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# Marketing tools to improve Tyrosine Kinase Inhibitors compliance for patients with Chronic Myeloid Leukemia: an achievable strategy for pharmaceutical industries?

Audrey Lagadec

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UNIVERSITÉ GRENOBLE ALPES  
UFR DE PHARMACIE DE GRENOBLE

Année : 2018

**L'OBSERVANCE CHEZ LES PATIENTS ATTEINTS DE LEUCEMIE MYELOIDE  
CHRONIQUE ET TRAITES PAR INHIBITEURS DE TYROSINES KINASES : ENTRE  
BESOINS PATIENTS ET STRATÉGIES DES LABORATOIRES  
PHARMACEUTIQUES**

THÈSE

PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN PHARMACIE

DIPLÔME D'ÉTAT

Audrey LAGADEC

[Données à caractère personnel]

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Dr. JOYEUX FAURE Marie

Membres :

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## KEY ABBREVIATIONS

ALD – Affection de Longue Durée

ARS – Agence Régionale de Santé

BMS – Bristol-Myers Squibb

CMD - Chronic Myeloproliferative Disorders

CML – Chronic Myeloid Leukemia

CMR – Complete Molecular Response

FISH – Fluorescence in situ hybridization

GERS – Groupement pour l'Elaboration et la Réalisation de Statistiques

HAS – Haute Autorité de Santé

HPST – Hôpital Patient Santé Territoire

MMR – Major Molecular Response

MRD – Minimal Residual Disease

PactOnco – Personnalisation de l'Accompagnement du patient en ONCOlogie

TKI – Tyrosine Kinase Inhibitor

UCD – Unité Commune de Dispensation (Dispensation common unit)

## INTRODUCTION

Les pratiques pharmaceutiques et médicales évoluent. En effet, depuis quelques années, les missions du pharmacien et du médecin sont de plus en plus centrées sur le patient. Les pharmaciens sont désormais en charge des entretiens pharmaceutiques avec les patients (exemple des entretiens sur les antagonistes de la vitamine K ou sur les chimiothérapies), à la recherche de contre-indications ou d'interactions médicamenteuses (1). Ils sont également responsables de l'éducation thérapeutique du patient, tout comme les médecins. Les pratiques médicales évoluent et placent les patients au cœur de leur prise en charge thérapeutique en leur donnant de plus en plus d'information et de pouvoir décisionnel sur certains aspects de leur prise en charge.

Notre système de santé français a subi de nombreuses évolutions au cours des dernières années. Le concept « d'autonomie du patient » n'est pas un concept récent. Depuis 2002, la loi sur les droits des patients et la qualité du système de santé fait du patient un acteur à part entière de sa prise en charge médicale et thérapeutique. En février 2018, le gouvernement a communiqué sur cinq axes de réforme du système de santé en France, dont le premier était « d'inscrire la qualité et la pertinence des soins au cœur des organisations et des pratiques médicales ». Plus récemment, en septembre 2018, la réforme "Ma santé 2022" qui vise à placer le patient au cœur du système de santé a été votée (2).

De plus, les médecins et même les autorités de santé sont de plus en plus exposés aux pressions des patients. Au fil des années, les patients ont acquis de plus en plus de pouvoir décisionnel. Le cas du Levothyrox® en France en est l'exemple parfait.

Ce changement des pratiques médicales et pharmaceutiques doit aujourd'hui être intégré par les laboratoires pharmaceutiques car les stratégies marketing sont dans la plupart des cas, essentiellement dirigées vers les médecins.

L'observance thérapeutique est aujourd'hui un enjeu majeur pour les autorités de santé, les médecins, les patients mais aussi les laboratoires pharmaceutiques. L'inobservance thérapeutique touche particulièrement les patients atteints de maladies chroniques. Les inhibiteurs de tyrosines kinases (ITK) utilisés dans le traitement de la leucémie myéloïde chronique (LMC) en sont le parfait exemple. L'inobservance thérapeutique est très présente chez les patients atteints de LMC en phase chronique et il est donc important de comprendre

comment cette problématique de santé pourrait être améliorée. En effet, cette inobservance peut être source de perte d'efficacité du traitement, mais aussi de l'apparition de résistances au traitement entraînant donc des dépenses de santé supplémentaires (hospitalisations, greffes etc.). Aujourd'hui, l'inobservance des patients atteints de LMC et traités par ITK est estimée à 30% en France. De plus, seulement 15 % des patients au maximum sont considérés comme totalement observant (3). Les laboratoires pharmaceutiques, et notamment le marketing, peuvent jouer un rôle dans cette éducation thérapeutique des patients, en finançant la création de nouveaux outils marketing pour améliorer l'observance médicamenteuse. Cependant, pour pouvoir y parvenir, l'équipe marketing doit connaître et comprendre les attentes et besoins non satisfaits des patients. Améliorer l'observance des patients est donc devenu un axe stratégique pour les laboratoires pharmaceutiques.

Dans un premier temps, cette thèse sera consacrée à la revue de la littérature scientifique, avec notamment un état des lieux des outils marketing actuellement disponibles pour les patients, portant sur l'observance et ayant été financés par les laboratoires pharmaceutiques commercialisant des ITK dans la LMC.

Dans un second temps, ce travail s'est attaché à répondre aux trois questions de recherche suivantes :

- 1) Quels sont les besoins patients actuels en termes d'outils marketing pour les aider à améliorer leur observance thérapeutique ?**
- 2) Comment segmenter les patients atteints de LMC et sur quel segment devraient se concentrer les laboratoires pharmaceutiques ?**
- 3) Concentrer sa stratégie sur l'observance du patient : est-ce une stratégie réalisable pour les laboratoires pharmaceutiques ?**

Un questionnaire permettra de recueillir les besoins patients en termes de nouveaux outils marketing. Puis une segmentation des patients atteints de LMC en phase chronique sera réalisée afin de mieux comprendre à quels types de patients ces outils peuvent s'adresser.

L'objectif est de rédiger des recommandations concernant les directions à suivre pour la construction de nouveaux outils marketing afin d'apporter de nouvelles solutions aux patients et de répondre à des besoins aujourd'hui encore insatisfaits. Ces outils doivent pouvoir aider le

patient à mieux comprendre son traitement et surtout de le sensibiliser à l'importance de prendre son ITK de façon régulière. Puis la question de faisabilité en termes de stratégie pour les laboratoires pharmaceutiques sera traitée grâce aux données de la littérature et des données recueillies dans les questions de recherche précédentes, mais aussi grâce aux témoignages de chefs de produits des laboratoires pharmaceutiques concernés. Les avantages et les inconvénients de cette stratégie seront passés en revue.

Enfin, la dernière partie de cette thèse sera consacrée à une discussion puis une conclusion générale.

## ETAT DES LIEUX ET PROBLEMATIQUE

L'observance thérapeutique est fréquente chez les patients atteints de LMC et sous traitement oral par ITK. La première partie de travail a consisté à dresser un état des lieux des outils marketing actuels proposés par l'industrie pharmaceutique afin d'amélioration de l'observance de ces patients vis-à-vis de leur traitement par ITK.

La proportion d'outils marketing actuellement disponibles sur le marché pour une maladie rare comme la LMC est élevée. Chaque laboratoire pharmaceutique commercialisant des ITK dans la LMC a développé sa propre stratégie en termes de projets financés.

Pfizer a misé sur le financement d'outils dans la prise en charge globale des patients en oncologie avec PactOnco™, un parcours de soin virtuel qui invite le patient et sa famille à prendre connaissance des différents interlocuteurs qu'ils vont rencontrer, à s'informer sur le cancer et sa prise en charge, à obtenir des réponses sur le plan administratif, juridique et social etc. Ce projet est disponible sur internet, et regroupe des témoignages patients, des vidéos ainsi que des brochures. PactOnco™ n'est pas centré sur l'observance des ITK ou sur la LMC mais intègre dans un seul et même outil le parcours de soins du patient en oncologie, ceci afin d'aider le patient mais également ses proches.

Novartis lui, a investi dans des applications mobiles ciblées sur la LMC comme "LMCoach" et Mon "Suivi BioMol". LMCoach est un service mobile d'accompagnement personnalisé à l'observance des patients atteints de LMC. Ce service est gratuit et a rencontré un franc succès depuis sa sortie. Aujourd'hui, 370 patients sont inscrits. Ce service de soutien personnalisé utilise la voie SMS en envoyant des messages types, conçus en fonction des différents profils

de patients et ayant été rédigés par un comité scientifique : rappels de traitement, rendez-vous de consultation, conseils sur le mode de vie diététique, activité physique adaptée, etc. En revanche, l'application « Mon suivi BioMol » est aujourd'hui peu utilisée par les patients. Cette application cible également l'observance thérapeutique mais avec une approche différente du service LMCoach en permettant au patient de rentrer ses résultats de PCR pour suivre leurs évolutions.

Bristol Myers Squibb (BMS) est quant à lui plus diversifié en termes de types d'outils, avec des vidéos, des brochures en version papier pour les patients et des gadgets de type « nudges » pour améliorer l'observance thérapeutique.

BMS, Pfizer, Novartis et Incyte apportent également de façon fréquente leur soutien aux réunions patients organisées par l'association Fi-LMC chaque année dans toute la France.

## QUESTIONS POSEES ET RESULTATS

Trois questions de recherche ont ensuite été explorées dans ce travail :

- Quels sont les besoins patients actuels en termes d'outils marketing pour les aider à améliorer leur observance thérapeutique ?
- Comment segmenter les patients atteints de LMC et sur quel segment devraient se concentrer les laboratoires pharmaceutiques ?
- Concentrer sa stratégie sur l'observance du patient : est-ce une stratégie réalisable pour les laboratoires pharmaceutiques ?

### **1. Méthodologie et limites**

Pour répondre à la première question de recherche, un questionnaire à destination des patients atteints de LMC (en phase chronique) et traités actuellement ou ayant été traités dans le passé par ITK a été élaboré. L'objectif était de recueillir leurs besoins en se basant en partie sur les outils préexistants et financés par les laboratoires pharmaceutiques (outils ayant été identifiés dans la partie « Littérature Review » de cette thèse). Le questionnaire était composé de 20 questions (cf. annexe 1) et envoyé aux patients par des hématologues du CHU de Grenoble.



Dix questionnaires ont été retournés entièrement complétés par les patients. Ces dix questionnaires ont donc été inclus dans ce travail de recherche.

Pour répondre à la seconde question de recherche, une segmentation des patients atteints de leucémie myéloïde chronique a été réalisée en se basant sur les données de la littérature ainsi que sur des échanges avec des chefs de produits travaillant dans l'industrie pharmaceutique sur les ITK indiqués dans la LMC.

Enfin, pour répondre à la dernière question de recherche, des interviews avec des chefs de produits travaillant dans l'industrie pharmaceutique sur les ITK dans la LMC ont été conduites (cf. annexe 2). Deux chefs de produits de deux ITK différents ont pu être interviewés sur les cinq ITK commercialisés dans la LMC. Les avantages et inconvénients d'adopter une stratégie centrée sur le patient et sur l'observance thérapeutique pour les laboratoires pharmaceutiques ont également été identifiés grâce aux données de la littérature. Enfin, le témoignage d'une personne travaillant dans un laboratoire pharmaceutique dans le domaine de « patient advocacy » a également été source d'information pour répondre à cette dernière question de recherche.

Ce travail comporte cependant certaines limites :

- Taille de la population : la LMC est une maladie rare et il est donc difficile d'avoir accès à des patients et de recueillir de nombreuses réponses. Le nombre de questionnaires analysés dans cette thèse est donc faible. La taille de l'échantillon de patients est un obstacle à l'obtention de résultats statistiquement significatifs et ne peut que fournir une tendance.
- Subjectivité des réponses des patients : analyse qualitative qui reste donc subjective
- Secret professionnel des chefs de produits travaillant dans l'industrie pharmaceutique : cela a constitué un frein pour l'obtention de certaines réponses.
- Temps et prise de contact : la prise de contact avec les différents interlocuteurs (chef de produits, personnes travaillant en « Patient Advocacy » etc.) a été difficile. Le réseau web professionnel LinkedIn a été utilisé mais les chefs de produits sont peu disponibles et ne répondent pas toujours aux sollicitations la plupart du temps.

Afin de minimiser ces limites, un questionnaire destiné aux hématologues aurait pu être créé afin de recueillir les deux points de vue (traitant/traité) sur les besoins en termes d'outils pour l'amélioration de l'observance du patient. A l'avenir, une autre recommandation serait de créer un second questionnaire. Celui-ci serait plus complet et basé sur les grandes directives à

adopter ayant été identifiées grâce à ce travail concernant la création d'un nouvel outil pour améliorer l'observance patient dans la LMC.

## 2. Principaux résultats

Concernant l'enquête basée sur le **questionnaire pour recueillir les besoins patients**, 80% des patients souhaiteraient avoir un outil pour les aider à mieux gérer les effets secondaires du traitement. 70% d'entre eux souhaiteraient également avoir un outil leur donnant plus d'informations sur le médicament (mécanisme d'action, mode de prise etc.). Et seulement 30% des patients souhaiteraient avoir un outil avec des informations sur la LMC.

Le besoin est donc plutôt tourné vers un outil sur la prise en charge globale du patient et prenant en compte différents aspects du traitement pour aider à améliorer leur observance.

De plus, les patients sont, pour une large majorité, plus intéressés par un outil en version numérique (70%) que par un outil papier (30%).

Ajouté à cela, la communication à propos de ces outils doit passer par les hématologues qui restent les interlocuteurs privilégiés des patients. En effet, 89% des patients interrogés souhaiteraient que les informations papiers soient diffusées préférentiellement par leur hématologue contre 56% par leur généraliste, 22% par les organisations de patients et 11% par leur pharmacien.

Par ailleurs, 70% des patients interrogés ont déjà consulté le site de l'association « LMC France ». Ils étaient 100% à être satisfaits de leurs recherches sur ce site.

Concernant la **segmentation des patients** atteints de LMC en phase chronique et actuellement traités par ITK, ce questionnaire a permis l'identification de 5 segments :

- Le premier segment est celui des patients âgés de plus de 45 ans.
- Le second segment regroupe les patients avec un diagnostic récent, datant de moins de six mois.
- Le troisième segment regroupe les patients recevant plusieurs traitements chroniques. En effet, le nombre de médicaments pris de façon chronique peut impacter négativement l'observance thérapeutique du patient.

- Le quatrième segment regroupe les patients qui reçoivent pour la première fois un ITK (1<sup>ère</sup> ligne de traitement).
- Enfin, le cinquième et dernier segment identifié regroupe les patients ayant accepté leur maladie (patients en phase d'acceptation et non de déni).

Selon les **interviews avec des chefs de produits**, pour des produits matures comme les ITK qui sont actuellement sur le marché, peu d'initiatives sont prises aujourd'hui pour créer de nouveaux outils marketing destinés aux patients afin de les aider à améliorer leur observance thérapeutique. De plus, les médecins connaissent maintenant très bien les ITK et les actions de sensibilisation (sur le traitement ou la maladie) mises en place par les laboratoires pharmaceutiques sont moins nombreuses à leur égard aujourd'hui.

Selon les **interviews avec des responsables « Patient Advocacy »** d'un laboratoire pharmaceutique, les réglementations qui encadrent les programmes d'éducation thérapeutique et les actions d'accompagnement sont peu précises concernant les actions autorisées et non autorisées par les laboratoires pharmaceutiques dans ce type d'initiative. Les laboratoires sont donc hésitants à s'impliquer dans le financement de ces programmes. De plus, le domaine de la santé publique manque de moyens financiers et humains pour développer ces actions. Tout ceci amène donc à un manque d'initiatives en termes de création de programmes basés sur l'éducation et l'observance thérapeutique. Néanmoins, les associations de patients restent pour la plupart conciliantes concernant la mise en place de partenariats avec les laboratoires pharmaceutiques afin de recevoir leur soutien institutionnel.

## DISCUSSION ET CONCLUSION

La proportion d'outils marketing actuellement disponibles sur le marché pour une maladie rare comme la LMC est élevée. Chaque laboratoire pharmaceutique commercialisant des ITK dans la LMC a développé sa propre stratégie en termes de projets financés. Pfizer a misé sur le financement d'outils dans la prise en charge globale des patients en oncologie avec PactOnco® alors que Novartis a investi dans des applications mobiles ciblées sur la LMC comme "LMCoach" et Mon "Suivi Biomol". BMS est plus diversifié avec des outils vidéo, des brochures papiers patients et des gadgets de type « nudges » pour améliorer l'observance thérapeutique.

Concernant la partie segmentation, les laboratoires pharmaceutiques devraient cibler le segment basé sur l'année du diagnostic du patient. En effet, les patients à inclure dans ce segment sont faciles à identifier. Ce segment représente une part de marché suffisamment importante car il regroupe l'ensemble des nouveaux diagnostics et ce segment est stable dans le temps. Enfin, les patients débutant un traitement sont, la plupart du temps, plus faciles à éduquer en termes d'observance par rapport à des patients traités depuis plus d'un an et qui auraient déjà pu acquérir des automatismes plus difficiles à changer...

Lorsque l'on interroge les patients, 90% d'entre eux estiment que l'information médicale leur ayant été dispensée à l'annonce du diagnostic et lors des mois qui ont suivi est de bonne qualité. Cependant, grâce au questionnaire patient, des recommandations concernant le développement de nouveaux outils patients ont pu être élaborées. L'objectif serait donc de créer des outils numériques (application mobile de préférence, car très accessible et ludique), qui tiendraient compte non seulement du problème de l'inobservance thérapeutique, mais également de la prise en charge globale du patient. La stratégie de communication concernant ces outils doit inclure l'hématologue qui reste l'interlocuteur privilégié des patients, mais également impliquer les associations de patients très actives dans l'environnement associatif. En effet, ces associations représentent un élément clé dans le succès d'un outil marketing. Une autre recommandation serait d'inclure dans ces outils un volet destiné aux aidants ou de créer un nouvel outil directement destiné aux aidants. En effet, selon le livre blanc de LMC France en 2016 et son « enquête patient », plus de 73% des patients interrogés sont insatisfaits ou très insatisfaits du niveau d'accès au soutien psychologique pour leurs proches (38,4% sont très insatisfaits). Pourtant, les aidants sont ce qu'il y a de plus important en termes de soutien au patient. Travailler sur une application mobile pour sensibiliser la famille et les proches pourrait aider le patient à améliorer son observance thérapeutique, son bien-être général et à maintenir l'équilibre de la famille et du couple fragilisé par la maladie.

Néanmoins, le nombre d'outils axés uniquement sur l'observance du traitement reste faible. La plupart du temps, il s'agit d'outils complets concernant la maladie, les traitements et les effets indésirables, etc. Les associations doivent donc continuer à développer de nouveaux outils grâce au soutien institutionnel des laboratoires pharmaceutiques.

Enfin, concernant la dernière question de recherche, les avantages et inconvénients d'adopter une stratégie centrée sur le patient et sur le financement de nouveaux outils ou programmes à

destination des patients par les laboratoires pharmaceutiques ont été analysés et regroupés dans l'analyse SWOT présentée ci-dessous :

<b>FORCE</b>	<b>FAIBLESSES</b>
<ul style="list-style-type: none"> <li>- Améliorer l'observance thérapeutique</li> <li>- Améliorer l'efficacité du traitement</li> <li>- Impacter positivement le prix lors de l'évaluation post AMM</li> <li>- Apporter un service aux patients</li> <li>- Améliorer l'image du laboratoire pharmaceutique</li> </ul>	<ul style="list-style-type: none"> <li>- Image négative des laboratoires pharmaceutiques</li> </ul>
<b>OPPORTUNITES</b>	<b>MENACES</b>
<ul style="list-style-type: none"> <li>- Intérêts économiques partagés avec l'état et les autorités de santé (coûts supplémentaires des hospitalisations, greffes, effets secondaires des ITK etc.)</li> <li>- Lois en santé de plus en plus centrées vers le patient (cf. Loi HPST, Plan Cancer etc.)</li> </ul>	<ul style="list-style-type: none"> <li>- Lois floues concernant l'encadrement des pratiques autour de la mise en place des programmes d'éducation thérapeutique et des actions d'accompagnement, et contraignantes</li> <li>- Nouvelle priorité pour les médecins et les autorités de santé : les interruptions de traitement par ITK chez les patients en réponse moléculaire profonde.</li> <li>- Arrivée des génériques : impact négatif sur l'observance des traitements ?</li> </ul>

En conclusion, l'offre existe aujourd'hui, mais elle n'est pas suffisante. Les programmes d'éducation thérapeutique et les actions d'accompagnement sont encore trop peu développés au regard de l'inobservance encore élevée chez les patients atteints de LMC. Les laboratoires pharmaceutiques doivent donc continuer dans cette direction en continuant à apporter de nouvelles solutions et outils aux patients et à leurs aidants, même si les réglementations sont contraignantes en ce qui concerne les actions d'accompagnement et les programmes d'éducation thérapeutique.

## LITTERATURE REVIEW

### **1. The Chronic Myeloid Leukemia**

#### 1.1 Epidemiology (3)

Chronic myeloid leukemia (CML) is a rare disease (4). Global incidence of CML in France is 1-2 cases per 100,000 per year. The average age of CML patients is 55 years old, but the disease can occur at every age (even for Children, but it is very rare). There is also a discreet male predominance (sex ratio: 1.2). Today, no precise etiology is known. There are however, promoting factors like exposure to benzene, ionizing radiations etc.

#### 1.2 Physiopathology

The CML is also known as myelogenous leukemia. It belongs to the chronic myeloproliferative disorders (CMD), which are malignant blood diseases characterized by a clonal and deregulated proliferation of the hematopoietic stem cells, with no maturation block of the myeloid lineage. A normal blood marrow produces red blood cells for carrying oxygen, white blood cells to protect the body from infections, and platelets involved in blood clotting. The type of myeloproliferative disorder is based on whether too many white blood cells, red blood cells or platelets are being made.

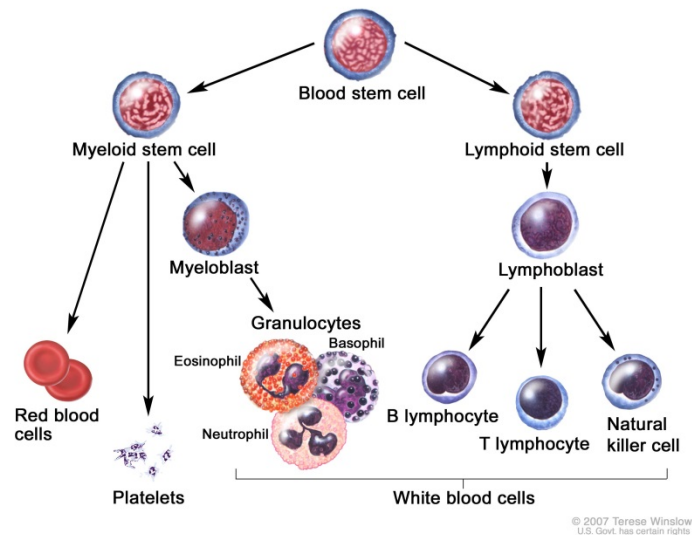


Figure 1: Hematopoietic Progenitors & CMD (from the National Cancer Institute)

The CML is a disorder characterized by a dominant proliferation of granulocytes, a type of white blood cells. Initially, these cells are functioning normally. But after a certain period of time, the immature white blood cells (called myeloblast – see figure 1) are accumulating in the blood and bone marrow. This abnormal proliferation of granulocytes results from a reciprocal translocation between the long arms of chromosomes 9 and 22. The genetic material from part of chromosome 9 is missing from its usual location and appears attached on the chromosome 22. This translocation is known as “Philadelphia chromosome” and leads to production of the fusion onco-protein BCR-ABL, a constitutively active tyrosine kinase. This protein transforms normal blood-forming cells into malignant ones.

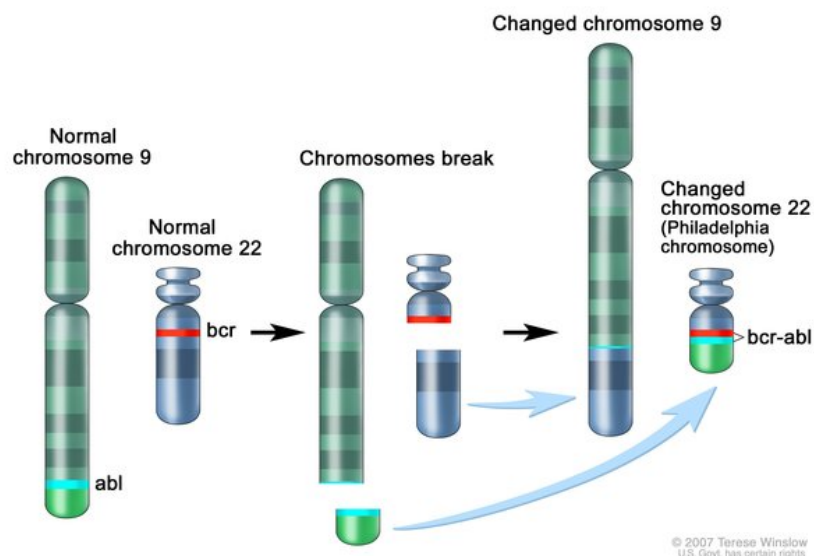


Figure 2: Mechanism of BCR-ABL Translocation (5)

The BCR-ABL protein (210 kDa being the most frequent form) with her constitutive activation of tyrosine kinase activity, has the effects below:

- Deterioration of the cell's stroma adhesion, leading to presence of myelocytes in the blood flow.
- Cell proliferation (for myeloid cells)
- Anti-apoptotic action (for myeloid cells)
- Genomic instability

However, gene translocation effects are not immediately clinically expressed in the patient. Most of the time, diagnosis of CML is incidental, by doing a simple routine blood test: it is during the chronic phase of the disease. But this gene is unstable and is accumulating numerous mutations over a period of year, until the disease enters to an accelerated phase. At this stage, there is more abnormal and immature cells than normal cells in the bone marrow (6). The disease can evolve at this stage, into acute myeloid leukemia.



To conclude, 3 phases are existing for CML (5):

Phase	Name	Length	Details
1	Chronic	Months to years	<ul style="list-style-type: none"> <li>- Number of mature white blood cells are high</li> <li>- Myeloblast &lt; 10% of total blood cells</li> <li>- Symptoms: mild, absent or worsen slowly</li> </ul>
2	Accelerated	3 to 9 months without treatment	<ul style="list-style-type: none"> <li>- Myeloblast rate (in blood or marrow): between 10% and 19% (see other biologic criteria from the World Health Organisation)</li> <li>- Symptoms: night sweats, loss weight, bone pain etc...</li> </ul>
3	Blast (or Blast crisis)	Median survival: 3 to 6 months	<ul style="list-style-type: none"> <li>- Lower risk since the arrival of Tyrosine Kinase Inhibitor therapies</li> <li>- Myeloblast rate &gt; 20%</li> <li>- Clinical picture (life threatening): like an acute leukemia (tumoral syndrome, anemia, infections, hemorrhages, enlarged spleen etc...)</li> </ul>

*Table I: The different phases of the Chronic Myeloid Leukemia*

### 1.3 Diagnosis

First, diagnosis can be raised in front of a clear hyperleukocytosis (> 100 Giga/Liter) on a complete blood count. Myelogram is essential to define the phase of the leukemia (blast cell rate) and for the cytogenetics (medullary karyotype). Then, cytogenetics is completed. The cytogenetics is the standard method to detect Philadelphia chromosome. The fluorescence in situ hybridization (FISH) technic enables physicians to see the BCR-ABL1 fusions, unseen on the medullary karyotype (3).

Test	Target	Tissue	Sensitivity (%) *	Use
<b>Cytogenetics</b>	Ph chromosome t(9 ;22)(q34 ;q11) presents in 95% of cases	BM	1-10	<ul style="list-style-type: none"> <li>- Confirm diagnosis of CML</li> <li>- Evaluate karyotypic abnormalities other than Ph chromosome (ie, clonal evolution)</li> </ul>
<b>FISH</b>	Juxtaposition of <i>bcr</i> and <i>abl</i>	PB/BM	0.5-5	<ul style="list-style-type: none"> <li>- Confirm diagnosis of CML</li> <li>- Routine monitoring of cytogenetic response in clinically stable patients</li> <li>- Routine measurement of MRD</li> </ul>
<b>RT-PCR</b> <b>RT-qPCR</b>	<i>bcr-abl</i> mRNA	PB/BM	0.0001- 0.001	<ul style="list-style-type: none"> <li>- RT-PCR for the diagnosis</li> <li>- RT-qPCR for the follow up and measurement of the minimal residual disease</li> </ul>

\*Number of leukemic cells detectable per 100 cells ; BM = bone marrow; FISH = fluorescence in situ hybridization; MRD = Minimal Residual Disease; PB = peripheral blood ; Ph = Philadelphia; RT-PCR = reverse transcriptase polymerase chain reaction; RT-qPCR = Quantitative reverse transcriptase polymerase chain reaction

Table II: Diagnosis Methods of CML adapted from Dale Bixby presentation (7)

Abnormal BCR-ABL molecule level is measured thanks to a highly sensitive technique called polymerase chain reaction (PCR). The most precise way of assessing how well CML is responding to treatment is to use PCR. Physicians are also looking for the exact mutations that have been developed by the BCR-ABL gene. They will check results before the start of the tyrosine kinase inhibitor (TKI) treatment, or if initial therapy does not produce a good response, and periodically afterwards. Mutations search is decisive in the choice of the treatment.

## 2. Therapeutic options in Chronic Myeloid Leukemia

### 2.1 Drugs overview

Before the 2000s, initial treatment for CML was based on bone marrow transplants for some patients or treatment with alpha interferon. Since the 2000s, CML care has been evolving a lot with the introduction of TKI (8).

In 2001, the first TKI introduced into clinical practices was imatinib (GLIVEC® from Novartis). This drug was the first inhibitor of tyrosine kinase used to treat CML. It has revolutionized the treatment of this disease. Before introducing TKI therapies for CML, overall survival of patients was about 3-4 years, whereas current overall survival is now such general population. CML has been considered now as a chronic disease (9). Over years, new and so-called second generation TKI have been introduced:

- Nilotinib (TASIGNA® from Novartis),
- Dasatinib (SPRYCEL® from Bristol-Myers Squibb (BMS))
- Bosutinib (BOSULIF® from Pfizer).

TKI of second generation were originally used for second-line treatment in cases of ineffectiveness and or intolerance of Imatinib. Nilotinib and Dasatinib have been approved in 2010 in first line treatment of patient newly diagnosed with CML. Imatinib, Nilotinib and Dasatinib differ in some ways by their toxicity profiles and their ability to target specific gene mutations. There are now several options from which to choose initial treatment and as back-up if the CML develops resistance to the first-line drugs (6). In 2013, Bosutinib was commercialized for patients with resistance or intolerance to Imatinib, Nilotinib or Dasatinib (8). A third generation with Ponatinib (ICLUSIG®) appeared in the end of 2013, for patients resistant or intolerant to first and second TKI generations. Ponatinib is particularly helpful when the malignant cells develops the T315I mutation since none of the other TKI are effective in these circumstances (6).

The different presentations of TKI and their market authorization date are reported in table III.

Product	Presentation	Market Authorization date	EPhMRA class (level n°3) (FRANCE)	Pharmaceutical company
TASIGNA	TASIGNA 200MG GELU* BT 28	03/07/2012	L01X - ANTINEOPLASIQ.AUTRES	NOVARTIS PHARMA
TASIGNA	TASIGNA 150MG GELU BT 28	24/02/2012	L01X - ANTINEOPLASIQ.AUTRES	
GLIVEC	GLIVEC 100MG GELU BT 120	25/04/2003	L01H - ANTINEOPLASIQ. INHIB.PROTEINE KINASE	
GLIVEC	GLIVEC 100MG CPR** BT 60	22/11/2004	L01H - ANTINEOPLASIQ. INHIB.PROTEINE KINASE	
GLIVEC	GLIVEC 400MG CPR BT 30	22/11/2004	L01H - ANTINEOPLASIQ. INHIB.PROTEINE KINASE	
ICLUSIG	ICLUSIG 15MG CPR FL 60	03/10/2013	L01H - ANTINEOPLASIQ. INHIB.PROTEINE KINASE	INCYTE BIOSCIENCES
ICLUSIG	ICLUSIG 45MG CPR FL 30	03/10/2013	L01H - ANTINEOPLASIQ. INHIB.PROTEINE KINASE	
ICLUSIG	ICLUSIG 15MG CPR FL 30	01/09/2016	L01H - ANTINEOPLASIQ. INHIB.PROTEINE KINASE	
ICLUSIG	ICLUSIG 30MG CPR FL 30	01/09/2016	L01H - ANTINEOPLASIQ. INHIB.PROTEINE KINASE	
BOSULIF	BOSULIF 100MG CPR BT 28	05/06/2013	L01H - ANTINEOPLASIQ. INHIB.PROTEINE KINASE	PFIZER
BOSULIF	BOSULIF 500MG CPR BT 28	05/06/2013	L01H - ANTINEOPLASIQ. INHIB.PROTEINE KINASE	
SPRYCEL	SPRYCEL 20MG CPR BT 60	05/01/2007	L01H - ANTINEOPLASIQ. INHIB.PROTEINE KINASE	BRISTOL MYERS SQUIBB
SPRYCEL	SPRYCEL 50MG CPR BT 60	05/01/2007	L01H - ANTINEOPLASIQ. INHIB.PROTEINE KINASE	
SPRYCEL	SPRYCEL 70MG CPR BT 60	05/01/2007	L01H - ANTINEOPLASIQ. INHIB.PROTEINE KINASE	
SPRYCEL	SPRYCEL 100MG CPR D.U BT 30	30/06/2009	L01H - ANTINEOPLASIQ. INHIB.PROTEINE KINASE	
SPRYCEL	SPRYCEL 140MG CPR D.U BT 30	04/10/2011	L01H - ANTINEOPLASIQ. INHIB.PROTEINE KINASE	

\* CPR: tablet; \*\* GELU: Capsule

Table III: TKI used for patients with CML (data from the Groupement pour l'Elaboration et la Réalisation de Statistiques (GERS))

Other therapeutic approaches are existed like the Omacetaxine mepesuccinate (Synribo™) (used in Temporary Use Authorization for patients with refractory CML). If the patient with CML does not respond effectively to drug therapy, the physician may suggest other options, such as participating in a clinical trial or allogeneic stem cell transplant. Other treatment options include a second allograft or lymphocyte transfusion from a donor.

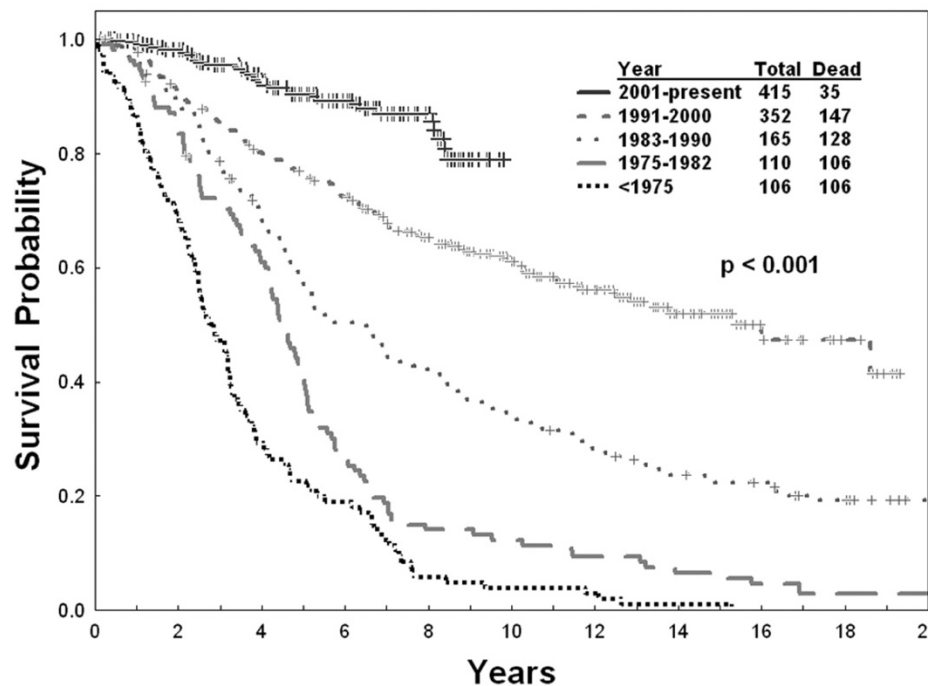


Figure 3: Survival in newly diagnosed CML (Chronic Phase) by year of therapy (10)

The figure 3 shows how Imatinib (GLIVEC®) improved overall survival for patients with newly diagnosed CML. Indeed, the estimated 8-year survival rate has increased from 6% before 1975 up to 87% since 2001 (10).

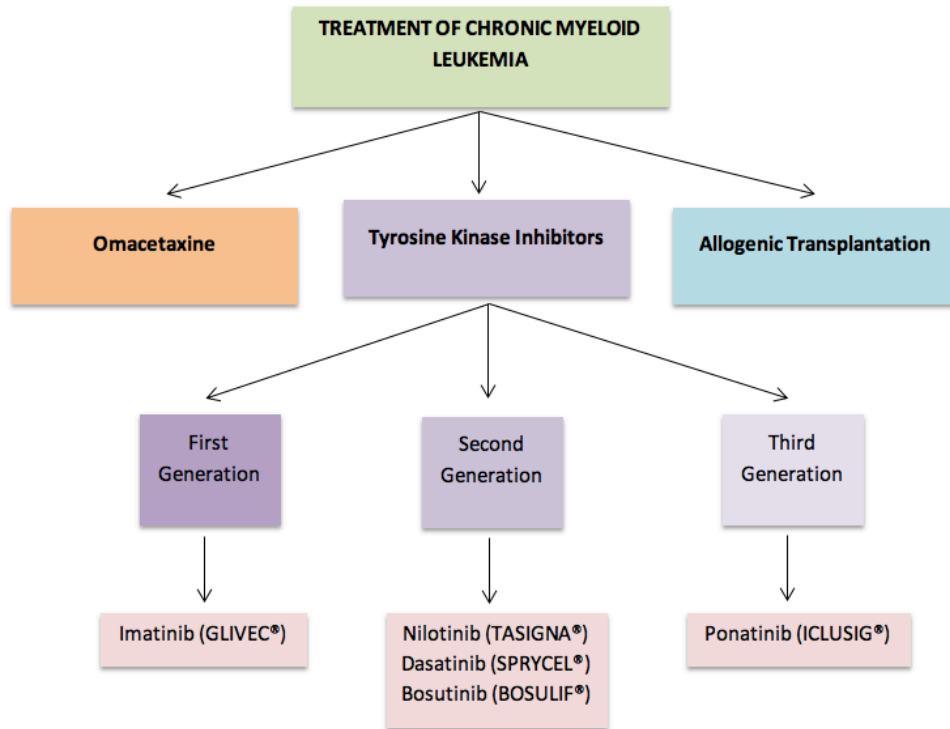


Figure 4: The different therapeutic options to treat CML

## 2.2 Tyrosine kinase inhibitors: Mechanism of action

TKI are drugs that block the tyrosine kinase activity of the enzyme, by competitive inhibition of ATP at the catalytic site of it. Indeed, inside the catalytic domain of ABL protein, there is a pocket composed of amino-acids. Some of those amino-acids are involved in ATP interactions and the others bind Imatinib, thus preventing phosphorylation of the substrate. It triggers to an autophosphorylation inhibition, proliferation inhibition and induction of apoptosis (see figure 5 below).

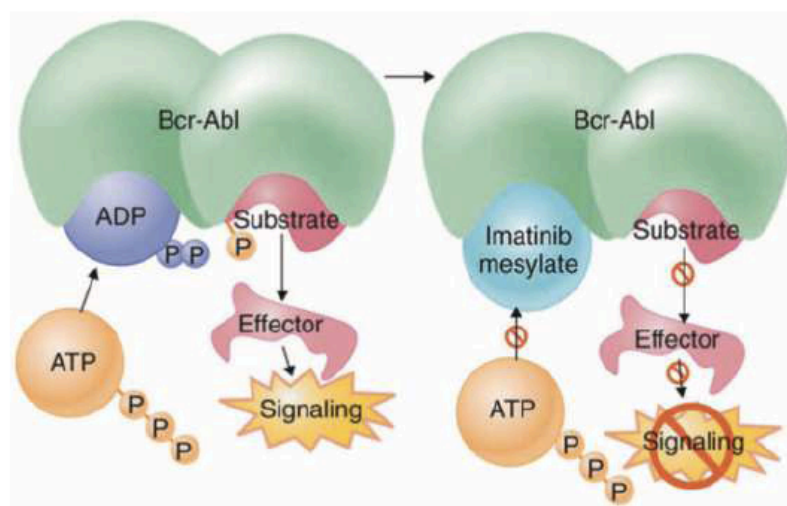


Figure 5: Imatinib mechanism of action on BCR-ABL protein (11)

Nevertheless, this action does not allow to eradicate all the CML cells, so it cannot by itself, lead to the healing of CML.

Dasatinib is a strong TKI, with over 300 times the in vitro activity of Imatinib. It inhibits BCR-ABL oncoprotein and Src pathway. Dasatinib is active on most of the mutations of the BCR-ABL protein, excepting T351I. The drug can fix active or inactive form of the oncoprotein. There is a high probability of resistance for F371I/V/S and V299L after failure of Imatinib. Dasatinib can also overcome Imatinib resistance caused by hyperexpression of BCR-ABL and MDR gene.

Nilotinib has over 25 times the in vitro activity of Imatinib. It fixes only the active form of the BCR-ABL protein, and like the Dasatinib, it is active on most of the Imatinib's resistances, excepting T351I mutation (12).

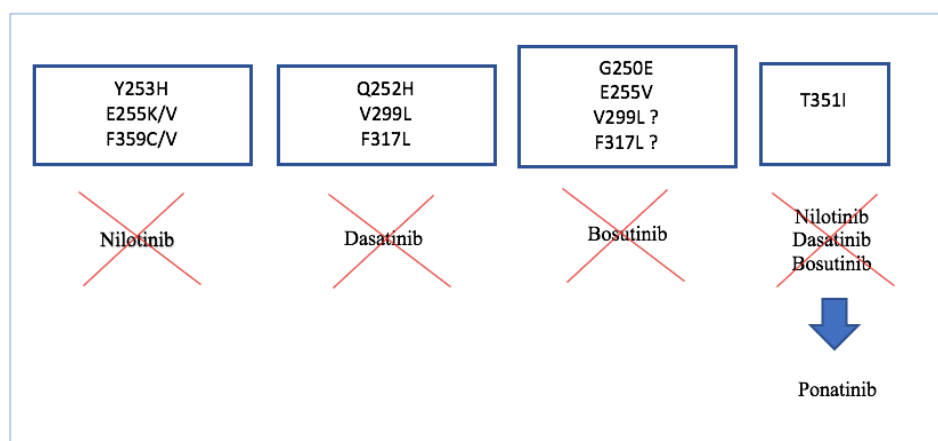


Figure 6: Mutation profiles and ITK inefficiencies (13)

### 2.3 Overview of the TKI market (Annex 3)

Numbers of sales for each TKI have been collected from the database of the Groupement pour l'Elaboration et la Réalisation de Statistiques (GERS). On the graphs below (figures 7 to 11), revenues coming from hospitals and pharmacies' sales have been combined.

The goal of this part is to give an overview of which company is currently leading the market, and which TKI makes the higher source of income. Indeed, the five TKI studied here are heterogeneous in terms of presence in the market and position in the treatment strategy. This could be linked to marketing tools developed in collaboration with patient organization for improving treatment adherence (investment degree of the pharmaceutical company depending on how much sales do the drug, or watching if the pharmaceutical company leading the market is producing the higher number of tools etc...).

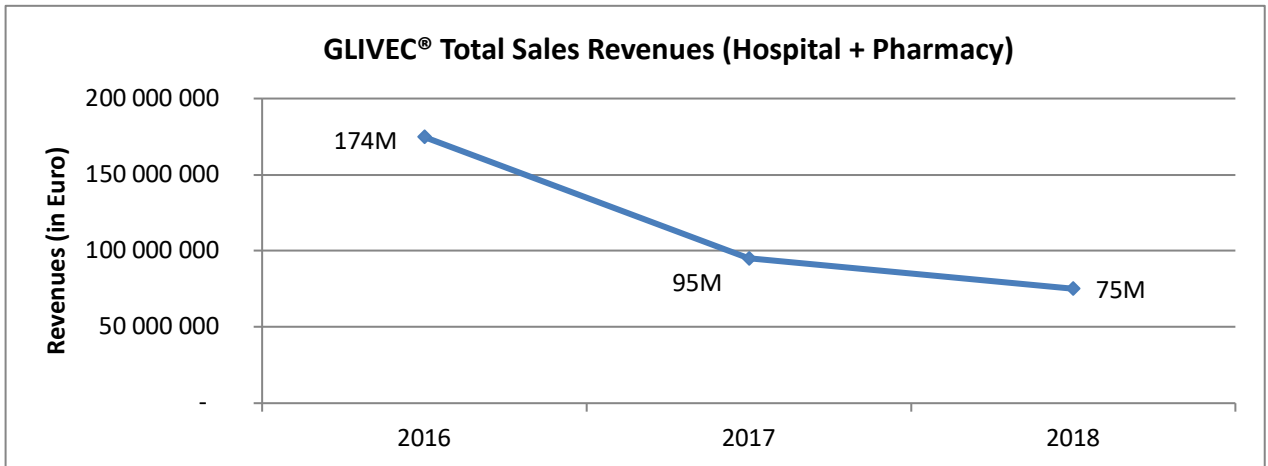


Figure 7: GLIVEC® Total Sales Revenues

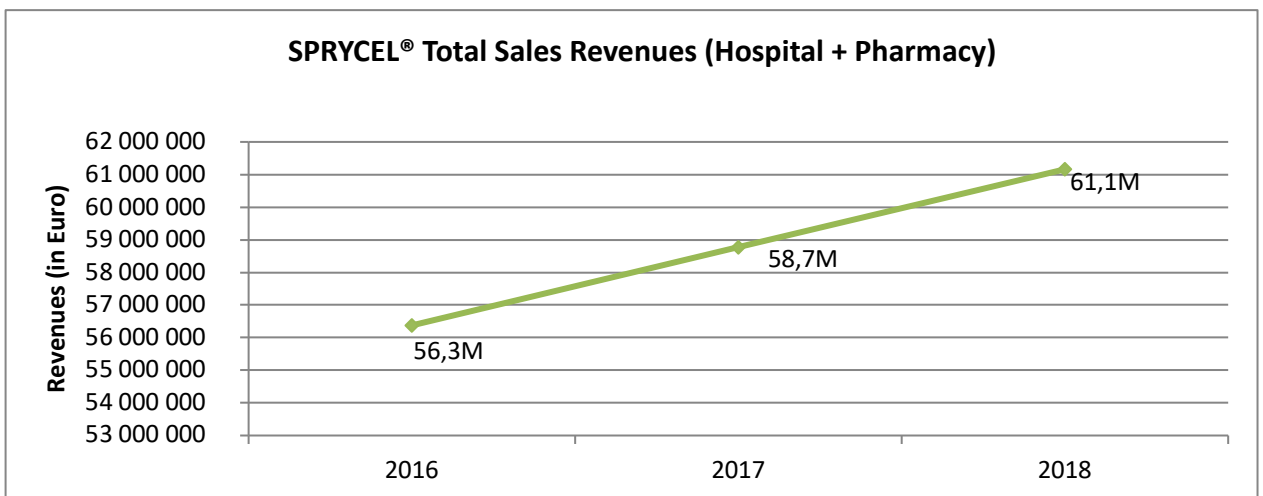


Figure 8: SPRYCEL® Total Sale Revenues



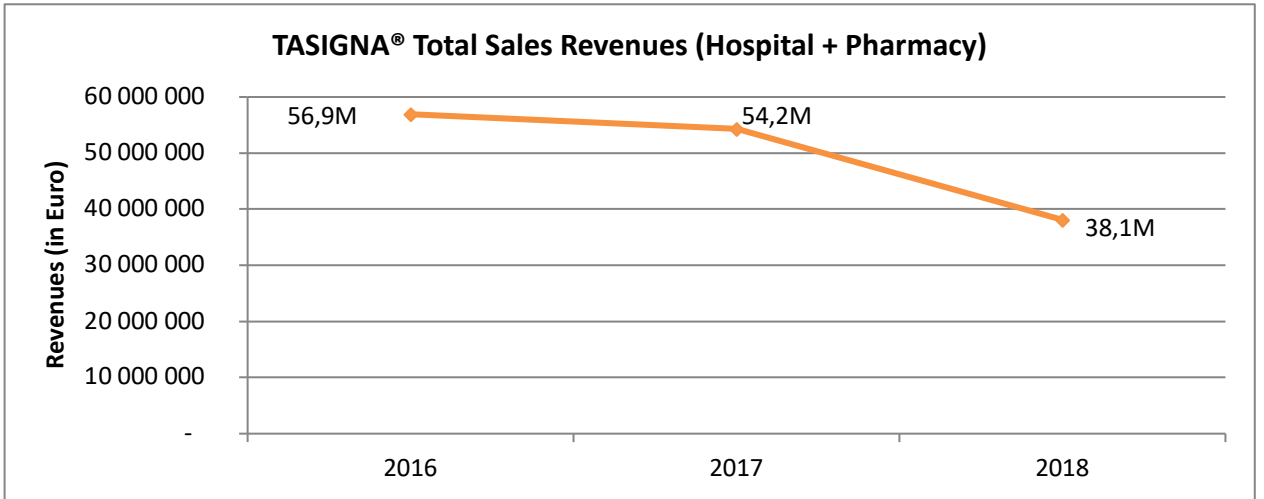


Figure 9: TASIGNA® Total Sales Revenues

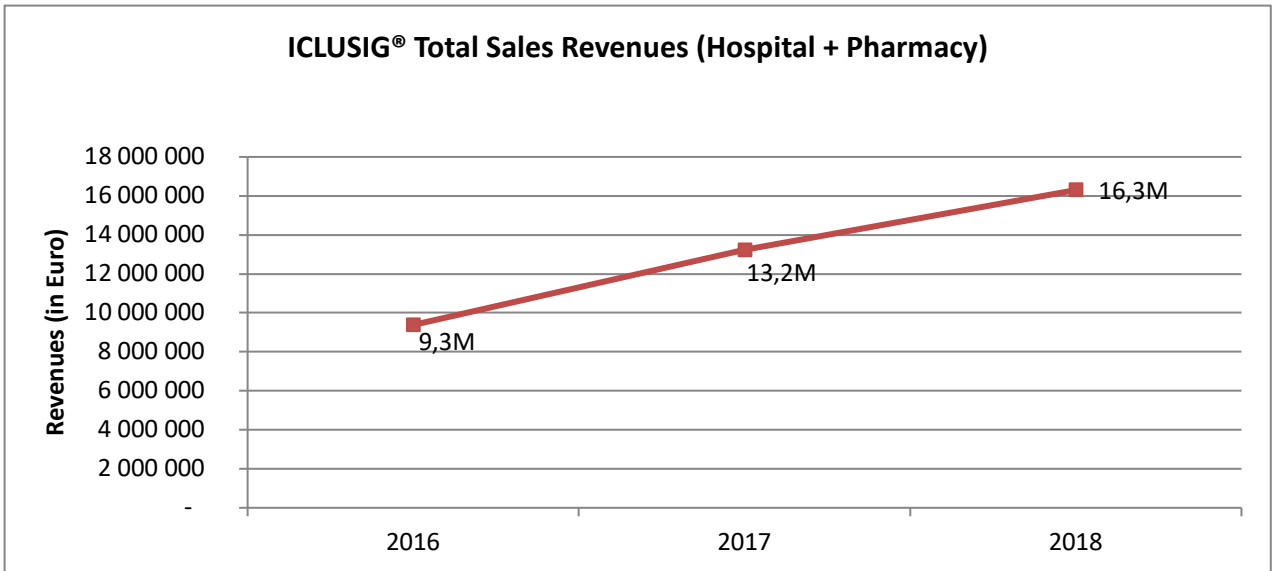


Figure 10: ICLUSIG® Total Sales Revenues

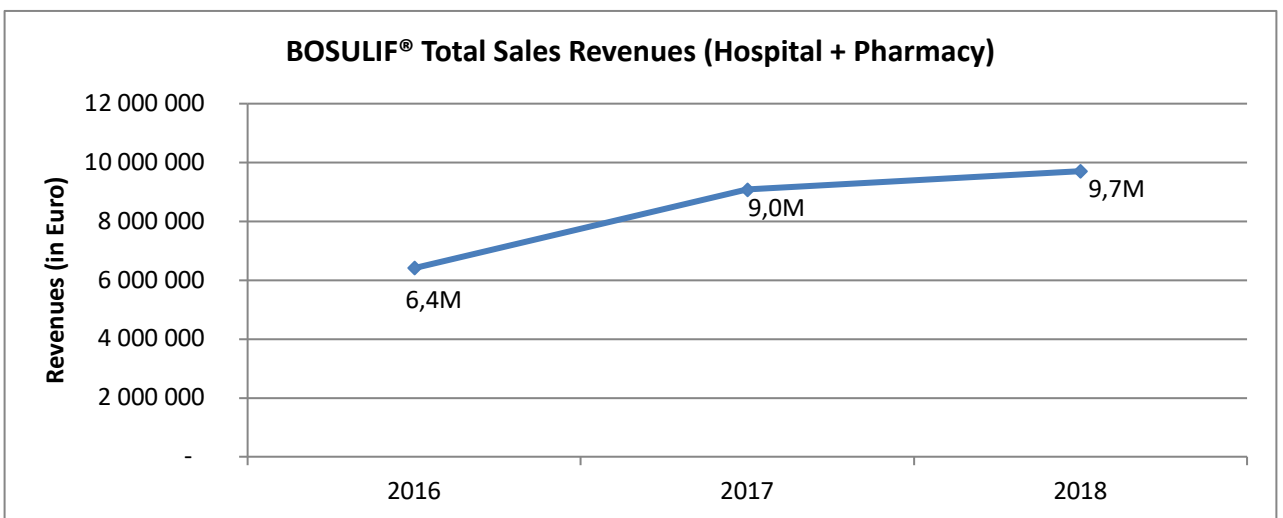


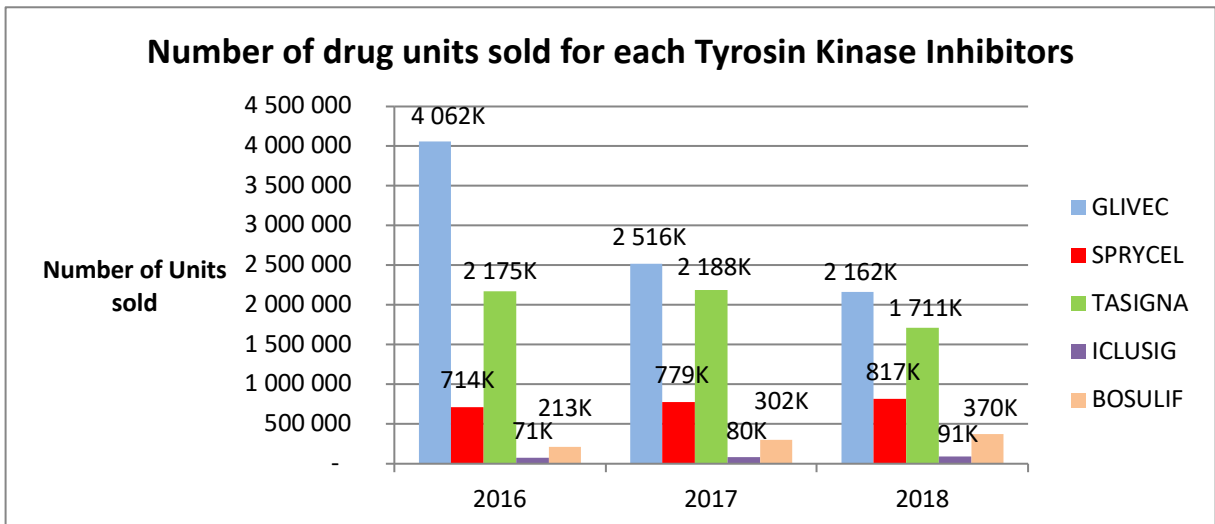
Figure 11: BOSULIF® Total Sales Revenues

GLIVEC® and TASIGNA® sales are decreasing, whereas meanwhile, SPRYCEL®, ICLUSIG® and BOSULIF® are increasing. Nevertheless, number interpretation has to be done carefully because CML are not the only medical indication for these treatments and therefore, not the only source of income.

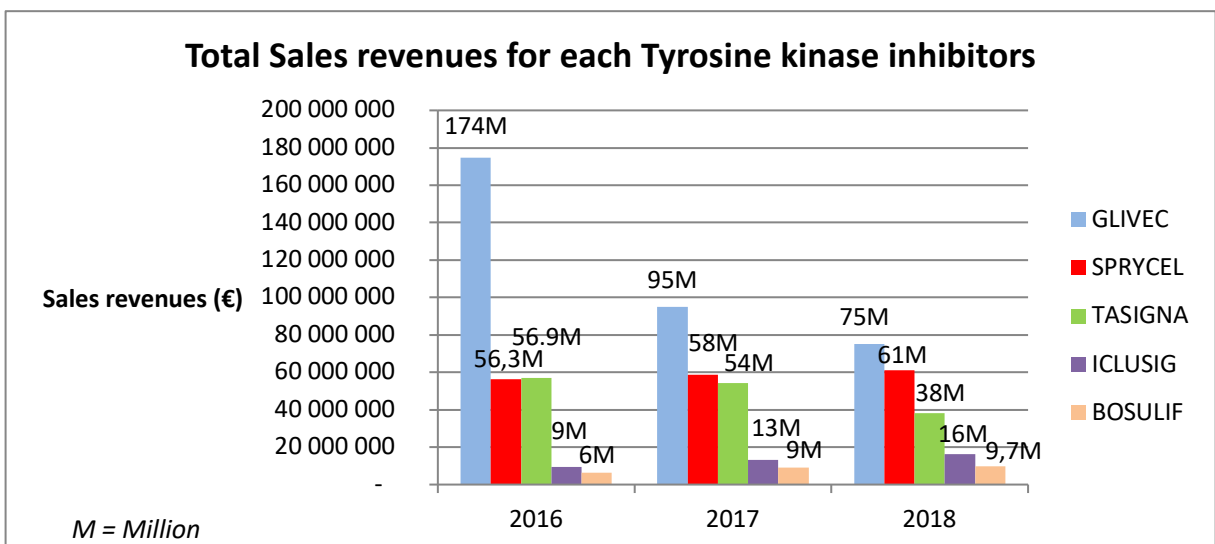
TASIGNA® have been impacted in the end of 2016 by price decreases (14) (example: €3 621,240 to €3 317,060 in November 2016 for the 200mg form (box of 112 capsules), but it is not the only dosage form impacted). This price decline can partly explain the decrease of the revenue. SPRYCEL® suffered from the same price decline in 2016 and revenue are still increasing, but drug price is higher than TASIGNA®. Indeed, in January 2018, the price of a box of 112 capsules of TASIGNA® 150mg was €2 487,860 or €22,21 for one capsule. At the same date, the price for 60 pills of SPRYCEL® 50mg was €3 321,530 or €55,35 for one pill. This price could offset the difference in terms of number of units sold between TASIGNA® and SPRYCEL® (see the figure below).

Nevertheless, BOSULIF® and SPRYCEL® have the market authorization in first-line treatment of CML but they are not yet reimbursed in this therapeutic indication in France. Today, most of the newly diagnosed patients are therefore under GLIVEC® or TASIGNA®.

All those price decreases are also linked to the arrival of generic drugs. Indeed, Novartis patent for GLIVEC® (Imatinib) expired in 2016 (15). The pharmaceutical company launched his own generic drug under their generic brand name SANDOZ in 2016. GLIVEC® is the only TKI with generics.



*Figure 12: Total Drug's units sold by TKI*



*Figure 13: Total Sales Revenues for each TKI*

Any medical indication taken together, GLIVEC® is the TKI who realize the higher number of drug units sold and the higher revenue for three years. TASIGNA®'s units sold are much higher than SPRYCEL® but because of a lower price, revenues are lower than SPRYCEL®. TKI from the third generation are much more recent in the medical practices and despite expensive prices, number of sales are lower than the others TKI.

To conclude, market share based on total sales in 2018 for each TKI are represented in the figure 14 below.

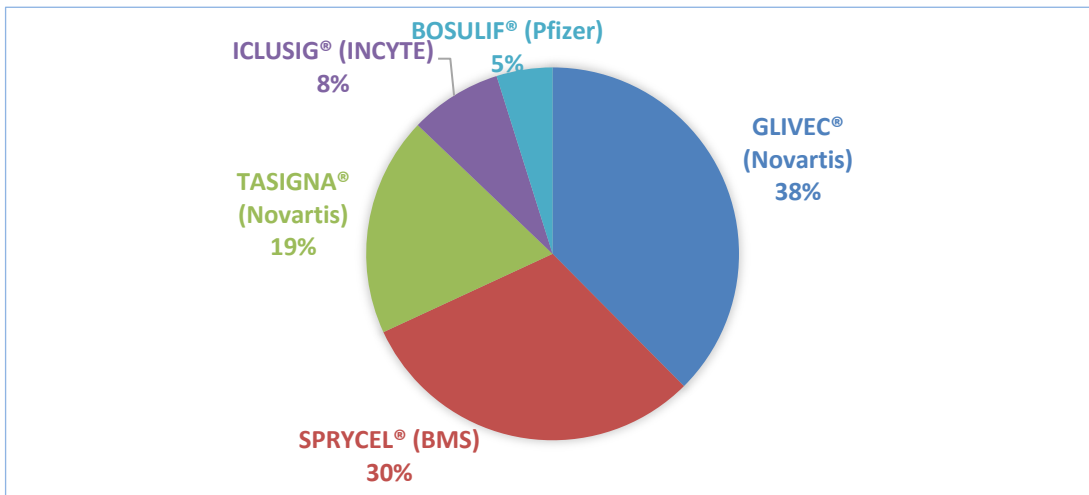


Figure 14: TKI Market Shares in 2018 (based on Total Sales Revenues)

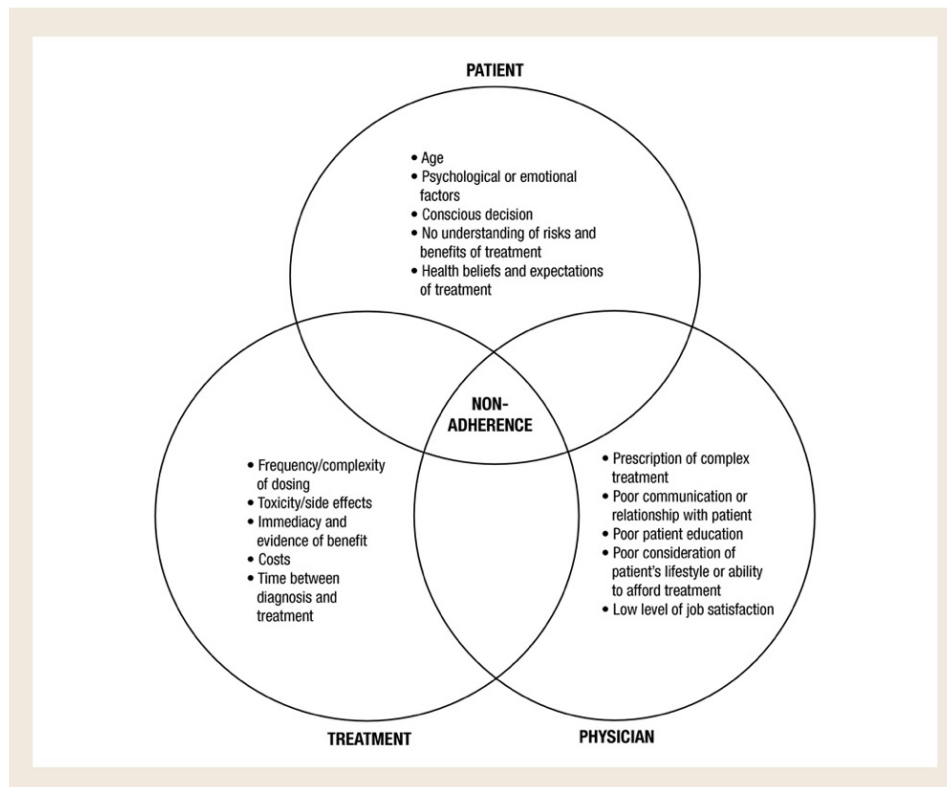
### 3. Failures in TKI adherence: reasons and impacts

#### 3.1 Overview of non-treatment adherence

Non-treatment adherence is regarding about 30% of patients with CML. A maximum of 15% of patients are completely compliant (16). Regarding the Hammersmith Hospital study, 25% of patients have no TKI adherence (threshold sets at 90%) (17). In a very recent study (Rychter et al. 2017), results show that half of the patients (51.4%) admitted to skipping doses. The same study also reported that among 54 patients who reported skipping at least on dose in the month prior to follow-up doctor's appointment, 63% felt they "always" followed instructions and 31.5% "almost always" (9). All these results show a significant proportion of patients treated by TKI therapies and who was found not to adhere to prescriptions. In addition, patient self-assessment overestimate adherence: 60% of patients who reported skipping doses admitted that they are "always" following therapeutic recommendations. Lastly, over the whole period of treatment, rates of skipping doses were 11.2% during the first two years of treatment, and 88.8% after two years of TKI treatment (9). To conclude on these numbers, rate of patient treatment adherence is low, and also overestimated by physicians (18).

#### 3.2 Reasons of non-treatment adherence

Barriers to treatment adherence can be divided into three areas: the patient – the treatment – and physician related (see figure 15 below).



*Figure 15: Factors affecting treatment adherence of chronic disease (19)*

BCR-ABL inhibitors therapies have numerous side effects. Most of them are hematological effects (anemia, thrombocytopenia, neutropenia...) but there are also asthenia, muscular disorders like cramps or myalgia, digestive disorders (diarrheas, abdominal pain), skin disorders etc. (8). All these side effects have a significant impact on treatment adherence by reducing its effects. Also, these drugs have a lot of drug interactions. Imatinib, Dasatinib, Bosutinib and Nilotinib are hepatic CYP3A4 substrates. Therefore, all drugs and even food that interact with this CYP3A4 will impact on the BCR-ABL inhibitor therapy. If they inhibit CYP3A4, it could increase TKI exposure and increase the risk of toxicity. On the contrary, if they activate CYP3A4, they will reduce efficacy of the TKI therapies. Food restriction also increases this treatment complexity. For patients with CML in chronic phase and treated by Nilotinib, eating lead to an increase of Nilotinib bioavailability and a strict fasting period is required 1 hour before or 2 hours after administration. This is a major constraint for patient schedule and life and this factor could decrease treatment adherence (20).

<b>Tyrosine Kinase inhibitor</b>	<b>Administration requirement regarding meals</b>
Imatinib	Possible during meals
Dasatinib	Possible during meals
Nilotinib	Must be taken away from meals
Bosutinib	Must be taken during meals
Ponatinib	Possible during meals

*Table IV: Drug's administration modalities regarding meals*

To conclude, non-adherence reasons are much diversified, and patient's treatment non-adherence is most of the time, a combination of most of these factors.

### 3.3 Impact of non-treatment adherence

TKI therapies are oral therapies, taken on one's own by the patient. In order to obtain an optimal effect of the treatment, these oral therapies have to be taken at the correct dose, at the correct time (right time in relation to meals and at appropriate intervals), and regularly; this is what we call "Patient adherence". Nevertheless, non-adherence is very common in patients with chronic diseases (diabetes, dyslipidemia etc.) and treated by oral therapies, and has a major impact on treatment response (molecular and cytogenetic). The first and major study that demonstrates this impact is the ADAGIO study (2009). This study evaluated 169 CML patients treated by Imatinib (GLIVEC®) from 34 Belgium centers over a 90 days period. Only 14.2% of all patients were found to be perfectly adherent to GLIVEC®. 70% of patients took less than the prescribed dose and 14.8% took more. This study also estimated that non-adherence in TKI therapy increases up to three times the risk of poor treatment outcomes of patient with CML (in chronic phase). In another study (on 87 patients from Hammersmith Hospitals which assessed adherence to Imatinib using the Medical Event Monitor System method (MEMS) (17), the probability of achieving major and complete molecular responses was significantly better in patients with more than 90% of treatment adherence (see table below). No patients with an adherence under or equal to 80% achieved a molecular response (21). Moreover, the degree of adherence in multivariate analysis was an independent predictor for achieving complete molecular response.

Response	Rate of Treatment Adherence		
	$\leq 90\%$	$> 90\%$	
<b>MMR</b>	14%	94%	p < 0.001
<b>CMR</b>	0%	44%	p = 0.002

CMR: Complete Molecular Response; MMR: Major Molecular Response

Table V: Probable rates of 6 years MMR and CMR by level of adherence to Imatinib from Jabbour et al. (19)

More recent clinical studies are showing similar rates (high rates) of treatment adherence to obtain good biological responses. For example, in 2017, a retrospective study (22) found that patients with treatment adherence equal or higher than 90% (indicating high medication adherence), had a mortality rate of 20.4/1000 person-years versus 27.0/1000 person-years for patients with treatment adherence under 90%. In the same time, patients with treatment adherence under 90% had a progression to Accelerated Phase (AP) or Blast Crisis rate of 15.8/1000 person-years versus 7.2/1000 person-years for patient with treatment adherence over 90%.

#### 4. Existing Marketing Tools about compliance and developed in collaboration with pharmaceutical companies

##### 4.1 Novartis

Novartis is the pharmaceutical industry who owns the majority of the TKI market shares (38% market shares with GLIVEC®, and 19% market shares with TASIGNA® or 57% of the TKI total market shares). But how many tools are developed by this company to improve patient compliance?

In November 2017, Novartis announced a **video** released about the sensitive question of patient compliance for patients with cancers and treated by oral therapies (23). The video is named “**A life under prescription**” (or in French, “**Une vie sous ordonnance**”). This documentary was produced in partnership with ten patient organizations: APTED (Association of Patients with Digestive Endocrine Tumors), CCM (Know and Fight Myelodysplasias), Etincelle IDF, Europa Donna, France Lymphome Espoir, Info Sarcomes, LMC France, Patient en réseau, SILLC

(Association of Support and Information for Leukemia, Chronic Lymphoid and Waldenström Disease) and Vaincre le Mélanome. The objectives are to shatter the stigma of patient and family's difficulties about this new type of care, and cancer noncompliance. The video presents patient testimonies. The main objective and the key message of this video are to encourage patients to talk about their treatment adherence difficulties, to their physicians, pharmacists and to their families. Through this video, Novartis is releasing information to patients in order to improve patient compliance.

Novartis also financed a project developed by "LMC France": a free **mobile application** named "**LMCoach**". The mobile application was entirely financed by Novartis until 2018 (24). Since then, LMC France is now financing the program. The tool was launched in October 2014, and the 15<sup>th</sup> of February 2016, 155 patients had been subscribed to this mobile app (25). Today, 194 patients have been enrolled in this program by their physicians and 176 self-registered patients (so 370 patients in total).



Figure 16: "LMCoach" website interface (26)

The free personalized LMCoach support service uses the SMS route to fill the gap between two consultations, often spaced three to six months apart. Typical messages, designed to address different patient profiles, were written by a Scientific Committee: treatment reminders, consultation appointments, dietetic lifestyle advice, adapted physical activity etc. (27).

"**Mon suivi Bio Mol**" is another tool developed in collaboration with the patient organization LMC France, to help patients following their PCR results, but not only. It is a free **mobile application**, like LMCoach, created in 2015. This app allows the patient to provide information on his PCR results, to establish a curve with these data and thus, to follow his results evolution



since the date of his diagnosis. It also includes a "treatment adherence journal", to record medication intake and display adherence monitoring to treatment over the long term. Information on molecular biology and disease are also available, as well as tips and advices (28).

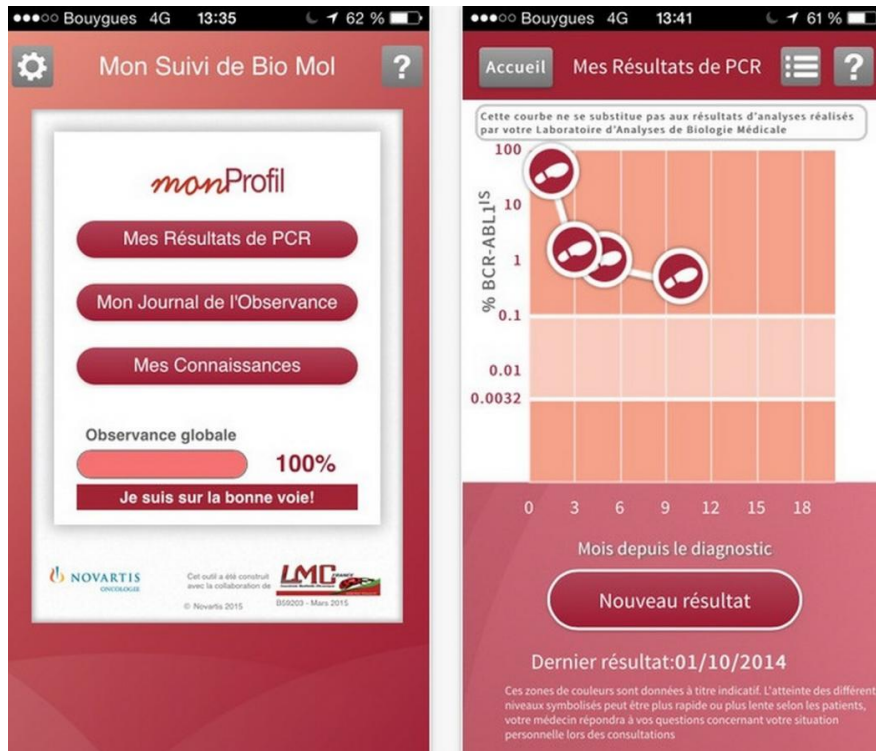


Figure 17: "Mon Suivi Bio Mol" mobile application (29)

To conclude, Novartis financed two digital daily tools for patients to help them to improve their treatment adherence. These tools have a real practical utility for patients. They have been developed by the patient organization "LMC France" and Novartis provided institutional support to these projects.

#### 4.2 Pfizer

"My Log Book" is a tool developed by LMC France with the institutional support of Pfizer. It allows patient to log, day after day, the history of the disease, its follow-up, the treatments, their side effects, the medical appointments, questions to physicians and to easily find the contact details of the different interlocutors involved in the LMC care. Register day after day in a **paper tool** (brochure) drug intakes and sides effects can improve treatment adherence by

being a sort of “reminder”. Nevertheless, this type of method seems not very interactive for patients. Add to this, the patient has to have the brochure with him on an ongoing basis.

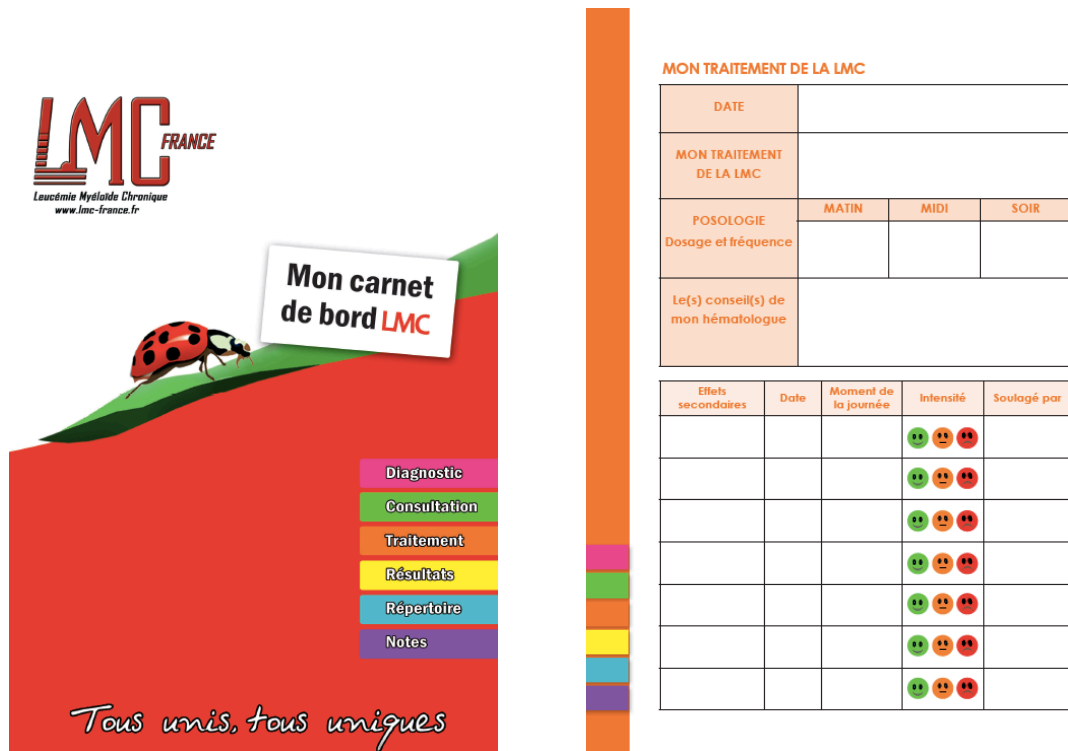


Figure 18: The "log Book"

The follow-up of side effects (see figure above), thanks to this “log book”, can help the patient to talk about his potential lack of compliance caused by side effects. The physician will be able then to adjust the dosing of the medication and/or manage side effects to improve patient’s quality of life. By managing patient’s side effects, physicians avoid voluntary treatment interruption by the patient.

DATE : .....

RDV AVEC : .....

PROBLÈMES (d'ordre médical, familial, social, professionnel, économique) DEPUIS LA DERNIÈRE CONSULTATION : .....

.....

.....

RITUEL QUE J'AI MIS EN PLACE POUR PENSER À BIEN PRENDRE MON TRAITEMENT : .....

.....

.....

QUESTIONS À POSER : .....

.....

.....

À RETENIR DE LA CONSULTATION : .....

.....

.....

Je note un mot, une citation ou un proverbe que j'apprécie, qui reflète mon état d'esprit ou qui m'aide à garder le moral

Figure 19: Medical consultation section of the « Log Book »

This section (in red on the figure above) reminds the patient not to forget his treatment by asking him what types of tips he implements to think about his drug intake.

Nevertheless, this brochure is no longer available. Pfizer is currently working on a new version of this tool in partnership with physicians. The new brochure will be launched in 2019.

To conclude on Pfizer, excepted with this brochure, the pharmaceutical company doesn't have specific tools targeting patient treatment adherence. However, Pfizer created a program, named **PactOnco™** (Personalization of Patient's support in Oncologie) in 2011 (30). Originally, this program was created to inform all the different actors of the care pathway, the oncologist, the patient, from the hospital to the home, and through the general practitioner and the pharmacist. The goal was to train health professionals by managing their professional stress, by implementing therapeutic education programs, and implementing a better communication between patients and physicians. The goal was also to inform the pharmacist, to help them giving the best advices to the patient during the delivery of the drug at the pharmacy and help oncology services to adapt their functioning for a better follow-up of patients under oral treatments.

In 2015, a new version of PactOnco™ was launched, created in collaboration with patient organizations. This version integrates brochures, patient's testimonies and videos. PactOnco™ is a virtual care pathway (31). By inviting, in a virtual way, the patient and his/her family to better understand the role of each interlocutor, the specificities of places that are more or less familiar to them, the services that are available to support them, PactOnco™ try to make patients their own actors in their everyday care, in the real world.

This program is not focused on treatment adherence and CML but incorporate oncology and all its different actors (patients, physicians, pharmacists, patient's close relatives etc..) in one tool, to help them about all the issues that they have to face in their lives and professional activities.

#### 4.3 Bristol-Myers Squibb

The patient organization "LMC France", in partnership with BMS, created a **video about CML and side effects**. This video is explaining why it is important to talk about side effects to physicians in order to manage them. This video encourages patients to write during the day what kind of side effects they had, the time and the intensity for each of them. The objective of this video is to drive home to patient that side effects can be managed, and they should not stop their treatment by themselves (32).

A **compliance Kit** was also developed by "LMC France", in partnership with BMS in September 2012 (see figure 20). This kit contains documents about compliance, a memo with useful website links, and a little game "Mem'Observance" to sensitize patients to compliance and encourage patients to speak freely with physicians about compliance obstacles (33). But today, this tool is no longer available and was not been renewed.



Figure 20: Compliance kit from (33)

BMS has been also developing nudges for patients. This project was set up in collaboration with physicians. The goal is to provide reminders for patients, to help them remember to take their treatment. Nudges have been created for each moment of the day (morning, evening etc.) and patient can choose the nudge he need according to his own rhythm.

Finally, BMS also supported another project in July 2013: **a video about drug compliance** (34). The objective of this tool is to sensitize patient with CML about treatment adherence thanks to advices, and to inform patients on the fact that forgot two or three drug intakes have an impact on treatment efficacy.

To conclude, all these tools have been developed by “LMC France”, a very active patient organization. Pharmaceuticals industries only financed these projects and bring an institutional support. Nevertheless, Incyte Biosphere is the only pharmaceutical industry who commercialize TKI to treat CML and who have never been implicated in a project with LMC France. Regarding Novartis, it is the only pharmaceutical industry supporting projects on digital tools and directly useable by patients. BMS was involved also in many projects like Novartis, but most of them are not very recent and excluding videos, there is no digital tools useable directly by patients.

# EXPERIMENTATION

## 1. Methodology

### 1.1 Patient survey

In order to make recommendations for pharmaceutical industries about tools that can be developed to help patients improving their treatment adherence, a data collection by a short questionnaire has been conducted (twenty questions in total, see annex 1). This questionnaire has been created at the end of September 2018. The questions were based on discussions with hematologists, based on my pharmaceutical experience and on literature review (PubMed Articles and patient's testimonies on Internet).

This survey is presented in the annex 1. The first part of the questionnaire was mainly focused on patient status (year of diagnosis, drug etc...). The second part was focused on which drivers could be used to improve treatment adherence and what are the communication lines to use. The third and last part was focused on patient experience with tools already on the market and existing websites to try to analyze which one is best perceived and what could be improved?

Hematologists sent this survey to their patients with CML. This survey respected patient's confidentiality. The main goal of this survey was to answer to the research question number one: what are patient's expectations in terms of tools to improve their treatment adherence?

This part was conducted from end of September to the beginning of November 2018. Two hematologists sent the questionnaires to their patients, by email. Ten responses were obtained (response rate of 70%) and all the questionnaires have been fully completed (completion rate of 100%).

The first limitation is linked to patient population. Indeed, CML is a rare disease, and about 12 000 patients in France have this disease in 2018. It is so extremely difficult to have access to these patients and send questionnaires. Consequently, numbers of questionnaires analyzed in this thesis are quite low. Therefore, the analysis of these results should be interpreted with caution. The size of patient sample is an obstacle for having statistically significant results and could only provide a trend.

Furthermore, patient's feedbacks are very subjective. It is therefore difficult to analysis precisely and makes guidance based on very subjective point of views. A suggestion regarding this part of the analysis could have been to create another one intended for hematologists. Collect feedbacks from hematologists could have been very interesting too and it would have been easier to have more answers (compared to patients).

To conclude about limitations, questionnaires for patients were maybe too short, with a majority of closed questions. The goal was to have few questionnaires, but all 100% completed. I would not create a questionnaire too long and too difficult for patients... But afterthought, in doing this, the questionnaire may not be complete enough. A recommendation is that this questionnaire should be followed in the future of another questionnaire, based on the first survey's results to develop ideas and trends raised in this one.

## 1.2 Segmentation of the patients

The benefits of market segmentation have been long established. Market segmentation allows marketers to better understand the market and give competitive advantages (35).

Market segmentation is a fundamental mainstay of marketing in industrialized countries. Companies have to consider customer's needs and have to recognize the heterogeneity of those needs. Market segmentation has been introduced by Smith in 1956, with the development of marketing. It has become a central concept, in theoretical or practical marketing. Smith brought to light the heterogeneity of consumer needs. According to Smith: "Market segmentation involves viewing a heterogeneous market as a number of smaller homogeneous markets, in response to differing preferences, attributable to the desires of consumers for more precise satisfaction of their varying wants". Identification of specific needs of groups of customers allows companies to develop the right offer and consequently, obtains a competitive advantage. A lot of definitions for market segmentation have been suggested but Smith definition is the major one. With this definition, segments derive directly from the heterogeneity of customer needs. Smith's approach led to a segmentation that divides market into homogeneous sub-market groups (Dickinson and Ginter 1987). From this segmentation, we can identify groups of customers, who respond likely to the marketing mix. This reflection triggers to a market orientation rather than a product orientation of the segmentation, according to (35).

The recent development of databases or information technologies had allowed marketers to be more efficient and accurate in market segmentation. Consequently, marketers are focusing on smaller segments and apply direct marketing approaches. To determine the effectiveness and profitability of marketing strategies, six criteria have been highlighted: identifiability, substantiality, accessibility, stability and responsiveness and actionability (35):

- **Identifiability:** marketing manager should be able to identify customers in each segment, and be able to “measure the segment” (how many patients in each segment?)
- **Substantiality:** this criterion can be satisfied if each segment represents a large enough proportion of the market to ensure profitability. Each segment has to be vast enough to justify the elaboration of a specific marketing strategy.
- **Accessibility:** manager should reach the targeted segment through his marketing efforts, by knowing price sensibility of the segment, consumption habits of the segment etc....
- **Responsiveness:** is it a key criterion concerning the effectiveness of any market segmentation strategy. A segmentation strategy will be effective only if each segment is homogeneous in its response to the strategy. This criterion is based on the fact that each segment should react uniquely.
- **Stability:** segments have to be stable in time. It is a key point in the effectiveness of the marketing strategy. Indeed, if the identified segments change their composition, behavior during the implementation of the marketing strategy, marketing efforts could become not successful. The stability should be present at least, in a period long enough to identify the segments and implement the marketing strategy.
- **Actionability:** segments are actionable if they can provide guidance for decisions (35).

The segments don't need to be real physical entities. The objective of these segments is to help managers to best serve their customers. “Market segmentation is a theoretical concept involving artificial groupings of customers, in order to help managers to design a marketing strategy and take tactical decisions”, said Michel Wedel and Wagner Kamakura (35). Market segments identification are dependent of used methods and variables or criteria. The choice of a segmentation base is directly linked to the market (and health market is a very specific one) and to the purpose of the study.

Today, product differentiation is a key point to reach success. «There has been a switch from ‘sell products we develop’ to ‘develop products we can sell’» said Kathryn Greengrove (36).



Pharmaceutical industries have to focus on value. By increasing the understanding of patient needs, pharmaceutical industries will increase the probability for their products to meet those needs.

Health products are very specific, with strict regulations. Marketing segmentation is therefore specific and segmentation models applied to other products like cars, phones or any other objects cannot be applied to them. Patients are all different, but they have common characteristics. McDonald (1999) defined a market segment as “a group of customers or consumers who share the same or similar needs”. Two main segmentation approaches exist: the needs-based and the characteristics-based segmentations. The needs-based segmentation is based on understanding the needs of the customers (here the patient), while characteristic based segmentation consists in segmenting customers based on their attitudes, behavior. The needs-based segmentation drives product development and brand strategy.

By doing a segmentation based on expectations/patient needs, marketers could understand how to package its messages. It triggers better messages constructions and targeting (36).

About our research question number two on segmentation, all the results from the questionnaire previously described were used and segmentation has been made on this and thanks to the literature review.

Limitation identified was about questions asked to product managers. Professional confidentiality was an obstacle for some questions and not all the questions have been answered. Moreover, not all the product managers answered to my contact request and especially Novartis, the leader in the market for TKI. It could have been very interesting to have their feedbacks on mobile applications co-developed with “LMC France”.

### 1.3 Feedbacks from TKI managers and patient advocacy

The last challenge was to collect data and feedbacks from TKI product managers to answer to the question of strategy (research question number three, see annex 2). These persons were targeted on LinkedIn and contacted via this website. The goal was to interview all the product managers working for TKI previously cited, so five product managers in total. Add to this, a person working in patient advocacy in rare disease have also been contacted, to collect

information about the link between pharmaceutical companies and patient organizations in those types of projects, and about specific laws.

Relating to product manager, out of five managers contacted in total, only two persons agreed to answer to my questions and accepted an interview. They were from Pfizer and BMS, so product managers of BOSULIF® and SPRYCEL®. The interviews lasted about 45 minutes each (see annex 2).

A person working in patient advocacy in rare disease had been also interviewed. The interview lasted 45 minutes. The goal was to have his feedbacks on his work with patient organizations, and to understand what challenges the pharmaceutical industries have to face. It was also important to understand what pharmaceutical companies could do and could not do.

The patient organization LMC France has been contacted in order to collect data on patient needs and understand what could improve patient's treatment adherence, but without success.

## **2. Results**

### **2.1 Patient survey**

Regarding questionnaires that have been sent to patients, ten answers have been collected (see annex 1 for an example). The objective of this questionnaire was not to determine if patients were compliant to their treatment by TKI or understand the reasons of non-treatment adherence. The goal was to understand what type of tool could become available for patients to help them improving their treatment adherence? The objective of this questionnaire was to collect patient's needs and make guidelines of which directions could take pharmaceutical industries and patient organization to create a marketing tool for improving treatment adherence of patients with chronic myeloid leukemia.

Data from the 10 questionnaires completed showed that 80% of patients are currently still under TKI treatment and 20% of patients had interrupted their treatment (one patient has no treatment since more than one year, but less than 3 years and one patient has no treatment since more than three years).

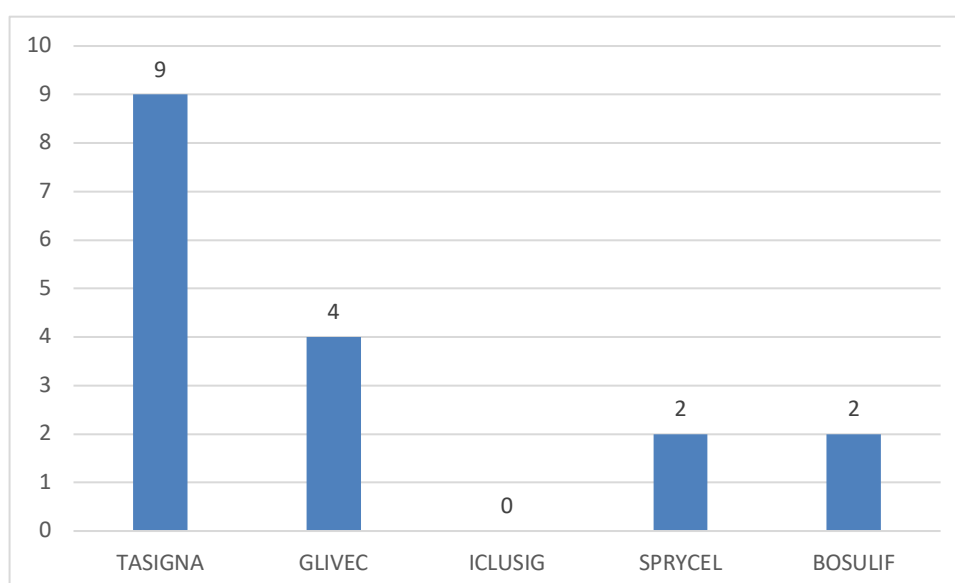
In total, year of diagnosis were between 2006 and 2018. There are one diagnosis in 2006, 2008, 2009, 2010, 2017, two diagnoses in 2012 and three diagnoses in 2018.

<b>Duration since the beginning of treatment for patients currently under medication</b>	<b>Percentage of patients</b>
< 1 month	38%
Between 1 and 6 months	13%
> 6 months	0%
> 1 year	50%

*Table VI: Profiles of patients currently under TKI medication*

A majority of patients are under treatment since more than one year. But also, 40% of patients interrogated are under treatment since less than one month. It is therefore very recent diagnosis. Three patients out of eight have been diagnosed in 2018.

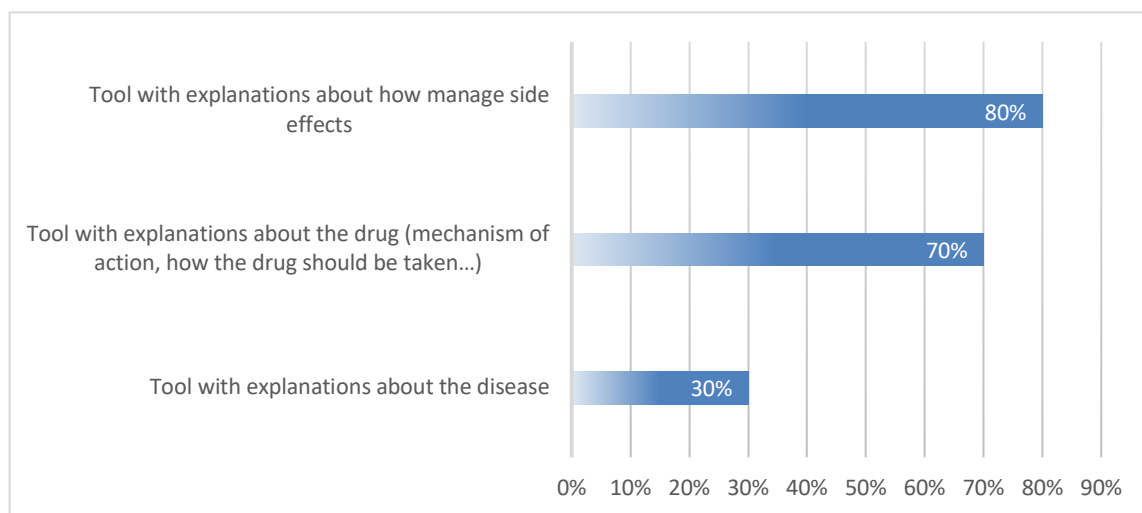
Three patients out of ten have been treated by more than one TKI. One patient received GLIVEC® and TASIGNA®. The two other patients received both first and second generation of TKI: GLIVEC®, TASIGNA®, SPRYCEL® and BOSULIF®. For the rest of patients, six patients are treated (or had been treated) by TASIGNA® only and one patient is under GLIVEC® since the diagnosis.



*Figure 21: Number of patients currently under medication or treated in the past by TKI therapies*

When we asked patients about information they received about their treatments (mechanism of action, how and when should they take the drug, and TKI's possible side effects), 90% of patients are satisfied for each of these criteria.

In terms of tools that could help patients to improve their treatment compliance, three options with a possibility of multiple answers were available. 80% of patients are looking for something who explain better how to manage side effects and 70% are looking for a tool giving more information about the drug (mechanism of action, how they should take it, at which time etc.). Only 30% of patients want a tool with more explanations about the CML.



*Figure 22: Type of tool for improving treatment adherence according to patients*

Today, the health is becoming more and more digital. When patients had been interrogated on “what do they prefer to have between a digital or a paper tool”, 70% of patients answered digital tools against 30% only for a paper tool.

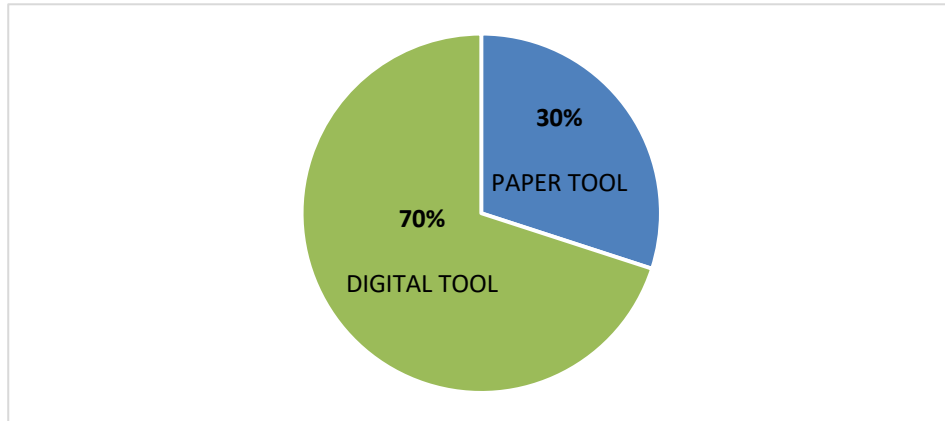


Figure 23: Type of tool preferred by patients

If we talk about broadcast channels, patients who choose digital tools at the previous question could choose between three answer propositions. Do they prefer?

- A mobile application (like “LMCoach” or “Mon Suivi BioMol”)
- A tool available on Patient organization’s website
- A tool available on Pharmaceutical industry website

However, some patients who tick the box “paper” at the previous question also answered to this one. Therefore, two analyses have been conducted: the first one is taking into account only patients who ticked the box “digital tool” and a second analysis taking into account all answers combined (see table below).

Type of tool preferred by patient	First analysis	Second analysis (All answers combined)
Mobile application	86%	90%
Patient Organization’s website	43%	30%
Pharmaceutical company’s website	29%	20%
<b>TOTAL</b>	<b>7 patients</b>	<b>10 patients</b>

Table VII: Broadcast channels preferred by patients for digital tools

86% of patients in the first analysis would like to have a mobile application and 90% in the second analysis. In the first analysis, 43% of patients would like to have a tool available on a patient organization’s website and all answers combined, a lower percentage with only 30% of patients. Concerning a possible tool available on a pharmaceutical industry’s website, 29% of patients who ticked the digital tool box could be interested and all answers combined, only 20% of patients. To conclude, a vast majority of patients could be interested in a mobile application.

For patients who ticked the box “paper tool”, the next question relating to these types of tools asked about where could be the best place to find these tools for patients? Four positions were possible:

- At the General Practitioner office
- At the Medical Specialist office (Hematologist or Oncologist)
- At the Pharmacy
- available by sending or for printing on the patient organization’s website.

Two analyses have been conducted like in the previous case, because patients who ticked the box “digital tool” also ticked boxes for this question.

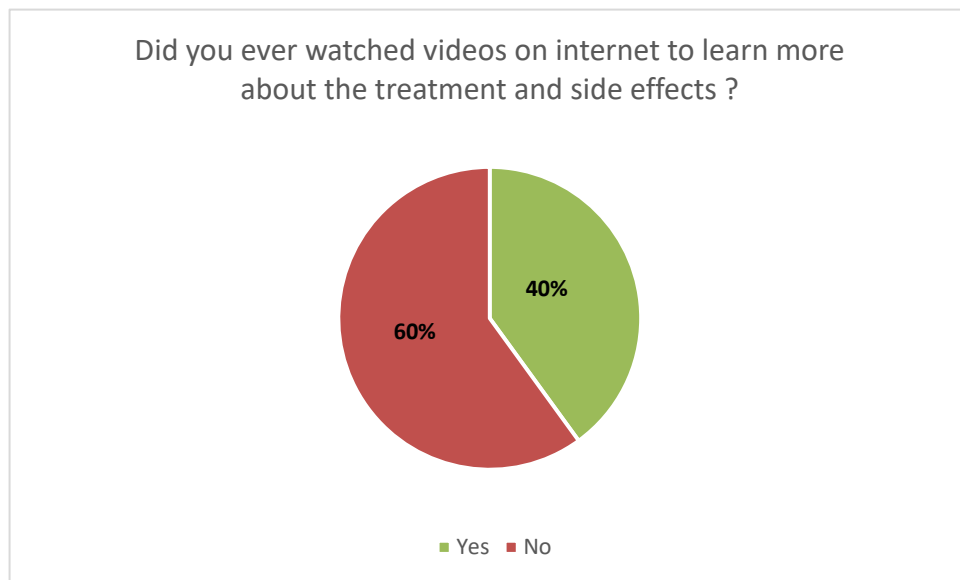
<b>Place where patient could find a paper version of a tool</b>	<b>First analysis</b>	<b>Second analysis (All answers combined)</b>
General Practitioner	33%	56%
Medical Specialist (Hematologist or Oncologist)	<b>100%</b>	<b>89%</b>
Pharmacist	33%	11%
Patient Organization	0%	22%
<b>TOTAL</b>	<b>3 patients</b>	<b>9 patients</b>

*Table VIII: Broadcast channels preferred by patients for paper tools*

For patients who prefer a paper version of the tool (representing three patients in total out of ten), 33% would like to have a tool available at the general practitioner office, 100% at the medical specialist office, 33% at the pharmacy, and no patients have ticked the patient organization box (0%).

If results are analyzed with all answers combined, nine patients in total answered to this question. 56% of patients would like to have a tool available at the general practitioner office, 89% at the medical specialist office, 11% at the pharmacy and 22% would like to have a tool available via patient organization.

Regarding the learning videos for patients explaining the disease or the possible side effects for example (short videos with animations), only 40% of them have already watched these videos.



*Figure 24: Percentage of patients who have ever watched learning videos on internet*

For patients who answered no at this question, 33% were aware of these videos but did not want to watch them. The majority (67% of patients) was not aware but might be interested to watch them. And no patient answered that they are not interested in this type of communication.

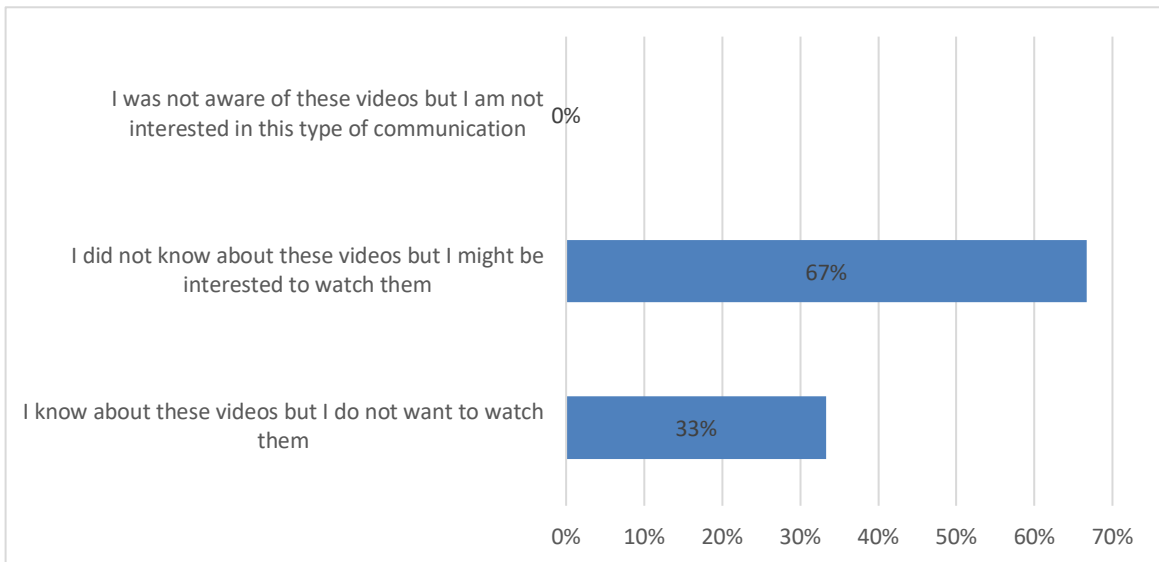


Figure 25: Patient's answers about videos on internet

When patients were interrogated about existing tools like the compliance kit or the mobile application “Mon Suivi BioMol”, only one patient out of ten have already eared about the compliance kit but never used it (it was during a patient day organized by LMC France in Lyon). And only one patient out of ten have already eared about the mobile application “Mon Suivi BioMol” but never used it also. It was his medical specialist who informed him about this tool.

Regarding website consulted by patients, only 20% of patients have already visited the pharmaceutical company’s website. And no patients of these 20% were satisfied about their researches on it.

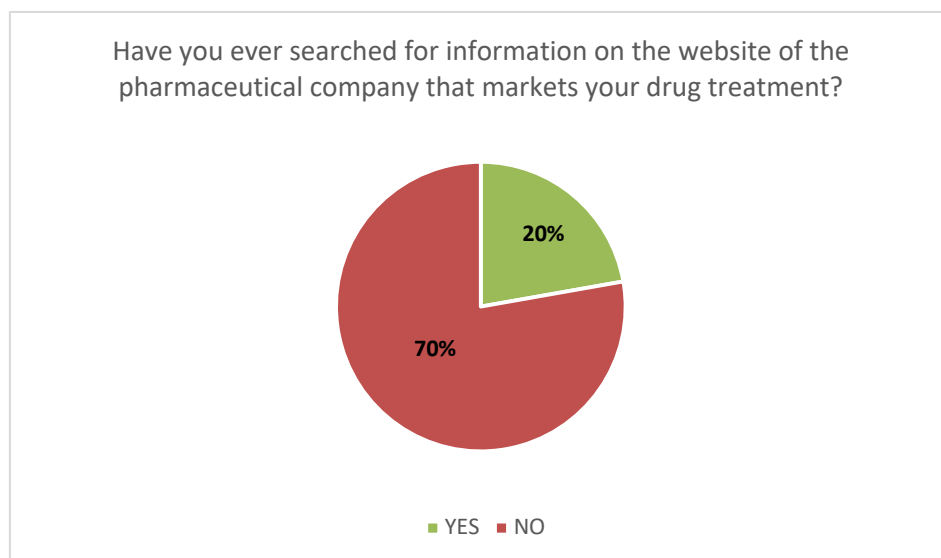
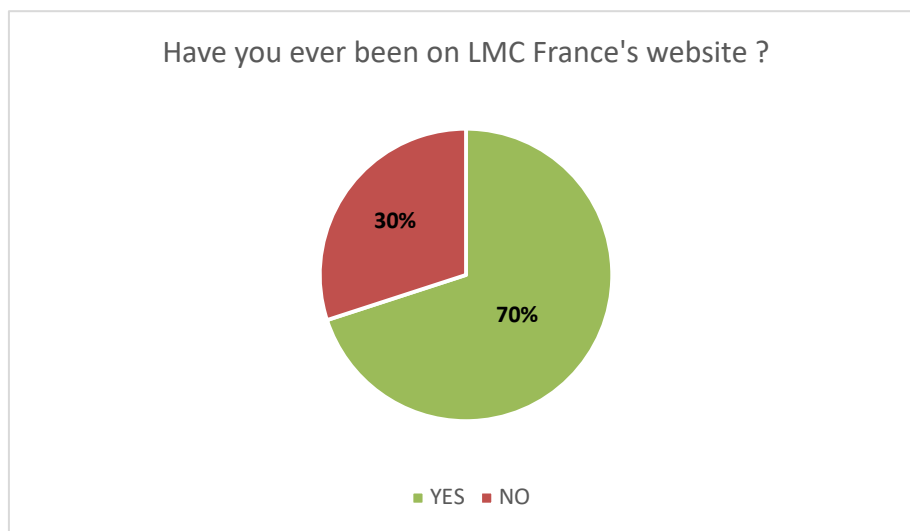


Figure 26: Percentage of patients who have already visited pharmaceutical company's website



However, regarding LMC France's website, 70% of patients interrogated have been doing researches on it. And 30% of patients have never been on this website.



*Figure 27: Percentage of patients who have already visited LMC France's website*

In this 30%, one patient was diagnosed in 2008 and knows the existence of the website and would like to go on it since a long time, and the two other patients were diagnosed in 2018, and are treated since less than one month. It is therefore very recent diagnosis.

For patients who visited the website of LMC France, 100% of them have been satisfied of their researches on this website.

To conclude on the patient survey, 100% of patients were satisfied about their researches on LMC France website while 0% of patients were satisfied about their researches on pharmaceutical companies' websites.

## 2.2 Segmentation

A patient segmentation has been made. In the table below, all the possible groups of patients have been gathered.

The segmentation is based on this following population basis: patients with CML and in chronic phase, and currently treated by TKI.

Five criteria have been identified to be common characteristics shared by groups of patients with CML. In order to create a relevant segmentation, segments have been evaluated according to the six criteria described in the market segmentation part.

Number of the segment	Segment Based on	Characteristics	Comments
1	Patient's age	Patient > 45 years old	Irrelevant. The majority of patient is over 45 years old.
2	Year of diagnosis	Patient with recent diagnosis (under six months)	Patient attitude and habits are different at the beginning, comparing to one year after the diagnosis
3	Medication status	Polymedicated patients	Number of prescribed drugs can influence patient's treatment adherence. Non polymedicated patients have a lower probability of having a poor treatment adherence.
4	Therapeutic situation of the patient	Patient with his first TKI	Patient who has already received multiple treatment lines can be in a situation of treatment failure or drugs are not well tolerated by the patient.
5	Status regarding disease acceptance level	Patient who has accepted the disease	Patient who doesn't have accepted the disease (denial stage) will not be receptive to therapeutic education

*Table IX: Patient segmentation*

The first group has been made based on age criteria. Segmentation is generally based on socio-demographic characteristics. For CML, the mean age at diagnosis is 45 years old. The first segment is therefore patients over 45 years old.

In the second segment, a common characteristic has been identified within CML patient population. It is the year of diagnosis for patients. A patient diagnosed six months ago or one year ago can completely change the strategy in terms of therapeutic education. Habits taken by patients are differently rooted according to the year of diagnosis, and therapeutic education is generally easier with patient recently diagnosed.

The third segment has been made based on patient's medication status. Be treated by TKI is constraining (everyday, depending on meals for some TKI etc...). For patients who have, add to CML, other chronic diseases (like hypertension, hypercholesterolemia etc.) they have to take several drugs each day. This factor is impacting treatment adherence. It is why this third segment has been identified. The marketing strategy could target polymedicated patients that mean patients with higher risk of low treatment adherence.

The segment number four refers to the therapeutic situation of the patient. Patient receiving his first TKI treatment is not as sensitive as patients who have already received multiple treatment lines, in terms of therapeutic education. Two main reasons can explain a situation of patients treated by several TKI:

- Failure in terms of drug's efficacy (apparition of drug resistance etc.)
- Drug intolerance (too many side effects, from clinical to biological)

This segment gathers patients who receive their first line treatment. This group of patients don't used to take TKI and need to be informed on how to take it, when, and why (therapeutic education).

The last segment who has been identified is the segment number five. This segment is focusing on patient's status regarding patient's disease acceptance level. A patient who has not accepted the disease will, in the majority of cases, not take correctly his treatment and have a low treatment adherence. The segment which could be targeted by pharmaceutical industries is therefore patients who have accepted the disease.

### 2.3 Product manager's interviews and literature review about the "patient-centered" strategy

According to interviews with product managers, for mature products like the TKI actually on the market, not a lot of initiatives are being made today to create new marketing tool for patient to help them improve their treatment compliance. Add to this, physicians know very well TKI today and less awareness actions (about treatment or disease) are set up by pharmaceutical companies for them (in the CML field). For pharmaceutical companies, working with physicians is more for raising issues with them, and try to solve these issues. The new priority for physicians today is when the treatment can be interrupted and how interrupts it.

Non-compliance is a multifactorial issue. It is hard to say for product managers if it is side effects or treatment omission or intentional treatment omissions which are at the origin of non-treatment adherence. It is a combination of numerous factors. Add to this, problematic is different depending on TKI used. For example, BMS with SRYCEL® don't have any issue regarding time of the drug intake. That is different from TASIGNA® that needs to be taken away from meals. These constraint levels trigger different interests for pharmaceutical companies to develop compliance tools. Focusing actions on patients is still very important for pharmaceutical companies and they should continue to work on how improve treatment adherence.

Regarding laws that frame creation and development of these types of tools by pharmaceutical companies, legal texts had been analyzed.

According to the HPST law ("Hôpital Patient Santé Territoire law), therapeutic education has been registered in the Public Health Code (Article 84), giving to this practice a legislative framework. The law divides the therapeutic education into three different modalities (37):

- **Therapeutic education programs:** they are suggested to the patient by the prescribing physician and lead to the development of a personalized program; these programs are evaluated by the HAS (Haute Autorité de Santé). An independent operator, financed by a pharmaceutical company, set up the program by means of health professionals.
- **Learning programs:** They aimed at the appropriation, by the patients, of technical gestures allowing the use of a drug requiring it. Unlike therapeutic education program, they are set up at a regional level, after the authorization of the ARS agency ("Agence

Régionale de Santé”). These types of programs have to be set up by at least, two health professionals, including one physician. They must concern a long-term disease (or ALD disease in France).

- **Actions of support:** Their purpose is to provide assistance and support to patients, or their relatives, in the management of their illness.

An important point is that actions of support are part of therapeutic education (according to law definition).

Six enforcement texts had been published about Therapeutic education programs. However, for actions of support, no enforcement text has been published at this time (37).

Based on Saout-Charbonnel-Bertrand supplementary report page 19 and 20 (38), actions of support for patients, like disease management, cannot be directly set up by pharmaceutical companies, except if it is about skill (technical gesture). Pharmaceutical companies have to respect three limits to be able on working for support actions or therapeutic education programs:

- They cannot have direct contacts with patients
- They cannot create, develop or execute the action
- They have to work with health professionals and organizations in some conditions

Consequently, financial support from pharmaceutical companies is possible (in some conditions, see above) and non-financial participation is theoretically also possible, but pharmaceutical companies have to respect the three rules above.

## DISCUSSION

The proportion of marketing tools currently available on the market, for a rare disease like CML, is high. Each big pharmaceutical company is involved in treatment compliance tools and have been developed its own strategy. Pfizer have staked on the global oncology patient care with PactOnco® whereas Novartis staked on mobile applications like “LMCoach” and Mon “Suivi Biomol”. BMS is more diversified with tools like videos, brochure and nudges. Nevertheless, the number of tools only focused on treatment adherence is low. Most of the time, it is comprehensive tools talking about the disease, treatments and side effects etc.

Regarding the patient segmentation and taking into account criteria to choose a relevant segment, the segment number two have been retained. Selecting patients based on the age category is not relevant because most of patients are diagnosed around 45-55 years old. Regarding the substantiality criterion, the segment number three about medication status could be relevant. Indeed, according to a French national survey about observance named “Vos traitements et vous”, the number of medications taken have an impact on treatment adherence (39). Under four drugs taken per day, there is no significant impact on treatment adherence (15% of patients forgot to take their treatments), but over five drugs taken per day, there is a significant impact on patient’s compliance (37,2% of patients taking five drugs per day forgot their treatments). Nevertheless, this segment will represent a lower proportion of the market compares to the segment number two. It is therefore less interesting than the second one. About the segment number four, based on therapeutic situation of the patient, patients who have already received multiple lines of treatment could be, most of the time, far from the diagnosis in terms of years. It means that patients would already adopt habits in terms of treatment adherence behaviors. Finally, the segment number five, based on status regarding disease acceptance level of patients, has not been retained too. Indeed, population of this segment is very difficult to identify. Even for physicians, levels of disease acceptance of patients are very hard to determine. Therefore, this segment is not responding to the criterion of “identifiability” described in the segmentation part.

To conclude, the best segment that should be targeted by marketers to develop a new marketing tool is the segment number two, based on patient year of diagnosis. Indeed, the segment is easy is to identify. Patient’s year of diagnosis is not a hard criterion to identify. This segment represents a large enough proportion of the market to ensure profitability, because it represents all the new diagnostics. This segment is also stable. There will be all the time new diagnosis

and old diagnosis. Finally, patients with recent diagnosis don't have bad habits in terms of compliance, except if they are already taking chronic treatment. But in the majority of cases, patients starting a chronic oral therapy like TKI for CML are easier to educate in terms of therapeutic adherence behaviors (comparing to a patient treated since more than one year and who have already entrenched habits).

Regarding to the patient survey, number of answers are low (10 answers) but it is a rare disease and the sample of patients who answered are well representing the population. Indeed, recent and old diagnoses are composing this patient's sample. It allows a better analysis of patient's needs by having both viewpoints from patients with old and recent diagnosis.

According to the questionnaire, most of patients have been treated by TASIGNA® (currently or in the past). Nine over ten patients received TASIGNA®. Nilotinib is known to be very constraining in terms of time for drug intake. Indeed, Nilotinib need to be taken away from meals. For patients going to the restaurant one night, or invited for dinner by friends, all these things can change the time that patient have to take his medication and the patient could forgot to take it, or just skip the taking to go to sleep earlier for example. Effects of the treatment are not visible by the patient. There is no clinical improvement by taking the drug. It is generally even worse: there is a physical deterioration caused by side effects. All these things are not encouraging the patient to take his medication.

To conclude, patients treated by TASIGNA® have to be followed in their treatment, and requires a special attention from physicians, health professionals and pharmaceutical companies.

The second point highlighted by this survey is that patients are very satisfied about medical information they received. In this survey, 90% of interrogated patients are satisfied. According to the White Paper of LMC France (Second edition, 2016, page 29 (40)), 42.6% of interrogated patients are satisfied about medical information received, and 30.5% very satisfied. It means that more than 73% of patients are satisfied about information received by health professionals. These results confirm the results obtained here.

Add to this, the hematologist stays the privileged interlocutor for patients. Indeed, we observed that 100% of patients interrogated would like to have a tool available at the medical specialist office (if paper version). This is confirmed by the White Paper of LMC France where the hematologist is, for 39,4% of patients, with the spouse (48,3%), the best source of

psychological support (40). The medical specialist is therefore a key part of the patient health care and pharmaceutical companies should focus their actions on this interlocutor in priority.

The goal of this survey was to understand what types of needs do patients have today and what type of tool pharmaceutical companies could create to improve patient's treatment adherence? Non-treatment adherence is a multifactorial event. The survey highlights the fact that patients need a complete tool to understand each aspect of the treatment. 80% of patients would like to have a tool to better understand how the drug works, how it should be taken (time), and why it is important to take the medication very regularly. In parallel, 70% of patients are looking for a tool explaining how to manage side effects. Only 30% would like to have some explanations about the disease. All of this shows that needs are diversified. Patients need to have a global view of their health care, and better understand all the aspects regarding the TKI prescribed.

The perfect example is the success of the mobile application LMCoach. The tool tackles all patient's issues (reminders for medical appointments, advices for patients, and personalized reminders about drug intake). The tool was created by "Observia" with the institutional support of Novartis. The mobile application was launched in October 2014, and the 15th of February 2016, 155 patients had been subscribed to this mobile app (25). Today, 194 patients have been enrolled in this program by their physicians and 176 patients self-registered (so 370 patients in total). It is a great success for a rare disease. By providing complete mobile applications, talking about many aspects of the CML health care, pharmaceutical companies provide indirect services to patients. It is not just about selling drugs. This is also for pharmaceutical companies, a strategy of differentiation from their competitors.

However, side effects are still concerning patients. In this survey, the need with the higher percentage is "manage side effects" (80%). The side effects have a special place in terms of needs. This issue is concordant with the issue presented in the White paper of LMC France. In 2016, more than 62% of patients are not satisfied or very unsatisfied by how side effects are managed (39.4% are unsatisfied and 23.2% are very unsatisfied) (40). An observational study conducted in 2008 over 355 patients showed that 80% of patients with CML have been faced with impacting side effects. In this same study, 25% of these same proportion of patients did not receive any information about possible side effects of TKI, at the beginning of the treatment (41). Side effects are still today, not enough well known and managed. According to another study (31), three quarters of physicians are under estimated their patient's side effects. Patients



can interrupt a treatment in order to stop side effects. By sensitizing more hematologists and physicians about side effects, and encourage patients to talk about this subject, pharmaceutical companies will avoid treatment interruption caused by side effects and improve patient's treatment adherence.

Regarding the questionnaire, 70% of patients would like to have a digital tool. It is a clear majority. For 90% of them (all answers combined), a mobile application is preferred. A phone could be taken everywhere, compares to website which are not accessible everywhere (for example in holidays etc.). Add to this, videos could be a good broadcast channel for pharmaceutical companies because, even if the majority of interrogated patients did not have seen videos (60%), 67% of them might be interested to watch videos about the treatment (how to take it, side effects etc.). However, this diffusion channel is less practical than mobile application and stays unsteady in terms of patient's demand.

Pharmaceutical companies' websites are not often visited by patients. Only two patients interrogated out of ten have been on those websites and did not visit LMC France's website. These two patients are patient with a very recent diagnosis (less than one month, and even less than two weeks). Nevertheless, 70% of patients have been on the LMC France website. All these results show that patient organization can have a big impact in terms of visibility and communication. Having a strong organization in the field is very important to change things and to communicate about treatment adherence to patients for pharmaceutical industries. LMC France is very active in terms of event organization, communication, and the website is very complete (advices, tools to help patients, links, patient's testimonies, white papers etc.)

To conclude, global guidance for pharmaceutical companies would be to create a digital tool (mobile application preferred, because very accessible and playful), which taking into account not only treatment adherence issue but the global health care of the patient. The hematologist stays the privileged interlocutor for patients and pharmaceutical companies must include these health professionals in their communication strategy. The communication strategy should include also patient organization with a strong presence in the public environment. Having a strong organization like LMC France helped a lot the development of the mobile application LMCoach. A lot of communication has been done by the organization and patients were very aware of the existence of this tool.

Another recommendation would be to redirect patients visiting the pharmaceutical company's website towards the patient organization website. The satisfaction level about researches on the

pharmaceutical company's website will increase and her brand image too. The last recommendation would be to include in this new tool the patient's close circle. According to the white paper of LMC France in 2016 and their study, more than 73% of the interrogated patient are unsatisfied or very unsatisfied about the level of access regarding psychological support for their close circle (38.4% are very unsatisfied). Yet, patient's close circle is however, the most important part concerning patient support. Working on a mobile application to help family and close relatives of the patient will help him to improve his treatment adherence, his global wellness, and keep the family and couple balance unaffected by the disease.

For pharmaceutical companies, treatment adherence is a real issue and challenge. There are a lot of pros to justify involvement in compliance for pharmaceutical companies but there are also important barriers to implement these types of actions (marketing tools about treatment adherence, therapeutic education programs etc.)

According to Eric Baseilhac, former director of the LEEM ("Les Entreprises du Médicament"), drugs prices are negotiated with the CEPS (Comité Economique des Produits de Santé) according to agreements. An initial price is determined by the CEPS but this price is subject to change according to the drug efficacy "in real life". Therefore, taking the case of patient with CML, a lot of patients decide to stop their treatments because of side effects or mere oversight. Efficacy of TKI is linked to compliance and the treatment needs to be taken very regularly for a long time, to be effective (see part 3.3). Non-compliance patients will therefore decrease statistics on "real life efficacy" and price of the drug could be reevaluated downward. It also impacts indirectly brand image. If a drug is not enough effective and have goods results after it launch, the medication will stop being used. For pharmaceutical companies, manage compliance becomes strategic (42).

The efficacy of the drug is directly linked also to the number of switch or treatment interruption. Indeed, if the drug is not enough effective, physicians will switch for another drug and that is a loss for pharmaceutical companies. In CML, forget only one to three drug intakes during one-month impact drastically the treatment response. It is therefore essential to focus action on treatment adherence, to avoid switch or treatment interruption.

Add to this, by doing marketing tools to help patients in their health care, pharmaceutical companies are providing indirect services. This is a good strategy to differentiate from competitors. Second generation TKI are now mature products. It is therefore important for pharmaceutical companies to implement differentiation strategies.

Today, regulations are going more and more present in this patient focus initiative. For example, it started with the HPST law in 2009, create to modernize public health establishments (functioning and organization, care quality, safety of care, cooperation and performance), to improve access to care, prevention and public health and finally to improve territorial organization of the health system (creation of ARS, regional health policies etc.) (43). Later, this regulation had been following by the Plan Cancer between 2014 and 2019, with 17 objectives in total. This new plan is completely focusing on patients in oncology and aims to meet the needs and expectations of patient, patient's families and all citizens. The goal is to provide support to patients and their loved ones, reduce inequalities and loss of chance face to cancer and improve patient's access to innovation and improve quality of care. Add to regulations, hospitals are setting up some special programs to improve patient treatment adherence. Indeed, some patient's program supports are settled up to support patient under oral therapies at the beginning of the treatment. An example is ONCORAL settled up in Lyon by the "Hospices Civils" (41). This program consists of nurse and hospital pharmacist doing the link with the care out of hospital since the patient's treatment initiation. They can also provide therapeutic education and phones calls to the patients. Another program named ARIANE has been settled up by Cochin Hospital in Paris (41). In conclusion, patient programs are more and more created and health regulations are taking more and more into account the patient and his action in his own health care. Pharmaceutical industries can therefore take benefits from this enabling environment to create new actions around the patient and his close relatives.

To conclude about advantages of the "patient focus strategy", there are some shared interests between pharmaceutical companies and health authorities and French government about the treatment adherence subject. Indeed, beyond this public health issue, the non-treatment adherence triggers costs for the French health system. In November 2014, an important study was conducted by IMS Health Corporate about therapeutic compliance (44). This report describes that nine billion dollars could be saved by the social security in France by improving compliance of patient with chronic diseases in general. According to this study, only 40% of the patient population in average is compliant. To be more precise, the white paper edited in November 2016 by a group of patient organization (41) reported page 51 that the main economic lever is treatment interruption in the CML. Indeed, a patient's follow-up program will improve treatment adherence and therefore will improve too the sustainability of the complete cytogenic response and the major molecular response. Recent studies show that maintaining major molecular response for 3.4 years (median) and after 6.6 years of treatment

allows treatment interruption. And for patients who interrupted the treatment, 56% of them do not take it again (41). Add to this, a patient who is followed in his treatment, with a good treatment adherence, will prevent the transition to subsequent lines treatment and especially blast phase and transplant. All of these will prevent from extra costs. By estimating the average duration under treatment at ten years, savings for the 3.4 years with a compliant patient and followed for two years are estimated to 59 000 euros. In other words, by allowing treatment interruption, a follow-up program could generate 63 euros of savings for one euro invested. To conclude, treatment adherence is a real issue for pharmaceutical companies but not only for them. Health authorities and government are interested in this compliance issue to save money and reduce health costs for patients with CML. They are therefore shared interests between pharmaceutical companies and health authorities and French government.

Creating partnerships with patient organizations could help pharmaceutical industries to have a better brand image and maximize the understanding of patient needs. But create marketing tools, programs on compliance is achievable? Is it easy to set up partnerships with them? What can be done and what the laws say about these practices?

The observation today highlights the need for patient organization to find financial support. The goal of patient organization like LMC France is to provide help and support for patients with CML. Without the help of pharmaceutical companies like Novartis, LMC France would have significant difficulties in completing the LMCoach project. By talking with product managers and people working in patient advocacy for pharmaceutical industries in rare disease, most of patient organizations agree to receive institutional support from pharmaceutical companies. It is therefore not too difficult to set up partnership with them, even if patient organization still wants to stay away from financial support of pharmaceutical companies. In theory, it is the patient organization who asks for pharmaceutical companies an institutional support and companies answer positively or not to patient organization's requests, depending on interest level for the project.

Nevertheless, even if creating partnership with patient organization is possible, creation of marketing tools, therapeutic education programs and other solutions are not yet done...Indeed, these actions are strictly framed by laws and regulations (see HPST law). Like it was said in the result part, pharmaceutical companies have three limits to work on support actions or therapeutic education programs:

- They cannot have direct contacts with patients
- They cannot create, develop or execute the action
- They have to work with health professionals and organizations in some conditions

Consequently, financial support from pharmaceutical companies is allowed (according to the three conditions above) and non-financial participation is also possible, but pharmaceutical companies have to respect the three rules above too and in this last situation, the three rules are making the last possibility almost impossible. Pharmaceutical companies are not allowed to act directly into programs conception or redaction (42). They need to find strategy to avoid direct link with patients. To protect themselves and be in accordance with the law, pharmaceutical companies have to use an intermediate to communicate and create a patient tool. For example, some companies like Teva and Sandoz developed software helping pharmacists to conduct therapeutic interviews of patients. Another example is the arrival of companies working for pharmaceutical industries like “Patient connect”. This type of company offers to pharmacists a remuneration if they accept to use their software. This software delivers messages about compliance. Pharmacy seems to be a good front door for pharmaceutical companies to deliver key messages about compliance (42).

Nevertheless, laws are still very unclear (37). According to a decree with the article L.1161-3 CSP, actions of supports are under the therapeutic education program qualification and therefore, restricted to ALD diseases. But according to the HSPT law, actions of support are part of the education therapeutic programs (article L.1161-3 CSP) but the law distinguish patient’s therapeutic education program in the article L.1161-2 CSP from actions of support in the article L.1161-3 CSP. Add to this, the legislator has provided a separate legal status for actions of support. Actions of support are not subject to criminal sanctions in case of missing authorization. (37). Actions of support have therefore an autonomous status from therapeutic education programs and could be therefore applicable for other diseases in the ALD list. But nonetheless, these types of actions could be also attached to therapeutic education programs as defined in the Saout-Charbonnel-Bertrand report in June 2010 and be applicable only for ALD diseases. Add to this, requirement specifications for actions of support have never been defined, unlike therapeutic education program. Health actors are therefore reluctant to go for actions of supports or therapeutic education programs because the implementing decree related to actions of supports have never been published.

Add to this unclear legislative framework and despite the willingness instilled by the HPST law and “Plan Cancer”, there is still a lack of unique health policy strategy to improve the monitoring of oral therapies, and a lack of sustainable resources (41).

A pharmaceutical company’s image does not work in its favor either. It is difficult to set up actions with patients and laws are very constraining about their scope in terms of actions. Pharmaceutical companies are therefore less inclined to set up and develop therapeutic education programs for patients.

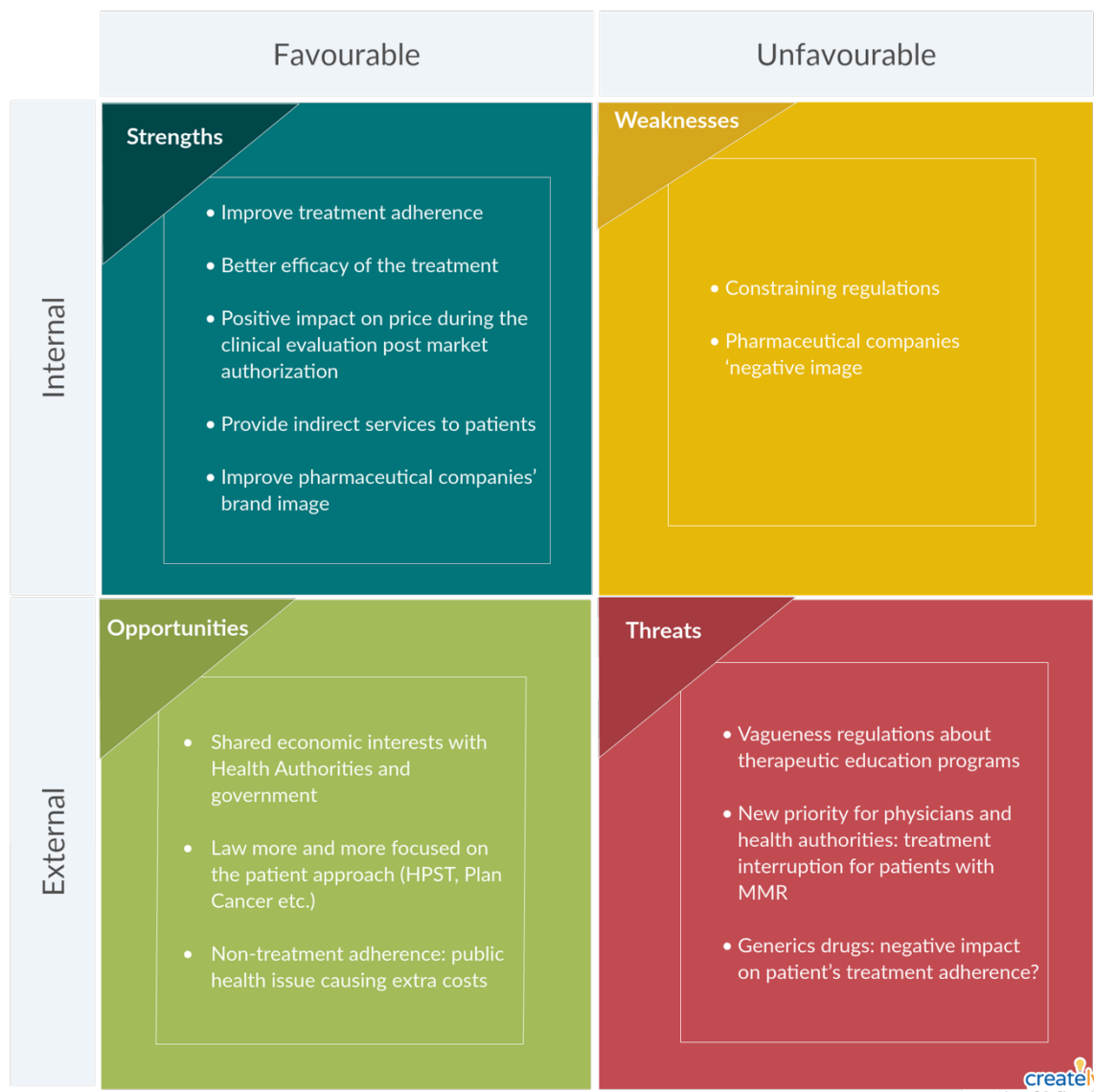


Figure 28: SWOT Analysis about the "patient-centered" strategy

To conclude about strategies, there are a lot of pros but also some cons. Nonetheless, pharmaceutical companies have to continue their efforts to create and provide some tools and programs to improve patient's treatment adherence. Even if laws are constraining, patient organization need the institutional support of pharmaceutical companies and patients too. Focusing strategies on patients and their close relatives are a good strategy for pharmaceutical companies and health authorities have to work with these pharmaceutical companies to improve the public health issue of treatment adherence. Non-treatment adherence is still a current issue. Therapeutic education programs could be the next step for pharmaceutical companies. In the white paper of LMC France in 2016 (40), more than 8 out of 10 patients did not know the existence of these therapeutic education programs. And 91% of interrogated

patients would be interested by therapeutic education modules available for patients and their closes relatives on internet. The results of the survey highlight a near-universal lack of knowledge on patients' therapeutic education among patients and close relatives. These types of programs are not well known, and few people are taking advantage of it. Today, actions about therapeutic education are at a very early stage and deserve to be developed and financed by pharmaceutical companies.

In conclusion, non-treatment adherence is still today a public health issue. This issue is relating to all the chronic diseases, and especially those where patients receive outpatient treatment. CML is one of the diseases concerned and non-treatment adherence has a drastic impact on treatment efficacy and patient survival. To improve this health issue, pharmaceutical companies have been financing marketing tools developed by patient organization to help patients improving their treatment adherence in the CML. Novartis, leading the TKI market in terms of sales, is the company who provide the most complete offer in terms of tools, with two mobile applications and videos. Each pharmaceutical company is offering diversified tools: some tools are focused on treatment adherence, but some other tools are taking into account the whole patient's health care. Today, the offer is existing, but it is not enough sufficient. Therapeutic education programs and actions of support should be more developed and patient organization need the institutional support of pharmaceutical companies.

Guidance for pharmaceutical companies would be to create digital tools (mobile application preferred, because very accessible and playful), which taking into account not only treatment adherence issue but the global health care of the patient. Communication strategy about these tools should include the hematologist, who stays the privileged interlocutor for patients. The communication strategy should include also proactive patient organization with a strong presence in the public environment. The patient organization is a key element in the success of a tool.

However, pharmaceutical companies have to move forward into this direction of bringing solutions to patients. Even if regulations are constraining and unclear about actions of support or therapeutic education programs, focusing strategy on patient stays a good strategy. Excepted constraining regulation, the health environment is moving into this same direction of bringing patient at the center of his own health care. However, government and health authorities should



encourage pharmaceutical company by doing clearer regulations about therapeutic education programs and actions of support.

The next step for pharmaceutical companies would be would be to finance therapeutic education programs and develop tools to support patients' close relatives.

**THÈSE SOUTENUE PAR : LAGADEC Audrey**

**TITRE :**

L'OBSERVANCE CHEZ LES PATIENTS ATTEINTS DE LEUCEMIE MYELOIDE CHRONIQUE ET TRAITES PAR INHIBITEURS DE TYROSINES KINASES : ENTRE BESOINS PATIENTS ET STRATÉGIES DES LABORATOIRES PHARMACEUTIQUES

**CONCLUSION :**

Aujourd'hui encore, l'inobservance est un problème de santé publique d'actualité. Il concerne les maladies chroniques, et en particulier celles où les patients reçoivent un traitement en ambulatoire. C'est le cas des patients atteints de LMC et traités par inhibiteurs de tyrosines kinases. Chez ces patients, l'inobservance thérapeutique a un impact considérable sur l'efficacité du traitement et la survie du patient. Pour remédier en partie à ce problème de santé, les laboratoires pharmaceutiques ont financé des projets de développement d'outils marketing (développements réalisés par les associations de patients), afin d'aider les patients atteints de LMC à améliorer leur observance. Novartis, leader sur marché des TKI en termes de revenus et de ventes, est le laboratoire pharmaceutique qui propose l'offre la plus complète en termes d'outils (applications mobiles, vidéo etc.). Chaque laboratoire pharmaceutique commercialisant des TKI propose des outils diversifiés. Certains outils sont axés sur l'observance du traitement, mais d'autres outils ont une approche beaucoup plus globale en incluant le patient et son parcours de soin dans sa globalité (cf. PacteOnco de Pfizer). Aujourd'hui, l'offre existe, mais elle n'est pas suffisante. Les programmes d'éducation thérapeutique et les actions d'accompagnement sont encore trop peu développés au regard de l'inobservance encore observée aujourd'hui chez les patients atteints de LMC.

Les recommandations émises dans ce travail sont destinées aux laboratoires pharmaceutiques. Elles sont basées sur le recueil des besoins patients, et portent sur la création de nouveaux outils numériques (applications mobiles de préférence, car très accessibles et ludiques) qui tiendront compte non seulement du problème de l'inobservance thérapeutique, mais également de la prise en charge globale du patient. La stratégie de communication concernant ces outils doit inclure l'hématologue qui reste l'interlocuteur privilégié des patients, mais également impliquer les associations de patients très actives dans l'environnement associatif. En effet, elles représentent un élément clé dans le succès d'un outil marketing.

Les laboratoires pharmaceutiques doivent donc continuer dans cette direction en continuant à apporter de nouvelles solutions et outils aux patients et à leurs aidants, même si les réglementations sont contraignantes en ce qui concerne les actions d'accompagnement.

**VU ET PERMIS D'IMPRIMER**

Grenoble, le : 14/11/2018

**LE DOYEN**



**Pr. Michel SÈVE**

Pour la Présidence  
et par délégation  
Le Doyen de Pharmacie  
Pr. Michel SÈVE

**LE PRÉSIDENT DE LA THÈSE**



**Dr. Marie JOYEUX FAURE**

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## APPENDICES

### ANNEX 1: QUESTIONNAIRES COMPLETED BY PATIENTS WITH CHRONIC MYELOID LEUKEMIA.

Patient n°1

1) Année de diagnostic de votre Leucémie Myéloïde Chronique : 2018

2) Êtes-vous actuellement sous traitement médicamenteux ?

OUI                       NON

3) Si oui, depuis combien de temps prenez-vous votre traitement ?

- < 1 mois  
 Entre 1 et 6 mois  
 > 6 mois  
 > 1 an

4) Si non, depuis combien de temps avez-vous arrêté votre traitement ?

- < 3 mois  
 Entre 3 et 6 mois  
 > 1 an  
 > 3 ans

5) Par quel médicament êtes-vous actuellement/ou avez-vous été traité dans le passé, pour votre leucémie ?

- TASIGNA® (Nilotinib)  
 GLIVEC® (Imatinib)  
 ICLUSIG® (Ponatinib)  
 SPRYCEL® (Dasatinib)  
 BOSULIF® (Bosutinib)

6) Selon vous, estimez-vous avoir été suffisamment informé sur votre traitement actuel à propos :

Du mécanisme d'action :  OUI  NON

Du mode de prise (heure de prise, moment de la prise etc.) :  OUI  NON

Des effets indésirables possibles :  OUI  NON

**7) Quel(s) support(s) vous aiderai(en)t à mieux comprendre l'importance de votre médicament et l'importance de la régularité de prise de vos comprimés ou gélules ?**

Un support expliquant plus en détails la maladie

Un support expliquant plus en détails votre médicament (mode d'action, effets indésirables, conseils sur les moments et mode de prise de votre médicament)

Un support contenant des conseils afin d'apprendre à mieux gérer les effets indésirables de votre traitement

Autre :

**8) Quel mode de support mis à votre disposition préféreriez-vous ?**

Support Papier

Support Digital/Numérique (Site internet, application mobile, etc...)

**9) Si l'outil était développé en version papier, souhaiteriez-vous qu'il soit disponible chez :**

Médecin Généraliste

Médecin Spécialiste (Cancérologue/Hématologue)

Pharmacien

Association de Patients

Autre :

**10) Si l'outil était développé en version numérique, souhaiteriez-vous qu'il soit disponible chez :**

En version « application mobile » à installer sur votre téléphone portable (alarme de rappel de la prise, rdv médicaux etc..)

Sur le site internet d'une association de patient

Sur le site internet du laboratoire pharmaceutique qui commercialise votre médicament

Autre :

11) Connaissez-vous l'outil « Mon suivi Bio Mol », une application mobile vous permettant de rentrer vos résultats PCR et de tenir un journal d'observance ?

OUI  NON

12) Si oui, comment l'avez-vous connu ?

13) L'avez-vous déjà utilisé ?

OUI  NON

14) Connaissez-vous la mallette observance ?

OUI  NON



15) Si oui, comment l'avez-vous connue ?

16) L'avez-vous déjà utilisée ?

OUI  NON

17) Avez-vous déjà visionné sur internet des vidéos explicatives sur la maladie, les effets indésirables des traitements etc. ?

OUI  NON

18) Si non, pour quelle(s) raison(s) ?

- J'ai connaissance de ces vidéos mais je ne souhaite pas les visionner
- Je n'avais pas connaissance de ces vidéos mais je pourrais être intéressé pour les visionner
- Je n'avais pas connaissance de ces vidéos mais je ne suis pas intéressé par ce mode d'information

**19) Vous êtes-vous déjà rendu sur le site internet du laboratoire pharmaceutique qui commercialise votre médicament pour rechercher des informations sur le médicament, ses effets indésirables ou tout autre information :**

OUI                       NON

**20) Si oui, avez-vous été satisfait de vos recherches sur ce site ?**

OUI                       NON

**21) Vous êtes-vous déjà rendu sur le site internet de l'association de patient « LMC France » ?**

OUI                       NON

**22) Si oui, avez-vous été satisfait de vos recherches sur ce site ? Avez-vous trouvé ce site utile ?**

OUI                       NON

Commentaires :

## **ANNEX 2: Questionnaire for Product Managers of TKI treatments:**

- For how long times are you working on this product?
- Currently, what are the marketing tools available for patients and created by your company?
- What feedbacks did you get on those?
- What percentage of all of your projects represents marketing tools for patients?
- Digital or paper tools: which one is the most wanted?
- Regarding your experience, what patients need to improve their treatment compliance according to you? (a better understanding of the disease, of the drug, others?)
- What do you think about industrial strategies to develop tools for patients on treatment compliance?
- Is it difficult to set up partnerships with patient organizations?
- After the launch of these tools, did you see any results/difference on your sales?
- What impact these tools had on pharmaceutical company brand image?
- Do you have some new marketing tools about compliance ongoing?
- Do you think you will continue to work on these types of projects?
- If yes, in same quantity or do you think you will increase marketing tools for patients?
- Do you think that focusing on patients and compliance is a good strategy? Could it be a strategy for differentiation?

### ANNEX 3: TYROSINE KINASE INHIBITORS SALES (PHARMACY & HOSPITAL)

All these data are extracted from the GERS database.

For year “2018” (an incomplete year) numbers are the results of sales from July 2017 to July 2018 (it is named in French “Cumulé mobile sur 12 mois”), in order to be able to compare 2017 and 2018 numbers.

Pharmaceutical forms that have been considered in the numbers for pharmacy sales are the following:

- GLIVEC 100MG GELU\* BT\*\* 120
- GLIVEC 100MG CPR\*\*\* BT 60
- GLIVEC 400MG CPR BT 30
- SPRYCEL 20MG CPR BT 60
- SPRYCEL 50MG CPR BT 60
- SPRYCEL 70MG CPR BT 60
- SPRYCEL 100MG CPR D.U BT 30
- SPRYCEL 140MG CPR D.U BT 30
- TASIGNA 200MG GELU BTE 28
- TASIGNA 200MG GELU BTE 112
- TASIGNA 150MG GELU BT 28
- TASIGNA 150MG GELU BT 112
- ICLUSIG 15MG CPR FL\*\*\*\* 60
- ICLUSIG 45MG CPR FL 30
- ICLUSIG 15MG CPR FL 30
- ICLUSIG 30MG CPR FL 30
- BOSULIF 100MG CPR BT 28
- BOSULIF 500MG CPR BT 28

\* Capsule

\*\* Pills

\*\*\* Box

\*\*\*\* Bottle

One “Unité Commune de Dispensation” (UCD) represent one drug’s unit. For drugs formulated in pill (for example), sales in UCD represents the number of pills sold.

<b>2016</b>	<b>Hospital Sales (in UCD)</b>	<b>Pharmacy Sales (in UCD)</b>	<b>Hospital Sales (€)</b>	<b>Pharmacy Sales (€)</b>	<b>TOTAL SALES (in UCD)</b>	<b>TOTAL SALES (€)</b>
GLIVEC® (Imatinib)	91 290	3 971 340	3 157 714	171 554 269	4 062 630	147 711 983
SPRYCEL® (Dasatinib)	14 730	699 150	859 334	55 516 493	713 880	56 375 827
TASIGNA® (Nilotinib)	27 020	2 148 160	798 158	56 129 712	2 175 180	56 927 870
ICLUSIG® (Ponatinib)	38 910	32 550	4 511 155	4 869 683	71 460	9 380 838
BOSULIF® (Bosutinib)	1 960	211 540	67 760	6 341 720	213 500	6 409 480

\* GLIVEC 100mg et 400mg (pills)

\* SPRYCEL 20mg, 50mg, 70mg, 100mg and 140mg (pills)

\* TASIGNA 150mg and 200mg (capsules)

\* ICLUSIG® 15mg, 30mg and 45mg (pills)

\* BOSULIF 100mg and 500mg (pills)

<b>2017</b>	<b>Hospital Sales (in UCD)</b>	<b>Pharmacy Sales (in UCD)</b>	<b>Hospital Sales (€)</b>	<b>Pharmacy Sales (€)</b>	<b>TOTAL SALES (in UCD)</b>	<b>TOTAL SALES (€)</b>
GLIVEC® (Imatinib)	59 010	2 456 760	1 856 661	92 541 330	2 515 770	95 057 100
SPRYCEL® (Dasatinib)	16 824	762 360	1 002 879	57 989 764	779 184	58 768 948
TASIGNA® (Nilotinib)	21 448	2 166 220	579 672	52 077 444	2 187 668	54 265 112
ICLUSIG® (Ponatinib)	6 570	73 440	1 175 811	13 143 312	80 010	13 223 322
BOSULIF® (Bosutinib)	3 752	301 616	87 472	8 771 752	302 368	9 074 120

<b>2018</b>	<b>Hospital Sales (in UCD)</b>	<b>Pharmacy Sales (in UCD)</b>	<b>Hospital Sales (€)</b>	<b>Pharmacy Sales (€)</b>	<b>TOTAL SALES (in UCD)</b>	<b>TOTAL SALES (€)</b>
GLIVEC® (Imatinib)	33 720	2 128 380	1 024 532	74 112 222	2 162 100	75 136 754
SPRYCEL® (Dasatinib)	16 950	800 070	999 879	60 160 541	817 020	61 160 420
TASIGNA® (Nilotinib)	19 264	1 691 592	524 726	37 576 588	1 710 856	38 101 314
ICLUSIG® (Ponatinib)	7 530	83 550	1 347 619	14 952 665	91 080	16 300 284
BOSULIF® (Bosutinib)	4 452	365 848	96 887	9 608 386	370 300	9 705 273





# **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 ».**

L'OBSERVANCE CHEZ LES PATIENTS ATTEINTS DE LEUCEMIE MYELOIDE  
CHRONIQUE ET TRAITES PAR INHIBITEURS DE TYROSINES KINASES : ENTRE  
BESOINS PATIENTS ET STRATÉGIES DES LABORATOIRES PHARMACEUTIQUES

RÉSUMÉ

L'inobservance thérapeutique est fréquente chez les patients atteints de leucémie myéloïde chronique et recevant un traitement oral par inhibiteurs de tyrosines kinases. L'objectif de ce travail est d'étudier le rôle de l'industrie pharmaceutique dans la création de nouveaux outils marketing pour l'amélioration de l'observance, mais aussi les besoins actuels et encore non satisfaits des patients. Dans un premier temps, une revue de la littérature sur les outils actuels traitant de l'observance et ayant reçu le support des laboratoires pharmaceutiques sera réalisée. Dans un second temps, une segmentation des patients sera effectuée ainsi qu'une analyse des résultats de questionnaires patients afin de recueillir leurs besoins et d'élaborer des pistes de réflexion pour la création de nouveaux outils marketing sur l'observance. Enfin, cette thèse abordera les avantages et inconvénients de la « stratégie patient » adoptée par les laboratoires pharmaceutiques afin d'améliorer l'observance de leurs traitements par voie orale.

ABSTRACT

Non-treatment adherence is common in patients with chronic myeloid leukemia and receiving oral treatment with tyrosine kinase inhibitors. The objective of this work is to understand the place of the pharmaceutical industry in the creation of new compliance marketing tools, but also to understand the current and unmet patient's needs. As a first step, a literature review on compliance tools available to patients and who have received support from pharmaceutical companies will be conducted. In a second step, patient segmentation will be carried out as well as an analysis of the results of patient questionnaires, in order to collect their needs and to develop guidance for the creation of new marketing tools on treatment adherence. Finally, this thesis will focus on the "patient strategy" adopted by pharmaceutical companies to improve treatment adherence with their oral treatments. The advantages and disadvantages of this strategy will be studied.

MOTS CLÉS : Leucémie Myéloïde Chronique – Inhibiteurs de Tyrosines Kinases – Inobservance – Stratégie – Segmentation – Laboratoires Pharmaceutiques – Outils marketing

FILIÈRE : Industrie