Tyrosine Kinase Inhibitors without Radiation Therapy for Brain Metastases from EGFR-mutant Adenocarcinoma of Lung

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Disclosure

We have no conflict of interest to declare.

Background (1)
Standard Treatment of Metastatic Brain Tumors

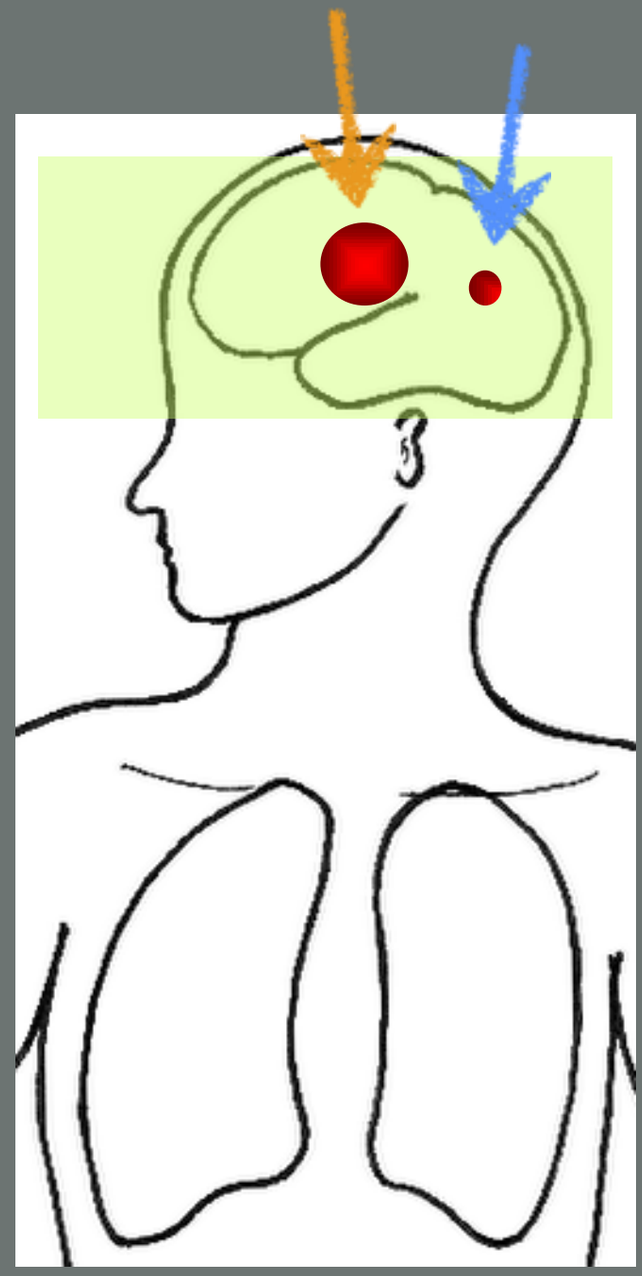
Surgical Removal of large lesions

and/or

Stereotactic Radiosurgery for small lesions

followed by

WBRT (Whole Brain Radiation Therapy)

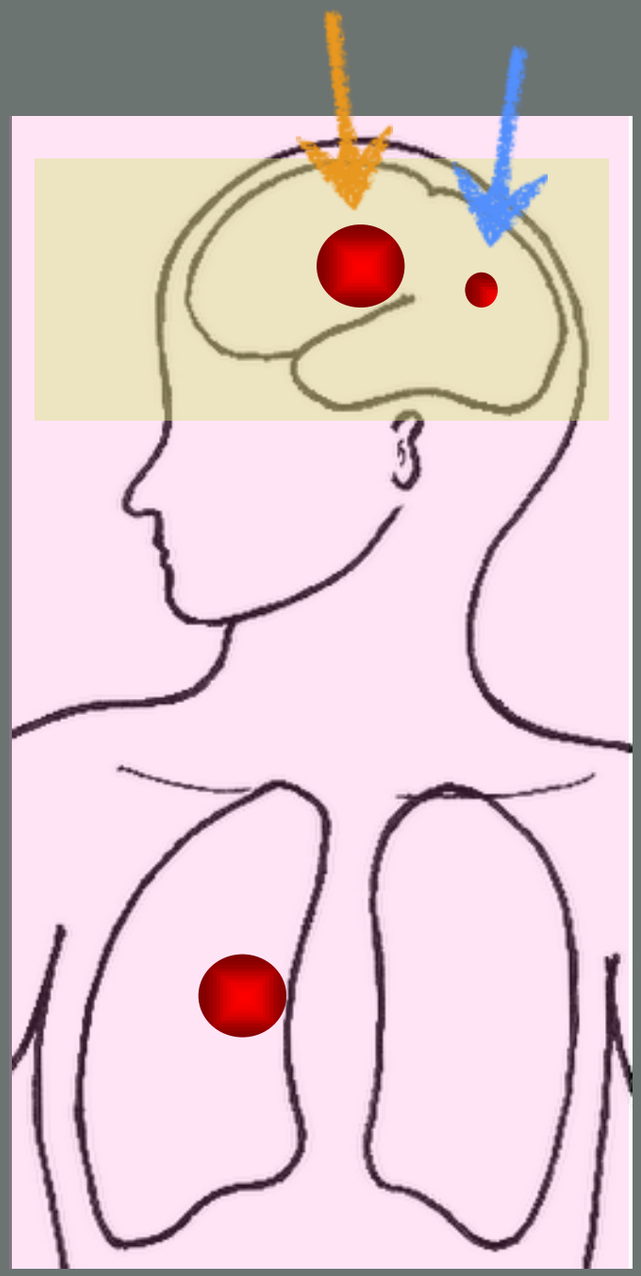


WBRT increased the risk of decline in learning & memory functions at 4 months

Chang EL et al., Lancet Oncology 2009

VIENNA 2012 ESMO congress

Background (1)
Standard Treatment of Metastatic Brain Tumors



Surgical Removal of large lesions

and/or

Stereotactic Radiosurgery for small lesions

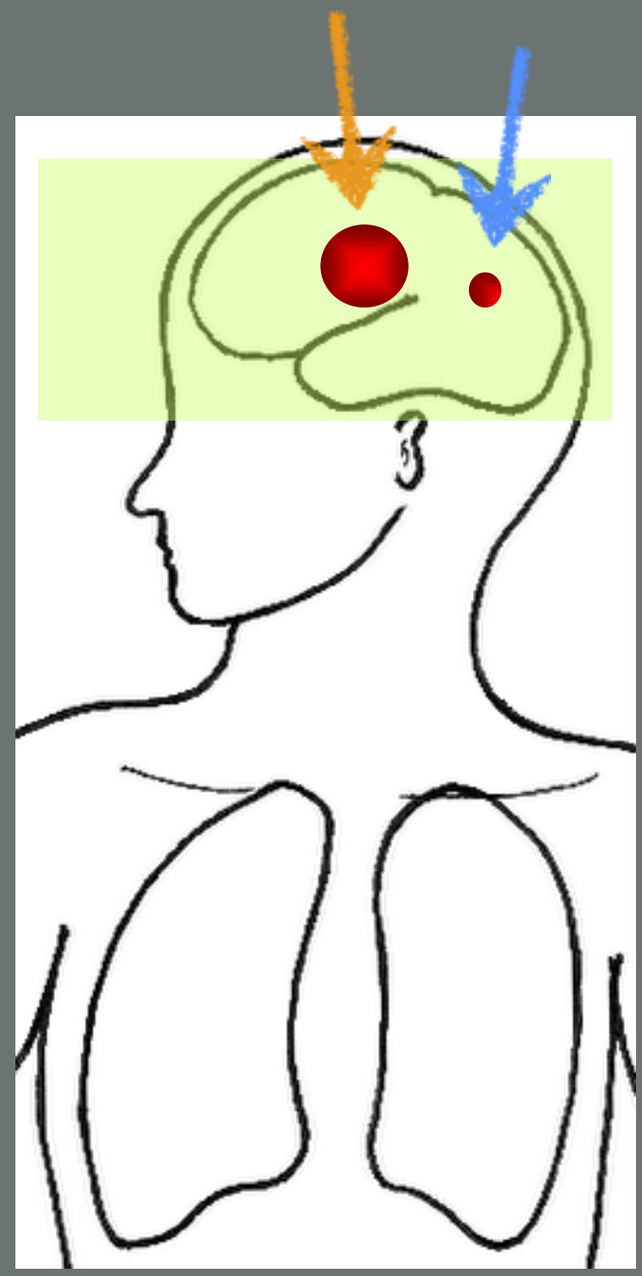
followed by

WBRT (Whole Brain Radiation Therapy)

followed by

Systemic Chemotherapy

for systemic lesions



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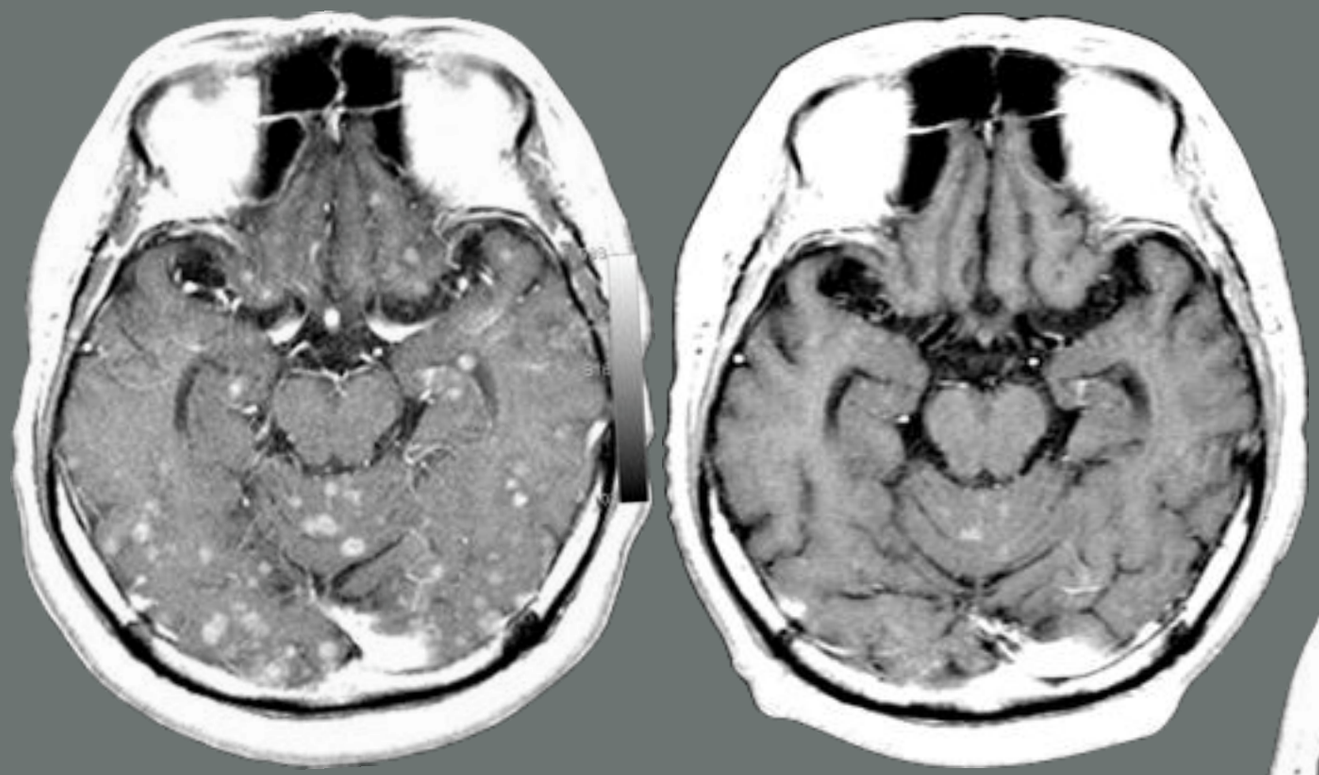
Background (2)
Effect of Chemotherapy for Brain Metastases

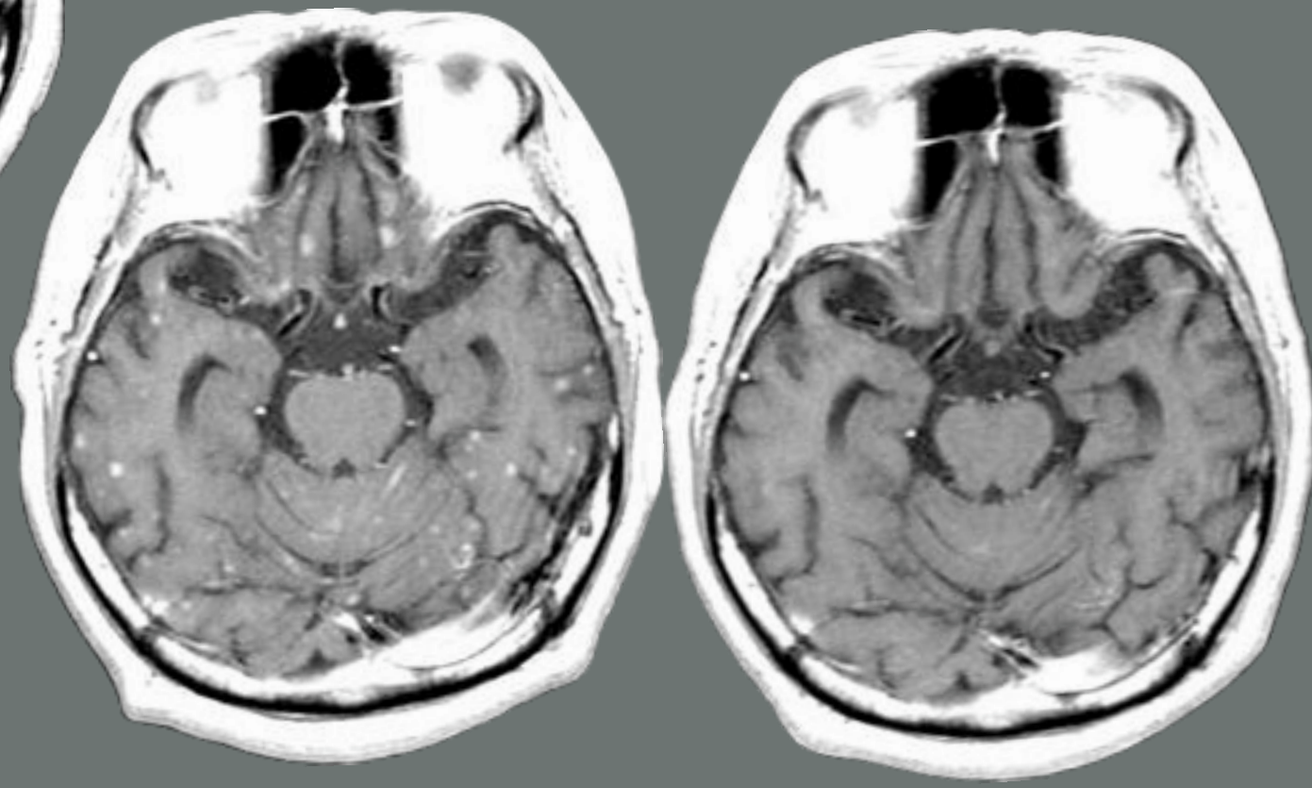
before Treatment

after WBRT



Relapse after WBRT

after Chemotherapy



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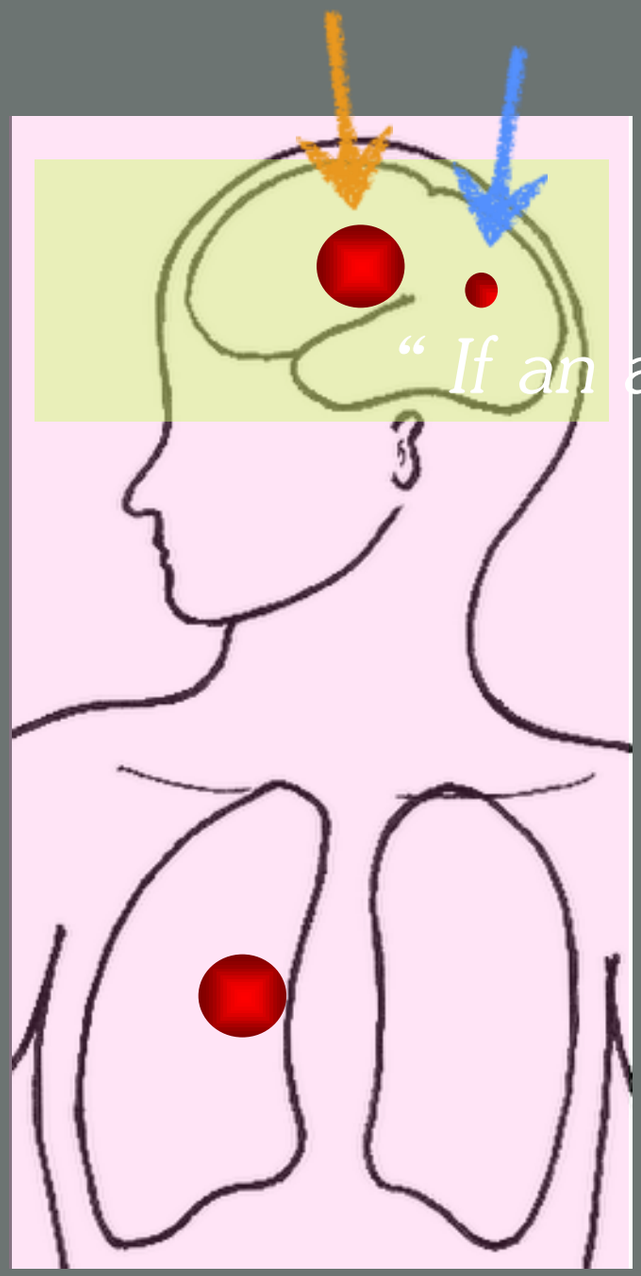
Hypothesis



" If an anti-cancer agent is effective for systemic lesions, it is also effective for intracranial lesions"

Surgical Removal of large lesions and/or

Stereotactic Radiosurgery for small lesions

followed by

WBRT

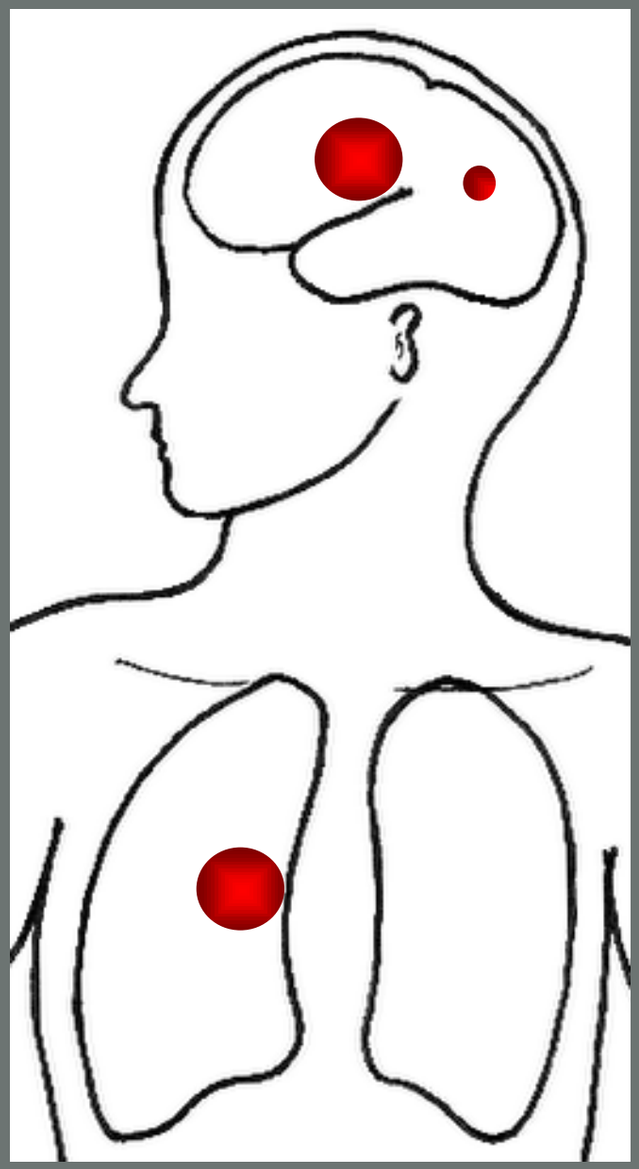
Stereotactic Radiosurgery and/or WBRT

followed by

if necessory...

Systemic Chemotherapy

Inclusion Criteria



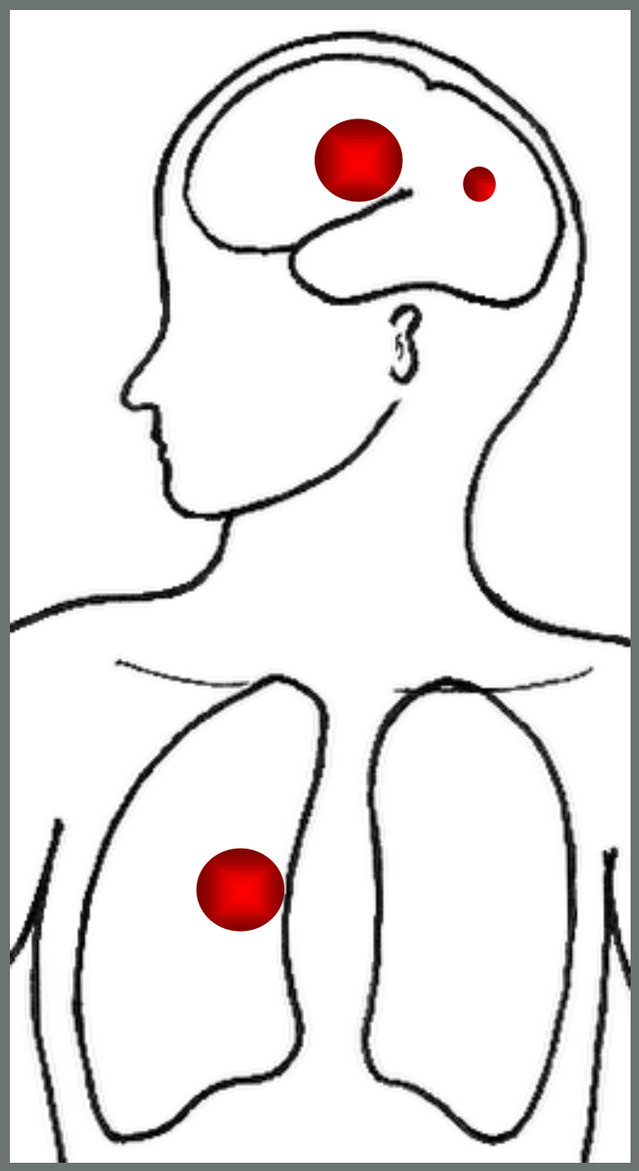
1) Metastatic brain tumors from lung adenocarcinoma

2) EGFR mutation (+)

3) Systemic lesions which require TKIs (+)

4) PS 0-2

Treatment



Brain Metastases (EGFR mutant)

↓

Gefitinib

Tm. Progression
(intracranial/systemic)

↓

Erlotinib

Tm. Progression
(intracranial/systemic)

↓

SRS/SRT and/or WBRT

No indication of CHT
for Systemic Lesions

↓

SRS/SRT and/or WBRT

Follow up & Endpoints

Follow up

MRI: 1.5T, CE, 1.8mm slice thickness, gapless

intervals: 2-3 months

Endpoints

Primary Endpoint: Survival after brain metastases

Secondaly Endpoints: Progression-free Survival

Response to TKIs

Patients

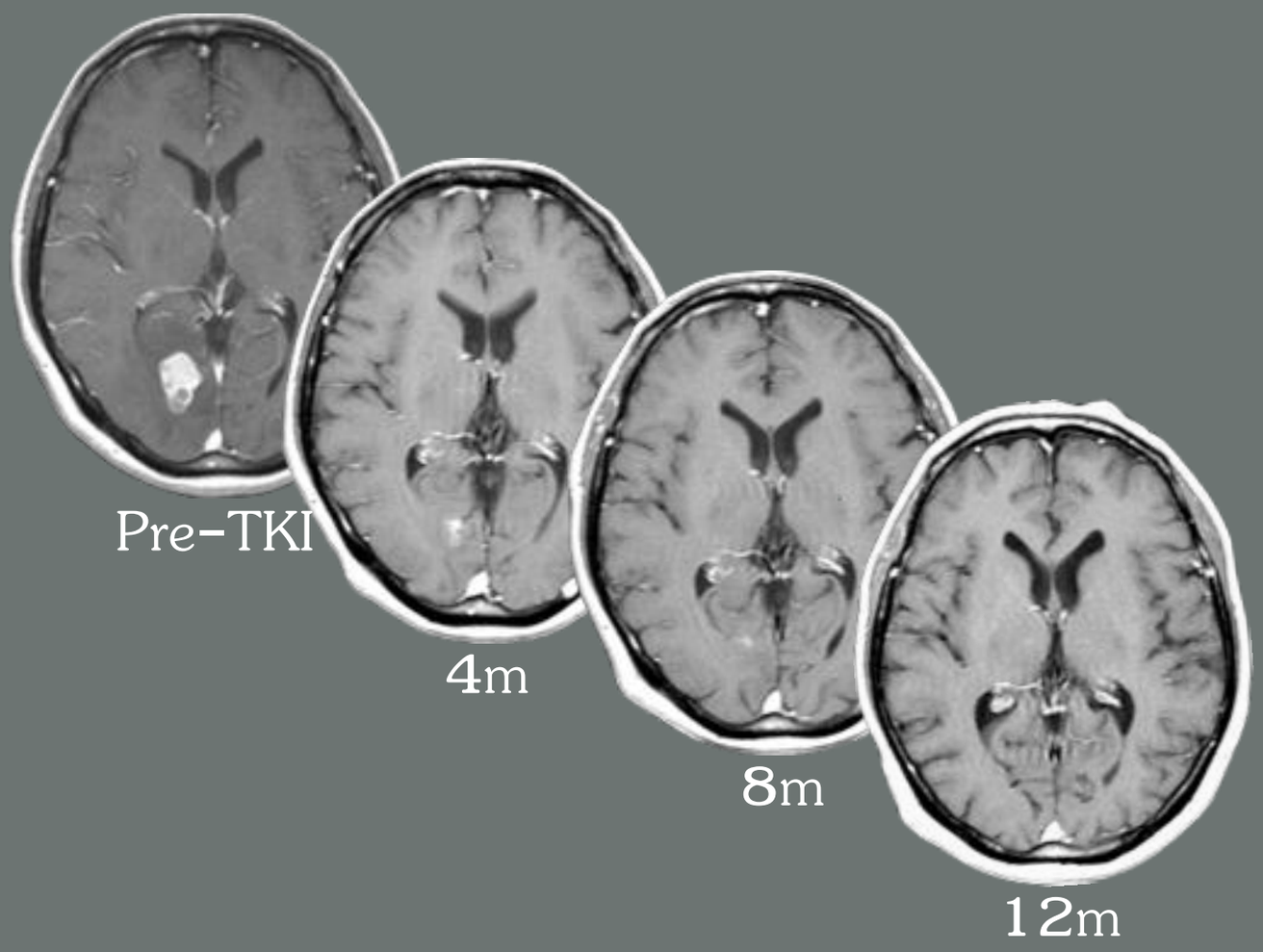
37 Cases

Age (y.o.)	65 (46-81)
Sex (F/M)	26 / 11
No. of Lesions	3 (1-20)
Tm. Size (mm)	7.5 (1.9-25.9)
Previous CHT (yes/no)	8 / 29
Gefitinib	2
CBDCA/GEM	4
CBDCA/PTX	1
CBDCA/VNR	1

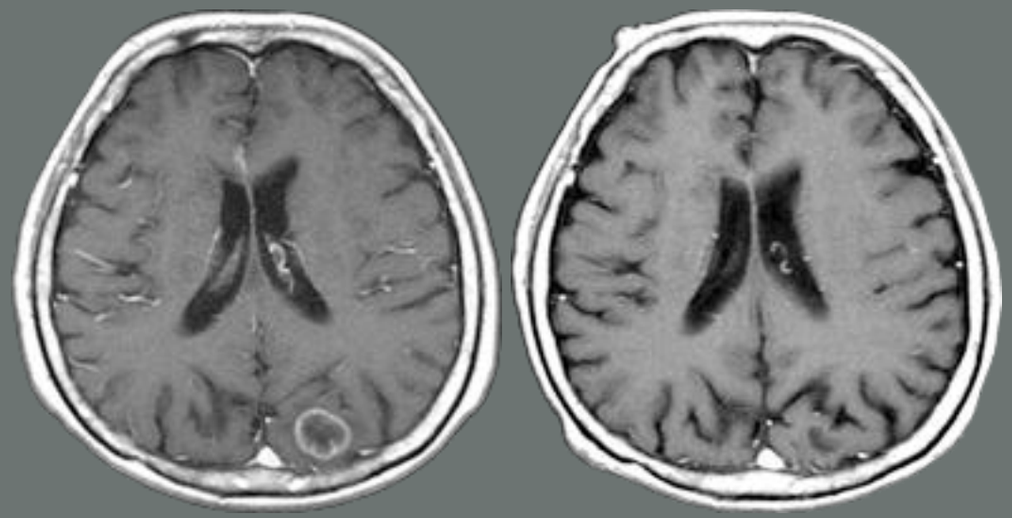
Response

Representative Cases (TKI alone)

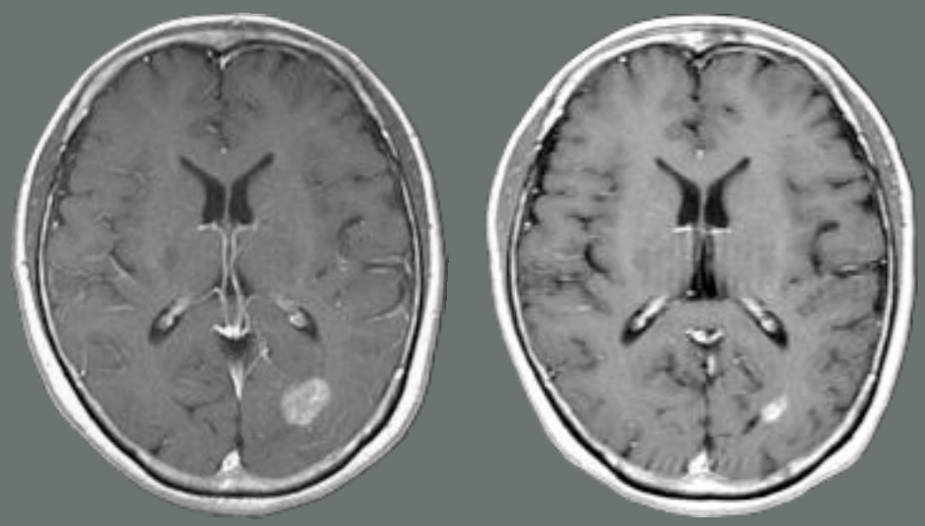
53f Ex21 L858R



73f Ex21 L858R

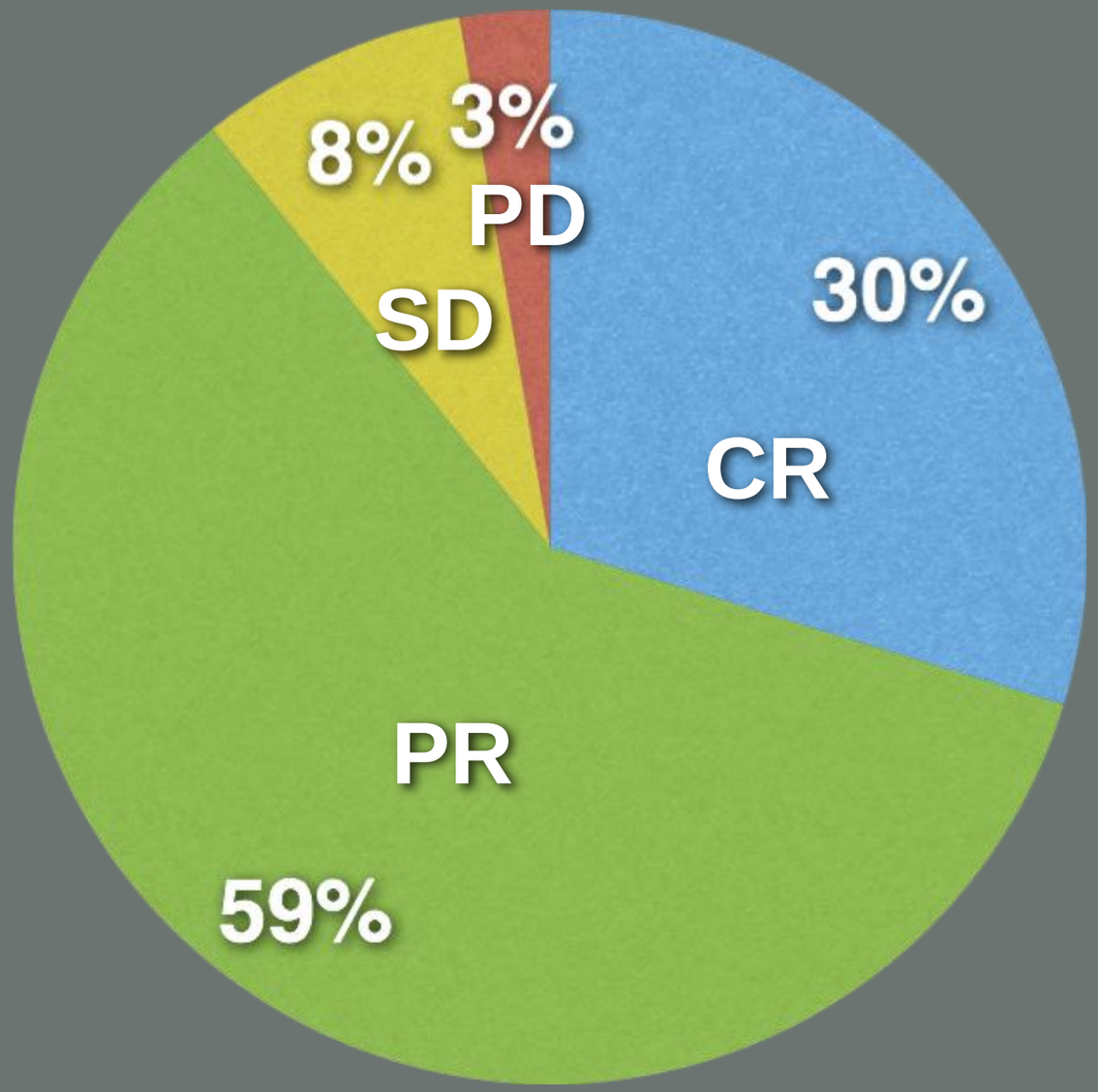


64f Ex19del



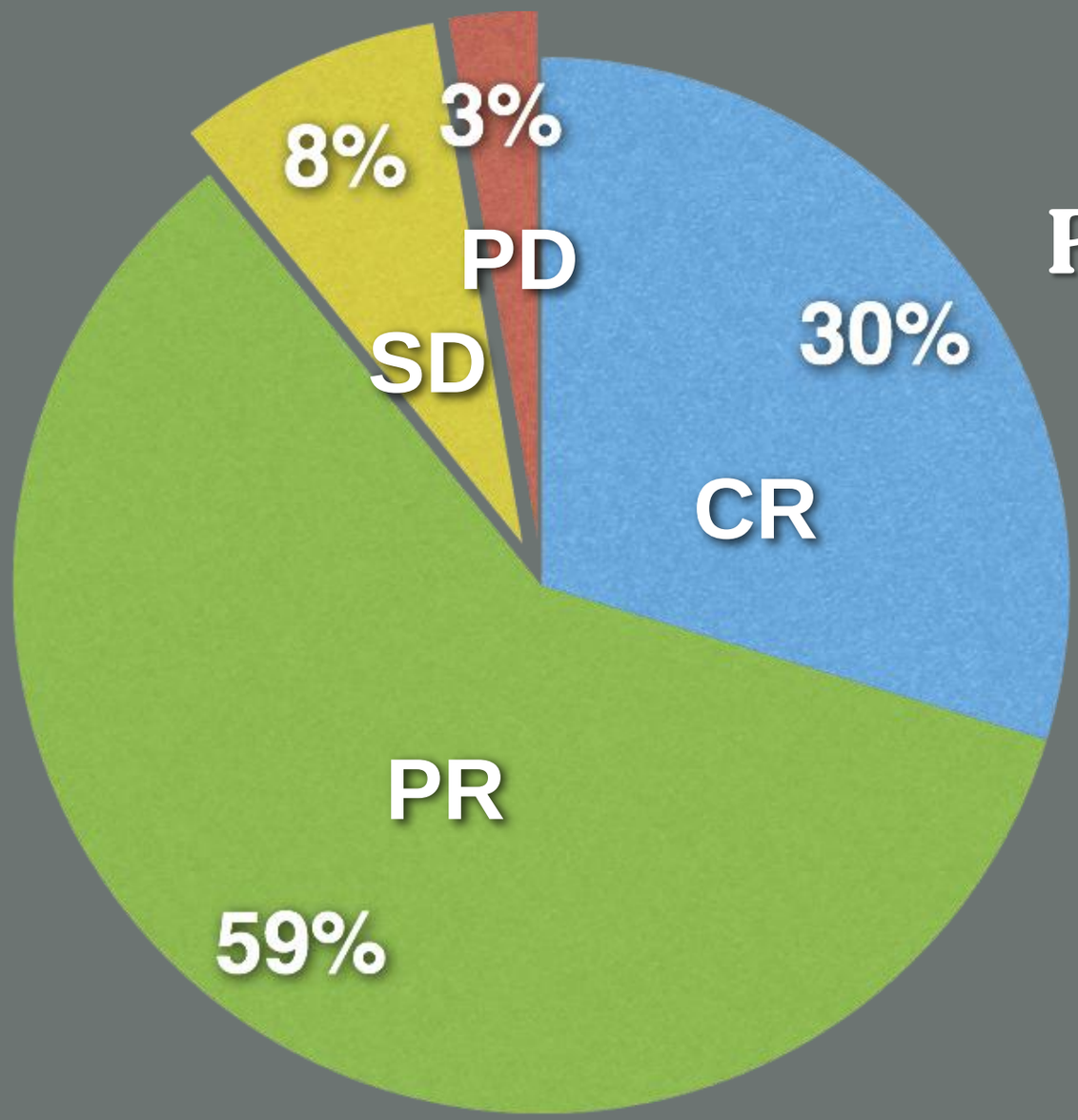
Response

37 Cases



Response

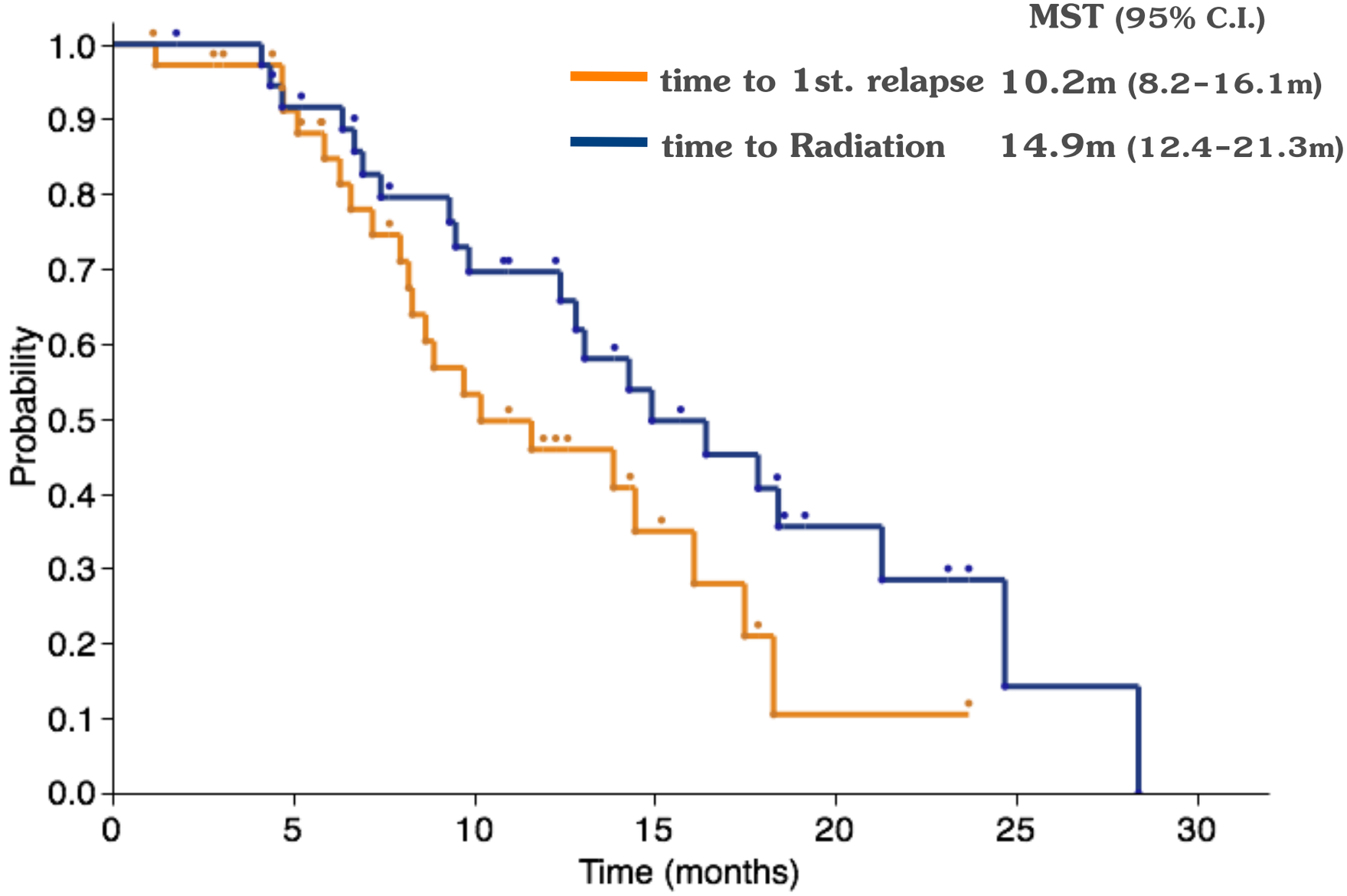
37 Cases



Response Rate

89.2%

Lesion Control



Lesion Control

Variables	High-risk Group	Monovariate			Multivariate		
		R.R.	(95% C.I.)	p	R.R.	(95% C.I.)	p
Age (y.o.)	<60	2.47	(0.90-6.29)	0.076			
Sex (f/m)	f	3.37	(1.27-10.67)	0.014	2.85	(1.03-9.25)	0.044
No. of Lesions	3<	1.95	(0.82-4.97)	0.133			
Max. Size (mm)	<15	1.12	(0.43-3.45)	0.829			
Ex19del/others	others	5.73	(2.00-18.95)	0.001	5.03	(1.71-17.2)	0.003
History of CHT	yes	1.82	(1.61-7.86)	0.309			

Cox's Proportional Hazard Model

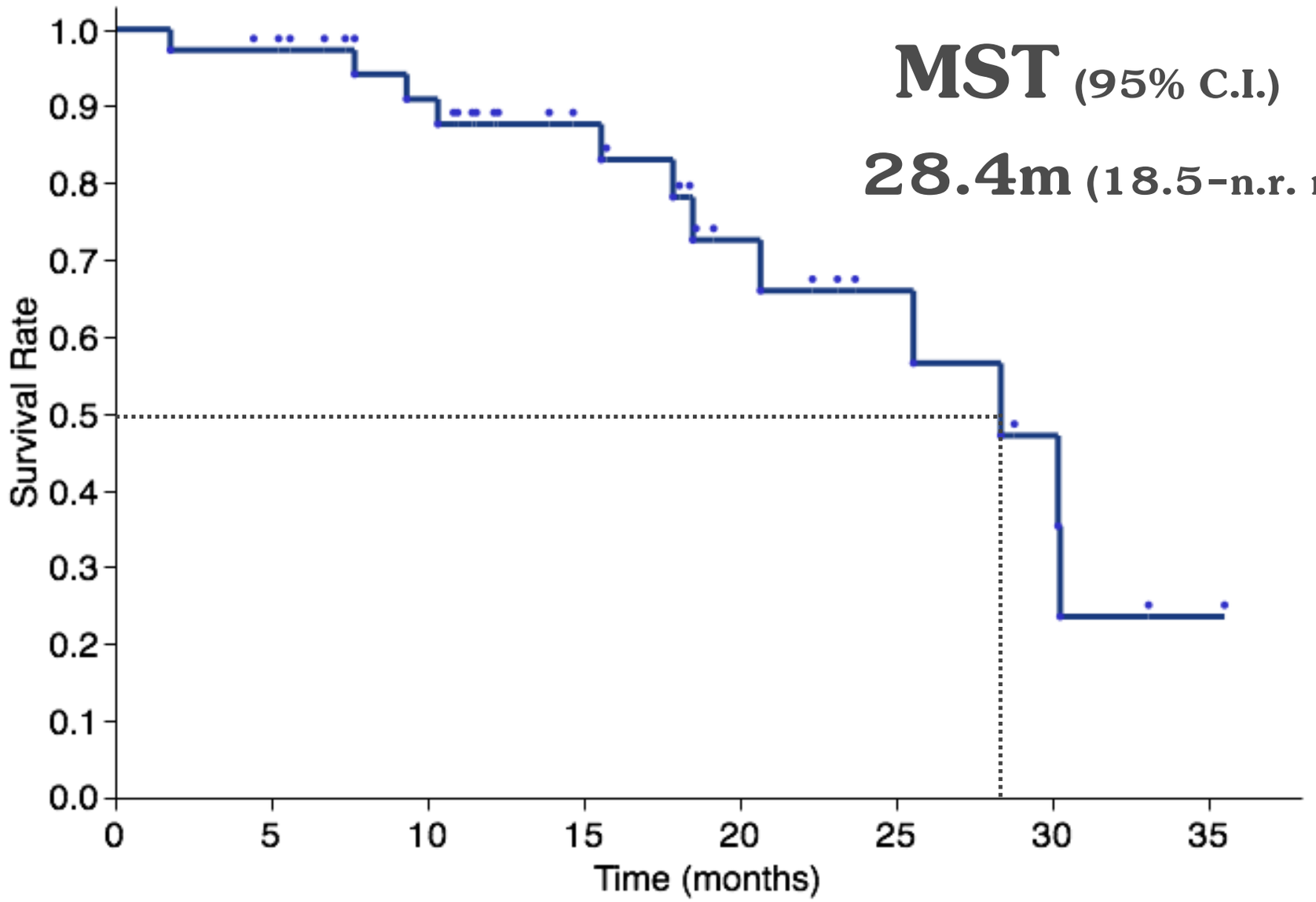
Cause of Withdrawal

30/37 Cases

Progression of Intracranial Lesions	14
Progression of Extracranial Lesions	13
No Extracranial Lesions to Treat	1
Adverse Events	2

Survival

Survival after brain metastases



MST (95% C.I.)

28.4m (18.5-n.r. m)

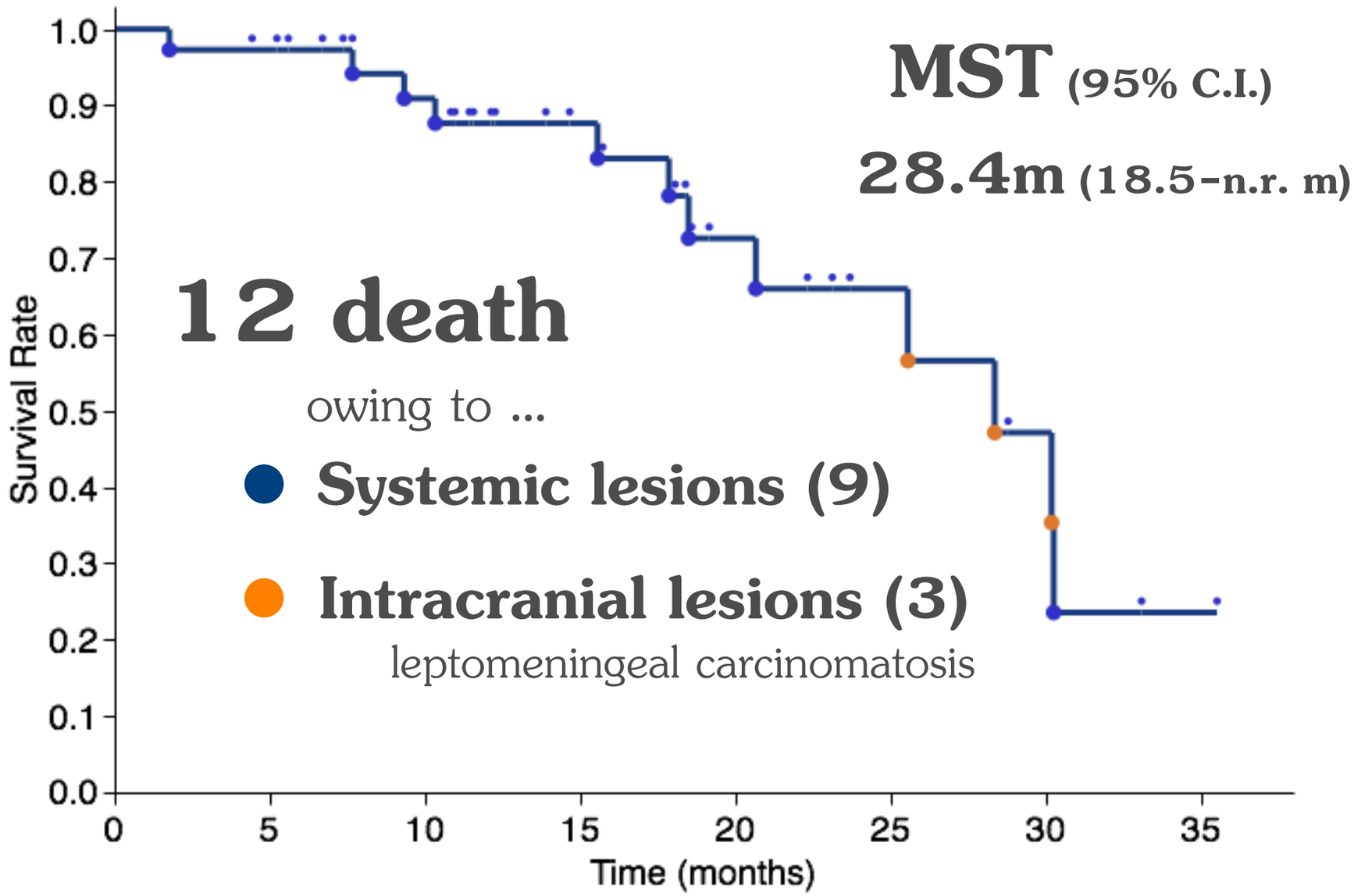
Survival

Variables	High-risk Group	Monovariate R.R. (95% C.I.)		p	Multivariate R.R. (95% C.I.)	p
Age (y.o.)	<60	1.72	(0.45-5.92)	0.392		
Sex (f/m)	f	1.61	(0.50-6.09)	0.434		
PS (0-1/2)	2	9.29	(2.26-45.6)	0.003		
No. of Lesions	<4	1.43	(0.45-4.95)	0.544		
Max. Size (mm)	15<	1.59	(0.42-10.41)	0.528		
Ex19del/others	others	2.23	(0.52-9.15)	0.269		
History of CHT	yes	2.07	(0.29-9.88)	0.417		

Cox's Proportional Hazard Model

Survival

Survival after brain metastases



MST (95% C.I.)

28.4m (18.5-n.r. m)

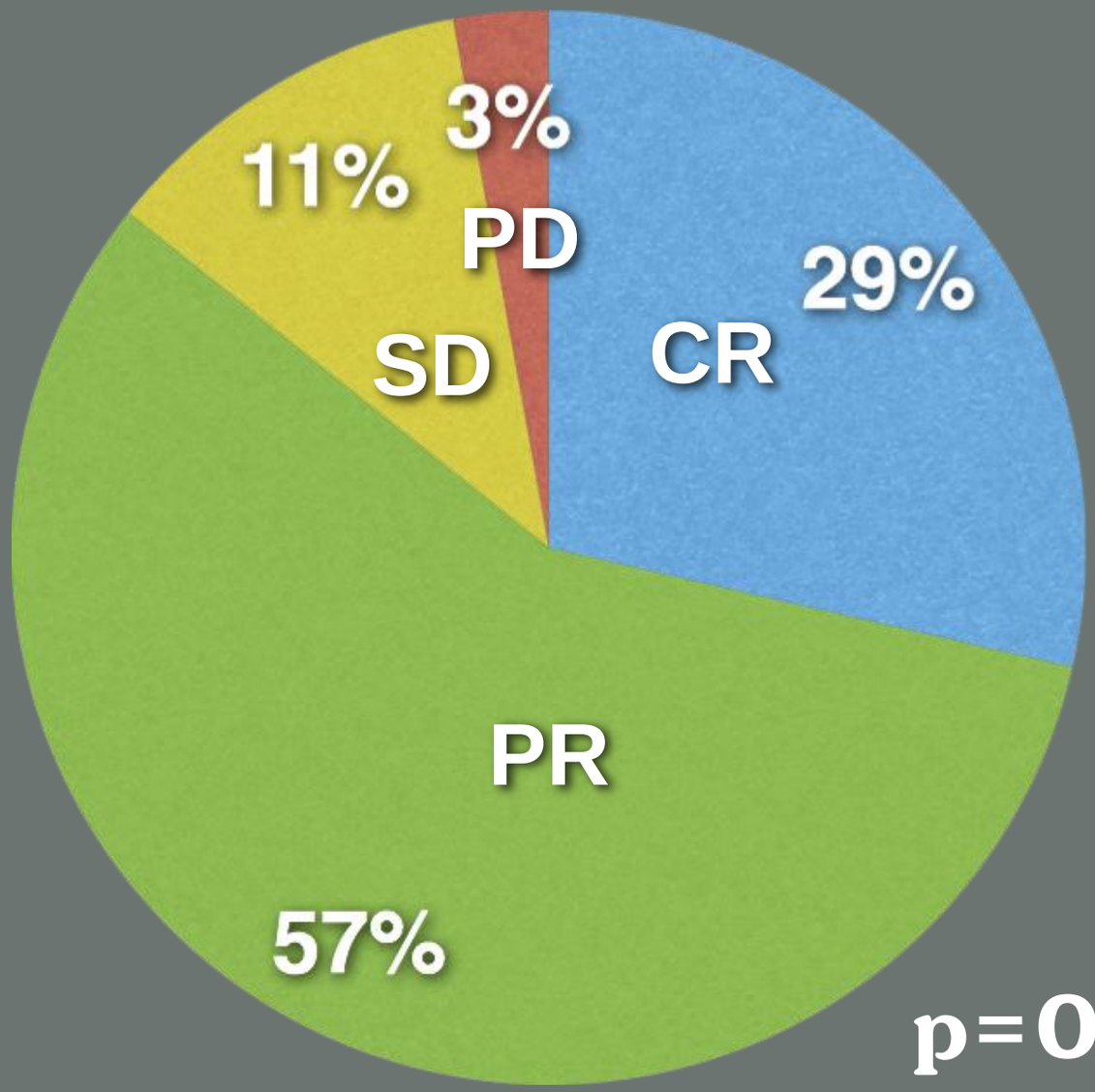
12 death

owing to ...

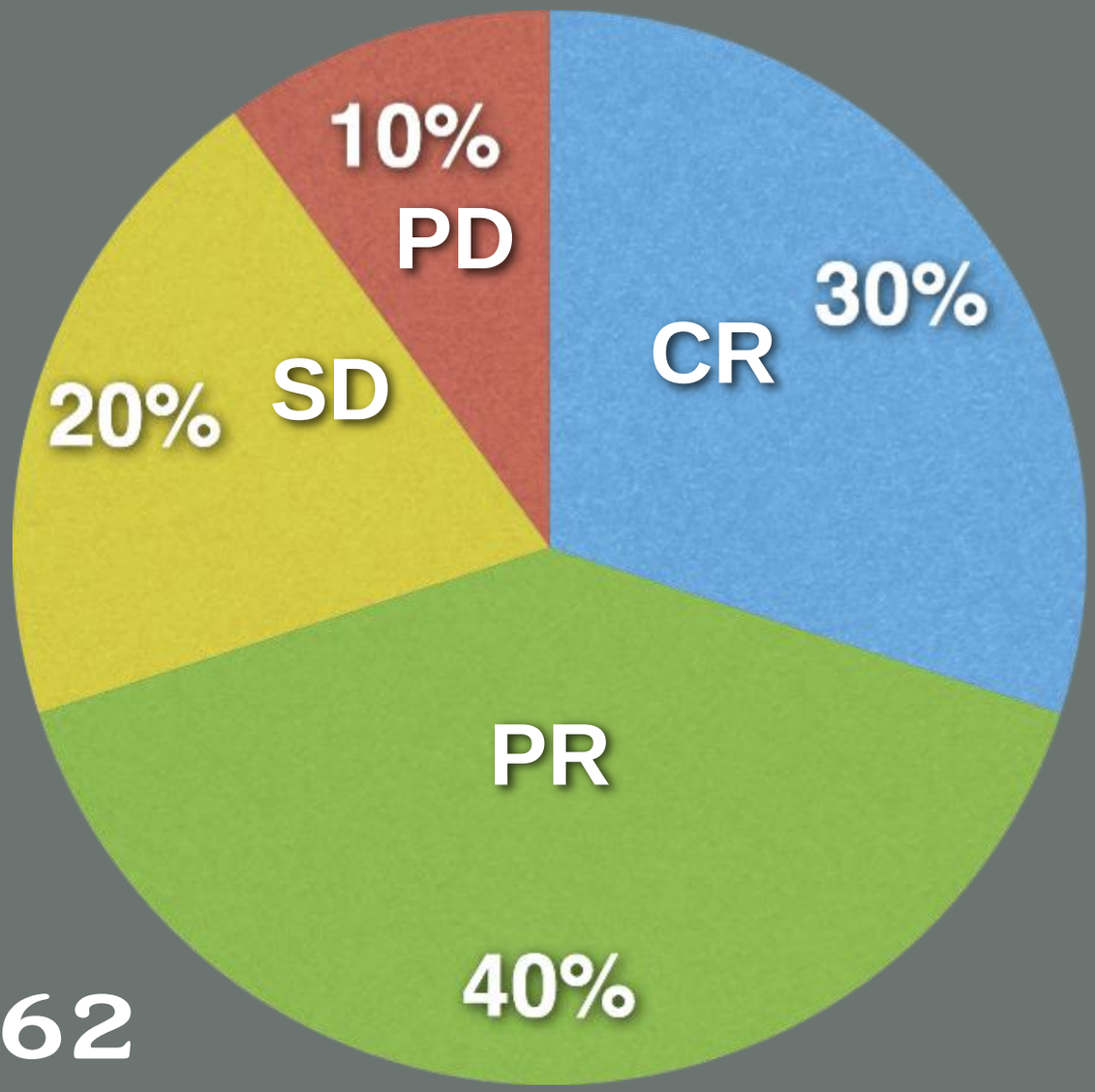
- **Systemic lesions (9)**
- **Intracranial lesions (3)**
  leptomeningeal carcinomatosis

Tyrosine Kinase Inhibitors

Gefitinib



Erlotinib

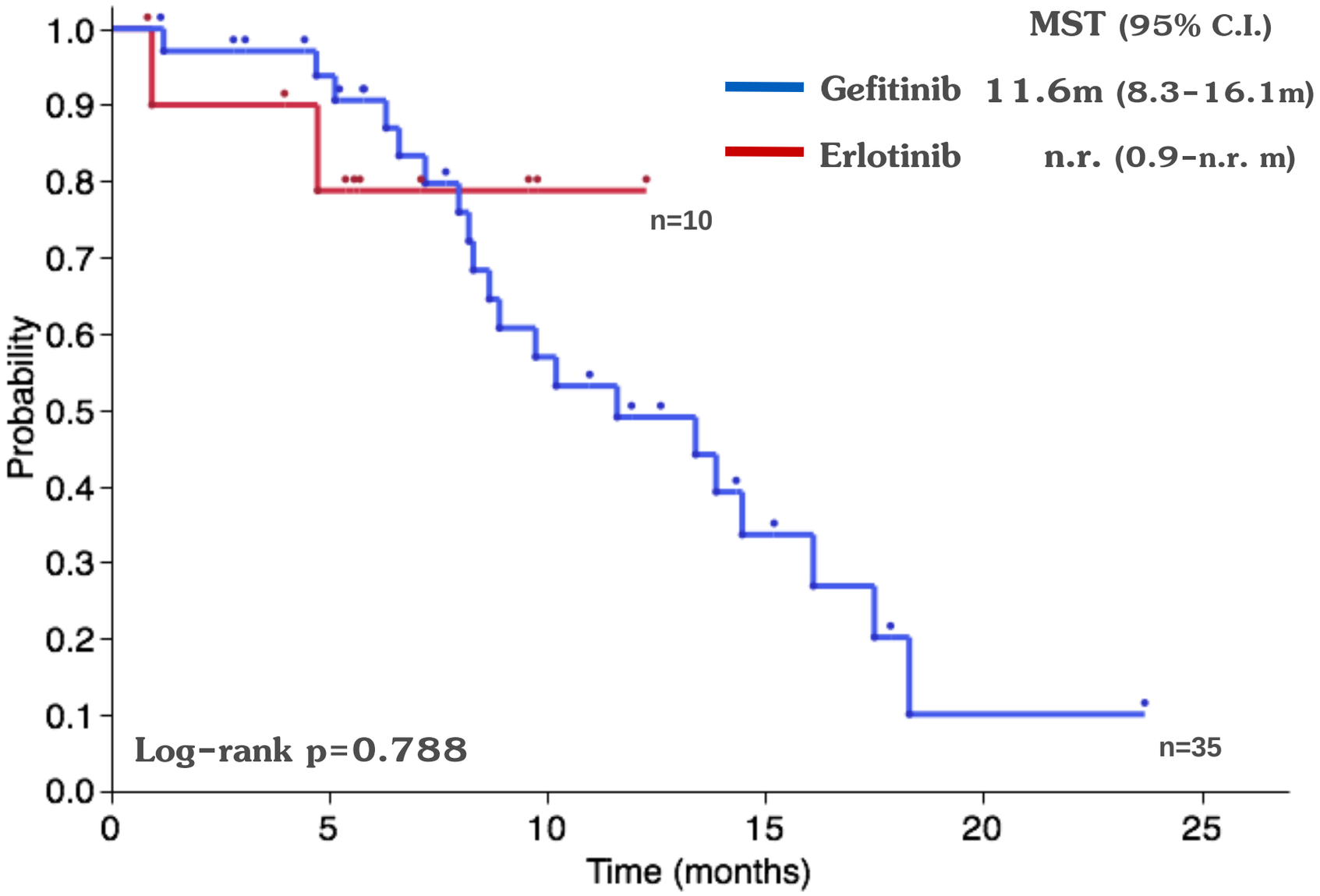


p=0.662

Erlotinib was administrated for relapsed cases after gefitinib...

Tyrosine Kinase Inhibitors

Progression-free Survival



Erlotinib was administrated for relapsed cases after gefitinib...

EGFR mutations

37 Cases

Exon 18 G718A	1
Exon 18 G719X	1
Exon 19 del	**21**
Exon 21 L858R	**13**
Exon 21 L861Q	1

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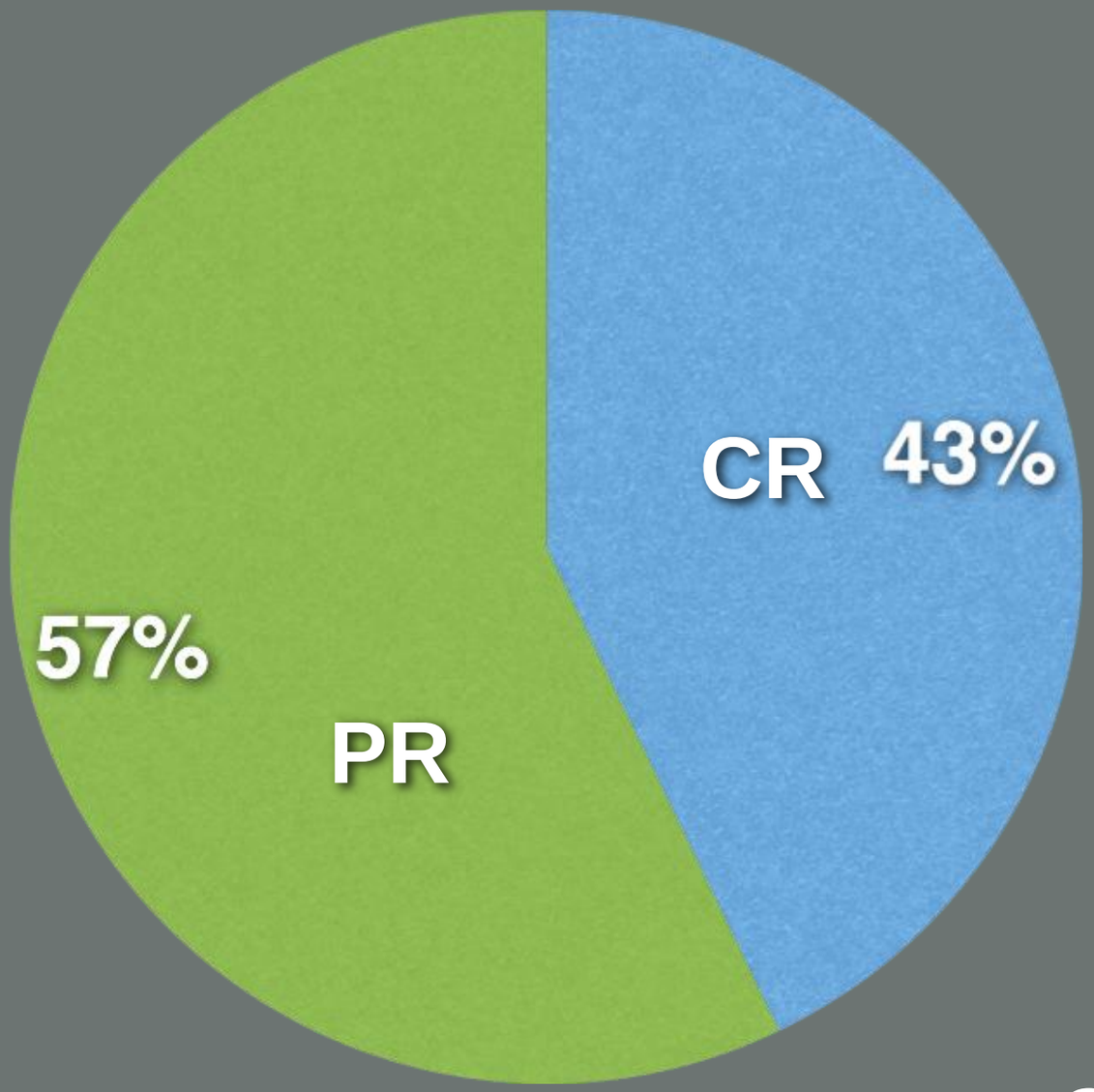
EGFR mutations

37 Cases

	Ex19del n=21	Others n=16	p
Age (y.o.)	63 (47-81)	66 (46-79)	0.878
Sex (f/m)	**12/9**	**14/2**	**0.048**
No. of Lesions	3 (1-20)	4 (1-20)	0.311
Max. Tm. Size (mm)	6.8 (1.9-25.9)	7.9 (2.4-22.7)	0.951
Diagnosis of brain metastases			0.461
at onset	14	13	
during the treatment	7	3	

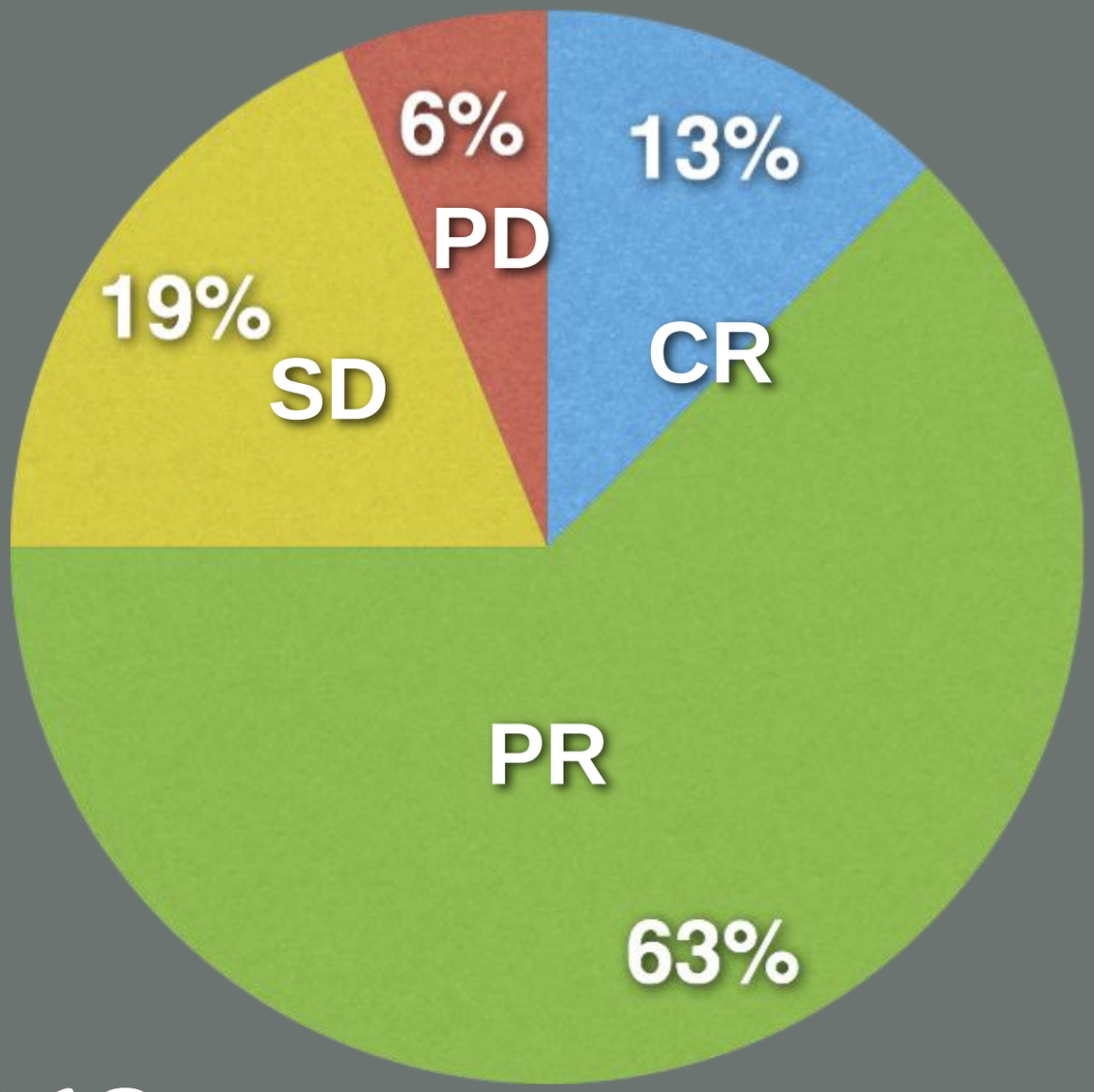
EGFR mutations

Ex19del



21 Cases

Others

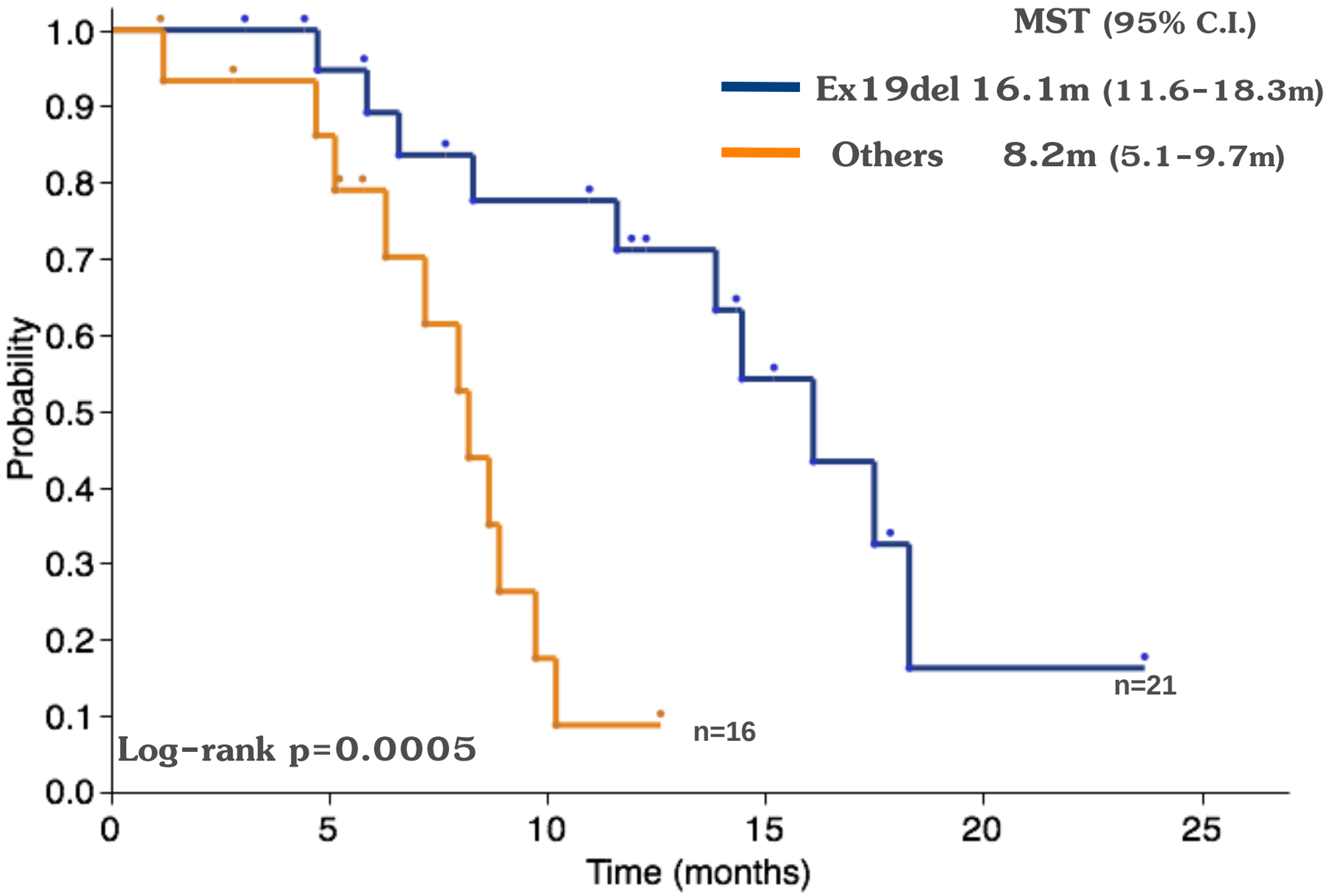


16 Cases

p=0.049

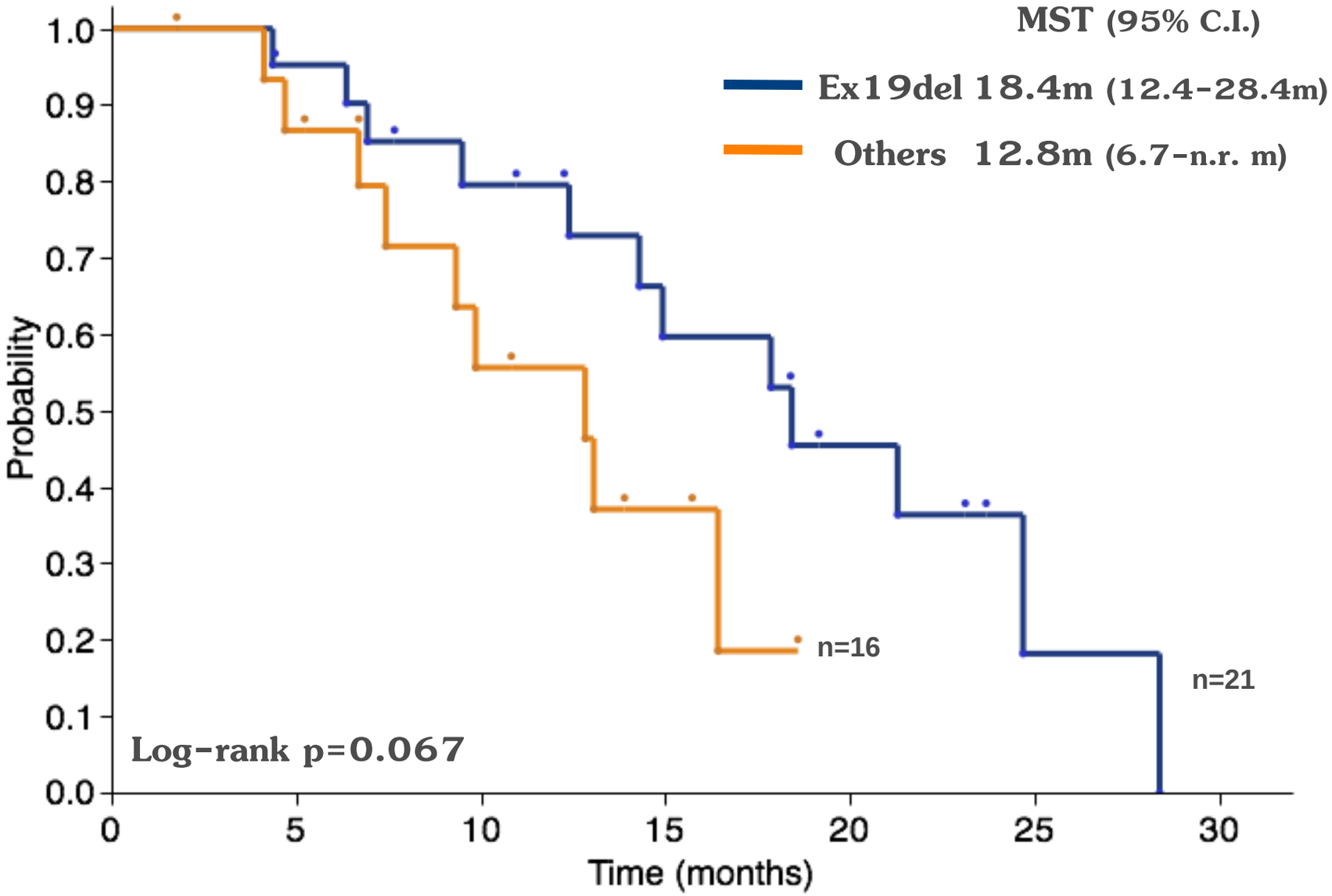
EGFR mutations

Progression-free Survival



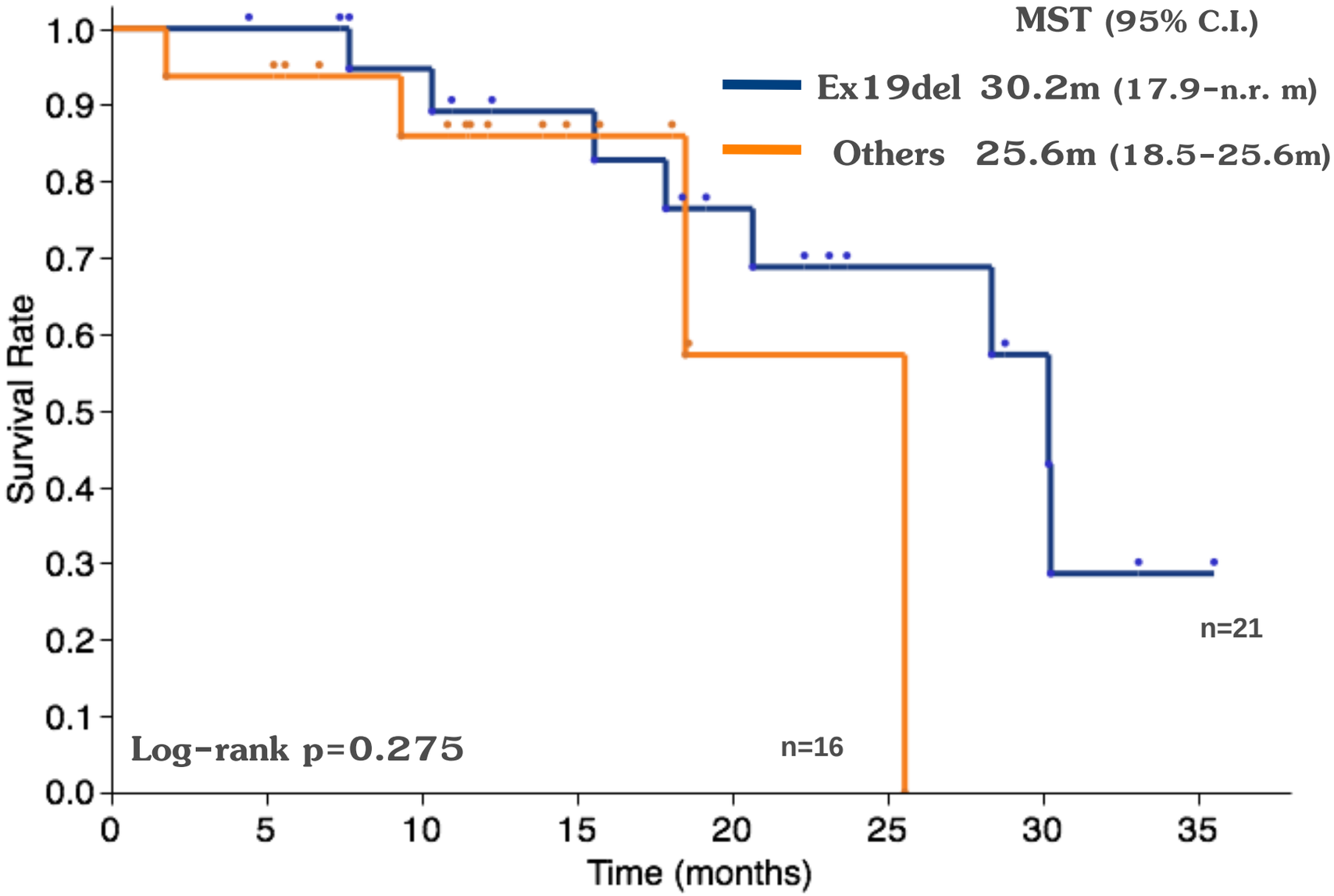
EGFR mutations

Time to Radiation Therapy



EGFR mutations

Survival after brain metastases



Adverse Events

37 Cases

No Grade 4 Adverse Event

Grade 3 Adverse Events

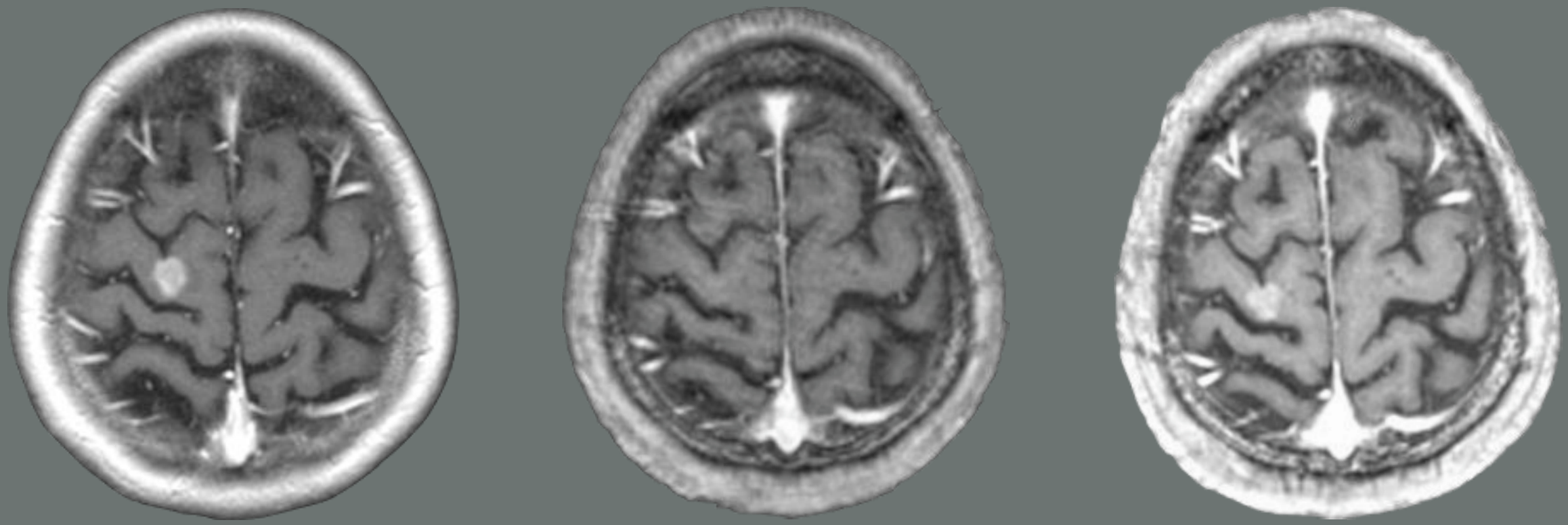
Pneumonitis	1	2.7%
Skin Rash	8	21.6%
Blood toxicity	2 lymphocytopenia (1) Neutorpenia (1)	5.4%
Liver dysfunction	4	10.8%
Renal dysfunction	0	0.0%

Remaining Problems

Regrowth after Withdrawal

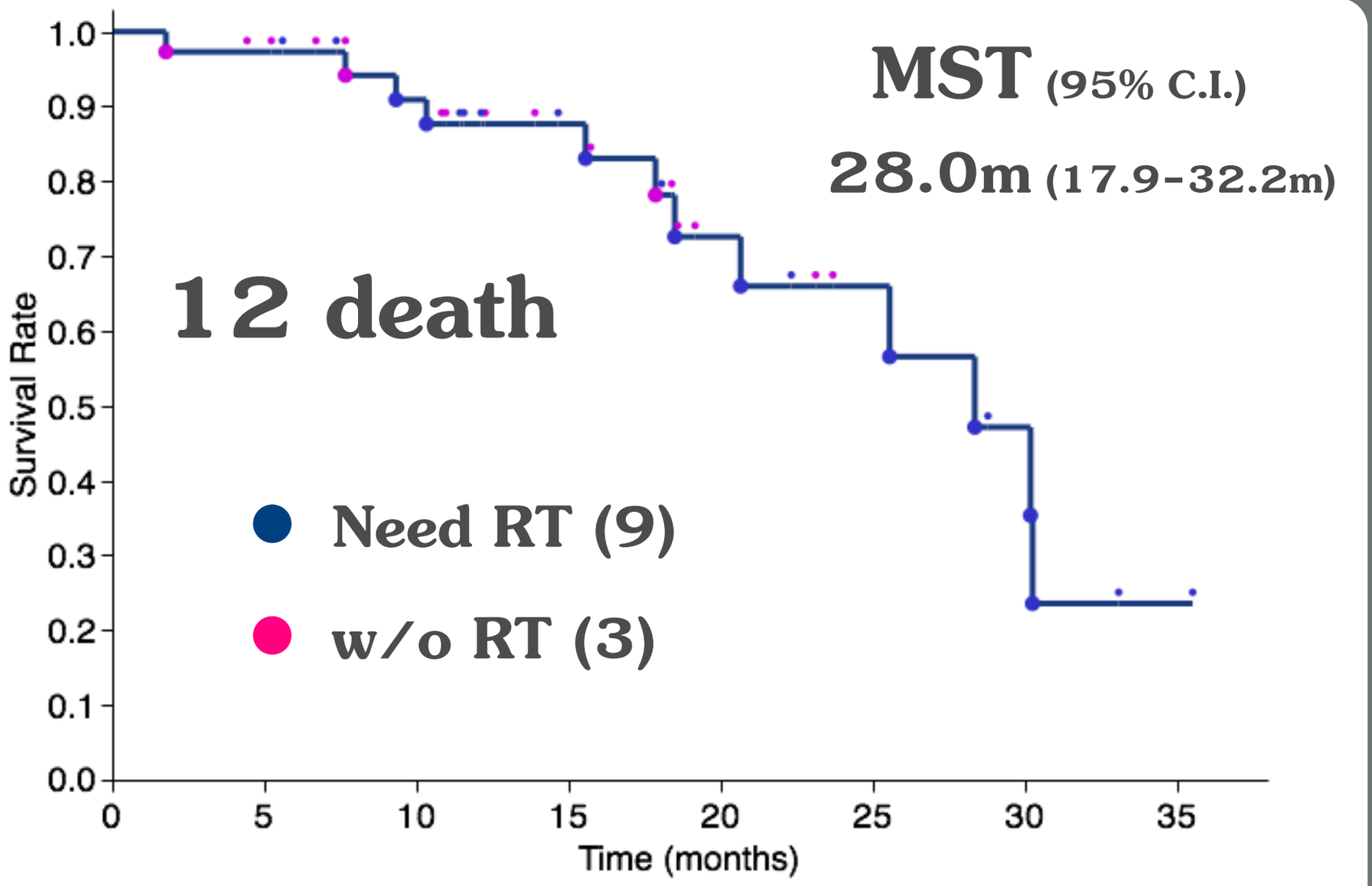
75f Ex19del

before TKI | **after TKI** | **after withdrawal**



Remaining Problems

Salvage RT

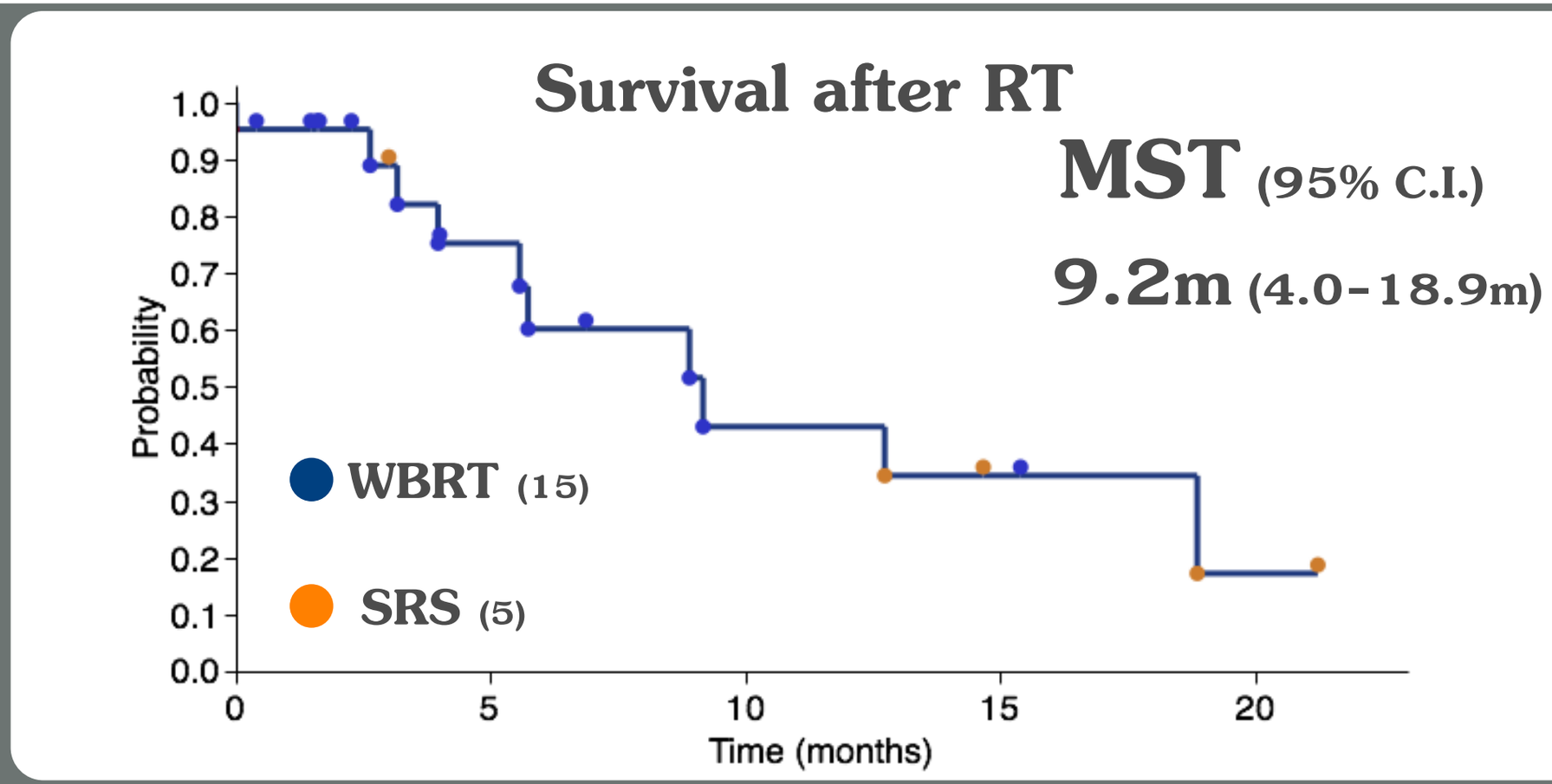


Remaining Problems

Salvage RT

20 / 37 Cases

Whole Brain Radiation Therapy	15
Stereotactic Radiosurgery	5



Conclusions

#1 TKIs showed favorable effect on control of EGFR-mutant brain metastases, and it could delay RT for more than one year.

#2 Ex19 del. was not prognostic but predictive of sensitivity to TKIs.

#3 Erlotinib still had sufficient effect on control of intracranial lesions which relapsed after gefitinib.

#4 Overall survival after brain metastases of our Pts. was excellent (28 months after metastases).