A Statistician's Reflections on the Tivozanib Experience

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Tivozanib
For the treatment of advanced Renal Cell Carcinoma

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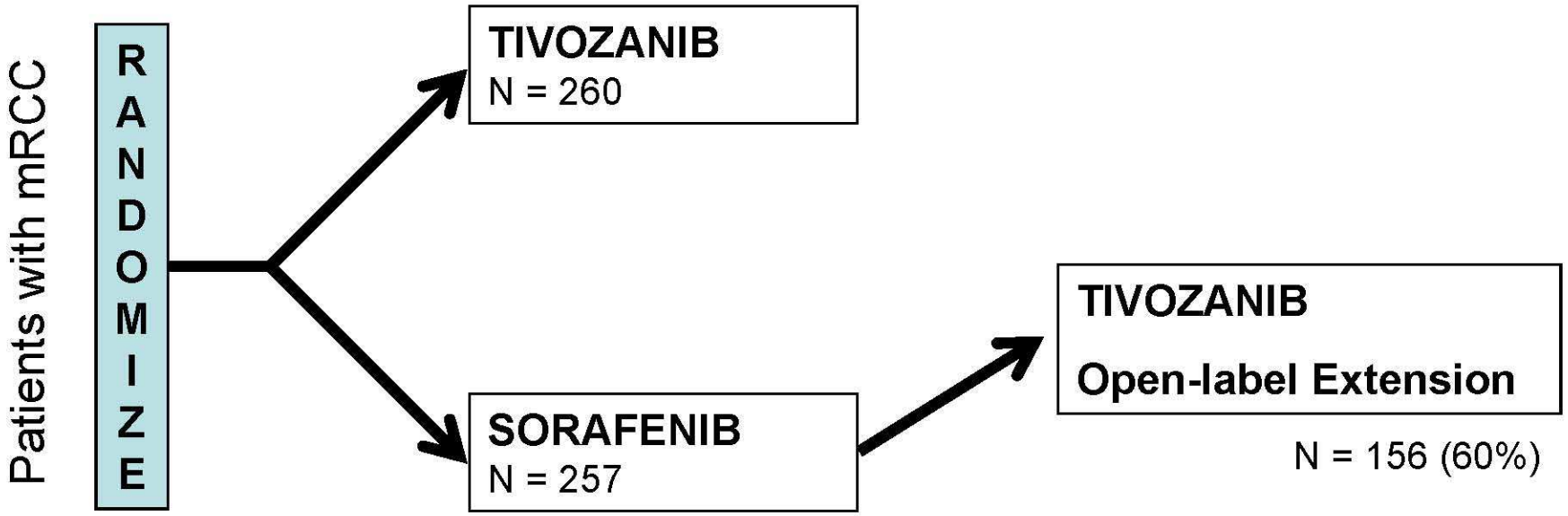
Source: ODAC slide deck - FDA

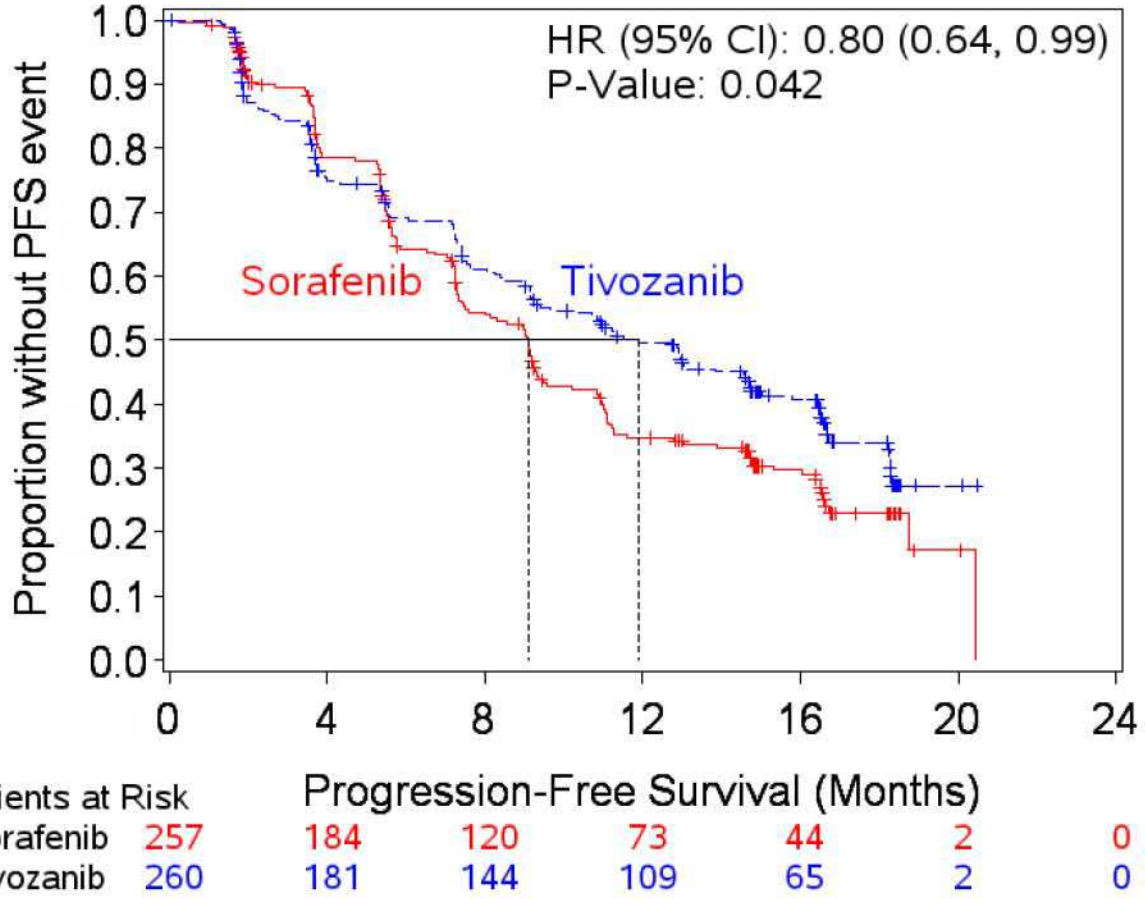
Trial Schema



Primary endpoint: PFS

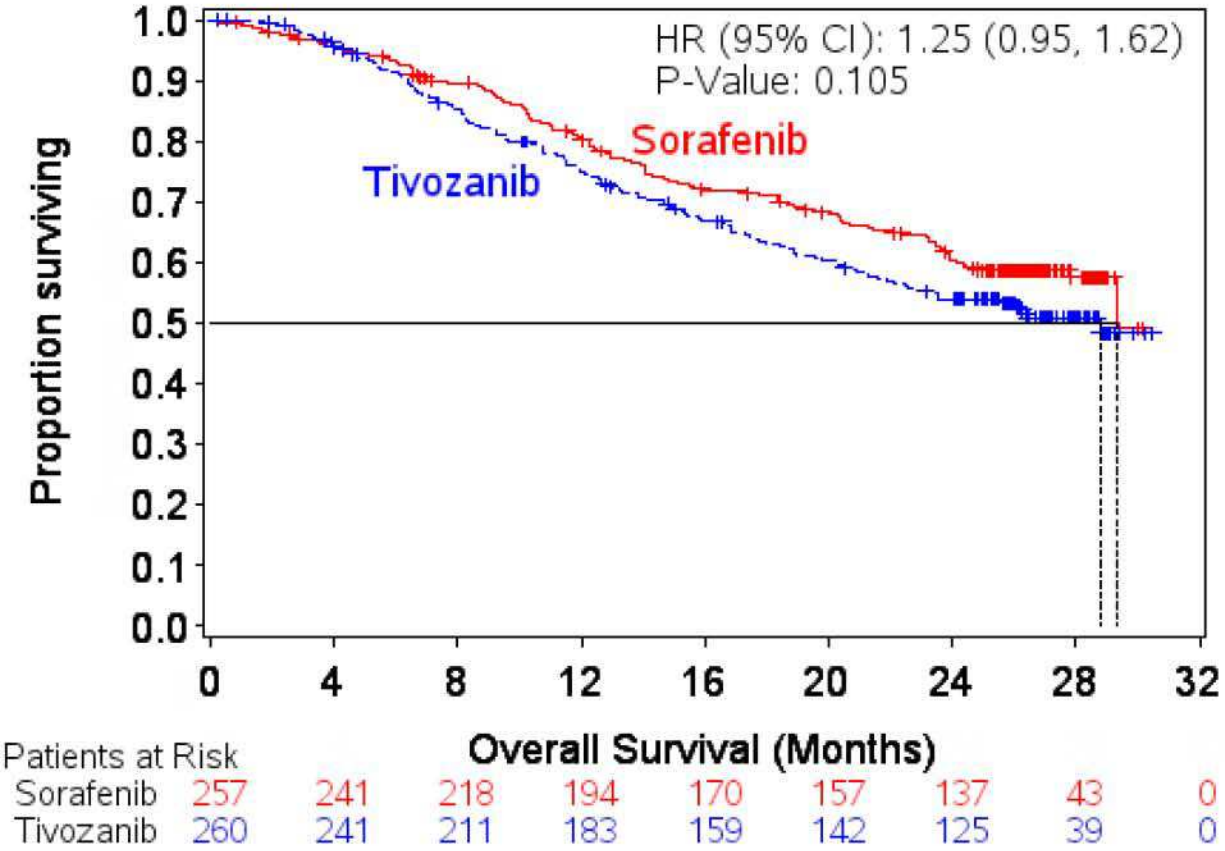
Source: ODAC slide deck - FDA

Improvement in PFS



Source: ODAC slide deck - FDA

Increase in risk of death



Source: ODAC slide deck - FDA

Concerns

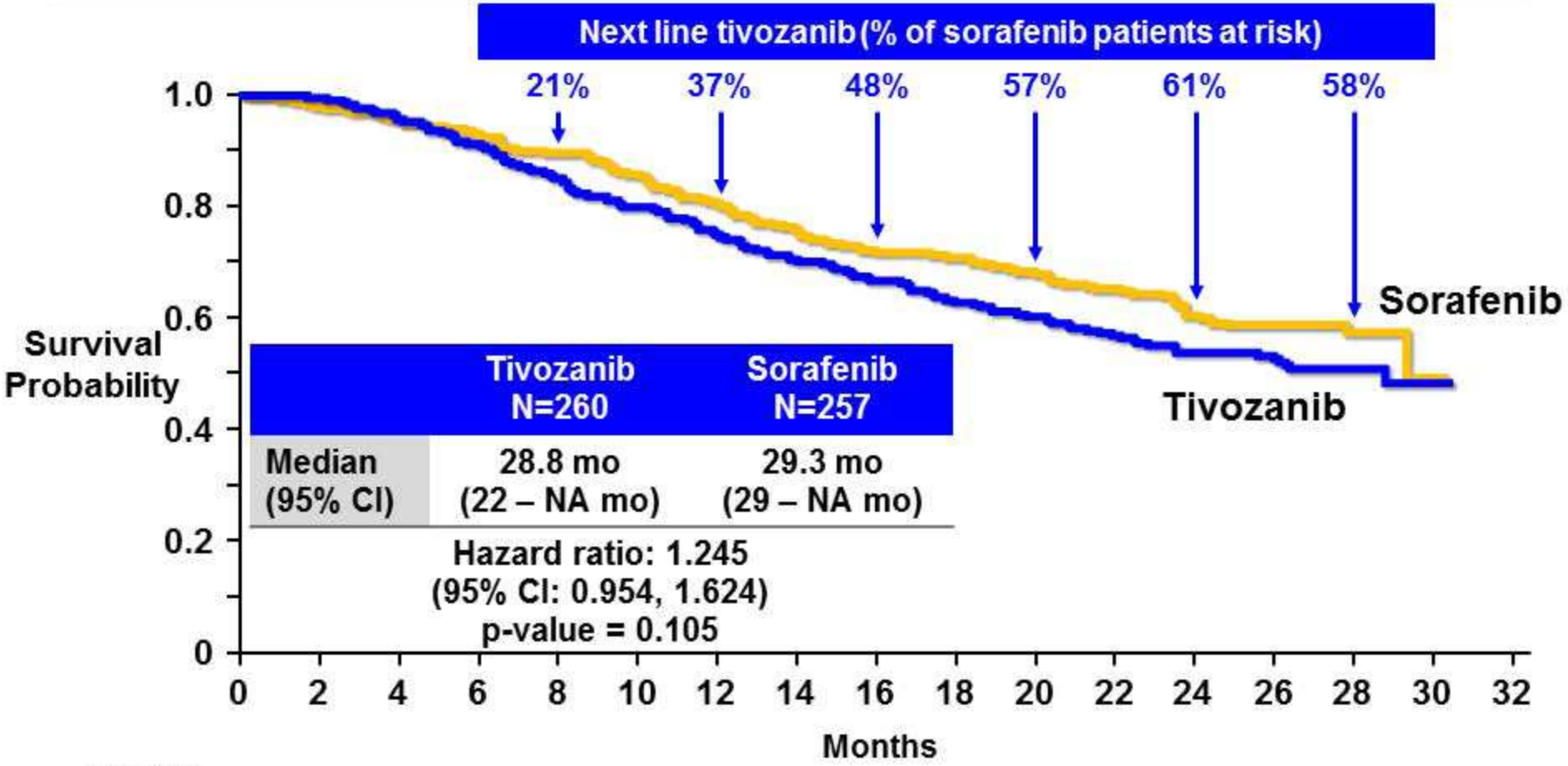
- The inconsistent PFS and OS results and imbalance in post study treatments makes the trial results inconclusive when making a risk-benefit assessment necessary for approval of a drug

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

Source: ODAC slide deck - FDA

Do AVEO and Astellas offer an explanation?

Overall Survival in Study 301



# At Risk																
Tivozanib 260	256	241	227	211	198	183	170	159	148	142	133	125	89	39	2	0
Sorafenib 257	249	241	232	218	208	194	181	170	167	157	151	137	98	43	3	0

Source: ODAC slide deck – Sponsor

Next-Line Targeted Therapy

ITT Population	Tivozanib Study 301 (N=260)	Sorafenib Study 301 (N=257)
Next-line targeted therapy (%)	34 (13%)	162 (63%)
Tivozanib (Study 902)	0	156
Off-protocol	34	6

Source: ODAC slide deck - Sponsor

Study 301 Stratified Based on 3 Criteria

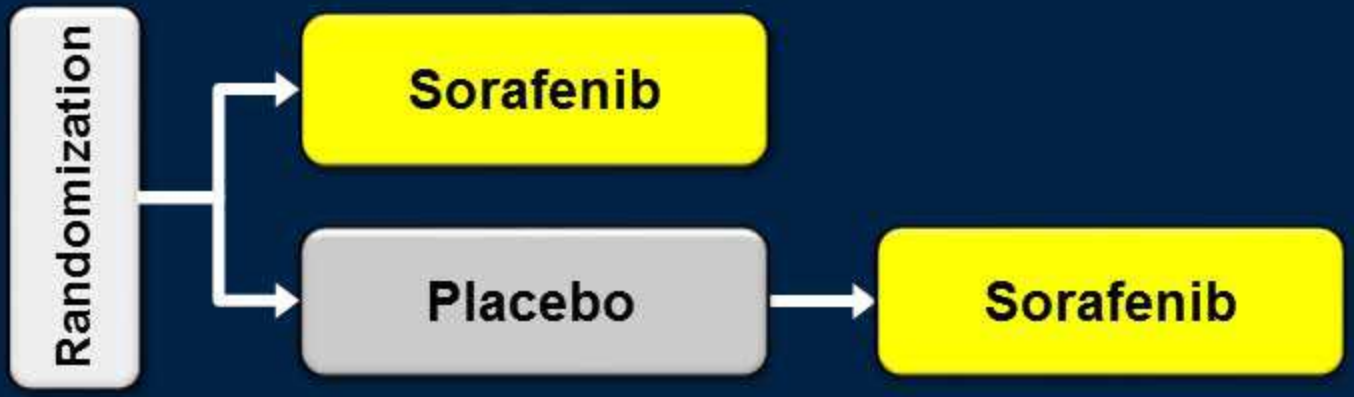
- Prior treatment for RCC (0 or 1)
- # of metastatic sites (1 or ≥ 2)
- Geographic region
  - Central / Eastern Europe (CEE) = 88%
  - N. America* / Western Europe = 8%
  - Rest of World = 4%

Source: ODAC slide deck - Sponsor

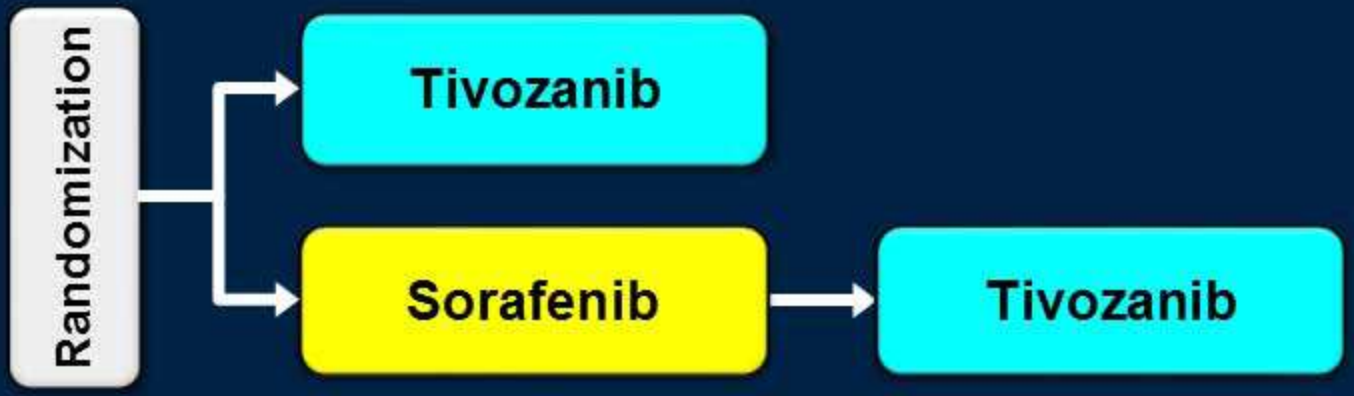
* 16 (3%) from US

Subsequent TKI Use Confounds OS

1. 1 TKI vs 1 TKI (e.g., Sorafenib Trial[1])



2. 1 TKI vs 2 TKIs (Study 301)



1. Escudier, NEJM 2007

Source: ODAC slide deck - Sponsor

Reflections

- You can’t analyze your way out of a study design flaw
- It’s not just about the primary endpoint
- Think through – and model/simulate – all aspects of your design
- Be wary of design changes intended to stimulate enrollment