# Tivozanib
# For the treatment of advanced Renal Cell Carcinoma

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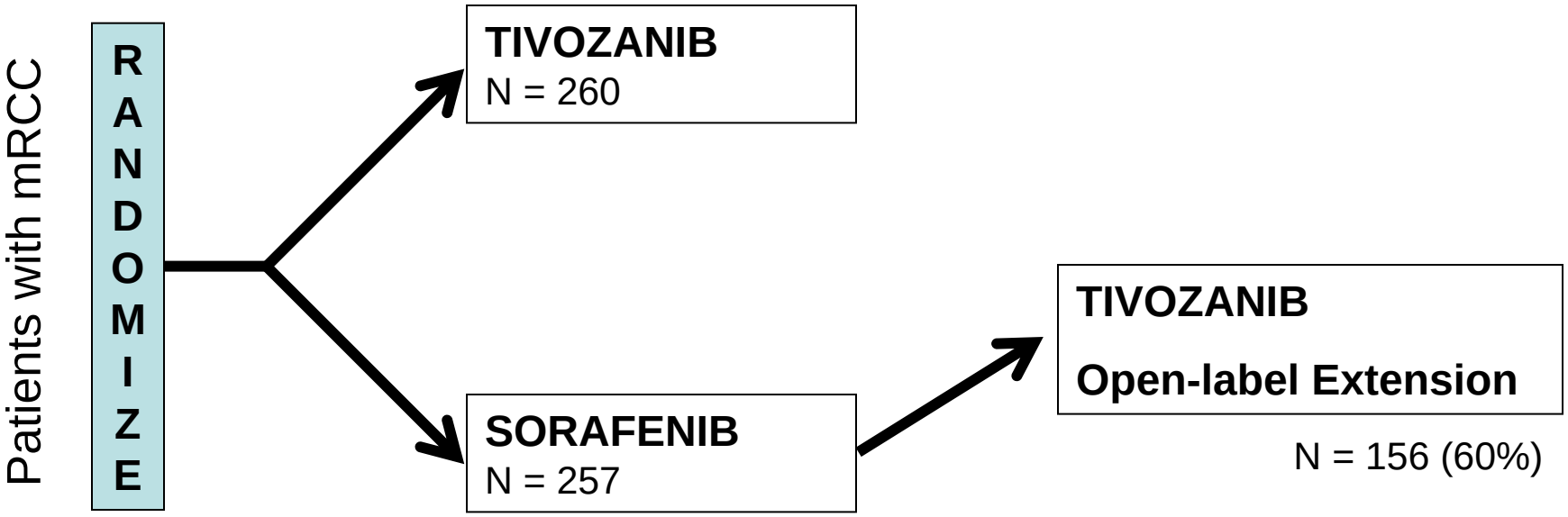
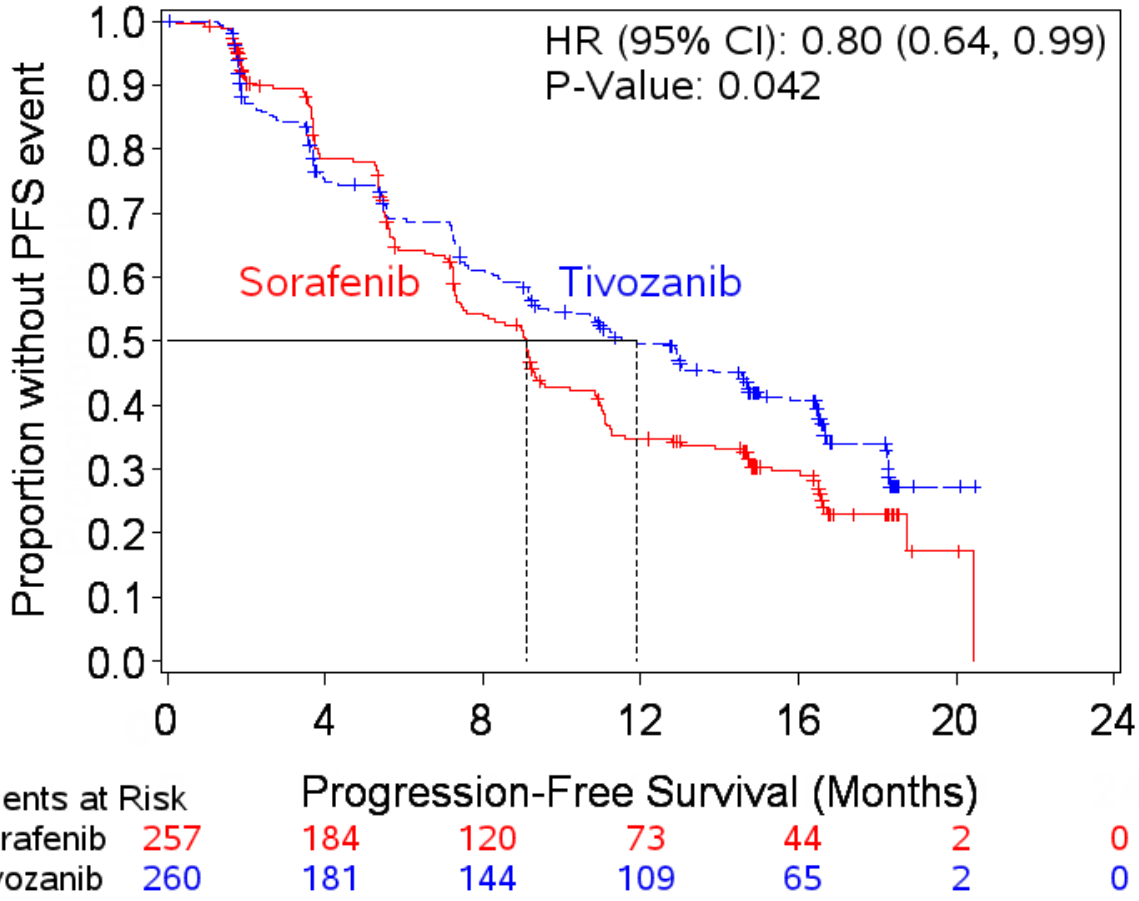
# Trial Schema

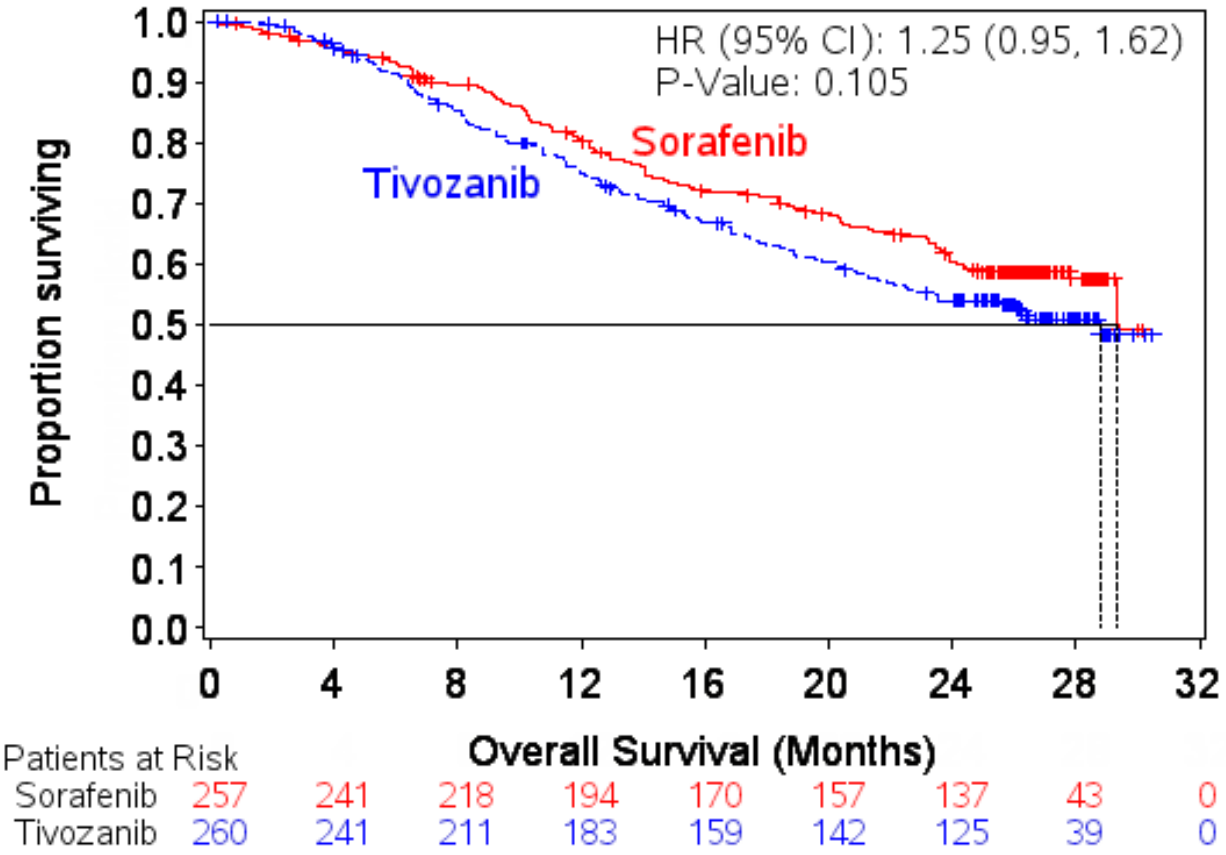



Primary endpoint: PFS

# Improvement in PFS



# Increase in risk of death

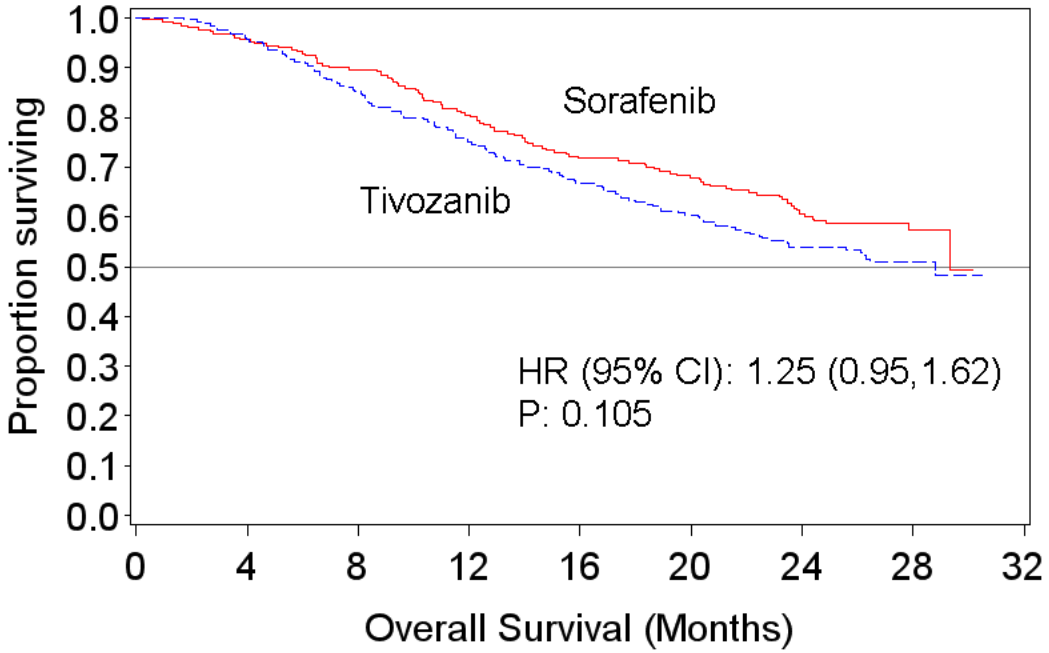


# Concerns

- The inconsistent PFS and OS results and imbalance in post study treatments makes the trial results inconclusive when making a risk-benefit assessment necessary for approval of a drug

- Has the Applicant demonstrated a favorable benefit to risk evaluation for the treatment of renal cell carcinoma in an adequate and well-controlled trial?

# Tivozanib
# Advanced Renal Cell Cancer

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# Outline

- Current Available Therapies
- Trial Design and Conduct
- Applicant's Exploratory Analyses
- Comparable Toxicity Profile
- Question to ODAC

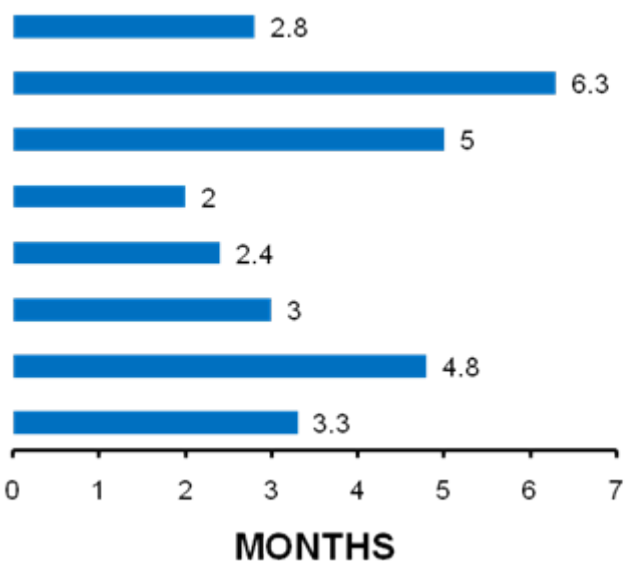
# Currently Approved Targeted Therapies

| Drug | Comparator | Endpoint | Prior Targeted Rx |
|---|---|---|---|
| Sorafenib | Placebo | PFS | No |
| Sunitinib | IFN-α | PFS | No |
| Pazopanib | Placebo | PFS | No |
| Bevacizumab (+ IFN-α) | IFN-α alone | PFS | No |
| Temsirolimus | IFN-α | OS | No; poor prognosis |
| Everolimus | Placebo | PFS | Yes |
| Axitinib | Sorafenib | PFS | Yes |

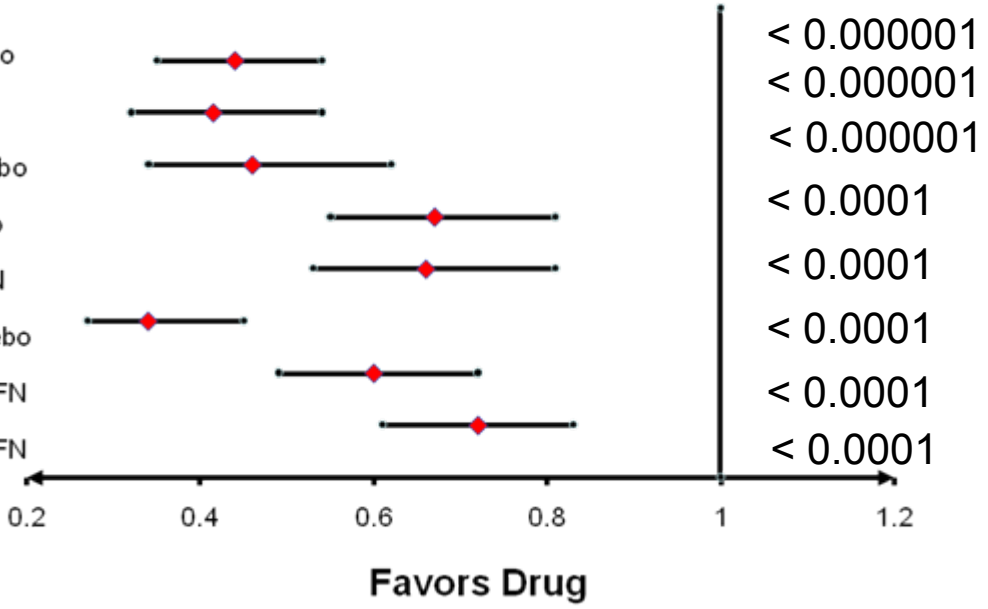
# Progression-Free Survival

## Basis for Prior Approvals

Median PFS Δ

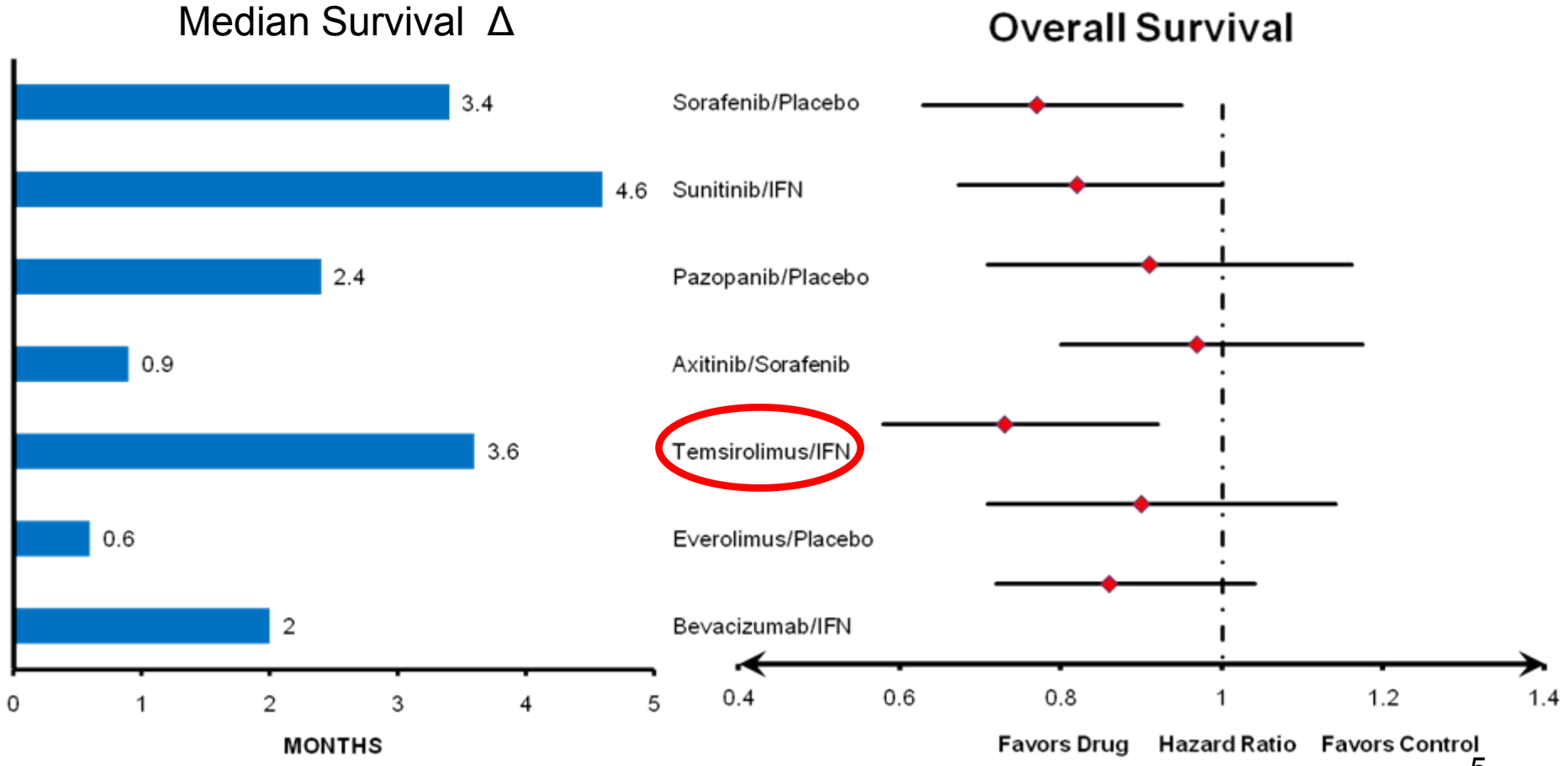



Progression-Free Survival



# Overall Survival

## Basis for Approvals



# Many Trials Have Imbalanced Subsequent Therapy

| | Post-Progression Crossover | | Subsequent Targeted Therapy* | |
|---|---|---|---|---|
| | Allowed | % | **Study Arm** | **Comparator Arm** |
| **Sorafenib**/Placebo | Yes | 48% | --- | --- |
| **Sunitinib**/ IFN-α | Yes | 39% | 53% | 69% |
| **Bevacizumab**/IFN-α | Yes | 4% | 54% | 62% |
| **Pazopanib**/Placebo | Yes | 54% | 22% | 63% |
| **Temsirolimus**/IFN-α | No | --- | --- | --- |
| **Everolimus**/Placebo | Yes | 80% | --- | --- |
| **Axitinib**/Sorafenib | No | --- | --- | --- |

* Includes both study drug and subsequent use of VEGF or MTOR therapies off protocol

# Main Findings

- Phase 2 randomized withdrawal data
- Single Phase 3 trial with inconsistent results
- Advantage in progression-free survival against an active comparator
- Potential increased risk of death
- Should another trial be performed before approval?

# Trial Schema

**517 Patients**
- **Metastatic RCC**
- **Measurable disease**
- **≤ 1 prior therapy**

**RANDOMIZE**

**Study 301**

**TIVOZANIB**
N = 260
1.5 mg daily X 3 weeks then 1 week off

**SORAFENIB**
N = 257
400 mg BID

**Study 902**

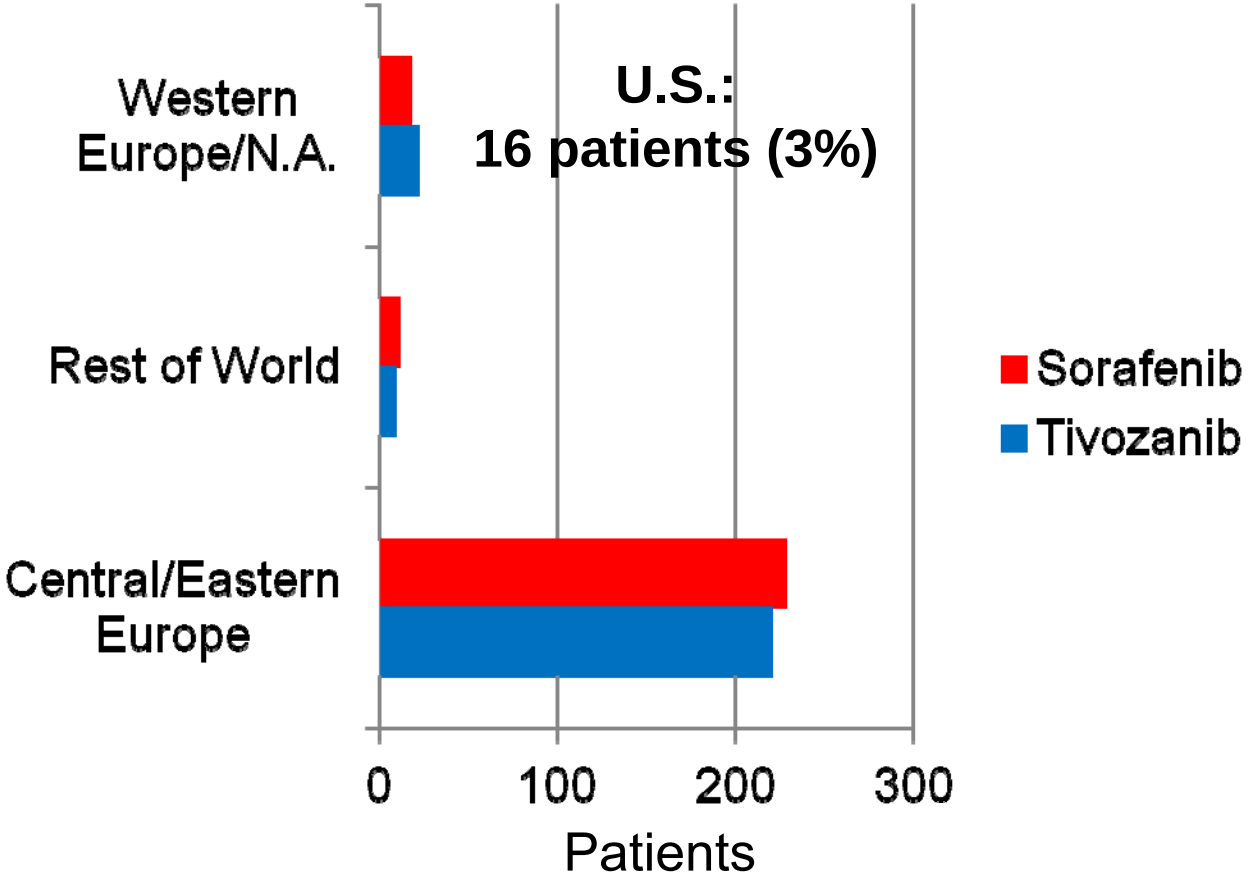
**TIVOZANIB**

**Open-label Extension**

**N = 156 (60%)**

**STRATIFICATION**
1. Geographic Region
2. Prior Treatments
3. Metastatic Sites

# Less than 10% of Patient Population from U.S. or Western Europe



# Subsequent Targeted Therapy

- **Sorafenib arm: 163 (63%)**
  - "Crossover" to tivozanib: 156
  - Subsequent therapy off protocol: 8*
- **Tivozanib arm: 41 (16%)**
  - Subsequent therapy off protocol: 41
    - Western Europe/N.A.: 10/22 **(45%)**
    - Central/Eastern Europe: 30/229 **(13%)**
    - Rest of World: 1/9 **(11%)**

* Some patients who crossed over also received subsequent targeted therapies off-protocol

# Statistical Analysis Plan

- Primary endpoint: Progression-free survival by independent radiologist in the ITT population
  - Stratified (# of prior treatments, # metastatic organs) log-rank test
  - 90% power with 310 PFS events
- First secondary endpoint: Overall survival
- Duration of response and objective response rates

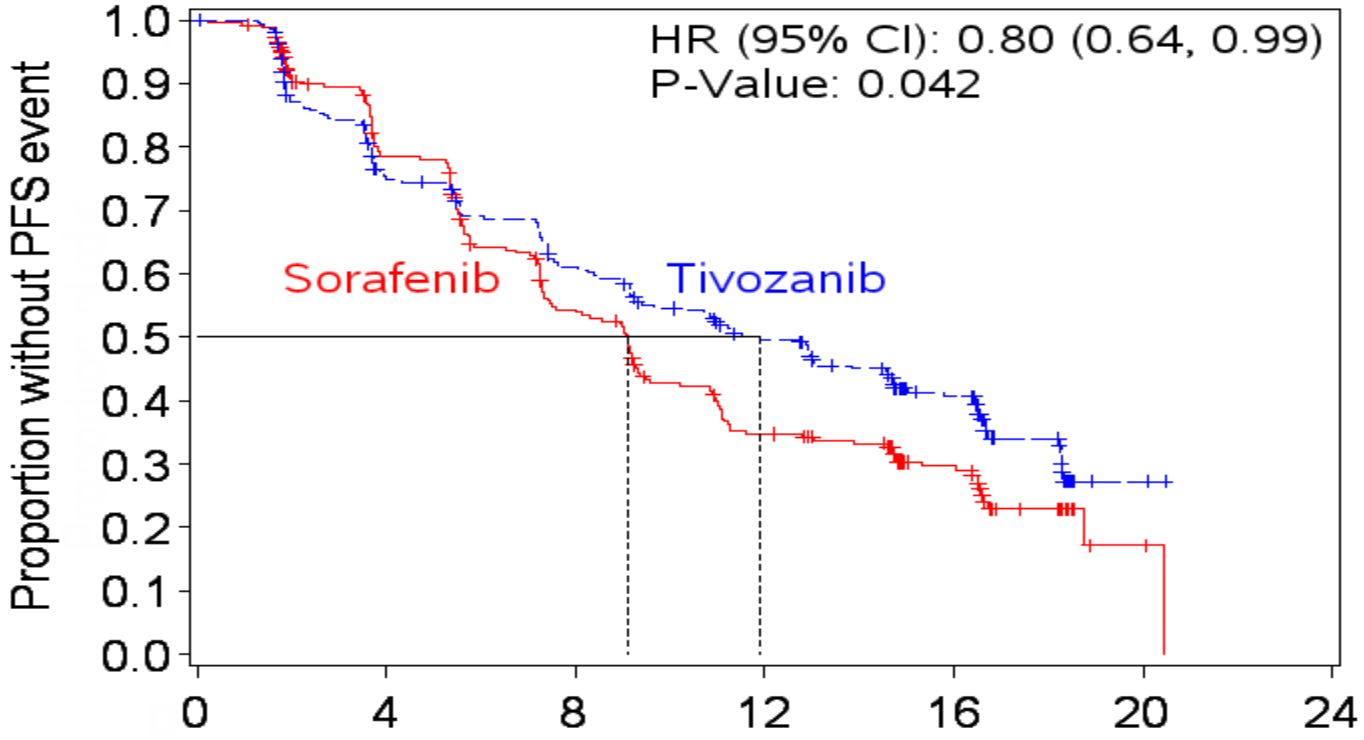
# Baseline Disease Characteristics

| | **Tivozanib** (N = 260) | **Sorafenib** (N = 257) |
|---|---|---|
| Median Time Since Diagnosis | 15 mos | 17 mos |
| Prior Treatments | | |
| 0 | 70% | 70% |
| ≥ 1 | 30% | 30% |
| MSKCC Prognostic Group | | |
| Favorable | 54% | 60% |
| Intermediate | 45% | 39% |
| Poor | 0.8% | 0.4% |

# Progression-Free Survival
## Primary Efficacy Endpoint

| | Tivozanib N=260 | Sorafenib N=257 |
|---|---|---|
| PFS event (%) | 153 (59) | 168 (65) |
| Number of patients with progression (%) | 139 (54) | 156 (61) |
| Number of patients with deaths (%) | 14 (5) | 12 (5) |
| Median PFS in months (95% CI) | 11.9 (9.3, 14.7) | 9.1 (7.3, 9.5) |
| Hazard ratio (95% CI) | 0.80 (0.64, 0.99) | |
| P-value | 0.042 | |

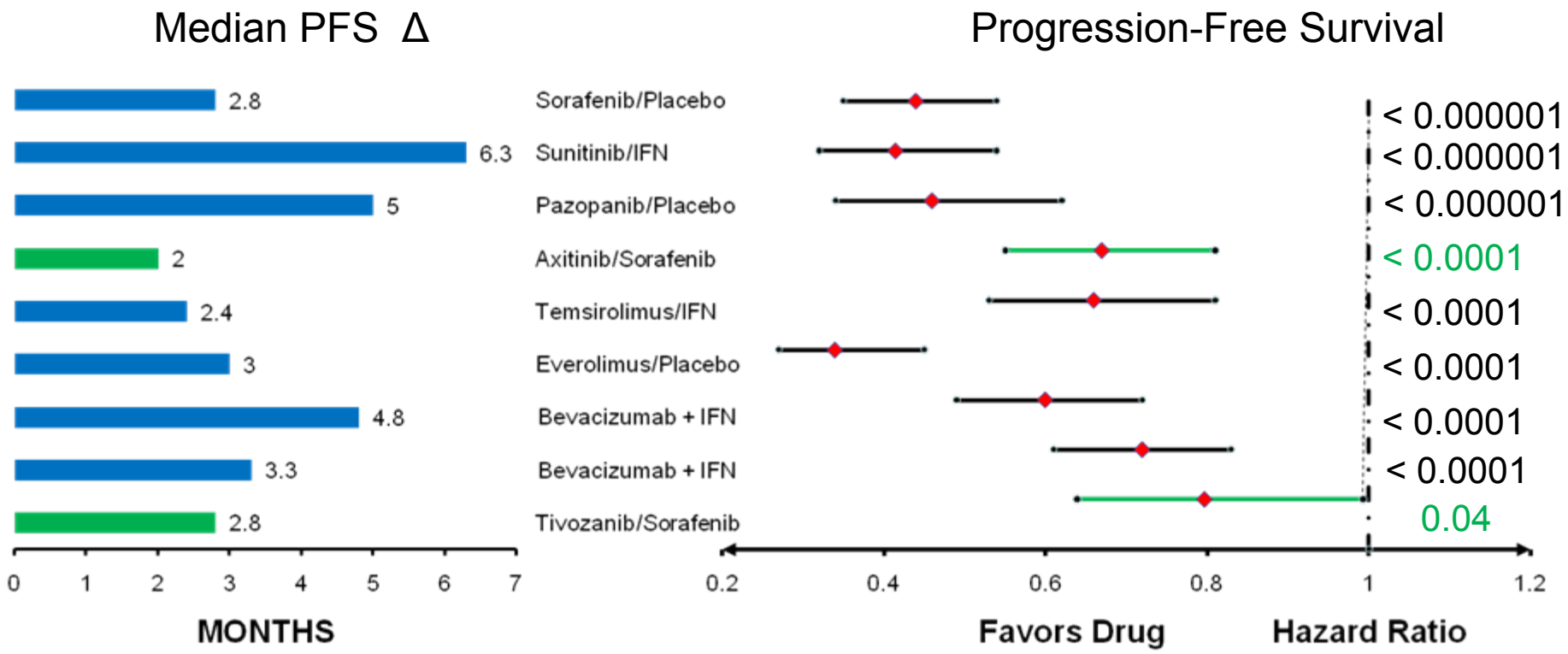
# Kaplan-Meier Plot for PFS




| Patients at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Sorafenib | 257 | 184 | 120 | 73 | 44 | 2 | 0 |
| Tivozanib | 260 | 181 | 144 | 109 | 65 | 2 | 0 |

# Progression-Free Survival

## (Not for Comparison)

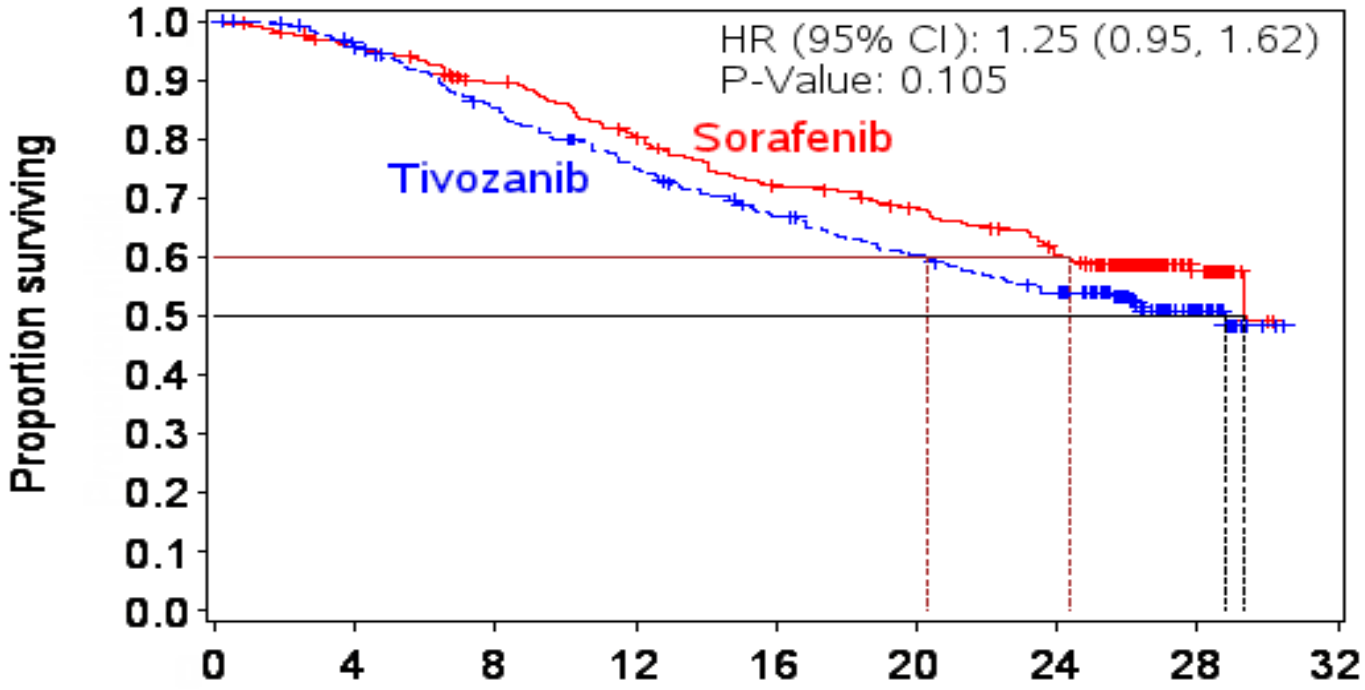



Trials in green were the only ones to use a targeted therapy (Sorafenib) as an active comparator

# Overall Survival

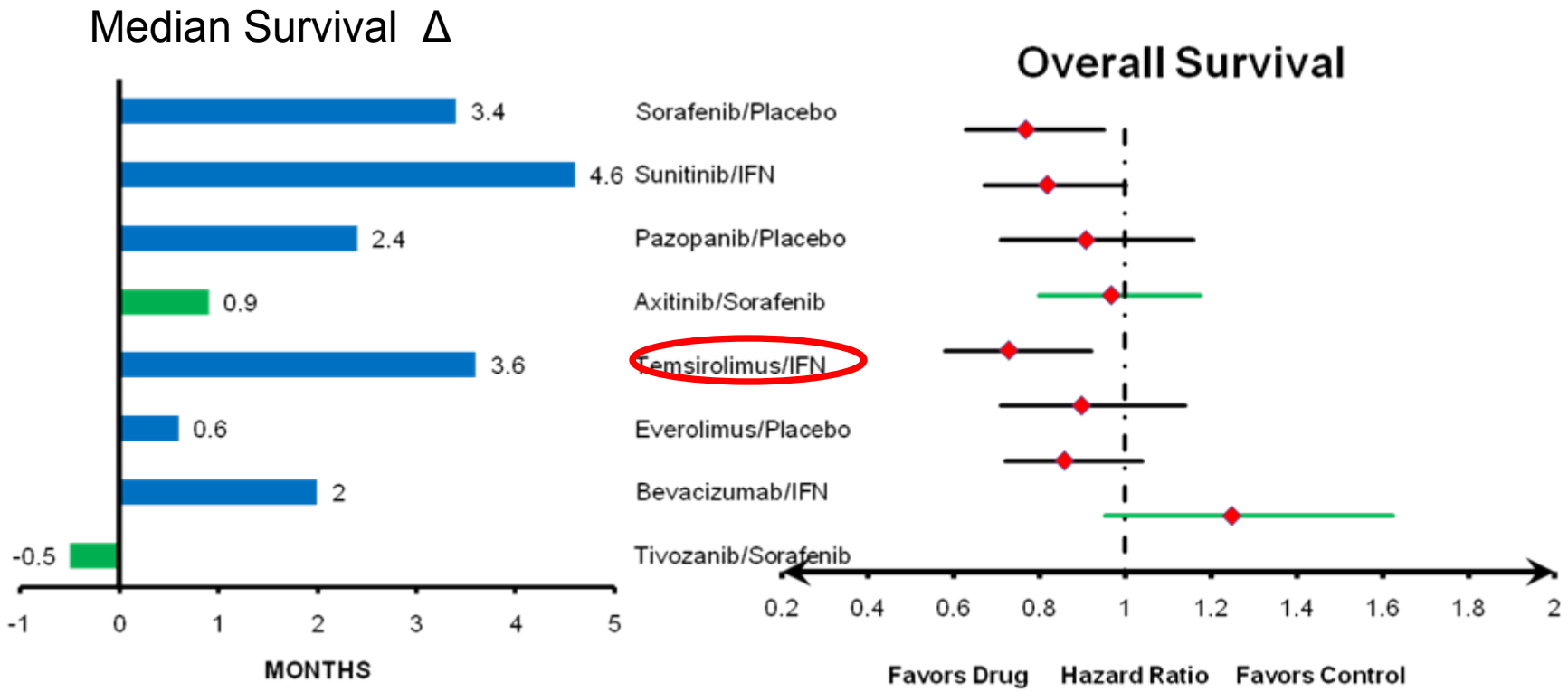
| | **Tivozanib** N = 260 | **Sorafenib** N = 257 |
|---|---|---|
| Events | 118 (45%) | 101 (39%) |
| Median (months) (95% CI) | 28.8 (22.5, NE) | 29.3 (29.3, NE) |
| Hazard Ratio (95% CI) | 1.25 (0.95, 1.62) | |
| p-value | 0.105 | |

# Kaplan-Meier Plot for Overall Survival



# Targeted Therapies: Overall Survival

## (Not for Comparison)

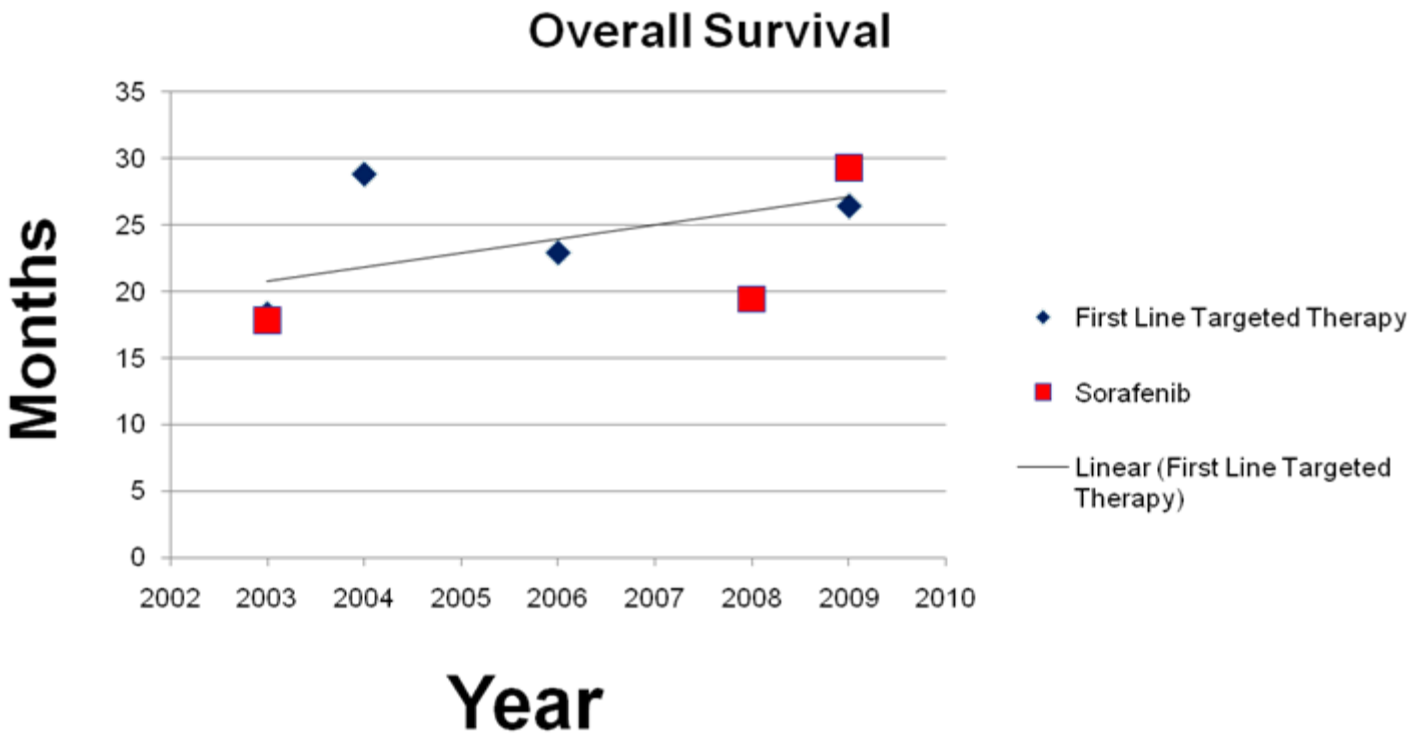


# *Post Hoc* Exploratory Analyses

- Post-progression survival
- Subgroup analyses
  - Region
  - Exposure
  - Subsequent therapy
- Long median survival

**Hypothesis Generating**

# Effect of Year of Study on Overall Survival

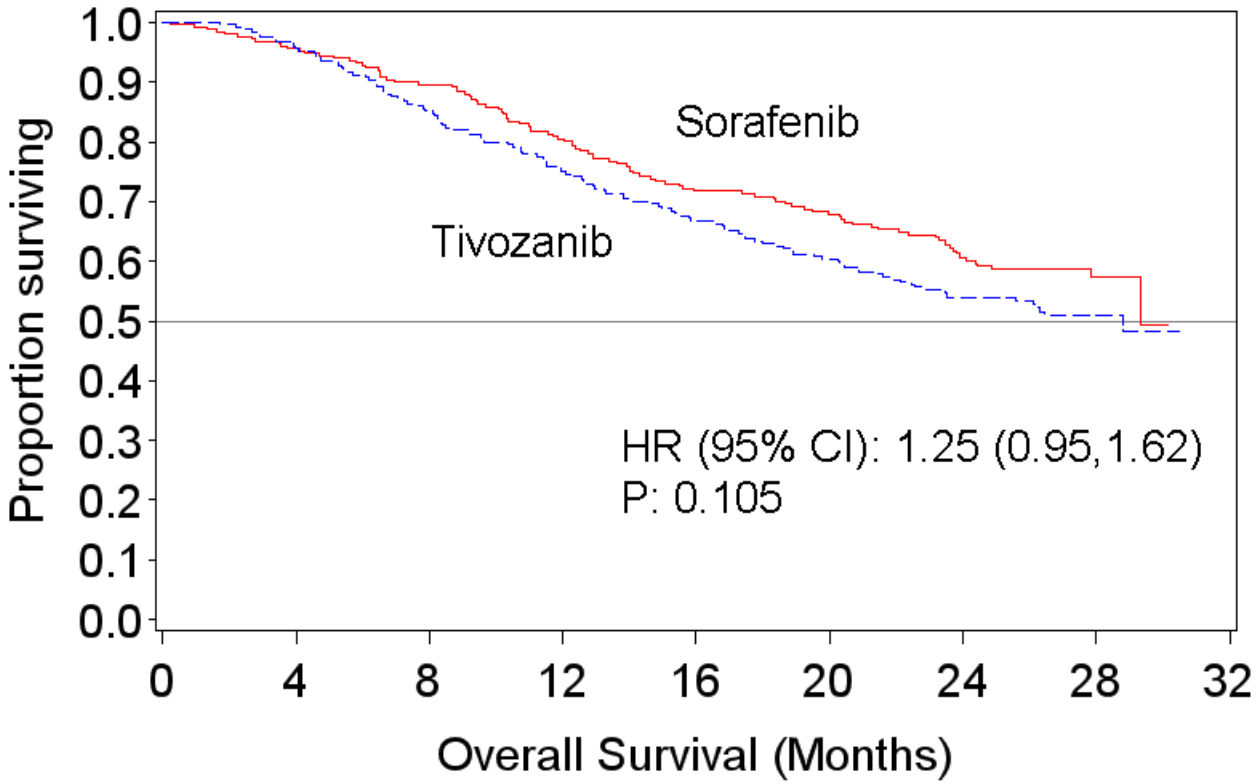


# Efficacy Summary

- Improved progression-free survival against active comparator
  - H.R.: 0.8  p value: 0.042
- Negative trend in overall survival
  - H.R.: 1.25  p value: 0.1

# SAFETY

# Increase in Risk of Death



# Deaths in the Phase 3 Trial

| **Deaths** | **Tivozanib N=259 (%)** | **Sorafenib N=257 (%)** |
|---|---|---|
| All Deaths (data cutoff 8-27-2012) | 118 (45) | 101 (39) |
| Deaths within 30 days of treatment (data cutoff 6-1-12) | 21 (8.1) | 14 (5.4) |
| Deaths attributed to PD within 30 days | 8 (3) | 2 (0.1) |
| Deaths attributed to AEs within 30 days | 13 (5) | 12 (4.7) |

# Adverse Events by Region

| | Central/Eastern Europe N = 456 | North America/ Western Europe N = 40 | Rest of World N = 20 |
|---|---|---|---|
| Grade 1-4 | 93% | 100% | 90% |
| Grade 3-4 | 59% | 88% | 75% |

# Adverse Events in > 10% of Patients

| | Tivozanib N = 259 | | Sorafenib N = 257 | |
|---|---|---|---|---|
| | Grade 1-4 | Grade 3-4 | Grade 1-4 | Grade 3-4 |
| All | 90% | 57% | 97% | 68% |
| Hypertension | 46% | 27% | 36% | 18% |
| Diarrhea | 22% | 2% | 33% | 7% |
| Dysphonia | 21% | 0 | 5% | 0 |
| Fatigue | 19% | 5% | 16% | 4% |
| Weight Decreased | 18% | 3% | 21% | 4% |
| Asthenia | 15% | 4% | 17% | 3% |
| Stomatitis | 15% | 0.8% | 12% | 0.8% |
| Infections | 15% | 2% | 17% | 4% |
| Back Pain | 13% | 3% | 8% | 2% |
| PPE | 13% | 2% | 54% | 17% |
| Abdominal Pain | 12% | 1% | 11% | 0.8% |
| Nausea | 12% | 0.4% | 8% | 0.4% |
| Dyspnea/Exertional Dyspnea | 12% | 2% | 10% | 2% |
| Decreased Appetite | 11% | 0.4% | 10% | 0.4% |

# Adverse Events in > 10% of Patients

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| Decreased Appetite | 11% | 0.4% | 10% | 0.4% |

# Adverse Events of Concern*

| | Tivozanib N = 259 | | | Sorafenib N = 257 | | |
|---|---|---|---|---|---|---|
| Grade | All | 3-4 | 5 | All | 3-4 | 5 |
| Hypertension | 120 | 71 | 1 | 96 | 47 | 0 |
| Hemorrhagic Events | 28 | 5 | 1 | 14 | 2 | 1 |
| Arterial Events | 20 | 12 | 4 | 19 | 8 | 4 |
| Venous Events | 6 | 1 | 1 | 3 | 1 | 2 |
| Cardiac Failure | 4 | 2 | 2 | 7 | 3 | 2 |

* These adverse events are on-therapy or within 30 days following discontinuation

# Safety Summary

OS most important safety (and efficacy) endpoint

- Potential decrement in OS
  - HR 1.25, p = 0.11
  - 25% increase in the potential risk of death on the tivozanib arm
- AE profile is comparable to other drugs for mRCC
- Serious toxicities. Hypertension, cardiac dysfunction, thromboembolism, hepatic dysfunction and pancreatitis have caused deaths on tivozanib

# Summary

- 20% improvement in PFS against sorafenib
- 25% potential increase in death compared to sorafenib
- Comparative safety profile
  - **Tivozanib**: higher HTN, hemorrhage, and dysphonia
  - **Sorafenib**: higher PPE, diarrhea

# Why do we care about Overall Survival?

- Progression-free survival is primarily a radiological endpoint
- Overall survival assures both safety and efficacy
- Critical for the risk-benefit analysis
- Important endpoint for patients

# Hypotheses

- Sequential therapy versus monotherapy
- Sorafenib is more effective than tivozanib for overall survival endpoint
- Tivozanib has greater delayed toxicity or toxicity not recognized

# Conclusion

- Flawed trial design
- Internal inconsistency
- Uninterpretable Overall Survival results
- Inconclusive risk-benefit assessment

# FDA Review Team

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