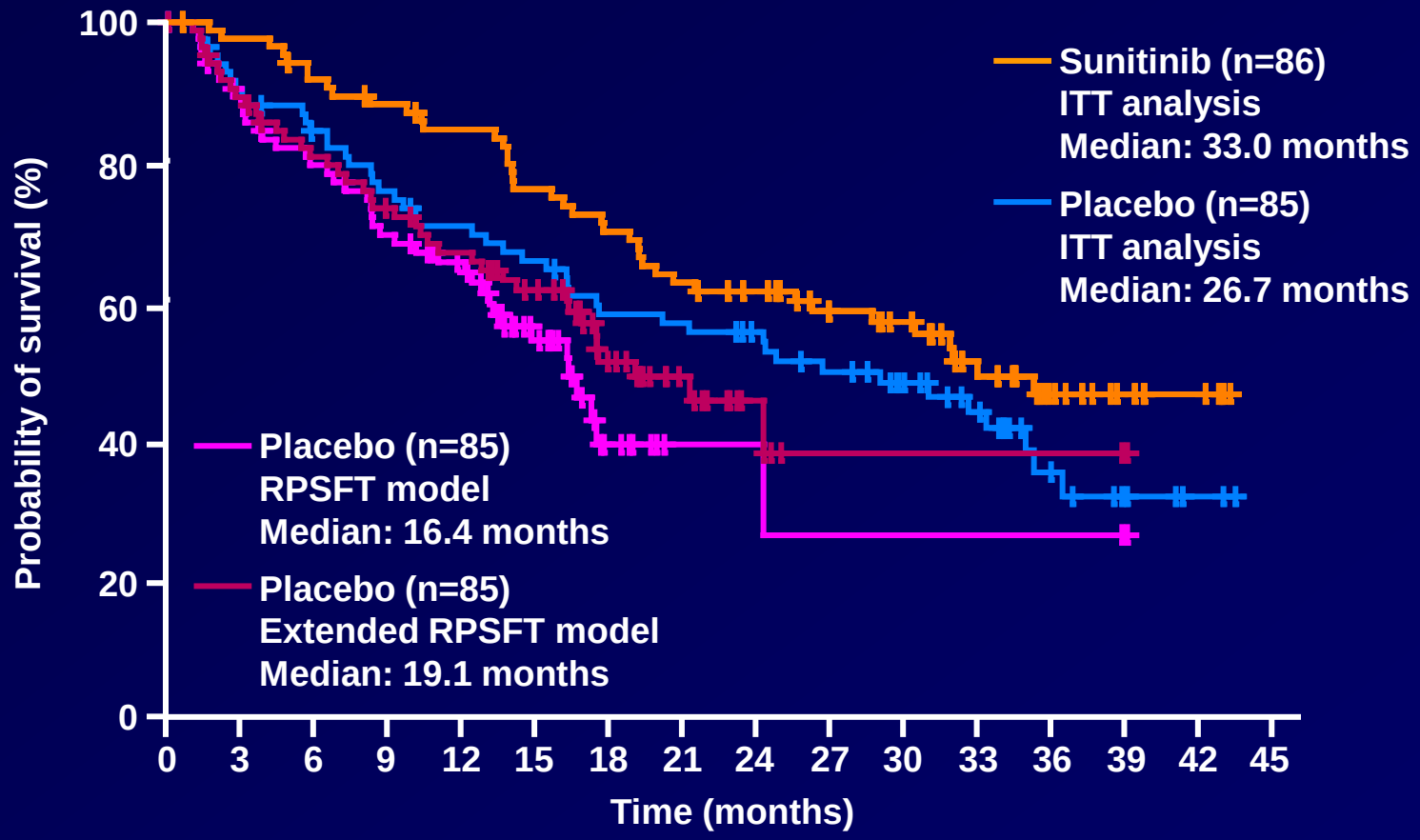

Conclusions

- **In this phase III study, updated OS based on ITT analysis continued to favor sunitinib, with a clinically meaningful improvement of 6.3 months in median OS**

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  - treatment crossover
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- This result was not statistically significant for reasons that may include:
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- Four different methods of adjusting for crossover suggested that the effect of sunitinib on OS may have been more pronounced had no crossover occurred

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- In this phase III study, updated OS based on ITT analysis continued to favor sunitinib, with a clinically meaningful improvement of 6.3 months in median OS
- This result was not statistically significant for reasons that may include:
  - treatment crossover
  - limited statistical power
- Four different methods of adjusting for crossover suggested that the effect of sunitinib on OS may have been more pronounced had no crossover occurred
- These analyses demonstrate a survival advantage and further support the clinical benefit of sunitinib for patients with advanced, progressive pancreatic NET

We would like to thank all of the participating patients and their families, as well as the global network of investigators, research nurses, study coordinators, and operations staff

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