Biotech and Breakthroughs in Immuno-Oncology

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KEYWORDS

• Immunotherapy • Immuno-oncology • Checkpoint inhibitors • Tumor microenvironment
• Urologic oncology

KEY POINTS

- Paradigm-shift in disease management with the approval of immuno-oncology agents, namely, checkpoint inhibitors, created a major shift in how patients with cancers are treated.
- The significant clinical impact of checkpoint inhibitors led to what some have seen as a goldrush, others as a bubble, toward clinical development of immunotherapies.
- Immuno-oncology agents have not by and large cured most patients in most cancers, hence new immunotherapeutic agents and combinations are needed.
- Over the past 5 years, much of the BioPharma industry's focus has been on expanding the range of immuno-oncology agents and combinations.

The age of immunotherapy has been a century in the making, from the first published reports of Dr Coley through the approvals in the late 1980s, of interferon-alpha in hairy cell leukemia, follicular non-Hodgkin lymphoma, melanoma, and AIDS-related Kaposi sarcoma, to the approvals in the early 1990s of IL-2 for and metastatic renal cell carcinoma (RCC) and melanoma, to the long-standing standard of care use of Bacillus of Calmette and Guerin in non–muscle-invasive bladder cancer and formal approval by the US Food and Drug Administration in 1990 for carcinoma in situ of the bladder. Over this time, despite these approvals and notwithstanding the problematic therapeutic index of these agents and generally limited efficacy, the belief in the role of the immune system fighting off cancer remained by and large suspect within the pharmaceutical industry. Those scientists and clinicians researching and believing in the potential, known then as "tumor immunologists," worked against the prevailing dogma of direct killing of cancer cells, whether by radiation, chemotherapy, or later "targeted" therapies, ranging from early antibodies like *Herceptin* (trastuzumab) for $HER2^+$ breast cancer and rituximab (Rituxan) for $CD20^+$ non-Hodgkin's lymphoma or small molecule mostly kinase inhibitors like imatinib (Gleevec) targeting bcr-abl fusions for chronic myeloid leukemia and erlotinib (Tarceva) for epidermal growth factor receptor-driven non–small cell lung cancer (NSCLC).

With the approvals of sipuleucel-T (Provenge), the first cancer vaccine approved in the United States, for prostate cancer, and ipilimumab, anti-CTLA-4 (Yervoy), the first checkpoint inhibitor (CPI) approved in the world, both in 2011, followed by the first anti-programmed death 1 (PD-1) CPIs approved in 2014, nivolumab (Opdivo) and pembrolizumab (Keytruda), so begins the new age of immunotherapy as not only a validated anticancer approach but as a significant blockbuster category within the pharmaceutical industry (**Fig. 1**).

As shown in **Fig. 1**, sales of leading oncology drugs worldwide, one can readily see the extent to which the anti–PD-1 and anti–PD-ligand 1 agents define the immuno-oncology (IO) space now and going forward over the next 5 years, and in fact by 2024 pembrolizumab becomes the largest pharmaceutical product in the world, surpassing the anti-inflammatory anti-tumor necrosis

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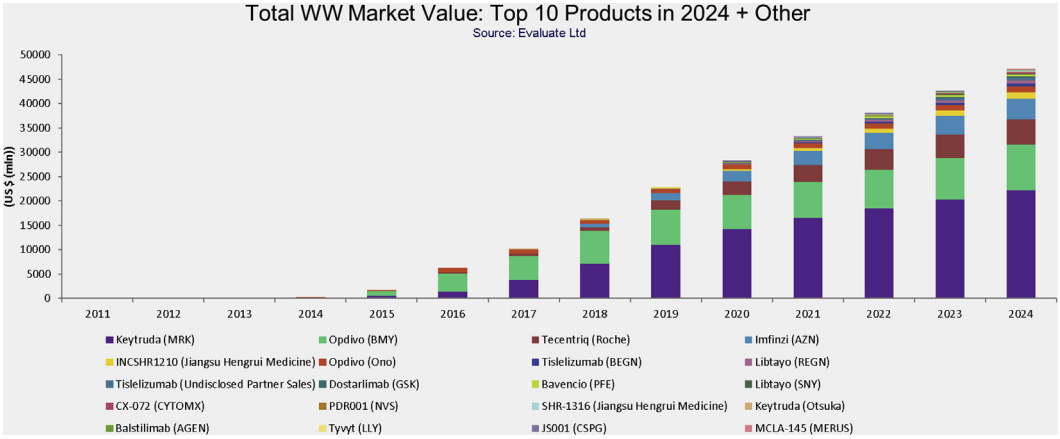


Fig. 1. Sales of leading immuno-oncology agents. (*From* EvaluatePharma, Cello Health BioConsulting (previously Defined Health) analysis.)

factor product adalimumab (Humira) that has been the biggest selling drug for some time. Nivolumab becomes the fourth-leading product.

That pembrolizumab and nivolumab are among the top selling pharmaceutical products is significant because it reflects the degree to which this class of immunotherapy agents, the CPIs, have become a new foundational component of therapeutic regimens across multiple tumor types. Such a role for CPIs is akin to that of the taxanes like paclitaxel (Taxol) and docetaxel (Taxotere) in the first decades of the modern age of oncology. CPIs are approved or in development for a wide range of tumors. Most activity is in solid tumors, especially those with good clinical activity and extent approvals, such as melanoma, NSCLC, and the urologic oncology indications of RCC and bladder cancer (Fig. 2).

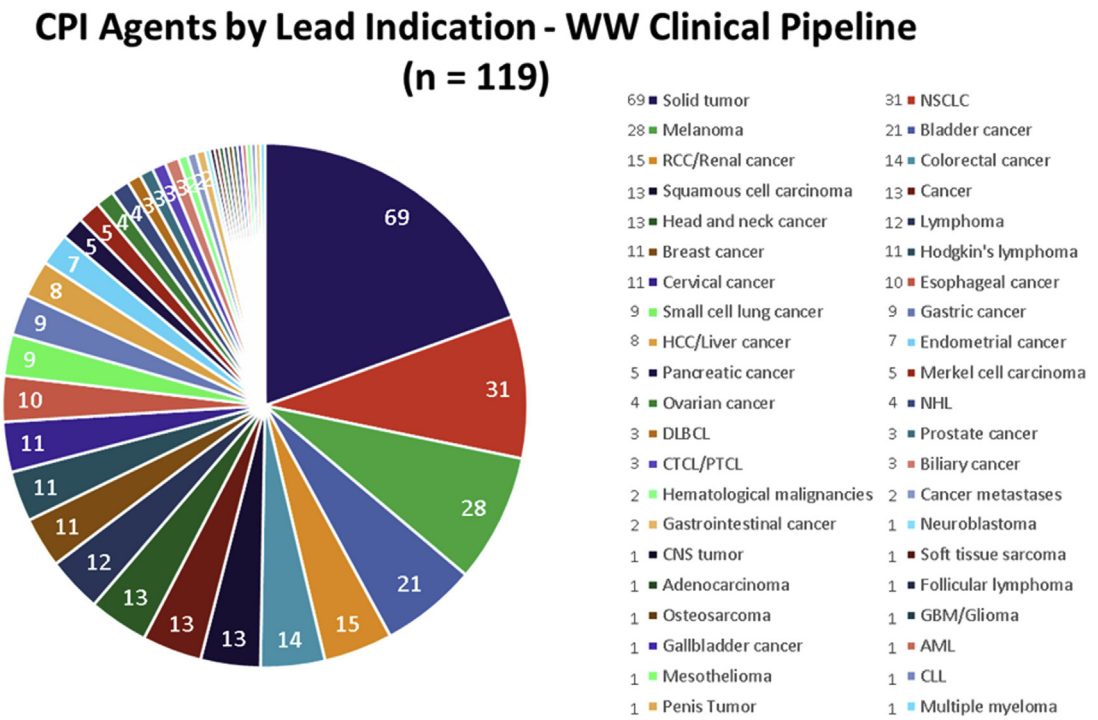


Fig. 2. CPIs in clinical development across all cancers. CTCL, cytotoxic T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; HCC, hepatocellular carcinoma; PTCL, peripheral T-cell lymphoma; RCC, renal cell carcinoma. (*From* Adis R&D Insight, Clarivate Analytics Cortellis, Cello Health BioConsulting (previously Defined Health) analysis.)

Number of Assets in Clinical Development	Cancer	Solid Tumor	GBM/Glioma	Neuroblastoma	CNS Tumor	Head and Neck Cancer	Breast Cancer	Ovarian Cancer	Cervical Cancer	Endometrial Cancer	Prostate Cancer	Penis Tumor	RCC/Renal Cancer	Bladder Cancer	Colorectal Cancer	NSCLC	Small Cell Lung Cancer	Mesothelioma	Melanoma	Merkel Cell Carcinoma	Squamous Cell Carcinoma	Pancreatic Cancer	Gallbladder Cancer	Biliary Cancer	HCC/Liver Cancer	Esophageal Cancer	Gastric Cancer	Gastrointestinal Cancer	Osteosarcoma	Soft Tissue Sarcoma	Adenocarcinoma	Cancer Metastases
PD-1	2	18				4	1	2	4		1		5	8	4	9	4		9	2	4				4	3	3	1		1		1
PD-L1	1	13				1	2		3	1	1	1	2	6	3	8	1		3	1	2	2	1	3		1	1		1			
LAG-3	1	4	1				2	1	1	1			1	1	1	2	1	1	4	1	1				1	1	1					
PD-L1 / 4-1BB		4				2	1		1	1			1	2		2			1		1					1	1					
TIGIT		5					1	1		1			1	1	1	2			1	1	1					1		1				
PD-1 / CTLA-4	1	3				1	1			1			1	1	1	1			1		1				1	1	1				1	
CTLA-4 / LAG-3		1				2	1		1	1			1	1	1	1	1		1		1	1			1	1	1					
PD-1 / ICOS		1				1	1		1	1			1	1	1	1	1		1		1	1			1		1					
CTLA-4		4											1		1	2	1		5													
TIM-3	3	5																														
PD-L1 / CTLA-4	1	1					1									1					1					1						
PD-1 / DLL1											1		1		1				1			1										
B7-H3		2		1	1																											
PD-1 / TIM-3		1														1			1													
PD-1 / PD-L1		2																														
NKG2A						1										1																
VISTA	1																															
CTLA-4 / OX40		1																														
PD-L1 / TGF-B		1																														
PD-L1 / VISTA	1																															
LAG-3 / PD-L1																																1
KIR						1																										
TIM-3 / PD-L1		1																														
CTLA-4 / CD80		1																														
PD-1 / OX-40L		1																														
PD-1 / LAG-3	1																															
Undefined	1																															

Legend
Highest Count Key
1 5 10 15 20

Fig. 3. Heat map of immunomodulatory antibodies across cancer settings. HCC, hepatocellular carcinoma; RCC, renal cell carcinoma. (*From* Adis R&D Insight, Clarivate Analytics Cortellis, Cello Health BioConsulting (previously Defined Health) analysis.)

As shown in Fig. 3, a heat map of the count of currently marketed and development stage immunomodulatory antibodies, one can readily see the intense competitive clinical development in the validated setting of anti–PD-1/ligand 1 inhibitors, as well as the high level of activity in next-generation CPIs against new targets and that of the costimulatory agonists of various classes. The excitement around immunotherapies, or IO as the space is increasingly referred to, is reflected in various analytics of pipeline and clinical trial activity. As our analysis shows (Fig. 4), the clinical development pipeline is increasingly a diverse range of IO targets and therapeutic modalities.

The intensity of IO development, specifically around the anti–PD-1/PD-ligand 1 agents, is underscored in the analysis by the Cancer Research Institute of clinical trials from 2017 to 2019. As shown in Fig. 5, combinations studies of the now 9 approved CPIs is nearly 3000 active studies. Such competitive intensity starts with patient enrollment and continues into the clinical development strategy and ultimately commercialization, with extensive investment by the leading CPI players in life cycle management to expand

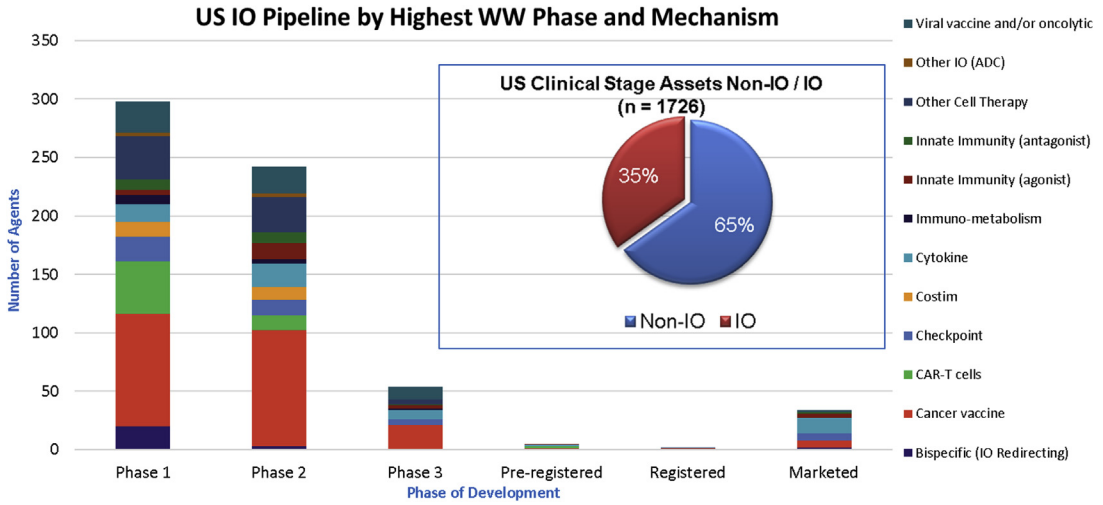


Fig. 4. Oncology clinical development pipeline (US only). ADC, antibody-drug conjugate. (*From* Adis R&D Insight, Clarivate Analytics Cortellis, Cello Health BioConsulting (previously Defined Health) analysis.)

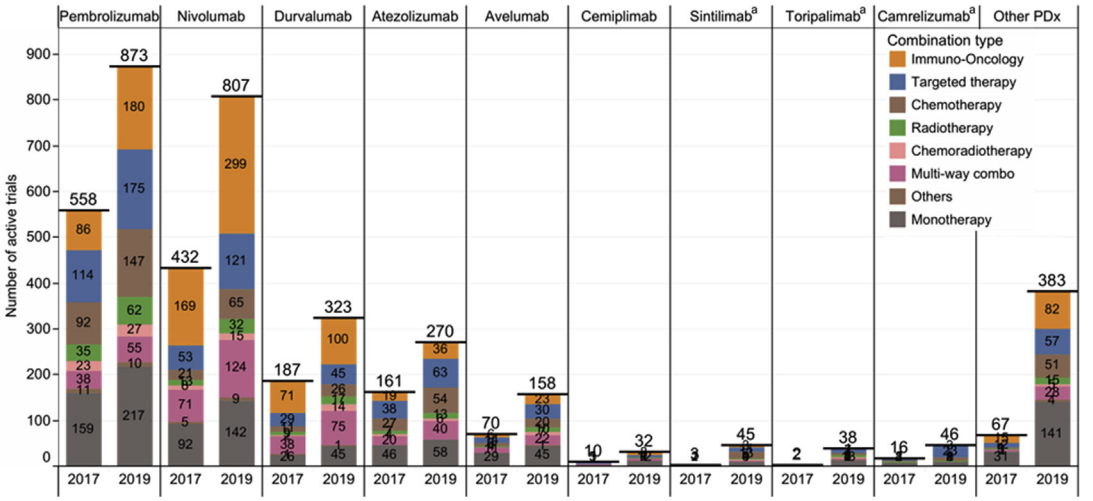


Fig. 5. Clinical trials with CPIs, 2017 versus 2019. [a] Approved in China only. PDx, products. (*From* Jia Xin Yu, Jeffrey P. Hodge, Cristina Oliva, Svetoslav T. Neftelinov, Vanessa M. Hubbard-Lucey & Jun Tang. Trends in clinical development for PD-1/PD-L1 inhibitors. Nature Reviews Drug Discovery 19, 163-164 (2020); with permission.)

the labels by settings within indications (vertical franchise expansion) and across more tumor types (horizontal franchise expansion).

The sheer number of combination trials highlights both the strengths and weaknesses of the CPIs: they have been paradigm-changing in selected settings for 20% to 60% of patients, in tumors like melanoma and NSCLC, but they are not working in all patients even in the more "immunoresponsive" or "hot" cancers and there are key, high unmet need cancers like pancreatic, where they have little to no activity, the so-called "cold" tumors. Hence, the need for layering on other agents with overlapping and distinct mechanisms of action (MOA), both IO agents and, if we may use the colloquial coinage, "non-IO" agents. As

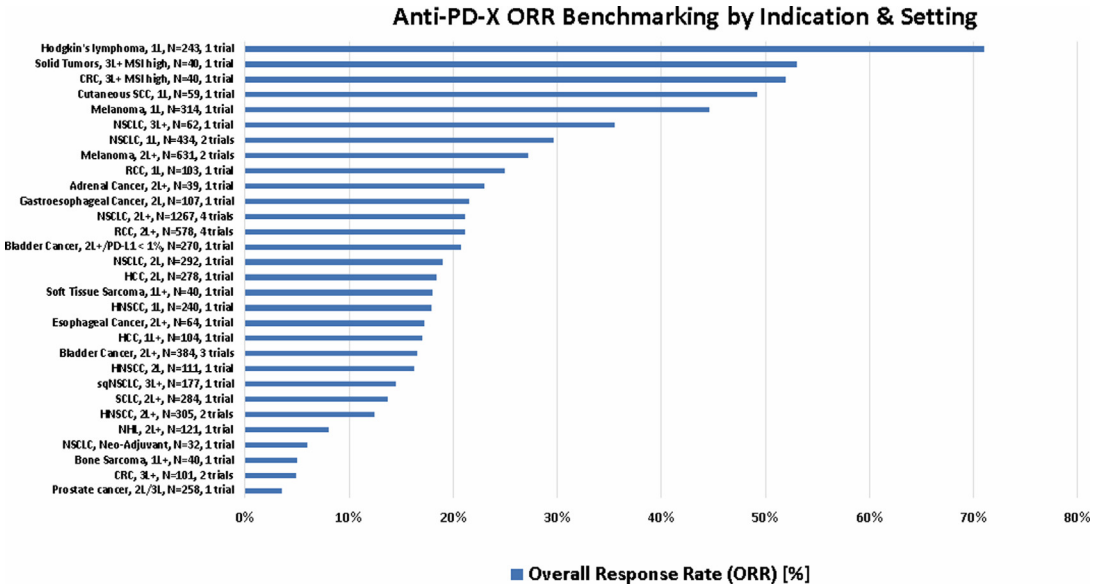


Fig. 6. Aggregate overall response rates (ORR) per tumor type and line of therapy across monotherapies. CRC, colorectal cancer; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; MSI, microsatellite instability; SCC, squamous cell carcinoma; SCLC, small cell lung cancer. (*From* Adis R&D Insight, Clarivate Analytics Cortellis, Beacon Targeted Therapies, Cello Health BioConsulting (previously Defined Health) analysis.)

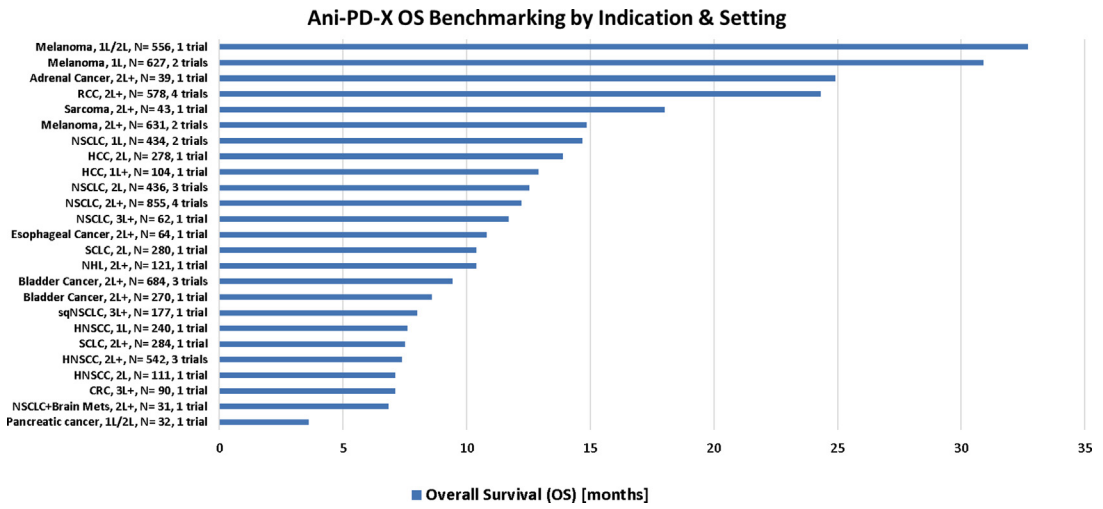


Fig. 7. Aggregate overall survival (OS) per tumor type and line of therapy across monotherapies. CRC, colorectal cancer; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; NHL, non-Hodgkin lymphoma; SCLC, small cell lung cancer. (*From* Adis R&D Insight, Clarivate Analytics Cortellis, Beacon Targeted Therapies, Cello Health BioConsulting (previously Defined Health) analysis.)

Figs. 6 and 7 show in terms of the clinical activity of CPIs, the range of efficacy as expressed by overall response rate or my overall survival with CPIs varies widely, from low single digit to nearing 70% overall response rate for monotherapy use, and from more than 30 months in melanoma to less than 5 months for pancreatic cancer as a monotherapy.

As is readily apparent, RCC is near the top of the more immunoresponsive cancers, bladder, at least for activity of CPIs, is in the lower middle (but is muddied by specific setting of bladder cancer and line, such as whether it is Bacillus of Calmette and Guerin refractory), and at the other end of the spectrum is prostate cancer, one of the least immunoresponsive tumors. It is worth noting, however, that prostate cancer was the first tumor type to get an IO agent approved since the times of IL-2 and interferon, and although melanoma is as expected near the top, the activity of CPIs in NSCLC was really not anticipated, although in retrospect through the lens of tumor mutational burden, this now makes sense.

As one can see in Fig. 8, cold tumors are being heavily studied in combination with CPIs, especially small molecule combinations.

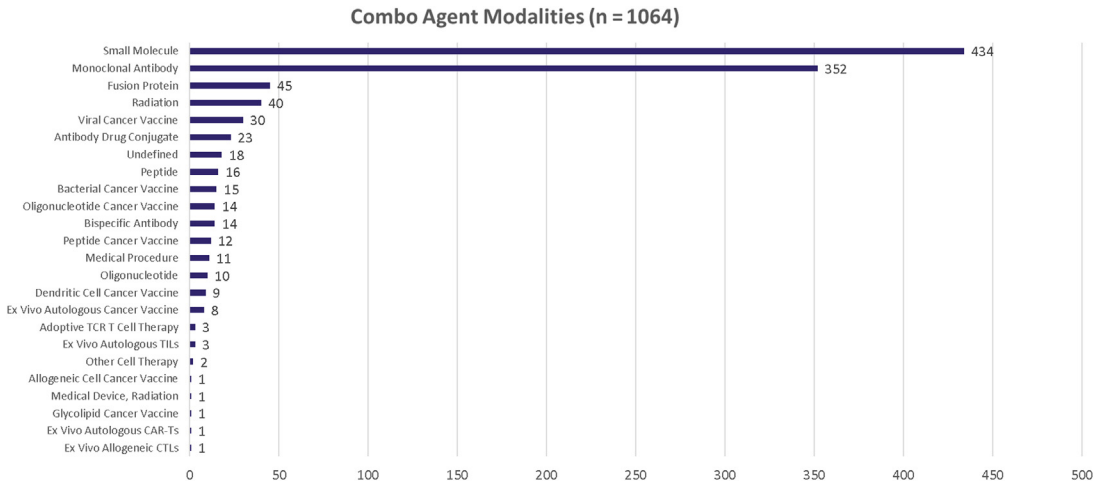
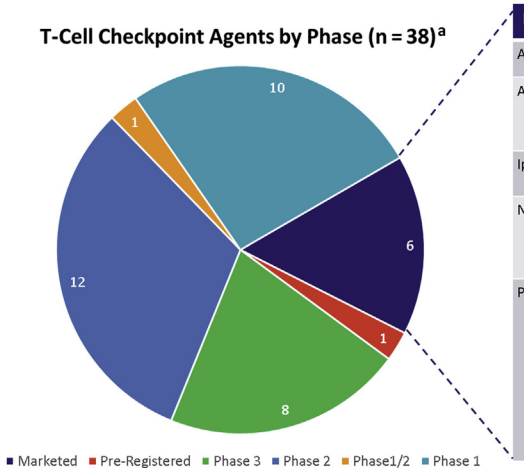


Fig. 8. Combinations by therapeutic modality. CAR-Ts, chimeric antigen receptor technology; CTLs, cytotoxic T cells; TCR, T-cell receptor. (*From* Adis R&D Insight, Clarivate Analytics Cortellis, Beacon Targeted Therapies, Cello Health BioConsulting (previously Defined Health) analysis.)



Marketed Agent	Approved Indications	Line of Therapy / Setting
Atezolizumab	Urothelial Carcinoma	Locally advanced or metastatic
Avelumab	Urothelial Carcinoma	Locally advanced or metastatic
	RCC	1L in combination with Axitinib
Ipilimumab	RCC	Previously untreated advanced RCC in combination with Nivolumab
Nivolumab	RCC	Advanced RCC (monotherapy)
	RCC	Previously untreated advanced RCC in combination with Ipilimumab
Pembrolizumab	Urothelial Carcinoma	- Locally advanced or metastatic, ineligible for cisplatin-chemo, PD-L1+ - Advanced or metastatic, following or within 12 mo of platinum-chemo treatment
	Non-Muscle Invasive Bladder Cancer	With or without papillary tumors who are ineligible for cystectomy
	RCC	1L in combination with Axitinib

Fig. 9. Leading CPIs, from Phase 1 through Marketed for top 3 urology settings of kidney, prostate and bladder cancers. [a] Products in development for multiple indications are double-counted. (*From* Adis R&D Insight, Clarivate Analytics Cortellis, Cello Health BioConsulting (previously Defined Health) analysis.)

Turning now specifically to analysis of the oncology and IO for urologic cancers, as Fig. 9 shows, this has been an active area for CPI approvals, with 5 unique programs currently approved and several others in late-stage development. Of course, the activity includes life cycle management among the 5 agents shown that are approved in urologic cancers, as well as the marketed CPIs not yet approved in any urologic setting, and follow-on CPIs not yet approved for any indication.

Looking at all clinical development activity in oncology for the 3 lead indications of kidney, bladder, and prostate cancers (Fig. 10), the snapshot of the pipeline reflects substantive activity for immunotherapy agents versus "nonimmunotherapy" programs. In fact, there is more IO activity as a percentage in these 3 indications than broadly for oncology overall (43% vs 35%, respectively; see Fig. 4). The diversity of overall anticancer approaches is not unexpected, with cell signaling kinase inhibitors, epigenetic inhibitors, hormonal modulation, antiangiogenics, and still a good and quite active development of cytotoxic agents (next generation, reformulations, drug delivery, etc).

Diving more specifically into the pipeline for each of these 3 main tumor types, as shown in Fig. 11, one can see a large bolus of phase II agents IO agents that are moving toward

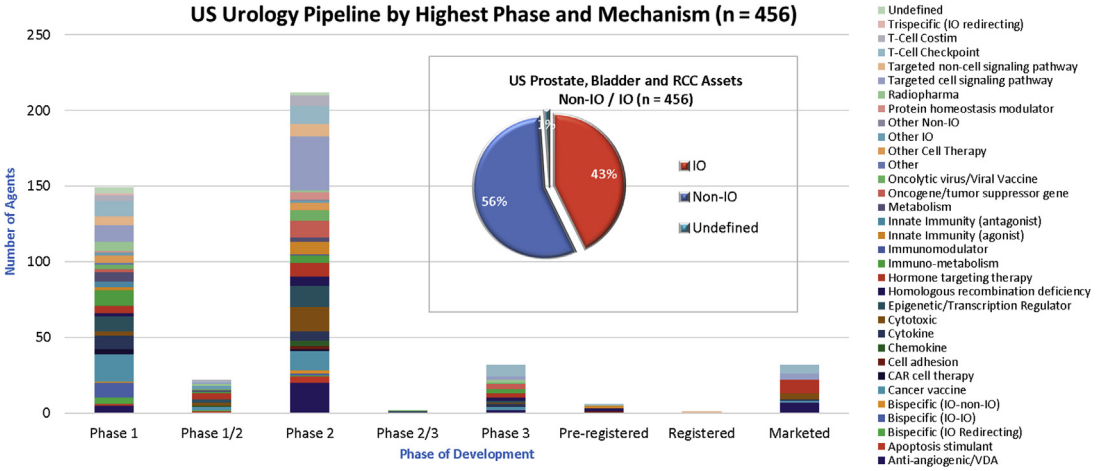


Fig. 10. Clinical development pipeline for prostate, bladder, and kidney cancers. Products in development for multiple indications are double counted. VDA, vascular disrupting agent. (*From* Adis R&D Insight, Clarivate Analytics Cortellis, Cello Health BioConsulting (previously Defined Health) analysis.)

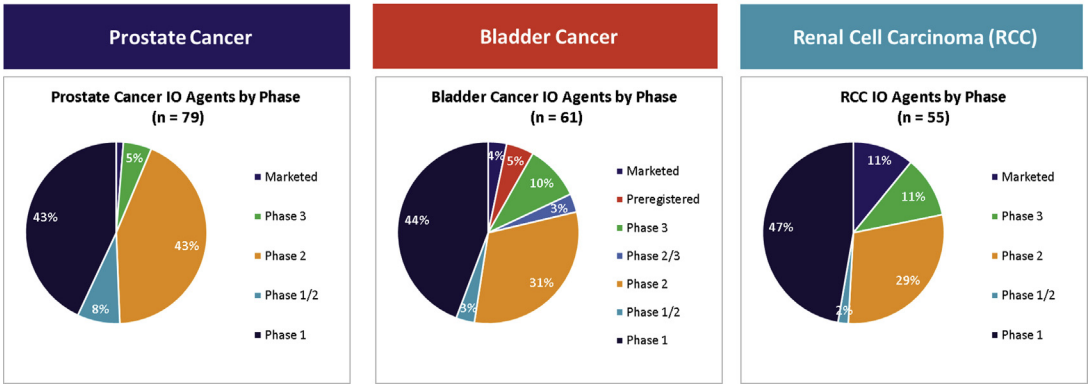


Fig. 11. IO agent development across the prostate, bladder and kidney cancer indications. (*From* Adis R&D Insight, Clarivate Analytics Cortellis, Cello Health BioConsulting (previously Defined Health) analysis.)

registration. As shown in the next several figures of our analytics, many of the IO agents for urologic cancers, as is true of the broad IO pipeline, whether CPIs or other MOAs, are looking to combine with small molecule kinase inhibitors of various sorts and with multiple chemotherapy agents regimens.

Antibodies are the leading therapeutic modality for development across the leading urologic cancers (Fig. 12). And although small molecule agents are generally the second most common approach, cancer vaccines remain a major focus of development; in fact, in prostate cancer it is the most active IO modality. That cancer vaccines remain such an active category in prostate cancer may reflect their safety profile and the ability to position them at either end of the spectrum from earlier stage disease, for example, as a maintenance adjunctive to an androgen receptor antagonist, or in late stage disease where the therapeutic options are more limited and patient's performance status more compromised.

As an example of these combination approaches, Fig. 13 shows late stage agents for RCC. As is evident, IO agent, primarily anti–PD-1 or anti–PD-ligand 1, are being combined with validated MOAs like antiangiogenic agents, which may also have immunomodulatory effects on the tumor microenvironment, as well as novel targets like inhibitors of c-met, given hepatocyte growth factor (HGF)/mesenchymal epithelial transition factor (c-MET) seems to have a an immunosuppressive role in through the direct inhibition of dendritic cells and an indirect inhibition of T-cell proliferation.

Fig. 14 shows a comparable analysis for prostate cancer, but of the entire clinical stage pipeline. There is a fairly robust pipeline with a few promising agents on the immediate horizon. Of note, there is increasing trial focus on targeted therapies

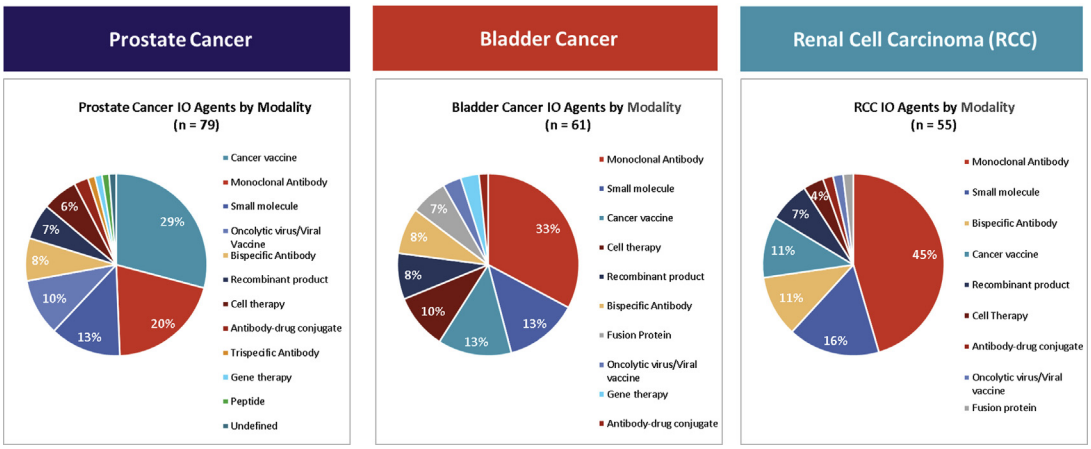


Fig. 12. IO pipeline activity in prostate, bladder, and kidney cancer indications. (*From* Adis R&D Insight, Clarivate Analytics Cortellis, Cello Health BioConsulting (previously Defined Health) analysis.)

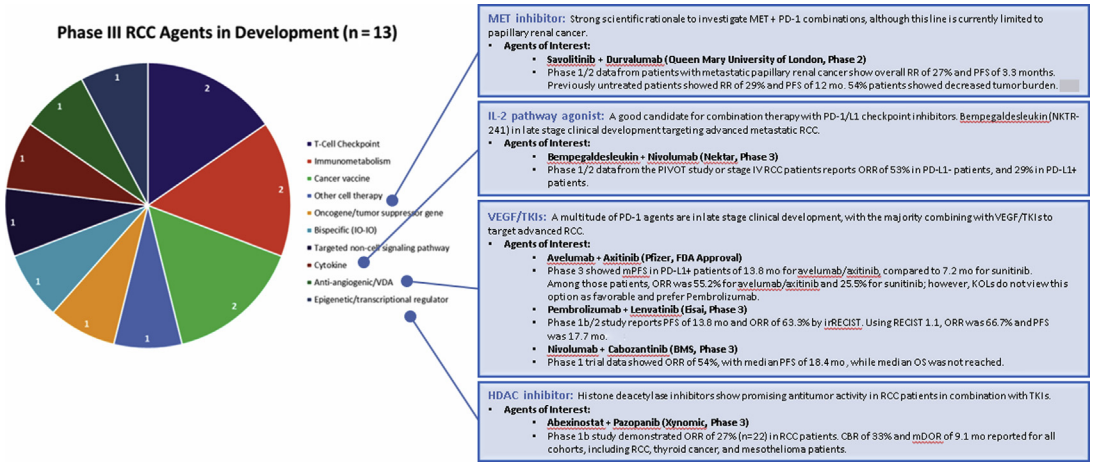


Fig. 13. Late stage RCC programs. FDA, US Food and Drug Administration; HDAC, histone deacetylase; KLOs, key opinion leaders; mDORs, mouse delta-opioid receptors; RR, relative risk; TKI, tyrosine kinase inhibitor; VDA, vascular disrupting agent; VEGF, vascular endothelial growth factor. (*From* Adis R&D Insight, Clarivate Analytics Cortellis, Cello Health BioConsulting (previously Defined Health) analysis and Primary Research. https://ir.nektar.com/news-releases/news-release-details/preliminary-data-nktr-214-combination-opdivo-nivolumab-patients, https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.3022, https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.7_suppl.545?af=R, https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.4560, https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.6_suppl.515, www.ClinicalTrials.gov, Cancer Discov. 2019; 9(6):711:721. J. Clin. Onco. 2018; 36(15). NEJM 2019; 380:1103-1115.)

and IO/non-IO combinations, as well as biomarker-selected, late stage programs for metastatic castrate-resistant prostate cancer including 177Lu-PSMA-617 for PSMA + patients, ipatasertib for PTEN-negative patients, and PARP inhibitors for homologous repair–deficient patients.

Last, I turn to some of the deals and investments that have been going into IO, because this reflects opportunities for academics and their institutions to put into a proper context potential early stage collaborations or new company ("newco") formation. In viewing IO through the twin lenses of investing and deal-making perspective, some interesting trends become apparent (**Fig. 15**).

First and foremost, what strikes one looking at these metrics is the size of the investments in IO

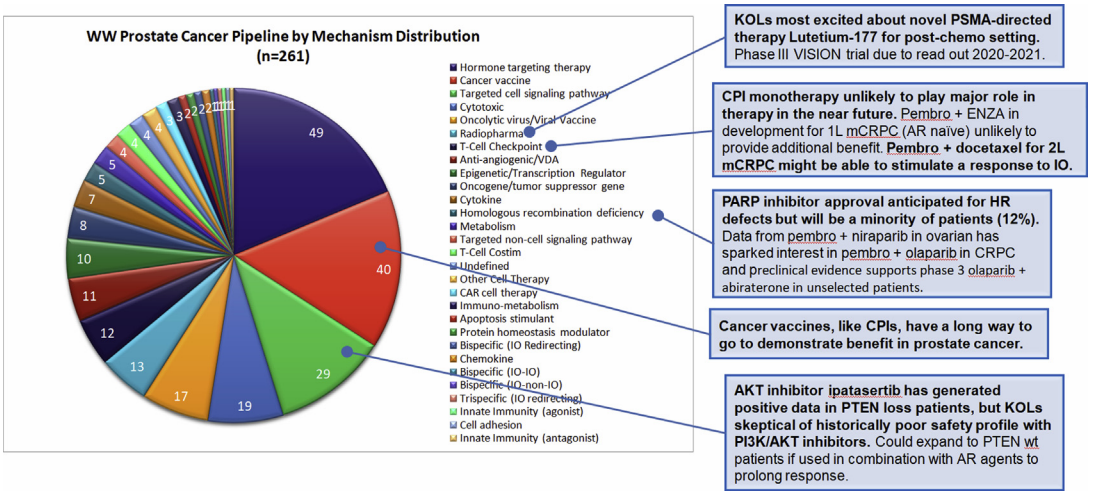


Fig. 14. Prostate cancer clinical stage pipeline. AR, androgen receptor; CPI, checkpoint inhibitors; CRPC, castration-resistant prostate cancer; KLOs, key opinion leaders; mCRPC, metastatic castration-resistant prostate cancer; PSMA, prostate-specific membrane antigen; VDA, vascular disrupting agent. (*From* Adis R&D Insight, Clarivate Analytics Cortellis, Cello Health BioConsulting (previously Defined Health) analysis and Primary Research.)

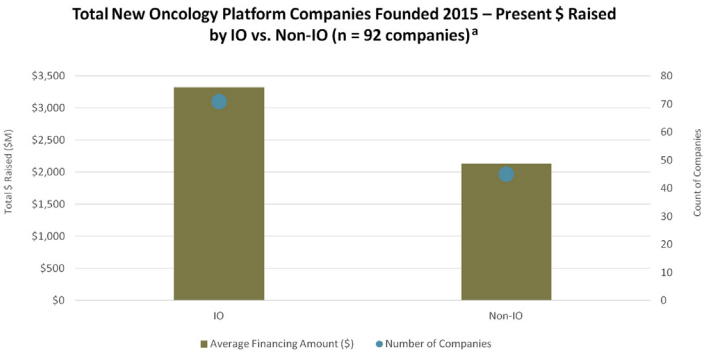


Fig. 15. Oncology company investments (indication agnostic). [a] Companies with platform(s) that are applicable to both IO or non IO approaches are double counted. Only venture funding data points were used to calculate the total amount raised. (*From* BCIQ, Cello Health BioConsulting (previously Defined Health) analysis.)

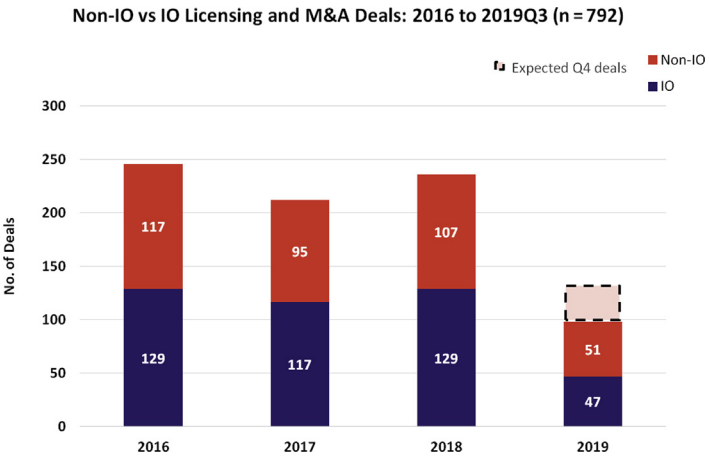


Fig. 16. IO deal making 2016 to quarter 3 of 2019. (*From* BCIQ, Cello Health BioConsulting (previously Defined Health) analysis.)

Top 10 Deals by Upfront Value ($M): 2018

Rank	Company	Deal Partner/ Product Source	Product(s)	Phase	Upfront[a]	Milestones	Total (Upfront + Milestones)
1	Celgene	Juno Therapeutics	Multiple	Phase 1/2	9,000	Undisclosed	9,000
2	GSK	Tesaro	Multiple	Marketed	5,100	Undisclosed	5,100
3	Sanofi	Ablynx N.V	Multiple	Registration	4,800	Undisclosed	4,800
4	Servier	Shire	Pegaspargase, Multiple	Marketed	2,400	Undisclosed	2,400
5	Novartis	Endocyte	Multiple	Registration	2,100	Undisclosed	2,100
6	Bristol-Myers Squibb	Nektar Therapeutics	NKTR-214	Phase 3	1,850	1,800	3,650
7	Eli Lilly	Armo Biosciences	Multiple	Phase 3	1,600	Undisclosed	1,600
8	Seattle Genetics	Cascadian Therapeutics	Multiple	Phase 3	614	Undisclosed	614
9	Johnson & Johnson	Argenx S.E	Cusatuzumab	Phase 2	500	1,300	1,800
10	Merck & Co.	Viralytics	Cavatak	Phase 2	371	Undisclosed	371

Top 10 Deals by Total Value ($M): 2018

Rank	Company	Deal Partner/ Product Source	Product(s)	Phase	Upfront[a]	Milestones	Total (Upfront + Milestones)
1	Celgene	Juno Therapeutics	Multiple	Phase 1/2	9,000	Undisclosed	9,000
2	Merck & Co.	Eisai	Lenvatinib mesylate	Marketed	300	4,385	5,785
3	GSK	Tesaro	Multiple	Marketed	5,100	Undisclosed	5,100
4	Genentech	Affimed N.V.	Multiple	NA	96	4,950	5,046
5	Sanofi	Ablynx N.V	Multiple	Registration	4,800	Undisclosed	4,800
6	Bristol-Myers Squibb	Nektar Therapeutics	NKTR-214	Phase 3	1,850	1,800	3,650
7	Gilead	Sangamo	Multiple	Preclinical	150	3,000	3,150
8	Allogene Therapeutics	Pfizer	UCART19	Phase 1	0	185	2,800
9	Shire	Servier	Pegaspargase, Multiple	Marketed	2,400	0	2,400
10	Novartis	Endocyte	Multiple	Registration	2,100	Undisclosed	2,100

Contains IO program

Fig. 17. Top deals in 2018 as grouped by IO and non IO. [a] Upfront includes upfront cash and upfront equity; NA (not applicable) = can include deals with multiple agents or portfolio where phase is not applicable. (*From* BCIQ, Evaluate Pharma, Cello Health BioConsulting (previously Defined Health) analysis.)

Top 10 Deals by Upfront Value ($M): 2019							
Rank	Company	Deal Partner/ Product Source	Product(s)	Phase	Upfront[a]	Milestones	Total (Upfront + Milestones)
1	BMS	Celgene	Multiple	NA	35,000	Undisclosed	74,000
2	Pfizer	Array BioPharma	Multiple	NA	11,400	Undisclosed	11,400
3	Eli Lilly	Loxo Oncology	Multiple	NA	7,234	Undisclosed	7,234
4	AstraZeneca	Daiichi Sankyo	Trastuzumab deruxtecan	Phase 3	1,350	5,550	6,900
5	Merck & Co.	Peloton Therapeutics	Multiple	NA	1,050	1,150	2,200
6	GSK	Merck KGaA	Bintrafusp alfa (M7824)	Phase 2	344	3,871	4,214
7	Merck & Co.	Immune Design	Multiple	NA	248	Undisclosed	248
8	Clinigen Group	Novartis AG	Proleukin, aldesleukin (Macrolin)	Marketed	180	30	210
9	Amgen	Nuevolution AB	Multiple	NA	167	Undisclosed	167
10	Aurobindo Pharma	Spectrum Pharmaceuticals	Multiple	NA	160	140	300

Top 10 Deals by Total Value ($M): 2019							
Rank	Company	Deal Partner/ Product Source	Product(s)	Phase	Upfront[a]	Milestones	Total (Upfront + Milestones)
1	BMS	Celgene	Multiple	NA	35,000	Undisclosed	74,000
2	Pfizer	Array BioPharma	Multiple	NA	11,400	Undisclosed	11,400
3	Eli Lilly	Loxo Oncology	Multiple	NA	7,234	Undisclosed	7,234
4	AstraZeneca	Daiichi Sankyo	Trastuzumab deruxtecan	Phase 3	1,350	5,550	6,900
5	GSK	Merck KGaA	Bintrafusp alfa (M7824)	Phase 2	344	3,871	4,214
6	Abpro Corporation	Chia Tai Tianqing Pharmaceutical	Multiple	NA	Undisclosed	Undisclosed	4,000
7	Gilead	Nurix Therapeutics	Multiple	NA	45	2,300	2,345
8	Merck	Peloton Therapeutics	Multiple	NA	1,050	1,150	2,200
9	Codiak BioSciences	Jazz Pharmaceuticals	Multiple	NA	56	Undisclosed	1,076
10	Cytovant Sciences	Medigene AG	Multiple	NA	10	1,000	1,010

Contains IO program

Fig. 18. Top deals in 2019 as grouped by IO and non IO. [a] Upfront includes upfront cash and upfront equity; NA (not applicable) = can include deals with multiple agents or portfolio where phase is not applicable. (*From* BCIQ, Evaluate Pharma, Cello Health BioConsulting (previously Defined Health) analysis.)

over the past 5 years, with roughly 50% more money raised and more companies funded for IO-centric platform companies than non-IO ones. Although these analyses are not specific to urologic cancers, but rather to oncology broadly, nevertheless the general conclusion seems to be that the appeal of immunotherapy within the health care ecosystem remains strong.

As shown in Fig. 16, IO deals actually slowed in 2019, with less than 50% of the prior year, raising the question of whether a spate of failures (IDO inhibitors, for example) has led to some maturing in understanding and a higher bar, or just fatigue in IO along with a renewed interest, perhaps owing to this fatigue, in non-IO options.

However, a drill down into the data reveals a somewhat more nuanced picture. Using the top deals, licensing or M&A, as a surrogate of industry interest, the years 2015 to 2018 displayed intense "IO frenzy" with the majority of the top deals as defined by total deal value (which includes upfront and milestones, plus any equity) or simply by the size of the upfront payments would be categorized as IO. Looking only at 2018, for example, in Fig. 17, it is clear the extent to which deals in the IO space commanded more real and prospective dollar value than non-IO deals.

However, using this same approach to look at 2019 (Fig. 18), one might conclude that perhaps some maturing of vision has begun, with a more balanced view of the need for diverse IO and non-IO approaches to tackle cancer. The apparent renewed interest in non-IO options reflects in part a return to precision medicine agents (eg, NTRK inhibitors from LOXO, for example). Many in the industry have observed that the intense focus in IO spurred by the clinical (and financial) performance of the CPIs ultimately led to a situation within the BioPharma and investor community where these successes overshadowed some important

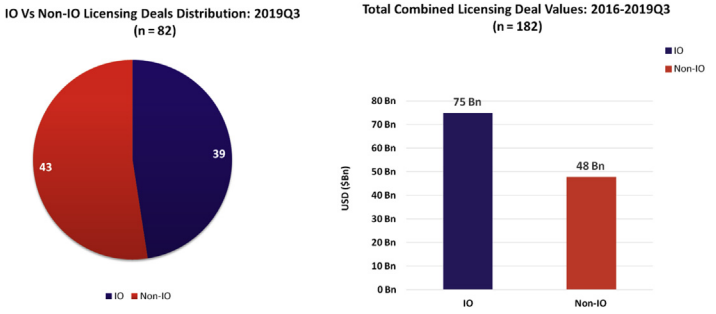


Fig. 19. Total licensing deals and value, 2016 to quarter 3 of 2019, by IO and non IO. *Note left graph = all counts include undisclosed and missing deal values, whereas the right graph excludes them. (*From* BCIQ, Cello Health BioConsulting (previously Defined Health) analysis.)

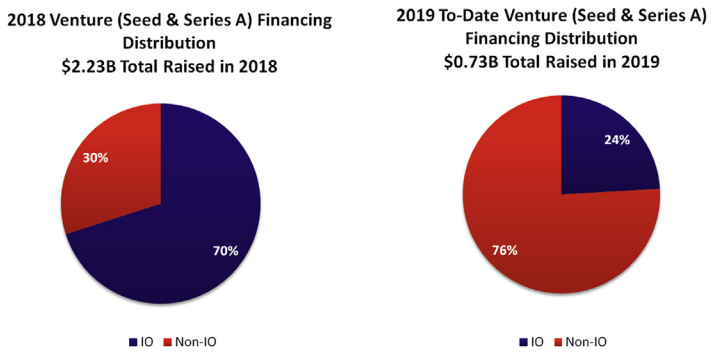


Fig. 20. Venture funding in oncology, seed and series A, 2016 to quarter 3 of 2019, by IO and non IO. (*From* BCIQ, Cello Health BioConsulting (previously Defined Health) analysis.)

limitations of the rush into the space, such that business strategy overruled translational science, leading to a number of clinical trial stumbles we have seen with novel MOAs attempting to follow in the footsteps of the CPIs.

Looking cumulatively from 2016 through the third quarter of 2019, one can see how the number of IO and non-IO deals were nearly equal, but the total deal value for IO was more than 50% greater than for non-IO deals (Fig. 19). This underscores the hope, and the hype, around immunotherapies being true paradigm changing therapies. However, as noted elsewhere in this article, there was a noticeable change from 2018 to 2019 in oncology funding and startups (series A and seed), essentially an inversion from being IO dominant in 2018 to being non-IO dominant in 2019, while at the same time far less monies were invested into oncology in 2019. Although certainly macro trends drove the overall lower investment in oncology newcos, the switchover from IO to non IO again highlights a potential realignment, what might be called a return to a more reasoned and balanced (in terms of MOAs) investing strategy (Fig. 20).

In conclusion, for all the successes that the CPIs have had over the past 9 years since their first approvals, and all the industry noise around partnerships and newcos in IO, it can seem at times that more of the talk is around what is not working in IO. The high-profile failure of the IDO inhibitors, along with underperformance or safety issues with other novel MOAs being combined with CPIs, has added a strain of skepticism to what some had long felt to be an overhyped space. Thinking of this rather as the maturing of the field, the issue remains as to how best to move novel IO programs forward. Certainty, a reemphasis on reasonable single-agent activity is a the top of correctives, but there is still more to be done in more fully interrogating the biology and doing the translational work around these novel targets and pathways, their role in combination with CPIs, and how best to position them for clinical development and for optimal patient benefit.

DISCLOSURE

CHBC works for many BioPharma companies developing immuno-oncology therapies on a project fee basis. Neither I nor the company has any financial stake in any of these clients.