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HUMIRA BIOSIMILARS:
Battle Lines Shift From Education To Sustainability

BY MELANIE SENIOR

Immuno-Oncology: Unicorns, China And The Perfect Storm

There is a unique phenomenon being realized in immuno-oncology deal-making compared with other segments in the life sciences sector – an apparent uncoupling between risk and return on invested capital, as early assets provide similar liquidity to more mature assets.

BY SWARNA MEHROTRA, ODED BEN-JOSEPH AND ELLEN BARON

Unicorn transactions have emerged in the IO sector, as well as never seen before partnerships, financing deals that regularly hit above $200 million, and multibillion-dollar acquisitions and IPO valuations.

The market is optimizing multiple paths to liquidity at all stages of development and experiencing a shortening in time to exit, which is further propelling investor appetite.

So what? As IO drugs demonstrate robust clinical potential and early movers reap market rewards, the segment continues to attract significant interest from the investor community as well as pharma and biotech players, triggering highly competitive behavior and intense transactional activity.

The biopharma IPO window is rewarding investors with rapid valuation step-ups and a shortened trajectory to an exit (some companies have gone public two to three years post-Series A). This path to liquidity is translating into renewed excitement by limited partners who are eager to keep the investment cycle going by supporting larger venture financings at a faster pace. At the halfway point of 2018, the US venture capital market continues to see the crystallization of a new normal where capital is concentrated into fewer, larger deals.

At the same time, the improved access to the IPO market, particularly for immuno-oncology (IO) companies, has been a welcome trend. This, coupled with healthy M&A activity, results in a lucrative exit landscape. The global IO segment is expected to remain the highest grossing therapy area, exceeding $100 billion by 2024. There is good reason to believe that this market will not turn down anytime soon as big pharma remains desperate to boost growth rates and companies are willing to pay up for IO opportunities.

However, in 2018, there also have been significant, late-stage clinical failures. One of which, **Merck & Co. Inc./Incyte Corp.**'s indoleamine 2,3-dioxygenase(IDO) inhibitor trial, created ripples in the market and impacted several other late-stage clinical programs, leaving a trail of destruction. **Bristol-Myers Squibb Co.** terminated its late-stage combination trial for its IDO inhibitor (acquired from Flexus Biosciences Inc. for a whopping $1.25 billion in 2016) and **Genentech Inc.** terminated its IDO inhibitor partnership with **NewLink Genetics Corp.**, a collaboration that could have generated over $1.15 billion for NewLink. Although IDO has seen a setback, other immuno-metabolism pathways have received significant investment, including those of **Agios Pharmaceuticals Inc.**, **Kyn Therapeutics**, **IDEAYA Biosciences Inc.**, **Rheos Medicines Inc.** and **Dracen Pharmaceuticals Inc.** There are multiple approaches currently under investigation targeting the metabolism of other

amino acids such as glutamine, arginine and particularly adenosine, known to be harnessed by the tumor microenvironment and in inflammatory conditions.

Transaction Trends

IO is one of the most promising advances in the treatment of cancer in recent times, as such it has completely dominated biopharma's transaction landscape in the past three-and-a-half years. Beyond the impressive number of IO transactions, deal terms have far exceeded the amounts paid for comparable deals in other therapeutic areas. Moreover, despite that most of the transactions were early-stage, pre-proof of concept, they were able to garner an average up-front payment of roughly $150 million and total deal value close to $1 billion. To understand the unique dynamics and transaction trends in the IO segment, Outcome Capital tracked a total of 244 venture-backed companies (pure-play or lead IO asset) from January 1, 2015, through to June 30, 2018. The group analyzed various market parameters including invested capital, stage of investment, path to liquidity, acquisition and partnership transactions, and IPOs. The data gathered also highlight the behavior of individual sub-sectors such as immune modulators and adoptive cell therapy.

Investor Appetite

The IO segment has attracted significant interest by institutional investors, with nearly $1.5 billion in invested capital in the first half of 2018 alone. For the first time in 2018, we saw unicorn deals (greater than $1 billion valuation) with more than $200 million venture investments rounds (iMab Pharma, **CStone Pharmaceuticals Co. Ltd.**, **BioNTech AG** and **Allogene Therapeutics Inc.**). IO continues to follow the global venture investing trends where capital invested continues to rise. However, a rise in early-stage investing and early exits, a phenomenon unique to the IO segment, has been observed. This signifies confidence in the underlying science and excitement in the potential for IO segment growth.

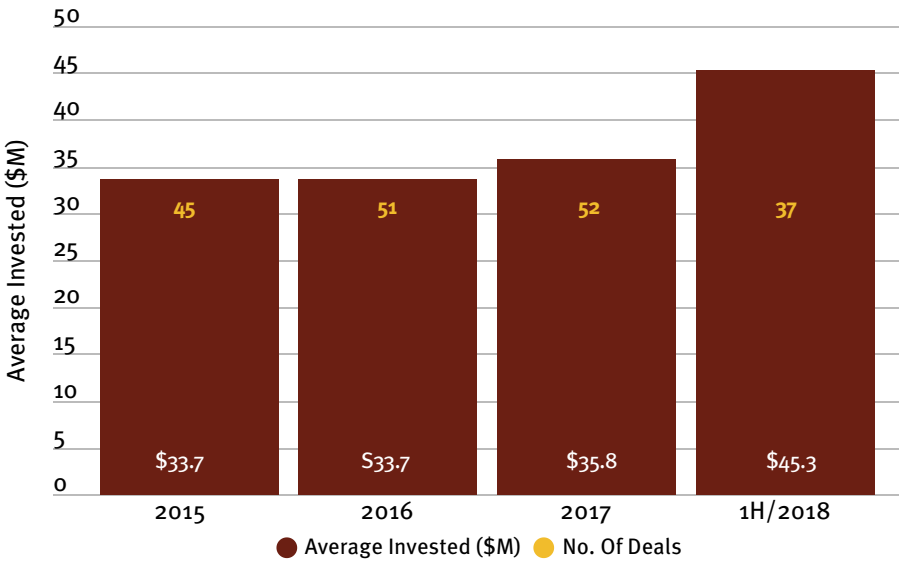
The exit timelines have shortened to around three to five years in this segment, providing comfort to the investors and creating a favorable fund-raising environment.

There was robust year-over-year growth in total invested capital. The first half of 2018 saw larger venture investments, with a 27% increase in average investment size compared with the prior year (*see Exhibit 1*) and a robust VC appetite for early-stage companies, investing heavily in Series A and B (*see Exhibit 2*). Larger Series A and B is a key risk mitigation driver, because it allows CEOs to focus on execution rather than a continual effort to raise capital. In addition, access to capital is likely to increase the probability of meeting meaningful value-inflection milestones. Undercapitalization continues to plague the life sciences sector, often leading to unnecessary failure.

As expected for a rapidly growing segment with a multitude of early-stage companies entering the space, there has been a massive increase in clinical trial activity with consequent negative impact on patient enrollment rates. According to *ClinicalTrials.gov*, there are more than 6,200 industry-sponsored oncology clinical trials ongoing. Due to the massive increase in IO clinical activity, trials are taking longer as a result of the fierce competition in patient recruitment. This represents a challenge for

Exhibit 1

IO Attracts Larger Investments in 1H/18

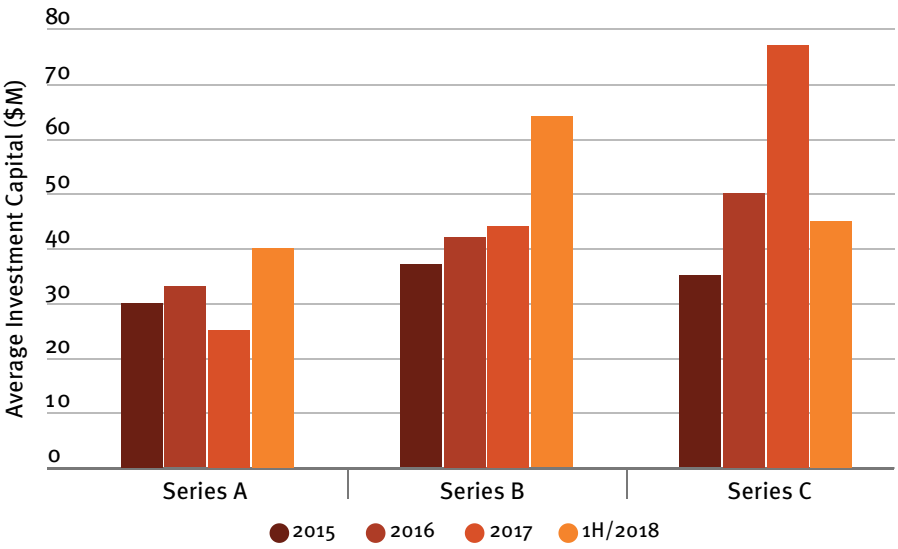


METHODS

A broad search was conducted using PitchBook to capture the majority of IO companies; search terms included "oncology" or "cancer" or "tumor" or "immuno oncology" or "immune therapy" or "immunotherapy" or "tumor microenvironment" for different deal types, VC financings, M&As and IPOs. All companies were screened using company descriptions and an analysis of their pipeline to determine whether they fall under the IO category and if they are pure-play or have IO as their lead asset.

Financing encompassed all VC stages with deals above $5 million included for analysis. Phase of development was found from *ClinicalTrials.gov* and company press releases. Exit timelines were calculated as the time from company founding to exit. Deal size was not always available for all companies, resulting in some exits being excluded from the analysis. For M&A exits, outliers (Juno-Celgene and Kite-Gilead) were excluded when calculating averages. For IPO exit values, market capitalization at IPO and post-IPO (six months; the typical lock-up) were captured using PitchBook and Capital IQ platforms. The list of active investors in IO was pulled from PitchBook.

Exhibit 2
Investors Show Appetite For Early-Stage In 1H/18



management teams and is likely to prolong returns on invested capital for investors.

Outcome Capital has ranked the top 10 active investors based on the number of investments in unique IO companies in the last three-and-a-half years (*see Exhibit 3*). OrbiMed led the list, with 18 IO investments totaling 19% of its total investments during this time frame. MPM Capital and Atlas Ventures also invested heavily with 35% and 26%, respectively, of their total investments. Interestingly, New Enterprise Associates and Flagship Pioneering, two of the largest life sciences venture firms, exhibit little presence in the segment. Crossover funds like Cormorant Asset Management, Redmile Group and Foresite Capital Management have a dominant presence in this segment as a result of the early public liquidity (last money in before IPO). Corporate VCs (CVC) investments

THE EMERGENCE OF IO

The approval of first-generation checkpoint inhibitors, Merck's Keytruda and Bristol-Myers Squibb's Opdivo in the second half of 2014, catalyzed a wave of deal-making, not only around other checkpoint inhibitors, but also for molecules and technologies that could offer synergistic benefits when used in combination with these drugs.

The underlying rationale of immuno-oncology (IO) therapeutic approaches is to take the brakes off the immune system or boost its ability to detect and destroy tumor cells. The approval of first-generation checkpoint inhibitors, Merck & Co. Inc.'s Keytruda (pembrolizumab) and Bristol-Myers Squibb Co.'s Opdivo (nivolumab) in the second half of 2014, catalyzed a wave of deal-making, not only around other checkpoint inhibitors, but also for molecules and technologies that could offer synergistic benefits when used in combination with these drugs. These two checkpoint inhibitors alone generated a combined $12 billion in sales this year. This has translated into a patenting frenzy as players seek to stake their claim in this wide commercial landscape and has resulted in large pharma and biotech stumbling over each other to acquire or partner with companies developing IO assets.

Late-comers who were behind the curve in identifying novel drug candidates to augment their pipelines, are now paying top dollar, thereby further propelling the proliferation of checkpoint transactions, creating a competitive and crowded marketplace. Given the impressive overall survival data of some of the combination trials with checkpoint inhibitors, partnering transactions are gaining significant momentum, with total values in excess of $1 billion dollars. In early 2018, BMS entered a co-development deal with Nektar's lead IO program in combination therapies with BMS' marketed cancer immunotherapy Opdivo and Yervoy (ipilimumab), in more than 20 indications for a whopping $3.6 billion-plus, including $1.8 billion up front. Merck & Co. partnered with Eisai to co-develop its marketed cancer treatment Lenvima (lenvatinib mesylate) for additional oncology indications, both alone and in combination with Merck's Keytruda, a potential $5.77 billion dollar deal, including $300 million up front.

In 2017, Celgene Corp.entered into a strategic partnership with BeiGene Ltd. for a total of $1.4 billion ($411 million in up-front cash and equity and $980 million in milestones) for acquisition of worldwide rights to develop its PD-1 inhibitor BGB-A317. Similarly, Servier SA partnered with Pieris Pharmaceuticals Inc. in a broad co-development deal including Pieris' preclinical dual-checkpoint inhibitor PRS-332 and up to seven other IO bispecific drug candidates in a collaboration that could generate up to $1.8 billion.

Oncology remained the most competitive area for deal-making in 1H-2018, with IO therapeutics continuing to be the principal driver, as clinical evidence emerges to support next-generation technologies such as chimeric antigen receptor cell therapies (CAR-T), antibody-drug conjugates and bispecific antibodies. Indeed, one of the largest deals of 2018 so far is Celgene's $9 billion acquisition of the CAR-T cell company Juno Therapeutics Inc.

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show an upward trend with **Celgene Corp.** investing heavily to maintain its strategic focus – with 33% of its total investments focused on IO in the last few years.

However, big players, such as Merck, BMS, **AstraZeneca PLC**/Medimmune LLC and **Roche**, already possessing approved IO drugs, are barely investing in early assets. Instead, these players are focusing efforts on clinical trial partnerships (supplying compound but little or no dollars). This strategy allows them to combine and test their approved drugs with different compounds for enhanced efficacy in different modalities in a cost-contained manner. Meanwhile, CVC group Boehringer-Ingelheim Venture Fund doubled its investable capital to €250 million following recent successes in IO, and it currently has five IO companies in its portfolio.

Interestingly, there has been a surge in Chinese venture (6 Dimensions Capital, Lilly Asia Ventures, Wuxi Ventures) investing in US biotechs with IO assets constituting 20% to 40% of their active portfolio. Thus, Chinese investors appear to have become important drivers of the rush into the IO segment, providing biotech companies multibillion-dollar valuations. Beijing launched an ambitious industrial policy in 2015 (Made in China 2025), making biotech eligible for greater government backing. China once lagged in drug spending but by allowing more investment in US biotech, the country is now gaining earlier and easier access to novel therapies and a share in the potential high returns. According to health information and technologies and clinical research company IQVIA, China's pharmaceutical spending will reach $170 billion by 2021, compared with $117 billion in 2016. As China attempts to migrate the country's pharmaceutical sector beyond low-cost generic medications, this investment wave is likely to continue (unless the current US administration levies unsustainable taxes and tariffs).

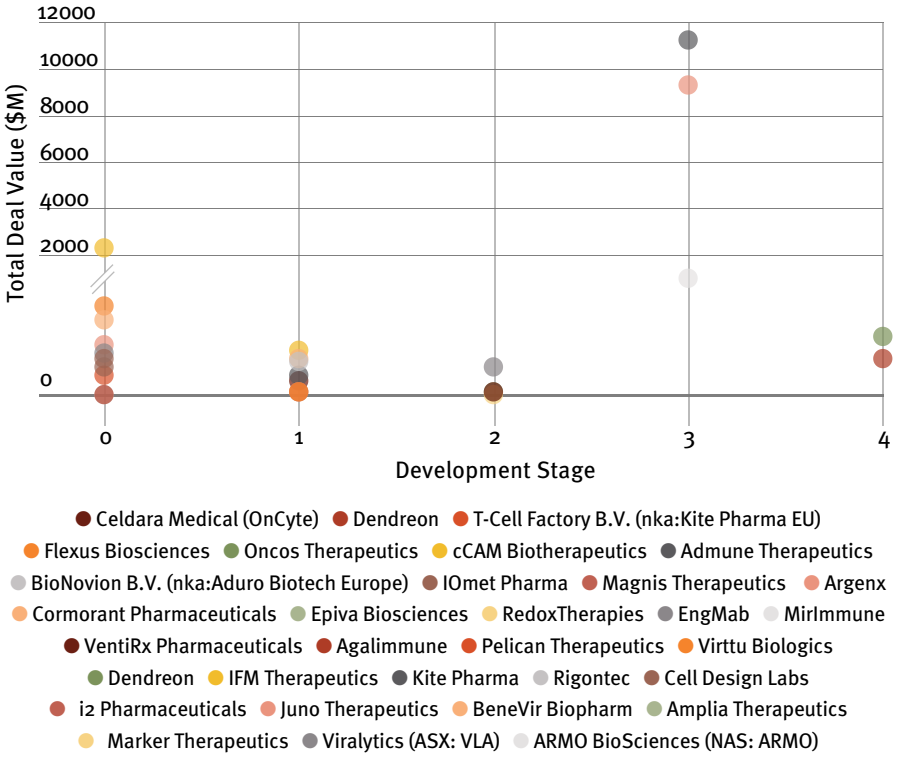
Exit Landscape

The IO segment demonstrated robust merger and acquisition activity in the time period tracked with major headline acquisitions: **Juno Therapeutics Inc.**-Celgene ($9 billion) and **Kite Pharma Inc.-Gilead**

Exhibit 3
OrbiMed Leads On Individual Company Investments

INVESTORS	NO. OF INVESTMENTS (IO)	NO. OF INVESTMENTS (ALL INDUSTRIES)	% OF TOTAL INVESTMENTS IN IO
OrbiMed	18	94	19%
Cormorant Asset Management	14	45	31%
MPM Capital	11	31	35%
Google Ventures	11	198	6%
Lilly Asia Ventures	9	25	36%
Atlas Venture	9	35	26%
Novo Holdings	9	59	15%
Celgene	8	24	33%
Redmile Group	8	28	29%
Foresite Capital Management	7	40	18%

Exhibit 4
Distinct Preference For EarlyStage M&A



Development stage: 0=preclinical, 1=Phase I, 2=Phase II, 3=Phase III, 4=Marketed

Sciences Inc. ($11 billion). There were 32 acquisitions with an aggregate total capital return of about $15 billion (excluding outliers, Juno-Celgene and Kite-Gilead) with around one third of which ($5.8 billion) were in up-front cash payments. The yearly breakdown of the aggregate and average total and upfront values are shown in *Exhibit 6*. (These are approximate numbers as some transaction financials were not disclosed and therefore not included in our calculations.)

The first half of 2018 continued to demonstrate strong interest in IO assets with a total of seven M&As with higher mean transaction and up-front values compared with the previous years. Three of seven M&A transactions were unicorn (greater than $1 billion) deals: **Janssen Biotech Inc.** paid $140 million up front for BeneVir Biopharma Inc., with a total value of around $1.04 billion, to acquire its preclinical assets and T-stealth platform; **Eli Lilly & Co.** paid $1.53 billion up front to acquire **Armo BioSciences Inc.**'s Phase III asset; and Celgene paid a hefty $9 billion to add Juno Therapeutics' CAR-T platform to its pipeline.

These acquisitions suggest a distinct preference for early-stage assets as evidenced by the intense M&A activity around preclinical assets. There seems to be little or no correlation between risk and return on invested capital (ROIC) as early-stage assets (*see Exhibit 4*), a phenomenon provided similar liquidity compared with later-stage assets, a phenomenon unique to this segment. Big pharmas that had existing commitments in the segment (Merck, BMS) are buying early assets to extend or diversify their pipelines (Merck-Rigontec GMBH, BMS-IFM Therapeutics) or dramatically expanding their franchises (BMS-Nextar, Merck-**Eisai Co. Ltd.**). Others are in catch-up mode, paying top dollar to build a presence in the segment (Celgene-Juno, Gilead-Kite Pharma, Lilly-Armo, AZ-**Compugen Ltd.**, **Johnson & Johnson**-Benevir).

IPOs continue to perform strongly in the first half of 2018 with a total of eight public debuts raising around $104 million with a market capitalization of around $538 million, clearly exceeding the numbers from the previous years (*see Exhibit 5*). For the first time, companies saw market capitalizations reaching $1 billion at IPO (**Aduro BioTech Inc.** and **NantKwest Inc.**), indicating aggressive market uptake of IO assets and comfort to both private and public investors.

Phase I assets dominate the public markets with 10 IPOs pulling $968 million in value out of the marketplace and there seems to be no difference in market capitalization for early- versus late-stage assets, again, a phenomenon unique to the IO segment (*see Exhibit 7*).

The first half of 2018 saw shortening of the exit window to about four years for IPOs and six years for M&As with significantly faster ROIC to investors compared with previous years (*see Exhibit 8*).

Exhibit 5
IPO Trends Similar For Early-Stage & Late-Stage Assets

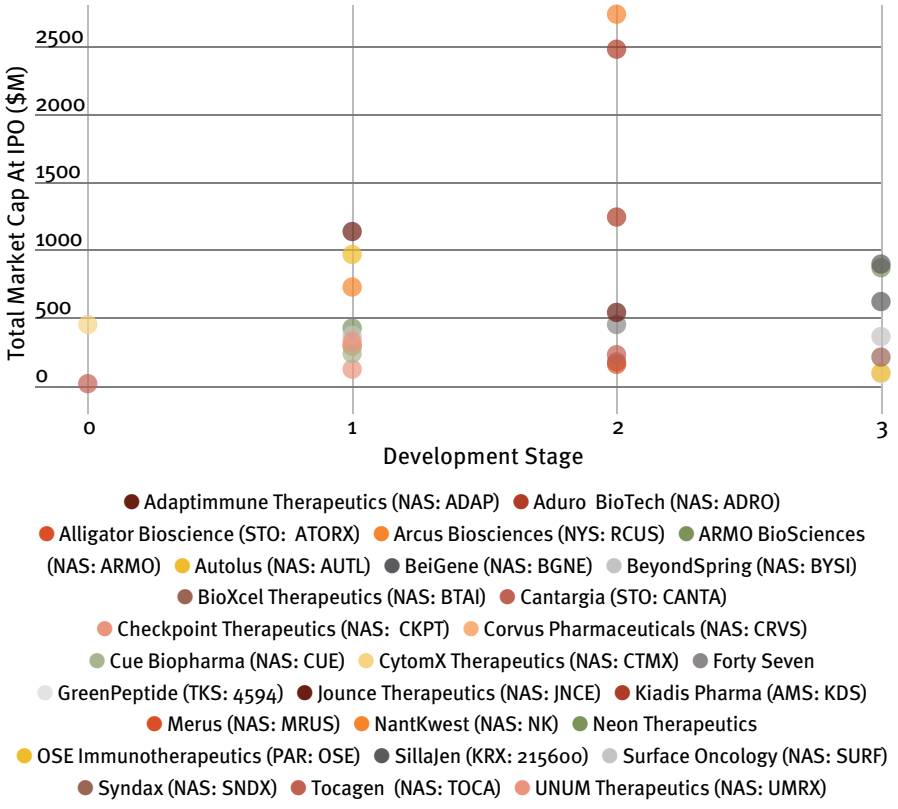
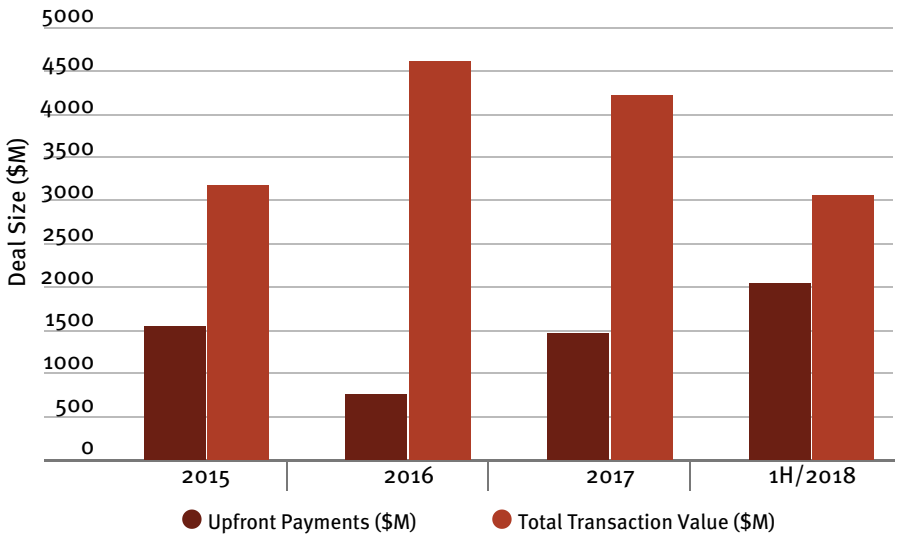


Exhibit 6
Robust Growth In M&A Transactions



Sub-Segment Analysis

Outcome Capital analyzed the disposition of capital in different IO sub-segments. Sub-segments were divided broadly into six classes:

- Immune-modifying factors, which boost the immune response, including soluble factors, for example, cytokines, immune-metabolic regulators and adenosine antagonists to name a few;
- Engineered T cells;
- Checkpoint inhibitors, for example, PD-1, PD-L1, CTLA-4, TIM-3 and IDO;
- Antibody-based therapeutics, for example, bispecific antibodies and antibody platforms;
- Innate immunity targeting natural killer (NK) cells and dendritic cell populations; and
- Cancer vaccines, for example, genetically engineered viruses and vaccines expressing specific antigens.

In the first half of 2018, adoptive cell therapy remained the most attractive segment with an average investment of $71 million (*see Exhibit 9*); with two CAR-T US FDA approvals last year (*Kymriah* [tisagenlecleucel] and *Yescarta* [axicabtagene ciloleucel]), and large transactions such as Juno-Celgene and Kite-Gilead, investors are perceiving CAR-T assets as less risky with greater return on invested capital and greater exit values, with an average market cap of $783 million.

Current exit trends suggest increasing interest in bispecifics and antibody platforms and innate immunity assets targeting NK cells, dendritic cells and CD47-directed therapies with total transaction values of $3.9 billion and $2.9 billion, respectively (*see Exhibit 10*). Aduro Biotech, with its lead assets in the STING pathway, soared in the public market with a $1 billion market cap and FortySeven, a clinical stage IO company founded in 2015, with an anti-CD47 antibody as its lead asset, made its public debut in June 2018, raising $113 million with a market cap of $450 million at IPO – a quick return of capital to investors.

Additionally, 2017 saw large acquisitions in the innate immunity space by some of the established players with approved drugs in IO; Merck's acquisition of Rigontec for its Phase I asset targeting the RIG pathway for $554 million with a $137 million up-front value, and BMS' acquisition of IFM therapeutics for its preclinical STING programs for a total value of $2.3 billion and a $300 million up-front payment. This suggests an interesting trend that big pharmas are looking to expand their current IO products by combining them with some early-stage assets in newer sub-segments to create better clinical efficacy and to target different modalities (*see Exhibit 8*).

While the approved immune checkpoints and CAR-T therapies continue to expand their indications, adoptive cell therapy followed by innate immunity and bispecifics as well as other antibody platforms are attracting the most investment activity and are the sub-segments to watch for through 2019. We believe exciting innovations in cancer will continue to be found in the IO space, yielding successful clinical results and commercial partnerships and exit opportunities for investors.

Exhibit 7

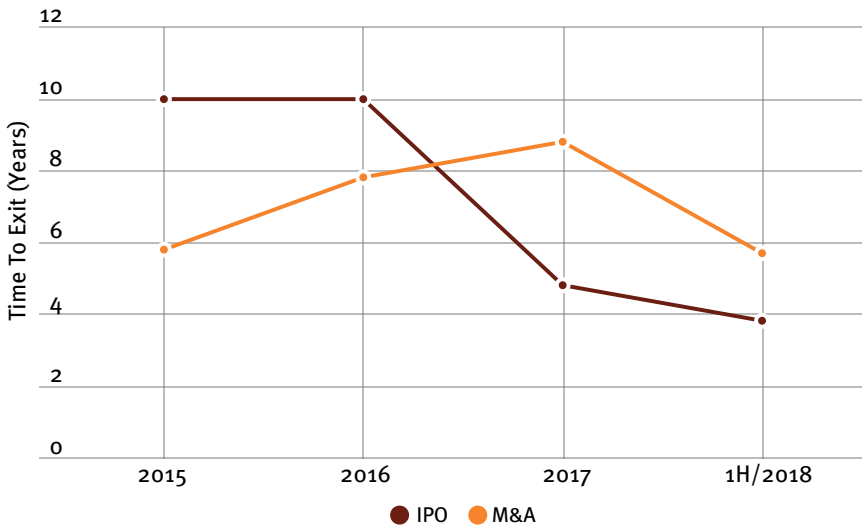
Phase I Dominates The IPO Exit

STAGE OF LEAD ASSET	TOTAL NO. OF TRANSACTIONS	GROSS PROCEEDS ($M)	AVERAGE PROCEEDS ($M)	TOTAL MARKET CAP ($M)	AVERAGE MARKET CAP AT IPO
Preclinical	2	85	43	464	232
Phase I	10	968	97	4887	488
Phase II	8	773	97	2789*	465
Phase III	7	582	83	3135	448

*Deleted two deals with market cap >$2 billion (Aduro Biotech and NantKwest)

Exhibit 8

Early Exits Translate Into Faster Returns



Key Takeaways

IO may be the perfect storm for venture returns. It represents a radical change from traditional cytotoxic drugs, the capital markets are booming, and traditionally slow regulators have catalyzed meaningful new product approvals based on unprecedented clinical data. This is driving VCs flush with cash to engorge new IO market entrants with capital to hit value-inflecting milestones. Coupled with large players jumping at early M&As,

biotech companies are enjoying a high probability to exit early. These catalysts are the lifeblood of venture capital returns.

In the first half of 2018, the size and number of venture financings and M&A deals in IO increased to new heights. The sector hit new high-water marks in IO deal-making: unicorn valuations, acquisitions of early assets for multibillions of dollars and public debuts with market capitalization of over $1 billion. IO R&D is on an upward surge due to massive interest by big pharma and large biotech in clinically effective drug combinations. This is creating a voracious investor appetite as IO assets are generating lucrative and faster returns with shortening of exit timelines and higher exit multiples. Notably, unique to this segment compared with other segments in the life sciences sector is the apparent uncoupling between risk and ROIC as early-stage assets are providing similar liquidity to mature assets.

Buying innovation will not come cheap in this sector and geopolitical forces have played a role in the continued influx of China-based capital in US IO companies. The raising of sizeable war chests from venture and corporate investors, the availability of public capital and the exciting science will propel the next wave of innovation, investor enthusiasm for the space and early returns on invested capital. Overall, a rather optimistic outlook for the remainder of 2018 and into the near future.

The question that remains: are we in the midst of a transformational inflection point in scientific progress leading to meaningful improvements in clinical outcomes or are we witnessing irrational exuberance by investors and strategic players leading to unduly escalated asset values? Time will tell.

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Exhibit 9

Stong Investor Interest In Adoptive Cell Therapy In 1H2018

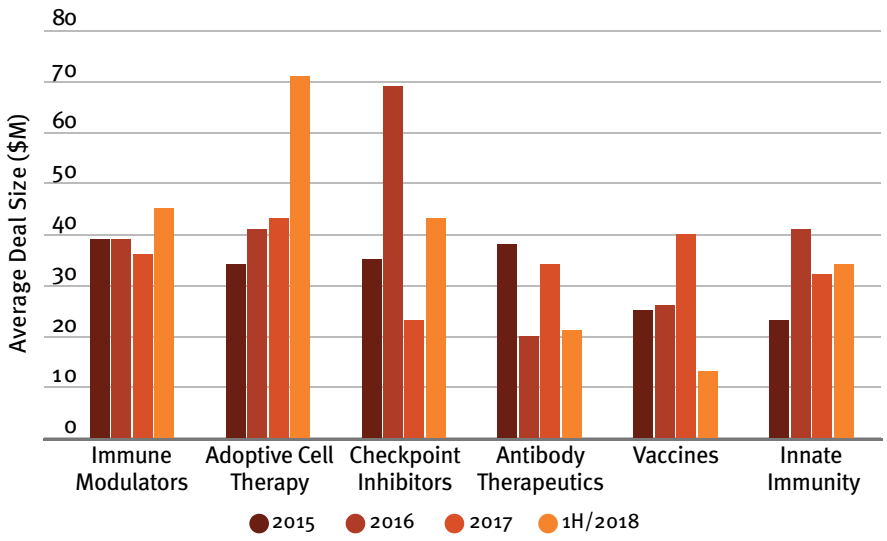
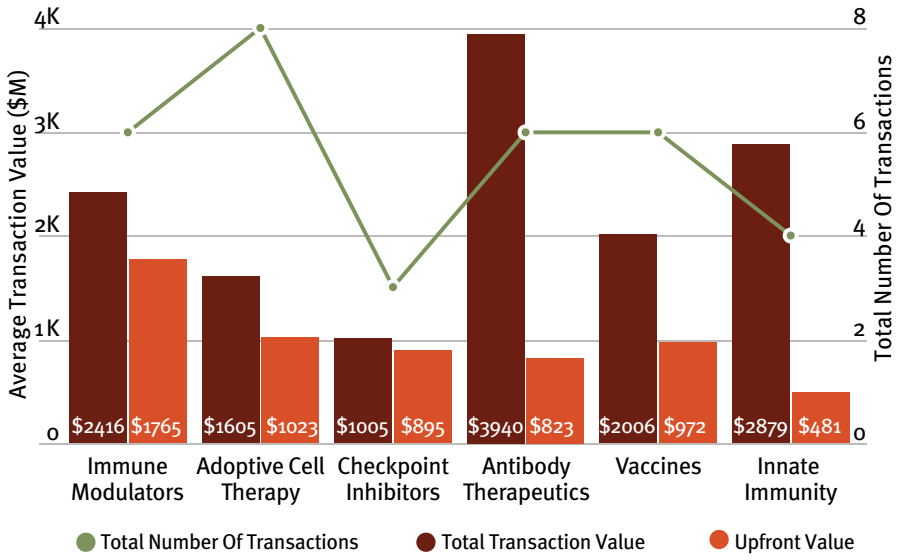


Exhibit 10

Antibody Therapeutics, Innate Immunity Top M&A List



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