# INNOVATIONS EN PNEUMOLOGIE

Samedi 19 Mars 2016
Espace du Centenaire - 189 rue de Bercy 75012 Paris

SPIF
La Société de Pneumologie d'Île-de-France

# La biologie moléculaire : une innovation dans le diagnostic et le traitement des CBNPC

Hôpitaux Universitaires Paris Est
ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

THERANOSCAN
GRC-UPMC

UPMC
PARIS UNIVERSITAS

# Conflict of interest disclosure

I have the following, real or perceived direct or indirect conflicts of interest that relate to this presentation:

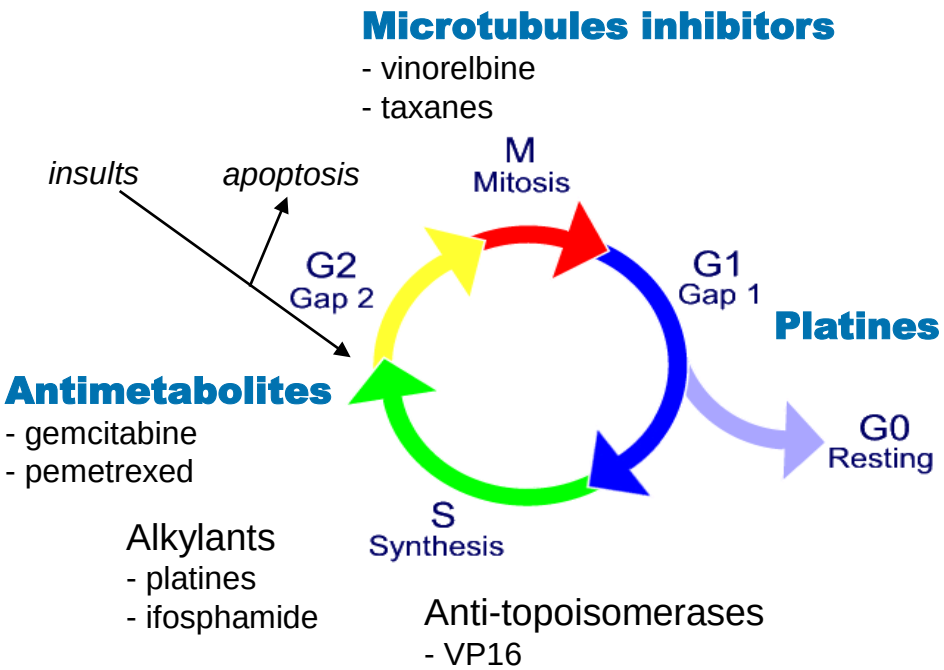
| Affiliation / financial interest | Nature of conflict / commercial company name |
|---|---|
| Tobacco-industry and tobacco corporate affiliate related conflict of interest | **NO** |
| Grants/research support (to myself, my institution or department): | Research supports in thoracic oncology from BI, Novartis, Pfizer for my institution |
| Honoraria or consultation fees: | AZ, BI, BMS, Lilly, Novartis, Roche |
| Participation in a company sponsored bureau: | **NO** |
| Stock shareholder: | **NO** |
| Spouse/partner: | **NO** |
| Other support or other potential conflict of interest: | **NO** |

This event is accredited for CME credits by EBAP and speakers are required to disclose their potential conflict of interest going back 3 years prior to this presentation. The intent of this disclosure is not to prevent a speaker with a conflict of interest (any significant financial relationship a speaker has with manufacturers or providers of any commercial products or services relevant to the talk) from making a presentation, but rather to provide listeners with information on which they can make their own judgment. It remains for audience members to determine whether the speaker's interests or relationships may influence the presentation. Drug or device advertisement is strictly forbidden.

# Effet plateau de la chimiothérapie[2000]

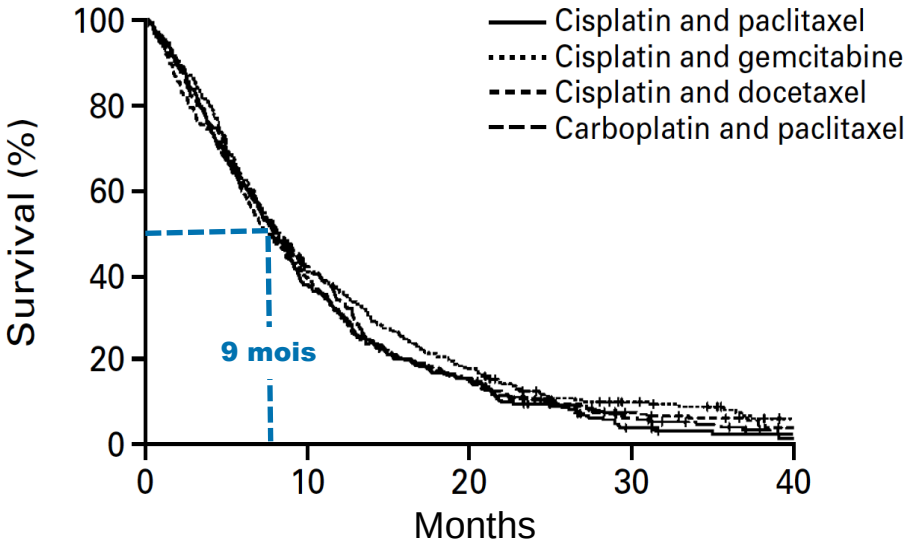
COMPARISON OF FOUR CHEMOTHERAPY REGIMENS FOR ADVANCED NON–SMALL-CELL LUNG CANCER

JOAN H. SCHILLER, M.D., DAVID HARRINGTON, PH.D., CHANDRA P. BELANI, M.D., COREY LANGER, M.D., ALAN SANDLER, M.D., JAMES KROOK, M.D., JUNMING ZHU, PH.D., AND DAVID H. JOHNSON, M.D., FOR THE EASTERN COOPERATIVE ONCOLOGY GROUP




**ECOG trial, Phase III, OS**

**1st line, non-selected population**




*Schiller J, N Engl J Med 2002, 346:92, Kelly K, J Clin Oncol 2001,19:3210*

# Effet modeste des 2éme et 3éme lignes2000-2005

| Study | Treatment | Median OS (mo) |
|---|---|---|
| Tax 317 | Docetaxel (D75/100) vs BSC | 7.5 (D75) vs 4.6 |
| BR.21 | Erlotinib vs placebo | 6.7 vs 4.7 |
| JMEI | Pemetrexed vs docetaxel | NS |
| Tax 320 | Docetaxel (D75/100) vs ifosfamide or vinorel | |
| ISEL | Gefitinib vs placebo | |
| ZODIAC | Vandetanib + docetaxel vs docetaxel | |
| ZEAL | Vandetanib + pemetrexed vs pemetrexed | |
| ZEST | Vandetanib vs erlotinib | |
| VITAL | Aflibercept + docetaxel vs docetaxel | |
| BETA | Bevacizumab + erlotinib vs erlotinib | |
| TAILOR | Docetaxel vs erlotinib, non-EGFR mutations | |
| TITAN | Docetaxel/pemetrexed vs erlotinib | |
| Vinflunine | Vinflunine vs docetaxel | |
| Topotecan | Oral topotecan vs docetaxel | |
| SUN1087 | Sunitinib + erlotinib vs erlotinib | |
| BR 26 | Dacomitinib vs placebo | |

Histoguidage

Maintenance

Traitements ciblés

2éme et 3éme ligne

Anti-angiogéniques

Immunothérapie

# Essais thérapeutiques

↓

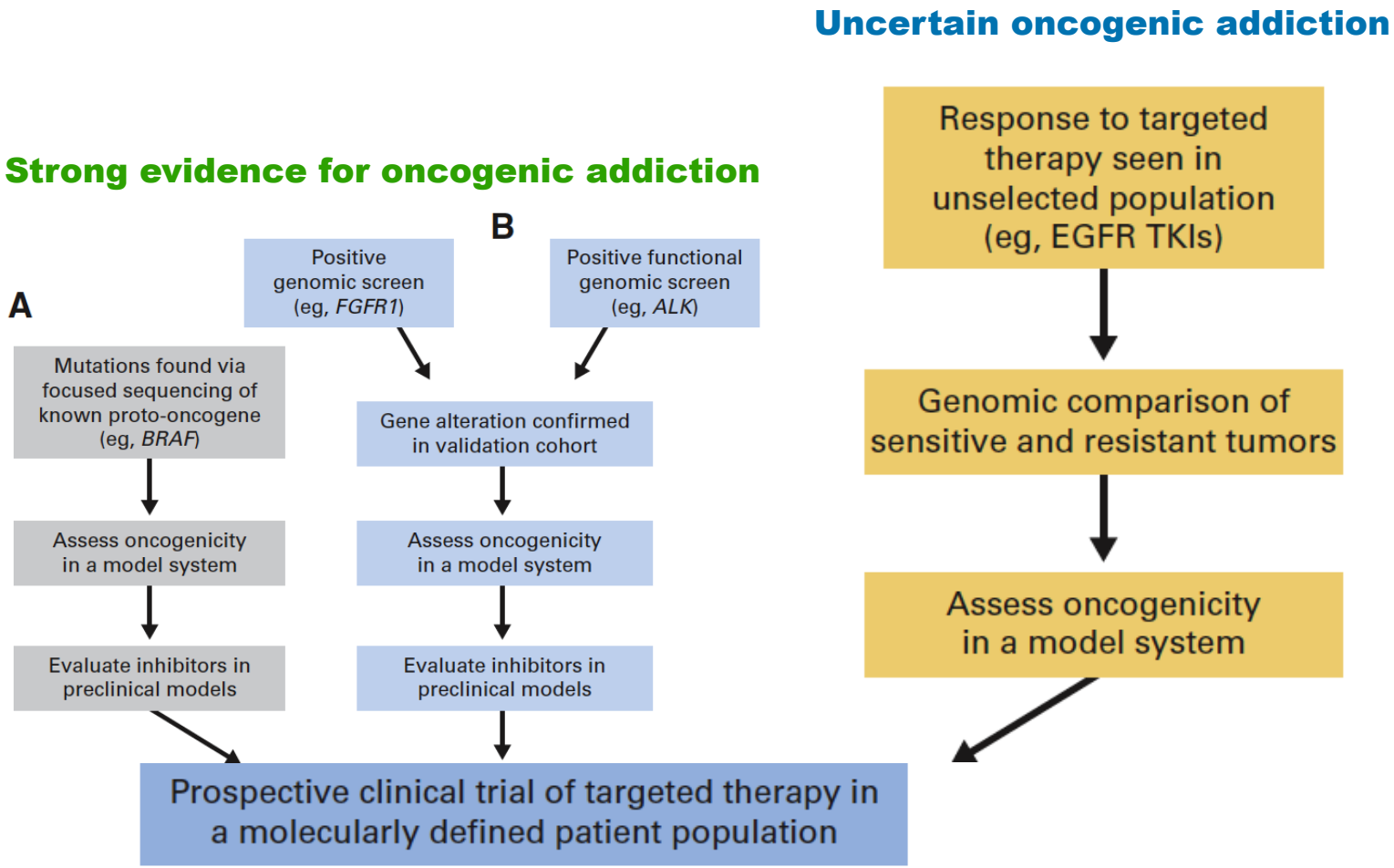
**Survie x 3 dans les 5 dernières années**

# Effet des TKI-EGFR dans populations ciblées[2005-2009]

**Table 3. Analysis of Survival.***

| Factor | No. of Patients | Univariate Hazard Ratio (95% CI)† | P Value | Multivariate Hazard Ratio (CI)‡ | P Value§ |
|---|---|---|---|---|---|
| Treatment group | | | | | |
| Erlotinib | 488 | 0.7 (0.6–0.9) | <0.001 | 0.7 (0.6–0.9) | 0.002 |
| Placebo | 243 | | | | |
| Pathological subtype | | | | | |
| Adenocarcinoma | 365 | 0.7 (0.6–0.9) | 0.008 | 0.8 (0.6–0.9) | 0.004 |
| Other | 366 | 0.8 (0.6–1.0) | 0.07 | | |
| EGFR expression | | | | NA | |
| Positive | 184 | 0.7 (0.5–0.9) | 0.02 | | |
| Negative | 141 | 0.9 (0.6–1.4) | 0.70 | | |
| Unknown | 406 | 0.8 (0.6–1.0) | 0.03 | | |
| Smoking status | | | | | |
| Current smoker or ever smoked | 545 | 0.9 (0.7–1.0) | 0.14 | Reference group | |
| Never smoked | 146 | 0.4 (0.3–0.6) | <0.001 | 0.8 (0.6–1.0) | 0.048 |
| Unknown | 40 | 1.1 (0.5–2.6) | 0.80 | 1.0 (0.7–1.5) | 0.89 |
| Race or ethnic group | | | | | |
| Asian | 91 | 0.6 (0.4–1.0) | 0.06 | 0.7 (0.5–0.9) | 0.01 |
| Other | 640 | 0.8 (0.7–0.9) | 0.01 | | |

# A la recherche des biomarqueurs[2005-2009]




*Oxnard J, J Clin Oncol 2013, 31:1097*

# A la recherche des biomarqueurs 2005-2009

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.

PNAS

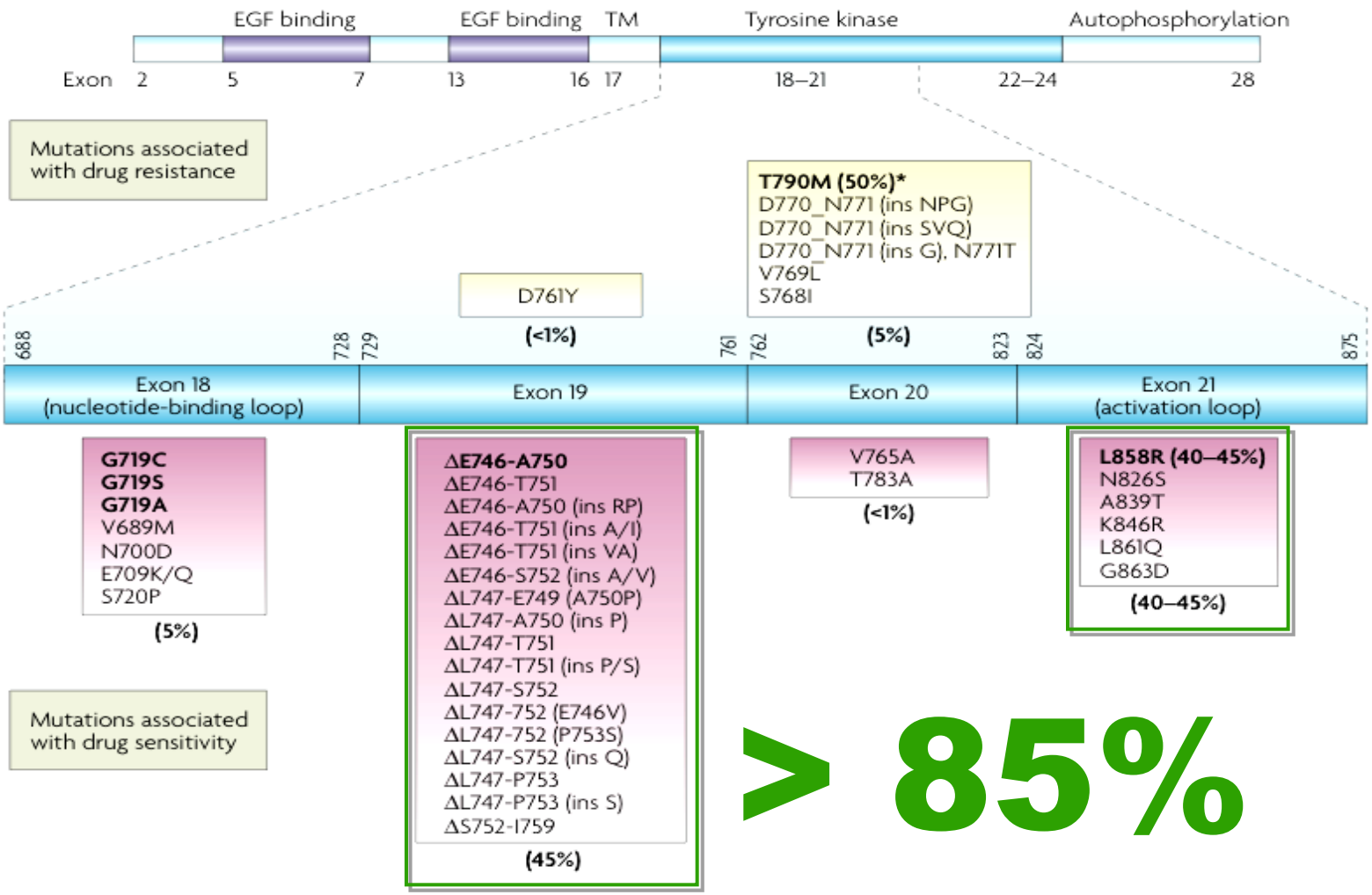
## EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib

William Pao*†‡, Vincent Miller†§, Maureen Zakowski¶, Jennifer Doherty*, Katerina Politi*, Inderpal Sarkaria‖, Bhuvanesh Singh‖, Robert Heelan**, Valerie Rusch‖, Lucinda Fulton††, Elaine Mardis††, Doris Kupfer††, Richard Wilson††, Mark Kris†§, and Harold Varmus*

*Program in Cancer Biology and Genetics and Departments of †Medicine, ‖Surgery, ¶Pathology, and **Radiology, Memorial Sloan–Kettering Cancer Center, 1275 York Avenue, New York, NY 10021; and ††Genome Sequencing Center, Washington University School of Medicine, 4444 Forest Park Boulevard, St. Louis, MO 63108

13306–13311 | PNAS | September 7, 2004 | vol. 101 | no. 36 www.pnas.org/cgi/doi/10.1073/pnas.0405220101

# Les mutations de l'EGFR[2005-2009]



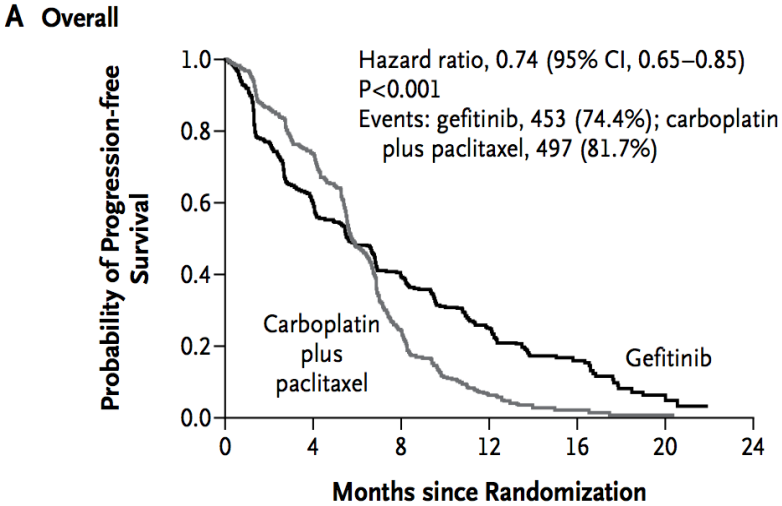

*Sharma SV, Nature Reviews Cancer 2007, 7:169*

# Les plateformes de l'INCa 2005-2009

## AMM Iressa®

### IPASS, Phase III

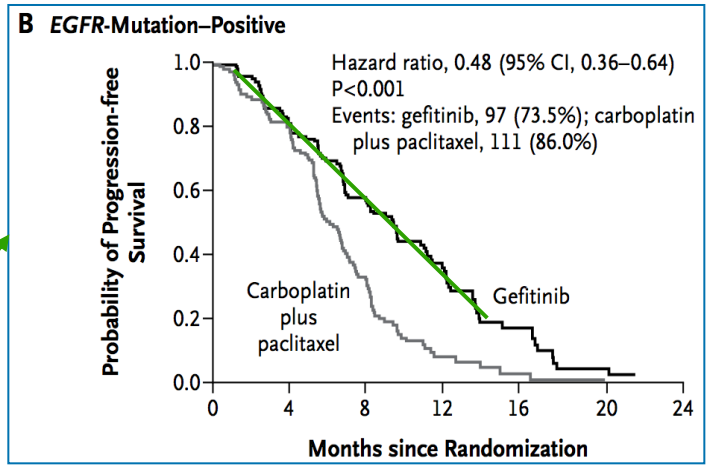
**1st line, enriched population**
**Asian, female, non smoker, ADC**



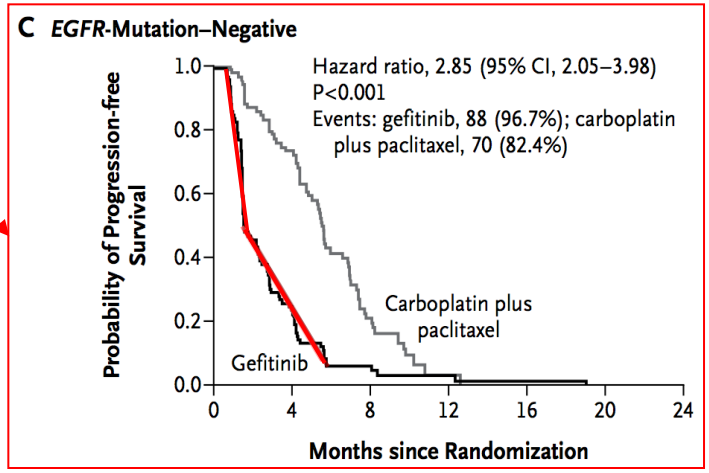

**No. at Risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Gefitinib | 609 | 363 | 212 | 76 | 24 | 5 | 0 |
| Carboplatin plus paclitaxel | 608 | 412 | 118 | 22 | 3 | 1 | 0 |

**EGFR+ 59.7%**



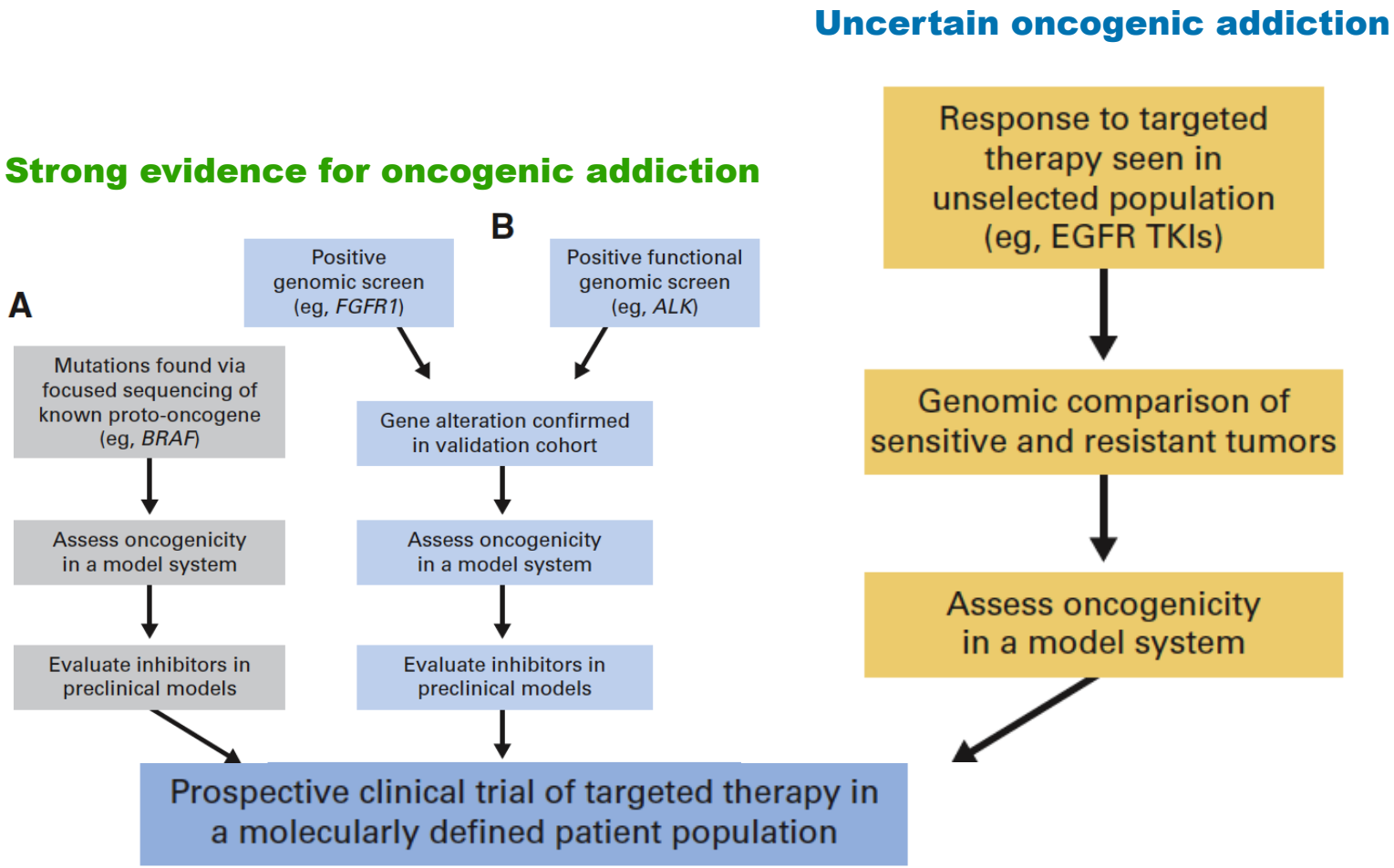

**EGFR- 40.3%**




*Mok T N Engl J Med 2009, 361:947*

# Les plateformes de l'INCa 2005-2009

# A la recherche des biomarqueurs[2009-2012]

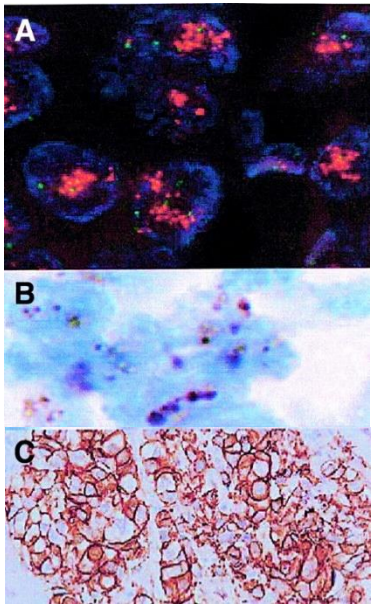



*Oxnard J, J Clin Oncol 2013, 31:1097*

# Les autres addictions oncogéniques 2009-2012

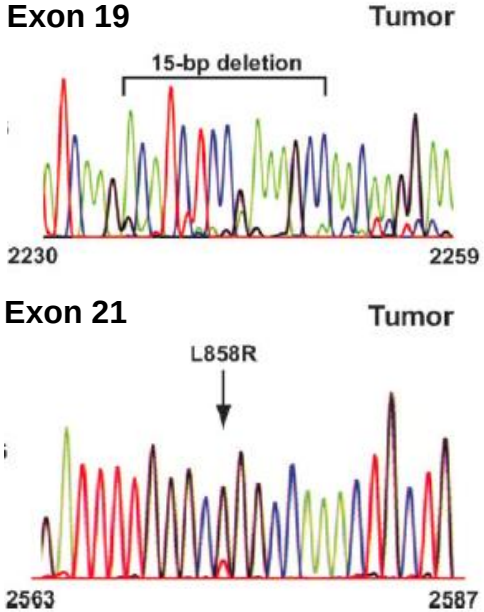
**Amplification génique**
**Surexpression protéique**

? FGFR
MET/HGFR
HER2…



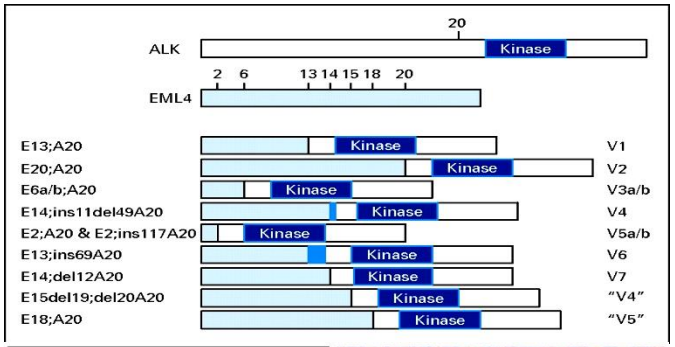

**Gain de fonction**
**Mutation dans la kinase**

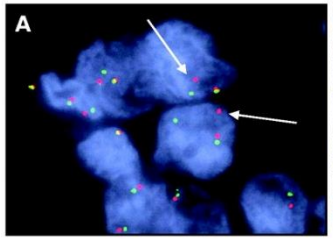
**EGFR, HER2, BRaf…**

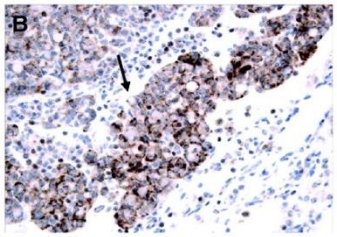



**Réarrangement chromosomique**
**Protéine de fusion oncogénique**

**ALK…**

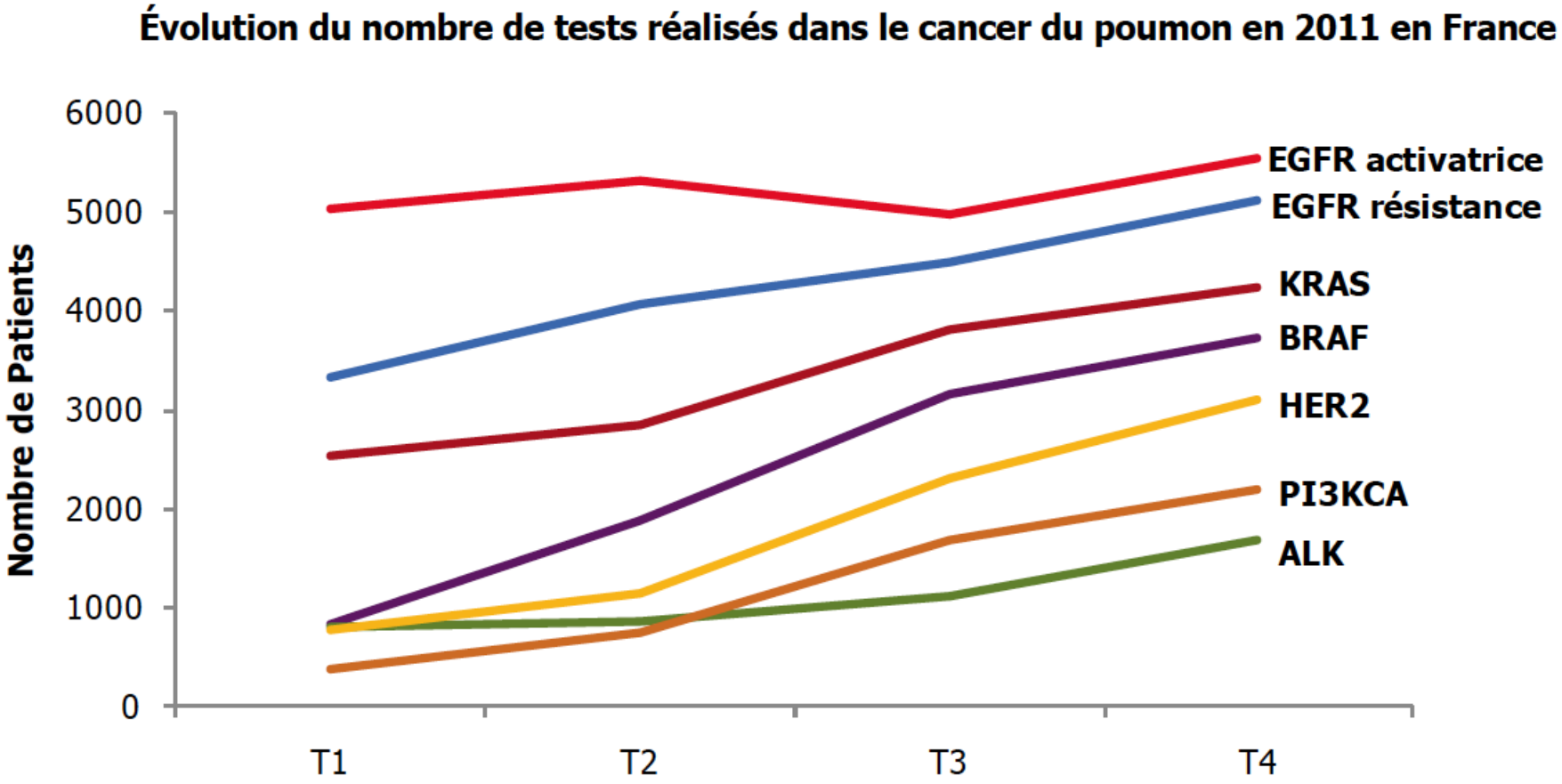



*Blume-Jensen P, Nature 2001, 411:355*

# Les plateformes de l'INCa 2009-2012

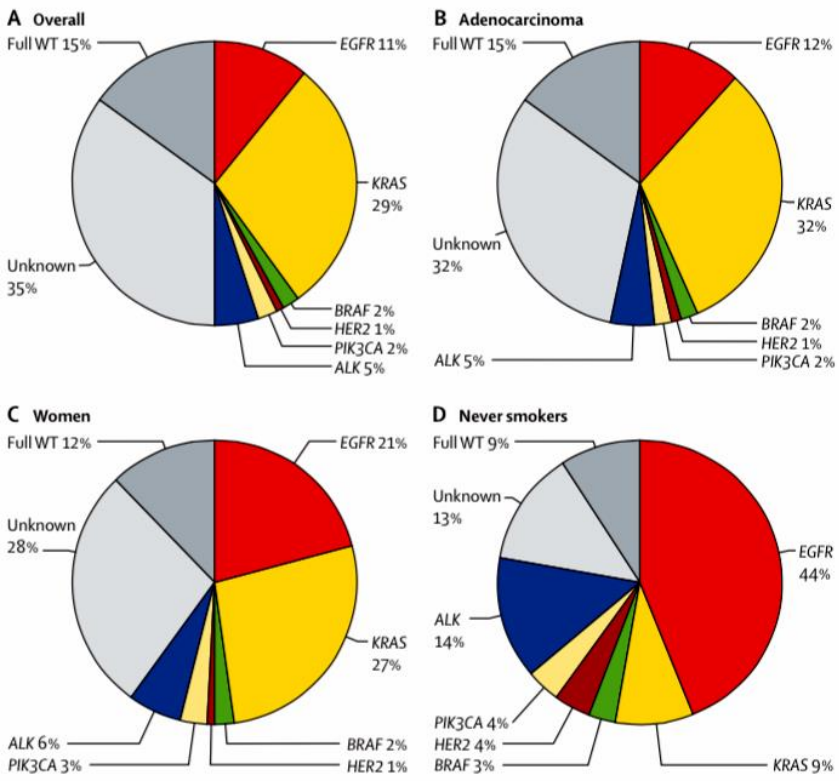


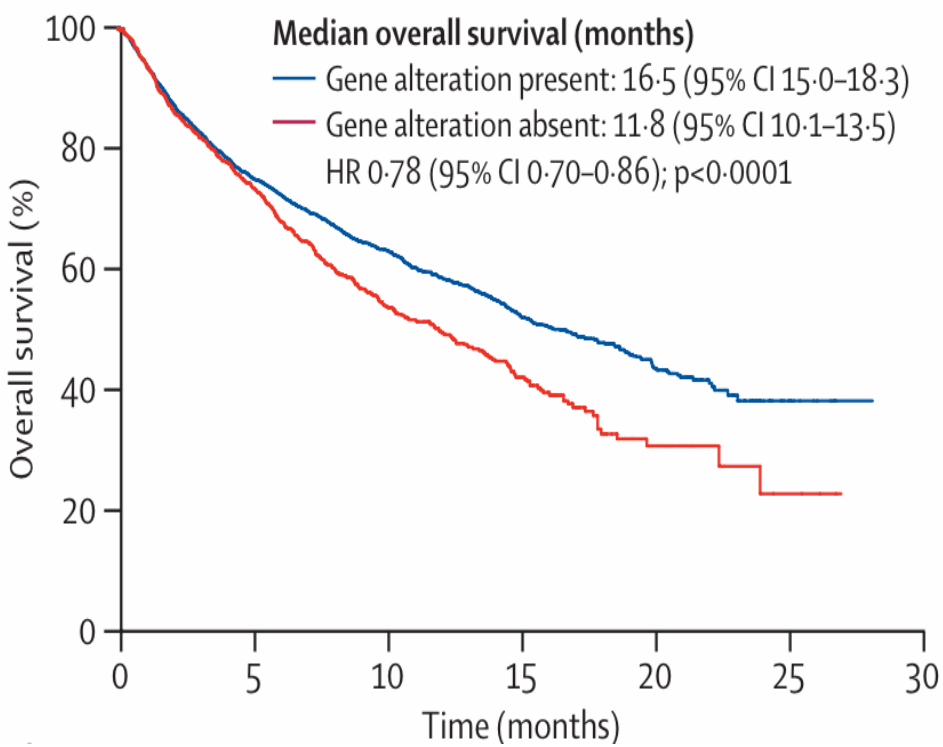

*Les tests de génétique moléculaire pour l'accès aux thérapies ciblées en 2012*

# Les plateformes de l'INCa[2009-2012]

## Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT)

*Fabrice Barlesi, Julien Mazieres, Jean-Philippe Merlio, Didier Debieuvre, Jean Mosser, Hervé Lena, L'Houcine Ouafik, Benjamin Besse, Isabelle Rouquette, Virginie Westeel, Fabienne Escande, Isabelle Monnet, Antoinette Lemoine, Rémi Veillon, Hélène Blons, Clarisse Audigier-Valette, Pierre-Paul Bringuier, Régine Lamy, Michèle Beau-Faller, Jean-Louis Pujol, Jean-Christophe Sabourin, Frédérique Penault-Llorca, Marc G Denis, Sylvie Lantuejoul, Franck Morin, Quân Tran, Pascale Missy, Alexandra Langlais, Bernard Milleron, Jacques Cadranel, Jean-Charles Soria, Gérard Zalcman, for the Biomarkers France contributors**

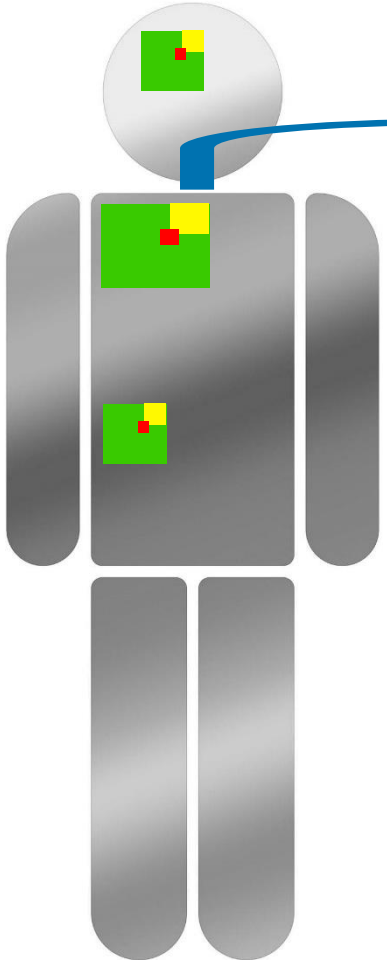



*18 679 patients in 2012*

*Lancet 13/01/2016*

# Les autres addictions oncogéniques 2012-2016



**ADC**

Genome instability & mutation

**NSCLC samples tested for EGFR mutations by 15 French NCI plateforms**

10,117 NSCLC samples tested *(2005-2008)*

**EGFR wild-type samples**
*9,070 (90%)*

EGFR-mutated samples
*1047 (10%)*

**Exons 19 and 21 EGFR-mutated samples**
*945 (90%)*

**Rare EGFR-mutated samples**
(exon 18; exon 20)
*102 (10%)*

Exon 18 EGFR mutations *41 (4%)*

Exon 20 EGFR mutations *49 (5%)*

Exon 18 and/or exon 20 complex EGFR mutations *12 (1%)*

?

*Beau-Faller M, Ann Oncol 2014, 25:126*

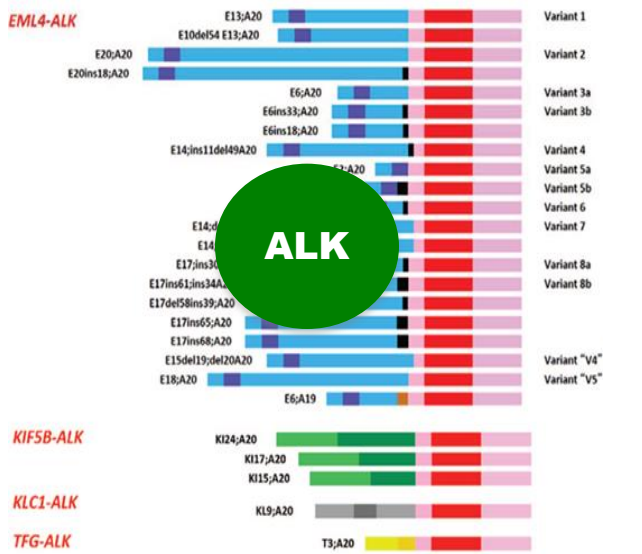
# Les autres addictions oncogéniques[2012-2016]

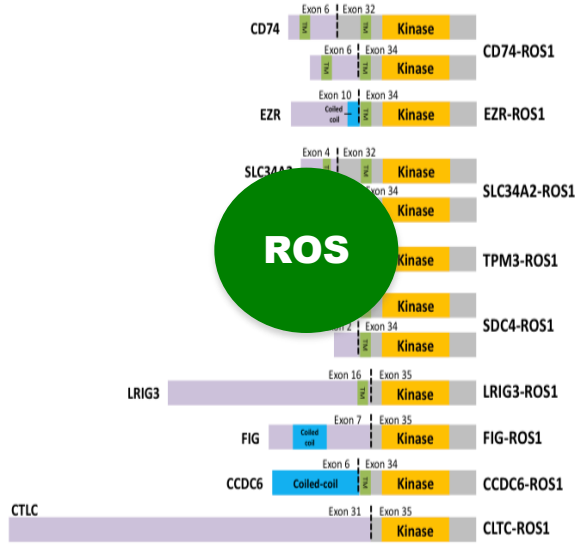
**EGFR TKI efficacy in rare and complex mutations**

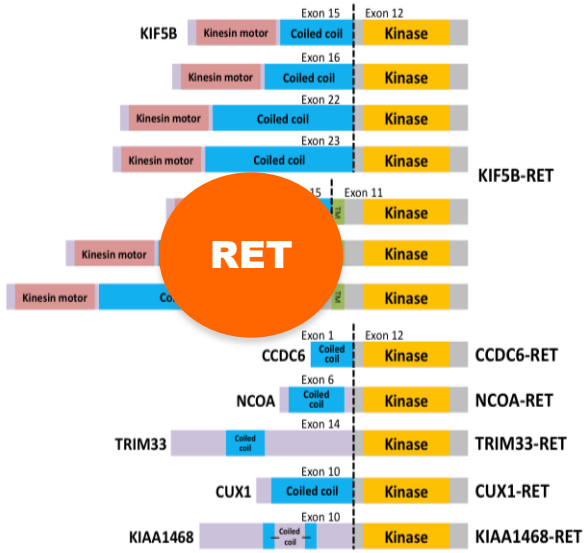
| No. of patients | | *EGFR* mutation | RR (%) | PFS (mo) | OS (mo) |
|---|---|---|---|---|---|
| 278 | | Single classical mutation (deletions in exon 19 or L858R) | 74.1 | 8.5 | 19.6 |
| **Gefitinib, n=60; Erlotinib, n=11** | | | | | |
| 11 | **Exon 20** | Insertions in exon 20 | 0 | 1.4 | 4.8 |
| 15 | **Exon 18** | G719 (single or complex) | 53.3 | 8.1 | 16.4 |
| 15 | **Exon 21** | L861 (single or complex) | 60.0 | 6.0 | 15.2 |
| 20 | **Complex** | Uncommon mutations with combination with deletions in exon 19 or L858R | 60.0 | 5.3 | 18.8 |
| 15 | **Complex** | Uncommon mutations without combination with deletions in exon 19 or L858R or G719 or L861 | 20.0 | 1.6 | 11.1 |

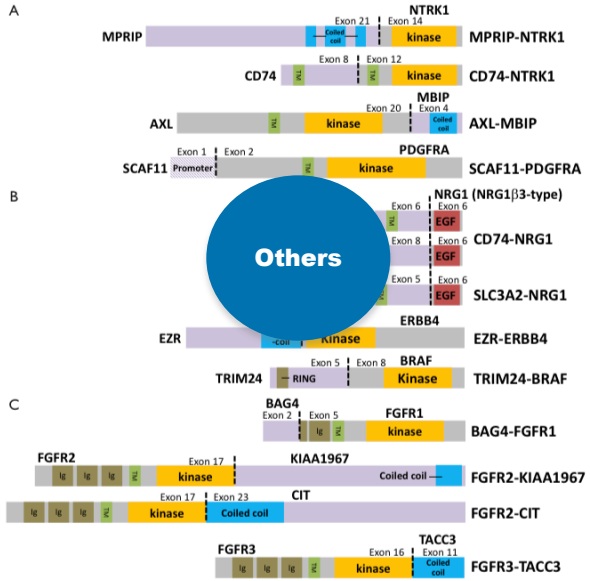
*Yu JY, Clin Cancer Res 2011, 17:381*

# Les autres addictions oncogéniques 2012-2016



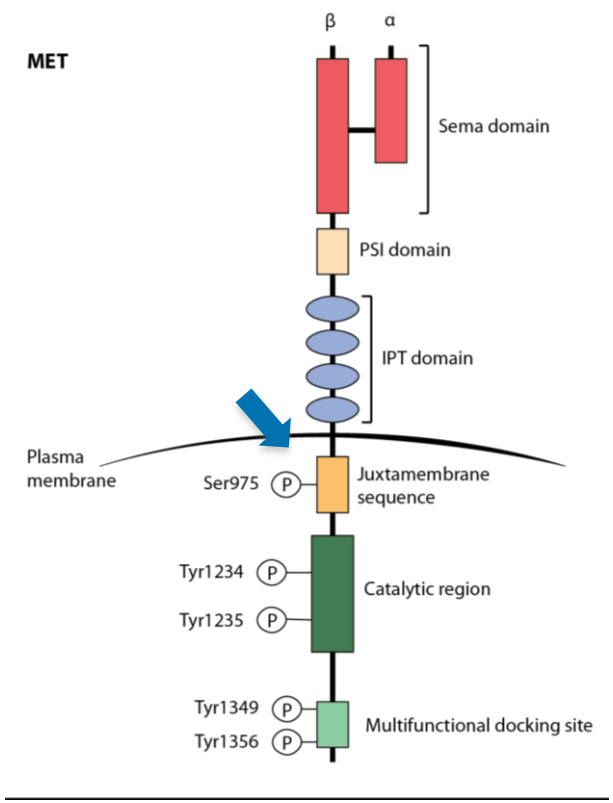



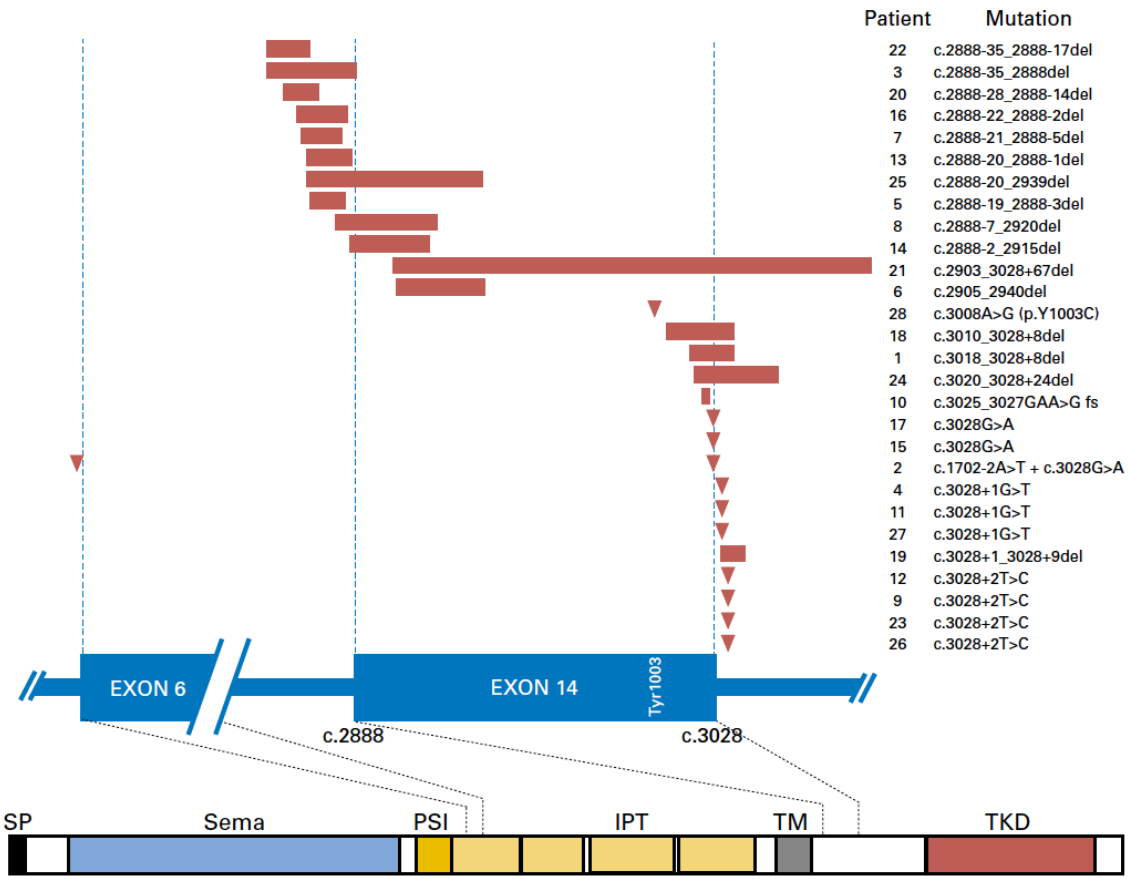




*Khono T, Trans Lung Cancer Res 2015,4:156*

# Les autres addictions oncogéniques[2012-2016]

**C-met exon 14 (intron) mutation/deletion**

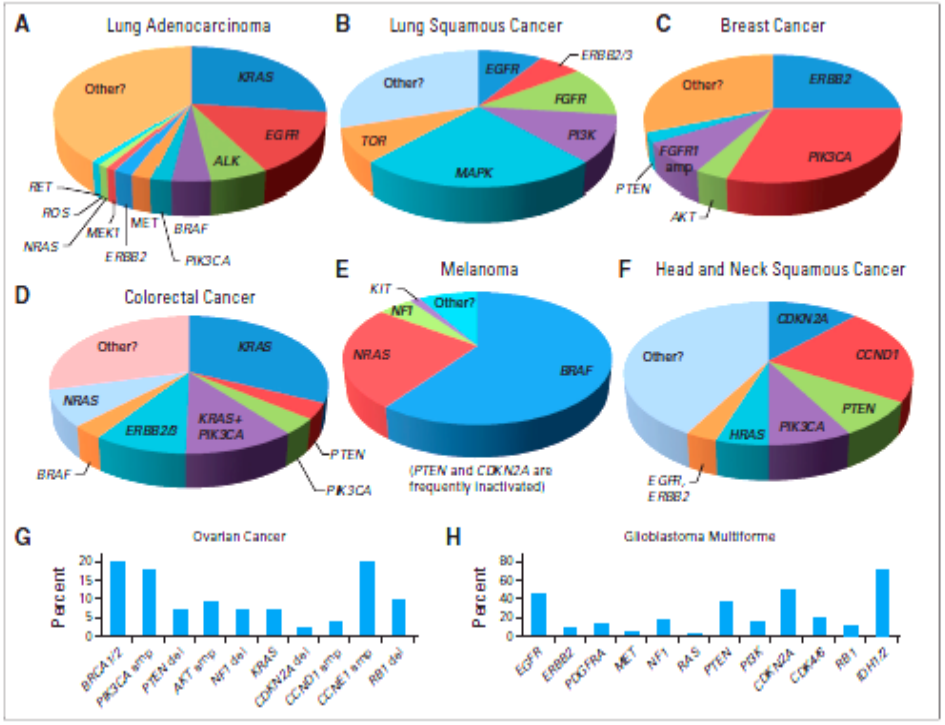


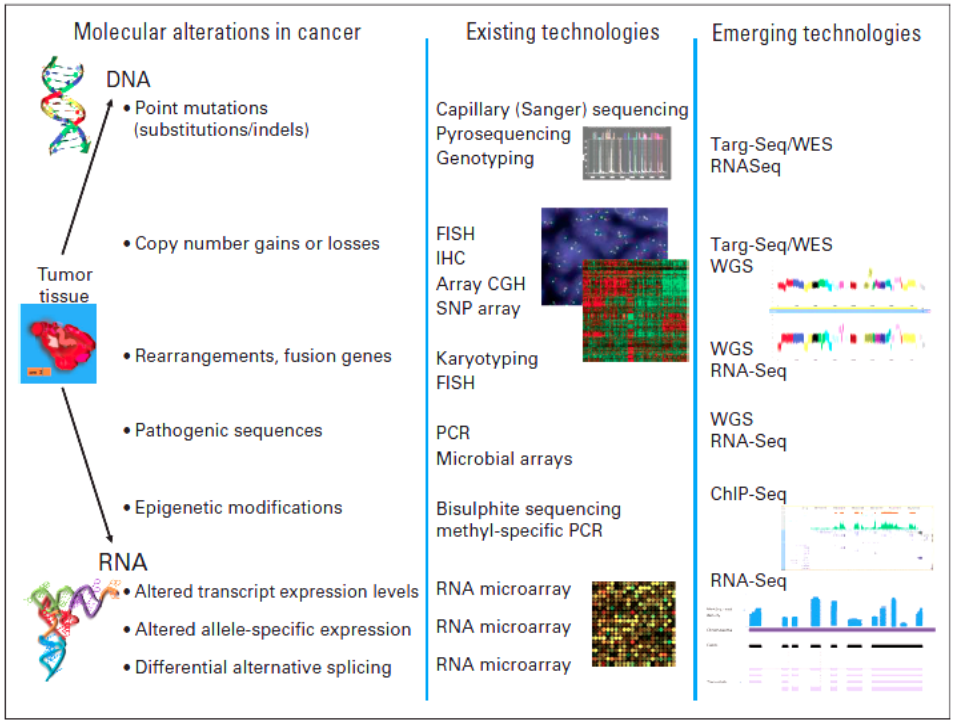

*Awad AM, J Clin Oncol 2016*

# Les défis de l'innovation diagnostique moléculaire 2015-2020

## Increased number of patients




## Increased number of rare addictions



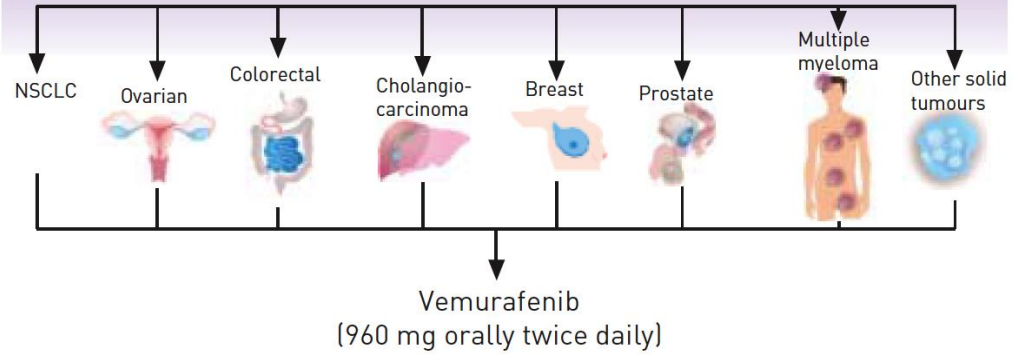

*Garraway LA, J Clin Oncol 2013, 31:1806; MacConaill LE, J Clin Oncol 2012, 31:1815*

# Les défis de l'innovation diagnostique moléculaire 2015-2020

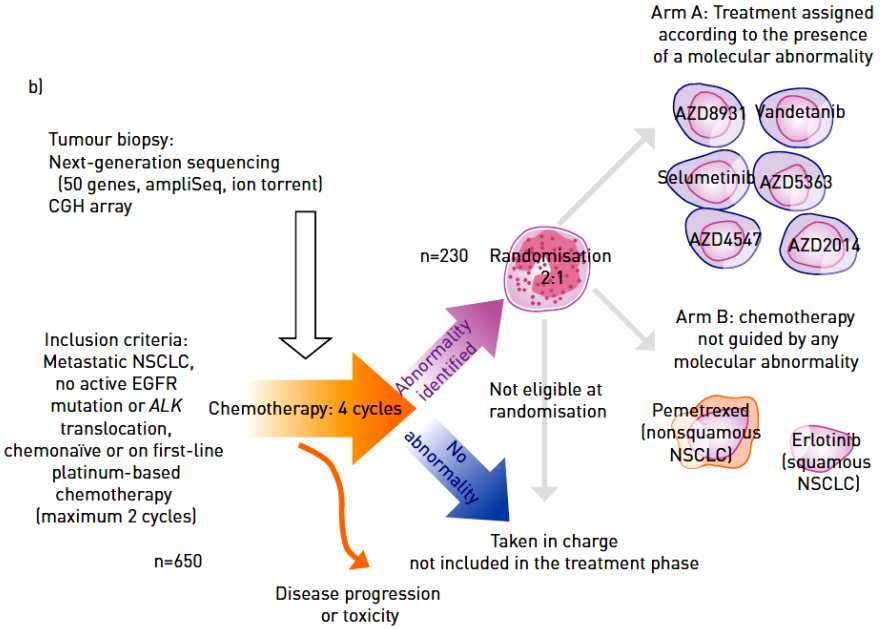
## Basket trial

8 cohorts *BRAF*$^{V600}$ positive cancers:
Metastatic solid tumors
Multiple myeloma

*BRAF*$^{V600}$ testing
All *BRAF*$^{V600}$ mutations
Tested by local routine methods
Retrospective optional evaluation with cobas 4800 *BRAF* mutation test



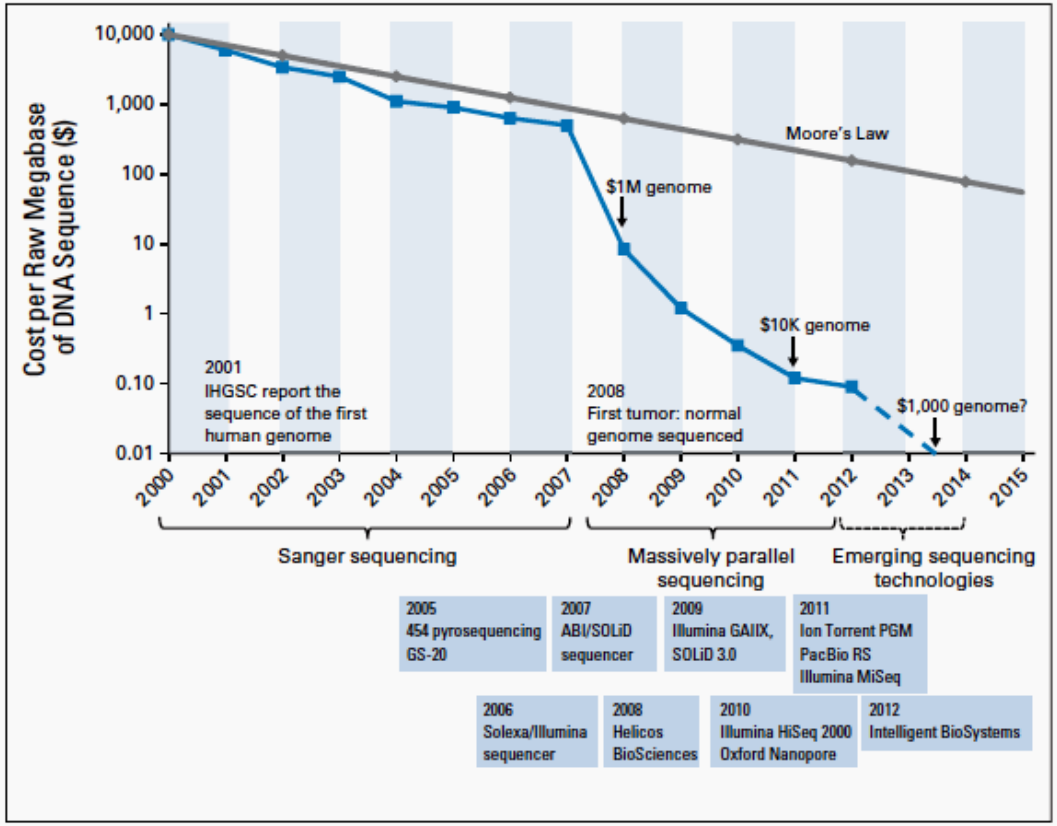

## Umbrella trial




*Menis J, Eur Respir Rev 2014, 23:376*

# Les défis de l'innovation diagnostique moléculaire[2015-2020]

**3 milliards de paires de base**




**Profondeur: nombre de fois ou l'exome (les**
**X100= 100 fois**

Box 1 | **Barriers for clinical translation**

**Molecular diagnostics**

- Choice of assay and design
- Cost
- Tissue quality
- Tumour content
- Analytical validity
- Clinical Laboratory Improvements Amendment (CLIA) certification
- Turnaround time
- Bioinformatics analysis

**Clinical implementation**

- Tissue acquisition
- Heterogeneity
- Expert interpretation
- Pathway versus tissue of origin
- Availability of broad panels of drugs
- Trial design and end points
- Clinical validity and utility

*Simon R, Nat Rev Drug Disc 2013:12,569*

# Les défis de l'innovation diagnostique moléculaire 2015-2020

Ion AmpliSeq™ Colon and Lung Cancer Research Panel v2 and
Ion AmpliSeq™ RNA Fusion Lung Cancer Research Panel
Now with NGS workflows and analysis for both DNA and RNA

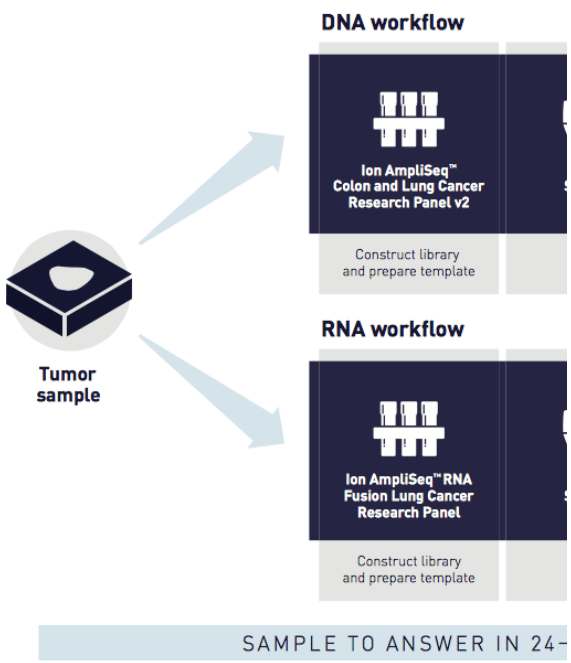


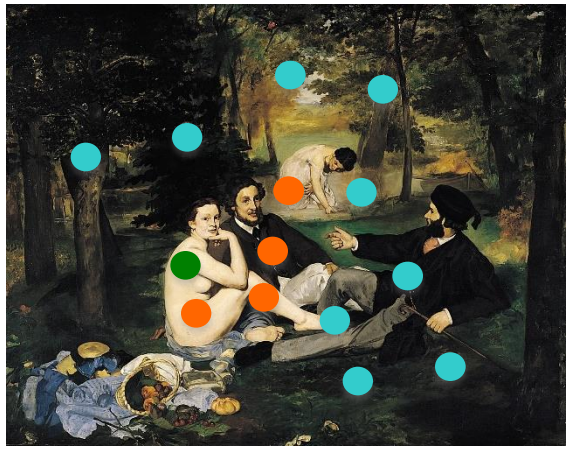

**Table 1. Ion AmpliSeq™ Colon and Lung Cancer Research Panel v2.**

| | |
|---|---|
| **Sample type** | FFPE samples |
| **Application** | Somatic m[illegible]te[illegible] 91% 46% |
| **Genes** | *KRAS, EGFR, BRAF, PIK3CA, AKT1, ERBB2, PTEN, NRAS, STK11, MAP2K1, ALK, DDR2, CTNNB1, MET, TP53, SMAD4, FBX7, FGFR3, NOTCH1, ERBB4, FGFR1, FGFR2* |
| **Pairs of primers and amplicon length** | 92 pairs of primers in a single pool<br>92 amplicons with an average length of 162 bp |
| **Input DNA required** | 10 ng |
| **Observed performance** | Percent of amplicons with the target base coverage at 500X: >95%<br>Average panel uniformity: 95%<br>Average percent reads on target: 98% |
| **Multiplexing** | 2 samples per Ion 314™ Chip with at least 500X sequencing coverage<br>8 samples per Ion 316™ Chip with at least 500X sequencing coverage<br>16 samples per Ion 318™ Chip with at least 500X sequencing coverage |

Sustaining proliferative signaling
Evading growth suppressors
Avoiding immune destruction
Enabling replicative immortality
Tumor-promoting inflammation
Activating invasion & metastasis
Inducing angiogenesis
Genome instability & mutation
Resisting cell death
Deregulating cellular energetics
Cellules normales
Clone 3

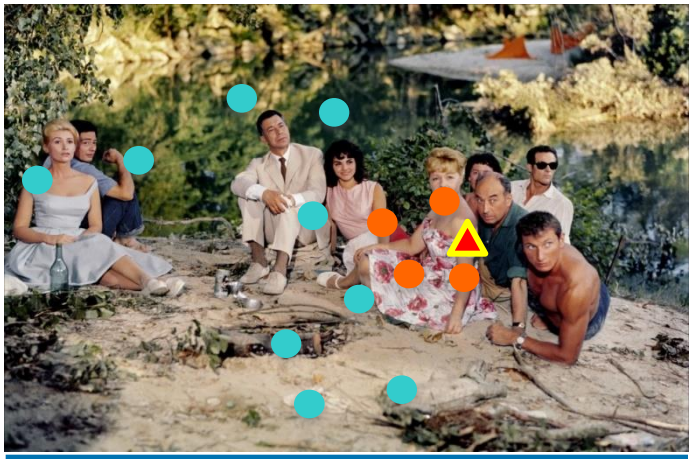
# Les défis de l'innovation diagnostique moléculaire 2015-2020

**ADC 1**



**ADC 2**

**ADC 3**



Séquençage exon :

PCR spécifique ciblée :

NGS ciblé :

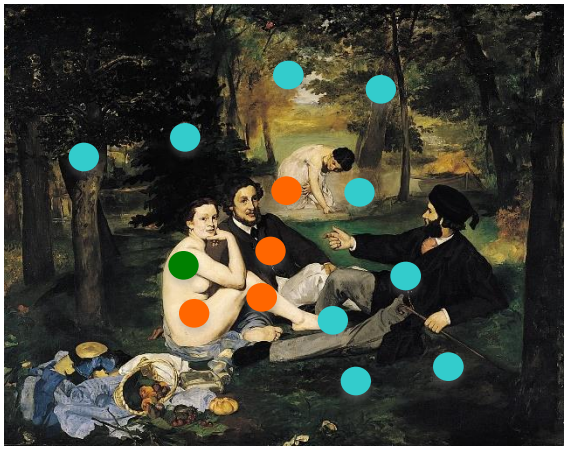
NGS whole exome :

NGS whole RNA :

NGS sang :

# Les défis de l'innovation diagnostique moléculaire 2015-2020

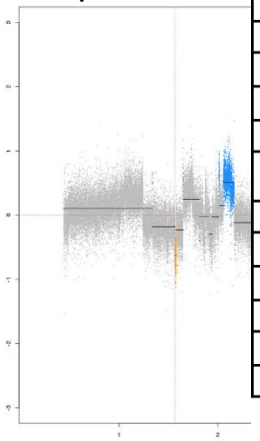
**Mr BAL Gal**



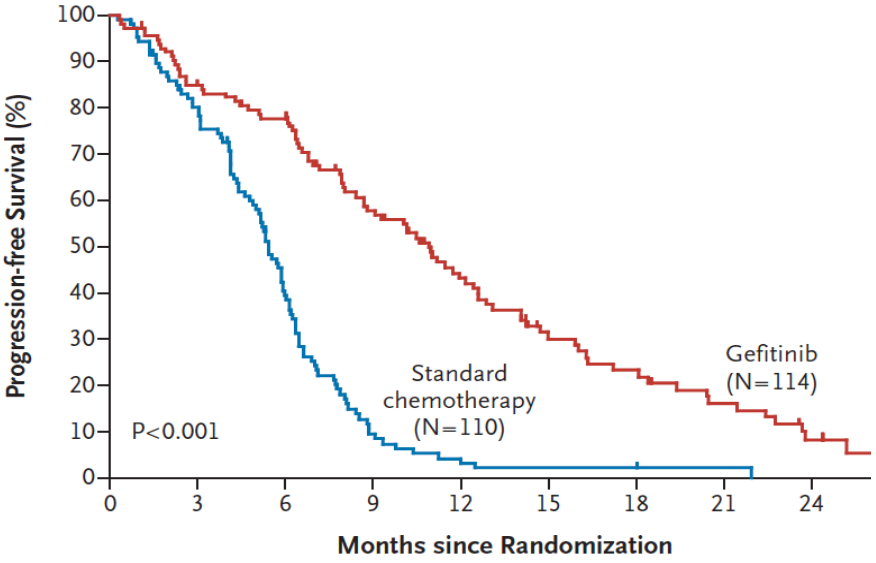
Gènes du cancer

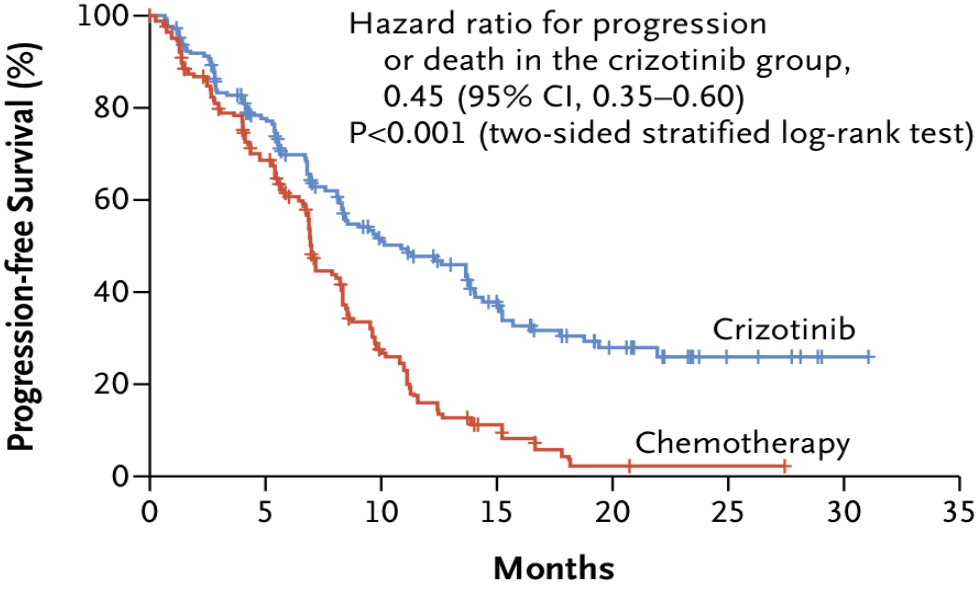
| gene | Niveau cDNA | Niveau gDNA(GRCh37) | Protéine | % | LOH |
|---|---|---|---|---|---|
| **ARID2** | NM_152641.2:c.1459G>T | Chr12:g.46233240G>T | p.Glu487* | 61% | NON |
| CAP2 | NM_006366.2:c.1291G>C | Chr6:g.17551776G>C | p.Glu431Gln | 16% | NON |
| **CREBBP** | NM_004380.2:c.1473del | Chr16:g.3832785del | p.Tyr492fs | 23% | NON |
| DDR2 | NM_001014796.1:c.2476A>T | Chr1:g.162749944A>T | p.Lys826* | 42% | NON |
| DIAPH1 | NM_005219.4:c.1801G>T | Chr5:g.140953616C>A | p.Ala601Ser | 63% | NON |
| EPHA3 | NM_005233.5:c.989G>T | Chr3:g.89390923G>T | p.Arg330Ile | 75% | OUI |
| ERCC4 | NM_005236.2:c.1476G>T | Chr16:g.14029265G>T | p.Leu492Phe | 29% | NON |
| FANCI | NM_001113378.1:c.2912G>A | Chr15:g.89844579G>A | p.Ser971Asn | 44% | NON |
| FANCM | NM_020937.3:c.172C>G | Chr14:g.45605406C>G | p.Leu58Val | 15.5 | NON |
| **FN1** | NM_212482.1:c.1186C>T | Chr2:g.216288899G>A | p.Gln396* | 50% | NON |
| **GRIN2A** | NM_000833.3:c.1279G>T | Chr16:g.9943662C>A | p.Glu427* | 35% | NON |
| HDAC5 | NM_001015053.1:c.1883A>G | Chr17:g.42164784T>C | p.Lys628Arg | 61.5% | NON |
| IGF1R | NM_000875.3:c.3515G>T | Chr15:g.99486209G>T | p.Gly1172Val | 14% | NON |
| KDR | NM_002253.2:c.464C>T | Chr4:g.55981473G>A | p.Ser155Leu | 19% | NON |
| **KEAP1** | NM_012289.3:c.340G>T | Chr19:g.10610370C>A | p.Gly114Trp | 55% | NON |
| MED23 | NM_004830.3:c.1723G>C | Chr6:g.131925351C>G | p.Glu575Gln | 32.5% | NON |
| MGA | NM_001164273.1:c.5411C>G | Chr15:g.42041033C>G | p.Pro1804Arg | 19% | OUI |
| **MSH2** | NM_000251.2:c.1757C>T | Chr2:g.47698199C>T | p.Ser586Leu | 22% | NON |
| **MUTYH** | NM_001128425.1:c.789G>A | Chr1:g.45797982C>T | p.Trp263* | 8% | NON |
| MYOCD | NM_001146312.2:c.2202+3A>T | Chr17:g.12659877A>T | p.? | 72% | NON |
| **ODAM** | NM_017855.3:c.648+1G>T | Chr4:g.71068047G>T | p.? | 60% | NON |
| PDGFRA | NM_006206.4:c.2926G>A | Chr4:g.55156525G>A | p.Ala976Thr | 19% | NON |
| SMARCA4 | NM_001128849.1:c.3478G>A | Chr19:g.11141501G>A | p.Gly1160Arg | 9.2% | NON |
| TMPRSS2 | NM_001135099.1:c.1138A>G | Chr21:g.42843781T>C | p.Asn380Asp | 10% | NON |
| ***TP53** | NM_000546.4:c.880G>T | Chr17:g.7577058C>A | p.Glu294* | 70% | OUI |
| XIRP2 | NM_152381.5:c.7550C>T | Chr2:g.168105452C>T | p.Pro2517Leu | 42% | NON |
| XIRP2 | NM_001199143.1:c.2720G>T | Chr2:g.168115677G>T | p.Arg907Met | 20% | NON |
| XIRP2 | NM_152381.5:c.8803C>G | Chr2:g.168106705C>G | p.Arg2935Gly | 50% | NON |

Amplifications



# Les défis de l'innovation diagnostique moléculaire[2015-2020]

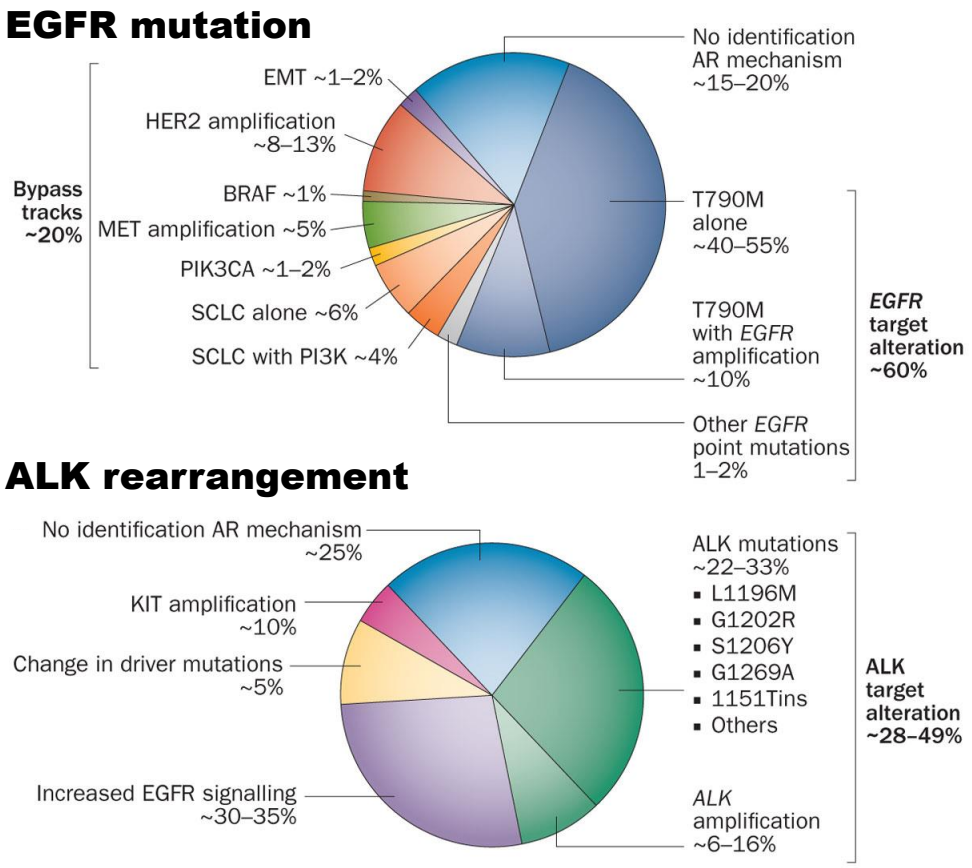





*Maemondo M, New Engl J Med 2010, 362:25; Solomon BJ, N Engl J Med 2014, 371:2*

# Les défis de l'innovation diagnostique moléculaire 2015-2020

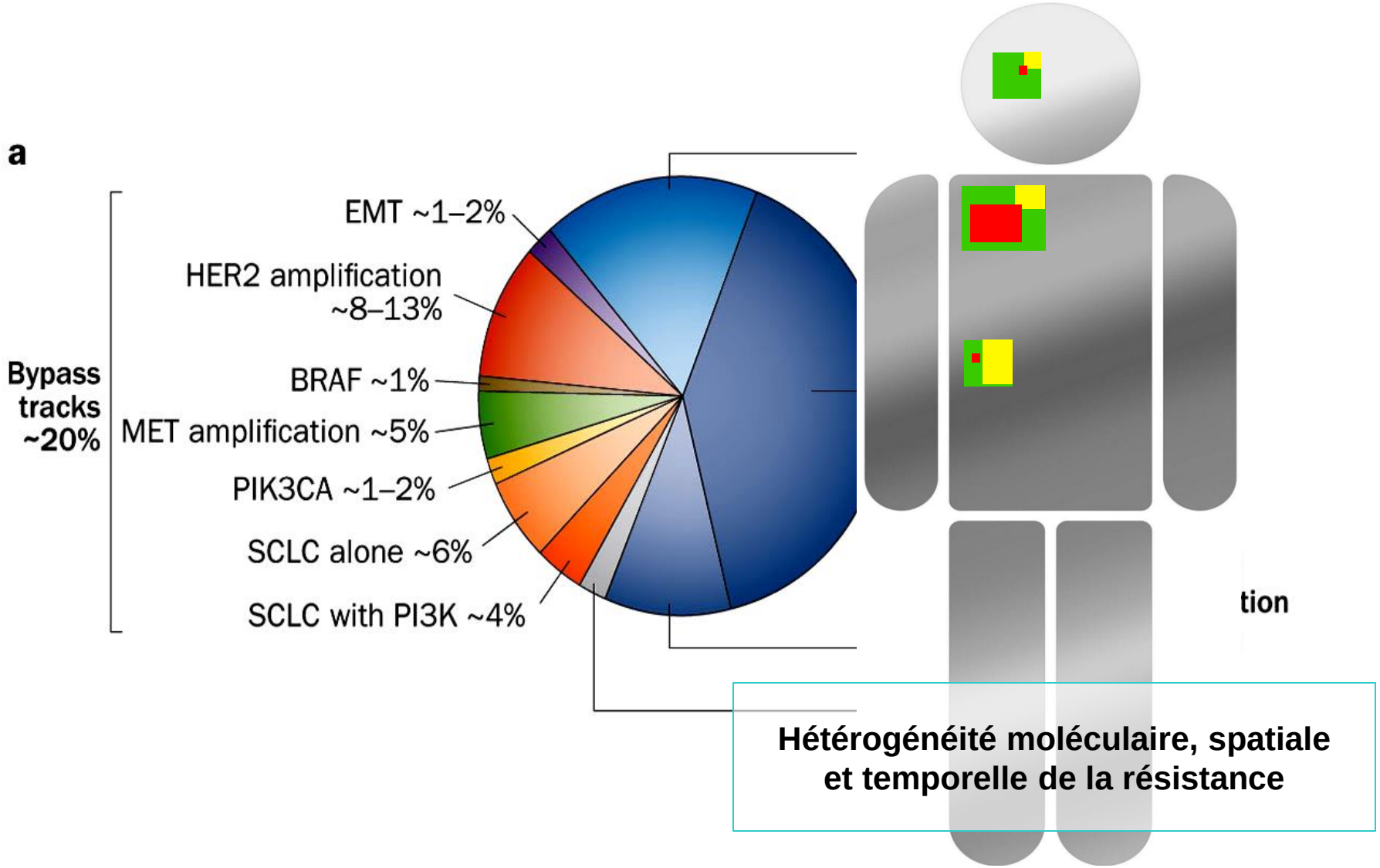



→ **AZ9291, rociletinib**

→ **ceritinib, alectinib, PF06463922**

*Camidge R, Nat Rev Clin Oncol 2014, 11:473*

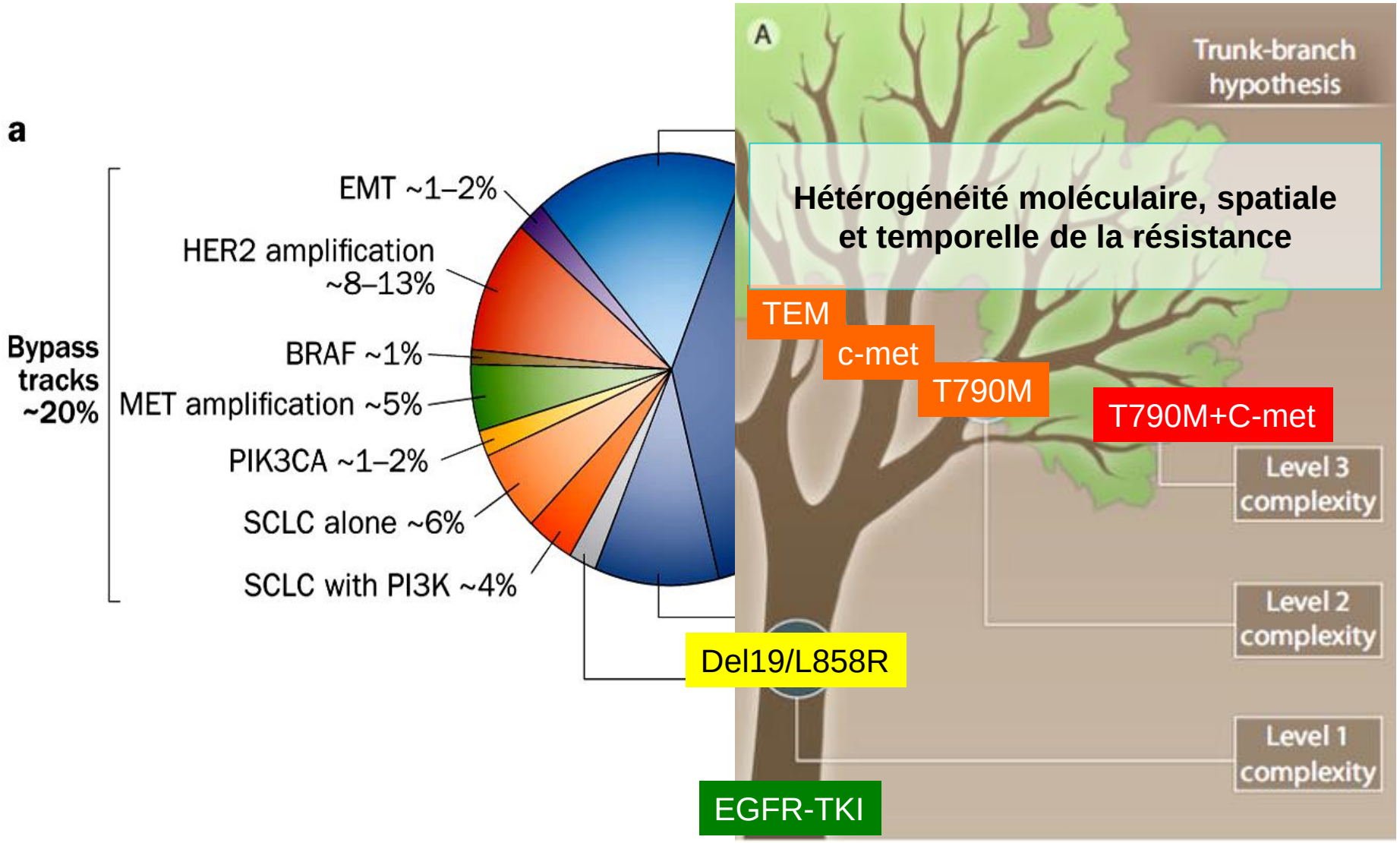
# Les défis de l'innovation diagnostique moléculaire 2015-2020




**Hétérogénéité moléculaire, spatiale et temporelle de la résistance**

*Camidge R, Nat Rev Clin Oncol 2014, 11:473; Yap TA, Sci Transl Med 2012, 127:3*

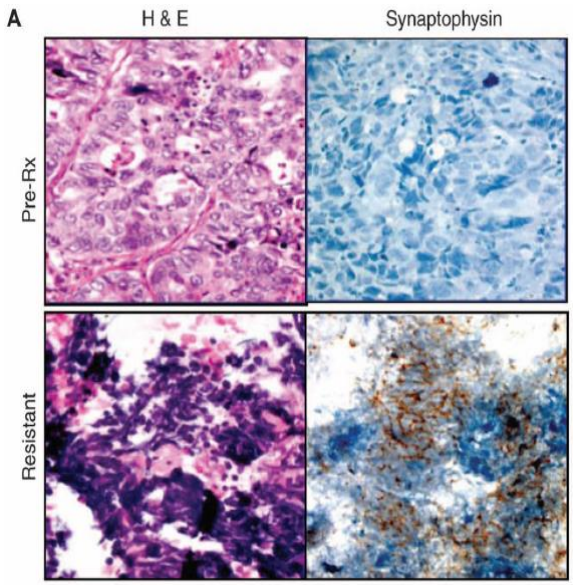
# Les défis de l'innovation diagnostique moléculaire[2015-2020]




*Camidge R, Nat Rev Clin Oncol 2014, 11:473; Yap TA, Sci Transl Med 2012, 127:3*

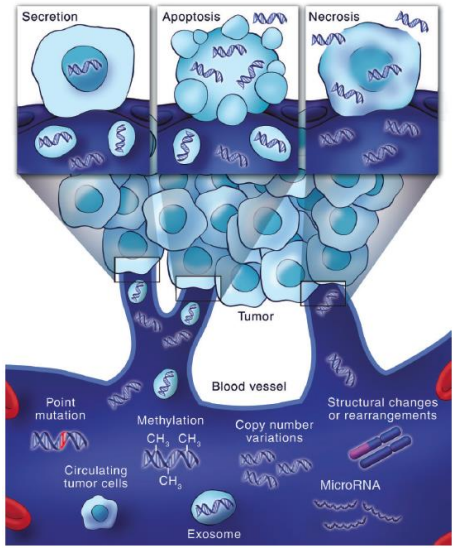
# Les défis de l'innovation diagnostique moléculaire 2015-2020

## Biopsy



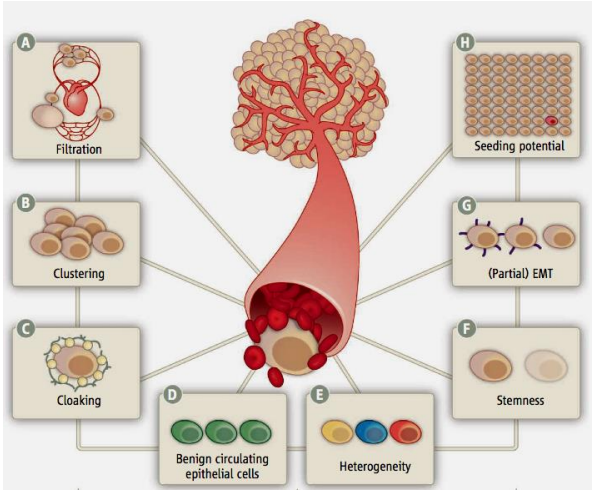

Invasive
Poorly repeatable
Heterogeneity
All techniques
Phenotype
Micro-environment

## Circulating Tumoral DNA




Non invasive
Easy repeatable
Heterogeneity
No phenotype
No micro-environment
Not all techniques

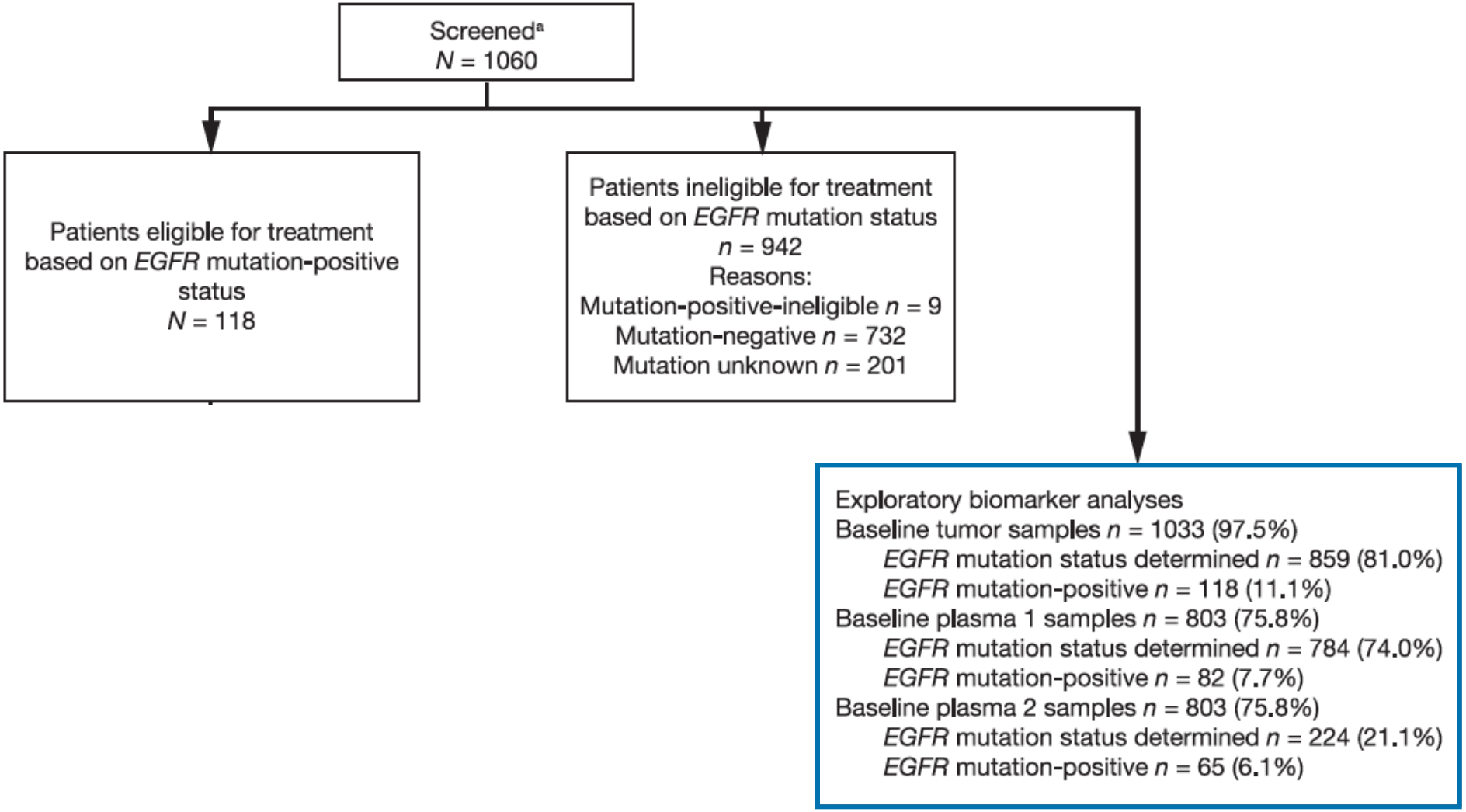
## Circulating Tumoral Cells




Non invasive, complex
Repeatable
Heterogeneity
No phenotype
No micro-environment
Some techniques

*Sequist L, Sci Transl Med 2011, 3:75ra26; Diaz LA, J Clin Oncol 2014, 32:579; Plaks L, Science 2013, 341:1186*

# Les défis de l'innovation diagnostique moléculaire[2015-2020]




*Douillard JY, J Thorac Oncol 2014, 9:1345*

# Les défis de l'innovation diagnostique moléculaire[2015-2020]

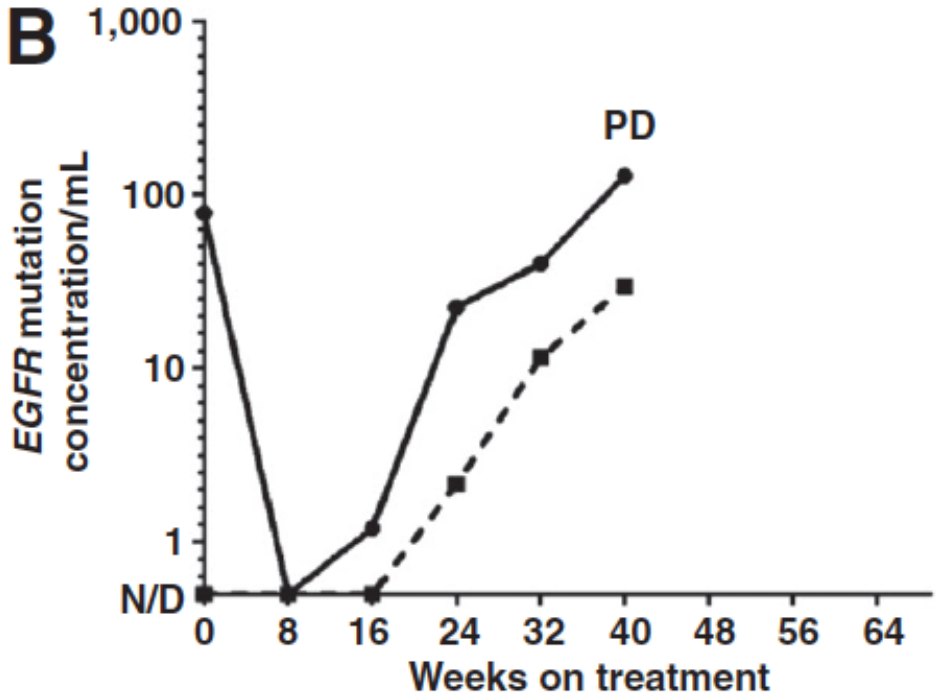
| | Plasma 1 *EGFR* Mutation Status, *n* | | |
|---|---|---|---|
| | Positive | Negative | Total |
| Tumor *EGFR* mutation status, *n*[a] | | | |
| Positive | 69 | 36 | 105 |
| Negative | 1 | 546 | 547 |
| Total | 70 | 582 | 652 |

| | *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 |

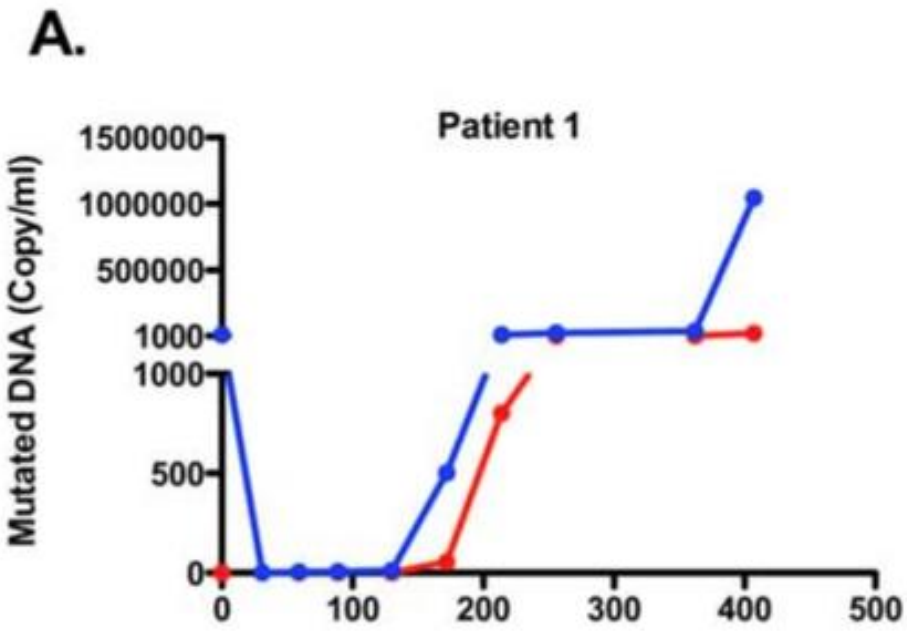
*Douillard JY, J Thorac Oncol 2014, 9:1345*

# Les défis de l'innovation diagnostique moléculaire[2015-2020]

**Digital PCR, CT-DNA pre/post TKI**
**6/9 (60%) T790M à progression**




**COBAS, CT-DNA pre/post TKI**
**9/23 (39%) T790M à progression**




*Oxnard G, Clin Cancer Res 2014, 20:1698; Sorensen BS, Cancer 2014, 120:3896*

# Les défis de l'innovation diagnostique moléculaire[2015-2020]

**Meta-analyse detection mutations EGFR sur ADN circulant, n=3110**
*(pas de précision sur le type de mutation)*

| | Studies | AUSROC | Sensitivity | Specificity |
|---|---|---|---|---|
| Overall | 27 | 0.91 (0.89–0.94) | 0.620 (0.513–0.716) | 0.959 (0.929–0.977) |
| Format of blood sample | | | | |
| Plasma | 18 | 0.92 (0.89–0.94) | 0.599 (0.468–0.717) | 0.960 (0.925–0.979) |
| Serum | 9 | 0.90 (0.87–0.92) | 0.658 (0.463–0.811) | 0.954 (0.864–0.986) |
| Detection methods | | | | |
| ARMS | 9 | 0.88 (0.85–0.91) | 0.549 (0.419–0.672) | 0.975 (0.937–0.991) |
| AS-APEX | 2 | 0.96 (0.94–0.98) | 0.859 (0.189–0.994) | 0.935 (0.527–0.995) |
| DHPLC | 2 | 0.82 (0.78–0.85) | 0.628 (0.572–0.681) | 0.846 (0.813–0.874) |
| HRM | 2 | 0.91 (0.88–0.93) | 0.887 (0.402–0.989) | 0.736 (0.042–0.994) |
| ME-PCR | 3 | 0.97 (0.95–0.98) | 0.556 (0.290–0.794) | 0.975 (0.906–0.994) |
| Collection time of blood sample | | | | |
| Before CT | 6 | 0.89 (0.86–0.91) | 0.647 (0.375–0.848) | 0.967 (0.773–0.996) |
| After CT | 2 | 0.81 (0.78–0.85) | 0.307 (0.149–0.528) | 0.961 (0.732–0.995) |

*Qiu M, Cancer Epidemiol Biomarkers Prev 2014, 24:1*

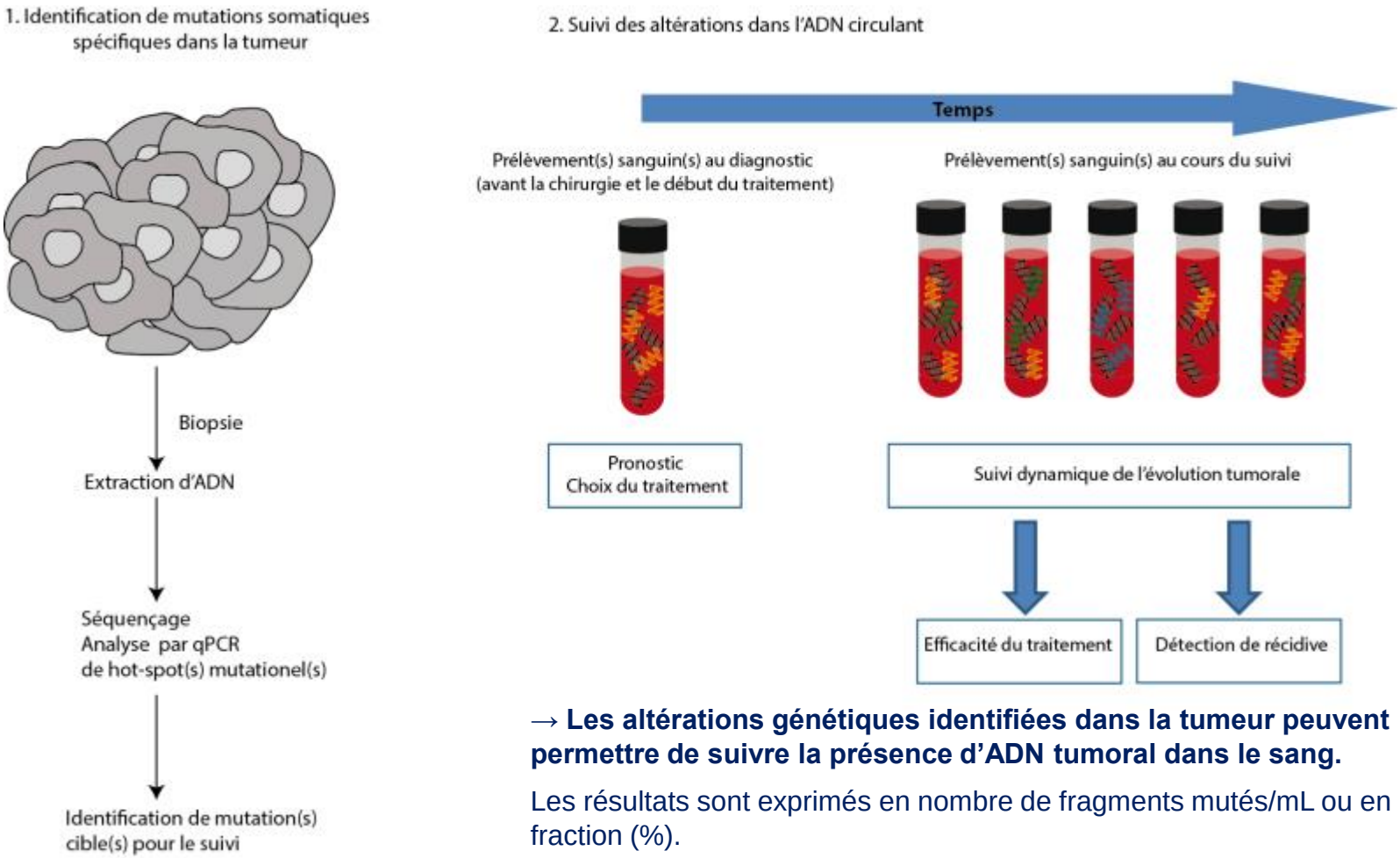
# Les défis de l'innovation diagnostique moléculaire 2015-2020

| | Séquençage de nouvelle génération (NGS) | PCR digitale en microcompartiments |
|---|---|---|
| **Sensibilité** | >10% pour le séquençage d'exomes<br>1-5% pour le NGS ciblé classique<br>(séquençage profond, >1000 reads)<br><0,1% pour les méthodes optimisées (Tam-Seq, Safe-Seq, etc.) | Dépend principalement du nombre de compartiments analysés, de la quantité d'ADN amplifiable disponibles et du taux de faux positif du test utilisé.<br><0,001% |
| **Capacité de multiplexage** | >100 amplicons (150-200 pb) pour les procédures de séquençage ciblé classiques | 5-10 cibles maximum |
| **Facilité d'analyse des résultats** | Complexe mais de nombreux logiciels ont été développés | Relativement simple |
| **Applications** | Analyse de génome tumoral et de ses évolutions sans *a priori*, analyse et suivi de l'hétérogénéité tumorale | Analyse et suivi d'un ou plusieurs marqueurs génétiques, analyse de sous-clônes tumoraux rares, validation de résultats de séquençage |

**→ Le séquençage de nouvelle génération et la PCR digitale peuvent permettre de suivre l'ADN tumoral circulant**

*D'après Pierre Laurent Puig*

# Les défis de l'innovation diagnostique moléculaire 2015-2020



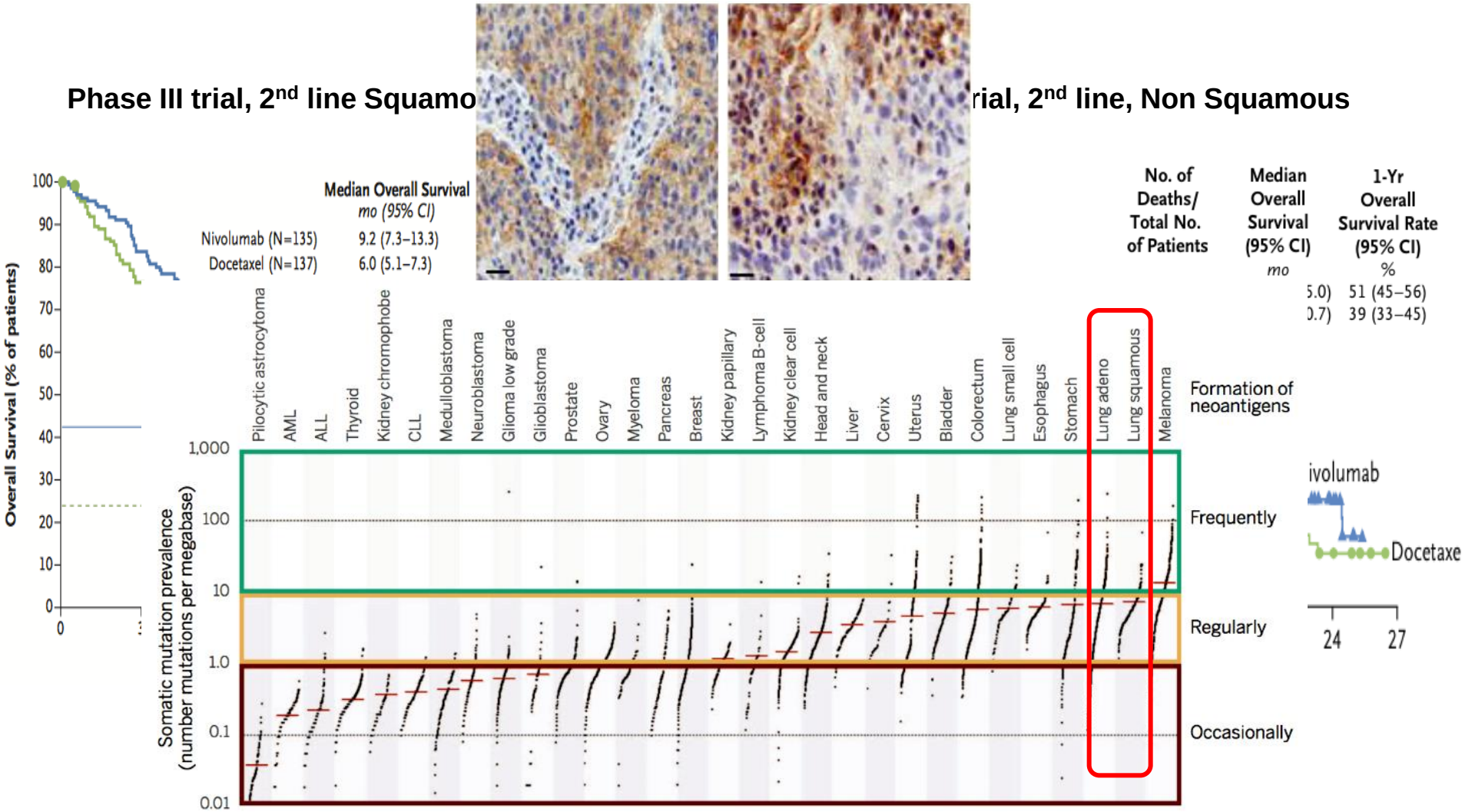

→ **Les altérations génétiques identifiées dans la tumeur peuvent permettre de suivre la présence d'ADN tumoral dans le sang.**

Les résultats sont exprimés en nombre de fragments mutés/mL ou en fraction (%).

*D'après Pierre Laurent Puig*

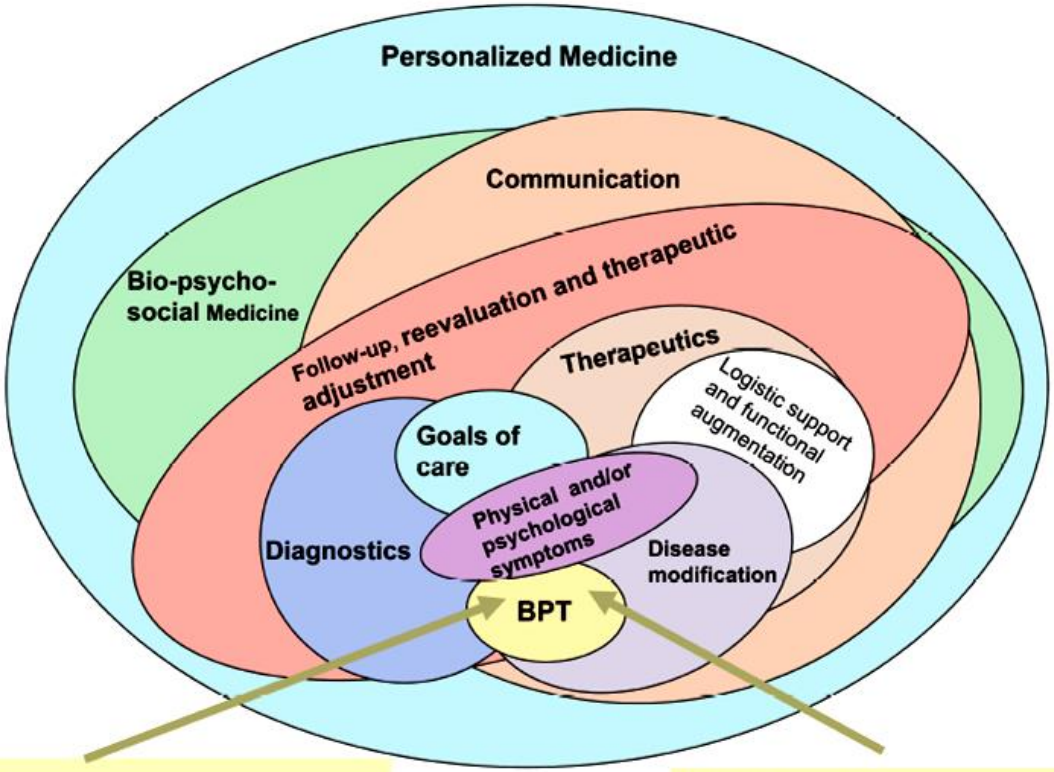
# Les défis de l'innovation diagnostique moléculaire[2015-2020]

**Phase III trial, 2nd line Squamo** **rial, 2nd line, Non Squamous**




*Brahmer J, N Engl J Med 2015, 373: 123; Borghaei H, N Engl J Med 2015, 373:1627*

# Les défis de l'innovation diagnostique moléculaire 2015-2020




**Disease Specific**

target specific identifiable molecular targets or receptors

genomic analysis for positive or negative predictive indicators for specific therapeutic options

individualized drug selection based on sophisticated in-vivo drug testing on individual patient's tumor clones

identification of rare altered molecules in bodily fluids to monitor disease burden and response to treatment

others

**Host Specific**

germline polymorphisms and pharmacogenomics to select drugs and avoid toxicity

others

*Cherny NI, J Natl Cancer Inst 2014,106:1*