Emerging Therapies for Blood Cancer indications

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Emerging therapies for blood cancer indications

Unravelling the best hematological antitumor therapies in terms of underlying biology, clinical trial design and their implications on treatment guidelines.

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Preface

At the beginning of my academic career, I was sure I would have dedicated my entire life to the Biomedical Research, in order to understand the intricate and complex interconnectivity between cancer and aging. Later on, even though I had so far just hands-on-experience in the scientific research, I decided to take as a Specialization for my Master the Science+ Business & Policy track. I thought that investigational research might be the first fundamental step in order to make a difference to improve – or even save – people's lives, but that application and implementation of science are the actual forces that make a change possible.

I'm really glad I had such an opportunity to collaborate with CATO-SMS. With this experience I understood the challenges associated to the arduous and long drug development path, together with the opportunities and the benefits that this field constantly offers to cancer-affected patients worldwide. The qualities of the company that astonished me the most are the high-performance culture that is constantly nurtured at CATO SMS, and the ambition of the employees to be on a continuous learning and development path.

I would like to thank all the employees at CATO SMS that made me feel part of the team since the very first day of my internship. In addition, I would like to thank my daily supervisor Inka Pawlitzky for giving me the opportunity to join the ODDA department and for constantly supporting me during this wonderful experience. I admire her in-depth oncology knowledge and expertise and I will always feel grateful for her proactive and positive attitude that gave me the motivation to achieve my best until the last day of my internship. To Bram Piersma, my SBP supervisor, who always saw the "bigger picture" of my project and that acted as a guidance whenever I felt lost on the way. To Frank Kruyt, my scientific supervisor for the educational support in the scientific part of the report. Last but not least, to my fellow intern Circe, who gave me a fundamental moral support during these unprecedented times of Covid-19.

I hope you will enjoy reading my report.

Irene Vetrugno

Amsterdam, NL.

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Executive summary

CATO SMS is a contract research organization that conducts clinical studies on behalf of other biomedical and biotechnological companies and offers drug development advice. This company is highly valued for being one of the fewest CROs in the world solely dedicated to oncology. **CATO SMS has the ambition of integrating into its oncology portfolio the potential leading antitumor therapies in the field of hematological malignancies**.

This advisory report has the objective of describing the evolution of the hematological anti-tumor therapies landscape in the past five years, in order to identify recent trends in therapies and to anticipate new developments in the field. The biological background of the different blood cancer indications is uncovered together with the scientific rationale and mode-of-action of current anti-tumor therapies. Furthermore, novel therapeutic strategies that have the potential to achieve extraordinary results in the treatment of hematological malignancies are highlighted. These findings are integrated with business factors derived from an internal analysis of the company, in order to evaluate how CATO SMS internal aspects – structure, style, systems, shared values, strategy, staff and skills – fit with the company ambition to invest into this project. Macroenvironmental factors such as political, economic, social, technological, ethical and legal factors that have an effect on the conduct of hematological malignancies clinical studies are evaluated.

The in-depth analysis of the biology of hematological malignancies reveals that these indications are caused by a malignant transformation of hematopoietic stem cells that acquire successive genomic alterations. The molecular heterogeneity of mutations that characterizes hematological malignancies determine the resistance of malignant cells towards therapy. The trends analysis shows that important aspects of current research for the treatment of blood cancers include understanding the genomic background of the different indications and investigating the molecular mechanisms initiated by each mutation that lead to the disease. Therefore, although the majority of marketed drugs for the treatment of hematological malignancies consists of chemotherapeutic agents, the pipeline drugs activity is currently focusing on targeted therapies and immunotherapeutic approaches. In particular, CAR-T cells and immune checkpoint inhibitors solutions are coming to the forefront for the clinical management of acute myeloid leukemia, chronic lymphocytic leukemia and multiple myeloma. In accordance with these results, technological trends from the external analysis reveal that precision medicine is currently changing the course of blood cancer treatments by including genetic databases, medical record, tissue banks, and other clinical sources of ‘big data’.

The final advice addressed to CATO SMS is composed of two central evaluations. One consideration regards the intrinsic challenges related to the hematological malignancies field. CATO SMS should **improve its network** across Europe and in the US and strengthen collaborations with KOLs and specialists in a competitive “niche” field. The company should also consider **patients engagement** as a valuable strategy to ensure patients recruitment and retention in hematological malignancies studies. **Tailored trainings** should be provided by a hematological malignancies expert focusing on target disease, investigational agents, protocols and data management. The second part of the advice highlights the advantages and potential opportunities for CATO SMS to integrate the future leading hematological therapies in its oncology portfolio. In particular, CATO SMS would broaden its expertise in the field of **personalized medicine**, which is revolutionizing the clinical approaches for blood cancer indications. The company would also consider **innovative clinical trials design**, including umbrella, basket and adaptive trials approaches. Finally, CATO SMS would also have the opportunity to **collaborate with academia**, having a close eye on novel drug targets, validation of targets, animal models, specialized disease expertise and biomarkers discovery.

List of abbreviations

AA: Accelerated approval

ACR: Adoptive T cell therapy

AE: Adverse events

AML: Acute myeloid leukemia

BTD: Breakthrough therapy designation

CARs: Chimeric antigen receptors

CHIP: Clonal hematopoiesis of indeterminate potential

CLL: Chronic lymphocytic leukemia

CNS: Central nervous system

CR: Complete remission

CRO: Contract research organization

CRS: Cytokine release syndrome

CSF: Cerebrospinal fluid

DFS: Disease-free survival

DLT: Dose-limiting toxicity

DoR: Duration of response

EDC: Electronic data capture

FC: Constant fragment

FDA: US Food and Drug Administration

FT: Fast track

GCP: Good clinical practice

GI: Gastrointestinal

HLA: Human leukocyte antigen

HSCs: Hematopoietic Stem Cells

LoA: Likelihood of approval

mAbs: Monoclonal antibodies

MGUS: Monoclonal Gammopathy of Uncertain Significance

MHC: Major Histocompatibility Complex

MM: Multiple Myeloma

MRD: Minimal residual disease

NGS: Next generation sequencing

ObRR: Objective response rate

ORR: Overall response rate

OS: Overall survival

PCs: Plasma cells

PFS: Progression-free survival

PTSR: Phase transition success rate

QoF: Quality of life

RBC: Red blood cells

SAR: Survival after relapse

T1/2: Terminal half life

TCR: T cell receptor

TIL: Tumor-infiltrating lymphocytes

t-MNs: Therapy related myeloid malignancies

TSAs: Tumor surface antigens

TTNT: Time to next treatment

TTP: Time to progression

WBC: White blood cells

Glossary of terms

Endpoint	Definition
Adverse event	Any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment*.
Biomarkers	Characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention*.
Chemotherapy	Use of anti-cancer drugs injected into a vein, under the skin, into the cerebrospinal fluid, or orally, in order to destroy or control the growth of cancer cells. All chemotherapeutic agents are characterized by their ability to inhibit mitosis, or cell division.
Combination therapy	Refers to the simultaneous administration of two or multiple agents.
Complete remission	No detectable evidence of tumor **.
Disease-free survival	Time from randomization until disease recurrence or death from any cause **.
Duration of response	Time interval between the date of initial documentation of a response (partial response or better) and the date of first documented evidence of pharmacodynamics, death, or date censoring for the participants not progressed/died **.
Immunotherapy	Therapy that aims at boosting the activation of the immune system in order to target and eliminate malignant cells through natural mechanisms.
Minimal residual disease	Persistence or re-emergence of very low levels of cancer cells **.
Objective response rate	Percentage of patients whose disease decreased (Partial response – PR) and/or disappears (Complete response – CR) after treatment *.
Overall response rate	Proportion of patients with tumor size reduction of a predefined amount and for a minimum time period. Generally, the FDA has defined ORR as the sum of partial responses plus complete responses **.
Overall survival	Time from randomization until death from any cause **.
Progression-free survival	Time from randomization until objective tumor progression or death, whichever occurs first **.
Quality of life	Outcome self-reported by patients using wellness scales, presence of adverse effects and toxicity therapeutic*.
Targeted therapy	Therapy that exploits particular molecular characteristics that are unique to a specific tumor.
Terminal half-life	Time required for half of the drug to be eliminated from the serum*.
Time to next treatment	Time from end of primary treatment to institution of next therapy*.
Time to progression	Time from randomization until objective tumor progression **.

*Definition retrieved by *GlobalData*.

** Definition retrieved by **Food and Drug Administration. (2019). Clinical trial endpoints for the approval of cancer drugs and biologics guidance for industry.**

Bookmark: Reading guide

1 Introduction

About the CATO SMS enterprise, the internship formal framework, the project challenge

1. Introduction

1.1 CATO SMS at a glance

CATO SMS comes from the recent merger of two enterprises, SMS-oncology and CATO Research. SMS-oncology is a full-service contract research organizations (CROs) particularly dedicated to oncology. This company offers drug development advice and provides clinical development plans covering the complete chain of clinical studies, from the design and preparation to the conduct and completion of early and late phase studies. Its main area of expertise concerns early phase and immune-oncology studies. SMS-oncology clients, also called sponsors, include emerging small and mid-size biotech companies, as well as large pharmaceutical corporations and research groups and investigators. Since its foundation in 2007, SMS-oncology committed to excel in oncology trials; on October 28th 2019, SMS-oncology announced its merger with CATO Research. Cato Research is a full-service contract research organization dedicated to helping pharmaceutical and biotechnology companies to navigate the regulatory approval process to bring new drugs, biologics, and medical devices on the market. By joining forces, CATO SMS is now aiming to expand its presence across Europe and North America, to deepen its oncology and regulatory expertise, and to broaden its suite of services.

Figure 1.1 CATO SMS Headquarters (Amsterdam)

Full-service clinical & regulatory CRO

320+ employees

Offices & operations in Europe, N-America (US, CA), Israel, South-Africa

High performance culture

1.2 Mission of the company

CATO SMS mission is to contribute to the development of innovative cancer therapies that will benefit patients worldwide. CATO SMS has the ambition to grow and become the leading European oncology CRO by:

- Providing direction along the complex path of oncology drug development
- Being valued for its in-depth oncology expertise and high-quality services
- Nurturing a stimulating working environment

1.3 Project challenge

Novel therapy strategies for the treatment of hematological malignancies achieved extraordinary results in the recent years. Therefore, in the context of a recent outbreak of important achievements in the hematological community, CATO SMS aims to actively integrate blood cancer indications in its oncology portfolio. In order to do that, the company has the objective of being of top of the leading hematological anti-tumor therapies and to anticipate

future developments of the field. As a result, CATO SMS wants to develop an in-depth oncology drug development expertise for blood cancer indications and to provide expert advice to its sponsors in order to navigate the best way forward in the highly competitive hematological area.

1.4 Formal Framework

1.4.1 The internship

- The internship takes place in **the context** of the specialization in Science+ Business & Policy. This specialization track is part of the Master's degree in Biomedical Sciences at the University of Groningen (*Groningen, NL*), and encloses a strong focus on the unification of business aspects with (biomedical) scientific knowledge.
- **The main aim** is applying scientific expertise into enterprises and governing bodies.
- **The project** is commissioned by CATO SMS and specifically established and guided by the consultancy department, called Oncology Drug Development Affairs. The internship takes place in the period 15Jan2020 to 08Jul2020 for exactly 24 weeks.
- **The pursuit** is an integration of 60% scientific and 40% business aspects.
- **The end product** concerns strategic business advice exclusively addressed to CATO SMS with the ambition of uncovering insights in the field of hematological anti-tumor therapies in terms of drug development strategies.

1.4.2 The student

The project is performed individually by the intern Irene Vetrugno, currently a second year Master student at the University of Groningen (Groningen, NL), studying Biomedical Sciences and with a previous degree in Biotechnology (Milan, IT).

1.4.3 Supervision

The internship takes place under a threefold supervision (**Table 1**); Inka Pawlitzky (PhD), director of the Oncology Drug Development Affairs department at CATO SMS, acts as a daily supervisor. Dr. Bram Piersma, lecturer in the Science+ Business & Policy track at the University of Groningen, acts as a supervisor of Professional Training SBP. The scientific supervisor is Prof. Dr. Frank A.E. Kruyt, professor in the field of experimental oncology at the department of Medical Oncology, UMCG Groningen.

Name	Institute	Function	Role in supervision
PhD Inka Pawlitzky	CATO-SMS	Director of Oncological Drug Development Affairs	Daily supervisor
Dr. Bram Piersma	University of Groningen	Docent	SBP teacher
Prof. Dr. Frank A.E. Kruyt	University of Groningen	Docent	Science teacher

1.5 Central question

As already mentioned, with this project, CATO SMS aims to acquire insight into clinical trials and product development approaches covering specifically therapies used as

treatments of hematological tumors. The objectives of the company can be integrated into a unique research question:

"How should CATO SMS differentiate and develop strategies to implement the current leading hematological tumor therapies into their oncology portfolio?"

In order to derive an extensive and substantiated answer to this question, the approach method will rely on dividing the main question into different sub-questions:

- *What is the status of oncology and of hematological therapies in 2020?*
  Analyze the rising role of oncology and of hematological anti-tumor therapies in the recent years (**Chapter 3**).

- *How are clinical trials designed and conducted?*
  Describe the long and challenging road of biopharmaceutical drug development (**Chapter 4**).

- *What is the biologic background of blood cancer indications? What is the scientific rationale and mode-of-action of the hematological anti-tumor therapies?*
  Analyze how the anti-tumor therapies rapidly changed from 2014 to 2018 under the light of the increased knowledge of the pathology and development of blood cancers (**Chapter 5 & 6**).

- *How did the therapies landscape evolve in the past five years? What are the potential leading therapies for the future?*
  Identify recent trends in therapies and anticipate potential future directions for blood cancer treatments (**Chapter 7**).

- *What are the macroenvironmental factors that affect CATO SMS ambition to invest in this project?*
  Consider the political, economic, social, technological, ethical and legal factors that have an effect on the conduct of hematological malignancies clinical studies (**Chapter 8**).

- *How does the internal organizational structure of the company fit with CATO SMS ambition to start this project?*
  Perform an internal analysis in order to understand CATO SMS structure, core principles and business strategies (**Chapter 9**).

- *Does CATO SMS have sufficient previous experience in hematology?*
  Analyze the company's position and level of expertise in the hematological oncology area (**Chapter 10**).

- *What does CATO SMS need to acquire in order to prepare for the expansion of its hematological malignancies' portfolio?*
  Integrate the findings derived from the external and internal analyses and drive the final conclusions (**Chapter 11**).

- *How should CATO SMS proceed?*
  Formulate a feasible advice for CATO SMS and define potential future directions (**Chapter 12**).

2 Research Methodology

Approach method, analysis and reporting of data

2. Research Methodology

As already mentioned in the Introduction (Chapter 1), the main goal of this advice-report is applying scientific expertise into enterprises and governing bodies. The end result aims at offering an advice to CATO SMS in order to uncover significant insights in the field of hematological antitumor therapies. In order to solve the central question of the project, different sub-questions have been formulated. The strategy for approaching these tasks relies on an integration of 60% scientific aspects and 40% business aspects (**Figure 2**).

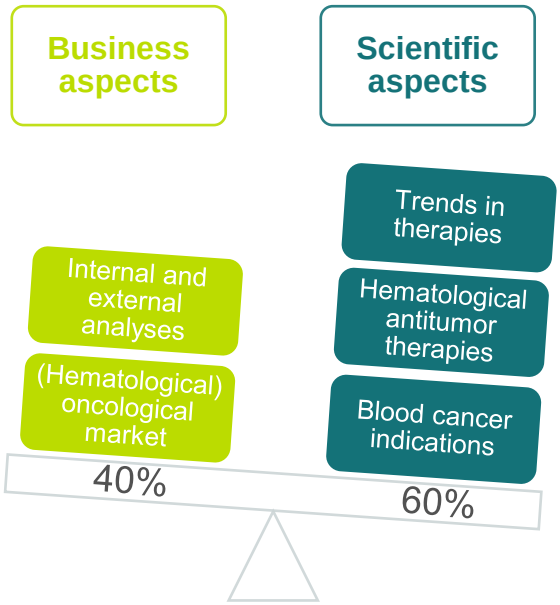


Figure 2. Integration of Scientific and Business aspects

2.1 Becoming an expert

Both the scientific and the business aspects are researched by performing an extensive literature analysis. This analysis includes an overview of business reports in order to depict the current situation of the (hematological) oncology market, specifically focusing on drug development and clinical trials. Furthermore, a literature research of scientific papers allows to acquire in-depth-knowledge about blood cancer indications and current anti-tumor treatments. In addition, internal oncology trainings organized monthly by internal and external specialists at CATO SMS offer direct experience on the field of oncology drug development and clinical trials.

2.2 Sources of data

One of the main sources of data is available at *GlobalData Plc. GlobalData* is a leading global provider of business intelligence in the healthcare industry. Thanks to its broad team of analyst and consultants, *GlobalData* can provide up-to-date information regarding the latest achievements in the field of drug development. (**Figure 2.1**).

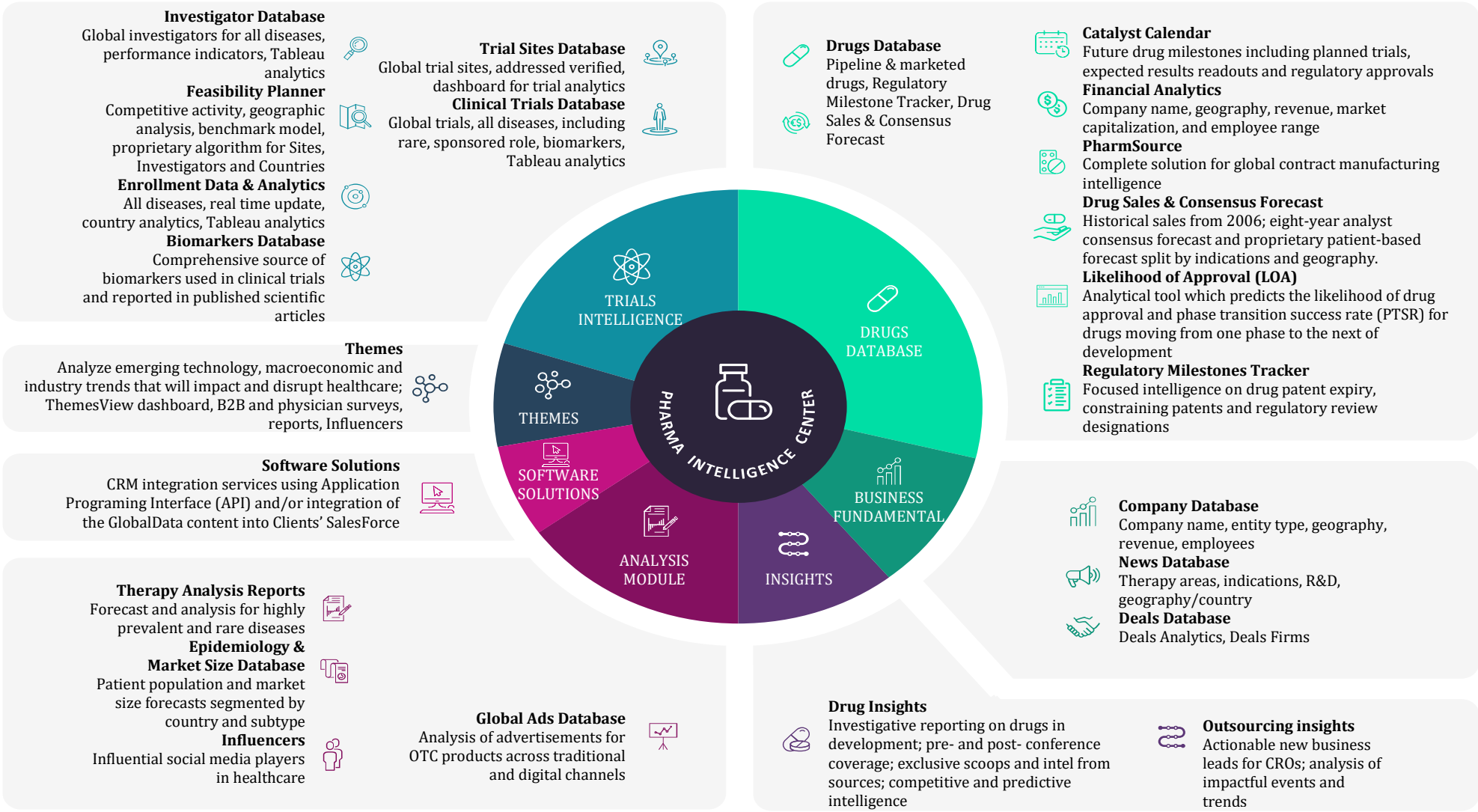


Figure 2.1 GlobalData services.

2.3 Inclusion criteria

In order to select and obtain reports on trials of interest, the database research on *GlobalData* is refined by search options and inclusion criteria:

- Therapy area
  Oncology
- Indication
  Blood Cancer (Leukemia: AML, CLL; Multiple Myeloma)
- Trial Start Date – Trial End Date
  Jan2014 – Dec2014
  Jan2015 – Dec2015
  Jan2016 – Dec2016
  Jan2017 – Dec2017
  Jan2018 – Dec2018
- Trial Phase
  Phase 0
  Phase I
  Phase II
  Phase III
  Phase IV
- Trial Status
  Ongoing, not recruiting
  Ongoing, recruiting
  Ongoing, recruiting by invitation

2.4 Analysis of data

The obtained trials are further analysed by their specific indication, and the different types of drugs were categorized according to:

- Molecule type
  Small Molecule
  Monoclonal Antibody; Bispecific Monoclonal Antibody; Monoclonal Antibody Conjugated
  Cellular Immunotherapy, Stem Cell Therapy
- Drug Descriptor
  Chemotherapy
  Stem Cell Therapy
  Targeted Therapy
  Immunotherapy

2.5 Reporting

Search refinement is determined and applied to selectively obtain an overview of the trials of interest. Data sheets are exported to and further analysed in Microsoft Excel.

3 Clinical Oncology

A comprehensive overview of clinical trial phases, an evaluation of the current status of therapies and recent advances in the hematological cancers area.

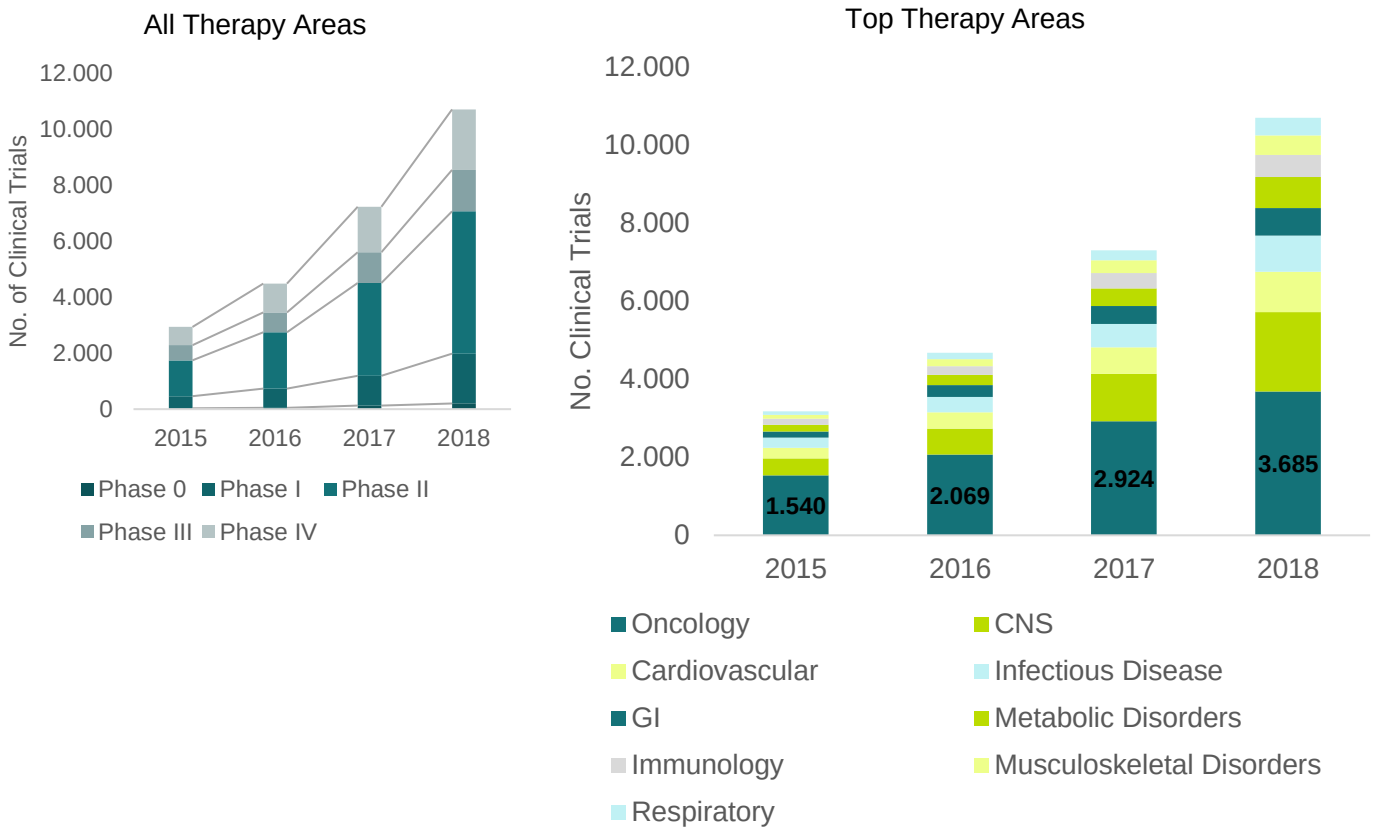
3. Clinical Oncology

> *What is the status of oncology and of hematological therapies in 2020?*
> Analyze the rising role of oncology and of hematological anti-tumor therapies in the recent years.

3.1 Oncology dominates the therapy market

The development of innovative medicines has evolved dramatically over the past decade. Recent advances in science, technology and data management gradually contributed to the improvement of clinical development, and lead to a shift with different impacts depending on the therapy area [1]. According to recent R&D trends, cancer is the top disease in terms of new drug development projects [2]. Oncology has been the leading field of the major therapy areas, and it is currently dominating the pharmaceutical industry as never before (**Figure 3**).

Figure 3. Oncology dominates the top therapeutic areas

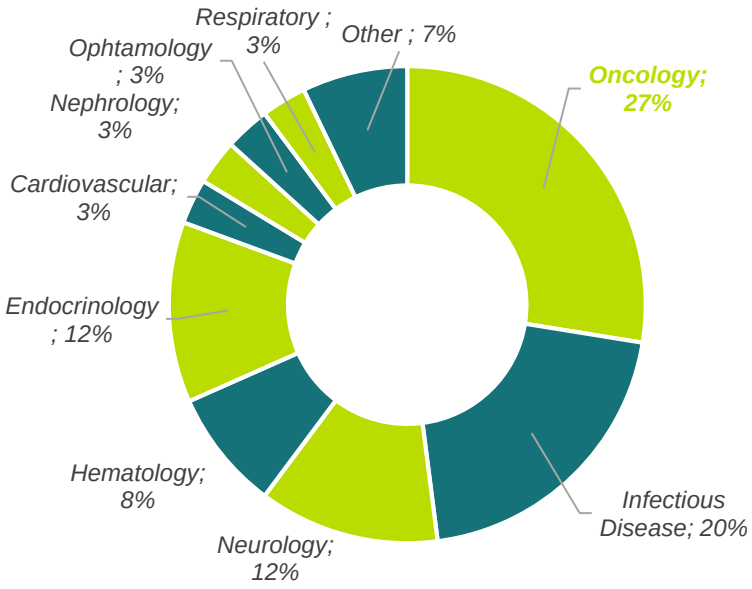


Over the past year, the therapeutic areas that received the biggest increase in activity are those focused on oncology. **Source: GlobalData.**

In the past years, a surprisingly high number of novel oncology drugs have been approved, giving hope to over 20 different tumor types that now have new potential treatment options [3]. In 2018, the oncology therapeutics constituted almost 30% of all innovative medicines launched during that year (**Figure 3.1**). In the same year, out of 711 companies working in

oncology late-stage development, 65% were emerging biopharma [4]. To date, successful oncology treatments have promised some of the highest returns for pharmaceutical manufacturers investments [5].

Figure 3.1. Oncology has the highest number of novel therapeutic launches



The number of new substances launched in 2018 was higher than in any of the past five years. Oncology differentiated itself with the highest number of launches [4].

3.2 The oncology landscape is more difficult and has lower success

Oncology presents high levels of pipeline activity; however, factors such as risk of failure and long trials duration make oncology as one of the most challenging area for research and development [4]. Barriers for approval of new drugs create remarkable difficulties, delaying patient benefit from treatment advances. **Figure 3.2** illustrates the central challenges faced in oncological R&D.

Figure 3.2. Oncology is the one of the most challenging areas for R&D

Oncological clinical trial activity is high-risk

The success rate associated to oncological clinical trials completion fell from 11.7% to 8.0% in 2017 - 2018 [4]. In addition, clinical trial duration for oncological studies has declined over the years, but it still remains higher compared to other therapeutic areas.

The R&D spending for oncological drugs is on rise

The costs required by the oncology care are far higher compared to the treatment costs of any other disease, in terms of expenditure for diagnosis, surgery, hospitalization, and palliative end-of-care. It has been estimated that oncology spend has risen by 53% from 2015 to 2020.

Oncology is characterized by an intense competition

Multiple manufacturers studying similar therapeutic mechanisms of action create an intense competitive landscape. This aspect confers limitations on the depths of market penetration expected with the development of these therapies. These factors, in combination with an environment requiring increasing R&D spending, threaten profitability [5].

Personalized medicine reduces the patients eligibility for anti-tumor treatments

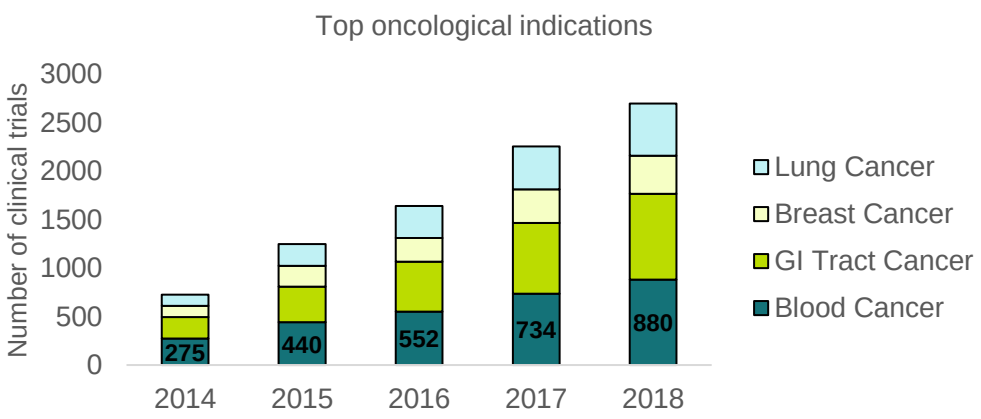
A dramatic reduction in eligible patients populations for novel treatments is caused by the therapeutic revolution in the oncological field brought by personalized medicine. Despite being one of the greatest trends that provide substantial patient benefits, personalized medicine comprises labels that are suitable only for highly-responding patients.

Factors that lead to a high competitivity in the oncological area.

3.3 Hematology is the leading area

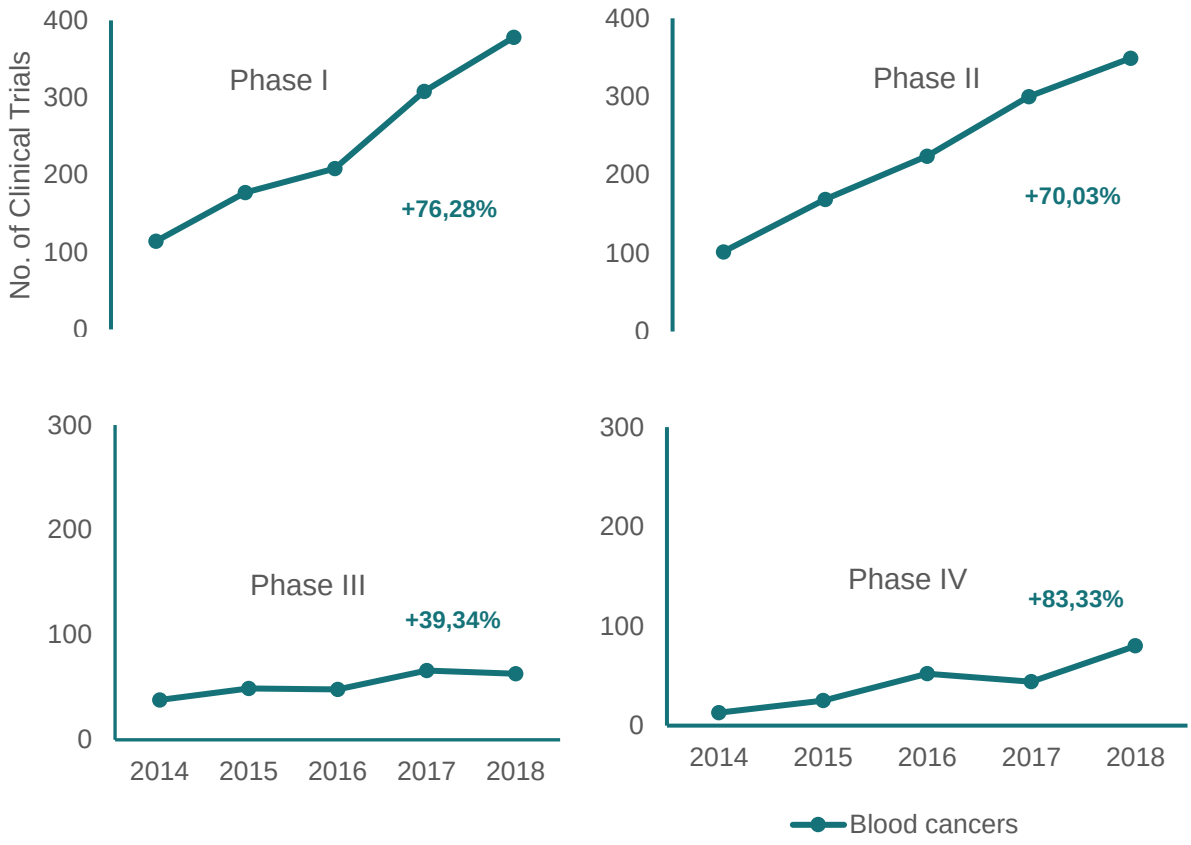
In 2018, remarkable advances in understanding the underlying cause and progression of blood cancer diseases, gave rise to new potential opportunities for novel therapeutic treatments. Novel drugs for the treatment of non-solid tumors – leukemia, lymphoma and myeloma – constituted almost one-third of all approved indications [4]. The number of clinical trials dedicated to hematological indication reached a record number of 880 clinical trials in 2018 (**Figure 3.3**). Moreover, hematology was the area that saw one of the biggest improvements in all clinical trials phases, from phase I to phase IV (**Figure 3.4**). Finally, in the recent years, hematological indications outplaced the most common cancers for survival rates. Lymphoma reached 71% of survival rate in the USA [6] (**Figure 3.5**). A detailed description about hematological clinical trials will be offered in the following chapter.

Figure 3.3. Hematology takes the lead for oncological clinical trials



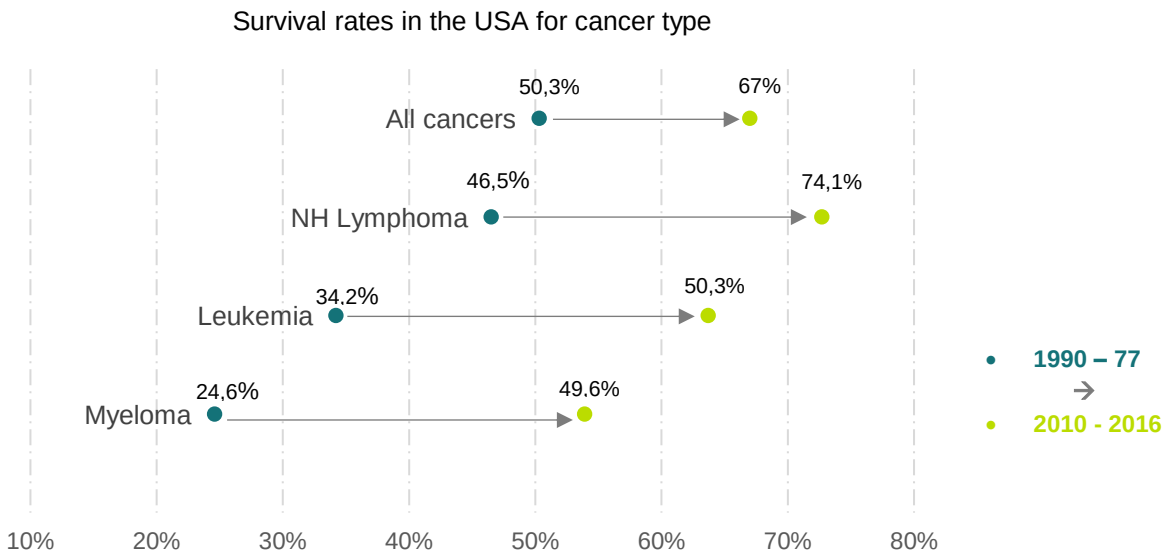
The number of blood cancer clinical trials increased from 275 in 2014 to 880 in 2018, leading the hematological malignancies area to constitute almost 33% of all oncological clinical trials. **Source: GlobalData**.

Figure 3.4. Blood Cancer clinical trials improve in all phases



In the past five years, drug development for the treatment of blood cancer indications saw an unprecedented growth in all the different phases (Phase 0 – Phase IV). Phase IV trials saw the biggest improvement, with an increase of ***+83,33****%. In addition, drugs in development phases (Phase I and Phase II) expanded significantly (****+76,28%*** *and +****70,03%*** *respectively). Finally, Phase III was the one that saw the smallest increase (****+39,34%****).* **Source: GlobalData**.

Figure 3.5. Blood Cancer survival rates significantly increased over time



Since the early 1990s, progress in 5-year survival for the most common blood cancers, outplaced other cancers such as colon, ovary, stomach and brain cancers (not shown here). The biggest increase in survival was for NH lymphoma, followed by leukemia and multiple myeloma [6], [7].

3.4 Conclusions – Chapter 3

The purpose of this chapter was to illustrate the main role that oncology played in the past years and the rising importance of hematology.

- Oncology is the leading area for new drug development projects, with a record of 70 new oncology treatments that have been launched in the past five years.
- Oncology is still considered as one of the most challenging areas for research and development, due to a high-risk clinical trial activity, expensive R&D associated costs and low level of patients eligibility.
- Hematology represented the leading area for oncological treatments in 2018.
- In the past five years, drug development for hematological indications saw an unprecedented growth in all the different phases of clinical studies, from phase I to phase IV.
- These progresses led to an increase of blood cancer survival rates.

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4 Clinical Trials

The long road of biopharmaceutical drug development

4. Clinical Trials

> *How are clinical trials designed and conducted?*
> Describe the long and challenging road of biopharmaceutical drug development.

4.1 The biopharmaceutical drug development

A novel therapeutic agent has to face a long and arduous travel from inception to commercial availability. The development process typically costs a pharmaceutical or biotechnology company an estimated $1 billion and it usually takes from 10 up to 15 years to be completed [1]. Moreover, apart from being costly and time consuming, the development of therapeutics has also high attrition rates. In order to be approved, a drug must show efficacy and acceptable toxicity in both preclinical and clinical trials. The licensing and approval for marketing of an agent is a role appointed to specific regulatory bodies. Out of every 5,000 new compounds identified during the discovery process, approximately only five are considered safe for testing in human volunteers after preclinical evaluation. After years of further clinical testing in patients, only one of these compounds on average is ultimately approved as a marketed drug (**Figure 4**). By definition, a clinical trial is a research study conducted in patients, with patients and for patients, to answer specific questions about their treatment diagnosis or follow-up. Clinical trials – also called interventional studies – are used to determine whether new biomedical or behavioral interventions are both safe and effective for patients in treating their disease [2]. Drug development undergo a structured sequence of four different phases ensuring safety and aiming at a therapeutic progress.

Phase I

During phase I, pharmacokinetics and pharmacodynamic measures are assessed in detail in order analyze safety and tolerability of the candidate drug [3]. They typically can take from six up to nine months. A small number of subjects, usually from 20 to 100 volunteers, are recruited to test the drug for short periods of time. Analyses are conducted in order to describe how the investigational drug acts in the body – the way it is absorbed, distributed, metabolized and excreted. Repeated dosing protocols are explored to determine the maximum tolerated dose in consecutive cohorts of individuals [1].

Phase II

Clinical studies in this phase are designed to determine the effectivity and to further assess the safety of the candidate drug in several hundred patients. Selected doses and regimens are compared to placebo or standard treatment, in a randomized, double-blind manner [1]. Confirmation of the appropriate dose is then used to support drug registration. Depending upon the type of investigational drug and the conditions of testing, this phase of development can take from six months up to three years.

Phase III

Phase III trials are important to prove the investigational agent efficacy and safety in larger number of subjects (up to several thousand patients). In these studies patients are randomized between an established standard therapy and a novel therapy that resulted promising in the phase II setting. These studies are usually multi-institutional involving large national and international cooperative groups [3].

Phase IV

This stage involves post-marketing surveillance in order to assess any unexpected adverse events or toxicity caused by the medication. Late-stage drug development studies of approved, marketed drugs may continue for several months up to several years.

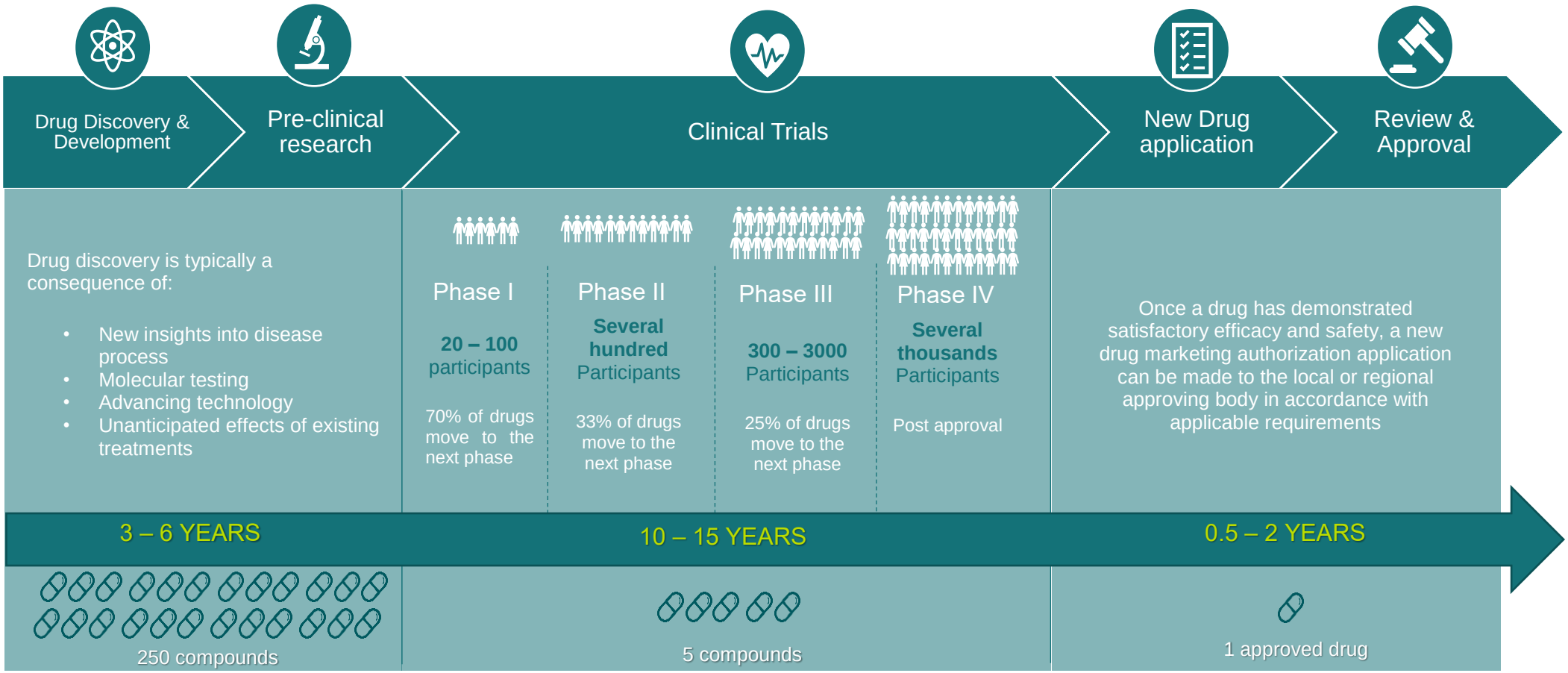


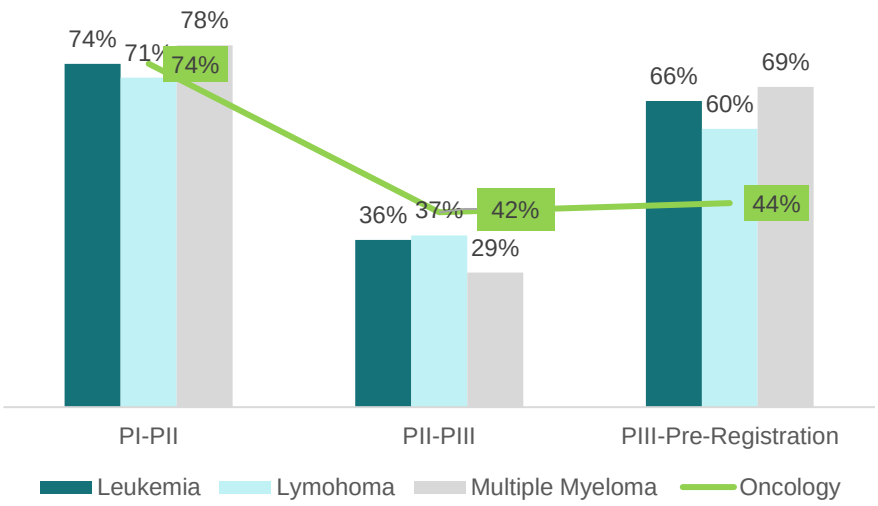
Figure 4. The long path of drug development. Adapted from Janssen EMEA [4].

4.2 Clinical Development Success Rates

Within the past two decades, clinical research has expanded globally and became more complex. Every year, a number of novel drugs are evaluated based upon the safety and efficiency data provided by sponsors running clinical trials all over the world. These innovative new products offer potential new treatments to multiple therapeutics areas, involving hundreds of clinical trial sites and tens of thousands of people globally. Compared to other therapeutic areas, clinical trial duration remains higher for oncology trials. However, trial duration has declined over the years [5]. Moreover, the average number of patient-years included in trials has been declining. This factor is due to an increasing number of specialty drugs, such as niche and orphan drugs, which typically require a fewer subjects in the clinical testing and have shorter trial durations [6].

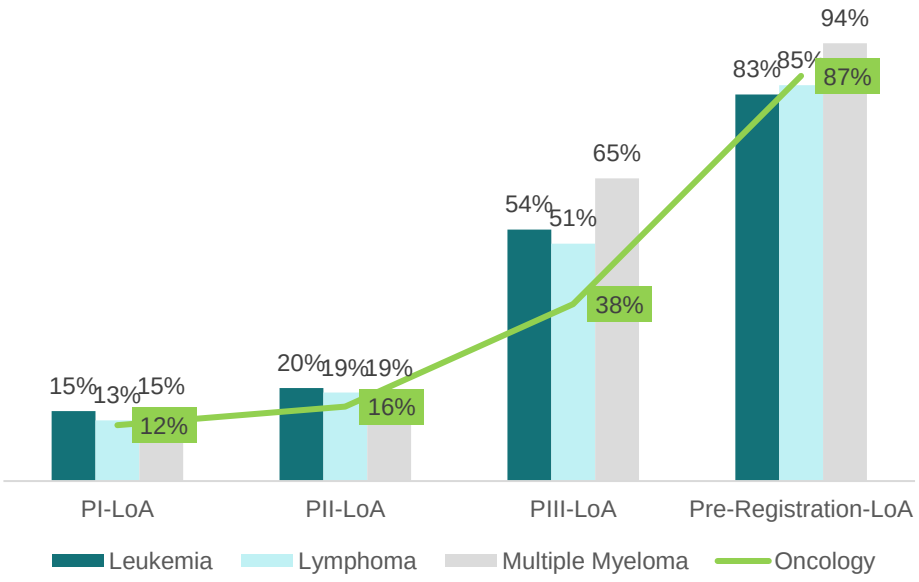
Interestingly, the phase transition success rate (PTSR) and the likelihood of approval (LoA) for hematological malignancies clinical trials look more encouraging compared to other oncological indications (**Figure 4.1** and **Figure 4.2**). PTSR and LoA determine the probability of success of a clinical trial, which is an important variable for clinical researchers and biopharma investors that need to take scientific and economic decisions.

Figure 4.1. PTSR is higher for hematological malignancies clinical trials



*Phase transition success rate (PTSR) for hematological malignancies clinical trials is higher compared to other oncological indications. The highest rate of approval between phase I and phase II is represented by multiple myeloma (**78%**), followed by leukemia (**74%**) and lymphoma (**71%**). Phase II-phase III transition is the only stage where oncology exceeds blood cancer indications (**42%**). Finally, phase III - phase IV transition for hematological malignancies clinical trials is on average 20% higher compared to other oncological indications, with a maximum of **69%** success rate for multiple myeloma. Phase I transition success rate is typically higher since phase I clinical trials are conducted for safety testing and therefore are not dependent on efficacy results for candidates to advance. Phase II – phase III has the lowest success rate of all phases. Indeed, this is the point in development where sponsors evaluate whether to initiate a large and expensive phase III study. Finally, the second lowest phase transition success rate is represented by phase III- phase IV transition. Usually, phase III trials are the longest and more expensive trials to conduct.* **Source: GlobalData.**

Figure 4.2. LoA is significantly higher for hematological malignancies clinical trials



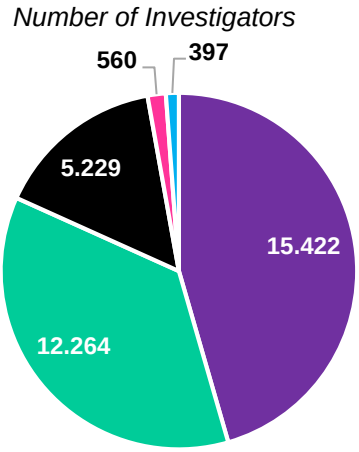
*Likelihood of approval (LoA) is remarkably higher for hematological malignancies clinical trials compared to other oncological indications. The higher the phase reached prior approval, the higher the probability of approval of the drug under development. The greatest value is represented by multiple myeloma clinical trials in pre- registration phase (**94%**), followed by lymphoma (**85%**) and leukemia (**83%**).* **Source: GlobalData**.

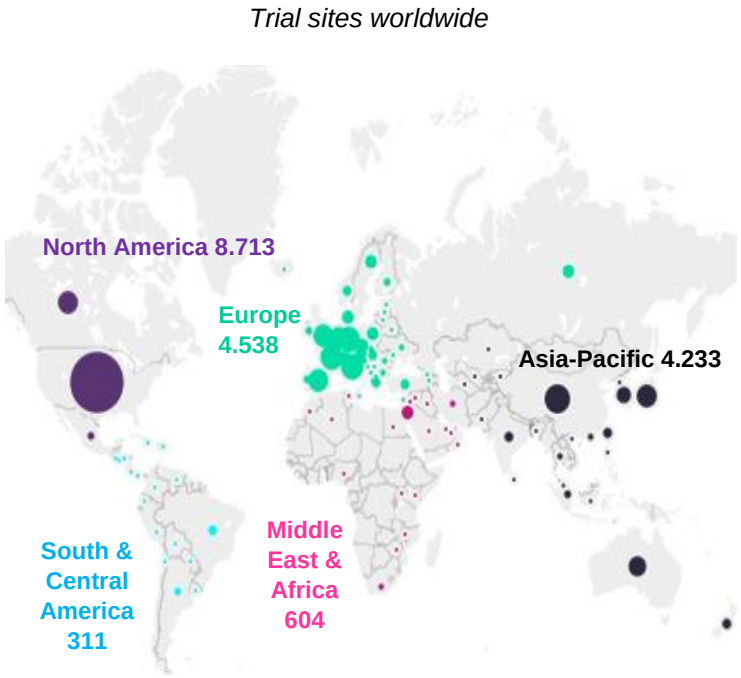
4.3 Clinical Trials analysis by country

An analysis of hematological malignancies clinical trials was performed on *GlobalData* for different countries. As key findings, North America accounts for the highest number of hematological malignancies clinical trials and for the most elevated number of investigators conducting studies on blood cancers (**Figure 4.3**). However, Asia-Pacific records the fastest growth rate for hematological anti-tumor therapies, for both development and late phases (**Figure 4.4**). North America is also the country with the greatest amount of blood cancer trial sites worldwide, and France in Europe (**Figure 4.5**).

Figure 4.3. Investigators and Hematological malignancies Clinical Trials by country

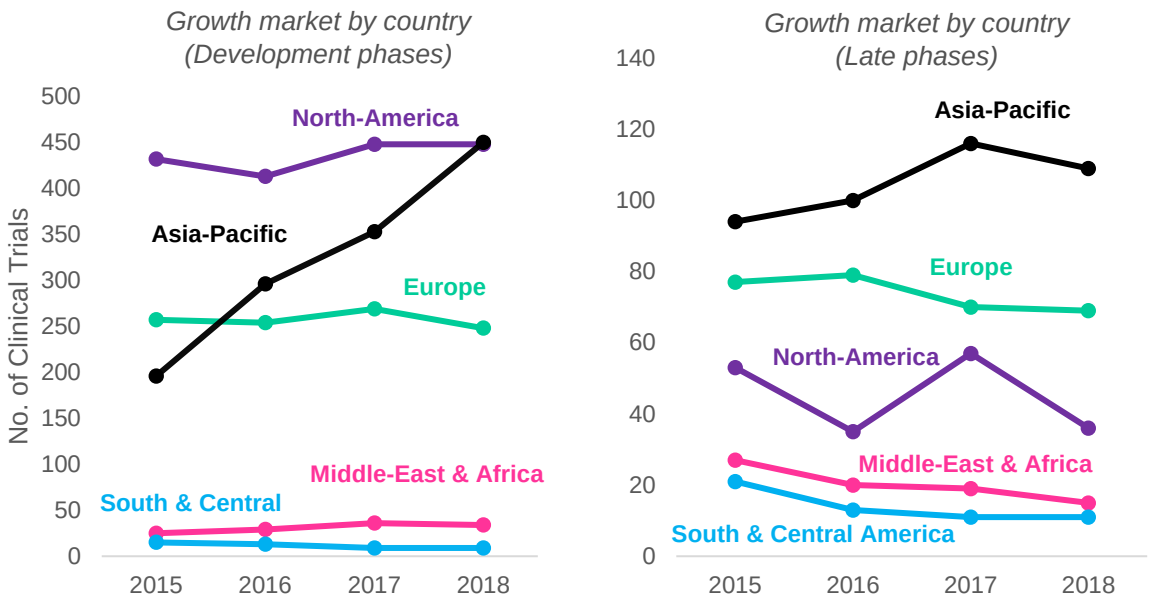
- North America
- Europe
- Asia-Pacific
- Middle East & Africa
- South & Central America





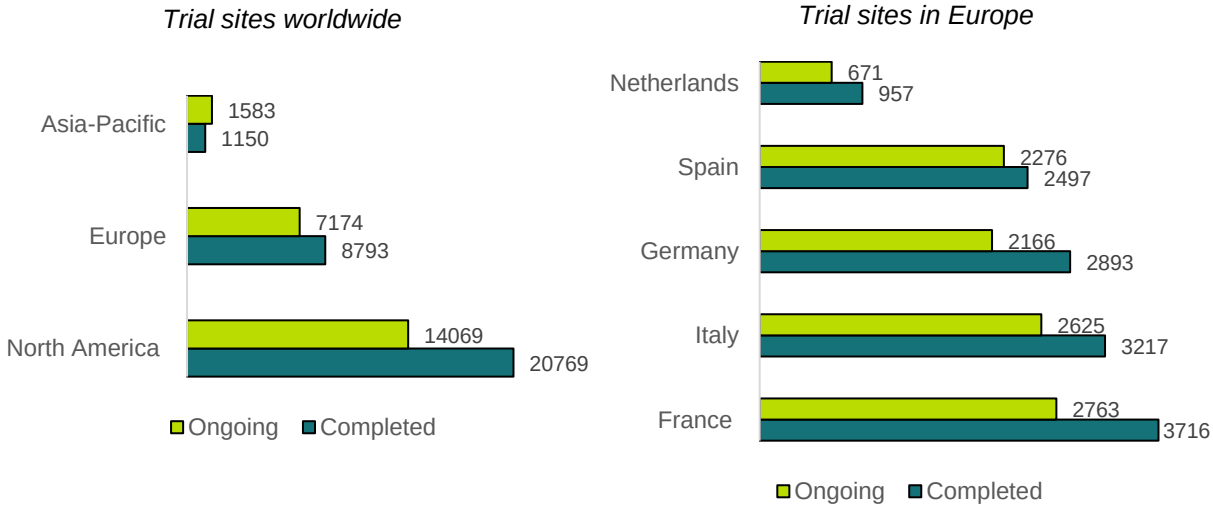
***Pie chart**: North America is the country with the highest number of investigators involved with hematological malignancies (**15.422**), followed by Europe (**12.264**) and Asia-Pacific (**5.229**). **Geographical map:** North America is also the country that account for the highest number of clinical trials (**8.713**), followed by Europe (**4.538**) and Asia-Pacific (**4.233**). **Source: GlobalData**.*

Figure 4.4. Hematological malignancies market growth



North America took the lead for hematological malignancies clinical trial in development phases (phase 0, phase I, phase II). However, Asia-Pacific saw an unprecedented growth in the number of clinical trials, reaching almost 450 clinical trials in 2018. Asia Pacific is also the country with the highest number of late phases clinical trials (phase III and phase IV) for the treatment of blood cancers. Europe saw a decrease in both development and late phases. **Source: GlobalData.**

Figure 4.5. Trial sites for the treatment of blood cancers worldwide and in Europe



North America accounts for the highest number of trial sites for the treatment of blood cancers. In Europe, France is the top country, followed by Italy, Germany, Spain and finally Netherlands. **Source: GlobalData.**

4.4 Conclusions – Chapter 4

- The arduous drug development path comprises a sequence of clinical studies ensuring safety and aiming at a therapeutic progress. This process usually costs a biopharmaceutical company an estimated value of $1 billion and it usually takes an average of 10 to 15 years.
- Compared to other therapeutic areas, clinical oncological studies have the highest duration. However, the average number of patient-years included in clinical studies has been decreasing.
- PTSR for hematological malignancies clinical trials is higher compared to other oncological indications. The highest rate of approval is achieved between phase I and phase II. Phase II – phase III has the lowest success rate of all phases.
- LoA is remarkably higher for hematological malignancies compared to other oncological studies. The greatest value is represented by multiple myeloma clinical trials in pre- registration phase.
- North America accounts for the highest number of hematological malignancies clinical trials and for the most elevated number of investigators conducting studies on blood cancers. In Europe, France is the top country for number of trial sites.

4.5 References

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5 Hematological Malignancies

An overview of the main blood cancer indications

5. Hematological Malignancies

> *What is the biologic background of blood cancer indications?*
> Define pathogenesis, underlying causes, and progression of the diseases.

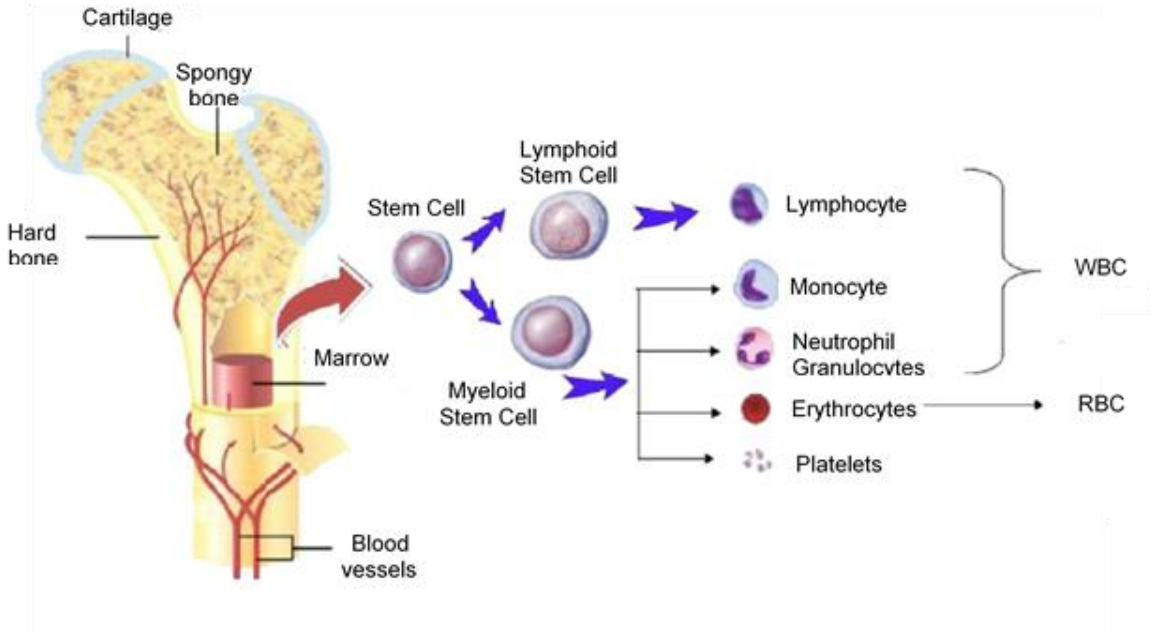
5.1 Introduction

The current chapter aims at providing an extensive overview of hematological malignancies indications, including their pathogenesis, incidence rate and genomic associated mutations. Three specific indications (acute myeloid leukemia, chronic lymphocytic leukemia and multiple myeloma) will be thoroughly analyzed. Acute myeloid leukemia is the most common leukemia in adults and it is the indication that constituted the majority of previous hematological malignancies projects at CATO SMS (refer to Chapter 10). Chronic lymphocytic leukemia has been recently considered as one of the most dynamic fields in clinical research, due to a therapeutic landscape that is constantly changing. Multiple myeloma is still an incurable disease and it constitutes the minority of hematological malignancies projects conducted at CATO SMS.

5.2 The field of Hematological Malignancies

Hematology is a branch of medicine concerning the study of blood, the blood-forming organs, and blood diseases. The word "*heme*" comes from the Greek for blood. More precisely, hematology refers to the study of the hematopoietic system. All cellular blood components are derived from hematopoietic stem cells (HSCs) through the hematopoiesis process (**Figure 5**). HSCs reside in the medulla of the bone (bone marrow) and have the unique ability to give rise to all the different mature blood cell types: erythrocytes (red blood cells), myeloid and lymphoid leukocytes (white blood cells) and megakaryocytes (which produce platelets).

Figure 5. Inside the bone marrow



During the hematopoiesis process, stem cells in the bone marrow give rise to red blood cells (RBC), white blood cells (WBC) and platelets.

The early history of blood cancer rates back 200 years. In 1845 John Bennet, a Scottish physician, described in his manuscript an examination of a young patient with hypertrophy of the spleen and liver [1]. Bennet noticed at autopsy that in the patient's blood there were present white blood cells densely packed; however, he could not detect any sign of infection (**Figure 5.1**). Bennet was the first physician that recognized that the accumulation of leucocytes in the blood was related to a systemic blood disorder. A little while later, Rudolf Virchow was the first one to name this disease as 'leukamie', from the Greek word *leukos* (white), which is still used nowadays [2]. The field of hematology had greatly increased since the first description of leukemia by Bennet and Virchow in the 19th century. It now includes additional disease of the bone marrow, such as multiple myeloma, myeloproliferative neoplasms and myelodysplastic syndrome, as well as disease that originate in the lymph nodes (Hodgkin's lymphoma and non-Hodgkin's lymphoma).

Figure 5.1. Bennet's colorless blood corpuscles described in his manuscript in 1845

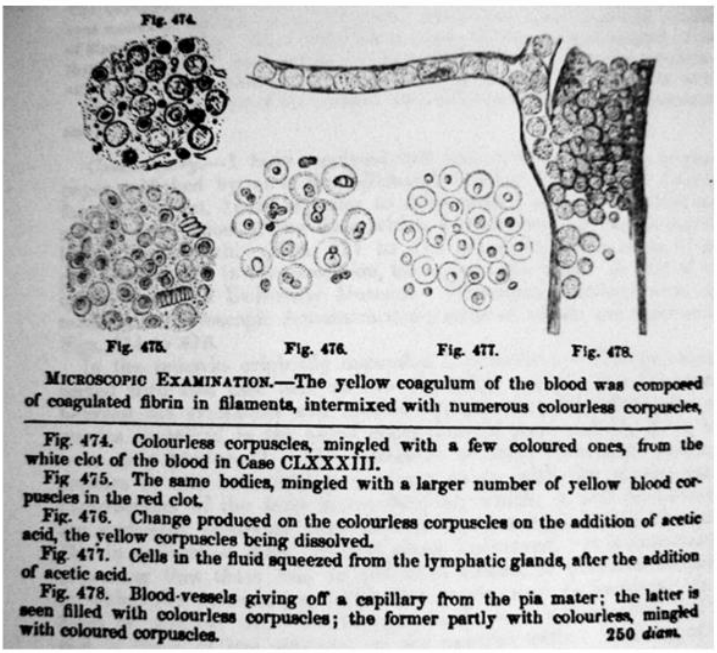


Fig. 474. Fig. 475. Fig. 476. Fig. 477. Fig. 478.

MICROSCOPIC EXAMINATION.—The yellow coagulum of the blood was composed of coagulated fibrin in filaments, intermixed with numerous colourless corpuscles,

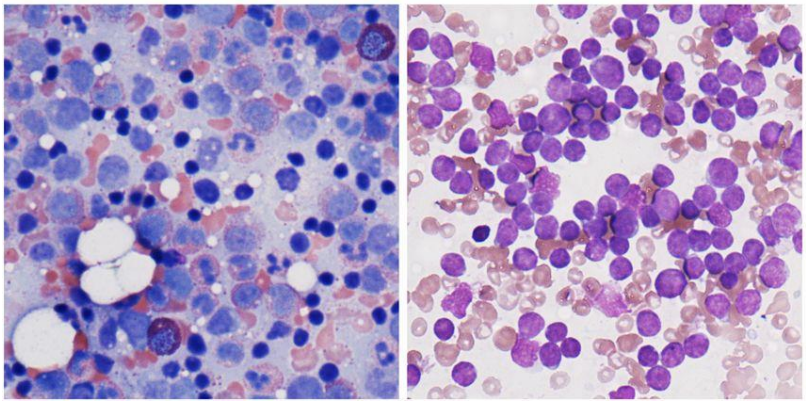
Fig. 474. Colourless corpuscles, mingled with a few coloured ones, from the white clot of the blood in Case CLXXXIII.
Fig. 475. The same bodies, mingled with a larger number of yellow blood corpuscles in the red clot.
Fig. 476. Change produced on the colourless corpuscles on the addition of acetic acid, the yellow corpuscles being dissolved.
Fig. 477. Cells in the fluid squeezed from the lymphatic glands, after the addition of acetic acid.
Fig. 478. Blood-vessels giving off a capillary from the pia mater; the latter is seen filled with colourless corpuscles; the former partly with colourless, mingled with coloured corpuscles. 250 *diam.*

Bennet was the first one to recognize an association of the corpuscles accumulation in the circulatory system with a systemic disease of the blood.

5.3 Leukemia

Leukemia is a malignant proliferation of abnormally differentiated leukocytes in the blood. The disease originates in the bone marrow, from where it spreads to the blood and subsequently to other tissues. Leukemia manifests in different forms, including a chronic and indolent form, termed chronic leukemia, and the more aggressive form known as acute leukemia. The disease is caused by a malignant transformation of hematopoietic stem cells that acquire successive genomic alterations. These alterations, besides allowing stem cells to proliferate at an uncontrolled pace, consequently induce an arrest of normal cell maturation. This process leads to an accumulation of immature, rapidly expanding cells, also known as blasts [3] (**Figure 5.2**). Due to their inability to mature, these cells cannot fulfill their normal function in fighting microbes. Therefore, patients affected by leukemia are exposed to an increased risk of infections.

Figure 5.2. Normal bone marrow vs acute leukemia



*Normal bone marrow (**left**) contains hematopoietic cells in the various stage of maturation. Bone marrow of a patient with leukemia (**right**) is filled with monotonously appearing large leukemic blasts*.

5.3.1 Acute Myeloid Leukemia (AML)

Introduction

The clonal and abnormal proliferation of blood cells coming from the myeloid lineage is considered as the main cause of acute myeloid leukemia (AML). These immature cells, called blasts, infiltrate the bone marrow, blood and other tissues, causing an impairment of normal hematopoiesis. This process is the cause of severe infections, anemia, and hemorrhage **[4]**. Acute myeloid leukemia is considered as the most common type of leukemia in adults **[5]**. Unfortunately, for several decades, patients affected by AML saw few therapeutic advances available for the treatment of their disease. However, in 2017 an unprecedented growth in the therapeutic armamentarium for the treatment of AML was registered, and great achievements in understanding the biological and genomic background of the disease have been made since then **[4]**.

Epidemiology

AML is a disease that can occur in any age group. However, it usually characterizes older patients, with a median age at diagnosis of 68 years. The incidence of AML is rising, due to the aging of the population and to an increasing number of patients affected by cancer treated with cytotoxic chemotherapy **[6]**. People are predisposed to this disease by several genetic and environmental risk factors, such as germline predisposition. However, the majority of the patients still do not show clear predisposing factors for the development of AML **[7]**.

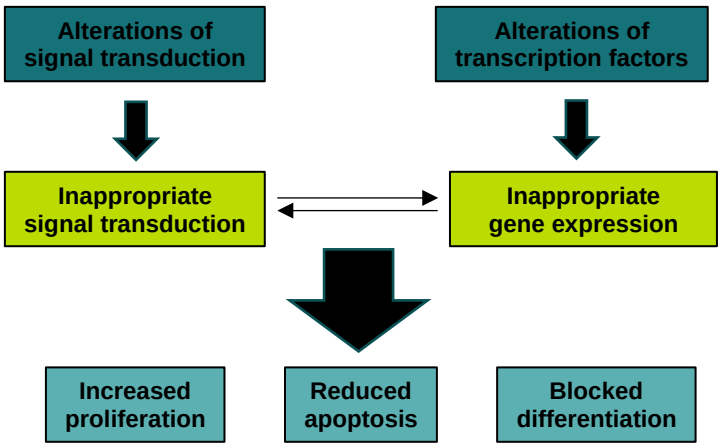
Pathogenesis

During the last years, the molecular pathogenesis of AML has been better understood thanks to the advances achieved with genomic analyses. Indeed, the oncogenic transformation of hematopoietic stem cells is now believed as the leading cause for the development of AML [8]. Leukemic stem cells with self-renewing capacity are capable of resisting to cytotoxic chemotherapy, driving relapse of the disease [9]. Further genetic events cause karyotype abnormalities and heterogeneity, with different competing clones detected at the diagnosis time [10]. Different subtypes of AML may have different pathogenesis, and therefore it hasn't been identified a singular model of pathogenesis for all cases of AML yet **[11]**.

Genomics

Response to therapy and the eventual risk of relapse of the disease are influenced by the molecular heterogeneity of mutations [12]. Identifying the interaction behaviors of these mutations that determine the disease phenotype and response to therapy is a priority of current research [13]. It has been reported that 96% of patients present at least one driver mutation, and two or more driver mutations are present in 86% of patients [14]. The investigation of new potential targets for AML targeted therapies focuses on these driver mutations (refer to Chapter 6) [15]. Specific mutations occur early in leukemogenesis providing a selective advantage for stem cells clonal expansion. Moreover, most AML-typical chromosomal alterations cause fusion genes involving signal transduction mediators and transcription factors important for myeloid differentiation [11]. These alterations lead on the one hand to an inappropriate signal transduction, and on the other hand to an inappropriate gene expression (**Figure 5.3**)

Figure 5.3 Different molecular alterations contribute to the development of AML



Alterations of signal transduction and of transcription factors may drive the development of AML. These alterations cause an inappropriate signal transduction and inappropriate gene expression. Both mechanisms together contribute to the pathogenesis of AML by inducing increased proliferation, reduced apoptosis and blocked differentiation. **Adapted from Steffen et al., 2005 [11].**

Furthermore, mutations of epigenetic factors such as DNMT3A, TET2, and ASXL1 are considered as the fundamental events that lead to the malignant transformation [16], [17]. As already mentioned, in some cases the genotoxic effects of chemotherapeutic treatments may lead to the development of AML. Patients that develop AML due to the effects of cytotoxic chemotherapy represent 10% of AML cases [6].

5.3.2 Chronic Lymphocytic Leukemia (CLL)

Introduction

Chronic Lymphocytic Leukemia (CLL) is a disease that primarily affect elderly patients, and it is reported as the most common type of leukemia in developed countries [18], [19]. Advanced targeted therapies have been developed thanks to remarkable progress in understanding the molecular mechanisms involved in the pathogenesis of the disease.

Epidemiology

CLL is the most common type of leukemia in western countries. More than 15000 newly diagnosed cases and approximately 450 deaths are currently estimated [18]. This type of leukemia predominantly affects the older populations, with the median age at diagnosis being 72 years old. More male than female patients (1.7,1) are affected [20]. As the incidence rate

rises with age, the prevalence and mortality of CLL are likely to further increase due to the demographic increases in society in the forthcoming decades (refer to Chapter 8) [18].

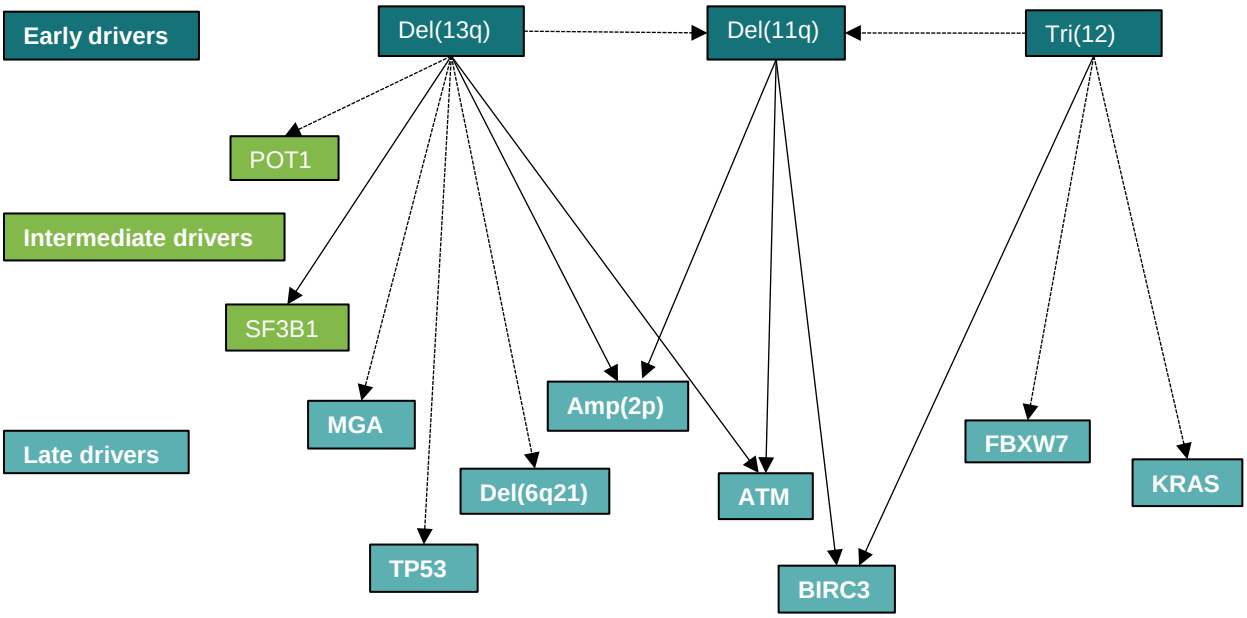
Pathogenesis

Differentiated and often CD5- positive B cells clonally proliferate and accumulate in a number of organs – bone marrow, lymph nodes and spleen [21]. As for what regards AML, also in CLL primary mutational events might involve hematopoietic stem cells with a self-renewing capacity [18]. Despite the strong inherited predisposition of CLL [22], a limited number of risk factors have clarified the development of CLL [23].

Genomics

Comprehensive genomic analyses showed that karyotypic abnormalities initiate the leukemic transformation in most patients affected by CLL (**Figure 5.4**). The aggressivity of the disease may be increased by the loss or addition of chromosome material followed by later additional mutations [24].

Figure 5.4. Genetic drivers of CLL



Deletion of chromosome 13q and acquisition of chromosome 12 constitute the majority of early drivers of mutational events for the development of CLL [18]. Other aberrations comprise deletion of chromosome 13q and deletion of chromosome 17p. Deletion of chromosome 13q may cause the loss of miRNAs; deletion of chromosome 11q drives the deletion of the ATM gene, an important factor involved in DNA damage [26]. The majority of deletions of chromosome 17p causes additional mutations in the TP53 allele [27]. Other important somatic mutations involve NOTCH1, XPO1, KLHL6, MYD88 and SF3B1 [28]. A permissive microenvironment also play an important role in CLL development, by favoring clonal expansion and therapy resistance [29]. **Adapted from Hallek M. et al., (2018) [21].**

5.4 Multiple Myeloma

Introduction

Multiple myeloma is characterized by an uncontrolled proliferation of plasma cell clones in the bone marrow. Subsequently, it is followed by the secretion of monoclonal immunoglobulins [30]. MM usually is associated with end-organ damage that can include lytic bone lesions, anemia,

immunodeficiency, and decreased renal function. MM continues to be considered as an incurable disease, but the median survival has increased from three to over six years [31]. Ongoing research is focusing on investigating the interactions between tumor cells and the bone marrow niche. This interaction has a fundamental role for disease progression and therapy resistance.

Epidemiology

Multiple myeloma (MM) can lead to severe clinical features such as anemia, lytic bone lesions, hypercalcemia, and renal disease [32]. This indication affects approximately 4 in every 100000 individuals in Europe [33]. African Americans are the most affected population, with an incidence two to three times higher in this ethnic group [30]. The median age at diagnosis is 69 years, with the majority of patients being men [34]. Response to anti-MM therapies are still variable. Although some treated patients survive progression-free for more than 10 years [35], approximately 10% die within 1 year of diagnosis [36], [37]**.** Furthermore, most patients relapse and usually die of refractory disease because there is currently no effective cure [38], [39].

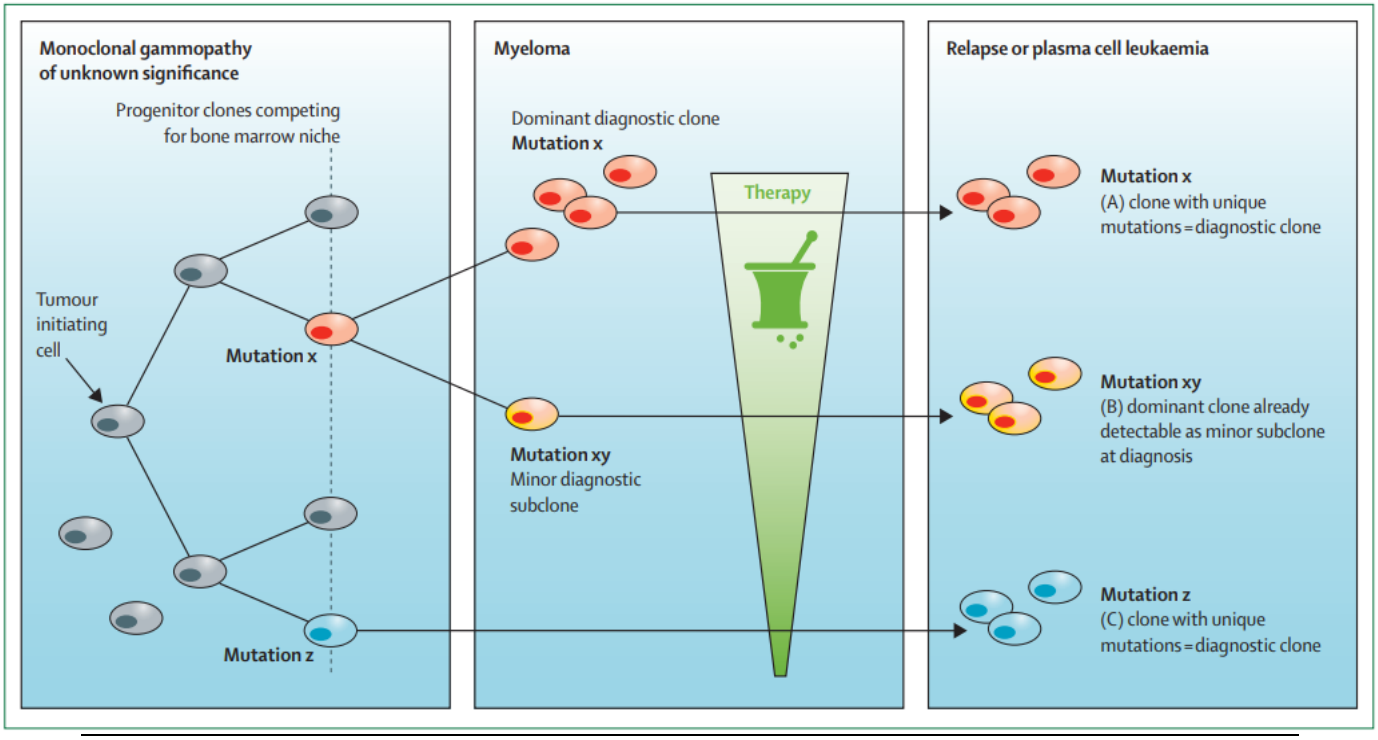
Pathogenesis

Multiple myeloma cells are characterized by a strong bone marrow dependence and interaction, and by an extensive somatic hypermutation of Ig genes often causing an absence of IgM expression [31]. Moreover, MM cells have the potential to retain a lower proliferative state compared to healthy plasma cells. As already mentioned, current research for the treatment of multiple myeloma is focusing on investigating the interaction between malignant cells and their bone marrow niche, especially on cell-cell and cell-matrix interactions, growth factors and cytokines. The bone marrow transforms into a tumor-promoting and immune-suppressive microenvironment thanks to the interactions between MM cells and surrounding cells [40]. The therapies that are currently implemented for the treatment of other hematological malignancies, such as stem cell transplantation, don't have the same outcomes in the clinical management of multiple myeloma. Novel high-resolution genomic studies have revealed that tumors like multiple myeloma are composed by clonally diverse groups of tumor cells showing an enormous genetic heterogeneity [30] (**Figure 5.5**).

Genomics

About 40% of cases present chromosome translocations resulting in overexpression of genes such as CCMD1, CCND3, MAF, MAFB, WHSC1 and FGFR3 [41]. Other cases exhibit hyperdiploidy. However, these abnormalities alone are probably not sufficient for malignant transformation because they are also observed in the pre-malignant syndrome known as monoclonal gammopathy of uncertain significance (MGUS). Malignant progression events include activation of MYC, FGKR3, KRAS and NRAS and activation of the NF-kB pathway [42]. In addition to that, loss-of-function mutations in the histone demethylase UTX have also been reported [43].

Figure 5.5. Clonal composition of MM during disease progression

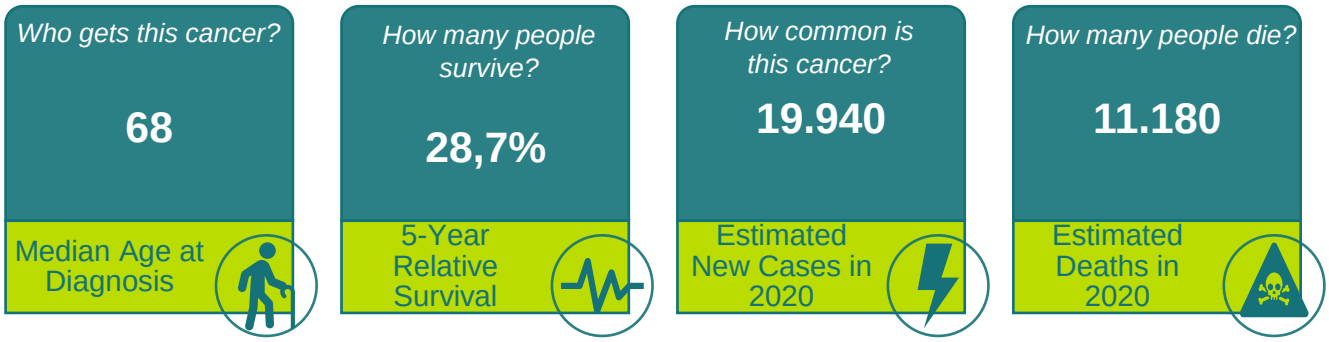


During the progression of the disease, tumor initiating cells can give rise to different subclones. A mutation x can be detectable at the time of initial diagnosis. However, it might acquire additional driving mutations xy during the therapy that might contribute to relapse. Other mutations, z, are not detectable at the time of initial diagnosis but might arise later and evolve as dominating clone at relapse. **Rolling C. et al., 2014 [21].**

5.5 Conclusions – Chapter 5

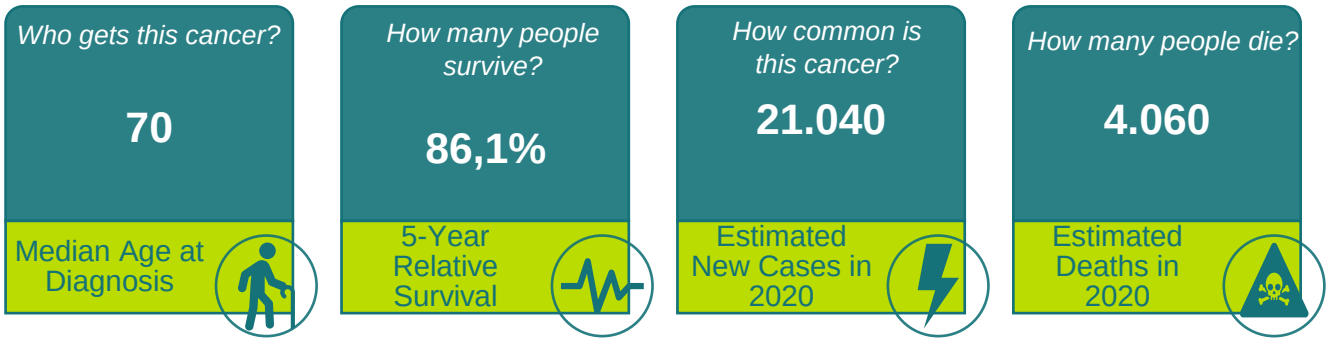
Acute Myeloid Leukemia (AML)

The most common type of leukemia in adults



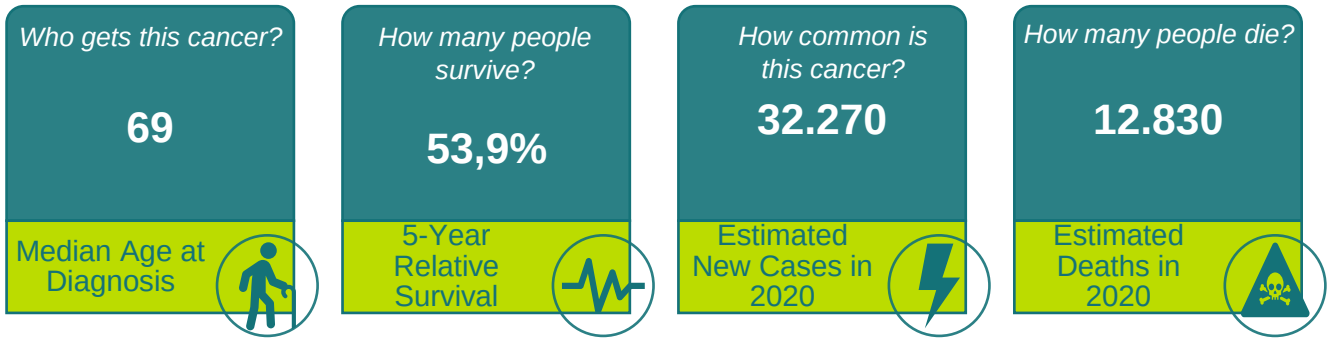
Chronic Lymphocytic Leukemia (CLL)

The most common type of leukemia in western countries



Multiple Myeloma (MM)

Considered as an incurable onco-hematological disease



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6 Blood Cancer Therapies

Anti-tumor treatments for blood cancer indications

6. Blood Cancer Therapies

> *What is the scientific rationale and mode-of-action of the hematological anti-tumor therapies?*
> Analyze how the anti-tumor therapies rapidly changed from 2014 to 2018.

Introduction

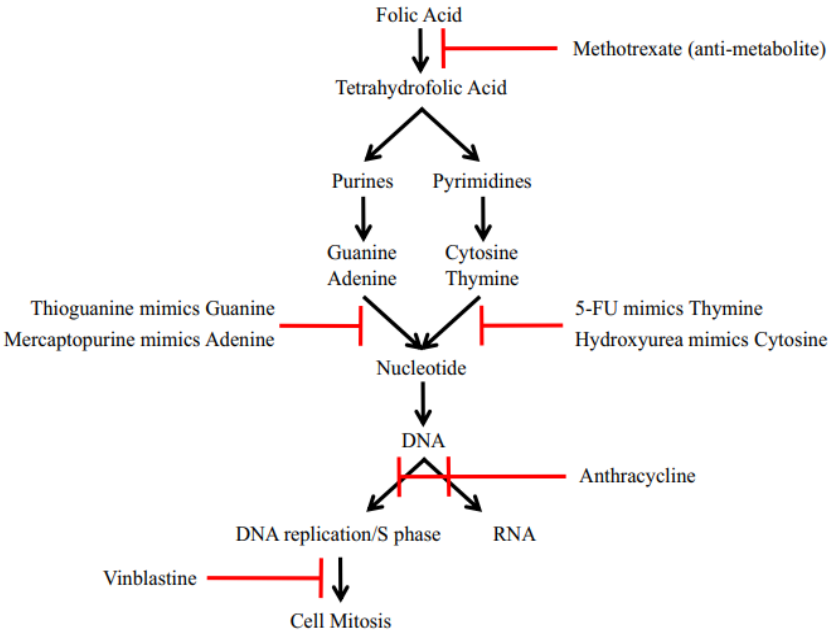
Novel therapeutic targets have been identified revolutionizing the treatment of hematological malignancies over the past decades. The investigations have spawned the discovery, clinical evaluation, and US Food and Drug Administration (FDA) approval of new mechanistic-based therapeutic agents. A surprising number of these agents have progressed from the discovery phases to validation, animal modeling, and successful clinical testing. This chapter provides an overview of the traditional and novel therapeutic agents available for the treatment of patients affected by blood cancers. Particularly, the chapter describes on the one hand how “classic” chemotherapeutic agents still constitute the backbone of treatment of hematological indications. On the other hand, the chapter also presents newly developed, targeted- cancer therapies that constitute a new generation of cancer treatment for blood cancer indications. Finally, it will discuss research advances, opportunities and challenges of (cellular) immunotherapies, in order to critically analyze the outlook of this emerging area.

6.1 Chemotherapy

Survival rates for hematological malignancies have improved significantly throughout the past century. One of the main reasons for the surprising achievements in blood cancer treatments is the advent of chemotherapy, which represents the therapeutic backbone for hematological malignancies nowadays [1]. Chemotherapy is the use of anti-cancer drugs injected into a vein, under the skin, into the cerebrospinal fluid (CSF), or orally, in order to destroy or control the growth of cancer cells. Except when given into the CSF, these drugs enter the bloodstream and reach all areas of the body. All chemotherapeutic agents are characterized by their ability to inhibit mitosis, or cell division. Indeed, cancer cells, characterized by uncontrolled and rapid division are very susceptible to the chemotherapy mechanism of action. Most chemotherapeutic agents inhibit cell division by damaging the DNA, which they achieve through different mechanisms (**Figure 6**). For example, antimetabolites inhibit cell division by blocking enzymes or incorporating itself into the DNA. Anti-microtubule agents disturb microtubule function, hereby preventing the completion of mitosis. Topoisomerase inhibitors cause single or double stranded DNA breaks [2].

While much research has been conducted for the development of targeted therapies - therapies designed to exploit a specific vulnerability of cancer cells - chemotherapy continues to be the mainstay of hematological cancer treatment today. With most agents used today being the same as those used fifty years ago, improved survival has mainly been the result of optimized dosing schedules and combination therapy.

Figure 6. Chemotherapeutic agents mechanisms of action



Most chemotherapeutic agents drive cells to apoptosis by disrupting DNA replication in dividing cells. **Adapted from Baudino, T. et al., (2015)** [2].

6.1.1 Side Effects

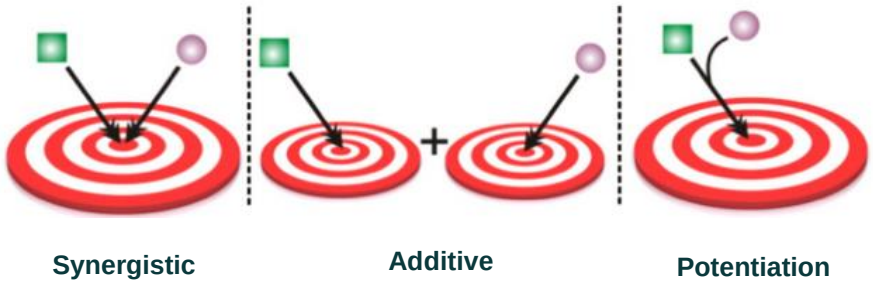
The ability of chemotherapy to kill rapidly dividing cells is the main reason for its success. However, this aspect is also the main reason for its limitation in cancer treatment. Indeed, apart from cancer cells, other innocent cells in our body divide rapidly, such as hair cells, cells part of the gastro-intestinal tract, even cells in the hematopoietic system. Unfortunately, none of the chemotherapeutic agents used to date are able to distinguish between rapidly dividing cancer cells and rapidly dividing non-cancerous cells [1]. As a result, one of the most commonly encountered side effects of chemotherapy is bone marrow suppression. Because cells of the hematopoietic system divide rapidly, they are particularly susceptible to chemotherapy. Suppression of the hematopoietic system leads to a severe risk of infections, anemia and thrombocypenia. Other commonly encountered side effects are alopecia, nausea and vomiting. Depending on the specific type of chemotherapeutics, additional side effects might occur, including neurotoxicity, renal failure, hearing problems and pulmonary fibrosis. In addition to that, others side effects might include therapy-related myeloid malignancies (t-MNs).

6.2 Combination Therapy

It is well known that tumors are physiologically very complex. Indeed, a therapy that involves a single drug may not be efficient to achieve a functional treatment. Combination therapy have been designed to provide solutions for drug resistance and tumor recurrence often encountered in cancer affected patients. Combination therapy refers to the simultaneous administration of two or multiple chemotherapeutic agents. The role of combination therapy became increasingly important in cancer treatments in the clinics [3]. Combination therapies can achieve durable responses by disrupting different signaling pathways in cancer cells. Favorable outcomes can be achieved through various mechanisms of combination

chemotherapy, including synergistic effects, additive effects and potentiation effects (**Figure 6.1**).

Figure 6.1 Schematic illustration of combination chemotherapy



When two drugs are administered simultaneously, the combination of their therapeutic effects can generate a synergistic, additive or potentiation effect. A synergistic effect is achieved when the combination of two agents generate a greater effect compared to the summed effect of the individual drugs acting on the same pathway. The combination effect is additive when the effects is greater than or equal to the summed effect of the partner drugs acting on different targets; potentiation effects can be achieved on the circumstance that the therapeutic effect/activity of one rug is enhanced or the side effect is reduced by another drug via regulation of its absorption, metabolism and excretion. **Adapted from Hu, Q. et al., (2016)** [3].

6.2.1 Resistance

Patients diagnosed with acute leukemia often undergo two rounds of treatment. The first round of treatment, called induction therapy, consists of killing about 99,9% of these leukemic cells. Following induction chemotherapy, an intensive program of consolidation treatment is employed to kill the remaining cancer cells. However, despite the intensive induction and consolidation treatment regimens, some cells may survive therapy [1]. This survival capability may be due to an acquired or innate resistance phenotype, or because of the inability of the drug to reach the cancer cell. Relapsed leukemia refers to the presence of leukemia in patients who initially achieved complete remission – a state in which the disease is undetectable - but in whom the disease returned. Non-response is distinct from relapse, as it refers to a state in which complete remission is never achieved despite intensive treatment. The study of chemotherapy resistance and relapse in leukemia relies heavily on analysis of genetic alterations in patients with relapsed disease. For example, it has been reported that pre-existing somatic mutations may be present in some older individuals. It has been demonstrated that the risk of developing blood cancer highly increases with the presence of particular mutations called clonal hematopoiesis of indeterminate potential (CHIP) mutations [4], [5], [6].

6.3 Targeted therapies: The Achille's heel of mutant cells?

As mentioned before, chemotherapeutic drugs act by targeting highly proliferative cells. However, these drugs are not capable of distinguishing malignant cells from healthy cells that are undergoing a normal cell division. The current anti-tumor therapies research, after identifying genes involved in chemotherapy resistance and relapse of the hematological diseases, is mainly focusing on the identification of novel treatment options. The concept of targeted therapies consists of identifying specifying molecular mechanisms that are unique to cancer cells, instead of using broad base cancer treatments [1]. After all, instead of killing every fast-replicating cell, targeted therapies – as the name implies – only target the cancerous ones. Particularly, since pathogenic mutations will have an effect on cellular homeostasis, targeted therapies are designed to exploit an acquired favorable characteristic of the cancer cell to its

disadvantage [2]. Hence, the search for targeted therapies can be compared to a search for the 'Achilles heel' of mutant cells. The benefit of this therapeutic approach is that targeted therapies imply less side effects compared to classic cytotoxic therapies. The two treatment options that are currently playing an important role in the clinical management of hematological malignancies are small molecules inhibitors and monoclonal antibodies. The role of small molecule inhibitors is affecting molecular pathways that are not regulated during tumor development by inhibiting specific kinases. Monoclonal antibodies, by binding specific antigens that characterize the surface of cancer cells, are capable of mediating different mechanisms of action.

6.3.1 Small Molecule Inhibitors

One of the main characteristics that allow cells to become cancerous is an inappropriate kinase activity. Small molecules inhibitors bind in a competitive manner to a tyrosine kinase in its ATP binding site [2]. This way, they interact BCR-ABL, Akt or mTOR – factors that are usually not regulated during cancer development. The interaction with the tyrosine kinase domain causes a stop of the downstream signaling pathway. These molecules showed positive results when administered together with chemotherapeutic agents.

6.3.2 Monoclonal Antibodies

Nowadays monoclonal antibodies (mAbs) are a widespread tool for biomedical science, constituting the majority of targeted therapies. In the hematological cancer field, since rituximab became the first mAb approved by FDA for the treatment of B cells malignancies, other mAbs targeting lineage-specific antigens have been successfully developed [7]. The most commonly used mAbs in cancer immunotherapy are IgG antibodies, composed by two regions that determine their specific biologic properties. One region, the variable fragment (Fv), is responsible for interaction with the antigen. The second region called constant fragment (Fc), is instead responsible for communication with immune cells of innate or acquired immunity. Fv and Fc together determine the different characteristics of the mechanism of action displayed by a single mAb, enhancing its utility as immunotherapeutic agent in cancer. Briefly, a particular mAb may inhibit ligand-receptor interactions, and/or induce proapoptotic signaling, and/or activate innate immune cells to induce tumor cell killing. In the hematological malignancies field, therapeutic mAbs are especially relevant to identify specific targets and mechanisms of action, owing to accessibility to tumor cells and facilitating *in vitro* studies. Moreover, the deep knowledge about hematopoietic differentiation antigens has provided different classes of monoclonal antibodies for different targets: antibodies targeting glycoproteins and oncogenic receptors, antibodies targeting chemokine receptors, antibodies targeting the tumor niche, and antibodies targeting immune checkpoints. Immune checkpoints inhibitors will be discussed in Section 6.5.1.

6.4 Stem Cell Therapy

Just as in a normal hematologic system, leukemic cells comprise a hierarchy of cells at various levels of differentiation. Tumors arise from malignant stem cells generated from normal stem cells that retain the mechanism of self-renewal. Most leukemic cells have a limited capacity for proliferation, and therefore they are continuously replenished by leukemic stem cells. Only 1 in 1 million leukemic blasts appears to be a true stem cell, according to the capacity to propagate and sustain leukemia in immunologically susceptible mice [8]. Importantly, malignant stem cells result insensitive the chemotherapy. As normal stem cells, malignant stem cells can repair DNA efficiently and resist apoptosis. Therefore, if malignant stem cells are resistant to the therapy, they allow cancer to recur. Hematopoietic stem cells (HSCs) were first described by Till and McCulloch in 1961. Stem cells can be broadly defined by their ability of self-renewal

and potential to proliferate and differentiate into diverse cell types. HSCs comprise a very small, but critical sub-population of the total hematopoietic system, making up less than 0.01% of cells in the bone marrow [9]. In the hematopoietic system, there are three different populations of multipotent progenitors: stem cells with a capacity for long-term renewal, stem cells with a capacity for short-term renewal, and multipotent progenitors that cannot renew but differentiate into the varied lineages in the bone marrow [10]. From the hematopoietic stem cells descend primitive progenitors that give rise to less-differentiated precursors that produce mature blood cells. As all stem cells, hematopoietic stem cells have the ability to produce some daughter cells characterized by stem-cell properties, constituting an important source of blood cells. In fact, it has been demonstrated that a single stem cell can reconstruct the entire hematopoietic system of a lethally irradiated animal [11]. Hematopoietic stem cell transplantation (HSCT) involving the intravenous infusion of autologous or allogeneic stem cells might be a possibility to reestablish hematopoietic function in patients whose bone marrow or immune system are damaged or defective. There are different sources of stem cells available for transplant. Peripheral blood is an accurate source of hematopoietic stem cells [8]. Cord blood is another good source, especially when transplantation is urgent and no suitable donors can be found.

6.4.1 Side Effects

Family members or unrelated bone marrow and peripheral blood donors serve as source of stem cell transplants. The donation of healthy stem cells can restore hematopoiesis and control tumor development. However, two immunological barriers constitute the main problematic side effects of stem cell transplantation. The first one, called host-versus-graft reaction, is related to a complex mechanism initiated by the glycoproteins present on HLA cell surface of the recipient that recognize the foreign donor antigens. An immune reaction is initiated by the recipient patient and the graft is rejected. Graft rejection is always associated with detrimental effects for the patients, and remains the most important direct or indirect cause for mortality related to allogeneic HSCT [12]. In contrast, the second barrier, the graft-versus-host reactions, is caused by a mechanism initiated by the donor's T cells that causes graft-versus-tumor. Hematopoietic stem-cell transplantation results can offer more efficient cures and remissions compared to other alternative treatments, but it is also a cause of morbidity and mortality. Although the mortality rate is less than 2 percent for some autologous transplantations and less than 10 percent for some allogeneic transplantations, about 40 percent of patients with advanced cancer who undergo allogeneic transplantation die from complications related to transplantation [8]. Reducing toxicities of the preparative regimen is critical in order to improve the safety of this practice.

6.5 Immunotherapies

In recent years, the potential of the immune system to control cancer development and progression has been extensively investigated. Immunotherapies used to treat cancer aim at boosting the activation of the immune system to specifically target tumorigenic cells [13]. Immunotherapies have the capability of improving immune responses against cancer with less invasive side effects compared to chemotherapies. Over the past decade, a growing number of immunotherapies have been investigated and approved for clinical management of cancer affected patients. The first approved immunotherapeutic treatment was a recombinant version of the cytokine interferon-α for hairy cell leukemia in 1986 [14]. Afterwards, recombinant interleukin-2 (IL-2) immunotherapeutic approaches have been discovered to induce durable complete responses in some cancer affected patients [15]. However, although there were promising results from cancer immunotherapies, the failure of many clinical trials focused on

cancer vaccines provoked the interruption of immunotherapy investigations in the 2000s [16]. However, the important discovery of checkpoint inhibitors established a new beginning for the treatment of cancer in the field of immunotherapy. The advent of *ipilimumbab* and CAR-T cell therapies was regarded as a milestone in cancer treatments, and reported as the breakthrough of 2013 by *Science* [17]. Nowadays, dozen immunotherapies are available for cancer treatment, and even more are currently under investigation in clinical trials.

6.5.1 Checkpoint Inhibitors

Checkpoint inhibitors represent one of the most remarkable newly developed immunotherapies for cancer treatment, particularly represented by anti-CTLA-4 and anti-PD therapy. In 2018 James Allison and Tasuku Honjo were awarded with the Nobel Prize for their contributions in the investigation of immune checkpoint-based immunotherapies. Immune checkpoints are important factors of immunity that regulate the stimulatory or inhibitory state of T cells. Activation of T cells include two signals. The first one, provided by the TCR and the second one by the stimulatory checkpoints. High levels of IL-2 production by T cells can be achieved only after the interaction of CD28 with B7-1 and B7-2 ligands [18]. Other negative regulators such as CTLA-4 and PD-1 control the excessive response to infection of T cells in order to maintain the cellular homeostasis. For example, CTLA-4 compete with CD28 for the binding of B7 ligands, resulting in the inhibition of CD28 signaling pathway [19]. The immune homeostasis is determined by the balance between the stimulatory and inhibitory signals provided by the immune checkpoints. CTLA-4, PD-1/PD-L1, LAG-3/FGL1 and other inhibitory immune checkpoints provide an inhibitory state [20], [21], [22], [23]. Following this rationale, cancer cells can be attacked by immune cells through the suppression of the inhibitory immune checkpoints and the activation of the stimulatory immune checkpoints. So far, the blockade of CTLA-1 or PD-1/PD-L1 antibodies are the ones that reported the best therapeutic effect (**Table 6.1**).

Brand name	Generic name	Target	Description	Indication(s)
Opdivo	nivolumab	PD1	Tumor cells have been demonstrated to escape from the immune system by upregulating the expression of PD-L1 (B7-H1) and promoting T cell apoptosis. Blocking antibodies that inhibit PD-1/PD-L1 interaction were shown to enhance the efficacy of T cell immunotherapy [24].	Hodgkin Lymphoma (B-Cell Hodgkin Lymphoma)
Keytruda	pembrolizumab			

Table 6.1. Top marketed immunotherapeutic agents for hematological malignancies in 2018. Source: GlobalData.

6.5.2 Adoptive T cell therapy

Complexes of MHC-peptides present on the surface of tumor cells are recognized by T cell receptor, which triggers a cascade of immune responses in order to recognize and eliminate the tumor. The aim of adoptive T-cell therapy (ACT) is to artificially enrich T cells that are capable of recognizing tumor surface antigens (TSAs) and destroy tumor cells. Therefore, the rationale behind T cell enrichment or manipulation is to enhance antigenic specificity and potency towards cancer cells [25]. Currently, there are three main classes of ACT, each one

characterized by its own mechanism of action: ACT with tumor-infiltrating lymphocytes (TIL), ACT using T cell receptor (TCR) gene therapy, and ACT with chimeric antigen receptor (CAR) modified T cells [26]. Rosenberg and coworkers were the first researchers to perform studies with TIL, and demonstrated that TIL grown from different murine tumors reported anti-tumor activity *in vivo* [27]. A growing number of tumor responses after *in vivo* expansion of TIL from resected tumor material and adoptive transfer have been registered in different clinical trials [26], [28], [29]. However, the modified TCR require the presentation of the antigen by the major histocompatibility complex (MHC) in order to specifically recognize the tumor. It has been demonstrated that some tumors are able to evade the immune responses initiated by T cells because of their capability of downregulation or loss of MHC expression. Chimeric antigen receptors (CARs) have been specifically designed to overcome this dependency of antigen presentation by the MHC complex. CARs are recombinant proteins that are composed by two domains: a portion that recognizes the antigen - the TCR - and a portion that mediates the internal signaling - the cytoplasmatic domain. According to this approach, T cells are collected from blood of the patients, and are subsequently genetically modified to express CARs specific to recognize an antigen present on the surface of tumor cells. Therefore, once the antigen is targeted, tumor cell death is initiated. It has been demonstrated that long time responses can be achieved through CAR-T cells administration, compared to other treatments [13]. A growing number of surface antigens expressed on hematologic cells have been discovered; in addition, it has been demonstrated the T cells homing preference to hematologic organs. It's not surprising that CARs came to the forefront for the treatment of hematologic malignancies [30]. In 2018 the top marketed adoptive cellular therapies were represented by CAR-T cells treatments (**Table 6.2**).

Brand name	Generic name	Target	Description	Indication
Yescarta	axicabtagene ciloleucel	CD19	Autologous T cells modified to express a chimeric antigen receptor (CAR) targeted to CD19 induce high rates of remissions in patients with refractory B-cell hematologic malignancies [31].	Diffuse Large B-Cell Lymphoma
Kymriah	tisagenlecleucel			Acute Lymphocytic Leukemia (ALL, Acute Lymphoblastic Leukemia); Diffuse Large B-Cell Lymphoma

Table 6.2. Top marketed adoptive cellular therapies for hematological malignancies in 2018. Source: GlobalData.

6.5.3 Toxicities

Engineered immune cells have the benefit of an increased precision in the recognition of targets, and therefore have a potential to increase treatment-associated toxicities that are usually experienced with chemotherapies. However, it has to be considered that severe immune-mediate adverse events have been registered after CAR-T cells administration [32]. The long-term persistence that has been reported in human trials [33] [34] is considered as the main cause of toxicities. These adverse events associated with T cell-based therapies can be immediate or delayed, mild or severe. So far, the main adverse event registered after CAR-T

administration is the cytokine release syndrome (CRS). Particularly, high levels of inflammatory cytokines, IL-10 and IL-6 have been related to CRS [35].

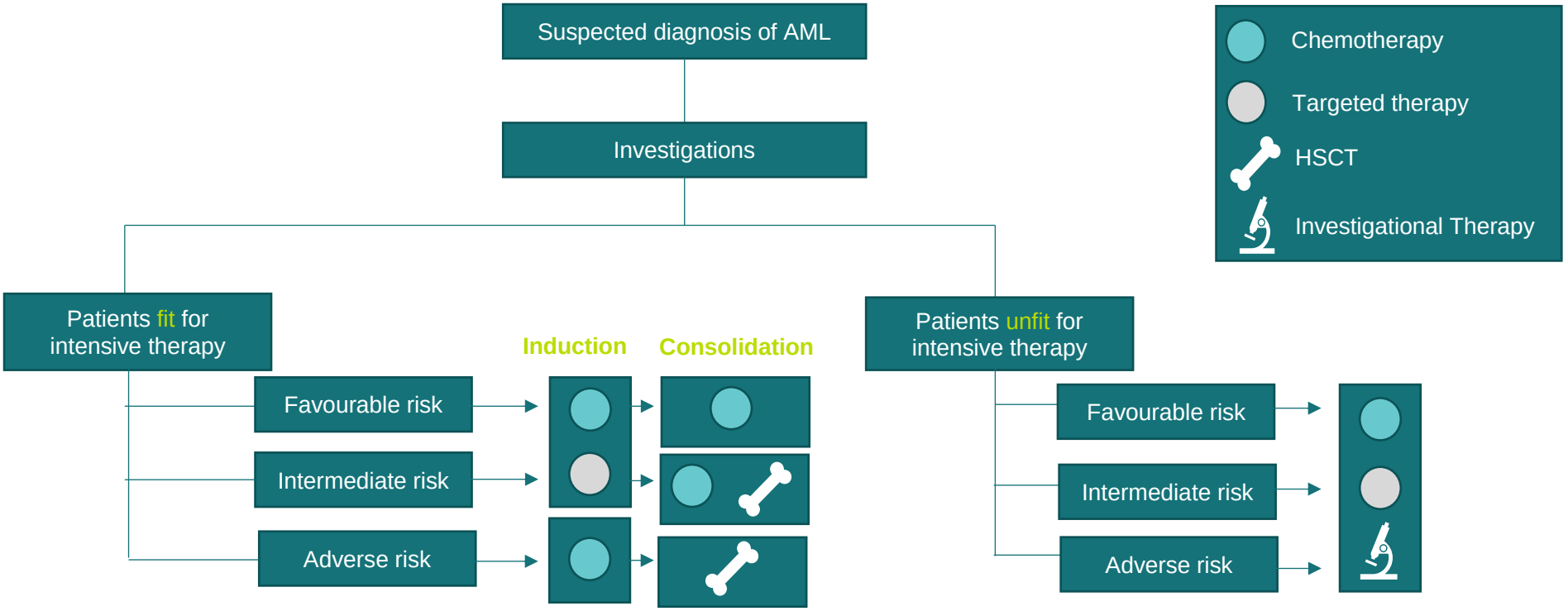
6.6 AML, CLL and MM

6.6.1 Current therapeutic approach: AML

Before designing a treatment plan for AML, it is important to consider important patients-related factors such as advanced age and performance status that may render them not suitable to receive intensive chemotherapy. **Figure 6.2** illustrates the current general approach for the management of AML in adults, mainly constituted by an induction and consolidation phases. Induction phase for intensive therapy-fit patients usually comprises the use of chemotherapeutic (e.g. *midostaurin*) o targeted agents (e.g. *gemtuzumab*, especially in case of CD33 positive). Consolidation phase for favorable and intermediate risk patients includes high and medium dose of cytotoxic agents, or allogeneic stem cell transplantation for intermediate and adverse risk patients (for detailed information see **Supplementary Figure 1**). Patients unfit for intensive therapy usually undergo cytotoxic and targeted agent treatments for favorable and intermediate risk cases. Investigational therapy is encouraged for adverse risk patients.

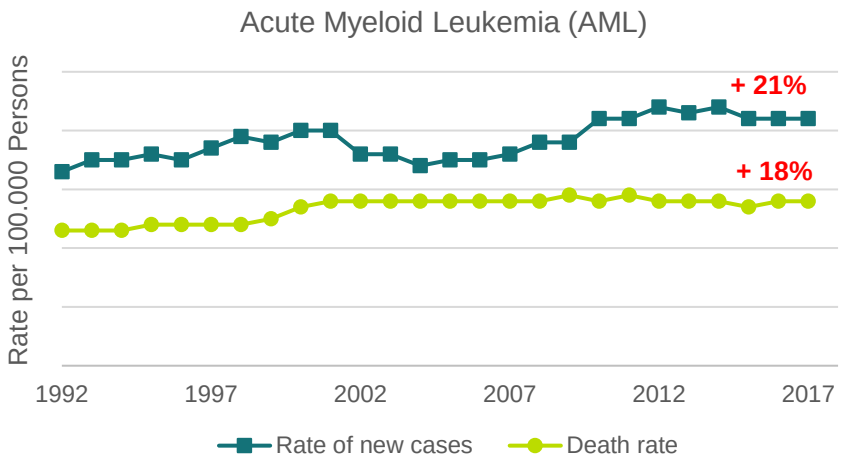
Of the patients that receive standard chemotherapy, only 40% of adult patients and 15% of old patients achieve long-term survival [36]. Indeed, despite promising progresses in the field of AML treatments, the outcomes of patients treated in clinical trials is still not satisfactory. The death rate increased in the past years, due to an increased incidence rate of new cases and to a poor prognosis for patients (**Figure 6.3**) [37]. However, due to a remarkable growth in the number of new available drugs in 2017, the frontline treatments for AML are rapidly changing. Particularly, new approaches rely on precise genomic analyses that identify genomic and molecular changes.

Figure 6.2 General therapeutic approach for AML affected patients



Patients affected by AML are divided into those that are fit or unfit for intensive therapy, based on patient-related factors. Patients that are fit for intensive therapy at favorable risk undergo chemotherapeutic induction and consolidation phases. Patients at intermediate risk undergo targeted agents based – induction therapy followed by cytotoxic agents and if possible stem cell transplantation. Patients at adverse risk undergo chemotherapy induction phase and stem cell transplantation consolidation phase. Patients that are unfit for intensive therapy have the options of chemotherapeutic or targeted agents-based therapies. However, investigational therapy for patients at adverse risk is highly recommended.

Figure 6.3. Rate of new cases and death rate for AML

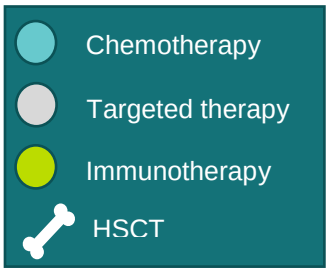


*The rate of new cases and the death rate for AML greatly increased from 1992, respectively with an increase of **+21%** and **+18%**. The growing rate of new cases is mainly due to the fact that AML is an age-associated disease and the population is currently facing a demographic shift towards aging (see Chapter 10). The increment of the death rate is due to the increase of the rate of new cases and the concomitant poor prognosis for AML affected patients.* **Source: National Cancer Institute** [37].

6.6.2 Current therapeutic approach: CLL

Important advances in therapeutic approaches for CLL brought different benefits in the clinics for cancer affected patients. Novel prognostic tools and the development of new targeted therapies are rapidly improving clinical outcomes. **Figure 6.4** describes the current general approach for the management of CLL affected patients. Similarly to AML, patient-related factors (fitness, age, comorbidities and TP53 genetic status) are considered before choosing the optimal treatment [38]. For detailed information see **Supplementary Figure 2**. Together with a slight decrease of the incidence rate of CLL in the past ten years, the death rate sharply decreased [39] (**Figure 6.5**).

Figure 6.4. General clinical approach for CLL affected patients

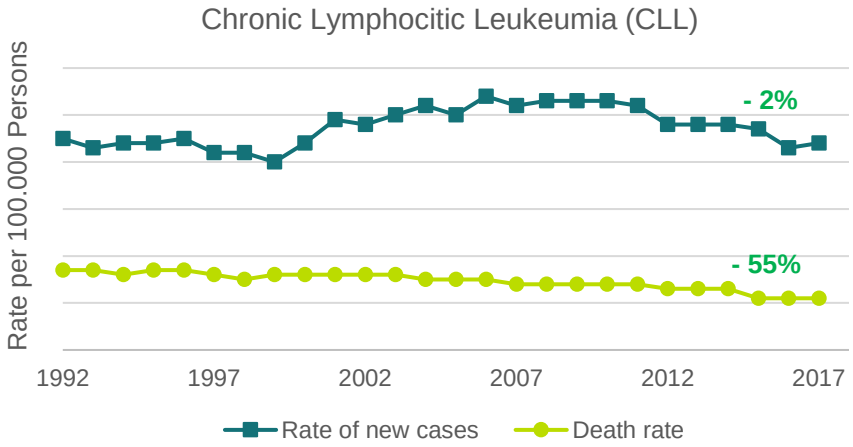


	No TP53 aberration	TP53 aberration
First-line treatment		
Physically fit	+	+
Physically unfit	+	+

		Standard therapy	Alternative therapies
Second-line treatment	Refractory or progression within 3 years		
	Physically fit		
	Physically unfit	Change therapy	
	Progression after 3 years		
	All fitness levels	Repeat front-line therapy	Change to another immunotherapy

The first-line treatment for CLL affected patients comprises the use of combination of cytotoxic drugs, cytotoxic and targeted drugs and targeted and immunotherapeutic agents. The decision regarding the second-line treatment approach is based on progression of the disease within or after 3 years. Patients physically fit undergo a combination of targeted agents and stem cell transplantation or combination of targeted agents or immunotherapeutic solutions alone.

Figure 6.5. Rate of new cases and death rate for CLL



*The rate of new cases for CLL slightly decreased from 1992 (**-2%**). In addition to that, the death rate remarkably dropped by half (**-55%**).* **Source: National Cancer Institute** [39].

6.6.3 Current therapeutic approach: MM

Multiple myeloma is still considered as an incurable disease, despite the rapid development of novel effective compounds based on an increased knowledge of the disease pathogenic mechanisms. Allogeneic stem cell transplantation has become part of standard care for MM, and the safety of this approach is often compromised by complications related to graft-versus-host disease reactions. The risk of disease progression is 10% per year for the first 5 years, and then it decreases subsequently [40]. Since a definitive cure is impossible even using multiple interventions, patients with old age are treated according to a disease control plan, including achievement of non-progression of the disease with marginal toxic effects and good quality of life. Current clinical studies are focusing on providing different patient subgroups in order to prevent over-treatment patients that are not suitable for intensive interventions. **Figure**

6.6 illustrates the general approach for first line and second line treatment for patients affected by MM (for more detailed information see **Supplementary Figure 3**). Finally, despite the incidence rate of new cases for MM greatly increased, the death rate slightly improved from 1992 but it remained fairly steady in the past ten years [41] (**Figure 6.7**).

Figure 6.6. General clinical approach for MM affected patients

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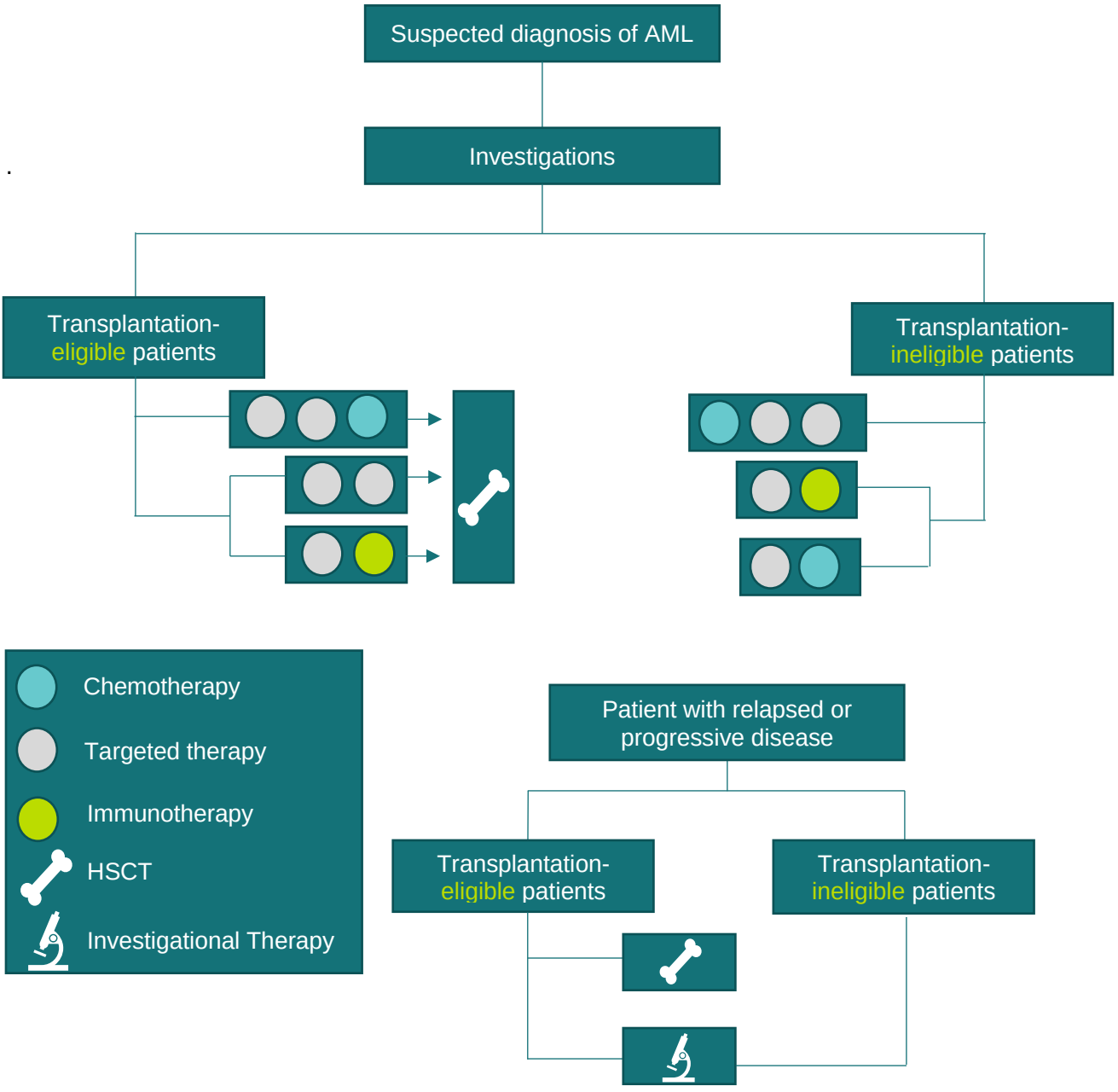
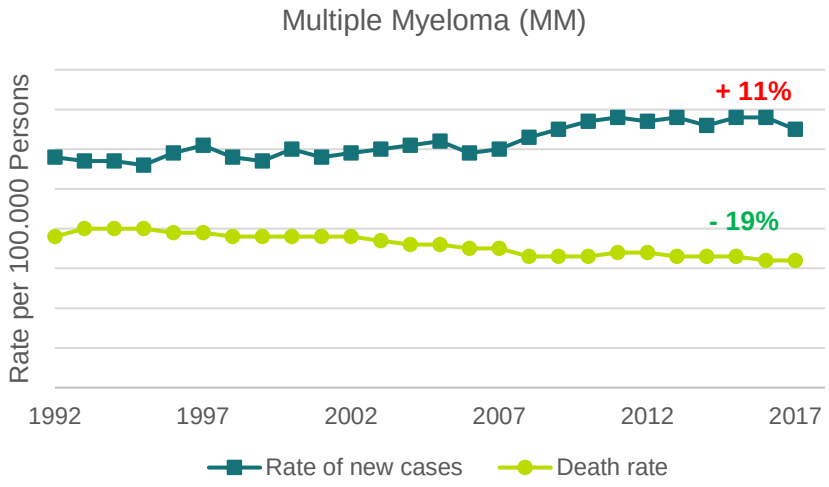


Patients affected by MM are divided according to their eligibility to stem cell transplantation. Transplantation-eligible patients undergo a three-drug or two-drug regimen followed by stem cell transplantation. Transplantation-ineligible patients undergo a three-drug or two-drug regimen alone. Second-line treatment comprises stem cell transplantation if the patient is eligible or a treatment based on a novel drug.

Figure 6.7. Rate of new cases and death rate for MM



*The rate of new MM cases considerably increased **+11%** until 2017. Despite this fact, effective therapies promoted an improved survival, with a decreased death rate **-19%** since 1992.* **Source: National Cancer Institute [41].**

6.7 Conclusions – Chapter 6

- Chemotherapy represents the therapeutic backbone for hematological malignancies nowadays. All cytotoxic agents are characterized by their ability to inhibit mitosis, or cell division. Unfortunately, none of the chemotherapeutic agents used to date are able to distinguish between rapidly dividing cancer cells and rapidly dividing non-cancerous cells.
- Combination chemotherapy refers to the simultaneous administration of two or multiple chemotherapeutic agents.
- The aim of targeted therapies is exploiting cancer specific mechanisms. Two treatment options that are currently been investigated in research are small molecules inhibitors and monoclonal antibodies.
- Stem cell therapy might be a possibility to reestablish hematopoietic function in patients whose bone marrow or immune system are damaged or defective. Immunological barriers to stem cells transplantation comprise host-versus-graft (graft rejection) and graft-versus-host reactions.
- Immunotherapy is now regarded as a powerful weapon for the clinical management of blood cancer indications. The rationale behind this therapy type is to boost the immune system in order to specifically attack cancer cells.

- Despite the promising progresses, the outcomes of patients with AML remain unsatisfactory. On the other hand, the outcomes of CLL affected patients tremendously improved. Finally, despite a sharp increase of the incidence rate of new cases for MM, the death rate improved in the past two decades.

- The general approach for AML mainly comprises cytotoxic agents and monoclonal antibodies (such as anti-CD33). Before deciding the therapeutic strategy, patients-fit to intensive therapy is evaluated.

- The general approach for CLL includes the use of cytotoxic and targeted agents in the first line treatment (including monoclonal antibodies anti-CD20). In the second line treatment one immunotherapeutic solution is considered (*Lenalidomide*).

- MM is still considered as an incurable disease. Ongoing efforts for the clinical management of the disease include the use of cytotoxic and targeted approaches followed by stem cell transplantation (according to patients eligibility).

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7 The current Status

Recent hematological advances and trends in therapies

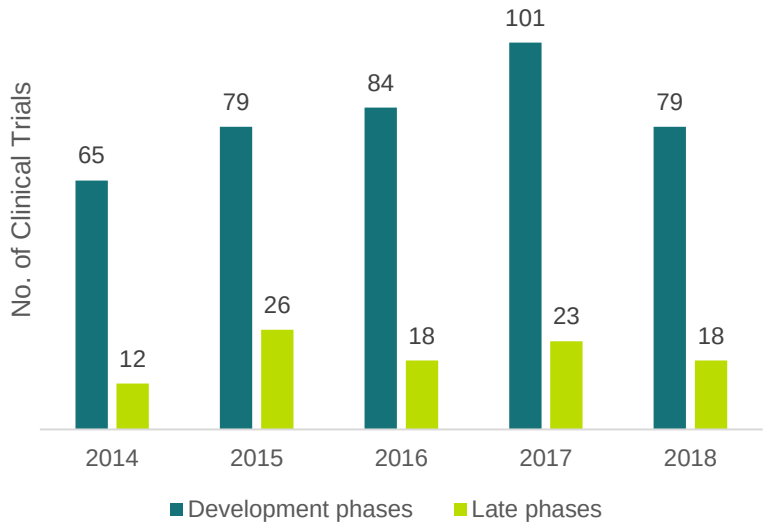
7. The Current Status

> *How did the therapeutic landscape evolve in the past five years? What are the potential leading therapies for the future?*
> Identify recent trends in therapies and anticipate potential future directions.

7.1 Trends in Therapies

As already discussed in the previous chapter, cytotoxic chemotherapy has been traditionally considered as the preferred weaponry for all cancers. Although chemotherapy remains the primary support of the current treatments in onco-hematology, the side-effects and long-term sequelae of anti-cancer chemotherapy remain a major source of concern for both patients and clinicians. Chemotherapeutic drugs while targeting rapidly dividing mitotic cells may attack normal tissues in the physiological growing phase. As a result, these serious toxicities lead to treatment discontinuations and frequently acquired resistance.
In recent years, due to the remarkable advances in the fields of targeted therapies and immunotherapies, the number of clinical trials investigating the efficacy and safety of cytotoxic drugs greatly decreased (**Figure 7**). The number of clinical trials in development phases decreased with 42% in phase I clinical trials and 8% phase II clinical trials. Late phases clinical trials decreased with 44% in phase III.

Figure 7. The decreasing investigation of chemotherapy for blood cancers

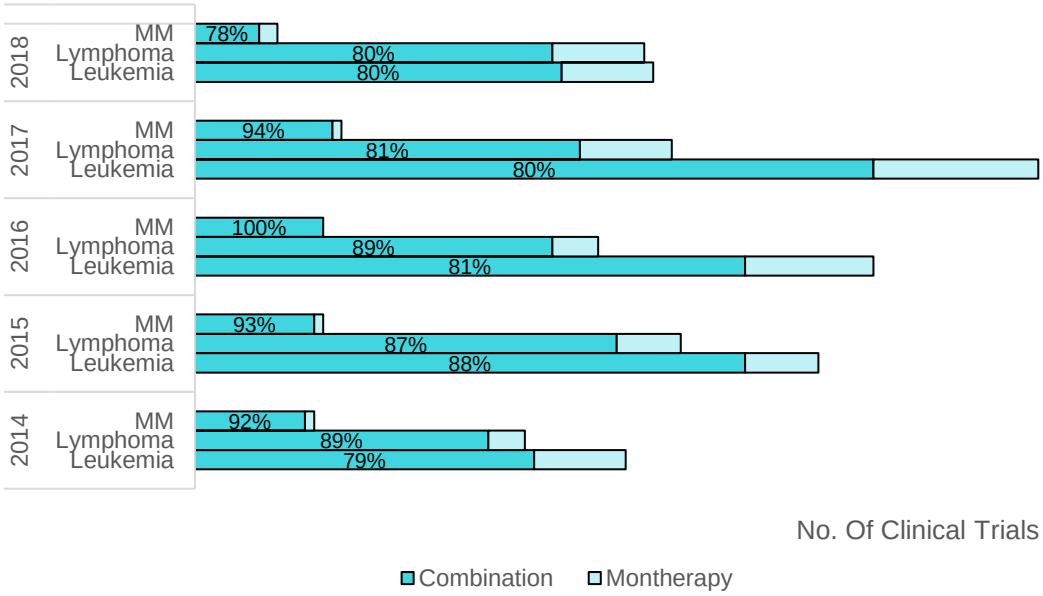


The graph above shows the number of ongoing clinical trials focused on chemotherapy treatments for hematological malignancies from 2014 to 2018. Due to the significant enhancements in targeted therapies and in immunotherapies, the number of clinical trials investigating chemotherapeutic drugs remarkably decreased from 2017 to 2018. ***Development phases****: phase 0, phase I, phase II clinical trials.* ***Late phases****: phase III, phase IV clinical trials.* **Source: GlobalData**.

Studies using combinations of chemotherapeutic agents demonstrated evidence for synergy or additive effects. As already explained in Chapter 6, the rationale behind chemotherapy combination is tumor cell heterogeneity and its implication for drug resistance [1]. In fact, it has

been demonstrated that heterogeneity among tumor cells increases the number and diversity of potential target sites for chemotherapy and the need for combining therapeutic agents. Consequently, the number of clinical trials testing combinations of chemotherapeutic drugs dominate over monotherapy – based treatments (**Figure 7.1**).

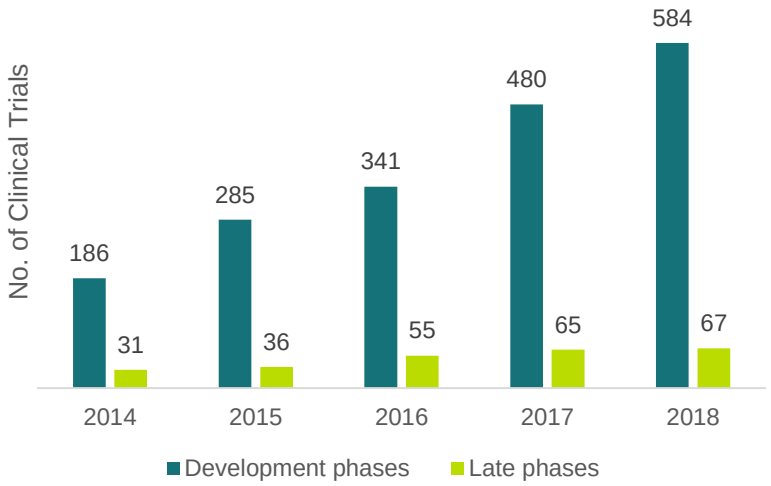
Figure 7.1. Combination therapies for cytotoxic drugs dominate over monotherapies



The graph reports the number of ongoing clinical trials from 2014 till 2018 focused on combination chemotherapy approaches. Clinical trials using combination of multiple chemotherapeutic drugs greatly overcame the number of clinical trials centered in monotherapy, in all the three different indications (Leukemia, Lymphoma and Multiple Myeloma). **Source: GlobalData**.

Chapter 6 reported the importance of targeting the characteristics specific to neoplastic cells, given the upgraded knowledge of tumor biology and microenvironment. Targeted therapies are an effective approach to differentiate molecular changes that are unique to cancer, with less toxic therapeutic effects in onco-hematology. In contrast to the decrease of chemotherapy – centered clinical trials, the number of targeted therapy investigations greatly expanded in the recent years (**Figure 7.2**). The latest generations of precision medicines changed the course of cancer treatment by reducing toxicity and improving outcome, extending patients lives beyond what could be achieved by the use of nontargeted therapies (refer to Chapter 8, Technological section). Compared to chemotherapy, combinations of drugs in targeted therapies currently play a smaller role (**Supplementary Figure 4**).

Figure 7.2. The advent of targeted therapies in onco-hematology

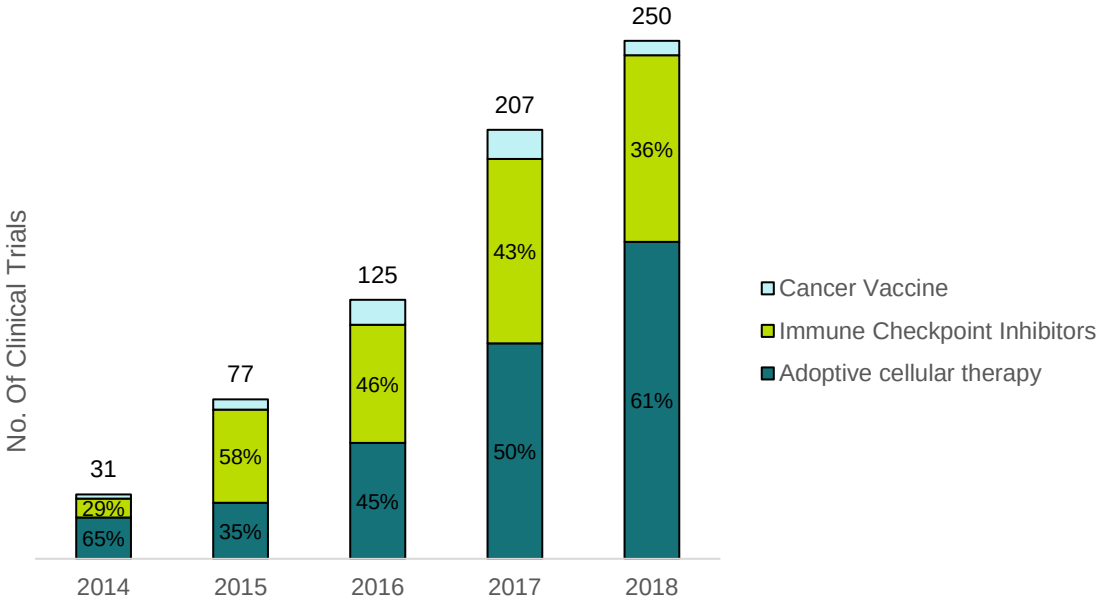


*The graph describes the number of ongoing clinical trials focused on targeted therapies for the treatment of hematological malignancies from 2014 till 2018. Clinical trials in development phases (phase 0, phase I, phase II) have been distinguished from late phases (phase III and phase IV) clinical trials. Targeted therapies rapidly expanded in the past five years, counting more 600 clinical trials in 2018. Phase I increased by **35%** and phase II increased by **26%.** Phase IV increased by **83%** (not shown here).* **Source: GlobalData**.

Targeted therapies comprise small molecule inhibitors and monoclonal antibodies. The unique mechanisms of action of these agents drove the inclusion of these drugs in many protocols designed to treat cancer affected patients. From 2014 until 2018 the number of clinical trials focused on monoclonal antibodies greatly increased, almost reaching the number of small molecules-based treatment options (**Supplementary Figure 5 and 6**).

Recent success of novel anticancer immunotherapies has led to a new era of cancer treatment. Immunotherapies have been reported to enhance durable responses for multiple hematological malignancies. However, the response rates achieved with immunotherapies still need improvements that can be achieved through multiple combination strategies [2]. For example, the inclusion of predictive biomarkers could help overcome limitations related to immunotherapeutic approaches (refer to Chapter 8). However, immunotherapies are increasingly used for blood cancer indications (**Figure 7.3**) compared to other solid tumors, due to specific characteristics of hematological malignancies [3].

Figure 7.3. Immunotherapy as a powerful clinical strategy for treating Blood Cancers.

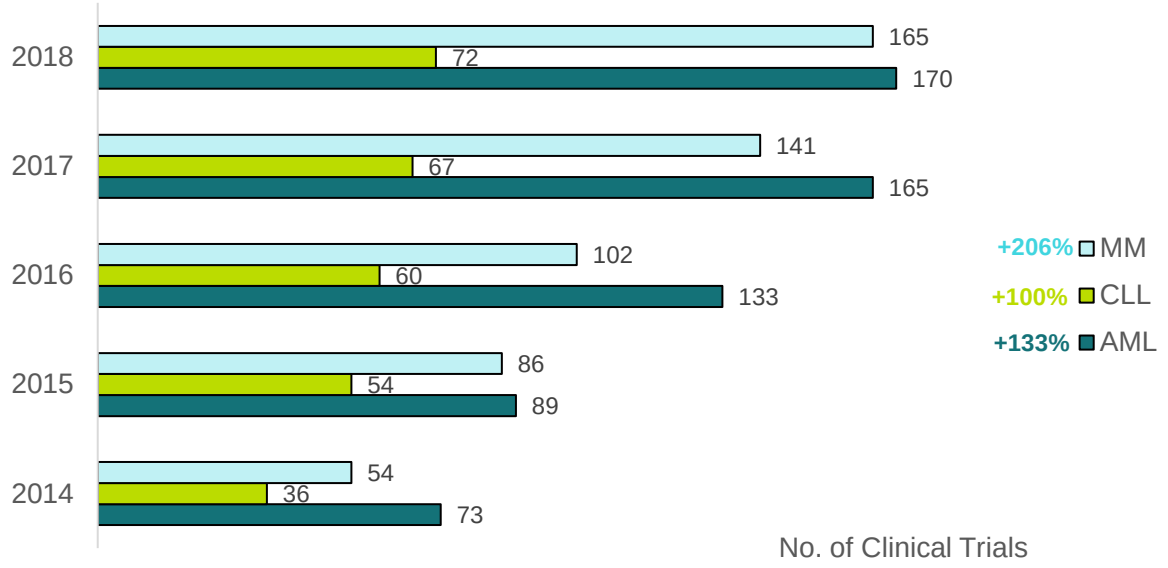


*Graph showing the number of ongoing clinical trials focused on immunotherapy approaches for the treatment of hematologic malignancies from 2014 to 2018. The immunotherapy field greatly expanded reaching a number of 250 clinical trials in 2018. Adoptive cellular therapy increased to reach **61%** of all immunotherapy – based clinical trials in 2018. The number of clinical trials investigating CAR – T cells increased from 16 in 2014 to 118 in 2018 (not shown here).* **Source: GlobalData**.

7.2 Trends in AML, CLL and MM treatment modalities

A number of therapeutic approaches are being evaluated for the treatment of AML, CLL and MM, with very promising assets in the pipeline. These investigations have spawned the discovery, clinical evaluation and marketing approval of novel therapeutic agents, thus leading to a dynamic change of the treatments landscape. The number of the ongoing clinical trials investigating new therapies in the past five years have been analyzed (**Figure 7.4**). AML counted the highest number of clinical trials, due to the aggressiveness of the disease and the high mortality rate. Indeed, the outcomes of patients suffering from AML remain unsatisfactory, despite the remarkable growth of the drugs available for treatment [4]. Concerning multiple myeloma, that is still considered as an incurable disease, remarkable improvements have been made in terms of effective treatment strategies and enhanced supportive care. In 2014 multiple myeloma counted for 56 ongoing clinical trials, but it has been the central indication in a total of 165 clinical trials in 2018. The broad pipeline of potential novel treatment together with ongoing efforts in clinical trials are giving hope for improvements in the treatment of patients affected by multiple myeloma. Important progresses have been achieved in the field of CLL.

Figure 7.4. Clinical Trials for AML, CLL and MM

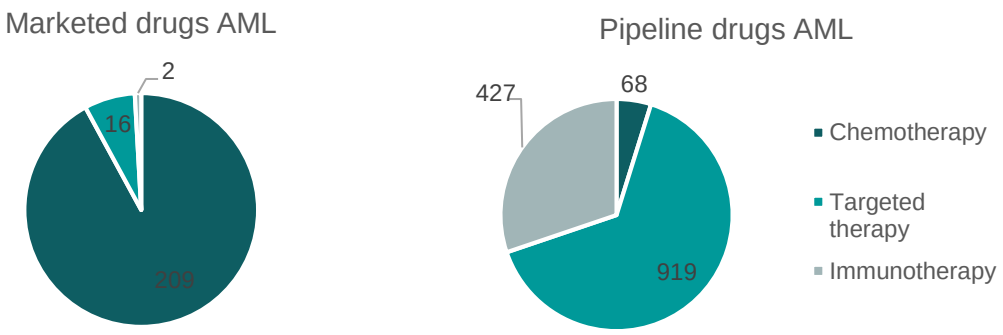


*The number of clinical trials focused on AML, CLL and MM clearly increased in the past 5 years, from 163 clinical trials in 2014 to 407 in 2018. Clinical trials investigating therapies for the treatment of AML constituted the majority of trials from 2014 to 2018, due to the aggressivity of the disease and of the high mortality of the disease. However, MM is the indication that saw the biggest increase (**+206%**).* **Source: GlobalData**.

Acute Myeloid Leukemia (AML)

The majority of marketed drugs for the treatment of AML consists of chemotherapeutic agents (**Figure 7.5**), **that still constitute the backbone of induction therapies**. Despite the remarkable progresses reached in the clinical management of the disease, many important questions remain. Current research for the treatment of AML is focusing on understanding the genomic background of the disease, including the way each mutation leads to the development of AML and the mechanism by which different mutations affect each other's in driving the disease relapse. An increased understanding of the heterogeneous nature of the disease is supporting the development of future therapies. Particularly, novel compounds showing different mechanisms of action are currently being tested – such as monoclonal antibodies that have the capability of targeting specifically leukemic stem cells. In addition, thanks to the remarkable achievements reached in the field of immunotherapies, current efforts are also taking place in order to investigate immune-base therapies, such as the use of immune checkpoint inhibitors [5] and chimeric antigen receptor T-cell therapies (CAR-T) that act by targeting specific epitopes that are expressed on AML blasts.

Figure 7.5. Marketed vs pipeline drugs for the treatment of AML

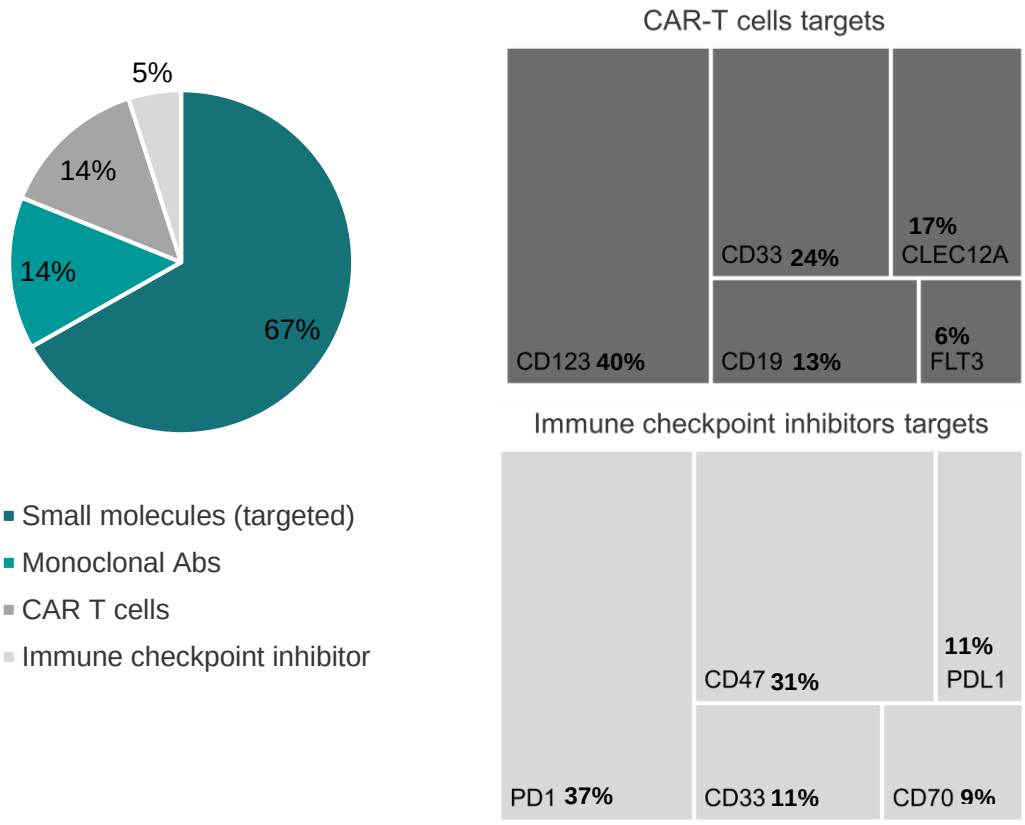


*Pie charts showing the number of marketed and pipeline drugs for the treatment of AML. The majority of marketed drug relies on chemotherapeutic agents. However, chemotherapy represents a really low percentage of drugs under investigation. The majority of pipeline drugs is constituted by targeted therapies (**919**) and immunotherapies (**427**). The ongoing trials and well-designed correlative interrogation of the immune system in patients treated on such trials will further enhance the understanding and clinical application of immune therapies as single agent and combination approaches for the treatment of AML.* **Source: GlobalData.**

The main conclusion of the results obtained from the trend analysis for the treatment of AML is that small molecules for targeted therapies constitute the majority of the pipeline drugs (Figure 7.6). Concerning immunotherapeutic approaches, a leading target for CAR-T cells and monoclonal antibodies therapies has not yet been identified. For what regards CAR-T cell therapy, several factors currently limit the use of CAR-T cells for patients affected by AML, such as biological barriers, technical and manufacturing issues, patient-related factors, and limitation in deliverability of therapy for all patients with AML [6]. Indeed, the ideal target for CAR-T cell therapy is an antigen highly expressed on the surface of all malignant cells, but absent from all healthy cells. CD123 (**40%** of the pipeline drugs estimated on GlobalData, **Figure 7.6**) is the transmembrane alpha chain of the interleukin 3 receptor. Due to its surface expression and its overexpression on AML blasts and leukemic stem cells, as well as its low expression on normal hematopoietic stem cells, CD123 qualifies as a suitable target [7], [8]. A recent study [9] demonstrated that CARs can be engineered using VH and VL chains derived from different CD123-specific mAbs to generate a specific combination that reduces toxicity for normal hematopoietic stem cells while ensuring their toxic effects on leukemic cells. CD33 represents another attractive target for immunotherapy against AML, comprising **24%** of pipeline drugs reported on GlobalData (**Figure 7.6**). CD33 is expressed in up to 90% of leukemic blast cells but also on healthy myeloid and myeloid progenitor cells. It is not expressed on early pluripotent CD34-positive hematopoietic stem cells, though it is expressed by hepatocytes, which determines the non-hematological toxicity in the form of veno-occlusive liver disease (VOD) [10]. Although *gemtuzumab* (m*ylotarg,* Pfizer, Berlin, Germany), a humanized drug-conjugated anti-CD33-antibody was first approved in 2000 by the FDA, it was withdrawn by the European and US markets in 2010 due to bone marrow toxicity and VOD. It was then reintroduced in 2018 thanks to a meta-analysis by Hills et al. that demonstrated that a low, fractionated dose of m*ylotarg* in combination with chemotherapy led to an improved OS of 280 treated AML patients [11]. Looking further at the monoclonal antibodies approach, the PD-1/ PD-L1 pathway (comprising **37%** and **11%** of the pipeline drugs respectively on GlobalData, **Figure 7.6**) is thought to play a role in immune evasion and cytotoxic T-cell exhaustion in AML, and it may be associated with the progression of the disease. Finally, CD47 (**31%** of the pipeline drugs on GlobalData, **Figure 7.6**) is

considered as a novel macrophage immune checkpoint that plays an important role in cancer immune evasion across multiple cancer types, and it has been particularly been identified as a leukemic stem cell marker in AML [12]. Therapeutic blockade of the CD47-SIRPα pathway has led to remarkable pre-clinical efficacy in vivo with robust developments in clinics [13]. Initial data with *magrolimab*, a first-in-class anti-CD47 antibody, has been shown encouraging efficacy results when combined with *azacytidine* in AML patients. Future efforts will be necessary to highlight the clinical importance of targeting immune checkpoints such as CD47 and the critical role for macrophages in the pathophysiology of leukemic disease.

Figure 7.6. Targeted therapy and immunotherapy pipeline drugs for AML

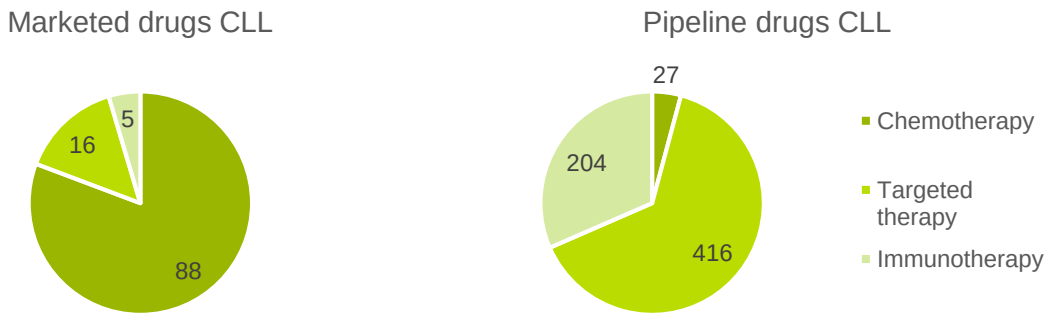


***Pie chart**: Targeted therapy, which represents the main area of pipeline treatments for AML, is constituted by small molecules (**67%**). For what regards immunotherapy, CAR-T cells constitute **14%** of AML therapeutic approaches. **Tree map**: The most frequent targets for CAR-T cell therapy are CD123 (**40%**) and CD33 (**24%**). The common targets for immune checkpoint inhibitors are PD1 (**37%**) and CD47 (**31%**).* **Source: GlobalData**.

Chronic Lymphocytic Leukemia (CLL)

Similarly to AML, although the majority of the marketed drugs for the treatment of CLL are chemotherapeutic agents, these drugs represent just a small percentage of the pipeline drugs (**Figure 7.7**). New drugs under development comprise mainly targeted therapies and immunotherapies. Novel approaches including immune checkpoint inhibitors and CAR-T cells are giving hope for providing an alternative treatment to stem cell transplantation practices in the future.

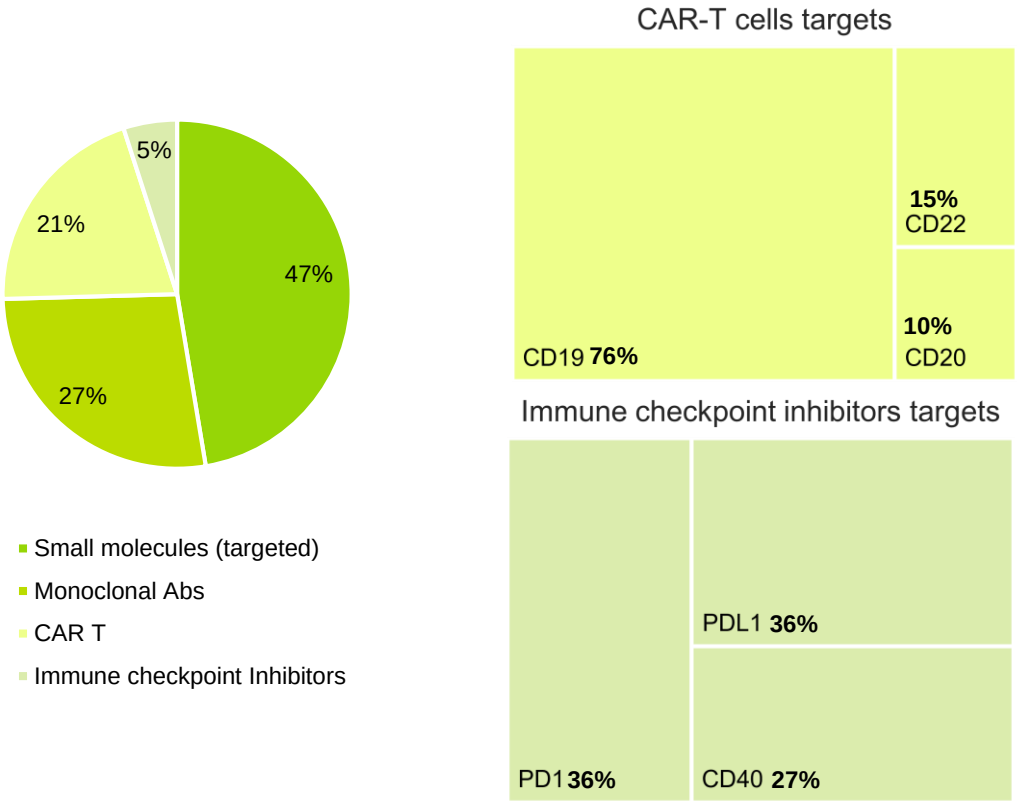
Figure 7.7. Marketed and pipeline drugs for the treatment of CLL



*The majority of marketed drug for the treatment of AML relies on chemotherapeutic agents. However, chemotherapy represents a really low percentage of drugs under investigation. The majority of pipeline drugs is constituted by targeted therapies (**416**) and immunotherapies (**204**).* **Source: GlobalData**.

The trends analysis showed that small molecules constitute the main area of pipeline drugs for the treatment of CLL, followed by monoclonal antibodies, CAR-T cells and immune checkpoint inhibitors (Figure 7.8). CD19 and PD-1/PD-L1 are the top targets for CAR-T cells and monoclonal antibodies respectively. The most advanced CAR-T cells developed to date are directed against CD19 [14]. Since the first report about the efficacy of second-generation CAR-T cells against CLL in 2011 [15], other results have been published or reported for the injection of CAR-T cells [16]. Patients with poor prognosis still show a low response rate, but there are signs of efficacy and the absence of graft-versus-host disease is highly promising. However, CAR-T cells therapy has a lower efficacy compared to other hematological indications. This aspect may be partly due to the intrinsic characteristics of the immune system in CLL, that include particular mechanisms that lower CAR-T cell activation and transduction [17]**.** Moreover, it has been showed that CLL patients already display immune defects at early disease stages, which might prevent the initiation of a strong antitumor response [18]. Recent studies reported a novel link between the immune checkpoint axis PD-1/PD-L1 on metabolic programming of T cells. Particularly, it has been demonstrated that PD-1 ligation causes a weaker antitumor response. PD-L1 is highly expressed on CLL cells and PD-1 on patrolling immune cells of CLL patients. Therefore, blocking PD-L1/PD-1 signaling might prevent these immunosubversion mechanisms. Monoclonal antibodies designed to block the interactions between PD1 and its ligands have shown significant clinical activity in solid tumors and Hodgkin lymphoma, but has yet to be extensively demonstrated for CLL [19].

Figure 7.8. Targeted therapy and immunotherapy pipeline drugs for CLL



***Pie chart**: Small molecules represent the main areas of pipeline drugs for the treatment of CLL (**47%**), followed by monoclonal antibodies (**27%**), and immunotherapeutic approaches such as CAR-T cells (**21%**) and immune checkpoint inhibitors (**5%**). **Tree map**: The most frequent targets for CAR-T cell therapy is CD19 (**76%**). The common targets for immune checkpoint inhibitors are PD-1 and PD-L1 (**36%**).* **Source: GlobalData**

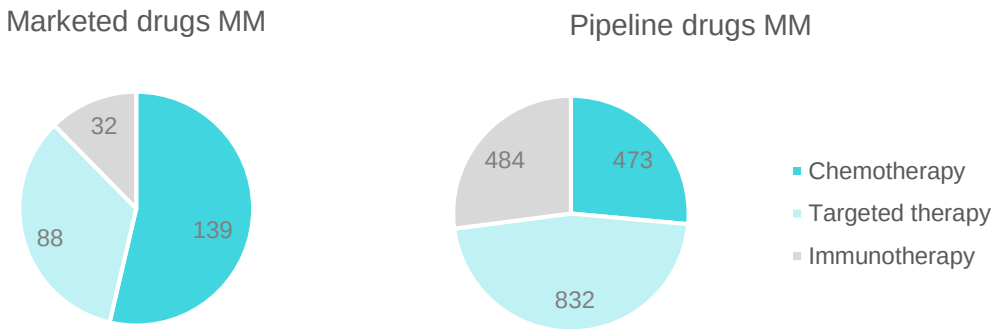
Multiple Myeloma (MM)

Differently from the before mentioned indications, a great percentage of marketed drugs for the treatment of multiple myeloma are targeted therapies, besides the traditional chemotherapeutic approaches (**Figure 7.9**). Indeed, one of the key challenges in the MM space is that patients develop drug resistance very easily, triggering the need for different therapeutic modalities to be evaluated. Multiple innovative drugs for the treatment of multiple myeloma with different mechanisms of action have been developed in the past decade. Important achievements have been particularly made in understanding the biological background of the disease, leading to improved tools designed for disease prognostication [20] [6]. Although MM remains an incurable disease for most patients [21], the overall progress led to improved survival for patients with MM.

The trends analysis showed that small molecules constitute the biggest area of pipeline treatments for MM, followed by monoclonal antibodies and CAR-T cells, and immune checkpoint inhibitors. The antigen that has been most frequently targeted with CAR-T cells based therapies for MM is the B-cell maturation antigen (BCMA) or CD269 (counting **74%** of CAR-T cells targets on GlobalData, **Figure 7.10**). BCMA is a transmembrane glycoprotein from the tumor necrosis factor receptor superfamily. It is an important player in long-term plasma cell survival and B-cell differentiation into plasma cells [22]. Its expression

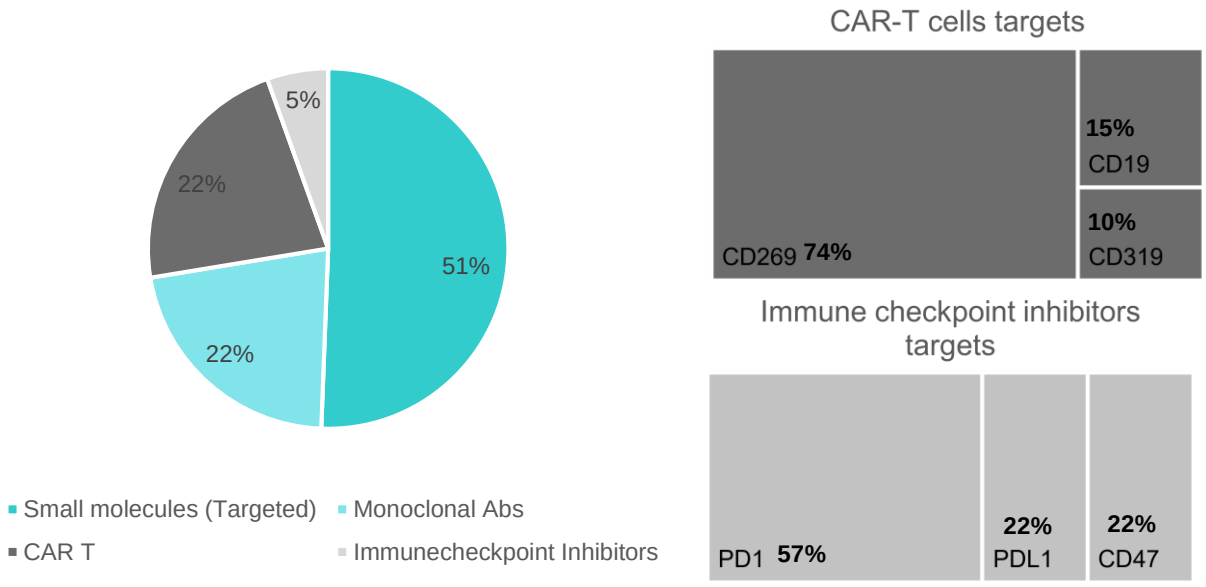
increases during B-cell differentiation and can be found only in late memory B cells and plasma cells. However, BCMA is also an important factor for the survival of malignant plasma cells, as malignant plasma cells usually express higher BCMA levels compared to normal plasma cells [23]. Anti-BCMA CAR T-cell therapy has shown safety and efficacy in heavily pretreated MM patients, and the field is rapidly evolving towards strategy optimization worldwide [24]. **Specifically for the field of monoclonal antibodies, the role of PD-1/PD-L1 pathway** (constituting **57%** and **22%** respectively of monoclonal antibodies on GlobalData, **Figure 7.10**) **in mediating immune escape in MM and the corresponding therapeutic efficacy of PD-1/PD-L1 blockade has risen as an area of great interest**. Patients with advanced MM present high levels of PD-L1. On the contrary, PD-L1 is not expressed on normal plasma cells [25].

Figure 7.9. Marketed and pipeline drugs for the treatment of MM



*Differently from AML and CLL, targeted therapies-based drugs (**88**) constitute a great percentage of marketed drugs together with chemotherapeutic agents (**139**) for the treatment of MM. However, the treatment solutions in the pipeline comprise mainly targeted therapies (**832**) and immunotherapies (**484**). Still a lot of chemotherapeutic drugs are under development (**473**) due to the high risk of patients resistance to common cytotoxic induction therapies.* **Source: GlobalData**.

Figure 7.10. Targeted therapy and immunotherapy pipeline drugs for MM



***Pie chart**: Small molecules (**51%**) constitute the biggest area of pipeline treatments for MM, followed by monoclonal antibodies and CAR-T cells (**22%**), and immune checkpoint inhibitors (**5%**). **Tree map**: The most frequent targets for CAR-T cell therapy is CD269 (**74%**). The common target for immune checkpoint inhibitors is PD-1 (**57%**).* **Source: GlobalData**.

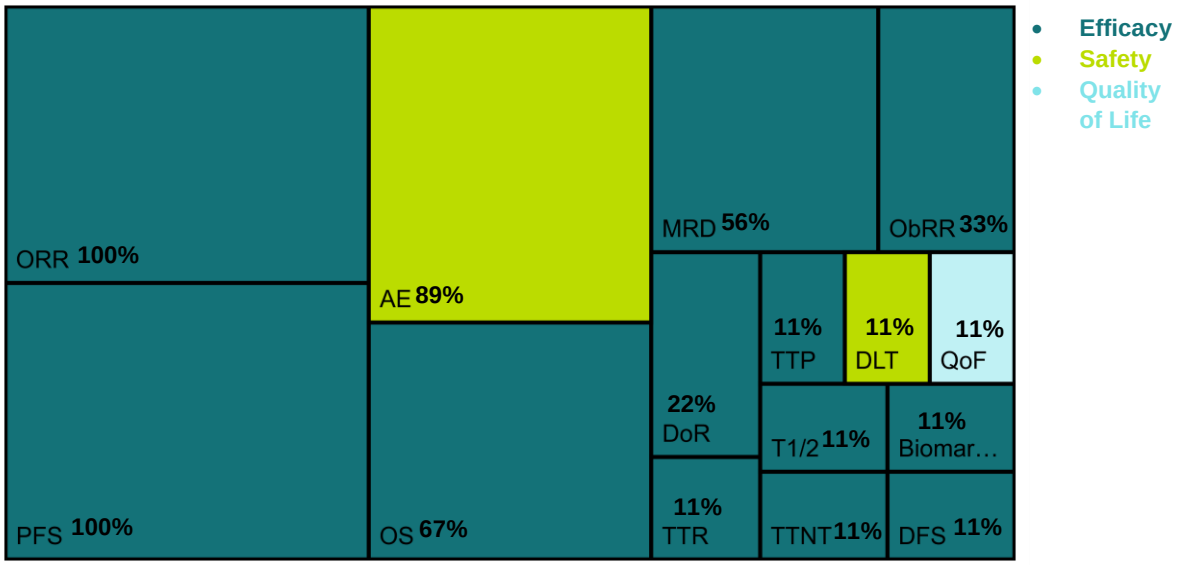
7.3 Defining Endpoints

As already explained in Chapter 4, new treatments for cancer derive through a series of clinical trials. In phase I trials the tolerable dose of a drug or a combination of drugs is assessed; in phase II trials it is investigated whether the experimental therapy may or may not work. Phase II trials constitute a crucial step in the development process of oncological drugs, because at the end of these trials it is not established a new stander of care, but it is rather provided important efficacy data that is fundamental to allow the study to access phase III [26]. In other words, phase II trials are useful instruments to screen whether drugs are worth to be tested in a large phase III trial. Indeed, the transition phase of between phase II and phase III trials became a critical step in clinical drug development. In phase II studies, analyses are conducted with a critical eye before navigating an expensive, time and resource consuming phase III trial. According to the FDA, only 33% of drugs move from phase II to phase III [27], meaning that many phase II trials don't receive approval to succeed to the next phase. To estimate the premature signals of efficacy of a new treatment investigator have to define endpoints. According to the FDA, primary endpoints in clinical trials are objective, clinically meaningful, and reproducible measures of patient outcomes [28]. **Response rate (RR) and progression-free survival (PFS) are frequently used as primary endpoints in oncology clinical trials. Common secondary endpoints include toxicity assessments**. These endpoints determine specific outcomes that are fundamental to decide go *versus* no-go to promote a clinical study to a late phase. Of important note, the determination of endpoints differs significantly between solid tumors and hematologic oncology [29]. The assessment of a participant's improvement/response for most solid tumors is based on the Evaluation Criteria in Solid Tumors (RECIST). In contrast, blood cancers rely on different measurements to determine changes and disease progression related to the investigational agent, which can complicate the trial design, conduct and assessment. For these reasons, an analysis was performed on *GlobalData* in order to highlight the most frequent endpoints assessed in AML, CLL and MM phase II studies that were successfully approved to phase III. The clinical trials were selected from the top selling drugs in 2018 for AML, CLL and MM (**Supplementary Figure 7**). The final aim was to delineate a common trend for these clinical trials in order to understand the basics for decision to promote a clinical trial to the later phase. **On a general base, overall survival (OS) remains the gold standard when evaluating the effectiveness of any anti-cancer investigational agent. However, progression-free survival (PFS) is the most commonly used surrogate endpoint for trials involving advanced cancers**. **Other surrogate endpoints comprise disease-free or event-free survival, response rate or objective response rate and time to progression** (**Figure 7.11, 7.12, 7.13**).

Figure 7.11. Endpoints assessed during AML phase II studies

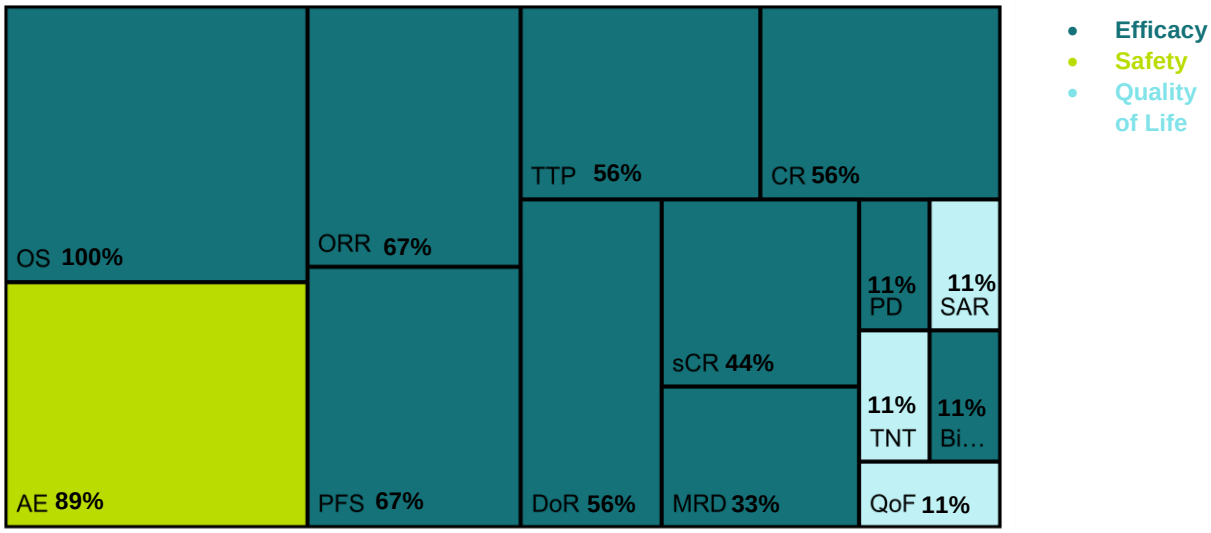
*Nine successfully approved phase II clinical trials from the top 3 drugs for the treatment of AML (Vidaza, Venetoclax, Vyxeos) were analyzed and the main endpoints were highlighted. Primary outcomes of early-phase AML trials assess drug tolerability and safety (**AE**, **89%**). Particularly, drug development in acute leukemias result complicated by the baseline morbidity of these diseases that relates directly to leukemia-associated bone marrow failure with an expectedly high risk for overwhelming infection and attendant multiorgan dysfunction [30]. Efficacy is less evaluated, since it is a primary outcome pf phase III trials that generally form the basis of new drug approvals.* **Source: GlobalData**.

Figure 7.12. Endpoints assessed during CLL phase II studies



*Nine successfully approved phase II clinical trials from the top 2 drugs for the treatment of CLL (Rituximab, Imbruvica) were analyzed and the main endpoints were highlighted. The two endpoints that were evaluated in all the analyzed clinical trials were assessing the efficacy of the treatment, (**ORR** and **PFS**, **100%**). In addition to that, safety (**AE**, **89%, DLT 11%**) is another central endpoint for early phase CLL clinical trials [31].* **Source: GlobalData.**

Figure 7.13. Endpoints assessed during MM phase II studies



*Nine successfully approved phase II clinical trials from the top 5 drugs for the treatment of MM (Revlimid, Velcade, Pomalyst, Darzalex, Kyprolis) were analyzed and the main endpoints were highlighted. OS is the gold standard endpoint for MM clinical trials, due to the substantial improvements in survival for MM affected patients over the recent years. In addition to that, the increasing complexity of the novel recommended regimens and their prolonged use, warrant a heightened vigilance for early and late side effects (***AE*, *89%*). **Source: GlobalData.**

7.4 Conclusions – Chapter 7

- The invasive side-effects often associated to chemotherapeutic treatments remain the main point of concern in clinical trials. The number of clinical trials investigating cytotoxic agents decreased remarkably between 2017 and 2018.
- Combination chemotherapies dominate over monotherapies due to synergy and additive effects.
- Targeted therapies constitute a promising approach to improve outcomes of cancer affected patients while reducing treatments associated toxicities. The number of clinical trials investigating targeted agents increased to almost 600 clinical trials in 2018.
- Anticancer immunotherapies led to a new era of cancer treatment, becoming particularly popular for hematological indications.
- Chemotherapies still constitute the backbone of induction therapies for AML, CLL and MM. However, the majority of pipeline drugs is constituted by targeted therapies and immunotherapies for all the three indications.
- Phase II – Phase III transition is considered as a critical step in clinical drug development. According to the FDA, only 33% of drugs in Phase II move to the next phase.
- For evaluations regarding the effectiveness of the treatment, overall survival (OS) remains the gold standard in clinical trials. Progression-free survival (PFS) is another central endpoint in oncological clinical trials. Other surrogate endpoints comprise disease-free or event-free survival, response rate or objective response rate and time to progression. In addition to that, safety (AE, DLT) is often assessed.

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8 External analysis

Macroenvironmental factors affecting the conduct of hematological malignancies clinical trial

8. External analysis

> *What are the macroenvironmental factors that affect CATO SMS ambition to invest in this project?*
> Consider the political, economic, social, technological, ethical and legal factors that have an effect on the conduct of hematological malignancies clinical studies.

8.1 PESTEL analysis

Performing an external analysis is important in order to evaluate the macroenvironmental factors that affect CATO SMS ambition to integrate hematological malignancies clinical trials in its oncological portfolio. This analysis usually consists of six factors, abbreviated with the acronym PESTEL, which stands for: **political**, **economic**, **social**, **technological**, **ethical** and **legal** factors [1].

Political

Brexit consequences on regulations, access to medicines and funding of clinical trials.

Since January 31st 2020, the UK is no longer a member of the European Union. UK and EU agreed that until 31st December 2020 UK won't be considered as a Member State, but market access for medicines will continue in the same way [2]**.** In addition to that, the EU's Clinical Trials Regulation (CTR) [3], which is expected to be implemented in 2020, will enable an application process for drug development, involving a single portal for EU clinical trials. However, it has to be considered that **Brexit introduced significant short- and long-term political instability and uncertainty** in a broad set of areas including **regulations**, **access to medicines**, **data**, **workforce** and **funding of clinical trials**. Many pharmaceutical companies running clinical trials through contract research organizations and contract manufacturing organizations based in UK and being no longer part of EU, will face negative consequences on testing and distributing investigational medicinal products. Finally, it seems clear that many scientific disciplines will lose EU funding post-Brexit as will cancer research [4]. **In conclusion, the impact of Brexit on the supply chain of clinical trials for CATO SMS will have significant financial and economic consequences on the development of new drugs.**

Economic

The rising drug prices and financial implications of Covid19 pandemic on (hematological) oncology clinical trials

Over the past 15 years, treatment outcomes for hematologic malignancies have improved remarkably. However, **cancer drug prices** have also risen dramatically [5]. Given the fact that cancer is estimated to affect 1 in 3 individuals in their lifetime, an increasing number of families will at some point face a situation of cancer diagnosis within the family and need a cancer treatment. Studies have reported that 10% to 20% of patients cannot afford the therapeutic treatments [6]. Even thought many progresses have been made in the diagnosis and clinical

management of cancers, medical experts often question the value of cancer treatments at their current high prices [7]. Particularly, it has been demonstrated that in the field of hematological malignancies the majority of drug prices are not justified [5]. Drug price should reflect its value in terms of the benefit given to patients – such as **survival prolongation**, **degree of tumor elimination**, or **improved quality of life**. However, drugs developed for the treatment of cancers provide minor benefits, especially for the most aggressive indications. In a health care delivery system relying on **third-party payers** (private or government) covering the costs of cancer treatment for the public - that has a presumed and possibly legal right to access to all approved drugs - the unaffordable price of cancer drugs places major problems. For example, insurance companies don't know how to correctly price policy premiums because the approval and clinical usage of new expensive drugs is very unpredictable and geographically variable [8]. In addition to that, there's the risk that approved cancer drugs may be used for indications and conditions not agreed by the FDA. Therefore, **off-label use** may increase. The issue of soaring and unsustainable drug prices began to attract the attentions of policymakers [9], [10].
Other economic implications that need to be considered concern the **coronavirus disease 2019** (**COVID-19**) outbreak, that has rapidly escalated into a global pandemic. With the COVID-19 pandemic turning the world upside down, it's hard to think of an activity or business that hasn't been influenced – with no exception for clinical trials. A survey published on April 23rd 2020 by Medidata [11] revealed that the top four concerns expressed by respondents there were working on clinical trials sites included **financial implications for cancelled studies** and financial implications **from delayed milestones**. Another study recently reported that COVID-19 pandemic is currently disrupting clinical research in much of the world [12]. This study performed between March and April 2020 was conducted in order to show the effect of this crisis on the management of oncology clinical trials. During the survey assessment period, factors such as **patient enrolment** were severely impacted by the COVID-19 pandemic. The type of cancer therapy, including route of administration was a key consideration, and the survey revealed concerns about patient safety and a potential lack of research staff and resources. Another study [13] reported that patients suffering from hematological malignancies, and in particular recipients of hematopoietic stem cell transplantation (HSCT) could be at increasing risk from COVID-19. Indeed, these patients are usually at an advanced age, have multiple comorbidities, and are often immunosuppressed by their disease or therapy. Patients with leukemia, lymphoma, or myeloma; those who receive radical radiotherapy, cytotoxic chemotherapy, immunotherapy, antibodies, protein kinase inhibitors, or poly ADP ribose polymerase (PARP) inhibitors; and those with recent bone marrow or stem cell transplants could be especially vulnerable to COVID-19 [14]. The COVID-19 pandemic had serious consequences on the conduct of hematology clinical trials, as evidenced by Aveo Pharmaceuticals Inc. appointing COVID-19 as a reason for the study failure of *ficlatuzumab* in acute myeloid leukemia [15]. **For these reasons, CATO SMS has to consider the evident difficulties and the growing risks associated with new hematological malignancies study starts, trials progression and completion, as well as the financial and work safety impacts on the trial sites.**

Social

Demographic shift and practical implications for an ageing population

Many nations are currently facing challenges due to the ongoing **increasing demographic shift in age** among their populations. The United Nations reported that the world's population

of elderly who are 60 years old will double and those who are 80 years old will triple during the next 30 years at the same time as other age groups will decrease in number [16]. Populations ageing is not only one of the most significant social phenomenon of this century, it is also one of the greatest challenges facing humanity, say agencies as the World Health Organization [17], the European Medicines Agency [18] and the Centers for Disease Control and Prevention [19]. Particularly, an aging population place an unprecedented demand for healthcare systems. In accordance with the demographic shift, age-related chronic diseases – cardiovascular diseases, diabetes, cancer and chronic respiratory diseases – are currently rising. Regarding blood cancer indications, the median age at diagnosis for AML, CLL and MM are **68**, **72** and **69** years respectively [20], [21], [22]. For example, as the risk of developing MM increases with age, due to the demographic shift the number of diagnosed cases of MM is expected to spike from 354,000 cases to 555,000 at an Annual Growth Rate (AGR) of 5.69% (**Supplementary Figure 8**) [23]. Therefore, novel efficient therapeutic approaches are required to offer a clinical treatment to these diseases. Practical guidance is also required when treating ageing populations. For example, it has been estimated that twice as many patients aged 65-plus are hospitalized due to adverse drug events conditions compared to younger people [24]. In conclusion, the **demographic shift of the population represents a positive incentive for CATO SMS to integrate hematological malignancies in its oncological portfolio**. Indeed, since blood cancers affect specifically old patients, these indications will become more and more frequent and an increasing number of anti-tumor hematological clinical trials will be needed. However, it will be important to consider the **difficulties and practical implications** of performing clinical trials on older patients.

Technological

Personalized Medicine: The future of Blood Cancer indications

The cancer therapy landscape has been revolutionized by the concept of treatment personalization and by the development of specific treatments for particular tumor types. **Precision medicine** takes advantage of an innovative strategy of treatment selection by evaluating patient's specific immune markers, biological features and comorbidities [25]. Personalized medicine's rise began with oncology, in order to target tumors and their underlying genetic profiles. Oncology remains the main area of interest (**Supplementary Figure 9**), and there's potential for the treatment of blood cancers. For example, the identification of **Philadelphia chromosome** [t(9;22)] in patients with chronic myeloid leukemia [26] led to the discovery of *imatinib mesylate*, approved in 2002 by the FDA. Following this example, groundbreaking discoveries in the field of genomics and high-throughput technologies allowed the identification of multiple molecular alterations in hematological indications. Personalized and precision medicine seeks to build a foundation for cancer treatment through a broad spectrum of information. Potential inputs for advancing precision medicine include longitudinal tracking of healthy individuals to better understand the transition from non-diseased to diseased states; identifying with higher precision individuals at risk for disease; finally, tailoring treatments based on diverse and growing data information gathered during individual trials as well as population-based studies [27]. The data flowing into precision medicine will come from genetic databases, medical record, tissue banks, and other clinical sources of '**big data'**. Since most hematologic malignancies are caused by **genomic alteration** (point mutation, chromosomal aberrations, copy number variations), a complete understanding of these diseases can only be achieved by comprehensive screening of a large

number of clinical samples [28]. Massive parallel sequencing, the improvements in **next generation sequencing** (**NGS**), allows researchers to sequence the entire exome of leukemia or lymphoma cells, and it can be combined with RNA-Seq to evaluate the transcriptome. These techniques allow them to search for mutations, indels, gene fusions, copy number alterations, alternative splicing, and gene expression profiles from a blood sample of a person affected by leukemia [29]. Particularly, for hematologic indications such as AML, CLL and MM, once mutations in leukemic cells are identified, it is important to assess the temporal order in which mutations are acquired. Particularly, some leukemias first acquire important driver mutations, with substantial transforming ability such that additional mutations are dispensable. Targeting the earliest driver mutations holds the greatest therapeutic promise when they carry a relevant transforming potential.

In recent years, the term "precision medicine" is used to indicate **targeted and immunotherapeutic approaches** that act on biological abnormalities involved in carcinogenesis. Particularly, **adoptive T-cell therapy** represents nowadays a field of great interest for the treatment of hematological malignancies. Often these therapeutic approaches include a genetic manipulation of T cells, in order to enable a specific recognition of tumor antigens (discussed in Chapter 6). However, it is important to consider the multiple challenges that come with the implementation of clinical trials in precision oncology. For example, researchers are currently taking advantage of targeted NGS in order to uncover the genomic background of blood cancer indications; however, there will be a need for whole-genome sequencing. Bioinformatics tools are currently limited and will need to be optimized. Resistance to treatment is detected inefficiently, and tumor biopsies will be needed in order to allow a real-time monitoring. Predictive biomarkers are currently not available for all patients, and optimized technologies will be important to identify fundamental tumor markers in patients [25]. Only with these advances it will be possible to assess in all patients at the time of diagnosis their immune markers and genomic background in order to determine the optimal treatment. It is estimated that there will be a need in the future for phase II studies with innovative designs, such as adaptive, umbrella and N-of-1 trials that take into account the dynamic biological changes and complex features of cancers (for more information about innovative clinical trial design refer to internal report of **van der Heide C.**, **'Trends in adaptive oncology clinical trial design, and its implications for CATO SMS'** [30]). The future treatments for blood cancer indications will focus on enhancing the single patient's response based on their **unique genetic makeup**, along with targeting the driver event. Personalized oncology has been broadly defined as "getting the right treatment to the right patient at the right time, dose and schedule" [31]. The clinical management of hematologic malignancies will rely on targeted therapies and immunotherapeutic approaches alone or in combination with chemotherapies. Therefore, if CATO SMS is willing to actively approach the hematological malignancies clinical trials field, **it will be necessary to deepen its knowledge about patient's specific molecular and biological features, such as the use of biomarkers. During the conduct of clinical trials, it would be interesting to perform personalized treatments to different patients based on their genetic mutations and see if there's an improvement on the outcomes of the treatment.**

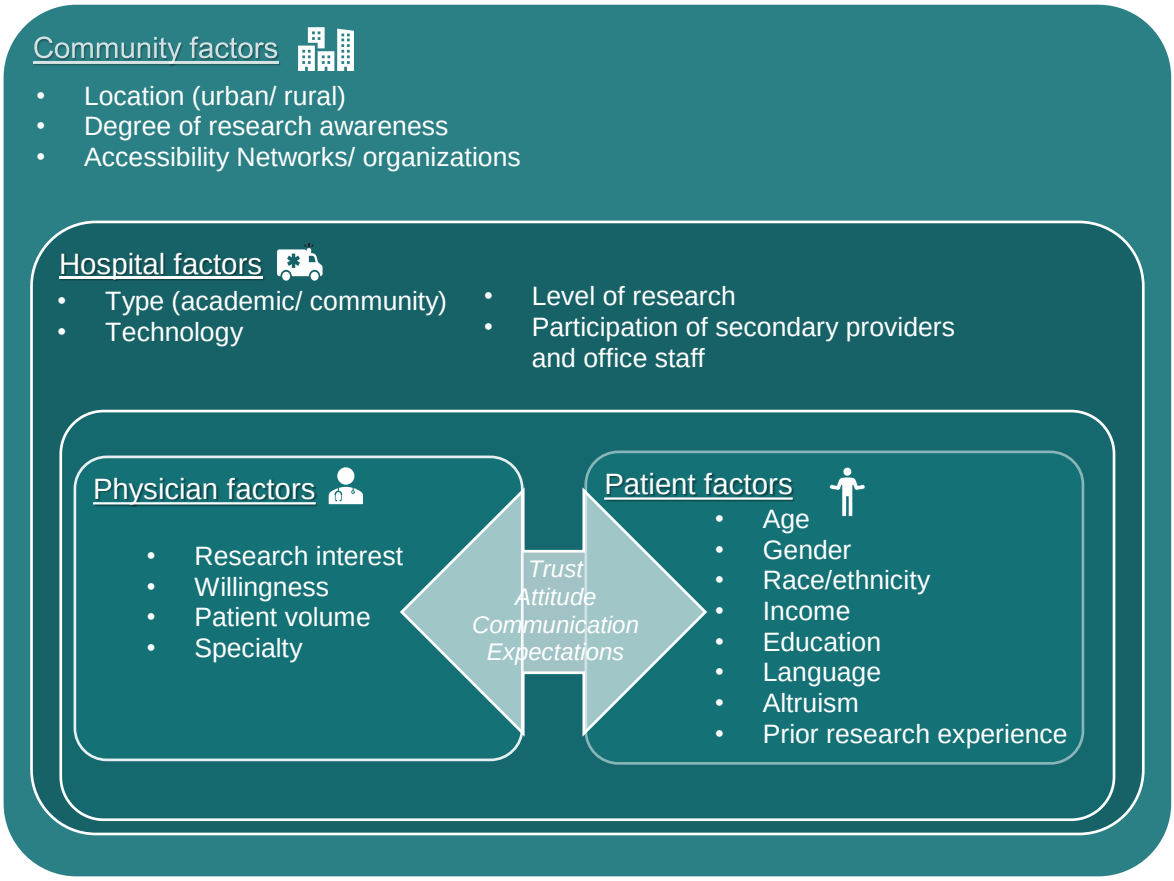
Ethical

Patients engagement: considering patients' needs and experiences

The design and conduct of cancer clinical trials implies special ethical responsibilities to safeguard the interests of research participants and to ensure that they represent an informed

partner in the efforts for improving cancer care. Standards of medical ethics and regulatory codes for protection of human research subjects require that the rights and interests of trial participants are considered and protected before, during and after the conduct of research [32]. Of important note, in recent years **patient engagement** in clinical trials has risen as an increasingly meaningful aspect of successful clinical trials [33]**.** From the 2007 inception of the Clinical Trials Transformation Initiative in a multi-stakeholder engagement model, patients have been included as valued partners. Patients engagement can be defined as a commitment to increase the benefits, desires and preferences of patients, in both the research and development process through collaborative relationships. Particularly regarding hematological malignancies clinical trials, sponsors have understood that it is important to take into consideration the patient needs when **recruiting**, **enrolling** and **retaining patients** [34]. Indeed, trials teams should be aware that patients affected by blood cancers make different considerations and decisions compared to patients affected by solid tumors. For example, patients diagnosed with a chronic hematologic disease are interested in the benefit that a clinical trial can offer; however, they are also aware that the disease may extend for years or even decades, and therefore they are also concerned about invasive procedures (such as **repeat biopsies** and **bone marrow exams**) that are likely to highly interfere with their lifestyle. On the other hand, the opposite is true for patients affected by acute cancers such as acute myeloid leukemia. Time is of essence, and they perceive available clinical trials as possibilities of life extension, even if trials involve more invasive interventions, multiple clinical visits or radiographic studies. As a result, it is necessary to clearly communicate trial's educational materials, providing information regarding **potential risks of the disease**, the **benefits** and the **impacts** study participation might have on one's **quality of life**. Patients engagement is considered as an important factor for successful patients recruitment and trial completion. A **patient-centered approach** [35] reported that multilevel factors such as, **trust** enhanced by the patient-physician relationship, **altruistic attitude** of the patient and provider, **clear communication** regarding details of the study, and **aligning expectations** of the study outcomes have relevant effects on the patients recruitment and retention. Therefore, **CATO SMS should consider a patient-centered recruitment and retention strategy** (**Figure 8**) **in order to achieve targeted sample in terms of number or timespan, ensuring the significance of the research findings**.

Figure 8. Conceptual model of patient-centered recruitment and retention



In this multicenter, longitudinal randomized controlled trial in localized prostate cancer patients, Chhatre S. et al., present a conceptual model of patient-centered recruitment and retention. According to this model, patient-centered recruitment and retention are affected by patient-, physician-, hospital-, and community factors. Strategies related to concepts such as trust (e.g. physician involvement, ensuring protection and information), trial details communication (through informative brochures and pamphlets), attitude (e.g. emphasizing altruistic value of research, positive attitude of providers and research staff), and expectations (e.g. clearance about study requirements and time commitment, update letters), are demonstrated to facilitate recruitment and retention. **Adapted from Chhatre et al., 2018 [35].**

Legal

Novel regulatory approvals constitute an advantage for hematological malignancies drugs

The US Food and Drug Administration (FDA) is entitled of approving drugs developed by pharmaceutical sponsors. It has been reported a growing FDA's flexibility in partnering with pharmaceutical sponsors in order to develop products useful for patients that are affected by a life-threatening disease [36]. There are two available approval pathways for drugs developed to treat life-threatening disease. In a regular approval, the demonstration of clinical benefit for patients is required (e.g. prolongation of life or better quality of life). In order to accelerate the development of drugs, four accelerating programs exist to ensure that clinical therapies are available earlier to patients affected by a serious disease that have few or no other options of treatment available. These programs are named **Fast Track** (**FT**) **Designation**, **Breakthrough Therapy Designation** (**BTD**), **Accelerated approval** (**AA**), and **priority review** [37] (**Table**

8.1). Particularly, a great number of new drugs approved for the treatment of hematological malignancies took advantage of these accelerating programs. For example, the BCL-2 inhibitor *Venetoclax* was approved for CLL affected patients with 17p deletion. Since it has been reported that patients with a 17p deletion have a poorer prognosis compared with CLL patients without this particular mutation, *Venetoclax* could benefit from an accelerated approval. In addition, the majority of the 59 BTW products that have been approved since 2012 **regarded hematology and oncology indications** [38]. In conclusion, hematologic malignancies affect a big amount of the population, and some patients have few options of treatment available for their disease. Therefore, **gathering accelerated approvals is an opportunity that can be reached through innovative scientific approaches and regulatory flexibility. This aspect might represent an incentive for CATO SMS to conduct hematological malignancies clinical trials for the benefit of rare and ultrarare populations.**

Table 8.1. FDA expedited review programs

Program	Features
AA	Accelerated approval is granted to a drug based on a surrogate endpoint that is considered to give a clinical benefit. Post-marketing clinical trials are required to the applicant in order to investigate the drug further [39], [40].
FT	Fast track designation is granted for drugs treating life-threatening diseases that show the potential to address unmet medical needs for patients that have no other cures available [41].
BTD	Breakthrough therapy designation is granted for drugs designed to treat serious conditions that show a remarkable improvement of a significant endpoint [41].
Priority review	Granted for drugs intended to treat serious conditions that provide clinical evidence of a significant improvement in safety or effectiveness [41].

AA: Accelerated approval. FT: Fast track designation. BTD: Breakthrough therapy designation. For specific information, consult US Food and Drug Administration [41]. Adapted from Farrell et al., 2017 [36].

8.2 Conclusions – Chapter 8

- Performing a PESTEL analysis is important in order to evaluate the macroenvironmental factors that affect CATO SMS ambition to integrate hematological malignancies clinical trials in its oncological portfolio. As a result, CATO SMS should consider:

- Short-term effects:

  - The COVID-19 pandemic has immediate disruptive effects on the conduct of oncology and specifically hematology clinical trials.

  - Patients affected by blood cancers have different potential viewpoints that set them apart from solid tumor patients, and it is fundamental to guarantee them while recruiting patients for clinical studies. Patients engagement can be considered as a successful strategy for significant patients recruitment and retention.

  - An important number of drugs designed to treat hematological malignancies use accelerated approval – programs. This aspect may constitute an incentive for developing novel therapies for blood cancer indications affecting rare and ultra-rare patients populations.

- Long-term effects:

  - The impact of Brexit on the supply chain of clinical trials for CATO SMS will have significant financial and economic consequences on the conduct of clinical studies for sponsors based in the UK.

  - The ongoing and increasing demographic shift in age of the population will place the need for an increasing number of oncological clinical trials, and specifically for hematological malignancies that have an increased risk of incidence in older people.

  - The future treatments for blood cancer indications will rely on precision medicine approaches that use the patient's tumor and cell-free DNA analysis, immune markers, and other biological features and comorbidities to determine and offer optimal therapy.

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9 Internal analysis

CATO SMS internal design and structure analyzed through the 7S Model

9. Internal analysis

> *How does the internal organizational structure of the company fit with CATO SMS ambition to start this project?*
> Perform an internal analysis in order to understand CATO SMS structure, core principles and business strategies.

9.1 The enterprise

CATO SMS comes from the merger of two **Contract Research Organizations** (**CROs**). CROs are private corporations that conduct a wide variety of clinical research-related activities and functions on behalf of biotechnology, pharmaceutical, and medical device companies sponsoring studies in human subjects. High-quality CROs have the potential to add remarkable benefit to the clinical trial process, including improving the quality of data collection and trial standardization.

SMS-oncology was founded in 2007 and was initially based at the Science Park in Amsterdam. By then, the company was conducting two departments, including Consultancy and Clinical Operations. As the enterprise started its growth, the oncological services expanded, introducing the Medical Affairs department in 2010, when for the first time a full-service study was conducted. A remarkable step was made in 2015, when SMS-oncology initiated a 4D service – providing a direction to sponsors along the entire drug-data-dossier path.

In October 2019, SMS-oncology announced its merger with **CATO Research**. CATO is a full-service contract research and development organization specialized in all areas of product development and regulatory strategy. By joining forces, CATO and SMS-oncology aimed to expand their presence across Europe and North America, while deepening their oncology and regulatory expertise and broadening their suite of services. Nowadays, CATO SMS counts more than 320 employees and a number of full range of personalized, high-touch services:

- Consultancy
- Medical writing
- Project management
- Regulatory affairs
- Site and investigator selection
- Site management and monitoring
- Medical affairs
- Pharmacovigilance
- Data management
- Insights & analytics reports

9.2 McKinsey 7S Model

The McKinsey 7S Framework is a management model developed by business consultants Robert H. Waterman, Jr. and Tom Peters in the 1980s [1]. The model is based on the theory that, an organization needs to align seven specific elements to perform well. Peters and Waterman described a company comprised of three “hard” (**Strategy**, **Structure**, **Systems**) and four “soft” elements (**Shared values**, **Style**, **Skills** and **Staff**) [2], represented in **Figure 9**. The model is most often used as an organizational analysis tool to assess and monitor changes in the internal situation of an organization. Whatever the type of change – restructuring, new processes, organizational merger, new systems, change of leadership, and so on – the model

can be used to understand how the organizational elements are interrelated, and so to ensure that the wider impact of changes made in one area is taken into consideration.

The internal analysis of this Report was conducted through interviews with employees working in different departments at CATO SMS, specifically at **Business Development**, **Oncology Drug Development Affairs**, **Medical Affairs** and **Data Management**. The information derived from the interviews was integrated with internal records and training materials at CATO SMS.

Figure 9. McKinsey 7S model applied to CATO SMS

The three "hard" and four "soft" elements that compose the 7S Model.

Strategy

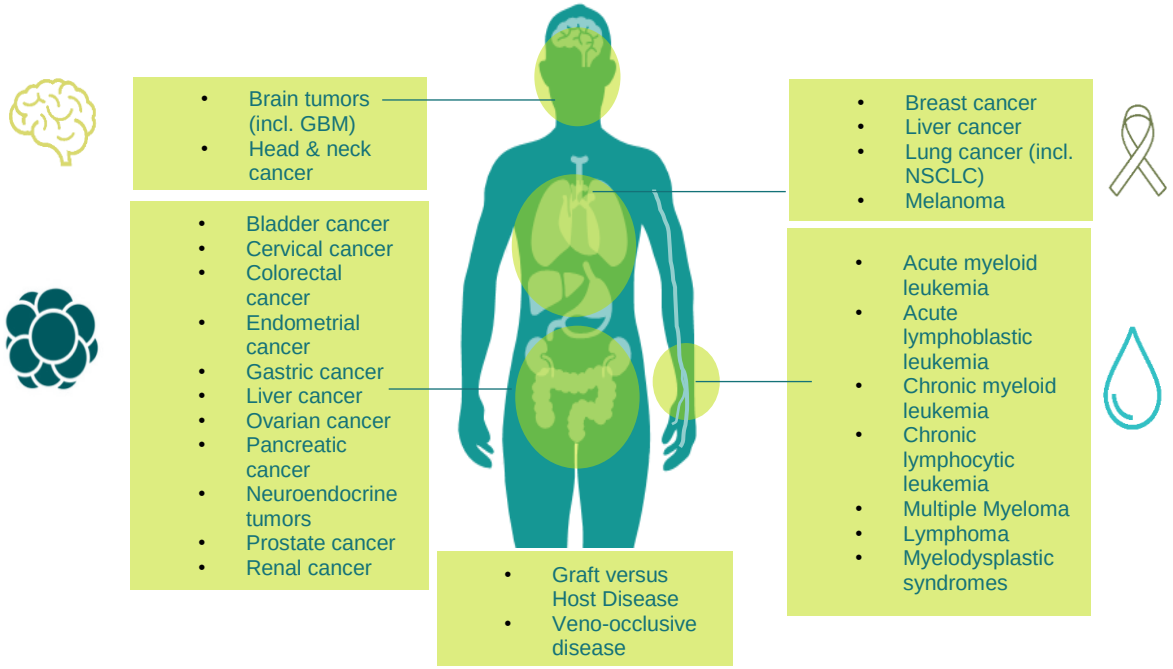
The must-win Is.

Invest in oncology knowledge and expertise

The main characteristic that sets CATO SMS apart from competition is the **strong oncology knowledge and expertise**. Teams of dedicated oncology professionals believe that strong passion and devotion are the true key to excel in clinical trials. One of the main objectives of the enterprise is to develop processes that establish and maintain a "**Culture of Quality**", in order to have a reputation of being valued for its in-depth oncology expertise and high-quality services. CATO SMS takes pride for currently conducting more than 300 oncology programs, working with different therapeutic approaches, such as chemotherapies, targeted therapies, gene therapies, radiotherapies, immunotherapies and hormonal therapies (**Figure 9.1**). The main strategy to support sponsors in the challenging drug development path consists not only in **recognizing the recent advances of oncological treatments**, but also **being ahead of**

future trends in therapies. For this reason, the initiative of starting this project reflects completely the strategy of the company.

Figure 9.1. Different cancer types included in CATO SMS projects



Illustrative figure showing the broad range of cancers involved in CATO SMS projects.

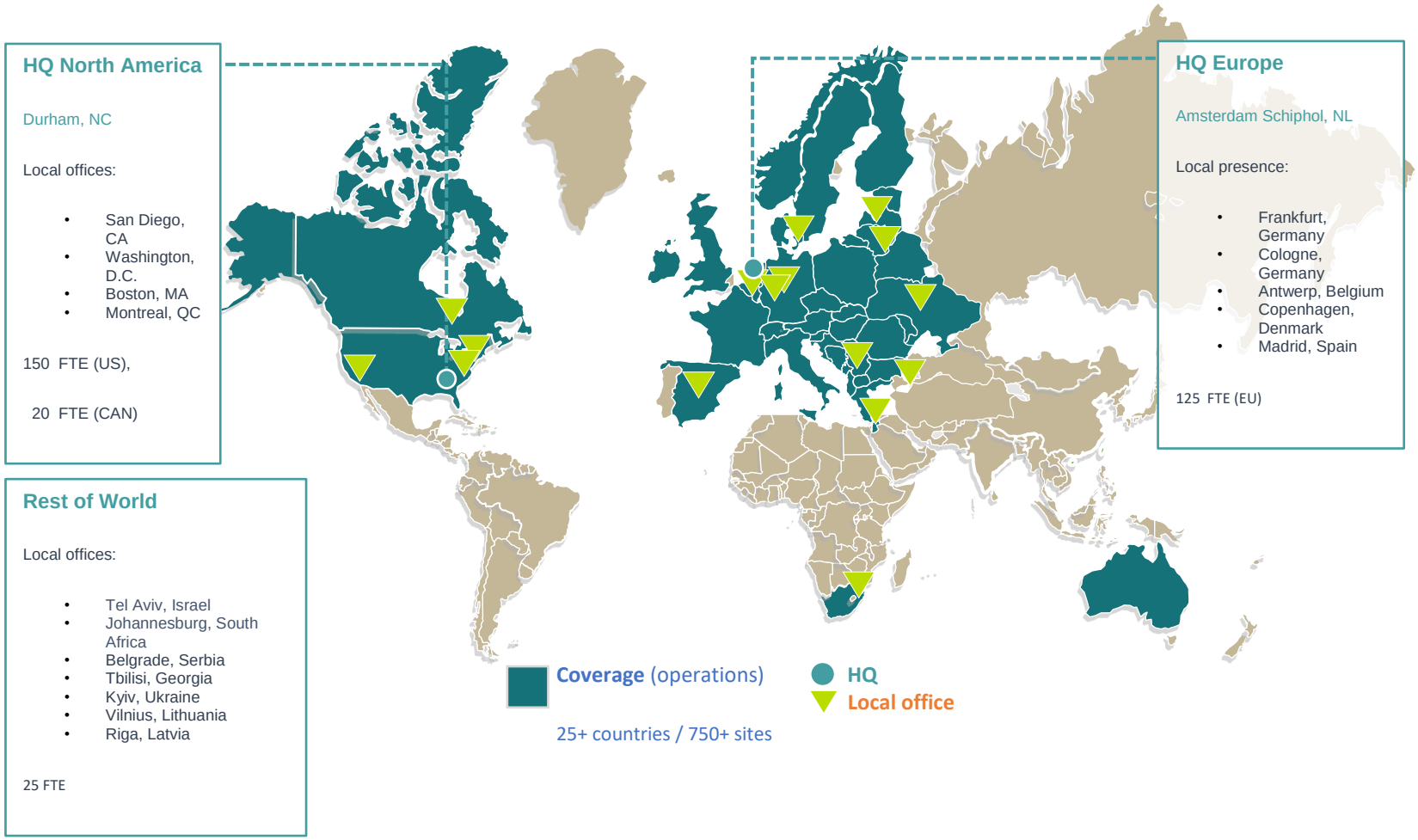
Increase patients recruitment

CATO SMS dedicated a whole **department of Patient Inclusion** to support communication between patient and doctor, enhancement of trial awareness amongst patients and to offer support to clinical investigators to lower trial workload. However, the company should consider that **patient population availability is at disadvantage if related to hematological oncology**. Given the fact that incident rates for blood cancers are lower compared to solid tumors, patient access for hematological clinical trials is more difficult [3]. Of particular importance, a large number of trials are dependent on the willingness of patients and professional to invest their time and effort to participate. If high levels of participation (through recruitment to the study and longer-term retention) are not accomplished, negative implications can have effect on statistical power, internal and external validity. Recruitment problems have also practical and financial repercussions, as they can delay completion of research or reduce its timely impact on patient health and wellbeing [4]. Strategies to improve patients recruitment and retention are displayed in Chapter 8, Ethical section.

Reach an International expansion

CATO research and SMS-oncology by joining forces expanded their headquarters in **Europe** and **North America**. Offices and operations are currently being carried on in Europe, North America (US, CA), Israel and South-Africa (**Figure 9.2**).

Figure 9.2. The recent expansion of CATO SMS

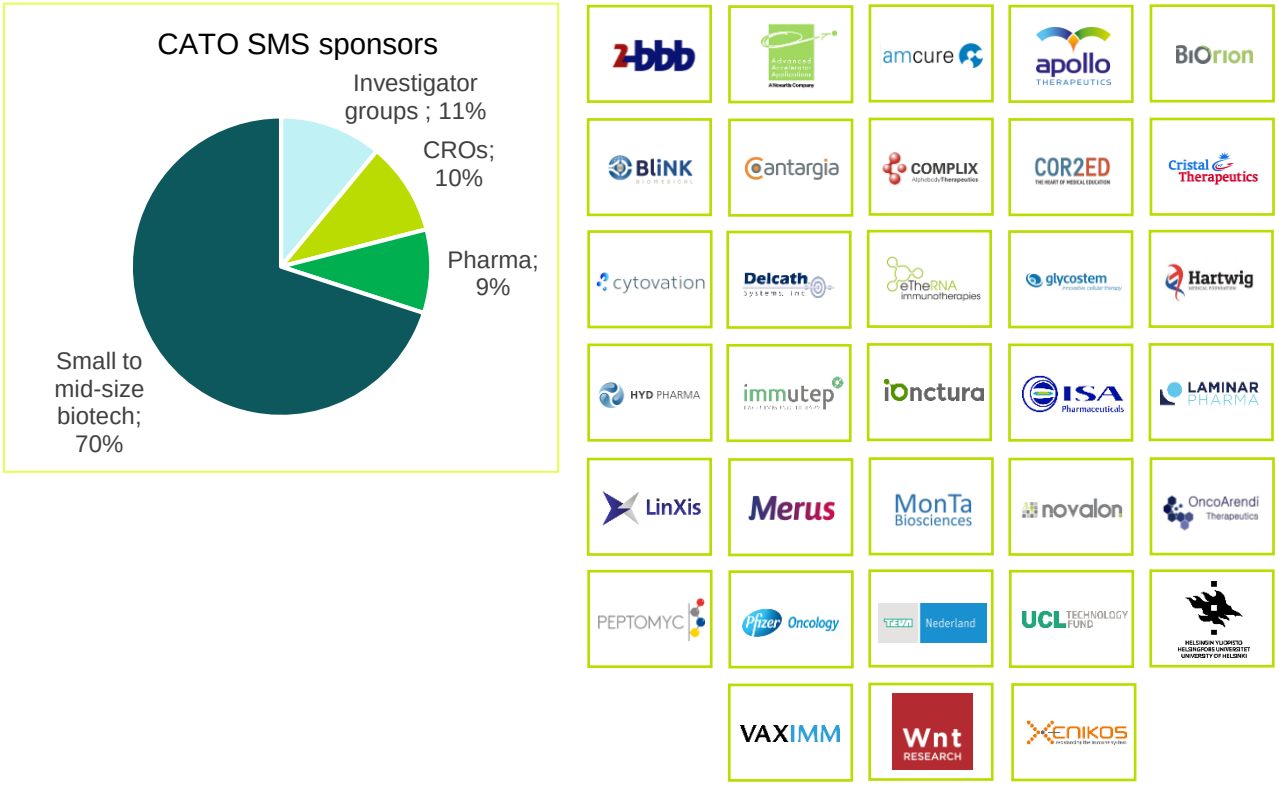


With the ambition to grow and to reach an international expansion CATO SMS aims to broaden its area of expertise, in order to contribute to the successful oncology drug development for the benefit of their sponsors and cancer patients worldwide.

Improve project win rates

Being a highly competitive field, oncology requires a robust stakeholder engagement. In order to improve project win rates it's important to **engage partnerships** and establishing **long-term relationships** with sponsors. The majority of CATO SMS sponsors comprises emerging **small to midsize biotech companies** (**Figure 9.3**). While larger pharmaceutical companies typically have in-house experience to navigate complex regulatory processes, smaller biotech companies tend to lack this expertise due to their size and focus on niche indications. For this reason, sponsors need help for specific capabilities to respond to the industry trends and to provide differentiated value. Once a partnership is established, CATO SMS aims to offer a proactive guidance in the drug development path, from the design of oncology studies to their full execution. Progress is tracked frequently and interventions are made where value is at potential risk (delays to clinical programs, misalignment in the development or commercialization strategy). The client satisfaction results are the reflection of feeling of joint commitment and collaboration, a strong knowledge and oncology expertise, and a flexible and tailor-made approach to meet specific needs of every project.

Figure 9.3. CATO SMS sponsors



Ensure an Internal organization health

CATO SMS has the objective of establishing a linkage between health and performance, at both the corporate and subunit level. An aspect that can be improved is **employee involvement**, particularly regarding the finalization of new ideas, due to a lack of focus and or time. However, CATO SMS has the potential to enhance this aspect thanks to the continuous growth of the company and the subsequent growing number of career opportunities. In addition to that, as a result of the recent merger, it's important that CATO SMS ensure a good integration of the different departments of the two enterprises, due to the different educational and working backgrounds cultures and styles of the companies.

Shared values

Core-guiding principles at CATO SMS

On top, Go-for-it, Eager to learn, Loyalty to mission and goals

At CATO SMS a **high-performance culture** is nurtured. Particularly, with a constant training and process alignment the employees are inspired to accomplish operational excellence and extraordinary results. All employees at CATO SMS are trained to conduct clinical trials according to the **Good Clinical Practice** (**GCP**), an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects [5]. AT CATO SMS there's a strong emphasis on **team work**, and as a central feature each employee of the team functions as a customer and supplier to other workers in the facility. Therefore, in this chain of internal customers and suppliers each operational unit ensures the quality of their own work. Thanks to this effective interaction between different teams, CATO SMS results proactive and responsive to the demands of the sponsors. Ensuring a clear and constant communication with the client is very important for a qualitative conduct of clinical trials. It allows to align expectations from both sides, and offer meaningful insights to data. The employees at CATO SMS are on a continuous learning and development path. Particularly, next to in-house knowledge, the company also collaborates with **external experts** in the respective field, such as oncologists in hospitals and pre-clinical researchers, often called **Key Opinion Leaders** (**KOLs**). CATO SMS explores exciting new frontiers of cancer treatments through the publication of white papers and webinars. Employees are valued for their **loyalty**, **integrity** and accountability.

Staff

Number and types of employees at CATO SMS

CATO SMS encounters a number of 320 employees. At the Amsterdam headquarters, 95% are oncology dedicated experts, 25% have a Master Degree and/or PhD. Specifically, regarding hematological malignancies it's fundamental to work with experts that have a deep understanding of the pathology, clinical manifestations, current treatment guidelines, study parameters and endpoints. For this reason, **CATO SMS that doesn't have yet a senior figure with specific experience with hematological malignancies**, should consider to invest in hiring an expert that can act as guidance for the other employees. In alternative, the company should provide tailored trainings to the staff by inviting Key Opinion Leaders (KOLs) or organizing webinars and white papers related to the recent advances in the hematological malignancies field.

Skills

Early phase oncology trials

The main area of expertise regards **early phase oncology trials**, with Phase I and II studies comprising 64% of CATO SMS work. Many of these Phase I/II trials involved first-in-human, followed a dose-escalation study design, and/or involved other multifaceted procedures. In contrast to late phase trials, detailed data are collected from a relatively low number of patients. However, these early phase oncology trials often recruit heavily pre-treated patients with advanced disease.

Inhouse data management

One of the strongest selling point for CATO SMS is the **robust inhouse data management department** that ensure a full-service management of clinical trials, including the delivery of high-quality validated data in compliance with industry and regulatory standards. CATO SMS has extensive experience in working with various **electronic data capture** (**EDC**) **platforms**. Managing data with a proven and reliable electronic data capture system significantly benefits hematologic oncology trials, ensuring a complete integration of data from local sites and central laboratories in an accurate and timely manner [3]. However, it has to be considered that data management is far more complex in hematologic oncology trials, compared to solid tumor studies. CATO SMS encountered **a number of challenges and milestones in data management during the conduct of blood cancer studies**, due to the multiplicity of definitions, classifications and clinical measurements. The main impacts regarded data collection, review and analyses. Reconciliation of data points including adverse events, medical history and chronology of study procedures are key to appropriately drive development strategy in hematologic oncology. In addition to that, data cleaning strategy and plan is needed to ensure clinical database quality.

Style

The matrix organization allows a **clear and easy communication style** between multiple departments and with the management team. Because employees answer to multiple managers, issues can be resolved in a **flexible way** and the interaction is enhanced at a company level. This aspect is fundamental to shape the actions of people in the organization to drive high performance and ensure strong motivation. It's important that these leaders in the organization ensure individuals understand what is expected of them, have sufficient authority and feel accountable for delivering results.

Systems

Procedures within CATO SMS, including management information systems and project management systems

CATO SMS takes advantage of **clinical data management system** (**CTMS**), a software that supports data management in clinical trials. This system represents an effective support for clinical trials under all aspects, including patient data, scheduling, reporting, analysis, and data management. In this system, the effective support of clinical data management dimensions leads to the increased accuracy of results and prevention of diversion in clinical trials.
In addition to that, CATO SMS works under **Standard Operating Procedures** (**SOPs**), that are specific methods employed to express policies in action during day-to-day operations. SOPs defines the activities requested to complete tasks for business processes, the associated resources and responsibilities.

Structure

The way CATO SMS is organized, including the types of departments and the structure of decision-making authorities regarding the allocation of resources and responsibilities.

CATO SMS structure follows a **matrix organizational structure**. In this company structure the reporting relationships are set up as a grid, or matrix, rather than in the traditional hierarchy. In other words, employees have dual reporting relationships - generally to both a functional manager and a product manager. Matrix structures are useful for the management of large-scale projects that require an efficient processing of a very large amounts of information. This way, the information while conducting a clinical trial can flow rapidly from and to different departments. In addition to that, the matrix organizational structure is considered as an advantage from CATO SMS employees, since it enhances a direct communication with the Management Team.

9.3 Conclusions – Chapter 9

- The McKinsey 7S Framework is a management model based on the theory that an organization needs to align seven specific elements – Strategy, Structure, Systems, Shared values, Style, Skills and Staff – to perform well.
- CATO SMS ambition to integrate the leading hematological anti-tumor therapies reflects completely the strategy of the company: recognize the recent advances of oncological treatments, while being ahead of future trends in therapies.
- CATO SMS should consider that aspects such as patient population availability, resources at the site, and data collection procedures constitute a disadvantage if related to hematological oncology. Therefore, it's important for CATO SMS to set the dedicated department of Patient Inclusion and Data Management as a priority to excel with hematological malignancies clinical trials
- In order to provide an internal organization health after the merger, it's important for CATO SMS to ensure an efficient integration of different departments coming from the two enterprises, that have different educational and working backgrounds cultures and styles of the companies.
- The inhouse Data Management department is a factor that set CATO SMS apart from competition.
- The matrix organizational structure that characterizes CATO SMS is considered as an advantage to provide a fast exchange of information about the trial from and to different departments. In addition, it allows a direct communication between the employees and the Management Team.

9.4 References

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10 Experience

Previous collaborations with sponsors interested in hematology

10. Experience

> *Does CATO SMS have sufficient previous experience in hematology?*
> Analyze the company's position and level of expertise in the hematological oncology area.

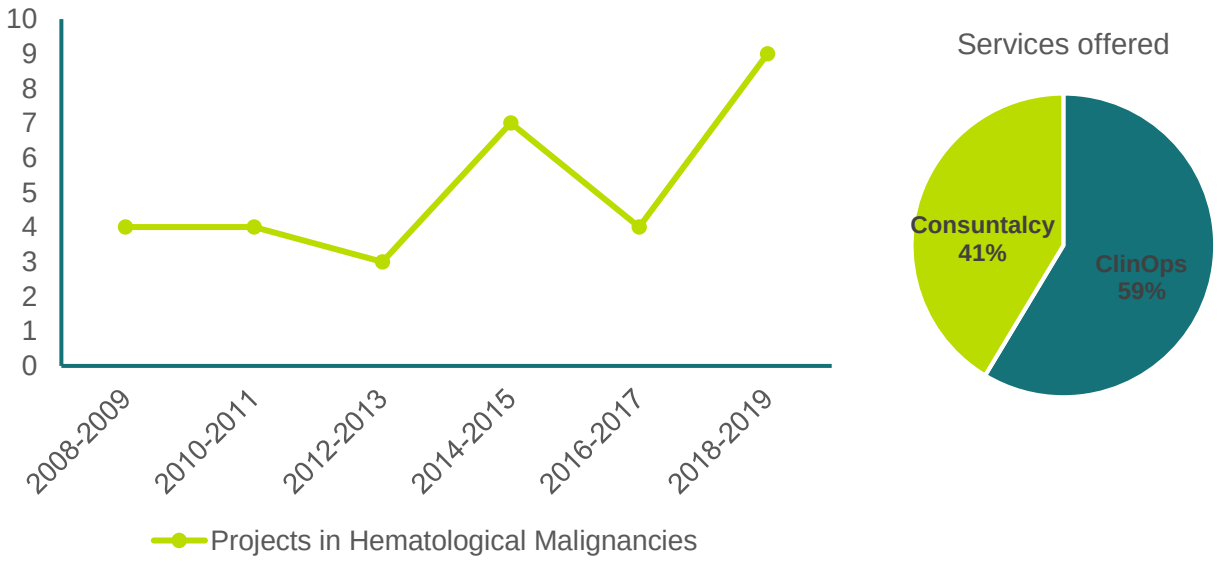
10.1 Introduction

The initial purpose of this chapter was to analyze the experience of CATO SMS concerning blood cancer indications. Therefore, the original plan of action was to conduct separate analyses for SMS-oncology and CATO Research hematological malignancies projects started before the merger. However, due to time constraints it wasn't possible to include information related to CATO Research experience. Therefore, the data contained in his Chapter regard only SMS-oncology experience with hematological malignancies projects.

10.2 Hematological malignancies projects

From the analysis regarding SMS-oncology experience, it emerged that the company worked on an increasing number of projects related to blood cancer indications in the past years (**Figure 10**). Particularly, between 2018 and 2019 SMS-oncology worked on 9 projects for sponsors interested in blood cancer indications. This finding is consistent with the rising growth of the hematological field described in Chapter 3. Of these projects, 41% were consultancy projects and 59% were clinical operations (ClinOps) projects.

Figure 10. Hematological malignancies projects conducted by SMS-oncology

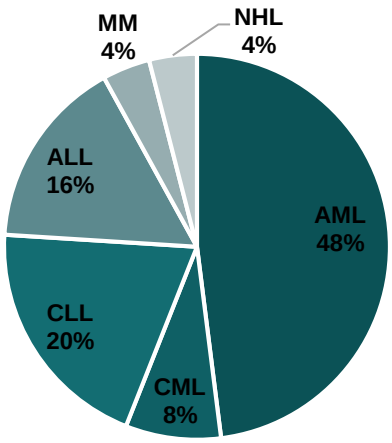


Analysis of SMS-oncology experience, including consultancy and clinical operation (ClinOps) projects.

SMS-oncology focused its attention on a number of blood cancer indications. The majority of projects concerned acute myeloid leukemia (AML) (**Figure 10.1**). For what regards the types

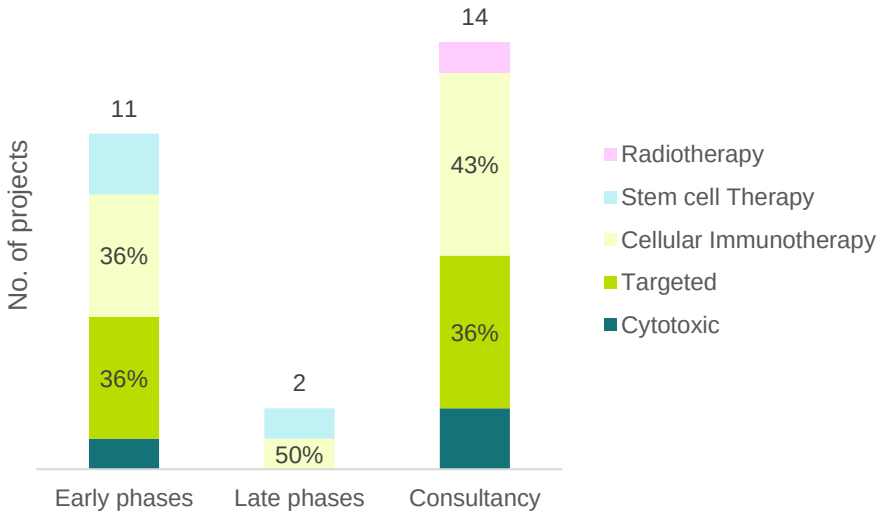
of therapies conducted during the clinical studies, cellular immunotherapies comprised the majority of the treatments for early phase and consultancy projects. Late phase trials included mainly cellular immunotherapies and stem cell therapies (**Figure 10.2**).

Figure 10.1. SMS-oncology experience with blood cancer indications



*Pie chart showing the number and types of blood cancer indications included in SMS-oncology projects. SMS-oncology acquired specific expertise in acute myeloid leukemia (**AML**, **48%** of the blood cancer projects) and chronic lymphocytic leukemia (**CLL**, **20%**). Unfortunately, the company doesn't have a lot of experience with multiple myeloma studies (**MM**, **4%**).*

Figure 10.2. SMS-oncology experience with hemato-oncological therapies



Bars chart displaying the different types of therapies used in SMS-oncology hematological malignancies projects classified in therapies for early phases or late phases trials, and consultancy.

10.3 Conclusions – Chapter 10

- The number of hematological malignancies projects conducted by SMS-oncology remarkably increased in the past years, starting from a number of 4 hematological malignancies projects in 2008-2009 to 9 projects in 2018-2019.
- SMS-oncology gained meaningful expertise with AML and CLL, but had a more limited experience with MM projects.
- SMS-oncology experience with hematological anti-tumor therapies mainly comprises targeted agent-based therapies and cellular immunotherapies.

10.4 References

The data illustrated in this Chapter have been retrieved by internal records at SMS-oncology.

11 Integration

Internal and external aspects integrated through a SWOT analysis

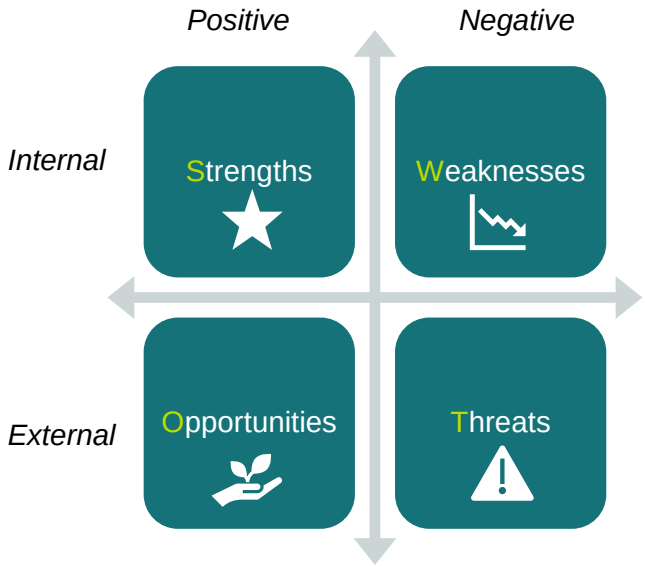
11. Integration

> *What does CATO SMS need to acquire in order to prepare for the expansion of its hematological malignancies' portfolio?*
> Integrate the findings obtained from the external and internal analyses and derive the final conclusions.

11.1 SWOT analysis

In order to provide a final advice for CATO SMS it is necessary to perform a summary analysis of observed or supposed internal strengths and weaknesses and external opportunities and threats (**Figure 11**) [1].

Figure 11. The SWOT matrix



The positive and negative, internal and external elements assessed in the SWOT analysis.

Strengths

Strong oncology expertise, Eager to learn, Inhouse data management

One of the most valuable capabilities of CATO SMS that emerged from the internal analysis (Chapter 8) is the **strong oncology expertise** that characterizes the company and that sets CATO SMS apart from competition. This aspect constitutes a valuable advantage for the company that is willing to integrate further the hematological malignancies in its oncological portfolio. Indeed, in order to conduct a successful study in this area it is required an understanding of the particular nature of blood cancers, current treatment guidelines and clinical practices. In addition to that, to appropriately plan a development strategy in hematologic oncology, it is necessary to have knowledge about the investigational agent's effect on the underlying disease, and not just the patient's symptoms, so as to discern efficacy and safety in comparison with current practices. At CATO SMS the **thirst for knowledge** is highly encouraged, as it constitutes a building block of the core values for the company

(Chapter 8). The employees have the opportunity to be on a continuous learning and development path, through activities with external experts, KOLs, conferences and trainings. This **proactive attitude** is fundamental to successfully conduct hematological malignancies clinical trials. Trainings about the selection of proper study design, endpoints and data capture strategy are essential in order to help sponsors bringing their innovative therapies to market and improving the treatment options and quality of life for patient affected by blood cancers. Finally, the **inhouse data management department** represents a competitive advantage for CATO SMS. This way, sponsors can rely on the generation of high-quality, reliable, and statistically sound data for clinical research.

Weaknesses

As highlighted in the internal analysis (Chapter 9) CATO SMS is currently **missing a leading senior figure with specialized experience in the field of hematological malignancies**. As previously underlined in the analysis, this aspect has a negative impact on the ambition of CATO SMS to actively integrate blood cancer indications in its oncological portfolio. A deep understanding of the pathology, clinical manifestations and treatment guidelines is important to discern efficacy and safety in comparison to current practices. Moreover, a correct assessment of study parameters and endpoints as well as data management are important for a strategic clinical trial design. Finally, the company is also lacking of **a shared vision and clarity of the future directions after the merger**. Some departments are concerned that the focus on oncology won't be as evident as it was before the collaboration with CATO, and about the integration of the different enterprises departments.

Opportunities

A good number of opportunities give CATO SMS the incentive to integrate hematological malignancies clinical trials in their expertise. One of the most remarkable factors is the rising field of hematology (discussed in Chapter 3). The **growing hematologic oncology therapy market** is fueled by the success of a number of investigational agents, driven in part by the application of new scientific knowledge and technology to isolate the biology of malignant cells. Particularly, what emerged from the trends (Chapter 7) and external (Chapter 8) analyses is that advances in hematological antitumor therapies are perfectly in line with a continued trend towards **personalized medicine approvals**. Personalized medicine constitutes a particularly novel and exiting topic in the healthcare industry, and it is currently revolutionizing the treatment approaches for cancer. Particularly, it provides an opportunity for pharma and biotech companies to develop targeted therapies and identify biomarkers involved in hematological malignancies. Another aspect that provides potential to invest in hematological antitumor therapies, is the **demographic shift** (discussed in the external analysis, Chapter 8) towards aging. Indeed, since the risk of developing blood cancer increases with age, with an increase in the aging population the number of diagnosed prevalent cases is expected to spike in the future years; therefore, an increasing number of anti-tumor hematological clinical trials will be needed. Other two aspects that constitute a potential incentive for CATO SMS to implement this project, come from the merger of the two enterprises. Particularly, thanks to

this merger the two CROs will have the possibility to extend their presence in the US and Europe, with the potential of **starting new partnerships** with sponsors interested in the hematological malignancies field. Finally, this merger will allow CATO SMS to strengthen its expertise in clinical trials, integrating **two robust data management teams** that will be fundamental for the successful conduct of hematological studies.

Threats

Political instability after Brexit, Financial and practical implications in hematological clinical trials due to Covid-19 pandemia, Intrisic difficulties of hematological studies.

However, potential threats need to be considered before giving future directions. The political and economic sections from the external analysis (Chapter 8) revealed a **political instability after Brexit**, that is reflecting negative consequences on general regulations, access to medicines, data, workforce and funding of clinical trials. In addition to that, financial implications for cancelled studies and from delayed milestones caused by the **Covid-19 global pandemia** are negatively affecting the conduct of hematological malignancies clinical trials. As highlighted in the analysis, patient enrolment for hematological studies appears to be severely affected, due to the increased risk faced by older patients that are already immunosuppressed by their hematological disease or anti-tumor therapy. Finally, it has to be recognized the intrinsic difficulties of conducting effective clinical trials in hematologic malignancies. Numerous factors and complexities are addressed by these studies, and set them apart from solid tumors. **Challenging patients access**, evidenced by the relatively low incidence rates of blood cancers compared to solid tumor, impacting statistical power and study validity. **Paucity of knowledgeable investigators and specialized trial sites** due to the rarity of some hematologic oncology diseases, with implications for trial conduct and regulatory clearance plans. **Arduous data management** because of the complexity of definitions, classifications and clinical measurements, with consequent impacts on data collection as well as review and analyses.

11.2 References

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12 Advice

Action plan for CATO SMS

12. Advice

How should CATO SMS proceed?
Formulate a feasible advice for CATO SMS and define potential future directions.

12.1 Introduction

In the context of important achievements in the hematological community, with novel therapy strategies developed for the treatment of blood cancer indications, CATO SMS is aiming to gain an in-depth knowledge in hematological malignancies clinical trials strategy design. Novel approaches achieved extraordinary results and allowed blood cancers to outplace the most common cancers for survival rates. The advice addressed to CATO SMS comprises on the one hand an evaluation of the intrinsic challenges of hematological studies, in terms of field competition, patients access, data management and trials strategic design. On the other hand, it highlights the advantages and potential opportunities for the company investing in this project (**Figure 12**).

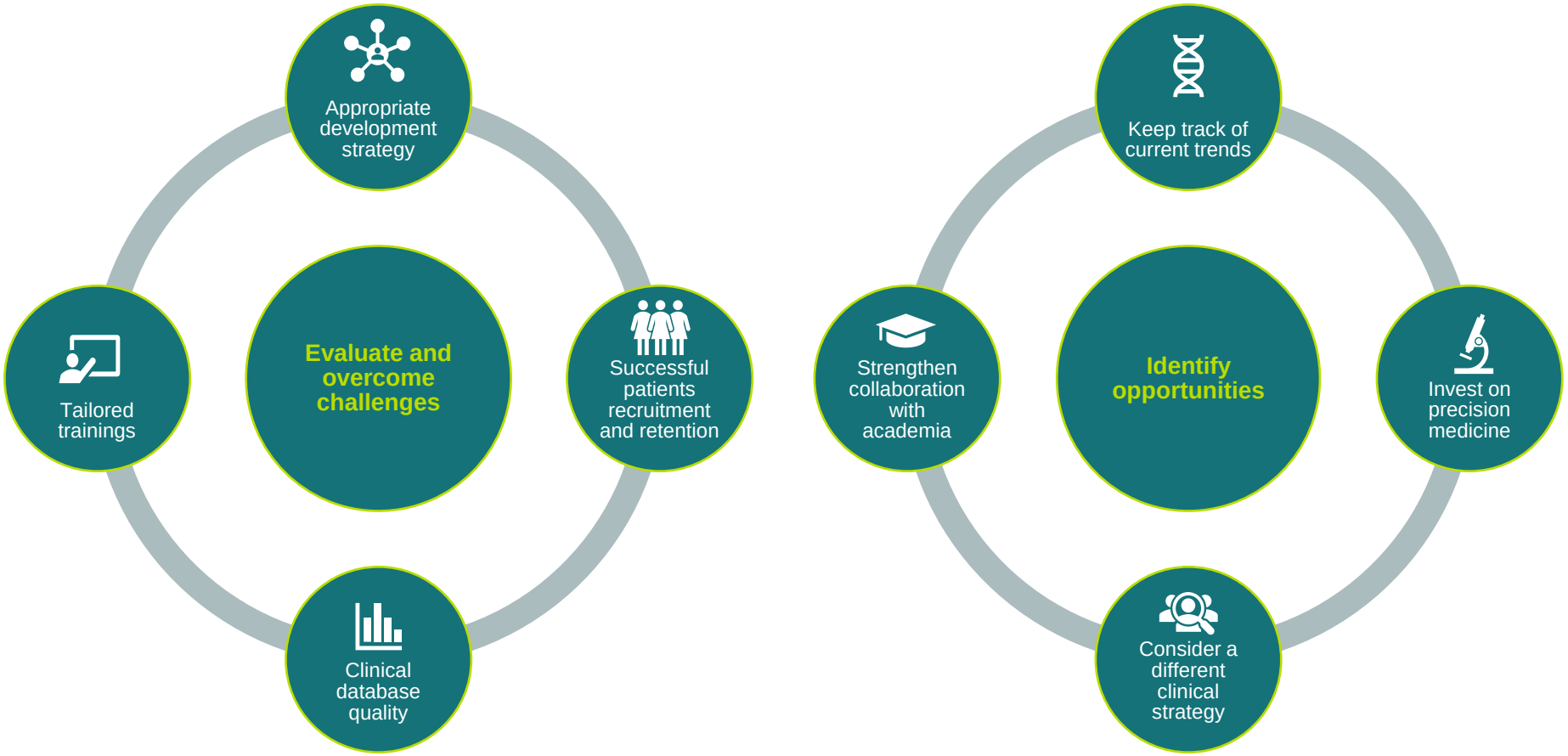
12.2 Evaluate and overcome the intrinsic challenges associated to hematological studies

Despite the global market growth for approved hematologic cancer drugs constitutes an incentive for CATO SMS to actively integrate blood cancer indications in its oncological portfolio, the intrinsic challenges of hematologic oncology studies need to be evaluated. First of all, in order to appropriately drive development strategy in the field of hematologic oncology it is important to assess not only the patient's symptoms but also the agent's effect on the underlying disease and the disease progression, in order to discern efficacy and safety. In addition to that, the very nature of blood- based cancers require that clinical trials rely on different measurements to determine changes and disease progression related to the investigational agent. Therefore, the determination of endpoints which differs significantly from solid tumors add more complexity to trial design, conduct and assessment. Patients access is more difficult due to the relatively low incidence rates of blood cancers compared to solid tumors. Finally, data management is more challenging due to the complexity of definitions, classifications and clinical measurements.

Higher competition in the niche-field of Hematology:
Conduct an appropriate development strategy.

Improve network across Europe and in the US and strengthen collaborations with KOLs and specialists in hematology in order to guide clinical trial sponsors to the investigators and facilities with the appropriate hematologic oncology expertise and knowledge of the biology of the disease. Highly knowledgeable and experienced oncologists and hematologists practicing in community settings represent a significant source of referrals for clinical trials. This specific objective can be achieved by participating to international conferences, enhancing collaborations with external experts for the development of webinars and CATO SMS blog, or investing in hiring senior hemato-oncological experts and physician specialists. An important upcoming congress that **CATO SMS should participate to is the "16th World Congress on Blood Cancer"** which is going to be held on September 14-15 2020 in Vienna, Austria.

Figure 12. Schematic illustration of the final advice addressed to CATO SMS



Difficult patients access in hematological studies:
Enhance successful patients recruitment and retention.

Patients recruitment and retention represent a fundamental aspect for successful clinical trials completion. If high levels of participation are not achieved, statistical power, internal and external validity may be at risk. Recruitment obstacles can cause also financial implications, as they can delay completion of research or determine a timely impact on patient health and wellbeing. Patients recruitment and retention are challenging processes in all therapeutic areas, but for hematological malignancies they are even more difficult, due to the low incidence rates of blood cancers compared to solid tumors. For these reasons, **CATO SMS should consider patients engagement as a valuable strategy**. Core concepts of patients recruitment and retention strategies [1] include:

- **Gaining patients trust** through a continued involvement of physicians in the study. Physician should introduce patient to research staff and should be up to date with the study in order to answer any questions. Also, ensuring protection of health information and identity privacy is another important aspect to develop patient's trust.
- **Ensuring a positive attitude of providers and research staff**, by emphasizing the importance and the altruistic value of the research study.
- **Enhancing communication** by explaining the study protocol in a way that patients can understand. Trial's educational materials should report all information about potential benefits and risks regarding the patient's disease, and include an evaluation of the potential impact study participation might have on one's quality of life.
- **Defining expectations, role and responsibilities of all partners** from the very beginning, including the application of resources, data sharing, and objectives of the program.

CATO SMS has already made improvements to enhance patient recruitment and retention in clinical trials. A dedicated department of Patient Inclusion is involved in both the design and conduct of clinical trials to ensure maximal patient recruitment at trial sites. CATO SMS should consider this department as a priority to ensure recruitment and retention of hematological malignancies affected patients. Trial teams **should evaluate the different needs and viewpoints of hematological malignancies patients, including their concerns about invasive procedures, such as bone marrow exams and repeat biopsies that might interfere with their lifestyle**.

Complex data management for hematological malignancies:
Ensure clinical database quality

Data management is fundamental to produce trials outcomes and to help managing trials efficiency and conduct. CATO SMS has experience in working with two electronic data capture (EDC) systems, named IBM Clinical Development and Viedoc. **CATO SMS should ensure an accurate data integration from local sites and central laboratories, by capturing real-time status of study conduct.** The reports generated from the EDC system should include data related to each patient visit, ranging from laboratory results analyses to dosing records and adverse events. In addition to that, electronic medical records (EMR) are an additional powerful tool for data collection and input. Thanks to the recent merger, **CATO SMS has the**

opportunity to integrate two robust data management departments and to use this advantage in order to set itself apart from competition. The two enterprises can ensure a data cleaning strategy with the aim of interpreting data and assisting the site staff in order to understand how to minimize data discrepancies.

Missing a senior expertise in hematological studies:
Provide tailored trainings

In order to achieve high performance hematologic oncology trials, CATO SMS should be able to evaluate for its sponsors the hematologic oncology study design relative to the feasibility of executing the trial, and, if possible, offer modifications or alternative approaches that will lead to successful enrollment. To do so, it is necessary to work with a highly trained staff that is able to adapt endpoints, study designs and data management, in order to fully cover all aspects of the most appropriate trial design. Therefore, if CATO SMS aims to actively integrate hematological malignancies in its oncological portfolio, **should offer specific trainings in order to ensure a highly qualified staff that has the potential to excel in hematologic malignancies clinical trials**.

- **Therapeutic trainings on a target disease** (such as Multiple Myeloma) conducted by a certified hematologist/oncologist in order to ensure a better understanding of the pathology, clinical manifestations, and current treatment guidelines of the specific hematologic cancer under study.
- **Investigational agents trainings** (such as CAR-T cells and immune checkpoint inhibitors therapeutic approaches) in order to ensure the team has expert knowledge of the study drug's scientific foundation, mechanism of action and preclinical testing results.
- **Protocol trainings** (including the objective(s), design, methodology, statistical considerations and organization of a successful clinical trial) in order to achieve accuracy and efficiency with enrollment, data collection and other trial aspects.
- **Data management trainings** about collection, integration and availability of data in order to define line listings needed to support clinical data reviews, to accurately evaluate and interpret data.

12.3 Identify opportunities

Navigating the ever-changing field of hematological malignancies offers to CATO SMS different opportunities. First of all, it allows the company to support its central strategy of being on top of current oncological trends, while anticipating future developments in anti-tumor treatments. In addition to that, investigating the recent advances of hematological anti-tumor therapies expose CATO SMS to the emerging field of personalized medicine, which is currently revolutionizing the clinical approach of blood cancer indications. Personalized medicine places the need of developing an advanced clinical design strategy and offers to CATO SMS the possibility to collaborate with academia, in order to enable truly personalized treatments.

Keep track of current trends in therapies

From the trends analysis it became clear that remarkable advances have been achieved in the treatment of Acute Myeloid Leukemia, Chronic Lymphocytic Leukemia and Multiple Myeloma. The number of clinical trials conducted to investigate these indications increased exponentially in the past 5 years, with AML taking the lead due to the aggressivity of the disease and the high mortality rate. However, MM that is still considered incurable, is the indication that saw the biggest growth, with an increase of +200% clinical trials focused on this disease in 2018. From the analysis of the previous hematological malignancies projects conducted at SMS-oncology, it emerged that the company had little experience with multiple myeloma, constituting only 4% of blood cancer indications centered projects. Under the light of the advances that have been achieved for the treatment of this disease and of the promising pipeline of potential new treatments, the company should join forces with CATO in order to **deep its knowledge and expertise in the treatment of multiple myeloma**. For what regards the types of therapeutic agents available for the treatment of patients affected by blood cancers, it emerged that chemotherapies still constitute the backbone of hematological anti-tumor therapies, with the majority of marketed drugs for the treatment of AML, CLL and MM being cytotoxic agents. However, **CATO SMS should focus its attention on targeted therapies and immunotherapies approaches** that hold promise for improving clinical outcomes for blood cancer affected patients, while reducing toxicities associated to the treatment. In terms of targets, **CATO SMS should consider small molecules targeting FLT3** as the preferred therapeutic approach for the treatment of AML. **Autologous T cells modified to express CAR targeted to CD19** are currently demonstrating high rates of remission and meaningful antitumor efficacies in adults affected by CLL. Finally, **CAR-T cells targeting BCMA (CD269)** are believed to be the first cellular immunotherapies that will be implemented into the clinics to treat MM.

Invest in precision medicine

As shown in the trends and external analyses, new generations of precision medicines changed the course of blood cancer treatments by reducing toxicity and improving outcome, extending patients lives beyond what could be achieved by the use of nontargeted therapies. Since most of the hematological malignancies are caused by genomic alterations, targeting the earliest driver mutations that might be the potential carrier of the transforming potential is fundamental to appreciate the heterogeneity and sub clonal nature of hematological malignancies indications. For these reasons, **CATO SMS should aim at including into clinical practice discovery platforms that provide genomic information, proteomics and medical and family history data related to the patient.** Next-generation sequencing (NGS) analyses have already been introduced in most specialized hematologic laboratories with various NGS platforms now being commercially available (**Table 12**) [2]. These panels analyze different categories of genes ranging from the splicing machinery, epigenetic modifiers, cohesins, transcription factors, signaling molecules and chromatin modifiers. Implementing personalized approaches will give the opportunity to CATO SMS to facilitate earlier disease detection while reducing time expenditure in disease management and potentially increase patients quality of life.

Table 12. Databases currently available for the characterization of genetic variants

Database	URL	Description
cBioPortal	www.cbioportal.org	Free database for cancer genomics
My Cancer Genome	www.mycancergenome.org	Free database for cancer genomics
COSMIC	cancer.sanger.ac.uk/cosmic	Free database for somatic mutations in cancer
dbSNP	ww.ncbi.nlm.nih.gov/SNP	Free database for short genetic variations
ExAC Browser	exac.broadinstitute.org	Freely available exome sequencing data from the Exome Aggregation Consortium
ClinVar	www.ncbi.nlm.nih.gov/clinvar	Free database for information about genomic variation and their relationship with human health
gnomAD	gnomad.broadinstitute.org	Free database for genome sequencing data
ESP	evs.gs.washington.edu/EVS	Free database for exome sequencing data
LOVD	www.lovd.nl	Freely available tool for gene-centered collection and display of DNA variations
HGMD Professional	www.hgmd.cf.ac.uk	Database for gene mutations causing inherited diseases

Adapted from Bacher et al., 2018 [1].

Consider a different clinical trial design strategy

Endpoints that are frequently included in successful phase II clinical trials for hematological malignancies are overall survival (OS) and progression free survival (PFS). The discovery of novel biomarkers currently constitutes a field of great interest in order to enable oncological personalized treatments. However, in order to account for the unpredictable variability in tumor markers, microenvironmental characteristics and patients' biological and genomic backgrounds, **CATO SMS should evaluate advanced trial design strategies such as adaptive design trials, "basket" or "umbrella", and "N-of-1" trials.** These innovative trials designs are currently coming to the forefront especially in the oncological field.

Strenghten collaboration with academia

The ambition of characterizing the drivers for carcinogenesis in blood cancer indications through precision medicine approaches will not be possible without specific diagnostic tools, including NGS analysis, sensitive bioinformatic analysis and AI. Nowadays, collaborations

between academia and pharmaceutical companies through open innovation models, public-private partnerships, and industry-academic partnerships are becoming more and more common (**Table 12.1**). This cooperation enables sponsors to get access to novel drug targets, validation of targets, animal models, disease expertise and biomarkers. For this reason, **CATO SMS should evaluate how to best engage with academia and not-for-profit research organization**. On the one hand, by strengthening collaborations and partnerships with academic institutions CATO SMS services would act as support for scientists that usually don't have experience with strategic planning needed for translational purposes, allowing them to license their discoveries to pharma or spin out start-ups based on their novel ideas or technology. On the other hand, engaging these partnerships will allow CATO SMS to support its main strategy to anticipate trends for (hematological) cancer therapies, having a close eye on academia, the greatest engine for scientific innovation.

Table 12.1 Examples of academia-industry partnerships

Institute / Centre	Description
Lead Discovery Center (Max-Plank-Innovation)	Fully operational drug discovery organization acting as a translational bridge between Max-Plank scientists and applied pharmaceutical research.
California Institute for Biomedical Research (Merck & Co)	Translational medical center for programs in immunology, autoimmune and metabolic disorders, cardiovascular disease, regenerative medicine, cancer biology, and neurodegenerative disease.
Pfizer Cambridge	Translational medical center bringing together employees from Pfizer with famous universities such as the Massachusetts Institute of Technology (MIT) or Harvard University.
Oncode	Independent institute dedicated to understanding cancer and translating research into practice, joining forces of 61 research groups at 12 different institutes across The Netherlands.
GSK- Harvard Stem Cell Institute	$25 million funding from GSK in order support research at the university and in at least four Harvard-affiliated hospitals in neuroscience, heart disease, cancer, diabetes, musculoskeletal diseases, and obesity.
CRUK–AstraZeneca Antibody Alliance Laboratory	Collaboration that brings together Cancer Research UK's cancer biology expertise with the world-class antibody engineering technology of AstraZeneca to support antibody discovery.

12.4 References

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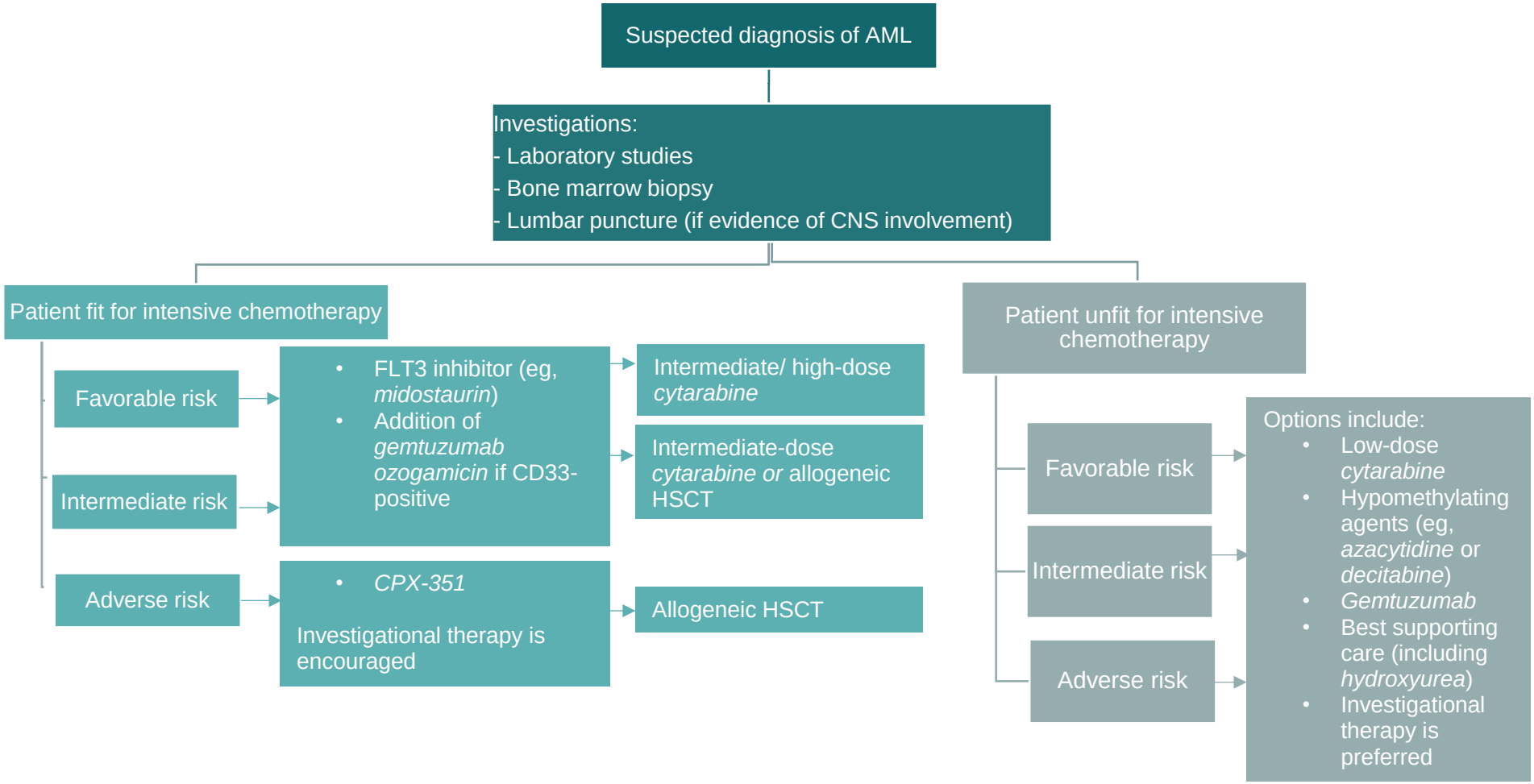
Supplementary Figures

Supplementary Figure 1. General clinical approach for AML affected patients



The standard approach for AML intensive therapy is a combination of cytarabine and anthracycicline. Gemtuzumab is an anti-CD33 antibody that acts as a potent DNA damaging agent. CPX-351 is a liposomal encapsulated formulation of cytarabine and daunorubicin. Patients that achieve remission thanks to chemotherapy undergo through a consolidation phase with a cytarabine-based approach. Allogeneic HSCT may be useful to avoid relapse in high-risk patients. Patients unfit for chemotherapy undergo a low-dose cytarabine and hypomethylating based treatments. **Adapted from Short N. et al., (2018)**.

Supplementary Figure 2. General clinical approach for CLL affected patients

First line treatment for CLL

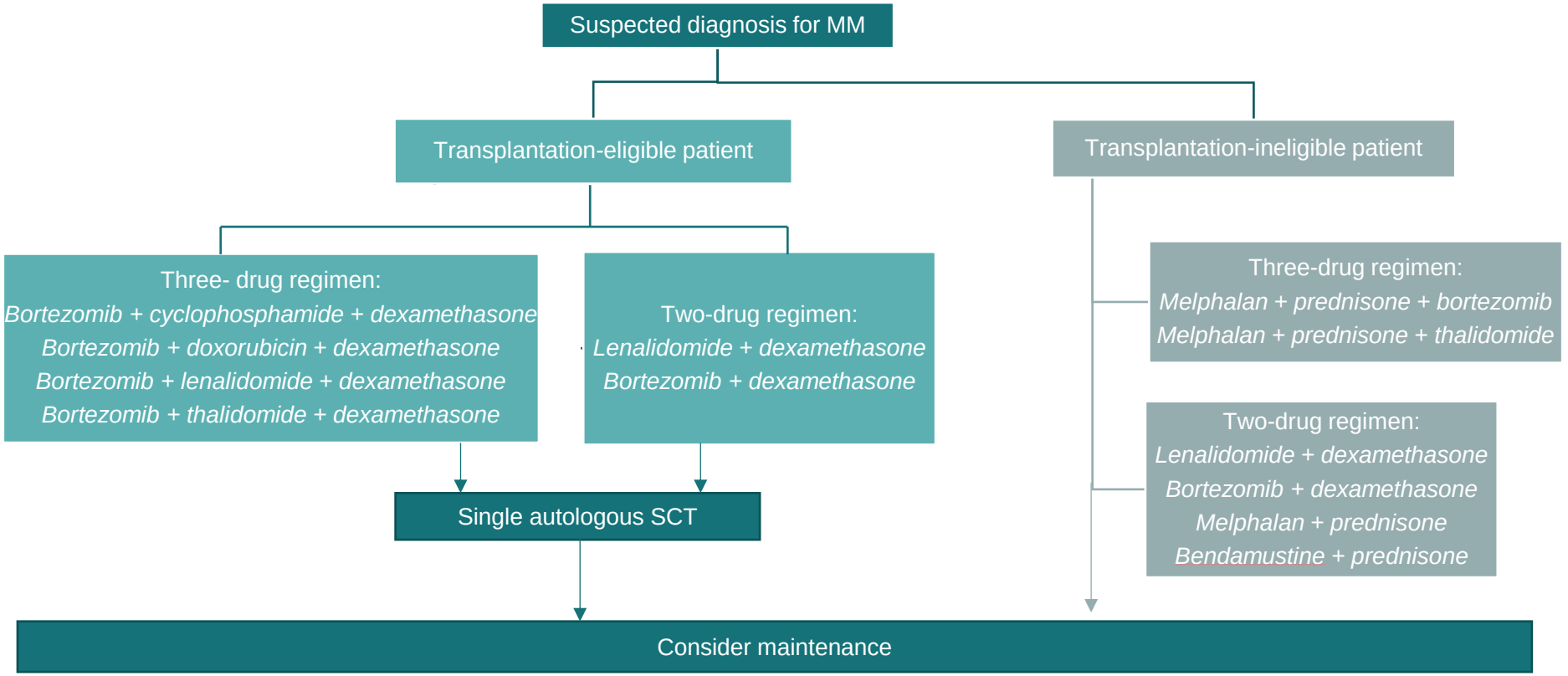
	No TP53 aberration	TP53 aberration
Physically fit	*Fludarabine* + *cyclophosphamide* + *rituximab* (age ≤ 65 years); or *bendamustine* + *rituximab* (age > 65 years)	*Ibrutinib* or *idelalisib* + *rituximab* or *venetoclax*
Physically unfit	*Chlorambucil* + *obinutuzumab*; or *chlorambucil* + *rituxumab*; or *ibrutinib monotherapy*	*Ibrutinib* or *idelalisib* + *rituximab* or *venetoclax*

Second line treatment for CLL

	Standard therapy	Alternative therapies
Refractory or progression within 3 years		
Physically fit	*Ibrutinib* + possibly HSCT	*Idelalisib* + *rituximab*; *venetoclax*; *lenalidomide*
Physically unfit	Change therapy	*Ibrutinib; idelalisib* + *rituximab*; *venetoclax*; *lenalidomide*; Anti-CD20 antibody alone
Progression after 3 years		
All fitness levels	Repeat front-line therapy	Change to another chemoimmunptherapy; *ibrutinib*; *idelalisib* + *rituximab*

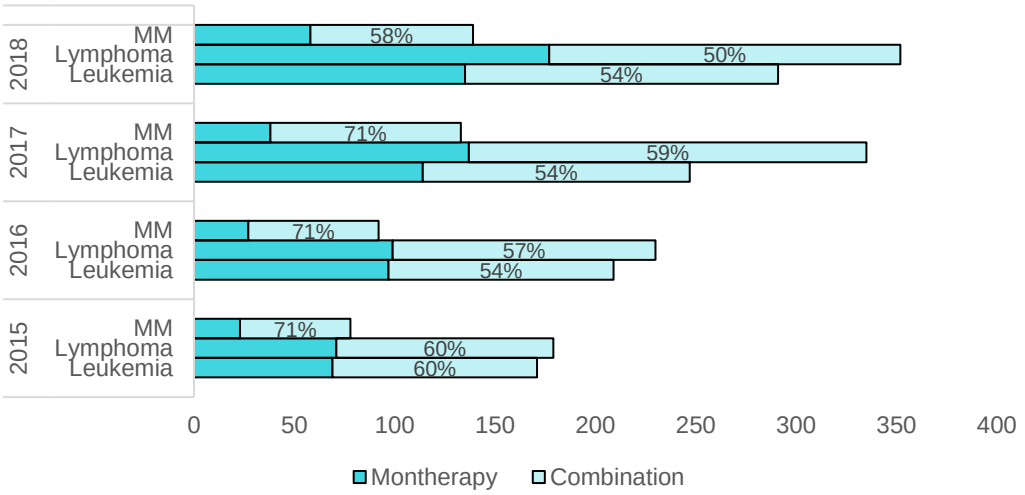
First line treatments for CLL mainly rely on cytotoxic or targeted agents. The most common targeted agents include monoclonal antibodies Anti-CD20. The only immunotherapeutic approach implemented into practice comprises the use of lenalidomide, a TNF inhibitor still under development for the treatment of CLL. The choice of both first-line and second-line therapies are guided by the evaluation of the patients fitness together with genetic defects (such as TP53). **Adapted from Hallek M. et al., (2018).**

Supplementary Figure 3. General clinical approach for MM affected patients



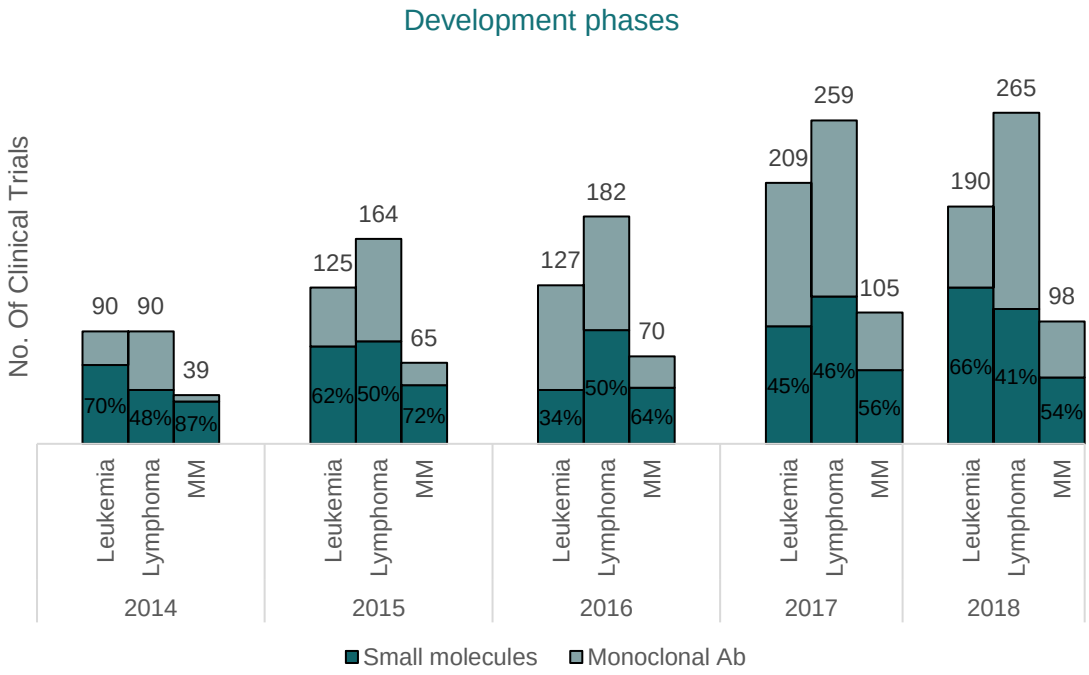
Combinations with novel drugs is used for first-line treatment. These novel drugs mainly comprise cytotoxic and targeted agents. High-dose therapy with autologous stem cell transplantation prolongs survival substantially compared with conventional cytostatic treatments. **Adapted from Röllig C. et al., (2015).**

Supplementary Figure 4. Combination of drugs for Targeted Therapies



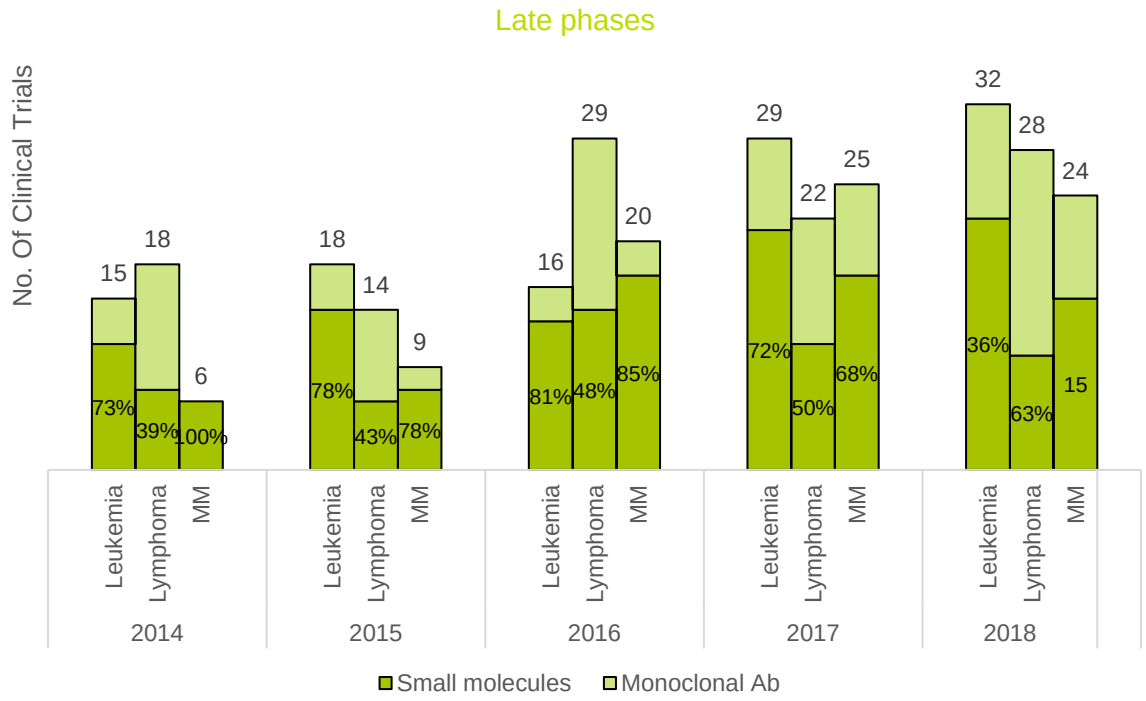
For targeted therapies combination of drugs played a smaller role compared to chemotherapy, indeed, the amount of clinical trials investigating targeted drugs in combination was comparable to the number of clinical trials using monotherapies. **Source: GlobalData**.

Supplementary Figure 5. Small molecules vs Monoclonal Antibodies (Development phases)



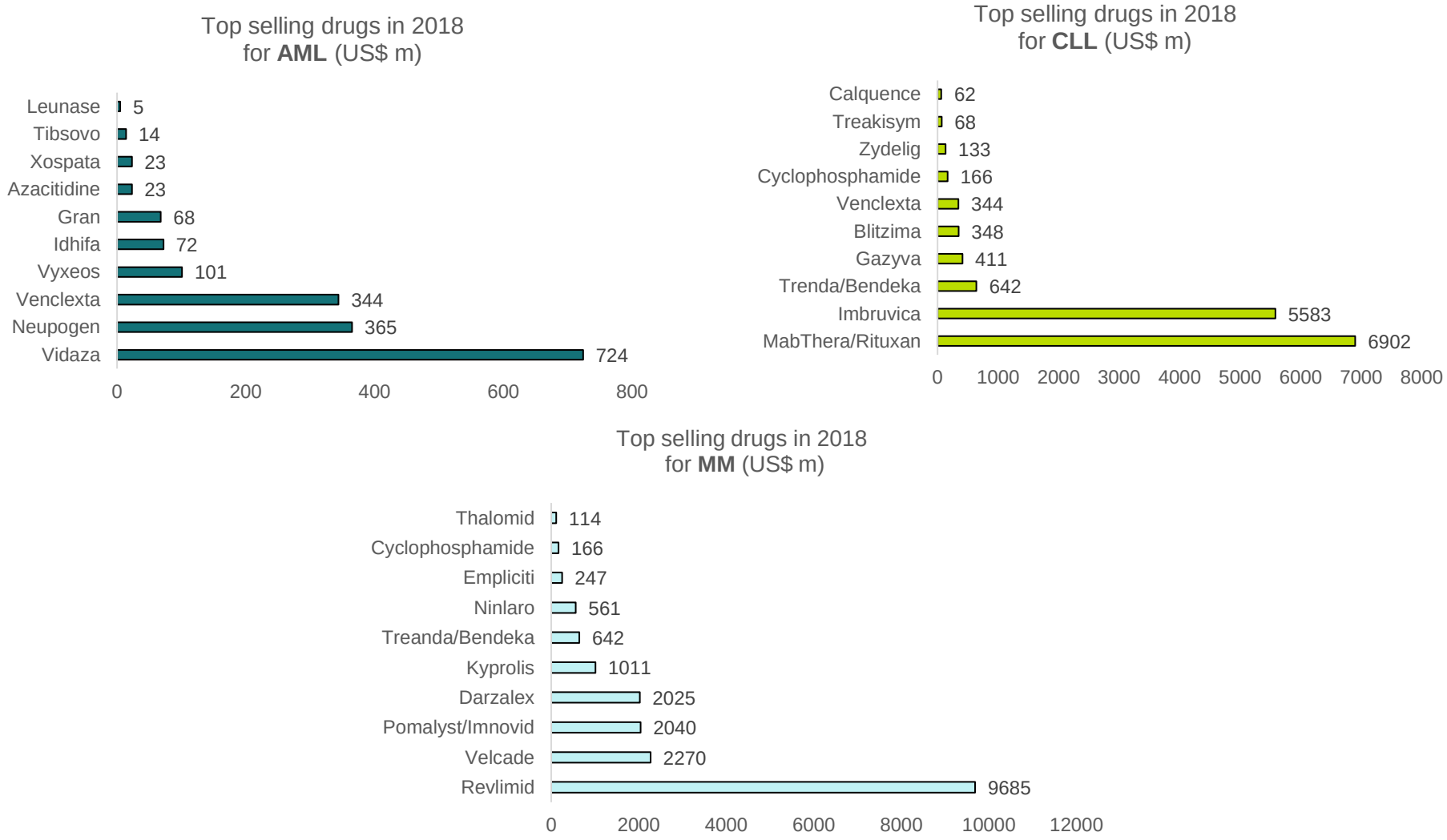
The use of Monoclonal Antibodies took over the Small molecules-based therapies for Lymphoma and Multiple Myeloma (MM) development phases. **Source: GlobalData**.

Supplementary Figure 6. Small molecules vs Monoclonal Antibodies (Late phases)



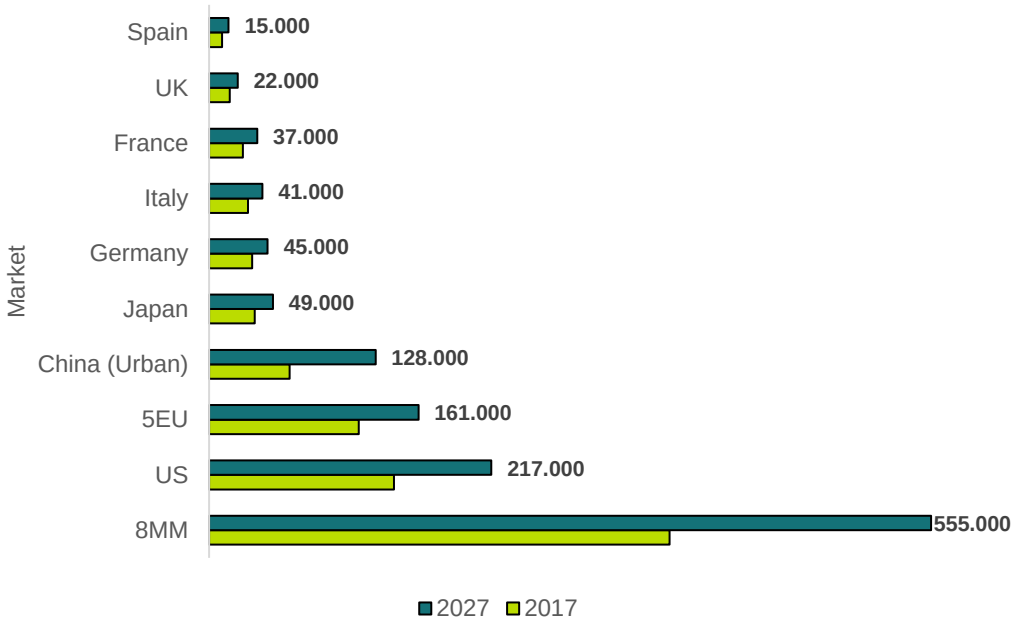
Small molecules based targeted therapies registered a higher number for Leukemia and Multiple Myeloma in late phases. **Source: GlobalData**

Supplementary Figure 7. Top selling drugs in 2018 (US$ m) for AML, CLL and MM



Illustrative graphs representing the top selling drugs for AML, CLL and MM in 2018 (US$ m). **Source: GlobalData**

Supplementary Figure 8. The increasing diagnosed prevalent cases of MM in the 8MM



Diagnosed prevalent cases of MM, both sexes, ages ≥ 40 years, 2017 and 2027. In 2017, the US accounted for 40% of the diagnosed prevalent cases of MM in the 8MM, with 142,000 diagnosed prevalent cases. China (Urban) is expected to see the largest growth in MM diagnosed prevalent cases, from 62,000 cases in 2017 to 128,000 cases in 2027, at an AGR of 10 %. **Adapted from Qaisrah K. (2019)**.

Supplementary Figure 9. Oncology remains the top therapeutic area for personalized approaches

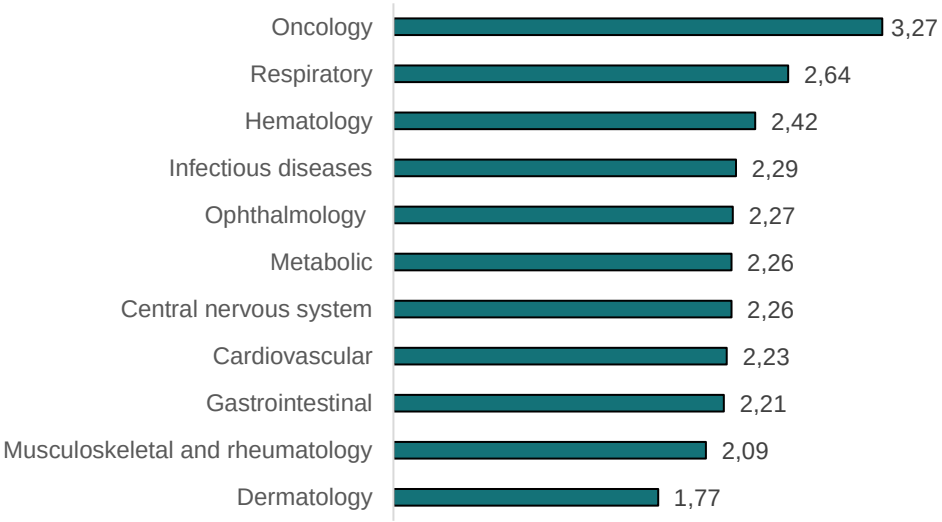


Figure that represents the average scores given by survey respondents on a scale of 1 to 5. N= 114. Oncology remains the main area of interest for personalized approaches and this trend should continue. Lower involvement in dermatology, musculoskeletal and rheumatology areas can be explained due to

their partial heritability; that is, an individual's genes are not entirely responsible for development of these diseases, that can be rather influenced by lifestyle and environmental factors. **Adapted from GlobalData (2019). The state of Personalized/Precision Medicine. Report Code: GDHCHT02.**