L'oncologie en 2030

LA RÉVOLUTION NUMÉRIQUE A ATTEINT L'ONCOLOGIE

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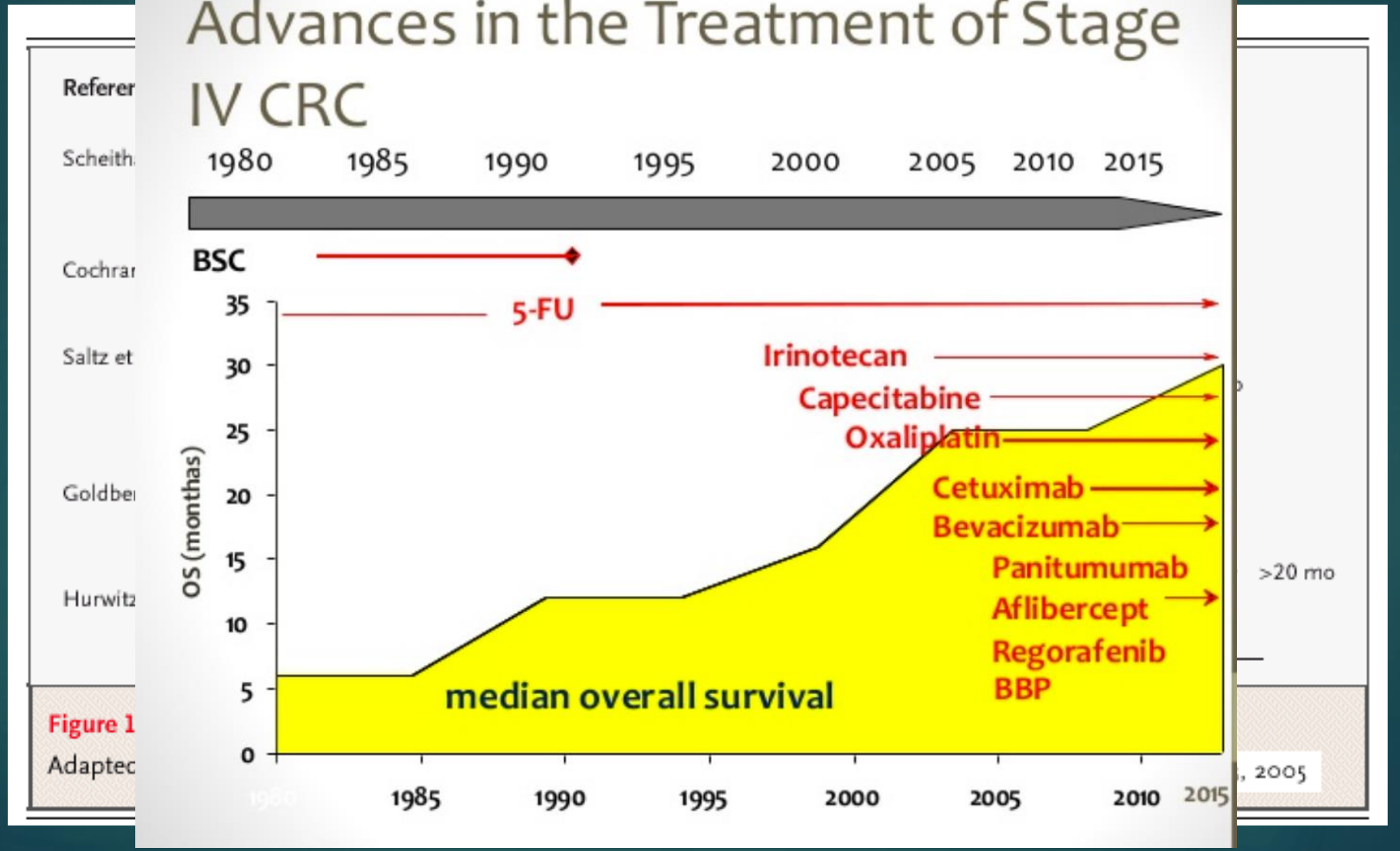
Centre Hospitalier de Luxembourg

Président, Institut National du Cancer

L'oncologie: evolution en 30 ans… en 10 dias ☺

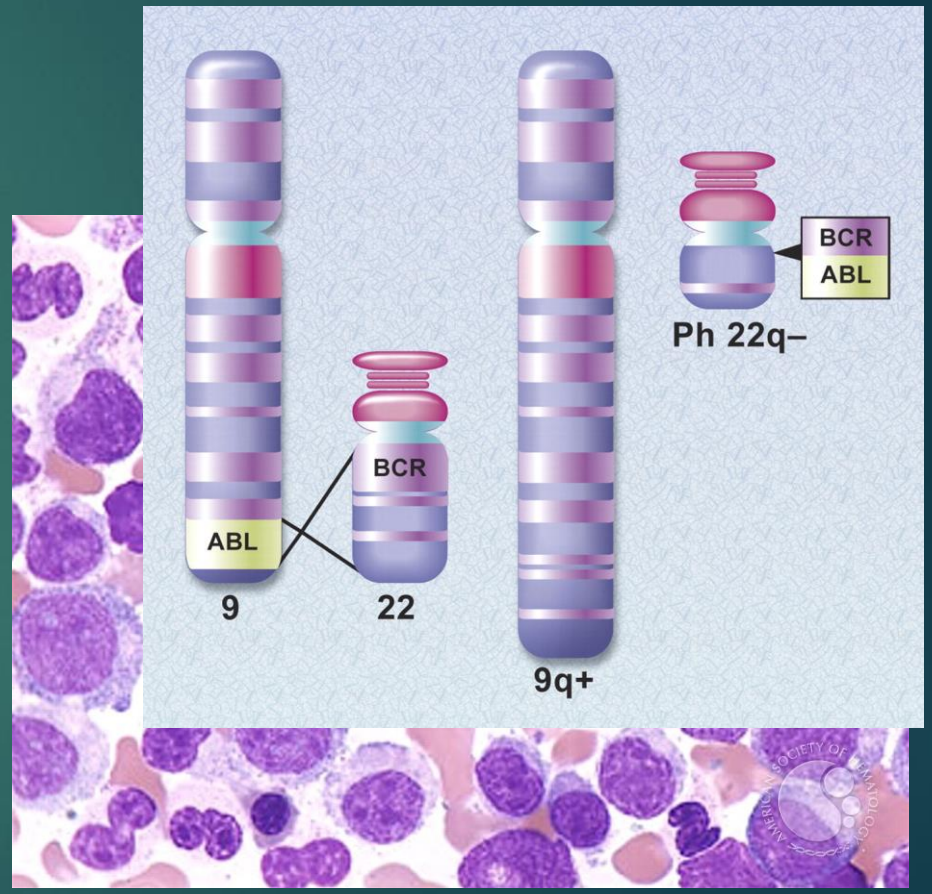
- du concept de "mouroir" à une possibilité de "guérison" dans un nombre significatif de cas….
- Leucémie chez l'enfant
- Tumeurs du testicule
- Lymphomes de Hodgkin
- Leucémie myéloïde chronique
- Autres: Sein, colon…

Le cancer du colon métastatique



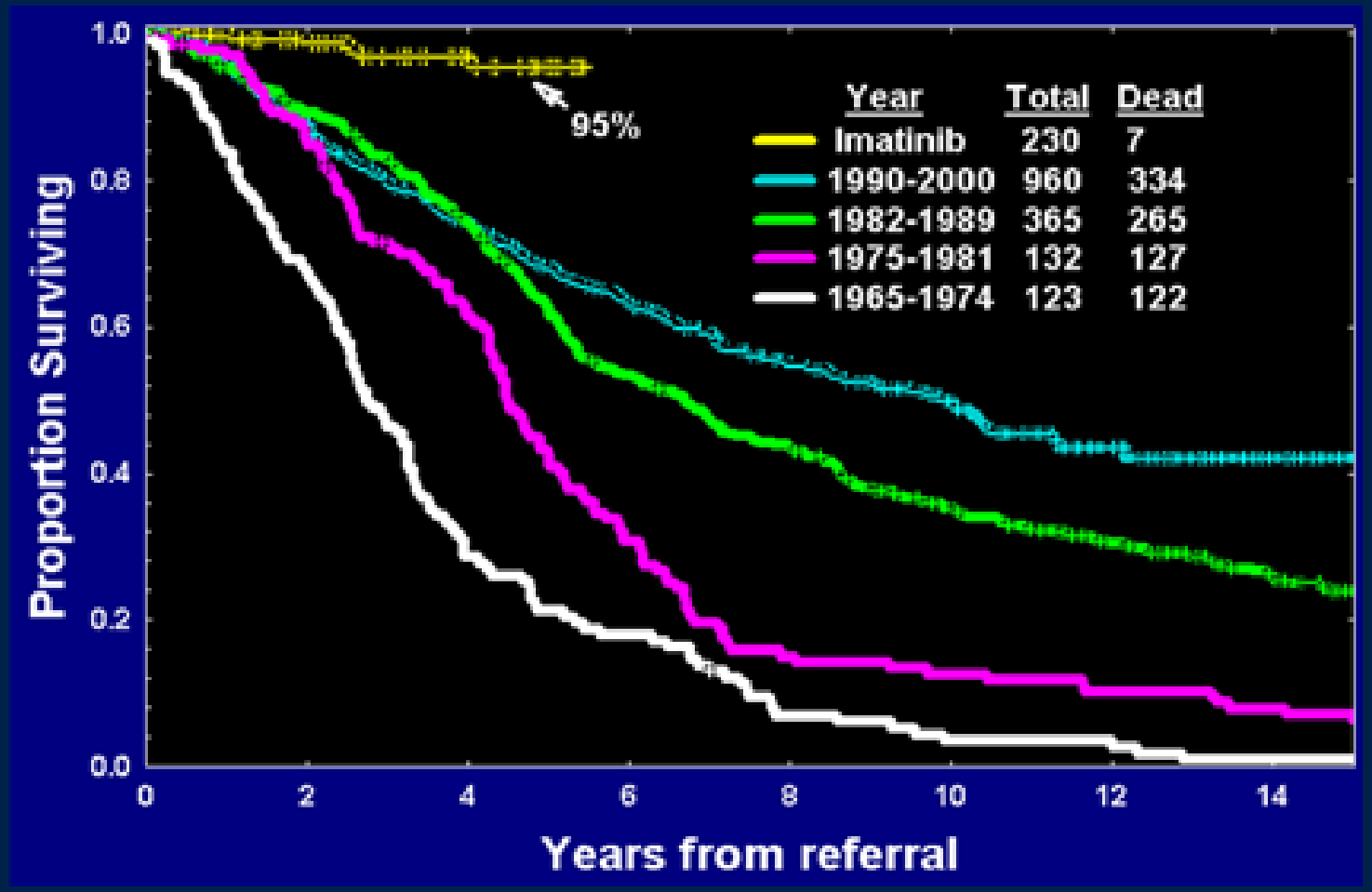
Médicaments ciblés
Leucémie Myéloïde chronique

- La cible => altération moléculaire spécifique (translocation chromosomique 9;22 (BCR-ABL))
- Oncogène puissant faisant se multiplier les cellules de la moëlle



Leu

Survival in Early Chronic Phase CML

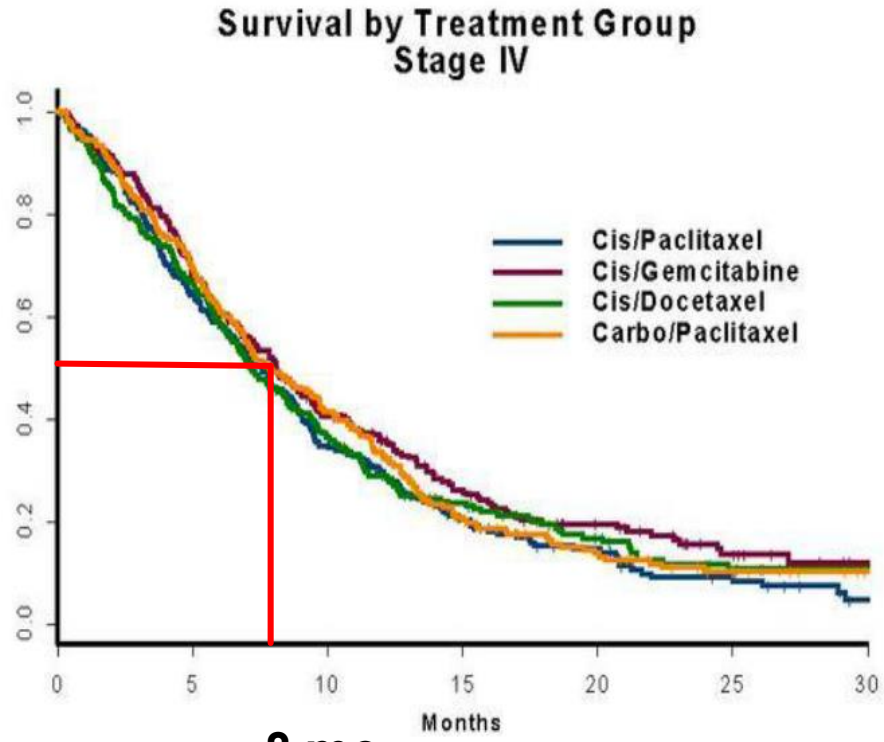


Quintás-Cardama A, Cortes JE. *Mayo Clin Proc*. 2006;81:973-988.

Cancer du Poumon

Platinum-Based Doublets for NSCLC

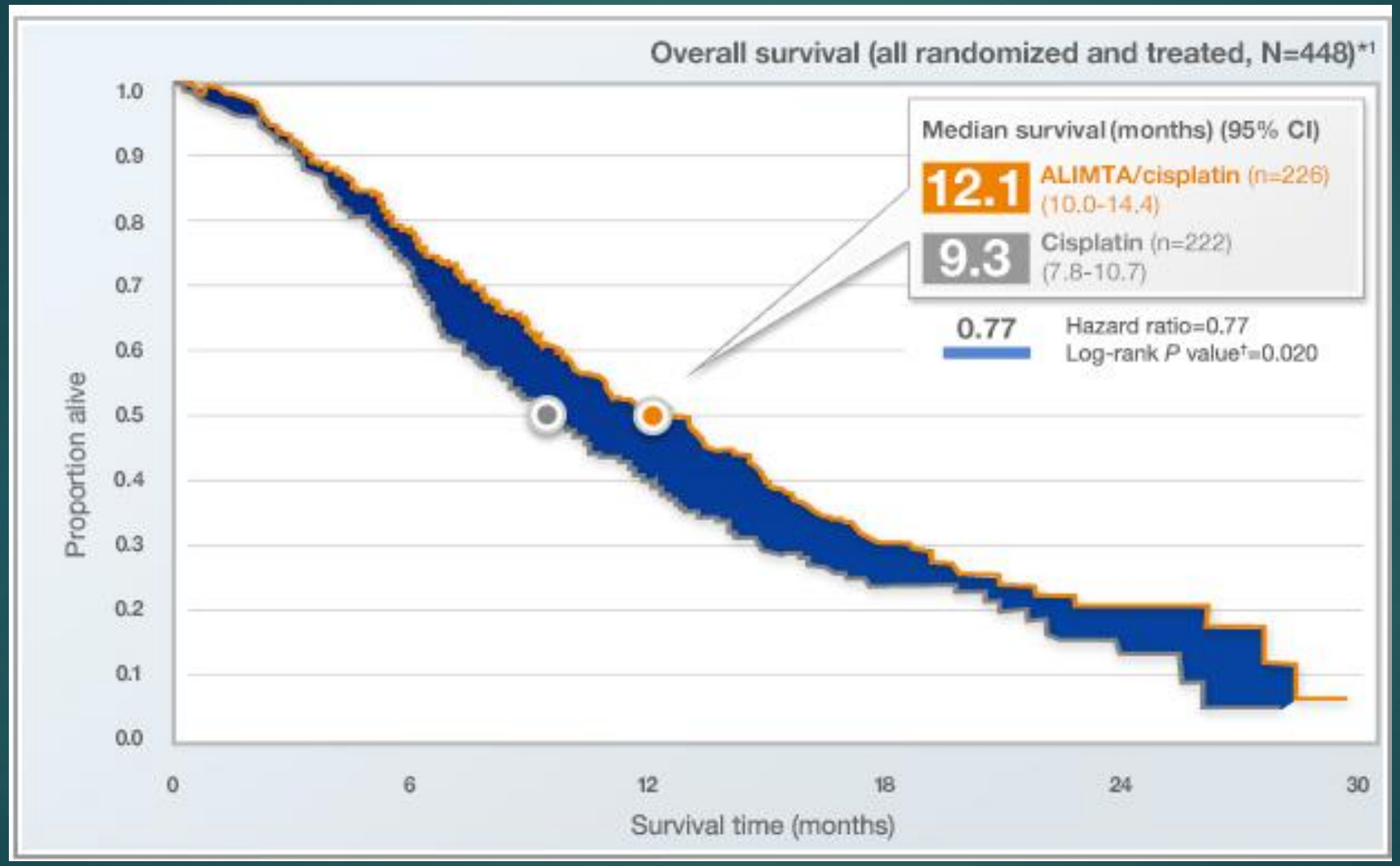
North American Experience (ECOG)



8 mo

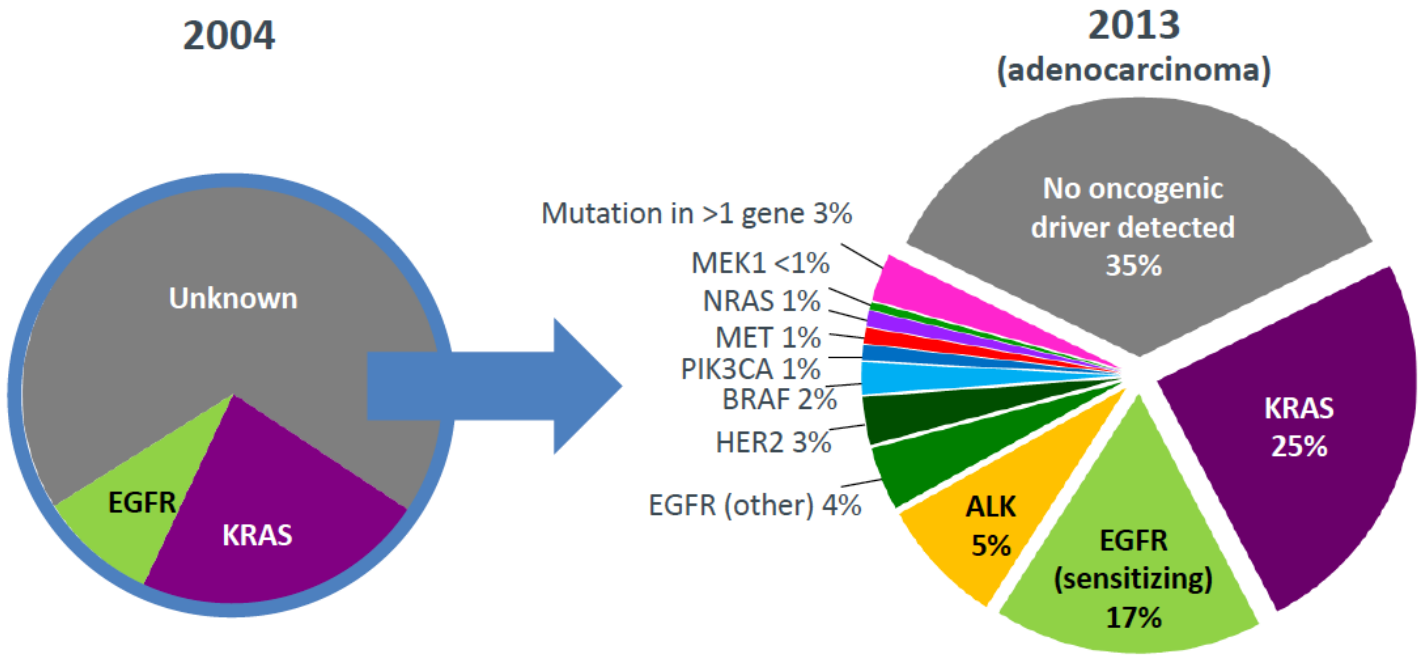
Schiller JH, et. al. *N Engl J Med.* 2002;346(2):92-98.

Meilleure chimiothérapie



Meilleurs biomarqueurs

Evolving Molecular Classification of NSCLC Over the Last Decade

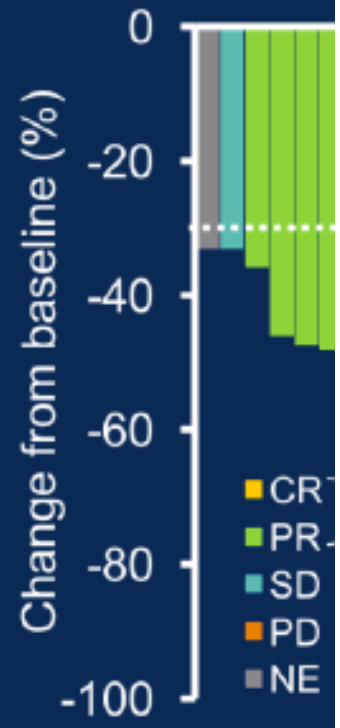


- Clinical practice has moved into an era of precision medicine in which many cancer patients are treated with targeted therapies (TKIs)

Pao & Girard. Lancet Oncol 2011; Blakely & Bivona. Cancer Discov. 2012; Johnson, et al. ASCO 2013

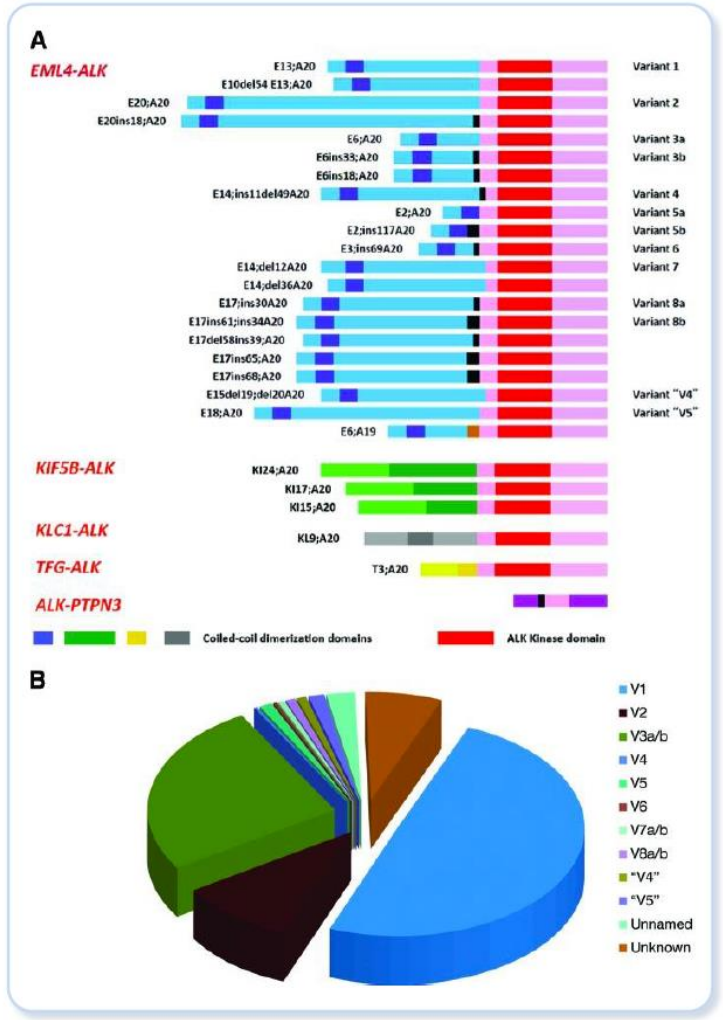
ALK

ORR: 93.5% (95%CI: 82.1 - 98.6)



ALK Rearrangements

At least 30 different ALK gene rearrangement variants have been described in lung cancer and an EML4 is the main fusion partner



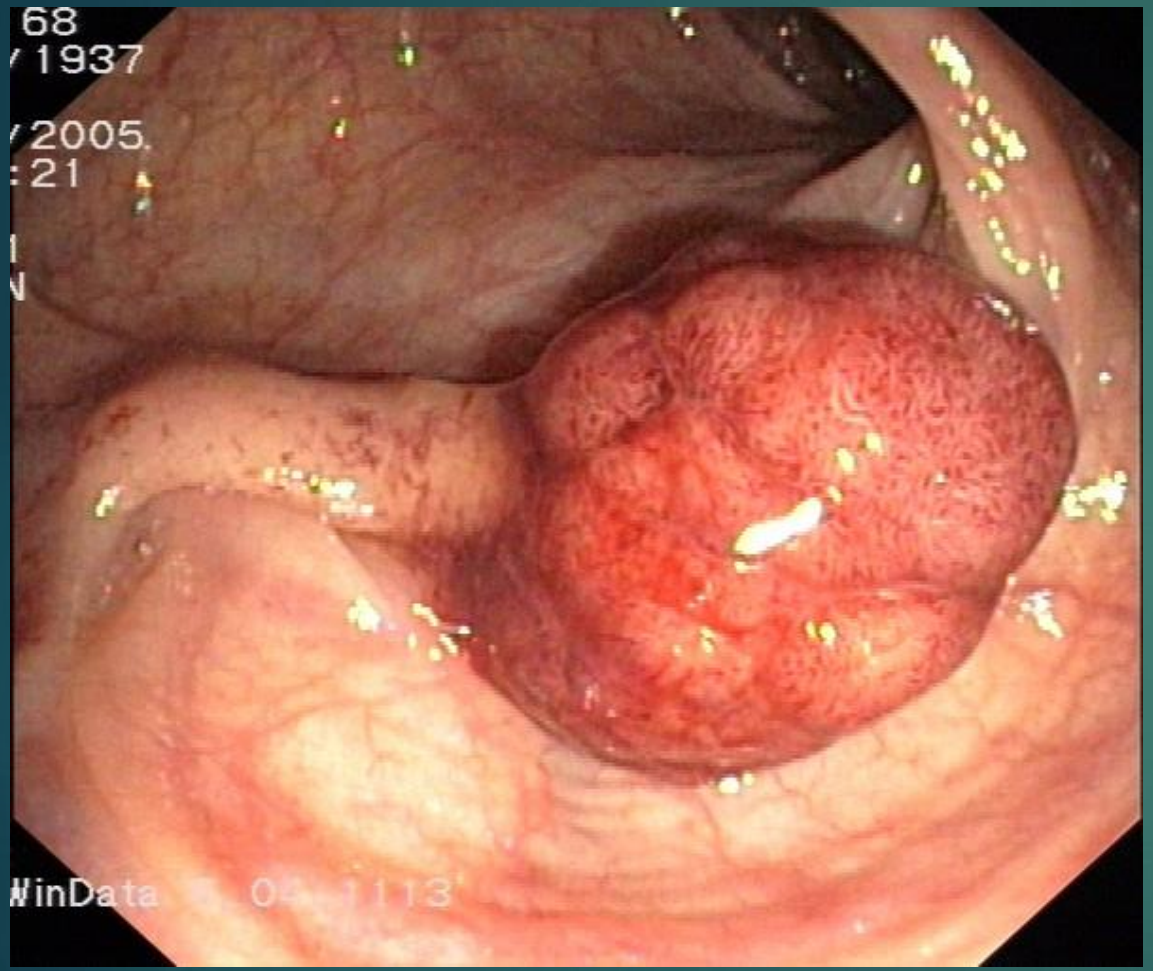
Ou et al., Oncologist. Nov 2012; 17(11): 1351–1375

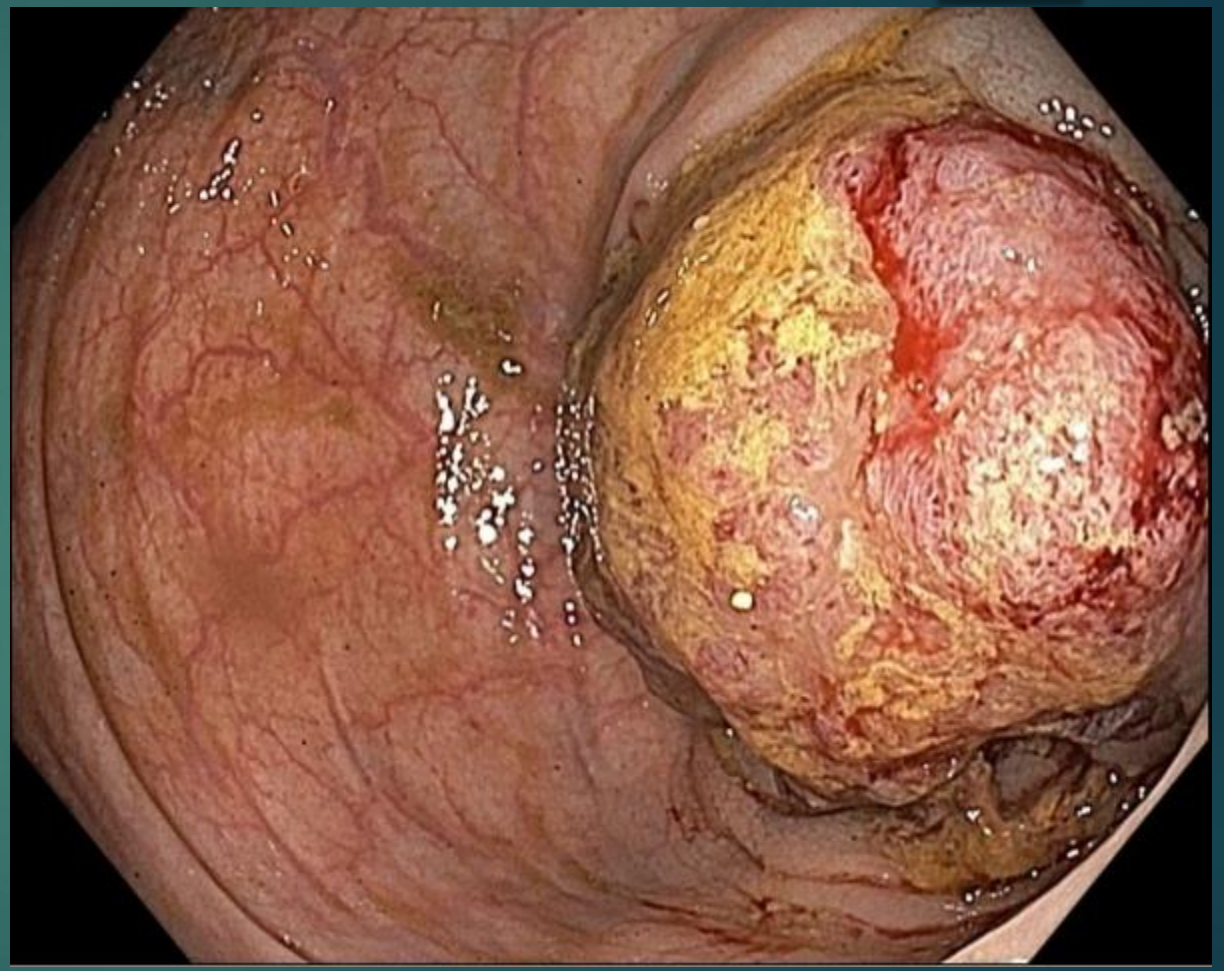
Crizotinib Resistance Mutations

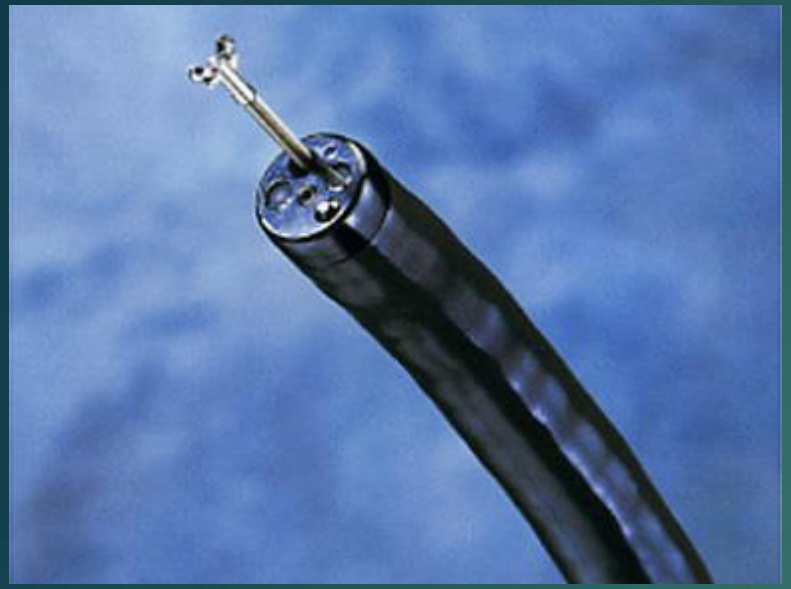
Mutation Status	Cell Line	Cellular ALK Phosphorylation Mean IC_{50} (nM)			
		PF-06463922	Crizotinib	Ceritinib (LDK-378)	Alectinib (CH-5424802)
EML4-ALK v1	NIH3T3	1.3	80	NA	62
	BaF3	3.6	90	41	24
EML4-ALK L1196M	NIH3T3	21	843	NA	250
	BaF3	43	1154	70	113
EML4-ALK G1269A	NIH3T3	15	605	NA	NA
	BaF3	80	689	134	112
EML4-ALK G1202R	NIH3T3	77	1003	>1000	>10,000
	BaF3	113	562	549	362
EML4-ALK I1151Tins	NIH3T3	38	1268	1066	1770
	BaF3	50	902	296	126
EML4-ALK S1206Y	NIH3T3	4.2	626	NA	NA
	BaF3	3.2	152	60	29
EML4-ALK C1156Y	NIH3T3	1.6	478	NA	NA
	BaF3	15	406	177	21
EML4-ALK F1174L	NIH3T3	0.2	165	NA	NA
	BaF3	4.0	150	161	26

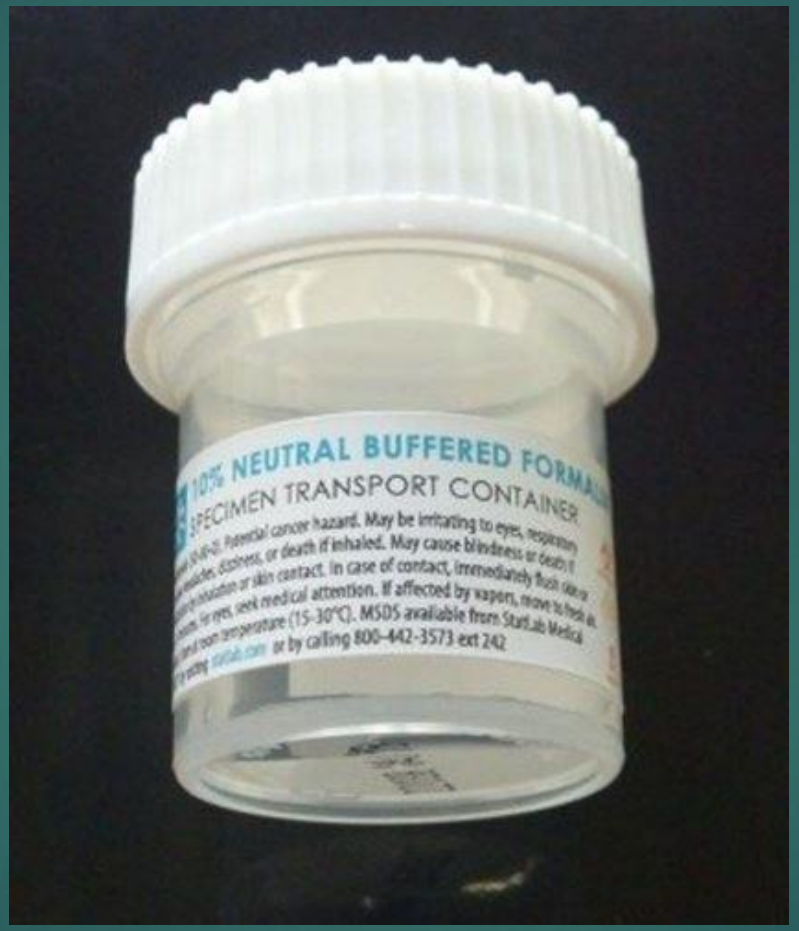
And now the Future!

Le Profilage moléculaire

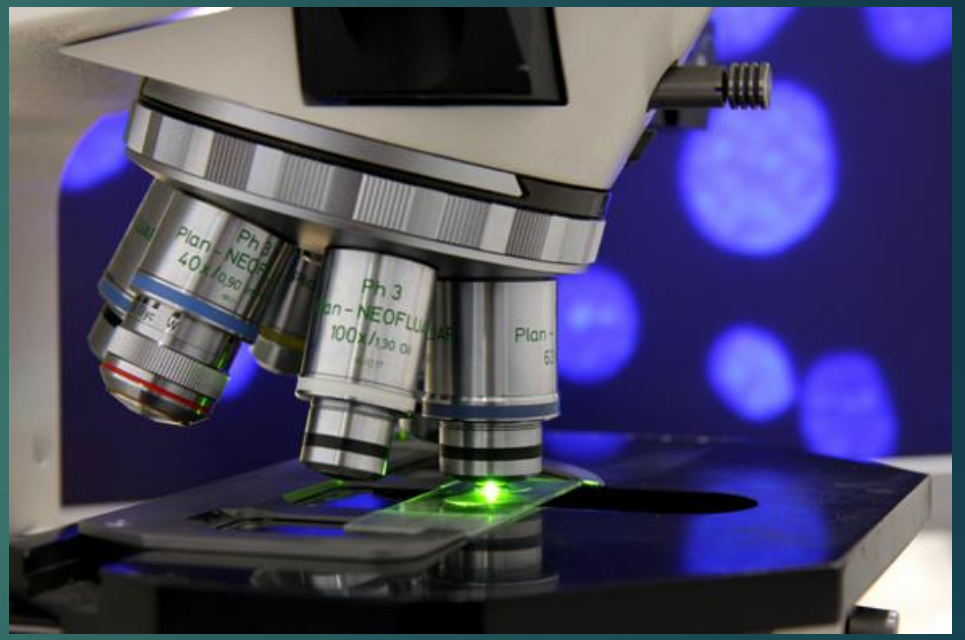

68
1937
2005
21
WinData

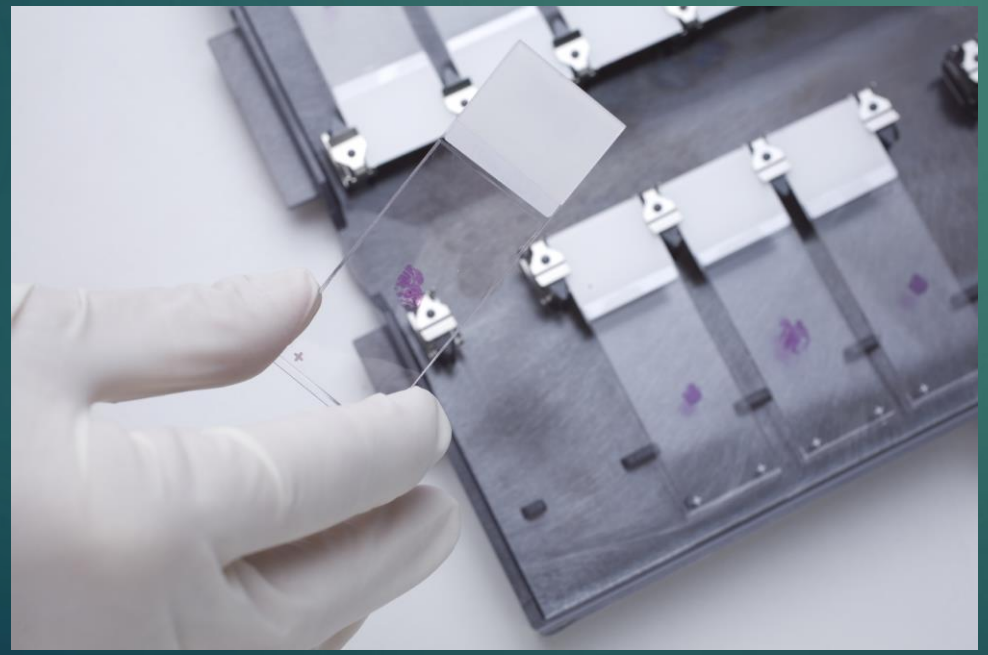


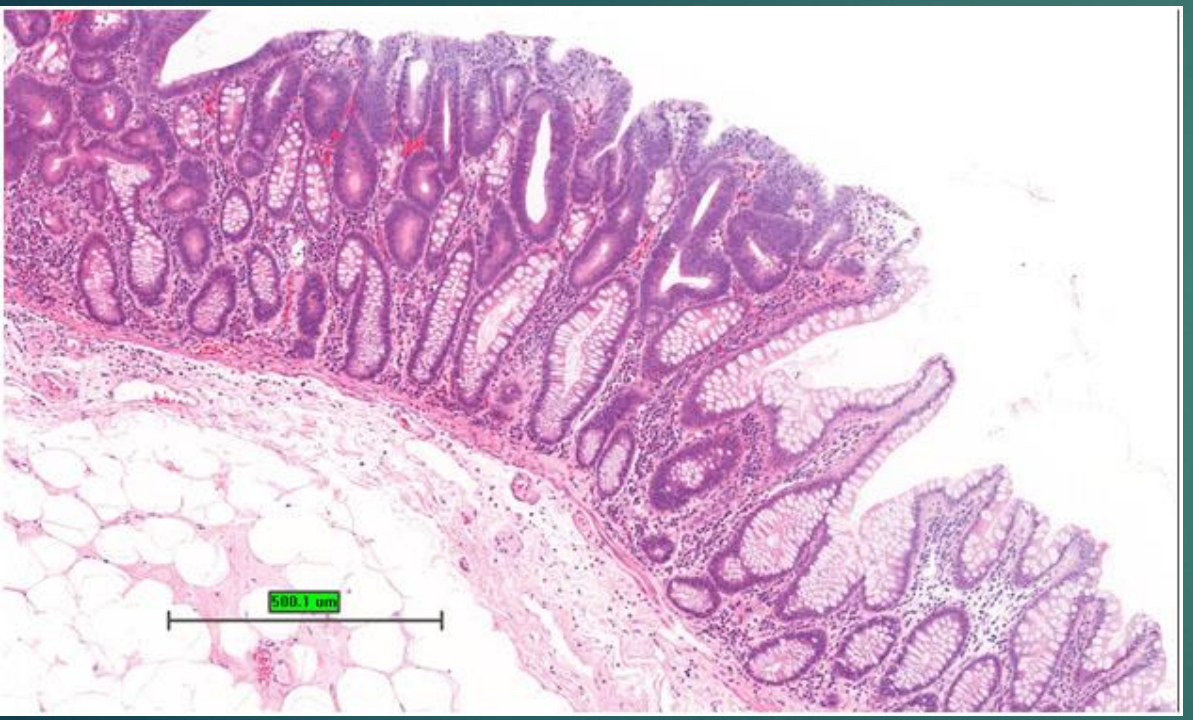


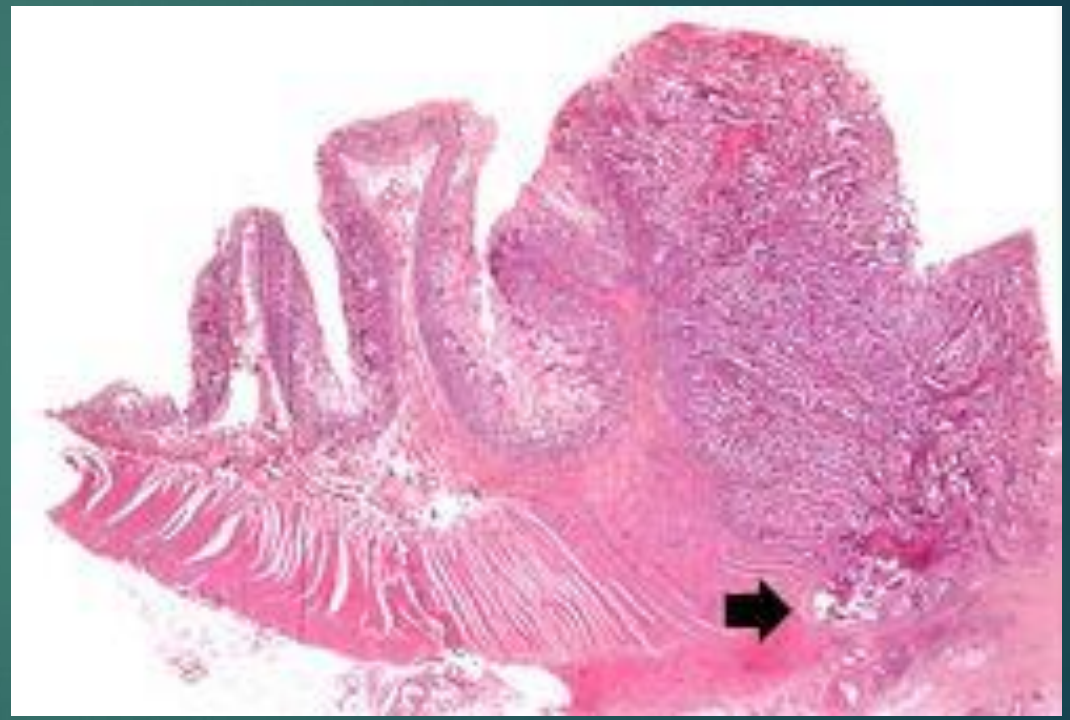

10% NEUTRAL BUFFERED FORMA
SPECIMEN TRANSPORT CONTAINER

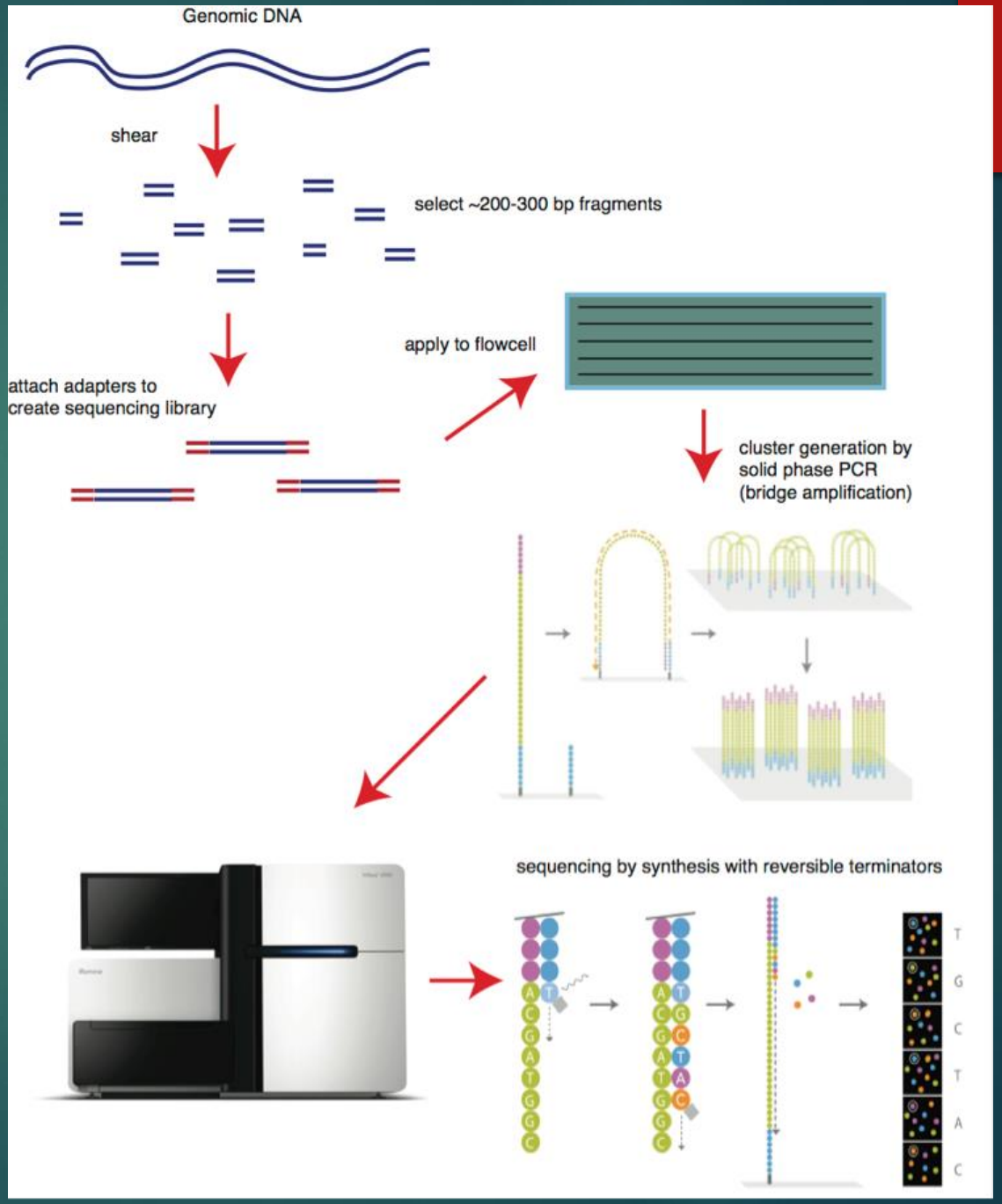

Leica
MEDICAL EQUIPMENT SOURCE, LLC

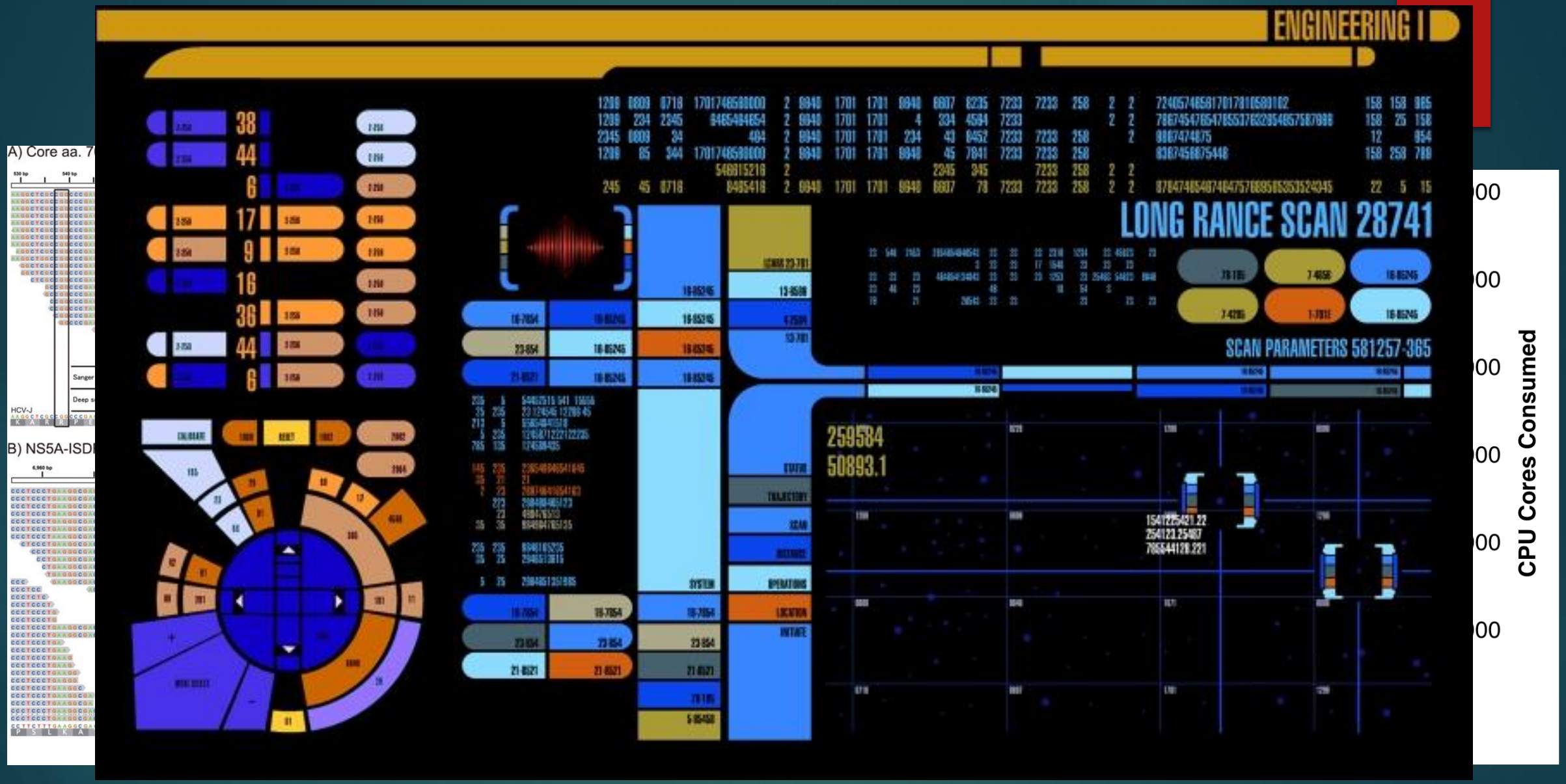

Ph 3
100x/1,30 Oil




500.1 um

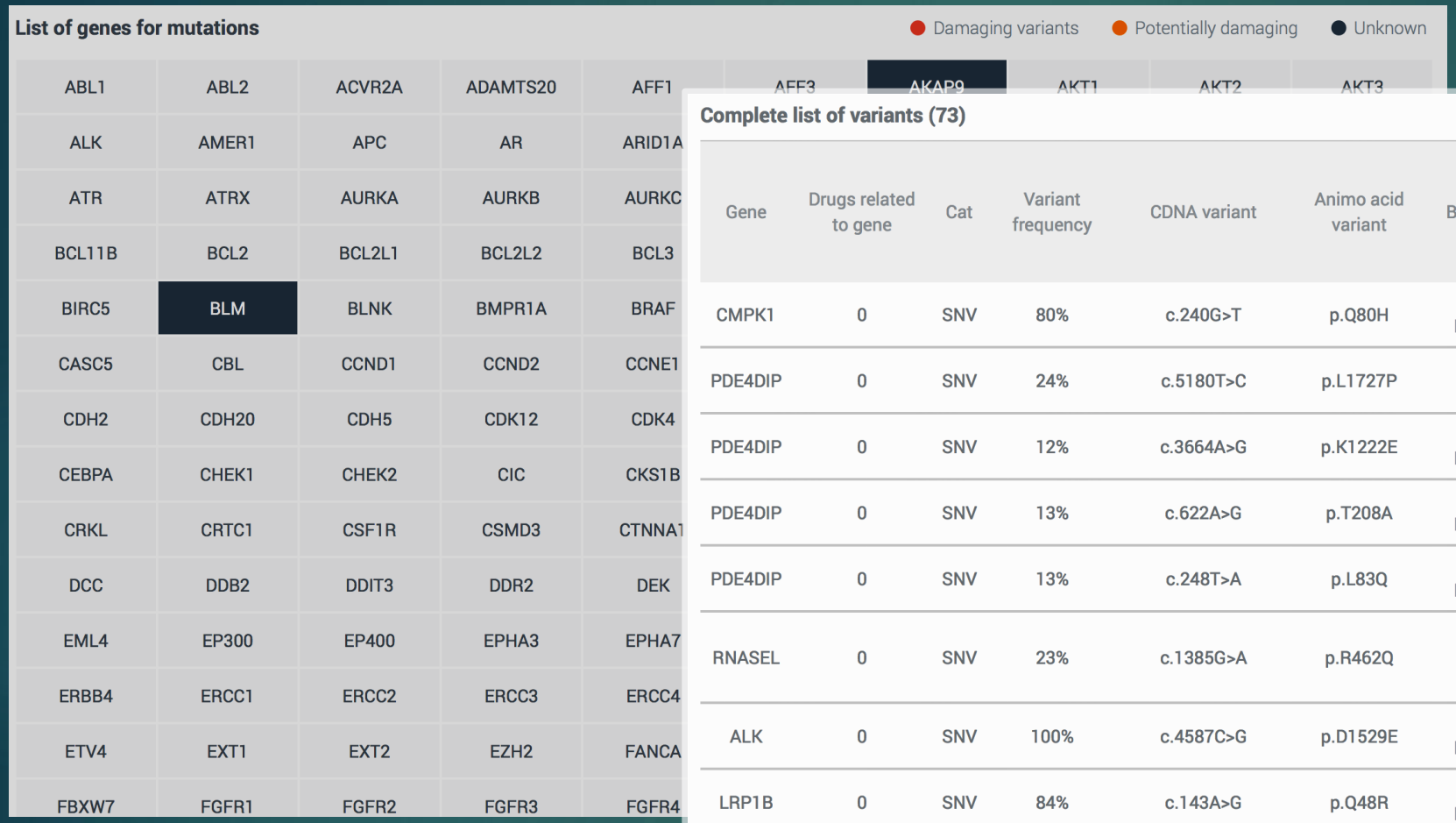



Genomic DNA
shear
select ~200-300 bp fragments
apply to flowcell
attach adapters to
create sequencing library
cluster generation by
solid phase PCR
(bridge amplification)
sequencing by synthesis with reversible terminators
T
G
C
T
A
C



=> Des « tonnes » de données

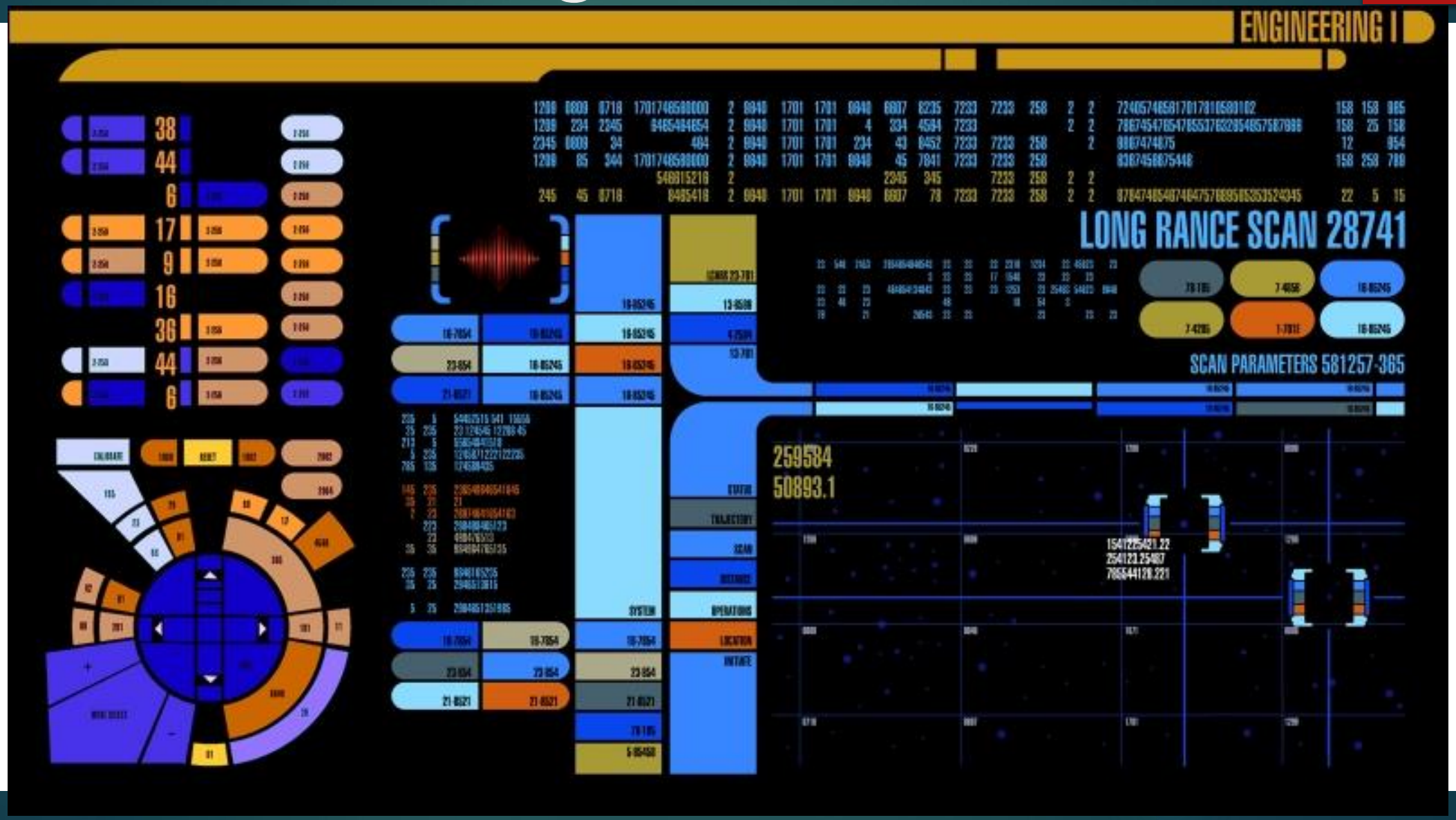
Molecular testing:



Complete list of variants (73)

Gene	Drugs related to gene	Cat	Variant frequency	CDNA variant	Animo acid variant	Biological impact	Therapeutical impact	Medically actionable incidental findings	Drugs related to your patient
CMPK1	0	SNV	80%	c.240G>T	p.Q80H	Probably Polymorphism		No	0
PDE4DIP	0	SNV	24%	c.5180T>C	p.L1727P	Unknown		No	0
PDE4DIP	0	SNV	12%	c.3664A>G	p.K1222E	Probably Polymorphism		No	0
PDE4DIP	0	SNV	13%	c.622A>G	p.T208A	Probably Polymorphism		No	0
PDE4DIP	0	SNV	13%	c.248T>A	p.L83Q	Probably Polymorphism		No	0
RNASEL	0	SNV	23%	c.1385G>A	p.R462Q	Unknown			0
ALK	0	SNV	100%	c.4587C>G	p.D1529E	Probably Polymorphism		No	0
LRP1B	0	SNV	84%	c.143A>G	p.Q48R	Probably Polymorphism		No	0
FANCD2	13	SNV	25%	c.4356+3C>T	-	Unknown		No	3
TGFBR2	0	SNV	24%	c.263 7A>G	-	Probably Polymorphism		No	0
GATA2	0	SNV	77%	c.490G>A	p.A164T	Probably		No	0

Molecular testing:



Results

Integrated Biological Review

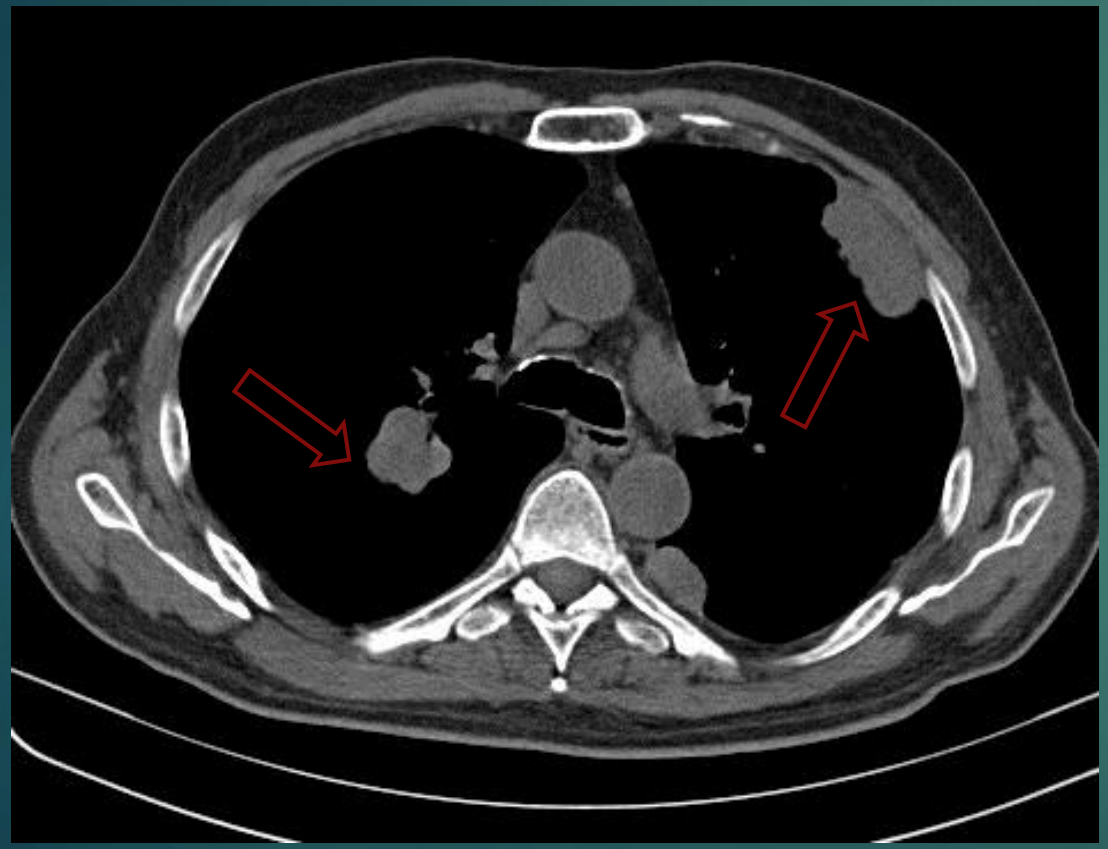
Treatments associated with Potential Clinical Benefit	Treatments associated with Potential Lack of Clinical Benefit	Treatments associated with Undetermined Clinical Benefit	Treatments associated with toxicity
Gemcitabine (RRM1 IHC)	Platinum based chemotherapy (ERRC1 IHC)		
Anthracycline based chemotherapy (TOP2A IHC)	5-FU based chemotherapy (TS IHC)		
Angiogenesis inhibitors (VEGFR2 IHC)	KIT inhibitors (cKIT IHC)		
	Taxane based chemotherapy (TUBB3 IHC)		
	alkylating agent (MGMT)		
	PD-1/PD-L1 inhibitors (PD-L1 & CD8 IHCs)		

- Patient discussion molecular tumor board

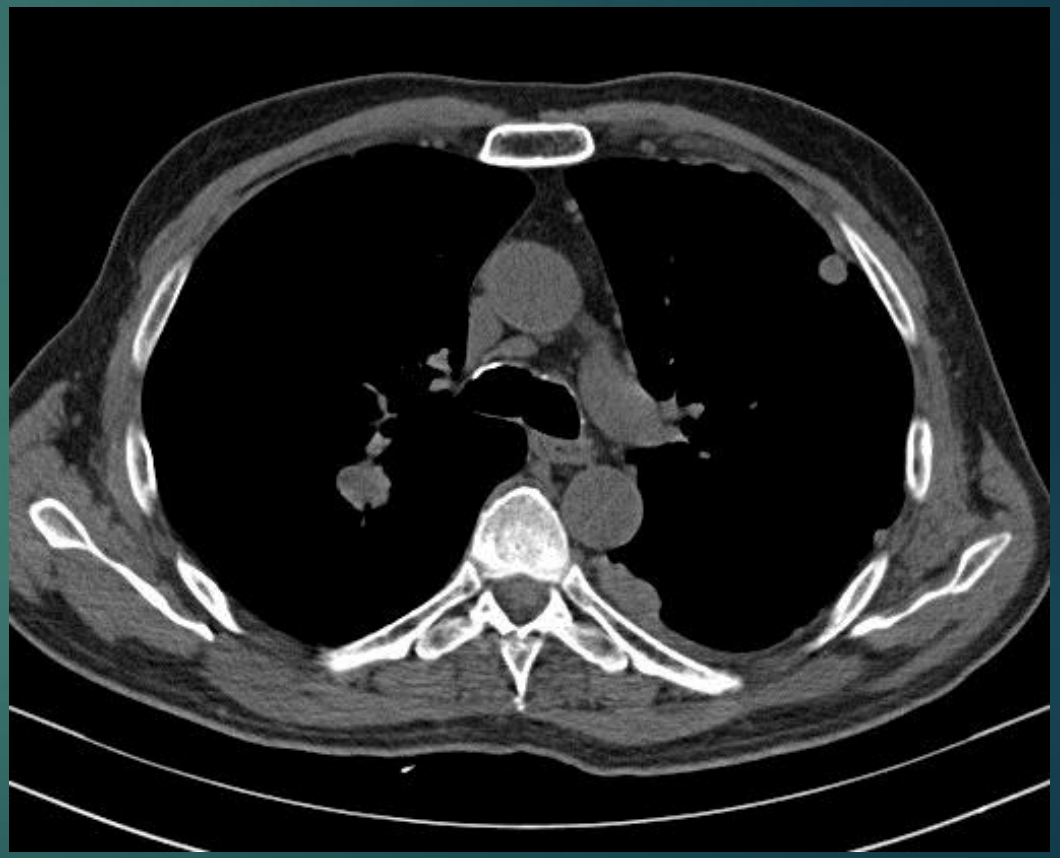
Et maintenant?

- Après les résultats sont discutés au sein du Molecular Tumor Board et il a été décidé de le mettre sous un médicament antiangiogénique qu'on n'aurait jamais utilisé sinon…

Exemple d'un patient réel



10/2015



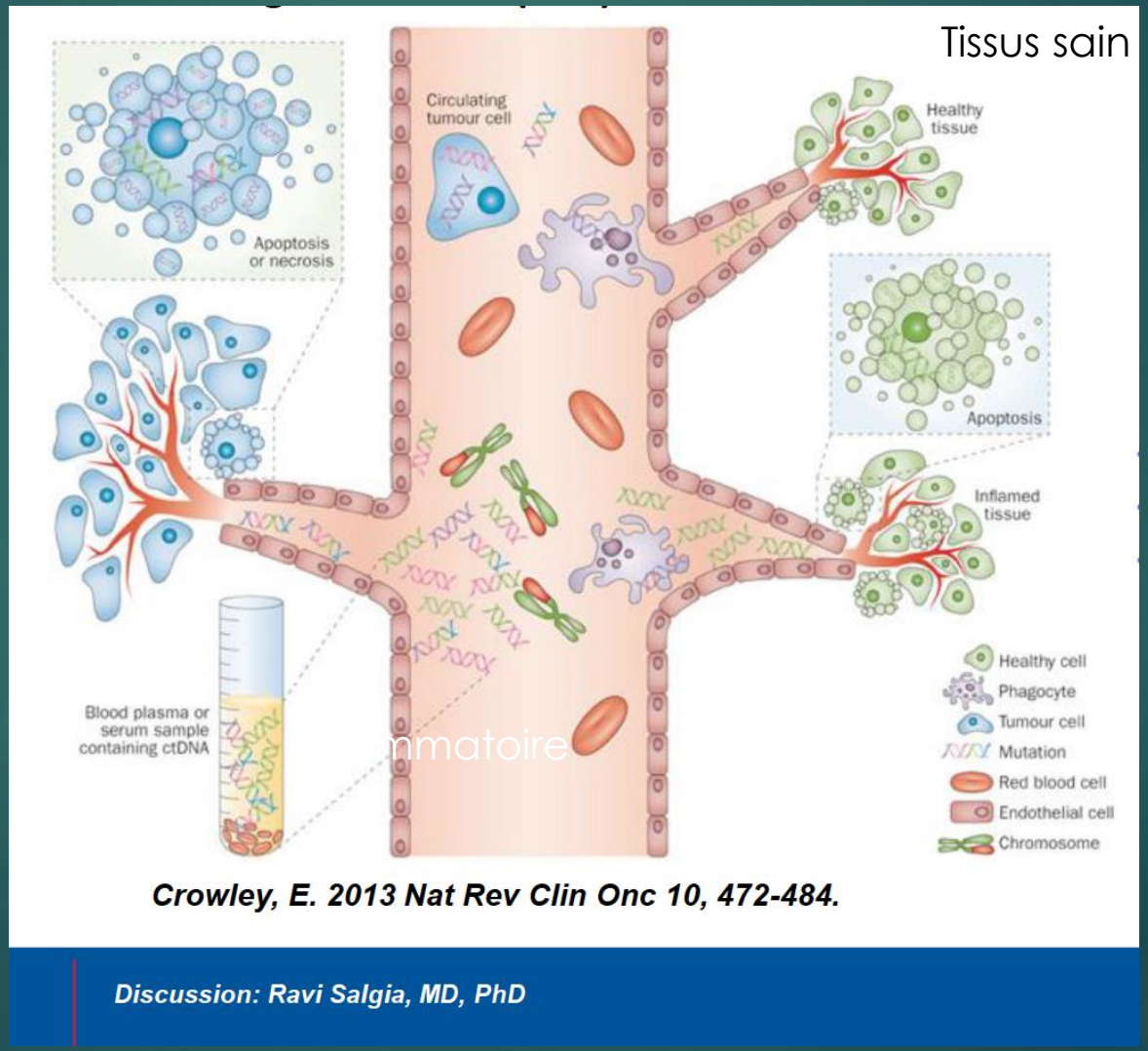
3/2016

Comment suivre ces altérations moléculaires dans le temps?

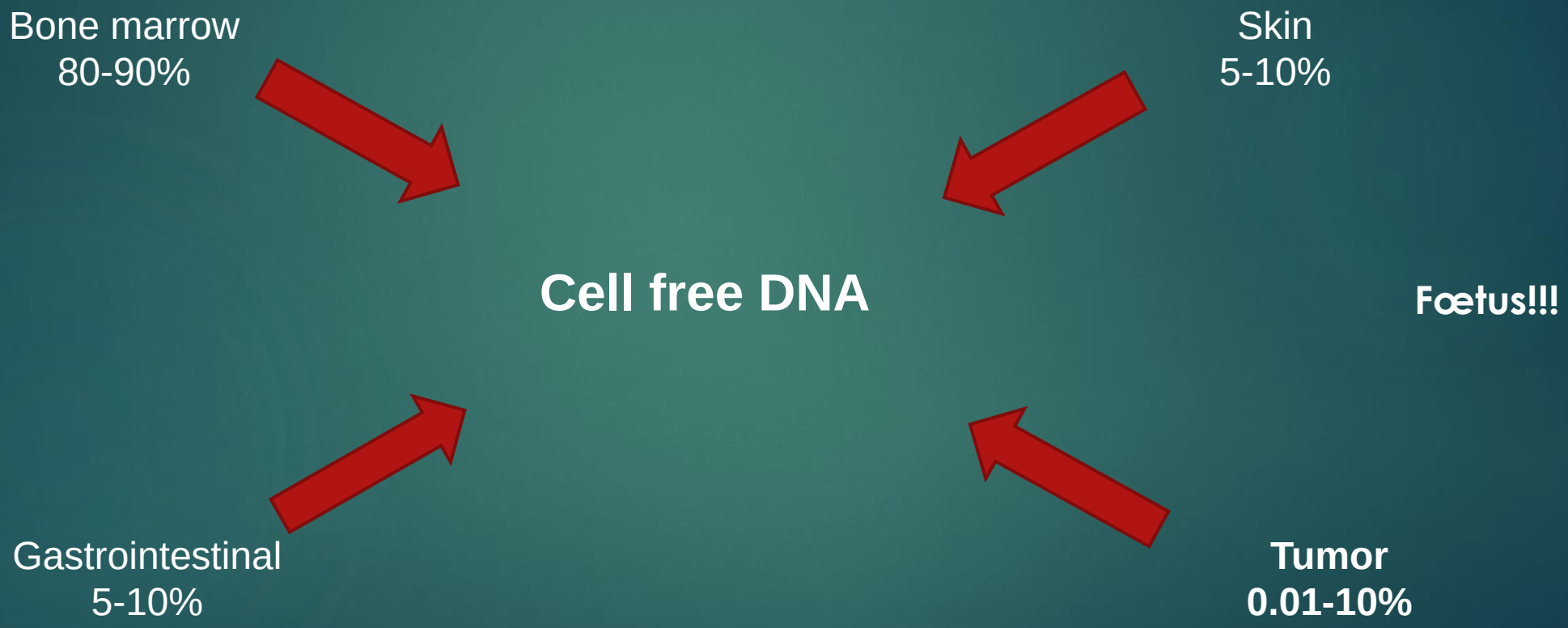
- Afin de voir ce que ces variants moléculaires deviennent avec le temps de nombreuses biopsies de la tumeur seraient nécessaires au cours du temps…
- Non éthique et non faisable!
- Quelle autre possibilité avons nous?

DNA circulant !!!

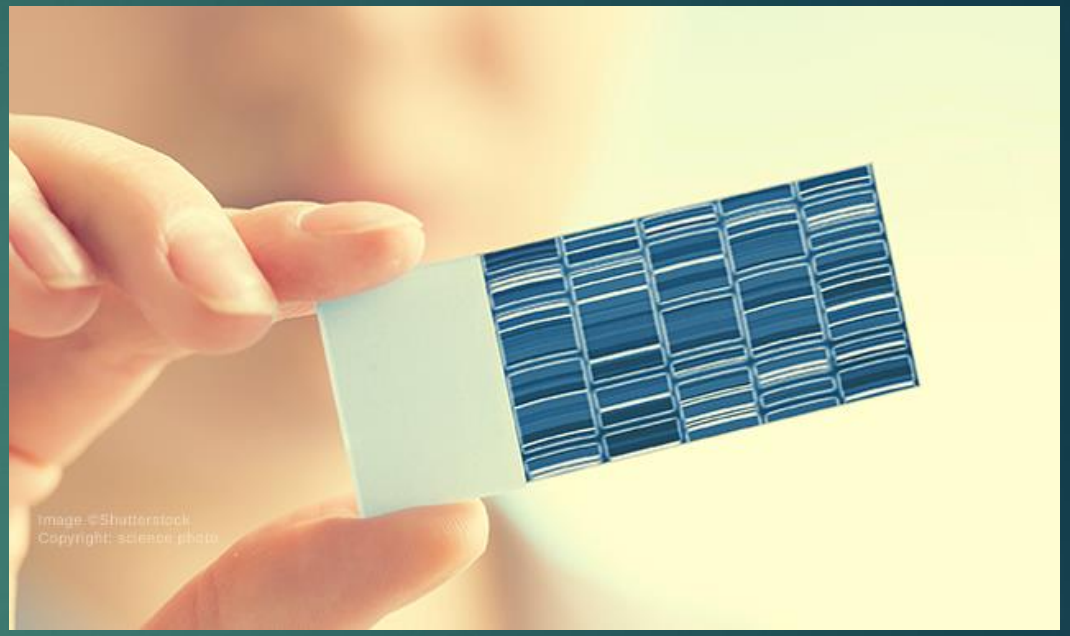
Tissus cancéreux



Origin of cfDNA



Analyse



=> A nouveau… des « tonnes » de données

DNA circulant

- **Va permettre de suivre toutes les mutation intéressantes**
- **On pourra alors changer de traitement sans devoir faire de biopsie à chaque fois…**

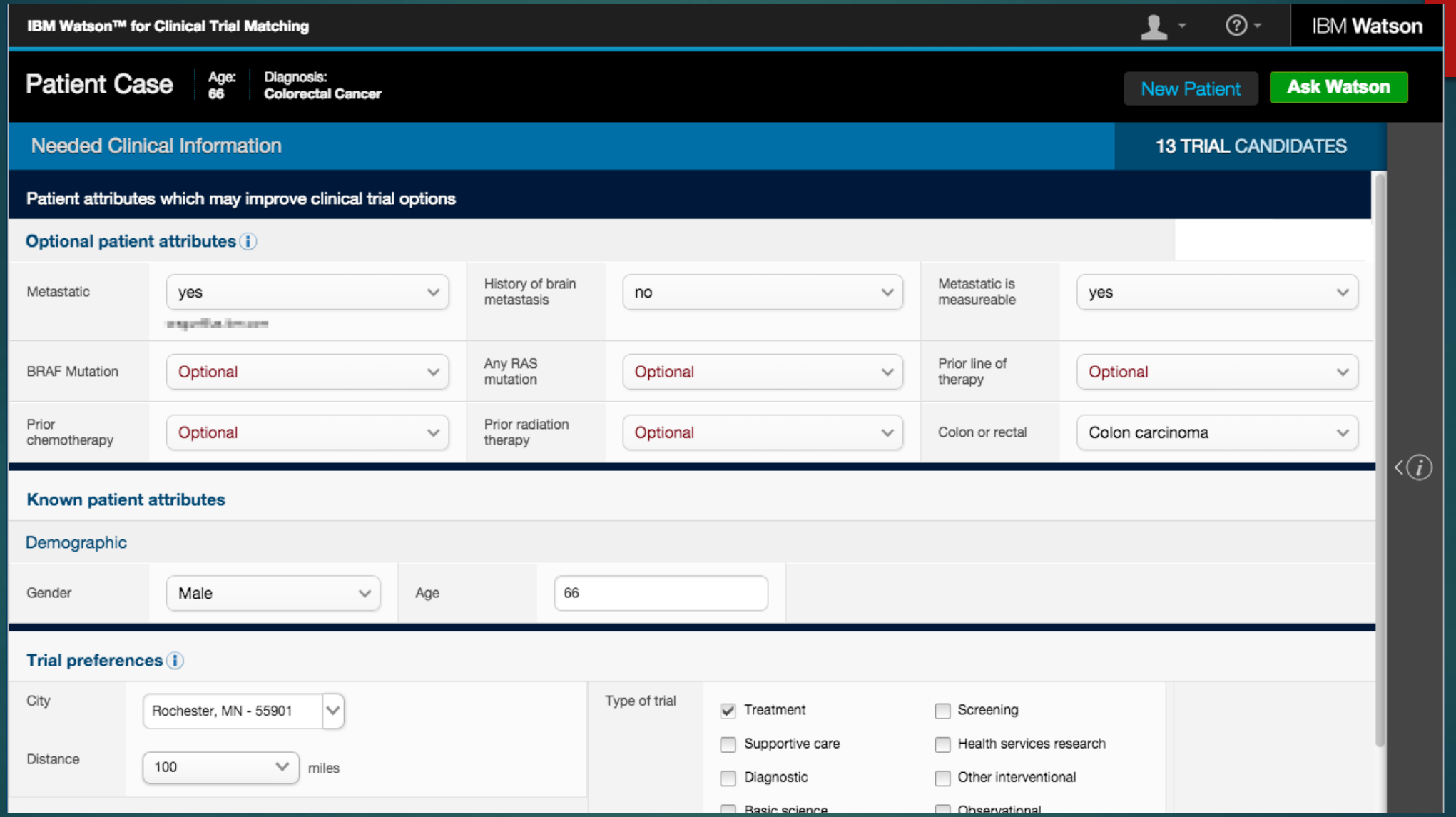
L'intelligence artificielle

IBM-Watson


PIENSE
THINK
ΣΚΕΨΟΥ
DENKE
PENSER
$300,000
$1,000,000
$200,000
KEN
WATSON
BRAD

Que sait faire Watson?

- Watson est une intelligence artificielle dévelopée par IBM (Deep Blue)
- Sait lire et comprendre du texte libre….
- Connaît toute la littérature médicale…
- Il est programmé pour proposer des décisions médicales.
- Il peut être paramétré pour respecter des « guidelines » nationales
- Existe pour cancer du sein, colon, poumon
- Bientôt maladies rares comme sarcomes
- Module Médecine personnalisée moléculaire


IBM Watson™ for Clinical Trial Matching
IBM Watson
Patient Case
Age: 66
Diagnosis: Colorectal Cancer
New Patient
Ask Watson
Needed Clinical Information
13 TRIAL CANDIDATES
Patient attributes which may improve clinical trial options
Optional patient attributes
Metastatic
yes
History of brain metastasis
no
Metastatic is measureable
yes
BRAF Mutation
Optional
Any RAS mutation
Optional
Prior line of therapy
Optional
Prior chemotherapy
Optional
Prior radiation therapy
Optional
Colon or rectal
Colon carcinoma
Known patient attributes
Demographic
Gender
Male
Age
66
Trial preferences
City
Rochester, MN - 55901
Distance
100
miles
Type of trial
Treatment
Screening
Supportive care
Health services research
Diagnostic
Other interventional
Basic science
Observational


IBM Watson for Oncology
Treatments
CMF (Cyclophosphamide/ Methotrexate/ Fluorouracil)
TC (Docetaxel/ Cyclophosphamide)
CEF (Cyclophosphamide/ Epirubicin/Fluorouracil)
CAF (Cyclophosphamide/ Doxorubicin/
Details for CMF
Rationale
Additional Publications
Administration
Rationale supporting this treatment
This is recommended when the patient has a high Oncotype DX
MSK curated literature about this treatment
Two months of doxorubicin-cyclophosphamide with
reinduction therapy compared with 6 months of cyc
methotrexate, and fluorouracil in positive-node brea
tamoxifen-nonresponsive tumors: results from the N
Breast and Bowel Project B-15.

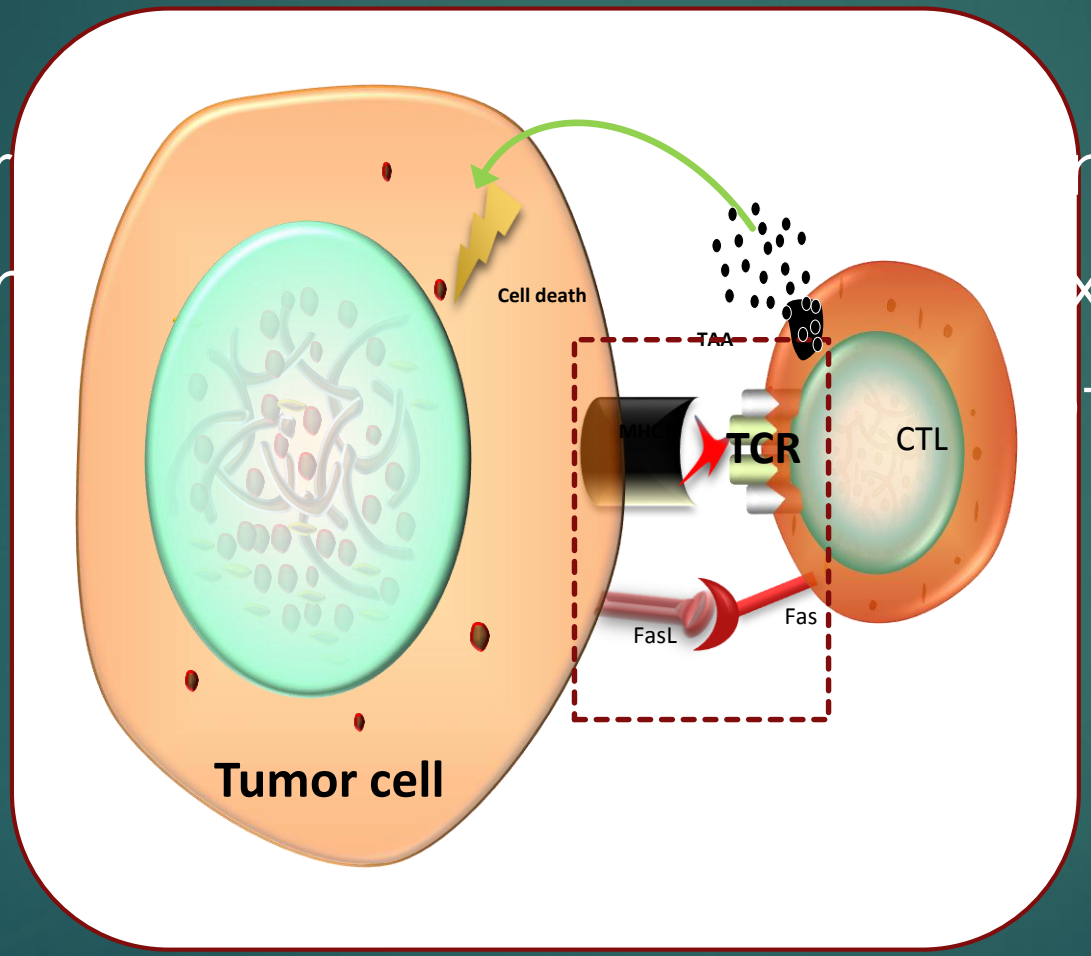
IBM WATSON GENOMIC ANALYTICS AT SANFORD CANCER CENTER

A New Era in Personalized Cancer Treatment

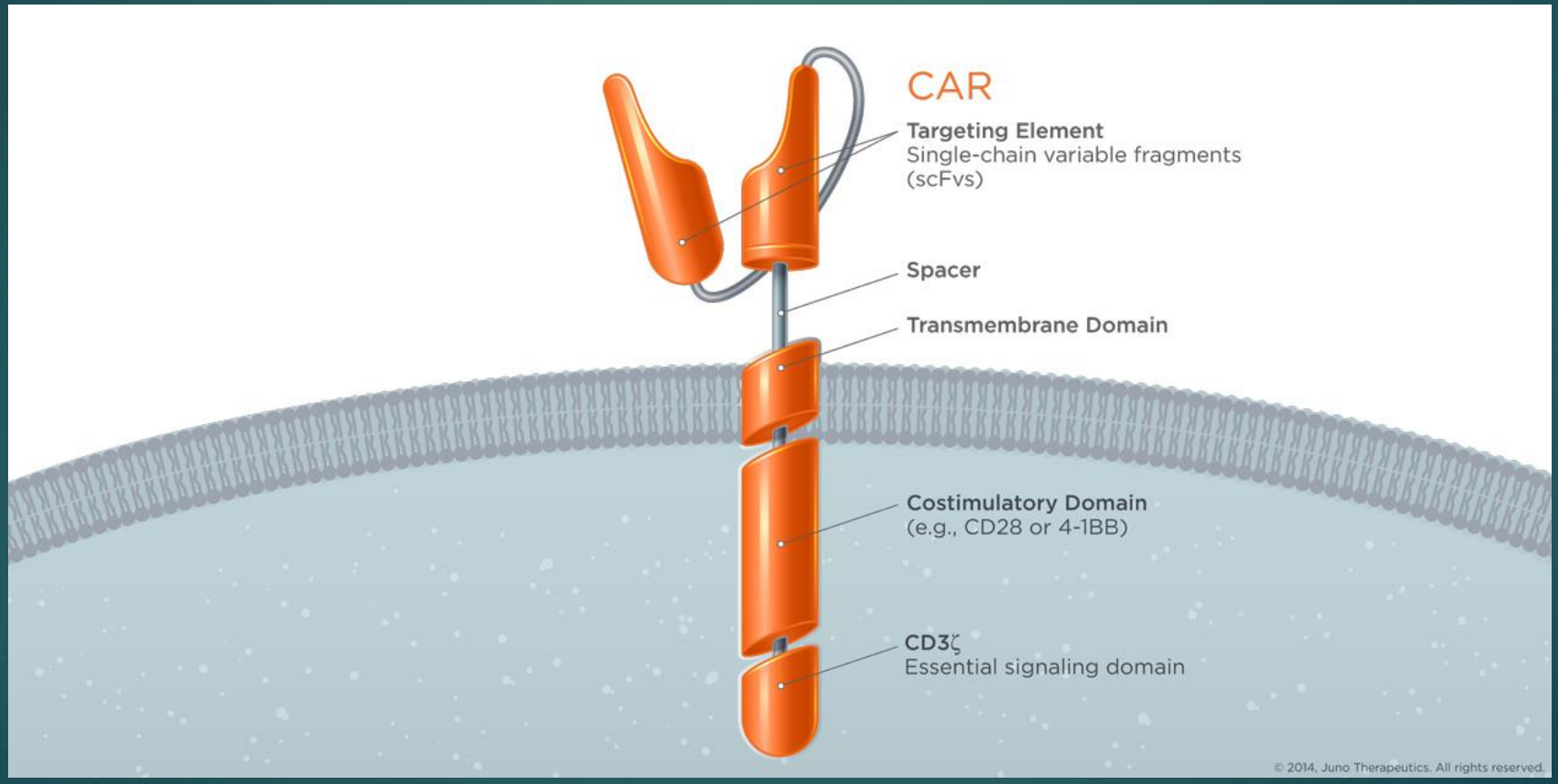
What took weeks, now takes minutes. IBM Watson Genomic Analytics is able to sort through and analyze the DNA data of cancer patients and quickly provide comprehensive insights on cancer-causing mutations faster than ever before. The

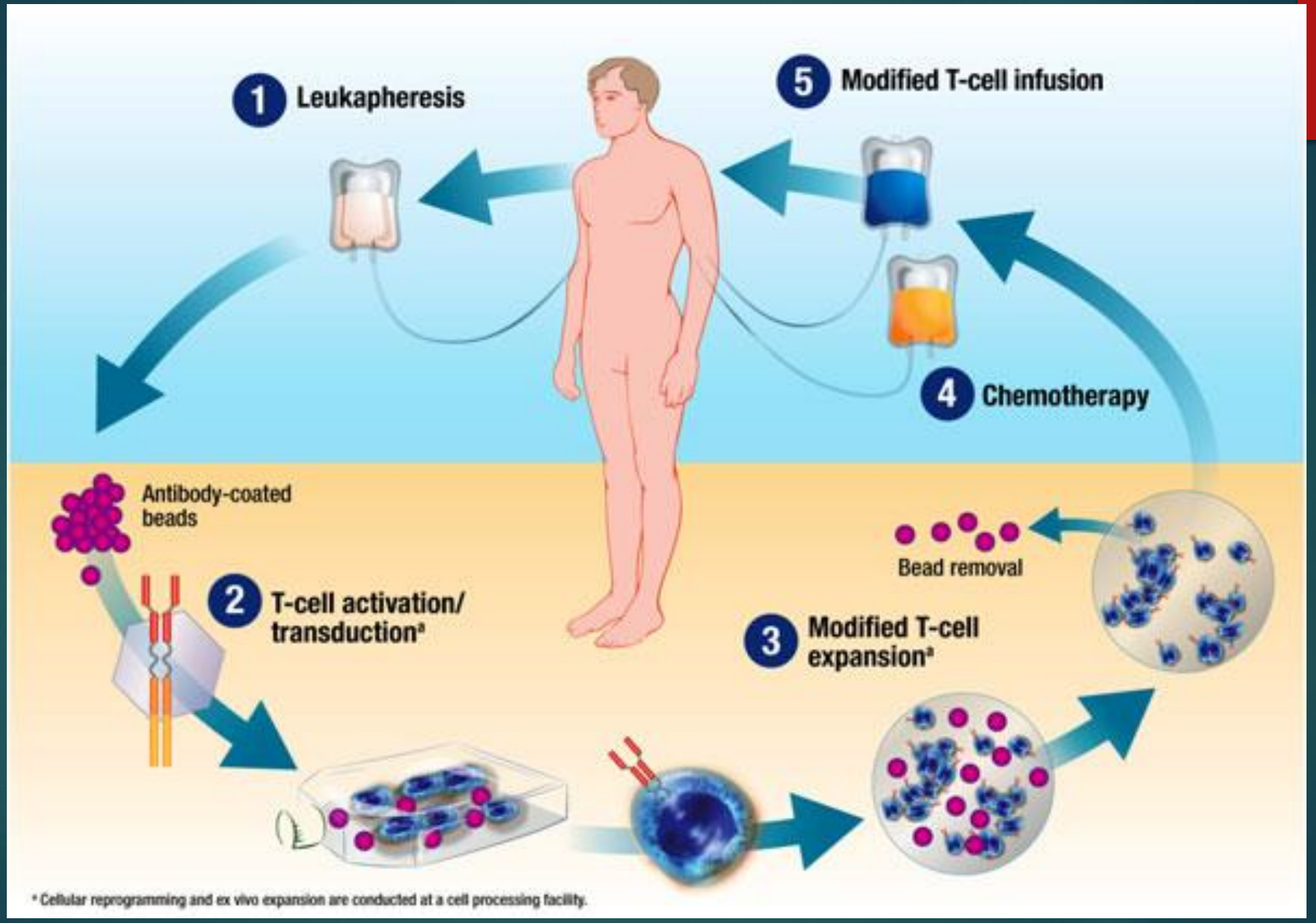
Façonnage moléculaire

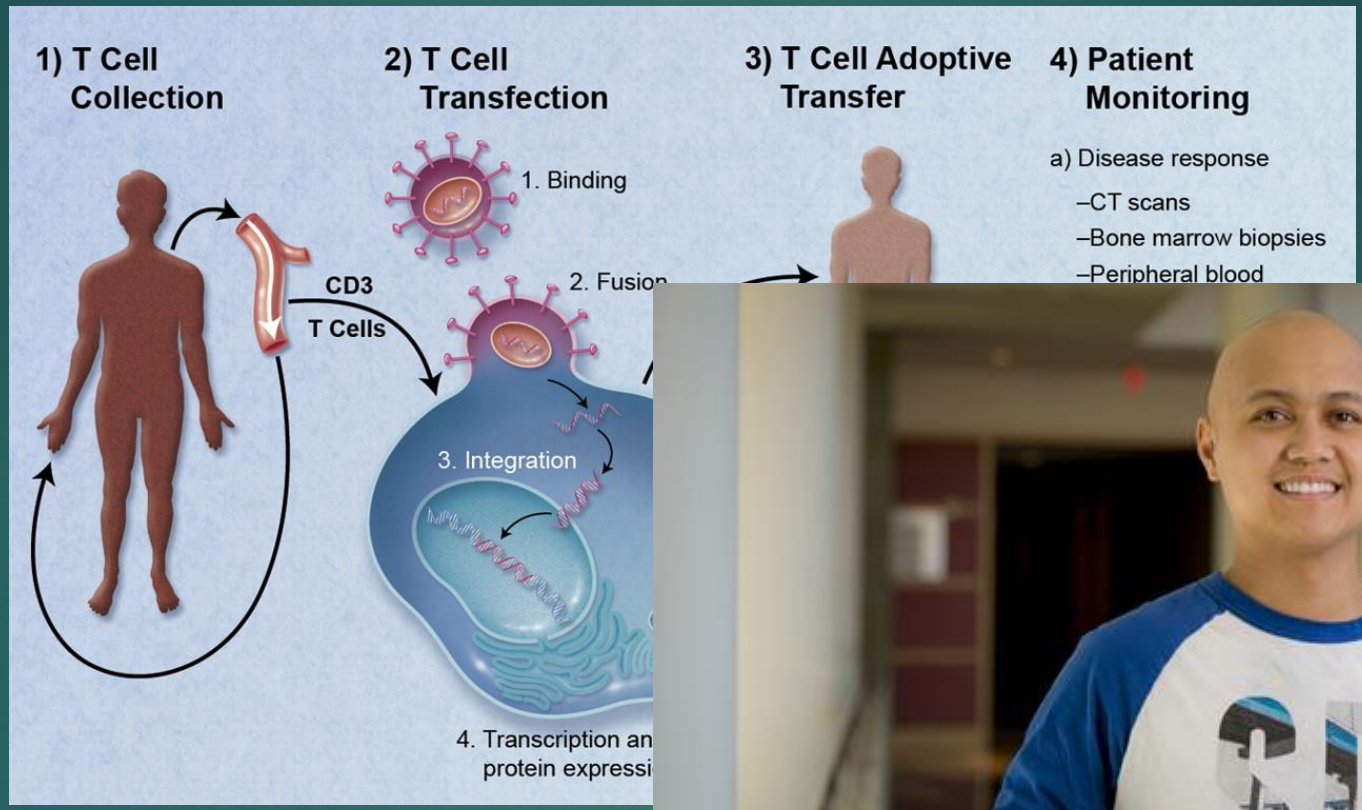
- Créer … nt artificiels
- Comm … x…
- P. ex. … toxiques…



CAR-T
chimeric antigen receptor




1 Leukapheresis
5 Modified T-cell infusion
4 Chemotherapy
Antibody-coated beads
2 T-cell activation/ transduction*
Bead removal
3 Modified T-cell expansion*
* Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.


1) T Cell Collection
2) T Cell Transfection
3) T Cell Adoptive Transfer
4) Patient Monitoring
a) Disease response
–CT scans
–Bone marrow biopsies
–Peripheral blood
1. Binding
2. Fusion
CD3
T Cells
3. Integration
4. Transcription an
protein expressi

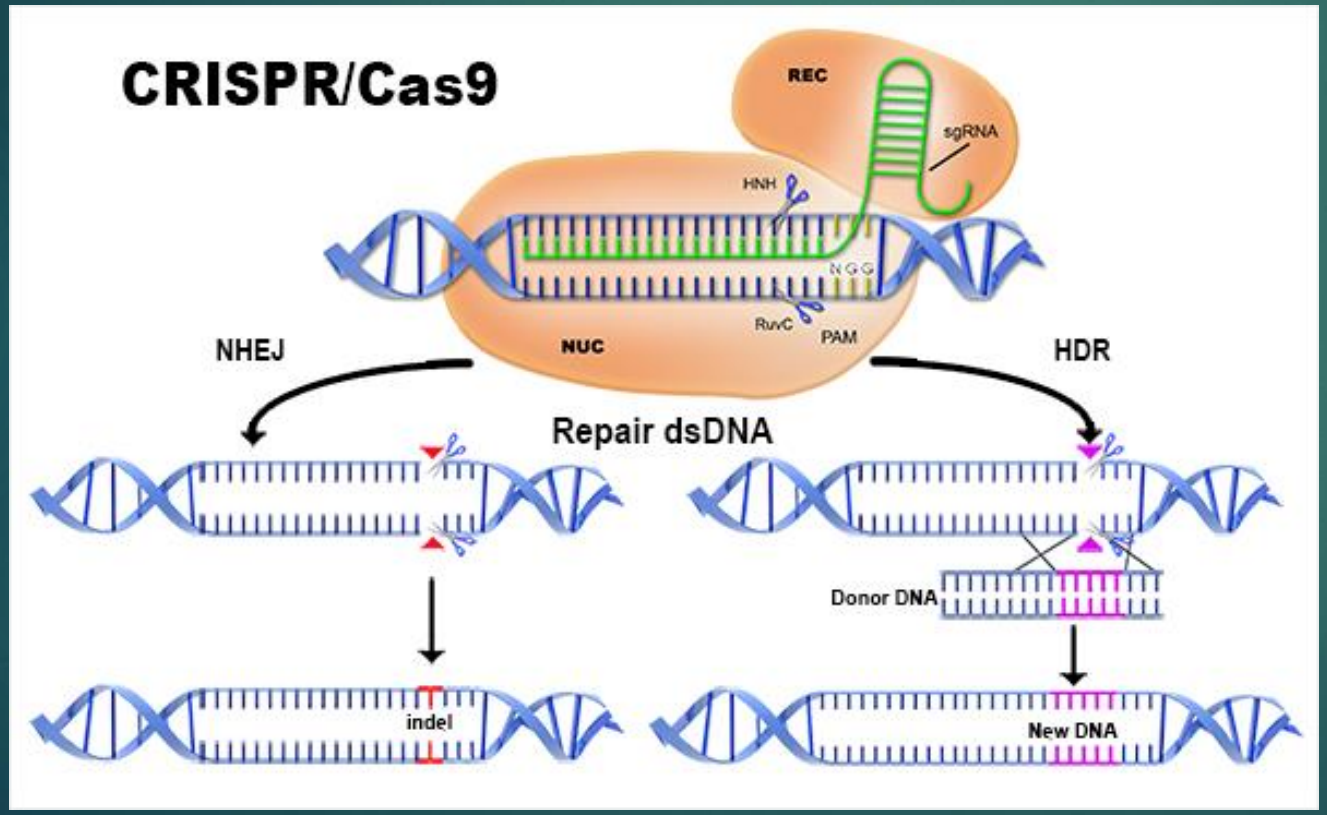

SAN DIEGO·CA

- Ceci est en cours d'essai chez LLA réfractaires
- Toxique… mais redoutablement efficace
- Pourrait être imaginé dans tous les cancers…
- Aussi longtemps qu'on connaît un antigène tumoral

CRISPR cas9….

Clustered Regularly Interspaced Short Palindromic Repeats

- *Clustered Regularly Interspaced Short Palindromic Repeats*

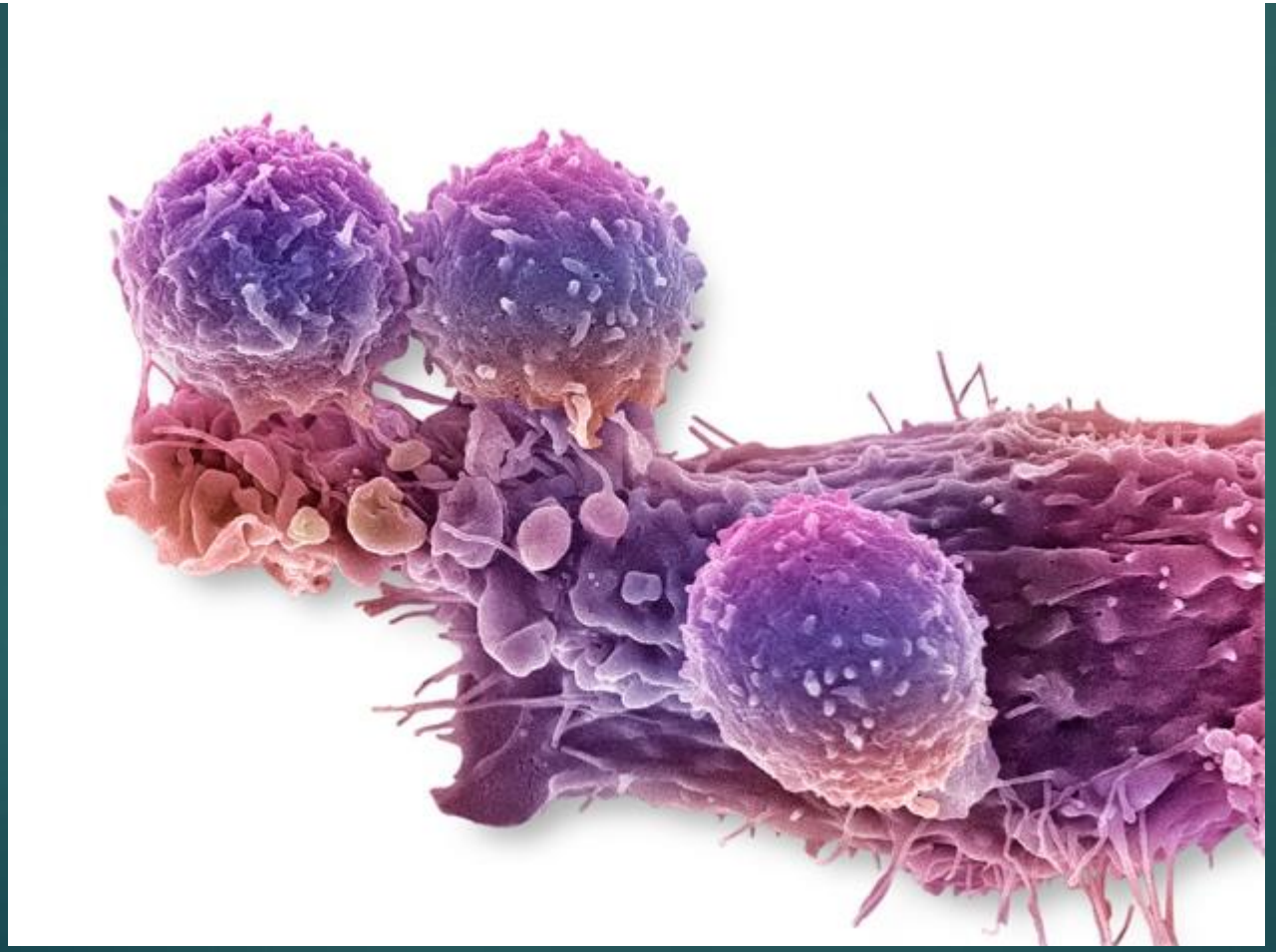


On utilise les mécanismes de réparation du DNA pour le changer…

BIOMEDICINE

First trial of CRISPR in people

Chinese team approved to test gene-edited cells in people with lung cancer.



nature

Gene editing could improve the ability of immune cells (spherical) to attack cancer.

BIOTECHNOLOGY

CRISPR gene editing tested in a person

Trial could spark biomedical duel between China and US.

BY DAVID CYRANOSKI

A Chinese group has become the first to inject a person with cells that contain genes edited using the revolutionary CRISPR–Cas9 technique.

On 28 October, a team led by oncologist Lu You at Sichuan University in Chengdu delivered the modified cells into a patient with aggressive lung cancer as part of a clinical trial at the West China Hospital, also in Chengdu.

Earlier clinical trials using cells edited with a different technique have shown promise at treating disease. The emergence of CRISPR, which is simpler and more efficient than other techniques, will probably accelerate the race to get gene-edited cells into the clinic, says Carl June, who specializes in immunotherapy at the University of Pennsylvania in Philadelphia and led one of the earlier trials.

"I think this is going to trigger 'Sputnik 2.0', a biomedical duel on progress between China and the United States, which is important since competition usually improves the end product," he says.

June is also the scientific adviser for a planned US trial that will use CRISPR to target three genes in cells extracted from participants, with the goal of treating various cancers. He expects the trial to start early next year. In March 2017, a group at Peking University in Beijing hopes to start three clinical trials using CRISPR against bladder, prostate and renal-cell cancers. Those trials do not yet have approval or funding.

Lu's trial received ethical approval from a hospital review board in July. Injections into participants were supposed to begin in August but the date was pushed back, Lu says, because culturing and amplifying the cells took longer than expected and then the team ran into China's October holidays.

The researchers removed immune cells from the recipient's blood and then disabled a gene in them using CRISPR–Cas9, which combines a DNA-cutting enzyme with a molecular guide that can be programmed to tell the enzyme precisely where to cut. The disabled gene codes for the protein PD-1, which normally puts the brakes on a cell's immune response: cancers take advantage of that function to proliferate.

Lu's team then cultured the edited cells, increasing their number, and injected them back into the patient, who has metastatic non-small-cell lung cancer. The hope is that, without PD-1, the edited cells will attack and defeat the cancer.

Lu says that the treatment went smoothly, and that the participant will get a second injection, but declined to give details because of patient confidentiality. The team plans to treat ten people in total; each will receive either two, three or four injections. It is primarily a safety trial, and participants will be monitored for six months to determine whether the injections are causing serious adverse effects. Lu's team will also watch them beyond that time to see if they seem to be benefiting from the treatment.

Other oncologists are excited about CRISPR's entry onto the cancer scene. "The technology to be able to do this is incredible," says Naiyer Rizvi of Columbia University Medical Center in New York City. Antonio Russo of Palermo University in Italy notes that antibodies that neutralize PD-1 have successfully kept lung cancer in check, bodes well for a CRISPR-enabled attack on the protein. "It's an exciting strategy," he says. "The rationale is strong."

But Rizvi questions whether this particular trial will succeed. The process of extracting, genetically modifying and multiplying cells is "a huge undertaking and not very scalable", he says. "Unless it shows a large gain in efficacy, it will be hard to justify moving forward." He doubts it will be superior to the use of antibodies, which can be expanded to unlimited quantities in the clinic. Lu says that this question is being evaluated in the trial, but that it's too early to say which approach is better. ■

- First patient NSCLC 28th of October 2016
- CRISPR-Cas9 adressing PD-1 in T cells, then expanded ex vivo and reeinjected
- … results of first 10 patients will be published soon….

Gene editing could improve the ability of immune cells (spherical) to attack cancer.

BIOTECHNOLOGY

CRISPR gene editing tested in a person

Trial could spark biomedical duel between China and US.

BY DAVID CYRANOSKI

A Chinese group has become the first to inject a person with cells that contain genes edited using the revolutionary CRISPR–Cas9 technique.

On 28 October, a team led by oncologist Lu You at Sichuan University in Chengdu delivered the modified cells into a patient with aggressive lung cancer as part of a clinical trial at the West China Hospital, also in Chengdu.

Earlier clinical trials using cells edited with a different technique have shown promise at treating disease. The emergence of CRISPR, which is simpler and more efficient than other techniques, will probably accelerate the race to get gene-edited cells into the clinic, says Carl June, who specializes in immunotherapy at the University of Pennsylvania in Philadelphia and led one of the earlier trials.

"I think this is going to trigger 'Sputnik 2.0', a biomedical duel on progress between China and the United States, which is important since competition usually improves the end product," he says.

June is also the scientific adviser for a planned US trial that will use CRISPR to target three genes in cells extracted from participants, with the goal of treating various cancers. He expects the trial to start early next year. In March 2017, a group at Peking University in Beijing hopes to start three clinical trials using CRISPR against bladder, prostate and renal-cell cancers. Those trials do not yet have approval or funding.

Lu's trial received ethical approval from a hospital review board in July. Injections into participants were supposed to begin in August but the date was pushed back, Lu says, because culturing and amplifying the cells took longer than expected and then the team ran into China's October holidays.

The researchers removed immune cells from the recipient's blood and then disabled a gene in them using CRISPR–Cas9, which combines a DNA-cutting enzyme with a molecular guide that can be programmed to tell the enzyme precisely where to cut. The disabled gene codes for the protein PD-1, which normally puts the brakes on a cell's immune response: cancers take advantage of that function to proliferate.

Lu's team then cultured the edited cells, increasing their number, and injected them back into the patient, who has metastatic non-small-cell lung cancer. The hope is that, without PD-1, the edited cells will attack and defeat the cancer.

Lu says that the treatment went smoothly, and that the participant will get a second injection, but declined to give details because of patient confidentiality. The team plans to treat ten people in total; each will receive either two, three or four injections. It is primarily a safety trial, and participants will be monitored for six months to determine whether the injections are causing serious adverse effects. Lu's team will also watch them beyond that time to see if they seem to be benefiting from the treatment.

Other oncologists are excited about CRISPR's entry onto the cancer scene. "The technology to be able to do this is incredible," says Naiyer Rizvi of Columbia University Medical Center in New York City. Antonio Russo of Palermo University in Italy notes that antibodies that neutralize PD-1 have successfully kept lung cancer in check, bodes well for a CRISPR-enabled attack on the protein. "It's an exciting strategy," he says. "The rationale is strong."

But Rizvi questions whether this particular trial will succeed. The process of extracting, genetically modifying and multiplying cells is "a huge undertaking and not very scalable", he says. "Unless it shows a large gain in efficacy, it will be hard to justify moving forward." He doubts it will be superior to the use of antibodies, which can be expanded to unlimited quantities in the clinic. Lu says that this question is being evaluated in the trial, but that it's too early to say which approach is better. ■

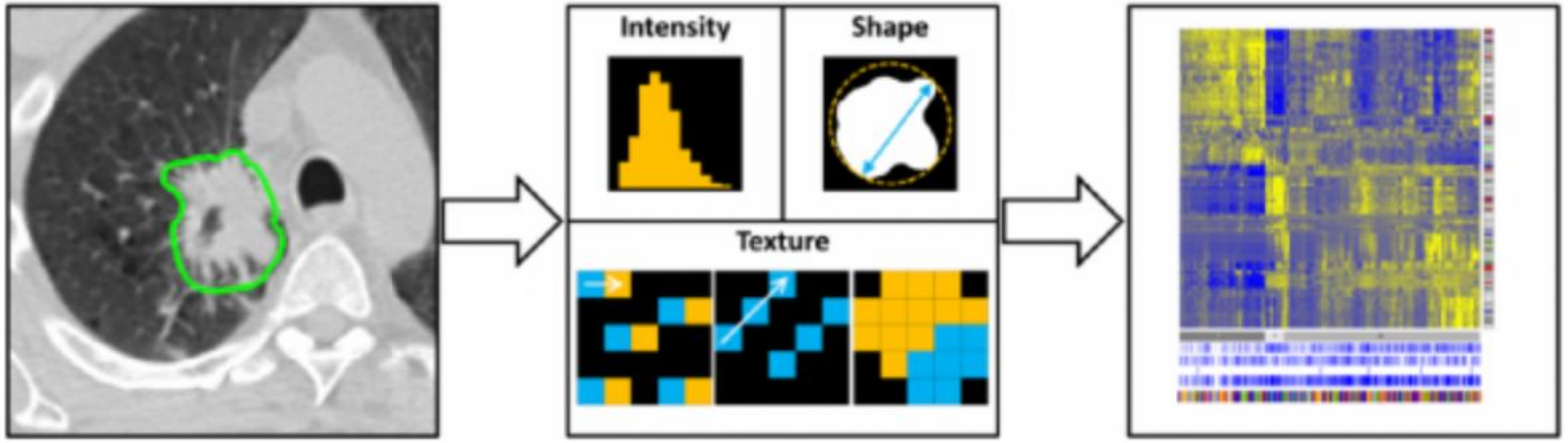
- Premier patient NSCLC traité 28 Oct 2016
- CRISPR-Cas9 altérant PD-1 dans des cellules T, puis cultivées et réinjectées….
- … résultats publiés après les 10 premiers patients

Radiomics

- Utilisation des données informatiques des images radiologiques.

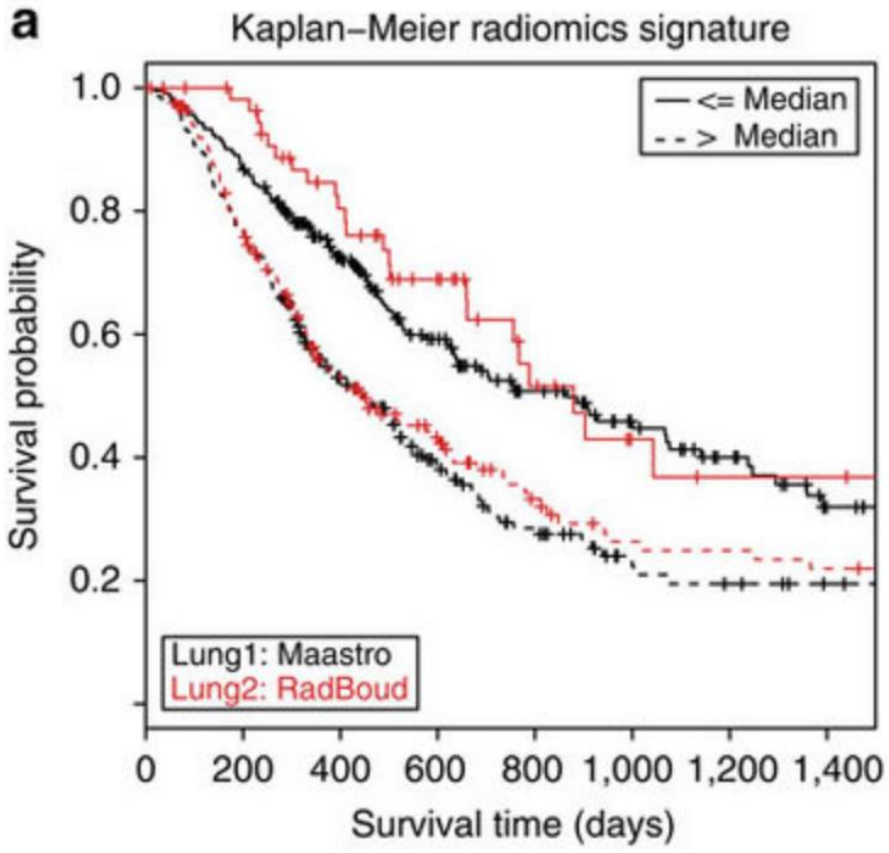
Radiomics: What is it about?

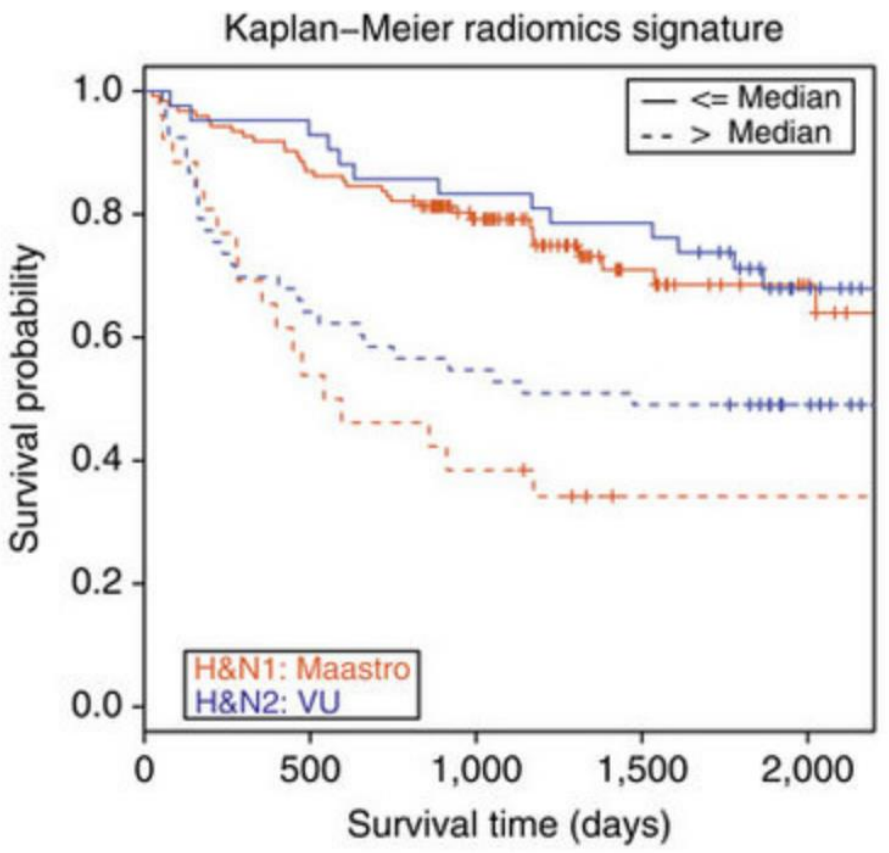
A high throughput approach to convert



medical images to minable data

Résultats…





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Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach.

Merci !