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Outcome, quality of life and cognitive function of patients with brain metastases from non-small cell lung cancer treated with whole brain radiotherapy combined with gefitinib or temozolomide. A randomised phase II trial of the Swiss Group for Clinical Cancer Research (SAKK 70/03)

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ABSTRACT

Purpose: Patients with brain metastases (BM) rarely survive longer than 6 months and are commonly excluded from clinical trials. We explored two combined modality regimens with novel agents with single agent activity and radiosensitizing properties.
Patients and methods: In this randomised phase II trial patients with BM from NSCLC were randomly assigned to 30 Gy WBRT with either concomitant gefitinib (GFT) 250 mg/day continuously or temozolomide (TMZ) 75 mg/m^2 for 21/28 days. The primary end-point was overall survival, with quality of life and cognitive function as secondary end-points.
Results: We enrolled 59 patients (GFT 16, TMZ 43), and 56 patients have died, mainly (80%) from disease progression. Four patients succumbed complications of the disease or corticosteroids (intestinal perforation (2), CNS haemorrhage and pulmonary emboli). Median overall survival in the gefitinib arm was 6.3 months (95% CI 2.1–14.6), and 4.9 months (95% CI 2.3–5.6) in TMZ treated patients. Fatigue was the main complaint.

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Conclusions: No relevant toxicity with those therapeutic regimens was observed. Fatal outcome in three patients may have been related to corticosteroids. Cognitive function improved during treatment. However, median overall survival for all patients was only 4.9 months (95% CI 2.3–5.7) and 1-year survival 25.4% (95% CI 15.4–37.0%).

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1. Introduction

Non-small cell lung cancer (NSCLC) is the most frequent cause of cancer death in Europe [http://www-dep.iarc.fr/]. Distant metastases are present in 30–40% of patients at initial diagnosis, and up to half of the patients will develop brain metastases (BM) with a poor overall survival of only 3–6 months, and profoundly disabling symptoms.[1–3] Whole brain radiotherapy (WBRT) is the treatment of choice for the majority of patients.[4–6] Radiosensitisers added to WBRT have been evaluated in randomised trials without impact on survival.[5,6]

Both temozolomide (TMZ) and gefitinib (GFT) are potentially useful agents in combination with radiation. TMZ, an alkylating agent with favourable distribution through the blood brain barrier has shown efficacy in combination with radiotherapy in the treatment of glioblastoma.[7] Preliminary reports suggest activity of TMZ in metastatic NSCLC,[8] and the combination with radiotherapy was tested in patients with BM.[9,10,17–20] GFT, a tyrosine kinase inhibitor against the epidermal growth factor receptor (EGFR) has demonstrated activity in *EGFR*-mutated NSCLC. Synergy of EGFR-inhibition and radiotherapy has also been shown[11,12] and responses of BM in various solid adult tumours including NSCLC have been reported.[13]

Most clinical trials on BM focused on selected subgroups of patients with limited disease extension, or on the contrary included very heterogeneous groups of patients of various primary tumours. Little prospective clinical data are available on the management and outcome of treatment of unselected patients with BM. Our trial aimed at evaluating the addition of a chemotherapeutic or targeted agent with single agent activity to standard hypofractionated radiotherapy; and to evaluate the benefits and limitations of standard WBRT in the management of BM from NSCLC.

2. Patients and methods

2.1. Trial design and end-points

In this multicentre, randomised, open-label, 2-stage phase II trial patients were randomly assigned to receive WBRT (10×3 Gy) in combination with either GFT (250 mg p.o. daily continuously) or TMZ 75 mg/m^2 p.o. daily $\times$ 21/28 days, starting on day 1 of RT and to be continued until disease progression or intolerance. Primary end-point was overall survival (OS). Secondary end-points were time to progression (TTP), or neurological progression, or extracranial disease progression, and quality of life including cognitive function as well as safety and tolerability.

The trial, developed within the framework of the Swiss Group of Clinical Cancer Research (SAKK), was registered with clinicaltrials.gov (#NCT00238251).

2.2. Eligibility

Adult patients with multiple BM from NSCLC were eligible. Patients had to be on a stable or decreasing dose of corticosteroids for at least 4 days. Staging with MRI/CT of the brain, chest and upper abdomen was required within 6 weeks. Other inclusion requirements were a WHO performance status 0–2, adequate haematological (haemoglobin $\geqslant$100 g/l, neutrophils $\geqslant 1.5 \times 10^9$/l, thrombocytes $\geqslant 100 \times 10^9$/l), hepatic (bilirubin $\leqslant 1.5 \times$ ULN, ASAT, ALAT, and alkaline phosphatase $\leqslant 2.5 \times$ ULN) and renal (calculated creatinine clearance $\geqslant$40 ml/min) function. No prior irradiation to the brain was allowed, prior chemotherapy was allowed except GFT or TMZ. Patients receiving hepatic enzyme inducing drugs (e.g. antiepileptics) were not eligible. All patients gave written informed consent, and the trial was approved by the ethics committees of the participating institutions and the Swissmedic.

2.3. Treatment

2.3.1. Radiotherapy

WBRT consisted in standard cranial irradiation (6–10 MV photons) of 10×3 Gy, without cone down or boost. Central axis dose calculations were considered sufficient for dosimetry. The reference dose was the isodose ICRU point (ICRU-62). Minimum and maximum doses had to be defined according to ICRU-62 recommendations.

2.3.2. Gefitinib

Patients randomised to GFT (Iressa®, Astra Zeneca, Macclefield, UK) received 250 mg p.o. daily from day 1 of radiotherapy without interruption until disease progression.

2.3.3. Temozolomide

TMZ (Temodal®, Temodar®, Schering-Plough, Kenilworth, NJ) was prescribed at a daily dose of 75 mg/m^2 p.o. daily for 21 days continuously every 28 days (1 cycle), beginning on day 1 of radiotherapy.

During radiotherapy, GFT or TMZ was to be taken at least 1 h before radiotherapy. GFT or TMZ administration was intended to be continued until disease progression or intolerance and toxicity.

2.3.4. QoL and cognitive function

QoL and cognitive function were assessed prior to treatment start, and on day 1 of cycles 2, 3, and 5. Only QoL forms completed at the scheduled visits were analysed. The European Organisation for Research and Treatment of Cancer (EORTC) quality of life core questionnaire (QLQ-C30 – Aaronson et al., 1993) was complemented with two global indicators for overall treatment burden[14] and coping/perceived adjust-

ment.[15] Higher scores on the functional/global QoL scales but lower scores on the symptom scales represent a better condition. For each time point and QoL score, the median value of the difference from baseline was calculated. A change of $\geqslant 8$ points was considered as clinically meaningful.[16] Due to decreasing number of patients over time the analysis remains descriptive with the two arms pooled.

Cognitive function was measured by the Mini Mental State Examination (MMSE – Folstein, 1975), and the Trailmaking Test, Part B (Trails B – Reitan, 1958), which is more sensitive to mild cognitive impairment. MMSE scores of 23 or lower (range 0–30) were considered as "impaired". Subjective cognitive functioning (SCF, range 0–100) was measured by the EORTC QLQ-C30 cognitive function subscale. Scores were dichotomised according to 'no impairment' (SCF score = 100) and 'impairment' (SCF score <100).

2.3.5. *Statistical considerations and randomisation*

For two parallel treatment arms, Simon's optimal two-stage design was applied with a 3-months survival rate of 55% considered insufficient and a rate of 75% considered promising. With a power of 80% and a significance level of 5% a total of 43 patients had to be accrued per treatment arm. An interim analysis for futility and toxicity was performed after treatment of the first 15 patients per arm.

Randomisation was performed using the minimisation method. Patients were stratified according to the number of BM (1–3 versus multiple ($\geqslant 4$)), prior chemotherapy, WHO performance status (0–1 versus 2) and institution.

Survival was calculated from the date of randomisation according to the Kaplan–Meier method. The two subjective cognitive functioning groups were compared using the log-rank test. Exploratory analyses aimed at identifying associations between various predictors and OS used univariate Cox regression models.

Symptoms and toxicities were assessed according to the NCI Common Terminology Criteria for Adverse Events v3.0 (CTCAE).

All p-values are two-sided and not adjusted for multiple testing. Analyses have been performed using SAS 9.2 (SAS Institute Inc.) and R 2.12.0 (www.r-project.org).

3. Results

3.1. *Patient characteristics*

From April 2005 until April 2009 a total of 59 patients were included; 43 patients were treated with TMZ/WBRT, and 16 with GFT/WBRT.

Median age was 61 years (range 46–82) and performance status was 0 or 1 in 83% of patients. All but 1 patient had extracranial disease, only 9 patients had previously received chemotherapy (Table 1).

3.2. *Treatment delivery and toxicity*

All patients received radiotherapy as prescribed. The median duration of chemotherapy was 1.6 (range 0.3–7.6) months in the TMZ arm, and 1.8 (range 0.3–10.5) months in the GFT arm.

Treatment-emergent toxicities are summarised in Table 2, treatment was well tolerated and severe toxicity rare.

Treatment was discontinued due to disease progression in 43 patients (73%). Other reasons included toxicity: 6 patients (GFT 3 {asthenia, mucositis, diarrhoea}, TMZ 3 {asthenia, anorexia and nausea}; deterioration in performance status: three patients (all TMZ arm); patients' wish in the absence of toxicity: three patients (GFT 1, TMZ 2). Four patients died while receiving therapy (intestinal perforation 2 {GFT 1, TMZ 1}, pulmonary embolism {TMZ}, haemorrhage {TMZ}). Delays in the administration of chemotherapy were recorded in 8 patients.

One patient in the TMZ arm received second-line chemotherapy in the absence of disease progression. Overall, 26 patients (GFT 7, TMZ 19) received a subsequent line of chemotherapy.

3.3. *Survival analyses*

At a median follow-up of 34 months, 56/59 patients have died. At the planned interim analysis after the first 15 patients per arm treated, only 9 patients in the GFT arm and 10 in the TMZ arm were alive at 3 months. With a preset boundary for futility of $\geqslant 10$ patients, the GFT arm was closed early (see CONSORT statement, (Fig. 1). In the TMZ arm additional 28 patients were accrued in stage II. Among all 43 patients in the TMZ arm, 25 (58.1%, exact 95% CI 42.1–73.0%) survived at least 3 months. At least 29 successes were required by the design to judge the treatment as promising. The median and 1-year survival is 6.3 months (95% CI 2.1–14.6) and 37.5% (95% CI 15.4–59.8%), for the GFT arm, and 4.9 months (95% CI 2.3–5.6 months) and 20.9% (95% CI 10.4–34.0%) for the TMZ arm, respectively (Fig. 2). For other end-points see Table 3 and Supplementary Figs. 1 and 2.

3.4. *Cause of death*

Disease progression was the cause of death in 45/56 (80%) patients, with systemic disease progression as primary site of failure in 43%, progression within the CNS in 27%, and a combination of both in 8%, unspecified in 1 patient (2%) (Table 4). Three patients died of infectious complications, and 2 patients of bowel perforation, all complications associated with high-dose corticosteroids.

3.5. *QoL and cognitive function*

Baseline QoL and the MMSE were available from all patients, the Trails B from 38 patients (64%, missing in 1 patient and invalid [incorrect test performance] in 20). Submission remained high (over 90%) during therapy, with a major proportion of patients off-study due to tumour progression beyond cycle 2. Baseline scores of the QL indicators are presented in Supplementary Table S1 (online only). Mean scores were substantially impaired for role, emotional, social functioning, and for global health status/QoL. Mean symptom burden at baseline was rather low except for fatigue. Regarding cognitive function 92% ($n = 54$) had a normal MMSE score, 74% ($n = 28$) had a normal Trails B score. Of the 38 patients with both tests completed, 27 had normal scores in both tests,

Table 1 – Patient and treatment characteristics.

	TMZ ($n = 43$)		GFT ($n = 16$)	
	No. pts	%	No pts.	%
Age, years				
Median (range)	63 (45–79)		57 (46–82)	
Gender (female/male)	16/27	37/63	7/9	44/56
Smoking status in pack years				
Median (range)	45 (10–120)		45 (5–70)	
WHO performance status				
0	10	23	8	50
1	25	58	6	38
2	8	19	2	12
No. of brain metastases				
1	4	9	3	19
2	6	14	4	25
3	8	19	1	6
$\geqslant 4$	25	58	8	50
Brain metastases' locations				
Supratentorial	39	91	12	75
Infratentorial	14	33	11	69
No. of extracranial metastases				
0	0	0	1	6
1	12	28	4	25
$\geqslant 2$	31	72	11	69
Administration of steroids	40	93	15	94
Histological type				
Adenocarcinoma	33	77	15	94
Squamous cell carcinoma	2	5	1	6
Large cell carcinoma	1	2	0	0
Undifferentiated carcinoma	4	9	0	0
Other	3	7	0	0
Cognitive function, Trails B score				
Median	182		182.5	
Range	45–453		75–630	

Table 2 – Toxicity and treatment related adverse events.

	TMZ ($n = 43$) No. of patients				GFT ($n = 16$) No. of patients			
Adverse event	Grade 2	Grade 3	Grade 4	% All grades	Grade 2	Grade 3	Grade 4	% All grades
Haemoglobin*	–	0	0	0	–	0	0	0
Lymphopaenia*	–	4	0	9	–	0	0	0
Low CD4*	–	1	0	2	–	0	0	0
Platelets*	–	0	0	0	–	0	0	0
Hyperglycaemia*	–	0	0	0	–	0	0	0
Transaminases*	–	4	0	9	–	0	0	0
Nausea/vomiting	6	0	0	14	0	0	0	0
Diarrhoea	0	0	0	0	0	1	0	6
Skin rash	1	0	0	2	2	0	0	13
Fatigue	12	7	1	47	2	2	1	31
Mucositis	0	0	0	0	0	1	0	6
Dysponea	0	0	0	0	1	1	0	13

* Grade 2 toxicities for laboratory values were not recorded.

2 were deficient in both tests, 8 were deficient in Trails B only, 1 in the MMSE only. During the first month of treatment, emotional functioning improved (median change: 8.3), while fatigue worsened (median change: 11.1); physical functioning tended to worsen (median change: −6.7). After 2 months, emotional functioning remained higher (median change:

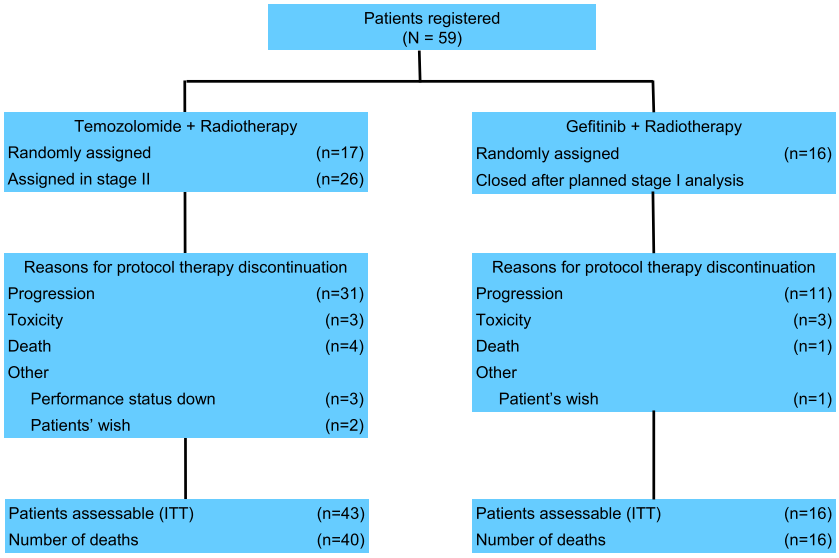

Fig. 1 – CONSORT chart.

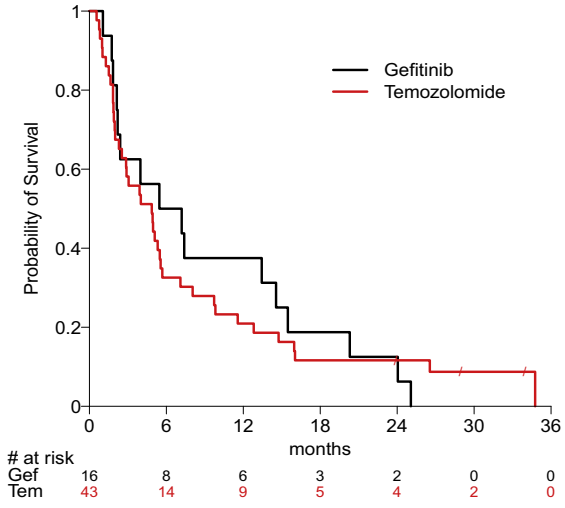

Fig. 2 – Overall survival by treatment arm; Gef = Gefitinib, Tem = Temozolomide.

8.3) while fatigue (median change 11.1) remained lower than at baseline; a similar tendency was seen for physical functioning (median change: −6.7). For all other QoL indicators no relevant changes were observed during this period. The proportion of patients with normal cognitive function remained stable while on treatment with a tendency to improved scores in both MMSE and the Trails B test.

Univariate Cox regression models revealed that subjective cognitive functioning was only associated with overall survival (log-rank p-value 0.008). For age, performance status, the number of BM, and several QoL measures not significant association could be found. Median overall survival was 10.1 months (95% CI 2.3–16.0) for patients with SCF not impaired, and 3.1 months (95% CI 2.1–5.0) for patients with impaired SCF (Fig. 3). The risk of a shorter survival time for patients with impaired SCF was twice as high as for those with SCF not impaired (HR = 2.1 [95% CI 1.2–3.7], $p = 0.009$). Other factors such as age, performance status, more than 4 BM, MMSE score or global health status/QoL have no significant impact on survival.

4. Discussion

Combination of WBRT with TMZ or GFT was well tolerated with no unexpected or added substantial toxicity, but with no indication of a beneficial effect neither. Overall outcome remains particularly poor. Despite the fact that the majority of patients were previously untreated and with a relatively good performance status at enrollment, median survival was only 4.9 (95% CI: 2.5–5.7) months. At the time of the conception of our trial, the association between *EGFR* mutations and response to GFT was not known, and may in part explain the early closure of the GFT arm.

Our results are in line with other reports. A randomised study from Hong Kong reported on 95 patients randomised to WBRT ± concomitant TMZ, median survival was 4.4 and 5.7 months (95% CI not reported, p = NS), respectively.[17] Similarly, a Spanish report on 82 patients with BM (42 from NSCLC) failed to demonstrate an advantage by the addition of TMZ to WBRT.[18] Solely Antonadou reported in 2002 (abstract only) on a small ($n = 134$, 25% solitary BM) randomised phase III trial adding TMZ to WBRT and found a significantly increased median survival of 8.6 months in the TMZ/RT arm compared to 7 months with RT alone.[10] Activity for GFT in central nervous system (CNS) disease was reported on 41 NSCLC patients unselected for EGFR mutations.[13] Response rate was 10%, disease control rate 27%, with a median survival of 5 months (CI not reported). Twenty-one Chinese patients received WBRT (20×2 Gy) with concomitant GFT, followed by GFT alone. Overall survival was 13 months (95% CI 8.2–17.8)[19].

In our study, the primary site of failure was systemic tumour progression, isolated CNS failure was reported in 27% patients. This indicates that improved treatments are required for both local and systemic control. Importantly, 8% of patients succumbed to complications (intestinal perfo-

Table 3 – Survival analyses.

	GFT (n = 16)	TMZ (n = 43)	All (n = 59)
Median overall survival	6.3 mo (95% CI 2.1–14.6 mo)	4.9 mo (95% CI 2.3–5.6 mo)	4.9 mo (95% CI 2.5–5.7 mo)
Median time to progression	1.8 mo (95% CI 1.1–3.9 mo)	1.8 mo (95% CI 1.5–1.8 mo)	1.8 mo (95% CI 1.5–1.8 mo)
1-year survival rate	37.5% (95% CI 15.4–59.8%)	20.9% (95% CI 10.4–34.0%)	25.4% (95% CI 15.2–37.0%)
Median time to neurological progression	4.8 mo (95% CI 3.9–10.5 mo)	8.0 mo (95% CI 2.2–n.a. mo)	5.1 mo (95% CI 3.6–12.6 mo)
Median time to extracranial disease progression	2.0 mo (95% CI 1.1–6.1 mo)	1.8 mo (95% 1.7–1.9 mo)	1.8 mo (95% 1.7–1.9 mo)

Table 4 – Causes of death.

	TMZ (n = 40/43)		GFT (n = 16/16)		All 56/59	
Cause	No. pts	%	No. pts	%	No pts	%
Progressive disease						
CNS	8	20	7	44	15	27
Systemic	19	48	5	31	24	43
CNS + systemic	3	8	2	13	5	8
unspecified	1	2	0	0	1	2
Toxicity[a]						
Bowel perforation	1	2	1	6	2	3
Infection (pneumonia, sepsis)[b]	3	8	0	0	3	5
Other						
Epileptic seizure	0	0	1	6	1	2
Pulmonary haemorrhage	1	2	0	0	1	2
Pulmonary embolism	2	5	0	0	2	3
Unknown	2	5	0	0	2	3

[a] Steroid related, *not* related to study drugs.
[b] In the absence of neutropenia.

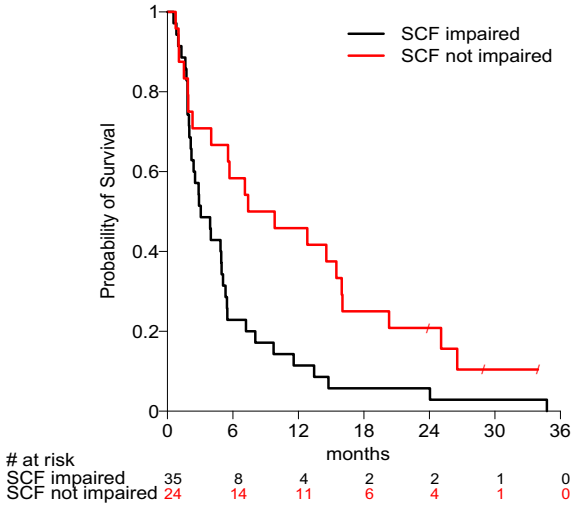

Fig. 3 – Overall survival and cognitive function; SCF = subjective cognitive functioning.

rations and infections) likely related to supportive steroid use. This underscores the importance of careful patient management and restrictive use of corticosteroids.

A prognostic scoring system, known as recursive partitioning analysis (RPA) based on age, performance status, and presence of extracranial disease has been established previously.[3] Our patients corresponded to RPA class II, with no single clinical prognostic factor predictive for outcome. Interestingly, the patients' perception of their subjective cognitive function was predictive for survival; this may indicate that the subjective estimation of cognitive function is a sensitive indicator of the underlying disease status.

Quality of life and preservation of cognitive function is one of the main objectives treating patients with BM. Our patients reported substantially impaired QoL scores for role, emotional and social functioning, fatigue and global health status/QoL at baseline and no substantial changes in QoL during the first two months of treatment. While emotional functioning improved, fatigue worsened over this period. Addeo et al. evaluated the effect on QoL of concomitant WBRT and TMZ[20] in patients with BM and reported QoL to be stable or significantly improved following treatment.

Cognitive function was impaired in only a minority at baseline, and both MMSE and Trails B scores tended to improve over the course of treatment. This suggests that cog-

nitive function was not negatively affected by the treatment at short-term.

5. Conclusions

The survival of patients treated with GFT or TMZ and concurrent WBRT was a disappointing and an unsatisfactory treatment for unselected patients with BM. The correlation of the patients' subjective perception of cognitive function with outcome warrants confirmation. With a median survival of only 4–5 months, the indication and patient selection for brain irradiation should be revisited. The study does not support the use of TMZ or GFT with concurrent radiotherapy in the treatment of BM in NSCLC. Particular attention should be given to supportive care measures, dosing and duration of corticosteroid therapy, and signs of infection. Prospective trials using new approaches in this common condition are urgently needed.

Conflict of interest

G.A.P. declares a consultant/advisory role and other remuneration with Essex/MSD, Switzerland and Roche, Switzerland.

R.M. declares a consultant/advisory role and honoraria with Amgen and Roche, and a consultant/advisory role with Novartis.

M.S., and R.C. and M.P. declare a consultant/advisory role with Essex Chemie and Astra Zeneca, respectively.

R.S. declares a consultant/advisory role and honoraria with Schering-Plough/MSD and Merck KGaA, Darmstadt, Germany, and a consultant/advisory role with OncoMethylome Sciences and Roche, Basel, Switzerland.

All the remaining authors have declared no conflict of interest.

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These additional investigators contributed to patient accrual: Dr. C. Uhlmann, Dr. L. von Rohr, Dr. P. Schmid, Dr. W. Mingrone and Prof. S. Bodis from the Aarau Kantonsspital; Dr. J. Lukaschek from the Baden Kantonsspital; Dr. C. Rothermund, Dr. P. Schmid, Dr. Seifert, Prof. A. Zippelius, and Prof. R. Herrmann from the Basel Universitätsspital; Dr. A. Lohri from the Liestal Kantonsspital; Dr. U Mey, Dr. M. Fehr, and Dr. R. Inauen from the Chur Kantonsspital; Dr. M. Früh from the St. Gallen Kantonsspital; Dr. Th. Lippuner from the Winterthur Kantonsspital; Dr. S. Mauri, from Oncology Institute of Southern Switzerland, all in Switzerland.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2011.10.016.

REFERENCES

1. Chang J. Thoracic tumors. In: Perez CA, Brady LW, editors. *Principles and practice of radiation oncology*. Lippincott and Williams; 2008. p. 1078–108.
2. Posner JB. *Neurologic complications of cancer*. Philadelphia: Davies FA editors; 1995.
3. Gaspar L, Scott C, Rotman M. Et al: Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys* 1997;**37**:745–51.
4. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 Study. *J Clin Oncol* 2010;**29**:134–41.
5. Videtic GM, Gaspar LE, Aref AM, et al. American College of Radiology appropriateness criteria on multiple brain metastases. *Int J Radiat Oncol Biol Phys* 2009;**75**:961–5.
6. Tsao MN, Lloyd N, Wong R, et al. Whole brain radiotherapy for the treatment of multiple brain metastases. *Cochrane Database Syst Rev* 2006;**3**:CD003869.
7. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;**352**:987–96.
8. Adonizio CS, Babb JS, Maiale C, et al. Temozolomide in non-small-cell lung cancer: preliminary results of a phase II trial in previously treated patients. *Clin Lung Cancer* 2002;**3**:254–8.
9. Antonadou D, Paraskevaidis M, Sarris G, et al. Phase II randomized trial of temozolomide and concurrent radiotherapy in patients with brain metastases. *J Clin Oncol* 2002;**20**:3644–50.
10. Antonadou D, Coliarakis N, Paraskevaidis M, et al. Whole brain radiotherapy alone or in combination with temozolomide for brain metastases. A phase III study. *Int J Radiat Oncol Biol Phys* 2002;**54**(Suppl.):93–4 [abstract].
11. Kelly K. Huang C: Biological agents in non-small cell lung cancer: a review of recent advances and clinical results with a focus on epidermal growth factor receptor and vascular endothelial growth factor. *J Thorac Oncol* 2008;**3**: 664–73.
12. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006;**354**:567–78.
13. Ceresoli GL, Cappuzzo F, Gregorc V, et al. Gefitinib in patients with brain metastases from non-small-cell lung cancer: a prospective trial. *Ann Oncol* 2004;**15**:1042–7.
14. Bernhard J, Maibach R, Thurlimann B, et al. Patients' estimation of overall treatment burden: why not ask the obvious? *J Clin Oncol* 2002;**20**:65–72.
15. Hurny C, Bernhard J, Bacchi M, et al. The Perceived Adjustment to Chronic Illness Scale (PACIS): a global indicator of coping for operable breast cancer patients in clinical trials. Swiss Group for Clinical Cancer Research (SAKK) and the International Breast Cancer Study Group (IBCSG). *Support Care Cancer* 1993;**1**:200–8.

16. Sloan JA. Assessing the minimally clinically significant difference: scientific considerations, challenges and solutions. *COPD* 2005;**2**:57–62.
17. Chua D, Krzakowski M, Chouaid C, et al. Whole-brain radiation therapy plus concomitant temozolomide for the treatment of brain metastases from non-small-cell lung cancer: a randomized, open-label phase II study. *Clin Lung Cancer* 2010;**11**:176–81.
18. Verger E, Gil M, Yaya R, et al. Temozolomide and concomitant whole brain radiotherapy in patients with brain metastases: a phase II randomized trial. *Int J Radiat Oncol Biol Phys* 2005;**61**:185–91.
19. Ma S, Xu Y, Deng Q, et al. Treatment of brain metastasis from non-small cell lung cancer with whole brain radiotherapy and Gefitinib in a Chinese population. *Lung cancer* 2009;**65**:198–203.
20. Addeo R, Caraglia M, Faiola V, et al. Concomitant treatment of brain metastasis with whole brain radiotherapy [WBRT] and temozolomide [TMZ] is active and improves quality of life. *BMC Cancer* 2007;**7**:18.