Erasmus MC
Universitair Medisch Centrum Rotterdam

Cancer Institute

brain tumor center

Neurocognitive assessment and patient reported outcomes

ESMO preceptorship programme: Brain tumours
Athens, 28-29 September

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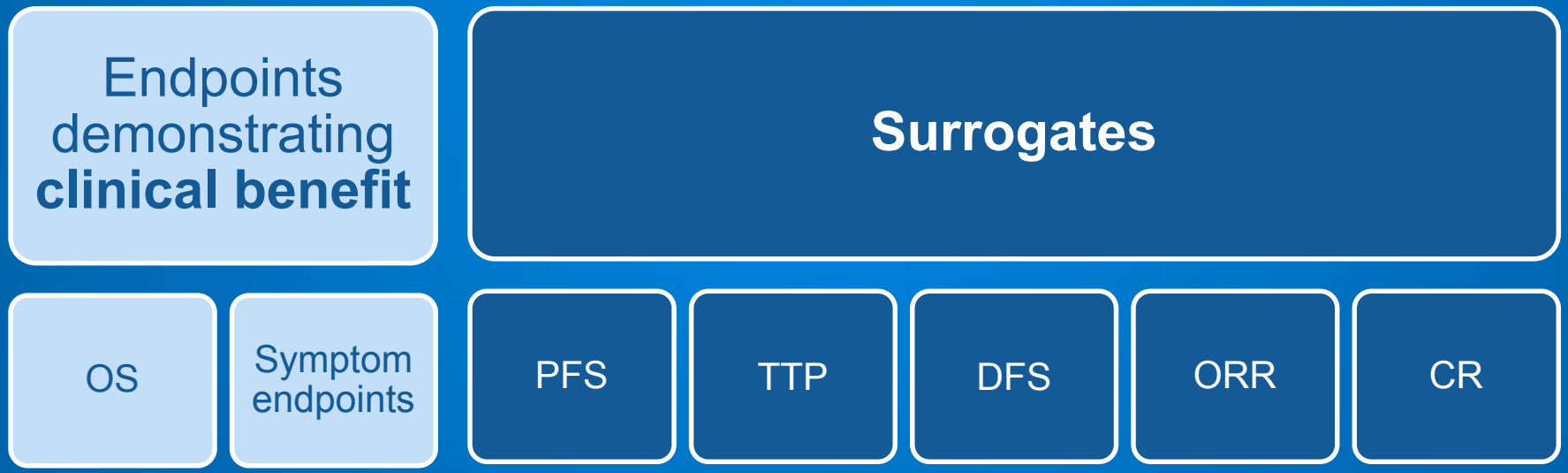
disclosures

- Grant/research support from Abbvie
- Honoraria from Celgene, BMS, Abbvie, Agios, Daichi Sankyo

FDA opinion on oncology endpoints

- Only OS and symptom endpoints are sufficient to demonstrate **clinical benefit** for regular approval[1]
- Improvement in surrogate endpoints reasonably likely to predict benefit may be sufficient to gain accelerated approval
  - Adequacy of surrogates is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy[1]
- Tumor-specific guidance on endpoints still awaited[2]

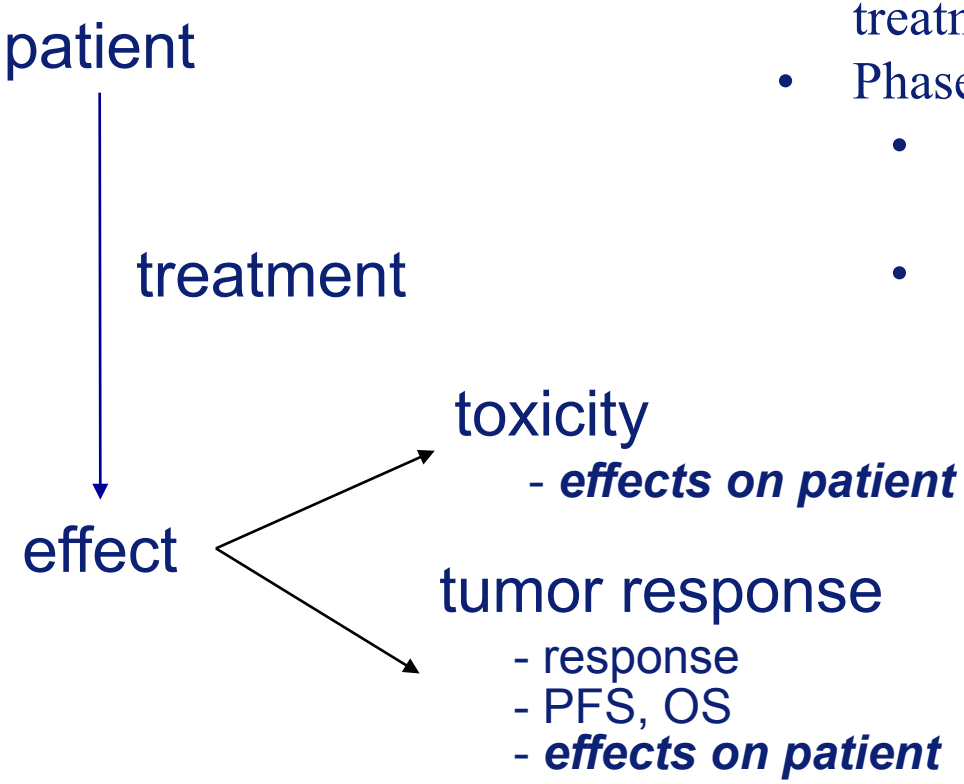


CR: complete response.; ORR: objective response rate; TTP: time to progression

1. www.fda.gov/cder/guidance/index.htm;
2. www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/CancerDrugs/ucm094586.htm

Outcome assessment in primary brain tumors: The GIGA rule

- Every day clinical practice: guidance of treatment: response
- Phase II trials: evaluation of novel treatments: ORR, PFS
- Phase III trials: PFS, OS
  - Reliability depends on design & conduct of the trial
  - Garbage In is Garbage Out



Measuring changes over time

Bacchus and Ariadne
Carle van Loo (Nice 1705 - Paris 1765)

Jan Brueghel II, Jan van Balen
The Feast of Bacchus 1640

Drunken bacchus – PP Rubens

Young sick bacchus
Caravaggio, 1593

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Auxiliary Endpoints
Patient Function and Well-Being

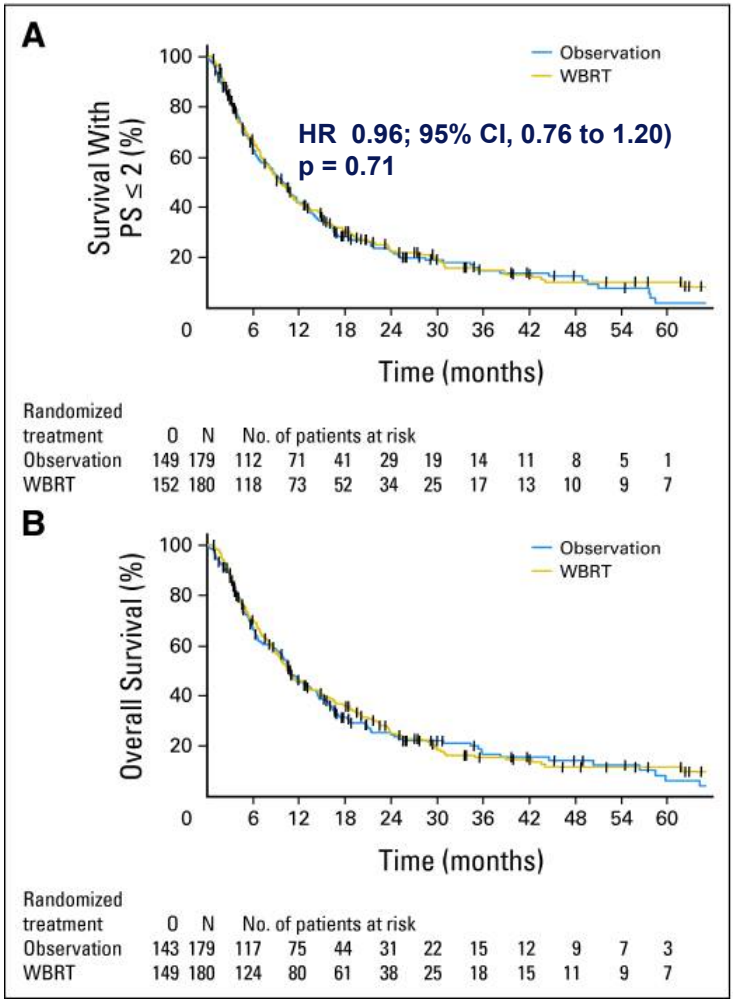
- Tumor specific
  - May address disease specific clinical issues
- Candidates in neuro-oncology
  - Corticosteroid use
  - Neurocognitive assessment
  - Health-related quality of life
  - Performance status change over time
  - Seizures
- Patient derived vs doctor derived
  - **Patient Reported Outcome (PRO)**

Par example: management of brain metastases after surgery or SRS

- Resection or SRS of 1-3 brain metastases improves outcome of patients with controlled systemic disease
- OS is determined by systemic disease in majority of patients
- WBRT administered after surgery or SRS improves local and brain control
- WBRT given after surgery or SRS of 1-3 brain metastases does not improve OS
- Does improved local control matter?

EORTC 22952: WBRT vs observation (OBS) after surgery or SRS for 1-3 brain metastases

- n = 359, eligible with PS 0-2
- Primary endpoint: time to PS WHO > 2
- The median time to WHO PS > 2
  - Obs: 10.0 mo (95% CI, 8.1 to 11.7)
  - WBRT: 9.5 mo (95% CI, 7.8 to 11.9)
- 2 years: OBS 22.3% and WBRT 22.6% alive and functionally independent
- Extracranial progression (death as competing risk) at 2 yrs:
  - OBS: 63% (95% CI, 56% to 70%)
  - WBRT 65% (95% CI, 58% to 72%) (p = 0.73)



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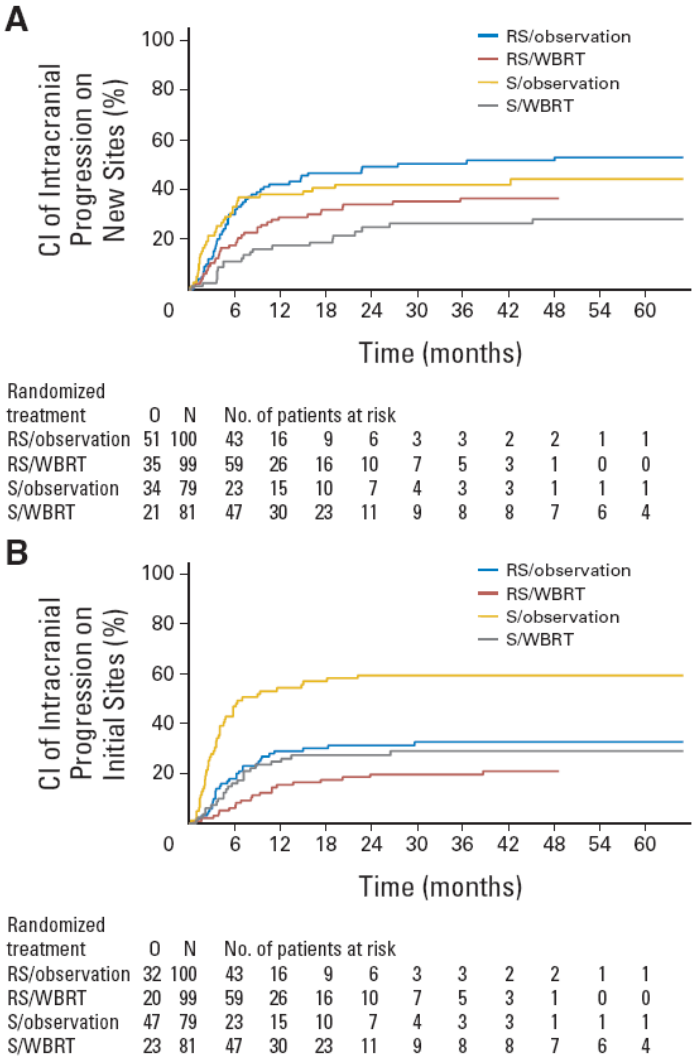
Kocher et al, *J Clin Oncol 2010 29:134-141*

Risk of intracranial PD

- At 2 yrs: WBRT reduced after radiosurgery reduced the probability of relapse at
  - initial sites: from 31% (95% CI, 22%to 40%) to19%(95% CI,11%to 27%; *P* = .040)
  - at new sites: from 48% (95% CI, 38% to 58%) to 33% (95% CI, 24% to 43%; p = 0.0023



Kocher et al, *J Clin Oncol 2010 29:134-141*

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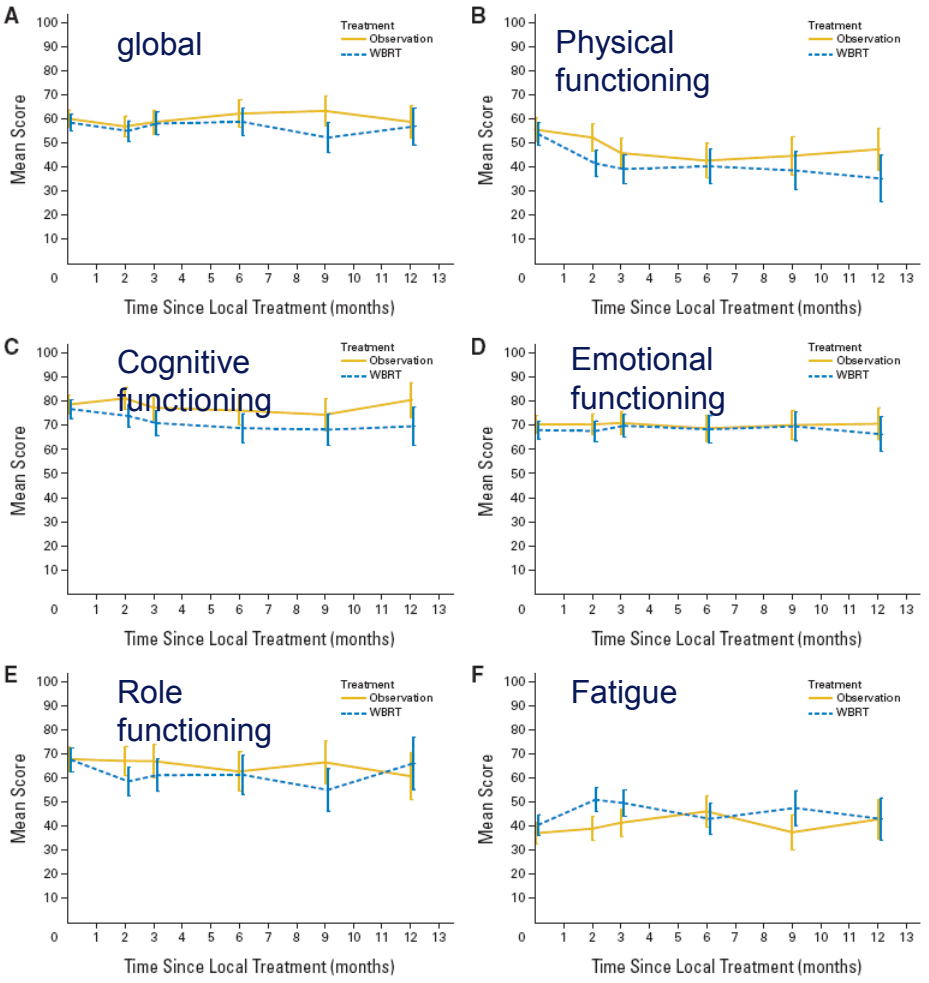
EORTC 22952: WBRT vs observation (OBS) after surgery or SRS for 1-3 brain metastasesL QoL

- Health related quality of life using QoL C30 and BCM20
- Change of 10 points considered clinically relevant
- OBS patients better HRQOL scores than WBRT patients
- Statistically significant and clinically relevant
  - global health status at 9 mo,
  - physical functioning at 8 wks
  - cognitive functioning at 12 mo
  - fatigue at 8 wks



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Soffietti et al, *J Clin Oncol 2012;31:65-72*

SRS vs no SRS after resection brain metastases

- N = 132 patients, 4 ineligible
- Primary endpoint: time to local recurrence
- 12-mo freedom from local PD:
  - 43% (95% CI 31–59) without SRS
  - 72% (60–87) in the SRS group
- median overall survival
  - 18 mo (95% CI 13 months to NR) without SRS
  - 17 mo (13–22) in the SRS group
- 12-mo freedom from distant brain PD
  - 33% (95% CI 22–49) without SRS
  - 42% (30–58) in SRS group

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Mahajan et al, Lancet Oncol 2017; 18: 1040–48

Conclusion

- SRS of the surgical cavity in patients who have had complete resection of one, two, or three brain metastases significantly lowers local recurrence compared with that noted for observation alone.
  - Thus, the use of SRS after brain metastasis resection could be an alternative to whole-brain radiotherapy
  - Treating the surgical cavity postoperatively with SRS is an appealing strategy to limit the neurocognitive insult while improving local tumour control.
- Burning question: does local control matter?
  - No impact OS
  - No impact on distant brain control (WBRT does!)
  - Impact on patient functioning not reported

WBRT revisited: SRS vs WBRT

- 194 patients randomized to SRS or WBRT
- The co-primary endpoints were overall survival and cognitive-deterioration-free survival
- Cognition assessed with 6 well established cognitive tests to assess learning and immediate memory
- Median OS 12·2 months (95% CI 9·7–16·0, 69 deaths) for SRS and 11·6 months (9·9–18·0, 67 deaths) for WBRT
- Cognitive-deterioration-free survival longer after SRS (median 3·7 months [95% CI 3·45-5·06]) compared to WBRT (median 3·0 months [2·86–3·25])

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Brown et al, Lancet Oncol 2017; 18: 1049–60

Conclusion

- Decline in cognitive function was more frequent with WBRT than with SRS and there was no difference in overall survival between the treatment groups
- Objective outcome assessment beyond survival
- How does that relate to patient quality of life symptoms?

Assessment cognition

- 6 tests: Hopkins Verbal Learning Test-Revised [HVLT-R] Immediate Recall), verbal fluency (Controlled Oral Word Association Test [COWAT]), processing speed (Trail Making Test part A [TMT-A]), executive function (Trail Making Test part B [TMT-B]), delayed memory (HVLT-R Delayed Recall), and recognition (HVLT-R Recognition).
- Cognitive-deterioration-free survival: the time from randomisation to a drop of greater than 1 SD from baseline in at least one of the six cognitive tests (all tests are standardised on the basis of published norms
- Secondary endpoints were quality of life (change from baseline to 6 months in FACT-Br and LASA), functional independence (assessed by the Barthel ADL index), local surgical bed recurrence, local recurrence of unresected metastases, distant brain recurrence, development of leptomeningeal disease, intracranial progression (time from randomisation to recurrence in the local surgical bed, progression of unresected metastases, distant brain recurrence, or development of leptomeningeal disease), long-term cognitive status, and toxicity.

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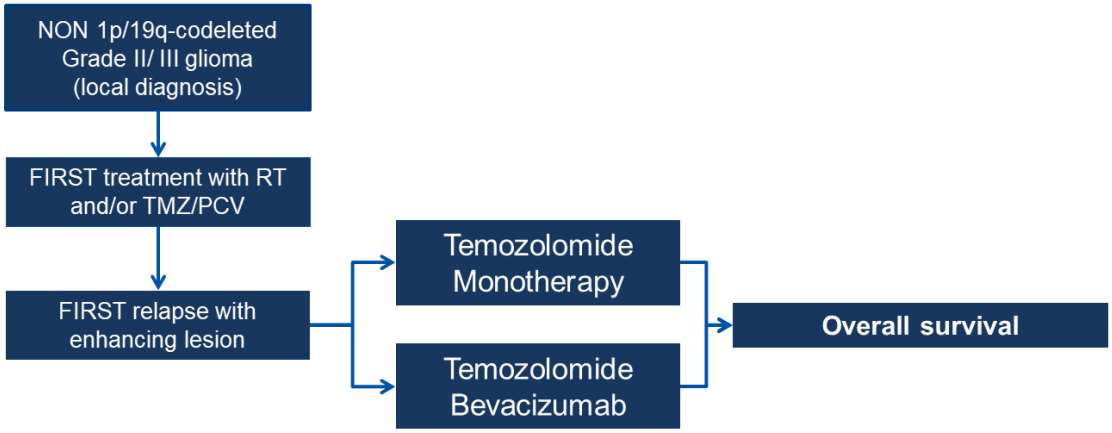
Cognitive Domain	Test	Time to Administer (minutes)
Memory	Hopkins Verbal Learning Test–Revised	8
Visual-motor processing speed	Trail Making Test Part A	5
Executive Function	Trail Making Test Part B	7
Verbal fluency	Controlled Oral Word Association	5
		Total time: 25 minutes

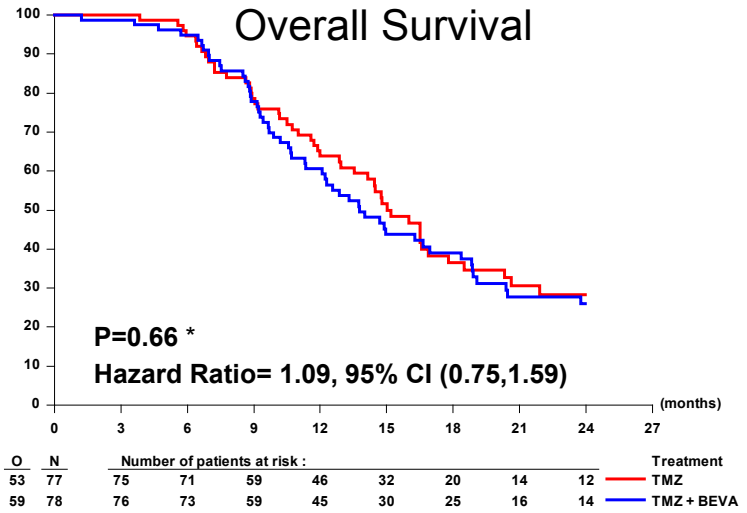
- Dutch, English (US, UK), French, German, Italian, Spanish, Catalan, Hebrew, Turkish, Portuguese
- 6 parallel versions
- Sensitive to the impact of cancer & neurotoxic effects of cancer treatment

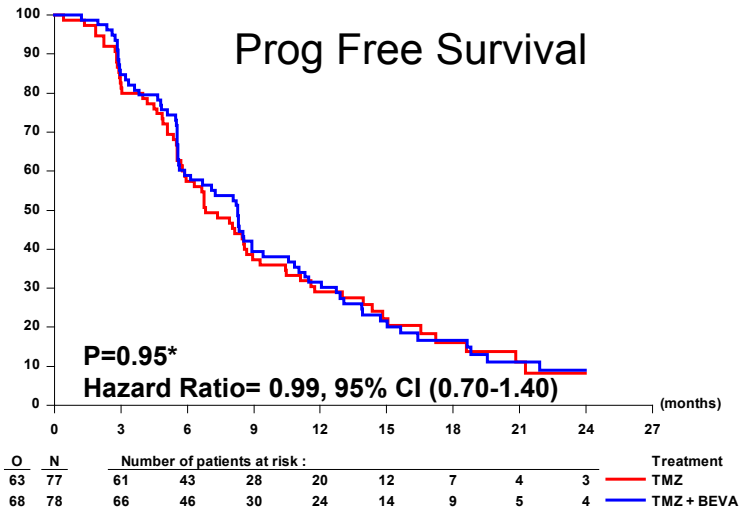
Determine NCF – EORTC Battery

- EORTC, NCCTG, NCI-C, RTOG, and MRC multisite clinical trials:
  - **EORTC 26053 - 22054 RTOG 0834** - The CATNON Intergroup trial. Phase III trial on Concurrent and Adjuvant TMZ chemotherapy in non-1p/19q deleted anaplastic glioma.
  - **EORTC 26081-22086** - The CODELETED trial. Phase III Intergroup Study of Radiotherapy versus TMZ versus Radiotherapy with Concomitant and Adjuvant TMZ for Patients with Newly Diagnosed Anaplastic Oligodendroglioma or Anaplastic Mixed Glioma with Chromosomal co-deletions of 1p and 19q.
  - **EORTC 26091** - Bevacizumab in recurrent grade II and Grade III gliomas
  - **EORTC 26101** - Phase II trial exploring the sequence of bevacizumab and lomustine in patients with first recurrence of a glioblastoma
  - **EORTC 1419 -** Molecular genetic, host-derived and clinical determinants of long-term survival in glioblastoma

EORTC TAVAREC trial: bevacizumab and temozolomide in recurrent 1p/19q intact grade II / III glioma







PP population		TMZ alone N=73	TMZ + BEV N=70
Primary endpoint	**Patients alive at 12m***	**44:72st (61%)**	**39:70 (56%)**

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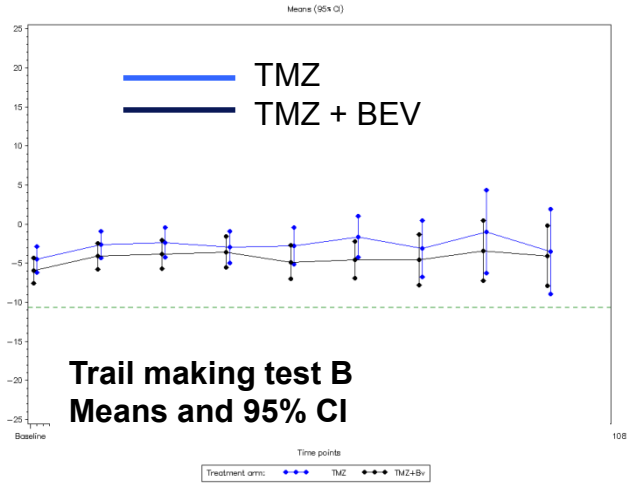
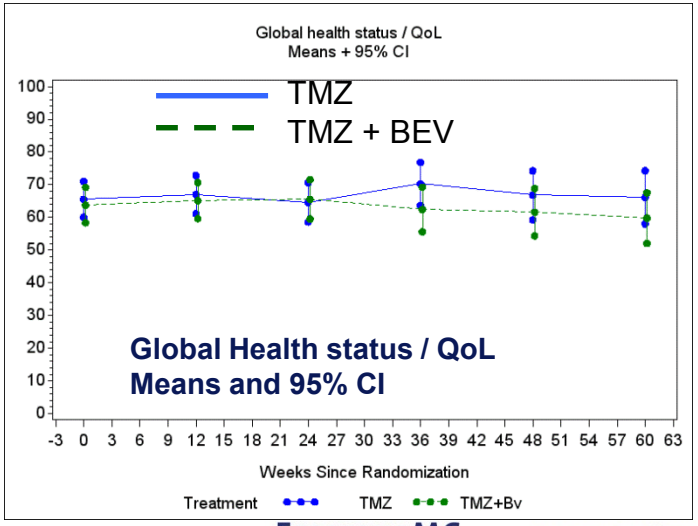
van den Bent et al, Lancet Oncol 2018doi: 10.1016/S1470-2045(18)30362-0

EORTC TAVAREC: Analysis QoL, cognition

- No clinical significant differences (ie > 10 points) were found at any time point for Global Health (p = 0.26), Cognitive Functioning (p = 0.13) or Pain (p=0.24)
- No impact on Cognition
  - For all 6 tests: none of the null hypothesis of no difference (H0) rejected
- TAVAREC conclusion:
  - No difference OS, PFS
  - No clinically better functioning in BEV/TMZ arm





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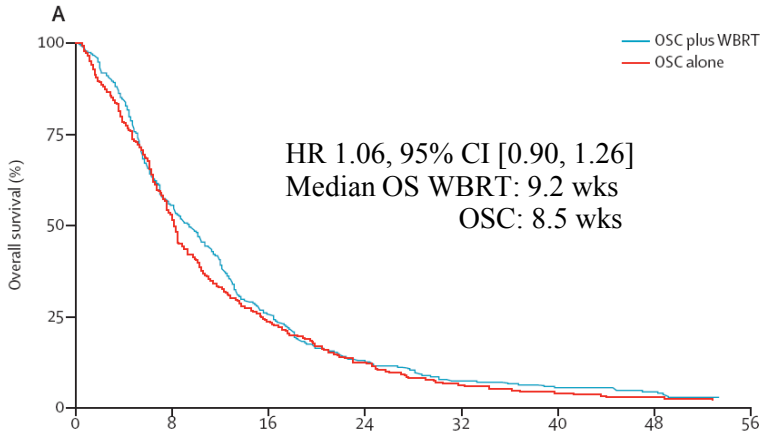
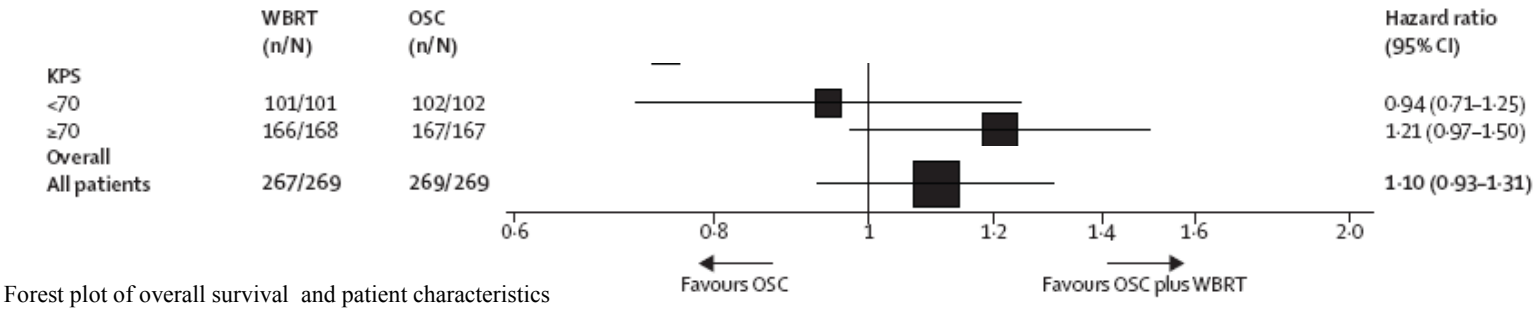
van den Bent et al, Lancet Oncol 2018doi: 10.1016/S1470-2045(18)30362-0

The QUARTZ trial: a new perspective on WBRT in NSCLC

- Design: optimal supportive care vs OSC with WBRT 20 Gy in 5 fractions
- Eligible: NSCLC patients with radiologically proven brain mets
  - Not candidate for surgery or SRS
- N = 538
  - KPS < 70 38%, ≥ 70 62%
  - Uncontrolled primary: 64%
- Non-inferiority trial, primary endpoint: QALY

➢ No OS difference in outcome between arms





Forest plot of overall survival and patient characteristics

➢ Still to be considered for good KPS patients

Mulvenna et al, Lancet 2016;388:2004-14

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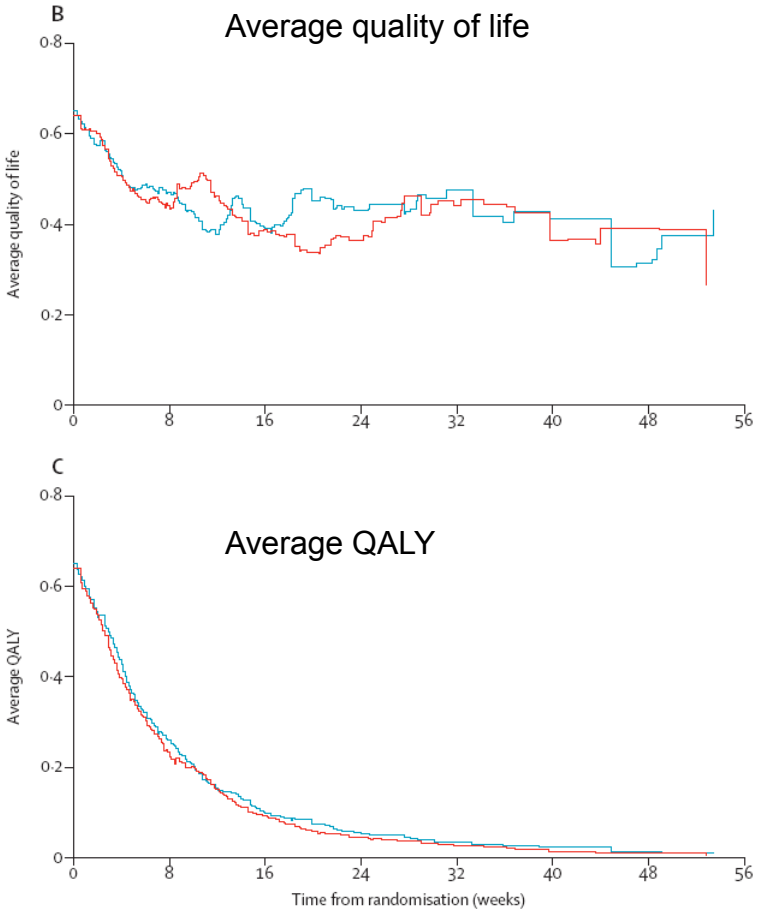
QUARTZ trial: primary endpoint

- Primary endpoint was quaity-adjusted life years
  - Combined measure of survivor function and utility
- Assessed with EuroQol EQ-5D 3L questionnaire
- Non-inferiority design
- No differernce between groups



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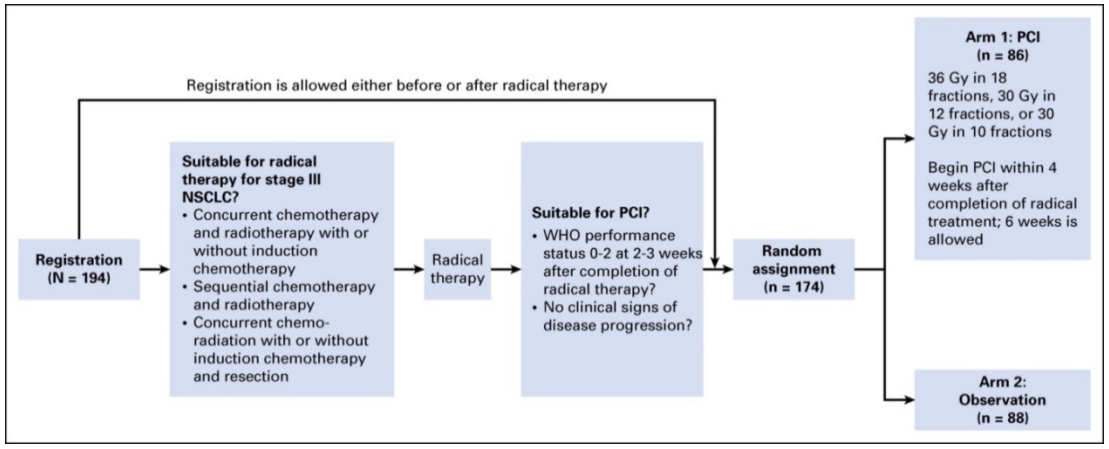
Mulvenna et al, Lancet 2016;388:2004-14

New trial on PCI for radically treated stage III NSCLC

- Primary end point: development of symptomatic brain metastases at 24 mo
  - Key symptoms: one or a combination of signs of increased intracranial pressure, headache, nausea and vomiting, cognitive or affective disturbances, seizures, and/or focal neurologic symptoms
  - Mandated imaging
- AE event assessment CTC for adverse events 3.0
- QoL assesssment with QoL C30 and BN20, EuroQol 5D
- n = 172



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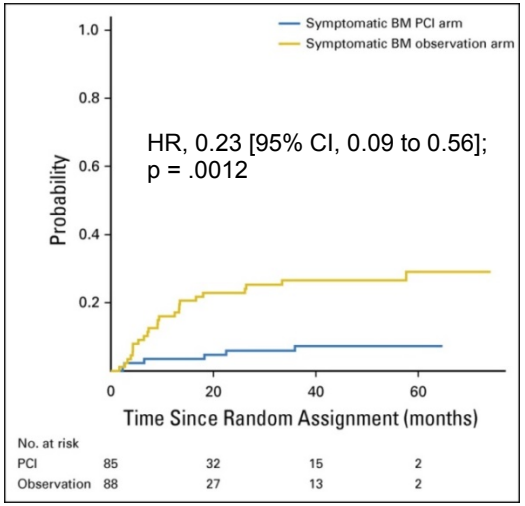
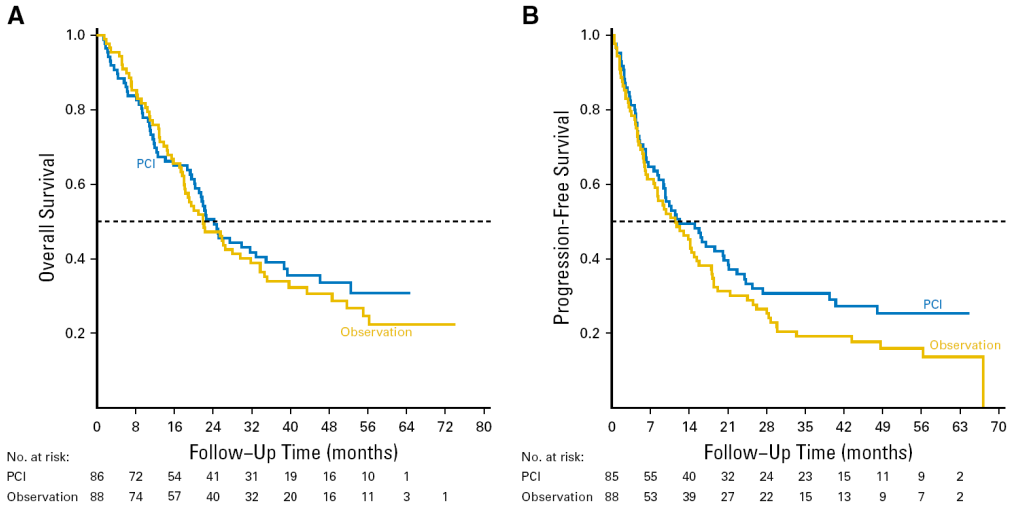
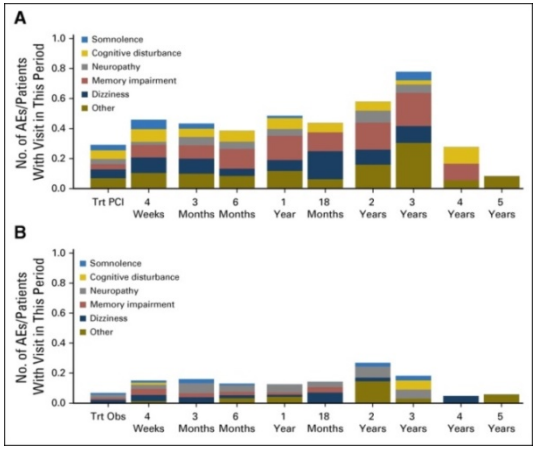
Ruysscher et al, J Clin Oncol Clin Oncol 2018;36:2366-2377

New trial on PCI for radically treated stage III NSCLC

- 6 (7.0%) of 86 patients PCI group vs 24 (27.2%) of 88 patients control group symptomatic brain metastases (p = .001)
- PCI increased time to develop symptomatic brain metastases (hazard ratio, 0.23; [95%CI, 0.09 to 0.56]; p = .0012).
- Less symptomatic brain metastases but no difference in Overall Survival







- After PCI more neurologic AEs, most low grade (grade 1 and 2)

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PCI: quality of survival

- Significantly increased: grade 1 / 2 memory impairment (30% v 8%, respectively) and cognitive disturbance (19% v 3%, respectively
- Virtually all AEs under-reported by physicians compared with patients
  - Fatigue and memory impairment more under-reported by physicians in the observation arm than in the PCI arm.
  - memory impairment was reported by 57% and 54% of patients in the PCI arm and observation arm
- Reflecting bias of physicians? **Requires PRO's…**
- OS and progression-free survival similar in both arms
  - PCI is efficacious in reducing the incidence of brain metastases
  - majority of patients developed extracranial recurrences, thus lowering the potential effect of PCI on OS
  - Effect of treatment of symptomatic (CNS) metastases

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Some conclusions

- Non-survival endpoints may help to assess quality of survival
  - As another measure of patient benefit
- Challenge: patient, physician compliance
- Different tools, different advantages
- Especially relevant in treatments that
- Improve survival by intensified treatment: impact functioning
- Similar OS but different PFS
- Different tools

Cornelis de Vos, 1651 – El triumfo de baco…

Peter Paul Rubens, 1613 . Venus, Cupid, Bacchus and Ceres.

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