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Agathe Plichta

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UNIVERSITÉ GRENOBLE ALPES
UFR DE PHARMACIE DE GRENOBLE

Année : 2018

**IMPACT MEDICO-ECONOMIQUE DES THERAPIES CIBLEES ET DES
TRAITEMENTS IMMUNO-ONCOLOGIQUES DANS LA PRISE EN CHARGE DES
CANCERS BRONCHO-PULMONAIRES AVANCES OU METASTATIQUES EN
FRANCE**

THÈSE
PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN PHARMACIE
DIPLOME D'ÉTAT

Agathe PLICHTA

[Données à caractère personnel]

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UMR: Unité Mixte de Recherche
UVHCI: Unit of Virus Host Cell Interactions

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Abréviations Françaises

ACPR : Autorité de Contrôle Prudentiel et de Résolution - Prudential Control and Resolution Authority

ALD : Affection Longue Durée – Long-Term Affection

AME : Aide Médicale d’Etat – State Medical Assistance

AMM : Autorisation de Mise sur le Marché – Market Authorization

ANAP : Agence Nationale d’Appui à la Performance des établissements de santé et médico-sociaux - National Agency to Support the Performance of Health and Health and Social Care Institutions

ANESM : Agence Nationale de l’Evaluation de la qualité des Etablissements et Services sociaux et Médico-sociaux - Agency for the Quality Assessment of Health and Social Care Organizations and Services

ANSES : Agence Nationale de Sécurité Sanitaire de l’Alimentation, de l’Environnement et du travail - French Agency for Food, Environmental and Occupational Health Safety

ANSM : Agence Nationale de Sécurité du Médicament et des produits de santé - French National Agency for Medicines and Health Products Safety

ARS: Agence Régionale de Santé – Regional Centralized Healthcare Authority

ASMR: Amélioration Service Medical Rendu - Improvement of the Rendering Medical Service

ATIH : Agence Technique de l’Information sur l’Hospitalisation - Agency for Information on Hospital Care

AURA : Auvergne Rhône Alpes (Référentiel)

CBNPC : Cancer Bronchique Non à Petites Cellules

CEPS : Comité Économique des Produits de Santé – Economic Committee for Health Products

CMU : Couverture Maladie Universelle

CNAMTS : Caisse nationale d'assurance maladie des travailleurs salariés – General SHI Scheme

CSP : Code de la Santé Publique – Public Health Code

CT : Commission de Transparence – Transparency Committee

DG : Dotation Globale - Global Endowment

EFS : Établissement Français du Sang - French Blood Agency

EPRUS : Établissement de Préparation et de Réponse aux Urgences Sanitaires - Health Emergency Preparedness and Response Agency

GHM : Groupe Homogène de Malades - Homogeneous Group of Patients

GHS : Groupe Homogène de Séjour - Homogenous Groups of Stay

HAS : Haute Autorité de Santé - National Authority for Health

HCAMM : Haut conseil pour l'avenir de l'assurance maladie - High Council for the Future of Health Insurance report

HCSP : Haut Conseil de la Santé Publique - High Council for Public Health report

INCa : Institut National du Cancer - National Institute for Cancer

INPES : Institut National de Prévention et d'Education pour la Santé - Institute of Health Prevention and Education

InVS : Institut de Veille Sanitaire - National Institute for Health Surveillance

IRSN : Institut de Radioprotection et de Sécurité Nucléaire - Radioprotection and Nuclear Safety Institute

JO : Journal Officiel – Official Journal

MCO : Médecine, Chirurgie, Obstétrique - Medicine, Surgery and Obstetrics

MIB : Modèle d'Impact Budgétaire

ONDAM : Objectifs Nationaux des Dépenses de l'Assurance Maladie - National Objectives of the Health Insurance Expenditure

OQN : Objectif Quantifié National - National Quantified Objective

PMSI : Programme de Médicalisation de Systèmes d'Information - Program of Medicalization of Information Systems

RATP : Régie autonome des Transports Parisiens

SMR: Service Medical Rendu - Rendering Medical Service

SNCF : Société Nationale des Chemins de fer Français – Railway French National Society

T2A : Tarification à l'Activité - Pricing Activity

UNCAM: Union Nationale des Caisses d'Assurance Maladie - National Union of Health Insurance Funds

UNOCAM: Union Nationale des Organismes d'Assurance Maladie Complémentaire - National Union of Complementary Health Insurance Organizations

Abréviations Anglaises

ACTH: Adrenocorticotrophic hormone

ADC: Adenocarcinoma

ADC-BA: Adenocarcinoma Bronchioalveolar

ALK: Anaplastic Lymphoma Kinase

APC: Antigen-Presenting Cell

ASCO: American Society of Clinical Oncology

BBB: Blood Brain Barrier

CHMP: Committee for Medicinal Products for Human Use

CIT: Cancer Immunotherapy

CNS: Central Nervous System

CNG: Copy Number Gain

DAR: Draft Assessment Report

EGFR: Epidermal Growth Factor Receptor

EMA : European Medicines Agency – Agence Européenne du Médicament

EPAR: European Public Assessment Report

ESMO: European Society for Medical Oncology

FISH: Fluorescence In-Situ Hybridization

IHC: Immunohistochemistry

LCC: Large Cell Carcinoma

LCNEC: Large Cell Neuroendocrine Carcinoma

MAPK: Mitogen-activated Protein Kinase

MHC: Major Histocompatibility Complex

MK: Midkine

MRI: Magnetic Resonance Imaging

NHS: National Health Service – Service National de Santé

NGS: Next-Generation Sequencing

NSCLC: Non-Small Cells Lung Cancer

OOP: Out-Of-Pocket - Reste à charge

OS: Overall Survival

PAH: Polycyclic Aromatic Hydrocarbons

PD-1: Programmed death 1

PD-L1: Programmed Death Ligand 1

PFS : Progression Free Survival

P-GP : Protein P-Glycoprotein

PTN : Pleiotrophin

RMS : Reference Member State – Etat Membre de Référence

RT-PCR: Reverse-transcriptase polymerase chain reaction

SCC: Squamous Cell Carcinoma

SCLC: Small Cells Lung Cancer

SHI: Statutory Health Insurance - Assurance Maladie

SmPC: Summary of Product Characteristic

SoC: Standard of Care

TCR: T Cell Receptor

VHI - Voluntary health insurance - Assurance complémentaire

VIP: Vasoactive Intestinal Polypeptide

WHO: World Health Organization

WT: Wild Type

Glossaire

Médico-économie : la médico-économie correspond à l'économie appliquée au domaine de la santé. Elle permet d'analyser des interventions de santé avec les ressources consommées pour la produire. Cela suppose que les interventions de santé soumises à la décision publique soient comparées, sur la base de leurs résultats et de leurs coûts respectifs (1).

Modèle d'impact budgétaire (MIB) : une approche financière destinée à estimer, sur un horizon temporel à court ou à moyen terme, les conséquences budgétaires annuelles de l'adoption d'une intervention de santé. Cette estimation résulte du calcul de la différence entre les prévisions de dépenses associées à des scénarios intégrant ou non l'intervention de santé étudiée (2). L'objectif du MIB n'est pas normatif et ne conduit pas à une recommandation formelle de prise en charge ou de tarification (3).

Introduction

Au cours des dernières décennies, malgré la prise en charge thérapeutique et les campagnes de prévention contre les facteurs de risques, le cancer broncho-pulmonaire reste aujourd'hui une maladie avec un mauvais pronostic à 5 ans. Cette survie à 5 ans n'a pas vu d'amélioration, d'après les résultats de l'étude de l'Institut National du Cancer (INCA) (4). En effet, les personnes diagnostiquées entre 2005 et 2010 ne présentent pas d'amélioration en termes de survie nette standardisée à 5 ans par rapport aux patients diagnostiqués entre 1989 et 2010, celles-ci étant respectivement de 17% et 15%. Ce mauvais pronostic peut être expliqué par le fait que 68% des cancers sont diagnostiqués d'emblée au stade avancé (IIIB) ou métastatique (IV) et que dans la population résiduelle, 40% progresseront vers un stade avancé ou métastatique dans l'année (5,6).

Le cancer du poumon représente un problème de santé publique mondial majeur avec la plus forte incidence de cancer soit 1,8 million de nouveaux cas par an (13% des nouveaux cas de cancer total) et le taux de mortalité le plus élevé avec 1,6 million de décès par an (19% des décès par cancer) (7). En France, le cancer du poumon représente le quatrième cancer le plus fréquent avec un peu plus de 45 000 nouveaux cas par an et le taux de mortalité le plus élevé (environ 30 500 décès par an, soit 20% de cancers) (4,5). Parmi ceux-ci, environ 82,4% sont des cancers du poumon non à petites cellules, soit 37 263 nouveaux cas par an (8). Entre 2005 et 2012, les taux d'incidence et de mortalité ont augmenté chez les femmes d'environ 5% par an et ont diminué chez les hommes (entre -0,3% et -2,2%) (4). Cette augmentation chez la femme est liée à l'évolution du statut des femmes dans la société et son association avec le tabagisme (9).

Grâce à de nombreuses découvertes dans le domaine de la génomique (techniques de détection et découvertes d'addictions oncogéniques) et des nouvelles thérapeutiques (thérapies

ciblées et immunothérapies) au cours des 10 dernières années, un changement de paradigme conduit à de nouvelles opportunités et possibilités pour mieux prendre en charge le cancer du poumon. L'arrivée ces dernières années des thérapies ciblées, des immunothérapies et bientôt de la médecine personnalisée offre un espoir grandissant pour la prise en charge du cancer bronchique. Ces biothérapies, révolutions thérapeutiques sont plus onéreuses que la chimiothérapie conventionnelle. De plus, une nouvelle aire commence peu à peu à faire son chemin et l'on commence à voir fleurir les combinaisons pour la prise en charge des patients : biothérapies en association avec une chimiothérapie, biothérapies avec d'autres biothérapies, mais également des combinaisons plusieurs biothérapies et chimiothérapie. Ces traitements, aussi efficaces soient-ils, ajoutent des coûts non négligeables pour le système de santé actuel.

Développement de la Thèse en Français

1. Problématique

En France, le cancer bronchique fait partie des pathologies que l'on appelle « Affection Longue Durée » (ALD). Cela signifie que cette pathologie est prise intégralement en charge par le système de soin français : l'Assurance Maladie ; et n'est donc pas à la charge du patient. Le financement de la prise en charge de cette pathologie est assuré par des fonds publics. Le cancer broncho-pulmonaire ne représente que l'une des multiples pathologies prise en charge intégralement par le système de santé français.

Les thérapies innovantes représentent cependant des coûts plus élevés que les chimiothérapies actuelles. Cela conduit donc à se poser la question de l'impact de ces nouveaux coûts médicaux dans la prise en charge du cancer du poumon et ce, dans une optique d'évaluation pour l'assurance maladie. Dans un contexte de financement public aux ressources limitées, l'évolution des traitements, de la prise en charge et des techniques de diagnostic ont augmenté le coût de la prise en charge des patients atteints de cette pathologie. Ce modèle peut donc montrer aujourd'hui des limites. Une des questions qui se dresse est de savoir comment maintenir un système de santé durable et égalitaire ?

Cette problématique nous amène donc à nous questionner sur la difficile notion de prix et de financement en santé afin de préserver un système de santé éthique et égalitaire. L'objectif de ce travail est de formuler des hypothèses à 5 ans, pour 2022, de l'évolution de la prise en charge du cancer du poumon, des coûts médicaux réels de la maladie afin d'identifier des points de contrôle à l'aide d'un modèle d'impact budgétaire.

2. Méthodologie

L'évaluation médico-économique est une discipline récente, (2) qui a pris de l'importance ces dernières années, notamment au niveau des politiques de santé, due à l'augmentation des dépenses de santé dans des modèles de financements restreints. En France, la Loi a permis en 2008 d'intégrer dans les missions de la Haute Autorité de Santé (HAS) la publication de recommandations et d'évaluations médico-économiques sur les stratégies de soins, de prescription ou de prise en charge les plus efficaces (3). Et plus récemment, en 2016, l'Accord Cadre entre le Comité d'Evaluation des Produits de Santé (CEPS) et Les Entreprises du Médicaments (LEEM), (10) demandent parfois aux laboratoires pharmaceutiques de fournir des dossiers d'efficacité lors de demande d'Amélioration du Service Médical Rendu (ASMR) de niveaux I, II ou III pour des traitements onéreux (11). L'objectif de ces évaluations étant de s'informer sur les coûts impliqués et de trouver des solutions pour maintenir un système de santé égalitaire et éthique en optimisant les ressources allouées. Il existe aujourd'hui des guides méthodologiques, proposés par la HAS, pour conduire des analyses médico-économiques (2).

L'ensemble de l'étude a été effectuée à l'aide de Microsoft® Office Excel, les analyses et résultats bruts sont présentés dans la section Annexes.

2.1 *Analyse Primaire*

Cette analyse suppose qu'en 2022 le système de prise en charge par l'assurance maladie sera équivalent à celui en place actuellement. L'objectif ici est de créer un modèle d'impact budgétaire pour l'ensemble des thérapies disponibles pour la prise en charge du cancer bronchique non à petites cellules avancés ou métastatiques et non pas uniquement pour un traitement.

Afin de quantifier les coûts totaux du cancer du poumon avancé et métastatique au cours des prochaines années, un modèle est créé pour ce travail en intégrant un certain nombre de paramètres décrits ci-dessous. Le modèle dans ce travail est statique et évalue les coûts du cancer du poumon en un an pour la population incidente. Cela signifie que le modèle porte sur le nombre de patients dans une ligne thérapeutique particulière avec un traitement particulier sans tenir compte de son évolution dans le temps ou de sa voie thérapeutique. L'objectif ici est de formuler des hypothèses sur l'évolution de la prise en charge du cancer broncho-pulmonaire en fonction de l'évolution du marché. Les hypothèses sont formulées à 5 ans, donc pour l'année 2022.

Les principales hypothèses de ce modèle sont les suivantes :

- Les patients sont classés par histologie et mutation ou translocation existante,
- Un taux de mortalité identique est appliqué à tous les patients du modèle,
- Les patients sont évalués de manière statique, à un instant donné,
- Pour les événements indésirables, un coût global est appliqué à tous les patients traités par le même traitement afin de simplifier le modèle,
- Il est supposé que tous les patients soient pris en charge dans le cadre de leur maladie à long terme (ALD).

- Les algorithmes de prise en charge sont formulés en fonction des résultats disponibles et en supposant que les études de phase III actuellement en cours atteindront leurs objectifs principaux.

Les coûts pris en compte dans le modèle sont des coûts directs médicaux conformément aux recommandations de la HAS (12).

Les coûts inclus dans le modèle sont les suivants et les références qui les suivent sont les sources des données brutes. Les coûts généraux ont ensuite été adaptés à la population et la méthodologie est détaillée dans la partie Primary Analysis:

- Les coûts liés à la consultation (13,14),
- Les coûts liés au testing (13–15),
- Les coûts liés aux transports sanitaires (14,17),
- Les coûts liés à l’acquisition des traitements sont basés selon les tarifs de l’Assurance Maladie (14),
- Les coûts liés à l’administration du traitement (14,18),
- Les coûts liés au suivi spécifique pour chaque traitement (14,16,19,20),
- Les coûts liés aux événements indésirables (14,21),
- Les coûts liés à l’hospitalisation pour soins palliatifs (14,19,21,22),

Tous ces coûts sont calculés par cycle et ensuite rapportés au mois ou bien à l’année.

2.2 *Analyse Secondaire - Etudes de Sensibilité*

Afin d'évaluer de manière critique les résultats qui ont été formulés à partir d'hypothèses, une analyse de sensibilité a été conduite en deux parties.

2.2.1 *Analyse de sensibilité sur le résultat global : hypothèses d'évolution des coûts*

La première partie porte sur l'analyse et la variation des résultats dans leur globalité. Les valeurs en ce qui concernent les différents coûts ont été reportés à l'identique entre 2017 et 2022. Ainsi, l'analyse primaire laisse à penser que les coûts sont identiques entre 2017 et 2022 ce qui est peu probable. Avec l'évolution de la prise en charge et avec le temps, les coûts auront plutôt tendance à aller à la baisse. L'analyse primaire de 2022 est donc surestimée par rapport aux coûts probables réels. Ainsi une pondération de chaque poste de dépense a été effectuée en tenant compte des potentielles baisses de prix, que ce soit par réévaluation ou bien par l'entrée des génériques sur le marché pour ce qui est des coûts d'acquisition, mais aussi de l'évolution des techniques et de la prise en charge pour ce qui est des autres postes de dépenses.

Lors de cette première analyse de sensibilité, les paramètres ont été modifiés avec 2 amplitudes pour obtenir au final 3 hypothèses de base pour 2022, une première hypothèse, celle de l'analyse de base qui est surestimée, c'est l'hypothèse maximale ; une seconde hypothèse avec une variation moyenne des prix à la baisse, qui correspond à l'hypothèse moyenne et enfin une troisième hypothèse avec une variation à la baisse des prix plus importante, celle-ci correspond à

l'hypothèse minimale. Les taux de variations pour les hypothèses moyenne et minimale par rapport à l'hypothèse maximale sont résumés dans les Tableau 1 et Tableau 2. Ces taux de variations ont été choisis en fonction des impacts monétaires pressentis en fonction des coûts actuels, des arrivées des concurrents sur le marché ou bien de la perte d'exclusivité de certains traitements (génériques).

Généralement, lors d'une évaluation médico-économique, une actualisation des coûts est réalisée afin d'évaluer plusieurs stratégies thérapeutiques qui n'auraient pas le même horizon temporel et pour ne pas favoriser une stratégie thérapeutique par rapport à une autre (3). C'est le cas par exemple d'un traitement oral journalier à vie versus une chirurgie avec un effet bénéfique à vie. Si l'on compare les traitements sur 1 année, le coût global sera en défaveur de la chirurgie qui a un effet bénéfique qui s'étale pourtant sur plus d'une année. Il faut donc de ce cas rapporter le bénéfice de la chirurgie à celui de la thérapie orale à un horizon temporel cohérent.

Pour ce qui est des thérapies dans le CBNPC avancés et métastatiques, les enjeux sont différents et les horizons temporels comparables, le cancer du poumon à ces stades ne présentant qu'un taux de survie à 5 ans très limité (inférieur à 5%) cf. partie Diagnostic. Le choix a donc été fait dans cette analyse de ne pas tenir compte de la durée du traitement et de considérer chaque traitement de manière comparable sur une prise en charge annuelle ou mensuelle.

Tableau 1. Taux de variation des coûts à la baisse des hypothèses minimale et moyenne par rapport à l'hypothèse maximale pour les coûts liés aux traitements (%)

	Chimiothérapie		Afatinib		Alectinib		Atezolizumab		Bévacizumab	
	Min %	Moy %	Min %	Moy %	Min %	Moy %	Min %	Moy %	Min %	Moy %
Coût d'acquisition	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%	50%	25%
Coût d'administration	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%
Coût de monitoring	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%
Coût des EIs	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%
	Brigatinib		Ceritinib		Crizotinib		Erlotinib		Gefitinib	
	Min %	Moy %	Min %	Moy %	Min %	Moy %	Min %	Moy %	Min %	Moy %
Coût d'acquisition	0%	0%	5%	2.5%	0%	0%	50%	25%	50%	25%
Coût d'administration	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%
Coût de monitoring	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%
Coût des EIs	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%
Alectinib	Lorlatinib		Nivolumab		Osimertinib		Pembrolizumab		Pemetrexed	
	Min %	Moy %	Min %	Moy %	Min %	Moy %	Min %	Moy %	Min %	Moy %
Coût d'acquisition	0%	0%	5%	2.5%	5%	2.5%	5%	2.5%	10%	5%
Coût d'administration	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%
Coût de monitoring	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%
Coût des EIs	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%

Tableau 2. Taux de variation des coûts à la baisse des hypothèses minimale et moyenne par rapport à l'hypothèse maximale pour les autres coûts de prise en charge (%)

	Min %	Moy %
Coûts de consultation	10%	5%
Coûts des soins palliatifs	10%	5%
Coûts du testing	10%	5%
Coûts du transport sanitaire	10%	5%

2.2.2 Analyse de sensibilité sur l'influence de chaque paramètre sur l'hypothèse globale

Chaque poste de dépense influence de manière autonome le coût total de la prise en charge moyenne du CBNPC avancé ou métastatique. L'objectif de cette deuxième partie est donc d'analyser comment chaque paramètre influence indépendamment des autres sur le coût total et de déterminer quels paramètres ont le plus d'influence sur la prise en charge et le coût global de la pathologie. Pour cela, chaque poste de dépense a été varié de plus ou moins 2,5% jusqu'à plus ou moins 50%. Les variations ont été rapportées en coût par mois par patient. En ce qui concerne les coûts liés au traitement, ceux-ci ont été tout d'abord analysés de manière globale par traitement (cela représente le coût total de chaque traitement en intégrant le coût d'acquisition, les coûts de gestion des effets indésirables, etc...) puis séparément pour chaque poste de dépenses liés aux traitements (ex. impact des différents traitements en fonction du coût d'acquisition).

3. Résultats

L'ensemble des hypothèses de populations, de prise en charge et des résultats de l'analyse primaire et secondaire sont réunies en annexe :

- *Annex 5. Study population evolution until 2022*
- *Annex 6. Algorithm of NSCLC IIIB/IV treatment in 2017 (%)*
- *Annex 7. Algorithm of NSCLC IIIB/IV treatment in 2017 (number of patients)*
- *Annex 8. Algorithm of NSCLC IIIB/IV treatment in 2022 (%)*
- *Annex 9. Algorithm of NSCLC IIIB/IV treatment in 2022 (number of patients)*
- *Annex 10. Analysis of costs in stage IIIB/IV NSCLC per treatment and for other costs for 2017 and 2022*
- *Annex 11. Hypothesis 2022 for costs in stage IIIB/IV NSCLC per treatment and for other costs*
- *Annex 12. Evolution of the total cost per patients per month when modifying each other costs from 0% to 50%: price variation comparing to med hypothesis*
- *Annex 13. Evolution of the total cost per patients per month when modifying treatment costs from 0% to 50%: price variation comparing to med hypothesis*
- *Annex 14. Evolution of the total cost per patients per month when modifying acquisition costs from 0% to 50%: price variation comparing to med hypothesis*
- *Annex 15. Evolution of the total cost per patients per month when modifying administration costs from 0% to 50%: price variation comparing to med hypothesis*

- *Annex 16. Evolution of the total cost per patients per month when modifying monitoring costs from 0% to 50%: price variation comparing to med hypothesis*
- *Annex 17. Evolution of the total cost per patients per month when modifying Adverse Events costs from 0% to 50%: price variation comparing to med hypothesis*

3.1 Analyse Primaire

Les résultats suivants représentent tout d'abord un état des lieux du marché actuel (Cf. Tableau 3). Le coût mensuel total en 2017 par patient s'élève à environ €4,400. Si seul le coût du traitement (intégrant le coût d'acquisition, d'administration, de monitoring et de gestion des effets indésirables) est pris en compte, le coût moyen par mois par patient s'élève à environ €4,000 et représente à lui seul 93.19% des coûts médicaux de la prise en charge des patients. Une étude menée en France entre 1998 et 2001 a démontré que le coût moyen annuel par patient du CBNPC, tout stade, était d'environ €23,300 soit €2,000 par patient par mois (23). Ces résultats sont cohérents avec l'évolution du paysage thérapeutique, et l'arrivée des thérapies ciblées mais également de nivolumab et pembrolizumab. De plus il est important de rappeler que ce travail n'inclut que les cancers bronchiques non à petites cellules avancés et métastatiques ce qui n'est pas le cas l'étude de *Chouaid et al.* qui évalue l'ensemble du CBNPC et CBPC à tous stades. Cette différence influence à la hausse le coût moyen de la prise en charge.

Tableau 3. Tableau récapitulatif des coûts annuels et mensuels engagés dans le CBNPC avancés ou métastatiques en France (*Annex 10*)

	2017	2022
<i>Coûts totaux de tous les traitements par an</i>	€ 1,519,258,196.50	€ 2,467,454,940.56
<i>Coûts de consultation par mois</i>	€ 961,178.40	€ 1,053,380.16
<i>Coûts des soins palliatifs par an</i>	€ 104,636,220.00	€ 98,301,548.00
<i>Coûts du testing par mois</i>	€ 2,723,338.80	€ 3,277,182.72

<i>Coûts du transport sanitaire par mois</i>	€ 2,278,030.95	€ 2,496,552.78
TOTAL PAR MOIS	€ 141,287,082.86	€ 220,640,156.37
TOTAL PAR AN	€ 1,695,444,994.30	€ 2,647,681,876.48
TOTAL PAR MOIS PAS PATIENT	€ 4,445.09	€ 6,334.05
TOTAL PAR AN PAR PATIENT	€ 53,341.04	€ 76,008.55

Les “autres coûts médicaux”, intégrant les coûts de consultation, les coûts des soins palliatifs, les coûts de testing ainsi que les coûts du transport sanitaire n’influencent finalement que peu le coût total de prise en charge, que ce soit en 2017 ou en 2022, ne représentant tous ensemble respectivement que 10% et 7% du coût total de prise en charge.

Si les coûts médicaux totaux de 2017 et 2022 de cette première analyse sont comparés, une évolution d’environ €1,900 est constatée en 5 ans, soit un peu plus de 42% d’augmentation.

Cette première analyse est cependant à interpréter avec prudence, les coûts généraux étant conservés dans le même état qu’en 2017. Hors, il est peu probable que les coûts actuels restent les mêmes pour les traitements actuellement sur le marché, l’arrivée de certains génériques tirant à la baisse le prix de certains traitements et des réévaluations possibles par le CEPS peuvent également influencer les prix à la baisse. Dans une moindre mesure, les autres coûts médicaux peuvent également être diminués dus à une meilleure connaissance des techniques mais également une optimisation des coûts. Ceci ne se révélera pas forcément vrai à horizon plus lointain pour, par exemple, les coûts du testing pouvant augmenter ou bien être plus facilement intégré dans le remboursement par l’assurance maladie. Ainsi cette première analyse, basée sur une population fictive mais avec des coûts réels actuels est surestimée.

Une analyse secondaire de sensibilité avec une actualisation des coûts à horizon à 5 ans permettra d'obtenir un coût total plus cohérent avec ce qui pourrait être attendu. C'est l'objet de cette deuxième partie des résultats qui est détaillée dans la partie suivante.

3.2 Analyse Secondaire - Etudes de Sensibilité

3.2.1 Analyse de sensibilité sur le résultat global : hypothèses d'évolution des coûts

L'hypothèse d'évolution des coûts permet d'éviter les biais de comparaison lorsque les coûts d'un même facteur sont évalués à des horizons temporels différents, ici 2017 et 2022. L'imputation des différentes variations de coûts est détaillée dans la partie Analyse Secondaire - Etudes de Sensibilité . Le Tableau 4 résume les données des hypothèses minimale, moyenne et maximale. L'hypothèse maximale correspond à l'hypothèse formulée dans la première partie de l'analyse de sensibilité pour les raisons décrites plus haut (Analyse de sensibilité sur le résultat global : hypothèses d'évolution des coûts). L'hypothèse moyenne correspond à l'analyse la plus réaliste pour 2022 (les coûts ont été ajustées pour 2022 qui ne correspondent plus aux coûts en 2017) et c'est de cette hypothèse que seront menées les analyses de la deuxième partie de l'étude de sensibilité.

Tableau 4. Tableau récapitulatif des hypothèses de coûts engagés dans le CBNPC avancés ou métastatiques en France (Annex 11)

	min	moy	max
<i>Coûts totaux tous les traitements par an</i>	€ 2,121,966,611.83	€ 2,225,802,183.17	€ 2,467,454,940.56
<i>Coûts de consultation par mois</i>	€ 948,042.14	€ 1,000,711.15	€ 1,053,380.16
<i>Coûts des soins palliatifs par an</i>	€ 88,471,393.20	€ 93,386,470.60	€ 98,301,548.00
<i>Coûts du testing par mois</i>	€ 2,686,119.41	€ 3,113,323.58	€ 3,277,182.72
<i>Coûts du transport sanitaire par mois</i>	€ 2,246,897.50	€ 2,371,725.14	€ 2,496,552.78

TOTAL PAR MOIS	€ 190,084,226.14	€ 199,751,481.02	€ 220,640,156.37
TOTAL PAR AN	€ 2,281,010,713.68	€ 2,397,017,772.30	€ 2,647,681,876.48
TOTAL PAR MOIS PAS PATIENT	€ 5,456.86	€ 5,734.38	€ 6,334.05
TOTAL PAR AN PAR PATIENT	€ 65,482.31	€ 68,812.59	€ 76,008.55

Si les nouvelles hypothèses de 2022 sont comparées à l'analyse de 2017, il est constaté une évolution du coût par patient de 29% et 23% pour les hypothèses moyenne et minimale respectivement. Pour l'hypothèse moyenne, cela représente un coût de près de €1,290 par patient par mois. Avec ce nouvel ajustement, le coût imputé par les thérapies représente 92.86% des coûts totaux médicaux de cette étude, ce qui ne change pas l'ordre de grandeur de l'impact des thérapies dans la prise en charge des patients CBNPC avancés ou métastatiques. Ainsi le plus grand poste de dépense de prise en charge médicale reste le coût de la thérapie utilisée et notamment les coûts d'acquisition des traitements représentent à eux seuls 65,50% de la prise en charge médicale.

Tous les patients n'étant pas sous les mêmes thérapies ou combinaison de thérapies, certains traitements onéreux ne sont donnés qu'à un nombre limité de patient. Ainsi si l'on regarde uniquement la notion de coût du traitement, l'analyse est erronée car la population est différente pour chaque traitement. L'objectif de l'analyse secondaire de sensibilité est de connaître quelle thérapie impacte le plus la prise en charge globale des patients CBNPC mais également de déterminer quel poste de dépense pour chaque traitement est celui qui influence le plus les coûts médicaux totaux. Tout cela est réalisé en considérant la population spécifique de chacun des

traitements. L'analyse a également été réalisée sur les autres coûts médicaux (c'est-à-dire les coûts hors traitements).

3.2.2 Analyse de sensibilité sur l'influence de chaque paramètre sur l'hypothèse globale

Les traitements qui impactent le plus la prise en charge du CBNPC IIIB/IV sont pembrolizumab et atezolizumab suivi par la chimiothérapie et nivolumab (Cf. Figure 1). Dans chacun des graphiques qui suivent dans l'analyse de sensibilité, chaque barre correspond à un taux de variation du coût total de la prise en charge du CBNPC stade IIIB/IV par patient et par mois. La barre la plus grande correspond à l'impact sur le cout total d'une variation de plus ou moins 50% du prix du traitement considéré. Les plus petites barres correspondent a des variations moindre du cout du traitement (40%, 30%, 25%, 20%, 15%, 10%, 5%, 3%). Les chiffres détaillés de chacun des graphiques sont intégrés dans les annexes. (A partir d'Annex 12)

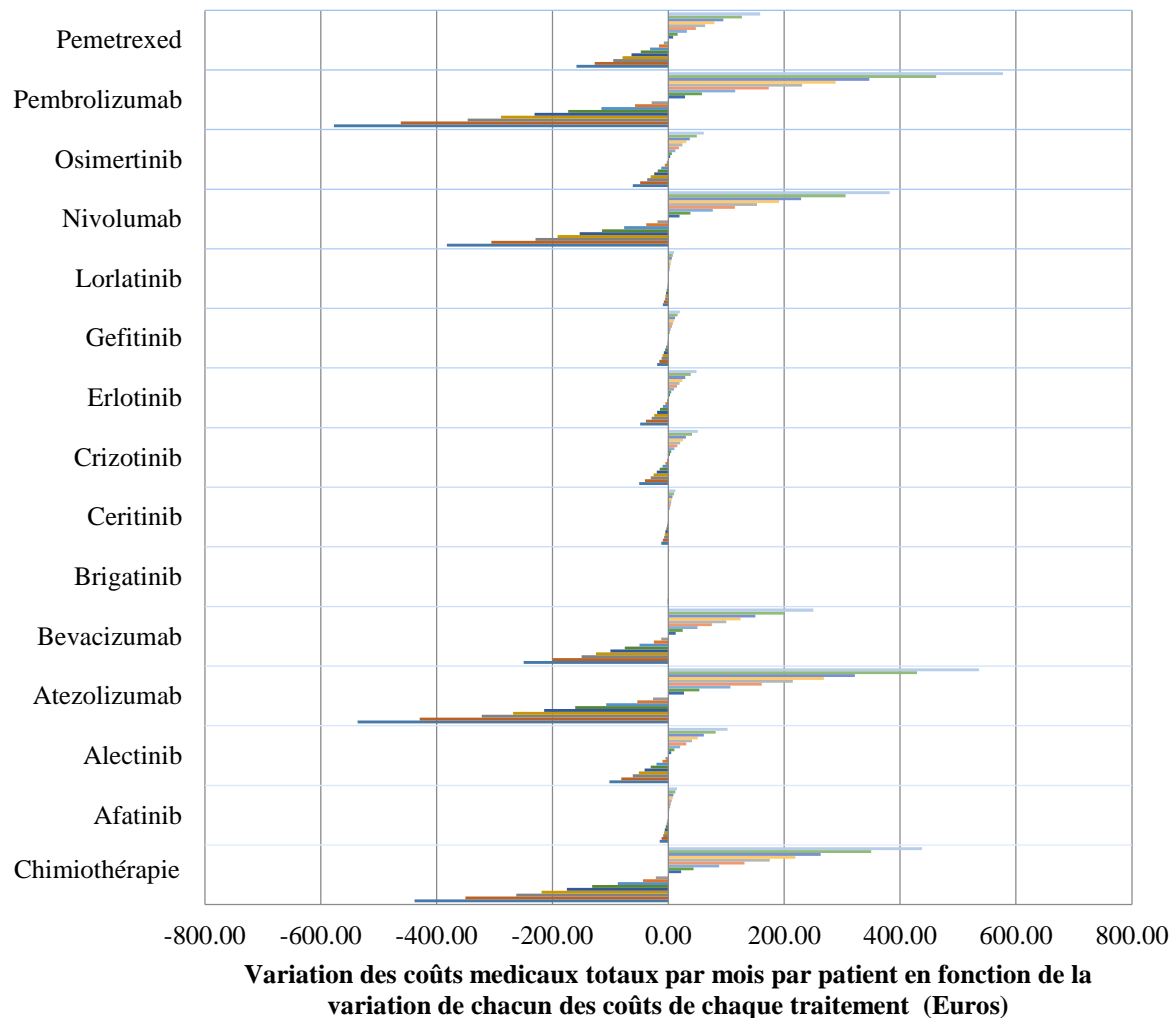


Figure 1. Analyse de sensibilité de l'impact des coûts totaux des thérapies sur les coûts médicaux totaux du CBNPC IIIB/IV en France en 2022 (Annex 13)

Lorsque l'on regarde plus en détail les traitements et que l'on s'intéresse à l'impact des différents postes de dépenses, concernant les coûts d'acquisition, les immunothérapies pembrolizumab en premier lieu, atezolizumab et nivolumab arrivent en tête de liste des traitements pour lesquels le coût d'acquisition impacte fortement le coût total de prise en charge (Cf. Figure 2). Cela s'explique en grande partie par, effectivement, un coût d'acquisition élevé mais également

une population importante (6043 patients, 6110 patients et 4776 patients respectivement). D’après les hypothèses, une variation de 10% du prix de pembrolizumab change de 1,75% le coût total de prise en charge. La chimiothérapie reste tout de même le quatrième traitement dont le coût impact de manière importante le coût total de prise en charge du CBNPC IIIB/IV ayant pourtant un coût d’acquisition d’environ €650, donc bien inférieur à celui des immunothérapies mais une population hypothétique encore très importante en 2022 (près de 23,700 patients). Ainsi une variation de 10% du prix de la chimiothérapie fait varier de 0.74% le coût total de prise en charge.

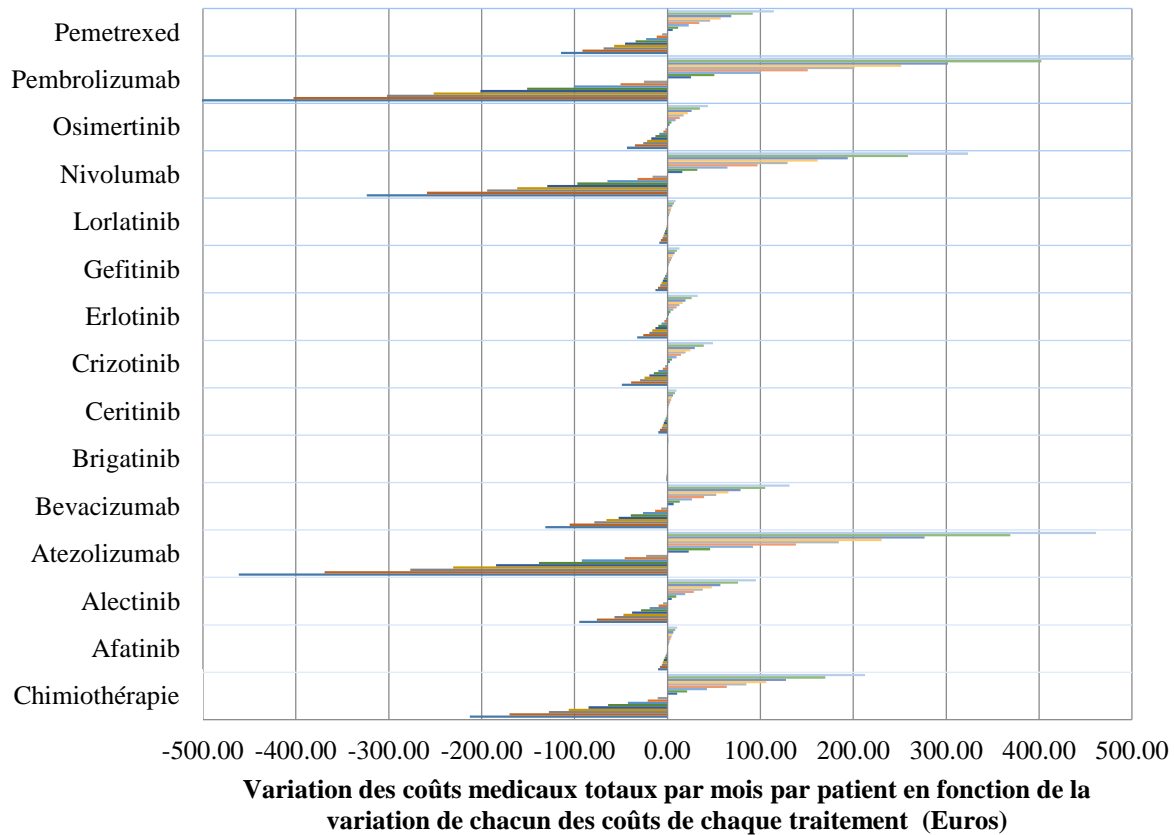


Figure 2. Analyse de sensibilité de l’impact des coûts d’acquisition des thérapies sur les coûts médicaux totaux du CBNPC IIIB/IV en France en 2022 (Annex 14)

Les coûts d'administration sont bien évidemment induits par les thérapies qui requièrent une hospitalisation temporaire avec perfusion (chimiothérapies et immunothérapies). Les autres traitements, étant administrés par voie orale, ne présentent pas de coûts supplémentaires d'administration. Pour ce qui concerne les chimiothérapies et les immunothérapies, les variations des coûts d'administration ne représentent qu'une faible partie des coûts médicaux totaux (Cf. Figure 3). Une variation de 50% des coûts d'administration de la chimiothérapie, thérapie qui a le coût d'administration le plus important, ne représente qu'une variation de 2% des coûts médicaux totaux. Or une diminution des coûts d'administration de 50% en 5 ans est peu probable.

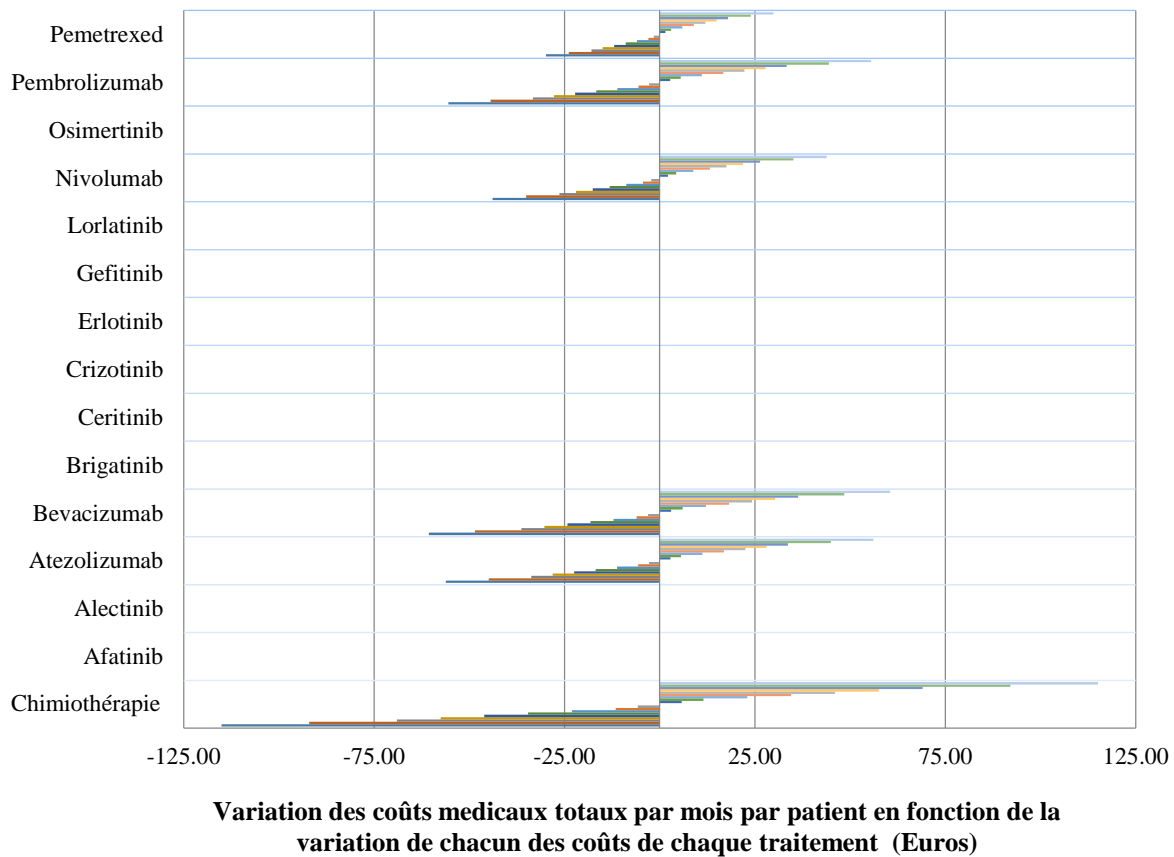


Figure 3. Analyse de sensibilité de l'impact des coûts d'administration des thérapies sur les coûts médicaux totaux du CBNPC IIIB/IV en France en 2022 (Annex 15)

Concernant les coûts de monitoring, il est constaté, avec les hypothèses, que même une variation importante des coûts, n'impacte que de peu les coûts médicaux totaux. Par exemple, une variation de 50% de chacun des postes de dépenses impactera de moins de €30 le coût total de €5,734.38 (0,5%) (Cf. Figure 4). Ce poste de dépense à lui seul n'impacte donc pas de manière importante les coûts médicaux totaux.

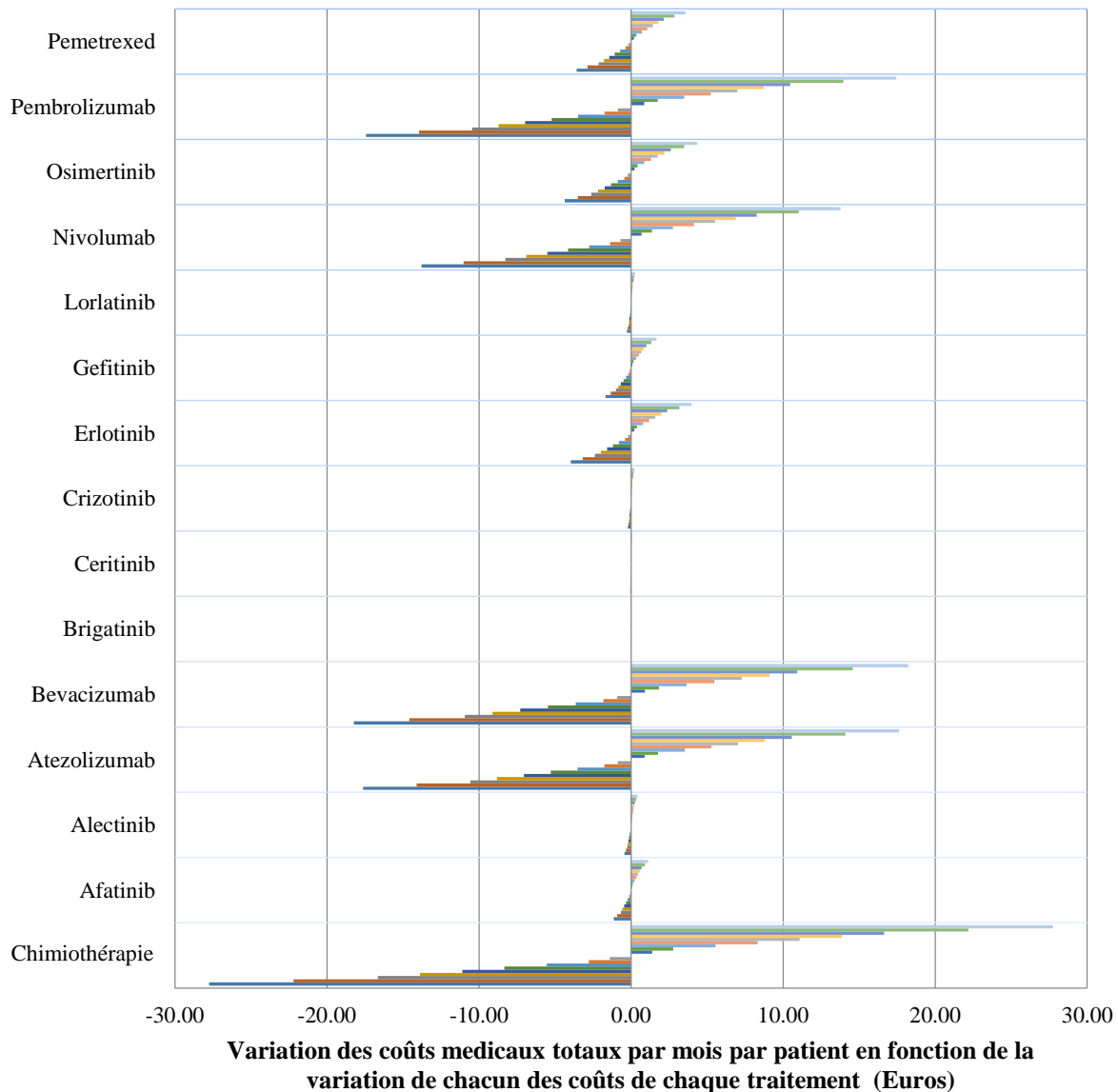


Figure 4. Analyse de sensibilité de l'impact des coûts de monitoring des thérapies sur les coûts médicaux totaux du CBNPC IIIB/IV en France en 2022 (Annex 16)

Le poste de dépense lié à la gestion des effets indésirables est essentiellement impacté par les chimiothérapies et le bévacizumab. Mais ces coûts impactent également que peu les coûts totaux médicaux (Cf. Figure 5).

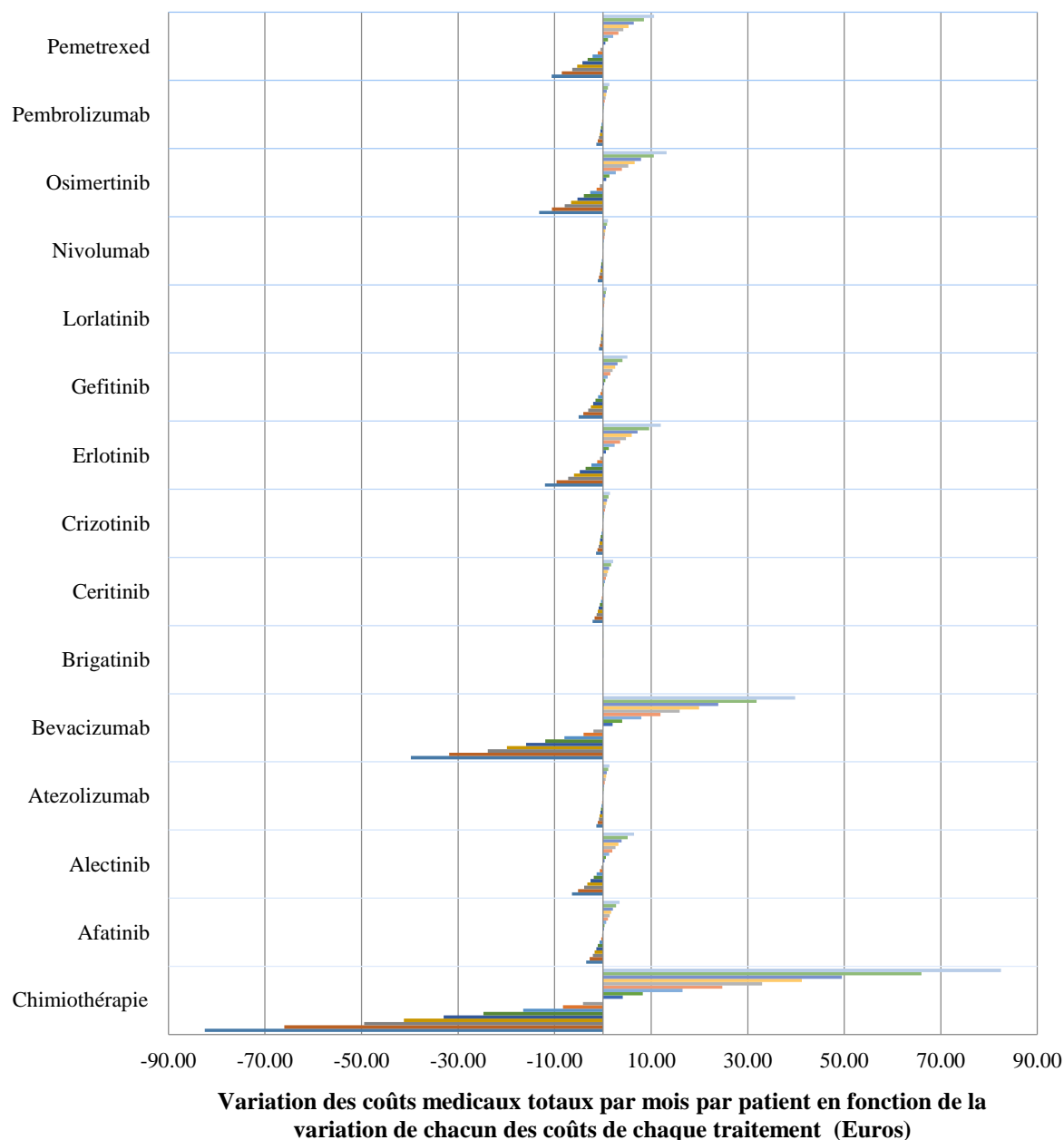


Figure 5. Analyse de sensibilité de l'impact des coûts des effets indésirables des thérapies sur les coûts médicaux totaux du CBNPC IIIB/IV en France en 2022 (Annex 17)

Lorsque l'on s'intéresse de plus près aux autres coûts médicaux totaux, le poste de dépense qui impacte fortement la prise en charge totale du CBNPC IIIB/IV est celui qui correspond aux soins palliatifs. En effet ce poste de dépense influe autant sur les coûts car il correspond à une majorité de la population (en 2022, selon les hypothèses, environ 60% des patients auront recours à une hospitalisation pour soins palliatifs durant l'année). Ainsi une variation de 10% des coûts des soins palliatifs correspond à une variation de près de 4,7% des coûts totaux du CBNPC IIIB/IV (Cf. Figure 6 et Annex 12). C'est le poste de dépense qui impacte le plus la prise en charge, devant le coût des thérapies. Ainsi une optimisation des coûts des soins palliatifs pourrait améliorer fortement le budget total de prise en charge du CBNPC IIIB/IV. Si l'on regarde cette diminution de 10%, cela correspond à une variation d'environ €268 par patient et par mois, soit une économie potentielle de €112 millions par an. Les coûts médicaux liés au transport, au testing et à la consultation impactent pour leur part d'une manière bien plus faible les coûts totaux. (Cf. Figure 6)

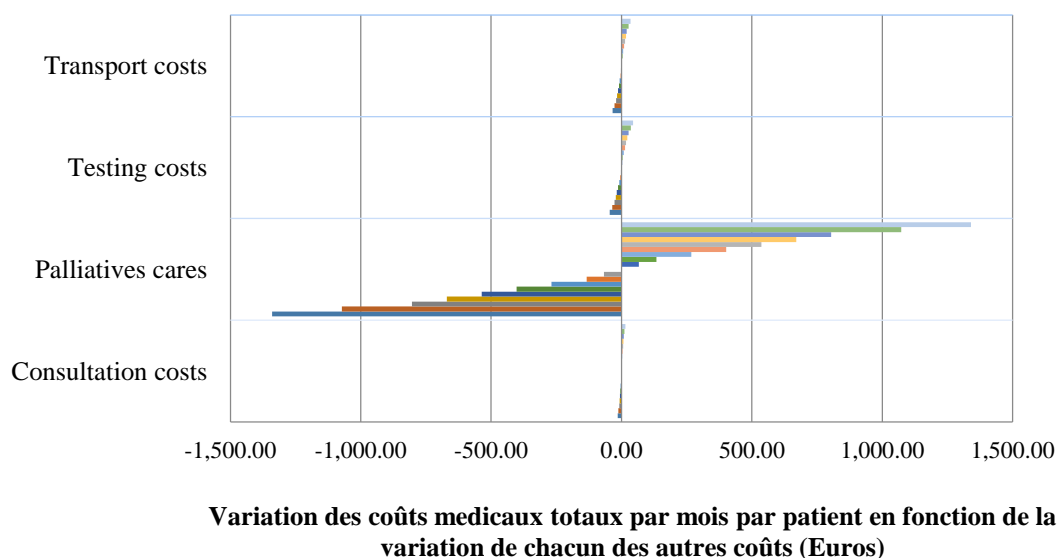


Figure 6. Analyse de sensibilité de l'impact des autres coûts médicaux sur les coûts médicaux totaux du CBNPC IIIB/IV en France en 2022 (Annex 12)

4. Discussion

Dans cette étude, nous avons vu que les coûts engendrés par les soins palliatifs et les coûts d'acquisition des thérapies sont les postes de dépenses qui impactent le plus la prise en charge du CBNPC IIIB/IV. Les traitements qui impactent le plus la prise en charge du CBNPC IIIB/IV sont essentiellement les immunothérapies pembrolizumab et atezolizumab suivi par la chimiothérapie et nivolumab.

L'ensemble de ces résultats ont pour objectif de présenter l'impact des évolutions des coûts sur les dépenses de santé pour la prise en charge du cancer du poumon CBNPC Stade IIIB/IV. Seuls les résultats pour 2017 sont des résultats avec des données réelles. L'ensemble du reste des résultats est basé sur des hypothèses de résultats cliniques (supposés positifs pour les études actuellement en phase III et qui n'ont pas encore de résultats). Des hypothèses de prescription par les médecins sont également incluses avec les choix des molécules au sein d'une même classe (TKI, anti-PD1, etc..), le choix de l'utilisation d'une monothérapie ou bien de la prescription d'une combinaison. Les évolutions des coûts sont également basées sur des hypothèses formulées selon l'histoire connue pour des cas similaires. L'ensemble de ces hypothèses apportent des biais au niveau de l'analyse des chiffres pour l'analyse primaire. Premièrement un biais de sélection qui implique que les patients seraient mal sélectionnés (hypothèse de projection de la population erronée) et mal répartis dans les différents groupes de traitements. D'un autre côté, le biais au niveau des coûts avec une potentielle sur- ou sous-estimation de ceux-ci (nouveaux prix, ajustement des prix, entrée des génériques sur le marché, etc..)

C'est pour s'affranchir au maximum de ces biais que l'analyse de sensibilité a été conduite. Tout d'abord avec une première partie qui permet de comparer trois hypothèses générales (minimale, moyenne et maximale). La première partie de l'analyse de sensibilité porte sur les résultats dans leur globalité. L'ensemble des coûts ont été reportés à l'identique entre 2017 et 2022. Une pondération de chaque poste de dépense a été effectuée en tenant compte des potentielles baisses de prix, que ce soit par réévaluation ou bien par l'entrée des génériques sur le marché pour ce qui est des coûts d'acquisition, mais aussi de l'évolution des techniques et de la prise en charge pour ce qui est des autres postes de dépenses.

La deuxième partie de l'analyse cible quant à elle chaque poste de dépense et leur influence sur le coût total de la prise en charge moyenne du CBNPC avancé ou métastatique. Cette partie de l'analyse permet de pondérer l'impact en s'affranchissant des chiffres grâce notamment aux graphiques qui montrent quel poste de dépenses a l'impact le plus important sur la prise en charge globale.

L'objectif de cette étude était donc d'avoir une vision du coût global du CBNPC stade IIIB/IV en 2022 mais dans l'état actuel de nos connaissances. En effet, les connaissances sur les immunothérapies n'en sont qu'à leur début et plusieurs points concernant leurs utilisations sont encore à étudier. Parmi ces points, certains sont détaillés ci-dessous.

La dose et la fréquence d'utilisation des immunothérapies ne sont à ce jour pas encore clairement connues. La question se pose donc actuellement sur l'utilisation d'une dose fixe ou variable mais également sur l'espacement de chaque injection et de leur impact sur la réponse du

patient. En effet, certaines immunothérapies sont commercialisées à doses variables et d'autres à doses fixes. Le laboratoire MSD qui commercialise pembrolizumab a lancé son programme de recherche avec une dose variable, en mg/kg, mais revoit celui-ci dans ses nouvelles études et soumet actuellement aux autorités sanitaires un dossier de modification visant à transformer l'utilisation du pembrolizumab 2 mg/kg en dose fixe à 200 mg par injection. Pour ce qui concerne la fréquence d'injection, le laboratoire BMS est en train de comparer l'impact d'une injection toutes les 2 semaines ou toutes les 4 semaines sur l'efficacité de son immunothérapie. Ces modifications pourraient impacter les coûts de prise en charge pour l'assurance maladie sans causer de perte de bénéfice clinique pour le patient.

La durée d'utilisation des immunothérapies est également challengée. Les laboratoires MSD et BMS ont lancé des études comparant l'utilisation continue de l'immunothérapie jusqu'à progression de la maladie versus une utilisation à durée fixe. Le laboratoire MSD est même allé plus loin en l'intégrant dans les critères de réponses dans ses études pivotales en traitant les patients jusqu'à progression de la maladie ou 2 ans après le début de l'immunothérapie.

L'évaluation de la réponse au traitement est encore actuellement questionnée. En effet, certains experts commencent à s'interroger sur la notion d'évaluation de la progression à l'aide de critères RECIST reposant uniquement sur des critères radiologiques, tandis que les patients continuent à en tirer un bénéfice clinique. La nouvelle évaluation et les nouvelles études tendent à l'appréciation de la réponse au traitement par l'évaluation du bénéfice clinique et non seulement radiologique. Cela pourrait changer la durée des traitements et donc impacter les coûts médicaux.

Au niveau du séquençage des thérapies, le problème du re-challenge peut également être discuté. Le retraitement avec une molécule qui a la même cible moléculaire, n'est pas vraiment développée actuellement dans les essais cliniques. Lorsqu'un patient progresse sous un traitement, le changement de classe de traitement est le plus souvent utilisé. Si les patients bénéficient d'une immunothérapie de première intention, l'arsenal thérapeutique en cas de non-réponse ou rechute du patient après ce traitement est très limité. La question de la séquence thérapeutique est donc importante et reste un défi pour les cliniciens afin d'assurer la survie la plus longue dans les conditions les plus favorables pour les patients.

Les réponses des patients aux immunothérapies ne sont pas toujours bien connues ni prédites. Tous les patients ne répondent pas forcément de la même manière aux immunothérapies et certains présentent des réponses atypiques. Cela commence à être décrit par l'étude de certains cas cliniques avec des cas de patients hyper-progressifs (14–16) et des cas de patients pseudo-progressifs par exemple (bien observés dans le cas de mélanome notamment) (18–21). Il n'est actuellement pas possible de prédire ce type de réaction avant l'introduction du traitement. La découverte de biomarqueurs permettant de prédire l'efficacité mais également la tolérance des immunothérapies représente un potentiel important pour l'évolution de la prise en charge des patients et permettrait de tendre vers une médecine plus adaptée au patient, une médecine personnalisée.

Le gouvernement travaille sur la loi de financement de la sécurité sociale effective depuis 2018 (LFSS 2018 - Loi sur le financement de la sécurité sociale) afin de trouver des solutions pour améliorer le système actuel de santé. Certains laboratoires pharmaceutiques commencent à

proposer des initiatives concernant le modèle de remboursement. C'est le cas, par exemple, du laboratoire ROCHE avec son initiative PRM (Personalized Reimbursement Medicine), un système offrant un remboursement adapté aux différents critères de patients et aux bénéfices qu'ils peuvent obtenir.

L'on peut imaginer un système de prise en charge à 100% du traitement par l'assurance maladie pour les patients bénéficiant de meilleures réponses, par rapport aux patients qui bénéficierait d'un avantage plus limité du traitement. Les frais d' « efficacité limitée » seraient imputés au laboratoire. Ainsi, le remboursement s'adapterait aux réponses des patients. Ce type de proposition représente un projet de financement très complexe, car spécifique à chacun et potentiellement difficilement applicable.

L'objectif de l'État est essentiellement d'optimiser le financement des thérapies dans un contexte d'enveloppe monétaire limitée. Il est indéniable que le coût des traitements augmente avec l'évolution des connaissances sur la biologie, l'ingénierie de ces molécules biologiques mais aussi l'arrivée de la médecine personnalisée. L'éthique de notre profession de santé ne peut nous amener à limiter dans un objectif purement économique l'accès à des thérapeutiques innovantes. Le système de santé ne peut pas se réguler lui-même et nécessite une surveillance de chaque partenaire. Un système de santé durable est donc possible, mais le système actuel semble montrer des limites à long terme. Chaque acteur a donc un rôle clé à jouer pour assurer une gestion efficace et éthique des dépenses de santé.

Développement de la Thèse en Anglais

1. Introduction

During the last decades, despite of therapeutic evolutions and prevention, the lung cancer stills nowadays a widespread disease with a poor prognosis at 5 years. With numbers of discoveries in the domain of genomics and therapeutic in the last 10 years, a change of paradigm leads to a new opportunities and possibilities to support lung cancer: the personalized medicine.

The French healthcare system offers a single public payer financing model: the Statutory Health Insurance (SHI; Assurance Maladie). This system avoids a high Out-of-Pocket (OOP) for the population and tries to ensure a most egalitarian healthcare system smoothing differences (social, territorial, etc.). This model can show limitation when considering new treatments and therapeutic costs evolution as the SHI fund has not unlimited resources. One of the concerns is how to maintain a sustainable and equalitarian healthcare system?

In France, lung cancer is classified as a long-term affection (ALD; Affection Longue Durée). This pathology is hundred percent supported by the SHI. In this context of public financing with limited resources, treatment and diagnostics methods leaded by the personalized medicine increased considerably the price of lung cancer support. This problematic carries to the notion of fair price determination and the fair financing in order to preserve an ethical and egalitarian healthcare system. The objective of this work is to understand evolutions in lung cancer and actual costs of the disease in order to identify checkpoints, discuss about financing model and management to keep a sustainable healthcare system integrating the medical innovation for the country.

2. History and General Knowledges

2.1 *The Challenges of Drug Financing System and Market Access*

2.1.1 *French Health Care System Story*

Evolution

The actual French Healthcare model results in a mix between Bismarck model which preach a collective social protection inspired from the German health system and a Beveridge model based on single public payer model with a social security system inspired from the United Kingdom health system. This system leads to high medical care utilization with limited OOP costs for the French population. Financing health care comes essentially from tax-based revenue of employer, employee and retiree contributions (28).

The Bismarck model is the oldest social protection system (29) created by Chancellor Otto von Bismarck (1815-1898) in Germany in the 1880's. It established the obligation of health insurance coverage only with labor incomes by employees and companies financing. The Bismarck model offers an important pluralism for health offer with public and private possibilities, but the financing is instable with variations regarding the repartition between employee portion and company portion. Each part being treated separately, health costs can be impacted with different proportion following the decisions taken. This lead to some variation in the purchasing power for employees and benefits for industrials.

In this model, there is essentially an economic decentralization with competition between different insurances thanks to a plurality system (prices negotiation, reimbursement rates variation, etc.) (30).

The Beveridge model is characterized as a national model with public financing. It has appeared later than the Bismarck model with Lord William Beveridge (1879-1963), an English politician and economist, during the Second World War. Lord Beveridge has written the Report to the Parliament on Social Insurance and Allied Services for the United Kingdom Government (31) to develop a mandatory fee system for all the population and cover health costs. Nationalization of all health facilities, in 1948, by the creation of the National Health Service (NHS) provides free healthcare to the entire population (30). This organization leads to a poor plurality of the health offer with national monopoly although tax financing ensures a better homogeneity than Bismarck model in financing costs of health by a general tax (See Table 5).

Table 5. Comparison of Bismarck and Beveridge model

	Bismarck model	Beveridge model
Objective	Health insurance model	National model
Gouvernance	Economic decentralization with organisms under public control	Economic centralization with State control
Financement	Employees and companies financing	Taxes
Health offer	Private and public plurality	Public monopoly

Historically, the actual Social Security System (32) was established after the Second World War by Pierre Laroque (1907-1997), president of the Social Security System during the General de Gaulle government (30). Prior to this, during the long period of the 30 glorious, the French society was living in a context of modernism and emerging spirit of egalitarianism in its multiple dimensions (social, financing, cultural and geographical) (25,26).

In this context, the ancestor of social security emerged in 1930 with a compulsory protection paid by employers for employees whose earning under a certain level. This old social insurance included 5 branches, mixing areas of the actual social security, including illness, maternity, disability, old age and death. This system had well evolved with a high coverage of the French population thanks to the management by association and organization leading in 1945 to the creation of the Social Security System (Ordinance n°45-2259 of October 4, 1945 on the organization of social security) (27,28).

The current system was deeply removed by the creation of structured and well-defined entities. The Social security becomes the institution which included four areas: health, worked-related illness and injuries, retirement and family (28).

SHI is the area of the Social Security System covering four branches of the health security known as disease, maternity, incapacity and death (20,25).

Organization

All the population is affiliated to different schemes of the SHI following the employment status ensuring no competition among different schemes. There are three mains schemes financing by national SHI fund and numerous of other specific which are independent for a minority of the

population financing respecting geographical distribution (for marines, miners, employees of the national railway company (SNCF; Société Nationale des Chemins de fer Français / RATP; Régie autonome des Transports Parisiens), the national bank, the clergy and notary, the National Assembly, people from the Alsace and Moselle regions, etc.) (Assurance Maladie - ameli.fr, 2012) (20,29).

- The general SHI scheme (CNAMTS; Caisse nationale d'assurance maladie des travailleurs salariés) covers employees in commerce and industry and their families, non-working people and also people eligible for CMU basic coverage (Couverture Maladie Universelle). Sixty million beneficiaries accounting for 90% of the population benefit from general SHI scheme.

The CMU Fund was created following the 1999 Universal Health Coverage Act (Act No.99-641 from July 27, 1999) in order to provide free public coverage for people with incomes below a certain level. The access of the CMU is not eligible for undocumented immigrants, however, for these latter who have lived in France for at least three months are eligible for free coverage under the State Medical Assistance (AME; aide médicale d'état) (28).

- The agricultural SHI fund (Mutualité Sociale Agricole) covers farmers and agricultural employees and their families (3.4 million beneficiaries, 5.1% of the population) (28).
- The SHI scheme for self-employed people (régime social des indépendants) covers artisans and self-employed people (4 million beneficiaries, 6% of the population) (28).

The 3 main schemes are represented by the National Union of Health Insurance Funds (UNCAM; Union Nationale des Caisses d'Assurance Maladie), instance created in August 2004 by the reform act of the SHI. Objectives of the UNCAM are to lead the convention politic, to define reimbursement policy and rates for healthcare. The director-general of UNCAM is also the director of CNAMTS, Mr. Nicolas Revel until 2014 (32).

The financing

Until 2003, the method of financing in hospitals was different according to their legal nature (public, private and private non-profit). Funding for public health facilities was done under a system called Global Endowment (DG; Dotation Globale) and according to the National Quantified Objective (OQN; Objectif Quantifié National) for private institutions (38).

The principle is that the share of expenses covered by the health insurance schemes is subject to a global allocation for the benefit of each institution and paid monthly by health insurance organizations. The amount of the allocation is revised every year according to the previous year's expenditure and according to the National Objectives of the Health Insurance Expenditure (ONDAM; Objectifs Nationaux des Dépenses de l'Assurance Maladie) (see Governance section) set according to the general economic assumptions (39). The overall allocation is a fixed envelope provided to health facilities, the distribution of expenses being managed by the institution itself. Unfortunately, the system was not optimal because it was not scalable and penalized hospitals with efficient management. Indeed, the overall endowment does not include changes in establishments in terms of type of activity, volume of activity but also the arrival of expensive molecules, the

budget being determined according to the previous year's expenditure. Establishments that have saved money and have effectively managed the allocated budget, are not favored the amount of the envelope being readjusted downward if it has not been fully used (39).

The financing system has been redesigned and modified to provide funding based on an estimate of activities and revenues: the Pricing Activity (T2A; Tarification à l'Activité). This system has been harmonized and is therefore a unique funding method for medicine, surgery and obstetrics (MCO; Médecine, Chirurgie, Obstétrique) activities. The price of each activity is set annually by the Minister of Health. The activities are divided into homogenous groups of stay (GHS; Groupe Homogène de Séjour) associated with a homogeneous group of patients (GHM; Groupe Homogène de Malades). The whole is classified in the Program of Medicalization of Information Systems (PMSI; Programme de Médicalisation de Systèmes d'Information). However, some expensive drugs and medical devices cannot be integrated in the GHS because they introduce a strong heterogeneity. These products can therefore be listed on a list in addition to the GHS; this list is limited and fixed by a decree. To integrate this list, products must meet a number of cumulative criteria:

- The product must be used mainly in the hospital
- The product must provide an important Rendering Medical Service (Service Medical Rendu; SMR) (see Market Access section)
- The product must have an Improvement of the Rendering Medical Service (Amélioration Service Medical Rendu; ASMR) higher than III (see Market Access section)
- The cost of the product must exceed 30% of the GHS package

Since 2014, after the social security financing law products are listed in addition to the GHS indication by indication to ensure better management of funding of molecules. Products added to

the list may be deleted when the re-evaluation of the SMR and ASMR by the National Authority for Health (HAS; Haute Autorité de Santé) no longer allows the product to fulfill the necessary criteria, when the price of the product has been sufficiently reduced to be included in the GHS or well when stopping marketing it (39) (40).

The governance

Policy and regulation of the health care system is ensured by the state with the government, the parliament, SHI and regional authorities. The government thanks to different reports purpose public health act and the annual social security finance act:

- The Auditor's Office report (Cours des comptes) is built in order to ensure the control of public funds regarding the use of it during the last years (35).
- The High Council for the Future of Health Insurance report (HCAMM; Haut conseil pour l'avenir de l'assurance maladie)
- The High Council for Public Health report (HCSP; Haut Conseil de la Santé Publique)
- The National Health Conference (Conférence National de Santé)

Studying these acts, the parliament vote for the government purposes and pass public health acts in order to control healthcare system and resources thanks to the ONDAM, which is the projected target spending for health insurance for the upcoming year, and also approved the revenue calculates regarding the employers, employees and other specific earmarked taxation calculate by the government. The first Public Health Act was passed in 2004 (Act n°2004–806 of August 9, 2004 on public health policy) and a new act was passed in 2016 in order to (Act n°2016-41 of January 26, 2016 for the modernization of the health system) (35).

Once acts passed, the Ministry of Health is responsible for the preparation and the implementation of the government policy (28).

Some reforms since 1995, regional institutions were created to build closer health policy decision-making respecting the national governance and national health expenditure objectives. The 2009 HPST acts to ensure high efficiency of this aspect and lead to a regional centralized healthcare authority named the ARS (Agences Régionales de Santé) (28).

The Health Ministry relies upon a number of health agencies and public bodies in the development and implementation of policies for which it is responsible: (28)

- National Institute for Cancer (INCa; Institut National du Cancer),
- French Biomedicine Agency (Agence de la biomédecine),
- French National Agency for Medicines and Health Products Safety (ANSM ; Agence Nationale de Sécurité du Médicament et des produits de santé),
- French Blood Agency (EFS ; Etablissement Français du Sang),
- National Institute for Health Surveillance (InVS ; Institut de Veille Sanitaire),
- Institute of Health Prevention and Education (INPES ; Institut National de Prévention et d'Education pour la Santé),
- Health Emergency Preparedness and Response Agency (EPRUS ; Établissement de Préparation et de Réponse aux Urgences Sanitaires),
- French Agency for Food, Environmental and Occupational Health Safety (ANSES ; Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail),
- Radioprotection and Nuclear Safety Institute (IRSN ; Institut de Radioprotection et de Sécurité Nucléaire),

- Agency for Information on Hospital Care (ATIH; Agence Technique de l'Information sur l'Hospitalisation),
- National Agency to Support the Performance of Health and Health and Social Care Institutions (ANAP; Agence Nationale d'Appui à la Performance des établissements de santé et médico-sociaux),
- The previously named National Agency for the Quality Assessment of Health and Social Care Organizations and Services (ANESM; Agence Nationale de l'Evaluation de la Qualité des Etablissements et services sociaux et médico-sociaux) which was incorporated in the HAS in 2018.
- The HAS which is an independent public body with financial autonomy.

A summary of information provided above about the French healthcare system are summarized in the Figure 7.

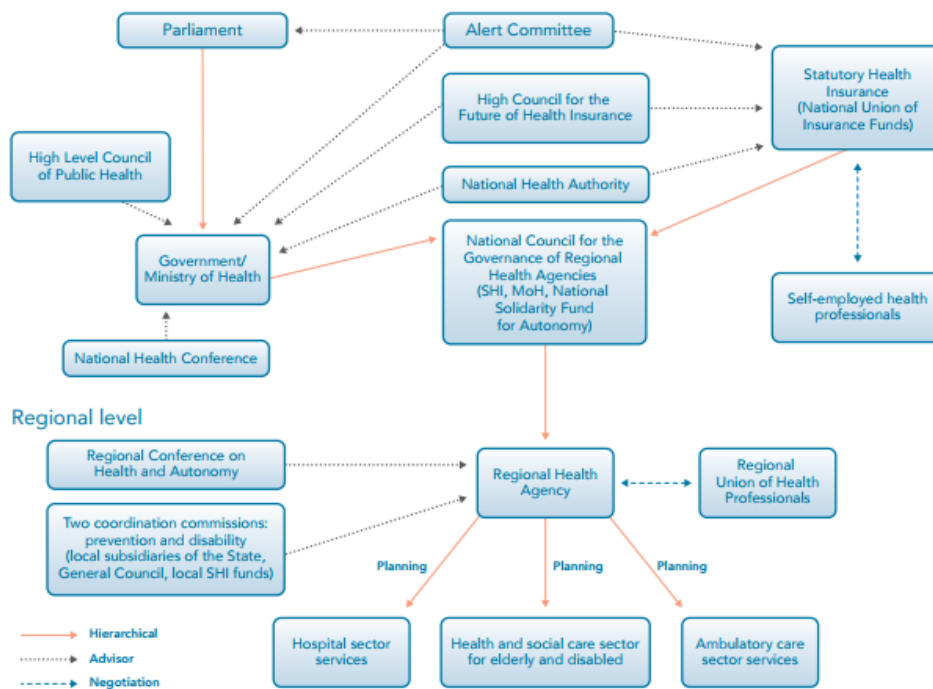


Figure 7. Organization of the Health System in France (43)

Voluntary health insurance (VHI) (Assurance complémentaire)

Three types of VHI suppliers operate with proper sets of regulation but the same supervision and governance. Regarding the regulation part, the mutual insurance companies are regulated by the mutual insurance code, the commercial insurance companies are regulated by the commercial insurance code, and the provident institutions are regulated by the social security code. The supervision is ensured by the Prudential Control and Resolution Authority (ACPR; Autorité de Contrôle Prudentiel et de Résolution) and the governance by the health care system through the National Union of Complementary Health Insurance Organizations (UNOCAM; Union Nationale des Organismes d'Assurance Maladie Complémentaire) which is consulted for fund regulations and establishment of annual Social Security Finance Act and all health care reforms (28).

This first part was presented in order to explain how the French healthcare system works. Its organization ensures a high coverage of the population for health protection but still a complicated model with multiple instances and multiple interactions. The T2A funding method shows some limitation when considering new treatments which are nowadays more big molecules and no more small molecules. These treatments are for the moment far more expensive than small molecules and will probably exceed 30% of the GHS package. Majority of new therapies could not be integrated in the list in *sus* of the GHS. An adjustment of the GHS package will be an option, but this means that this money needs to be withdrawn to another financing part.

The complexity of the French healthcare system is also nourished by specific steps for a treatment to access of the market. The next part is dedicated to the market access cycle for a treatment.

2.1.2 The Market Access

Since drugs are not common products, they comply with regulations requiring a Market Authorization (Autorisation de Mise sur le Marché; AMM) in order to be sold. This requirement is the result of article 6 of directive 2011/83/CE on the community code relating to drug products for human use and transposed to article L.5121-8 of the Public Health Code (Code de Santé Publique; CSP) (41).

In Europe, there are four different procedures to obtain a market authorization including the centralized procedure, the mutual recognition, the decentralized procedure and the national one. Even if there are 4 procedures; quality, safety and efficacy criterion are harmonized at the European level and need to be followed by all European countries for all application (41).

A file containing the information and documents submitted in accordance with Annex I to Directive 2001/83/EC (transposed into French law to Article R. 5121-25 of the Health Code and the Order of April 23, 2004 amending the standards and protocols for analytical, toxicological and pharmacological tests and clinical documentation to which the medicinal products or products referred to in Article L. 5121-8 of the public health Code) accompanied these procedures (42).

The European Public Assessment Report (EPAR) is published by the European Medicines Agency (EMA). The EMA publishes an EPAR for every medicine granted a central marketing authorization by the European Commission following an assessment by the EMA's Committee for Medicinal Products for Human Use (CHMP). EPARs are full scientific assessment reports of medicines authorized at a European Union level. The EPAR includes different annexes, such as annex I which integrates the Summary of Product Characteristics (SmPC), annex II, annex IIIA for the labelling and annex IIIB for the notice and patient information (43). The Market

Authorization is granted for five year for the first inscription and at these five years a re-evaluation is applied with no time limitation except for treatments with a particular pharmacovigilance where a re-evaluation with five-year availability.

Centralized procedure

The centralized procedure is based on the evaluation of a single rapport forwarded to all Member States and coordinated by the EMA. Following the evaluation of the data in the rapport and on the basis of the opinion of the CHMP according to Article 5.R 726/2004 of March 31, 2004, the European Commission may grant a single marketing authorization valid in all the Member States under a single brand name (Cf. Figure 8). This marketing authorization confers the same rights and obligations as the marketing authorizations issued by the competent national authorities. Certain national specificities in conformity with the marketing authorization, in particular concerning the conditions of prescription, issuance, price and reimbursement, may be incorporated (43).

The centralized procedure is compulsory for certain applications, in particular:

- Medicines from biotechnologies;
- Innovative therapy medicinal products (defined in Article 2 of Regulation (EC) No 1394/2007);
- Medicinal products containing a new active substance not yet authorized on the date of entry into force of the Regulation and indicated for the treatment of AIDS (Acquired Immune Deficiency Syndrome), cancer, neurodegenerative disease, diabetes, autoimmune diseases and other immune dysfunctions as well as viral diseases;

- Medicinal products designated as orphan medicinal products (in accordance with Regulation (EC) No 141/2000).

In other cases, the submission with a centralized procedure is optional (43). In the case of this work, treatments for the NSCLC (Non-Small Cells Lung Cancer) are, for the majority, subject to the centralized procedure by excluding chemotherapies. Indeed, most new cancer therapies are derived from biotech engineering.

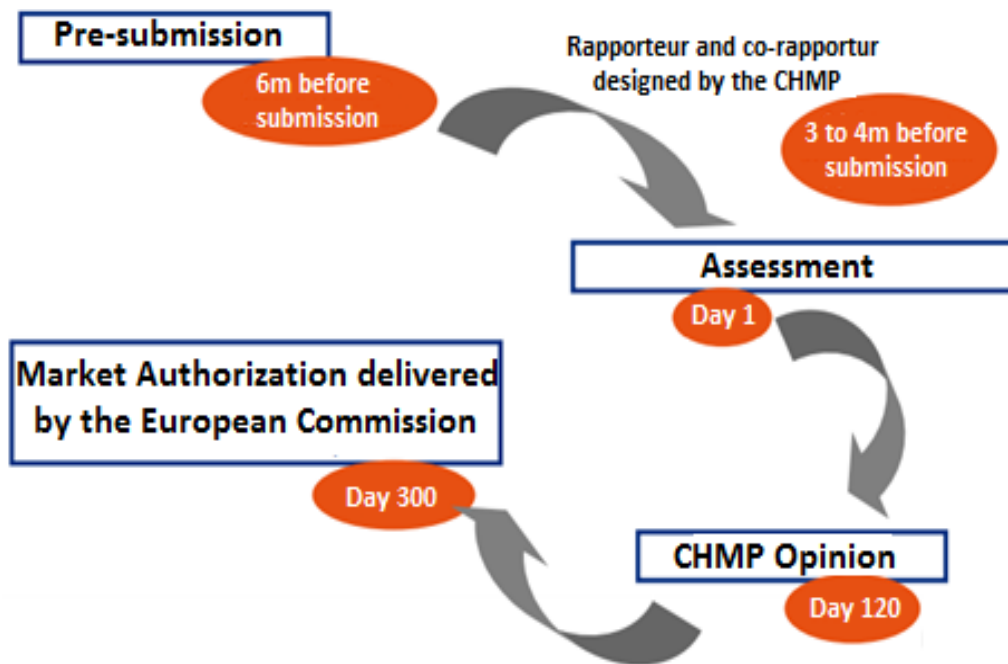


Figure 8. Organization of the centralized procedure (47)

Mutual recognition

The mutual recognition procedure is laid down Article 39 (2) of Directive 2001/83 / EC and states that the mutual recognition procedure is compulsory if the applicant has already obtained a marketing authorization in a Member State of the European Union. The procedure allows the

applicant to apply for marketing authorization in more than one Member State of the European Union, except for medicinal products falling within the scope of the centralized procedure. The Member State that has already obtained the marketing authorization will be the Reference Member State (RMS) and must submit in support of his application an identical dossier in the Member States. The Member States concerned shall recognize the authorization already issued by the RMS within 90 days (without clock-stop). At the end of this procedure, an agreement will have to be reached between all the Member States involved and will result in a summary of the product's characteristics, labeling and a common notice. The market authorization shall be issued at the national level within 30 days following the conclusion of this procedure by each competent authority (41).

Decentralized procedure

This procedure was introduced in European pharmaceutical legislation in 2004 when Directive 2004/27/EC was adopted, amending Directive 2001/83/EC. It was implemented as from 30 October 2005 (41). Article 28 of the directive states that the decentralized procedure may be used when the applicant wishes to authorize a medicinal product in more than one Member State. The difference with the mutual recognition is that in the decentralized procedure the medicinal product is not already authorized in a Member State of the European Union. The choice of the RMS is the responsibility of the applicant. This procedure is carried out in 210 days, with five steps including two-phase evaluation.

- ⇒ The pre-procedural step allows the RMS to inform the Member State and to submit the application to each National Competent Authorities. After verification of legal basis validity each Member State notified the successful passage for the initial validation phase.
- ⇒ Assessment step I – The first round lasts 120 days for preparing Draft Assessment Report (DAR) and comments on draft SmPC, draft of Package Leaflet and draft labelling (44).
- ⇒ The Clock-stop allows the RMS to submit new data in reply to the questions raised by the Member State at the end of the first round. The applicant can supplement the dossier by providing updated SmPC, Package Leaflet and labelling proposals (41).
- ⇒ The start of the assessment step II corresponds to Day 0 of the 90-day period mentioned in 28 of Dir. 2001/83/EC. The RMS cannot submit new data and studies (44).
- ⇒ For the national step, at the end of all the procedure, an agreement will have to be reached between all the MS involved and will result in a summary of the product characteristics, a common Annex II, a labeling and a package leaflet. The marketing authorization shall be issued nationally within 30 days following the completion of this procedure by each competent authority (41). (See Figure 9)

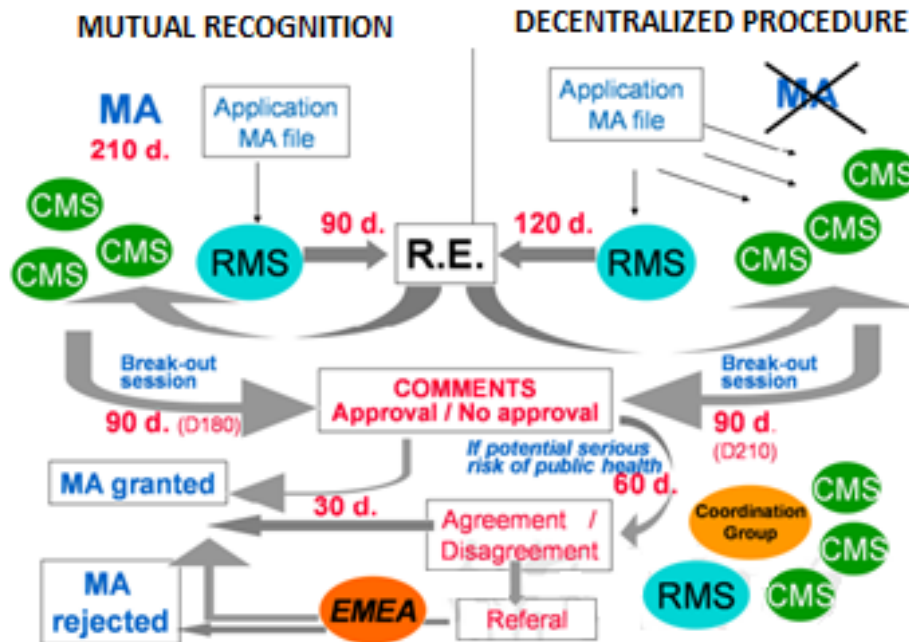


Figure 9. Organization of the mutual recognition and decentralized procedure (47)

National procedure

This procedure applies only to applications for drugs whose marketing is limited to the national territory and which are not authorized in another Member State of the European Union. The maximum deadline for the application by ANSM is 210 days from the submission of a complete application file. This delay may be suspended by a "clock stop" in order to obtain additional information from the applicant (R. 5121-35), in which case the schedule of the instruction shall be restarted as soon as the applicant submits the supplements of information. At the end of the evaluation of the data in the file, the Director General of ANSM, Sir Dominique Martin until 2014, may grant a Market authorization (41). (See Figure 10)

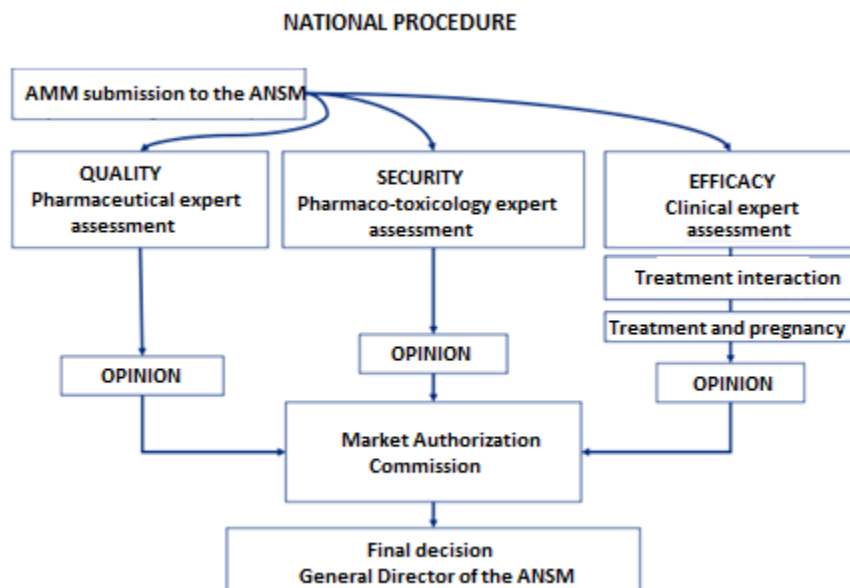


Figure 10. Organization of the national procedure (47)

Price and reimbursement procedure

Once the Market Authorization has been obtained, the drug must be evaluated by the Transparency Committee (Commission de Transparence; CT) in order to evaluate the intrinsic value and its value in comparison with other drugs with same indications. The CT is one of the specialized committees of the HAS, its president, is a member of the college of the HAS.

The Transparency Committee is a scientific body composed of twenty-eight members chosen for their scientific competence (physicians, pharmacists, methodology and epidemiology specialists), each has a deliberative voice. It assesses medicinal products which have obtained marketing authorization, when the laboratory marketing them wishes to obtain their inclusion on the list of reimbursable medicinal products (Articles L.162-17 of the Social Security Code and L.5123 -2 of the Public Health Code). The composition of the CT is fixed by decree (Article R.163-

15 of the Social Security Code) for a period of three years. It includes twenty-one regular members in addition to its President, Professor Christian Thuiller, chosen from the HAS College, including two vice-presidents and seven alternate members, one of whom is chosen from among the members of an association of patients and Health system users. Seven members have a consultative voice and represent the Directorate of Social Security, the Directorate-General for Health, the Directorate-General for Health Care, the ANSM, The general SHI scheme, The agricultural SHI fund, The SHI scheme for self-employed people. Law No 2007-248 of 26 February 2007 laying down various provisions for adapting Community law in the field of medicinal products in Article 28 requires the HAS to make public the minutes containing the details and explanations of the votes meetings of the CT (44).

Objectively, the CT evaluates in a first time the Rendering Medical Service (Service Medical Rendu; SMR) of the drug. This assessment considers, in particular, the effectiveness and undesirable effects of the medicinal product, the seriousness of the condition for which it is intended, and its interest in public health. This evaluation has to evaluation if the drug provides a sufficient interest to be reimbursed by national insurance. This assessment has 4 levels to determine the reimbursement rate. Three of them are sufficient to allow the inscription on the list of reimbursable drugs:

- Significant SMR: 65% reimbursement;
- Moderate SMR: 30% reimbursement;
- SMR low: 15% reimbursement;

An "insufficient" SMR means a negative opinion to the inscription on the list of reimbursable drugs.

Once the SMR is determined the CT states on the Improvement of the ASMR by establishing a comparison with drugs of the same therapeutic class in the same indication. The ASMR allows engaging negotiation between the laboratory and the ANSM to assess the price of the new drug.

Five levels of ASMR assessment of progress against existing treatments are established:

- ASMR I: Major; it means a major evolution in the therapeutic management of a disease,
- ASMR II: Important; for important progresses,

Today, it is becoming increasingly rare for cancer treatments to obtain a level II ASMR and even less level I, already existing therapies for these conditions. These high-grade ASMRs are generally reserved for molecules with a high impact on populations, such as vaccines.

- ASMR III: Moderate,
- ASMR IV: Minor,
- ASMR V: Lack of progress or non-existent. This ASMR means no evolution regarding drugs already on the market. To be on the reimbursement list, these drugs need to bring an economic advantage, so the price cannot be higher to the actual price of marketed drugs.

In general, this ASMR applies for “me too” drugs and generics drugs.

The assessment for inscription on the reimbursement list is carried out by the Economic Committee for Health Products (Comité économique des produits de santé; CEPS) which determines the price of the drug according to the ASMR allocated by the CT and the UNCAM which sets on the reimbursement rate according to the SMR allocated by the CT (See Figure 11). The final registration decision is the responsibility of the Minister of Health and is published in the Official Journal (Journal Officiel, JO).

A Medico-Economic Assessment is planned alongside the transparency file for SRM and ASMR for expensive products that can have a significant impact on health finances.

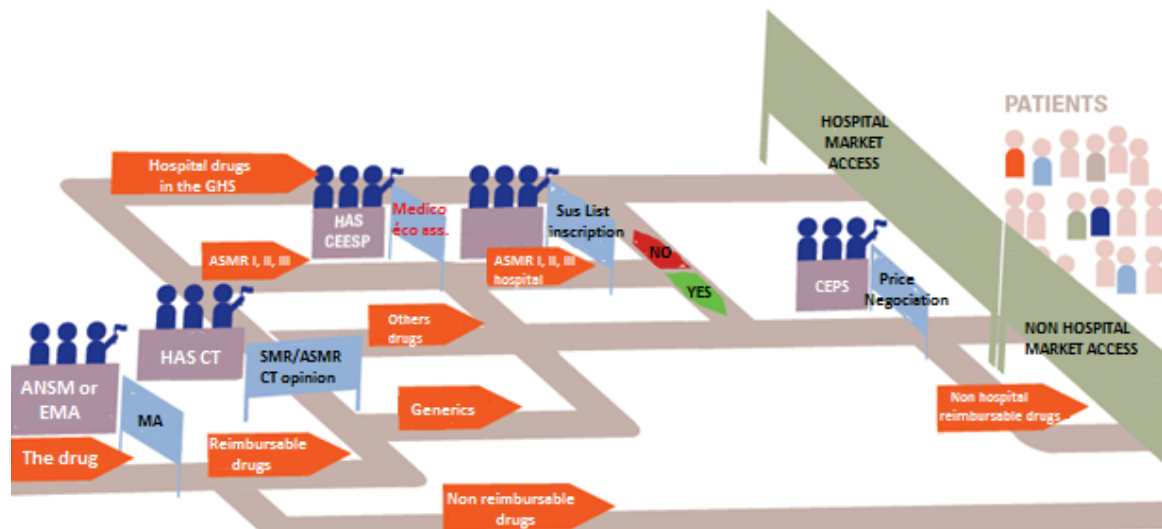


Figure 11. Summary of the administrative procedure for drug market access in France (47)

The current financing in France with T2A is a system that was effective for inexpensive products and punctual innovations. The arrival of new therapies, particularly from biotechnology engineering, is causing a real paradigm shift in the management of broncho-pulmonary cancer, among other pathologies with expensive therapeutics, future associations, the multiplication of therapeutic algorithms with an increasingly adaptable pathology management to patients but also increases patient survival and therefore increases in the duration of treatment. The current system tends to reduce access to reimbursement to ensure sustainable and equitable care by national solidarity, but innovations is multiplying, and the prices of therapeutics are exploding. An ethical challenge therefore arises to ensure equitable access for all to the national solidarity, while respecting the budget allocated for care, but in pathologies with a limited vital prognosis, such as bronchopulmonary cancer where innovations evolve at a blazing speed with prices taking the same path, access for all to these new therapeutics is a real challenge.

The next part of this work presents the lung cancer pathology to well understand the importance of development of new therapeutics for this disease which nowadays as already a poor prognosis despite the marketed drugs.

2.2 *Lung Cancer: The Pathology*

2.2.1 *Epidemiology*

Lung cancer represents a major global public health issue with the highest incidence of cancer: 1.8 million new cases per year (13% of new cases of total cancer) and the highest mortality rate: 1.6 millions of deaths per year (19% of cancer deaths) (7).

In France, lung cancer represents the fourth highest incidence of cancer (slightly more than 45,000 new cases per year) and the highest mortality (around 30,500 deaths per year) (7),(4). Of these, approximately 82.4% are non-small cell lung cancers meaning 37,263 new cases per year (8). Between 2005 and 2012, rates of incidence and mortality increased in women by about 5% per year and decreased in men (between -0.3% and -2.2%) (4). Women's death rates in lung cancer increase until 2000, reflecting an increase in smoking behavior in women following the evolution of women's position in the society (9).

The issue is still important as the 5-year standardized net survival in persons diagnosed between 2005 and 2010 compared to the 5-year standardized net survival in persons diagnosed between 1989 and 2010 has not changed considerably (17% and 15% respectively) (4). The opinion of the CT for the specialty ZYKADIA® states that 68% of cancers are diagnosed from the outset at the advanced (IIIB) or metastatic (IV) stage and that in the residual population, 40% progress to an advanced stage or metastatic in the year (44). Evolution at these advanced stages is at the origin of this high mortality because the only way of cure is surgery at early stages, but few patients can benefit from the present due to diagnostic methods that do not allow early diagnosis. At these stages, only palliative therapies can be purposed for the patient.

Thus, bronchial cancer remains today a serious disease affecting a large number of patients and with an extremely limited 5-year prognosis despite therapeutic changes.

2.2.2 Risk Factors

Numbers of cases are attributable to individual behaviors (45). The causal relationship between lung cancer and smoking was demonstrated in epidemiological studies in 1950s (40,41) but was only recognized by public health authorities in the 1960s (48). The proportion of lung cancer due to active or passive smoking was over 85-90% (11). The relative risk among smokers versus non-smokers is in the order of 8 to 15 for men and 3 to 10 for women (48). The risk of lung cancer in smokers depends on the smoking behavior, including the duration of exposition, the number of cigarettes smoked, the type of cigarette smoked and also the inhalation. Deep inhalation compared to medium or light inhalations have shown an increased risk of cancer development and also the localization of cancer is not the same. Duration of exposition to the cigarette is the strongest determinant (49). Many carcinogens agents are present in tobacco smoke. More than 4,000 chemicals have been identified in cigarette smoke. Approximately 2500 come from natural tobacco processed, while the rest comes from additives, pesticides and other metallic and organic. Known carcinogens include polycyclic aromatic hydrocarbons (PAHs), N-nitrosamines, aromatic amines, aldehydes, organic components (eg benzene, vinyl chloride) and inorganic components (eg arsenic, chromium, radion, lead 210, polonium 210). PAH compounds and tobacco-specific nitrosamines are the most potent carcinogens in tobacco smoke. These can induce a genetic modification of the bronchial or alveolar cells by following a multistep process, characterized by a progression towards an invasive phenotype of one or a small number of cells "initiated" by the acquisition of alterations genetic advantage giving them a proliferative advantage (50). These agents often affect the bronchopulmonary tree as a whole and the upper aero-digestive tract and may lead

to the formation of several concomitant primary lesions. This phenomenon is described under the name of "field carcinogenesis" which can eventually lead to a malignant evolution (50).

Other environmental or occupational factors are recognized as carcinogenic agents as asbestos, diesel engine exhaust, radon, arsenic, nickel, cobalt, chromium, exposure to certain ionizing radiation, silica, cadmium. For a person exposed to asbestos, the risk of bronchopulmonary cancer is multiplied by 5 in a non-smoking patient and multiplied by 50 in a smoking patient.

Other factors appear to be involved in bronchopulmonary cancer:

- Inhaled cannabis;
- History of thoracic irradiation for Hodgkin's disease or for breast cancer;
- Professional or accidental exposure to ionizing radiation (11).

The deposition of particles containing PAHs, polonium 210 or lead 210 in the bronchi strains is associated with the development of squamous cell carcinomas, while inhalation depletion of volatile nitrosamines results in their deposition in the terminal bronchioles and alveoli and thus to the development of adenocarcinomas. Histologies of lung cancer are described in the part below.

2.2.3 Histologies: WHO Classification

The majority of lung cancers are carcinomas that develop from the bronchial epithelium, the other histological types represent less than 1% of cases (51). The histology of bronchial cancer depends on the histology of the bronchial and pulmonary tree which is characterized by the gradual change of a type of epithelium plus one goes down into the bronchial tree. The tracheal epithelium, pseudo-stratified, ciliated and containing goblet cells,

changes at the level of the terminal bronchioles to give way to a simple cylindrical epithelium without goblet cells and characterized by a specialized cell type, Clara's cell. Then, the terminal bronchioles open on the pulmonary alveoli, lined with type I and II pneumocytes (42,46).

Lung cancers are often histologically heterogeneous with variations in appearance from one microscopic field to another (51). This shows the plastic character of the differentiation of lung cancers. However, it has been possible to classify anatomically 4 major types of bronchial cancer divided in two major classes. The next part describes the different type of lung cancer according to the WHO classification established in 2004 (48). There is thus small-cell lung cancer (SCLC) as opposed to NSCLC, which is subdivided into 3 groups: squamous cell carcinoma, adenocarcinoma and large cell cancer. Other types of tumors are neuroendocrine carcinomas including large cell neuroendocrine carcinomas (LCNEC) and typical carcinoid. The origin, diversity and typology of neuro-endocrine tumors remain questionable (52). These tumors are thought to be derived from specific precursor cells with neuroendocrine characteristics (Kulchitzky-Masson cells). These neuroendocrine carcinomas are strongly associated with smoking. Due to their high mitotic activity, these cancers have a very fast growth and a frequent metastatic evolution. This strong mitotic activity seems to be at the origin of a good initial response to chemotherapy (52).

Small Cell Lung Carcinoma, SCLC

Small Cell Lung Carcinoma (SCLC) is a group of cancers with common morphological, histological and structural features, including a small amount of cytoplasm, a granular-like chromatin, a high mitotic activity, and the presence of large beaches of necrosis. SCLCs have a neuroendocrine origin. Like the neuroendocrine tumors described earlier in this section, the SCLC is an aggressive fast-growing lung cancer type due to a high mitotic activity, it is

therefore often diagnosed at an extended stage. It has a very poor prognosis and usually develops in the main bronchi (48),(52).

Non-Small Cell Lung Carcinomas, NSCLC

Non-Small Cell Lung Carcinoma (NSCLC) are derived from epithelial stem cells of the bronchopulmonary mucosa. NSCLC accounts for 80% of cases, and can adopt an epidermoid (Squamous Cell Carcinoma, SCC), glandular (AdenoCarcinoma, ADC and AdenoCarcinoma BronchioAlveolar, ADC-BA) or undifferentiated (Large Cell Carcinoma, LCC) architecture, depending on the etiology and the location in the bronchial tree (48),(52).

- SCC develops from the pseudo-stratified bronchial epithelium by a process of squamous metaplasia, followed by a hyperplasia-dysplasia-carcinoma sequence (52). It involves cells of the squamous epithelium (reserve cells, which replace damaged cells in the bronchi lining) which are usually flat and line the airways. (See Figure 12) Squamous cell carcinoma represents approximately 30% of cases and is characterized by keratin synthesis by tumor cells and by intercellular bridges. It is a well-differentiated cancer that also develops in the proximal parts of the lung. Most cases are caused by smoking.

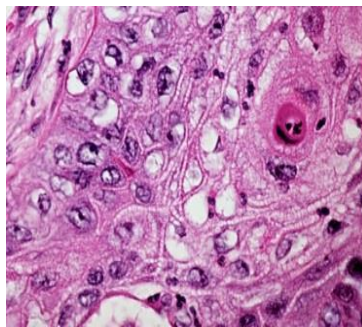


Figure 12. Squamous Cell Carcinoma histology (Scale: x550) (57)

Adenocarcinoma affects about 40% of patients and originates from glandular cells, which are derived from epithelial stem cells. The tumor cells of adenocarcinoma secrete intra cytoplasmic mucus. Although it is linked to tobacco, it also has a greater expression in non-smokers and women than other types of lung cancer. Likewise, unlike other types of bronchial cancer, it develops in more distal parts. There are 5 different types of adenocarcinoma: acinar, solid, mixed, papillary, all 4 links together under the term adenocarcinoma (ADC). ADC are derived from the transformation of type I and II pneumocytes. The fifth type of ADC with bronchoalveolar origin, ADC-BA, develops primarily from the Clara cell lining of small peripheral bronchioles (See Figure 13). This last subtype deserves to be individualized because of a distinct oncogenesis not link with tobacco but with frequent mutations of the EGF receptor (EGFR). This subtype is most common in Asian populations and has a better prognosis during early diagnosis (51–53)

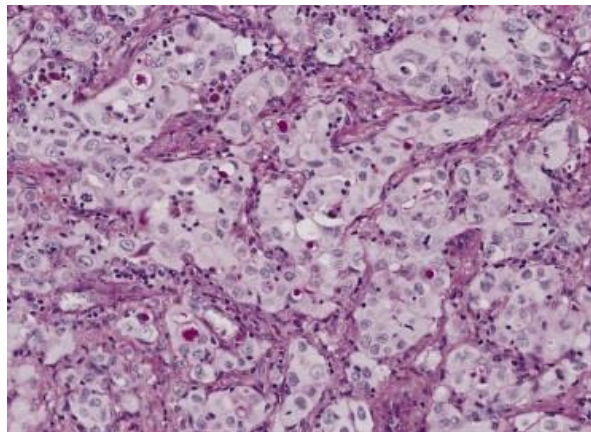


Figure 13. Adenocarcinoma histology (Scale: x400) (55)

However, for the adenocarcinoma, the World Health Organization (WHO) classification of 2004 was too global and offers only an overview. Regarding evolution in different sectors imply in lung cancer cares as medical oncology, radiology and mostly in molecular biology the

classification for adenocarcinoma was reviewed in 2011 by the International Association for the Study of Lung Cancer, the American Thoracic Society and the European Respiratory Society. For this analysis, this overview is sufficient because treatments are not yet developed at this level (56).

- Large cell carcinoma accounts for 10% of patients with bronchial cancer. It groups together undifferentiated LCC and large cell neuroendocrine carcinomas. It is an aggressive cancer which tends to grow and spread quickly, so it has a poor prognosis. It is usually peripherally located and involves large cells (subtypes include basaloid and clear cell) with large nuclei (See Figure 14).

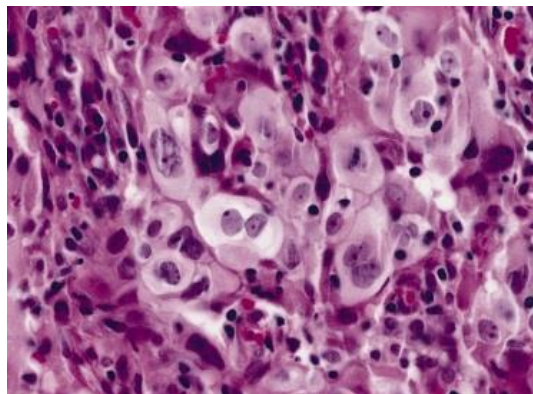


Figure 14. Large cell carcinoma histology (Scale: x550) (55)

The affiliation between lung carcinomas and cells histology is resumed in the Figure 15. The sagging arrow illustrates the hypothetical character of the filiation between the precursor cell of neuroendocrine carcinomas and the epithelial stem cells (52).

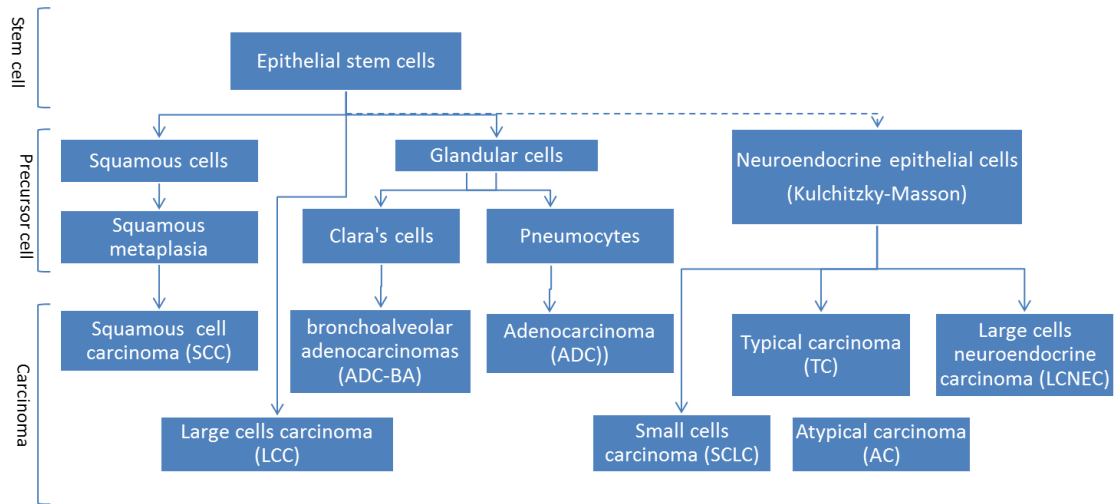


Figure 15. Histopathogenesis of bronchopulmonary carcinomas (56)

In this work, we will concentrate on the NSCLC which represents the majority of lung cancer. In addition to histology, lung cancer expressed molecular alterations and some of them are characteristic and can be target by targeted therapy. The next session developed different molecular alterations which are every time developed and some other which are particulars.

2.2.4 Molecular Alterations

As in most cancers, bronchopulmonary carcinomas develop various alterations during their development; first, genetic alterations such as mutations, gene amplifications, allele losses and chromosomal instabilities; and also, epigenetic alterations with gene overexpression or suppression of expression by hyper-methylation of promoters (57). If the frequency and type of alterations differ from one histology to another, involving different mechanisms, it is often the same pathways that are affected by these evolutionary phenomena. These pathways seem to be the pathways that play a fundamental role in the regulation of morphogenesis, the protection against physiological stress and the mechanisms of regeneration of the normal

epithelium after the appearance of lesions. The mechanisms of regulation of these pathways involve proliferation, apoptosis, differentiation and responses to. Thus, it is understood that the molecular alteration causes the affected cell to become able to proliferate beyond its normal replicative limit, to remain alive in conditions where normal physiology leads to cell death, to avoid involvement in terminal differentiation, and to develop according to altered differentiation patterns. These effects are involved in all carcinogenic processes. What is unique about bronchopulmonary carcinomas lies in a twofold characteristic: the histological plasticity of the bronchopulmonary epithelium, described above, which confers on this epithelium a form of tissue instability expressed by the frequent formation of metaplasias, and the particular weight of environmental risk factors, including tobacco smoke, which act not only as mutagens but also as remodeling factors for the bronchial epithelium (52).

As explained above, some mutations of the very common way in lung cancer. These are described in the following paragraphs.

TP53 Mutation

The most common genetic alteration is the mutation of the TP53 suppressor gene at chromosome 17P13, it is detected in 50% of the NSCLCs. The p53 protein ensure genetic and tissue stability. It is specialized in the response to a broad spectrum of physical, chemical or biochemical stresses like carcinogen exposures by arresting cell cycle and allow DNA repair or apoptosis following the differentiation grade and the stress. TP53 mutations are mainly due to non-sense substitutions that inactivate the protein by preventing its folding into an active conformation (56,62).

TP63 and TP73 Dysregulation

Two other members of the TP53 family, TP63 and TP73, are expressed in a complex manner during morphogenesis and differentiation of the bronchial tree. They are also involved in bronchogenic carcinogenesis by a possible pro-oncogenic effect (52).

Rb Pathway Alteration

The keystone of a systematically altered signaling pathway in lung cancer is the Rb protein, a product of the retinoblastoma RB1 gene (chromosome 13q14). The Rb protein is a tumor suppressor and acts as a limiting factor for controlling cell progression in the G1 and S phases of the cell cycle. The inactivation of RB1 leads to a stop of the transition between G1 and S phase of the cell cycle and ensure an uncontrolled proliferation (52).

MEN1 Alterations

The MEN1 gene, located on chromosome 11q13, encodes for a protein that functions as a modulator of mitogenic transcription factors. The mutations and loss of MEN1 are responsible of the formation of neoplastic lesions. This phenomenon is observed in the majority of atypical bronchial carcinoids. This is the only known genetic alteration to date that distinguishes SCLCs from NSCLCs (52).

Inactivation de p14ARF

The INK4 / CDKN2a locus has a complex structure and is involved in the repression of proliferation. In most cases, the deletion of the INK4 locus leads to an excessive proliferation (52).

Wnt/BetaCatenine/MYC Pathways

Factors of the Wnt family are secreted proteins involved in the regulation of proliferation, morphogenesis, cell adhesion, differentiation and apoptosis. They bind to a family of surface receptors whose stimulation induces a signaling cascade involving the increased expression of many genes. The components of this cascade are altered with heterogeneous manner in pulmonary carcinogenesis. The amplification of this pathway could be associated with the highly mitotic nature of lesions (52).

Alleles Loss in 3p

One of the most common genetic alterations in bronchopulmonary carcinomas, regardless of their histological type, is the loss of alleles in a specific region of chromosome 3, observed in nearly 80% of NSCLC and SCLC. This chromosomal region contains several gene-suppressor candidates. Some of these gene-suppressors are located in a highly fragile chromosomal region, which is conducive to the formation of deletions under the direct effect of carcinogenic agents of tobacco smoke. This deletion could lead to a dysregulation of intracellular nucleotide levels and in the control of DNA synthesis (59).

Other mutations are non-constitutional and presents only in certain patients with NSCLC. These mutations are important because some are the target of treatments studied in this work.

EGFR mutation

The prevalence of EGFR mutations in NSCLC varies widely with population ethnicity. Estimation from observational studies ranged from 4.5% in a study conducted in Italy to approximately 40% in two studies conducted in Japan and Taiwan (53,54). EGFR alterations

are almost known as HER1 and ERBB1 alteration. They are common in non-smokers ADC. EGFR is a transmembrane receptor with an intracellular tyrosine kinase domain which can be activated by some ligands (EGF, TGFalpha, etc...). Following this step, a signal transduction cascade modulating proliferation, survival, adhesion, migration, epithelial cell differentiation, and angiogenesis is activated. Some genetic mutations affect the structure of protein loops surrounding the ATP binding domain that is the active site of the enzyme (60) causing a constitutive activation of the receptor without the need of a ligand. Effects are different regarding the nature and position of the mutation.

ALK Translocation

The anaplastic lymphoma kinase (ALK) gene is localized on chromosome 2. ALK is primarily expressed in the developing Central Nervous System (CNS) and is also expressed to a lesser extent in the adult CNS. Some studies suggest that ALK plays a role in the development of the CNS (61). ALK codes for a receptor tyrosine kinase, a member of the insulin receptor subfamily (56,62). This ALK protein is a membrane-bound protein and it is constituted from an extracellular domain, a transmembrane domain and a kinase domain. When the extracellular domain is binding of its ligands, the growth factors midkine (MK) and pleiotrophin (PTN) the ALK dimerization is induces. The dimerization promotes ALK autophosphorylation on the intracellular domain. The ligand-dependent activates downstream intracellular signaling pathways notably MAPK pathway which activate the proliferation and also STAT3 and PI3K/AKT pathways which promote the cell survival. In some cases, the ALK gene undergoes a rearrangement, within a second gene on the chromosome and resulting in a structural alteration of the chromosome and in the expression of an ALK fusion protein (63). The ALK rearrangements can occur with different genes, the most common rearrangement is between EML4 and ALK, EML4 having several variants. The breakpoint of ALK gene occurs at exon

20 (A20) (See Figure 16). The EML4-ALK is totally localized in the cytoplasm, this translocation results in a constitutive activation of the ALK kinase domain and the dysregulation of the signaling cascades of proliferation and cell survival. This promotes tumor cell growth and survival. ALK translocation was first discovered as part of a chromosomal rearrangement in anaplastic large-cell non-Hodgkin's lymphoma (64).

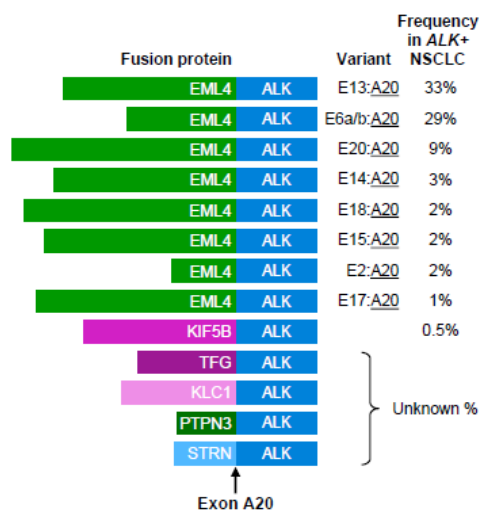


Figure 16. Common variants of the ALK fusion protein (69)

After biopsy, the suspect sample is sent for analysis. In addition to the pathological evaluation, various molecular biology tests are performed to identify ALK translocations routinely in addition to the identification of EGFR mutations. The different methods of testing are the Fluorescence in-situ hybridization (FISH), Immunohistochemistry (IHC), Reverse-transcriptase polymerase chain reaction (RT-PCR) and the Next-Generation Sequencing (NGS).

The FISH test uses red and green fluorescence of specific regions of the ALK gene. When a cell has not been translocated, the ALK gene is whole, so the red and green colored fluorescent parts appear side by side in the FISH test. When the cells have been translocated, the ALK gene

is cut into two parts. Part of the ALK gene is found fused with another part of the EML4 gene (See Figure 17 and Figure 18). Thus the two parts with different fluorescence appear remotely to the FISH test. The FISH test, however, requires a minimum of 50 tumor cells, which is not always possible for some biopsies. It takes a lot of time in terms of achievement but also for training teams in this technique, the test procedures are not standardized. It is also an expensive test.

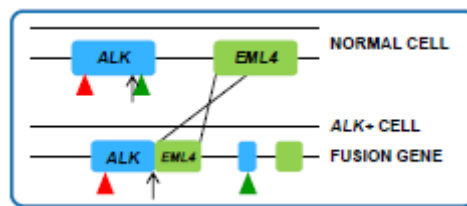


Figure 17. Explanation of the FISH fluorescence in the ALK translocations (70)

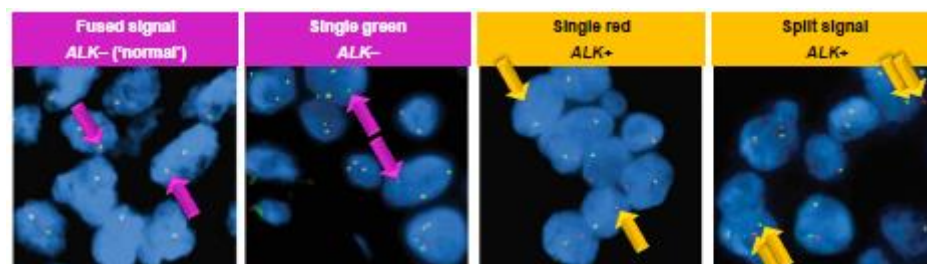


Figure 18. Example of FISH test results (70)

The IHC test is used to detect the expression of the ALK fusion protein using specific antibodies directed against epitopes conserved by the ALK protein. IHC uses the principle that the ALK protein is physiologically not or weakly expressed. Thus, after revelation by IHC, the visualization of a highly granular and highly colored cytoplasm proves the presence of ALK translocation at the tumor level. This technique is most often used in clinical routine because it is fast, inexpensive and does not require a large amount of biological material (See Figure 19).

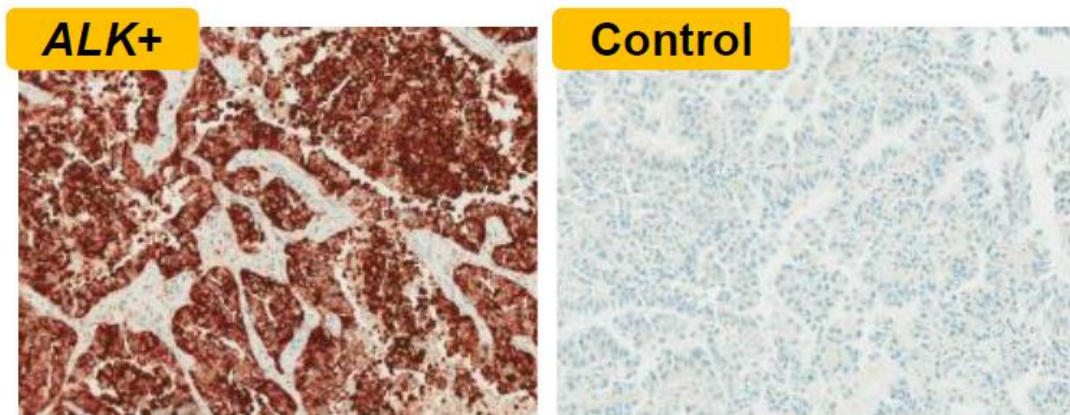


Figure 19. Example of results with IHC test (65)

RT-PCR is used to detect RNA expression levels. The principle is the same as with the IHC, that is to say the detection of the number of copies of mRNA from the ALK-EML4 translocation gene. High RNA quality is required to perform a quality test, so this test is rarely performed and is not recommended routinely because of a constraint on the quality of the sample.

The test by NGS is the most complete and the most efficient. It provides information on the entire transcriptome in a single analysis and can be used on biopsies with a small amount of DNA. However, it is still very expensive and is therefore not recommended for ALK testing routinely for clinical practice.

KRAS Mutation

Unlike EGFR mutations, which are found mainly in non-smokers, KRAS mutations appear to predominate in smokers and ex-smokers. In normal cells, RAS is present in the intracellular part of the plasma membrane in an inactive, GDP-related form. RAS proteins play a role of relay and enhancer of intracellular signals triggered by the activation of tyrosine kinase receptors and notably EGFR. After stimulation by an extracellular signal, RAS interacts with

guanidine nucleotide exchange factors causing its conversion to an active GTP-related form. The mutation at codon 12 blocks KRAS2 protein in the active configuration, resulting in the production of a constitutive signal, independent of the activation of the upstream receptors (66).

2.2.5 Symptoms

Most patients with lung cancer do not experience any symptoms until the disease has reached an advanced stage. Symptoms can be mistaken for other health problems, delaying diagnosis. All signs and symptoms of lung carcinoma are resumed in the Table 6. The information is extracted from the WHO Classification (48).

Table 6. Symptoms of lung cancer (52)

<p><u>Systemic symptoms</u></p> <ul style="list-style-type: none"> • Weight loss, loss of appetite, malaise, fever <p><u>Local /direct effects</u></p> <ul style="list-style-type: none"> • From endobronchial growth and/or invasion of adjacent structures • including chest wall and vertebral column • Cough, dyspnea, wheeze, stridor, hemoptysis • Chest pain/back pain • Obstructive pneumonia (+/- cavitation) • Pleural effusion <p><u>Extension to mediastinal structures</u></p> <ul style="list-style-type: none"> • Nerve entrapment: recurrent laryngeal nerve (hoarseness), phrenic • nerve (diaphragmatic paralysis), sympathetic system (Horner syndrome), • brachial plexopathy from “superior sulcus” tumors 	<p><u>Endocrine syndromes</u></p> <ul style="list-style-type: none"> • Parathormone-like substance: hypercalcemia • Inappropriate antidiuretic hormone: hyponatremia • Adrenocorticotrophic hormone (ACTH): Cushing syndrome, hyperpigmentation • Serotonin: carcinoid syndrome • Gonadotropins: gynecomastia • Melanocyte-stimulating hormone: increased pigmentation • Hypoglycemia, hyperglycemia • Hypercalcitonemia • Elevated growth hormone • Prolactinemia • Hypersecretion of vasoactive intestinal polypeptide (VIP): diarrhea <p><u>Hematologic/coagulation defects</u></p> <ul style="list-style-type: none"> • Disseminated intravascular coagulation • Recurrent venous thromboses
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<ul style="list-style-type: none"> • Vena cava obstruction : superior vena cava syndrome • Pericardium: effusion, tamponade • Myocardium: arrhythmia, heart failure • Esophagus: dysphagia, bronchoesophageal fistula • Mediastinal lymph nodes: pleural effusion <p><u>Metastatic disease</u></p> <ul style="list-style-type: none"> • Direct effects related to the organ(s) involved <p><u>Paraneoplastic syndromes</u></p> <ul style="list-style-type: none"> • Dermatomyositis/polymyositis • Clubbing • Hypertrophic pulmonary osteoarthropathy • Encephalopathy • Peripheral neuropathies • Myasthenic syndromes (including Lambert-Eaton) • Transverse myelitis • Progressive multifocal leukoencephalopathy 	<ul style="list-style-type: none"> • Nonbacterial thrombotic (marantic) endocarditis • Anemia • Dysproteinemia • Granulocytosis • Eosinophilia • Hypoalbuminemia • Leukoerythroblastosis • Marrow plasmacytosis • Thrombocytopenia <p><u>Miscellaneous (very rare)</u></p> <ul style="list-style-type: none"> • Henoch-Schönlein purpura • Glomerulonephritis, Nephrotic syndrome • Hypouricemia, Hyperamylasemia • Amyloidosis • Lactic acidosis • Systemic lupus erythematosus
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As stated in the table above, patients do not only have bronchial involvement but more general deterioration. The alteration of the general condition of the patient can be measured using a performance scale of the WHO called "performance index" it is divided into different scores:

- PS0: the patient keeps a normal activity
- PS1: the patient experiences minor symptoms but this does not affect his ability to maintain a professional activity
- PS2: the symptoms experienced by the patient are more important, it is still ambulatory with less than 50% of his time spent in bed

- PS3: the symptoms are very important and require the patient to spend more than 50% of his time bedridden
- PS4: The patient is in a serious condition preventing him from performing any activity.

2.2.6 Diagnosis

Bronchopulmonary cancer is evoked by the presence or persistence of respiratory symptoms (cough, dyspnea, hemoptysis, etc.), especially in a smoker or former smoker. The diagnosis is often of poor prognosis notably due to the late detection of bronchial cancer which is, for most of the time, discovered at a metastatic stage (See Table 7). Sites of metastatic dissemination are numerous, but the main sites are the viscera, the central nervous system, liver, bone, adrenal and ganglion. Metastatic lung cancer is usually visceral, and it is most often brain metastases that are at the origin of the diagnosis causing possible epileptic seizures and therefore additional radiological examinations.

Table 7. 5-years survival regarding lung cancer stage (67)

	Stage I and II localized	Stage III locally advanced	Stage IV metastatic
Frequency at diagnosis	15 to 30%	20%	40 to 55%
5-years survival	52.6%	23.7%	3.8%

Different types of exams aimed at exploring the respiratory system can guide the diagnosis. The basic inescapable review for directing the diagnosis remains the frontal and lateral chest

x-ray. It makes it possible to visualize hilar, peripheral or sometimes excavated opacities but also to highlight other signs such as atelectasis; which corresponds to a retraction of the pulmonary alveoli by an obstruction of the bronchi; and adenopathies including mediastinal. Other examinations such as computed tomography, PET scan, ultrasound, MRI (Magnetic Resonance Imaging) allow carrying out an extension assessment to assess lymph node and visceral involvement. The extension assessment and stage of the disease is codified by an official classification called the "TNM Classification". This will be discussed in the next subpart.

After radiography, if a bronchial cancer is suspected, an examination allowing the collection of potentially malignant material must be carried out. A bronchoscopy and thoracoscopy allow performing a biopsy of suspect material for sending and confirmation of the diagnosis by an anatomic pathologist. Only the anatomo-pathological examination makes it possible to affirm the diagnosis and also to provide the histological status of pulmonary cancer.

2.2.7 TNM Classification

The TNM classification makes it possible to graduate the evolution of the disease. The T of this classification corresponds to the primary tumor, that is to say the home of origin of the cancer. As cancer is a progressive disease, it is necessary to determine the size and extent of the tumor in the tissue and its environment. This T classification of the tumor can range from T1 to T4. As cancer is a progressive disease but also a disseminator, two criteria make it possible to evaluate the spread of cancer. The N of the classification makes it possible to determine if there is lymph node involvement and, in this case, make it possible to judge the size, the number of adenopathies and their location (more or less complicated). This classification N evolves from N0 to N3. With regard to metastatic evolutions, it is the M

classification that makes it possible to say whether or not metastases exist. This grade contains only two possibilities M0 and M1, because the number of metastases does not really influence the prognosis, the cancer being anyway generalized.

After performing this classification in each of the areas of cancer evolution, all the criteria are cross-checked (as shown in Table 8) and can be used to determine a stage from IA-1 to IV-B. Details of the TNM classification are integrated in annex of this thesis (Annex 1). The actual TNM classification is the 8th edition of the AJCC Cancer Staging Manual and was implemented with the new system and represents the standard of NSCLC staging since 2017 (65–67). It replaces the 7th edition which was established in 2010 and based on the AJCC Cancer Staging Manual (68,69).

Table 8. Cancer stage classification following the 8th edition of the TNM classification (from (75))

	N0	N1	N2	N3	M1a-b Tout N	M1c Tout N
T1a	IA-1	IIB	IIIA	IIIB	IV-A	IV-B
T1b	IA-2	IIB	IIIA	IIIB	IV-A	IV-B
T1c	IA-3	IIB	IIIA	IIIB	IV-A	IV-B
T2a	IB	IIB	IIIA	IIIB	IV-A	IV-B
T2b	IIA	IIB	IIIA	IIIB	IV-A	IV-B
T3	IIB	IIIA	IIIB	IIIC	IV-A	IV-B
T4	IIIA	IIIA	IIIB	IIIC	IV-A	IV-B

The TNM classification is a crucial step because it determines the therapeutic strategy. In this work we will focus on stages IIIB and IV which correspond at advanced and metastatic lung cancer because most of the patient are diagnose at these stages. For these patients, chemotherapy remains historically a base for the management of advanced lung cancer, new therapies push for change in the treatment of bronchial cancer.

The next part will discuss the evolution of lung cancer management in recent decades and future developments.

2.3 Evolution of the Lung Cancer Management towards Personalized Medicine

2.3.1 Generalist Treatment

Chemotherapy is a group of treatments for the purpose of cytotoxic action. Chemotherapies, by different mechanisms of action, prevent cell growth or cause cell death. Cell growth is dictated by a multi-stage cell cycle regulated by many factors. A cancer cell has a capacity for reproduction and development by this cell cycle much more developed than a normal cell that is regulated. Some chemotherapies have the ability to disrupt this cell cycle such as ant microtubule agents, topoisomerases II inhibitors, antimetabolites as well as antitumor antibiotics.

The cytotoxic activity of cisplatin was discovered in 1965 by Rosenberg et al. and its first phase I clinical trials in 1971. Cisplatin is now one of the most used cytotoxic agents for different types of cancer (70). Before the 1990s, the use of chemotherapy in NSCLC has long been controversial providing a limited benefit in terms of overall survival time, indeed from chemotherapy, the gain counted in days of survival and not yet in months (71). (Cf. Figure 20)

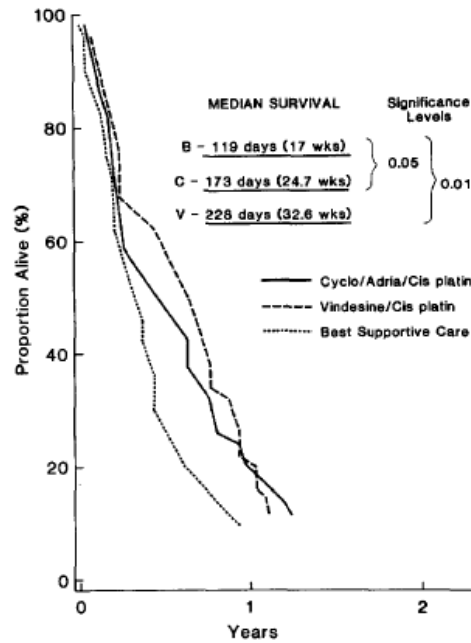


Figure 20. Median Survival of patients with NSCLC with cisplatin combination vs. Best Supportive Care (71)

The addition of many side effects is also an argument that weighs against chemotherapy. The problem with cytotoxic agent is that it has a lack of tumor tissue selectivity leading to severe side effects (nephrotoxicity, neurotoxicity and ototoxicity, myelotoxicity). Second and third generation platinum-based drugs have been synthesized to create new cisplatin analogues over the last past 30 years in order to fight against these side effects. Different clinical trials have tried to find a solution to improve the fight of this pathology but despite the attempts, no agent or combination does better than cisplatin. But since the 1990s, new agents have been developed, including paclitaxel, docetaxel, gemcitabine and vinorelbine (71,72).

2.3.2 Treatment by Histology

Studies comparing different combinations of chemotherapies have highlighted the interest of treating patients according to their histology. This is particularly the case of the JMDB study, which aimed to compare two first-line combinations (chemo-naive patients) in patients with stage IIIB or IV bronchial cancer. These two associations were cisplatin + gemcitabine versus cisplatin + pemetrexed. In analyzing the results in the general population, no statistically significant difference in overall survival was found with median overall survival (OS) at 10.3 months for both associations and HR at 0.94 (95% CI: 0.84-1.05). However, looking at the OS analysis performed in patients with non-small-cell non-squamous cell lung cancer and in more detail, those with adenocarcinoma, statistically significant results were found in favor of the combination cisplatin + pemetrexed with median OS at 11.0 months versus 10.1 months (HR = 0.84, 95% CI: 0.74-0.96) in non-squamous NSCLC patients and at 12.6 months versus 10.9 months and an HR of 0.84 (95% CI: 0.71-0.99). Conversely, in patients with squamous NSCLC, the cisplatin + gemcitabine combination is more effective in terms of OS compared to the cisplatin + pemetrexed combination (73,74).

2.3.3 Targeted Treatment / Molecular Biology

The advent of molecular biology has led to research and discovery of targeted therapies for specific mutation as explain in the section Mutation.

EGFR Mutation

TARCEVA® Erlotinib

Erlotinib inhibits signaling from both wild type (WT) and mutated EGFR by binding reversibly to the intracellular tyrosine-kinase domain. In three separate studies, EURTAC, OPTIMAL and ENSURE, assessing first-line erlotinib versus standard platinum-doublet chemotherapy in patients with EGFR Mut+ NSCLC, erlotinib significantly prolonged progression free survival (PFS) compared with chemotherapy with between a median PFS from 10.4 to 13.7 months for erlotinib versus 4.6 to 5.5 months for standard platinum-doublet chemotherapy (38,75–77). (See Figure 21)

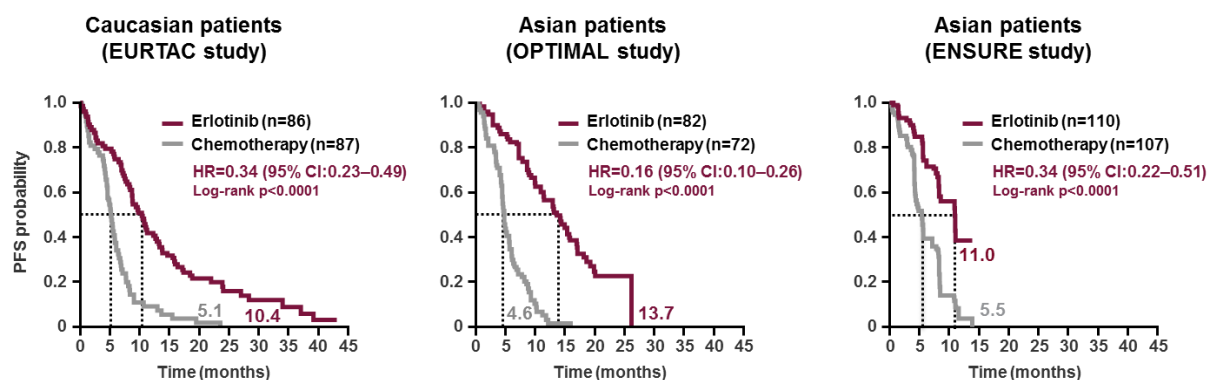


Figure 21. Erlotinib vs. Chemotherapy PFS assessment in 3 studies (57–59)

IRESSA® Gefitinib Gefitinib inhibits signalling from both wild type and mutated EGFR by binding reversibly to the intracellular tyrosine-kinase domain. The pivotal clinical trial development includes a phase III, IPASS, for the first line comparing gefitinib vs carboplatin/paclitaxel in Asian, never or light ex-smokers with adenocarcinoma and a phase IV, IFUM, for 1L Caucasian patients with EGFR Mut+ NSCLC (78,79). The median PFS in the study IPASS is included in a comparison between EGRF TKI in the figure 19 and 20. The

phase IV study, IFUM showed that for 1L Caucasian patients with EGFR Mut+ NSCLC, the median PFS is 9.7 months and the mOS 19.2 months.

GIOTRIF® Afatinib

Afatinib binds irreversibly to the WT and mutated EGFR, inhibiting signalling. However, continuous synthesis of new, unbound receptors necessitates once daily dosing of afatinib. The irreversible inhibitor afatinib is associated with higher rates of toxicity compared with other approved EGFR TKIs. Pivotal clinical trials of afatinib are the phase III LUX-Lung 3 which is a global registration study for the 1L comparing afatinib vs cisplatin/pemetrexed in patients with EGFR Mut+ NSCLC (80). For Asian registration, the phase III study LUX-Lung 6 evaluates 1L afatinib vs cisplatin/gemcitabine in Asian patients with EGFR Mut+ NSCLC (81). LUX-Lung 7 a phase IIb for the 1L comparing afatinib vs gefitinib in patients with EGFR Mut+ advanced adenocarcinoma of the lung is also part of the development program (82). Another pivotal study, LUX-Lung 8, is the phase III for advanced squamous cell carcinoma in 2L comparing afatinib vs erlotinib (83).

These three molecules are engaged in a strong competition in order to dominate the EGFR market. Regarding study results and a pooled analysis of data from over 90 published studies showed that median PFS is longer with erlotinib than with gefitinib in EGFR Mut+ NSCLC (84).

EGFR TKIs demonstrate significantly prolonged PFS and QoL benefit compared with chemotherapy. In pooled analyses and meta-analysis of first-line studies of EGFR Mut+ NSCLC, erlotinib demonstrates improved median PFS compared with chemotherapy, gefitinib or afatinib.

TAGRISSO® Osimertinib

Osimertinib is also a third generation irreversible TKI (Tyrosine Kinase Inhibitor) that selectively targets both activating EGFR mutations and the T790M resistance mutation, while sparing WT, or normal, EGFR. The pivotal clinical trials program includes:

- AURA (phase I/II): open-label, multicentre dose escalation/expansion trial of osimertinib in patients with advanced EGFR Mut+ NSCLC (includes previously-treated and treatment-naïve cohorts) (85)
- AURA2 (phase II): open label trial of 2L osimertinib in patients with EGFR T790M+ locally advanced/metastatic NSCLC (86)
- AURA3 (phase III): open label, randomised trial to assess efficacy of 2L osimertinib vs chemotherapy in patients with advanced or metastatic EGFR T790M+ NSCLC (87)
- FLAURA (phase III): double-blind, randomised trial to assess 1L efficacy and safety of osimertinib vs standard of care (géfitinib or erlotinib) in patients with advanced or metastatic EGFR Mut+ NSCLC. In results of this study, presented at the 2017 and 2018 ESMO Congress, osimertinib demonstrated a progression-free survival (PFS) rate of 18.9 months (95% CI, 12.5-21.4) versus 10.2 months (95% CI, 9.6-11.1) for standard therapy (HR, 0.46; 95% CI, 0.37-0.57; P <.0001). The median duration of response was 17.2 months versus 8.5 months. The objective response rate was similar in the two groups. Overall survival was not yet reached at the interim analysis had not yet been reached (88,89).

All of the EGFR TKI treatments cited above have an oral administration. Some characteristics of each molecule are summarized in the Table 9 .

Rociletinib (CO-1686), also a 3rd gen EGFR TKI, was under investigation in this setting but its development was terminated by Clovis Oncology in May 2016 following concerns over its benefit-risk profile.

Table 9. Characteristics summarize of erlotinib, gefitinib, afatinib and osimertinib (91–94)

Company	Roche	AstraZeneca	Boehringer Ingelheim	AstraZeneca
Generic name	Erlotinib	Gefitinib ZD1839	Afatinib BIBW 2992	Osimertinib AZD-9291
Brand name	TARCEVA®	IRESSA®	GIOTRIF®	TAGRISSO®
Class	Small molecule reversible TKI	Small molecule reversible TKI	Small molecule irreversible TKI	Small molecule irreversible TKI
Target	EGFR	EGFR	EGFR, HER2, ErbB4	EGFR, T790M resistance mutation
Dosing	150mg/day	250mg/day	40mg/day	80mg/day
Formulation	25mg, 100mg and 150mg film-coated tablets	250mg fil-coated tablets	20mg, 30mg, 40mg, 50mg film-coated tablets	40mg and 80mg film-coated tablets
Administration	Oral	Oral	Oral	Oral
Indications/ approvals in EU (EMA)	<p>Sep 2005: treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen</p> <p>Sep 2011: First-line treatment of EGFR Mut+ NSCLC</p> <p>Jan 2016: switch maintenance treatment of EGFR Mut+ NSCLC in patients with stable disease after first-line chemotherapy</p>	<p>Jul 2009: Treatment of EGFR Mut+ NSCLC in any line of therapy</p>	<p>Sep 2013: first-line treatment of EGFR Mut+ NSCLC</p> <p>Apr 2016: locally advanced or metastatic squamous NSCLC progressing on or after platinum-based chemotherapy</p>	<p>Feb 2016: for the treatment of T790M+ NSCLC after progression with a previous EGFR TKI</p> <p>April 2017: for treatment of T790M Mut+ NSCLC, irrespective of previous treatment with an EGFR TKI</p> <p>April 2018: 1L EGFR Mut+</p>

ALK Translocation

The rationale of ALK-inhibitors is that the proliferation and survival of cells in NSCLC expressing ALK fusion proteins are dependent on ALK signaling, named “oncologic addiction”. Preclinical models have shown that inhibition of ALK in cells expressing EML4-ALK induces apoptosis. So, the ALK fusion proteins have therefore been proposed as therapeutic targets, ALK inhibitors promoting cancer cell death by restoring apoptosis and inhibiting tumor cell growth and proliferation.

The evolution of ALK inhibitors is ALK-inhibitors marked by the development of different generations of ALK inhibitors. The last generations are more and more targeted on the translocation ALK.

XALKORI® Crizotinib

Crizotinib is a small molecule inhibitor of the tyrosine kinase activity of MET, ALK, ROS1 and RON. It is a first generation ALK inhibitor (See Table 10). Crizotinib inhibits ALK receptor activation by blocking the ATP binding site. The results of the Phase III PROFILE 1007 study demonstrate the superiority in terms of progression-free survival of crizotinib versus chemotherapy (pemetrexed or docetaxel) in ALK + patients who have already received first-line chemotherapy (94). This superiority was confirmed in the first line, in patients who did not receive chemotherapy with PROFILE 1014 (95).

Therefore, Crizotinib enters the brain by crossing the blood-brain barrier (BBB). The drug-efflux-transport protein P-glycoprotein (P-gp) is expressed in several tissues, including the liver, pancreas, kidney, colon and at high levels in the brain. Crizotinib is effectively exported to the BBB in the bloodstream by P-gp in an ATP-dependent manner and therefore has a low brain-to-plasma ratio. In the PROFILE 1014 study of first-line crizotinib vs. chemotherapy in patients with ALK + NSCLC, crizotinib demonstrated modest activity in the CNS. The active

transport of crizotinib out of the brain by P-gp may result in a low brain-to-plasma ratio of crizotinib, and therefore explain why the CNS is a frequent site of relapse in crizotinib-treated patients.

Unfortunately the use of crizotinib leads to certain resistance mechanisms with, in particular, secondary mutations in the ALK gene, an increase in the number of copies (copy number gain, CNG) of EML4-ALK per cell or other oncogenic drivers are at the origin of crizotinib resistance.

Table 10. Summary of XALKORI® (Crizotinib) characteristics (96)

Company	Pfizer
Generic name	Crizotinib PF-2341066
Brand name	XALKORI®
Class	TKI
Target	ALK, MET, ROS1 and RON
Dosing	250 mg twice a day
Formulation	200mg and 250 mg capsules
Administration	Oral (with or without food)
Indications/ approvals in EU (EMA)	October 2012: Patient with metastatic NSCLC ALK or ROS-1 positive disease; all line

ZYKADIA® Céritinib

Ceritinib is an inhibitory ALK, 2nd generation, developed by Novartis (See Table 11). Its ASCEND clinical program, a set of phase I to III clinical trials, has demonstrated the benefit of using ceritinib in patients with first- and second-line NSCLC, and particularly in post-progression use with crizotinib in the first line. As a substrate of P-gp, ceritinib is exported from the brain via the blood-brain barrier. Like crizotinib, ceritinib does not have a high CNS

/ plasma ratio. A control of brain metastases with these treatments seems difficult. Preclinical studies have also shown a high incidence of cerebral relapse (97).

Table 11. Summary of ZYKADIA® (Ceritinib) characteristics (97)

Company	Novartis
Generic name	Ceritinib LDK-378
Brand name	ZYKADIA®
Class	TKI
Target	ALK
Dosing	750 mg once daily
Formulation	150 mg capsules
Administration	Oral without food (1 hour before or 2 hours after meal)
Indications/ approvals in EU (EMA)	May 2015: Patient with metastatic NSCLC ALK positive disease; all line

ALECENSA® Alectinib (2G)

Alectinib prevents autophosphorylation of the ALK receptor, and therefore inhibits intracellular signaling involved in tumor proliferation and survival (See Table 12). By studying preclinical models, alectinib has good penetration of the brain. Indeed, unlike crizotinib and ceritinib, alectinib is not a substrate for P-gp and therefore shows a high-brain-to-plasma ratio (98).

All the clinical trials of the clinical program seem to confirm the good brain penetration of alectinib. The ALUR study is a phase III, randomized, multicenter open. This is a comparison to evaluate the efficacy and safety of alectinib (72 patients) versus standard chemotherapy (docetaxel or pemetrexed) (35 patients) in patients with non-small-sized bronchial cancer. ALK+ NSCLC previously treated with platinum-based chemotherapy and crizotinib. At the January 26, 2017 cut-off date, the median progression-free survival assessed by the

investigators in the ITT population was 9.6 months (95% CI: [6.9-12.2], $p < 0.001$) in the alectinib arm and 1.4 months in the chemotherapy arm (95% CI: [1.3-1.6], $p < 0.001$) (99).

The ALEX study is a randomized, multicentre, open-label, phase III study comparing alectinib (152 patients) versus crizotinib (151 patients) for ALK + NSCLC-naive patients. The median progression-free survival assessed by the investigators was not achieved for patients on the alectinib arm and was 11.1 months for crizotinib arm patients (9.1 - 13.1). The hazard ratio is evaluated at 0.47 (95% CI: 0.34 - 0.65), $p < 0.0001$). The median progression-free survival assessed by an independent committee was achieved for both treatment arms with 10.4 months (7.7 - 14.6) for the crizotinib arm and 25.7 months (19.9 - not estimated) for the alectinib arm. The hazard ratio is 0.50 (95% CI 0.36-0.70, $p < 0.0001$). Median overall survival is not achieved for both treatment arms (100).

Table 12. Summary of ALECENSA® (Aletinib) characteristics (101)

Company	Roche (Chugai)
Generic name	Alectinib RG7853
Brand name	ALECENSA®
Class	TKI
Target	ALK and RET
Dosing	600mg twice a day
Formulation	20mg, 40mg and 150mg capsules
Administration	Oral with food
Indications/ approvals in EU (EMA)	February 2017: Patient with metastatic NSCLC ALK; 1L or after crizotinib failure

Two others treatments are forthcoming: brigatinib (2G TKI) and lorlatinib (3G TKI).

Wild Type Patients

AVASTIN® Bévacicizumab

VEGF, a diffusible glycoprotein produced by normal and neoplastic cells, is an important regulator of physiologic and pathologic angiogenesis. Increased levels of VEGF expression have been found in most human malignancies examined to date, including tumors of the lung, breast, thyroid, gastrointestinal tract, kidney, bladder, ovary, cervix and pancreas, as well as angiosarcomas and glioblastomas. Increased VEGF serum levels have been correlated with poor survival. Bévacicizumab is a recombinant humanized anti-vascular endothelial growth factor (anti-VEGF) monoclonal immunoglobulin G1 (IgG1) antibody. Bévacicizumab binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralizing the biological activity of VEGF regress the vascularization of tumors, normalizes remaining tumor vasculature, and inhibits the formation of new tumor vasculature, thereby inhibiting tumor growth (102).

A phase III study, ECOG 4599, was conducted in patients with non-squamous NSCLC comparing the efficacy of carboplatin and paclitaxel plus or minus bévacicizumab. The results of this study were favorable for the combination carboplatin + paclitaxel + bévacicizumab in the general population of the study in terms of overall survival (HR = 0.79, 95% CI: 0.67-0.92) (103). (See Figure 22)

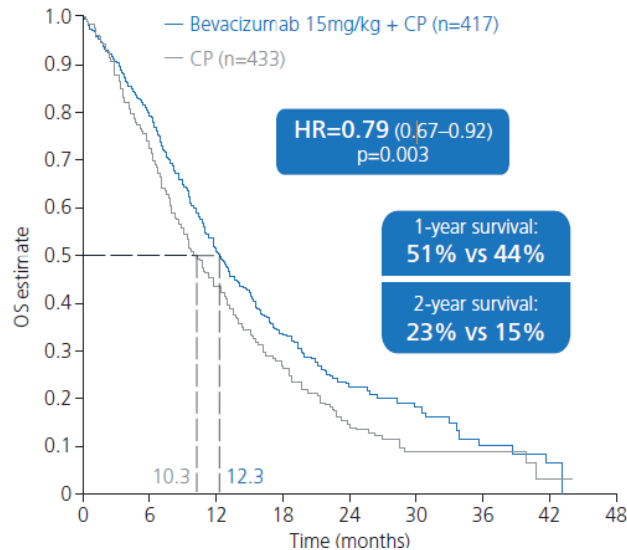


Figure 22. OS with b vacizumab + platine doublet versus platine doublet in 1L non squamous NSCLC (103)

Paradigm Shift: Cancer Immunotherapy (CIT)/ Phenotypes

The evolution of therapies could have suggested that only targeted therapies were beginning to take their place in the cancer landscape, but that is without counting on the arrival of immunotherapy, causing a paradigm shift. CIT changes the vision of the cancer treatment. While chemotherapy and targeted therapy are targeting directly the cancer cells, CIT are molecules targeting the immune system in order to increase its efficiency against the cancer. The genetic and cellular alterations that characterized cancer cells can be recognized by the immune system as foreign, resulting in T cells being able to kill cancer cells. The entire process by which the immune system recognizes targets and kills cancer cells is described by the cancer-immunity cycle. For an anticancer immune response to lead to effective killing of cancer cells, a series of stepwise events must be initiated and allowed to proceed and expand iteratively (the cancer-immunity cycle):

- Step 1 : Release of cancer cell antigens

- Oncogenesis (the formation of cancer) can produce tumor-specific antigens: neoantigens which are mutated or overexpressed proteins that are released by tumor cells
- Step 2 : Cancer antigen presentation
 - Tumor-specific antigens are captured by antigen presenting cells (APCs) for processing
 - Antigens originating from within the epithelia are captured by APCs in the tissue
 - Antigens that enter the bloodstream are captured by APCs in the spleen
 - APCs transport the tumor-associated antigens through the lymphatic system to the lymph nodes
 - APCs present tumor-associated antigens, to T cells via MHC molecules
- Step 3 : Priming and activation
 - When a T cell encounters an antigen-presenting cell to which it can bind, it will initiate an activation program, requiring three sets of signals: a cascade generated by the TCR, a cascade generated through the costimulatory molecules (B7:CD28) and cytokines
 - T-cell activation is regulated by immune checkpoints: costimulatory and inhibitory interactions that protect against auto-immunity and excessive immune responses
- Step 4 : Trafficking of T cells to tumors

- Activated T cells enter the bloodstream and traffic to the site of the tumor, migrating across the endothelial barrier into the tumor bed
- T cells are attracted to the site of action by selectins

- Step 5: Infiltration of T cells into tumors
 - T cells roll along the endothelial layer until chemokines trigger firm adhesion
 - T-cell adhesion occurs through binding of T-cell integrin to endothelial molecules
 - T cells migrate through the endothelial layer to the site of action
 - T-cell trafficking can be impaired by the tumor microenvironment

- Step 6 : Recognition of cancer cells by T cells
 - T cells recognize tumor cells through binding of the T Cell Receptor (TCR) to its specific antigen presented by major histocompatibility complex (MHC) class I molecules
 - Interactions between the peptide:MHC complex and the TCR can be costimulated or inhibited by a wide range of immune checkpoint interactions

- Step 7: Killing of cancer cells
 - Activated effector T cells directly kill target cells by cell-mediated cytotoxicity
 - Killing of cancer cells releases additional tumor-associated antigens
 - This reinitiates the cancer-immunity cycle, with an increased depth and breadth of responses in subsequent cycles, a process called epitope or antigen spreading

Tumors can inhibit the antitumor response by disrupting the balance governing the steps of the cancer-immunity cycle through a specific pathway or a combination of pathways, known as

immune checkpoints. Cancer can grow when the immune system is unable to generate an effective anti-cancer immune response. There are a number of mechanisms through which tumor cells can escape immune destruction (See Figure 23).

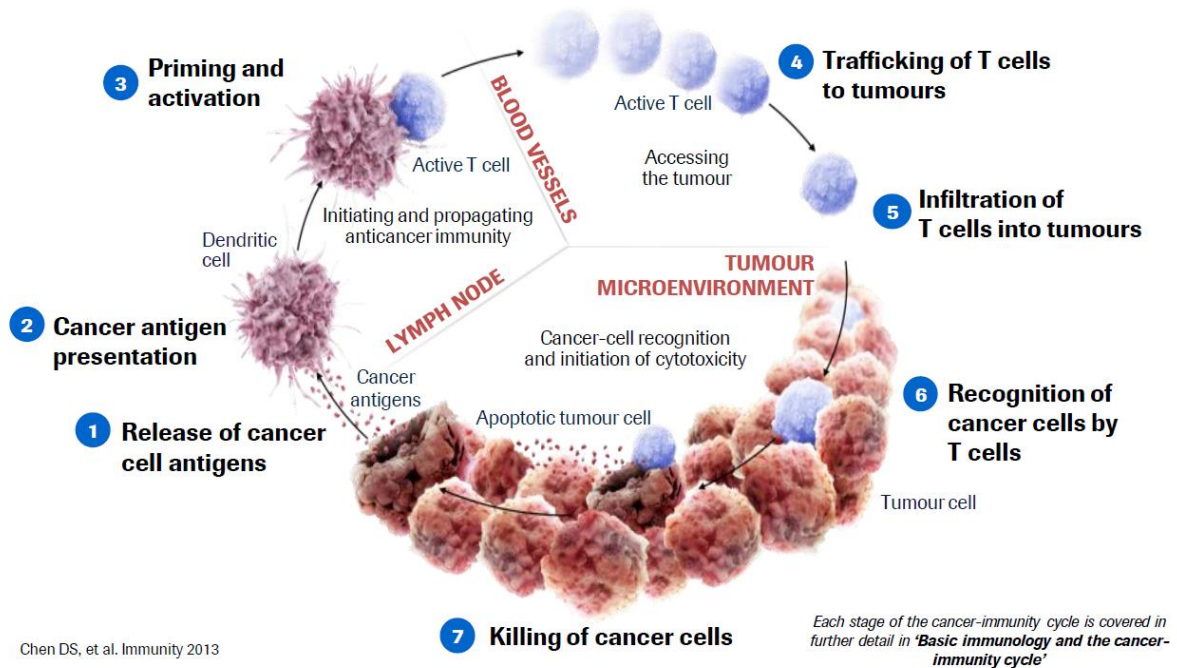


Figure 23. Cancer immunity circle (from (104))

Immune checkpoints are regulatory pathways in the immune system that ensure an appropriate duration and amplitude of immune response and therefore are crucial for modulating immune responses, preventing autoimmunity, minimizing collateral damage. Tumors can inhibit the antitumor response by disrupting the balance governing the steps of the cancer immunity cycle through specific checkpoints (such as the PD-L1 pathway). Therefore, the anticancer immune response can potentially be enhanced by activating stimulatory checkpoints that promote the immune response and blocking inhibitory checkpoints that downregulate the immune response, such as the PD-L1 pathway (See Figure 24).

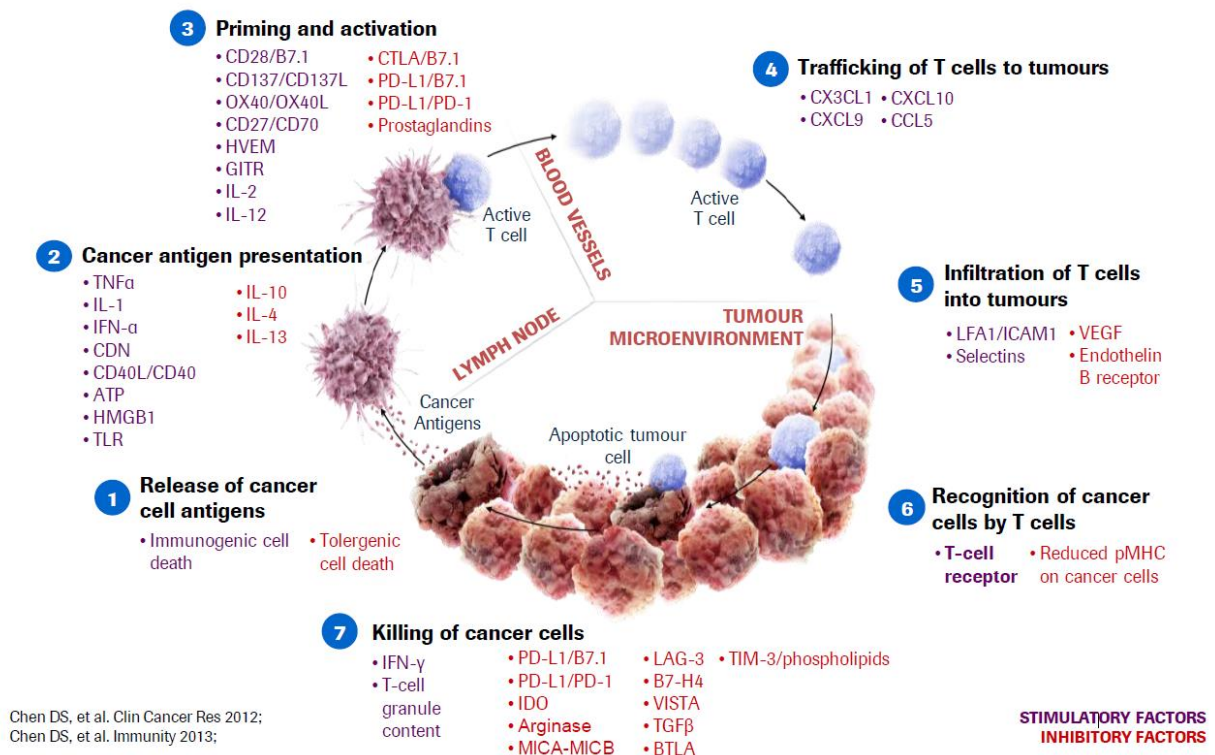


Figure 24. Possible checkpoint inhibitor in the cancer immune cycle (from (94))

Anti-PD1

Nivolumab (OPDIVO®) and Pembrolizumab (KEYTRUDA®) are anti-PD1 drugs. Targeting of PD-1 blocks co-inhibitory signaling between the tumor cell and PD-1, sparing the interaction between the tumor cell and B7.1. Blocking PD-L2/PD-1 interactions involved in immune homeostasis and can potentially increase autoimmunity. In lung cancer, nivolumab is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Pembrolizumab is indicated in second line of NSCLC for patients with PDL1 status superior at 1% following results of the pivotal study KEYNOTE-010 and in first line for patients with a PDL1 status superior at 50% following results of the pivotal phase III study KEYNOTE-024 (107–110).

Anti-PDL1

Targeting PD-L1 can block co-inhibitory signaling between the tumor cell and both PD-1 and B7.1, preventing down-regulation of T-cell activity. The preservation of PD-L2/PD-1 interaction can minimize effects on immune homeostasis but no clinical data can have yet show this possibility. This interaction may contribute to the prevention of autoimmune responses, particularly in the lung to avoid pneumonitis.

Atezolizumab (TECENTRIQ®) is a humanized immunoglobulin (IgG1) monoclonal antibody that is produced in Chinese hamster ovary cells. Atezolizumab targets programmed death ligand 1 (PD-L1) on tumor-infiltrating immune cells (ICs) or tumor cells and prevents interaction with the programmed death-1 (PD-1) receptor and B7.1 (CD80), both of which function as inhibitory receptors expressed on T cells and other immune cells. Interference of the PD-L1:PD-1 and PD-L1:B7.1 interactions may enhance the magnitude and quality of the tumor-specific T-cell response through increased T-cell priming, expansion, and/or effector function. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and, consequently, eliminates detectable Fc-effector function. By eliminating Fc-effector function and antibody-dependent cell-mediated cytotoxicity, antibody-mediated clearance of activated effector T cells is also eliminated (109). And forthcoming, durvalumab (IMFINZI®) has shown impressive a result for stage IIIA patients with is last study PACIFIC. Avelumab (BAVENCIO®) is also in development in lung cancer and already have market authorization in other diseases (110,111).

The following Table 13 show the different immunotherapies currently involved in phase III clinical trials.

Table 13. Summary of immunotherapy characteristic in NSCLC IIB/IV (110–114)

Company	Bristol-Myers Squibb	MSD	Roche	AstraZeneca	Merck KGaA/Pfizer
Generic name	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab	Avelumab
Brand name	OPDIVO®	KEYTRUDA®	TECENTRIQ®	IMFINZI®	BAVENCIO®
Class	mAb (IgG4)	mAb (IgG4)	mAb (IgG1)	mAb (IgG1)	mAb (IgG1)
Target	PD-1	PD-1	PD-L1	PD-L1	PD-L1
Dosing	3mg/kg q2w (EU) or 240mg q2w (US)	2mg/kg q3w (EU in $\geq 2L$) Up to come: 200mg q3w (EU in 1L; US 1L and $\geq 2L$)	1200mg q3w	20mg/kg q4w	10mg/kg q2w
Administration	Intravenous infusion (60 minutes)	Intravenous infusion (30 minutes)	Intravenous infusion (30 minutes)	Intravenous infusion	Intravenous infusion
Indications/approvals in previously treated NSCLC	June 2015: metastatic NSCLC after prior chemotherapy <i>No diagnostic required</i>	Sept 2016: metastatic NSCLC PD-L1 positive NSCLC after prior chemotherapy <i>Diagnostic required: PD-L1 TPS $\geq 1\%$ with Dako 22C3</i>	Sept 2017: metastatic NSCLC after prior chemotherapy <i>No diagnostic required</i>	Not yet approved	Not yet approved
Indications/approvals in first-line NSCLC	Not yet approved	FDA/EMA: previously untreated, metastatic NSCLC with high PD-L1 expression [‡] <i>Diagnostic required: PD-L1 TPS $\geq 50\%$ (Dako 22C3)</i> FDA (accelerated approval): in combination with pemetrexed and carboplatin for previously untreated, metastatic, non-squamous NSCLC regardless of PD-L1 expression <i>No diagnostic required</i>	Not yet approved	Not yet approved	Not yet approved
Diagnostic assay	28-8 (Dako platform)	22C3 (Dako platform)	SP142 (Ventana platform)	SP263 (Ventana platform)	73-10 (Dako platform)

Regarding the development plan of the laboratory, most of the laboratories engaged in the immunotherapy development in NSCLC are expecting Phase III pivotal study results during the 201 and the upcoming years.

Following the evolution of molecules development, the landscape will radically move in the upcoming years. Actually, 100% of patients in 2nd line or more are eligible for immunotherapy in 2017 and 80% in 2018. Indeed, the arrival of immunotherapies in first line, modifies the landscape of the second line, because for now no study was conducted on the possible succession of lines and a re-challenge of immunotherapies. Thus, patients who have received first-line immunotherapy are not eligible for second-line immunotherapy. Following the commercialization of pembrolizumab in 1L, the proportion of naïve immunotherapy patients who arrive in second line from 2019 is 25%. The new data concerning associations in the first instance of PD-L1 status tend towards a wide use of immunotherapy in the first line.

Upcoming Combinations with Immunotherapies

The association of different therapy can enhance the cancer immunity profile. Inflamed, or immunologically responsive, tumors have specific features that differentiate them from immunologically unresponsive tumors. Understand tumor immune biology drives identification of potential targets and biomarkers. (112,113) (See Figure 25)

Different immune profiles of patients with cancer have been discovered:

- Inflamed profile when T cells infiltrated the tumor but are non-functional. Checkpoint inhibition is adapted therapy because it can stand the inhibition by cancer cells.

- Immune excluded profile show accumulated T cells around the cancer but cannot infiltrate the cancer. For this profile, therapy allowing the infiltration can be a solution to enhance the CIT and can be potentialized by immune checkpoint in order to limit tumor inhibition.
- Immune desert profile show the absence of T cells in the tumor and the environment of the tumor. Treatments which increase the number of T-cells can be an interesting pathway to develop the immune fighting against cancer.

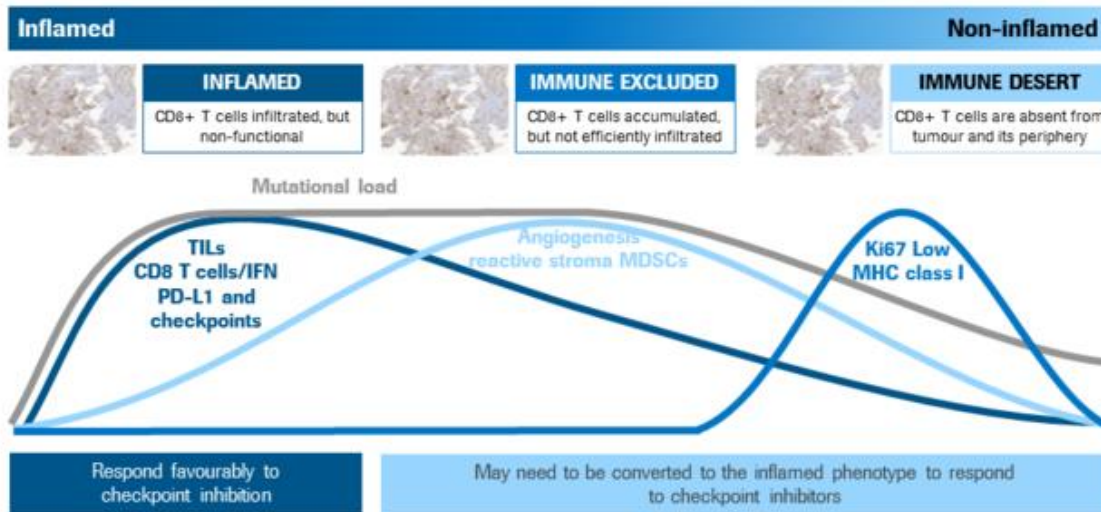


Figure 25. Three identified profiles of cancer immunity (112,113)

These possible associations and personalized care for lung cancer can in the long run lead to a sharp increase in the impact of cancers on health care costs. Ongoing studies and the results of a first phase III study of combination therapies have shown promising early results.

MSD will probably extend nivolumab indication for treatment naïve NSCLC patient probably in Q3 2018 with its pivotal Phase 3 CheckMate-227 which reached its co-primary endpoints. CheckMate-227 study met the PFS with the association of nivolumab plus ipilimumab versus chemotherapy, the median PFS was 7.2 months versus 5.5 months ($P < 0.001$) and the ORR was respectively 45.3% versus 26.9%. Biomarkers represent a notable evolution in this study as these results are significant in patients following their Tumor Mutation Burden (TMB) and not their PD-L1 expression. This study shows the interest of the TMB as potential new biomarker to identify responding patient for immunotherapies. Nivolumab will probably never obtain MA in monotherapy for the first line as the pivotal Phase III study CheckMate 026 evaluating nivolumab monotherapy versus chemotherapy did not reach its primary endpoint (114,115).

This is the same for IMpower150 study, evaluating the combination of atezolizumab associated with bévacizumab and a platine doublet versus bévacizumab with a platine doublet standard of care (SoC). The median progression-free survival in the WT population was 8.3 months with atezolizumab-bévacizumab-chemotherapy versus 6.8 months with bévacizumab-chemotherapy with a statistically significant improvement (Hazard Ratio 0.62, $p < 0.001$). This study also focus on patient with Tef-high WT population which can be a new possibility to classify patient and also be a potential biomarker to predict the response of the patient (116).

The results of the KEYNOTE-189 study evaluating the combination of chemotherapy with pembrolizumab in the first line are also under study. The estimated rate of OS at 12 months was 69.2% in the pembrolizumab-combination group versus 49.4% in the placebo-combination group

(HR = 0.49; $p < 0.001$). The improvement in OS was seen in all PD-L1 categories that were evaluated. The PFS was also statistically significant (HR = 0.52; $p < 0.001$) (117).

A summary of all therapies and studies with immunotherapies are available in the Annexes (Annex 2 and Annex 3).

2.4 Guidelines

Different guidelines are currently available. At an international level, the ASCO (American Society of Clinical Oncology) guidelines (118) are the most following and known. In the Europe, most known guidelines are the ESMO (European Society for Medical Oncology) guidelines (119). In France we used the AURA (Auvergne Rhône-Alpes) guidelines (120) which are reviewed every year by a committee of French expert in the domain. These last guidelines, from 2018, are included in the *Annex 4*.

3. Material and Methods

3.1 Objectives

Non-small cell lung cancer (NSCLC) is a cancer with a high incidence and therefore a significant impact on public health expenditures. The prevalence will probably increase in the coming years thanks to the positive effect of the arrival of new therapies. These innovative therapies, however, represent a higher cost than current chemotherapy. This therefore raises the question of the impact of these new medical costs in the management of lung cancer, with a view to evaluating health insurance. This analysis assumes that in 2022 the system of coverage by health insurance will be equivalent to that currently in place. The goal here is to create a budget impact model for all therapies available for the management of non-small cell advanced or metastatic lung cancer and not just for treatment.

Medico-economic assessment is a new discipline, (2) which has become more important in recent years, particularly for health policy, due to the increase in health expenditure in a limited funding models. In France, in 2008, Act allowed HAS missions to publish recommendations and medico-economic assessments on the most efficient cares, prescribing or care strategies (3). More recently, in 2016, the Framework Agreement between the CEPS and the LEEM, (10) planned the requirement of an assessment of efficiency for pharmaceutical companies which request I, II or III ASMR levels for expensive treatments (11). The objective of these evaluations is to learn about the costs involved and to find solutions to maintain an egalitarian and ethical health system by

optimizing the allocated resources. There are now methodological guides, proposed by the HAS, to conduct medico-economic analyzes (2).

In order to quantify the total costs of advanced and metastatic lung cancer over the next few years, a model is created for this work incorporating a number of parameters described below. The model in this work is static and assesses the costs of lung cancer in one year for the incident population. This means that the model relates to the number of patients in a particular therapeutic line with a particular treatment regardless of its evolution over time or its therapeutic pathway. The objective here is to formulate hypotheses on the evolution of the management of bronchopulmonary cancer according to the evolution of the market. The assumptions are formulated at 5 years, so for the year 2022.

The main assumptions of this model are:

- Patients are classified by histology and existing mutation or translocation,
- An identical mortality rate is applied to all patients in the model,
- Patients are assessed statically, at a given time,
- For adverse events, an overall cost is applied to all patients treated with the same treatment to simplify the model,
- It is assumed that all patients are managed as part of their long-term illness (ALD).
- Management algorithms are formulated based on available results and assuming that current Phase III studies will meet their primary criteria.

The costs taken into account in the model are direct medical costs in accordance with the recommendations of the HAS (12)

The costs included in the template are as follows:

- Costs related to the consultation (13,14),
- Costs related to testing (13–15),
- Costs related to medical transport (14,17),
- Costs related to the acquisition of treatments (14),
- The costs of administering the treatment (14,18),
- Costs related to the specific follow-up for each treatment (14,16,19,20),
- Costs related to adverse events (14,21),
- The associated costs of palliative hospitalization (14,19,21,22),

All these costs are calculated per cycle and then reported to the month or year.

3.2 Primary Analysis

3.2.1 Study Population

Table 14 identifies the repartition of lung cancer in the French population and the target population of the analysis (See Results Regarding Lung Cancer Financing: State of Art and Upcoming Evolution (2017 – 2022)) (4).

Table 14. Study population evolution until 2022 (Annex 5)

Population projection	2017	2018	2019	2020	2021	2022
INCIDENCE						
NSCLC IIIB-IV (67,5% NSCLC) + NSCLC I-IIIa with an evolution to IIIB-IV during the year (40% of stage I-IIIa)	31785	32327	32901	33509	34153	34834
NSCLC IIIB-IV with ALK+ rearrangement (5% NSCLC)	1589	1616	1645	1675	1708	1742
NSCLC IIIB-IV with EGFR+ mutation (11% NSCLC)	3496	3556	3619	3686	3757	3832
NSCLC IIIB-IV with ROS1 mutation (1% NSCLC)	318	323	329	335	342	348
NSCLC IIIB-IV wild type (83%)	26382	26831	27308	27813	28347	28912
NSCLC IIIB-IV wild type squamous (26,3%)	6938	7057	7182	7315	7455	7604
NSCLC IIIB-IV wild type non-squamous (73,7%)	19443	19775	20126	20498	20892	21308

3.2.2 Diagnosis Costs

A diagnostic test should be performed upstream of the treatment to identify ALK + translocation and EGFR + mutations. A 100% test rate should therefore be achieved for each center, however, considering the variability with the sites and sometimes the absence of ALK and

EGFR test for some patients, a value of 90% of test performed on patients is ALK and 95% for the EGFR for 2017 and 2018. The assumption is also that the test rates for these mutations should evolve with routine integration and equipment in the laboratory. Rates are therefore increased to 99% for the following years in the study. Regarding the PD-L1 diagnostic test, that is not always routinely done, but also tends towards a generalization of this test. It is therefore assumed in this study that from 2017 to 2018, 85% of diagnosed patients will be tested and that by 2019, approximately 90% of patients will be tested. All information is summarized in the following Table 15 (13–15).

Table 15. Diagnostic test evolution of use and costs (IHC)

Diagnostic test	2017-2018	Price (€)	2019-2022	Price (€)
EGFR	95%	€ 7.00/test € 6.30/patient	99%	€ 7.00/test € 6.93/patient
ALK	90%	€ 73.96/test € 66.56/patient	99%	€ 73.96/test € 73.22/patient
ROS1	90%	€ 9.58/test € 8.62/patient	99%	€ 9.58/test € 9.48/patient
PD-L1	85%	€ 4.94/test € 4.20/patient	90%	€ 4.94/test € 4.45/patient
TOTAL	/	€ 85.68/patient	/	€ 94.08/patient

Regarding the costs of these diagnosis tests, the majority is not standardized and sometimes hospitals used their own antibodies in order to reduced costs. These costs are currently at the change of the hospital, but the hypothesis is made that in the upcoming years, the diagnosis test can be included in the reimbursement model.

3.2.3 Acquisition Costs

Acquisition costs are calculated according to the recommended dosage in the Summary of Product Characteristics (SmPC) of the molecules, and to the cost per dose. Regarding the intravenous (IV) administered molecules, the model does not take into account the remainders (units not consumed but invoiced). The benchmark analysis therefore considers that there is a loss of product for these molecules. For the different treatment lines included in the model it is necessary to estimate treatment duration. Thus, the average treatment times of the different molecules are based on the progression-free survival data obtained in the clinical trials.

The acquisition costs are expressed in € 2017. They are based on health insurance rates (PPTTC) for the molecules administered in the city and the molecules of the list in addition. For the rest, the treatments used in hospitals are included in the homogeneous hospital stay groups (Groupe Homogène de Séjour; GHS). Note that in this analysis the difference between the actual price and the negotiated price is not integrated. In fact, in negotiations between the state and the pharmaceutical companies, two prices are determined: the face price and the net price of the drug. The net price of the medicine corresponds to the actual price fixed with the CEPS. The face price corresponds to the negotiated price, perceived by the laboratories and really assumed by the insurance. Pharmaceutical companies agree to reimburse the difference between the 2 to the health insurance. This mechanism is part of a set of provisions used to limit price increases and ensure compliance with the Schengen Agreement. This agreement nevertheless has an impact on price inflation because the costs are negotiated and reimbursed to the health insurance, but this is not the case for the voluntary health insurance with the city treatments with a 65% reimbursement. Difference in prices is not reimbursed by the laboratories to the voluntary health insurance.

Summary of acquisition costs of drugs used in this model is reported in the Table 16 (14).

Table 16. Summary of acquisition costs used in the model

Costs Item	Acquisition mensual Costs	Dosage	Schema
Atezolizumab TECENTRIQ	€ 5,394.75 (hypothesis)	1200mg IV	Q3W until PD
Nivolumab OPDIVO	€ 4,839.846	3mg/kg IV	Q2W until PD
Pembrolizumab KEYTRUDA	€ 5,949.655	2mg/kg IV	Q3W until PD
Chemotherapy /	€ 2,341.52	Variable regarding the treatment used, majority of time in mg/m ² IV.	21 days cycle 4 to 6 cycles
Pemetrexed ALIMTA	€ 2,752.56	500 mg/m ² IV	21 days cycle 4 to 6 cycles Possible maintenance
Erlotinib TARCEVA	€ 2,195.88	100mg PO	until PD
Alectinib ALECENSA	€ 6,455.32 (hypothesis)	600mg PO	2x/day Every day until PD
Crizotinib XALKORI	€ 5,238.72	500mg PO	until PD
Ceritinib ZYKADIA	€ 4,983.42	750mg PO	until PD
Brigatinib ALUNBRIG	€ 4,983.42	180 mg PO	until PD

Bévacizumab AVASTIN	€ 1,930.48	7,5mg/kg or 15mg/kg	21 days cycle Possible maintenance
Afatinib GIOTRIF	€ 1,870.48	40mg PO	until PD
Gefitinib IRESSA	€ 2,059.74	250mg PO	until PD
Osimertinib TAGRISSO	€ 2,059.74	80mg PO	until PD
Lorlatinib /	€ 6,500.00 (hypothesis)	100mg PO	until PD

3.2.4 Costs Associated With Medical Transportations

It is considered that each IV administration is accompanied by a transport of the patient. On average, in France, between 50 and 70% of patients use a medical transport. For this study, a percentage of 60% of patients who come with a medical transport is retained. According to a report by the Court of Auditors (Cour des Comptes), 50.1 million professionalized seated transports were covered by health insurance in 2010. This corresponded to an amount of 1.9 billion euros. The estimated average cost associated with a medical transport, all types of medical transport combined, is therefore € 37.92 (in € 2010). Considering the health sector CPI between 2010 (value in June 2010: € 104.31) and today (value in May 2017: € 98.57), the average cost of a health transport, discounted in € 2017 is € 35.83. Considering that a sanitary transport always consists of

one way and one return, the average cost of round trip, in sanitary transport, is € 71.67. It is important to note that this cost is not specific to the patients of the indication under study. (14,17)

3.2.5 Costs of Drug Administration

The valuation of the cost of an intravenous (IV) injection of chemotherapy is globalized and based on the price of GHS MCO 2016 (Homogeneous Stay Groups Medical Surgery and Odontology; Groupe Homogène de Séjour Médical, Chirurgie et Odontologie) associated with GHM (Homogeneous medical group; Groupe Homogène de Maladie) 28Z07Z "Chemotherapy for tumor in sessions" and 17M06T "Chemotherapy for another tumor, very short term. These GHMs were found from the ATIH site, using the main diagnosis Z511 "Tumor Chemotherapy Session". (12) Here, the difference in calculation and support has been incorporated into the model to account for differences in private and public sector costs, and the distribution of staff between GHM is used to estimate a weighted average.

For the treatments include in the GHS, the weighted costs of GHM 28Z07Z and 17M06T for a session is estimated at € 347.03 (€ 2017). For treatments include in the GHS sus list, specific costs are described in the Table 17 (14,18).

Table 17. Administration costs regarding the drug administrated

Costs Item	Costs
Atezolizumab / Nivolumab / Pembrolizumab /Gemcitabine / Docetaxel administration costs	€ 656.58 (per administration)
Bévacizumab administration costs	€ 685,33 (per administration)
Pemetrexed administration costs	€ 700.04 (per administration)

Platinum doublet administration cost	€ 347.03 (per administration)
Alectinib / Crizotinib / Ceritinib / Brigatinib / Lorlatinib / Erlotinib / Afatinib / Gefitinib / Osimertinib administration costs	€ 0.00

Some of the treatments for the management of bronchopulmonary cancer require premedication (eg docetaxel). This premedication incorporates mainly anti-pain and corticosteroids. Reported cost includes the cost of the molecule used (prednisone 100 mg, paracetamol 1000mg) in PPTTC, from the database of medicaments for health insurance, and the cost of pharmacist dispensing fees (€ 1.02/ packaging). Since these costs have a low impact on care, the choice has been made not to include it in the model.

3.2.6 Costs of Treatment Monitoring

The costs of treatment follow-up are calculated from the recommended follow-up in the SmPCs of the molecules. The costs of biological acts are based on the National Biology Coding Table (Table Nationale de Codage Biologique) and associated costs (121). Table 18 shows the necessary follow-up for each molecule. The tests performed during the chemotherapy session are not taken into account because they are included in the GHS costs. For the combination pemetrexed + platinum salt, the monitoring of pemetrexed is included in that of platinum salt.

The security packages for the treatment of a blood sample, the preanalytical treatment package for the patient and the cost of the blood sample are included in the cost of the biological examinations. These packages for all biological acts identified in the SmPC.

The supplement for acts of medical medicine carried out urgently, outside work periods, and travel allowances are not considered in the valuation. It is assumed that biology-related samples are not

taken at the patient's home during work periods. It is assumed that patients do not use medical transportation for performing their biological examinations (14,16,19,20).

Table 18. Biological monitoring associated with each molecule

Treatment	Type of follow-up	Frequency
Xalkori® (Crizotinib)	Liver function	Once a week for 2 months, then once a month if clinically indicated, and more frequently if there is an increase of grade 2, 3 or 4 (hypothesis of 2 times per month)
Chemotherapy Platinum doublet Gemcitabine Docétaxel	Kidney function Liver function Hematopoietic function (Blood Cell Count) Ionograms	Before each administration, so every 3 weeks
Alimta® (Pemetrexed)	Blood Cell Count Kidney function Liver function	Before each administration, so every 3 weeks
Avastin® (bévacizumab)	Proteinuria before and then during treatment	At initiation then every 3 months (hypothesis)
Alecensa® (Alectinib)	Liver function	Twice the first month and once a month (hypothesis once a month)
	Measurement of fasting blood glucose	Periodic (hypothesis once a month)
Alunbrig® (Brigatinib)	Not available	Hypothesis: identical to the new TKI alectinib and ceritinib
Zykadia® (Ceritinib)	Liver function	Twice the first month and once a month (hypothesis once a month)

	Measurement of fasting blood glucose	Periodic (hypothesis once a month)
Tecentriq® (Atezolizumab)	To be determined Thyroid assessment (according to expert opinion)	To be determined At the initiation
Opdivo® (Nivolumab)	No one according to the SmPC Thyroid assessment (according to expert opinion)	At the initiation
Keytruda® (Pembrolizumab)	None in the treatment of myeloma Thyroid assessment (according to expert opinion)	At the initiation
Tarceva® (Erlotinib)	No one	No one
Giotrif® (Afatinib)	No one	No one

After a synthesis and a compilation of all the different costs of monitoring, the costs are resumed in the *Table 19*.

Table 19. Medical costs of monitoring

Costs Item	Medical monitoring costs
Atezolizumab	€ 206.15
Nivolumab	€ 206.15
Pembrolizumab	€ 206.15
Durvalumab	€ 206.15
Chemotherapy	€ 83.67
Erlotinib	€ 206.15
Alectinib	€ 28.89
Crizotinib	€ 24.30
Ceritinib	€ 28.89
Brigatinib	€ 28.89
Bévacizumab	€ 206.15
Afatinib	€ 0.00
Gefitinib	€ 0.00
Osimertinib	€ 0.00
Lorlatinib	€ 0.00

3.2.7 Costs of Consultation

Costs of consultation vary depending on whether the patient is going to a general practitioner, a pulmonologist or an oncologist. Indeed, each doctor has a different remuneration according to his specialty (See costs on Table 20) (13,14).

Table 20. Costs of consultation regarding physician specialization

Physicians	Total costs of consultation	Total number of realized acts	Average cost calculated per consultation
Oncologist	29 329 060	868 034	33.79 €
Pneumologist	201 607 254	3 603 224	55.95 €
General practitioner	6 797 036 243	227 932 645	29.82 €
TOTAL	7 027 972 557	232 403 903	30.24€

After studying the total numbers of acts performed, a compilation of data to determine an average cost of a consultation is performed. The average cost of a consultation selected for this analysis is € 30.24.

It is assumed that each patient makes a first visit after the diagnosis of his illness.

3.2.8 Adverse Events Costs Related

The valuation was made from the point of view of health insurance. For the public sector T2A tariffs are considered and for the private sector the rates associated with the amount of fees estimated in the national study of the common methodology costs of the sector (ENCC) MCO were added to the T2A costs.

Treatment follow-up costs are calculated from the recommended monitoring in the PCR of the molecules. The costs of biological acts are based on the National Biology Coding Table and associated costs. Table 21 shows the necessary follow-up associated with each molecule. It should be noted that tests performed directly during the chemotherapy session are directly considered because they are included in the GHS costs. For pemetrexed + cisplatin combination, pemetrexed monitoring is included in cisplatin.

A special case is that of ALK positive patients who have a higher risk of brain metastases. An additional cost related to the monitoring of brain metastases is therefore applied for these patients as part of this study. All additional costs including intensive care, and continuous monitoring and GHS radiotherapy are considered as well as packages and rates for stays (14,21).

Table 21. Adverse events, medical monitoring and brain metastasis costs according to the molecule

Costs Item	AE Mensual Costs	Medical monitoring costs
Atezolizumab	€ 15.84	€ 206.15
Nivolumab	€ 15.84	€ 206.15
Pembrolizumab	€ 15.84	€ 206.15
Durvalumab	€ 15.84	€ 206.15

Chemotherapy	€ 248.68	€ 83.67
Erlotinib	€ 623.38	€ 206.15
Alectinib	€ 437.44	€ 28.89
Crizotinib	€ 157.41	€ 24.30
Ceritinib	€ 1067.19	€ 28.89
Brigatinib	€ 526.00	€ 28.89
Bévacizumab	€ 450.00	€ 206.15
Afatinib	€ 623.38	€ 0.00
Gefitinib	€ 623.38	€ 0.00
Osimertinib	€ 623.38	€ 0.00
Lorlatinib	€ 623.38	€ 0.00

3.2.9 Costs of Palliative Hospital Stay

The cost estimate for palliative care was based on diagnosis CIM 10 of palliative care: Z515. With the help of the ATIH website, the most associated stay in 2015 for this main diagnosis was found: GHM 23Z02Z "Palliative care, with or without act". The distribution of this GHM between the public and private sector was sought for the year 2014, as well as their survey rate to determine their representativeness in the T2A. This distribution is shown in Table 22 (14,19,21,22).

Table 22. Estimation of palliative hospital stay

	Effectives in 2014	Distribution (%)	Cost of the stay according to T2A	Medical fees (ENCC 2014)	Total costs
Public sector	67 972	77%	€ 4,295	Included in the cost of the stay	€ 291,939,740
Private sector	19 758	23%	€ 4,792	€ 1,341	€ 120,709,130

The assumption is therefore made that the average cost per stay is € 4,703. A fixed rate of mortality is applied per year; it is further assumed that a stay in palliative care before the death of the patient is performed for only 70% of patients at the end of life in 2017 and for only 60% of patients in 2022 (See

Table 23).

Table 23. Consumed volumes and unit costs for estimating end-of-life support costs

Ressources	Volume/Frequency	Unitary cost	Total cost
Palliative cares in 2017	1 stay for 70% of patients	€ 4,703	€ 3,292/patient
Palliative cares in 2022	1 stay for 60% of patients	€ 4,703	€ 2,822/patient

3.3 Secondary Analysis – Sensitivity Analysis

In order to critically evaluate the results that were formulated from assumptions, a sensitivity analysis was conducted in two parts.

3.3.1 Sensitivity Analysis on the Overall Result: Cost Evolution Assumptions

This first part deals with the analysis and the variation of the results in their entirety. The values for the different costs were reported identically between 2017 and 2022, only the population changes. Thus, the primary analysis suggests that the costs are identical between 2017 and 2022 which is unlikely. With the evolution of cares and over time, costs will tend to go down. This primary analysis for 2022 is therefore overestimated. Thus a weighting of each item was made taking into account potential price decreases, whether by re-evaluation or by the entry of generics on the market in terms of acquisition costs, but also of the evolution of technics and other costs.

In this first sensitivity analysis, parameters were modified with 2 amplitudes to finally obtain 3 basic assumptions for 2022, a first hypothesis, the one of the first analysis which is overestimated, it is the maximum hypothesis; a second hypothesis with a lower average price variation, which corresponds to the mean hypothesis and finally a third hypothesis with a larger downward price variation, which corresponds to the minimum hypothesis.

The rates of change for the mean and minimum assumptions relative to the maximum assumption are summarized in Table 24 and Table 25. These rates of change were selected based on expected monetary impacts based on current costs, competitors' arrivals on the market or the loss of exclusivity of certain treatments (generics).

Generally, during a medico-economic assessment, an update of the costs is carried out in order to evaluate several therapeutic strategies that do not have the same time horizon and not to favor a therapeutic strategy compared to another one (3). This is the case, for example, of daily oral treatment for life versus surgery with a beneficial effect for life. If we compare the treatments over 1 year, the overall cost will be against the surgery which has a beneficial effect that spreads over more than a year. It is therefore necessary to report the benefit of surgery and oral therapy in a coherent time horizon.

For advanced and metastatic NSCLC therapies, the stakes are different and time horizons comparable, with lung cancer at these stages showing only a very limited 5-year survival rate (<5%). The choice was therefore made in this analysis not to take into account the duration of the treatment and to consider each treatment in a similar way on an annual or monthly coverage.

Table 24. Down rates in costs for the minimum and the main assumptions from the maximum assumption for treatment costs (%)

	Chemotherapy		Afatinib		Alectinib		Atezolizumab		Bévacizumab	
	Min %	Main %	Min %	Main %	Min %	Main %	Min %	Main %	Min %	Main %
Acquisition Costs	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%	50%	25%
Administration Costs	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%
Monitoring Costs	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%
AEs Costs	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%
	Brigatinib		Ceritinib		Crizotinib		Erlotinib		Gefitinib	
	Min %	Moy %	Min %	Moy %	Min %	Moy %	Min %	Moy %	Min %	Moy %
Acquisition Costs	0%	0%	5%	2.5%	0%	0%	50%	25%	50%	25%
Administration Costs	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%
Monitoring Costs	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%
AEs Costs	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%
	Lorlatinib		Nivolumab		Osimertinib		Pembrolizumab		Pemetrexed	
	Min %	Moy %	Min %	Moy %	Min %	Moy %	Min %	Moy %	Min %	Moy %
Acquisition Costs	0%	0%	5%	2.5%	5%	2.5%	5%	2.5%	10%	5%
Administration Costs	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%
Monitoring Costs	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%
AEs Costs	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%	5%	2.5%

Table 25. Down rates in costs for the minimum and the main assumptions from the maximum assumption for other medical costs (%)

	Min %	Main %
Consultation Costs	10%	5%
Palliative Costs	10%	5%
Testing Costs	10%	5%
Medical Transport Costs	10%	5%

3.3.2 Sensitivity Analysis: Influence of Each Parameter on the Global Hypothesis

Each expense item independently influences the total cost of average management of advanced or metastatic NSCLC. The objective of this second part is to analyze how each parameter influences independently of the others on the total cost and to determine which parameters influence the most on the management and the overall cost of the disease. For this, each item has been varied from plus or minus 2.5% to plus or minus 50%. The variations were reported in cost per month per patient. In terms of treatment costs, these were analyzed generally and independently. Thus, the results will be presented by the impact of each treatment in the overall care and by the impact of each in the cost items related to treatment (eg. impact of different treatments based on the cost of acquisition).

The next part looks at the results compiling all the data presented in this section. The purpose of analyze aggregates the various areas of costs for health insurance.

4. Results Regarding Lung Cancer Financing: State of Art and Upcoming Evolution (2017 – 2022)

The set of population hypothesis, management and results of the primary and secondary analysis are presented in appendix:

- *Annex 5. Study population evolution until 2022*
- *Annex 6. Algorithm of NSCLC IIIB/IV treatment in 2017 (%)*
- *Annex 7. Algorithm of NSCLC IIIB/IV treatment in 2017 (number of patients)*
- *Annex 8. Algorithm of NSCLC IIIB/IV treatment in 2022 (%)*
- *Annex 9. Algorithm of NSCLC IIIB/IV treatment in 2022 (number of patients)*
- *Annex 10. Analysis of costs in stage IIIB/IV NSCLC per treatment and for other costs for 2017 and 2022*
- *Annex 11. Hypothesis 2022 for costs in stage IIIB/IV NSCLC per treatment and for other costs*
- *Annex 12. Evolution of the total cost per patients per month when modifying each other costs from 0% to 50%: price variation comparing to med hypothesis*
- *Annex 13. Evolution of the total cost per patients per month when modifying treatment costs from 0% to 50%: price variation comparing to med hypothesis*
- *Annex 14. Evolution of the total cost per patients per month when modifying acquisition costs from 0% to 50%: price variation comparing to med hypothesis*
- *Annex 15. Evolution of the total cost per patients per month when modifying administration costs from 0% to 50%: price variation comparing to med hypothesis*

- *Annex 16. Evolution of the total cost per patients per month when modifying monitoring costs from 0% to 50%: price variation comparing to med hypothesis*
- *Annex 17. Evolution of the total cost per patients per month when modifying Adverse Events costs from 0% to 50%: price variation comparing to med hypothesis*

4.1 Primary Analysis

The following results represent first an inventory of the current market (Cf. Table 26). The total monthly cost in 2017 per patient is around € 4,400. If only the cost of treatment (including the cost of acquisition, administration, monitoring and management of adverse effects) is taken into account, the average cost per month per patient is around € 4,000 and represents to itself 93.19% of the medical costs. A study conducted in France between 1998 and 2001 demonstrated that the average annual cost per patient of NSCLC at any stage was approximately € 23,300 or € 2,000 per patient per month (23). These results are consistent with the evolution of the therapeutic landscape and the arrival of targeted therapies, but also nivolumab and pembrolizumab. Moreover, it is important to remember that this work only includes advanced non-small cell lung cancer and metastatic cancer, which is not the case of *Chouaid et al.* study that assesses all NSCLC and SCLC at all stages. This difference has an upward influence on the average cost of care.

Table 26. Summarizing table of annual and monthly costs incurred in advanced or metastatic NSCLC in France (*Annex 10*)

	2017	2022
<i>Treatment Costs per year</i>	€ 1,519,258,196.50	€ 2,467,454,940.56
<i>Consultation Costs per month</i>	€ 961,178.40	€ 1,053,380.16
<i>Palliative Costs per year</i>	€ 104,636,220.00	€ 98,301,548.00
<i>Testing Costs per month</i>	€ 2,723,338.80	€ 3,277,182.72
<i>Medical Transport Costs per month</i>	€ 2,278,030.95	€ 2,496,552.78
TOTAL PER MONTH	€ 141,287,082.86	€ 220,640,156.37

TOTAL PER YEAR	€ 1,695,444,994.30	€ 2,647,681,876.48
TOTAL PER MONTH PER PATIENT	€ 4,445.09	€ 6,334.05
TOTAL PER YEAR PER PATIENT	€ 53,341.04	€ 76,008.55

"Other medical costs", including consultation costs, palliative care costs, testing costs as well as medical transport costs, have little impact on the total cost of care, whether in 2017 or in 2022, representing together only 10% and 7% respectively of the total cost of care.

If the total medical costs of 2017 and 2022 of this first analysis are compared, a change of approximately € 1,900 is recorded in 5 years, a little more than 42% increase.

However, this primary analysis should be interpreted with caution, since the general costs are kept in the same condition as in 2017. Current costs are unlikely to remain the same for treatments on the market, the arrival of certain generics lowering the price of certain treatments and possible revaluations by the CEPS may also influence prices downward. To a lesser extent, other medical costs can also be reduced due to better knowledge of techniques but also cost optimization. This will not necessarily prove to be true in the distant future for, for example, the costs of testing, the cost may increase or be more easily integrated into the reimbursement by health insurance. Thus this first analysis, based on a fictitious population but with actual current costs is overestimated.

A secondary sensitivity analysis with a 5-year cost update will result in a total cost more consistent with what might be expected. This is the purpose of this second part of the results which is detailed in the following section.

4.2 Second Analysis – Sensibility Analysis

4.2.1 Sensitivity Analysis on the Overall Result: Cost Evolution

Assumptions

The cost evolution assumption avoids the comparison bias when the costs of the same factor are evaluated at different time horizons, in 2017 and 2022. The imputation of the different cost variations is detailed in the section Secondary Analysis – Sensitivity Analysis. Table 27 summarizes the data for the minimum, main and maximum assumptions. The maximum hypothesis corresponds to the hypothesis formulated in the first part of the sensitivity analysis for the reasons described above. The main hypothesis corresponds to the most realistic analysis for 2022 and it is from this hypothesis that analyzes of the second part of the sensitivity study will be conducted.

Table 27. Summary table of cost assumptions incurred in advanced or metastatic NSCLC in France (Annex 11)

	min	moy	max
<i>Treatment Costs per year</i>	€ 2,121,966,611.83	€ 2,225,802,183.17	€ 2,467,454,940.56
<i>Consultation Costs per month</i>	€ 948,042.14	€ 1,000,711.15	€ 1,053,380.16
<i>Palliative Costs per year</i>	€ 88,471,393.20	€ 93,386,470.60	€ 98,301,548.00
<i>Testing Costs per month</i>	€ 2,686,119.41	€ 3,113,323.58	€ 3,277,182.72
<i>Medical Transport Costs per month</i>	€ 2,246,897.50	€ 2,371,725.14	€ 2,496,552.78
TOTAL PER MONTH	€ 190,084,226.14	€ 199,751,481.02	€ 220,640,156.37
TOTAL PER YEAR	€ 2,281,010,713.68	€ 2,397,017,772.30	€ 2,647,681,876.48

TOTAL PER MONTH PER PATIENT	€ 5,456.86	€ 5,734.38	€ 6,334.05
TOTAL PER YEAR PER PATIENT	€ 65,482.31	€ 68,812.59	€ 76,008.55

If the new assumptions for 2022 are compared to the analysis of 2017, an increase in the cost per patient of 29% and 23% is found for the main and minimum assumptions respectively. For the main hypothesis, this represents a cost of around € 1,290 per patient per month. With this new adjustment, the cost attributed to therapies represents 92.86% of the total medical costs of this study, which does not change the order of magnitude of the impact of therapies in the management of advanced or metastatic NSCLC patients. Thus, the largest expense item of medical expense is the cost of the therapy used, and in particular the costs of treatment acquisition alone. It accounts for 65.50% of medical care.

Not all patients are under the same therapies or combinations of therapies, some expensive treatments are only given to a limited number of patients. So if we look only at the notion of cost of treatment, the analysis is wrong because the population is different for each treatment. The objective of the secondary sensitivity analysis is to know which therapy has the greatest impact on the overall management of NSCLC patients but also to determine for each treatment which specific cost has the greatest impact on total medical costs. All this is achieved by considering the specific population of each treatment. The analysis was also performed on other medical costs (ie. non-treatment costs).

4.2.2 Sensitivity Analysis: Influence of Each Parameter on the Main Hypothesis

Treatments that most impact the management of NSCLC IIB/IV are pembrolizumab and atezolizumab followed by chemotherapy and nivolumab (Cf. Figure 26).

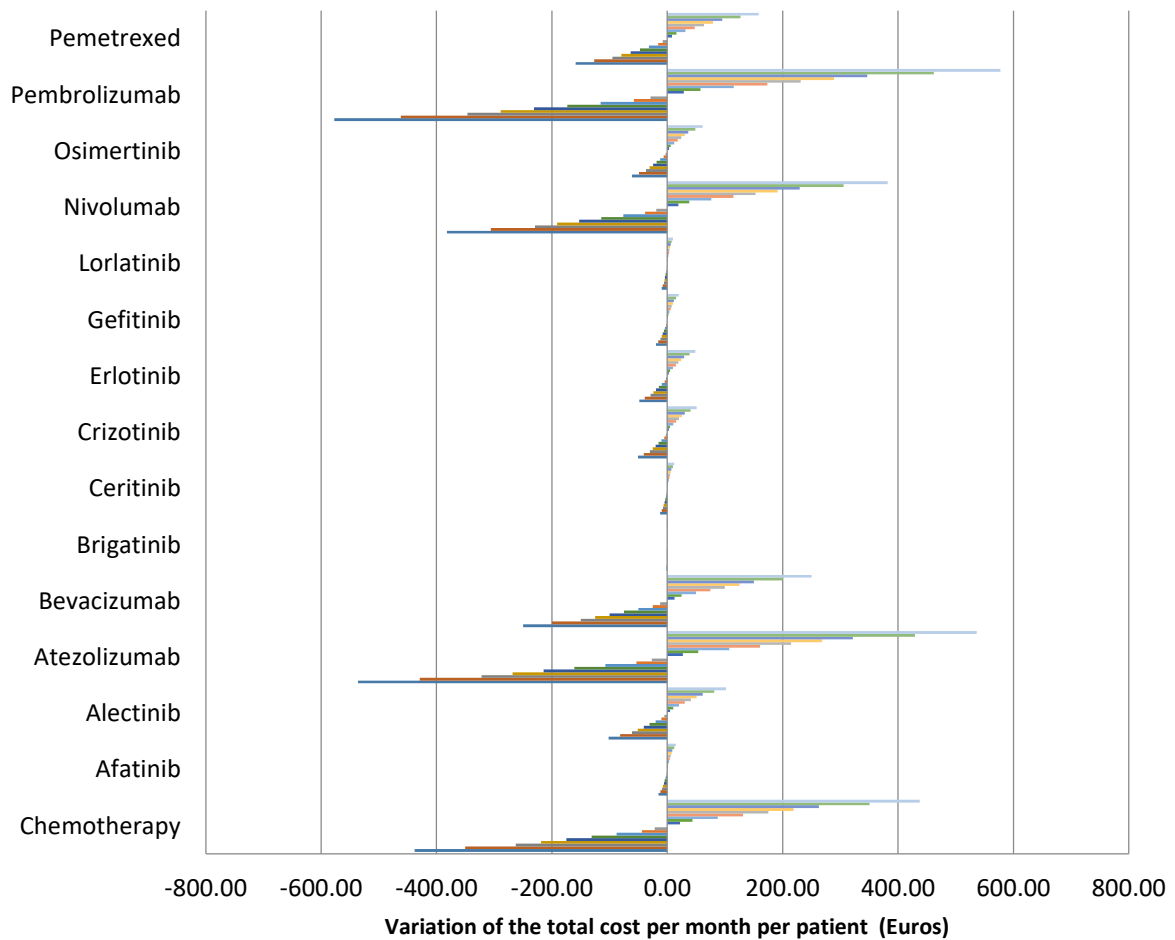


Figure 26. Sensibility analysis of the impact of costs per treatment in the total cost of NSCLC Stage IIB/IV in France in 2022 (*Annex 13*)

When we look deeply at the treatments and at the impact of the various items, regarding the acquisition costs, not surprisingly pembrolizumab is in the first place, atezolizumab and nivolumab arrive also at the top of the list of treatments for which the acquisition cost has a strong impact on the total cost of care (See Figure 27). This is largely due to a high cost of acquisition but also a large population (6043 patients, 6110 patients and 4776 patients respectively). Based on the assumptions, a 10% change in the price of pembrolizumab changes the total cost of management by 1.75%. Nevertheless, chemotherapy remains the fourth treatment whose cost has a significant impact on the total cost of NSCLC IIB / IV with an acquisition cost of around € 650, which is much lower than immunotherapy. Hypothetical population is still very important in 2022 (about 23,700 patients). Thus a variation of 10% of the price of chemotherapy varies by 0.74% the total cost of care.

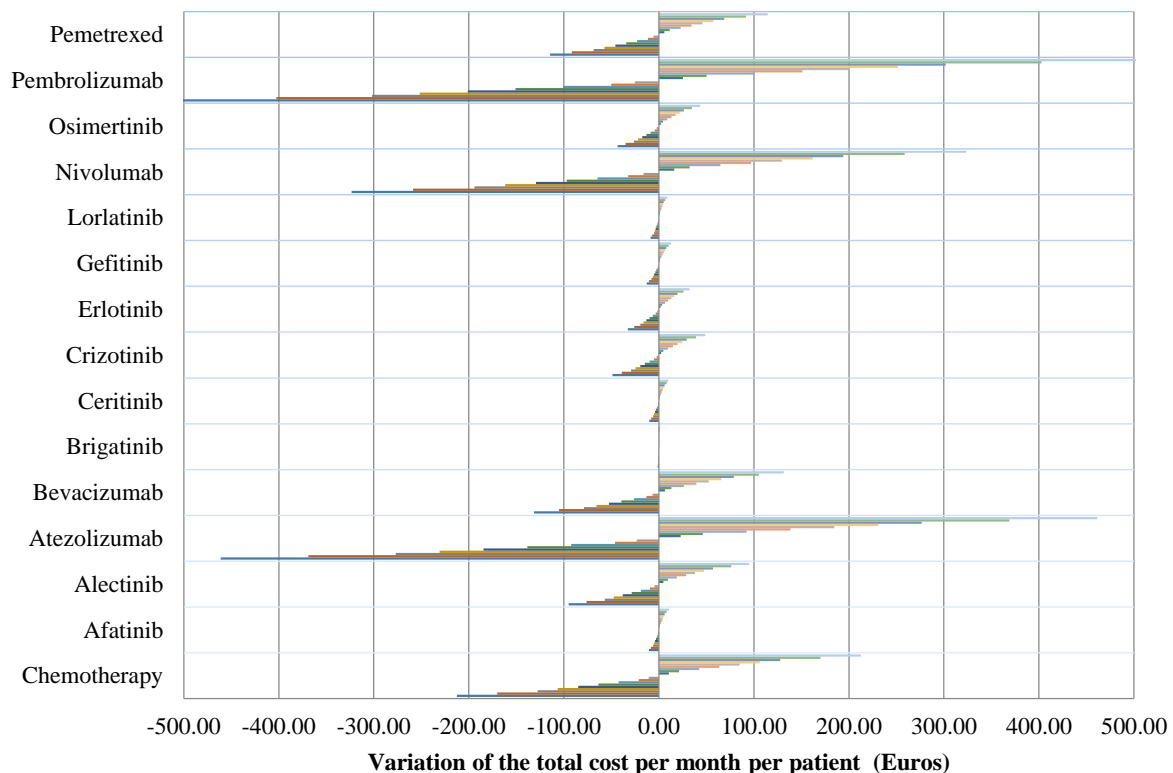


Figure 27. Sensibility analysis of the impact of acquisition costs per treatment in the total cost of NSCLC Stage IIB/IV in France in 2022 (*Annex 14*)

Administration costs are obviously induced by therapies that require temporary hospitalization with infusion (chemotherapy and immunotherapy). The other treatments, being administered orally, do not present additional costs of administration. For chemotherapies and immunotherapies, variations in the cost of administration represent only a small amount of total medical costs (See Figure 28). A 50% change in chemotherapy administration costs, which has the highest cost of administration, represents only a 2% change in total medical costs. A decrease of 50% in administration costs in 5 years is unlikely to happen.

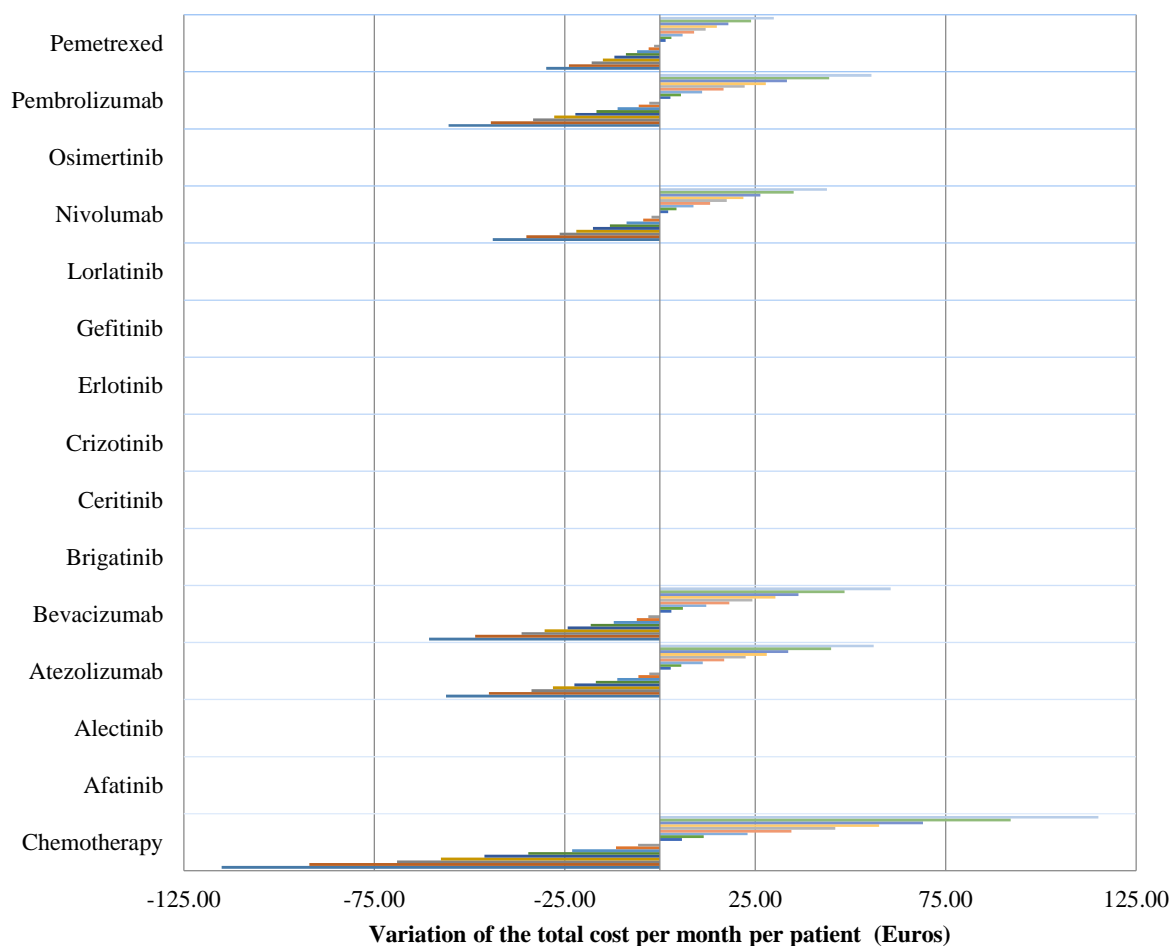


Figure 28. Sensibility analysis of the impact of administration costs per treatment in the total cost of NSCLC Stage IIB/IV in France in 2022 (*Annex 15*)

Regarding monitoring costs, it is found, with assumptions that even a significant variation in costs, slightly impacts the total medical costs. For example, a 50% change in each item will impact the total cost of € 5,734.38 (0.5%) by less than € 30 (See Figure 29). This item alone does not have a significant impact on total medical costs.

Concernant les coûts de monitoring, il est constaté, avec les hypothèses, que même une variation importante des coûts, n'impacte que de peu les coûts médicaux totaux. Par exemple, une variation de 50% de chacun des postes de dépenses impactera de moins de €30 le coût total de €5,734.38 (0,5%) (Cf. Figure 29). Ce poste de dépense à lui seul n'impacte donc pas de manière importante les coûts médicaux totaux.

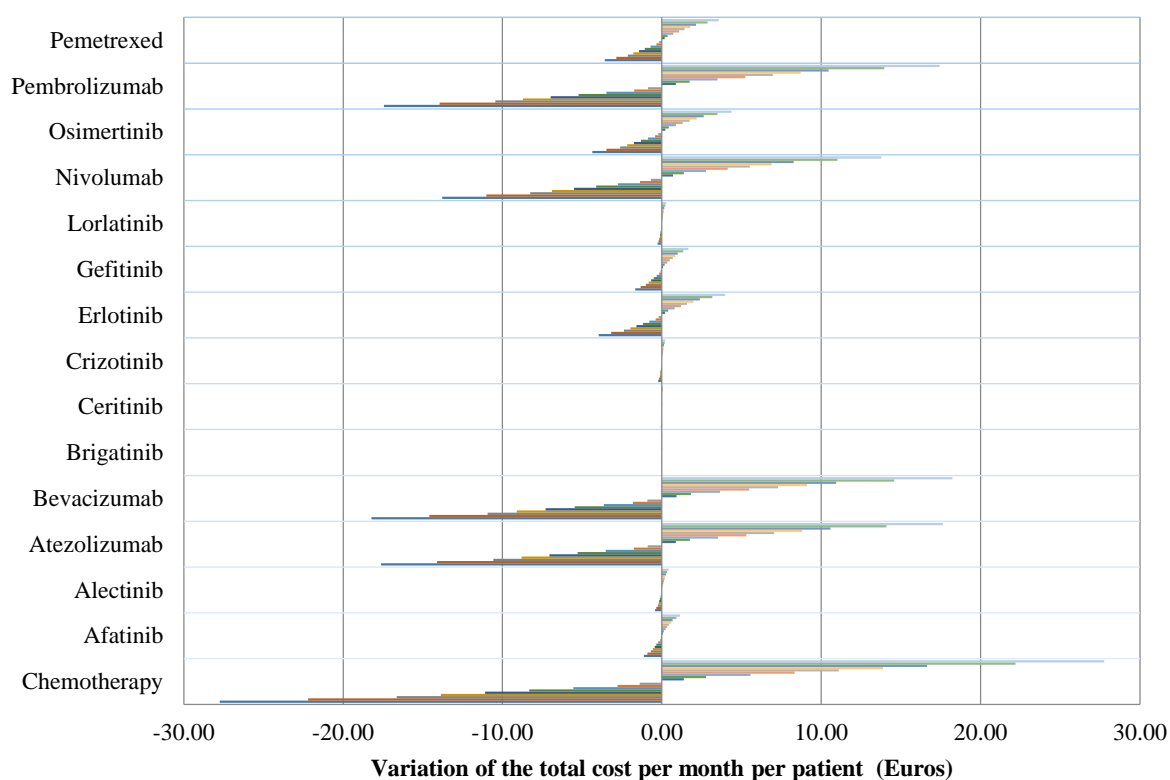


Figure 29. Sensibility analysis of the impact of monitoring costs per treatment in the total cost of NSCLC Stage IIB/IV in France in 2022 (*Annex 16*)

Costs of adverse effects are mainly impacted by chemotherapy and b vacizumab. But these costs do not have a strong impact on the total medical costs. (See Figure 30)

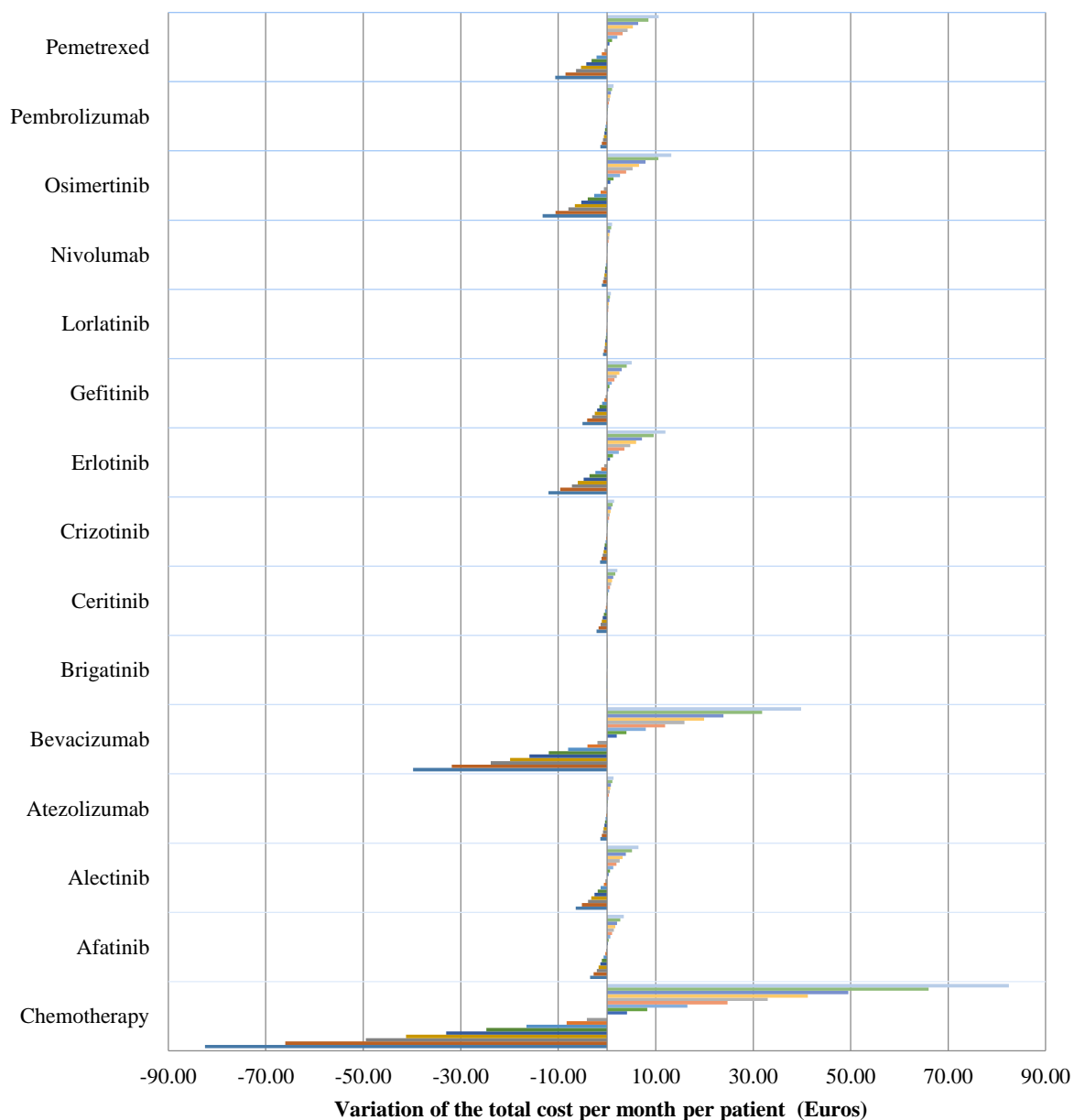


Figure 30. Sensibility analysis of the impact of adverse events costs per treatment in the total cost of NSCLC Stage IIB/IV in France in 2022 (*Annex 17*)

When one takes a closer look at other medical costs, the item that strongly impacts the total management of NSCLC IIB / IV is the one that corresponds to palliative care. Indeed, this post affects the costs as much as it corresponds to a majority of the population (in 2022, according to the hypotheses, about 60% of the patients will resort to hospitalization for palliative care during the year). Thus, a variation of 10% in palliative care costs corresponds to a variation of almost 4.7% in the total costs of NSCLC IIB / IV. (See Figure 31) It is the medical cost that has the greatest impact on the treatment, given the cost of the therapies. Thus an optimization of the costs of palliative care could greatly improve the total budget for the management of NSCLC IIB / IV. If we look at this 10% decrease, this corresponds to a variation of around € 268 per patient per month, a potential saving of € 112 million per year.

The medical costs of transport, testing and consulting have a much lower impact on total costs. (See Figure 31)

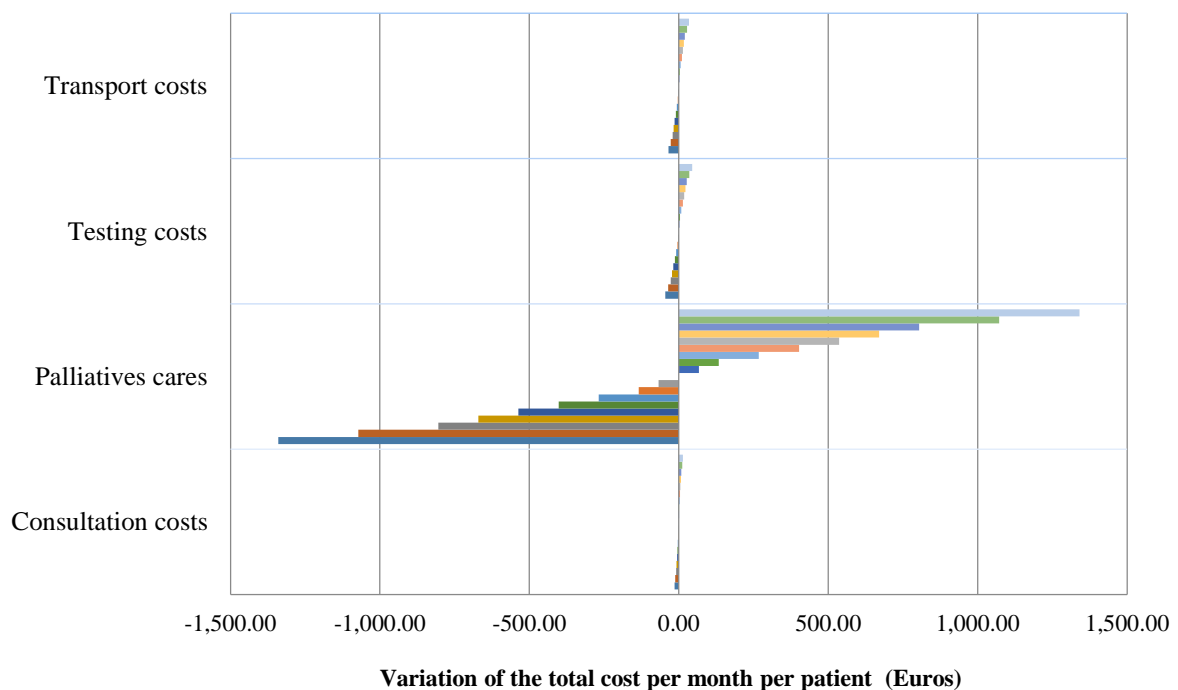


Figure 31. Sensibility analysis of the impact of other medical costs per treatment in the total cost of NSCLC Stage IIB/IV in France in 2022 (*Annex 12*)

5. Discussion

We have seen in this study that palliative care costs and acquisition costs are the cost items that have the most significant impact on the management of NSCLC IIB / IV. Treatments that have the most significant impact on the management of NSCLC IIB / IV are essentially immunotherapies, with pembrolizumab and atezolizumab followed by chemotherapy and nivolumab.

The purpose of these results is to present cost trends impact on health expenditure for the management of stage IIB / IV NSCLC. Only results for 2017 are results with existing data. The rest of the results are based on clinical results hypotheses (assumed to be positive for studies currently in phase III and which have not yet results). Prescription hypotheses by physicians are also included with the choice of molecules within the same class (TKI, anti-PD1, etc.), the choice of the use of a monotherapy or the prescription of 'a combination. (See Annex 6, Annex 7, Annex 8, Annex 9). Cost developments are also based on known historical assumptions for similar cases. All of these assumptions provide biases in the analysis of primary analysis figures. Firstly, a selection bias which implies that patients would be wrongly selected (hypothesis of projection of the false population) and wrongly distributed in the different treatment groups. On the other hand, the cost bias with a potential over- or underestimation of these (new prices, price adjustment, entry of generics into the market, etc.)

To overcome as much as possible these biases, a sensitivity analysis was conducted. First of all, with a first part that compares three general hypotheses (minimum, average and maximum). The first part of the sensitivity analysis focuses on the whole results. All costs have been reported as identical between 2017 and 2022. Each costs were weighted, regarding of

potential price reductions, either by re-evaluation or by the entry of generics on the market for acquisition costs, but also the evolution of techniques and support for other expenditure items.

The second part of the analysis targets each expenditure item and their influence on the total average cost for advanced or metastatic NSCLC. This part of the analysis allow to weight the impact by getting rid of the figures, in particular with graphs which show which item of expenditure has the most significant impact on the overall care cost.

The advent of these innovative therapies represents promising changes and hope for patients. Further studies could further improve care, especially at the research and development activities level to, of course, ideally discover therapies that could one day treat NSCLC IIIB / IV, but also in the shorter term with a potential use of curative treatments.

The objective of this study was therefore to have a global vision of Stage IIIB / IV NSCLC total cost in 2022 but in the current state of our knowledge. The knowledge on immunotherapies is indeed only at its beginning and several points concerning their use are still to be studied. Of these, some are detailed below.

The dose and frequency of use of immunotherapies are not yet clearly known. The question therefore arises about the use of a fixed or variable dose but also about the spacing of each injection and their impact on the patient's response. Some immunotherapies are indeed marketed at variable doses and others at fixed doses. MSD, which markets pembrolizumab, has launched its research program with a variable dose, in mg / kg, and is reviewing it through its new studies. It is also currently submitting to health authorities an amendment package to transform the use of pembrolizumab 2 mg / kg fixed dose at 200 mg per injection. Regarding the frequency of injection, the BMS laboratory is comparing the impact of an injection every

2 weeks or every 4 weeks on the effectiveness of its immunotherapy. These changes could impact the costs of care for health insurance without causing loss of clinical benefit to the patient.

The duration of use of immunotherapies is also being challenged. MSD and BMS laboratories have initiated studies comparing the continued use of immunotherapy to disease progression versus fixed-duration use. The MSD laboratory went even further by integrating it into the response criteria in its pivotal studies by treating patients until disease progression or 2 years after starting immunotherapy.

The treatment response evaluation is still being questioned. Some experts are beginning to question the notion of progression assessment using RECIST criteria based solely on radiological criteria, while patients continue to derive clinical benefit. The new evaluation and studies tend to evaluate the treatment response by assessing the clinical benefit and not just the radiological benefit. This could change treatments duration and thus impact medical costs.

The problem of re-challenge can also be highlighted in the sequencing of therapies. The use of new treatments with the same molecular target is currently not really being developed in clinical trials. If patients benefit from first-line immunotherapy, the therapeutic arsenal is very limited in case of no response or relapse of the patient after this treatment. The issue of the therapeutic sequence is therefore important and remains a challenge for clinicians to ensure the longest survival within the most favorable conditions for patients.

Patient responses to immunotherapies are not always well known or predicted. Not all patient respond in the same way to immunotherapies and some have atypical responses. This

is starting to be described through the study of specific clinical cases with, for instance, cases of hyper-progressive patients (13-15) and cases of pseudo-progressive patients (well observed in the case of melanoma in particular) (16-19). It is currently not possible to predict this type of reaction before the introduction of the treatment. The discovery of biomarkers to predict not only the efficacy but also the tolerance of immunotherapies, represents an important potential for the evolution of patient care and would make it possible to tend towards a more adapted medicine for the patient, a personalized medicine.

The government has been working on the effective social security financing law since 2018 (LFSS 2018 - Social Security Financing Act) to find solutions in order to improve the current health system. Some pharmaceutical companies are starting to propose initiatives regarding the reimbursement model. Such is the case, for instance, of the laboratory ROCHE with its PRM initiative (Personalized Reimbursement Medicine): a system offering a reimbursement adapted to the different criteria of patients and the benefits they can obtain.

One can imagine a 100% coverage health insurance system treatment for patients with better responses, compared to patients who would benefit from a more limited benefit of treatment. The "limited efficiency" fee would be charged to the laboratory. The reimbursement would adapt to patient responses. Because it is specific to each patient and potentially difficult to implement, this type of proposal represents a very complex financing project.

The government's objective is essentially to optimize funding of therapies in a context of limited resources and budget cuts. It is undeniable that the cost of treatments increases with the evolution of biology knowledge, the engineering of these biological molecules but also the less and less hypothetical arrival of personalized medicine. Ethics related to our healthcare profession cannot lead us to limit access to innovative therapies for a purely economic purpose.

The healthcare system cannot regulate itself and requires monitoring of each partner. A sustainable healthcare system is therefore possible, but the current system seems to show some long-term limitations. Each actor therefore has a key role to play in ensuring effective and ethical management of health expenditure.

6. Conclusion

Based on forecast hypotheses for the management of advanced or metastatic non-small cell lung cancer by 2022, this study shows a budgetary impact of therapeutic innovations on the health system. Indeed, the average one-year cost of treatment for a patient with advanced or metastatic non-small cell lung cancer was around € 53,000 in 2017 and would approach € 76,000 in 2022. This trend is consistent with the hypothesis of the increasing use of targeted therapies and immunotherapies with interesting clinical. The concomitant use of chemotherapies, immunotherapies and targeted therapies to potentiate patients' response, also raises the average cost per patient. When looking closer at the impact of the various medical expenditure items, the costs of palliative care and acquisition costs of therapies are the expenditure items that have the most significant impact on the management of NSCLC IIB / IV.

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Annexes

Annex 1. The TNM Classification 8th edition (based on the AJCC Cancer Staging Manual) (from (120))

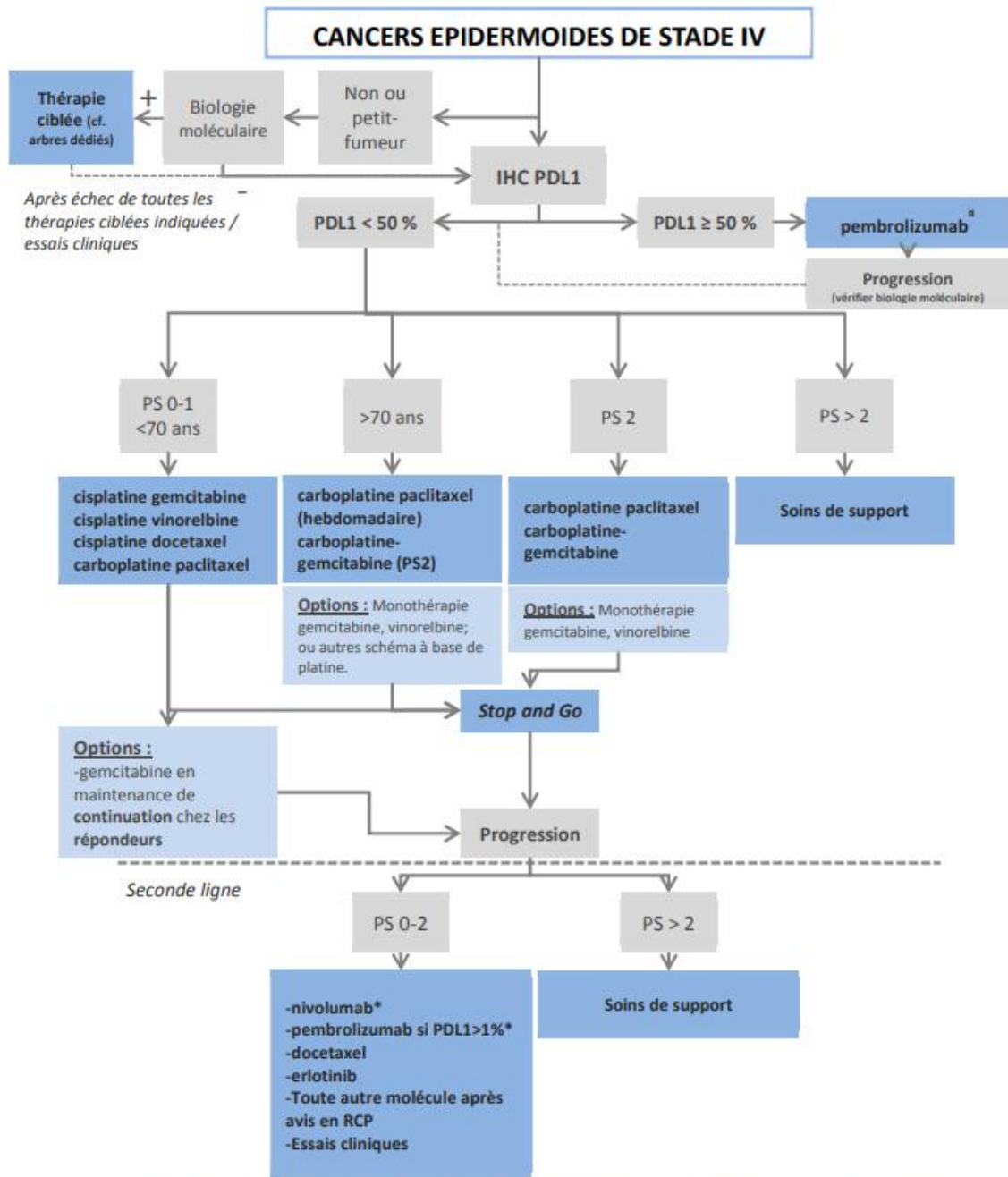
T - Tumeur	Tx	Tumeur primaire non connue ou tumeur prouvée par la présence de cellules malignes dans les sécrétions broncho-pulmonaires mais non visible aux examens radiologiques et endoscopiques.
	T0	Absence de tumeur identifiable.
	Tis	Carcinome <i>in situ</i> .
	T1	Tumeur de 3 cm ou moins dans ses plus grandes dimensions, entourée par du poumon ou de la plèvre viscérale, sans évidence d'invasion plus proximale que les bronches lobaires à la bronchoscopie (c'est-à-dire pas dans les bronches souches).
	T1a(mi)	Adénocarcinome minimalement-invasif
	T1a	≤ 1cm
	T1b	> 1 cm et ≤ 2 cm
	T1c	> 2 cm et ≤ 3 cm
	T2	Tumeur de plus de 3 cm, mais de 5 cm ou moins , avec quelconque des éléments suivants : -envahissement d'une bronche souche quelle que soit sa distance par rapport à la carène mais sans envahissement de la carène, -envahissement de la plèvre viscérale, -existence d'une atelectasie ou pneumonie obstructive s'étendant à la région hilare ((sub)lobaire ou pulmonaire)
	T2a	> 3 cm mais ≤ 4 cm
T2b	> 4 cm mais ≤ 5 cm	
T3	Tumeur de plus de 5 cm et de 7 cm ou moins , ou associée à un(des) nodule(s) tumoral(aux) distinct(s) et dans le même lobe, ou ayant au moins l'un des caractères invasifs suivants : -atteinte de la paroi thoracique (incluant les tumeurs du sommet), -atteinte du nerf phrénique, -atteinte de la plèvre pariétale ou du péricarde.	
T4	Tumeur de plus de 7 cm ou associée à un(des) nodule(s) pulmonaire(s) distinct(s) comportant un envahissement quelconque parmi les suivants : -médiastin, -cœur ou gros vaisseaux, -trachée, -diaphragme, -nerf récurrent, -œsophage, -corps vertébraux, -carène, -nodules tumoraux séparés dans deux lobes différents du même poumon.	
N - Adénopathies	Nx	Envahissement locorégional inconnu.
	N0	Absence de métastase dans les ganglions lymphatiques régionaux.
	N1	Métastases ganglionnaires péri-bronchiques homolatérales et/ou hilaires homolatérales incluant une extension directe.
	N2	Métastases dans les ganglions médiastinaux homolatéraux ou dans les ganglions sous-carénaux
	N3	Métastases ganglionnaires médiastinales controlatérales ou hilaires controlatérales ou scaléniques, sus-claviculaires homo- ou controlatérales.
Métastases	M0	Pas de métastase à distance.
	M1	Existence de métastases :
	M1a	Nodules tumoraux séparés dans un lobe controlatéral, ou nodules pleuraux ou pleurésie maligne ou péricardite maligne
	M1b	1 seule métastase dans un seul site métastatique
M1c	Plusieurs métastases dans un seul site ou plusieurs sites atteints	

Annex 2. Summary of treatments used in NSCLC

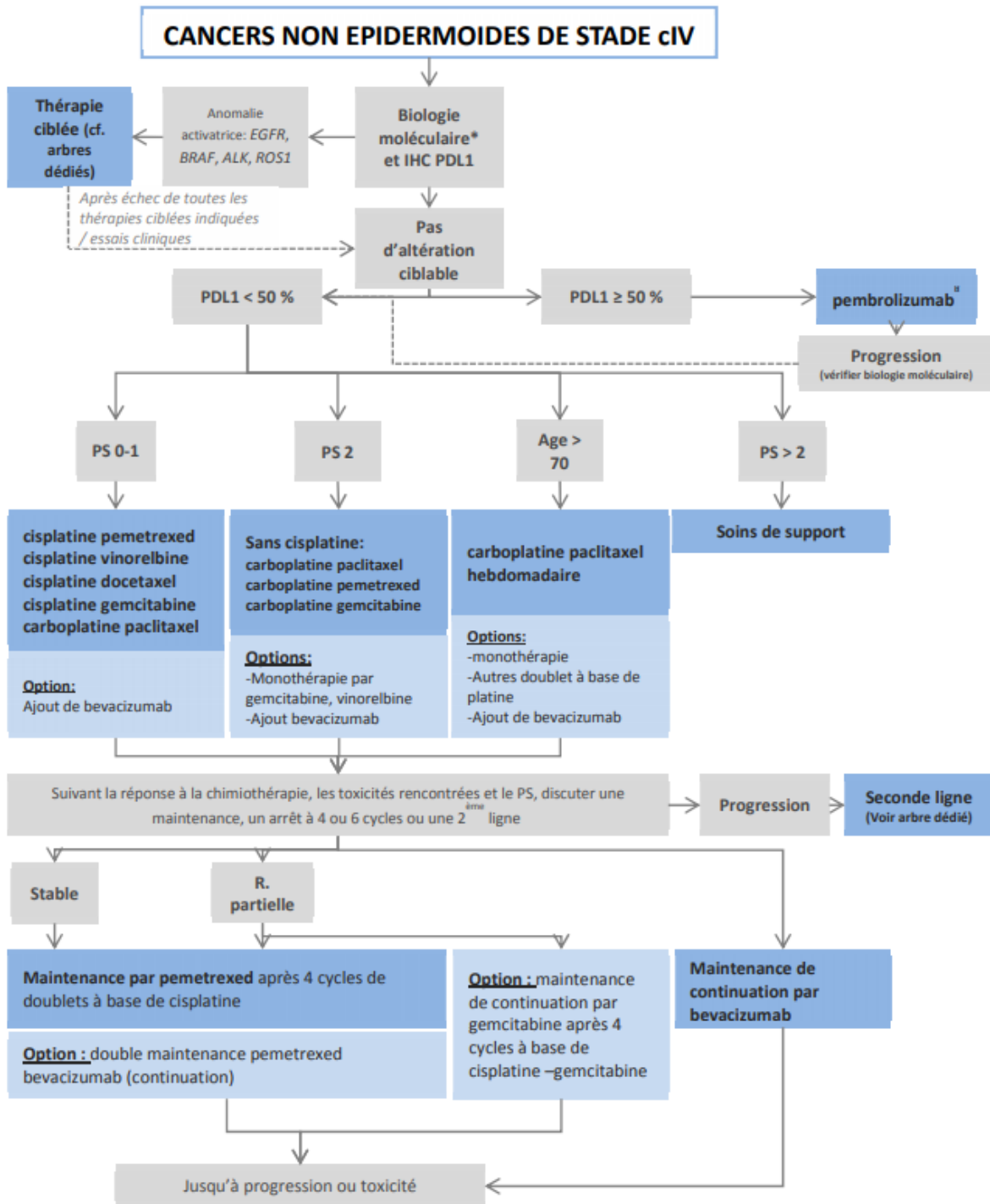
	Treatment	Brand Name in France	Laboratory	Family
CHEMOTHERAPY	Cisplatine	CISPLATYL		Sel de platine
	Carboplatine	CARBOPLATYL		
	Vinorelbine	NAVELBINE		Vinca alcaloïdes
	Paclitaxel	TAXOL		Taxane
	Docétaxel	TAXOTERE		
	Etoposide	/		Dérivé podophyllotoxine
	Gemcitabine	GEMZAR		Analogue pyrimidine
	Pemetrexed	ALIMTA		Analogue acide folique
TARGETED THERAPIES	Bévacizumab	AVASTIN	ROCHE	AcM anti-VEGF
	Ramucirumab	CYRAMZA	LILLY	
	Erlotinib	TARCEVA	ROCHE	EGFR TKI
	Afatinib	GIOTRIF	BOEHRINGER	
	Géfitinib	IRESSA	ASTRA ZENECA	
	Osimertinib	TAGRISSE	ASTRA ZENECA	
	Crizotinib (TKI 1G)	XALKORI	PFIZER	ALK TKI
	Alectinib (TKI 2G)	ALECENSA	ROCHE	
	Céritinib (TKI 2G)	ZYKADIA	NOVARTIS	
	Brigatinib (TKI 2G)	/	ARIAD Pharma	
	Lorlatinib (3G)	/	PFIZER	
CANCER IMMUNOTHERAPIES	Atezolizumab	TECENTRIQ	ROCHE	Anti PD-L1 IgG1
	Nivolumab	OPDIVO	BMS	Anti-PD1 AcM H type IgG4
	Pembrolizumab	KEYTRUDA	MSD	Anti-PD1
	Durvalumab	IMFINZY	ASTRA ZENECA	Anti-PDL1
	Avelumab	BAVENCIO	PFIZER	Anti-PDL1

Annex 3. Studies of CIT in first line of NSCLC Stage IIIB/IV

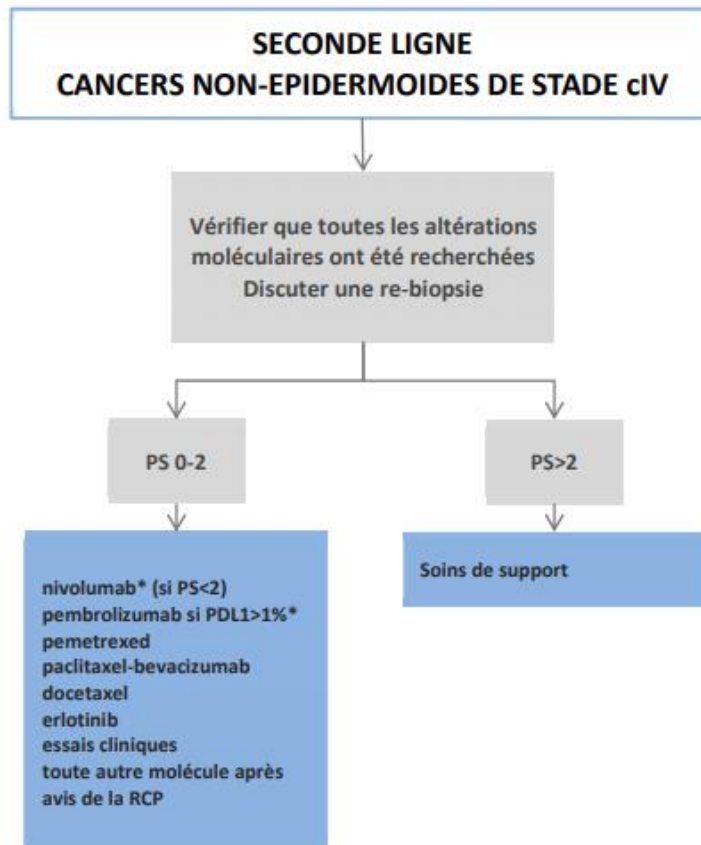
Annex 4. 2018 AURA guidelines (French Guidelines) for the Stage IIIB/IV NSCLC squamous and non-squamous (from (120))



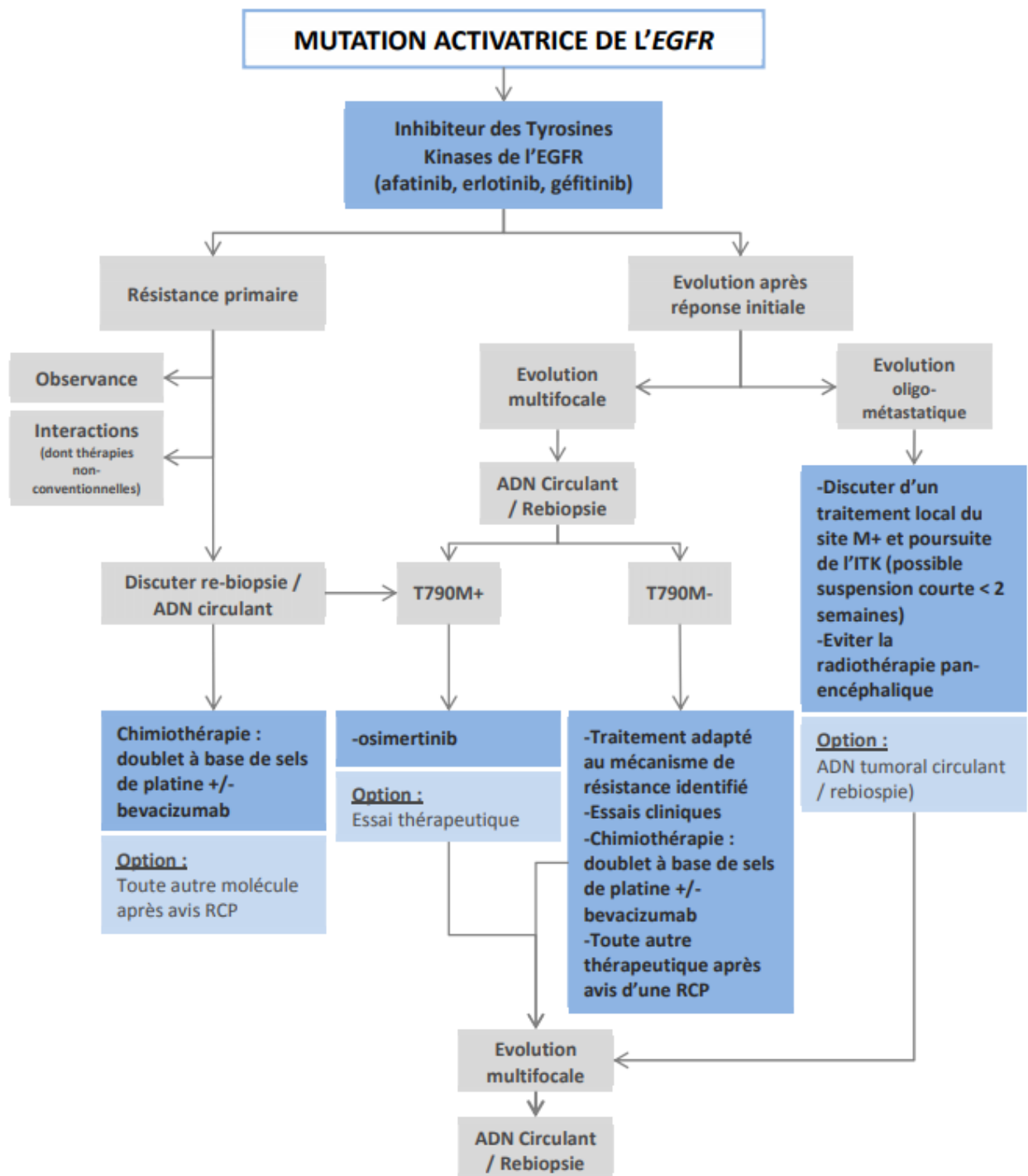
* Hors PS>2, option pour les >70ans et PS2 - * si immunothérapie non utilisée précédemment

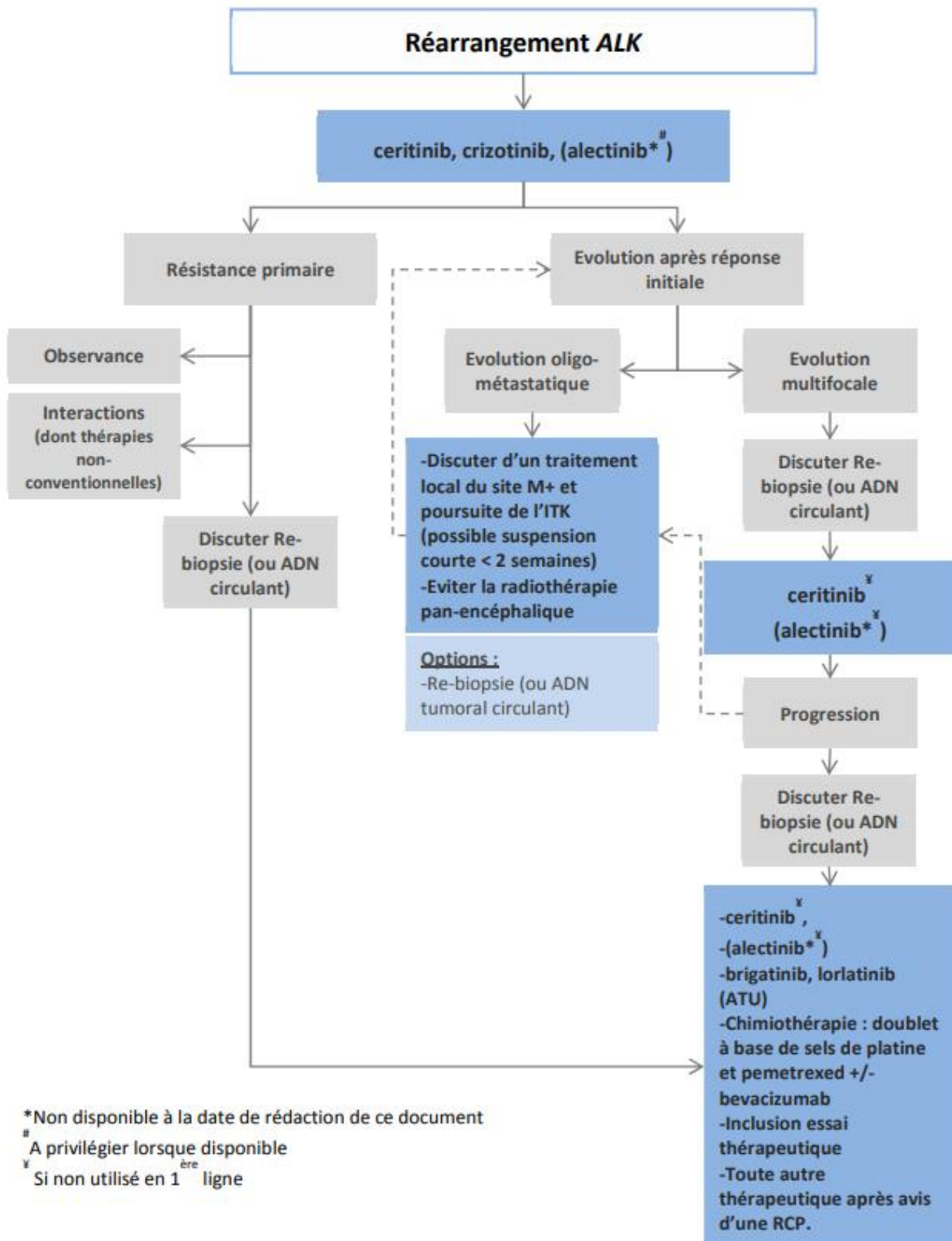


*Sur échantillon tissulaire ou sur ADN circulant si échec / insuffisance - Hors PS>2, option pour les >70ans et PS2



*Si immunothérapie non utilisée en première ligne





Annex 5. Study population evolution until 2022

Population projection	2017	2018	2019	2020	2021	2022
Growing rate of the French population (%)	0,3971%	0,3971%	0,3971%	0,3971%	0,3971%	0,3971%
French population size (n)	66 990 826	67256847	67523924	67792061	68061263	68331535
French male population size (n)	32 455 859	32584741	32714135	32844043	32974467	33105408
French female population size (n)	34 534 967	34672105	34809788	34948018	35086797	35226126

MORTALITY	2017	2018	2019	2020	2021	2022
LC mortality	29 933	29 944	29 986	30 059	30 164	30 302
Male LC mortality	20 086	19644	19212	18789	18376	17972
Female LC mortality	9 847	10300	10774	11269	11788	12330
Male Annual death rate	-0,022	-0,022	-0,022	-0,022	-0,022	-0,022
Female Annual death rate	0,046	0,046	0,046	0,046	0,046	0,046

PREVALENCE	2017	2018	2019	2020	2021	2022
Lung cancer population size	79 500	79 489	79 447	79 374	79 269	79 131
Male Lung cancer population size	60 700	61 142	61 574	61 997	62 410	62 814
Female Lung cancer population size	18 800	18 347	17 873	17 378	16 859	16 317
NSCLC prevalence (85% of LC)	67575	67566	67530	67468	67379	67262
NSCLC localized or locally advanced (I-IIIa) (32,5%)	21962	21959	21947	21927	21898	21860
NSCLC localized or locally advanced with an evolution during the year (40%)	8785	8784	8779	8771	8759	8744
NSCLC advanced or metastatic (IIIB-IV) (67,5%)	45613	45607	45583	45541	45481	45402
NSCLC advanced or metastatic (67,5%) + NSCLC localized or locally advanced with an evolution during the year (40% of 32,5%)	54398	54390	54362	54312	54240	54146
NSCLC IIIB-IV with ALK+ rearrangement (5% NSCLC)	2720	2720	2718	2716	2712	2707
NSCLC IIIB-IV with EGFR+ mutation EGFR (11% NSCLC)	5984	5983	5980	5974	5966	5956
NSCLC IIIB-IV with ROS1 mutation (1% NSCLC)	544	544	544	543	542	541
NSCLC IIIB-IV wild type (83%)	45150	45144	45120	45079	45019	44941
NSCLC IIIB-IV wild type squamous (26,3%)	11875	11873	11867	11856	11840	11819

CBNPC IIIB-IV wild type non-squamous (73,7%)	33276	33271	33254	33223	33179	33121
INCIDENCE	2017	2018	2019	2020	2021	2022
LC incidence	46452	47 244	48 083	48 972	49 913	50 908
Male LC incidence	29 820	29731	29642	29553	29464	29376
Female LC incidence	16 632	17514	18442	19419	20449	21532
Male Annual incidence rate of LC	-0,003	-0,003	-0,003	-0,003	-0,003	-0,003
Female Annual incidence rate of LC	0,053	0,053	0,053	0,053	0,053	0,053
NSCLC incidence (85% Cancer du poumon)	39485	40158	40871	41626	42426	43272
NSCLC I-IIIa (32,5%)	12832	13051	13283	13529	13788	14063
NSCLC I-IIIa with an evolution to IIIB-IV during the year (40% of stage I-IIIa)	5133	5221	5313	5411	5515	5625
NSCLC IIIB-IV (67,5% NSCLC)	26652	27107	27588	28098	28637	29208
NSCLC IIIB-IV (67,5% NSCLC) + NSCLC I-IIIa with an evolution to IIIB-IV during the year (40% of stage I-IIIa)	31785	32327	32901	33509	34153	34834
NSCLC IIIB-IV with ALK+ rearrangement (5% NSCLC)	1589	1616	1645	1675	1708	1742
NSCLC IIIB-IV with EGFR+ mutation (11% NSCLC)	3496	3556	3619	3686	3757	3832
NSCLC IIIB-IV with ROS1 mutation (1% NSCLC)	318	323	329	335	342	348
NSCLC IIIB-IV wild type (83%)	26382	26831	27308	27813	28347	28912
NSCLC IIIB-IV wild type squamous (26,3%)	6938	7057	7182	7315	7455	7604
NSCLC IIIB-IV wild type non-squamous (73,7%)	19443	19775	20126	20498	20892	21308

Annex 6. Algorithm of NSCLC IIIB/IV treatment in 2017 (%)

2017 Stage IIIB/IV	31785	Wild-type						EGFR +			ALK+			ROS1	
	Nb of patients	26382													
		Non squamous			Squamous										
	Nb of patients	19443			6938			3496			1589			318	
Brand name	DCI	1L	2L	3L	1L	2L	3L	1L	2L	3L	1L	2L	3L	1L	TOTAL
	%	61%	26%	14%	61%	26%	14%	51%	28%	22%	41%	33%	26%	100%	
	Nb of patients	11845	4963	2635	4227	1771	940	1767	972	757	651	521	417	318	
GIOTRIF	Afatinib	0	0	0	0	0	0	0.19	0.03	0.08	0	0	0	0	0.3
ALECENSA	Alectinib	0	0	0	0	0	0	0	0.00	0.00	0	0.03	0.06	0	0.09
TECENTRIQ	Atezolizumab	0	0	0	0	0	0	0	0.00	0.00	0	0	0	0	0
ALUNBRIG	Brigatinib	0	0	0	0	0	0	0	0.00	0.00	0	0	0	0	0
ZYKADIA	Ceritinib	0	0	0	0	0	0	0	0.00	0.00	0	0.28	0.43	0	0.71
XALKORI	Crizotinib	0	0	0	0	0	0	0	0.00	0.00	0.9	0.60	0.40	1	2.9
	CT	1	0.4	0.39	1	0.1	0.39	0.02	0.24	0.18	0.1	0.09	0.11	0	4.02
AVASTIN	Bévacizumab	0.22	0.05	0.02	0.00	0	0	0.00	0.07	0.02	0.08	0.03	0.00	0	0.49
TARCEVA	Erlotinib	0	0.15	0.14	0	0.15	0.14	0.37	0.15	0.08	0	0	0	0	1.18
IRESSA	Gefitinib	0	0	0	0	0	0	0.42	0.07	0.00	0	0	0	0	0.49
/	Lorlatinib	0	0	0	0	0	0	0.00	0.00	0.00	0	0	0	0	0
OPDIVO	Nivolumab	0	0.35	0.37	0	0.65	0.37	0.00	0.02	0.13	0	0	0	0	1.89
TAGRISO	Osimertinib	0	0	0	0	0	0	0.00	0.50	0.52	0	0	0	0	1.02
KEYTRUDA	Pembrolizumab	0	0.1	0.1	0	0.1	0.1	0.00	0.00	0.00	0	0	0	0	0.4
ALIMTA	Pemetrexed	0.56	0	0	0.56	0	0	0.00	0.19	0.06	0.1	0.00	0.00	0	1.47
		1.78	1.05	1.02	1.56	1	1	1	1.27	1.07	1.18	1.03	1	1	

Annex 7. Algorithm of NSCLC IIIB/IV treatment in 2017 (number of patients)

2017 Stage IIIB/IV	31785	Wild-type						EGFR +			ALK+			ROS1	
	Nb of patients	26382													
		Non squamous			Squamous										
	Nb of patients	19443			6938			3496			1589			318	
Brand name	DCI	1L	2L	3L	1L	2L	3L	1L	2L	3L	1L	2L	3L	1L	TOTAL
	%	61%	26%	14%	61%	26%	14%	51%	28%	22%	41%	33%	26%	100%	
	Nb of patients	11845	4963	2635	4227	1771	940	1767	972	757	651	521	417	318	
GIOTRIF	Afatinib	0	0	0	0	0	0	336	29	61	0	0	0	0	426
ALECENSA	Alectinib	0	0	0	0	0	0	0	0	0	0	16	25	0	41
TECENTRIQ	Atezolizumab	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ALUNBRIG	Brigatinib	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ZYKADIA	Ceritinib	0	0	0	0	0	0	0	0	0	0	146	179	0	325
XALKORI	Crizotinib	0	0	0	0	0	0	0	0	0	586	313	167	318	1383
347.29	CT	11845	1985	1028	4227	177	367	35	233	136	65	47	46	0	20191
AVASTIN	Bévacizumab	2606	248	53	0	0	0	0	68	15	52	16	0	0	3058
TARCEVA	Erlotinib	0	744	369	0	266	132	654	146	61	0	0	0	0	2371
IRESSA	Gefitinib	0	0	0	0	0	0	742	68	0	0	0	0	0	810
/	Lorlatinib	0	0	0	0	0	0	0	0	0	0	0	0	0	0
OPDIVO	Nivolumab	0	1737	975	0	1151	348	0	19	98	0	0	0	0	4329
TAGRISO	Osimertinib	0	0	0	0	0	0	0	486	394	0	0	0	0	880
KEYTRUDA	Pembrolizumab	0	496	264	0	177	94	0	0	0	0	0	0	0	1031
ALIMTA	Pemetrexed	6633	0	0	2367	0	0	0	185	45	65	0	0	0	9295
		21084	5211	2688	6594	1771	940	1767	1234	810	769	537	417	318	

Annex 8. Algorithm of NSCLC IIIB/IV treatment in 2022 (%)

2022 Stage IIIB/IV	34834	Wild-type						EGFR+			ALK+			ROS1	
	Nb of patients	28912													
		Non Squamous			Squamous										
	Nb of patients	21308			7604			3832			1742			348	
Nom commercial	DCI	1L	2L	3L	1L	2L	3L	1L	2L	3L	1L	2L	3L	1L	TOTAL
	%	69%	29%	2%	67%	28%	5%	54%	30%	16%	64%	25%	10%	100%	
	Nb of patients	14739	6176	393	5091	2133	380	2078	1143	610	1120	439	183	348	
GIOTRIF	Afatinib	0	0	0	0	0	0	0.15	0.03	0.08	0	0	0	0	0.26
ALECENSA	Alectinib	0	0	0	0	0	0	0	0	0	0.9	0.1	0	0	1
TECENTRIQ	Atezolizumab	0.3	0.05	0	0.25	0.05	0	0	0	0	0	0	0	0	0.65
ALUNBRIG	Brigatinib	0	0	0	0	0	0	0	0	0	0	0	0.1	0	0.1
ZYKADIA	Ceritinib	0	0	0	0	0	0	0	0	0	0	0.20	0.30	0	0.5
XALKORI	Crizotinib	0	0	0	0	0	0	0	0	0	0.05	0.50	0.15	1	1.7
347.29	CT	0.8	0.85	0.9	0.8	0.65	0.8	0.01	0.24	0.18	0	0.20	0.25	0	5.68
AVASTIN	Bévacizumab	0.40	0.05	0	0.00	0	0	0.00	0.07	0.02	0	0.03	0.05	0	0.62
TARCEVA	Erlotinib	0	0.05	0.1	0	0.05	0.2	0.30	0.15	0.08	0	0	0	0	0.93
IRESSA	Gefitinib	0	0	0	0	0	0	0.24	0.07	0	0	0	0	0	0.31
/	Lorlatinib	0	0	0	0	0	0	0.00	0	0	0.05	0	0.2	0	0.25
OPDIVO	Nivolumab	0.15	0	0	0.4	0.2	0	0.00	0.02	0.13	0	0	0	0	0.9
TAGRISO	Osimertinib	0	0	0	0	0	0	0.30	0.50	0.52	0	0	0	0	1.32
KEYTRUDA	Pembrolizumab	0.33	0.05	0	0.15	0.05	0	0.00	0	0	0	0	0	0	0.58
ALIMTA	Pemetrexed	0.1	0	0	0.26	0	0	0.00	0.19	0.06	0	0	0	0	0.61
		2.08	1.05	1	1.86	1	1	1	1.27	1.07	1	1.03	1.05	1	

Annex 9. Algorithm of NSCLC IIIB/IV treatment in 2022 (number of patients)

2022 Stage IIIB/IV	34834	Wild-type						EGFR +			ALK +			ROS1	
	Nb of patients	28912													
		Non Squamous			Squamous										
	Nb of patients	21308			7604			3832			1742			348	
Nom commercial	DCI	1L	2L	3L	1L	2L	3L	1L	2L	3L	1L	2L	3L	1L	TOTAL
	%	69%	29%	2%	67%	28%	5%	54%	30%	16%	64%	25%	10%	100%	
	Nb of patients	14739	6176	393	5091	2133	380	2078	1143	610	1120	439	183	348	
GIOTRIF	Afatinib	0	0	0	0	0	0	312	34	49	0	0	0	0	395
ALECENSA	Alectinib	0	0	0	0	0	0	0	0	0	1008	44	0	0	1052
TECENTRIQ	Atezolizumab	4422	309	0	1273	107	0	0	0	0	0	0	0	0	6110
ALUNBRIG	Brigatinib	0	0	0	0	0	0	0	0	0	0	0	18	0	18
ZYKADIA	Ceritinib	0	0	0	0	0	0	0	0	0	0	88	55	0	143
XALKORI	Crizotinib	0	0	0	0	0	0	0	0	0	56	219	27	348	651
347.29	CT	11792	5249	354	4072	1386	304	21	274	110	0	88	46	0	23696
AVASTIN	Bévacizumab	5896	309	0	0	0	0	0	80	12	0	13	9	0	6319
TARCEVA	Erlotinib	0	309	39	0	107	76	624	171	49	0	0	0	0	1375
IRESSA	Gefitinib	0	0	0	0	0	0	499	80	0	0	0	0	0	579
/	Lorlatinib	0	0	0	0	0	0	0	0	0	56	0	37	0	93
OPDIVO	Nivolumab	2211	0	0	2036	427	0	0	23	79	0	0	0	0	4776
TAGRISSE	Osimertinib	0	0	0	0	0	0	624	572	317	0	0	0	0	1512
KEYTRUDA	Pembrolizumab	4864	309	0	764	107	0	0	0	0	0	0	0	0	6043
ALIMTA	Pemetrexed	1474	0	0	1324	0	0	0	217	37	0	0	0	0	3051
		30658	6485	393.024591	9468	2133	380	2078	1452	653	1120	452	192	348	

Annex 10. Analysis of costs in stage IIIB/IV NSCLC per treatment and for other costs for 2017 and 2022

Years	2017		2022 max	
Total number of patients	31785		34834	
Chemotherapy				
Number of patients	20191		23696	
Acquisition costs	€	641.00	€	641.00
Administration costs	€	347.03	€	347.03
Monitoring costs	€	83.67	€	83.67
AEs costs	€	248.68	€	248.68
TOTAL	€	26,660,369.82	€	31,288,124.42
Afatinib				
Number of patients	426		395	
Acquisition costs	€	1,870.48	€	1,870.48
Administration costs	€	-	€	-
Monitoring costs	€	206.15	€	206.15
AEs costs	€	623.38	€	623.38
TOTAL	€	1,148,881.80	€	1,066,156.26
Alectinib				
Number of patients	41		1052	
Acquisition costs	€	6,455.32	€	6,455.32
Administration costs	€	-	€	-
Monitoring costs	€	28.89	€	28.89
AEs costs	€	437.44	€	437.44
TOTAL	€	281,317.93	€	7,282,891.08
Atezolizumab				
Number of patients	0		6110	
Acquisition costs	€	-	€	5,394.75
Administration costs	€	656.58	€	656.58
Monitoring costs	€	206.15	€	206.15

AEs costs	€	15.84	€	15.84
TOTAL	€	-	€	38,329,481.92
Bévacizumab				
Number of patients		3058		6319
Acquisition costs	€	1,930.48	€	1,930.48
Administration costs	€	685.33	€	685.33
Monitoring costs	€	206.15	€	206.15
AEs costs	€	450.00	€	450.00
TOTAL	€	10,004,452.69	€	20,675,808.82
Brigatinib				
Number of patients		0		18
Acquisition costs	€	4,983.42	€	4,983.42
Administration costs	€	-	€	-
Monitoring costs	€	28.89	€	28.89
AEs costs	€	237.29	€	237.29
TOTAL	€	-	€	95,933.64
Ceritinib				
Number of patients		325		143
Acquisition costs	€	4,983.42	€	4,983.42
Administration costs	€	-	€	-
Monitoring costs	€	28.89	€	28.89
AEs costs	€	1,067.19	€	1,067.19
TOTAL	€	1,976,722.14	€	866,577.06
Crizotinib				
Number of patients		1383		651
Acquisition costs	€	5,238.72	€	5,238.72
Administration costs	€	-	€	-
Monitoring costs	€	24.30	€	24.30
AEs costs	€	157.41	€	157.41
TOTAL	€	7,498,794.30	€	3,529,045.28
Erlotinib				
Number of patients		2371		1375

Acquisition costs	€	2,195.88	€	2,195.88
Administration costs	€	-	€	-
Monitoring costs	€	206.15	€	206.15
AEs costs	€	623.38	€	623.38
TOTAL	€	7,173,153.18	€	4,158,799.25
Gefitinib				
Number of patients		810		579
Acquisition costs	€	2,059.74	€	2,059.74
Administration costs	€	-	€	-
Monitoring costs	€	206.15	€	206.15
AEs costs	€	623.38	€	623.38
TOTAL	€	2,341,186.87	€	1,672,409.37
Lorlatinib				
Number of patients		0		93
Acquisition costs	€	6,500.00	€	6,500.00
Administration costs	€	-	€	-
Monitoring costs	€	206.15	€	206.15
AEs costs	€	623.38	€	623.38
TOTAL	€	-	€	678,475.10
Nivolumab				
Number of patients		4329		4776
Acquisition costs	€	4,839.85	€	4,839.85
Administration costs	€	656.58	€	656.58
Monitoring costs	€	206.15	€	206.15
AEs costs	€	15.84	€	15.84
TOTAL	€	24,755,712.15	€	27,310,763.36
Osimertinib				
Number of patients		880		1512
Acquisition costs	€	2,059.74	€	2,059.74
Administration costs	€	-	€	-
Monitoring costs	€	206.15	€	206.15
AEs costs	€	623.38	€	623.38

TOTAL	€	2,541,611.72	€	4,369,715.35
Pembrolizumab				
Number of patients		1031		6043
Acquisition costs	€	5,949.66	€	5,949.66
Administration costs	€	656.58	€	656.58
Monitoring costs	€	206.15	€	206.15
AEs costs	€	15.84	€	15.84
TOTAL	€	7,039,722.10	€	52,748,038.13
Pemetrexed				
Number of patients		9295		3051
Acquisition costs	€	2,752.56	€	2,752.56
Administration costs	€	700.04	€	700.04
Monitoring costs	€	83.67	€	83.67
AEs costs	€	248.68	€	248.68
TOTAL	€	35,182,925.00	€	11,549,026.01
ALL TREATMENT TOTAL PER MONTH	€	126,604,849.71	€	205,621,245.05
ALL TREATMENT TOTAL PER YEAR	€	1,519,258,196.50	€	2,467,454,940.56
<i>Consultation costs per patient per month</i>			€	30.24
Consultation costs per month	€	961,178.40	€	1,053,380.16
<i>Palliatives cares per patient</i>			€	2,822.00
Palliatives cares	€	104,636,220.00	€	98,301,548.00
<i>Testing costs per patient per month</i>		85.68		94.08
Testing costs per month	€	2,723,338.80	€	3,277,182.72
<i>Transport costs per patient per month</i>			€	71.67
Transport costs per month	€	2,278,030.95	€	2,496,552.78
TOTAL PER MONTH	€	141,287,082.86	€	220,640,156.37
TOTAL PER YEAR	€	1,695,444,994.30	€	2,647,681,876.48
TOTAL PER PATIENT PER MONTH	€	4,445.09	€	6,334.05
TOTAL PER PATIENT PER YEAR	€	53,341.04	€	76,008.55

Annex 11. Hypothesis 2022 for costs in stage IIIB/IV NSCLC per treatment and for other costs

Years			min	med	max
Total number of patients	Min	Med			
	%	%			
Chemotherapy					
Number of patients			23696	23696	23696
Acquisition costs	5%	2.5%	€ 608.95	€ 624.98	€ 641.00
Administration costs	5%	2.5%	€ 329.68	€ 338.35	€ 347.03
Monitoring costs	5%	2.5%	€ 79.49	€ 81.58	€ 83.67
AEs costs	5%	2.5%	€ 236.25	€ 242.46	€ 248.68
TOTAL			€ 29,723,718.19	€ 30,505,921.30	€ 31,288,124.42
Afatinib					
Number of patients			395	395	395
Acquisition costs	5%	2.5%	€ 1,776.96	€ 1,823.72	€ 1,870.48
Administration costs	5%	2.5%	€ -	€ -	€ -
Monitoring costs	5%	2.5%	€ 195.84	€ 201.00	€ 206.15
AEs costs	5%	2.5%	€ 592.21	€ 607.80	€ 623.38
TOTAL			€ 1,012,848.45	€ 1,039,502.35	€ 1,066,156.26
Alectinib					
Number of patients			1052	1052	1052
Acquisition costs	5%	2.5%	€ 6,132.55	€ 6,293.94	€ 6,455.32
Administration costs	5%	2.5%	€ -	€ -	€ -

Monitoring costs	5%	2.5%	€ 27.45	€ 28.17	€ 28.89
AEs costs	5%	2.5%	€ 415.57	€ 426.50	€ 437.44
TOTAL			€ 6,918,746.52	€ 7,100,818.80	€ 7,282,891.08
Atezolizumab					
Number of patients			6110	6110	6110
Acquisition costs	5%	2.5%	€ 5,125.01	€ 5,259.88	€ 5,394.75
Administration costs	5%	2.5%	€ 623.75	€ 640.17	€ 656.58
Monitoring costs	5%	2.5%	€ 195.84	€ 201.00	€ 206.15
AEs costs	5%	2.5%	€ 15.05	€ 15.44	€ 15.84
TOTAL			€ 36,413,007.83	€ 37,371,244.87	€ 38,329,481.92
Bévacizumab					
Number of patients			6319	6319	6319
Acquisition costs	50%	25%	€ 965.24	€ 1,447.86	€ 1,930.48
Administration costs	5%	2.5%	€ 651.06	€ 668.20	€ 685.33
Monitoring costs	5%	2.5%	€ 195.84	€ 201.00	€ 206.15
AEs costs	5%	2.5%	€ 427.50	€ 438.75	€ 450.00
TOTAL			€ 14,152,524.03	€ 17,414,166.42	€ 20,675,808.82
Brigatinib					
Number of patients			18	18	18
Acquisition costs			€ 4,983.42	€ 4,983.42	€ 4,983.42
Administration costs	5%	2.5%	€ -	€ -	€ -

Monitoring costs	5%	2.5%	€ 27.45	€ 28.17	€ 28.89
AEs costs	5%	2.5%	€ 225.43	€ 231.36	€ 237.29
TOTAL			€ 95,690.43	€ 95,812.04	€ 95,933.64
Ceritinib					
Number of patients			143	143	143
Acquisition costs	5%	2.5%	€ 4,734.25	€ 4,858.83	€ 4,983.42
Administration costs	5%	2.5%	€ -	€ -	€ -
Monitoring costs	5%	2.5%	€ 27.45	€ 28.17	€ 28.89
AEs costs	5%	2.5%	€ 1,013.83	€ 1,040.51	€ 1,067.19
TOTAL			€ 823,248.21	€ 844,912.64	€ 866,577.06
Crizotinib					
Number of patients			651	651	651
Acquisition costs			€ 5,238.72	€ 5,238.72	€ 5,238.72
Administration costs	5%	2.5%	€ -	€ -	€ -
Monitoring costs	5%	2.5%	€ 23.09	€ 23.69	€ 24.30
AEs costs	5%	2.5%	€ 149.54	€ 153.47	€ 157.41
TOTAL			€ 3,523,130.04	€ 3,526,087.66	€ 3,529,045.28
Erlotinib					
Number of patients			1375	1375	1375
Acquisition costs	50%	25%	€ 1,097.94	€ 1,646.91	€ 2,195.88
Administration costs	5%	2.5%	€ -	€ -	€ -

Monitoring costs	5%	2.5%	€ 195.84	€ 201.00	€ 206.15
AEs costs	5%	2.5%	€ 592.21	€ 607.80	€ 623.38
TOTAL			€ 2,592,530.72	€ 3,375,664.98	€ 4,158,799.25
Gefitinib					
Number of patients			579	579	579
Acquisition costs	50%	25%	€ 1,029.87	€ 1,544.81	€ 2,059.74
Administration costs	5%	2.5%	€ -	€ -	€ -
Monitoring costs	5%	2.5%	€ 195.84	€ 201.00	€ 206.15
AEs costs	5%	2.5%	€ 592.21	€ 607.80	€ 623.38
TOTAL			€ 1,052,276.97	€ 1,362,343.17	€ 1,672,409.37
Lorlatinib					
Number of patients			93	93	93
Acquisition costs			€ 6,500.00	€ 6,500.00	€ 6,500.00
Administration costs	5%	2.5%	€ -	€ -	€ -
Monitoring costs	5%	2.5%	€ 195.84	€ 201.00	€ 206.15
AEs costs	5%	2.5%	€ 592.21	€ 607.80	€ 623.38
TOTAL			€ 674,635.73	€ 676,555.41	€ 678,475.10
Nivolumab					
Number of patients			4776	4776	4776
Acquisition costs	5%	2.5%	€ 4,597.85	€ 4,718.85	€ 4,839.85
Administration costs	5%	2.5%	€ 623.75	€ 640.17	€ 656.58

Monitoring costs	5%	2.5%	€ 195.84	€ 201.00	€ 206.15
AEs costs	5%	2.5%	€ 15.05	€ 15.44	€ 15.84
TOTAL			€ 25,945,225.19	€ 26,627,994.27	€ 27,310,763.36
Osimertinib					
Number of patients			1512	1512	1512
Acquisition costs	5%	2.5%	€ 1,956.75	€ 2,008.25	€ 2,059.74
Administration costs	5%	2.5%	€ -	€ -	€ -
Monitoring costs	5%	2.5%	€ 195.84	€ 201.00	€ 206.15
AEs costs	5%	2.5%	€ 592.21	€ 607.80	€ 623.38
TOTAL			€ 4,151,229.59	€ 4,260,472.47	€ 4,369,715.35
Pembrolizumab					
Number of patients			6043	6043	6043
Acquisition costs	5%	2.5%	€ 5,652.17	€ 5,800.91	€ 5,949.66
Administration costs	5%	2.5%	€ 623.75	€ 640.17	€ 656.58
Monitoring costs	5%	2.5%	€ 195.84	€ 201.00	€ 206.15
AEs costs	5%	2.5%	€ 15.05	€ 15.44	€ 15.84
TOTAL			€ 39,200,108.99	€ 40,231,690.81	€ 52,748,038.13
Pemetrexed					
Number of patients			3051	3051	3051
Acquisition costs	10%	5%	€ 2,477.30	€ 2,614.93	€ 2,752.56
Administration costs	5%	2.5%	€ 665.04	€ 682.54	€ 700.04

Monitoring costs	5%	2.5%	€ 79.49	€ 81.58	€ 83.67
AEs costs	5%	2.5%	€ 236.25	€ 242.46	€ 248.68
TOTAL			€ 10,551,630.10	€ 11,050,328.06	€ 11,549,026.01
ALL TREATMENT TOTAL PER MONTH			€ 176,830,550.99	€ 185,483,515.26	€ 205,621,245.05
ALL TREATMENT TOTAL PER YEAR			€ 2,121,966,611.83	€ 2,225,802,183.17	€ 2,467,454,940.56
Consultation costs per patient per month				€ 28.73	
Consultation costs per month	10%	5%	€ 948,042.14	€ 1,000,711.15	€ 1,053,380.16
Palliatives cares per patient				€ 2,680.90	
Palliatives cares	10%	5%	€ 88,471,393.20	€ 93,386,470.60	€ 98,301,548.00
Testing costs per patient per month				€ 89.38	
Testing costs per month	10%	5%	€ 2,686,119.41	€ 3,113,323.58	€ 3,277,182.72
Transport costs per patient per month				€ 68.09	
Transport costs per month	10%	5%	€ 2,246,897.50	€ 2,371,725.14	€ 2,496,552.78
TOTAL PER MONTH			€ 190,084,226.14	€ 199,751,481.02	€ 220,640,156.37
TOTAL PER YEAR			€ 2,281,010,713.68	€ 2,397,017,772.30	€ 2,647,681,876.48
TOTAL PER PATIENT PER MONTH			€ 5,456.86	€ 5,734.38	€ 6,334.05
TOTAL PER PATIENT PER YEAR			€ 65,482.31	€ 68,812.59	€ 76,008.55

Annex 12. Evolution of the total cost per patients per month when modifying each other costs from 0% to 50%: price variation comparing to med hypothesis

<i>Price variation comparing to med hypothesis</i>	± 0 %	$\pm 3\%$	$\pm 5\%$	$\pm 10\%$	$\pm 15\%$	$\pm 20\%$	$\pm 25\%$	$\pm 30\%$	$\pm 40\%$	$\pm 50\%$
<i>Consultation costs</i>	0.00	0.72	1.44	2.87	4.31	5.75	7.18	8.62	11.49	14.36
<i>Palliatives cares</i>	0.00	67.0 2	134.0 5	268.0 9	402.1 4	536.1 8	670.2 3	804.2 7	1,072.3 6	1,340.4 5
<i>Testing costs</i>	0.00	2.23	4.47	8.94	13.41	17.88	22.34	26.81	35.75	44.69
<i>Transport costs</i>	0.00	1.70	3.40	6.81	10.21	13.62	17.02	20.43	27.23	34.04

Annex 13. Evolution of the total cost per patients per month when modifying treatment costs from 0% to 50%: price variation comparing to med hypothesis

<i>Price variation comparing to med hypothesis</i>	<i>±0%</i>	<i>±3%</i>	<i>±5%</i>	<i>±10%</i>	<i>±15%</i>	<i>±20%</i>	<i>±25%</i>	<i>±30%</i>	<i>±40%</i>	<i>±50%</i>
<i>Chemotherapy</i>	<i>0.00</i>	<i>21.89</i>	<i>43.79</i>	<i>87.58</i>	<i>131.36</i>	<i>175.15</i>	<i>218.94</i>	<i>262.73</i>	<i>350.30</i>	<i>437.88</i>
<i>Afatinib</i>	<i>0.00</i>	<i>0.75</i>	<i>1.49</i>	<i>2.98</i>	<i>4.48</i>	<i>5.97</i>	<i>7.46</i>	<i>8.95</i>	<i>11.94</i>	<i>14.92</i>
<i>Alectinib</i>	<i>0.00</i>	<i>5.10</i>	<i>10.19</i>	<i>20.38</i>	<i>30.58</i>	<i>40.77</i>	<i>50.96</i>	<i>61.15</i>	<i>81.54</i>	<i>101.92</i>
<i>Atezolizumab</i>	<i>0.00</i>	<i>26.82</i>	<i>53.64</i>	<i>107.28</i>	<i>160.93</i>	<i>214.57</i>	<i>268.21</i>	<i>321.85</i>	<i>429.14</i>	<i>536.42</i>
<i>Bévacizumab</i>	<i>0.00</i>	<i>12.50</i>	<i>25.00</i>	<i>49.99</i>	<i>74.99</i>	<i>99.98</i>	<i>124.98</i>	<i>149.98</i>	<i>199.97</i>	<i>249.96</i>
<i>Brigatinib</i>	<i>0.00</i>	<i>0.07</i>	<i>0.14</i>	<i>0.28</i>	<i>0.41</i>	<i>0.55</i>	<i>0.69</i>	<i>0.83</i>	<i>1.10</i>	<i>1.38</i>
<i>Ceritinib</i>	<i>0.00</i>	<i>0.61</i>	<i>1.21</i>	<i>2.43</i>	<i>3.64</i>	<i>4.85</i>	<i>6.06</i>	<i>7.28</i>	<i>9.70</i>	<i>12.13</i>
<i>Crizotinib</i>	<i>0.00</i>	<i>2.53</i>	<i>5.06</i>	<i>10.12</i>	<i>15.18</i>	<i>20.25</i>	<i>25.31</i>	<i>30.37</i>	<i>40.49</i>	<i>50.61</i>
<i>Erlotinib</i>	<i>0.00</i>	<i>2.42</i>	<i>4.85</i>	<i>9.69</i>	<i>14.54</i>	<i>19.38</i>	<i>24.23</i>	<i>29.07</i>	<i>38.76</i>	<i>48.45</i>
<i>Gefitinib</i>	<i>0.00</i>	<i>0.98</i>	<i>1.96</i>	<i>3.91</i>	<i>5.87</i>	<i>7.82</i>	<i>9.78</i>	<i>11.73</i>	<i>15.64</i>	<i>19.55</i>
<i>Lorlatinib</i>	<i>0.00</i>	<i>0.49</i>	<i>0.97</i>	<i>1.94</i>	<i>2.91</i>	<i>3.88</i>	<i>4.86</i>	<i>5.83</i>	<i>7.77</i>	<i>9.71</i>
<i>Nivolumab</i>	<i>0.00</i>	<i>19.11</i>	<i>38.22</i>	<i>76.44</i>	<i>114.66</i>	<i>152.89</i>	<i>191.11</i>	<i>229.33</i>	<i>305.77</i>	<i>382.21</i>
<i>Osimertinib</i>	<i>0.00</i>	<i>3.06</i>	<i>6.12</i>	<i>12.23</i>	<i>18.35</i>	<i>24.46</i>	<i>30.58</i>	<i>36.69</i>	<i>48.92</i>	<i>61.15</i>
<i>Pembrolizumab</i>	<i>0.00</i>	<i>28.87</i>	<i>57.75</i>	<i>115.50</i>	<i>173.24</i>	<i>230.99</i>	<i>288.74</i>	<i>346.49</i>	<i>461.98</i>	<i>577.48</i>
<i>Pemetrexed</i>	<i>0.00</i>	<i>7.93</i>	<i>15.86</i>	<i>31.72</i>	<i>47.58</i>	<i>63.45</i>	<i>79.31</i>	<i>95.17</i>	<i>126.89</i>	<i>158.61</i>

Annex 14. Evolution of the total cost per patients per month when modifying acquisition costs from 0% to 50%: price variation comparing to med hypothesis

<i>Price variation comparing to med hypothesis</i>	$\pm 0\%$	$\pm 3\%$	$\pm 5\%$	$\pm 10\%$	$\pm 15\%$	$\pm 20\%$	$\pm 25\%$	$\pm 30\%$	$\pm 40\%$	$\pm 50\%$
<i>Chemotherapy</i>	0.00	10.63	21.26	42.51	63.77	85.03	106.29	127.54	170.06	212.57
<i>Afatinib</i>	0.00	0.52	1.03	2.07	3.10	4.13	5.17	6.20	8.27	10.34
<i>Alectinib</i>	0.00	4.75	9.51	19.01	28.52	38.02	47.53	57.03	76.05	95.06
<i>Atezolizumab</i>	0.00	23.06	46.13	92.26	138.39	184.52	230.65	276.78	369.04	461.29
<i>Bévacizumab</i>	0.00	6.57	13.13	26.27	39.40	52.53	65.66	78.80	105.06	131.33
<i>Brigatinib</i>	0.00	0.07	0.13	0.26	0.39	0.52	0.65	0.78	1.05	1.31
<i>Ceritinib</i>	0.00	0.50	0.99	1.99	2.98	3.98	4.97	5.96	7.95	9.94
<i>Crizotinib</i>	0.00	2.45	4.90	9.79	14.69	19.58	24.48	29.37	39.17	48.96
<i>Erlotinib</i>	0.00	1.62	3.25	6.50	9.75	13.00	16.25	19.50	26.00	32.50
<i>Géfitinib</i>	0.00	0.64	1.28	2.57	3.85	5.13	6.42	7.70	10.27	12.83
<i>Lorlatinib</i>	0.00	0.43	0.86	1.73	2.59	3.45	4.32	5.18	6.91	8.64
<i>Nivolumab</i>	0.00	16.17	32.35	64.70	97.05	129.40	161.75	194.09	258.79	323.49
<i>Osimertinib</i>	0.00	2.18	4.36	8.72	13.08	17.44	21.80	26.16	34.88	43.60
<i>Pembrolizumab</i>	0.00	25.16	50.32	100.63	150.95	201.27	251.59	301.90	402.54	503.17
<i>Pemetrexed</i>	0.00	5.73	11.45	22.91	34.36	45.81	57.26	68.72	91.62	114.53

Annex 15. Evolution of the total cost per patients per month when modifying administration costs from 0% to 50%: price variation comparing to med hypothesis

<i>Price variation comparing to med hypothesis</i>	$\pm 0\%$	$\pm 3\%$	$\pm 5\%$	$\pm 10\%$	$\pm 15\%$	$\pm 20\%$	$\pm 25\%$	$\pm 30\%$	$\pm 40\%$	$\pm 50\%$
<i>Chemotherapy</i>	0.00	5.75	11.51	23.02	34.53	46.03	57.54	69.05	92.07	115.09
<i>Afatinib</i>	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
<i>Alectinib</i>	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
<i>Atezolizumab</i>	0.00	2.81	5.61	11.23	16.84	22.46	28.07	33.69	44.91	56.14
<i>Bévacizumab</i>	0.00	3.03	6.06	12.12	18.18	24.24	30.30	36.36	48.49	60.61
<i>Brigatinib</i>	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
<i>Ceritinib</i>	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
<i>Crizotinib</i>	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
<i>Erlotinib</i>	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
<i>Géfitinib</i>	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
<i>Lorlatinib</i>	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
<i>Nivolumab</i>	0.00	2.19	4.39	8.78	13.17	17.55	21.94	26.33	35.11	43.89
<i>Osimertinib</i>	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
<i>Pembrolizumab</i>	0.00	2.78	5.55	11.11	16.66	22.21	27.76	33.32	44.42	55.53
<i>Pemetrexed</i>	0.00	1.49	2.99	5.98	8.97	11.96	14.95	17.94	23.91	29.89

Annex 16. Evolution of the total cost per patients per month when modifying monitoring costs from 0% to 50%: price variation comparing to med hypothesis

<i>Price variation comparing to med hypothesis</i>	$\pm 0\%$	$\pm 3\%$	$\pm 5\%$	$\pm 10\%$	$\pm 15\%$	$\pm 20\%$	$\pm 25\%$	$\pm 30\%$	$\pm 40\%$	$\pm 50\%$
<i>Chemotherapy</i>	0.00	1.39	2.77	5.55	8.32	11.10	13.87	16.65	22.20	27.75
<i>Afatinib</i>	0.00	0.06	0.11	0.23	0.34	0.46	0.57	0.68	0.91	1.14
<i>Alectinib</i>	0.00	0.02	0.04	0.09	0.13	0.17	0.21	0.26	0.34	0.43
<i>Atezolizumab</i>	0.00	0.88	1.76	3.53	5.29	7.05	8.81	10.58	14.10	17.63
<i>Bévacizumab</i>	0.00	0.91	1.82	3.65	5.47	7.29	9.12	10.94	14.58	18.23
<i>Brigatinib</i>	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01
<i>Ceritinib</i>	0.00	0.00	0.01	0.01	0.02	0.02	0.03	0.03	0.05	0.06
<i>Crizotinib</i>	0.00	0.01	0.02	0.04	0.07	0.09	0.11	0.13	0.18	0.22
<i>Erlotinib</i>	0.00	0.20	0.40	0.79	1.19	1.59	1.98	2.38	3.17	3.97
<i>Géfitinib</i>	0.00	0.08	0.17	0.33	0.50	0.67	0.83	1.00	1.34	1.67
<i>Lorlatinib</i>	0.00	0.01	0.03	0.05	0.08	0.11	0.13	0.16	0.21	0.27
<i>Nivolumab</i>	0.00	0.69	1.38	2.76	4.13	5.51	6.89	8.27	11.02	13.78
<i>Osimertinib</i>	0.00	0.22	0.44	0.87	1.31	1.75	2.18	2.62	3.49	4.36
<i>Pembrolizumab</i>	0.00	0.87	1.74	3.49	5.23	6.97	8.72	10.46	13.95	17.43
<i>Pemetrexed</i>	0.00	0.18	0.36	0.71	1.07	1.43	1.79	2.14	2.86	3.57

Annex 17. Evolution of the total cost per patients per month when modifying Adverse Events costs from 0% to 50%: price variation comparing to med hypothesis

<i>Price variation comparing to med hypothesis</i>	$\pm 0\%$	$\pm 3\%$	$\pm 5\%$	$\pm 10\%$	$\pm 15\%$	$\pm 20\%$	$\pm 25\%$	$\pm 30\%$	$\pm 40\%$	$\pm 50\%$
<i>Chemotherapy</i>	0.00	4.12	8.25	16.49	24.74	32.99	41.23	49.48	65.98	82.47
<i>Afatinib</i>	0.00	0.17	0.34	0.69	1.03	1.38	1.72	2.07	2.76	3.44
<i>Alectinib</i>	0.00	0.32	0.64	1.29	1.93	2.58	3.22	3.86	5.15	6.44
<i>Atezolizumab</i>	0.00	0.07	0.14	0.27	0.41	0.54	0.68	0.81	1.08	1.35
<i>Bévacizumab</i>	0.00	1.99	3.98	7.96	11.94	15.92	19.90	23.88	31.84	39.80
<i>Brigatinib</i>	0.00	0.00	0.01	0.01	0.02	0.02	0.03	0.04	0.05	0.06
<i>Ceritinib</i>	0.00	0.11	0.21	0.43	0.64	0.85	1.06	1.28	1.70	2.13
<i>Crizotinib</i>	0.00	0.07	0.14	0.29	0.43	0.57	0.72	0.86	1.15	1.43
<i>Erlotinib</i>	0.00	0.60	1.20	2.40	3.60	4.80	6.00	7.20	9.59	11.99
<i>Géfitinib</i>	0.00	0.25	0.50	1.01	1.51	2.02	2.52	3.03	4.04	5.05
<i>Lorlatinib</i>	0.00	0.04	0.08	0.16	0.24	0.32	0.40	0.48	0.65	0.81
<i>Nivolumab</i>	0.00	0.05	0.11	0.21	0.32	0.42	0.53	0.64	0.85	1.06
<i>Osimertinib</i>	0.00	0.66	1.32	2.64	3.96	5.28	6.60	7.92	10.56	13.19
<i>Pembrolizumab</i>	0.00	0.07	0.13	0.27	0.40	0.54	0.67	0.80	1.07	1.34
<i>Pemetrexed</i>	0.00	0.53	1.06	2.12	3.19	4.25	5.31	6.37	8.50	10.62

THÈSE SOUTENUE PAR : Agathe PLICHTA

TITRE :

IMPACT MEDICO-ECONOMIQUE DE LA MEDECINE PERSONNALISEE ET DES TRAITEMENTS IMMUNO-ONCOLOGIQUES DANS LA PRISE EN CHARGE DES CANCERS BRONCHO-PULMONAIRES AVANCES OU METASTATIQUES EN FRANCE

CONCLUSION :

Cette étude basée sur des hypothèses de projection de la prise en charge du cancer bronchique non à petit cellules avancé ou métastatique pour 2022 montre un impact budgétaire des innovations thérapeutiques pour le système de santé. En effet pour une année de traitement, les coûts moyens de prise en charge d'un patient atteint d'un cancer bronchique non à petit cellules avancé ou métastatique s'élevait à environ € 53,000 en 2017 et s'approcherait de €76,000 en 2022. Cette évolution est cohérente avec l'hypothèse de l'utilisation de plus en plus importante des thérapies ciblées et des immunothérapies qui présentent des résultats cliniques intéressants. L'utilisation concomitante de chimiothérapies, immunothérapies et thérapies ciblées, pour potentialiser la réponse des patients, tire également à la hausse le coût moyen par patient. Les coûts engendrés par les soins palliatifs et les coûts d'acquisition des thérapies sont les postes de dépenses qui impactent le plus la prise en charge du CBNPC IIIB/IV.

VU ET PERMIS D'IMPRIMER

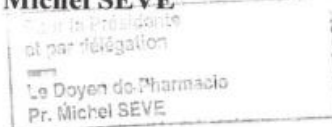
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LE DOYEN

LE PRÉSIDENT DE LA THÈSE



Pr. Michel SÈVE



Dr. Jean BRETON

*Faculté de Pharmacie,
Université Grenoble Alpes*



Serment de Galien



« Je jure en présence des Maîtres de la Faculté, des Conseillers de l'Ordre des Pharmaciens et de mes condisciples :

D'honorer ceux qui m'ont instruit(e) dans les préceptes de mon art et de leur témoigner ma reconnaissance en restant fidèle à leur enseignement.

D'exercer, dans l'intérêt de la santé publique, ma profession avec conscience et de respecter non seulement la législation en vigueur, mais aussi les règles de l'honneur, de la probité et du désintéressement.

De ne jamais oublier ma responsabilité et mes devoirs envers le malade et sa dignité humaine ; en aucun cas, je ne consentirai à utiliser mes connaissances et mon état pour corrompre les mœurs et favoriser des actes criminels.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert(e) d'opprobre et méprisé(e) de mes confrères si j'y manque ».

Agathe PLICHTA

THE HEALTH-ECONOMIC ISSUES OF TARGETED THERAPIES AND IMMUNO-ONCOLOGY THERAPIES IN THE MANAGEMENT OF ADVANCED OR METASTATIC LUNG CANCERS IN FRANCE

SUMMARY :

Lung cancer is the fourth most common cancer with the highest mortality rate in France. The French healthcare system offers a mainly public funding model, and medical costs generated by this pathology are fully covered by Health Insurance. The arrival of immunotherapy has modified the management of advanced or metastatic non-small cell lung cancer. This analysis aims to assess whether therapeutic innovations in lung cancer have a budgetary impact on the health system. For that purpose, the 2017 actual medical costs of this pathology were studied, as well as the coming years' costs within a specific forecast analysis to 2022. A model integrating medical parameters, changes in treatment, care and testing was built and studied. This study shows a budgetary impact of therapeutic innovations on the health system. The average one-year cost of treatment for a patient with advanced or metastatic non-small cell lung cancer was approximately € 53,000 in 2017 and would approach € 76,000 by 2022. This trend is consistent with the assumption of the increasingly important use of targeted therapies and immunotherapies. The associated costs for palliative care and acquisition costs of therapies are the most significant expenses in the management of NSCLC IIIB / IV.

KEY WORDS : Broncho-pulmonary cancer, health-economic, immunotherapies

SPECIALIZATION : Industry Field

Agathe PLICHTA

IMPACT MEDICO-ECONOMIQUE DES THERAPIES CIBLEES ET DES TRAITEMENTS IMMUNO-ONCOLOGIQUES DANS LA PRISE EN CHARGE DES CANCERS BRONCHO-PULMONAIRES AVANCES OU METASTATIQUES EN FRANCE

RÉSUMÉ :

En France, le cancer du poumon représente le quatrième cancer le plus fréquent et avec le taux de mortalité le plus élevé. Le système de santé français propose un modèle de financement essentiellement public et les coûts médicaux engendrés par cette pathologie sont intégralement pris en charge par l'Assurance Maladie car le cancer bronchique fait partie des Affections Longues Durées. L'arrivée de l'immunothérapie a modifié la prise en charge du cancer bronchique non à petites cellules avancé ou métastatique. Cette analyse vise à évaluer si les innovations thérapeutiques dans le cancer du poumon ont un impact budgétaire pour le système de santé. Pour cela, les coûts réels médicaux de cette pathologie en 2017 ont été étudiés mais également ceux au cours des prochaines années et notamment une projection à 2022. Un modèle intégrant des paramètres médicaux, l'évolution des traitements, de la prise en charge et des techniques de diagnostic a été étudié. Cette étude montre un impact budgétaire des innovations thérapeutiques pour le système de santé. Pour une année de traitement, les coûts moyens de prise en charge d'un patient atteint d'un cancer bronchique non à petit cellules avancé ou métastatique s'élevait à environ € 53,000 en 2017 et s'approcherait de € 76,000 en 2022. Cette évolution est cohérente avec l'hypothèse de l'utilisation de plus en plus importante des thérapies ciblées et des immunothérapies. Les coûts engendrés par les soins palliatifs et les coûts d'acquisition des thérapies sont les postes de dépenses qui impactent le plus la prise en charge du CBNPC IIIB/IV.

MOTS CLÉS : Cancer broncho-pulmonaire, médico-économie, immunothérapie

FILIÈRE : Industrie