

Optimize Immuno-oncology Drug Discovery and Development Using Quantitative Systems Pharmacology

By Piet van der Graaf & Andrzej Kierzek

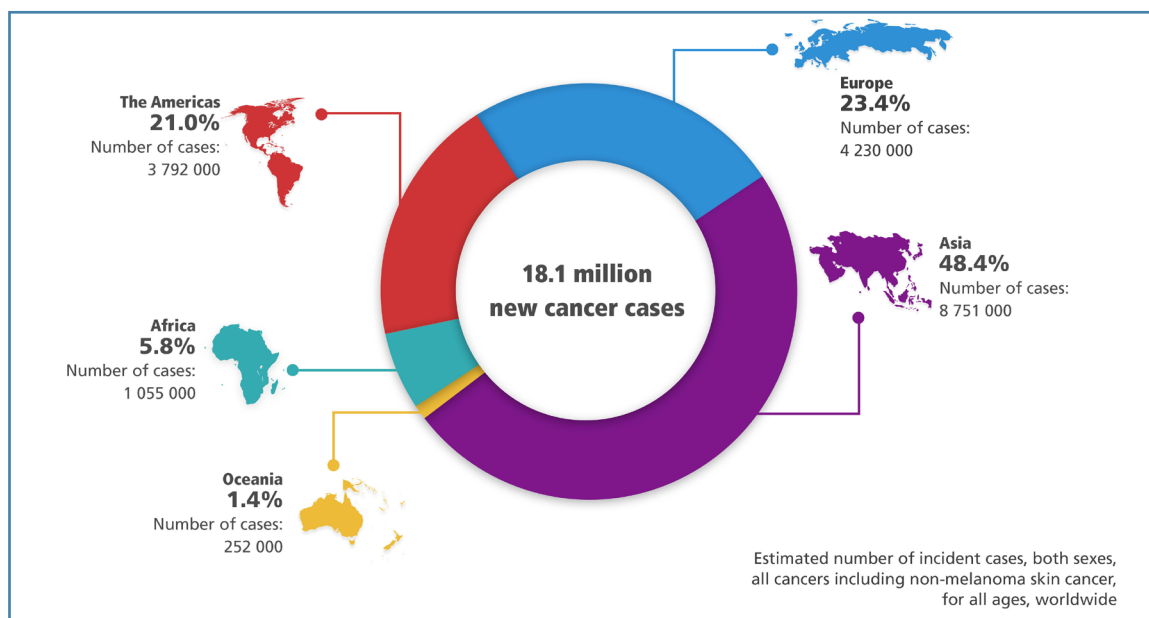


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Background

According to the Institute of Health Metrics and Evaluation, cancer was the second leading cause of death in 2018 with an estimated 9.6M deaths worldwide. Although significant advances have been made in cancer diagnostics and therapeutics, the high death rates can be attributed to the unmet medical need of cancer patients for targeted and more efficacious therapies that can improve the patient's quality of life by decreasing severe adverse effects, increasing survival rates, and reducing disease burden. 18 million cancer diagnoses were estimated in 2018 and this number is expected to reach to nearly 28 million by 2040 - a staggering increase of 60% (Figure 1). Factors contributing to the rise in cancer incidence and prevalence include increased exposure to physical, chemical and biological carcinogens, hormonal imbalances in the body, and an increase in the geriatric population since approximately 84% of the recognized cancer cases occur in people aged 50 years and greater.

Figure 1. Global Cancer Incidence



Source: World Health Organization and American Cancer Society

Immuno-oncology: The Game Changer in Cancer Therapy

Cancer immuno-oncology (IO) is a unique approach that uses the body's natural defenses to combat cancer. These therapies stimulate an individual's immune system, and act to restore the ability of the immune system to identify and destroy cancer cells that are inhibited during the spread of cancer. Ultimately, IO therapy expedites long term responses against cancer by contributing long-lasting memory to the immune system.

The global cancer therapeutic market was valued at over \$100B in 2018, about 50% of that in IO. The IO market is expected to reach \$170B with a compound annual growth rate of 14.2% by 2028. This trend is attributed to more sensitive early detection techniques, greater patient awareness, a growing aging population, greater survival rates versus traditional cancer treatments, and acceleration of development and regulatory approvals, particularly with the FDA's pro-science directive (see sidebar). Advancements in IO therapeutics with lesser side effects, combined with precision medicine, greater in-depth

understanding of disease pathophysiology, and improved cancer bioinformatics are expected to fuel the rapid expansion of this market.

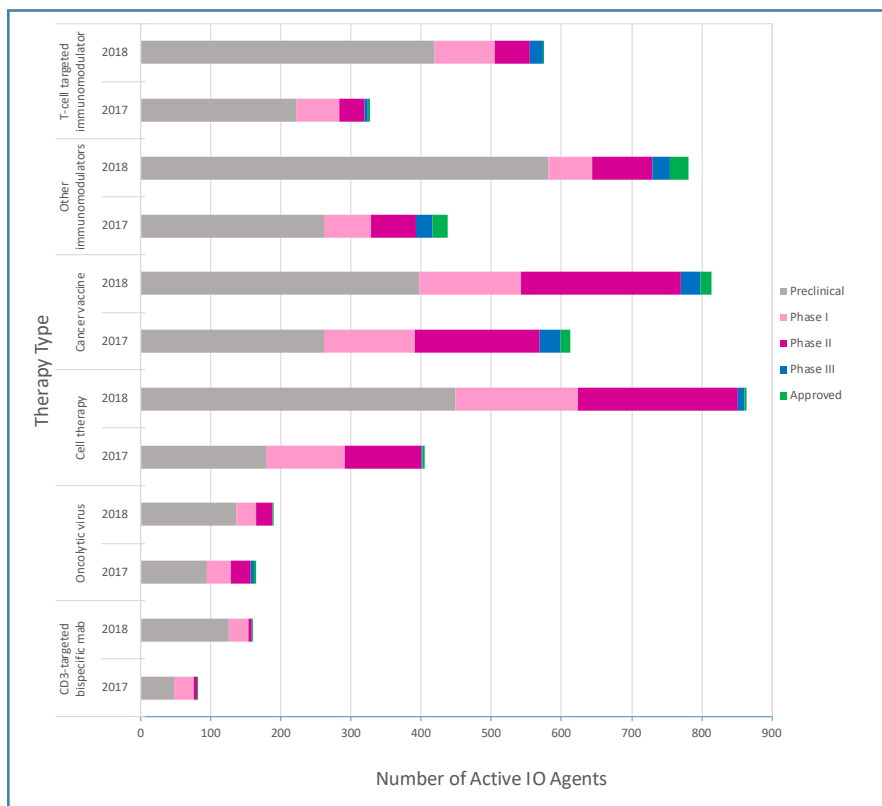
Since the 2014 breakthrough approvals for the treatment of advanced melanoma with the IO drugs pembrolizumab (Keytruda®) and nivolumab (Opdivo®), the IO drug market has continued to transform the oncology therapeutics landscape. These and subsequent IO therapies have delivered long-lasting anti-cancer benefits to patients who previously had very few options available to them.

It is now about five years since the introduction of checkpoint inhibitors Keytruda and Opdivo, a fact highlighted at the 2019 ASCO conference. Data shared at ASCO showed that nearly one fifth of advanced lung cancer patients treated with Keytruda in an early study of the therapy are alive today, a figure that is quadruple that prior to its introduction. A combination of Opdivo and Yervoy® also showed a significantly improved survival rate in previously treated or untreated metastatic melanoma.

The Immuno-oncology Drug Pipeline

Based on data obtained by the Cancer Research Institute (CRI), the IO Landscape has experienced an unprecedented number of new investigational agents and companies. Compared to 2017, the number of IO targets and agents currently under investigation has increased by nearly 60% and 70%, respectively (Figure 2). Today, nearly 3,400 IO therapies are in the current global drug development pipeline with 1,300 in clinical studies. 2,250 clinical trials focused on IO were conducted in 2018 – representing a 50% year-over-year increase versus 2017. IO company partnerships are also on the rise – a recent report indicates that in 2018 IO collaborations have increased 16% year-over year, with the top ten collaborations valued at nearly \$40B.¹

Figure 2. Comparison of 2017 and 2018 Global IO Drug Pipelines



Source: The Cancer Research Institute

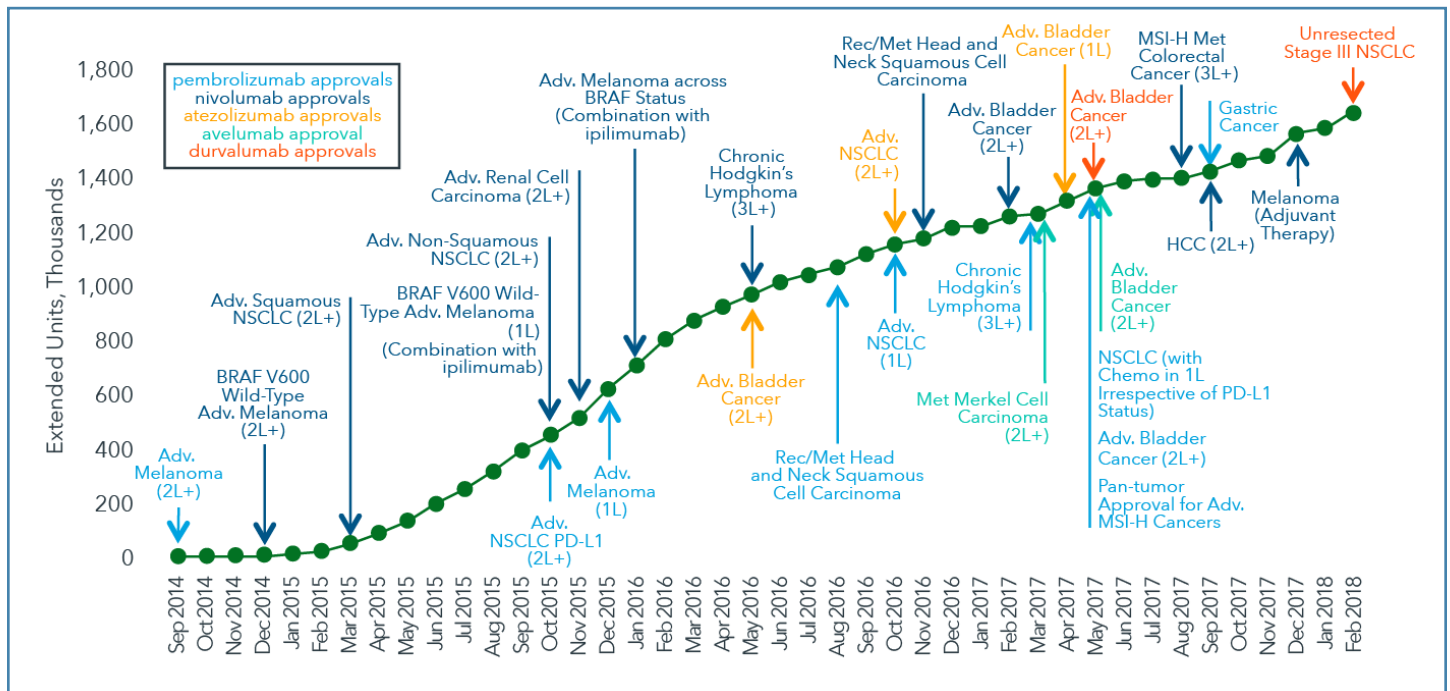
Key Factors Contributing to the Rise of the IO Therapeutic Market

- Rising incidence of cancer
- Targeted and exquisite specificity
- Enhanced survival rates
- Fewer side effects
- Long-lived effects
- Lower recurring chance of cancer
- Increased R&D investments
- Strong emerging IO drug pipelines
- Enhanced IO drug discovery and development with bioinformatics tools
- Increase in precision medicine approaches
- Accelerated regulatory approvals

Immune checkpoint inhibitors have emerged as a novel IO therapy option for certain cancers. As described by the National Cancer Institute (NCI), checkpoint inhibitors are “drugs that block certain proteins made by some types of immune system cells, such as T cells, and some cancer cells. These proteins help keep immune responses in check and can keep T cells from killing cancer cells”. According to the NCI, when these proteins are blocked, the “brakes on the immune system are released and T cells are able to kill cancer cells better”. Checkpoint inhibitors are currently categorized into three groups: programmed cell death-1 (PD-1), PD-ligand 1 (PD-L1), and cytotoxic T-lymphocyte– associated antigen 4 (CTLA-4) inhibitors. PD-1 is a cell-surface receptor expressed by T cells during priming or expansion and binds to either the PD-L1 or PD-L2 ligand. CTLA-4 is a negative regulator of T cells during T-cell activation by antigen-presenting cells.

PD-1 and PD-L1 in particular have demonstrated clinical efficacy for certain types of cancers including non–small cell lung cancer, melanoma, urothelial cancer, Hodgkins and non-Hodgkins lymphoma, head/neck cancer, subsets of colon and breast cancers and most notably, solid tumors with microsatellite instability-high (MSI-H) mutations and mismatch repair deficient (dMMR) mutations.² As evident of their sustained uptake, ability to prevent autoimmune responses and limit cell-mediated tissue damage, checkpoint inhibitors continue to demonstrate extraordinary clinical profiles and extended indications (Figure 3).³

Figure 3: Immuno-oncology PD-1 and PD-L1 Inhibitor Uptake in the United States



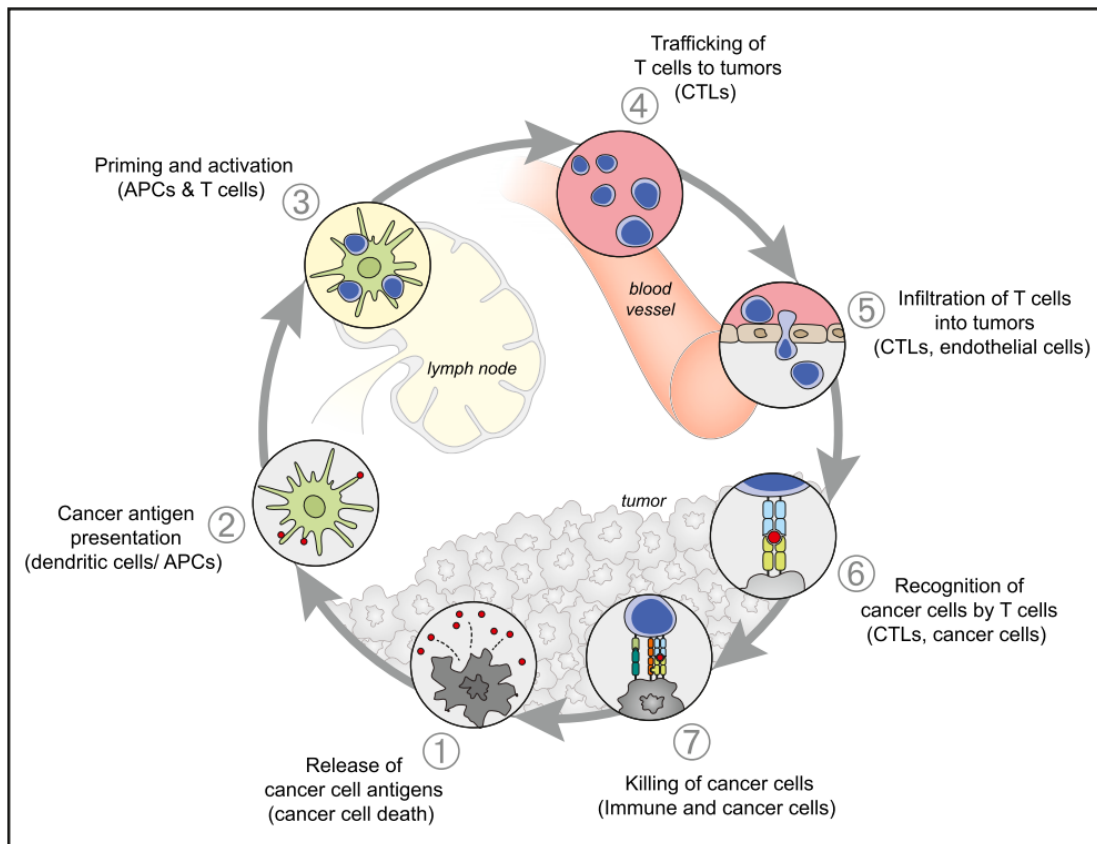
Source: U.S. FDA, IQVIA, National Sales Perspectives, Feb 2018; IQVIA Institute, Apr 2018

The Cancer Immunity Cycle

Immuno-oncology is the fastest growing area in drug discovery. Rapidly developing insights into immune system biology have led to treatments that mobilize the patients' own immune system to fight cancer and provide lasting therapeutic benefit. Technological advancements in molecular and cellular biology provided the scientific background required to exploit the immune system in oncology drug development. IO drugs target various stages of the Cancer Immunity Cycle, described by Daniel Chen and Ira Mellman in Figure 4.⁴

The contemporary knowledge on the molecular and cellular players participating in the Cancer Immunity Cycle lay the foundation for advancing immunotherapy research. There is also growing anticipation of the complexity of patient-specific factors which determine why some patients respond or do not respond to IO therapies. These factors – known as the cancer-immune set point - take into account individual tumor properties and extrinsic factors (e.g., gut microbiome that has been implicated in regulating immunotherapy responses and carcinogenesis, the presence of infection, exposure to sunlight, etc.). The cancer-immune set point combines elements which produce “an equilibrium between the factors that promote or suppress anticancer immunity of an individual”⁵

Figure 4: The Cancer Immunity Cycle



Source: *Immunity Review* 2019; 39, 1-10.

Advancing Combination Therapy Drug Development

PD-1 and CTLA-4 inhibitors and other IO agents as monotherapies have provided momentous advances in treating cancers. However, while complete regression and higher long-term survival rates is achieved in some patients, only a subset of people exhibit durable responses.⁶ Alternatively, combination therapies using checkpoint inhibitors have been shown to be a viable approach to developing IO therapies with higher responses, as is evident by its highly competitive market landscape.

While combination therapies are successfully being leveraged, they can also result in higher toxicities. Developing more efficacious checkpoint inhibitor therapies require a better approach to patient selection through simplified biomarker development and other factors, comprehension of the disease pathophysiology, and optimized clinical trial design to identify:

- who will respond to the therapy,
- how these drugs and drug combinations work and why some tumors respond or do not respond,
- who will be at greater risk of toxicity or immunogenicity,
- how to design and test balanced, safe, and effective combination therapies.

A better comprehension of the multifaceted interaction between a tumor and the immune system will lead to the development of greater efficacious treatments.

With the pace of IO R&D on the rise, the Clinical Accelerator team at the Cancer Research Institute actively monitors the rapidly evolving landscape to source novel agents that can be evaluated and studied.

Figure 5 shows 38 different clinical-stage agents that could be used to support various combination immunotherapy trials.

Figure 5: Clinical Stage Agents to Support Combination IO Therapies Based on Mechanism of Action

Immunomodulator Targets			Cancer Vaccine		Oncolytic Virus	Bispecific Antibody	Targeted Therapy		
PD-1	PD-L1	CTLA-4	SURVIVIN	TLR-4	CSF2RA	CEA	STAT3	HER3	KIT
CSFL1R	IDO1	KIR	MAGE-C1	NY-ESO-1			CD22	ALK	AKT
FLT3	CD73	TLR-3	MAGE-C2				MEK-1/2	EGFR	cMET
4-1BB	GITR	LAG-3					MUCIN-1	mTOR	PARP
CD27	ICOS	OX40					PI3K delta	WEE-1	gpNMB
							FGRF1/2/3		

Source: The Cancer Research Institute Clinical Accelerator

Second Generation Combination IO Drug Development

A 2018 article in *Frontiers in Oncology* assesses recent advances in current IO therapy development, providing an evaluation of second generation IO therapies that can be synergistically combined with other immunotherapies, or non-IO strategies.⁷ These include targeted therapies, co-stimulatory mAbs, bifunctional agents, epigenetic modulators, vaccines, nanoparticles, adoptive T-cell therapy, oncolytic viruses, and synthetic gene circuits. The review also places a significant emphasis on immunotherapy personalization, which requires the identification and use of reliable biomarkers. Ideally, biomarkers are “ideally screened simultaneously in multiplexed assays” to enhance broader treatment efficacy, and are “essential to identify patients likely to give the best response to a given immunotherapy regimen with minimal toxicity.” Most importantly, to maximize patient benefits, the potential of IO requires a greater emphasis on cross-disciplinary work.

Approaches to treat hot, altered and cold tumors with combination immunotherapy, including checkpoint inhibitors, has been a focus of recent research.⁸ In colorectal cancer (CRC), the type, density and location of immune cells within the tumor site enhances patient stratification and helps to predict survival. CRC tumor classification is designated as “Hot” (highly infiltrated) or “Cold” (non-infiltrated), a distinction that is immune-versus cancer-based. Such stratification supports personalized cancer immunotherapeutic therapies. For example, cold tumors are hard to eliminate and associated with poor prognosis, require more combinatorial approaches to achieve clinical benefit. Furthermore, priming therapies, e.g., radiotherapy, chemotherapy, targeted therapies, DNA-repair-based therapies, oncolytic therapies, and vaccine-based therapies, may prove to be beneficial in cases of non-inflamed cold tumors.

The Challenge of Combination IO Therapy Drug Development

According to Dr. Andrzej Kierzek, Head of Certara’s Systems Modeling, QSP, many companies have redirected their IO therapy focus on combining existing targets, a strategy where mechanistic modeling can become an important tool. Due to the vast number of possible drug combinations, coupled with the complexity of biological and pathological processes involved in IO, the development of IO combination therapies that are more efficacious than the current monotherapy, particularly in patient cohorts that are not responding to current treatment, is a daunting, complex, and difficult goal.

The level of complexity in developing combination IO therapies could be unprecedented since it is likely that different modalities (biologicals, small molecules, gene therapies, vaccines) targeting diverse biological pathways (IO and non-IO) will be combined in different cancer types. A major challenge, according to Dr. Piet van der Graaf, SVP Quantitative Systems Pharmacology at Certara, is that choosing successful combinations cannot be done randomly, but requires knowledge-based guidance. Further, the potential number and types of IO combinations cannot possibly be tested clinically, simulation using mechanistic models representing current knowledge is a viable method for combination analysis.

Despite the initial success of checkpoint inhibitors, further development of novel, differentiated IO therapies in this highly competitive and rapidly evolving landscape will be challenging, as illustrated by recent clinical trial failures. We use these examples to learn, helping us to inform the next iterations of combinations. (see box below)

Recent Learnings: IO Combination Challenges

- The BMS Phase III trial that combined the PD-1 inhibitor nivolumab with radiation to treat newly-diagnosed patients with MGMT-unmethylated glioblastoma multiforme (GMB), an aggressive, incurable and fatal form of brain cancer that has a median survival of less than two years, failed to meet its primary endpoint of improving overall survival.⁹ Learning from this, BMS had another Phase III study underway for the treatment of methylated GMB – which has a better prognosis - using the combination of nivolumab with radiation and temozolomide, an oral alkylating chemotherapy drug used to treat brain cancers.
- Astra Zeneca’s MYSTIC lung cancer trial using their two CTLA-4 checkpoint inhibitors, Imfinzi, used as a monotherapy against non-small cell lung cancer, combined with tremelimumab, was halted after it missed their primary endpoint of progression-free survival.¹⁰ According to management, “although statistical significance for overall survival had not been met, the data merited further analysis in exploratory subgroups. We will continue to evaluate its potential in combinations with other chemotherapies.”
- Last year, Merck and Incyte halted a late-stage study using Merck’s checkpoint inhibitor, pembrolizumab, with Incyte’s indoleamine 2,3-dioxygenase (IDO) inhibitor, epacadostat, to treat people with metastatic melanoma. IDO inhibitors block the enzyme which is responsible for initiating the breakdown of tryptophan into metabolites that suppress the immune system.¹¹

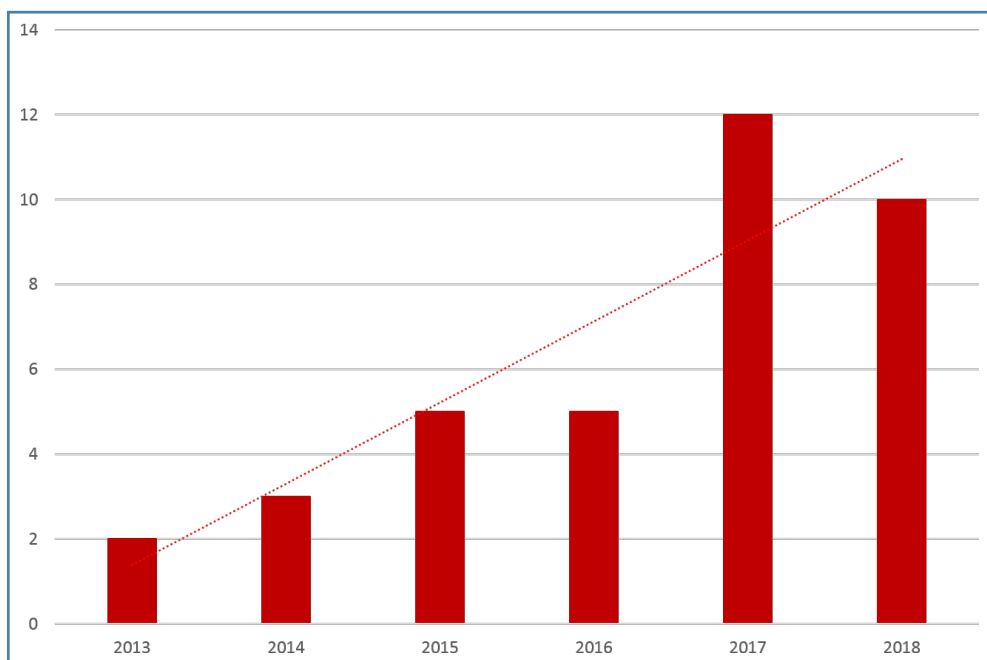
Using a Quantitative Systems Pharmacology Approach to Advance Combination IO Therapy

Traditionally, pre-clinical studies are used to test various potential IO combinations, typically focusing on one arm using an existing monotherapeutic agent, e.g. PD-1, combined with a test compound(s). Promising data from these potential combination preclinical studies can then be moved into clinical development. Dr. van der Graaf believes that a Quantitative Systems Pharmacology (QSP) approach for developing combination IO therapies can be used to better predict effective drug combinations, especially to more accurately correlate the physiological differences between preclinical models and human patients. Unlike other therapeutic areas where preclinical models can be used fairly confidently to guide the development program, oncology models combined with immunological complexities have limited translational value.

QSP combines computational modeling and experimental data to examine the relationships between a drug, the biological system, and the disease process. QSP models are built using human physiology and pathology and provide an *in silico* framework for constructing mechanistic, mathematical models of drug action. QSP focuses on the area between pharmacokinetics/pharmacodynamics (PK/PD) and systems biology. QSP translates PK or exposure into pharmacological effect and builds on gaining insights from pharmacometric, PK/PD, and physiologically-based PK (PBPK) approaches with systems biology models of biological and biochemical processes.

As evident with increasing submissions to the FDA, QSP has already shown promise for increasing the probability of success in R&D by bridging scientific gaps between disciplines to enable target validation. QSP is recognized by sponsors and global regulatory agencies as a valuable scientific approach to increase understanding of disease biology, improve target selection, and help to ensure drug safety and efficacy in clinical trials (figure 6).¹² QSP can also be used in the efficient design of First-in-Human (FIH) clinical trials to help determine the starting dose and subsequent dose escalations to ensure the best possible protection for human subjects.

Figure 6: QSP Submissions to the US Food and Drug Administration



Source: CPT Pharmacometrics Syst. Pharmacol. 2019, Epub ahead of print

A recent regulatory perspective describes how QSP, similar to other recognized emerging regulatory pharmacometric sciences (exposure/response modeling, pharmacogenomics and precision medicine, and PBPK modeling), follows a Hope-Hype Lifecycle. As suggested, QSP best practices “at a minimum, is predicted to lower the peak of inflated expectations and may facilitate more integration of QSP in drug discovery, development, and regulatory evaluation.”¹³ Per FDA’s Zineh, “QSP is arguably on an expedited pathway because of the very thoughtful work being conducted by drug development, regulatory and academic scientists. The impact of QSP is to de-risk a drug development program as it progresses.”

QSP can help answer the following questions: How will the drug modulate cellular signaling to exert a pharmacological effect? What pharmacological action will it have at that particular organ? Answering these questions will provide insight into the mechanisms of drug efficacy. This approach can be used to predict how drugs modify cellular networks and how drugs impact and are impacted by human pathophysiology. QSP can also facilitate evaluating complex, heterogeneous diseases such as cancer, immunological, metabolic, and CNS diseases that commonly require combination therapies to control disease progression. QSP is distinct from other Model-informed Drug Development (MIDD) approaches, such as pharmacometrics, since it helps to fill in the gaps between the early-stage PK and late-stage drug efficacy using a mechanistic approach.

The key to successfully developing IO therapies will be the selection of optimal combination therapies and dosing regimens, tailored to specific cancers and patient populations. The development of QSP models of interactions between tumor, the immune system, and therapies will be the requirement for rational development decisions and the regulatory approval process.

The Use of Virtual Twin Technology in Model-informed Precision Dosing

Model-informed Precision Dosing (MIPD) is a modeling and simulation (M&S) approach in healthcare that is used to predict the most effective and/or least toxic drug dose for a patient. The ability to leverage key “hidden” factors that alter drug exposure and/or response distinguishes MIPD from current attempts in clinical practice to do precision dosing. The hidden factors that can drive intra-subject variability include Drug Metabolizing Enzymes and Transporter (DMET) genotype and/or phenotype, organ sizes and blood flows, inflammatory status, and DDIs. MIPD can consider these factors simultaneously to support a quantitative approach to selecting the right drug at the right dose at the right time for an individual patient. Importantly, MIPD can simulate the multiple factors that determine clinical outcomes to identify a better tactic to individualize treatment.

Quantitative M&S methods provide a more predictive approach to precision dosing and include the use of basic nomograms, population PK (PopPK), and PBPK. Certara’s Simcyp Simulator®, the basis for the Virtual Twin™ Technology, includes extensive demographic, physiologic, molecular and genomic databases. The Simulator links *in vitro* data to *in vivo* ADME (absorption, distribution, metabolism, and excretion) and PK/PD outcomes to help explore potential clinical complexities prior to human studies and support decision-making in drug development. This enables the user to predict drug behavior in virtual populations, identifying the types of individuals who could be at extreme risk of ADRs.

Certara has developed a Sim-Cancer population with a focus on solid tumor types.

The Simcyp Simulator helps to quantify how much drug is getting to the target site within the tumor. The Simulator’s permeability limited tumor models combine knowledge of the tumor composition with the drug’s physicochemical properties to simulate the distribution of small molecule drugs or biologics.

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The impact of QSP is to de-risk a drug development program as it progresses.”

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– Issam Zineh - US FDA

These drug distribution models can also be combined with other tumor growth models, allowing a drug's concentration in the tumor and the resulting tumor growth or inhibition to be factored in. The Simcyp Simulator can model the impact of a single drug or a combination therapy on the tumor. It can also simulate target-mediated drug disposition in tumor for biologics.

The Future of Virtual Twin Technology in IO Drug Development

Virtual Twin technology incorporates knowledge of biological and physiological functions and creates a computer-simulated model of each patient, replicating the patient's various attributes that affect drug exposure and/or response. These attributes include the patient's age, weight, height, gender, ethnicity and genetics of DMETs. The Virtual Twin model has the potential to account for the patient's fed or fasted state, co-morbid conditions and co-medications that affect the activity of DMETs, and their level of organ function.

The Virtual Twin concept simply adapts some of the biological and physiological data used to build a base PBPK model representative of the population, with individual information about these parameters that better matches the patient e.g., specific renal, liver, and cardiac function, hematocrit, DMET genotype and phenotype. Monte Carlo simulation can be used to understand the extent of variability attributed to parameters that are not known for that patient (e.g., any missing information that might be important in predicting dose). Recent publications have demonstrated the use of this technology to (1) predict olanzapine systemic exposure predicted in Virtual Twins when compared to actual drug concentrations in the corresponding patients¹⁴, and (2) to develop an *in silico* quantitative systems toxicology (QST) model for citalopram to predict the likely occurrence of cardiotoxic events in real patients under different clinical conditions.¹⁵

Van der Graaf and Kierczek believe that the future for IO combination drug development lies with an equivalent of a "clinical" Virtual Twin Technology. The Virtual Twin technology will allow clinicians to predict the optimal drug dosing regimen for an individual patient—one that maximizes therapeutic benefit while minimizing side effects—by evaluating the impact of different drug doses, schedules, and combinations in the patient's *in silico* 'virtual twin' first.

Creating a Consortium to Tackle IO Combination Drug Development through Cooperation and Expertise

Certara formed a QSP IO Consortium in 2018 that brought together leading biopharmaceutical companies in a pre-competitive environment to cooperatively develop a robust Immuno-oncology Simulator, based on state-of-the-art QSP science and methods. The resulting IO simulator will be used to predict optimal combinations, dose regimens, and biomarkers in computer-generated diverse virtual patient populations. By capturing the complexity of biology, together with the pharmacology and PBPK involved in IO, at a sufficient level of mechanistic detail, a technology to simulate virtual clinical populations (including inter-individual variability) to guide and improve the drug discovery and clinical development of combination IO therapies will be created.

The QSP IO Simulator will be a multi-scale model which allows for continuous and seamless integration, analysis and simulations of relevant emerging biology at the intracellular, cytokine/chemokine, cellular, tumor, and whole-body level. The IO Simulator focuses is on clinical development and human data, with the ability to translate to and from preclinical models for validation purposes.

An important element of the IO Simulator is that, to a large extent, it is agnostic to what is fed into the model. Currently, combinations of small molecules with antibodies, and antibodies to antibodies have

been used in the model, however since the core of the model is the immune system, it will be feasible to add other modalities, e.g. cell therapy, CAR-T, or radiation, providing all possibilities that can be researched and tested in the clinic.

The QSP IO Consortium is Certara's second consortium, following the success of the QSP immunogenicity (IG) Consortium formed in 2017, which is developing a Simulator that can predict immunogenicity of biologics and its impact on the PK, efficacy, and safety in diverse patient populations. The IG simulator has already demonstrated its ability to impact go/no go decisions by identifying those biologic drug candidates that could impact PK, and hence dosing versus those without correlation. This could markedly improve success rates in clinical development of compounds negatively affected by IG.

The cooperative development of the IO Simulator provides significant benefit by being part of the Certara family of Simulators, including the original Simcyp Simulator, Cardiac Safety Simulator, Pediatric Simulator, Dermal Simulator, and QSP IG Simulator. All simulators communicate seamlessly with each other – a major advantage for data sharing for more complex drug development.

Next Steps

The rapid rise of IO drug development has led to notable success and regulatory approvals of oncological monotherapies. However, for the majority of patients who do not respond to current treatments, it is critical that alternate approaches must be investigated to develop more efficacious and long-acting therapies to further advance the potential of IO-based treatments for a broader population of cancer patients. Although notable challenges are associated with developing combination IO therapies - a direction now taken by most IO developers - a quantitative and mechanistic approach can be used to help better predict optimal drug combinations. The IO Simulator will help to guide IO combination therapies by predicting optimal combinations, dose regimens, and biomarkers using the Virtual Twin Technology.

The key to successfully developing IO therapies will be the selection of optimal combination therapies and dosing regimens, tailored to specific cancers and patient populations. According to Dr. van der Graaf, the QSP IO Simulator will enable researchers to explore therapeutic combinations, even drugs using different modalities with a virtual population. It will help sponsors to answer "what if" questions, providing input and guidance for clinical development. The development of QSP models of interactions between tumor, the immune system, and therapies will be the requirement for rational drug development decisions and facilitating the regulatory approval process.

The QSP IO Simulator combines rigorous science with a focus on drug discovery, development, and regulatory needs including:

- Validation of novel targets and optimal dosing regimens for combination therapies
- Individualized dosing and prediction of efficacy in different cancer types and special patient populations
- Guiding identification of patient subgroups most likely to benefit through the use of biomarkers, diagnostics, and precision medicine

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