Phase II Trial of Atezolizumab Combined with Carboplatin and Pemetrexed for Patients with Advanced Non-Squamous NSCLC with Untreated Brain Metastases (Atezo-Brain, GECP17/05). Ernest Nadal et al.

Supplementary Methods

Safety and efficacy were assessed in the intention-to-treat population cohort of 40 patients using the Bayesian approach of Thall, Simon, Estey[1,2] and further developed by Thall and Sung.[3] Historical data on similar patients showed a 12-weeks PFS rate of 40% and a toxicity rate of 35%.[4-6] We assumed independence between efficacy and toxicity. We expected that atezolizumab plus chemotherapy would improve the PFS rate at 12 weeks to 50%, while the grade 3 or higher toxicity rate would be 35% or below during the first 9 weeks. A sample size of 40 patients ensured that, if the trial is not terminated early, a posterior 90% credibility interval (CrI) for ORR would have width of 0.257 at most, under the assumption of 50% of PFS at 12 weeks. The probabilities of efficacy and toxicity for the historical data are modeled by beta distributions (Beta(14,26) and Beta(9,16), respectively). The prior probabilities of PFS rate at 12 weeks and toxicity for the experimental regimen are also modeled by beta distributions (Beta(0.4,0.6) and Beta(0.35,0.65), respectively), which have the same means as the corresponding beta distributions for the historical data, and an Effective Sample Size of 1. Sample size analysis was based on the assumptions of an accrual time of 18 months with an additional 36 months of follow-up.

The Kaplan–Meier method was used to estimate PFS and OS. Data for patients who were alive or lost to follow-up were censored for OS at the time they were last known to be alive. Data for patients who were alive and did not have disease progression or who were lost to follow-up were censored for the analysis of PFS

at the time of the last imaging assessment. The stratified log-rank test was used to assess between-group differences in PFS and OS. Hazard ratios and associated 95% confidence intervals were calculated with the use of a stratified Cox proportional-hazards model.

References:

1. Thall PF, Simon RM, Estey EH: Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Stat Med 14:357-79, 1995

2. Thall PF, Simon RM, Estey EH: New statistical strategy for monitoring safety and efficacy in single-arm clinical trials. J Clin Oncol 14:296-303, 1996

3. Thall PF, Sung HG: Some extensions and applications of a Bayesian strategy for monitoring multiple outcomes in clinical trials. Stat Med 17:1563-80, 1998

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5. Barlesi F, Gervais R, Lena H, et al: Pemetrexed and cisplatin as first-line chemotherapy for advanced non-small-cell lung cancer (NSCLC) with asymptomatic inoperable brain metastases: a multicenter phase II trial (GFPC 07-01). Ann Oncol 22:2466-70, 2011

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Supplementary Tables and Figures

Supplementary Table S1. Number or patients included per investigator and site.

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Supplementary Figure S1. Study design.

Supplementary Figure S2. Stopping rules based on boundaries defined for efficacy (R: number of patients free of intracranial or systemic tumor progression or death) during the first 12 weeks and toxicity (Tox: number of patients with grade 3 or higher adverse events) during the first 9 weeks.

Supplementary Figure S3. Posterior distribution of the progression-free survival (PFS) rate. The overall PFS rate at 12 week was 62.2% (95% credibility interval 47.1 to 76.2%) above the expected 50%.

Supplementary Figure S4. Kaplan-Meier estimates of duration of intracranial response.

Supplementary Figure S5. Best percentage change from baseline by target lesion. Waterfall plot displaying the maximum percentage change in sum of the diameters of target lesions in the brain (a) or in the body (b) according to PD-L1 expression.

Supplementary Figure S6. Kaplan-Meier estimates of overall survival according to PD-L1 expression (a) and dose of corticosteroids at baseline (b). Two patients were not included in the analysis since PD-L1 expression was not evaluable.

Supplementary Figure S7. Kaplan-Meier estimates of time to brain radiotherapy (a) and event-free survival (b). Dotted lines indicate 95% confidence intervals. Swimmer plot showing the time from treatment initiation to any brain radiotherapy or death (c).

Supplementary Figure S8. Kaplan-Meier estimates of time to appearance of treatment-related neurological adverse events (a) and time to appearance to neurological adverse events regardless of their relationship to treatment (b).

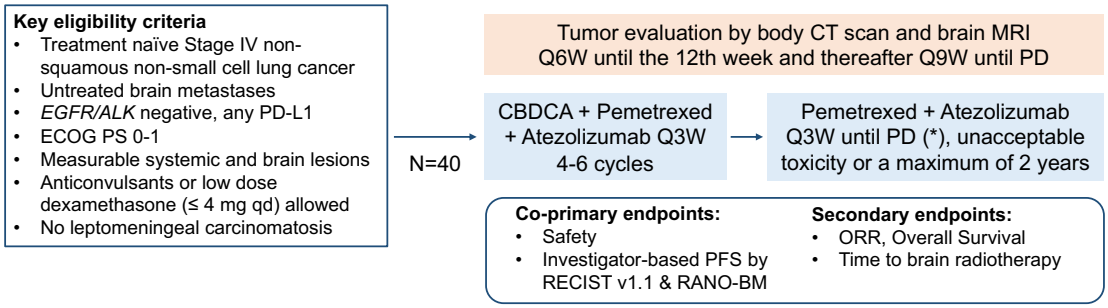
Supplementary Table S1. Number or patients included per investigator and site.

Site	Principal Investigator	Number of patients included
Institut Català d'Oncologia, L'Hospitalet	Dr. Nadal	8
H. Insular de Gran Canaria, Las Palmas	Dr. Rodríguez	8
H. General de Alicante, Alicante	Dr. Massutí	6
H. Universitari la Fe, Valencia	Dr. Juan	3
Complejo Hospitalario de Vigo, Vigo	Dr. Huidobro	3
H. Clínico Universitario de Valladolid, Valladolid	Dr López	2
H. Universitario La Paz, Madrid	Dr. De Castro	2
Institut Català d'Oncologia, Badalona	Dra. Estival	2
Complejo Hospitalario de A Coruña, A Coruña	Dra. Garcia Campelo	2
H. de Sant Pau, Barcelona	Dra. Sullivan	1
H. Universitario Vall d'Hebrón, Barcelona	Dra. Felip	1
H. General Universitario de Valencia, Valencia	Dra. Blasco	1
H. Universitario de Elche, Elche	Dra. Guirado	1

Supplementary Table 2. List of grade ≥3 adverse events related to treatment (N=40).

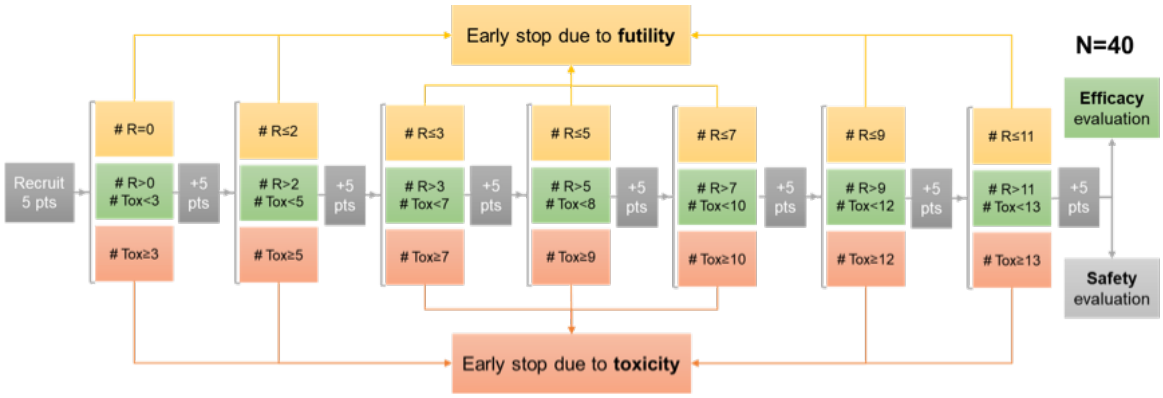
Adverse Events	Grade 3	Grade 4	Grade 5
Anemia	8 (20%)	0	0
Platelet count decreased	3 (7.5%)	0	0
Alanine aminotransferase increased	1 (2.5%)	0	0
Lipase increased	1 (2.5%)	0	0
Blood and lymphatic system disorders	2 (5.0%)	0	0
Hypomagnesemia	2 (5.0%)	0	0
Febrile neutropenia	1 (2.5%)	0	1 (2.5%)
Acute kidney injury	2 (5.0%)	0	0
Neutrophil count decreased	1 (2.5%)	0	0
Pneumonitis	1 (2.5%)	0	0
Respiratory, thoracic	1 (2.5%)	0	0
Renal and urinary disorders	1 (2.5%)	0	0
Thromboembolic event	1 (2.5%)	0	0
Upper respiratory infection	1 (2.5%)	0	0
Vascular disorders - Other, specify	1 (2.5%)	0	0
Gamma-glutamyl transferase increased	1 (2.5%)	0	0

Supplementary Figure S1. Study design.

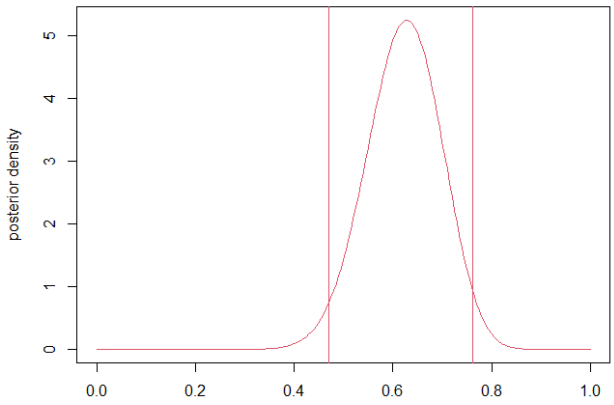


Abbreviations: CBDCA, carboplatin; CT, computerized tomography; DoR, duration of response; MRI, magnetic resonance imaging; OS, overall survival; ORR, overall response rate; PFS, progression-free survival; PD, progressive disease; qd, once daily; Q3W, every three weeks; Q6W, every 6 weeks; Q9W, every 9 weeks; RANO-BM, response assessment criteria for brain metastases; RECIST, response evaluation criteria in solid tumors.

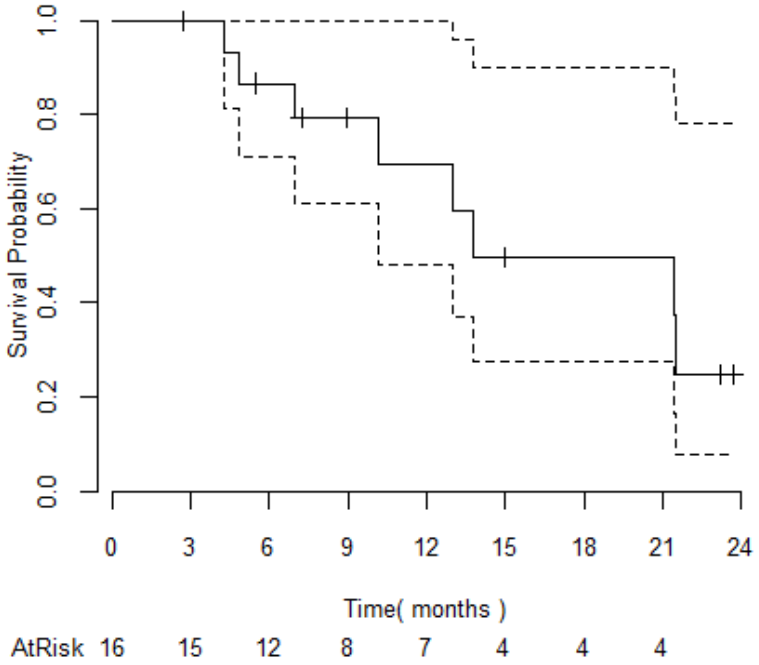
Supplementary Figure S2. Stopping rules based on boundaries defined for efficacy (R: number of patients free of intracranial or systemic tumor progression or death) during the first 12 weeks and toxicity (Tox: number of patients with grade 3 or higher adverse events) during the first 9 weeks.



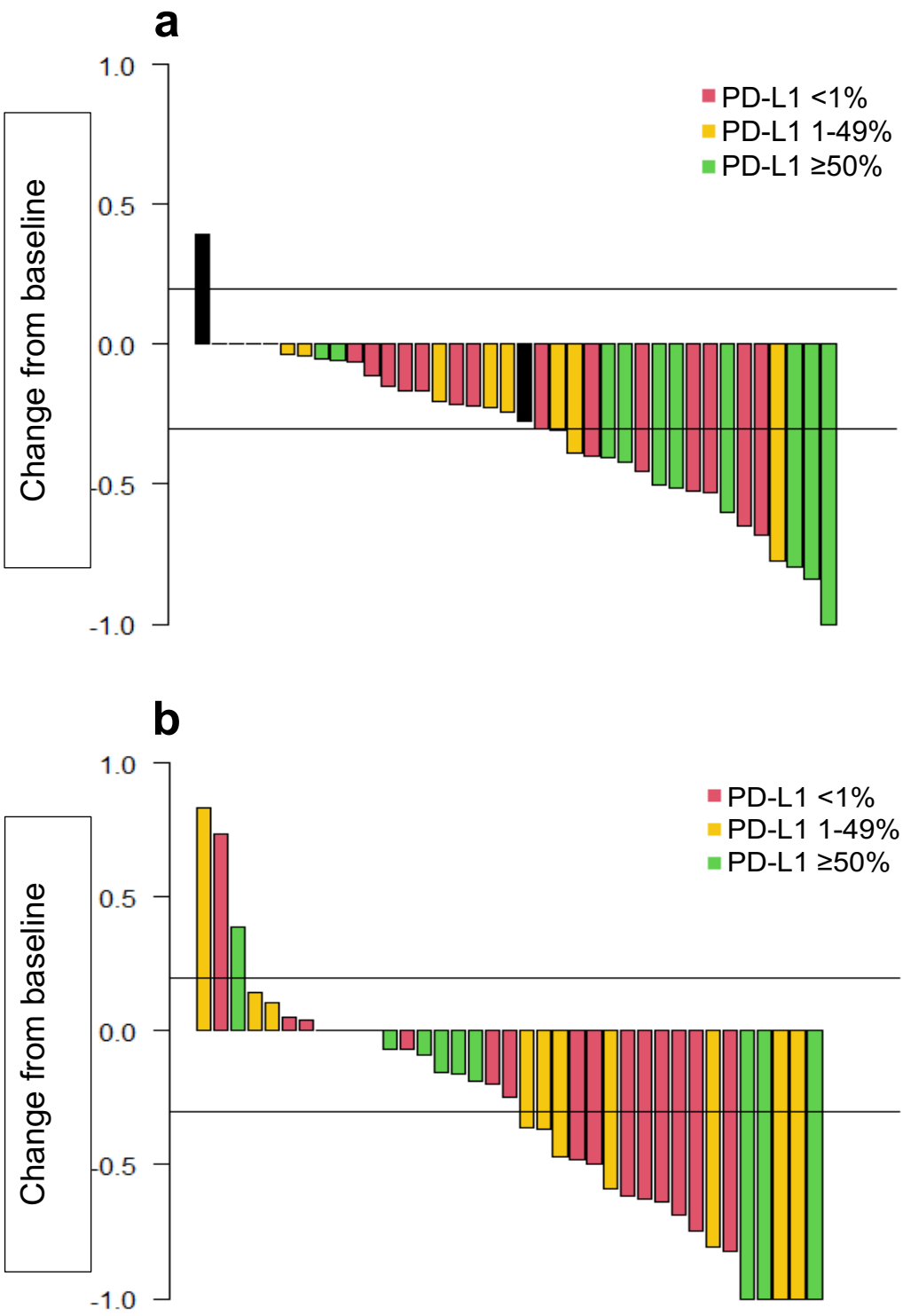
Supplementary Figure S3. Posterior distribution of the progression-free survival (PFS) rate. The overall PFS rate at 12 week was 62.2% (95% credibility interval 47.1 – 76.2%) above the expected 50%.



Supplementary Figure S4. Kaplan-Meier estimates of duration of intracranial response. Dotted lines indicate 95% confidence intervals.



Supplementary Figure S5. Best percentage change from baseline by target lesion. Waterfall plot displaying the maximum percentage change in sum of the diameters of target lesions in the brain (a) or in the body (b) according to PD-L1 expression. Black bars represent two patients in whom PD-L1 was unknown.



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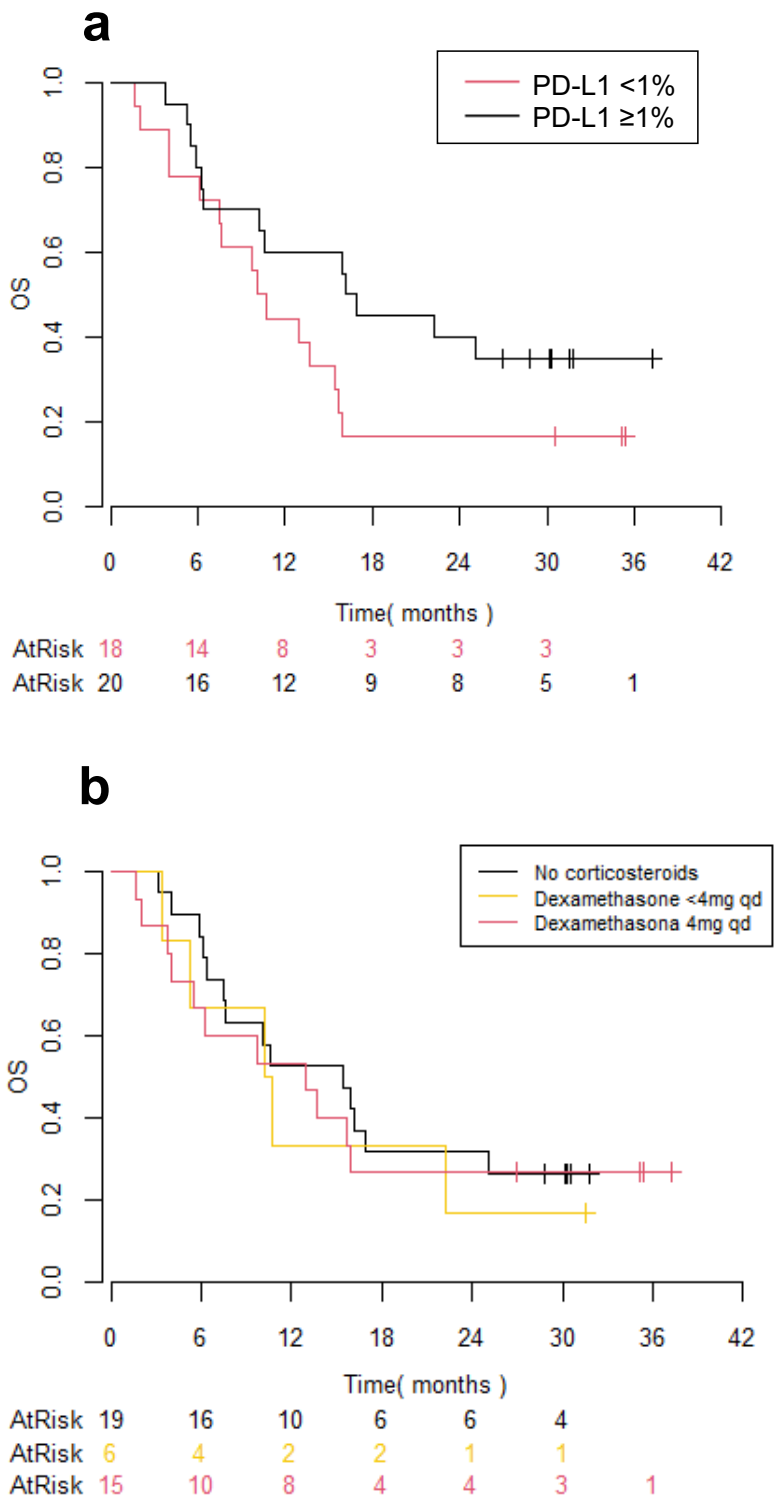
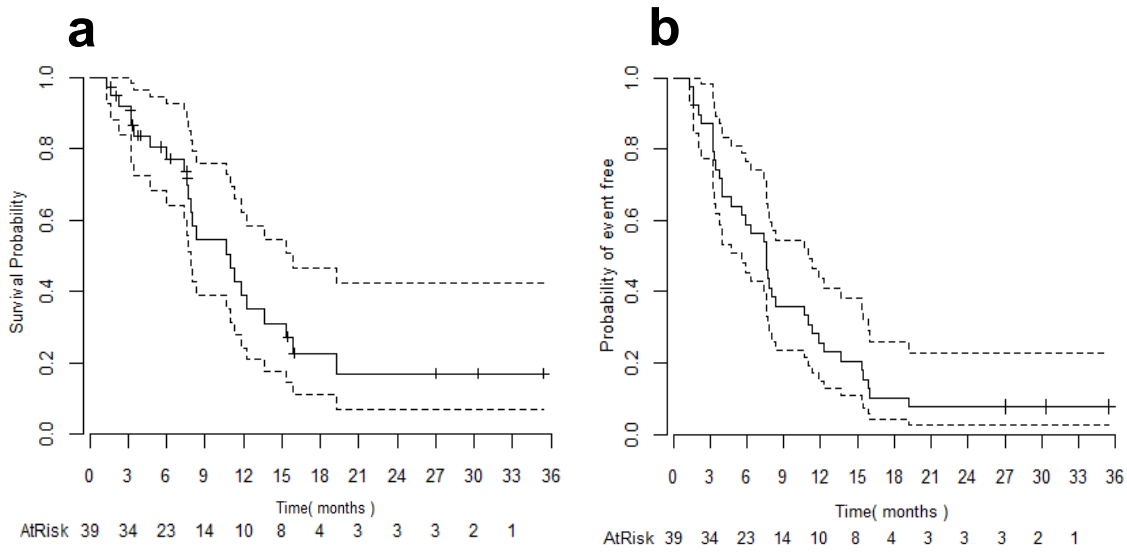
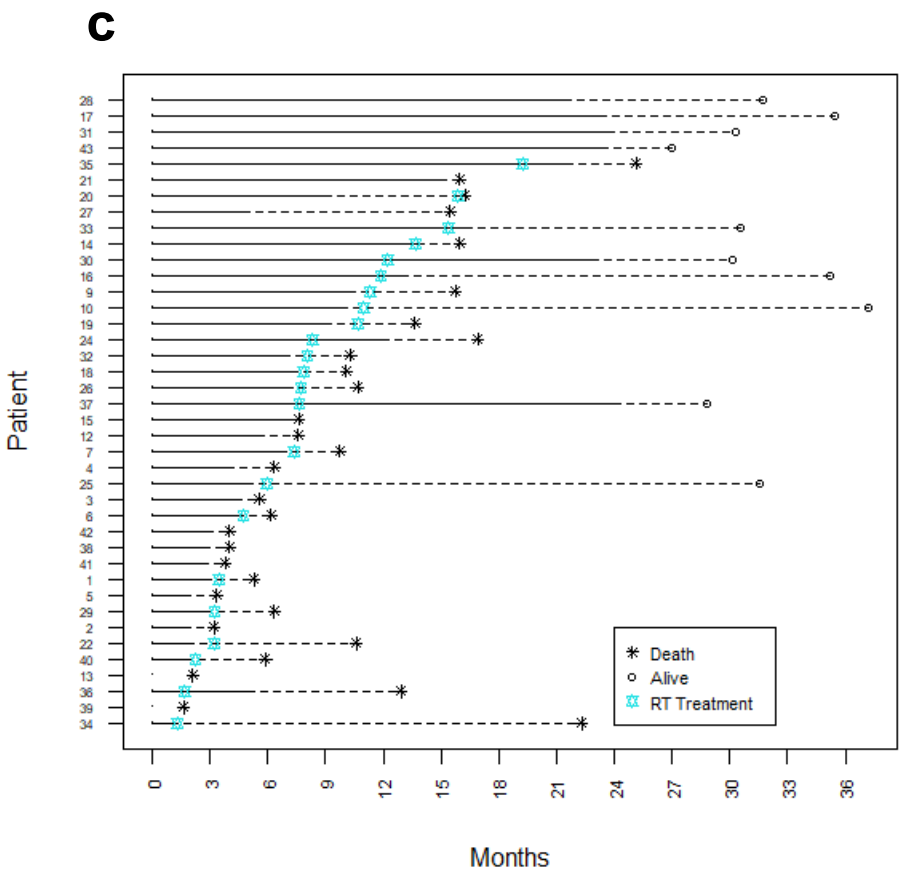


Supplementary Figure S7. Kaplan-Meier estimates of time to brain radiotherapy (a) and event-free survival (b). Dotted lines indicate 95% confidence intervals. Swimmer plot showing the time from treatment initiation to any brain radiotherapy or death (c). Continuous lines represent follow-up within the study, while dashed lines represent survival follow-up after disease progression. In two patients, in which tumor assessment was not performed, the continuous lines were not depicted.





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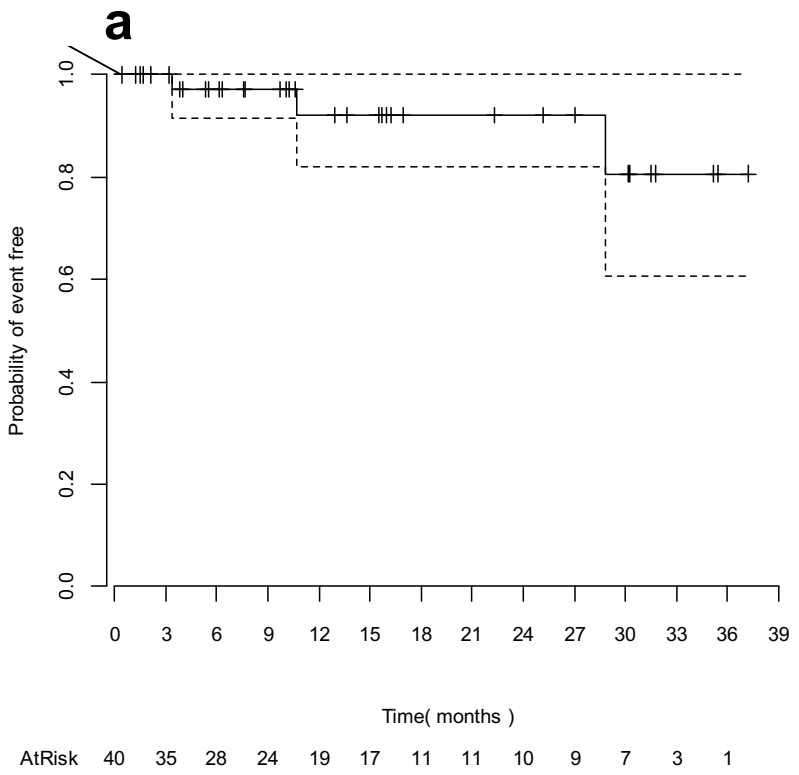

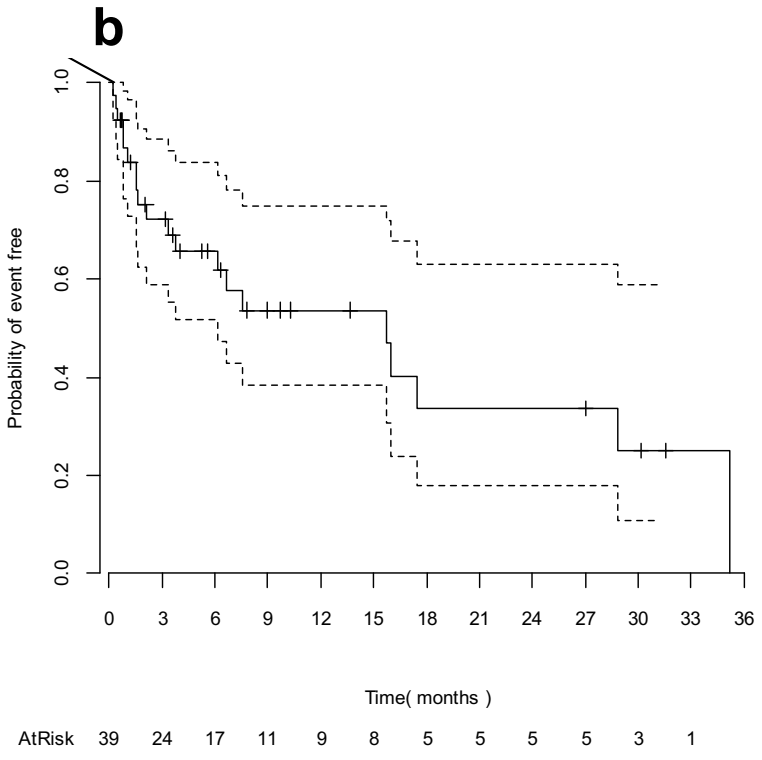

Supplementary Figure S9. Assessment by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30 (QLQ-C30) of Global Health Status (a) and Quality of Life in the previous week (b) at distinct study timepoints. Higher scores indicate a better level of functioning and quality of life.