Cancers bronchiques :

La personnalisation jusqu'où ?

Cours du GOLF

Strasbourg – 19 Novembre 2015

Fabrice Barlesi, MD, PhD

Multidisciplinary Oncology
& Therapeutic Innovations Dept
INSERM U911
Marseille - France

Assistance Publique
Hôpitaux de Marseille

Aix*Marseille université

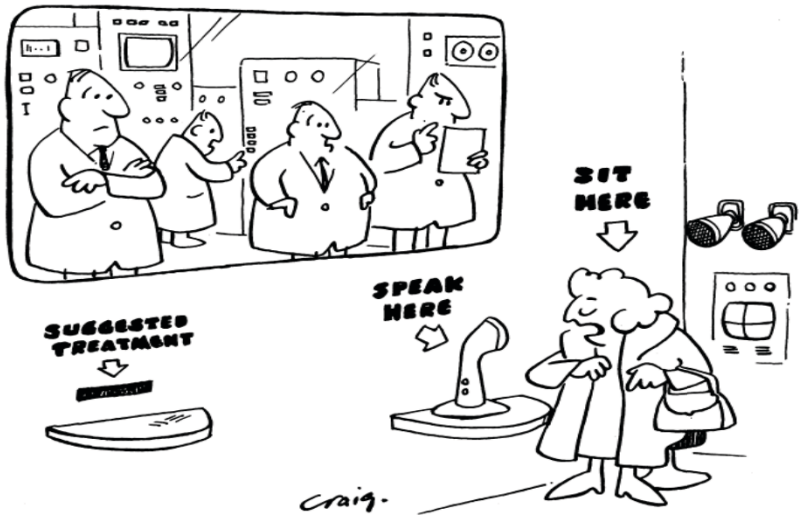
Disclosure slide

I provided consultations for Astra-Zeneca, Bristol-Myers Squibb, Boehringer–Ingelheim, Clovis Oncology, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Novartis, Merck, MSD, Pierre Fabre and Pfizer.

Préambule

- **Médecine**
  - **Personnalisée**
  - **Individualisée**
- **Médecine de précision**

Une question ancienne



IN HIS BOOK *Morals and Medicine*, Joseph Fletcher describes medicine as a "human art for human beings", and says that just as human beings increase in wisdom and stature, so must the ethics of medical care change, grow and engage in self-correction.

Without commenting on man's growth for the better, I feel it is true that few of us can remain indifferent to the climate of change around us.

What future is there for family practice, and in particular, what future is there for solo practice? Is solo practice dying of inanition? Is it something that already belongs to the past? Or will it vanish, like the horse and buggy doctor who typified it, into the mists of antiquity, lamented only by rising in public esteem for their unique qualities of personal care?

We live in times of great change and it would probably be true to say that within the span of a single lifetime, medicine has left medievalism behind it. Certainly within my medical lifetime, the advances in the science — as opposed to the art — of medicine, have been astounding. Looking back at

Can Personalized Medicine Survive?

by W. M. GIBSON, MB, ChB

that our profession, especially that part of it engaged in family practice, is going through a period of evaluation not only of its ethics, but of its methods of practice. Those we serve, the "consumers of health services", take a considerable interest in our doings, and we can rely on the politicians to keep them well-informed, so that

the sentimental few? Or will the solo practitioner's demise be welcomed, his replacement being a battery of experts in the fields of medicine, surgery, psychiatry and all the new allied health sciences, infinitely better trained than their singlehanded predecessor? Or will solo and family practice go from strength to strength,

some of these changes over 30 years of practice helps me to predict a future for medicine. Naturally, I hope that we will retain the good, discard the bad, after an objective deliberation that becomes us in our modern role as scientist-physicians.

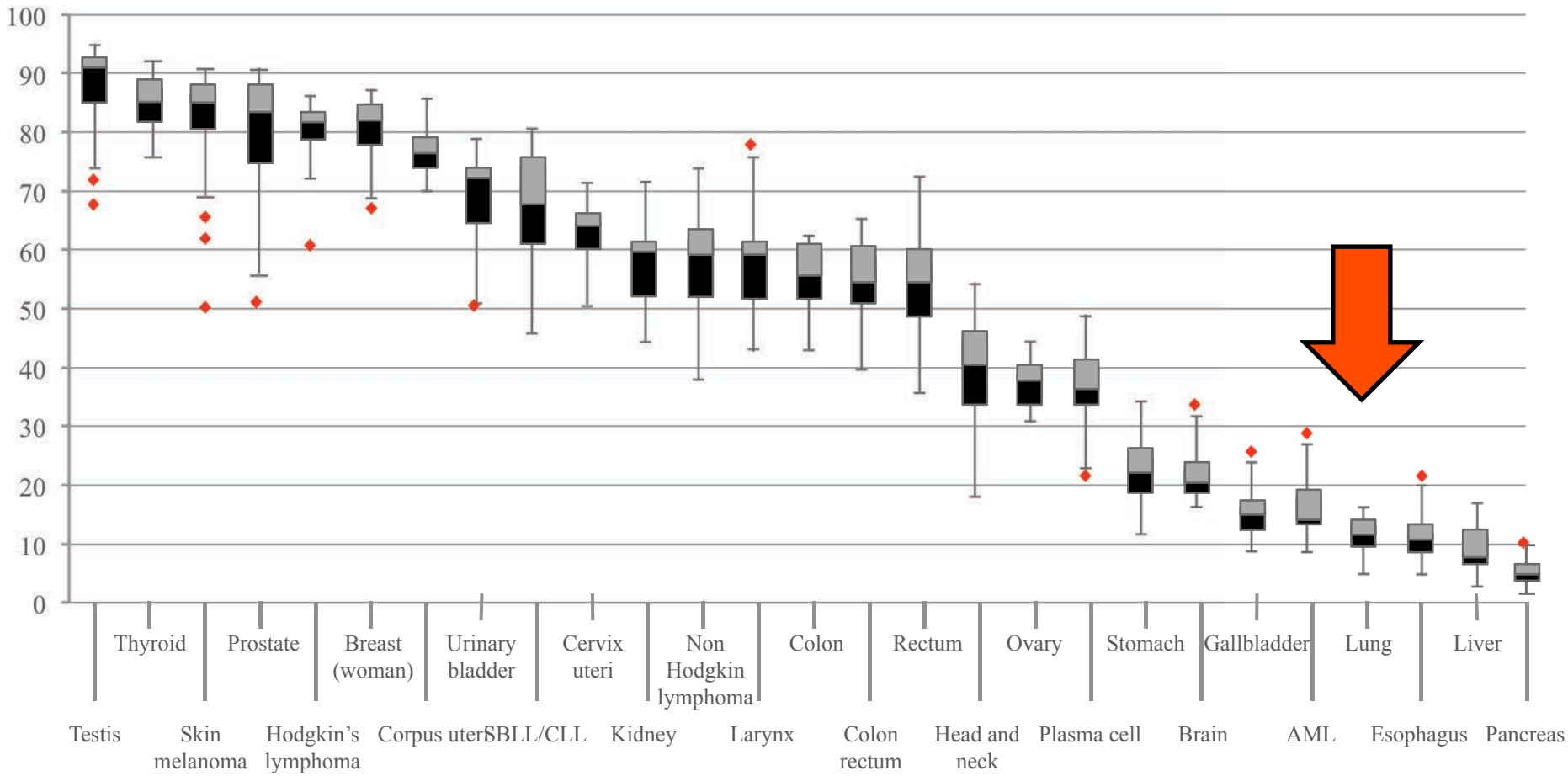
However, the essence of survival, it has been said, is adaptability, and on

CANADIAN FAMILY PHYSICIAN • AUGUST, 1971 29

Agenda

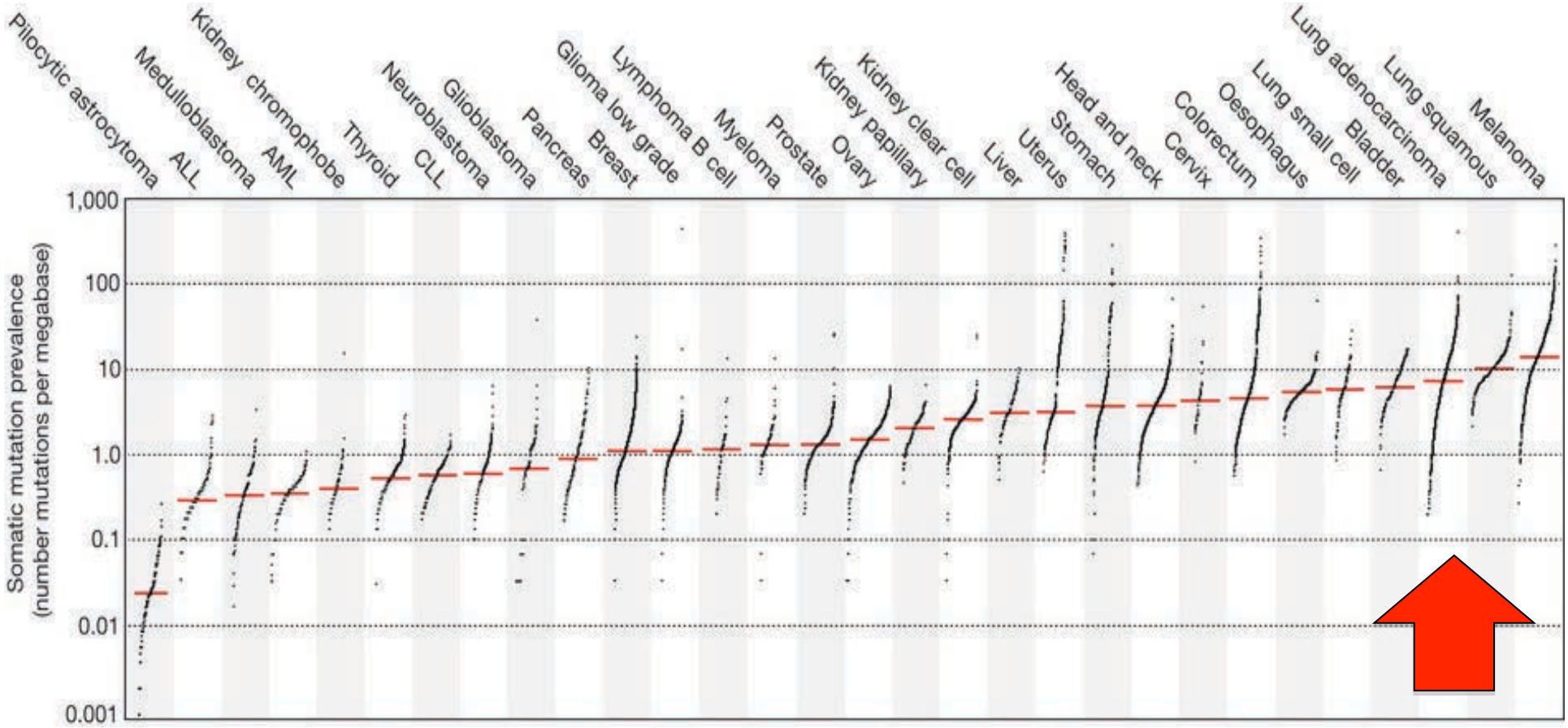
- **Pharmaco-génomique**
- Pharmaco-cinétique
- Pharmaco-génétique
- Perspectives

Le cancer du poumon



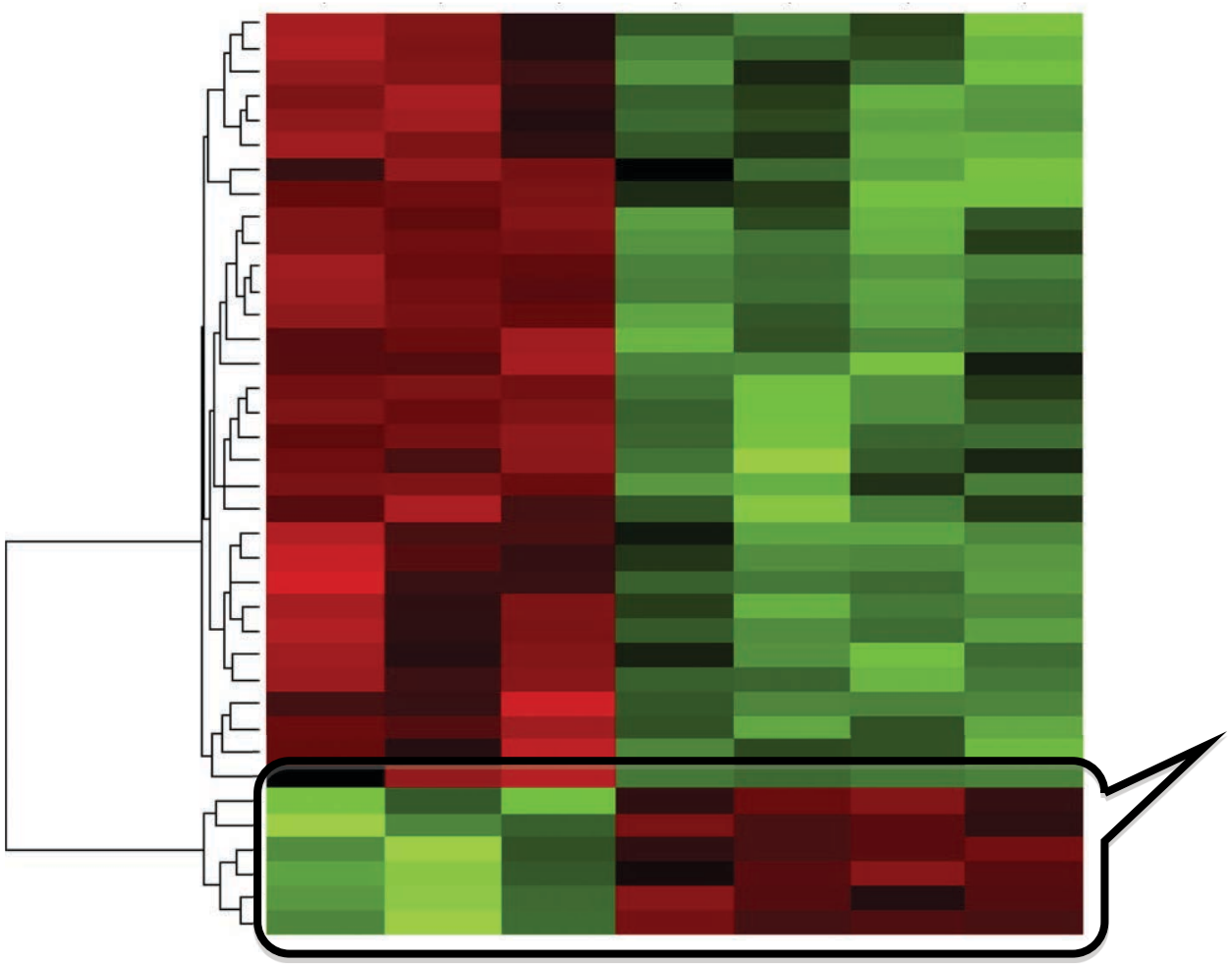
Sant M. et al. (Eurocare 5) - ESMO® 2015 – Abs. #LBA1

Mean number of genetic alteration / tumor



Alexandrov L, Nature 2013

Objectif de la cancérologie moderne



Caractéristique(s) génétique(s) commune(s) = traitement commun ?

La première démonstration

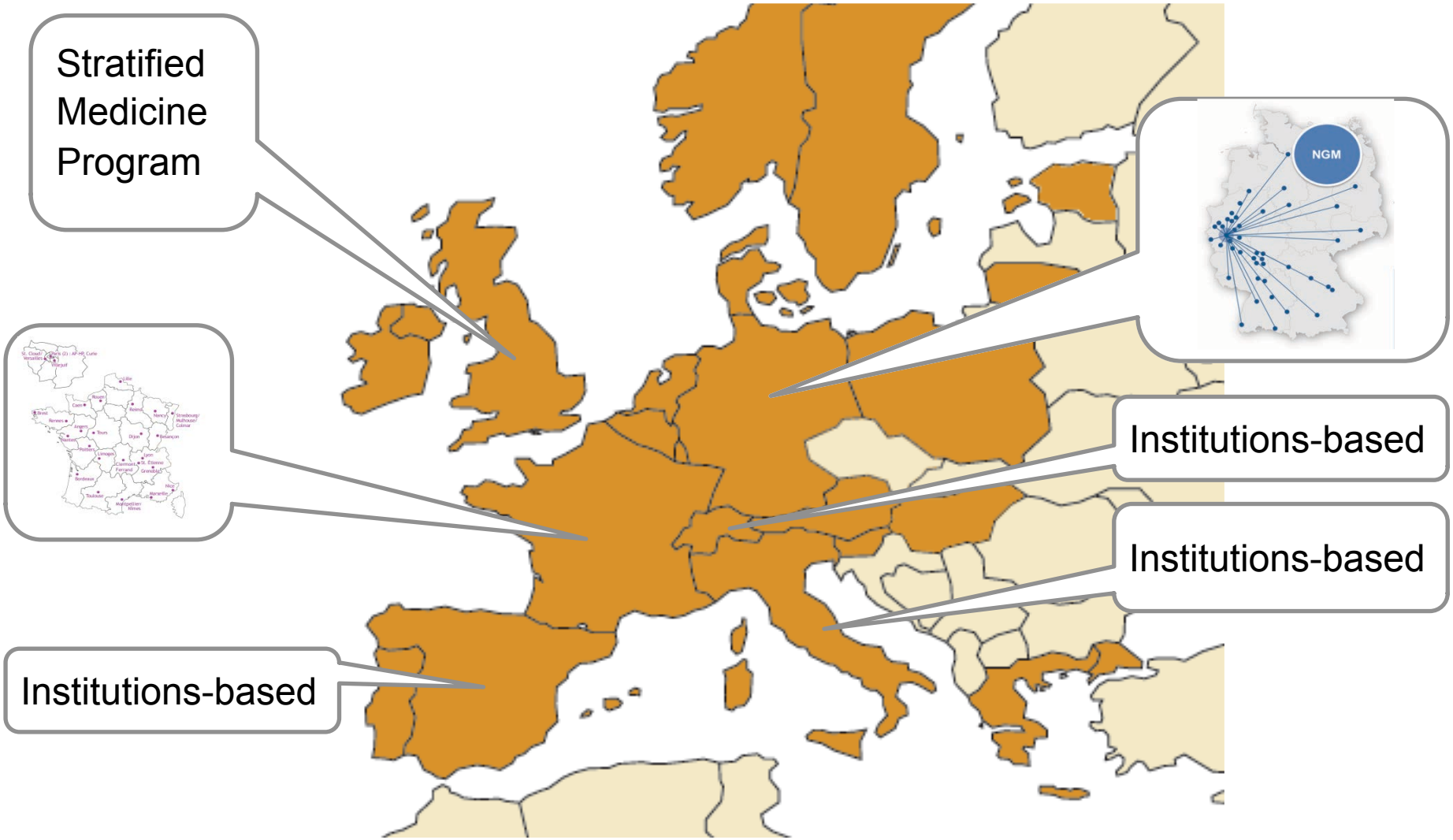
The NEW ENGLAND JOURNAL of MEDICINE

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.

Examples of EU's LC genotyping programs



Un profil moléculaire … pour tous

- **28 platforms (2006)**

** i.e. Regional molecular genetics centers*

- **10 biomarqueurs de routine (+ 6 émergents)**

Tableau 1. Nombre de recherches de marqueurs prédictifs de la réponse à une thérapie ciblée en 2013

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

Available at www.ecancer.fr

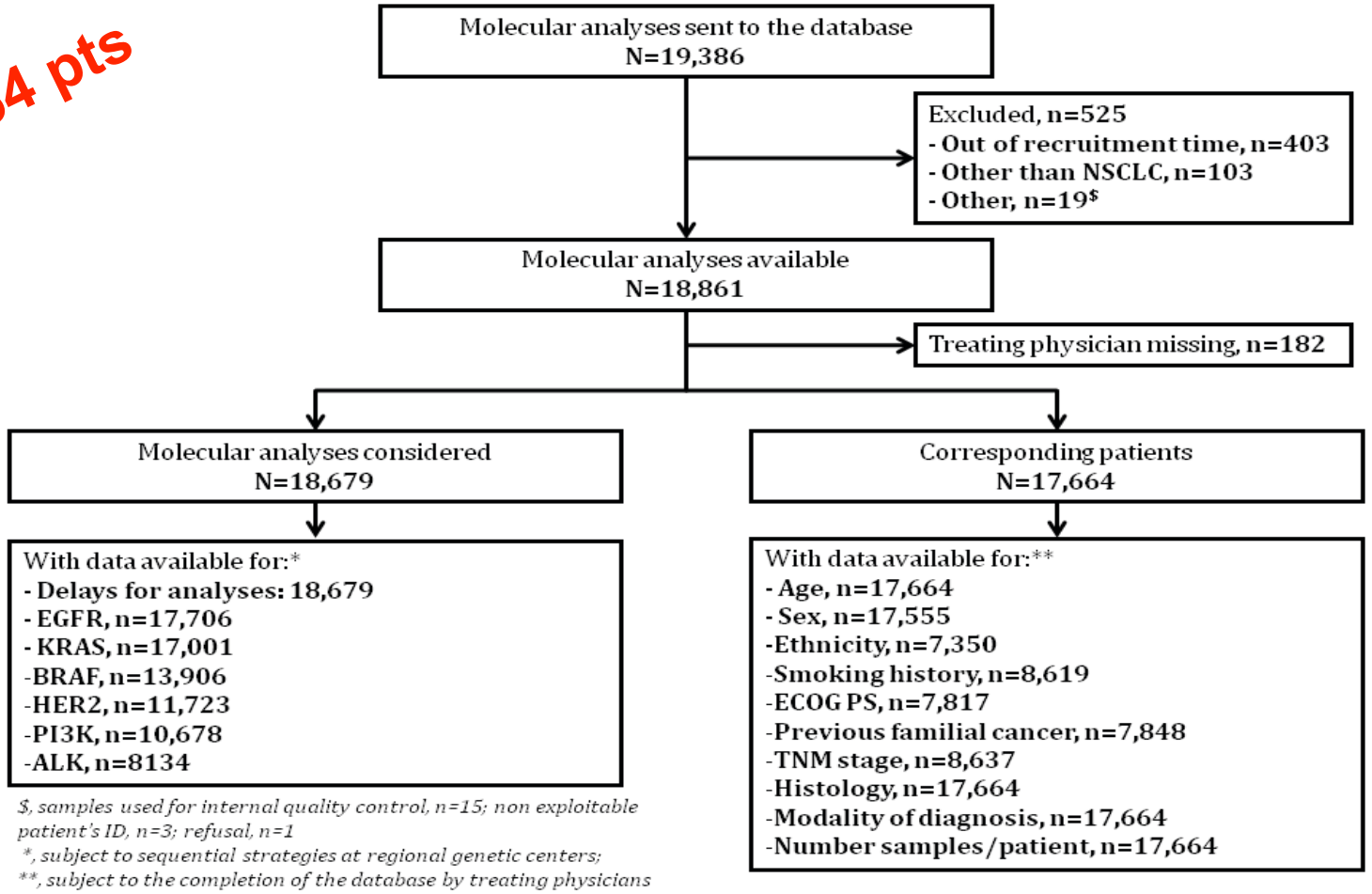
Profil moléculaire et C. du poumon (2015)

Cancer	Molecular Target	Treatment
Lung Non-sq NSCLC	**Programme INCa**	
	EGFR mutations (activating and resistant)	1stG: EGFR-TKIs 3rdG: AZD9291, CO1686 (ATU) & trials
	EML4-ALK transloc.	Crizotinib Ceritinib (ATU), Clinical Trials
	ROS1 rearrangement	Crizotinib
	KRAS mutations	Clinical trials
	HER2 ex20 mutations	HER2 inhib, Clinical trials
	BRAF mutations	Vemurafenib (Acsé), Clin. trials
	MET mutations/amplification	Crizotinib, Clinical trials

Available at www.ecancer.fr

Biomarkers France

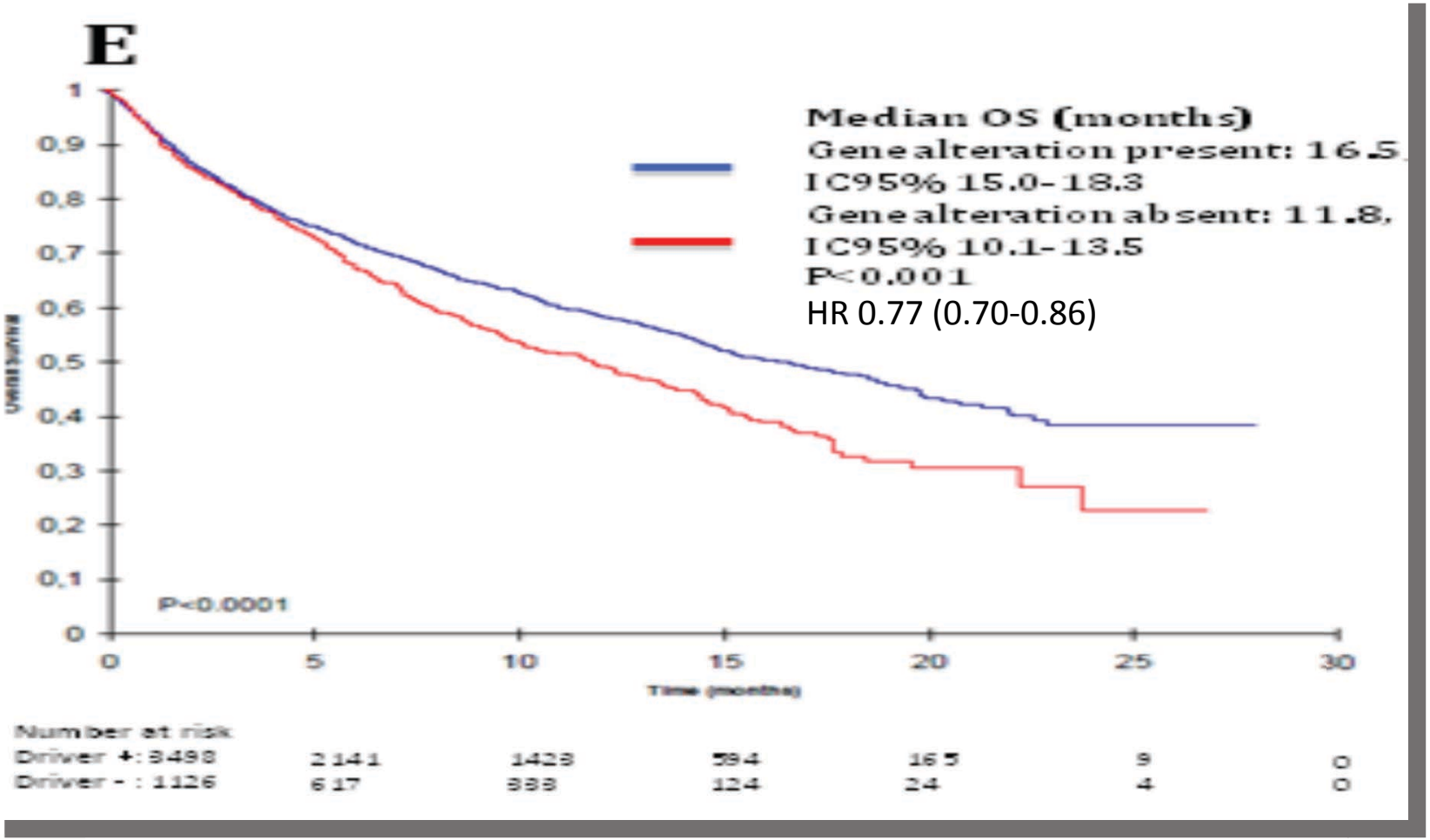
17,664 pts



$, samples used for internal quality control, n=15; non exploitable patient's ID, n=3; refusal, n=1
**, subject to sequential strategies at regional genetic centers;*
***, subject to the completion of the database by treating physicians*

Barlesi et al, Biomarkers France, Lancet 2015 (in press)

Biomarkers France



Barlesi et al, Biomarkers France, Lancet 2015 (in press)

La précision jusqu'où ?

http://www.phgfoundation.org

Sampling?

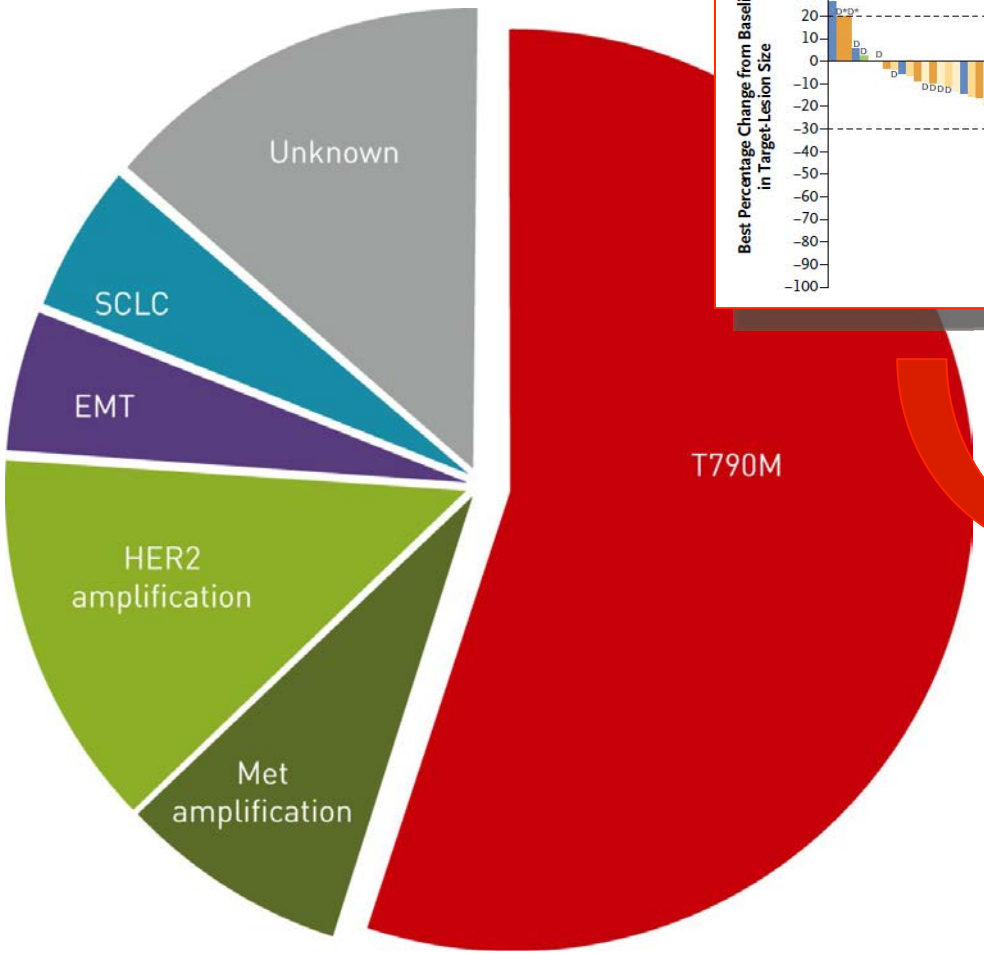
- **Daily practice – Lung Cancers (2013)**

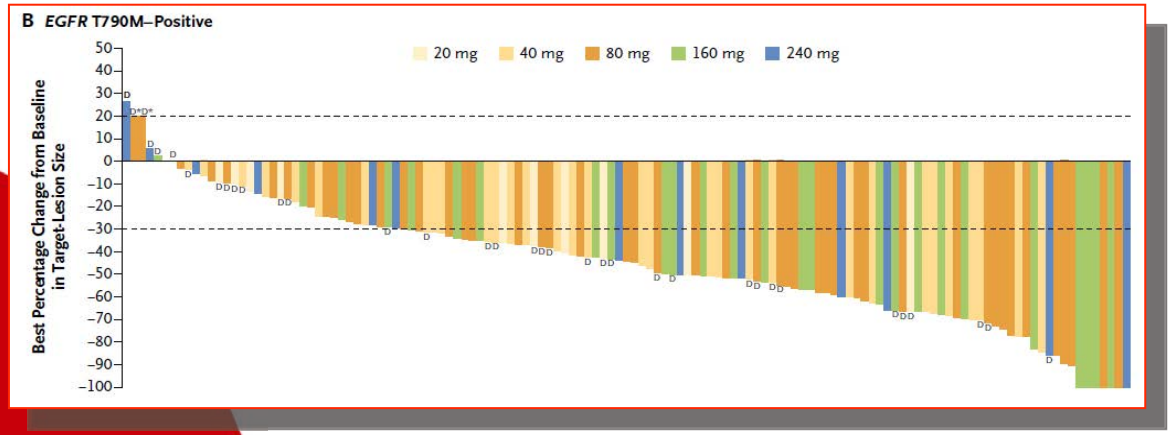
Biomarker	Number of tests	Non interpretable (%)
EGFR mut	23,386	8.0
ALK rearrang*	18,861	13.4
KRAS mut	22,958	7.9
BRAF mut	20,100	8.9
HER2 mut	17,843	10.1
PI3K mut	17,375	10.4

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

Available @ www.ecancer.fr

EGFR TKI (1G) acquired resistance

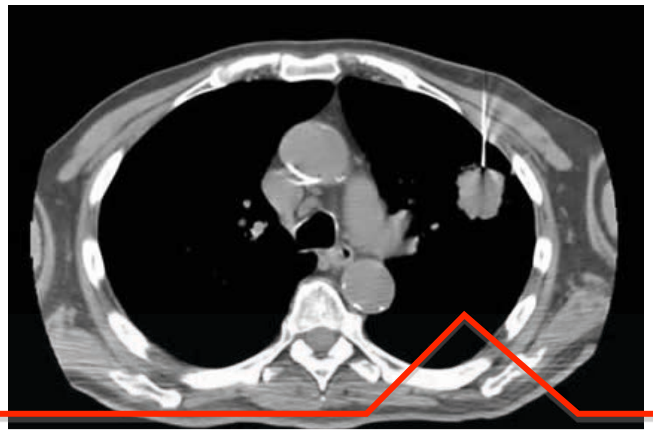




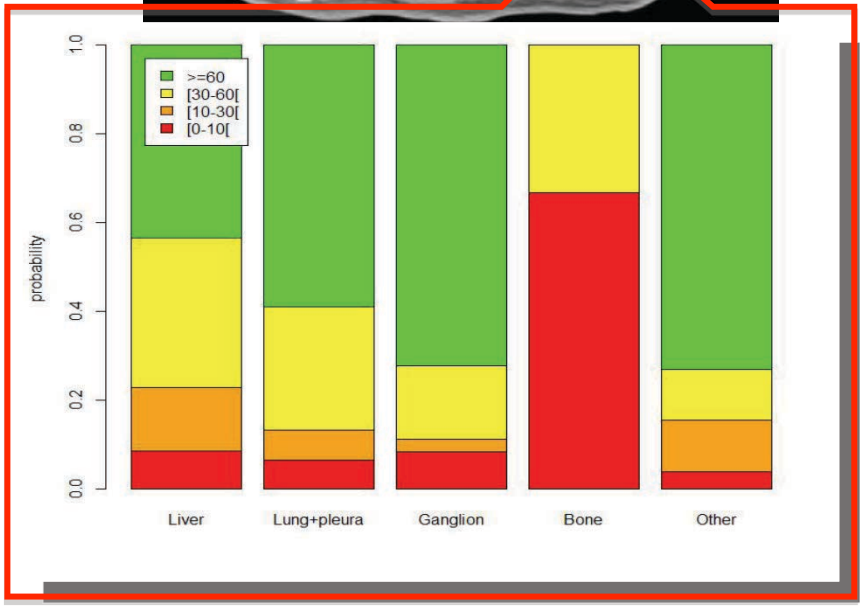
Cortot A & Janne PA, Eur Respir Rev 2014;

Janne P et al, NEJM 2015

Sampling?



vs



	Plasma 1 *EGFR* Mutation Status, *n*		
	Positive	**Negative**	**Total**
Tumor *EGFR* mutation status, *n*[a]			
Positive	69	36	105
Negative	1	546	547
Total	70	582	652

	n	**Rate, %**	**95% Confidence Interval**
Concordance	652	94.3	92.3–96.0
Sensitivity	105	65.7	55.8–74.7
Specificity	547	99.8	99.0–100.0
Positive-predictive value	70	98.6	92.3–100.0
Negative-predictive value	582	93.8	91.5–95.6

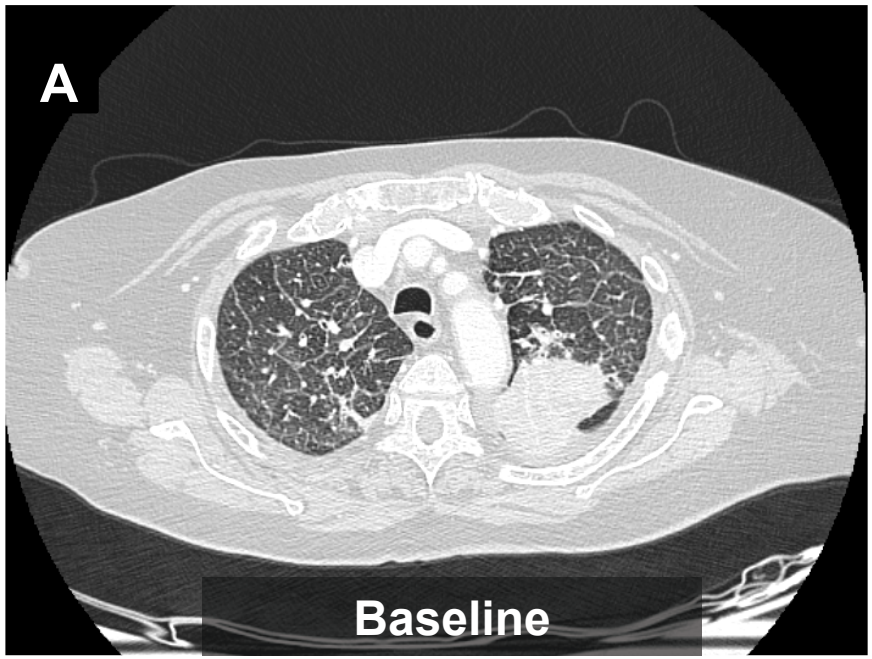
Antoine Hollebecque et al, EORTC NCI AACR 2013; Douillard JY et al, J Thorac Oncol 2014

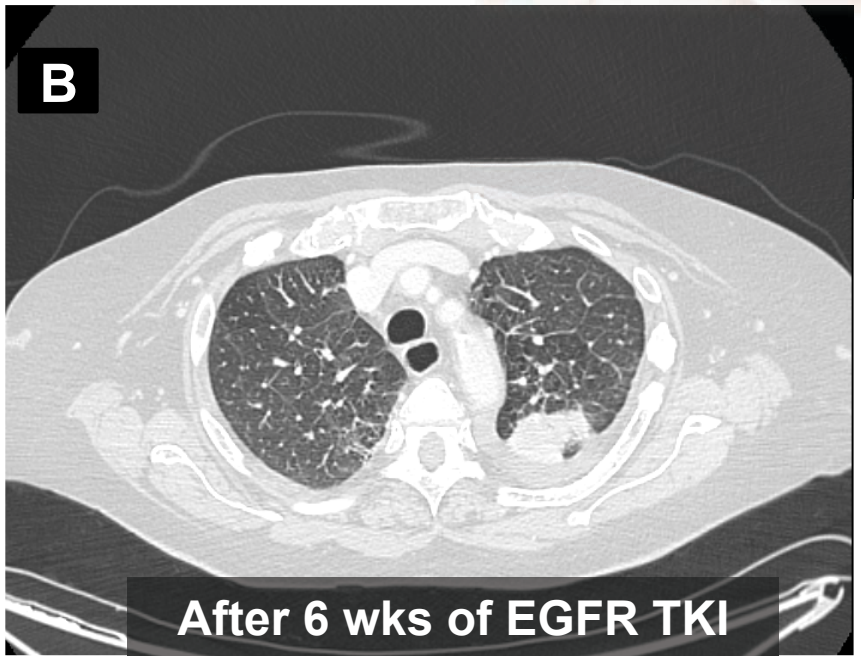
Diagnostic sur ADN circulant

Patiente 76 ans, ATCD vasculaire cérébral

Etat général dégradé (PS 4), pas d'examen invasif possible

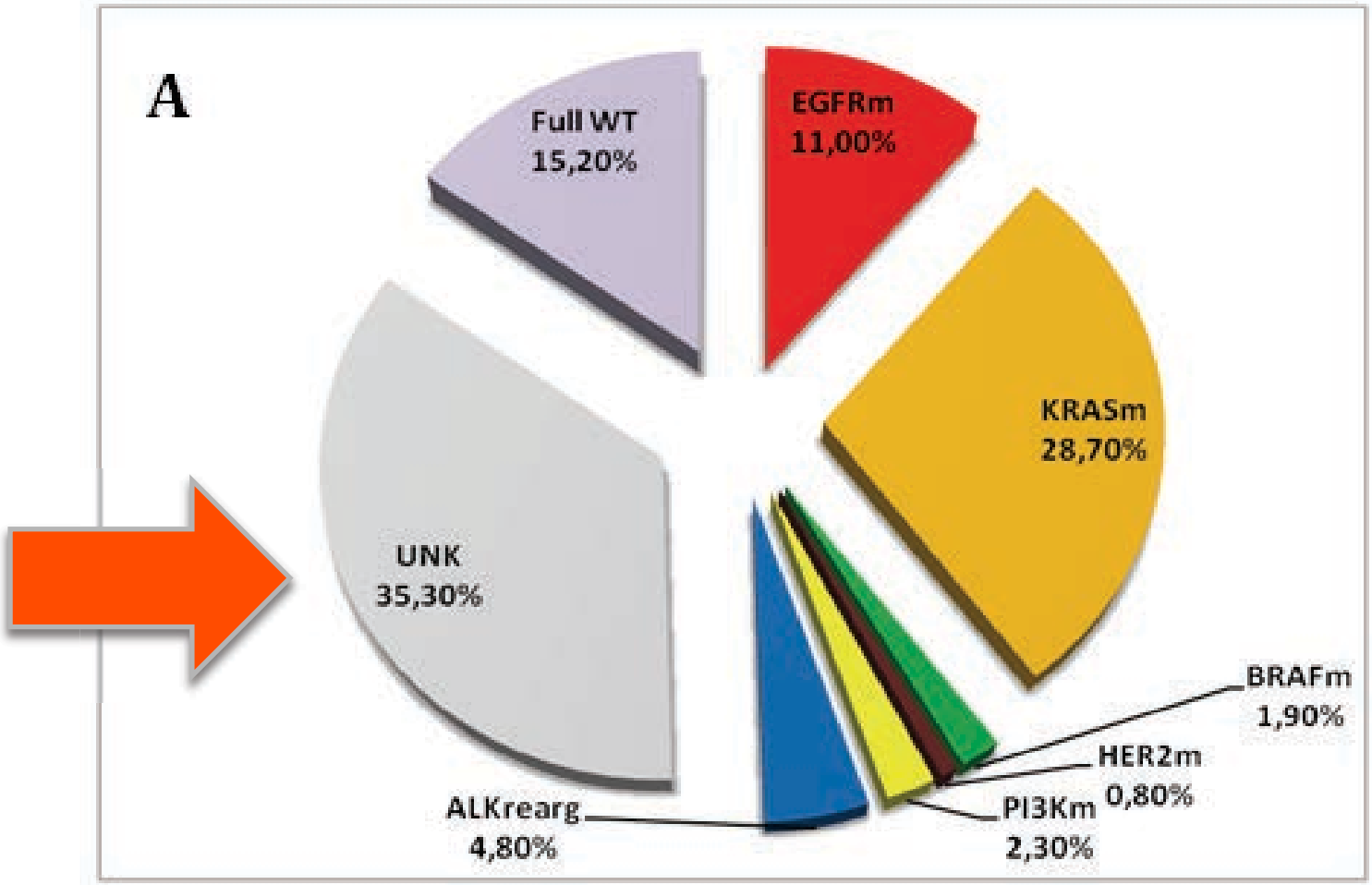
ADN circulant: mutation EGFR del 19





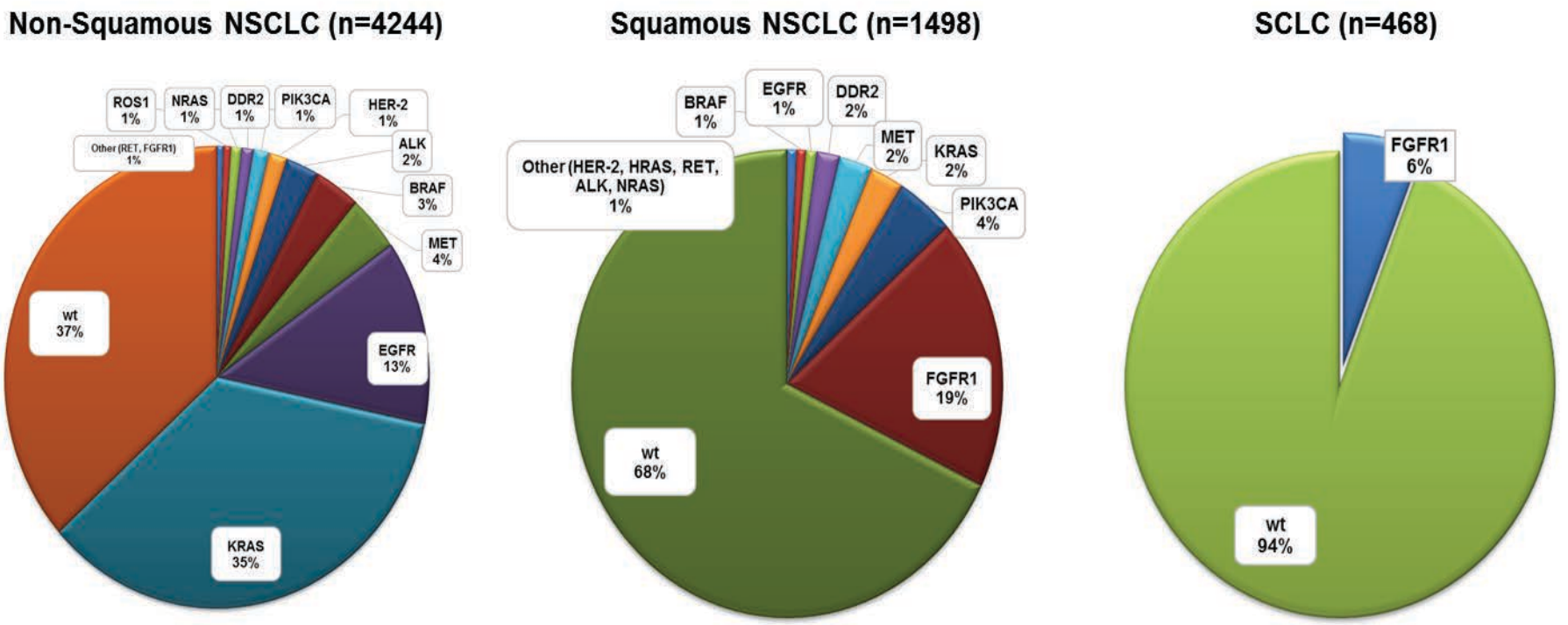
Tomasini et al, submitted

Profil moléculaire et C. du poumon: résultats



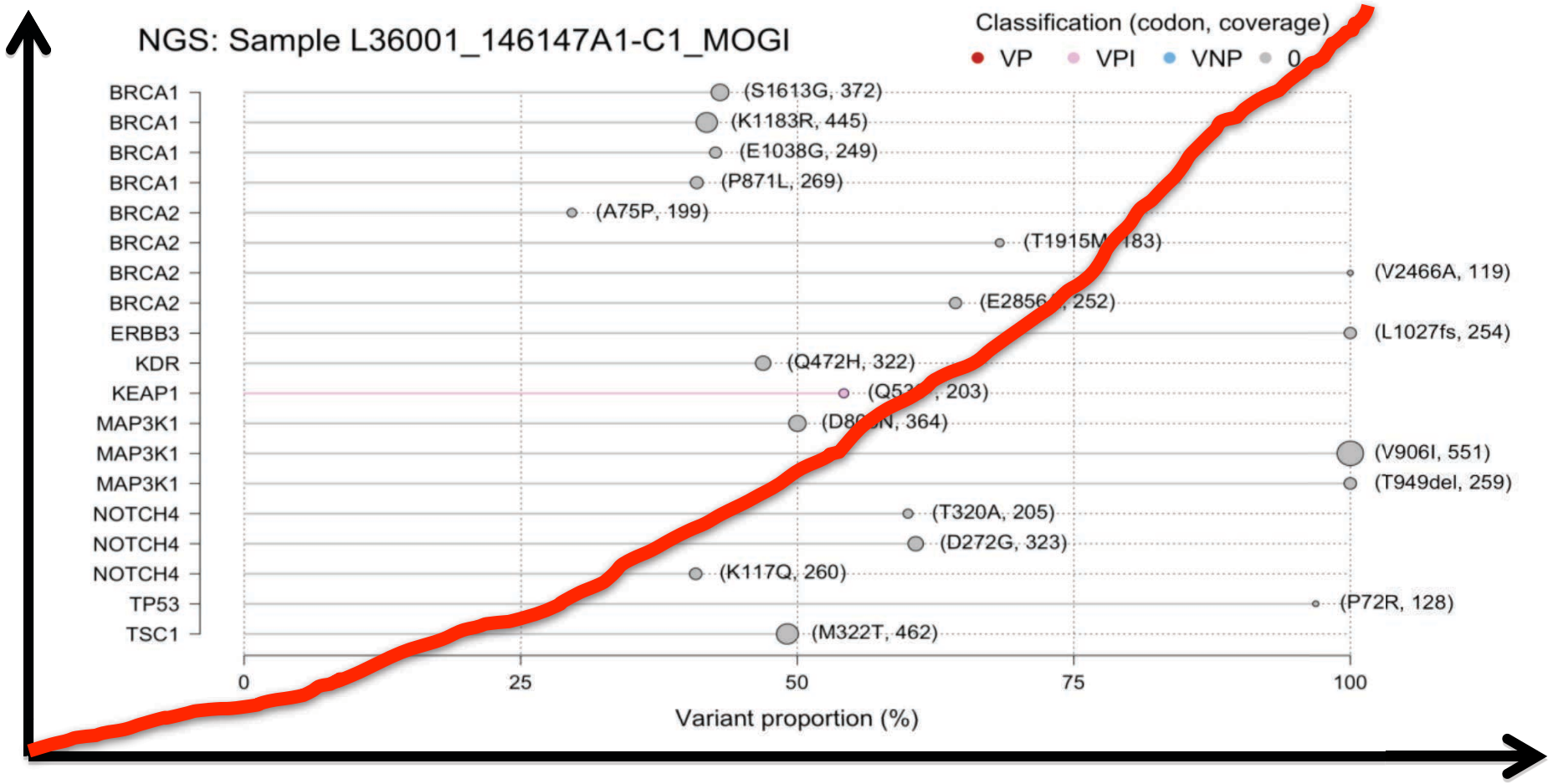
Barlesi et al, Biomarkers France, Lancet 2015 (in press)

Molecular profiling of cancer



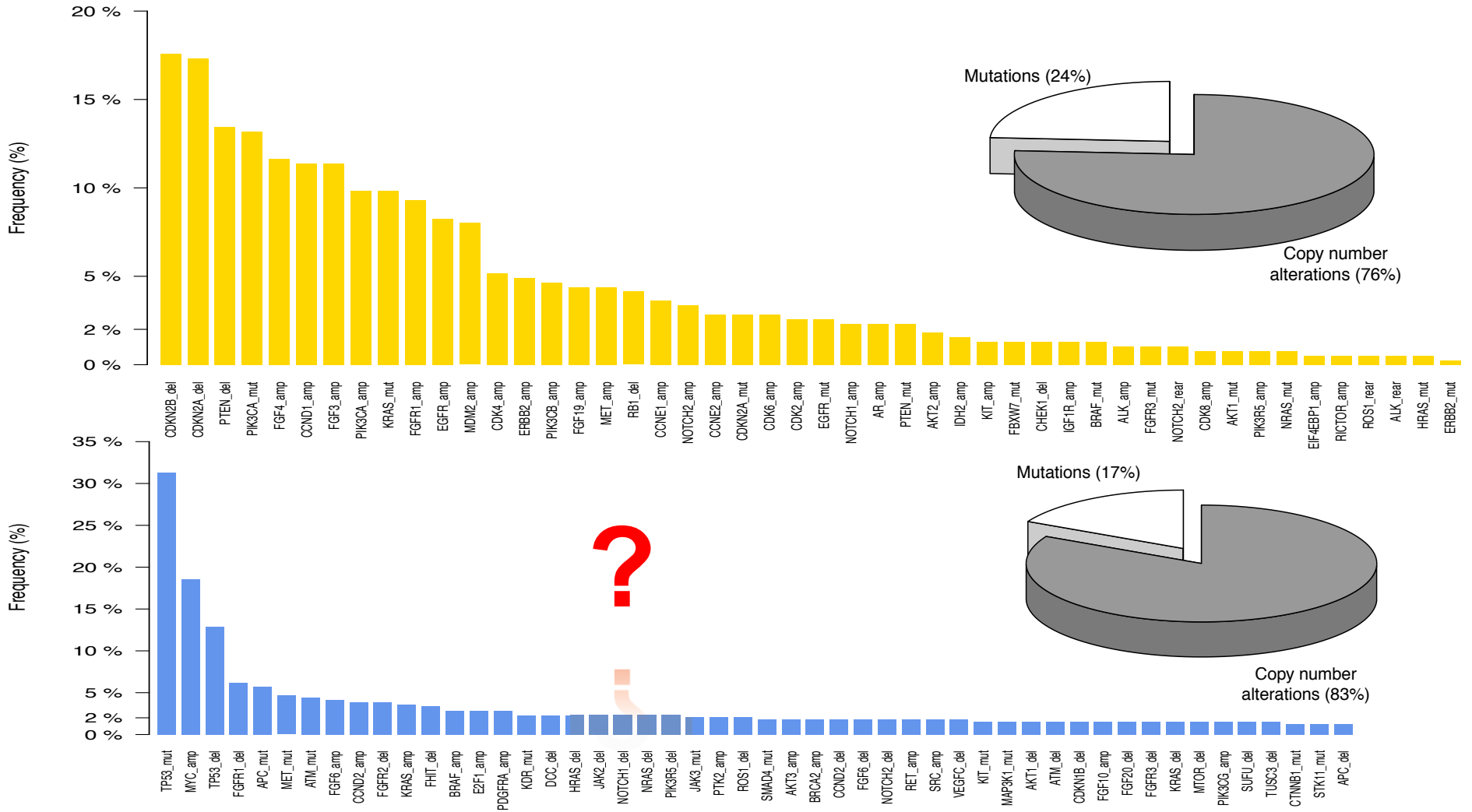
Kostenko A et al. - ESMO® 2015 – Abs.

High througpout molecular genotyping



Images: CGH and NGS analyses from the SAFIR lung Unicancer IFCT trial
PIs: JC Soria / F Barlesi

How large should be the analysis?



Ferte C et al, AACR 2014

How deep should be the analysis?

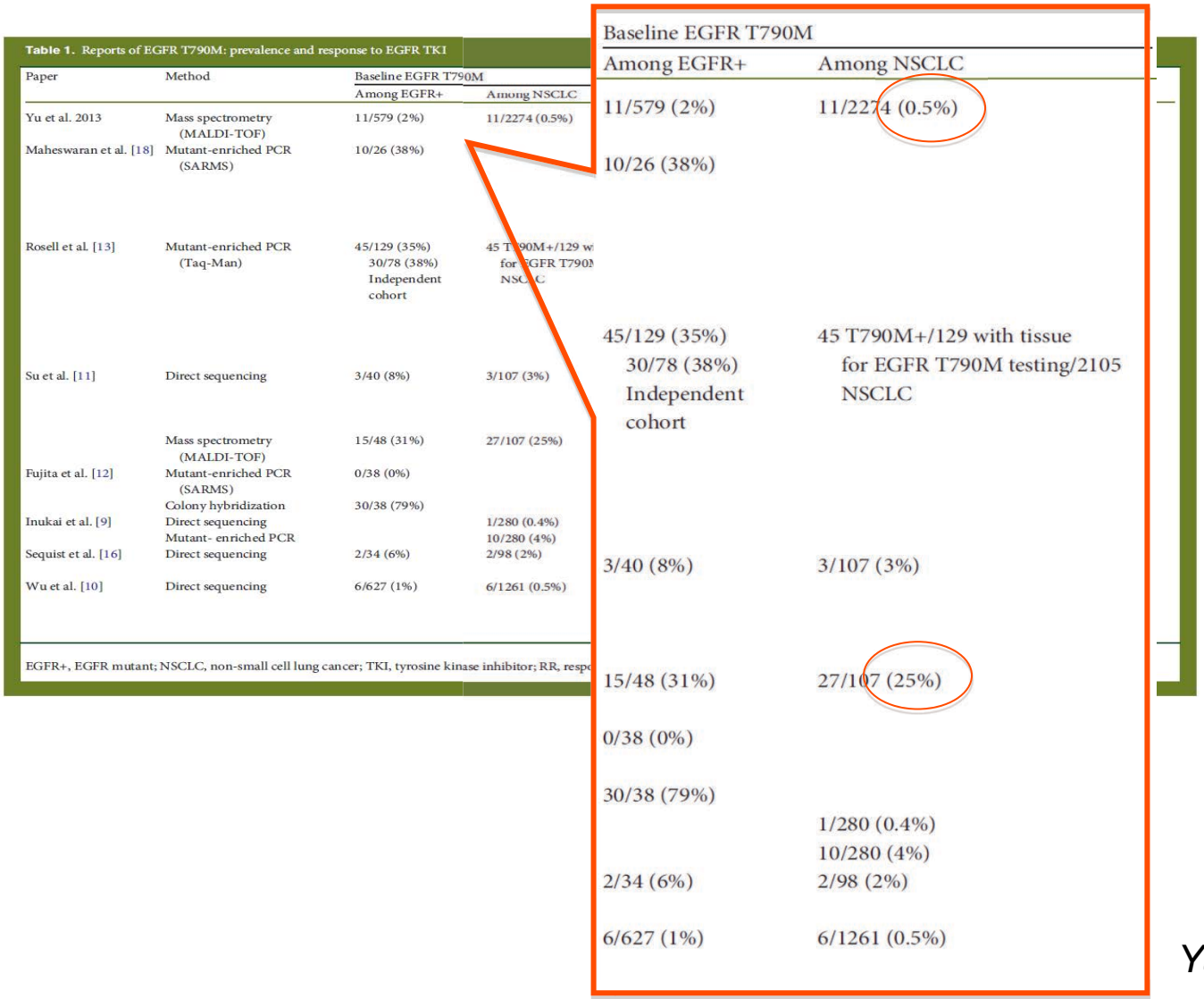


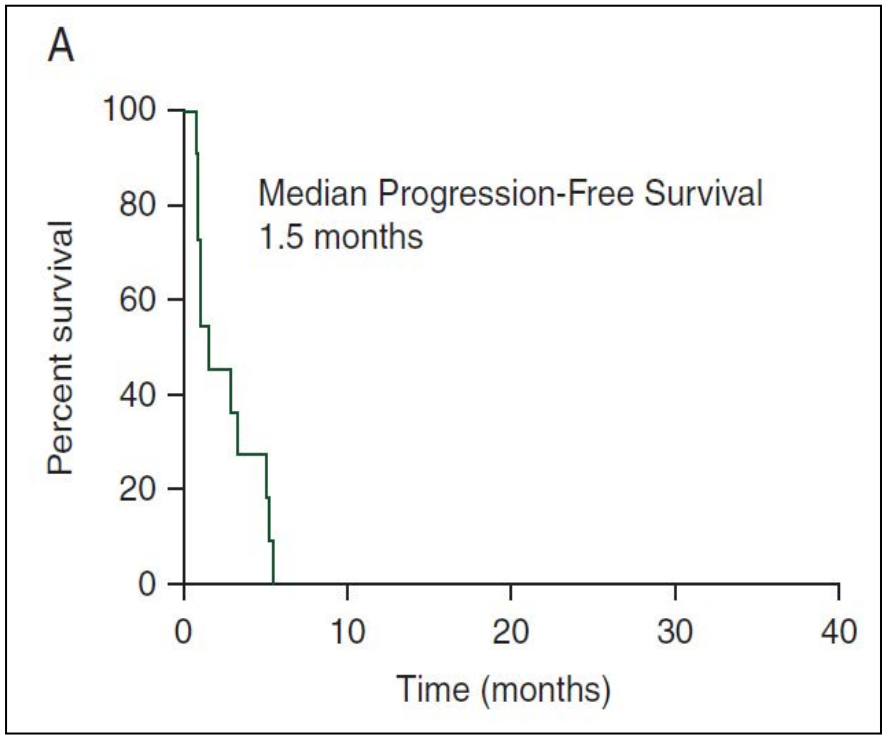
Table 1. Reports of EGFR T790M: prevalence and response to EGFR TKI

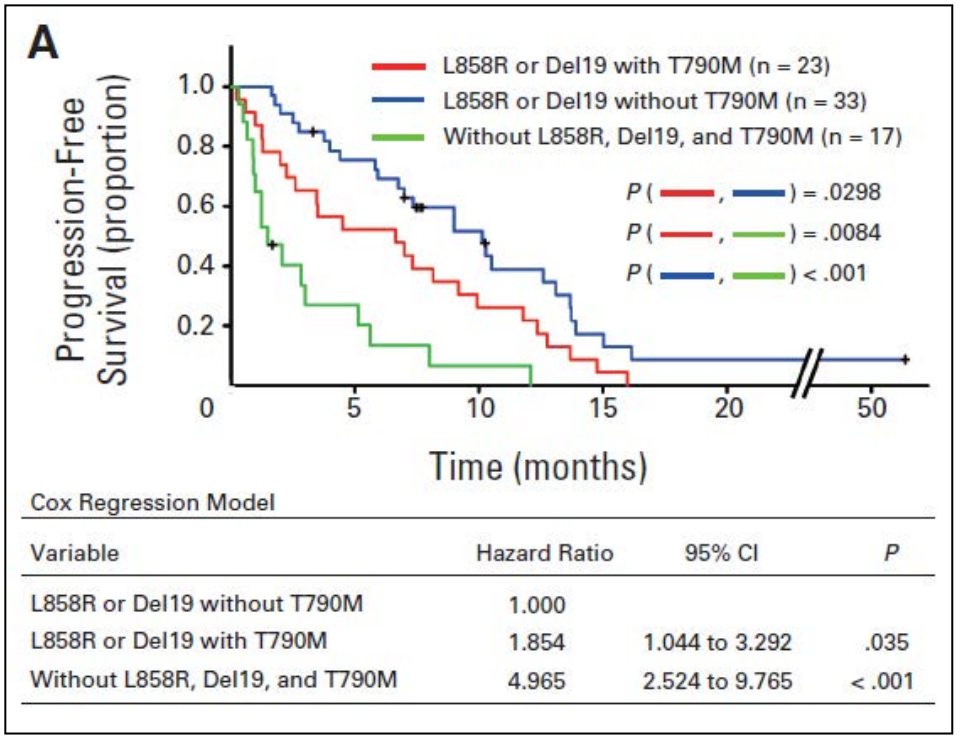
Paper	Method	Baseline EGFR T790M	
		Among EGFR+	Among NSCLC
Yu et al. 2013	Mass spectrometry (MALDI-TOF)	11/579 (2%)	11/2274 (0.5%)
Maheswaran et al. [18]	Mutant-enriched PCR (SARMS)	10/26 (38%)	
Rosell et al. [13]	Mutant-enriched PCR (Taq-Man)	45/129 (35%) 30/78 (38%) Independent cohort	45 T790M+/129 w for EGFR T790 NSCLC
Su et al. [11]	Direct sequencing	3/40 (8%)	3/107 (3%)
	Mass spectrometry (MALDI-TOF)	15/48 (31%)	27/107 (25%)
Fujita et al. [12]	Mutant-enriched PCR (SARMS)	0/38 (0%)	
	Colony hybridization	30/38 (79%)	
Inukai et al. [9]	Direct sequencing		1/280 (0.4%)
	Mutant- enriched PCR		10/280 (4%)
Sequist et al. [16]	Direct sequencing	2/34 (6%)	2/98 (2%)
Wu et al. [10]	Direct sequencing	6/627 (1%)	6/1261 (0.5%)

EGFR+, EGFR mutant; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; RR, respo

Yu HA et al, Ann Oncol 2014

How deep should be the analysis?





Cox Regression Model

Variable	Hazard Ratio	95% CI	P
L858R or Del19 without T790M	1.000		
L858R or Del19 with T790M	1.854	1.044 to 3.292	.035
Without L858R, Del19, and T790M	4.965	2.524 to 9.765	< .001

PFS of EGFRmut patients w de novo T790M mutation by **standard sequencing** (1.5 months)

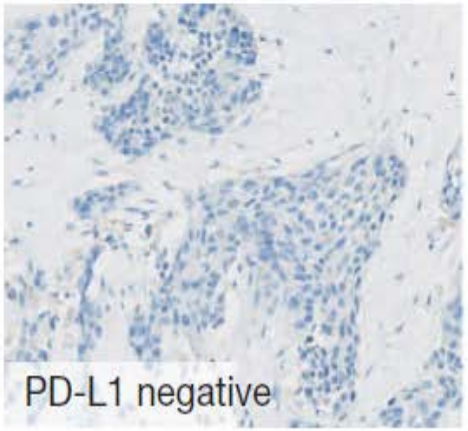
PFS of EGFRmut patients w de novo T790M mutation by **highly sensitive technics** (6.7 months)

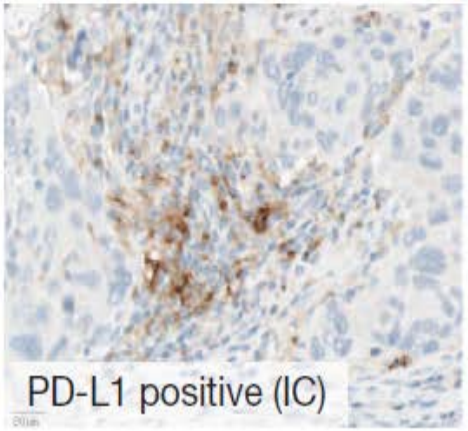
Yu HA et al, Ann Oncol 2014; Su KY et al, J Clin Oncol 2012

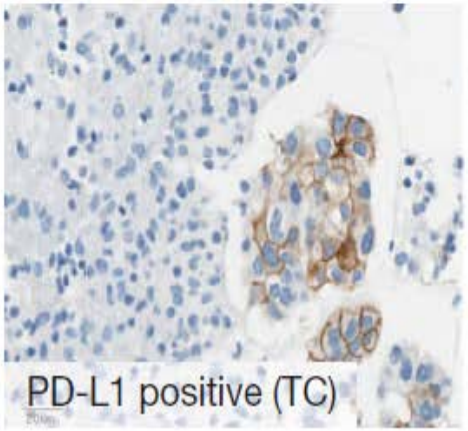
PD-L1 expression (example)

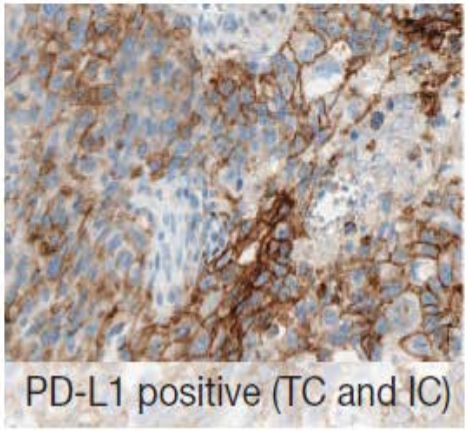
PD-L1 prevalence determined with a Genentech/Roche anti-PD-L1 IHC assay

Indication	*n*	Percentage of PD-L1 positive (IC)	Percentage of PD-L1 positive (TC)
NSCLC	184	26	24
RCC	88	25	10
Melanoma	58	36	5
HNSCC	101	28	19
Gastric cancer	141	18	5
CRC	77	35	1
Pancreatic cancer	83	12	4


PD-L1 negative


PD-L1 positive (IC)


PD-L1 positive (TC)


PD-L1 positive (TC and IC)

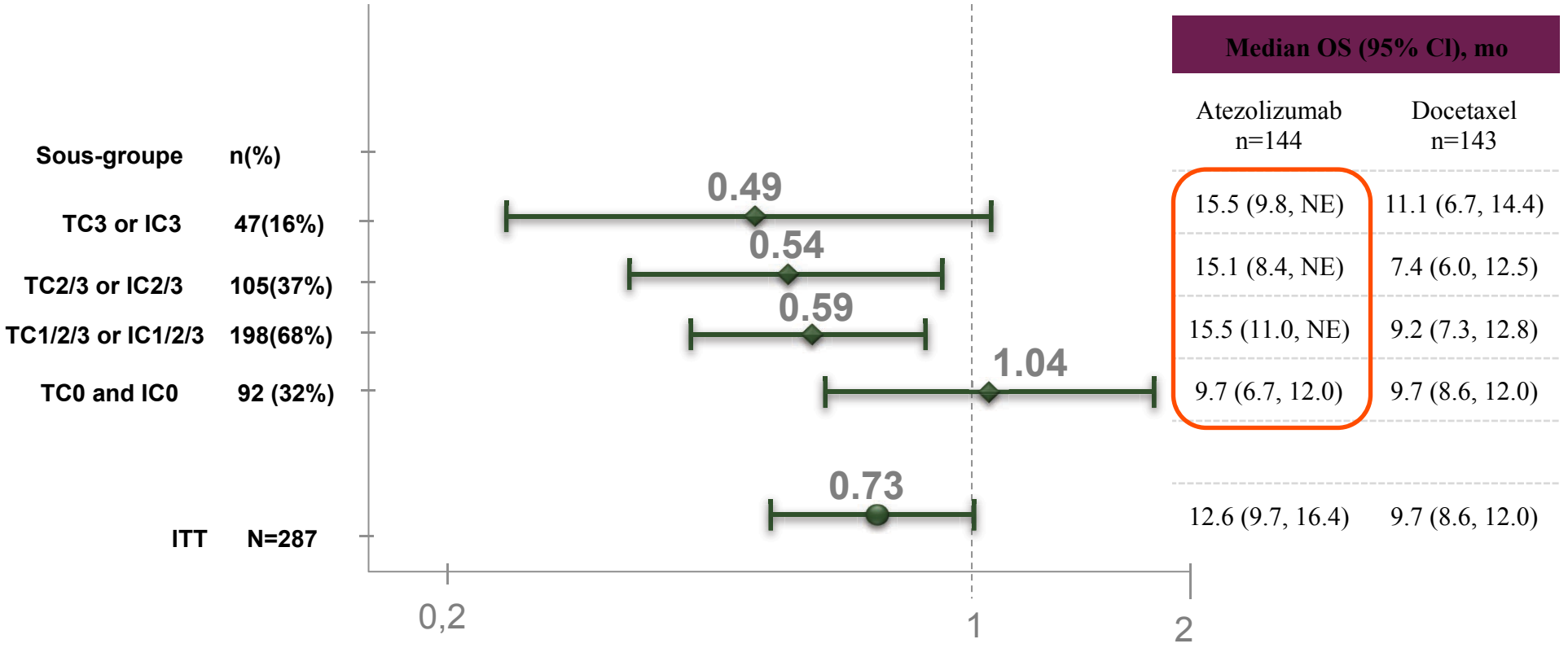
Herbst R et al, Nature 2015

PD-L1 expression (heterogeneity)

Drug	Biomarker antibody	Rx line	Definition of 'Positive' #	N Positive %	Positive Predictive outcome	ORR % IHC pos cases	ORR % IHC neg cases
Nivolumab	Dako 28-8	1st	≥5% in >100 cells	59%	Yes	31%*	10%
Nivolumab	Dako 28-8	≥2nd	≥5% ≥1%	49% 56%	No	15% 13%	14% 17%
Nivolumab + Ipilimumab	Dako 28-8	1st	≥5% in >100 cells	42%	No	19%	14%
Nivolumab	Dako 28-8	≥2nd	≥5%	33%##	Yes	24%	14%
Nivolumab	5H1 **	≥2nd	≥5% Also studied TIICs	67%	Yes	*No data For lung*	*No data For lung*
Pembrolizumab	Dako 22C3	any	'Strong' ≥50% 'Weak' 1-49%%	25% 70%	Yes Yes	37% 17%	9%
Pembrolizumab	Dako 22C3	1st	≥50% ≥1%	?	Yes	47% 26%	?
MPDL3280A	Roche Ventana SP142	≥2nd	≥10% TIICs*** ≥5% TIICs ≥1% TIICs	13% 28% 56%	Yes	83% 46% 31%	18% 18% 20%
MEDI-4736	Roche Ventana SP263	≥2nd	*Data not available*	41%	yes	25%	3%

Kerr K et al, J Thorac Oncol (in press)

PD-L1 expression (prediction/POPLAR)



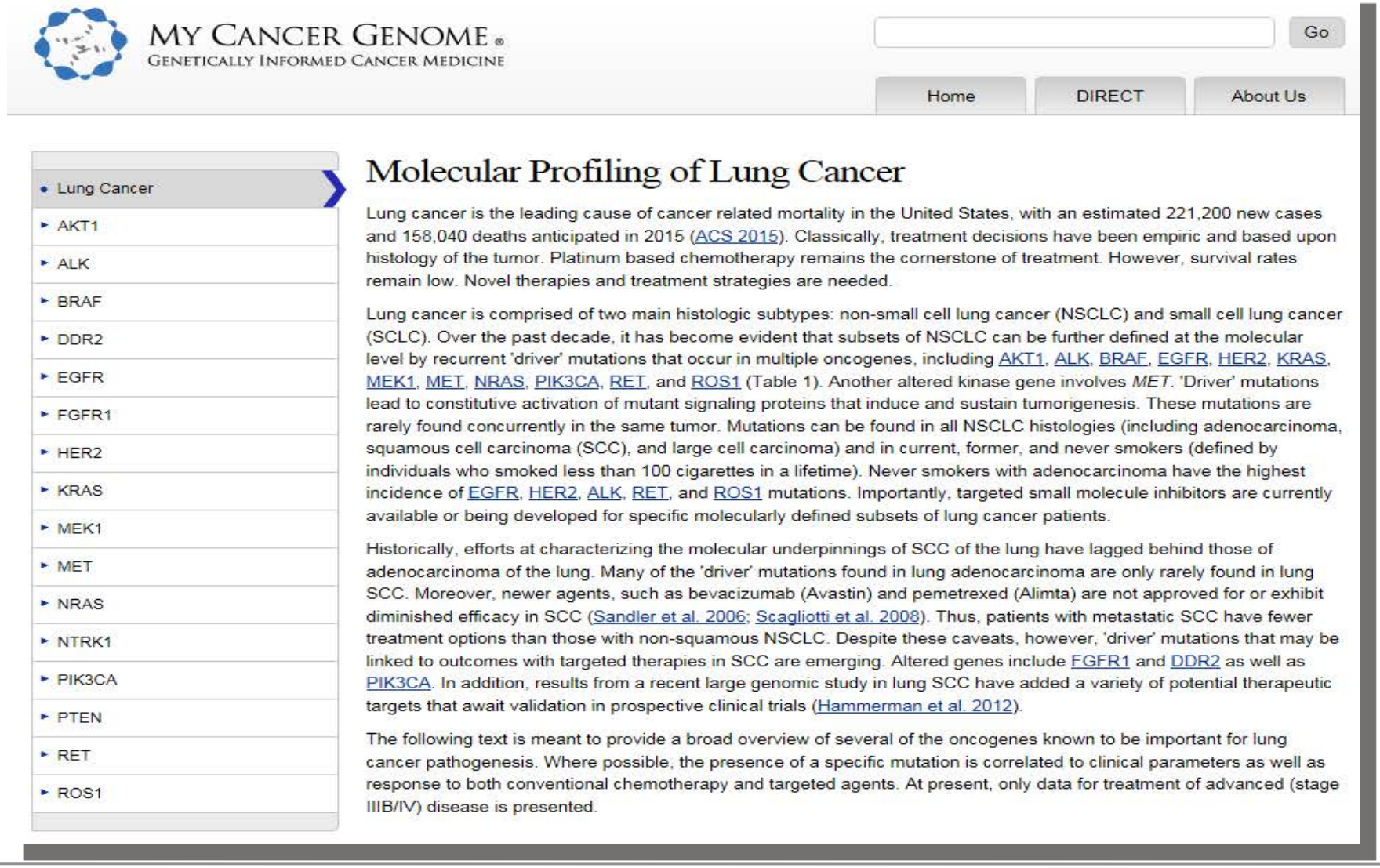
Vansteenkiste J. et al. - ESMO® 2015 - Abs. LBA 14

Target(s) choice(s)

Gene	Status (M, C or F)*	Frequency (%)		Available GEMMs	Currently available targeted therapies	Selected potential targeted therapies
		ADC	SCC			
Receptor tyrosine kinases						
EGFR	M or C	10 (M)	2–3	L858R, Del19, T790M and Ins20	Erlotinib, gefitinib and afatinib	AZD9291, CO-1686 and HM61713
FGFR1	C	N/A	20	N/A	N/A	Dovitinib, ponatinib, AZD4547 and BGJ398
FGFR2	M or C	3 (M)	3	N/A	N/A	Dovitinib, ponatinib, AZD4547 and BGJ398
ALK	F	3–5	<1	ALK fusion, L1196M and F1174L	Crizotinib and ceritinib	AP26113, alectinib, ganetespib and PF-06463922
MET	C	2–4	N/A	Overexpression	Crizotinib	Tivantinib, cabozantinib, INC280 and onartuzumab
ROS1	F	1–2	N/A	N/A	Crizotinib	PF-06463922
NTRK1	F	1–2	N/A	N/A	N/A	Crizotinib and lestaurtinib
RET	F	1	N/A	N/A	N/A	Carbozantinib and vandetanib
HER2	M or C	2–4 (M)	N/A	HER2-YVMA insertion	N/A	Neratinib, afatinib, lapatinib and trastuzumab
DDR2	M	N/A	2–3	N/A	N/A	Dasatinib
PDGFRA	M	6–7	4	N/A	N/A	Sunitinib
Signalling						
KRAS	M	15–25	1–2	G12D, G12C and G12V	N/A	Selumetinib plus docetaxel combination
NF1	M	12	10	Null	N/A	
BRAF	M	1–6	4–5	V600E	N/A	Vemurafenib, dabrafenib and trametinib
PIK3CA	M	5	15	p110α	N/A	BEZ235, BKM120 and GDC0941
MEK1	M	1	N/A	N/A	N/A	Selumetinib and trametinib
NOTCH1	M	8	1	Conditional null	N/A	N/A
Epigenetic factors						
MLL2	M	9	20	N/A	N/A	N/A
EZH2	M	2	2	N/A	N/A	N/A
TET2	M	3	2	N/A	N/A	N/A
DNMT3A	M	4	1	N/A	N/A	N/A
Transcription factors						
SOX2	C	6	65	Overexpression	N/A	N/A
MYC	C	25	N/A	Overexpression	N/A	N/A
Proteolysis						
KEAP1	M	17	12	N/A	N/A	N/A
Cell cycle						
CDKN2A	M	7	15	Null	N/A	N/A
Ligand						
NRG1	F	<1	N/A	N/A	N/A	N/A
Tumour suppressor						
TP53	M	52	79	Conditional null and R172H	N/A	N/A
LKB1	M	9	2	Conditional null	N/A	N/A
PTEN	M	2	8	Conditional null	N/A	BEZ235, BKM120 and GDC0941

Chen Z et al, Nat Rev Cancer 2014

Target(s) choice(s)?



MY CANCER GENOME ®
GENETICALLY INFORMED CANCER MEDICINE

Go

Home | DIRECT | About Us

- Lung Cancer
- AKT1
- ALK
- BRAF
- DDR2
- EGFR
- FGFR1
- HER2
- KRAS
- MEK1
- MET
- NRAS
- NTRK1
- PIK3CA
- PTEN
- RET
- ROS1

Molecular Profiling of Lung Cancer

Lung cancer is the leading cause of cancer related mortality in the United States, with an estimated 221,200 new cases and 158,040 deaths anticipated in 2015 (ACS 2015). Classically, treatment decisions have been empiric and based upon histology of the tumor. Platinum based chemotherapy remains the cornerstone of treatment. However, survival rates remain low. Novel therapies and treatment strategies are needed.

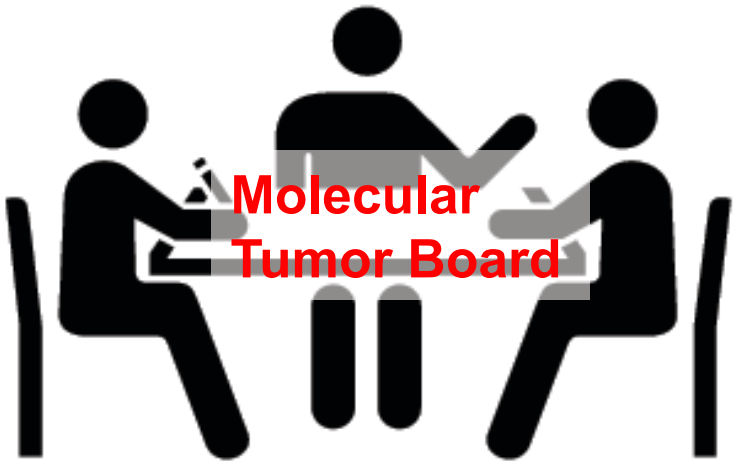
Lung cancer is comprised of two main histologic subtypes: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Over the past decade, it has become evident that subsets of NSCLC can be further defined at the molecular level by recurrent 'driver' mutations that occur in multiple oncogenes, including AKT1, ALK, BRAF, EGFR, HER2, KRAS, MEK1, MET, NRAS, PIK3CA, RET, and ROS1 (Table 1). Another altered kinase gene involves *MET*. 'Driver' mutations lead to constitutive activation of mutant signaling proteins that induce and sustain tumorigenesis. These mutations are rarely found concurrently in the same tumor. Mutations can be found in all NSCLC histologies (including adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma) and in current, former, and never smokers (defined by individuals who smoked less than 100 cigarettes in a lifetime). Never smokers with adenocarcinoma have the highest incidence of EGFR, HER2, ALK, RET, and ROS1 mutations. Importantly, targeted small molecule inhibitors are currently available or being developed for specific molecularly defined subsets of lung cancer patients.

Historically, efforts at characterizing the molecular underpinnings of SCC of the lung have lagged behind those of adenocarcinoma of the lung. Many of the 'driver' mutations found in lung adenocarcinoma are only rarely found in lung SCC. Moreover, newer agents, such as bevacizumab (Avastin) and pemetrexed (Alimta) are not approved for or exhibit diminished efficacy in SCC (Sandler et al. 2006; Scagliotti et al. 2008). Thus, patients with metastatic SCC have fewer treatment options than those with non-squamous NSCLC. Despite these caveats, however, 'driver' mutations that may be linked to outcomes with targeted therapies in SCC are emerging. Altered genes include FGFR1 and DDR2 as well as PIK3CA. In addition, results from a recent large genomic study in lung SCC have added a variety of potential therapeutic targets that await validation in prospective clinical trials (Hammerman et al. 2012).

The following text is meant to provide a broad overview of several of the oncogenes known to be important for lung cancer pathogenesis. Where possible, the presence of a specific mutation is correlated to clinical parameters as well as response to both conventional chemotherapy and targeted agents. At present, only data for treatment of advanced (stage IIIB/IV) disease is presented.

Target(s) choice(s)

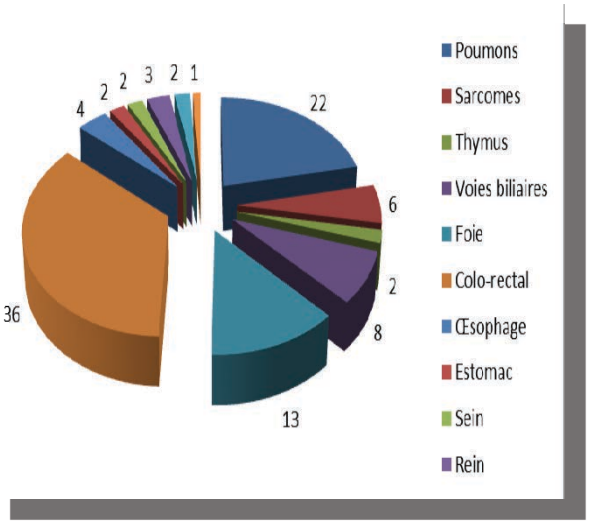
Oncologists

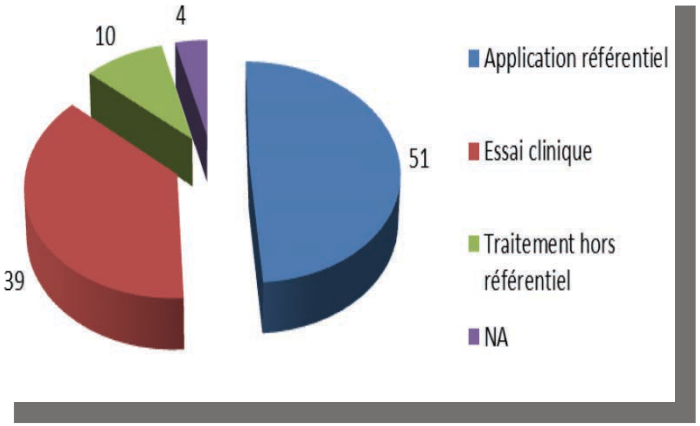


Bio-mathematicians

Biologists

Pathologists





RCPbiomol@ap-hm.fr *; Coordination F Barlesi, S Garcia, C Mascaux, L Ouafik*

Centres Labélisés INCa de Phases Précoces

INSTITUT NATIONAL DU CANCER

Appel à candidature 2015 " Labellisation de centres d'essais cliniques de phase précoce en cancérologie adulte/pédiatrique (CLIP² 2015-2019)"

Centres d'essais cliniques de phase précoce labellisés par l'INCa

Etablissement de Rattachement du CLIP²	CLIP²	Site principal du CLIP²	Coordonnateur du projet CLIP²	Services ou Sites Partenaires
Centre Léon Bérard LYON	Adultes/Enfants	Unité de Phase Précoce Adulte Centre Léon Bérard	Dr Philippe CASSIER Dr Didier FRAPPAZ (Pédiatrie)	- Unité de Phase Précoce Pédiatrique, Institut d'Hématologie et d'Oncologie Pédiatrique - Centre Léon Bérard
Institut Gustave Roussy VILLEJUIF		Département d'Innovations Thérapeutiques et d'Essais Précoces (DITEP) Gustave Roussy	Pr Jean-Charles SORIA Dr Birgit GEOERGER (Pédiatrie)	- Département de Cancérologie de l'enfant et de l'adolescent, Gustave Roussy - Département d'Hématologie et d'Oncologie Pédiatrique, Hôpital Armand Trousseau, AP-HP - Département d'Hématologie et d'Immunologie Pédiatrique, Hôpital Robert Debré, AP-HP
Centre de Référence Régional en Cancérologie - GCS C2RC LILLE		- Centre d'Investigation Clinique, CIC 1403 INSERM, Hôpital Cardiologique, CHRU Lille - Unité de Recherche Clinique - Centre Oscar Lambret	Pr Thierry FACON Dr Brigitte NELKEN (Pédiatrie) Dr Nicolas PENEL Dr Pierre LEBLOND (Pédiatrie)	- Département d'Hématologie, Hôpital Claude Huriez, CHRU Lille - Département de Pneumologie et d'Oncologie Thoracique, Hôpital Albert Calmette, CHRU Lille - Département d'Oncologie Médicale, Hôpital Claude Huriez, CHRU Lille - Département de Dermatologie, Hôpital Claude Huriez, CHRU Lille - Centre d'Investigation Clinique - CIC 1403, unité pédiatrique, Hôpital Jeanne de Flandres, CHRU Lille - Unité de Recherche Clinique et Unité Pédiatrique, Centre Oscar Lambret
Assistance Publique des Hôpitaux de Marseille (AP-HM) MARSEILLE		Unité de Phase I d'Oncologie Hôpital de la Timone, AP-HM	Pr Fabrice BARLESI Dr Nicolas ANDRE (Pédiatrie)	- Unité d'Hématologie et d'Oncologie Pédiatrique, Hôpital de La Timone Enfants, AP-HM - Département de Dermatologie et Cancérologie Cutanée, Hôpital de La Timone, AP-HM - Département d'Oncologie Digestive et Hépato-Gastro-Entérologie, Hôpital de La Timone, AP-HM - Département d'Oncologie Médicale, Hôpital de La Timone, AP-HM - Département d'Oncologie Multidisciplinaire et Innovations Thérapeutiques, Hôpital Nord, AP-HM - Département de Neuro-Oncologie, Hôpital de La Timone, AP-HM - Unité d'Hématologie et Thérapie Cellulaire, Hôpital de La Conception, AP-HM
Institut Curie PARIS		Unité d'essais Cliniques Institut Curie	Dr Christophe LE TOURNEAU Pr François DOZ (Pédiatrie)	- Département d'Oncologie Pédiatrique, Adolescents et Jeunes Adultes, Institut Curie
Groupement de coopération sanitaire - Institut régional du cancer Nantes-Atlantique (GCS IRCNA) NANTES		- Département d'Hématologie Hôtel Dieu, CHU Nantes - Unité de Développement Thérapeutique Précoce Institut de Cancérologie de l'Ouest	Pr Steven LE GOUILL Pr Mario CAMPONE Dr Nadège CORRADINI (Pédiatrie)	- Département d'Oncologie Pédiatrique, Hôtel Dieu, CHU Nantes - Département d'Onco-Dermatologie, Hôtel Dieu, CHU Nantes - Département d'Oncologie Nucléaire, CHU Nantes et Institut de Cancérologie de l'Ouest

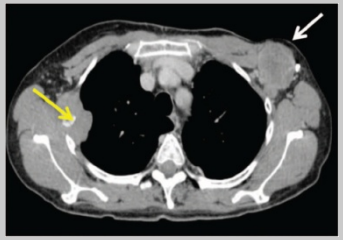
CENTRE D'ESSAIS PRÉCOCES EN CANCÉROLOGIE DE MARSEILLE

CUP 2

IFCT – Unicancer SAPHIR02L trial

Stage IV
NSCLC
No EGFRm
No ALK

Fresh biopsy @ 2 cycles max
- CGH
- NGS



@ 4 cycles

R

Bioguided Rx
(AZ pipeline: AZD2014, AZD4547, AZD5363, AZD8931, selumetinib, vandetanib)

Until PRG

Standard Cx
PMX (nSQ)
ERL (SQ)

EXIT

No molecular alteration *or* Progression

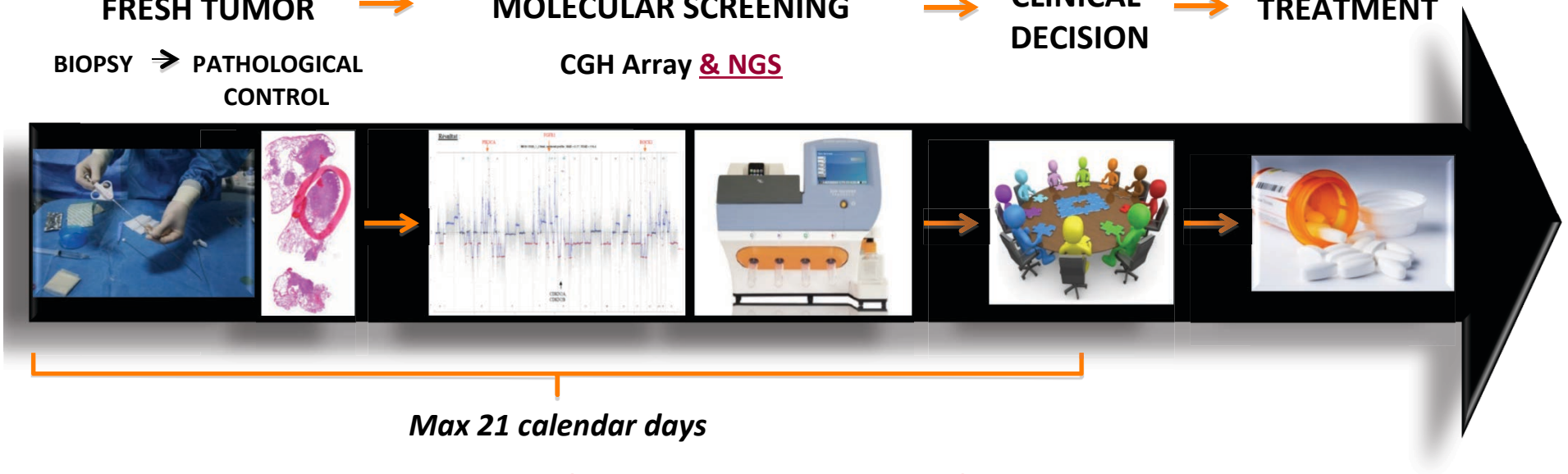
Pis JC Soria / F Barlesi

Turn around time: MOSCATO trial (G Roussy)

FRESH TUMOR → **MOLECULAR SCREENING** → **CLINICAL DECISION** → **TREATMENT**

BIOPSY → PATHOLOGICAL CONTROL

CGH Array & NGS



Max 21 calendar days

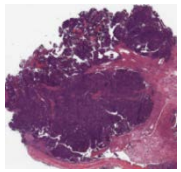
Median 14 days (95% CI: 7-35 days)

Hollebecque A et al, ASCO 2013

Turn around time: Match trial (NCI)

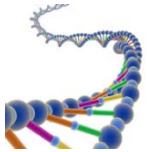
Biopsy Received

Tissue Fixation Path Review



Tumor content >70%

1 DAY **Nucleic Acid Extraction**



DNA/RNA yields > 20 ng

1 DAY **Library/Template Prep**

Library yield > 20 pM

1 DAY **Sequencing , QC Checks**

Test fragments
Total read
Reads per BC
Coverage
NTC, Positive, Negative Controls

1 DAY **Centralized Data Analysis** aMOIs identified

3 DAYS **Clinical Laboratory aMOI Verification**

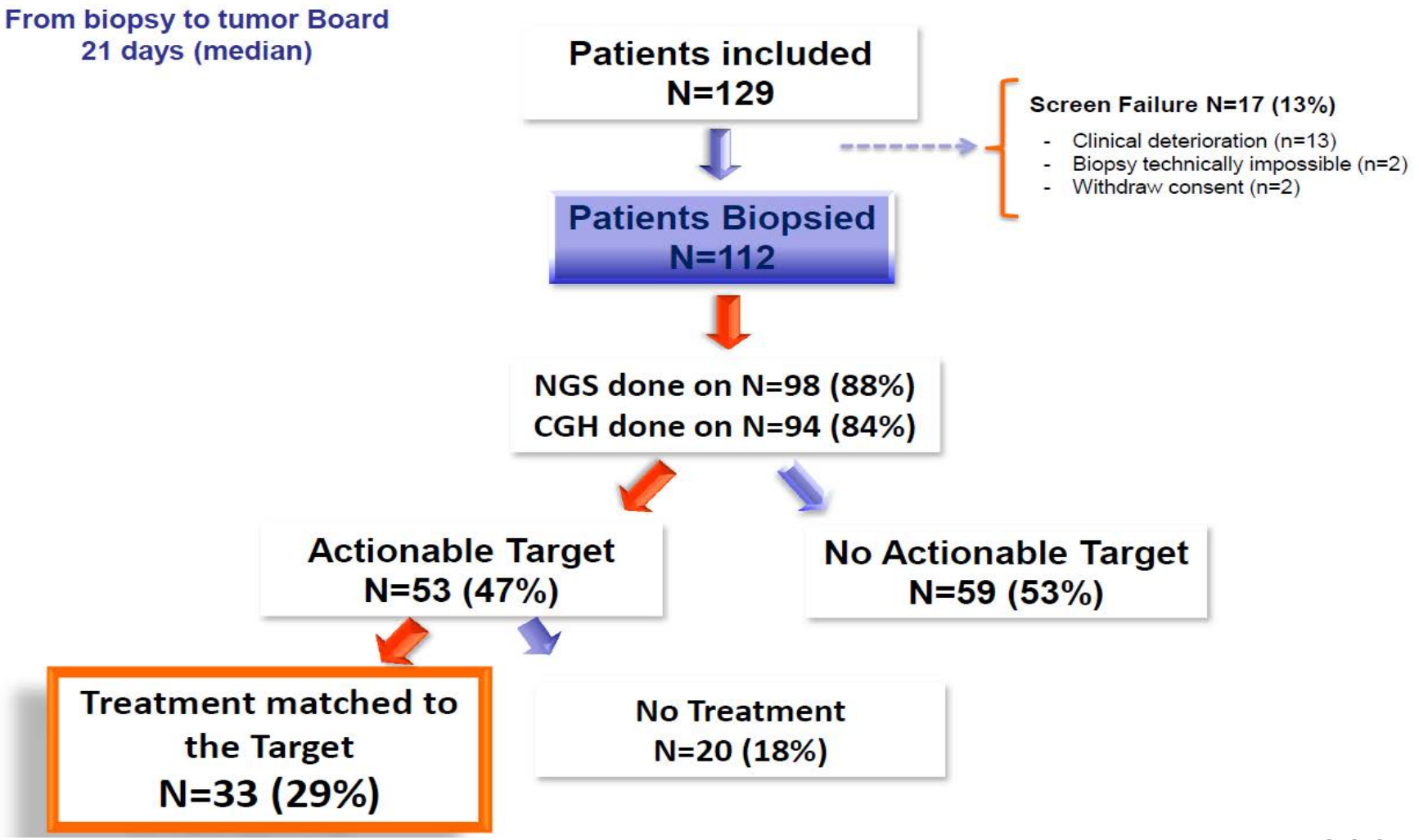
10-14 days **Treatment Selection**

Turn around time: experience in France

- **Daily practice (standard sequencing)**
  - Bringing the sample to the lab(s): 8 days
  - Report of analyses results: 11 days
- **SAFIR 02 lung trial (NGS and CGH)**
  - Maximum of 6 wks to get the MTB decision
  - To date: less than 0.5% failure rate

Barlesi et al, Biomarkers France, Lancet 2015 (in press); Unicancer, data on file

Targeted drugs access



Hollebecque A et al, ASCO 2013

Agenda

- Pharmaco-génomique
- **Pharmaco-cinétique**
- Pharmaco-génétique
- Perspectives

Un nouvel outil de personnalisation

Evidence for Therapeutic Drug Monitoring of Targeted Anticancer Therapies

Bo Gao, Shang Yeap, Arthur Clements, Bavanthi Balakrishnar, Mark Wong, and Howard Gurney

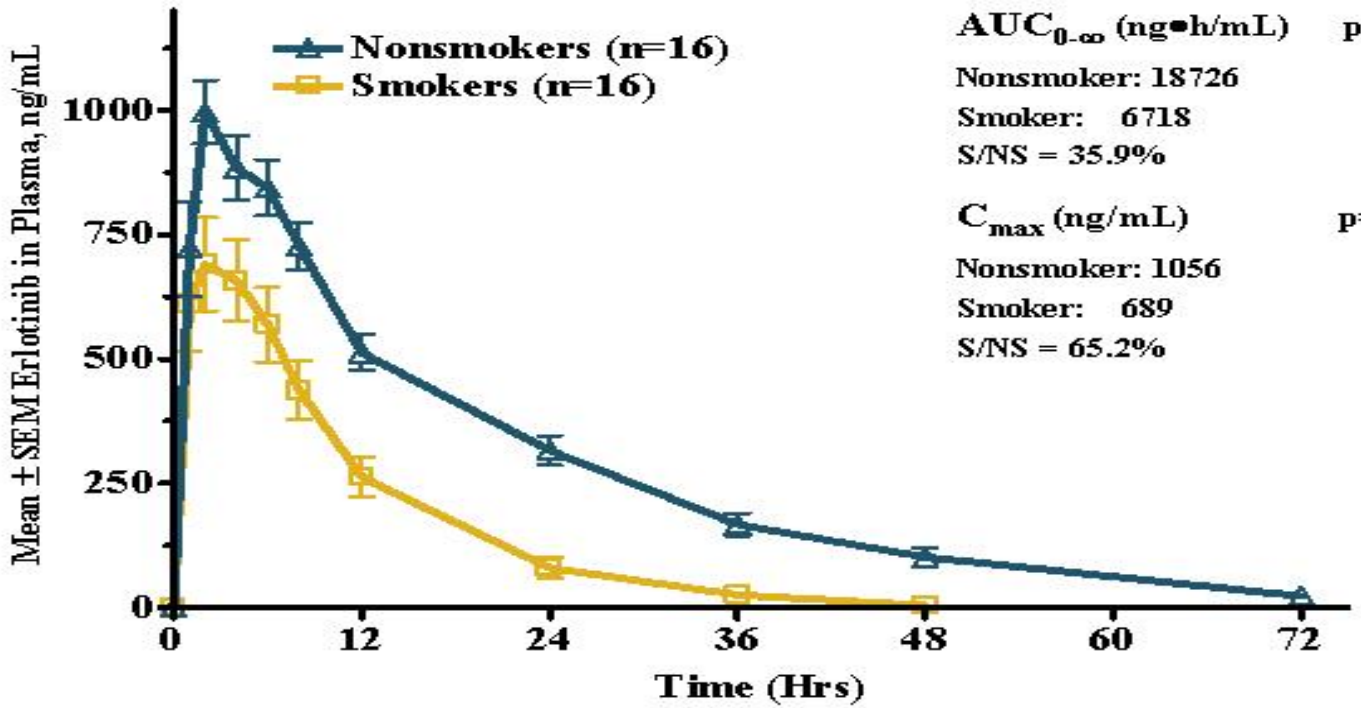
A B S T R A C T

Therapeutic drug monitoring (TDM) provides valuable guidance for dose adjustment of antibiotics, immunosuppressives, antiepileptics, and other drugs, but its use for traditional anticancer therapies has been limited. Perhaps the most important obstacle is the impractical requirement of multiple blood samples to adequately define systemic exposure of drugs that have a short elimination half-life and are given by intermittent intravenous injections. However, the newer targeted anticancer therapies have different pharmacokinetic (PK) and dosing characteristics compared with traditional cytotoxic drugs, making it possible to estimate the steady-state drug exposure with a single trough-level measurement. Recent evidence indicates that certain PK parameters, including trough levels, are correlated with clinical outcomes for many of these agents, including imatinib, sunitinib, rituximab, and cetuximab. Although the current evidence is insufficient to mandate TDM in routine practice, a concerted investigation should be encouraged to determine whether the steady-state trough measurements of targeted agents will have a practical place in the clinical care of patients with cancer.

Gao et al, J Clin Oncol 2012

Impact du tabac sur la dose de médicament

Single 150 mg Dose in Healthy Male Subjects



$AUC_{0-\infty}$ (ng•h/mL) p=<0.0001

Nonsmoker: 18726

Smoker: 6718

S/NS = 35.9%

C_{max} (ng/mL) p=0.0310

Nonsmoker: 1056

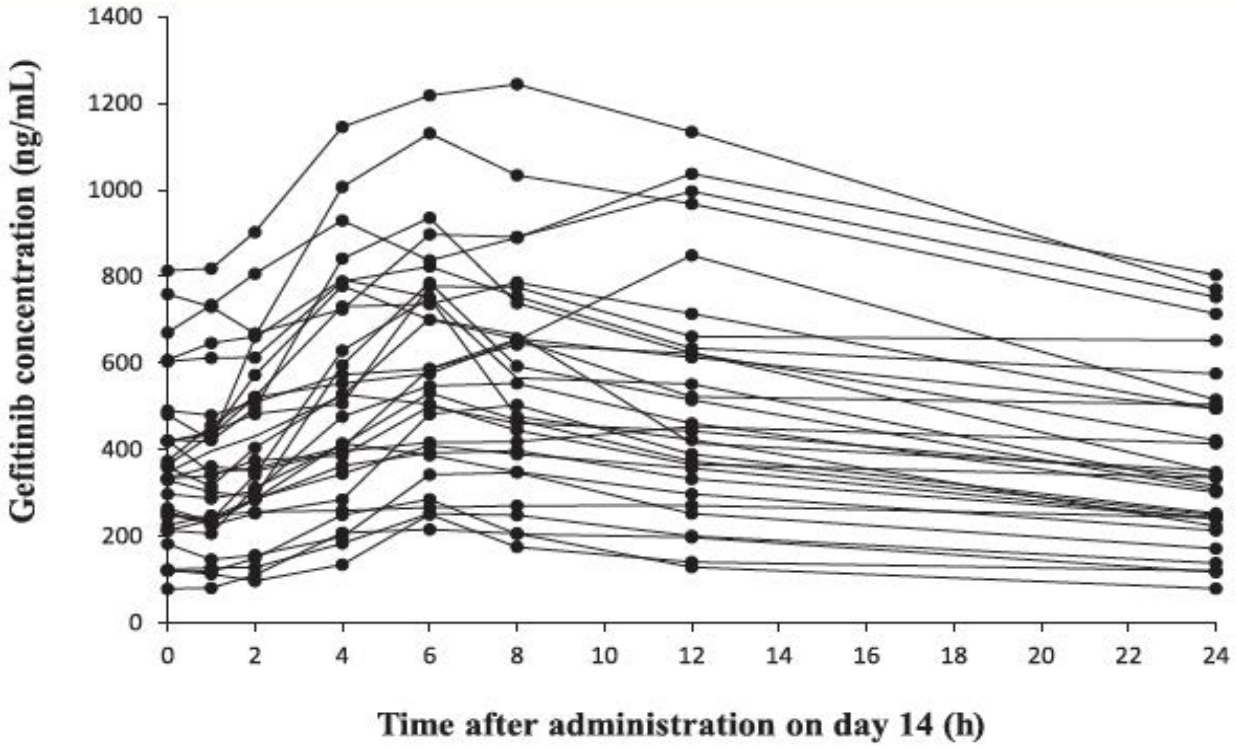
Smoker: 689

S/NS = 65.2%

Hamilton, CCR 2006

Impact de la dose sur la toxicité

Figure 1 Plasma Concentration-Time Profiles of Gefitinib in 31 Patients With Non–small-cell Lung Cancer Administered 250 mg of Gefitinib



Kobayashi H et al, Clin Lung Cancer 2015

Impact de la dose sur la toxicité

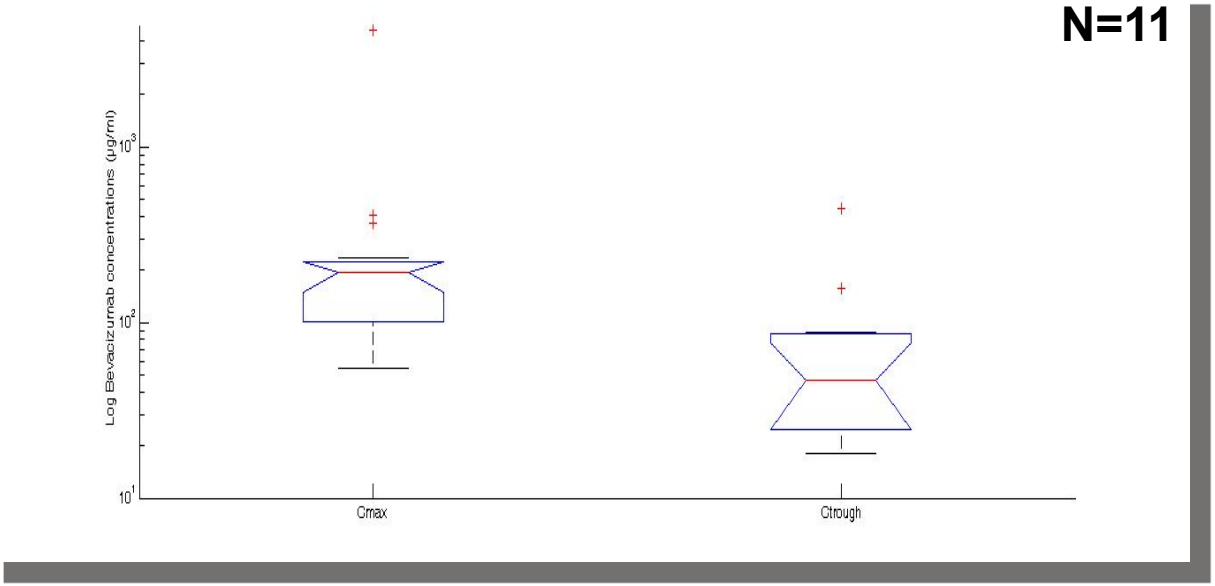
Table 2 Comparison of Pharmacokinetics Parameters of Gefitinib Among Cytochromes P450 and Drug-Transporter Genotype Groups

Study Group	Patients (n)	Gefitinib (250 mg/d)			
		AUC_{0-24} (ng·h/mL)	*P* Value	C_0 (ng/mL)	*P* Value
Gender			.242[a]		.211[a]
Male	13	9794 (3247-24,726)		329 (78-813)	
Female	18	11,396 (4360-21,591)		389 (120-759)	
EGFR mutation status			.710[a]		
Exon 19	14	10,565 (3247-21,591)		340 (78-670)	.710[a]
Exon 21	17	10,086 (3450-24,726)		334 (120-813)	
Side effects					
Diarrhea	15	14,246 (6226-24,726)	.006[a]	421 (213-813)	.002[a]
No diarrhea	16	8918 (3247-15,487)		261 (78-490)	
Skin rash	20	11,246 (3450-24,726)	.476[a]	341 (120-813)	.761[a]
No skin rash	11	9433 (3247-21,338)		333 (78-607)	
Hepatotoxicity (all grades)	17	12,967 (5634-21,591)	.024[a]	420 (182-759)	.002[a]
No hepatotoxicity	14	8473 (3247-24,726)		248 (78-813)	

Kobayashi H et al, Clin Lung Cancer 2015

Impact de la dose sur l'efficacité

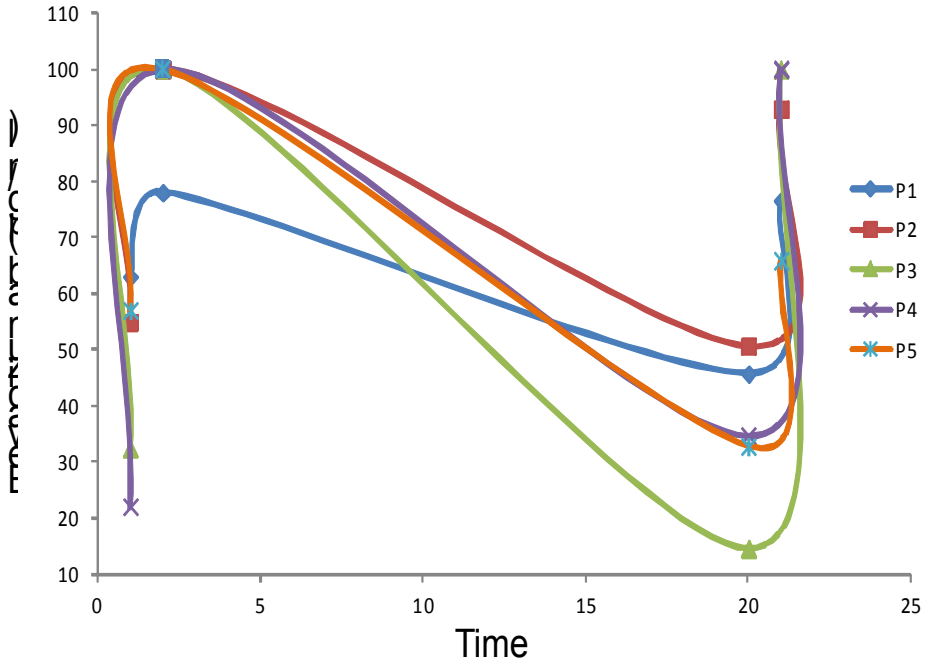
- **Variabilité (PK)**



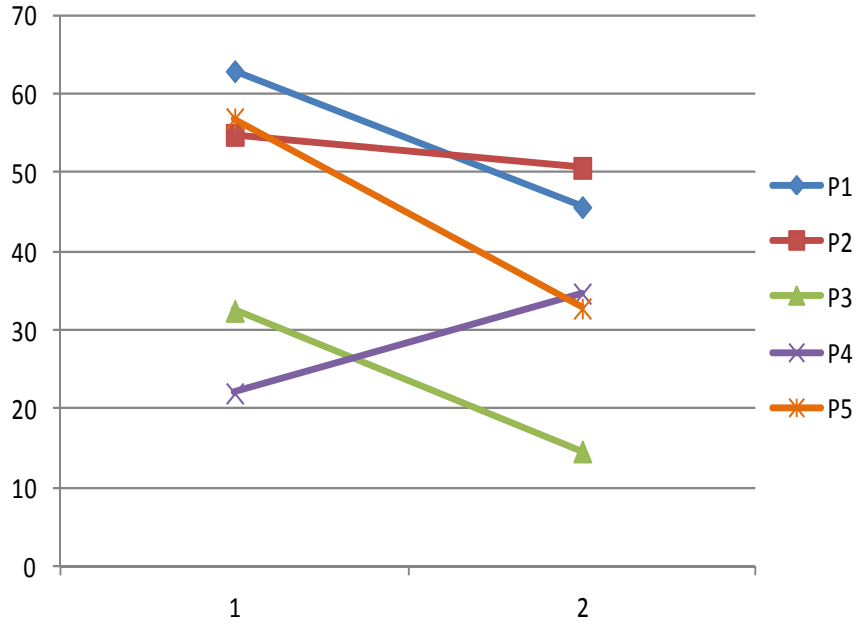
Inter-patient variability
242% (Cmax) and 133% (Ctrough)

Barlesi F / Ciccolini J, en cours

Impact de la dose sur l'efficacité



Variabilité inter-patient

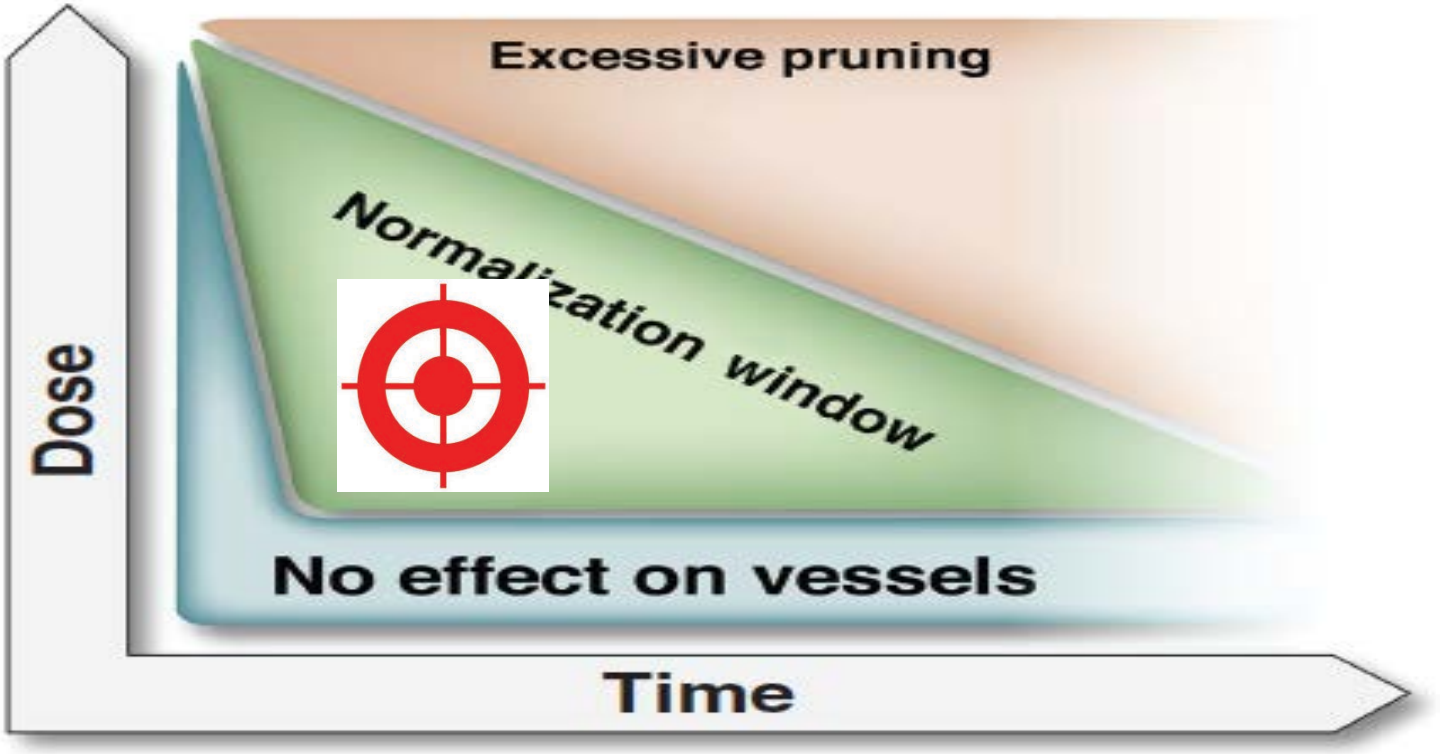


Variabilité intra-patient

Courtesy Joseph Ciccolini, presented at AACR 2014

Impact de la dose sur l'efficacité

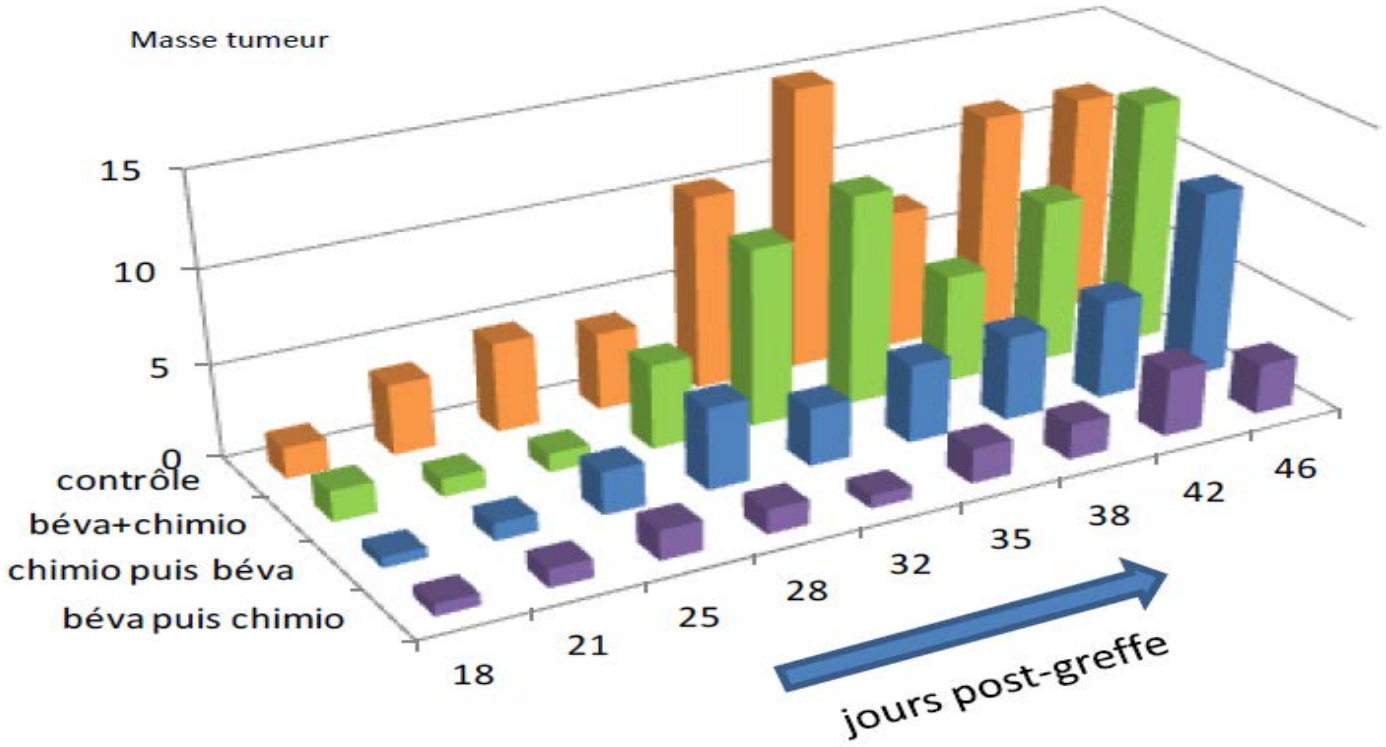
- **Dose optimale: drug monitoring?**



Jain R, J Clin Oncol 2013

Impact de la dose sur l'efficacité

- **Concept de normalisation vasculaire**



H460 Lung Cancer model

Serdjebi C/Ciccolini J, Lab Pharmacocinétique SMARTc, Inserm S_911

La précision jusqu'où ?

https://adrafinil.com

Agenda

- Pharmaco-génomique
- Pharmaco-cinétique
- **Pharmaco-génétique**
- Perspectives

Avons-nous tous le même métabolisme ?

Pharmacogenomic and Pharmacokinetic Determinants of Erlotinib Toxicity

Charles M. Rudin, Wanqing Liu, Apurva Desai, Theodore Karrison, Xuemin Jiang, Linda Janisch, Soma Das, Jacqueline Ramirez, Balasubramanian Poonkuzhali, Erin Schuetz, Donna Lee Fackenthal, Peixian Chen, Deborah K. Armstrong, Julie R. Brahmer, Gini F. Fleming, Everett E. Vokes, Michael A. Carducci, and Mark J. Ratain

A B S T R A C T

Purpose
To assess the pharmacogenomic and pharmacokinetic determinants of skin rash and diarrhea, the two primary dose-limiting toxicities of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor erlotinib.

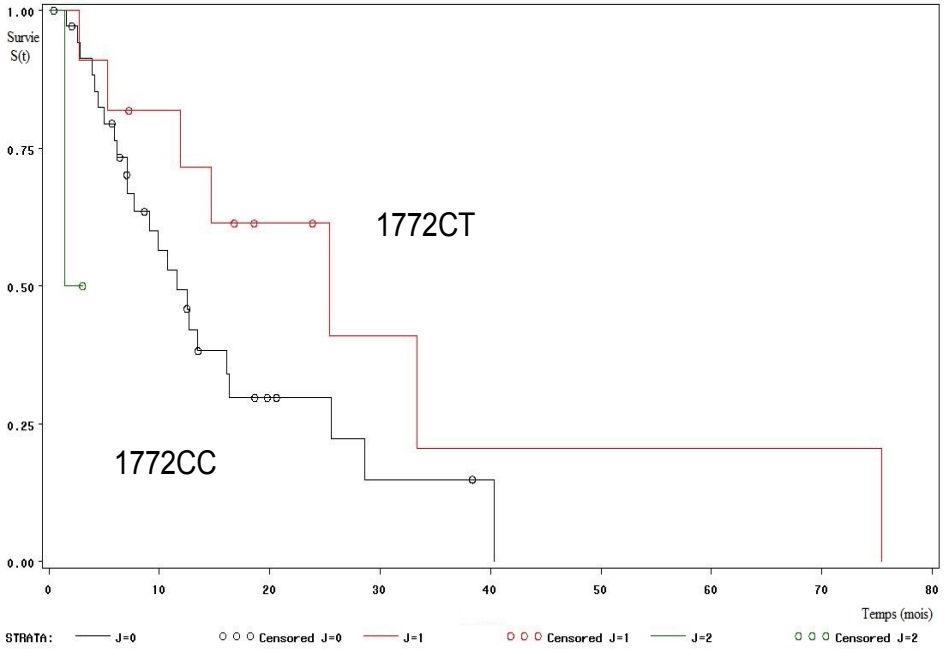
Patients and Methods
A prospective clinical study of 80 patients with non–small-cell lung cancer, head and neck cancer, and ovarian cancer was performed. Detailed pharmacokinetics and toxicity of erlotinib were assessed. Polymorphic loci in *EGFR*, *ABCG2*, *CYP3A4*, and *CYP3A5* were genotyped, and their effects on pharmacokinetics and toxicities were evaluated.

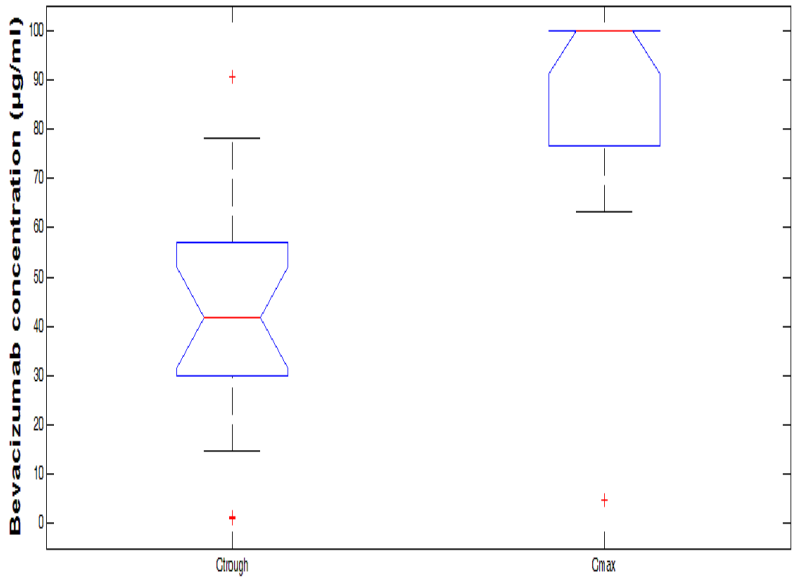
Results
A novel diplotype of two polymorphic loci in the *ABCG2* promoter involving −15622C/T and 1143C/T was identified, with alleles conferring lower ABCG2 levels associated with higher erlotinib pharmacokinetic parameters, including area under the curve ($P = .019$) and maximum concentration ($P = .006$). Variability in skin rash was best explained by a multivariate logistic regression model incorporating the trough erlotinib plasma concentration ($P = .034$) and the *EGFR* intron 1 polymorphism ($P = .044$). Variability in diarrhea was associated with the two linked polymorphisms in the *EGFR* promoter ($P < .01$), but not with erlotinib concentration.

Conclusion
Although exploratory in nature, this combined pharmacogenomic and pharmacokinetic model helps to define and differentiate the primary determinants of skin and gastrointestinal toxicity of erlotinib. The findings may be of use both in designing trials targeting a particular severity of rash and in considering dose and schedule modifications in patients experiencing dose-limiting toxicities of erlotinib or similarly targeted agents. Further studies of the relationship between germline polymorphisms in *EGFR* and the toxicity and efficacy of EGFR inhibitors are warranted.

J Clin Oncol 26:1119-1127.

Impact des caractéristiques génétiques





génotype 1772CC HIF1α associé à DFS

>60% de variabilité expositions sériques

Courtesy Joseph Ciccolini, presented at AACR 2014

Avons-nous tous le même métabolisme ?

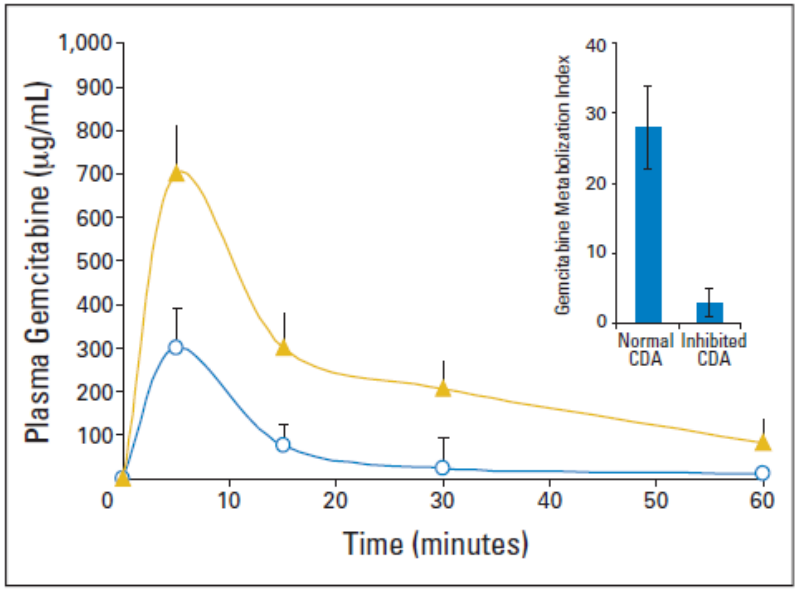


Fig 1. Plasma drug monitoring of gemcitabine in mice with normal cytidine deaminase (CDA; blue circle) and inhibited CDA (gold triangle). Gemcitabine (100 mg/kg) was administered intraperitoneally. CDA inhibition was achieved by pretreatreating animals with tetrahydrouridine (100 mg/kg). Inset: metabolization index of gemcitabine in mice with or without cytidine deaminase (CDA) inhibition. Metabolization index was calculated as the ratio of difluorodeoxyuridine to gemcitabine × 100.

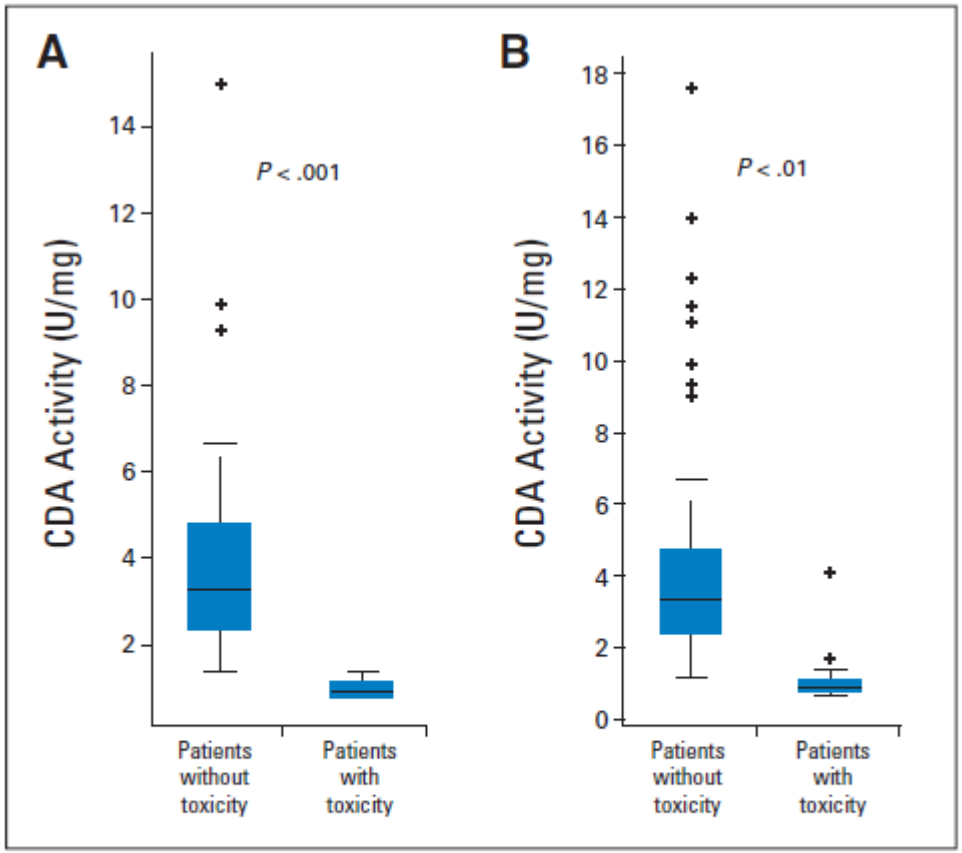


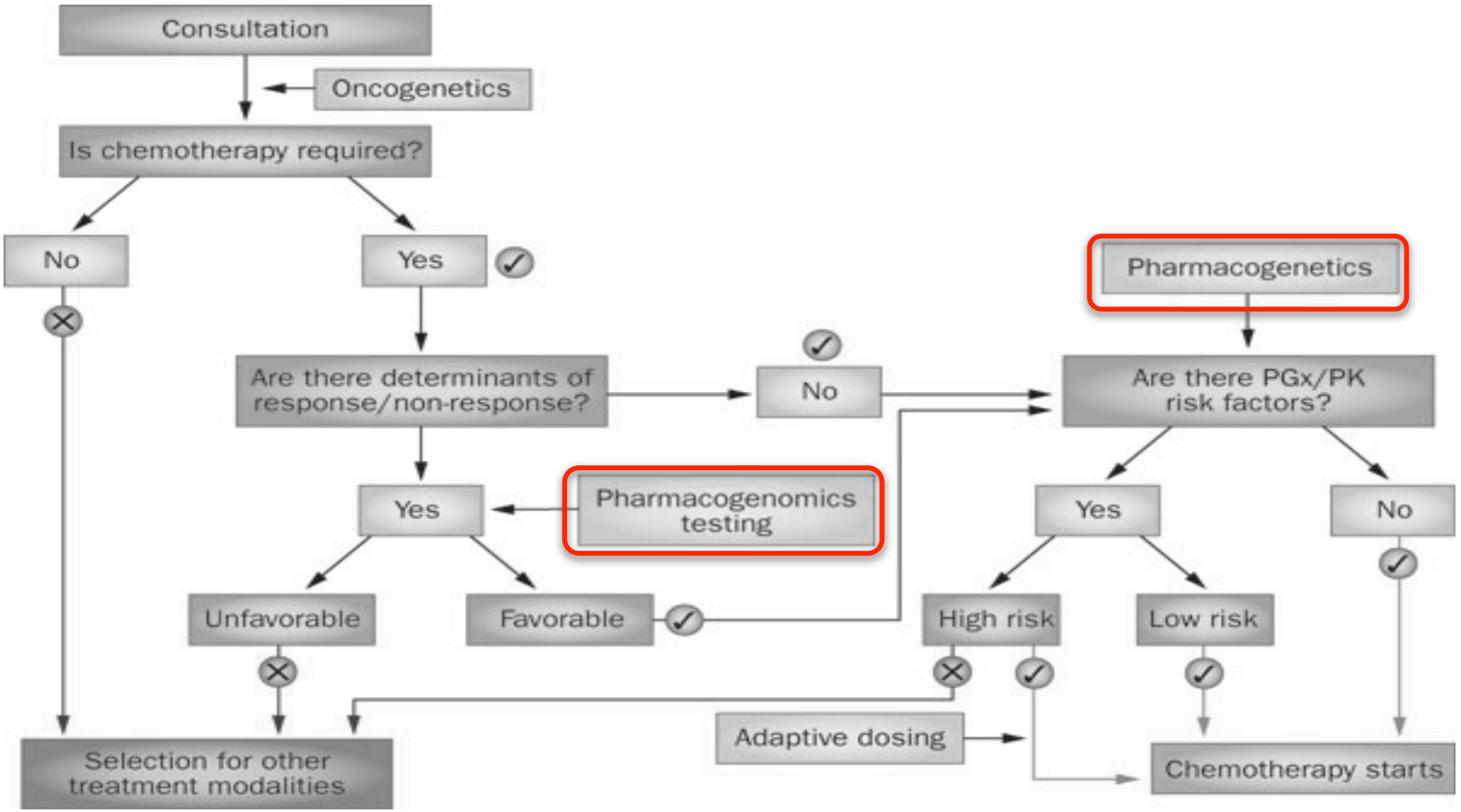
Fig 2. Distribution of cytidine deaminase (CDA) activities in patients with or without early severe toxicities in (A) subset 1 (3.9 ± 2.4 U/mg *v* 1 ± 0.2 U/mg; $P < .001$ by Mann-Whitney rank sum test; n = 64) and in (B) subset 2 (4 ± 2.6 U/mg *v* 1.2 ± 0.8 U/mg; $P < .01$; n = 130).

Ciccolini et al, J Clin Oncol 2010

Agenda

- Pharmaco-génomique
- Pharmaco-cinétique
- Pharmaco-génétique
- **Perspectives**

Améliorer encore la précision



Ciccolini et al, Nat Rev Clin Oncol 2011

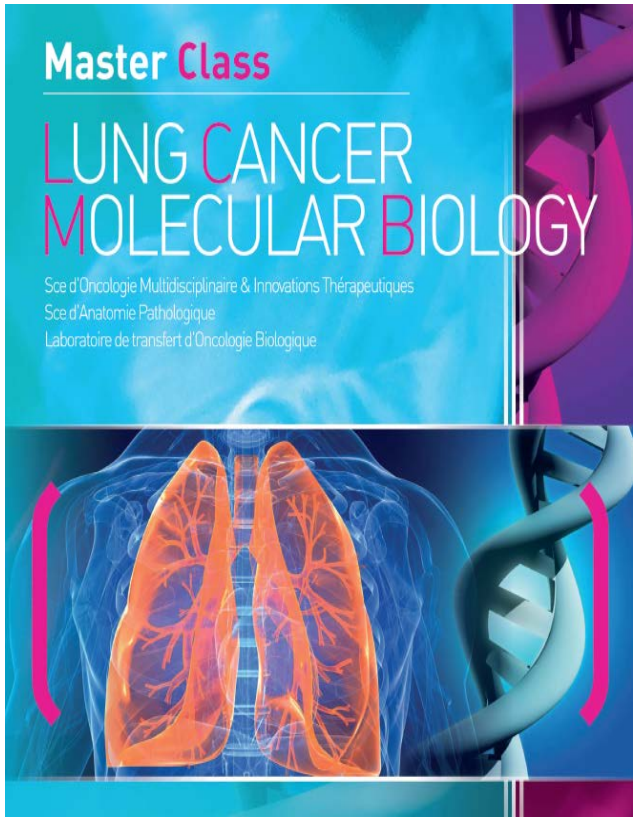
Conclusions

- **Médecine personnalisée**
  - Faisable pour tous, partout
  - Impact réel sur la survie des patients
- **Limites de développement**
  - Hétérogénéité tumorale
- **Prise en compte autres facteurs**
  - Monitoring des médicaments ?

Lung Cancer Molecular Biology Masterclass

- **20 participants max.***
- **Principes**
  - Matin: formation technique théorique
  - Après midi: manips laboratoires
- **Faculty**
  - J Mazieres
  - G Zalcman
  - J Ciccolini
  - MS Tsao
  - F Cappuzzo
  - M Beau-Faller
  - J Cadranel
  - P Hofman
  - S Lantuejoul
  - D Adam
  - F Sheperd
  - C Massard

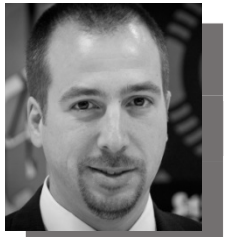
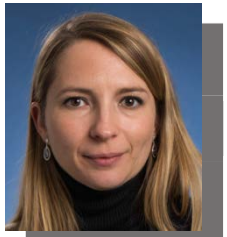
02-04 DEC 2014

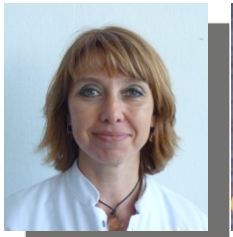
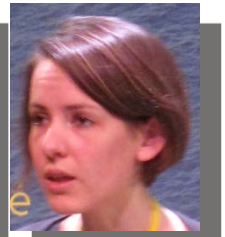


masterclass@atout-org.com

** Ouvert à un public international de médecins, biologistes, responsables industriels, etc*

- **Oncologie Multidisciplinaire AP-HM**
  - Laurent Greillier
  - Pascale Tomasini
  - Celine Mascaux
  - Marjorie Baciuchka
  - Marie Eve Garcia
  - Clothilde Fournier
- **Equipe de Recherche Clinique**
  - Julie Biemar
  - Maryline Blanchon
  - Christelle Deschamps
  - Sandrine Jourdan
  - Rocqya Nouar
  - Fabienne Palmerini
  - Aurélie Roger
- **Chirurgie Thoracique**
  - Pascal Thomas
  - Christophe Doddoli
  - Benoit Djourno
  - Deplhine Trousse
  - Geoffrey Brioude
- **Endoscopies et Radiologie**
  - Jerome Soussan
  - Caroline Prost
  - Hervé Dutau
  - Philippe Astoul
  - Sophie Laroumagne
- **Laboratoire d'Anatomie Pathologique**
  - Stéphane Garcia
  - Véronique Secq

- **Laboratoire de Cytologie Pathologique**
  - Patrice Roll
  - André Robaglia
- **Centre Essais Précoces en Cancérologie de Marseille CLIP²**
  - Clarisse Maurin
  - Annick Pelletier
- **Lab. Pharmacologie**
  - Joseph Ciccolini
  - Bruno Lacarelle
  - Cindy Serdjebi
- **Modélisation**
  - Dominique Barbolosi
  - Sébastien Benzekry
  - Christophe Meille
- **Laboratoire de Transfert**
  - Frederic Fina
  - Isabelle Nanni-Metellus
  - Lhoucine Ouafik
- **Sponsors**