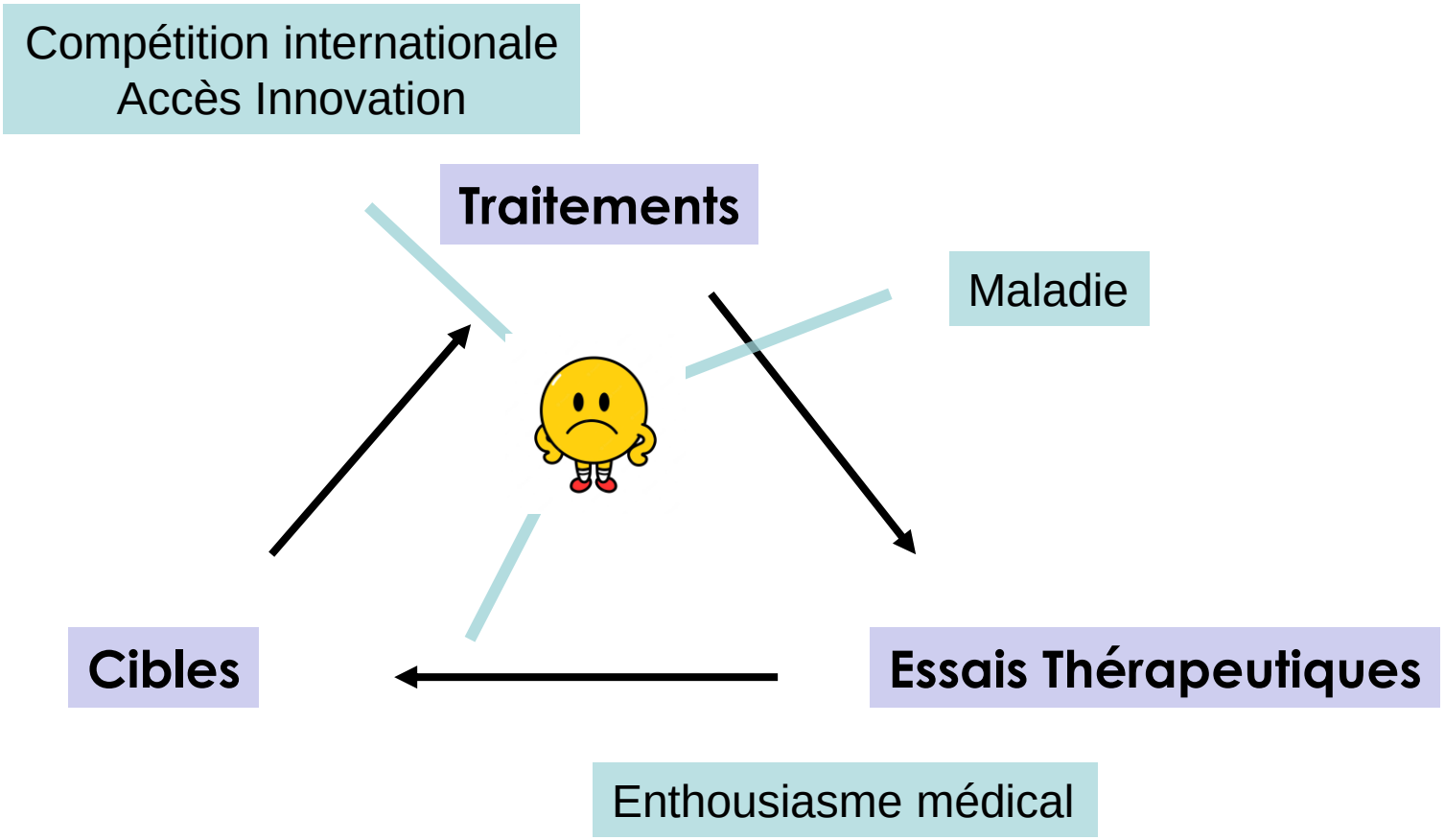
Participation des patients aux études de phase I : enjeux et défis

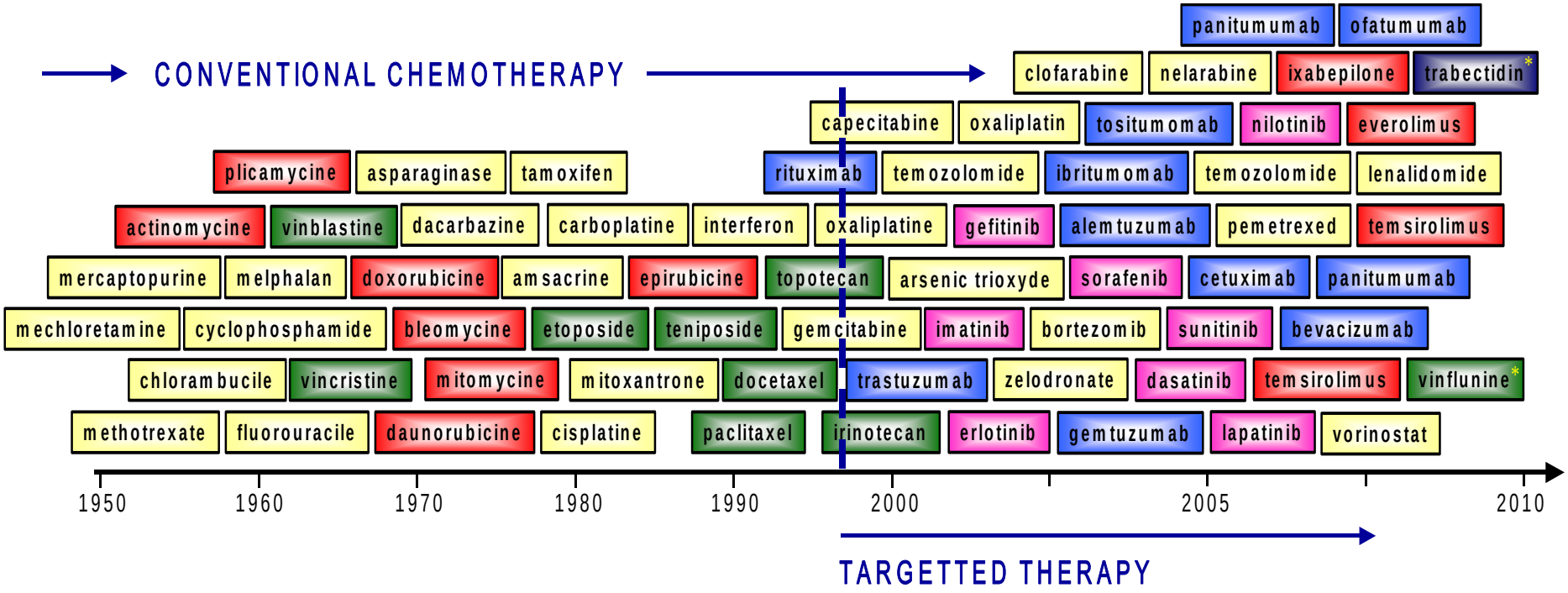
Jean-Pierre Delord

Colloque CNCP 2023

Le cycle du développement thérapeutique

Le patient est au cœur d'un triple enjeu

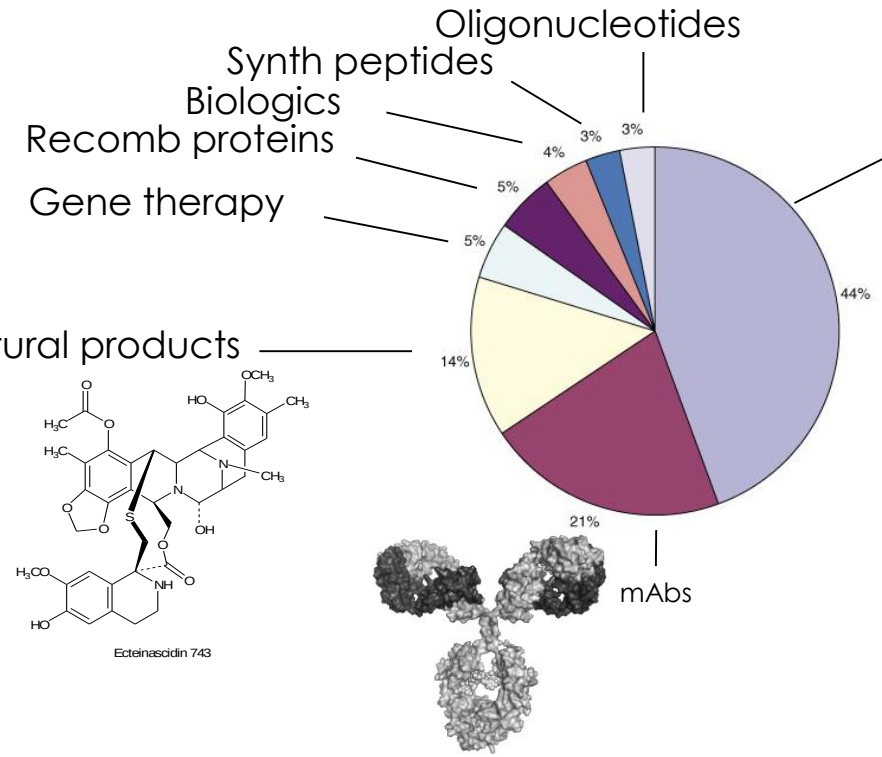


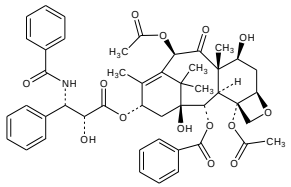


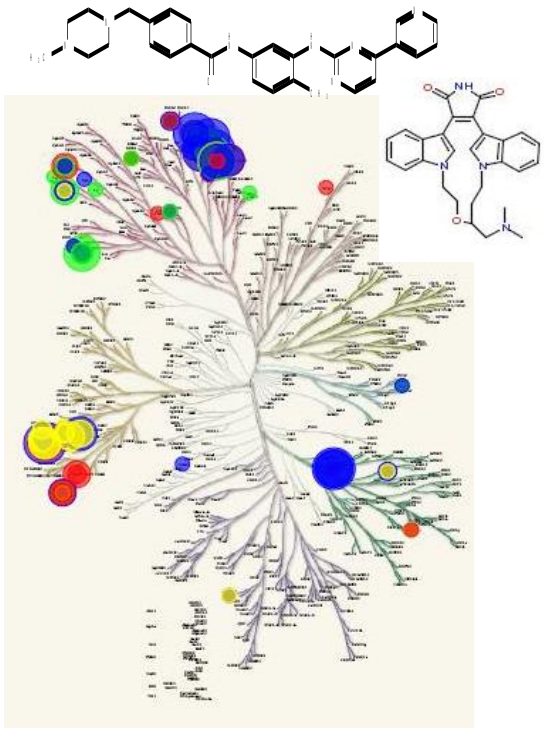
Bailly C. *Biochem. Pharmacol*. 2009, *77*, 1447

Nouveaux traitements et vaccins (2006-2016)

	Tous	% Enregistrés
Total	920	8
petites molecules	405	10
mAbs	190	9
vaccins	191	0,5

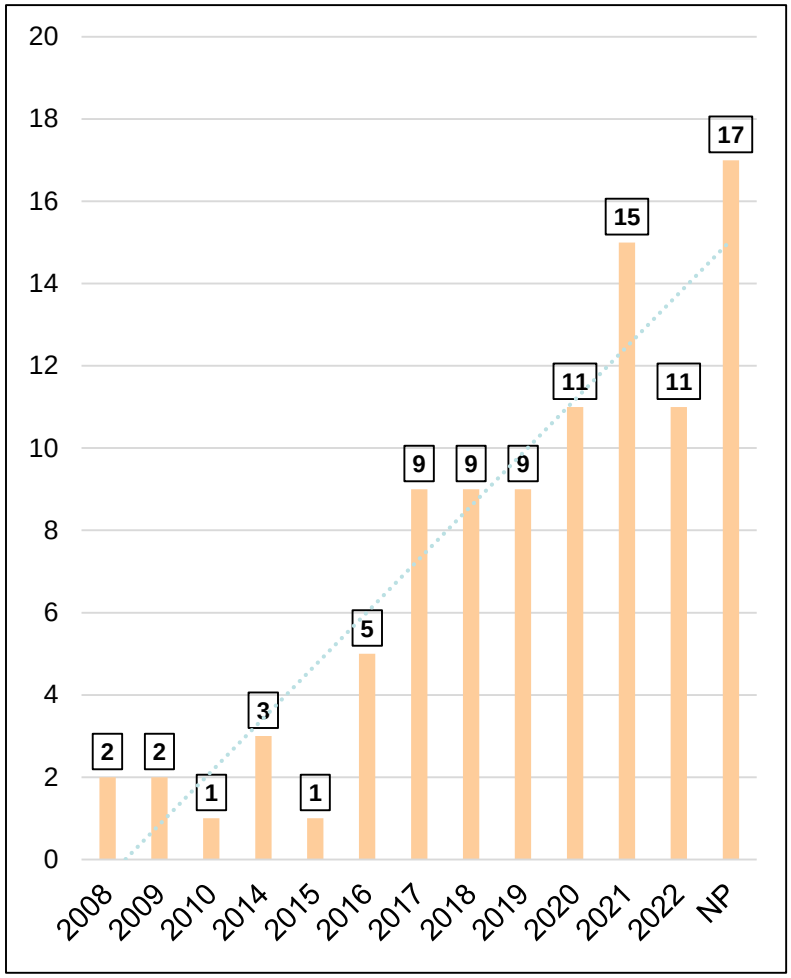




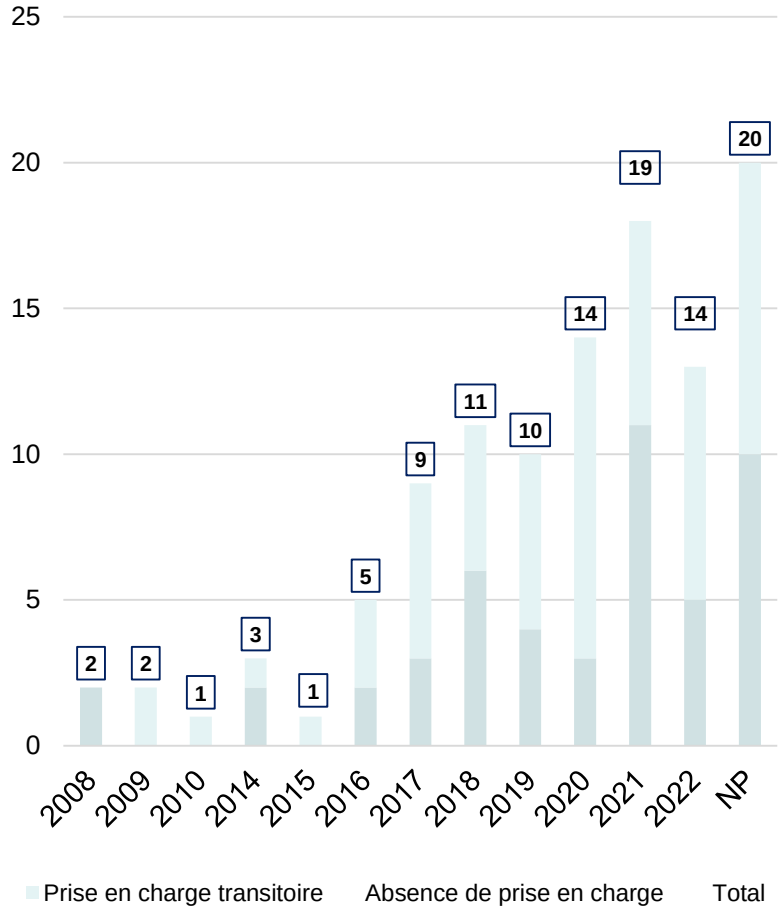


targeted/selective therapies: a revolution in patient care & cancer biology paradigms

Depuis 2008, forte augmentation du nombre de thérapies ciblées disponibles en France et du besoin de prise en charge des actes



Nombre de thérapies ciblées dans de nouvelles indications en France

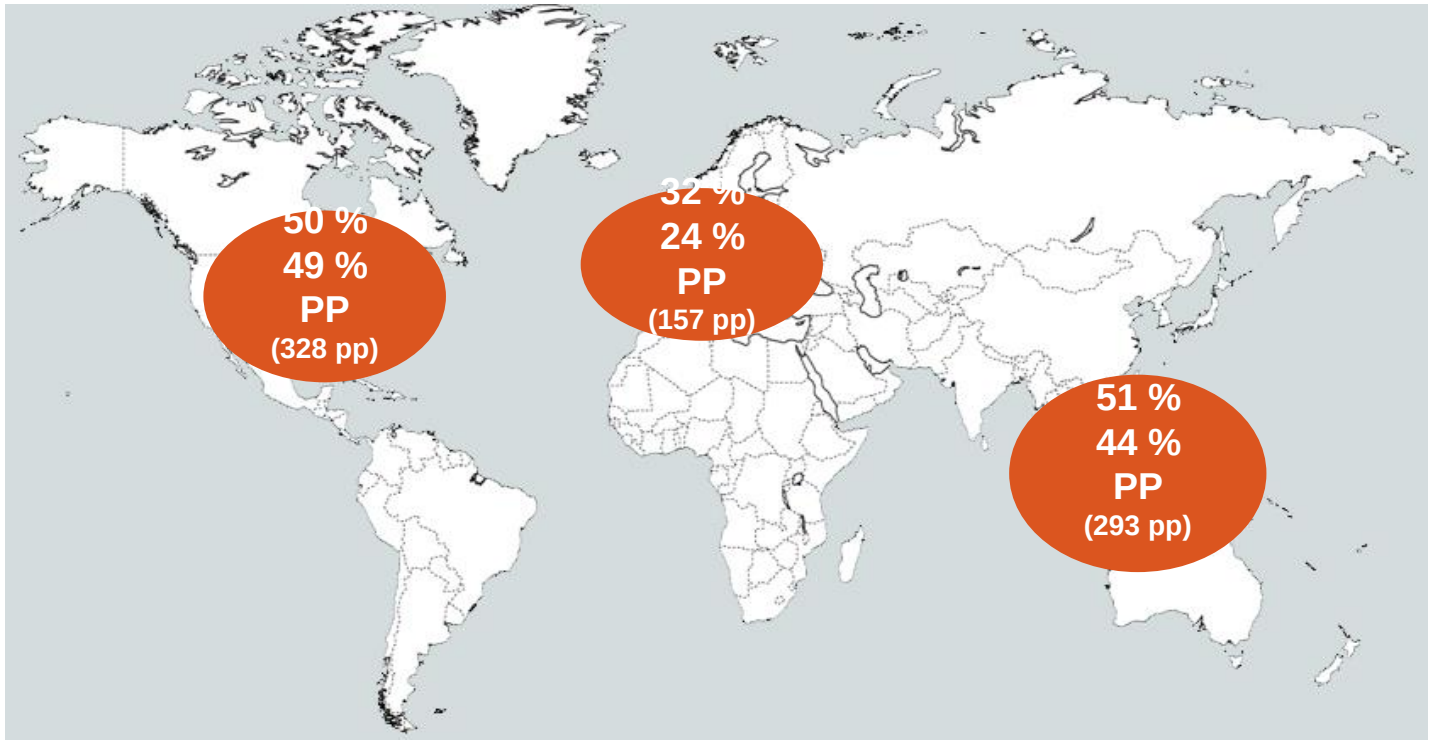


Répartition du nombre de marqueurs et du niveau de prise en charge (N=111)

La France positionnée au 2ème rang européen en oncologie

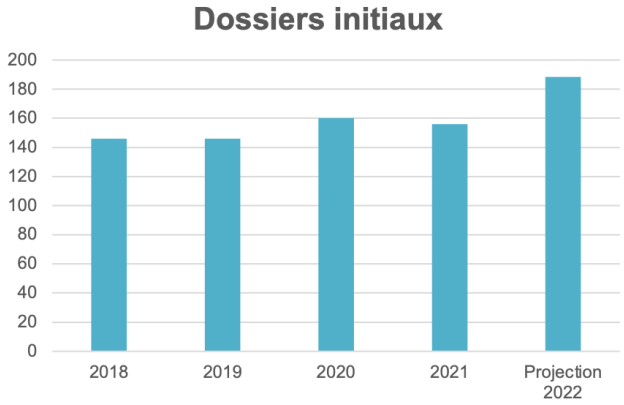
	1er	2ème	3ème	4ème	5ème
Cancers (solides et liquides) N=1 137	Espagne (19%)	**France (15%) =**	Italie (12%)	Royaume-Uni (12%)	Allemagne (9%)
Healthy, In Vivo, Safety, PK, bioavailability, bioequivalence N= 665	Royaume-Uni (10%)	Allemagne (7%)	Belgique (4%)	Pays-Bas (4%)	Espagne (3%)
Maladies virales N= 271	Espagne (11%)	Russie (8%)	Pologne (8%)	Ukraine (8%)	Italie (7%)
Maladies métaboliques et nutritionnelles N= 225	Allemagne (14%)	Espagne (13%)	Pologne (12%)	Royaume-Uni (11%)	Russie (6%)
Maladies du système nerveux N= 194	Espagne (22%)	Allemagne (18%)	Pologne (17%)	Royaume-Uni (16%)	**France (15%)** ↑
Maladies de la peau et du tissu conjonctif N= 190	Pologne (23%)	Allemagne (23%)	Espagne (18%)	**France (14%) =**	Italie (11%)
Maladies du système digestif N= 137	Pologne (26%)	Belgique (16%)	Allemagne (15%)	Royaume-Uni (13%)	**France (12%)** ↑
Maladies cardiaques et cardiovasculaires N= 119	Allemagne (18%)	Royaume (Uni (13%)	Espagne (13%)	**France (12%)** ↑	Italie (12%)
Maladies des yeux N= 107	Allemagne (7%)	Royaume-Uni (7%)	Italie (6%)	Espagne (5%)	**France (4%) =**

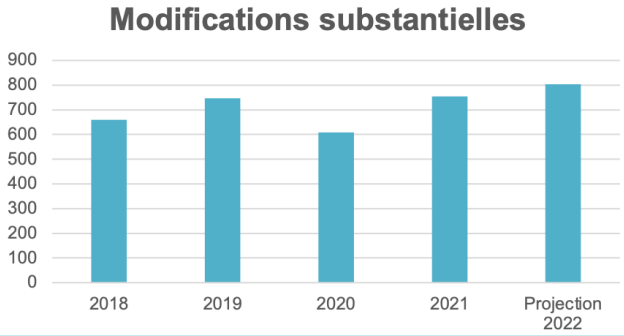
L'Asie passe au 1er rang des grandes régions en cancérologie, l'Amérique du Nord conserve le *lead* pour les phases précoces

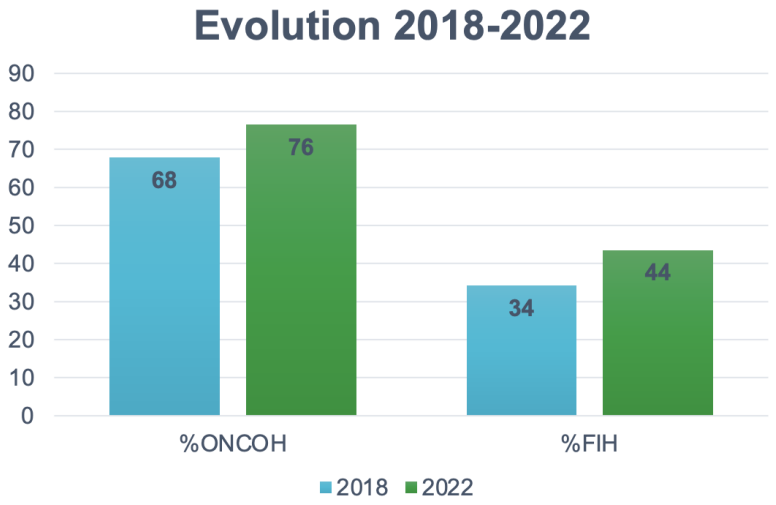


1 137 essais cliniques industriels sur le médicament en cancérologie initiés en 2021 dont 663 phases précoces

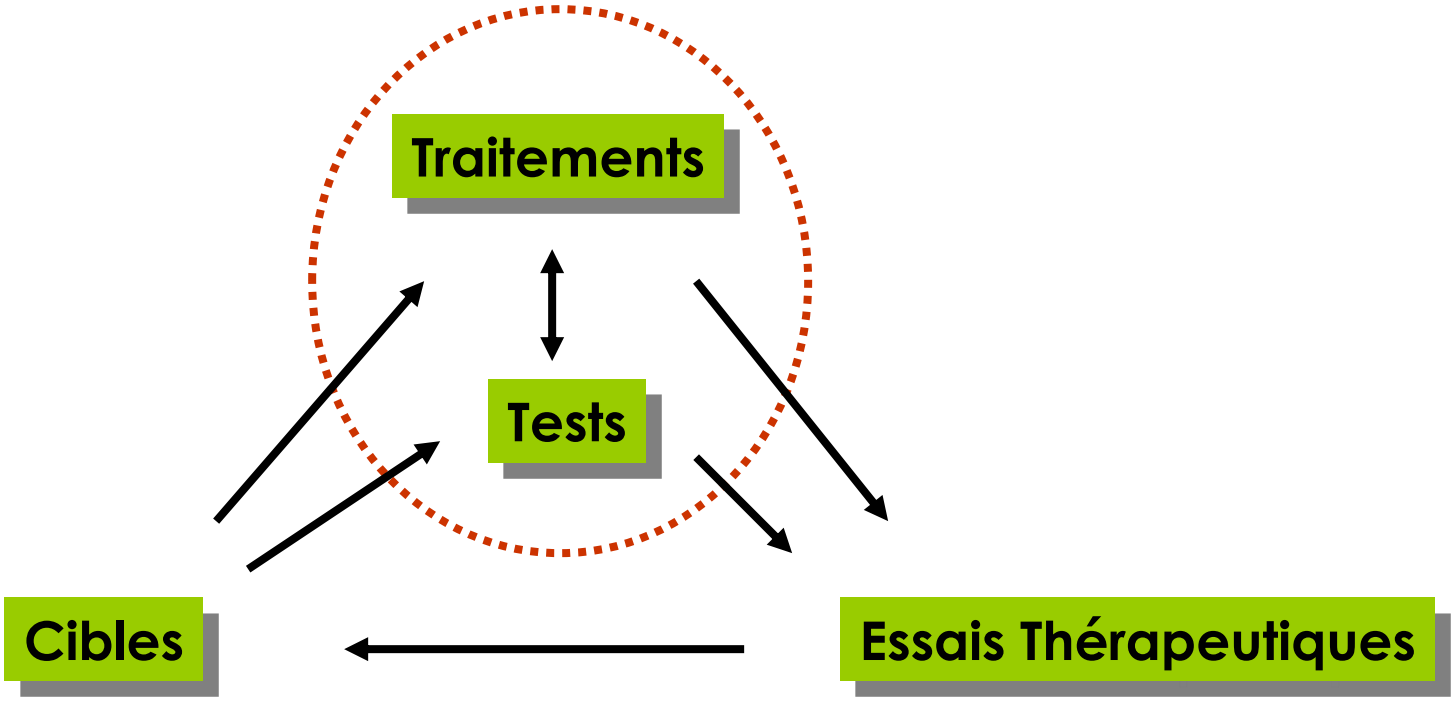
Activité de la cellule Essais Précoces ANSM



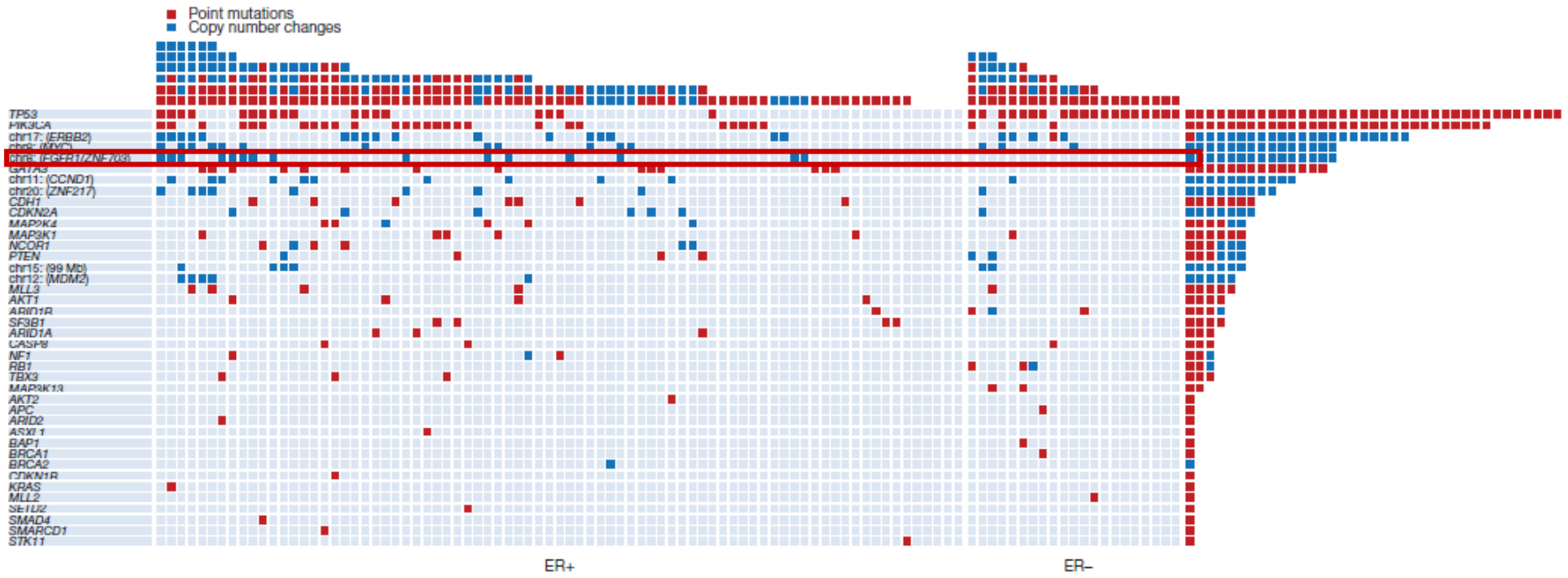




La médecine personnalisée



Genomic segmentation of breast cancer



Breast cancer disease includes a large number of RARE genomic segments
Treatment should include specific agent for each segment

Stephens, Nature, 2012

70%

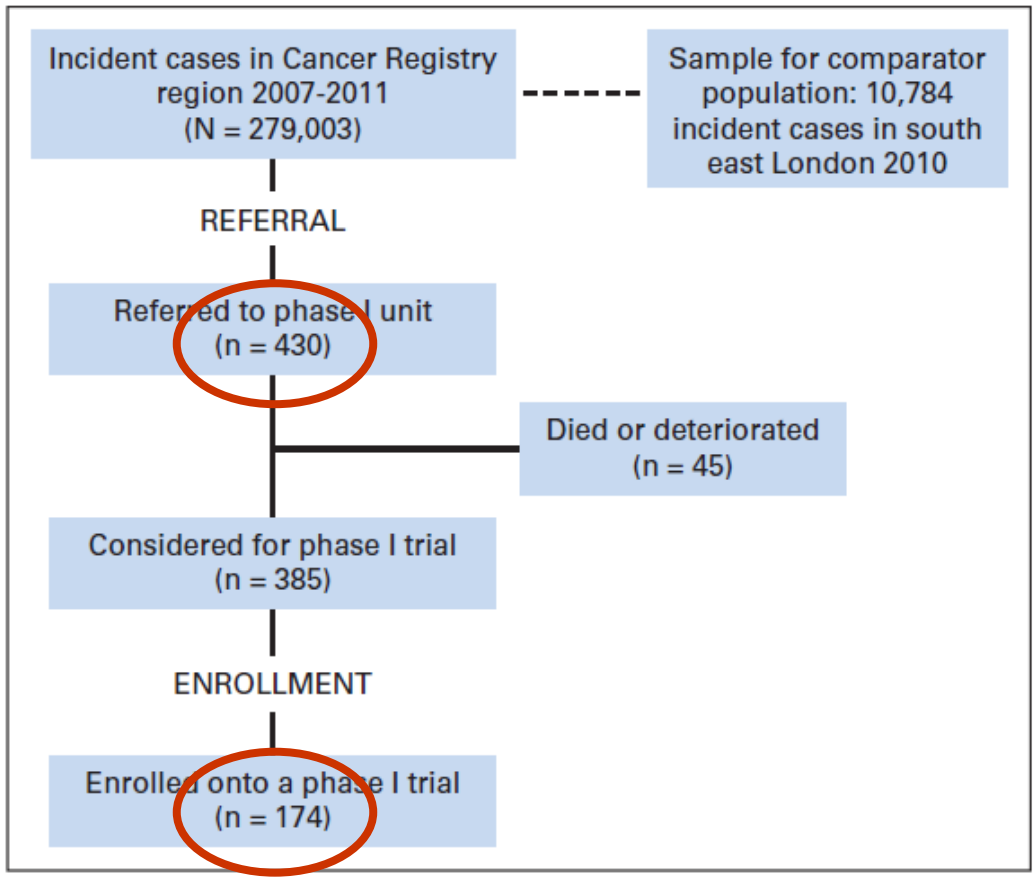


Fig 1. Schema showing the three populations studied. In this analysis, we compared incident cancer cases in the referral region, those referred and considered for a trial, and finally those actually enrolled (bottom box). The deprivation analysis for the incident population was confined to a representative year (10,784 patient cases diagnosed in 2010). Forty-five patients (10.5%) referred were not considered for recruitment to a phase I trial because of clinical deterioration or death in the intervening period.

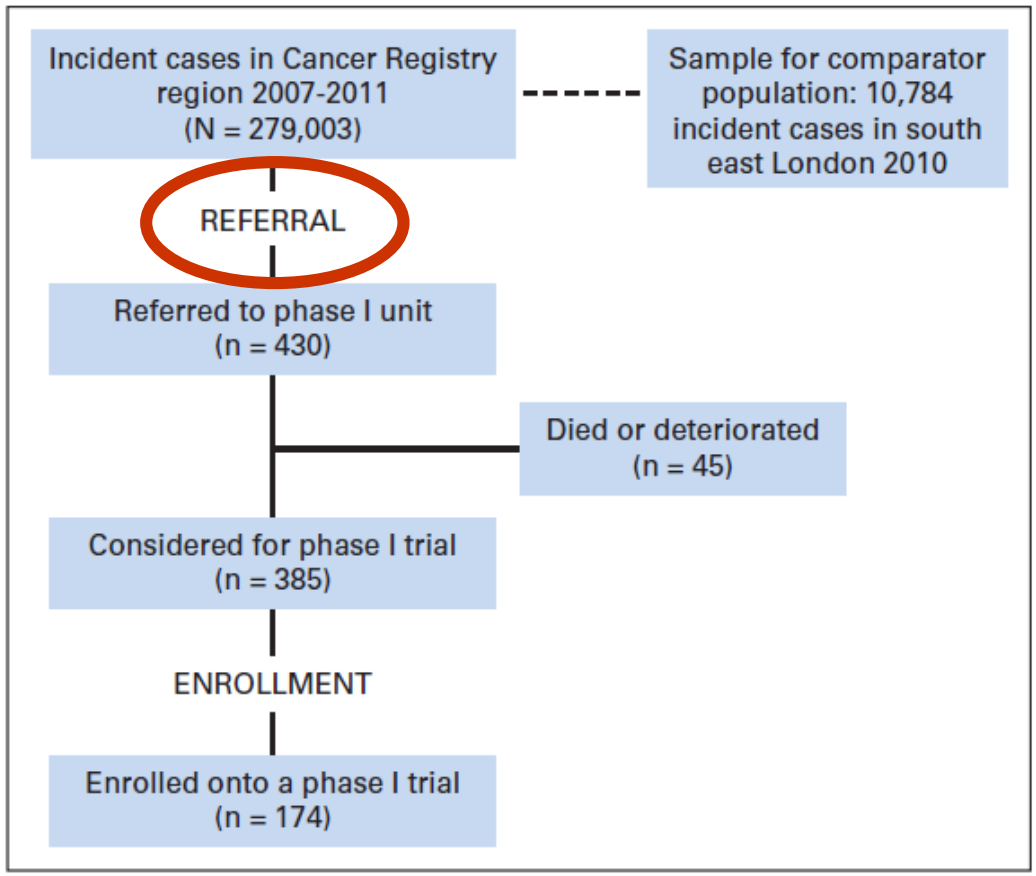


Fig 1. Schema showing the three populations studied. In this analysis, we compared incident cancer cases in the referral region, those referred and considered for a trial, and finally those actually enrolled (bottom box). The deprivation analysis for the incident population was confined to a representative year (10,784 patient cases diagnosed in 2010). Forty-five patients (10.5%) referred were not considered for recruitment to a phase I trial because of clinical deterioration or death in the intervening period.

VOLUME 31 · NUMBER 2 · JANUARY 10 2013

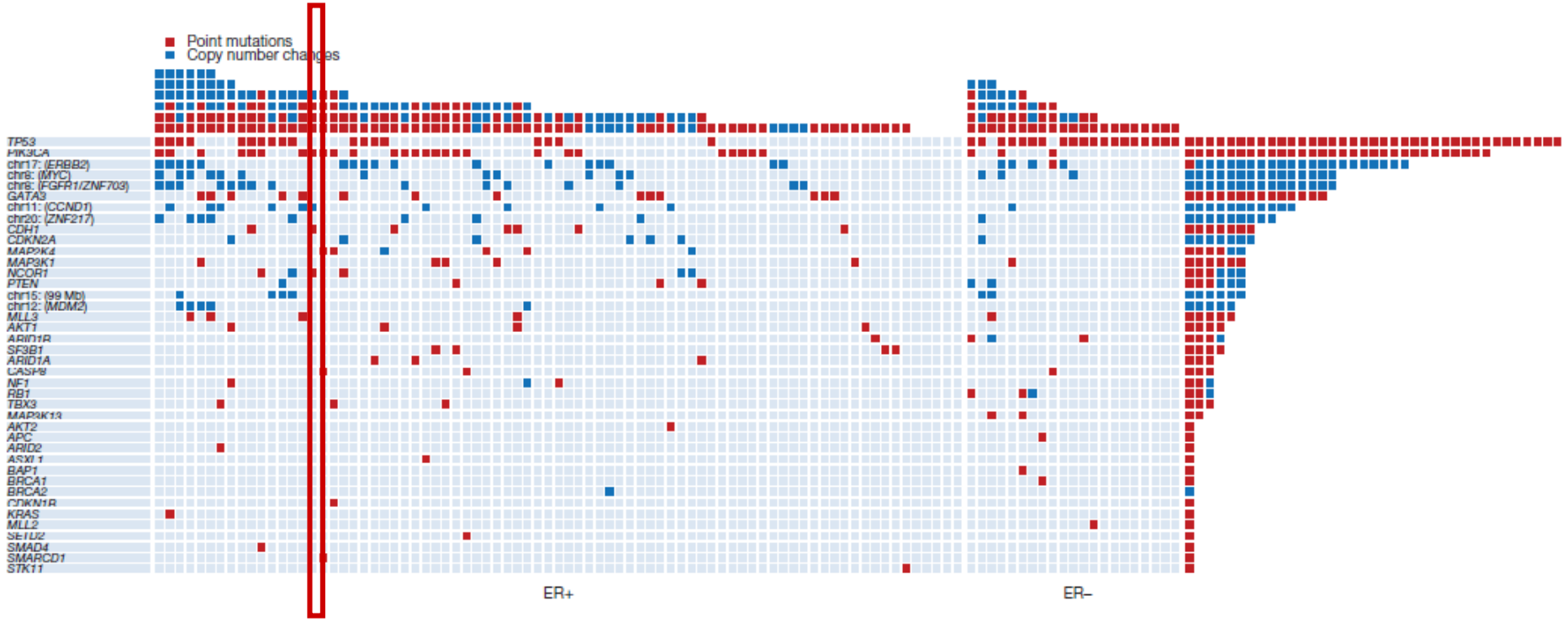
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Effect of Patient Socioeconomic Status on Access to Early-Phase Cancer Trials

Aisyah Mohd Noor, Debashis Sarker, Suzanne Vizor, Blair McLennan, Sarah Hunter, Aneta Suder, Henrik Moller, James F. Spicer, and Sophie Papa

L’enjeu véritable de « médecine personnalisée »



Breast cancer disease includes a large number of RARE genomic segments
Treatment should include specific agentS for each PATIENT

Stephens, Nature, 2012

Evolution majeure de la recherche clinique

- Evolution des connaissances, des technologies
- Démembrement moléculaire et identification de nouvelles cibles thérapeutiques
- Présence d'anomalie rare
  - ✓ Exemple: **fusion** du **gène NTRK** présent dans 0.3% des cancers
- Le Gold Standard (RCT) n'est pas réalisable
- Etude monobras avec Contrôle Externe

External control arms in oncology: current use and future directions

P. S. Mishra-Kalyani[1*], L. Amiri Kordestani[2], D. R. Rivera[3], H. Singh[2,3], A. Ibrahim[2], R. A. DeClaro[2,3], Y. Shen[1], S. Tang[1], R. Sridhara[3], P. G. Kluetz[2,3], J. Concato[4], R. Pazdur[2,3] & J. A. Beaver[2,3]

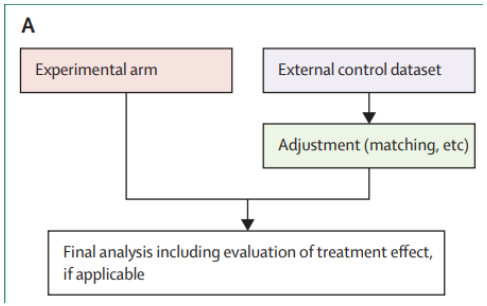
[1]Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring; [2]Office of Oncologic Diseases, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring; [3]Oncology Center of Excellence, U.S, Food and Drug Administration, Silver Spring; [4]Office of Medical Policy, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, USA

(Annals of Oncology 2022)

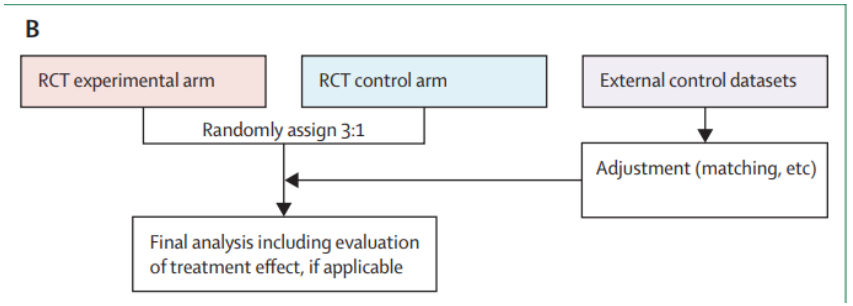
Sélection du Bras Contrôle Externe

- Typologie des données: Données Individuelles vs Agrégées
- Différentes sources de données:
  - ✓ Essai thérapeutique vs Cohorte ou registre prospectif vs RWD

Stratégie classique



Stratégie Hybride

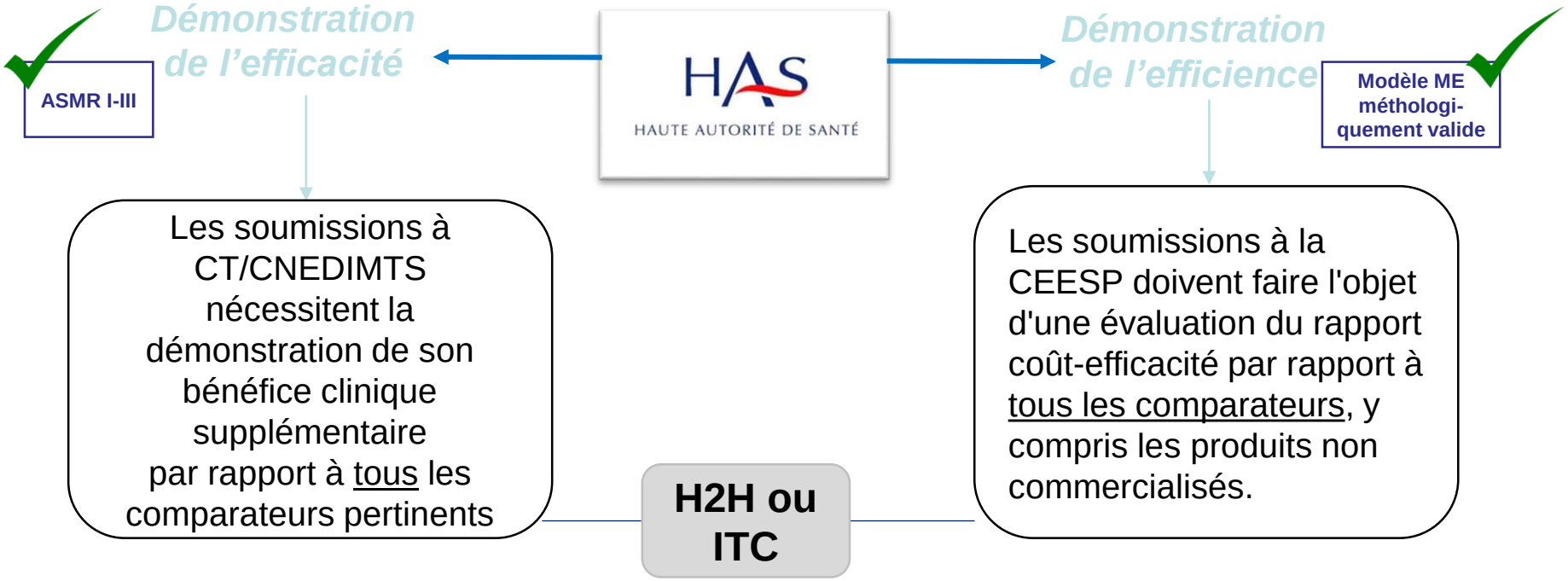


(Rahman, Lancet Oncol 2023)

S’ils avaient tous la même maladie….

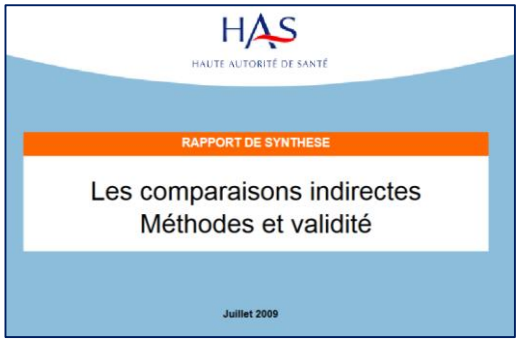
Contexte : quel bénéfice du traitement ?

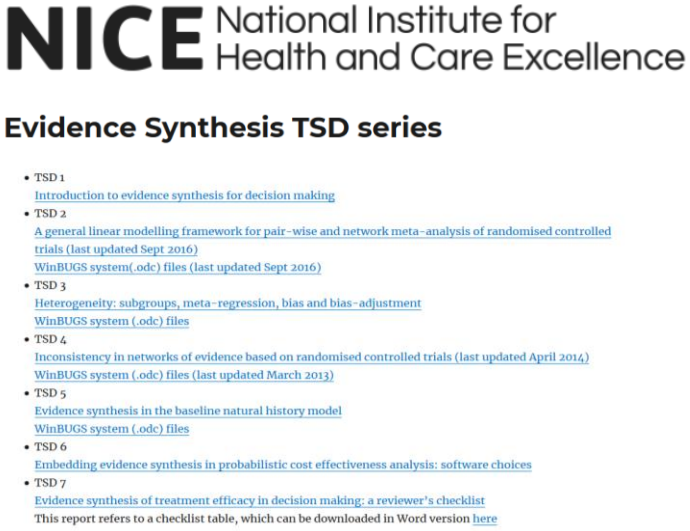
- Dans les dossiers soumis à la HAS



CT: commission de transparence **; CNEDIMTS:** commission nationale d'évaluation des dispositifs médicaux et des technologies de santé
ASMR: amélioration du service médical rendu ; **ITC**: indirect treatment comparison; **H2H**: Head-To-Head treatment comparison

Les recommandations actuelles





Lignes directrices de la HAS depuis 2009 :
- Peu technique
- Générales et non détaillées

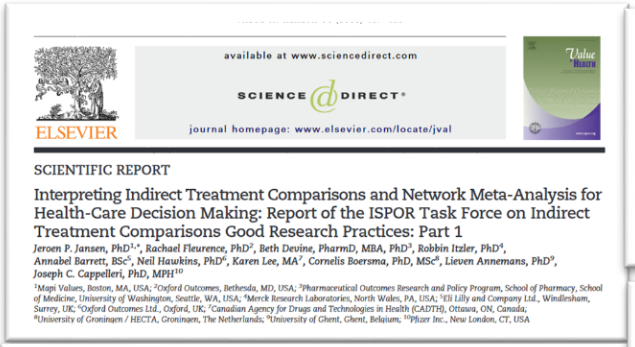
Lignes directrices de l'eunethta depuis 2022 :
- Quelques recommandations, générales
- Permet de cibler les grandes attentes

NICE :

Très détaillé et technique, mais non exhaustif

HORIANA

Une littérature riche et diverse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journal homepage: www.elsevier.com/locate/jval
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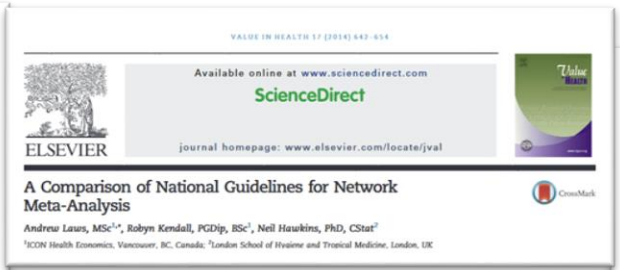
SCIENTIFIC REPORT
Interpreting Indirect Treatment Comparisons and Network Meta-Analysis for Health-Care Decision Making: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 1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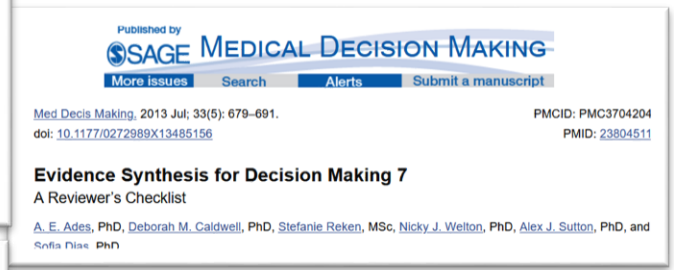
A Comparison of National Guidelines for Network Meta-Analysis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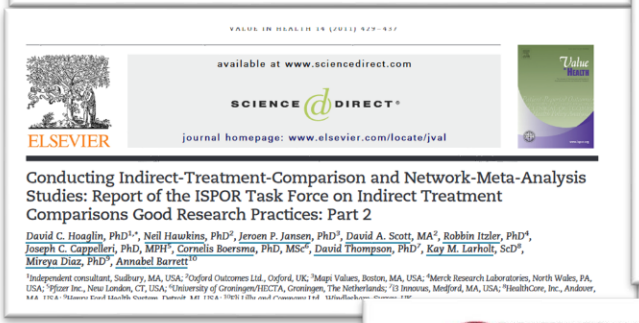
Med Decis Making. 2013 Jul; 33(5): 679–691.
doi: 10.1177/0272989X13485156
PMCID: PMC3704204
PMID: 23804511
Evidence Synthesis for Decision Making 7
A Reviewer's Checklist
A. E. Ades, PhD, Deborah M. Caldwell, PhD, Stefanie Reken, MSc, Nicky J. Welton, PhD, Alex J. Sutton, PhD, and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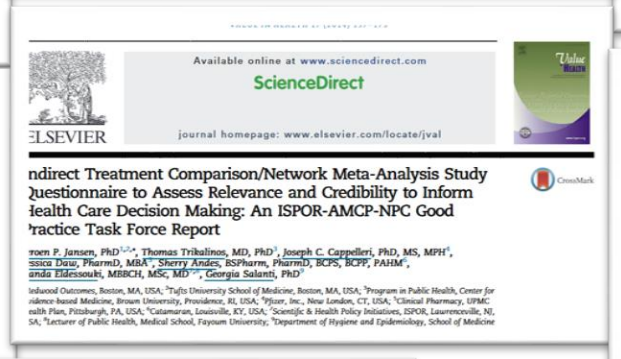
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Questionnaire to Assess Relevance and Credibility to Inform
Health Care Decision Making: An ISPOR-AMCP-NPC Good
Practice Task Force Report


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Clinical pharmacology
From single-arm studies to externally controlled studies. Methodological considerations and guidelines ☆


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A checklist for critical appraisal of indirect comparisons
A. Ortega, M. D. Fraga, E. J. Alegre-del-Rey, F. Puigventós-Latorre, A. Porta, P. Ventayol, J.M. Tenias, N. S. Hawkins, D. M. Caldwell
First published: 01 October 2014 | https://doi.org/10.1111/iicp.12487 | Citations: 2


OPEN ACCESS Freely available online
PLOS ONE
Evaluating the Quality of Evidence from a Network Meta-Analysis
Georgia Salanti[1], Cinzia Del Giovane[2], Anna Chaimani[1], Deborah M. Caldwell[3], Julian P. T. Higgins[3,4]*

Le point de vue des méthodologistes de la HAS

« Position paper » récent, mentionnant les attentes sur les comparateurs externes

EBM analysis

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

Antoine Vanier,[1,2] Judith Fernandez ,[1] Sophie Kelley,[1] Lise Alter,[1] Patrick Semenzato,[1] Corinne Alberti,[3,4] Sylvie Chevret,[5] Dominique Costagliola,[6] Michel Cucherat,[7] Bruno Falissard,[8] François Gueyffier,[9] Jérôme Lambert,[5] Etienne Lengliné,[10] Clara Locher ,[11] Florian Naudet ,[12,13] Raphael Porcher,[14] Rodolphe Thiébaut,[15] Muriel Vray,[16] Sarah Zohar,[17,18] Pierre Cochat,[19] Dominique Le Guludec[19]

Gathering source(s) of data for external comparison

Performing an adequate comparison vs an external control, using for example data from cohorts or other clinical trials, can be an option for mitigating uncertainties in the absence of RCTs. Availability of external controls may be scarce (eg, in case of targeted therapies for very rare mutation(s) in oncology). Real-world data generation should therefore be anticipated by the manufacturer during the early stages of the clinical development if no pre-existing data set has been identified for the comparison.

Bras comparateur externe

Des recommandations plus claires, mais très exigeantes

Box 1 Methodological points of attention HAS should consider when assessing an external comparison between an uncontrolled trial and an external control

1. Justification of the lack of randomisation
   - A rationale appraised as acceptable by Haute Autorité de santé is provided.
2. Study design
   - Early planning during clinical development and before the conduct of the uncontrolled trial of the treatment of interest.
   - A priori definition of the clinical question, study population, intervention, comparator and outcomes in a protocol and statistical analysis plan.
   - An emulation of a target trial can enhance eliciting the appropriate clinical question (estimand) and designing the external comparison.
3. Search and selection of relevant sources of data
   - Well-performed systematic review identifying relevant prognostic variables, confounders and effect modifiers.
   - Well-performed systematic review (with eligibility criteria defined a priori) identifying relevant sources for external control.
4. Choice of the external control
   - The comparator and external source(s) of data has been chosen independently of the results of the uncontrolled trial, fit best the clinical question (does not arbitrarily favour the treatment of interest) and correspond to standard of care.
5. Analysis of the results
   - The study protocol, statistical analysis plan and report allow a transparent and appropriate assessment of the study.
   - A model for causal inference controlling an appropriate set of confounders and targeting the predefined estimand has been properly specified and estimated.
   - The model is preferably based on a method using individual patient data only such as propensity scores, g-computation or doubly robust estimation.
   - Underlying assumptions have been explored and seems to be met (such as positivity, sufficient overlap and sufficient balance for propensity scores).
   - If 'trimming' (ie, excluding patients in areas of the propensity score without overlap) have been performed, the resulting target population for which results can apply is described.
   - Residual confounding has been explored with analyses such as the use of negative and positive controls, consistency in results when using other external controls, or quantitative bias analysis and excludes a conclusion of no treatment effect.
   - Study characteristics of the uncontrolled trial and external control are sufficiently similar for excluding other sources of bias such as selection bias, attrition bias, measurement bias.
   - Safety can be properly documented for both groups.
6. Grading the clinical added value
   - The clinical added value of the treatment of interest is appraised considering the certainty of results, the relevance and magnitude of treatment effect and safety.

Quelles sont les meilleures méthodes ? Sont-elles toujours applicables ?

HORIANA

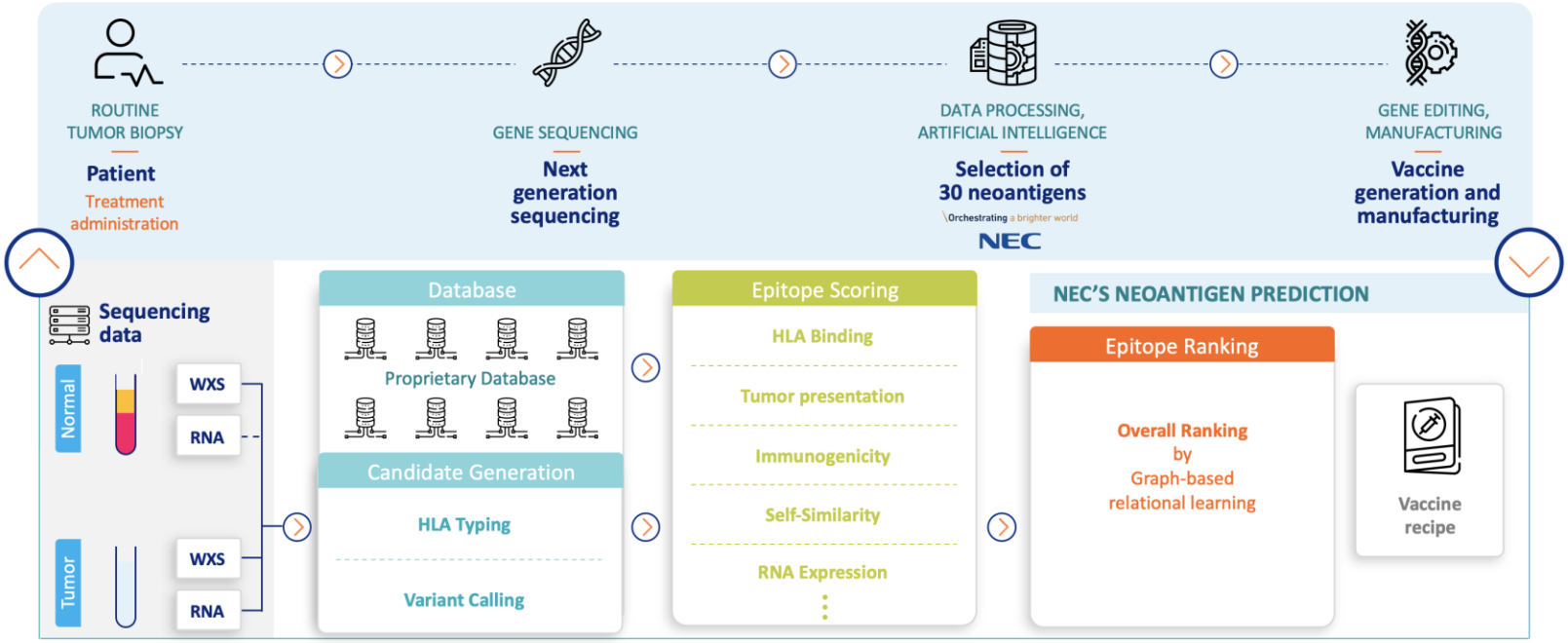
Optimisation du design et de l'analyse des essais avec bras comparateurs externes : application en oncologie

Plan de recherche

1. Evaluer les méthodes existantes permettant de minimiser les biais (indication, confusion)
    a. IPD et/vs données agrégées
    b. Méthodes existantes de quantification des biais résiduels (e-value, etc)
    c. Définir les limites des méthodes
    d. Problématique small sample size, hétérogénéité, intégration de données externes sur le bras expérimental
2. Elaborer des solutions pour un design hybride, sur les axes :
    a. Schéma Bayesien - Choix du prior (poids des info externes)
    b. Méthode d'estimation de la taille d'étude
    c. Méthode d'analyses
    d. Quantification des biais résiduels

Vaccins personnalisés anti-néoantigènes

TG4050 : Une phase 1...en situation adjuvante !

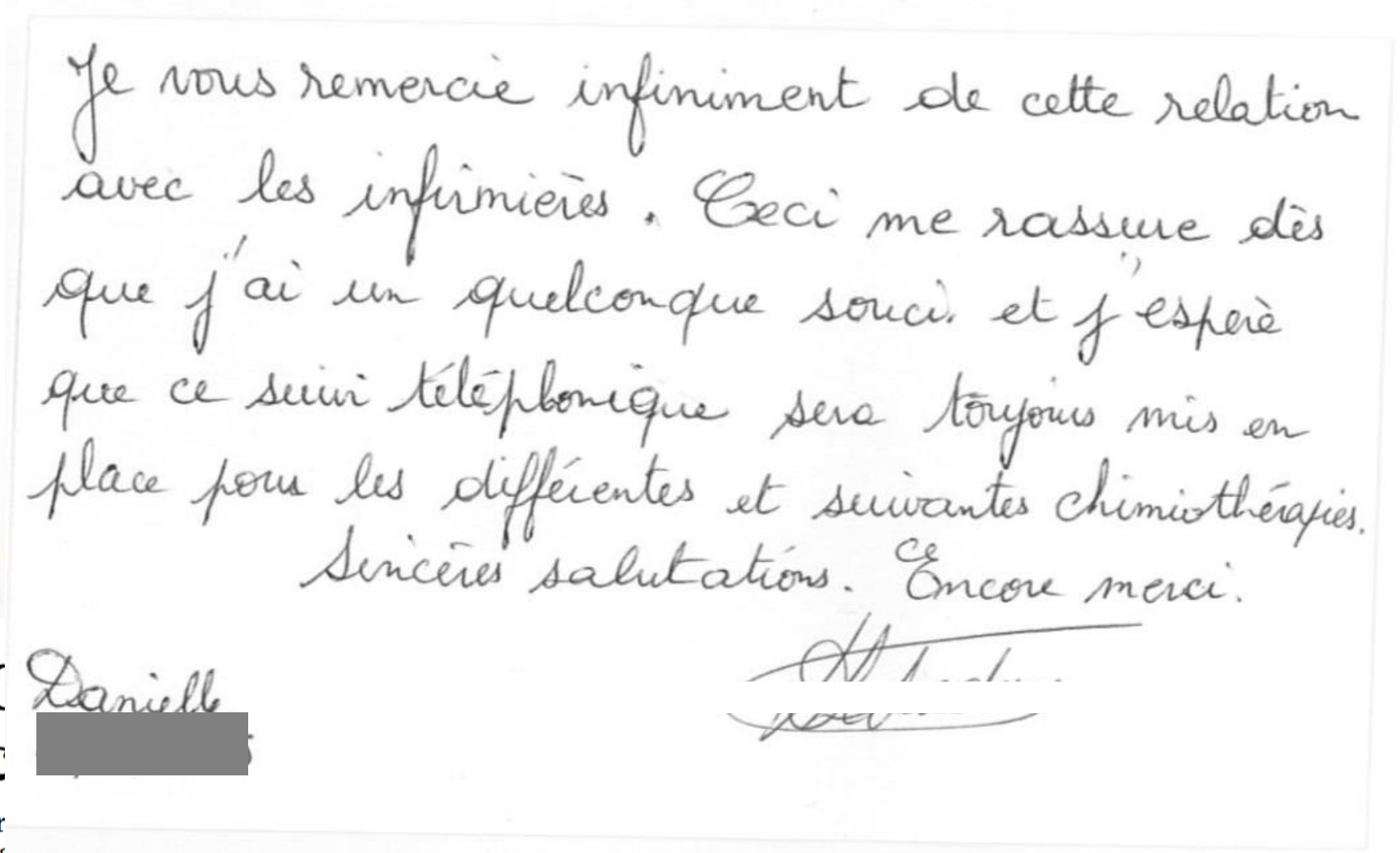


Misconception...

	Oncologues	Onco-pédiatres
Pour améliorer le traitement de futurs patients...	40%	32%
Pour m ’assurer que mes patients seront traités correctement...	43%	64%

S Joffe, JC Weeks JNCI Dec 2002

Notre objectif : la recherche au bénéfice des patients.

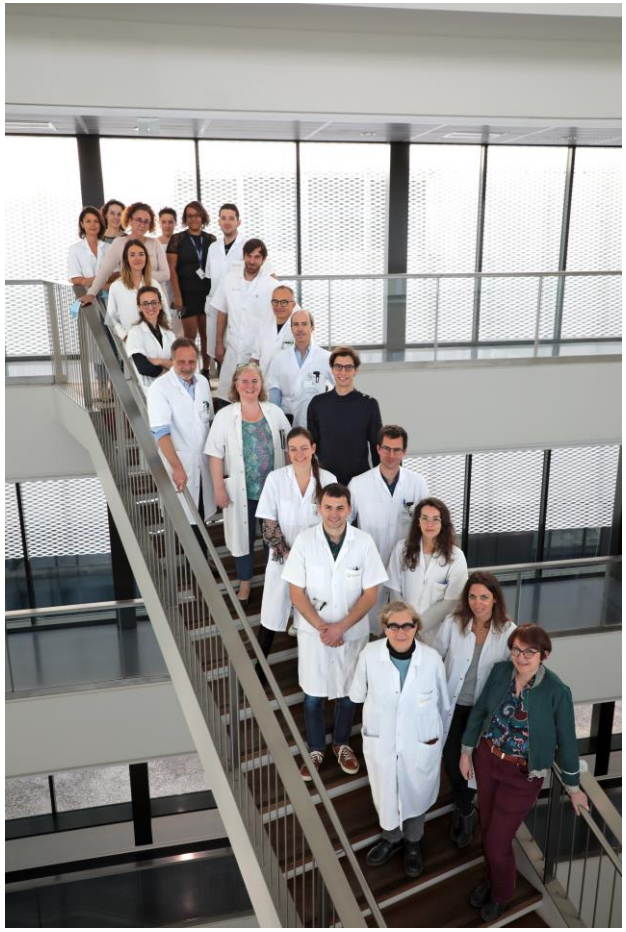


Je vous remercie infiniment de cette relation avec les infirmières. Ceci me rassure dès que j'ai un quelconque souci et j'espère que ce suivi téléphonique sera toujours mis en place pour les différentes et suivantes chimiothérapies.

Sincères salutations. Encore merci.

Danielle [redacted]

Marta Jimenez[13], Semih Dogan[14], Benjamin Verret[14], Max Chaffanet[1], Thomas Bachelot[15], Mario Campone[4,5], Claudia Lefeuvre[16], Herve Bonnefoi[17], Florence Dalenc[18], Alexandra Jacquet[13], Maria R. De Filippo[2], Naveen Babbar[19], Daniel Birnbaum[1], Thomas Filleron[18,26], Christophe Le Tourneau[20,21,22,26] & Fabrice André[9,14,23,26]*



“ Comité ORL”

T2I

PRESENTIEL

Phases Précoces en Cancérologie

Avec le parrainage de SCOPP

Le rendez-vous annuel de tous les acteurs des phases précoces en cancérologie pour faire de la France le pays le plus attractif !

PROGRAMME

Jeudi 30 novembre 2023

Palais des Congrès d'Issy-Les-Moulineaux

JE M'INSCRIS

CRCT
Centre de Recherches en Cancérologie Toulouse
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INSTITUT UNIVERSITAIRE DU CANCER DE TOULOUSE
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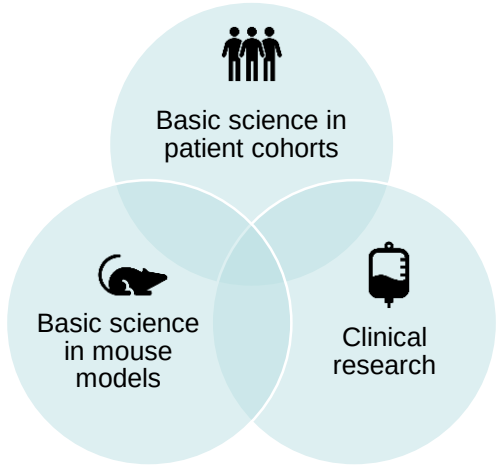

LA LIGUE CONTRE LE CANCER

FONDATION ARC POUR LA RECHERCHE SUR LE CANCER
Reconnue d'utilité publique

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