

Department of Radiation Oncology

Chairman: Prof. Dr. Matthias Guckenberger

Crizotinib-controlled ALK positive disease and three brain metastases

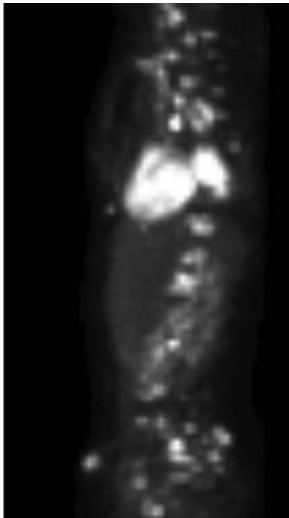
Matthias Guckenberger



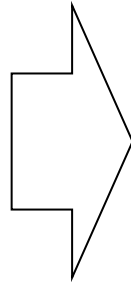
UniversityHospital
Zurich

The (typical) case

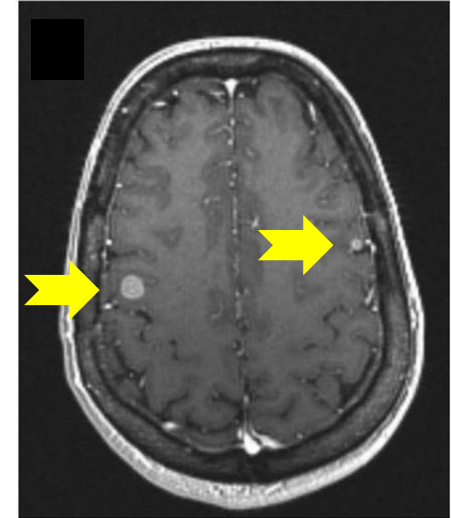
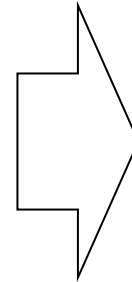
- 64 y.o. male; former smoker 5 p.y.; no relevant comorbidities
- ECOG 1, no weight loss
- Newly diagnosed stage IV NSCLC, adenocarcinoma, ALK positive



Disseminated
Metastatic
Disease



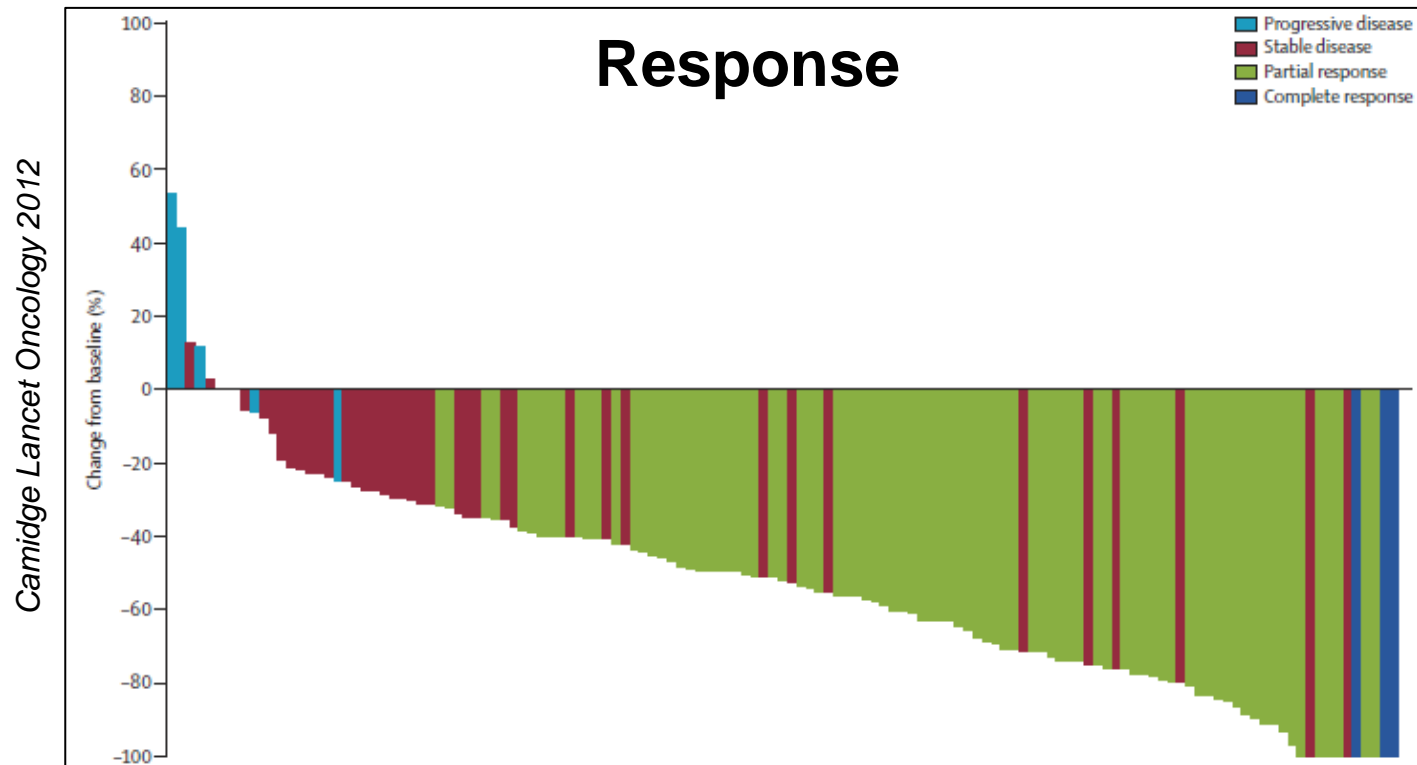
Very good
partial response
to Crizotinib



CNS progression only:
3 brain mets 0.7 – 1.2cm

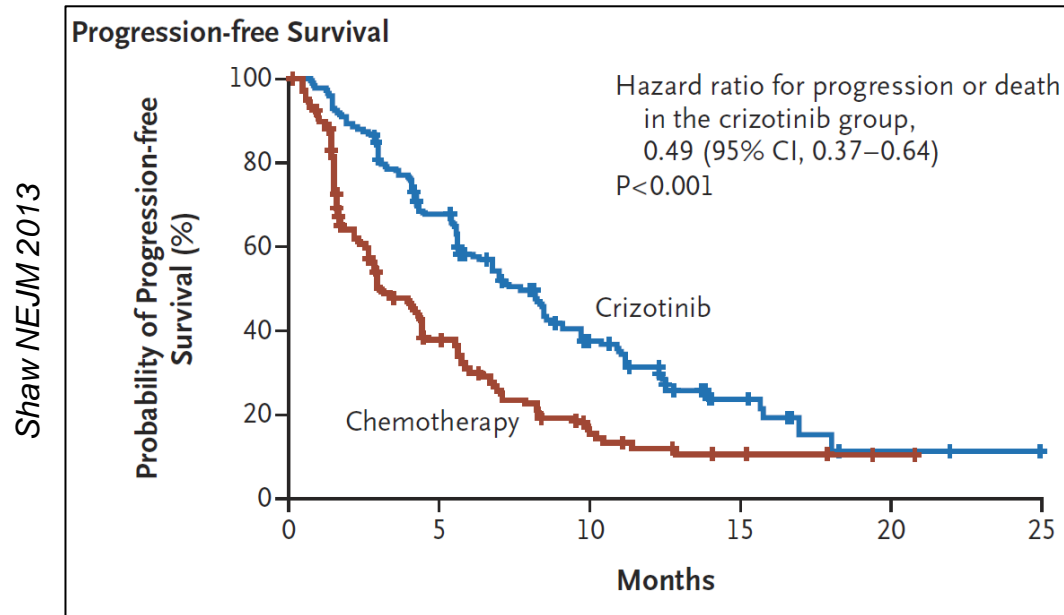
Chun Cancer Biol Ther 2012

Efficacy of Crizotinib in ALK positive NSCLC



- **Toxicity:** visual disorder, gastrointestinal side effects, and elevated liver aminotransferase levels

Reasons for Crizotinib failure: resistance



	Crizotinib	Pemetrexed Docetaxel	P-value
OS	12.2 months	12.1 months	NS

- All patients will develop progressive disease & no improvement of OS
- Multiple resistance mechanisms to Crizotinib

CNS failure during Crizotinib treatment



Crizotinib treatment with wice daily 250mg

➤ CSF-to-plasma ratio of 0.0026

Costa JCO 2011

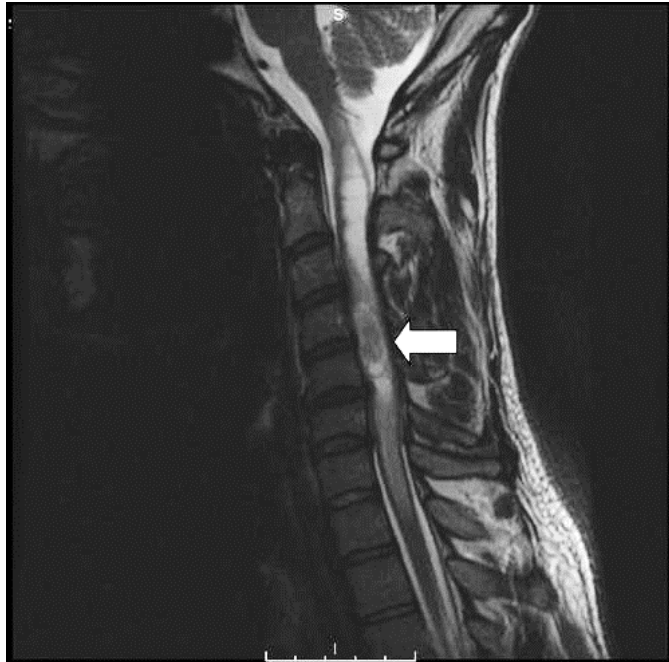
CNS progression during Crizotinib treatment

➤ 10 / 39 patients with extended Crizotinib treatment

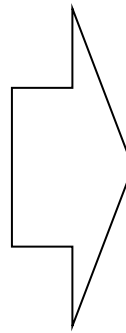
Camidge Lancet Oncology 2012

- CNS as a frequent site of Crizotinib treatment failure

CNS failure during Crizotinib treatment



Intramedullary spinal metastases
after ~ 2.5 years Crizotinib

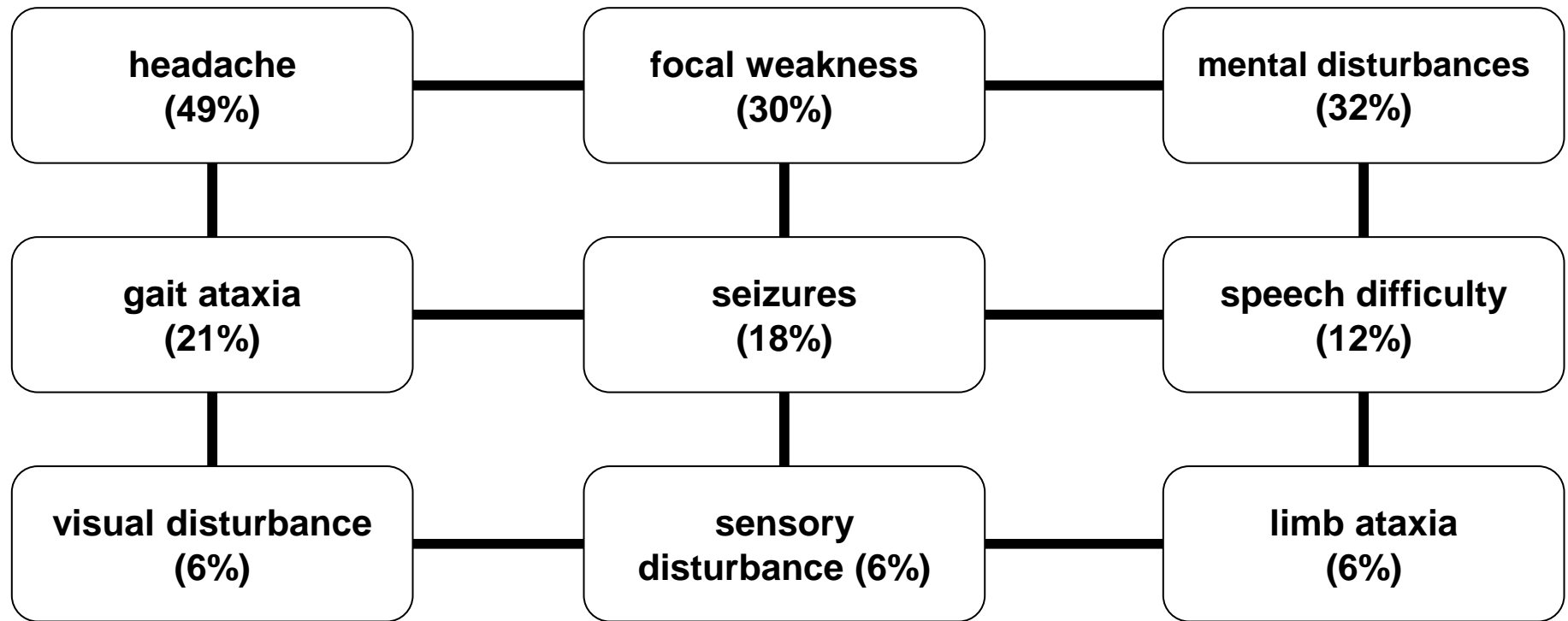


Radiological and clinical response
after 30Gy radiotherapy

Gainor JTO 2013

- CNS failures not only in the brain but also spinal cord

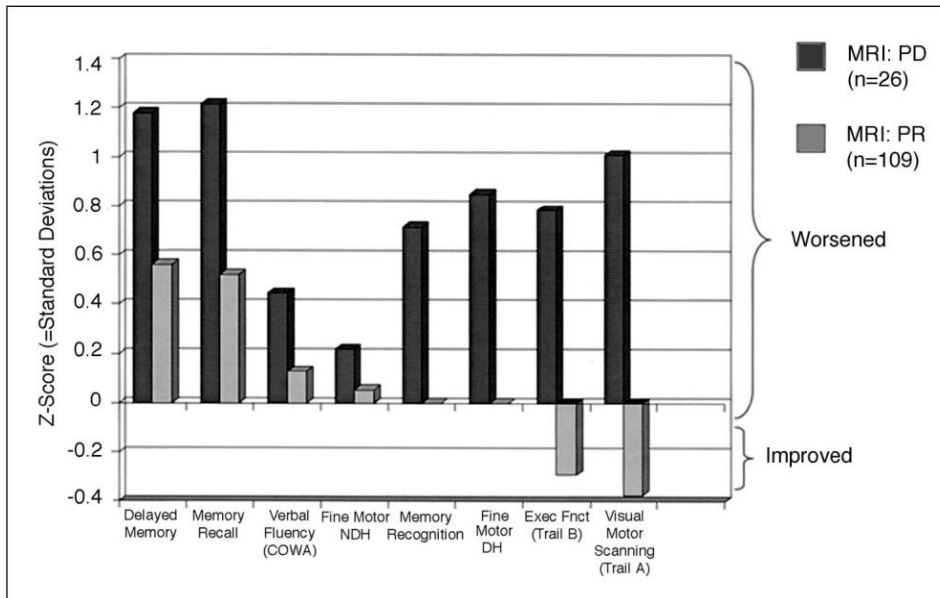
Symptoms of brain metastases



Tremendous impact on Quality of life

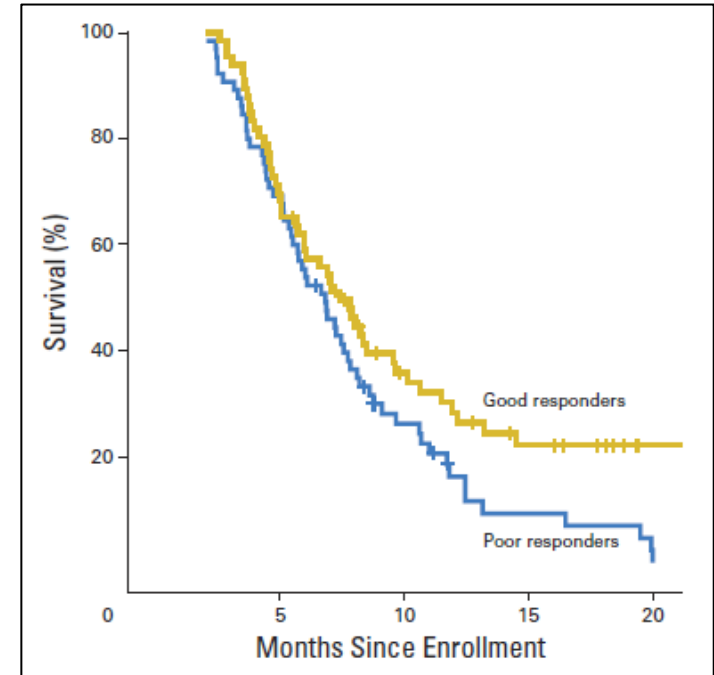
Importance of achieving maximum response

Neurocognitive function



Meyers JCO 2004

Overall survival



Li JCO 2007

Improved LOCAL intracranial tumor response

➤ Improved neurocognitive function & improved OS

Aims of treatment

- 1. Maximize response of brain metastases**
- 2. Maintain systematic disease stability**

CNS failure during Crizotinib treatment

Therapeutic options:

Systemic:

- *Change to Chemotherapy*
- *Continue Crizotinib*
- *Change to second-line ALK inhibitor*

Local:

- *Neurosurgery & Radiotherapy*
- *Whole brain irradiation*
- *Whole brain irradiation & Radiosurgery*
- *Radiosurgery only*

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Change to Chemotherapy and delayed local Tx

Randomized trials comparing CT alone versus CT & WBI

Study	CT	OS	RR after CT alone
Postmus 2000	Teniposide	NS	22%
Robinet 2001	Cisplatin and vinorelbine	NS	-
Mornex 2003	Fotemustine	NS	7%

- Low response rates of brain metastases to „classical“ CT
- Remaining extra-CNS efficacy of Crizotinib making it difficult to abandon ALK targeting treatment

CNS failure during Crizotinib treatment

Therapeutic options:

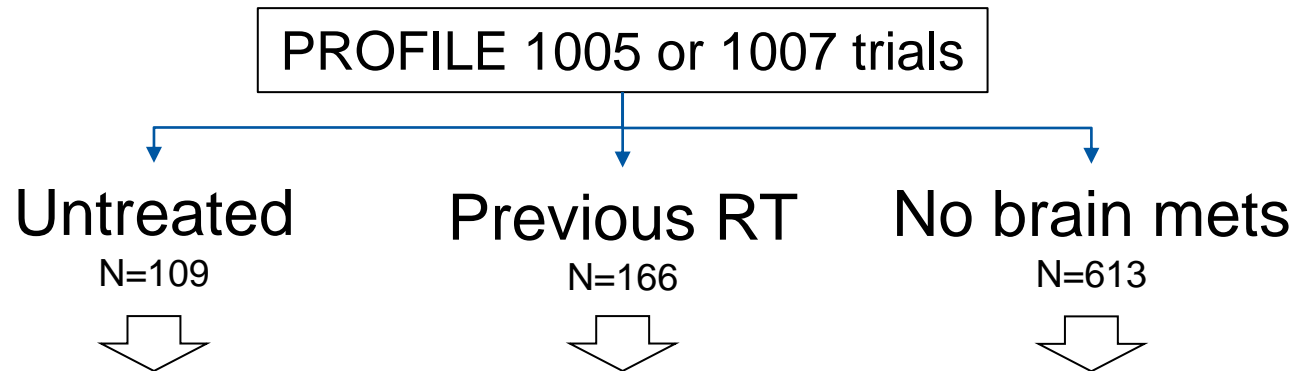
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Continuation of Crizotinib after diagnosis of asymptomatic brain mets



Disease control rate @ 12 weeks			
IC Systemic	56%	62%	
	63%	65%	71%

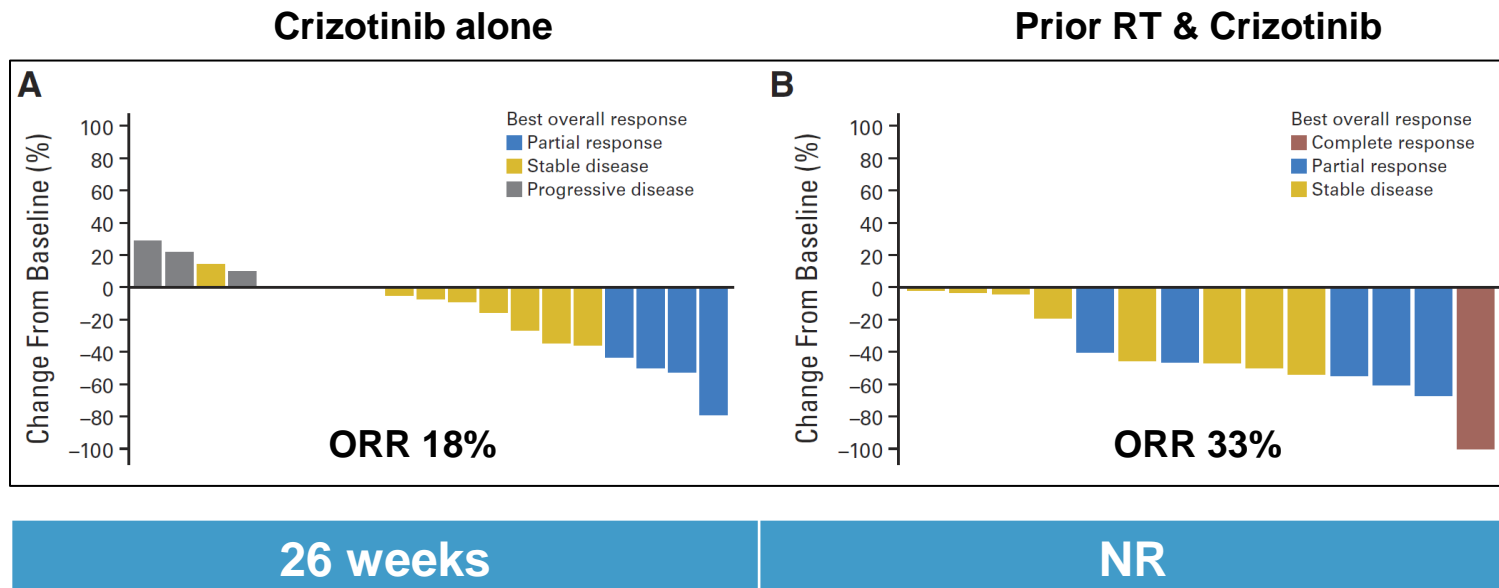
Costa JCO 2015

Even short term:

- Insufficient control of asymptomatic brain metastases with Crizotinib

Continuation of Crizotinib after diagnosis of brain mets

Intra-cranial response

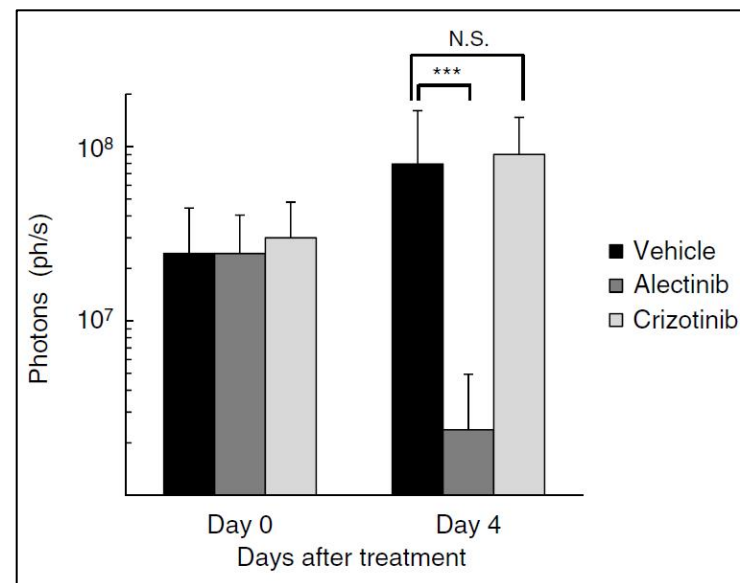
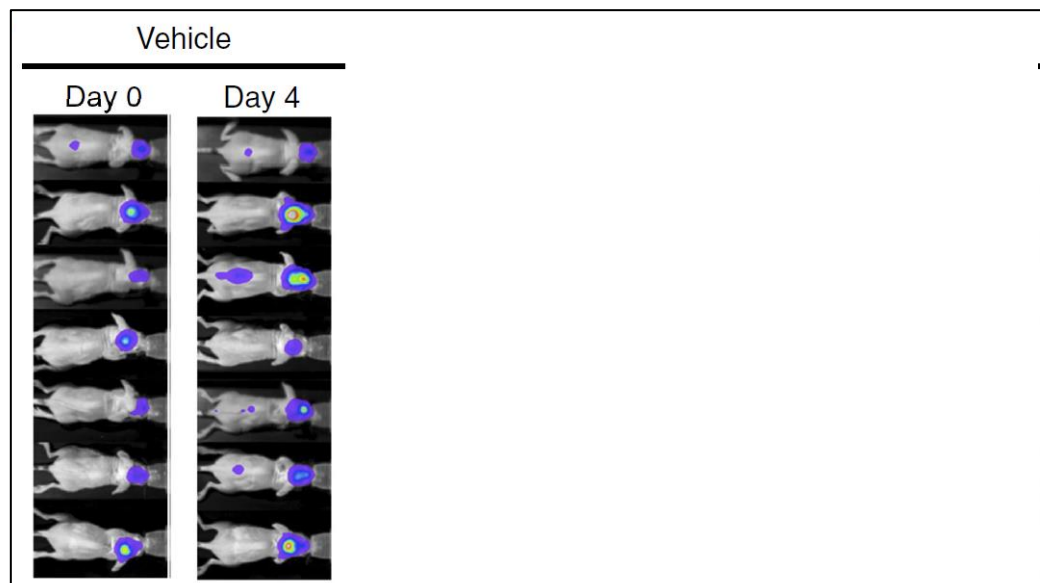


Costa JCO 2015

- Improved response of brain metastases to Crizotinib when combined with radiotherapy

CNS activity of ALK targeting agents

ALK positive mouse model of implanted brain metastases



Kodama Cancer Chemother Pharmacol 2014

- No CNS activity of Crizotinib
- High CNS activity of Alectinib

CNS failure during Crizotinib treatment

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- *Continue Crizotinib*
- *Change to second-line ALK inhibitor*

Local:

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Targeting of ALK positive NSCLC

First-generation ALK inhibitors

Crizotinib

- Oral tyrosine kinase inhibitor targeting ALK, MET, and ROS1

Second-generation ALK inhibitors

Ceritinib

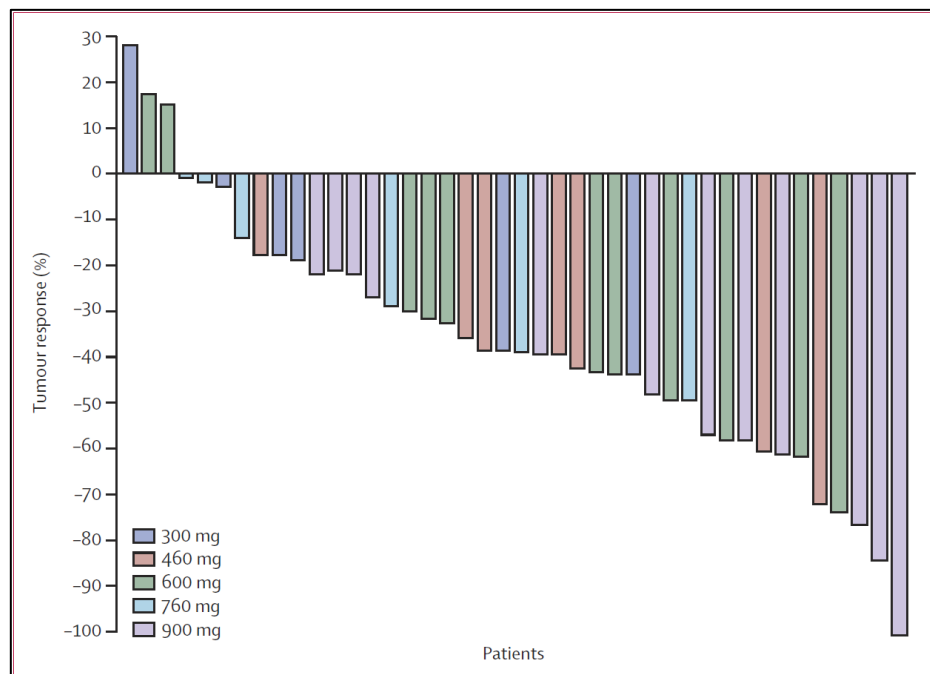
- selective small-molecule tyrosine kinase inhibitor of ALK

Alectinib

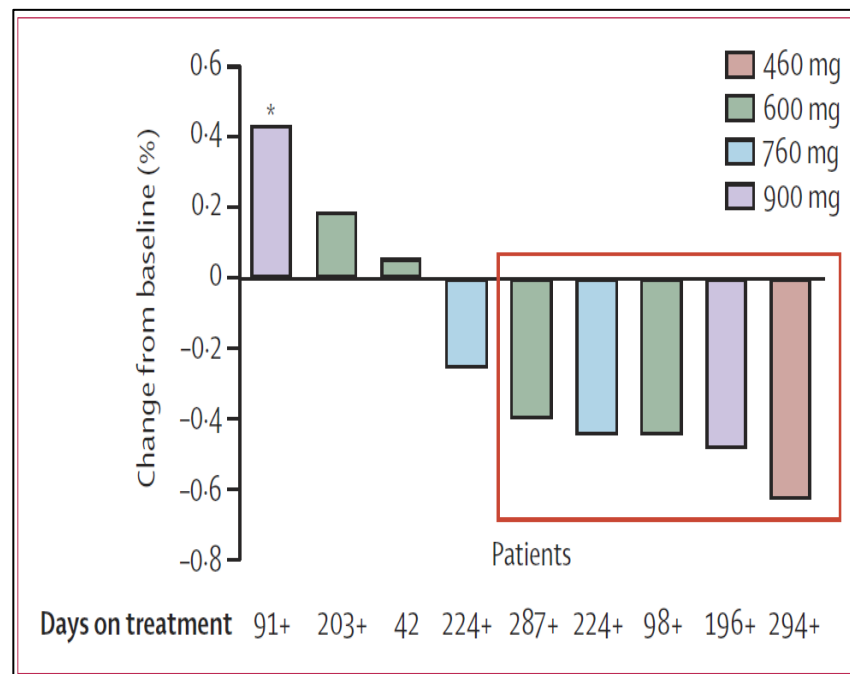
- highly selective ALK inhibitor

Alectinib after Crizotinib progression

Overall response



CNS response



Gadgeel Lancet Oncology 2014

- Dose reduction required in 26% due to adverse events
- Intra-cranial response in only 5 / 9 patients

CNS failure during Crizotinib treatment

Therapeutic options:

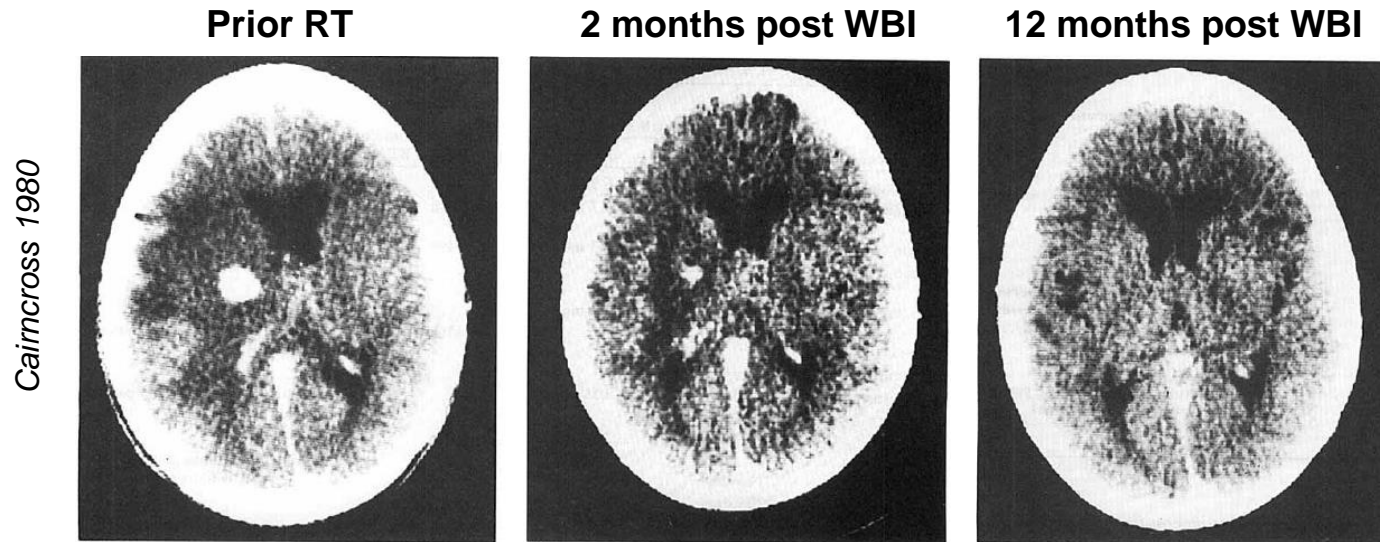
Systemic:

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Local:

- *Whole brain irradiation*
- *Neurosurgery*
- *Whole brain irradiation & Radiosurgery*
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Facts about whole brain irradiation only: Symptom improvement



61 y.o. female with RCC; WBI 10 x 3Gy

- Response rates > 50% independently from histology
- Symptom improvement in 60 – 85%

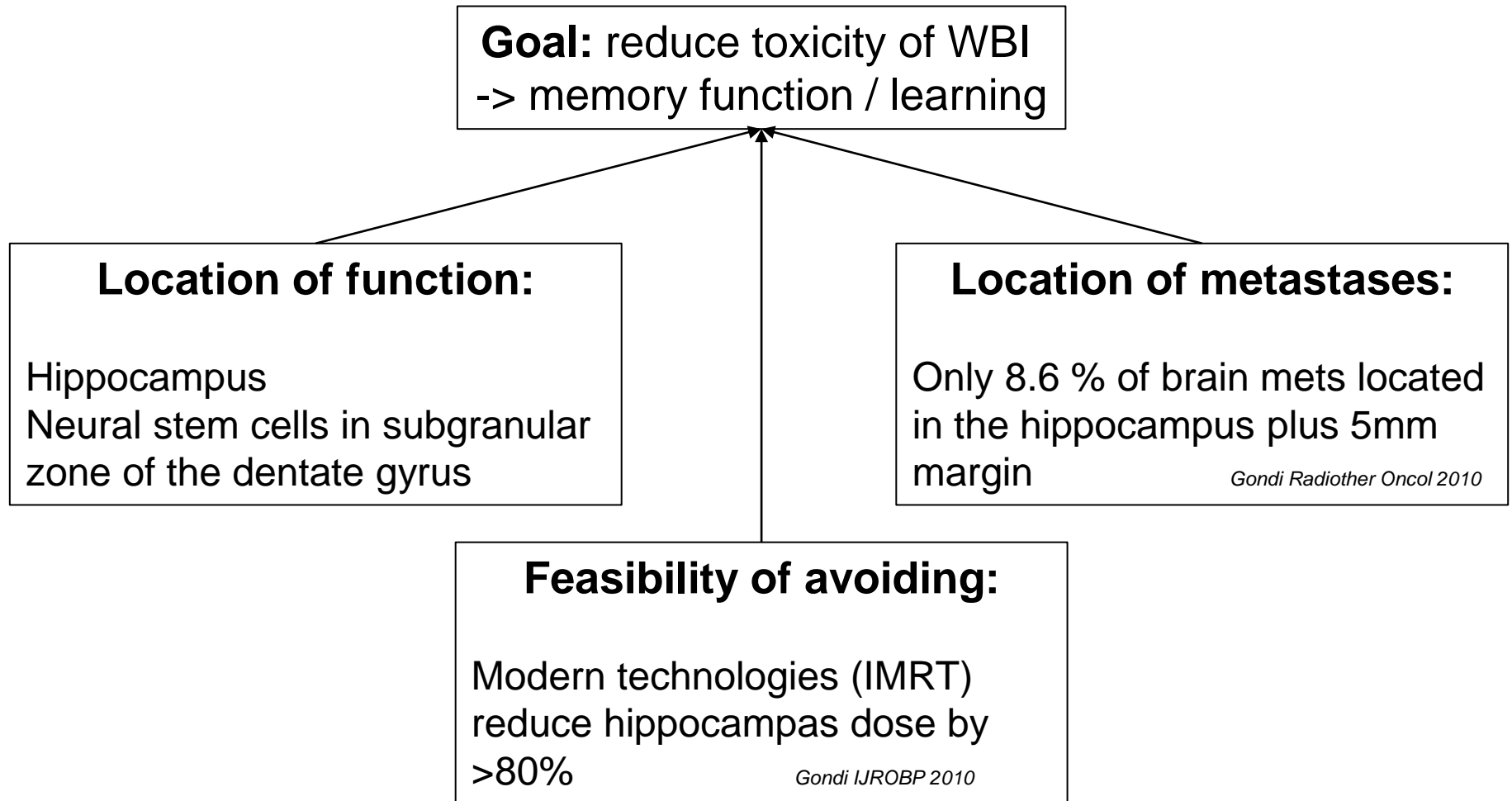
Facts about whole brain irradiation only: Impact on OS

Best supportive care	Corticosteroids	Whole brain irradiation
OS: 1 month	OS: 2 months	OS: 3 – 6 months

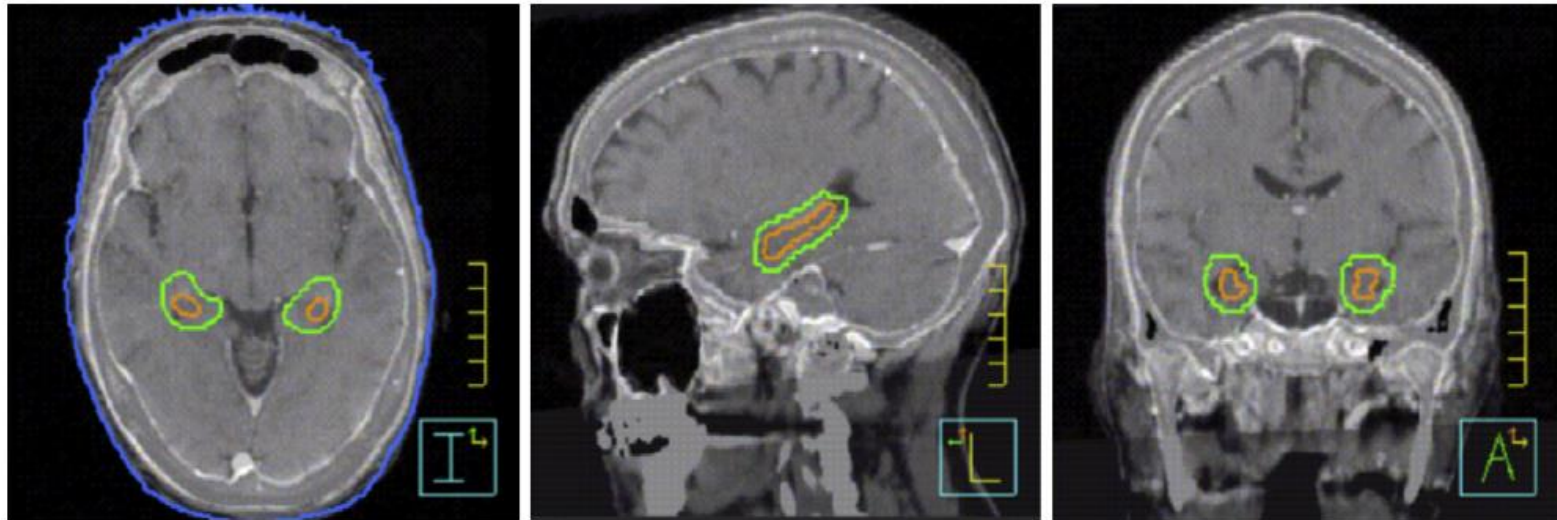
*Chao 1954
Katz 1981
Zimm 1981*

- No randomized controlled trials, retrospective data only
 - Despite WBI: neurological progression cause of death in up to 50%
 - Neurocognitive function impairment in patients with longer OS

WBI with hippocampus sparing



WBI with hippocampus sparing



RTOG 0933

- Prospective phase II trial of hippocampus sparing during WBI with 10 x 3Gy
- The primary endpoint was the Hopkins Verbal Learning Test Delayed Recall (HVLT-DR) at 4 months
- N=113
- Metastatic progression in hippocampus: 4.5%
- Mean relative decline in HVLT-DR from baseline to 4 months: 7.0%

Gondi IJROBP 2013

CNS failure during Crizotinib treatment

Therapeutic options:

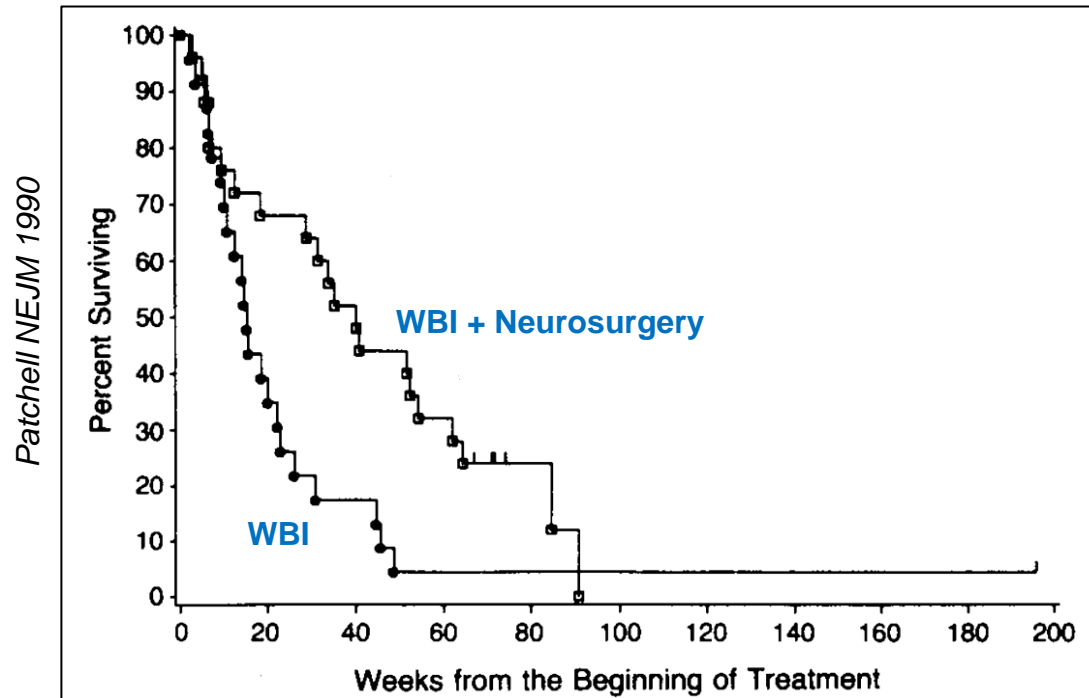
Systemic:

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- *Change to second-line ALK inhibitor*

Local:

- *Whole brain irradiation*
- **Neurosurgery**
- *Whole brain irradiation & Radiosurgery*
- *Radiosurgery only*

Surgical resection of solitary brain metastases



Study	Inclusion criteria	OS
Patchell 1990	KPS \geq 70	40 vs 15 weeks
Noordijk 1994	WHO \leq 2	10 mo vs 6 mo
Mintz 1996	KPS \geq 50	6 mo vs 6 mo

CNS failure during Crizotinib treatment

Therapeutic options:

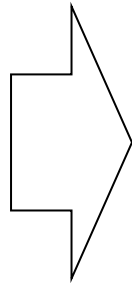
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Local:

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- *Neurosurgery*
- **Whole brain irradiation & Radiosurgery**
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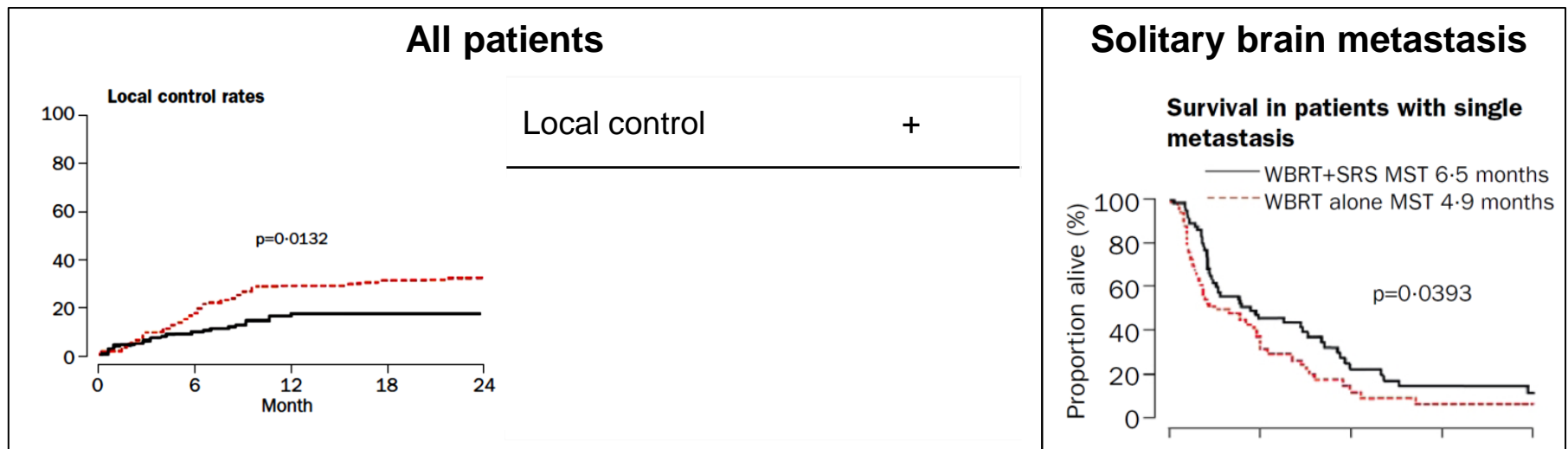
radiosurgery: From frame-based to image-guided



Radiosurgery of brain metastases

RTOG 95-08: *Andrews Lancet 2004*

- RCT: WBI vs WBI & SRS
 - 1 – 3 brain metastases (333 patients)
 - KPS ≥ 70



➤ SRS improves OS in RPA class I patients compared to WBI only

CNS failure during Crizotinib treatment

Therapeutic options:

Systemic:

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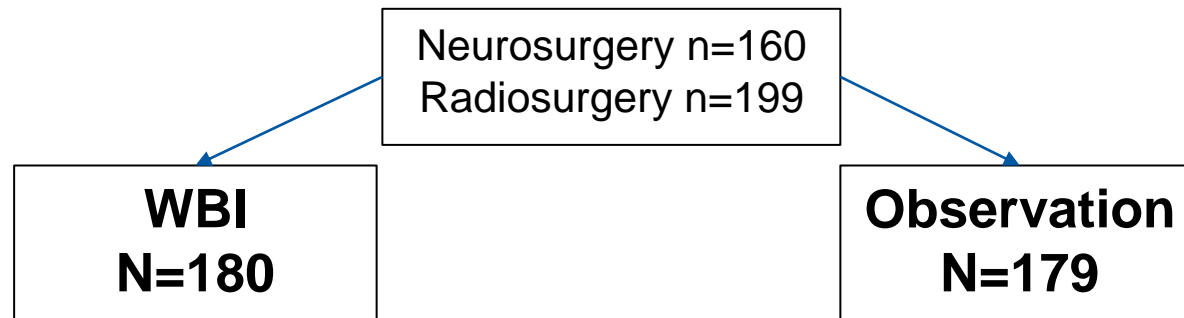
Local:

- *Whole brain irradiation*
- *Neurosurgery*
- *Whole brain irradiation & Radiosurgery*
- ***Radiosurgery only***

SRS w/o WBI for 1 – 3 brain metastases

- 1- 3 brain metastases
- stable systemic disease or asymptomatic primary tumors
- WHO performance status (PS) of 0 to 2

Kocher JCO 2011



Primary EP:

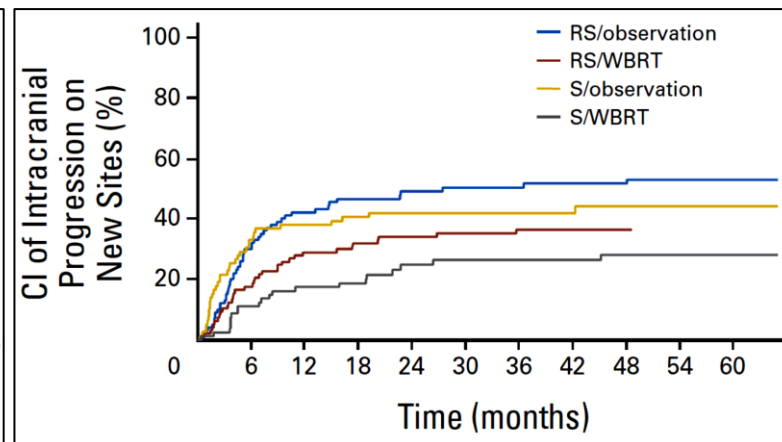
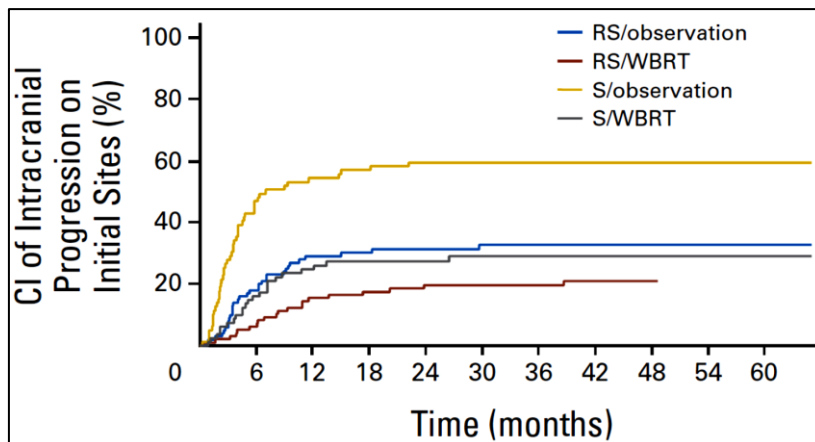
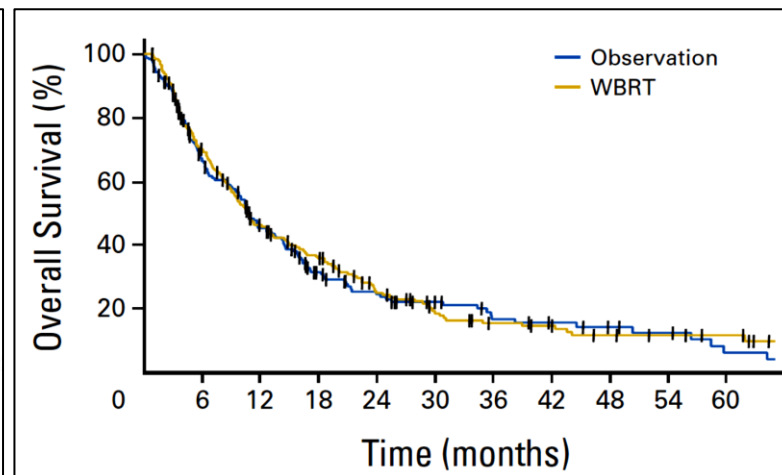
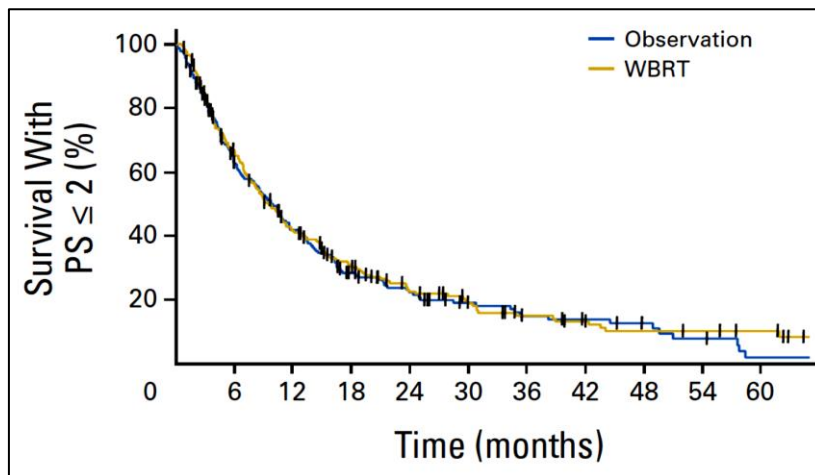
- duration of functional independence

Secondary EP:

- frequency of intracranial relapse at initially
- treated and at new sites
- progression-free
- overall survival
- late toxicities
- quality of life

SRS w/o WBI for 1 - 3 brain metastases

Kocher JCO 2011



SRS w/o WBI for >3/4 brain metastases

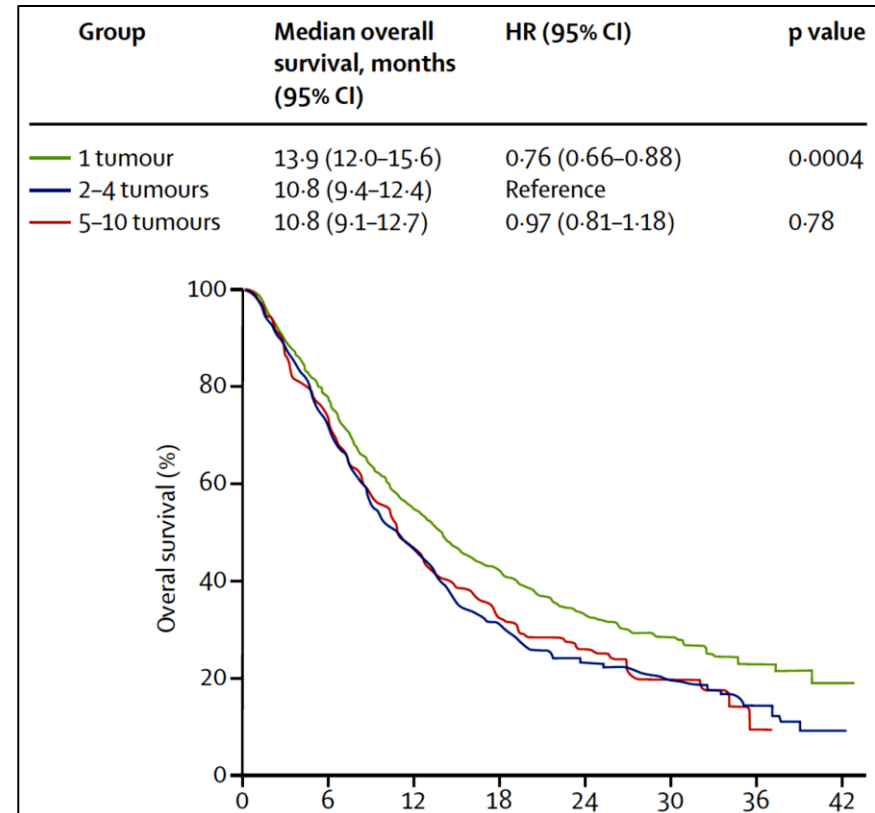
Prospective observational study

Inclusion criteria: n=1194

- SRS only for 1 – 10 brain metastases
- Largest tumor <10ml, <3cm
- Total cumulative volume 15ml
- KPS ≥ 70

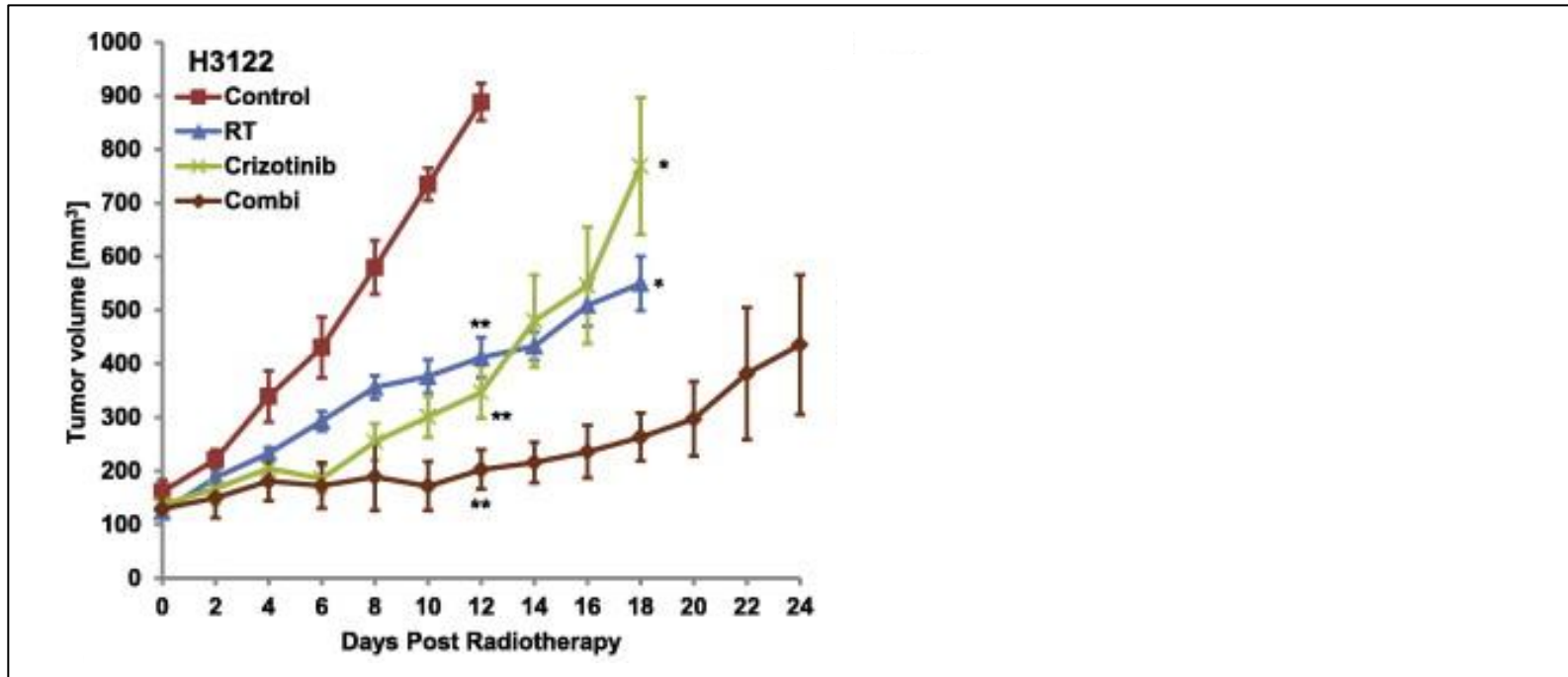
SRS with 1 x 20-22Gy
MRI FU every 3 months

Yamamoto Lancet Oncol 2014



➤ OS identical in patients with 2-4 and 5-10 metastases

Interaction of Crizotinib & radiotherapy



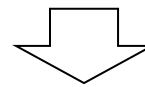
Xenograft model in ALK+ (H3122)

- Synergistic anti-proliferative and pro-apoptotic effect between RT and Crizotinib
- Effect on normal tissue ?

Local ablative radiotherapy for oligo-progressive ALK+ NSCLC

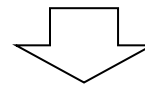
Weickhardt JTO 2012

Retrospective study n=38
ALK+ Crizotinib



PFS 9 months

15 / 28 suitable for local RT
50% CNS progression



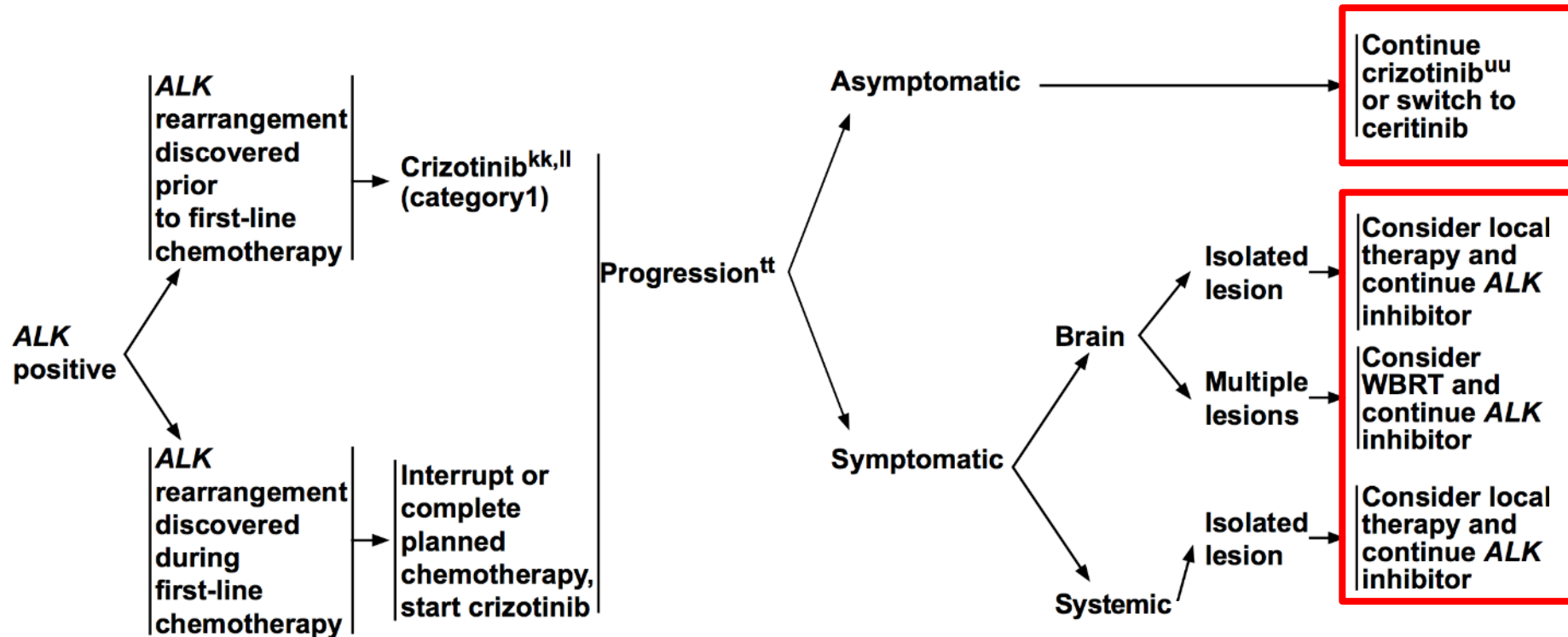
WBI & SRS & SBRT
Continuation of Crizotinib

Time to further progression:	6 months
RT to CNS:	7.1 months
RT to eCNS:	4 months

- Six additional months of disease control
- No grade 3/4 toxicity **except** fatigue in patients receiving WBI

What is stated in the guidelines for this situation ...

NCCN Guidelines Version 5.2015



- Continue Crizotinib beyond progression
- Symptomatic vs asymptomatic the indication for local TX ?

So how would my treatment look like

Interpretation of clinical situation:

- CNS failure due to inability of Crizotinib to cross the blood-brain barrier
- No acquired extra-CNS Crizotinib-resistance, yet

Recommendations:

Systemic:

- Proceed with Crizotinib
 - Continuous extra-CNS activity
 - Change to second-generation ALK inhibitor -> systemic failure

CNS:

- Asymptomatic lesions <5mm: close MRI follow-up
- Large lesions not responding to steroids: neurosurgery
- Large majority of patients: radiosurgery only