TRENDING UPDATES IN RADIATION ONCOLOGY –WEBINAR SERIES
PART 3 – November 26th 2021, Friday

CATNON and CODEL – Update in Mx Anaplastic Glioma

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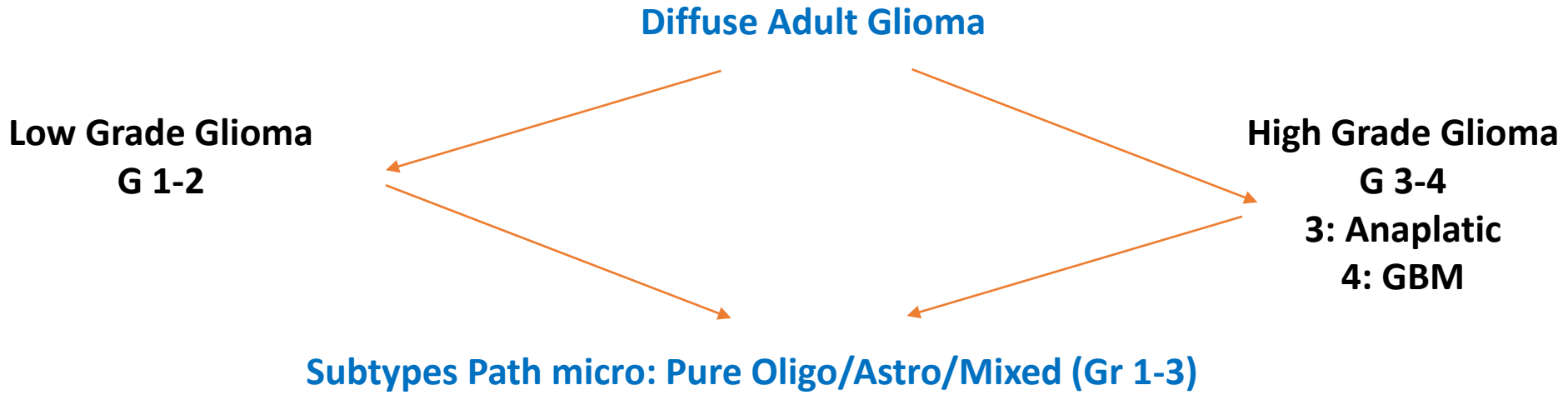
Anaplastic glioma

- About 20-30% of all newly diagnosed primary brain tumors in adults
  - Anaplastic Astrocytoma,
  - Anaplastic Oligoastrocytoma
  - Anaplastic Oligodendroglioma.



Anaplastic glioma

- Traditionally treated similar to GBM
  - Maximum safe resection followed by RT (60Gy EQD2) with TMZ f/b adj TMZ 6 cycles or similar regimens as per institutional choices
    - RT alone
    - RT & concurrent CT
    - RT + adjuvant CT
    - RT & concurrent CT + adjuvant CT
  - CT: PCV variations to TMZ
- Reason for lack of clarity / consensus
  - Heterogeneous group
    - Pathologically: Astrocytoma, Oligodendroglioma, Mixed (AA, AO, AOA)
    - Biologically: IDH, 1p19q, MGMT, PTEN, P53 etc
    - Clinical outcomes 2 years median values to 12-15 years PFS / OS
      - Vary from grade to GBM outcomes.

Anaplastic glioma

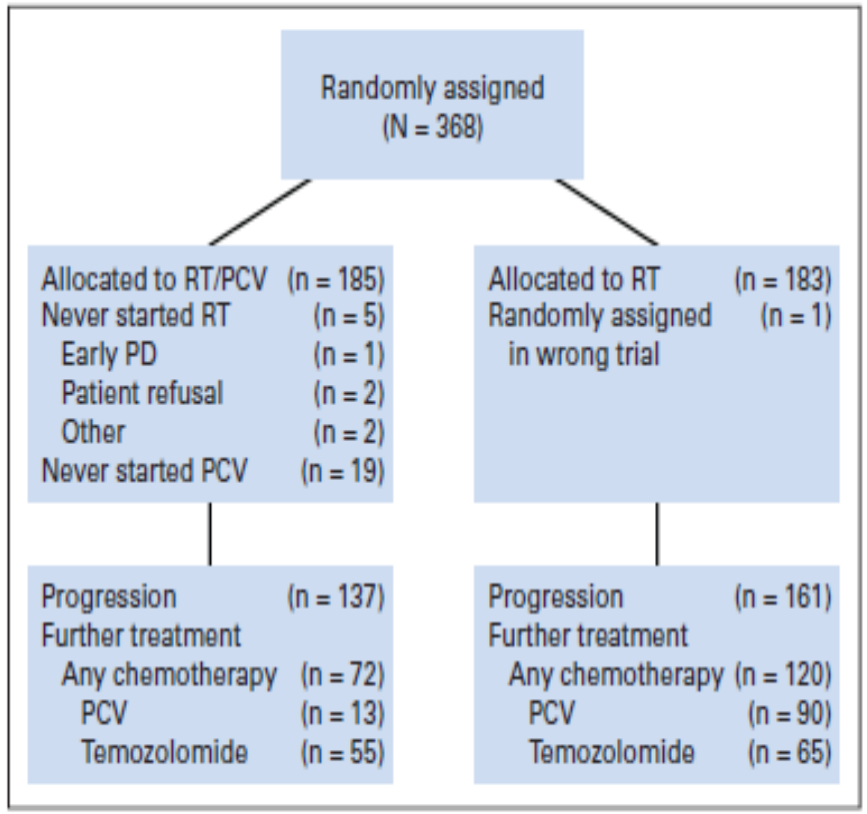
- **Objectives:**
  - Briefly discus **historical data**:
    - EORTC 26951 & RTOG 9402
  - **Latest studies** available outcomes and their implication on current practice:
    - CATNON & CODEL

EORTC 26981 and of EORTC 26951

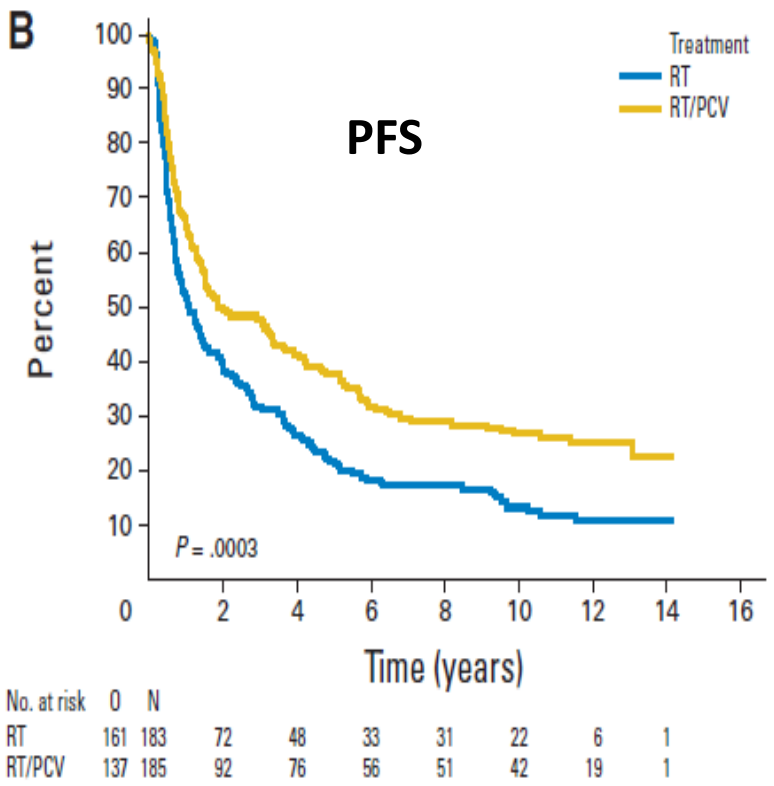
- To assess whether concurrent radiotherapy with daily temozolomide chemotherapy improves overall survival as compared to no daily temozolomide in non-1p/19q deleted anaplastic glioma.
- To assess whether adjuvant temozolomide chemotherapy improves survival as compared to no adjuvant temozolomide chemotherapy in non-1p/19q deleted anaplastic glioma

EORTC study 26951

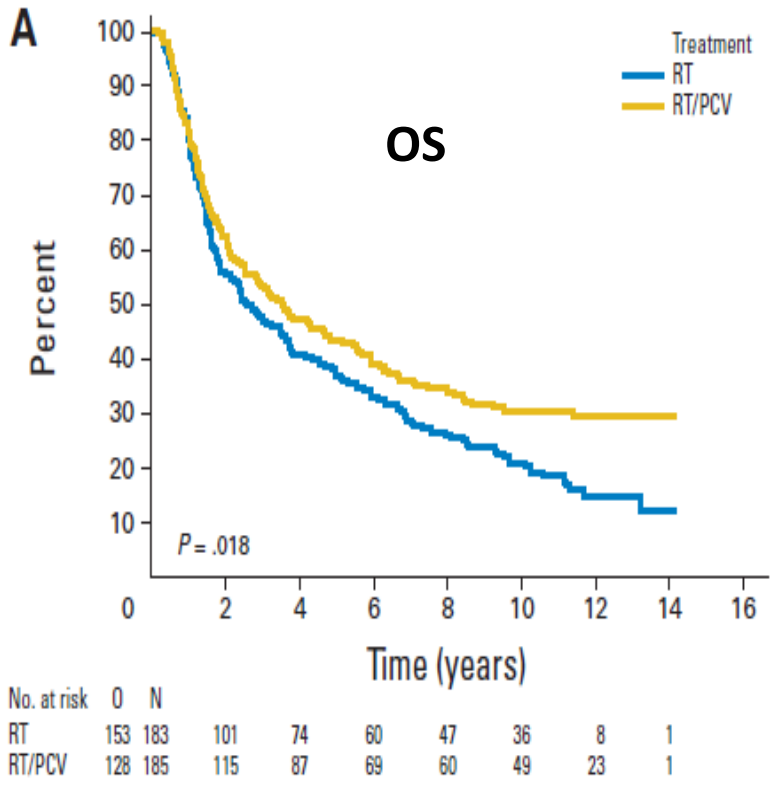
Anaplastic ODG : RT alone 59.4 Gy vs RT f/b 6 adj std PCV



Median follow-up of 140 months



24.3 vs 13.2 m
HR, 0.66; 95% CI, 0.52 to 0.83



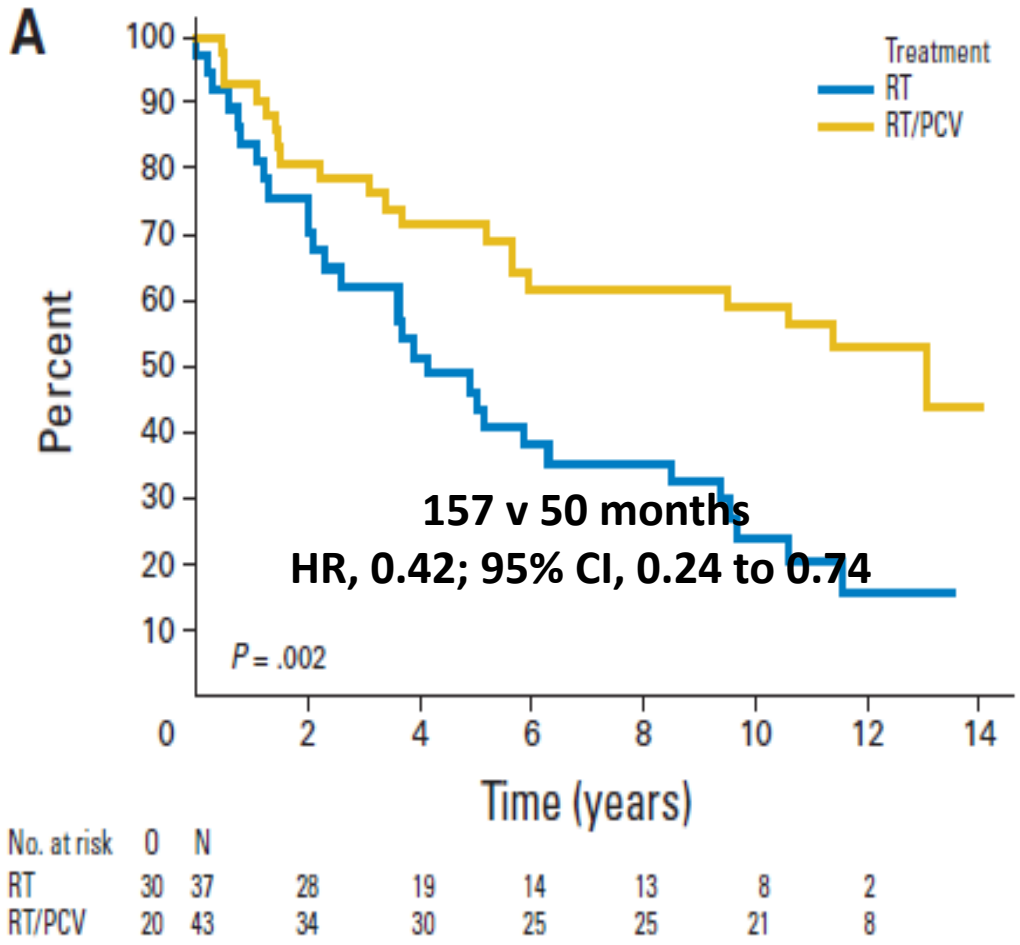
42.3 *v* 30.6 m
HR: 0.75; 95% CI, 0.60 to 0.95)

DOI: 10.1200/JCO.2012.43.2229

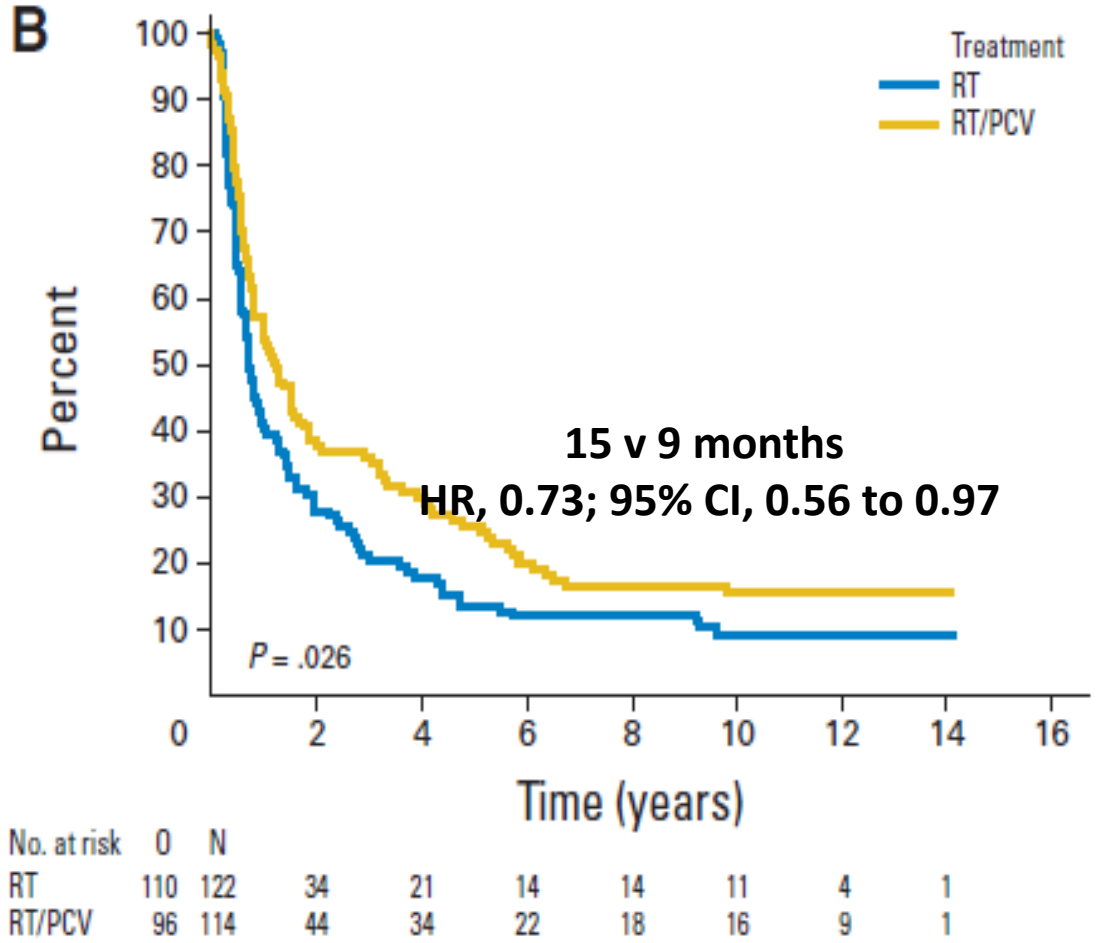
EORTC study 26951

PFS

1p/19q-codeleted tumors



non–1p/19qcodeleted tumors



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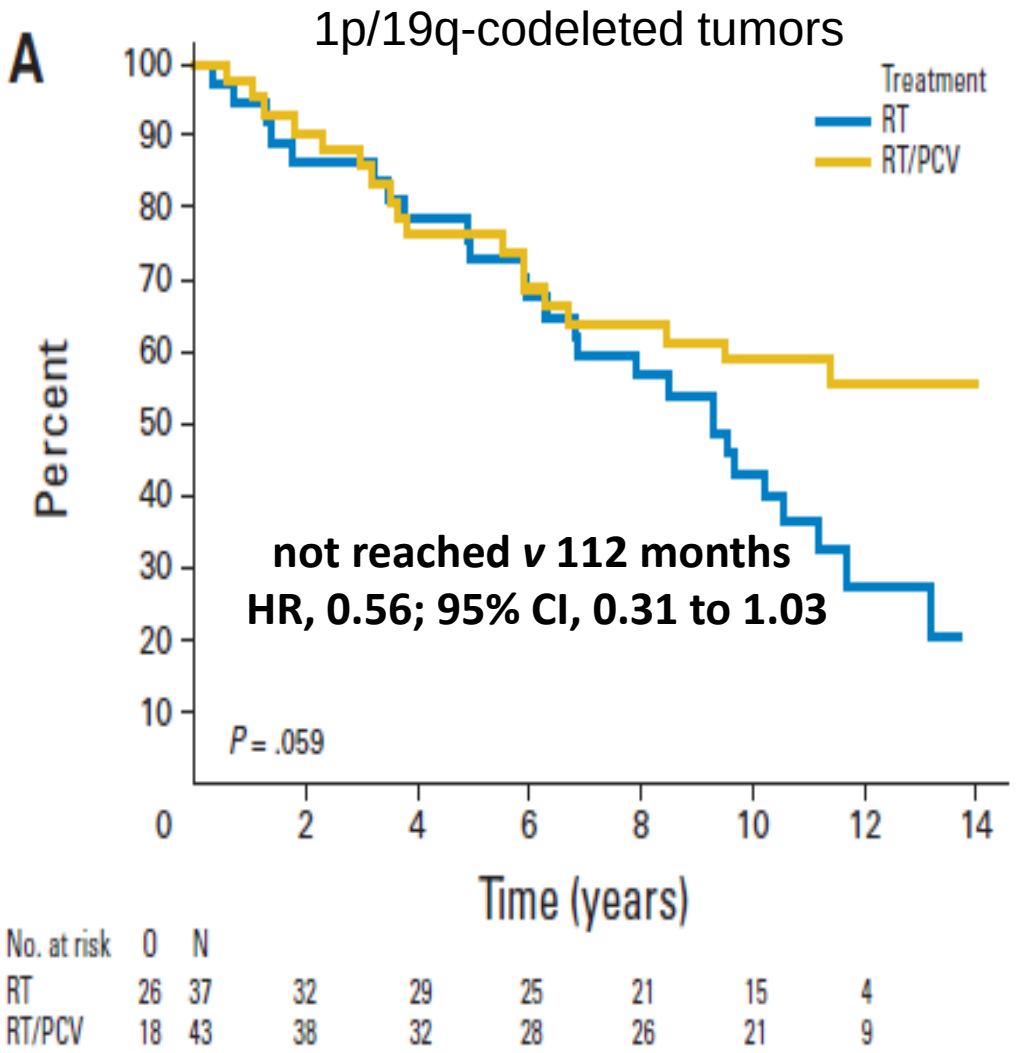
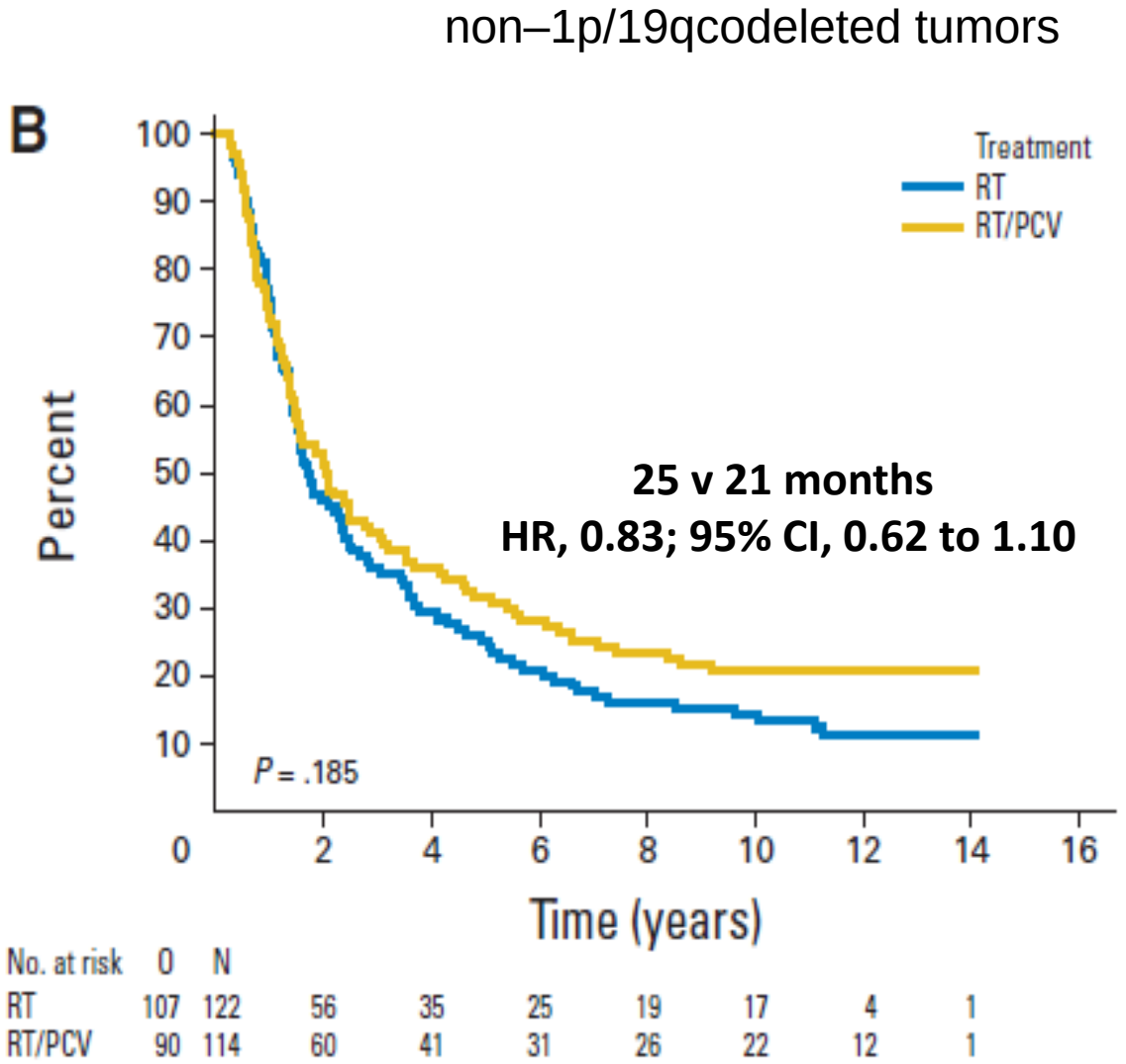
EORTC study 26951

OS

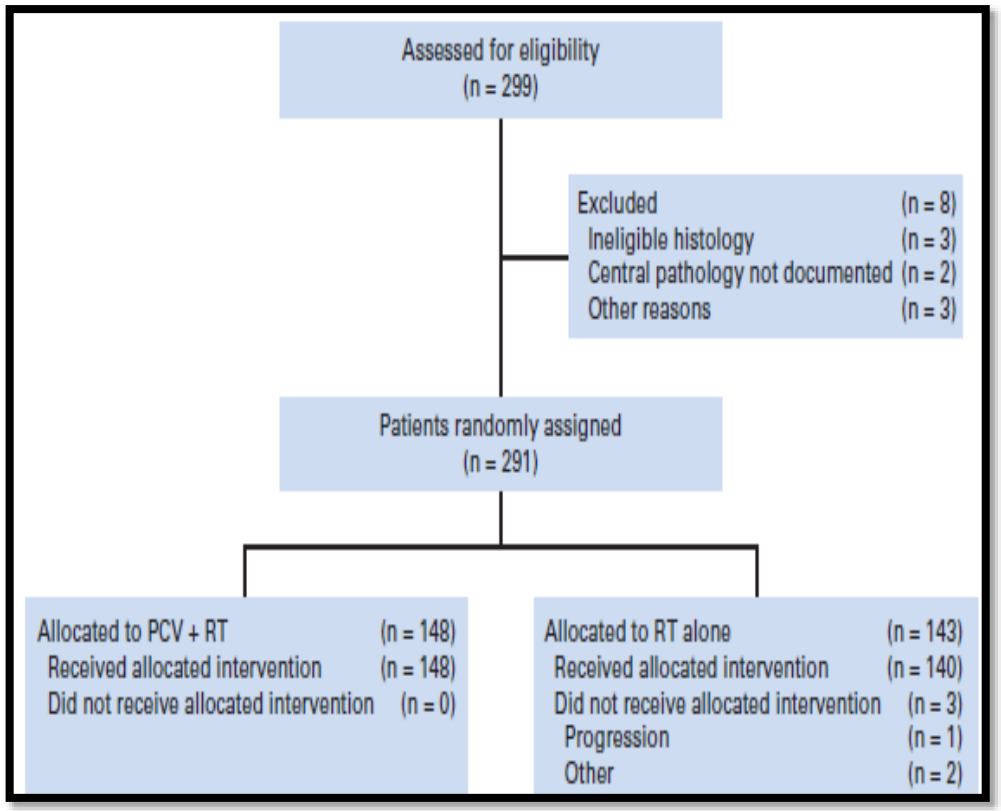




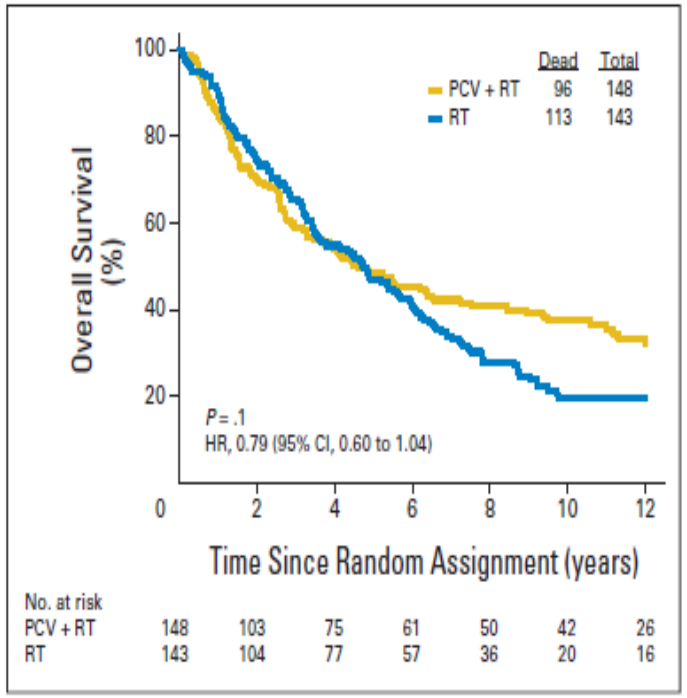
DOI: 10.1200/JCO.2012.43.2229

RTOG 9402

AO/AOA: intense PCV f/b RT versus RT alone.

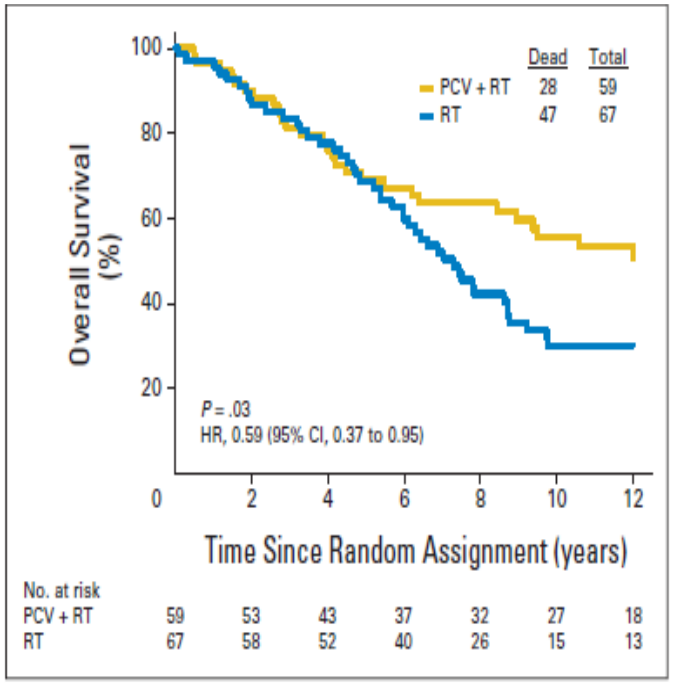


Whole Cohort OS



4.6 *v* 4.7 yrs

Codel OS



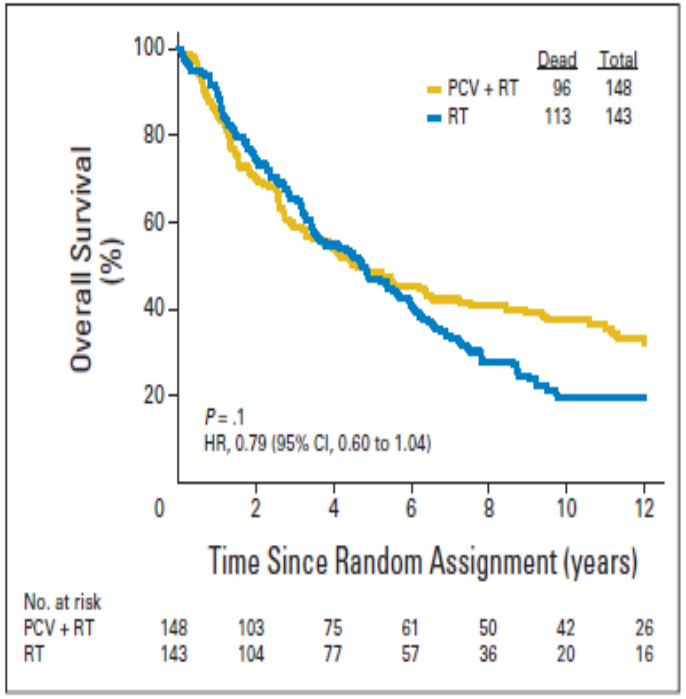
14.7 *v* 7.3 years

DOI: 10.1200/JCO.2012.43.2674

RTOG 9402

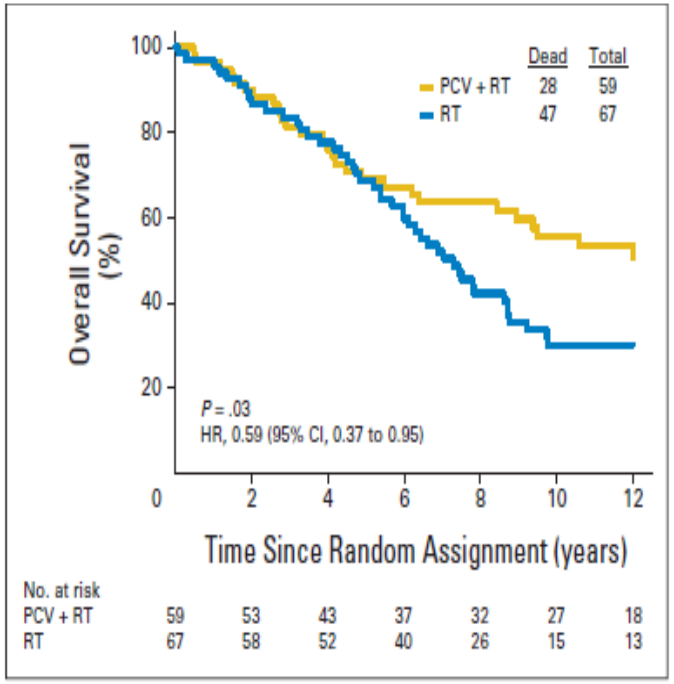
AO/AOA: intense PCV f/b RT versus RT alone.

Whole Cohort OS



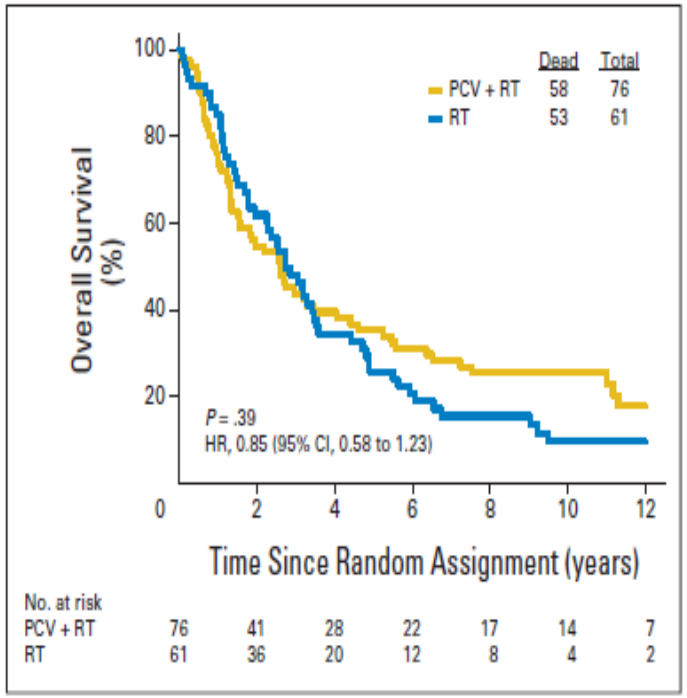
4.6 *v* 4.7 yrs

Codel OS



14.7 *v* 7.3 years

Non-codel

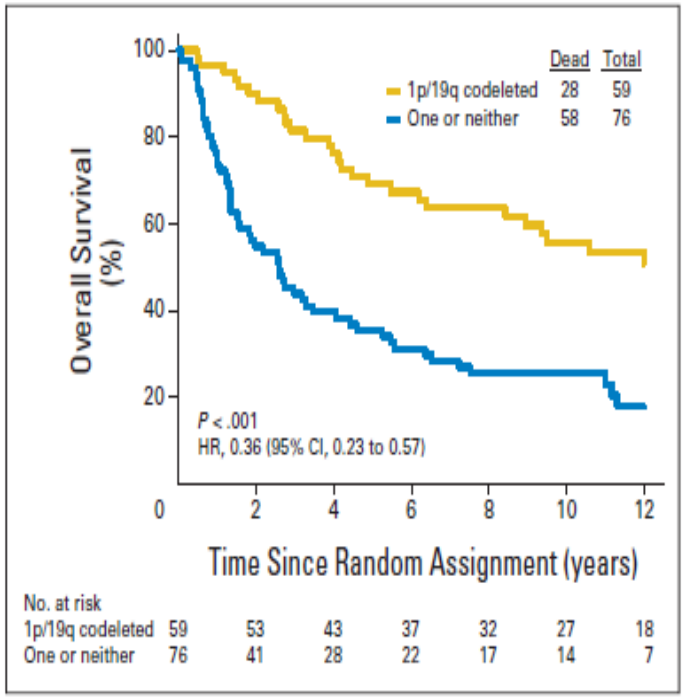


DOI: 10.1200/JCO.2012.43.2674

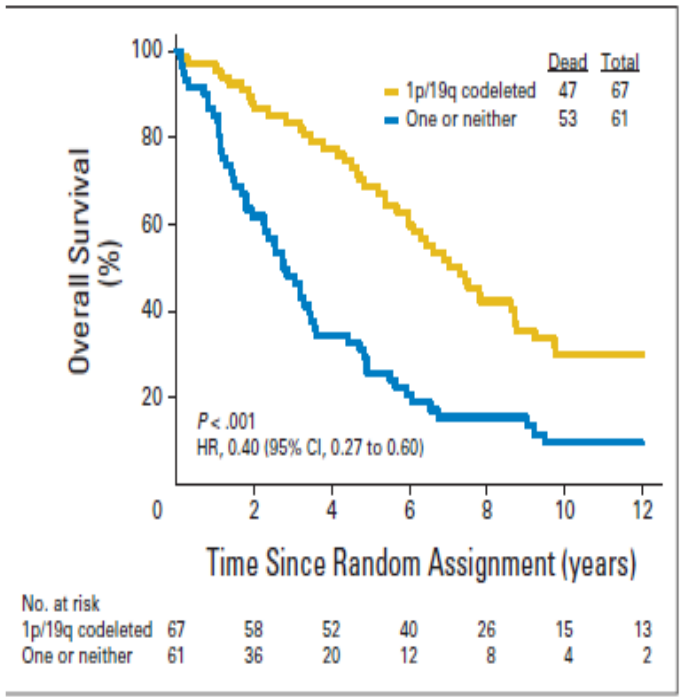
RTOG 9402

AO/AOA: intense PCV f/b RT versus RT alone.

Whole Cohort

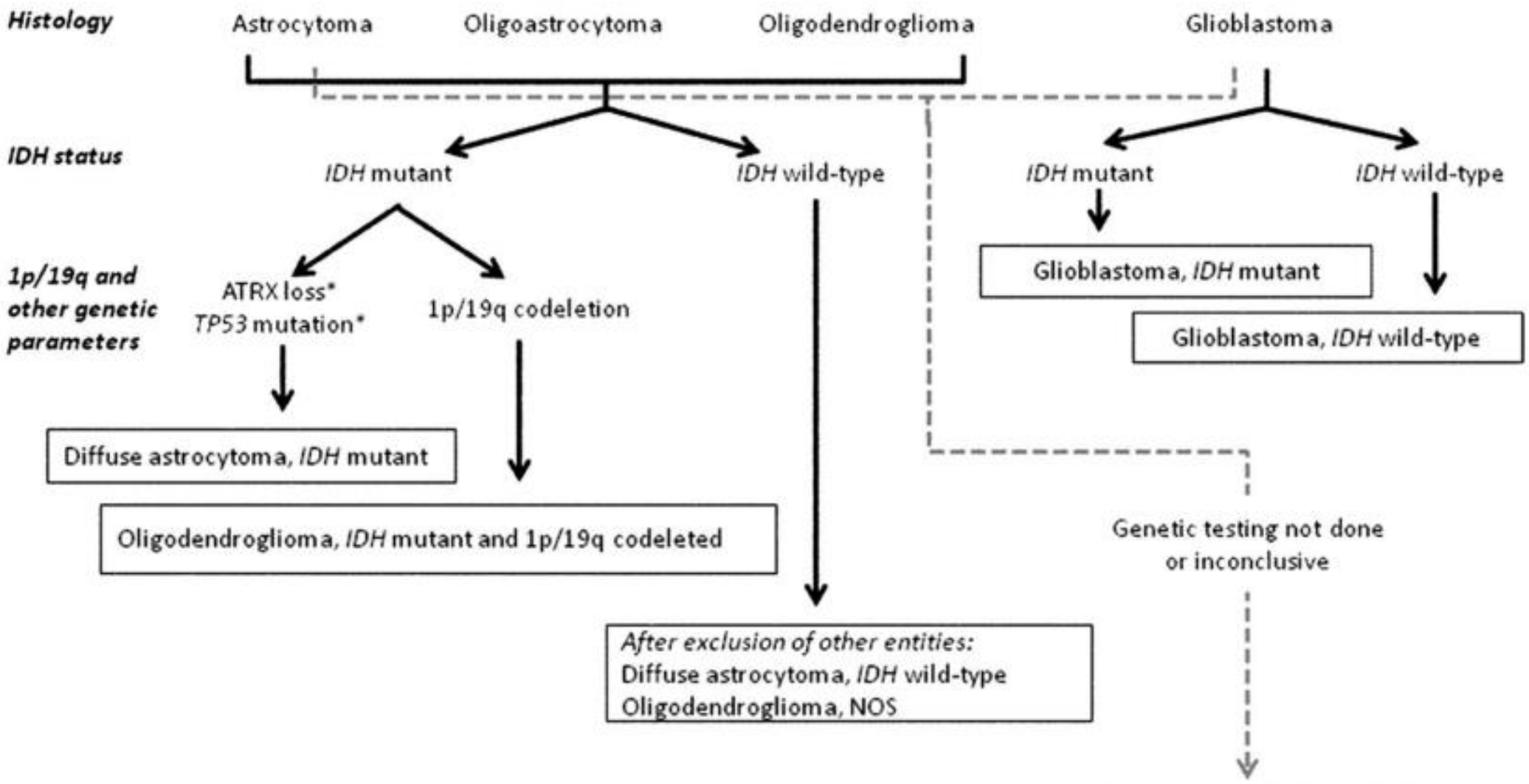


RT alone



DOI: 10.1200/JCO.2012.43.2674

Diffuse Adult Glioma: 2016 WHO update



DOI 10.1007/s00401-016-1545-1

Issues with PCV: Toxicity

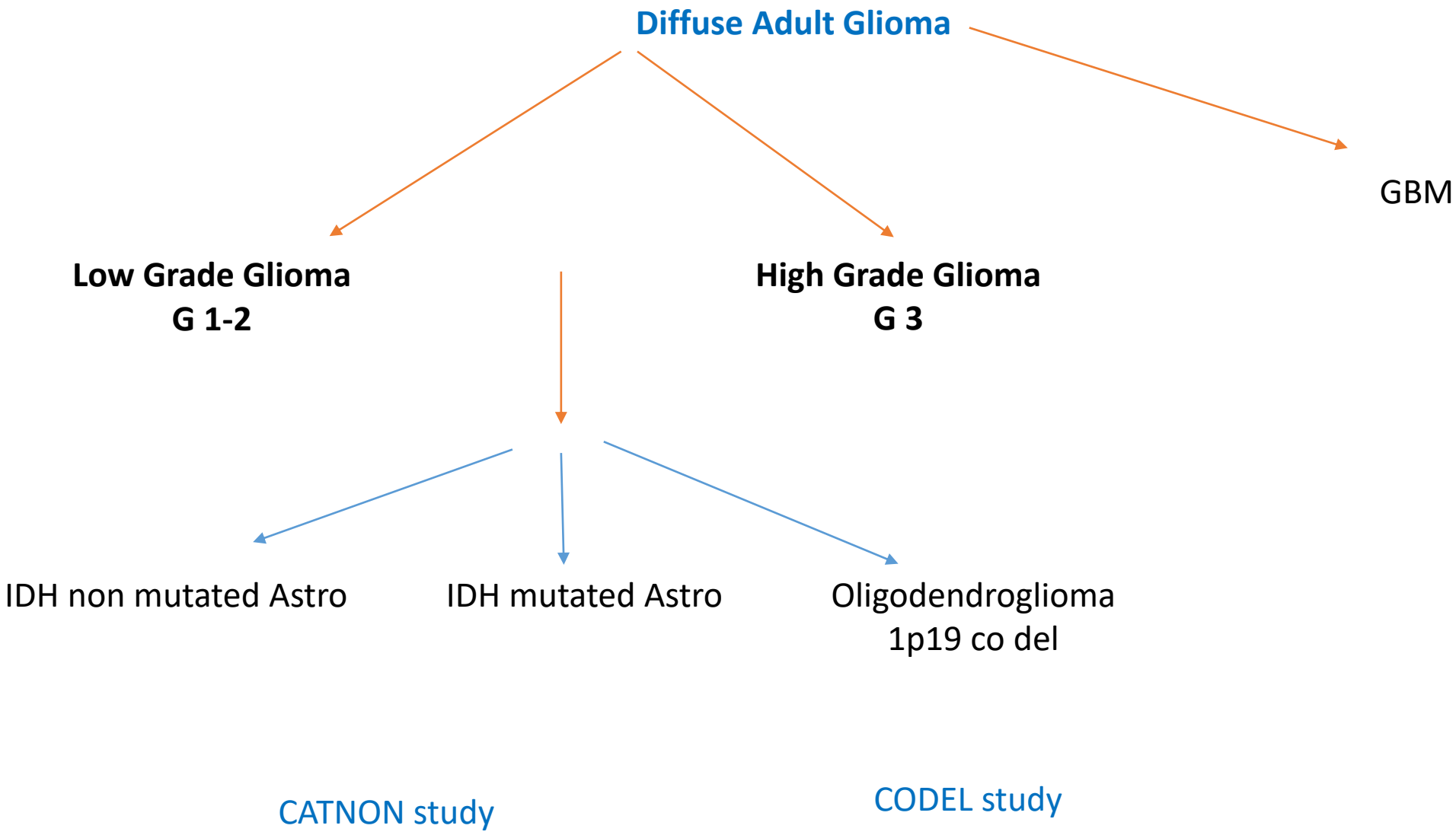
- **RTOG:**
- PCV
  - Lomustine 130 mg/m2 PO D1
  - Procarbazine 75 mg/m2 PO D8-21
  - Vincristine 1.4 mg/m2 i/v D 8
- RT + PCV: G3: 34%, G4: 32%, 1 death
- Percentage receiving four, three, two, one, and no cycles was 54%, 22%, 9%, 12%, and 2%,
- PCV stopped:
  - Progression or death in 17%,
  - Toxicity in 20%,
  - Other reasons in 15%.

- **EORTC:**
- PCV
  - Lomustine 110 mg/m^2 PO D1
  - Procarbazine 60 mg/m^2 PO D 8 - 21,
  - Vincristine 1.4 mg/m^2 i/v D 8 & 29
- 13% of patients randomized to RT/PCV that did not actually receive
- 37% completed at least five cycles, and 30% completed six cycles
- Reasons for premature discontinuation
  - Hematologic toxicity in 33%
  - Nonhematologic toxicity in 5%,
  - Tumor progression in 24%,
  - Patient refusal in 5%,
  - Other reasons in 4%.

Lack of evidence make science into art

- Current Practice survey
  - RT only
  - RT – Adj CT
  - cCT-RT + Adj CT
  - cCT-RT only

- Variability in CT
  - PCV and its variations
  - TMZ


Diffuse Adult Glioma
GBM
Low Grade Glioma
G 1-2
High Grade Glioma
G 3
IDH non mutated Astro
IDH mutated Astro
Oligodendroglioma
1p19 co del
CATNON study
CODEL study

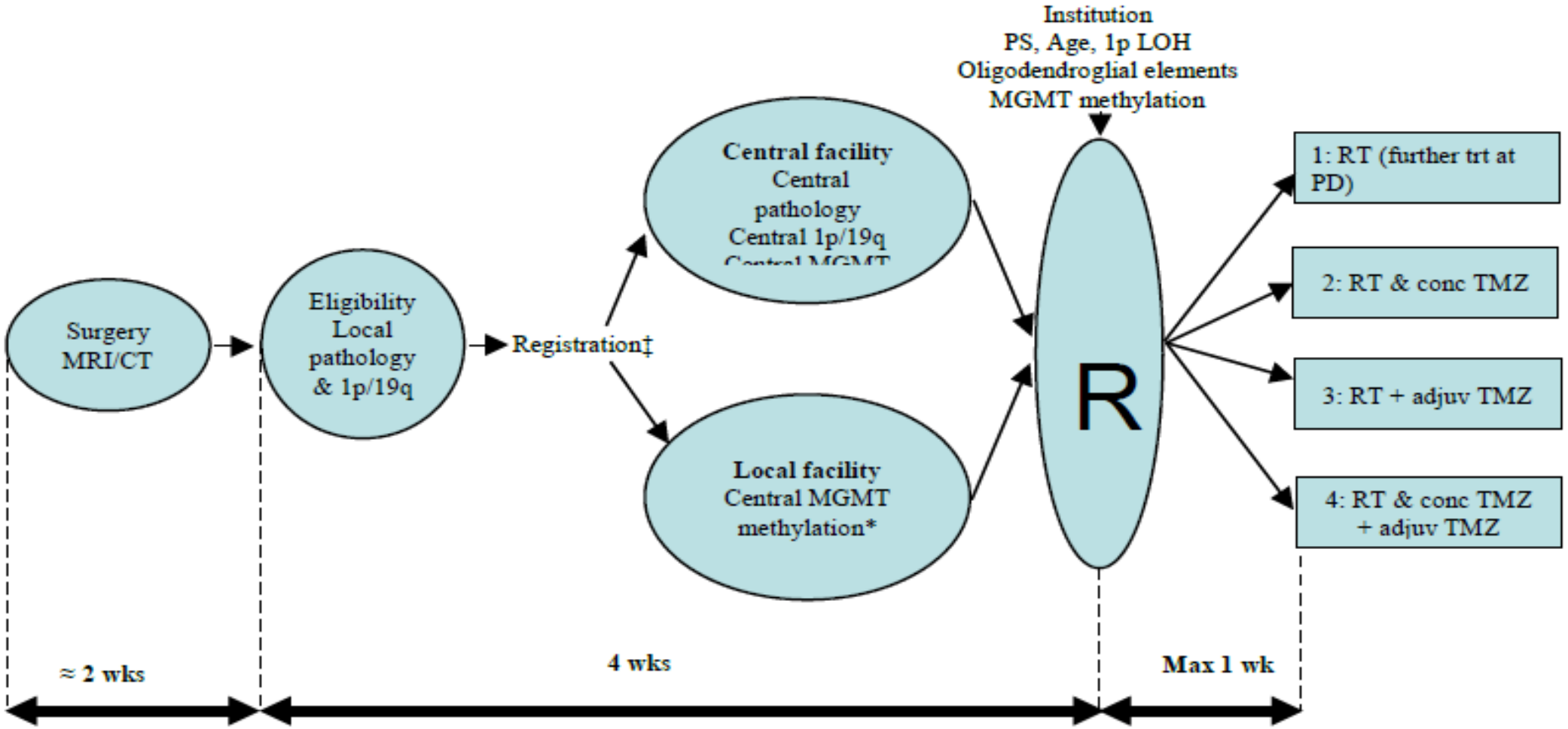
Intergroup Study (EORTC 26053_22054)

(EudraCT number 2006-001533-17)
(NCT00626990)

Phase III trial on Concurrent and Adjuvant Temozolomide chemotherapy in non-1p/19q deleted anaplastic glioma. The CATNON Intergroup trial.

Collaborative Groups/Co-Chairs:

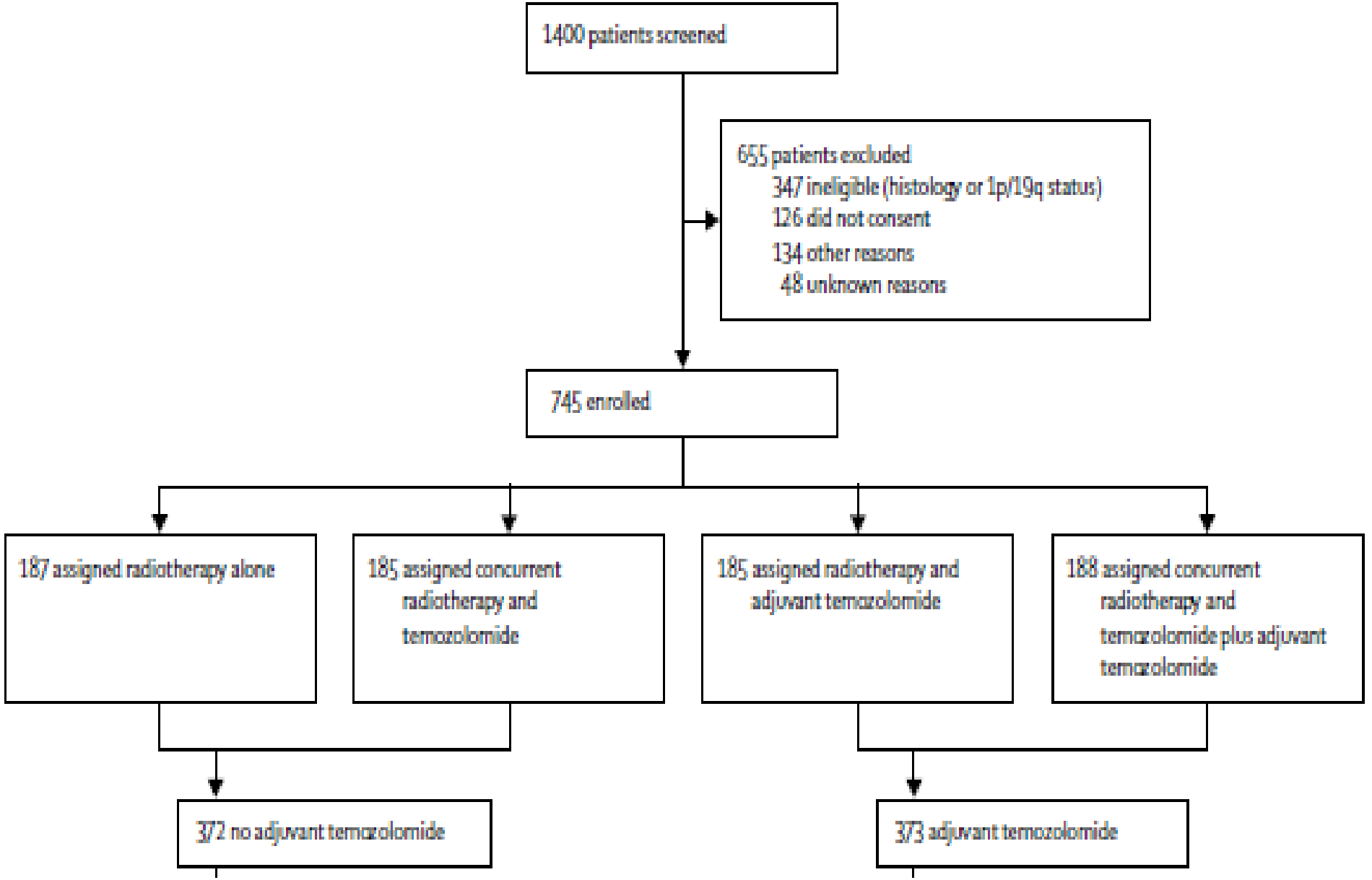
EORTC Brain Tumor Group/W. Wick, A. Omuro, R. Soffietti
EORTC Radiation Oncology Group/ B. Baumert
NCI-C/ J.G. Cairncross, W. Mason
RTOG/M. Metha, M. Vogelbaum
MRC/NCRI Brain tumor Clinical Studies Group/S. Erridge
COGNO CTC/A. Nowak



† Institution must choose to evaluate 1p/19q LOH locally or use central facility.

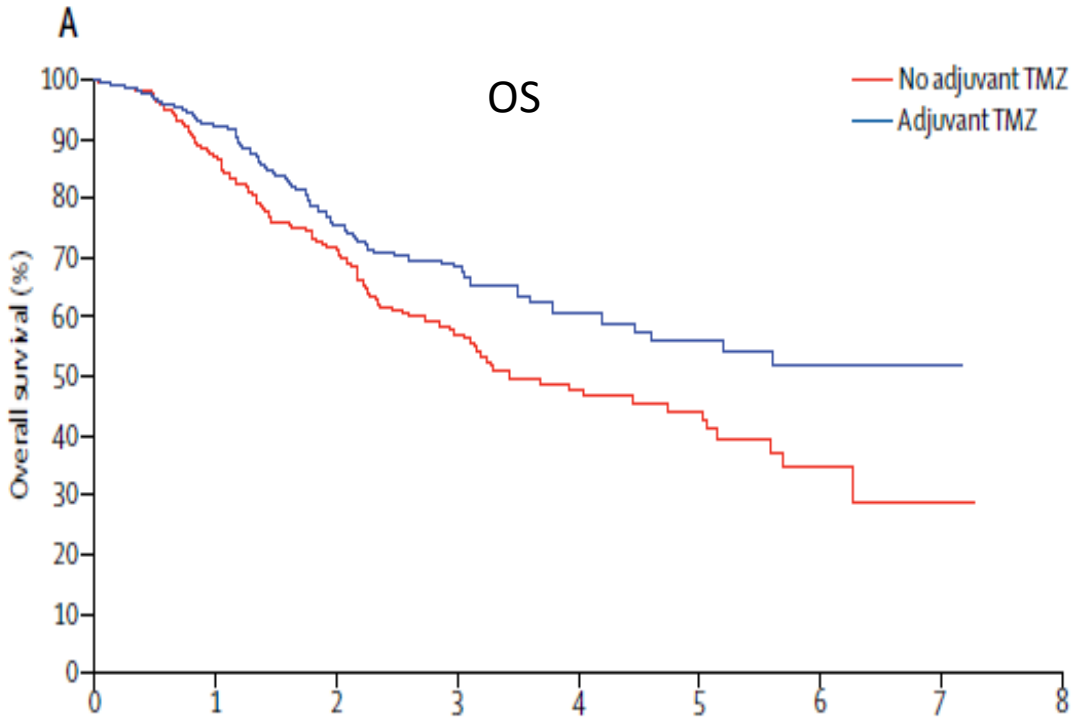
‡ After registration, all material is centrally reviewed for MGMT methylation status.

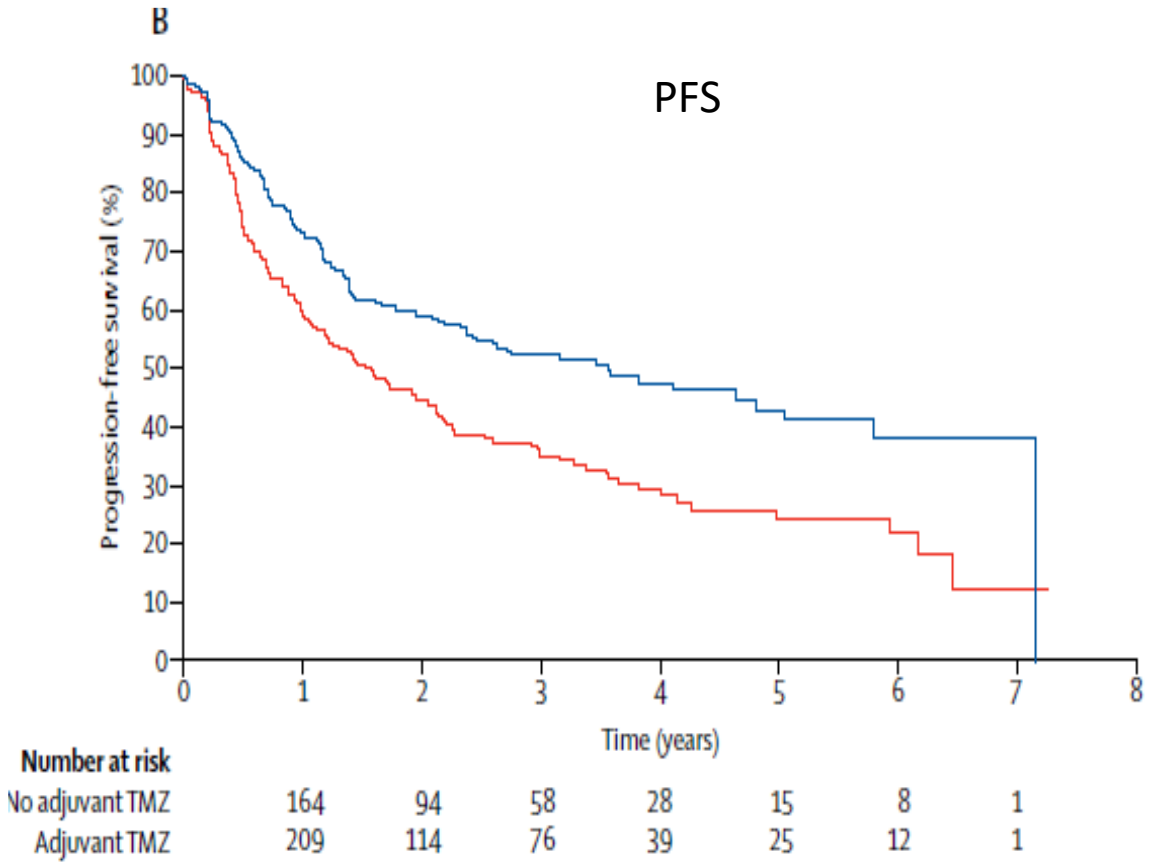
* Investigators can't randomize a patient:


1400 patients screened
655 patients excluded
347 ineligible (histology or 1p/19q status)
126 did not consent
134 other reasons
48 unknown reasons
745 enrolled
187 assigned radiotherapy alone
185 assigned concurrent radiotherapy and temozolomide
185 assigned radiotherapy and adjuvant temozolomide
188 assigned concurrent radiotherapy and temozolomide plus adjuvant temozolomide
372 no adjuvant temozolomide
373 adjuvant temozolomide

	Hazard ratio (99·145% CI)	p value
Adjuvant temozolomide	0·65 (0·45–0·93)	0·0014
Age (>50 years *vs* ≤50 years)	4·04 (2·78–5·87)	<0·0001
WHO performance status score (>0 *vs* 0)	1·36 (0·94–1·96)	0·0273
1p loss of heterozygosity (yes *vs* no)	1·56 (0·84–2·88)	0·0572
Presence of oligodendroglial elements (yes *vs* no)	1·20 (0·81–1·76)	0·2230
MGMT promotor methylation before randomisation		
Methylated *vs* unmethylated	0·49 (0·26–0·93)	0·0031
Indeterminate or invalid *vs* unmethylated	0·81 (0·54–1·21)	0·1606

Table 2: Cox proportional hazards model of overall survival in patients receiving adjuvant temozolomide, adjusted by baseline stratification factors


A
OS
No adjuvant TMZ
Adjuvant TMZ
Overall survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8
Number at risk
No adjuvant TMZ 240 150 93 48 30 9 1
Adjuvant TMZ 266 152 99 50 34 17 1


B
PFS
Progression-free survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8
Time (years)
Number at risk
No adjuvant TMZ 164 94 58 28 15 8 1
Adjuvant TMZ 209 114 76 39 25 12 1

	Overall survival			Progression-free survival		
	Number of deaths	Median (95% CI) survival (months)	5-year survival (95% CI)	Number of patients with disease progression	Median (95% CI) survival (months)	5-year survival (95% CI)
Received adjuvant temozolomide	92	Not reached	55·9% (47·2–63·8)	144	42·8 (28·6–60·6)	43·1% (35·0–50·9)
Did not receive adjuvant temozolomide	129	41·1 (36·6–60·7)	44·1% (36·3–51·6)	200	19·0 (14·4–24·6)	24·3% (17·7–31·6)

Table 3: Median and 5-year overall and progression-free survival

TMZ Tolerance

- Relative dose intensity was
  - > 90% in concurrent phase
  - 92% in adj patients

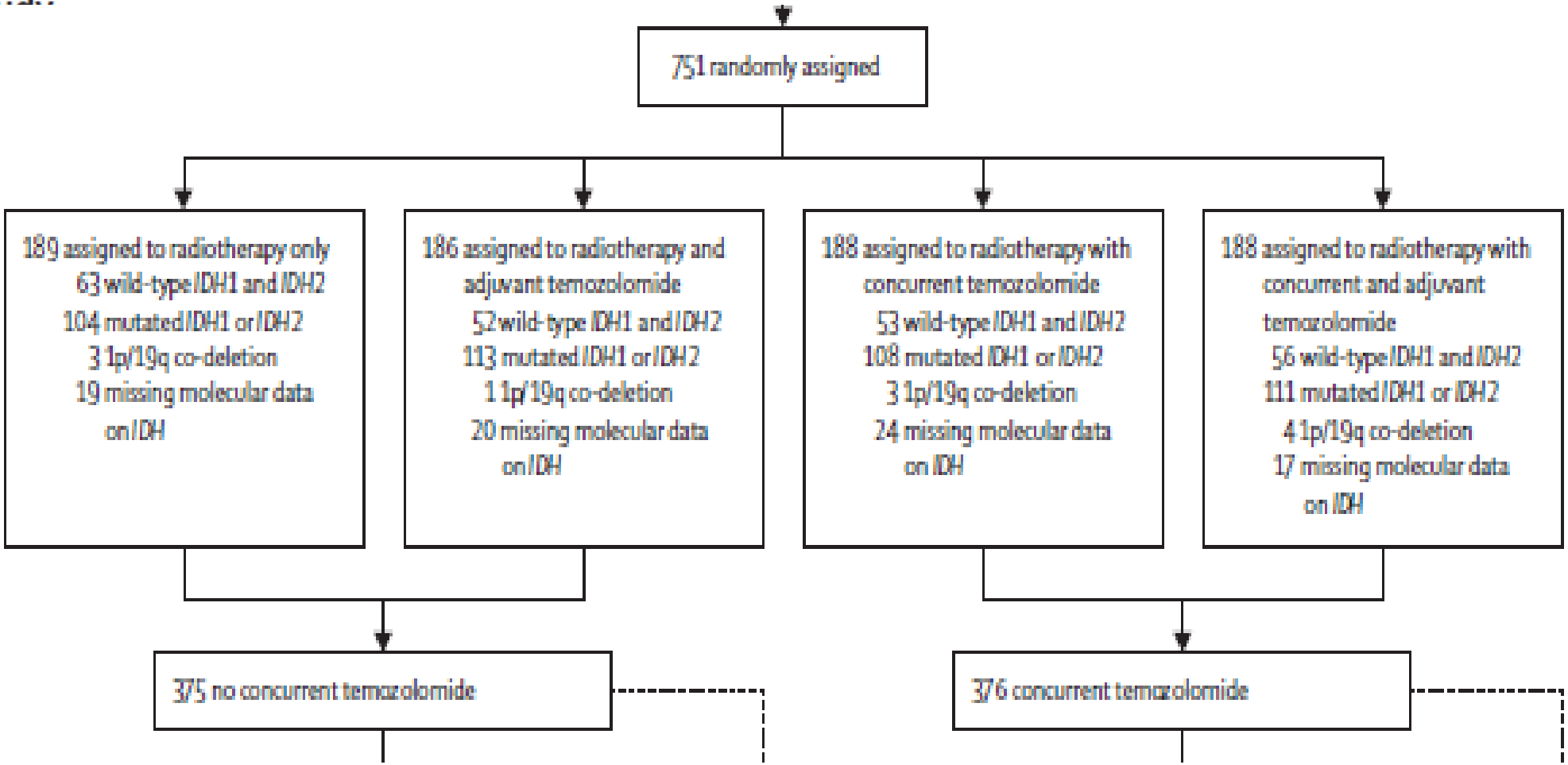
- one cycle delayed
  - 74 (28%) : HT
  - 16 (6%) non HT
  - 8 (3%) both
  - 123 (47%) : NR

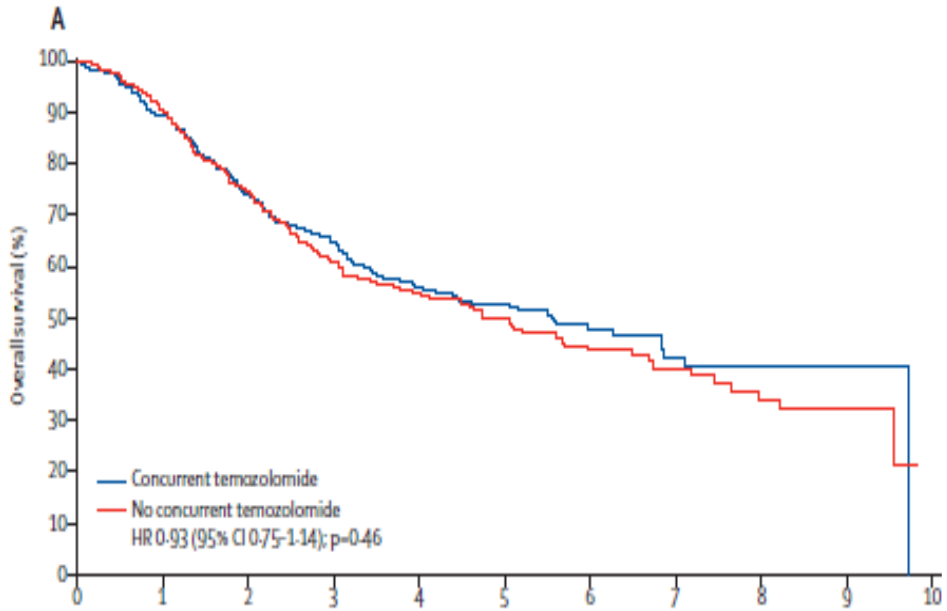
- Overall G 3-4 toxicity : 8–12%
  - Thrombocytopenia : 7–9%
  - GI: 1-2%

Take home message

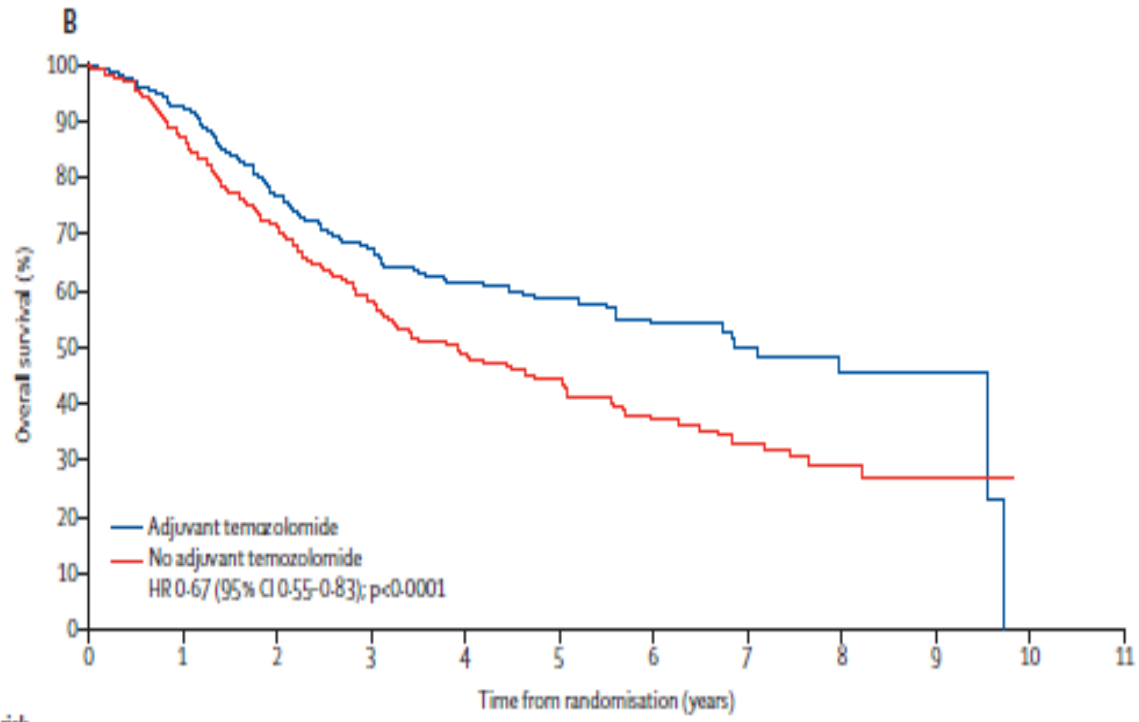
- RT + 12 4-week cycles of adj TMZ (150–200 mg/m2 given on days 1–5) improved PFS and OS in 1p/19 non-co-deleted anaplastic glioma.

Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase 3 st[illegible]



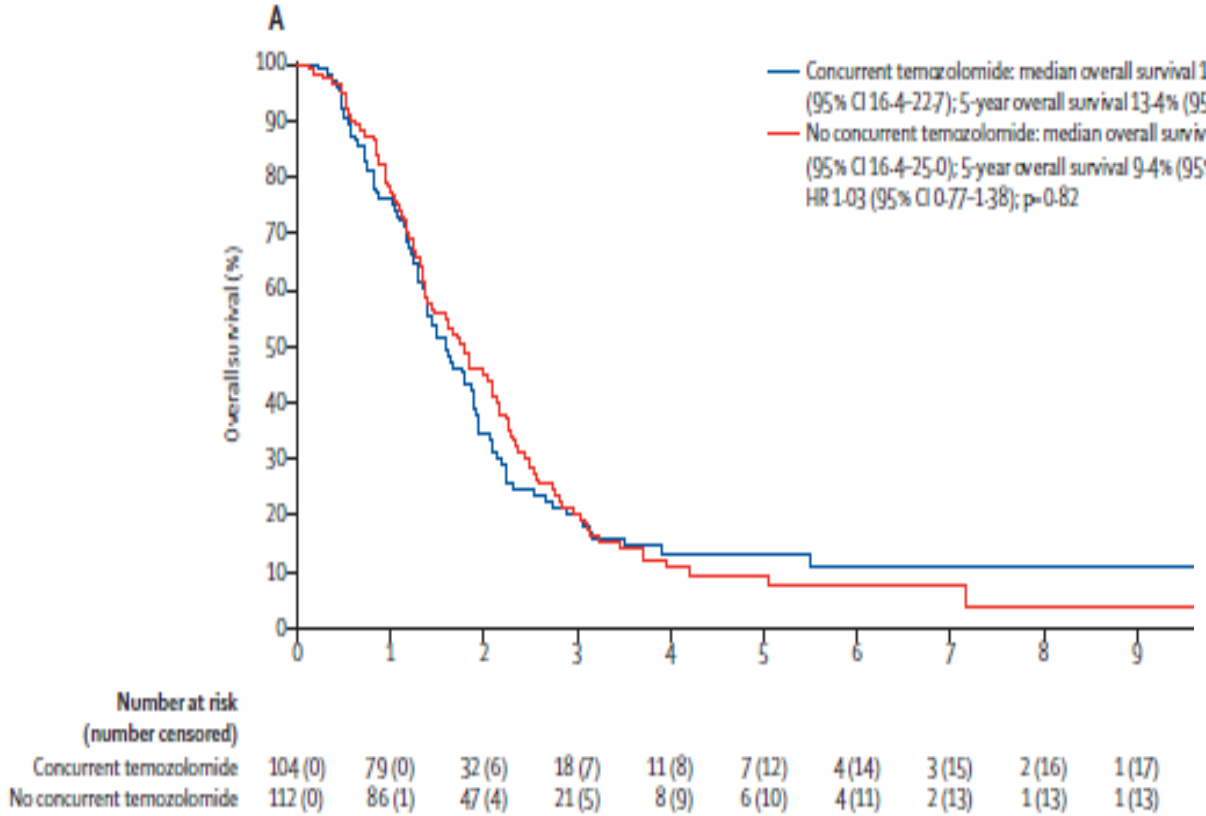


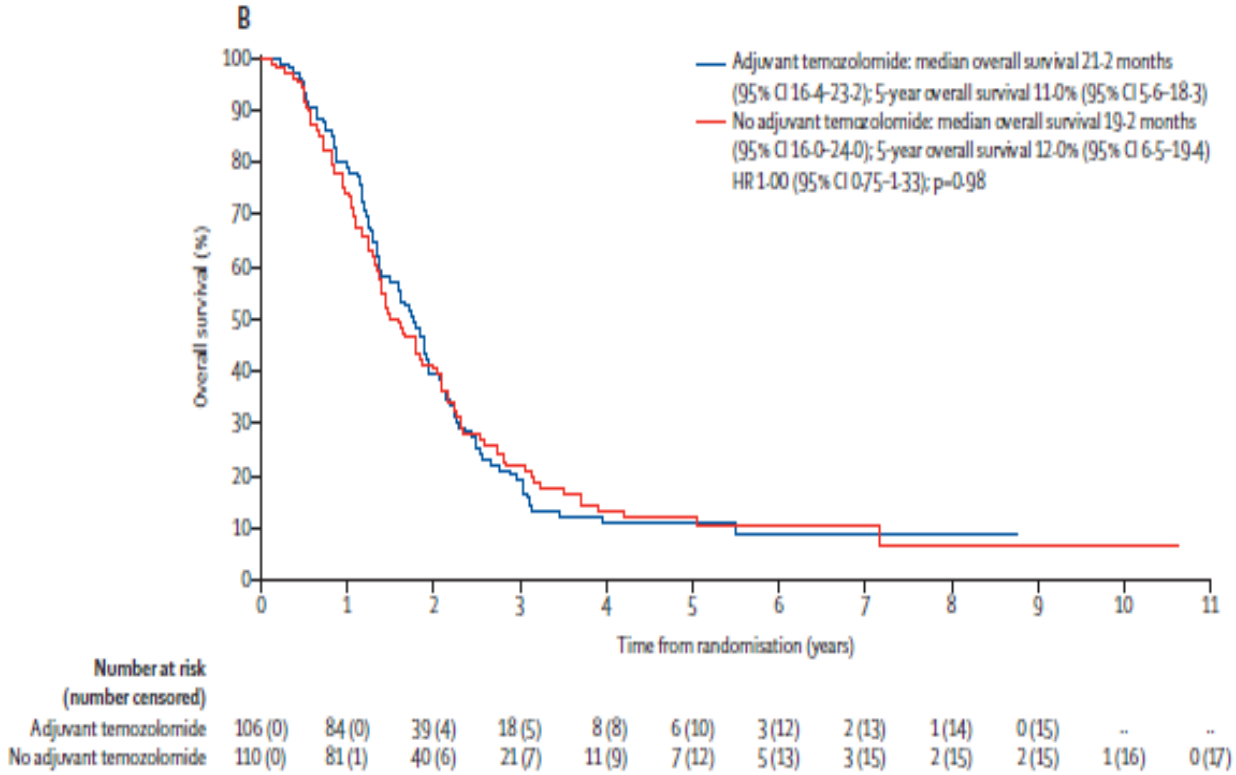
Number at risk (number censored)											
Concurrent temozolomide	376 (0)	332 (5)	259 (21)	197 (53)	130 (94)	87 (131)	53 (158)	28 (179)	15 (191)	6 (200)	0 (20
No concurrent temozolomide	375 (0)	332 (7)	263 (18)	186 (49)	126 (92)	84 (125)	54 (145)	30 (166)	20 (172)	9 (182)	0 (19



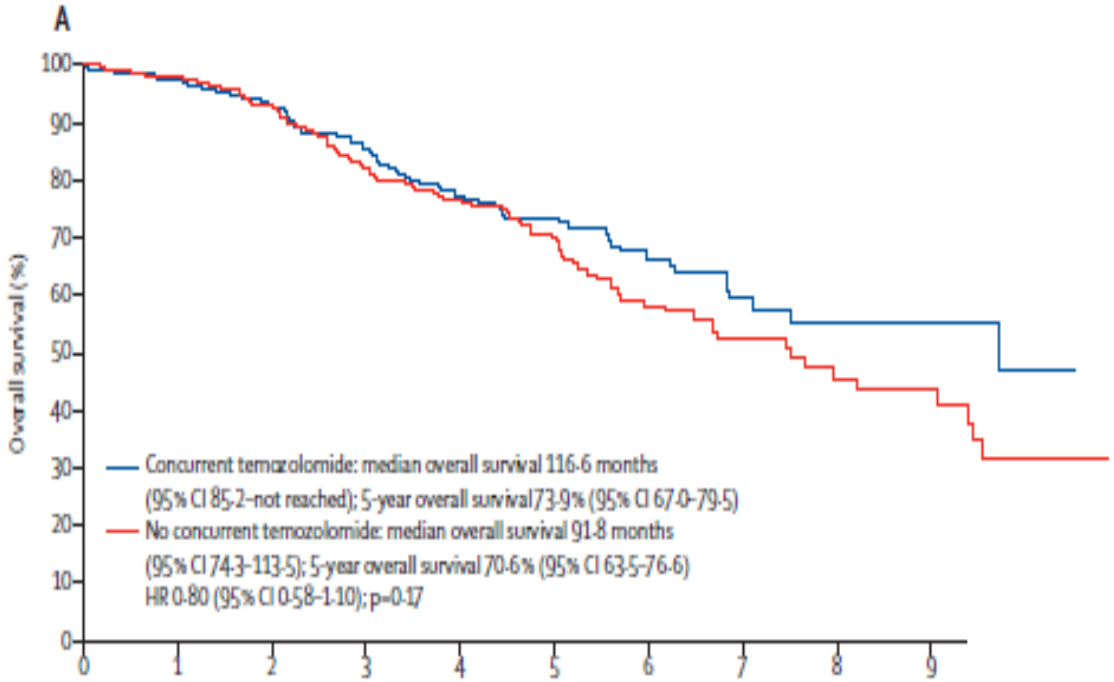
Number at risk (number censored)												
Adjuvant temozolomide	374 (0)	339 (7)	272 (18)	206 (51)	143 (98)	94 (141)	58 (171)	30 (196)	20 (204)	12 (212)	0 (222)	..
No adjuvant temozolomide	377 (0)	325 (5)	250 (21)	177 (51)	113 (88)	77 (115)	49 (132)	28 (149)	15 (159)	3 (170)	0 (173)	..

Non IDH mutated

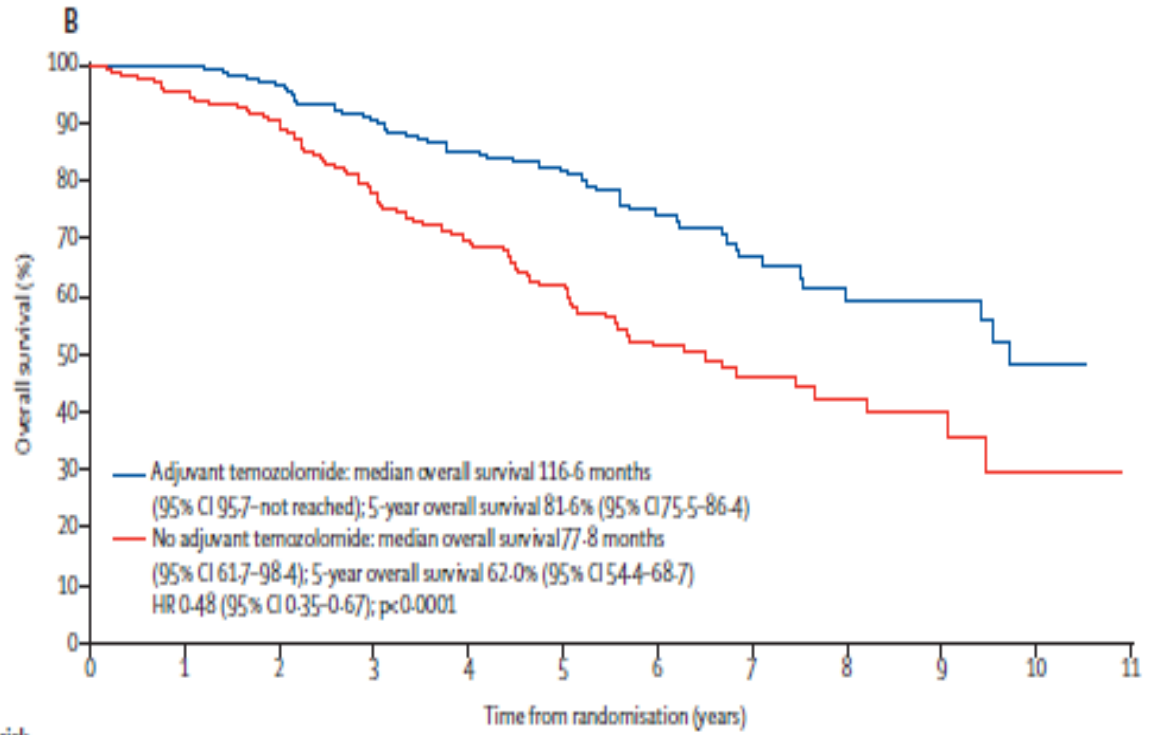




IDH mutated



Number at risk (number censored)										
Concurrent temozolomide	224 (0)	214 (4)	198 (11)	175 (19)	134 (44)	92 (80)	60 (105)	34 (126)	20 (138)	13 (145)
concurrent temozolomide	220 (0)	211 (4)	195 (11)	166 (17)	136 (37)	94 (69)	59 (90)	40 (104)	25 (115)	18 (121)



Number at risk (number censored)												
Adjuvant temozolomide	226 (0)	220 (5)	207 (11)	189 (16)	156 (38)	108 (81)	70 (110)	45 (129)	27 (143)	20 (150)	8 (159)	0 (167)
No adjuvant temozolomide	218 (0)	205 (3)	186 (11)	152 (20)	114 (43)	78 (68)	49 (85)	29 (101)	18 (110)	11 (116)	2 (123)	0 (125)

Take Home message

- TMZ given simultaneously with RT does not improve overall survival compared to RT alone
- Clinical benefit of adding adjuvant TMZ to RT is limited to patients with *IDH1* or *IDH2* mutant tumours only

N0577 TITLE PAGE

CODEL: phase III study of RT, RT + TMZ, or TMZ for newly diagnosed 1p/19q codeleted oligodendroglioma. Analysis from the initial study design

Alliance for Clinical Trials in Oncolog

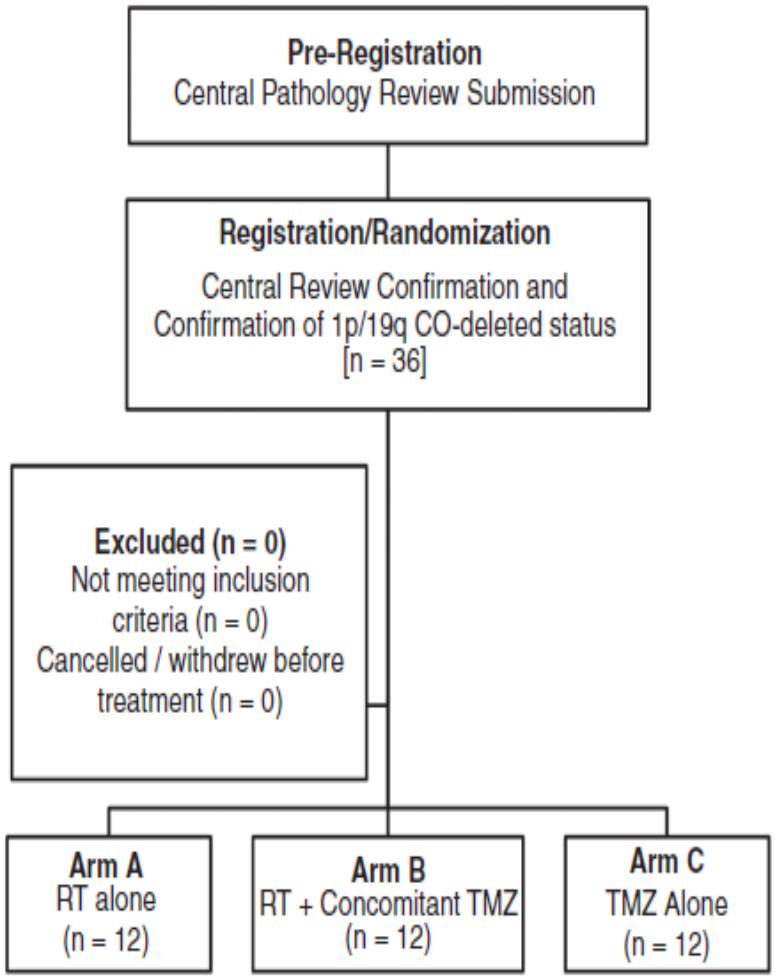
N0577 (CODEL): Phase III Intergroup Study of Radiotherapy wi Temozolomide versus Radiotherapy with Adjuvant PCV Chemotherapy in Patients with 1p/19q Co-deleted Anaplastic Glioma or Low Grade Glioma

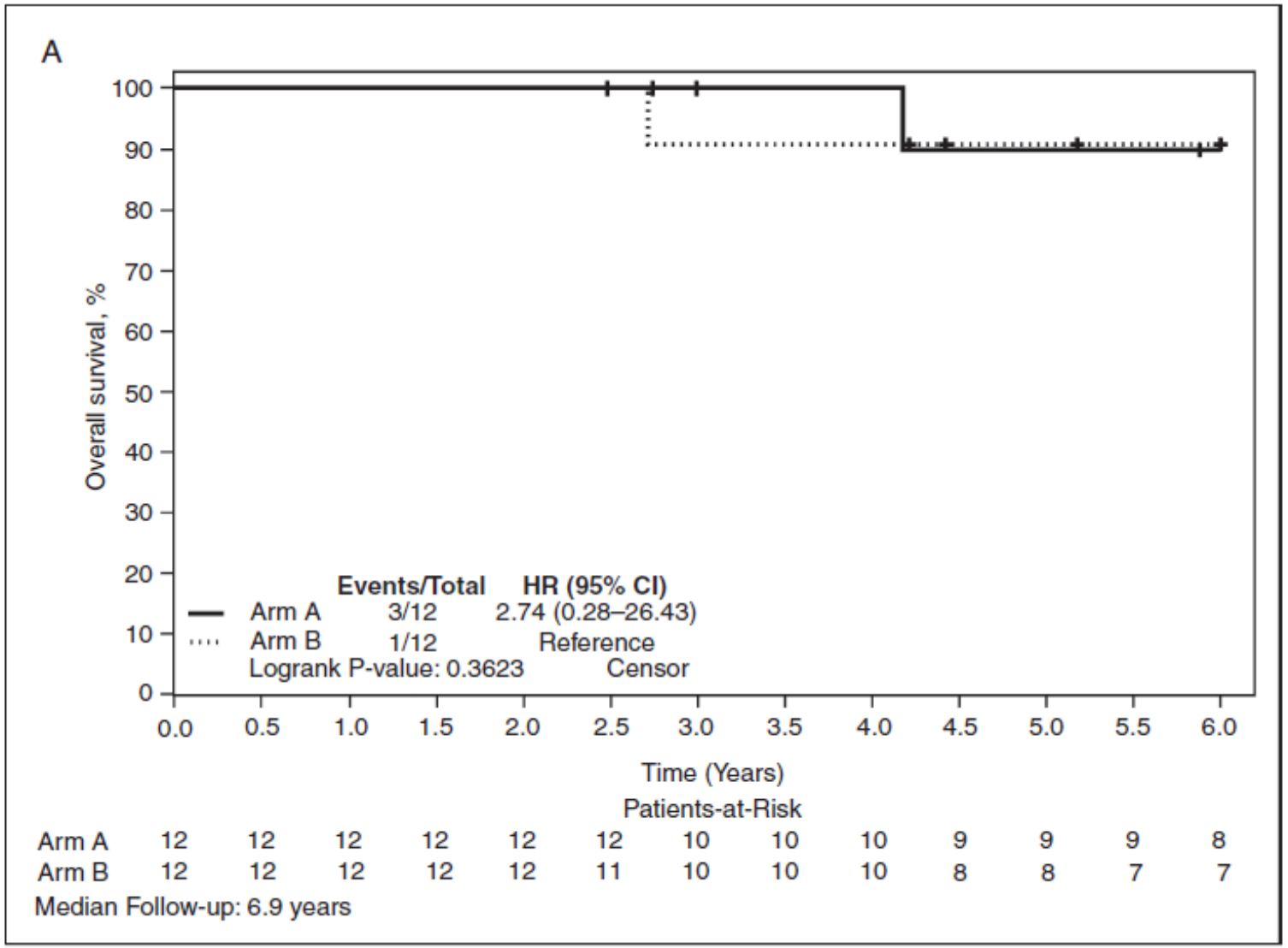
ClinicalTrials.gov Identifier: NCT00887146

Background. We report the analysis involving patients treated on the initial CODEL design.
Methods. Adults (>18) with newly diagnosed 1p/19q World Health Organization (WHO) grade III oligodendroglioma were randomized to

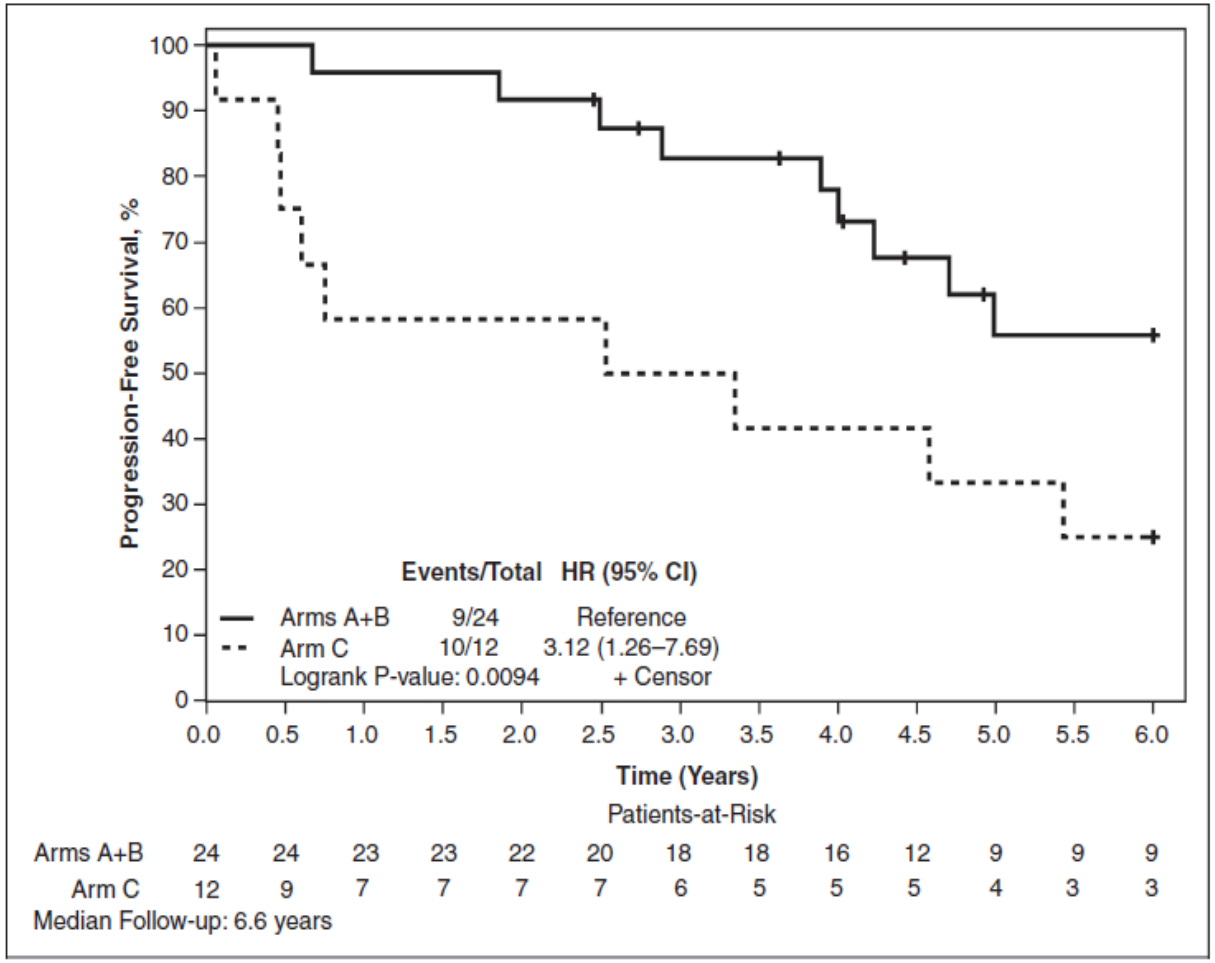
1. RT (RT; 5940 centigray) alone (arm A); RT followed by adjuvant PCV
2. RT with concomitant and adjuvant temozolomide (TMZ) (arm B);
3. TMZ alone (arm C).

Primary endpoint was overall survival (OS), arm A versus B.
Secondary comparisons were performed for OS and PFS, comparing pooled RT arms versus TMZ-alone arm.

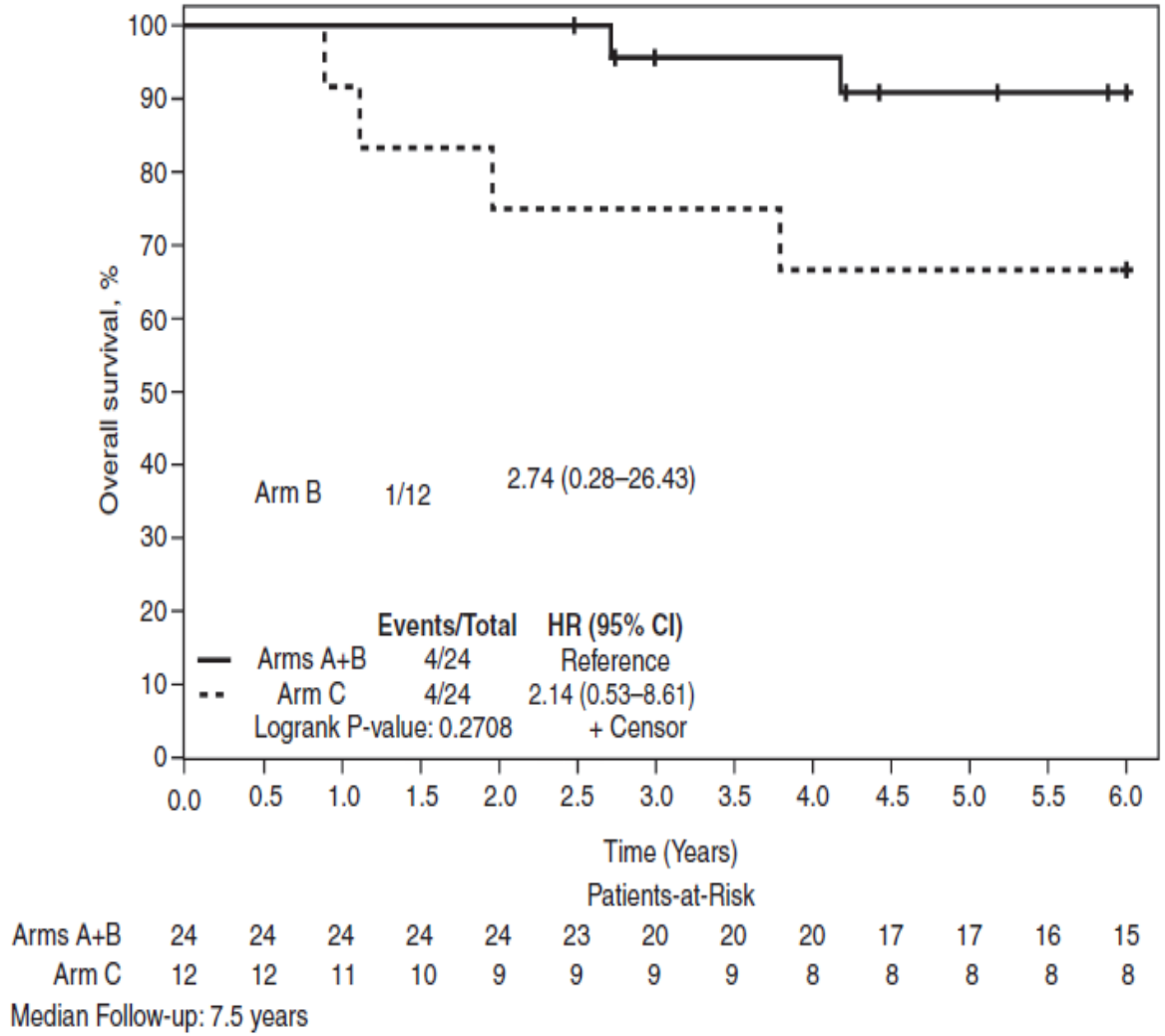




RT alone = RT + TMZ



B



TMZ alone not as good as RT or RT + TMZ

Table 3. Progression outcome following initial chemotherapy alone: patients with newly diagnosed, 1p/19q codeleted anaplastic oligodendrogliomas

Authors	Study Type	*N*	Initial Treatment	Median PFS or Median TTP, y
Lassman et al[15]	Case Series	124	TMZ	3.3
			PCV	7.6
Mikkelsen et al[16]	Case Series	36	TMZ	2.4
Thomas et al[18]	Phase II	33	TMZ → ASCT[b]	5
Wick et al[19,a]	Phase III	17	TMZ	4.5
		16	PCV	9.4

AO, anaplastic oligodendroglioma; AOA, anaplastic oligoastrocytoma; HDC-ASCT, high dose chemotherapy with autologous stem cell transplant; TTP, time to progression.

[a]1p/19q codeleted, CpG island methylator phenotype + patients.

[b]Responders to TMZ subsequently received ASCT.

Table 2. Cognitive progression at 3 months

	Arm A: RT Alone ($N = 9$)	Arm B: RT + Concomitant TMZ ($N = 11$)	Arm C:TMZ Alone ($N = 9$)	Total ($N = 29$)	*P*-value
Median Days to Testing (range)	87 (84–105)	85 (73–130)	82 (59–97)	86 (59–130)	0.13[e]
Frequency of Deterioration[a]					
HVLT-R Immediate Recall, *n* (%)	1 (11.1)	1 (9.1)	1 (11.1)	3 (10.3)	0.93[d]
COWAT, *n* (%)	0 (0.0)	1 (9.1)	1 (11.1)	2 (6.9)	0.20[d]
Trail Making A, *n* (%)	1 (12.5)	0 (0.0)	3 (37.5)	4 (15.4)	0.18[d]
Trail Making B, *n* (%)	5 (71.4)	3 (33.3)	3 (42.9)	11 (47.8)	0.29[d]
HVLT-R Delayed Recall, *n* (%)	3 (33.3)	1 (9.1)	0 (0.0)	4 (14.3)	0.18[d]
HVLT-R Delayed Recognition, *n* (%)	2 (22.2)	2 (18.2)	1 (12.5)	5 (17.9)	0.24[d]
Progression Determination					
Neurocognitive Progression[b], *n* (%)	7 (77.8)	8 (72.7)	6 (66.7)	21 (72.4)	0.87[d]
Clinical Progression[c], *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	NA

RCI, reliable change index; HVLT-R, Hopkins Verbal Learning Test–Revised; COWAT, Controlled Oral Word Association Test.
[a]>RCI90 value decrease from baseline.
[b]Number deteriorating on any one subtest >RCI90 value decrease from baseline.
[c]Defined by clinical exam and/or radiographic progression at 3 months after registration.
[d]Chi-square.
[e]Kruskal–Wallis.

Take home message

- For anaplastic ODG (1p19q co del):
  - TMZ alone should be avoided.
  - RT + TMZ vs RT vs PCV is not known