Oncogenic mutations of the EGFR pathway in lung adenocarcinoma

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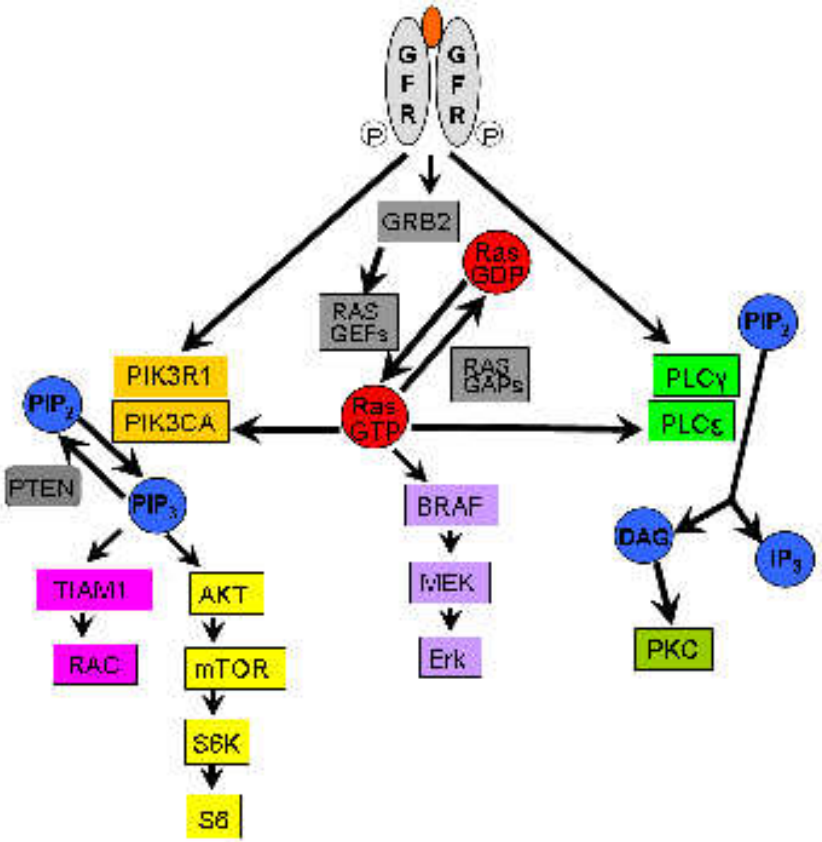
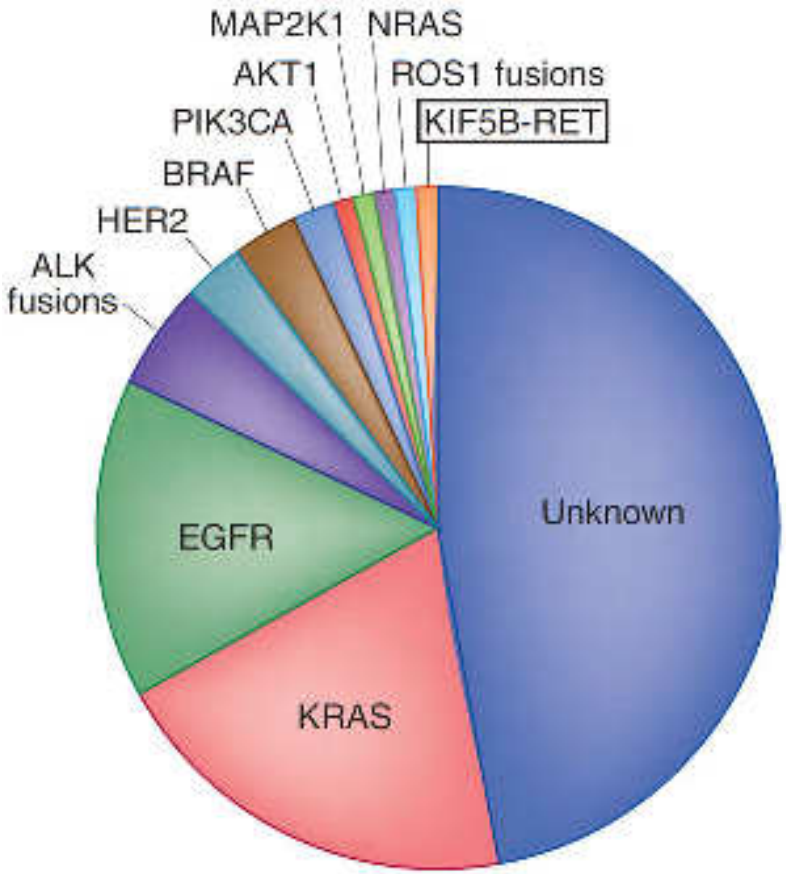
MEDICAL UNIVERSITY OF VIENNA

Growth factor receptor signaling





	EGFR	KRAS	BRAF	PI3KCA	NF1 (GAP)	PTEN
Lung adenocarcinoma	8-20%	20-30%	1-3%	3-8%	??	11%

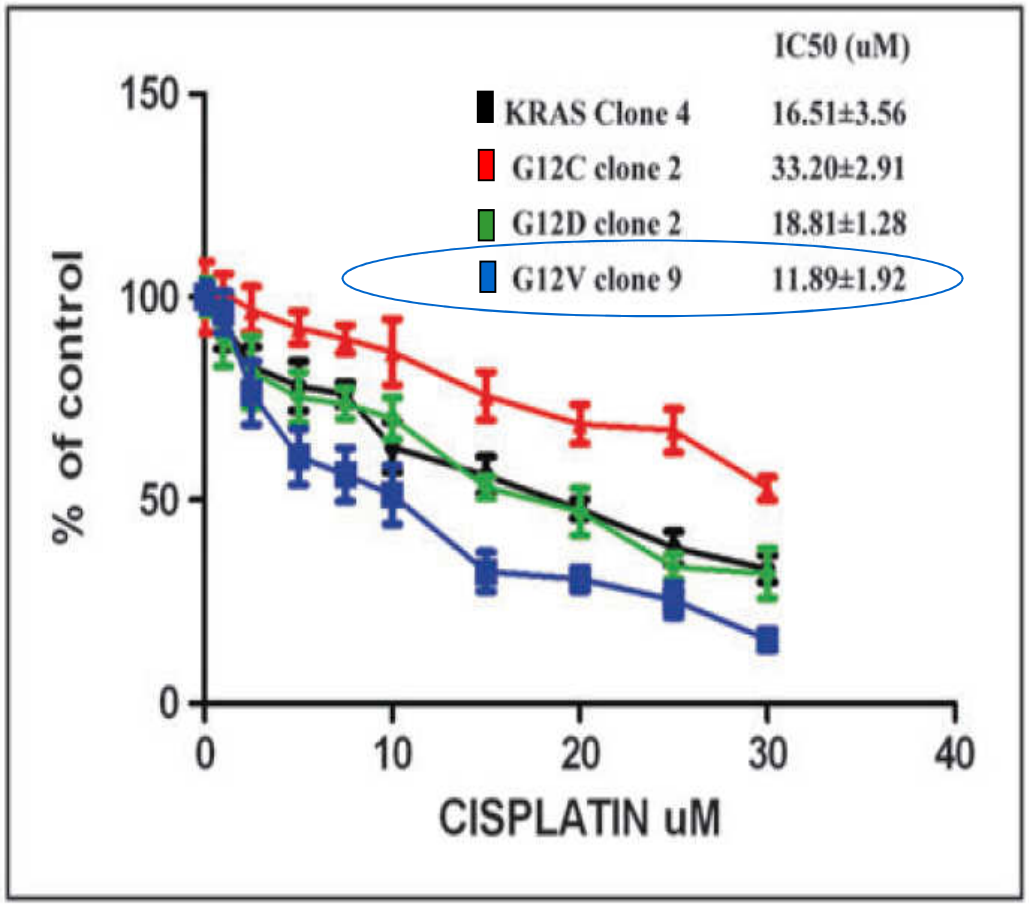
Response to Platinum-Based Chemotherapy and Subtype-Specific KRAS Mutations in Advanced Lung Adenocarcinoma

The most frequent oncogenic mutations of KRAS in lung adenocarcinoma

Nucleotide change	Amino acid change		Mutation
GGT>TGT	Glycin	Cystein	**G12C**
GGT>GTT	Glycin	Valin	**G12V**
GGT>GAT	Glycin	Aspartat	**G12D**
GGT>GCT	Glycin	Alanin	**G12A**
GGT>AGT	Glycin	Serin	**G12S**
GGT>CGT	Glycin	Arginin	**G12R**
GGC>GAC	Glycin	Aspartat	**G13D**

Dogan S, Shen R, Ang DC, Johnson ML, D'Angelo SP, Paik PK, Brzostowski EB,Riely GJ, Kris MG, Zakowski MF, Ladanyi M. Molecular epidemiology of EGFR andKRAS mutations in 3,026 lung adenocarcinomas: higher susceptibility of women tosmoking-related KRAS-mutant cancers. Clin Cancer Res. 2012 Nov 16;18(22):6169-77.

Biological effect of the amino acid change



Garassino MC, Marabese M, Rusconi P, Rulli E, Martelli O, Farina G, Scanni A, Broggini M. Different types of K-Ras mutations could affect drug sensitivity and tumour behaviour in non-small-cell lung cancer. Ann Oncol. 2011 Jan;22(1):235-7.

Patient population and enrollment criteria

- Single center study (National „Koranyi" Institute of Pulmonolgy and TB)
- 1125 patient with KRAS mutation analysis
- 01/01/2009 - 31/12/2012

- **505** patients met the requirements of inclusion criteria:
  - III-IV stage lung adenocarcinoma
  - ECOG: 0-1
  - platinum based chemotherapy

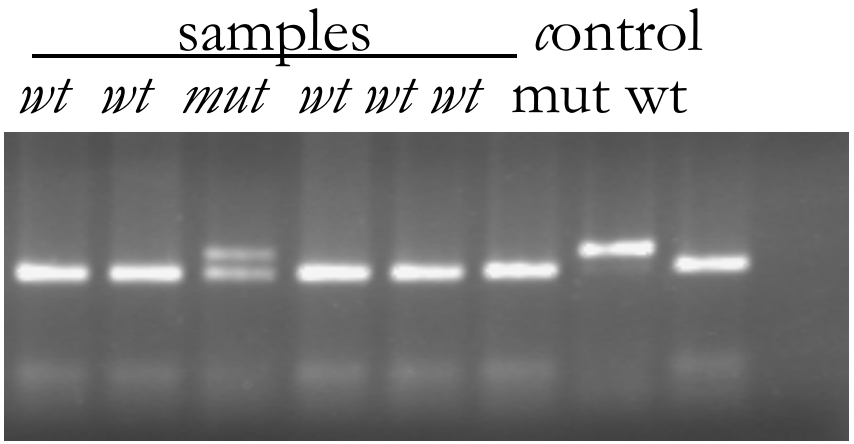
  (adjuvant chemo treatment was excluded)

Cserepes et al, European Journal of Cancer, 2014

KRAS mutation analysis

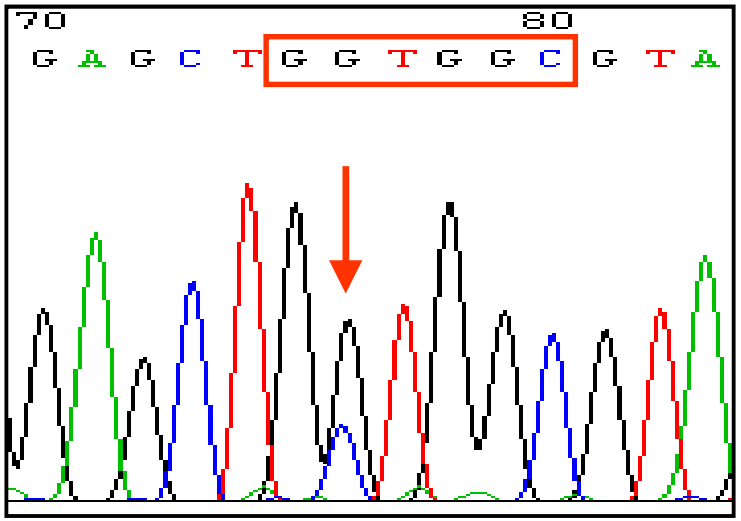
- **RFLP**

  Detection of wild-type and mutant alleles.



- **Direct sequencing**

  validation of the mutation and the accurate nucleotide change detection



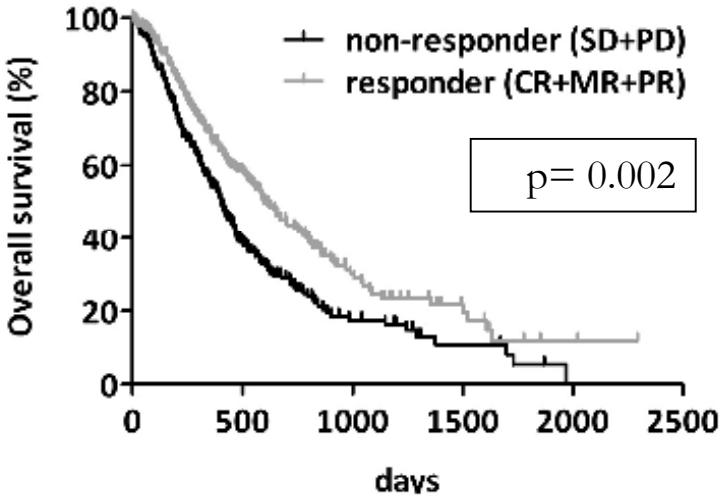
Prevalence of KRAS mutations

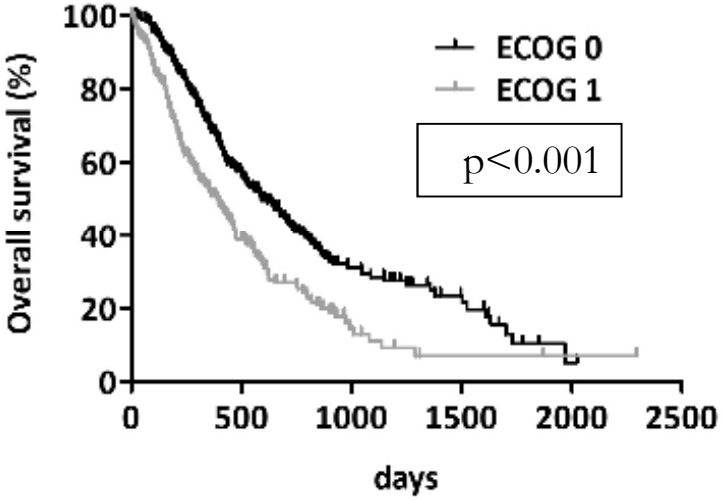
Entire patient population			
KRAS status	Number	%	Mutant %
Total	**1125**	100	-
Wild type	764	67.91	-
KRAS12 mut	335	29.78	92.8
KRAS13 mut	26	2.31	7.2

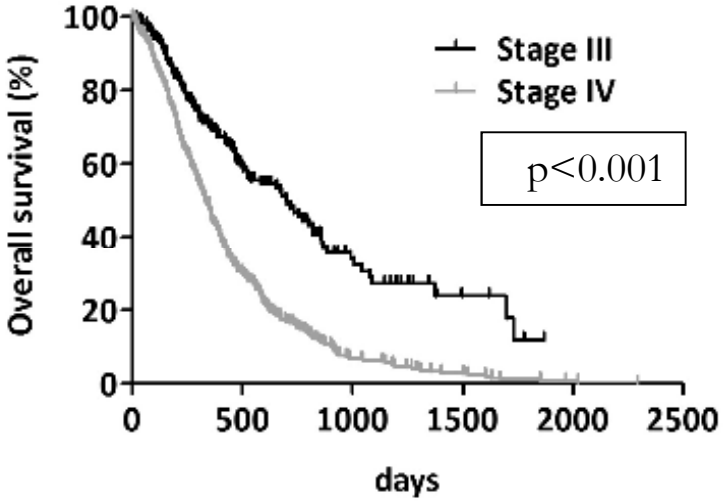
Patients with full clinical follow-up		
Number of patients		**505**
Wild type		**338**
Codon13 mutation		**20**
Codon12 mutation	all	**147**
	G12C	61
	G12V	29
	G12D	27
	G12A	8
	G12S	6
	G12R	3
	Not identified	11

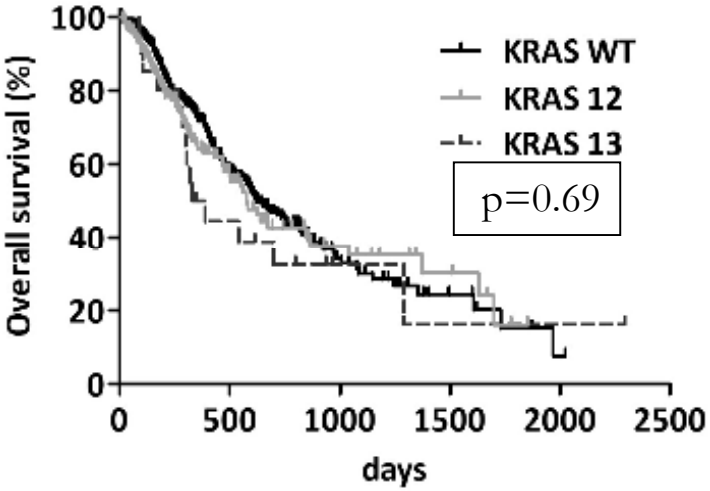
	COSMIC*	**Current cohort**
G12C	42%	38,61%
G12V	20%	18,35%
G12D	15%	17,09%
G12A	7%	5,06%

Prognostic / predictive factors

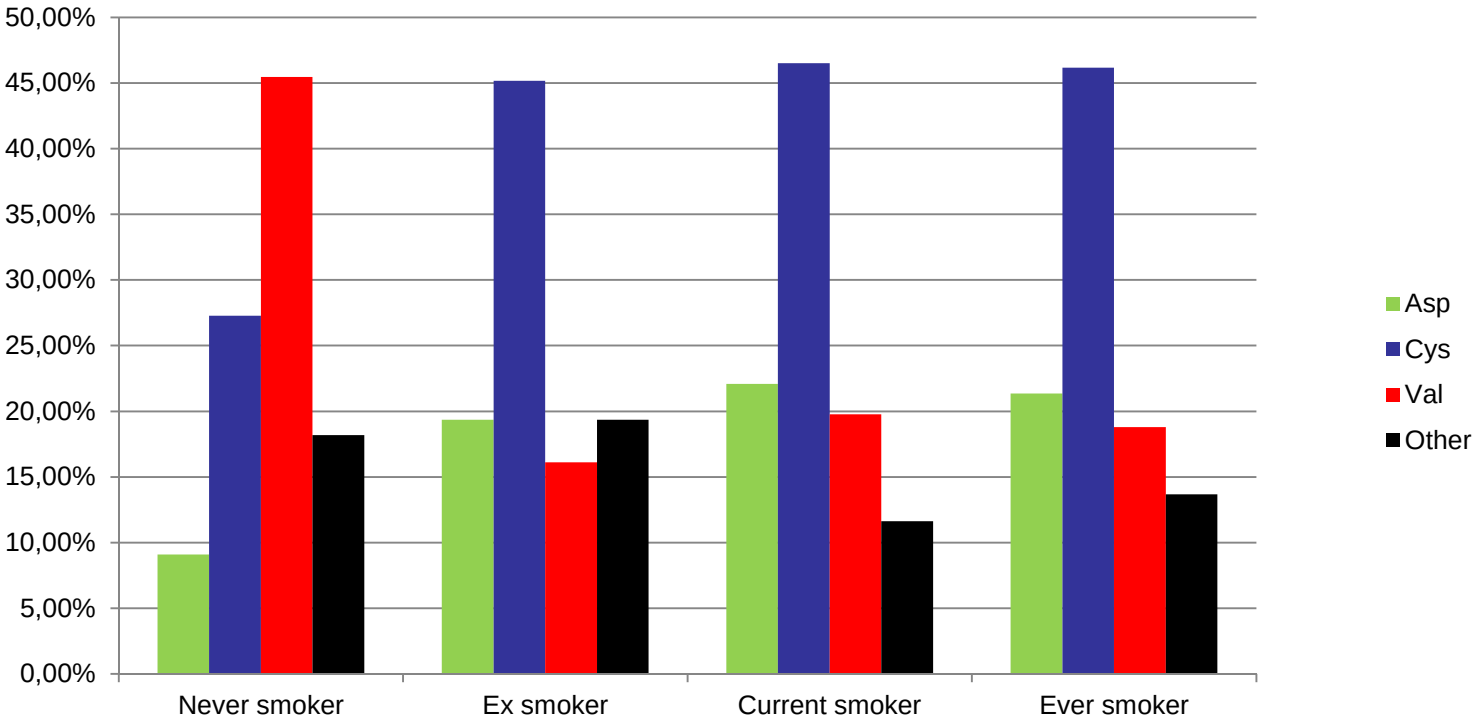




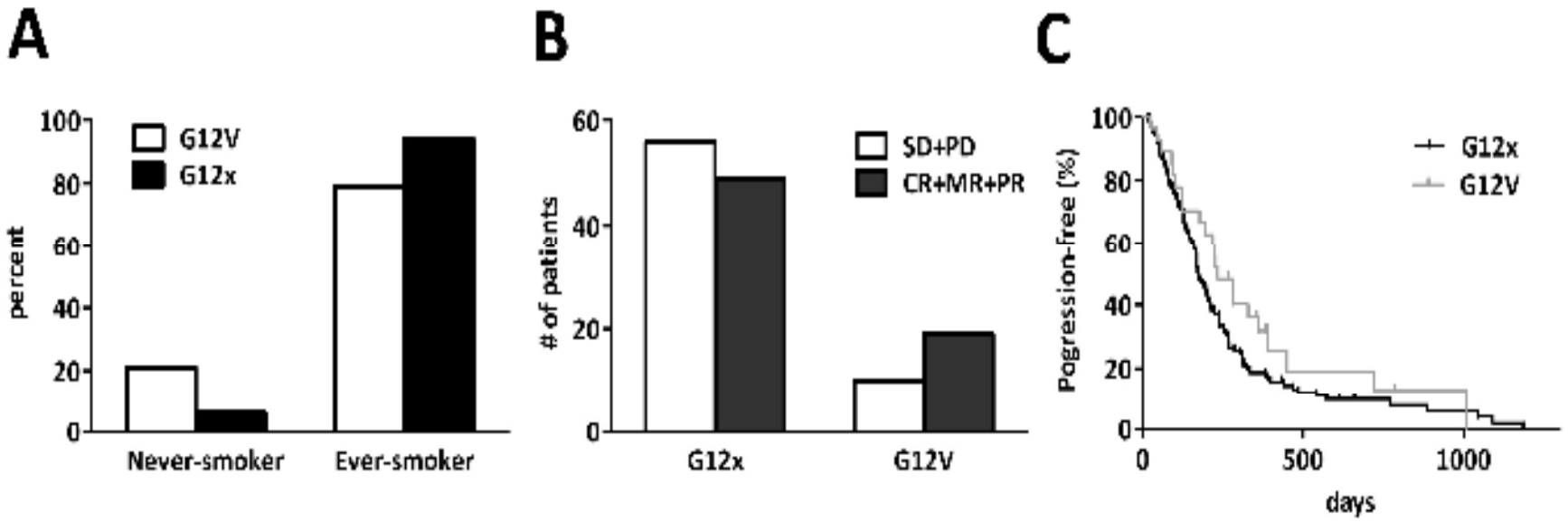




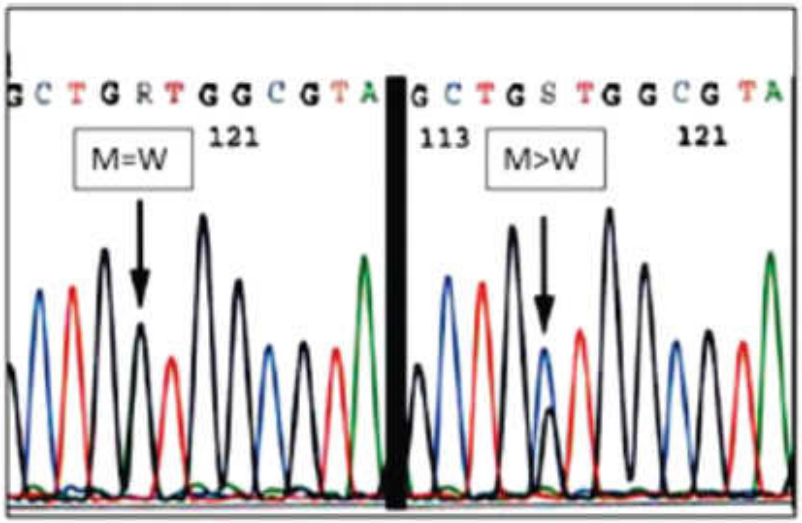
KRAS mutation subtype and smoking history

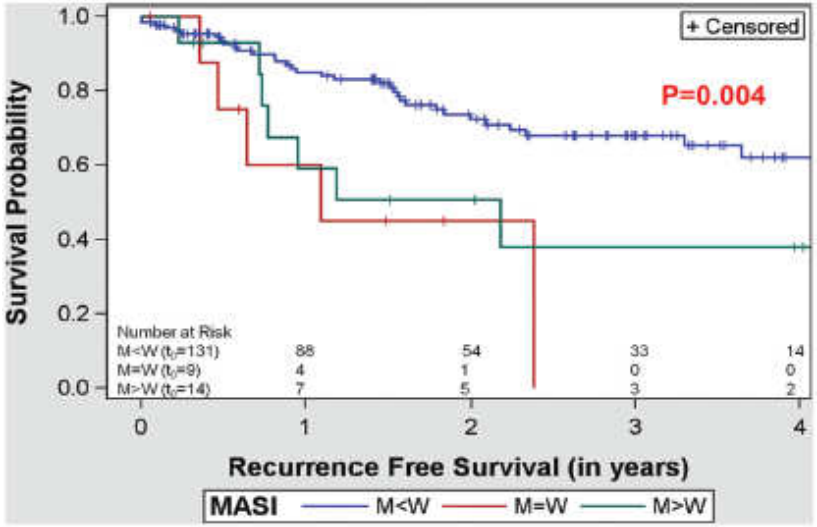


Comparison of G12V versus all other G12 KRAS mutant



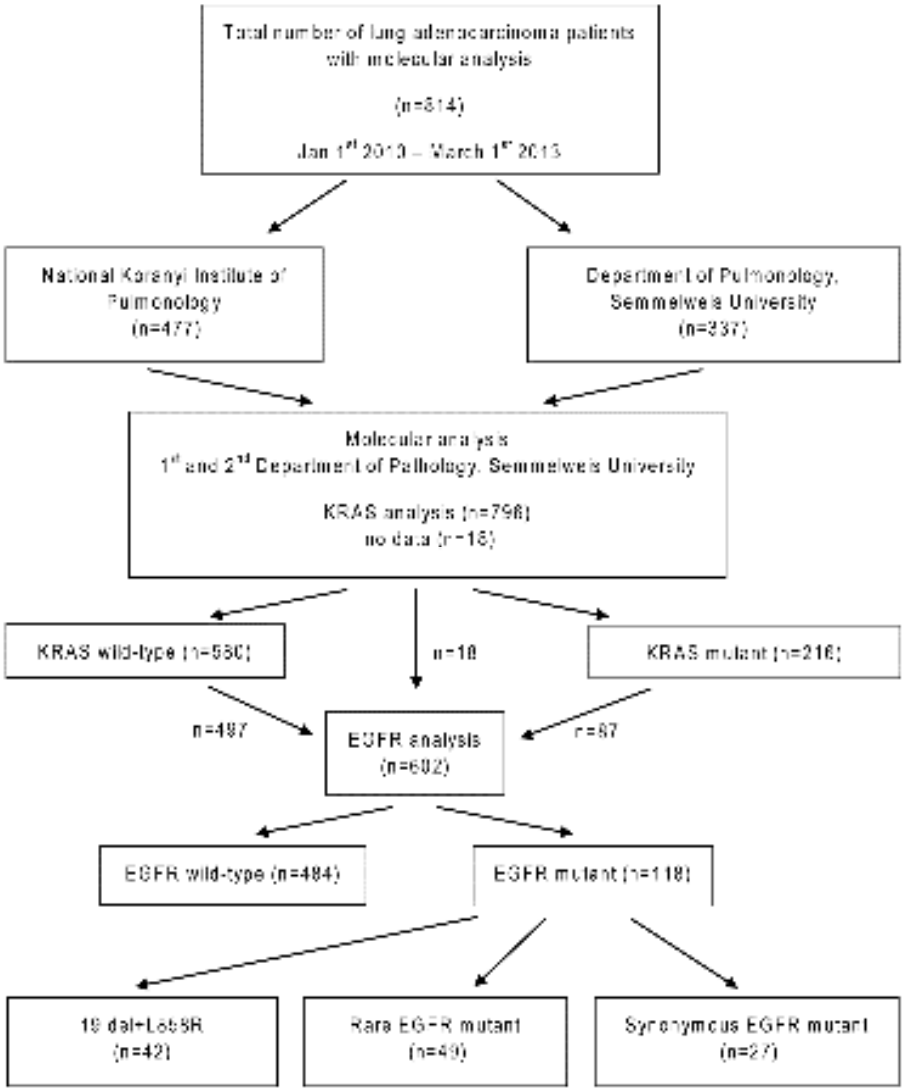
Perspective: mutant allele specific imbalance (MASI)





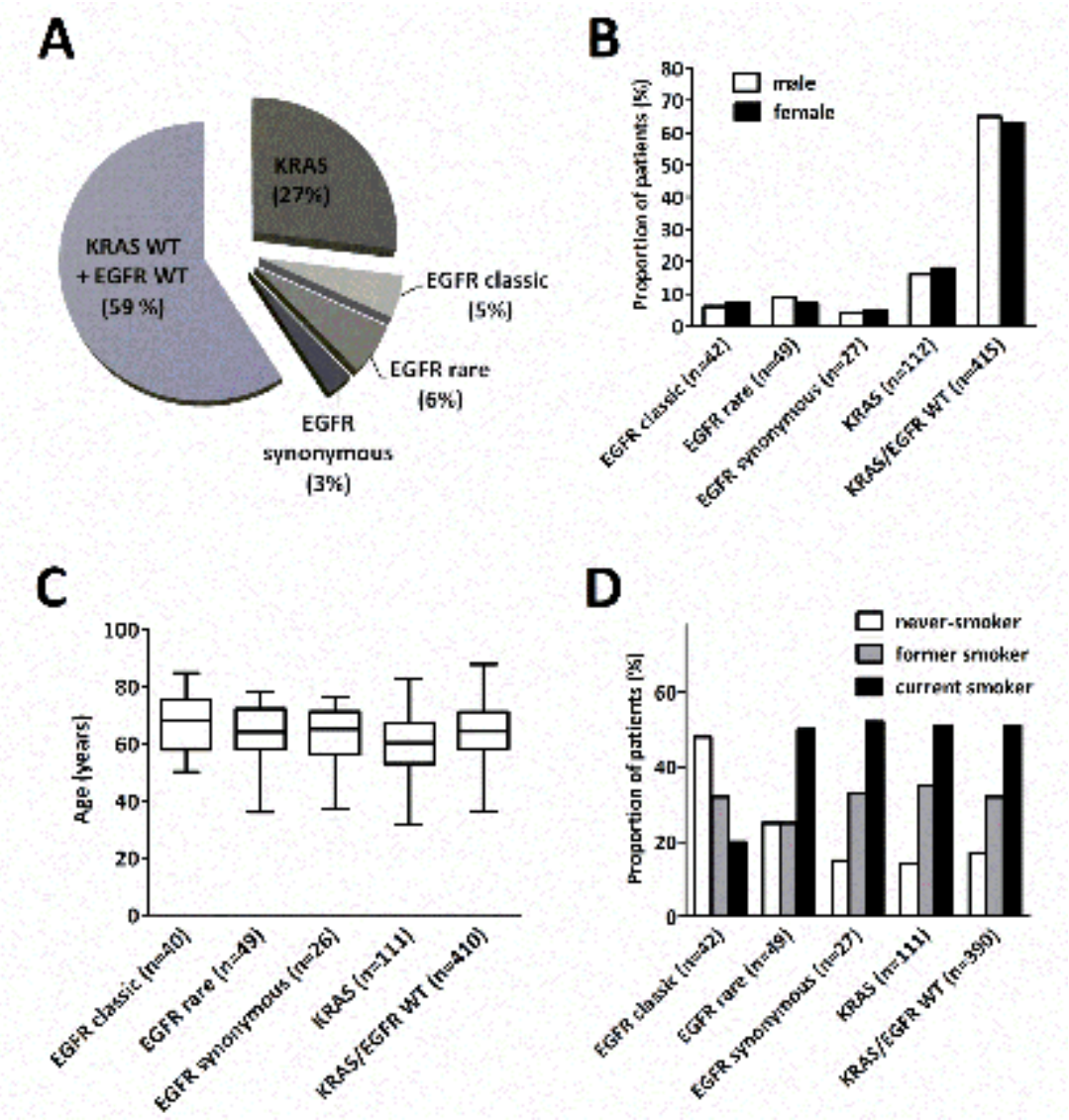
Villaruz LC, Socinski MA, Cunningham DE, Chiosea SI, Burns TF, Siegfried JM, Dacic S. The prognostic and predictive value of KRAS oncogene substitutions in lung adenocarcinoma. Cancer. 2013 Jun 15;119(12):2268-74. doi: 10.1002/cncr.28039. Epub 2013 Mar 22. PubMed PMID: 23526491

Epidemiology of rare EGFR mutations

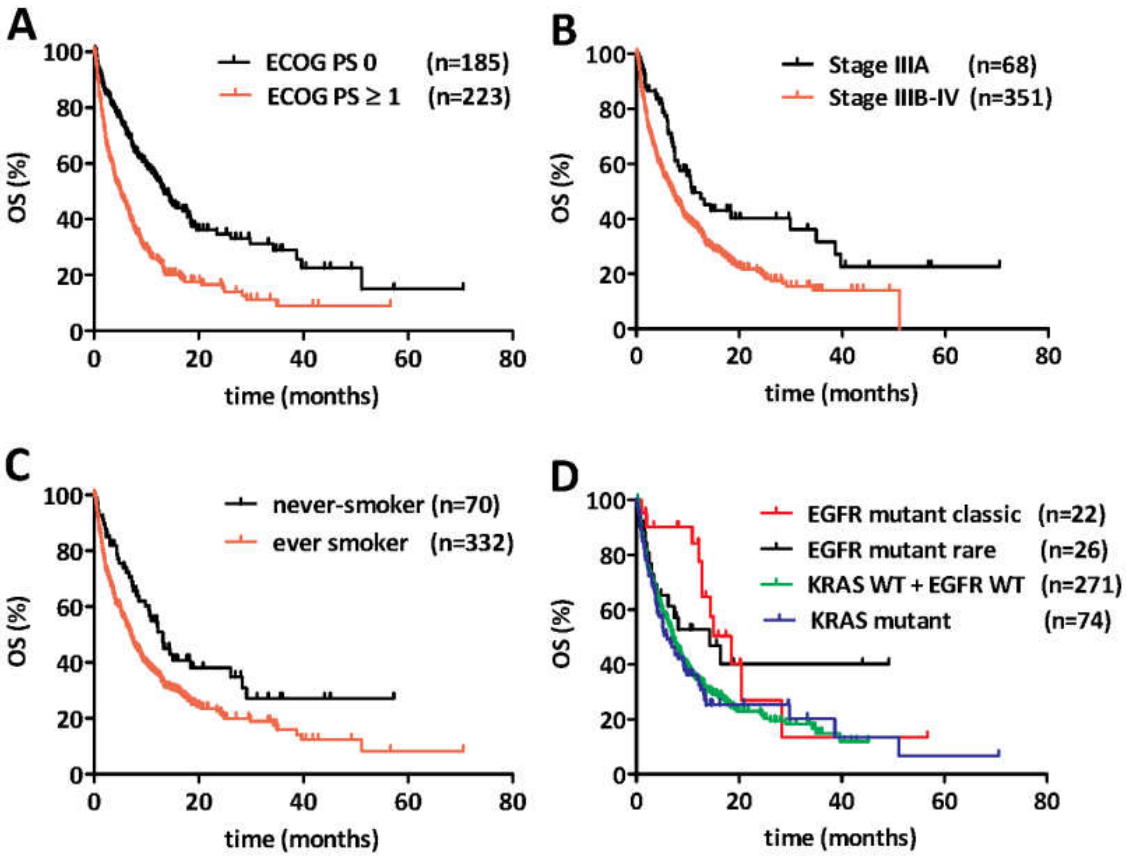


Lohinai et al, Journal of Thoracic Oncology, 2015

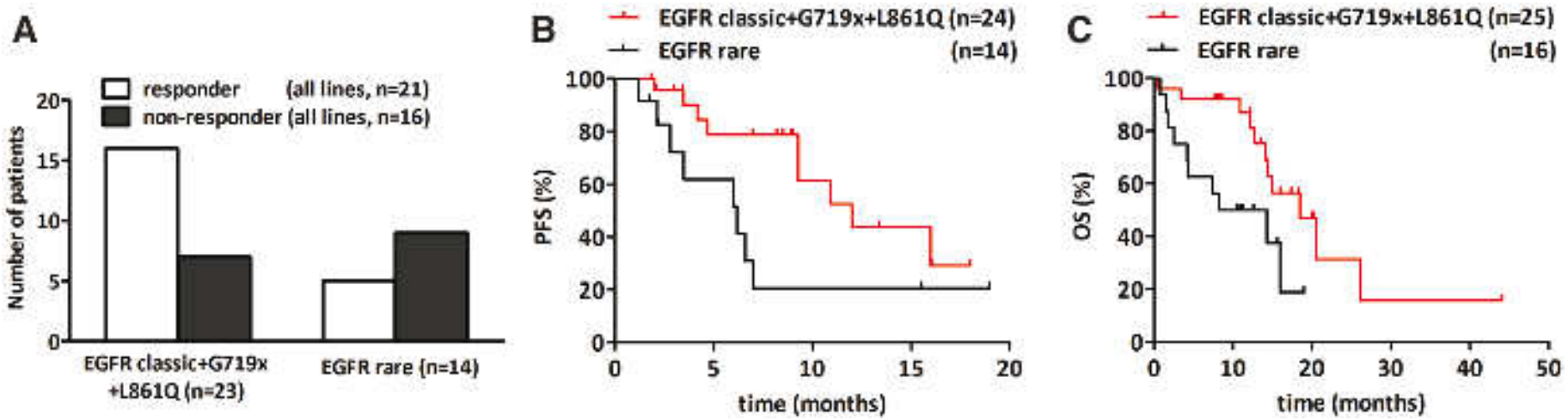
Epidemiology of rare EGFR mutations



Prognosticators in lung adenocarcinoma



EGFR TKI treatment



DIRECT database

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  - DIRECT
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  - Glossary
  - Cancer Resources
  - Videos
- Newsletter
- News & Press Releases
- MCG Publications and Abstracts
- Release Notes
- Articles of Interest
- Contributors
- Development Team
- Acknowledgments

DNA-mutation Inventory to Refine and Enhance Cancer Treatment (DIRECT)

What is DIRECT?

The Vanderbilt–Ingram Cancer Center Personalized Cancer Medicine Initiative (PCMI) team has established a database entitled DNA-mutation Inventory to Refine and Enhance Cancer Treatment (DIRECT) that contains information about the potential clinical significance of specific tumor mutations. DIRECT may enable a genetically informed approach to cancer medicine—in other words, cancer therapy tailored according to the genetic makeup of individual tumors.

Currently, DIRECT catalogues drug response data from patients with non-small cell lung cancer (NSCLC) whose tumors harbor mutations in:

- Epidermal growth factor receptor (EGFR)

How does DIRECT work?

To compile the information in DIRECT, the PCMI team used a retrospective PubMed medical subject heading (MeSH) search to identify patient-level, mutation-specific, drug response data from different studies in NSCLC (Horn et al. 2011; Yeh et al. 2013). As of January 1, 2013, more than 1,800 individual patient entries including patient demographics, tumor mutations, and drug response data have been extracted from 165 papers and catalogued in the DIRECT database. DIRECT currently has information on 188 different primary EGFR mutations and 4 secondary EGFR mutations (Yeh et al. 2013).

If you wish to query DIRECT for more information about a specific mutation of interest, please

Fill Out This Form.

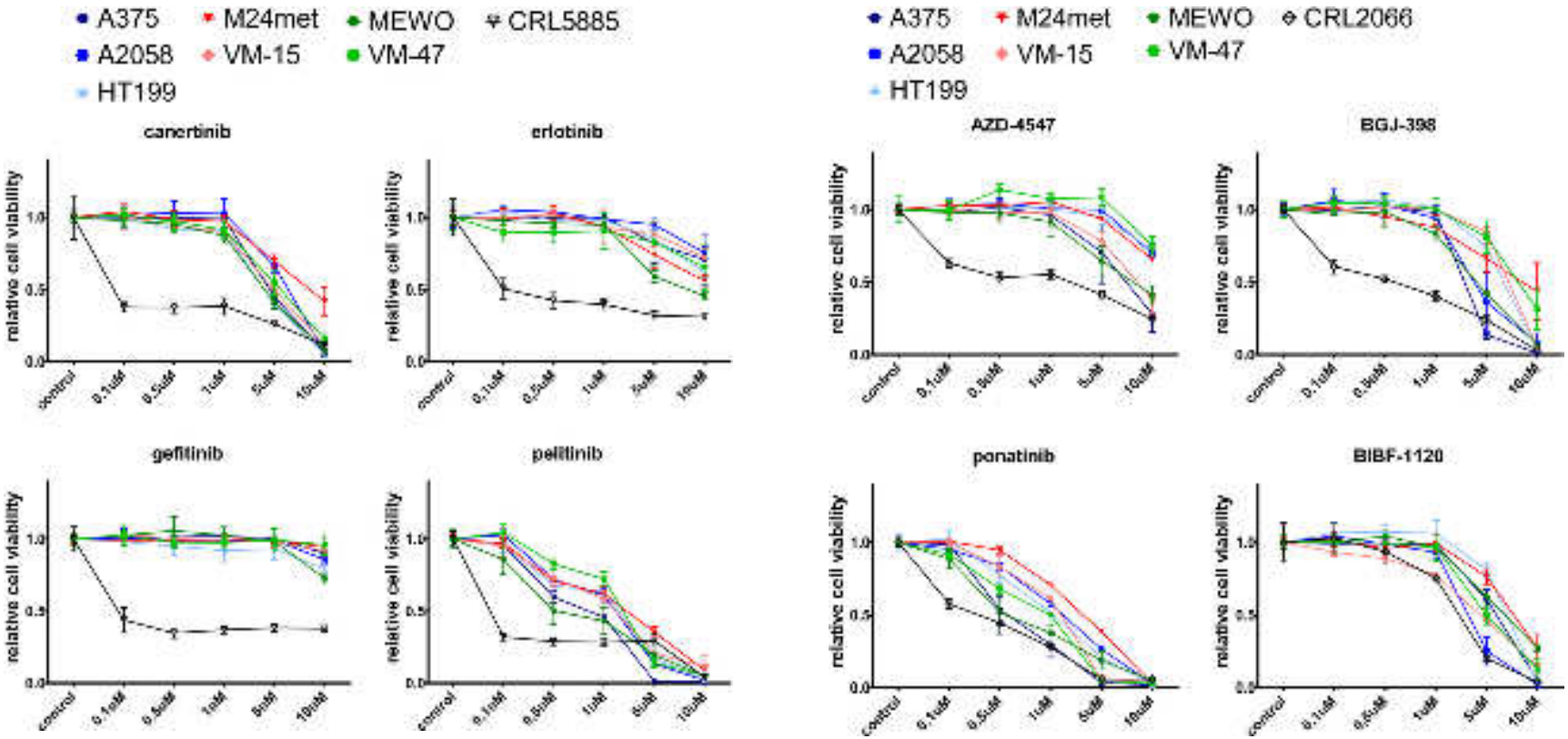
If the mutation is in DIRECT, we will provide you with a customized report detailing patient-level, mutation-specific drug response data.

Pathol. Oncol. Res.
DOI 10.1007/s12253-015-9916-9

RESEARCH

Sensitivity of Melanoma Cells to EGFR and FGFR Activation but Not Inhibition is Influenced by Oncogenic BRAF and NRAS Mutations

Tamás Garay · Eszter Molnár · Éva Juhász · Viktória László · Tamás Barbai · Judit Dobos · Karin Schelch · Christine Pirker · Michael Grusch · Walter Berger · József Tímár · Balázs Hegedűs



EGFR mutation, TKI treatment and immunotherapy

Original Study

Programmed Death-Ligand 1 Expression Predicts Tyrosine Kinase Inhibitor Response and Better Prognosis in a Cohort of Patients With Epidermal Growth Factor Receptor Mutation-Positive Lung Adenocarcinoma

Cheng Lin,[1] Xiong Chen,[1] Meifang Li,[2] Jingnan Lin,[1] Xingfeng Qi,[3] Wenting Yang,[3] Hairong Zhang,[4] Zhonglu Cai,[5] Yun Dai,[6] Xuenong Ouyang[1]

original articles

Annals of Oncology 25: 1935–1940, 2014
doi:10.1093/annonc/mdu242
Published online 9 July 2014

Association of PD-L1 overexpression with activating EGFR mutations in surgically resected nonsmall-cell lung cancer

K. Azuma[1], K. Ota[2], A. Kawahara[3], S. Hattori[4], E. Iwama[2], T. Harada[2], K. Matsumoto[2], K. Takayama[2], S. Takamori[5], M. Kage[3], T. Hoshino[1], Y. Nakanishi[2,6] & I. Okamoto[6*]

[1]Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Kurume; [2]Research Institute for Disease of the Chest, Graduate School of Medical Sciences, Kyushu University, Fukuoka; [3]Department of Diagnostic Pathology, Kurume University Hospital, Kurume; [4]Biostatistics Center, Kurume University, Kurume; [5]Department of Surgery, Kurume University School of Medicine, Kurume; [6]Center for Clinical and Translational Research, Kyushu University Hospital, Fukuoka, Japan

Biochemical and Biophysical Research Communications 463 (2015) 95–101

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journal homepage: www.elsevier.com/locate/ybbrc

EGFR-TKI down-regulates PD-L1 in EGFR mutant NSCLC through inhibiting NF-κB

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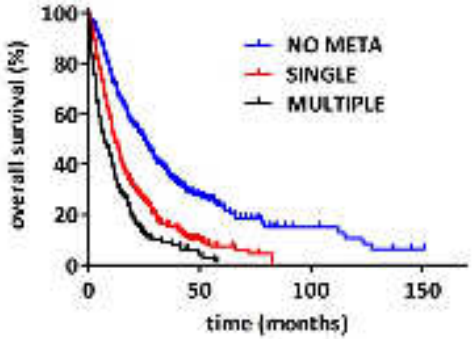
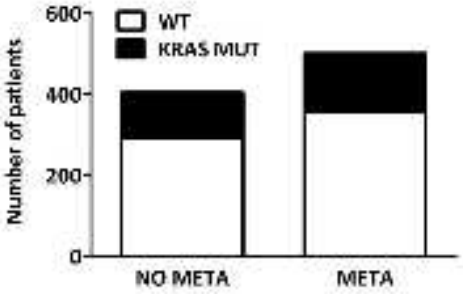
Institute of Cancer, Xinqiao Hospital, Third Military Medical University, Chongqing 400037, China

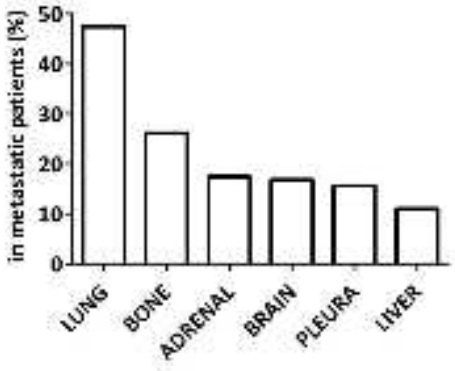
Metastatic site-specific variation of KRAS status in lung adenocarcinoma

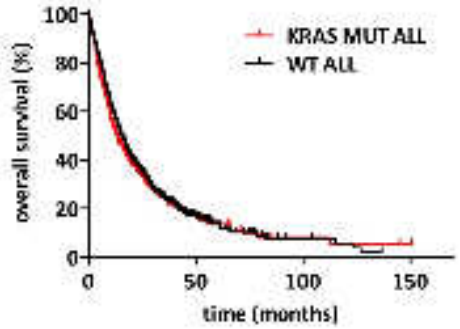
Metastatic site		Multiple	Single	Lung	Bone	Adrenal	Brain	Pleura	Liver	Non-metastatic
Total		138	362	228	131	87	84	78	55	403
Age (mean±SD)		60.8±8.7	62.4±9.3	62±9.0	60.7±10.2	61.1±9.6	59.2±9.3	64.5 ±10.5	62.2±9.9	61.8±8.9
Gender	**Male**	64 (46%)	181 (50%)	102 (45%)	74 (56%)	34 (39%)	36 (43%)	38 (49%)	26 (47%)	190(49%)
	Female	74 (54%)	181 (50%)	126 (55%)	57 (44%)	53 (61%)	48 (57%)	40 (51%)	29 (53%)	213 (51%)
ECOG	**0-1**	124 (92%)	335 (94%)	218 (97%)	115 (91%)	75 (87%)	77 (93%)	71 (91%)	48 (91%)	382 (96%)
performance status	**>1**	11 (8%)	21 (6%)	7 (3%)	11 (9%)	11 (13%)	6 (7%)	7 (9%)	5 (9%)	15 (4%)
	Unknown data	3	6	3	5	1	1	0	2	6
Smoking status	**Never-smoker**	15 (12%)	52 (16%)	29 (14%)	18 (16%)	7 (9%)	7 (9%)	20 (27%)	4 (8%)	66 (17%)
	Former smoker	37 (30%)	104 (31%)	61 (29%)	32 (28%)	20 (25%)	25 (32%)	23 (32%)	20 (41%)	115 (30%)
	Current smoker	71 (58%)	179 (53%)	117 (57%)	65 (58%)	52 (66%)	45 (58%)	30 (41%)	25 (51%)	203 (53%)
	Unknown data	15	27	21	16	8	7	5	6	19
KRAS	**Wild-type**	94 (68%)	263 (73%)	148 (65%)	94 (72%)	58 (67%)	60 (71%)	65 (83%)	46 (84%)	290 (72%)
	Mutant	44 (32%)	99 (27%)	80 (35%)	37 (28%)	29 (33%)	24 (29%)	13 (17%)	9 (16%)	113 (28%)

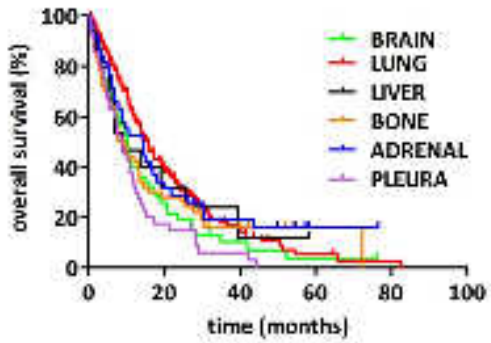
KRAS status in metastatic lung adenocarcinoma

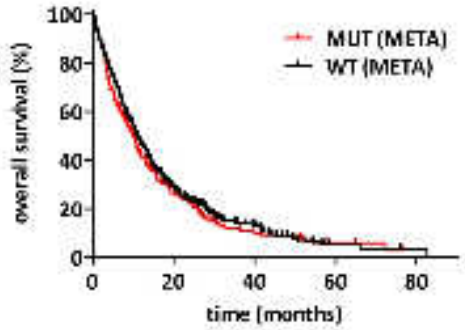




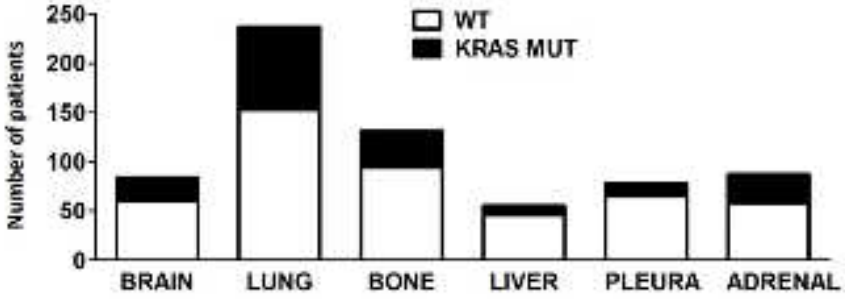


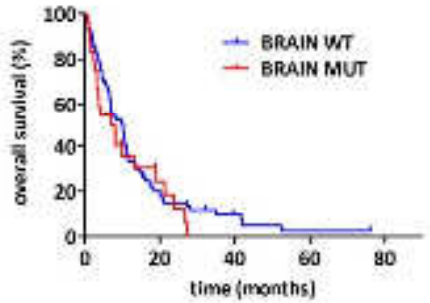


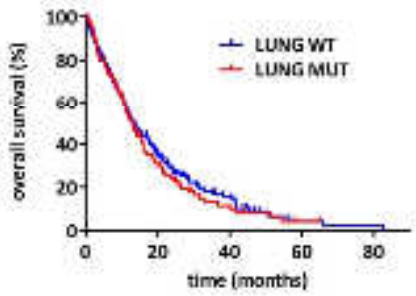


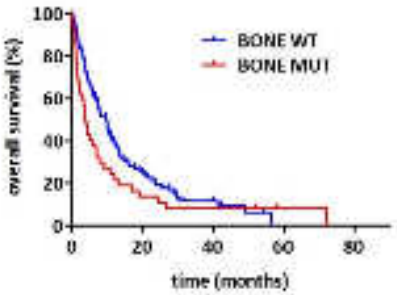


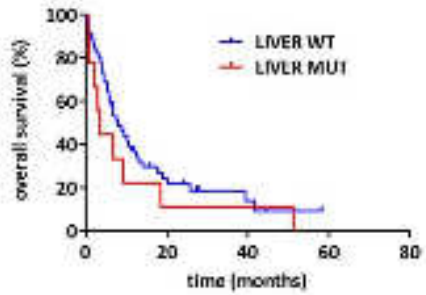
Metastatic site-specific variation of KRAS status in lung adenocarcinoma











Repurposing bisphosphonates

PNAS

Repurposing of bisphosphonates for the prevention and therapy of nonsmall cell lung and breast cancer

Agnes Stachnik[a,1], Tony Yuen[a,1], Jameel Iqbal[a], Miriam Sgobba[b], Yogesh Gupta[a], Ping Lu[a], Graziana Colaianni[a,c], Yaoting Ji[a,d], Ling-Ling Zhu[a,d], Se-Min Kim[a], Jianhua Li[a], Peng Liu[a], Sudeh Izadmehr[a], Jaya Sangodkar[a], Thomas Scherer[a], Shiraz Mujtaba[a], Matthew Galsky[a], Jorge Gomez[a], Solomon Epstein[a], Christoph Buettner[a], Zhuan Bian[d], Alberta Zallone[c], Aneel K. Aggarwal[a], Shozeb Haider[b], Maria I. New[a,2], Li Sun[a,3], Goutham Narla[a,e,3], and Mone Zaidi[a,2,3]

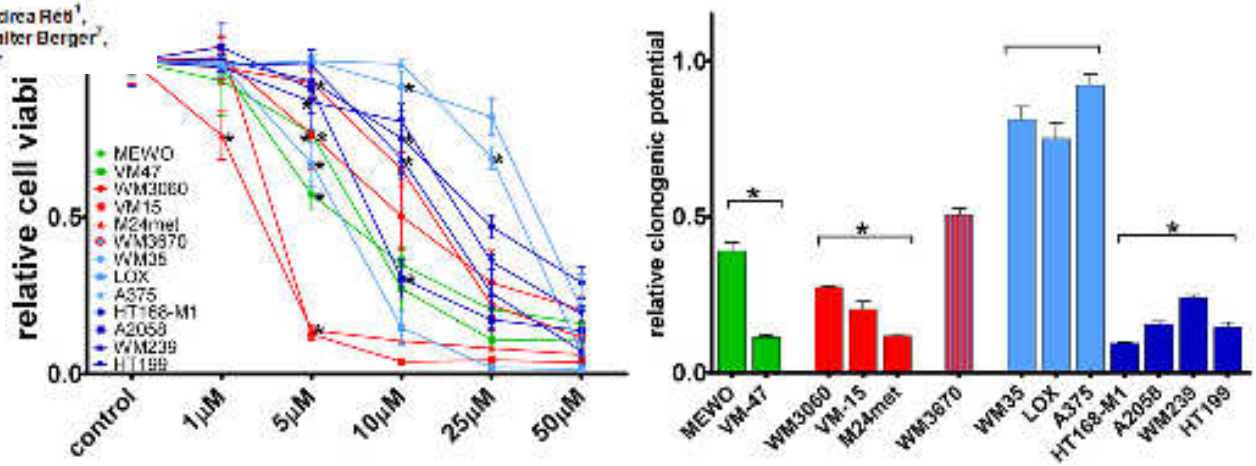
[a]Departments of Medicine, Pediatrics, and Chemical and Structural Biology, and the Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029; [b]Department of Pharmaceutical and Biological Chemistry, School of Pharmacy, University College, London WC1N 1AX, United Kingdom; [c]Department of Histology, University of Bari, Bari 70121, Italy; [d]Department of Research, School of Stomatology, Wuhan University, Wuhan 430079, China; and [e]Department of Medicine and Institute for Transformative Molecular Medicine, Case Western Reserve University, Cleveland, OH 44106

Contributed by Maria I. New, November 11, 2014 (sent for review October 2, 2014; reviewed by Wafik El-Deiry and H. Michael Shepard)

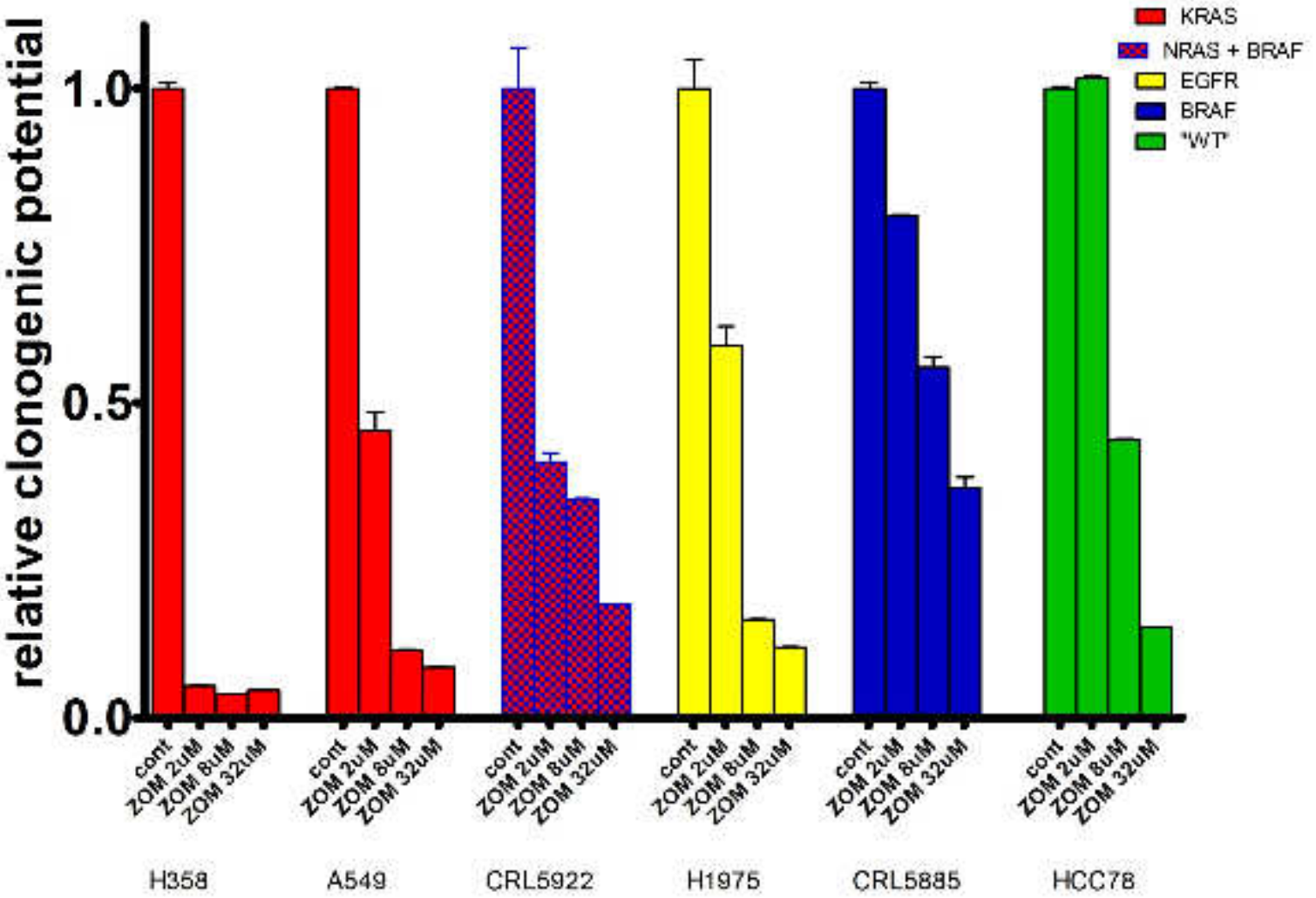
RESEARCH ARTICLE

Prenylation Inhibition-Induced Cell Death in Melanoma: Reduced Sensitivity in BRAF Mutant/PTEN Wild-Type Melanoma Cells

Tamás Garay[1,2,4], István Kenessey[1], Eszter Molnár[1], Éva Juhász[1], Andrea Reti[1], Viktoria László[1], Anita Rozsás[3,4], Judit Dobos[2,4], Balázs Dome[3,4,5], Walter Berger[7], Walter Klepetko[8], József Tóvári[6], József Tímár[1,4], Balázs Hegedüs[3,4]*



KRAS mutation and bisphosphonate treatment sensitivity



Garay, Lohinai et al, unpublished data

Personalised (precision) medicine in lung adenocarcinoma

- Subtypes of molecular alterations, especially of so-called ‘driver mutations’, must be used as markers that determine the selection of patients who most likely can benefit from therapy.

- The clinical consequence of molecular alterations are context (e.g. metastatic site) dependent.

- The translation of our knowledge about molecular mechanisms and signaling networks to predict therapeutic consequences is a very delicate task and requires thorough preclinical and clinical investigations.

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Anita Rozsas
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