Long term follow-up results of EORTC 26951: a randomized phase III study on adjuvant PCV chemotherapy in anaplastic oligodendroglial tumors

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DIFFUSE GLIOMAS: infiltrative glial tumors
15.000 new cases each year in the USA

Grade	Survival
Grade II (low grade)	5 - 15 years
Grade III (anaplastic)	3 - >7 years
Grade IV glioblastoma	12 - 15 months

Gliomas: most frequent adult primary brain tumor

Histological subtypes

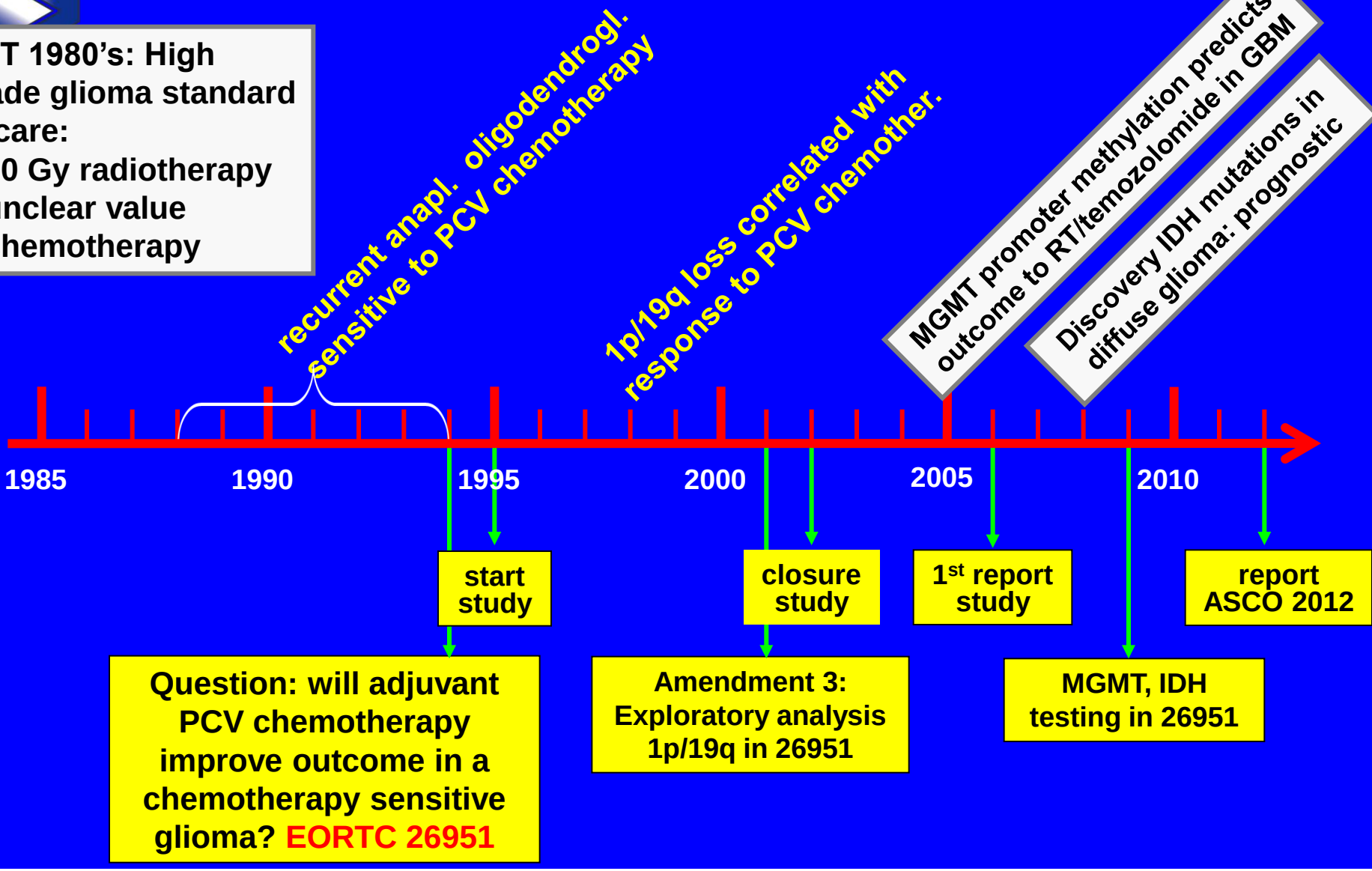
5 -10 % of all gliomas

anaplastic astrocytoma
oligodendroglioma
oligoastrocytoma

EORTC 26951 on anaplastic oligodendroglial tumors

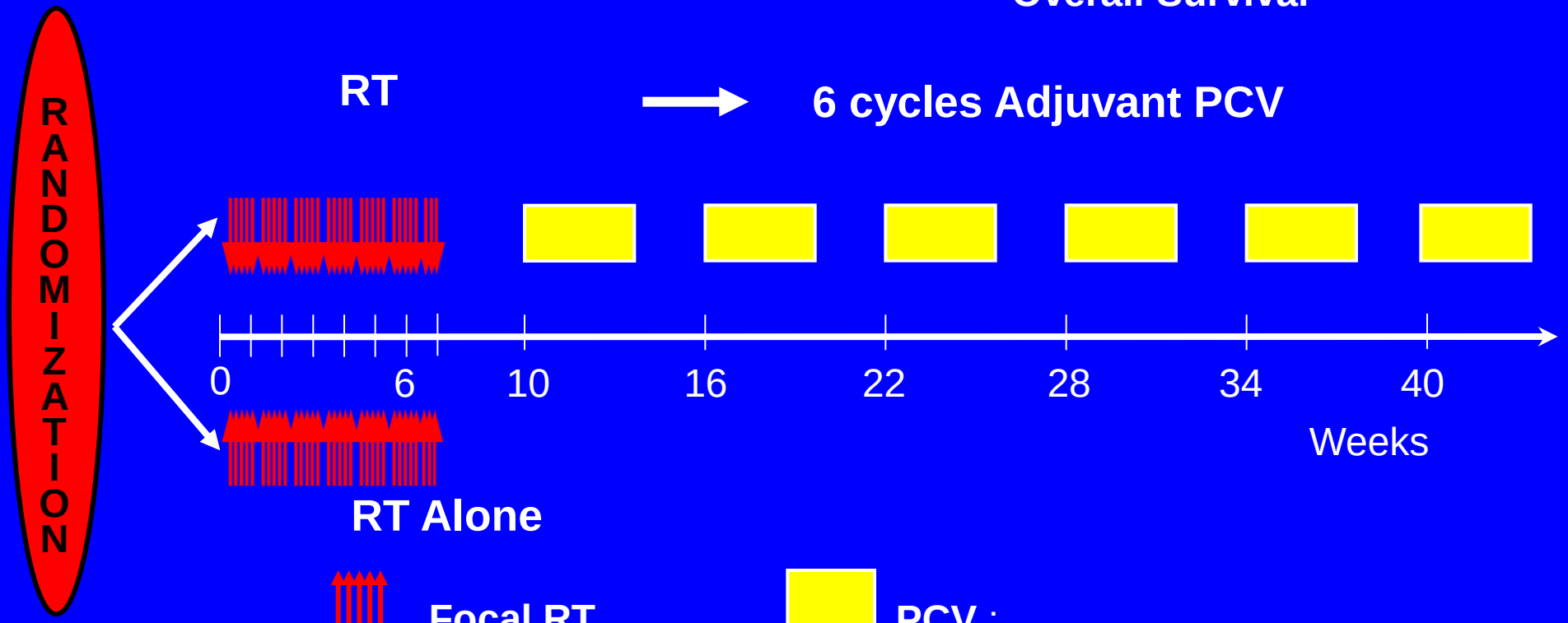
EORTC 26951: 2 decades of timelines and events

RCT 1980's: High grade glioma standard of care:
- **60 Gy radiotherapy**
- **unclear value chemotherapy**



Treatment Schedule EORTC 26951

Primary endpoints:
Progression Free Survival
Overall Survival



Focal RT
daily - 33 x 1,8 Gy
Total dose 59,4 Gy

PCV :
CCNU (lomustine) 110 mg/m^2 day 1
Procarbazine 60 mg/m^2 day 8-21
Vincristine 1.4 mg /m^2 day 8 + 29
Planned: 6 cycles of 6 weeks

Trial details

- Protocol emphasized (PCV) chemotherapy at progression in the RT arm: ‘cross over’
- Eligible:
  - Newly diagnosed Anaplastic Oligodendroglial tumors, as diagnosed by the local pathologist
  - ≥Age 16–70 years, WHO PS 0-2
- 368 patients enrolled (1995 – 2002)
  - Prognostic factors well balanced between arms
  - In 70% confirmation of histology at review

First report EORTC 26951 in 2006
(median follow- up: 60 months)

- Adjuvant PCV increases progression free survival, not overall survival
- Combined 1p/19q loss
  - Is of prognostic significance (2 yrs versus > 6 yrs)
  - Not predictive for benefit to adjuvant PCV
- Median survival was not reached in the 1p/19q co-deleted tumors (more than 6 years)

EORTC 26951: long term follow-up

ASCO 2012, June 3rd 2012

Some details

At the time of this report (February 20, 2012):

- **Median follow-up: 140 months**
  - **Progression in 298 patients (81.0%)**
  - **87 patients (24.6%) still alive**

Chemotherapy at progression

Progression RT/PCV arm
n = 137 (74%)

Further treatment:

- Any chemotherapy: 72 (53%)
  - PCV: 13 (9%)
  - Temozolomide: 55 (40%)

Progression RT alone arm
n = 161 (88%)

Further treatment:

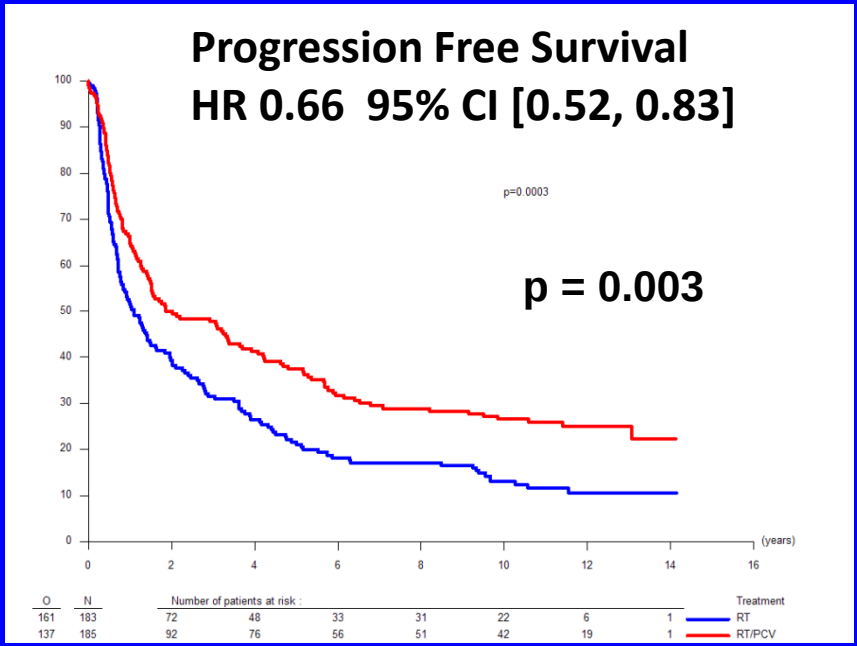
- Any chemotherapy: 120 (75%)
  - PCV: 90 (56%)
  - Temozolomide: 65 (40%)

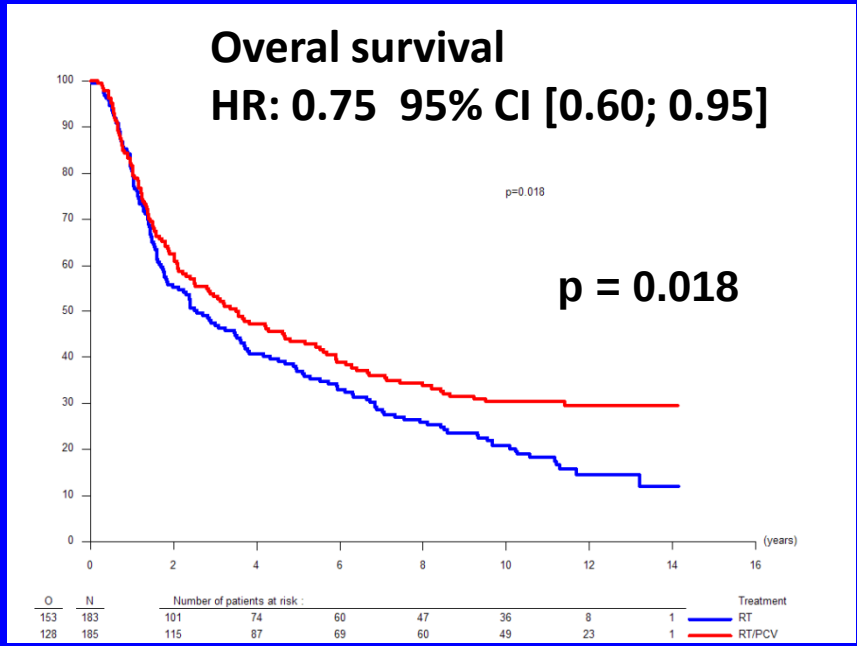
Conclusion: as planned the trial compared adjuvant chemotherapy to chemotherapy at progression

PFS and OS in the intent to treat population

Conclusion: clinically and statistically significant increase in PFS and OS after adjuvant PCV chemotherapy

Median	PFS	OS
RT	13 mo	31mo
RT/PCV	24mo	42 mo





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*[ ]:95% Confidence Interval

EORTC 26951: Risk adjusted analysis

- **Risk adjusted analysis including:**
  - **Age (≤40, >40 years)**
  - **Surgery (biopsy versus resection)**
  - **WHO performance status (0, 1 versus 2) P**
  - **Previous surgery for low grade glioma (yes/no)**

<u>Assigned treatment remained independent factor for Overall Survival:</u>

- **Adjusted HR similar to unadjusted HR in ITT analysis: 0.76 (compared to 0.75 unadjusted)**

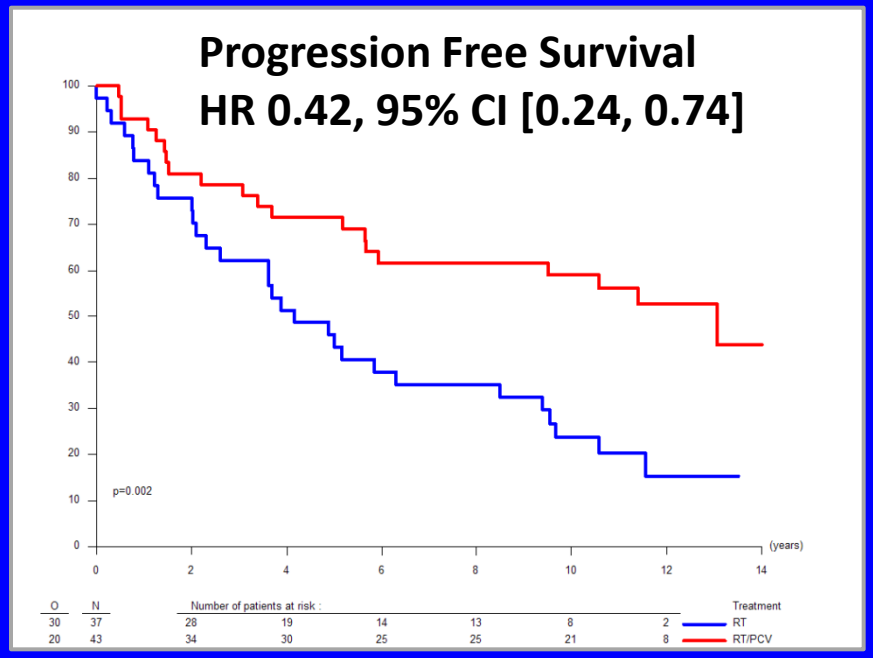
Molecular testing

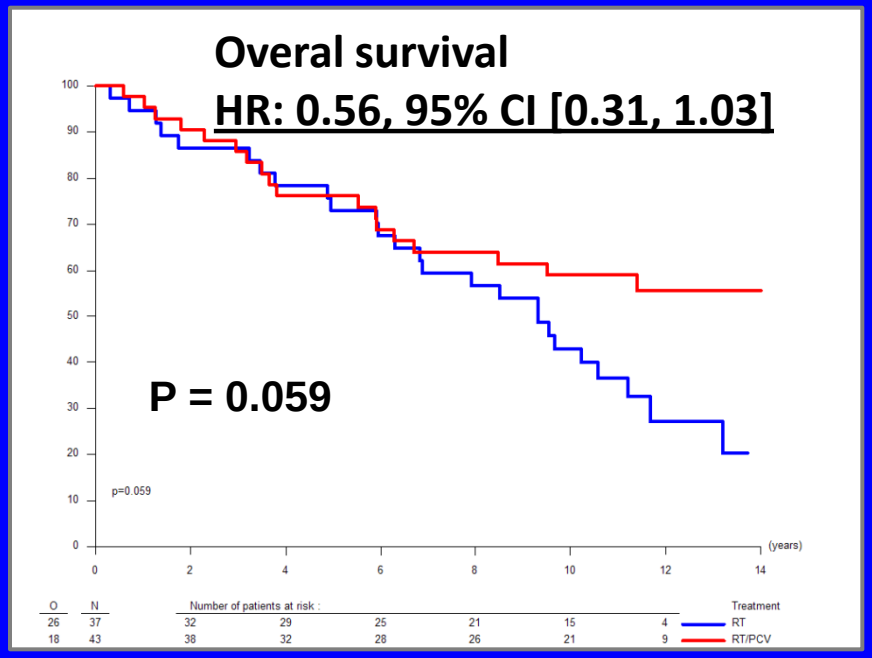
- Can we identify particular molecular subgroups that benefit from adjuvant PCV?
- Preplanned analysis for 1p/1q co-deletion:
  - 316 patients tested, 80 patients (25%) co-deleted
- Post hoc testing for IDH, MGMT:
  - 178 patients tested for IDH mutations, 81 (46%) mutated
  - 183 patients tested for MGMT methylation, 136 (74%) methylated

PFS and OS in 1p/19q co-deleted patients (n = 80)

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

Median	PFS	OS
RT (37)	50 mo	112 mo
RT/PCV (43)	157 mo	Not Reached





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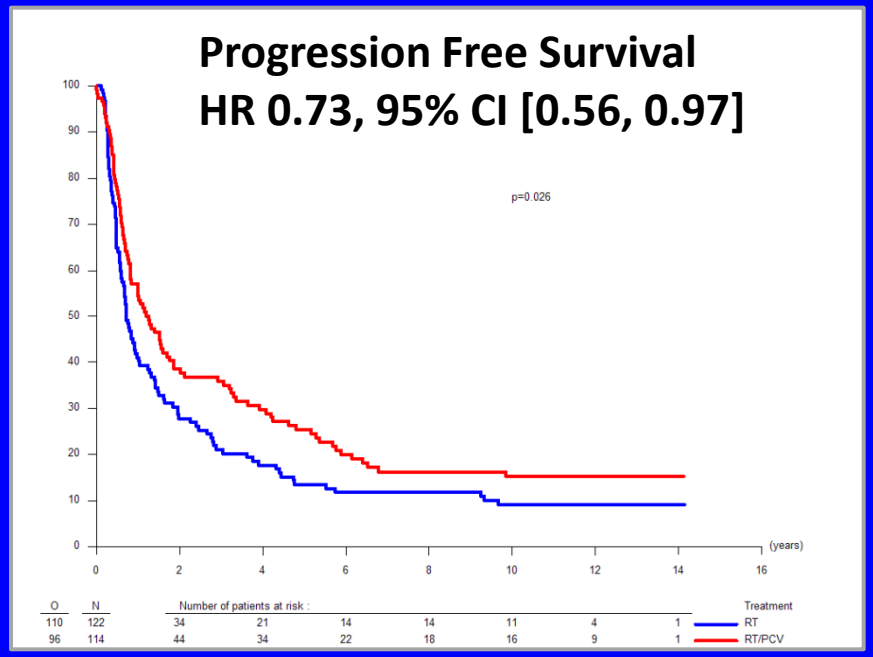
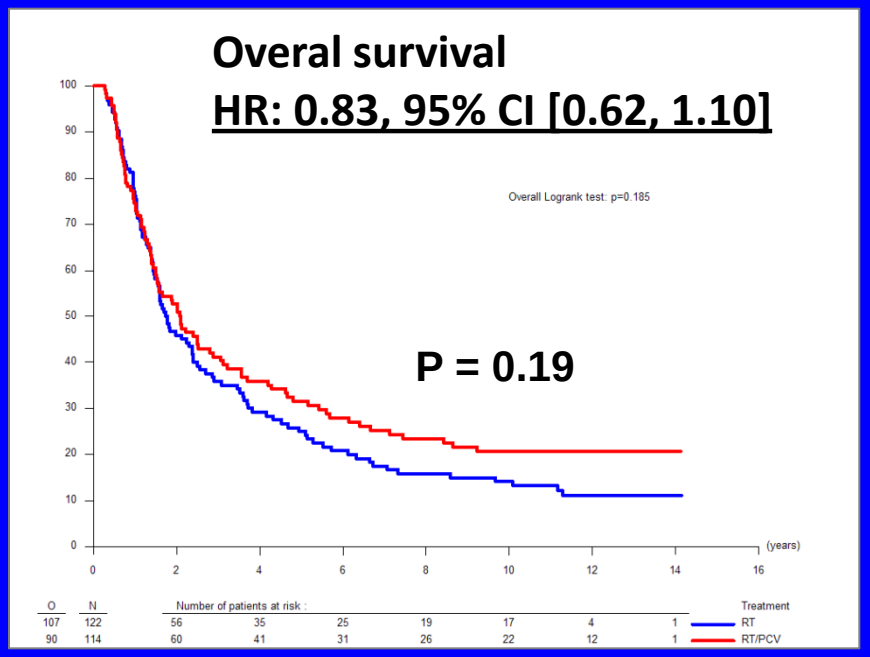
PFS and OS in the non-deleted patients (n = 236)

Conclusion:
With addition of PCV no statistically significant OS benefit

Median	PFS	OS
RT (n = 122)	9 mo	21 mo
RT/PCV (n = 114)	15 mo	25 mo





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Further molecular analysis on IDH, MGMT (post hoc)

- In univariate analysis: 1p/19q, IDH and MGMT status of prognostic significance ($p < 0.0001$)
- But: 1p/19q, IDH and MGMT are correlated:
  - Virtually all 1p/19q codeleted tumors show IDH mutation
  - Virtually all IDH mutated tumors show MGMT promoter methylation (as part of genome wide methylation)
- 158 cases with 1p/19q, IDH and MGMT available
  - Multivariate analysis:

<u>1p/19q and IDH are of independant prognostic value</u>

Post-hoc analyses IDH,MGMT

- Both in IDH mutated and in MGMT promoter methylated tumors trend towards more benefit of adjuvant PCV

But: two limitations

- In all molecular subgroups: tests for interaction remain negative
  - Limited sample size
- Post-hoc testing for both MGMT and IDH

<u>Confirmation is needed in a prospective dataset</u>

Conclusions EORTC 26951 in 2012

- Adjuvant PCV improves Overall Survival in anaplastic oligodendroglial tumors
- 1p/19q co-deletion identifies patients with increased benefit after PCV (HR: 0.56)
  - No proven benefit of PCV in non-deleted tumors
- Findings confirmed by RTOG study 9402 (PI G Cairncross, abstract # 2008b)
  - HR risk reduction in 120 co-deleted patients: 0.59, 95% CI (0.37, 0.95)

<u>RT/PCV new standard of care in 1p/19q co-deleted patients</u>

Questions after EORTC 26951

What about the non-deleted tumors?

- In other molecular subtypes no definitive conclusion
- Ongoing intergroup CATNON trial (EORTC) in non-1p/19q co-deleted grade III tumors must further define which patients benefit from chemotherapy

Adjuvant PCV or concurrent chemo-irradiation with temozolomide?

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