elcc European Lung Cancer Conference

Tumor burden and tyrosine kinase inhibitors benefit in advanced NSCLC patients with EGFR sensitizing mutations or ALK rearrangement

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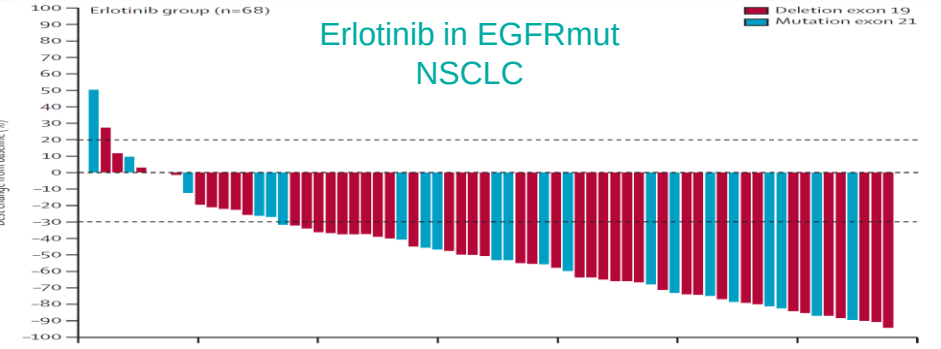
GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

DISCLOSURE SLIDE

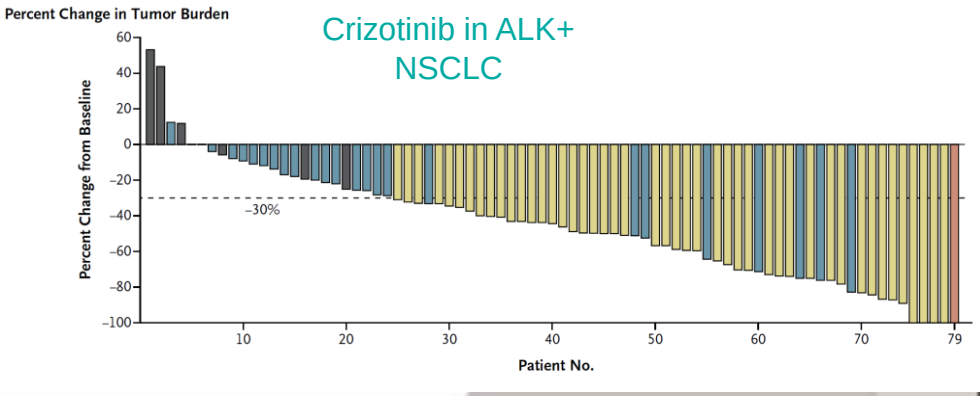
- **None**

INTRODUCTION (1)

- EGFR sensitizing mutations (EGFRmut): 10-30% NSCLC
- ALK rearrangement (ALK+): 3-7% NSCLC
- Highly sensitive to Tyrosine Kinase Inhibitors (TKI) therapy with a response rate around 60%



Erlotinib in EGFRmut NSCLC



Crizotinib in ALK+ NSCLC

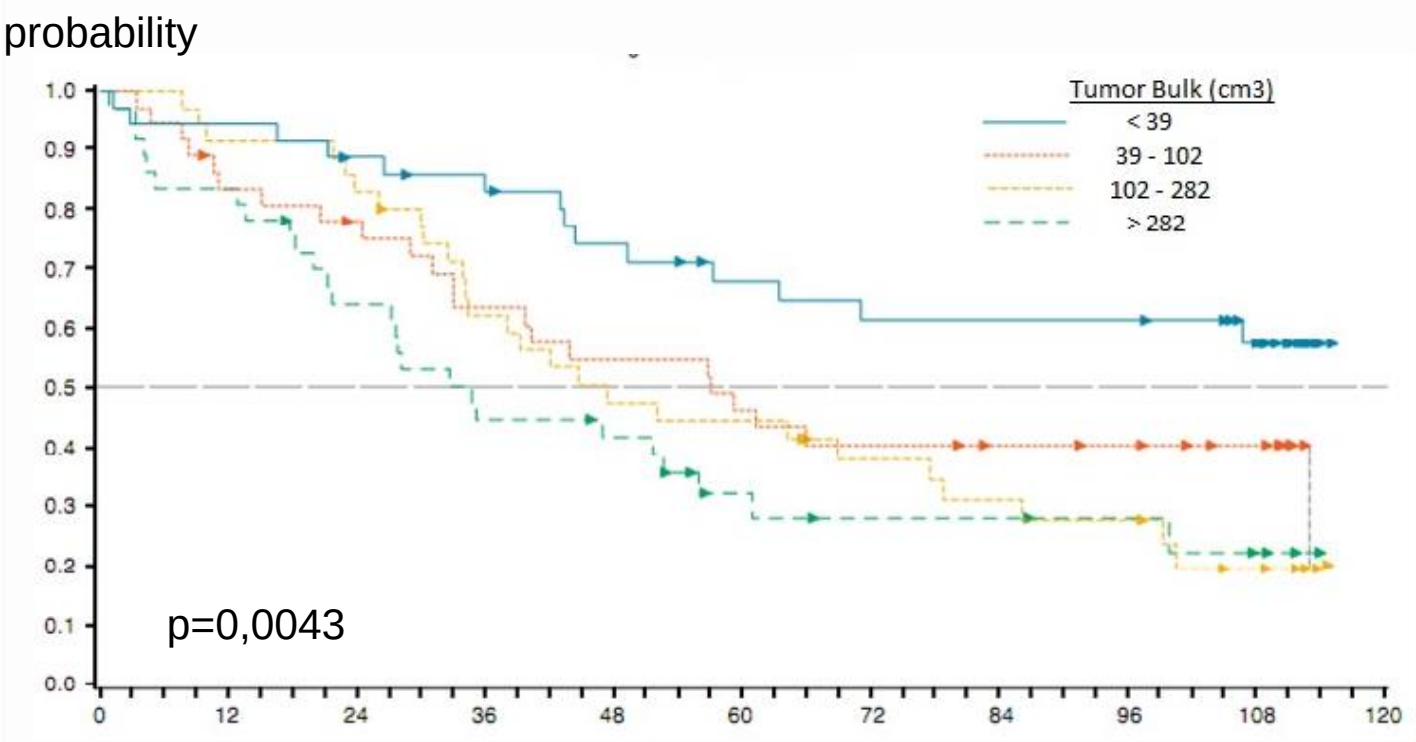
Rosell Lancet Oncol 12, Kwak NEJM 10

INTRODUCTION (2)

- The rate of response to TKI is related to :
  - clinical factors (never-smoker status, female gender, adenocarcinoma subtype, asian ethnicity)
  - molecular factors (L858R point mutation or E746-A750 deletion, amplification of EGFR gene)
- The other predictive factors of response to TKI are poorly known

RATIONALE AND OBJECTIVE

- In GIST: significant correlation between tumor bulk at baseline and 9-yr OS (58% if <39 mm^2 *vs* 23% if ≥262 mm^2)



Phase II B2222 trial
n = 147

- Objective of our study: define the impact of initial tumor volume on TKI benefit in advanced NSCLC EGFRmut or ALK+

Blanke et al. J Clin Oncol 2009;26:620-625 ; Von Mehren et al J Clin Oncol 2011; 29: (abstr 10016)

PATIENTS AND METHODS

- Retrospective single center study, from June 2006 to November 2013

- **Inclusion criteria:**
  - Advanced NSCLC (stage III/IV)
  - Harboring EGFRmut or ALK+
  - Treated with TKI (EGFRmut : erlotinib or gefitinib ; ALK+ : crizotinib)

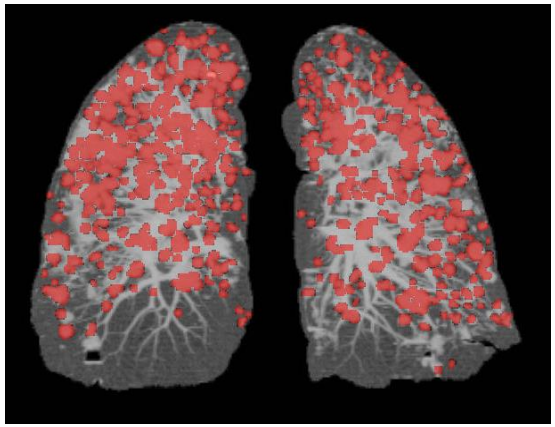
- **Statistics**: univariate and multivariate using Cox analyses

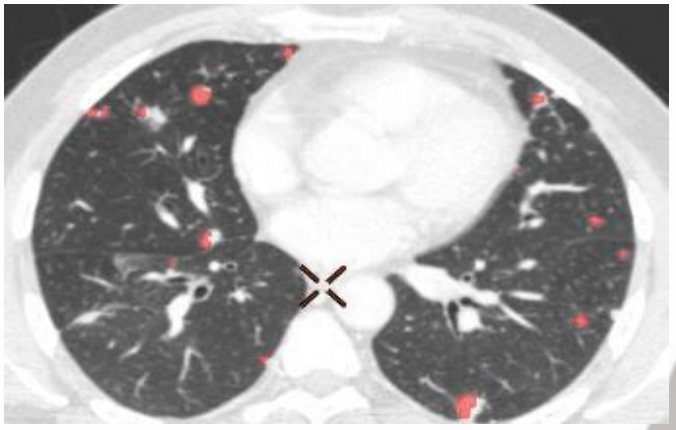
- **End points:**
  - Primary : Correlation of initial tumor burden
  - Secondary : Progression Free Survival (PFS) and Overall Survival (OS)

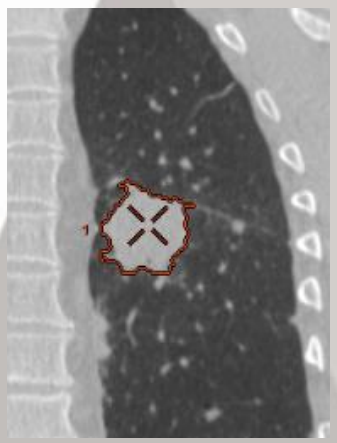
PATIENTS AND METHODS

Tumor volume measurement:

- Baseline CT scans
- All primary and metastatic measurable lesions
- Automatic or semi automatic measurement
- By contouring the whole tumor volume







volume analysis software, LungVCAR, GE

RESULTS: Patients characteristics (1)

	No. (%) n = 97
Sex	
Male	29 (30%)
Female	68 (70%)
Age (median, range)	57 (24, 85)
Clinical Stage at diagnosis	
IIIa	1 (1%)
IIIb	1 (1%)
IV	95 (98%)
Genomic Alteration	
ALK translocation	14 (14%)
EGFR mutation	80 (82%)
Both	3 (3%)

	No. (%) n = 97
Resistant Mutation	
No	92 (95%)
Yes	5 (5%)
Smoker status	
No	59 (59.8%)
< 10 PA	25 (25.8%)
≥ 10 PA	13 (13.4%)
Histology	
Adenocarcinoma	84 (86.8%)
Epidermoïde	12 (12.4%)
Poorly differentiated	1 (1%)

RESULTS: Patients characteristics (2)

Initial tumor volume (cm^3)	No. (%) – n = 97
≤ 35	33 (34%)
35 - 74	31 (32%)
> 74	33 (34%)

RESULTS: Patients characteristics (3)

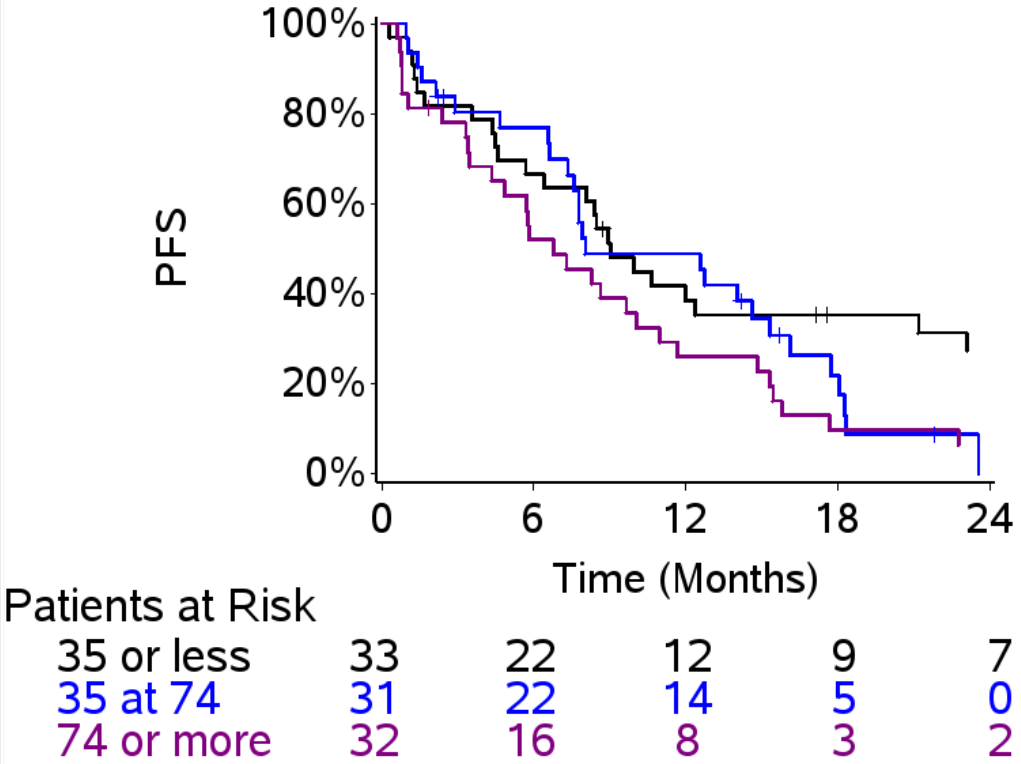
Number of metastatic sites	No. (%) – n = 97
0 or 1	26 (27%)
2 or 3	54 (56%)
≥ 4	17 (18%)

RESULTS: Survival

	Months (median)
Follow-up	31
PFS	
Global	8.5
EGFRmut	9.02
ALK+	6.62
OS	
Global	25
EGFRmut	25.5
ALK+	14.1

RESULTS: PFS

PFS decreases with increasing initial tumor volume (test for trend: p=0.04)



	Median PFS (IC95%)	HR (p=0.04*)
≤ 35 cm3	9.02 (5.67-21.18)	1
35 – 74 cm3	8.03 (7.34-15.31)	1.34 [0.77-2.33]
> 74 cm3	7.28 (4.33-10.07)	1.70 [1.01-2.84]

*** Test for trend**

RESULTS: multivariate analysis

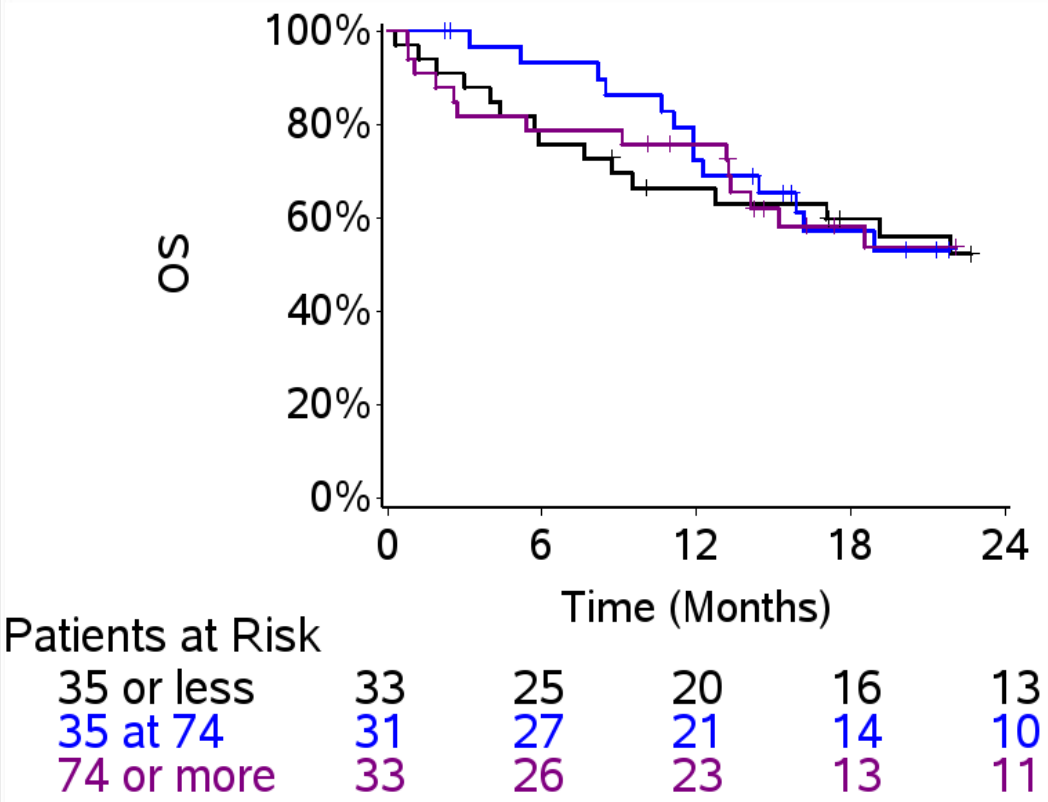
- Results were similar when including the number of metastatic sites and genomic alterations
- Results were not significant when gender and presence of liver metastasis were included

	HR [95% IC]	p
Genomic Alterations		
EGFRmut	1	0.053
ALK+	1.24 [0.68-2.28]	
Both	4.37 [1.29-14.76]	
Number of metastatic sites		
0-1	1	0.004
2-3	1.33 [0.78-2.27]	
4-5	3.20 [1.6-6.4]	
Total Metastases volume (in cm^3)		
≤35	1	0.04*
>35 and ≤74	1.54 [0.87-2.72]	
>74	1.73 [1.01-2.96]	

*** Test for trend**

RESULTS: OS

Tumor volume was not associated with OS in univariate (p for trend= 0.72) and multivariate analysis (p for trend= 0.87)



	Median OS (IC95%)	HR (p=0.72*)
≤ 35 cm3	24.85 (9.51-36.07)	1
35 – 74 cm3	27.02 (12.23-31.34)	1.02 [0.54-1.93]
> 74 cm3	24.3 (13.25-32.49)	1.12 [0.61-2.05]

*** Test for trend**

CONCLUSION

- In EGFRmut and ALK+ advanced NSCLC treated by TKI, PFS decreases with increasing initial tumor volume
- OS is not influenced by initial tumor volume
- Number of metastatic sites is a stronger survival predictor
- TKI onset should not be delayed after diagnosis or begun after a cytoreductive treatment such as chemotherapy
- Validation on a bicentric cohort is ongoing