

Are there new targets in advanced NSCLC?

Update on the French genetic centers

Fabrice BARLESI

Aix Marseille University

Assistance Publique Hôpitaux de Marseille

Marseille, France



15-18 April 2015, Geneva, Switzerland

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Disclosure slide

- Astra-Zeneca, Boehringer–Ingelheim, Daichii Saiko, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Glaxo-Smithkline, Novartis, Pfizer et Pierre Fabre



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Background

- **Lung Cancer in France**



- **39,495** new cases (4th)
- **29,949** deaths (1st)



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Les cancers en France en 2013, INCa 2014

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Background

- **2004:** Discovery of oncogene addictions

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

MAY 20, 2004

VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D.,
Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A.,
Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D.,
Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.



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Background

- **2006:** Genetic centers' network launched by the French NCI
 - Routine
 - Clinical trials
 - #9M€ investment



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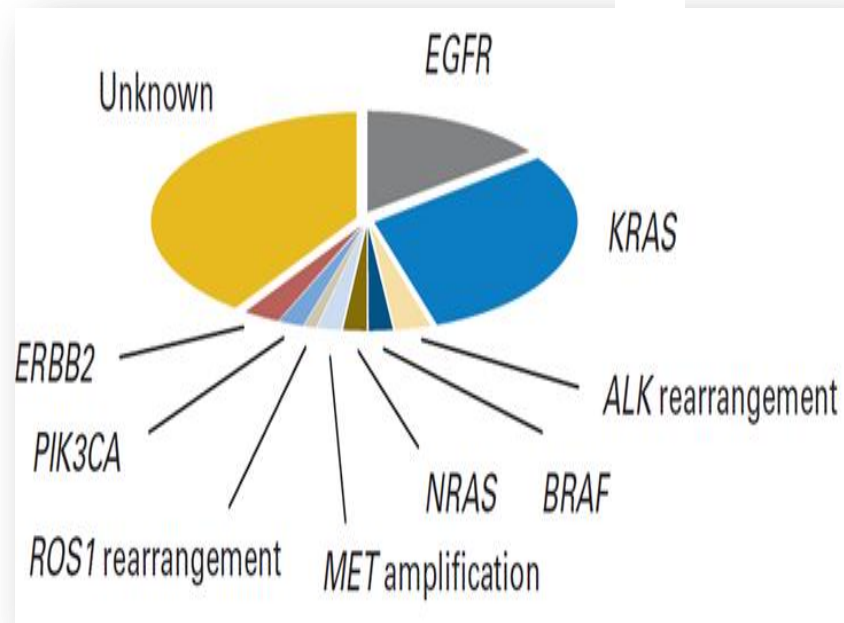


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Background

- **2011:** Assessment of emerging biomarkers
 - Clinical trials
 - Anticipate new biomarkers



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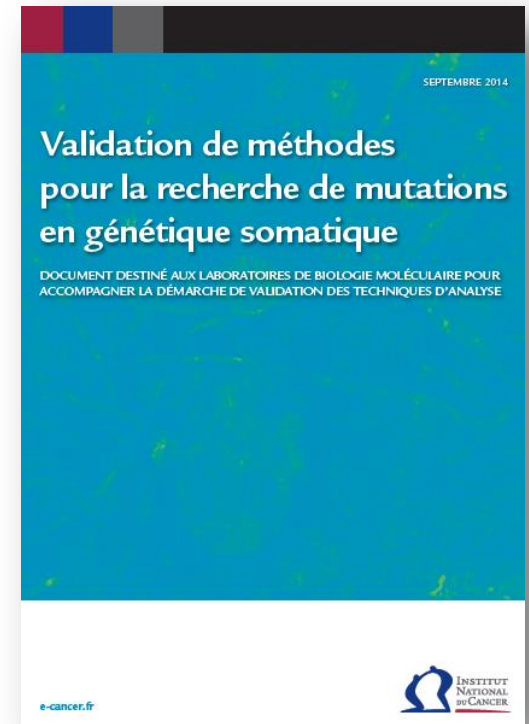
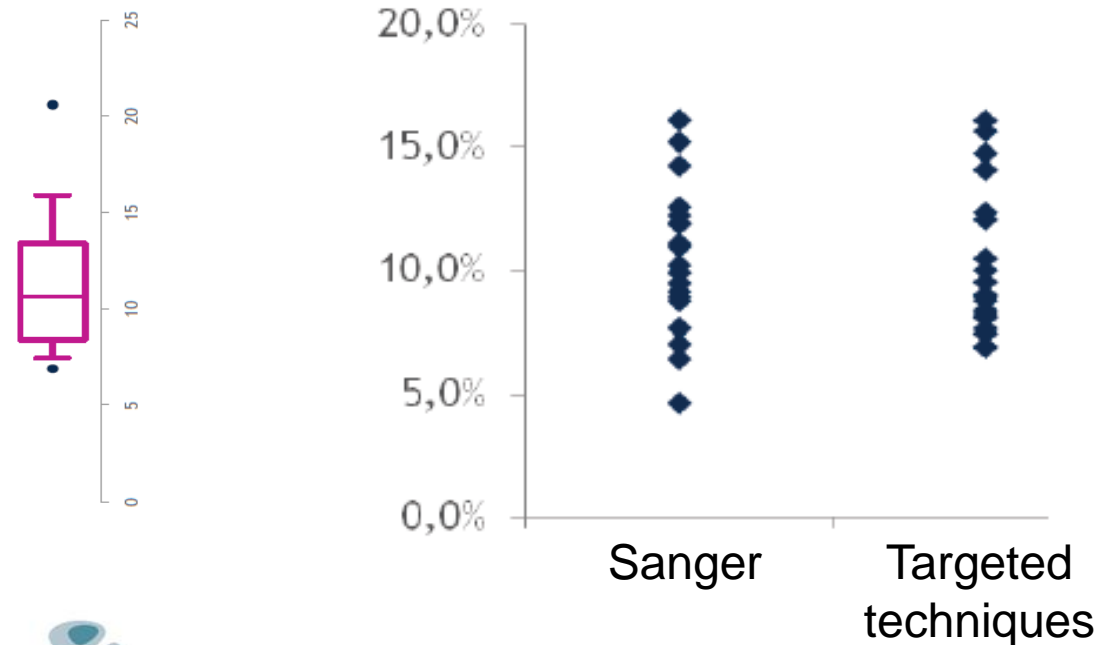
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Janne P et al, JCO 2012

Background

- Quality control (internal)



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Background

• Quality control (external)

ORIGINAL ARTICLE

Cross-Validation Study for Epidermal Growth Factor Receptor and KRAS Mutation Detection in 74 Blinded Non-small Cell Lung Carcinoma Samples

A Total of 5550 Exons Sequenced by 15 Molecular French Laboratories (Evaluation of the EGFR Mutation Status for the Administration of EGFR-TKIs in Non-Small Cell Lung Carcinoma [ERMETIC] Project—Part 1)

Michèle Beau-Faller, MD, PhD,^{1,††} Armelle Degeorges, PhD,[§] Estelle Rolland, MSc,^{||} Mounia Mounawar, PhD,[‡] Martine Antoine, MD,^{‡,¶} Virginie Poullet, LabTec,^{¶¶} Audrey Mauguen, MSc,^{||} Véronique Barbu, MD, PhD,^{††} Florence Coulet, PharmD, PhD,^{††} Jean-Luc Prêtre, PhD,^{§§} Ivan Bièche, PharmD, PhD,^{||} Hélène Blons, PharmD, PhD,^{¶¶} Jean-Christophe Boyer, PharmD, PhD,^{¶¶} Marie-Pierre Buisson, PharmD, PhD,^{***} Florence de Fraipont, PharmD, PhD,^{†††} Sarah Léard, PhD,^{†††} Sylviane Olschwang, MD, PhD,^{§§§} Patrick Saulnier, PhD,^{|||} Delphine Pronier-Mercœur, MD, PhD,^{¶¶¶} Nicolas Richard, PharmD, MSc,^{¶¶¶} Claire Danet, MD,^{†,***} Elisabeth Brambilla, MD, PhD,^{†††††} Christos Chouaid, MD, PhD,^{†,††††} Gérard Zalcman, MD, PhD,^{†,§§§§§} Pierre Hainaut, PhD,[¶] Stefan Michiels, PhD,^{||} and Jacques Cadranel, MD, PhD,^{¶¶||}

Introduction: The Evaluation of the epidermal growth factor receptor (EGFR) mutation status for the administration of EGFR-tyrosine kinase inhibitors in non-small cell lung carcinoma (NSCLC) (ERMETIC) project part 1 assessed the accuracy of

EGFR and KRAS mutations detection in NSCLC among 15 French centers.

Methods: The 15 ERMETIC centers selected 74 NSCLC surgical specimens from previously untreated patients. Paraffin and paired frozen DNA were sequenced for EGFR exons 18 to 21 and KRAS exon 2 by an external molecular laboratory, yielding a gold standard. The 74 blinded paraffin DNAs were redistributed to the 15 ERMETIC laboratories for sequencing of a total of 5550 exons. Results were compared with the gold standard and between centers by discordance rates and kappa statistics.

Results: The gold standard included 39 mutated samples with 22 EGFR and 17 KRAS mutated samples. Kappa statistics showed that 10, 6, and 6 of the 15 ERMETIC centers had a moderate to good kappa score, when compared with external laboratory for EGFR exon 19, EGFR exon 21, and KRAS exon 2, respectively. Kappa statistics showed moderate score between centers which increased to good for EGFR exon 19 mutation when removing 16 poor-quality samples with high nonamplifiable rates.

Conclusions: Paraffin-embedded specimens may represent a suitable source of DNA for sequencing analyses in ERMETIC centers. EGFR exon 19 deletions were most accurately detected by ERMETIC centers. Ease and accuracy of results, depended more on the quality of sample than on the difference in molecular sequencing procedures between centers, emphasize the need of primary-level quality control programs.

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Journal of Thoracic Oncology • Volume 6, Number 6, June 2011

The Journal of Molecular Diagnostics, Vol. 16, No. 1, January 2014



the Journal of
Molecular
Diagnostics
jmd.elsevier.org

A Multicenter Blinded Study Evaluating EGFR and KRAS Mutation Testing Methods in the Clinical Non-Small Cell Lung Cancer Setting—IFCT/ERMETIC2 Project Part 1

Comparison of Testing Methods in 20 French Molecular Genetic National Cancer Institute Platforms

Michèle Beau-Faller,^{1,§} Hélène Blons,² Caroline Domerg,³ Dorota Gajda,⁴ Nicolas Richard,⁵ Fabienne Escande,⁶ Jérôme Solassol,⁷ Marc G. Denis,⁸ Anne Cayre,⁹ Isabelle Nanni-Metellus,¹⁰ Sylviane Olschwang,¹¹ Sarah Lizard,¹² Fabienne Pard,¹³ Jean-Luc Prêtre,¹⁴ Florence de Fraipont,¹⁵ Ivan Bièche,¹⁶ Patricia de Cremona,¹⁷ Isabelle Rouquette,¹⁸ Pierre-Faël Bringuier,¹⁹ Jean-Marc,²⁰ Michèle Legrain,²¹ Anne-Elise Voegelé,²² Patrick Saulnier,²³ Francis Morin,²⁴ Jean-Pierre Pignon,²⁵ Gérard Zalcman,²⁶ and Jacques Cadranel²⁴

From the Department of Molecular Biology,¹ Strasbourg University Hospital, EA 3483, Strasbourg University, Strasbourg; the Francophone Interagency of Thoracic Oncology,² Paris; the Department of Molecular Biology,³ Georges Pompidou European Hospital, AP-HP, Paris; Université Paris Descartes, Paris; the Department of Biostatistics and Epidemiology,⁴ Institut Gustave Roussy, Villejuif; the Department of Genetics,⁵ Laboratory of Medical Genetics, CHU de Caen, Caen; the Oncology and Molecular Genetics Laboratory,⁶ Division of Biochemistry and Molecular Biology, Center for Disease Biology, CHU de Lille, Lille Cedex; the Molecular Biology Laboratory,⁷ CHU de Montpellier, Montpellier; the Biochemistry Laboratory,⁸ CHU de Nantes, Nantes; the Molecular Biology Laboratory,⁹ CHU de Clermont-Ferrand, Clermont-Ferrand; the Laboratory of Oncology and Biological Transfer,¹⁰ CHU de Marseille, Marseille; Medical Genetics and Functional Genomics,¹¹ INSERM UMR 5015, Marseille; the Molecular Biology Unit,¹² Centre GIP Leclerc, Dijon; the Molecular Biology Laboratory,¹³ CHU de Dijon, Dijon; the Unit Francophone Centre,¹⁴ EA 3151, FRED2M, and CHU Rouen, Rouen; the UM Biochemistry and Cancer Biophysics,¹⁵ Division of Biology, CHU Grenoble, Grenoble Cedex 09; the Oncogenetics Laboratory,¹⁶ Plateforme HUGEGEN, Institut Curie-Hopital René Huguier, Saint-Cloud; the Pharmacology Unit,¹⁷ Department of Tumor Biology, Institut Curie, Paris; the Unit of Lung Molecular Pathology for the Hospital/Epidemiology of Cancer Molecular Genetics and Pathology,¹⁸ Pathological Anatomy Service, CHU Toulouse Rangueil, Toulouse; the Department of Anatomy and Pathological Cytology,¹⁹ Hôpital Cochin de Lyon, Hôpital Edouard Belin, Lyon; the Laboratory of Sarcoma Genetic Genomics,²⁰ CHU de Rennes, Rennes; the Molecular Biology Laboratory,²¹ Hôpital de Beaupré, Strasbourg; the Translational Research Laboratory,²² Institut Gustave Roussy, Villejuif Cedex; UMR 106 INSERM and the Department of Pneumology and Thoracic Oncology,²³ Caen University Hospital, Caen; and the Pneumology Service,²⁴ Assistance Publique Hôpitaux de Paris, Hôpital Tenon, GRC-04 Thorax, Université Paris VI, Paris Cedex 20, France.

Accepted for publication July 30, 2013.

Address correspondence to: Michèle Beau-Faller, MD, PhD, Department of Molecular Biology, Strasbourg University Hospital, 1 avenue Moltke, F-67088 Strasbourg. E-mail: michele.beau-faller@unistra.fr.

Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors have limited use as first-line treatment for mutated EGFR metastatic non-small cell lung cancer. The French National Cancer Institute has installed molecular genetics platforms implementing EGFR and KRAS testing. However, there is considerable uncertainty as to which detection methods should be applied for routine diagnosis. This study aimed to compare the EGFR and KRAS genotyping methods developed by the IFCT/ERMETIC2 network platforms in two blind panels: 25 samples of serial dilutions of cell line DNA (20 centers) and 74 FFPE lung tumor samples (10 centers). The best threshold of mutation detection on cell lines was obtained using allele-specific amplification-based technologies. Nonamplifiable tissue samples were significantly less common when using alternative testing versus direct sequencing (15%; 95% confidence interval [CI], 14%-16% versus 40%; 95% CI, 39%-42%; $P < 0.001$). Mutated cases increased from 42% (95% CI, 31%-54%) to 53% (95% CI, 41%-64%), with three supplementary EGFR mutations (p.L858R at exon 18 and p.L858R and p.L858R at exon 21) and five supplementary KRAS mutations, when using alternative testing instead of direct sequencing. False-positive results were observed when using a PCR-based testing assay, high-resolution melting, or pyrosequencing. Concordance analysis returned good kappa test scores for EGFR exon 19 and KRAS analysis when comparing sequencing with alternative methods and revealed no

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Beau-Faller et al,
J Thorac Oncol 2011;
Beau-Faller et al,
J Mol Diagn 2014

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Updated results

- Daily practice – All Cancers (2013)

Pathologie	Biomarqueur	Nombre de tests
Cancer du sein	Amplification d' <i>HER2</i>	8 924
Cancer de l'estomac	Amplification d' <i>HER2</i>	709
Cancer colorectal	Mutations de <i>KRAS</i>	19 347
	Mutations de <i>NRAS</i>	3 330
GIST	Mutations de <i>KIT</i>	1 105
	Mutations de <i>PDGFRA</i>	1 005
Cancer du poumon	Mutations d' <i>EGFR</i>	23 336
	Translocation d' <i>ALK</i>	18 861
Mélanome	Mutation de <i>BRAF</i> V600	5 026
Leucémies	Détection de <i>BCR-ABL</i>	6 750
	Mutations d' <i>ABL</i>	861
TOTAL		89 254

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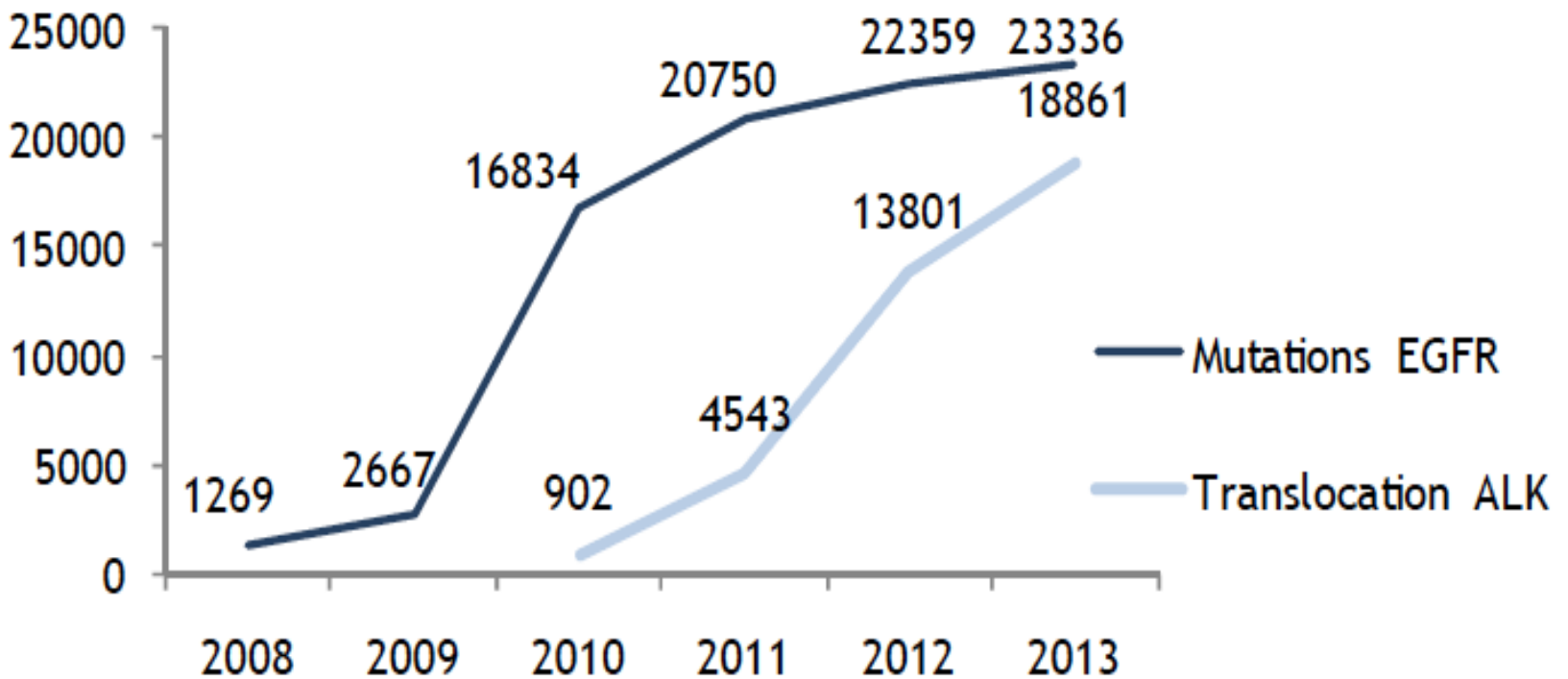


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Updated results

- Daily practice – Lung Cancers (2013)



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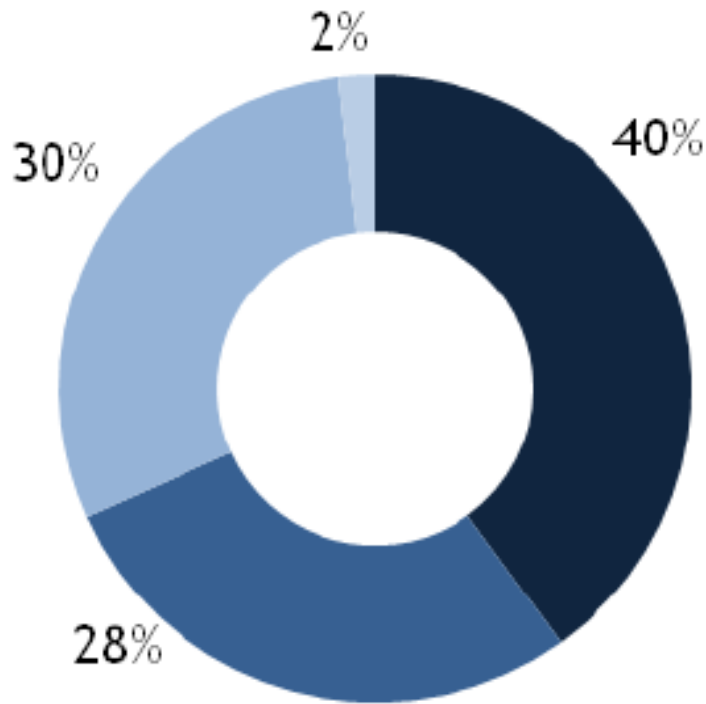


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Updated results

- **Daily practice – Lung Cancers (2013)**



- Pts treated at the site of the genetic center
- Pts treated in a public hospital (outside GC)
- Pts treated in a private center
- Samples referred from another lab

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Updated results

- Daily practice – Lung Cancers (2013)

Marqueur	Nombre de patients	% d'altérations moléculaires
Mutations <i>EGFR</i>	23 336	10,0 %
Translocation <i>ALK</i>	18 861	3,5 %
Mutations <i>KRAS</i>	22 958	27,0 %
Mutations <i>BRAF</i>	20 100	2,0 %
Mutations <i>HER2</i>	17 843	0,7 %
Mutations <i>PI3KCA</i>	17 375	2,4 %



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Updated results

- **Daily practice – Lung Cancers (2013)**

Biomarker	Number of tests	Non interpretable (%)
EGFR mut	23,386	8.0
ALK rearrang*	18,861	13.4
KRAS mut	22,958	7.9
BRAF mut	20,100	8.9
HER2 mut	17,843	10.1
PI3K mut	17,375	10.4

**, mainly assessed by FISH only at this time (2013)*

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Updated results

- Daily practice – Total costs (2006-2012)

Plateforme	Estomac	Mélanome	Colorectal		Poumon		TOTAL
	HER2	BRAF	MSI	KRAS	EGFR	ALK	
CHU-CLCC de Strasbourg ; CH de Colmar ; CH de Mulhouse	2 000 €	6 500 €	27 000 €	60 000 €	80 500 €	34 000 €	546 000 €
CHU-CLCC de Bordeaux	3 500 €	29 500 €	232 000 €	140 000 €	235 000 €	99 000 €	1 505 500 €
CHU-CLCC de Clermont-Ferrand	2 000 €	9 500 €	5 000 €	59 000 €	78 500 €	33 000 €	464 500 €
CHU-CLCC de Caen	4 000 €	5 500 €	3 500 €	47 000 €	55 500 €	23 500 €	348 000 €
CHU-CLCC de Dijon	2 000 €	8 500 €	17 000 €	65 000 €	100 000 €	41 000 €	557 000 €
CHU de Brest	12 500 €	9 500 €	16 000 €	25 000 €	74 000 €	31 000 €	411 500 €
CHU-CLCC de Rennes		18 500 €	34 000 €	118 000 €	201 000 €	84 500 €	954 333 €
CHRU de Tours ; CH d'Orléans		7 500 €	30 000 €	81 000 €	83 500 €	35 000 €	451 000 €
CHU-CLCC de Reims		8 000 €	18 000 €	47 000 €	65 000 €	25 500 €	369 500 €
CHU de Besançon		6 000 €	22 000 €	40 000 €	61 500 €	26 000 €	410 500 €
CHU-CLCC de Rouen		11 500 €	38 000 €	85 000 €	97 500 €	41 000 €	578 000 €
AP-HP	5 000 €	54 000 €	198 000 €	405 000 €	544 500 €	229 000 €	4 109 500 €
Institut Curie ; CLCC de Saint Cloud ; CH de Versailles	2 000 €	6 000 €	18 000 €	107 000 €	95 000 €	36 500 €	762 500 €
Institut Gustave Roussy		21 500 €	3 500 €	47 000 €	79 500 €	33 500 €	501 500 €
CHU-CLCC de Montpellier ; CH de Nîmes	2 000 €	11 500 €	31 000 €	118 000 €	168 000 €	70 500 €	793 000 €
CHU de Limoges		6 500 €	9 000 €	25 000 €	41 000 €	17 000 €	215 000 €
CHU-CLCC de Nancy		9 500 €	21 000 €	94 500 €	113 500 €	47 500 €	601 500 €
CHU-CLCC de Toulouse	3 500 €	12 500 €	34 000 €	118 000 €	116 500 €	49 000 €	1 082 833 €
CHRU-CLCC de Lille		14 500 €	40 000 €	178 500 €	183 000 €	77 000 €	1 599 333 €
CHU-CLCC de Marseille	4 000 €	19 500 €	21 000 €	138 500 €	236 500 €	99 000 €	
CHU-CLCC de Nice		15 000 €	6 000 €	70 500 €	68 500 €	29 000 €	
CLCC d'Angers		11 500 €	8 000 €	80 000 €	49 000 €	20 000 €	
CHU-CLCC de Nantes	2 500 €	26 500 €	46 000 €	57 000 €	102 000 €	43 000 €	
CHU d'Amiens			31 000 €	75 000 €	71 500 €		
CHU de Poitiers		5 000 €	28 000 €	80 000 €	83 000 €	35 000 €	
CHU de Grenoble		4 500 €	4 000 €	40 000 €	95 000 €	40 000 €	
CHU-CLCC de Lyon	4 000 €	25 500 €	80 000 €	138 500 €	161 000 €	68 000 €	
CHU de Saint-Etienne		6 500 €	3 000 €	35 500 €	30 000 €	13 000 €	222 000 €
TOTAL	49 000 €	370 500 €	824 000 €	2 575 000 €	3 369 500 €	1 381 500 €	21 973 000 €

21 973 000 €

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Updated results

- Impact on patients /outcomes?



**Reality of
bioguided
treatments?**

Efficacy?



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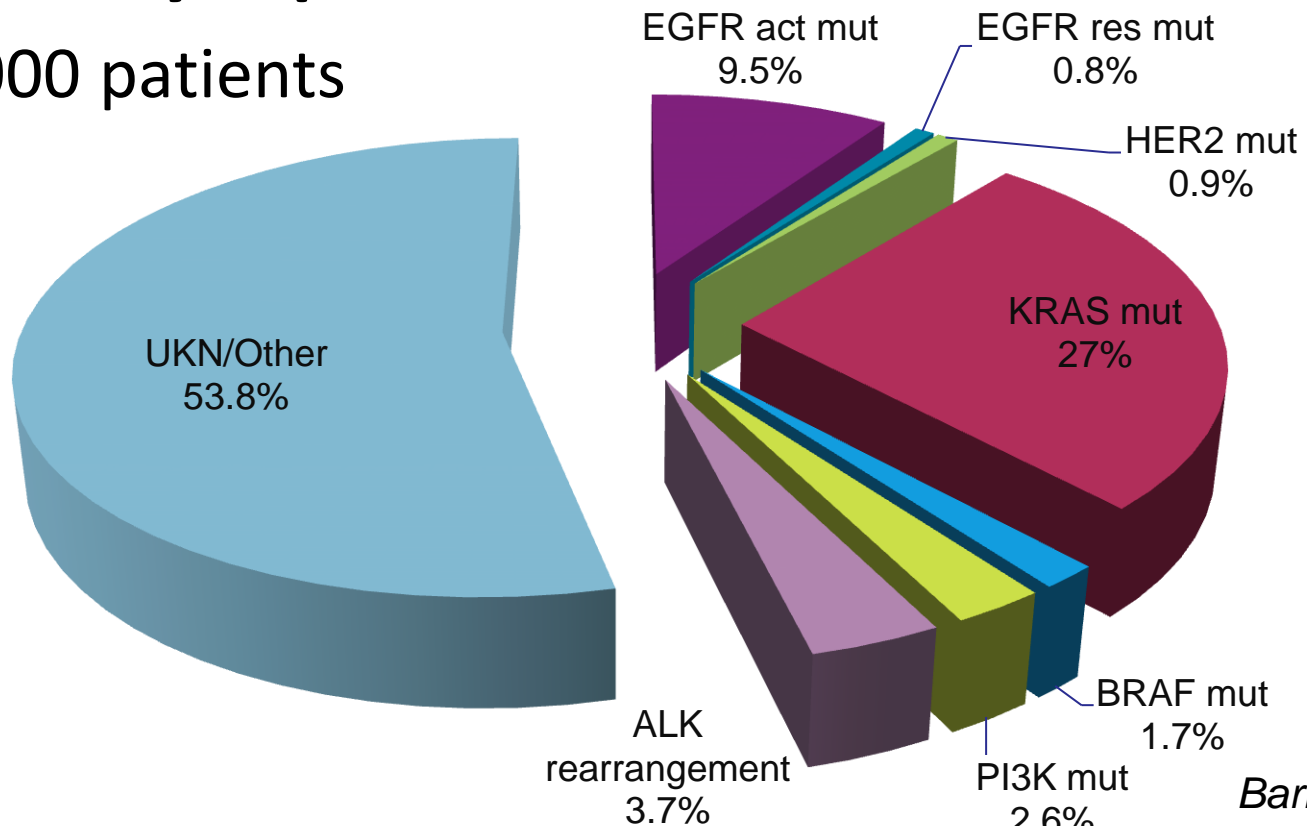


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Results

- **Preliminary report**
 - 10,000 patients



*Barlesi F et al,
ASCO 2013 (#8000)*

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Updated results

- **Final cohort**
 - One full year of recruitment
 - Data cut-off for analysis: Jul. 2014
 - Median follow-up of #25 months



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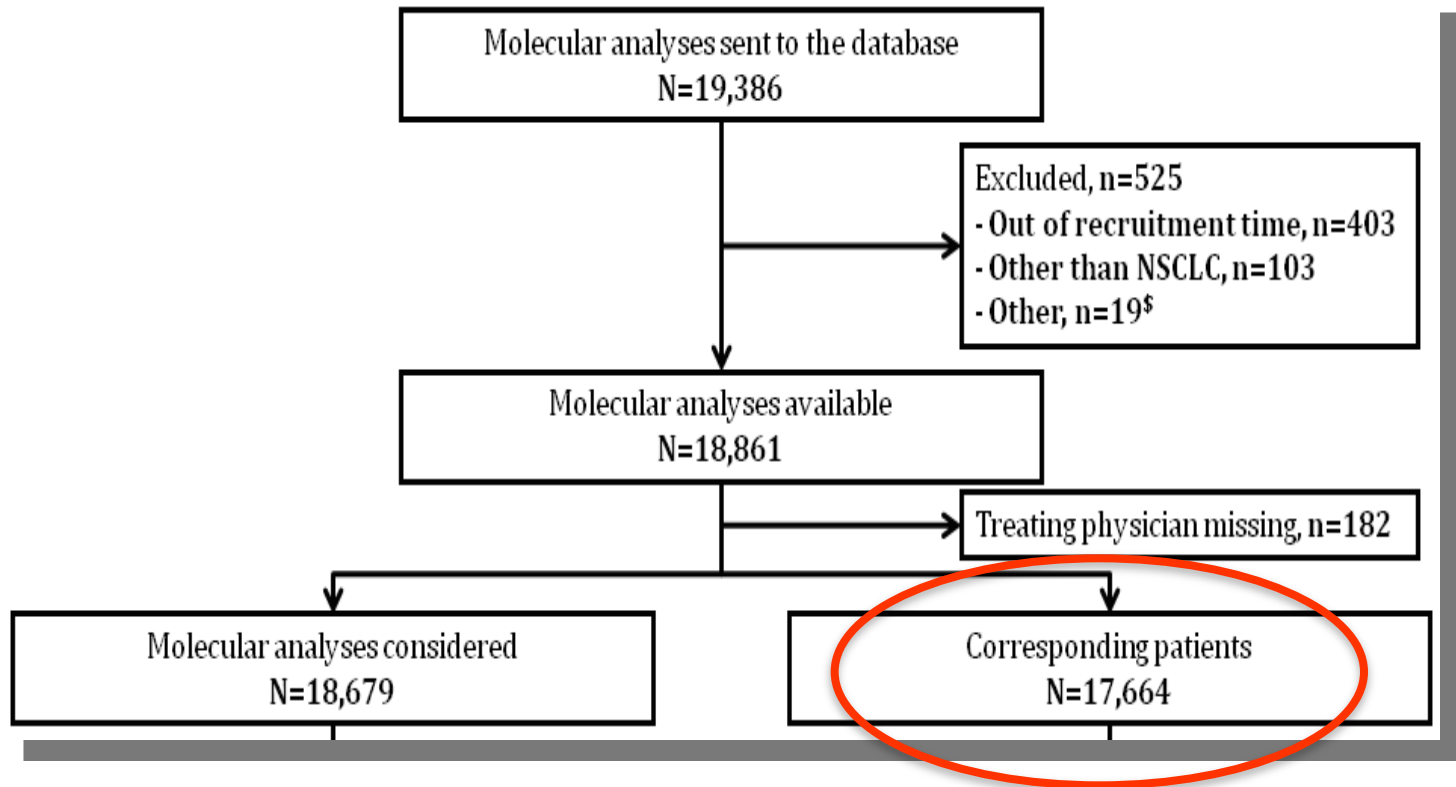
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Barlesi et al, submitted

Updated results

- Final cohort



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Barlesi et al, submitted

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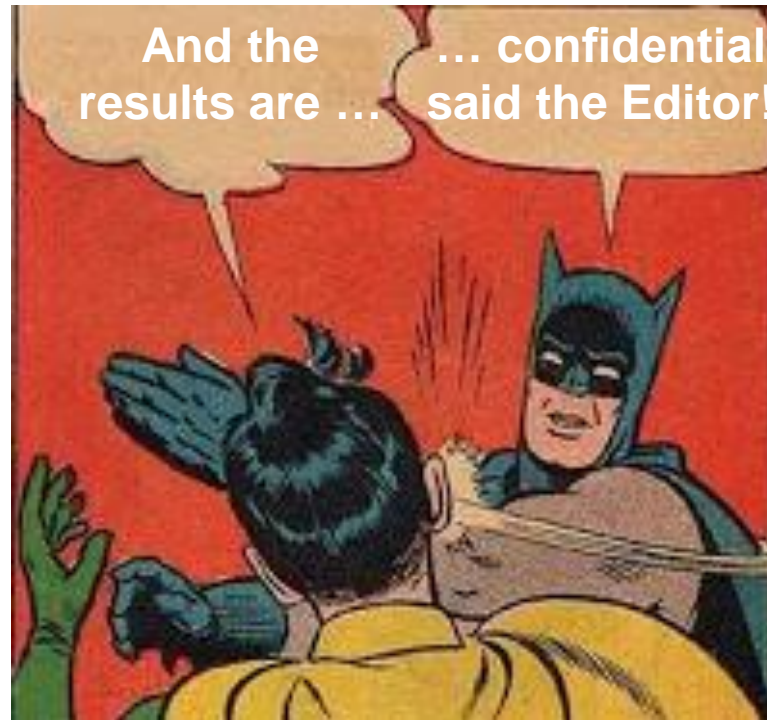


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Updated results

- Final cohort



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Barlesi et al, submitted

Expected results

- **A local example of achievement**
 - Initial diagnosis during 2012-2013
 - Stage IV ADC patients
 - Molecular profile?
 - Type of treatment?
 - Outcomes?



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Fournier C & Barlesi F (unpublished data)

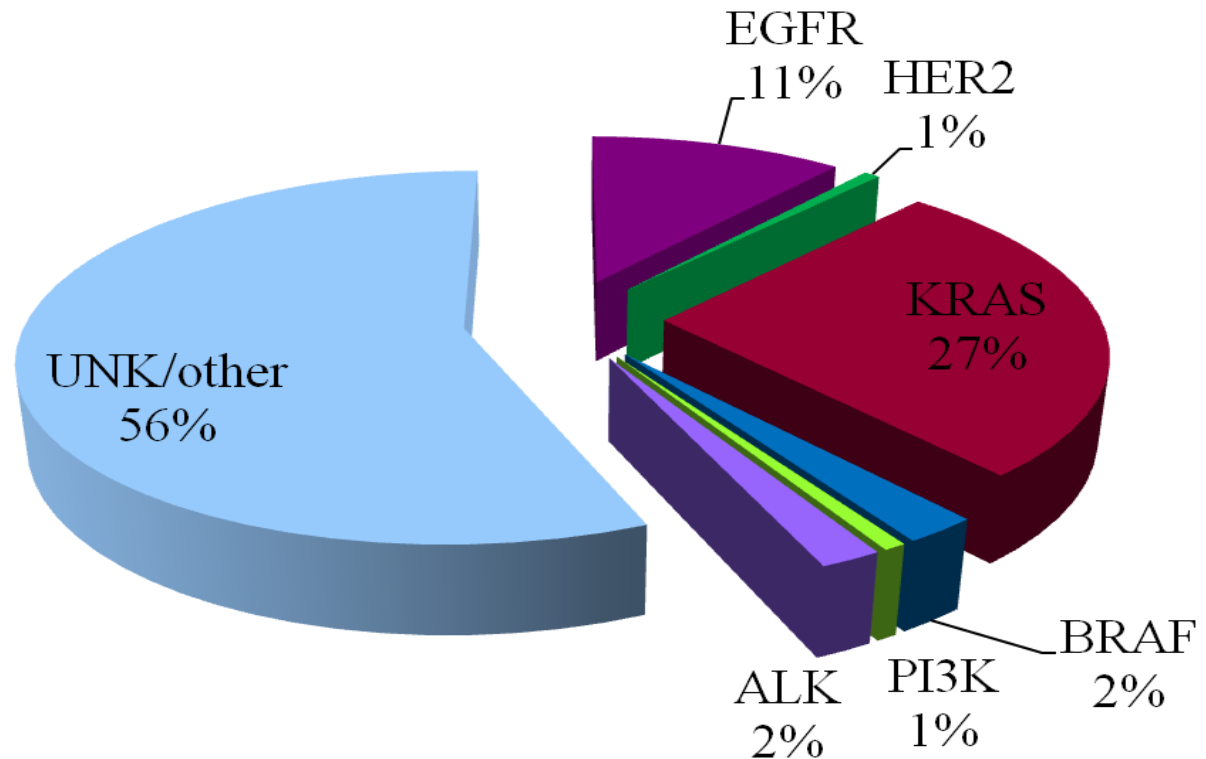
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Expected results

- A local example of achievement

- N=262 pts



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Fournier C & Barlesi F (unpublished data)

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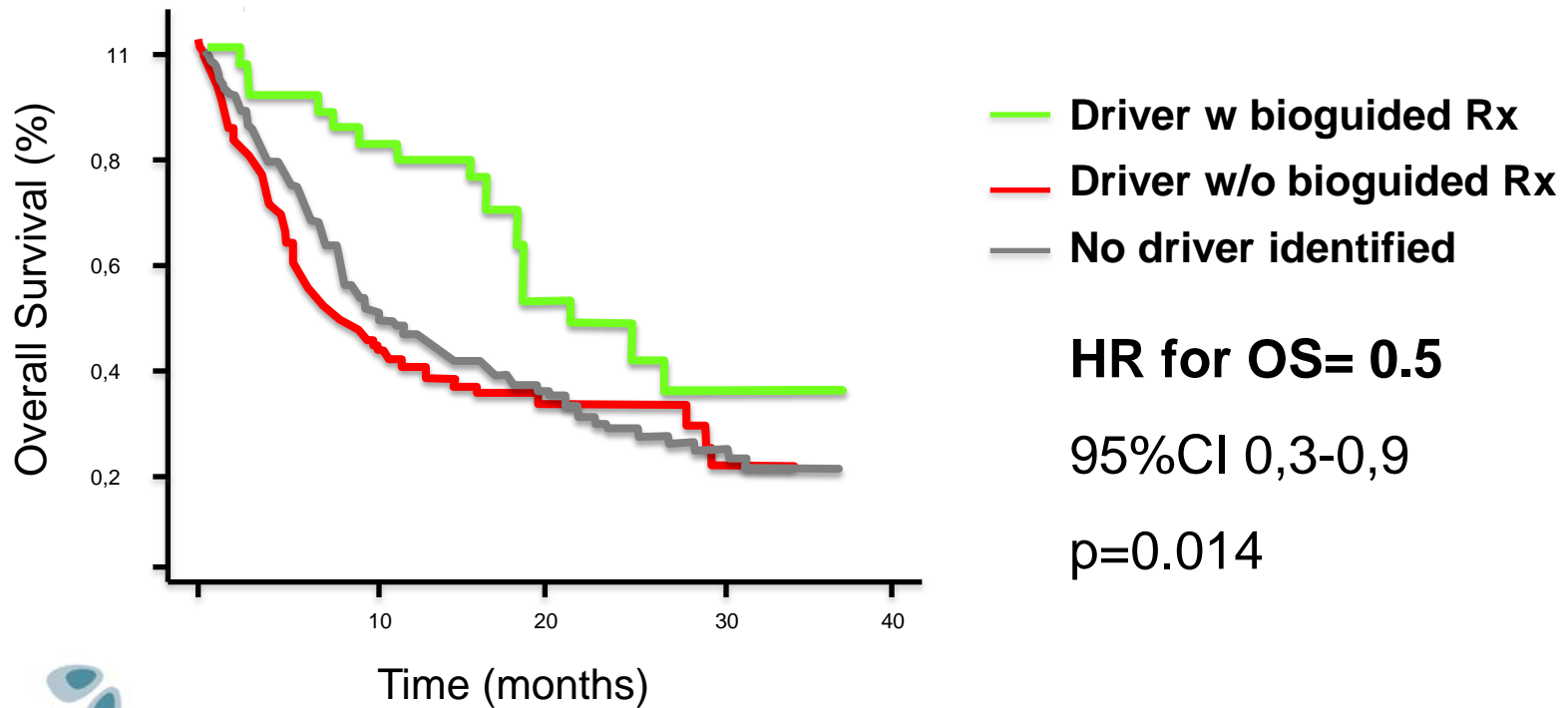


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Expected results

- A local example of achievement



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Fournier C & Barlesi F (unpublished data)

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Expected results

- A local example of achievement

		No driver N=150 (%)	Driver w Bioguided Rx N=32 (%)	Driver w/o bioguided Rx N=79 (%)
Gender	Men	75	37	65
	Women	25	63	35
Age	< 70yrs	72	81	75
	> 70yrs	28	19	25
Smoking	<10 PA	13	53	39
	>10 PA	84	47	59
Comorbidities	COPD	11	9	7
	Diabetes	10	12	5
	HTA	18	22	25
ECOG PS	0 or 1	75	94	68
	2	13	3	16
	3 or 4	9	0	13
Brain mets +		47	44	40

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Fournier C & Barlesi F (unpublished data)

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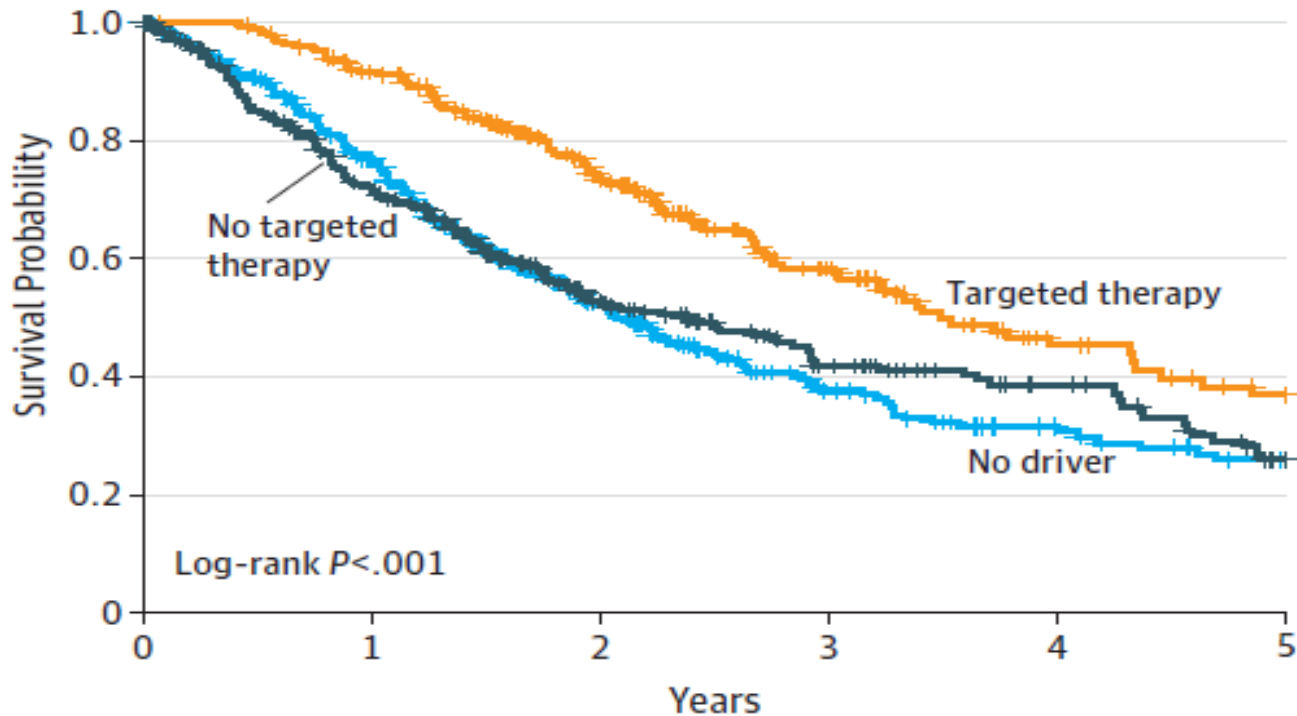


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Perspectives

- Biomarkers France *versus* LCMC?



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Kris MG et al, JAMA 2014

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Perspectives

- **Biomarkers France: ancillary studies**
 - BRAF mutated pts
 - KRAS mutated pts
 - HER2 mutated pts
 - ALK rearranged pts
 - Pts w rare EGFR mutations
 - Pts w double mutations
 - Medico-economics



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Perspectives

- From the 2015' routine testing (Lung cancers)

Cancer	Molecular Target	Treatment
Lung Non-sq NSCLC	EGFR activating mutations	Afatinib, Erlotinib, Gefitinib
	EGFR resistant mutations	Clinical trials
	EML4-ALK transloc.	Crizotinib, Ceritinib [£]
	ROS1 rearrangement	Crizotinib*
	KRAS mutations	Clinical trials
	HER2 ex20 mutations	Clinical trials
	BRAF mutations	Clinical trials, Vemurafenib*
	MET amplification	Crizotinib*

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[£], ATU (#EAP); *, Acsés programs

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Perspectives

- **To the 2017' routine testing (Lung cancers)**
 - NGS
 - Liquid biopsies: ctDNA



Appel à projets 2013

**Structuration du séquençage
de nouvelle génération
à visée diagnostique en cancérologie**



Action 21



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Perspectives

- **Biomarkers France #2**
 - NGS to be widely implemented in 2017
 - More drugs available through the network of 2015' certified phases I depts (CLIP²)
 - Support will depend on the Biomarkers France #1 results



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Conclusions

- **French NCI certified genetic centers**
 - Accomplish a great daily work for patients
 - Evolve regularly (biomarkers, techniques)
 - Are subject to several quality controls
- **The updated results of Biomarkers France study**
 - Are still embargoed for OS
 - A NGS Biomarkers France #2 study will be conducted in case of encouraging results



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Acknowledgements

- **INCa**
 - Dominique Maraninchi
 - Agnès Buzyn
 - Frédérique Nowak
- **IFCT**
 - Franck Morin
 - Pascale Missy
 - Quan Tran
 - Antoine Deroy
 - Alexandra Langlais
 - ARCs
- **Steering Committee**
- **Genetic centers**
- **Clinicians**
- **Sponsor & support**



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