

# A Tale Of Two Pipelines



Immuno-oncology has produced some exciting successes, but the field has become intensely crowded. Enormous resources are being poured into duplicative work and shaky hypotheses – overshadowing other pursuits in cancer research while producing limited results. It is time to re-evaluate how the sector should be pursuing innovation in cancer and how it can be smarter in its use of resources – financial investment, talent, bandwidth, patients and data.

## BY DENNIS CHANG, KEITH FLAHERTY, AND UCIANE SCARLETT

Rethinking translational models: shifting towards greater use of patient-derived explants, organoids and xenografts in humanized mice, as well as leveraging tumor atlas datasets.

Rethinking data ownership: leveraging the power of the patient to drive data sharing and building platforms for companies to collaborate on key challenges in a pre-competitive setting.

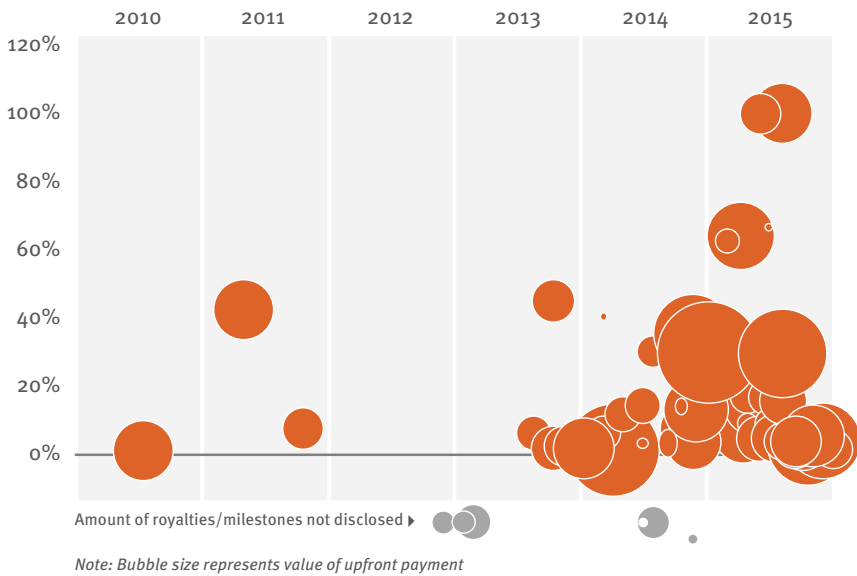
Rethinking the clinical paradigm: raising the bar and focusing on cancer clearance rather than merely delaying progression in both clinical trials and clinical practice.

In oncology clinical development, every year brings new breakthroughs: drugs that can put previously intractable cancers into remission, or double the duration of remission, or even cure cancers that were previously incurable.

At the forefront of the excitement is immuno-oncology (IO), the harnessing of the body's immune system to fight cancer—and potentially eradicate it. The successes of immunotherapy are breathtaking. Analysis of SEER data shows that a decade ago, metastatic melanoma used to have a dismal median survival of only 7 months. Now, immune checkpoint blockade (ICB) with regimens such as anti-PD1 nivolumab (Opdivo) combined with anti-CTLA4 ipilimumab (Yervoy) – or “nivo + ipi” – enables most patients to survive five years or more, as shown in the CheckMate 067 study. Similarly, relapsed/refractory acute lymphoblastic leukemia (r/r ALL) in children used to have a five-year disease-free survival of only 10-20%. However, when extrapolating from available clinical studies, CD19-targeted chimeric antigen receptor T (CAR-T) cell therapy tisagenlecleucel (Kymriah) may cure as many as 40% of these patients. The first child treated with Kymriah in 2012, Emily Whitehead, remains alive and cancer free today.

These successes have fueled an explosion of IO investment and R&D activity. The first dramatic efficacy signals of ICB and CAR-T were reported in 2010 and 2011, respectively. An analysis, conducted by Uciane Scarlett, of the number of licensing deals and acquisitions for IO assets and companies over the approximately five years since the landmark publication of ipilimumab data in mid-2010 (*see Exhibit 1*) showed that every metric soared over this time period: the number of deals, the average size of IO deals and the average proportion of deals paid up-front. The IO pipeline has grown even more extraordinarily. The Cancer Research Institute has shown that from 2017 to 2018, the IO pipeline has grown across all dimensions: clinical assets, preclinical assets, targets and clinical trial sponsors (*see Exhibit 2*). Since 2014, there have been approximately 60 US FDA approvals for immunotherapies, including multiple indi-

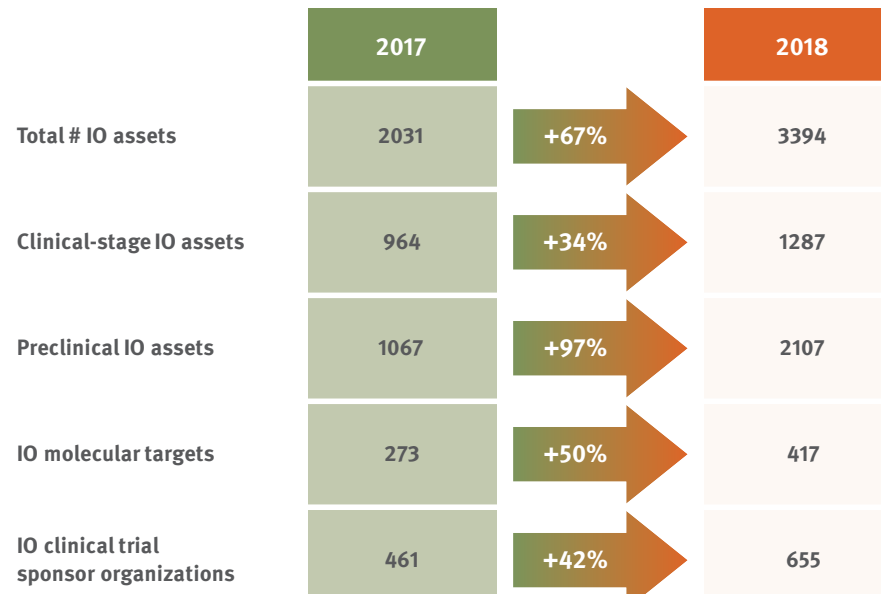
**Exhibit 1**  
**An Explosion In IO Deals**



NOTE: All licensing, research, collaboration and acquisition transactions with publicly disclosed financial terms for IO assets and companies from 2010 through June 30, 2015. Data were compiled from news media sources. Bubble size represents the total deal amount (\$) and may include upfront payment, shares, milestones/royalties and payments for research. Approximations were made in some instances where only partial information was available.

SOURCE: Uciane K. Scarlett, PhD

**Exhibit 2**  
**Growth Of The IO Pipeline**



NOTE: Cancer Research Institute (CRI) analysis of the global IO preclinical and clinical pipeline shows substantial increases in assets, targets and trial sponsors in a single year.

SOURCE: Tang 2018 Nat Rev Drug Discov 17:783

cations for anti-PD-1 agents nivolumab (Opdivo), pembrolizumab (Keytruda) and cemiplimab (Libtayo); anti-PD-L1 agents atezolizumab (Tecentriq), durvalumab (Imfinzi) and avelumab (Bavencio); and CAR-T cell therapies tisagenlecleucel and axicabtagene ciloleucel (Yescarta).

However, a tremendous amount of capital and human resources has been consumed with IO, and there are signs that exuberance for immunotherapy has become unsustainable. The most glaring is the proliferation of copycat approaches: a lot of resources are going towards replication of previous efforts. As CRI reported in September 2018, the number of CD19-targeted CAR-T cell therapies in the global pipeline was 106, and the number of anti-PD1/PD-L1 assets was 167. “Me-too” drugs are not new to the pharma industry, but the imitative extremes in IO have never been seen before. The corresponding inefficiency of resource use poses potential harm to patients and to non-IO programs in the near term, as well as the potential lack of incentivization for trial participation and investment in the long term.

As Rick Pazdur, director of the FDA’s Oncology Center of Excellence (OCE) cautioned at the 2019 American Association for Cancer Research conference, “Patients – whether they be worldwide patients or the US patients – are not a company’s resource, they’re a global resource... And when we have a sub-optimal way of developing drugs with a lot of duplication, that can result into [sic] a lack of confidence in the system of clinical trials, for example, or a lot of unnecessary duplication and expense.”

Moreover, the clinical trial failures and disappointments continue to accumulate. The first immunotherapy doublet combination to be approved, nivo + ipi in 2015, remains the *only* immunotherapy doublet combination to be approved (by the FDA). Failed regimens include combinations of anti-PD-1 or PD-L1 agents with IDO1 inhibitor epacadostat, BTK inhibitor ibrutinib, vaccines, multiple T-cell costimulatory agonists and many other IO mechanisms. There have been a handful of successes combining anti-PD-(L)1 agents with cytotoxic chemotherapy (e.g., in lung, head and neck, and triple-negative breast cancers) and with tyrosine

kinase inhibitors (TKIs) (e.g., in renal and endometrial cancers), and there are other promising IO + targeted combinations in the pipeline. Still, the failures of IO far exceed the successes. Even for the FDA approvals of IO treatments, the vast majority involve incremental clinical efficacy – the transformative efficacy seen in melanoma is limited to only a few other, rare tumor types.

Meanwhile, the field continues to produce important advances in non-IO targeted therapies. For example, a University of Colorado study showed that non-small cell lung cancer (NSCLC) patients harboring ALK fusions now have a median overall survival exceeding seven years, thanks to the availability of multiple potent ALK inhibitors. Inhibitors of NTRK fusion proteins like larotrectinib (Vitrakvi) produce objective responses in more than 80% of patients harboring NTRK fusions, regardless of the tumor site or histology. Multiple combinations of targeted agents can produce around 100% response rates in chronic lymphocytic leukemia (CLL). PARP inhibitors like olaparib (Lynparza) can dramatically improve progression-free survival in patients with BRCA mutations across multiple cancer types, including pancreatic adenocarcinoma (in the POLO study) and prostate cancer (in the PROfound study). And these are just a few examples.

The success of targeted therapies reflects the fact that the field has been working assiduously on developing targeted therapies for far longer than the recent

boom in IO. Typically, drug discovery starts with biological concepts; then tools and models are developed that are relevant for testing those concepts; then those insights are translated into therapeutic advances. For targeted therapies (as for the cytotoxic chemotherapies that preceded them), the concepts and thus the tools and models are focused on the tumor cells. Over time, those tools and models have become better and more sophisticated and even more importantly, we have learned vast amounts from decades of clinical findings. For IO, the concept is radically different: engaging and modulating immune cells rather than the tumor cells directly. The tools and models are far less developed, hindering progress, and while the clinical data are accumulating rapidly, it will take time to process, draw connections and gain insights.

Considering the challenges of taking IO to the next level, the clear inefficiencies of current IO efforts, and the promise of alternative approaches, it is worth re-evaluating how the sector should be pursuing innovation in cancer. There are lessons and insights that have been gained from past successes and failures. From an analysis of these events, three key themes have emerged that highlight how industry can be smarter in resource allocation and its approaches to oncology innovation (see Exhibit 3):

1. Rethinking translational models
2. Rethinking data ownership
3. Rethinking the clinical development and treatment paradigm

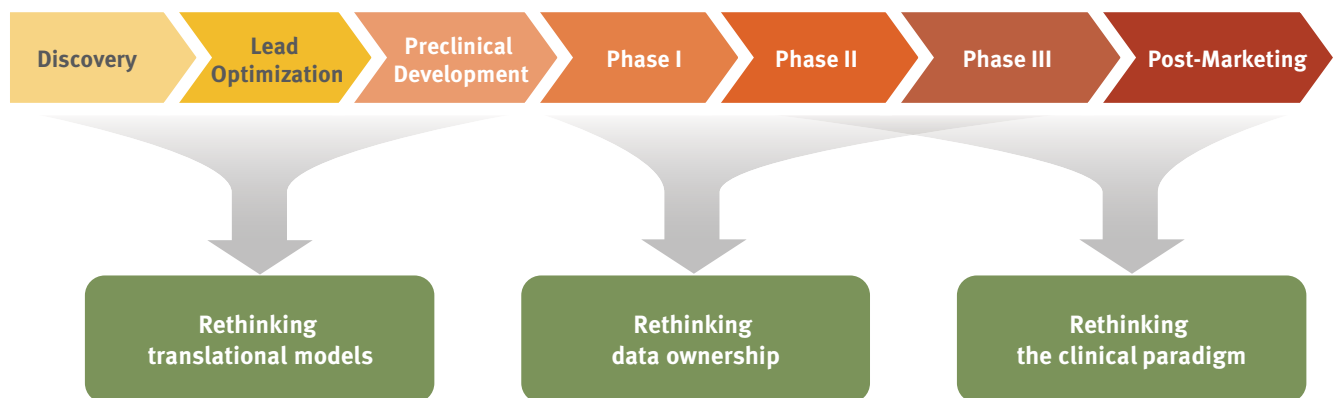
These were three areas raised by a panel of oncology innovators – clinical researchers, biopharma executives, venture capitalists and others – who gathered on May 8, 2019 at a summit called Emerging Frontiers in Oncology (Cambridge, MA), an event to raise funds for cancer research at the Fred Hutchinson Cancer Research Center. Each recommendation has the potential to transform the development of new and better cancer therapies.

**Rethinking Translational Models**

An MIT analysis found that only 3.4% of cancer drugs that enter Phase I are eventually approved and marketed, and yet virtually all these agents are supported by preclinical data. Thus, current preclinical models have a >96% rate of “false positives” and are a critical weak link in oncology research and development. Biopharma’s tremendous failure rate creates huge costs to the system in the form of failed clinical trials and capital/human investments that could have gone elsewhere.

IO is no exception. Indeed, as noted above, it is even more challenging to develop preclinical models for IO, which involves activation of immune cells to fight cancer, than for treatments that target tumor cells directly. Cell lines in culture and in mouse xenografts are not highly predictive in any case but do have some relevance for studying targets or pathways that are tumor cell intrinsic. These models are, however, inadequate for IO. Conventional xenografts involve

**Exhibit 3**  
**Three Proposals For Smarter Oncology Innovation**



SOURCE: Emerging Frontiers In Oncology Summit, May 8, 2019

immunodeficient mice, because a mouse with a competent immune system will recognize human-derived cancer cells as foreign and eliminate them too easily. However, immunodeficient mice are obviously not viable models for immunotherapy. Syngeneic mouse models, where mouse cancer cell lines are implanted into immunocompetent mice, seem reasonable in principle, but have proven to be poorly predictive of clinical responses. Furthermore, a very narrow repertoire of these models (e.g., CT26 and MC38), have been used as the basis for nominating many novel immune agents for development in combination with PD-1/PD-L1 antibodies. The repeated failure of those combinations indicate that we need to look elsewhere.

Many experts consider certain newer models – focusing on patient-derived tissue – as promising approaches for better evaluating preclinical immunotherapies:

- **Patient-derived xenografts in humanized mice:** Multiple groups now have methodologies for producing mice with a humanized immune system produced from human-derived stem cells. Patient-derived cancer cells (if at least partially HLA-matched) can be implanted and then studied in the context of functioning human immune cells. Further refinements may include less cumbersome/more efficient stem cell engraftment and extending the humanization, which may be achieved through gene editing and microbiome replacement.

- **Patient-derived tissue explants:** An alternative approach to using patient-derived tumor samples in mice is to test them in culture. Tissue explant cultures include both tumor cells and non-tumor cells (including immune cells) and preserve structural features of the tumor microenvironment (TME). Some systems (e.g., from Mitra Biotech) also include peripheral blood from the same patient in the culture. Dividing the tumor sample into multiple culture dishes allows for parallel testing of numerous drug regimens on a single patient tissue sample. However, given the differences in growth kinetics of tumor cells versus stroma and immune cells, explants can only provide very short-term evaluations of a drug regi-

men’s impact. After a few days in culture, the explant no longer resembles the in vivo TME. Thus, rather than measuring immune-mediated killing of the cancer cells, surrogate markers of efficacy are required, and must be validated.

- **Patient-derived organoids:** Organoids are 3-D multicellular cultures; in cancer research, most organoids consist purely of cancer cells on a 3-D scaffold. However, it may also be possible to assemble artificial tumors that consist of multiple cell types: not just tumor cells, but also various immune cells and stroma cells. Although more artificial than tissue explants or humanized mice, organoids have the potential for greater multiplicity/throughput.

- **Tumor atlas approaches** may involve systematic assessment of in vivo TME profiles and mapping them to clinical responses. Many initiatives have already conducted molecular profiling studies of thousands of cancer samples, but the focus to date has been largely on the genomes and transcriptomes of the cancer cells. Expanded, systematic study of the immune contexture in the TME is needed. Artificial intelligence platforms may be used to analyze the datasets and fuel IO hypothesis generation. Unlike the platform categories above, this is not an option for preclinical drug screening, but a means to produce better biological insights to inform preclinical research.

These are enabling technologies that may greatly elevate the success rate and ROI for oncology drug development broadly. We must continue to develop and enhance these and other preclinical models.

### Rethinking Data Ownership

Many leaders and advocates have called on biopharma companies to more rapidly and consistently make clinical trial data available, even when the results are negative. Greater data transparency would help to reduce replication and increase the impact of research efforts. For example, there is often a reluctance to publish failed studies, but such studies provide very useful data and new learnings. Open-source, public data resources are already starting to emerge, but more can certainly be done.

(Also see “Coordinated Open Data Will Drive Next-Level Health Research” - *In Vivo*, 1 Oct, 2019.) Two proposals may open the data floodgates:

- **Leveraging the power of the patient:** Although the exuberance in IO and the rapid proliferation of the pipeline is associated with certain risks and challenges, it also presents potential opportunities. One key dynamic is the shift in power to the patient. The demand for clinical trial patients and tissue specimens has never been higher, giving patients an opportunity to drive a change in the research system. Errik Anderson, CEO and founder, Alloy Therapeutics, proposed a policy that links patient consent for research participation to a requirement for public access to clinical data. This is an appropriate demand given the risk and burden that patients take on by participating in clinical trials; they should expect that maximal scientific advancement should be gained from their sacrifice. If this becomes a standard box to be checked for every clinical trial, then a wealth of clinical data would become more widely available to guide the sector’s collective efforts.

- **Building platforms for pre-competitive collaboration:** The unprecedented demand on human and capital resources also means that the incentive for research collaboration has also never been higher. One of the lessons of past failures is that identifying the best combination regimens and patient selection approaches is exceptionally difficult. Greater data sharing in the pre-competitive setting would serve to advance the science and make all research efforts more efficient and productive. Platforms for pre-competitive collaboration include tumor atlas initiatives for pooling biomarker data, harmonization of biomarker testing methodologies, and collaborative combination trials.

### Rethinking The Clinical Paradigm

In the traditional paradigm of treating metastatic cancer, the focus has been on delaying disease progression. Patients receive a line of therapy, and any tumor response or shrinkage (sometimes even stable disease) is considered of clinical

benefit. If the tumor grows or spreads, that progression triggers a new line of therapy. However, this algorithm is the legacy of the era of cytotoxic chemotherapy, when curing metastatic cancer was generally viewed as impossible.

The paradigm in much of hematologic oncology has already evolved, as improved combination regimens with or without stem cell transplantation may produce multi-year remissions or cures in many cases. The goalpost has begun to shift away from mere response to eradicating all detectable traces of disease. Accordingly, the molecularly defined minimal residual disease (MRD) endpoint is increasingly used to evaluate efficacy.

It is overdue for this concept to be applied to solid tumors as well, for 3 reasons. First, given the unprecedented proliferation of pipeline programs, we need to prioritize the very best regimens for resource and time investment; we need to set the bar higher. Second, the emergence of potentially curative immunotherapy and next-generation targeted therapies provide proof of principle that reaching a higher bar is possible. Third, the biology suggests that treating prior to disease progression may produce greater efficacy; a cancer that has evolved to a point where it is actively progressing despite ongoing treatment tends to be more aggressive and challenging to treat than one that is still partially under control.

This has critical implications for how we conduct clinical research and clinical practice:

- Should clinicians redefine the trigger for the next line of therapy (non-CR rather than progression)?
- Should clinical trial investigators increase the use of different endpoints (CR or even MRD-negative rates, rather than ORR)?
- Should drug developers make more use of neoadjuvant/presurgical studies to gain direct pathologic evidence of efficacy?

This new paradigm would redefine what the industry views as the unmet need and opportunity for new drug development and could drive bolder approaches and greater clinical impact.

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**What Is Next For IO?**

Robust implementation of the changes listed above would reshape the oncology R&D sector. The future vision is one in which:

- Thanks to better preclinical models, the free flow of data, and widespread inter-company collaborations, science and medicine rise to meet the new clinical bar.
- The IO pipeline is more sophisticated and diverse. Instead of 100+ anti-PD-(L)1

single agents redoing prior trials, there is a proliferation of innovative mechanisms and combination/sequencing approaches.

- The relatively higher success rates of IO clinical trials enable a more cost-efficient R&D model and may potentially lower the cost for novel drugs, enabling better patient access to the more effective combination approaches that will emerge.
- Every drug developer – and eventually every oncologist – strives for long-term survival for every patient, not merely delaying tumor growth by a few months.

None of this will occur overnight, and the challenges are steep, but this is an exciting time to be in the oncology field. The sector’s successes with immune checkpoint blockade and CAR-T cell therapy mean it is no longer unrealistic to anticipate “cures.” Breakthroughs in drugging traditionally “undruggable” targets are emerging. New targeted therapies aimed at tumor cell-intrinsic vulnerabilities that might also potentiate immunotherapy are beginning to arise. The tremendous infusion of capital investment and talent into the field, and the enthusiastic engagement of industry, health care providers and patients, all present us with an opportunity to conquer cancer if we deploy those resources well.

Moreover, we have at least a partial map of how to pursue cancer innovation in a smarter, more effective way – by leveraging better, patient-derived translational models; driving clinical data sharing and collaboration; and redefining clinical success. Through these efforts, the biopharma industry can do far, far better than it has ever done. ❦

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*Dennis Chang, PhD, (dchang@clarion-healthcare.com) is a principal at Clarion, A Life Sciences Consultancy located in Boston, MA. Keith T. Flaherty, MD, (kflaherty@mgh.harvard.edu) is the director of clinical research at Massachusetts General Hospital and a professor of medicine at Harvard Medical School. Uciane K. Scarlett, PhD, (uscarlett@oxfordsciences.com) was an associate at Atlas Venture and is currently a principal at Oxford Sciences Innovation.*