Réseau de Cancérologie d'Aquitaine

ROHLim
Réseau d'Oncologie - Hématologie du Limousin

Réseau Onco Poitou Charentes

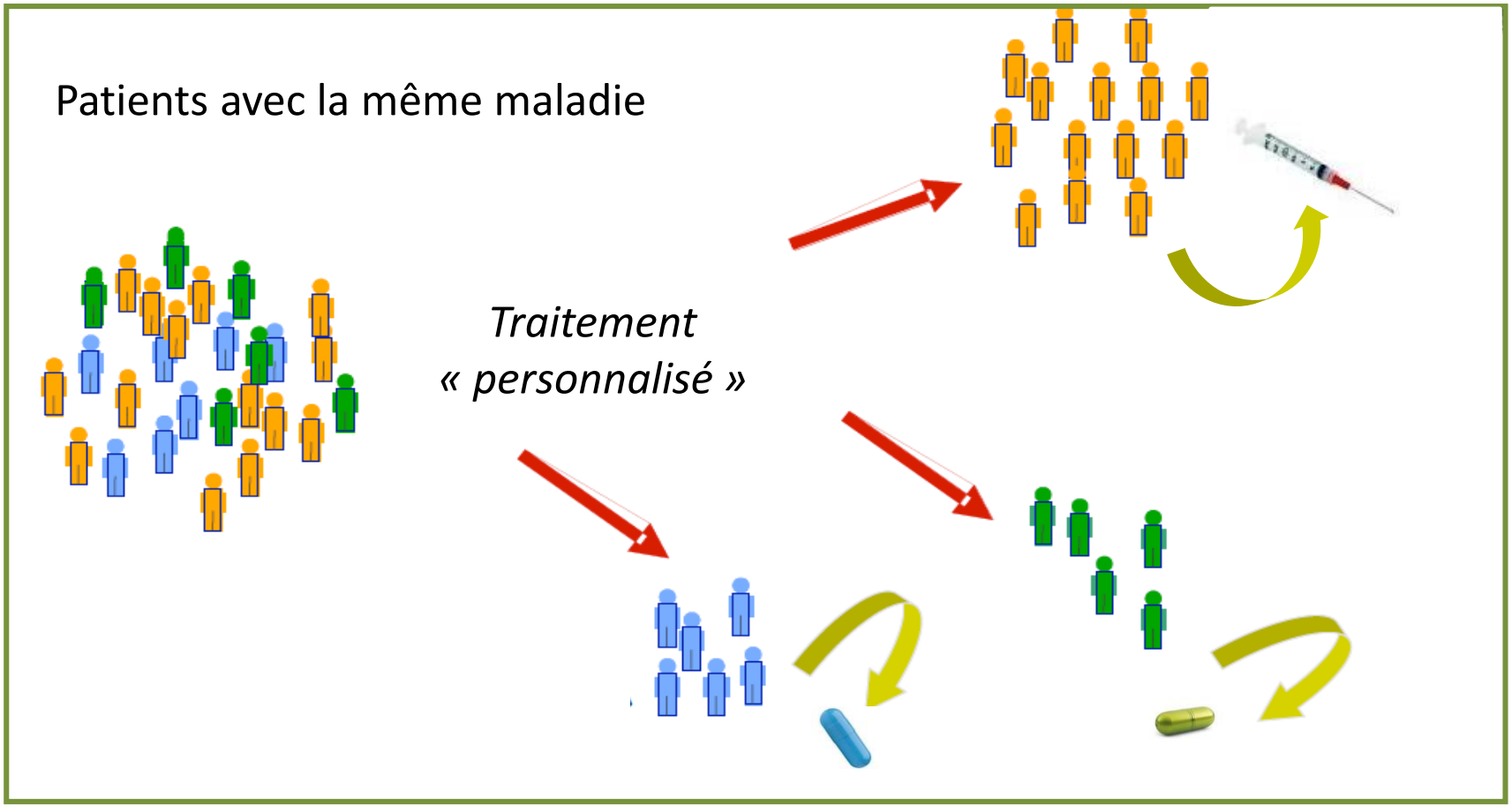
Apport de la biologie moléculaire avec le séquençage du génome

Dr Isabelle Soubeyran

Unité de Pathologie Moléculaire

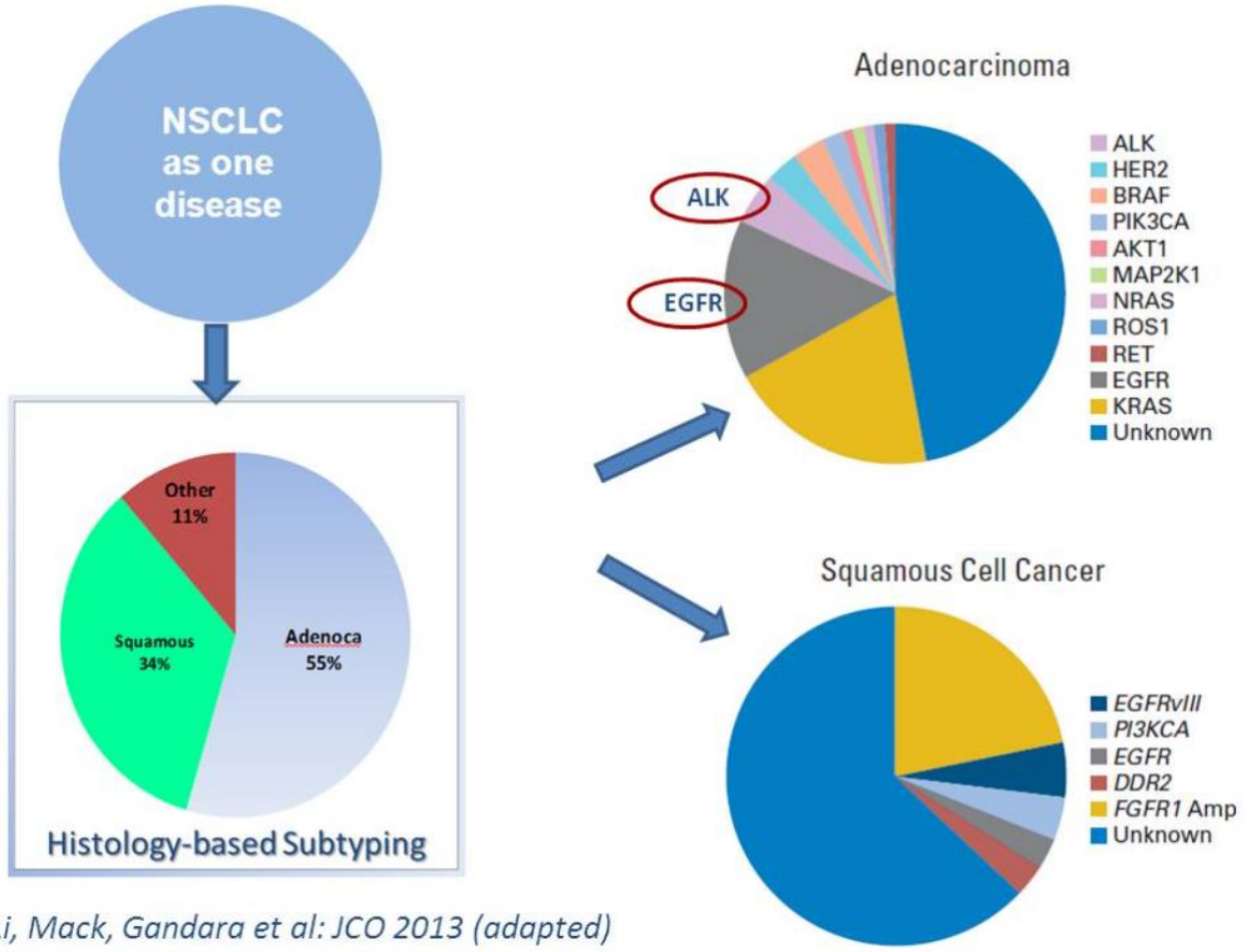
Institut Bergonié

Cancers et médecine de précision



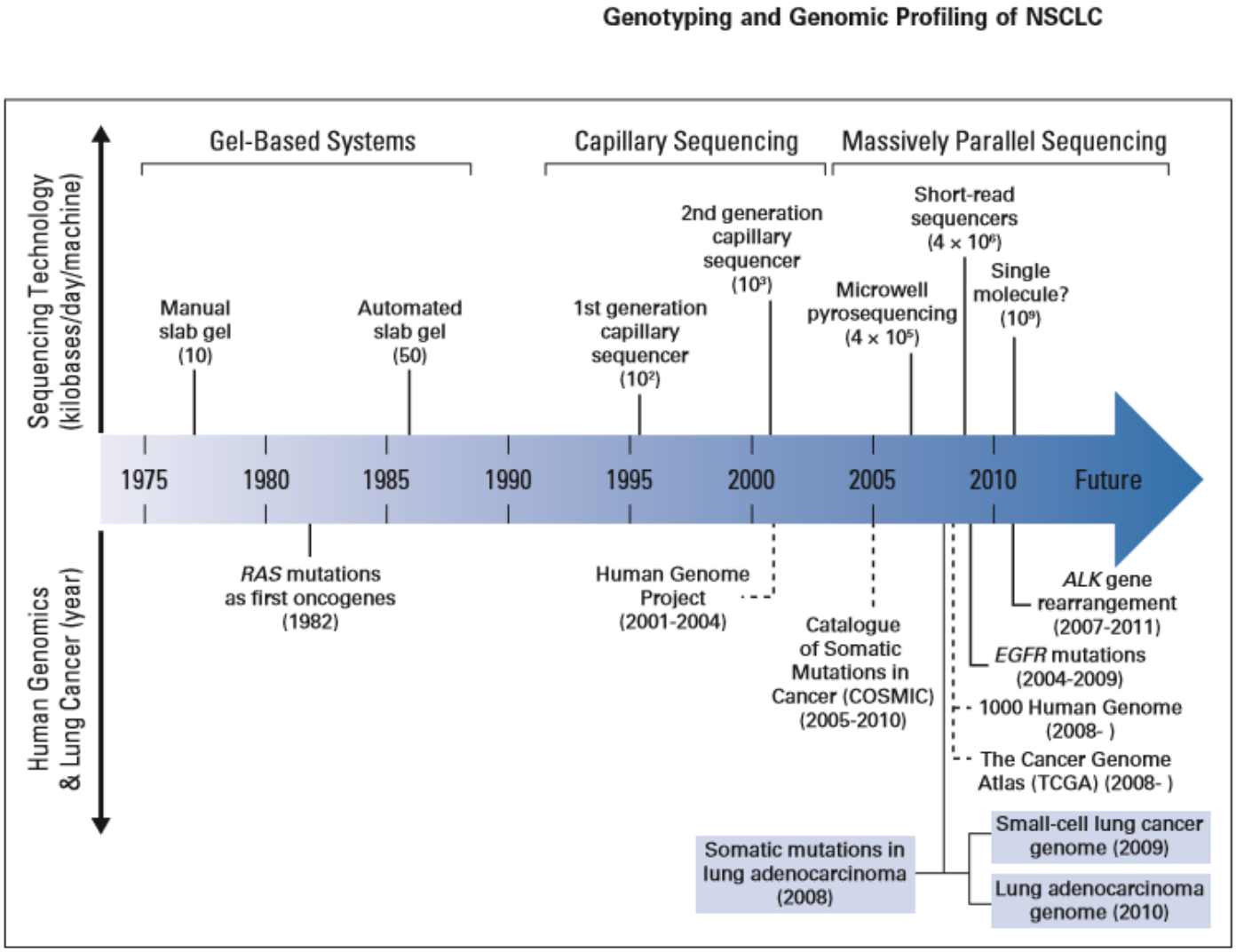
CBNPC : Intégration des données moléculaires à la classification histologique traditionnelle

ASCO Meeting Library



Li, Mack, Gandara et al: JCO 2013 (adapted)

Evolution technologique
Séquençage nouvelle génération



Les différents types de NGS

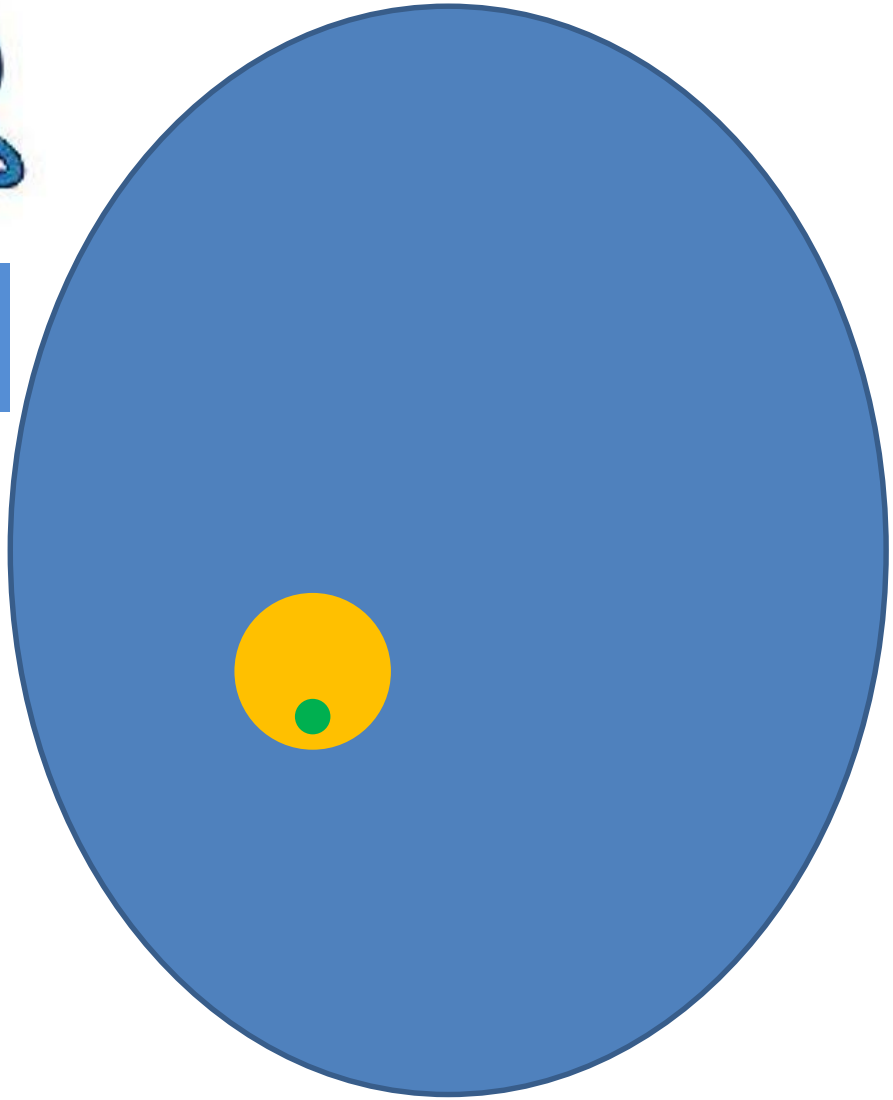
(séquençage nouvelle génération)

ADN génomique

Génome – WGS
3000Mb

Exome – WES
30Mb

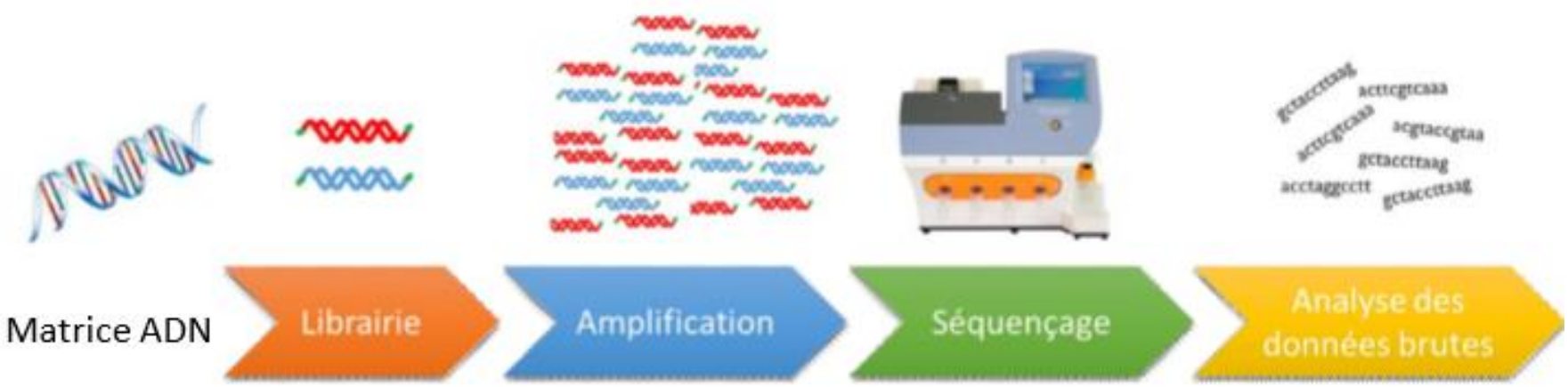
Ciblé



ARN

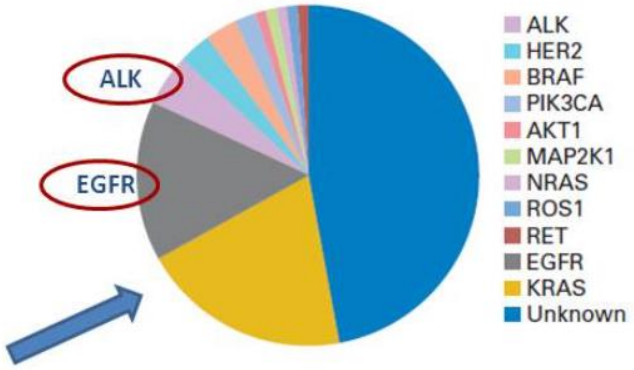
RNA-seq
- **total**
- **ciblé**

Principes du NGS
(séquençage nouvelle génération)



Screening NGS et CBNPC en 2018

NGS ciblé

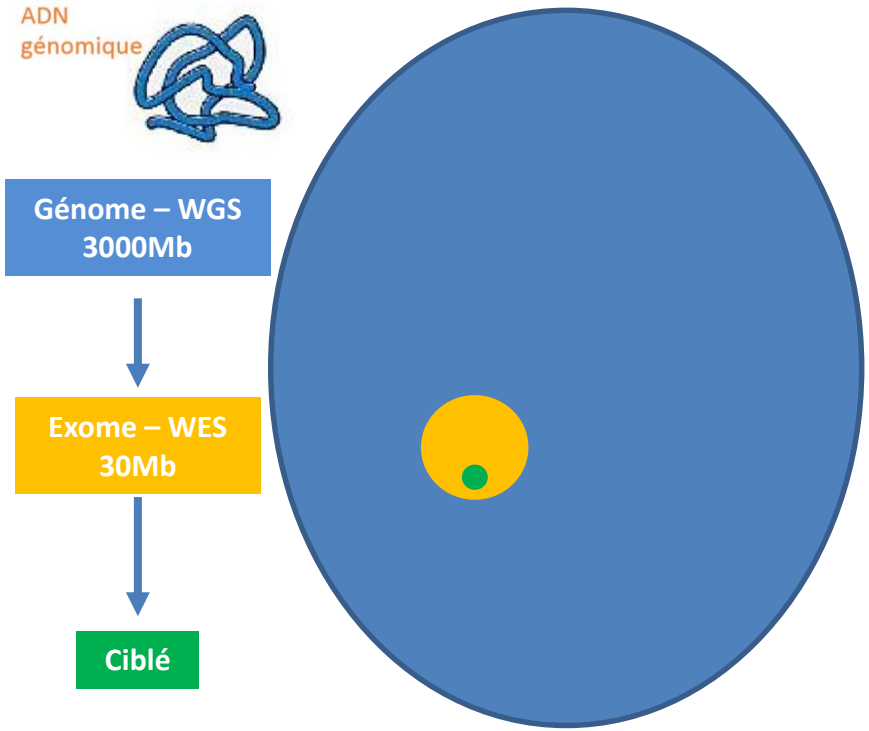


INSTITUT NATIONAL DU CANCER

Listes de gènes minimales à analyser dans le cadre d'un usage à visée diagnostique du NGS (février 2016)

Panel tumeurs solides				
Gène	**Exons / hotspots**	**Transcrit de référence**	**Molécule associée**	**utilité clinique**
AKT1	3	NM_001014431.1	AKT inhibitors	essais cliniques
ALK	23+24+25	NM_004304.1	crizotinib, ALK inhibitors	AcSé, essais cliniques
BRAF	11+15	NM_004333.4	vemurafenib, dabrafenib	AMM
EGFR	18+19+20+21	NM_005228.3	anti EGFR	AMM
ERBB2 (HER2)	20	NM_004448.2	trastuzumab, neratinib	essais cliniques
ERBB4	E452K et R393W	NM_005235.2	Afatinib	essais cliniques
FGFR2	S252, N549, K659	NM_000141.4	FGFR inhibitors	essais cliniques
FGFR3	7+9+14 (R248 àS249 et G370 à Y373)	NM_000142.4	FGFR inhibitors	essais cliniques
HRAS	2+3+4	NM_005343.2	inhibiteurs de MEK	essais cliniques
KIT	8+9+11+13+17+18	NM_000222.2	imatinib	AMM
KRAS	2+3+4	NM_033360.2	panitumumab et cetuximab	AMM
MAP2K1 (MEK1)	2	NM_002755.3	inhibiteurs de MEK	essais cliniques
MET	2 + 14 (de c.2942-63 en 5' à c.3082+20 en 34) à 20	NM_001127500.1	crizotinib	AcSé
NRAS	2+3+4	NM_002524.3	panitumumab, MEK inhibitors, BRAF inhibitors	pré-AMM, essais cliniques
PDGFRA	12+14+18	NM_006206.4	imatinib	AMM
PIK3CA	9 + 20	NM_006218.2	PI3K inhibitors	essais cliniques

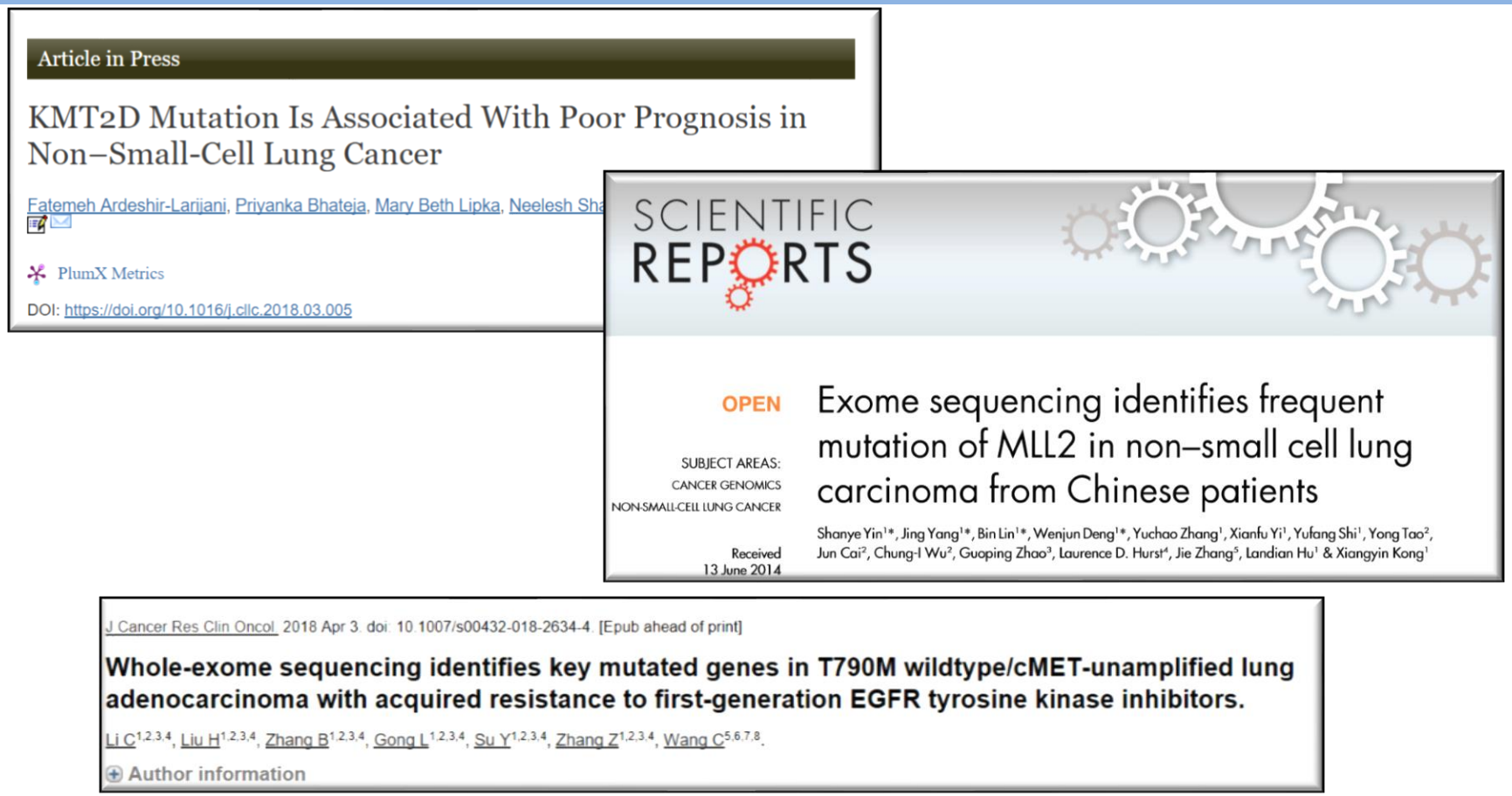
Apport de l'exome au diagnostic moléculaire des CBNPC



- Exome
  - Partie codante du génome
  - 1% du génome
  - 30Mbases
  - 20 000 gènes

Apport de l'exome au diagnostic moléculaire des CBNPC

Découverte de biomarqueurs pronostiques ou thérapeutiques ou de résistance



Article in Press

KMT2D Mutation Is Associated With Poor Prognosis in Non–Small-Cell Lung Cancer

Fatemeh Ardeshir-Larijani, Priyanka Bhateja, Mary Beth Lipka, Neelesh Sha

PlumX Metrics

DOI: https://doi.org/10.1016/j.cllc.2018.03.005

SCIENTIFIC REPORTS

OPEN

SUBJECT AREAS:
CANCER GENOMICS
NON-SMALL-CELL LUNG CANCER

Received
13 June 2014

Exome sequencing identifies frequent mutation of MLL2 in non–small cell lung carcinoma from Chinese patients

Shanye Yin[1]*, Jing Yang[1]*, Bin Lin[1]*, Wenjun Deng[1]*, Yuchao Zhang[1], Xianfu Yi[1], Yufang Shi[1], Yong Tao[2], Jun Cai[2], Chung-I Wu[2], Guoping Zhao[3], Laurence D. Hurst[4], Jie Zhang[5], Landian Hu[1] & Xiangyin Kong[1]

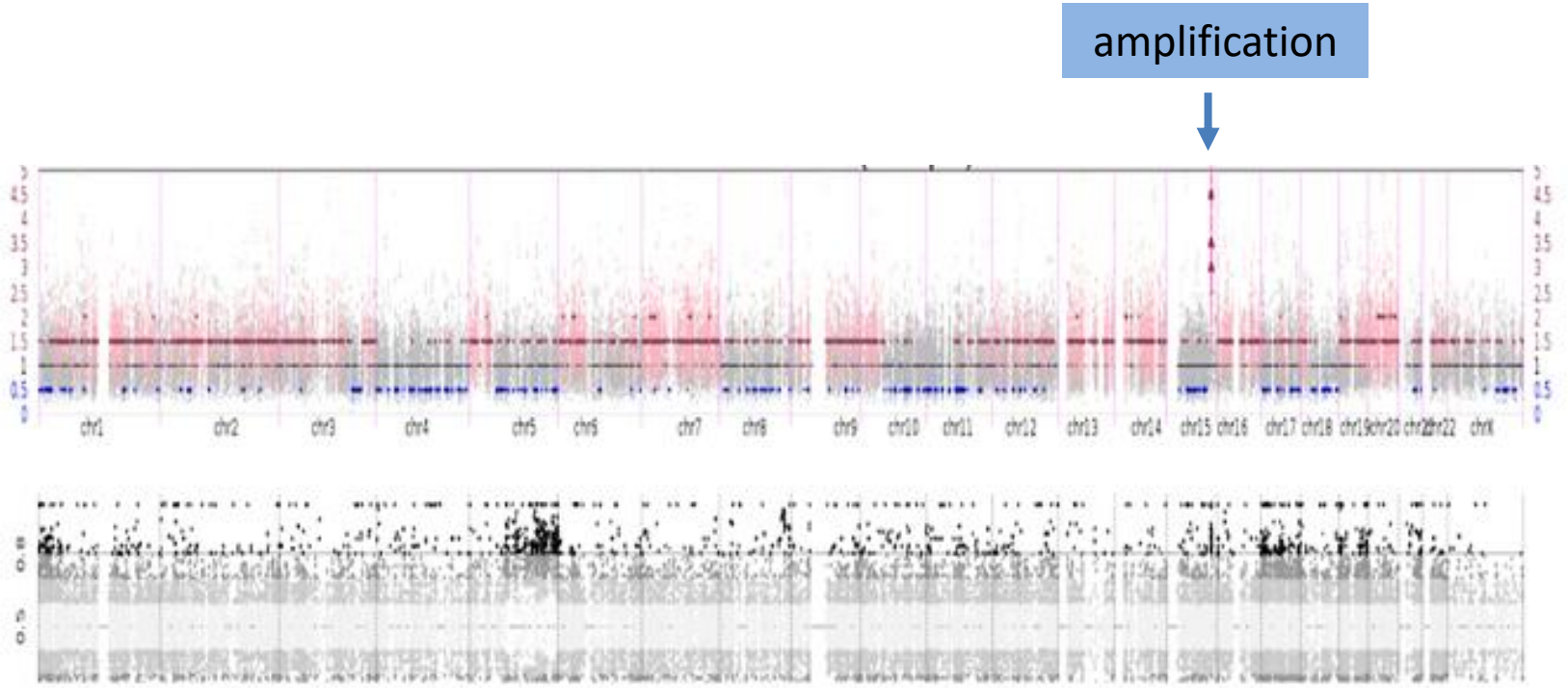
J Cancer Res Clin Oncol. 2018 Apr 3. doi: 10.1007/s00432-018-2634-4. [Epub ahead of print]

Whole-exome sequencing identifies key mutated genes in T790M wildtype/cMET-unamplified lung adenocarcinoma with acquired resistance to first-generation EGFR tyrosine kinase inhibitors.

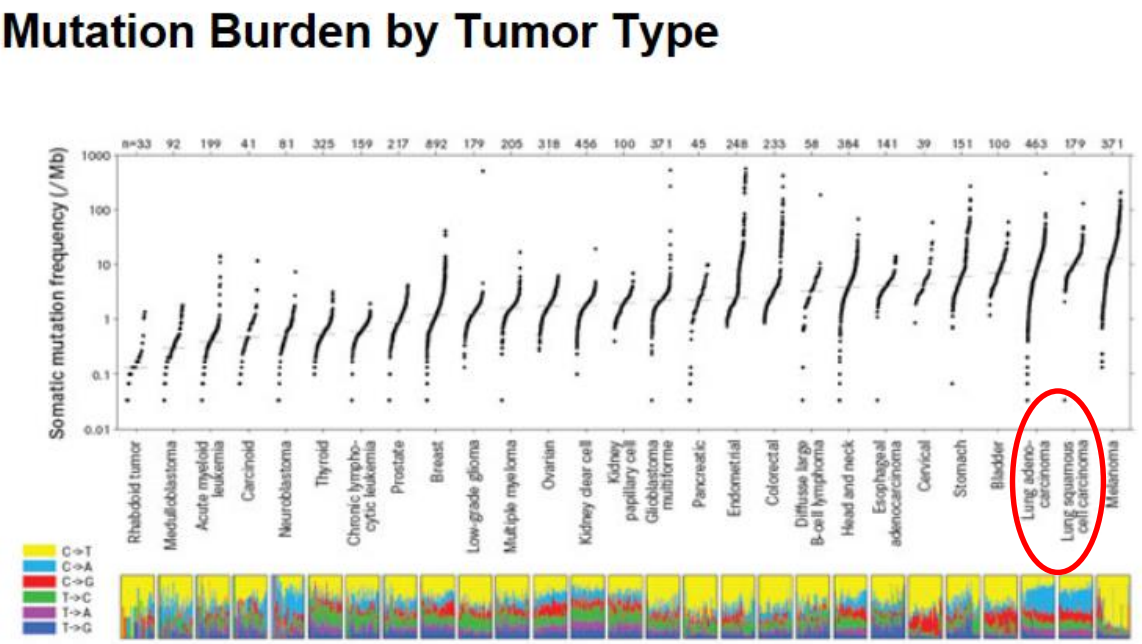
Li C[1,2,3,4], Liu H[1,2,3,4], Zhang B[1,2,3,4], Gong L[1,2,3,4], Su Y[1,2,3,4], Zhang Z[1,2,3,4], Wang C[5,6,7,8].

Author information

Apport de l'exome
Etude des variations du nombre de copies des gènes



Apport de l'exome :
Evaluation de la charge mutationnelle
(nombre de mutations somatiques/Mb)

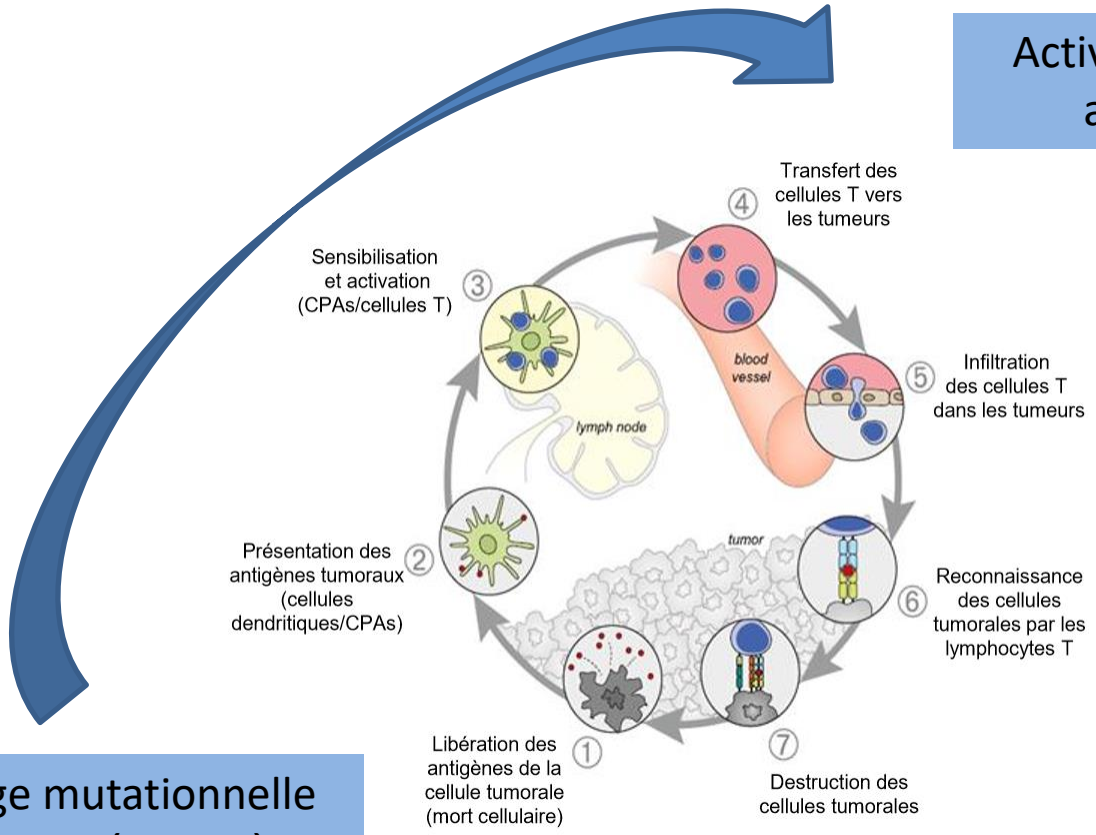


This graphic depicts the median frequencies of somatic mutations in the exome (horizontal lines) across multiple tumor types from the lowest frequencies, left, to the highest frequencies, right, as measured in mutations per megabase (Mb). The dots represent tumor-normal pairs. The colored panel at bottom illustrates the distribution of 6 possible base-pair substitutions in key at left.

Broad Institute of MIT and Harvard. Reprinted with permission.

Impact de la charge mutationnelle

Activation immunité antitumorale



Charge mutationnelle élevée => Néoantigènes

Apport de l'exome au diagnostic moléculaire des CBNPC

Charge mutationnelle et prédiction réponse immunothérapie

Please cite this article in press as: Hellmann et al., Genomic Features of Response to Combination Immunotherapy in Patients with Advanced Non-Small-Cell Lung Cancer, Cancer Cell (2018), https://doi.org/10.1016/j.ccell.2018.03.018

Cancer Cell

Article

CellPress

Genomic Features of Response to Combination Immunotherapy in Patients with Advanced Non-Small-Cell Lung Cancer

Matthew D. Hellmann,[1,2,3,4,17,*] Tavi Nathanson,[5] Hira Rizvi,[3] Benjamin C. Creelan,[6] Francisco Sanchez-Vega,[7,8] Arun Ahuja,[5] Ai Ni,[9] Jacki B. Novik,[5] Levi M.B. Mangarin,[10] Mohsen Abu-Akeel,[10] Cailian Liu,[10] Jennifer L. Sauter,[11] Natasha Rekhtman,[11] Eliza Chang,[5] Margaret K. Callahan,[1,2,4] Jamie E. Chaft,[1,2,3] Martin H. Voss,[1,2] Megan Tenet,[3] Xue-Mei Li,[12] Kelly Covello,[12] Andrea Renninger,[12] Patrik Vitazka,[12] William J. Geese,[12] Hossein Borghaei,[13] Charles M. Rudin,[1,2,3] Scott J. Antonia,[6] Charles Swanton,[14,15] Jeff Hammerbacher,[5,16] Taha Merghoub,[1,2,4,10] Nicholas McGranahan,[14] Alexandra Snyder,[1] and Jedd D. Wolchok[1,2,4,10]

Genomic Features of Response to Combination Immunotherapy in Patients with Advanced Non-Small-Cell Lung Cancer

Matthew D. Hellmann,[1,2,3,4,17,*] Tavi Nathanson,[5] Hira Rizvi,[3] Benjamin C. Creelan,[6] Francisco Sanchez-Vega,[7,8] Arun Ahuja,[5] Ai Ni,[9] Jacki B. Novik,[5] Levi M.B. Mangarin,[10] Mohsen Abu-Akeel,[10] Cailian Liu,[10] Jennifer L. Sauter,[11]

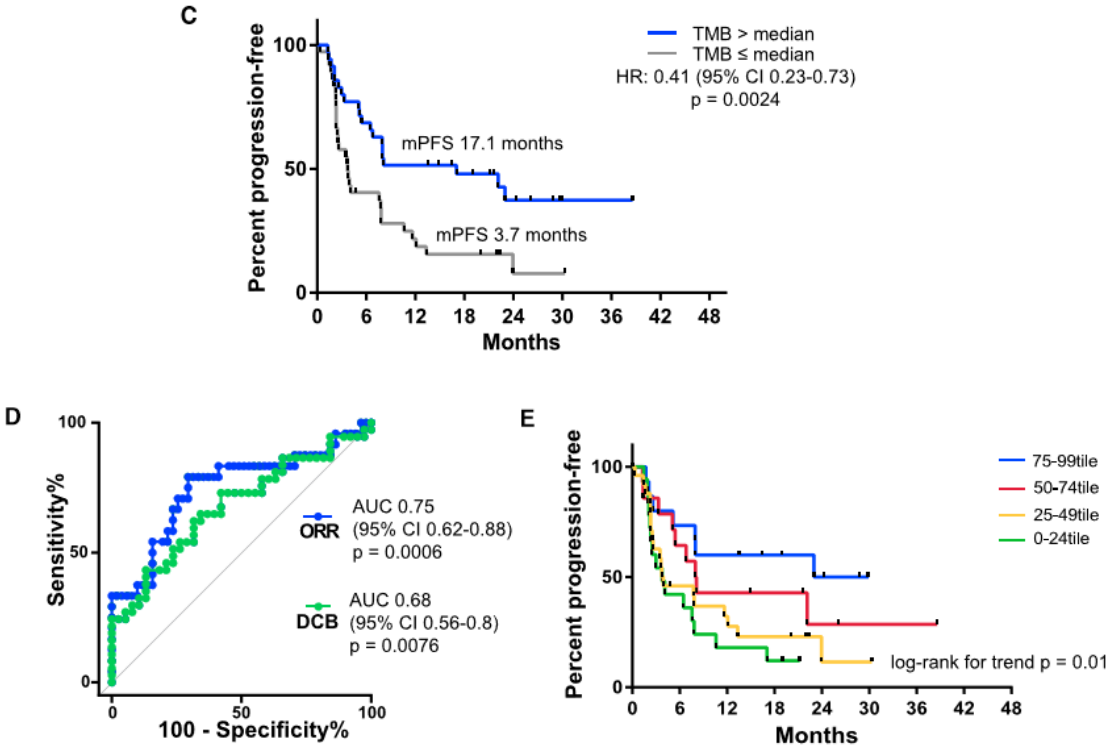


Figure 1. TMB Correlates with Efficacy in Patients with NSCLC Treated with Nivolumab Plus Ipilimumab

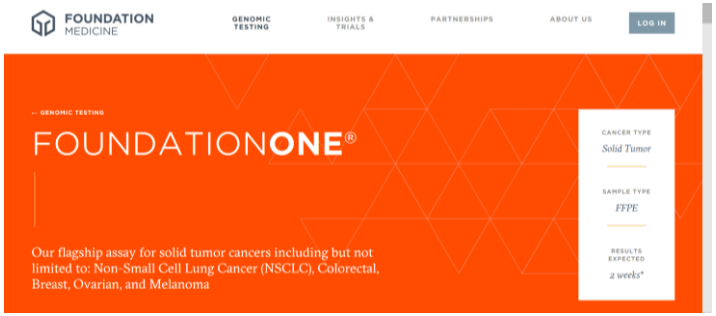
(A) TMB in patients with complete response (CR)/partial response (PR) (n = 24, blue) versus stable disease (SD)/progressive disease (PD) (n = 51, red) (median 273 versus 114 mutations, Mann-Whitney p = 0.0004) and TMB in patients with DCB (green, n = 37) versus those with NDB (purple, n = 38) (median 210 versus 113 mutations, Mann-Whitney p = 0.0071). Medians, interquartile ranges, and minimum/maximum shown in boxplots.

(legend continued on next page)

Alternative à l'exome?

Les panels de grande taille (300 à 400 gènes; 1 à 1,5Mb)

Exemple:



Published in final edited form as:
Nat Biotechnol. 2013 November ; 31(11): 1023–1031. doi:10.1038/nbt.2696.

Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing

Garrett M Frampton[1,9], **Alex Fichtenholtz**[1,9], **Geoff A Otto**[1], **Kai Wang**[1], **Sean R Downing**[1], **Jie He**[1], **Michael Schnall-Levin**[1], **Jared White**[1], **Eric M Sanford**[1], **Peter An**[1], **James Sun**[1], **Frank Juhn**[1], **Kristina Brennan**[1], **Kiel Iwanik**[1], **Ashley Maillet**[1], **Jamie Buell**[1], **Emily White**[1], **Mandy Zhao**[1], **Sohail Balasubramanian**[1], **Selmira Terzic**[1], **Tina Richards**[1], **Vera Banning**[1], **Lazaro Garcia**[1], **Kristen Mahoney**[1], **Zac Zwirko**[1], **Amy Donahue**[1], **Himisha Beltran**[2,3], **Juan Miguel Mosquera**[3,4], **Mark A Rubin**[3,4], **Snjezana Dogan**[5], **Cyrus V Hedvat**[5], **Michael F Berger**[5], **Lajos Pusztai**[6], **Matthias Lechner**[7], **Chris Boshoff**[7], **Mirna Jarosz**[1], **Christine Vietz**[1], **Alex Parker**[1], **Vincent A Miller**[1], **Jeffrey S Ross**[1,8], **John Curran**[1], **Maureen T Cronin**[1], **Philip J Stephens**[1], **Doron Lipson**[1], and **Roman Yelensky**[1]

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[2]Department of Medicine, Division of Hematology and Medical Oncology, Weill Medical College of Cornell University, New York, New York, USA

[3]Institute for Precision Medicine, Weill Cornell Medical College and New York-Presbyterian Hospital

[4]Department of Pathology and Laboratory Medicine, Weill Medical College of Cornell University, New York, New York, USA

[5]Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

[6]Yale Cancer Center Genetics and Genomics Program, Yale School of Medicine, New Haven, Connecticut, USA

[7]UCL Cancer Institute, University College London, London, UK

[8]Department of Pathology and Laboratory Medicine, Albany Medical College, Albany, New York, USA

Alternative à l'exome?

Les panels de grande taille (300 à 400 gènes; 1 à 1,5Mb)

Validation pour charge mutationnelle et prédiction immunothérapie

Companion Diagnostic, Pharmacogenomic, and Cancer Biomarkers

Molecular Cancer Therapeutics

Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers

Aaron M. Goodman[1,2,3], Shumei Kato[1,2], Lyudmila Bazhenova[1], Sandip P. Patel[1], Garrett M. Frampton[4], Vincent Miller[4], Philip J. Stephens[4], Gregory A. Daniels[1], and Razelle Kurzrock[1,2]

Abstract

Immunotherapy induces durable responses in a subset of patients with cancer. High tumor mutational burden (TMB) may be a response biomarker for PD-1/PD-L1 blockade in tumors such as melanoma and non–small cell lung cancer (NSCLC). Our aim was to examine the relationship between TMB and outcome in diverse cancers treated with various immunotherapies. We reviewed data on 1,638 patients who had undergone comprehensive genomic profiling and had TMB assessment. Immunotherapy-treated patients ($N = 151$) were analyzed for response rate (RR), progression-free survival (PFS), and overall survival (OS). Higher TMB was independently associated with better outcome parameters (multivariable analysis). The RR for patients with high (≥20 mutations/mb) versus low to intermediate TMB was 22/38 (58%) versus 23/113 (20%; $P = 0.0001$); median PFS, 12.8 months vs. 3.3 months ($P \leq 0.0001$); median OS, not reached versus 16.3 months ($P = 0.0036$). Results were similar when anti-PD-1/PD-L1 monotherapy was analyzed ($N = 102$ patients), with a linear correlation between higher TMB and favorable outcome parameters; the median TMB for responders versus nonresponders treated with anti-PD-1/PD-L1 monotherapy was 18.0 versus 5.0 mutations/mb ($P < 0.0001$). Interestingly, anti-CTLA4/anti-PD-1/PD-L1 combinations versus anti-PD-1/PD-L1 monotherapy was selected as a factor independent of TMB for predicting better RR (77% vs. 21%; $P = 0.004$) and PFS ($P = 0.024$). Higher TMB predicts favorable outcome to PD-1/PD-L1 blockade across diverse tumors. Benefit from dual checkpoint blockade did not show a similarly strong dependence on TMB. *Mol Cancer Ther; 16(11); 2598–608. ©2017 AACR.*

Intérêt du RNA-seq et CBNPC

Signature pronostique

ARN

OXFORD

JNCI J Natl Cancer Inst (2017) 109(1): djw200

doi: 10.1093/jnci/djw200
First published online October 5, 2016
Article

ARTICLE

Development of a RNA-Seq Based Prognostic Signature in Lung Adenocarcinoma

Sudhanshu Shukla*, Joseph R. Evans*, Rohit Malik, Felix Y. Feng, Saravana M. Dhanasekaran, Xuhong Cao, Guoan Chen, David G. Beer†, Hui Jiang†, Arul M. Chinnaiyan†

RNA-seq
- **total**
- **ciblé**

Intérêt du RNA-seq et CBNPC

Découverte de nouveaux transcrits de fusion

Lung Cancer. 2018 Feb;116:15-24. doi: 10.1016/j.lungcan.2017.12.004. Epub 2017 Dec 8.

ALK fusion variants detection by targeted RNA-next generation sequencing and clinical responses to crizotinib in ALK-positive non-small cell lung cancer.

McLeer-Florin A[1], Duruisseaux M[2], Pinsolle J[2], Dubourd S[3], Mondet J[4], Phillips Houlbracq M[2], Magnat N[3], Fauré J[5], Chatagnon A[6], de Fraipont F[7], Giaj Levra M[2], Toffart AC[8], Ferretti G[9], Hainaut P[10], Brambilla E[11], Moro-Sibilot D[8], Lantuejoul S[12].

An ALK status could be assigned by RNA-seq in 10/10 of the equivocal and/or borderline-positive IHC/FISH cases, 2/7 IHC/FISH discordant cases

Med Oncol. 2017 Jun;34(6):105. doi: 10.1007/s12032-017-0967-5. Epub 2017 Apr 25.

Targeting NTRK fusion in non-small cell lung cancer: rationale and clinical evidence.

Ricciuti B[1], Brambilla M[2], Metro G[2], Baglivo S[2], Matocc

BRIEF REPORT

FAST TRACK

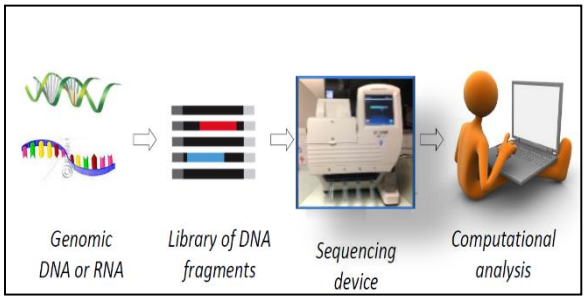
OPEN

Durable Clinical Response to Entrectinib in *NTRK1*-Rearranged Non-Small Cell Lung Cancer

Anna F. Farago, MD, PhD, Long P. Le, MD, PhD,† Zongli Zheng, PhD,† Alona Muzikansky, MA,* Alexander Drilon, MD,‡ Manish Patel, MD,‖ Todd M. Bauer, MD,§ Stephen V. Liu, MD,¶ Sai-Hong I. Ou, MD, PhD,# David Jackman, MD,** Daniel B. Costa, MD, PhD,†† Pratik S. Multani, MD,‡‡ Gary G. Li, PhD,‡‡ Zachary Hornby, MBA,‡‡ Edna Chow-Maneval, PhD,‡‡ David Luo, MPH,‡ Jonathan E. Lim, MD,‡‡ Anthony J. Iafrate, MD, PhD,† and Alice T. Shaw, MD, PhD**

Place des techniques très haut débit dans le parcours du patient

Discussion en RCP



Validation indication → NGS → Décision traitement

Faisabilité des techniques

Plateformes « INCa » actuelles	Futures plateformes France Médecine Génomique
NGS panel ciblé	Exome
NGS panel grande taille	Genome
RNA-seq ciblé	RNA-seq total
Exome	
RNA-seq total	

Financement RIHN :

- Facturation de l'établissement effecteur à l'établissement prescripteur (circulaire 2018)
- Déclaration dans FICHSUP

Conclusions- perspectives

- Evolution des techniques nécessaire
  - Charge mutationnelle
  - Transcrits de fusion
- Perspectives : Plateforme France Médecine Génomique 2025
  - projet commun région Nouvelle Aquitaine (Bordeaux-Limoges-Poitiers)
  - En attente nouvel appel d'offre
- Difficultés :
  - ↗ Temps biologiste pour validation et interprétation des analyses

MERCI DE VOTRE ATTENTION