La médecine personnalisée en oncologie

Denis MORO-SIBILOT
SHUPP CHU de Grenoble-Alpes

DMSLung

Liens d'intérêts

- Au cours des 3 dernières années avec les sociétés Pharmaceutiques suivantes

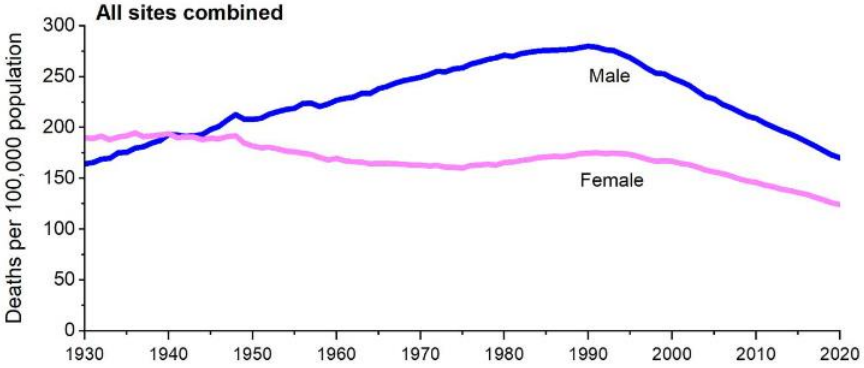
- Recherches cliniques : Roche, Pfizer, BMS, MSD, Boehringer Ingelheim, Astra Zeneca, Abbvie, Takeda, Lilly

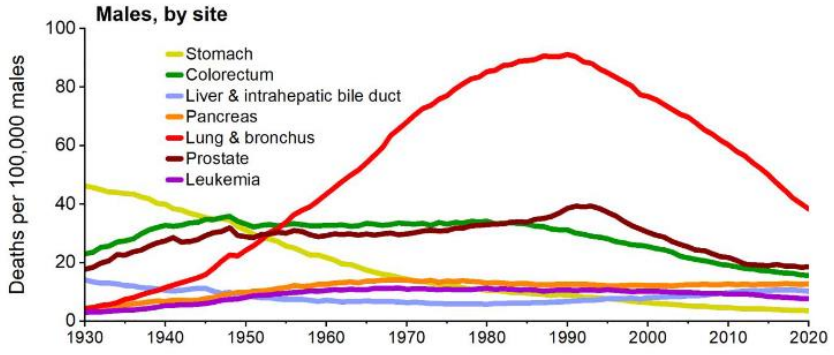
- Advisory Boards : Roche, Pfizer, BMS, MSD, Boehringer Ingelheim, Astra Zeneca, Abbvie, Takeda, Lilly, Amgen, Becton Dickinson, Mylan

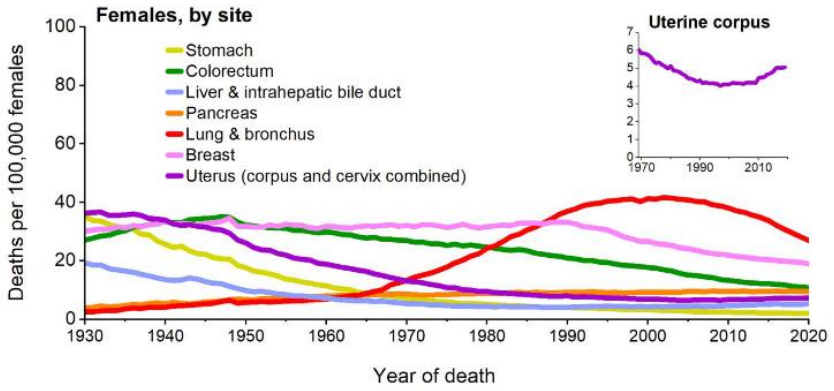
- Cours, formations : Roche, Pfizer, BMS, MSD, Boehringer Ingelheim, Astra Zeneca, Abbvie, Takeda, Lilly

- Aides pour des recherches : Roche, Pfizer, BMS, Boehringer Ingelheim, Astra Zeneca, Abbvie

Des progrès dans la prise en charge des cancers







Siegel RL et al. Cancer statistics, 2023. CA Cancer J Clin. 2023

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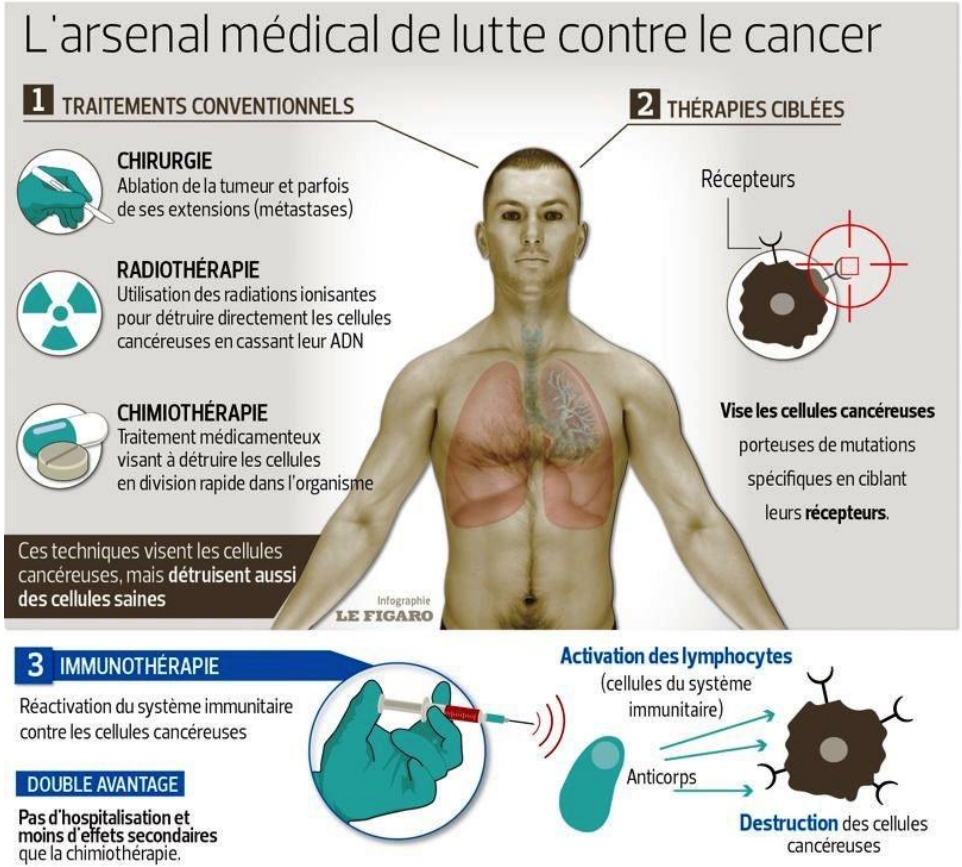
Révolution des traitements du cancer



Le figaro on line 14/10/2016

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Révolution des traitements du cancer

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.

ABSTRACT

BACKGROUND

Most patients with non–small-cell lung cancer have no response to the tyrosine kinase inhibitor gefitinib, which targets the epidermal growth factor receptor (EGFR). However, about 10 percent of patients have a rapid and often dramatic clinical response. The molecular mechanisms underlying sensitivity to gefitinib are unknown.

METHODS

We searched for mutations in the *EGFR* gene in primary tumors from patients with non–small-cell lung cancer who had a response to gefitinib, those who did not have a response, and those who had not been exposed to gefitinib. The functional consequences of identified mutations were evaluated after the mutant proteins were expressed in cultured cells.

RESULTS

Somatic mutations were identified in the tyrosine kinase domain of the *EGFR* gene in eight of nine patients with gefitinib-responsive lung cancer, as compared with none of the seven patients with no response ($P<0.001$). Mutations were either small, in-frame deletions or amino acid substitutions clustered around the ATP-binding pocket of the tyrosine kinase domain. Similar mutations were detected in tumors from 2 of 25 patients with primary non–small-cell lung cancer who had not been exposed to gefitinib (8 percent). All mutations were heterozygous, and identical mutations were observed in multiple patients, suggesting an additive specific gain of function. In vitro, EGFR mutants demonstrated enhanced tyrosine kinase activity in response to epidermal growth factor and increased sensitivity to inhibition by gefitinib.

CONCLUSIONS

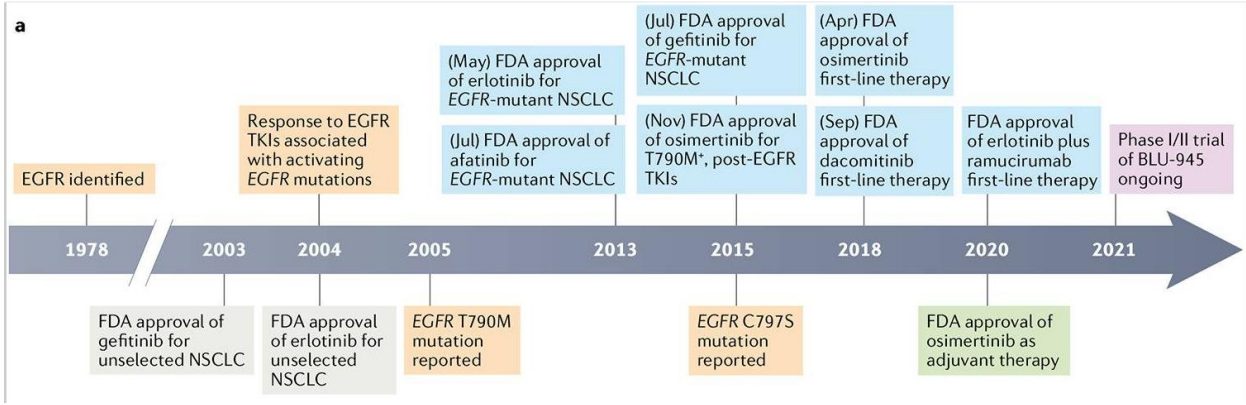
A subgroup of patients with non–small-cell lung cancer have specific mutations in the EGFR gene, which correlate with clinical responsiveness to the tyrosine kinase inhibitor gefitinib. These mutations lead to increased growth factor signaling and confer susceptibility to the inhibitor. Screening for such mutations in lung cancers may identify patients who will have a response to gefitinib.

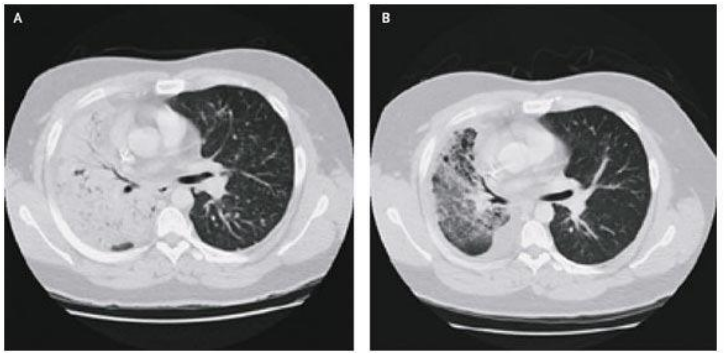
From the Cancer Center (T.J.L., D.W.B., R.S., S.G., R.A.O., B.W.B., P.L.H., S.M.H., J.G.S., F.G.H., D.N.L., D.C.C., J.S., D.A.H.) and the Departments of Medicine (T.J.L., D.W.B., J.G.S., F.G.H., D.C.C., J.S., D.A.H.) and Pathology (D.N.L.), Massachusetts General Hospital and Harvard Medical School; and the Harvard School of Public Health (S.G., D.C.C.) — all in Boston. Address reprint requests to Dr. Haber at MGH Cancer Center, Bldg. 149, 13th St., Charlestown, MA 02129, or at haber@helix.mgh.harvard.edu.

Drs. Lynch, Bell, and Sordella contributed equally to the article.

This article was published at www.nejm.org on April 29, 2004.

N Engl J Med 2004;350:2129-39.





Lynch T et al, NEJM 2004, Cooper AJ et al. Nat Rev Clin Oncol. 2022 DMSLung

Révolution des traitements du cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q.M. Chow, M.D., Wen-Jen Hwu, M.D., Ph.D., Suzanne L. Topalian, M.D., Patrick Hwu, M.D., Charles G. Drake, M.D., Ph.D., Luis H. Camacho, M.D., M.P.H., John Kauh, M.D., Kunle Odunsi, M.D., Ph.D., Henry C. Pitot, M.D., Omid Hamid, M.D., Shailender Bhatia, M.D., Renato Martins, M.D., M.P.H., Keith Eaton, M.D., Ph.D., Shuming Chen, Ph.D., Theresa M. Salay, M.S., Suresh Alaparthy, Ph.D., Joseph F. Grosso, Ph.D., Alan J. Korman, Ph.D., Susan M. Parker, Ph.D., Shruti Agrawal, Ph.D., Stacie M. Goldberg, M.D., Drew M. Pardoll, M.D., Ph.D., Ashok Gupta, M.D., Ph.D., and Jon M. Wigginton, M.D.

ABSTRACT

BACKGROUND

Programmed death 1 (PD-1) protein, a T-cell coinhibitory receptor, and one of its ligands, PD-L1, play a pivotal role in the ability of tumor cells to evade the host's immune system. Blockade of interactions between PD-1 and PD-L1 enhances immune function in vitro and mediates antitumor activity in preclinical models.

METHODS

In this multicenter phase 1 trial, we administered intravenous anti–PD-L1 antibody (at escalating doses ranging from 0.3 to 10 mg per kilogram of body weight) to patients with selected advanced cancers. Anti–PD-L1 antibody was administered every 14 days in 6-week cycles for up to 16 cycles or until the patient had a complete response or confirmed disease progression.

RESULTS

As of February 24, 2012, a total of 207 patients — 75 with non–small-cell lung cancer, 55 with melanoma, 18 with colorectal cancer, 17 with renal-cell cancer, 17 with ovarian cancer, 14 with pancreatic cancer, 7 with gastric cancer, and 4 with breast cancer — had received anti–PD-L1 antibody. The median duration of therapy was 12 weeks (range, 2 to 111). Grade 3 or 4 toxic effects that investigators considered to be related to treatment occurred in 9% of patients. Among patients with a response that could be evaluated, an objective response (a complete or partial response) was observed in 9 of 52 patients with melanoma, 2 of 17 with renal-cell cancer, 5 of 49 with non–small-cell lung cancer, and 1 of 17 with ovarian cancer. Responses lasted for 1 year or more in 8 of 16 patients with at least 1 year of follow-up.

CONCLUSIONS

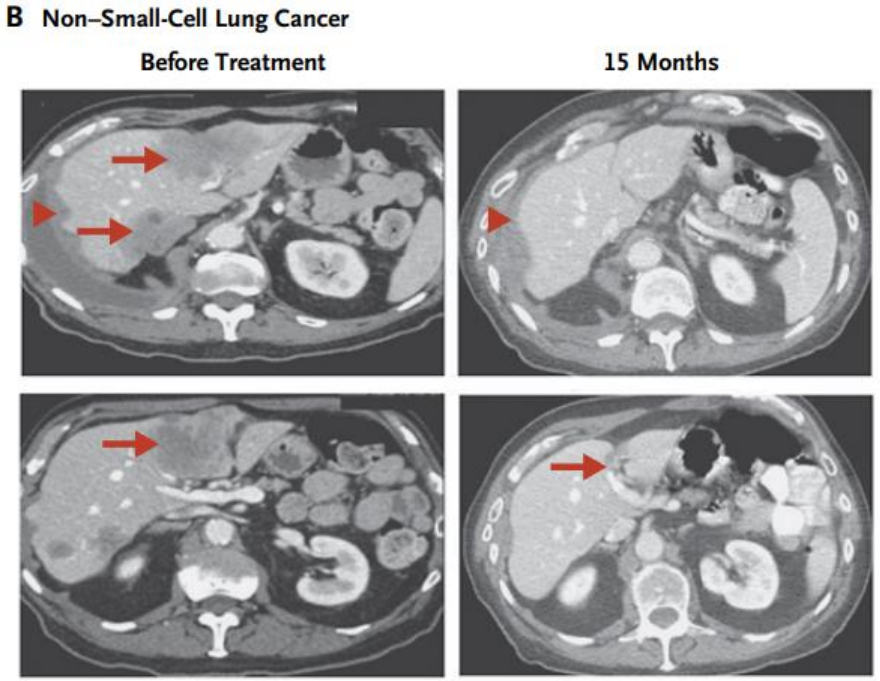
Antibody-mediated blockade of PD-L1 induced durable tumor regression (objective response rate of 6 to 17%) and prolonged stabilization of disease (rates of 12 to 42% at 24 weeks) in patients with advanced cancers, including non–small-cell lung cancer, melanoma, and renal-cell cancer. (Funded by Bristol-Myers Squibb and others; ClinicalTrials.gov number, NCT00729664.)

From Johns Hopkins University School of Medicine and the Sidney Kimmel Comprehensive Cancer Center, Baltimore (J.R.B., S.L.T., C.G.D., S.C., T.M.S., D.M.P.); University of Washington and Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, Seattle (S.S.T., L.Q.M.C., S.B., R.M., K.E.); M.D. Anderson Cancer Center (W.-J.H., P.H.) and St. Luke's Episcopal Hospital Cancer Center (L.H.C.) — both in Houston; Winship Cancer Institute of Emory University, Atlanta (J.K.); Roswell Park Cancer Institute, Buffalo, NY (K.O.); Mayo Clinic College of Medicine, Rochester, MN (H.C.P.); Angeles Clinic, Santa Monica (O.H.), and Bristol-Myers Squibb, Milpitas (A.J.K.) — both in California; and Bristol-Myers Squibb, Princeton, NJ (S.A., J.F.G., S.M.P., S.A., S.M.G., A.G., J.M.W.). Address reprint requests to Dr. Brahmer at the Sidney Kimmel Comprehensive Cancer Center, Bunting/Blaustein CRB G94, 1650 Orleans St., Baltimore, MD 21231.

Drs. Brahmer and Tykodi contributed equally to this article.

This article (10.1056/NEJMoa1200694) was published on June 2, 2012, and updated on June 28, 2012, at NEJM.org.

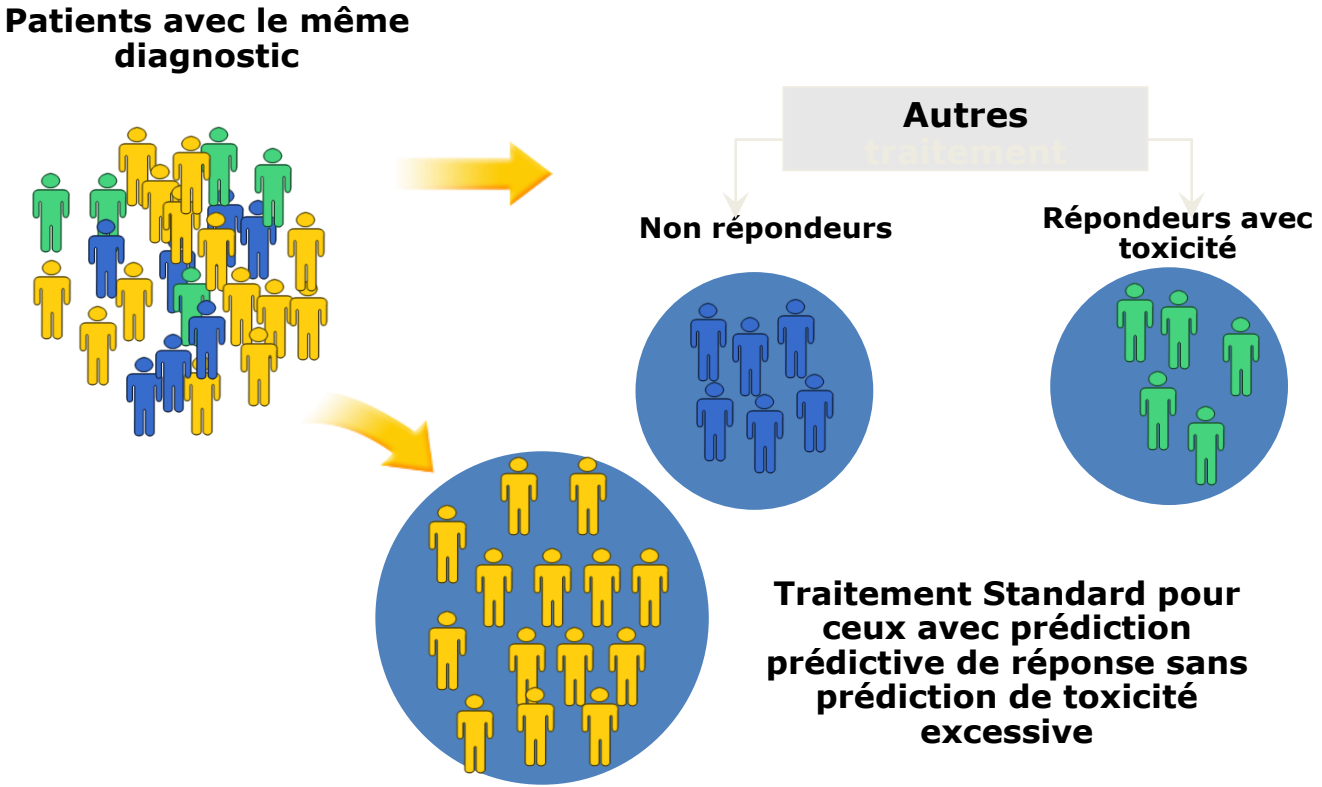
N Engl J Med 2012;366:2455-65.



Brahmer JR et al. N Engl J Med. 2012;366:2455-65.

Bénéfice de la médecine personnalisée

Point de vue des patients……



Prescrire pour chaque patient le meilleur traitement

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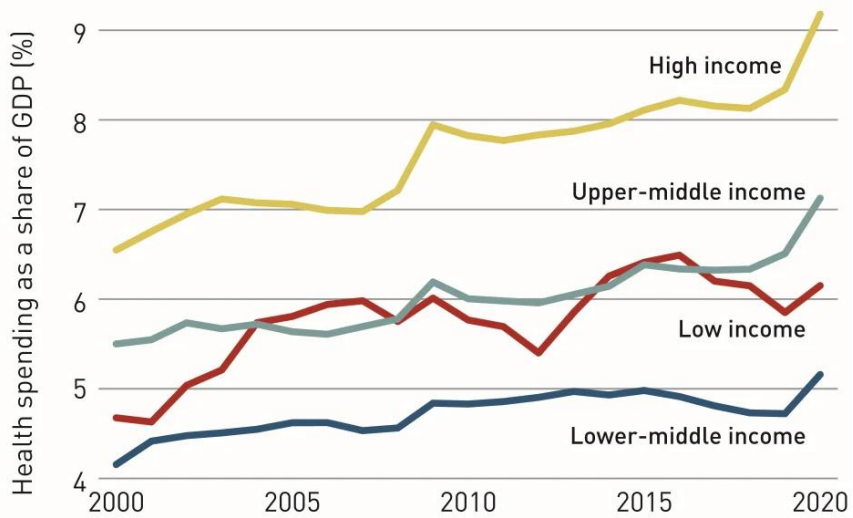
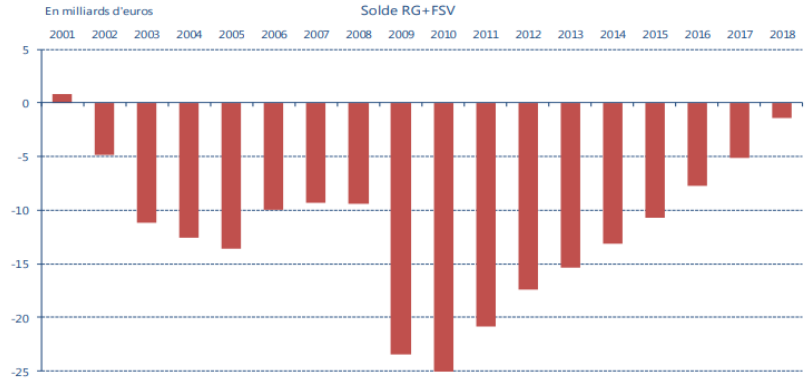
Point de vue des organismes payeurs……





Solde du régime général de la sécurité sociale et du fonds de solidarité vieillesse depuis 2001

- Maintenir l'innovation thérapeutique en maitrisant les coûts
- Réserver certains médicaments innovants à ceux qui en bénéficient le plus

WHO 2023 Global Health Expenditure Database, www.securite-sociale.fr

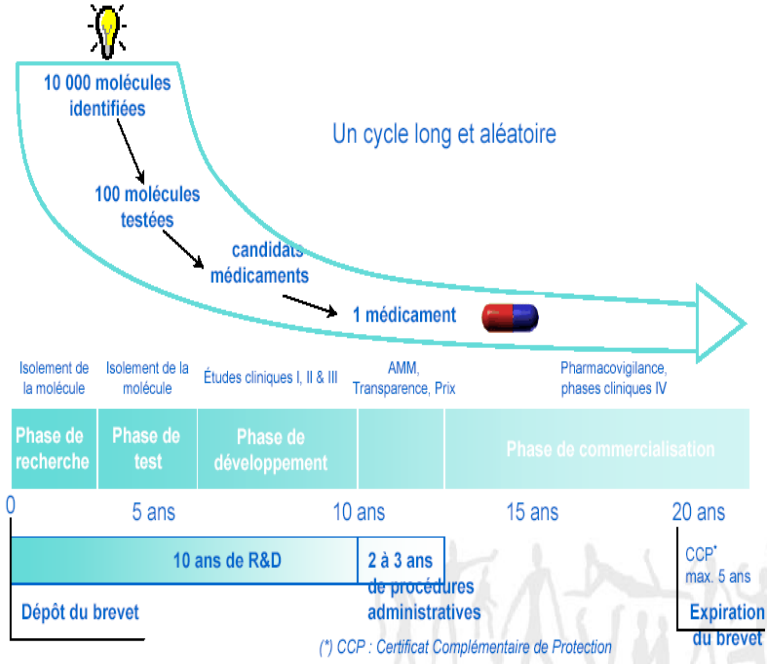
Point de vue des industriels……

- En 2000 la FDA, l'Université d'Arizona, le Stanford Research Institute publient un rapport: « Critical Path Initiative List ».
  - Inquiétude face au faible taux de rentabilité du développement classique
  - Limites des essais avec augmentation du risque d'erreur car comparaisons statistiques multiples, analyses intermédiaires inopinées)

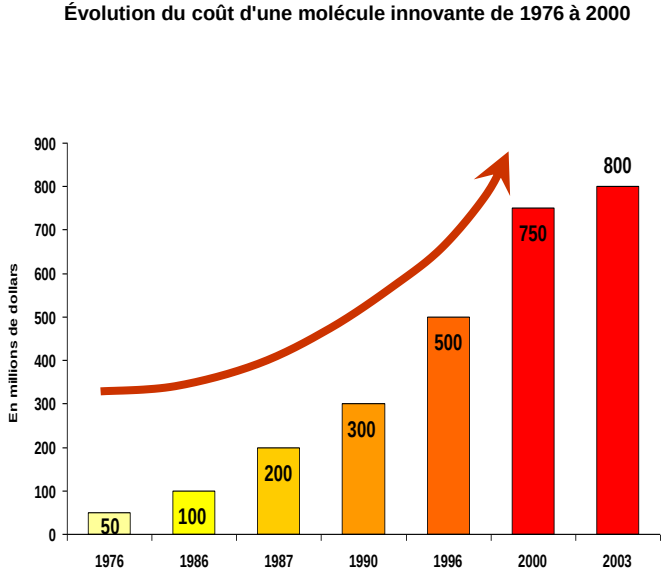
- En 2004 :
  - développement d'un nouveau médicament 10 à 15 ans
  - coût moyen de développement d'un médicament = 1,5 Milliard $
  - faible productivité (1 mise sur le marché pour 5000 composés testés)

Point de vue des industriels…… la recherche et le développement des nouveaux médicaments, un processus long et coûteux

De l'idée au produit : genèse d'un médicament



Le coût de l'innovation en croissance exponentielle depuis 20 ans (US$)



Sources : Arthur D. Little

Point de vue des industriels……

Réduire le taux d'attrition des médicaments

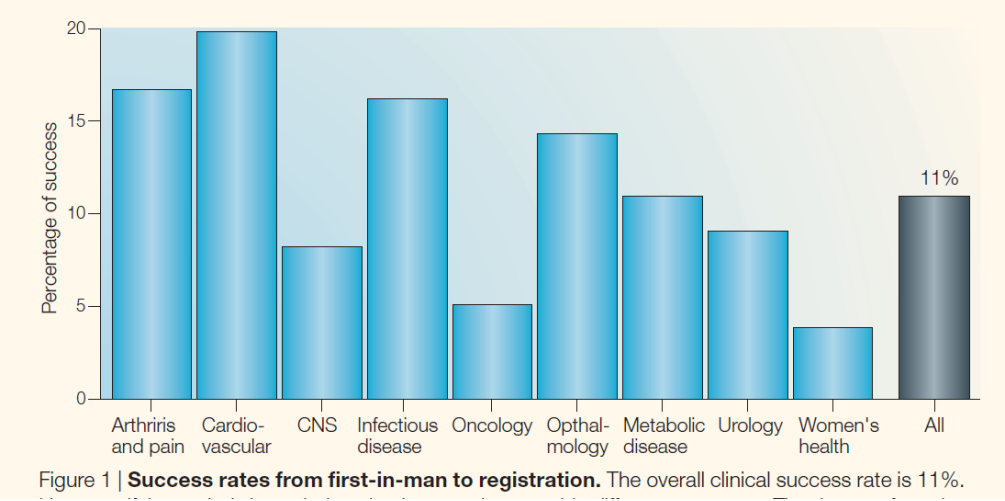
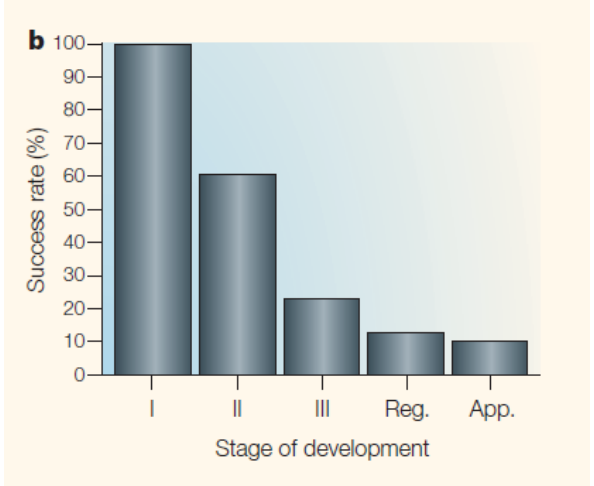


Figure 1 | **Success rates from first-in-man to registration.** The overall clinical success rate is 11%.

Taux de succès par spécialité



Taux de succès par phase de développement

Kola I Nat Rev Drug Discov. 2004 Aug;3(8):711-5.

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Recommandations du « Critical Path Opportunities Report » de 2006

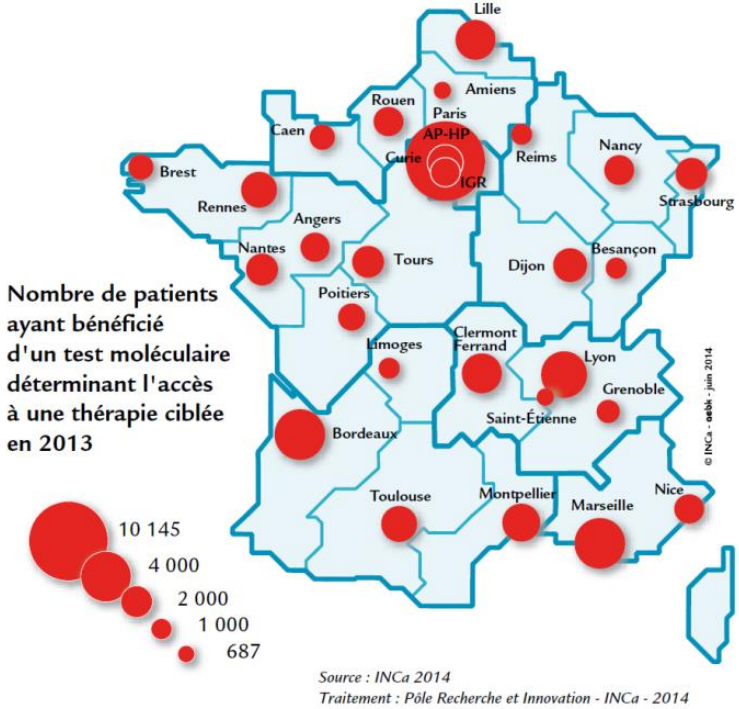
- FDA, l'Université d'Arizona, le Stanford Research Institute publient un rapport: « Critical Path Initiative List ».
  - Développement de biomarqueurs « surrogates endpoints » prédictifs de l'efficacité et de la tolérance
  - Rationalisation clinique efficace : sécurisation des patients, avec contrôle d'innocuité (méthodologies probabilistes modernes)
  - Bioinformatique
  - Qualité de fabrication
  - Lutte contre les infections émergentes
  - Recherche clinique en pédiatrie

Comment passer du monde probabiliste au monde personnalisé ?

- Identifier des biomarqueurs : ADN, ARN, protéines, méthylome …..
  - Plan Cancer 2003 et plateformes de biologie moléculaire des cancers
  - « Biopsies liquides »
- Traitements ciblés :
  - ITK
  - Immunothérapies
  - Nouvelles molécules de ciblage
- Nouvelle méthodologie des essais cliniques

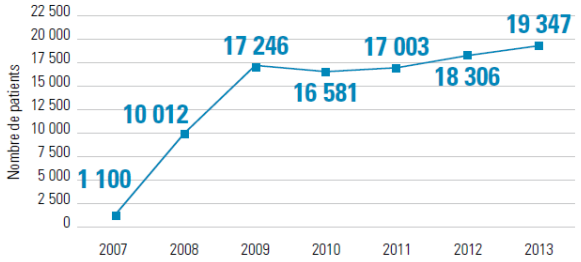
Plan Cancer 2003 : Les plateformes de biologie moléculaire des cancers

Dépistage moléculaire prédictif en France en 2013 : activité des 28 centres de génétique moléculaire

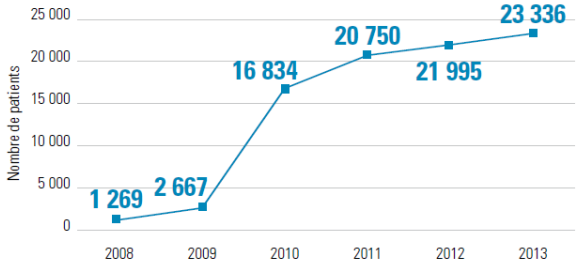


Source : INCa 2014
Traitement : Pôle Recherche et Innovation - INCa - 2014

DÉPISTAGE K-RAS POUR LES PATIENTS ATTEINTS D'UN CANCER DU CÔLON ET DU RECTUM

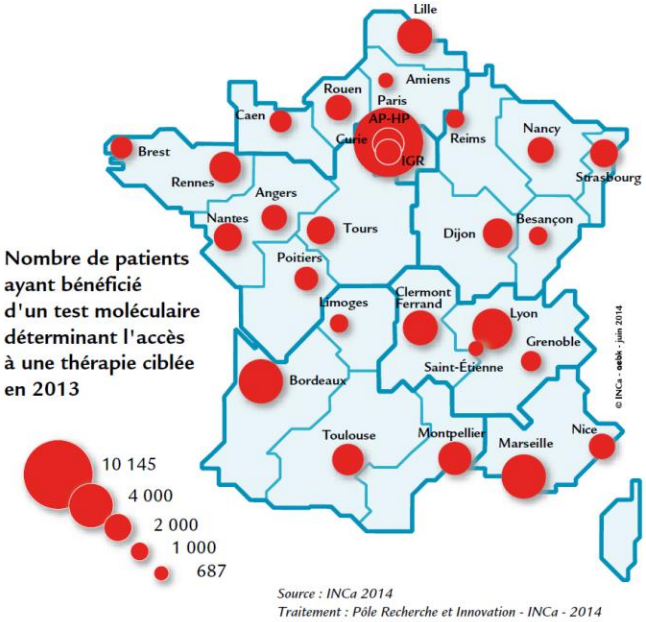


DÉPISTAGE EGFR POUR LES PATIENTS ATTEINTS D'UN CANCER DU POUMON



Etude Biomarker France

Dépistage moléculaire prédictif en France en 2013 : activité des 28 centres de génétique moléculaire



Source : INCa 2014
Traitement : Pôle Recherche et Innovation - INCa - 2014

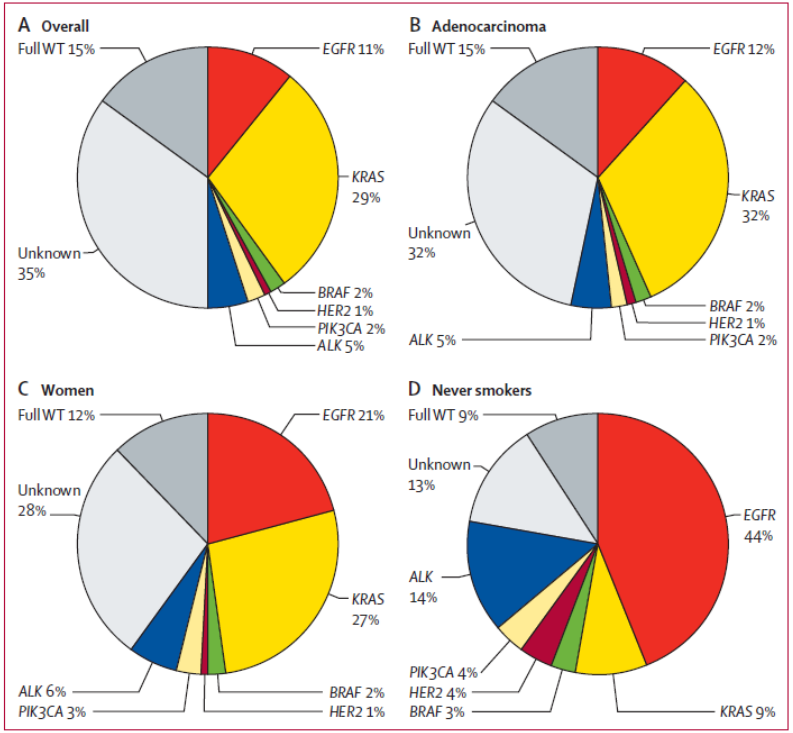


Figure 2: **Frequency of genetic alterations**
Frequency of molecular alterations in six genes from 18 679 analysed samples (expressed as the percentage of positive samples for each molecular alteration relative to the number of available analyses, with unknown representing the cases with at least one unknown result after assessment of the six genes). Full WT=patients with an established molecular profile without an *EGFR*, *KRAS*, *BRAF*, *HER2* (*ERBB2*), or *PIK3CA* mutation or *ALK* rearrangement. (A) Overall population, (B) adenocarcinoma only, (C) women only, and (D) never smokers only.

Barlesi F et al. Lancet. 2016;387:1415-1426.

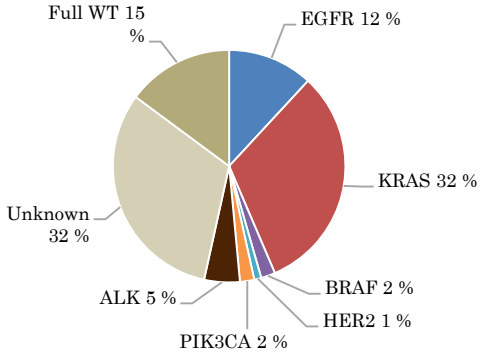
Révolution du testing moléculaire

2005

Chimiothérapie

2015

N = 17 664 (76 % ADC)
6 cancer-associated genes



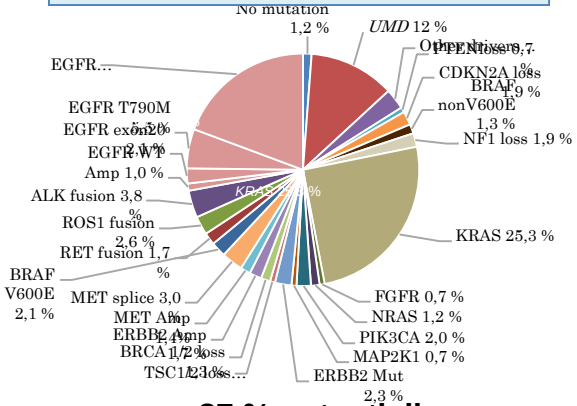
→ 21 % potentially actionable alterations

Barlesi, Mazières. Lancet 2015

Chimiothérapie
Thérapies ciblées
(EGFR, ALK)

2020

N = 860 ADC
≥ 300 cancer-associated genes



→ 87 % potentially actionable alterations

Jordan. Cancer Discovery 2017

Chimiothérapie
Immunothérapie
Thérapies ciblées

Réponse, survie

Courtoisie la lettre du cancérologue

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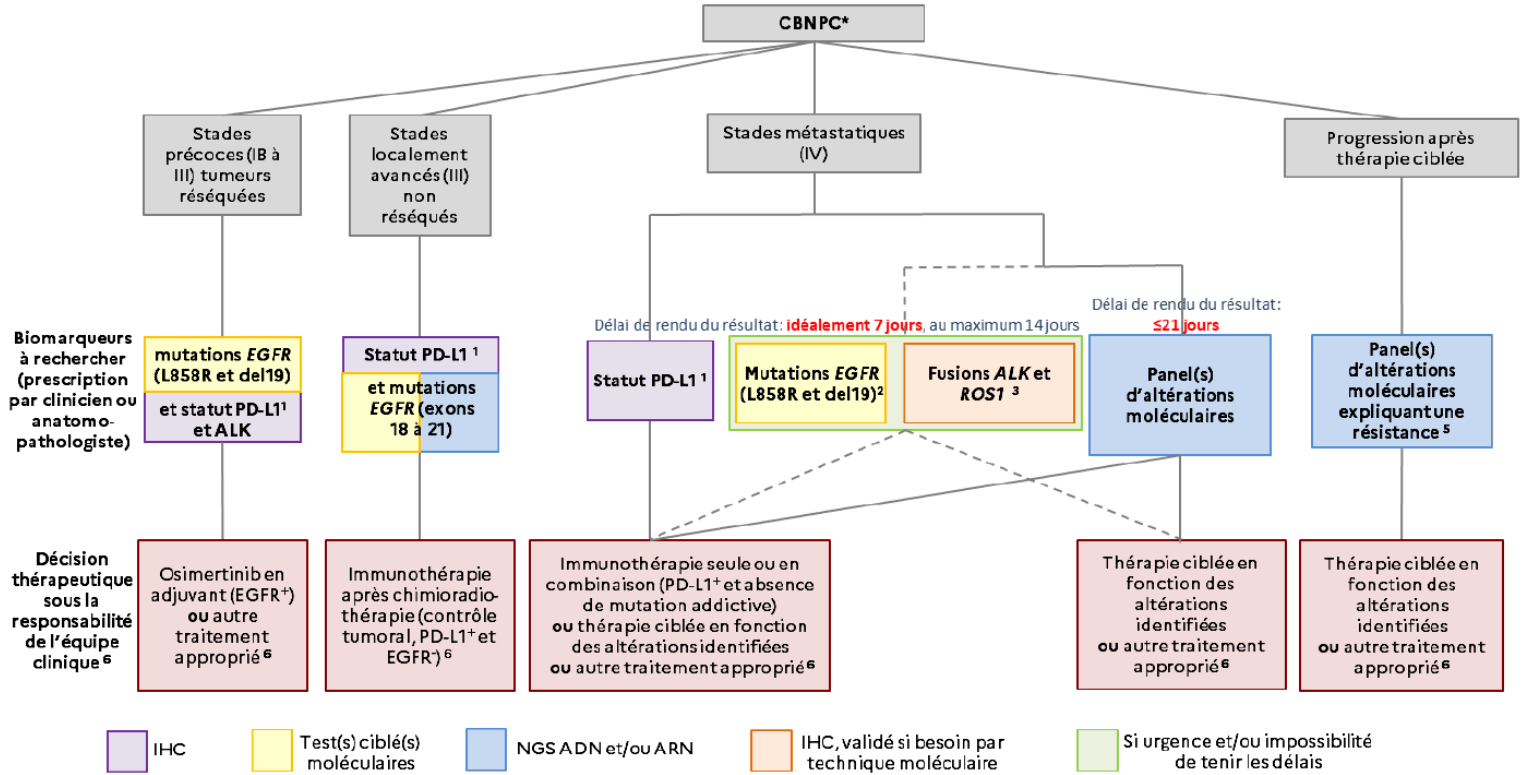
RECOMMANDATIONS ET RÉFÉRENTIELS

PATIENTS ATTEINTS D'UN CANCER BRONCHIQUE NON À PETITES CELLULES

/ Indications des tests moléculaires en vue de la prescription de traitements de précision

Arbre décisionnel : biomarqueurs nécessaires au traitement des patients atteints de cbnpc



INCa 2023

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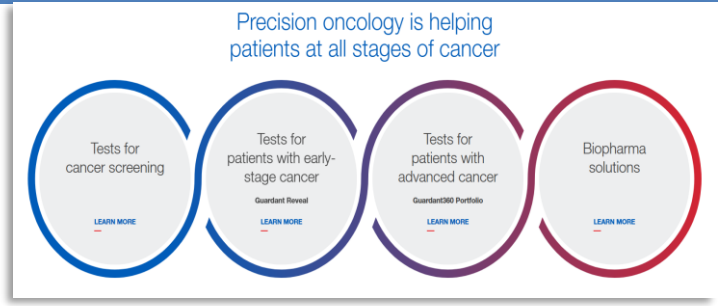
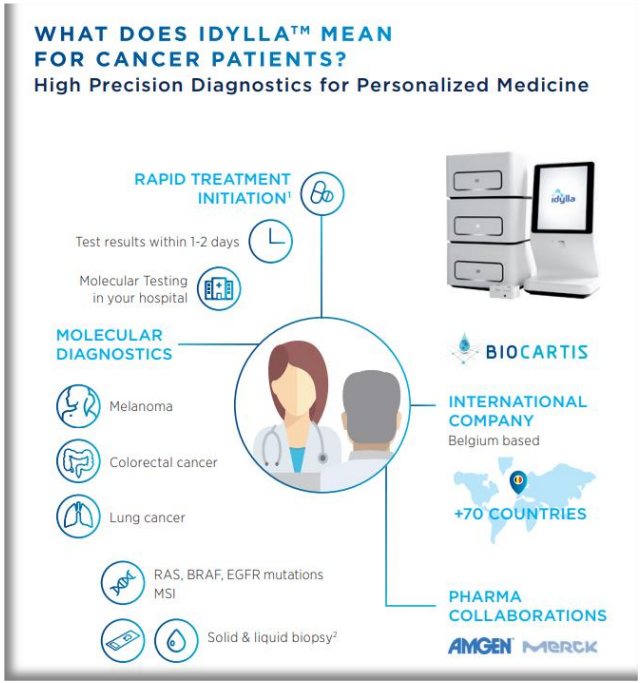
Une concurrence importante pour les plateformes





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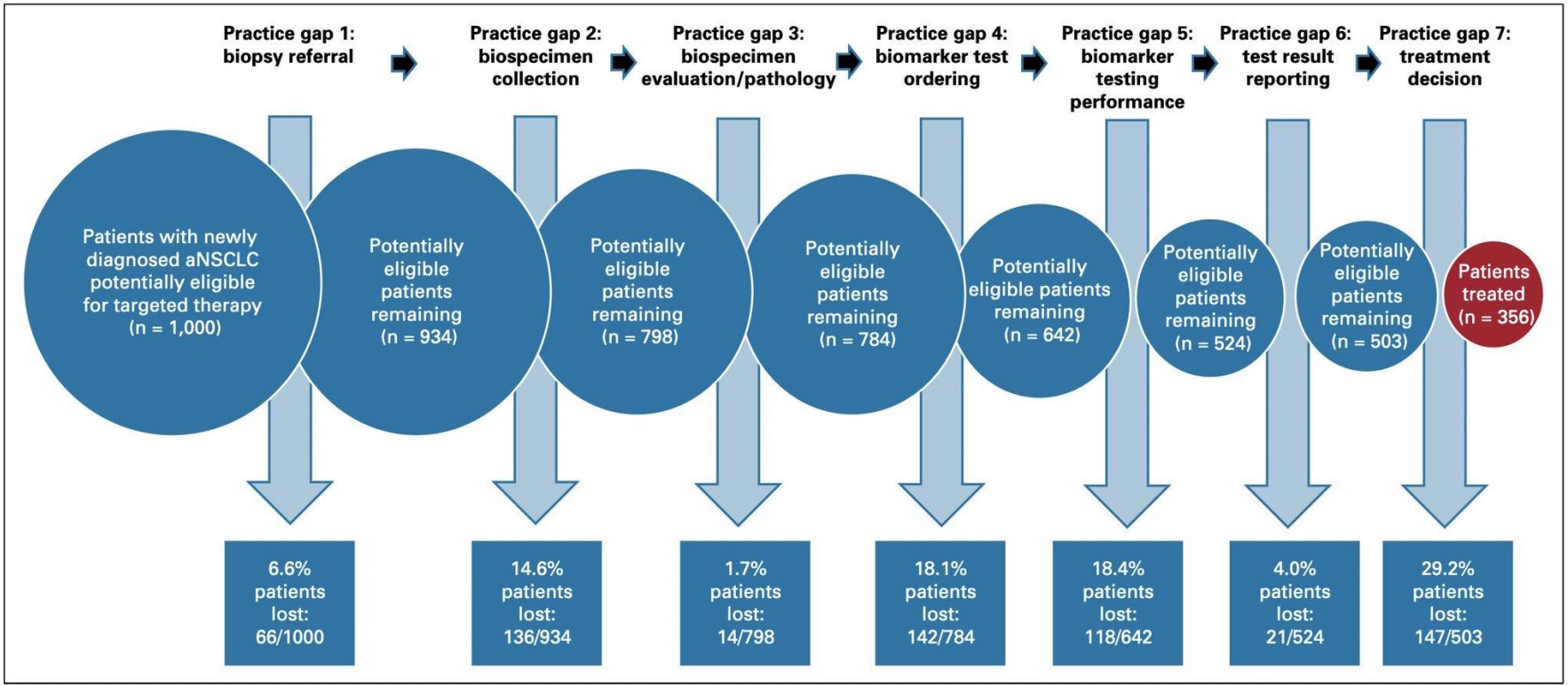
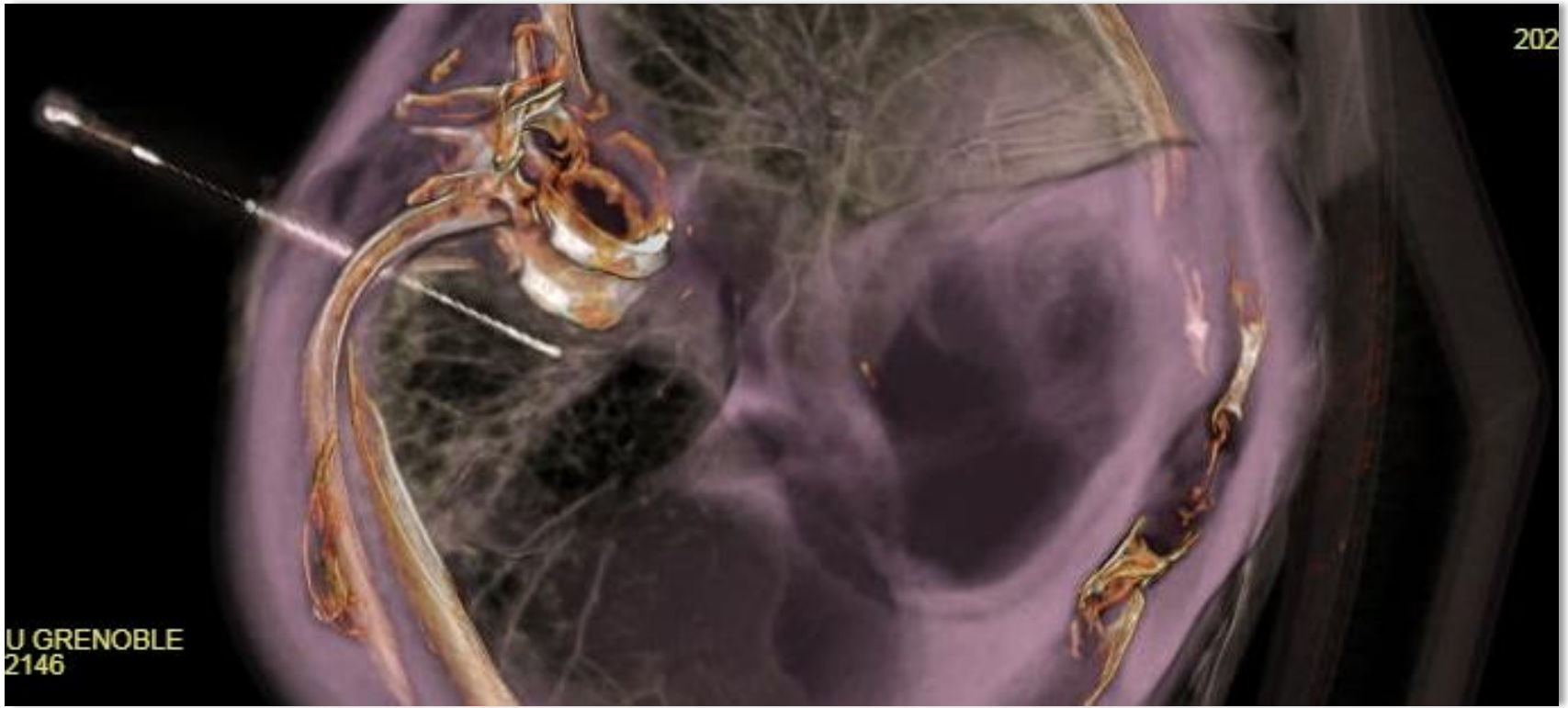
Un défi : l'équité d'accès à la biologie moléculaire



J Oncol practice 2023 DMSLung

Difficultés d’accés à la biologie moléculaire



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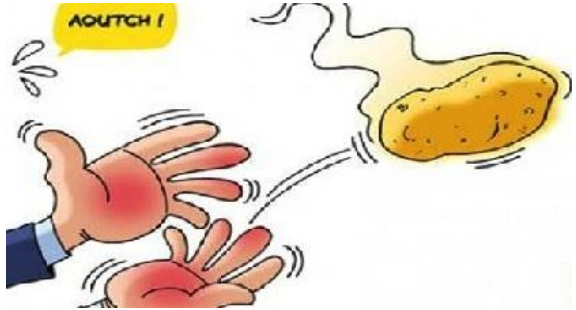
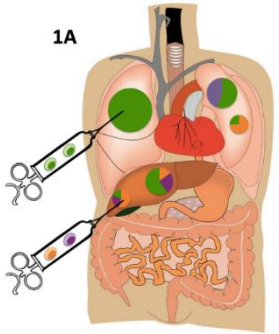
Un défi : l'équité d'accès à la biologie moléculaire

- Raisons médicales
  - Tumeurs peu accessibles (cerveau, poumon unique etc)
  - Obstacle anatomique
  - Contre indication (hémostase..)
  - Exiguïté du matériel biopsique
  - Épuisement et qualité du matériel
  - Refus du patient
    - ✓ Accès à la sédation
  - Pression patient /famille pour débuter un traitement le plus vite possible

- Raison logistiques et humaines
  - Délais d'accès au plateau technique
  - Délais d'accès à la sédation
  - Délais de transfert des biopsies
  - Délais de réalisation des analyses
  - Délais de rendu de résultat
  - Concurrence des plateformes
  - Coût des analyses et mode de prescription

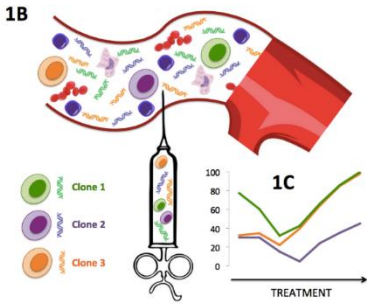


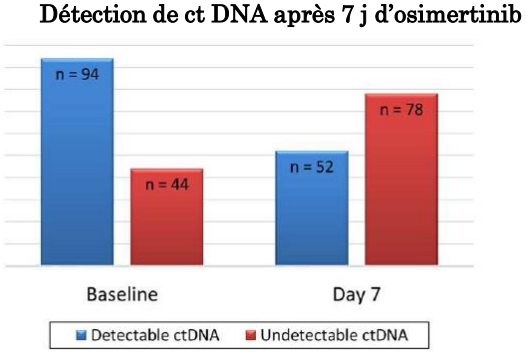
Biopsies et biopsies liquides



Biopsie

- Procédure invasive
- Nécessité d'un plateau technique
- Risques et contre indications
- Potentiel de répétition limité
- Indispensable pour l'histologie





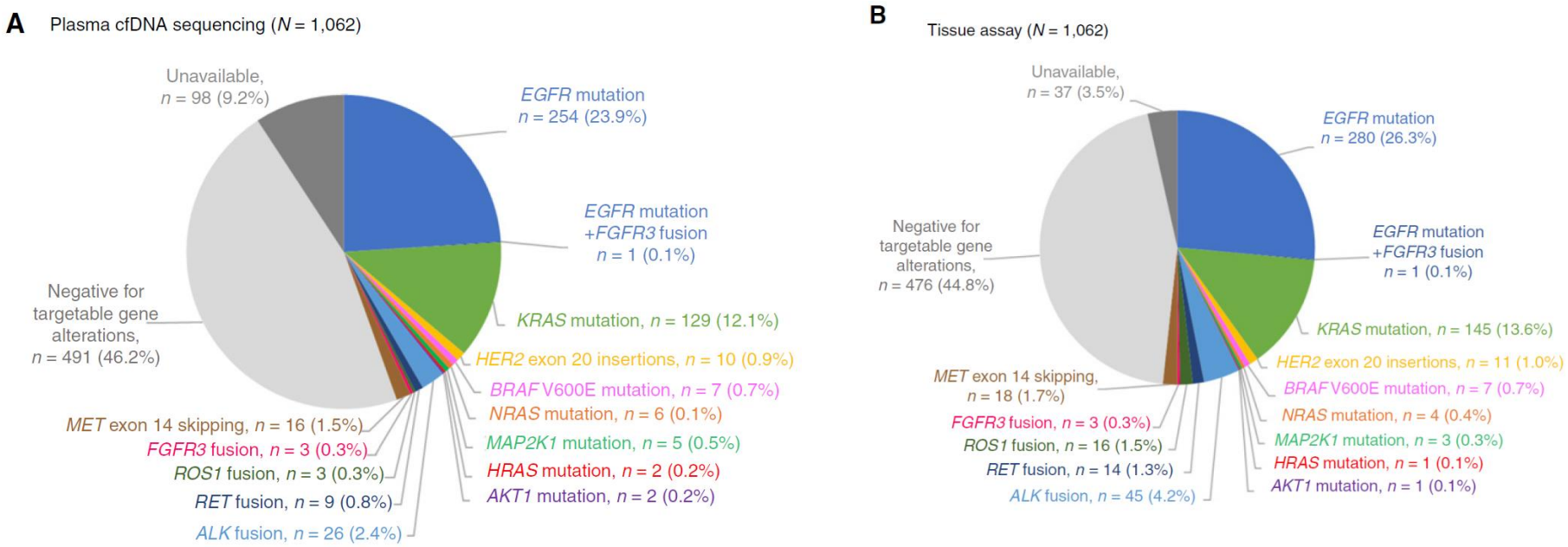
Biopsie liquide

- Procédure Non invasive
- Procédure ambulatoire
- Aucun risques et contre indications
- Potentiel de répétition infini
- Suivi moléculaire, pronostic, rechute
- Sensibilité à améliorer

Denis M ESMO 2022, Guibert N. Eur Resp Rev 2020 et Ann Oncol 2018.

DMSLung

Concordance analyses tissu & ADNtc - larges cohortes

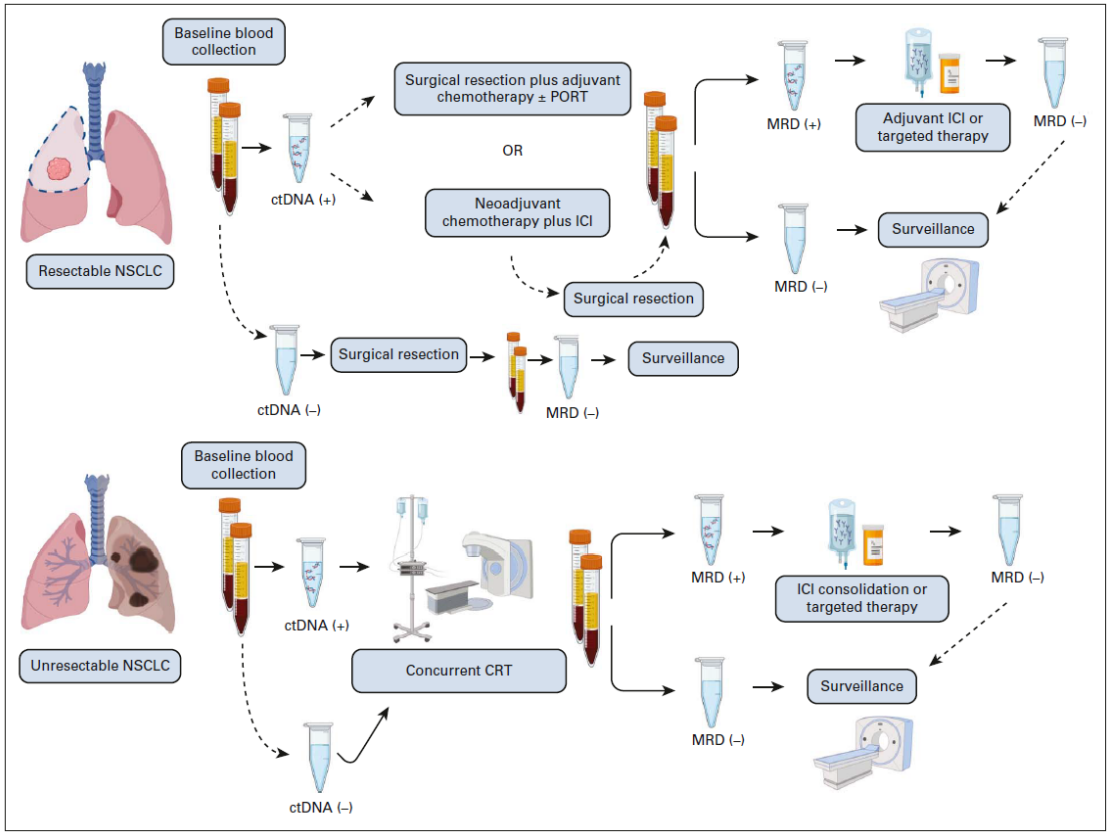


	Plasma	Tissu
Analyse réalisable	91%	97%
TAT (jours)	10 (6-27)	22 (12-57)
Altération ciblable détectée	473 / 44,5%	549 / 51,7%

Sugimoto et al Clin Cancer Res 2022

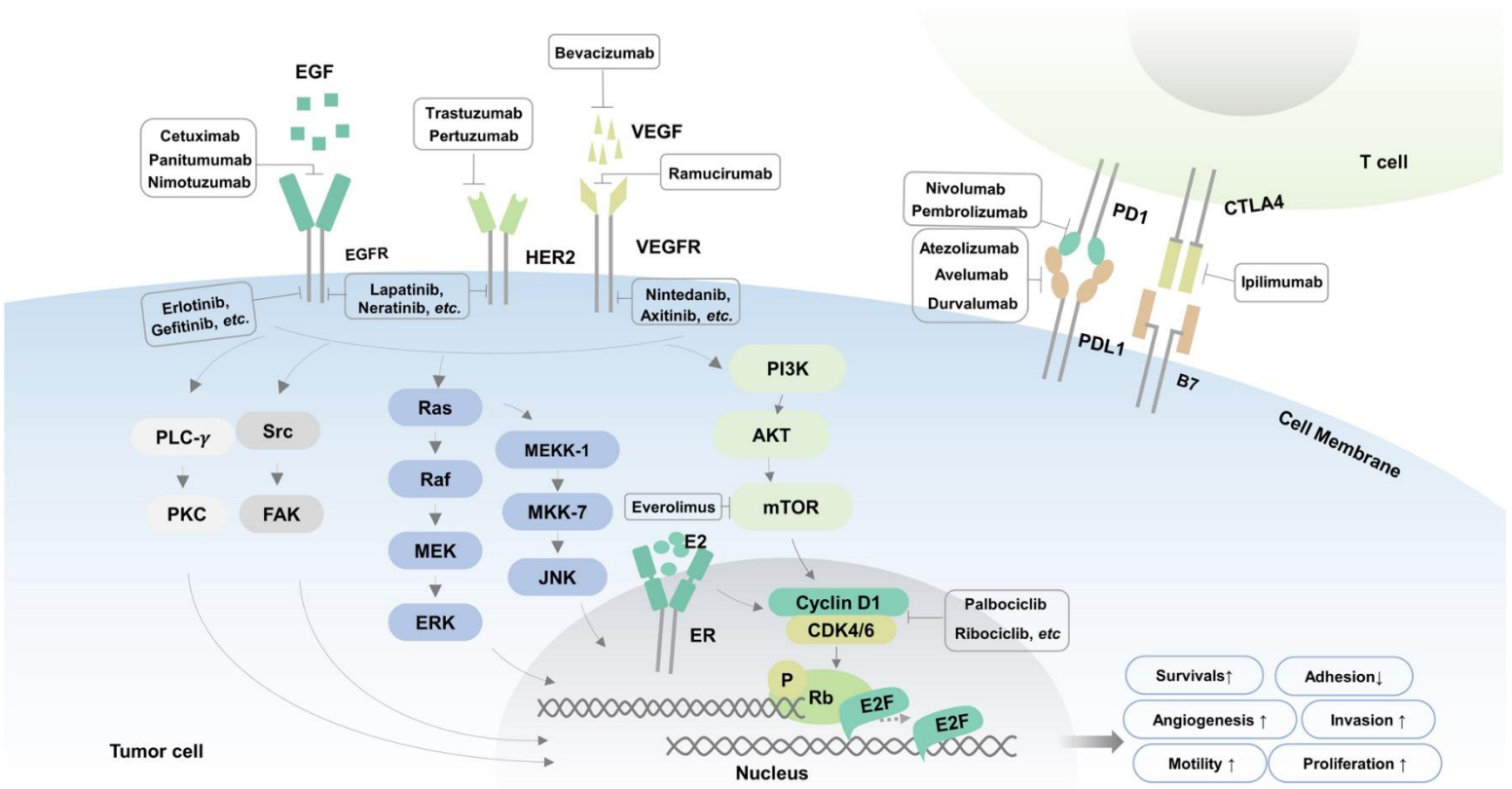
DMSLung

Futur des biopsies liquides : la maladie résiduelle



Pellini B et al J Clin Oncol 2022

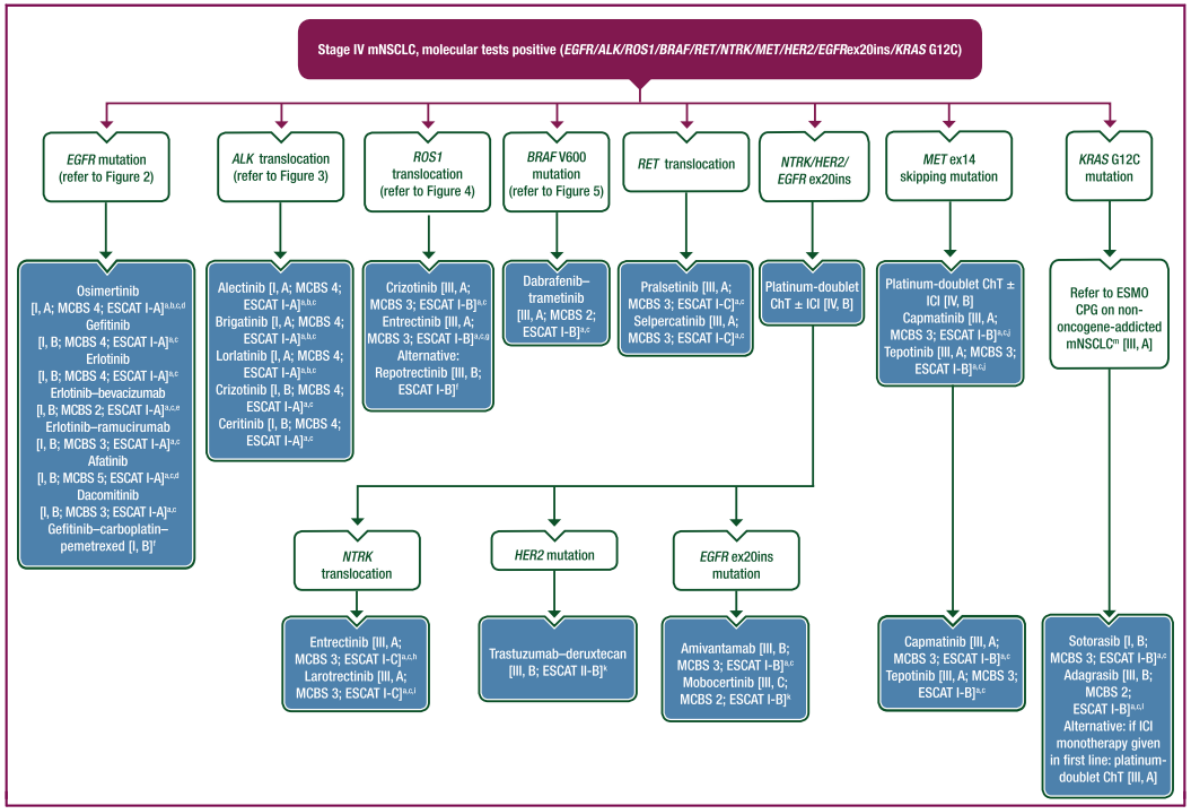
Les traitements ciblés



Bai JW et al . Signal Transduction and Targeted Therapy 2023

DMSLung

Les traitements ciblés : les petites molécules , ITK et autres

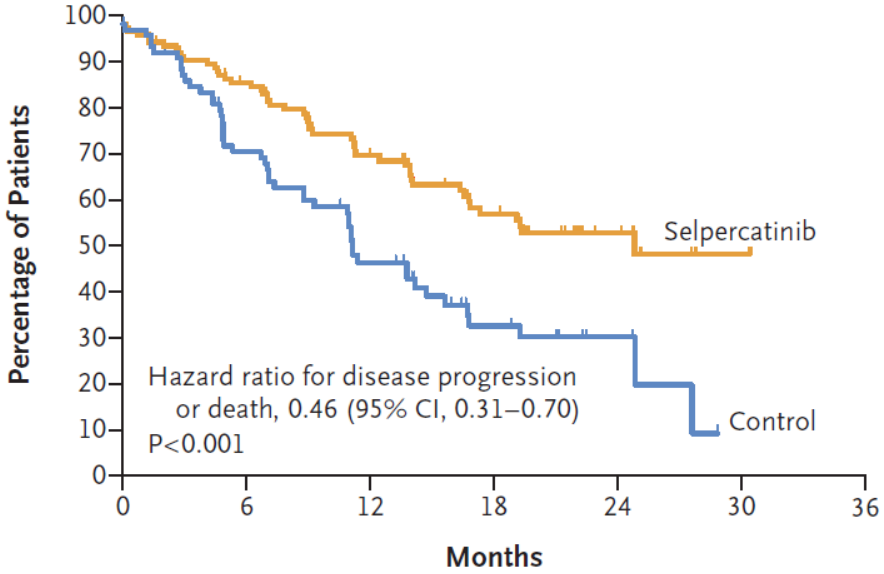


Hendriks LE et al . Ann Oncol. 2023 :S0923-7534 : 04781.

DMSLung

Les traitements ciblés : Ciblage des réarrangements de RET

A Progression-free Survival, Intention-to-Treat–Pembrolizumab Population



No. at Risk							
Selpercatinib	129	105	72	44	16	2	0
Control	83	55	29	15	6	0	0

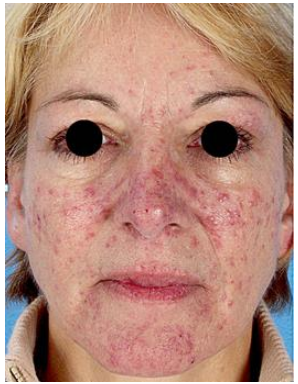
Zhou C et al . NEJM 2023.

DMSLung

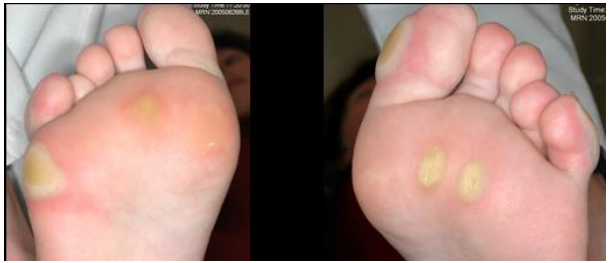
Les addictions oncogéniques

Anomalie moléculaire	impact	fréquence	traitement
Mutations EGFR ex 19 , ex 21	Très fort	10-15%	ITK première , seconde ligne
Mutations insertion EGFR ex 20	Très fort	1%	Amivantamab ?
Mutations Braf V600E	fort	1%	Anti Braf et anti MEK
Mutations HER2	fort	1%	Trastuzumab deruxtecan ?
Mutations Ras G12C	fort	10%	Sotorasib, adagrasib
Fusion ALK	Très fort	5%	ITK première , 3 ème ligne
Fusion ROS1	Très fort	1%	ITK première , 3 ème ligne
Fusions RET	Très fort	1%	ITK non remboursé
Fusions NTRK	fort	rarissime	ITK non remboursé
Mutation MET exon 14	fort	3%	ITK
Autres anomalies de MET	À déterminer	-	-

Toxicités modérées et souvent tardives : Sévérité *vs* tolerabilité



Folliculite Grade 2 ITK EGFR



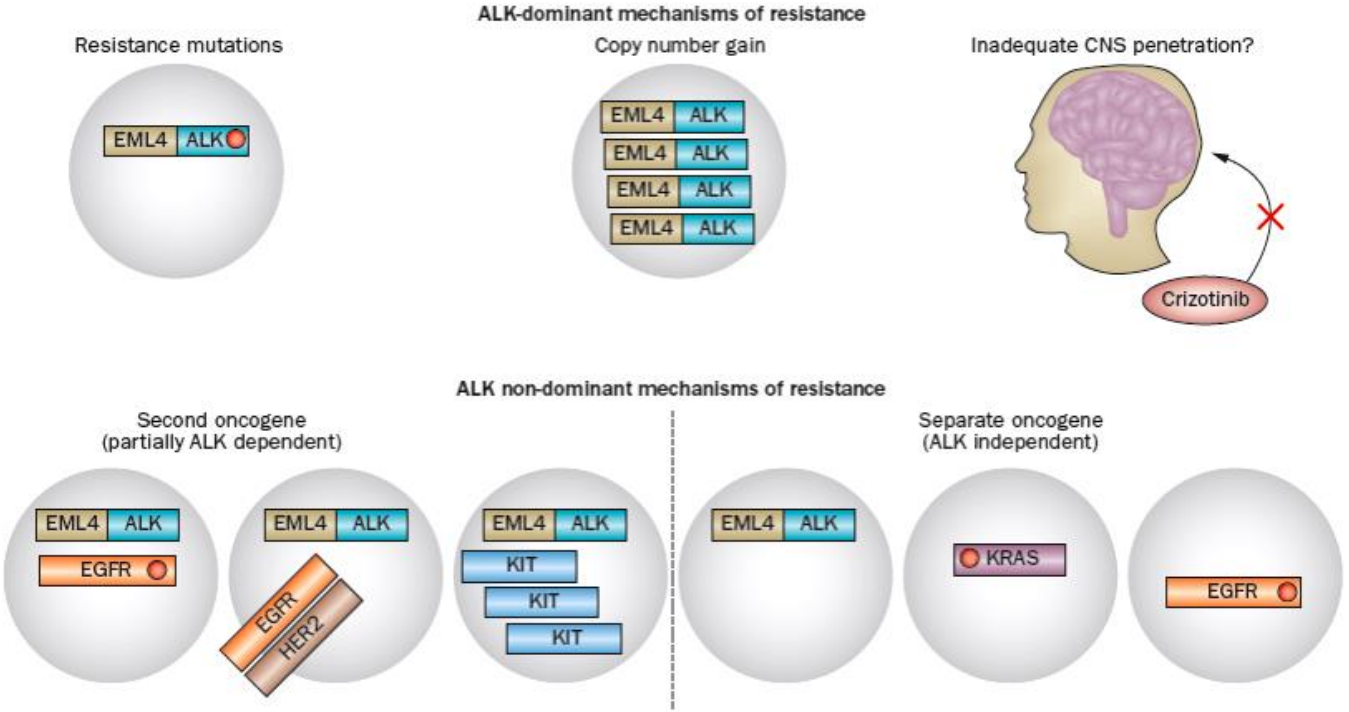
Grade 2 Syndrome main-pied sorafenib

Tolerable?

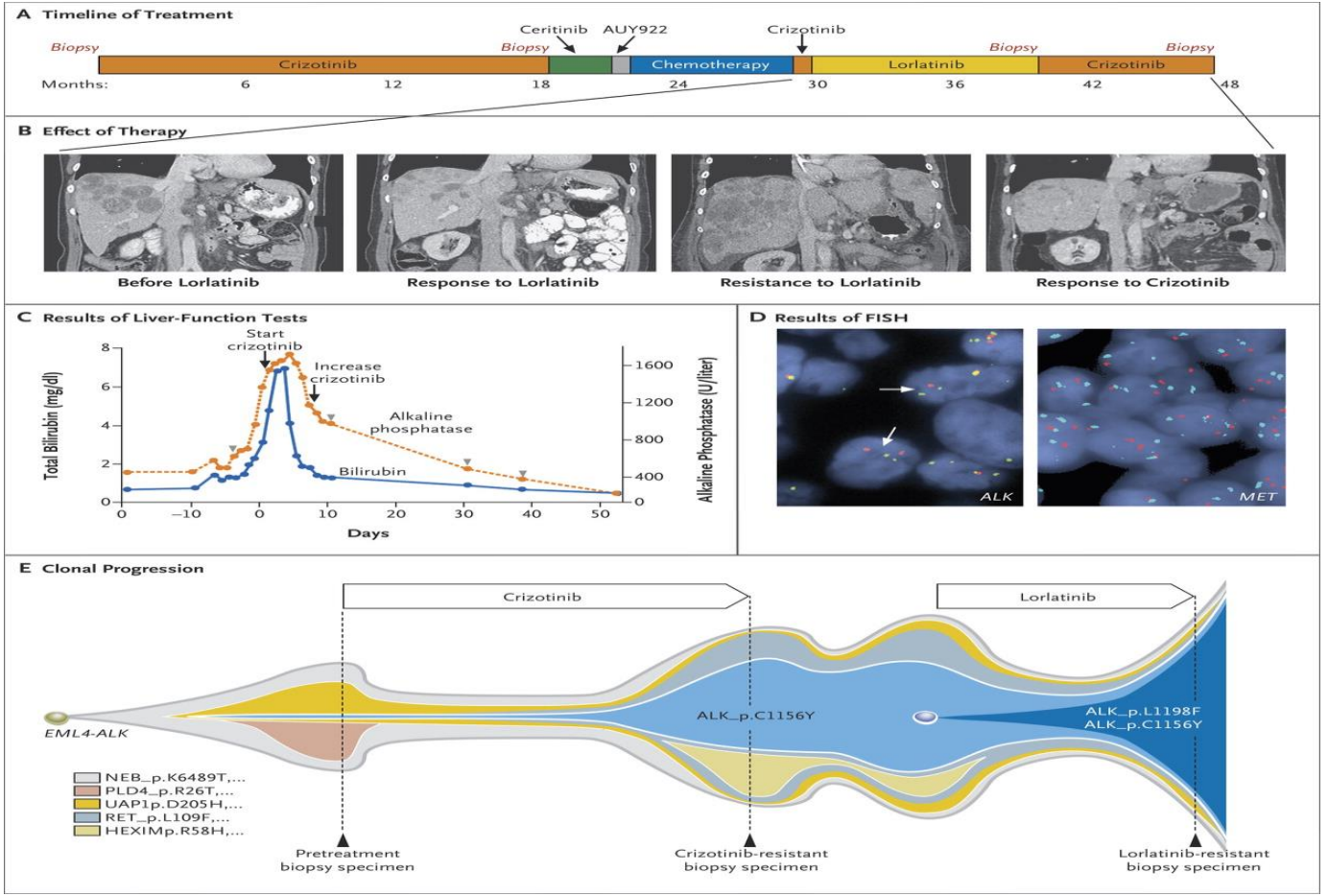
Effet indésirable	Grade 2
Diarrhées	Augmentation de 4-6 selles / j
Bouche sèche	Apports alimentaires.. Boissons… Choix alimentaires..

Soria JC GIRC Grenoble 2012 Robert C, Semin Oncol 2012

traitements ciblés : les résistances



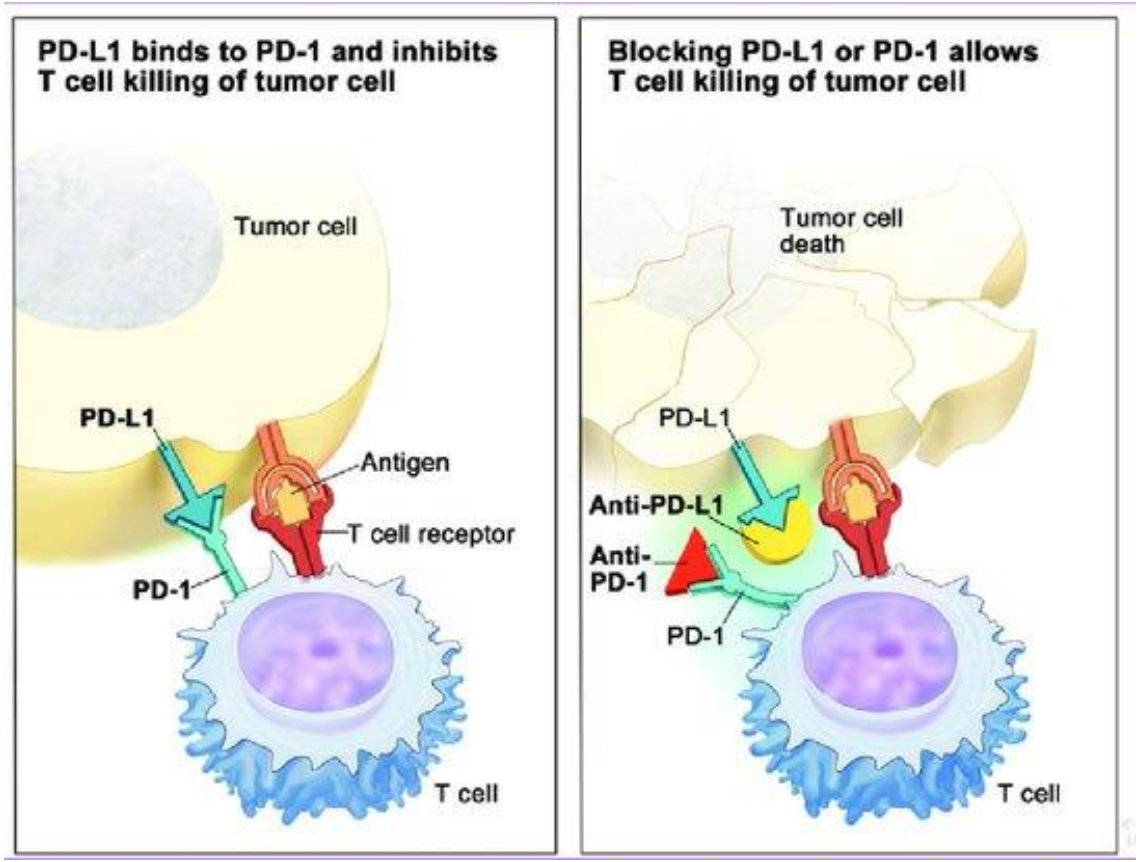
Camidge DR, Nat Rev Clin Oncol 2012, 9:268



Shaw AT et al, N Engl J Med 2016

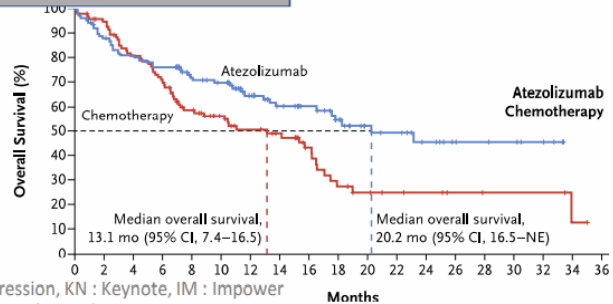
DMSLung

Immunothérapie : le ciblage PD1/PD-L1



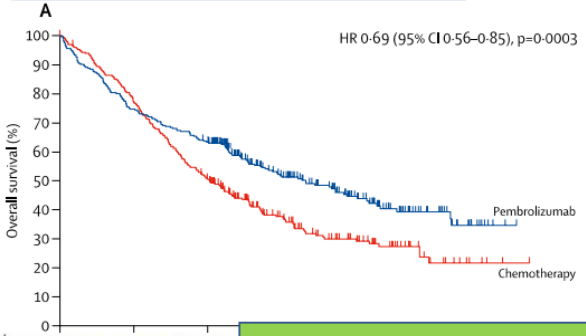
Immunothérapie : le ciblage PD1/PD-L1

IM 110 : 20.2 mois, mFU 15.7

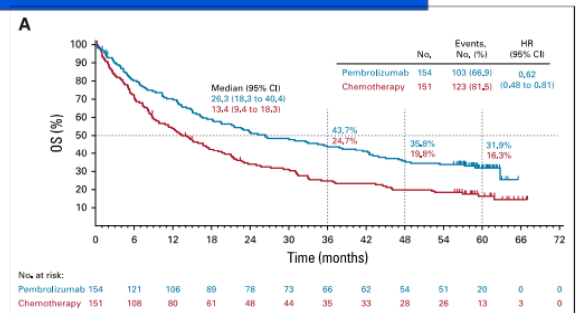


PFS: Survie Sans Progression, KN : Keynote, IM : Impower

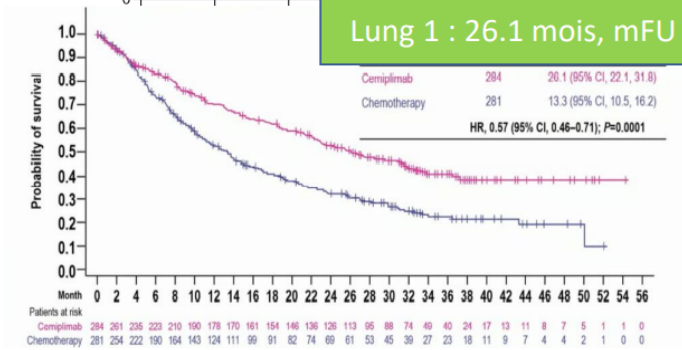
KN 042 : 20 mois, mFU 12.8



KN 024 : 26.3 mois, mFU* 59.9



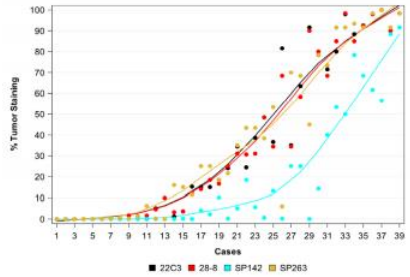
Lung 1 : 26.1 mois, mFU 37.1



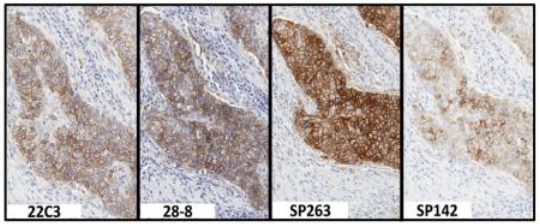
Reck JCO 2021, Mok Lancet 2019,Herbst NEJM octobre 2020, Ozguroglu ESMO 2022

DMSLung

Choix thérapeutique en fonction de l'expression du PD-L1



Each dot represents the mean score of 3 pathologists



3 assays showed similar staining characteristics for PD-L1 staining on tumor cells, but SP142 comparatively showed less tumor cells stained

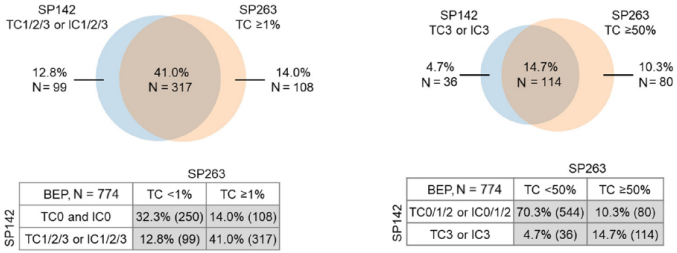
- L'expression de PD-L1 est une variable continue
- Expression associée à la survie à long terme en mono IO
- Expression évaluable sur tous types de prélèvements : cytoblocs, biopsies, pièces opératoires
- Contexte de variabilité de l'expression dans le temps et d'hétérogénéité de l'expression
- Variabilité des techniques et des anticorps

Kerr K JTO 2017

DMSLung

Choix thérapeutique en fonction de l'expression du PD-L1

- Variabilité des techniques et des anticorps
- Etude IMPower 150

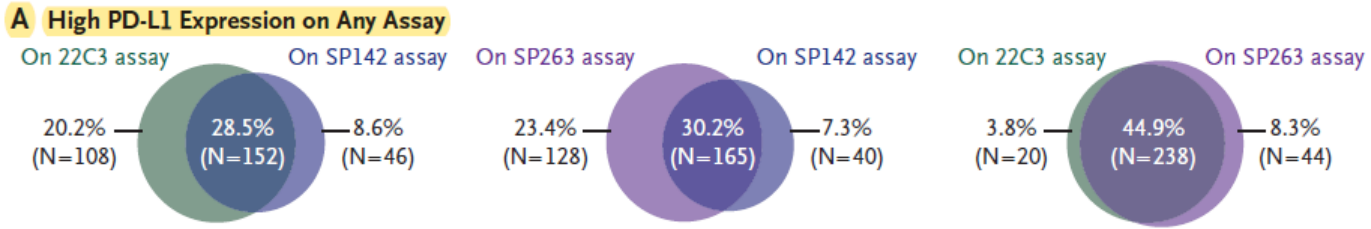


SP142 \ SP263	BEP, N = 774	TC <1%	TC ≥1%
	TC0 and IC0	32.3% (250)	14.0% (108)
	TC1/2/3 or IC1/2/3	12.8% (99)	41.0% (317)

SP142 \ SP263	BEP, N = 774	TC <50%	TC ≥50%
	TC0/1/2 or IC0/1/2	70.3% (544)	10.3% (80)
	TC3 or IC3	4.7% (36)	14.7% (114)

Figure 4. Concordance between SP142 and SP263 PD-L1-defined subgroups. Venn diagrams of overlapping and unique populations for SP142 and SP263 according to (*A*) PD-L1 positive and (*B*) PD-L1 high expression status. BEP, biomarker-evaluable population; IC, tumor-infiltrating immune cells; PD-L1, programmed death-ligand 1; TC, tumor cells.

- Etude IMPower 110



Herbst R NEJM 2020, Socinski M J Thor Oncol 2021

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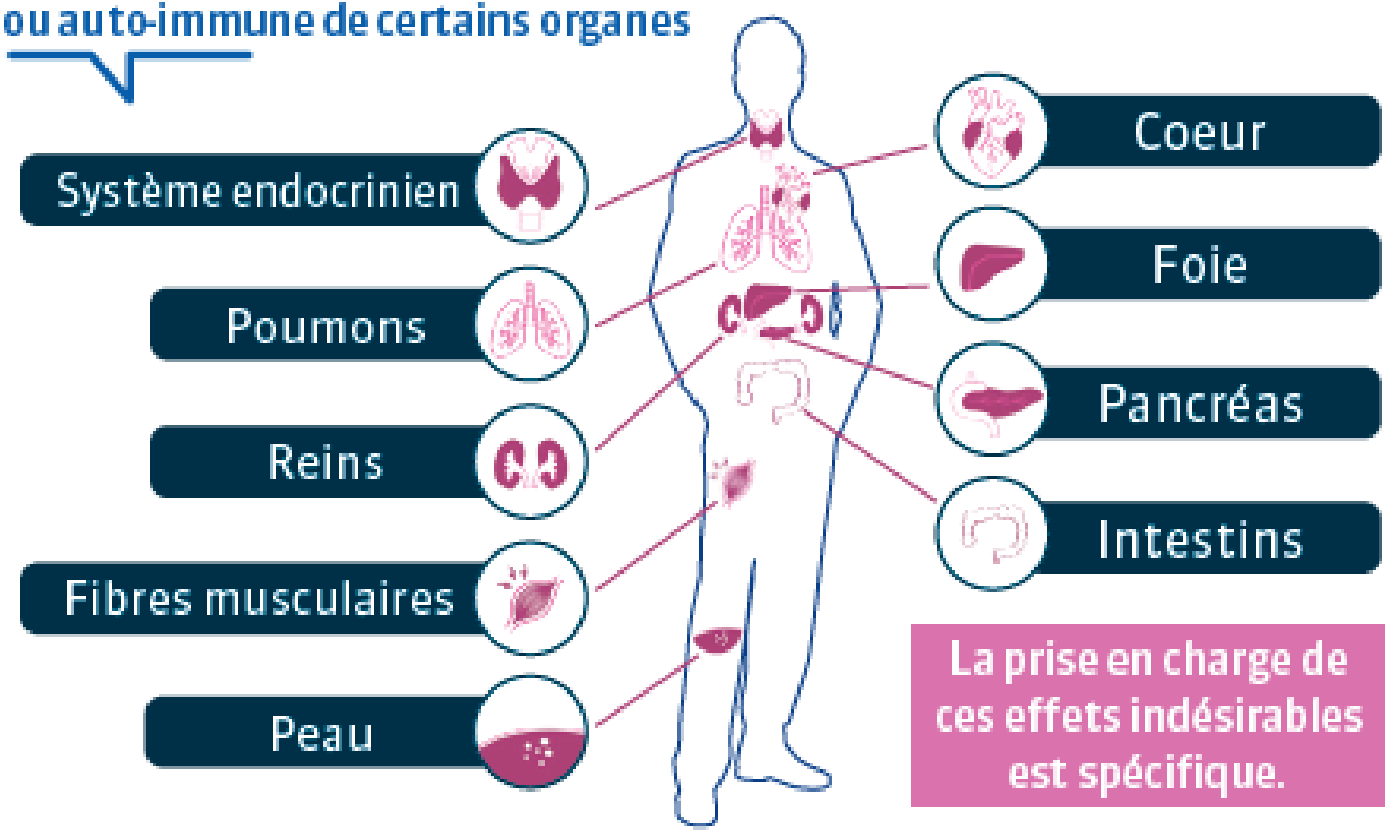
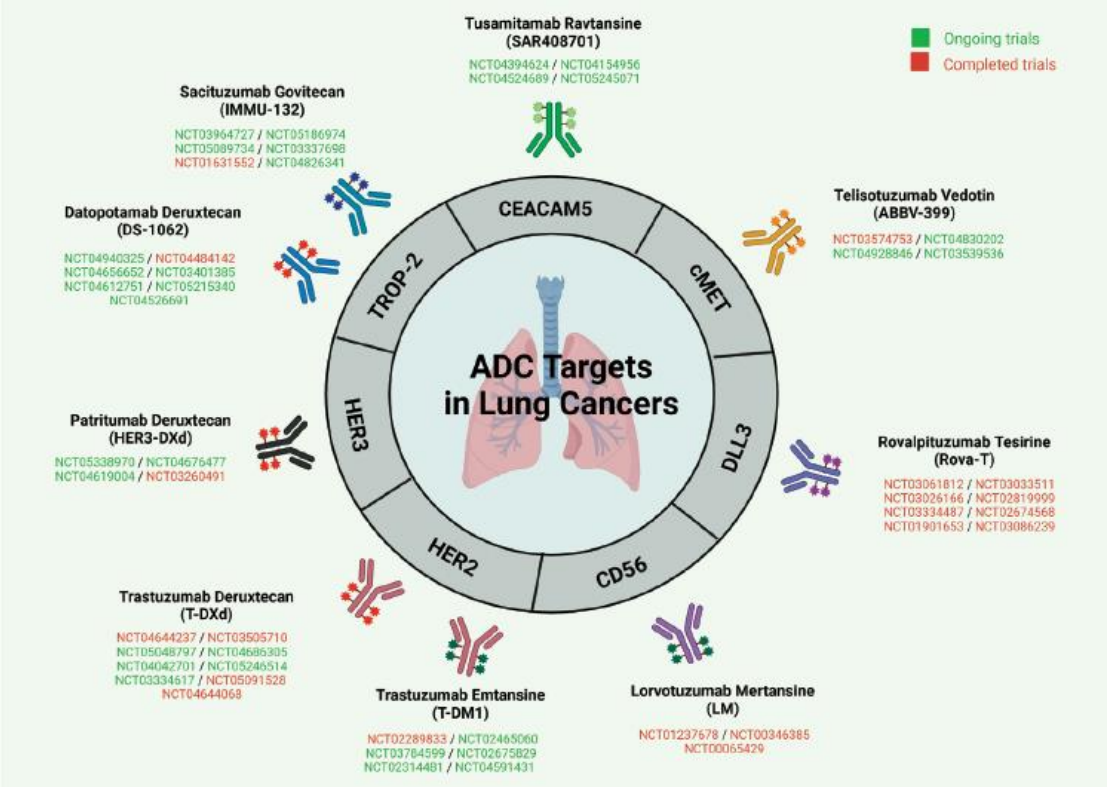
Je reçois une immunothérapie qui peut générer une toxicité inflammatoire ou auto-immune de certains organes

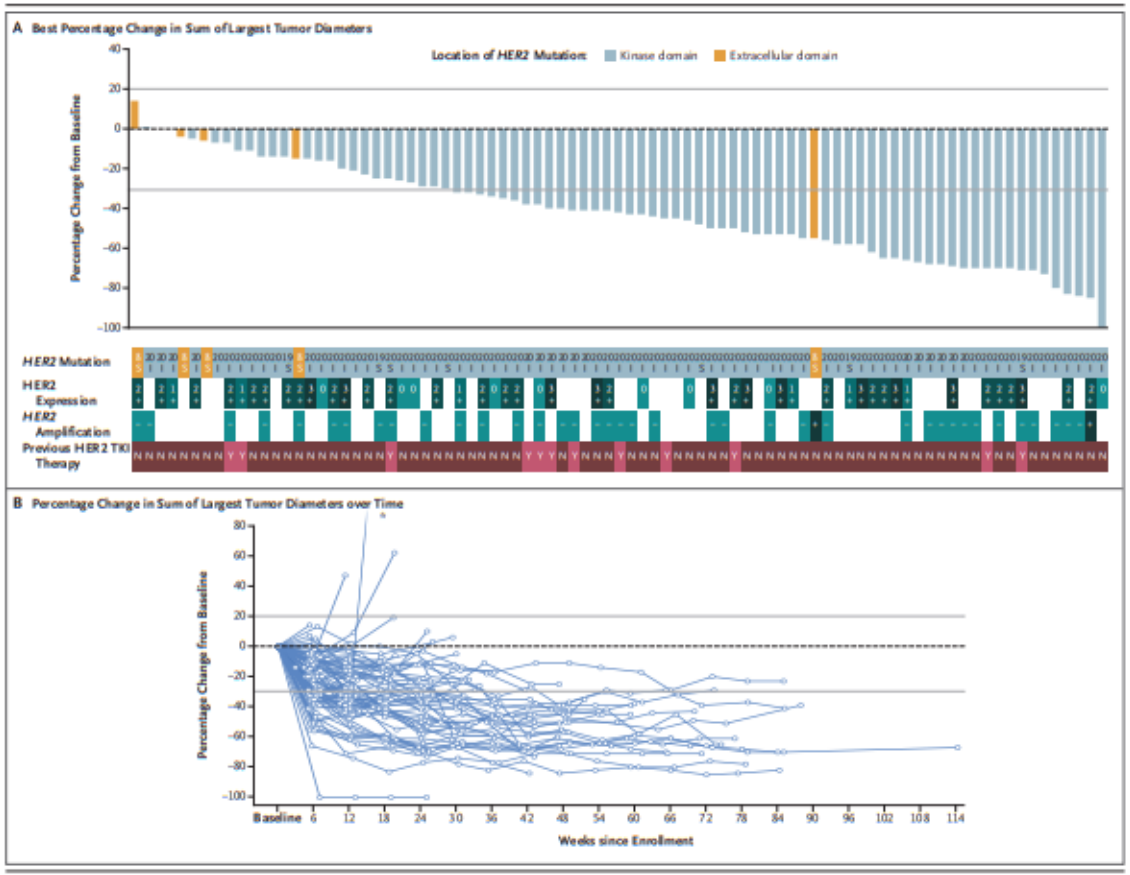


La prise en charge de ces effets indésirables est spécifique.

Nouveaux traitements ciblés : les anticorps chargés



Nouveaux traitements ciblés : les anticorps chargés



Li B et al . N Engl J Med. 2022 Jan 20;386(3):241-251.

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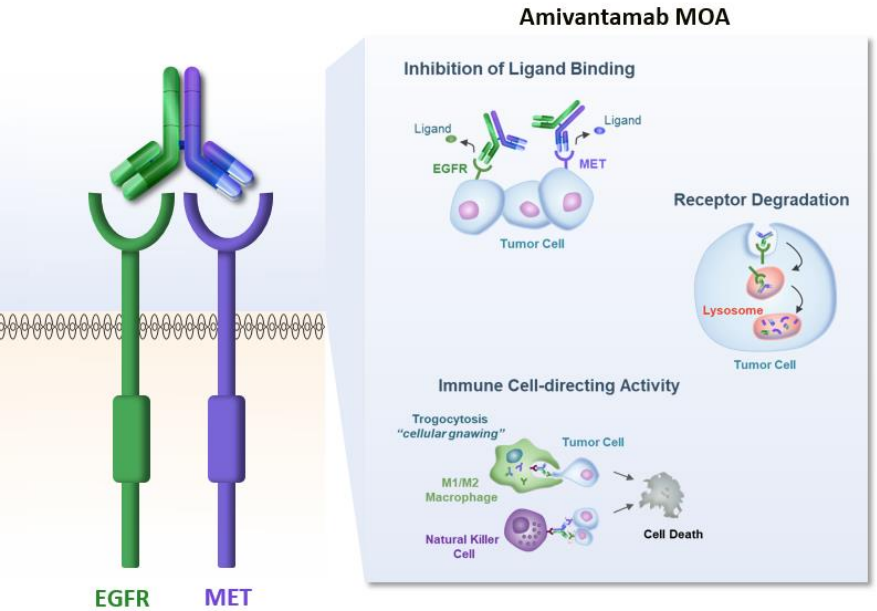
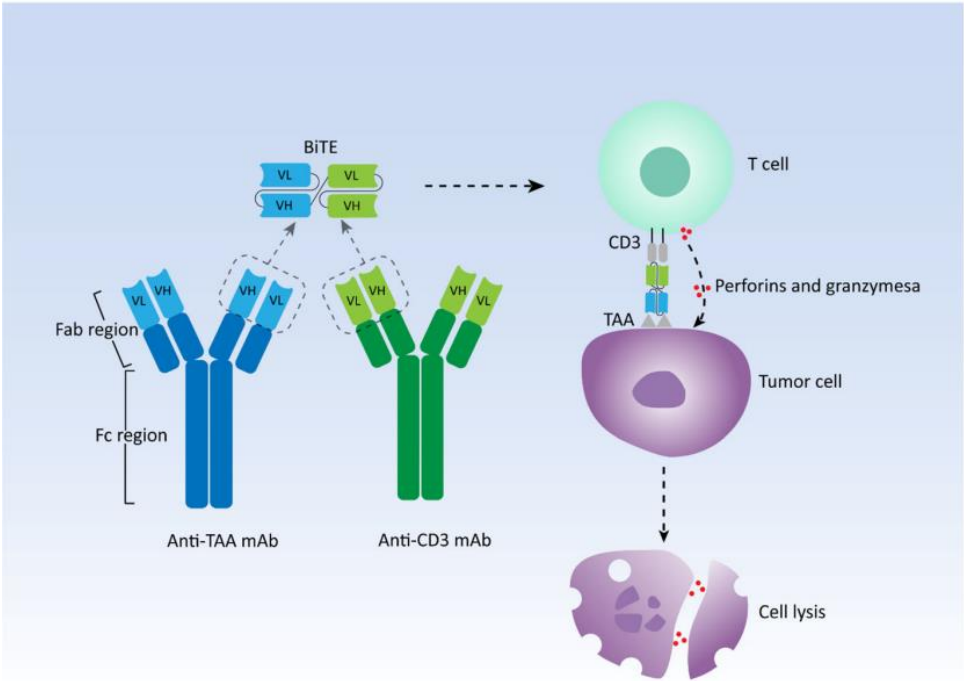
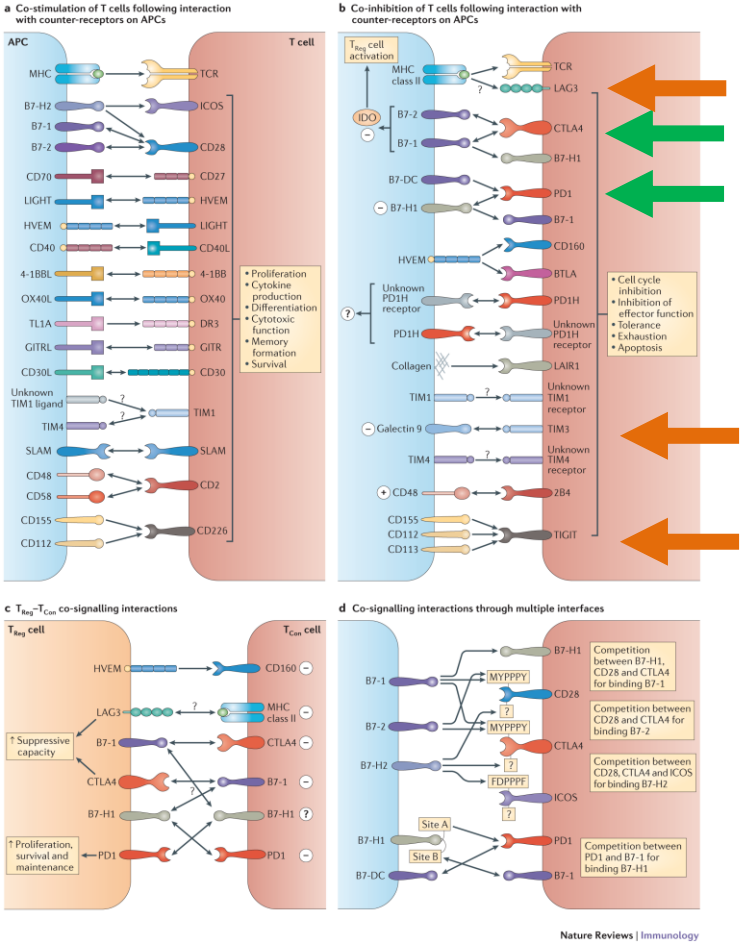
Nouveaux traitements ciblés : les anticorps bispécifiques et T Cell engagers





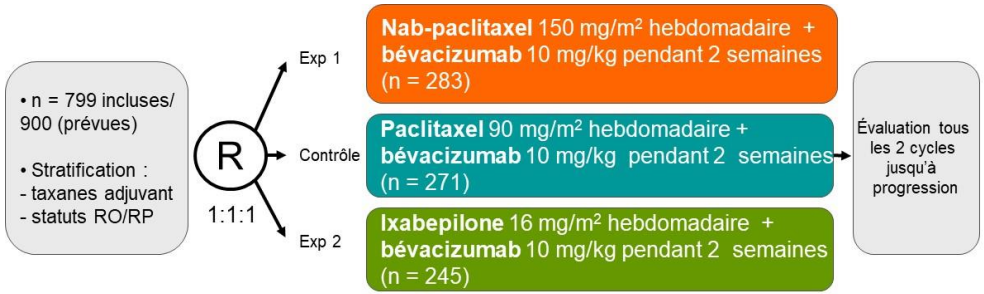
Cho, et al. ASCO 2021. Zhou S et al. Biomark R[illegible] 2024;9:38

Nouveaux ICI



Pardoll DM. Nat Rev Cancer. 2012;12:252-6

Adapter la recherche clinique a ce nouveau contexte



- Durée des études, selection des patients
- Adapter les méthodes statistiques
- Professionalisation de la recherche clinique (ICH BPC …)
- Couts de la recherche

Modification du design des études cliniques (avant)

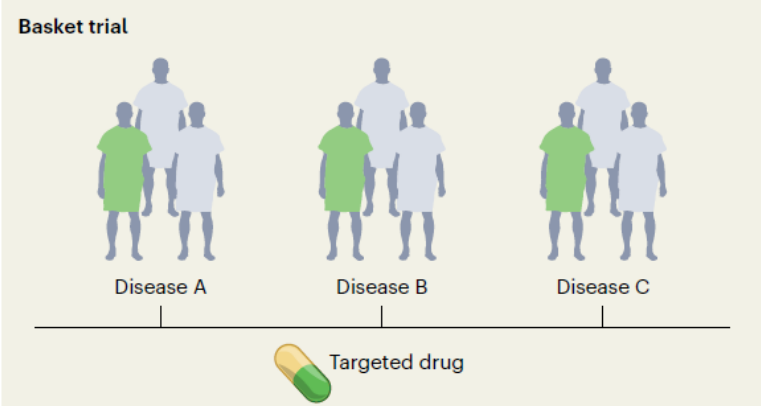
	Phase I	Phase II	Phase III
RATIONNEL	Établir la DMT	Établir l'activité	Comparer
THEME PRINCIPAL	Tolérance	Activité	Efficacité
OBJECTIF	Toxicité (DLT)	Réponse (RO%)	Survie (SSP, SG)
N (patients)	20-60	20-200	200-2000
VALEUR POUR L'ENREGISTREMENT	Nulle	Limitée	Majeure

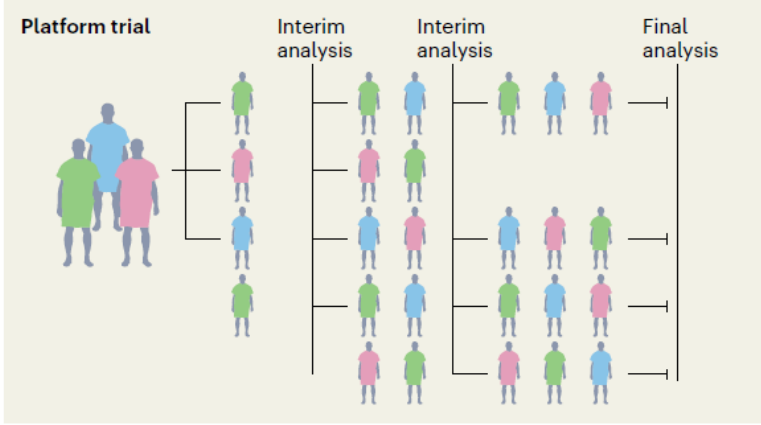
ESMO 2015 - D'après Soria JC et al., Keynote lecture

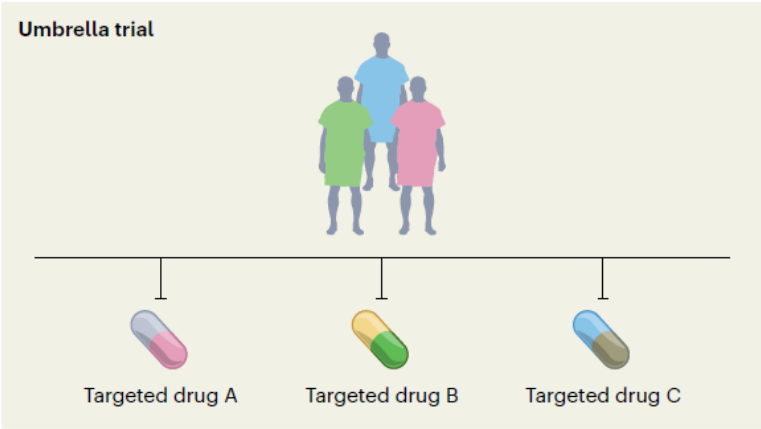
Modification du design des études cliniques (maintenant)

	Phase I/II	Phase III
RATIONNEL	DMT et activité	Comparer
THEME PRINCIPAL	Tolérance & activité & biomarqueurs	Efficacité
OBJECTIF	Toxicité & réponse (tous et populations sélectionnées) & données préliminaires de survie	Survie (SSP, SG)
N (patients)	100-1000+	200-2000
VALEUR POUR L'ENREGISTREMENT	Reelle (conditional, breakthrough)	Majeur

ESMO 2015 - D'après Soria JC et al., Keynote lecture

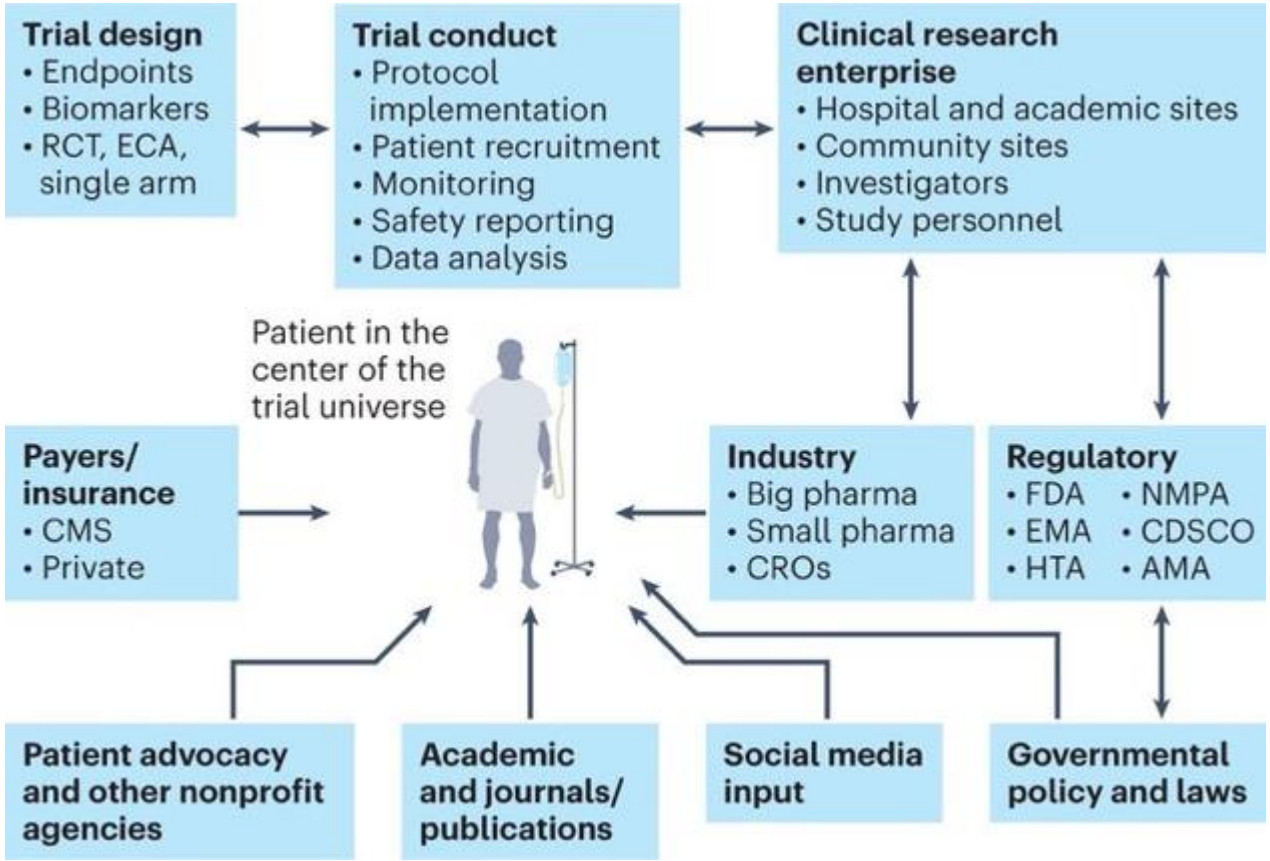






- Statistiques hiérarchisées
- Objectifs multiples
- HR avec impact clinique
- ESMO-Magnitude of Clinical Benefit Scale

Subbiah V. Nat Med. 2023;29:49-58



Subbiah V. Nat Med. 2023;29:49-58

DMSLung

IFCT Intergroupe Francophone de Cancérologie Thoracique

A propos de l'IFCT | Etudes cliniques | Publications | Formations & évènements | Espace patients | Espace membres | EN

FAVORISER L'ACCÈS À L'**INNOVATION THÉRAPEUTIQUE** AU BÉNÉFICE DES **PATIENTS** ATTEINTS D'UN **CANCER DU POUMON**

L'IFCT en chiffres

402 membres

330 centres

52 études terminées ou en suivi

10 études en cours d'inclusion

La recherche

Nos essais cliniques

Publications

Toutes nos publications

Actualités

21 Mar 2023 — Signature d'une convention de partenariat entre La Ligue contre le cancer et les GCO

EN SAVOIR +

14 Mar 2023 — Formation INVEST (24 mars) : inscriptions

Être investigateur au quotidien : Bonnes Pratiques Cliniques Partages d'expériences pratiques

EN SAVOIR +

28 Fév 2023 — Indication de tests moléculaires dans le CBNPC

Voir le référentiel INCa réalisé avec la participation de l'IFCT au sein du groupe d'experts

EN SAVOIR +

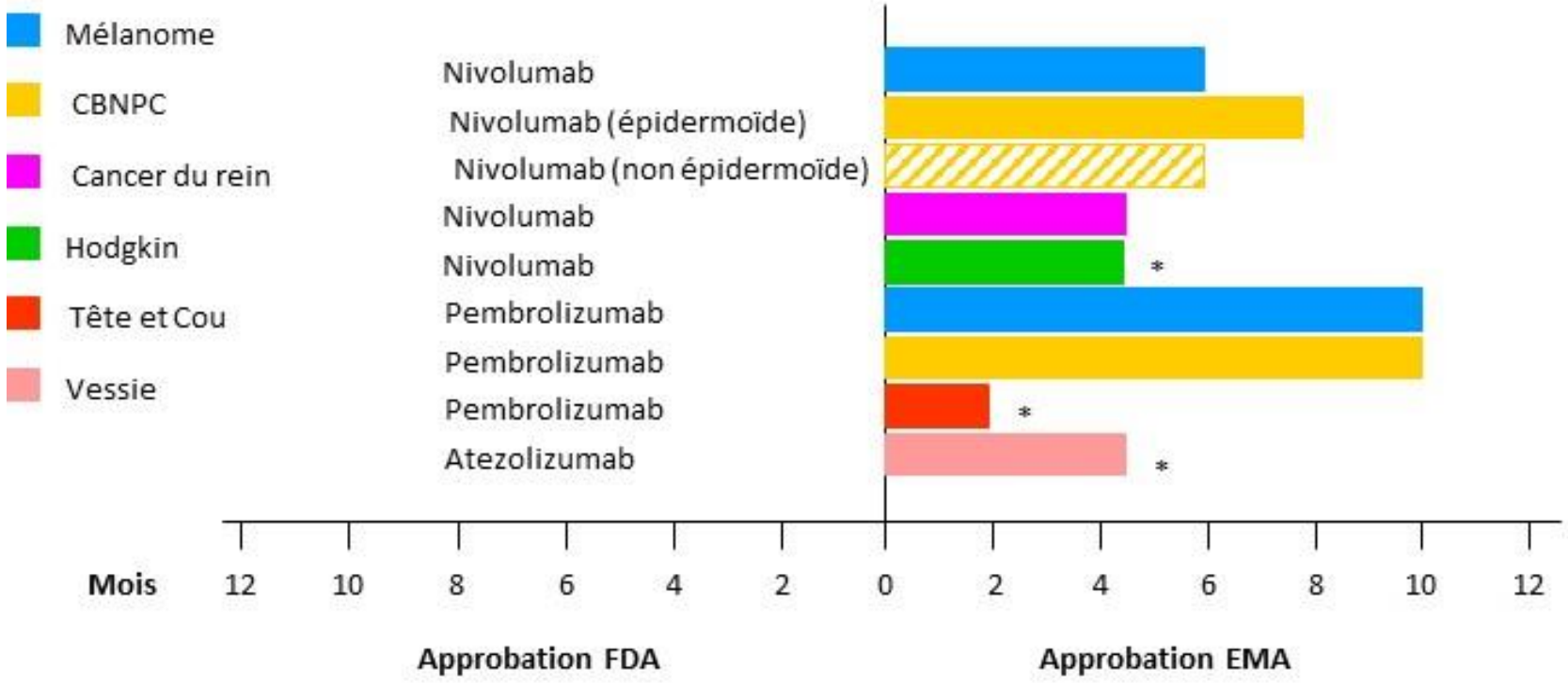
27 Fév — Transparence des résultats des essais cliniques

Adapter le progrès au monde réel

- Education thérapeutique, FMC
  - Effets secondaires
  - Interactions médicamenteuses, alimentaires …
- Adapter les structures académiques au changement
  - Risque majeur de perte de savoir faire
- Adapter la société au concept de « cancer orphelin »
- Adapter les agences réglementaires au changements actuels

FDA contre EMA pour les AMM en immunothérapie

Différence dans la durée d'approbation des enregistrements AMM entre l'EMA et la FDA



* En attente

ESMO 2016 - D'après Soria JC et al., Keynote lecture

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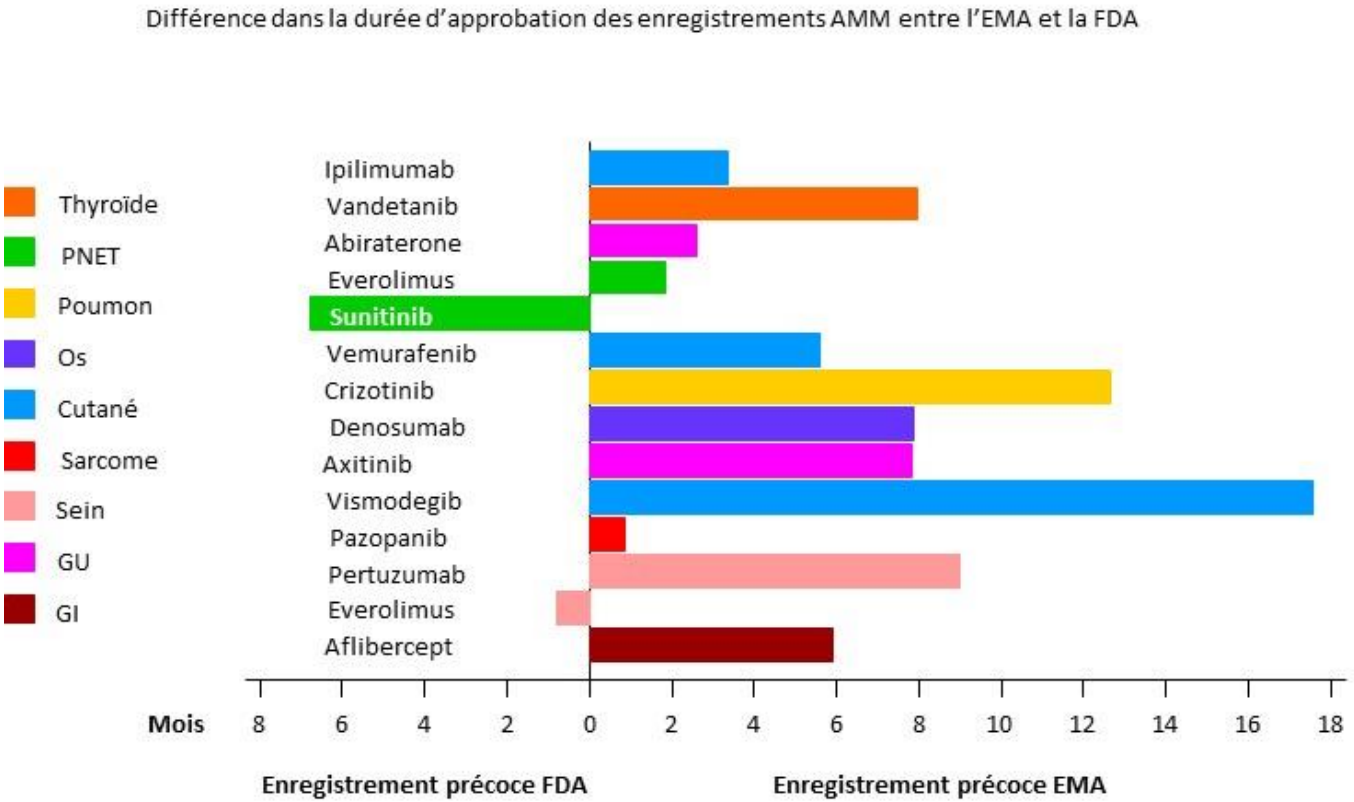
Durées d'enregistrement FDA contre EMA : traitements ciblés



ESMO 2016 - D'après Soria JC et al keynote lecture

Limitation of wordwide access to targeted therapies

EFPIA patients W.A.I.T indicator 2021 Survey

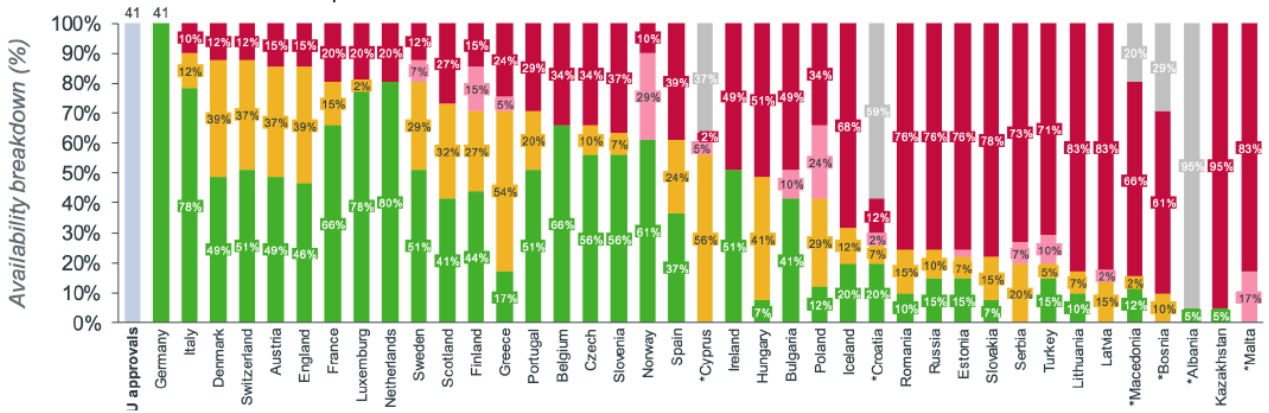
Updated July 2022

Availability definition

Description	Status
Full reimbursement through a national reimbursement system	Available
Full automatic reimbursement by a hospital budget (e.g. Nordic system)	
Limited reimbursement to specific subpopulations of approved indication	Available (marked LA*)
Limited reimbursement on a national named patient basis (individual patient)	
Limited reimbursement while decision is pending (where system permits)	
Availability through a special program (e.g. managed entry agreements)	
Available only within the private market at the patients expense	Only privately available
Not reimbursed, or not reimbursed while awaiting decision	Not available

% of oncology drugs available by UE-Countries after EMA authorization

100% 66% 40%



Newton M, IQWIA July 2022

Limitation of wordwide access to targeted therapies

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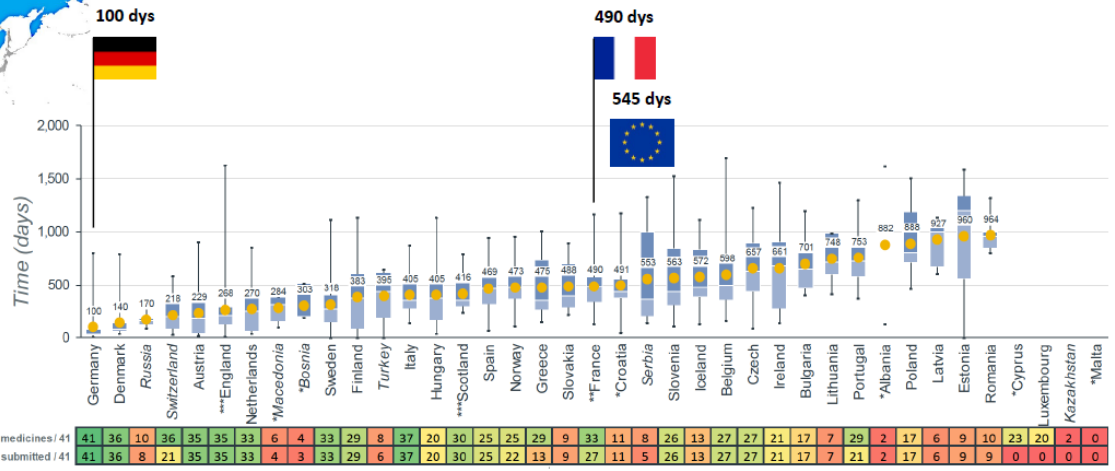
Delay for oncology drugs availability in UE-Countries after EMA authorization



Newton M, IQWIA July 2022

DMSLung

Le Parisien

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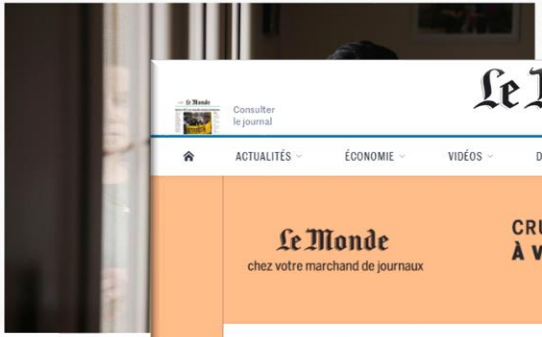
Société, Santé

Cancer : la difficulté d'accès aux médicaments innovants, « une perte de chance énorme pour les patients »

Des médecins réputés de la cancérologie s'insurgent de récents avis défavorables des autorités de santé pour le remboursement de médicaments anticancéreux, alors même qu'ils présentent des résultats parfois spectaculaires. Des patients qui en ont bénéficié, comme Suzanne, veulent également faire entendre la voix des malades.



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24 FÉVRIER 2023

INTERVIEW

Accès aux médicaments innovants en oncologie : "On y est toujours pas"

Après avoir rendu 7 avis défavorables pour des traitements contre le cancer, la HAS publie une révision de sa méthode d'évaluation des médicaments innovants. L'aboutissement d'un travail de 17 mois qui ne va pas assez loin selon le Pr Pascal Pujol, président de la Société française de médecine prédictive et

Le Monde

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TRIBUNE

Hervé Avet-Loiseau
Professeur

Laurent Gillot

Les patients atteints de cancer doivent avoir accès à l'innovation thérapeutique

Dans une tribune au « Monde », un médecin spécialiste du myélome, Hervé Avet-Loiseau, et un représentant d'une association de patients, Laurent Gillot, regrettent l'avis défavorable donné à un nouveau médicament traitant ce cancer de la moelle osseuse.

Publié le 03 mars 2023 à 12h00, mis à jour le 03 mars 2023 à 17h04 | Lecture 3 min.

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Article réservé aux abonnés

Goulot d'étranglement au niveau de la HAS

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- Quasi impossible en situation de maladie rare
  - exemple fusion NTRK <1% des CBNPC
  - Moins de 75 cas/an en France

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Rapid access to innovative medicinal products while ensuring relevant health technology assessment. Position of the French National Authority for Health

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The challenge of accelerated clinical developments

In France, decisions for reimbursement taken by the Ministry of Health are based on appraisal by an independent Health Technology Assessment body (HTA*h*): the 'Haute Autorité de santé' (HAS). HAS grades the clinical added value of any medicinal product for which a manufacturer seeks reimbursement. This appraisal considers different types of clinical and patient-centred outcomes, including patient-reported ones. Under certain conditions, a concomitant economic assessment which accounts for patients' preferences in the form of utility values is also performed.

As providing fast access to breakthrough therapies is a critical expectation from patients, clinicians and health policy makers, the European Medicines Agency and the Food and Drug Administration have established various accelerated approval pathways. These procedures lead to conditional approvals frequently based on uncontrolled (ie, single arm) pivotal trials.[1-4] Approvals based on uncontrolled trials are also motivated by randomisation sometimes being considered unfeasible or unethical, or because the pathophysiological rationale is assumed to be important when proving effectiveness (eg, a treatment with molecular target in oncology).[5-6]

However, expected benefits based on uncontrolled trials as evidence are frequently not confirmed. The results of meta-epidemiological studies illustrate that appraisals based on such evidence entail a high level of uncertainty leading to ethical concerns.[7-8] For patients, this may have deleterious consequences such as the use of products for which the benefits remain unknown,[9-10] the overestimation of benefits with no further confirmation[11-12] or the increased risks of adverse events.[13-15] This high level of uncertainty may also impact health system sustainability.

While ensuring rapid access to valuable treatments is of utmost importance to patients, maintaining an adequate balance with the performance of relevant HTA in this context is highly challenging. Thus, the French Minister of Health requested HAS to provide recommendations. A consultation of patient associations, academics, manufacturers and various institutions was conducted from October 2021 to January 2022. With the support of an expert committee, a qualitative summary of the consultation has led to the prioritisation of recommendations, which are developed below (details on the consultation process are available in an online supplemental appendix 1).

Need for evidence from comparative designs allowing causal interpretation of treatment effect estimation

Performing relevant HTA requires that an unbiased estimate of the treatment effect is available. Thus, the additional effect must be disentangled beyond effects due to the natural course of the medical condition, the placebo effect, various sources of bias and the effect of alternative(s). To produce such an estimate, the simplest and most consensual methodological choice is a comparison of the treatment of interest to a control by conducting a randomised controlled trial (RCT). Randomising treatment allocation balances both known and unknown confounders between groups, which enables the causal attribution of an observed effect to the investigated treatment. Other characteristics such as blinding and intention to treat analysis principles reduce the risk of bias and thereby lead to an estimation of treatment effect with the highest certainty of results.

Therefore, RCTs should still be systematically considered by manufacturers during clinical development.

Accelerating rapid access to innovative treatments by adapting the traditional RCT design

While RCTs are the gold standard for producing clinical evidence, HAS acknowledges that the strict

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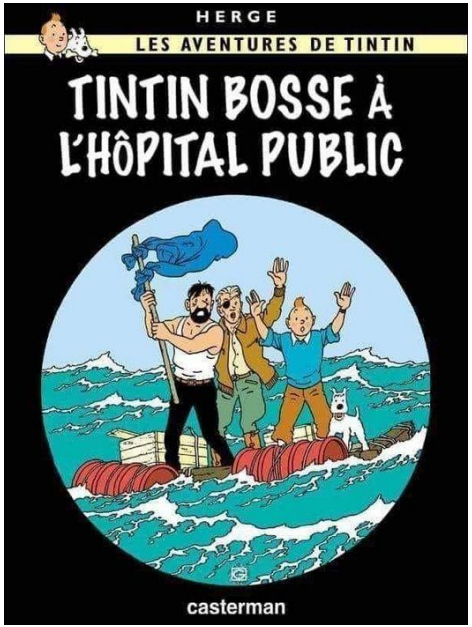

- Nouvelles modalités d'accès à l'innovation complexes, illisibles parfois
- Doctrine de la HAS révisée mais peut mieux faire…