GOLF 2016

Métastases cérébrales
Quelle stratégie?

Benjamin Besse

Oncologue médical

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GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

IOT | Institut d'Oncologie Thoracique

Disclosures

- **No personal financial disclosures**
- **Institutional grants for clinical and translational research**
  - AstraZeneca, BMS, Boehringer-Ingelheim, Lilly, Pfizer, Roche-Genentech, Sanofi-Aventis, Clovis, GSK, Servier, EOS, Onxeo, OncoMed, Inivata, OSE Pharma

Brain metastases managment

- Brain mets in NSCLC
- Blood Brain Barrier
- Radiotherapy
- Chemotherapy and antiangiogenic drugs
- Specific targeted therapies
- Immunotherapy
- Leptomeningeal carcinomatosis
- Conclusion

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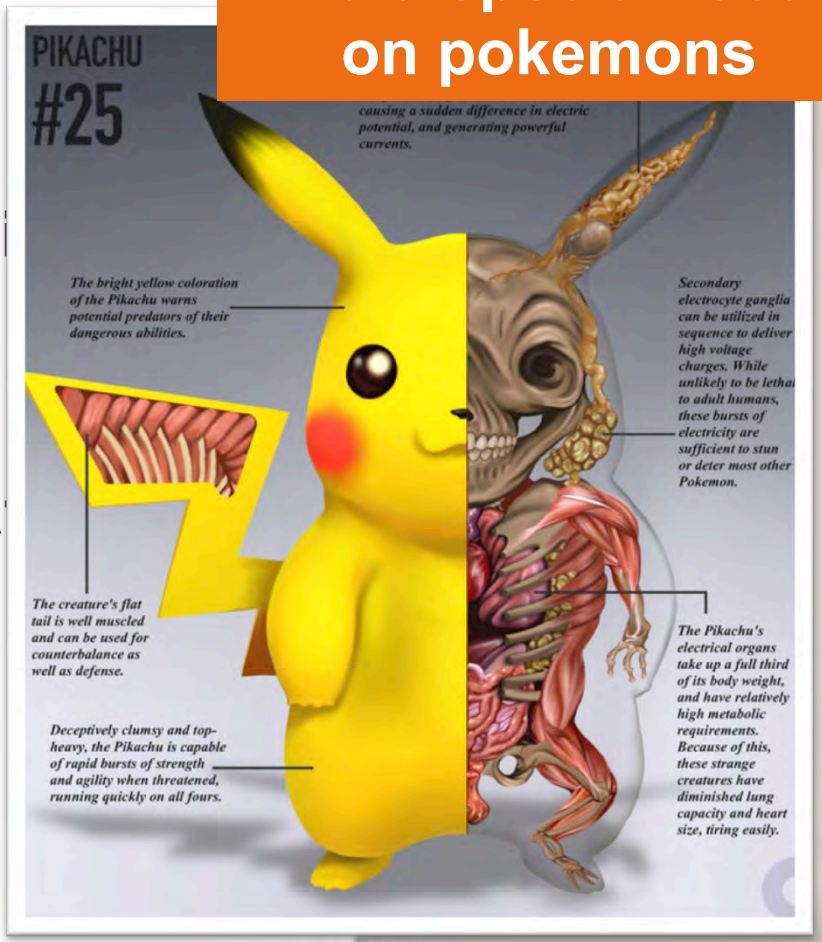
And a special focus on pokemons



Brain metastases managment

- **Brain mets in NSCLC**
- Blood Brain Barrier
- Radiotherapy
- Chemotherapy and antiangiogenic drugs
- Specific targeted therapies
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Brain mets in lung Cancer

- ✓ Median OS advanced NSCLC = 13 months
- ✓ First cause of brain mets
  - 10 - 18% at the time of diagnosis, 40% in total
- ✓ Median OS advanced NSCLC + brain mets = 4 - 16 months

Median OS from trials investigating WBRT, chemotherapy regimens and molecularly targeted treatments.

Regimen	Median OS range, months	Regimen	Median OS range, months	Regimen	Median OS range, months
WBRT regimens	3.7–13.4	**Chemotherapy regimens**	7.6–8.2	**Targeted therapies**	5–18.9
WBRT alone	5.2–7.2			Gefitinib	5–15
WBRT + SRS	10.3–13.4			Erlotinib	9.1–19.1
WBRT + chemotherapy	3.7–12.6			Erlotinib in *EGFR* positive	18.9–19.1

EGFR, epidermal growth factor receptor; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy.

Vallières E et al. J Thorac Oncol 2009; 4:1049-1059; Gaspar LE. Expert Rev Anticancer Ther 2002; 4:259-270
Chaubet-Houdu M. Bull Cancer 2013; 100:95-98; Peters – Cancer Treat Reviews 2016

Brain mets in lung Cancer

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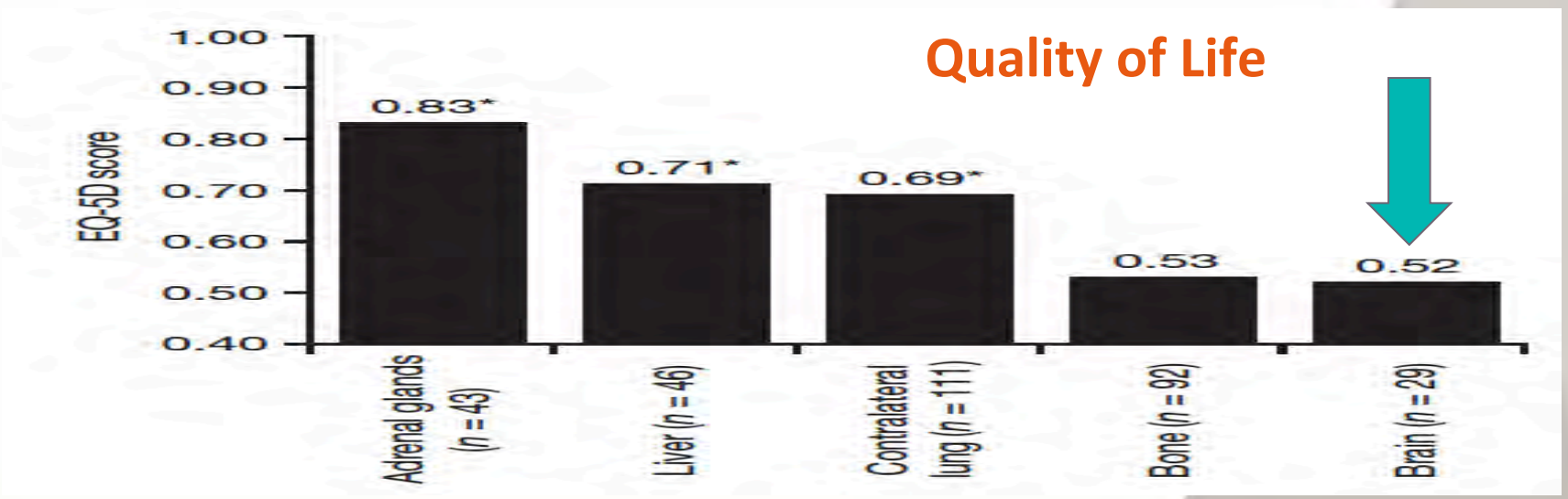

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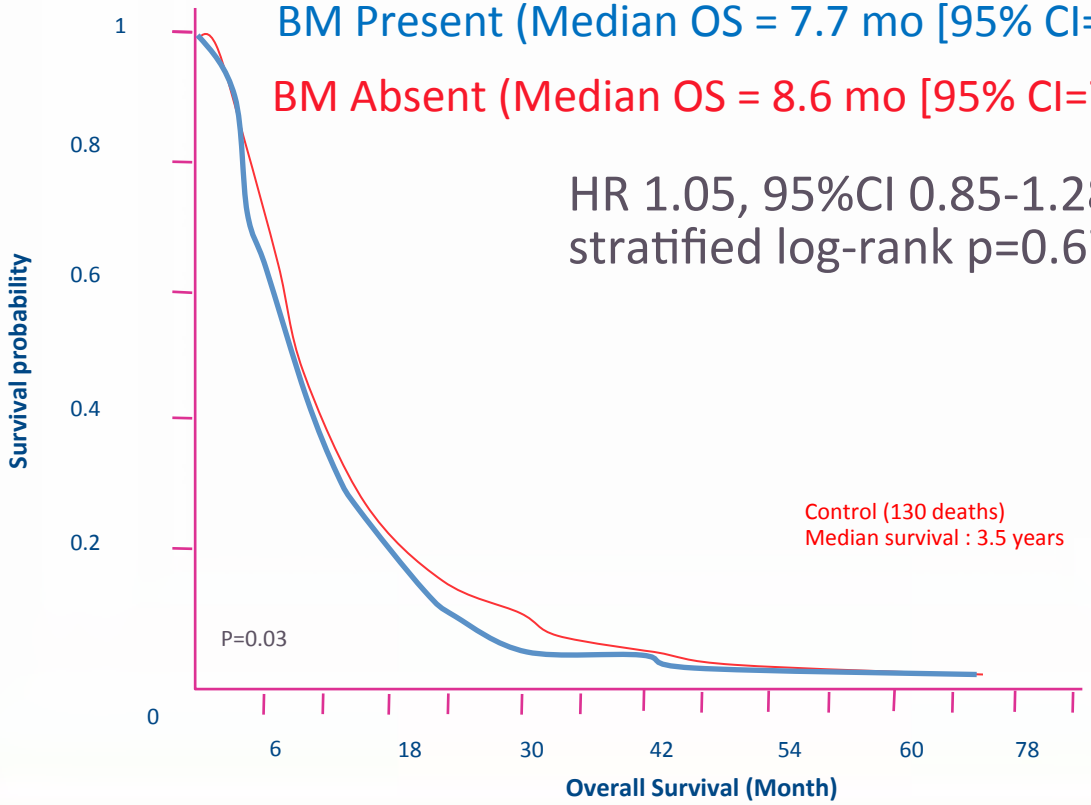
OS in brain mets patients

- Canadian cohort
- 3 RCT (BR.18, BR.21, BR.24)
- N=131(BM+)/1218(BM-)



P.A. Bradbury et col. ASCO 2009 Abs 8075
M.J.Edelman et col. ASCO 2009 Abs 8076

Brain metastases managment

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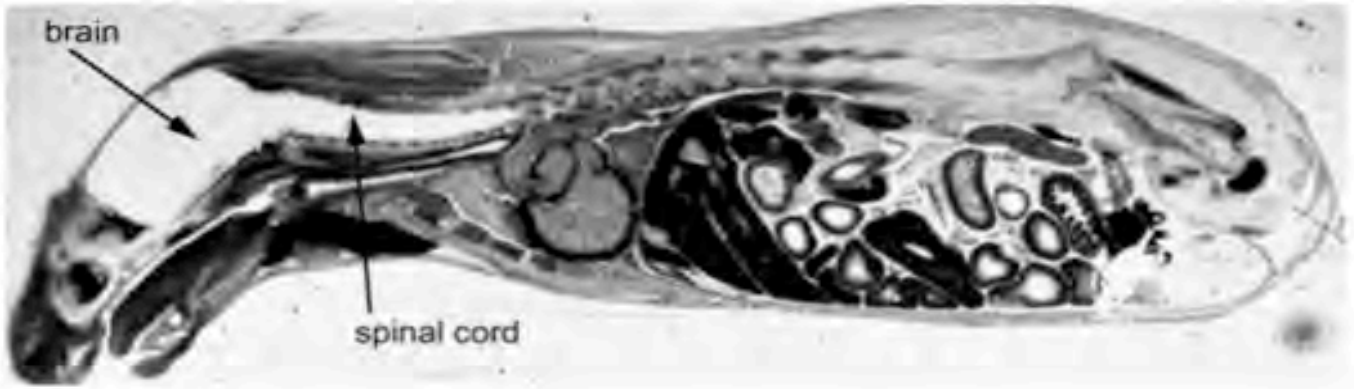
Why is it difficult to treat brain metastases?

The Blood-Brain Barrier: Bottleneck in Brain Drug Development



> 98 % of small molecule drugs do not cross the BBB	~100 % of large molecule drugs do not cross the BBB	<1 % of drug companies have a BBB drug targeting program	<1 % of academic neuroscience programs emphasize BBB transport biology

FIG. 1. Whole body autoradiogram of an adult mouse sacrificed 30 min after intravenous injection of radiolabeled histamine, a small molecule that readily enters all organs of the body, except for the brain and spinal cord.

Pardridge WM et al ,NeuroRX 2005: 2, 3

Blood Brain Barrier
The art of illusion

Table 4 Metastatic brain tumor tissue concentration of agents

Drug	MW	Lipophilicity[a]	N	O	TBR	*n*	Primary cancer
Cisplatin [30]	298	−2.1939	2	0	0.78	18	Lung
					1.68[b]	9	Lung
Liposomal Daunorubicin [31, 32]	564	0.1[c]	1	10	8.36	1	Adenocarcinoma NOS
Estramustine [34]	440	5.7	1	3	17.8	2	Melanoma, Thyroid
Etoposide [35–37]	589	1	0	13	0.116	1	Adenocarcinoma NOS
					0.155	5	Not stated
					0.199	3	Lung, Melanoma
Idarubicin [39]	497	0.2	1	9	5.6	1	Breast
Mitoxantrone [42]	444	−3.1	4	6	32.02	5	Multiple[d]
Paclitaxel [43, 44]	854	3	1	14	0.77	8	Lung, Melanoma
Teniposide [33, 45, 46]	657	1.5	0	13	1.03	8	Lung, melanoma, colon
					4.95	2	Breast, Melanoma
Temozolomide [25]	194	−2.8	6	2	0.118	5	NSCLC

Studies sorted alphabetically by agent name. *TBR* tissue to blood ratio, *MW* molecular weight rounded to nearest g mol^{-1}, *N* number of nitrogen atoms, *O* number of oxygen atoms, *n* sample size; MW, N, O, log(p) data from http://pubchem.ncbi.nlm.nih.gov unless otherwise referenced

[a] Lipophilicity measured as log(p)

[b] Cisplatin administered intra-arterially

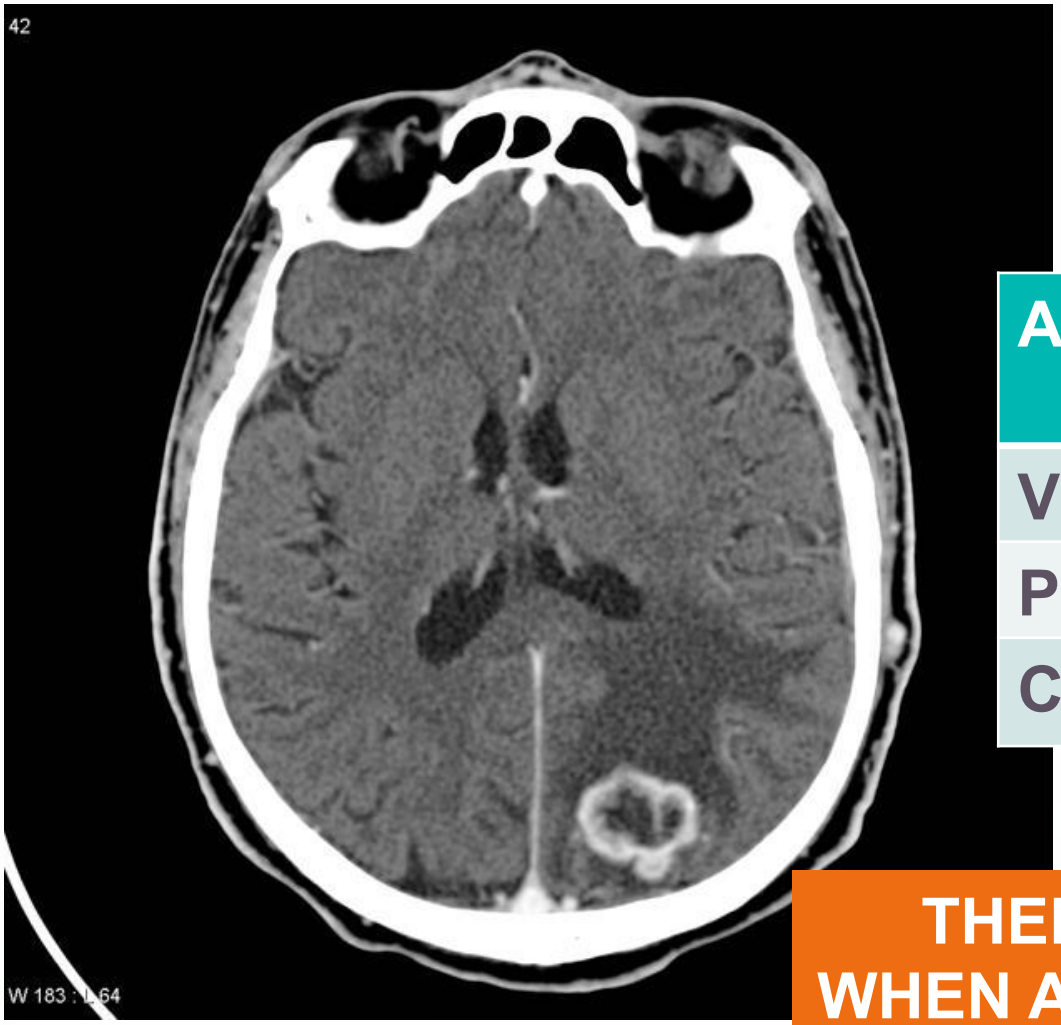
[c] Chemical data shown is for daunorubicin hydrochloride

[d] Breast, lung, paraganglioma, teratocarcinoma

Adapted from E. Le Rhun

Pitz et al. 2011

Brain CT Scan



Agent	Moleculat Weight
Visipaque™	1550
Paclitaxel	854
Cisplatin	298

THERE IS NO MORE BBB WHEN A BRAIN MET IS THERE!!

Brain metastases managment

- Brain mets in NSCLC
- Blood Brain Barrier
- Radiotherapy
  - WBRT
  - SABR
- Chemotherapy and antiangiogenic drugs
- Specific targeted therapies
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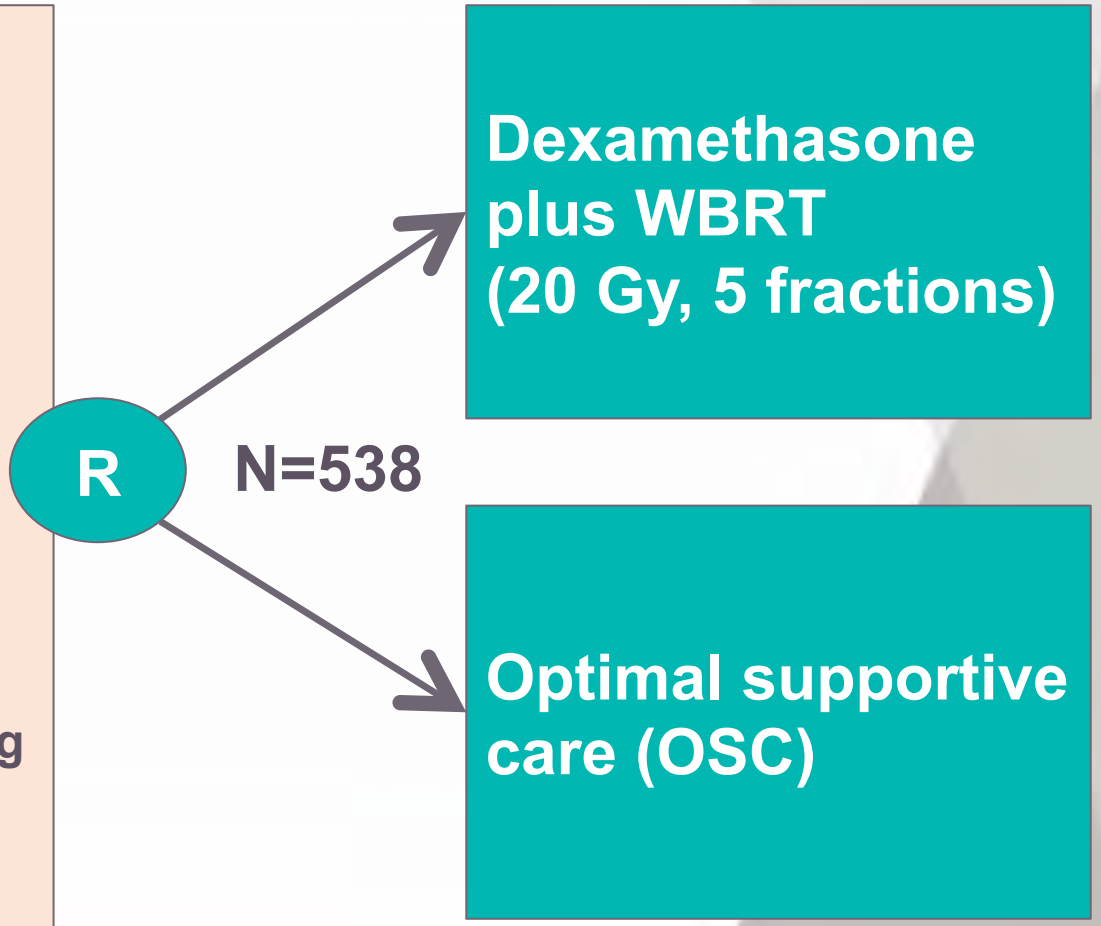
WBRT – Phase III trial QUARTZ

NSCLC &
BM unsuitable for Surgery or SABR

Stratification :
- Centre
- PS
- Gender
- status of BM
- status of primary lung cancer

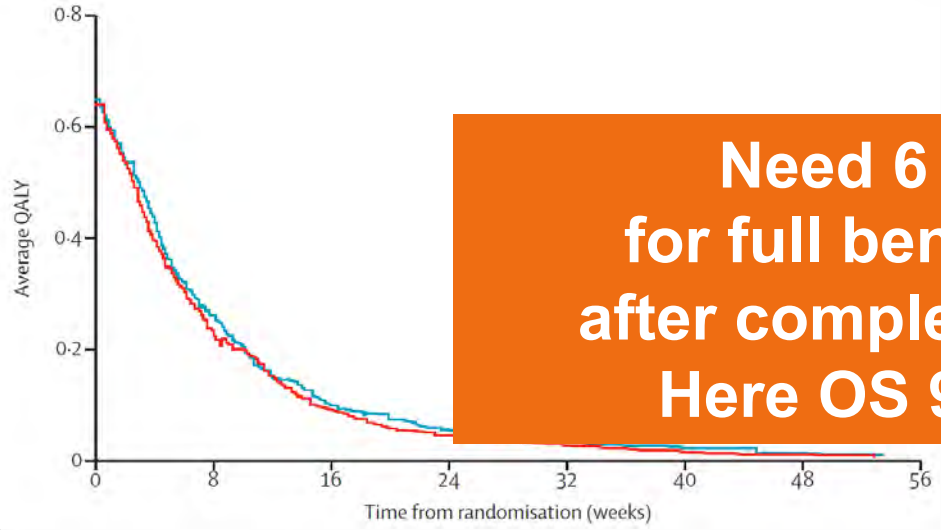


The primary outcome measure was quality-adjusted life-years (QALYs). QALYs = OS + EQ-5D questionnaire.

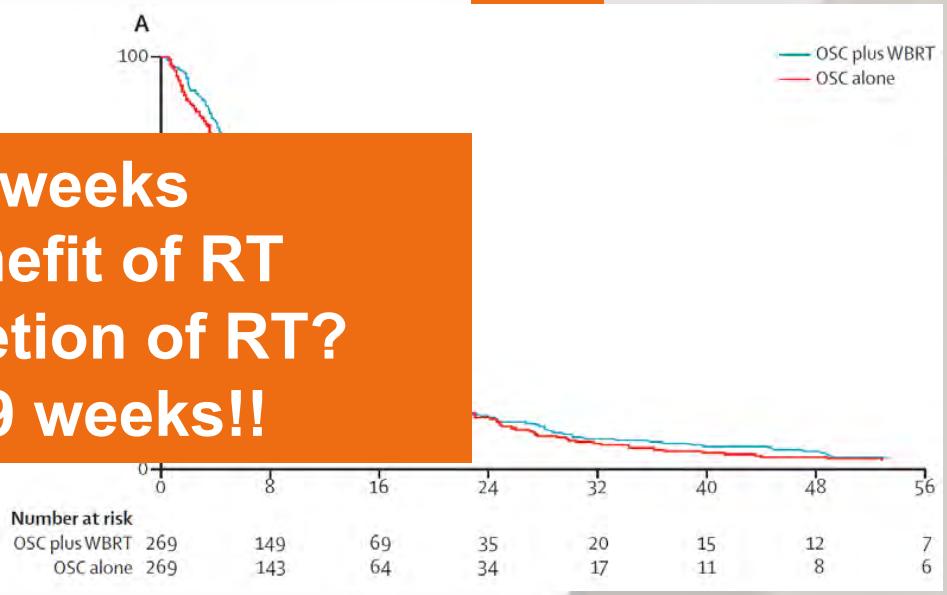
Mulvena, The Lancet 2016

QUARTZ

QALY



OS



Need 6 weeks for full benefit of RT after completion of RT? Here OS 9 weeks!!

Non-inferiority trial
1-week non-inferiority boundary
Delta QALYs = 4,7 days

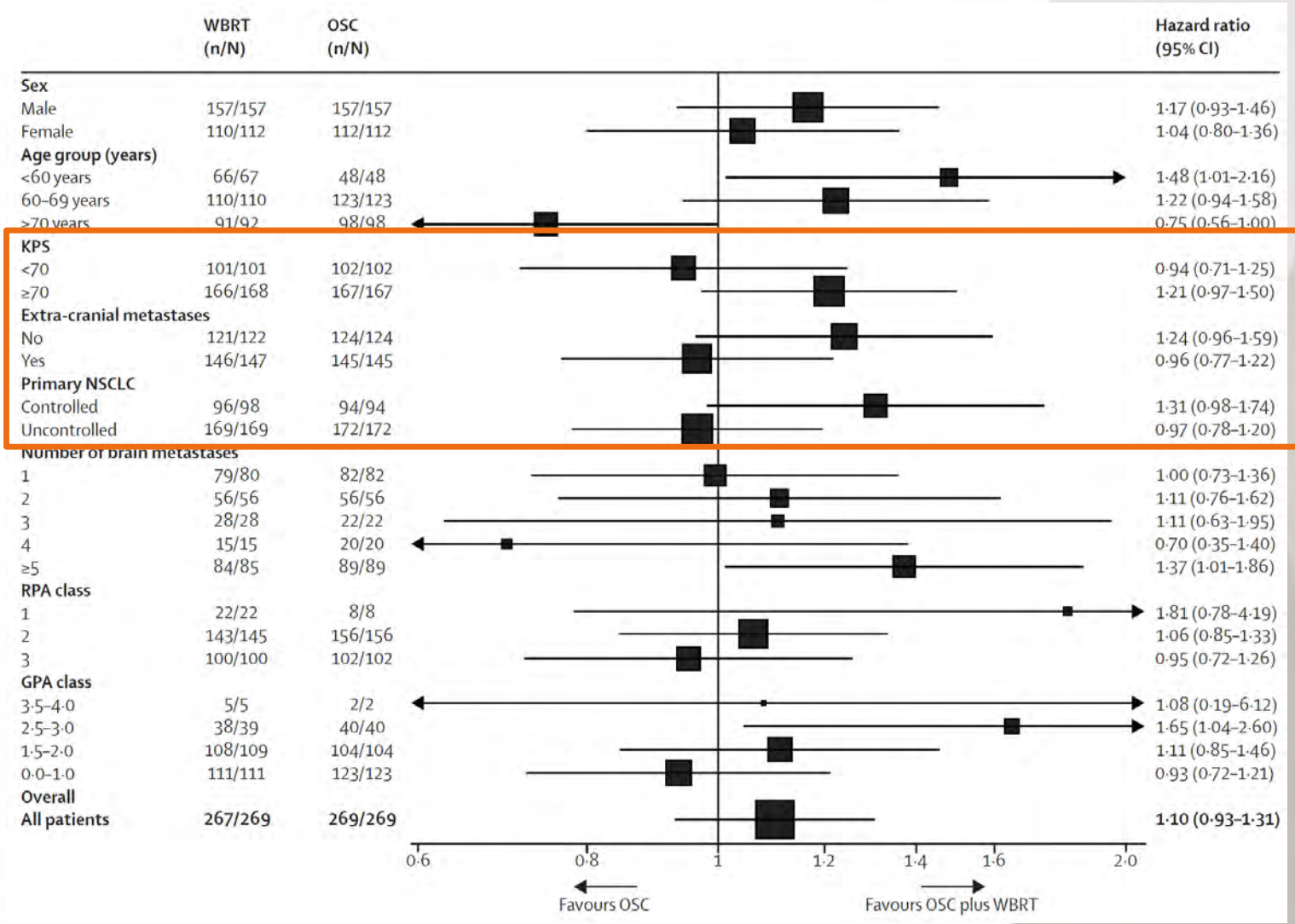
46,4 QALY days (WBRT) *vs* 41,7 QALY days(OSC)
Two-sided 90% CI of –12,7 to 3,3

OS = 9,2 wks (WBRT)
vs. 8.5 wks (OSC)
HR 1,06

(95% CI 0,90–1,26, p=0·8084)

Mulvena, The Lancet 2016

QUARTZ



Mulvena, The Lancet 2016

WBRT toxicity

Table 4. Testing of Deterioration Status From Baseline in Hopkins Verbal Learning Test During Follow-up Using Reliable Change Index

Component by Time Point	PCI				Observation					
	Deterioration		No Deterioration		Deterioration		No Deterioration			
	No.	%	No.	%	No.	%	No.	%	*P**	Adjusted *P*†
3 months										
Recall	28	45	34	55	10	13	66	87	< .001	< .001
Delayed recall	25	44	32	56	7	10	64	90	< .001	< .001
6 months										
Recall	11	19	46	81	3	5	58	95	.02	.045
Delayed recall	8	15	44	85	8	14	50	86	.81	.81
12 months										
Recall	10	26	28	74	3	7	42	93	.01	.03
Delayed recall	10	32	21	68	2	5	38	95	.003	.008

- Phase III PCI vs observation in locally advanced NSCLC
- First prospective 'Neurocognitive' trial focused on NSCLC
- Significant # favors *Observation, mostly at 12 mths*
- ***Main differences* in Short & Delayed *Memory***

Courtesy of F.Dhermain

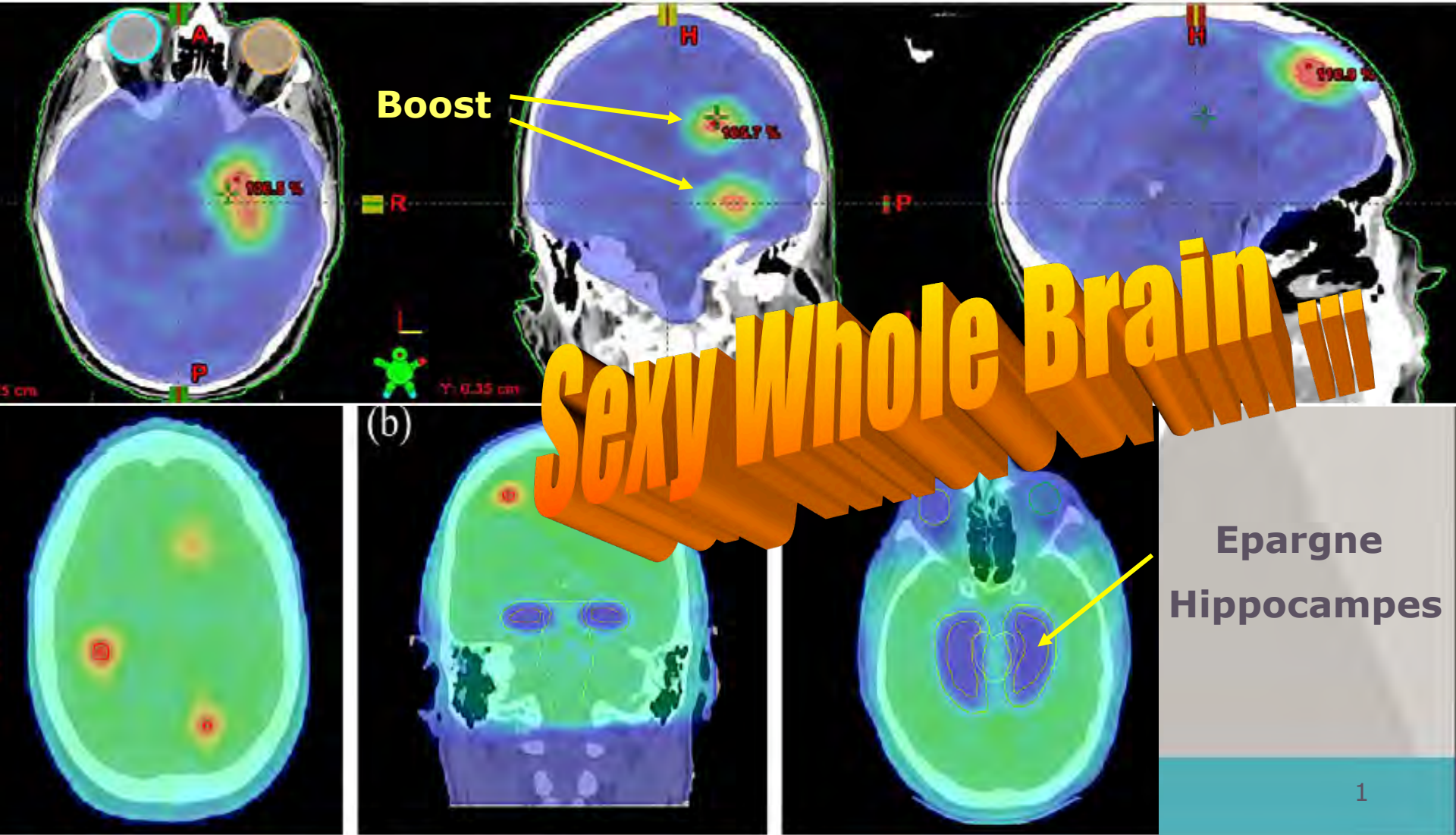
Sun, JCO 2011

PHYSICS CONTRIBUTION

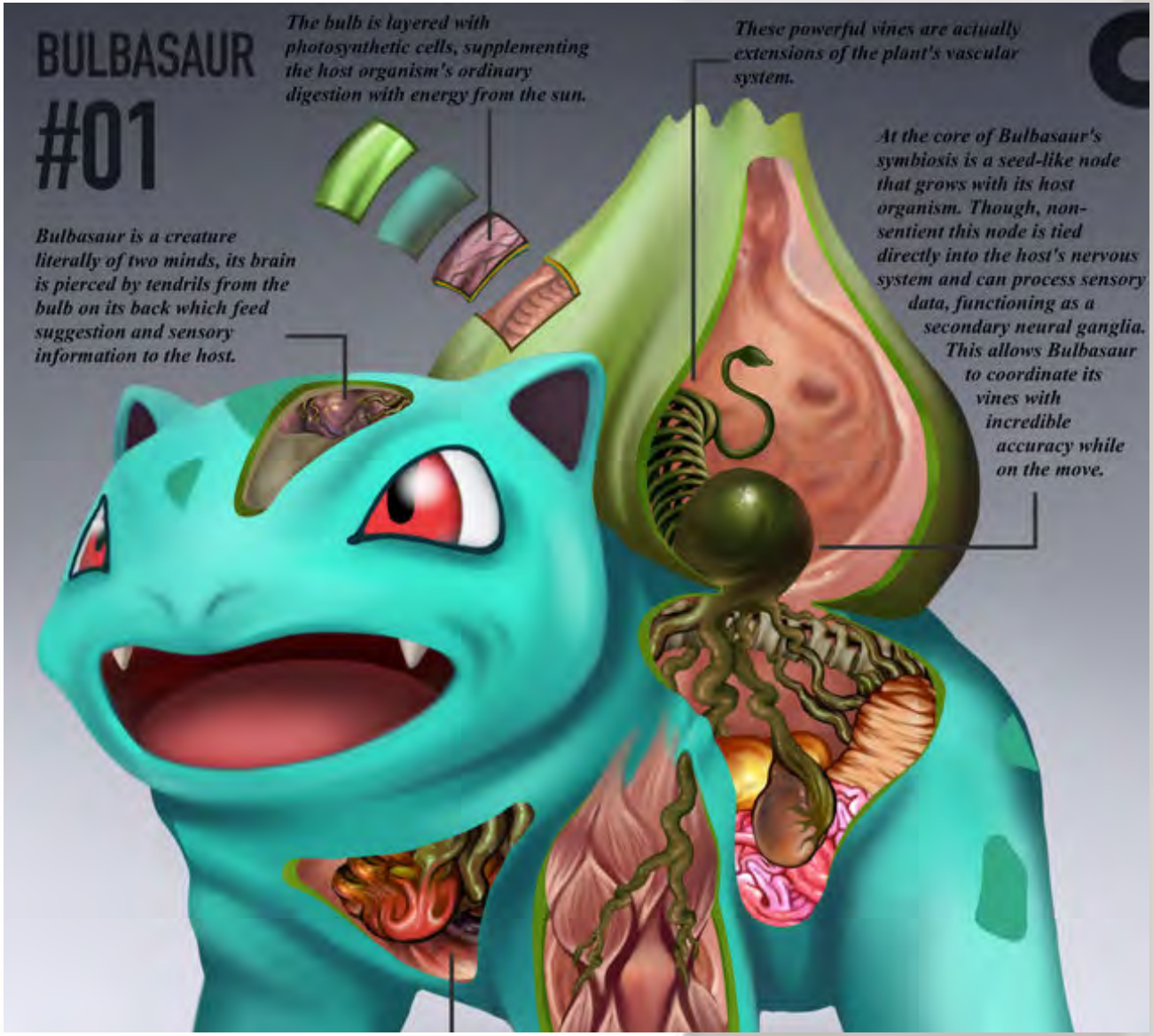
WHOLE-BRAIN RADIOTHERAPY WITH SIMULTANEOUS INTEGRATED BOOST TO MULTIPLE BRAIN METASTASES USING VOLUMETRIC MODULATED ARC THERAPY

FRANK J. LAGERWAARD, M.D., PH.D., ELLES A. P. VAN DER HOORN, WILKO F. A. R. VERBAKEL, PH.D., CORNELIS J. A. HAASBEEK, M.D., BEN J. SLOTMAN, M.D., PH.D., AND SURESH SENAN, M.R.C.P., F.R.C.R., PH.D.

Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands



ATTENTION!
LE BULBIZARRE
A 2 CERVEAUX



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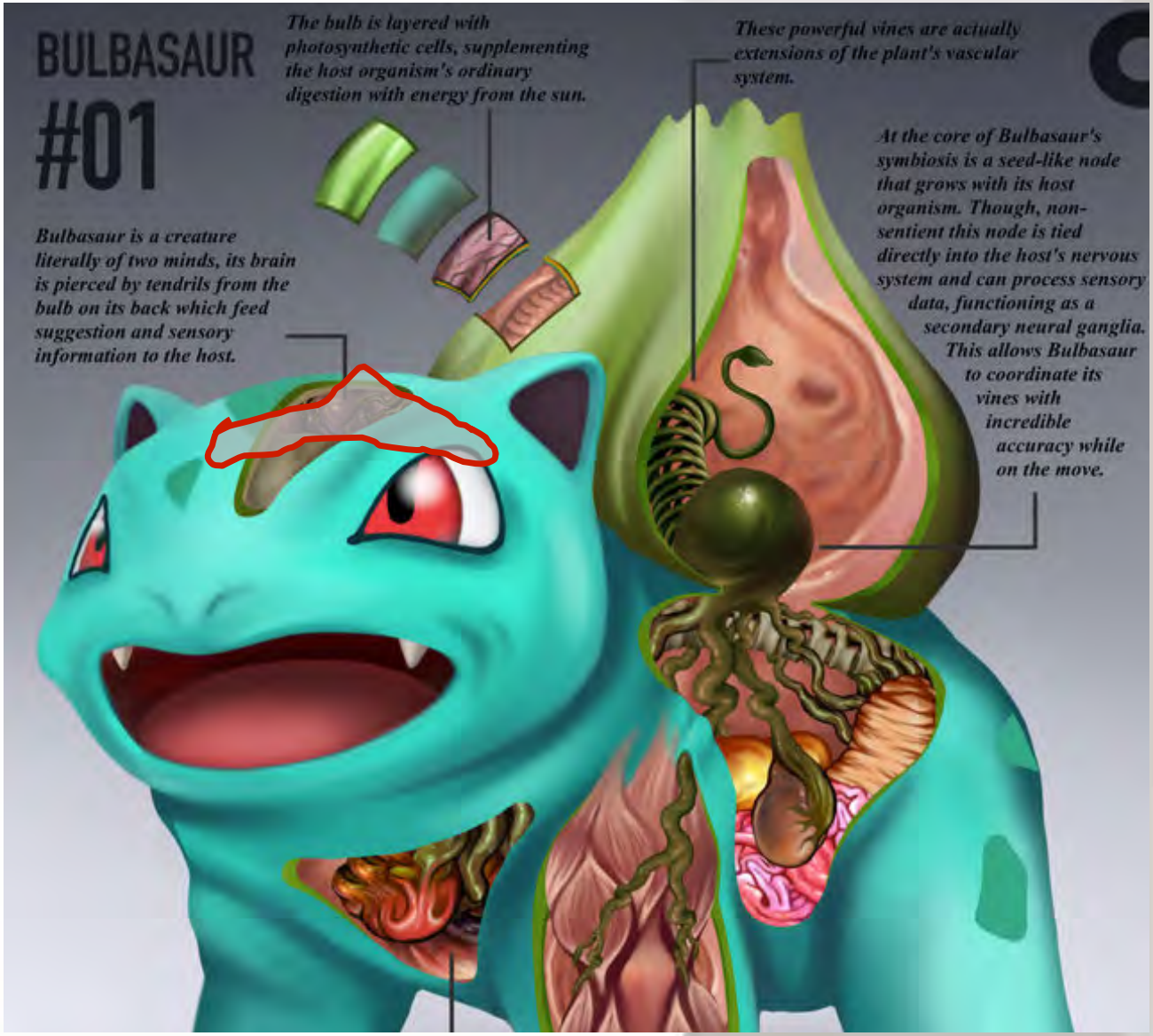

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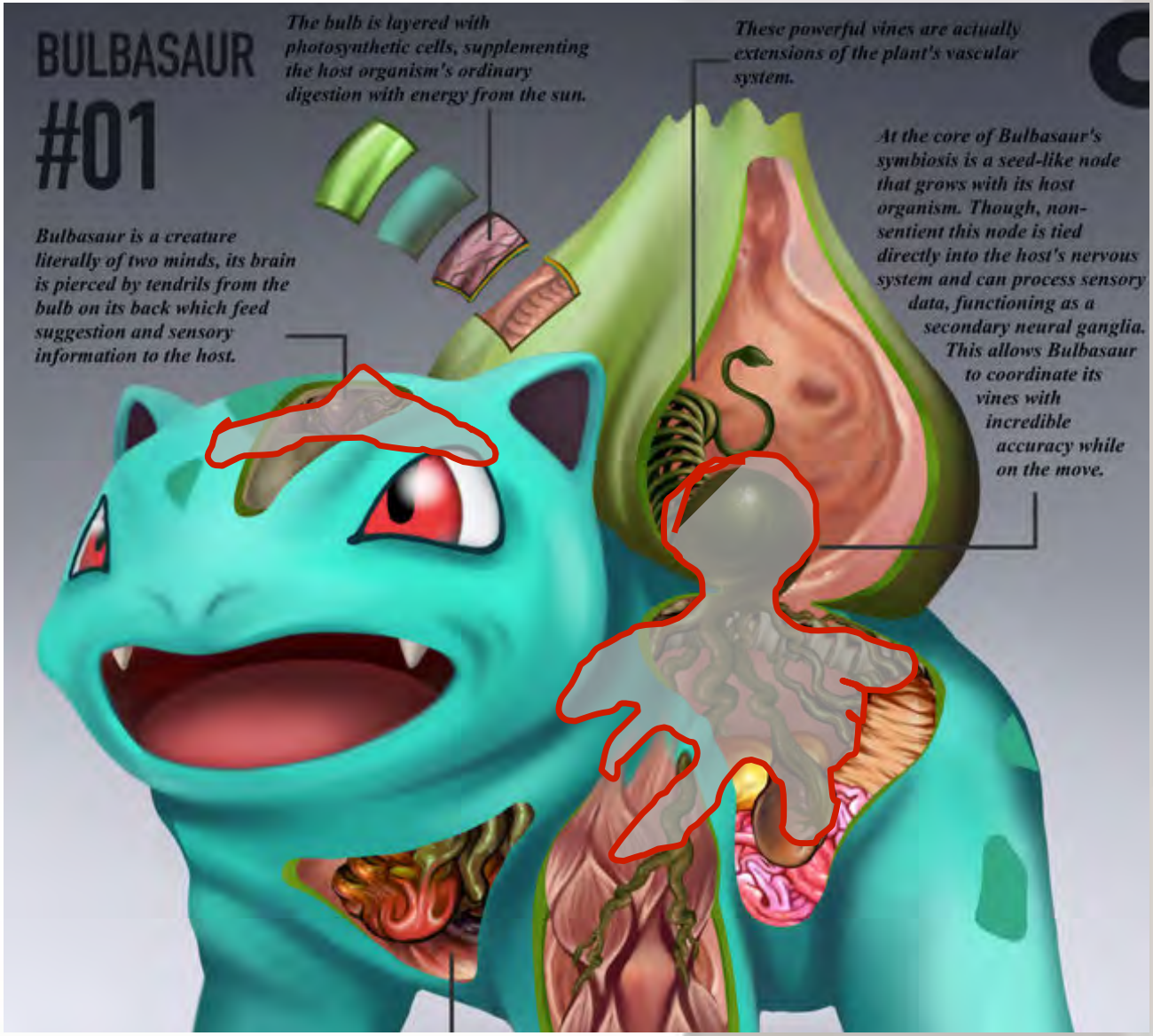
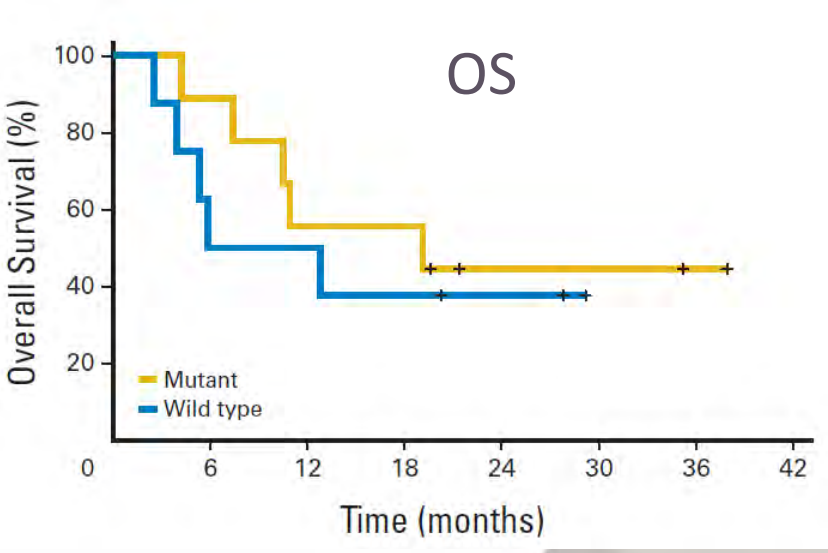
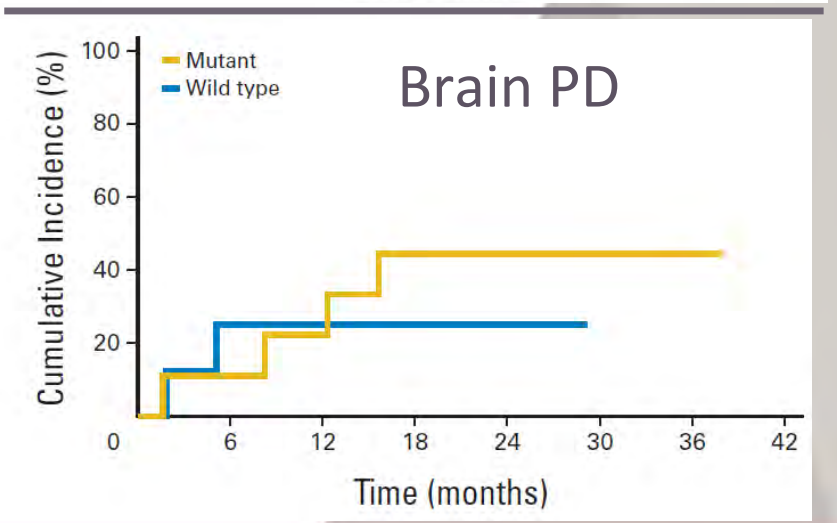


WBRT and EGFR TKI ?

- Phase II study
- 40 pts with brain mets
- Not selected on EGFRmut
- Erlotinib 1 wk then
  Erlotinib 100mg/d
  + WBRT (35Gy/14f)
  then erlotinib 150 mg/d
- Median age : 59,
  Median GPA :1.5
- ORR 86%
- No unusual toxicity





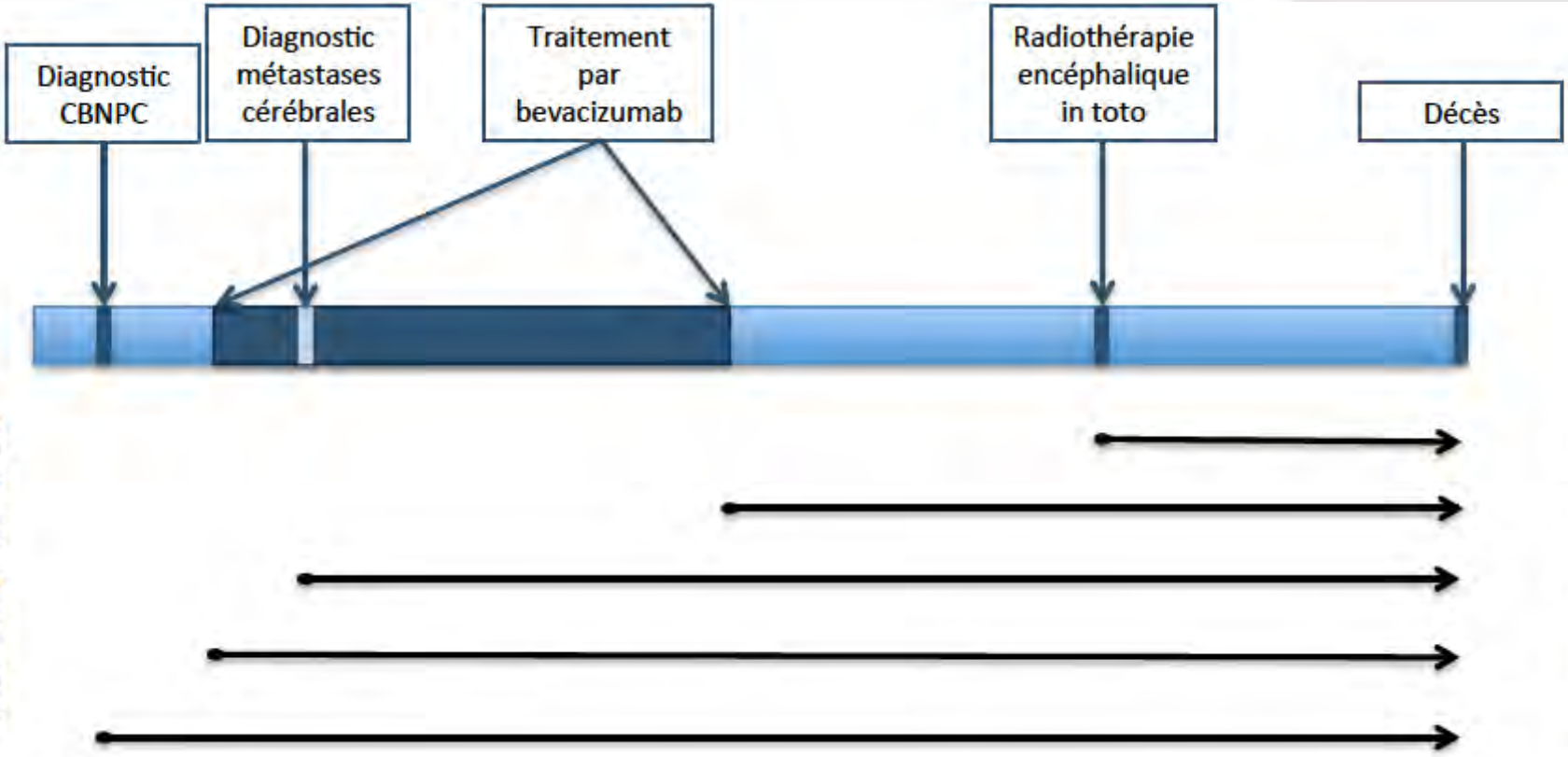
Bevacizumab and WBRT?

- Retrospective, multicenter study
- NSCLC patients with inoperable brain metastasis
- Bevacizumab followed by WBRT ≤ 6 months
- N=41

- 10 neurologic events (22%)
  - 5 cerebral hemorrhages (11%)
  - 2 deaths
  - no link with time between infusion of bevacizumab and toxicity

Arrondeau et al. ESMO 2013

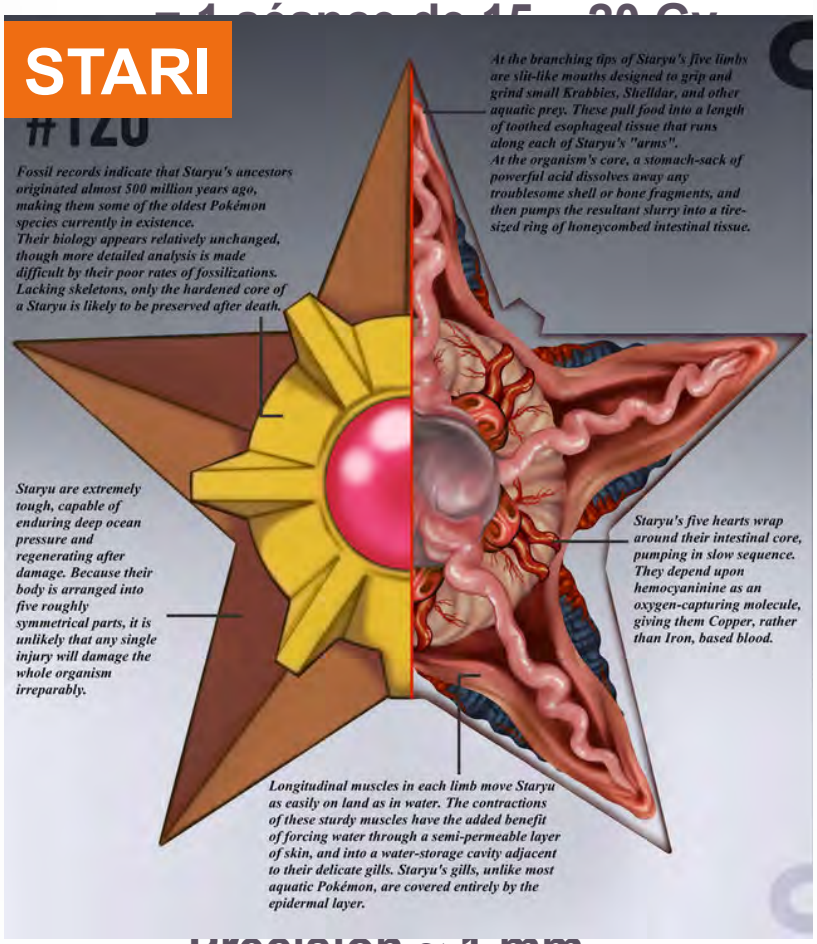
Bevacizumab and WBRT?



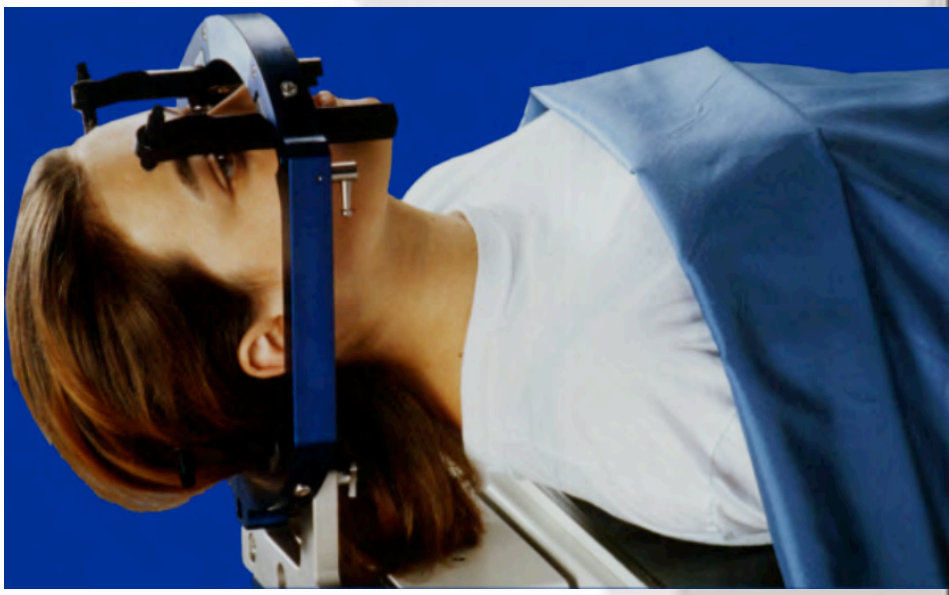
Arrondeau et al. ESMO 2013

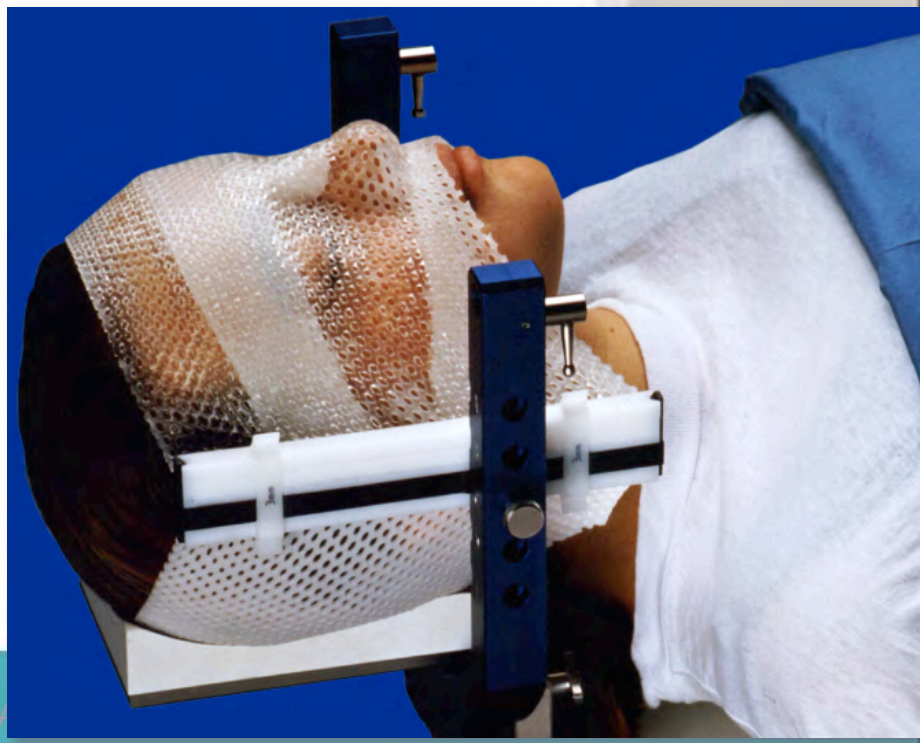
Contention *Invasive*

STARI

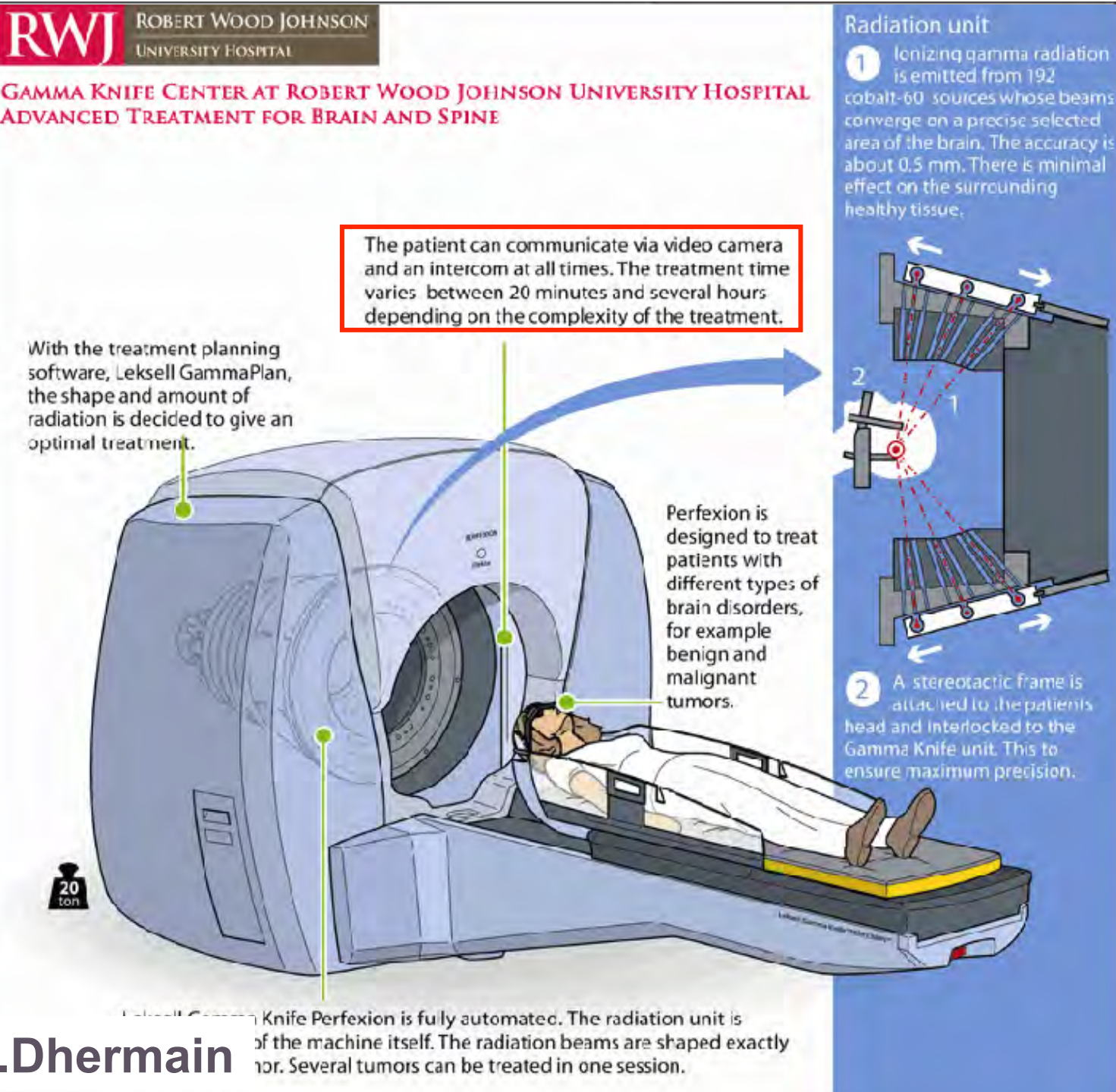


Précision ~ 1 mm



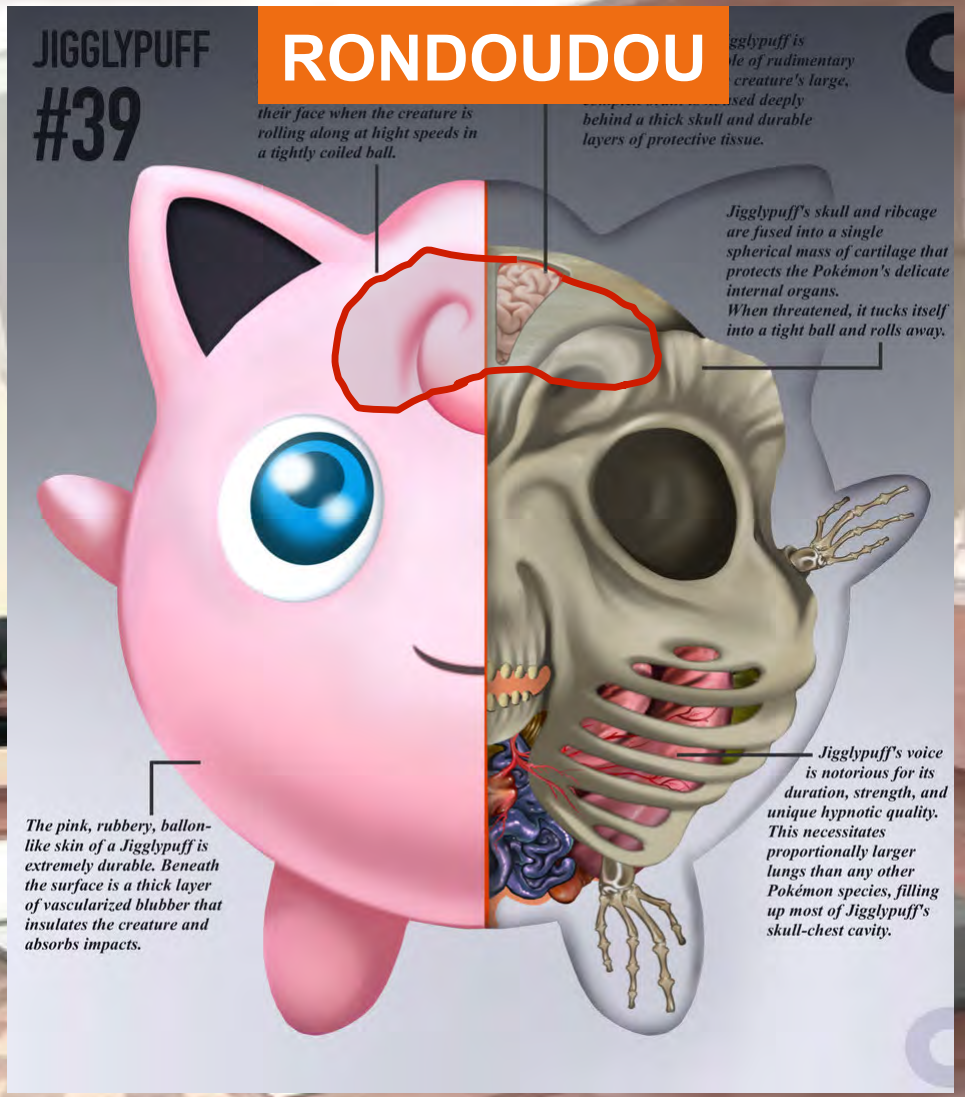


Gamma-Knife



Courtesy of F.Dhermain

Cyberknife



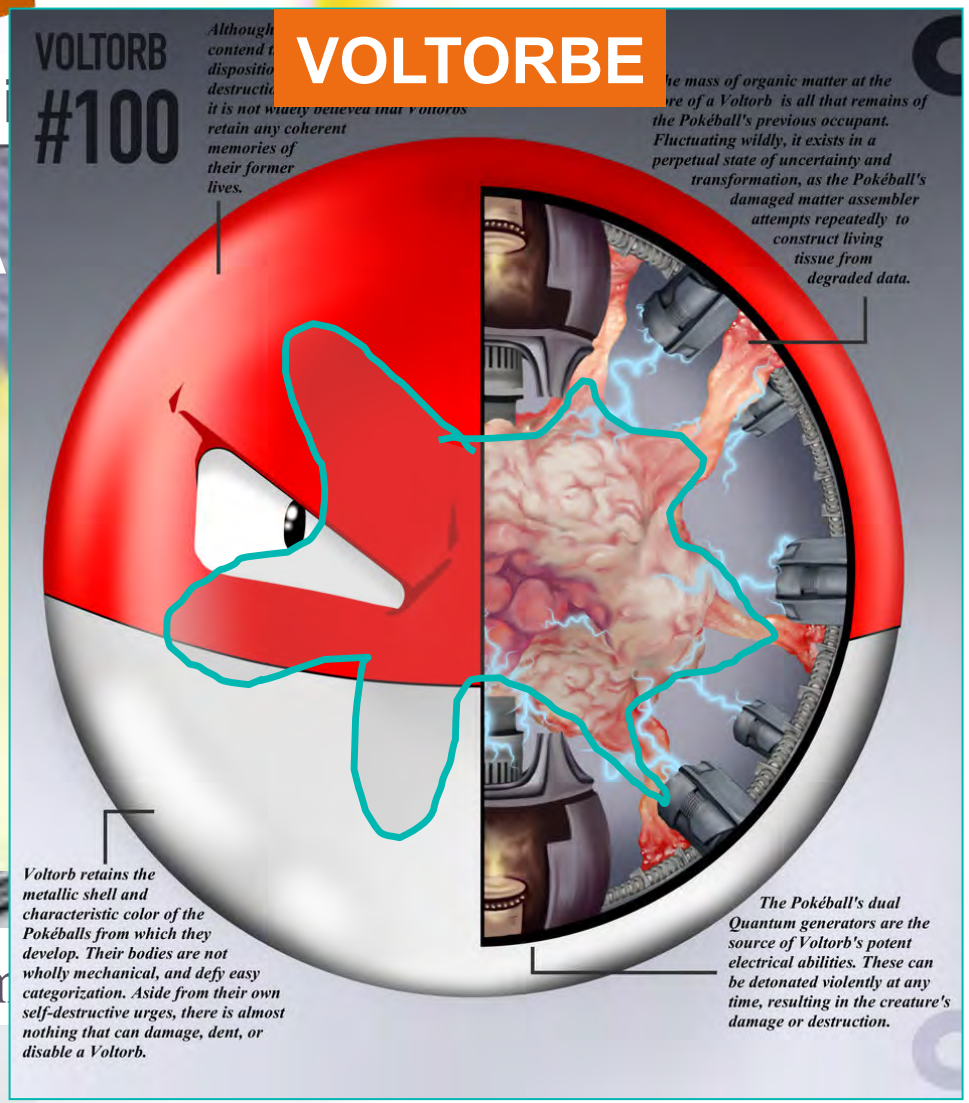
Courtesy of F.Dhermain

Novalis TX

Colli

+ IMRT & A

Couch with 6 degrees of freedom



Courtesy of F.Dhermain

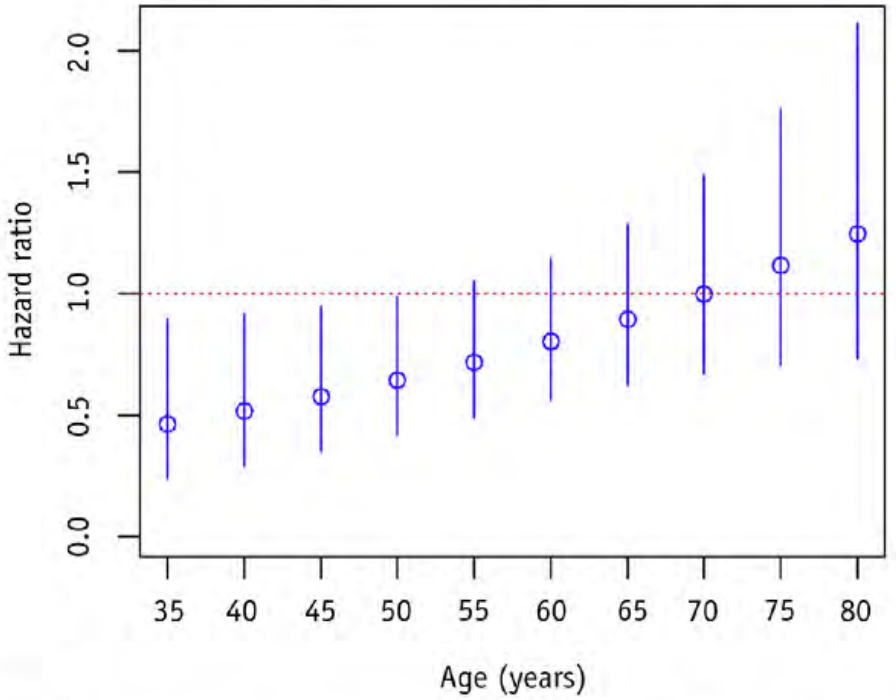
SRS +/- WBRT : meta-analysis of 3 RCT

69 studies identified based on search of key words:

57 were not RCT
2 RCT excluded as WBRT vs. SRS plus WBRT
3 RCT excluded as WBRT plus surgery vs. WBRT
1 RCT excluded as WBRT plus surgery vs. surgery
1 RCT excluded at WBRT plus surgery vs. SRS
1 RCT excluded as WBRT plus SRS vs. WBRT plus surgery
1 RCT excluded as WBRT plus SRS vs. WBRT plus SRS plus systemic therapy

3 Search results limited to only RCTs comparing SRS vs. SRS plus WBRT
-Chang et al. (4)
-Kocher et al. (5)
-Aoyama et al. (3)

! BM < 3.5 cm



Favors SRS alone, in particular if less than 50 y/o

Courtesy of F.Dhermain

Sahgal, IJROBP 2015

Choosing Wisely®

An initiative of the ABIM Foundation

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Resources > News Archive > ASTRO releases second list of five radiation oncology treatments to question, as part of national *Choosing Wisely®* campaign

SEARCH:

ASTRO releases second list of five radiation oncology treatments to question, as part of national *Choosing Wisely®* campaign

Encourages more detailed conversations between physicians and patients

Don't routinely add adjuvant whole brain radiation therapy to stereotactic radiosurgery for limited brain metastases.

Randomized studies have demonstrated no overall survival benefit from the addition of adjuvant whole brain radiation therapy (WBRT) to stereotactic radiosurgery (SRS) in the management of selected patients with good performance status and brain metastases from solid tumors. The addition of WBRT to SRS is associated with diminished cognitive function and worse patient-reported fatigue and quality of life. These results are consistent with the worsened, self-reported cognitive function and diminished verbal skills observed in randomized studies of prophylactic cranial irradiation for small cell or non-small cell lung cancer. Patients treated with radiosurgery for brain metastases can develop metastases elsewhere in the brain. Careful surveillance and the judicious use of salvage therapy at the time of brain relapse allow appropriate patients to enjoy the highest quality of life without a detriment in overall

Courtesy of F.Dhermain ir radiation oncologist.

Radionecrosis

160 pts, 271 BM, median FU 17 months

% radionecrosis

17% at 1 yr, **34% at 2 yrs**

SYMPTO: 12% at 1 yr

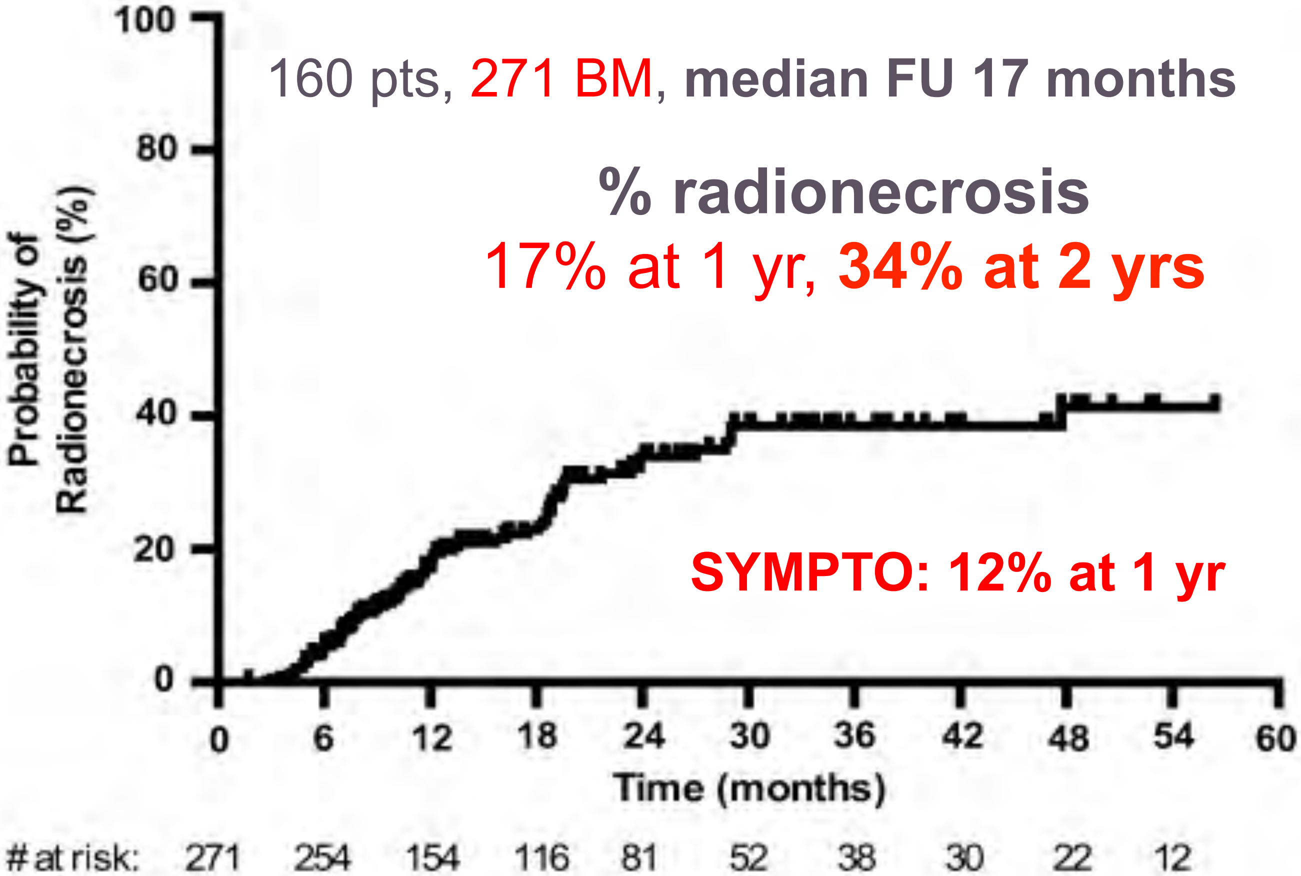


Fig. 1 Actuarial incidence of radionecrosis

FU < 6 months : patients excluded

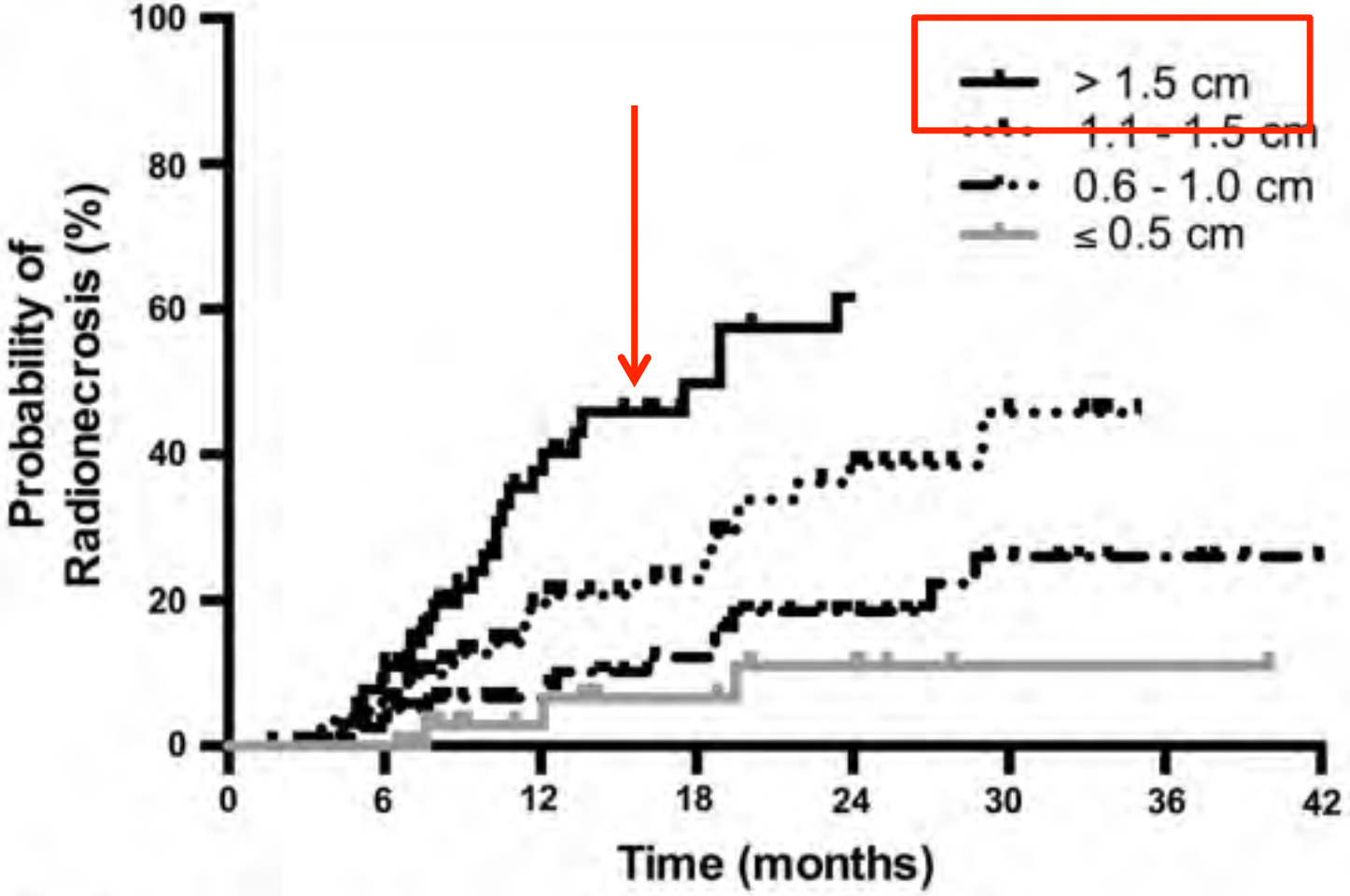
Courtesy of F.Dhermain

Kohutec, J Neurooncol 2015

Délai médian à la Nécrose: **11 mois**

Table 2 Characteristics of radionecrosis diagnosis

Necrosis characteristics	Number (%) of lesions
Time to necrosis (months), median (range)	10.8 (2.7–47.7)
Presence of symptoms	
Yes	47 (67.1 %)
No	23 (32.9 %)
Method of diagnosis	
Pathologic	22 (31.4 %)
Radiographic	48 (68.6 %)
MRI alone	27 (38.6 %)
MRI with PET	21 (30.0 %)



# at risk							
> 1.5 cm:	64	59	27	14			
1.1 - 1.5 cm:	84	78	49	38	26	15	
0.6 - 1.0 cm:	79	76	54	44	30	20	14
≤ 0.5cm:	44	44	27	23	18	12	12

Courtesy of F.Dhermain

Kohutec, J Neurooncol 2015

Brain metastases managment

- Brain mets in NSCLC
- Blood Brain Barrier
- Radiotherapy
- **Chemotherapy and antiangiogenic drugs**
  - Chemo first? or RT first?
  - Bevacizumab and brain mets
- Specific targeted therapies
- Immunotherapy
- Leptomeningeal carcinomatosis
- Conclusion

GFPC1 95-01

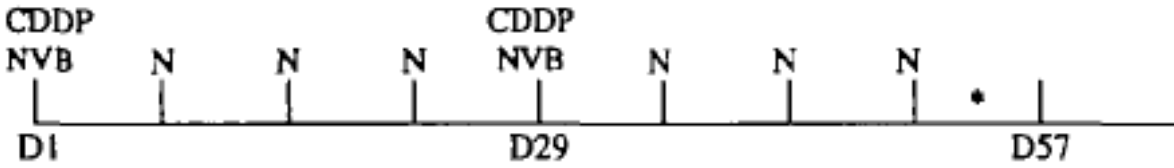
NSCLC & BM

>50% symptomatic

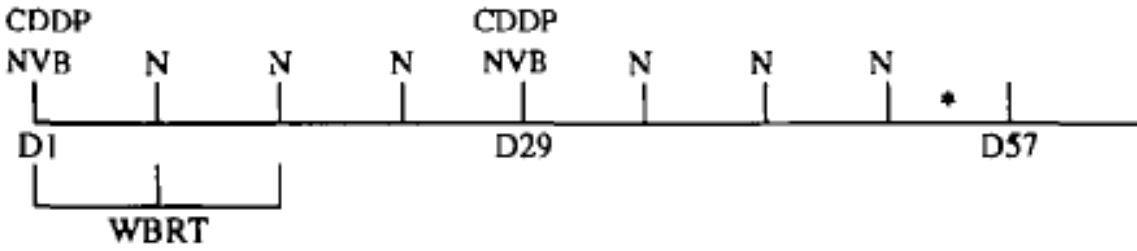
R

N=171

Arm A

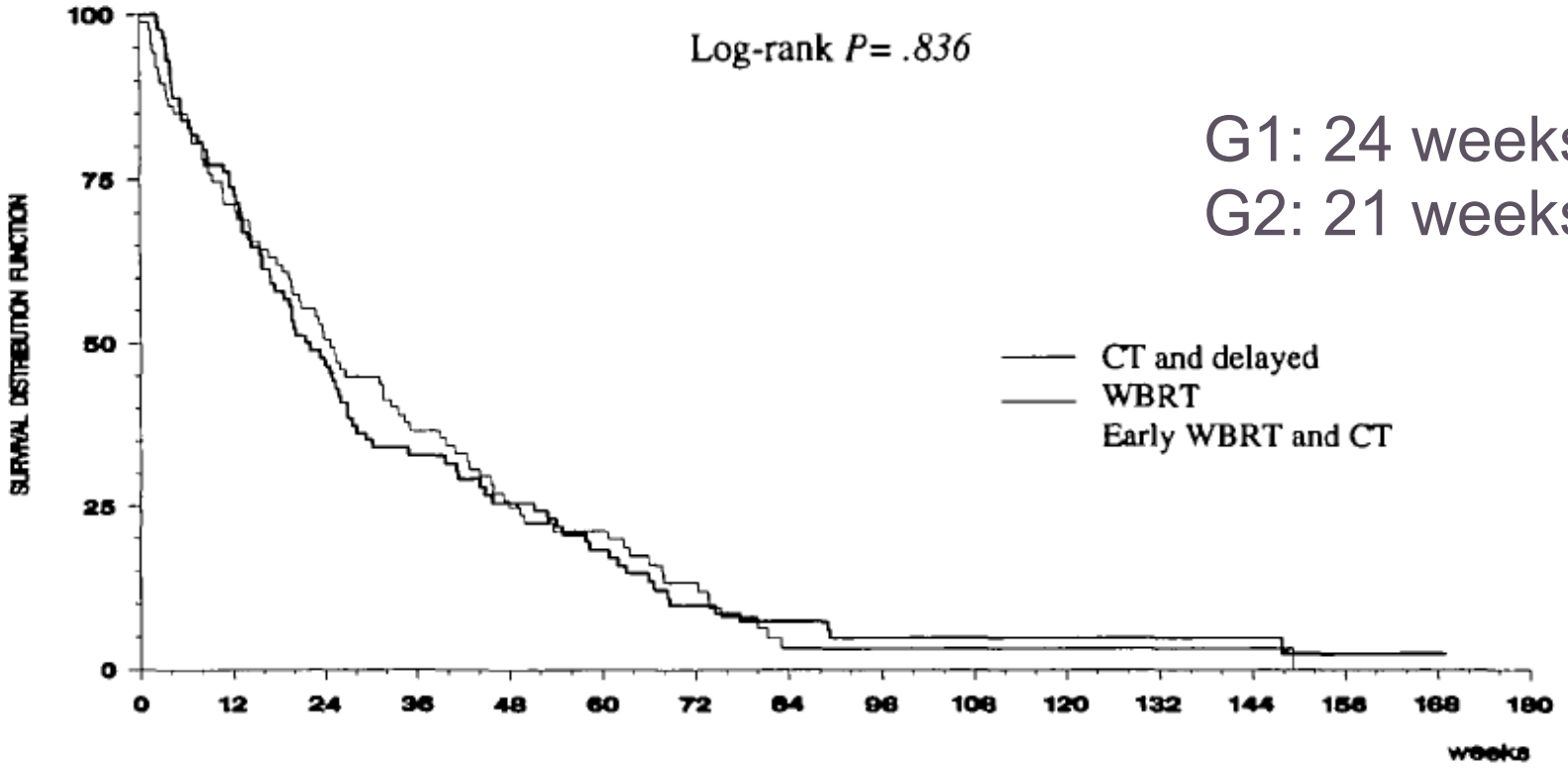


Arm B



Robinet, Ann Oncol 2001

Overall Survival

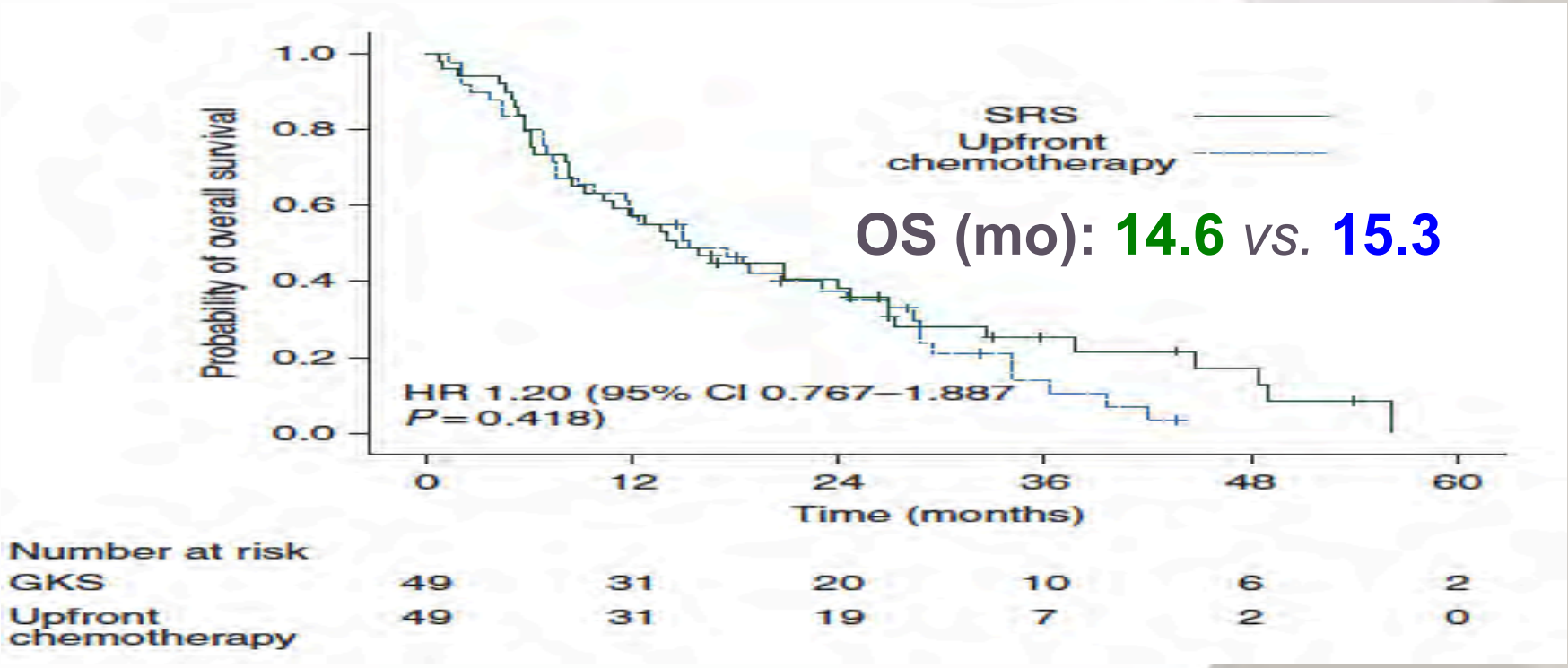


G1: 24 weeks
G2: 21 weeks

Robinet, Ann Oncol 2001

SRS *vs*. Observation

- 105 patients with **1 to 4** brain metastases, never-S
- SRS → CT *vs.* CT upfront End-point: OS



OS (mo): 14.6 *vs.* 15.3

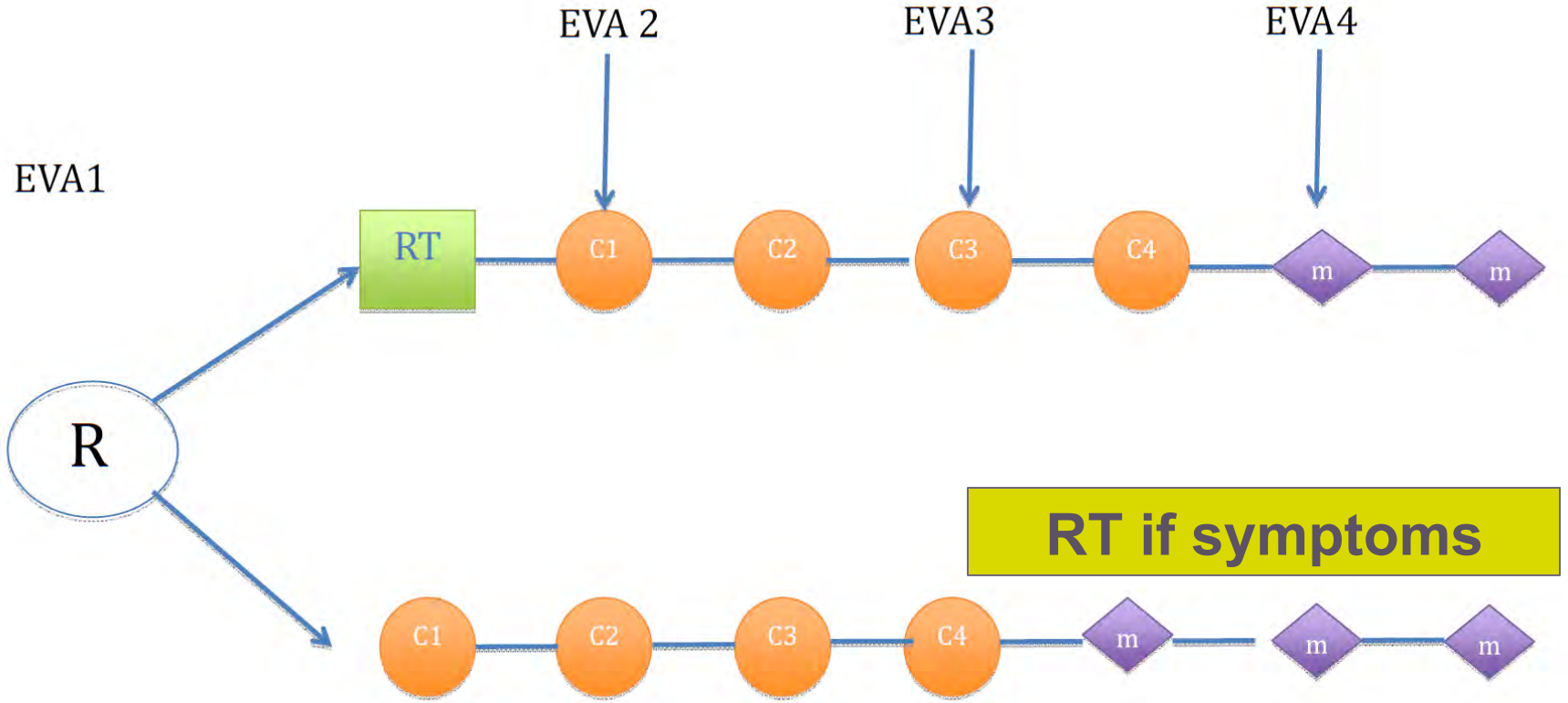
~30% of *EGFR*mut in both arms

Chemotherapy – 1st line

Authors	Regimen	N	ORR (%) Cerebral	ORR (%) Extra-Cerebral	PFS (m)	OS (m)
Cotto et al, 1996	Cisplatine fotemustine	31	23	Nr	5	4
Minotti et al, 1998	Cisplatine Teniposide	23	35	26	7	5
Franciosi et al, 1999	cisplatine etoposide	43	30	Nr	4	8
Fujita et al, 2000	Cisplatine ifosfamide CPT11	30	50	62	4.6	12
Bernardo et al, 2002	Carboplatine, navelbine, gemcitabine	22	45	NR	6.2	8.2
Cortes et al, 2003	Cisplatine taxol	26	38	50	3.2	5.3
Galetta et al, 2011	Cisplatine fotemustine	25	NR	NR	2.6	4.7
Barlesi et al, 2011	Cisplatine Pemetrexed	43	41.8	34.9	4.0	7.4
Bailon et al, 2012	Carboplatine Pemetrexed	26	40	40	7.7	9.7

GFPC 02-2013 METAL 2

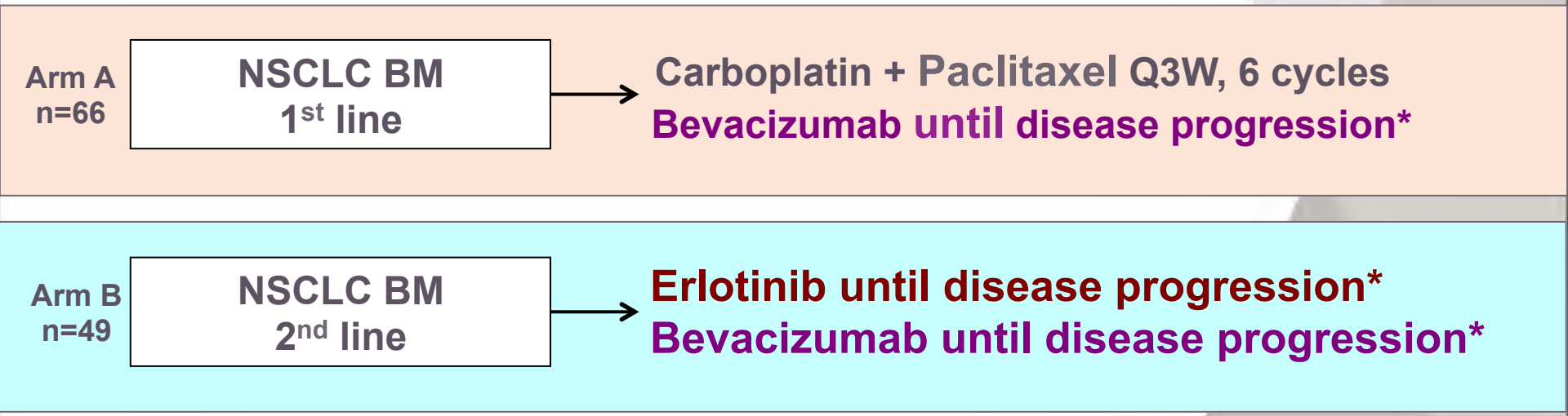
non squamous, asymptomatic BM
CT = pemetrexed/cisplatin



RT= radiothérapie
C= chimiothérapie d'induction
m= chimiothérapie de maintenance

Phase II study BRAIN

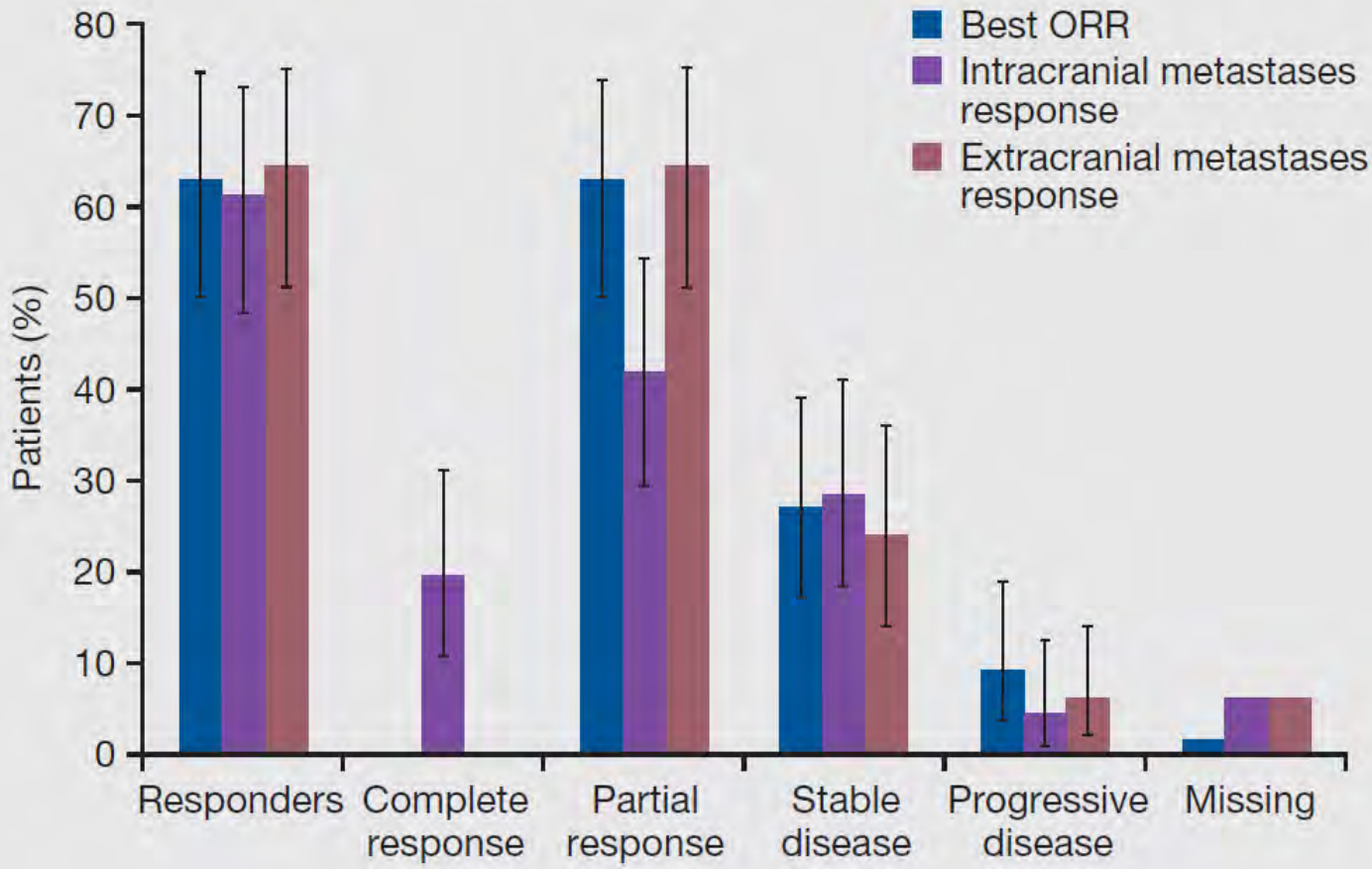
- Non squamous NSCLC
- Asymptomatic, non treated brain mets
- Mandatory RMI



Post-therapeutic follow-up until death or end of study

Besse et al. CCR 2016

ORR – Paclitaxel carboplatine bevacizumab



*all arms, n=91

Besse et al. CCR 2016

Efficacy

	B+CP (n=67)
6-month PFS rate, % (95% CI)	56.5 (43.8–67.4)
Median PFS, months (95% CI)	6.7 (5.7–7.1)
Median OS, months (95% CI)	16.0 (12.0–21.0)

- The most frequent cause for bevacizumab withdrawal was progression:
  - intracranial progression in 20.9% (B+CP) and 16.0% (B+E) of patients
  - extracranial progression in 50.7% (B+CP) and 54.2% (B+E) of patients.

Besse et al. CCR 2016

Efficacy

	B+CP (n=67)	B+E (n=24)
6-month PFS rate, % (95% CI)	56.5 (43.8–67.4)	57.2 (37.0–76.3)
Median PFS, months (95% CI)	6.7 (5.7–7.1)	6.3 (3.0–8.4)
Median OS, months (95% CI)	16.0 (12.0–21.0)	12.0 (8.9–20.2)

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  - intracranial progression in 20.9% (B+CP) and 16.0% (B+E) of patients
  - extracranial progression in 50.7% (B+CP) and 54.2% (B+E) of patients.

Cerebral Hemorrhage Rate : 1,5% (1pt, grade I)*

Besse et al. CCR 2016

Brain metastases managment

- Brain mets in NSCLC
- Blood Brain Barrier
- Radiotherapy
- Chemotherapy and antiangiogenic drugs
- Targeted therapies
  - EGFR
  - ALK
- Immunotherapy
- Leptomeningeal carcinomatosis
- Conclusion

EGFR TKI and Brain Mets

Author (Ref.)	*N*	Selection	Prior treatment	Treatment	Brain RR (%)	MST (months)
Porta et al. [65]	17 (subset)	*EGFR* mutated	No	Erlotinib	82	NR
Park et al. [66]	28	*EGFR* mutated	No	Gefitinib or erlotinib	83	15.9
Li [68]	9	*EGFR* mutated	No	Gefitinib	89	NR
Kim et al. [67]	23	Asian never-smokers	No	Gefitinib or erlotinib	74	18.8
Welsh et al. [78]	40	Unselected	Yes	Erlotinib	86	11.8
Luchi et al. [80]	41	*EGFR* mutated	No	Gefitinib	87.8	21.9

Brain mets

- **ORR 74-89%**
- **OS 15.9-21.9 m**

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Brain mets

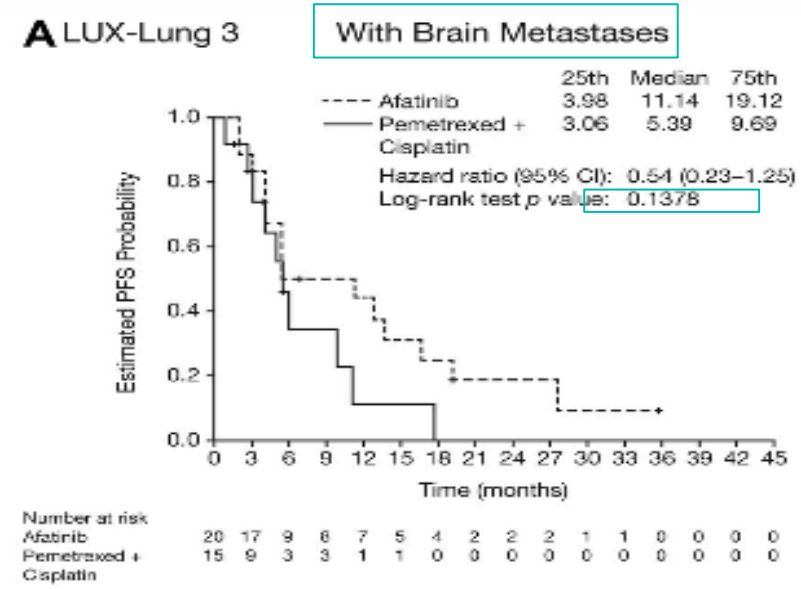
- **ORR 74-89%**
- **OS 15.9-21.9 m**

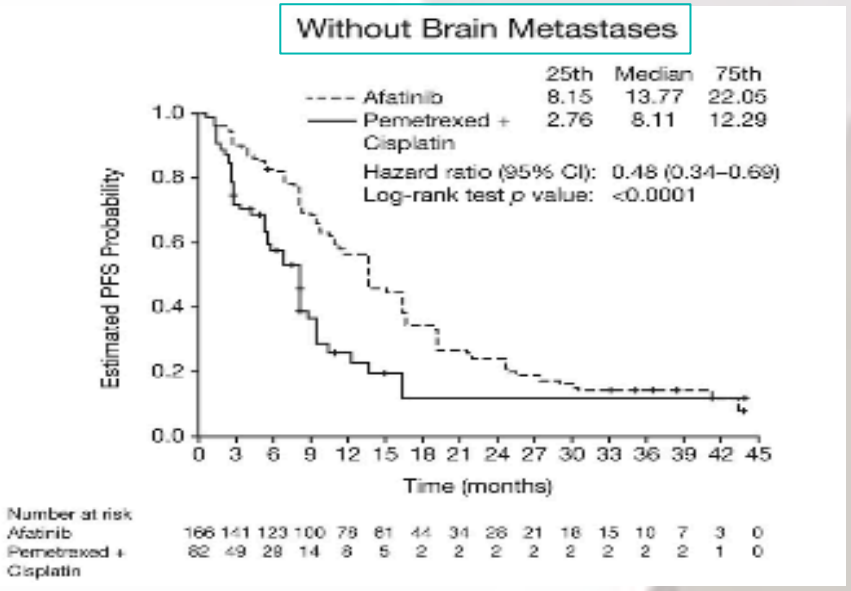
Phase III studies – all comers

ORR 56-84%

OS 19.3 – 28.1 m

Afatinib (LUX-Lung 3&6): brain metastases





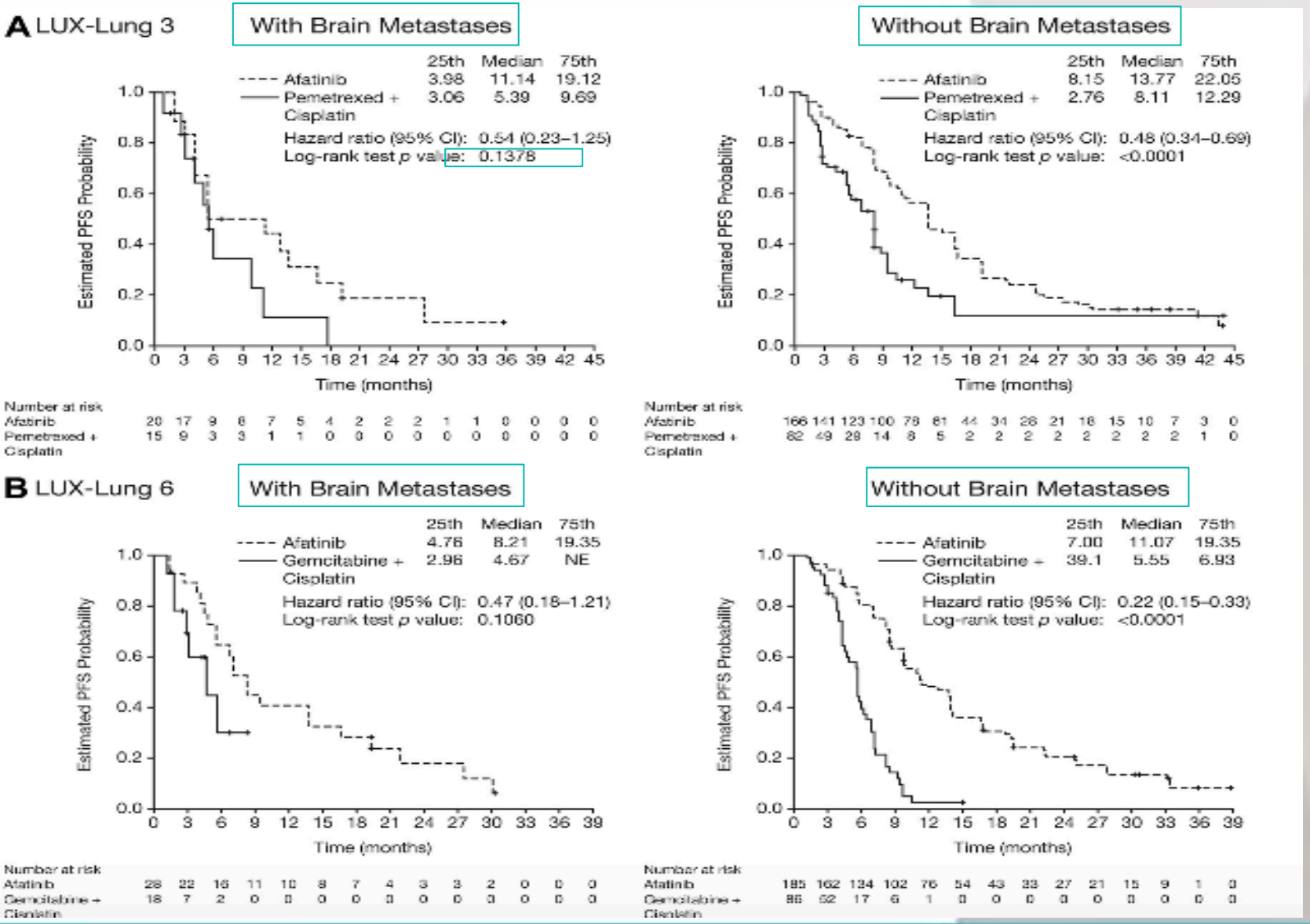
HR=0.54

HR=0.48

The magnitude of PFS improvement similar to pts without BM

Schuler – J Thorac Oncol 2016

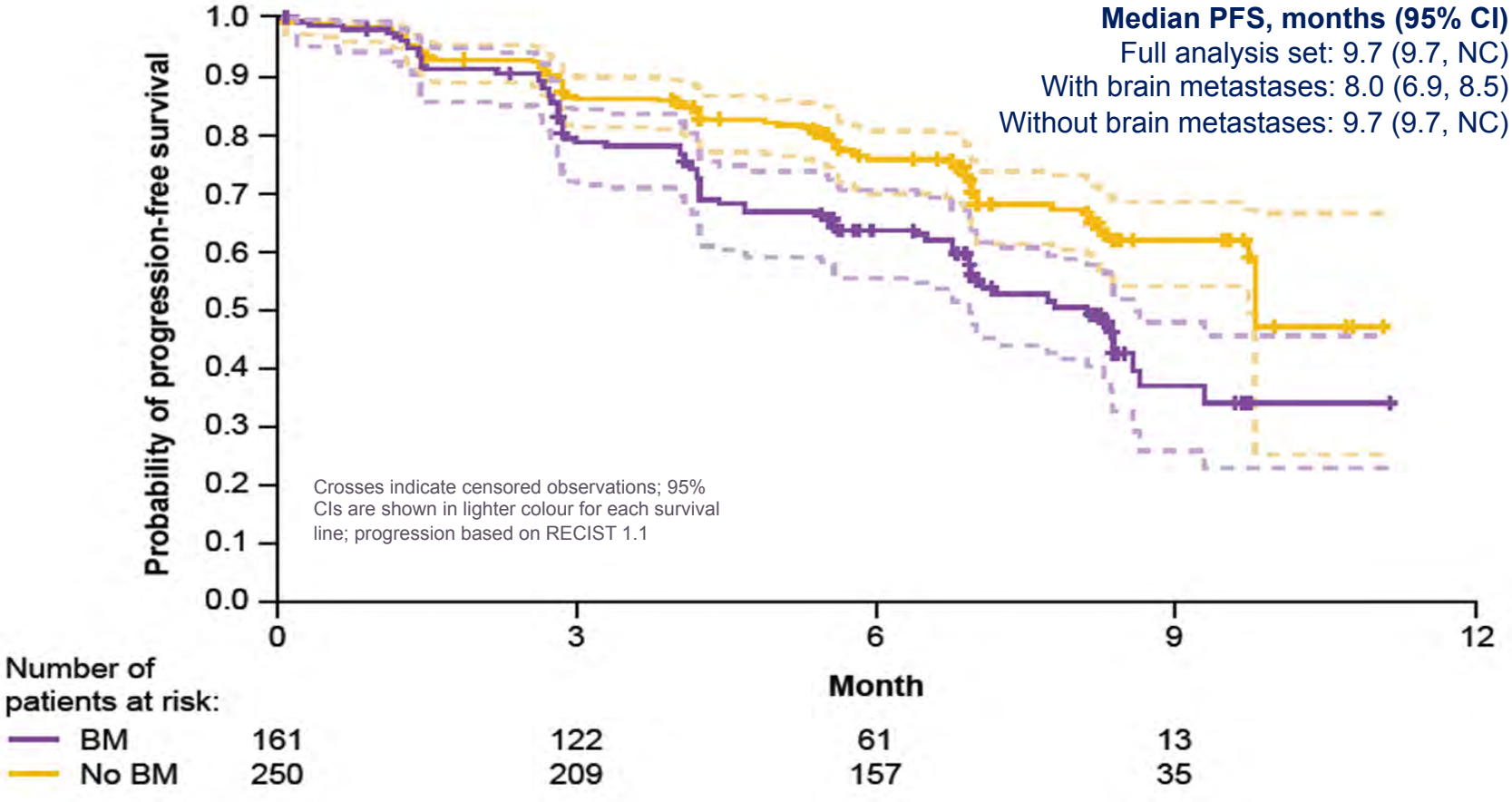
Afatinib (LUX-Lung 3&6): brain metastases



Schuler – J Thorac Oncol 2016

Pooled analysis AURA trials

- **PFS by medical history of brain metastases**



Maturity of PFS data in the full analysis set is 39%; median follow-up for PFS was 6.8 months

Ahn M-J, et al. ECC 2015; abstract 3083

Brain metastases managment

- Brain mets in NSCLC
- Blood Brain Barrier
- Radiotherapy
- Chemotherapy and antiangiogenic drugs
- Targeted therapies
  - EGFR
  - ALK
- Immunotherapy
- Leptomeningeal carcinomatosis
- Conclusion

CNS involvement: the example of NSCLC

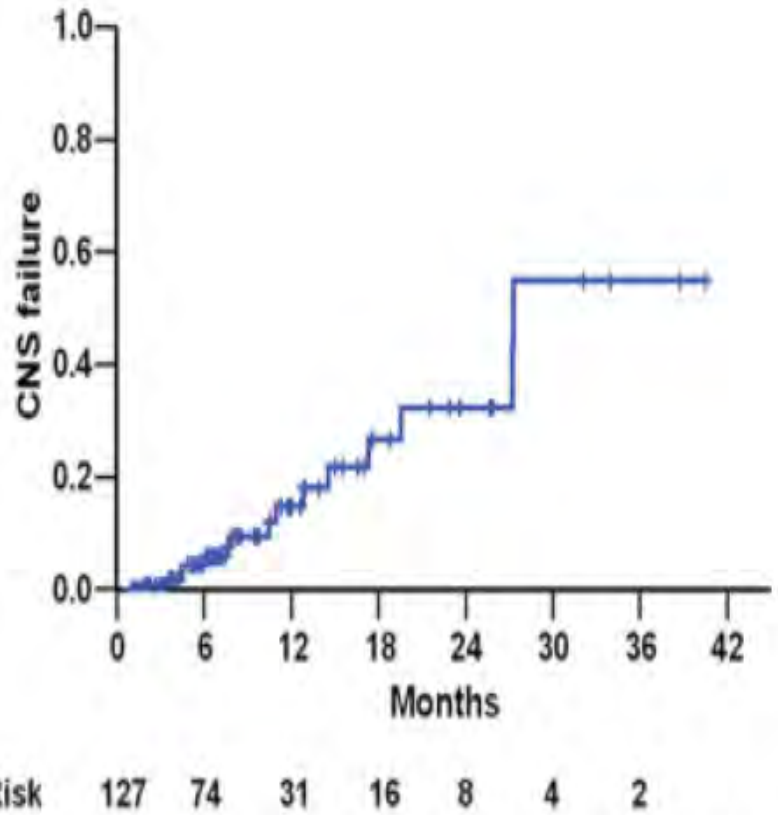
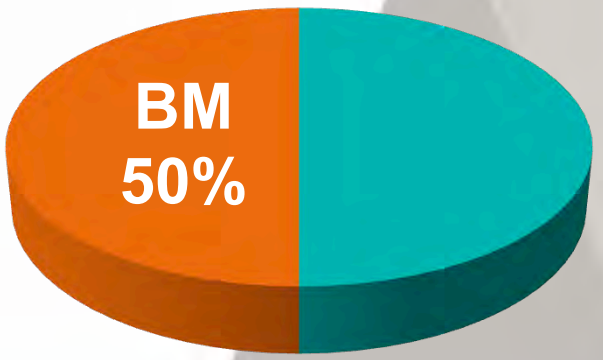


Figure 1. The actuarial incidence of isolated central nervous system failure, measured by the Kaplan-Meier method, in patients with clinical benefit from epidermal growth factor tyrosine kinase inhibitors.

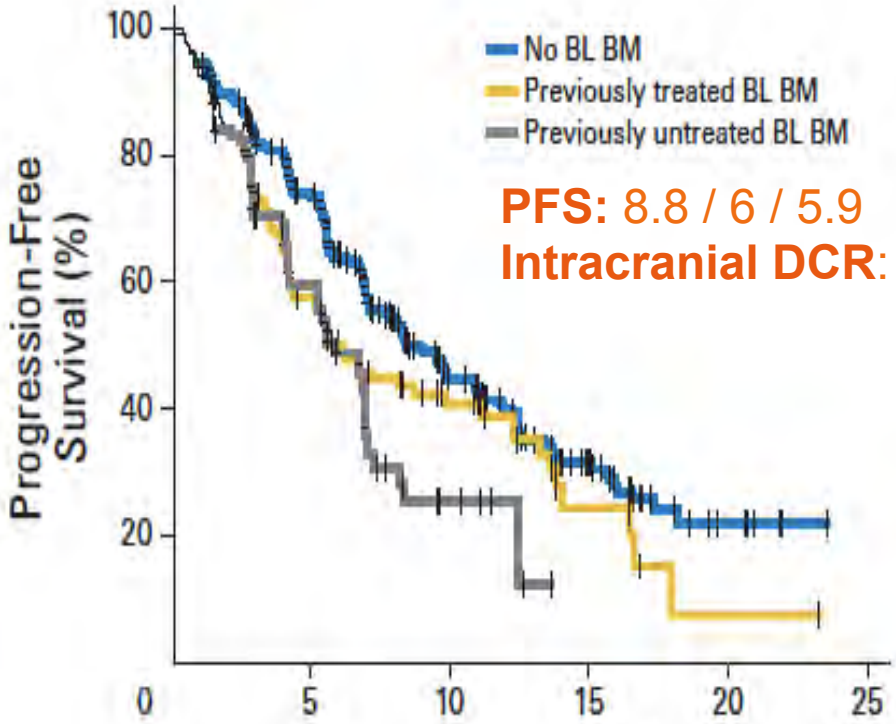
30% of *ALK*+ patients had brain metastasis at baseline and 35-50% develop brain metastases



Shaw AT et al, Lancet Oncol 2011: 12, 1004
Camidge R et al, Nat Rev Clin Oncol 2014: 11, 473 - Costa – JCO 2015

Crizotinib and efficacy in brain

- Crizotinib has a poor CNS penetration with a CSF-to-plasma ratios of 0.026
- Retrospective study of PROFILE 1005, 1007



PFS: 8.8 / 6 / 5.9
Intracranial DCR: ~60%

N=275 (Treated /Untreated: 109/166)

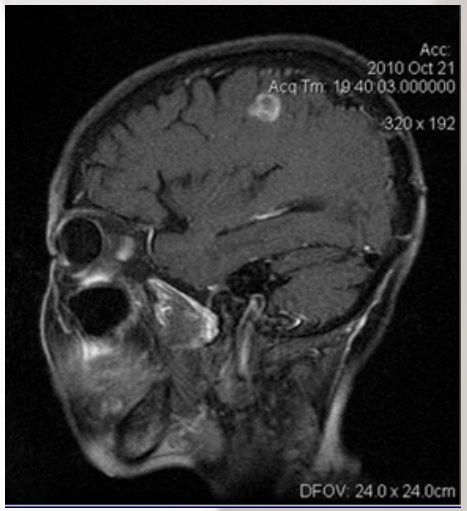
ALK inhibitors and RR to brain

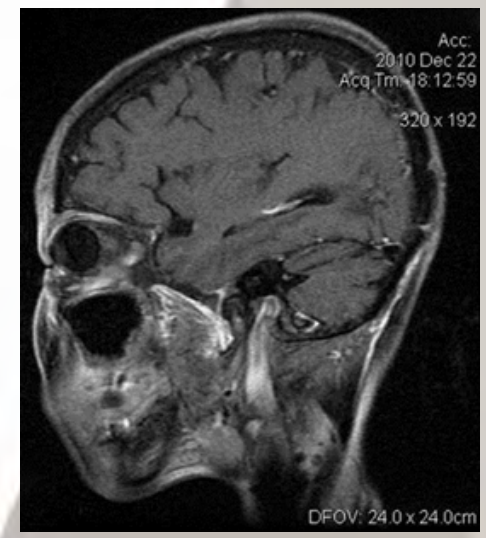
Author	Medicament	N	Réponse intracrânienne
***ALK* réarrangé**			
Kim et al.	Ceritinb* (phase I)	75	65% (disease control rate)
Ou et al.	Alectinib* (phase II)	35	57%
Shaw et al.	Alectinib* (phase II)	16	75%
Gadgeel et al	Alectinib* (phase I/II)	21	52%
Kim et al.	Brigatinib* (phase II)	21	67%

*Patients crizotinb-resistant

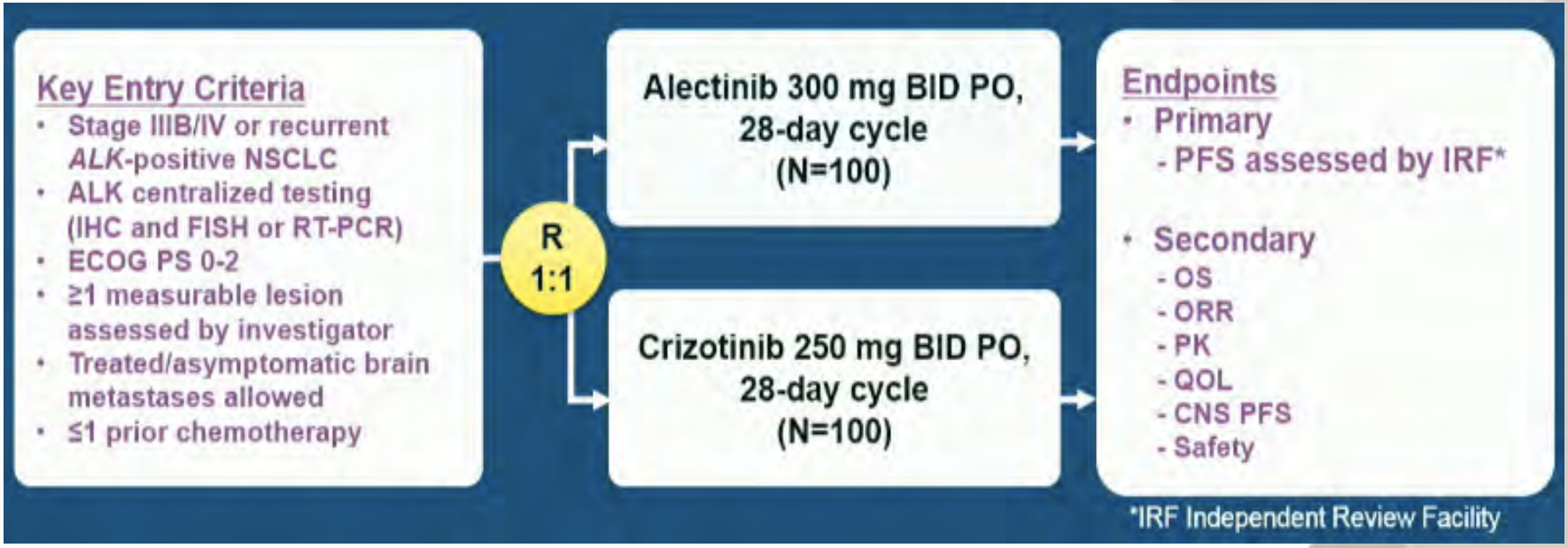
Crizotinib activity on brain mets

- **Retrospective analysis of patients with (n=275) or without (n=613) brain mets from PROFILE 1005 and PROFILE 1007**
- **Intracranial DCR at 12 weeks ~ 60% in patients with brain metastases**
  - 56% if untreated BM
  - 62% if previously treated BM
- **Intracranial ORR ~ 25% in 40 patients with ≥1 brain metastasis identified as a target lesion at baseline**
  - 18% if untreated BM
  - 33% if previously treated BM

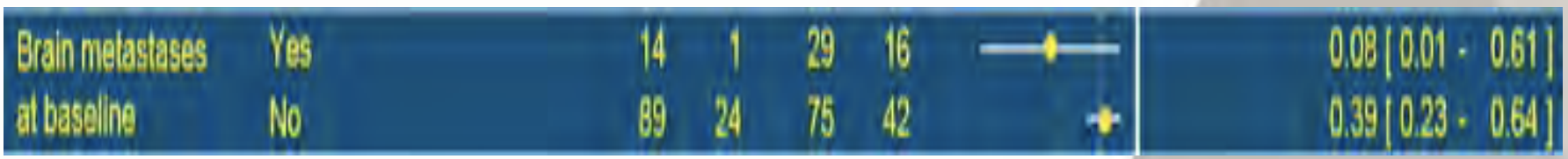




J-ALEX phase III study in *ALK*+

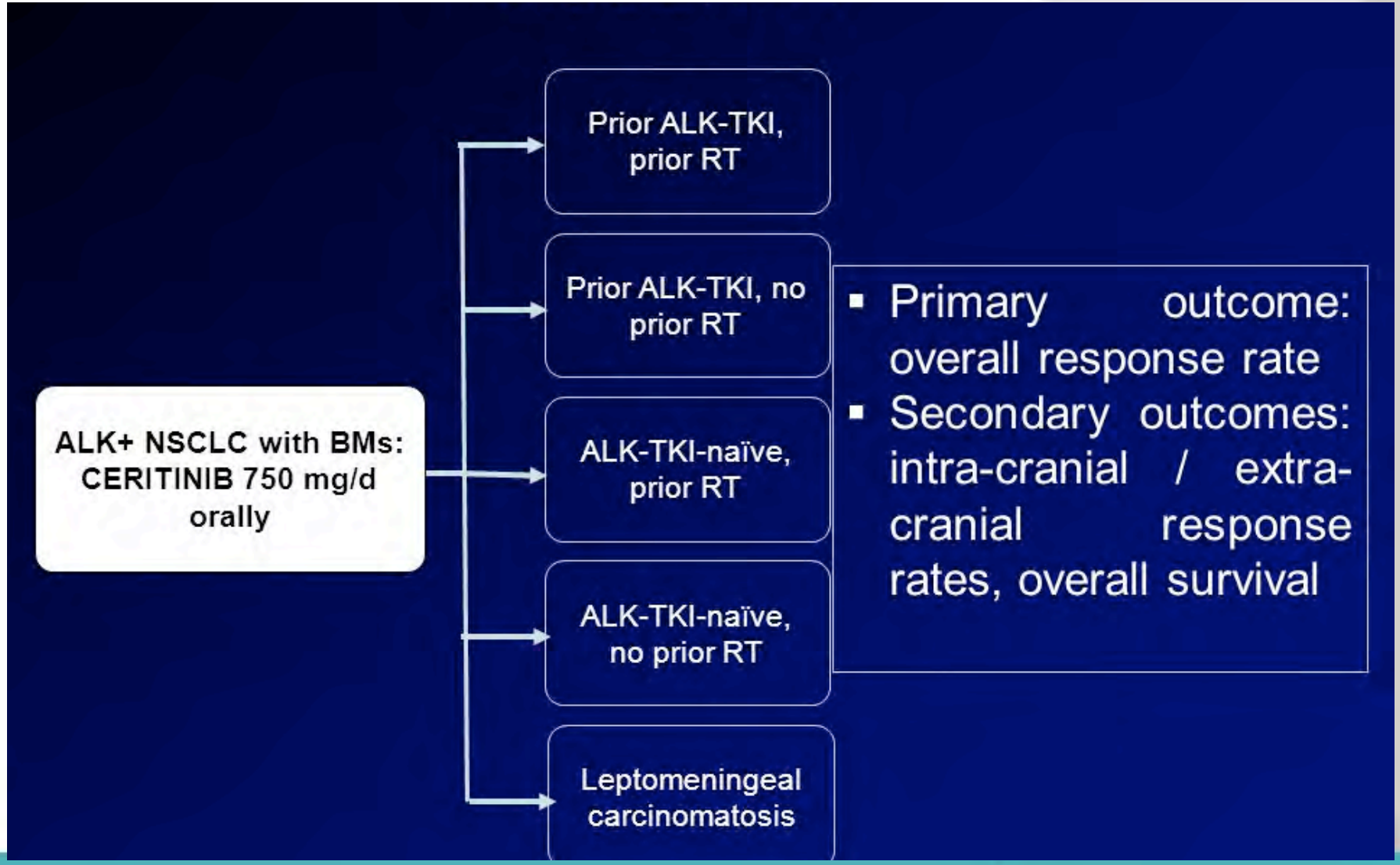


	Alectinib	Crizotinib	p
RR (independent)	91.6%	78.9%	
PFS	NR	10.2	HR:0.34, p<0.001



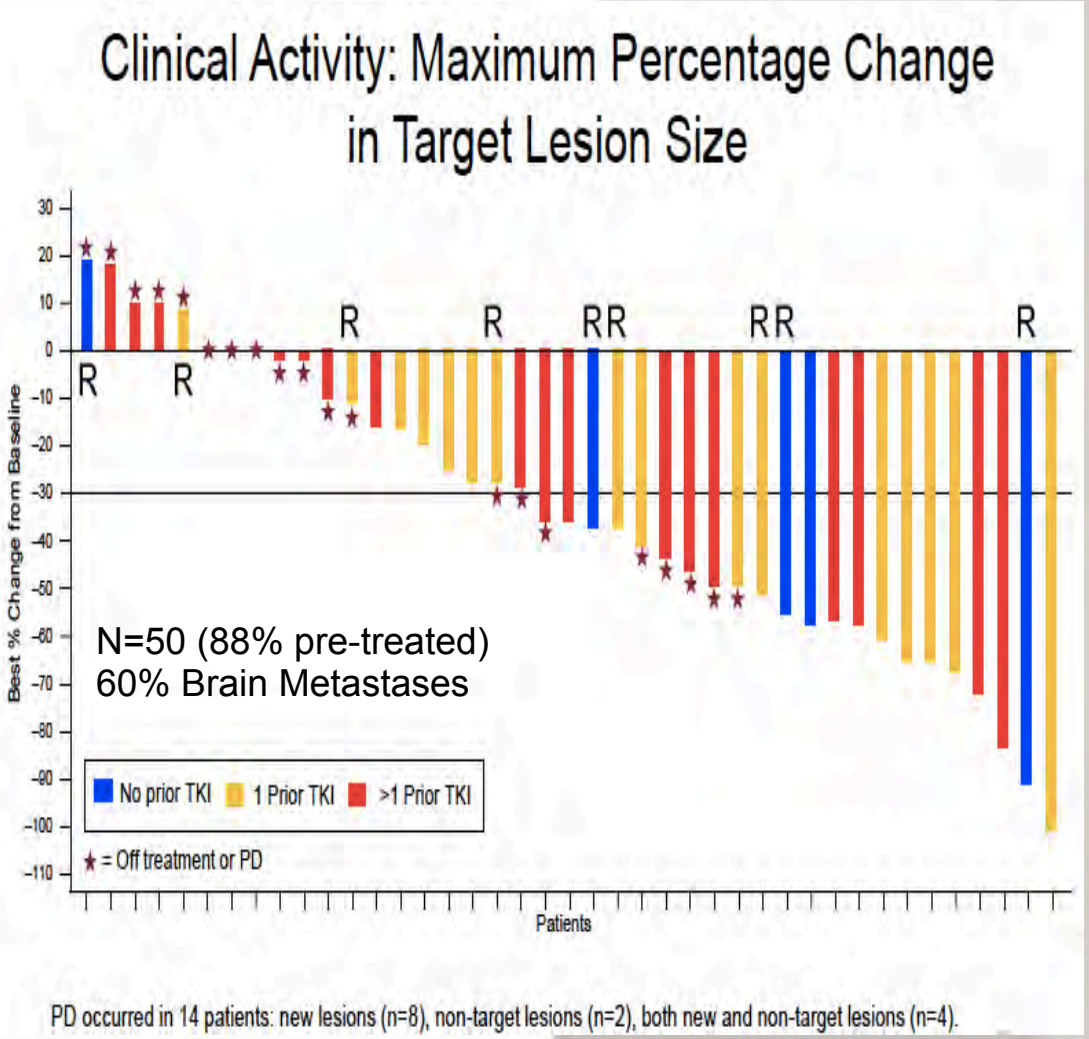
Yang – ASCO 2016 (Abstract 9008)

ASCEND 7 trial ongoing



Lorlatinib (PF06463922)

Mutation Status	Cell Line	Cellular ALK Phosphorylation Mean IC_{50} (nM) Lorlatinib PF-06463922	Crizotinib	Ceritinib (LDK-378)	Alectinib (CH-5424802)
EML4-ALK v1	NIH3T3	1.3	80	NA	62
	BaF3	3.6	90	41	24
EML4-ALK L1196M	NIH3T3	21	843	NA	250
	BaF3	43	1154	70	113
EML4-ALK G1269A	NIH3T3	15	605	NA	NA
	BaF3	80	689	134	112
EML4-ALK G1202R	NIH3T3	77	1003	>1000	>10,000
	BaF3	113	562	549	362
EML4-ALK I1151Tins	NIH3T3	38	1268	1066	1770
	BaF3	50	902	296	126
EML4-ALK S1206Y	NIH3T3	4.2	626	NA	NA
	BaF3	3.2	152	60	29
EML4-ALK C1156Y	NIH3T3	1.6	478	NA	NA
	BaF3	15	406	177	21
EML4-ALK F1174L	NIH3T3	0.2	165	NA	NA
	BaF3	4.0	150	161	26

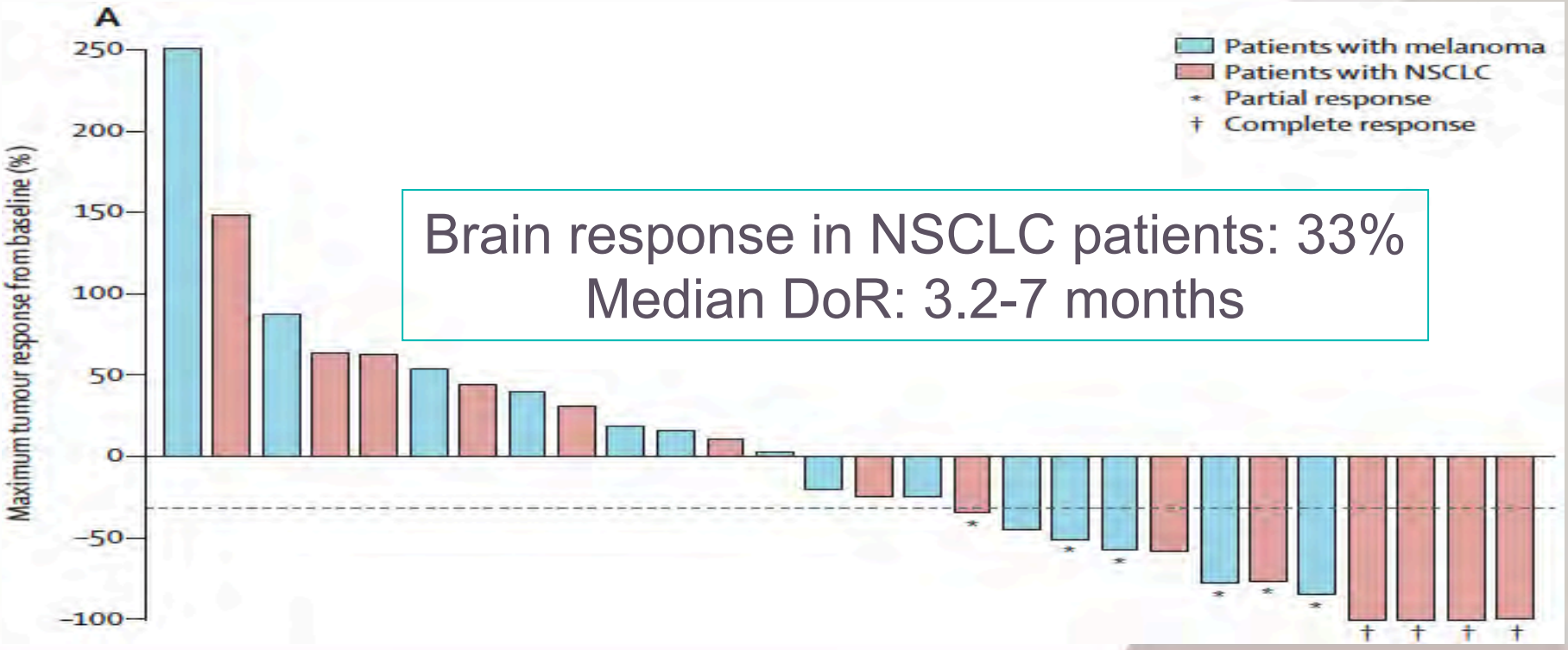


Brain metastases managment

- Brain mets in NSCLC
- Blood Brain Barrier
- Radiotherapy
- Chemotherapy and antiangiogenic drugs
- Targeted therapies
- Immunotherapy
- Leptomeningeal carcinomatosis
- Conclusion

Immunotherapy: Pembrolizumab

- N=36 (18 melanoma, 18 PD-L1+* NSCLC patients)
- 1 untreated or progressive brain metastasis (5 and 20 mm in diameter) <u>without</u> associated neurological symptoms or the need for corticosteroids.



Brain response in NSCLC patients: 33%
Median DoR: 3.2-7 months

*>1% tumoral cell +

Goldberg -Lancet Oncol 2016

Brain metastases managment

- Brain mets in NSCLC
- Blood Brain Barrier
- Radiotherapy
- Chemotherapy and antiangiogenic drugs
- Targeted therapies
- Immunotherapy
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- Conclusion

Leptomeningeal metastasis

- **Incidence 3.8% in NSCLC.** *Liao – JTO 2015*
- **Median OS 3.6-11 months.** *Umemura – Lung Cancer 2012*
- **Performance status is the best prognosis factor**
- **ITC improve OS: 7.5 vs. 3.6 mo.** *Wu – Oncol Letter 2016*
- **Incidence in *EGFR*-mutant pt: 9%.** *Kuiper – Lung Cancer 2015*

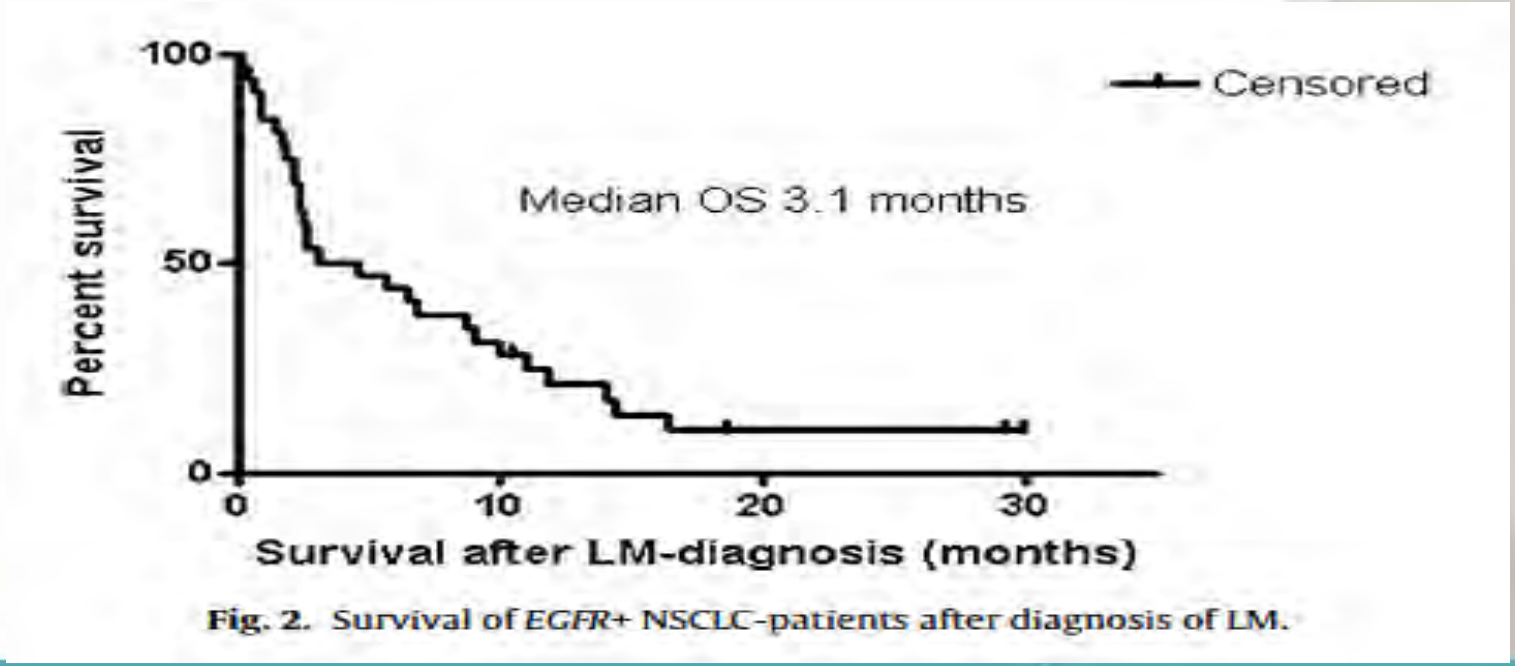


Fig. 2. Survival of *EGFR*+ NSCLC-patients after diagnosis of LM.

Osimertinib LM metastases: BLOOM study

First patient dosed: April 14, 2015

Osimertinib LM cohort 1

Advanced or metastatic EGFRm NSCLC and confirmed diagnosis of LM by positive CSF cytology

Key inclusion criteria:

- Primary tumor with EGFR L858R or exon 19 deletion
- Prior EGFR-TKI treatment
- ECOG PS 0–2
- Stable extracranial disease
- At least one LM lesion by MRI scan

Osimertinib 160 mg QD

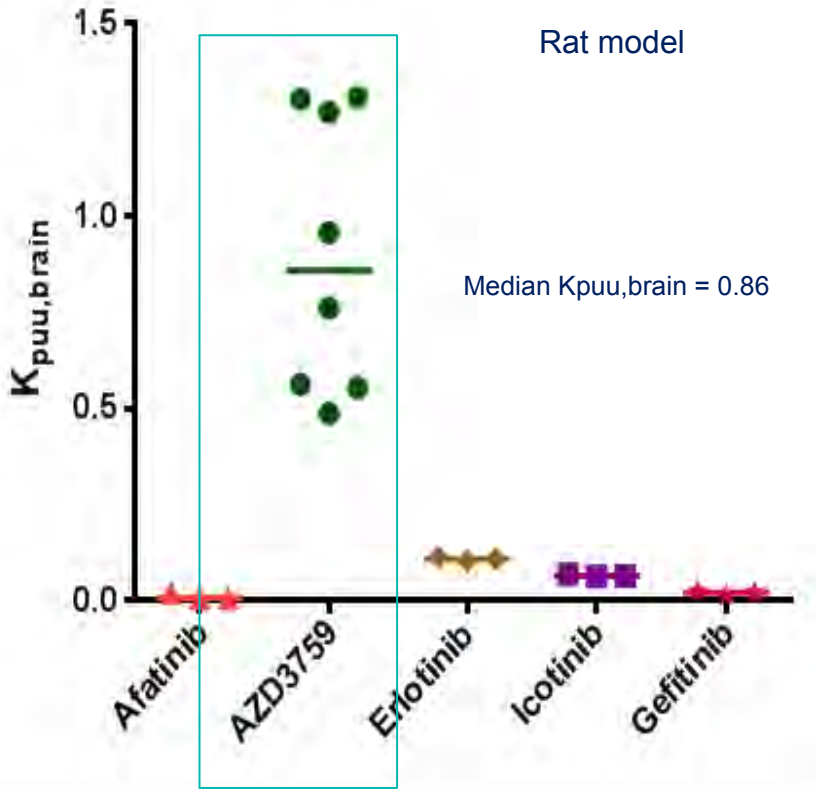
Data cut-off: March 10, 2016

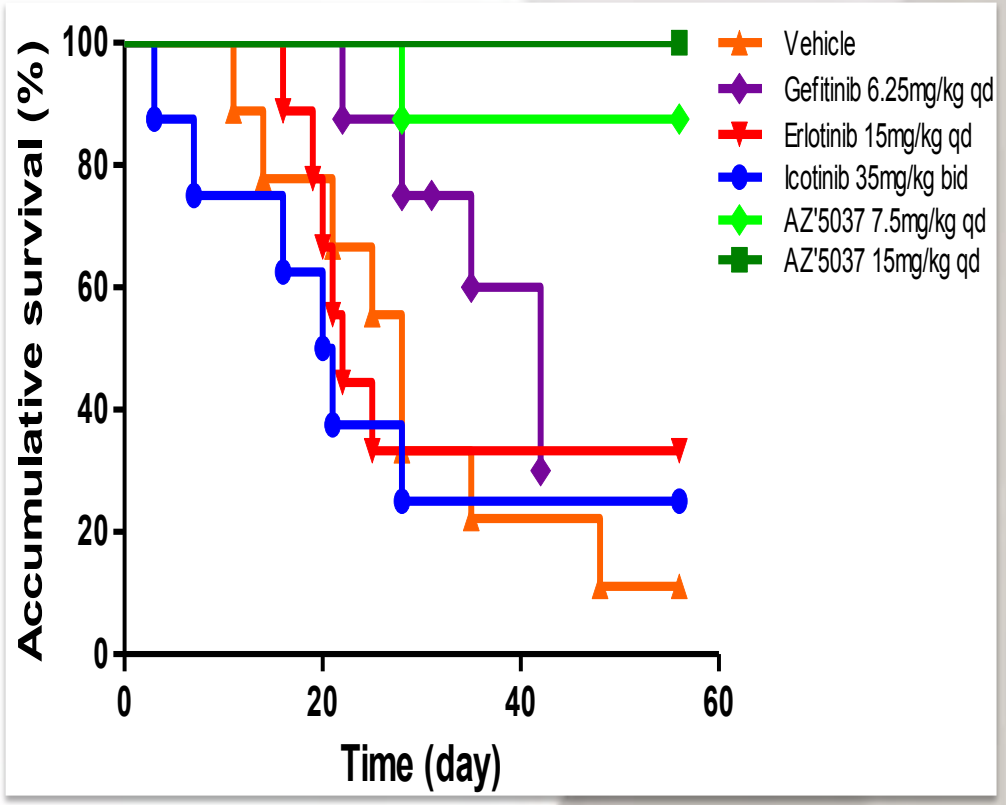
Assessments

- Adverse events*
- Efficacy assessment:
  - OS
  - Brain MRI and extracranial MRI or CT scan*†
  - CSF cytology
  - Neurological exam*
  - CNS symptoms*
- PK in CSF
- Quantification of EGFRm DNA in CSF

Best MRI imaging intracranial response, n (%)	N=21	
	Confirmed*	Unconfirmed
Responding	7 (33)	1 (5)
Stable disease	9 (43)	2 (10)
Early withdrawal	2 (10)	

Low CSF penetration with current EGFR TKI



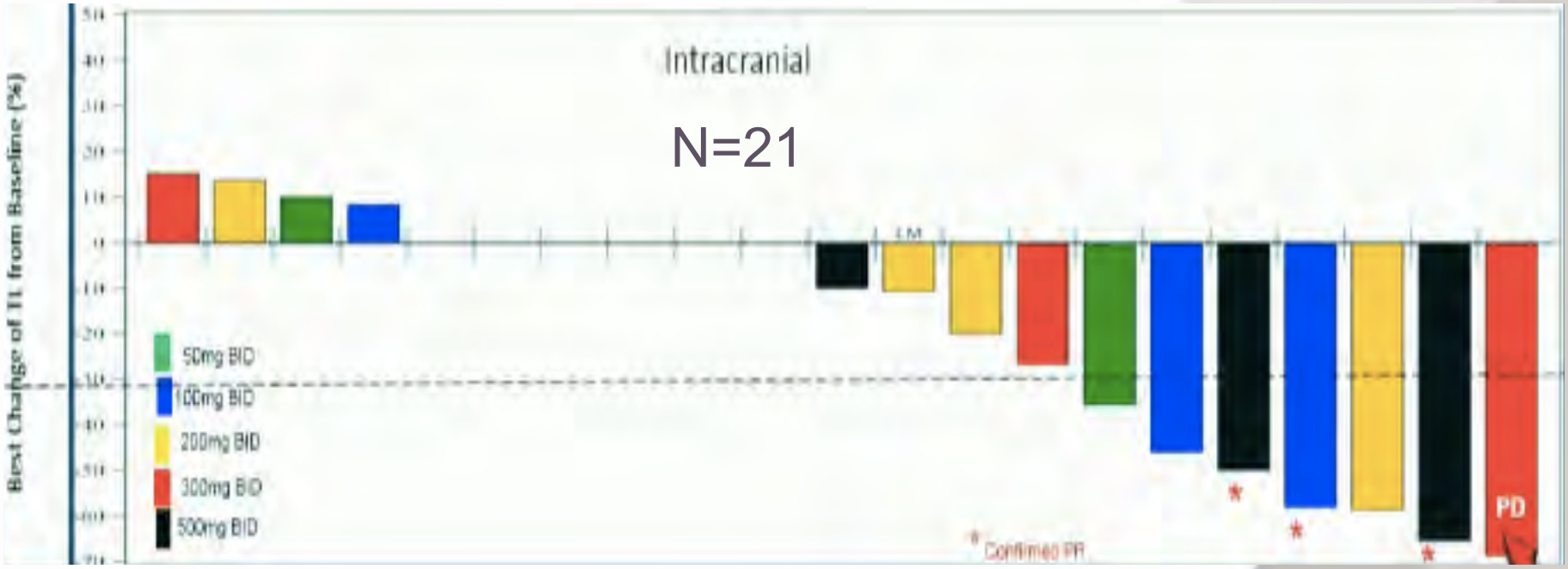


AZD3759 is not a substrate
- of PGP
- and BCRP efflux transporters

Significantly prolonged animal survival in **PC-9 BM model,** compared with gefitinib, erlotinib, icotinib

Kim – ASCO 2015, Abstract 8016

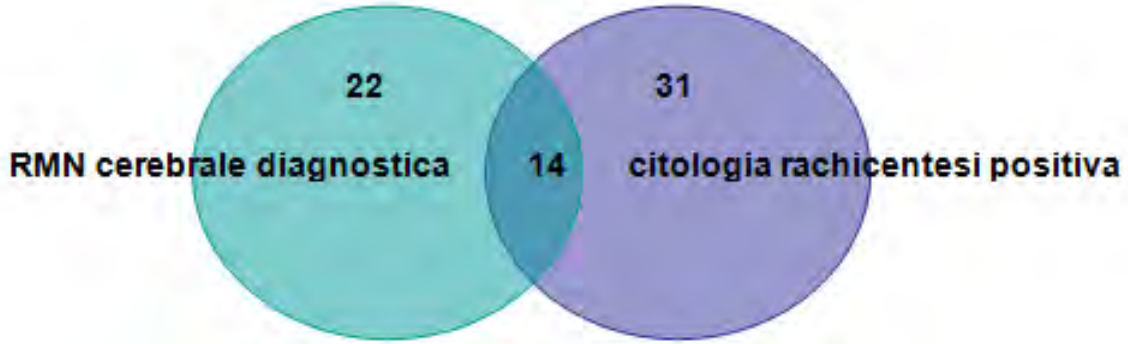
New EGFR TKI: AZD3759 (not *T790M*)



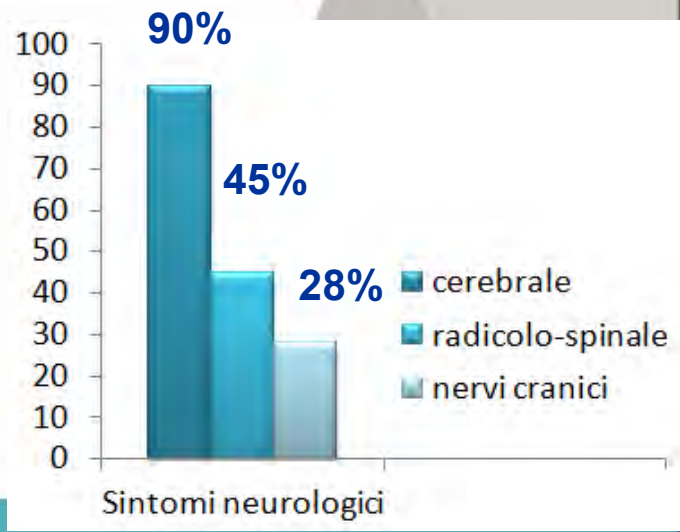
- Long lasting activity
- Drug-related adverse events: rash and diarrhea
- ADZ3759 achieved concentrations above IC50 for target inhibition in CSF in all patients ≥ 200 mg BID

Carcinomatous meningitis (French experience)

40 pts - EGFRmut



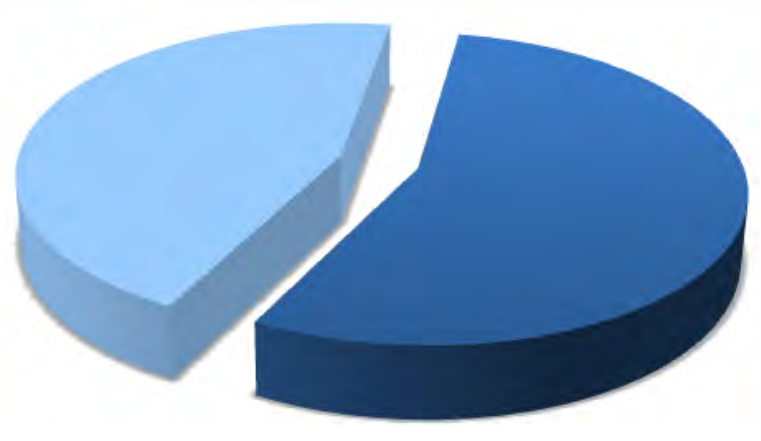
Symtoms



Biondani et al.

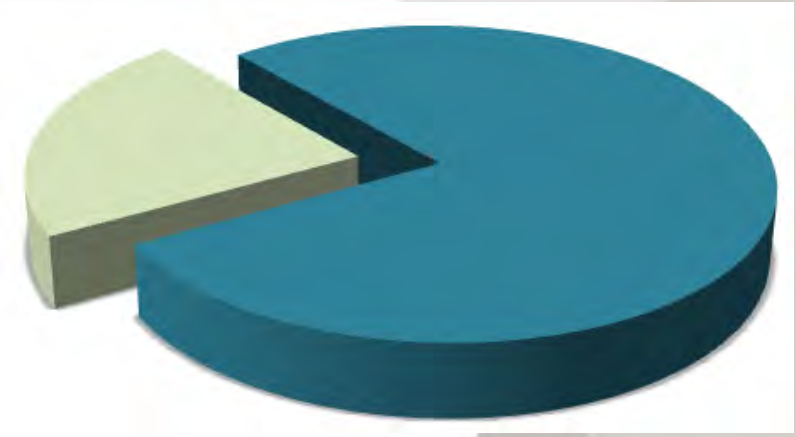
ORR to EGFR TKI

ORR



RP: 55%

DCR



RP + SD: 78%

- IF RP or SD: improvement of symptoms
- OS 6 mois

Increase TKI dose ?

- **N=14 (36%)**

1) Erlotinib increase (n=8)

- 150mg to 300mg (n=7)
- Weekly high dose (n=1)

2) Switch from gefitinib to erlotinib (n=6)

- **ORR=29%**
- **DCR=64%**

Conclusion

- BLOOD BRAIN BARRIER DOES NOT EXIST IN BRAIN METS
- SABR and surgery are key players
- WBRT can be delayed
- ORR to chemotherapy : same as extra-cranial disease
- Bevacizumab, a good partner for brain mets?
- EGFRmut and ALK+ population : TKI should be offered upfront if brain mets
- Carcinomatous meningitis: increase TKI dose is an option