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

On behalf of the EORTC Brain Tumor group:
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DIFFUSE GLIOMAS: infiltrative glial tumors
15,000 new cases each year in the USA

Gliomas: most frequent adult primary brain tumor

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

Histological subtypes:
- 5-10% of all gliomas
- anaplastic astrocytoma
- oligodendroglioma
- oligoastrocytoma

EORTC 26951 on anaplastic oligodendroglial tumors

EORTC 26951 ASCO 2012
Question: will adjuvant PCV chemotherapy improve outcome in a chemotherapy sensitive glioma? EORTC 26951

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

- 1p/19q loss correlated with response to PCV chemotherapy
- MGMT, IDH testing in 26951
- Discovery IDH mutations in diffuse glioma: prognostic

- Amendment 3: Exploratory analysis 1p/19q in 26951
- MGMT, IDH testing in 26951

EORTC 26951: 2 decades of timelines and events
Primary endpoints:
Progression Free Survival
Overall Survival

**Treatment Schedule EORTC 26951**

**Focal RT**
daily - 33 x 1,8 Gy
Total dose 59.4 Gy

**RT Alone**

**RT**

6 cycles Adjuvant PCV

**PCV:**
CCNU (lomustine) 110 mg/m² day 1
Procarbazine 60 mg/m² day 8-21
Vincristine 1.4 mg/m² 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


- 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
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

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<th>Median</th>
<th>PFS</th>
<th>OS</th>
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<tr>
<td>RT</td>
<td>13 mo</td>
<td>31mo</td>
</tr>
<tr>
<td>RT/PCV</td>
<td>24mo</td>
<td>42mo</td>
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**Progression Free Survival**
- HR 0.66  95% CI [0.52, 0.83]
- p = 0.003

**Overall survival**
- HR: 0.75  95% CI [0.60; 0.95]
- p = 0.018

*[ ]:95% Confidence Interval

EORTC 26951 ASCO 2012
EORTC 26951: Risk adjusted analysis

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

**Assigned treatment remained independent factor for Overall Survival:**

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

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<th>Median</th>
<th>PFS</th>
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<tr>
<td>RT (37)</td>
<td>50 mo</td>
<td>112 mo</td>
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<tr>
<td>RT/PCV (43)</td>
<td>157 mo</td>
<td>Not Reached</td>
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**Progression Free Survival**
HR 0.42, 95% CI [0.24, 0.74]

**Overall survival**
HR: 0.56, 95% CI [0.31, 1.03]

P = 0.059

*[*]: 95% Confidence Interval

EORTC 26951 ASCO 2012
Conclusion:

With addition of PCV no statistically significant OS benefit

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<th>PFS</th>
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<tr>
<td>RT (n = 122)</td>
<td>9 mo</td>
<td>21 mo</td>
</tr>
<tr>
<td>RT/PCV (n = 114)</td>
<td>15 mo</td>
<td>25 mo</td>
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Progression Free Survival

HR 0.73, 95% CI [0.56, 0.97]

Overall survival

HR: 0.83, 95% CI [0.62, 1.10]

P = 0.19
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:

1p/19q and IDH are of independent prognostic value
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

Confirmation is needed in a prospective dataset
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)

RT/PCV new standard of care in 1p/19q co-deleted patients
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?
Acknowledgements

Co-investigators

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