Brain metastases (BM)

Local therapies in oncogenic-driven diseases

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Disclosures:

- Boehringer-Ingelheim
- ROCHE
- Pfizer
- Novartis
- Astra-Zeneca

Treatment options for NSCLC patients with brain metastases

- Whole brain radiotherapy (WBRT)
- Stereotactic radiotherapy
- Surgery
- Chemotherapy
- Targeted therapies
- Best supportive care

Stratification of cancer patients with brain metastases
RPA classes I - III

	Median OS
KPS≥70 Age<65 and Controlled primary site and No mets outside CNS	**7.1 months**
KPS ≥ 70 Primary site active and/or Mets outside CNS present Age ≥ 65	4.2 months
KPS< 70	2.3 months

Gaspar IJROBP 1997;37:745-751

Stratification of cancer patients with brain metastases: Graded Prognostic Assessment (GPA) Score

Non–small-cell and small-cell lung cancer

Prognostic Factor	0	0.5	1.0	Patient Score
Age, years	> 60	50-60	< 50	____
KPS	< 70	70-80	90-100	____
ECM	Present	—	Absent	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) by GPA: 0-1.0 = 3.0; 1.5-2.0 = 5.5; 2.5-3.0 = 9.4; 3.5-4.0 = 14.8

Melanoma

Prognostic Factor	0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 4.7; 2.5-3.0 = 8.8; 3.5-4.0 = 13.2

Breast cancer

Prognostic Factor	0	0.5	1.0	1.5	2.0	Patient Score
KPS	≤ 50	60	70-80	90-100	n/a	____
Subtype	Basal	n/a	LumA	HER2	LumB	____
Age, years	≥ 60	< 60	n/a	n/a	n/a	____
Sum total						____

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 7.7; 2.5-3.0 = 15.1; 3.5-4.0 = 25.3

Renal cell carcinoma

Prognostic Factor	0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) by GPA: 0-1.0 = 3.3; 1.5-2.0 = 7.3; 2.5-3.0 = 11.3; 3.5-4.0 = 14.8

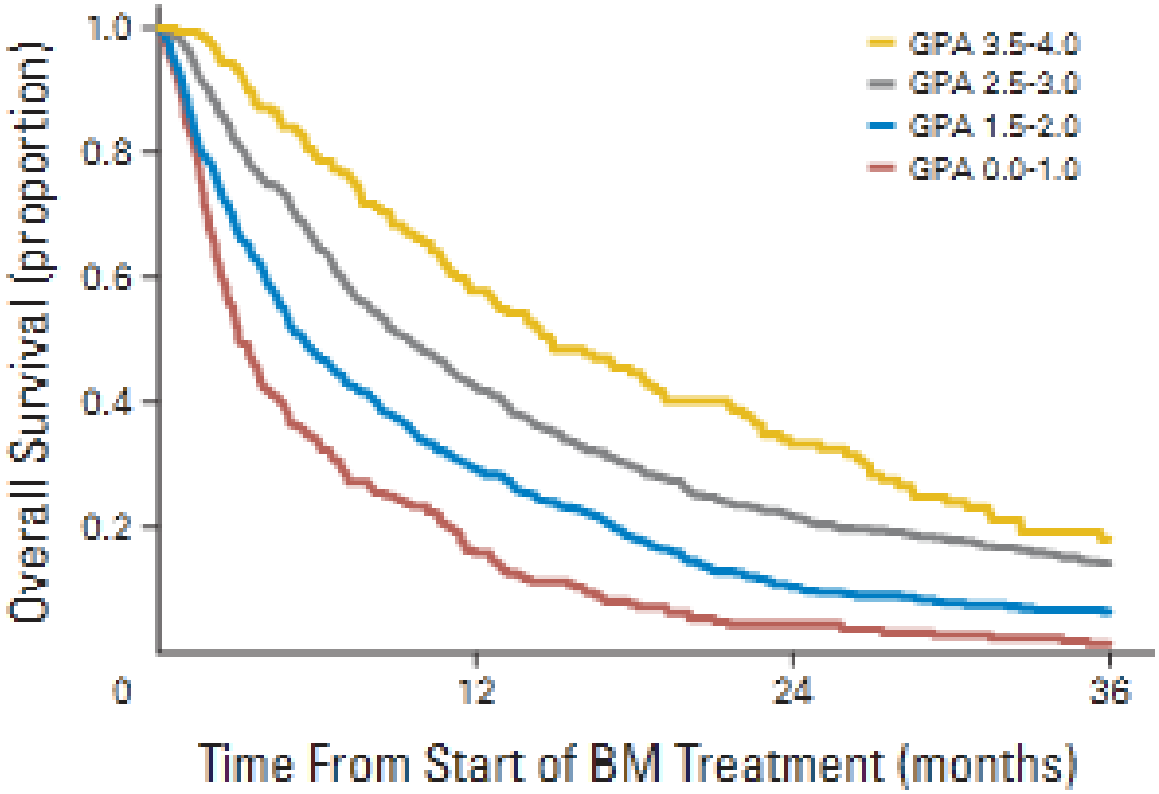
GI cancers

Prognostic Factor	0	1	2	3	4	Patient Score
KPS	< 70	70	80	90	100	____

Median survival (months) by GPA: 0-1.0 = 3.1; 2.0 = 4.4; 3.0 = 6.9; 4.0 = 13.5

Sperduto JCO 2012;30:419-425

Stratification of NSCLC patients with brain metastases: Graded Prognostic Assessment (GPA) Score



Sperduto JCO 2012;30:419-425

NSCLC patients with 1-3 metastases: Indications for surgery vs. SRS

Surgery

- Single lesions
- Larger lesions w/mass effect
- Outside „vulnerable” surgical areas
- No contraindications to surgery

SRS

- Smaller lesions
- Multiple lesions (1 – 3?)
- All locations in the brain, including brain stem
- Patients who are not surgical candidates

Key evidence: WBRT vs. SRS + WBRT
RTOG 9508 trial (N=331)

- 1-3 metastases, < 40 mm
- WBRT 37,5 Gy/15 fx
- Local control 71% vs 82%; p<0,05
- Overall survival 6,5 vs 5,7 months; NS
- Subset of pts with single metastasis:
  OS 4,9 vs 6,5 months; p<0,05
- 6-month KPS improvement
  and steroid intake favors SRS+WBRT

Andrews DW Lancet 2004

Key evidence: WBRT vs. SRS + WBRT
RTOG 9508 trial – 2013 GPA update

- 252/331 patients re-analyzed according to GPA

Median OS according to treatment arm and GPA score

GPA < 3,5 (N=205)

WBRT	WBRT+SRS
5,4	5,0

GPA = 3,5 – 4,0 (N=47)

WBRT	WBRT+SRS
10,3	21,0

Sperduto et al., ASTRO 2013: abstr 123

Key evidence: Surgery / SRS with or without WBRT EORTC 22952-26001 trial (N=359)

VOLUME 29 · NUMBER 2 · JANUARY 10 2011

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

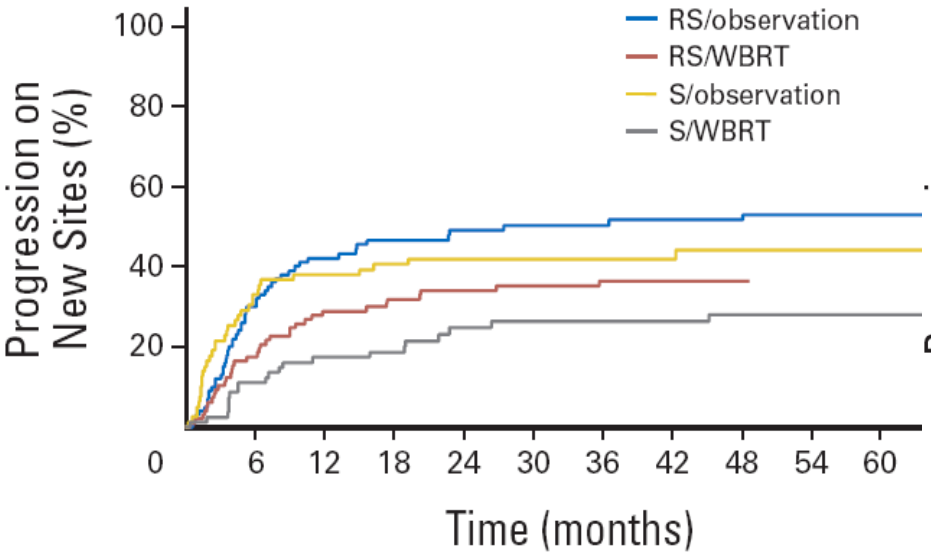
Adjuvant Whole-Brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Results of the EORTC 22952-26001 Study

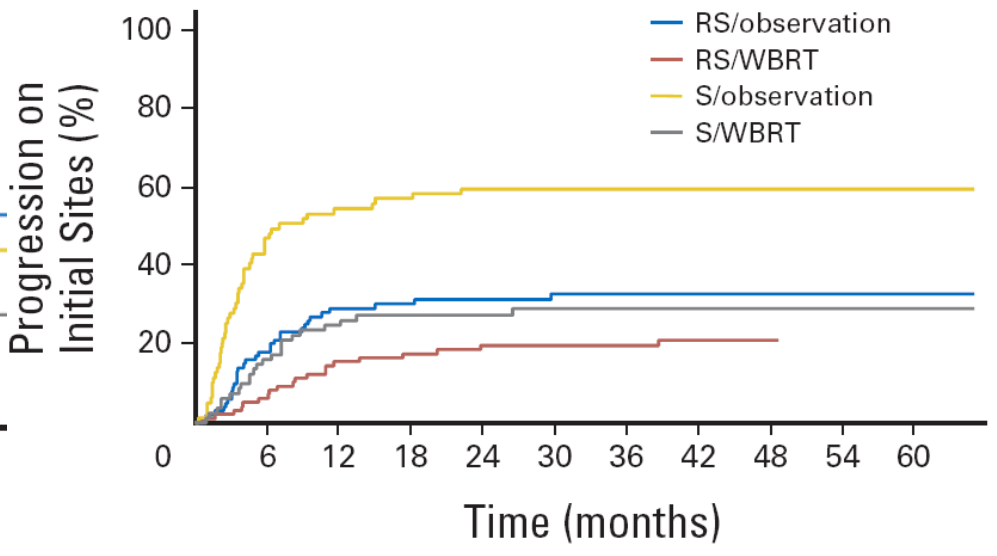
Martin Kocher, Riccardo Soffietti, Ufuk Abacioglu, Salvador Villà, Francois Fauchon, Brigitta G. Baumert, Laura Fariselli, Tzahala Tzuk-Shina, Rolf-Dieter Kortmann, Christian Carrie, Mohamed Ben Hassel, Mauri Kouri, Egils Valeinis, Dirk van den Berge, Sandra Collette, Laurence Collette, and Rolf-Peter Mueller

- 1-3 brain metastases <30 mm
- Disease control outside CNS
- WHO PS 0-2
- Randomizations after surgery or SRS: WBRT vs observation
- WBRT 30 Gy/10 fr

Kocher M JCO 2011

Key evidence: Surgery / SRS with or without WBRT
EORTC 22952-26001 trial (N=359)





Kocher M JCO 2011

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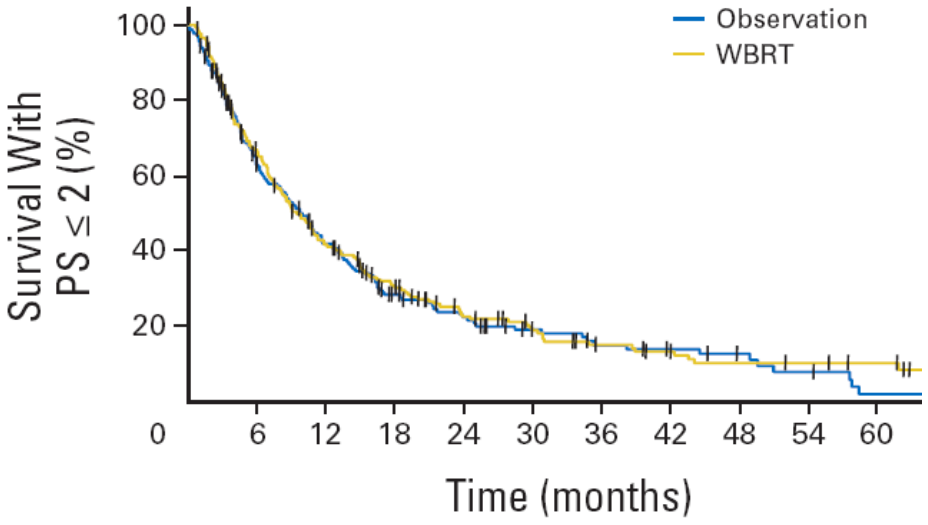
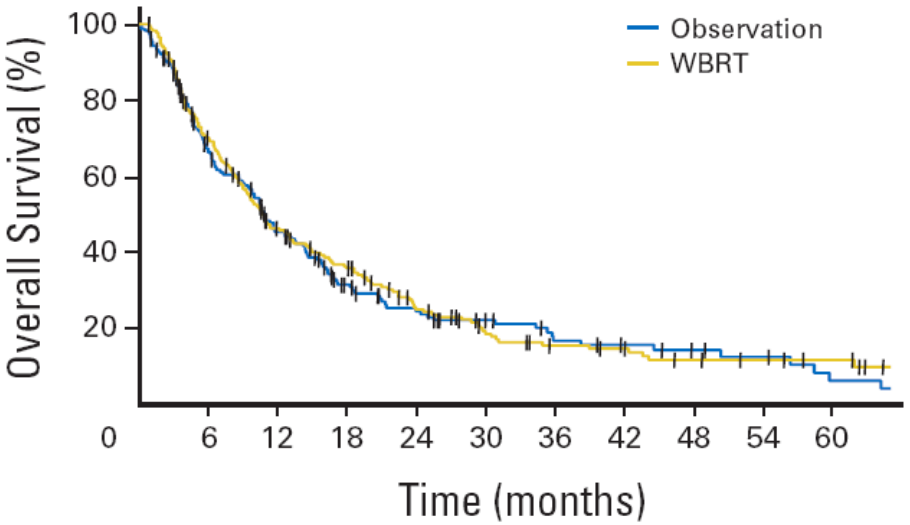




Kocher M JCO 2011

WBRT: Cognitive function deficit

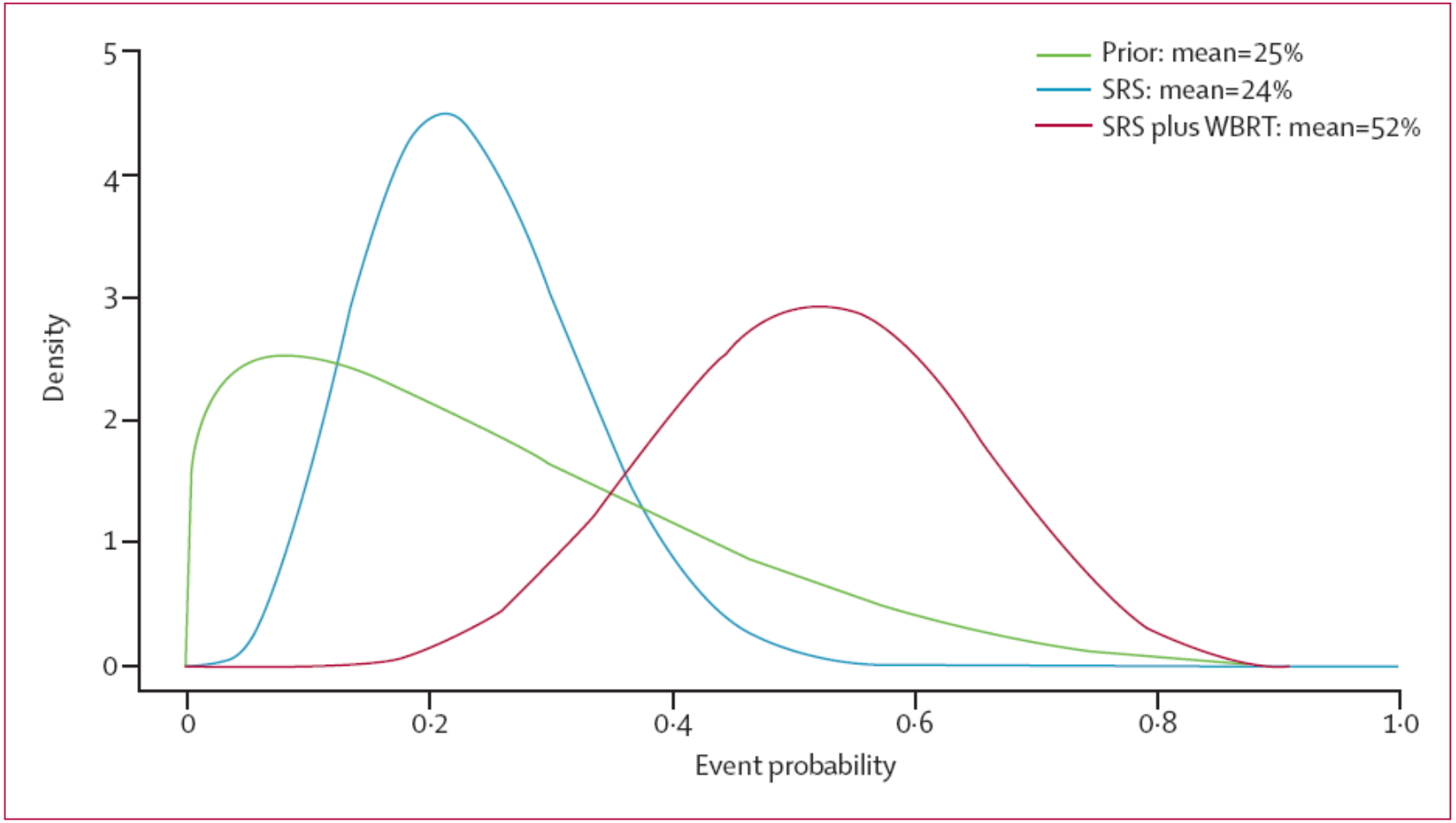


Figure 2: Prior and posterior distributions of probability of cognitive decline (5 points or greater fall from baseline) assessed by HVLT–R (total recall)

Chang et al., Lancet 2009

Surgery or SRS: Summary

- Should be considered in selected good prognosis patients with 1 – 3 brain metastases
- SRS improves survival when added to WBRT in patients with single metastasis / GPA 3,5 - 4
- WBRT improves local control but not survival when added to surgery or SRS
- WBRT associated with moderate cognitive disfunction
- In most patients with GPA 3,5 – 4: consider surgery or SRS without WBRT, particularly if effective systemic tx exist

Local treatment - new approaches

- Hippocampal-sparing RT
- Whole brain radiotherapy (WBRT) with simultaneous integrated boost (SIB) to BM
- Brain protective agents

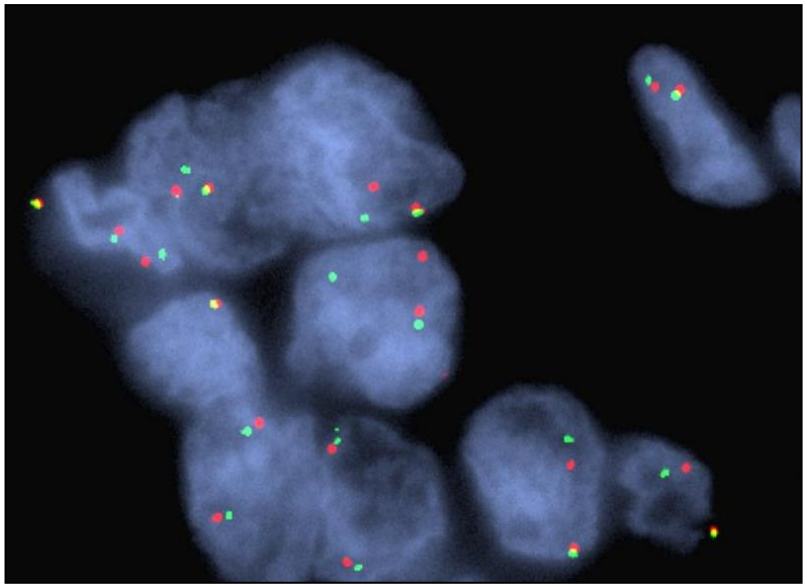
Does targeted therapy change the BM landscape in oncogenic-driven NSCLC subsets?

Targeted therapies and BM

- Targeted therapies are more effective than chemotherapy in specific subsets of NSCLC patients
- Pharmacokinetic properties of targeted agent in relation to blood-brain barier (BBB) are extremely important
- Better systemic control with targeted agents may significantly prolong survival of NSCLC patients with BM and influence the prognostic scoring systems

ALK+/ROS1+

NSCLC

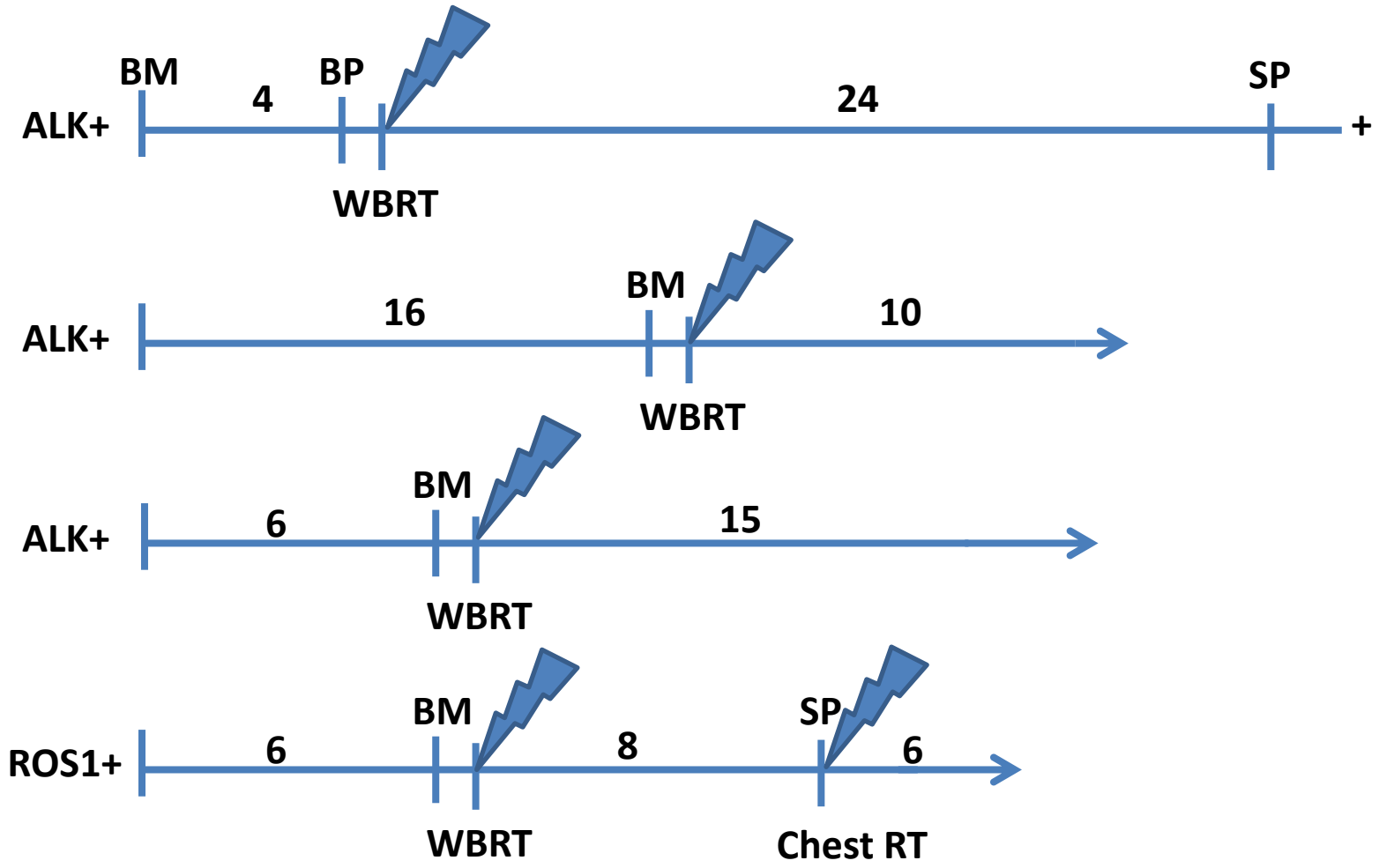


Pharmacokinetic brain relapse

- ALK+ NSCLC has propensity for early brain dissemination (~30% of pts participating in PROFILE 07 trial)
- Crizotinib penetration to CSF <1%
- Many progressions occur exclusively in the CNS (brain, meninges, spinal cord) – „pharmacokinetic relapses”
- With continued systemic control, crizotinib may be considered in pts with isolated BM after WBRT and/or SRS, with case stories of prolonged second remissions in the CNS

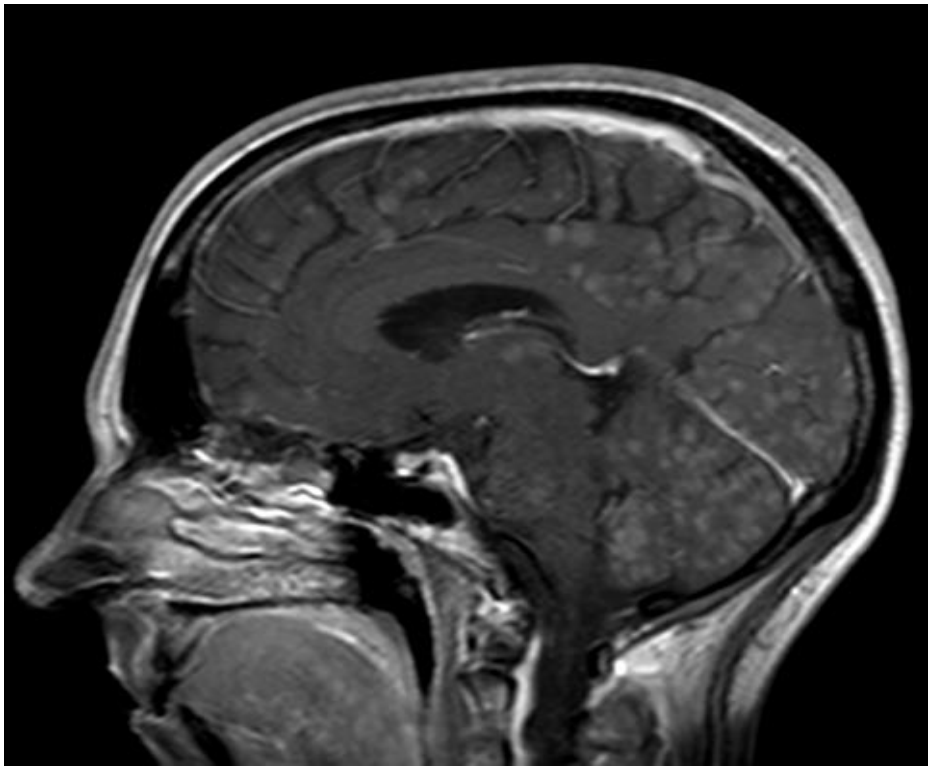
ALK+/ROS1+ patients and BM

Gdańsk experience with crizotinib

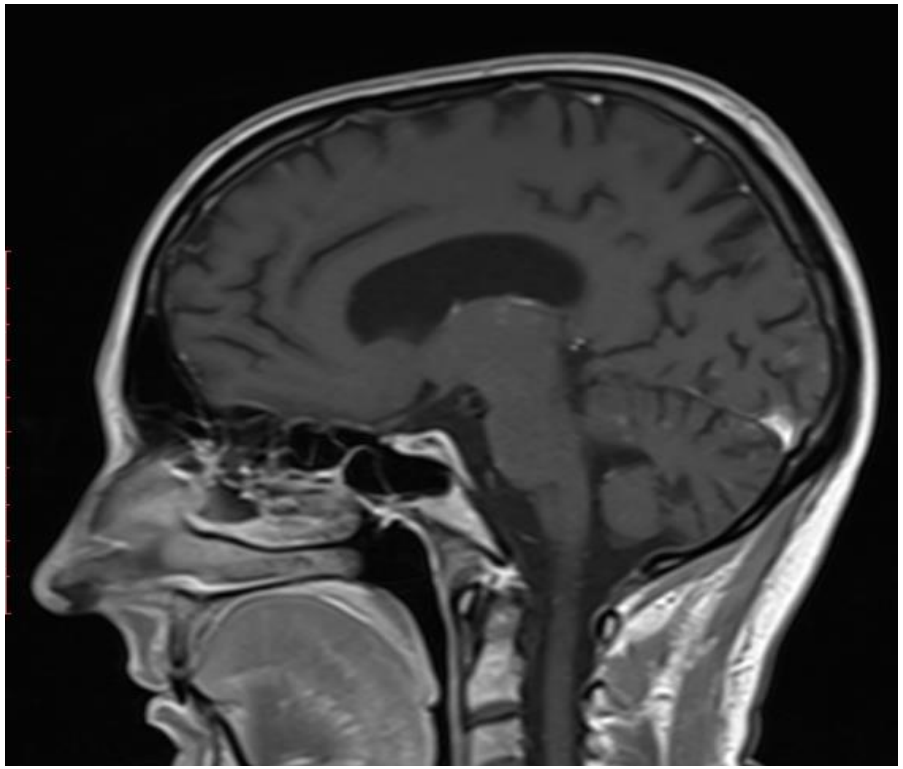


BM=brain metastasis; BP=brain progression; SP=systemic progression; WBRT=whole brain RT

Miliary brain metastases in a patient with *ROS1* rearrangement



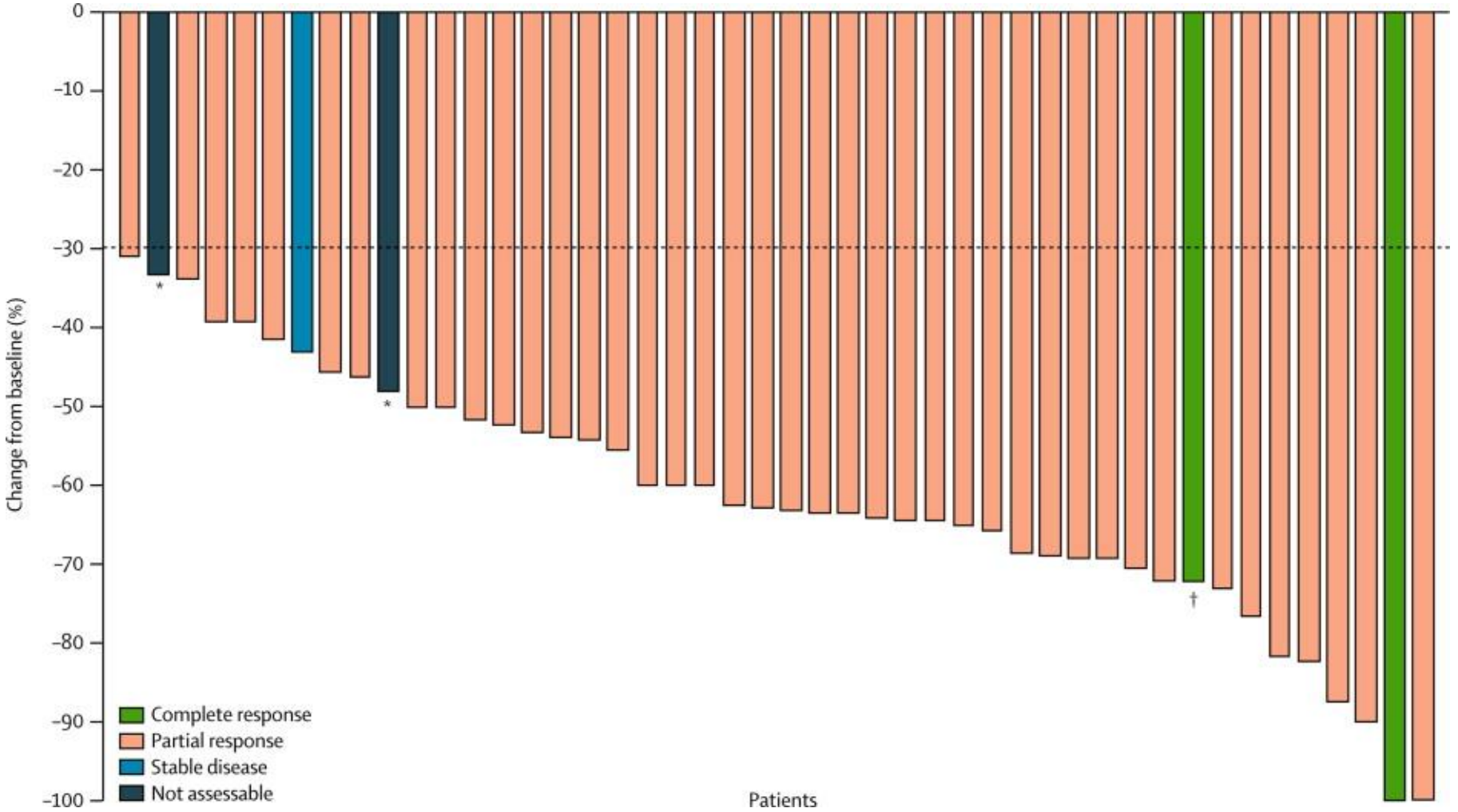
After 6 months on crizotinib



After WBRT and another
4 months on crizotinib

Dziadziuszko K, J Thorac Oncol, in press

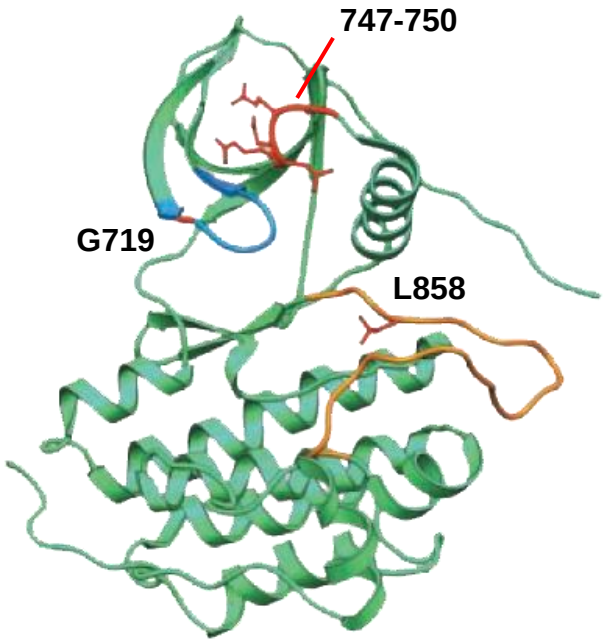
CH5424802 (RO5424802) for patients with *ALK* + NSCLC: single-arm, open-label, phase 1–2 study (AF-001JP)



Seto et al., The Lancet Oncology, 2013, 14: 590 - 598

EGFR mutation +

NSCLC



Efficacy of reversible EGFR tyrosine kinase inhibitors (TKIs) in patients with brain metastases

Table 1. Trials studying the efficacy of EGFR tyrosine kinase inhibitors in non–small cell lung cancer with central nervous system metastases

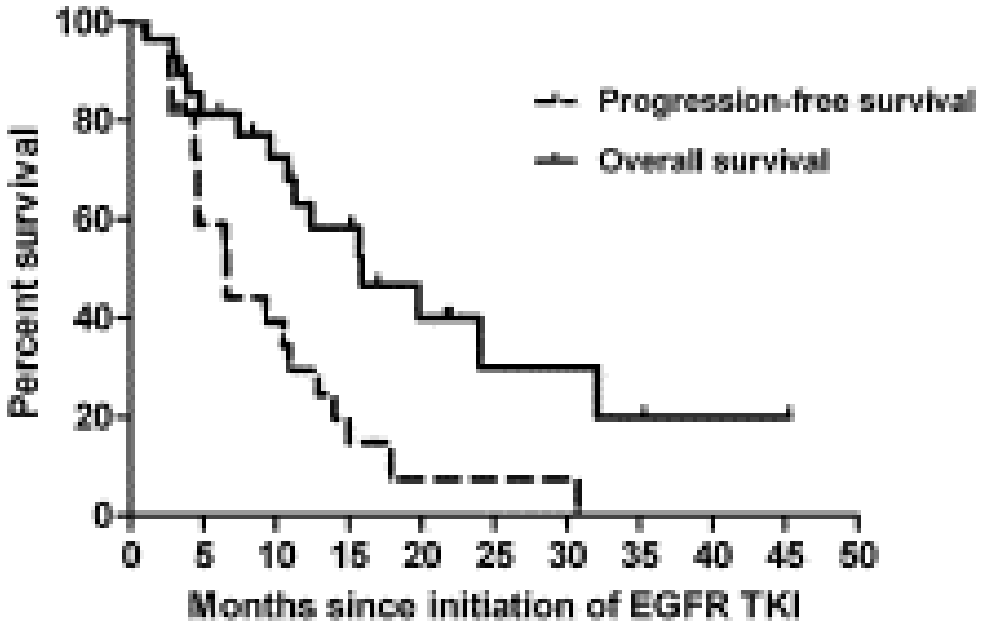
Study	Treatment	Selection	Phase	*N*	RR (%)	Survival
Unselected patients						
Ceresoli et al. (51)	Gefitinib	European	II	41	27	PFS 3 mo
Wu et al. (52)	Gefitinib	East Asian, adenocarcinoma	II	40	32	PFS 9 mo
Selected patients						
Hotta et al. (53)	Gefitinib	East Asian	II	57	43	
Porta et al. (54)	Erlotinib	*EGFR* mutation	II	69	82	OS 12.9 mo
Kim et al. (55)	Gefitinib or erlotinib	*EGFR* mutation, East Asian, adenocarcinoma	II	23	70	PFS 6.6 mo, OS 19.8 mo
Li et al. (41)	Gefitinib	*EGFR* mutation, East Asian	II	110	89	
Wu et al. (57)	Erlotinib	East Asian, *EGFR* mutation, and/or adenocarcinoma	II	48	56	PFS 23.2 mo
Kim et al. (60)	Gefitinib or erlotinib	East Asian, never-smoker, adenocarcinoma	II	23	74	PFS 7.1 mo, OS 18.8 mo

Abbreviations: mo, months; OS, overall survival; PR, partial response; RR, response rate; TTP, time to progression.

Jamal-Hanjani M. CCR 2011; 18:938

EGFR TKIs in patients w/brain metastases

- 28 NSCLC patients with EGFR M+ NSCLC and brain mets
- Phase II study with either gefitinib or erlotinib
- RR = 83%, median PFS = 6.6 months,
  median OS = 15.9 months



Park SJ et al., Lung Cancer 2012

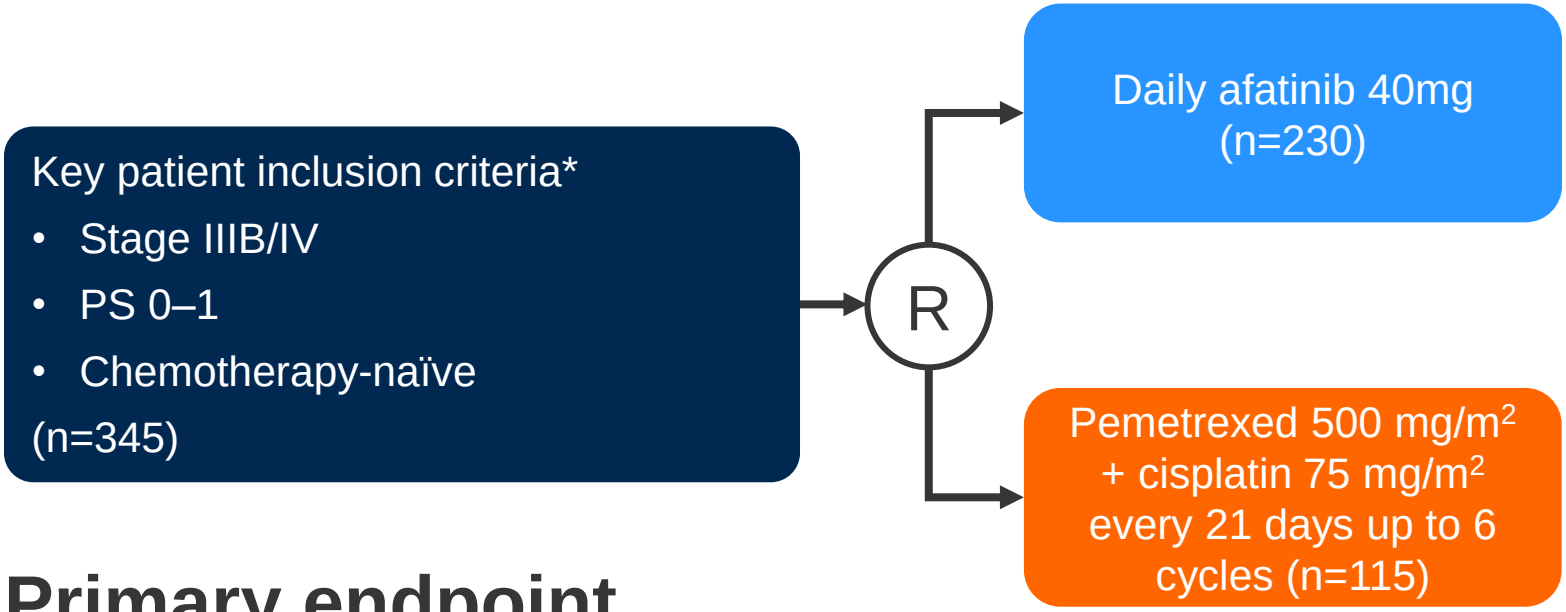
Pharmacokinetics of EGFR inhibitors in NSCLC 15 patients w/EGFR mutant tumors and brain metastases

	Mean concentration	CSF penetration
Gefitinib	3.7ng/mL	1.13%
Erlotinib	28.7ng/mL	2.77%

Togashi Y et al., Cancer Chemother Pharmacol 2012

LUX-Lung 3: A randomised, open-label, phase III study of afatinib versus pemetrexed and cisplatin as first-line treatment for patients with advanced adenocarcinoma of the lung harboring EGFR-activating mutations

Randomised, open-label, Phase III study,
patients with asymptomatic brain metastases were allowed to participate



Primary endpoint

- **PFS**

Sequist et al. *J Clin Oncol*. 2013;31:3327

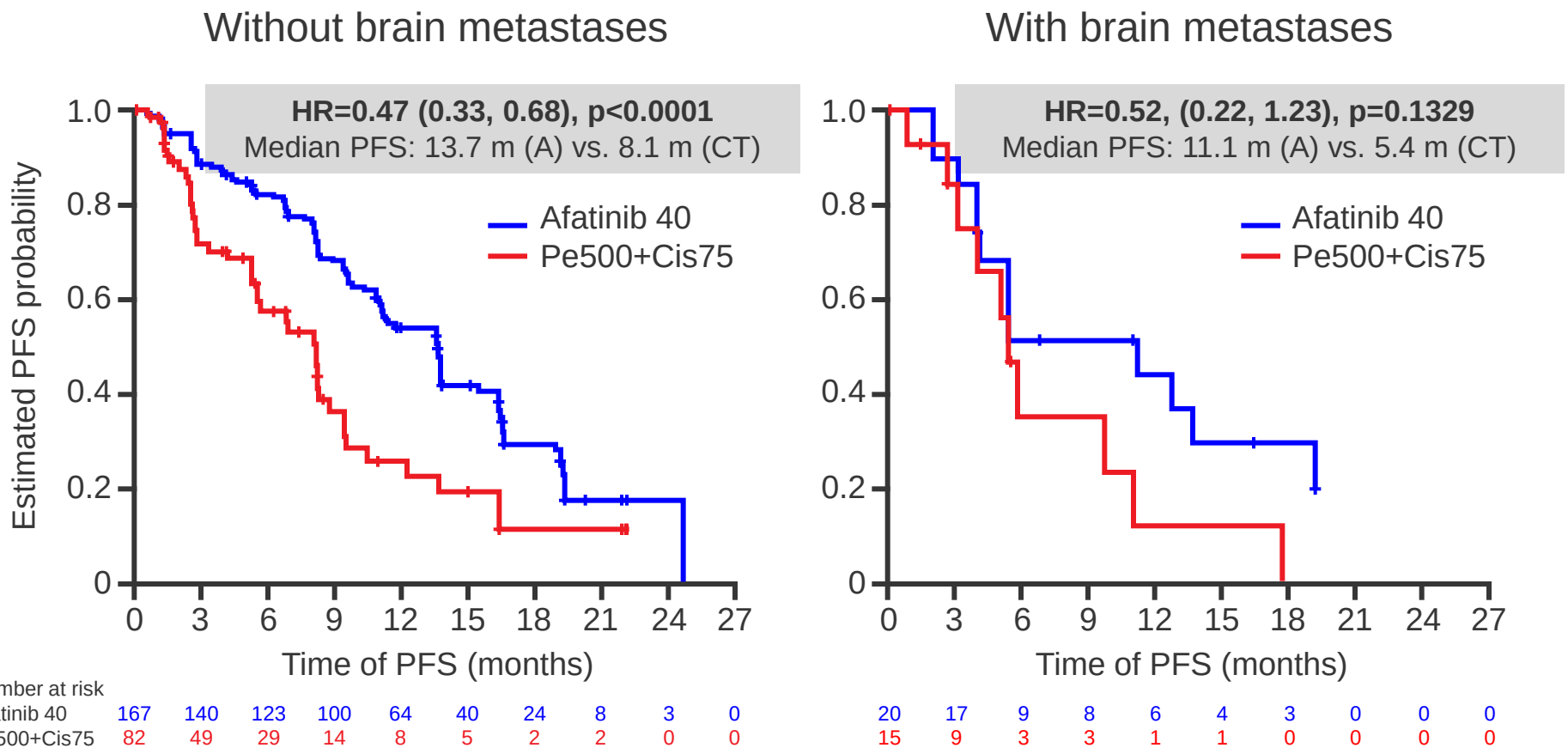
LUX-Lung 3: Patients with common EGFR mutations with or without asymptomatic brain metastases

	Without brain metastases*		With brain metastases*	
	Afatinib n=167	Pem/cis n=82	Afatinib n=20	Pem/cis n=15
Age, median	63.0	61.0	60.5	63.0
Females, %	65.9	67.1	70.0	80.0
Never smoked, %	67.7	65.9	70.0	86.7
Asian, %	70.1	68.3	85.0	80.0
ECOG PS 0, %	43.1	35.4	20.0	46.7
Stage IV, %	89.2	84.1	100.0	100.0
Del19, %	53.9	56.1	55.0	53.3
L858R, %	46.1	43.9	45.0	46.7

*Patients with unknown brain metastatic disease at baseline were excluded (n=24)

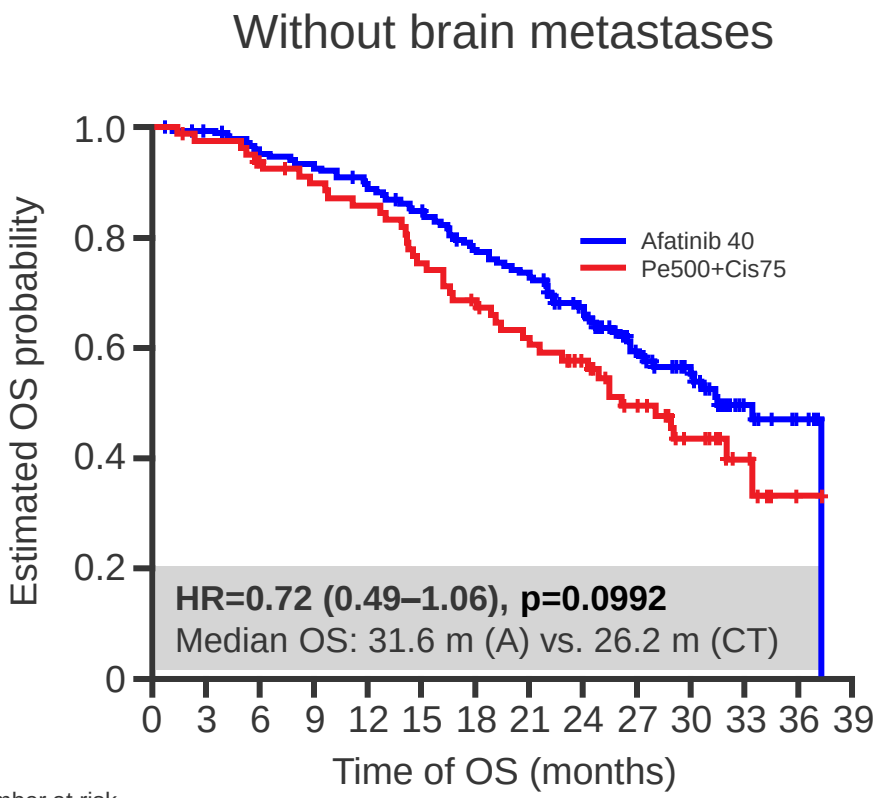
Schuler M. et al., WCLC 2013, slide courtesy of Boehringer-Ingelheim

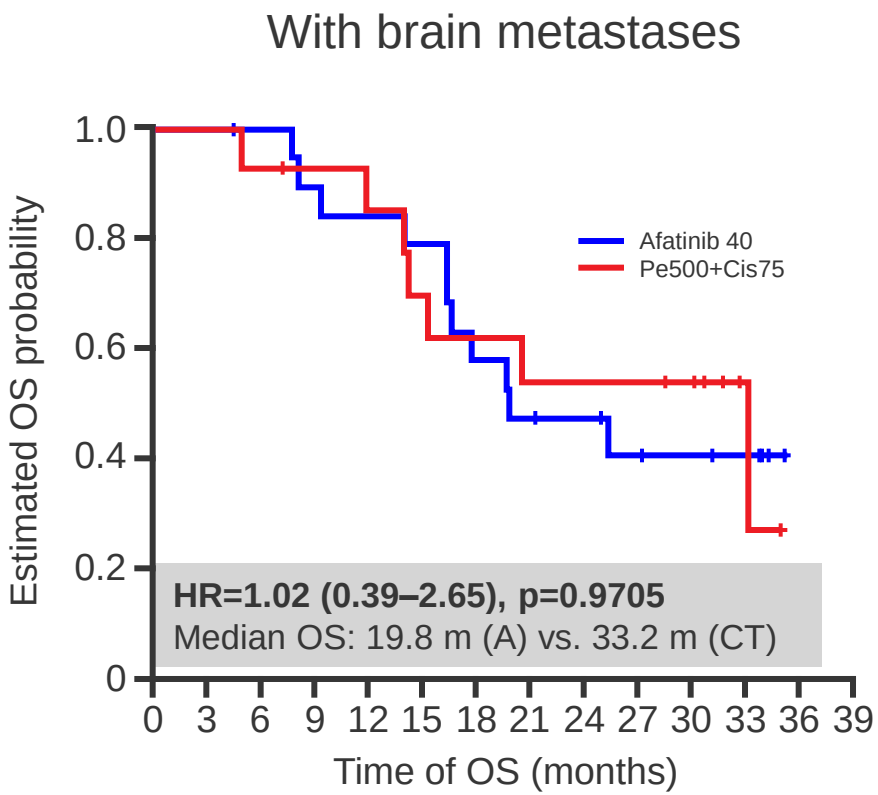
LUX-Lung 3: Progression-free survival in patients with or without brain metastases



Schuler M. et al., WCLC 2013, slide courtesy of Boehringer-Ingelheim

LUX-Lung 3: Overall survival in patients with or without brain metastases





Number at risk

Afatinib 40	167	163	155	152	145	136	123	116	94	66	48	20	6	0
Pe500+Cis75	82	77	72	68	65	57	51	45	37	28	17	7	2	0

Afatinib 40	20	20	19	17	16	15	11	9	8	6	5	4	0	0
Pe500+Cis75	15	14	13	12	11	9	8	7	7	7	6	2	0	0

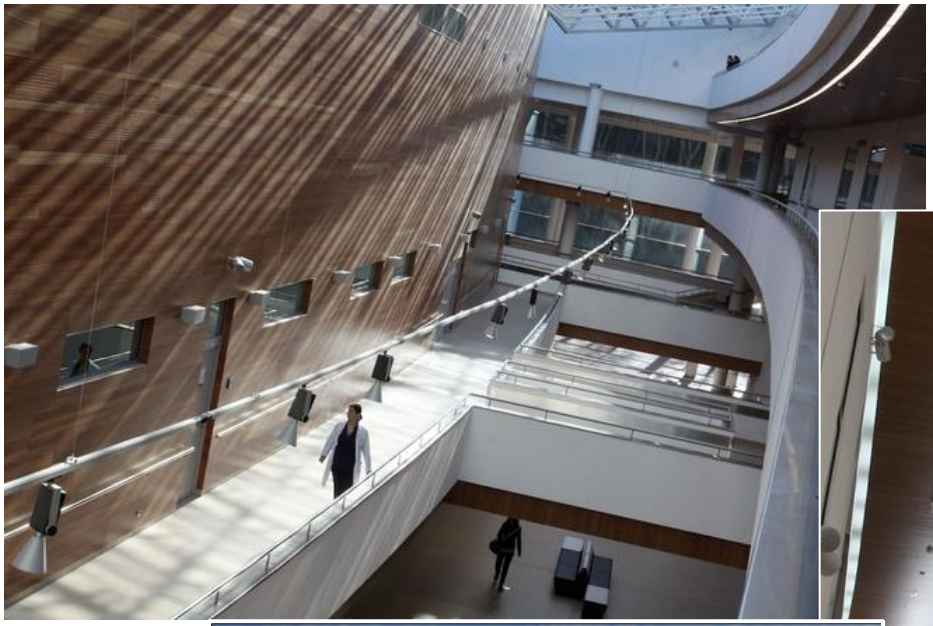
Schuler M. et al., WCLC 2013, slide courtesy of Boehringer-Ingelheim

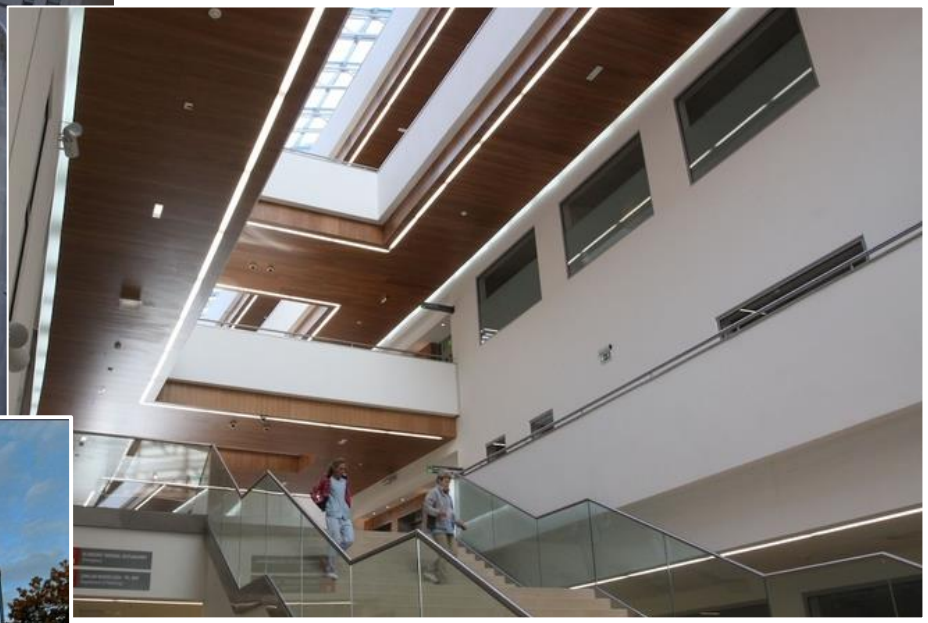
CNS progression on EGFR or ALK inhibitors

- Mechanism could be pharmacokinetic → local treatment essential
- In a gefitinib treated patient, consider switch to erlotinib or afatinib to achieve higher CSF concentrations
- Several retrospective series demonstrate some efficacy of erlotinib pulse-dosing,
  e.g. erlotinib 300mg every other day or
  erlotinib 600mg every 4 days
- Similar observation of efficacy of crizotinib pulse-dosing (500mg OD) was published in ALK+ NSCLC

Take-home messages

- Stratification of BM patients according to prognostic models is useful in clinical practice
- WBRT remains the standard of care in most patients
- Surgery or SRS should be considered in selected good prognosis patients with 1 – 3 (?) brain metastases; WBRT may be deferred in these patients until progression in the brain
- Targeted therapies can significantly prolong survival of NSCLC patients with BM.
- Brain penetration of particular compound in relation to local therapies is extremely important





Thank you for your attention!