BRAIN TUMOUR INFORMATION & SUPPORT
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Regional Neuro-Oncology Service Information Evening

Dr Jackie Harney

Information Evening hosted by Brainwaves NI, in partnership with the Northern Ireland Regional Neuro-Oncology Multi Disciplinary Team.

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HSC Belfast Health and Social Care Trust

Brain Tumour Awareness Meeting

Updates in Neuro-Oncology

13/06/13

Dr Jackie Harney

Summary

(Potential)Changes in Practice

- Anaplastic Oligodendroglioma (AO)
- Malignant Glioma in the elderly

Anaplastic Oligodendroglioma

Tale of Two Studies and a Lonely Tumour

- Anaplastic Oligodendroglioma
- Uncommon (5-10%) brain tumour with distinctive histopathological features
- Long recognized as a more favorable diagnosis
- Characterized by a balanced translocation of chromosomes 1 and 19 (≈ 70%)
- Prognostic favorable if 1p/19q deleted
- Predictive value uncertain

Anaplastic Oligodendroglioma

- Historically treatment consisted of maximal safe resection followed by radiotherapy
- The suggestion that some tumours were chemo-sensitive prompted 2 studies in the 1990's
  - **RTOG 9402** - 1994
  - **EORTC 2691** - 1995

EORTC 26951

368 patients (AO)

Maximal safe resection

RT Alone
60Gy

RT + PCV x 6 cycles
60Gy

- Study initially published in 2006 with a median follow-up of 5 years
- Results subsequently updated & published in 2012 with a median FU of 12 years
- Patients were eligible to receive additional treatment after progression following their initial management.

EORTC 26951

- Median follow-up of 5 years (2006)
  - Progression-free survival (PFS) was already significantly prolonged with adjuvant PCV c/w RT alone (23 vs. 13 months, P=0.0018), **but** the difference in overall survival at that time was not statistically significant (40mths vs. 31mths).

- With more prolonged follow-up (2012)
  - the survival curves with the two initial treatment regimens diverged
  - the benefit from initial combined chemotherapy (PCV) and RT was seen primarily in patients whose tumors contained the **1p/19q co-deletion**.

EORTC 26951

- Samples from 316/368 patients (86%) available for analysis for 1p/19q co-deletion.

- 80 (25%)patients contained the 1p/19q co-deletion
  - PFS was **significantly increased** with RT + PCV c/w RT alone (median PFS - 157mths vs. 50mths)
  - There was a trend toward increase in overall survival (median not reached vs. 112 months).

- 236 (75%) non-codeleted patients,
  - the prognosis was substantially worse and the impact of adding chemotherapy to RT was limited (median PFS 15mths vs. 9 mths and median OS 25mths vs. 21 mths)

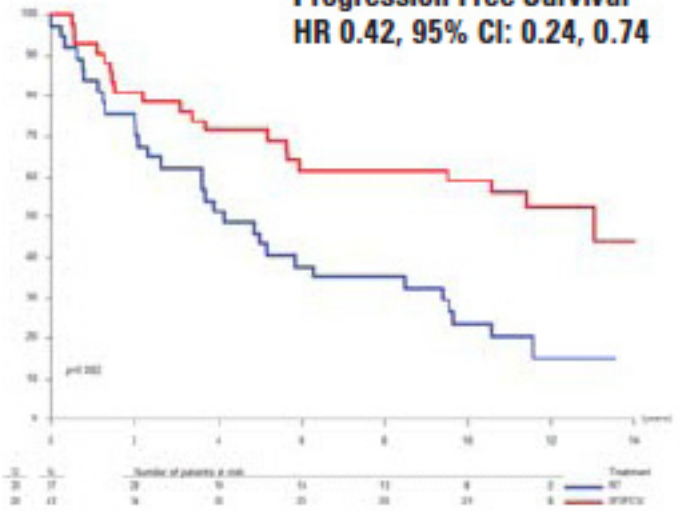
EORTC 26951

PFS and OS in 1p/19q Codeleted Patients (80 Patients)

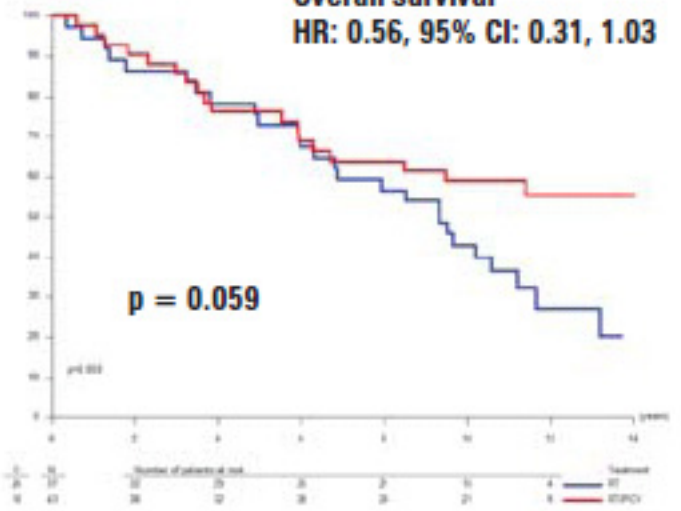
With addition of PCV:
OS increase from 9 yrs
after RT alone to > 12 yrs

Median	PFS	OS
RT (37)	50 months	112 months
RT/PCV (43)	157 months	Not reached

Progression Free Survival
HR 0.42, 95% CI: 0.24, 0.74



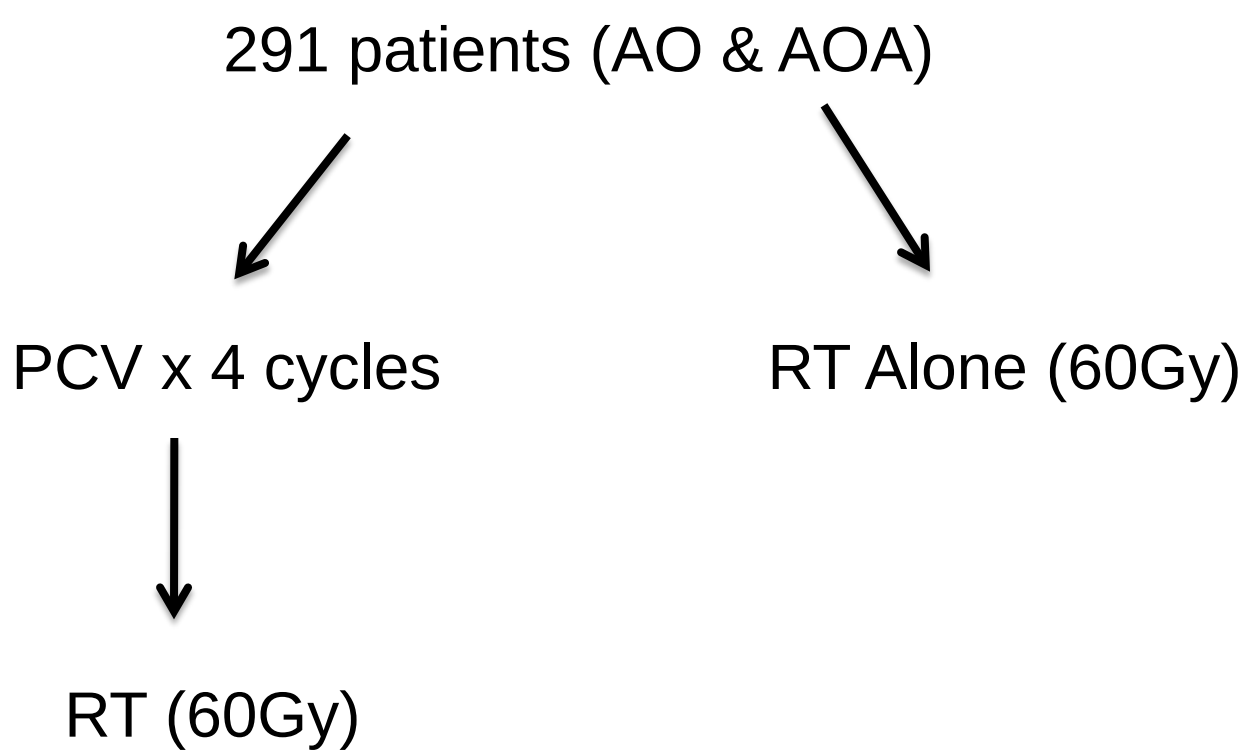
Overall survival
HR: 0.56, 95% CI: 0.31, 1.03



*95% Confidence Interval

Abbreviations: PFS, progression-free survival; OS, overall survival; PCV, combination procarbazine, lomustine, and vincristine; RT, radiation therapy.

RTOG 9402



Results initially published in 2006
Results updated & published in 2012 with a median follow-up of 11.3 yrs

RTOG 9402

- **2006** – median PFS was significantly increased with PCV + RT c/w RT alone (2.6yrs vs. 1.7 yrs), ***but*** the difference in median OS was not significant (4.9yrs vs. 4.7 yrs)
- **2012** - Results were dependent upon the molecular characteristics of the tumor and were consistent with those seen in the EORTC 26951 trial.
- **1p/19q co-deleted tumours**
  - Median OS was significantly prolonged in patients treated with intensified PCV followed by RT c/w those given RT alone (median OS 14.7yrs vs. 7.3 yrs).
- **Non co-deleted tumours**
  - Prognosis was again substantially worse, and the impact of therapy was not statistically significant (median OS 2.6 vs. 2.7 years)

RTOG 9402

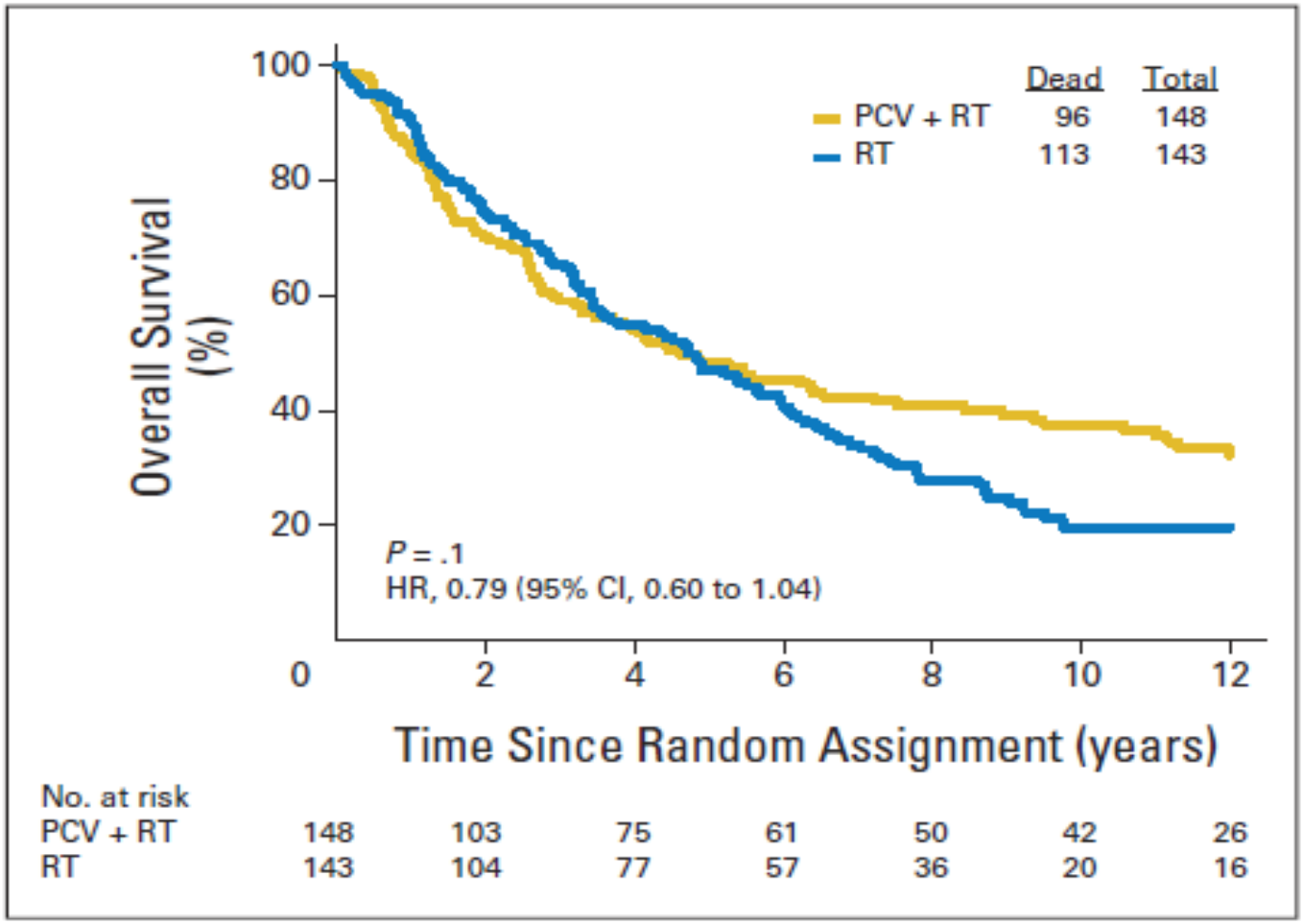


Fig 2. Kaplan-Meier estimates of overall survival by treatment group. The hazard ratio (HR) for survival of patients treated with procarbazine, lomustine, and vincristine (PCV) plus radiotherapy (RT) compared with RT alone was 0.79 (95% CI, 0.60 to 1.04; *P* = .1).

RTOG 9402

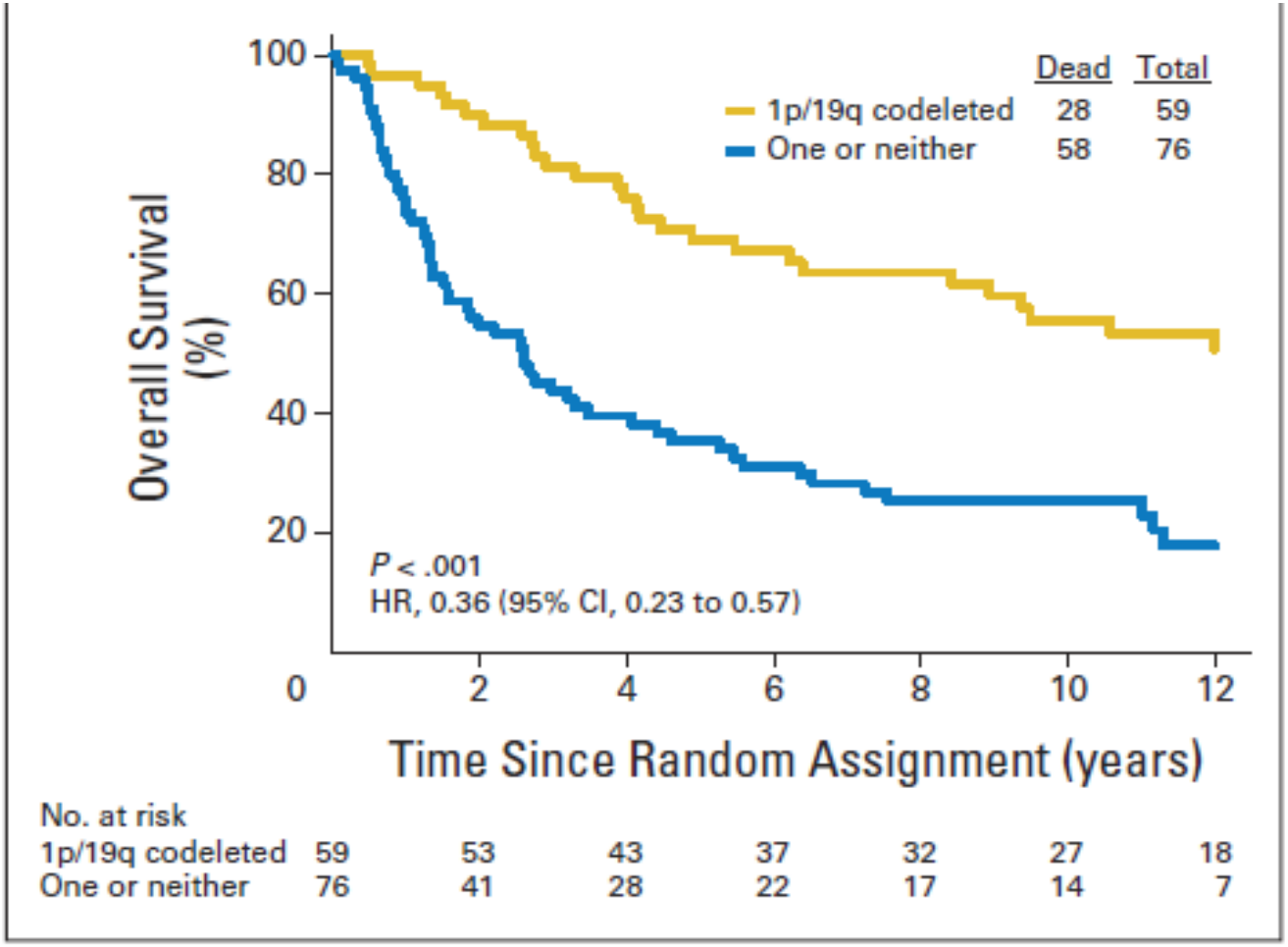


Fig 3. Kaplan-Meier estimates of overall survival by genotype for procarbazine, lomustine, and vincristine plus radiotherapy arm. The hazard ratio (HR) for overall survival of patients with 1p/19q codeleted anaplastic oligodendroglioma (AO)/ anaplastic oligoastrocytoma (AOA) compared with those with AO/AOA in whom one or neither allele was deleted was 0.36 (95% CI, 0.23 to 0.57; $P < .001$).

Summary

	RTOG 9402	EORTC 26951
Median Follow-up	11.3 years	140 months
<u>All patients – median OS</u> RT RT + PCV	 4.6 years 4.7 years	 31 months 42 months
<u>Co-deleted – median OS</u> RT **RT + PCV** HR	 7.3 years **14.7 years** .55	 112 months **NR** .56
<u>Non Co-deleted – median OS</u> RT RT + PCV	 2.7 years 2.6 years	 21 months 25 months

Significance

- New standard of care for co-deleted anaplastic oligodendrogliomas
- Patients with co-deleted AO **should** receive chemotherapy

- **International CODEL study**
  - Patients with co-deleted AO randomized to
  - RT alone
  - RT/TEM followed by TEM
  - TEM alone
  - *BUT*
- **STUDY CURRENTLY ON HOLD**

Significance

STUDY CURRENTLY ON HOLD

Why?

- Issues
  - Back to PCV?
  - Role of Temozolomide?
  - Concurrent and adjuvant?
  - Chemo alone for chemo-sensitive tumor?

Malignant Glioma in Elderly Patients

- Malignant glioma common in the over 60's
- Median OS < 1 year
- Standard of care since 2004 – Concurrent chemo/RT + adjuvant chemotherapy
- But – based on a population of < 70 yrs
- & - increasing age a negative prognostic feature
- Elderly patients might not be offered/fit for combined therapy
- Alternatives treatments sought
  - Hypofractionated RT – 6 fractions over 2 weeks
  - Temozolomide

2 large studies performed

Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial

Wolfgang Wick, Michael Platten, Christoph Meisner, Jörg Felsberg, Ghazaleh Tabatabai, Matthias Simon, Guido Nikkhah, Kirsten Papsdorf, Joachim P Steinbach, Michael Sabel, Stephanie E Combs, Jan Vesper, Christian Braun, Jürgen Meixensberger, Ralf Ketter, Regine Mayer-Steinacker, Guido Reifenberger, Michael Weller, for the NOA-08 Study Group of the Neuro-oncology Working Group (NOA) of the German Cancer Society*

Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial

Annika Malmström, Bjørn Henning Grønberg, Christine Marosi, Roger Stupp, Didier Frappaz, Henrik Schultz, Ufuk Abacioglu, Björn Tavelin, Benoit Lhermitte, Monika E Hegi, Johan Rosell, Roger Henriksson, for the Nordic Clinical Brain Tumour Study Group (NCBTSG)

NOA Study

- 584 patients with grade 3/4 malignant glioma
- >65 years
- KPS >/= 60
  - Randomised
    - Temozolomide 100mg/msq, week on, week off
    - RT 60Gy in 30# over 6 weeks
    - Endpoint – OS

NORDIC Study

- 342 patients with GBM
- >60 years
- PS 0-2
  - Randomised
    - Temozolomide 200mg/msq x 5 days every 28 days
    - RT 34Gy in 10#
    - RT 60gy in 30#
    - Endpoint - OS

NOA-08 Results

Overall Survival

Event Free Survival

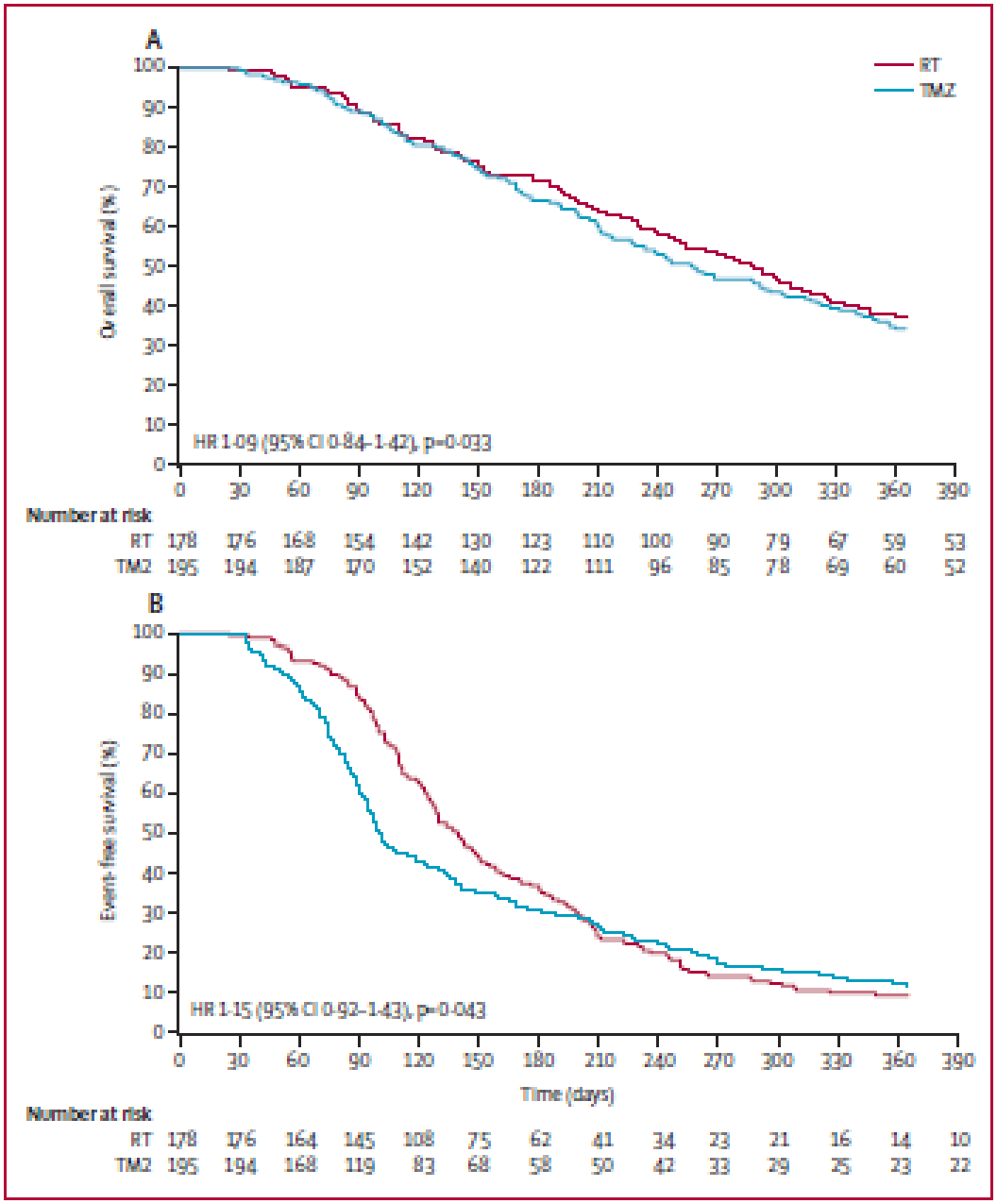


Figure 2: Kaplan-Meier analysis of overall and event-free survival
(A) Overall survival. (B) Event-free survival presented as non-proportional curves, which are deemed non-problematic in the context of non-inferiority. RT=radiotherapy. TMZ=temozolomide. HR=hazard ratio.

NOA-08 Results -Methylation Status

Overall Survival

Event free survival

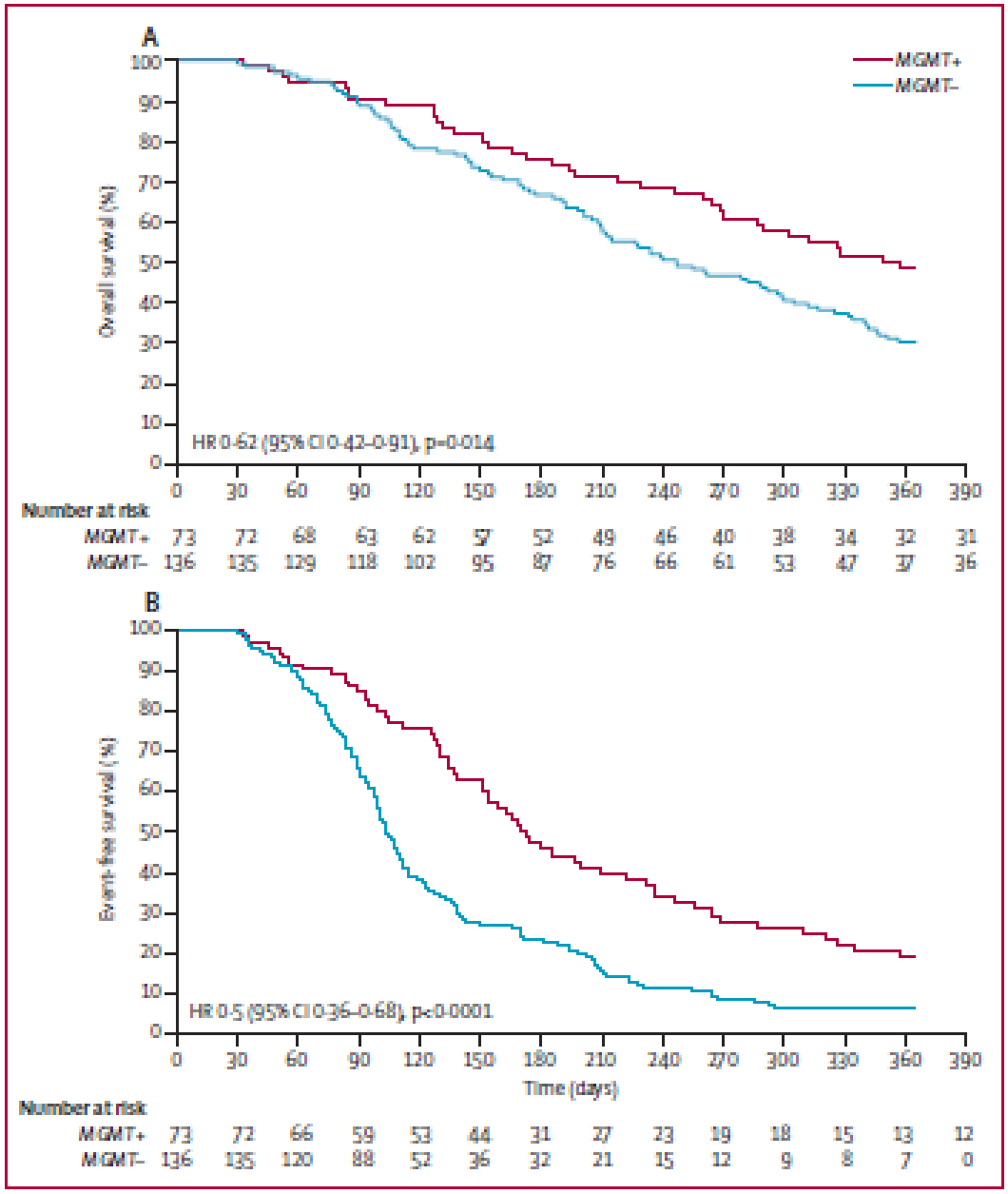
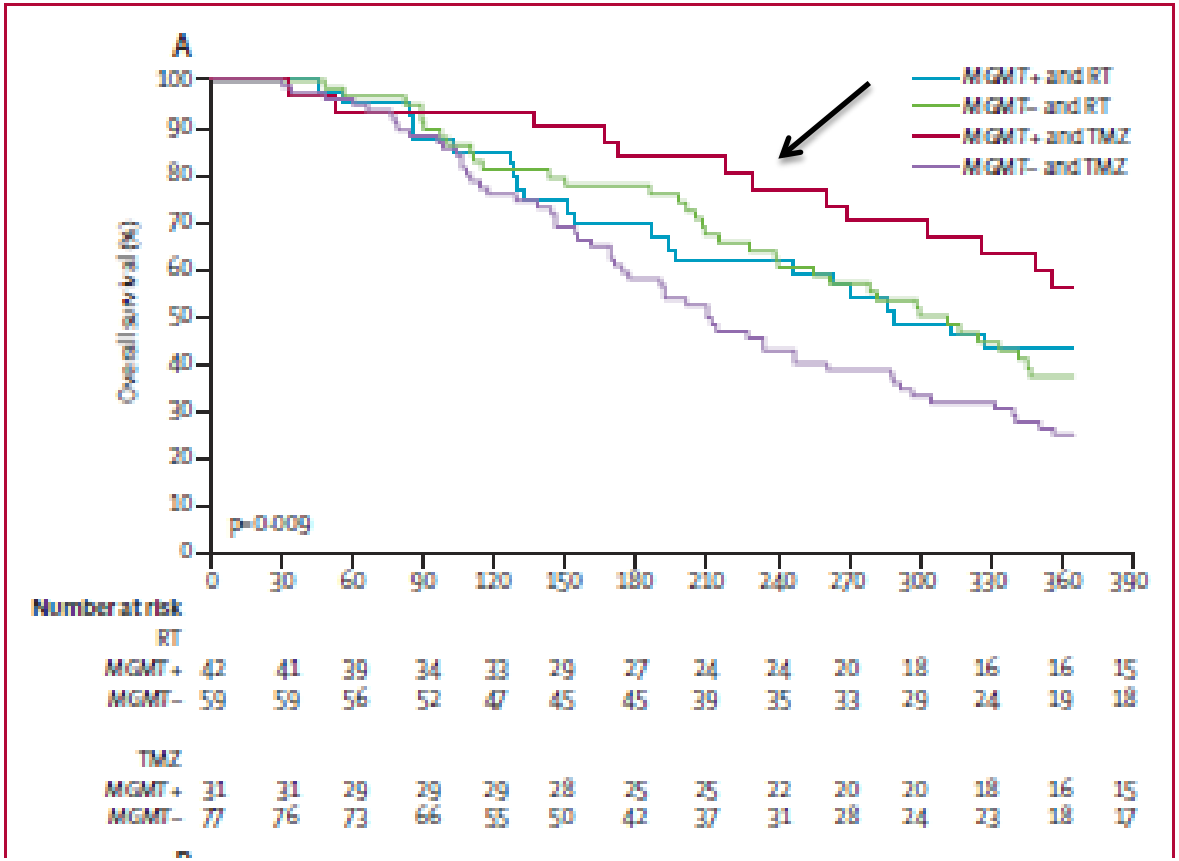


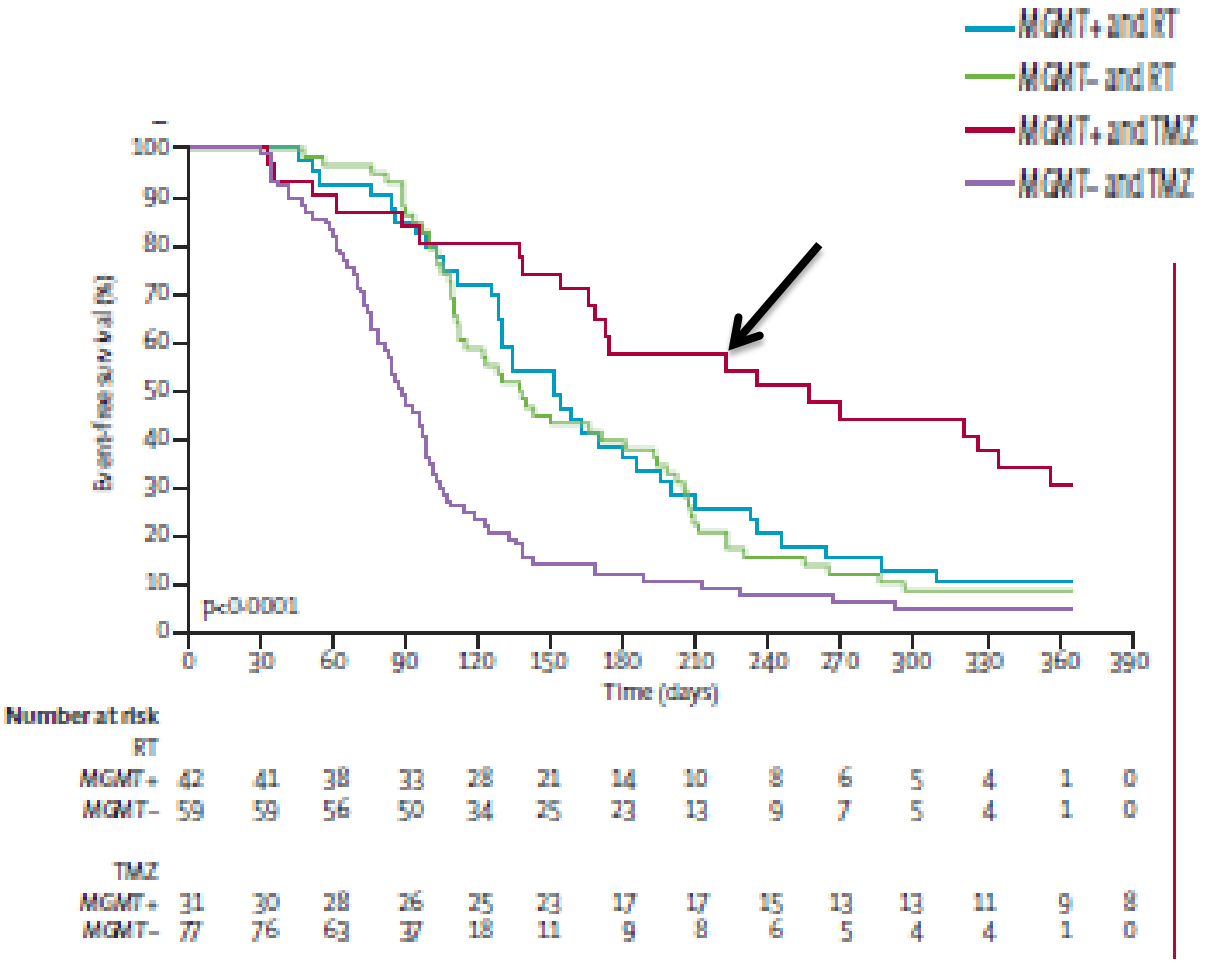
Figure 3: **Kaplan-Meier analysis of overall and event-free survival in relation to *MGMT* promoter methylation status**
(A) Overall survival. (B) Event-free survival. HR=hazard ratio.

NOA-08 Results - Methylation Status & Treatment modality



Overall Survival

NOA-08 Results - Methylation Status & Treatment modality

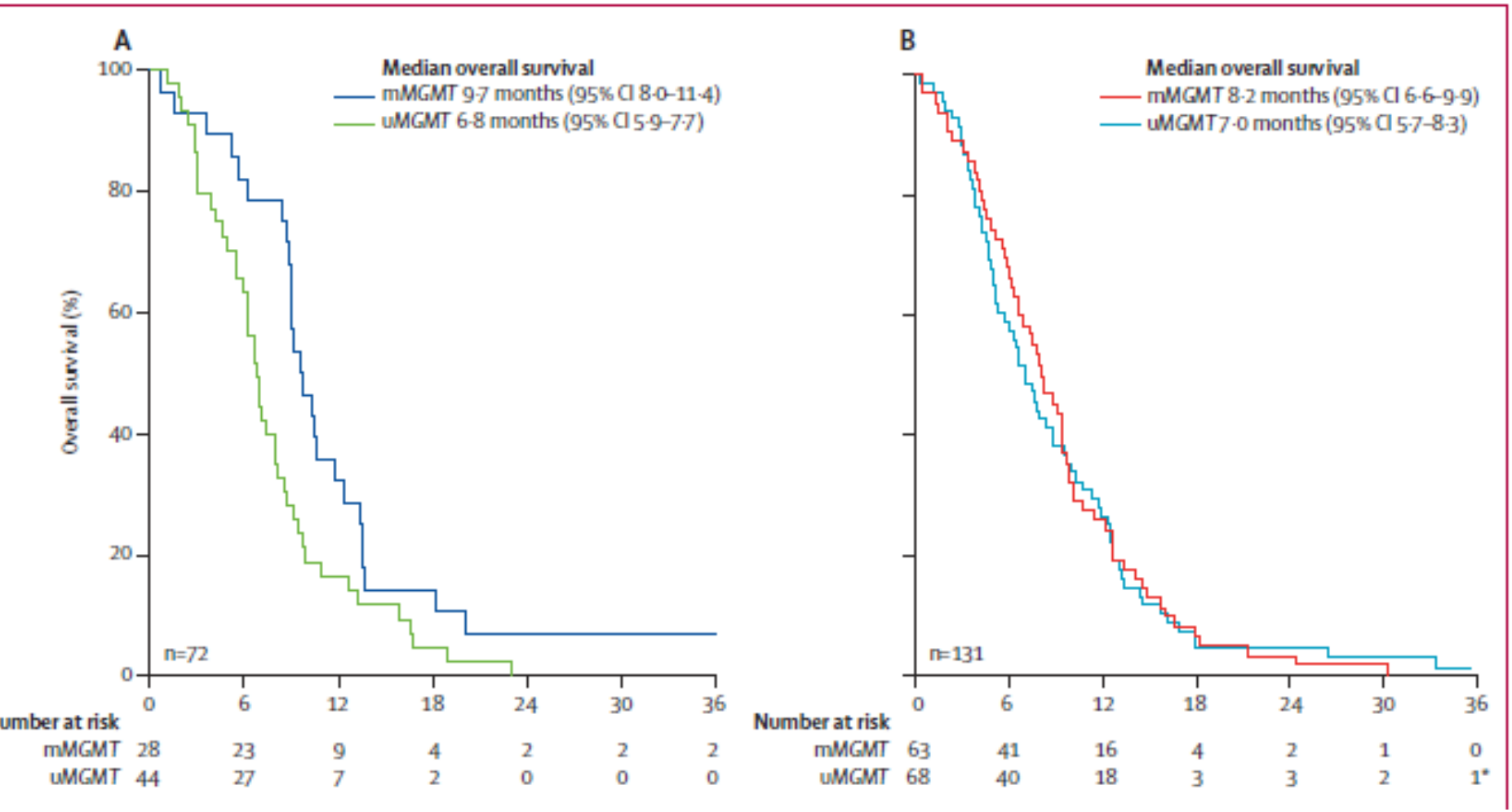


Event Free Survival

NOA-08

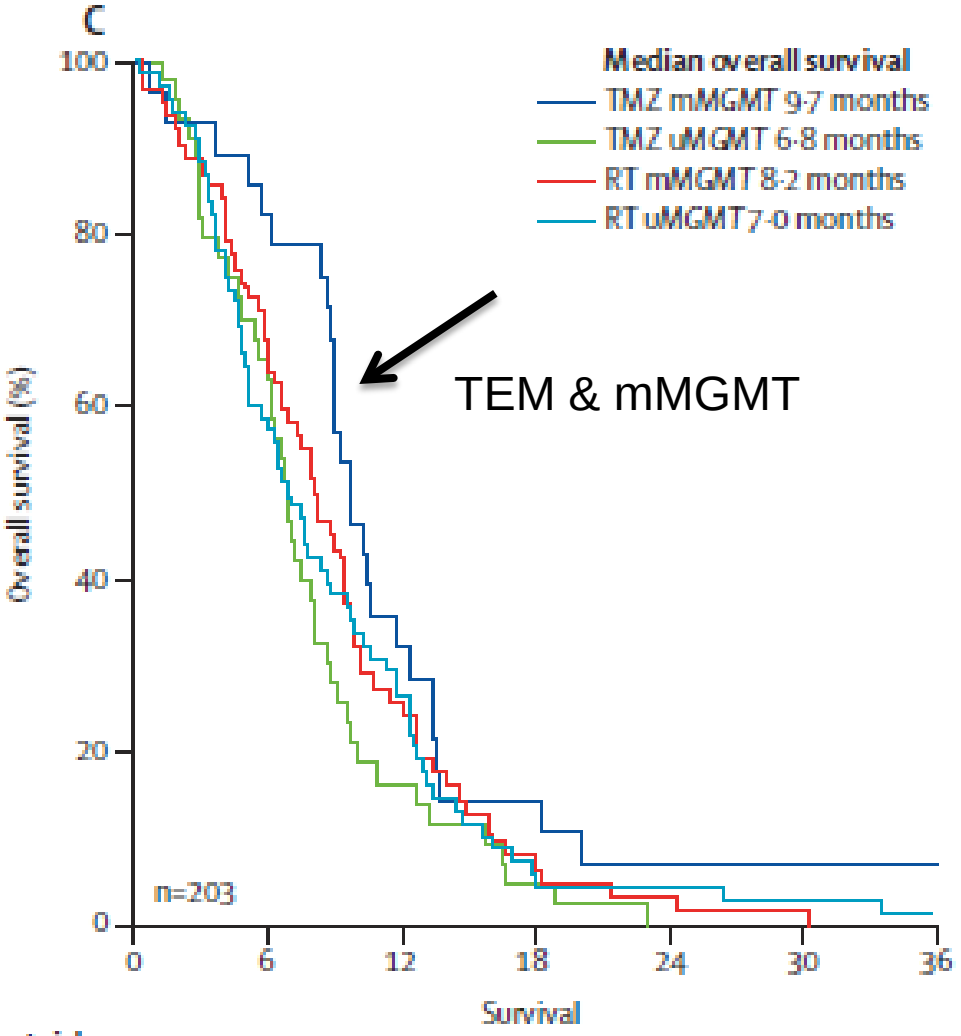
Interpretation Temozolomide alone is non-inferior to radiotherapy alone in the treatment of elderly patients with malignant astrocytoma. *MGMT* promoter methylation seems to be a useful biomarker for outcomes by treatment and could aid decision-making.

NORDIC Study



Temozolomide

Radiotherapy (pooled)



Number at risk								Number
TMZ mMGMT	28	23	9	4	2	2	2	m
TMZ uMGMT	44	27	7	2	0	0	0	u
RT mMGMT	63	41	16	4	2	1	0	
RT uMGMT	68	40	18	3	3	2	1*	

NORDIC Study

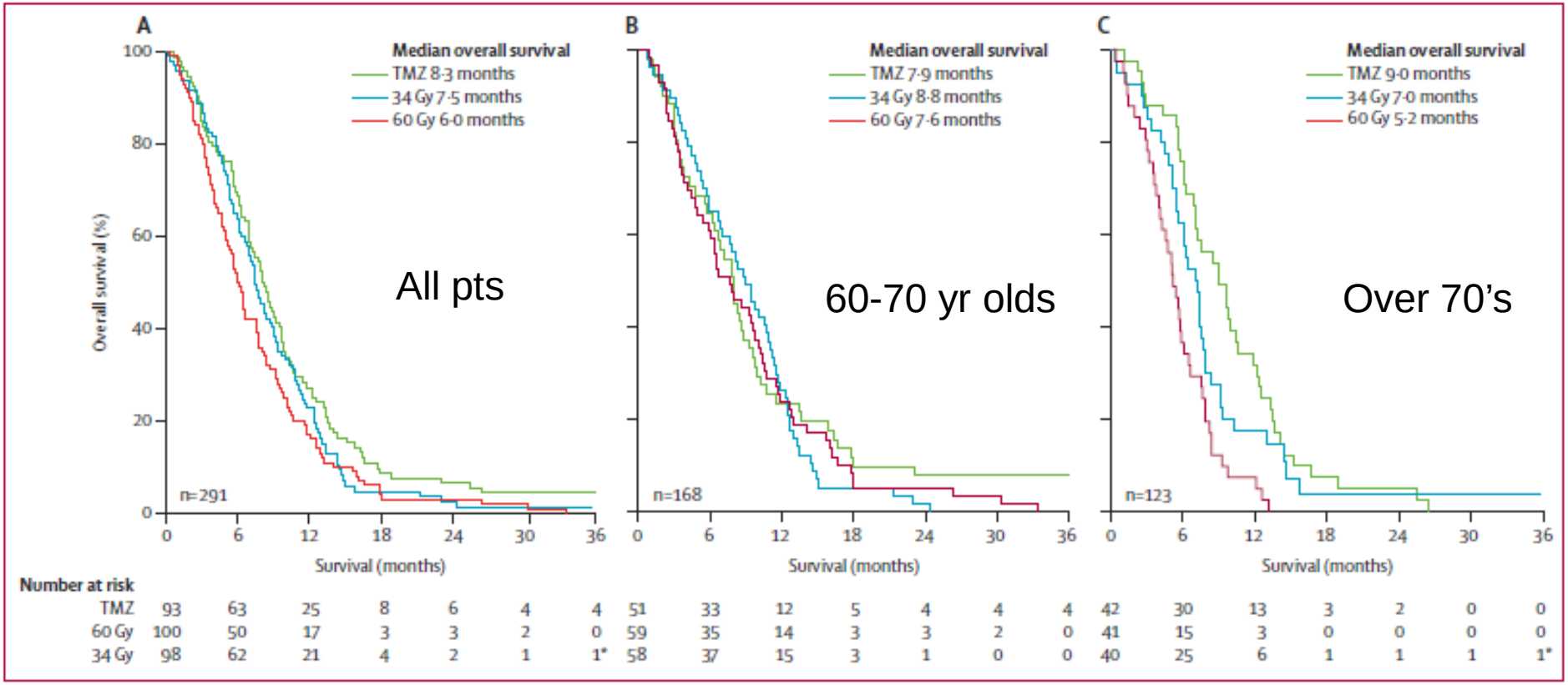


Figure 2: **Kaplan-Meier analysis of overall survival in patients randomised across three treatment groups**
(A) All patients. (B) Patients aged 60–70 years. (C) Patients older than 70 years. TMZ=temozolomide. 34 Gy=hypofractionated radiotherapy. 60 Gy=standard radiotherapy. *Patient censored at 35 months.

NORDIC Study

	Number of deaths/ patients	Hazard ratio (95% CI)	Log-rank p value	Median (95% CI) survival (months)	1-year (95% CI) survival (%)
Temozolomide or hypofractionated radiotherapy vs standard radiotherapy*					
Overall					
Standard radiotherapy	100/100	1·0	..	6·0 (5·1–6·8)	17% (10–24)
Hypofractionated radiotherapy	94/98	0·85 (0·64–1·12)	0·24	7·5 (6·5–8·6)	23% (14–31)
Temozolomide	90/93	0·70 (0·52–0·93)	0·01	8·3 (7·1–9·5)	27% (18–36)
Age 60–70 years					
Standard radiotherapy	59/59	1·0	..	7·6 (5·2–10·1)	24% (13–35)
Hypofractionated radiotherapy	57/58	1·06 (0·73–1·54)	0·77	8·8 (6·9–10·8)	26% (15–38)
Temozolomide	49/51	0·87 (0·59–1·28)	0·48	7·9 (6·5–9·3)	24% (12–35)
Age >70 years					
Standard radiotherapy	41/41	1·0	..	5·2 (4·0–6·3)	7% (0·6–15)
Hypofractionated radiotherapy	37/40	0·59 (0·37–0·93)	0·02	7·0 (5·2–8·8)	18% (6–29)
Temozolomide	41/42	0·35 (0·21–0·56)	<0·0001	9·0 (6·2–11·8)	32% (18–46)

NORDIC Study

MGMT status‡					
Unmethylated					
Any radiotherapy	67/68	1·0	..	7·0 (5·7–8·3)	26% (16–37)
Temozolomide	43/44	1·16 (0·78–1·72)	0·46	6·8 (5·9–7·7)	16% (5–27)
Methylated					
Any radiotherapy	62/63	1·0	..	8·2 (6·6–9·9)	26% (15–37)
Temozolomide	26/28	0·64 (0·39–1·04)	0·07	9·7 (8·0–11·4)	32% (15–49)
Temozolomide					
Unmethylated	43/44	1·0	..	6·8 (5·9–7·7)	16% (5–27)
Methylated	26/28	0·56 (0·34–0·93)	0·02	9·7 (8·0–11·4)	32% (15–49)
Any radiotherapy					
Unmethylated	67/68	1·0	..	7·0 (5·7–8·3)	26% (16–37)
Methylated	62/63	0·97 (0·69–1·38)	0·81	8·2 (6·6–9·9)	26% (15–37)

*Three-group randomisation (n=291). †n=242. ‡MGMT analysis stratified for randomisation to three or two groups.

NORDIC

Interpretation Standard radiotherapy was associated with poor outcomes, especially in patients older than 70 years. Both temozolomide and hypofractionated radiotherapy should be considered as standard treatment options in elderly patients with glioblastoma. *MGMT* promoter methylation status might be a useful predictive marker for benefit from temozolomide.

Interpretation

Our results are in concordance with those in previous reports, but additionally highlight that standard radiotherapy seems poorly tolerated in patients older than 70 years and can be avoided in those with predicted short survival. A high number of patients were unable to complete the standard radiotherapy schedule compared with the 2-week hypofractionated schedule. Our findings support the predictive value of *MGMT* promoter methylation status for response to temozolomide chemotherapy, but we found no similar predictive value for response to radiotherapy. Our data, as well as those of the NOA-08 trial, suggest that testing of *MGMT* promoter methylation status would be useful in elderly patients with glioblastoma to facilitate treatment recommendations. The European Organisation for