FDA U.S. FOOD & DRUG ADMINISTRATION

Sutent

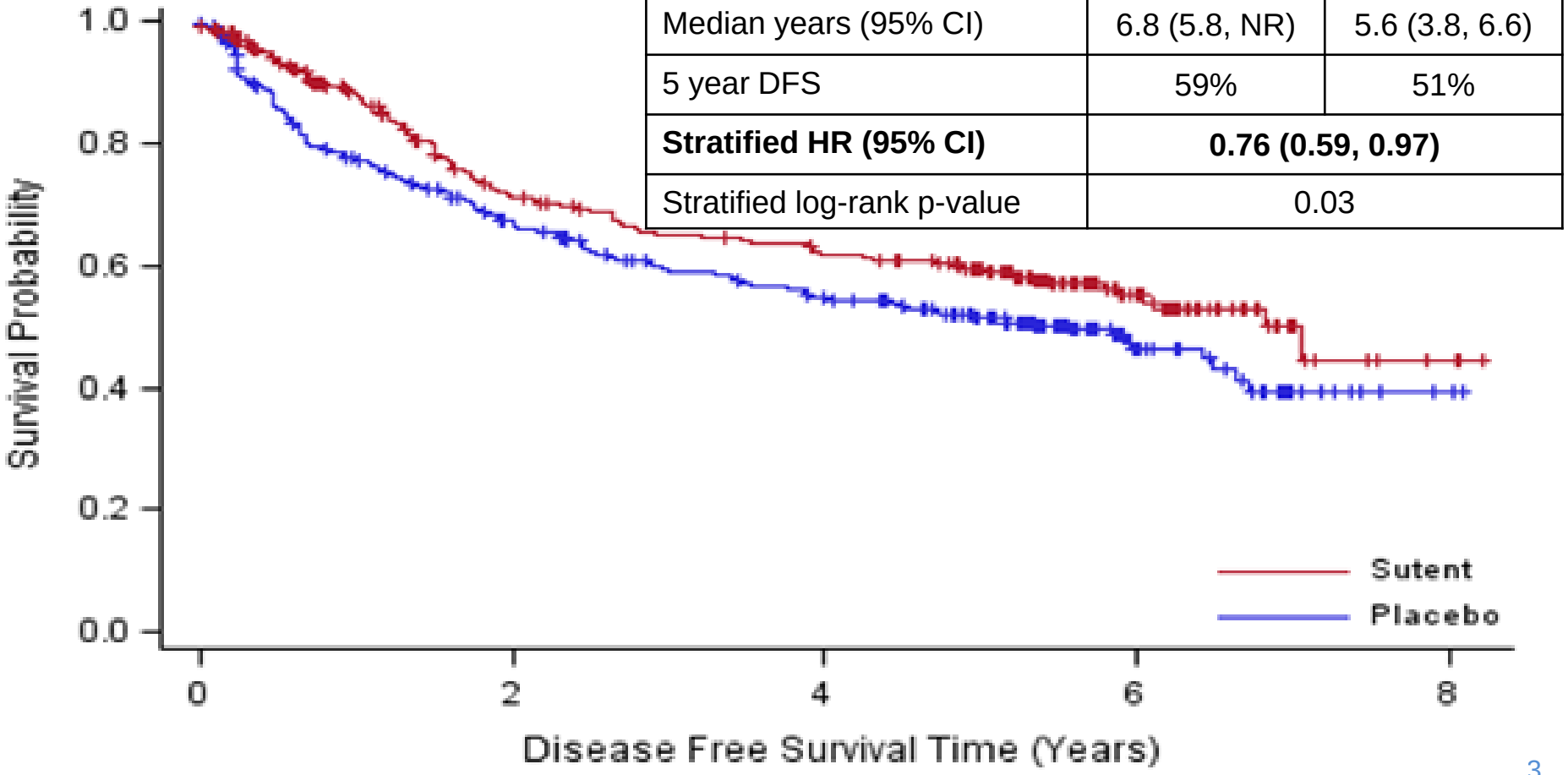
for adjuvant treatment of adult patients at high risk of recurrent Renal Cell Carcinoma (RCC) following nephrectomy

Adjuvant Treatment of RCC

- No approved therapies
- Standard of care is partial or radical nephrectomy followed by surveillance
- High unmet medical

S-TRAC Primary Analysis
Disease Free Survival (DFS) by IRC*

	Sutent (N=309)	Placebo (N=306)
Events	113 (37%)	144 (47%)
Median years (95% CI)	6.8 (5.8, NR)	5.6 (3.8, 6.6)
5 year DFS	59%	51%
Stratified HR (95% CI)	**0.76 (0.59, 0.97)**	
Stratified log-rank p-value	0.03	



*IRC: independent review committee

Safety/Tolerability

- More toxicities on Sutent vs. placebo
- 1 year of treatment
- No new safety signals adjuvant vs. metastatic setting
- Most toxicities appear reversible

S-TRAC vs. ASSURE

- ASSURE
  - Sutent vs. placebo in adjuvant setting
  - No disease free or overall survival difference

- Different population and different dose

- No definitive conclusion can be drawn from exploratory analyses of the two trials

Adjuvant Approvals

- Breast Cancer
  - Disease Free Survival (DFS) considered direct measure of clinical benefit
  - Standardized DFS definitions/biopsy
- Colon Cancer, Gastrointestinal stromal tumors, Melanoma
  - DFS/Relapse Free Survival considered direct measure of clinical benefit (or surrogate for OS in colon cancer)
- Magnitude of DFS
  - DFS Hazard Ratios ranged 0.4-0.87
  - Absolute improvements in 3 to 5 year DFS ranged from 2-11%

DFS endpoint in S-TRAC

- Patients not biopsied (5% biopsied to confirm recurrence)
- Recurrence criteria on S-TRAC are reasonable
- Subsequent systemic/surgery/radiation therapy at time of recurrence
  - 80% of patients treated for recurrence;
    78% Sutent and 76% placebo
- Large magnitude of DFS improvement
  - 8% absolute difference in 5 year DFS
  - HR 0.76
  - 1 year difference in median DFS

Question for the Committee

- **VOTE:** Is the benefit-risk profile of Sutent acceptable for the adjuvant treatment of patients at high risk of recurrent renal cell carcinoma following nephrectomy?

U.S. FOOD & DRUG ADMINISTRATION

Sutent

Adjuvant Treatment of Renal Cell Carcinoma

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Outline

- Background
- Improvement in DFS on S-TRAC
- Differences between S-TRAC and ASSURE
- Adverse event profile of Sutent
- DFS as an endpoint in the adjuvant setting
- Summary

Proposed Indication

SUTENT is a kinase inhibitor indicated for adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy

Sutent Background

- Approved January 2006 for treatment of advanced renal cell carcinoma
- Acts primarily through vascular endothelial growth factor receptor (VEGFR)
- Acts through other tyrosine kinase receptors
- Dose-response in trials of metastatic disease

Prognosis Post-Nephrectomy

- UISS* risk stratification post-nephrectomy
  - T stage
  - Grade
  - Performance status

- 5 year freedom from failure
  - UISS Intermediate Risk: 64%
  - UISS High Risk: 37%

- 5 year disease-specific survival
  - UISS Intermediate Risk: 80%
  - UISS High Risk: 55%
  - Node positive: 0-32%

*UCLA Integrated Staging System

JCO 2002 20:2559

Adjuvant Trials of VEGFR Inhibitors in Renal Cell Cancer

- Did not demonstrate benefit in RCC
  - ASSURE:
    - Sutent vs. Placebo, DFS: HR 1.02, p = 0.80
    - Sorafenib vs. Placebo, DFS: HR 0.97, p = 0.72
  - PROTECT:
    - Pazopanib 600 mg vs. Placebo, DFS: HR 0.86, p = 0.165
- Ongoing trials in renal cancer
  - Axitinib, everolimus, sorafenib

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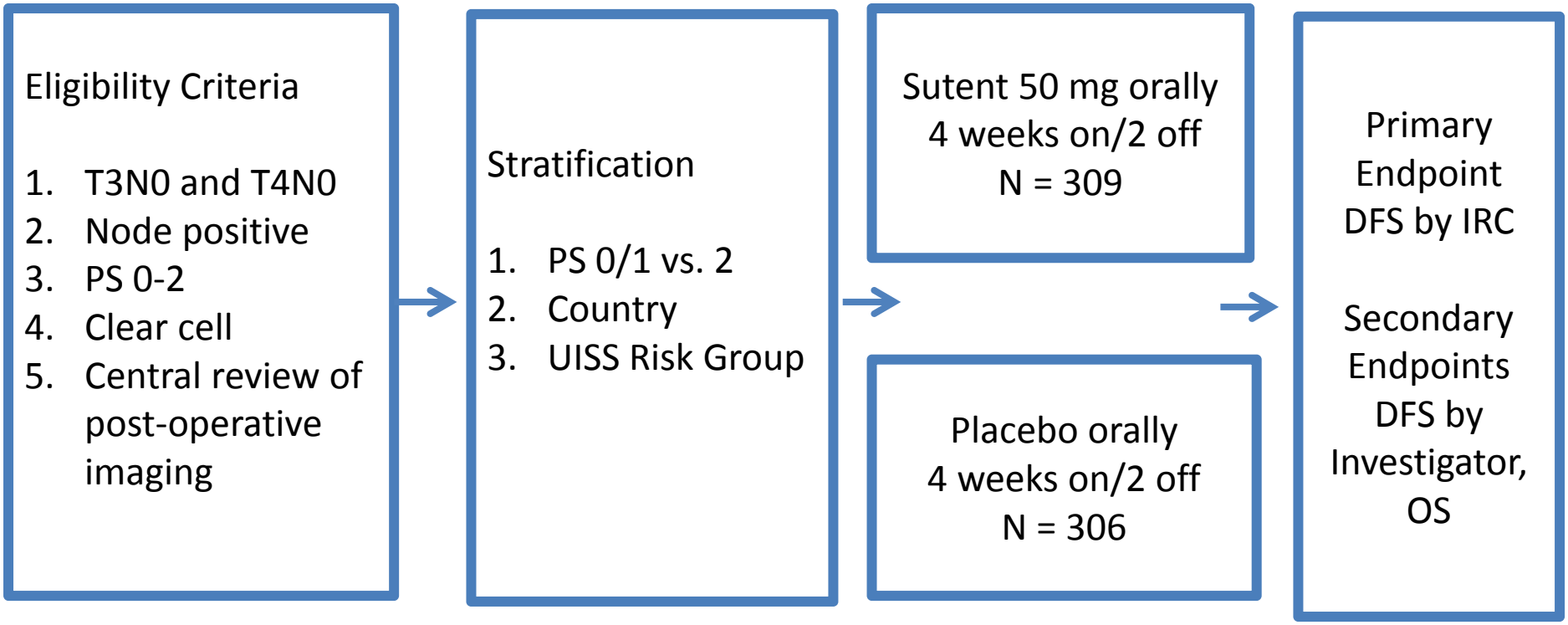
S-TRAC Trial Design



Scans every 3 months for 3 years then every 6 months

Baseline Disease Characteristics

	Sutent N = 309	Placebo N = 306
UISS Risk Strata		
Intermediate Risk	37%	37%
High Risk	53%	54%
T4 and Node Positive	9%	9%
Histology		
Clear Cell	99%	100%
Other	1%	0

Disease Recurrence by IRC

- Similar definitions: Independent and Investigator
- No consensus definition of DFS in renal cell
- Investigators asked to obtain IRC review prior to treatment decisions
- Detailed, reasonable IRC definition
- IRC could override the criteria in the definition
- Many of the lesions were small

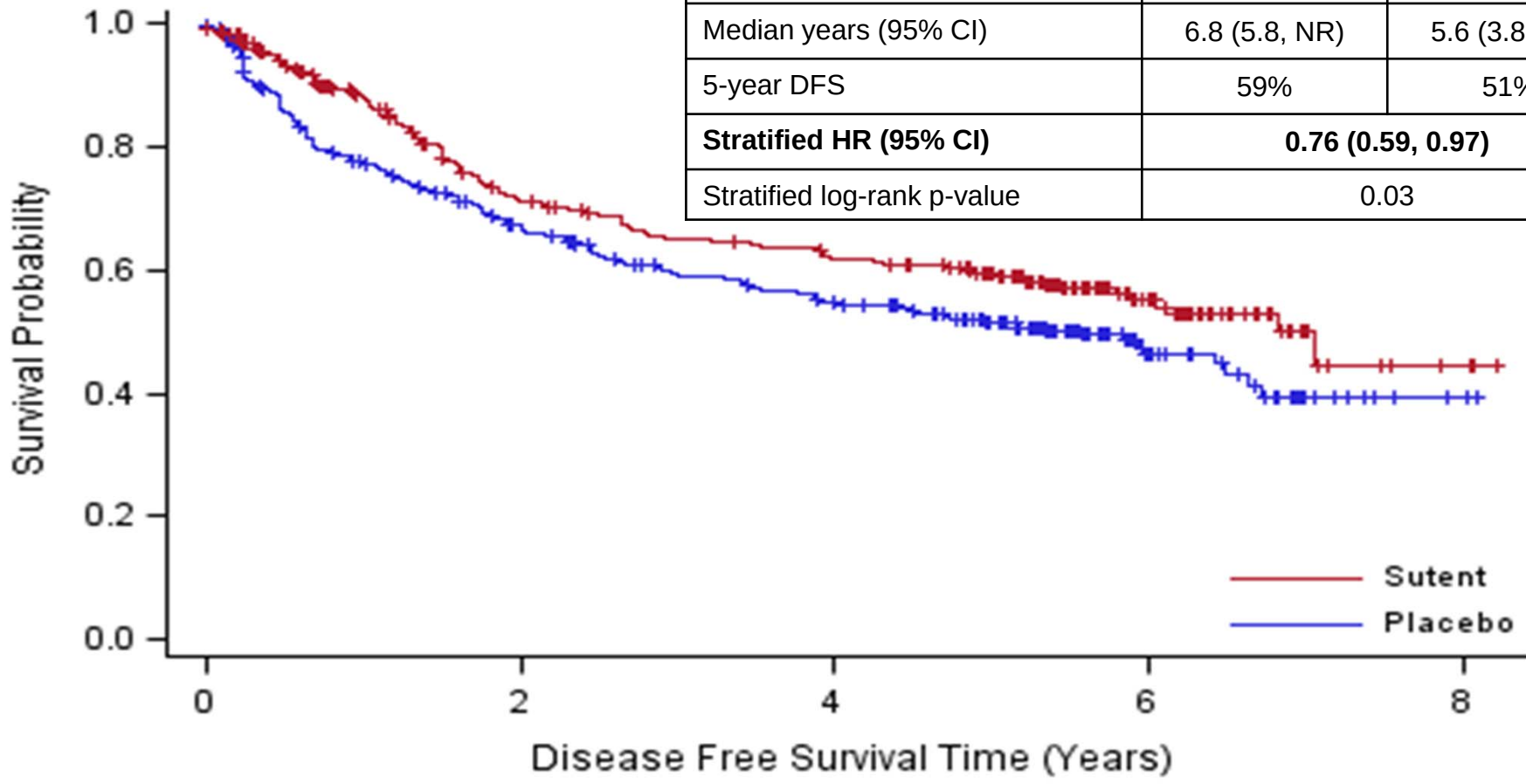
S-TRAC Statistical Analysis Plan

Primary endpoint	DFS by IRC
Secondary endpoint	OS
Supportive endpoints	• DFS per INV • EORTC* QLQ-C30 • EuroQol EQ-5D
Interim Analyses	• Initial sample size: N=228 with 127 DFS events • Final sample size: N=615 with 258 DFS events to provide 84% power to detect a HR of 0.69 • Primary DFS analysis changed from event-driven to 5 years after last subject first visit or when approx. 258 DFS events were observed • Neither of the two interim analyses resulted in early stopping
Alpha allocated for final DFS analysis	0.0476

*European Organization for Research and Treatment of Cancer

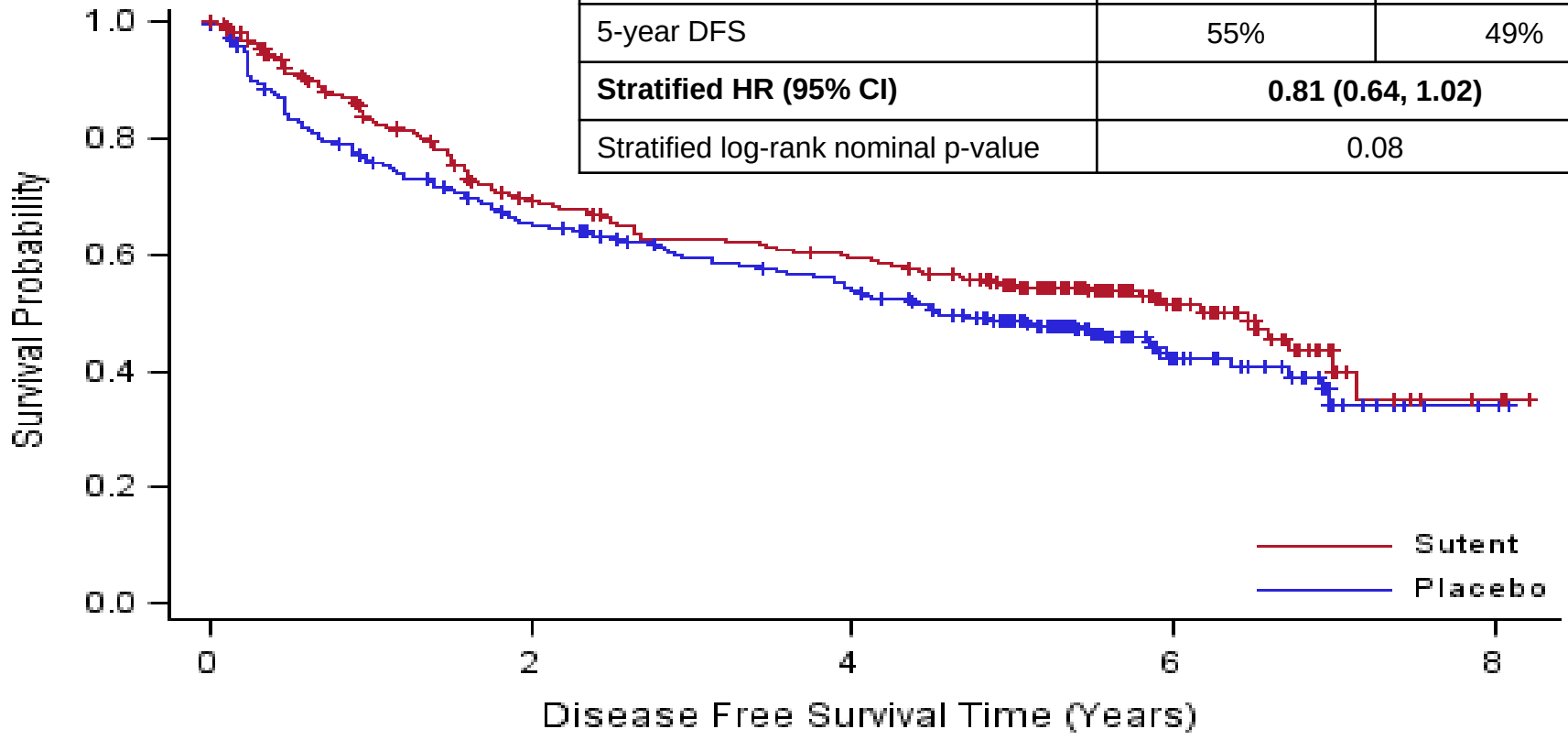
Primary Analysis-DFS by IRC

	Sutent (N=309)	Placebo (N=306)
IRC Events	113 (37%)	144 (47%)
Median years (95% CI)	6.8 (5.8, NR)	5.6 (3.8, 6.6)
5-year DFS	59%	51%
Stratified HR (95% CI)	**0.76 (0.59, 0.97)**	
Stratified log-rank p-value	0.03	



Supportive Analysis-DFS by Investigator

	Sutent (N=309)	Placebo (N=306)
Investigator Events	132 (43%)	158 (52%)
Median years (95% CI)	6.5 (4.7, 7.0)	4.5 (3.8, 5.9)
5-year DFS	55%	49%
Stratified HR (95% CI)	**0.81 (0.64, 1.02)**	
Stratified log-rank nominal p-value	0.08	



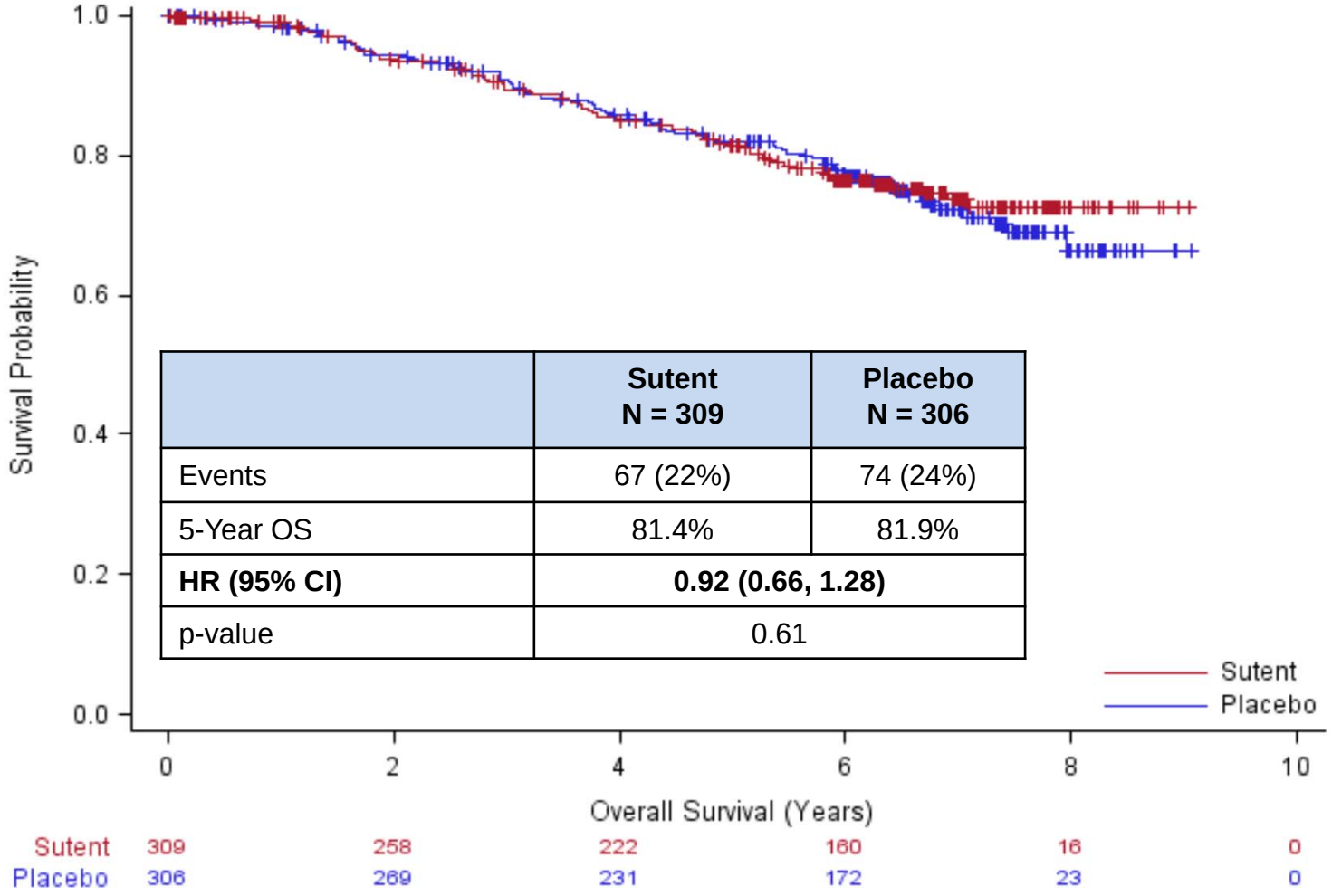
Sensitivity Analyses of DFS

Applicant Analyses	Hazard Ratio (95% CI)
DFS analysis, including events: • confirmed by IRC • occurring after anti-cancer therapy • occurring after ≥2 missed visits	0.81 (0.64,1.02)
Time to recurrence: • Censors deaths and second primary malignancies unrelated to RCC	0.78 (0.60, 1.01)
FDA Analysis	
• First scan date, if equivocal • Biopsy date, if available • Additional 2nd primaries	0.76 (0.59, 0.97)

- These and other sensitivity analyses support the primary analysis.

Overall Survival

(As of January 2017)



	Sutent N = 309	Placebo N = 306
Events	67 (22%)	74 (24%)
5-Year OS	81.4%	81.9%
HR (95% CI)	**0.92 (0.66, 1.28)**	
p-value	0.61	

- Estimated median follow-up time was 6.6 and 6.7 years for Sutent and placebo, resp.
- Final OS analysis planned to occur in 2019

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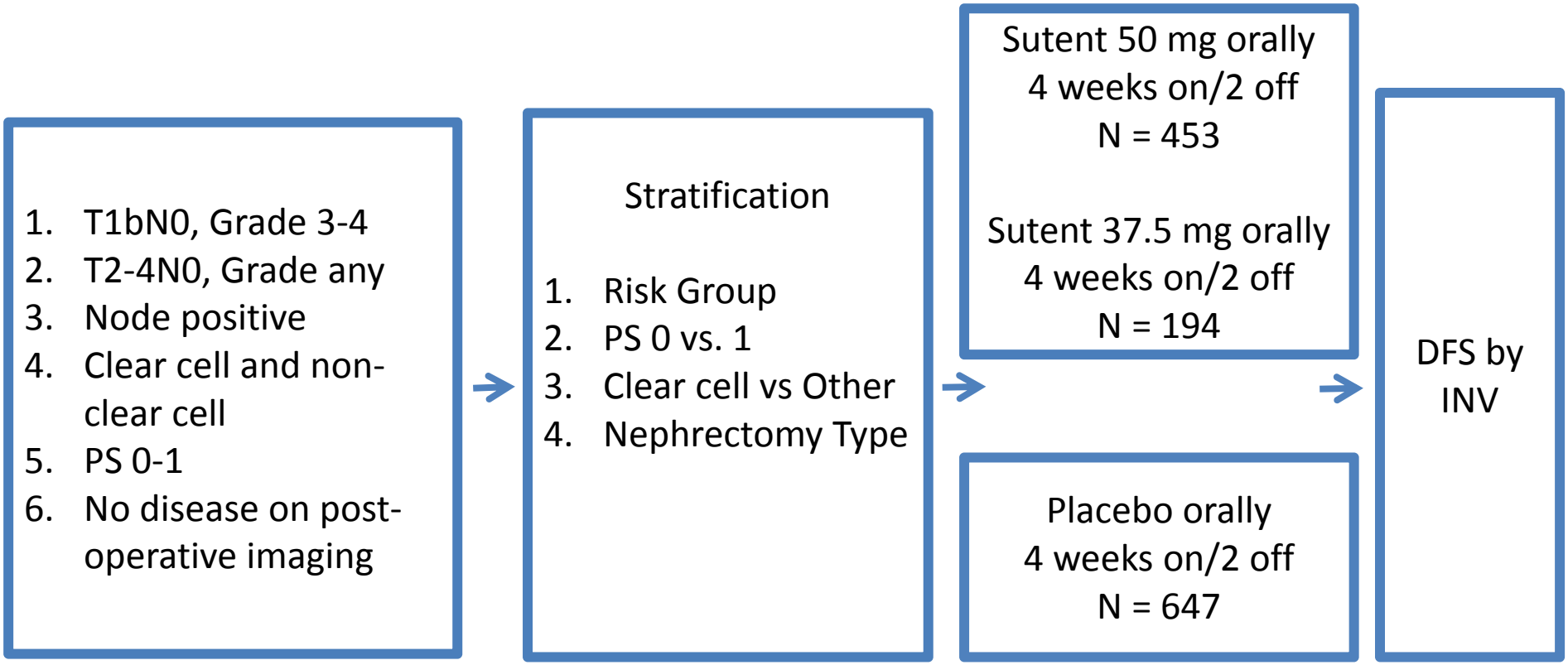
ASSURE Trial Design



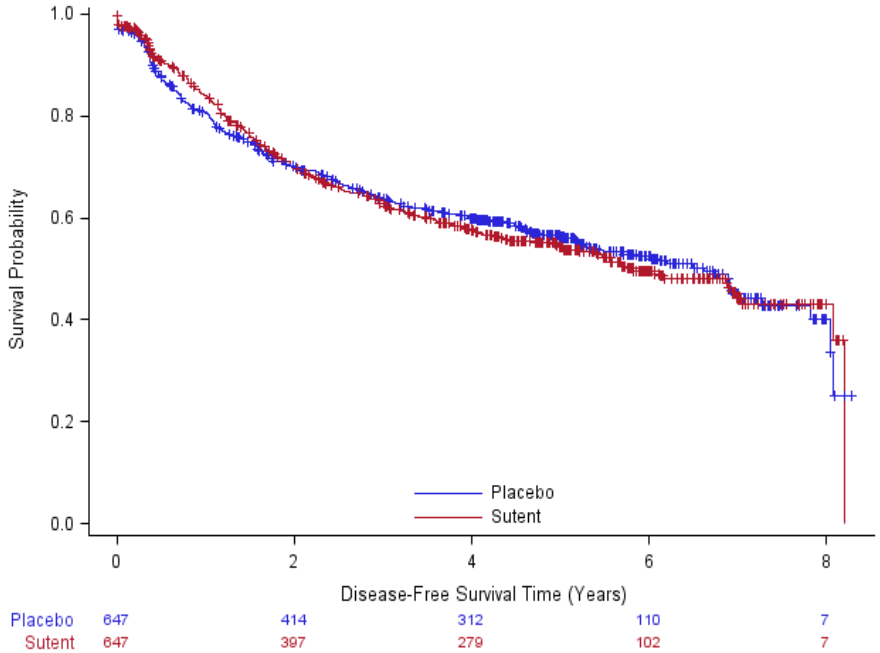
- Scans every 3 months during dosing, 6 weeks after last dose, every 6 months for 2 years, then yearly to year 8
- ASSURE also contained a sorafenib arm, N = 649

ASSURE Trial Results

DFS per Investigator

- HR=1.02 (95% CI: 0.87, 1.20)
- Median DFS (95% CI):

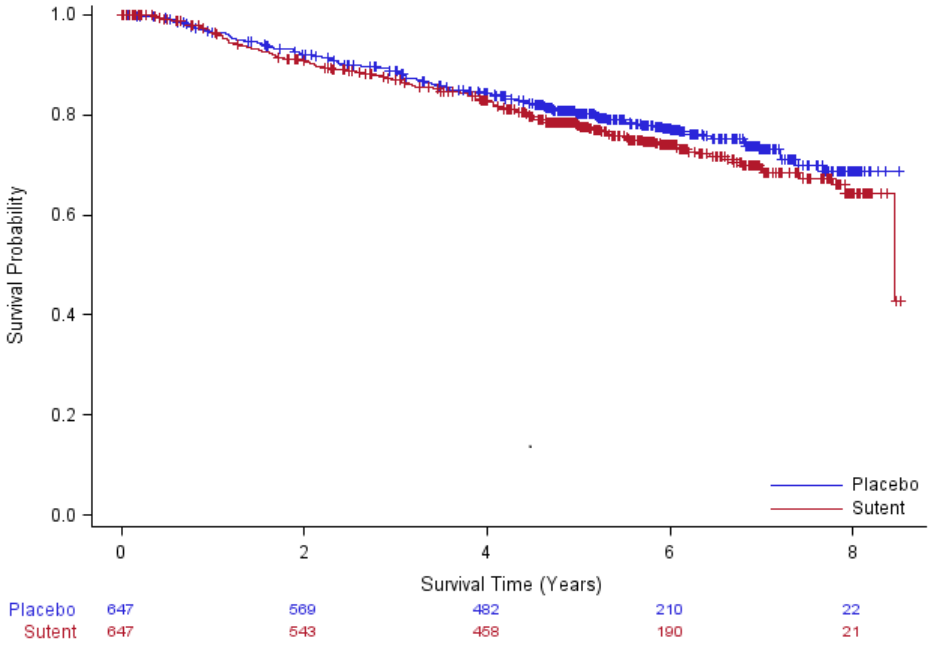
  Sutent: 5.8 yrs (5.0, 7.0)
  Placebo: 6.6 yrs (5.3, 7.0)



Overall Survival

- HR=1.17 (95% CI: 0.93, 1.47)
- 5 year survival probability:

  78% Sutent vs 80% Placebo



S-TRAC vs ASSURE: Key Differences

	S-TRAC N=615	ASSURE N =1294
Countries	20 countries ex-US US (8%)	Canada US (92%)
Accrual Period	September 2007 – April 2011	April 2006 – September 2010
Tumor Staging	T3-T4	T1b-T4
Histology	Clear cell RCC	Clear/Non-clear cell RCC
Sutent Starting Dosage	50 mg	50 mg 37.5 mg
Primary Endpoint	DFS per IRC	DFS per Investigator
Discontinuation	50 mg – 36%	50 mg – 44% 37.5 mg – 34%
UISS Risk Category	Intermediate – 37% High – 63%	Low-Intermediate – 33% Intermediate – 47% High – 20%

Exploratory Comparison S-TRAC vs ASSURE Subgroup

- Selected ASSURE subgroup that met S-TRAC entry criteria:
  - T3N0, T4N0, TanyN1-2
  - Clear cell pathology
  - Without metastatic disease at baseline
  - Starting dose 50mg Sutent

- 460 out of 1294 patients in ASSURE met these criteria

Does this subgroup help to explain the difference in results?

S-TRAC and ASSURE Subgroup Risk Categories

	S-TRAC N=615		ASSURE Subgroup N=460	
	Sutent N = 309	**Placebo N = 306**	**Sutent N = 229**	**Placebo N = 231**
Intermediate Risk	37%	37%	76%	75%
High Risk (including node positive)	63%	63%	24%	25%

S-TRAC vs ASSURE Subgroup Exploratory Results

	S-TRAC N=615		ASSURE Subgroup N=460	
	Sutent N = 309	**Placebo N = 306**	**Sutent N = 229**	**Placebo N = 231**
Disease Free Survival				
Events, n (%)	113 (37)	144 (47)	110 (48)	119 (52)
Hazard Ratio[1] (95% CI)	0.76 (0.59, 0.98)		0.98 (0.75, 1.28)	

[1] Stratified by UISS risk strata

Note: S-TRAC investigator DFS - HR=0.81 (95% CI: 0.64, 1.02)

Efficacy Summary

- Statistically significant improvement in DFS in S-TRAC
  - HR = 0.76 (95% CI: 0.59, 0.97)
  - Median DFS of 6.8 with Sutent vs 5.6 years with placebo
  - Sensitivity analyses of DFS showed consistent benefit

- ASSURE did not demonstrate improvement in DFS
  - HR = 1.02 (95% CI: 0.87, 1.20)

- No difference in OS has been observed in S-TRAC or ASSURE

- The difference in the two trial results could not be explained by the exploratory subgroup of patients in ASSURE meeting the S-TRAC entry criteria; however there are limitations to this exploratory subgroup analysis

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Safety Overview of S-TRAC

	Sutent N = 306 (%)	Placebo N = 304 (%)
Deaths*	3 (1%)	0
Permanent Discontinuation	85 (28%)	15 (5%)
Dose Reduction	106 (35%)	6 (2%)
Dose Interruption	142 (46%)	40 (13%)
Grade 3-4 Adverse Events	183 (60%)	46 (15%)

*Deaths due to an adverse event and within 28 days of last dose

Patient Reported Outcomes

- Instruments used: EORTC QLQ-C30 and EQ-5D
  - Over 89% on-treatment completion rate
- Domain-level analyses:
  - Patients receiving Sutent reported a decrement in health related quality of life and several domains including the physical function domain, compared to placebo
- Item-level analyses from QLQ-C30:
  - FDA selected additional PRO items for further analysis based on adverse event profile including nausea, weakness, work or daily activities, appetite loss, and diarrhea
  - These were consistently worse on the Sutent arm through the treatment cycles

Safety Summary

- Adverse events less frequent in the adjuvant setting vs. metastatic setting
  - Exception: palmar-plantar erythrodysesthesia (PPE)

- No new safety signals in S-TRAC
  - Sutent administered for 1 year
  - Cardiotoxicity same in each arm

- Data limited on long-term toxicities

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DFS as an Endpoint in the Adjuvant Setting

- No adjuvant approvals in RCC

- Breast Cancer, Colon Cancer, Gastrointestinal Stromal Tumors, Melanoma
  - DFS/Recurrence-free survival used as primary endpoint for regular approval
  - Many approvals based on DFS without OS detriment

Treatment after Recurrence

- IRC-determined recurrence

- Subsequent treatment
  - 78% of patients in Sutent and 76% in the placebo arm
    - Systemic: 44% Sutent and 43% placebo
    - Surgery: 28% in both arms
    - Radiation: 6% Sutent and 5% placebo

Overall Conclusions

- S-TRAC demonstrated a statistically significant and substantial difference in DFS
- Differences in patient population and Sutent dose prevent a conclusion regarding differences in results of S-TRAC and ASSURE
- The adverse events associated with the use of Sutent are substantial, but may be acceptable in a high-risk population
- Magnitude of benefit seen in DFS similar to other adjuvant approvals

Question for the Committee

- **VOTE:** Is the benefit-risk profile of Sutent acceptable for the adjuvant treatment of patients at high risk of recurrent renal cell carcinoma following nephrectomy?

Back up Slides Shown

Exploratory Subgroup Analysis Difference in Dose

- S-TRAC: DFS by Dose Intensity
  - HR: 0.84 (95% CI: 0.64, 1.09)-dose intensity > 75% (N = 232 pts on Sutent)
  - HR: 0.55 (95% CI: 0.34, 0.88)-dose intensity < 75% (N = 74 pts on Sutent)
- S-TRAC: DFS by Occurrence of Hypertension
  - HR: 0.73 (95% CI: 0.55, 0.96)-with hypertension (N = 207 on Sutent)
  - HR: 0.87 (95% CI: 0.60, 1.26)-without hypertension (N = 99 on Sutent)

Time to First Intervention Post Adjuvant Therapy

	Sutent (N=309)	Placebo (N=306)
Interventions	125 (41%)	138 (45%)
Median (years)	7.42 (6.49,NR)	7.23 (5.80, NR)
HR (95% CI)	0.88 (0.69, 1.13)