BRYAN, GARNIER & CO

Oncology Day

Perspectives on Cancer Treatment Paradigm Shift

September 2016

Healthcare

Healthcare White Paper

Immuno-oncology has become in recent years a sub-specialty within oncology owing to its unique science and its potential for substantial and long-term clinical benefit. Among all available immune therapeutic options, checkpoint inhibitors monoclonal antibodies are the fastest growing segment and have the potential to become standard of care.

- Since first approval in 2011, checkpoint inhibitors have generated impressive clinical results and achieved significant patient benefits for challenging tumour types (such as metastatic melanoma). Increasing competition in the field will force innovation and differentiation: beyond the now well established anti-PD-1/PDL-1 and CTLA-4 backbone, a wide variety of other checkpoint and immune blocker/activator therapies are currently being developed in clinic by several key pharmaceuticals players including Bristol-Myers Squibb, Roche, Merck & Co and AstraZeneca.

- Recently demonstrated limitation of checkpoint inhibitor monotherapy approach in lung cancer underlines the fact that combination therapies are likely to reach the best outcomes, as they allow the targeting of several fronts/pathways. Evaluating tumour specificities, and especially its micro-environment, will thus be key to gauge and select the best agents or targets in a given indication. In this context, the development of biomarkers will increasingly become of importance.

- The growing importance of biological and immunology therapies is expected to drive global market for immuno-oncology drugs to reach c. $30 billion by 2020, and eventually represent between 30% and 50% of the total oncology drug market by the end of the 2020's decade.

- 2015 and 2016 YTD immuno-oncology funding and deal activities have been stellar, and should continue to grow at a steady pace given the increasing number and high variety of clinical and preclinical programs. Main partnership deals drivers were acquisition of new targets or new technologies such as combination and/or bispecific antibodies. However, increasing competition in the field pushes technologies' price tag up. Investors education appears therefore as key to accurately identify future high return opportunities.

Corporate Finance Executive Insights

1. Introduction

Bryan, Garnier & Co Oncology Day, the first event of its kind held in Paris, brought together at Institut Curie last June both public & private investors as well as corporate decision-makers, around four first-class scientists, to get an in-depth insight into the area of immuno-oncology. The event was attended by more than 100 participants including venture capitalists and private equity funds, institutional funds managers and small/mid cap quoted and non-quoted oncology companies.

Investors found actionable intelligence for their existing and future portfolios, while Corporate attendees gained a deeper understanding of how the financial community perceives and approaches the immuno-oncology sector from an investment perspective.

This white paper summarizes key topics discussed during the scientific plenary and extended Q&A sessions, focusing on the four themes covered during the day: 1/ how our immune system can kill cancer cells; 2/ the importance of the tumour micro-environment (TME); 3/ the place of immune checkpoint blockers and bispecifics within this nascent paradigm; and 4/ the challenges and futures development of immune-therapy. This review also analyses the current market and transactional conditions in the immuno-oncology sector.

Scientific Speakers Profiles

Olivier Lantz

Olivier Lantz is head of the clinical immunology laboratory of the Insitut Curie, co-Director of the Institut Gustave Roussy (IGR)–Institut Curie (IC) INSERM biotherapy investigational unit, chairman of the Institut Curie Immunotherapy Network and CD4 Lymphocyte and Anti-Tumoral Response Group Leader at the INSERM U932. Olivier and his team of 12 dedicated scientists focus on the studies of in vivo T cell biology in mouse and human models by investigating three main topics: (1) Mucosal associated invariant T (MAIT) cells, an evolutionarily conserved T cell subpopulation; (2) Interactions between tumors expressing nominal antigens and specific T cells population; and (3) CD4 T cells mediated immune response during the treatment of cancer patients. Olivier authored over 150 scientific publications in international peer-reviewed journals.

Vassili Soumelis

Vassili Soumelis is senior physician in immunology and hematology and Integrative Biology of Human Dendritic Cells and T Cells Group Leader at the INSERM U932. Vassili and his team of 10 dedicated scientists focus on understanding the reciprocal interactions between immune cell state/behavior and their environment. The research is organized in three interconnected programs using dendritic cells (DC) and T cells as preferred cellular models: (1) Systems and integrative biology of human immune cells; (2) Global analysis of human tissue inflammation and tumor microenvironment; and (3) Biology of human TSLP (a cytokine - i.e. signaling molecule - produced by epithelial cells and targeting DC in order to modulate their behavior). Vassili authored over 55 scientific publications in international peer-reviewed journals.

Eliane Piaggio

Eliane Piaggio is INSERM Research Director (DR2) and head of the Translational Research in Immunotherapy Team (INSERM / IC). The translational research department is a hub for biomedical research at the Institut Curie. Its mission is to promote collaborative projects that associate researchers and physicians. Located within the hospital, the department's goal is to apply basic research discoveries to innovative care. Within this department, the Translational Research in Immunotherapy Team focus on cancer immunotherapy through 3 main areas of research: (1) Analysis of human tumor-draining lymph nodes (LNs), with a focus on tumor neo-epitopes for future personalized anti-cancer vaccines; (2) Translation of IL-2/antI-IL-2 Ab complexes immunotherapy to the clinics, as monotherapy or in combination with other immunotherapies in different tumor mouse models; and (3) Immunotherapies in optimized in vivo models for cancer to improve therapeutic effect and define rationalized drug combinations. Eliane authored over 40 scientific publications in international peer-reviewed journals.

Delphine Loirat

Delphine Loirat is a Medical Oncologist and Co-Principal Investigator of the Translational Research in Immunotherapy Team (IC), working in close collaboration with Eliane Piaggio. As medical oncologist, Delphine is involved in day-to-day cancer patient management at Curie hospital and is a specialist of clinical trials in immunotherapy. Delphine authored over 20 scientific publications in international peer-reviewed journals.

About Institut Curie

Created in 1909 on the basis of the « basic research to innovative care » model originally devised by Marie Curie, Institut Curie is a private charitable foundation since 1921. Institut Curie operates one of the largest cancer research centers in Europe and a leading-edge hospital group that treats all types of cancer, including its rarest forms. Institut Curie regroups more than 14'300 active patients and has 3'300 employees. In 2014, the Insitut had c. €350m of resources, invested for 80% in Hospital operations, including clinical research, and for 20% in Research activities.

2. Cancer Immuno-Therapy

2.1. From oncology to immuno-oncology

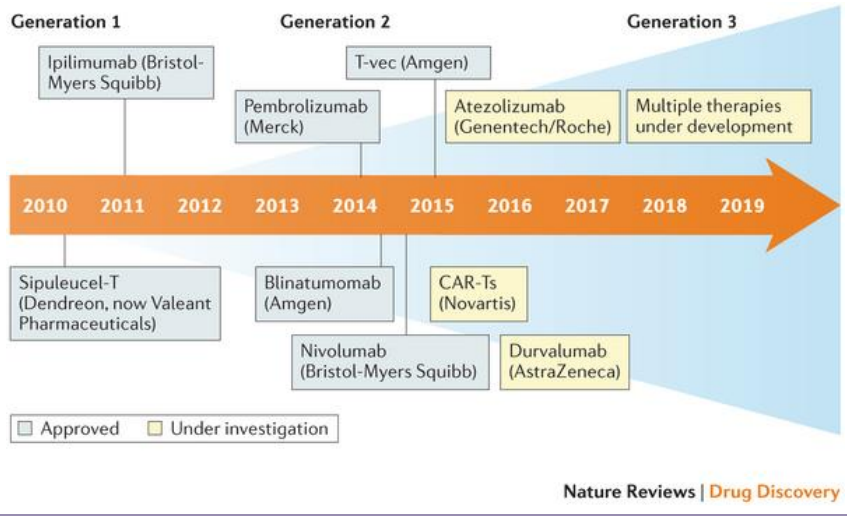
Immuno-oncology (IO) refers to **all therapies mobilising the immune system to fight cancers**, encompassing plethora of approaches that can be divided into two main types: 1/ active immunotherapies, like cancer vaccines, which regroup the compounds that stimulate the immune system (e.g. by enhancing the presentation of tumour-associated antigens); and 2/ passive immunotherapies which are instead solutions that improve the pre-existing immune responses.

For almost 60 years, the scientific community demonstrated scepticism when it came to immuno-oncology, mainly driven by the lack of understanding of the ability of the immune system to elicit an effective response against malignant tumours. "*One central question is how the immune system is able to recognize tumour antigen originated from "normal" tissue, using receptors able to react against specifities to which they have not been "educated" during their development in the thymus"* explained Olivier Lantz. "*Another difficulty is the understanding of the negative feedback loops operating at all stage of the immune response*".

Immuno-oncology appears as a relevant therapeutic alternative since the approval of ipilimumab in 2011…

However, compelling evidences in favour of effective tumour-specific immunity accumulated in recent years. "*Since the late 2000's, it has become clear that modulation of a patient's immune system can result in effective cancer immunotherapy*" says Eliane Piaggio. "*The regulatory approval of ipilimumab (an anti-CTLA-4 mAb) in 2011 let the field experience a complete renaissance*" added Delphine Loirat. "*A large variety of approaches has since emerged, including small molecules, other monoclonal antibodies, CAR-T cells and bispecific molecules*" listed Olivier Lantz. "*Deeper and longer-lasting responses, and thus largely improved overall survival rates, have since then been achieved with this increasingly exhaustive IO portfolio*" concluded Delphine Loirat.

Fig. 1: IO drugs since the approval of Sipuleucel-T and ipilimumab



Source: Nature

…But progresses remain to be done in order to take full advantage of this approach

But the "Holy Grail" is far from being achieved due to the extreme complexity and heterogeneity of antigens, tumour micro-environments, genomics and immune-system/cancer interrelations. And the more we know, the more complex it looks, with key questions being: (i) how an effective immune response is mounted? (ii) what is the so-called tumour micro-environment and why is it becoming so important? (iii) what is a checkpoint blocker and why such a buzz around it?

2.2. The Immune System Role Against Cancer

The immune system: a complex and dynamic network

"*The immune system is a highly organized liquid organ, representing between 1.5 and 2kg of body mass, dispersed throughout the all body, mainly in lymphoid organs, such as lymphatics, lymph nodes, thymus, spleen and bone marrow*" described Olivier Lantz. It has to be seen as a dynamic and complex network in which many different cells, chemicals and hormones constantly interact to protect our body in the best possible way, be it against pathogens, tumours or other malignancies, without destroying the surrounding normal tissues. Main effectors of the immune systems are immune cells (such as dendritic cells, macrophages, T and B lymphocytes) and antibodies (Y shaped proteins produced by B cells). "*The immune system is subdivided into two interdependent and equally important subparts: the innate and the adaptive systems*" explained Olivier Lantz.

2.2.1. Innate and Adaptive Immune System

- The innate immunity serves as the very first barrier of defence; with an ability to induce rapid and non-specific attacks against a wide range of invaders and send signals to the rest of the system. Its objective is to immediately and non-specifically eradicate the pathogen and initiate the development of the adaptive response.
- The adaptive immunity, on the other hand, is a delayed (7-10 days), cell-based, potent yet specific response, restricted to subset of antigens recognized by lymphocytes (B cells and T cells) and antibodies with high affinity, and leading to long-lasting protection through the emergence of memory cells.

Fig. 2: Innate and adaptive immunity

	Innate immunity	Adaptive immunity: specificity
Examples	Dendritic cells, Natural Killer cells, macrophages	T and B cells
Development	Bone marrow then tissues	BM and thymus, then lymphoid organs
Lag phase	Immediate response	Response takes a few days
Specificity	Limited, same response mounted to a wide range of agents	High, response directed only to the agents that initiated it
Diversity	Limited, hence limited specificity	Extensive, and resulting in a wide range of antigen receptors
Memory	Absent, subsequent exposures generate the same response	Present, subsequent exposures to the same agent induce amplified responses

Source: Curie Institute; Bryan, Garnier & Co ests.

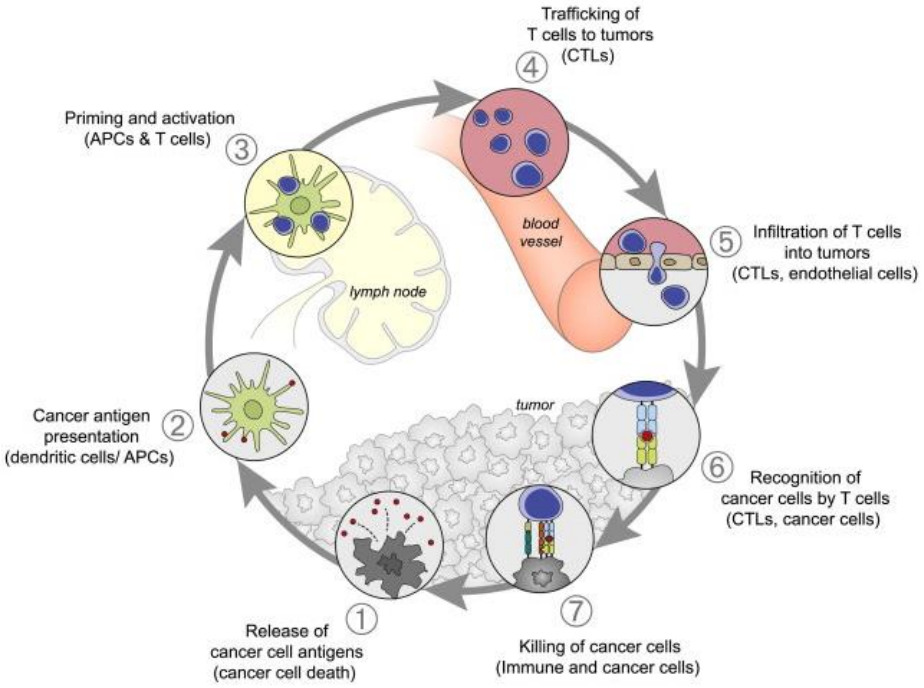
2.2.2. Immune Response against Cancer

An effective immune response can be mounted against tumour…

The immune response against cancers can roughly be divided into three big steps ultimately leading to the death of cancer cells:

- **Initiating the anti-tumour response**. Neoantigens (i.e. antigens encoded by tumour-specific mutated genes) created by oncogenesis have to be recognised by innate cells before 1/ pro-inflammatory cytokines and factors are released to stimulate the overall system, and 2/ effector T lymphocytes (which by definition are the most potent of our immune cells) are activated by dendritic cells through cell-cell interaction and antigen presentation in the lymph nodes.
- **Trafficking to the tumour.** The activated effector T cells then migrate and infiltrate the tumour micro-environment (which is comprised of non-cancer cells and small proteins).
- **Recognising cancer cells and initiating cytotoxicity.** Once within the tumour bed, these immune cells specifically recognise/bind cancerous ones thanks to a specific receptor (known as TCR), and kill them… and, after that, more tumour-associated antigens are released, recognised, etc.

Fig. 3: The immune response cycle



Source: Research Cancer Immunotherapy; adapted from Chen et al*., 2013.*

On paper, such a cycle looks pretty well-rounded, but the reality is quite different, especially when it comes to cancer patients. The cancer-immunity cycle does not perform optimally due to a multiplicity of issues (non-detection of tumour antigens, generation of a Treg response following the recognition of the antigen as "self", loss of MHC expression, etc.) which could be explained by numerous potential distorts in the cancer immuno-surveillance process leading to immune escape. Such a concept is currently known as **"the three Es of cancer immuno-editing"** and suggest that there are three phases of relation between cancer and our immune system: elimination, equilibrium and escape.

…But the tumour manages to escape the immune system

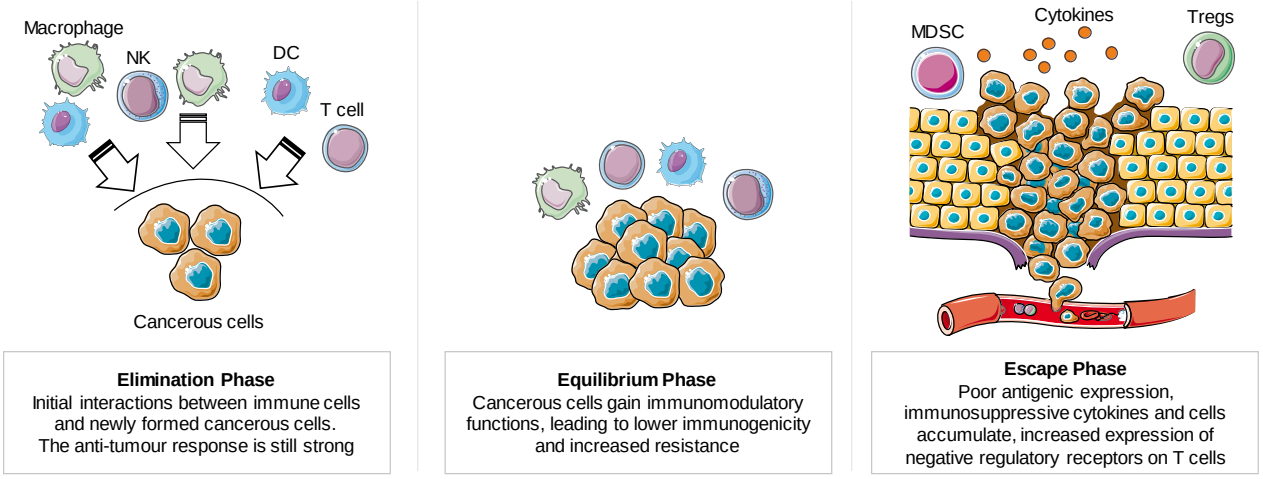
2.2.3. The three Es of cancer immuno-editing

- In the **Elimination** phase, malignant cells are quickly recognised and killed by immune cells for a wide range of reasons: antigens are significantly expressed and in a wide variety, few immune cells are "corrupted", etc.

- In the **Equilibrium phase,** our immune system is still able to recognise cancer cells and continue to exert its pressure. But while many of the original variants are destroyed, new variants actually arise, and appear to be much more resistant to immune attacks.

- **Escape**: tumour cell variants that have so far survived are completely resistant to immune detection and elimination thanks to a variety of mechanisms… and, in this case, the concept of tumour micro-environment appears to be key.

Fig. 4: From immuno-surveillance to immune escape (the three Es)



Source: Adapted from Kim et al., *2007; Bryan, Garnier & Co. ests.*

"*Objective of the current immuno-therapeutic strategies in oncology is to break the cancer immune-editing concept, and identify approaches/therapeutic agents able to sustain the anti-tumour immune response*" said Olivier Lantz.

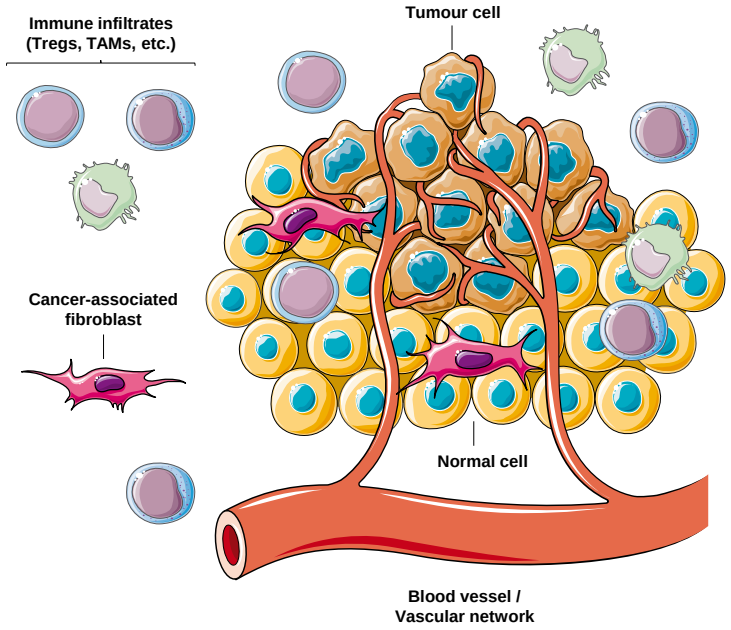
2.3. The tumour micro-environment: an increasingly key concept

Tumour micro-environment is an immune-suppressive network of cells and signalling components

"*Any biological system is a hierarchical organization of interconnected networks of biological components including cells, signalling molecules and metabolites. Dysregulation of signalling inside a network of biological components give rise to an environment supporting disease or tumour emergence and maintenance (through immune editing-mechanisms in the case of cancer for example)*" explained Vassili Soumelis. As such, identifying and understanding signalling cascades (from receptor recognition to final biological effect) in relevant biological networks appears as a key prerequisite for developing efficient therapeutic approaches.

One key network of interest in immune-oncology is the Tumour Micro-Environment (TME), a network of both malignant and non-malignant elements (immune cells, vasculature, cytokines and chemokines, etc.) forming an immuno-suppressive environment. This environment has caught significant momentum in the recent years and is now recognised as: 1/ **a key factor in multiple stages of the disease progression (e.g. local resistance, immune-escaping and metastasis)**; and 2/ an important "missing link" in the quest for more effective anti-cancer treatments.

Fig. 5: The TME: a quite complex ecology



Source: Adapted from Nature; Bryan, Garnier & Co. ests.

Basically, communication and signalling within the TME occurs through two major mechanisms: (1) Cell-cell interaction through **cell surface molecules** like specific cell receptors (such as TCR and BCR), adhesion molecules & immune checkpoints ligands; and (2) Distant communication through **soluble mediators** such as cytokines (interleukins), hormones, chemokines and inflammatory mediators. "*In the TME, this signalling molecules are acting as break or accelerators for the anti-cancer immune response*" stated Vassili Soumelis.

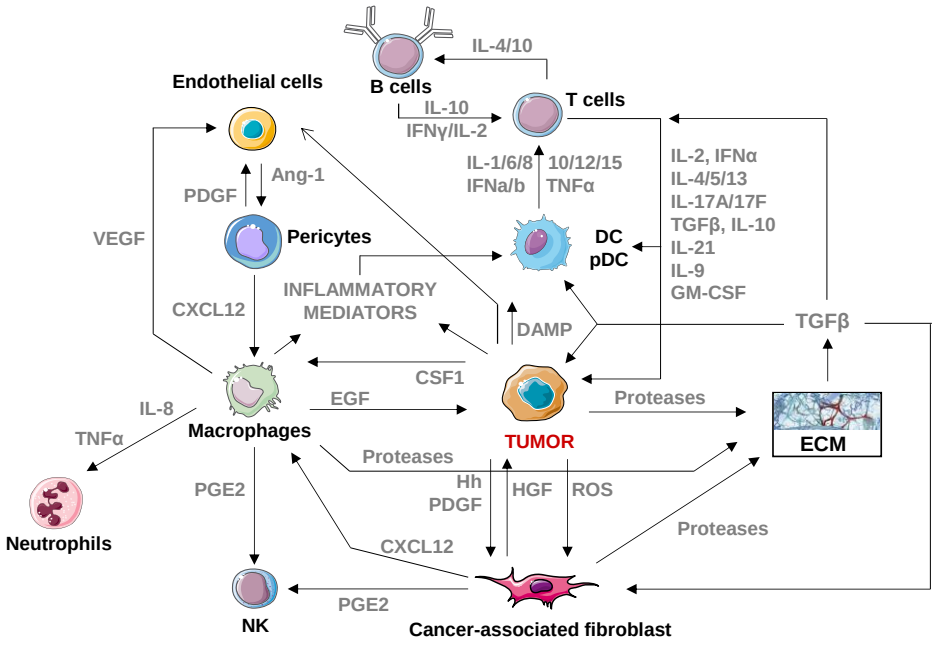
As example, gliomas/brain tumours are known to: 1/ secrete immuno-suppressive factors such as TGF-β, IL-10 and CCL-2; 2/ recruit immune cells like regulatory T cells (Tregs) and myeloid-derived suppressive cells (MDSCs) to cancer cells, thus further developing a tumour-promoting milieu. In addition, these malignant cells express surface molecules such as Fas-ligand, B7-1/B7-2 and PD-L1/PD-L2 which, when bound to their respective receptors (Fas, CTLA-4 and PD-1) on tumour-infiltrating lymphocytes, alter and dampen their effector functions...

Tumour micro-environment understanding will be key for successful cancer immuno-therapy

"*Network analysis will help predict potential drug effects and identify new pathways to target to generate therapeutics through a rational approach based on patient segmentation to increase probability of success*" said Vassili Soumelis

Soluble signalling mediators, such as cytokines, display two key features which prevents them for being relevant targets for therapeutic development: (1) they elicit their biologic effect through several receptors in a variety of biological pathways, with potential additive or opposite effects, depending on the involved receptor (a mechanism known as "pleiotropy"), and (2) several cytokines may elicit the same biological effect (a mechanism known as "redundancy"). Such features question the ability to elicit a biological effect by blocking or administering cytokines, and underline the potential risks of unwanted adverse events associated with such approach. For example, high-dose IL-2 has been considerably underused in the treatment of patients with metastatic renal cell carcinoma (RCC) in spite of its clinically demonstrated efficacy, because it is inconvenient to administer and often results in types of toxicity not common in the practice of medical oncologists.

Fig. 6: TME – Multiple soluble activating and inhibitory intercellular signals

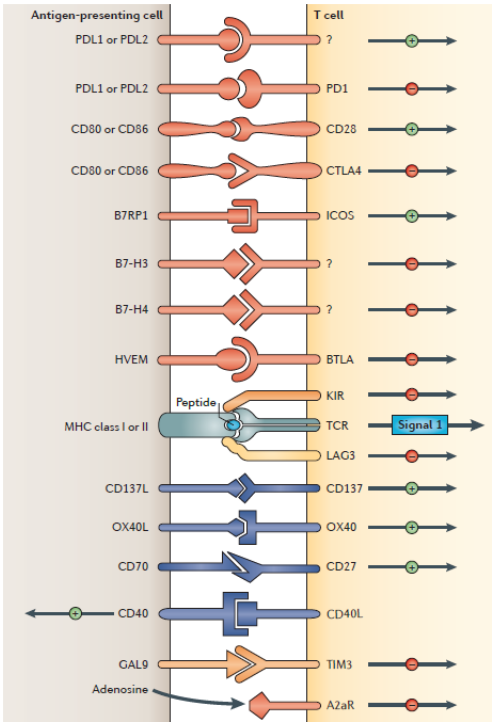


Source: Curie Institute; Bryan, Garnier & Co. ests.

T-cell activating and inhibitory surface receptors are priority targets for current immune modulator drug development

On the other hand, **cell surface molecules** don't have the pleiotropy feature, thus defining more relevant targets with more predictable biological effects, and as such more suited for the development of new therapeutic approaches. Within this category, immune checkpoint molecules define a promising subset of targets.

Fig. 7: TME – Multiple T-cell surface activating and inhibitory intercellular signals



Source: Adapted from Nature (Pardol, 2012), Curie Institute; Bryan, Garnier & Co. ests.

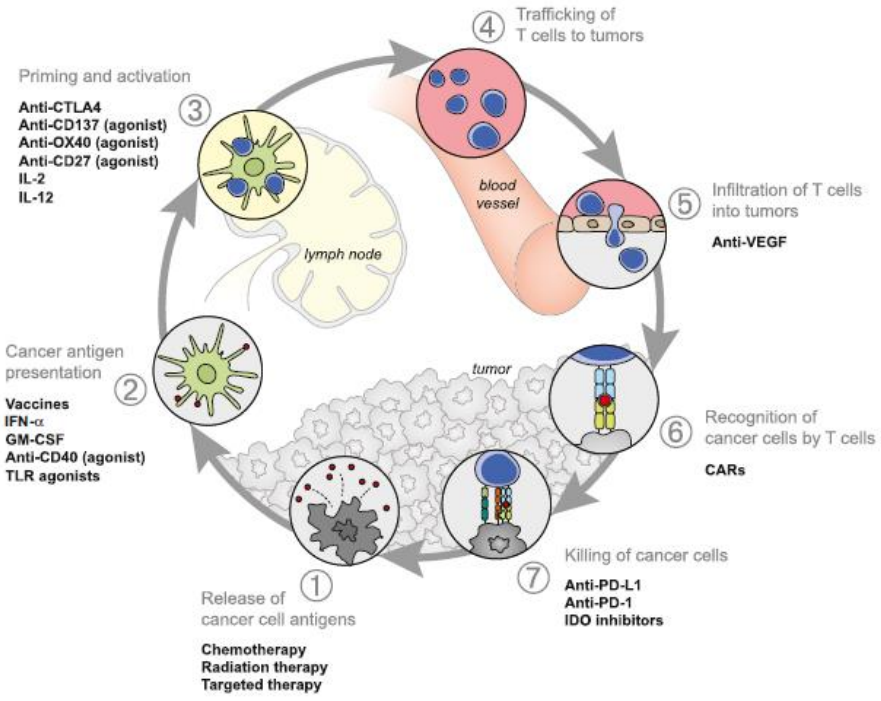
Immune checkpoints are key signalling pathways, triggered by specific surface molecule recognition during cell-to-cell interaction, able to modulate the immune response. To put it in simple words, they work the same as "police roadblocks": each cell is controlled by our immune cells and has to present some surface proteins that act as ID cards. And if such a protein suggests that the cell is infected/dangerous, an immune attack is unleashed, leading to the target infected/dangerous cell's death. That said, cancer cells are foxy, and sometimes act as normal ones to survive, by presenting false ID cards. Hence, the aim to prevent this through some specific immune checkpoint blockers/inhibitors.

2.4. Current Strategies in Cancer Immuno-Therapy

The breadth of potential targets opens a wide range of immune therapeutic options

"The numerous factors involved in the cancer-immunity cycle and the regulation of the TME provide a wide range of potential therapeutic targets" stated Eliane Piaggio. The main current immune-therapies currently assessed in clinical and preclinical settings or already used in clinic are: (1) monoclonal antibodies able to target either tumour antigens or immune signalling receptors (including checkpoint inhibitors), (2) small molecule able to selectively inhibit cell signalling, (3) adoptive cell transfer approach, including the CAR-T cells strategy, (4) bispecific molecules (including BiTES), (5) oncolytic viruses and (6) anti-tumour vaccination.

Fig. 8: Current Immuno-Therapy Strategies



Source: Research Cancer Immunotherapy; adapted from Chen et al., 2013.

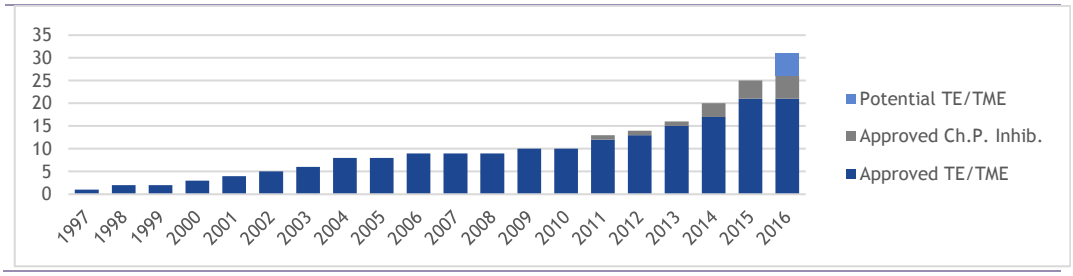
Discussion during the day focused on the most advanced therapeutic strategy which already demonstrated clinical proof of efficacy and successful clinical use: the monoclonal antibodies approach, with a specific emphasis on immune checkpoint inhibitor antibodies.

3. Monoclonal Antibodies as Cancer Therapies

Monoclonal antibodies are one of the most successful cancer therapy strategy to date

"*Monoclonal antibody-based treatment of cancer has been established as one of the most successful therapeutic strategies for both hematologic malignancies and solid tumors in the last 20 years*" said Delphine Loirat. Aside from targeting antigens that are involved in cancer cell proliferation and survival, antibodies can also function to either activate or antagonize immunological pathways that are important in cancer immune surveillance. "*Since 1997, 26 monoclonal antibodies have been approved for tumour indication, and we could reasonably expect an acceleration of antibodies approval for the treatment of cancer*" stated Delphine Loirat.

Fig. 9: FDA Approved mAbs for Cancer Therapy



Note: Ch.P. Inhib.: Checkpoint Inhibitor; TE/TME: Tumor Epitope/Tumor Micro-Environment

Source: Curie Institute; Bryan, Garnier & Co. ests.

Immune checkpoint inhibitors are approved since 2011 and progressively shift cancer treatment paradigm

Before 2011, antibodies approved for oncology indication are only targeting receptors on tumour or microenvironment of the tumour (angiogenesis). Since 2011, a new class of mAb targeting not protein on tumour nor the tumour microenvironment, but the anti-tumour immune response microenvironment is also approved.

Fig. 10: FDA Approved mAbs for Cancer Therapy – Detailed List

Year	Anti-Tumor/TME	Company	Target	Checkpoint Inhibitor	Company	Target
1997	Rituximab	Roche (Genentech)	CD20			
1998	Trastuzumab	Roche (Genentech)	HER2/neu			
2000	Gemtuzumab Ozogamicin	Wyeth (now Pfizer)	CD33			
2001	Alemtuzumab	Genzyme (now Sanofi)	CD52			
2002	Ibritumomab Tiuxetan	Biogen Idec	CD20			
2003	Tositumomab	Corixa (now GSK)	CD20			
2004	Cetuximab	Merck Serono	EGFR			
	Bevacizumab	Roche (Genentech)	VEGF			
2006	Panitumumab	Amgen	EGFR			
2009	Ofatumab	GSK	CD20			
2011	Denosumab	Amgen	RANKL	Ipilimumab	BMS	CTLA-4
	Brentuximab vedotin	Takeda (Millenium)	CD30			
2012	Pertuzumab	Roche (Genentech)	HER2			
2013	Obinutuzumab	Roche	CD20			
	Ado-trastuzumab emtansine	Roche (Genentech)	HER2/neu			
2014	Siltuximab	Janssen	IL-6	Pembrolizumab	Merck & Co	PD-1
	Ramucirumab	Eli Lilly	VEGFR2	Nivolumab	BMS	PD-1
2015	Dinituximab	United Therapeutics	GD2	Ipilimumab+nivolumab	BMS	PD-1+CTLA-4
	Daratumumab	Janssen	CD38			
	Necitimumab	Eli Lilly	EGFR			
	Elotuzumab	BMS	SLAMF7			
2016				Atezolizumab	Roche	PD-L1
potential 2016	Farletuzumab	Morphotek	FRA			
	Inotuzumab ozogamicin	Pfizer	CD22			
	Xilonix	Xbiotech	IL-1alpha			
	Begelomab	Adienne	CD26			
	Oralatumab	Eli Lilly	PDGFRα			

Source: Curie Institute; Bryan, Garnier & Co. ests.

3.1. Antitumor/TME Antibodies

The killing of tumor cells using monoclonal antibodies can result from direct action of the antibody (through receptor blockade, for example), immune-mediated cell killing mechanisms, payload delivery, and specific effects of an antibody on the tumor vasculature and stroma. Tumor antigens that have been successfully targeted include epidermal growth factor receptor (EGFR), ERBB2, vascular endothelial growth factor (VEGF), CD20, CD30 and CD52.

3.2. Immune Checkpoint Inhibitor Antibodies

Since 2011, a new type of antibodies, able to target immune system modulation molecules on surface of immune cells (mainly T-cell) are available on the market. "*The modulation of immune system interplay with tumour cells through targeting of T cell immune checkpoint receptors has emerged as a powerful new therapeutic strategy for tumour therapy*" said Delphine Loirat.

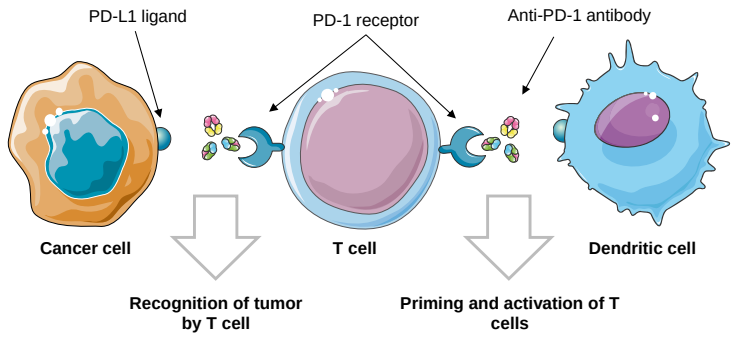
Immune checkpoint blockers are currently among the most promising anti-cancer approaches. CTLA-4 was the very first target that significantly improved overall survival in patients with a quite challenging tumour type (metastatic melanoma), and led to the approval of the very first compound within this novel therapeutic class (BMS's Yervoy, also known as ipilimumab). But even better outcomes have now been reached with anti-PD-1/PD-L1 in a range of different indications, and especially in patients overexpressing the ligand PD-L1.

3.2.1. PD-1/PD-L1 inhibitors as strong backbones

Checkpoint inhibitors, and particularly anti-PD-1/PD-L1s, are likely to be part of the future SOC

PD-1 is a checkpoint protein expressed on the surface of T cells. It normally acts as a type of "off switch" that helps keep the T cells from attacking other cells in the body. It does this when it attaches to PD-L1, a protein on some normal cells. When PD-1 binds to PD-L1, it triggers a signalling cascade preventing the T cell to kill the target cell. Some cancer cells express large amounts of PD-L1, which helps them evade immune attack. Targeting the PD1/PD-L1 pathway with blocking antibody aims at preventing the blockade signalling and promoting the elimination of tumour cells by T-cells.

Fig. 11: Mechanism of action for a checkpoint inhibitor targeting PD-1



Source: Bryan, Garnier & Co. ests.

Several molecules targeting the PD1 receptor are already approved or in development for a large panel of tumor types. Nivolumab, an Anti-PD1 drug developed by Bristol-Myers Squibb, is approved for previously treated metastatic melanoma and squamous non-small cell lung cancer. Another anti-PD1 drug, Pembrolizumab, developed by Merck, is approved for previously treated metastatic melanoma. Similar strategies are being explored targeting PD-L1 to treat other cancer types including non-squamous NSCLC, renal cell carcinoma and bladder cancer. Roche's leading anti-PD-L1 candidate drug,

Atezolizumab has been approved in May 2016 by the FDA for the treatment of locally advanced or metastatic urothelial carcinoma.

Fig. 12: Selected PD1 / PD-L1 monoclonal antibodies

Antibody	Target	Company	Tumor Type	Clinical Development Stage
Nivolumab	PD-1	Bristol Myers Squibb	Melanoma, NSCLC, RCC	Approved (US)
			Hodgkin lymphoma	Breakthrough Therapy (US)
			Bladder/urothelial, brain, gastric/GEJ, HCC, HNSCC, SCLC	Phase 3
Pembrolizumab	PD-1	Merck & Co	Melanoma, NSCLC	Approved (US)
			mCRC (MSI-high)	Breakthrough Therapy (US)
			Breast, bladder/urothelial, gastric/GEJ, HNSCC, multiple myeloma	Phase 3
Pidilizumab	PD-1	Medivation	Pancreatic, CRC, RCC, prostate, CNS	Phase 2
Atezolizumab	PD-L1	Roche (Genentech)	Bladder/urothelial	Approved (US)
			NSCLC	Breakthrough Therapy (US)
			Breast, RCC	Phase 3
Durvalumab	PD-L1	Astrazeneca (Medimmune)	Bladder, NSCLC, HNSCC	Phase 3
Avelumab	PD-L1	Pfizer/Merck KGaA	Merkel cell	Breakthrough Therapy (US)
			NSCLC, gastric, ovarian, urothelial	Phase 3

Note: GEJ: gastroesophageal junction; HCC: hepatocellular carcinoma; HNSCC: head and neck squamous cell carcinoma; mCRC: metastatic colorectal cancer; MSI: microsatellite instability; NSCLC: non-small-cell lung cancer; SCLC: small-cell lung cancer. - Source: Bryan, Garnier & Co. ests.

According to cancer type, response rate to PD-1/PD-L1 inhibitor may vary.

That said, these blockers are far from perfect as the overall response rates vary between 15% and 30% in solid tumours. And: 1/ these quite low levels can certainly be explained by the fact that these approaches solely target one immune axis; and 2/ such heterogeneity is also attributable to the inter-tumour heterogeneity and the complexity of the tumour micro-environment.

Fig. 13: Anti-PD-1/PD-L1 – Overall response rates (%)

Indication	Response rate (%)
Non-small cell lung cancer (NSCLC), squamous and non-squamous	15-20%
Small cell lung cancer (SCLC)	15%
Renal cell Carcinoma (RCC)	15-20%
Bladder cancer	25%
Head & neck squamous cell carcinoma (HNSCC)	15-25%
Gastric cancer	20%
Hepatocellular carcinoma (HCC)	20%
Hodgkin's Lymphoma (HL)	65-85%
Ovarian cancer	15%
Triple negative breast cancer (TNBC)	20%

Source: Curie Institute; Bryan, Garnier & Co.ests.

Targeting PD-1/PD-L1 alone may not be sufficient to treat a large variety of cancers

In August, BMS announced that Opdivo (nivolumab, anti-PD-1 mAb) as monotherapy did not meet its primary endpoint of progression-free survival in patients with previously untreated advanced non-small cell lung cancer (NSCLC) whose tumours expressed PD-L1 at ≥ 5%. This is the first set back of the anti-PD-1 approach, resulting in an instant drop of almost 20% in BMS share price. Although disappointing, this failure may not be a total surprise as overall response rate to anti-PD-1/PD-L1 in lung cancer was already low (between 15-20%). This results underlines the fact that combination therapy may provide an important opportunity to address the needs of cancer patient.

"*It remains surprising that mono-target approaches (like the anti-PD1 antibodies) demonstrates such patient benefits in the view of TME network complexity*" premonitory shared Vassili Soumelis during our discussions. Recent BMS' setback is the demonstration that monotherapy could be limited in its application because of its inability to address the complexity of signal integration at the TME level, and brutally reminds of the necessity to take into account the diversity of TME signalling to propose efficient therapies.

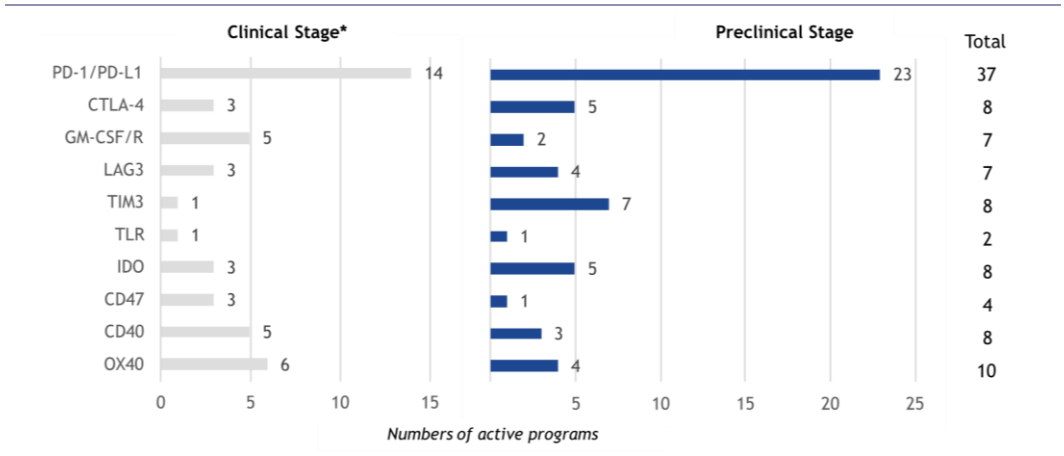
Additionally, this results may advocate for the importance of testing other checkpoint inhibitors on the back of the growing understanding of the numerous immune-tumour interactions, notably to identify best combination regimens.

3.2.2. Other checkpoint inhibitors strategies

Several other T-cell checkpoint inhibitors are being developed beyond PD-1/PD-L1

Although PD-1 and CLTA-4 checkpoint inhibitors have grabbed the attention of scientists and oncologists in recent years, a wide variety of other checkpoint and immune blocker/activator therapies may hold promise in cancer treatment, although their potential in the clinic is yet to be developed. Most novel checkpoints and immune blockers/activators currently under investigation for the development of new therapeutic antibodies target T-cell activation as well as the TME through the following molecules: GM-CSF/GM-CSFR, LAG3, TIM3, TLR, IDO, CD40, CD47 and OX40.

Fig. 14: Selected Active Immuno-Oncology Programs



*including approved drugs - Source: BioMedTracker

"*Although these new targets hold promise for cancer treatment alone or in combination, priorities need to be made to test the list of available anti-check point Abs in the clinics*", said Eliane Piaggio. "*In this respect, translational immunology will be key for concept validation and clinic transposition*".

"*One key question to answer is the place of each of these additional potential targets in the therapeutic strategy, aside from already available checkpoint inhibitors and more traditional options such as chemotherapy*", added Delphine Loirat.

3.3. Bi-specifics: early promises

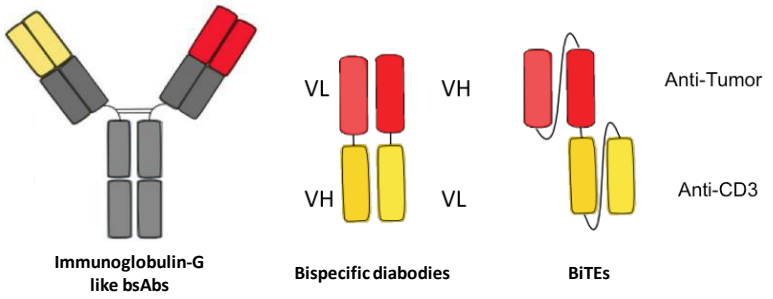
Bispecific antibodies may open a new era of anti-tumour immunity modulation

Currently, the vast majority of monoclonal antibodies are "monospecific", with a defined specificity for a given molecular part of one antigen/one epitope. But, as previously seen, these approaches struggle to address the multifactorial state of cancer cells. Combining therapies is obviously an answer, but then their consequent cost is just another issue.

In this context, **bispecific antibodies (bsAbs) are of increasing interest given their ability to simultaneously bind to two different epitopes on the same or on different antigens**.

There are two classes of bsAbs: (1) Immunoglobulin-G (IgG)-like bsAbs, large molecule having a conserved immunoglobulin constant domain, thus able to exhibit Fc-mediated activities and having similar half-life as monoclonal Abs; (2) Small bsAbs: genetically engineered recombinant antibodies lacking a constant domain and primarily designed as effector cell recruiters (diabodies), and T-cell engagers (Bispecific T-cell Engager Antibodies, BiTEs).

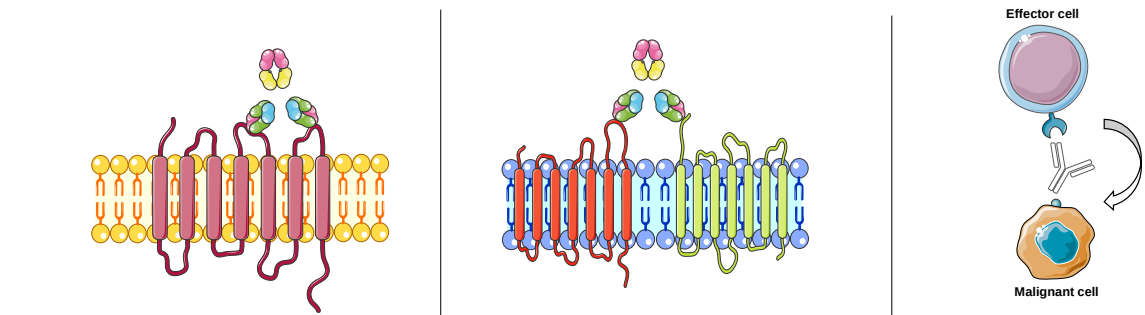
Fig. 15: Types of bsAbs



Source: Curie Institute, Bryan, Garnier & Co. ests.

The ability of bsAbs to simultaneously bind to two different epitopes confers at least two advantages compared to more traditional mAbs: 1/ they can engage immune effector cells like T-cells, and promote tumour destruction (these types of cells cannot be recruited by conventional mAbs due their lack of Fc receptors); and 2/ they allow the concurrent blockade of two pathways (thus improving the therapeutic efficacy while reducing the risk of resistance formation).

Fig. 16: Bispecifics – How they work



Source: Bryan, Garnier & Co. ests.

Bispecific T-cell Engager Antibodies (BiTEs) are single-chain antibodies designed for polyclonal activation and redirection of cytotoxic T-cells to tumour cells. One of the antibody's arms recognize CD3, a cluster of differentiation for T-cells, and the other one detects tumour cells. The small design of BiTEs is optimal to enable an interaction between both cells, ensuring the formation of a lytic immunological synapse.

BiTEs demonstrated clinical efficacy

The very first T-cell engagers that reached the market, blinatumomab (Blincyto), bsAbs anti-CD19/CD3 developed by Amgen, and catumaxomab (Removab), bsAbs anti-EpCAM/CD3 developed by Neovii Biotech, displayed quite deep response rates in haematological malignancies, but many intrinsic factors are impairing their commercial penetration; the main problem being the limited half-life (c. 2 hours for Blincyto) and, consequently, the need for continuous infusions, because of their small size and lack of constant domain.

Fig. 17: Blincyto – Phase II results in adults with R/R ALL

Efficacy endpoints	%
Complete response/complete response with partial hematologic recovery	43%
o/w Complete response (CR)	33%
o/w Complete response with partial hematologic recovery (CRh)	10%
MRD response during first 2 cycles CR/CRh	82%
Hematopoietic stem cell transplant after CR/CRh	40%
. Most frequent grade ≥ 3 AE: febrile neutropenia (25%), neutropenia (16%)	
. Serious AE included Cytokine Release Syndrome (CRS) and nervous system AE	

Source: Company Data.

Efforts are thus being made to improve the design of these molecules (e.g. IgG-like with deeper tissue penetration/better interaction profiles, or smaller with increased serum half-life), and/or increase the number of potential bonds.

Aside from the two bsAbs currently approved, over 30 bispecific molecules are in different stages of clinical trials and more than 70 are in preclinical phase.

4. Challenges and Future Development of Immunotherapy

The new generation of immunotherapies represent a breadth of opportunities, but this diversity may become a challenge to efficient development of relevant therapeutic alternatives. From discussion with Curie's specialists, several key messages arose:

- **Understanding the mechanism of action of each compound, and thus their impact on the cancer-immune system interrelations (especially the TME), is key**, knowing that some pathways might be more important than others.

- **Monotherapies are not a panacea, and the best outcomes are likely to be achieved by combination therapies**; but :1/ obviously, not all of them will yield positive results; and 2/ each and every one of them are more susceptible to succeed in a given milieu/indication.

- Apart from a "simple" stratification of the patients depending on the characteristics of the tumour milieu, **we see molecules with potential predictive biomarkers as the ones with better probability of success**.

- Efficacy is of course of essence, but **one should not turn a blind eye to safety**.

4.1. Combining to better address a tumour's heterogeneity and complexity

Going from the tumour specifics to choosing the right combination

The optimal anti-tumour response will require the successful modulation of several pathways/fronts. There is no "one-fits-all" strategy (and that's why some approaches long failed as a monotherapy, e.g. cancer vaccines); and the best outcomes will probably be achieved by attacking multiple fronts in a targeted manner.

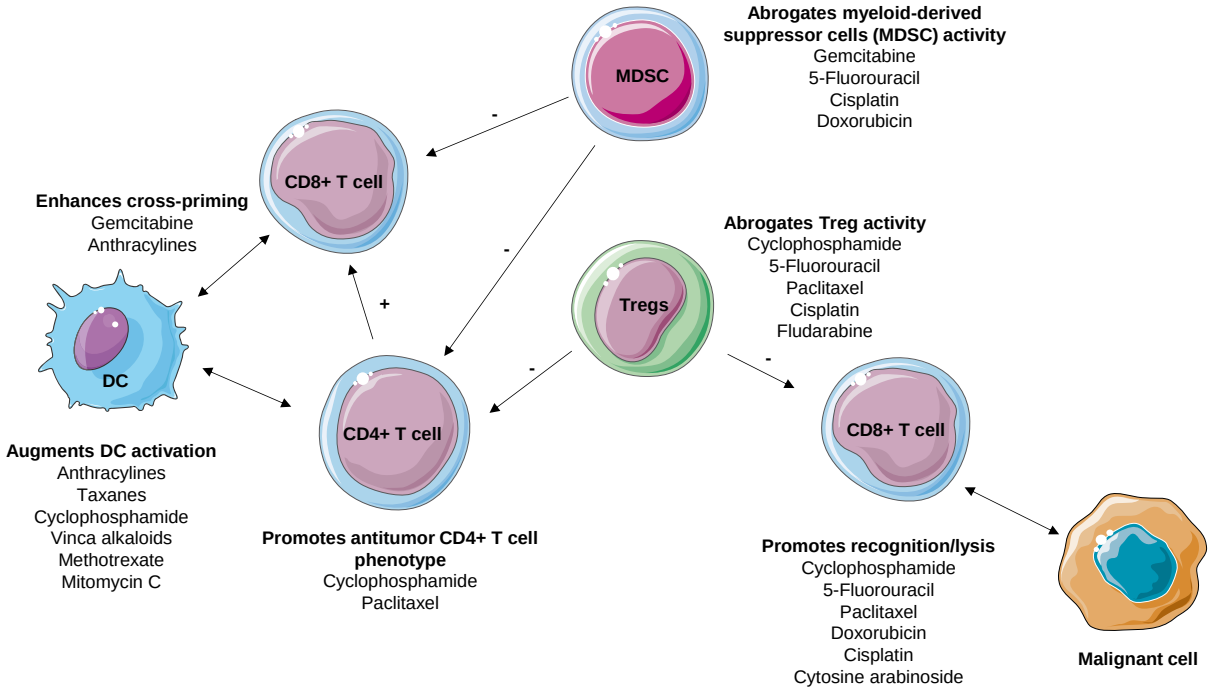
Evaluating the cancer micro-environment will be key to gauging/selecting the best agents to be used; all the more so as: 1/ the efficacy profile of a given agent can be significantly impacted by the TME (e.g. checkpoint blockers are less likely to generate responses in lowly inflamed tumours); 2/ simply adding a compound to another is clearly not the right strategy; and 3/ analysing the tumours will be key to know which immuno-suppressive pathway is hampering the cocktail's effects.

Compounds targeting a unique factor within the TME may fail, as recently demonstrated by the inability of anti-PD-1 monotherapy to address lung cancer for example… and unfortunately giving an estimation of its relative importance is no easy task.

More "traditional" therapies (e.g. chemo, radiation, etc.) will play a key role in the future paradigm, be it because: 1/ some of them are much more affordable than their more innovative counterparts… or 2/ their mechanism of action is pretty synergistic with IO agents. Chemotherapies are immune suppressive and thus were long considered as contra-productive in the current paradigm. It is now widely accepted that some of these can actually augment tumour immunity; be it: 1/ by inducing immunogenic cell death and leading to the release of cancer antigens ("debulking"), or 2/ by disrupting strategies that cancer cells use to evade immune suppression (including the abrogation of immuno-suppressive cells within the TME, such as Tregs).

Targeted therapies (e.g. anti-ALK, anti-EGFR) are also believed to afford a favourable window for immunotherapy to achieve more cytotoxicity due to: 1/ their ability to rapidly induce pretty deep responses, and 2/ their potential impact on the TME (reduced immuno-suppression, unleashing of neoantigens, etc.). That said, these approaches are likely to be considered solely if the genetic profile of the patient corresponds with the afferent classification.

Fig. 18: How chemotherapies modulate tumour immunity



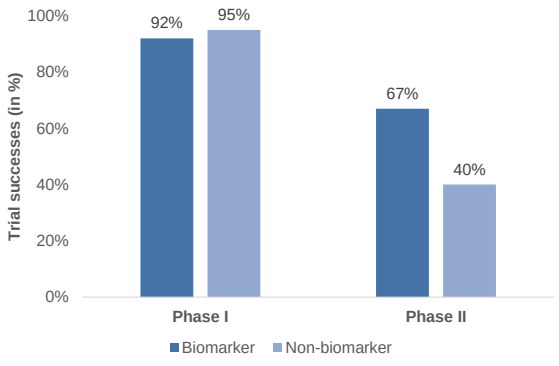
Source: Adapted from Emens et al. *2015, Bryan, Garnier & Co. ests.*

4.2. The quest for biomarkers continues

Predictive biomarkers as must-haves

The quest for biomarkers dates back to the development of the first targeted therapies directed at tumours with specific mutation types. Today, the development of a drug is often associated with the hunt for a predictive biomarker which helps to stratify patients better and maximise the success of clinical trials. IO is no exception to the rule, and **biomarkers are believed to become must-haves in the development of oncology treatments going forward**.

Fig. 19: NSCLC trial success for molecules with and without biomarkers



Source: Journal of Thoracic Oncology, 2014; 9 (2): 163.

■ **PD-L1 expression as a primary basis for stratification**

Responses to PD-1/PD-L1 blockers are positively correlated to the expression of PD-L1…

The initial data collected by BMS, Merck & Co., Roche and AstraZeneca look fairly unanimous: the response along with its duration tend to be much more significant when patients over-express the PD-L1 ligand (be it solid tumours or haematological malignancies). And that's why some of these companies have decided to use this first element of stratification as a key cornerstone in designing their trials.

Fig. 20: PD-L1 expression depending on the type of tumour

Cancer type	PD-L1 expression	Tumour-infiltrated immune cells?
Melanoma	40-100%	Yes
Non-small cell lung cancer	35-95%	Yes
Nasopharyngeal	68-100%	Yes
Glioblastoma	100%	Yes
Colon adenocarcinoma	53%	Yes
Hepatocellular carcinoma	45-93%	Yes
Urothelial/bladder	28-100%	Yes
Multiple myeloma	93%	Yes
Ovarian	33-80%	Yes
Gastric carcinoma	42%	Yes
Oesophageal	42%	Yes
Pancreatic	39%	Yes
Renal cell carcinoma	15-24%	Yes
Breast	31-34%	Yes
Lymphomas	17-94%	Yes
Leukaemias	11-42%	No

Source: Research Cancer Immunotherapy; Bryan, Garnier & Co. ests.

… But such a basis for stratification is far from perfect

However, **simply retaining the PD-L1 status might not be the right strategy** as: 1/ its expression can apparently vary over time, and even within different regions of the same tumour, under the influence of different factors (e.g. IFN-γ); 2/ as previously underlined, PD-1/PD-L1 is just one immune checkpoint among others; 3/ patients diagnosed in late stages of a cancer (III-IV) might have inaccessible tissues or a sample that cannot be evaluated; e.g. in advanced or metastatic NSCLC, 31% of patients have inaccessible tissue and 25% of sample tissues cannot be processed because of their heterogeneity, improper conservation or instability; and 4/ PD-1/PD-L1 might not be a sufficient target on its own to obtain clinical efficacy.

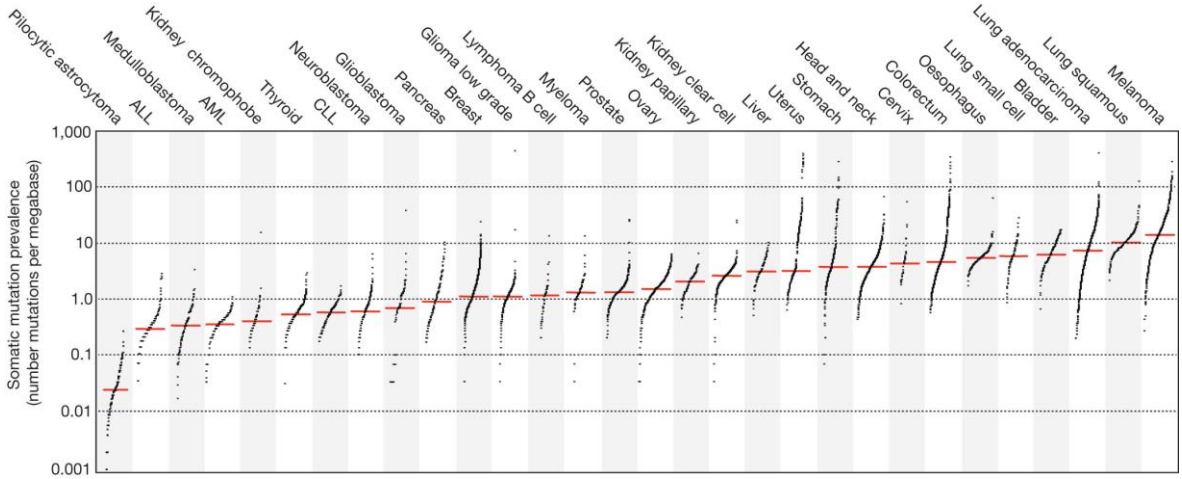
Note that a liquid biopsy might be a first answer to the latter issue and, particularly, the analysis of cell free DNA currently investigated in clinical trials. This approach focuses on the analysis of cell free nucleic acids which are thought to originate from dead cells and which have been shown to contain cancer-related mutations. However, the variation of concentration in the bloodstream raises challenges with regard to the enrichment of the sample and the sensitivity of the test.

■ **Other potential markers are currently under investigation**

Other promising markers are under investigation

The use of MMR deficiency (DNA mismatch repair) as a potential predictive marker for checkpoint blockers, for example, has gained traction immensely over the past few months; particularly following the publication of an ORR of 62% in heavily pre-treated patients with metastatic colorectal cancer exhibiting such a deficiency (5-10% of them). That said, other alternatives are needed for the remaining 90-95%... And that's why Merck & Co is investigating a wide range of other possibilities (e.g. the IFN-γ signature).

Fig. 21: Mutation frequencies in protein-coding regions



Source: LB Alexandrov et al.*, Nature (2013)*

4.3. And don't forget the safety belt!

One should not turn a blind eye to safety

Delphine Loirat made a particular focus on the importance of anticipating and managing immune-related adverse events, all the more so as: 1/ oncologists practicing in small clinics are probably not yet accustomed to such toxicity profiles; and 2/ such risks are exacerbated with combinations. As an example, nivo/ipi did significantly improve response rates vs either nivo or ipi as single-agents… But at the expense of a nearly exponential increase in Grade 3-4 adverse events (55% vs 16% and 27% respectively); and ultimately more discontinuations.

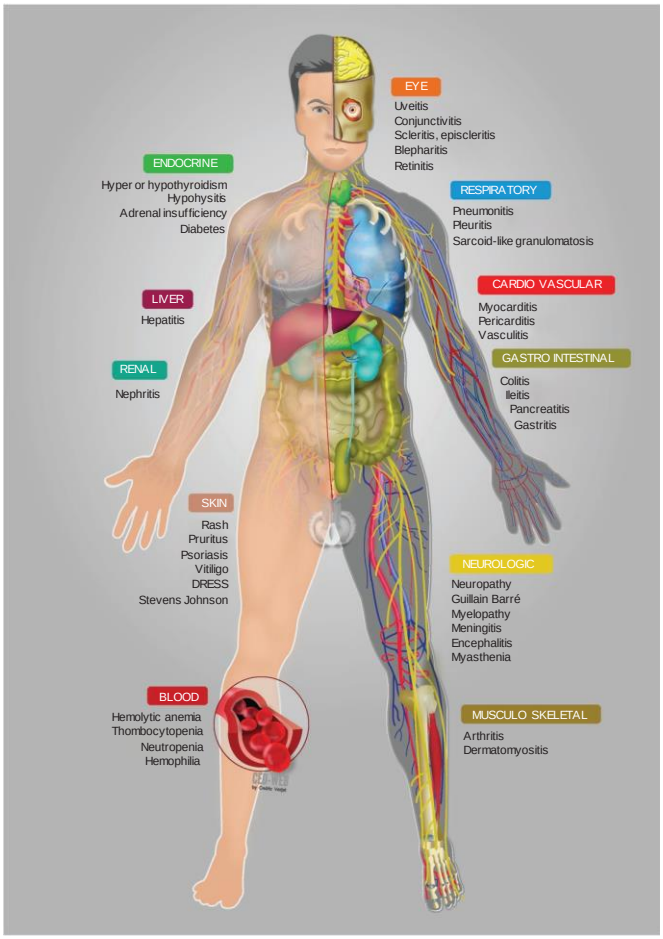
Obviously, a balance has to be found to minimise toxicity while preserving efficacy, be it through changes in administration sequences (Weber *et al.*, 2016) or the combination with other compounds.

Fig. 22: Nivo/ipi in untreated melanoma – Adverse events

Event	Nivolumab		Ipilimumab		Nivo/Ipi	
	Any	Grade 3-4	Any	Grade 3-4	Any	Grade 3-4
Treatment-related adverse events	**82%**	**16%**	**96%**	**55%**	**86%**	**27%**
Diarrhea	19%	2%	44%	9%	33%	6%
Fatigue	34%	1%	35%	4%	28%	1%
Pruritus	19%	0%	33%	2%	35%	0%
Rash	26%	1%	40%	5%	33%	2%
Nausea	13%	0%	26%	2%	16%	1%
Pyrexia	5%	0%	19%	1%	7%	0%
Decreased appetite	11%	0%	18%	1%	13%	0%
Increase in alanine amino-transferase level	4%	1%	18%	8%	4%	2%
Vomiting	6%	0%	15%	3%	7%	0%
Increase in aspartate amino-transferase level	4%	1%	15%	6%	4%	1%
Hypothyroidism	9%	0%	15%	0%	4%	0%
Colitis	1%	1%	12%	8%	12%	9%
Treatment-related AE leading to discontinuation	**8%**	**5%**	**36%**	**29%**	**15%**	**13%**

Source: NJEM; Bryan, Garnier & Co ests.

Fig. 23: Spectrum of toxicity of immune checkpoint blockade agents

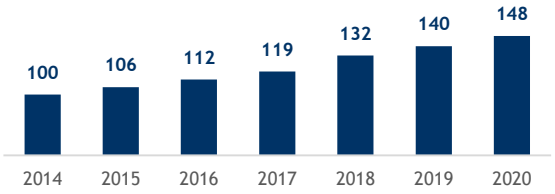


Source: Champiat et al.*, 2015*

5. IO Drug Market Overview

The global market for cancer drugs has hit $100 billion in annual sales in 2014, growing from $75 billion five years earlier.

Fig. 24: Global Oncology Drug Market ($Bn)



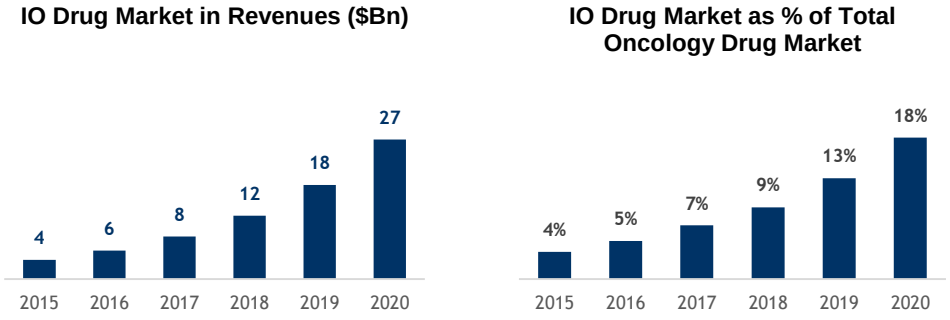
Source: IMS Institute for Healthcare Informatics.

The plethora of cancer therapies being developed and commercialised is set to sustain high growth in the market in the next five years, with the market estimated to be worth c. $150 billion in 2020, growing at a c. 7% CAGR over the period. Approximately 50% of the oncology market is concentrated in the US and Europe, a share expected to remain stable over the period.

Global immuno-oncology drug market could reach up to 50% of global oncology market by end 2029

The growing importance of biological and immunology therapies is a strong driver of the global oncology drug market. The total immuno-oncology drug market was worth approximately $4 billion in 2015, but is set to grow to $27 billion by 2020 at an impressive 49% CAGR over the period, to represent c. 20% of the total oncology market. Growth of the segment is expected to stabilize around 10-15% annually. Should this trend be confirmed, the IO market could represent up to 50% of the total oncology market by the end of the 2020's decade.

Fig. 25: Global Immuno-Oncology Drug Market

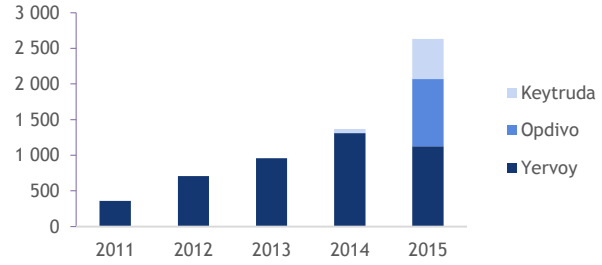


Source: Global Data, Bryan, Garnier & Co ests.

Keytruda and Opdivo are current market leaders thanks to their first in market position

Since 2011, three immune checkpoint antibodies have been successfully launched: Bristol-Myers Squibb's Yervoy, Ono/Bristol-Myers Squibb's Opdivo and Schering Plough/Merck and Co.'s Keytruda. In 2015, these products reached cumulated sales over $2.6 billion (a 92% increase as compared to 2014) representing more than 70% of the global immuno-oncology drug market.

Fig. 26: Cumulated Sales of Approved Checkpoint Inhibitors



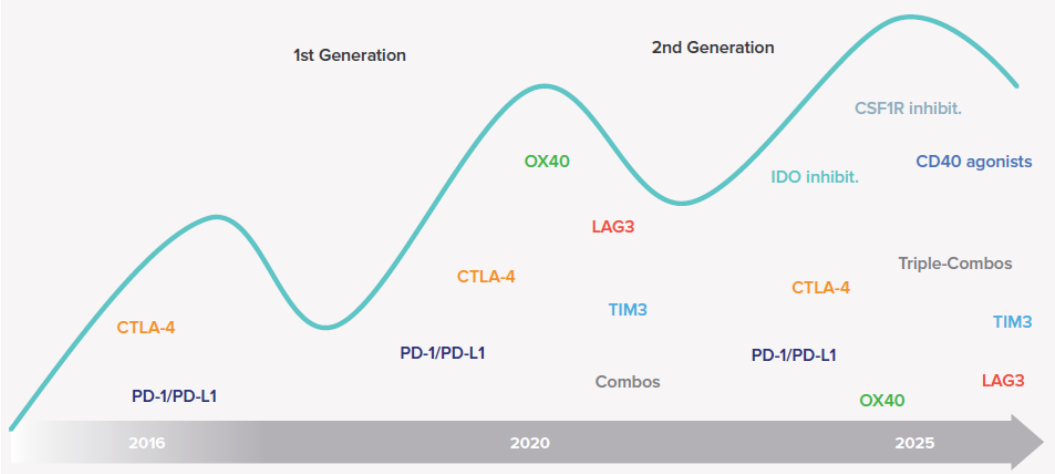
Source: Company Data

Opdivo and Keytruda are set to be the highest-selling immuno-oncology drugs, with forecasted sales of around $10 billion and $7 billion by 2024, respectively, thanks to their first-to-market position in many indications, enabling to leapfrog competition such as Roche's atezolizumab and AstraZeneca's durvalumab.

Immune checkpoint inhibitors are set to drive future immune-oncology drug market size and growth

PD-1/ PD-L1 and CTLA-4 inhibitors currently define most of the immune-oncology drug market, but companies are looking for new ways to differentiate, mainly by investigating other targets (OX40, LAG3, TIM3, CD40, IDO, etc.), and various combinations of immuno-oncology treatments, with either other immuno-oncology or non-immuno-oncology products.

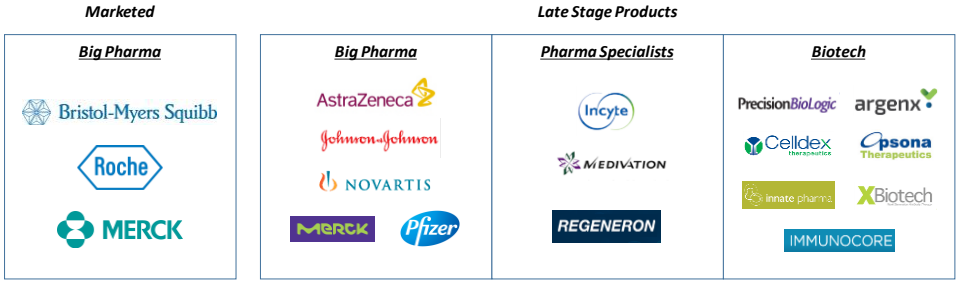
Fig. 27: Immune Checkpoint Inhibitor Drug Market Expected Evolution



Source: IMS Health

The market has become crowded and extremely competitive, with more than 130 biotechs and 20 pharmaceutical companies working on immuno-oncology therapies. Among them, c.20 companies were identified with marketed or late clinical stage (Phase 2 and beyond) immune checkpoint antibodies in their portfolio.

Fig. 28: Selected IO Companies with Late-Stage*/Marketed Checkpoint Abs



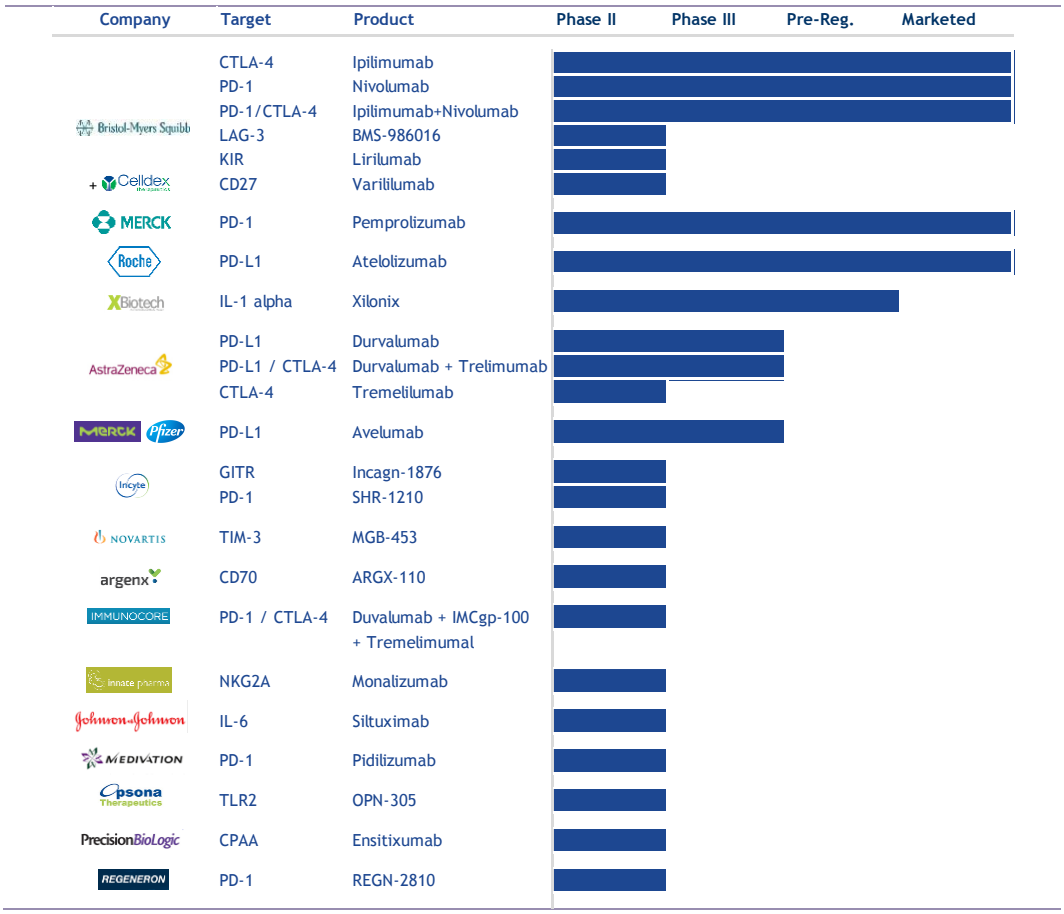
*Phase 2, Phase 3, Registration products (all indications) - Source: Global Data, Bryan, Garnier & Co. ests.

Bristol-Myers Squibb, Roche, Merck & Co and Astrazeneca are key players in the immune checkpoint inhibitor segment

As mentioned above, Merck's Keytruda (pembrolizumab) and Bristol-Myers Squibb's Opdivo (nivolumab) are two leading biologics in the immuno-oncology market, and Pfizer, AstraZeneca, Roche, Merck KGaA and Novartis are also seeking to be contenders. Additional smaller biopharmaceutical companies are also seeking a place in the market (Innate Pharma, Opsona, Celldex,etc.).

Late stage clinical pipeline of immune checkpoint antibodies reveals that PD-1/PD-L1 remain the current leading targets, in terms of number of programs (10) and clinical advancement of programs, but several additional targets are being pursued, with products such as XBiotech's anti-IL-1alpha Xilonix holding promises, notably for the treatment of advanced colorectal cancer.

Fig. 29: Late Stage Immune Checkpoint Inhibitor Pipeline*



*Most advanced phase of development for each molecule, including all indication under development
Source: Global Data, Bryan, Garnier & Co. ests.

Combination therapies in late stage development are currently limited to the CTLA-4 + PD-1/PD-L1 targets, and represent a very small portion of the current late stage pipeline of immune checkpoint inhibitors (only 2 programs having reached at least phase 2), but are set to take an increasingly importance, even more since Opdivo failed as monotherapy in lung cancer, underlining the fact that combination will be key to address additional tumour and expand products labels.

Amgen is leading the still relatively modest bispecific antibody market segment

According to Visiongain, the market for bispecific antibodies oncology drugs remains small as compared to the mAbs market, established at c. $60m in 2015, but highly dynamic, expected to reach c. $500m by 2020, at an impressive c. 155% CAGR over the period.

Two bsAbs reached the market in recent years, blinatumomab (Blincyto), bsAbs anti-CD19/CD3 developed by Amgen and approved in the US for ALL in 2014, and catumaxomab (Removab), bsAbs anti-EpCAM/CD3 developed by Neovii Biotech and approved in Europe for EpCAM positive tumors and malignant ascites in 2009.

The pipeline for bispecific antibodies is fairly less advanced than its mAbs counterpart but significant clinical progress should be expected in the coming years.

Fig. 30: Selected Late-Stage bsAb Pipeline

Company	Target	Product	Stage	Indication
neovii	EpCAM x CD3	Catumaxomab	Phase 2	Platinum refractory epithelial ovarian cancer Gastric adenocarcinoma Ovarian cancer
AMGEN	CD3 x CD19	Blinatumomab	Phase 2	B cell ALL Relapsed/refractory ALL
Roche	Angiopoietin2 x VEGF	RG7221	Phase 2	Neoplasms
MERRIMACK	IGF-1R x HER3	MM-141	Phase 2	Pancreatic cancer

Source: Clinicaltrial.gov, Bryan, Garnier & Co. ests.

6. Deal Environment Overview

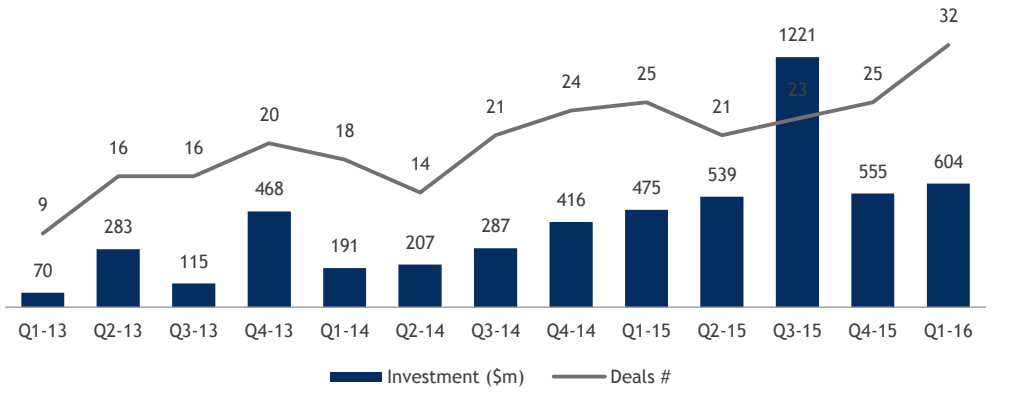
Although the immuno-oncology field is still in its infancy, the industry's high interest in the technology continues to rise, with significant investments and partnerships being announced repeatedly as biopharma companies look to add promising cancer therapeutics to their pipelines.

6.1. Financing

Immuno-oncology technologies attract significant growing private investments since 2013

Financing activity of private biotechnology and drug discovery companies focused on cancer treatment (including the use of immuno-oncology, oncolytic viruses and antibodies) reached new high in Q1-2016, confirming a global growing trend since 2013.

Fig. 31: Oncology Companies Funding Activity



Source: CB Insights

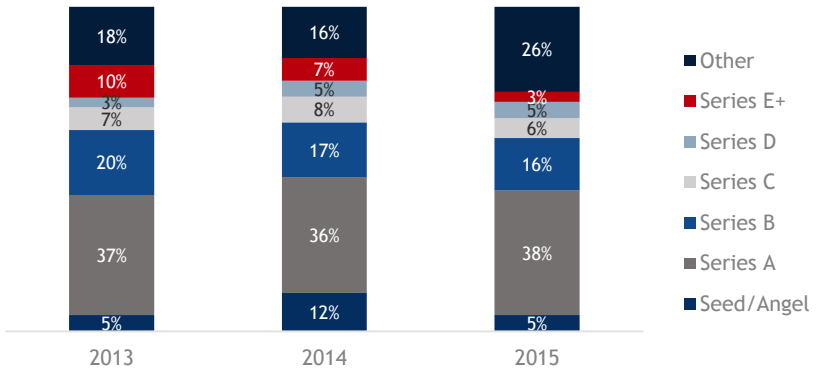
On an annual basis, equity funding to private cancer therapeutics companies was up 153% in 2015 as compared to 2014. Q3'15 was the quarter with the peak in funding, with total investment driven by 3 major rounds, including a $320m round raised by Immunocore. In Q1'16, the positive trend-lines continued, with deal activity rising 28% from Q4'16, to a new high of 32, more than triple the deal count seen in Q1'13.

Private immuno-oncology biotech funding are geared toward early stages

There is currently no need to be well established to attract significant money. Major investments have been directed to companies pursuing their series A or B rounds, with 54% of disclosed deals going to such rounds in 2015. Some of the largest funding rounds in Q1'16 include Series A rounds raised by immuno-oncology startups Forty Seven ($75m) and NextCure ($67m).

Late-stage deals (series E and above) dropped 7%, going from 10% of deals in 2013 to 3% in 2015.

Fig. 32: Deal Share by Stage



Source: CB Insights

Stemcentrx, valued at $5 billion, is the most well-funded oncology startup as of Q1'16, having raised a total of $373.5m in equity funding from investors including Elon Musk, Fidelity Investments, Founders Fund, Artis Ventures, and Sequoia Capital. The company develop conjugated monoclonal antibodies and its leading program, the anti-DLL3 antibody-drug conjugate Rovalpituzumab tesirine, is currently in Phase 1b for the treatment of small cell lung cancer.

Merus is one of the most successfully financed IO mAb company

One of the most active company in 2015 regarding fundraising was the Netherlands-based Merus, a clinical-stage immuno-oncology company developing bispecific antibody therapeutics. The company claimed in August the first tranche of a €72.8m series C financing led by Sofinnova Ventures and Novo A/S, with additional backing from RA Capital Healthcare Fund, Rock Springs Capital and Tekla Capital Management (to ultimately close a successful $65m IPO in May 2016).

7 out of the 10 most funded companies are developing mAbs or bsAbs.

Fig. 33: Top 10 Most Funded Oncology Start-ups as of Q1-2016

Company	Country	Type of Drug	Year Founded	# programs in clinical trials	Most advanced clinical phase	Most Advanced Indication	Partners
Stemcentrx	US	Conjugate mAb	2008	5	Ph1b	Small Cell Lung Cancer	-
Symphogen	Denmark	Recombinant antibody mixtures	2000	5	Ph2b	metastatic colorectal cancer	Baxalta, Genentech
Immunocore	UK	Bi-specific TCR-based targeting molecule with anti-CD3 effector function	2008	3	Ph3	cutaneous melanoma	AZ, Lilly, GSK, Genentech
GANYMED Pharmaceuticals	Germany	Ideal Monoclonal Antibodies (IMABs)	2001	2	Ph2	gastroesophageal cancer	-
NantCell	US	Nanoparticle chemotherapeutic agent & mAb	2015	1	na	cancer	Sorrento, Amgen
ADC Therapeutics	Switzerland	Antibody Drug Conjugates	2011	2	Ph1a	B-cell ALL, B-cell NHL	Cancer Research Technology, BZL Biologics, Genmab, Astrazeneca
Merus	The Netherlands	Bi-specific antibodies	2003	2	Ph1/2	breast, colorectal, ovrian, AML	ProBioGen
Kolltan Pharmaceuticals	US	Monoclonal antibody	2008	2	Ph1	cancer	-
Tocagen	US	Gene therapy	2007	1	Ph2	recurent high grade glioma	-
Isarna Therapeutics	Germany	TGF-ß-Selective Antisense Oligonucleotide	1998	1	Ph1	cancer, ophthalmology	-

Source: CB Insights, Bryan, Garnier & Co. ests

6.2. Partnership & M&A

The immuno-oncology space currently witnesses an increasing deal frenzy, big pharma companies being anxious not to miss out on that hot area of technology and thus continuing to be very active. According to Medtrack, by end 2015, 82% of immuno-oncology drugs were partnered, while only 48% of all cancer drugs involve a development collaboration.

Large Pharma interest for immuno-oncology technologies drives a strong partnership deal appetite

Between 2011 and 2015, there were far more deals for cancer (excluding immunotherapy agents) (c. 1280) than for immuno-oncology deals (c.230), but IO deals had higher average value per deal (c.$215m for cancer deals versus c.$240m for IO deals).

The majority of oncology deals involves programs at research-level collaborations (45% of all deals), while the immune-oncology deals mostly involved clinical stage assets (43% of all deals). Bristol-Myers Squibb and Merck & Co were not surprisingly the top immuno-oncology dealmakers over the 2011-2015 period, but several other large pharmaceutical companies are catching-up.

Deal activity for immune checkpoint antibodies in 2015 was mainly driven by combination

A large portion of partnership deals signed in 2015 involving immune checkpoint inhibitors were related to the development of either bispecific antibodies or combination of monoclonal antibodies. Companies relatively new to the field, such as Sanofi, relied on large development partnership with old partner (Regeneron) to try to anticipate the next "combination" revolution in the field. However, such strategy comes at a premium, Sanofi having paid its entry ticket c.$640m upfront… Other already well established players such as BMS, AstraZeneca and Merck & Co consolidated their grasps by enlarging their pipeline (BMS to collaborate with Five Prime to develop CSF1R targeting antibodies and thus diversifying the potential immune target) or anticipating on their key product's life cycle management (Merck & Co collaborating with Amgen to investigate Keytruda in combination with Blincyto).

Fig. 34: Key mAbs & bsAbs Partnership Deals in 2015

Companies	Date	Description	Product Technology	Targets	Potential Deal Value ($m)	Upfront ($m)
Amgen Merck & Co	Dec-15	Collaboration to investigate Amgen's CD19 bispecific T cell drug (blinatumomab) with Merck's PD-1 antibody (pembrulizumab) in non-Hodgkin's lymphoma	mAb-bsAb Combination	CD19 / CD3 / PD-1	-	-
Bristol-Myers Squibb Five Prime Therapeutics	Oct-15	Exclusive worldwide license and collaboration to co-develop CSF1R antibody program	mAbs	CSF1R	1740	350
Amgen Xencor	Sep-15	Strategic Collaboration on 6 drug discovery & development programs based on Xencor's XmAb bispecific technology platform	Bi Speficic antibodies	CD38 / CD3	45	45
Regeneron Sanofi	Jul-15	Exclusive collaboration to co-develop novel immuno therapeutics targeting the PD-1 pathway	mAbs & bsAbs	PD-1 / LAG3 / GITR	2170	640
Innate Pharma Astrazeneca	Apr-15	Co-development & co-commercialization on IPH 2201, anti-NKG2A mAb, notably in combination with MEDI4736, AZ anti-PD-L1 mAb	mAbs Combination	NKG2A / PD-L1	1275	250

Source: Company Press Releases, Bryan, Garnier & Co. ests

Despite increasing competition, deal flow continued to rapidly grow in 2016. At least 10 significant deals have been signed as of Q2'16, with a majority of them involving big pharma companies.

Year opened on a high note, with Symphogen and Baxalta signing a deal focused on up to six immune checkpoint targets, under which Symphogen gets $175m up front plus up to $1.6 billion more in option

fees and milestone payments. Symphogen will fund all preclinical research and clinical development through phase I, at which point Baxalta will be entitled to in-license each program, on a product-by-product basis.

January was a busy month for deal making, with Abbvie and Sanofi also completing transactions. Abbvie entered a collaboration and license agreement with F-star Biotechnology to research and develop bispecific antibodies in immuno-oncology. F-star's Modular Antibody Technology platform introduces an antigen-binding site into the constant region of an antibody to create a so-called Fcab (an Fc-domain with antigen binding activity). An Fcab can then be used to make many different bispecific antibodies using variable regions binding to second targets. F-star and Abbvie will create Fcabs against two immuno-oncology targets and generate several bispecific drug development candidates.

Deal activity for immune checkpoint antibodies in 2016 was mainly driven by new targets…

If 2015 deal activity was mainly focused on combination and bi-specifics, 2016 activity so far tends to reveal a focus on new immune modulatory targets, beyond the now established PD-1/PD-L1 and CTLA-4. Companies developing molecules able to target new immune checkpoints were getting high interest from large pharmaceutical companies in H1'16.

For example, Abbvie came out on top in a competitive bidding process triggered by broad industry interest in Argenx's program based around its potentially first-in-class, preclinical antibody, ARGX-115, which inhibits GARP (glycoprotein A repetitions predominant), a target involved in maintaining the immunosuppressive activity of regulatory T cells (Treg cells). Under the deal terms, Argenx got $40m upfront and is entitled to receive up to $645m in milestones.

Additionally, Jounce Therapeutics signed in July its first major R&D collaboration deal with Celgene for the development of five B-cell, Treg cell and tumor-associated macrophages targeting programs, including JTX-2011, a preclinical stage monoclonal antibody targeting ICOS. ICOS is an inducible T cell co-stimulatory molecule thought to be able, upon mobilization, to stimulate an immune response against tumour cells. The already planned phase 1/2 study for testing JTX-2011 as a single agent also includes an arm testing the antibody in combination with a PD-1 inhibitor. The deal could be worth up to $2.6Bn, including an already secured $225m upfront payment.

Fig. 35: Key mAbs & bsAbs Partnership Deals in 2016

Companies	Date	Description	Product Technology	Targets	Potential Deal Value ($m)	Upfront ($m)
Celgene Jounce Therapeutics	Jul-16	R&D collaboration on JTX-2011, anti-ICOS mAb, and up to 4 additional early stage programs of B cell, Treg cells and tumor associated macrophages targets	mAbs	ICOS	2600	225
AbbVie Argenx	Apr-16	Collaboration to develop and commercialize Argenx' GARP targeting antibody programs, including ARGX-115	mAbs	GARP	685	40
Sanofi Innate Pharma	Jan-16	Collaboration and license agreement to develop NK-cell recruiting bispecific antibodies, based on Innate Pharma proprietary technology platform	Bi Speficic antibodies	NKp46	-	-
Baxalta Symphogen	Jan-16	Co-development of novel therapeutics against six checkpoint targets	Biologics (mAbs)	-	1600	175
Abbvie F-Star Biotechnology	Jan-16	Collaboration and license agreement to research and develop bispecic antibodies based on F-Star's Modular Antibody Technology platform	Bi Speficic antibodies	-	-	-

Source: Company Press Releases, Bryan, Garnier & Co. ests

…Among which IDO1/TDO appear preeminent.

The past 18-month deal activity also reveals increasing interest of the pharmaceutical industry in IDO1 and TDO as new targets for anti-tumour immune response modulation.

Fig. 36: Selected Recent IDO1/TDO Deals

Companies	Deal Type	Date	Description	Product Technology	Targets	Potential Deal Value ($m)	Upfront ($m)
Merck & Co IOmet Pharma	M&A	Jan-16	Acquisition of full rights on IOmet's IDO and TDO programs	NCE (targeted inhibitor)	IDO1 / TDO	-	-
Roche Curadev Pharma	Collab.	Apr-15	R&D collaboration to develop new IDO1 and TDO targeted therapies	NCE (targeted inhibitor)	IDO1 / TDO	555	25
Bristol-Myers Squibb Flexus Biosciences	M&A	Feb-15	The transaction includes full rights to F001287, Flexus' lead preclinical, small-molecule IDO1-inhibitor and IDO/TDO discovery program	NCE (targeted inhibitor)	IDO1 / TDO	-	800

Source: Company Press Releases, Bryan, Garnier & Co. ests

IDO1 and TDO are key enzymes in the pathway that metabolizes the essential amino acid tryptophan, and have emerged as key targets for the pharmaceutical industry in the cancer immunotherapy field. Overexpression of these enzymes has been detected in a variety of cancers – including glioma, melanoma, lung, ovarian, and colorectal cancers – and is associated with poor prognosis and survival. Currently available preclinical and clinical data suggests that inhibition of IDO1 and/or TDO may synergize with, and help overcome resistance to, existing clinical cancer therapies, in particular other immunotherapy-based treatments. Three major deals involving IDO1/TDO inhibitors have been sealed in the last 18 months, signed by major players in the fields (Roche, BMS and Merck & Co). Interestingly enough, IDO1/TDO inhibitor currently developed are small molecules and not monoclonal antibodies. The BMS-Flexus Bioscience deal is particularly striking since, although F001287 is only in phase 1, Flexus got no less than $800m upfront from BMS…

New entrants in the field have often to pay a premium

The sizes of the aforementioned deals are indicatives not only of the amount of interest in immuno-oncology at the moment, but also demonstrate the premium that late-comers like Celgene and Sanofi are being forced to pay to ensure they will have a seat at a table already dominated by Bristol-Myers Squibb, Merck & Co., Roche and AstraZeneca. Indeed, the same could be said of Pfizer, which paid $850m to partner up with Merck KGaA in late 2014 on avelumab, a PD-L1 targeting mAb.

6.3. IPO

Public markets do not appear as a relevant funding option for the majority of mAbs players

Underwhelming market conditions coupled with exploding partnership opportunities don't stimulate companies to rely on public market to finance product development and future growth. Companies might also find more attractive to pair up with strategic partners rather than financial investors whose timelines for returns might be tighter. Only a handful of immuno-oncology antibody developers floated on public market between 2013 and 2016, with relative low average financial performance. Based on such observation, probability remains high in the future to see biotech companies with promising technology rather pursue partnership/M&A deals with large pharma companies rather than following the IPO path.

Fig. 37: Selected IO mAbs Developers IPO

Company	HQ	Exchange	IPO Year	Share Price IPO	Share Price IPO+3m	3m SP Performance	Market Cap (€m)
Merus	Canada	Nasdaq	2016	9,0	7,5	-17%	131,0
Nordic Nanovector	Norway	OSLO	2015	4,0	4,2	5%	1 110,5
TRACON Pharmaceuticals	US	Nasdaq	2015	8,3	13,2	59%	61,4
Affimed	US	Nasdaq	2014	4,4	3,8	-14%	89,8
arGEN-X	Netherlands	Euronext	2014	7,9	8,2	4%	254,3
OncoMed Pharmaceuticals	US	Nasdaq	2013	20,8	12,7	-39%	370,2
Average						*-0,2%*	

Source: Bloomberg, Company Data

7. Conclusion

The rapid expansion of immuno-oncology in the past five years has been exceptional: catalysed by striking clinical data, reflecting real changes in the survival curves of an ever-broader set of cancers, a huge number of IO programs have advanced across the industry, fuelled by prodigious amounts of capital and soaring collaboration activity between biotech and large pharmaceutical companies.

Monoclonal antibody-based immuno-oncology therapeutics are currently the fastest growing segment of this market. Since first immune checkpoint inhibitor approval in 2011, clinical and market success exponentially accumulated to position this approach as a potential future standard of care for cancer patient management.

As large pharmaceutical companies struggle to secure the technology that will allow them to enter or consolidate their position in this highly competitive field, opportunities seem still widely opened for promising biotech companies with sound technology to secure financing while offering visibility in exit strategy for investors.

However, current fierce competition may raise long term strategic questions. Future successful immune checkpoint inhibitors will have to stem from highly differentiated and strongly backed technology. The current plethora of checkpoint inhibitors development projects may bring the sentiment that a huge amount of (potentially redundant) investment and effort is focused on chasing the same set of cancer immunotherapy targets. Hence, new potent immune checkpoint identification, relevant biomarker development and combinatorial approaches will all participate in product differentiation and will be key to the IO future success. All this is further strengthened by the recent demonstration of the limitation of already well established monotherapy to treat some cancer type.

Other IO approaches beyond mAbs and bsAbs also represent relevant therapeutic options. Tumour vaccine (such as mRNA based solution currently developed by Moderna Therapeutics) or CAR-T cells, which, despite Juno's recent setback, are poised, along with checkpoint inhibitors, to shift current cancer treatment paradigm.

Overall, immuno-oncology agents have the potential to transform cancer care and it is likely that they will become the backbone of cancer therapy in the future. The potential for cure, either on a functional level by turning cancer into a controllable chronic disease (similar to achievements with HIV drugs) or in the true eradication of the disease, may now be a prospect for large numbers of cancer patients.

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- **Hervé Ronin** joined Bryan, Garnier & Co.'s Paris office in September 2010 as a Partner in Healthcare Investment Banking. Hervé has over 18 years of corporate finance experience, successfully advising M&A and ECM transactions across all healthcare segments. Prior to Bryan Garnier, Hervé worked for BNP Paribas Corporate Finance in the healthcare team.

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Please see the section headed "Important information" on the back page of this report.

About Bryan, Garnier & Co

Bryan, Garnier & Co is one of the leading independent investment banks specialized in European healthcare growth companies. We have a dedicated franchise of 20 senior professionals including investment bankers, equity research analysts and institutional sales professionals. Our team covers the key market sub-categories such as : biotechnology, large cap and specialty pharmaceuticals, life science tools, medical technology, diagnostics, healthcare information technology and services.

In 2015, Bryan, Garnier & Co completed over 10 transactions for European healthcare growth companies, raising a total of approximately $1 billion. We top the European healthcare fundraising league tables (number one Investment bank for Healthcare fund raising on Euronext) with landmark transactions such the IPOs of Bone Therapeutics and Amoeba on Euronext.

In the past 24 months, Bryan, Garnier & Co was the most active investment bank involved in the IPO of European healthcare growth companies on the US Nasdaq. We are the number one European investment bank on Nasdaq and in 2015 we achieved the largest ever IPO of European Biotech company on Nasdaq (Galapagos – $317 million).

Corporate Transaction

Bryan Garnier & Co leverage in-depth sector expertise to create fruitful and long lasting relationships between investors and European growth companies.

Initial Public Offering EURONEXT Paris €33 000 000 *April 2016* *Global Coordinator & Joint Bookrunner*	Follow-on Secondary Placement Euronext IPO €100 000 000 *Joint bookrunner*	Nasdaq IPO Follow-on $414 500 000 *July 2015* *Financial advisor*	Follow-on £21 000 000 *May 2015* *Lead Manager & Bookrunner*	Follow-on €45 000 000 *February 2013* *Joint Bookrunner*	Follow-On Offering & Issue of Preferred Equity Stock €50 000 000 *September 2011* *Co-advisor & Bookrunner*

Research

With seasoned research methodology and fundamental bottom-up approach, Bryan Garnier's analysts provide opinionated investment insights with leading perspective across all aspects of the healthcare sector. Bryan Garnier & Co developed the most dedicated healthcare research platform in Europe, with more than 40 stocks covered across the full market cap and sub-sector spectrum / therapeutic areas.

Bryan Garnier & Co, with more than 150 professionals based in London, Paris, New York and Munich, combines a range of services and expertise of top-tier investment banks with the level of attention to clients of a boutique.

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