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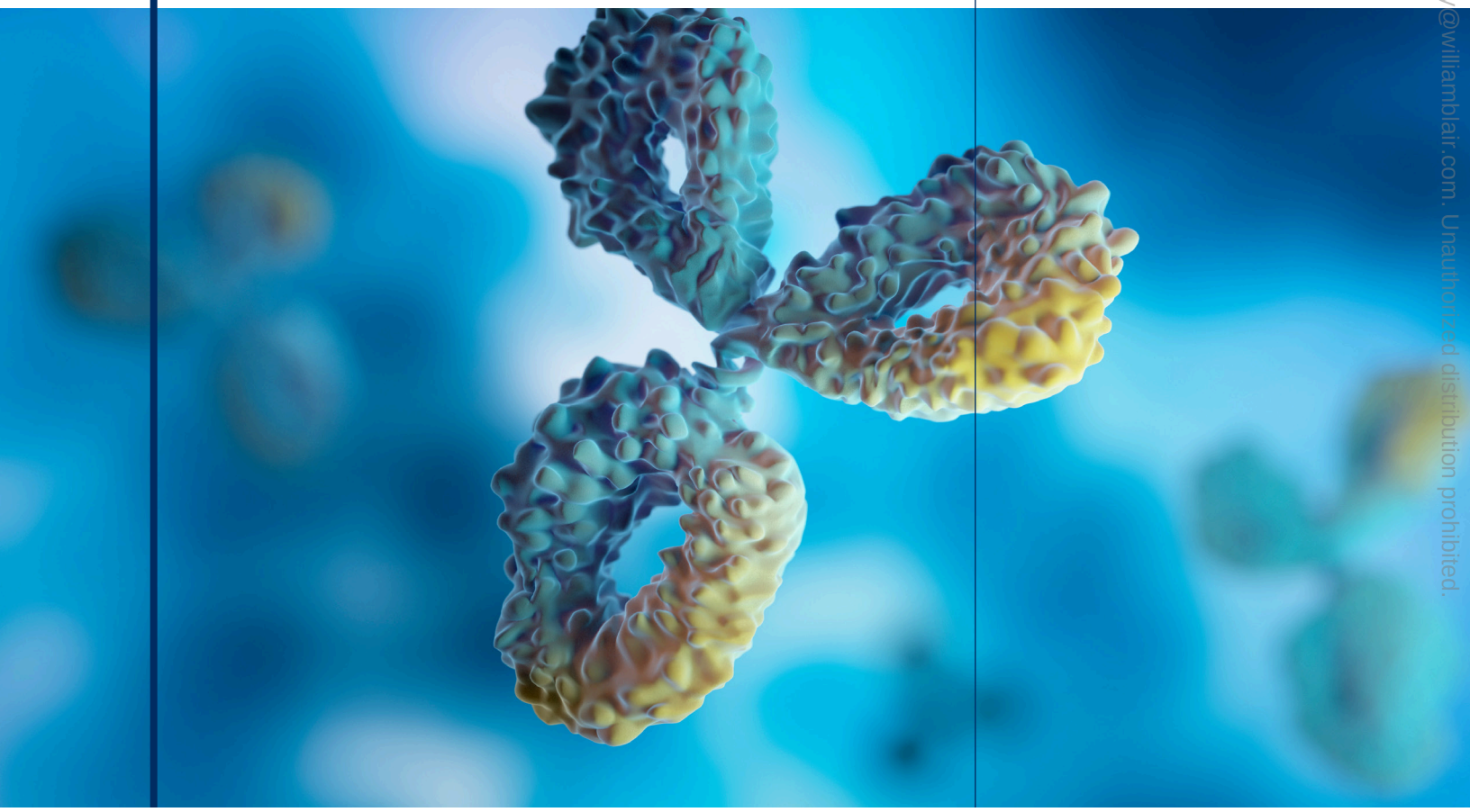
Getting Into (Bi)Specifics



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Executive Summary

In 2021, we published our first deep dive looking at key features of bispecific antibodies and the different platforms that build them. In our second issue on bispecifics, we took a deeper look at the effect of pharmacokinetics and drug exposure on safety and efficacy, with a focus on masking technologies and other novel bispecific approaches. Since that time, significant growth has occurred in the bispecific market, both in the number of approved bispecific therapies and in the scale of clinical research and targets and disease areas being evaluated. We believe this highlights the significant opportunities for novel bispecific therapies, particularly their ability to create novel or localized biology that cannot be achieved with other modalities.

In this issue of *Getting Into (Bi)Specifics*, we take a look at recent market trends and datasets with bispecific therapies, highlighting recent successes (and setbacks) in solid tumor indications, and how different approaches can impact the safety and efficacy of the therapy. Overall, we believe that growth of bispecific therapies will continue to outpace many other modalities, as more products reach commercialization and business development continues to expand, both in oncology and other disease settings. The success of T-cell engagers (TCEs) in solid tumors and continued improvements in cytokine release syndrome (CRS) management will drive greater adoption of this modality by physicians, including in the community settings. In particular, we focus on:

- Recent datasets with TCEs and how targeting CD3, CD28, and 4-1BB can impact the therapeutic profile but may be used in combination to drive greater antitumor durability. We look at specific instances where CD3, CD28, and/or 4-1BB TCEs have been investigated against the same antigen or indication, including recent data at ASH combining a CD20 TCE with CD28 or 4-1BB molecules to drive greater efficacy and durability;

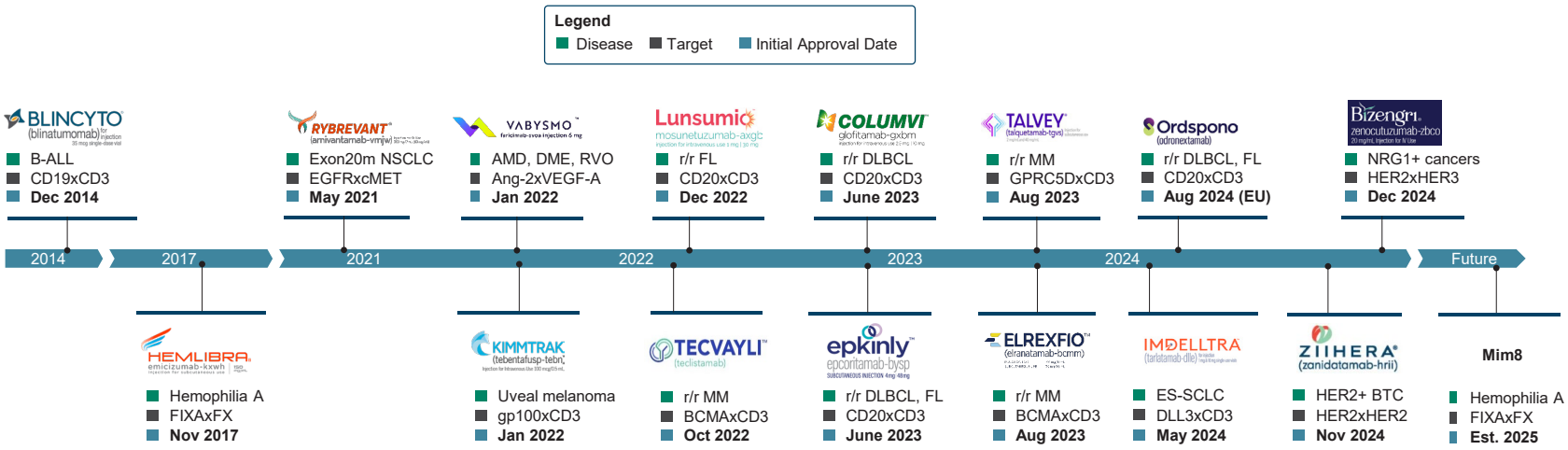
- The ups and downs of targeting dual "immuno-oncology" pathways (such as PD-L1x4-1BB) versus the recent surge of PD-L1xVEGF programs. While initial data with PD-L1xVEGF bispecifics has shown impressive responses and PFS, we still have some concerns on ability to drive meaningful survival benefit in global studies; and

- The growing trend of bispecifics in autoimmune indications, with modalities evaluating B-cell depletion and dual blockade of validated immune pathways. Building on the positive results of CD19 CAR-T and Blincyto treatment in autoimmune diseases and the VEGA trial in ulcerative colitis, business development in this area has been strong in 2024.

At the end of this report, we include updated tables looking at the landscapes for many popular bispecific targets and therapeutic indications.

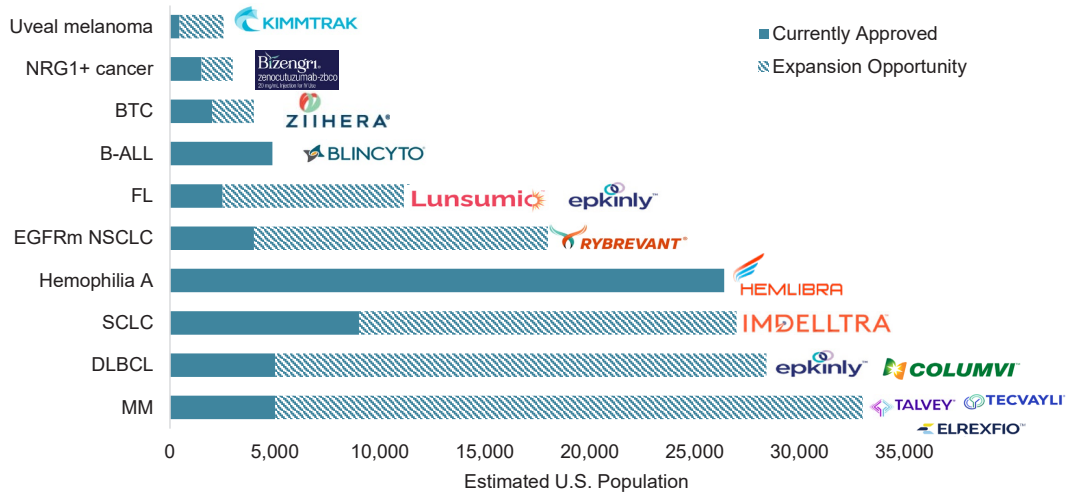
The number of approved bispecifics continues to increase, with 15 therapies now approved by the FDA or EMA, and one more with positive pivotal data likely to receive approval in the near term (exhibit 1). As bispecific therapies continue to move into earlier lines of therapy in approved settings and have breakthroughs into new indications, we see the market opportunity for this broad class of therapies growing significantly. As shown in exhibits 2 and 3, we attempt to summarize the number of patients with cancer (both solid tumors and hematologic malignancies) or hemophilia A in the United States annually who are currently eligible for bispecific therapies or have the potential to be eligible for those therapies that we believe have already shown compelling proof-of-concept data.

Exhibit 1
Approval Timeline for Bispecifics



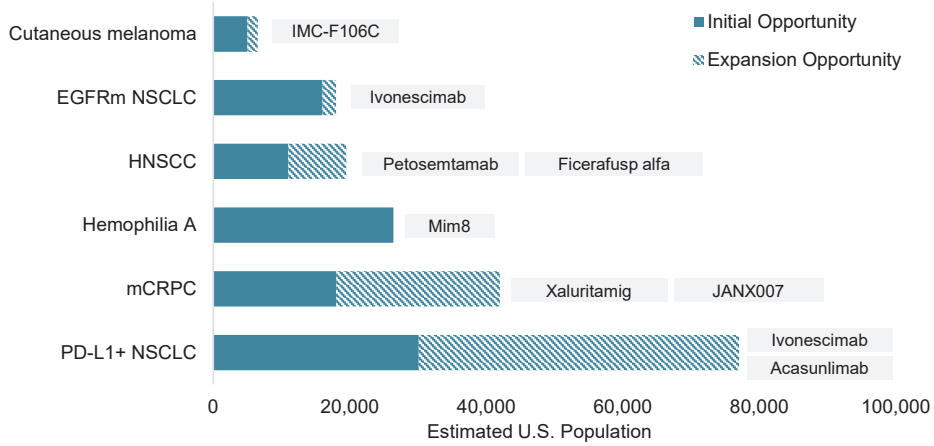
Future includes molecules with positive pivotal trial results
Sources: Company reports and William Blair Equity Research

Exhibit 2
Estimated Market Opportunity for Approved Bispecifics



Source: Company reports and William Blair Equity Research

Exhibit 3
Market Opportunity for Bispecifics in Development



Source: Company reports and William Blair Equity Research

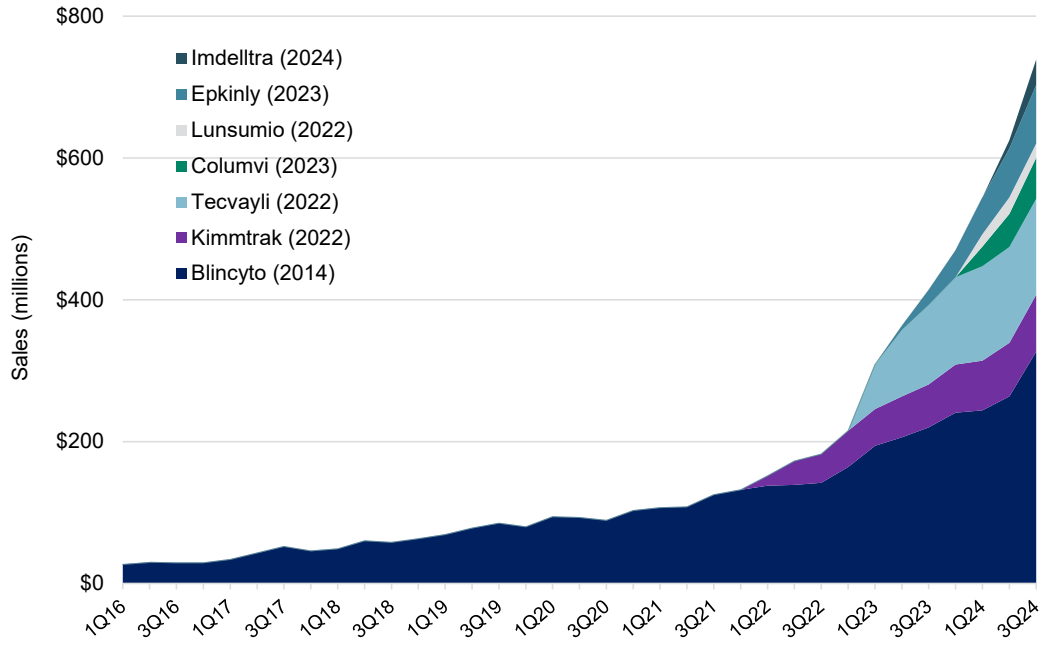
In looking at the market opportunity for bispecific therapies, we believe the class as a whole is still in its infancy with potential for significant expansion into larger market opportunities in the coming years, both from advancement into earlier lines of treatment and success of novel programs in ongoing pivotal trials. Currently, bispecific therapies generate quarterly sales of over $650 million in oncology indications and over $2.5 billion in non-oncology indications (based on publicly disclosed numbers, see exhibits 4 and 5). While there are many assumptions that go into an analysis of expansion opportunities for this broad class, we included estimates on targetable population for approved assets, those that are in ongoing Phase III trials, or those that we believe have shown

meaningful proof of concept and are likely to advance to pivotal trials (namely xaluritamig and JANX007). Expansion opportunities represent potential market expansion if the bispecific therapies are successful in earlier lines of treatment within the same indication.

Notably we have not included PD-1xCTLA-4 bispecifics in these charts, namely because we are not convinced the safety profile will be advantageous or efficacy will be greater than PD-1 plus CTLA-4 monoclonal antibodies. Similarly for AstraZeneca's rilvegostomig (PD-1xTIGIT) bispecific, which has generated some compelling data but is overshadowed by the lack of clinical success for TIGIT monoclonal antibodies.

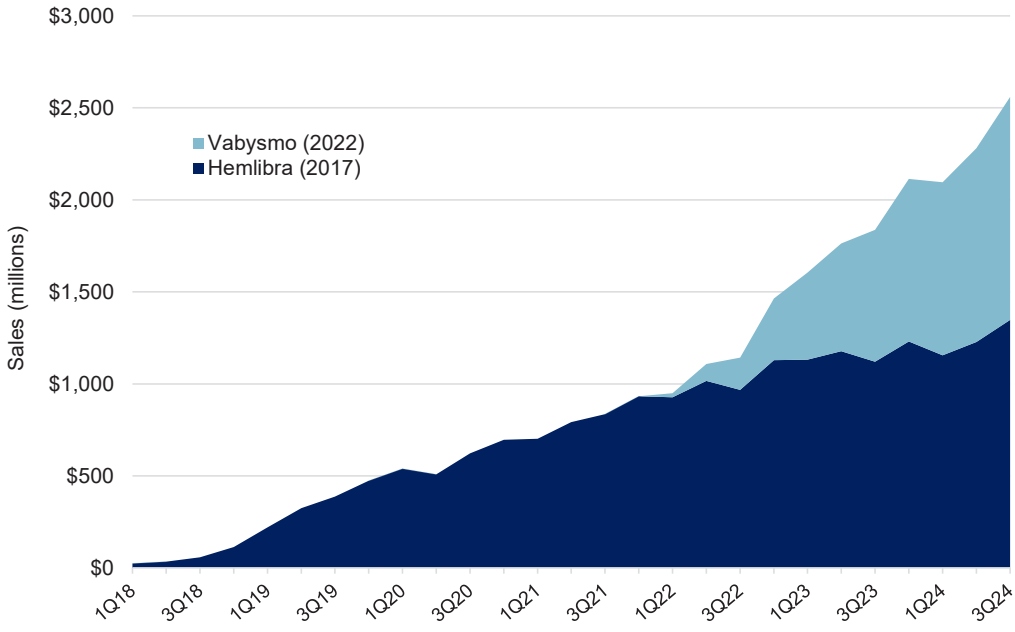
For sales of bispecifics approved in oncology, we note Johnson & Johnson has not broken out individual sales of Rybrevant or Talvey, although management commentary suggests these will be reported individually in future earnings releases.

Exhibit 4
Quarterly Commercial Sales of Approved Bispecific Therapies in Oncology Indications



Source: Company Reports and William Blair Equity Research

Exhibit 5
Quarterly Commercial Sales of Approved Bispecific Therapies in Non-Oncology Indications



Source: Company Reports and William Blair Equity Research

As bispecific therapies continue to expand into broader patient populations, we believe this broad class will continue to generate potential for business development deals between biotech companies and large biopharma. As shown in exhibit 6, business development for bispecifics continues to be active over the past two years, and we particularly call out a recent trend toward deals in the autoimmune space, with 5 of the last 10 deals including immunology as a potential indication.

Exhibit 6
Select Recent Bispecific and Multispecific Antibody Business Development

Date Announced	Lead Asset/Program	Acquirer	Target	Upfront Payment	Therapeutic Indication	Stage of Asset	Comments
17-Nov-22	Development collaboration with Probody and Veloci-Bi platforms	Regeneron	CytomX	$30M	Oncology	Discovery	Up to $2B in milestones
6-Dec-22	Ivonescimab (PD-1xVEGF)	Summit	Akeso	$500M	Oncology	Phase III	License agreement for ivonescimab rights in U.S., Canada, Europe, and Japan
4-Jan-23	Preclinical bispecific TCE	GSK	WuXi	$40M	Oncology	Preclinical	License agreement for a CD3 bispecific TCE, option for up to three other TCEs; up to $1.46B
5-Jan-23	Target identification using Caris Discovery platform	Xencor	Caris Life Sciences	ND	Oncology	Discovery	$187M in potential milestones; royalties on net sales
2-Feb-23	Trispecific T and NK cell engager (CD3x5T4xNKG2A)	Purple Biotech	Immunorizon	$7M	Oncology	Preclinical	Acquisition of trispecific antibody portfolio; up to $94M in milestones
14-Feb-23	CLN-418 (B7-H4x4-1BB)	Cullinan	Harbour Biomed	$25M	Oncology	Phase I	License agreement for U.S. rights; up to $563M in payments; royalties
5-Jul-23	Next-generation multispecific antibodies	Takeda	F-Star	ND	Oncology	Preclinical	Up to $1B in milestones
15-Aug-23	Multifunctional biologics for oncology and inflammation	Gilead Sciences	Tentarix	$66M	Oncology and inflammation	Discovery	Discovery collaboration for three programs; option to acquire for up to $240M
11-Sep-23	mRNA-enabled TCR bispecifics	Moderna	Immatics	$120M	Oncology	Preclinical	R&D collaboration combining mRNA and TCR technologies; up to $1.7B
12-Oct-23	FIT-Ig platform	AlmirAll	EpimAb Biotherapeutics	ND	Dermatology	Discovery	License agreement for up to three bispecific antibodies; up to $210M
6-Nov-23	PM8002 (PD-L1xVEGF)	BioNTech	Biotheus	$55M	NSCLC	Phase II	License agreement for PM8003 development excluding China; up to $1B in payments/royalties
27-Dec-23	Bispecific macrophage engager platform; ES019 (PD-L1xSIRPα)	Astellas	Elpiscience	$37M	Oncology	Preclinical	Research collaboration for ES019 and a second program; up to $1.7B
8-Jan-24	HPN328 (DLL3xCD3)	Merck	Harpoon	$680M	SCLC/NECs	Phase I/II	Company acquisition
13-Feb-24	Bifunctional fusion proteins in autoimmune and inflammatory disease	Ono Pharma	Shattuck Labs	ND	Immunology	Discovery	Two targets in autoimmune/inflammatory disease; up to $227 million in payments/royalties
22-Feb-24	Multispecific biologics in oncology and immunology	AbbVie	Tentarix	$64M	Oncology and immunology	Discovery	Discovery collaboration for two programs; option to acquire
6-Mar-24	Triclonics trispecific T-cell engager platform	Gilead Sciences	Merus N.V.	$81M	Oncology	Research	Two programs with the option for a third; up to $1.5 billion in payments and royalties
16-May-24	PX128 (IL-13xTSLP)	Johnson & Johnson	Proteologix	$850M	Atopic dermatitis	Phase I	Company acquisition
22-May-24	Anti-PD-1/cytokine bispecific, and expansion of an existing collaboration into CVD	Boehringer Ingelheim	OSE Immunotherapeutics	€13.5M	Oncology	Preclinical	Potential €17.5M near-term milestone for bispecific, up to €1.1B in payments
28-May-24	NM26 (IL-4RαxIL-31)	Johnson & Johnson	Yellow Jersey Therapeutics	$1.25B	Atopic dermatitis	Phase II	Acquisition of Yellow Jersey (a subsidiary of Numab Therapeutics) for the NM26 program; all-cash transaction
29-May-24	Restoret (EYE103; LRP5xFZD4)	Merck	EyeBio	$1.3B	Ophthalmology	Phase I/II	Acquisition of clinical and preclinical programs; up to $1.7B additional payments
7-Jun-24	Two candidates from TriSTAR platform	Ipsen	Marengo	ND	Cold tumors	Preclinical	Up to $1.2B in payments and royalties
17-Jun-24	IMB-101 (OX40LxTNF)	Navigator Medicines	IMBiologics	$20M	Autoimmune	Phase I	Ex-Asia license agreement for IMB-101 and IMB-102 (OX40L mAb); up to $925M in payments
10-Jul-24	CT-95 (MSLNxCD3)	Context Therapeutics	Link Immunotherapeutics	ND	Solid tumors	Preclinical	Asset purchase agreement for TCE CT-95
24-Jul-24	Anti-myeloid bispecific antibody platform	Novartis	Dren Bio	$150M	Hematologic malignancies & autoimmune	Phase I/II	Discovery and development collaboration; up to $2.85B in payments
1-Aug-24	IMM2510 (PD-L1xVEGF) IMM27M (CTLA-4 Ab)	Instil Bio	ImmuneOnco	$50M	Solid tumors, NSCLC	Phase I/II	Ex-China rights to IMM2510 and IMM27M; payments up to >$2B
1-Aug-24	SAR446309 (AMX-818; HER2xCD3) SAR446329 (AMX-500; PSMAxCD3) SAR446368 (AMX-525; EGFRxCD3)	Vir Biotech	Sanofi/Amunix	$100M	Solid tumors	Phase I	Rights for three masked TCEs and use of protease-cleavable masking platform. Up to $1.9B additional payments
5-Aug-24	GB261 CD20xCD3)	TRC 2004	Genor Biopharma	ND	Autoimmune disease	Phase I/II (in oncology)	Worldwide license (except China, HK, TW, Macau); up to $443 million
6-Aug-24	MK-6070 (HPN328; DLL3xCD3)	Daichii Sankyo	Merck	$170M	SCLC	Phase I/II	Expansion of existing co-development and co-commercialization agreement for 3 Dxd ADCs to include MK-6070. Merck to retain exclusive rights in Japan.
9-Aug-24	CN201 (CD19xCD3)	Merck	Curon	$700M	Oncology and autoimmune	Phase I/II	Asset acquisition; up to $600M in payments
4-Sep-24	EMB-06 (BCMAxCD3)	Vignette Bio	EpimAb Biotherapeutics	$60M	Autoimmune	Phase I/II	Ex-Greater China rights to EMB-06 development and commercialization; up to $575M in payments
9-Sep-24	GB261 CD20xCD3) EMB-06 (BCMAxCD3)	Candid Therapeutics	Vignette Bio and TRC 2004	ND	Autoimmune	Phase I/II	Three-way merger to acquire Vignette Bio and TRC 2004 for TCEs GB261 and EMB-06 for development in autoimmune disease. $370M capital raise in conjunction with the merger.
27-Sep-24	BA3362 (Nectin-4xCD3)	Context Therapeutics	BioAlta	$15M	Solid tumors	Preclinical	Worldwide development and commercialization license; up to $118.5M in payments
29-Oct-24	CMG1A46 (CD19xCD20xCD3)	GSK	Chimagen	$300M	Autoimmune (lupus)	Phase I	Asset acquisition; up to $550M in payments
7-Nov-24	LBL-051 (CD19xBCMAxCD3)	Oblenio Bio (Aditum Bio)	Leads Biolabs	$35M	Autoimmune		Company formation around license agreement for worldwide development and commercialization of LBL-051; up to $579M in payments
13-Nov-24	BNT327 (PM8002; PD-L1xVEGF)	BioNTech	Biotheus	$800M	Solid tumors	Phase III	Company acquisition; up to $150 in payments
14-Nov-24	LM-299 (PD-1xVEGF)	Merck	LaNova	$588M	Oncology	Phase I	Global development and commercialization license for LM-299; up to $2.7B in payments
3-Dec-24	BMX-502 (GPC3 MAIT engager)	Ipsen	Biomunex	ND	Solid tumors	Preclinical	Global license agreement for BMX-502; up to $610M in upfront and milestone payments

Sources: Company reports

Which T-Cell Redirector to Choose: CD3, 4-1BB, or CD28?

The first bispecific approved in the United States, Blincyto, was designed to bind to CD19 on leukemic cells and CD3 on T cells, forcing T-cell-mediated cytolysis of the leukemic cells. In addition, 8 other approved bispecifics (out of a total of 15 FDA- or EMA-approved bispecifics) use a CD3 binding domain. Therefore, this T-cell target has the most clinical experience to date and the most extensive development pipeline. This is why most people in the field associate bispecifics with those used to redirect T cells to tumor associated antigens (TAAs). However, many companies continue to explore the use of other T-cell targets, most notably CD28 and 4-1BB (also known as CD137). Divergent profiles are beginning to emerge for these novel therapeutics based on the T-cell target utilized, as summarized in exhibit 7 and discussed below.

Exhibit 7
Comparison of Pharmacokinetic Modifications of T-Cell Engager Bispecifics

	CD3	4-1BB	CD28
Function	T-cell activation and signal transduction following TCR binding	Co-stimulatory signal for T-cell proliferation, survival and cytotoxicity	Co-stimulatory signal for full T-cell activation and survival
Ligand	TCR Binding to pMHC results in phosphorylation of the CD3 ITAM domain	Binds to 4-1BBL on APCs and other cells	Binds CD80 (B7.1) and CD86 (B7.2) ligands on APCs
Signaling Pathway?	ITAM phosphorylation leads to downstream activation of pathways through ZAP70 including ERK, JNK, NF-κB and NFAT	4-1BB/4-1BBL interaction induces signaling through TRAF1/2 to activate NF-κB, AKT, p38 MAPK, and ERK pathways	Enhances TCR/CD3 complex and activates downstream pathways including PI3K and NF-κB
Number of Clinical Programs	>100	~26	~9
FDA Approvals	Blincyto (CD19xCD3); 2014 Kimmtrak (gp100xCD3); 2022 Tecvayli (BCMAxCD3); 2022 Lunsumio (CD20xCD3); 2022 Epkinly (CD20xCD3); 2023 Columvi (CD20xCD3); 2023 Talvey (GPRC5DxCD3); 2023 Elrexfio (BCMAxCD3); 2023 Imdelltra (DLL3xCD3); 2024	None	None
Dosing Constraints	Need for step dosing	Dosing 'sweet spot' to maximize 4-1BB agonism Dosing interval to prevent T-cell exhaustion	Potential need for step dosing
Safety Concerns	CRS ICANS	Hepatotoxicity HLH	CRS HLH

Abbreviations: CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; HLH, hemophagocytic lymphohistiocytosis; APCs, antigen presenting cells
Source: Company Reports and William Blair Equity Research

CD3

CD3 Remains the Most Clinically Validated, but Still Presents Challenges in Balancing Therapeutic Index

CD3 is among the most common targets used in bispecific therapies, leading to nine FDA-approved bispecific franchises to date, with many others in late-stage development. CD3 is a component of the T-cell receptor complex (TCR), which is present on all T cells and plays a pivotal role in T-cell activation and signaling. Bispecific antibodies targeting CD3 are designed to simultaneously bind TAA on cancer cells and CD3 on T cells. This dual binding in close proximity results in activation of the T cell and cytotoxicity against the cell type expressing the TAA and cytokine secretion.

One advantage of targeting CD3 is its universal expression on all T cells. This contrasts with other targets such as PD-1 or 4-1BB, which are selectively expressed on subsets of T cells. This widespread expression allows for bispecific-targeting CD3 to activate a broad range of T cells regardless of TCR target, reducing the need for an underlying T-cell immune response against the tumor cells.

However, there are drawbacks of CD3 targeting, most notably the release of inflammatory cytokines such as TNF-α, IFN-γ, and IL-6, which poses significant risks for CRS in patients. Consequently, all currently approved CD3 bispecifics have black box warnings for CRS and step-up dosing protocols to mitigate this risk. In addition, CD3 bispecifics targeting TAAs with broad expression not limited to just tumors can lead to on-target, off-tumor effects in healthy tissues.

Furthermore, the lack of costimulatory signaling (often termed signal 2) could result in rapid exhaustion or anergy of the activated T cells, which may limit the durability of the antitumor immune response. Lastly, CD3 bispecifics could potentially activate regulatory T cells (Tregs) within the tumor microenvironment given Tregs also express CD3. While this is a theoretical risk, we do not believe it has played out clinically, given the success of multiple programs to date.

Challenges with CD3-targeting in solid tumors

While CD3 bispecific antibodies have had success in hematological malignancies such as refractory B-cell lymphomas, lymphoblastic leukemias, and multiple myeloma, translating the success of CD3 bispecifics to solid tumors has proved more challenging for multiple reasons.

In contrast to hematologic malignancies, in which the lymph node tissue and bone marrow are often easily accessed by circulating T cells, solid malignancies often lack sufficient T-cell infiltration, creating an immunosuppressive tumor microenvironment (TME), especially in phenotypically "cold" tumors, which exhibit minimal immune cell presence. In addition, the on-target, off-tumor activity of CD3 targeting is less forgiving for solid tumor TAAs versus hematologic TAAs. In hematologic malignancies, depletion of B cells, plasma cells, or certain myeloid cells is reversible as long as hematopoietic stem cells are not targeted, which allows for replenishment of these blood cells. In contrast, solid tumor TAAs are often expressed on healthy organ tissue, which can cause immune-related organ damage. In addition, there are numerous factors within the TME that can hamper the efficacy of infiltrating T cells. Immunosuppressive cells in the TME produce factors like TGF-β, IL-10, indoleamine 2,3-dioxygenase (IDO), and arginase, which hinder T-cell metabolism and activation, for example. In addition, the continuous stimulation of T cells through CD3 targeting, particularly without the presence of a costimulatory second signal, can potentially lead to T-cell exhaustion and loss of T-cell efficacy.

To date, there have only been two CD3-targeting bispecific therapies approved for the treatment of solid tumors. Immunocore's Kimmtrak (gp100xCD3) was approved in 2022 for the treatment of HLA-A-A*201-positive uveal melanoma patients. Gp100 (also known as Pmel17) is a TAA highly expressed in melanocytes. In May 2024, Amgen's Imdelltra (DLL3xCD3) was approved for the treatment of extensive-stage small-cell lung cancer (ES-SCLC) with disease progression on or after

platinum-based chemotherapy. DLL3 is overexpressed in roughly 85% of SCLC tumors, and NEPC (neuroendocrine prostate cancer) and other NENs (neuroendocrine neoplasms) also have high expression levels where initial signs of activity have been observed for DLL3xCD3 TCEs.

At the end of this report, we provide additional tables outlining the CD3 bispecific landscape and clinical data reported to date across different indications. Recent updates with CD3-based TCEs that we believe demonstrated proof of concept or intriguing early signals include: Amgen's xaluritamig (STEAP1xCD3) and Janux's JANX007 (PSMAxCD3) in prostate cancer; Immunocore's brenetafusp (PRAMExCD3) and Immatics IMA402 (PRAMExCD3) in cutaneous melanoma; and I-Mab's IBI389 (CLDN18.2xCD3) and CytomX's CX-904 (EGFRxCD3) in pancreatic cancer.

Overall, CD3-based bispecifics have shown:

- Clear efficacy across hematologic malignancies with increasing success in solid tumors;
- A requirement for relatively "clean" TAAs, particularly in solid tumors, to avoid on-target, off-tumor toxicity, which can be mitigated with tumor-activated molecules, such as Janux's TRAC-Tr platform or CytomX's Probody platform;
- Step-up dosing and pre-medication can reduce CRS, but balancing efficacy with safety seems to require meaningful dose exploration with each novel program. We note that CRS risk, including the need for hospitalization during step-up dosing, remains a hindrance for community adoption of CD3-based TCEs, and overutilization of dexamethasone to treat low-grade CRS could have a negative impact on antitumor immunity, as suggested by recent update with JANX007 in mCRPC; and
- Emerging signs of combination ability with other approved agents, which could allow TCEs to move into earlier lines of treatment. It is unclear whether combinations with PD-(L)1 antibodies or other immune-targeted mechanisms will provide greater benefit or additive toxicities.

Adding "Signal 2" With Costimulation Target Has Potential to Improve Efficacy
As mentioned previously, engagement of CD3 and TCR complex provides the first signal necessary for T-cell activation. However, for full T-cell activation, a second costimulatory signal is required. This signal is antigen nonspecific and is provided by costimulatory molecules on APCs, which interact with specific costimulatory receptors on T cells. It has been shown that in the absence of this costimulatory signal, T cells may become anergic (unresponsive), undergo apoptosis, or acquire immune tolerance. While multiple costimulatory receptors have been identified, CD28 and 4-1BB have emerged as key targets in the development of therapeutic agonists.

As discussed below, while costimulatory agonist antibodies have been evaluated as monoclonal antibodies, the toxicity from overactivation of the immune system has significantly hampered development. Therefore, using a bispecific approach has been hypothesized to potentially limit the activation to only tumor-specific T cells within the tumor microenvironment, improving the therapeutic window of the therapies.

Adding CD28 Versus 4-1BB in Combination With CD20xCD3: Initial Case Study in Lymphoma
At the American Society of Hematology (ASH) meeting in 2024, Roche provided the first clinical data to our knowledge that looked at combining a CD3-based TCE against one TAA (Columvi; CD20xCD3 bispecific) with either a CD28- or 4-1BB-based TCE against a second TAA. Given Columvi is already approved in patients with relapsed or refractory (r/r) B-cell non-Hodgkin lymphoma (B-NHL), this provides a baseline dataset to compare the combination studies with to determine if greater efficacy or durability of responses can be achieved by providing either CD28 or 4-1BB costimulation.

Roche presented updated data for its novel costimulatory bispecifics RO7443904 (CD19xCD28) and englumafusp alfa (CD19x4-1BB). The presentation with englumafusp alfa was a follow-up to data previously presented at the 2024 European Hematology Association Congress in June, with longer follow-up and additional patients. Englumafusp alfa is a fusion protein combining 4-1BB ligand with a binder to CD19, with an Fc domain for improved half-life. Based on preclinical data, Roche did not expect englumafusp alfa to have single agent activity, and therefore the molecule was solely developed in combination with Columvi to provide costimulatory signaling and potentially enhance and prolong T-cell activity. The trial evaluated the approved step-up dose regimen of Columvi with the addition of englumafusp alfa during either cycle 1 or cycle 2, with the cycle 2 schedule selected for additional development.

The combination of englumafusp alfa plus Columvi resulted in greater expansion of activated and effector memory T-cells than Columvi monotherapy, and trends toward improved efficacy over the pivotal study of Columvi monotherapy (see exhibit 8). The efficacy was particularly strong in patients who were naive to prior CAR-T cell, with a 65.9% complete metabolic response rate (n=41), which compares favorably to a 42% CMR rate in the pivotal Columvi trial for CAR-T naive patients. The durability of responses also looks very encouraging, with a 25.9-month median duration of response for all patients and 32 months for CAR-T naive patients. The addition of englumafusp alfa does not appear to add any meaningful increase in adverse events, with rates of CRS coming in below the pivotal data with Columvi monotherapy.

As has been commonly observed with 4-1BB agonists, the dose escalation of englumafusp alfa resulted in a bell-shaped pharmacodynamic response, with doses in the middle-range of the dose escalation resulting in the greatest reduction in terminally differentiated T-cells and soluble CD25, markers of T-cell exhaustion. Therefore, these doses in the middle of the range will be taken forward into further development.

RO7443904 is being evaluated in a Phase I study in combination with Columvi in patients with r/r B-cell lymphomas. Notably, according to the clinical trial listing the study has been terminated due to portfolio realignment, so it is unclear what the next steps are for the molecule. Overall, the efficacy in patients with aggressive NHL looked relatively in line with Columvi monotherapy, with a 42.4% complete response rate across all patients and a 38.9% complete response rate in CAR-T naive patients. While the indolent lymphoma data does look particularly strong, with a 90% complete response rate and all patients still in response as of the cut-off date, the subset only included 19 patients, so additional patients may be needed to assess the profile in indolent lymphomas. The combination with RO7443904 did result in increased T-cell proliferation and expansion of effector memory over central memory T-cells, and a relatively similar tolerability profile to Columvi monotherapy.

Although some intriguing pharmacodynamic markers were observed with RO7443904 treatment (and included a bell-shaped relationship between dose and pharmacodynamic biomarkers), the efficacy in aggressive NHL patients appears similar to historical data with Columvi monotherapy, and therefore it appears additional development of englumafusp alfa is being prioritized at this time. Overall, it is unclear if 4-1BB costimulation with a bispecific is the optimal partner with CD3-based T-cell engagers, but the results with Columvi combinations do provide interesting data points and one of the few settings where different costimulatory bispecifics have been studied in the same indication.

Exhibit 8
Pivotal Results in LBCL With CD20xCD3 TCEs

	Columvi	Columvi + Englumafusp Alfa (CD19x4-1BBL)	Columvi + RO7443904 (CD19xCD28)
Phase	Phase II (NCT03075696)	Phase I/II (NCT04077723)	Phase I/II (NCT05219513)
Dose	C1 step up: D1 1000 mg Gazyva, D8 2.5 mg glofit., D15 10 mg glofit. Max. 12 cycles: 30 mg Q3W *median treatment cycles: 5 (1-13)*	C1 step up: D-7-4 1000mg Gazyva, D1 2.5 mg Columvi, D8 10 mg Columvi, C2D1: 30 mg Columvi C2D8: Dose Escalation of Englumafusp Alfa C3+: 30mg Columvi + Englumafusp Alfa	C1 step up: D-7-4 1000mg Gazyva, D1 2.5 mg Columvi, D8 10 mg Columvi, C2D1: 30 mg Columvi C2D8: Dose Escalation of RO7443904 C3+: 30mg Columvi + RO7443904
Enrollment	154 patients	83 patients aggressive NHL	33 patients aggressive NHL
Patient Characteristics	Median age: 66 ECOG 0: 45% Ann Arbor I/II/III/IV: 7%/16%/20%/55% DLBCL: 71%, tFL: 18%, HGBCL: 7%, PMBCL: 4% Bulky disease (>6cm): 53% Median prior lines: 3 (2-7) ≥3 prior lines: 61% Prior CAR-T: 33% CAR-T refractory: 30% Prior ASCT: 18% Refractory to last therapy: 86% Primary refractory: 58% Refractory to prior CD20: 83%	Median age: 63 Ann Arbor I/II/III/IV: 8%/22%/18%/52% DLBCL: 72% Transformed FL 22% Gr3B FL: 2.4% Bulky disease (>6cm): 38.6% Median prior lines: 3 (1-8) ≥2 prior lines: 84% Prior CAR-T: 50.6% CAR-T progression <6 months: 44.6% Refractory to last therapy: 78.3% Primary refractory: 54.2% Refractory to prior CD20: 80.7%	Median age: 66 ECOG 0: 60.6% Ann Arbor I/II/III/IV: 0%/6.5%/16.1%/77.4% DLBCL: 51.5% Transformed FL: 21.2% Bulky disease (>6cm): 30.3% Median prior lines: 3 (2-7) Prior CAR-T: 45% CAR-T progression <6 months: 73.3% Refractory to last therapy: 72.7% Primary refractory: 48.5% Refractory to prior CD20: 84.8%
ORR	51.6% CR: 39.4%	68.6% CR: 56.6% CAR-T Naïve CR: 65.9%	63.6% CR: 42.4% CAR-T Naïve CR: 38.9%
Median Duration of Response	18.4 months CR: 80% in response at cut off	25.9 months CAR-T Naïve: 32 months	57% Still in Response
Landmark Duration of Response	12 month: 63.6% CR 12 month: 77.6%		
Median PFS	4.9 months	9.9 months	5.4 months
Median OS	11.5 months	20.4 months	
Landmark OS	12 month: 49.8%	12 month: 61.1% 18 month: 51.9%	
All Grade CRS	64.0%	50.0%	61%
Grade ≥3 CRS	4.0%	1.5%	6%
Supportive Measures for CRS	Tocilizumab: 32% Steroids: 28%		
Other Toxicities (Grade ≥3)	Neutropenia: 37.7% (26.6%) Anemia: 30.5% Thrombocytopenia: 24.7% Pyrexia: 18.2% Hypophosphatemia: 17.5% Infections: 38.3% (14.9%) ICANS: 7.8% (2.6%)	Neutropenia: 41% Thrombocytopenia: 32.5% Hepatic Related: 19.3% Infections: 69.9%	Neutropenia: 24.2% Thrombocytopenia: 27.3%
Grade 5 Events	6% COVID: n=5, Sepsis: n=2, Delirium: n=1	2%	0%
Discontinuation	Any: 9.1% Treatment-related: 3.2%	2.4%	9.1%
Reference	ASCO 2022/ Dickinson et al., 2022. *NEJM*	ASH 2024	ASH 2024

NR = not reported; DLBCL = diffuse large B cell lymphoma; tFL = transformed follicular lymphoma; HGBCL = high-grade B cell lymphoma; PMBCL = primary mediastinal B cell lymphoma; ICANS = immune effector cell-associates neurotoxicity syndrome

Sources: Sources are shown in the body of the table

4-1BB

Intriguing Early Signals Seen With 4-1BB Bispecifics, but Questions Remain on Best Use-Case and Combination Strategy

In contrast to CD28, which is constitutively expressed, 4-1BB expression on T cells is generally considered to be transient and upregulated following TCR-mediated activation. Also known as CD137 or TNFRSF9, 4-1BB is a costimulatory molecule that belongs to the tumor necrosis factor receptor (TNFR) superfamily and is expressed on the surface of multiple immune cell types, including activated T-lymphocytes, NK cells, and dendritic cells. Binding of 4-1BB to its ligand 4-1BBL on APCs triggers a potent costimulatory signal to T cells.

While CRS appears to be less of a concern with 4-1BB targeting, there has been difficulty in reaching the optimal balance of antitumor activity and safety. Bristol Myers' urelumab (BMS-663513) was the first 4-1BB agonistic monoclonal antibody to enter the clinic in 2005. Urelumab showed dose-dependent and dose-limiting hepatoxicity, prompting investigators to discontinue study enrollment. Subsequent studies found the maximum tolerable dose of urelumab to be low at 0.1 mg/kg Q3W, which was subsequently studied in combination with cetuximab and Opdivo but showed limited additive antitumor activity. In contrast, Pfizer's utomilumab (PF-05082566), which entered clinical studies in 2011, showed a more favorable safety profile; utomilumab could be dosed up to 10 mg/kg Q4W without hepatoxicity. However, utomilumab showed limited efficacy, particularly in patients progressing on prior checkpoint inhibitor therapy. Subsequent work has shown utomilumab to be a less potent agonist of 4-1BB than urelumab; however, evidence has suggested that the activity of 4-1BB antibodies may depend more on Fc-mediated crosslinking and epitope binding rather than affinity for ligand binding (Ho et al., Mol Cancer Ther 2020). This could also play a role in the difference between the molecules, given urelumab is an IgG4 antibody, whereas utomilumab is an IgG2 antibody, which has lower affinity for Fc receptor IIB for IgG (FcγRIIB).

As discussed in greater detail below, the most clinical data to date has been generated with PD-L1x4-1BB bispecific therapies, although there is reported clinical experience with other TAA bispecifics, including those targeting HER2 (Pieris's PRS-343, which was discontinued) and Claudin18.2 (I-Mab's givastomig).

Phase I results for Claudin18.2 (CLDN18.2)-targeting bispecifics IBI-389 (CLDN18.2xCD3) and givastomig (CLDN18.2x4-1BB) provide a preliminary pair of datasets to compare immune cell targeting of CD3 versus 4-1BB for the same tumor target. See exhibit 9 for a comparison of early clinical data for the two CLDN18.2-directed bispecifics.

Innovent recently presented Phase I results for IBI-389 in patients with gastric cancer (GC), gastroesophageal junction adenocarcinoma (GEJC), pancreatic ductal adenocarcinoma (PDAC), and other CLDN18.2-expressing solid tumors at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting. Initial signals of efficacy were observed among GC/GEJC patients treated with at least 10 μg/kg IBI-389, with a disease control rate (DCR) of 73% (19/26) among 26 patients, including 8 PRs (31%). At the data cutoff, the duration of response data was immature, but median PFS was reported at 3.5 months and the 6-month PFS rate was 30.5%. The safety profile was considered manageable up to 600 μg/kg, with no dose-limiting toxicity. CRS events occurred in 60% of patients, with one patient experiencing grade 3 CRS and requiring treatment with tocilizumab. Treatment-related adverse events (TRAEs) occurred in 99.2% of patients, with grade 3 TRAEs in 58.3% of patients. The most common grade 3 AEs included gamma-glutamyltransferase (GGT) elevations (21.7%), lymphocyte count decreases (13.3%), and decreased appetite (5.0%).

Exhibit 9
Phase I Results With CLDN18.2 Bispecifics

	IBI-389 (CLDN18.2xCD3)	Givastomig (CLDN18.2x4-1BB)	
Company	Innovent	I-Mab Biopharma	
Phase	Phase I (NCT05164458)	Phase I (NCT04900818)	
Dosing	Dose escalation: 0.003-30 µg/kg Q3W Dose expansion: 10-600 µg/kg Q3W	Dose escalation: 0.1-15 mg/kg Q2W, 18 mg/kg Q3W Parallel dose expansion: 5, 8, 12, 15 mg/kg Q2W Dose expansion: 12 mg/kg Q2W	
Enrollment	120 patients	43 patients (CLDN18.2+ GEC treated at ≥5 mg/kg)	55 patients (dose escalation and parallel expansion)
Tumor Types	GC/GEJC: 30.8% PDAC: 60.0% Other solid tumors: 9.2%	EAC: 16% GC: 79% GEJ: 5%	GC: 38% GEJC: 4% EAC: 9% PDAC: 25% Other solid tumors: 24%
Baseline Characteristics	Age: 60 ECOG 0/1: 18.3%/81.7% CLDN18.2+ (IHC 2/3+) ≥10%: 76.7% Prior lines ≥2: 64.2%	Age: 59 ECOG 0/1: 28%/72% CLDN18.2+: 100% Median prior lines: 3.0 Prior PD-(L)1: 70%	Age: 66 ECOG 0/1: 30.9%/69.1% CLDN18.2+: 65.5% Median prior lines: 3.0 Prior PD-(L)1: 50.9%
Responses	31% PR (8/26) 42% SD (11/26) *(among CLDN18.2+ GC/GEJC patients at ≥10 µg/kg)*	16% PR (7/43) 33% SD (14/43) *(among CLDN18.2+ GEC patients at ≥5 mg/kg)*	15% PR (3/20) 20% SD (4/20) *(among efficacy-evaluable CLDN18.2+ GC/GEJC/EAC patients at 5-15 mg/kg)*
Treatment-Related Adverse Events (≥10%)	Pyrexia: 46.7% AST/ALT increase: 45.0%/44.2% Decreased appetite: 44.2% GGT increase: 40.8% Nausea: 36.7% Interleukin increase: 36.7% Hypoalbuminaemia: 35.0% CRP increase: 34.2% Anemia: 33.3% CRS: 32.5% Blood ALP increase: 28.8% Lymphocyte decrease: 27.5% Vomiting: 22.5%	Nausea: 26% Anemia: 23% WBC decreased: 23% Vomiting: 16% Decreased appetite: 14% ALT increased: 12% AST increased: 12% GGT increased: 12% Neutrophil count decreased: 12%	Nausea: 23.6% Vomiting: 16.4% Fatigue: 14.5% Anemia: 10.9%
Treatment-Related Adverse Events (Grade ≥3)	GGT increase: 21.7% AST/ALT increase: 0.8%/3.3% Decreased appetite: 5.0% Nausea: 4.2% Anemia: 3.3% CRS: 0.8% Blood ALP increase: 1.7% Lymphocyte decrease: 13.3% Vomiting: 3.3%	Nausea: 2.3% Anemia: 7.0% WBC decreased: 7.0% Vomiting: 2.3% Decreased appetite: 2.3% ALT increased: 2.3% AST increased: 4.7% GGT increased: 2.3% Neutrophil count decreased: 2.3% IRR: 2.3% Lymphocyte count decreased: 9.3% Lipase increased: 2.3% Platelet count decreased: 2.3%	Anemia: 1.8% ALT increase: 1.8% Lymphocyte decrease: 1.8% Pruritus: 1.8% WBC decrease: 1.8%
CRS	Any: 60.0% Grade 3: 0.8%	None	None
Reference	Zheng et al, ASCO 2024	Klempner et al, ESMO 2024	Ku et al, ESMO 2023

Source: William Blair Equity Research

For the CLDN18.2x4-1BB bispecific givastomig, I-Mab Biopharma reported clinical data from the Phase I study at the 2023 European Society of Medical Oncology (ESMO) Congress from the dose-escalation/expansion study evaluating givastomig as a monotherapy. The study included patients with CLDN18.2-expressing tumor types, including GC/GEJC, PDAC, and others. Initial signals of activity were reported, with a DCR of 35% (7/20), including 3 PRs (15%) among 20 patients treated in dose-expansion cohorts (5 to 15 mg/kg). With respect to safety, givastomig monotherapy was considered safe and well-tolerated up to 15 mg/kg, with no dose-limiting toxicity. The most common TRAEs were nausea (23.6%), vomiting (16.4%), fatigue (14.5%), and anemia (10.9%), which were almost all grade 1 or 2. Grade 3 events occurred in 10 subjects overall (18.2%), with each grade 3 event occurring in only 1 subject (1.8%). At ESMO 2024, I-Mab reported updated results from the Phase I dose expansion cohort in patients with CLDN18.2-positive gastroesophageal carcinoma (GEC) treated at dose levels ≥5 mg/kg. Among 43 patients, the DCR improved to 49%, including 7 PRs and 14 patients with stable disease. Safety was consistent with the initial dataset, with the most common TRAEs being GI-related (nausea, vomiting, appetite) or changes in blood cell and enzyme levels (see exhibit 9). Grade 3 TRAEs were relatively limited with the most common being lymphocyte and white blood cell decreases and anemia (<10%). There was no CRS with givastomig reported in either update.

As compared to the profile of the CD3-engaging bispecific IBI-389, givastomig has a relatively favorable safety profile, with fewer TRAEs overall, a much lower rate of grade 3 TRAEs, and no CRS, in support of an overall safer profile for 4-1BB-targeted versus CD3-targeted therapies. However, as expected, the antitumor activity of the 4-1BB-directed givastomig as a monotherapy does appear to be meaningfully lower than that of the CD3-directed IBI-389 in these initial datasets, although this could evolve with further dose optimization or in combination approaches. Givastomig is also being evaluated in combination with chemotherapy and Opdivo.

Overall, we believe 4-1BB bispecific therapies have shown that:

- Dosing to optimize 4-1BB agonism is not always straightforward and often requires additional mid-dose level exploration and various dose schedules to achieve desired pharmacodynamics;
- The safety profile appears generally manageable, though hepatotoxicity with the PD-L1x4-1BB bispecifics remains a concern; and
- Single-agent efficacy has been demonstrated, although 4-1BB bispecifics may be best used in combination regimens given their differentiated mechanism and general tolerability.

CD28

Attempting to Control the Power of CD28 Signaling With Bispecifics

CD28 is a costimulatory receptor that is constitutively expressed on activated and resting T cells and is significantly upregulated upon binding of the TCR to the target major histocompatibility complex (MHC). Binding of CD28 to ligands CD80 or CD86, such as those expressed on APCs, provides a critical second signal for activation and survival of naïve T cells. Historically, there have been safety challenges in targeting CD28 with monoclonal antibodies, which results in broad activation of T cells and CRS. In 2006, a Phase I study was conducted by TeGenero evaluating a novel superagonist anti-CD28 antibody, TGN1412, in 6 healthy participants, which resulted in a serious cytokine storm. Preclinically, TNG1412 did show preferential activation and expansion of T-helper and Tregs, resulting in transient lymphocyte count increases without detectable toxic or proinflammatory effects. However, shortly after administration of doses that were lower than those deemed safe in animal studies, all six patients in the Phase I study had life-threatening cytokine storm and severe depletion of lymphocytes and monocytes, requiring intensive care.

Current approaches targeting CD28 are largely focused on bispecific constructs in an attempt to reduce systemic CD28 agonism. Like CD3 bispecifics, CD28 bispecifics are designed to form a cross-link between CD28 on T cells and a TAA on tumor cells, resulting in more localized action in the tumor microenvironment. As highlighted in exhibit 10, there are multiple CD28 bispecific antibodies targeting various TAAs in early development, almost all of which are being evaluated in combination with other CD3 bispecifics and anti-PD-1 therapies. With this combination approach, the CD3-targeting component provides the primary activation signal and the CD28 component enhances this response via costimulation.

Still, targeting CD28 safely even in bispecific constructs has had challenges. The first meaningful data release with a CD28 bispecific was from Regeneron with nezastomig (REGN5678, PSMAxCD28) given in combination with the PD-1 antibody Libtayo in a Phase I/II study in patients with mCRPC. While the study initially showed some encouraging efficacy, including 3 out of 4 patients achieving a PSA50 response at the highest dose level, enrollment was subsequently stopped after two immune-mediated deaths were reported with the combination. One patient death was due to acute kidney injury, which was considered unrelated to treatment, and the other was due to hemophagocytic lymphohistiocytosis (HLH), which was deemed related to treatment. Grade ≥3 TEAEs occurred in 54% of patients, and 17% of patients had grade 1 CRS.

More recently, Regeneron presented data with REGN7075, an EGFRxCD28 bispecific antibody, in combination with Libtayo in patients with solid tumors at ASCO 2024. The study included 94 patients, the majority of which had microsatellite stable (MSS) colorectal cancer (CRC; n=61). Among 51 MSS CRC patients who achieved a REGN7075 dose of at least 100 mg, three patients achieved responses (5.9%), including one complete response and two partial responses. All three of these patients did not have liver metastasis, a subgroup of MSS CRC patients that have been reported to be more sensitive to immunotherapy treatments. REGN7075 did show a better-than-expected safety profile given the previously mentioned tolerability challenges of CD28 agonism, with only 14% of patients reporting rash maculopapular (1% grade 3 or 4) and 11% of patients reporting dermatitis acneiform (no grade 3), both of which are known epidermal growth factor receptor (EGFR)-related adverse events. The most common adverse event was infusion-related reactions, which occurred in 58% of patients, but only 2.4% were grade 3 or 4. Overall, while the safety profile of REGN7075 did appear better than expectations for CD28-based bispecifics, the efficacy is a little underwhelming, in our view—granted achieving clinical responses in MSS CRC patients is difficult. Expansion cohorts are ongoing in NSCLC, head and neck squamous cell carcinoma (HNSCC), cutaneous squamous cell carcinoma (CSCC), and CRC, which will provide a better idea of the profile of this therapy.

While a slightly different approach than those described previously, we note that Alpine Immune Sciences discontinued development of davoceticept (ALPN-202), a PD-L1-dependent CD28 costimulator and dual checkpoint inhibitor of PD-1 and CTLA-4, after safety concerns involving two patient deaths due to cardiogenic shock in a Phase I (NEON-2) study evaluating davoceticept in combination with Keytruda. A partial clinical hold was initially placed on the study after a first patient death due to cardiogenic shock, which the physicians deemed to be likely related to immune-mediated myocarditis or infection. A second patient death due to cardiogenic shock promoted the company to halt development of the asset completely.

As mentioned, ongoing programs with CD28 bispecifics are primarily focused on combination regimens, where the CD28 signaling has the potential to provide signal 2, while a CD3 bispecific or anti-PD-1 is used to help facilitate the underlying T-cell response. Whether these will be able to improve upon the efficacy or durability of the other components of the combination regimen without adding significant toxicity remains to be seen.

Exhibit 10
Select CD28-Based Bispecifics in Development for Oncology

Company	Technology/ Platform	Therapy	Tumor Target	Immune Cell Target	Valency (per target)	Stage	Indications	Study Start	NCT #	Status
REGENERON	-	Nezastomig (REGN5678)	PSMA	CD28	Monovalent	Phase I/II	Advanced prostate cancer	Aug-19	NCT03972657	Recruiting
						Phase I/II	Advanced prostate cancer	Nov-21	NCT05125016	Recruiting
						Phase I/II	Neoadjuvant prostate cancer	Dec-23	NCT06085664	Recruiting
		REGN5668	MUC16	CD28	Monovalent	Phase I/II	Recurrent ovarian or uterine cancer	Dec-20	NCT04590326	Recruiting
		REGN7075	EGFR	CD28	Monovalent	Phase I/II	Advanced solid tumors	Dec-20	NCT04626635	Recruiting
						Phase II	Early stage NSCLC	Aug-24	NCT06465329	Not yet recruiting
		REGN5837	CD22	CD28	-	Phase I	R/R B-NHL	Apr-23	NCT05685173	Recruiting
		REGN7945	CD38	CD28	-	Phase I/II	R/R multiple myeloma	Dec-24	NCT06669247	Not yet recruiting
Roche		RO7443904	CD19	CD28	-	Phase I	R/R B-NHL	Feb-22	NCT05219513	Terminated
Johnson&Johnson / xencor	XmAb	JNJ-87801493	CD20	CD28	-	Phase I	R/R B-NHL	Dec-23	NCT06139406	Recruiting
		JNJ-87189401	PSMA	CD28	-	Phase I	Advanced prostate cancer	Nov-23	NCT06095089	Recruiting
xencor	XmAb	XmAb808	B7-H3	CD28	2+1	Phase I	Solid tumors	Dec-22	NCT05585034	Recruiting
LIGHTCHAIN BIOSCIENCE / LamKap Bio	Kλ body	NI-3301	CEA	CD28	-	Preclinical	CEA+ solid tumors	-	-	-
		NI-3201	PD-L1	CD28	-	Preclinical	PD-L1+ tumors	-	-	-
		NILK-3801	GPC3	CD28	-	Discovery	GPC3+ solid tumors	-	-	-
RONDO therapeutics	-	RNDO-564	Nectin-4	CD28	-	Preclinical	Bladder cancer	-	-	-
		RNDO-Program 2	-	CD28		Preclinical	Ovarian cancer	-	-	-
zymeworks	Azymetric™ EFECT™	ZW209	DLL3	CD3, CD28	-	Preclinical	SCLC	-	-	-
sensei BIO	-	SNS-201	VISTA	CD28	-	Discovery		-	-	-

Sources: Company reports and William Blair Equity Research

CD28 Versus CD3: Case Studies With Initial Clinical Datasets

MUC16 and PSMA are two TAAs that have clinical datasets for both CD3 and CD28 bispecifics against the same target, enabling initial comparisons of the two T-cell targets. In this section we compare MUC16xCD3 versus MUC16xCD28 bispecifics in ovarian cancer (both in combination with PD-1 inhibition) and PSMAxCD3 versus PSMAxCD28 bispecifics in prostate cancer.

MUC16

Regeneron is evaluating two MUC16-targeting bispecifics in early clinical development including ubamatamab, a MUC16xCD3 bispecific, and REGN5668, a MUC16xCD28 bispecific. Both therapies were evaluated in Phase I/II studies in combination with Libtayo in patients with platinum-resistant ovarian cancer. Across 22 patients treated with doses of 10-250 mg of ubamatamab and at least one dose of Libtayo, the combination showed a 18% (4/22) overall response rate (ORR), with a median duration of response (DOR) of 8.3 months. Median PFS was 4.9 months, and 6- and 12-month PFS rates were 47.6% and 23.8%, respectively. Two dose-limiting toxicities (DLTs) occurred, including one grade 4 neutropenia case and one grade 4 HLH/macrophage activation syndrome case. Grade ≥3 TEAEs occurred in 48% of patients, and grade 1-2 CRS occurred in 69% of patients, with no cases of grade 3 CRS.

At ESMO-IO 2023, Regeneron presented initial data for REGN5668, a MUC16xCD28 bispecific antibody, in combination with Libtayo in patients with recurrent ovarian cancer. In contrast to ubamatamab, REGN5668 showed markedly lower efficacy, with only one partial response achieved in 28 patients treated with REGN5668 in combination with Libtayo (3.6% ORR). The safety profile of REGN5668 does appear more favorable than ubamatamab, with only one patient experiencing a grade 3 treatment-related adverse event, and only 3 patients (10.7%) experiencing grade 1 or 2 CRS (and no grade 3 CRS).

For ubamatamab, transient elevations in IFNγ and IL-6 were observed during step-up dosing, but increases were not observed after addition of Libtayo. For REGN5668 monotherapy, there were no elevations in cytokines, but slight increases in IFNγ and IP-10 were observed following the first dose of Libtayo at week 4, which is consistent with the anti-PD-1 mechanism.

Exhibit 11
Clinical Data With MUC16xCD3 and MUC16xCD28 Bispecifics

	Ubamatamab (REGN4018)	REGN5668
Format	MUC16xCD3 VelociBi	MUC16xCD28 VelociBi
Phase	Phase I/II (NCT03564340)	Phase I/II (NCT04590326)
Indication	Platinum-experienced recurrent, advanced ovarian cancer	Platinum-experienced recurrent, advanced ovarian cancer
Enrollment	35 patients	28 patients
Dosing	Ubamatamab dose escalation: 1-450 mg Libtayo 350 mg IV Q3W Days 29-36	REGN5668 dose escalation: 0.3-300 mg Libtayo 350 mg IV Q3W Days 21-28
Baseline Characteristics	Median age: 63 ECOG 0/1: 49%/51% High-grade serous histology: 89% BRCA1 and/or BRCA2: 26% Median baseline CA-125: 316 U/mL Visceral metastases: 43% Median prior lines: 5	Median age: 58 ECOG 1: 67.9% High-grade serous: 75.0% Other, mixed high-grade histology: 7.1% Clear cell: 17.9% BRCA1 and/or BRCA2: 14.3% Median baseline CA-125 (U/mL): 766 Visceral metastases: 21.4% Median prior lines: 3.5
Objective Response Rate	18% (4/22) *Efficacy analysis set (ubamatamab 10-250mg + ≥1 full dose Libtayo)*	ORR: 3.6% PR: 3.6%
Median DOR	8.3 mos	4.1 mos
Median PFS	4.9 mos	-
Landmark PFS	6-month PFS: 47.6% 12-month PFS: 23.8%	-
Grade ≥3 Adverse Events	Any grade 3-4 TEAE: 49% Pain: 20% Anemia: 26% Neutropenia: 11% Fatigue: 9% Hypophosphataemia: 6%	Treatment-related: 3.6% Fatigue: 3.6%
DLT	Two DLTs: grade 4 neutropenia; grade 4 HLH and macrophage activation syndrome	None
CRS	Grade 1-2: 69% Grade ≥3: 0%	All grades: 10.7% Grade 3: 0%
Reference	O'Cearbhaill et al., ESMO 2023	O'Cearbhaill et al., ESMO IO 2023

Sources: Company reports and William Blair Equity Research

PSMA

There are multiple datasets for both masked and unmasked approaches for CD3-based bispecific modalities that target PSMA. As mentioned, CD28 bispecifics are typically used in combination regimens where a CD3 bispecific or anti-PD-1 supplement the underlying T-cell response, and therefore it is difficult to make direct comparisons to a monotherapy CD3 bispecific. To our knowledge, data for Regeneron's nezastomig (REGN5678) is the only dataset available for a CD28 bispecific targeting PSMA. As briefly mentioned, nezastomig was evaluated in combination with Libtayo (PD-1 inhibitor) in patients with mCRPC. The study showed initial encouraging efficacy at the three highest dose levels, with roughly 38% (6/16) of patients achieving PSA30 response and roughly 31% (5/16) achieving PSA50 response. While CRS rates were encouraging, with 17% of patients experiencing CRS (all grade 1), grade ≥3 TRAEs occurred in 29% of patients and there

were two immune-mediated deaths, including acute kidney injury (unrelated to treatment) and HLH (deemed related to treatment), reported with the combination, which prompted investigators to stop enrollment in the study. Regeneron is currently evaluating nezastomig in combination with lower doses of Libtayo, as monotherapy in neoadjuvant prostate cancer, and in combination with the PSMAxCD3 bispecific, REGN4336.

As a comparison to nezastomig, Janux is advancing a masked PSMAxCD3 bispecific, JANX007, which is built on the company's TRACTr platform. At a high level, this platform facilitates the activation of JANX007 and the potent T-cell response against PSMA expressing cells, only upon cleavage of a peptide mask on the CD3 binding domain by proteases within the tumor microenvironment. This approach has allowed JANX007 to overcome challenges with prior unmasked TCE approaches, where further development has been hindered by suboptimal PK (pharmacokinetic) and toxicities, namely CRS.

Most recent data for JANX007 have shown highly encouraging efficacy and safety. Across 16 patients treated with target dose levels of JANX007, 100% of patients achieved a PSA50 response, 63% achieved a PSA90 response, and 31% achieved a PSA99 as best response. PSA50 and PSA90 responses were maintained in 75% and 50% of patients, respectively, at 12 weeks, and a 50% ORR (confirmed and unconfirmed) was also achieved among 8 evaluable patients. Importantly, this level of efficacy was achieved while maintaining a favorable and predictable safety profile. CRS events were primarily low grade and predictable, occurring largely in the first cycle and decreasing through the second step dose and target dose. There was one patient with a grade 3 CRS event in cycle 5, but this patient was on a prolonged treatment gap unrelated to JANX007 therapy and did not receive appropriate CRS mitigation protocols upon reinitiating treatment. A maximum tolerated dose (MTD) has not yet been reached up to target doses of 6 mg and 9 mg, which will be evaluated in expansion cohorts, and the company is also completing a 12 mg target-dose cohort. See additional details on the dataset in our note: Exceeding Investor Expectations and Raising the Bar in mCRPC; JANX007 Delivers on Efficacy and Safety.

We believe the strong profile of JANX007 is in large part due to the masking of the TCE with the TRACTr platform. Comparatively, unmasked PSMA-directed TCE approaches, such as with Harpoon's HPN424 (PSMAxCD3xalbumin, half-life extended trispecific) and Amgen's acapatamab (PSMAxCD3 half-life extended BiTE), showed efficacy on PSA response but were more limited by CRS, with roughly 4% and 20% of patients, respectively, having grade ≥3 CRS in initial dose-escalation studies. Development of both assets has been discontinued as a result.

Exhibit 12
Clinical Data With PSMAxCD3 and PSMAxCD28 Bispecifics

	JANX007		Nezastomig (REGN5678)
Format	PSMAxCD3 TRACTr		PSMAxCD28 bispecific
Phase	Phase I (NCT05519449)		Phase I (NCT03972657)
Indication	mCRPC		mCRPC
Regimen	JANX007 monotherapy		Nezastomig + Libtayo (anti PD-1)
Enrollment	23 patients	16 patients	35 patients
Dosing	Dose escalation up to 3 mg	Dose escalation (0.2-9 mg)	Dose escalation 0.1 - 300 mg Nezastomig + Libtayo 350 mg Q3W
Baseline Characteristics	Median age: 69 Median PSA: 158.5 ng/mL Median prior lines: 4 Prior taxane: 87%	Median age: 71.5 Median PSA: 80.9 Median prior lines: 4 Prior taxane: 63%	Median age: 67 ECOG 1: 63% Prior new hormonal agent: 100% Prior chemotherapy ≥1/≥2: 89%/40%
Objective Response Rate	-	50% (4/8) 1 cPR, 3 uPR	
PSA30 Response Rate	First dose ≥0.1mg: 78% First step dose ≥0.2mg 100%	100%	Dose levels 6-8 (30-300mg): 37.5% (6/16)
PSA50 Response Rate	First dose ≥0.1mg: 56% First step dose ≥0.2mg 83%	100%	Dose levels 6-8 (30-300mg): 31.3% (5/16)
PSA90 Response Rate	-	63%	-
PSA99 Response Rate	-	31%	-
Progression-Free Survival	-	7.4 months	-
Cytokine Release Syndrome (All Grade)	91%	100%	17% (all grade 1)
Cytokine Release Syndrome (Grade ≥3)	0%	6.25% (After treatment holiday without step-up)	0%
Serious Adverse Events (Grade ≥3)	0%	ALT increase: 19% AST increase: 38% Diarrhea: 13% Anemia: 13%	Any: 29% CIDP: 3% Encephalitis: 3% GBS: 3% Stomatitis: 3%
Deaths	0%	0%	6% (1 AKI, unrelated; 1 HLH, related)
Reference	Janux Presentation February 2024	Janux Presentation December 2024	Stein et al., ASCO GU 2023

Abbreviations: AKI, acute kidney injury; HLH, hemophagocytic lymphohistiocytosis
Sources: Company reports and William Blair Equity Research

While there seems to be less overall CRS risk in using CD28 bispecifics like REGN5668 or nezastomig as compared with CD3 bispecifics, the two immune-mediated patient deaths in the nezastomig study and minimal efficacy observed with REGN5668 suggest that effectively balancing safety and efficacy in targeting CD28 is still challenging. Regeneron has noted that in preclinical modeling, the immune-related adverse events seen with nezastomig in combination with Libtayo were not seen when combined with a CD3 bispecific, which highlights the clear differences in safety related to the method of T-cell activation used.

We believe CD28 bispecifics have shown:

- Better safety profile than the original CD28 superagonist, but there still seems to be significant safety risk with unmasked CD28 agonists; and

- There are still some questions on monotherapy efficacy and how to best design combination strategies (CD3 bispecific or PD-1?).

Exhibit 13
Overview of Immune and Tumor Targets for Approved or In-development Bispecific Therapies for Solid Tumors

Tumor Target \ Immune Target	CD3	CD28	4-1BB
PSMA	**Janux:** JANX007 (Phase I) **Academic:** CC-1 (Phase I) **Regeneron:** REGN4336 (Phase I/II) **Vir:** VIR-5500 (Phase I) **Aptevo:** APVO442 (Preclinical)	**JNJ/Xencor**: JNJ-87189401 (Phase I) **Regeneron**: Nezastomig (REGN5678) (Phase I)	**Crescendo Biologics:** CB307 (Phase I) **AbClon**: AFM109 (Research)
EGFR	**Amgen/CytomX:** CX-904 (Phase I/II) **Takeda**: TAK-186 (Phase I/II) **Janux:** JANX008 (Phase I) **Bioatla**: CAB-EGFR (Preclinical) **Adaptin**: APTN-101 (IND cleared)[5]	**Regeneron**: REGN7075 (Phase I/II)	**AbClon**: AM105 (Preclinical) **ABL Bio**: ABL 104 (IND-enabling)
MUC16	**Regeneron:** Ubamatamab (Phase I/II)	**Regeneron:** REGN5668 (Phase I/II)	-
CEA	**LamKap/Light Chain:** NILK-2301 (Phase I)	**LamKap/Light Chain:** NILK-3301 (Preclinical)	**BeiGene**: BGB-B167 (Phase I)[6]
B7-H3	**Takeda:** TAK-280 (Phase I/II)	**Xencor:** XmAb808 (Phase I)	-
GPC3	**Keymed:** CM350 (Phase I/II) **Chugai:** ERY974 (Phase I) **Abpro:** ABP-110 (Preclinical) **AstraZeneca:** AZD9793 (Preclinical) **LamKap/Light Chain:** NILK-2501 (Discovery)	**LamKap/Light Chain:** NILK-3801 (Discovery)	**Boston Pharmaceuticals:** BOS-342 (Phase I/II) **BeiGene:** BGB-B2033 (Phase I)
B7-H4	**Harbour:** HBM7004 (Preclinical)	-	**Harbour BioMed**: HBM7008 / CLN-418 (Phase I) **ABL**: ABL103 (Phase I)
5T4	**Chiome:** CBA-1535 (Preclinical) **Chiome:** PTRY (Preclinical)[2] **Purple:** IM1240 (Preclinical)[3]	-	**Alligator/Aptevo**: ALG.APV-527 (Phase I) **Crescendo:** Undisclosed (Preclinical)
HER2	**Roche**: Runimotamab (Phase I) **Vir**: VIR-5818 (Phase I) **Abpro**: ABP-102 (IND-enabling) **Adagene**: ADG138 (Preclinical)	-	**ABL:** ABL105 (Phase I) **AP**: AP402 (Phase I/II)
EpCam	**YZYBio**: M701 (Phase III) **Bioatla**: BA3182 (Phase I) **Merck:** HPN601 (Preclinical)	-	**Genmab/BioNTech**: GEN1059/BNT314 (Phase I/II)
Claudin18.2	**Astellas/Xencor:** ASP2138 (Phase I) **Innovent**: IBI-389 (Phase I) **Harbour/AstraZeneca**: AZD5863 (Phase I) **Abpro**: ABP-150 (Preclinical) **Genor**: GB264 (Preclinical)	-	**I-Mab**: Givastomig (Phase I)
MSLN	**Amgen:** AMG 305 (Phase I)[4] **JNJ:** JNJ-2421 (Phase I) **Zymeworks**: ZW171 (Phase I) **Context:** CT-95 (Phase I)	-	**Crescendo**: CB699 (IND-enabling)[1]
FAP	**Akamis:** NG-641 (Phase I)	-	**Roche:** RG7827 (Phase I/II)

1. CB699: CD40 x MSLN x CD137 (4-1BB) 2+1 immune cell engager; 2. PTRY: 5T4xPD-L1xCD3 TriBody; 3. IM1240 (5T4xCD3xNKG2A) TriBody; 4. AMG 305 (MSLNxCDH3xCD3) BiTE; 5. APTN-101 (EGFRvIIIxCD3); 6. BGB-B167 (CEACAM5x4-1BB)
Sources: Company reports and William Blair Equity Research

Can PD-(L)1-Based Bispecifics Break Through the PD-(L)1 Monoclonal Ceiling?

The advent of immune checkpoint inhibitors, particularly those targeting the PD-(L)1 axis, has transformed the treatment landscape for various cancers and led to blockbuster franchises including Keytruda and Opdivo. Through blocking the PD-(L)1 pathway, these therapies remove a gating mechanism on antitumor T cells, leading to meaningful clinical benefits in cancers including melanoma, non–small-cell lung cancer (NSCLC), bladder cancer, head and neck cancer, and renal cell cancer, among many others. Despite these advancements resulting in significant, durable responses for a select percentage of patients, most patients have primary resistance or eventually develop resistance to PD-1 blockade.

While a wide range of therapies have been developed in combination with PD-(L)1 antibodies to enhance and expand the therapeutic benefit to more patients, we are beginning to see clinical evidence of bispecific therapies where one arm targets the PD-(L)1 axis and another targets a second immune checkpoint or other relevant target. Unfortunately, it is unlikely that these bispecific therapies will be evaluated head-to-head versus a combination of monoclonal antibodies against the same targets, but investors and physicians will nonetheless attempt to extrapolate whether the bispecific is able to achieve greater efficacy, safety, or both, than could be achieved with a combination of monoclonal antibodies. We provide additional detail on a select number of bispecifics below and landscape tables in exhibits 14, 16, 18, 20, and 21.

PD-L1x4-1BB – Complex Dosing but Clear Clinical Activity; Will It Be Enough?

The most common dual-IO (immuno-oncology) bispecific approach based on the number of clinical programs is the combination of PD-L1 inhibition with 4-1BB activation. As described previously in this report, 4-1BB agonism has the potential to provide a costimulatory signal to activated T cells, thereby improving their antitumor activity and survival. However, systemic 4-1BB agonism resulted in significant immune-related adverse events, and therefore attempts now are being made to localize the 4-1BB agonism to the tumor microenvironment. By combining 4-1BB agonism with a PD-L1 binding arm, it is hypothesized that the bispecific will localize to PD-L1-positive tumors, thereby inhibiting the PD-1/PD-L1 inhibitory pathway and simultaneously providing a costimulatory signal for T cells.

Initial datasets from multiple programs suggested the dose at which optimal 4-1BB agonism was achieved would be insufficient to fully saturate the PD-1/PD-L1 axis, and therefore many of these programs moved into combination studies with a PD-1 antibody. Several recent datasets at the 2024 ASCO conference demonstrated activity with the class, with responses reported across multiple tumor types and potential survival advantages in NSCLC. However, some questions remain on the efficacy contribution of 4-1BB agonism over just PD-L1 inhibition, and these data further highlighted the complex PK/PD (pharmacodynamic) with targeting 4-1BB and the continued class effect of liver toxicity. As highlighted in exhibit 14, numerous PD-L1x4-1BB bispecific antibodies are in development.

Exhibit 14
PD-L1x4-1BB Bispecifics in Development

Company	Technology/ Platform	Therapy	First Target	Second Target	Valency (Per Target)	Stage	Indications	Study Start	NCT #	Status
Genmab	DuoBody	Acasunlimab (GEN1046)	PD-L1	4-1BB	Monovalent	Phase III	2L NSCLC	Nov-24	NCT06635824	Recruiting
						Phase I/II	Solid tumors	May-19	NCT03917381	Active, not recruiting
齐鲁制药 QILU PHARMACEUTICAL	-	QLF31907	PD-L1	4-1BB	Bivalent	Phase II	Advanced melanoma and urothelial carcinoma	Apr-23	NCT05823246	Recruiting
						Phase I/II	Solid tumors	Jun-24	NCT06394713	Not yet recruiting
						Phase I	Solid tumors	Oct-21	NCT05150405	Recruiting
Leads Biolabs	-	LBL-024	PD-L1	4-1BB	Bivalent	Phase I/II	Solid tumors	Jan-22	NCT05170958	Recruiting
						Phase I/II	Neuroendocrine carcinoma	Dec-23	NCT06157827	Recruiting
BIONTECH BIOTHEUS	-	PM-1003	PD-L1	4-1BB	Bivalent	Phase I/II	Solid tumors	Sep-21	NCT05862831	Recruiting
Merus	Biclonics	MCLA-145	PD-L1	4-1BB	Monovalent	Phase I	Solid tumors	May-19	NCT03922204	Active, not recruiting
I-MAB BIOPHARMA ablbio	Grabody-T	Ragistomig (TJ-L14B, ABL503)	PD-L1	4-1BB	Bivalent	Phase I	Solid tumors	Apr-21	NCT04762641	Recruiting
INVOX	mAb^2	FS222	PD-L1	4-1BB	Bivalent	Phase I	Solid tumors	Dec-20	NCT04740424	Recruiting
ablbio ATG 德琪医药 ANTENGENE	-	ATG-101	PD-L1	4-1BB	Bivalent	Phase I	Solid tumors and NHL	Jan-22	NCT05490043	Recruiting
						Phase I	Solid tumors and NHL	Oct-21	NCT04986865	Recruiting
AP Biosciences 国祥生技	T-cube	AP203	PD-L1	4-1BB	Bivalent	Phase I	Solid tumors	Feb-23	NCT05473156	Not yet recruiting

Sources: Company reports and William Blair Equity Research

Acasunlimab

Genmab is developing the PD-L1x4-1BB bispecific, acasunlimab (GEN1046), which has recently advanced to Phase III development. The ongoing Phase III study (NCT06635824) is evaluating acasunlimab in combination with Keytruda versus standard-of-care docetaxel, in patients with second-line, PD-L1-positive NSCLC. Acasunlimab was previously co-developed with BioNTech, but BioNTech opted out of acasunlimab development and Genmab has sole responsibility for late-stage development. Management of both companies noted the decision was purely driven by strategic portfolio prioritization in NSCLC, given the number of existing NSCLC programs in BioNTech's pipeline (such as the PD-L1xVEGF antibody BNT327). The Phase III study has an estimated primary completion in 2027, and Genmab plans to enroll 702 patients, with OS as a primary endpoint and PFS, ORR, DOR, and safety as secondary endpoints. Of note, the study will evaluate 100 mg acasunlimab in combination with 400 mg Keytruda, both given every 6 weeks (Q6W), which was the dosing regimen that generated the greatest efficacy in the initial ASCO dataset (see: Intriguing Updates for Acasunlimab and Complex 4-1BB Biology; Hope to See Longer OS Follow-Up to Better Gauge Phase III Odds).

- It has been determined by Genmab and others that the bell-shaped PD curves of T-cell activation with 4-1BB agonists requires a midlevel dose to achieve peak activation; however, there are still outstanding questions on the most optimal dosing frequency, particularly related to concerns with T-cell exhaustion with more frequent dosing. The Phase II study was designed with three arms to determine the most optimal dosing schedule: acasunlimab 100 mg Q3W for cycles 1-2, then 500 mg Q6W; acasunlimab 100 mg + Keytruda 200 mg IV Q3W; and acasunlimab 100 mg IV + Keytruda 400 mg IV Q6W.

- The Q6W regimen showed the greatest efficacy, with a 30% unconfirmed ORR, median DOR not reached, 24% 6-month PFS rate, and 69% 12-month OS rate. While the results are encouraging, we believe additional follow-up is needed to gain confidence in the survival curve (given the high number of censored patients), and historically beating docetaxel in second-line NSCLC has been difficult.

- The acasunlimab plus Keytruda Q6W regimen also showed the lowest incidence of liver function tests (LFT) elevations among all the arms, suggesting that less frequent dosing can improve safety. Additional PD analyses also showed that intermittent engagement and activation of 4-1BB with the Q6W regimen may be better at sustaining long-term T-cell functionality and reducing T-cell exhaustion as compared to the Q3W regimen.

- An encouraging 30% unconfirmed ORR was achieved for the Q6W regimen, but two unconfirmed responders discontinued due to LFT elevations. These patients were eventually rechallenged off-study and did not benefit, suggesting that a dosing window longer than six weeks is suboptimal. An updated LFT mitigation protocol was implemented during the study, and there were no discontinuations due to LFTs since implementation (compared to mandatory discontinuations upon grade 3 LFTs in the first portion of the study).

Since presenting the Phase II dataset, Genmab has presented additional translational analyses of the Phase II data.

- A poster presented at the 2024 World Conference on Lung Cancer (WCLC) showed that the Q6W combination regimen of acasunlimab and Keytruda exhibited intermittent induction of s4-1BB (surrogate for target engagement), allowing for a T-cell reset period, as opposed to chronic stimulation with the Q3W combination regimen. This allows for improved T-cell functionality versus the Q3W regimen, as shown by lower induction of co-inhibitory TIM3-expressing CD8+ T cells and greater proliferation of memory CD8+ T cells in subsequent cycles.

- In addition, increasing exposures of the acasunlimab and Keytruda combination were associated with a greater risk of grade ≥3 liver-related events and were indicated to be greater with the Q3W combination regimen than the Q6W regimen. More rapid resolution of grade ≥3 liver-related events was also observed in the Q6W regimen.

MCLA-145

Also at ASCO 2024, Merus presented results with MCLA-145, a PD-L1x4-1BB bispecific, as monotherapy and in combination with Keytruda in patients with solid tumors. Monotherapy responses were observed in two patients with gastrointestinal cancers, a patient with gynecological cancer, and a sarcoma patient. In combination with Keytruda, a complete response was achieved in a patient with lung cancer and a partial response in a patient with Merkel cell carcinoma. Notably, greater activity and safety and more sustained T-cell stimulation were observed with less frequent dosing with the Q3W dosing versus Q2W regimen.

Ragistomig

I-Mab presented first-in-human dose-escalation and initial dose-expansion data for ragistomig (PD-L1x4-1BB) at ASCO 2024. A maximum tolerated dose of 7 mg/kg Q2W was determined, but grade ≥3 LFT increases occurred across multiple dose levels and in 25% of patients overall. Among all 44 evaluable patients, the ORR was 15.9%. All responses were observed at the 5 mg/kg and 3 mg/kg expansion dose levels, where a 26.9% ORR (7/26) was achieved, including a complete response in ovarian cancer and partial responses in ovarian cancer, head and neck cancer, gastric cancer, melanoma, hepatocellular carcinoma, and esophageal cancer.

QLF31907

Qilu presented results for QLF31907 (PD-L1x4-1BB bispecific) in patients with solid tumors. QLF31907 was dose escalated up to 30 mg/kg, and DLTs were observed in one patient at the 20 mg/kg dose, which consisted of myalgia and platelet count decrease. The most common adverse events were anemia and hypertriglyceridemia, and we note that roughly a third of patients had LFT increases. Overall, six patients achieved partial responses: cervical cancer, head and neck cancer, melanoma, lung cancer, and two patients with endometrial cancer. The company also reported that at doses of 10 mg/kg Q2W and above, receptor occupancy for both PD-L1 and 4-1BB were both stabilized at 80% during the dosing interval.

LBL-024

Nanjing Leads Biolabs presented dose escalation and expansion of LBL-024, a PD-L1x4-1BB bispecific with lower affinity for 4-1BB. The study evaluated doses of 0.2 mg/kg up to 25 mg/kg, with a recommended Phase II dose of 15 mg/kg Q3W. Across 175 patients in dose escalation, 32.6% reported any grade AST increase and 27.4% reported any grade ALT increase, yet rates of grade 3 or higher were only roughly 1% for both. The efficacy analysis in this presentation focused on 45 patients with extrapulmonary neuroendocrine cancer (EP-NEC), where 33% achieved a response. Interestingly, responses were observed even in patients with PD-L1 CPS below 1% in this tumor type. Studies evaluating LBL-024 in EP-NEC are ongoing in monotherapy and in combination with chemotherapy.

FS222

InvoX Pharma presented initial data with FS222, which was evaluated in a Q4W regimen from 0.75 mg/kg mg up to 4.5 mg/kg. The company also explored 1 and 1.5 mg/kg in a Q3W regimen, although those will not be advanced further. In 114 patients, 100 received the Q4W regimen. Roughly a third of patients had grade 3 or higher AST or ALT increase. Of note, four patients experienced HLH, and one patient in the Q3W regimen died from HLH. Overall, 17 patients treated at the Q4W regimen responded, with responses observed across multiple tumor types. Notably, in melanoma patients who had previously been reported with a PD-1 inhibitor, 47% of patients achieved a response (across all doses), with a 6-month PFS rate of 53%.

Exhibit 15
Select Clinical Results for PD-L1 x 4-1BB Bispecific Antibodies in Development

	Genmab Acasunlimab (GEN1046)			Merus MCLA-145		I-Mab Biopharma Ragistomig	Qilu Pharmaceuticals QLF31907	Nanjing Leads Biolabs LBL-024	invoX Pharma FS222
Phase	Phase II (NCT05117242)			Phase I (NCT03922204)		Phase I (NCT04762641)	Phase I (NCT05150405)	Phase I/II (NCT05170958)	Phase I (NCT04740424)
Enrollment	22 patients **(16 PD-L1+)**	42 patients **(22 PD-L1+)**	49 patients **(24 PD-L1+)**	53 patients	19 patients	53 patients	38 patients	Total: n=175 Phase I: (n=64) Phase IIa: (n=111)	Total: n=114 Q4W mg/kg dose escalation and expansions: (n=100) Exploratory Q3W mg/kg: (n=14)
Dosage Arms	**Arm A** 100 mg acasunlimab Q3W x 2 cycles then 500 mg Q6W	**Arm B** 100 mg acasunlimab + Keytruda 200 mg Q3W	**Arm C** 100 mg acasunlimab + Keytruda 400 mg Q6W	MCLA-145 Q2W 0.4-75 mg (n=47) MCLA-145 Q3W 40 mg (n=6) **RDE**[1]: MCLA-145 40 mg Q3W (n=6)	Combination Q3W 10-40 mg (n=19) **RDE**: MCLA-145 40 mg + Keytruda 200 mg Q3W (n=9)	Dose escalation 0.7 - 10 mg/kg Dose expansion: 3 and 5 mg/kg	Dose escalation: 0.026 - 30 mg/kg	LBL-024 15 mg/kg	Q4W dose escalation: 0.75 - 4.5 mg/kg Q3W exploratory 1 and 1.5 mg/kg
ORR	Unconfirmed: 31.3% Confirmed: 12.5%	Unconfirmed: 20.8% Confirmed: 18.2%	Unconfirmed: 29.6% Confirmed: 16.7%	10% RDE ORR: 33%	11% RDE ORR: 11%	Dose expansion: 27% (7/26)	15.8% (6/38) PRs: CC, HNSCC, Melanoma, NSCLC, 2 EC	33.3% (15/45) PR: 33.3%	17% (17/100) CR: 1% PR: 16% cutaneous melanoma (9), ovarian cancer (2), NSCLC (2), mucosal melanoma (1), TNBC (1), mesothelioma (1), MSS CRC (1)
DCR	Confirmed: 50.0%	Confirmed: 59.1%	Confirmed: 75.0%	37%	68%	69%	60.5%	51.1%	45.0%
mDOR	2 months	5.2 months	NR	-	-	-	-	5.3 mos	5.5 mos
PFS	6-mo: 0%	6-mo: 14%	6-mo: 34%	-	-	mPFS: 3.9 months	-	Overall mPFS: 2.8 mos 2L: 4.1 mos 3L+: 2.7 mos	PD-1 experienced melanoma pts (n=19) 3-mo PFS: 92% 6-mo PFS: 53%
mOS	5.5 months	8.6 months	17.5 months	-	-	-	-	NR	-
Landmark OS	12-mo: 30%	12-mo: 26%	12-mo: 69%	-	-	-	-	6-mo OS Overall: 61.7% 2L: 72.7% 3L+: 52.0%	-
Adverse Events	Grade ≥3 liver-related events: 9.1% asthenia: 9.1% blood alkaline phosphatase increase: 9.1% anemia: 4.5%	Grade ≥3 Any: 28.6% liver-related events: 16.7% thrombocytopenia: 7.1% anemia: 2.4%	Grade ≥3 Any: 18.4% liver-related events: 12.2%	Grade ≥3 Any: 66% Serious: 40% Leading to d/c: 11% Neutropenia: 21% Anemia: 9% AST/ALT increase: 9% Fatigue: 4%	Grade ≥3 Any: 32% Serious: 16% Leading to d/c: 11% Neutropenia: 0% Anemia: 5% Dyspnea: 5% AST/ALT increase: 11% Fatigue: 11%	Grade ≥3 TRAEs: Any: 42% ALT increase: 23% AST increase: 21% Pyrexia: 2% Rash: 4% Fatigue: 2% Platelet decrease: 2% 5 DLTs	Any grade TRAEs: 92.1% Grade≥3 TEAEs: 63.2% TEASAEs: 52.6%	Grade≥3 TRAEs: 20.6% TRSAE: 16.6% TRAE leading to d/c: 4.0%	FS222-related TEAEs Any: 83% Grade≥3: 36% Serious AE: 28% Leading to d/c: 8% Grade≥3 TRAE AST increase: 33% ALT increase: 28% Thrombocytopenia: 22% Neutropenia: 19% Febrile neutropenia: 17%
Discontinuations		33.3%	24.5%	11%	11%	17%	15.8%	4%	8%
Source	Aerts et al., ASCO 2024			Kyi et al., ASCO 2024		Falchook et al, ASCO 2024	Lin et al. ASCO 2024	Lu et al., ASCO 2024	Garralda et al., ASCO 2024

1. Recommended dose for expansion
Source: William Blair Equity Research

PD-1xCTLA-4 – Clinical Activity but Can It Be Combined Safely in a Bispecific Format?

The use of monoclonal PD-(L)1 inhibitors in combination with CTLA-4 inhibitors is well established and capable of achieving greater efficacy than either alone in difficult-to-treat cancers, such as melanoma, NSCLC, renal cell carcinoma, and hepatocellular carcinoma, contributing to the success of the Opdivo (anti-PD-1) and Yervoy (anti-CTLA-4) franchises. Beyond Yervoy, AstraZeneca's Imjudo is the only other FDA-approved anti-CTLA-4 antibody, and similarly, is approved for use in combination with the PD-L1 antibody Imfinzi in hepatocellular carcinoma and NSCLC.

The combination of CTLA-4 and PD-1 inhibition targets different stages and mechanisms of T-cell regulation. Anti-CTLA-4 enhances the priming and activation of naïve T cells by allowing CD28 to bind to the activating ligands CD80 or CD86 on antigen presenting cells, facilitating the full activation of the T cells. In contrast, PD-1 blockade focuses on improving the activation and proliferation of both activated and exhausted T cells, boosting their cytotoxic function against cancer cells. Together, these mechanisms result in a more robust immune response but also result in substantially greater toxicity than either agent alone, particularly immune-related AEs.

It has been speculated that a bispecific antibody targeting CTLA-4 and PD-1 may potentially activate PD-1+/CTLA-4+ T cells within the tumor microenvironment, thereby reducing the systemic inhibition of CTLA-4 and subsequent rates of immune-related AEs. However, we highlight that clinical development of CTLA-4 antibodies in combination with PD-1 antibodies has demonstrated that low and infrequent dosage of the CTLA-4 antibody can add benefit on top of PD-1 antibodies, and continual CTLA-4 inhibition does not appear necessary. In addition, AEs experienced with PD-(L)1 plus CTLA-4 combinations often lead to discontinuation of the CTLA-4 antibody first, allowing the patient to stay on the PD-(L)1 antibody, whereas discontinuation of the bispecific therapy altogether would be required.

Therefore, we remain overall skeptical on the potential of PD-1xCTLA-4 bispecifics. A list of these assets in development are provided in exhibit 16, and recent updates from select programs are outlined below.

Exhibit 16
PD-(L)1xCTLA-4 Bispecifics in Development

Company	Technology/ Platform	Therapy	First Target	Second Target	Valency (Per Target)	Stage	Indications	Study Start	NCT #	Status
AstraZeneca	DuetMab	Volrustomig	PD-1	CTLA-4	Monovalent	Phase III	Locally advanced cervical cancer	Sep-23	NCT06079671	Recruiting
						Phase III	Unresected locally advanced HNSCC	Dec-23	NCT06129864	Recruiting
						Phase III	1L metastatic NSCLC	Oct-24	NCT05984277	Recruiting
						Phase III	1L unresectable malignant pleural mesothelioma	Nov-23	NCT06097728	Recruiting
						Phase I	advanced RCC	Aug-20	NCT04522323	Recruiting
						Phase Ib	Solid tumors	Apr-18	NCT03530397	Active, not recruiting
						Phase IIb	1L NSQ NSCLC	Aug-24	NCT06448754	Recruiting
Akesobio	-	Cadonilimab	PD-1	CTLA-4	Bivalent	Approved (China)	2L R/M cervical cancer	-	-	-
						Approved (China)	1L metastatic G/GEJ	-	-	-
						Phase III	1L R/M CC	Aug-21	NCT04982237	Recruiting
						Phase I/II	2L G/GEJ	Aug-21	NCT04982276	Recruiting
						Phase III	adjuvant HCC	Sep-22	NCT05489289	Enrollment in progress
						Phase II	1L PD1-negative NSCLC	Apr-23	NCT06424821	Recruiting
康宁杰瑞 ALPHAMAB ONCOLOGY	-	KN046	PD-L1	CTLA-4	Bivalent	Phase III	1L PDAC	Jan-22	NCT05149326	Active, not recruiting
						Phase II/III	Neoadjuvant NSCLC	Aug-23	NCT06020352	Recruiting
						Phase II	PD-1 resistant MSI-H GI tumors	Oct-23	NCT06099821	Recruiting
						Phase II	MSS CRC	Oct-23	NCT05985109	Recruiting
						Phase II	1L metastatic NSCLC	Jul-22	NCT05420220	Recruiting
						Phase III	1L Sq. NSCLC	Sep-20	NCT04474119	Unknown status
						Phase I/II	solid tumors	Nov-21	NCT04984668	Recruiting

Sources: Company reports and William Blair Equity Research

Exhibit 16 (Continued)
PD-(L)1xCTLA-4 Bispecifics in Development

Company	Technology/ Platform	Therapy	First Target	Second Target	Valency (Per Target)	Stage	Indications	Study Start	NCT #	Status
xencor	XmAb/Xtend	Vudalimab (XmAb2071)	PD-1	CTLA-4	Monovalent	Phase I/II	1L metastatic NSCLC	Dec-23	NCT06173505	Recruiting
						Phase II	mCRPC	Oct-22	NCT05005728	Recruiting
						Phase II	Gynecologic and genitourinary tumors	Jul-22	NCT05032040	Recruiting
MacroGenics	DART	Lorigerlimab	PD-1	CTLA-4	Bivalent	Phase II	mCRPC	Sep-23	NCT05848011	Recruiting
						Phase I	Solid tumors	Apr-22	NCT05293496	Active, not recruiting
						Phase I	Solid tumors	Dec-18	NCT03761017	Active, not recruiting
Systimmune	SEBA	SI-B003	PD-1	CTLA-4	Bivalent	Phase II	Solid tumors	Jul-24	NCT05965856	Recruiting
						Phase I/II	NSCLC	Oct-23	NCT05949606	Recruiting
						Phase I/II	HNSCC	Feb-23	NCT05668858	Recruiting
						Phase II	HER2- breast cancer	Dec-23	NCT06042894	Recruiting
						Phase II	SCLC	Nov-23	NCT05924841	Recruiting
						Phase I	Solid tumors	Nov-20	NCT04606472	Recruiting
GENOR BIOPHARMA	-	GB268	PD-1	CTLA-4, VEGF	-	Preclinical	-	-	-	-
		GBD209	PD-1	CTLA-4, TIGIT	-	Preclinical	-	-	-	-

Sources: Company reports and William Blair Equity Research

Cadonilimab

Akeso Bio is developing the tetravalent PD-1xCTLA-4 bispecific, cadonilimab (AK104). Cadonilimab was designed using Akeso's Tetrabody platform. Cadonilimab is being developed across multiple solid tumor indications, including cervical cancer (approved in recurrent/metastatic [R/M] cervical cancer in China), gastric cancer (approved in frontline gastric/GEJ cancer in China), hepatocellular carcinoma, lung cancer, esophageal cancer, pancreatic cancer, and other solid tumors.

Recent cadonilimab datasets presented at the ESMO 2024 include:

- ***Recurrent/metastatic cervical cancer.*** Single-arm Phase II data were presented for cadonilimab in combination with chemotherapy in 21 patients with R/M cervical cancer who failed previous immunotherapy or chemotherapy. With a median follow-up of 9.4 months, cadonilimab achieved a 52.4% ORR, and in patients treated with prior immunotherapy, the ORR was 25%. Median PFS was 6.2 months for all patients, and median PFS in patients receiving cadonilimab and chemotherapy as second-line and third-line or later treatment was 6.2 months and 4.8 months, respectively. Grade ≥3 adverse events occurred in 28.6% of patients, with the most common being leukopenia (19%), anemia (5%), and rash (5%). Cadonilimab is

approved in China, for use as monotherapy in second- and third-line cervical cancer. Cadonilimab is also being evaluated in combination with chemotherapy and/or Avastin in first-line cervical cancer.

- ***Advanced ovarian cancer*.** Data were also presented for neoadjuvant cadonilimab plus chemotherapy in advanced ovarian cancer. Notably, a 91.7% ORR was observed, including 2 complete responses. Grade ≥3 TRAEs occurred in 12.5% of patients, with the most common being thyroid dysfunction, skin rash, and bone marrow suppression. In this indication, a Phase III study evaluating neoadjuvant cadonilimab combined with chemotherapy versus chemotherapy alone has since been initiated.

- ***Advanced biliary tract cancer (BTC)*.** Akeso also presented data for cadonilimab combined with chemotherapy (gemcitabine and cisplatin) in first-line BTC. In 42 evaluable patients, a 61.9% ORR was observed including 2 complete responses in patients with intrahepatic and extrahepatic tumors. Median PFS was 9.0 months and 6-month PFS rate was 72.3%. Grade ≥3 TRAEs occurred in 60.5% of patients, and 9.3% of TRAEs led to treatment discontinuation.

- ***PD-1-refractory nasopharyngeal carcinoma (NPC)*.** Also highlighted were Phase II data for cadonilimab and chemotherapy (nab-paclitaxel, platin, and capecitabine) in patients with R/M NPC failing at least one prior line of systemic chemotherapy and anti-PD-1 therapy. In 24 evaluable patients, a 68% ORR was observed, including 3 patients with a complete response, and median DOR of 9.1 months. Median PFS was 10.6 months. Grade 3 or 4 TRAEs occurred in 48% of patients, which were primarily hematologic. In addition, one patient experienced a grade 3 immune-related rash and another a grade 3 immune-related lipase increase.

As mentioned, cadonilimab recently received NMPA approval in China, for use in combination with chemotherapy in frontline gastric/GEJ adenocarcinoma. The approval was based on results from the Phase III (COMPASSION-15/AK-104-302) study, which were recently presented at the 2024 American Association for Cancer Research (AACR) Annual Meeting:

- The study enrolled 610 patients, with 305 patients randomized to either cadonilimab plus chemotherapy followed by cadonilimab maintenance, or placebo plus chemotherapy followed by placebo. Notably, statistically significant and clinically meaningful OS and PFS benefit were achieved, with benefit maintained across PD-L1 expression levels.

- The combination of cadonilimab and chemotherapy achieved a median OS of 15.0 months versus 10.8 months with the chemotherapy control (HR 0.62). In patients with PD-L1 combined positive score (CPS) of 5 or greater, median OS was not reached versus median OS of 10.6 months for the control (HR 0.56, $p<0.001$). In patients with PD-L1 CPS less than 5, the cadonilimab/chemotherapy combination showed a 14.8-month median OS versus 11.1 months in the control arm (HR 0.70, $p=0.011$). Median PFS for the cadonilimab/chemotherapy regimen was 7.0 months versus 5.3 months for the control arm (HR 0.53), and similar benefit was maintained across PD-L1 CPS expression levels. A 62.5% ORR (8.8-month median DOR) and 48.9% ORR (4.4-month median DOR) was reported in the cadonilimab combination arm and control arm, respectively. Comparatively, in the CheckMate 649 study, Opdivo plus chemotherapy showed a 58% ORR (8.5-month median DOR), 8.1-month median PFS, and 13.8-month median OS. Opdivo plus chemotherapy is an approved first-line treatment for GEJ, but the combination of Opdivo and Yervoy (followed by Opdivo) in CheckMate 649 did not show meaningful efficacy improvements over chemotherapy alone, and therefore this regimen is not approved in the frontline setting. However, the combination of Opdivo and Yervoy is approved in the frontline esophageal squamous cell carcinoma setting based on results from the CheckMate 648 study.

Exhibit 17
Comparison of Clinical Results With Cadonilimab and Opdivo and Yervoy in Frontline Gastric Cancer

	COMPASSION-15 Cadonilimab + Chemo		CheckMate 649 Opdivo + Chemo and Opdivo + Yervoy			
Phase	Phase III (NCT05008783)		Phase III (NCT02872116)			
Disease	1L advanced unresectable or metastatic G/GEJ		1L advanced unresectable or metastatic G/GEJ			
Enrollment	305 patients	305 patients	789 patients	792 patients	409 patients	404 patients
Patient Characteristics	Age: 63.7 Female: 21.6% ECOG 0/1: 23.0%/77.0% GEJ adenocarcinoma: 20.7% Gastric adenocarcinoma: 79.3% Recurrent/locally advanced unresectable/primary metastasis: 21.3%/3.0%/75.7% Liver/lung/peritoneum mets: 47.2%/16.7%/14.1% PD-L1 vCPS ≥ 5%: 40.0% PD-L1 vCPS < 5%: 54.4%	Age: 64.3 Female: 23.0% ECOG 0/1: 23.6%/76.4% GEJ adenocarcinoma: 24.3% Gastric adenocarcinoma: 75.7% Recurrent/locally advanced unresectable/primary metastasis: 19.3%/4.6%/76.1% Liver/lung/peritoneum mets: 46.9%/15.1%/12.5% PD-L1 vCPS ≥ 5%: 40.3% PD-L1 vCPS < 5%: 56.7%	Age <65/≥65: 60%/40% Female: 32% ECOG 0/1: 41%/59% Gastric cancer: 70% GEJ cancer: 17% Esophageal adenocarcinoma: 13% Metastatic/locally advanced/locally recurrent: 96%/3%/1% Liver/peritoneum/CNS mets: 38%/24%/<1% PD-L1 <1%/≥1%: 84%/16%	Age <65/≥65: 62%/38% Female: 29% ECOG 0/1: 42%/57% Gastric cancer: 70% GEJ cancer: 16% Esophageal adenocarcinoma: 14% Metastatic/locally advanced/locally recurrent: 95%/4%/<1% Liver/peritoneum/CNS mets: 40%/24%/0% PD-L1 <1%/≥1%: 84%/16%	Age <65/≥65: 63%/37% Female: 32% ECOG 0/1: 41%/59% Gastric cancer: 69% GEJ cancer: 20% Esophageal adenocarcinoma: 11% Metastatic/locally advanced/locally recurrent: 96%/3%/1% Liver/peritoneum/CNS mets: 36%/23%/0% PD-L1 <1%/≥1%: 83%/17%	Age <65/≥65: 62%/38% Female: 31% ECOG 0/1: 46%/54% Gastric cancer: 70% GEJ cancer: 18% Esophageal adenocarcinoma: 12% Metastatic/locally advanced/locally recurrent: 96%/4%/0% Liver/peritoneum/CNS mets: 40%/24%/0% PD-L1 <1%/≥1%: 83%/17%
Regimen	cadonilimab + chemo followed by cadonilimab	placebo + chemo followed by chemo	Opdivo + chemo	chemo	Opdivo + Yervoy followed by Opdivo	Chemo
ORR	65.2%	48.9%	58%	46%	23%	47%
mDOR	8.8 mos	4.4 mos	8.5 mos	6.9 mos	13.8 mos	6.8 mos
Median Follow-Up	18.7 mos		13.1 mos	11.2 mos	11.4 mos	11.5 mos
mPFS	7.0 mos (HR 0.53)	5.3 mos	7.7 mos (HR 0.79)	6.9 mos	2.8 mos (HR 1.66)	7.1 mos
mPFS subgroup	*PD-L1 CPS ≥ 5: 6.9 mos (HR 0.51)* *PD-L1 CPS < 5: 6.9 mos (HR 0.60)*	*PD-L1 CPS ≥ 5: 5.5 mos* *PD-L1 CPS < 5: 4.6 mos*	PD-L1 CPS ≥ 5: 8.1 mos (HR 0.70)	PD-L1 CPS ≥ 5: 6.1 mos	PD-L1 CPS ≥ 5: 2.8 mos (HR 1.42)	PD-L1 CPS ≥ 5: 6.3 mos
mOS	15.0 mos (HR 0.62)	10.8 mos	13.8 mos (HR 0.79)	11.6 mos	11.7 mos (HR 0.91)	11.8 mos
Adverse Events	Any Grade ≥3: 65.9% Serious TRAEs: 30.5% TRAEs leading d/c: 23.9% Treatment-related deaths: 1.6%	Any Grade ≥3: 53.6% Serious TRAEs: 21.7% TRAEs leading d/c: 6.6% Treatment-related deaths: 2.3%	Grade 3-4 TRAEs: 60% Serious TRAEs: 17% TRAEs leading to d/c: 18%	Grade 3-4 TRAEs: 45% Serious TRAEs: 10% TRAEs leading to d/c: 9%	Grade 3-4 TRAEs: 38% Serious TRAEs: 23% TRAEs leading to d/c: 17%	Grade 3-4 TRAEs: 46% Serious TRAEs: 12% TRAEs leading to d/c: 10%
Source	Ji et al., AACR 2024		Shitara et al., *Nature* 2022			

Source: Company reports

- Investigators noted there were no new safety signals observed; however, there were considerably higher rates of TRAEs in the cadonilimab combination arm, with 65.9% of patients experiencing grade 3 or higher TRAEs versus 53.6% in the control arm. In addition, roughly 23.9% of patients in the cadonilimab combination arm discontinued therapy versus 6.6% in the control arm. In comparison, in the CheckMate 649 study, patients in the Opdivo and chemo combination arm had a 60% rate of grade 3 or 4 TRAEs, 17% rate of serious TRAEs, and 18% discontinuation rate due to TRAEs. In the same study, patients treated in a separate arm consisting of Opdivo plus Yervoy followed by Opdivo, had a 38% rate of grade 3 or 4 TRAEs, 23% rate of serious TRAEs, and 17% discontinuation rate due to TRAEs.

While the efficacy results in the COMPASSION-15 trial may be numerically greater than the results generated with Opdivo plus chemotherapy (CheckMate 649), we believe the safety profile does warrant caution, and given the trial was conducted solely in China, it remains to be seen how the regimen would perform in a global patient population.

Volrustomig

Also in late-stage development is AstraZeneca's monovalent PD-1xCTLA-4 bispecific, volrustomig (MEDI5752). Volrustomig comprises an anti-PD-1 mAb and the variable binding domains of Imjudo (tremelimumab; anti-CTLA-4 mAb) fused onto a DuetMab backbone and is designed with triple amino acid mutations of the human IgG1 constant heavy chain to reduce Fc-mediate immune effector functions.

AstraZeneca is conducting four Phase III studies evaluating volrustomig in locally advanced cervical cancer (eVOLVE-cervical), unresected locally advanced HNSCC (eVOLVE-HNSCC), frontline metastatic NSCLC (eVOLVE-Lung02), and frontline unresectable pleural mesothelioma (eVOLVE-meso). Initial data for these studies are expected in 2025 or later. The company also recently initiated two platform Phase II studies. One study (eVOLVE-01) is evaluating two dose levels of volrustomig in combination with chemotherapy in patients with NSCLC, with data expected in the second half 2025. The second study (eVOLVE-02) is evaluating volrustomig monotherapy in patients with cervical cancer and in patients with HNSCC.

Initial Phase I data for volrustomig were presented at ASCO 2022, where volrustomig monotherapy at 1,500 mg Q3W achieved a 58% ORR across 12 frontline, IO-naïve, clear cell RCC (ccRCC) patients. However, the 1,500 mg Q3W dose was limited by immune-related AEs, with roughly 25% of patients experiencing grade 3 or 4 liver toxicity and 70% of patients discontinuing treatment.

At ESMO 2023, the company presented updated data from the Phase I study evaluating volrustomig at 500 mg and 750 mg Q3W, which showed improved safety over the previously studied 1,500 mg dose and encouraging efficacy in frontline ccRCC patients.

- Efficacy data were presented for 65 evaluable patients randomized 1:1 to either volrustomig 750 mg Q3W or 500 mg Q3W arms.

- In 32 patients treated with the 750 mg dose, a 48.4% ORR was achieved, including 3 CRs, along with a 90.3% DCR. With a median follow-up of 22.7 months, a 17.0-month median DOR and 12.3-month median PFS were observed, along with a 51.7% 12-month PFS rate.

- In the 500 mg group, a 45.5% ORR was achieved, including 2 CRs, and a 69.7% DCR. With a median follow-up of 14.9 months, a median DOR of 11.5 months and median PFS of 9.5 months were observed, along with a 43.8% 12-month PFS rate.

- While greater efficacy was observed with the 750 mg dose, there were also greater safety liabilities with 62.5% of patients experiencing grade 3 or 4 TRAEs, versus 42.4% in the 500 mg arm. Discontinuation rates were also greater in the 750 mg arm at 46.9% (15 patients) versus 39.4% (13 patients), though there was one treatment-related death in the 500 mg arm due to bronchopulmonary aspergillosis with immune neutropenia.

As mentioned, volrustomig is being evaluated in a Phase III study (eVOLVE-Lung02) in the frontline metastatic NSCLC setting, specifically in patients with PD-L1 TC expression <50%. Phase I/II results for volrustomig in frontline NSCLC expansion cohorts were presented at the 2022 ESMO Congress.

- As of July 12, 2022, 105 patients were enrolled in two separate frontline non-squamous (NSQ) NSCLC dose-expansion cohorts: a single-arm cohort consisting of volrustomig 750 mg plus chemotherapy (n=64) or NSCLC combination cohorts (1:1 randomization) consisting of volrustomig 1,500 mg plus chemotherapy (n=20) or Keytruda 200 mg plus chemotherapy (n=21). At baseline, 45.0% of patients in the volrustomig 1,500 mg/chemotherapy group, 47.6% of patients in the Keytruda/chemotherapy group, and 72.0% in the volrustomig 750 mg single-arm group had PD-L1 expression <1. Of the 105 patients enrolled, data were presented for 91 patients, including 41 patients in the randomized cohorts and 50 patients in the single-arm cohort.

- In the randomized cohort, the volrustomig 1,500 mg/chemotherapy group achieved a 50% ORR across 20 evaluable patients. With a median follow-up of 22.8 months, median DOR was 20.5 months, median PFS was 15.1 months, and median OS was not reached. In patients with PD-L1 expression <1%, ORR was 55.6% (5/9 patients) and median PFS was 13.4 months.

- Comparatively, patients in the Keytruda/chemotherapy group (21 evaluable patients) had a median follow-up of 14.5 months and showed an ORR of 47.6%, median DOR of 9.9 months, median PFS of 8.9 months, and median OS of 16.5 months. In patients with PD-L1 expression <1%, ORR was 30.0% (3/10 patients) and median PFS was 9 months.

- Initial data from the single-arm volrustomig 750 mg/chemotherapy group (n=49) showed a 40.8% ORR (confirmed and unconfirmed responses). In patients with PD-L1 <1% (n=36), a 44.4% ORR was reported.

- Additional analyses showed the combination of both 750 mg and 1,500 mg volrustomig with chemotherapy resulted in greater T-cell proliferation compared to Keytruda/chemotherapy.

- Regarding safety, the 1,500 mg volrustomig dose was associated with greater toxicity than the 750 mg dose. Treatment-emergent adverse events leading to treatment discontinuation occurred in 70%, 28.6%, and 20.0% of patients in the volrustomig 1,500 mg/chemotherapy, Keytruda/chemotherapy, and volrustomig 750 mg/chemotherapy groups, respectively. In addition, grade 3 or 4 TRAEs occurred in 80.0%, 61.9%, and 50.0% of patients in the volrustomig 1,500 mg/chemotherapy, Keytruda/chemotherapy, and volrustomig 750 mg/chemotherapy groups, respectively. The most common grade 3 or 4 adverse events occurring in the volrustomig 1,500 mg/chemotherapy group were rash and ALT/AST increase.

Updated data from the single-arm cohort (volrustomig 750 mg/chemotherapy) of the Phase I/II study were recently presented at WCLC 2024:

- Data were presented for 140 patients treated in the frontline NSCLC setting with volrustomig 750 mg plus chemotherapy. Patients were divided into NSQ (n=120) and SQ (n=20) cohorts.

- With a median follow-up of 8.9 months, a 43.7% ORR and 84.9% DCR were reported in the NSQ cohort. In the SQ cohort, median follow-up was 17.6 months, and a 65.0% ORR and 95.0% DCR were reported.

- In patients with PD-L1 TC <1%, a 42.3% ORR in the NSQ group and 50.0% ORR in the SQ group were reported.

- Across all patients, TRAEs of any grade and grade 3 or 4, occurred in 97.1% and 75.7% of patients, respectively. TRAEs leading to discontinuation occurred in 30% of patients, and TRAEs leading to death occurred in 5% of patients (n=7). Of these patient deaths, 2 were deemed related to volrustomig alone (pneumonitis, hypophysitis), 1 related to volrustomig plus chemotherapy (septic shock), and 4 were related to chemotherapy alone (2 cases each of febrile neutropenia and septic shock).

To our knowledge, the volrustomig dose to be used in the Phase III eVOLVE studies has not been disclosed. The Phase III study is evaluating volrustomig plus chemotherapy head-to-head against Keytruda plus chemotherapy, as a frontline treatment in patients with metastatic NSCLC and PD-L1 expression <50%. Randomization will be stratified according to histology (SQ vs. NSQ), PD-L1 expression (<1% vs. 1%-49%), smoking status, and region. Of note, while patients with PD-L1 expression <50% are included in the study, the primary endpoints of PFS and OS are focused only on PD-L1-negative patients (PD-L1 <1% population).

KN046

AlphaMab Oncology is developing the tetravalent PD-L1xCTLA-4 bispecific, KN046. KN046 is a recombinant humanized bispecific antibody comprising two identical strands. Each strand comprises one PD-L1 single-domain antibody (dAb), one CTLA04 dAb, and one Fc domain, fused in tandem. Phase II results for KN046, in frontline triple-negative breast cancer (TNBC) and frontline metastatic NSCLC were recently published. In the TNBC study (Li et al., Nat Comm 2024), 27 patients with treatment-naïve locally advanced inoperable or metastatic TNBC were sequentially assigned to receive KN046 3 mg/kg Q2W plus nab-paclitaxel (n=16) or KN046 5 mg/kg Q2W plus nab-paclitaxel.

- Across 25 evaluable patients treated with KN046 at 3 mg/kg (n=15) and 5 mg/kg Q2W (n=10), in combination with chemotherapy, a 44% ORR was achieved, and median DOR was not reached with a median follow-up of 32.0 months. Across the ITT population, regardless of PD-1 expression, median PFS was 7.33 months and median OS was 30.92 months. In PD-L1 ≥1 patients, median PFS was 8.61 months (versus 4.73 months in PD-L1 <1) and median OS was 26.14 months (versus 30.92 months, respectively).

- Safety was generally consistent with other studies evaluating anti-PD-1 therapies in combination with chemotherapy in frontline TNBC. The majority of immune-related AEs were low grade, with 11.1% of immune-related AEs being grade ≥3 and occurring only in the higher 5 mg/kg dose arm.

These results compare favorably to current combination regimens of anti-PD-1 therapies and chemotherapy in the frontline setting.

- Keytruda in combination with chemotherapy is approved in the same setting, but the label is limited to patients with PD-L1 expression CPS ≥10. In the KEYNOTE-355 study supporting the regimen's approval, a 23-month median OS and 9.7-month median PFS was observed in PD-L1 CPS ≥10 patients. In the ITT population, median OS was 17.2 months and median PFS was 7.5 months.

- In addition, in the IMpassion130 study supporting initial accelerated approval for Tecentriq in combination with chemotherapy (nab-paclitaxel) in frontline TNBC, a median PFS of 7.2 months and median OS of 21.3 months were observed in the ITT population. However, the initial 2019 accelerated approval was withdrawn for Tecentriq in TNBC, following the failed IMpassion131 study (Tecentriq plus paclitaxel) where no survival advantage was observed in both PD-L1-positive patients and the ITT population.

- For a comparison on safety, grade ≥3 immune-related AEs occurred in 5% of patients in the KEYNOTE-355 study (Keytruda plus chemo), 8.7% in IMpassion130, and 11% in IMpassion131. Overall, the KN046 results do show encouraging initial efficacy and safety regardless of PD-1 expression, but similar to the study with cadonilimab, the KN-046 trial was conducted solely in China, and therefore the results will need to be confirmed in a global study.

In the frontline metastatic NSCLC study (Zhao et al., *Cell Rep Med* 2024), 51 patients with NSQ NSCLC (n=51) histology were treated with KN046 in combination with carboplatin and pemetrexed, and 36 SQ NSCLC patients received KN046 in combination with carboplatin and paclitaxel.

- In the overall population (n=87), a 46.0% ORR and 8.1-month median DOR were observed. Median PFS was 5.8 months, with 6- and 12-month PFS rates of 48.0% and 25.7%, respectively. Median OS was 26.6 months, and 12-month OS rate was 74.2%.

- Grade ≥3 KN046-related AEs occurred in 34.5% of patients, with the most common being IRRs (52.9%), pruritis (44.8%), rash (37.9%), and elevated LFTs (AST [34.5%], ALT [28.7%]). Grade ≥3 immune-related AEs were reported in 12.6% of patients on study, and there were 4 treatment-related patient deaths, including one case of immune-related pneumonia considered related to KN046. Across 87 patients, serious TRAEs grade 3 or higher occurred in roughly 30% of patients.

In comparison, in the CheckMate 227 study supporting approval of Opdivo in combination with Yervoy in frontline, PD-L1-positive metastatic NSCLC, an ORR of 33.4% and median OS of 17.1 months were recorded with the combination. In addition, in the Phase III POSEIDON study supporting approval of Imfinzi in combination with Imjudo and chemotherapy in frontline NSCLC, a 38.8% ORR and 14-month median OS were recorded.

Regarding safety, serious TRAEs grade 3 or higher occurred in 18.4% of patients in the CheckMate 227 study and 21.2% in the POSEIDON study comparatively. Again, while the results for KN-046 look encouraging, the trial was conducted solely in China, and therefore confirmation of the safety and efficacy in a global study is needed.

Vudalimab

Xencor is developing the PD-1xCTLA-4 bispecific, vudalimab, using the company's XmAb platform. Vudalimab is currently being evaluated in multiple clinical studies, including in patients with high-risk mCRPC (both monotherapy and in combination with standard of care) and in combination with chemotherapy in patients with NSCLC.

Interim data from the Phase II study were disclosed in February, with data for 14 high-risk mCRPC patients treated with vudalimab every 3 weeks at a flat dose of 1,000 mg (or 1,200 mg in patients >80 kg). These patients were heavily pretreated, with a median of four prior lines of therapy, and 79% having metastatic disease at diagnosis. As of a February 7 data cutoff, an ORR of 12% was observed across 12 evaluable patients, including 3 patients with confirmed PRs and 1 patient with an unconfirmed PR. PSA90 reductions were also observed in 25% (3/12) of patients.

Vudalimab was generally well tolerated, with the most common immune-related adverse events of any grade being rash (29%) and ALT increases (21%). Treatment-emergent events leading to vudalimab discontinuation occurred in two patients. In addition, there was one treatment-related adverse event of grade 5 autoimmune hepatitis (AIH), though Xencor notes that there have been no other cases of grade 5 AIH among over 240 patients treated with vudalimab across three clinical studies.

In the first half of 2025, Xencor will provide a clinical update and go/no-go decision on whether to advance vudalimab monotherapy or vudalimab in combination with chemotherapy in mCRPC. Vudalimab is also in a Phase Ib study in frontline metastatic NSCLC, which continues to enroll.

PD-1xLAG-3 – Appears Unable to Build on Success of Opdualag

The clinical success of the LAG-3 monoclonal antibody relatlimab when used in combination with Opdivo (Opdualag) in melanoma has increased interest in PD-1xLAG-3 bispecifics, although it remains to be seen if a bispecific approach offers any potential advantages over the fixed dose combination of relatlimab and Opdivo.

As highlighted below, a substantial number of PD-1xLAG-3 bispecific programs have been terminated or are not currently advancing in development.

AK129
Akeso is developing the PD-1xLAG-3 bispecific antibody, AK129. AK129 is being evaluated in a Phase I study across multiple solid tumors, though to our knowledge no clinical data for AK129 has been disclosed to date. Akeso recently posted two new Phase I/II clinical trials for AK129, though these studies have not begun recruiting yet. One study plans to evaluate AK129 in combination with chemotherapy and/or Akeso's cadonilimab (PD-1xCTLA-4), as a first-line treatment for patients with unresectable locally advanced or metastatic gastric or gastroesophageal junction cancer (GC/GEJC). The other study plans to evaluate AK129 as monotherapy or in combination with Akeso's AK117 (anti-CD47 antibody) in patients with r/r classic Hodgkin's lymphoma (cHL) who have failed prior anti-PD-(L)1 therapy.

Tobemstomig
Roche recently discontinued development of its PD-1xLAG-3 bispecific, tobemstomig, as disclosed in its 2024 third-quarter earnings release. Limited details were provided regarding the decision, though a media report quoting a Roche spokesperson noted the decision was based on comparisons to historical and control data, which suggested that tobemstomig was unlikely to "serve as a broad immune checkpoint inhibitor backbone to replace the current standard of care." At the time of discontinuation, tobemstomig was in multiple Phase II studies including in triple-negative breast cancer, renal cell carcinoma, melanoma, NSCLC, and other solid tumors.

IBI323
Innovent was also developing the PD-L1xLAG-3 bispecific, IBI323, which was in a Phase I study in advanced solid tumors. According to company reports, it appears that IBI323 is no longer in clinical development. However, there is a Phase II study sponsored by Hunan Province Tumor Hospital that is currently recruiting. The study is evaluating IBI-323 in combination with Avastin and platinum-based chemotherapy in patients with ALK-rearranged NSCLC who have failed frontline alectinib.

Tebotelimab
MacroGenics is developing the tetravalent PD-1xLAG-3 bispecific, tebotelimab (MGD-013), built upon the company's multispecific DART platform. Tebotelimab was previously being evaluated in combination with the anti-B7-H3 antibody, enoblituzumab, in a cohort of a Phase II study in the

frontline R/M HNSCC setting. However, the study was stopped in July of 2022, following a safety analysis that revealed 7 patient deaths across the two study arms, potentially linked to hemorrhagic events. In follow-up, investigators deemed 6 of 7 deaths as related to disease progression or unrelated to study treatment, with the other death possibly related to study treatment. While there is a clinical study in HER2+ gastric cancer listed as active on clinicaltrials.gov, MacroGenics does not currently have any active or ongoing tebotelimab studies, according to the company's latest reports.

FS118

InvoX was developing the PD-L1xLAG-3 bispecific antibody, FS118, which was originally developed by F-Star Therapeutics prior to the company's acquisition by InvoX. A Phase I study evaluating FS118 in solid tumors was terminated, with published results showing a 0% ORR and 46.5% DCR across 43 patients treated with FS118. InvoX's latest reports show that the asset is available for partnering, and there does not appear to be any ongoing studies.

ABL501

ABL Bio was developing the PD-L1xLAG-3 bispecific, ABL501, which was engineered using ABL's Grabody-I platform. ABL disclosed initial Phase I safety results for ABL501 in a public statement. Across 24 patients, drug-related AEs occurred in 75% of patients, of which 4.2% were grade ≥3, and the MTD was not reached. The company does not view the initial data as a failure but has since discontinued further development of ABL501 to focus resources on other pipeline programs.

Exhibit 18
PD-(L)1xLAG-3 Bispecifics in Development

Company	Technology/ Platform	Therapy	First Target	Second Target	Valency	Stage	Indications	Study Start	NCT #	Status
Akesobio	Tetrabody	AK129	PD-1	LAG3	Bivalent	Phase I	Solid tumors	Mar-23	NCT05645276	Recruiting
						Phase I/II	1L G/GEJ	Sep-24	NCT06586294	Not yet recruiting
						Phase I/II	PD-1 refractory cHL	Oct-24	NCT06642792	Not yet recruiting
MacroGenics	DART/ TRIDENT	Tebotelimab (MGD-013)	PD-1	LAG3	Bivalent	Phase I	Solid tumors, hematological malignancies	Aug-17	NCT03219268	Completed
						Phase I	HER2+ gastric cancer	Sep-19	NCT04082364	Active, not recruiting
InvoX	mAb^2	FS118	PD-L1	LAG3	Bivalent	Phase I	Solid tumors	Apr-18	NCT03440437	Available for partnering
Crescendo biologics	Humabody	CB213	PD-1	LAG-3	1+2	Preclinical	-	-	-	-
GENOR BIOPHARMA	-	GB266	PD-L1	LAG-3	1+2	Preclinical	-	-	-	-

Sources: Company reports and William Blair Equity Research

Exhibit 19
Clinical Results With PD-(L)1xLAG-3 Bispecific Antibodies

	Tebotelimab (2023)		FS118 (2023)	Tobemstomig (ESMO 2022)
Phase	Phase I (NCT03219268)		Phase I (NCT03440437)	Phase I/II (NCT04140500)
Disease	Advanced Solid Tumors and Hematologic Cancers		Advanced Solid Tumors	Advanced Solid Tumors
Enrollment	Monotherapy cohort expansion (n-216)	Combination all (tebotelimab dose escalation + cohort expansion) + margetuximab (n=84)	All cohorts (n=43)	35 patients
Patient Characteristics	Median Age: 60 Female: 62.0% ECOG 1: 74.5% Median prior lines: 2 Prior CPI: 61.0% Prior HER2: N/A	Median Age: 61 Female: 67.9% ECOG 1: 60.7% Median prior lines: 2 Prior CPI: 16.7% Prior HER2: 69.0%	All cohorts Median age: 59 Female: 39.5% ECOG 1: 76.7% Median prior lines: 4 Median prior lines for advanced/metastatic disease: 3 Median prior CPI lines: 1	Median age: 61 Female: 62.9% ECOG 0/1: 62.9%/37.1% Prior lines 0/1-2/≥3: 2.9%/57.1%/40.0% Prior CPI: 34.3% Prior radiotherapy: 54.3% Prior surgery: 65.7%
Dosing	Cohort expansion: tebotelimab 600 mg Q2W	tebotelimab 300 mg or 600 mg Q3W + margetuximab 15 mg/kg Q3W	Dose escalation (Cohorts 1-4): 800 µg to 0.3 mg/kg) Ascending 3+3 dose expansion (Cohorts 5-8): 1 to 20 mg/kg	Dose escalation Tobemstomig 50 mg to 2100 mg Q2W
Objective Response Rate (ORR)	EOC: 11% (4/36) TNBC: 6% (2/31) NSCLC: 7% (2/29) DLBCL: 50% (7/14)	HER2+ solid tumors: All Breast: 15% (5/33) GEJ/Esophageal: 20% (2/10) CRC: 50% (4/8)	0% (0/43) DCR: 46.5% (20/43)	17.1% DCR: 51.4%
Subgroup ORR	CPI-naïve NSCLC: 14% (2/14) CPI refractory NSCLC: 0% (0/15) CAR-T naïve DLBCL: 63% (5/8) Post CAR-T DLBCL: 33% (2/6)	No prior HER2: 33.3% (7/21 total) Prior HER2: 14.0% (7/50 total) CPI-naïve: 22.0% (13/59 total) CPI experienced: 8.3% (1/12 total)	-	CPI-naïve: 17.4% (4/23) CPI-experienced: 16.7% (2/12)
Duration of Response	Among 8 responses across EOC, TNBC and NSCLC: 12.1 months DLBCL: NR (95% CI: 3.55 - NE)	16.7 months	-	5.5 months
Adverse Event Rate (Grade 3-5)	Treatment-related: 21.3% Treatment-related serious: 6.9% AE leading to d/c: 11.1% Treatment related fatal: 0%	Treatment-related: 16.7% Treatment-related serious: 6.0% AE leading to d/c: 8.3% Treatment related fatal: 0%	Treatment-related: 58.1% Treatment-related lead to d/c: 2.3%	Treatment-related: 17.1% Leading to discontinuation: 5.7%
Source	Luke et al., *Nature Medicine* 2023		Yap et al., *Clin Cancer Res* 2023	Rohrberg et al., ESMO 2022

Sources: Company reports.

Other Dual-IO Targets

In exhibit 20, we summarize a variety of bispecific therapies generally characterized by targeting two different immune pathways potentially involved in antitumor immunity. While the majority of these programs do combine a PD-(L)1 targeting binder with a second immune target, there are some programs targeting two novel immune pathways in hopes of generating novel biology, such as localized activity within the tumor microenvironment, specific cis- or trans-signaling, or potentially an improved therapeutic index.

Exhibit 20
Other IO Bispecifics in Development

Company	Technology/ Platform	Therapy	First Target	Second Target	Valency	Stage	Indications	Study Start	NCT #	Status
Traditional IOxIO targets										
Genentech	CrossMab	Lomvastomig (RO7121661)	PD-1	TIM-3	Monovalent	Phase I	Solid tumors	Oct-19	NCT03708328	Completed
						Phase II	Esophageal cancer	Jun-21	NCT04785820	Active, not recruiting
AstraZeneca		Sabestomig (AZD7789)	PD-1	TIM-3	Monovalent	Phase I/II	Solid tumors	Sep-21	NCT04931654	Recruiting
						Phase I/II	R/R CHL	Mar-22	NCT05216835	Active, not recruiting
						Phase I	Advanced NSCLC	Feb-21	NCT04612751	Recruiting
AstraZeneca		Rilvegostomig (AZD2936)	PD-1	TIGIT	Monovalent	Phase III	1L PD-1+ NSCLC	Apr-24	NCT06357533	Recruiting
						Phase III	Adjuvant BTC	Dec-23	NCT06109779	Recruiting
						Phase I/II	Advanced NSCLC	Sep-21	NCT04995523	Active, not recruiting
						Phase II	GEJ	Jan-23	NCT05702229	Recruiting
						Phase II	HCC, BTC	Apr-23	NCT05775159	Recruiting
HARBOUR BIOMED	HBICE	HBM9027	PD-L1	CD40		Preclinical	-	-	-	-
Aptevo Therapeutics	ADAPTIR	APVO711	PD-L1	CD40		Preclinical	-	-	-	-
CENTESSA PHARMACEUTICALS	LockBody	LB101	PD-L1	CD47	Bivalent	Phase I	Solid tumors	Mar-23	NCT05821777	Recruiting
PharmAbcine		PMC-122	PD-L1	CD47		Preclinical	-	-	-	-
Innovent		IBI-322	PD-L1	CD47	2+1	Phase I	Hematologic malignancies	May-21	NCT04795128	Completed
						Phase II	ES-SCLC	Dec-21	NCT05296603	Recruiting
Akesobio	Tetrabody	AK129	PD-L1	LAG-3	Bivalent	Phase I	Solid tumors	Mar-23	NCT05645276	Recruiting
		AK131	PD-1	CD73	Bivalent	Phase I	Solid tumors	Jan-24	NCT06166888	Recruiting

Sources: Company reports and William Blair Equity Research

Exhibit 20 (Continued)
Other IO Bispecifics in Development

Company	Technology/ Platform	Therapy	First Target	Second Target	Valency	Stage	Indications	Study Start	NCT #	Status
Bristol Myers Squibb agenus	-	AGEN1777 (BMS-986442)	TIGIT	CD96	ND	Phase I	Solid tumors	Oct-21	NCT05025085	Completed
EpimAb Biotherapeutics	FIT-Ig	EMB-09	PD-L1	OX40	ND	Phase I	Solid tumors	Mar-22	NCT05263180	Recruiting
SUMGEN	BIMA	SG2501	CD38	CD47	ND	Phase I	R/R hematological malignancies and lymphoma	Aug-22	NCT05293912	Recruiting
Merus	-	ONO-4685	PD-1	CD3	ND	Phase I	Refractory T-cell lymphoma	Dec-21	NCT05079282	Recruiting
ONO PHARMA 百奥泰 BIO-THERA	-	BAT7104	PD-L1	CD47	ND	Phase I	Solid tumors	Apr-22	NCT05200013	Completed
						Phase I	Advanced malignant tumors	Jan-22	NCT05767060	Recruiting
COMPASS THERAPEUTICS	StitchMabs	CTX-8317	PD-1	PD-L1	ND	Preclinical	Solid tumors	-	-	-
xencor	-	XmAb22841	CTLA-4	LAG3	ND	Phase I	CPI refractory melanoma	Dec-25	NCT05695898	Active, not recruiting
IO x Cytokine										
Roche	-	Eciskafusp Alfa (RG6279)	PD1	IL2v	Fusion protein conjugate	Phase I	Solid tumors +/- Tecentriq	May-20	NCT04303858	Active, not recruiting
InnOvent	-	IBI-363	PD-1	IL2m	Fusion protein conjugate	Phase II	Solid tumors	Apr-24	NCT06281678	Recruiting
							Advanced melanoma	Oct-23	NCT06081920	Recruiting
YZY BIO	Check-BODY	Y101D	PD-L1	TGF-β	-	Phase II	Pancreatic cancer	Feb-23	NCT06266143	Active, not recruiting
						Phase Ib	Solid tumors	Aug-21	NCT05028556	Active, not recruiting
Akesobio	Tetrabody	AK130	TIGIT	TGF-β	Bivalent	Phase I	Solid tumors	Jan-23	NCT05653284	Completed
Incyte Merus	Biclonics	INCA33890	PD-1	TGF-βR2	Bivalent	Phase I	Solid tumors	Jul-23	NCT05836324	Recruiting
Other										
启愈 QureBio	-	Q-1802	PD-L1	Claudin1 8.2	-	Phase I/II	GI tumors	Jun-23	NCT05964543	Recruiting
						Phase I	Solid tumors	May-21	NCT04856150	Recruiting
MacroGenics	DART	MGD024	CD123	CD3	Monovalent	Phase I	R/R hematologic malignancies	Jul-22	NCT05362773	Recruiting
EpimAb Biotherapeutics	FIT-Ig	EMB-09	PD-L1	OX40	-	Phase I	Solid tumors	Jul-22	NCT05263180	Recruiting
Celldex therapeutics	-	CDX-585	PD-1	ILT4	-	Phase I	Solid tumors	May-23	NCT05788484	Recruiting
GENOR BIOPHARMA	-	GB262	PD-L1	CD55	-	Preclinical	-	-	-	-
	-	GBD201	CCR8	CTLA-4	-	Preclinical	-	-	-	-

Sources: Company reports and William Blair Equity Research

PD-1xVEGF – The New Shiny Object

Ivonescimab

Summit Therapeutics and Akeso Bio are developing the tetravalent PD-1xVEGF bispecific, ivonescimab (SMT112/AK112), which is in late-stage development in multiple lung cancer indications.

There has been recent excitement around the PD-1xVEGF bispecific class, following positive results from the HARMONi-2 study, where ivonescimab showed greater efficacy over Keytruda in advanced NSCLC. The HARMONi-2 study was a Phase III study designed to evaluate ivonescimab monotherapy against Keytruda monotherapy, in patients with locally advanced or metastatic NSCLC with positive PD-L1 expression. Positive results noting the beat on efficacy over Keytruda were initially disclosed in September, and shares are up nearly 600% year-to-date. Of note, the HARMONi-2 study was conducted solely in China, and therefore there are questions on how applicable the data is for a global population.

It is worth highlighting that previous studies combining Avastin plus chemotherapy versus chemotherapy alone in NSCLC have suggested improved outcomes in Asian patients over other demographics, including the subgroup analysis of the AVAiL study and the SAiL study. Overall survival benefit was only observed in the Asian subgroup analysis of the AVAiL study.

Full results from HARMONi-2 were presented at the International Association for the Study of Lung Cancer's World Conference on Lung Cancer 2024.

- The study enrolled 398 total patients, who were randomized 1:1 to either ivonescimab or Keytruda. Patients enrolled had stage IIIB to IV advanced NSCLC, with no prior systemic therapy, no EGFR or ALK mutations, and had PD-L1-positive status (TPS ≥1%).

- With a median follow-up of 8.67 months, ivonescimab demonstrated a statistically significant improvement over Keytruda on the primary endpoint of PFS, achieving an 11.1-month median PFS versus a 5.8-month median PFS for Keytruda (HR 0.51). Similar efficacy was observed across key subgroups, including patients with SQ (stratified HR 0.48) and NSQ histology (stratified HR 0.54), and patients with PD-L1 TPS ≥50% (stratified HR 0.46) and PD-L1 TPS 1%-49% (stratified HR 0.54). Of note, PFS slightly favored the Keytruda arm (HR 1.01) in patients with stage IIIB/C disease, but PFS benefit favored the ivonescimab arm in patients with stage IV disease (HR 0.49).

- OS was immature at the time of analysis and will be evaluated in the future.

- The ivonescimab group achieved a 50.0% ORR and 89.9% DCR, and median DOR was not reached. Comparatively, the Keytruda group showed a 38.5% ORR and 70.5% DCR, and median DOR was also not reached.

- Treatment-related grade ≥3 and serious adverse events occurred in 29.4% and 20.8%, respectively, of patients in the ivonescimab group, versus 15.6% and 16.1%, respectively, in the Keytruda group. AEs leading to discontinuation occurred in 1.5% of patients in the ivonescimab group versus 3.0% in the Keytruda group. AEs leading to death occurred in 0.5% of patients in the ivonescimab group versus 1.0% in the Keytruda group. Similar safety trends were also observed in the SQ subgroup. Notable differences in safety between the two treatment groups included greater rates of proteinuria, hypertension, and laboratory abnormalities (anemia, amylase increase, ALT increase) in the ivonescimab group.

Another notable Phase III readout for ivonescimab was the HARMONi-A study, which evaluated ivonescimab plus chemotherapy versus placebo plus chemotherapy in patients with EGFRm, locally advanced or metastatic NSQ NSCLC with progression following treatment with an EGFR tyrosine kinase inhibitor (TKI). Like the HARMONi-2 study, this study was conducted in China only, and therefore we also question the generalizability of the findings to a broader population. Full results from the study were presented at the 2024 ASCO conference:

- The primary endpoint of PFS was met, with a hazard ratio of 0.46 and a median of 7.1 months versus 4.8 months. Although immature, the overall survival is also trending in a positive direction, although that benefit has reduced with longer follow-up, with a hazard ratio of 0.72 after 30% of survival events and a hazard ratio of 0.8 with additional follow-up and 52% of events.

- There was an increase in serious adverse events, at 28.6% versus 16.1%; however, only 5.6% of patients discontinued ivonescimab, and overall, the bispecific does not appear to add significant immune-related adverse events.

- As mentioned by the discussant at the conference, the biggest limitation of the study was the lack of a control arm that evaluated a VEGF antibody or PD-(L)1 antibody alone in combination with chemotherapy, therefore making it difficult to know the contribution of each component of the bispecific antibody. Multiple prior studies have evaluated a PD-(L)1 antibody in combination with a VEGF antibody and chemotherapy in lung cancer and have shown benefits in response rates and progression free survival, including in EGFR-mutant subsets of the study. In a subgroup analysis of patients with EGFR mutations in the IMpower150 study, the combination of Tecentriq, Avastin, and platinum chemotherapy showed improved PFS over Avastin plus platinum chemotherapy alone, with a median PFS of 10.2 months versus 6.9 months (hazard ratio of 0.61). The hazard ratio was even higher in patients who had received previous EGFR TKI at 0.42.

- In contrast, there was no benefit for patients who received Tecentriq plus platinum chemotherapy versus those who received Avastin plus platinum chemotherapy. There was a slight improvement in the overall survival for patients on Tecentriq, Avastin, and platinum chemotherapy with a median OS of 26.1 months versus 20.3 months for patients on Avastin plus platinum chemotherapy; however, the hazard ratio for OS was only 0.91. The hazard ratio for patients with prior EGFR TKI therapy was better at 0.74, although the confidence intervals are wide given the small patient numbers available.

Ivonescimab is currently being evaluated in two registrational Phase III trials in lung cancer: HARMONi and HARMONi-3. Importantly, both these studies are being conducted globally.

The HARMONi study is evaluating ivonescimab plus chemotherapy in patients with EGFRm locally advanced or metastatic NSQ NSCLC, with progression following a third-generation EGFR TKI. Study enrollment has been completed (as of the company's third-quarter earnings release) and top-line data is expected in mid-2025.

The HARMONi-3 study is evaluating ivonescimab plus chemotherapy in frontline metastatic SQ NSCLC patients without actionable genomic alterations (AGAs). As of the company's third-quarter earnings update, Summit noted plans to amend the study protocol to include patients with both SQ and NSQ histology. The company also plans to update the primary endpoint to include two primary endpoints of PFS and OS, and the study size to include an estimated 1,080 patients.

- Akeso presented updated Phase II (AK112-201) data in this setting at the 2024 European Lung Cancer Conference, which evaluated ivonescimab in combination with chemotherapy in frontline, SQ and NSQ advanced/metastatic NSCLC without AGAs.

- A total of 135 patients were evaluated in cohort 1 of the study, with patients divided into NSQ (n=72) or SQ histology (n=63) cohorts. Both patients received a combination of ivonescimab in combination with platinum-based chemotherapy (NSQ group received pemetrexed plus carboplatin; SQ group received paclitaxel plus carboplatin).

- With a median follow-up of 21.3 months, patients in the NSQ group achieved a 54.2% ORR, 15.4-month median DOR, 13.3-month median PFS, and 58.9% estimated 9-month PFS. With a median follow-up of 22.1 months, median OS was not evaluable, and estimated 9-month OS was 81.9% in the NSQ group.

- With a median follow-up of 21.3 months, patients in the SQ group achieved a 71.4% ORR, 12.7-month median DOR, 11.1-month median PFS, and 65.1% estimated 9-month PFS. With a median follow-up of 22.1 months, median OS was not evaluable, and estimated 9-month OS was 90.4% in the SQ group.

- Grade ≥3 TRAEs occurred in 56.9% of patients in the NSQ group versus 66.7% in the SQ group. Treatment-related events leading to ivonescimab discontinuation occurred in 2.8% of patients in the NSQ group and 11.1% of patients in the SQ group. Treatment-related events leading to death occurred in 4.2% of patients in the NSQ group and no patients in the SQ group.

- Efficacy data were also reported for cohort 2 (EGFR-positive NSCLC with progression following EGFR-TKI) and cohort 3 (PD-1 and platinum-doublet chemotherapy refractory). With a median follow-up of 25.8 months, patients treated in cohort 2 achieved a 68.4% confirmed ORR, 8.7-month median DOR, 8.5-month median PFS, 22.5-month median OS, and 73.7% estimated 12-month OS. With a median follow-up of 24.7 months, patients treated in cohort 3 achieved a 40.0% confirmed ORR, 12.7-month median DOR, 7.1-month median PFS, 17.1-month median OS, and 65.0% estimated 12-month OS.

A third Phase III (HARMONi-7) study is planned to initiate in early 2025 to evaluate ivonescimab monotherapy in frontline metastatic NSCLC patients with high PD-L1 expression and without AGAs. The study plans to enroll an estimated 780 patients and has primary endpoints of PFS and OS.

BNT327/PM8002

BioNTech is developing the PD-L1xVEGF bispecific BNT327/PM8002. BNT327 was previously developed in collaboration with Biotheus; however, BioNTech announced plans to acquire Biotheus in November 2024. The acquisition will grant BioNTech full global rights to BNT327 and is expected to close in the first quarter of 2025.

BioNTech has noted the initial development strategy is focused on combining BNT327 with standard-of-care chemotherapy in potential fast-to-market indications. Multiple registrational studies for BNT327 are planned to start in 2024 and 2025.

BioNTech and Biotheus recently initiated two Phase II dose optimization studies for BNT327 in SCLC and TNBC.

- In October, the companies dosed the first patient in the Phase II dose-optimization study of BNT327 in combination with chemotherapy in patients with TNBC. These data are intended to inform a registrational Phase III study in first-line TNBC, which is expected to start in 2025.

- In September, the companies dosed the first patient in a Phase II trial evaluating BNT327 in combination with chemotherapy in patients with untreated ES-SCLC and second-line-plus SCLC. A Phase III registrational study in first-line SCLC is planned to start by year-end.

- A Phase II/III study in frontline NSCLC is also expected to start by year-end.

BioNTech also plans to evaluate BNT327 in novel combinations with ADCs. A cohort evaluating BNT327 alone or in combination with BNT325/DB-1305 (TROP2-targeted ADC) in various solid tumors was initiated in an ongoing Phase I/II study. Additional combination studies with ADCs are also planned to start in 2024 and 2025.

BNT327 has shown clinical activity across a broad range of tumors, including in NSCLC, EGFRm NSCLC, TNBC, cervical cancer, platinum-resistant ovarian cancer, clear cell renal cell carcinoma (ccRC), and non-clear cell RCC (nccRCC).

Phase I/II data across multiple indications were recently presented at the 2024 ESMO Congress:

BNT327 in combination with chemotherapy (nab-paclitaxel) in patients with EGFRm NSCLC with progression on prior EGFR-TKI treatment:

- A total of 64 patients were treated with BNT327 plus chemotherapy (carboplatin and pemetrexed) followed by BNT327 plus pemetrexed maintenance therapy, and patients were stratified by PD-L1 expression status (PD-L1 negative [TPS <1%]; PD-L1 low expression [TPS 1-49%] and PD-L1 high expression [≥50%]).

- Across 64 total patients treated with BNT327 and a median follow-up of 7.7 months, a confirmed 57.8% ORR (60.9% unconfirmed) was achieved, which comprised all partial responses. Unsurprisingly, confirmed response rates were greater in patients with PD-L1 low and high expression at 60.9% and 92.3%, respectively.

- Grade ≥3 TRAEs occurred in 61% patients, with hematological events being the most common. TRAEs leading to discontinuation of BNT327 only or chemotherapy only occurred in 6.3% of patients. Grade ≥3 immune-related and VEGF-related adverse events occurred in 6.3% and 10.9% of patients, respectively.

- Given the single arm nature of the study, it is again difficult to determine if the bispecific construct is truly adding any additional efficacy or safety benefit, though it has been previously demonstrated that combining a PD-1 and VEGF antibody separately does result in greater efficacy.

    – In a subgroup analysis of the IMpower150 study in patients with EGFR mutations, the combination of Tecentriq, Avastin, and platinum chemotherapy showed improvements in PFS (mPFS of 10.2 months) over Avastin and platinum chemotherapy alone (mPFS of 7.1 months) and Tecentriq and platinum chemotherapy alone (mPFS 6.9 months); and OS with 26.1-month mOS versus 20.3-month OS with Avastin/chemo alone and 21.4-month mOS with Tecentriq/chemo alone. In the same study however, the combination of Tecentriq, Avastin, and platinum chemotherapy did result in greater toxicity than either Tecentriq or Avastin alone (in combination with chemotherapy) with grade 3-4 TRAEs occurring in 66.7% of patients versus 56.8% and 55.8%, respectively.

BNT327 in combination with chemotherapy (nab-paclitaxel) in frontline locally advanced or metastatic TNBC:

- Data were presented for 42 patients treated and a median follow-up of 16.3 months. In the overall population, treatment with BNT327 and chemotherapy resulted in a 73.8% confirmed ORR (78.6% unconfirmed), including one complete response, and a mPFS of 13.5 months. In patients with PD-L1 CPS <1, PD-L1 CPS 1-10, and CPS ≥10, confirmed ORR was 76.9%, 56.3%, and 100%, respectively. Median PFS was not reached in patients with PD-L1 CPS <1, and was 14.0 months

and 10.8 months in patients with PD-L1 CPS 1-10 and CPS ≥ 10, respectively. ORR benefit was also observed regardless of FUDAN molecular subtype, including BLIS (basal-like and immune-suppressed), IM (immunomodulatory), LAR (luminal androgen receptor), MES (mesenchymal-like), and unclassified/unknown patients. Grade ≥3 TRAEs occurred in 57.1% of patients with the most common being hematological events, and serious adverse events occurred in 23.8% of patients. In addition, TRAEs led to treatment discontinuation in 4.8% of patients.

- Updated data from the study with roughly 3.5 months of additional follow-up, were recently presented at the San Antoni Breast Cancer Symposium. Across 42 patients, confirmed ORR was 73.8% (78.6% unconfirmed). In patients with PD-L1 CPS <1, PD-L1 CPS 1-10, and CPS ≥10, confirmed ORR was 76.9%, 56.3%, and 100%, respectively. Median PFS was 13.5 months across all patients, 18.1 months in patients with PD-L1 CPS <1, 14.0 months in patients with PD-L1 CPS 1-10, and 10.8 months in patients with CPS ≥10. Median OS was immature, though 12-month, 15-month and 18-month OS rates across all patients were 80.8%, 78.1%, and 69.7%, respectively. Safety was consistent with the ESMO dataset. Grade ≥3 TRAEs occurred in 59.5% of patients, and no grade 5 TRAEs were observed. TRAEs leading to discontinuation occurred in 9.5% of patients. The majority of grade ≥3 TRAEs were hematologic-related, and VEGF-associated AEs including hypertension and proteinuria were primarily low-grade.

- A Phase III study of BNT327 in combination with chemotherapy in first-line TNBC is ongoing in China, with an estimated primary completion in 2027. A global Phase II study evaluating BNT327 in combination with chemotherapy in both first- and second-line TNBC is also ongoing.

BNT327 monotherapy in patients with second-line clear cell renal cell carcinoma and first-line non-clear cell renal cell carcinoma:

- A total of 31 patients with ccRCC and 22 patients with nccRCC were enrolled, the majority of whom had intermediate- or poor-risk disease score. Median follow-up was 14.1 months in the ccRCC cohort and 9.0 months in the nccRCC cohort. In 28 evaluable patients in the ccRCC cohort, an ORR of 25.0% was observed (all partial responses) with a median DOR of 19.6 months and mPFS of 10.9 months. ORR was 36.4% in 22 evaluable nccRCC patients, and mPFS was 15.1 months.

- Grade ≥3 TRAEs occurred in 41.5% of all patients, with the most common being proteinuria (15.1%), hypertension (15.1%), and blood pressure increase (5.7%). Serious adverse events occurred in 15.1% of patients and TRAEs led to discontinuation in one patient.

HB0025

Huabo Biopharma is developing the PD-L1xVEGF bispecific, HB0025. Phase I data for HB0025 in patients with NSCLC were published in an online abstract at the 2024 ASCO conference:

- Data were presented for 12 NSCLC patients receiving various doses of HB00025 (3 mg/kg to 30 mg/kg). Patients had a median of four prior lines of treatment and included patients with both SQ and NSQ histology and with or without EGFR/ALK mutations.

- Among 12 evaluable patients, a 25% ORR (3/12; all PRs) and 66.7% DCR was achieved.

- TRAEs occurred in 91.7% of patients, with the most common being proteinuria, lymphocyte count decrease, blood bilirubin increases, and blood pressure increases. Grade ≥3 TRAEs occurred in 16.7% of patients. No TRAEs led to treatment discontinuation or death.

- A Phase II study in patients with advanced ccRCC is ongoing, with an estimated primary completion in early 2025.

IMM2510

ImmuneOnco and Instil Bio are developing the PD-L1xVEGF bispecific, IMM2510 (SYN-2510). Synbiotx (wholly owned subsidiary of Instil) in-licensed global development and commercialization rights for IMM2510 outside of China. ImmuneOnco plans to provide a Phase I clinical update for IMM2510 monotherapy in multiple solid tumors in the first half of 2025. The Phase I study is being conducted solely in China.

Phase I/II studies for IMM2510 in combination with chemotherapy in frontline NSCLC and TNBC are planned to start in late 2024 and early 2025, respectively. These studies are also planned to be conducted in China.

U.S. IND submission for IMM2510 is planned in late 2024, and a Phase II study of IMM2510 monotherapy in second-line NSCLC is planned to start in the second half of 2025.

Initial Phase I data for IMM2510 were published in an online abstract at ASCO 2024, and since then roughly 65 additional patients have been dosed. As mentioned, a clinical update of the study is expected in the first half of 2025.

- Data were presented for 33 patients treated with IMM2510 across 9 dose levels (0.007-20.0 mg/kg). Patients had a median of 3 prior lines of therapy, and 27% had prior treatment with an anti-PD-(L)1 therapy.

- In 25 evaluable patients, a 12% ORR (3/25) was observed. All responses were partial responses, including two PRs in SQ NSCLC patients and one PR in a patient with thymus-adenosquamous carcinoma.

- TRAEs occurred in 97% of patients, with most being grade 1 or 2. Grade ≥3 TRAEs occurred in 33.3% of patients, including IRR, platelet count decrease, lymphocyte count decrease, and diarrhea. TRAEs leading to discontinuation occurred in 9.1% of patients (hypersensitivity and pyrexia), and there were no DLTs.

LM-299

Merck and LaNova Medicines are developing the PD-1xVEGF bispecific LM-299. Merck recently entered into an exclusive global license agreement with LaNova for the development and commercialization of LM-299, expected to close in the fourth quarter of 2024. A Phase I study of LM-299 in advanced solid tumors in China is currently recruiting. Prior to announcement of the licensing agreement with Merck, LaNova noted that U.S. IND submission for LM-299 was planned in the second half of 2024.

Overall, while there are multiple datasets demonstrating clinical activity of PD-L1xVEGF bispecifics, we believe additional data from global studies, including demonstrating a survival advantage, will be key to establishing a new standard of care given the multiple disappointing datasets with PD-L1 plus Avastin combinations, including lack of meaningful overall survival advantages.

Exhibit 21
PD-(L)1xVEGF Bispecifics in Development

Company	Technology/ Platform	Therapy	First Target	Second Target	Valency (Per Target)	Stage	Indications	Study Start	NCT #	Status
Summit therapeutics / Akesobio	Tetrabody	Ivonescimab (SMT112/AK112)	PD-1	VEGF	Bivalent	Phase III	2L EGFRm NSCLC	May-23	NCT06396065	Active, not recruiting
						Phase III	2L EGFRm NSCLC	Jan-22	NCT05184712	Active, not recruiting
						Phase III	1L Squamous NSCLC	Oct-23	NCT05899608	Recruiting
						Phase III	1L NSCLC Stage IIIb/c or IV, TPS ≥1%	Nov-22	NCT05499390	Active, not recruiting
						Phase II	Advanced Gynecological Tumors	Mar-21	NCT04870177	Unknown status
						Phase II	Metastatic CRC	Jul-22	NCT05382442	Recruiting
						Phase II	Unresectable HCC	Aug-22	NCT05432492	Unknown status
BIONTECH / BIOTHEUS 普米斯生物技术	-	BNT327/PM8002	PD-L1	VEGF	Bivalent	Phase III	1L inoperable TNBC	Jun-24	NCT06419621	Recruiting
						Phase III	1L SCLC	Dec-24	NCT06712355	Not yet recruiting
						Phase II/III	1L NSCLC	Dec-24	NCT06712316	Not yet recruiting
						Phase II/III	1L ES-SCLC	Jun-23	NCT05844150	Recruiting
						Phase II/III	2L EGFRm NSCLC	Jun-23	NCT05756972	Active, not recruiting
						Phase II	1L HCC	Apr-22	NCT05864105	Recruiting
						Phase II	1L MPM	Aug-22	NCT05918107	Recruiting
						Phase II	2L SCLC	May-22	NCT05879068	Recruiting
						Phase II	2L NEN	May-23	NCT05879055	Recruiting
华博生物 HUABO BIOPHARM	-	HB0025	PD-1	VEGF	Bivalent	Phase II	ccRCC	Jan-23	NCT06222125	Recruiting
						Phase I	Solid tumors	Jun-22	NCT04678908	Unknown status
RemeGen 荣昌生物	HiBody	RC148	PD-L1	VEGF	-	Phase I	Solid tumors	Sep-23	NCT06016062	Recruiting
MERCK / LaNova 礼新医药	-	LM-299	PD-1	VEGF	-	Phase I	Solid tumors	Oct-24	NCT06650566	Recruiting
宜明昂科 ImmuneOnco / InstilBio	-	IMM2510 (SYN-2510)	PD-L1	VEGF	Bivalent	Phase I	Solid tumors	Aug-21	NCT05972460	Recruiting

Sources: Company reports and William Blair Equity Research

Exhibit 22
Clinical Results With PD-1 and VEGF Combination Modalities in Second-Line EGFR-mutant NSCLC

	IMpower150: EGFRm subgroup analysis			HARMONi-A (ASCO 2024)		ORIENT-31			Impower 151: EGFR/ALKm subgroup		ATTLAS	
Phase	Phase III (NCT02366143)			Phase III (NCT05184712)		Phase III (NCT03802240)			Phase III (NCT04194203)		Phase III (NCT03991403)	
Setting	EGFR-mutant NSCLC with progression on EGFR-TKI (10% of ITT population)			EGFR-mutant NSCLC with progression on EGFR-TKI		EGFR-mutant NSCLC with progression on EGFR-TKI			EGFR/ALK-mutant subgroup NSCLC with progression on EGFR TKI		EGFR/ALK-mutant NSCLC with progression on EGFR TKI	
Arms	Arm B: Tecentriq + Avastin + chemo	Arm A: Tecentriq + chemo	Control: Avastin + chemo	Ivonescimab (anti PD-1xVEGF bispecific) + chemo	Placebo + chemo	Sintilimab + IBI305 (VEGF) + chemo	Sintilimab + chemo	Chemo	Arm A: Tecentriq + Avastin (VEGF) + chemo	Arm B: Placebo + Avastin + chemo	Tecentriq + Avastin (VEGF) + chemo	Chemo
Enrollment	34	45	45	161	161	158	158	160	81 (53.3% of ITT population)	82 (53.6% of ITT population)	154	74
ORR	**71%**	36%	42%	**50.6%**	35.4%	**48.1%**	34.8%	29.4%			**69.5%**	41.9%
mPFS	**10.2 mos (HR 0.61)**	6.9 mos (HR 1.14)	6.9 mos	**7.1 mos (HR 0.46, p<0.001)**	4.8 mos	**7.2 mos (HR 0.51, p<0.0001)**	5.5 mos (HR 0.72)	4.3 mos	**8.5 mos (HR 0.86)**	8.3 mos	**8.5 mos (HR 0.62)**	5.6 mos
Landmark PFS				6-mo: 55.4% 9-mo: 37.9%	6-mo: 33.1% 9-mo: 18.3%							
mOS	NE (17.0, NE) (HR 0.61)	21.4 mos (HR 0.93)	18.7 mos	17.1 (14.6, NE) HR 0.72	14.5 (12.8, 18.1)	21.1 mos (HR 0.98, p=0.8883)	20.5 mos (HR 0.97, p=0.8202)	19.2 mos			20.6 mos (HR 1.01)	20.3 mos
Adverse Events	Any treatment-related: 100% Grade 3-4: 64% Grade 5: 0% Serious: 36% Leading to withdrawal from any treatment: 33% Immune-related in >5 pts in any arm Rash: 30% Hypothyroidism: 18%	Any treatment-related: 89% Grade 3-4: 57% Grade 5: 0% Serious: 34% Leading to withdrawal from any treatment: 14% Immune-related in >5 pts in any arm Rash: 36% Hypothyroidism: 2%	Any treatment-related: 96% Grade 3-4: 57% Grade 5: 2% Serious: 21% Leading to withdrawal from any treatment: 16% Immune-related in >5 pts in any arm Rash: 11% Hypothyroidism: 2%	Any grade: 98.1% Any grade≥3: 54.0% Grade≥3 immune-related: 6.2% Grade≥3 VEGF-related: 3.1% Serious: 28.6% Leading to discontinuation: 5.6% Leading to death: 0%	Any grade: 95.0% Any grade≥3: 42.9% Grade≥3 immune-related: 2.5% Grade≥3 VEGF-related: 2.5% Serious: 16.1% Leading to discontinuation: 2.5% Leading to death: 0%	Any TRAE: 98.7% Grade ≥3 TRAE: 55.7% Treatment-related serious AE: 31.6% TRAE leading to discontinuation: 15.8% TRAE leading to death: 3.8%	Any TRAE: 96.8% Grade ≥3 TRAE: 41.0% Treatment-related serious AE: 21.2% TRAE leading to discontinuation: 9.0% TRAE leading to death: 0.6%	Any TRAE: 96.9% Grade ≥3 TRAE: 49.4% Treatment-related serious AE: 23.8% TRAE leading to discontinuation: 5.0% TRAE leading to death: 0.6%	ITT population Any TRAE: 98.7% Grade ≥3 TRAE: 73.0% Treatment-related serious: 36.8% AE leading to Tecentriq d/c: 7.2% AE leading to Avastin d/c: 14.5%	ITT population Any TRAE: 100.0% Grade ≥3 TRAE: 68.6% Treatment-related serious: 32.0% AE leading to Tecentriq d/c: 5.2% AE leading to Avastin d/c: 10.5%	Any TRAE: 96.7% Grade ≥3 TRAE: 35.1% TRAEs leading to interruption or modification: 54.3% TRAEs leading to discontinuation: 1.3% TRAEs leading to death: 2.0%	Any TRAEs: 75.7%% Grade ≥3 TRAE: 14.9% TRAEs leading to interruption or modification: 13.5% TRAEs leading to discontinuation: 0% TRAEs leading to death: 0%
Source	Reck at al., ELCC 2019			Zhang et al., ASCO 2024		Lu et al., Lancet 2023			Zhou et al., IASLC 2023		Park et al., J Clin Oncol 2024	

Sources: Company reports.

Bispecifics in Autoimmune Disease

Deeper B-Cell Depletion in Hopes of an "Immune Reset"
B cells play a key role in numerous autoimmune diseases, resulting in CD20 antibodies such as Rituxan and Ocrevus being important aspects of treatment regimens across many autoimmune diseases. However, recent clinical and translational data have suggested achieving broader B-cell depletion through CD19 targeting and deeper depletion of B cells with more potent mechanisms can result in greater therapeutic benefit for patients. A major contributor to this renewed interest has been the exciting results from a series of case studies demonstrating the efficacy of CD19-directed CAR-T for the treatment of severe/refractory cases of lupus, myositis, and scleroderma from Dr. Georg Schett and colleagues at the University of Erlangen. Based on these results, several biotech companies are developing CAR-T cell therapies in various autoimmune indications.

As discussed in our initiation report for Cullinan Therapeutics and at our recent event focused on CD19-targeting therapies in autoimmune disease, many developers of B-cell depleting therapies including CAR-T and bispecific T-cell engagers (TCEs) have recently either entirely pivoted to focus on autoimmune indications or have added autoimmune programs for therapies already in development in oncology. Like CAR-Ts, B-cell targeting TCEs have the potential to be effective in B-cell driven autoimmune diseases by depleting the B-cell compartment, particularly in tissues where inflammation is occurring or being promoted. Bispecific TCEs could differentiate from cell therapies based on advantageous features with respect to convenience (subcutaneous administration), manufacturing (off-the-shelf), and safety (reduced CRS/ICANS, no secondary malignancy risk).

Cullinan Therapeutics pivoted its CD19xCD3 T-cell engager CLN-978 from oncology to autoimmune disease earlier this year. Cullinan has recently initiated a Phase I study in SLE (NCT06613360) and plans to initiate a Phase I study in rheumatoid arthritis in the second quarter of 2025. Initial results in SLE are expected in the fourth quarter of 2025. IGM Biosciences has also pivoted development of its CD20xCD3 IgM T-cell engager imvotamab to autoimmune indications including SLE, rheumatoid arthritis, and myositis after generating initial data in NHL. Similarly, Xencor has pivoted development of plamotamab (CD20xCD3) from oncology to autoimmune (rheumatoid arthritis) after Johnson & Johnson terminated its license agreement for the asset. Xencor is also developing a novel CD19xCD3 (XmAb657) specifically for autoimmune indications designed with a long half-life (with first-in-human study initiation expected in the second half of 2025). Novartis is testing a trispecific CD19xCD3xCD2 T-cell engager PIT565 in SLE, while continuing development in B-cell malignancies, according to the company's pipeline. We also note that Amgen is initiating a Phase IIa study evaluating both the subcutaneous formulation of Blincyto and the CD19 monoclonal antibody Uplizna in SLE (NCT06570798).

Roche is studying Lunsumio (CD20xCD3), which is already approved in follicular lymphoma, in a Phase I study in SLE (NCT05155345). The study is evaluating two doses of Lunsumio one week apart and will include 12 months of follow-up in roughly 50 patients. The study is estimated to be completed by mid-2025, and results could be presented at EULAR. Roche is also evaluating a CD19xCD3 T-cell engager RO7507062 optimized to drive deep B-cell depletion with low cytokine release. RO7507062 is also being evaluated in a two-dose regimen over one week, and a preclinical poster that included trial design for the Phase I SLE study (NCT05835986) was presented at the American College of Rheumatology (ACR) conference in 2024 (see additional details in our ACR recap).

A pair of academic case studies reported the use of Blincyto for the treatment of severe cases of autoimmune conditions including systemic sclerosis (Subklewe et al., EJC 2024) and rheumatoid arthritis (Bucci et al, Nature Medicine 2024), providing initial proof of concept for the CD19-directed TCE class in autoimmune disease. See additional details on these case reports in our notes shared at the time of publication here and here. Additional academic reports on the use of the BCMAxCD3 bispecific Tecvayli in patients with refractory autoimmune diseases (including SLE, rheumatoid

arthritis, Sjogren's syndrome, and systemic sclerosis) were published, providing additional support for B-cell depletion in the autoimmune setting (covered here). There may be certain diseases where BCMA targeting would be particularly beneficial if plasma cells are key drivers of disease, but overall, we believe that CD19 targeting offers the benefits of B-cell depletion, including targeting B-cell precursors that may lead to more durability, without the risks of long-lived plasma cell depletion and loss of vaccine protection.

At the ACR conference, iTabMed presented the first clinical results for the CD19xCD3 T-cell engager A-319 from a Phase I study in SLE. The initial data at ACR included six patients with SLE treated with very low doses (0.05 µg/kg priming for three doses followed by 0.3 µg/kg for three doses weekly during weeks 2 through 4). As discussed in additional detail here, while it was an early look at the data in small patient numbers with low dose levels in an IV formulation, there are signs of benefit across SLEDAI-2K scores and pharmacodynamic markers, which we view as encouraging for the potential of A-319 and bispecific T-cell engagers in SLE broadly. We hosted a fireside chat with iTabMed management following the update, where we discussed the results in detail and next steps for A-319 including the development of a SC formulation with additional data coming in early 2025 (takeaways summarized here).

There are outstanding questions on whether bispecifics will be able to lead to sufficiently deep and durable depletion of the B-cell compartment like CAR-T, given data for TCE use outside of patients with B-cell malignancies is limited to a handful of patients with limited follow-up. Nonetheless, there has been a flurry of business development activity focused on bispecifics in autoimmune disease in 2024, as shown in exhibit 6, on page 8. We highlight a few recent deals, including Merck's acquisition of Curon's CD19xCD3 bispecific CN201 for development in both oncology and autoimmune, and GSK's acquisition of Chimagen's CD19xCD20xCD3 trispecific CMG1A46 for development in lupus and other autoimmune indications. We also highlight the launch of private company Candid Therapeutics with two bispecific antibodies in autoimmune disease, including the BCMAxCD3 CND106 and the CD20xCD3 CND261. Candid was formed through acquiring both Vignette Bio for CND106 (formerly EMB-06, licensed from EpimAb) and TRC 2004 for CND261 (formerly GB261, licensed from Genor Biopharma) in a three-way merger.

Blocking Two Immunology and Inflammation Pathways to Break Through Monotherapy Efficacy Ceilings

Beyond the use of TCEs for B-cell depletion in autoimmune indications, there has also been an increased interest in bispecific therapies targeting two specific pathways involved in inflammation and autoimmunity, such as T-cell receptors or interleukins. These programs often target two independently validated mechanisms that have had successful monoclonal antibody development, with the goal of achieving greater efficacy.

These programs are largely in early stages of development, with limited clinical data publicly disclosed to date. It remains to be seen whether bispecific therapies for autoimmune diseases can achieve novel biology and greater efficacy than can be achieved with two separate monoclonal antibodies, or if new patent protection, manufacturing, and patient convenience (smaller injection volumes) will be the primary benefit.

A lot of the interest in these approaches comes from results generated in a Phase II study conducted by Johnson & Johnson combining two monoclonal antibodies in ulcerative colitis patients, the VEGA study. The study combined the TNFα monoclonal antibody Simponi with the IL-23 antibody Tremfya (during induction for 12 weeks followed by maintenance Tremfya), which are both approved as monotherapy in patients with ulcerative colitis, versus either drug alone. In the 214 patients randomized across the three treatment arms, the combination arm resulted in meaningfully higher rates of clinical remission after 38 weeks of treatment, at 48%, versus 21% for Simponi monotherapy and 31% for Tremfya monotherapy (Feagan et al., Lancet 2023).

As mentioned at the beginning of this report, bispecifics for autoimmune diseases have been a recent focus of business development activity for biopharma companies and will be an area to monitor as clinical data is generated.

Exhibit 23
Bispecifics in Development in I&I and Autoimmune Disease

Company	Technology/ Platform	Therapy	First Target	Second Target	Valency	Stage	Indications	Start Date	NCT #	Status
TCE Bispecifics										
AMGEN	BiTE	SC Blincyto	CD19	CD3	-	Phase IIa	SLE	Dec-24	NCT06570798	Not yet recruiting
igm Biosciences, Inc.	IgM	Imvotamab	CD20	CD3	10+1	Phase I	SLE	Aug-23	NCT06041568	Recruiting
						Phase I	Rheumatoid arthritis	Sep-23	NCT06087406	Recruiting
						Phase I	Myositis	Jul-24	NCT06524687	Recruiting
Roche	CrossMab	Lunsumio	CD20	CD3	Monovalent	Phase I	SLE	Jan-22	NCT05155345	Active, not recruiting
	-	RO7507062	CD19	CD3	-	Phase I	SLE	Dec-23	NCT05835986	Recruiting
cullinan THERAPEUTICS	-	CLN-978	CD19	CD3	-	Phase I	SLE	Nov-24	NCT06613360	Not yet recruiting
						Phase I	RA	2Q 25	-	-
NOVARTIS	-	PIT565	CD19	CD3, CD2	-	Phase I	SLE	Oct-24	NCT06335979	Recruiting
iTAb	iTab	A-319	CD19	CD3	Monovalent	Phase I	SLE	May-24	NCT06400537	Recruiting
		A-329	CD19	CD3	Bivalent	Preclinical	SLE	-	-	-
xencor	-	Plamotamab	CD20	CD3	Monovalent	Phase I/II	Rheumatoid arthritis	-	-	-
	XmAb	XmAb657	CD19	CD3	2+1	Preclinical	Autoimmune disease	-	-	-
MERCK CURON	-	CN201	CD19	CD3	-	Phase I/II (oncology)	Autoimmune disease	-	-	-
CandID EpimAb	-	CND106 (EMB-06)	BCMA	CD3	-	Phase I (oncology)	Autoantibody diseases (e.g., MG)	-	-	-
CandID GENOR	-	CND261 (GB261)	CD20	CD3	-	Phase I (oncology)	Autoimmune diseases (e.g., RA)	-	-	-
HARBOUR BIOMED	HBICE	HBM7020	BCMA	CD3	2+1	Preclinical	Autoimmune diseases	-	-	-
Aditum Bio Leads Biolabs	LeadsBody	LBL-051	BCMA, CD19	CD3	-	Preclinical	Autoimmune diseases	-	-	-
igm Biosciences, Inc.	IgM	IGM-2644	CD38	CD3	10+1	Preclinical	gMG	-	-	-

Sources: Company reports and William Blair Equity Research

Exhibit 23 (Continued)
Bispecifics in Development in I&I and Autoimmune Disease

Company	Technology/ Platform	Therapy	First Target	Second Target	Valency	Stage	Indications	Start Date	NCT #	Status
Non-TCE Bispecifics										
sanofi	-	SAR446422	CD28	OX40	-	Phase I	Inflammatory disease	May-23	ANZCTR: ACTRN12623001176651	Enrollment suspended
sanofi / MacroGenics	-	PRV-3279	CD32B	CD79b	-	Phase II	SLE	Jan-22	NCT05087628	Active, not recruiting
zurabio	-	Tibulizumab (ZB-106)	IL-17	BAFF	-	Phase II	Systemic sclerosis	4Q 24	-	-
						Phase II	Hidradenitis suppurativa	2Q 25	-	-
	-	Crebankitug (ZB-168)	IL-7R	TSLP	-	Preclinical	Inflammatory conditions (e.g., UC, AD, alopecia)	-	-	-
	-	Torudokimab (ZB-880)	IL-33	RAGE	-	Preclinical	Inflammatory conditions (e.g., asthma, COPD)	-	-	-
Alpine Immune Sciences	-	Acazicolcept	CD28	ICOS	-	Phase II	SLE	Jun-21	NCT04835441	Active, not recruiting
Pfizer	-	PF-07275315	IL-4, IL-13	TSLP	-	Phase II	Atopic dermatitis	Aug-23	NCT05995964	Recruiting
	-	PF-07264660	IL-4, IL-13	IL-33	-					
Navigator Medicines / IM Biologics	-	IMB-101	OX40L	TNF	-	Phase I	Rheumatoid arthritis	Dec-23	NCT06181786	Not yet recruiting
AstraZeneca	-	AZD1163	ND	ND	-	Phase I	Rheumatoid arthritis	Nov-23	NCT06103877	Recruiting
Pfizer	-	PF-07261271	p40	TL1a	-	Phase I	IBD	Oct-22	NCT05536440	Completed
Johnson&Johnson / numab	-	NM26-2198	IL-4Rα	IL-31	-	Phase I	Atopic dermatitis	May-23	NCT05859724	Terminated (completed study objectives)
InnoVent	-	IBI-3002	IL-4Rα	TSLP	-	Phase I	Asthma	Feb-24	NCT06213844	Recruiting
Celldex	-	CDX-622	TSLP	SCF	-	Phase I	Inflammatory and fibrotic disorders	Nov-24	NCT06650761	Recruiting
argenx	-	ARGX-121	FcRn	IgA	-	Preclinical	IgA-mediated disease	-	-	-
Santa Ana Bio	-	SAB01	cKIT	ND	-	Preclinical	Urticaria, allergy, asthma	-	-	-
triveni BIO	-	TRIV-573	KLK5/7	IL-13	-	Preclinical	I&I	-	-	-
xencor	XmAb	-	TL1A	IL-23	-	Preclinical	IBD	-	-	-
Attovia	ATTOBODY	ATTO-002	IL-31	IL-13	-	Preclinical	Immunology	-	-	-
Johnson&Johnson / Proteologix	-	PX128	IL-13	TSLP	-	Preclinical	Atopic dermatitis, asthma	-	-	-
	-	PX130	IL-13	IL-22	-	Preclinical	Atopic dermatitis	-	-	-
AbClon	AffiMab	AM201	IL-6	TNF-α	Bivalent	Preclinical	Rheumatoid arthritis	-	-	-

Sources: Company reports and William Blair Equity Research

Additional Updates Across Specific Solid Tumor Types

Prostate

PSMA has become a highly sought-after target in prostate cancer in recent years and represents an attractive target given its high expression level on the surface of prostate cancer cells. PSMA has been identified as an indicator of poor prognosis, with high expression associated with disease recurrence, tumor aggressiveness, and androgen independence. While PSMA is highly expressed on prostate cancer cells, there are also low levels of expression in normal tissues, including healthy prostate cells, brain, liver, kidney, and small intestine. While there have been signs of life in the initial data presented for the class, there have also been multiple discontinuations of PSMA T-cell engager (TCE) programs.

As mentioned above, Janux's PSMAxCD3 TCE JANX007 has shown highly encouraging efficacy and safety, likely attributed to its masking technology. In the Phase Ia study in mCRPC, JANX007 has shown potential best-in-disease clinical activity exemplified by impressive PSA responses including high rates of PSA50 (100%), PSA90 (63%), and PSA99 (31%) among a cohort of 16 patients at the most recent update, as well as a strong initial ORR of 50% (4/8) among RECIST-evaluable patients (Janux update, December 2024).

Recall that Johnson & Johnson's PSMAxCD3 bispecific JNJ-081 showed PSA50 response of 7.4% with the subcutaneous formulation and 0% with the infusion. Harpoon's HPN424 (PSMAxCD3x-albumin trispecific) was discontinued after showing just a 1.1% ORR, 2.7% PSA30 response, and 5.4% PSA50 response. Amgen has also evaluated multiple PSMAxCD3 bispecifics, including a continuous infusion BiTE (pasotuxizumab), which showed a 30% PSA50 rate, and the HLE-version acapatamab, which showed a 34% PSA50 rate. Overall, we view the results with xaluritamig as clear proof of concept for STEAP1 targeting with a CD3 bispecific. While PSMA-radioligands have set a new standard of care in chemotherapy-refractory prostate cancer patients, we believe there is still significant unmet medical need, particularly for an immunotherapy-based approach that offers the potential for durable clinical benefit.

Exhibit 24
PSMA-Targeting TCEs in Development

Company	Technology/ Platform	Therapy	Tumor Target	Immune Cell Target	Valency	Stage	Indications	Start Date	NCT #	Trial Status
Johnson&Johnson xencor	XmAb	JNJ-9401	PSMA	CD28	-	Phase I	Prostate cancer (+ JNJ-8343)	Nov-23	NCT06095089	Recruiting
Crescendo biologics	Humabody	CB307	PSMA	4-1BB	-	Phase I	mCRPC (+/- Keytruda)	Jun-21	NCT04839991	Recruiting
REGENERON	VelociBi	Nezastomig (REGN5678)	PSMA	CD28	Monovalent	Phase I	mCRPC (+/- Libtayo)	Aug-19	NCT03972657	Recruiting
		REGN4336	PSMA	CD3	-	Phase I/II	mCRPC (+/- Libtayo or REGN5678)	Nov-21	NCT05125016	Recruiting
dkfz. GERMAN CANCER RESEARCH CENTER	IgGsc	CC-1	PSMA	CD3	Monovalent	Phase I	Biochemical recurrent prostate cancer	Nov-22	NCT05646550	Recruiting
LAVA THERAPEUTICS	Gammabody	LAVA-1207	PSMA	Vγ9Vδ2 TCR	Monovalent	Phase I	Prostate cancer (+/- IL-2 or Keytruda)	Jun-22	NCT05369000	Recruiting
JANUX	TRACTr	JANX007	PSMA	CD3	Monovalent	Phase I	Solid tumors	Sep-22	NCT05519449	Recruiting
VIR	XPAT	VIR-5500 (SAR446329, AMX-500)	PSMA	CD3	-	Phase I	mCRPC	Aug-23	NCT05997615	Recruiting
AbClon	AffiMab	AFM109	PSMA	4-1BB	Bivalent	Research	mCRPC	-	-	-
Aptevo Therapeutics	ADAPTIR-FLEX	APVO442	PSMA	CD3	2+1	Preclinical	Prostate cancer	-	-	-

Sources: Company reports and William Blair Equity Research

Exhibit 25
Clinical Data for PSMA-Targeting T-Cell Engagers

	JANX007		CC-1	Nezastomig (REGN5678)	LAVA-1207	Pasotuxizumab (AMG 212)	Acapatamab (AMG 160)	AMG 340	HPN424	JNJ-8081
Company	Janux		Academic	Regeneron	Lava Therapeutics	Amgen	Amgen	Amgen	Harpoon	Johnson & Johnson
Format	PSMAxCD3 TRACTr		PSMAxCD3	PSMAxCD28	PSMAxVγ9Vδ2 TCR	PSMAxCD3 BiTE	PSMAxCD3 HLE-BiTE	PSMAxCD3 BiTE	PSMAxCD3xAlbumir	PSMAxCD3
Phase	Phase I (NCT05519449)		Phase I (NCT04104607)	Phase I/II (NCT03972657)	Phase I/IIa (NCT05369000)	Phase I (NCT01723475)	Phase I (NCT03792841)	Phase I (NCT04740034)	Phase I/IIa (NCT03577028)	Phase I (NCT03926013)
Status	Ongoing		Ongoing	Ongoing	Ongoing	Discontinued	Discontinued	Discontinued	Discontinued	Discontinued
Indication	mCRPC		mCRPC	mCRPC (3L+)	mCRPC	Advanced CRPC	Advanced mCRPC	mCRPC	Advanced prostate cancer (3L+)	Advanced mCRPC (2L+)
Enrollment	23 patients	16 patients	22 patients	35 patients (33 evaluable)	20 patients	47 patients	133 patients	42 patients	89 patients	39 patients
Baseline Characteristics	Median age: 69 Median PSA: 158.5 ng/mL Median prior lines: 4 Prior taxane: 87%	Median age: 71.5 Median PSA: 80.9 Median prior lines: 4 Prior taxane: 63%	Median age: 69 ECOG 0/1: 57%/43% Median PSA: 259.5 µg/mL LN metastases: 79%	Median age: 67 ECOG 0/1: 37%/63%	Median age: 68 Median prior lines: 4 Bone metastases: 95% LN metastases: 70%	Median age: 69 ECOG 0: 74%	Median age: 67 ECOG 0/1: 51%/48% ≥4 prior lines: 74% Prior taxane: 96%	Mean age: 68.5	Median age: 70 ECOG 0: 44% Median PSA: 129 ng/mL Median prior lines: 5 Prior IO: 33%	Median age: 67 ECOG 0: 41% Gleason score ≥8: 51.3%
Dosing	Dose escalation (0.1-3 mg)	Dose escalation (0.2-9 mg)	Dose escalation (28-826 µg) Dose expansion (826 µg)	Dose escalation (0.1-300 mg) plus Libtayo	Dose escalation (1.5-120 µg)	SC (up to 172 µg) and cIV (up to 80 µg) dose escalation of pasotuxizumab	Dose escalation up to 0.9 mg Dose expansion 0.3 mg	Dose escalation up to 800 mg Q3W	Dose escalation of HPN424 with either fixed dose (up to 160 ng/kg) or step dosing (up to 300 ng/kg)	SC (up to 60 µg/kg) and IV (up to 3 µg/kg) dose escalation of JNJ-081
Objective Response Rate		50% (4/8) 1 cPR, 3 uPR		DL 6-8 (30-300 mg): 1 CR, 1 PR, 1 uPR	0%	SC: 0% cIV: 0%	10.6%	0%	1.1%	0.0%
PSA50 Response Rate	First dose ≥0.1mg: 56% First step dose ≥0.2mg 83%	100%	16% (3/19)	DL 1-5 (0.1-10 mg): 0% DL 6-8 (30-300 mg): 31% (5/16)	0%	SC: 30% (9/30) cIV: 33% (3/9)	31.6%	10% (4/41)	5.4%	SC: 7.4% IV: 0%
PSA90 Response Rate		63%								
PSA99 Response Rate		31%								
PFS		7.4 months					3.1 months			
All Grade CRS	91%	100%	79%	17%	10%		97.7%	52%		
Grade ≥3 CRS	0%	6.25% (After treatment holiday without step-up)	0%	0%	0%	6.0%	20.3%	2%	4%	0%
Grade ≥3 Adverse Events	0%	ALT increase: 19% AST increase: 38% Diarrhea: 13% Anemia: 13%	Lymphopenia, leukopenia, neutropenia, thrombocytopenia, GGT increase	54%	Grade ≥3 TRAE: 0%	53%	CRS: 27.1%		AST increase: 21% ALT increase: 16% Anemia: 11%	43.6%
Discontinuations	0%	0%		2 AEs resulting in death (1 treatment-related)	0%	4%	96%			5.1%
Reference	Janux Presentation February 2024	Janux Presentation December 2024	Heitmann et al., ASCO 2024	Stein et al., ASCO GU 2023	ASCO GU 2023	Hummel et al., *Immunotherapy* 2021	Dorff et al., *Clin Cancer Res* 2024	Falchook et al., ASCO 2024	De Bono et al., ASCO 2021	Lim et al., ASCO-GU 2022

Source: William Blair Equity Research

Outside of PSMA, a handful of other targets are being explored in prostate cancer, including STEAP1, KLK2, and DLL3. The most advanced non-PSMA targeting TCE candidate in prostate cancer is Amgen's xaluritamig (STEAP1xCD3). The first clinical Phase I results of xaluritamig at ESMO 2023 demonstrated high levels of activity in heavily pretreated prostate cancer patients, showing encouraging prostate-specific antigen (PSA) and RECIST responses across all dose cohorts compared to established treatments. The study was designed as a two-part study, consisting of a monotherapy dose exploration with a step-dosing and prophylactic regimen to determine the MTD, followed by dose expansion. Pharmacokinetic findings prompted evaluation of efficacy across high-dose (target dose ≥0.75 mg) and low-dose (target dose <0.75 mg) cohorts. Specifically, treatment with xaluritamig exhibited PSA50 responses of 49% across all cohorts and 59% in high-dose cohorts, and RECIST ORR of 24% across all cohorts and 41% in high-dose cohorts. On the safety front, cytokine release syndrome (CRS) was the most common adverse event, occurring in roughly 70% of patients (but almost entirely grade 1 or 2), although fatigue, anemia, and myalgia were also reported. The company has evaluated multiple step-up dosing schemes, determining the maximum tolerated dose was 0.1 mg on day 1, 0.3 mg on day 8, 1.0 mg on day 15, and 1.5 mg for subsequent doses. Amgen has previously hinted at the potential of xaluritamig in mCRPC, noting a more tumor-specific expression profile of STEAP1, which has potential for improved safety and efficacy over PSMAxCD3 bispecifics.

At ESMO 2024, Amgen presented updated dose-expansion results for xaluritamig in mCRPC from the ongoing Phase I study. Patients with mCRPC were treated at the three expansion doses of 0.75 mg QW (n=35), 1.5 mg QW (n=35), and 1.5 mg Q2W (n=36). Safety for xaluritamig monotherapy was considered manageable and consistent. There were no fatal TRAEs, but grade 3 TRAEs were reported in 66% of patients and grade 4 TRAEs in 9% of patients. SAEs were reported in 60% of patients and the discontinuation rate due to TRAEs was 16%. Overall, the most common TRAE was CRS (76% overall; 9% grade 3), which was mainly grade 1-2 and most frequent in the first cycle, although CRS was also reported in cycle 2 or later (15% at 0.75 mg dose, 26% at 1.5 mg dose). Musculoskeletal inflammatory TRAEs (myalgia, arthralgia, and muscle weakness) were reported in the majority of patients (76% overall; 38% grade 3). The poster noted dose reductions and interruptions were utilized in reducing the musculoskeletal inflammatory TRAEs, but the rates of each were not disclosed.

PSA and RECIST responses were consistent with the initial update. PSA50 responses were reported in 49.5% of patients across the expansion doses, with the highest response rates in the 1.5 mg cohorts (60% and 53% at QW and Q2W, respectively), and PSA90 responses were reported in 28% of patients, similarly with higher response rates for the 1.5 mg cohorts (30% and 34% at QW and Q2W, respectively). Among RECIST evaluable patients (n=69), response rates were 15%, 19%, and 29% for 0.75 mg QW, 1.5 mg QW, and 1.5 mg Q2W, respectively. There was one complete response and 13 partial responses, for a response rate of 20% across the three dose levels. There were initial signs of durability, although follow-up was limited (median follow-up of 6.3 months) with 49% of PSA50 responses ≥3 months. Among radiographic PFS evaluable patients (n=106), the median PFS was 7.8 months.

Overall, the most favorable efficacy and safety in the dose expansion study was reported at the 1.5 mg Q2W xaluritamig dose regimen, where there was a 53% PSA50 response, 34% PSA90 response, and 29% ORR, including one complete response. This dose level also had a favorable safety profile, with the lowest rates of musculoskeletal AEs. Based on these results, the 1.5 mg Q2W was recommended as the Phase III dose for xaluritamig.

Amgen recently initiated a Phase III study evaluating xaluritamig monotherapy versus investigator's choice chemotherapy or androgen receptor therapy. Phase I studies are also ongoing for combination approaches (with abiraterone or enzalutamide) and earlier lines of mCRPC treatment, as well as treatment in neoadjuvant or biochemically recurrent, non-metastatic, castration-sensitive prostate cancer.

Small-Cell Lung Cancer

As mentioned earlier in this report, Amgen's Imdelltra (formerly tarlatamab) was recently approved by the FDA as the first TCE for small-cell lung cancer (SCLC) and the first TCE targeting delta-like ligand 3 (DLL3). DLL3 is a Notch inhibitory ligand and expressed on the majority of SCLC tumors, and the FDA label does not require diagnostic for confirming DLL3 expression. DLL3 is also expressed on other tumor types including neuroendocrine prostate cancer (NEPC) but has little to no expression in normal adult tissues outside the central nervous system.

Imdelltra was evaluated in the pivotal Phase II DeLLphi-301 study at two dose levels, 10 mg and 100 mg Q2W. Results presented at ESMO in 2023 demonstrated greater efficacy and safety at the 10 mg dose (all patients first dosed with 1 mg before step-up on dose 2), with a response rate of 40% versus 32%. However, more complete responses were observed at the higher dose, 1% for 10 mg versus 8% for 100 mg. This does raise the question of whether a dose in the middle of the range, or perhaps an additional step-up dose, may have improved tolerability over the 100 mg dose (grade 3-4 CRS and ICANS occurred most on first dose at 100 mg), yet still drive greater depth of responses than the 10 mg dose arm. The Phase I trial evaluated a wide dose range (0.003 mg to 100 mg), with the expansion cohort at 100 mg; a 23% response rate was reported across all patients, and a 26% response rate at 100 mg.

Dose reductions and interruptions were much more common at the 100 mg dose, at 29%, versus only 14% for the 10 mg arm. Outside of CRS and ICANS, other adverse event rates were similar between the two dosage arms.

Merck acquired Harpoon Therapeutics following the presentation of updated results with HPN328 (now MK-6070), the company's DLL3 TriTAC (CD3 bispecific that binds albumin for half-life extension), at ESMO in 2023. Updated results were presented at ASCO in 2024. A 2 mg priming dose was evaluated but determined to be intolerable, so the 1 mg dose was considered the maximum tolerated priming dose. Doses of 12 mg Q1W, 24 mg Q1W, 12 mg Q2W, and 24 mg Q2W with a 1 mg priming dose are being explored for dose optimization. DLTs were not observed at the target doses. Among all 97 participants, CRS was reported in 64% of patients with 2% grade 3 CRS and 1% grade 4 CRS. The rates of CRS have slightly increased from the last presentation at ESMO in 2023, where they were 59% in 71 patients. ICANS was reported in 7% of patients and was all grade 1 or 2, which is consistent with the prior update. In patients treated with a 1 mg priming dose and a 12 mg or 24 mg target dose with the opportunity to confirm responses, efficacy was reported in each tumor type. The ORR was 39% in SCLC patients (n=28) and 46% in other NENs (n=13). Overall, HPN328 was determined to be tolerable with the 1 mg step-up dose, and initial efficacy appears to be in line with Imdelltra in SCLC, which has a 40% ORR on the label, although further investigation will be needed to understand whether there are differentiating factors in other indications.

Boehringer Ingelheim is also developing the DLL3xCD3 TCE obrixtamig (BI 764532) in SCLC and other neuroendocrine cancers (NECs). Phase I dose-escalation results for obrixtamig in SCLC and other NECs were presented at ASCO in 2023, showing an ORR of 25% (at doses ≥90 µg/kg), coming in somewhat below the ORRs observed with Imdelltra and MK-6070. All-grade CRS was reported in 59% of patients (2% grade 3), in line with the other DLL3xCD3 TCEs. Obrixtamig is also being evaluated in combination with the PD-1 antibody ezabenlimab in DLL3-expressing tumors in an ongoing Phase I/II study.

Exhibit 26
Clinical Data for DLL3-Targeting T-Cell Engagers

	Imdelltra (tarlatamab)	MK-6070 (HPN328)			Obrixtamig (BI 764532)
Phase	Phase II DeLLphi-301 (NCT05060016)	Phase I/II (NCT04471727)			Phase I (NCT04429087)
Indication	SCLC	SCLC	NEPC	Other NEN	SCLC, Other NEC
Enrollment	Efficacy: 100 patients Safety: 187 patients	56 patients	23 patients	18 patients	107 patients
Baseline Characteristics	Median age: 64 Male: 72% ECOG 0/1: 26%/74% Median prior lines: 2 Prior PD-(L)1: 74% DLL3 expression >0%: 96%	Median age: 63.5 Male: 52% ECOG PS 0/1: 39%/61% Median prior lines: 2 Brain/liver mets: 57%/50%	Median age: 70.5 Male: 100% ECOG PS 0/1: 61%/33% Median prior lines: 3 Brain/liver mets: 11%/67%	Median age: 61 Male: 57% ECOG PS 0/1: 43%/57% Median prior lines: 3 Brain/liver mets: 43%/52%	Median age: 60 Male: 57% Median prior lines 1-2/≥3: 67%/31% ECOG PS 0/1: 26%/73% Prior PD-(L)1: 49% Brain/liver mets: 38%/56%
Design	10 mg Q2W IV	0.015 mg to 24 mg QW IV dose escalation 1 mg priming step dose escalation and optimization			Dose escalation Q3W IV, Q1W IV, Q1W IV with step dose
Objective Response Rate	40% (40/100)	SCLC: 39% (11/28) Other NEN: 46% (6/13)			25% (doses ≥90 µg/kg)
Disease Control Rate	70%	SCLC: 71% (20/28) Other NEN: 46% (6/13)			41%
Duration of Response	9.7 months	-			NR
Progression-Free Survival	4.3 months	-			-
Overall Survival	15.2 months	-			-
Median Follow-Up	10.6 months	-			-
CRS Events	All grade: 55% Grade 3-4: 1.6%	All grade: 63% Grade ≥3: 3%			All grade: 59% Grade ≥3: 2%
Adverse Events (Grade ≥3)	CRS: 1.6% Fatigue: 10% Decreased appetite: 2.7% Nausea: 1.6% Constipation: 0.5% Musculoskeletal pain: 1.1% Anemia: 6% Dyspnea: 2.1%	26%			27%
Leading to Discontinuation	7%	4%			4%
Reference	WCLC 2024; Imdelltra Label	ASCO 2024			ASCO 2023

Sources: Company reports and William Blair Equity Research

Colorectal Cancer

One novel approach in the bispecific TCE solid tumor landscape is the selective targeting and activation of T-cell subsets rather than the entire T-cell compartment. Marengo Therapeutics (private) is using this strategy to develop TCEs that target a subset of T cells expressing Vβ6 and Vβ10 TCRs, which have been shown to be enriched in tumor infiltration lymphocytes (TILs). The company's lead molecule invikafusp alfa (STAR0602) is an IL-2xTCRβ (Vβ6/10 selective) bispecific antibody that selective activates Vβ6/10 T cells, which are more likely to be selective for tumor antigens, reducing the systemic effects of cytokine therapies. Marengo's START-001 study, currently ongoing, is specifically enrolling patients with solid tumors with high mutation burden, based on the hypothesis that these tumors will have a higher proportion of TILs likely to respond to the therapy.

Marengo presented the first clinical results from the START-001 study of invikafusp alfa (STAR0602) at the SITC conference in 2024, providing the first validation of targeting TCR Vβ subsets to activate tumor-specific T cells with a bispecific therapy. The START-001 Phase I/II study evaluated monotherapy with invikafusp alfa in patients with PD-(L)1-resistant antigen-rich solid tumors. The presentation reported initial PK/PD data, which demonstrated dose-related Vβ6/10 T-cell expansion and identified an optimal dose range of 0.08-0.12 mg/kg. The safety profile for invikafusp alfa was consistent with its mechanism, reflecting T-cell activation/expansion similar to CAR-T cell therapy. CRS was reported in most patients in the dose escalation (75% grade 1-2, 18% grade 3). The safety profile was considered manageable, with no prophylactic use of corticosteroids, tocilizumab, or step-up dosing required. Invikafusp alfa demonstrated dose-dependent clinical activity, with tumor shrinkage reported in 50% (7/14) of patients treated at the optimal dose range, including two partial responses. Both partial responses were observed in microsatellite stable CRC patients with high tumor mutational burden (TMB-H). Based on the strongest efficacy signal being observed in TMB-H patients and specifically microsatellite stable CRC, Marengo has opened a CRC dose-expansion cohort and two tissue-agnostic dose-expansion cohorts in the Phase II portion of the START-001 study.

Head and Neck Cancer

Clinical results from novel EGFR-targeting bispecific antibodies including Merus's petosemtamab (EGFRxLGR5) and Bicara's ficerafusp alfa (EGFRxTGF-β) have demonstrated best-in-disease results in HNSCC in Phase I and II studies. The antibodies are progressing into Phase III development, with both being evaluated in Keytruda combination approaches in the frontline R/M HNSCC setting, and Merus also evaluating petosemtamab monotherapy in the second-line setting in Phase III. We described the HNSCC landscape in detail recently here and here, and we give a high-level summary below.

Merus most recently presented results for petosemtamab plus Keytruda in the frontline R/M HNSCC setting at ASCO 2024, showing a 67% ORR among 24 evaluable patients, including one CR and 15 PRs. Petosemtamab plus Keytruda led to a 75% (3/4) response rate among HPV-positive oropharyngeal cancer, a tumor type that has not historically responded to cetuximab (anti-EGFR antibody). Based on the results, Merus initiated a Phase III trial and is enrolling PD-L1-positive HNSCC regardless of HPV status (NCT06525220).

Bicara has most recently detailed results from its Phase I study of ficerafusp alfa in HNSCC in its recent S-1 filing. In frontline R/M HNSCC patients, ficerafusp alfa plus Keytruda led to a 54% ORR among 39 evaluable patients, including 6 CRs and 15 PRs. Among HPV-negative patients specifically, the ORR was higher at 64% (18/28). Bicara is initiating a pivotal Phase II/III study in HPV-negative frontline R/M HNSCC (expected to start in late 2024 or the first quarter of 2025).

In second-line R/M HNSCC at ESMO Asia 2024, Merus reported an ORR of 36% among 75 evaluable patients, with median DOR of 6.2 months, median PFS of 4.9 months, and median OS of 11.4 months. Merus has initiated a Phase III study (NCT06496178) for petosemtamab monotherapy in the second-line or later setting versus investigator's choice control arm.

Akeso and Summit's ivonescimab in combination with the anti-CD47 antibody, ligufalimab, has also shown encouraging initial activity in frontline R/M HNSCC. At the 2024 ESMO Congress, Akeso and Summit presented results from a Phase II trial evaluating the PD-1xVEGF bispecific ivonescimab as monotherapy and in combination with the CD47 antibody ligufalimab in frontline R/M HNSCC. The study enrolled 30 patients in China who received ivonescimab (n=10) or ivonescimab plus ligufalimab (n=20). Follow-up in the study was limited at only 3-4 months. The ORR for ivonescimab monotherapy was 30% (3/10) and for the ivonescimab/ligufalimab combination was 60% (12/20), with the median DOR not reached in either group. Median PFS was 5.0 months (monotherapy) and 7.1 months (combination therapy). Acknowledging the small patient enrollment numbers and limited follow-up so far, the results from the study do appear promising, particularly for the ivonescimab plus ligufalimab combination where a 60% ORR was reported, and further evaluation of the clinical profile of the combination will be interesting to monitor.

Conclusion

There has been substantial progress in the development of bispecific antibodies for the treatment of solid tumor types, alongside continued expansion into earlier lines of therapy and integration into the treatment paradigm across multiple hematological malignancies. Recent developments have included validation of novel technologies in the bispecifics space, such as TCE masking platforms or specific T-cell targeting, which have enabled superior clinical profiles for both antitumor activity and safety. Outside of the oncology space, we also see significant opportunity for bispecific antibodies in other disease areas including autoimmune, where there has been significant interest and dealmaking activity over the course of 2024. We believe that TCEs could play a key role in autoimmune indications by striking a balance between ease of use and manufacturing, and robust efficacy.

Landscape Tables

Exhibit 27
Non-PD-(L)1–Targeted 4-1BB Bispecifics in Development

Company	Technology/ Platform	Therapy	First Target	Second Target	Valency (Per Target)	Stage	Indications	Study Start	NCT #	Status
Genmab BIONTECH	DuoBody	GEN1042 (BNT312)	CD40	4-1BB	Monovalent	Phase I/II	Solid tumors (+ radiotherapy +/- Keytruda)	Mar-23	NCT05491317	Recruiting
						Phase I	Solid tumors	Sep-19	NCT04083599	Recruiting
						Phase I	Solid tumors	Nov-23	NCT06057038	Recruiting
Genmab BIONTECH	DuoBody	GEN1059 (BNT314)	EpCAM	4-1BB	Monovalent	Phase I/II	Solid tumors (+/- Keytruda)	Nov-23	NCT06150183	Recruiting
ALLIGATOR Aptevo	ADAPTIR	ALG.APV-527	5T4	4-1BB	Bivalent	Phase I	Solid tumors	Dec-22	NCT05934539	Recruiting
HARBOUR BIOMED	HBICE	HBM7008 (CLN-418)	B7-H4	4-1BB	Bivalent	Phase I	Solid tumors	May-22	NCT05306444	Completed
ablbio	Grabody-T	ABL103	B7-H4	4-1BB	Bivalent	Phase I	Solid tumors	Nov-23	NCT06126666	Recruiting
	MIRP	DSP107	CD47	4-1BB	1+3	Phase I	AML/MDS (+/- azacitidine)	Jan-22	NCT04937166	Recruiting
							Solid tumors (+/- Tecentriq)	Oct-20	NCT04440735	Recruiting
Pfizer	Anticalin	PF-08046049 (SGN-BB228)	CD228	4-1BB	Bivalent	Phase I	Melanoma, solid tumors	Jan-23	NCT05571839	Recruiting
astellas	-	ASP1002	Claudin4	4-1BB	ND	Phase I	Solid tumors	Mar-23	NCT05719558	Recruiting
I-MAB BIOPHARMA ablbio	Grabody-T	Givastomig (ABL111, TJ033721)	Claudin18.2	4-1BB	Bivalent	Phase I	Advanced solid tumors	Jun-21	NCT04900818	Recruiting
Roche	-	RG7827	FAP	4-1BB	1+3	Phase I/II MORPHEUS-UC	Urothelial carcinoma	Jun-19	NCT03869190	Active, not recruiting
						Phase I	CRC (+ cibisatamab)	Jul-21	NCT04826003	Active, not recruiting
ablbio	Grabody-T	ABL105 (YH32367)	HER2	4-1BB	Bivalent	Phase I	Solid tumors	Aug-22	NCT05523947	Recruiting
BeiGene	-	BGB-B2033	GPC3	4-1BB	-	Phase I	Solid tumors	Jul-24	NCT06427941	Recruiting
BOSTON Pharmaceuticals	Anticalin	BOS-342 (PRS-342)	GPC3	4-1BB	-	Phase I	HCC	Aug-23	ANZCTR: ACTRN12623000798662	Recruiting
bicycle therapeutics	Bicycle	BT7480	Nectin-4	4-1BB	Monovalent	Phase I	Nectin-4+ solid tumors	Nov-21	NCT05163041	Recruiting
AP Biosciences	T-cube	AP402	HER2	4-1BB	Bivalent	Phase I/II	HER2+ tumors	Dec-24	NCT06669975	Not yet recruiting
	T-cube	AP601	CD73	4-1BB	Bivalent	Preclinical	Solid tumors	-	-	-
invoX	mAb[2]	FS120	OX40	4-1BB	Bivalent	Phase I	Solid tumors +/- Keytruda	Nov-20	NCT04648202	Active, not recruiting

Sources: Company reports and William Blair Equity Research

Exhibit 27 (Continued)
Non-PD-(L)1–Targeted 4-1BB Bispecifics in Development

Company	Technology/ Platform	Therapy	First Target	Second Target	Valency (Per Target)	Stage	Indications	Study Start	NCT #	Status
BeiGene	-	BGB-B167	CEACAM5	4-1BB	Bivalent	Phase I	Solid tumors	Aug-22	NCT05494762	Active, not recruiting
Crescendo biologics	Humabody	CB307	PSMA	4-1BB	Monovalent	Phase I	PSMA+ tumors	Jun-21	NCT04839991	Recruiting
		CB699	MSLN x CD40	4-1BB	-	IND-enabling	-	-	-	-
		-	5T4	4-1BB	Monovalent	Preclinical	-	-	-	-
		-	ROR1	4-1BB	Monovalent	Preclinical	-	-	-	-
ablbio	Grabody-T	ABL102	ROR1	4-1BB	Bivalent	IND-enabling	Solid and hematological tumors	-	-	-
		ABL104	EGFR	4-1BB	Bivalent	IND-enabling	Solid tumors	-	-	-
AbClon	AffiMab	AM105	EGFR	4-1BB	Bivalent	Preclinical	CRC	-	-	-
bicycle therapeutics	Bicycle	BT7455	EphA2	4-1BB	-	IND-enabling	EphA2+ tumors			
Aptevo Therapeutics	ADAPTIR	APVO603	OX40	4-1BB	ND	IND-enabling	-	-	-	-

Sources: Company reports and William Blair Equity Research

Exhibit 28
T-Cell Engaging Bispecifics in Solid Tumors

Company	Technology/ Platform	Therapy	Tumor Target	Immune Cell Target	Valency	Stage	Indications	Start Date	NCT #	Trial Status
CHIOME	Tribody	CBA-1535	5T4	CD3	2+1	Preclinical	Solid tumors	-	-	-
CHIOME	Tribody	PTRY	5T4, PD-L1	CD3	-	Preclinical	Solid tumors	-	-	-
PURPLE	Tribody	IM1240	5T4	CD3, NKG2A	-	Preclinical	Solid tumors	-	-	-
Takeda	COBRA	TAK-280	B7-H3	CD3	4+2	Phase I/II	Solid tumors	Apr-22	NCT05220098	Recruiting
HARBOUR BIOMED	HBICE	HBM7004	B7-H4	CD3	-	Preclinical	Solid tumors	-	-	-
Boehringer Ingelheim	-	BI 765049	B7-H6	CD3	-	Phase I	B7-H6+ solid tumors (+/- anti-PD-1)	Jan-24	NCT06091930	Recruiting
							B7-H6+ solid tumors (+/- anti-PD-1)	May-21	NCT04752215	Active, not recruiting
ARBELE	TriAx	Cabotamig (ARB202)	CDH17	CD3	Bivalent	Phase I	Gastrointestinal tumors	May-22	NCT05411133	Recruiting
LIGHTCHAIN BIOTHERAPEUTICS / LamKap Bio	Kλ body	NILK-2301	CEA	CD3	-	Phase I	Low tumor volume CRC	Apr-24	NCT06663839	Recruiting
CHUGAI	Dual-Ig	SAIL66	Claudin6	CD3, 4-1BB	-	Phase I	CLDN6+ solid tumors	Apr-23	NCT05735366	Recruiting
ThirdArcBio	-	ARC101	Claudin6	ND	-	Phase I	CLDN6+ solid tumors	Feb-25	NCT06672185	Not yet recruiting
astellas	-	ASP1893	Claudin6	ND	-	Phase I	CLDN6+ solid tumors	Dec-24	NCT06681870	Not yet recruiting
xencor	XmAb	XmAb541	Claudin6	CD3	-	Phase I	Solid tumors	Apr-24	NCT06276491	Recruiting
context therapeutics	-	CTIM-76	Claudin6	CD3	-	Phase I	Solid tumors	Mid 2024	NCT06515613	Recruiting
astellas xencor	XmAb	ASP2138	Claudin18.2	CD3	2+1	Phase I	Gastric, pancreatic	Jun-22	NCT05365581	Recruiting
Innovent	-	IBI-389	Claudin18.2	CD3	-	Phase I	Solid tumors (+/- sintilimab)	Mar-22	NCT05164458	Recruiting
HARBOUR BIOMED AstraZeneca	HBICE	AZD5863 (HBM7022)	Claudin18.2	CD3	-	Phase I	Solid tumors	Jul-23	NCT06005493	Recruiting
abpro	-	ABP-150	Claudin18.2	CD3	-	Preclinical	Gastric	-	-	-
GENOR BIOPHARMA	-	GB264	Claudin18.2	CD3	-	Preclinical	-	-	-	-
AMGEN	HLE BiTE	Imdelltra (tarlatamab)	DLL3	CD3	Monovalent	Approved	R/R ES-SCLC	-	-	-
						Phase III	LS-SCLC	Feb-24	NCT06117774	Recruiting
							1L ES-SCLC	Jun-24	NCT06211036	Recruiting
							R/R SCLC	May-23	NCT05740566	Active, not recruiting
						Phase II	R/R SCLC	Dec-21	NCT05060016	Active, not recruiting
						Phase I	Prostate cancer	Jun-21	NCT04702737	Completed
							1L SCLC	Aug-22	NCT05361395	Active, not recruiting

Sources: Company reports and William Blair Equity Research

Exhibit 28 (Continued)
T-Cell Engaging Bispecifics in Solid Tumors

Company	Technology/ Platform	Therapy	Tumor Target	Immune Cell Target	Valency (per target)	Stage	Indications	Start Date	NCT #	Trial Status
Roche / Chugai	Dual-Ig	RG6524 (ALPS12)	DLL3	CD3, 4-1BB	-	Phase I	Solid tumors	Jan-23	NCT05619744	Recruiting
Merck	TriTAC	MK-6070 (HPN328)	DLL3	CD3	Monovalent	Phase I	SCLC	Nov-20	NCT04471727	Recruiting
Boehringer Ingelheim	-	Obrixtamig (BI 764532)	DLL3	CD3	Monovalent	Phase II	SCLC, NECs	Sep-23	NCT05882058	Active, not recruiting
						Phase I/II	SCLC, NECs (+ anti-PD-1)	May-23	NCT05879978	Recruiting
CytomX / Amgen	Probody	CX-904 (AMG 651)	EGFR		Monovalent	Phase I	Solid tumors	Feb-22	NCT05387265	Recruiting
Takeda	COBRA	TAK-186	EGFR	CD3	4+2	Phase I/II	HNSCC, NSCLC, CRC	Mar-21	NCT04844073	Recruiting
Janux	TRACTr	JANX008	EGFR	CD3	Monovalent	Phase I	Solid tumors	Apr-23	NCT05783622	Recruiting
VIR	XPAT	VIR-5525 (SAR446368, AMX-525)	EGFR	CD3	Monovalent	Preclinical	-	-	-	-
Pfizer	Gammabody	PF-08046052 (LAVA-1223)	EGFR	Vγ9Vδ2 TCR	-	Phase I	Solid tumors	Nov-23	NCT05983133	Recruiting
adaptin bio	BRiTE	APTN-101	EGFRvIII	CD3	-	IND cleared	Glioblastoma	-	-	-
Johnson&Johnson		JNJ-0387	ENPP3	CD3	-	Phase I	Solid tumors	Dec-23	NCT06178614	Recruiting
xencor	XmAb	XmAb819	ENPP3	CD3	2+1	Phase I	Renal cell carcinoma	Jun-22	NCT05433142	Recruiting
bioatla	CAB	BA3182	EpCAM	CD3	-	Phase I	Adenocarcinomas	Jul-23	NCT05808634	Recruiting
Merck	ProTriTAC	HPN601	EpCAM	CD3	-	Preclinical	EpCAM+ tumors	-	-	-
YZY BIO	YBODY	M701	EpCAM	CD3	-	Phase III	Malignant ascites	Mar-24	NCT06432296	Recruiting
						Phase II	Malignant ascites	Nov-21	NCT06266091	Active, not recruiting
						Preclinical	Solid tumors	-	-	-
Akamis Bio	T-SIGn	NG-641	FAP	CD3	Monovalent	Phase I	SCCHN (+ Keytruda)	Nov-21	NCT04830592	Active, not recruiting
						Phase I	Epithelial tumors (+ Opdivo)	Dec-21	NCT05043714	Active, not recruiting
						Phase I	Epithelial tumors	Jan-20	NCT04053283	Active, not recruiting

Sources: Company reports and William Blair Equity Research

Exhibit 28 (Continued)
T-Cell Engaging Bispecifics in Solid Tumors

Company	Technology/ Platform	Therapy	Tumor Target	Immune Cell Target	Valency (per target)	Stage	Indications	Start Date	NCT #	Trial Status
CHUGAI	TRAB	ERY974	GPC3	CD3	Monovalent	Phase I	Solid tumors	Aug-16	NCT02748837	Completed
							Hepatocellular carcinoma	Jun-21	NCT05022927	Active, not recruiting
康诺亚 KeyMed Biosciences	-	CM350	GPC3	CD3	-	Phase I/II	Solid tumors	Apr-22	NCT05263960	Recruiting
AstraZeneca	-	AZD9793	GPC3	CD3	-	Preclinical	-	-	-	-
abpro	MultiMab	ABP-110	GPC3	CD3	Bivalent	Preclinical	Hepatocellular	-	-	-
IPSEN BIOMUNEX pharmaceuticals	BiXAb MAIT engager	BMX-502	GPC3	MAIT TCR	-	Preclinical	Solid tumors	-	-	-
LIGHTCHAIN IMMUNOTHERAPEUTICS LamKap Bio	Kλ body	NILK-2501	GPC3	CD3	-	Discovery	GPC3+ solid tumors	-	-	-
IMMUNOCORE	ImmTAC	Kimmtrak (tebentafusp)	gp100	CD3	Monovalent	Approved	Uveal melanoma	-	-	-
						Phase III	Adjuvant uveal melanoma	Oct-24	NCT06246149	Not yet recruiting
						Phase II	Melanoma	Dec-22	NCT05549297	Recruiting
Genentech	CrossMab	Runimotamab (RG6194)	HER2	CD3	-	Phase I	HER2+ breast, gastric, solid tumors	Jun-18	NCT03448042	Active, not recruiting
abpro	TetraBi	ABP-102	HER2	CD3	Bivalent	IND-enabling	Breast, gastric cancer	-	-	-
VIR	XPAT	VIR-5818 (SAR446309, AMX-818)	HER2	CD3	Monovalent	Phase I	HER2+ solid tumors (+/- Keytruda)	Apr-22	NCT05356741	Recruiting
ADAGENE	POWERbody	ADG138	HER2	CD3	-	Preclinical	HER2+ solid tumors	-	-	-
Marengo	STAR	STAR0602	IL2	TCR Vβ	Monovalent	Phase I	Solid tumors	Nov-22	NCT05592626	Recruiting
Johnson&Johnson zymeworks	Azymetric	JNJ-8343	KLK2	CD3	-	Phase I	Prostate cancer	Jul-21	NCT04898634	Recruiting
						Phase I	Prostate cancer (+ JNJ-9401)	Nov-23	NCT06095089	Recruiting
						Phase I	mCRPC (+ JNJ-3283, chemo, or AR inhibitors)	Apr-23	NCT05818683	Recruiting
CDR-Life	M-gager	CDR404	MAGE-A4	CD3	-	Phase I	MAGE-A4+ solid tumors	May-24	NCT06402201	Recruiting
Bristol Myers Squibb immatics	TCER	IMA401	MAGE-A4/8	CD3	-	Phase I	Solid tumors	May-22	NCT05359445	Recruiting
context therapeutics	-	CT-95	MSLN	CD3	-	Phase I	Solid tumors	1Q 25	-	-
AMGEN	BiTE	AMG 305	MSLN, CDH3	CD3	-	Phase I	MSLN+ CDH3+ solid tumors	Jun-23	NCT05800964	Recruiting
Johnson&Johnson	-	JNJ-2421	MSLN	CD3	-	Phase I	Solid tumors	Feb-24	NCT06255665	Recruiting
zymeworks	Azymetric	ZW171	MSLN	CD3	2+1	Phase I	MSLN+ solid tumors	Sep-24	NCT06523803	Recruiting
REGENERON	VelociBi	Ubamatamab (REGN4018)	MUC16	CD3	Monovalent	Phase I/II	Ovarian, other MUC16+ cancers (+/- Libtayo)	May-18	NCT03564340	Recruiting
context therapeutics	-	CT-202	Nectin4	CD3	-	Preclinical	Solid tumors	-	-	-

Sources: Company reports and William Blair Equity Research

Exhibit 28 (Continued)
T-Cell Engaging Bispecifics in Solid Tumors

Company	Technology/ Platform	Therapy	Tumor Target	Immune Cell Target	Valency (per target)	Stage	Indications	Start Date	NCT #	Trial Status
SYSTIMMUNE	GNC	GNC-035	PD-L1, ROR1	CD3, 4-1BB	Bivalent	Phase I/II	CLL	Aug-23	NCT05944978	Recruiting
						Phase I/II	NHL	Nov-23	NCT06066203	Recruiting
						Phase I	Breast cancer	Nov-21	NCT05160545	Recruiting
						Phase I	Hematologic malignancies	Feb-22	NCT05104775	Recruiting
		GNC-039	PD-L1, EGFRvIII	CD3, 4-1BB	Bivalent	Phase I	Glioblastoma, solid tumors	Apr-21	NCT04794972	Recruiting
OXFORD BioTherapeutics		OBT700/PDL1	PD-L1	Undisclosed	-	Preclinical	Solid tumors	-	-	-
IMMUNOCORE	ImmTAC	IMC-R117C	PIWIL1	-	-	Preclinical	CRC and GI cancers	-	-	-
		Brenetafusp (IMC-F106C)	PRAME	CD3	Monovalent	Phase III	1L advanced melanoma (+ Opdivo)	Dec-23	NCT06112314	Recruiting
						Phase I/II	PRAME+ solid tumors (+/- anti-PD(L)1)	Feb-20	NCT04262466	Recruiting
		IMC-P115C	PRAME	-	-	Preclinical	Solid tumors	-	-	-
		IMC-T119C	PRAME	-	-	Preclinical	Solid tumors	-	-	-
immatics	TCER	IMA402	PRAME	CD3	-	Phase I/II	Solid tumors	Aug-23	NCT05958121	Recruiting
Traverse Biotech Genmab	DuoBody	-	ROR2	CD3	-	Preclinical	Ovarian cancer, NSCLC, lymphoma	-	-	-
AMGEN xencor	XmAb	Xaluritamig	STEAP1	CD3	2+1	Phase III	mCRPC	Jan-25	NCT06691984	Not yet recruiting
						Phase I	mCRPC	Mar-20	NCT04221542	Recruiting
						Phase I	Neoadjuvant in localized prostate cancer	Nov-24	NCT06613100	Not yet recruiting
						Phase I	Biochemically recurrent CSPC	Sep-24	NCT06555796	Recruiting
ARBELE	TriAx	ARB203	-	-	-	Preclinical	GI cancers	-	-	-
Phanes Therapeutics	-	PT950	-	CD3	-	Preclinical	Ovarian cancer	-	-	-
CDR-Life	M-gager	CDR813	PRAME	CD3	-	Preclinical	Solid tumors	-	-	-
		CDR505	KK-LC-1	CD3	-	Preclinical	Solid tumors	-	-	-

Sources: Company reports and William Blair Equity Research

Exhibit 29
Non-T-Cell–Engaging Bispecifics in Solid Tumors

Company	Technology/ Platform	Therapy	First Target	Second Target	Valency	Stage	Indications	Start Date	NCT #	Trial Status
TAA x TAA										
Innovent	-	IBI-334	EGFR	B7-H3	-	Phase I	Solid tumors	Aug-23	NCT05774873	Recruiting
Johnson&Johnson Genmab	DuoBody	Rybrevant (amivantamab)	EGFR	MET	Monovalent	Approved	NSCLC	-	-	-
						-	NSCLC, esophageal, CRC, HNSCC	-	Multiple	-
Merus	Biclonics	MCLA-129	EGFR	MET	Monovalent	Phase I/II	NSCLC and other solid tumors	Apr-21	NCT04868877	Recruiting
GENOR	-	GB263T	EGFR	MET	1+2	Phase I/II	NSCLC and other solid tumors	May-22	NCT05332574	Recruiting
Merus	Biclonics	Petosemtamab (MCLA-158)	EGFR	LGR5	Monovalent	Phase III	1L HNSCC (+ Keytruda)	Aug-24	NCT06525220	Recruiting
						Phase III	2L+ HNSCC	Jun-24	NCT06496178	Recruiting
						Phase I/II	HNSCC, CRC, solid tumors	May-18	NCT03526835	Recruiting
SYSTIMMUNE	SEBA	SI-B001	EGFR	HER3	Bivalent	Phase III	NSCLC (+ osimertinib)	Jan-22	NCT05020769	Recruiting
						Phase III	NSCLC (+ docetaxel)	Jul-23	NCT05943795	Recruiting
						-	Solid tumors	-	Multiple	-
Merus	Biclonics	Zenocutuzumab (MCLA-128)	HER2	HER3	Monovalent	Phase II	Solid tumors with NRG1 fusions	Jan-15	NCT02912949	Recruiting
						Phase II	NRG1+ NSCLC, mCRPC	Nov-22	NCT05588609	Active, not recruiting
Jazz Pharmaceuticals zymeworks	Azymetric	Ziihera (zanidatamab)	HER2	HER2	Monovalent	Approved	HER2+ biliary tract cancer	-	-	-
						Phase III	HER2+ gastric cancer	Dec-21	NCT05152147	Recruiting
						Phase III	HER2+ breast cancer	Aug-24	NCT06435429	Recruiting
						Phase II	HER2+ GI cancer	Aug-19	NCT03929666	Active, not recruiting
						Phase II	HER2+ breast cancer	-	Multiple	-
REGENERON	VelociBi	Davutamig (REGN5093)	MET	MET	Monovalent	Phase I/II	MET-altered NSCLC	Jan-20	NCT04077099	Active, not recruiting
TAA x Cytokine										
BICARA THERAPEUTICS	-	Ficerafusp alfa (BCA101)	EGFR	TGF-β	Bivalent	Phase I/II	1L HNSCC (+ Keytruda)	-	-	-
						Phase I	EGFR-driven solid tumors (+/- Keytruda)	Jun-20	NCT04429542	Recruiting
ablbio COMPASS THERAPEUTICS	Stitch-mabs	CTX-009 (ABL001)	DLL4	VEGF	Bivalent	Phase II/III	Biliary tract Cancer	Jan-23	NCT05506943	Active, not recruiting
						Phase II	Colorectal Cancer	Dec-22	NCT05513742	Active, not recruiting
						Phase I/II	Solid tumors	Jun-20	NCT04492033	Active, not recruiting

Sources: Company reports and William Blair Equity Research

Exhibit 29 (Continued)
Non-T-Cell–Engaging Bispecifics in Solid Tumors

Company	Technology/ Platform	Therapy	First Target	Second Target	Valency	Stage	Indications	Start Date	NCT #	Trial Status
TAA x CD47										
LIGHTCHAIN BIOSCIENCES / LamKap Bio		NILK-2401	CEA	CD47	-	Preclinical	CEA+ solid tumors	-	-	-
Phanes Therapeutics	PACbody	PT886	Claudin1 8.2	CD47	-	Phase I/II	Gastric, pancreatic (+/- Keytruda)	Mar-23	NCT05482893	Recruiting
Akesobio		AK132	Claudin1 8.2	CD47	-	Phase I	Solid tumors	Dec-23	NCT06166472	Not yet recruiting
Phanes Therapeutics	PACbody	PT217	DLL3	CD47	-	Phase I/II	SCLC, NEC	Sep-23	NCT05652686	Recruiting
LIGHTCHAIN BIOSCIENCES	Kλ body	NI-2801	HER2	CD47	-	Discovery	-	-	-	-
	MIRP	DSP-216	HLA-G	CD47	Bivalent	Preclinical	-	-	-	-
LIGHTCHAIN BIOSCIENCES	κλ	NI-1801	MSLN	CD47	-	Phase I	MSLN+ solid tumors	Apr-22	NCT05403554	Recruiting
NK Cell Engagers										
BeiGene		BGB-B3227	MUC1	CD16a	-	Phase I	Solid tumors (+/- Tevimbra)	Aug-24	NCT06540066	Recruiting
NAVA BIOSCIENCES / Cytovia Therapeutics	Flex-NK	NY-303 (CYT-303)	GPC3	NKp46	-	Preclinical	Hepatocellular carcinoma	-	-	-
AFFIMED	ICE	AFM24	EGFR	CD16a	-	Phase I/II	Solid tumors (+ Tecentriq)	Nov-21	NCT05109442	Recruiting
							Solid tumors	Apr-20	NCT04259450	Completed
		AFM32	FRα	CD16a	-	Preclinical	Solid tumors	-	-	-
Other										
MOLECULAR partners	DARPin	MP0317	FAP	CD40	-	Phase I	Solid tumors	Oct-21	NCT05098405	Terminated (adequate safety data)
YZY BIO	Nano-YBODY	Y332	VEGF	TGF-β	-	Preclinical	Solid tumors	-	-	-
Pfizer		PF-07826390	ILT2	ILT4	-	Phase I/II	Solid tumors (+/- chemo or sasanlimab)	Sep-24	NCT06546553	Recruiting
Genentech / xencor	XmAb	Efbalropendekin alfa (XmAb24306 / RG6323)	IL15	IL15Ra	Monovalent	Phase I	Multiple myeloma (+ daratumumab)	Apr-22	NCT05243342	Completed
						Phase I	Solid tumors (+ Tecentriq)	Mar-20	NCT04250155	Active, not recruiting
						Phase I	Multiple myeloma (+ cevostamab)	Mar-23	NCT05646836	Recruiting

Sources: Company reports and William Blair Equity Research

Exhibit 30
CD19 and CD20 Bispecifics in Development in Oncology

Company	Technology/ Platform	Therapy	Tumor Target(s)	Immune Cell Target(s)	Valency (per target)	Stage	Indications	Start date	NCT #	Trial Status
AMGEN	BiTE	Blincyto (blinatumomab)	CD19	CD3	Monovalent	Approved	B-ALL	-	-	-
						Phase I/II	B-ALL (subcutaneous)	Jan-21	NCT04521231	Recruiting
Genmab abbvie	DuoBody	Epkinly (epcoritamab)	CD20	CD3	Monovalent	Approved	R/R DLBCL, R/R FL	-	-	-
						Phase III	R/R DLBCL	Jan-21	NCT04628494	Active, not recruiting
							1L DLBCL (+ R-CHOP)	Feb-23	NCT05578976	Recruiting
							R/R FL	Sep-22	NCT05409066	Recruiting
							1L FL (+ R2)	Feb-24	NCT06191744	Recruiting
Roche	CrossMab	Lunsumio (mosunetuzumab)	CD20	CD3	Monovalent	Approved	R/R FL	-	-	-
						Phase III	R/R DLCBL	Apr-22	NCT05171647	Active, not recruiting
							R/R FL	Oct-21	NCT04712097	Recruiting
Roche	CrossMab	Columvi (glofitamab)	CD20	CD3	2+1	Approved	R/R DLBCL	-	-	-
						Phase III	R/R DLBCL	Feb-21	NCT04408638	Active, not recruiting
							1L LBCL	Sep-23	NCT06047080	Recruiting
							R/R MCL	Oct-23	NCT06084936	Recruiting
REGENERON	VelociBi	Ordspono (odronextamab)	CD20	CD3	Monovalent	Approved (EU)	R/R DLBCL and R/R FL	-	-	-
						Phase III	1L FL	Dec-23	NCT06091254	Recruiting
							1L FL	Nov-23	NCT06097364	Recruiting
							1L DLBCL	Dec-23	NCT06091865	Recruiting
							R/R B-NHL	Feb-24	NCT06230224	Recruiting
							R/R FL/MZL	Dec-23	NCT06149286	Recruiting
AstraZeneca	UniAb	AZD0486 (TNB-486)	CD19	CD3	Monovalent	Phase III	1L FL	Aug-24	NCT06549595	Recruiting
						Phase II	R/R NHL	Nov-24	NCT06526793	Recruiting
						Phase I/II	R/R B-ALL	Dec-23	NCT06137118	Recruiting
						Phase I	R/R NHL	Mar-21	NCT04594642	Recruiting

Sources: Company reports and William Blair Equity Research

Exhibit 30 (Continued)
CD19 and CD20 Bispecifics in Development in Oncology

Company	Technology/ Platform	Therapy	Tumor Target(s)	Immune Cell Target(s)	Valency (per target)	Stage	Indications	Start date	NCT #	Trial Status
GENOR	-	GB261	CD20	CD3	-	Phase I/II	R/R NHL + CLL	Aug-21	NCT04923048	Recruiting
MERCK / CURON	-	CN201	CD19	CD3	-	Phase I/II	B-ALL	Sep-22	NCT05579132	Recruiting
							B-NHL	Mar-21	NCT06189391	Recruiting
AstraZeneca	-	AZD5492	CD20	CD8 x TCR	-	Phase I/II	R/R B-cell malignancies	Sep-24	NCT06542250	Recruiting
宜明昂科 ImmuneOnco	-	IMM0306	CD20	CD47	-	Phase I/II	Indolent B-NHL	Mar-20	NCT05805943	Recruiting
						Phase I/II	B-NHL	May-23	NCT05771883	Not yet recruiting
NOVARTIS	-	PIT565	CD19	CD3, CD2	-	Phase I	R/R NHL, ALL	Oct-22	NCT05397496	Recruiting
Johnson&Johnson	-	JNJ-8780	CD22	CD3	-	Phase I	R/R NHL + CLL	Nov-20	NCT04540796	Active, not recruiting
	-	JNJ-8543	CD20, CD79b	CD3	Monovalent	Phase I	R/R NHL + CLL	Aug-22	NCT05424822	Recruiting
TG Therapeutics / LIGHTCHAIN BIOSCIENCE	κλ body	TG-1801 (NI-1701)	CD19	CD47	-	Phase I	B-cell lymphoma, CLL	Apr-21	NCT04806035	Terminated
						Phase I	B-cell lymphoma	Mar-19	NCT03804996	Completed
Roche	CrossMab	Englumafusp alfa (RG6076)	CD19	4-1BB	1+3	Phase I	NHL	Aug-19	NCT04077723	Recruiting
SYSTIMMUNE	GNC	GNC-038	CD19, PD-L1	CD3, 4-1BB	Bivalent	Phase I/II	R/R NHL	Sep-22	NCT05623982	Recruiting
							R/R lymphoma	Feb-23	NCT05627856	Recruiting
							R/R DLBCL	Aug-22	NCT05192486	Recruiting
							R/R CNS lymphoma	Feb-23	NCT05485753	Recruiting
ADAGENE	POWERbody	ADG152	CD20	CD3	-	Preclinical	B-cell lymphoma	-	-	-
iTAb	ITab	IM-1920	CD19, CD20	CD3	-	Preclinical	B-cell lymphoma	-	-	-
Protheragen	-	-	CD20	CD3	-	Preclinical	B-cell lymphoma	-	-	-

Sources: Company reports and William Blair Equity Research

Exhibit 31
TCE Bispecifics in AML

Company	Technology/ Platform	Therapy	Tumor Target	Immune Cell Target	Valency (per target)	Stage	Indications	Study Start	NCT #	Trial Status
sanofi innate pharma	ANKET	SAR443579	CD123	NKp46	-	Phase I/II	AML, B-ALL, HR-MDS, BPDCN	Dec-21	NCT05086315	Recruiting
Aptevo Therapeutics	ADAPTIR	APVO436	CD123	CD3	Bivalent	Phase I	AML	Dec-18	NCT03647800	Unknown
cullinan THERAPEUTICS	-	CLN-049	FLT3	CD3	-	Phase I	AML	Nov-21	NCT05143996	Recruiting
MOLECULAR partners	DARPin	MP0533	CD33 xCD70 xCD123	CD3	Monovalent	Phase I/II	AML, MDS	Dec-22	NCT05673057	Recruiting
LAVA THERAPEUTICS	Gammabody	LAVA-1266	CD123	Vγ9Vδ2 TCR	-	Preclinical	AML, MDS	-	-	-

Sources: Company reports and William Blair Equity Research

The prices of the common stock of public companies mentioned in this report follow:

Amgen (Outperform)	$270.62
AstraZeneca	$66.58
BioNTech	$120.38
Bicara Therapeutics	$17.50
Bristol Myers Squibb (Market Perform)	$55.78
Cullinan Therapeutics (Outperform)	$11.75
CytomX	$1.11
Genmab (Market Perform)	$20.17
GSK	$33.95
IGM Biosciences	$7.17
I-Mab Biopharma	$1.00
Immatics	$7.21
Immunocore	$28.91
Instil Bio	$21.97
Janux Therapeutics (Outperform)	$61.11
Johnson & Johnson	$146.62
MacroGenics	$3.20
Merck	$102.00
Merus (Outperform)	$42.83
Novartis	$98.36
Regeneron	$731.30
Roche	$35.39
Summit Therapeutics	$17.83
Xencor	$24.03

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