Prognostic and Predictive Values of *KRAS* in *EGFR*-based Subgroups and Combined with *TP53* in Completely Resected Non-Small Cell Lung Cancer (NSCLC): a LACE-Bio Study

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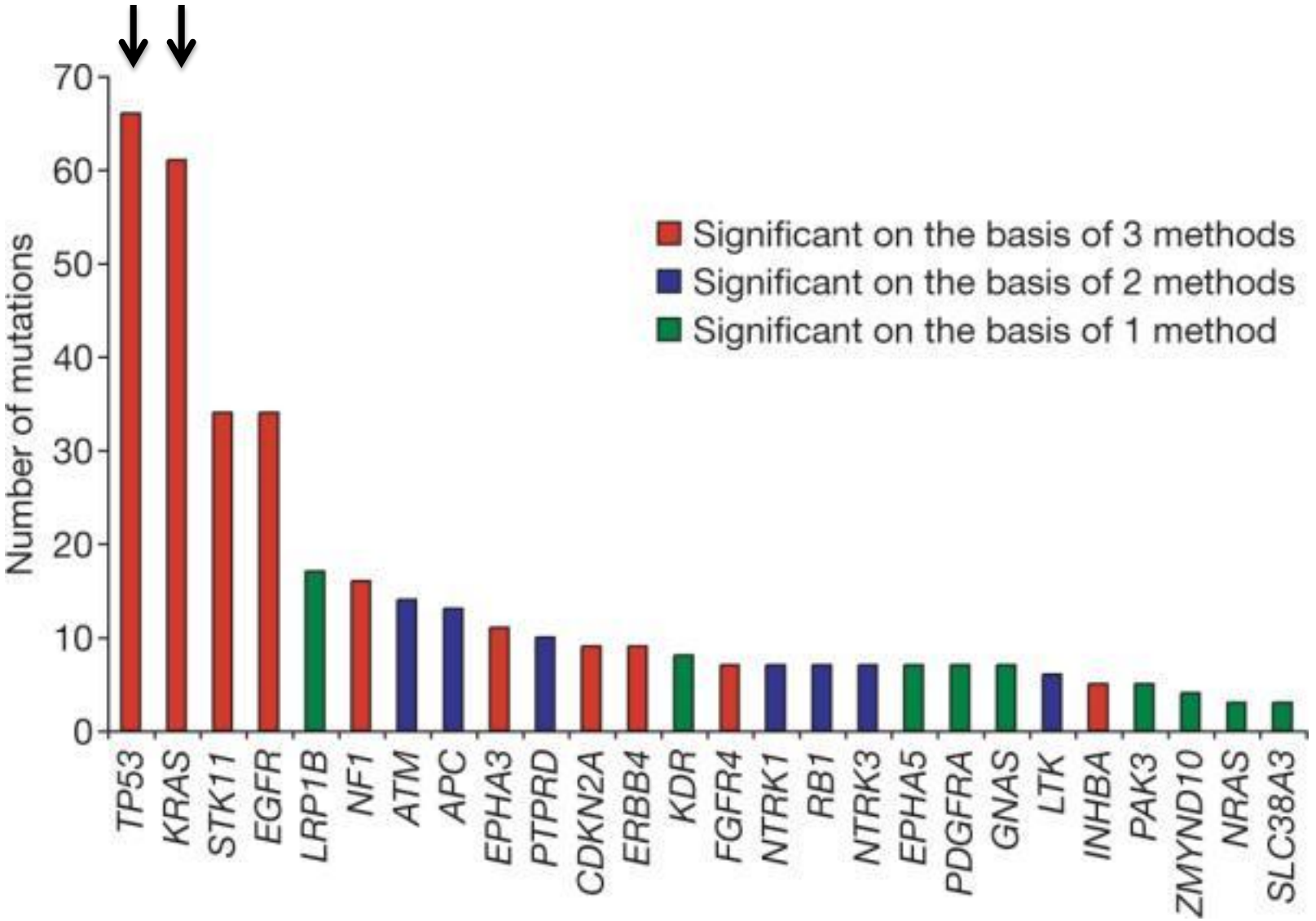
on behalf of the
LACE-Bio Collaborative Group

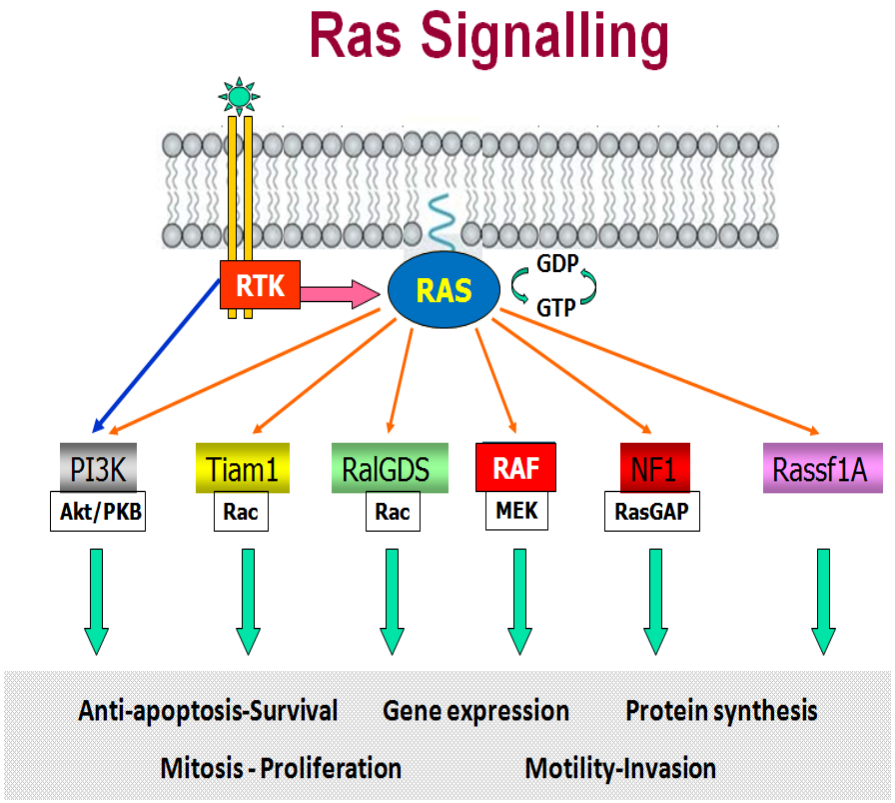
TP53 and *KRAS* Mutations are Common in NSCLC



Ding et al. Nature 2008

KRAS Mutation and NSCLC

- *RAS* mutations occur in 15-20% NSCLC, with >90% involving *KRAS*
- Associated with smoking and adenocarcinoma
- In 1990, *KRAS* mutation was first reported as a prognostic marker in lung adenocarcinoma



Previous *KRAS* results in LACE-Bio

Shepherd et al. ASCO 2012

- Pooled analysis of *KRAS* mutation status in 1543 patients from 4 randomized trials (ANITA, JBR10, IALT and CALGB 9633) of adjuvant platinum-based chemotherapy or observation

- No predictive nor prognostic significant value of *KRAS* mutation on OS and DFS

- Analysis according to the sub-type of mutation showed that codon 13 mutation was predictive of a deleterious effect of chemotherapy

Aims of the Current Study

- Assess the prognostic and predictive effects of *KRAS* mutations in 4 LACE-Bio trials of adjuvant chemotherapy versus observation
  - *KRAS* mutations in *EGFR* wild type (WT) adenocarcinoma
  - *KRAS* mutations combined with *TP53* mutations

Methods: *KRAS* Analyses

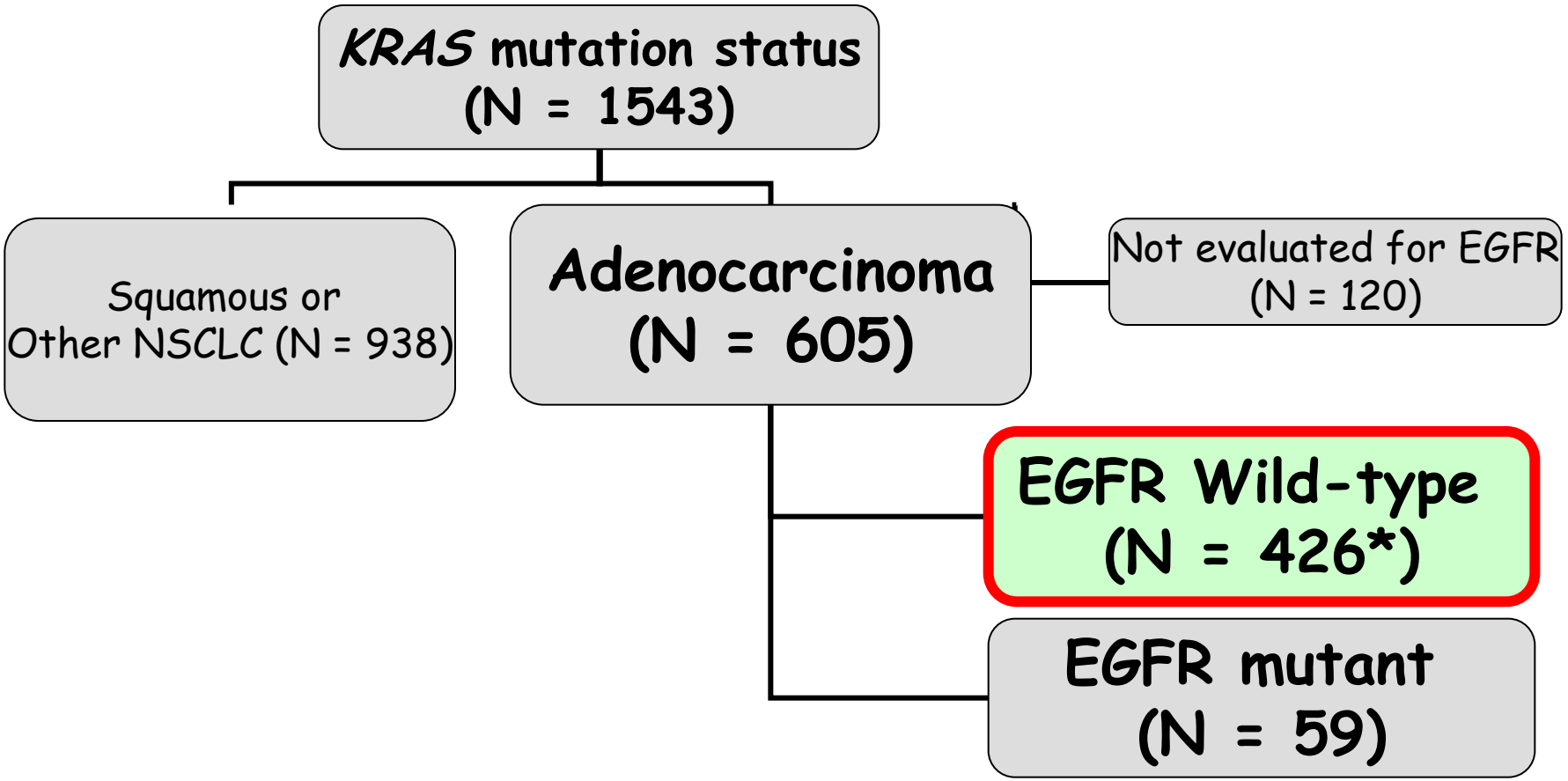
Trial	Analysis Method (All blinded)	*RAS* family	Codon
ANITA	Sequencing & RFLP & ARMS	K	12, 13
IALT	Sequencing & RFLP	K	12, 13
JBR.10	Sequencing & ASOH	K, H, N	12, 13, 61
CALGB	Mass spectrometry	K	12, 13, 61

RFLP: Restriction fragment length polymorphism
ASOH: Allelic specific oligonucleotide hybridization
ARMS: Allelic refractory mutation system analysis (DxS Kit)

Methods: *EGFR* and *TP53* analyses

EGFR exon 19 and 21 mutations and *TP53* were assessed by polymerase chain reaction / bidirectional sequencing in cases with DNA quality allowing also *KRAS* mutation search

KRAS Mutation in *EGFR* Wild-Type Adenocarcinoma Patients



* 27 ANITA patients were then removed of the analysis because of the uncertainty of the *EGFR* mutation detection

Prognostic Value of *KRAS* Mutation on Overall Survival in *EGFR* WT AdenoCa

Observation Arm*	No deaths / No patients	HR for death	95% CI	P
***KRAS* Status**				
KRAS wild-type	59 / 124	1	0.56-1.44	0.65
KRAS mutant	35 / 75	0.90		

* 5 patients had missing values for one or more covariates

Predictive Value of *KRAS* Mutation on Overall Survival in *EGFR* WT AdenoCa

	Chemotherapy (Deaths / Pts)	**Observation** (Deaths / Pts)	**HR for death** CT vs. no CT
***KRAS* wild-type** n=236*	44 / 112	59 / 124	0.74 [0.50 – 1.12] p = 0.16
***KRAS* mutant** n= 157*	35 / 82	35 / 75	0.91 [0.56 – 1.48] p = 0.69
HR *KRAS* mutant vs. wild-type	1.12 [0.71 – 1.76] p = 0.62	0.92 [0.59 – 1.44] p = 0.71	1.22 [0.64 – 2.31] p = 0.55

* 6 patients had missing values for one or more covariates

Prognostic Value of *TP53* and *KRAS* Mutations on OS in Observation Patients (n=587)

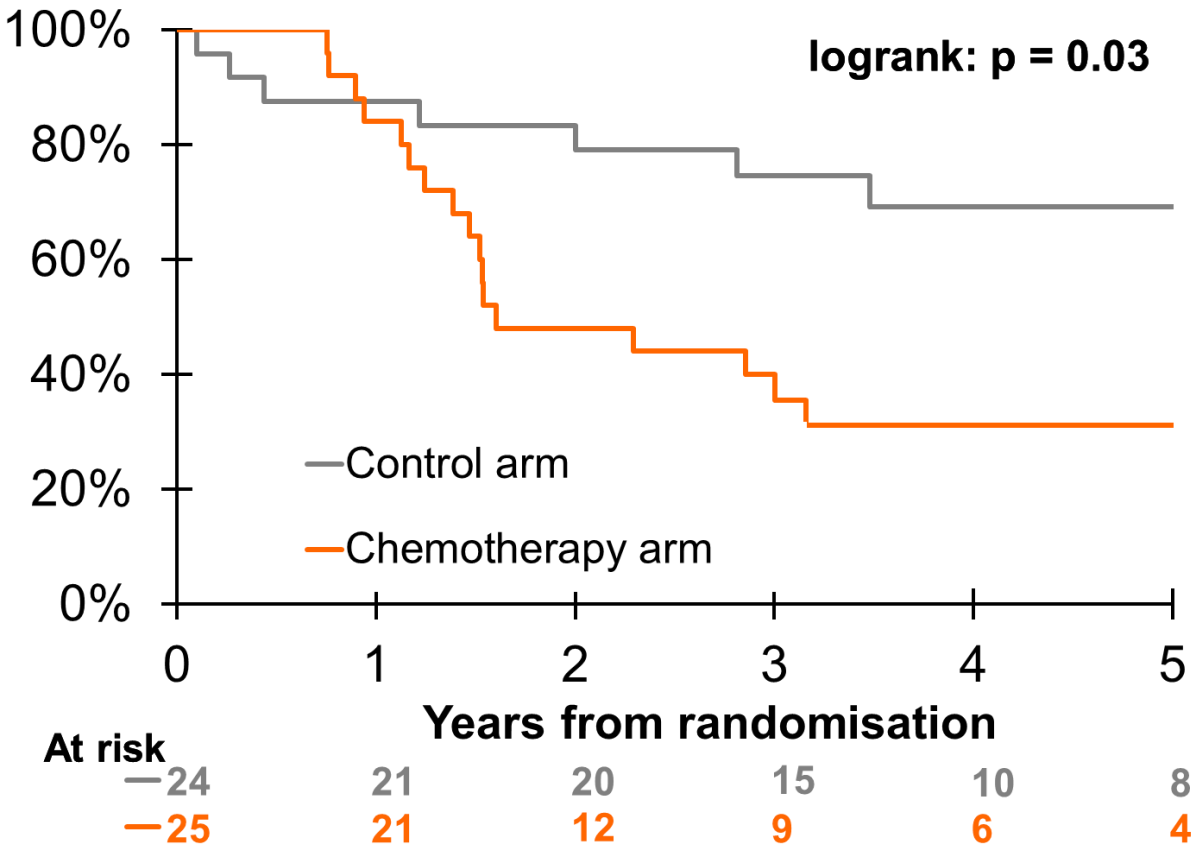
	No deaths / No patients	Multivariable		
		HR for death	95% IC	P value
***KRAS* mutation status**	280 / 580*			
Wild-type	141 / 299	1		0.58
KRAS mutant	41 / 86	1.25	[0.86 – 1.81]	
TP53 mutant	89/ 171	1.08	[0.82 – 1.53]	
Double mutation	9 / 24	0.85	[0.43 – 1.69]	

*7 patients with missing covariates are excluded

Predictive Value of *TP53* and *KRAS* Mutations on Overall Survival

	Chemotherapy (Deaths / Pts)	**Observation** (Deaths / Pts)	**HR for death** CT vs. no CT
***KRAS*/ *TP53* wild type** n=567*	109 / 268	141 / 299	0.82 [0.64 – 1.06] p = 0.13
***KRAS* mutant** n= 184*	41 / 98	41 / 86	0.73 [0.47 – 1.13] p = 0.16
***TP53* mutant** n= 373	108 / 202	89 / 171	0.97 [0.73 – 1.29] p = 0.84
Double mutant n=49	17 / 25	9 / 24	2.49 [1.10 – 5.66] p = 0.03
HR Double mutation vs. WT	2.76 [1.62 – 4.68] P = 0.0002	0.91 [0.46 – 1.80] P = 0.79	3.03 [1.29 – 7.15] P = 0.01

Predictive Value of *TP53* and *KRAS* *double* Mutations on Overall Survival



Interaction Treatment X type of Mutation (comparison of the treatment effect in the 4 groups): p=0.06

Prognostic Summary

- *KRAS* mutation in *EGFR* WT patients is not significantly prognostic in resected NSCLC

- *KRAS/TP53* mutations are not significantly prognostic in resected NSCLC

Predictive Summary

- *KRAS* mutation *overall* is *not* significantly predictive of survival benefit from adjuvant chemotherapy in *EGFR* WT AdenoCa resected NSCLC

- Patients with both *KRAS* and *TP53* mutations have a worse outcome when treated with adjuvant chemotherapy compared to those with WT/WT tumors

- Comparison of the effects of chemotherapy among the 4 groups defined by *KRAS* and *TP53* mutations was of borderline significance (p=0.06)

- *These results require validation in other data sets*

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