- Iuchi Toshihiko et al: Tyrosine kinase inhibitors for brain mets of EGRF mutant adenocarcinoma of the lung

- Bruno Chauffert et al: RCT phase II of irinotecan + Bev as neoadjuvant + adj. to TMZ treated unresectable GBM (TEMAVIR ANOCEF) study

- Emeline Tabouret et al: Association of a strong plasma biomarker level with response and survival in patients treated with Bevacizumab for recurrent HGG

Christine Marosi

Medical University of Vienna

Disclosures

Christine Marosi received previously travel support, lecture honoraria and research funding from Roche.

Tyrosine kinase inhibitors without radiation therapy for brain metastases from EGFR-mutant adenocarcinoma of the lung

Toshihiko Iuchi[1], M. Shingyoji[2], T. Sakaida[1], S. Yokoi[3], M. Itakura[2], K. Kawasaki[1], Y. Hasegawa[1], H. Kageyama[3], T. Iizasa[2]

1. Neurological Surgery, Chiba Cancer Center, Chiba, JAPAN,

2. Thoracic Disease, Chiba Cancer Center, Chiba, JAPAN,

3.Cancer Diagnosis, Chiba Cancer Center Research Institute, Chiba, JAPAN

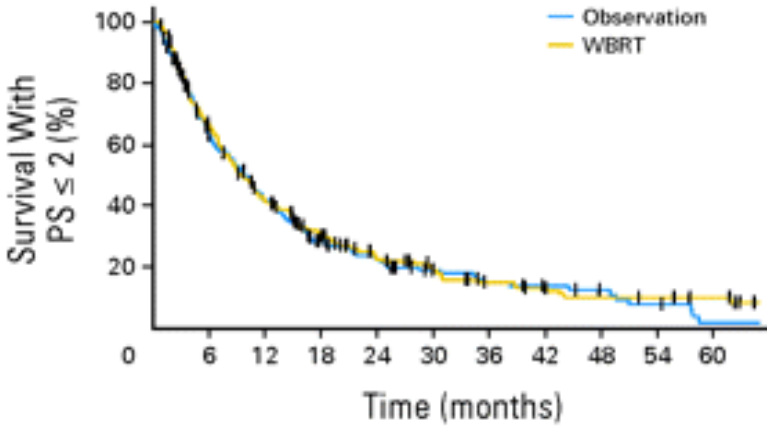
May radiotherapy be delayed to (certain) patients with brain metastases?

still a hot topic: brain metastases may affect 6% of the population

- ASCO 2006: W.Regine: The evidence favors whole brain radiotherapy
- Radiotherapy remains the mainstay of treatment of patients with BM
  - Gaspar LE et al:The role of whole brain radiation therapy in the management of newly diagnosed brain metastases:
  - Linskey ME, et al: The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases
  - both: J Neurooncology January 2010: systematic reviews and evidence-based clinical practice guideline.
- EORTC Study 22951/26001 Kocher et al:

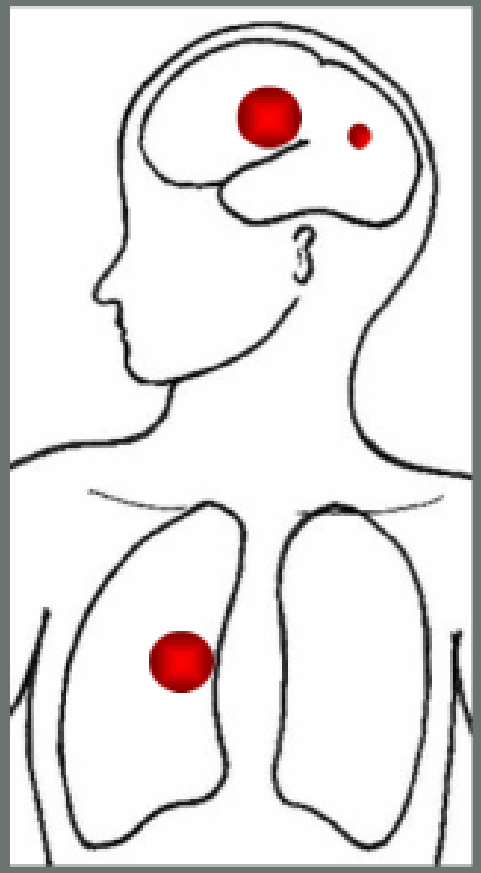
delay of WBRT in good prognostic patients

duration of independent SV similar



Kocher M, Soffietti R,
J Clin Oncol. 2011;29):134-41

Treatment



Brain Metastases (EGFR mutant)

↓

Gefitinib

↓

Tm. Progression
(intracranial/systemic)

↓

Erlotinib

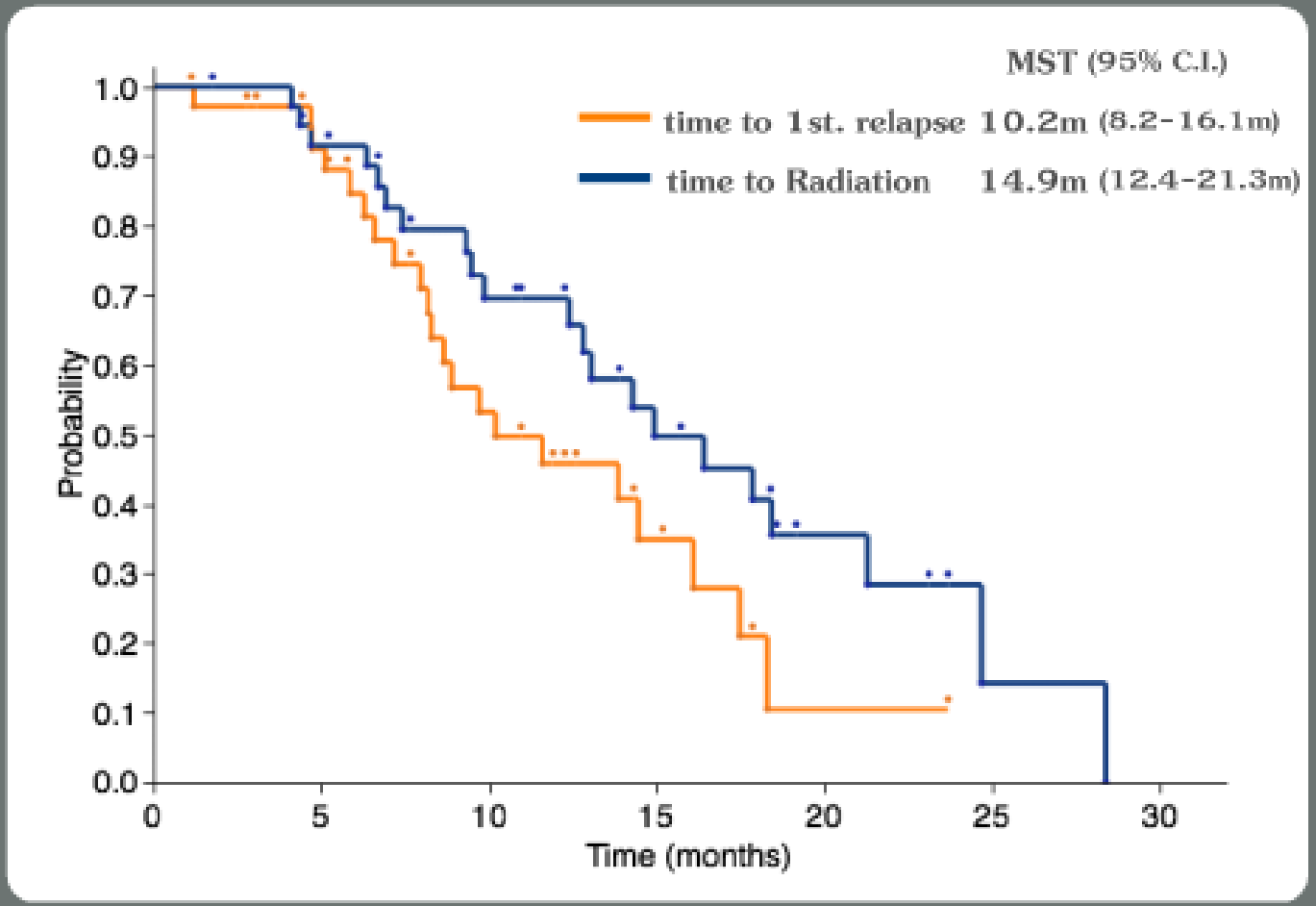
↓

Tm. Progression
(intracranial/systemic)

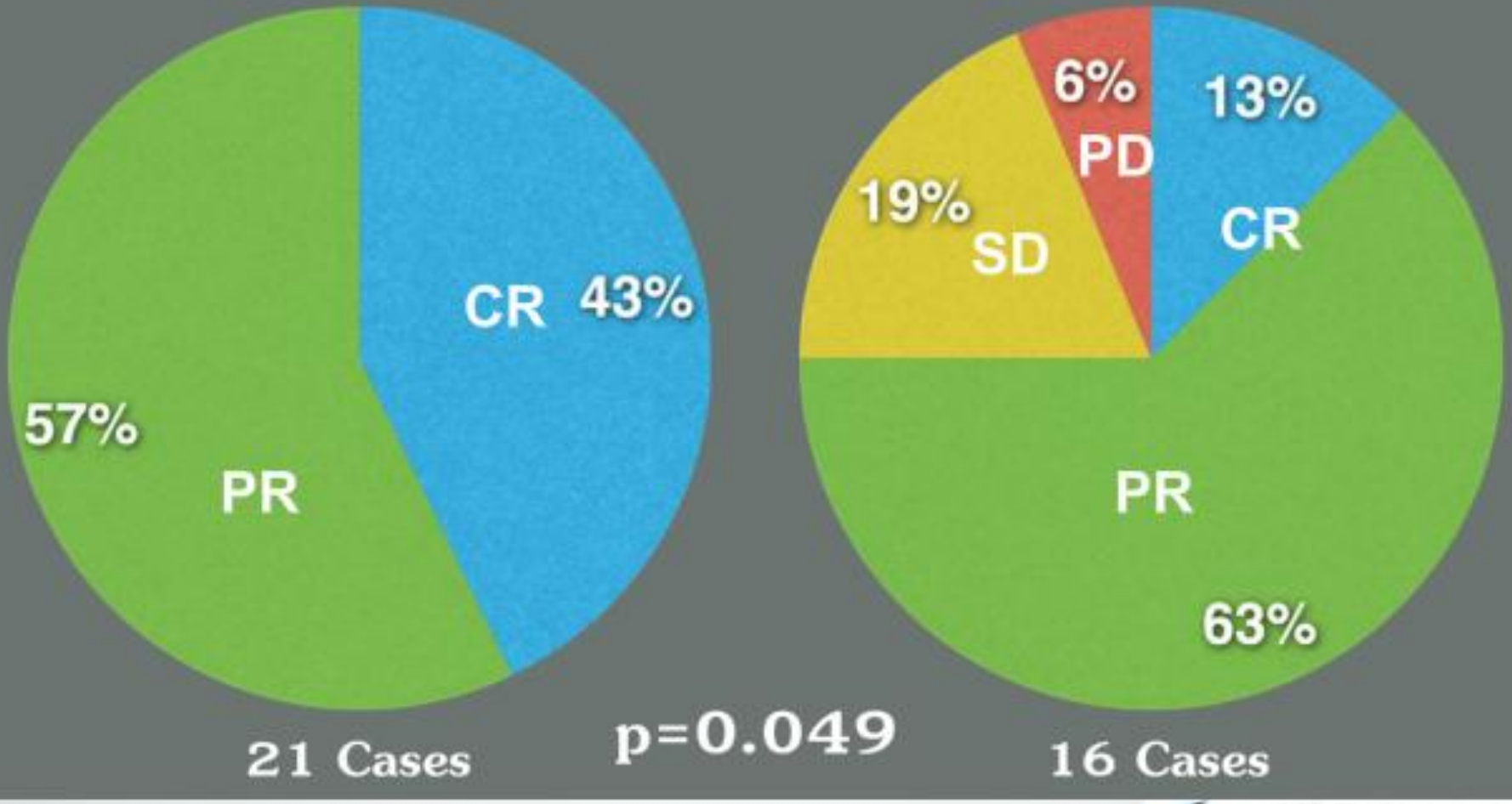
↓

SRS/SRT and/or WBRT

Lesion Control



EGFR mutations



Adverse Events

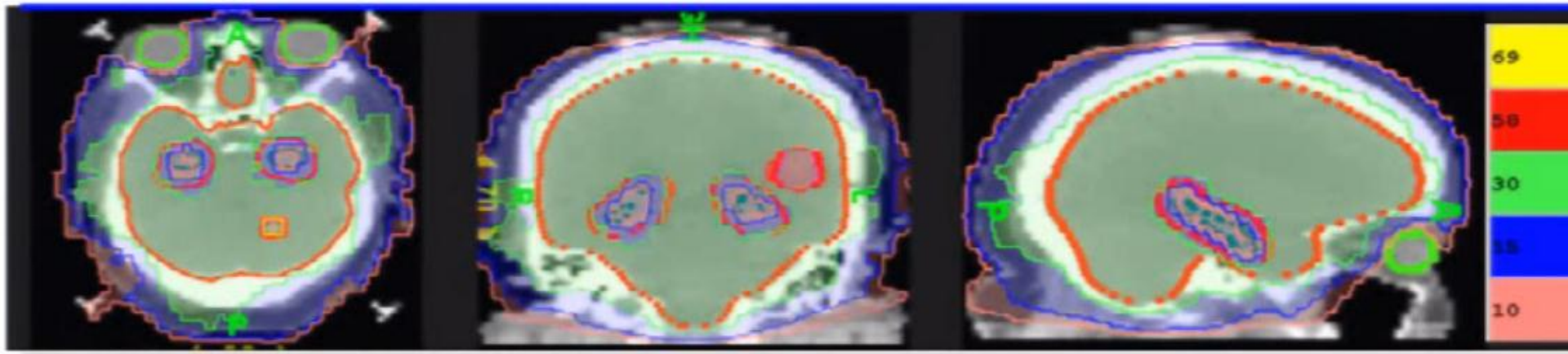
37 Cases

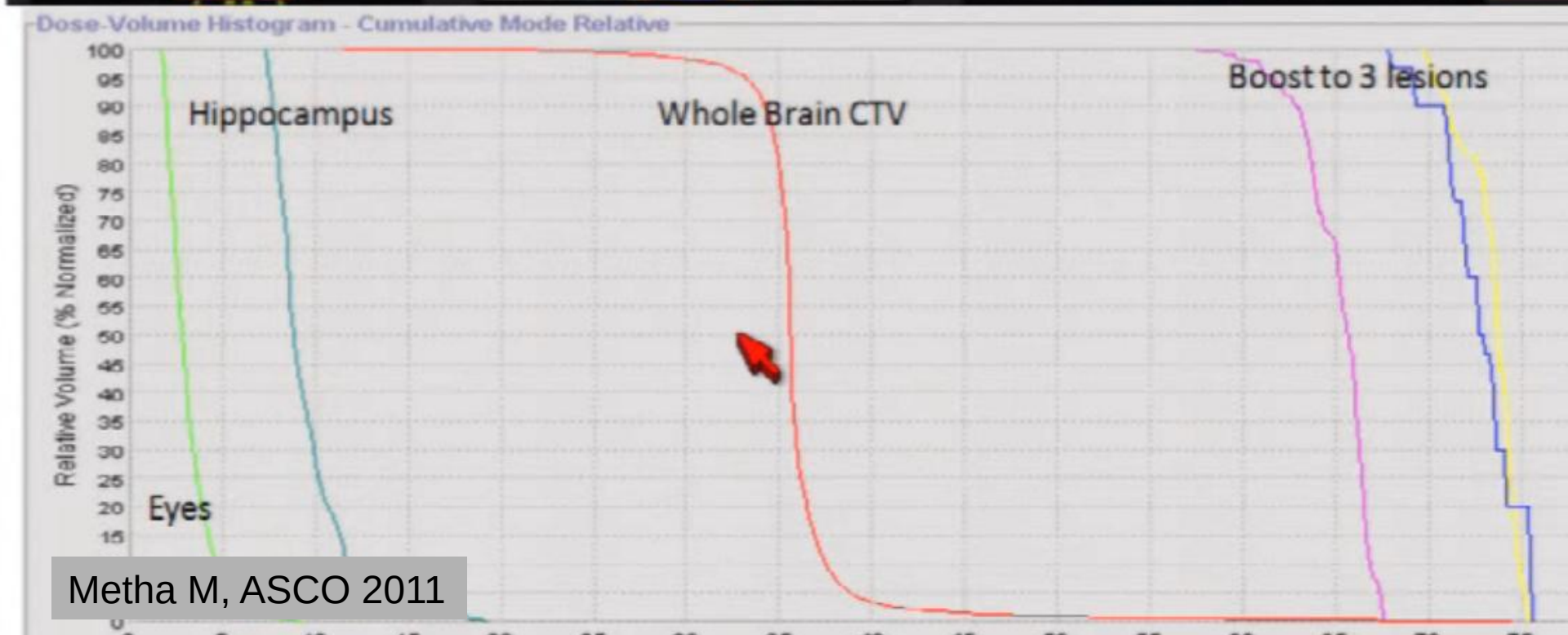
No Grade 4 Adverse Event

Grade 3 Adverse Events

Pneumonitis	1	2.7%
Skin Rash	8	21.6%
Blood toxicity	2 lymphocytopenia (1) Neutorpenia (1)	5.4%
Liver dysfunction	4	10.8%
Renal dysfunction	0	0.0%

HA-WBRT in conjunction with selective boosting





Metha M, ASCO 2011

Neurocognitive function impairment after WBRT: an actual assessment

Assessments of neurocognitive outcomes after WBRT+/- SRS in patients with brain metastases: 16 studies.1648 patients

- biphasic pattern of neurocognitive impairment:
  - subacute, transient decline with a peak at 4 months

    (31-57% patients impaired at three months)

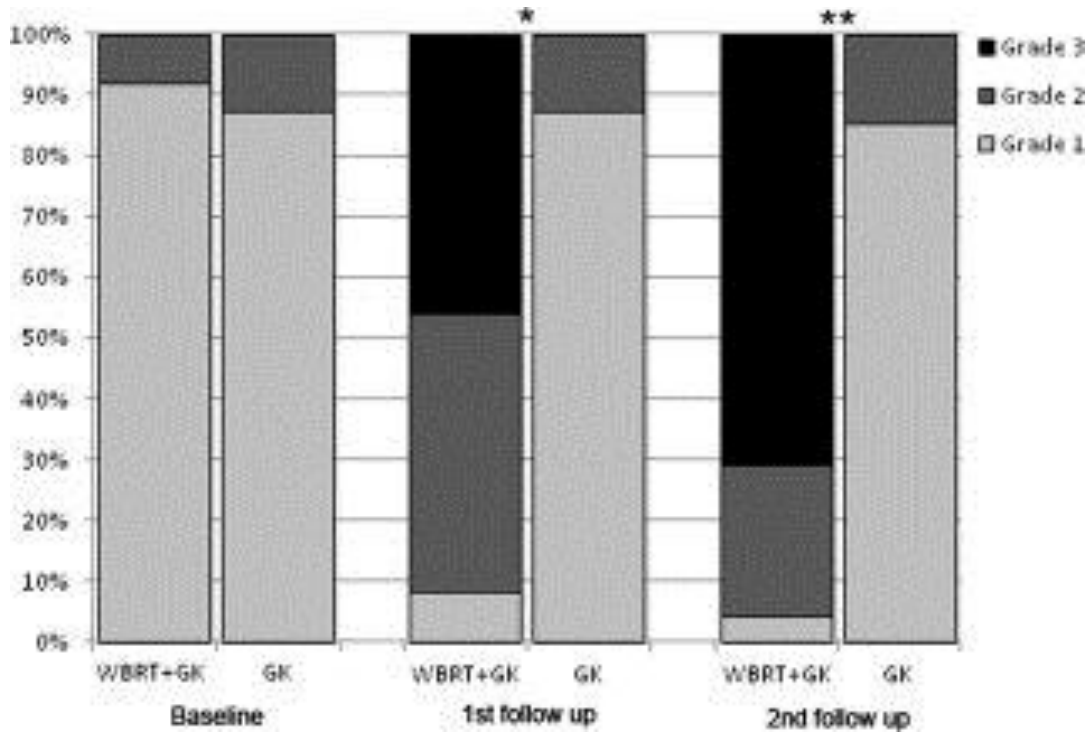
    > -4 points at MMSE, -2 SD at HVLT, COWA
  - late delayed irreversible impairment months or years after WBRT, affecting more memory than motor functions

    48-85% patients impaired at 12 months

- must be balanced against the detrimental cognitive effects of brain disease recurrence

Tallet et al. Radiation Oncology 2012,7:77

Leukencephalopathy after WBRT + SRS vs SRS alone for metatstatic lung cancer



similar initial white matter grading,
at 12 months: 40% grade, and 45% grade 3 white matter changes
at 24 months 25% grade 2 and 70% grade 3 white matter changes in the WBRT group

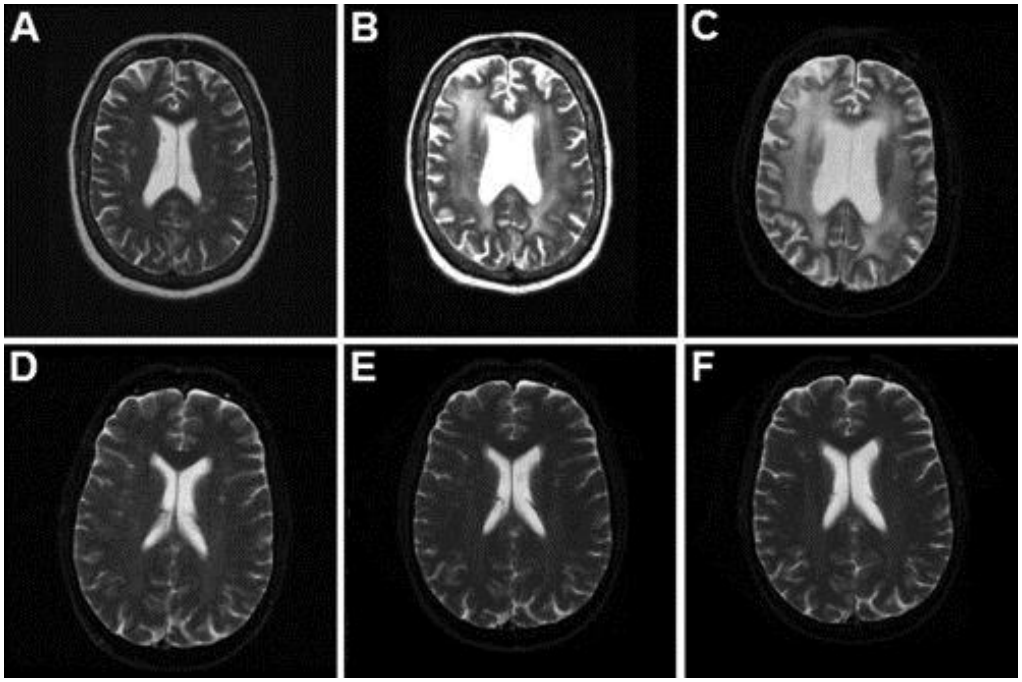
Monaco EA et al, Cancer June 15, 2012

Leukencephalopathy after WBRT + SRS vs SRS alone for metatstatic lung cancer

2 exemplary patients

WBRT + SRS

SRS



26.5 months

22.3 months

Monaco EA et al, Cancer June 15, 2012

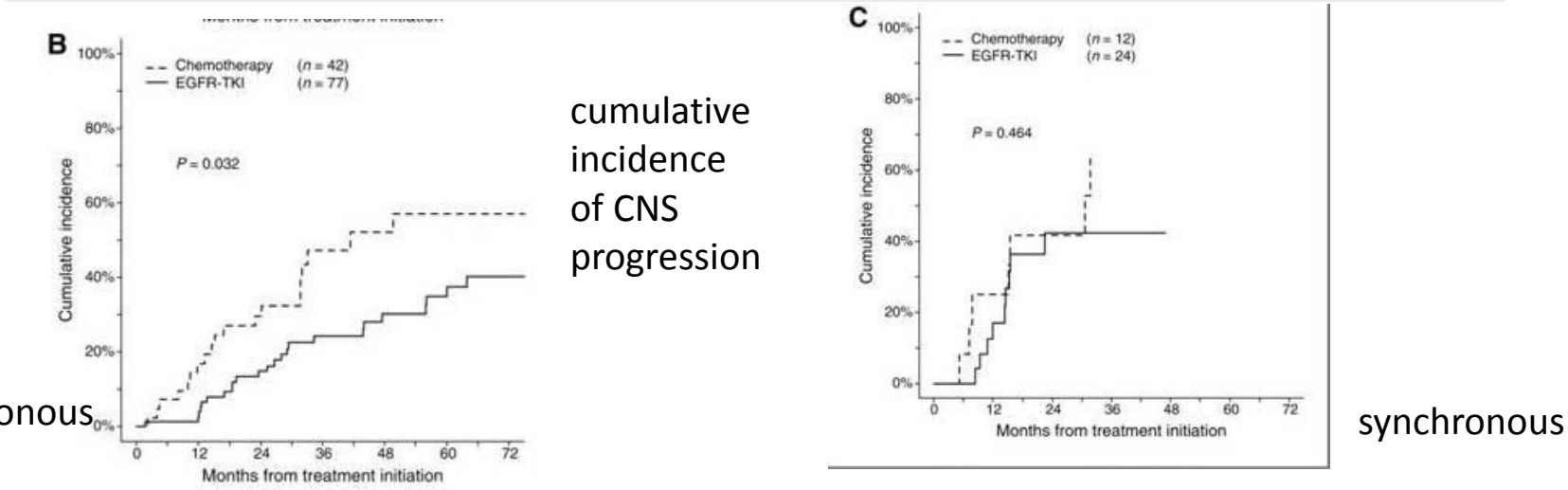
Published OnlineFirst June 25, 2012; DOI:10.1158/1078-0432.CCR-12-0357

Clinical Cancer Research

Cancer Therapy: Clinical

The Impact of Initial Gefitinib or Erlotinib versus Chemotherapy on Central Nervous System Progression in Advanced Non–Small Cell Lung Cancer with *EGFR* Mutations

Stephanie Heon[1,2,3], Beow Y. Yeap[2,4], Neal I. Lindeman[5,6], Victoria A. Joshi[5,6,7], Mohit Butaney[1], Gregory J. Britt[2,8], Daniel B. Costa[2,8], Michael S. Rabin[1,2,3], David M. Jackman[1,2,3], and Bruce E. Johnson[1,2,3]



cumulative incidence of CNS progression

metachronous

synchronous

TKIs prevented the formation of metachronous brain metastases (B), but not progression of established brain metastases (C) as compared to chemotherapy

RANDOMIZED MULTICENTER PHASE II TRIAL OF IRINOTECAN AND BEVACIZUMAB AS NEO-ADJUVANT AND ADJUVANT TO TEMOZOLOMIDE-BASED CHEMORADIATION VERSUS CHEMORADIATION FOR UNRESECTABLE GLIOBLASTOMA

DEFINITIVE RESULTS OF THE TEMAVIR ANOCEF STUDY

B. Chauffert

Medical Oncology, University Hospital, Amiens

FRANCE

Study design

Randomisation

EXPERIMENTAL GROUP : B/I

2 months — **Neo-adjuvant**
BVZ 10 mg/kg
IRI 125 mg/ m^2
D1, D15, D29 & D43

28 days — Therapeutic break-up
1st MRI

6 weeks — **Chemoradiation**
3D-RT 60 Gy : 2Gy/ fraction x 30
TMZ: 75mg/ m^2/ day
BVZ: 10mg/kg every 2 weeks

28days — Therapeutic break-up
2nd MRI

6 months — **Adjuvant**
BVZ: 10 mg/kg
IRI: 125 mg/ m^2
Every 2 weeks
MRI every 2 months

neoadjuvant phase
delays begin of RT
by 3 months
+ delay
since biopsy

CONTROL GROUP

Chemoradiation — 6 weeks
3D-RT 60 Gy : 2Gy/ fraction X 30
TMZ 75mg/ m^2/ day

Therapeutic break-up — 28 days
1st MRI

Adjuvant — 6 months
TMZ 150-200 mg/ m^2/ day
X 5 days/ month
MRI every 2 months

Patients were randomly assigned to experimental arm or control arm (1/1 ratio), and stratified by:
- ✓Mini Mental Status (MMSE) : < 27 *vs* ≥ 27
- ✓ Neurological Status: 0,1 ou 2 *vs* 3,4
- ✓ Gender men *vs* women
- ✓ Age : < 50 ans *vs* ≥ 50 ans
- ✓ Center

BVZ: bevacizumab, IRI: Irinotécan, TMZ: Témozolomide, MRI: Magnetic Resonance Imaging

Grade III-IV toxicities (%)

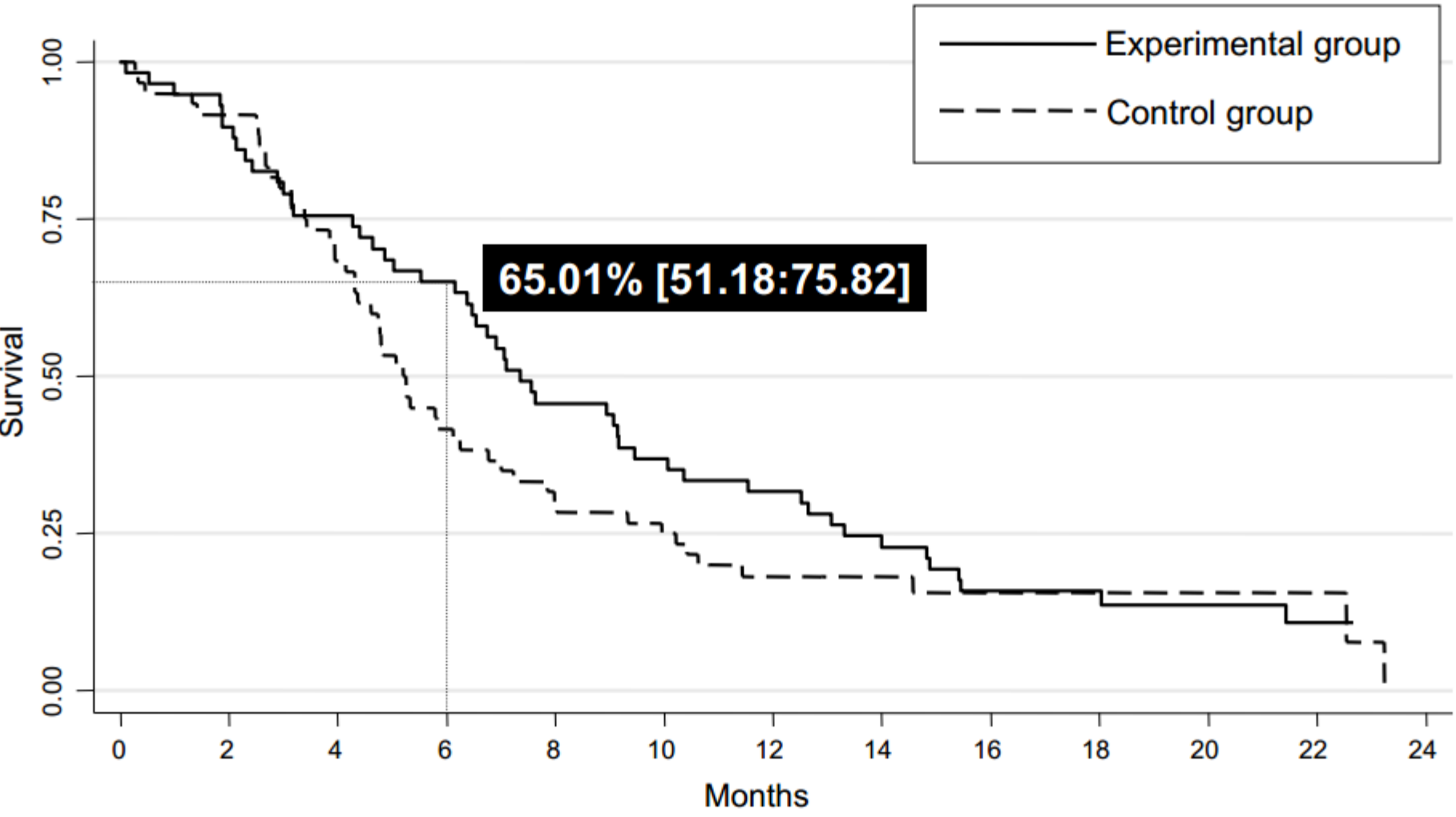
Control
Experimental

	Experimental group: B/I (60pts)	Control group *(60 pts)*
Overall toxicities	46.3	37.7
Hematological	12.3	14.8
Neutropenia	8.8	9.3
Febrile neutropenia	1.8	0.0
Anemia	0.0	0.0
Thrombocytopenia	3.5	14.8
Lymphopenia	12.3	13.0
Non Hematological	40	27.8
Other infections	8.8	3.7
Stomatitis	3.6	1.9
Nausea/vomiting	1.8	0.0
Diarrhea	7.1	0.0
Cutaneous	0.0	0.0
Renal	0.0	0.0
Neurotoxicity	0.0	1.9

Data presented above were censored the 31th of august 2012, two years follow-up is still ongoing.

Progression Free-Survival (PFS)

Kaplan Meier analysis was performed as secondary objective with an expected PFS at 6 months expected to be **≥ 66%.**



Comments

- Thanks ANOCEF!

You don´t avoid difficult questions

- „negative“ trial does just not meet the goals designed by youself (before)
  - impact of delaying RT in the experimental group
  - impact of cross over
- acceptable toxicity – interesting QoL data: how is systemic toxicity, e.g. hypertension, diarrhea, skin rasch perceived and managed by glioma patients and their relatives
  - How many patients stopped early in the experimental arm?
- Impressive TTP and OS data in a difficult patient population
  - Mc Namara: OS in patients with GBM and biopsy 4.5 mo, max: 6.3mo
- How would you design this trial today?

ASSOCIATION OF A STRONG CANDIDATE BIOMARKER PLASMA LEVEL WITH RESPONSE AND SURVIVAL IN PATIENTS TREATED WITH BEVACIZUMAB FOR RECURRENT HIGH GRADE GLIOMA

Emeline Tabouret[1]

F. Boudouresque[2], M. Barrié[1], M. Matta[1], C. Boucard[1], A. Loundou[3], M. Ouafik[2], O. Chinot[1]

1. Neurooncology, AP-HM Timone,
2. Umr 911, 3. Santé Publique, AMU,
Marseille
FRANCE

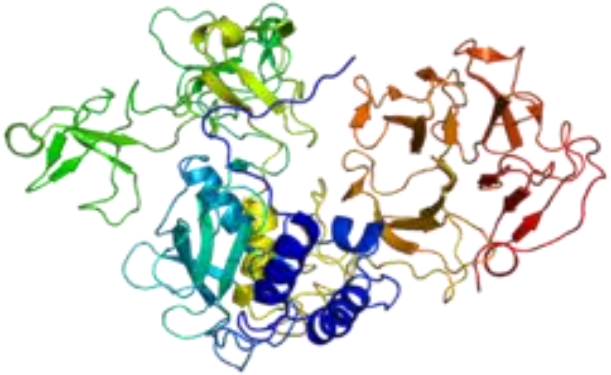
Circulating markers of angiogenesis, inflammation and coagulation in patients with glioblastoma

Reynes et al. J NeuroOncol 2011;102:35-41

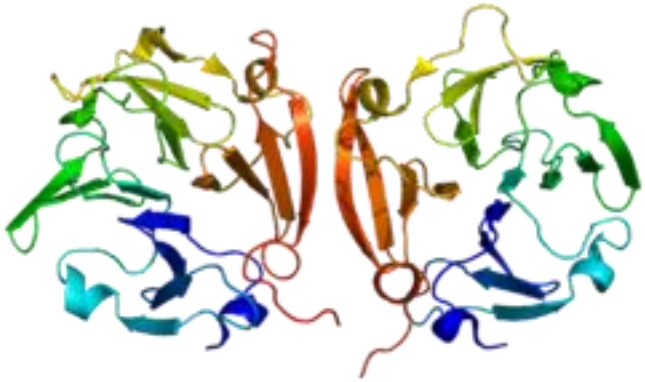
n	Patients 40	Controls 60	comment	p
COAGULATION				
Prothrombin factors 1&2 (nmol/l)	0.42 ± 0.5	0.2 ± 0.05	x2	<0.001
Tissue factor (pg/ml)	154 ± 93	153 ± 59	=	NS
Endogenous thrombin generation (UI/ml)	10.9 ± 3.4	8.7 ± 2.4	+25%	<0.01
INFLAMMATION				
IL-6 (pg/ml)	3.5 ± 7.1	0.7 ± 0.4	x7	<0.01
TNFalpha (pg/ml)	1.1 ± 0.9	0.6 ± 0.2	x2	<0.001
Fibrinogen (mg/dl)	300 ± 156	232 ± 31	+25%	<0.01
Sialic acid (mg/dl)	71 ± 22	55 ± 10	+40%	<0.001
CRP (mg/l)	17 ± 26.6	1.8 ± 2.7	x10	<0.001
ANGIOGENESIS				
VEGF (pg/ml)	268 ± 186	123 ± 64	x2	<0.001
sVEGF-R1 (pg/ml)	89 ± 29	77 ± 17	+15%	<0.05
Thrombospondin-1 (ug/ml)	47 ± 14	46 ± 10	=	NS

matrix metalloproteinases

- conserved in evolution from hydra to man
- depend on metal ions (zinc) for catalytic activity
- degrade structural proteins of the extracellular matrix & cell surface proteins, thus involved in signalling & motility



MMP-2: gelatinase A
expression significantly elevated
in glioma cells WHO II-IV
involved in glial invasion & angiogenesis



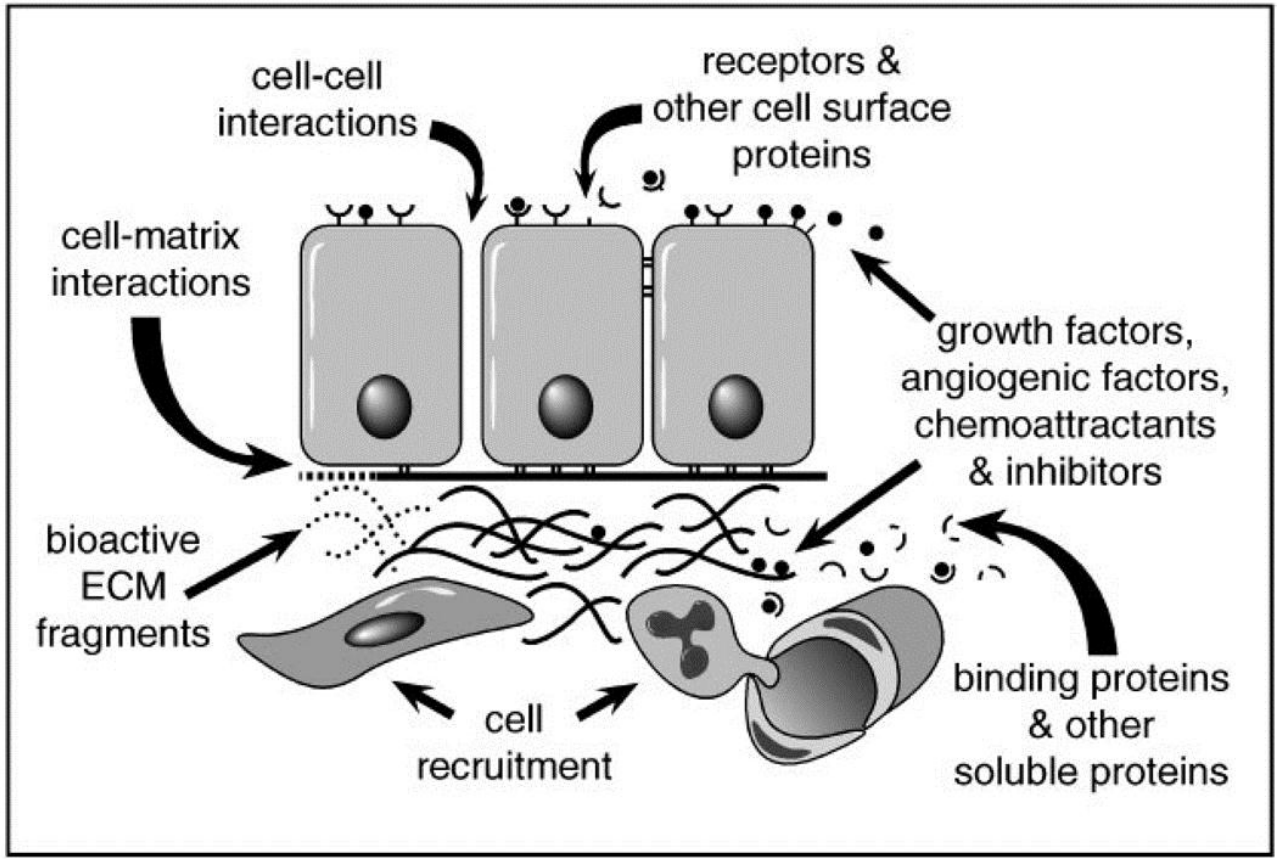
MMP-9: gelatinase B
expressed in blood vessels
at proliferating margins of glioma
Involved in neoangiogenesis

Forsyth et al, Brit. J Cancer 1999:79:1828-35

matrix metalloproteinases and glioma

- 640 hits in PUB Med
- involved in cell motility, invasiveness and angiogenesis – potential targets or markers?

- Zhao J, Li G, Zhao Z, Wang J, Gao G, He S. Matrix Metalloproteinase-9 Expression is Increased in Astrocytic Glioma and Associated with Prognosis of Patients.Jpn J Clin Oncol. 2012 Sep 12.



World Journal of Clinical Oncology

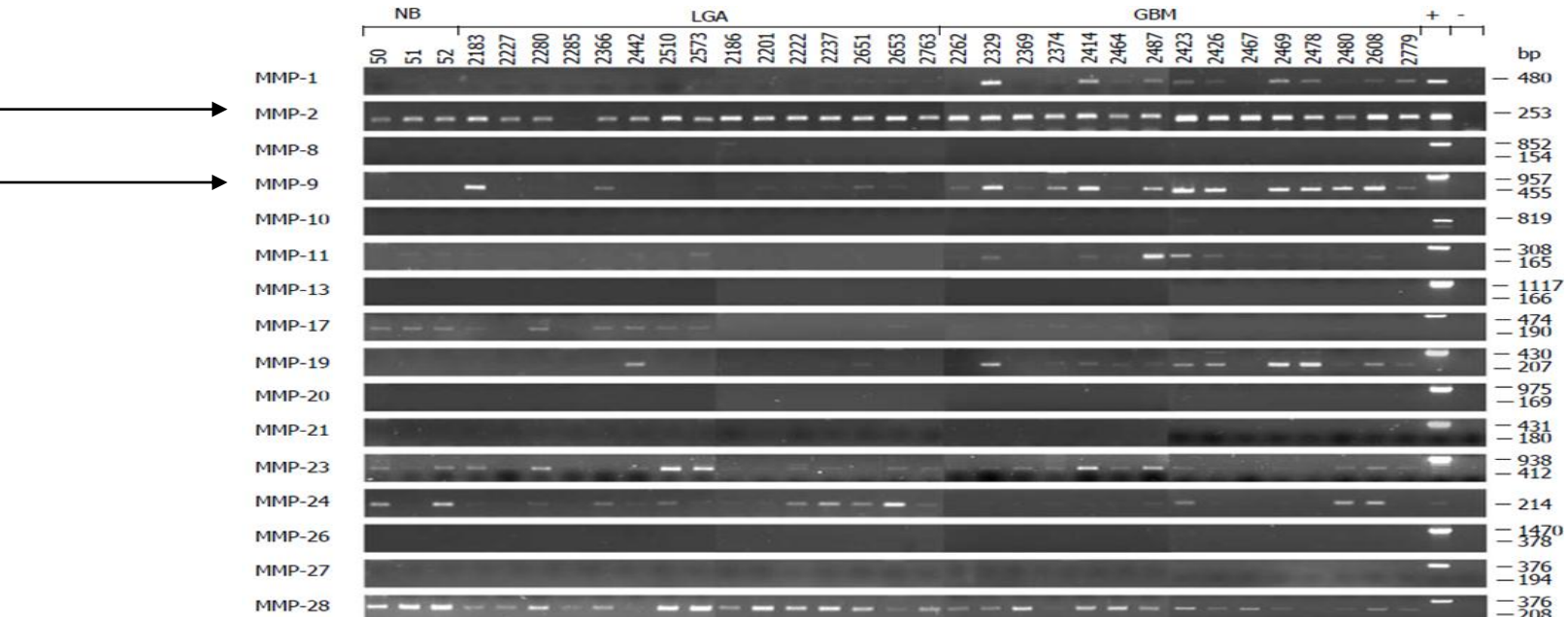
Online Submissions: http://www.wjgnet.com/2218-4333office
wjco@wjgnet.com
doi:10.5306/wjco.v3.i5.67

World J Clin Oncol 2012 May 10; 3(5): 67-79
ISSN 2218-4333 (online)

REVIEW

A complete compilation of matrix metalloproteinase expression in human malignant gliomas

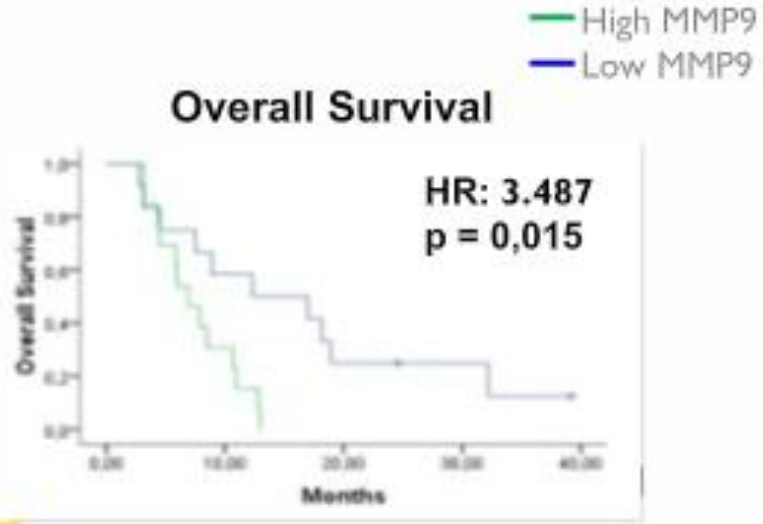
Carsten Hagemann, Jelena Anacker, Ralf-Ingo Ernestus, Giles H Vince



Results (cohort 1): **MMP 9** baseline level

Median:
234.8 ng/ml
N=26

	Low MMP9 N= 13	High MMP9 N=12	
Responders	8	4	
Non-Responders	3	9	
Response rate	61.5%	33.3%	p=0.041
PFS (months)	8.2	3.7	
95% CI	1.4-15.0	2.9-4.6	
OS (months)	12.3	6.9	
95% CI	0-26.1	4.6-9.3	



OK
cohort 2 showed no effect - so
no other cohorts, no hypothesis on MMP-9?

Aix Marseille université

+ Cohort 3

Results (cohort 1): **MMP 2** baseline level

Median:
227,2 ng/ml
N=26

ROC
AUC 0,827 (0,624-0,947)
p = 0,0017

Cut-off (227,2)
Se = 83,3 (51,6-97,9)
Sp=92,31 (64-99,8)

High MMP2
Low MMP2

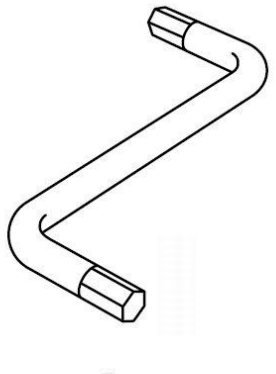
Cohort 3: without Bevacizumab

	Low MMP2 N= 13	High MMP2 N=12		Low MMP2 N= 17	High MMP2 N=3	
Responders	2	10		4	1	
Non-Responders	11	2		13	2	
Response rate	15.4%	83.3%	p=0.001	24%	3%	p=0.601
PFS (months)	3.0	5.9		3.1	7.7	
95% CI	2.5-3.5	4.0-7.8		1.0-5.1	4.0-11.4	
OS (months)	7.3	12.8		5.8	8.9	
95% CI	5.2-9.4	10.4-15.2		3.0-8.5	3.2-14.6	

MMP-2: elevated plasma levels

- acute cornary infarction
- acute coronary syndrome
- aortic dilatation
- emphysema, COPD
- infectious meningitis
- breast cancer, lung cancer
- bladder cancer
- viral liver disease
- acute pulpitis
- psoriasis
- venous ulcers
- macula degeneration
- arthritis, rheumatic diseases
- direct inguinal hernia…….
- any inflammatory reaction….

a single blood level – in 15 patients! - is not suitable to define „high level of MMP-2“ as a predictive marker given the lack of specificity….
But this remains an interesting finding & kinetics could be informative….



Thank you for your attention

any questions?