NCRI National Cancer Research Institute

MRC Clinical Trials Unit

A randomised trial of temozolomide vs PCV chemotherapy for recurrent malignant glioma (MRC BR12)

Siow Ming Lee PhD, FRCP
University College Hospital, London, UK
(sm.lee@uclh.org)

Authors: M Brada, R Gabe, S Stenning, L Thompson and SM Lee
on behalf of the MRC BR12 Collaborators

NCRI National Cancer Research Institute

Background – (1)

MRC Clinical Trials Unit

- Prognosis for recurrent high grade glioma (HGG) is poor with a median survival of <6mos for grade IVs and <15mos for grade IIIs.

- Although temozolomide (TMZ) is frequently used in patients with recurrent high grade glioma (HGG), it has never been directly compared with PCV chemotherapy.

- MGMT (O^6-methyguanine-DNA-methyltransferase) is an important DNA repair protein that contributes to resistance to TMZ and PC(V) by repairing the toxic O^6-alkylguanine lesion.

Background – (2)

NCRI National Cancer Research Institute

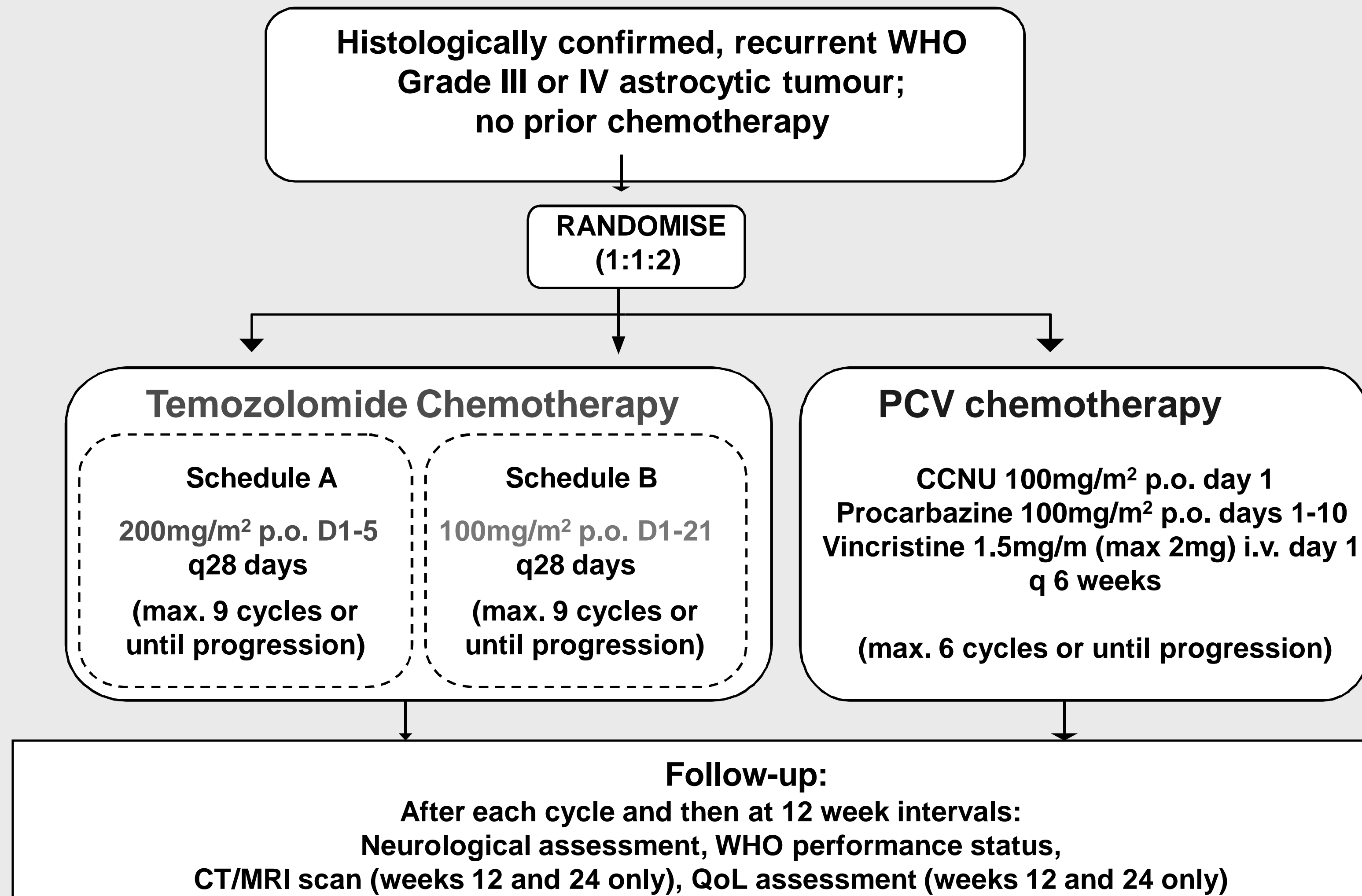
MRC Clinical Trials Unit

- We previously demonstrated the anti-tumour activity of the standard 5 day TMZ schedule was associated with progressive depletion of MGMT (Lee et al, BJC 1994).
- Prolonged TMZ dosing and dose intensification has the potential to improve efficacy by causing further MGMT depletion and/or preventing MGMT recovery.
- We report the first randomised comparison of PCV vs TMZ sub-randomised between 5 vs 21 day schedule in chemo-naïve pts with recurrent HGG.

Objectives

- PCV vs TMZ comparison:
  - Primary endpoint: Overall survival
  - Secondary endpoints: PFS, QoL
- TMZ-5 vs TMZ-21 comparison:
  - Primary endpoint: PFS at 12 weeks
  - Secondary endpoints: Overall survival, toxicity, QoL

Trial Design



NCRI National Cancer Research Institute

Sample size

MRC Clinical Trials Unit

- Trial was powered for the primary comparison of PCV vs TMZ (both arms combined) for overall survival
  - Sample size: ~500 patients (and ~380 deaths)
    - 95% power and 2-sided 5% level test to detect a 3 month increase in median survival (eg 6 to 9 months) or
    - 80% power to detect a 2 month increase in median survival
- Secondary comparison TMZ-5 vs TMZ-21
  - Sample size: 125 patients per arm
    - 80% power to detect 15-20% increase in PFS at primary assessment point at 12 weeks

Eligibility criteria

NCRI National Cancer Research Institute

MRC Clinical Trials Unit

- Histologically verified AA, GBM, gemistocytic, oligo-astrocytomas or gliosarcoma (WHO grade III/IV at diagnosis, relapse or a transformation). Oligodendroglioma excluded
- Primary treatment with radiotherapy, completed >2 months ago; no previous chemotherapy, radiosurgery or interstitial radiotherapy (brachytherapy) for glioma
- Evidence of first progression confirmed by CT or MRI and evaluable enhancing recurrent tumour on enhanced CT/MRI scan
- Considered fit for chemotherapy with age ≥18, WHO PS 0-3
- Adequate hepatic, renal and haematological function

Definition of progression: clinical/neurological criteria

NCRI National Cancer Research Institute

MRC Clinical Trials Unit

- Neurological deterioration
- Increased steroid requirements > 2 weeks
- Deterioration of WHO PS status ≥ 1
- Increased symptoms of raised intracranial pressure
- Imaging should be repeated on progression whenever possible

Results

- Accrual July 2003 – Jan 2008
- **447** patients randomised
  - **PCV: 224**
  - **TMZ: 223** (*TMZ-5: 112, TMZ-21: 111)*
- 382 deaths reported to 8.7.08
- Median follow-up of survivors =12 months

Baseline Characteristics – (1)

NCRI National Cancer Research Institute

MRC Clinical Trials Unit

		Allocated treatment					
		PCV (N=224)		TMZ - 5 (N=112)		TMZ - 21 (N=111)	
		n	*Col %*	n	*Col %*	n	*Col %*
% Male		**146**	**65%**	72	64%	70	63%
Mean (SD) age at entry		**52**	**(12.0)**	51	(11.6)	51	(12.1)
WHO tumour grade	Grade III	**51**	**23%**	26	23%	26	23%
	Grade IV	**166**	**74%**	83	74%	83	75%
	High grade (unspecified)	**7**	**3%**	3	3%	2	2%
WHO performance status	0/1	**142**	**63%**	70	63%	72	65%
	2/3	**82**	**37%**	42	38%	39	35%

Baseline Characteristics – (2)

NCRI National Cancer Research Institute

MRC Clinical Trials Unit

	PCV (N=224)		TMZ–5 (N=112)		TMZ-21 (N=111)	
	N	%	N	%	N	%
Type of Surgery						
• Total resection	30	15%	19	17%	12	13.5%
• Debulking	132	58.9%	63	56.3%	65	58.6%
• Biopsy	58	26.0%	29	25.9%	30	27%
• Missing	1	0.5%	1	0.9%	1	0.9%
Radiotherapy						
• > 55 Gy	143	64.1%	78	69.6%	71	64.5%
• ≤ 55 Gy	80	35.9%	34	30.4%	39	35.6%

Treatment received

NCRI National Cancer Research Institute

MRC Clinical Trials Unit

	Allocated chemotherapy treatment		
	PCV (N=224)	TMZ - 5 (N=112)	TMZ - 21 (N=111)
Median no. cycles received	4	6	5
% of patients completing at least 2x PCV and 3xTMZ	71%	73%	69%
% of patients completing at least 4x PCV and 6xTMZ	37%	49%	32%
% of patients completing full course i.e. 6x PCV, 9xTMZ	17%	26%	13%

NCRI National Cancer Research Institute

Toxicity

MRC Clinical Trials Unit

Worst toxicity throughout treatment period*

	Allocated Treatment					
	PCV (n=221)		TMZ – 5 (n=110)		TMZ – 21 (n=110)	
Grade 3/4 toxicity	n	%	n	%	n	%
At least one **haematological** toxicity	32	*16%*	20	*19%*	15	*14%*
At least one non-haem toxicity (**excluding** possibly) disease-related symptoms)	17	9%	7	7%	11	11%
Any toxicity (**including** possibly disease-related)	94	*43%*	49	*46%*	52	*47%*

* NB rows are not mutually exclusive

Quality of life

- EORTC QLQ C30 and brain tumour module required at baseline, 12 wks and 24 wks

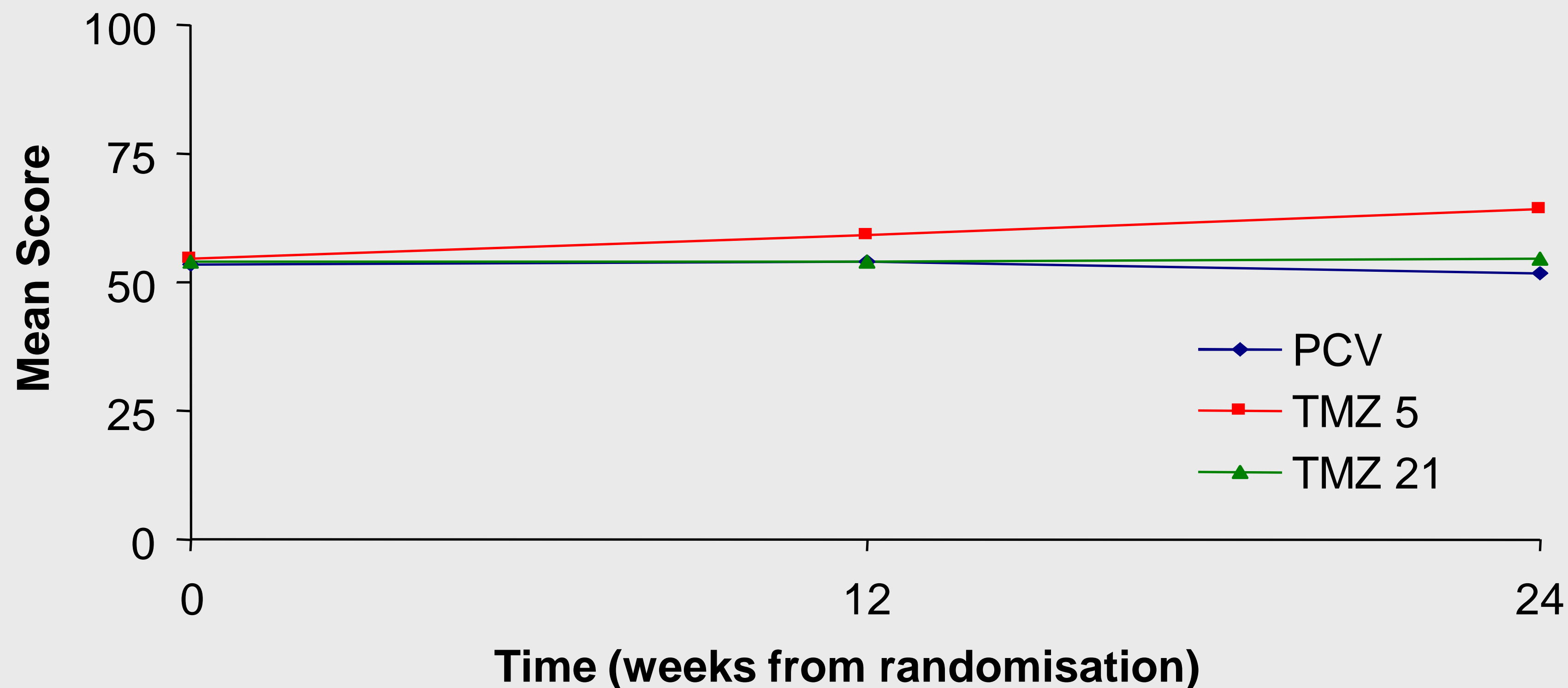
- Proportion of surviving (progression-free) patients completing questionnaires at:
  - Pre-randomisation 94% (94%)
  - 12 weeks 65% (74%)
  - 24 weeks 52% (68%)

- Global QL (0-100 scale) only presented today

Global Quality of Life - mean score (PCV vs TMZ 5 vs TMZ 21)

NCRI National Cancer Research Institute

MRC Clinical Trials Unit

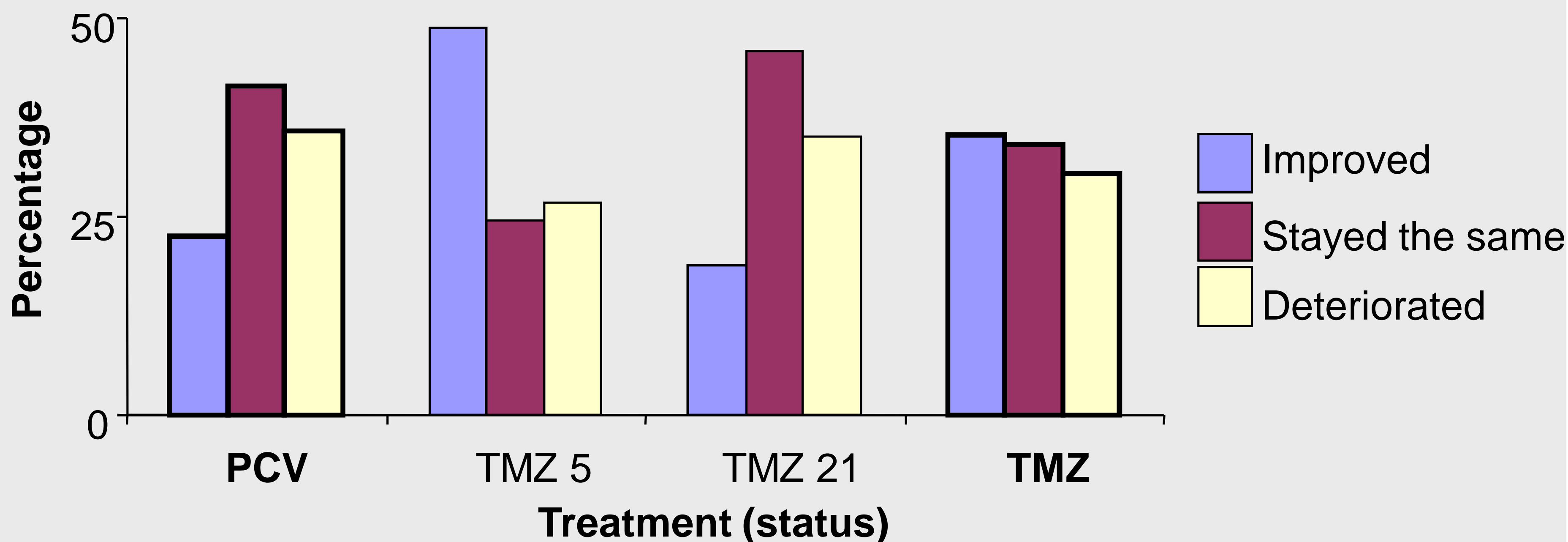


	0	12	24
PCV	211	101	54
TMZ 5	103	77	46
TMZ 21	101	60	38

Global QL Status: changes from baseline to 24 weeks

NCRI National Cancer Research Institute

MRC Clinical Trials Unit



PCV vs. TMZ	**Improved** (by>10 points):	**23% vs 35%**
	Stayed the same:	**42% vs 34%**
	Deteriorated (by>10 points):	**36% vs 31%**

Current status

NCRI National Cancer Research Institute

MRC Clinical Trials Unit

	Allocated treatment			
	PCV (N=224)	**TMZ – 5 (N=112)**	**TMZ – 21 (N=111)**	**TMZ all (N=223)**
Alive & progression-free	**16**	10	5	**15**
Alive with progression	**19**	7	8	**15**
Died	**189**	95	98	**193**
Disease related	*175*	*89*	*94*	*183*
Treatment related	*1*	*2*	*2*	*4*
Other	*13*	*4*	*2*	*6*

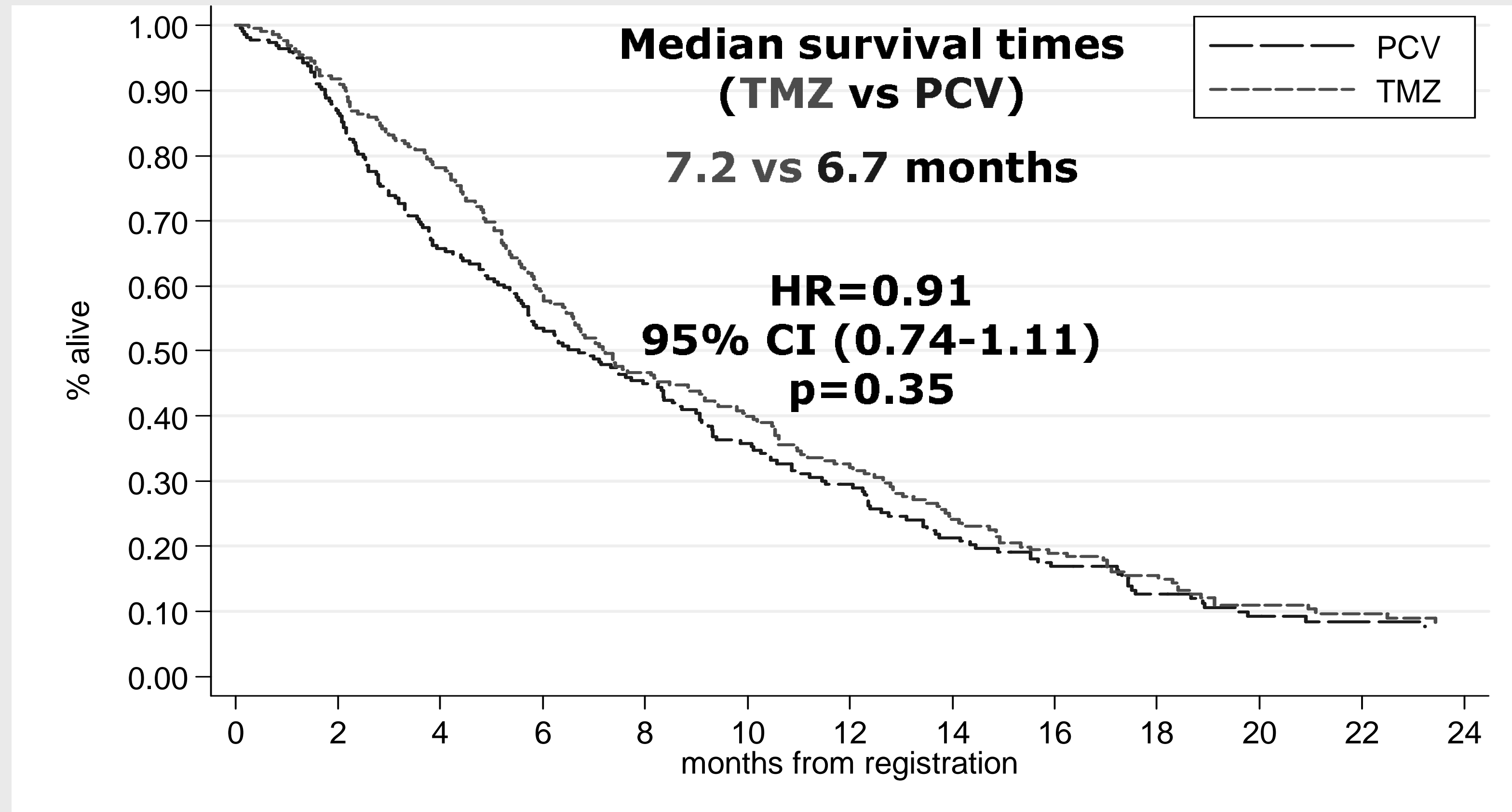
NCRI National Cancer Research Institute

Treatment on 1st progression

MRC Clinical Trials Unit

	Allocated treatment		
	PCV (n=156)	TMZ – 5 (n=83)	TMZ – 21 (n=81)
No further treatment	66	28	37
Further protocol chemotherapy	26	21	19
Other chemotherapy	56 (34% Temozolomide)	28 (30% PCV)	23 (25% PCV)
Other treatment	8	6	2

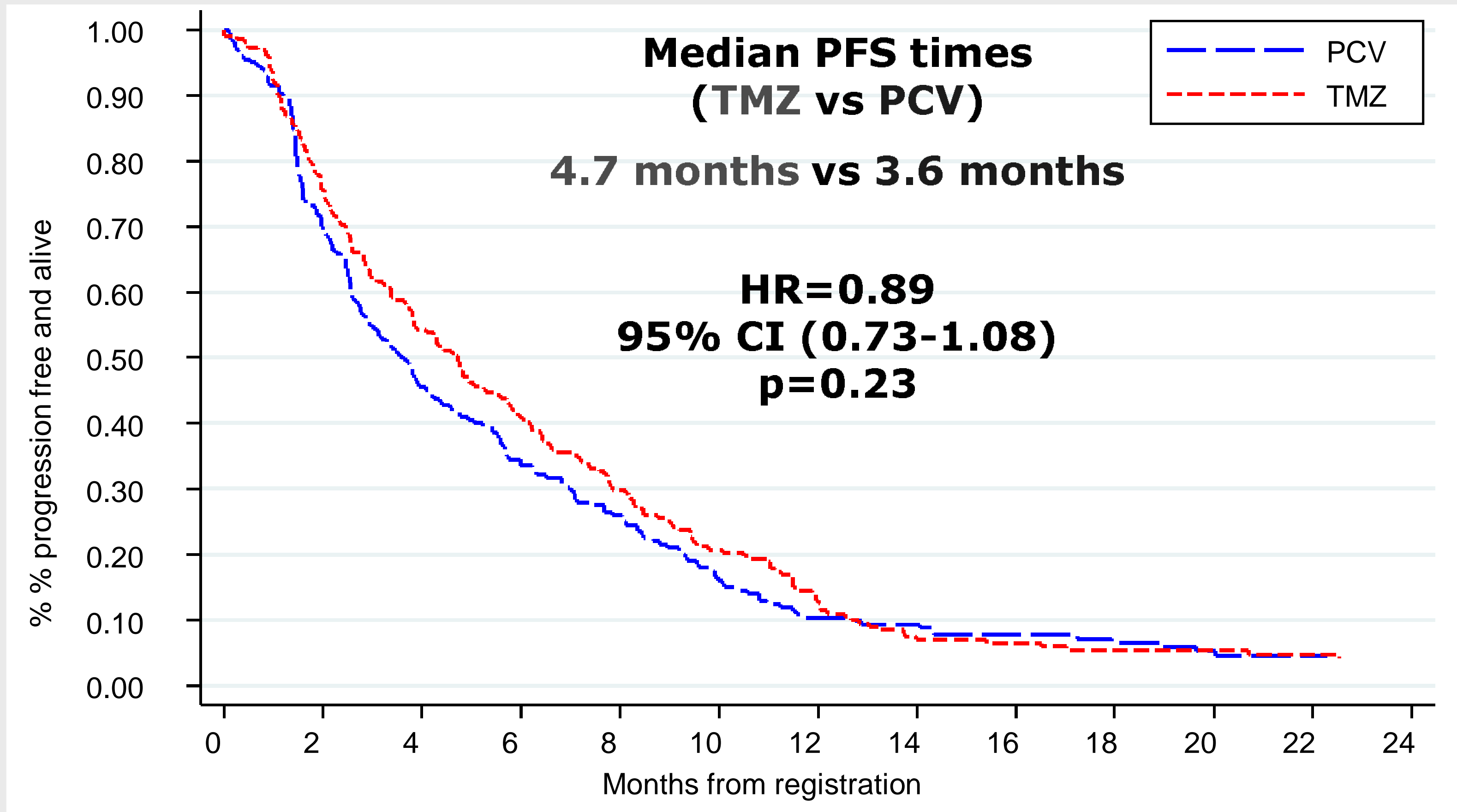
Survival: PCV vs TMZ



No. at risk

PCV	224	193	143	113	92	70	54	39	30	21	13	11	9
TMZ	223	203	171	125	97	82	65	48	36	27	18	14	12

PFS: PCV vs TMZ

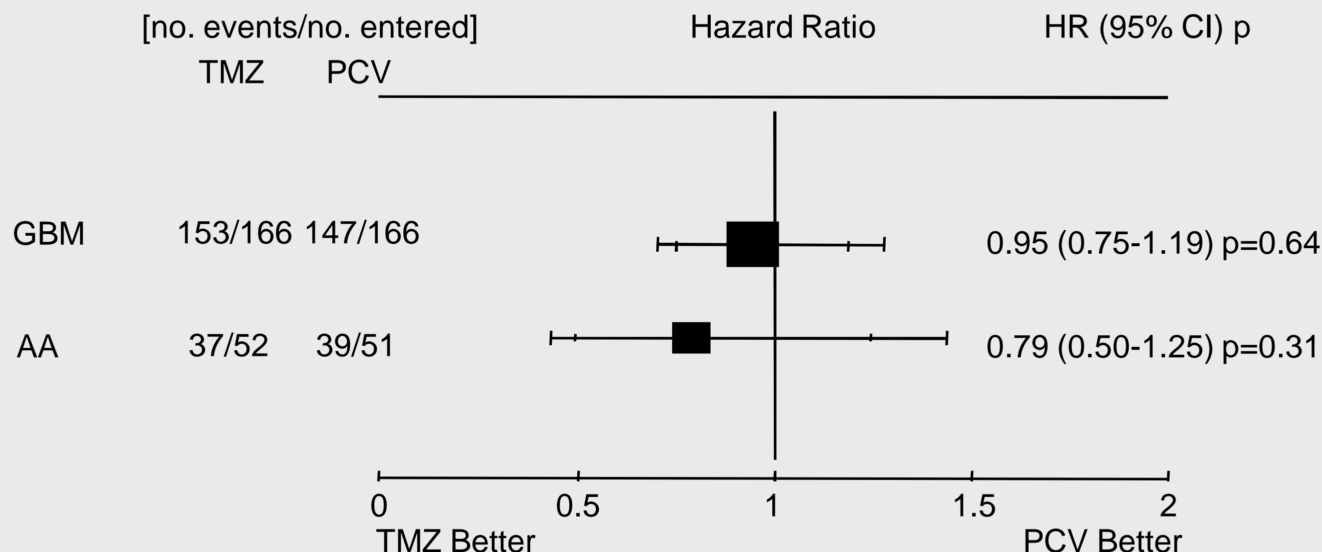


No. at risk

PCV	224	155	100	72	54	32	20	18	15	11	8	7	6
TMZ	223	167	120	89	63	43	26	14	13	9	8	7	6

Planned subgroup analysis: Treatment effect by tumour grade

- No clear evidence of differential treatment effect by tumour grade (test for heterogeneity, p=0.48)



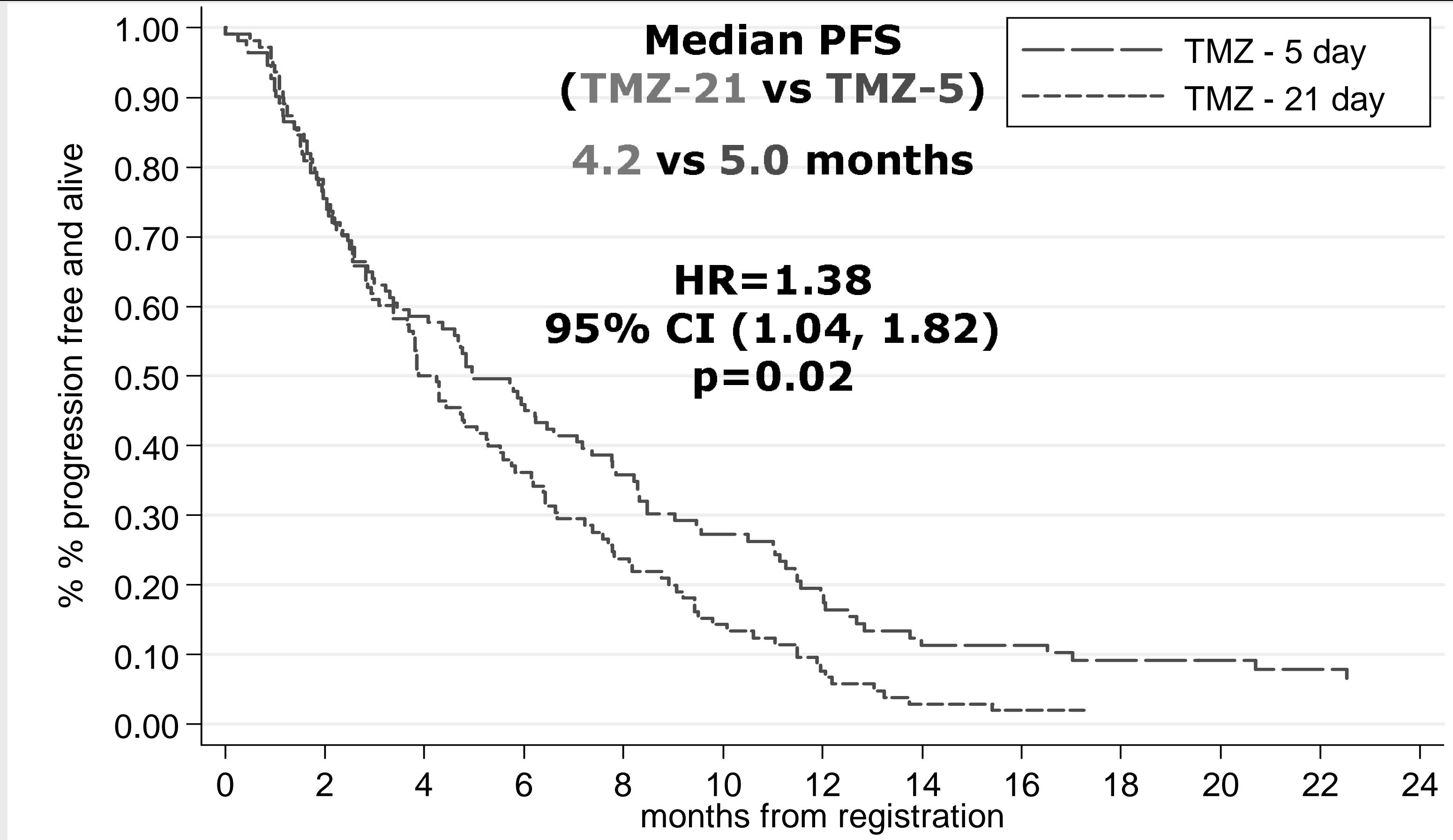
NCRI National Cancer Research Institute

PFS at 12 weeks

MRC Clinical Trials Unit

Event	PCV (n=224)	TMZ 5 (n=112)	TMZ 21 (n=111)	
Alive and progress^{n}- free at 12 wks	119 (54%)	70 (64%)	71 (66%)	TMZ 5 vs. TMZ 21: (64% vs. 66%) p=0.75
Scan at 12 wks showing progressive disease	17 (8%)	9 (8%)	7 (6%)	
Death prior to 12 weeks	30 (14%)	9 (8%)	11 (10%)	
Scan prior to 12 wks confirming a suspected progression	19 (9%)	4 (4%)	6 (6%)	
Clinically confirmed progression prior to 12 weeks - no scan	34 (16%)	18 (16%)	13 (12%)	

PFS: TMZ-5 vs TMZ-21



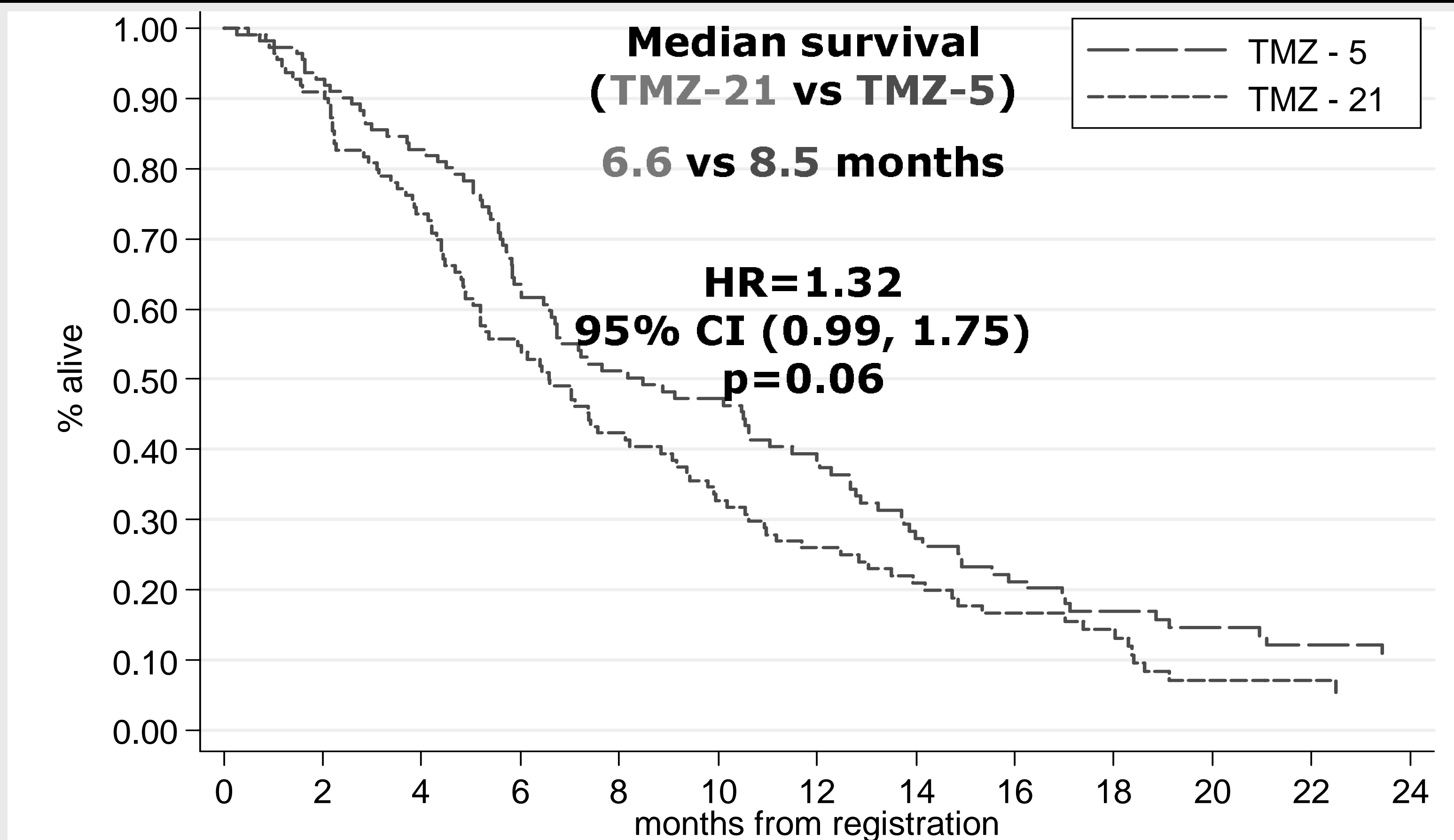
No. at risk

TMZ – 5day	112	84	65	51	38	28	18	11	11	8	7	6	5
TMZ – 21day	111	83	55	38	25	15	8	3	2	1	1	1	1

Survival: TMZ-5 vs TMZ-21

NCRI National Cancer Research Institute

MRC Clinical Trials Unit



No. at risk

TMZ – 5 day	112	103	91	68	53	48	38	27	21	15	12	10	9
TMZ – 21 day	111	100	80	57	44	34	27	21	15	12	6	4	3

Summary & Conclusion - 1

NCRI National Cancer Research Institute

MRC Clinical Trials Unit

In this large randomised trial in chemo-naïve, recurrent high grade glioma

- No clear survival benefit to TMZ over PCV was seen overall, however:
- TMZ-5 schedule was superior to TMZ-21 schedule with respect to progression-free and overall survival
- These results question the current basis of increasing TMZ 'dose intensity' by prolonged scheduling

NCRI National Cancer Research Institute

Summary & Conclusion - 2

MRC Clinical Trials Unit

- Concomitant chemoradiation with TMZ-5 schedule may further improve prognosis instead of TMZ-49 used currently for the primary treatment of GBM
- Translational works on-going in collected tumour specimens to examine whether MGMT expression and/or MGMT promotor methylation status are associated with survival

Acknowledgements

Many thanks to all the patients who took part, and all the clinicians and research staff in the 36 UK participating centres

Dr Colin Askill & Dr Kath Rowley, Singleton Hospital (Swansea); Dr Saif Awwad, Royal Shrewsbury Hospital; Dr Hugo Baillie-Johnson, Norfolk & Norwich University Hospital; Dr Ron Beaney, St. Thomas's Hospital; Dr Claire Blesing & Dr Nicola Warner, The Churchill Hospital (Oxford); Dr Peter Bliss & Dr Ingrid Koehler, Royal Devon & Exeter Hospital/ Torbay Hospital (Torquay); Prof Michael Brada & Dr Frank Saran, Royal Marsden Hospital (Sutton); Dr Cathryn Brock, Charing Cross Hospital, Dr Anthony Chalmers, Royal Sussex County Hospital (Brighton), Mr Charles Davis & Dr A Hindley, The Royal Preston Hospital; Dr Robert Dealey, The Princess Royal Hospital (Hull); Dr Peter Dunlop, The James Cook University Hospital (Middlesbrough);Dr Christine Elwell & Dr Hany Eldeeb, Northampton General Hospital; Dr Sean Elyan & Dr S Guglani, Cheltenham General Hospital; Dr Sara Erridge & Dr Anna Gregor, Western General Hospital (Edinburgh); Dr Rao Gattamaneni, The Christie Hospital, Dr Brian Haylock & Dr A Shenoy, Clatterbridge Centre for Oncology (Wirral); Dr Kirsten Hopkins, Bristol Haematology & Oncology Centre; Dr David C Hurman, Aberdeen Royal Infirmary, Dr Theodore Hurst, Royal Cornwall Hospital; Dr Sarah Jefferies, Dr N Burnet & Dr P Jones, Addenbrooke's Hospital; Dr Stephen Kelly & Dr S Pascoe, Derriford Hospital/Plymouth Onc Centre; Dr Siow Ming Lee & Dr Susan Short, UCLH NHS Trust; Dr David Levy, Weston Park Hospital (Sheffield); Dr Carmel Loughrey & Dr GE Gerrard, Cookridge Hospital (Leeds); Dr Hugh Newman, Royal United Hospital (Bath); Prof Roy Rampling, Beatson West of Scotland Cancer Centre (Glasgow); Prof Elaine M Rankin & Dr Douglas Adamson, Ninewells Hospital (Dundee); Dr Gill Sadler, Maidstone Hospital; Dr Eliot Sims, Queen's Hospital; Dr Michael Sokal, Nottingham City Hospital; Dr Paul Symonds, Leicester Royal Infirmary; Dr Owen Tilsley,Velindre Hospital (Cardiff); Dr Stephen Whittaker, St. Luke's Cancer Centre (Guildford); Dr Marie Wilkins, Sussex Oncology Centre; Dr Elena Wilson, Royal Free Hospital

Chief Investigator: Professor Michael Brada; **Co-chief investigator**: Dr Siow Ming Lee

Acknowledgements

- This NCRI trial was funded by a grant from Cancer Research UK and conducted by the MRC Clinical Trials Unit*

***CTU trial staff**: Statisticians - Lindsay Thompson, Sarah Kirk, Rhian Gabe, Sally Stenning; Trial managers - Sarah Beall, Claire Yule, Simon Clawson; Data managers - Kate Adams, Ellen Dyer