E2804
The BeST Trial

A randomized Phase II Study of VEGF, RAF Kinase and MTOR Combination Targeted Therapy with Bevacizumab, Sorafenib and Temsirolimus in Advanced Renal Cell Carcinoma

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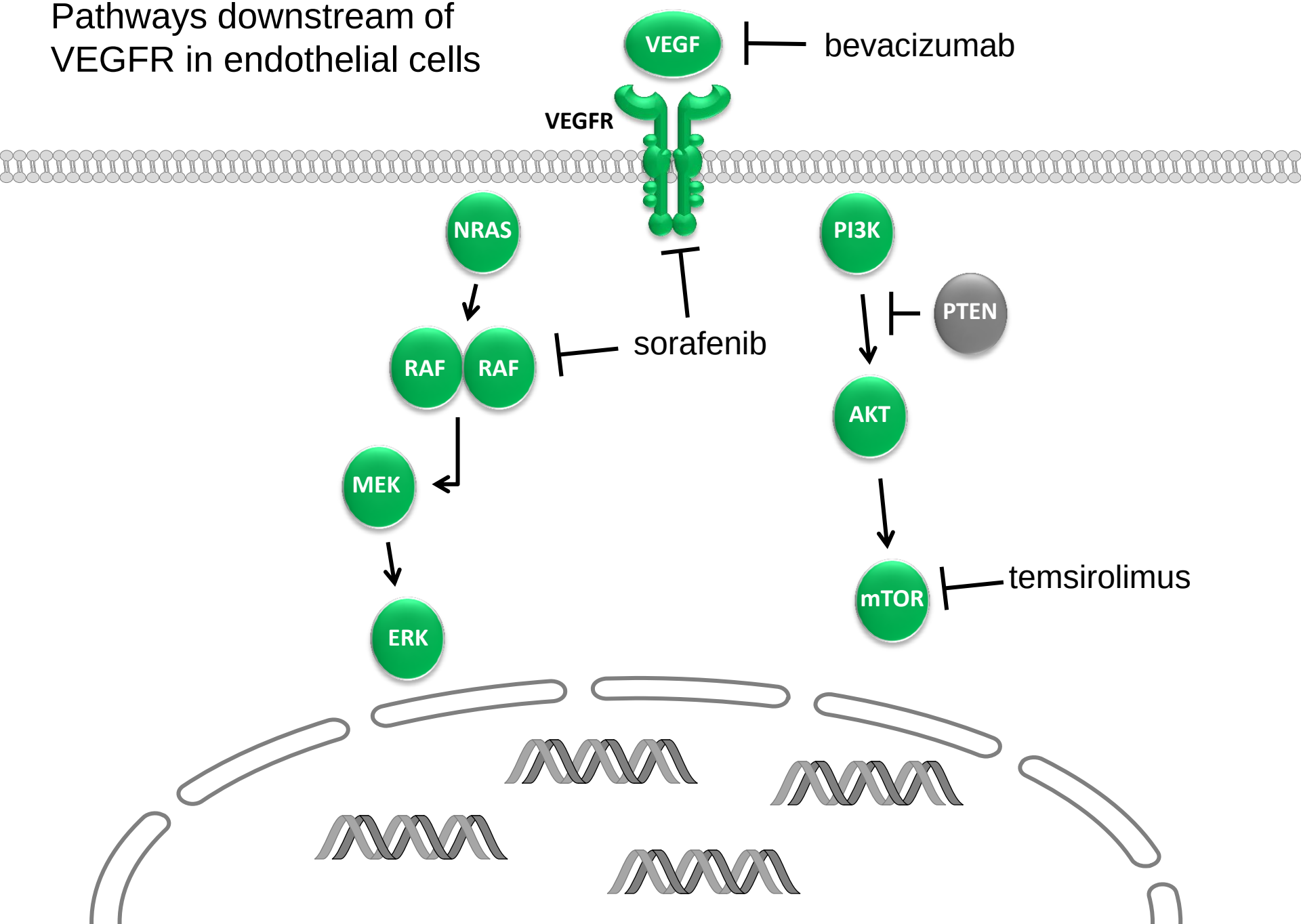
Hypothesis

- Targeting multiple growth and survival pathways in vascular endothelial cells will result in suppression of escape mechanisms to anti-angiogenic therapy in renal cell carcinoma

Pathways downstream of VEGFR in endothelial cells



Design

- Randomized phase II trial, designed to find the best combination regimen in comparison to bevacizumab alone for potential comparison to best available single-agent therapy in a phase III trial
  - Single-agent bevacizumab (Arm A) chosen as control because it is the most selective agent & known single-agent efficacy
- Incorporating combination regimens (dose & schedule) determined in previous phase I trials
  - Bevacizumab/temsirolimus (Arm B)
  - Bevacizumab/sorafenib (Arm C)
  - Sorafenib/temsirolimus (Arm D)

Yang JC et al. N Engl J Med. 2003 Jul 31;349(5):427-34.; Bukowski RM et al. J Clin Oncol. 2007 Oct 10;25(29):4536-41.; Moroney J et al. Clin Cancer Res. 2012 Sep 28. [Epub ahead of print]; Azad NS et al. J Clin Oncol. 2008 Aug 1;26(22):3709-14.; Davies MA et al. Clin Cancer Res. 2012 Feb 15;18(4):1120-8.

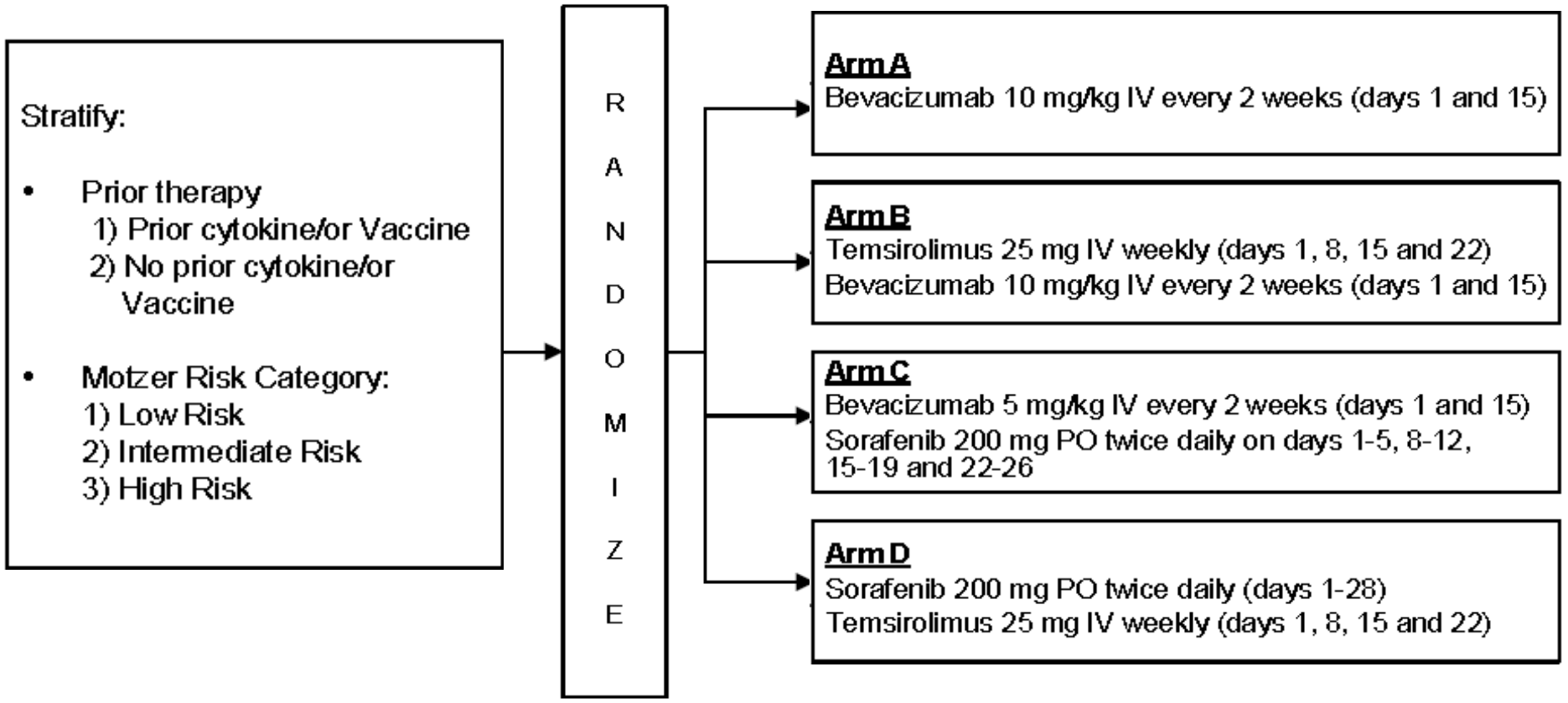
Statistical assumptions

- The study was designed to detect a 67% improvement in median PFS on the combination arms, compared to single-agent bevacizumab (median 9 vs. 15 months) using a one-sided log-rank test with 10% Type I error.

- To assure that there are 80 eligible patients per arm, total accrual of 90 patients per arm (360 total patients)

- Full information would exist when 104 of 160 eligible patients on a pair of arms had progressed or died.

Schema



Key eligibility: ≥ 75% clear cell, prior nephrectomy required unless high burden of disease elsewhere, no prior VEGF, VEGFR or mTOR inhibitors

Objectives

- Primary:
  - Progression-free survival
- Secondary
  - Safety
  - Response rate (tie-breaker if PFS no different)
    - In the absence of improved PFS, RR > 20% would be considered worthy of further study
  - Overall survival
  - Tissue-based predictive biomarker analysis (pending)

Study conduct

	Arm A bevacizumab	Arm B bevacizumab/ temsirolimus	Arm C bevacizumab/ sorafenib	Arm D sorafenib/ temsirolimus
Randomized	89	91	90	91
Ineligible	2	6	3	5
Withdrew before treatment	1	4	0	0
Eligible & treated	86	81	87	86

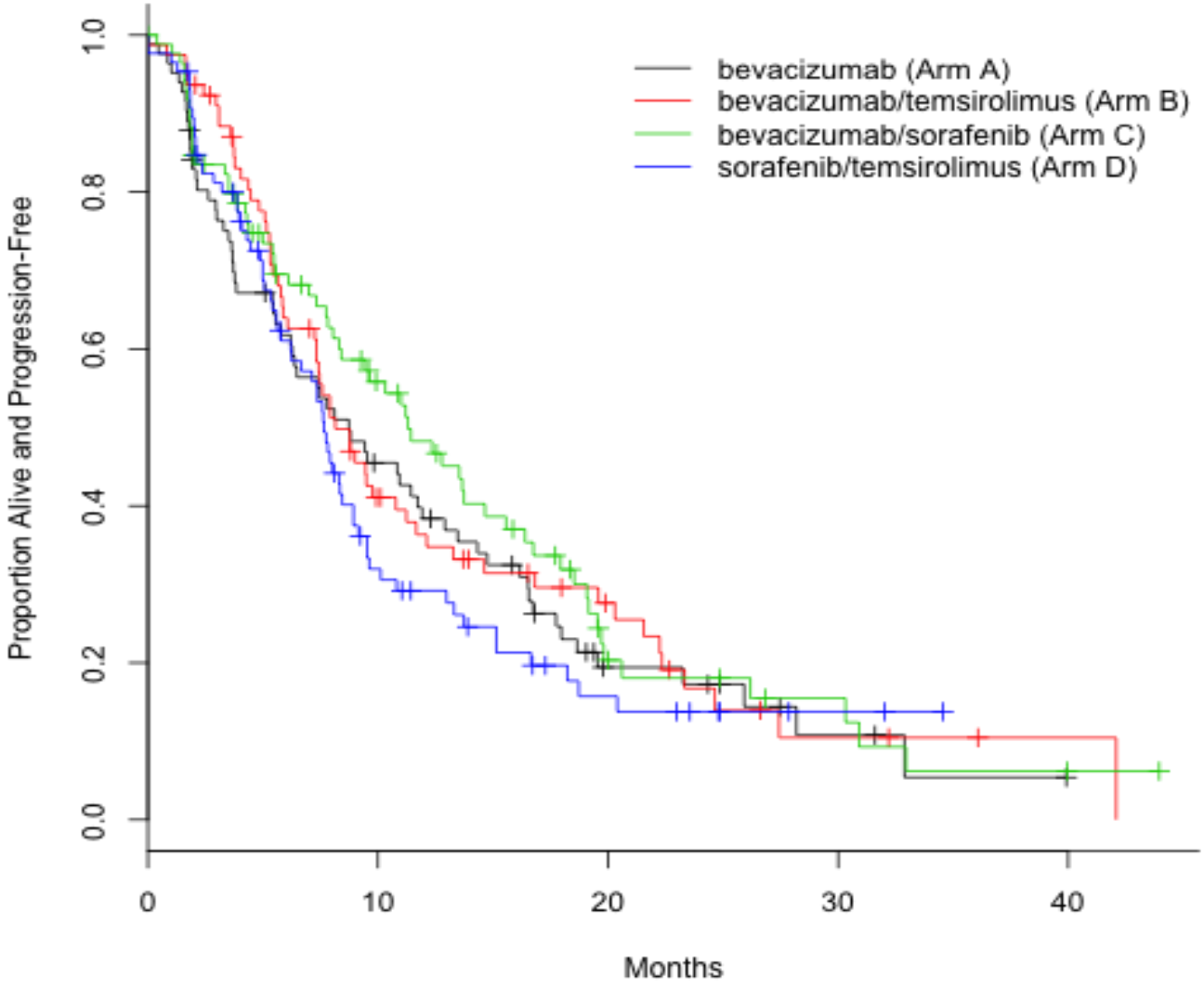
Reason for withdrawal	%
Disease progression	60
Adverse events	21
Patient refusal	7
Death on study	4
Other	8

Demographics

	Arm A bevacizumab	Arm B bevacizumab/ temsirolimus	Arm C bevacizumab/ sorafenib	Arm D sorafenib/ temsirolimus	Total
Male gender (%)	73	69	69	80	73
Age (median)	63	61	61	59	61
Histology (% clear cell)	95	98	93	91	94
MSKCC risk category (low/inter/high)	31 41 28	32 40 28	29 43 28	36 37 27	32 40 28
Prior nephrectomy (%)	86	90	87	85	87

Only prior therapy and MSKCC risk category were stratification factors

Progression-free survival



PFS hazard ratios

	Regimen	Hazard ratio	90% CI	P value	Median PF (months)
Arm A	bevacizumab	reference			8.7
Arm B	bevacizumab/temsirolimus	0.91	0.68-1.23	0.62	7.3
Arm C	bevacizumab/sorafenib	0.84	0.62-1.13	0.32	11.3
Arm D	sorafenib/temsirolimus	1.11	0.83-1.49	0.55	7.7

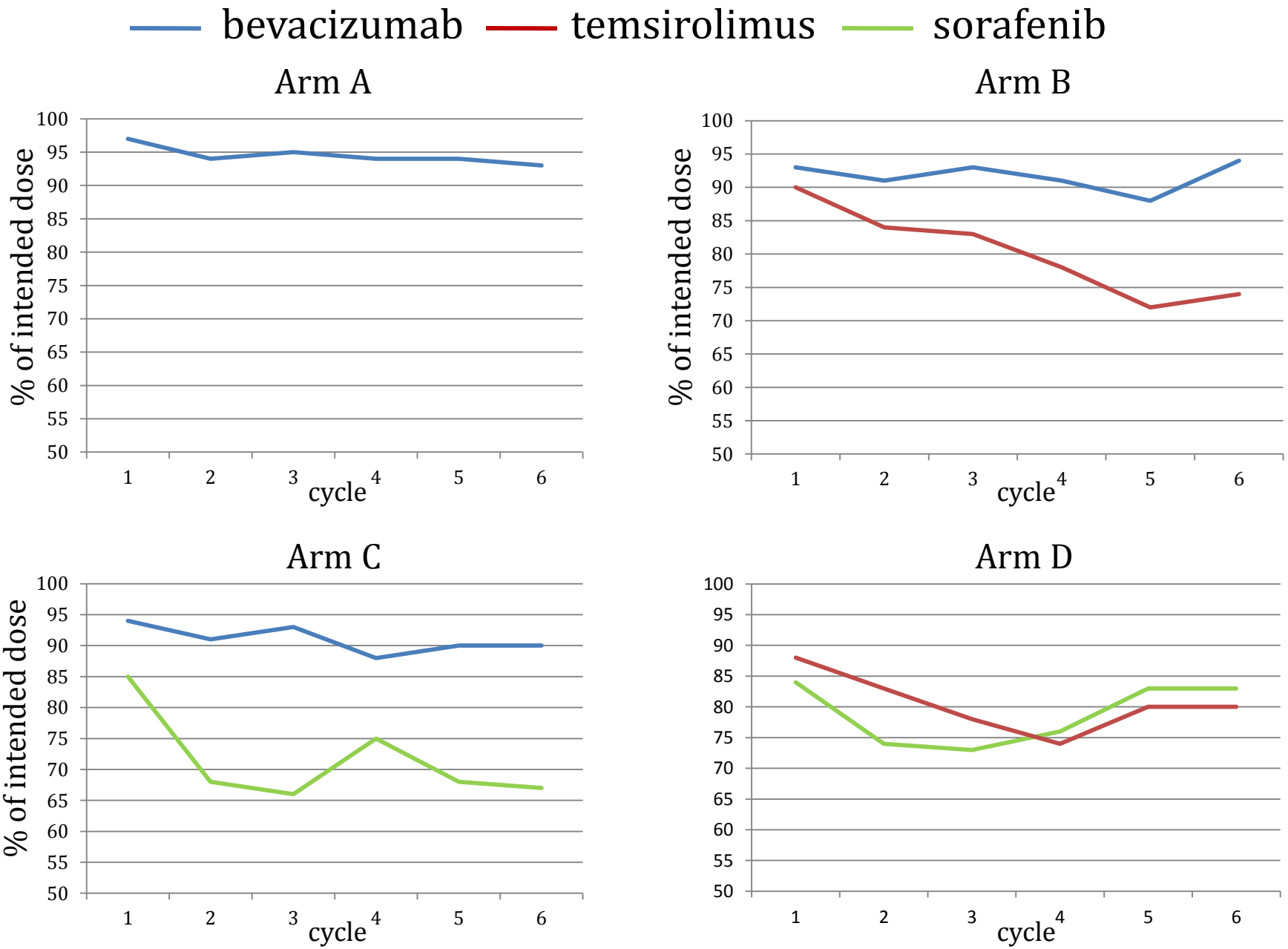
Severe toxicity

	Arm A (bev)	Arm B (bev/tem)	Arm C (bev/sor)	Arm D (sor/tem)
Grade 3 (%)	36	67	67	66
Grade 4 (%)	1	7	13	15
Grade 5 (%)	2	1	1	1

Grade 3/4 toxicity in > 10% of patients in at least one arm

	Arm A (bev) (%Gr 3/4)	Arm B (bev/tem) (Gr 3/4)	Arm C (bev/sor) (Gr 3/4)	Arm D (sor/tem) (Gr 3/4)
Hypertension	19/-	17/-	32/3	8/-
Fatigue	2/-	15/-	10/-	12/1
Hand-foot syndrome	-/-	1/-	22/-	3/-
Diarrhea	-/-	6/-	7/-	10/-
Hypophosphatemia	1/-	8/-	11/-	33/-
Proteinuria	9/-	23/-	9/-	1/-
Hyperglycemia	-/-	10/-	2/-	18/-

Dose intensity



Fatal events (at least possibly related to therapy)

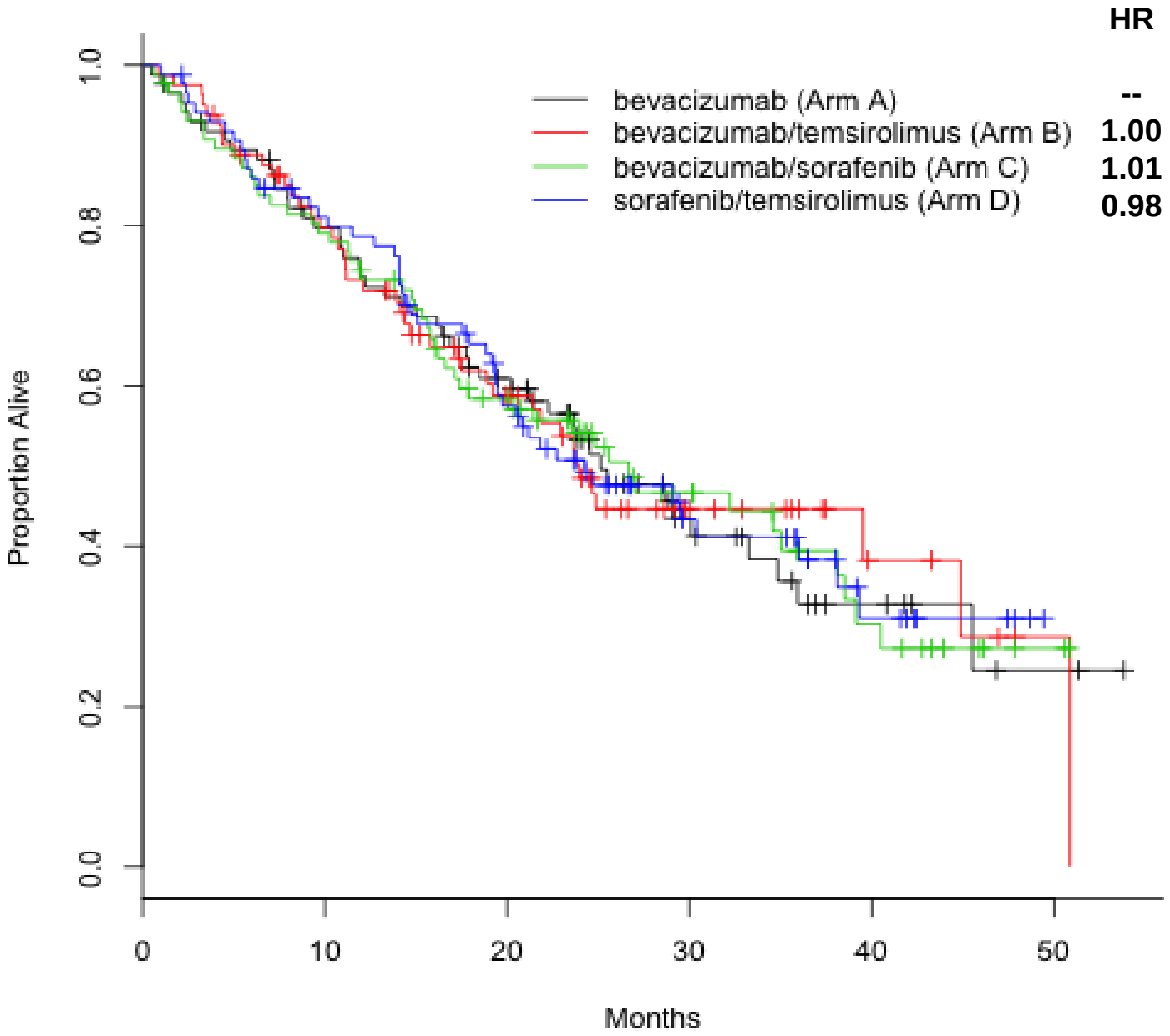
- Arm A (bevacizumab)
  - Obstructed colon, death probably due to disease
  - Myocardial infarction 3 days after starting therapy
- Arm B (bevacizumab/temsirolimus)
  - Cardiac ischemia
- Arm C (bevacizumab/sorafenib)
  - Severe hypertension and cerebral hemorrhage
- Arm D (sorafenib/temsirolimus)
  - Pneumonitis

Response rate

	Arm A bevacizumab	Arm B bevacizumab/ temsirolimus	Arm C bevacizumab/ sorafenib	Arm D Sorafenib/ temsirolimus
Assessed (n)	60	65	63	70
CR (%)	-	-	-	1
PR (%)	12	28	30	26
SD (%)	50	51	41	44
PD (%)	25	2	16	16
NE (%)	13	15	13	13

Pairwise comparison	Fisher's Exact p
A vs B	0.03
A vs C	0.02
A vs D	0.05

Overall survival



Conclusions

- No combination arm was superior to single-agent bevacizumab for the PFS primary endpoint
  - All 3 combination arms had a response rate >20%
- Common severe toxicities were expected, but more prevalent than single-agent bevacizumab (and sorafenib or temsirolimus, by historical control)
- Temsirolimus combined with bevacizumab or sorafenib offered no improvement in efficacy, but did add toxicity
- Bevacizumab/sorafenib had best efficacy, but was not tolerable; the VEGF/VEGFR co-inhibition strategy may warrant further investigation possibly with more selective VEGFR inhibitors

Acknowledgements

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