# Sunitinib Malate (SUTENT®)

***Sriram Krishnaswami, Ph.D.***
*Asset Team Leader Oncology*
*Pfizer Inc*

*Oncologic Drugs Advisory Committee Meeting*
*September 19, 2017*
*FDA White Oak Campus*
*Silver Spring, MD*

# Proposed Indication and Dosing Regimen

- Indication
  - SUTENT is indicated for the adjuvant treatment of adult patients at high risk of recurrent renal cell carcinoma (RCC) following nephrectomy
- Dosing Regimen
  - 50 mg taken orally once daily, on Schedule 4/2 (4 weeks on treatment, 2 weeks off)

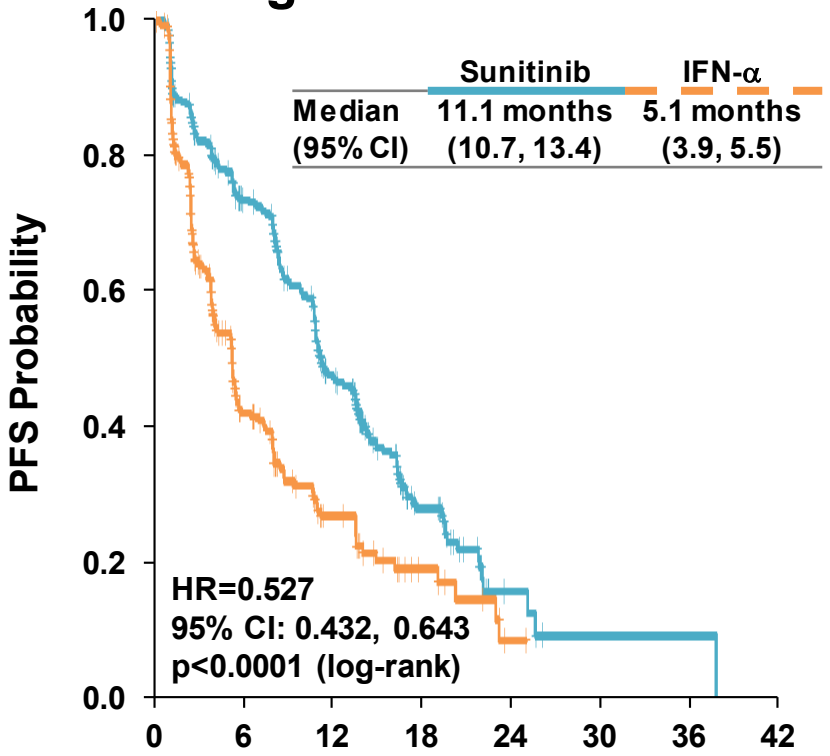
mg=milligrams

# SUTENT (sunitinib malate) Background

- Small molecule, anti-angiogenic multi-targeted tyrosine kinase inhibitor
- Approved in the United States in 2006
- Studied in >7000 patients in clinical trials
- >350,000 patients treated globally
- Approved indications
  - Gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate
  - Advanced renal cell carcinoma (RCC)
  - Progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease
- Dosing
  - RCC and GIST: 50 mg daily on Schedule 4/2
  - pNET: 37.5 mg continuous daily dosing

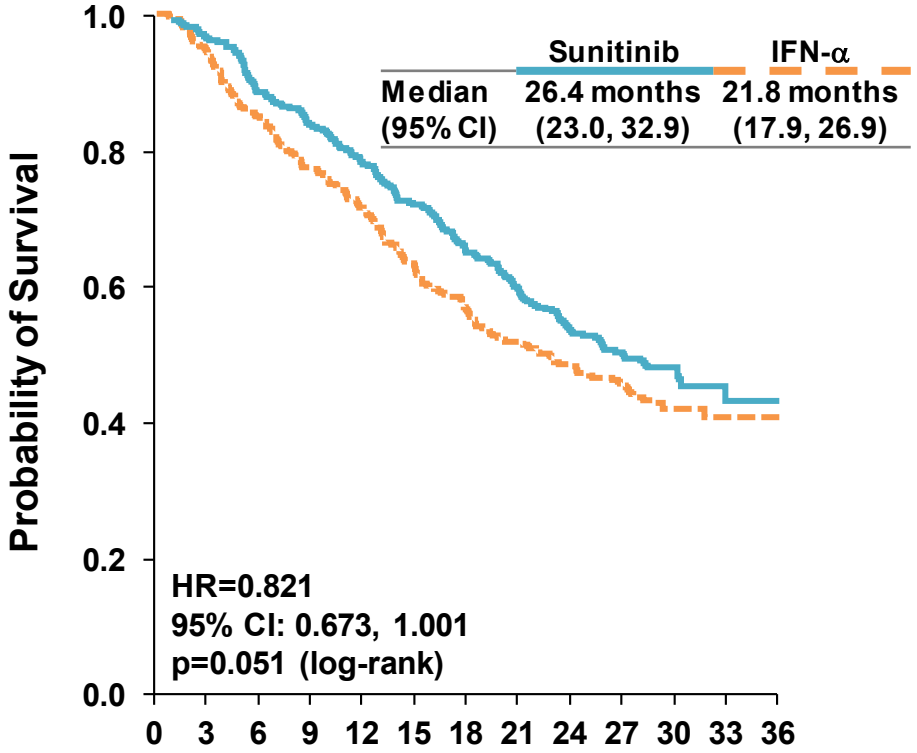
# Proven Efficacy in Metastatic RCC
# Study 1034: Sunitinib vs. IFN-α

## Progression-Free Survival




| No. at Risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Sunitinib | 375 | 224 | 119 | 34 | 5 | 1 | 1 | 0 |
| IFN-α | 375 | 80 | 32 | 10 | 1 | 0 | 0 | 0 |

## Overall Survival




| No. at Risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Sunitinib | 375 | 326 | 283 | 229 | 180 | 61 | 2 | |
| IFN-α | 375 | 295 | 242 | 187 | 149 | 53 | 1 | |

a. Independent central review for PFS

Motzer RJ, et al. *ASCO* 2007 Abstract 5024; Motzer RJ, et al. *J Clin Oncol* 2009;27:3584-90.

ASCO=American Society of Clinical Oncology; CI=Confidence Interval; HR=Hazard Ratio; IFN-α=Interferon alpha; No.=Number; PFS=Progression-Free Survival

# Why Sunitinib as an Adjuvant Treatment?

**Unmet Need**

- High-risk patients have a 60% risk of recurrence following nephrectomy and no available treatment options

**Efficacy**

- 24% relative DFS event risk reduction overall and 8% absolute DFS improvement at 5 years

**Safety**

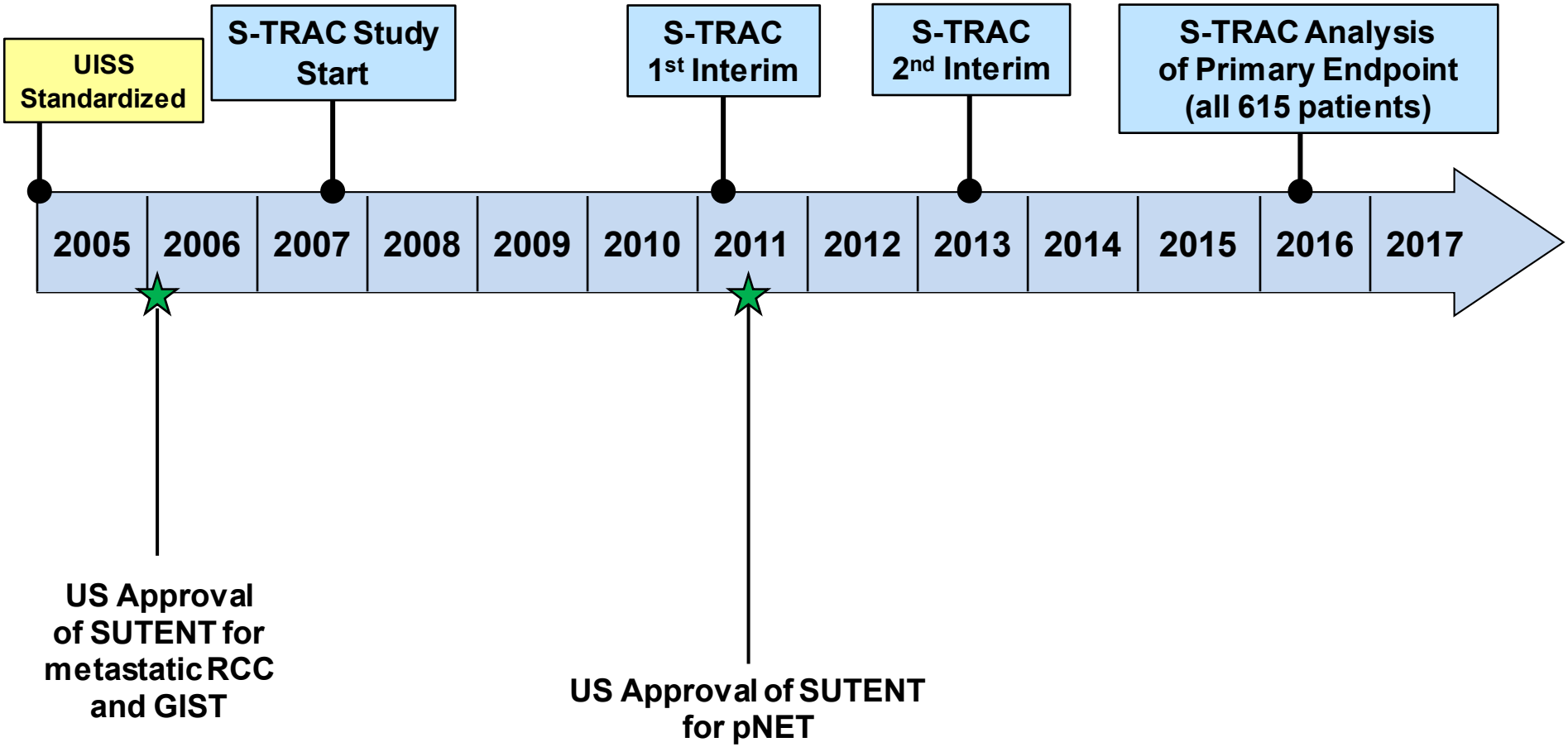
- Adverse events are predictable, manageable and reversible

**Benefit/Risk**

- Favorable for patients at high risk of recurrence

DFS=Disease-Free Survival

# Key Milestones in Adjuvant Renal Cell Carcinoma Therapeutics Development




ASSURE=Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma; ATLAS=Adjuvant Axitinib Therapy of Renal Cell Cancer in High Risk Patients; EVEREST=Everolimus in Treating Patients With Kidney Cancer Who Have Undergone Surgery; PROTECT=Pazopanib as Adjuvant Therapy for Subjects with Localized or Locally Advanced RCC Following Nephrectomy; SORCE=Sorafenib in Treating Patients at Risk of Relapse After Undergoing Surgery to Remove Kidney Cancer; S-TRAC=Sunitinib Treatment of Renal Adjuvant Cancer; UISS=UCLA Integrated Staging System for Renal Cell Carcinoma

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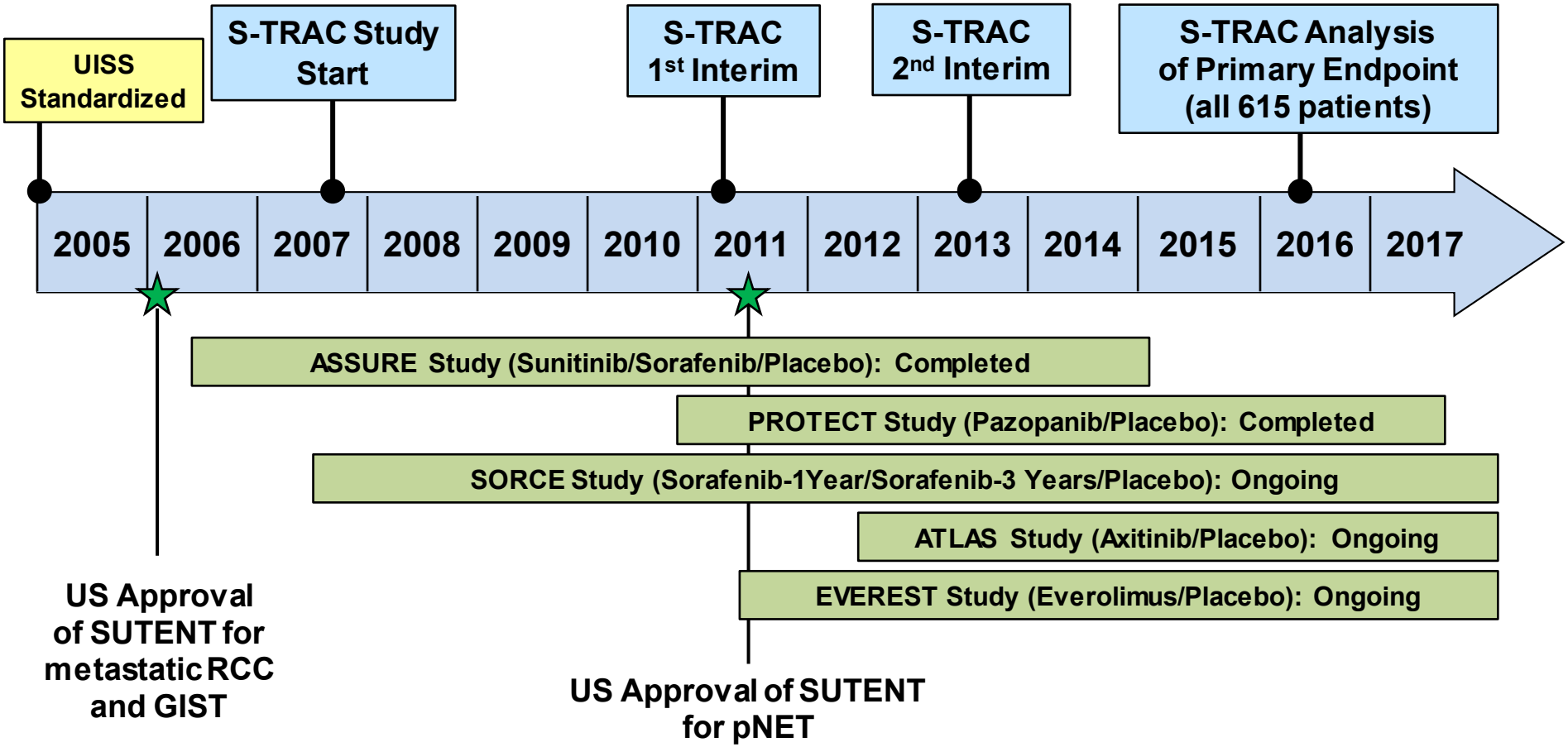


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# Presentation Overview

| Topic | Presenter |
|---|---|
| **Non-Metastatic RCC: Unmet Medical Need** | **Allan Pantuck, M.D.**<br>Professor of Urology<br>UCLA Medical Center, Los Angeles, CA |
| **Rationale for Adjuvant Treatment and Efficacy** | **Daniel George, M.D.**<br>Professor of Medicine and Surgery<br>Duke University Medical Center, Durham, NC |
| **Safety and Quality of Life** | **Liza DeAnnuntis, M.D.**<br>Safety Risk Lead/Pharmacovigilance, Pfizer Inc |
| **Benefit/Risk: Clinical Perspective** | **Robert A. Figlin, M.D., FACP**<br>Steven Spielberg Family Chair in Hematology Oncology<br>Professor of Medicine and Biomedical Sciences<br>Cedar-Sinai Medical Center, Los Angeles, CA |

# Additional Experts in Sponsor Section

| Expert | Area of Expertise |
|---|---|
| **Gary Koch, Ph.D.**<br>Professor of Biostatistics<br>University of North Carolina at Chapel Hill | **Statistical Consultant** |
| **Jean Paty, Ph.D.**<br>Practice Lead for Endpoint Strategy<br>Quintiles IMS | **Patient-Reported Outcomes Consultant** |

# Non-Metastatic RCC: Unmet Medical Need

***Allan Pantuck, M.D.***

*Professor of Urology*

*UCLA Medical Center, Los Angeles, CA*

# Why Sunitinib as an Adjuvant Treatment?

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**Efficacy**

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**Safety**

- Adverse events are predictable, manageable and reversible

**Benefit/Risk**

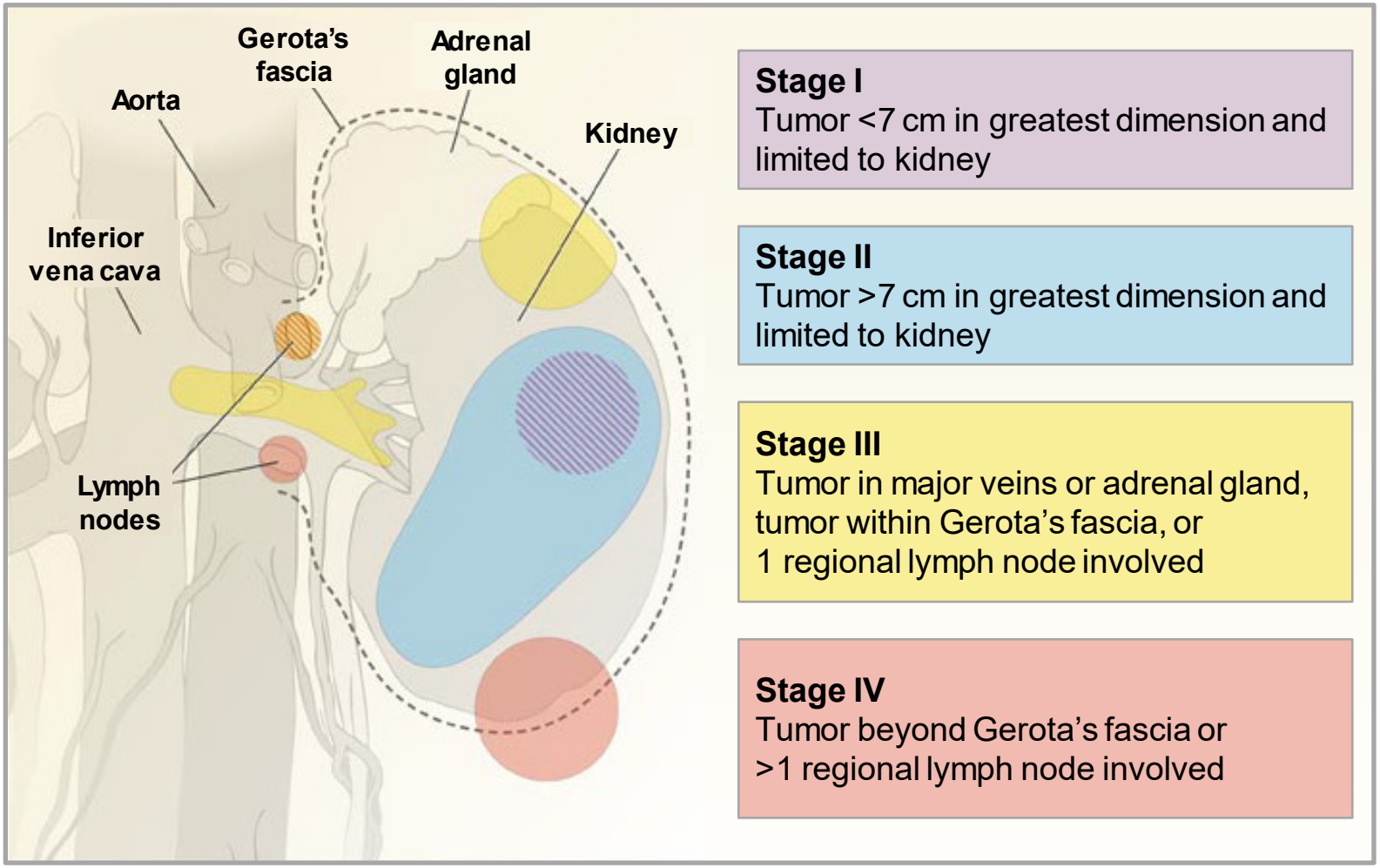
- Favorable for patients at high risk of recurrence

# Epidemiology

- US RCC incidence and death
  - 64,000 newly diagnosed and 14,000 deaths annually
- Surgical resection followed by observation is the standard of care
- Relapse rate after surgery remains high for sizable subset of patients
- Metastatic RCC (mRCC) remains a largely incurable disease with a 5-year survival rate as low as 12%

SEER Cancer Statistics Factsheets: Kidney and Renal Pelvis Cancer. 2016.

# Renal Cell Carcinoma Staging




**Stage I**
Tumor <7 cm in greatest dimension and limited to kidney

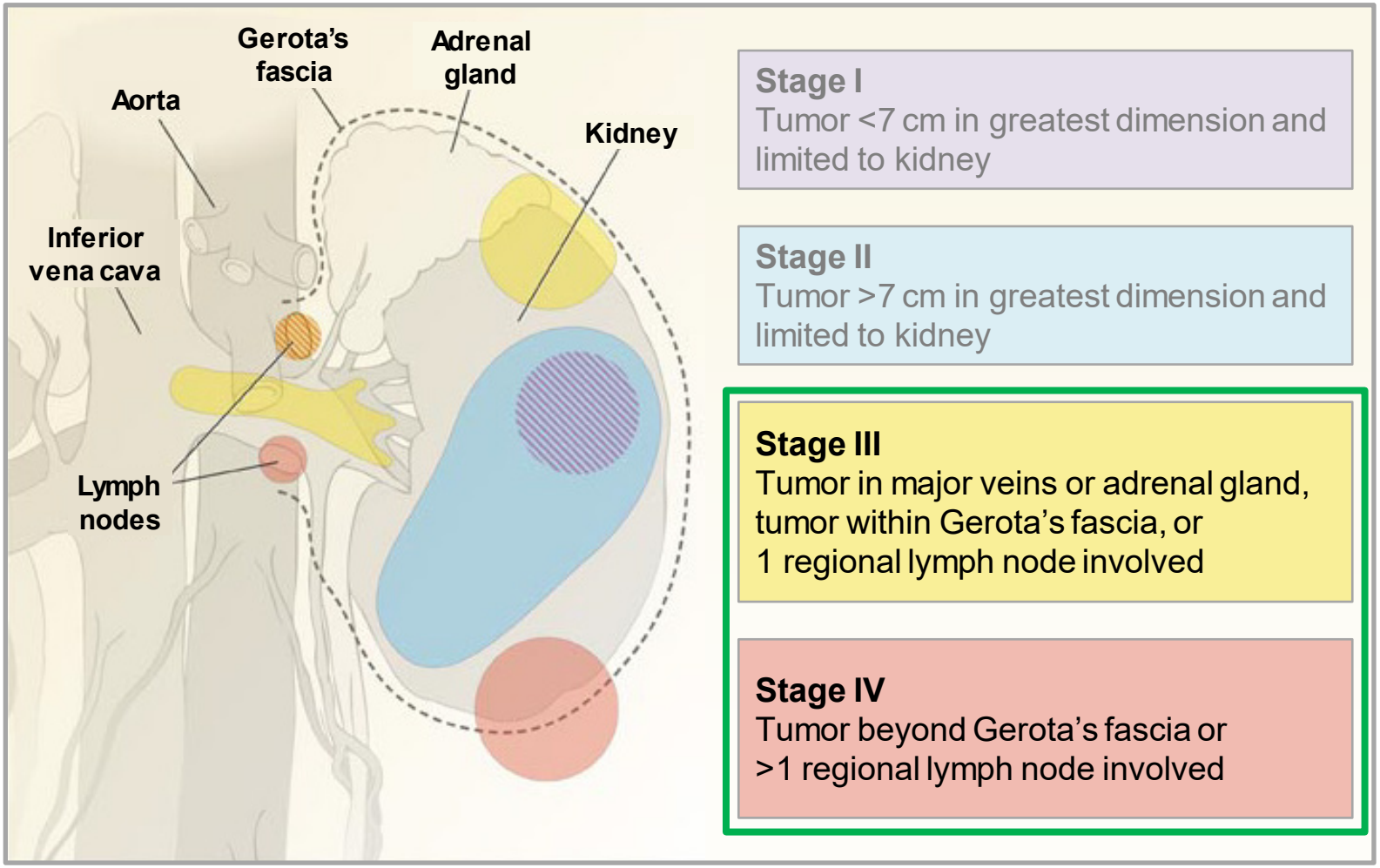
**Stage II**
Tumor >7 cm in greatest dimension and limited to kidney

**Stage III**
Tumor in major veins or adrenal gland, tumor within Gerota's fascia, or 1 regional lymph node involved

**Stage IV**
Tumor beyond Gerota's fascia or >1 regional lymph node involved

Adapted from Figure 1: Cohen et al. *NEJM* 2005;353:2477-90.
cm=centimeters

# Renal Cell Carcinoma Staging

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Tumor <7 cm in greatest dimension and limited to kidney

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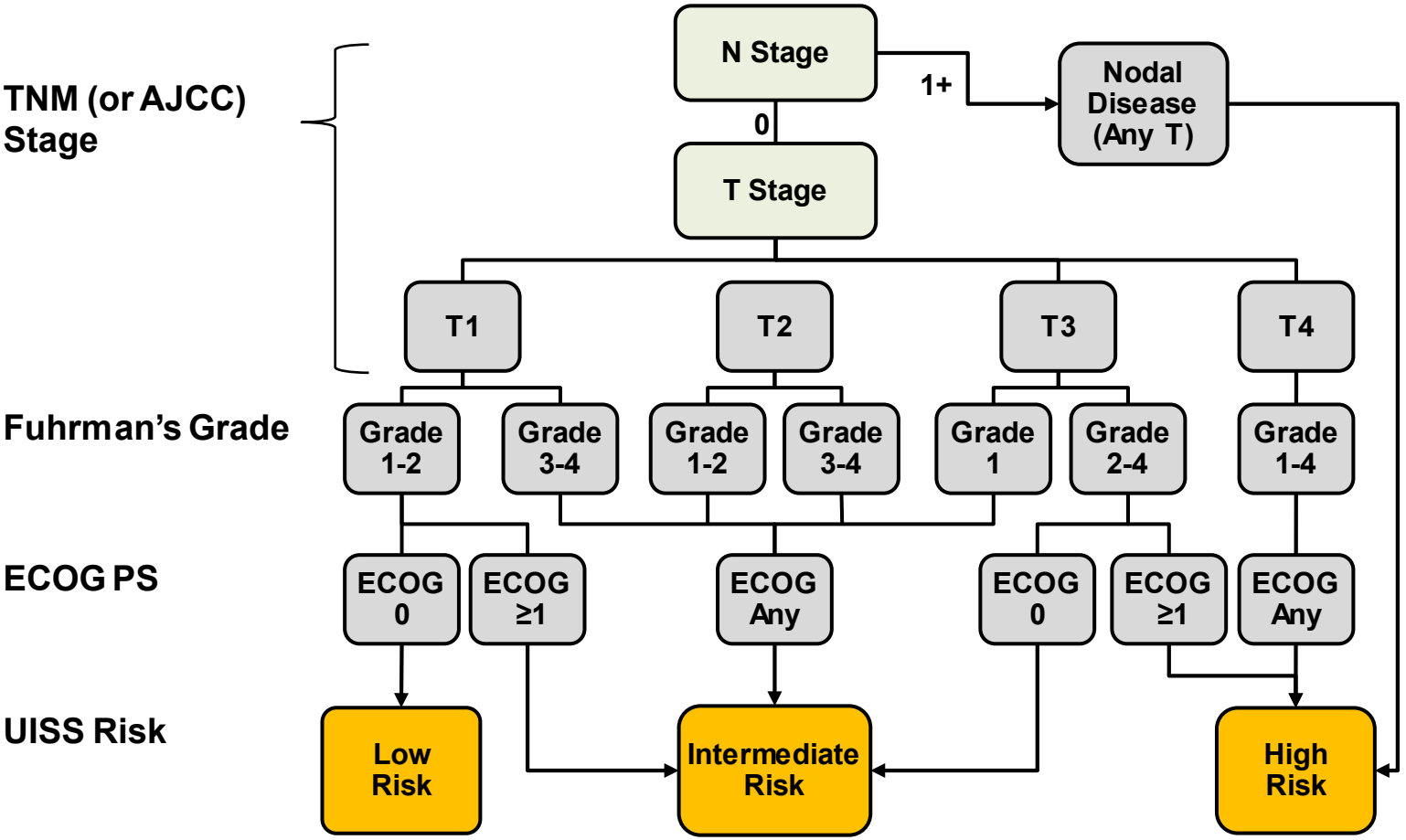
# UISS Risk Group Assignment in RCC




Adapted from: Zisman et al. *JCO* 2002;20:4561.; Lam JS, et al. *J Urol* 2005;74:466-472.
AJCC=American Joint Committee on Cancer; ECOG PS=Eastern Cooperative Oncology Group Performance Status; TNM=Tumor, Node and Metastasis

# Renal Cell Carcinoma Distribution and 5-Year Recurrence Rates by UISS Risk Group

| UISS Risk Group | Proportion of Patients % | 5-Year Recurrence Rate % |
|---|---|---|
| Low | 37.8 | 9.6 |
| Intermediate | 48.4 | 38.2 |
| High | 13.9 | 58.1 |

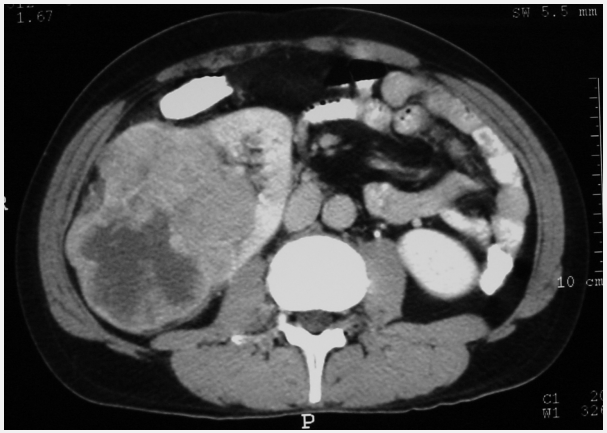
Lam et al. *J. Urol* 2005;174:466-472.

# Who Are My Patients?

## PATIENT

- 57 years old
- Male
- Active
- Busy work, family and social life

## DISEASE and TREATMENT



### Diagnosis

Presented to PCP with pain. Abdominal CT scan revealed primary tumor in his right kidney

| | |
|---|---|
| **Comorbidities** | Diabetes, controlled with antidiabetes medication<br>hypertension, controlled with antihypertensives |
| **Surgery** | Radical nephrectomy |
| **Pathology Report** | Tumor<br>• Size: 12x6x6 cm<br>• Directly invades perinephric fat but does not extend beyond Gerota fascia<br>• Type: clear cell<br>• Lymph nodes, regional<br>  • Number examined: 5<br>  • Number positive: 0 |

## RISK of RECURRENCE

**TNM Staging: T3a, N0, M0**

**Fuhrman Grade: 3**

**ECOG Performance Status: 1**

**HIGH RISK**

PCP=Primary Care Physician

# Efficacy of Sunitinib for Adjuvant Treatment of Renal Cell Carcinoma

***Daniel George, M.D.***

*Professor of Medicine and Surgery*

*Duke University Medical Center, Durham, NC*

# Why Sunitinib as an Adjuvant Treatment?

Unmet Need

**Efficacy**

Safety

Benefit/Risk

- High-risk patients have a 60% risk of recurrence following nephrectomy and no available treatment options
- 24% relative DFS event risk reduction overall and 8% absolute DFS improvement at 5 years
- Adverse events are predictable, manageable and reversible
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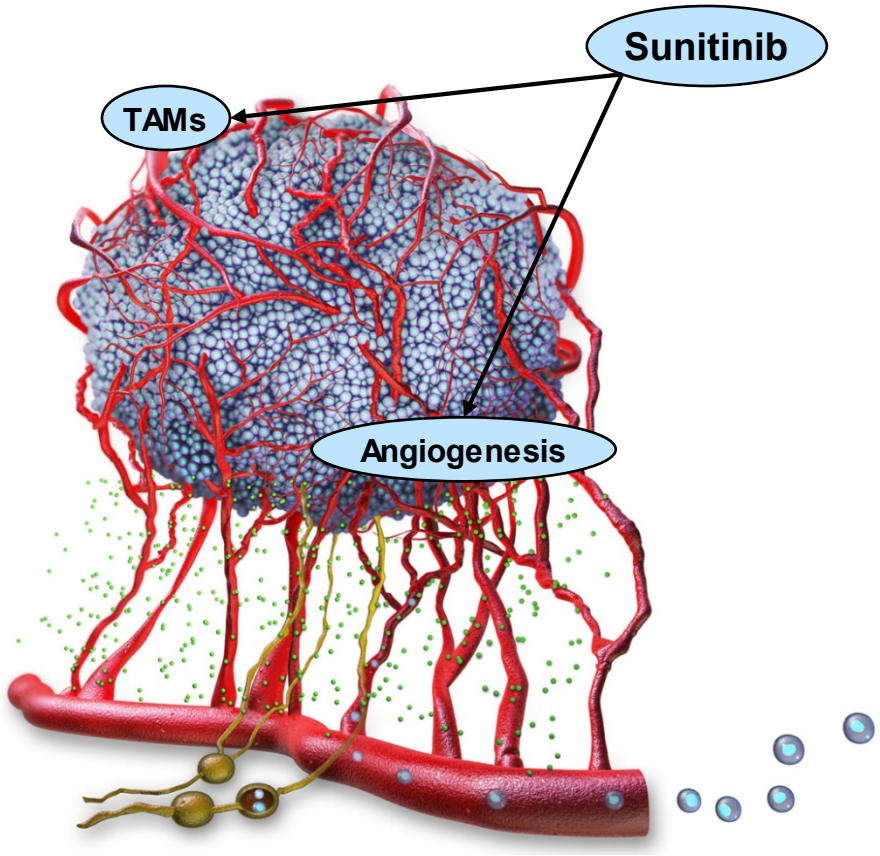
# Sunitinib Mechanism of Action

| Receptor | Biochemical $K_1$ (μM) | Cellular $IC_{50}$ (μM) | |
|---|---|---|---|
| | | Receptor Phosphorylation | Proliferation |
| VEGFR1[a] | 0.002 | – | – |
| VEGFR2[b] | 0.009 | 0.01 | 0.004 |
| VEGFR3[c] | 0.017 | – | – |
| PDGFRβ | 0.008 | 0.01 | 0.039 |
| PDGFRα | – | – | 0.069 |
| KIT | 0.004 | 0.001-0.01 | 0.002 |
| FLT3 (Wild-Type) | – | 0.25 | 0.01-0.05 |
| CSF1R | – | 0.05-0.1 | – |

Modified from: Faivre S et al. *Nat Rev Drug Disc* 2007;6:734-745.




Modified from:
Quail DF and JA Joyce *Nat Med* 2013;19(11):1423-1437.

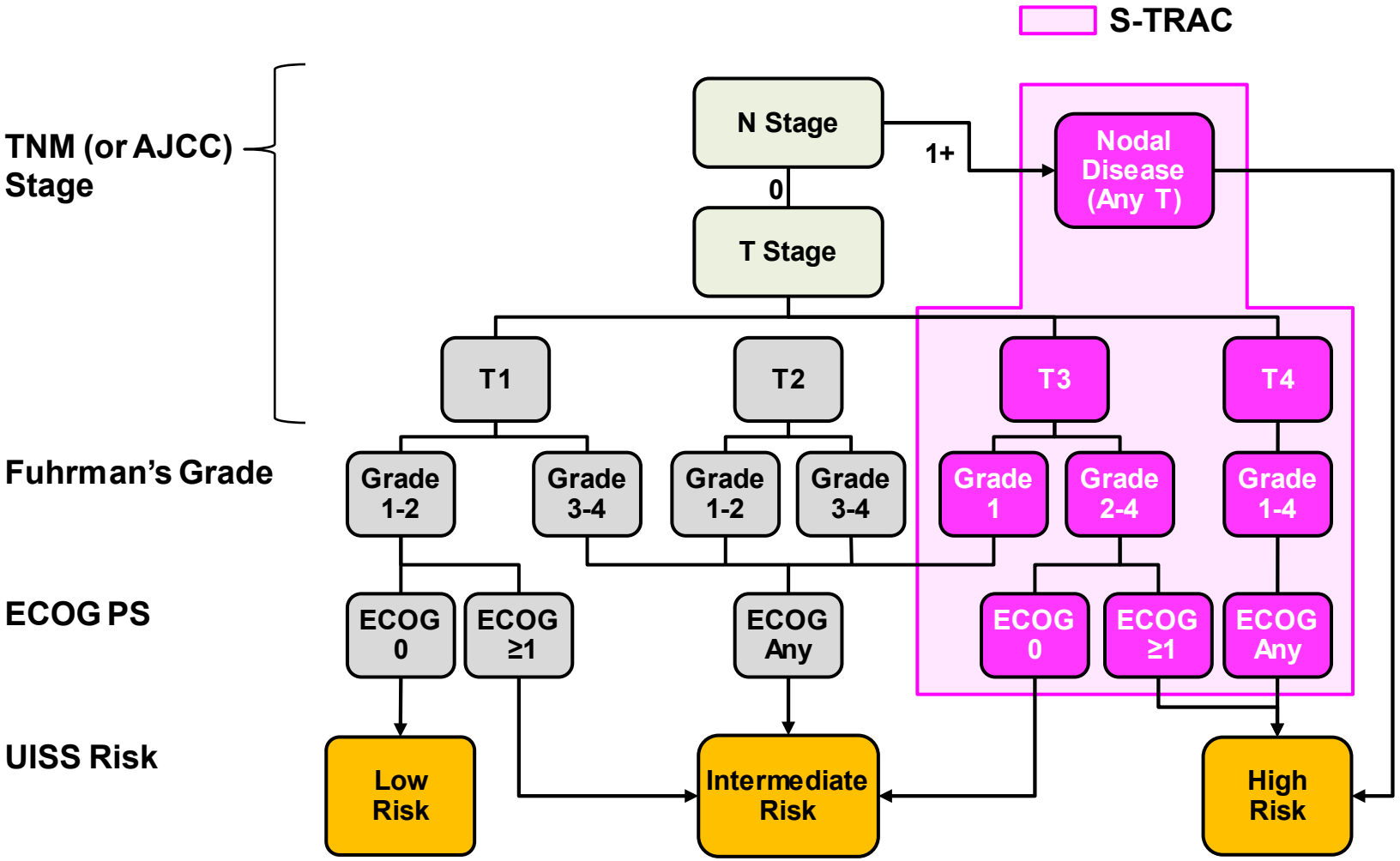
a. Also known as FLT1
b. Also known as FLK1 or KDR
c. Also known as FLT4
– indicates "Not determined"
CSF1R=Colony Stimulating Factor 1 Receptor; FLT=Fms-related Tyrosine kinase; KDR=Kinase-insert-domain-containing Receptor; KIT=stem-cell growth factor receptor; PDGFR=Platelet-Derived Growth Factor Receptor; TAM=Tumor Associated Macrophage; VEGFR=Vascular Endothelial Growth Factor Receptor

# Rationale for Disease-Free Survival (DFS) as a Primary Endpoint in Adjuvant RCC

- Patients want to remain disease-free, and DFS provides a direct real-time assessment of patient outcomes
- Long-term DFS is the primary goal for patients
- DFS is an earlier time point than OS in this patient population
- DFS is a consistent and accepted endpoint in many solid tumor adjuvant settings
  - Used for approval in various tumor types including colon cancer, breast cancer, melanoma, and GIST
  - Used in all current and planned adjuvant RCC studies

OS=Overall Survival

# Population Selected in S-TRAC
# UISS Risk Group Assignment

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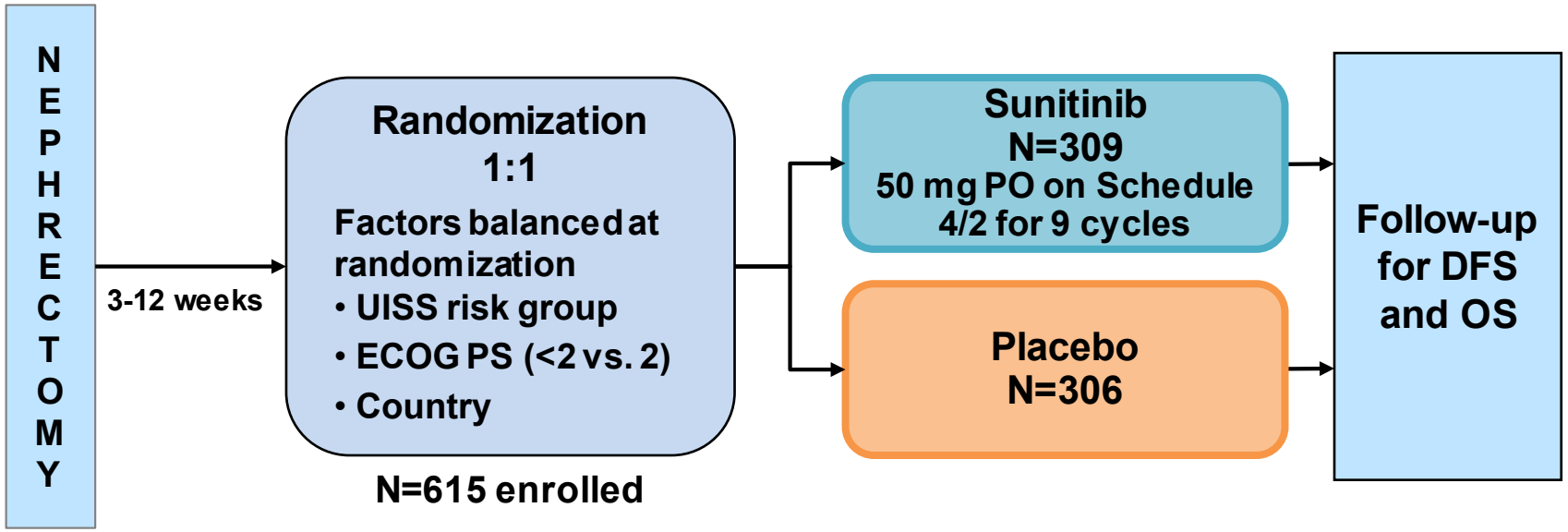
# Study 1109 (S-TRAC) Study Design




**Enrollment Criteria**
- Clear cell RCC
- ≥T3 and/or N+
- ECOG PS 0-2
- Lack of residual disease by BICR

**Primary Endpoint: Disease-Free Survival by Blinded Independent Central Review (BICR)**

External Data Monitoring Committee performed regular data reviews
PO=Per Orem (oral administration)

# S-TRAC
# Endpoints and Statistical Analysis

- Primary Endpoint: Disease-Free Survival (DFS) based on Blinded Independent Central Review
  - Two planned interim analyses
  - Final analysis after 5 years from last patient enrolled and ~258 DFS events
  - 84% power to detect a hazard ratio of 0.69 for DFS between the 2 treatment arms at a 2-sided significance level of 0.05
- Secondary Endpoints: Overall Survival (OS), Patient-Reported Outcomes (PROs), Safety

# S-TRAC
# Demographics and Baseline Characteristics by Treatment

| | Sunitinib N=309 | Placebo N=306 |
|---|---|---|
| Age, mean (range), years | 57 (25-83) | 58 (21-82) |
| <65 | 233 (75.4) | 224 (73.2) |
| ≥65 | 76 (24.6) | 82 (26.8) |
| Gender, n (%) | | |
| Male | 222 (71.8) | 229 (74.8) |
| Female | 87 (28.2) | 77 (25.2) |
| Race, n (%) | | |
| White | 254 (82.2) | 263 (85.9) |
| Black | 3 (1.0) | 1 (0.3) |
| Asian | 43 (13.9) | 33 (10.8) |
| Other | 9 (2.9) | 9 (2.9) |
| ECOG PS, n (%) | | |
| 0 | 228 (73.8) | 220 (71.9) |
| 1 | 79 (25.6) | 84 (27.5) |
| 2 | 1 (0.3) | 0 |
| Not reported | 1 (0.3) | 2 (0.7) |

# S-TRAC
# Disease Characteristics

| | Sunitinib N=309 n (%) | Placebo N=306 n (%) |
|---|---|---|
| Clear Cell RCC | 306 (99.0) | 306 (100.0) |
| UISS Risk Groups | | |
| T3 Overall | 280 (90.6) | 278 (90.8) |
| T3 low[a] | 115 (37.2) | 112 (36.6) |
| T3 high[b] | 165 (53.4) | 166 (54.2) |
| T4 N0 or NX[c] | 4 (1.3) | 4 (1.3) |
| Any T, N1-2[c] | 25 (8.1) | 24 (7.8) |
| Fuhrman's Grade | | |
| 1 | 11 (3.6) | 8 (2.6) |
| 2 | 104 (33.7) | 104 (34.0) |
| 3 | 139 (45.0) | 141 (46.1) |
| 4 | 54 (17.5) | 52 (17.0) |
| Not reported | 1 (0.3) | 1 (0.3) |

a. N0 or NX, M0, Any Fuhrman's grade, ECOG PS 0 or Fuhrman's grade 1, ECOG PS ≥1
b. N0 or NX, M0, Fuhrman's grade ≥2, ECOG PS ≥1
c. M0, Any Fuhrman's grade, any ECOG PS

# S-TRAC
# Patient Treatment

| Dosing Information | Sunitinib N=306 | Placebo N=304 |
|---|---|---|
| Treatment duration[a], median (range), months | 12.4 (0.13-14.9) | 12.4 (0.03-13.7) |
| Treatment duration, mean, months | 9.5 | 10.3 |
| Dose reductions, % | 45.8 | 4.9 |
| Dosing interruptions, % | 54.2 | 27.6 |
| Relative dose intensity, median (range)[b], % | 88.4 (15-106.2) | 99.7 (10-105.7) |

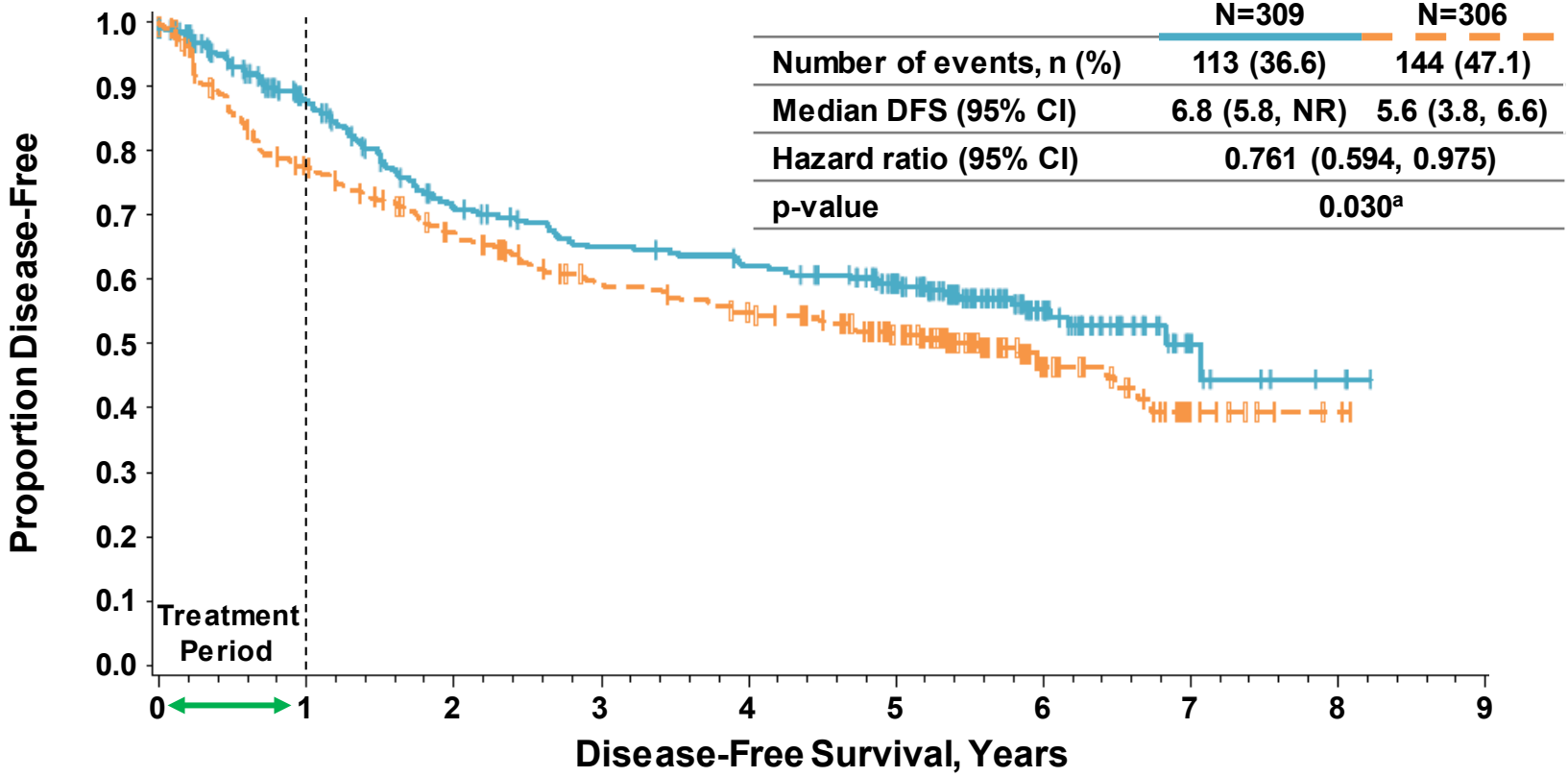
a. Duration of treatment was defined as the period between first and last doses of the drug and included dosing interruptions, cycle delays, and the scheduled 2-week off treatment
b. Relative dose intensity (%) >100 is due to >28 days of dosing within a cycle, <14 days off between cycles, and/or the cycle end date for the last cycle not accounting the 14 days off treatment period

# S-TRAC
# Patient Disposition

| Dosing Information | Sunitinib N=306 n (%) | Placebo N=304 n (%) |
|---|---|---|
| Treatment completion | 170 (55.6) | 212 (69.7) |
| Reasons for Discontinuation[a] | | |
| Adverse events | 84 (27.5) | 16 (5.3) |
| Disease progression/relapse | 22 (7.2) | 59 (19.4) |
| Patient died | 1 (0.3) | 0 |
| Global deterioration of health status | 1 (0.3) | 0 |
| Lost to follow-up | 1 (0.3) | 1 (0.3) |
| Protocol violation | 1 (0.3) | 1 (0.3) |
| Patient refused continued treatment for reason other than adverse event | 14 (4.6) | 8 (2.6) |
| Other | 12 (3.9) | 7 (2.3) |

a. Investigators had to select only one reason

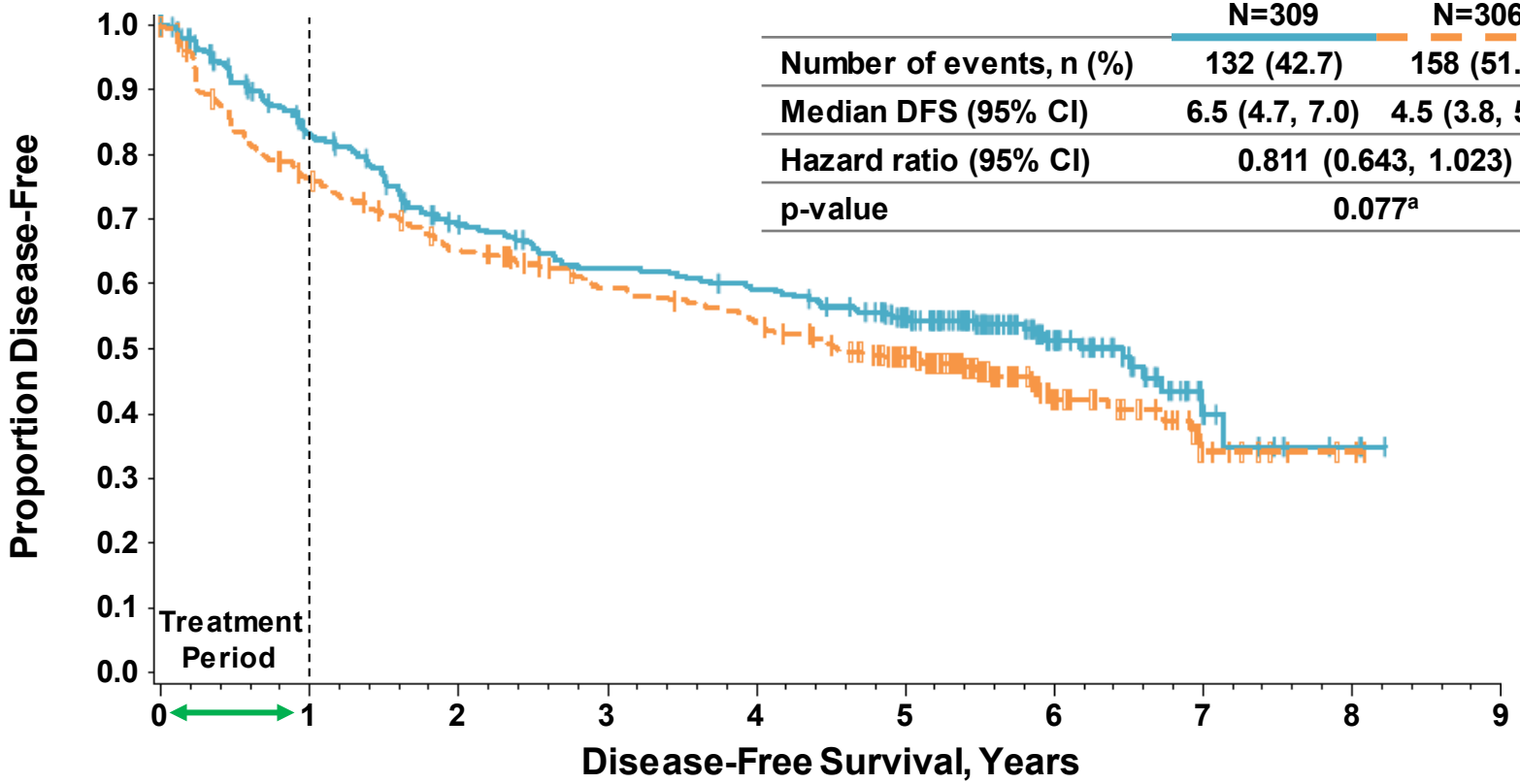
# S-TRAC
# Primary Endpoint: Disease-Free Survival By Blinded Independent Central Review




| Number at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Sunitinib | 309 | 225 | 173 | 153 | 144 | 119 | 53 | 10 | 3 | 0 |
| Placebo | 306 | 220 | 181 | 150 | 135 | 102 | 37 | 10 | 2 | 0 |

a. Two-sided p-value from log-rank test stratified by UISS high-risk group
NR=Not Reached

# S-TRAC
# Disease-Free Survival By Investigator Assessment

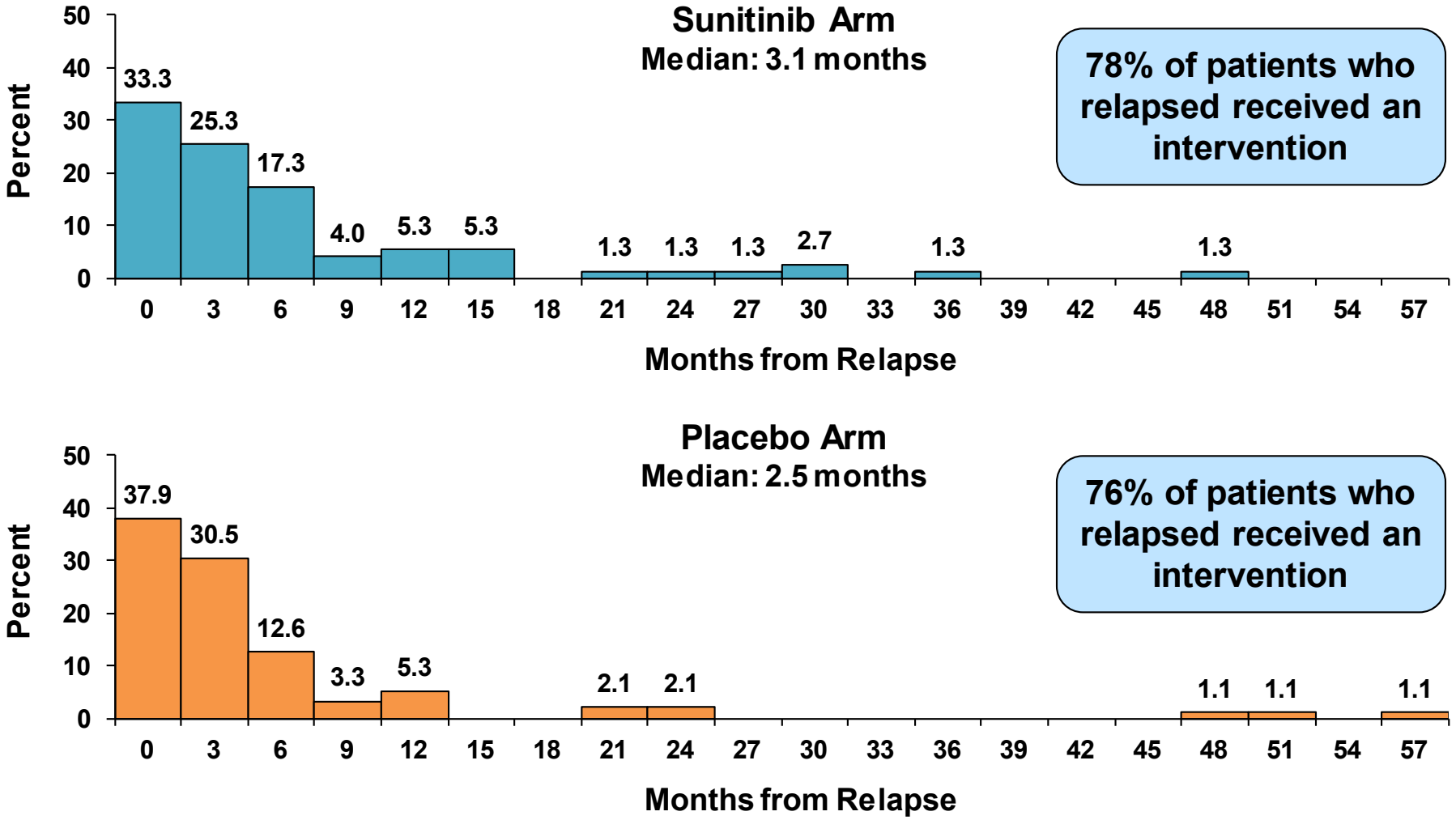



| | Sunitinib N=309 | Placebo N=306 |
|---|---|---|
| Number of events, n (%) | 132 (42.7) | 158 (51.6) |
| Median DFS (95% CI) | 6.5 (4.7, 7.0) | 4.5 (3.8, 5.9) |
| Hazard ratio (95% CI) | 0.811 (0.643, 1.023) | |
| p-value | 0.077[a] | |

| Number at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Sunitinib | 309 | 224 | 178 | 158 | 149 | 122 | 55 | 10 | 3 | 0 |
| Placebo | 306 | 219 | 184 | 158 | 142 | 106 | 37 | 10 | 2 | 0 |

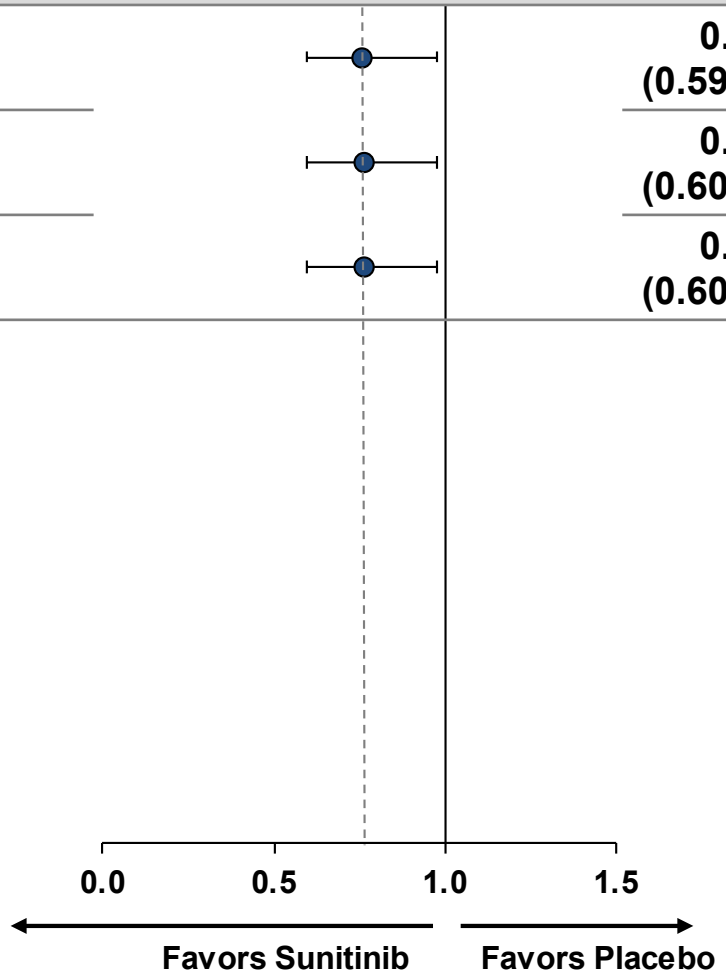
a. Two-sided p-value from log-rank test stratified by UISS high-risk group

# S-TRAC
# Time from BICR-Assessed Relapse to Intervention for Renal Cell Cancer



# S-TRAC
# Sensitivity Analyses of DFS

| | Events Sunitinib/Placebo | Hazard Ratio (95% CI) |
|---|---|---|
| Protocol specified (primary) analysis | 113/144 | 0.76 (0.59, 0.98) |
| Earliest scan date for equivocal lesions determined unequivocal | 113/143 | 0.77 (0.60, 0.98) |
| Earliest scan date equivocal and additional second primary malignancies | 114/144 | 0.76 (0.60, 0.98) |




CTX=anti-Cancer Therapy

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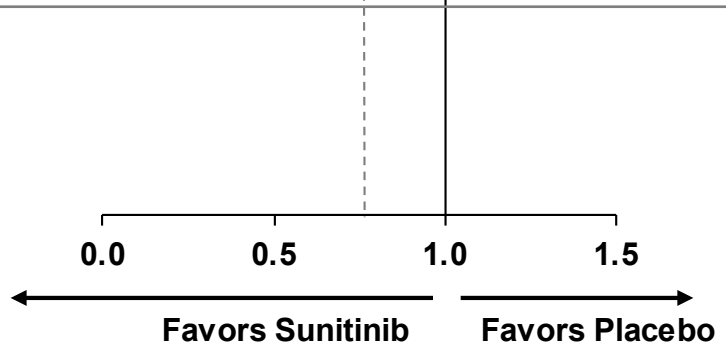
| Earliest scan date equivocal and additional second primary malignancies | 114/144 | 0.76 (0.60, 0.98) |
| Events regardless of missed visits/ new CTX | 133/156 | 0.81 (0.64, 1.02) |
| Including new CTX as an event | 125/157 | 0.77 (0.61, 0.97) |
| Excluding second primary malignancies and non disease related deaths | 104/129 | 0.78 (0.60, 1.01) |

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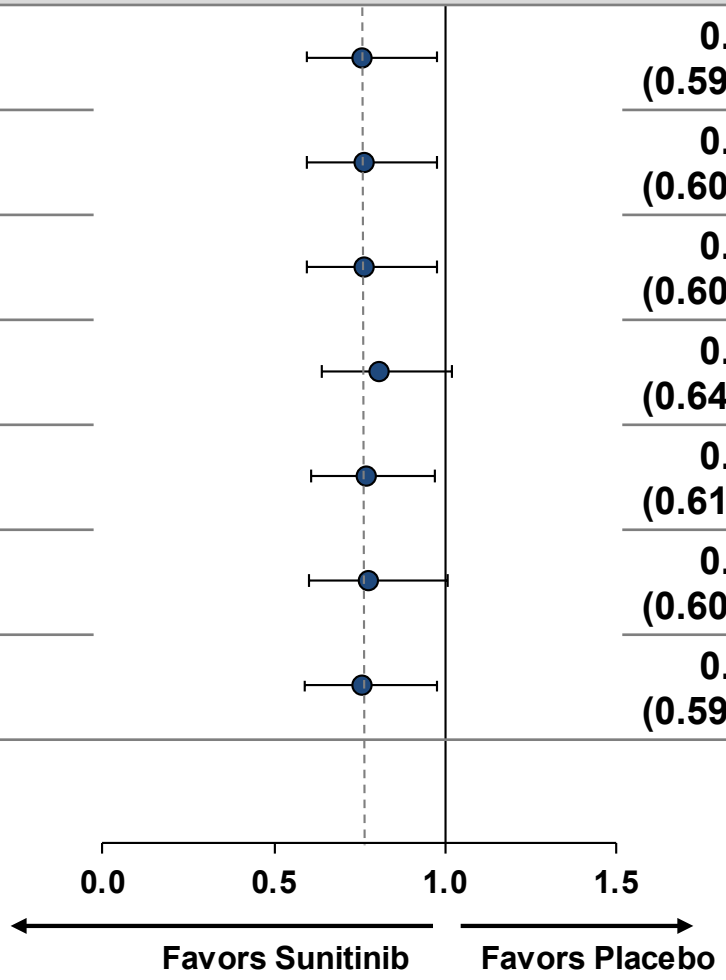
| Event/censoring at scheduled time points | 113/144 | 0.76 (0.59, 0.98) |

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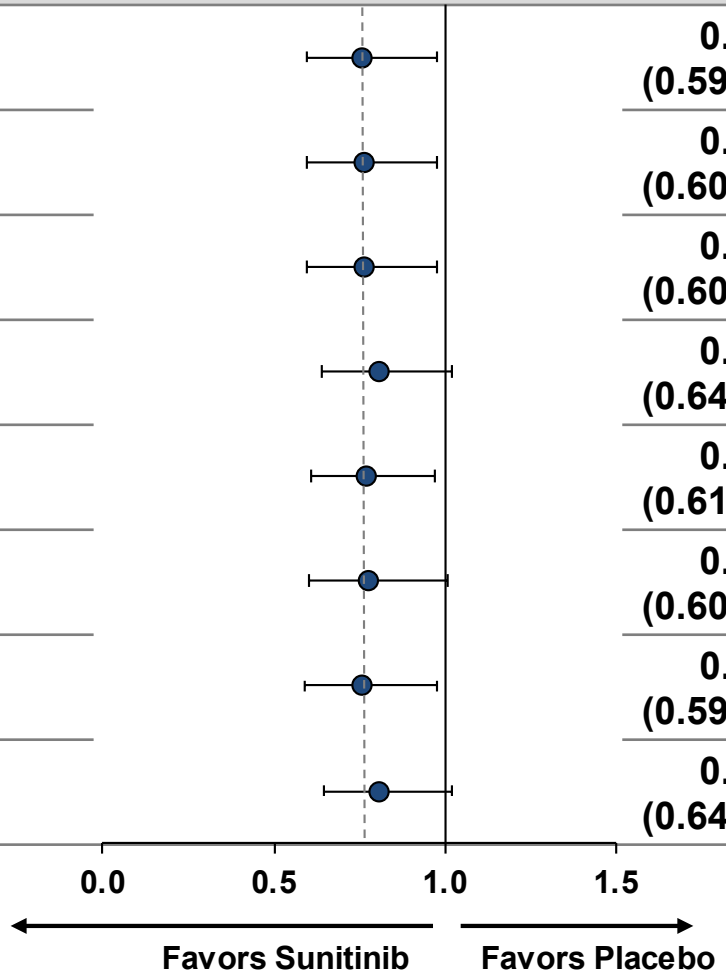
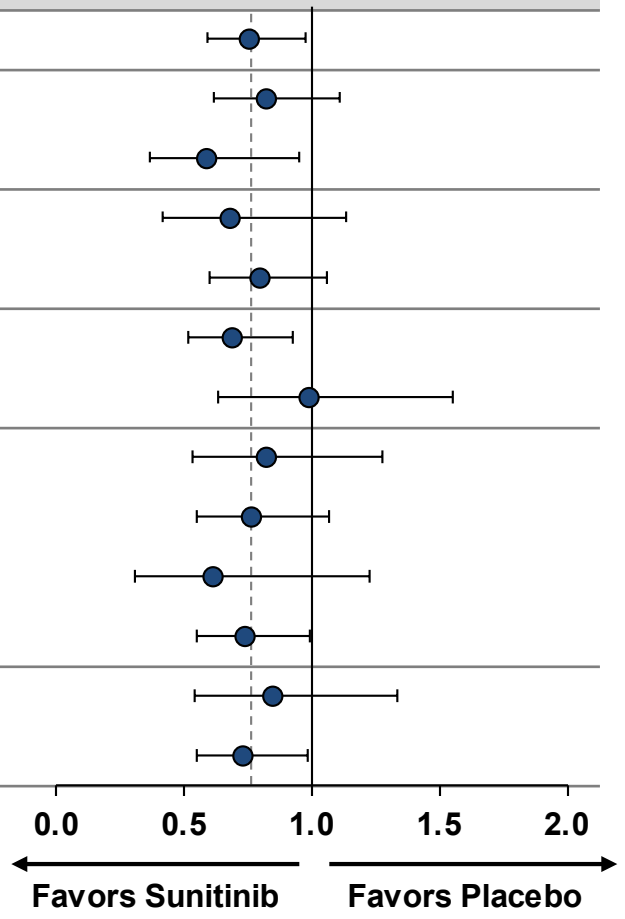
|---|---|---|
| Protocol specified (primary) analysis | 113/144 | 0.76 (0.59, 0.98) |
| Earliest scan date for equivocal lesions determined unequivocal | 113/143 | 0.77 (0.60, 0.98) |
| Earliest scan date equivocal and additional second primary malignancies | 114/144 | 0.76 (0.60, 0.98) |
| Events regardless of missed visits/ new CTX | 133/156 | 0.81 (0.64, 1.02) |
| Including new CTX as an event | 125/157 | 0.77 (0.61, 0.97) |
| Excluding second primary malignancies and non disease related deaths | 104/129 | 0.78 (0.60, 1.01) |
| Event/censoring at scheduled time points | 113/144 | 0.76 (0.59, 0.98) |
| Investigator assessment | 132/158 | 0.81 (0.64, 1.02) |



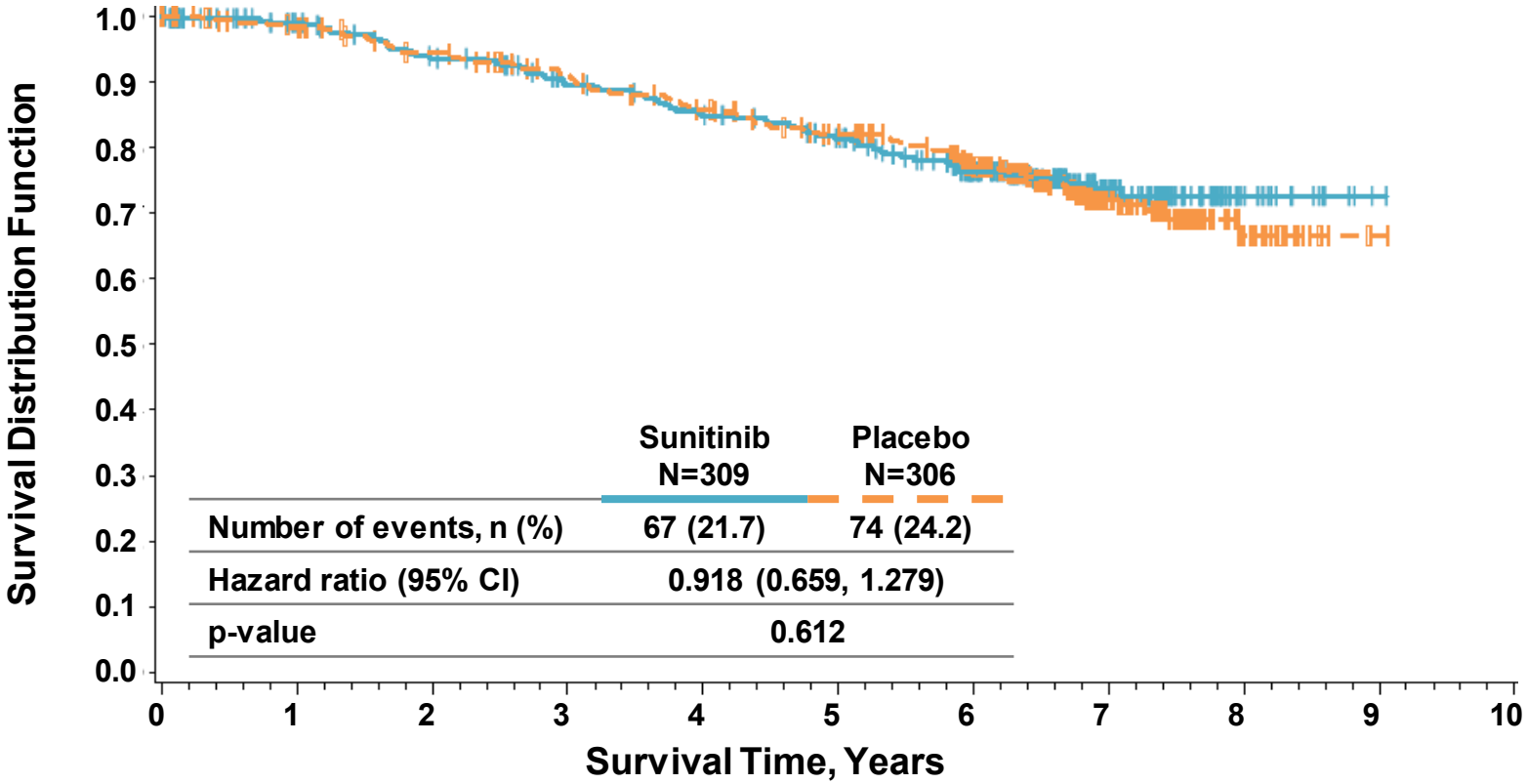

CTX=anti-Cancer Therapy

# S-TRAC
# Subgroup Analyses of DFS by BICR

| | | N | Events Sunitinib/Placebo | Hazard Ratio (95% CI) |
|---|---|---|---|---|
| Intent-To-Treat Patients (Primary) | | 615 | 113/144 | |
| Age, years | <65 | 457 | 86/99 | |
| | ≥65 | 158 | 27/45 | |
| Gender | Female | 164 | 27/33 | |
| | Male | 451 | 86/111 | |
| Performance Status | ECOG=0 | 448 | 76/104 | |
| | ECOG≥1 | 164 | 36/39 | |
| UISS | T3 Low | 227 | 35/46 | |
| | T3 High | 331 | 63/79 | |
| | Other (T4/Any T N+) | 57 | 15/19 | |
| | T3 High and Other | 388 | 78/98 | |
| Fuhrman's Grade | Grade 1/2 | 227 | 34/42 | |
| | Grade 3/4 | 386 | 79/102 | |



# S-TRAC
# Overall Survival




| Number at Risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Sunitinib | 309 | 278 | 258 | 236 | 222 | 205 | 160 | 82 | 16 | 1 | 0 |
| Placebo | 306 | 289 | 269 | 250 | 231 | 210 | 172 | 82 | 23 | 1 | 0 |

Data cutoff date: January 31, 2017

# S-TRAC
# Efficacy Conclusions

- In patients at high risk of recurrent RCC following nephrectomy, sunitinib demonstrated a statistically significant and clinically meaningful improvement in the primary DFS endpoint assessed by BICR compared with placebo

- The primary DFS result in favor of sunitinib was robust through the consistency of multiple sensitivity analyses

- No detrimental effect of sunitinib on overall survival observed

# Safety of Sunitinib for Adjuvant Treatment of RCC

***Liza DeAnnuntis, M.D.***

*Safety Risk Lead/Pharmacovigilance*

*Pfizer Oncology*

# Why Sunitinib as an Adjuvant Treatment?

Unmet Need

Efficacy

**Safety**

Benefit/Risk

- High-risk patients have a 60% risk of recurrence following nephrectomy and no available treatment options
- 24% relative DFS event risk reduction overall and 8% absolute DFS improvement at 5 years
- Adverse events are predictable, manageable and reversible
- Favorable for patients at high risk of recurrence

# Extensive Safety Experience for Sunitinib

- Sunitinib has been an available treatment in RCC for more than 11 years
- More than 350,000 patients have been treated with sunitinib globally since initial regulatory approval
- Most common AEs in clinical studies in approved indications (N=7115)
  - Diarrhea, Palmar-Plantar Erythrodysaesthesia syndrome (PPE), Hypertension, Fatigue/Asthenia, Nausea, Vomiting, Abdominal pain, Decreased appetite, Dysgeusia
- Well-characterized safety profile based on clinical studies and extensive post-marketing experience

AE=Adverse Event

# S-TRAC
# Overall Summary of Adverse Events (All Causality)[a]

| | Sunitinib N=306 n (%) | Placebo N=304 n (%) |
|---|---|---|
| Patients with AEs | 305 (99.7) | 269 (88.5) |
| Patients with Serious AEs | 67 (21.9) | 52 (17.1) |
| Patients with Grade 5 AEs | 5 (1.6) | 5 (1.6) |
| Patients with Grade 3 or 4 AEs | 189 (61.8) | 61 (20.1) |
| Patients temporarily discontinued due to AEs | 142 (46.4) | 40 (13.2) |
| Patients dose reduced due to AEs | 105 (34.3) | 6 (2.0) |
| Patients permanently discontinued due to AEs | 86 (28.1) | 17 (5.6) |

a. Includes all AEs collected throughout the follow-up period after last dose of study drug

# S-TRAC
# Common Treatment-Emergent Adverse Events (TEAEs)

| | Sunitinib N=306 % | | | Placebo N=304 % | | |
|---|---|---|---|---|---|---|
| | All Grades | Grade 3 | Grade 4 | All Grades | Grade 3 | Grade 4 |
| Any Adverse Event[a] | 99.7 | 48.4 | 12.1 | 88.5 | 15.8 | 3.6 |
| Diarrhea | 56.9 | 3.9 | 0 | 21.4 | 0.3 | 0 |
| PPE | 50.3 | 15.0 | 1.0 | 10.2 | 0.3 | 0 |
| Hypertension | 36.9 | 7.8 | 0 | 11.8 | 1.0 | 0.3 |
| Fatigue | 36.6 | 4.2 | 0.7 | 24.3 | 1.3 | 0 |
| Nausea | 34.3 | 2.0 | 0 | 13.8 | 0 | 0 |
| Dysgeusia | 33.7 | 0 | 0 | 5.9 | 0 | 0 |
| Mucosal inflammation | 33.7 | 4.6 | 0 | 8.2 | 0 | 0 |
| Dyspepsia | 26.8 | 1.3 | 0 | 6.3 | 0 | 0 |
| Stomatitis | 26.5 | 1.6 | 0.7 | 4.3 | 0 | 0 |
| Neutropenia | 23.5 | 7.5 | 1.0 | 0.7 | 0 | 0 |
| Asthenia | 22.5 | 3.6 | 0 | 12.2 | 0.7 | 0.3 |
| Hair color change | 22.2 | 0 | 0 | 2.3 | 0 | 0 |
| Thrombocytopenia | 20.9 | 4.9 | 1.3 | 1.6 | 0.3 | 0 |

a. Experienced by ≥20% of patients in the sunitinib arm. Includes all AEs collected throughout the follow-up period after last dose of study drug

# S-TRAC
# Common Treatment-Emergent Adverse Events (TEAEs)

| | Sunitinib N=306 % | | | Placebo N=304 % | | |
|---|---|---|---|---|---|---|
| | All Grades | Grade 3 | Grade 4 | All Grades | Grade 3 | Grade 4 |
| Any Adverse Event[a] | 99.7 | 48.4 | 12.1 | 88.5 | 15.8 | 3.6 |
| Diarrhea | 56.9 | 3.9 | 0 | 21.4 | 0.3 | 0 |
| PPE | 50.3 | 15.0 | 1.0 | 10.2 | 0.3 | 0 |
| Hypertension | 36.9 | 7.8 | 0 | 11.8 | 1.0 | 0.3 |
| Fatigue | 36.6 | 4.2 | 0.7 | 24.3 | 1.3 | 0 |
| Nausea | 34.3 | 2.0 | 0 | 13.8 | 0 | 0 |
| Dysgeusia | 33.7 | 0 | 0 | 5.9 | 0 | 0 |
| Mucosal inflammation | 33.7 | 4.6 | 0 | 8.2 | 0 | 0 |
| Dyspepsia | 26.8 | 1.3 | 0 | 6.3 | 0 | 0 |
| Stomatitis | 26.5 | 1.6 | 0.7 | 4.3 | 0 | 0 |
| Neutropenia | 23.5 | 7.5 | 1.0 | 0.7 | 0 | 0 |
| Asthenia | 22.5 | 3.6 | 0 | 12.2 | 0.7 | 0.3 |
| Hair color change | 22.2 | 0 | 0 | 2.3 | 0 | 0 |
| Thrombocytopenia | 20.9 | 4.9 | 1.3 | 1.6 | 0.3 | 0 |

a. Experienced by ≥20% of patients in the sunitinib arm. Includes all AEs collected throughout the follow-up period after last dose of study drug

# S-TRAC
# Serious Adverse Events Reported in ≥1% of Patients (All Causality)

| | Sunitinib N=306 n (%) | Placebo N=304 n (%) |
|---|---|---|
| **Patients with SAEs** | **67 (21.9)** | **52 (17.1)** |
| Hypertension | 8 (2.6) | 2 (0.7) |
| Thrombocytopenia | 7 (2.3) | 1 (0.3) |
| Pulmonary embolism | 5 (1.6) | 1 (0.3) |
| Pyrexia | 5 (1.6) | 0 |
| Abdominal pain | 3 (1.0) | 1 (0.3) |
| Myocardial infarction | 3 (1.0) | 1 (0.3) |
| Vomiting | 3 (1.0) | 0 |

SAE=Serious Adverse Event

# S-TRAC
# Summary of Deaths

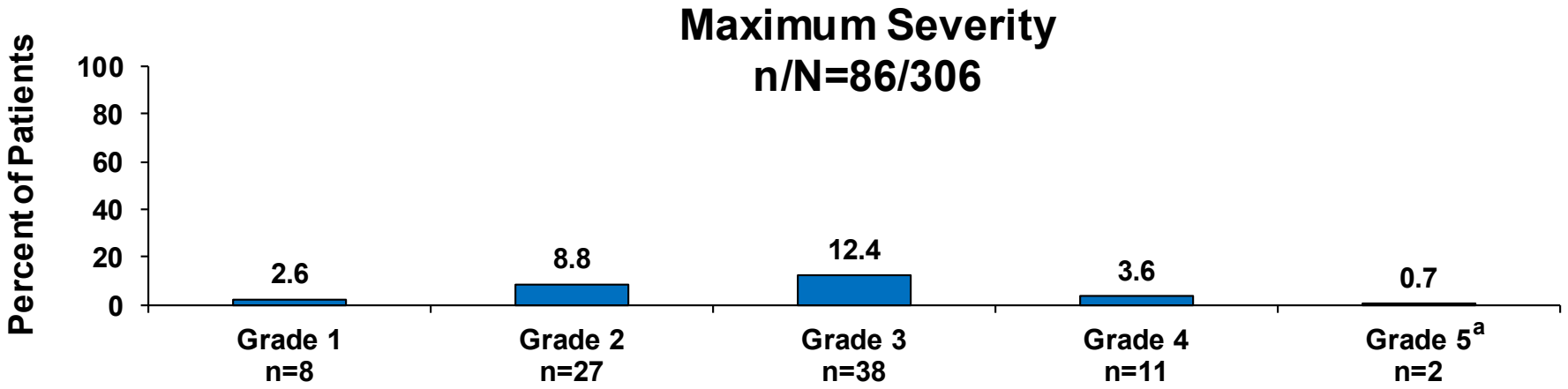
| | Sunitinib N=306 n (%) | Placebo N=304 n (%) |
|---|---|---|
| **Deaths** | 66 (21.6)[a] | 74 (24.3) |
| **Patients Who Died During Treatment Period[b]** | 2 (0.7) | 0 |
| Disease under study | 2 (0.7) | 0 |
| Study treatment toxicity | 0 | 0 |
| Unknown | 0 | 0 |
| Other | 1 (0.3) | 0 |
| **Patients Who Died During Follow-Up Period[c]** | 64 (20.9) | 74 (24.3) |
| Disease under study | 47 (15.4) | 50 (16.4) |
| Study treatment toxicity | 0 | 0 |
| Unknown | 9 (2.9) | 9 (3.0) |
| Other | 10 (3.3) | 16 (5.3) |

Some patients could have had multiple reasons for death
a. Number includes additional deaths from April 8, 2016 through January 31, 2017: 3 and 10 patients in the sunitinib and placebo arms respectively
b. Treatment period: Includes data up to 28 days after last dose of study drug
c. Follow-up period: Includes data from 28 days after last dose of study drug up to 9999 days

# S-TRAC
# Most Common TEAEs Experienced by ≥1% of Patients Leading to Permanent Discontinuation

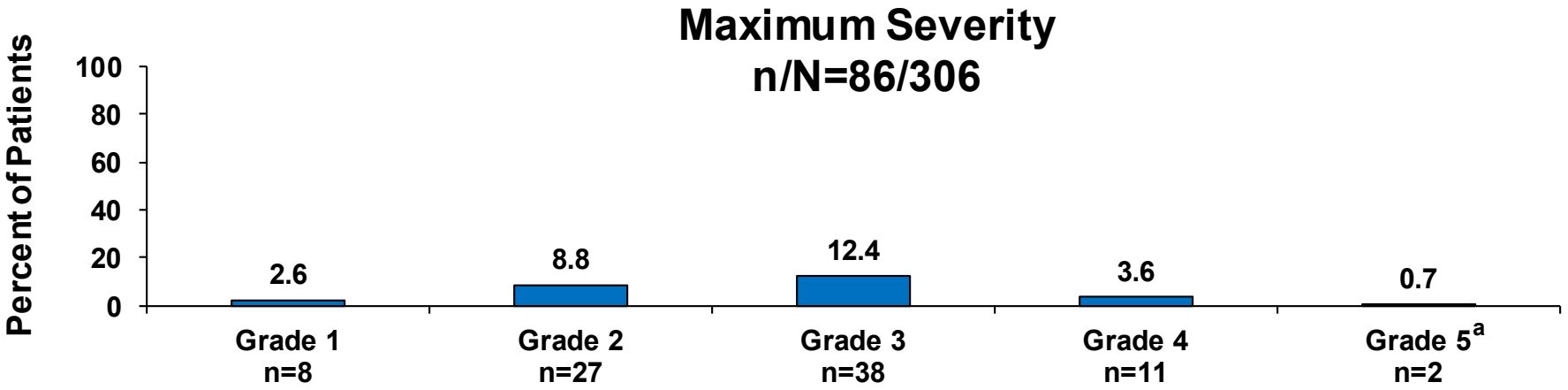
| | Sunitinib N=306 n (%) | Placebo N=304 n (%) |
|---|---|---|
| Any TEAE | 86 (28.1) | 18 (5.9) |
| PPE | 13 (4.2) | 0 |
| Hypertension | 6 (2.0) | 0 |
| Asthenia | 4 (1.3) | 0 |
| Fatigue | 3 (1.0) | 1 (0.3) |
| Pulmonary embolism | 3 (1.0) | 1 (0.3) |
| Gastroesophageal reflux disease | 3 (1.0) | 0 |

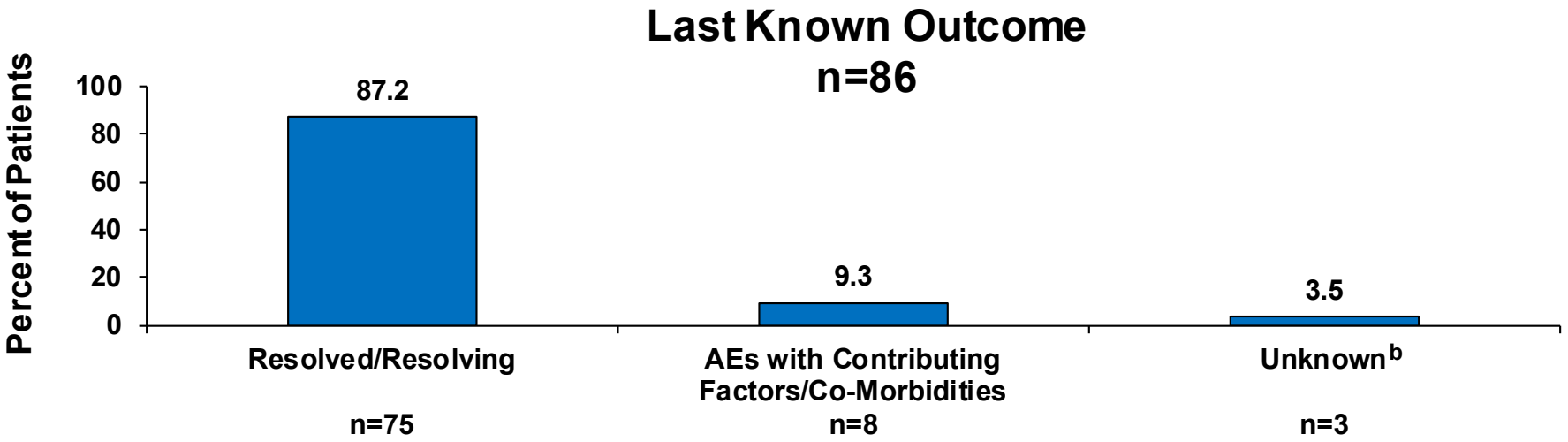
# S-TRAC
# Maximum Severity and Reversibility of TEAEs Leading to Permanent Discontinuation (All Causality)




a. Two Grade 5 events with fatal outcome unrelated to study treatment reported during active treatment period
b. Grade 2 and 3 PPE, Grade 2 unexpected therapeutic effect (increased thyroid function); AEs known to be manageable/reversible

# S-TRAC
# Maximum Severity and Reversibility of TEAEs Leading to Permanent Discontinuation (All Causality)



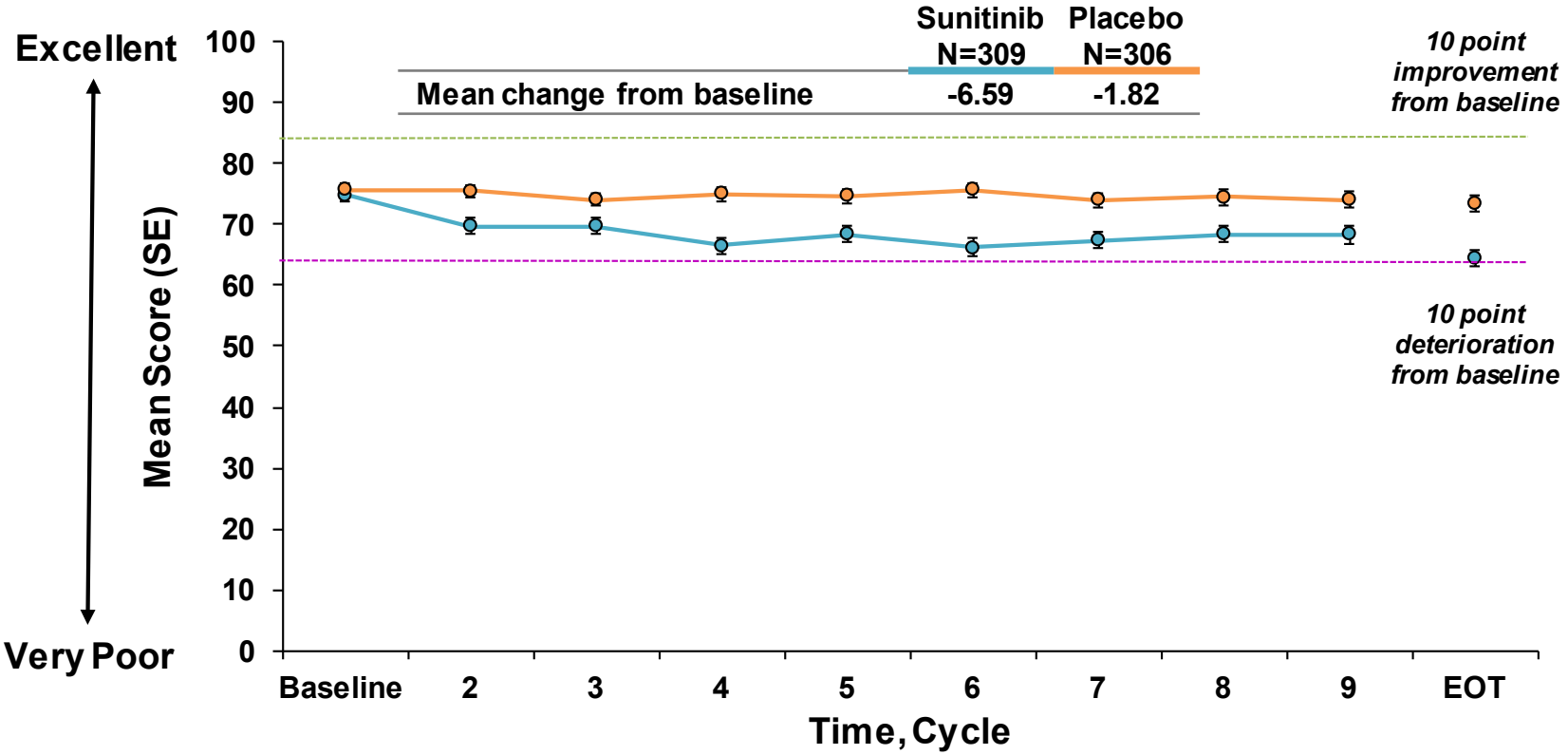

a. Two Grade 5 events with fatal outcome unrelated to study treatment reported during active treatment period
b. Grade 2 and 3 PPE, Grade 2 unexpected therapeutic effect (increased thyroid function); AEs known to be manageable/reversible

# S-TRAC
# Safety Conclusions

- Sunitinib adverse events are well understood
- Consistent with known safety profile
- No new safety signals observed
- No treatment-related deaths reported
- AEs were manageable and reversible via dosing interruption, dose reduction, and/or standard supportive treatment

# S-TRAC
# Patient-Reported Outcomes

# S-TRAC
# EORTC QLQ-C30 Mean Scores Over Time: Global Health Status/QoL Domain

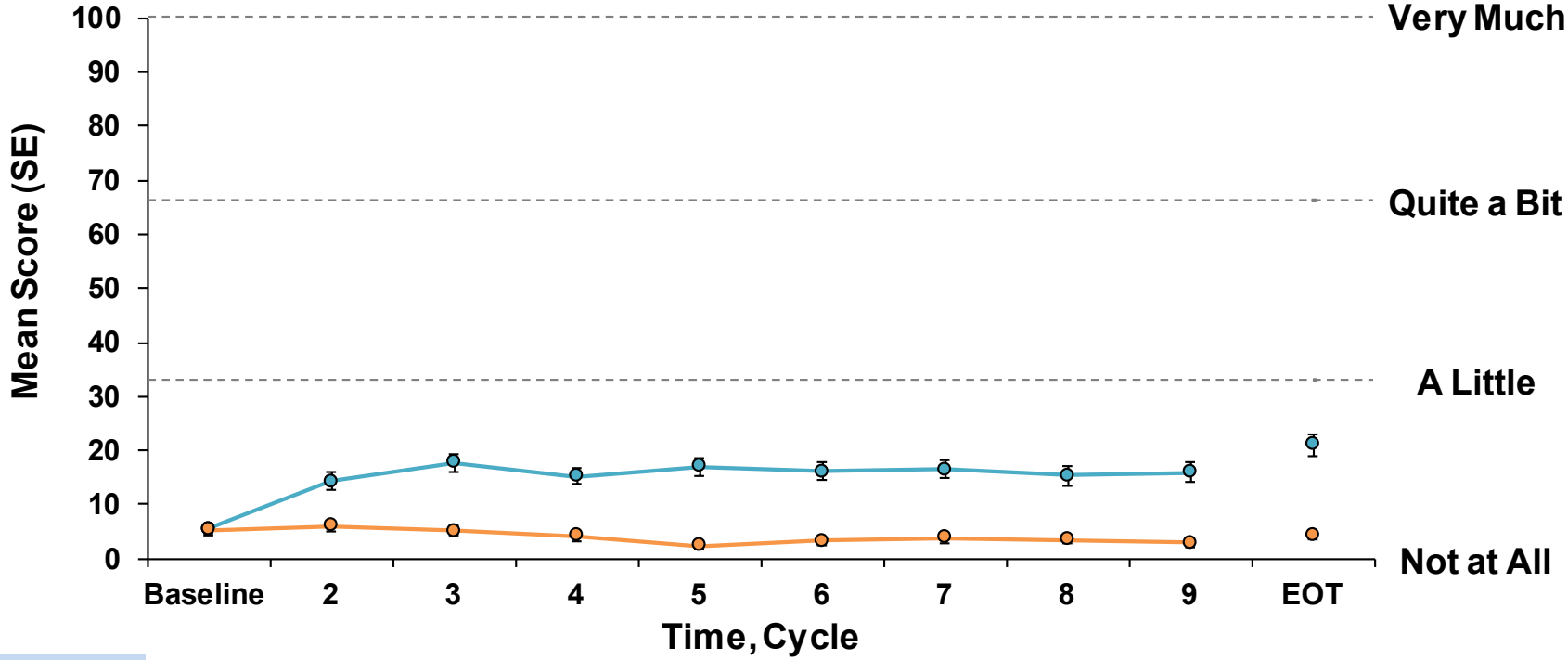



| Number at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Sunitinib | 292 | 260 | 241 | 227 | 219 | 210 | 200 | 185 | 177 | 250 |
| Placebo | 288 | 274 | 265 | 249 | 234 | 231 | 220 | 212 | 203 | 250 |

Intent-To-Treat Population
QLQ-C30 was measured on Day 1 of each cycle. Patients were responding using the recall period of 1 week. Mean change from baseline based on repeated measures longitudinal analysis
EORTC=European Organization for Research and Treatment of Cancer; EOT=End Of Treatment; QLQ=Quality of Life Questionnaire; QoL=Quality of Life; SE=Standard Error

# S-TRAC
# EORTC QLQ-C30 Mean Scores Over Time: Appetite Loss

| | Sunitinib N=309 | Placebo N=306 |
|---|---|---|
| Mean change from baseline | 9.18 | -0.86 |

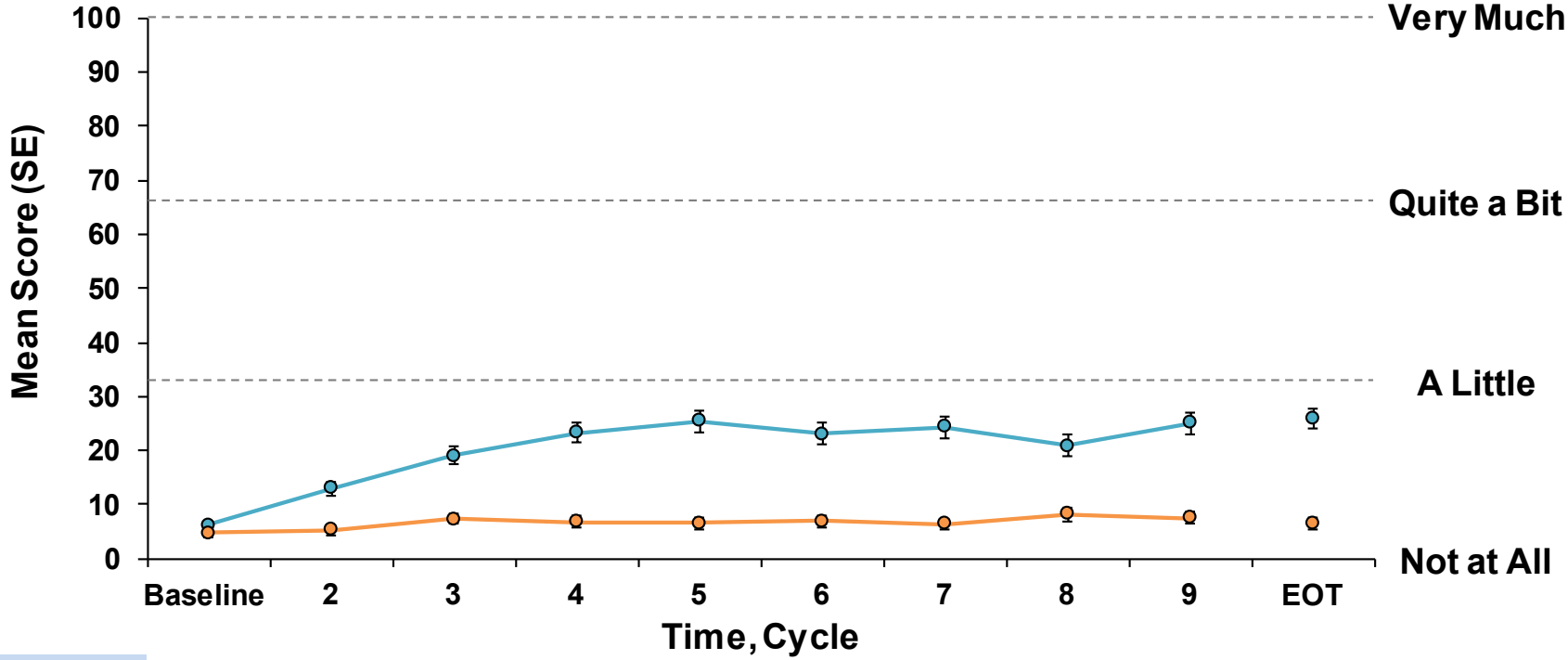



| Number at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Sunitinib | 294 | 260 | 241 | 228 | 222 | 211 | 200 | 185 | 177 | 251 |
| Placebo | 289 | 274 | 269 | 249 | 234 | 232 | 221 | 212 | 203 | 251 |

Intent-To-Treat Population
QLQ-C30 was measured on Day 1 of each cycle. Patients were responding using the recall period of 1 week. Mean change from baseline based on repeated measures longitudinal analysis

# S-TRAC
# EORTC QLQ-C30 Mean Scores Over Time: Diarrhea

| | Sunitinib N=309 | Placebo N=306 |
|---|---|---|
| Mean change from baseline | 13.32 | 1.32 |




| Number at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Sunitinib | 293 | 260 | 241 | 227 | 219 | 209 | 200 | 185 | 176 | 250 |
| Placebo | 288 | 274 | 264 | 249 | 234 | 231 | 220 | 212 | 203 | 249 |

Intent-To-Treat Population
QLQ-C30 was measured on Day 1 of each cycle. Patients were responding using the recall period of 1 week. Mean change from baseline based on repeated measures longitudinal analysis

# S-TRAC
# PRO Conclusions

- Patients at baseline reported few symptoms and high levels of functioning and global health status
- As expected, patients reported clinically meaningful worsening in diarrhea and loss of appetite, but no such worsening in other symptoms
- No clinically meaningful deterioration in functioning scales
  - Physical, Role, Emotional, Social, Cognitive
- No clinically meaningful deterioration in global health status/QoL

# Benefit/Risk of Sunitinib: Clinical Perspective

***Robert A. Figlin, M.D., FACP***

*Steven Spielberg Family Chair in Hematology Oncology*

*Professor of Medicine and Biomedical Sciences*

*Cedar-Sinai Medical Center, Los Angeles, CA*

# Why Sunitinib as an Adjuvant Treatment?

**Unmet Need**

- High-risk patients have a 60% risk of recurrence following nephrectomy and no available treatment options

**Efficacy**

- 24% relative DFS event risk reduction overall and 8% absolute DFS improvement at 5 years

**Safety**

- Adverse events are predictable, manageable and reversible

**Benefit/Risk**

- Favorable for patients at high risk of recurrence

# Previous Negative Adjuvant Trials of Non-Antiangiogenic Agents

| Author (Year) | Intervention |
|---|---|
| Kjaer (1987) | Radiation |
| Pizzocaro (1987) | Medroxyprogesterone |
| Galligioni (1996) | Tumor cells + BCG |
| Pizzocaro (2001) | IFN-α |
| Messing (2003) | IFN-α |
| Clark (2003) | IL-2 |
| Wood (2008) | HSPPC-96 |
| ARISER (2015) | Girentuximab |

- Many previous trials spanning 4 decades
- Different treatment approaches in varied patient populations
- High unmet medical need remains for patients with high risk of recurrence

BCG=Bacillus Calmette-Guerin; HSPPC=Heat Shock Protein Peptide Complex; IL=Interleukin

# Phase 3 Clinical Trials Evaluating Adjuvant Targeted Therapies in RCC

| Published Studies | Treatment Arms | Modified Dosing | Treatment Duration | Type of RCC[a] | Risk Group UISS |
|---|---|---|---|---|---|
| ASSURE | Sunitinib<br>Sorafenib<br>Placebo | Yes | 1 year | CC or nCC | ≥T1b, FG 3-4, PS0, and/or N+ |
| S-TRAC | Sunitinib<br>Placebo | No | 1 year | CC | ≥T3, FG any, PS0, and/or N+ |
| PROTECT | Pazopanib<br>Placebo | Yes | 1 year | CC | ≥T2, FG 3-4, PS0, and/or N+ |

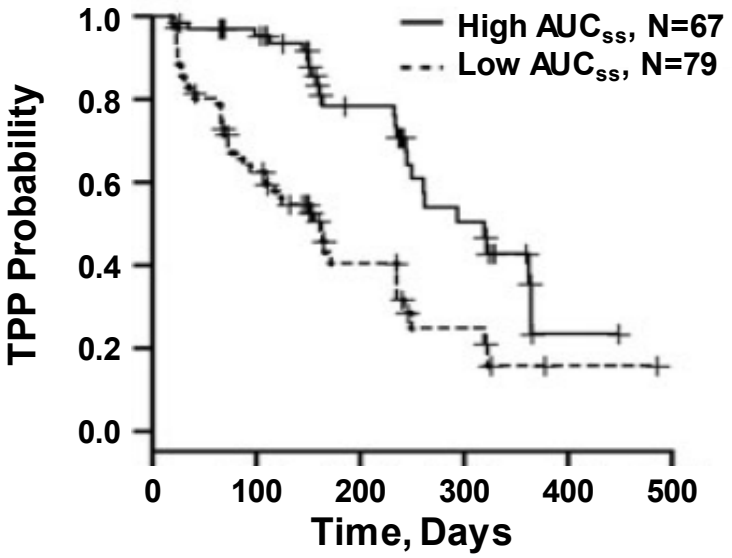
| Study Enrollment Complete | Treatment Arms | Modified Dosing | Treatment Duration | Type of RCC[a] | Risk Group |
|---|---|---|---|---|---|
| SORCE | Sorafenib 1 year<br>Sorafenib 3 years<br>Placebo | Yes | 1 or 3 years | CC or nCC | Leibovich (Score 3-11)[b] |
| ATLAS | Axitinib<br>Placebo | No | 1 (up to)<br>3 years | CC | ≥T2, FG any, PS0, and/or N+ |
| EVEREST | Everolimus<br>Placebo | No | 54 weeks | CC or nCC | ≥T1b, FG 3-4, PS0, and/or N+ |

Clinical Trials. www.clinicaltrials.gov. Date accessed: August 10, 2016
a. Varying % of clear cell
b. Leibovich=alternative scoring system based on Leibovich BC et al. *Cancer* 2003;97(7):1663-71.
CC=Clear Cell; nCC=Non-Clear Cell

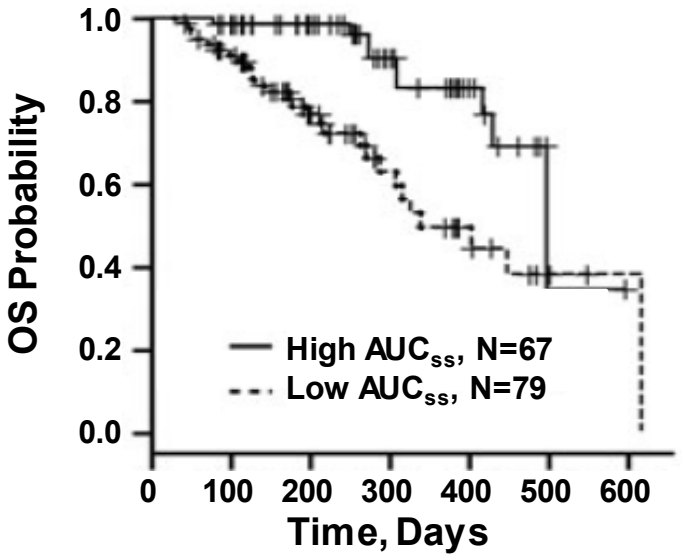
# S-TRAC: Why Did it Succeed?

- Unique patient population
  - Loco-regional RCC with ≥T3 and/or N+
  - Predominant (>50%) clear cell RCC
- Higher dose/treatment exposure to maintain dose intensity

**TTP in Advanced RCC[1]**




**OS in Advanced RCC[1]**




1. Houk BE et al. *Cancer Chemother Pharmacol* 2010;66(2):357-71.
$AUC_{ss}$=Area Under the Curve at Steady State; TTP=Time to Tumor Progression

# Differences in Study Design Drive Study Outcome

## S-TRAC

- Dosing
  - All patients started sunitinib at the full dose of 50 mg on Schedule 4/2
  - Dose reductions allowed to 37.5 mg

## ASSURE

- Dosing
  - ~1/3 of patients received a starting sunitinib dose of 37.5 mg on Schedule 4/2
  - Dose reductions allowed to 25 mg

# Differences in Study Design Drive Study Outcome

## S-TRAC

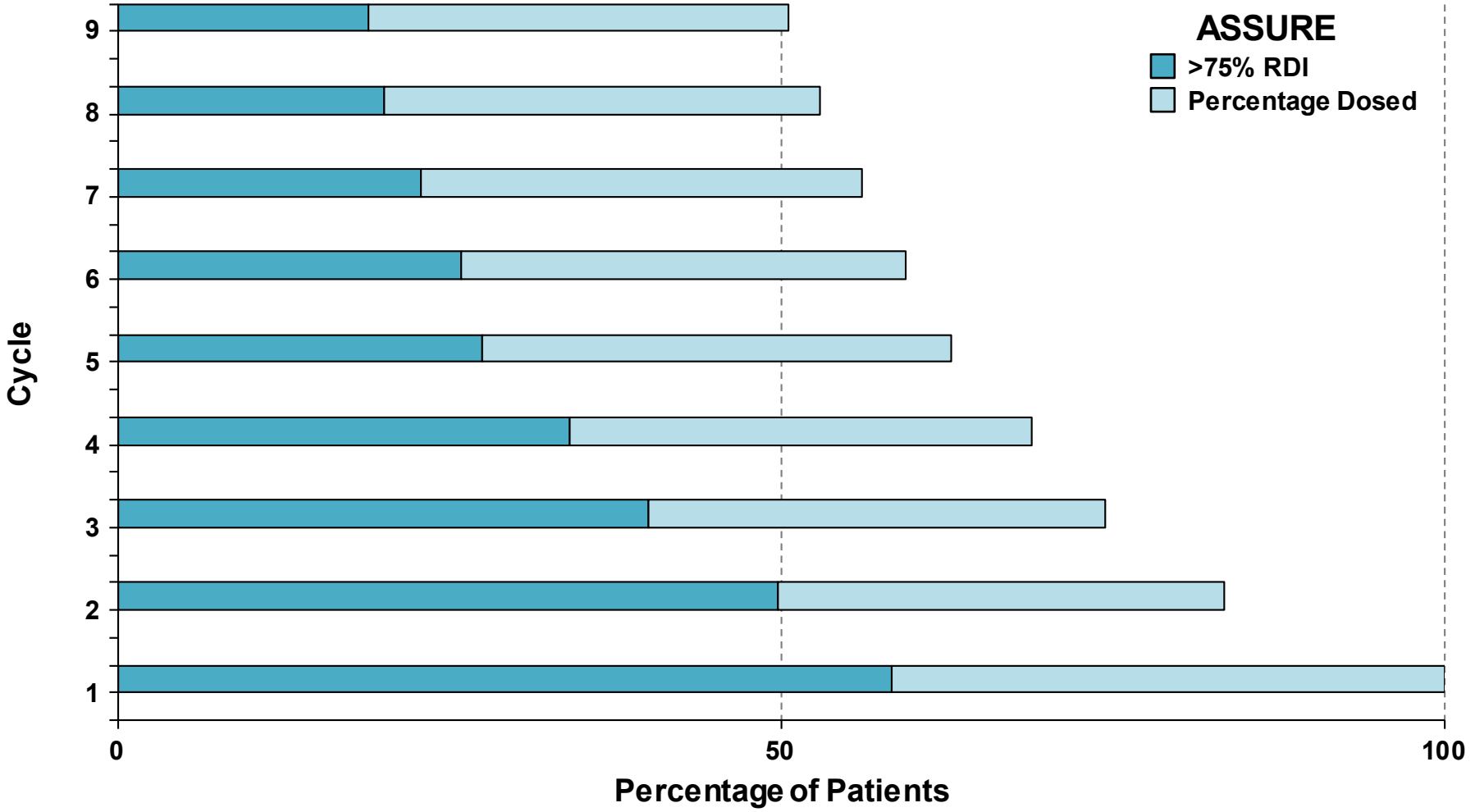
- Dosing
  - All patients started sunitinib at the full dose of 50 mg on Schedule 4/2
  - Dose reductions allowed to 37.5 mg

## ASSURE

- Dosing
  - ~1/3 of patients received a starting sunitinib dose of 37.5 mg on Schedule 4/2
  - Dose reductions allowed to 25 mg

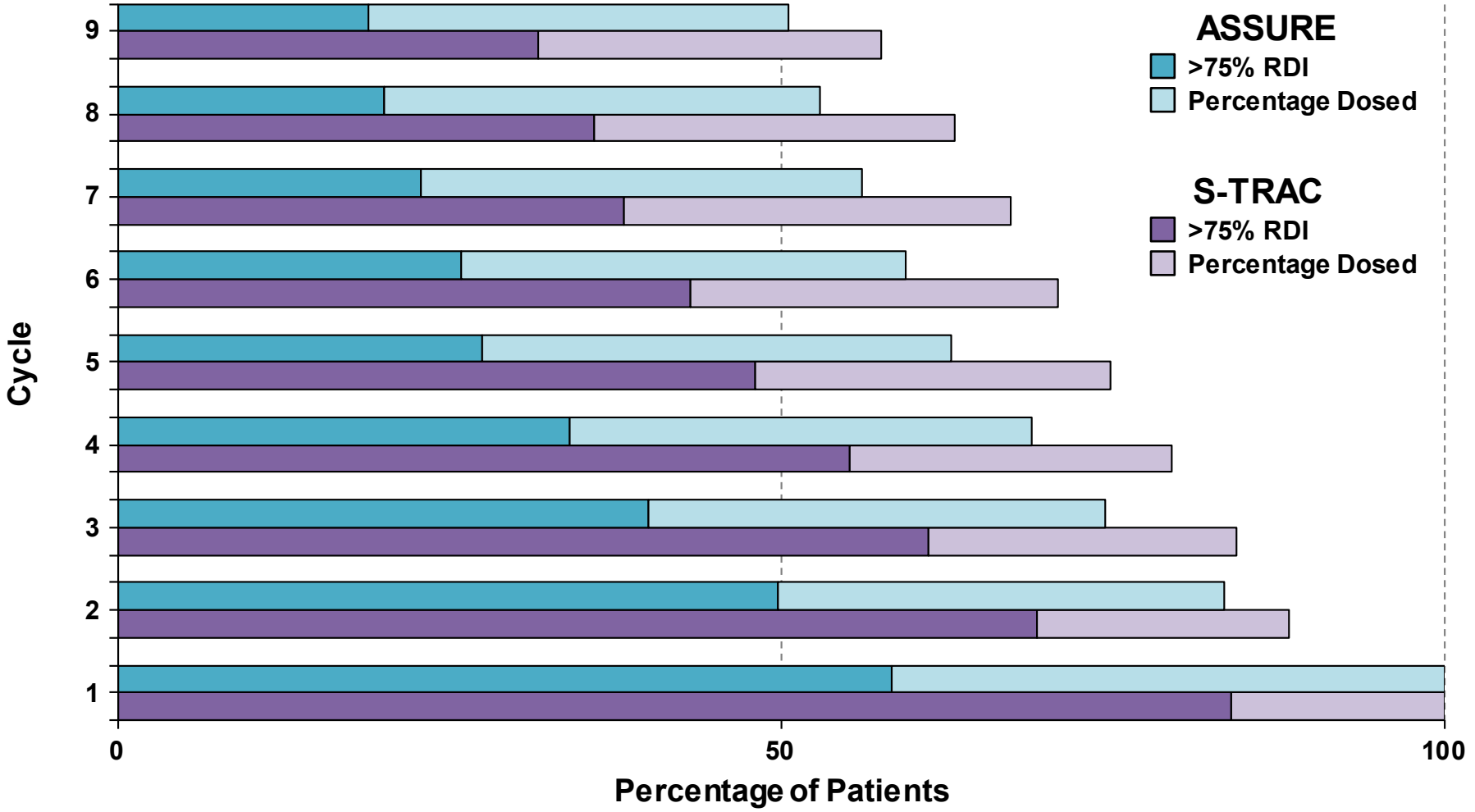
| | Sunitinib | |
|---|---|---|
| | **S-TRAC N=306** | **ASSURE N=629** |
| **Median average daily dose, mg** | **48.2** | **37.5** |
| **Median cumulative dose, mg** | **9637.5** | **6800.0** |
| **Mean duration of treatment, months** | **9.46** | **8.36** |
| **Completed 9 cycles of treatment, %** | **55.6** | **47.1** |

# ASSURE vs. S-TRAC
# Differences in Relative Dose Intensity




RDI=Relative Dose Intensity

# ASSURE vs. S-TRAC
# Differences in Relative Dose Intensity




RDI=Relative Dose Intensity

# Differences in Study Design Drive Study Outcome

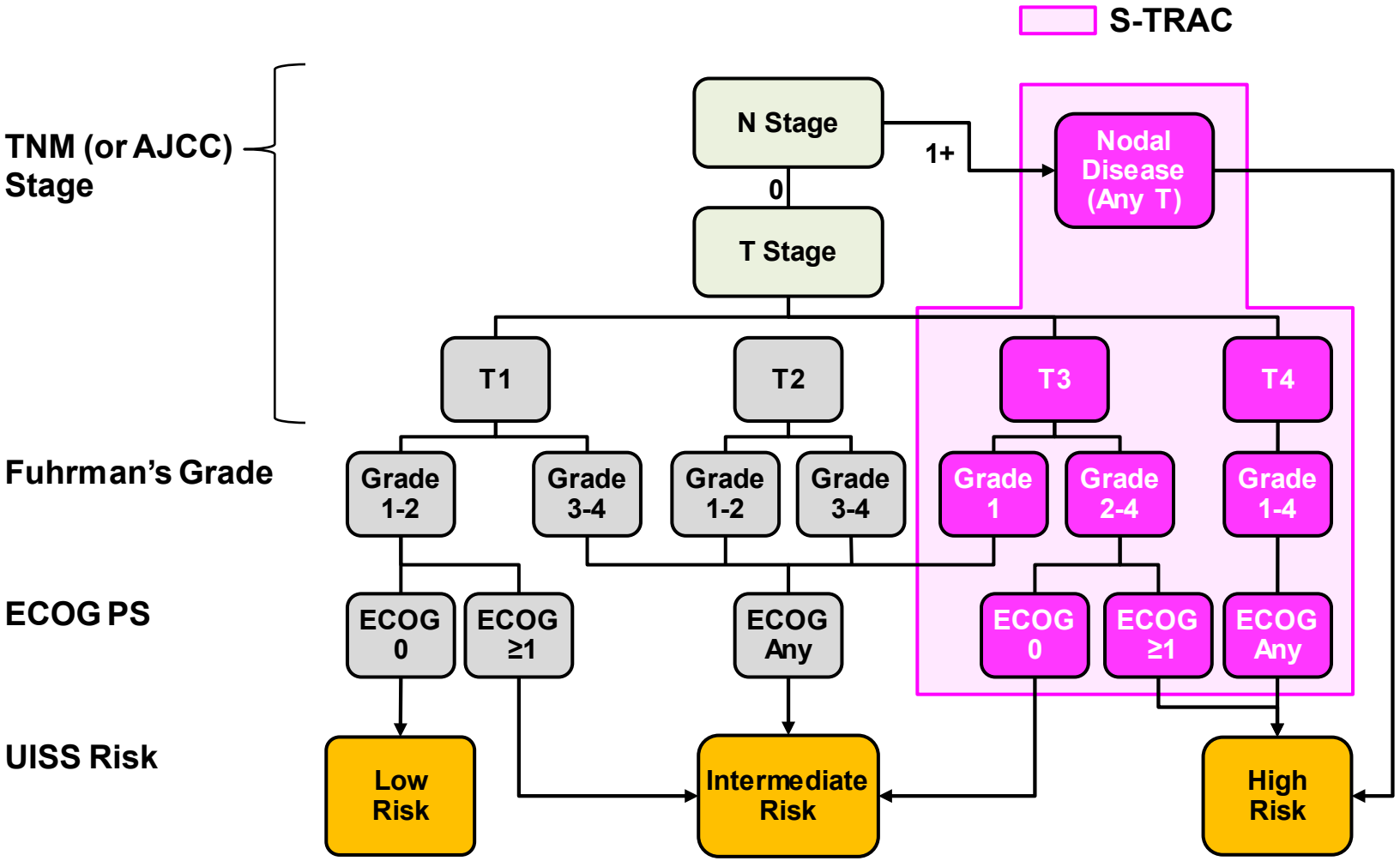
## S-TRAC

- Dosing
  - All patients started sunitinib at the full dose of 50 mg on Schedule 4/2
  - Dose reductions allowed to 37.5 mg
- Patients Included
  - Preponderant (defined as >50%) clear cell RCC
  - At high risk of recurrent RCC (locally advanced RCC, ≥T3 and/or N1-2)

## ASSURE

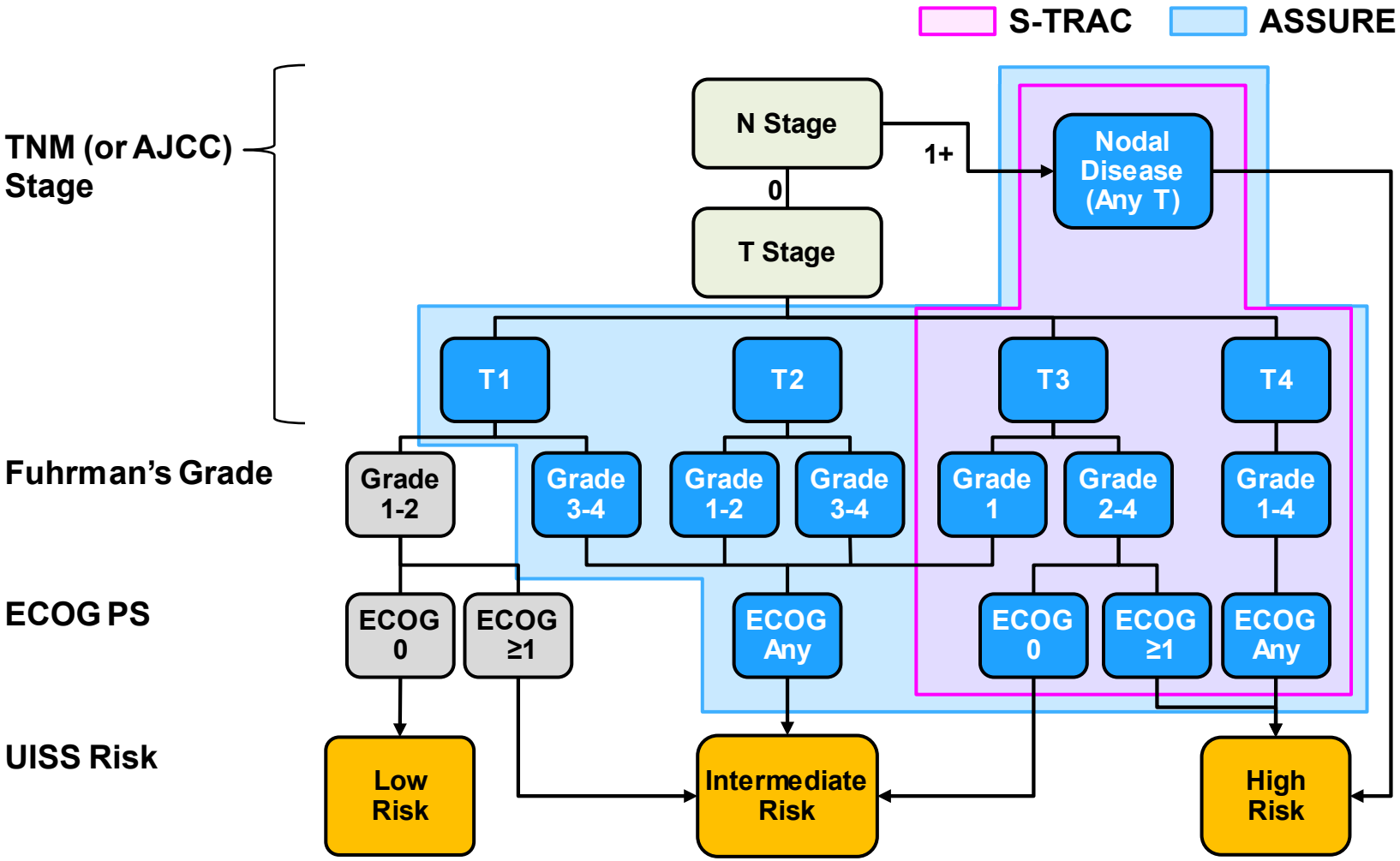
- Dosing
  - ~1/3 of patients received a starting sunitinib dose of 37.5 mg on Schedule 4/2
  - Dose reductions allowed to 25 mg
- Patients Included
  - ~21% of patients with a histology of non-clear cell RCC
  - 1/3 of patients with localized RCC (T1 and T2 without nodal involvement)

# S-TRAC
# UISS Risk Group Assignment




Adapted from: Zisman et al. *JCO* 2002;20:4561.; Lam JS, et al. *J Urol* 2005;74:466-472.

# ASSURE
# UISS Risk Group Assignment




Adapted from: Zisman et al. *JCO* 2002;20:4561.; Lam JS, et al. *J Urol* 2005;74:466-472.

# Patients in ASSURE Who Met S-TRAC Eligibility and Dosing Criteria

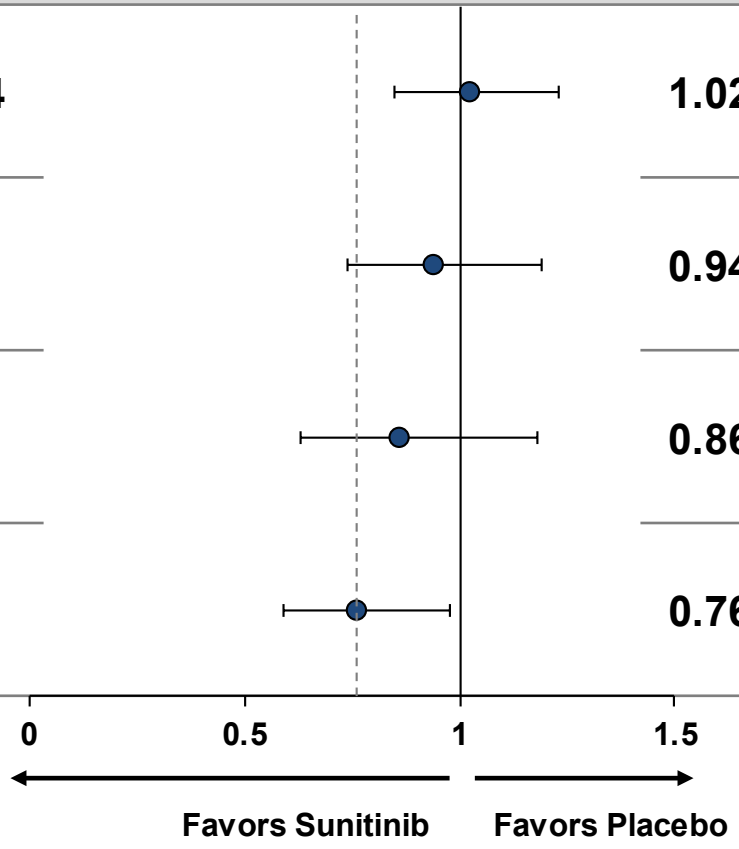
- Retrospective review by Pfizer Inc of the ASSURE database
- **30% (394/1294)** of the patients enrolled in the sunitinib and placebo arms of the ASSURE Study met the population and dosing criteria in S-TRAC Study

| | S-TRAC N=615 n (%) | ASSURE Subset N=394 n (%) |
|---|---|---|
| T3 Low[a] | 227 (36.9) | 293 (74.4) |
| T3 High[b] | 331 (53.8) | 57 (14.5) |
| T4 N0 or Nx, M0, any Fuhrman's grade, any ECOG status | 8 (1.3) | 1 (0.3) |
| Any T, N1-2, M0, any Fuhrman's grade, any ECOG status | 49 (8.0) | 38 (9.6) |
| T3 unknown (missing ECOG) | 0 | 5 (1.3) |

a. T3 Low=T3 N0 or Nx, M0, any Fuhrman's grade ECOG 0 or Fuhrman's grade 1 ECOG status ≥1
b. T3 High=T3 N0 or Nx, M0, Fuhrman's grade ≥2, ECOG status ≥1

# Sensitivity Analyses: Outcomes for Patients in ASSURE Who Met S-TRAC Eligibility and Dosing Criteria

| | Events/ Patients | Hazard Ratio (95% CI)[a] |
|---|---|---|
| **ASSURE ITT Population[1]** | **571/1294** | **1.02 (0.85, 1.23)** |
| **ASSURE T3/T4, Lymph Node Positive, Clear Cell[2]** | **NA/714** | **0.94 (0.74, 1.19)** |
| **ASSURE T3/T4, Lymph Node Positive, Clear Cell, Dosing[b]** | **217/410** | **0.86 (0.63, 1.18)** |
| **S-TRAC ITT Population** | **257/615** | **0.76 (0.59, 0.98)** |



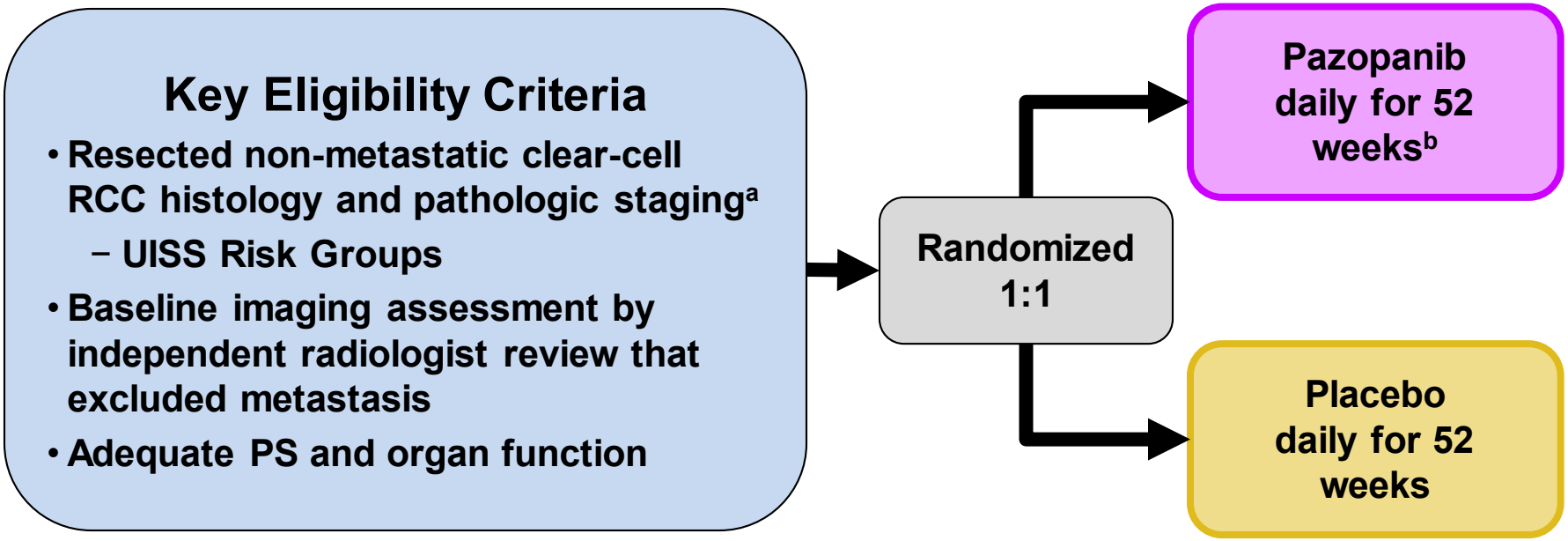

1. Haas NB et al. *Lancet* 2016;387;2008-16.
2. Haas NB et al. *JAMA Oncol* 2017:(Mar):e1-e4.

a. Confidence intervals are 95% for S-TRAC and 97.5% for ASSURE

b. Patients who started at 50 mg sunitinib and did not dose-reduce below 37.5 mg

ITT=Intent-To-Treat; NA=Not Available

# PROTECT Study Design

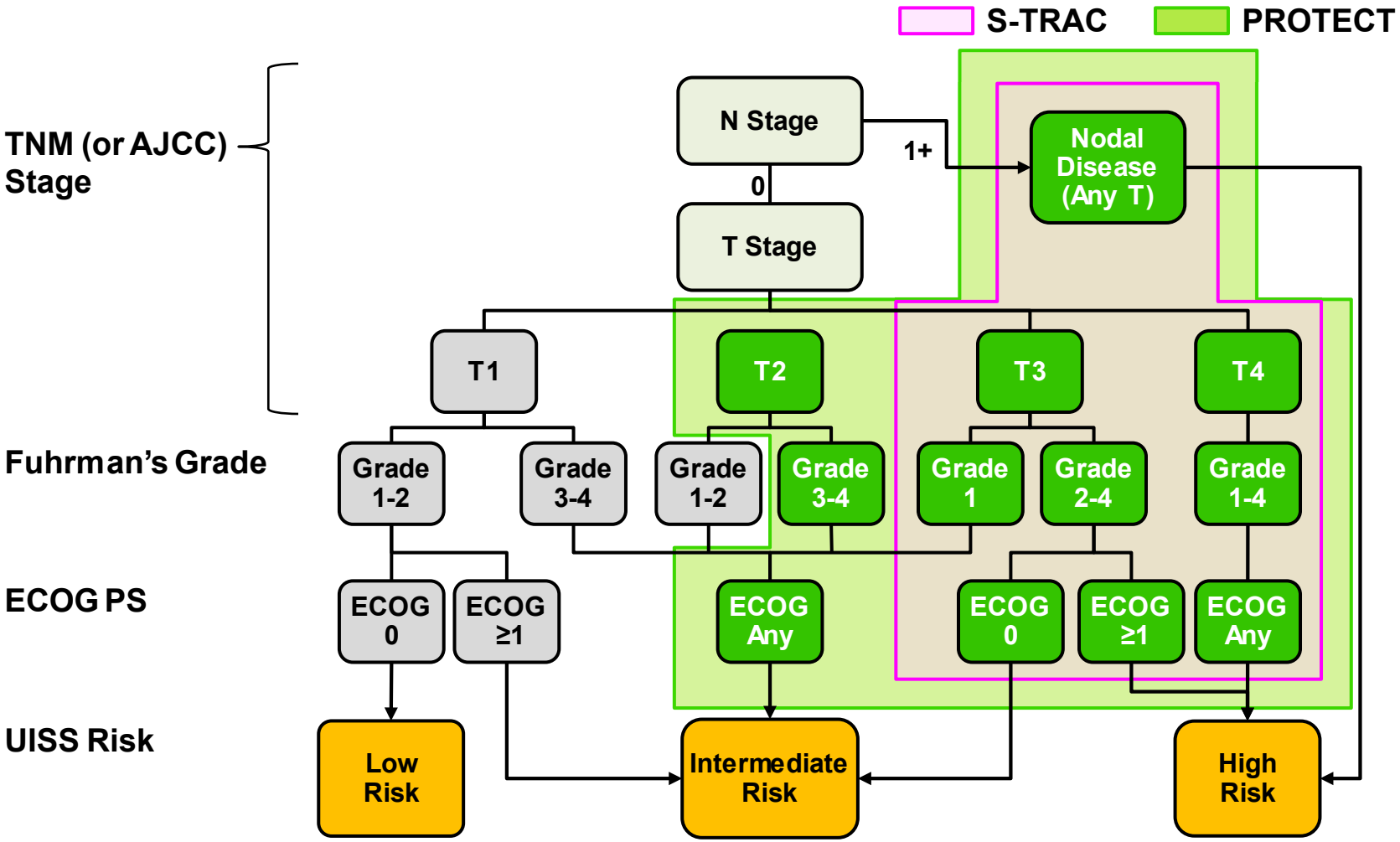



Stratification: partial vs. radical nephrectomy; pathologic staging

**Primary Endpoint: Disease-Free Survival**

a. Staging based on TNM classification per the American Joint Committee on Cancer (AJCC) 2010 version and Fuhrman nuclear grades
b. Starting dose 600 mg assessed for safety at 8-12 weeks and could be escalated to 800 mg or maintained at 600 mg based on patient's tolerability
Presented at ASCO 2017 by Dr. R. Motzer

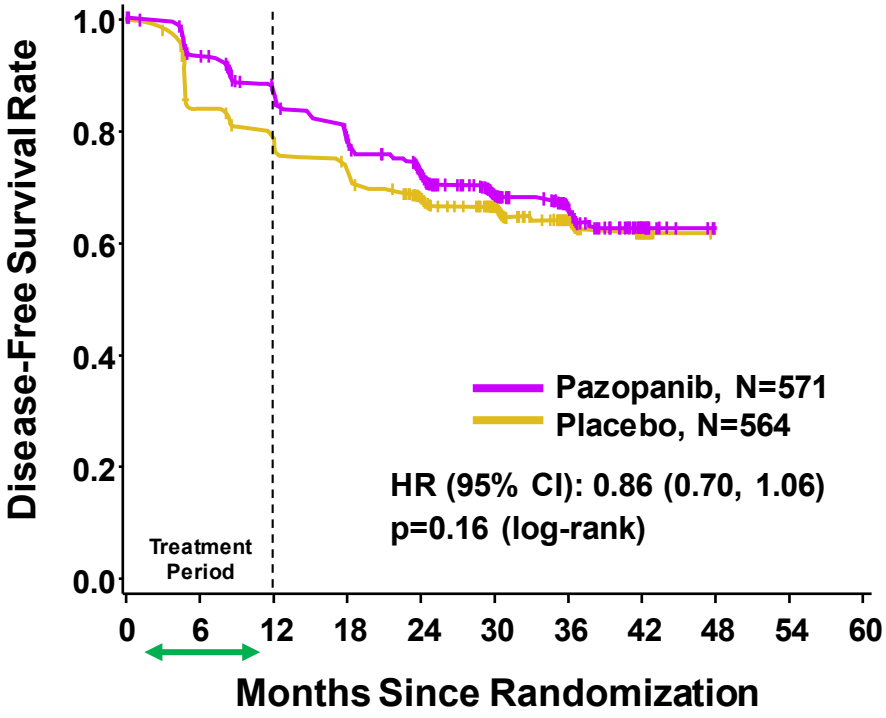
# PROTECT
# UISS Risk Group Assignment




Adapted from: Zisman et al. *JCO* 2002;20:4561.; Lam JS, et al. *J Urol* 2005;74:466-472.

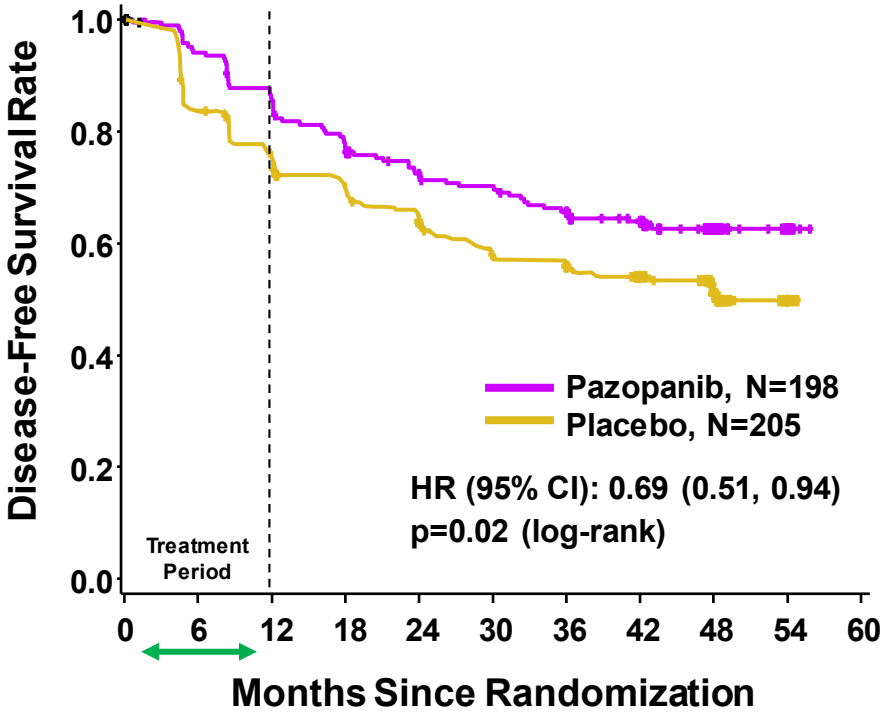
# PROTECT Study Results

## Primary Analysis
## $ITT_{600\ mg}$




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Pazopanib | 571 | 482 | 423 | 382 | 308 | 209 | 118 | 29 | 0 |
| Placebo | 564 | 443 | 394 | 372 | 300 | 213 | 118 | 37 | 0 |

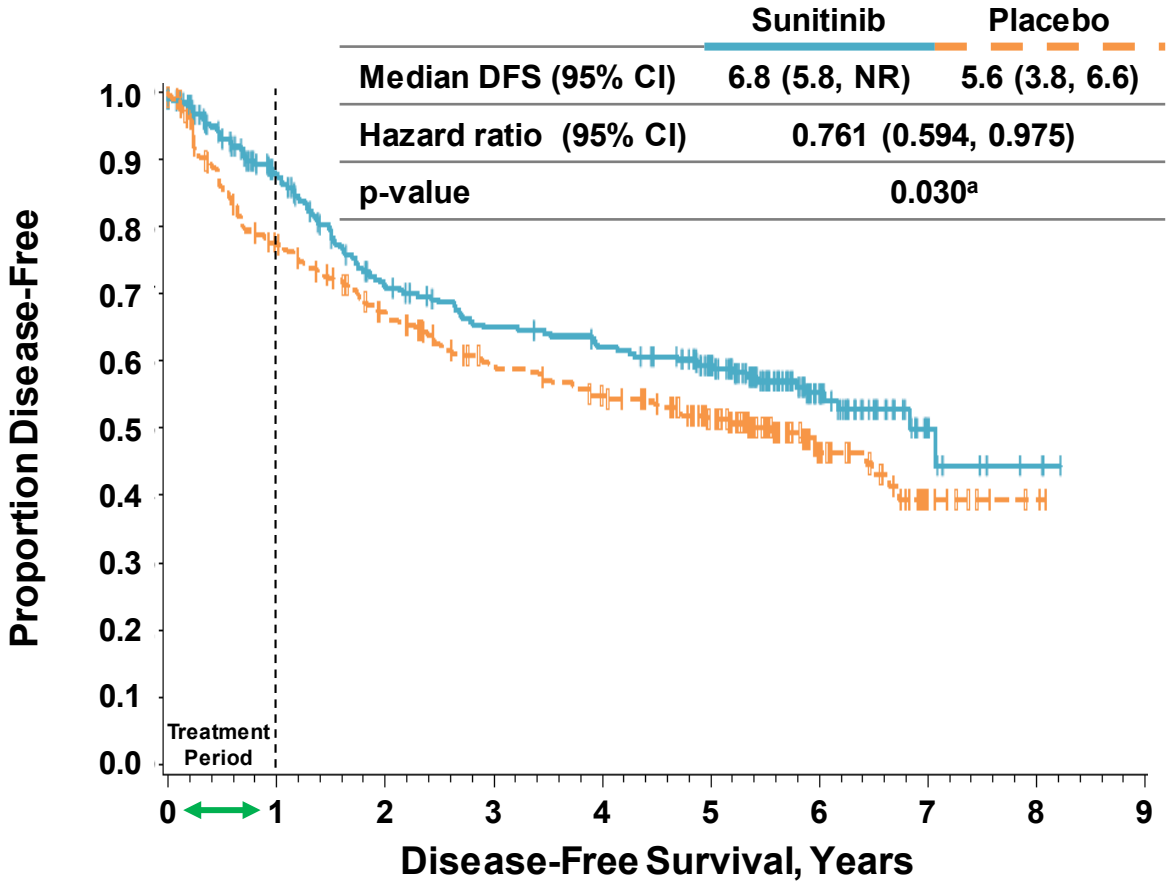
## Secondary Analysis
## $ITT_{800\ mg}$




| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pazopanib | 198 | 176 | 156 | 140 | 128 | 123 | 113 | 102 | 48 | 8 | 0 |
| Placebo | 205 | 169 | 144 | 134 | 119 | 106 | 97 | 85 | 46 | 3 | 0 |

Modified from Motzer RJ et. al. *J Clin Oncol*. doi:10.1200/jco.2017.73.5324.

# S-TRAC
# Primary Endpoint: Disease-Free Survival By Blinded Independent Central Review




| No. at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Sunitinib | 309 | 225 | 173 | 153 | 144 | 119 | 53 | 10 | 3 | 0 |
| Placebo | 306 | 220 | 181 | 150 | 135 | 102 | 37 | 10 | 2 | 0 |

- 24% reduction in relative risk of DFS events is clinically meaningful
- Persistent 8% absolute benefit
- Effect maintained over time

a. Two-sided p-value from log-rank test stratified by UISS high-risk group

# Sunitinib Adverse Events

- Sunitinib has a well-known safety profile
  - No new safety signals in S-TRAC
- Ability to reduce or interrupt dosing for patients who do not tolerate the full dose
- Side effects resolve after discontinuation of treatment
  - No known long-term sequelae
- Clinically manageable with early identification and monitoring

# Benefit/Risk Conclusion

- Favorable benefit/risk profile

- Sunitinib should be an adjuvant treatment option for patients at high risk of recurrent RCC following surgical resection

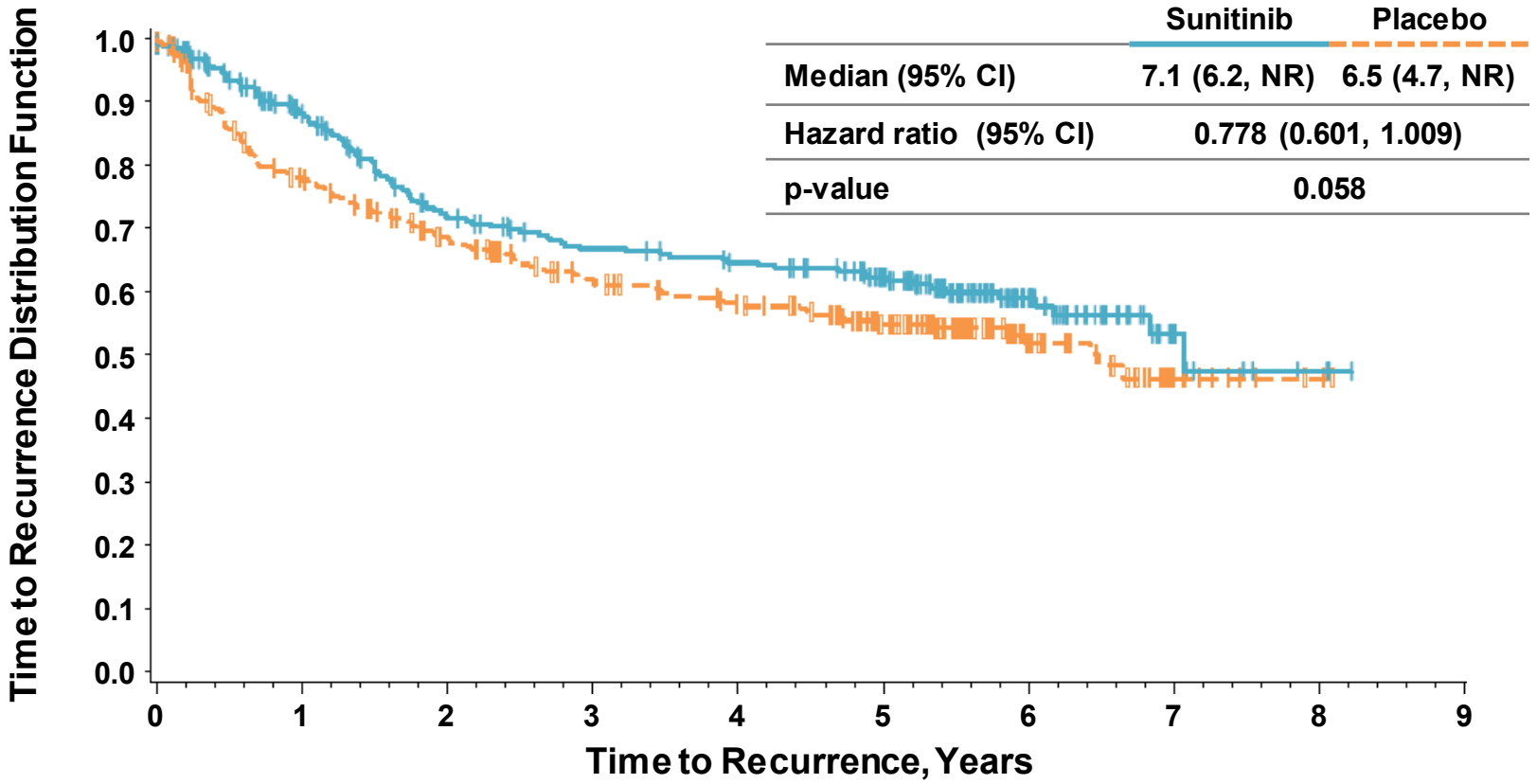
# What Does it Mean for the Patient with RCC at High Risk of Recurrence?

- High-risk patients have 5-year recurrence rate of approximately 60%
- Metastatic RCC is associated with substantial morbidity
- Survival after relapse remains unacceptably low
- No approved adjuvant therapy
- Patients want a higher chance of remaining disease-free

**Sunitinib is a valuable adjuvant treatment option for patients at high risk of recurrence**

# Backup Slides Shown

# S-TRAC ITT
# Time to Recurrence by BICR



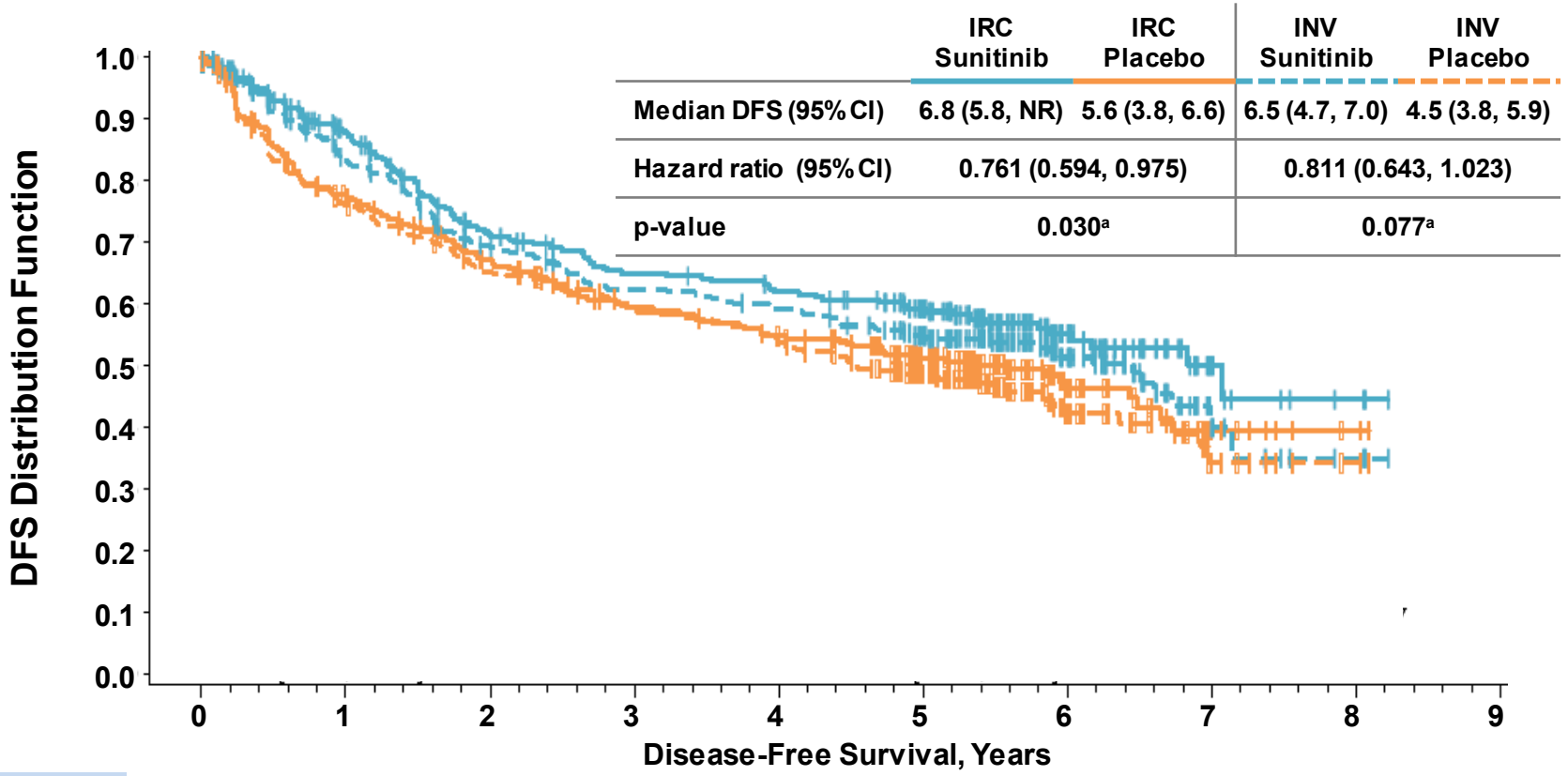

| Number at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Sunitinib | 309 | 226 | 173 | 154 | 145 | 120 | 53 | 10 | 3 | 0 |
| Placebo | 306 | 220 | 181 | 152 | 135 | 102 | 37 | 10 | 2 | 0 |

# Low Discordance in S-TRAC

| Parameter and Disagreement type | Sunitinib N=309 % | Placebo N=306 % | Difference % |
|---|---|---|---|
| Overall disagreement | 27.8 | 27.8 | 0 |
| Early disagreement rate | 36.4 | 24.7 | 11.7 |
| Late disagreement rate | 44.2 | 54.1 | -9.9 |
| Total event disagreement rate | 11.3 | 8.5 | 2.8 |

Intent to Treat Population

# S-TRAC ITT
# Disease-Free Survival by BICR or Investigator Assessment




| Number at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| IRC Sunitinib | 309 | 225 | 173 | 153 | 144 | 119 | 53 | 10 | 3 | 0 |
| IRC Placebo | 306 | 220 | 181 | 150 | 135 | 102 | 37 | 10 | 2 | 0 |
| INV Sunitinib | 309 | 224 | 178 | 158 | 149 | 122 | 55 | 10 | 3 | 0 |
| INV Placebo | 306 | 219 | 184 | 158 | 142 | 106 | 37 | 10 | 2 | 0 |

a. Two-sided p-value from the stratified log-rank test
IRC (BICR)=Blinded Independent Central Review; INV=Investigator Assessments
Patients with disease at baseline are included in the events and their DFS time is 1 day

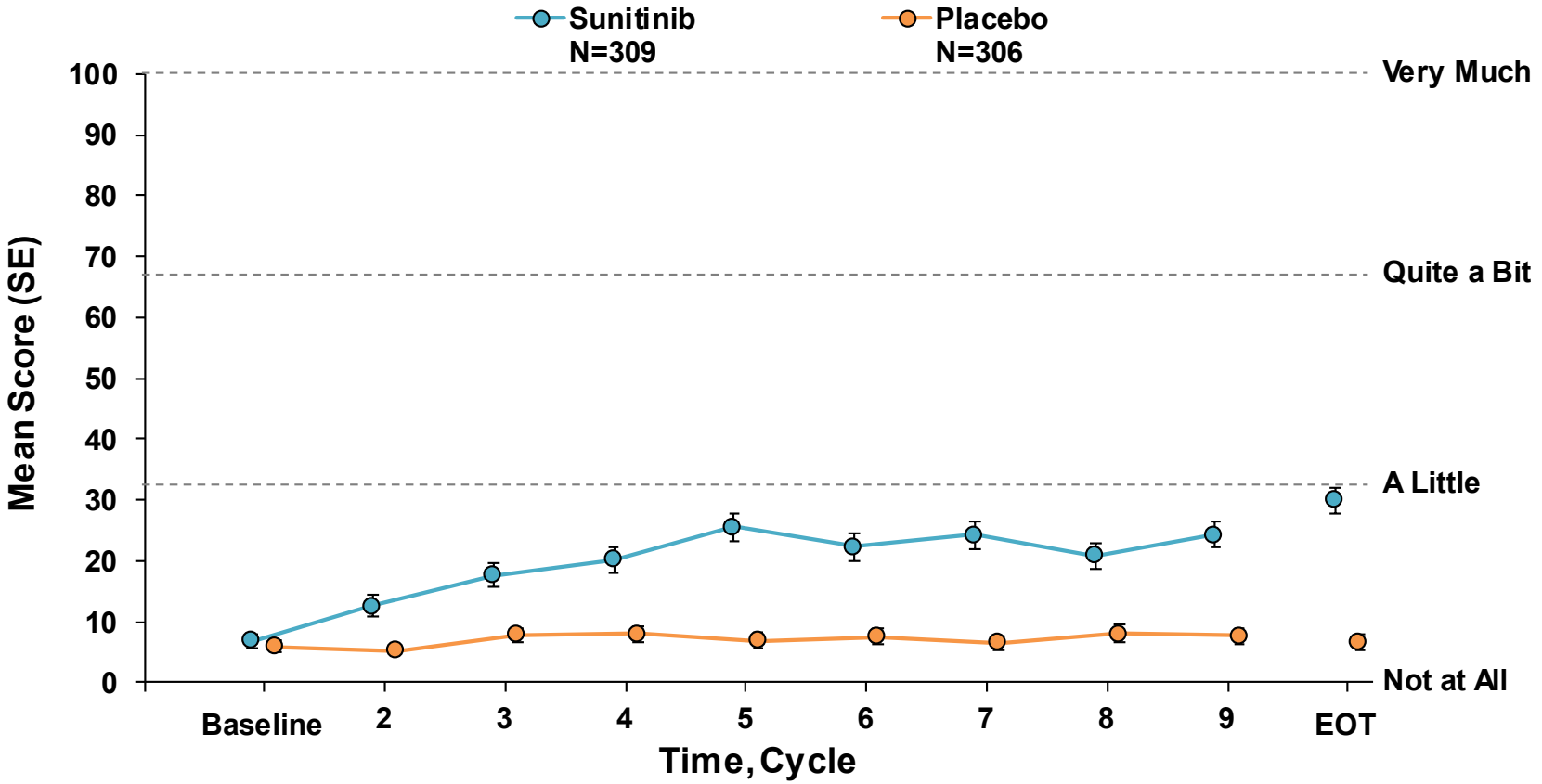
# S-TRAC
# Positive Association of DFS by BICR and OS

| | Overall Survival or Censored ≤5 Years n | Overall Survival >5 Years n |
|---|---|---|
| Disease-Free Survival or censored ≤2 years | 164 | 97 |
| Disease-Free Survival >2 years | 36 | 318 |

| | Statistic |
|---|---|
| Odds ratio | 14.9 |
| Positive predictive value | 0.90 |
| Negative predictive value | 0.63 |

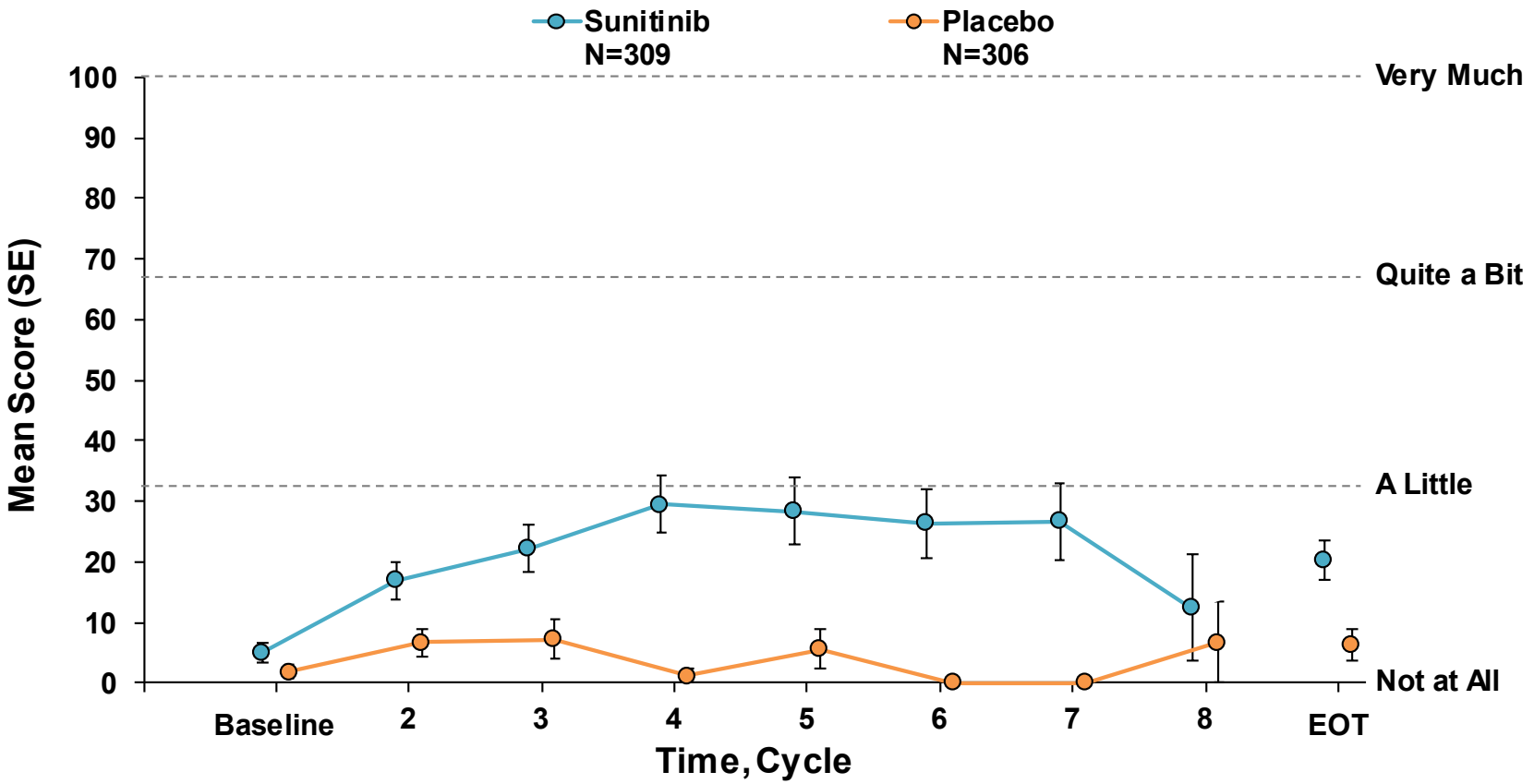
Sunitinib and placebo groups combined

# S-TRAC
# Completers QLQ-C30 Mean Scores – Symptom Scale: Diarrhea




| Number at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Sunitinib | 156 | 153 | 149 | 147 | 150 | 151 | 150 | 152 | 156 | 156 |
| Placebo | 178 | 166 | 174 | 173 | 168 | 175 | 173 | 173 | 178 | 178 |

# S-TRAC
# Discontinuers QLQ-C30 Mean Scores – Symptom Scale: Diarrhea




| Number at Risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Sunitinib | 84 | 67 | 54 | 44 | 34 | 24 | 20 | 8 | 84 |
| Placebo | 53 | 50 | 37 | 28 | 24 | 16 | 9 | 5 | 53 |

# ASSURE Dose Reductions to 25 mg and Amendment to the Starting Dose of 37.5 mg Led to Substantial Differences in Exposure

| | Sunitinib | |
|---|---|---|
| | S-TRAC N=306 | ASSURE N=629 |
| Median Average Daily Dose, mg | 48.2 | 37.5 |
| Median Relative Dose Intensity, % | 88.4 | 77.7 |
| Median Cumulative Dose, mg | 9637.5 | 6800 |
| Mean Duration of Treatment, months | 9.46 | 8.36 |
| Completed 9 Cycles of Treatment, % | 55.6 | 47.1 |
| **Quartiles of Cumulative Dose/Total Number of cycles, mg** | **S-TRAC N=306** | **ASSURE[a] N=334** |
| Q1 | <1052.8 | <827.8 |
| Q2 | 1052.8 to <1261.1 | 827.8 to <1031 |
| Q3 | 1261.1 to <1400 | 1031 to <1246 |
| Q4 | ≥1400 | ≥1246 |

As reported in JAMA from a subset of high-risk (pT3, pT4, node-positive) clear cell renal cancer (ccRCC) patients

# S-TRAC
# Sunitinib Dosing Analyses – As Treated

| | Events/Patients | | Hazard Ratio (95% CI) |
|---|---|---|---|
| Sunitinib completers/relapsed vs. Sunitinib discontinue | 82/193 | 31/113 | 0.95 (0.62, 1.44) |
| Sunitinib dose modifications vs. Sunitinib no dose modifications | 87/236 | 26/70 | 0.84 (0.54, 1.31) |
| Sunitinib dose reductions vs. Sunitinib no dose reductions | 54/140 | 59/166 | 0.84 (0.57, 1.22) |