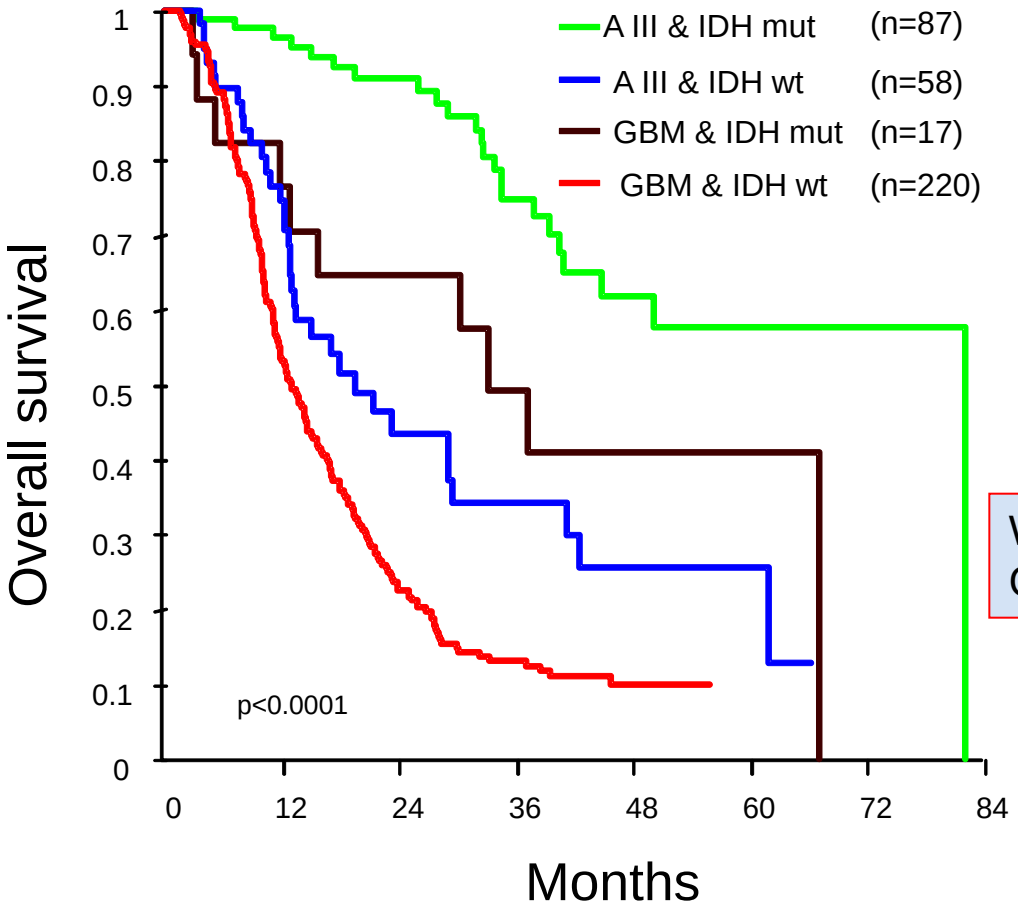
ESMO Congress 2012

Special Symposium – Molecular Neurooncology

Wolfgang Wick
Department Neurooncology & National Center for Tumor Disease Heidelberg
University Clinic Heidelberg & German Cancer Research Center

IDH1: better to discriminate high-grade glioma than WHO grade?



WHO-Grade

- Anapl. astrocytoma IDH1-mut
- GBM IDH1-mut
- Anapl. astrocytoma IDH1-wt
- GBM IDH1-wt

each

- MGMT meth.
- MGMT unmeth.

Hartmann et al., 2010

Deutsches Gliomnetzwerk

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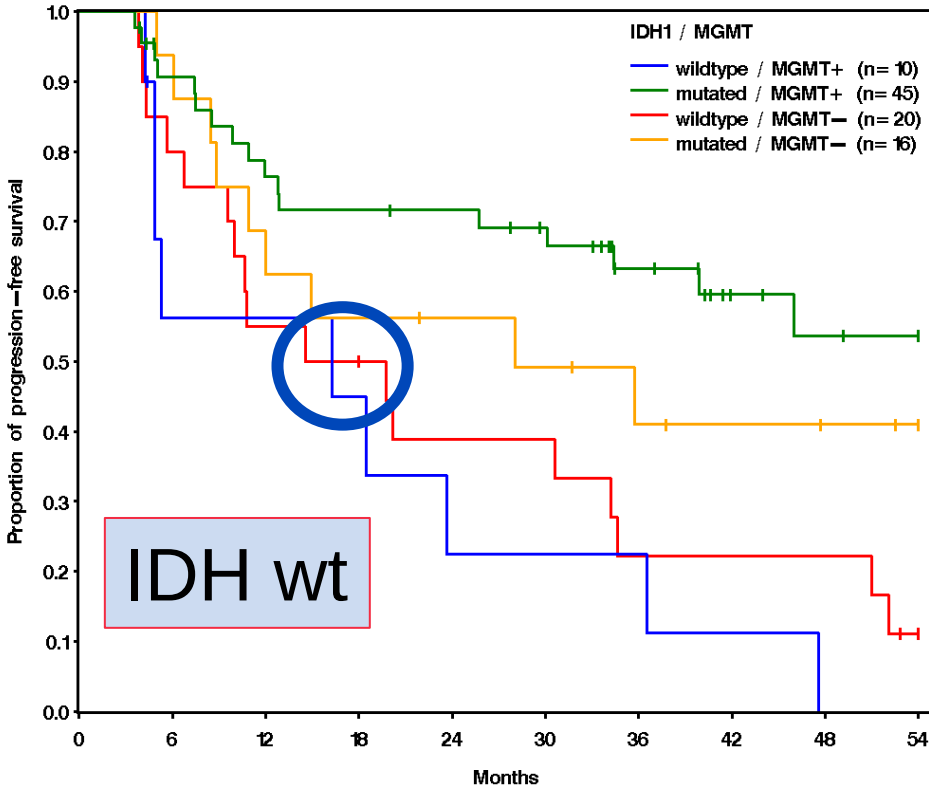
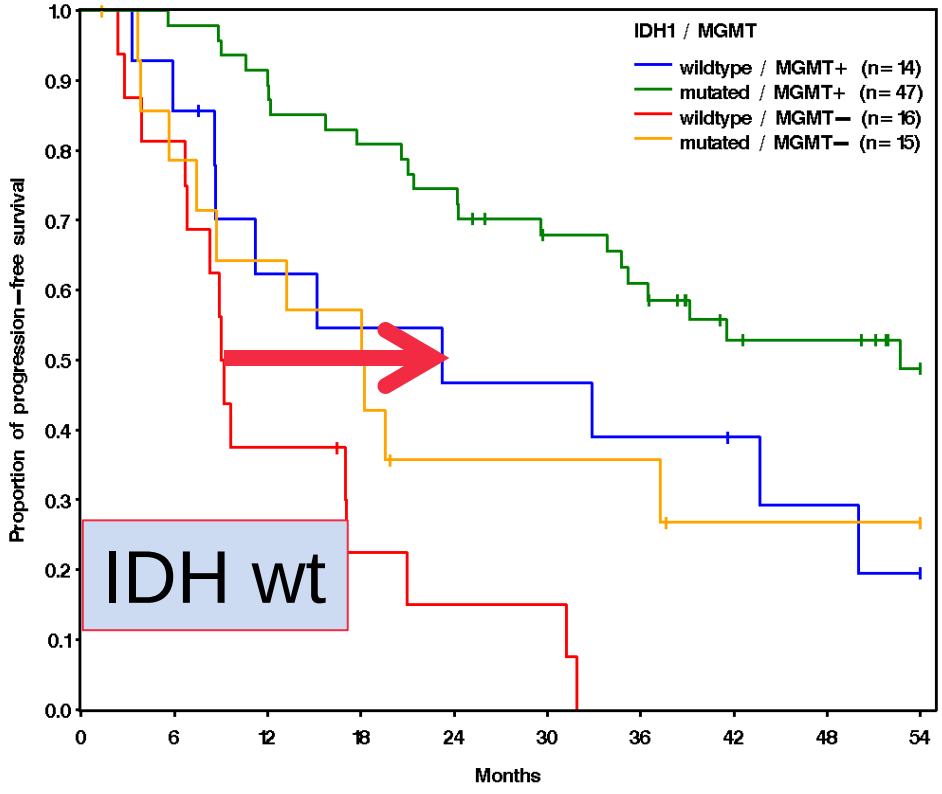
Interaction of *MGMT* and *IDH1?*

Radiotherapy

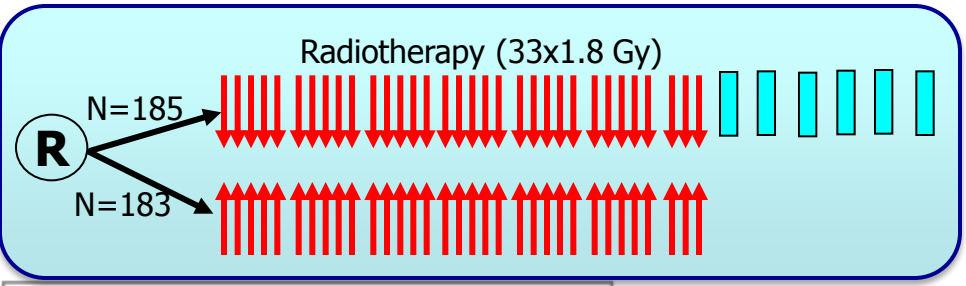


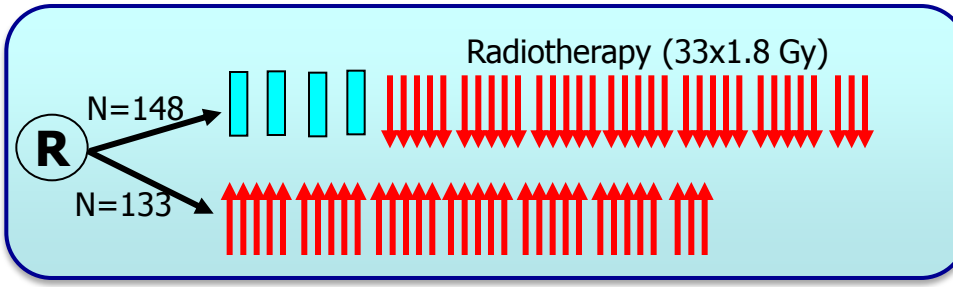
Alkylating CT

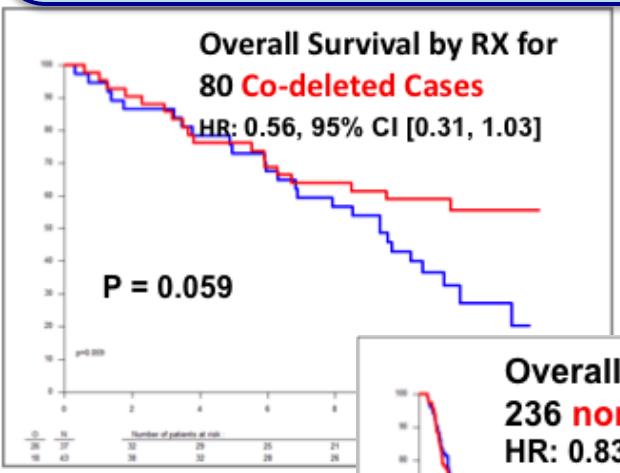


- Strong **prognostic** impact of IDH mutations for RT and chemotherapy
- **Prognostic** impact of MGMT for RT or chemotherapy in patients with IDH-mutated tumors
- **Predictive** role for MGMT for chemotherapy in patients with IDH-wt tumors

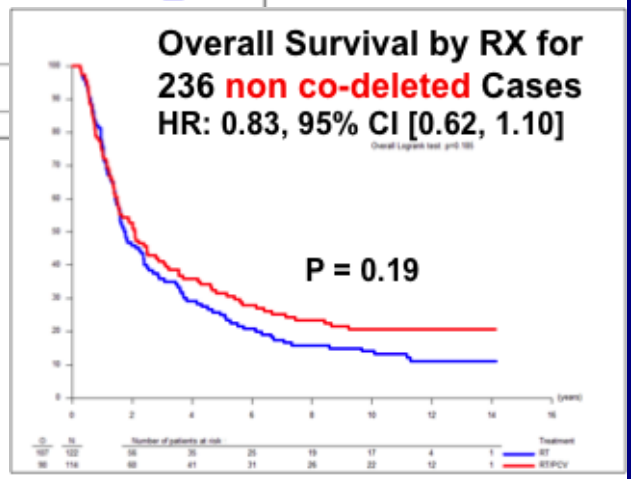
Prolonged survival with (neo-) adjuvant PCV chemotherapy



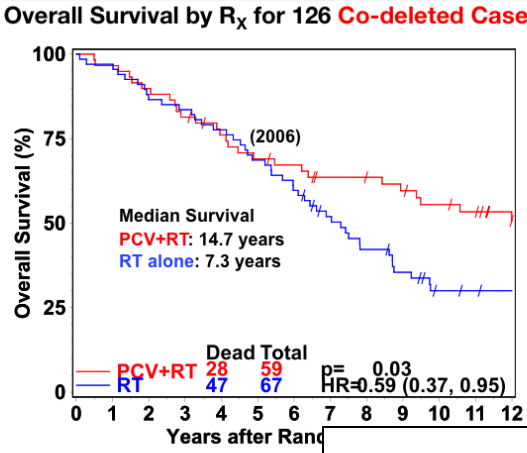




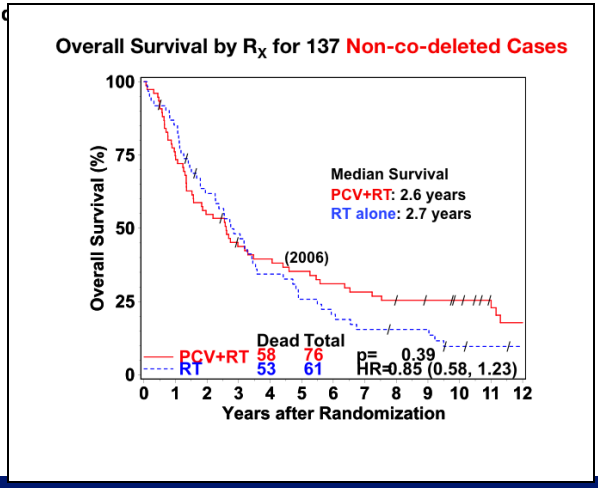
1p/19q codel



van den Bent for EORTC, Proc ASCO 2012, abstr # 2; J Clin Oncol 2006 vol. 24 (18) pp.2715-22



1p/19q codel



Cairncross for RTOG,

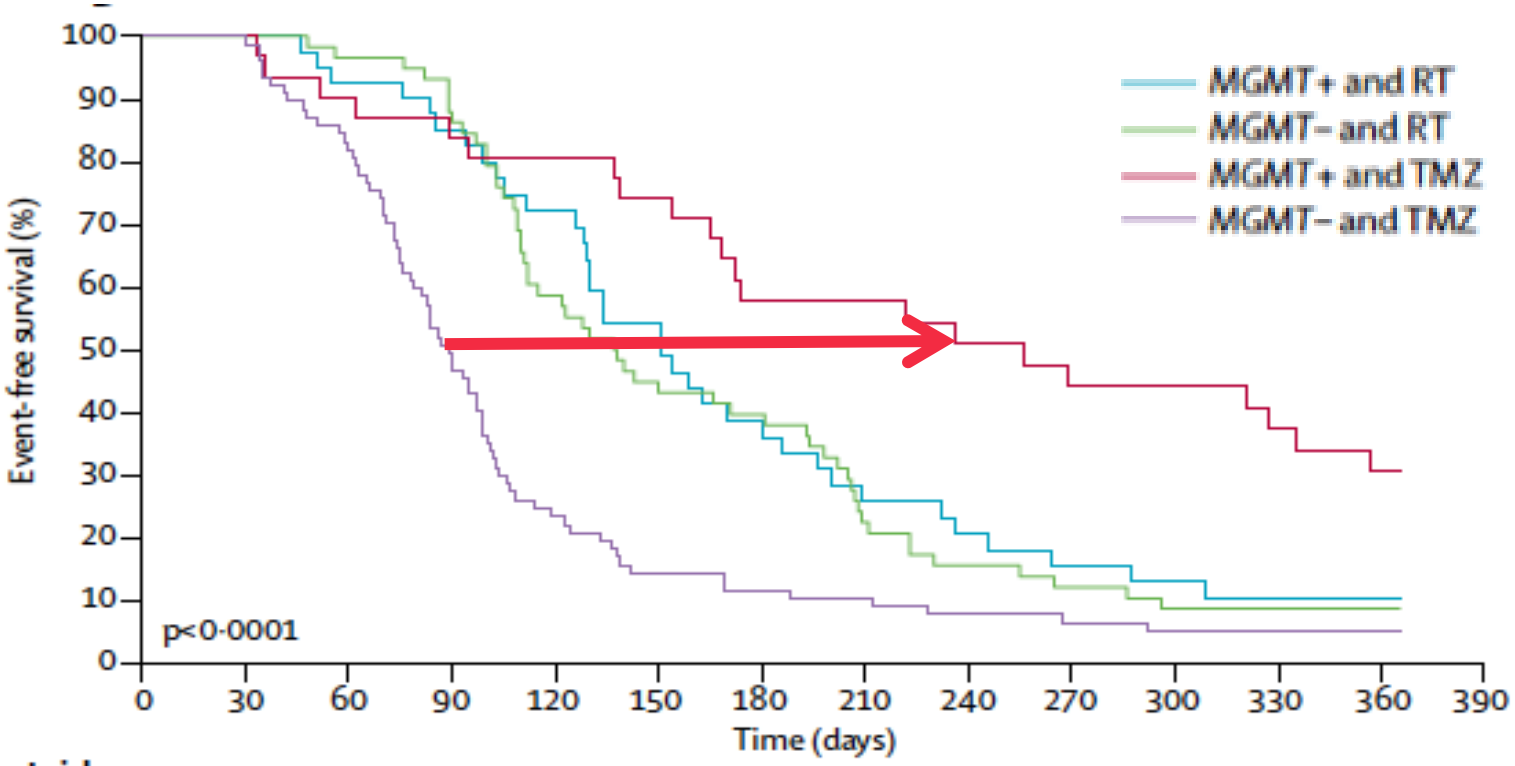
Proc ASCO 2012, abstr # 2008b; J Clin Oncol 2006;24:2707-14

1p/19q codeletion is a predictive biomarker in oligodendroglial tumors

	RTOG 9402		EORTC 26951	
	RT	PCV+RT	RT	RT+PCV
PFS, 1p/19q intact				
OS, 1p/19q intact	2.7	2.6	1.8	2.1
PFS, 1p/19q deleted				
OS, 1p/19q deleted	7.3	14.7	9.3	Not reached

van den Bent et al. ASCO 2012, abstract 2000; Cairncross et al. ASCO 2012, abstract 2010b

MGMT is a predictive biomarker in glioblastoma of the elderly



Number at risk

RT													
MGMT+	42	41	38	33	28	21	14	10	8	6	5	4	1	0
MGMT–	59	59	56	50	34	25	23	13	9	7	5	4	1	0
TMZ														
MGMT+	31	30	28	26	25	23	17	17	15	13	13	11	9	8
MGMT–	77	76	63	37	18	11	9	8	6	5	4	4	1	0

Wick et al. Lancet Oncol 2012

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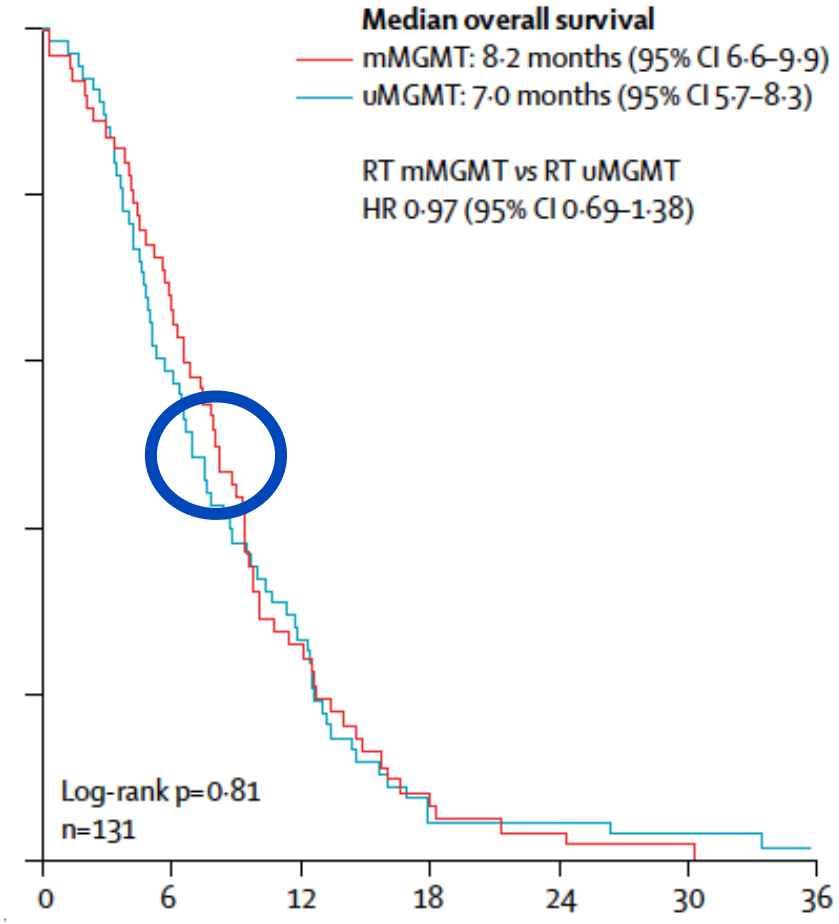
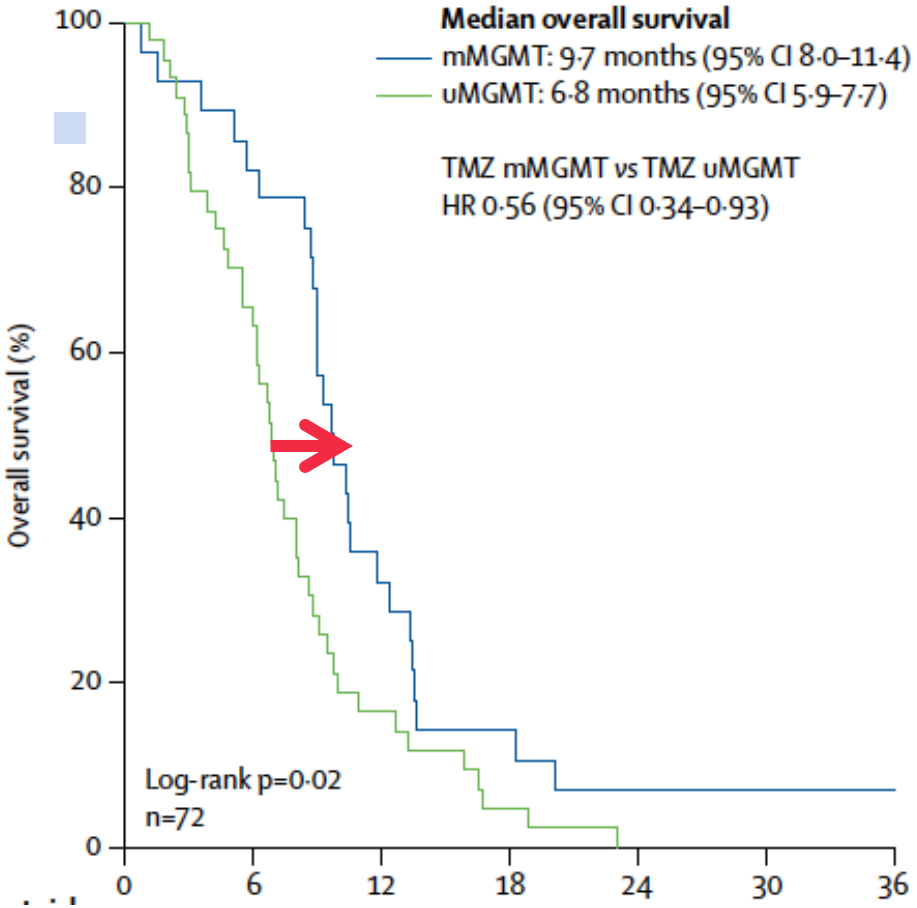
MGMT is a predictive biomarker in glioblastoma

Radiotherapy



Temozolomide



Malmström et al. Lancet Oncol 2012

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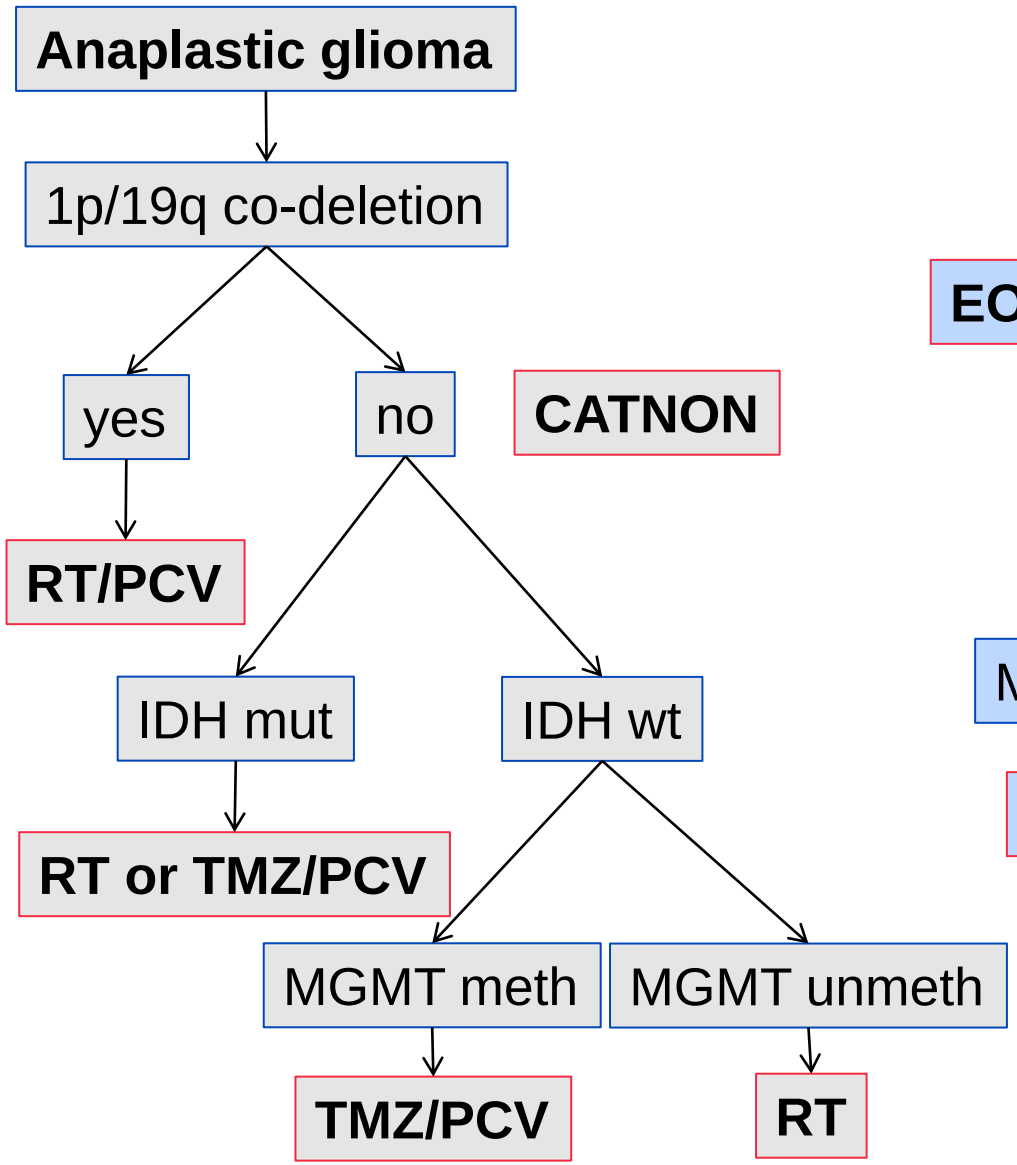
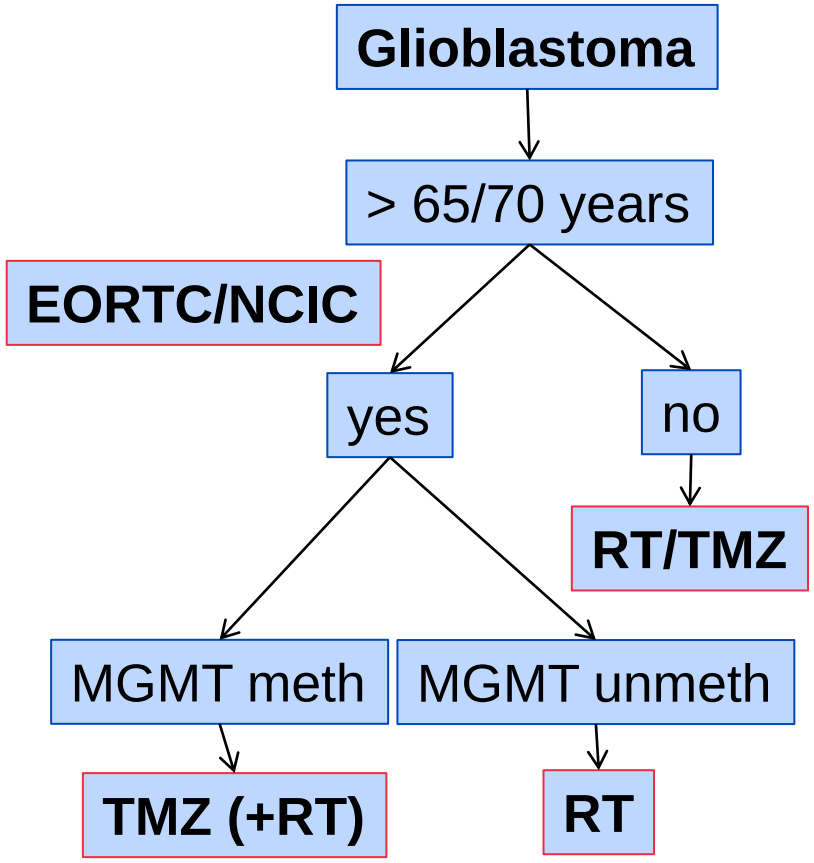
A practical approach to biomarker testing





Anaplastic glioma: what are the next questions?

Is radiotherapy necessary in 1p/19q co-deleted tumors?	NOA-04 might help to answer that question in some time from now
What does the next trial look like? **What is the biology behind the 1p/19q co-deletion?**	Is TMZ able to replace PCV in the EORTC/RTOG regimens? CIC, FUBP1, PRDX?
Does the 1p/19q status have a relevance beyond the WHO° III?	Maybe. RTOG 9802 might tell us in some years from now. The difficulties in grading in EORTC 26951 may point towards that notion.

Glioblastoma in the elderly: what are the next questions?

Can and should we use MGMT testing in the elderly?	NOA-08 and the Nordic Trial independently call for that.
Who is called elderly?	Further work on the biology of these tumors might tell us in the near future better than the passport.
What is the standard for MGMT meth patients?	RT or RT/TMZ? Will there be a trial to solve that question?
What are the next steps to improve survival?	Intensifying treatment separately for MGMT meth and unmeth patients.

Medulloblastoma: a paradigmatic disease for molecular neurooncology

- So far, the molecular classifiers have not translated into clinical trials
- *Although the data and tools allow stratification and in some instances prediction of rational drug targets*
- Analysis of primary and secondary resistance
  - To be tested now and applied in the upcoming trials, e.g. SHH inhibition

- Incidence of “sporadic” tumor syndroms may be more common than anticipated, which should lead to closer surveillance and diagnostics in relatives, e.g. of patients with SHH-medulloblastoma
  - Other pediatric tumors may also have an underlying hereditary basis

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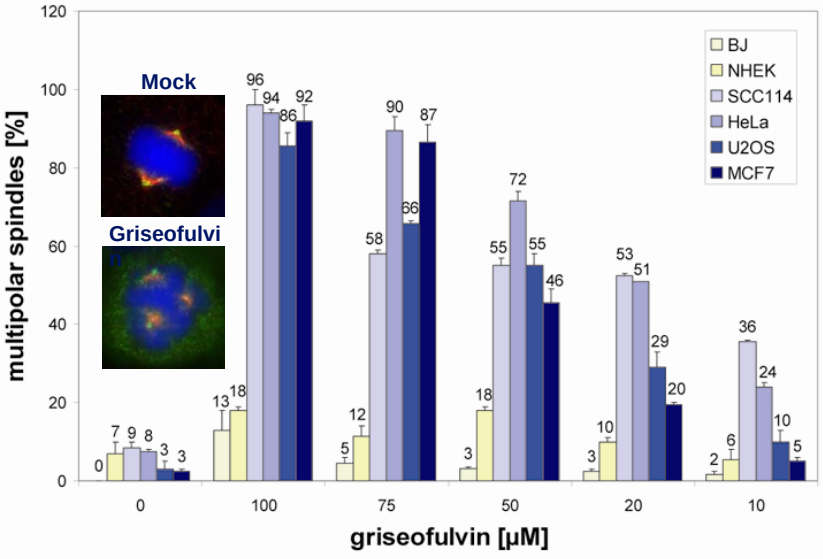
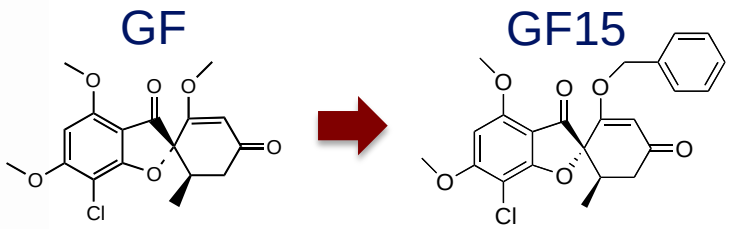
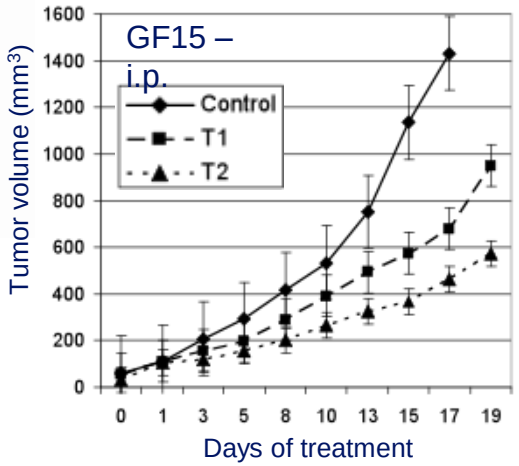
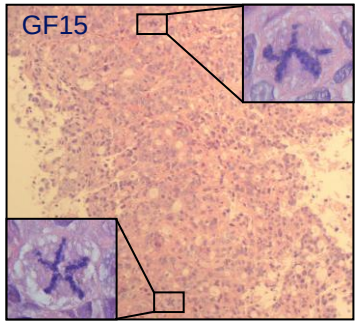
Genome-wide siRNA-screen for proteins involved in bundelling of extra centrosomes

Identification of therapeutic targets for 82 proteins identified to inhibit spindel multipolarity and induce cell death selectively in tumor cells (**Science Translational Medicine** 2010).







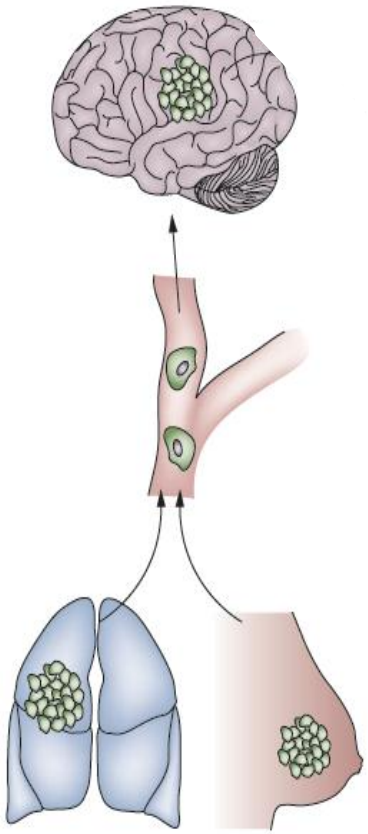


Tumor xenografts in mice

Griseofulvin analogues kill tumor cells with extra centrosomes *in vivo*

Best approach to brain metastases

❖ Regard them as one (important) feature of the diseases



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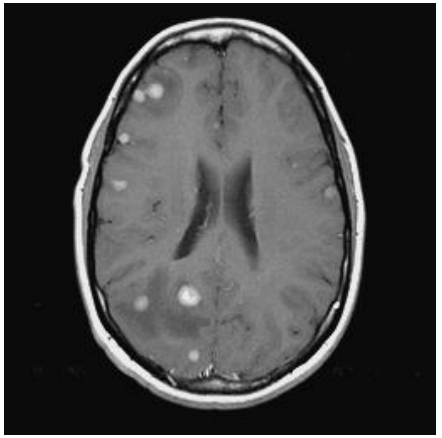
Prevention ⟷ Combat

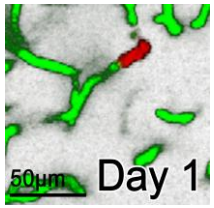
At which stage?
-> as early as possible
Which entity?
->nsNSCLC
->Biomarker-driven
Which endpoints?
->QoL
->OS
Which treatment?

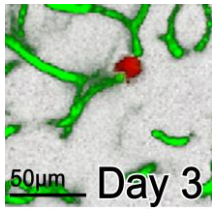


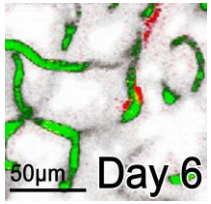
❖ New compounds
❖ New RT-strategies
(e.g. EORTC trial)

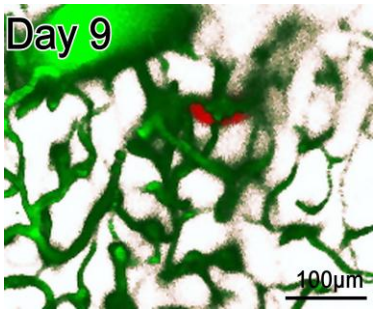
Different growth patterns

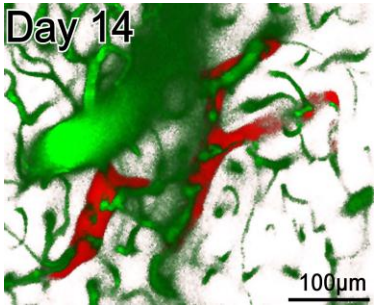
Melanoma – cooptive growth

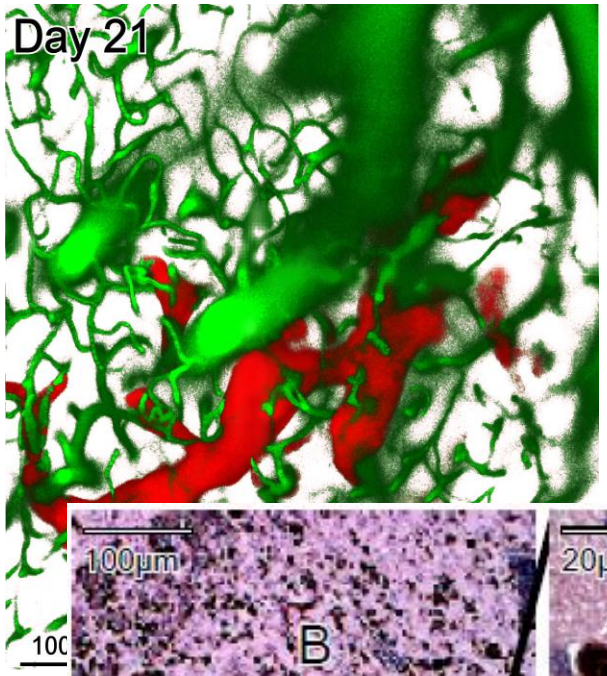


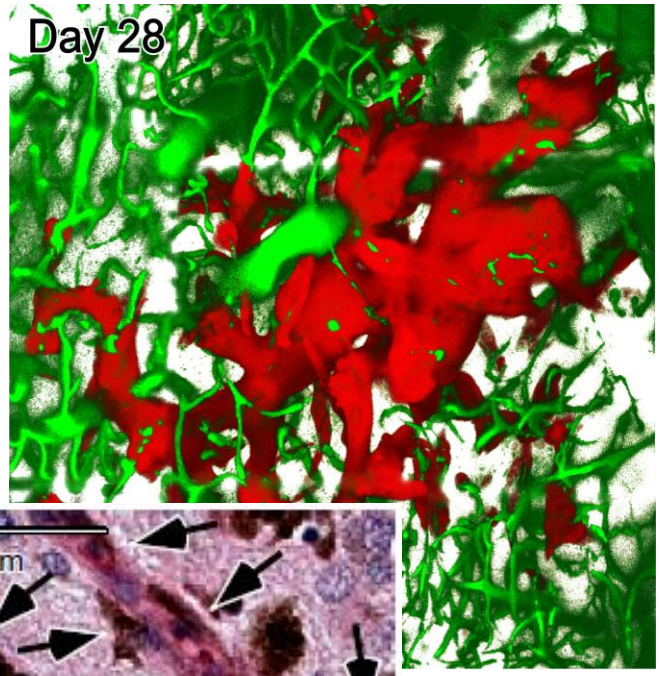




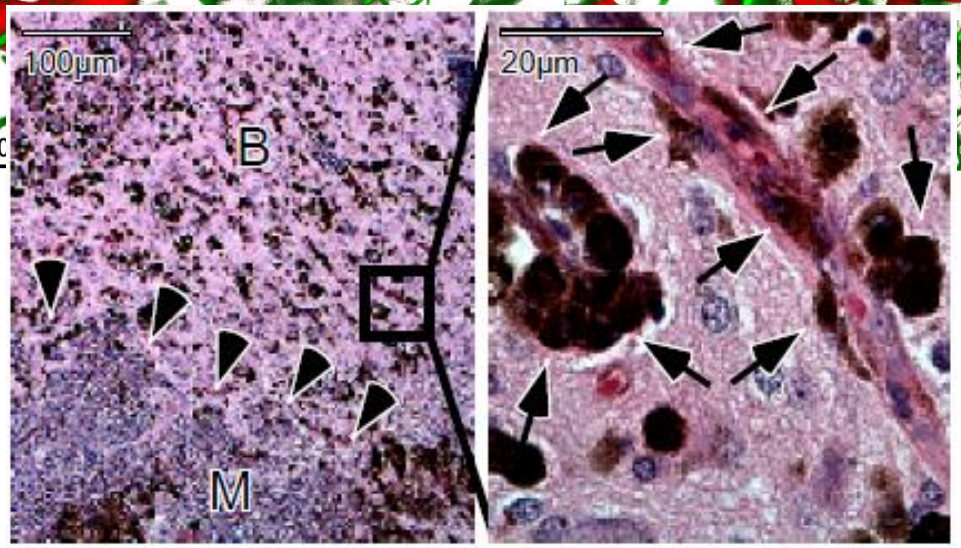






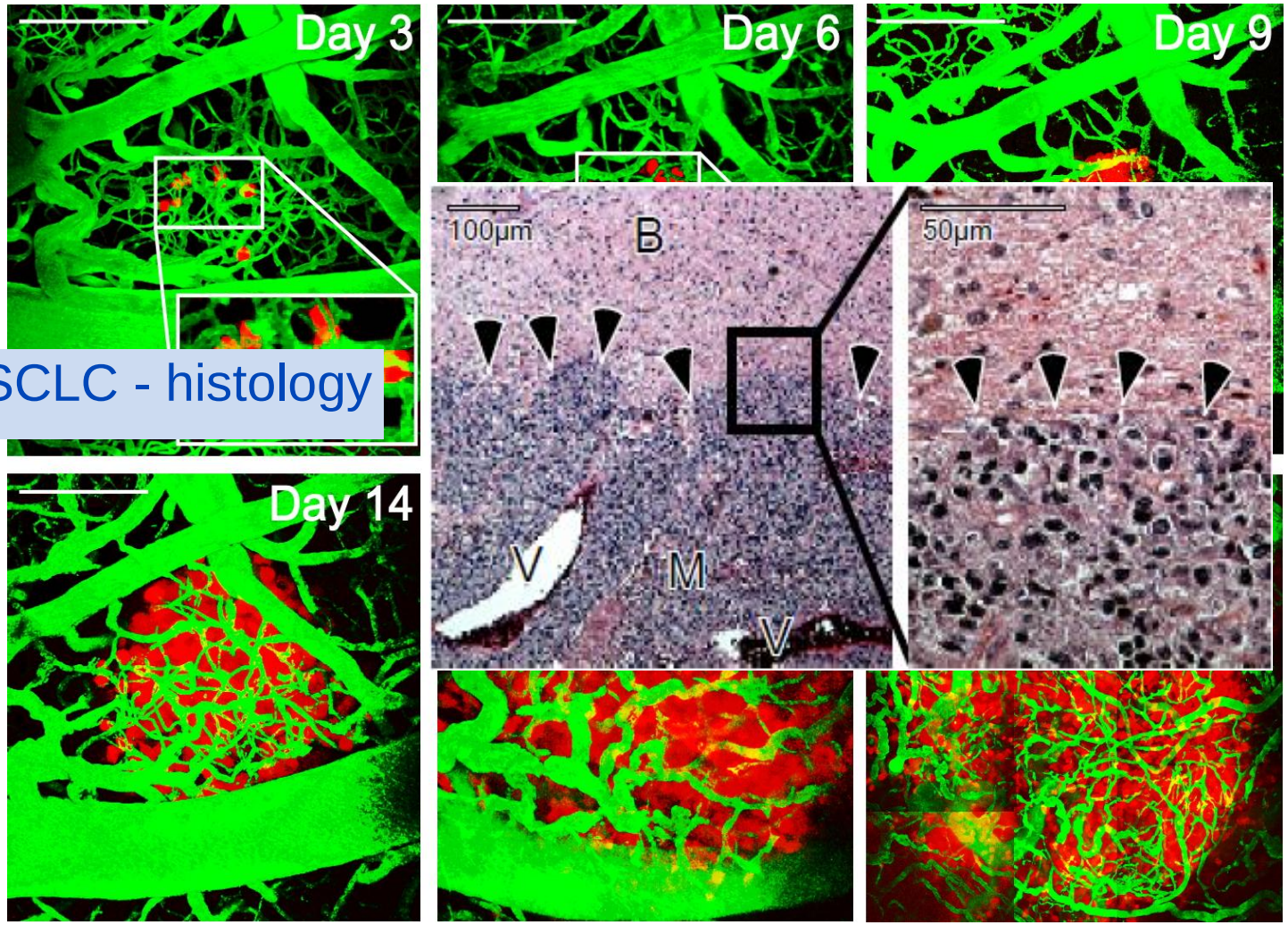


melanoma
(melanin: brown)



Different growth patterns

NSCLC– angiogenic growth



Brain metastases in nsNSCLS: proposal for a trial

- Stage III tumors
- Standard of care
- Randomized to bevacizumab at 5 mg/kg q 3 weeks for 2 years
- Endpoint: OS and time to formation of brain mets