

Targeted therapies and brain metastases in lung cancer patients

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19 septembre 2014



IOT

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Targeted therapies and brain mets

- **Brain mets in NSCLC**
- **Specific targeted therapies**
 - EGFR mutations
 - ALK rearrangements
 - Strategy in patients with PD after TKI
- **Unspecific targeted therapies**
 - Bevacizumab and brain mets
 - WBRT and bevacizumab
- **Conclusion**

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Lung Cancer

- ✓ Incidence in France - 2012:
 - 2nd cancer in men (28 200 new cases)
 - 3rd cancer in women (11 300 new cases)
- ✓ Mortality in France - 2012:
 - 1st cancer in men (21 300 death)
 - 2nd cancer in women (8 700 death)
- ✓ 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

Données InVS

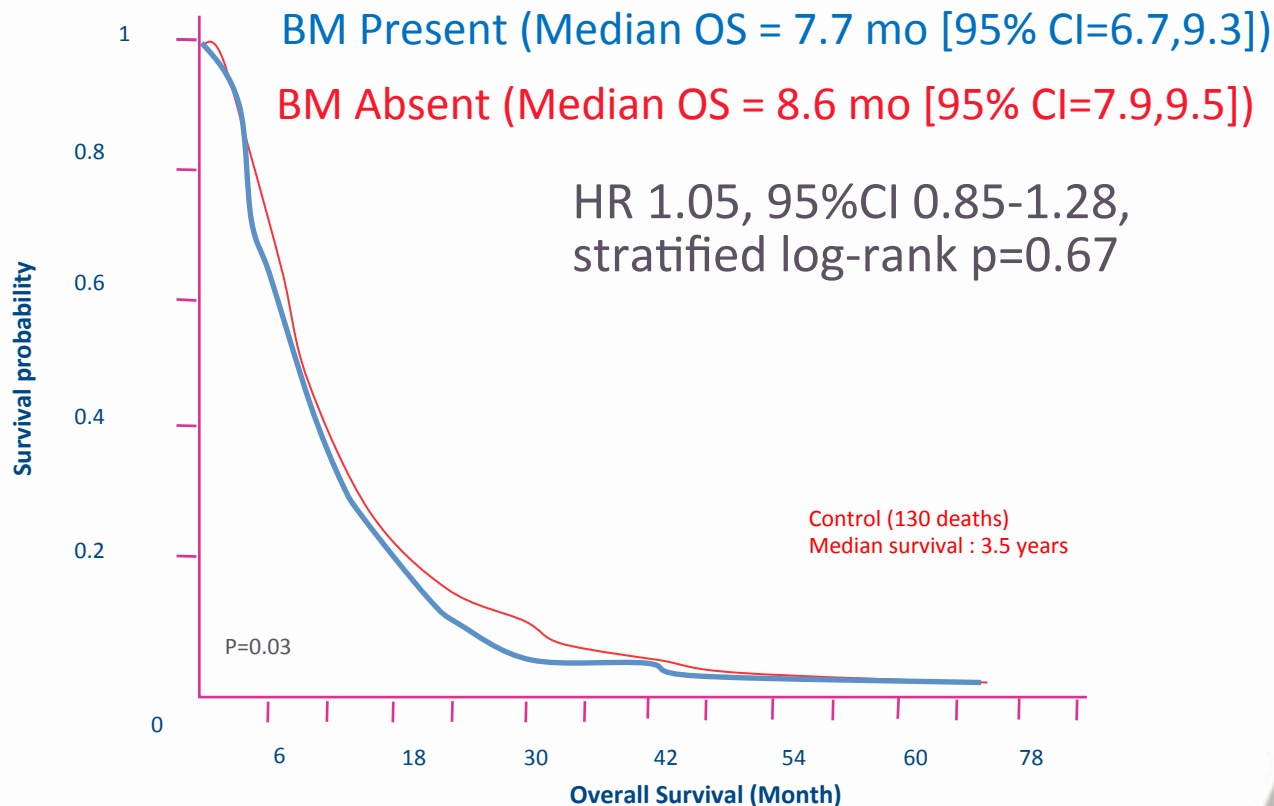
Vallières E et al. J Thorac Oncol 2009; 4:1049-1059

Gaspar LE. Expert Rev Anticancer Ther 2002; 4:259-270

Chaubet-Houdu M. Bull Cancer 2013; 100:95-98

OS in brain mets patients

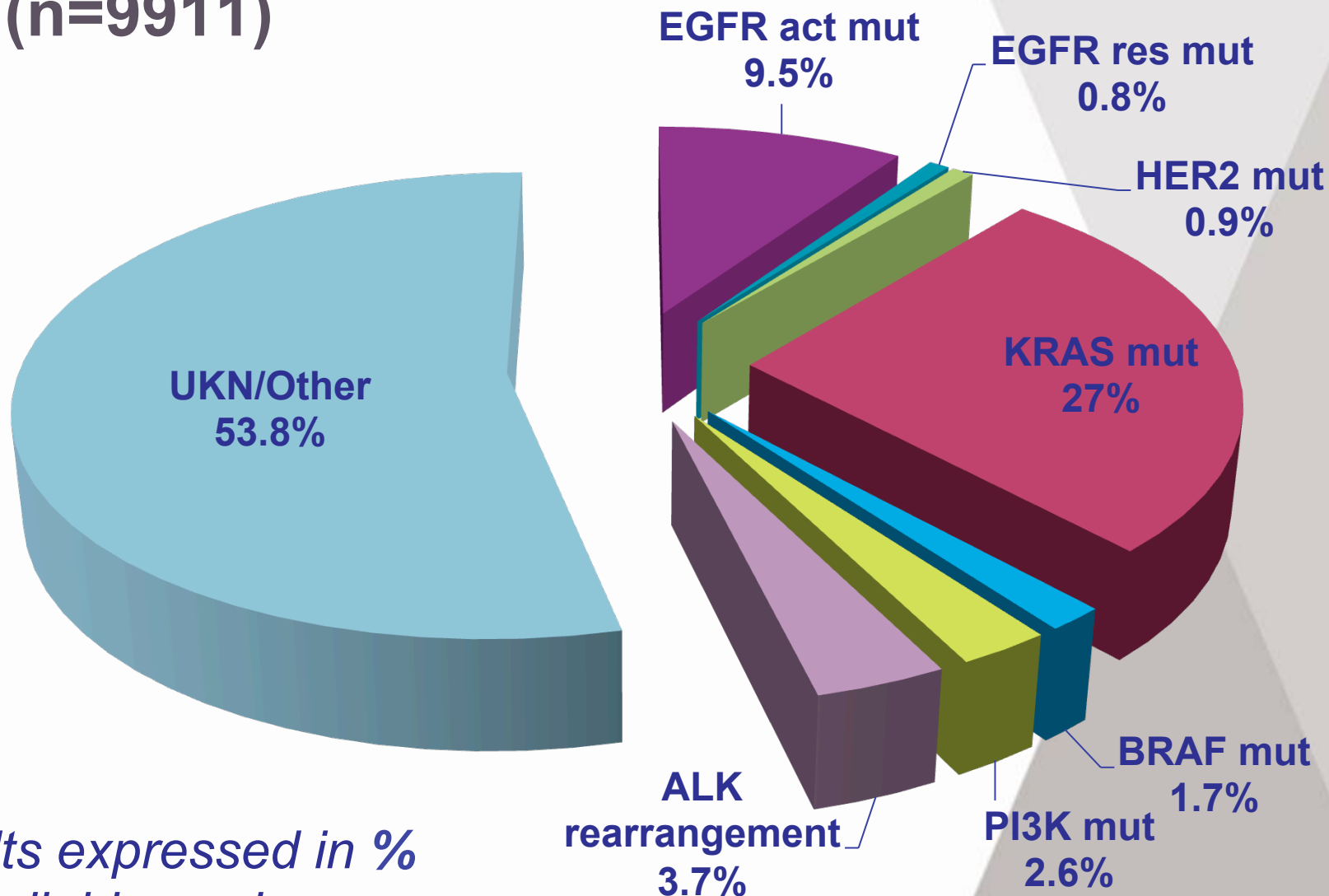
- Canadian cohort
- 3 RCT (BR.18, BR.21, BR.24)
- N=131(BM+)/1218(BM-)



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

Results: biomarkers assessment (n=9911)

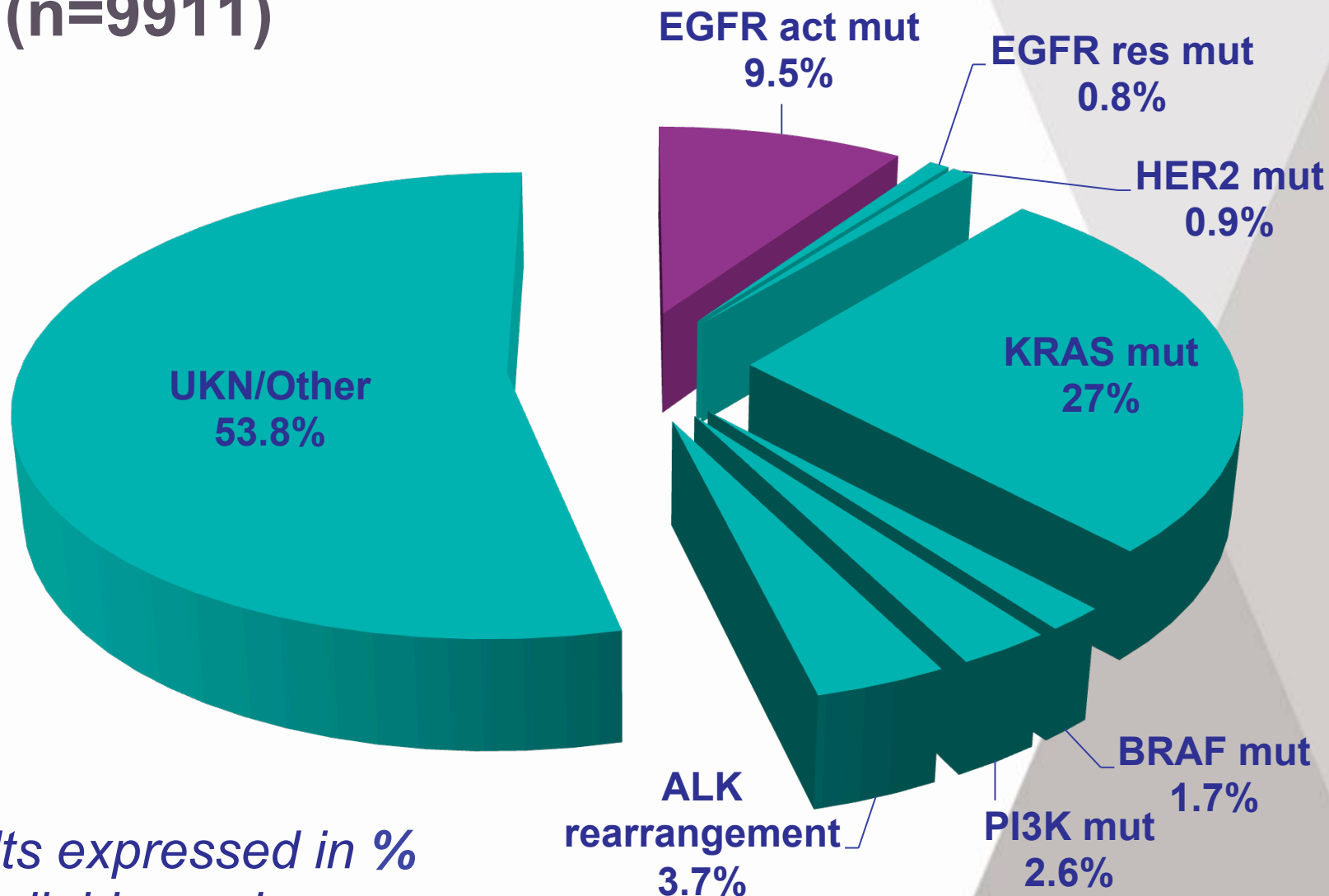


*Results expressed in %
on available analyses*

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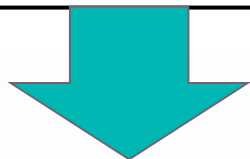
EGFR TKI in EGFRmut pts

Results of phase III studies

Study	Drug	N	ORR (%)	PFS (m)	OS (m)
IPASS	gefitinib	132	71,2	9,8	21,6
FIRST-SIGNAL	gefitinib		84,6	8,4	30,6
WJTOG 3405	gefitinib	51	62,1	8,4	35,5
NEJ 002	gefitinib	114	73,7	10,8	27,7
OPTIMAL	erlotinib	82	83,0	13,1	22,7
EURTAC	erlotinib	86	58	9,7	19,3
LUX-LUNG 3	afatinib	230	56	11,1	28,1
LUX-LUNG 6	afatinib	242	67	11,0	
ENSURE	erlotinib	110	63	11,0	

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

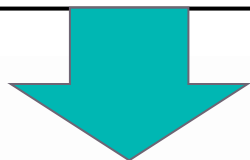


Brain mets

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

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Brain mets

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Phase III studies

ORR 56-84%
OS 19.3 – 28.1 m

TKI EGFR – largest cohort

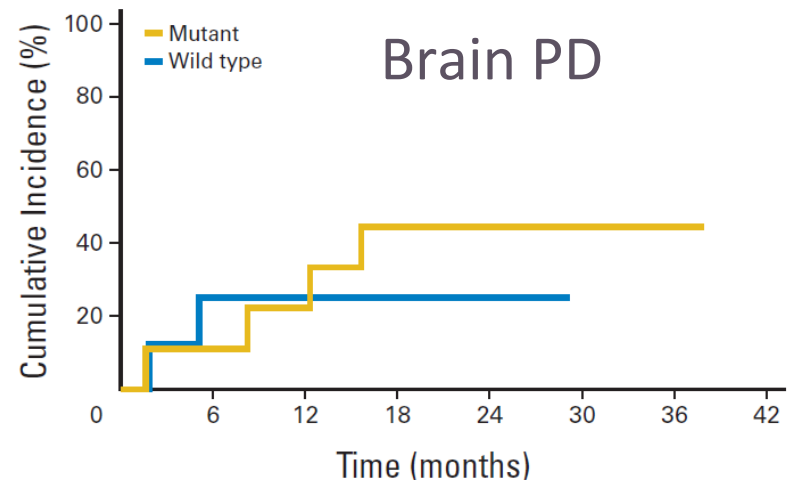
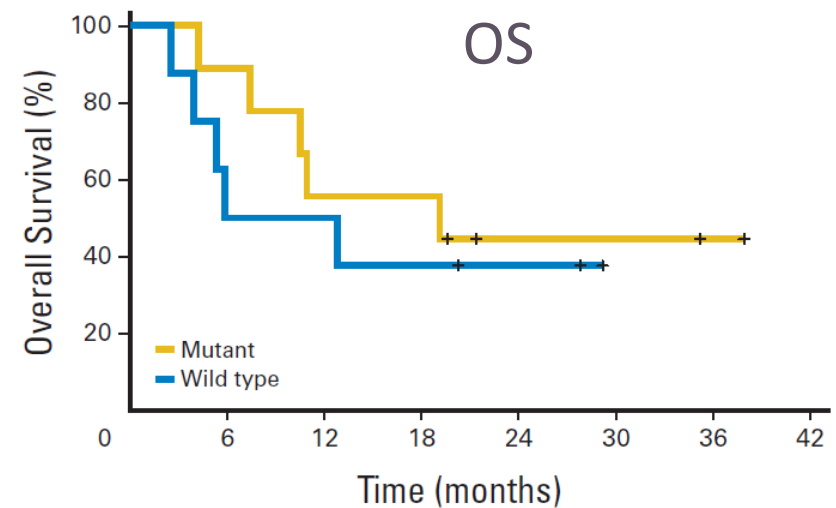
- Never smokers, asymptomatic, synchronone
- Gefitinib 250mg or erlotinib 150mg
- No WBRT

Best overall response	N = 28	(%)
Complete response	–	
Partial response	23	(83)
Stable disease	3	(11)
Progressive disease	1	(3)
Not available	1	(3)

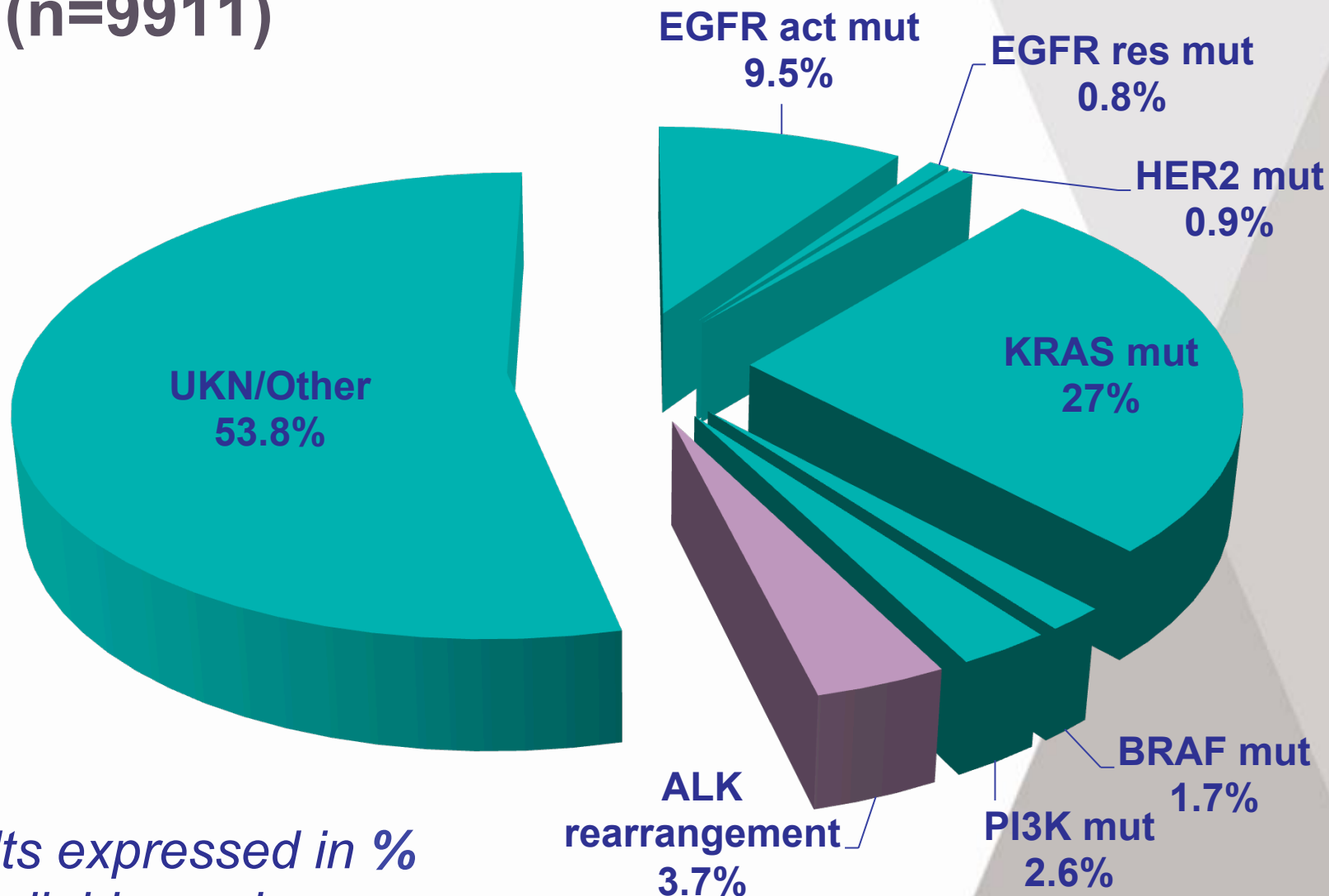
- Follow up 17,5 months
- PFS : 6,6 months - OS: 15,9 months
- Recurrence: Brain 13 pts, out of the brain 4 pts, both 4 pts
- WBRT in 14 patients at 12,6 months of diagnosis

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



Results: biomarkers assessment (n=9911)



*Results expressed in %
on available analyses*

ALK inhibitors in clinical development

- | | |
|--------------------------------------|-------------------------------------|
| ▶ Crizotinib (XALKORI, Pfizer) | approved |
| ▶ Ceritinib (ZYKADIA, Novartis) | approved (US only) + EAP |
| ▶ Alectinib (ALECENSA, Chugai/Roche) | phase III (approved in Japan, only) |
| ▶ AP26113 (Ariad) | phase II |
| ▶ ASP-3026 (Astellas) | phase I |
| ▶ PF-06463922 (Pfizer) | phase I |
| ▶ TSR-011 (Tesaro) | phase I |
| ▶ CEP-37440 (Teva) | phase I |
| ▶ X-396 (Xcovery) | phase I |
| ▶ RXDX (Ignyta) | phase I |

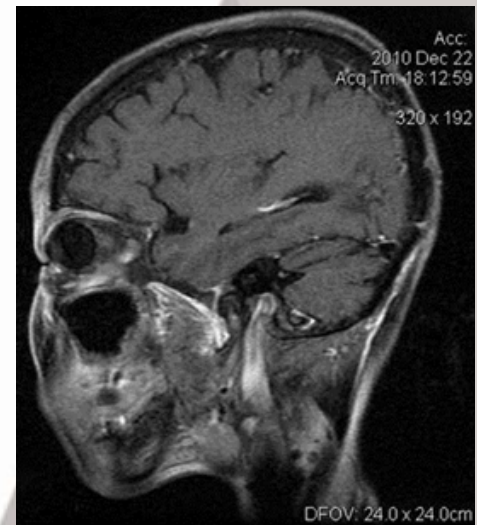
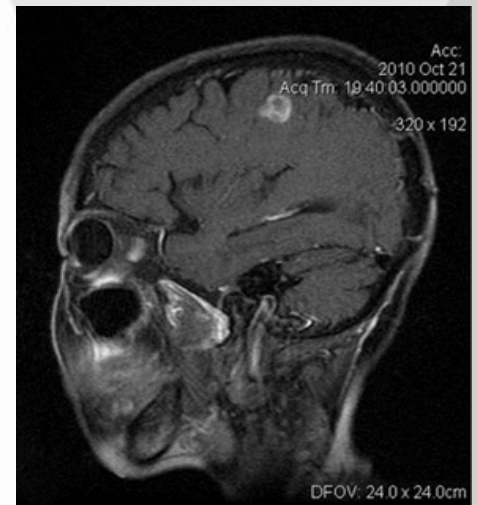
Crizotinib clinical trial efficacy data

	PROFILE 1001 ¹ N=143	PROFILE 1005 ² N=261	PROFILE 1007 ³ N=173	PROFILE 1014 ⁴ N=172
Line of therapy	Any line	Second-line and beyond	Second-line only	First line
ORR	60.8%	53%	65%	74%
Median duration of response, weeks	49.1	42.9	32.1	49.0
Median PFS, months	9.7	8.5	7.7	10.9
OS probability at 12 months	74.8%	61%	~70%	84%

1. Camidge RD, et al. Lancet Oncol 2012;10:1011–9; 2. XALKORI® Summary of Product Characteristics; 3. Shaw AT, et al. N Engl J Med 2013;368:2385–94; 4. Mok, T, et al. Presented at ASCO 2014, Abstract 8002

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

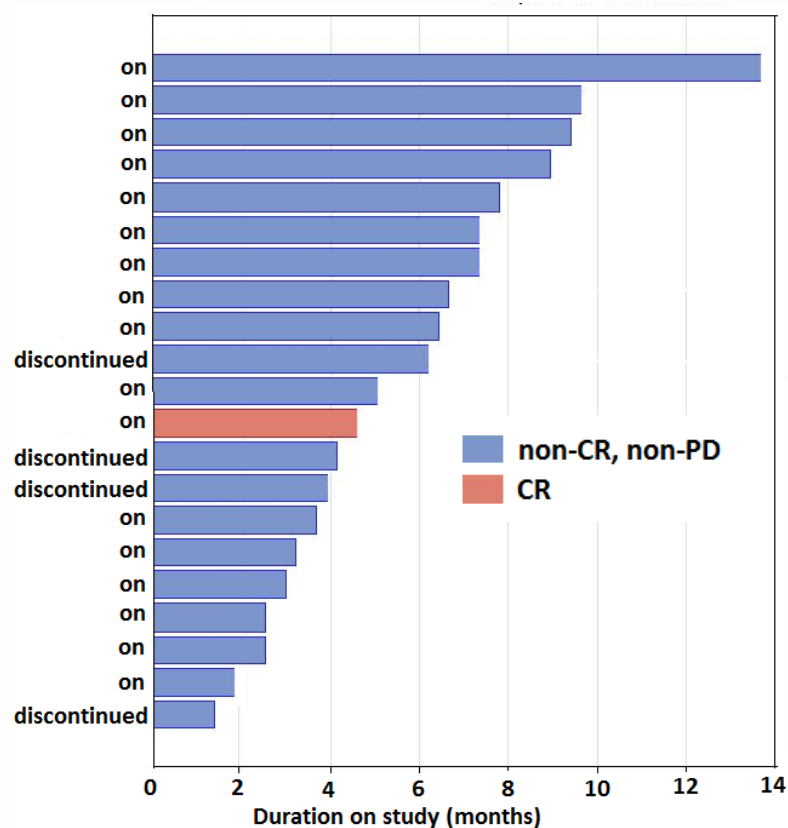


Crizotinib and brain mets

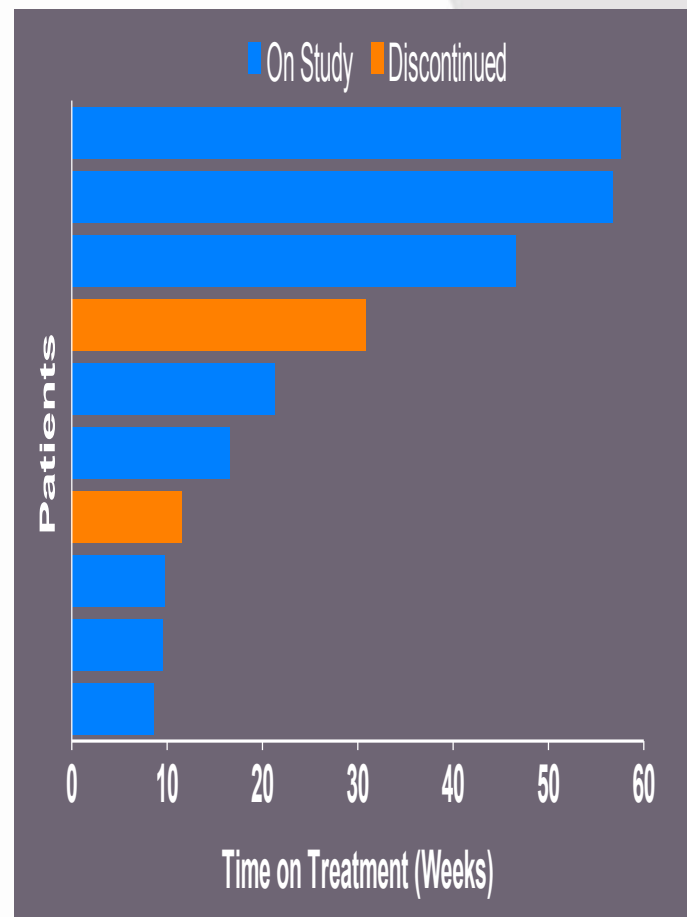
- **Crizotinib has real but decreased activity on brain mets**
 - ORR of 25%
 - to compare to a systemic ORR of 49%
- **CNS remains the dominant site of acquired resistance on therapy for ALK patients with or without brain metastasis**
 - 71% of PD in patients with baseline brain metastasis
 - 27% of PD in patients without baseline brain metastasis
- **Crizotinib has limited brain penetration (notably with an intact BBB) and may not be the best ALK inhibitor for brain metastasis**
 - Crizotinib CSF-to-plasma ratio of 0.0026 (Costa et al JCO 2011)
 - Carcinomatous Leptomeningeal responses reported with alectinib

2nd generation ALK TKI and Brain mets

Alectinib

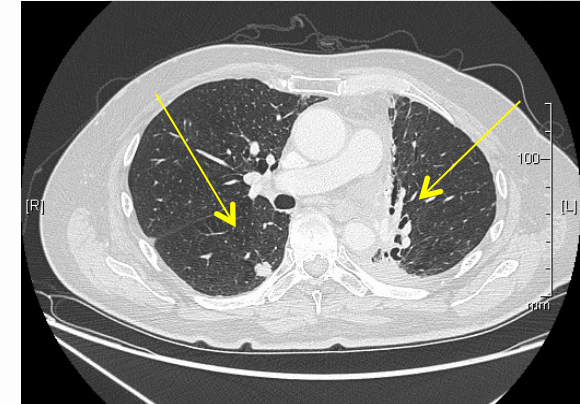
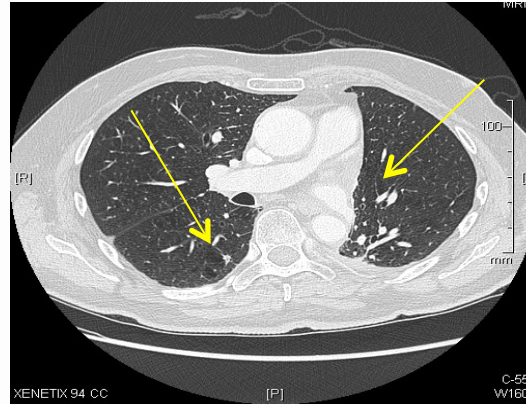


AP26113

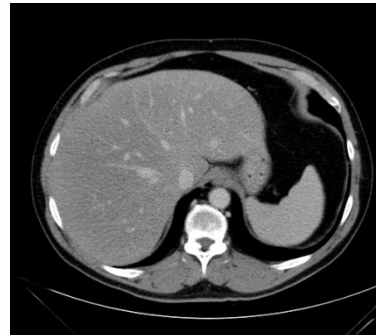


Types of progression

Asymptomatic,
indolent growth,
multiple sites



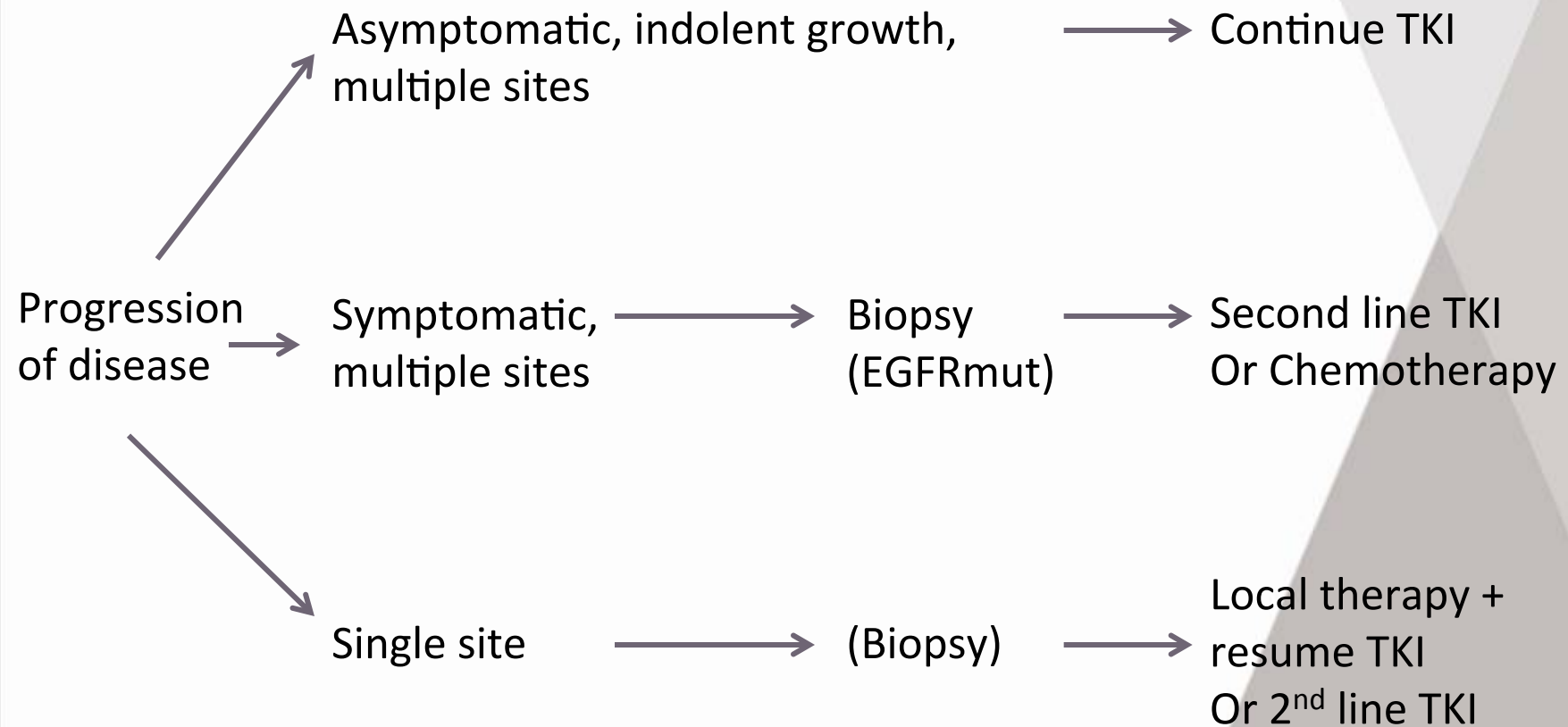
Single site



Symptomatic,
multiple sites



Approach to Management of Patients with TKI Acquired Resistance



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Bevacizumab

✓ Bevacizumab

- anti-VEGF monoclonal Ab
- half life 21 days (11-50)

Gordon MS et al. J Clin Oncol 2001; 19:843-850

✓ Approved in 1st line advanced NSCLC

	ECOG 4599 ¹	AVAiL ²
OS	12,3m vs 10,3m	13,1m vs 13,6m / 13,4m
PFS	6,2m vs 4,5m	6,6m / 6,5m vs 6,1m
ORR	35% vs 15%	34,1% / 30,4% vs 20,1%

¹Reck M et al. J Clin Oncol 2009; 27:1227-1234; ²Reck M et al. Ann Oncol 2010; 21:1804-1809

✓ Meta-analysis of randomized trials

- 1 yr absolute benefit : 4%
- Median OS at 1yr: 55%

Soria JC et al. Ann Oncol 2012; 24:20-30

Bevacizumab

✓ Bevacizumab toxicity

- frequent: HTA, proteinuria, epistaxis
- serious: hemorrhage, PE, wound healing issues

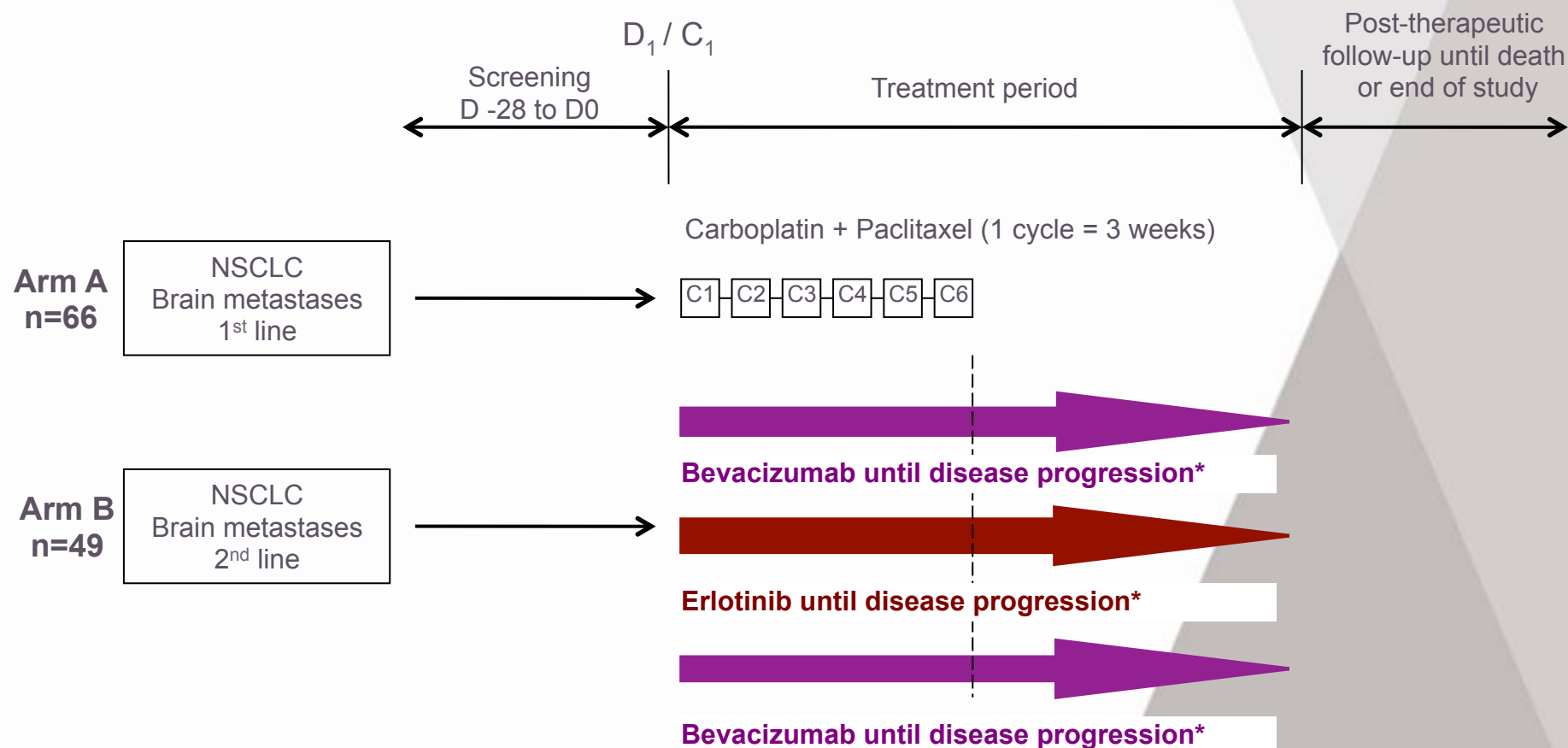
✓ Bevacizumab and Brain Mets (approved 2009 in EU)

Author	Phase	N	Cerebral Hemorrhage N (%)
Socinski et al. ¹	II	115	0 (0%)
Besse et al. ²	Méta-analyse	Groupe A: 187 Groupe B: 321 Groupe C: 131	3 (3,3%) 3 (0,9%) 1 (0,8%)
Crinò et al.	IV	2212	7 (2%)

¹J Clin Oncol 2009; 27:5255-5261; ²Clin Cancer Res 2010; 16:269-278; ³J Clin Oncol 2013; ⁴Lancet Oncol 2010; 11:733-740

Phase II study BRAIN

- Non squamous NSCLC
- Asymptomatic, non treated brain mets



- In the event of permanent discontinuation of chemotherapy due to toxicity, bevacizumab will be administered until disease progression, except in case of unacceptable toxicity or patient or investigator decision.

Patients Characteristics

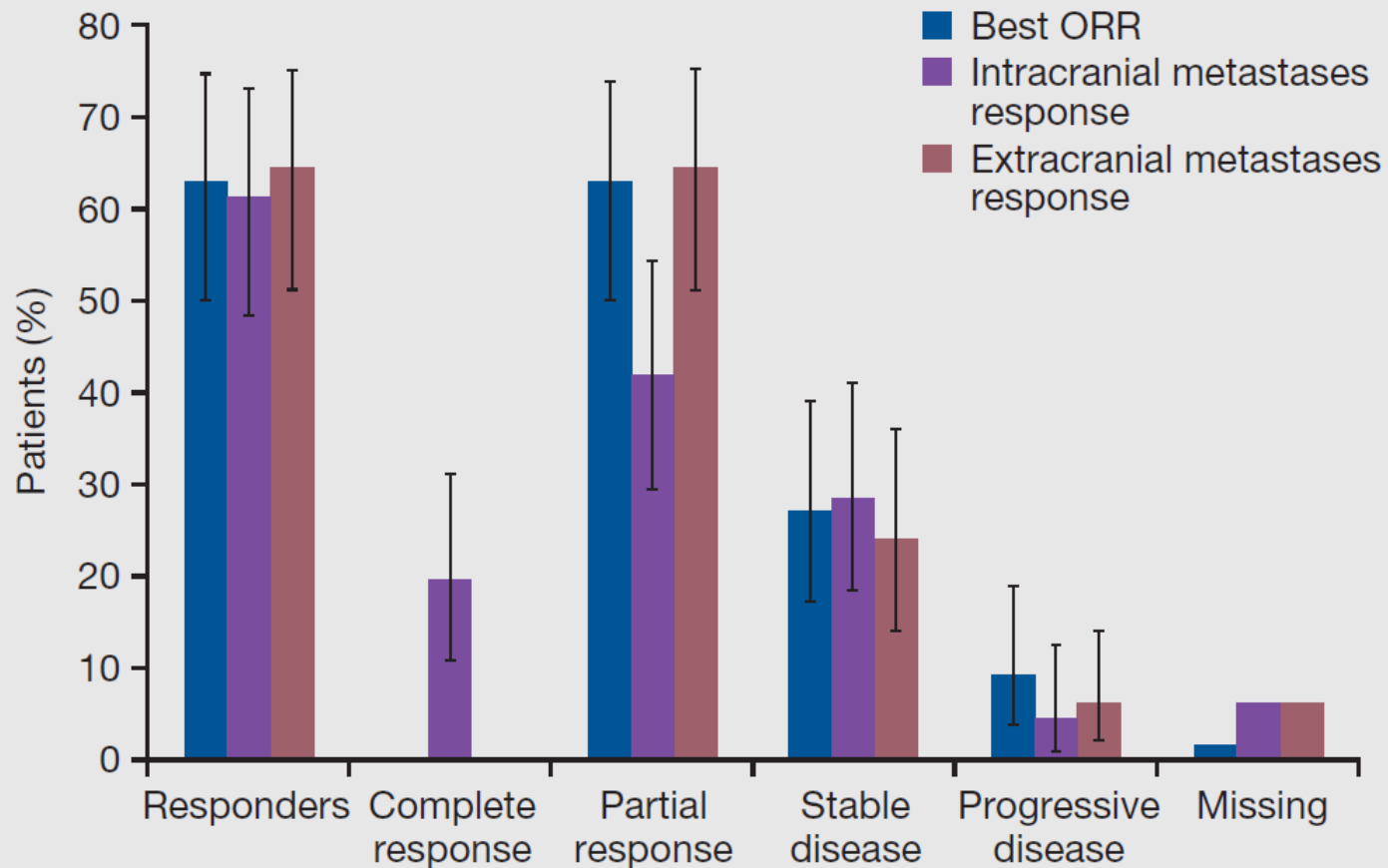
		B+CP (n=67)	B+E (n=24)
Gender, n (%)	Male	46 (68.7)	11 (45.8)
	Female	21 (31.3)	13 (54.2)
Median age, years (range)		61.0 (40–79)	54.0 (34–70)
ECOG PS, n (%)	0	37 (55.2)	13 (54.2)
	1	30 (44.8)	11 (45.8)
Histology, n (%)	Adenocarcinoma	59 (88.1)	23 (95.8)
	Large cell carcinoma	8 (11.9)	1 (4.2)
Recurrence of previous lung cancer, n (%)	No	61 (91.0)	N/A
	Yes	6 (9.0)	N/A
Metastatic sites, n (%)	Lymph nodes	36 (53.7)	13 (54.2)
	Liver	17 (25.4)	5 (20.8)
	Adrenal	14 (20.9)	9 (37.5)
	Pleura	4 (6.0)	–
	Bone	34 (50.7)	8 (33.3)
	Other	16 (23.9)	4 (16.7)
Smoking status, n (%)	Past smoker	33 (49.3)	17 (70.8)
	Current smoker	20 (29.9)	4 (16.7)
	Never smoker	14 (20.9)	3 (12.5)

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)

- 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.

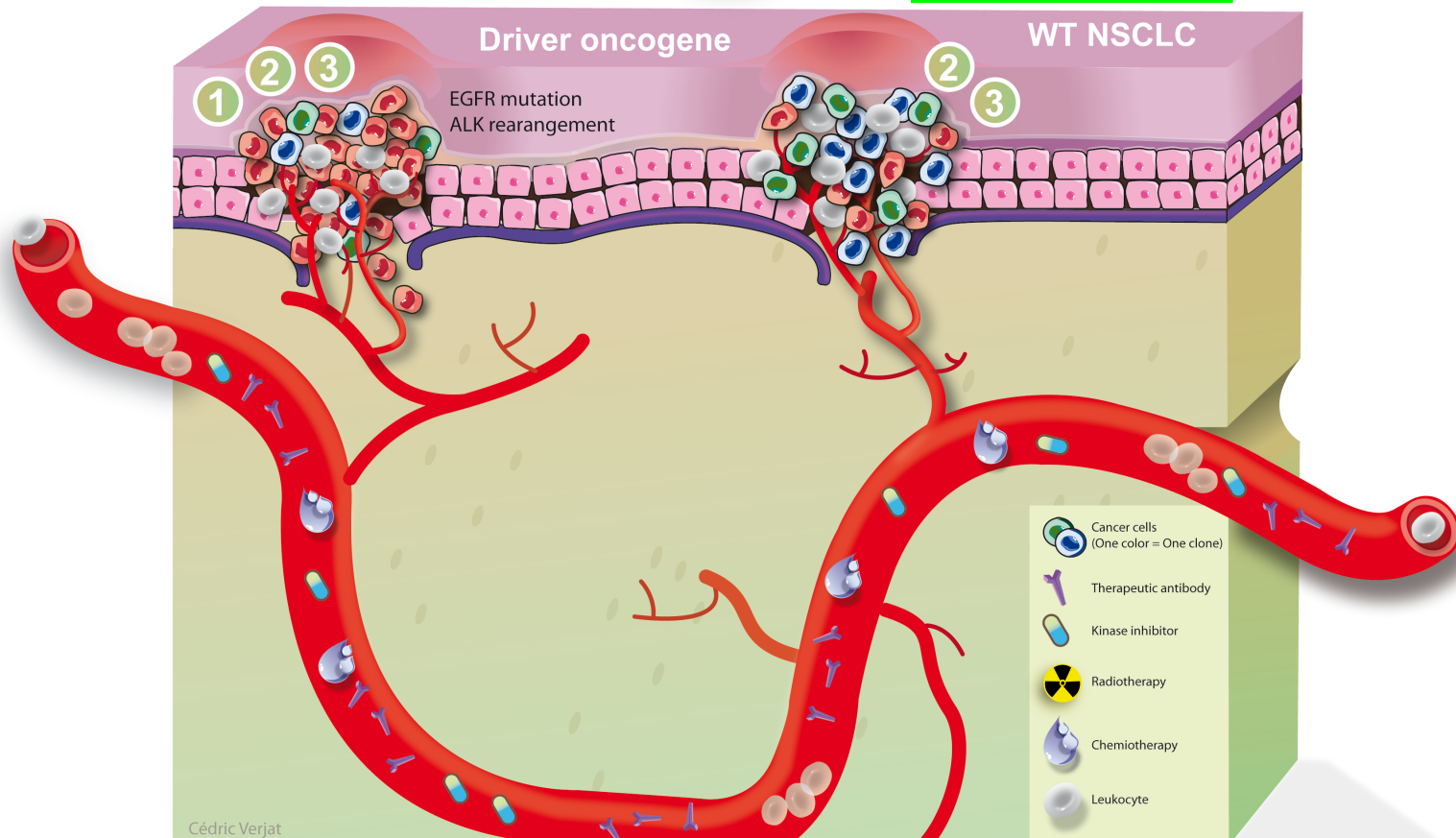
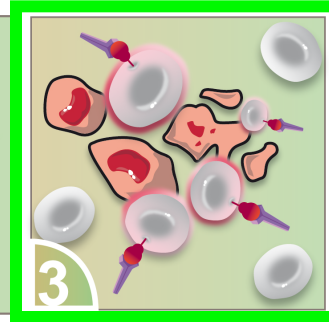
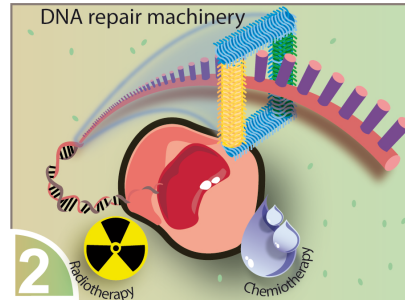
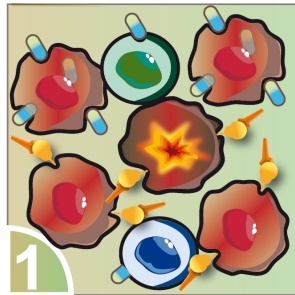
ORR – Paclitaxel carboplatine bevacizumab



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



Wt NSCLC vs oncogene addicted NSCLC



Conclusion

- **EGFRmut and ALK+ population**
 - TKI should be offered upfront if brain mets
 - TKI efficacy is not homogeneous (crizotinib less potent)
 - WBRT is safe with erlotinib low dose
- **Bevacizumab**
 - A 'good partner' for chemo in brain mets
 - WBRT + bevacizumab is feasible
- **Carcinomatous meningitis**
 - More frequent in EGFRmut/ALKmut population ?
 - A definitive issue in long survivor
- **Trial requirements**
 - Specific trials and open the in phase I studies to these pts