ENDPOINTS IN BRAIN METASTASIS TRIALS

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CONFLICT OF INTEREST

- I have received grants and honoraria for Lectures and Advisory Boards from MSD, Roche, Merck Serono, Celldex Therapeutics, Novartis and Mundipharma.

OUTLINE

- Review of endpoints used in trials on brain metastasis.

- New response criteria for brain metastasis trials proposed by the Response Assessment in Neuro-Oncology (RANO) Working Group.

Challenges relating to solid tumour brain metastases in clinical trials, part 1: patient population, response, and progression. A report from the RANO group

Nancy U Lin, Eudocia Q Lee, Hidefumi Aoyama, Igor J Barani, Brigitta G Baumert, Paul D Brown, D Ross Camidge, Susan M Chang, Janet Dancey, Laurie E Gaspar, Gordon J Harris, F Stephen Hodi, Steven N Kalkanis, Kathleen R Lamborn, Mark E Linskey, David R Macdonald, Kim Margolin, Minesh P Mehta, David Schiff, Riccardo Soffietti, John H Suh, Martin J van den Bent, Michael A Vogelbaum, Jeffrey S Wefel, Patrick Y Wen, for the Response Assessment in Neuro-Oncology (RANO) group

Therapeutic outcomes for patients with brain metastases need to improve. A critical review of trials specifically addressing brain metastases shows key issues that could prevent acceptance of results by regulatory agencies, including enrolment of heterogeneous groups of patients and varying definitions of clinical endpoints. Considerations specific to disease, modality, and treatment are not consistently addressed. Additionally, the schedule of CNS imaging and consequences of detection of new or progressive brain metastases in trials mainly exploring the extra-CNS activity of systemic drugs are highly variable. The Response Assessment in Neuro-Oncology (RANO) working group is an independent, international, collaborative effort to improve the design of trials in patients with brain tumours. In this two-part series, we review the state of clinical trials of brain metastases and suggest a consensus recommendation for the development of criteria for future clinical trials.

Lancet Oncol 2013; 14: e396–406

Challenges relating to solid tumour brain metastases in clinical trials, part 2: neurocognitive, neurological, and quality-of-life outcomes. A report from the RANO group

Nancy U Lin, Jeffrey S Wefel, Eudocia Q Lee, David Schiff, Martin J van den Bent, Riccardo Soffietti, John H Suh, Michael A Vogelbaum, Minesh P Mehta, Janet Dancey, Mark E Linskey, D Ross Camidge, Hidefumi Aoyama, Paul D Brown, Susan M Chang, Steven N Kalkanis, Igor J Barani, Brigitta G Baumert, Laurie E Gaspar, F Stephen Hodi, David R Macdonald, Patrick Y Wen, for the Response Assessment in Neuro-Oncology (RANO) group

Neurocognitive function, neurological symptoms, functional independence, and health-related quality of life are major concerns for patients with brain metastases. The inclusion of these endpoints in trials of brain metastases and the methods by which these measures are assessed vary substantially. If functional independence or health-related quality of life are planned as key study outcomes, then the reliability and validity of these endpoints can be crucial because methodological issues might affect the interpretation and acceptance of findings. The Response Assessment in Neuro-Oncology (RANO) working group is an independent, international, and collaborative effort to improve the design of clinical trials in patients with brain tumours. In this report, the second in a two-part series, we review clinical trials of brain metastases in relation to measures of clinical benefit and provide a framework for the design and conduct of future trials.

Lancet Oncol 2013; 14: e407–16

FACTORS INFLUENCING THE CHOICE OF ENDPOINTS IN CLINICAL TRIALS ON BRAIN METASTASES

- Patient population (differences in prognosis related to tumor type/ subtype, issues related to competing risks of extracranial progression)
- Trial setting (phase I vs phase II vs phase III)
- Type of intervention

ENDPOINTS

- Overall survival and functionally independent survival
- Response
- Progression-free survival
- Time to deterioration of performance status and time to neurological progression
- Neurological outcomes
- Neurocognitive outcomes
- Quality of Life

OVERALL SURVIVAL : PROS

- Almost universally chosen as primary endpoint in phase III brain metastasis trials
- Unambiguous endpoint
- Clinically meaningful (shared by both patients and providers)
- An alternative can be survival with functional independence

OVERALL SURVIVAL : CONS

- Frequent coexistence of extracranial disease which may exert a major effect on survival, regardless of intracranial disease control
  → improved intracranial control may not necessarily translate into improved overall survival.

- Influence of salvage treatments.

OBJECTIVE RESPONSE

- Commonly used as primary endpoint for phase II trials, including in patients with brain metastases

- To screen novel approaches ("activity") for eventual testing in a phase III setting

- A possible surrogate for other markers of clinical benefit, such as neurological symptoms, neurocognitive function, or survival: as an example, responders experienced a longer time to neurocognitive decline and improved survival after WBRT (*Li et al, 2007*) or a better improvement in neurological status after lapatinib for HER2+ breast cancer (*Lin et al, 2009*).

CRITERIA OF RESPONSE IN BRAIN METASTASIS TRIALS

- Not standardized the use of MRI thus far as the preferred modality for assessment response of brain metastases to treatments

- None of the Standard Response Criteria (Recist, WHO, MacDonald, RANO) were designed specifically to evaluate brain metastases, thus investigators have not consistently chosen one set over another, and in some instances have adopted existing criteria in differing ways.

↓

To date, consistent existing criteria have not been adopted across trials in brain metastasis patients.

MAJOR AREAS OF DIFFERENCE IN RESPONSE CRITERIA ACROSS TRIALS IN BRAIN METASTASIS PATIENTS

- Definition of a target lesion: not defined, ≥ 1 cm.
- Number of lesions : variable.
- Type of measurement: uni-dimensional, bi-dimensional, volumetric.
- Degree of tumor shrinkage required for response (≥ 30%, ≥ 50%).
- Requirement for confirmatory scans: more commonly non required.
- Use of steroids: more commonly not included.
- Neurological symptoms: more commonly not included.
- Extracranial disease: more commonly not included.

Response assessment criteria for brain metastases: proposal from the RANO group

Nancy U Lin, Eudocia Q Lee*, Hidefumi Aoyama, Igor J Barani, Daniel P Barboriak, Brigitta G Baumert, Martin Bendszus, Paul D Brown, D Ross Camidge, Susan M Chang, Janet Dancey, Elisabeth G E de Vries, Laurie E Gaspar, Gordon J Harris, F Stephen Hodi, Steven N Kalkanis, Mark E Linskey, David R Macdonald, Kim Margolin, Minesh P Mehta, David Schiff, Riccardo Soffietti, John H Suh, Martin J van den Bent, Michael A Vogelbaum, Patrick Y Wen, for the Response Assessment in Neuro-Oncology (RANO) group*

CNS metastases are the most common cause of malignant brain tumours in adults. Historically, patients with brain metastases have been excluded from most clinical trials, but their inclusion is now becoming more common. The medical literature is difficult to interpret because of substantial variation in the response and progression criteria used across clinical trials. The Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) working group is an international, multidisciplinary effort to develop standard response and progression criteria for use in clinical trials of treatment for brain metastases. Previous efforts have focused on aspects of trial design, such as patient population, variations in existing response and progression criteria, and challenges when incorporating neurological, neuro-cognitive, and quality-of-life endpoints into trials of patients with brain metastases. Here, we present our recommendations for standard response and progression criteria for the assessment of brain metastases in clinical trials. The proposed criteria will hopefully facilitate the development of novel approaches to this difficult problem by providing more uniformity in the assessment of CNS metastases across trials.

Lancet Oncology 2015; 16: e270–78

	Complete response	Partial response	Stable disease	Progressive disease
Target lesions	None	≥30% decrease in sum longest distance relative to baseline	<30% decrease relative to baseline but <20% increase in sum longest distance relative to nadir	≥20% increase in sum longest distance relative to nadir*
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal progressive disease*
New lesion(s)†	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	Not applicable‡
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse*
Requirement for response	All	All	All	Any‡

*Progression occurs when this criterion is met. †A new lesion is one that not present on prior scans and is visible in minimum two projections. If a new lesion is equivocal, for example because of its small size, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone to do not define progression. ‡Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

Table 2: **Summary of the response criteria for CNS metastases proposed by RANO-BM**

VOLUMETRIC CRITERIA FOR THE DEFINITION OF RESPONSE

- The existing data are not yet strong to justify the universal requirement of volumetric response criteria trials on brain metastases.

- However, the assessment and reporting of volumetric response in clinical trials (in addition to the unidimensional RANO Brain Metastasis criteria) is important and is encouraged its inclusion as a secondary end-point when feasible.

- The appropriate cutoff to define a partial response on the basis of volumetric measurements is still a matter of debate.

RANO Group Brain Metastasis, Lancet Oncology, 2015

VOLUMETRIC CRITERIA FOR THE DEFINITION OF RESPONSE

- When a tumor forms a perfect sphere, a 65% volumetric reduction corresponds to a 30% unidimensional reduction

Partial volumetric response should be defined as a 65% or greater decrease in the sum volume of CNS target lesions, in addition to the corticosteroid and clinical status criteria

- Volumetric changes of minimum 20% seem reproducible between readers and clinically meaningful

However, it is premature to formally define a category of a minor response

RANO Group Brain Metastasis, Lancet Oncology, 2015

CNS (RANO-BM)	Non-CNS (RECIST 1.1)	Response
Complete response, partial response, or stable disease	Complete response, partial response, or stable disease	Log as CNS and non-CNS complete response, partial response, or stable diseases
Complete response, partial response, or stable disease	Progressive disease	Log as CNS complete response, partial response, or stable disease; log as non-CNS progressive disease
Progressive disease	Complete response, partial response, or stable disease	Log as CNS progressive disease; log as non-CNS complete response, partial response, or stable disease
Progressive disease	Progressive disease	Log as both CNS and non-CNS progressive disease

Table 3: **CNS and non-CNS response assessment**

PROGRESSION- FREE SURVIVAL

- In trials of patients with metastatic solid tumors outside of the brain metastases setting, PFS is a commonly chosen as endpoint, with the definition of progression according to RECIST criteria

- In patients with brain metastases assessment of PFS (intracranial vs extracranial) is more challenging.

- The assessment of intracranial progression in case of lesions treated previously with radiosurgery is difficult $\longrightarrow$ problems of differential diagnosis between recurrence and radionecrosis

- The assessment of intracranial progression in patients on anti-VEGF therapies or immunotherapy is challenging

RECOMMENDATIONS FOR PROGRESSION- FREE SURVIVAL ANALYSIS IN FUTURE TRIALS ON BRAIN METASTSASES

- A uniform definition of progression must be developed, taking into account the neurological, neurocognitive status, and supportive care (steroids and antiepileptic drugs)
- A clear distinction between intracranial PFS, extracranial PFS and overall PFS should be done
- When considering CNS-directed therapies, collection of concurrent and subsequent systemic therapies is important
- The role of advanced imaging techniques (MRS, diffusion and perfusion MRI, PET with FDG and other tracers) for a better distinction of radiation necrosis from recurrence should be explored in specific studies.

RANO Group Lancet Oncology, 2015

CNS (RANO-BM)	Non-CNS (RECIST 1-1)	Bi-compartmental PFS	Note
Complete response, partial response, or stable disease	Progressive disease	Log as a progression-free survival event	Log as non-CNS progressive disease
Progressive disease	Complete response, partial response, or stable disease	Log as a progression-free survival event	Log as CNS progressive disease
Progressive disease	Progressive disease	Log as a progression-free survival event	Log as both CNS and non-CNS progressive disease

Table 4: **Bi-compartmental progression-free survival**

RANO Group Lancet Oncology, 2015

TIME TO DETERIORATION OF PERFORMANCE STATUS

- Time to deterioration of PS to WHO > 2 (as determined by locally responsible physician) has been used as primary endpoint in phase III EORTC 22952-26001 (*Kocher et al, 2011*).

Adjuvant Whole Brain Radiotherapy versus Observation after Radiosurgery or Surgical Resection of 1-3 Cerebral Metastases: Results of the EORTC 22952-26001 Study

M. Kocher[2], R. Soffietti[1], M.U. Abacioglu[3], S. Villa[4], F. Fauchon[5], B.G. Baumert[6], L. Fariselli[7], T. Tzuk-Shina[8], L. Collette[9], R.P. Mueller[2]

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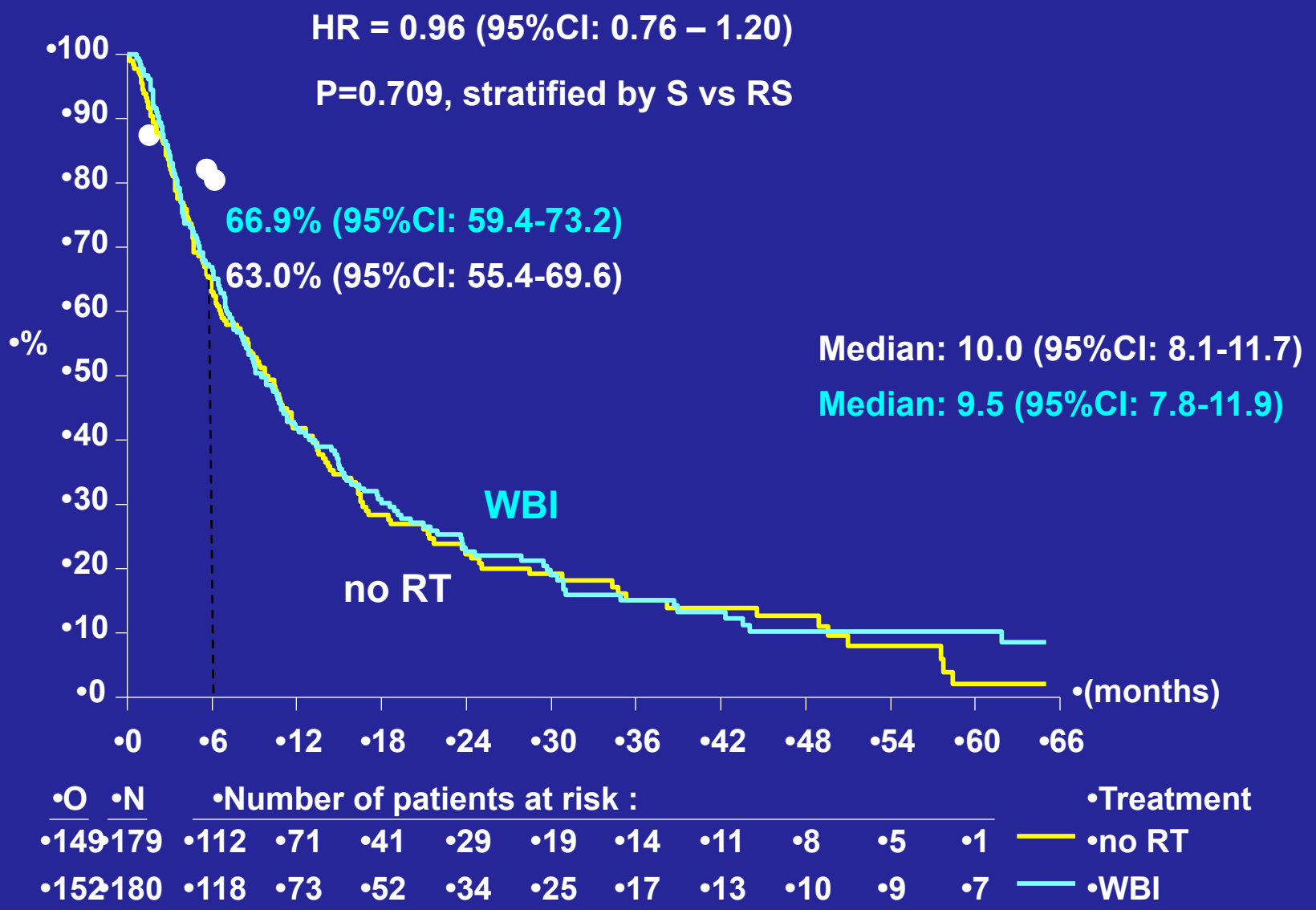
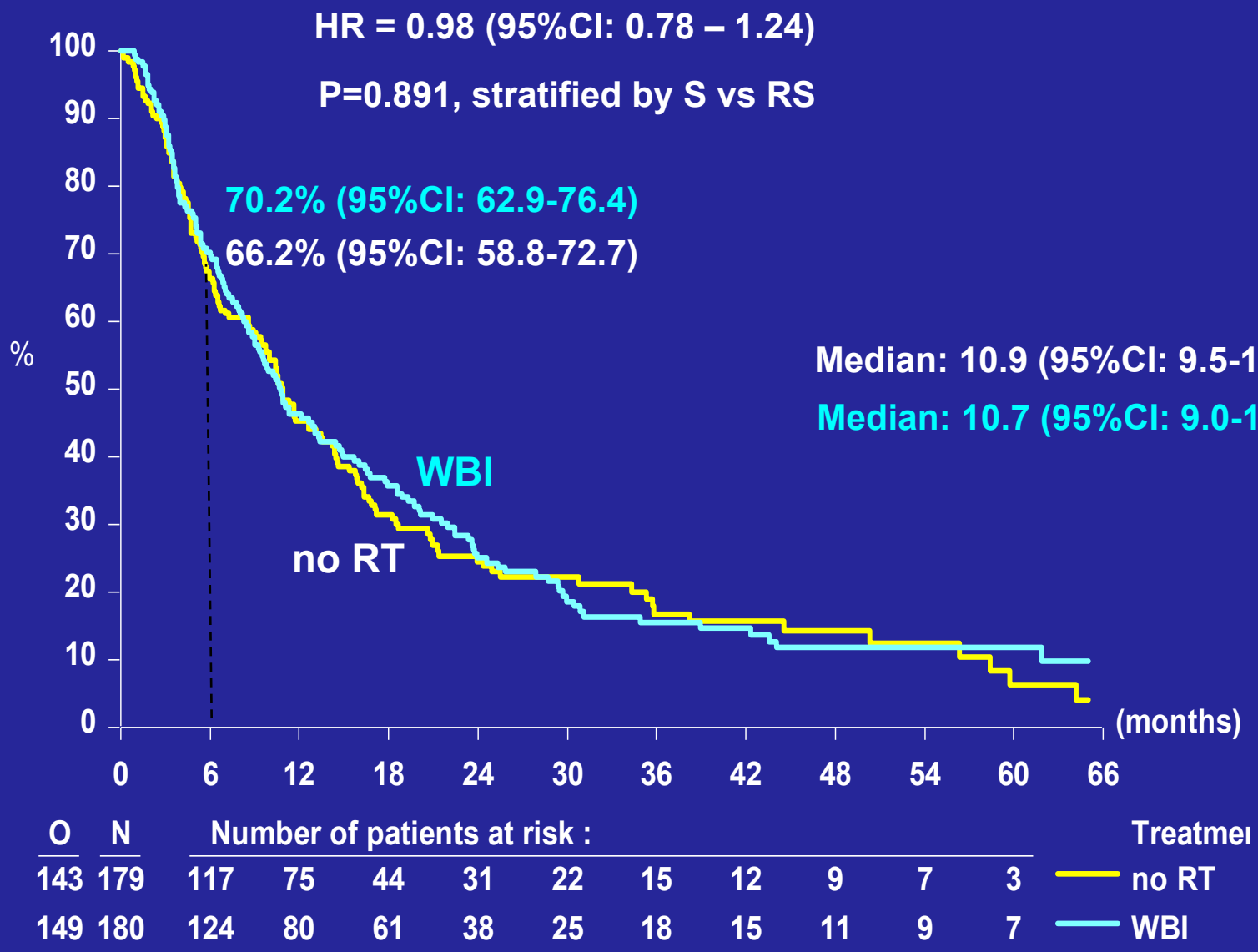
J Clin Oncol 29/2, 134-141, 2011

Primary endpoint:
Survival with PS ≤ 2 (ITT)



Overall Survival (ITT)



TIME TO NEUROLOGIC PROGRESSION

- Time to neurologic progression (as determined by a blinded events review Committee) has been used as co-primary endpoint in motexafin gadolinium trials (*Mehta et al, 2003*)

NEUROLOGICAL OUTCOMES

- The symptom burden elicited and reported in case report forms may vary tremendously according to the method of collection and type of physician ⟶ need for a standardization of the minimum components of a neurological examination when neurological symptoms are to be counted towards a primary endpoint.

- An alternative approach is to rely more heavily on patient reported outcomes (PRO), such as the MD Anderson Symptom Inventory Brain Tumor Module, etc

NEUROCOGNITIVE OUTCOMES

- Neurocognitive outcomes may serve as primary end-point when the treatment itself (i.e. WBRT) carries a risk of neurotoxicity (*i.e. Chang et al , 2009; Brown et al, 2013-2014; Gondi et al, 2014; MRG-CC 101 trial*)

- Neurocognitive outcomes may serve as secondary end-point to support the clinical benefit of a novel treatment approach (i.e. trials with motexafin gadolinium)

QUALITY OF LIFE

- HRQoL is a well established secondary endpoint in advanced cancer, including brain metastases

- A number of issues make HRQoL problematic as primary endpoint in brain metastases trials (*Soffietti et al, 2014*)
  - differential dropout, i.e. patients who have progressed or who experience clinical deterioration are the least likely to complete all of the assements, thus potentially rendering a treatment more favorable than it really is
  - confounding effect of extracranial disease and its treatments

EORTC 22952-26001
Quality of Life results of an EORTC phase III randomized trial of adjuvant Whole Brain Radiotherapy versus Observation after Radio surgery or Surgical Resection of 1-3 Cerebral Metastases of solid tumors
HRQOL results

R. Soffietti[1], M. Kocher[2], M. U. Abacioglu[3], S. Villa[4], F. Fauchon[5], B. G. Baumert[6], L. Fariselli[7], R. P. Mueller[2], G. Tridello[8], A. Bottomley[8]

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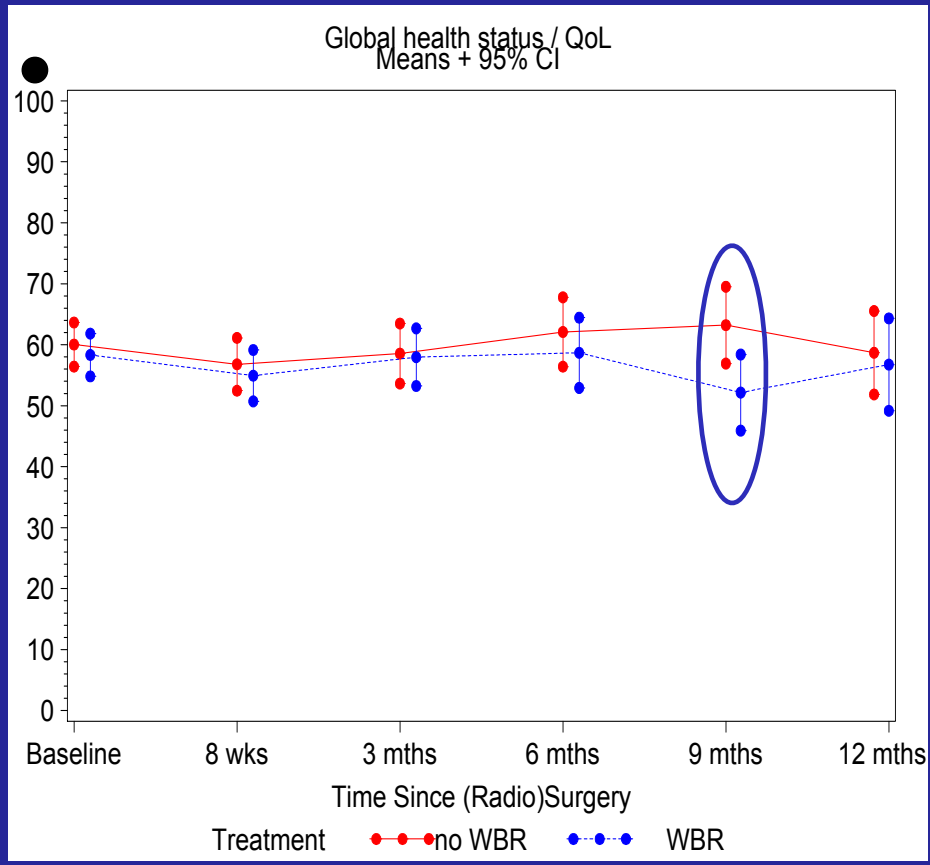
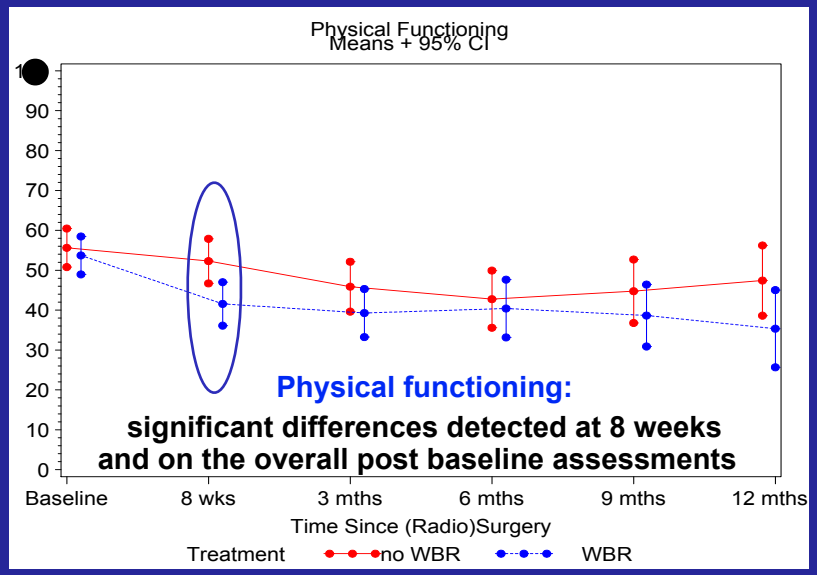
J Clin Oncol. 2013 Jan 1;31(1):65-72

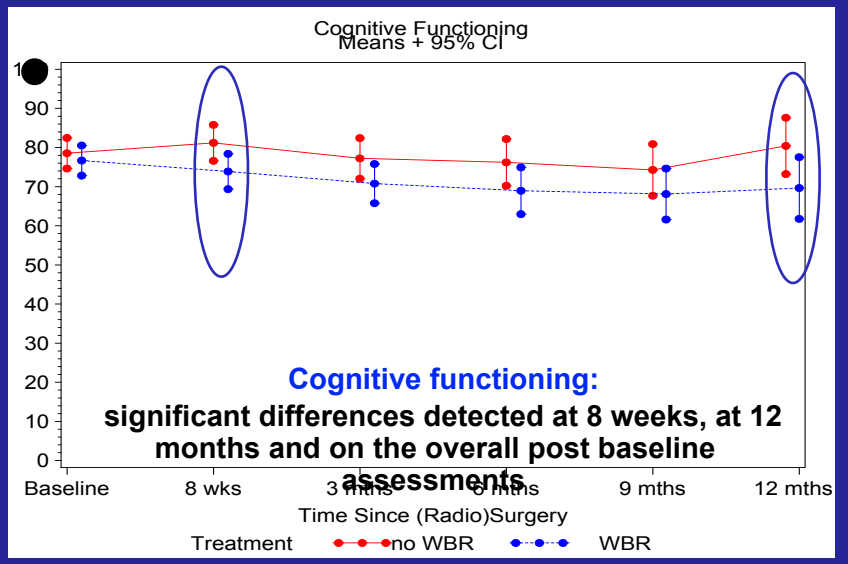
Results: Global health status / QoL

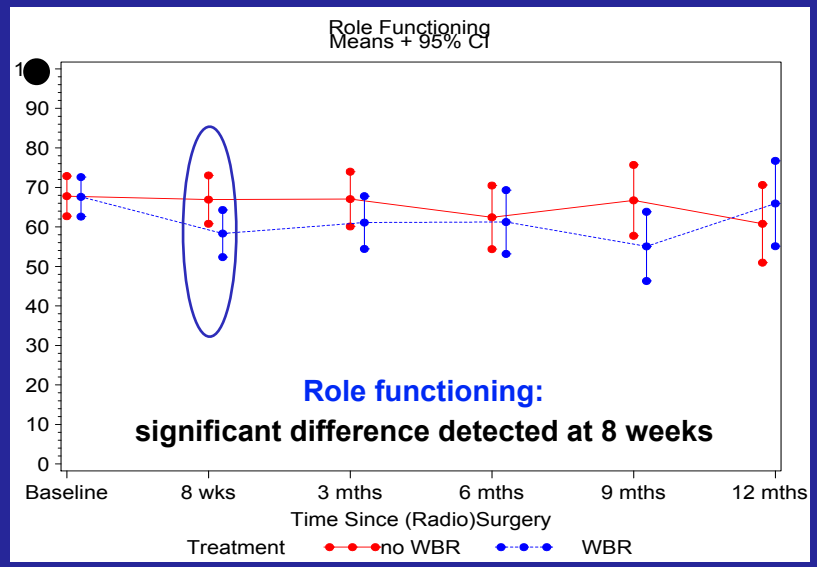
Timepoint	WBI Estimate (Std.Err.)	No WBI Estimate (Std.Err.)	Treatment difference p-value
Baseline	**58.3 (1.8)**	**60.0 (1.8)**	**0.5**
8 wks	**54.9 (2.1)**	**56.8 (2.2)**	**0.5**
3 mths	**58.0 (2.4)**	**58.6 (2.5)**	**0.9**
6 mths	**58.7 (2.9)**	**62.1 (2.9)**	**0.4**
9 mths	**52.2 (3.2)**	**63.2 (3.2)**	**0.01**
12 mths	**56.8 (3.9)**	**58.7 (3.5)**	**0.7**
Overall post baseline			**0.1**

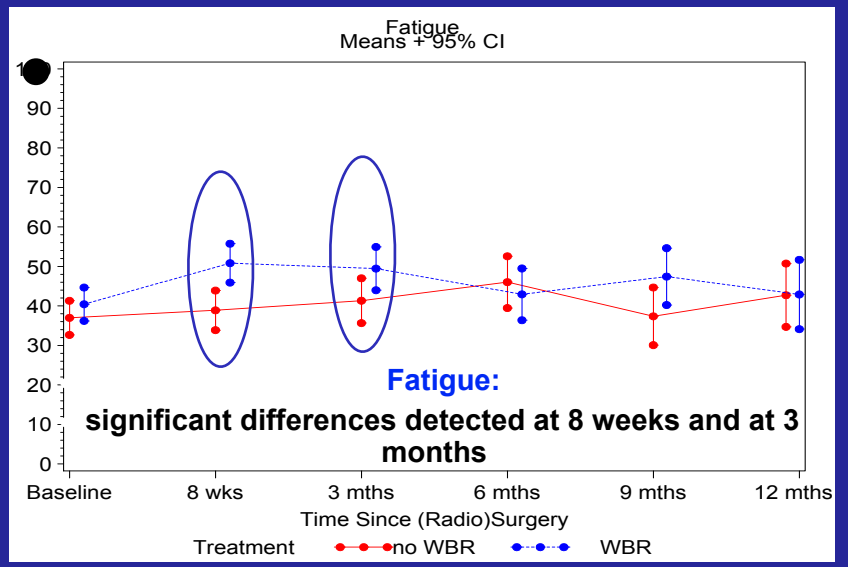


Results: secondary QoL endpoints









Emotional functioning: no differences were detected

QUALITY-ADJUSTED LIFE YEARS (QALYS)

- QALYS as a new endpoint to be validated (*Col et al, 2011*).

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journal homepage: www.clinicaloncologyonline.net

Original Article

Interim Data from the Medical Research Council QUARTZ Trial: Does Whole Brain Radiotherapy Affect the Survival and Quality of Life of Patients with Brain Metastases from Non-small Cell Lung Cancer?

R.E. Langley [*], R.J. Stephens [*], M. Nankivell [*], C. Pugh [*], B. Moore [†], N. Navani [*,‡], P. Wilson [§], C. Faivre-Finn [¶], R. Barton [‖], M.K.B. Parmar [*], P.M. Mulvenna [**]on behalf of the QUARTZ Investigators

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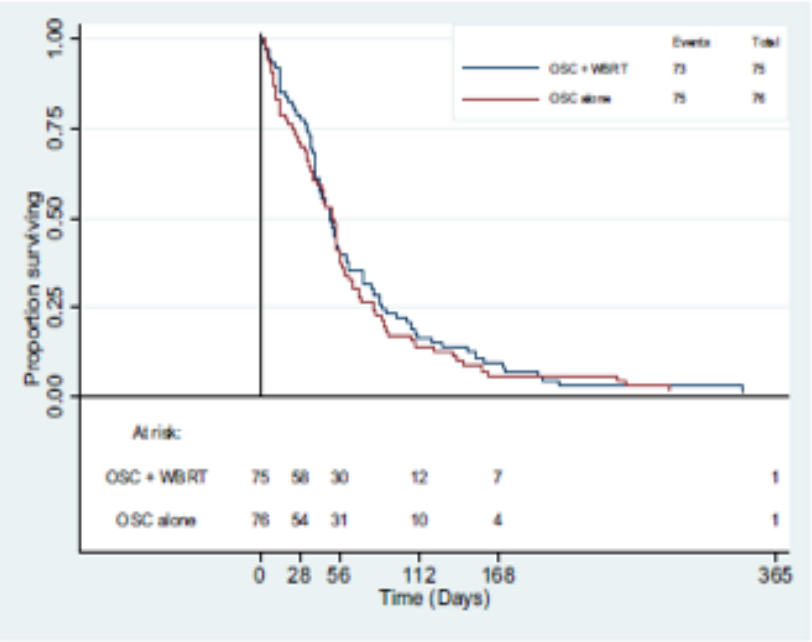

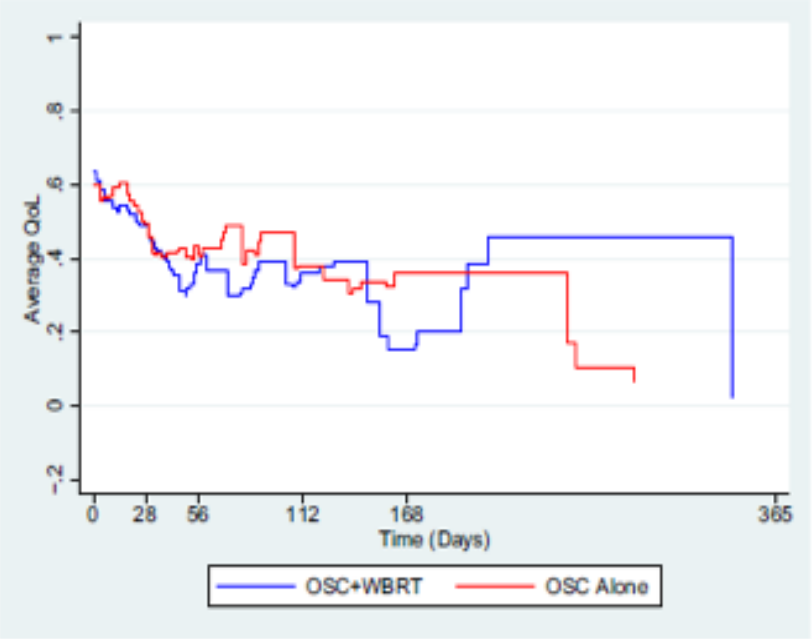

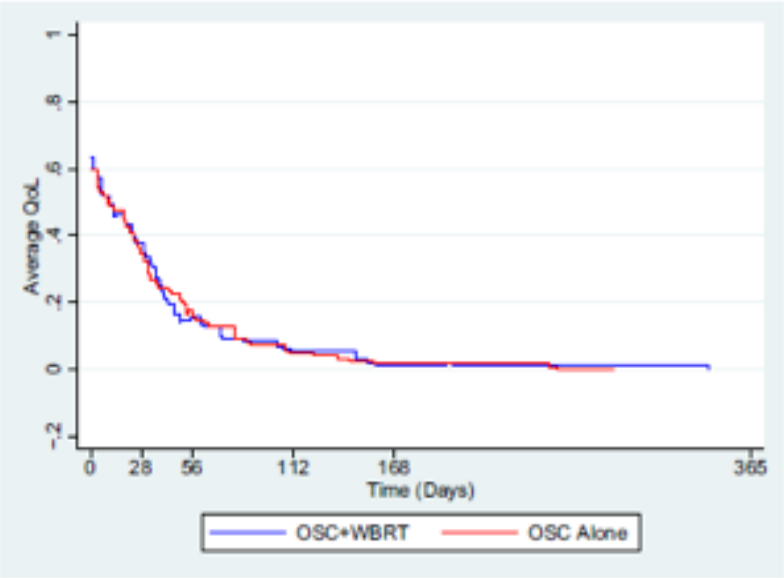

Fig 2. Overall survival, quality of life over time, and quality-adjusted life years (QALYs). Top: Kaplan–Meier plot of survival times for the two treatment groups, showing survival as the number of days from randomisation until death. Overall, 148 of the 151 patients had died at the time of the analysis, with a median survival of 49 days (optimal supportive care plus whole brain radiotherapy [OSC + WBRT]) and 51 days (OSC alone) and a hazard ratio of 1.11 (95% confidence interval 0.80–1.53). Middle: the average quality of life score over time for the two groups. The five questions from the EQ-5D questionnaire were combined to create a utility score, formed using the value a healthy population assigns to the 243 health states represented by each possible combination of EQ-5D questionnaire responses. Larger fluctuations in average scores are observed over time as fewer patients remain in the trial, with 61 patients still in follow-up after 56 days, and just 22 after 112 days. Bottom: a plot of QALYs for each treatment arm. Survival times and quality of life scores were combined to produce an estimate of the average QALY for each group. Due to the presence of censored survival data in this analysis, QALYs were estimated using the average quality of life score at each event time, with bootstrapping used to form confidence intervals for the difference between the treatment groups.

CRITICAL ISSUES FOR TRIALS ON TARGETED AGENTS IN ESTABLISHED BRAIN METASTASIS

- Uptake of the drug
- Presence of the molecular target
- Measurement of drug activity

Soffietti et al, Curr Opin Oncol, 2012, 24:679-86

Lin et al,Curr Treat Opt Neurol, 2014, 16:276-293

Neuro-Oncology

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Advance Access date 11 July 2014

Capecitabine and lapatinib uptake in surgically resected brain metastases from metastatic breast cancer patients: a prospective study

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Background. Breast cancer brain metastases (BCBM) are challenging complications that respond poorly to systemic therapy. The role of the blood–tumor barrier in limiting BCBM drug delivery and efficacy has been debated. Herein, we determined tissue and serum levels of capecitabine, its prodrug metabolites, and lapatinib in women with BCBM resected via medically indicated craniotomy.

Methods. Study patients with BCBM requiring surgical resection received either single-dose capecitabine (1250 mg/m^2) 2–3 h before surgery or 2–5 doses of lapatinib (1250 mg) daily, the last dose 2–3 h before surgery. Serum samples were collected serially on the day of surgery. Drug concentrations were determined in serum and BCBM using liquid chromatography tandem mass spectrometry.

Results. Twelve patients were enrolled: 8 for capecitabine and 4 for lapatinib. Measurable drug levels of capecitabine and metabolites, 5′-deoxy-5-fluorocytidine, 5′-deoxy-5-fluorouridine, and 5-fluorouracil, were detected in all BCBM. The ratio of BCBM to serum was higher for 5-fluorouracil than for capecitabine. As for lapatinib, the median BCBM concentrations ranged from 1.0 to 6.5 μM. A high variability (0.19–9.8) was noted for lapatinib BCBM-to-serum ratio.

Conclusions. This is the first study to demonstrate that capecitabine and lapatinib penetrate to a significant though variable degree in human BCBM. Drug delivery to BCBM is variable and in many cases appears partially limiting. Elucidating mechanisms that limit drug concentration and innovative approaches to overcome limited drug uptake will be important to improve clinical efficacy of these agents in the central nervous system.Trial registration ID: NCT00795678.

Keywords: blood–tumor barrier, brain metastases, breast cancer, capecitabine, lapatinib.

CRITICAL ISSUES FOR TRIALS ON TARGETED AGENTS IN THE PREVENTION OF BRAIN METASTASIS

- The identification of subgroups of patients at high risk of CNS relapse.
- The ability of a promising agent to adequately cross the BBB/BTB.

Soffietti et al, Curr Opin Oncol, 2012, 24:679-86

Lin et al,Curr Treat Opt Neurol, 2014, 16:276-293

CONCLUSIONS

- The evaluation of patients with brain metastases enrolled in clinical trials is complex.
- The choice of primary and secondary endpoints will naturally vary according to the treatment modalities and overall study goals and type; however, the definition of the endpoints should ideally remain constant.
- The new proposed criteria must be validated within future clinical trials.