Phase III Trial of Bevacizumab Added to Standard Radiotherapy and Temozolomide for Newly Diagnosed Glioblastoma: Final Progression-Free Survival and Interim Overall Survival Results in AVAglio

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Disclosures

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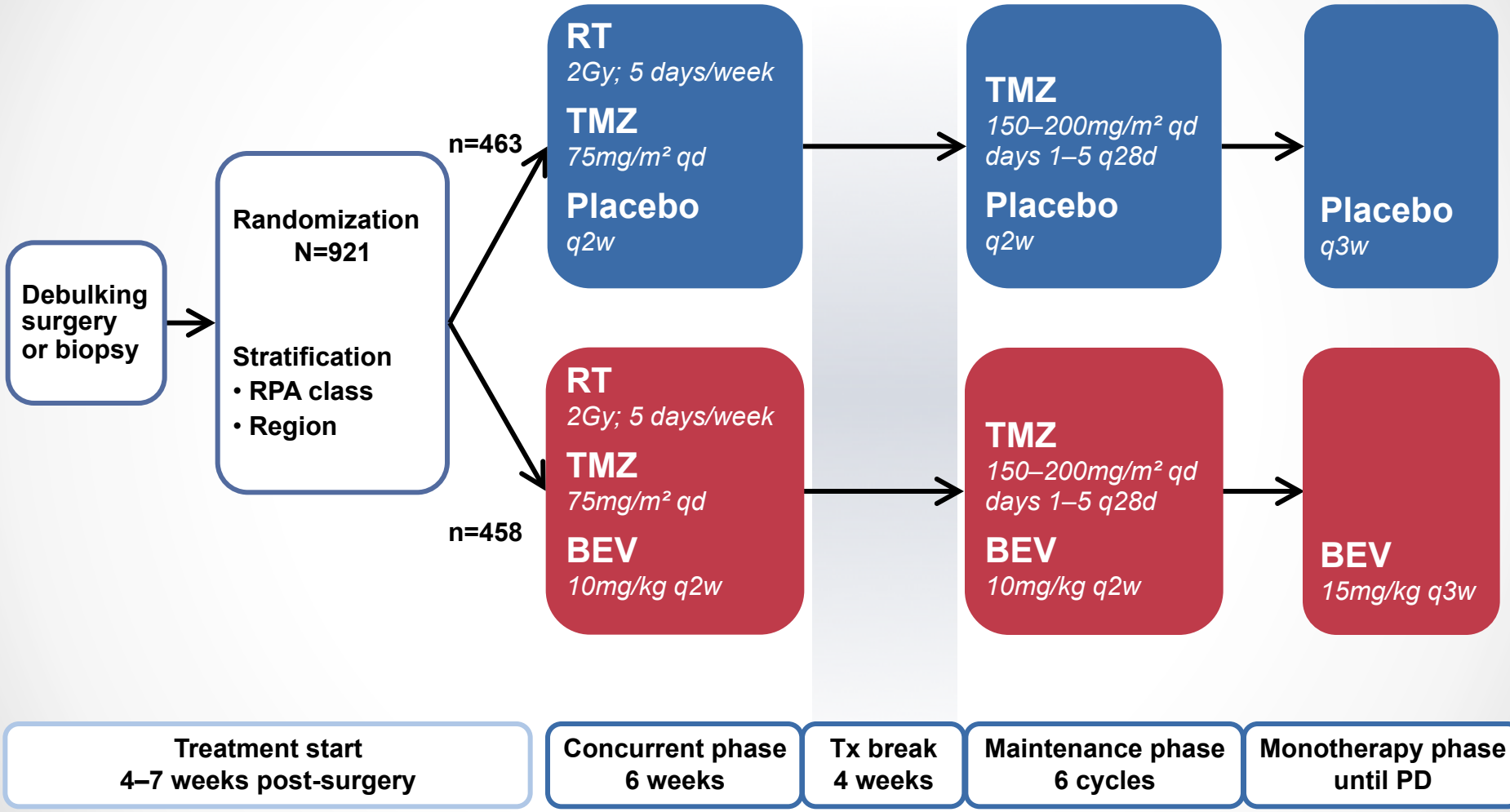
Introduction

- **Glioblastomas are highly vascularized tumors characterized by overexpression of VEGF-A**[1,2]
- **Bevacizumab (BEV) has shown activity in glioblastoma**
  - **Increased PFS and ORR vs historical controls in recurrent glioblastoma**[3–5]
  - **Phase II study results suggested that BEV plus standard frontline treatment may improve clinical outcomes in newly diagnosed glioblastoma**[6,7]
- **The phase III AVAglio study evaluated the efficacy and safety of BEV with RT and TMZ for newly diagnosed glioblastoma**
  - **Final PFS analysis positive, supported by measures of clinical benefit (HRQoL, KPS, steroid use)**
  - **Interim OS analysis not statistically significant**

HRQoL = health-related quality of life; KPS = Karnofsky performance status; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RT = radiotherapy; TMZ = temozolomide; VEGF-A = vascular endothelial growth factor-A

[1]Chi 2009; [2]Hicklin 2005
[3]Vredenburgh 2007; [4]Friedman 2009
[5]Kreisl 2009; [6]Lai 2011; [7]Narayana 2012

AVAglio Study Design



Last patient in: March 2011

BEV = bevacizumab; PD = progressive disease; RPA = recursive partitioning analysis; RT = radiotherapy; TMZ = temozolomide; Tx = treatment; qd = daily; q28d = every 28 days; q2w = every 2 weeks; q3w = every 3 weeks

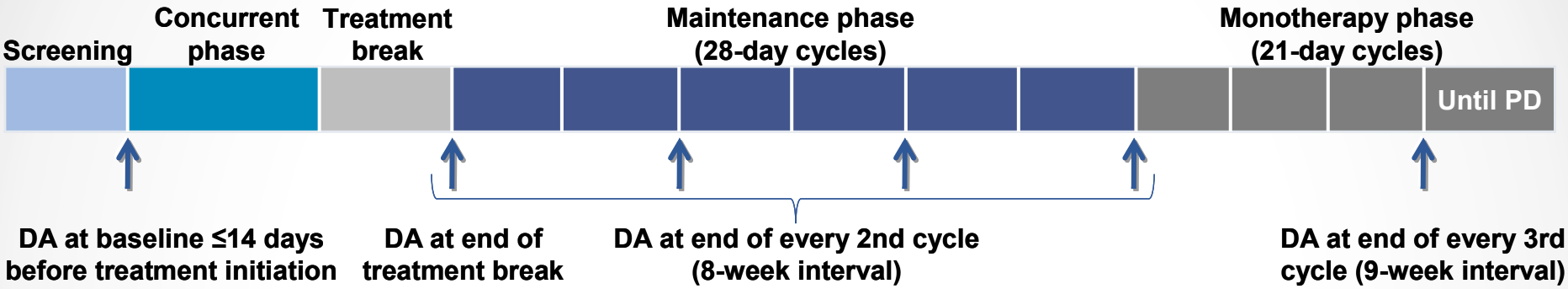
Study Objectives

- **Co-primary objectives**
  - **PFS (investigator assessed)**
  - **OS**
- **Secondary objectives**
  - **PFS (Independent Review Facility)**
  - **1-year and 2-year survival rates**
  - **Health-related quality of life (EORTC QLQ-C30 and BN20)**
  - **Safety**
- **Exploratory objectives included**
  - **Karnofsky performance status**
  - **Use of corticosteroids**

EORTC QLQ-C30 and BN20 = European Organization for Research and Treatment quality of life questionnaire core 30 and brain neoplasms 20; OS = overall survival; PFS = progression-free survival

Assessment of Progression

Timing



Criteria

Assessment	Definition of progression
Radiological	• ≥25% increase of enhancing lesions • Unequivocal progression of existing non-enhancing lesions • Any new lesion
Clinical	• Neurologic symptoms worsened
Corticosteroid use	• Stable or increased corticosteroid dose

DA = disease assessment; PD = progressive disease

Statistical Assumptions*

	Control arm, median	Assumed HR	Experimental arm, median	Log-rank test
PFS	7 months	0.769	9.1 months	Power = 80% 2-sided 1% α level
OS Expected 2013	14.6 months	0.80	18.3 months	Power = 80% 2-sided 4% α level

Planned sample size = 920

*Trial meets its primary objective if either one, or both, of the co-primary endpoints is statistically significant

HR = hazard ratio; OS = overall survival; PFS = progression-free survival

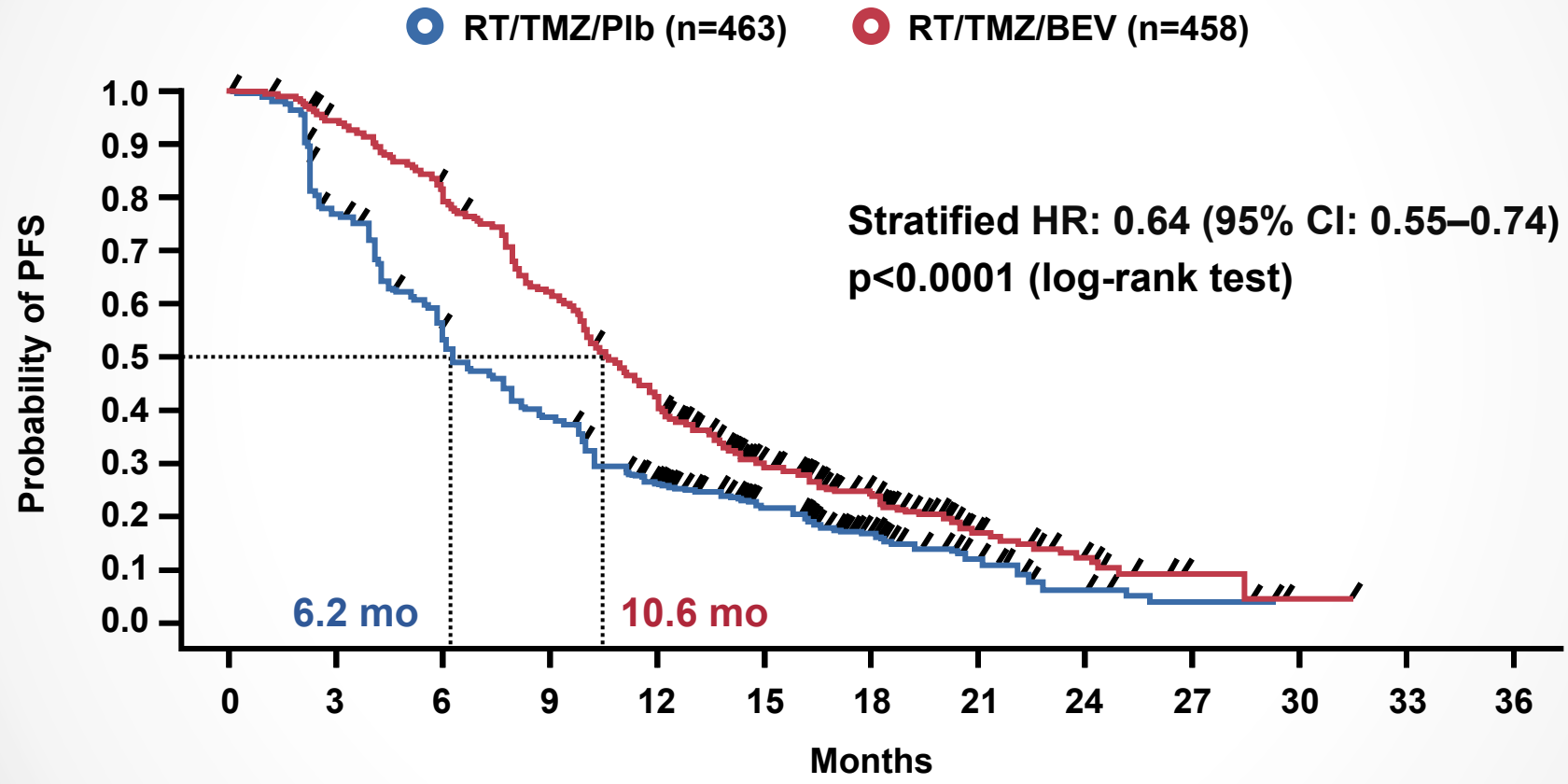
Baseline Characteristics*

Patients, %		RT/TMZ/Plb (n=463)	RT/TMZ/BEV (n=458)
Median age, years (range)		56.0 (18–79)	57.0 (20–84)
Gender	Male	64	62
WHO PS	0	52	50
	1–2	48	50
RPA class	III	16	17
	IV	60	57
	V	23	26
MGMT status	Methylated	26	26
	Non-methylated	51	49
	Missing	23	25
Surgical status	Biopsy	10	13
	Partial resection	48	46
	Complete resection	42	41
KPS	50–80	30	33
	90–100	70	67
MMSE score	<27	24	24
	≥27	76	76
Corticosteroids	On	45	41
	Off	55	59
EIAEDs	On	20	19
	Off	80	81

*Selected characteristics only

Results

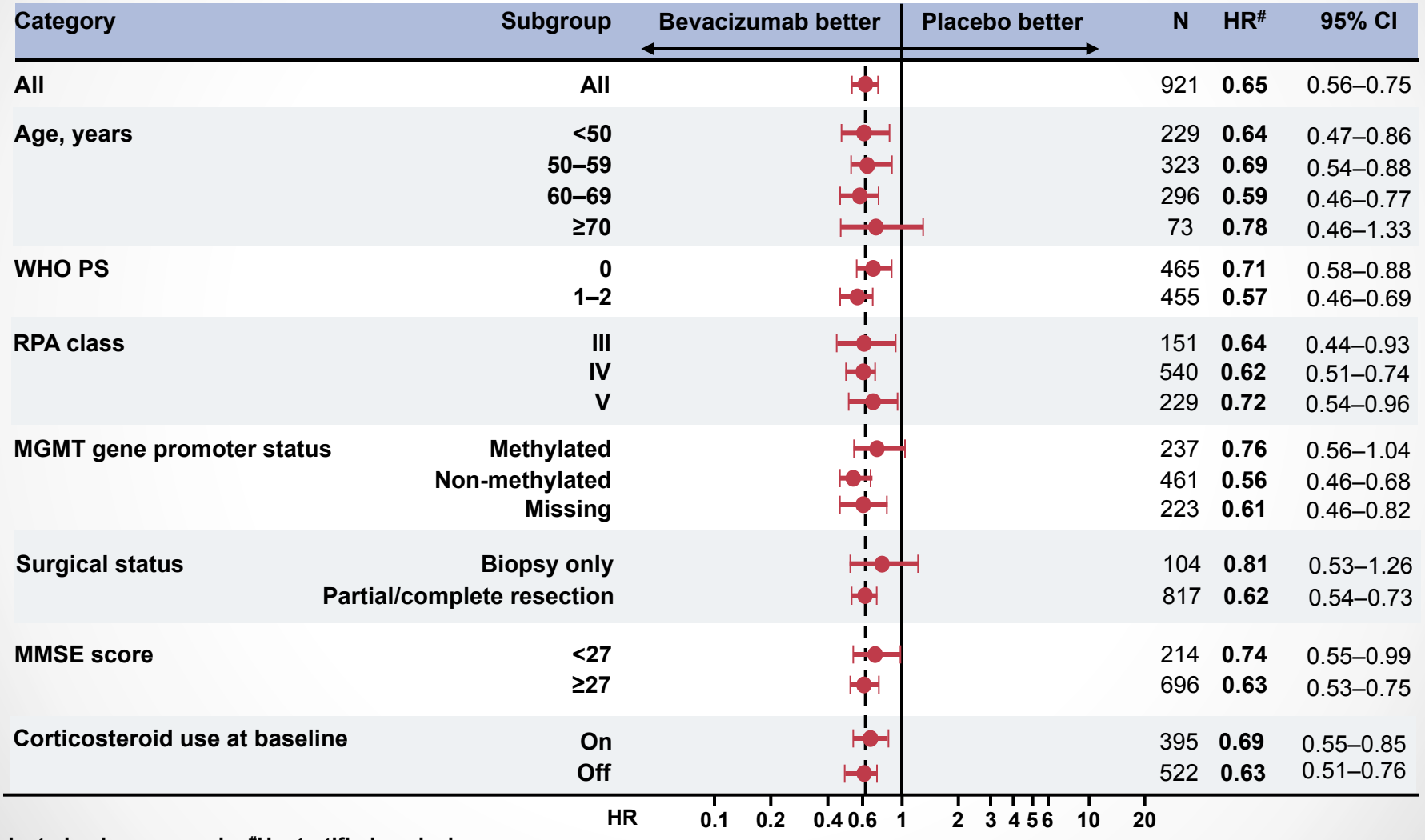
Investigator-Assessed PFS (Co-Primary Endpoint)



N at risk													
RT/TMZ/Plb	463	349	247	170	110	77	47	23	8	4	0	0	0
RT/TMZ/BEV	458	424	366	278	189	104	71	25	13	2	1	0	0

BEV = bevacizumab; CI = confidence interval; HR = hazard ratio; mo = months; PFS = progression-free survival; Plb = placebo; RT = radiotherapy; TMZ = temozolomide

Investigator-Assessed PFS: Subgroup Analyses*

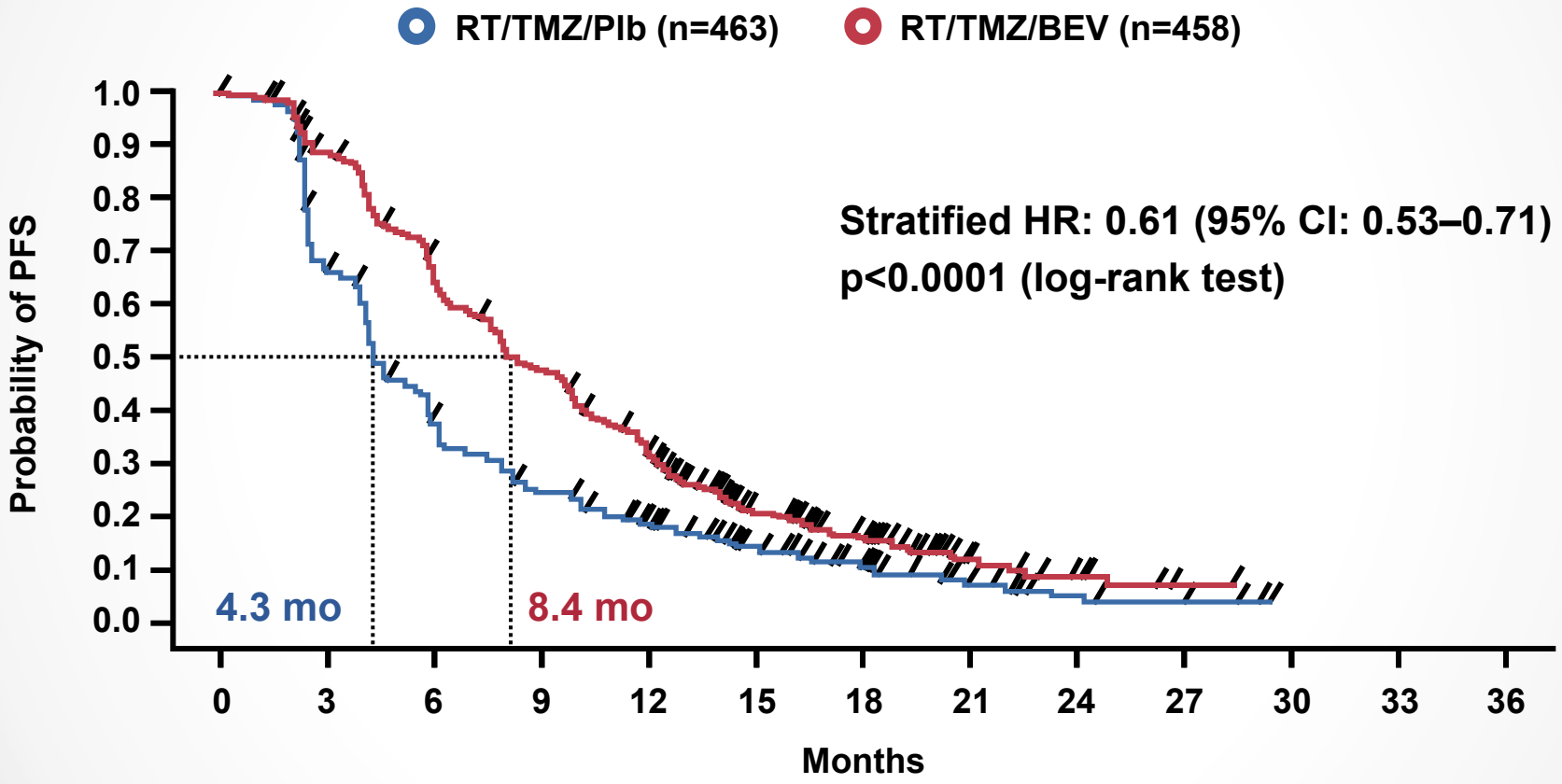


Category	Subgroup	N	HR#	95% CI
All	All	921	**0.65**	0.56–0.75
Age, years	<50	229	**0.64**	0.47–0.86
	50–59	323	**0.69**	0.54–0.88
	60–69	296	**0.59**	0.46–0.77
	≥70	73	**0.78**	0.46–1.33
WHO PS	0	465	**0.71**	0.58–0.88
	1–2	455	**0.57**	0.46–0.69
RPA class	III	151	**0.64**	0.44–0.93
	IV	540	**0.62**	0.51–0.74
	V	229	**0.72**	0.54–0.96
MGMT gene promoter status	Methylated	237	**0.76**	0.56–1.04
	Non-methylated	461	**0.56**	0.46–0.68
	Missing	223	**0.61**	0.46–0.82
Surgical status	Biopsy only	104	**0.81**	0.53–1.26
	Partial/complete resection	817	**0.62**	0.54–0.73
MMSE score	<27	214	**0.74**	0.55–0.99
	≥27	696	**0.63**	0.53–0.75
Corticosteroid use at baseline	On	395	**0.69**	0.55–0.85
	Off	522	**0.63**	0.51–0.76

*Selected subgroups only; #Unstratified analysis

CI = confidence interval; HR = hazard ratio; MGMT = methylguanine-DNA methyltransferase; MMSE = mini-mental state examination; PFS = progression-free survival; RPA = recursive partitioning analysis; WHO PS = World Health Organization performance status

IRF-Assessed PFS (Secondary Endpoint)



N at risk													
RT/TMZ/Plb	463	297	168	109	76	46	30	14	6	4	0	0	0
RT/TMZ/BEV	458	396	298	212	148	70	44	14	7	1	0	0	0

BEV = bevacizumab; CI = confidence interval; HR = hazard ratio; IRF = Independent Review Facility; mo = months; PFS = progression-free survival; Plb = placebo; RT = radiotherapy; TMZ = temozolomide

Interim OS Analysis

	RT/TMZ/Plb (n=463)	RT/TMZ/BEV (n=458)
Median follow-up, months	13.7	14.4
Events	263	254
Stratified HR (95% CI)	0.89 (0.75–1.07) p=0.2135	
1-year survival rate, % (95% CI)	66 (62–71)	72 (68–76) p=0.052

BEV = bevacizumab; CI = confidence interval; HR = hazard ratio; OS = overall survival; Plb = placebo; RT = radiotherapy; TMZ = temozolomide

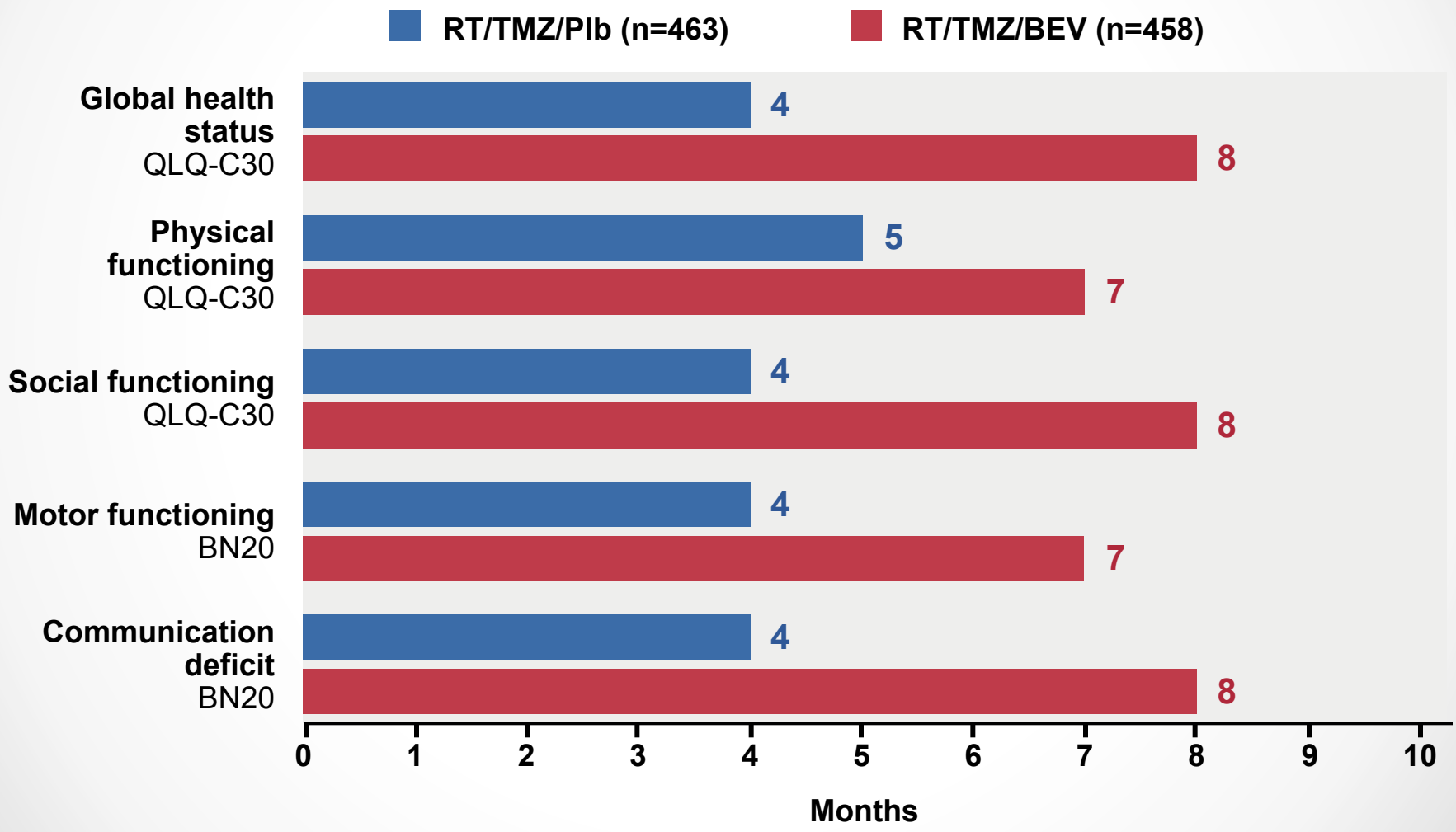
Health-Related Quality of Life

- **EORTC QLQ-C30 and BN20 (brain cancer-specific), validated HRQoL instruments[1–3]**
- **Five domains were pre-specified as secondary analyses based on relevance and importance in glioblastoma[2,4–10]**
  - **Global health status**
  - **Physical functioning**
  - **Social functioning**
  - **Motor functioning**
  - **Communication deficit**

EORTC QLQ-C30 and BN20 = European Organization for Research and Treatment quality of life questionnaire core 30 and brain neoplasms 20; HRQoL = health-related quality of life

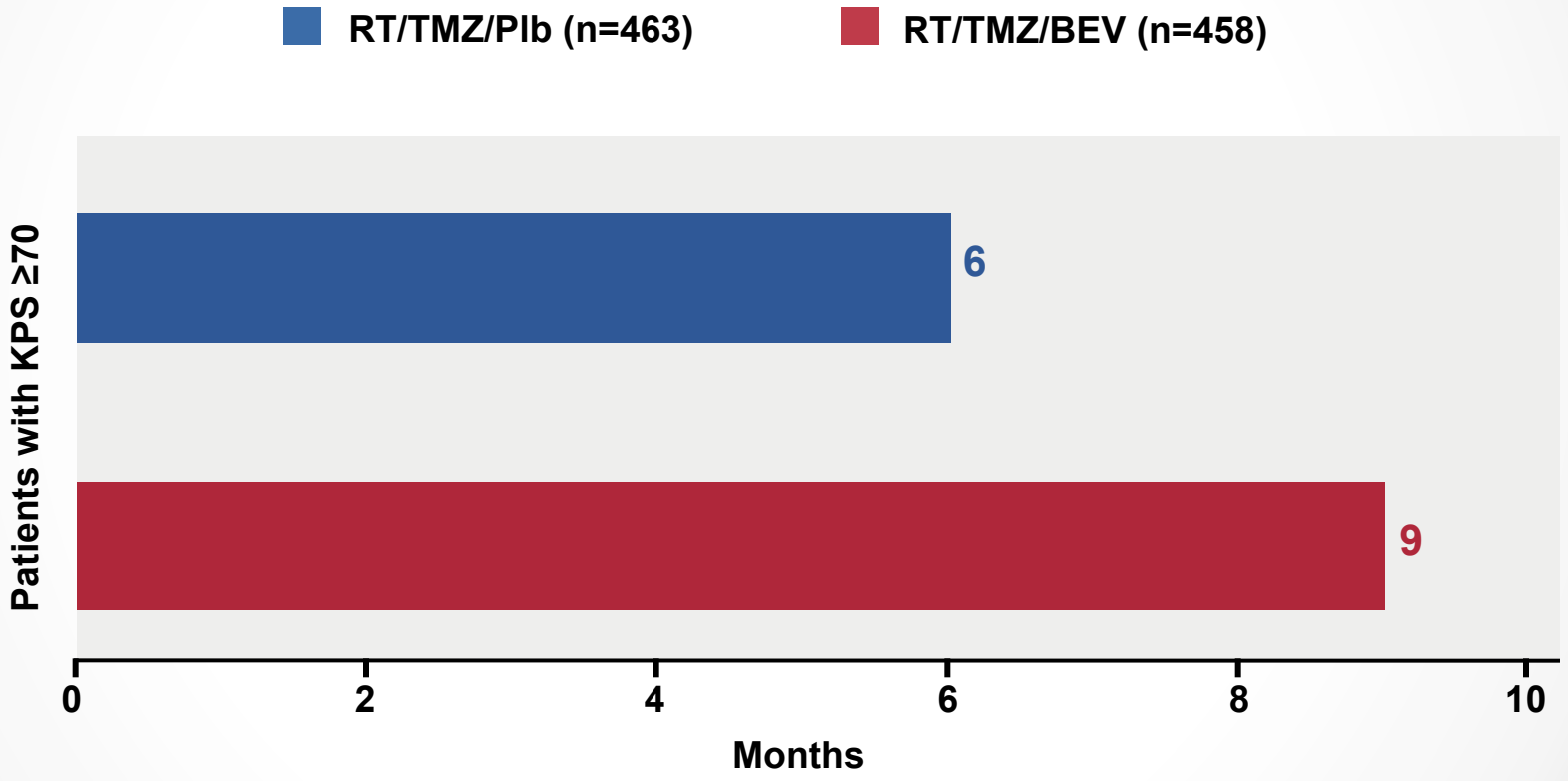
[1]Aaronson 1993; [2]Osoba 1996; [3]Taphoorn 2010
[4]Bottomley, Aaronson 2007
[5]Osoba 2000; [6]Taphoorn 2005
[7]Stupp 2005; [8]Taphoorn, Bottomley 2005
[9]Klein 2001; [10]Budrukkar 2009

HRQoL: Median Duration that Patients were Stable/Improved from Baseline



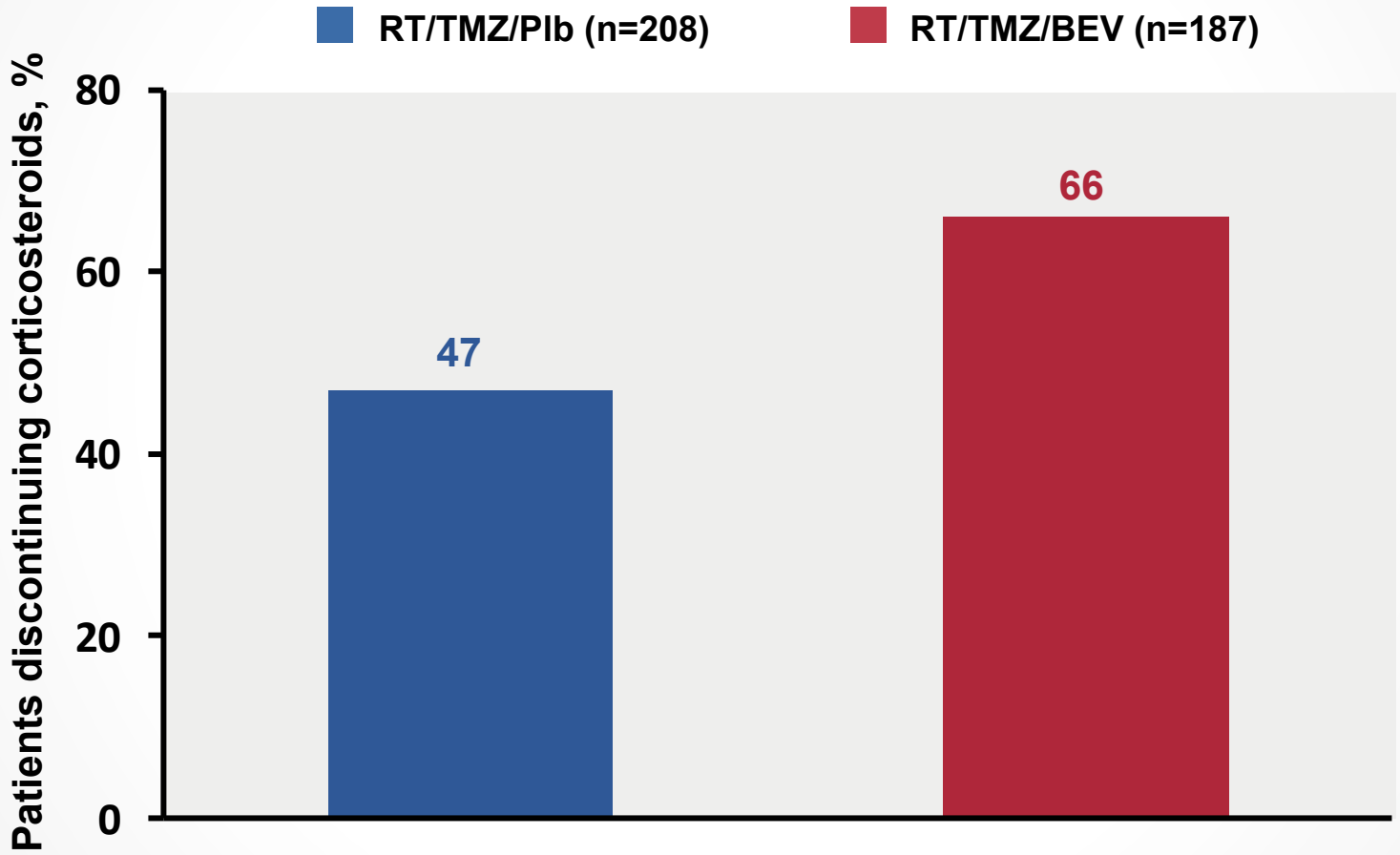
BEV = bevacizumab; BN20 = brain neoplasms 20; HRQoL = health-related quality of life; QLQ-C30 = quality of life questionnaire core 30; Plb = placebo; RT = radiotherapy; TMZ = temozolomide

Median Duration Patients Maintained a KPS ≥70



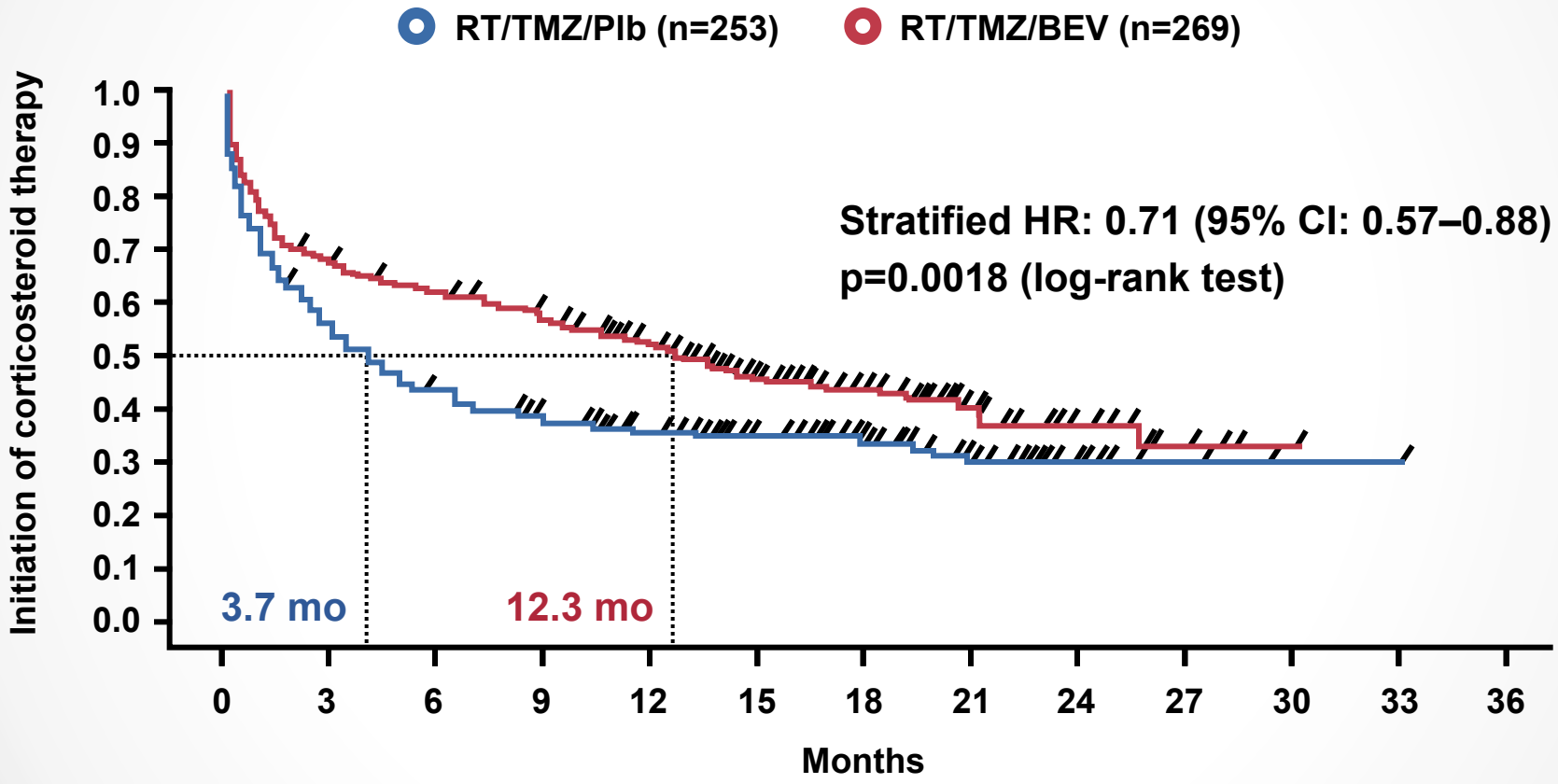
BEV = bevacizumab; KPS = Karnofsky performance status; Plb = placebo; RT = radiotherapy; TMZ = temozolomide

Corticosteroid Discontinuation* in Patients ON Steroids at Baseline



*Defined as no corticosteroid intake (0mg) for at least 5 consecutive days
BEV = bevacizumab; Plb = placebo; RT = radiotherapy; TMZ = temozolomide

Time to Steroid Initiation for Patients OFF Steroids at Baseline



N at risk													
RT/TMZ/Plb	253	133	106	88	77	56	34	17	5	2	1	0	0
RT/TMZ/BEV	269	179	163	146	125	76	47	20	11	5	0	0	0

BEV = bevacizumab; CI = confidence interval; HR = hazard ratio; mo = months; Plb = placebo; RT = radiotherapy; TMZ = temozolomide

Overview of Adverse Events

Patients, %	RT/TMZ/Plb (n=447)	RT/TMZ/BEV (n=464)
Any AE	95.7	98.1
Serious AE	25.7	36.6
Grade 3–5 AE	50.1	62.7
Grade 3–5 AE of special interest for BEV	15.2	28.7
Grade 5 AE	2.7	4.5
Discontinued any treatment due to AE	13.2	24.6

Safety population; AEs reported up until 90 days after last dose of study treatment

AE = adverse event; BEV = bevacizumab; Plb = placebo; RT = radiotherapy; TMZ = temozolomide

Adverse Events of Special Interest for BEV

Patients, %	RT/TMZ/Plb (n=447)		RT/TMZ/BEV (n=464)	
	All grades	Grade ≥3	All grades	Grade ≥3
Bleeding: cerebral haemorrhage	2.2	0.7	2.6	1.5
mucocutaneous bleeding	8.9	–	26.7	0.4
other	8.1	0.4	11.6	0.6
Wound-healing complications	2.2	0.7	3.7	1.5
Arterial thromboembolic events	1.6	1.3	5.0	4.1
Venous thromboembolic events	9.6	8.1	7.8	7.3
Hypertension	13.0	2.0	37.5	10.3
Proteinuria	4.0	–	14.0	3.7
GI perforation (including GI fistula/abscess)	0.2	0.2	1.7	1.1
Abscesses and fistulae	0.4	0.4	0.6	0.6
Congestive heart failure	0.2	–	0.4	0.4
Posterior reversible encephalopathy syndrome	–	–	–	–

Safety population

BEV = bevacizumab; GI = gastrointestinal; Plb = placebo; RT = radiotherapy; TMZ = temozolomide

Conclusions

- **The addition of BEV to RT/TMZ significantly extended PFS by 4.4 months in patients with newly diagnosed glioblastoma**
  - **36% relative reduction in the risk of progression or death**
  - **IRF assessment confirmed the magnitude of benefit, with an HR of 0.61**
  - **Subgroups analysis for PFS was consistent with the overall population**
- **HRQoL and KPS were stable or improved during PFS in both treatment arms, emphasizing the value of prolonging PFS in the BEV arm**
  - **Patients receiving BEV had a diminished steroid requirement**
- **Safety profile was consistent with the known side effects of BEV; no new safety signals observed**
- **At the interim analysis, OS did not cross the threshold for significance; final OS data expected in 2013**

BEV = bevacizumab; HR = hazard ratio; HRQoL = health-related quality of life; IRF = Independent Review Facility; KPS = Karnofsky performance status; OS = overall survival; PFS = progression-free survival; RT = radiotherapy; TMZ = temozolomide

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