

COURS DU GOLF

7 AU 10 OCTOBRE 2019

Groupe d'Oncologie de la Société de
Pneumologie de Langue Française



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Applications de la biopsie
liquide dans le cancer du poumon

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Applications de la biopsie liquide dans le cancer du poumon

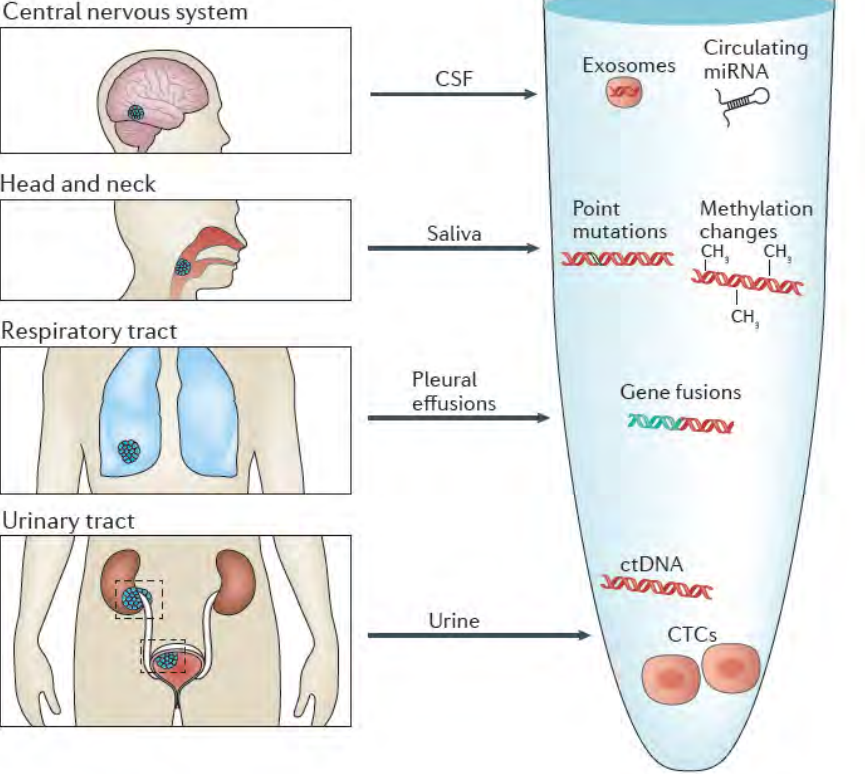
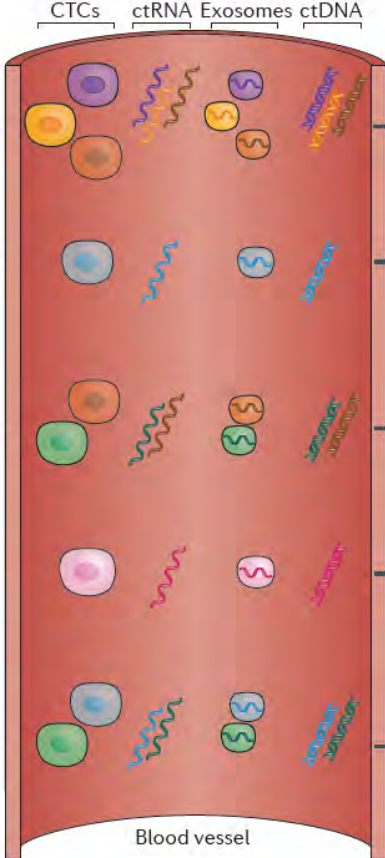
Nicolas Guibert
Hôpital Larrey, Toulouse
10 octobre 2019



Définitions

ADN libre circulant,
mais pas seulement !

Plasma,
mais pas seulement !

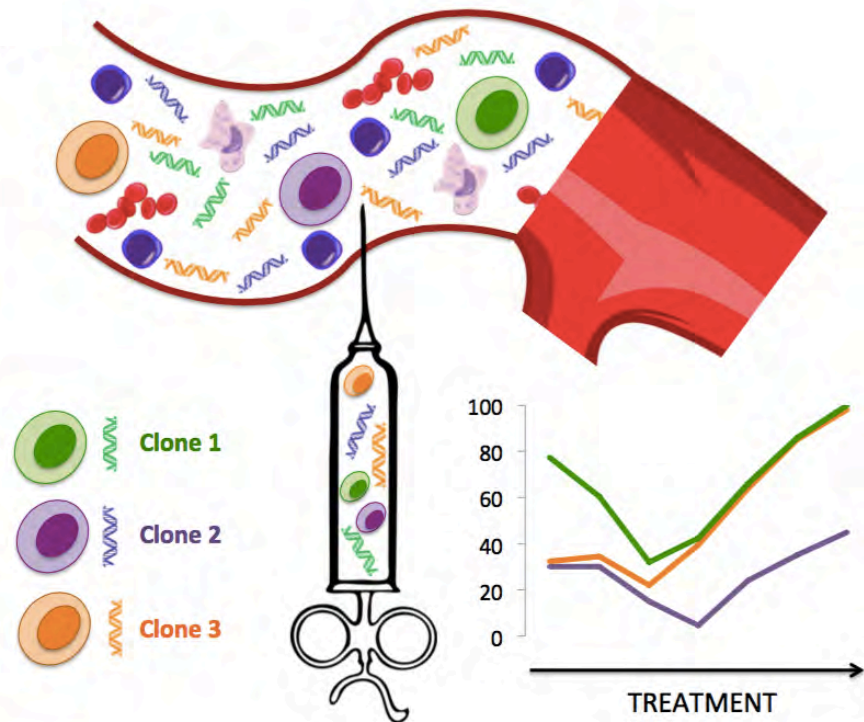
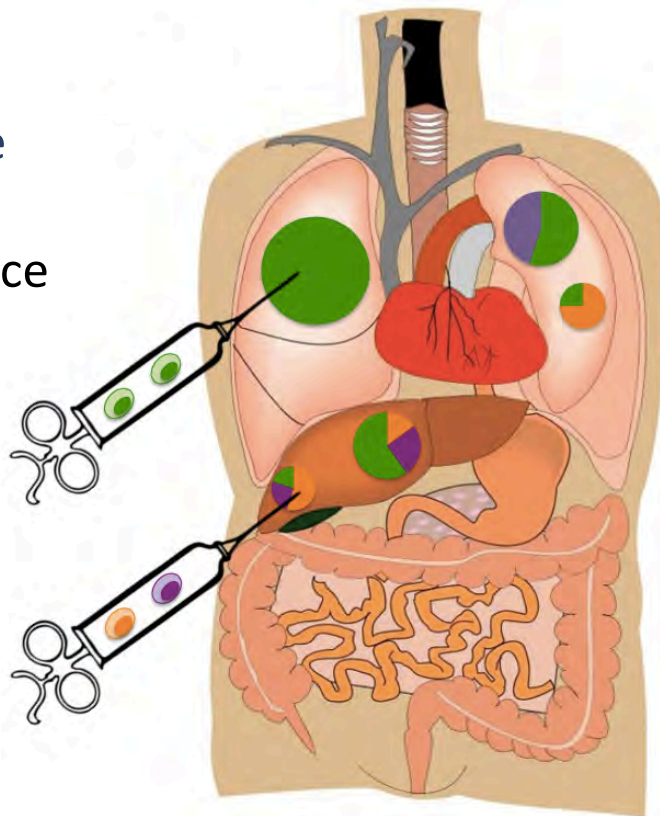


Avantages de la biopsie liquide

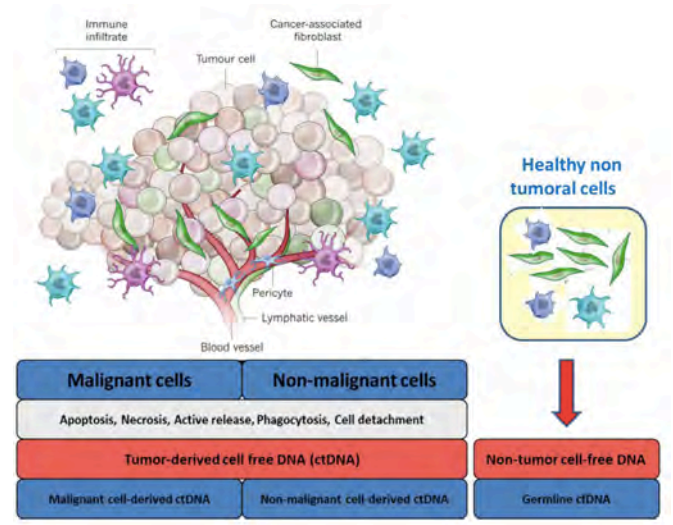
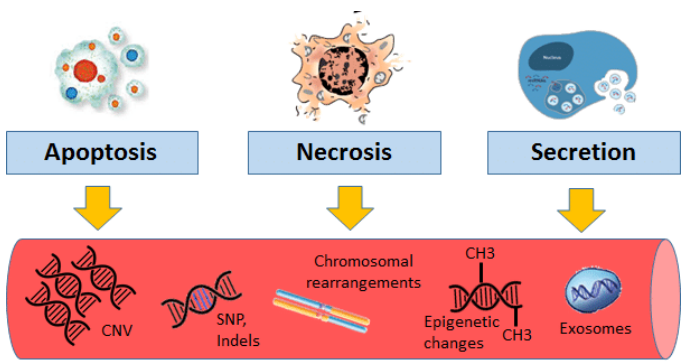
Non invasif

Hétérogénéité
tumorale
temps et espace

Suivi
évolution
subclonale



ADN tumoral vs ADN sauvage circulant



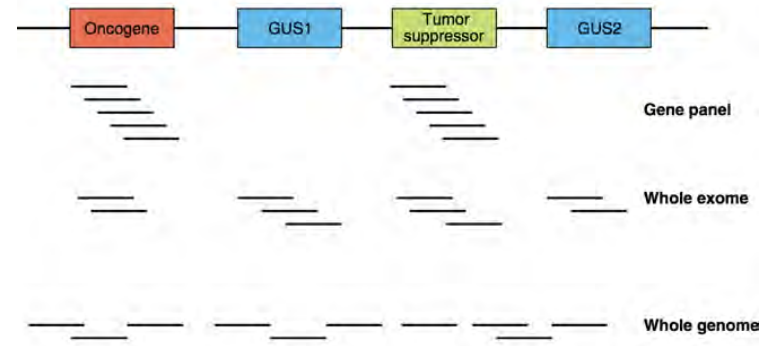
Présélection selon **propriétés biologiques** du ctDNA ?
 Puis recherche **aberration génomique**

Approche ciblée (EGFR)

Cobas, Therascreen, ddPCR, BEAMing ...

Approche multiplexe

Séquençage à haut débit (NGS)

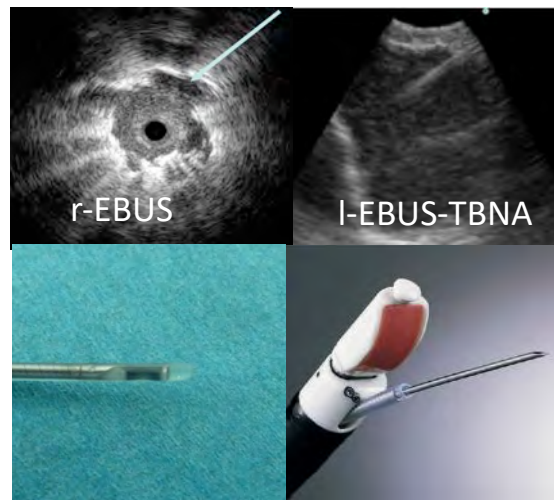
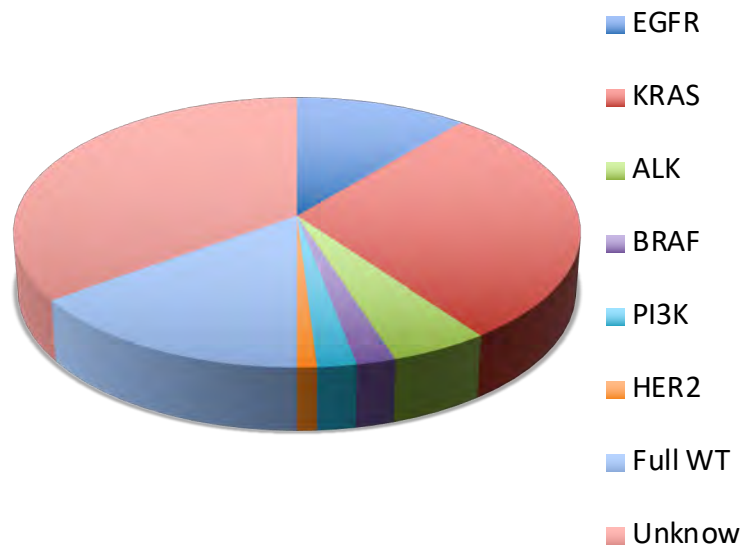


*Thierry Cancer Met Rev 2016, Oxnard CCR 2014, Sanchez Genomic Medicine 2018
 Gagan Genome Med 2015, Mouliere Sci Trans Med 2018*

I-Applications de la biopsie liquide (ADNtc) dans le cancer du poumon: **Thérapies ciblées**



Rationnel au diagnostic initial

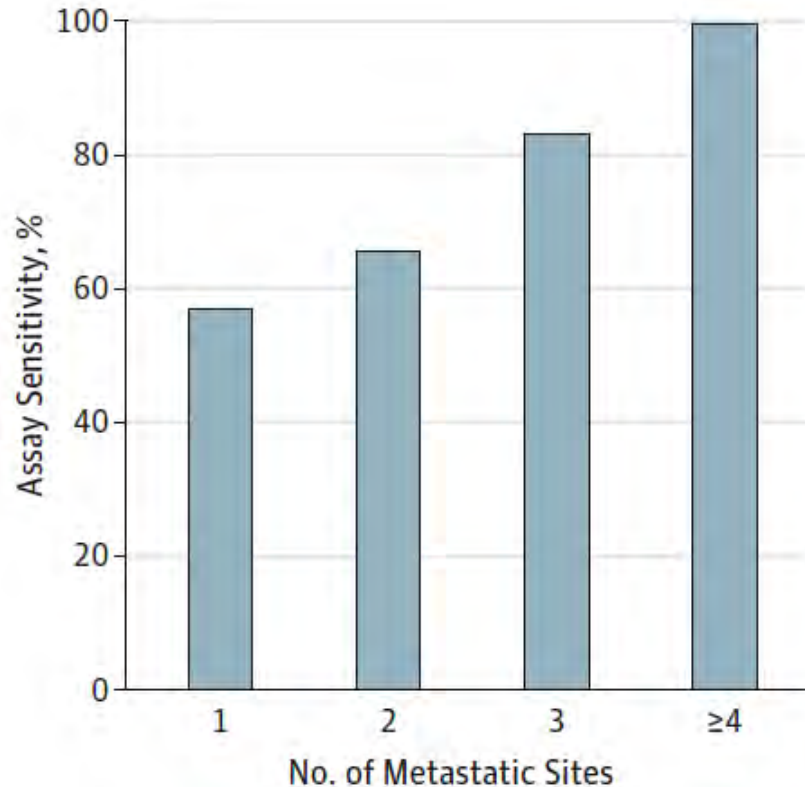


Paradoxe

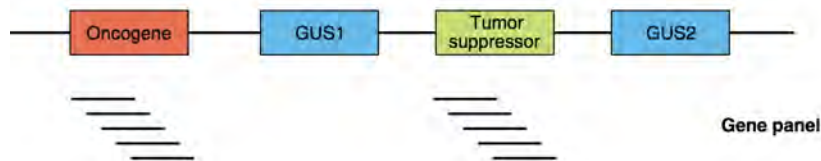
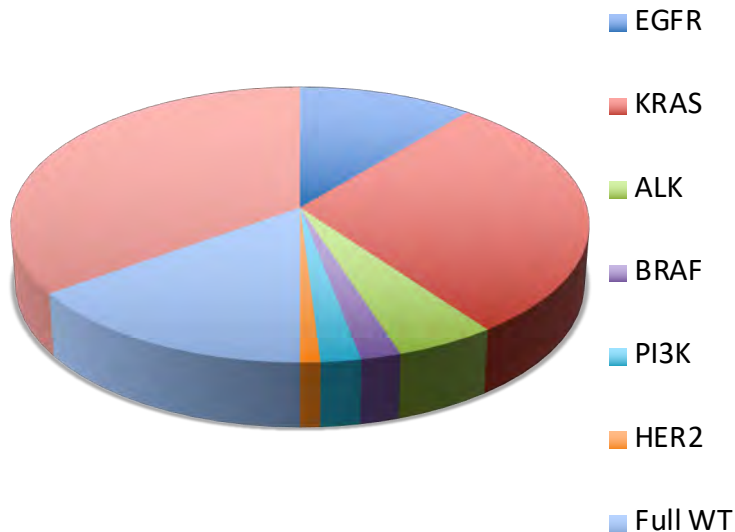
- Techniques mini-invasives: prélèvements de petite taille
- Nb croissant de cibles actionnables

Diagnostic initial: tests ciblés: ex *EGFR*

- Cobas, Therascreen, BEAMing, ddPCR: sensibilité **70%**, dépend masse tumorale
- Spécificité **100%** !



Diagnostic initial: NGS (séquençage à haut débit)



Tissue Genotype	Plasma NGS
<i>BRAF</i> V600E	<i>KRAS</i> G12D (0.18%)*
<i>BRAF</i> V600E	none
<i>BRAF</i> G469A	<i>BRAF</i> G469A (12.8%)
<i>MET</i> exon 14	<i>MET</i> exon 14 (1.4%)
<i>MET</i> exon 14	<i>MET</i> exon 14 (12.1%)
<i>HER2</i> exon 20 ins	<i>HER2</i> exon 20 ins (0.3%)
Sensitivity (rare SNVs) 66.7% (4/6)	
<i>EML4-ALK</i> fusion	<i>EML4-ALK</i> fusion
<i>EML4-ALK</i> fusion	<i>EML4-ALK</i> fusion
<i>EML4-ALK</i> fusion	<i>EML4-ALK</i> fusion
<i>EML4-ALK</i> fusion	<i>EML4-ALK</i> fusion
<i>EML4-ALK</i> fusion	<i>EML4-ALK</i> fusion
<i>EML4-ALK</i> fusion	<i>EML4-ALK</i> fusion
<i>EML4-ALK</i> fusion	<i>EML4-ALK</i> fusion
<i>EML4-ALK</i> fusion	none
<i>CD74-ROS1</i> fusion	<i>CD74-ROS1</i> fusion
<i>CD74-ROS1</i> fusion	<i>CD74-ROS1</i> fusion
Sensitivity (<i>ALK/ROS1</i>) 89% (8/9)	

Diagnostic initial: NGS (séquençage à haut débit)

Screening

GUARDANT HEALTH

GENOMICS GRAIL

myriad
WHEN DECISIONS MATTER

natera freenome
Conceive. Deliver.

AcuamarkDx CHRONIX
BIOMEDICAL

Biomarqueurs traitement

CARIS LIFE SCIENCES OncoDNA TEMBUS
ThermoFisher SCIENTIFIC GUARDANT HEALTH

IBM GENOMICS Biocept
biodesix NEO GENOMICS QIAGEN GENOPTIX

ONANT Genomic Health illumina
SOPHIA GENETICS Quest Diagnostics oncologica

new oncology PGD NAVICAN
Personal Genome Diagnostics PRECISION CANCER CARE
an Illumina/Jan HealthCare company

LabCorp nanoString Roche

Inivata admera health FOUNDATION MEDICINE BiOCARTIS

BGI BOREAL GENOMICS GENETRON HEALTH
sysmex cynvenio Agena
BIOSCIENCE

Monitoring

GUARDANT HEALTH

FOUNDATION MEDICINE GENOPTIX

GENOMICS

BOREAL GENOMICS

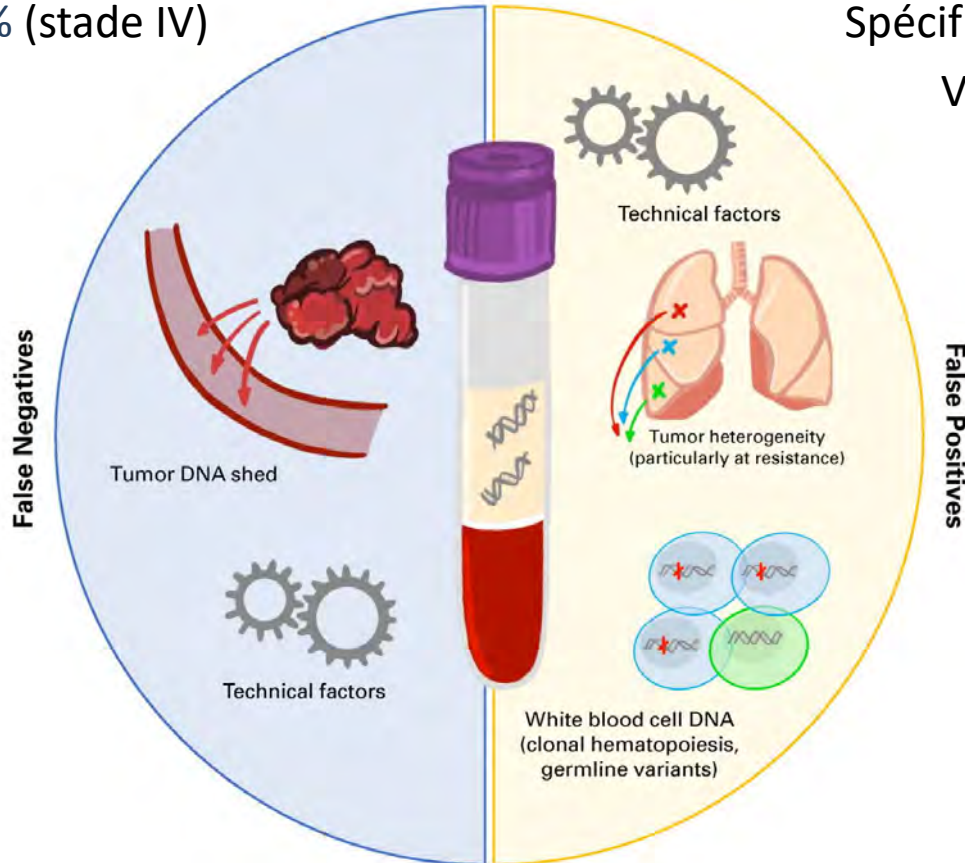
CHRONIX BIOMEDICAL

Performances et limites du NGS de l'ADNtc

Sensibilité 70-80% (stade IV)

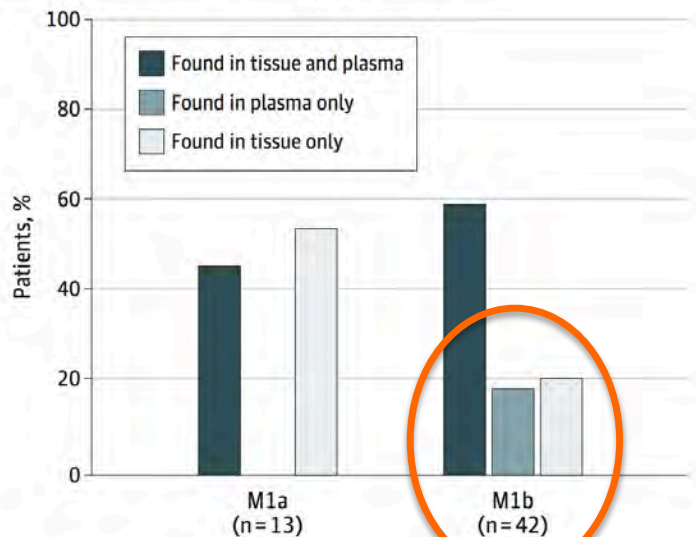
Spécificité dépend MAF

VPP 100% > 1%



Clinical Implications of Plasma-Based Genotyping With the Delivery of Personalized Therapy in Metastatic Non-Small Cell Lung Cancer

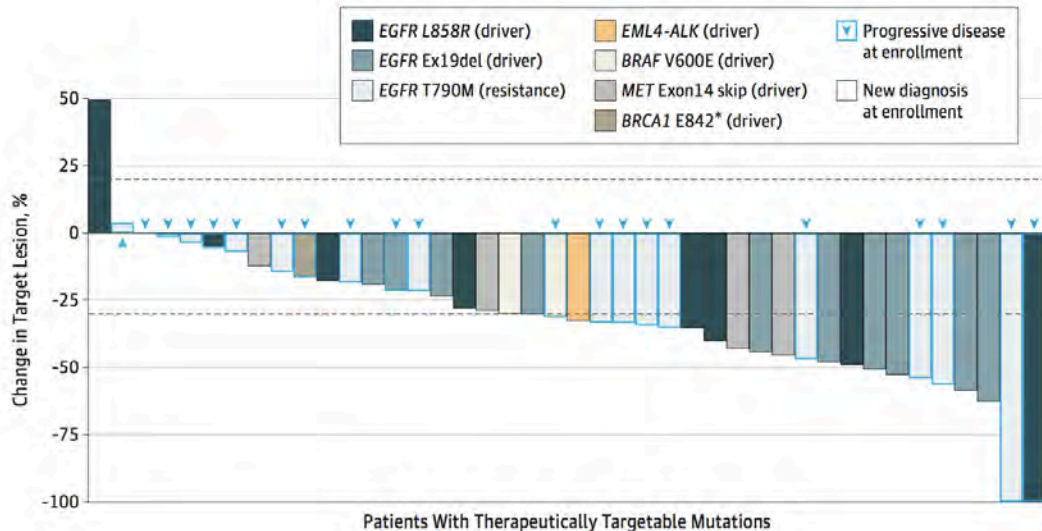
B Detection of therapeutically targetable mutation



Aggarwal, JAMA Oncol 2019

Plasma vs Tissue Next-Generation Sequencing in Non-Small Cell Lung Cancer—Either, Both, or Neither?

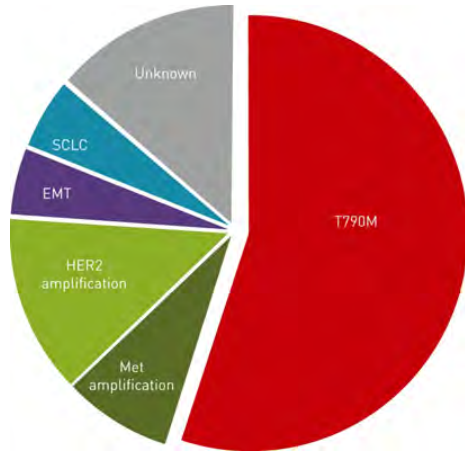
Bishal Gyawali, MD, PhD; Howard (Jack) West, MD



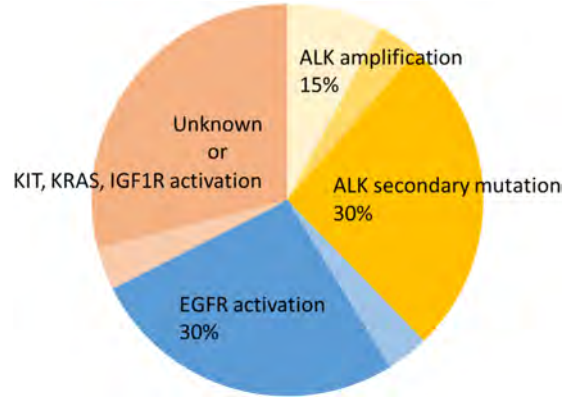
Gyawali, JAMA Oncol 2019

Rationnel à la résistance

Résistance EGFR-TKI

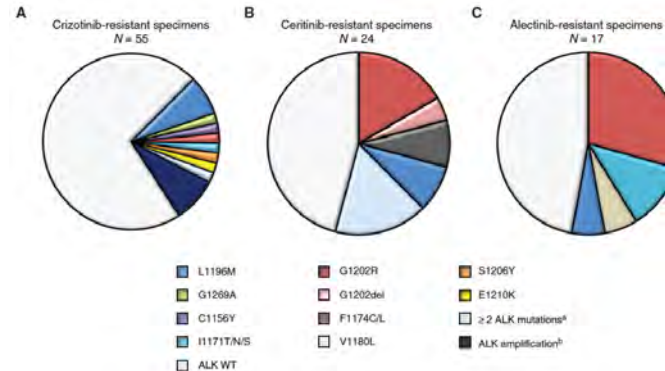
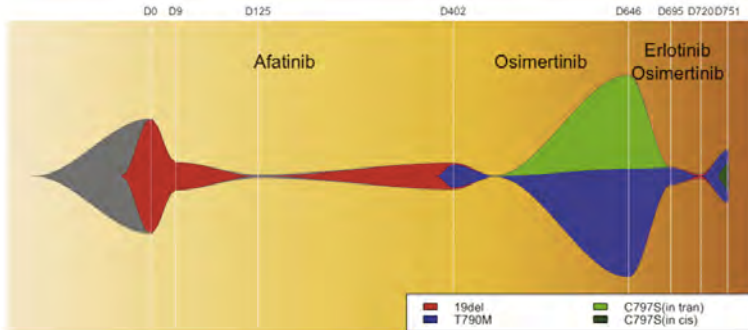


Résistance ALK-TKI

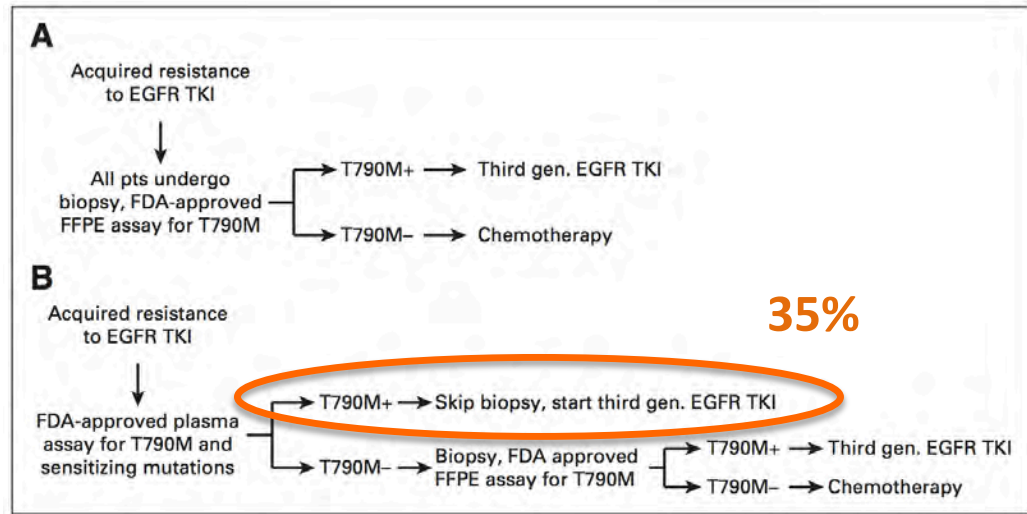
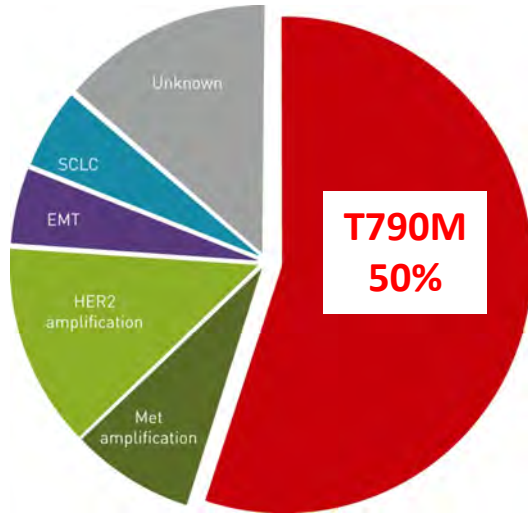


Biopsie liquide:

- Accès non invasif et rapide à la biologie de la tumeur
- Surveillance évolution clonale
- Tenant compte de l'hétérogénéité



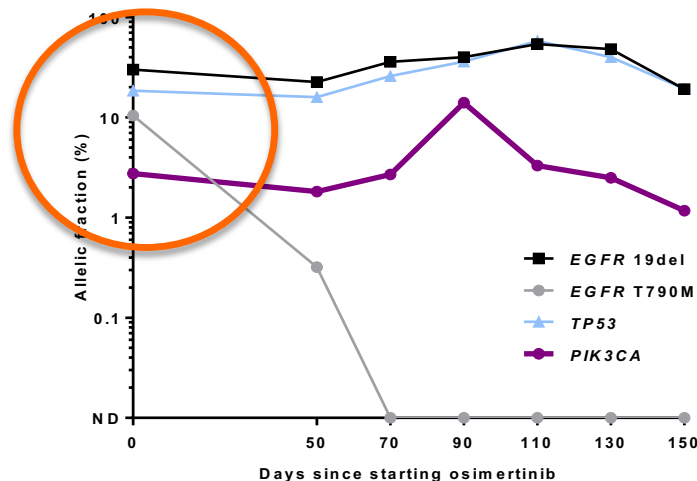
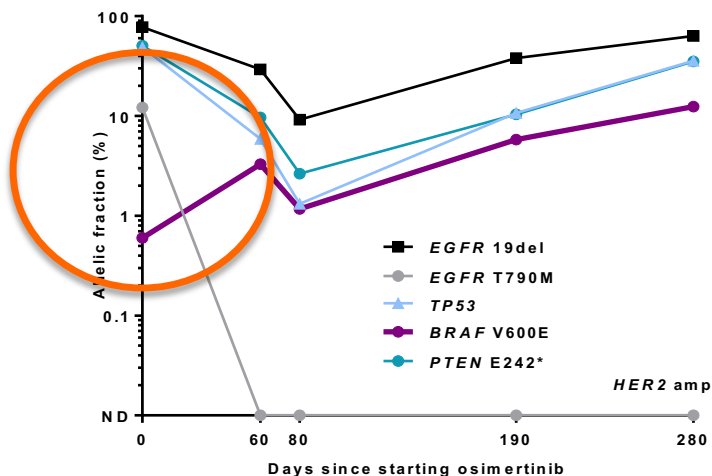
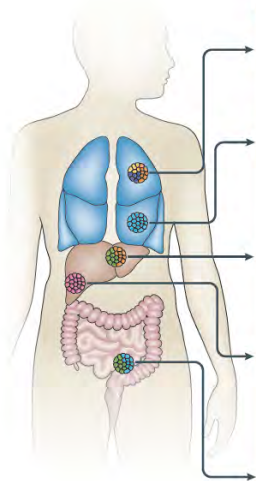
Limites des tests ciblés ex. *EGFR*



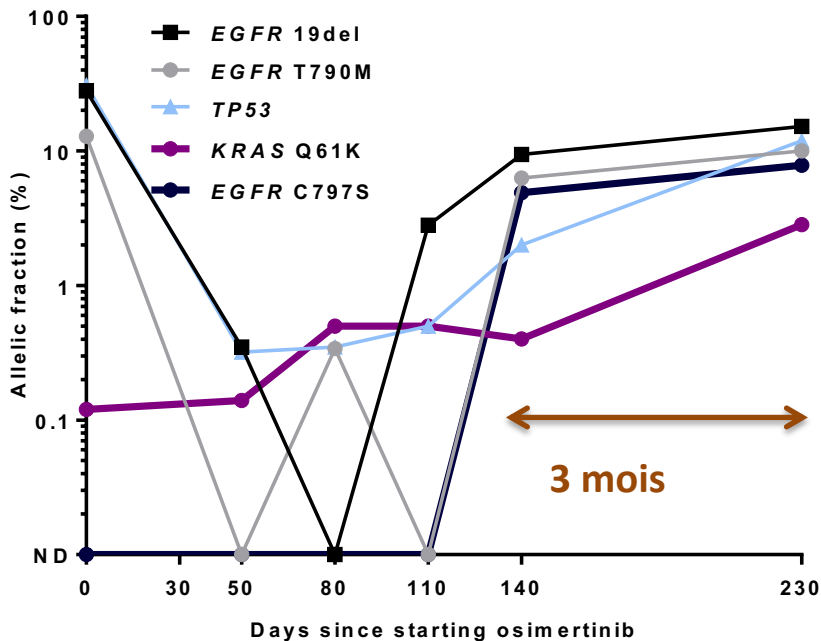
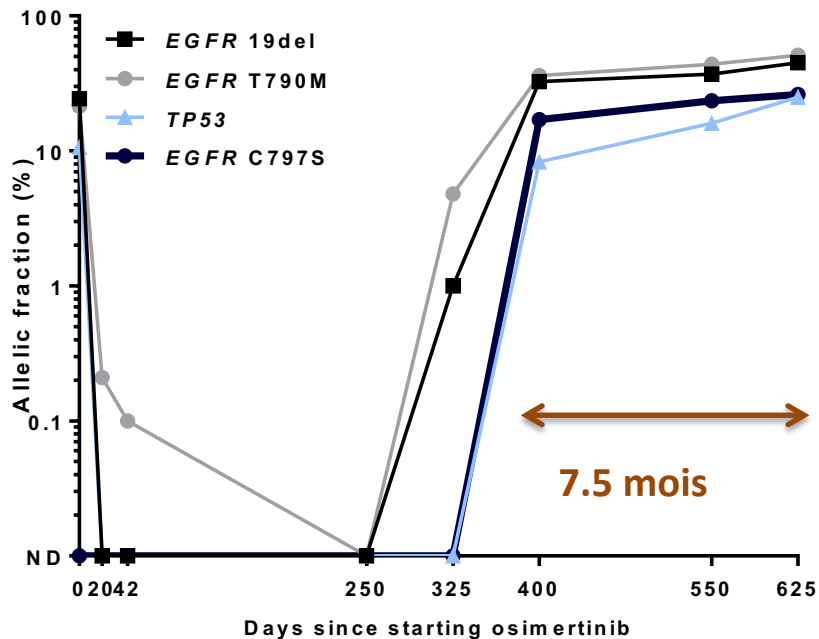
- Paradigme actuel de détection de T790M basé sur screening plasma (sensibilité **70%**)
- Intérêt du **séquençage à haut débit** pour éviter plus de rebiopsies

Limites des tests ciblés ex. *EGFR*: Séquençage à haut débit (NGS)

- **Hétérogénéité** de la résistance (45% mécanismes multiples)
- Importance AF relative T790M/driver



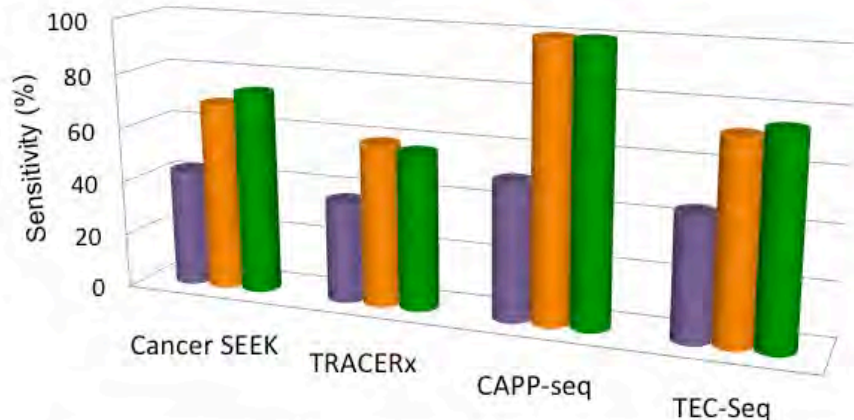
La progression plasmatique précède la progression radiologique



II-Applications de la biopsie liquide dans le cancer du poumon: **Stades précoces**



Dépistage



	Cancer SEEK	TRACERx	CAPP-seq	TEC-Seq
■ Stade I	43	37	50	45
■ Stade II	69	59	100	72
■ Stade III	74	57	100	75

Early stages
Hybrid Capture
Plasma NGS
(16 genes) and
8 protein markers

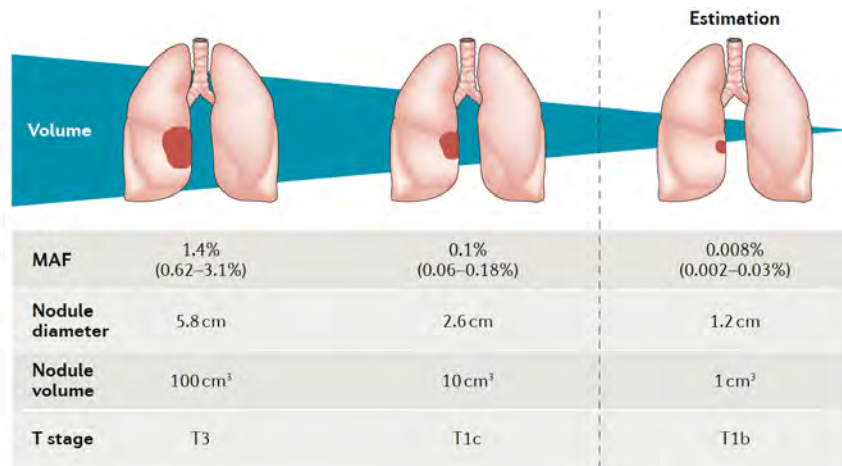
MRD
Plasma NGS
Patient-specific
multiplex PCR
(10 to 22 SNVs)
Subclonal evolution

**Early stages
MRD**
Hybrid Capture
Plasma NGS
(139 genes)

**Early stages
MRD**
Hybrid Capture
Plasma NGS
(58 genes)

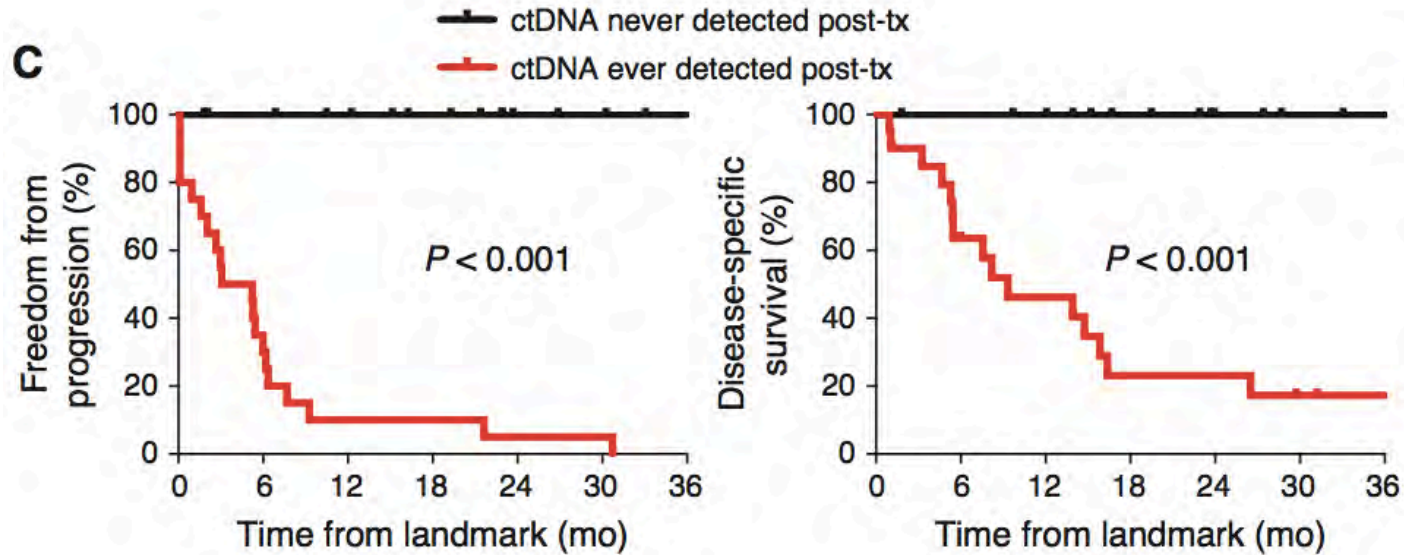
Early stage NSCLC — challenges to implementing ctDNA-based screening and MRD detection

Christopher Abbosh, Nicolai J. Birkbak and Charles Swanton



Maladie résiduelle

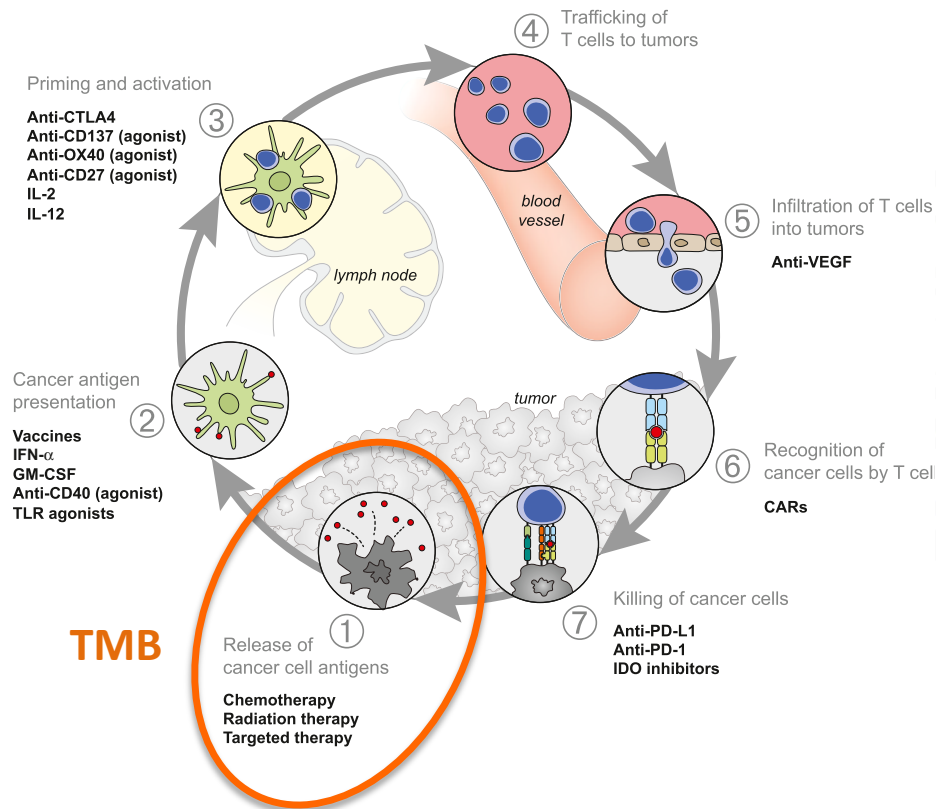
NGS plasmatique après traitement curatif d'un CBNPC localement avancé (33/40 stade II/III)



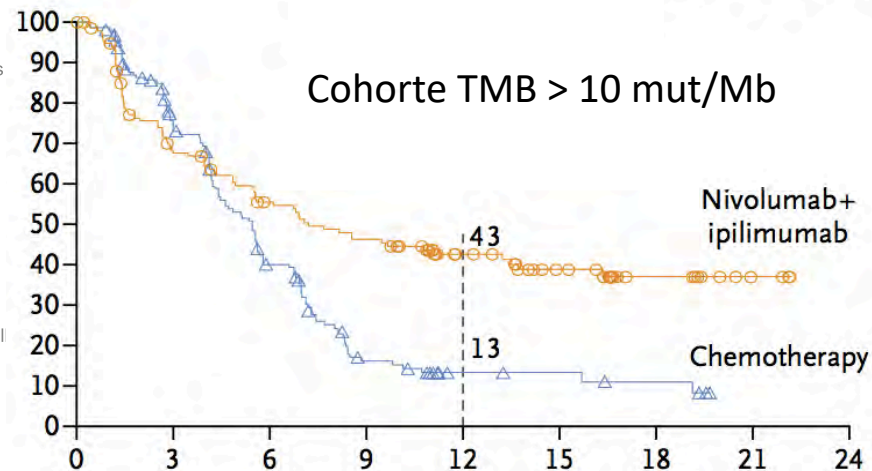


III- Applications de la biopsie liquide dans le cancer du poumon: **Immunothérapie**

ADN tumoral circulant et charge mutationnelle tumorale

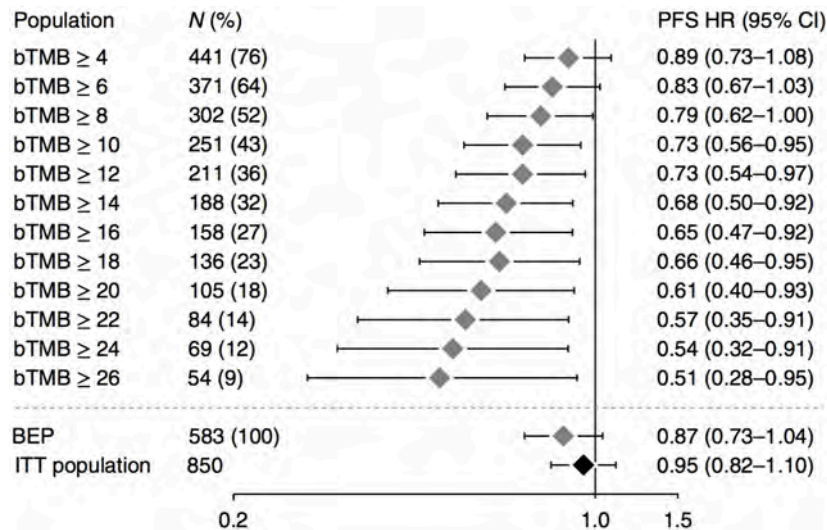


TMB: Charge mutationnelle tumorale

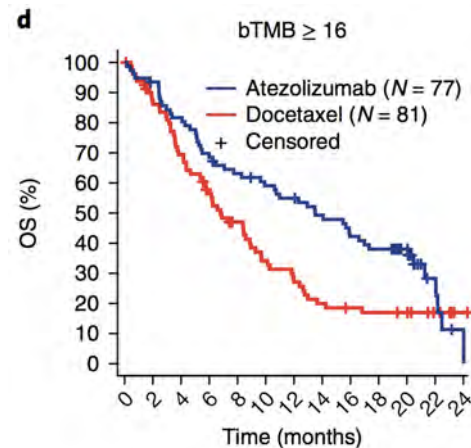
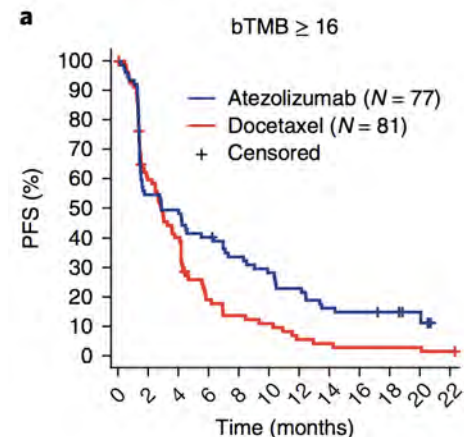


ADN tumoral circulant et charge mutationnelle tumorale

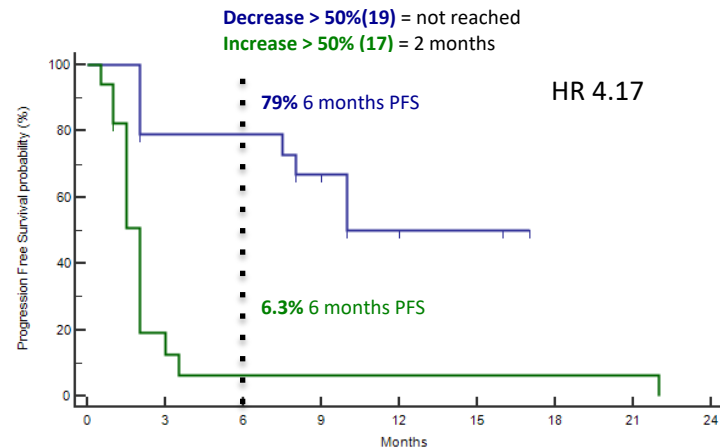
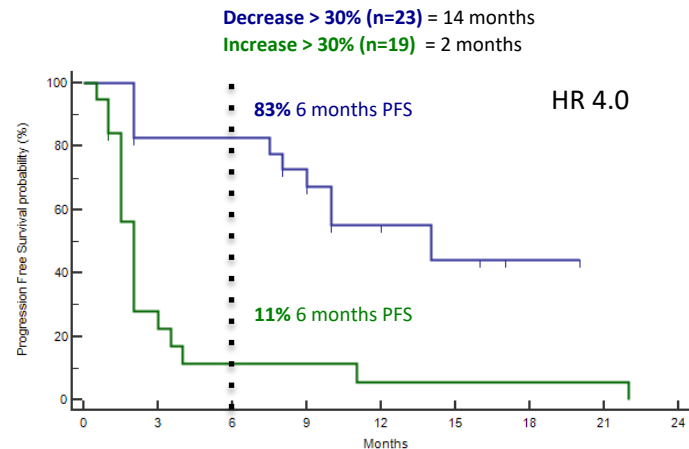
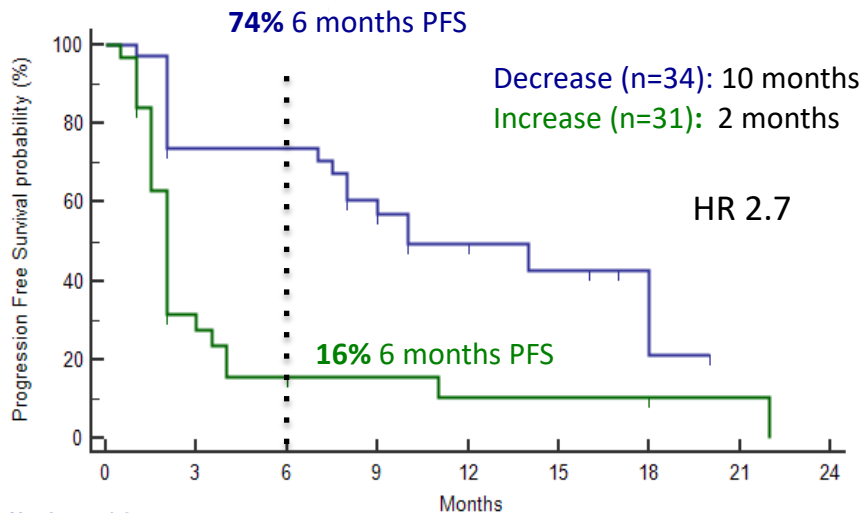
- Difficile en routine sur tissu (WES ou large panel): faisabilité limitée (60%)
- **b-TMB +++** (80% faisabilité, corrélée à tissu et à réponse)



Gandara Nature Med 2018



Corrélation cinétique précoce du ctDNA et réponse clinique



- Les **variations précoces** (1 mois) de l'ADN tumoral circulant est un bon indicateur de la réponse à 6 mois
- D'autant plus que les variations sont importantes (30%, 50%)

TUMOR BURDEN

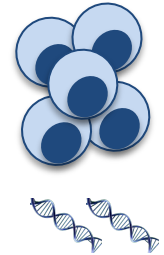
Level of ctDNA shed (variable)

Different tumor clones

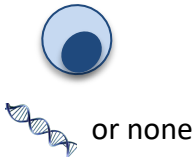
1.SCREENING
Large NGS panels



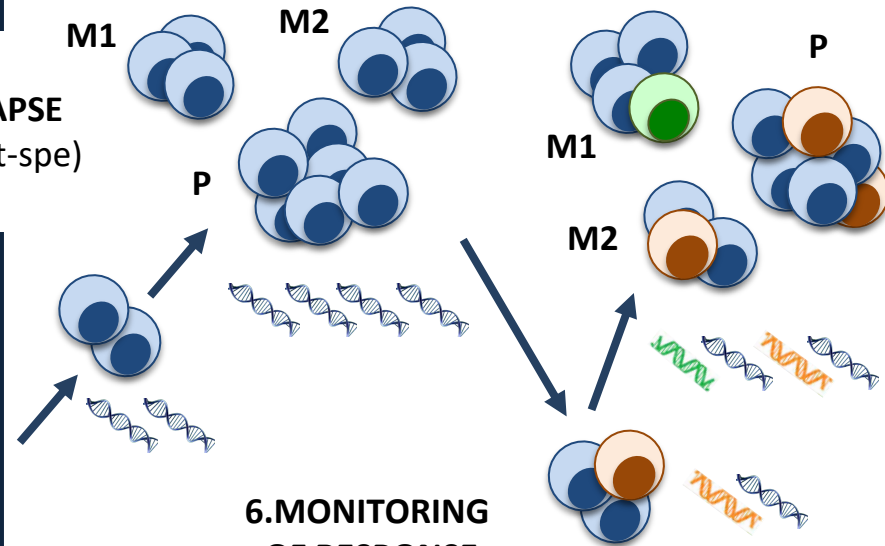
**2.BEFORE SURGERY:
NEOADJUVANT**
(NGS, Pt-spe if biopsy)



**3.POST-TREATMENT:
ADJUVANT (MRD)**
(NGS, Pt-spe)



4.RELAPSE
(NGS, Pt-spe)



5.ADVANCED STAGES: BIOMARKERS
Targeted therapies
(Targeted assays, limited NGS panels)

6.MONITORING OF RESPONSE
Pharmacodynamics (phase I)

7.EARLY DETECTION OF RESISTANCE CLONES
(Targeted assay, limited NGS panels)

EARLY STAGES

ADVANCED STAGES