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EUROPEAN LUNG CANCER CONFERENCE
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EUROPEAN LUNG CANCER CONFERENCE 2016

PCI IN SCLC AND NSCLC

Current Controversies in SCLC

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Multidisciplinary Interactive Session (MIS) ELCC 2016, 15.04.2016, 08:00 - 08:50, Room W

DISCLOSURE SLIDE

Honorarium

AstraZeneca K.K.
Chugai Pharmaceutical Co., Ltd.
Daiichi Sankyo Co. Ltd.
Eli Lilly Japan K.K.
Kyowa Hakko Kirin Co., Ltd.
Mochida Pharmaceutical Co., Ltd.
Nippon Boehringer Ingelheim Co., Ltd
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Research fund

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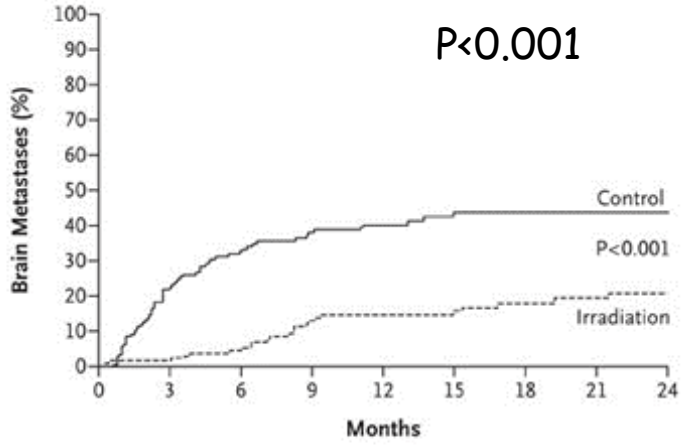
I have no COI on this presentation.

Background PCI-ED-SCLC 1

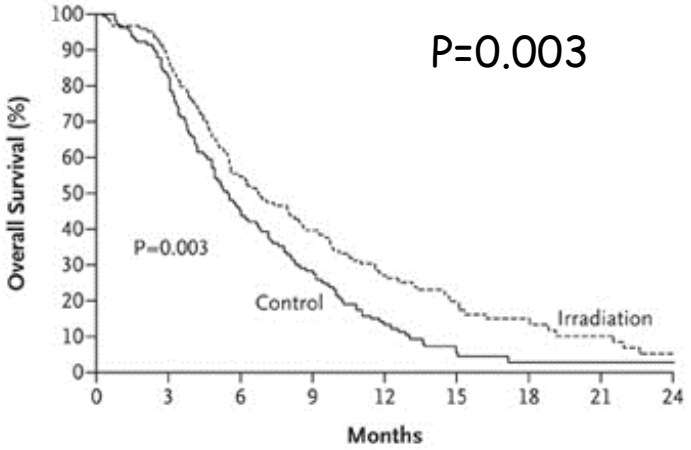
- Prophylactic cranial irradiation (PCI) reduces brain metastasis (BM) and prolongs overall survival (OS) for Limited Disease Small Cell Lung Cancer (LD-SCLC) who achieved a complete response to induction chemotherapy.
  - *Aupérin A, et al. New Engl J Med 1999*

- It has been reported that PCI also reduces the incidence of symptomatic BM and prolongs OS for Extensive Disease Small Cell Lung Cancer (ED-SCLC) who achieved any response to induction chemotherapy.
  - *Slotman B, et al. New Engl J Med 2007*

Time to Symptomatic Brain Metastasis

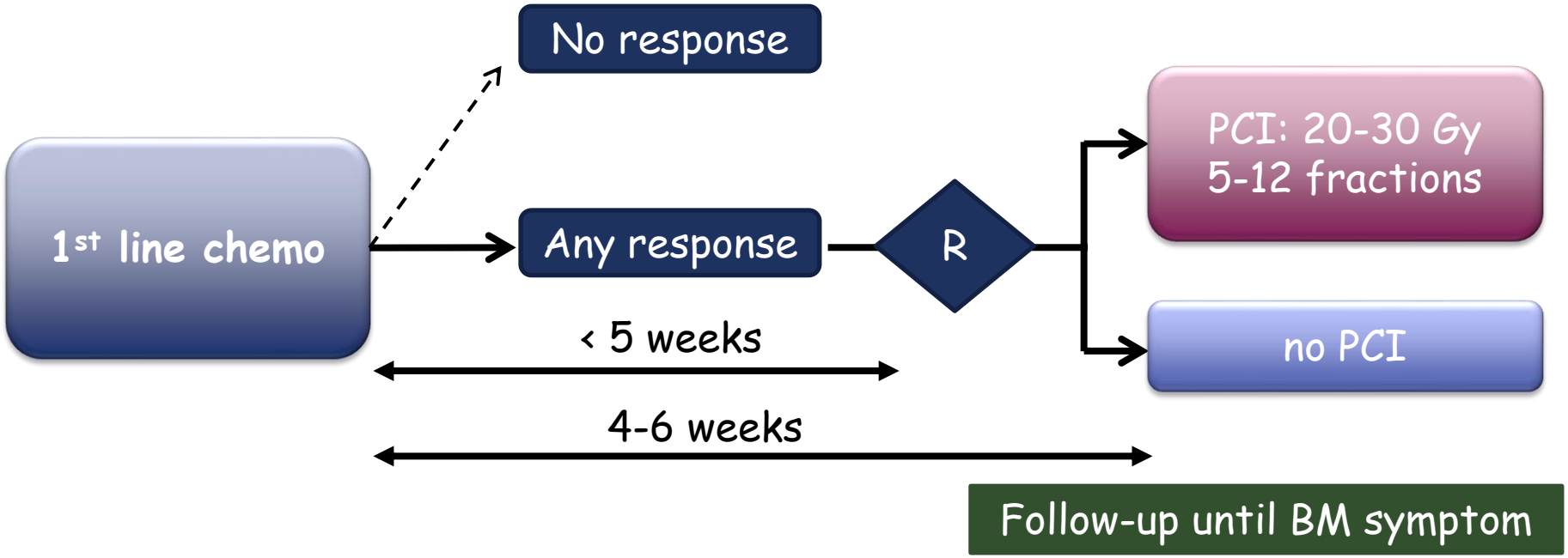


Overall Survival



Background PCI-ED-SCLC 2

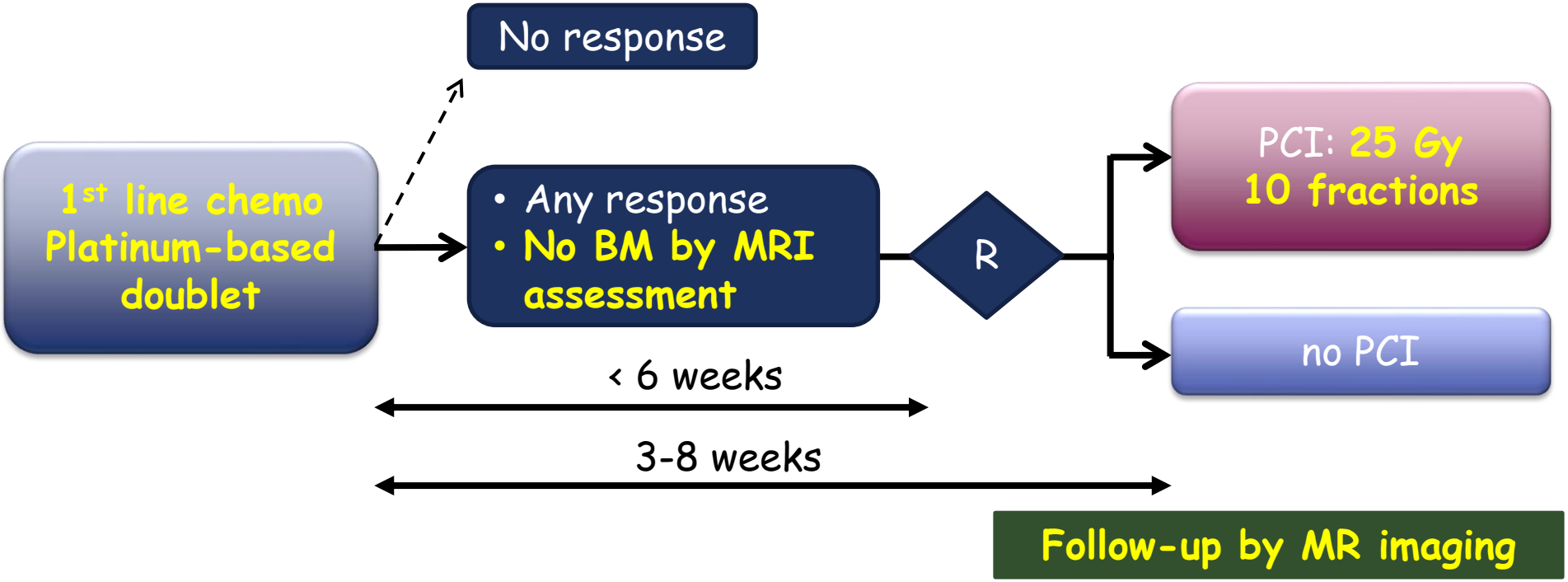
EORTC 22993-08993



Concerns for this study

- Use of 1st line chemotherapy other than platinum
- Lack of imaging assessment to confirm the absence of BM at study enrollment
- Various radiation doses/fractionation in PCI treatment
- Lack of follow-up imaging assessment for BM

Design of Japanese PCI Study



Stratification by Age (70≦ / <70), PS (0-1 / 2), Response (CR / PR+MR), Institutions

Primary endpoint: Overall Survival

Secondary endpoints: Time to BM (evaluated every 3 months)
Progression-Free Survival (PFS)
Safety
Mini Mental State Examination (MMSE)

Key Eligibility Criteria

Inclusion criteria

- Cytologically or Pathologically proven SCLC
- Extensive disease
- Response to 2 or more cycles of platinum-based doublets
- Absence of BM by MRI assessment within 4 weeks at enrollment
- Absence of tumor regrowth within 4 weeks at enrollment
- ECOG PS of 0-2
- Within 6 weeks from the start of last induction chemotherapy
- Written informed consent

Exclusion criteria

- History of irradiation for PCI field
- Double cancer

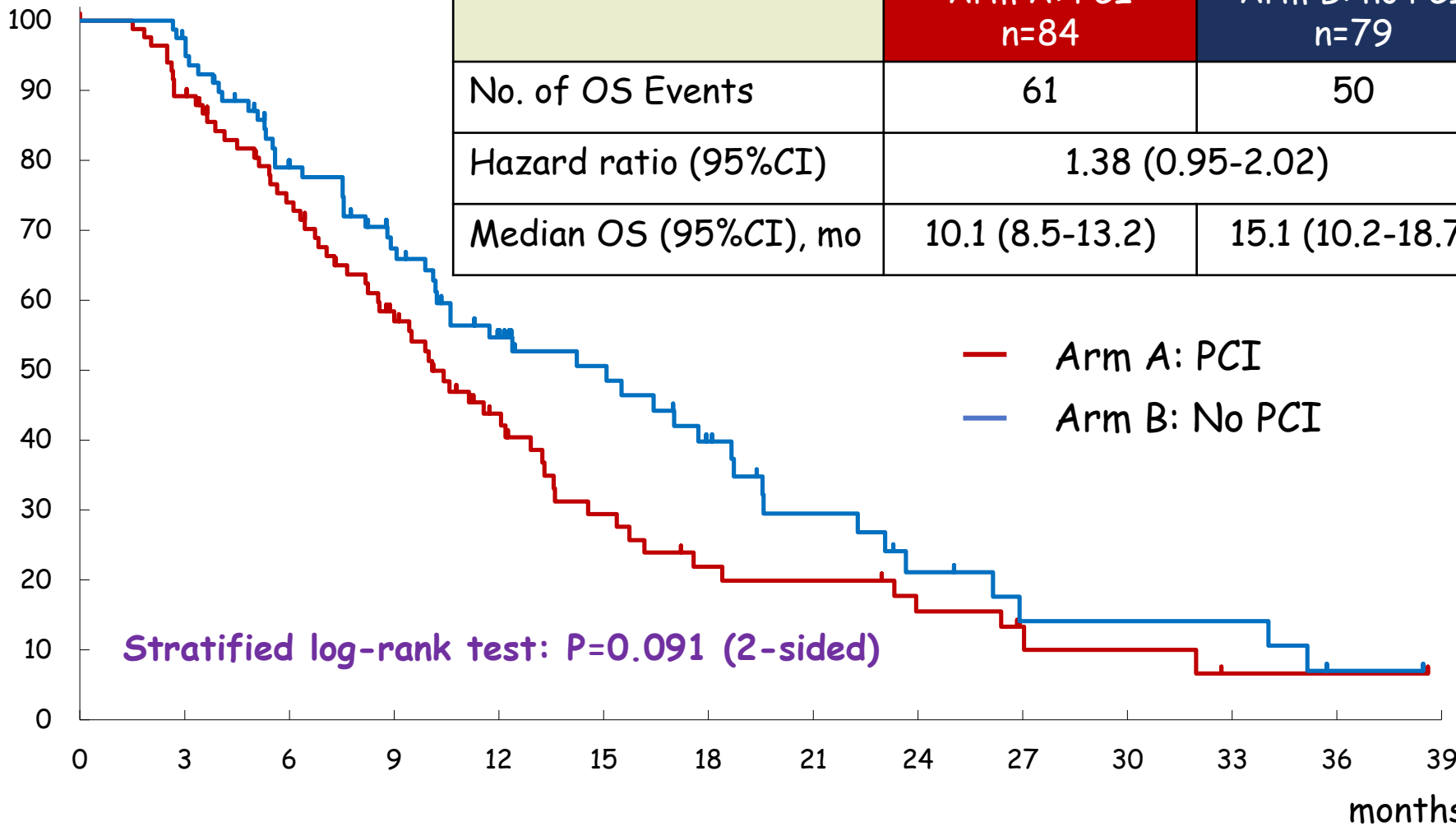
Statistical Considerations

- **Planned sample size**
  - N=330 (299 deaths) to detect a HR of 0.75 with 80% power by log-rank test at a significance level of 0.05
  - Accrual, 6 years; Follow-up, 2 years

- **Interim Analysis**
  - 1st interim analysis was planned when 50% of patients had been enrolled.
  - At this interim analysis, 111 out of 299 (37%) deaths were observed.
  - After IDMC review, this trial was stopped due to futility at 17 July 2013.

Overall Survival at 1st interim analysis

	Arm A: PCI n=84	Arm B: no PCI n=79
No. of OS Events	61	50
Hazard ratio (95%CI)	1.38 (0.95-2.02)	
Median OS (95%CI), mo	10.1 (8.5-13.2)	15.1 (10.2-18.7)



Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial

Ben J Slotman, Harm van Tinteren, John O Praag, Joost L Knegjens, Sherif Y El Sharouni, Matthew Hatton, Astrid Keijser, Corinne Faivre-Finn*, Suresh Senan*

Lancet 2015; 385: 36–42
Published Online

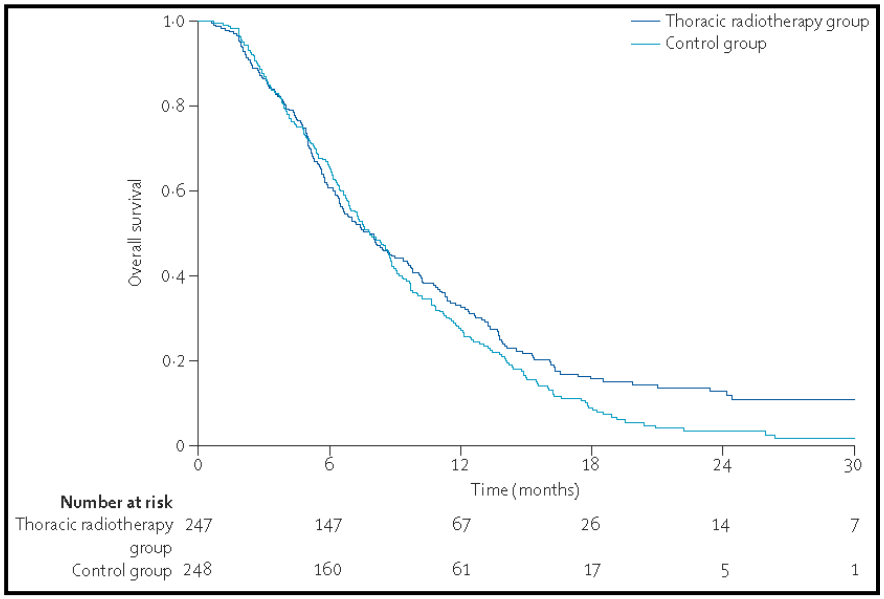
Summary

Background Most patients with extensive stage small-cell lung cancer (ES-SCLC) who undergo chemotherapy, and prophylactic cranial irradiation, have persistent intrathoracic disease. We assessed thoracic radiotherapy for treatment

- ✓ ED-small*
- ✓ ECOG PS 0-2
- ✓ age 18 years or older
- ✓ any response of CTx**

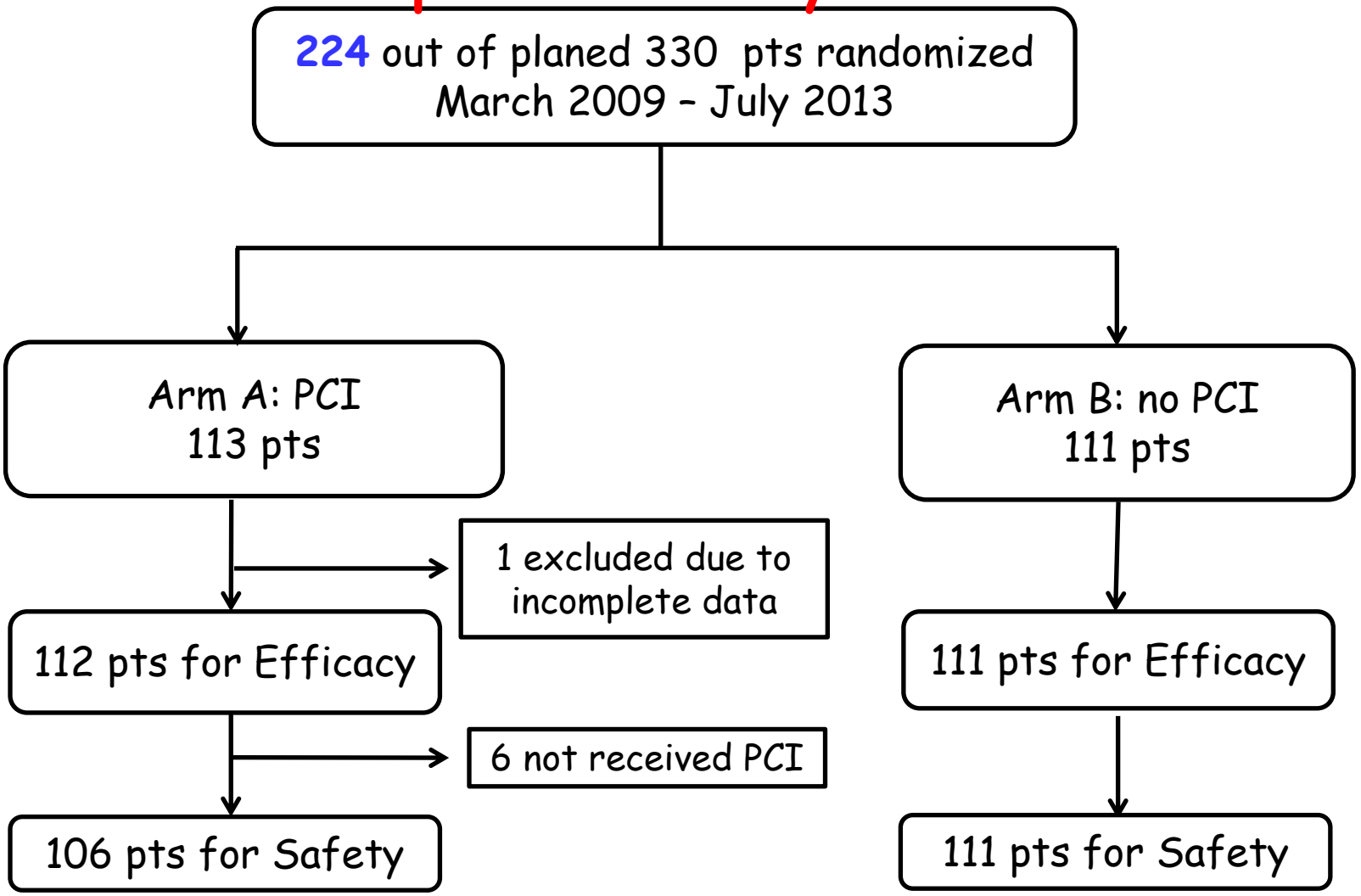
PCI → any response → R n=498

- Thoracic radiation 30 Gy/10 fr n=247
- Observation n=248



CONSORT Diagram

update analyses



Patients Characteristics

		Arm A: PCI n=113		Arm B: no PCI n=111	
Age					
	median	69		69	
	range	43-86		37-86	
Gender					
	man	94	83%	98	88%
	woman	18	17%	13	12%
ECOG PS					
	0-1	108	96%	107	96%
	2	5	4%	4	4%
Response to Chemotherapy					
	CR	13	12%	13	12%
	PR+MR	100	88%	98	88%

1st line Chemotherapy

Regimen	Arm A PCI n=113	Arm B no PCI n=111	Total n=224
CBDCA+etoposide	38	47	85
CDDP+irinotecan	40	32	72
CDDP+etoposide	21	19	40
CBDCA+irinotecan	3	3	6
CBDCA+etoposide -> CDDP+etoposide	4	1	5
CDDP+etoposide -> CBDCA+etoposide	2	2	4
CBDCA+etoposide -> CDDP+irinotecan	2	1	3
CBDCA+amrubicin	1	1	2
CDDP+irinotecan -> CBDCA+etoposide	1	1	2
CBDCA+irinotecan -> CBDCA+etoposide	0	1	1
CBDCA+irinotecan -> CDDP+irinotecan	0	1	1
CDDP+irinotecan -> CBDCA+irinotecan	0	1	1
CDDP+amrubicin	1	0	1
CDDP+topotecan	0	1	1

Delivery of PCI (25Gy in 10fr)

Total exposure	Arm A: PCI n=106
= 25 Gy	106
< 25 Gy	0
> 25 Gy	0

Duration of PCI	Arm A: PCI n=106
median	14 days
range	12-28 days

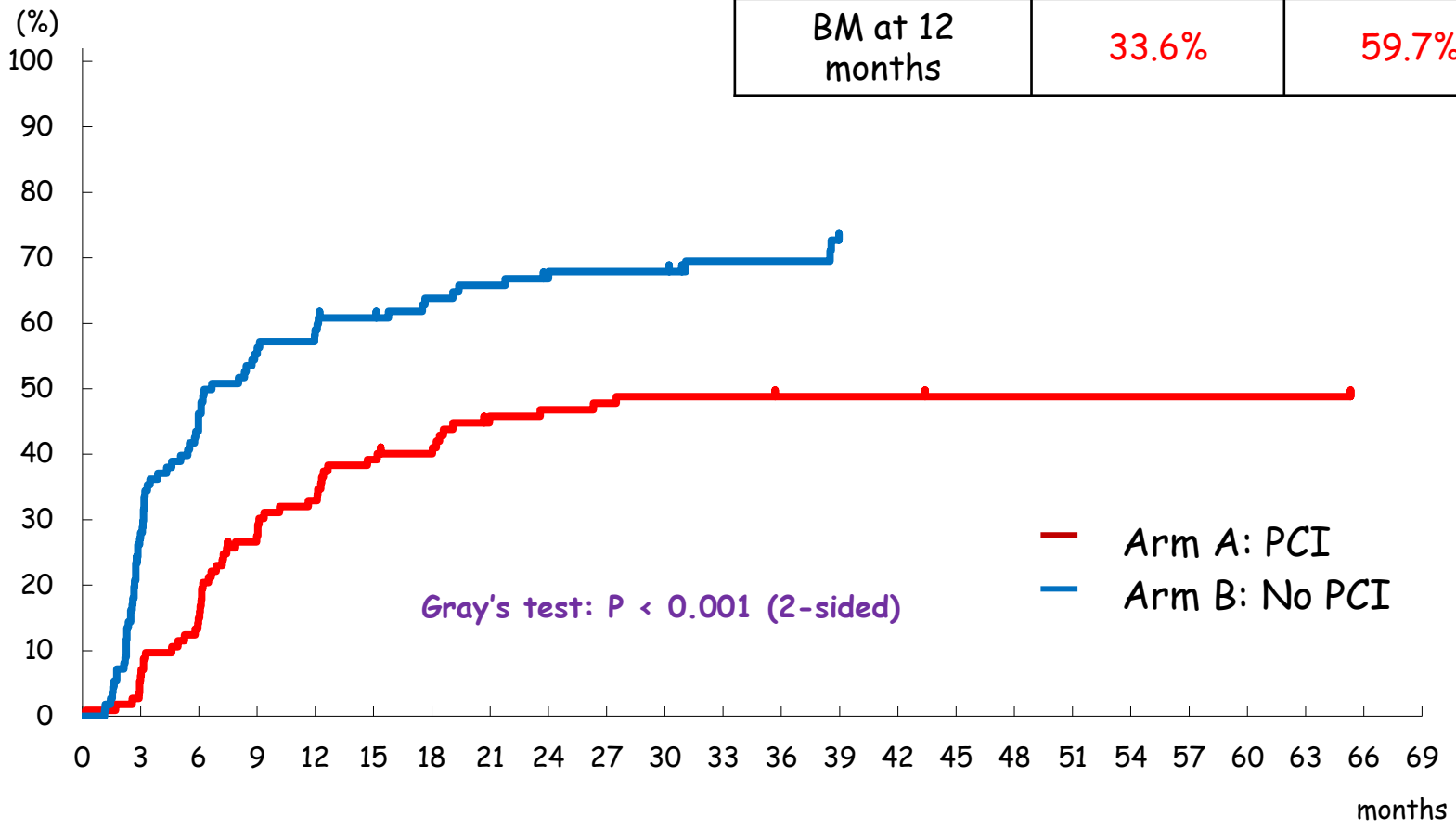
Adverse Events with PCI

	Arm A: PCI n=106 (At randomization)			Arm A: PCI n=106 (Worst Gr during PCI)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
alopecia	25%	0%	0%	25%	0%	0%
dermatitis	4%	0%	0%	4%	0%	0%
headache	3%	0%	0%	3%	0%	0%
anorexia	14%	5%	0%	21%	9%	1%
nausea	0%	1%	0%	13%	4%	0%
vomiting	0%	1%	0%	1%	2%	0%
dizziness	2%	1%	0%	2%	2%	0%
malaise	8%	4%	0%	17%	4%	0%
lethargy	2%	2%	0%	3%	3%	0%

CTCAE ver. 3.0

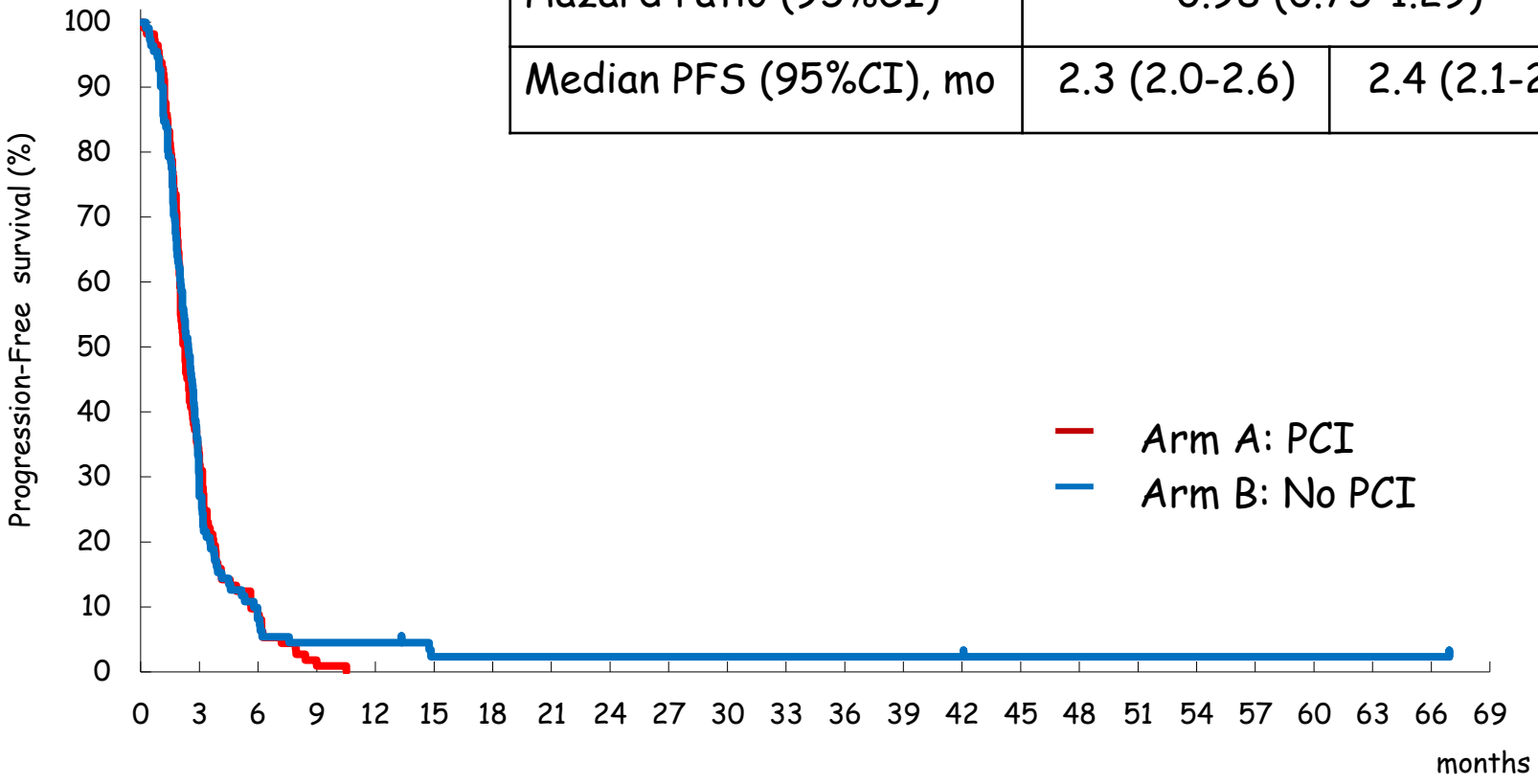
Time to Brain Metastasis

	Arm A: PCI n=113	Arm B: no PCI n=111
BM at 12 months	33.6%	59.7%



Progression-Free Survival

	Arm A: PCI n=112	Arm B: no PCI n=111
No. of PFS Events	113	108
Hazard ratio (95%CI)	0.98 (0.75-1.29)	
Median PFS (95%CI), mo	2.3 (2.0-2.6)	2.4 (2.1-2.7)

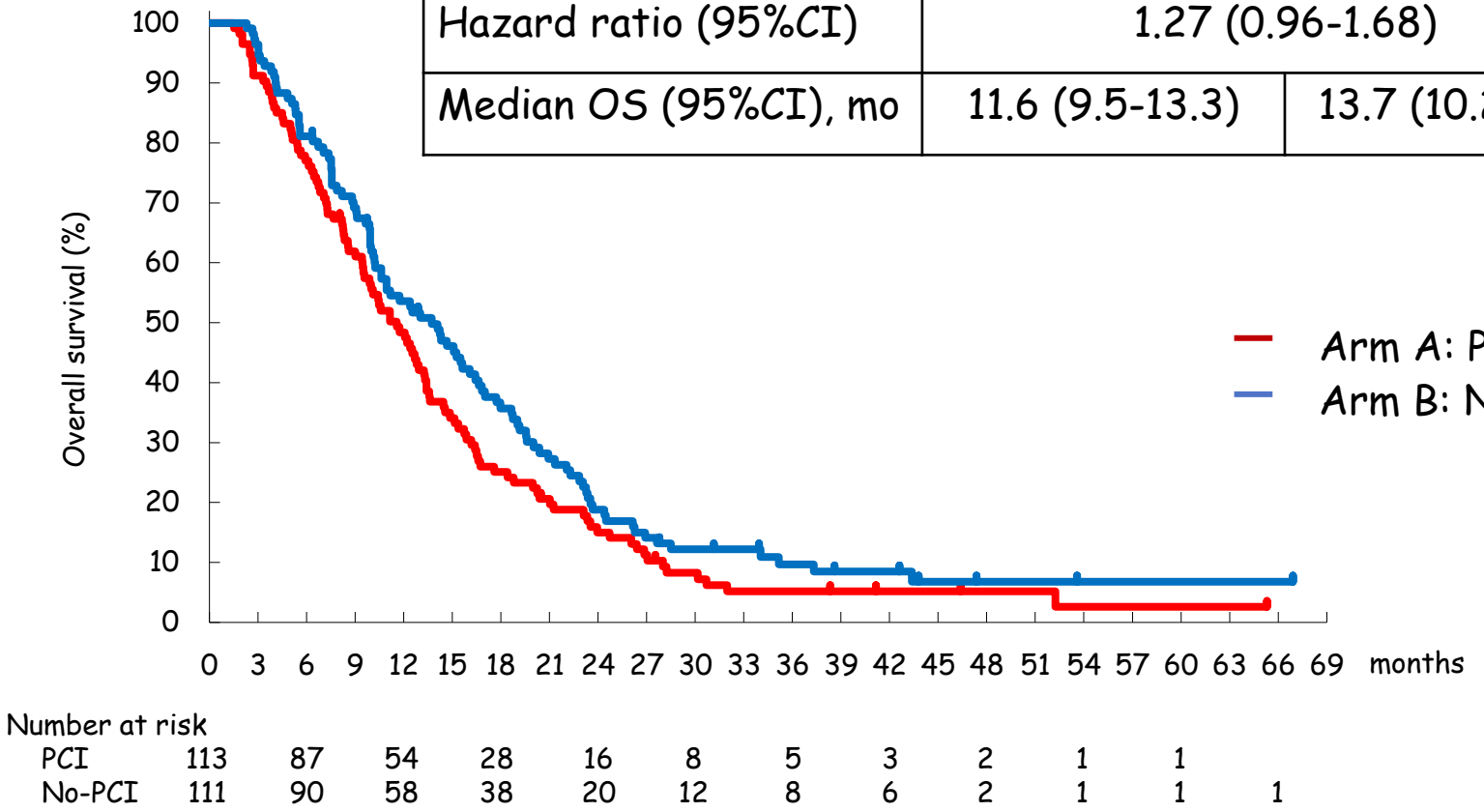


Post-Study Therapy

	Arm A: PCI n=113	Arm B: no PCI n=111
Brain Irradiation	25 (22%)	64 (58%)
2nd line chemotherapy	99 (88%)	99 (89%)
Single agent	69	67
Platinum-based doublet	24	29
Cisplatin + irinotecan + etoposide	5	3
Other	1	0
3rd line chemotherapy	56 (50%)	68 (61%)
Single agent	38	47
Platinum-based doublet	15	17
Other	3	4
4th line chemotherapy	29 (26%)	40 (36%)
Single agent	16	27
Platinum-based doublet	13	12
CODE	0	1

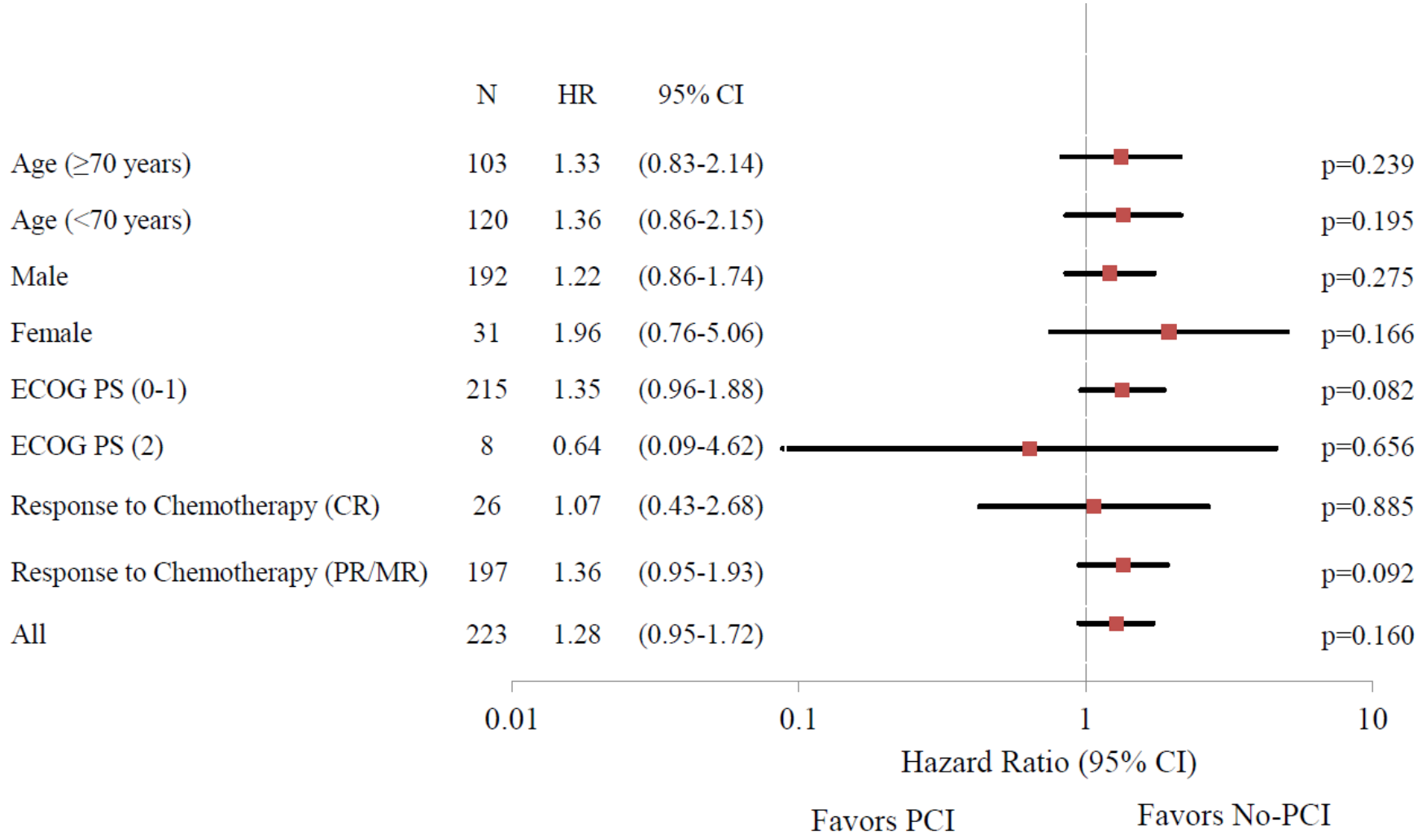
Overall Survival

	Arm A: PCI n=113	Arm B: no PCI n=111
No. of OS Events	106	99
Hazard ratio (95%CI)	1.27 (0.96-1.68)	
Median OS (95%CI), mo	11.6 (9.5-13.3)	13.7 (10.2-16.4)

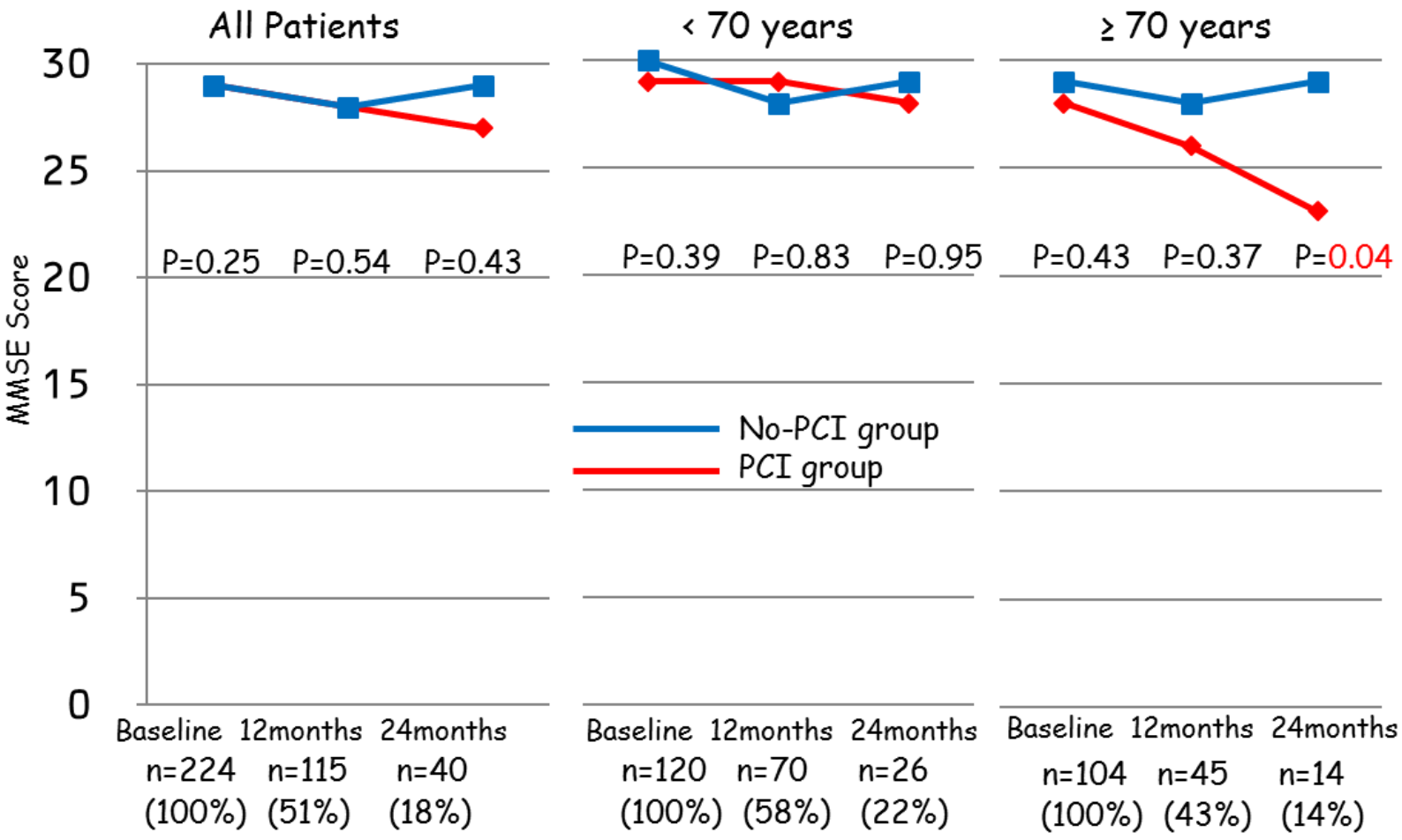


Stratified log-rank test: P=0.093 (2-sided)

Overall Survival subset analyses



Mini Mental State Examination



Summary

- Japanese study was early terminated because of futility based on the results of 1st interim analysis.
- Final data shows bellow.
- PCI significantly reduced the risk of BM.
  - 33.6% vs 59.7% at 12 months in the PCI and no PCI arms
- PFS was comparable between the two arms.
  - The median was 2.3 vs. 2.4 months. HR=0.98 (0.75-1.28)
- OS was not improved by PCI
  - The median was 11.6 vs. 12.1 months. HR=1.28 (0.95-1.72)
- Increase of AEs was observed in PCI arm.

Discussion

	EORTC	Japanese
Results		
Survival	better	not better
Progression free survival	better	comparable
Time to brain metastases	better	better
Study design		
Primary endpoint	QoL	survival
MRI at enrollment	no	yes
Induction chemotherapy	including non platinum	platinum doublets
PCI dose and fraction	various	2.5Gy x 10fr
Follow up	symptom	image

Major difference between EORTC and Japanese trials is exclusion of the pts with asymptomatic BM by MRI.

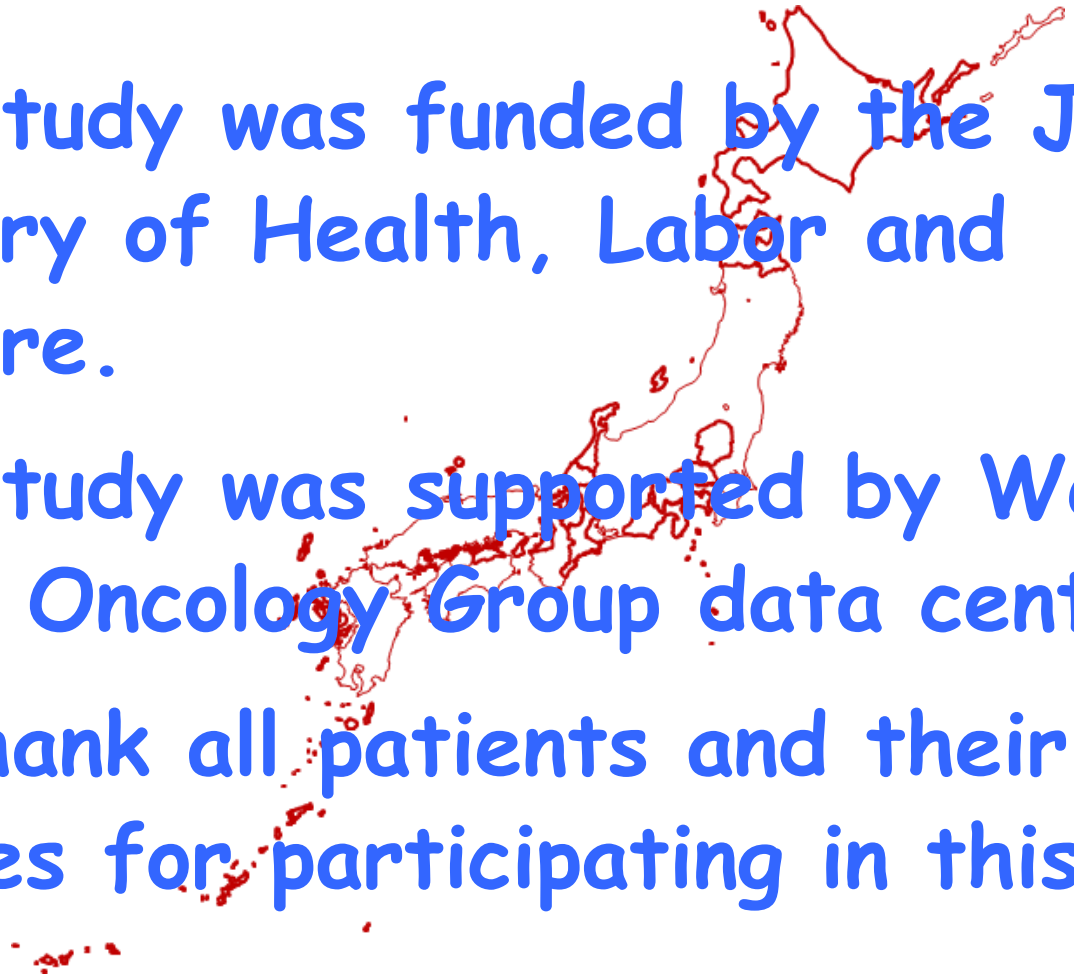
TAKE HOME MESSAGE

PCI did not show the survival benefit for

ED-SCLC patients with a confirmed absence of BM

by MRI.

Acknowledgements



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- We thank all patients and their families for participating in this trial.