COWEN
AND COMPANY

Biotechnology

Immune Design

Equity Research

Initiating Coverage

May 15, 2015

Price: $21.29 (05/14/2015)

Price Target: NA

OUTPERFORM (1)

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Key Data

Symbol	NASDAQ: IMDZ
52-Week Range:	$40.13 - 11.51
Market Cap (MM):	$423.2
Net Debt (MM):	$(75.4)
Cash/Share:	$4.46
Dil. Shares Out (MM):	19.9
Enterprise Value (MM):	$347.9
ROIC:	NA
ROE (LTM):	NA
BV/Share:	$3.93
Dividend:	NA

FY (Dec)	2014A	2015E	2016E
Earnings Per Share			
Q1	-	$(0.56)A	$(0.51)
Q2	-	$(0.47)	$(0.51)
Q3	-	$(0.49)	$(0.52)
Q4	-	$(0.54)	$(0.61)
Year	$(4.56)	$(2.05)	$(2.15)
P/E	NM	NM	NM
Consensus EPS	$(4.56)	$(2.51)	$(2.75)

Consensus source: Thomson Reuters

Revenue (MM)			
Year	$6.4	$7.8	$7.8
EV/S	54.4x	44.6x	44.6x

Initiation: Two Leading Immunotherapy Platforms Under One Roof

The Cowen Insight

We are initiating coverage of IMDZ with an Outperform rating. IMDZ is developing two proprietary immunotherapy platforms, both of which are off-the-shelf immunotherapies that have the potential to elicit an anti-tumor T-cell response. As data are reported in the next 12-18 months, we expect significant growth in investor interest and stock appreciation.

An Off-The-Shelf Vaccine That Targets Dendritic Cells In Vivo

Vaccines were once at the forefront of cancer therapeutics, but quickly fell out of favor after several disappointing results. Many experts believe vaccines are ready for a 2nd-life with the emergence of immune checkpoint inhibitors and we believe Immune Design is poised to become the leader in vaccine/CPI combination therapy. IMDZ has developed a novel technology that utilizes an engineered lentivirus to deliver tumor-associated antigens directly to dendritic cells in vivo. The ZVex platform is an off-the-shelf vaccine that can deliver antigenic peptide to initiate an immune response via an intra-dermal injection and establish anti-tumor immunity. IMDZ's lead ZVex product, LV305/CMB305, targets the proven tumor antigen NY-ESO-1. Prior attempts to vaccinate against NY-ESO-1 have yielded unimpressive results despite some signs of immune activation. We believe this was due to method of antigen delivery, length of peptide fragment and microenvironment in which dendritic cells were "activated", all things we believe IMDZ's platforms address. Initial data reported in ASCO abstracts was encouraging and updated results at ASCO could heighten investor interest.

ZVex Engineering Offers Unlimited Opportunity

While the NY-ESO-1 targeting ZVex has broad potential across numerous tumor indications, its real potential lies in the ease with which it can be engineered with new/multiple antigens or immune checkpoint antibody fragments and cytokines to enhance immune activity. We expect IMDZ to leverage the flexibility of the platform and rapidly develop additional single-antigen virus for clinical development either in-house or through licensing partnerships. IMDZ has also suggested the inclusion of a single-chain checkpoint inhibitor antibody into the single-antigen ZVex platform. This would make ZVex a 2-in-1 product, a vaccine through antigen delivery and an immune checkpoint inhibitor. We believe such a product would be of significant interest to physicians and patients, as well as investors.

G100 Provides In Situ Personalized Vaccination

G100 is a TLR4 agonist that IMDZ is developing as a potent activator of dendritic cells. In combination with antigen-release from dying tumor cells (caused by localized radiation), G100 can promote antigen uptake and dendritic cell activation to initiate a personalized anti-tumor T-cell response. Given G100's mechanism of action, we believe G100 has application in several indications where localized radiation, and even chemotherapy, is standard of care. The first data for G100 (monotherapy in MCC) was recently reported in an ASCO abstract, with additional details to be provided at the ASCO meeting.

At A Glance

Our Investment Thesis

We believe there are numerous factors supporting our positive investment opinion of Immune Design including: (1) The ZVex platform provides a novel mechanism of antigen delivery to elicit a robust anti-tumor T-cell response. (2) The NY-ESO-1 ZVex product utilizes a proven tumor antigen with opportunity in multiple indications. (3) The ability to integrate CPIs/cytokine into next-generation ZVex products to enhance efficacy. (4) G100 adjuvant provides a unique approach to generating personalized in situ vaccines. (5) G100's mechanism of action suggests application in wide variety of setting where localized radiation and/or chemotherapy are utilized.

Forthcoming Catalysts

- G305 dose-escalation data; ASCO
- LV305 dose-escalation data; ASCO
- G100 MCC data; ASCO
- CMB305 dose-escalation data; YE15

Base Case Assumptions

- CMB305 proof-of-concept/approval in myxoid/round cell and synovial sarcoma.
- G100 proof-of-concept/approval in MCC.
- '305 w/CPI shows tolerability and activity.

Upside Scenario

- '305/G100 platforms demonstrate activity in multiple indications in Phase I trials.
- Next-gen ZVex (w/two antigens, CPI, cytokine) demonstrate enhanced clinical activity.
- Adjuvant partnerships provide significant source of capital.

Downside Scenario

- Both platforms prove ineffective as monotherapies in early stage trials.
- '305 w/CPIs show no synergy.
- Adjuvant partnerships end with no significant milestone payments.

Price Performance

Source: Bloomberg

Company Description

Immune Design is a clinical-stage immunotherapy company. They are developing multiple product candidates from their two discovery platforms, ZVex and GLAAS. Their product candidates, LV305, CMB305 and G100, utilize multiple immuno-oncology approaches. LV305 and G100 are in Phase I clinical trials. CMB305 combines its two platforms, LV305 and a second agent G305, in a prime-boost approach that it believes should be more effective than LV305 alone. G305 is based on its GLAAS platform and is in a Phase 1 clinical trial. The Company has several collaborations in place with global pharmaceutical companies leveraging the GLAAS platform in infectious disease, and one of these programs has progressed into clinical development.

Analyst Top Picks

	Ticker	Price (05/14/2015)	Price Target	Rating
Celldex Therapeutics	CLDX	$25.75	$33.00	Outperform
Stemline Therapeutics	STML	$13.60	$NA	Outperform
Immune Design	IMDZ	$21.29	$NA	Outperform

Discussion of Investment Thesis

A Novel Targeting Platform To Deliver A Proven Antigen

Numerous preclinical studies have shown that genetically engineered dendritic cells are more potent activators of an anti-tumor response than dendritic cells (DCs) that have been pulsed with naked peptide antigen. IMDZ is developing a proprietary platform (ZVex) that delivers tumor-associated antigen specifically to dendritic cells via an engineered virus. This approach presents two features that we feel differentiates IMDZ's platform from previous approaches to develop a therapeutic vaccine. First, the virus is designed to infect only dendritic cells. This permits for direct in vivo delivery that should result in a high rate of infected dendritic cells. Prior attempts to engineer DCs for vaccines have either manipulated DCs ex vivo (with mRNA, DNA or virus) which is costly and time consuming or utilized virus that has broad infectivity which results in a low frequency of infected dendritic cells. The ZVex platform overcomes both of these hurdles. Second, viral delivery of the antigen results in continuous intracellular production of the tumor antigen. This allows a dendritic cell to process the full length peptide that contains multiple MHC-restricted epitopes. Presentation of antigen through both MHC class I and class II molecules results in an anti-tumor immune response that involves both CD4+ and CD8+ T-cells which has the potential for deeper, more durable responses.

IMDZ's initial target is the well-established NY-ESO-1 tumor antigen (LV305: ZVex-NY-ESO-1; G305: NY-ESO-1 peptide + adjuvant; CMB305: LV305 + G305). This antigen has been extensively studied, with expression in a broad range of tumor indications (melanoma, lung, ovarian, sarcoma) and normal expression restricted to select tissues (testes). There have been many attempts at therapeutically vaccinating against NY-ESO-1, but most have disappointed. While many studies have shown that vaccination, typically with NY-ESO-1 peptide, can elicit an antigen-specific immune response, this rarely translates to clinical activity. Often the immune responses were measured by an increase in antigen-specific CD4+ or CD8+ T-cells or an antibody response, but rarely has a full blown immune-response been observed. This is likely due to the fact that naked peptides still need to be actively taken up by dendritic cells and the peptide fragments taken up may be MHC class-restricted. This would ultimately result in a blunted immune response. The ZVex platform overcomes the need for active DC uptake by utilizing a viral delivery system, and again delivers a full-length peptide. The first data for LV305 and G305 are expected at ASCO and we expect any positive data to generate significant investor interest around the platform.

Off-The Shelf Immuno-Therapy Platform With Broad Potential

IMDZ's ZVex platform can be rapidly engineered to deliver different and/or multiple antigens. It can also be designed so that along with the delivery/expression of tumor antigen, it can also encode for co-stimulatory molecules or cytokines to enhance DC activity. We see the LV305 program as a proof-of-concept for the platform, with the potential for multiple ZVex-based products. IMDZ has indicated that they plan on exploring potential antigens from tumor indications that are known to be of viral origin. Given the wealth of already known tumor-associated viral-antigens, we believe such products can be quickly designed and developed by IMDZ. Moreover, IMDZ has indicated that NY-ESO-1 represents only 2Kb of a potentially 4-5Kb genomic backbone. This means that there is still plenty of genetic room for an additional antigen, co-stimulatory molecule, or cytokine.

Specifically, IMDZ has suggested the inclusion of a single-chain checkpoint inhibitor antibody into the ZVex platform. This will make ZVex a 2-in-1 product that will

stimulate DC-mediated antigen presentation while simultaneously releasing the checkpoint blockade on T-cells. We believe a product like this could elicit a robust anti-tumor response and will be of great interest to investors.

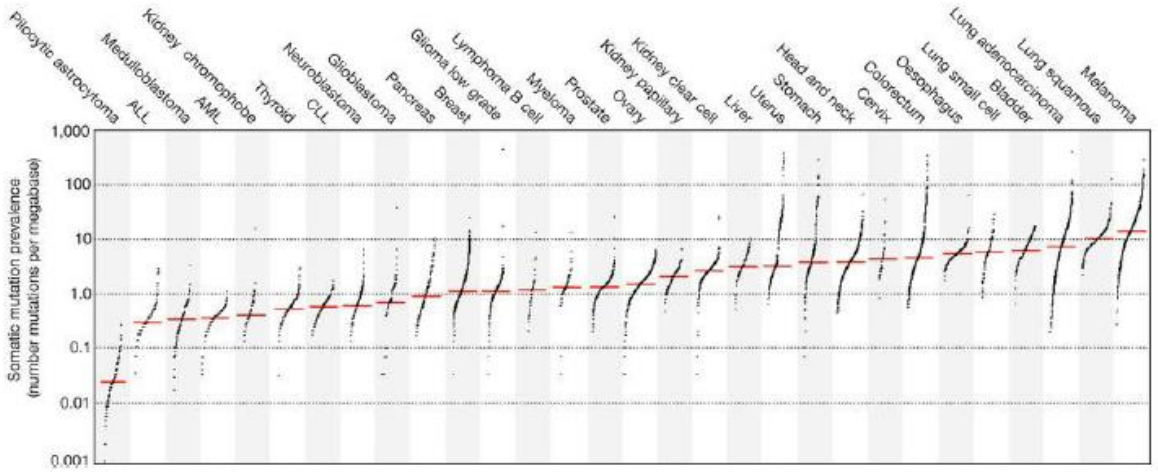
Vaccination Through Endogenous Antigen Release

At a recent meeting on emerging immuno-therapies, several presenters highlighted the idea of an "in-situ vaccine". The idea being to either increase the presence of antigen by causing tumor cells to release antigen or enhancing antigen uptake by dendritic cells. IMDZ is using both these approaches in their G100 adjuvant platform in hopes of generating a localized, tumor-generated, personalized vaccine. G100 is a formulation of their lipid A-based synthetic GLA adjuvant that is a potent TLR4 agonist and activator of dendritic cells. In combination with antigen release caused by radiation-induced tumor cell death, G100 is designed to promote antigen uptake by dendritic cells and ultimately trigger a T-cell response. Given G100's mechanism of action it has potential for application across a wide array of cancers that are treated with localized radiation. In addition, G100 has the potential to be used in combination with any cytotoxic drug. Like ZVex, the first data from G100 are expected at ASCO and again, any positive data should draw attention to the platform.

Both Platforms Offer Potential Synergy With CPIs

Many have now suggested that response to immune checkpoint inhibition is dictated in part by the mutagenic profile of the tumor. The tumors with the most mutations have the most neo-antigens and therefore, should have the most anti-tumor T-cells waiting to having their checkpoint lifted. This is highlighted by the often cited graph below, where tumor indications with the most mutations (those on the right side of the graph) have been those that have shown the most impressive rates of response to CPIs. Much focus has turned to how to sensitize or improve the response rates of tumors with few mutations/antigens to checkpoint inhibition. We believe both of IMDZ's programs offer the potential to increase the frequency and tumor-infiltration of antigen-specific T-cells. IMDZ will begin to explore this potential with a combination trial in sarcoma expected to initiate by YE15.

Prevalence Of Mutations Across Cancer Indications



Source: Lion Biotechnologies

Model Accelerated CMB305 Approval in Sarcoma Subtypes

IMDZ is evaluating the CMB305 (LV305+G305) product in several indications in their Phase I trial and include NSCLC, ovarian, melanoma and sarcoma, all in the advanced setting. Specifically, they have disclosed that their first Phase II trial will be in combination with a checkpoint inhibitor in soft tissue sarcoma. The expansion cohorts that IMDZ expects to enroll for their Phase I trial are synovial sarcoma and myxoid/round cell liposarcoma, two indications that we believe will qualify CMB305 for orphan drug designation and the potential for accelerated approval. While these indications provide modest revenue potential for CMB305, we view them as proof-of-concept indications that will provide a solid foundation for expansion into additional indications.

Liposarcomas represent 18% of soft tissue sarcomas and of those ~40% are myxoid/round cell sarcomas. We estimate that in 2015 there will be ~850 new cases of myxoid/round cell sarcomas, half of which will be diagnosed with advanced disease or refractory to standard of care, with nearly all (90%) considered NY-ESO-1 positive. Synovial sarcoma makes up ~8% of all new cases of soft tissue sarcoma, which translates to ~900 new diagnoses in the US in 2015. Half will be advanced or refractory disease, and of those 65% will be considered NY-ESO-1 positive. Like most other soft tissue sarcomas, standard of care for both myxoid/round cell and synovial sarcoma often includes surgical resection followed by radiation. There is no cure for metastatic sarcoma, and therefore the goal of treatment is often palliative. Most patients who develop metastatic sarcoma are given chemotherapy (doxorubicin/ifosfamide), and although it produces relatively short-lived responses, responses are seen in only a minority of patients. Given this, as well as the lack of a targeted therapy, these two indications represent a highly unmet clinical need.

Broad Potential For G100, Right Now Model Approval In Merkel Cell Carcinoma

We believe that given the development plan to combine G100 with traditional radiation, G100 has broad potential to be used in numerous cancer indications where localized radiation is standard of care. It is currently involved in two corporate sponsored trials (monotherapy in MCC and w/radiation in NHL) and an IST in combination with radiation in Sarcoma. While IMDZ's lead target indication for G100 is not yet clear (MCC data to be presented at ASCO), we expect it to move forward in MCC (as a monotherapy or in combination w/radiation or chemotherapy) given the one reported CR with monotherapy G100. Like myxoid/round cell and synovial sarcoma, MCC represents an orphan indication with only 1,500 new cases expected in 2015. As such, we model accelerated approval in 2019 and view MCC as a quick-to-market, proof-of-concept indication.

MCC is a highly malignant, rare cancer that quickly metastasizes to regional lymph nodes and distant organs and has no real standard of care. Surgical excision of the primary disease is usually followed by radiation and/or chemotherapy. Since G100's mechanism of action is independent of the tumor itself, we expect all MCC patients with advanced or refractory disease to be eligible for treatment. This translates to ~800 patients eligible for treatment in 2019.

Given the early stages of development for both the '305 and G100 platforms, we currently only model approval of CMB305 in STS indications and G100 in MCC. This is likely to change as additional data are reported over the next 12-18 months for LV305 in melanoma PD-1 failures, CMB305 in lung, ovarian and melanoma, as well as G100 in NHL and sarcoma.

CMB305 Revenue Model In Sarcoma

Year	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
US Incidence of STS																
Incidence of Sarcoma	11,930	12,169	12,412	12,660	12,913	13,172	13,435	13,704	13,978	14,257	14,543	14,833	15,130	15,433	15,741	16,056
% liposarcoma	*18.0%*	*18.0%*	*18.0%*	*18.0%*	*18.0%*	*18.0%*	*18.0%*	*18.0%*	*18.0%*	*18.0%*	*18.0%*	*18.0%*	*18.0%*	*18.0%*	*18.0%*	*18.0%*
# Patients w/liposarcoma	2,147	2,190	2,234	2,279	2,324	2,371	2,418	2,467	2,516	2,566	2,618	2,670	2,723	2,778	2,833	2,890
% myxoid/round cell	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*
# Patients myxoid/round cell liposarcoma	859	876	894	912	930	948	967	987	1,006	1,027	1,047	1,068	1,089	1,111	1,133	1,156
% advanced/refractory disease	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
# Patients w/advanced disease	429	438	447	456	465	474	484	493	503	513	524	534	545	556	567	578
% NY-ESO-1+	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*
# Patients w/NY-ESO-1+ myxoid/round cell	**387**	**394**	**402**	**410**	**418**	**427**	**435**	**444**	**453**	**462**	**471**	**481**	**490**	**500**	**510**	**520**
% synovial sarcoma	*7.5%*	*7.5%*	*7.5%*	*7.5%*	*7.5%*	*7.5%*	*7.5%*	*7.5%*	*7.5%*	*7.5%*	*7.5%*	*7.5%*	*7.5%*	*7.5%*	*7.5%*	*7.5%*
# Patients w/synovial sarcoma	895	913	931	950	969	988	1008	1028	1048	1069	1091	1113	1135	1157	1181	1204
% advanced/refractory disease	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
# Patients w/advanced disease	447	456	465	475	484	494	504	514	524	535	545	556	567	579	590	602
% NY-ESO-1+	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*
# Patients w/NY-ESO-1+ synovial	***291***	***297***	***303***	***309***	***315***	***321***	***327***	***334***	***341***	***348***	***354***	***362***	***369***	***376***	***384***	***391***
Projected # of myxoid/round cell eligible for CMB305	**387**	**394**	**402**	**410**	**418**	**427**	**435**	**444**	**453**	**462**	**471**	**481**	**490**	**500**	**510**	**520**
% Treated w/CMB305	***0%***	***0%***	***0%***	***0%***	***5%***	***15%***	***25%***	***35%***	***40%***	***40%***	***40%***	***40%***	***40%***	***40%***	***40%***	***40%***
Projected # of synovial eligible for CMB305	**291**	**297**	**303**	**309**	**315**	**321**	**327**	**334**	**341**	**348**	**354**	**362**	**369**	**376**	**384**	**391**
% Treated w/CMB305	***0%***	***0%***	***0%***	***0%***	***5%***	***10%***	***15%***	***20%***	***25%***	***25%***	***25%***	***25%***	***25%***	***25%***	***25%***	***25%***
Price per patient treated; Myxoid/Round Cell (000s)	**$60**	**$63**	**$66**	**$69**	**$73**	**$77**	**$80**	**$84**	**$89**	**$93**	**$98**	**$103**	**$108**	**$113**	**$119**	**$125**
Price per patient treated; Synovial (000s)	**$60**	**$63**	**$66**	**$69**	**$73**	**$77**	**$80**	**$84**	**$89**	**$93**	**$98**	**$103**	**$108**	**$113**	**$119**	**$125**
US Revenue in Myxoid/Round Cell ($MM)	0	0	0	0	2	5	9	13	16	17	18	20	21	23	24	26
Ex-US Revenue in Myxoid/Round Cell ($MM)	0	0	0	0	0	0	1	1	2	2	3	3	3	3	3	4
US Revenue in Synovial ($MM)	0	0	0	0	1	2	4	6	8	8	9	9	10	11	11	12
Ex-US Revenue in Synovial ($MM)	0	0	0	0	0	0	0	1	1	1	1	1	1	1	2	2
Total Milestone/Licensing	0	0	0	25	0	10	0	0	0	0	0	0	0	0	0	0
Total Revenue in Sarcoma ($MM)	**0**	**0**	**0**	**25**	**3**	**18**	**14**	**21**	**26**	**29**	**31**	**33**	**35**	**38**	**41**	**44**

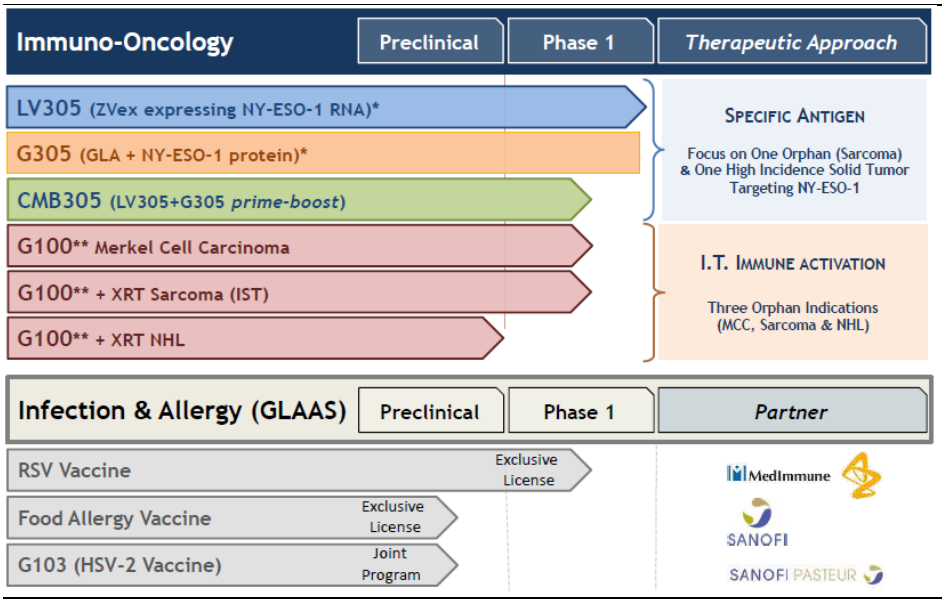
Source: Cowen and Company.

G100 Revenue Model In MCC

Year	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
US Incidence of MCC																
Incidence of MCC	1,500	1,530	1,561	1,592	1,624	1,656	1,689	1,723	1,757	1,793	1,828	1,865	1,902	1,940	1,979	2,019
% late stage (III/IV)	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
% recurrence w/metastases	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
# Patients w/advanced MCC	**765**	**780**	**796**	**812**	**828**	**845**	**862**	**879**	**896**	**914**	**933**	**951**	**970**	**990**	**1,009**	**1,030**
Projected # of MCC eligible for G100	**765**	**780**	**796**	**812**	**828**	**845**	**862**	**879**	**896**	**914**	**933**	**951**	**970**	**990**	**1,009**	**1,030**
% Treated w/G100	***0%***	***0%***	***0%***	***0%***	***3%***	***5%***	***10%***	***20%***	***30%***	***35%***	***35%***	***35%***	***35%***	***35%***	***25%***	***15%***
Price per patient treated; MCC (000s)	**$60**	**$63**	**$66**	**$69**	**$73**	**$77**	**$80**	**$84**	**$89**	**$93**	**$98**	**$103**	**$108**	**$113**	**$119**	**$125**
US Revenue in MCC ($MM)	0	0	0	0	2	3	7	15	24	30	32	34	37	39	30	19
Ex-US Revenue in MCC ($MM)	0	0	0	0	0	0	0	1	2	4	4	5	5	5	6	4
Total Revenue in MCC ($MM)	**0**	**0**	**0**	**0**	**2**	**3**	**7**	**16**	**26**	**33**	**36**	**39**	**42**	**45**	**36**	**24**

Source: Cowen and Company

Immune Design Pipeline



Source: Immune Design

Immune Design Upcoming Milestones

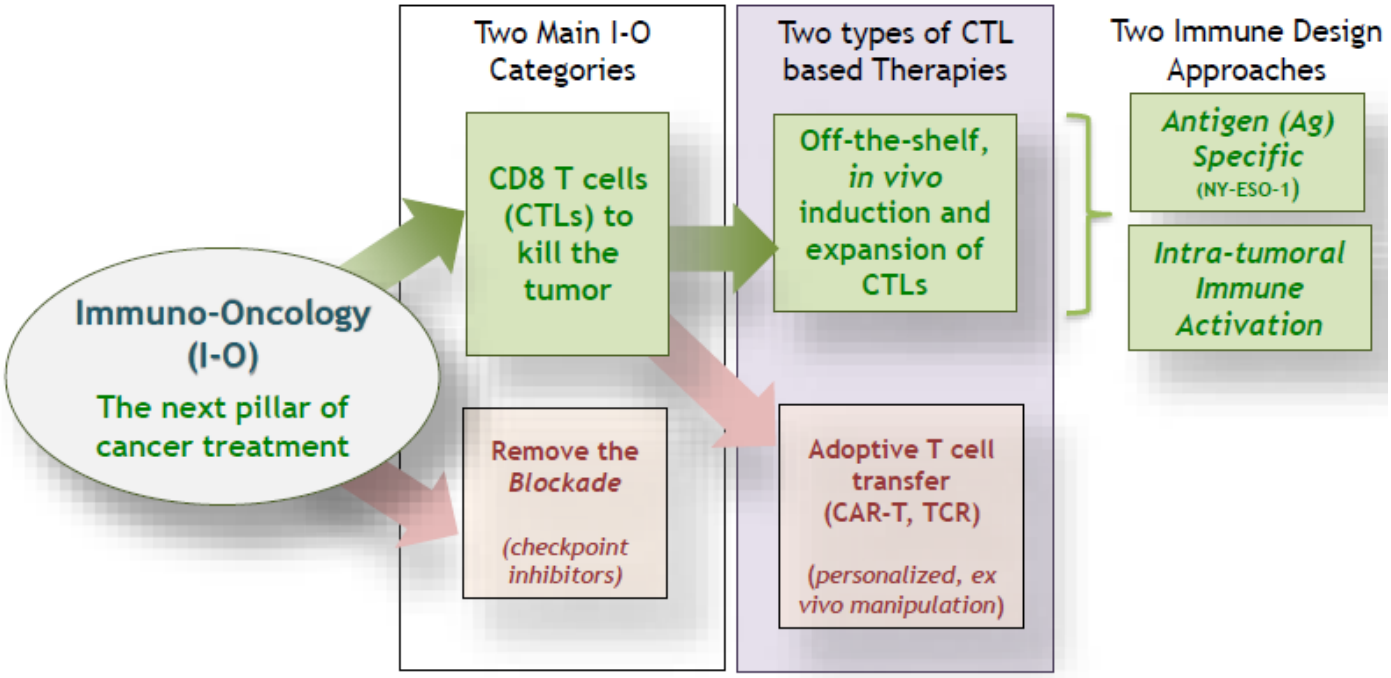
Date	Stage	Milestone
G305 (GLA+NY-ESO-1 Peptide)		
2Q15	Phase I	Dose-escalation data in solid tumors (ASCO)
LV305 (ZVex-NY-ESO-1)		
2Q15	Phase I	Dose-escalation data in solid tumors (ASCO)
2Q15	Phase I	Initiate expansion w/α-PD-1 in CPI melanoma failures
CMB305 (G305+LV305)		
3Q15	Phase I	Begin enrollment of expansion cohorts
2H15	Phase II	Initiate study in sarcoma w/CPI
YE15	Phase I	Dose-escalation data
G100 (Adjuvant for endogenous antigen)		
2Q15	Phase I	Data from study in Merkel Cell Carcinoma (ASCO)
2Q15	Phase I	Initiate study w/radiation in NHL
YE15	Phase I	Completion of study w/radiation in sarcoma (IST)

Source: Immune Design; Cowen and Company

A Two-Armed Approach To Anti-Tumor Immunity

Immune Design is utilizing two proprietary platforms to develop immune-based therapies for the treatment of cancer. With re-activation of the host anti-tumor immune response at the forefront of cancer therapy, Immune Design has developed novel methods of antigen delivery and modulation of dendritic cell activity. Both platforms converge on the central idea that eliciting an antigen-specific, anti-tumor T-cell response will produce complete, durable responses.

IMDZ Approach: Specific & Broad Immune Activation



Source: Immune Design

Mounting A Successful Immune Response

While the innate arm of immunity, consisting of macrophages, neutrophils and NK cells, has been shown to play a vital role in anti-tumor immunity, much effort has now turned to modulating adaptive immunity as a means of cancer therapy. The initiation of an adaptive immune response begins when a dendritic cell processes a foreign peptide or antigen. Most of these cells reside within tissues and persist for quite some time, constantly surveying the tissue microenvironment. For many infectious pathogens, dendritic cells recognize certain characteristics via specific receptors, that once engaged promote uptake of that pathogen, digestion and presentation of antigen. Dendritic cells are also continually ingesting material from the microenvironment, such as peptides and virus, which are processed and presented on the surface of the cell. Once internalized, peptides are digested, processed through the endoplasmic reticulum and delivered to the plasma membrane via peptide-MHC class I/II complexes. MHC class I molecules present degraded peptides that are found in the cytoplasm of the dendritic cell. Nearly every type of cell expresses MHC class I

molecules. MHC class II molecules present peptides that originate from extracellular material that has been internalized. These antigen complexes are found only in subsets of immune cells and include dendritic cells, macrophages and B-cells. Upon activation, dendritic cells, now considered professional antigen presenting cells (APCs), will up-regulate co-stimulatory molecules and shuttle to regional lymph nodes where they will interact with T-cells.

Once in local lymph nodes, APCs will present their antigen to T-cells, with each T-cell having different antigen specificity. As naïve T-cells migrate through lymph nodes, they encounter the activated APCs. Upon engagement of the T-cell receptor (TCR) with the antigen/MHC complex (as well as co-stimulatory molecules), intracellular signaling pathways are triggered and that T-cell will begin to rapidly proliferate, referred to as clonal expansion. Once activated, T-cells will migrate to sites containing antigen and perform effector functions that include production of cytokines and cell killing. Once antigen has been cleared, most effector T-cells will die off, though some will persist as memory T-cells ready to re-activate upon re-challenge.

Two distinct subsets of T-cells exist that can respond to antigen. CD4+ T-cells respond only to antigen in the context of MHC class II presentation, while CD8+ T-cells engage only MHC class I molecules. In the case of CD8+ T-cells, activation induces maturation into cytotoxic T lymphocytes (CTLs) that are capable of lysing antigen-expressing cells. In contrast, CD4+ cells will mature into T helper cells and will secrete cytokines that can stimulate the effector function of other T-cells and promote B-cell antibody production. T helper cells can be further subdivided based on their cytokine profiles. Th1 polarized T helper cells are characterized by production of IFNγ, IL-2, IL-12 and TNF-α and enhance the proliferation of CD8+ T-cells, killing activity of macrophages and production of opsonizing antibodies (to trigger antibody dependent cell killing). Th2 T helper cells are marked by IL-4 and IL-10 secretion and activate eosinophils, basophils and mast cells (involved in allergies and asthma) while directly suppressing Th1 polarization. Much work has now suggested that Th1 immunity is critical to eliciting an anti-tumor response, as well as generating immunological memory.

How Tumors Evade Immune Surveillance

Numerous studies have highlighted the idea that the immune system is designed to detect and destroy cancer cells. For the most part, our immune system is quite efficient at eliminating malignant and even pre-malignant cells, but cancerous cells have evolved mechanisms through which they can evade immune detection. Understanding and exploiting these mechanisms has uncovered viable and effective therapeutic options including the highly touted anti-PD-1/PD-L1 agents.

Immunosuppression In The Microenvironment

Much of the immunotherapies currently in development are based upon the idea that the immunosuppressive tumor microenvironment is inhibiting immune-mediated tumor cell killing. Malignancies have evolved several strategies to evade immune surveillance by recruiting immunosuppressive lymphocytes and inhibiting the function of otherwise anti-tumor immune cells. Several strategies to target these features of tumor development and progression have been developed with many more in clinical studies.

- **Disruption Of Antigen Presentation.** Again, for a T-cell to activate, it must be presented with the proper signals, including the correct antigen. A T-cell is presented with the proper antigen through antigen presentation mechanisms that

involve the coordination of several pathways that will ultimately display the antigen on the tumor cell surface. Cancer cells have evolved several mechanisms that include point mutations/deletions and transcriptional down-regulation through which they can perturb antigen presentation.

- **Impair Lymphocyte Infiltration.** Cancer cells can also alter the tumor vasculature and block the ability of lymphocytes to exit the blood stream and enter the tumor microenvironment. It has been reported in some tumors that the blood vessels surrounding the tumor have reduced levels of adhesion molecules required for immune cells to traverse the vessel and reach the malignant cells.

- **Resistance To Immune-Mediated Killing.** A signature feature of cancer cells is their ability to resist apoptosis and cell death. Similar to the way tumors develop resistance to chemotherapy during the course of treatment, tumors acquire resistance to immune killing during the course of development. A T-cell has two mechanisms by which it can destroy a tumor cell, by injecting killing enzymes and engaging extracellular death receptors. Cancer cells can express proteins that inhibit these killing enzymes, as well as express decoy receptors that a T-cell can engage but are non-functional.

- **Block T Cell Activation.** By far the greatest area of active research within immune evasion is that of inhibitory co-receptors such as CTLA-4 and PD-1. When engaged, these receptors inhibit T-cell activation and trigger immune tolerance. Patients with tumors that express the PD-1 ligand, PD-L1, and thus inhibit T cell activation, have been shown to have worse clinical outcomes. Indeed, the CTLA-4-targeting ipilimumab and PD-1-targeting pembrolizumab and nivolumab have all demonstrated clinical activity and have been approved for the treatment of melanoma.

  Another mechanism by which a tumor can inhibit T-cell activation is through amino acid depletion. Cancer cells have been shown to express the IDO enzyme that catalyzes the conversion of tryptophan to kynurenine. Studies have reported that both the depletion of tryptophan and accumulation of kynurenine results in cell cycle arrest of T-cells. Inhibitors of the IDO enzyme are currently in development at both NewLink and Incyte for the treatment of cancer.

- **Recruitment Of Immunosuppressive Lymphocytes.** Malignant cells can also inhibit lymphocytes indirectly by recruiting suppressive immune cells. One such cell type is regulatory T-cells (T_{regs}) which are characterized by their ability to inhibit the activation of effector T cells. High numbers of T_{regs} have been found in a variety of solid tumors, and like PD-L1 expression, are associated with poor outcomes. They are recruited to tumors through an unknown mechanism, but a conversion mechanism has also been postulated. In this model, the tumor microenvironment induces infiltrating effector T cells to adopt a T_{reg} phenotype.

Depletion Of Immunogenicity Through Immuno-Editing

Many of the above mechanisms of immune evasion all suggest that tumor cells are recognized by the immune system, but the tumor cells are in some way preventing the immune system from doing its job. Another possible mechanism by which a tumor cell can evade immune surveillance is by not being immunogenic enough or simply just not be recognized by the immune system. The theory of cancer immuno-editing has gained steam over the last couple of years with mounting evidence to support it. The theory suggests that early in the creation of the tumor the immune system efficiently removes malignant cells, so that it remains below the limit of detection. As the tumor

progresses through early development, the immune system acts as a selective pressure to remove the most immunogenic cells, while sparing those that are the least immunogenic. Some studies have shown that this early selective pressure is driven entirely by the recognition of tumor-specific antigens. In the end, those cells that go on to form clinically detectable tumors are those that are essentially non-immunogenic and tolerated by the immune system.

Many of the well-recognized tumor-associated antigens of solid tumors, like NY-ESO-1, are self-antigens that are aberrantly re-expressed. As a self-antigen, high-affinity TCRs against NY-ESO-1 should be eliminated during immune development to prevent autoimmunity. As such, it is predicted that anti-NY-ESO-1 immunity will not occur once a tumor begins to express the antigen. This however is not true, as anti-NY-ESO-1 (as well as other self-tumor antigens) T-cells are readily detectable in some patients. Unfortunately, despite the presence of antigen-specific T-cells, tumor cells continue to proliferate until becoming clinically detectable. Numerous studies have demonstrated that while antigen-specific T-cells are present, they may in fact be unresponsive to antigen in vivo. It has been suggested that a T-cell's decision to activate upon antigen recognition or not is determined by the APC. If a dendritic cell encounters antigen in an inflammatory environment it will become fully activated, express co-stimulatory molecules and elicit a fully functional T-cell response. In contrast, if that antigen is processed in non-inflammatory conditions, antigen will still be processed into MHC complexes, but the APC will lack the necessary co-stimulatory molecules. Presentation of antigen from an APC that is not fully activated will in fact tolerize that T-cell to that antigen.

Re-Educating The Immune System Through Dendritic Cells

Based on these assumptions, we believe there are three necessary steps to generating an APC that can elicit a robust anti-tumor immune response.

1. Efficient delivery of antigen to dendritic cells.

2. The presence of multiple MHC class-I/II epitopes on the antigenic peptide.

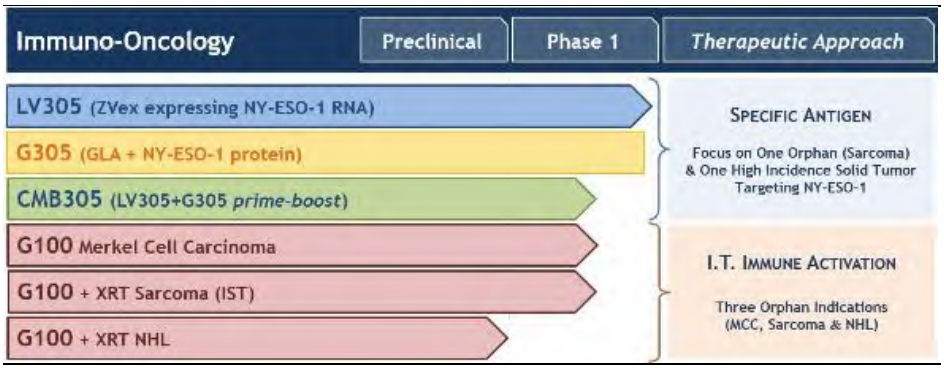
3. Delivery of antigen in the presence of danger/inflammatory signals.

We think prior in vivo vaccination approaches have failed to meet all three of these requirements and may be why therapeutic vaccines have demonstrated lackluster results in the clinic thus far. Preclinical studies demonstrate that IMDZ's ZVex and adjuvant platforms hit all three of these requirements and as such have the potential to be a best-in-class vaccine delivery strategy.

ZVex & GLA Immune-Oncology Programs

Immune Design is developing in vivo approaches to generating anti-tumor cytotoxic T-cells. They have engineered an immune activating adjuvant that activates dendritic cells via TLR4 and an antigen delivery method that utilizes a lentivirus vector to deliver tumor-specific antigen to dendritic cells. Both platforms are being tested as single-agents and in combination with one another in various tumor indications.

Clinical Stage Oncology Products



Source: Immune Design

Using their two platforms, Immune Design is taking a three-step approach to developing an NY-ESO-1-targeting immunotherapeutic. First, and recently completed, they evaluated G305 and LV305 as single agents. Once both agents were considered safe without dose-limiting toxicities, IMDZ initiated a Phase Ib study evaluating the two in combination, termed CMB305. Lastly, Phase II trials, expected to initiate in 2H15, will look at LV305 and CMB305 in combination with a checkpoint inhibitor. Pipeline description, as well as ongoing and expected trial details will follow.

ZVex: An Off-The Shelf DC Vaccine

Developed from technology licensed from Caltech, IMDZ's ZVex platform utilizes an engineered virus to deliver antigen specifically to dendritic cells. The platform has been extensively evaluated in vitro and has recently entered a Phase I trial as LV305 to deliver NY-ESO-1 antigen in NY-ESO-1 expressing tumor indications. On their 4Q14 call, IMDZ reported that LV305 has been well-tolerated with no dose-limiting toxicities and treated patients have shown increased levels of NY-ESO-1-specific CD8+ T-cells. Data included in the ASCO 2015 abstract provided more clarity on trial design and early results. The dose-escalation portion of the trial enrolled four cohorts of three patients who received three or four intradermal injections of LV305 every three weeks (10^8-10^{10} vector genomes/dose). No DLTs or SAEs were reported and all treatment related AEs were low grade (fatigue, injection site reaction and myalgia). In the initial 12 patients, eight SDs were observed (139-347+ days). Increased levels of NY-ESO-1-specific CD4+ and/or CD8+ T-cells were detectable in 73% of treated patients and four of the six patients treated at the highest doses develop a CD8+ NY-ESO-1+ T-cell response that was not detectable prior to vaccination. Moreover, TIL-specific TCR sequences were amplified following vaccination and T-cells to new epitopes became detectable. Expansion cohorts of up 53 patients are ongoing and are being treated at the highest dose level. Additional data is expected at ASCO. IMDZ will advance LV305 as single-agent, as well as in combination with G305 (NY-ESO-1 peptide + adjuvant) as CMB305.

Developmental Strategy:

1. **Phase I dose-escalation (NCT02122861) – COMPLETED:** This Phase I trial is designed to determine the MTD of LV305 in patients with advance NY-ESO-1+ cancers. LV305 will be dosed intradermally every three weeks across four doses. Once the MTD is established, indication-specific expansion cohort will open for enrollment. Updated data for the dose-escalation portion of this trial beyond the abstract described above will be presented at ASCO 2015.

2. **Phase I expansion cohorts at high-dose – ONGOING**

3. **Phase I DE in combination with G305 (CMB305) – ONGOING:** Detailed below.

4. **Phase I expansion with CPI in melanoma CPI-failures – EXPECTED 2Q15**

5. **Phase I CMB305 expansion cohorts at optimal dose – EXPECTED 3Q15**

Delivering Antigen Through An Engineered Virus

Approval of Dendreon's sipuleucel-T/Provenge in 2010 demonstrated that utilizing dendritic cells as a method of generating anti-tumor immunity was an effective approach. While Dendreon may have been the victim of many compounding factors, the ex-vivo education of dendritic cells proved to be a burdensome and expensive process that many felt wasn't justified by the clinical benefit. Briefly, generation of the sipuleucel vaccine involved harvesting autologous lymphocytes, presenting antigen to these cells, inducing maturation of dendritic cells and reinfusion. As a personalized vaccine, the process is quite time consuming and along with its questionable cost/benefit, sales have disappointed with Dendreon filing for bankruptcy in 2014. Immune Design is using the same basic principle of educating dendritic cells with tumor antigen to elicit a tumor-specific immune response, but do so in vivo via viral delivery.

ZVex is an engineered lentivirus that has been designed to specifically target and infect dendritic cells. Incorporated into the viral envelope is a modified glycoprotein from the Sindbis virus that has been altered, so that it only interacts with a surface-expressed dendritic cell protein. Specifically, the virus binds the DC-SIGN protein which when engaged causes the dendritic cell to envelope and engulf the virus. The virus has also been designed to encode the NY-ESO-1 protein within the viral genome. As the virus is processed by the cell, NY-ESO-1 protein is expressed, degraded and presented as antigen on the surface of the dendritic cell. As a safety precaution, the virus has also been engineered so that it is both replication and integration deficient.

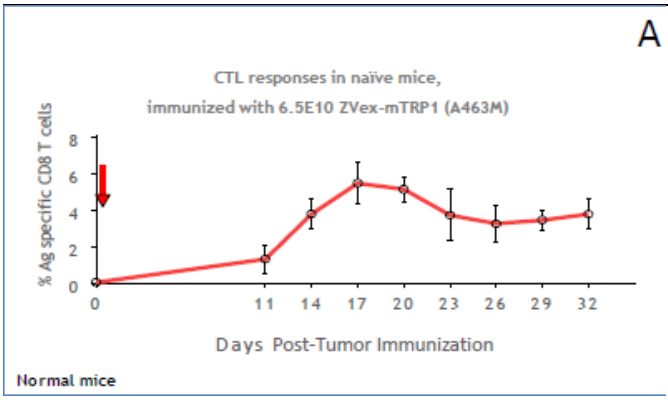
Using a virus expressing either the green fluorescent protein (GFP) or luciferase reporter as a proof of principle, investigators have demonstrated that the platform can effectively target and infect DC-SIGN expressing cells. Mice receiving a single subcutaneous dose of the GFP-virus had GFP+ dendritic cells 3 days post-treatment. The fact that GFP+ DCs were found in regional lymph nodes following treatment highlights the platform's ability to generate a systemic immune response. More than one month following dosing, lentivirus was undetectable in all isolated organs evaluated, confirming the specificity of the virus for dendritic cells. In an early model to assess whether the platform could generate systemic immunity, investigators utilized the well-characterized OVA antigen. Here, mice received a single dose of virus harboring the OVA antigen and were monitored for OVA-specific immunity. Compared

to mice who received a control virus, T-cells from mice treated with the OVA-virus robustly secreted IFNγ upon re-stimulation with the OVA antigen. The frequency of T-OVA-specific T-cells following a single injection was found to be dose-responsive, with a remarkable 15% of T-cells found to be OVA-specific at the highest dose tested. Moreover, an antibody response against OVA was also detected following a single dose of virus.

The platform's anti-tumor efficacy was first assessed in a vaccination model where mice were first immunized using the virus then challenged with OVA-expressing tumor cells. Mice receiving the vaccination were completely resistant to tumor challenge, while mice receiving a mock vaccination formed robust tumors. This immunity was OVA-specific, as immunized mice were not resistant to tumor cells that did not express the OVA antigen. In a therapeutic model, tumors were first established and mice then received two doses of OVA-virus on days 3 and 10 post-tumor implantation. Treated mice demonstrated tumor regression beginning at day 9 that resulted in a complete response beyond the level of detection. All mice remained tumor free for the duration of the experiment (>60 days). In stark contrast, tumors in untreated mice grew rapidly to the point where mice had to be sacrificed by day 16.

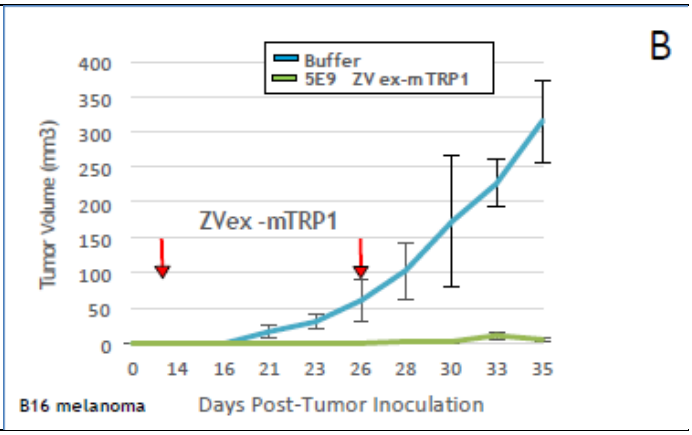
Immune Design has also evaluated their platform using tumor-specific antigens in murine mouse models. Using the B16 murine melanoma model and a ZVex virus designed to deliver the TRP1 antigen, IMDZ has demonstrated the platform to be a potent immuno-therapeutic. As shown in the figures below, the TRP1-virus was capable of generating a robust antigen-specific T-cell response in naïve mice that was detectable for >30 days following a single dose. Additionally, B16 melanoma tumor progression was completely abrogated in mice who received two doses of the therapeutic vaccine, while tumors grew unchecked in mice treated with placebo.

ZVex-TRP1 Generates Antigen-Specific CD8 T-Cells



Source: Immune Design

ZVex-TRP1 Inhibits B16 Melanoma Progression

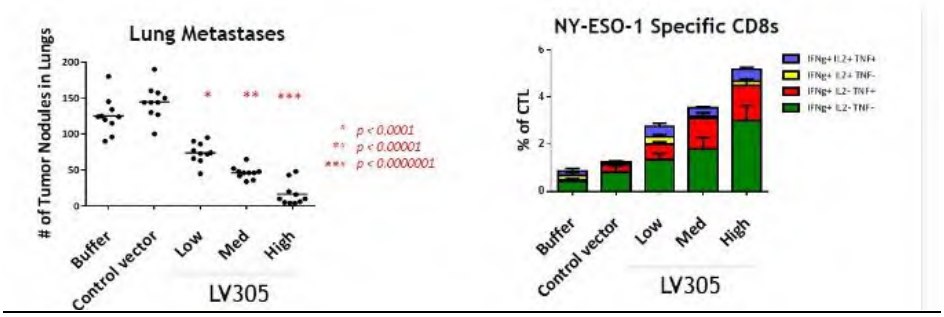


Source: Immune Design

Lastly, IMDZ has demonstrated in preclinical testing that LV305 is active against NY-ESO-1 expressing tumor cells and that efficacy is dependent on both a CD4+ and CD8+ T-cell response. Using a model of spontaneous metastases where NY-ESO-1+ tumor cells injected IV form lesions in the lung, LV305 exhibited dose-dependent activity and significantly reduced metastatic burden at all tested dosing levels. In response to a single dose of LV305, mice generated an impressive CD8+ T-cell

repertoire that was characterized by polyfunctional T-cells as demonstrated through the presence of INFγ+, IL2+ and TNF+ triple-positive T-cells.

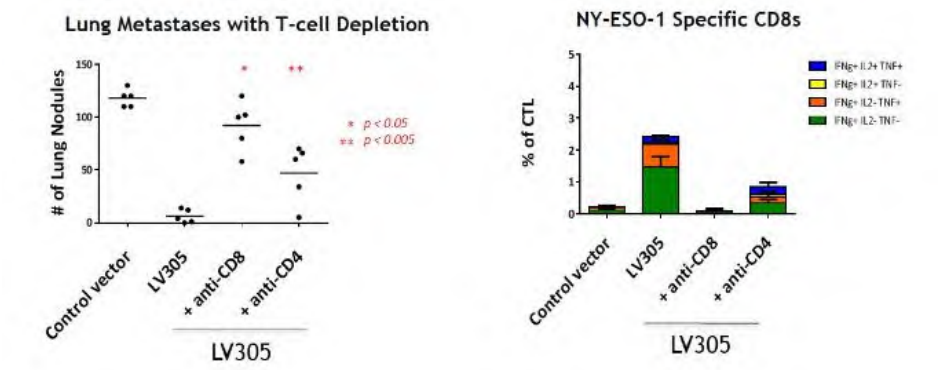
LV305 Blocks Spontaneous Mets & Elicits A Thorough T-Cell Response.



Source: Immune Design

Using the same model, IMDZ has shown that LV305 anti-tumor activity is mediated through a CD4/CD8 T-cell response. Again, while the lungs of control mice were littered with metastatic lesions, mice receiving the LV305 were nearly 100% protected. To elucidate the mechanism of activity, groups of mice either had their CD4+ or CD8+ T-cells depleted prior to LV305 immunization. Depletion of the CD8+ T-cell compartment resulted in near complete reversion of the protection offered by LV305. CD4+ depletion also significantly reduced the protective immunity of LV305, though to a lesser extent than CD8+ T-cell depletion. Further highlighting the importance of the CD4 T-cell compartment to LV305 activity, CD4+ depletion resulted in a marked reduction of polyfunctional CD8+ T-cells.

LV305 Activity Is Dependent On CD4+ & CD8+ T-Cells



Source: Immune Design

Possibilities Beyond A Single Antigen For ZVex

IMDZ's ZVex platform can be rapidly engineered to deliver different and/or multiple antigens. It can also be designed so that along with the delivery/expression of tumor antigen, it can also encode for co-stimulatory molecules or cytokines to enhance DC activity. IMDZ has indicated that NY-ESO-1 represents only 2Kb of a potentially 4-5Kb genomic backbone. This means that there is still plenty of genetic room to engineer in

an additional antigen, co-stimulatory molecule or cytokine. Specifically, IMDZ has suggested the inclusion of a single-chain checkpoint inhibitor antibody into the ZVex platform. This will make ZVex a 2-in-1 product that will stimulate DC-mediated antigen presentation while simultaneously releasing the checkpoint blockade on T-cells.

G305: GLA Adjuvant + NY-ESO-1 Peptide

G305 consists of IMDZ's GLA immune-adjuvant and a full-length NY-ESO-1 peptide. It is currently involved in a Phase I dose-escalation study. On their YE14 call, IMDZ reported that G305 was well-tolerated and able to elicit NY-ESO-1-specific immunity, though they did not release any data at that time. Data from this trial will be presented at ASCO 2015.

This trial is enrolling patients with advanced NY-ESO-1+ solid tumors who are dose intramuscularly once every three weeks in escalating dosing cohorts. In the 12 patients treated thus far in the ASCO abstract, injection site reactions were the most commonly reported AE and all other AEs have been low grade. There have been no DLTs or SAEs. SDs were observed in 67% of treated patients and ranged from 161-365+ days. Notably, 75% and 45% of evaluable patients developed an antibody or CD4+ NY-ESO-1 responses following vaccination, respectively. IMDZ has disclosed that they currently have no plans to develop G305 as a standalone product, but will instead move it ahead in development by combining with LV305, as CMB305.

Developmental Strategy:

1. **Phase I dose-escalation (NCT02015416) – COMPLETED:** This Phase I trial is designed to determine the MTD of G305 in patients with advanced NY-ESO-1+ cancers using a standard 3+3 design. G305 will be dosed intramuscularly across three doses. Updated data will be presented at ASCO.

The GLA Adjuvant

This immune adjuvant was licensed by IMDZ from the Infectious Disease Research Institute (IDRI). As an adjuvant, GLA is designed to strengthen vaccination efficacy through stimulation of the immune system. Adjuvants are frequently included in viral vaccination strategies and have been safely used in vaccines for decades. By combining a vaccine with an adjuvant, the immunogenicity of an antigen can be amplified and thus antigen-specific responses are robust and durable. This is especially important for recombinant protein-based vaccination strategies which have shown relatively low immunogenicity on their own.

Aluminum salt adjuvants were first discovered in the early 20th century and are the most widely utilized adjuvants in currently approved vaccines. For some time, many believed that precipitating antigens with these insoluble salts allowed them to persist for longer periods of time, as antigens were slowly released from the salt particles (a phenomenon referred to as the "depot effect"). More recently, data suggests that aluminum salts also promote up-regulation of co-stimulatory molecules on APCs, as well as drive Th2-type T-cell immunity.

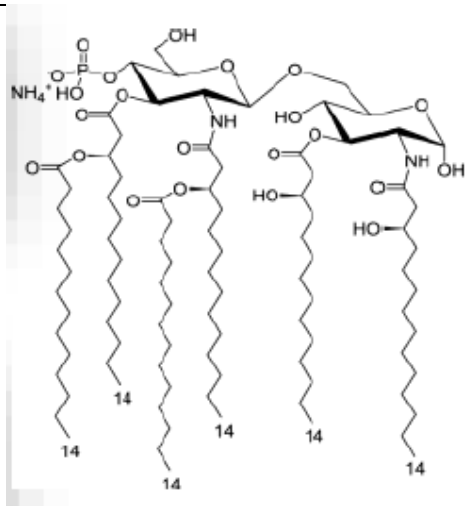
The generation of GLA (glucopyranosyl lipid A) was formed around the well-known immuno-stimulatory properties of the bacterial membrane polysaccharide LPS. In the 1950s, LPS was found to enhance antibody response to protein antigens and was later found to be a potent agonist of TLR4 signaling. While LPS was found to be too toxic to be used as an effective adjuvant in humans, a slight modification to the Lipid A

portion of LPS yielded a molecule that retained adjuvant activity, but with diminished toxicity. Monophosphoryl lipid A (MPL) has a single core carbohydrate removed and is capable of promoting Th1 T-cell immunity with only ~0.1% of the toxicity observed with LPS. This adjuvant has been tested in more than 300,000 patients and is approved for use in combination with an aluminum salt in GSK's HPV vaccine. While MPL has been successful, some studies have indicated its ability to drive a Th-1 response is dependent on both antigen and route of administration.

GLA is a lipid A derivative that consists of a two sugar backbone, a single phosphate and six fatty acid side chains (structure depicted below). As a synthetic lipid, GLA has been designed with several distinct differences to other lipid A molecules such as MPL. One significant feature is that GLA is synthesized with fatty acid side chains that have defined positions and lengths, so that a homogenous pool is produced. Since MPL is a naturally occurring lipid A, its fatty acid side chains are not defined and thus consist of heterogeneous pools of lipids. This is important as studies have demonstrated that in humans the length and number of fatty acid side chains can greatly affect the immune stimulating properties of a lipid A-based adjuvant.

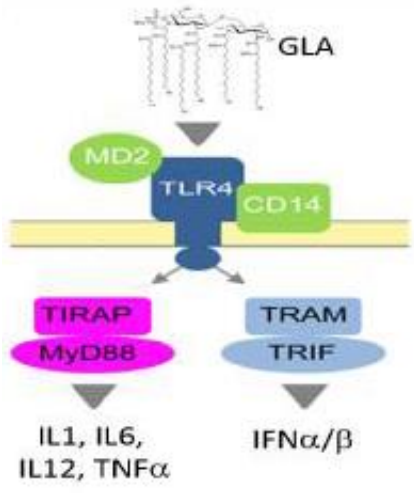
Many adjuvants exploit the family of Toll-like receptors (TLRs) which play a crucial in the innate arm of the immune system and are part of a larger family of pattern recognition receptors (PRRs) that recognize molecules expressed by infectious pathogens. TLR4 was first identified due its ability to bind bacterial LPS and promote inflammatory signaling. Upon ligand binding, TLR4 will dimerize and trigger two signaling pathways that promote dendritic cell activation and maturation. Specifically, activation of TLR4 results in MyD88- and TRIF-mediated signaling that elicits cytokine production to drive Th1-immunity, which again is characterized by cell-mediated immunity. Much research has shown that GLA is a potent activator of TLR4 signaling with a tolerable safety profile.

Structure Of GLA Adjuvant



Source: Immune Design

GLA Activates Two Pathways For DC Activation

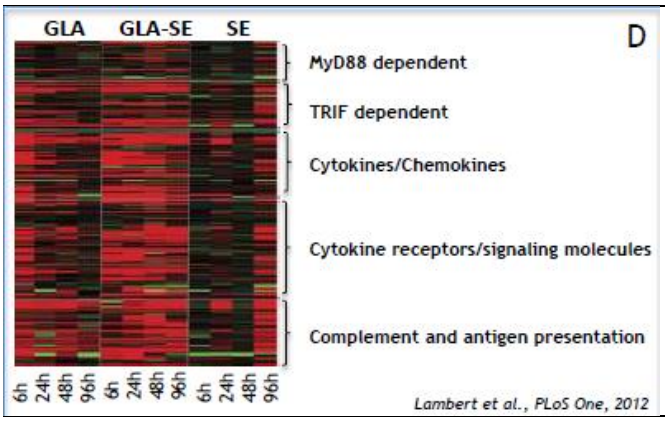


Source: Immune Design

Prior work has demonstrated that GLA stimulates MyD88- and TRIF-dependent cytokines and chemokines to levels that were nearly identical to MPL in murine bone marrow-derived dendritic cells (expected as difference in fatty acid side chains do not appear to affect mouse DCs). Moreover, dendritic cells from mice treated with GLA exhibited up-regulation of co-stimulatory molecules including CD40 and CD86 to

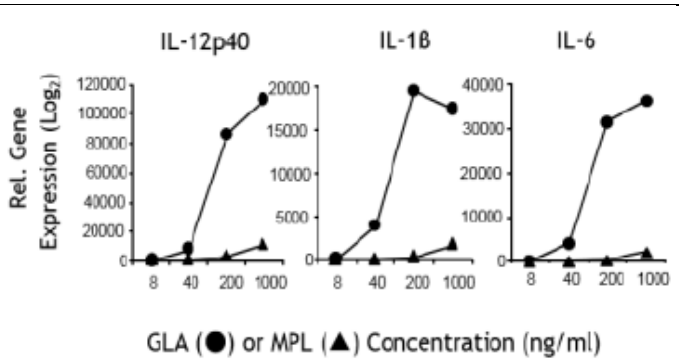
comparable levels of mice treated with either MPL or LPS. Moreover, in a vaccination model where vaccine-alone promotes a Th2-immune response, vaccinations in combination with GLA shifted T-cell responses to a Th1-immune response. This was characterized by elevated levels of IFNγ and TNFα and the absence of IL-5 and IL-13 Th2 cytokines. Highlighting the ability of human DCs to discern between fatty acid side chains, **GLA was superior to MPL in stimulating MyD88- and TRIF-dependent cytokines and chemokines, as well as promoting dendritic cell maturation.** Based on these data, GLA is thought to be 10-100X more potent than MPL as a TLR4 agonist.

GLA & GLA-SE (Stable Emulsion) Are Potent TLR4 Agonists



Source: Immune Design

GLA More Potent Than MPL

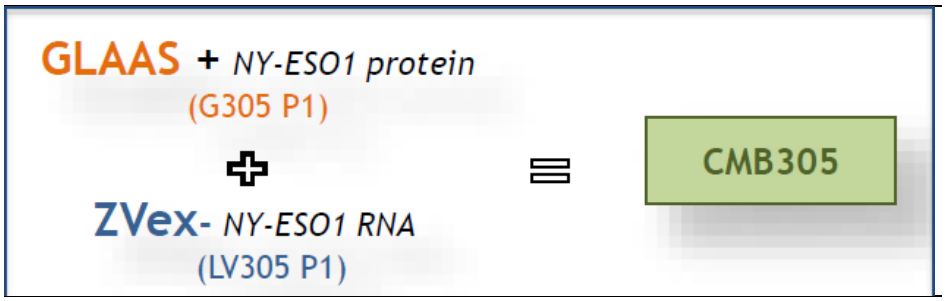


Source: Immune Design

CMB305 Prime-Boost: Testing Combinations Of In-House Assets

With G305 and LV305 deemed safe and tolerable, IMDZ has begun developing CMB305, a combination of the two NY-ESO-1 targeting vaccines.

CMB305 – Prime + Boost



Source: Immune Design

Developmental Strategy:

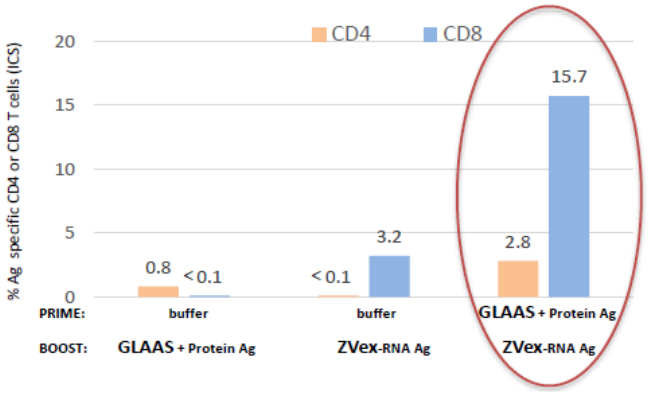
1. **Phase I dose-escalation (NCT02387125) – ONGOING:** This is open-label Phase Ib trial is dosing patients with advanced/relapsed NY-ESO-1+ melanoma, NSCLC, ovarian cancer or sarcoma sequentially with LV305 and G305. Data are expected by YE15.

2. **Phase I expansion cohorts at optimal dose – EXPECTED 3Q15.**

3. Phase II in combination w/CPI in STS – EXPECTED 4Q15.

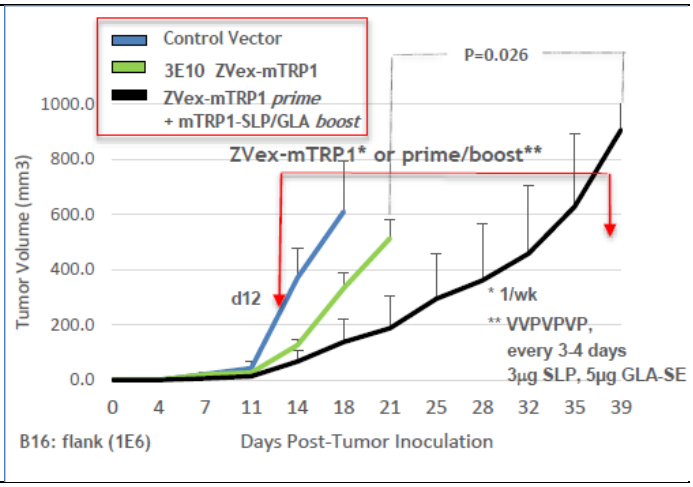
IMDZ has demonstrated the cooperativity of G305 and LV305 to formulate CMB305. They believe that sequential dosing of LV305 and G305 will amplify the antigen-specific T-cell response, as well as generate immunologic memory to produce durable, long-term responses. In preclinical studies, IMDZ has seen increased numbers of antigen-specific CD4+ and CD8+ T-cells when the GLA/peptide antigen platform is used in combination with ZVex, than when the two platforms are used on their own. Additionally, this effect on T-cells translates to improved control of tumor progression in the B16 murine melanoma model.

CMB305: Synergy Between G305 & LV305



Source: Immune Design

Prime-Boost: Enhanced Anti-Tumor Activity Over ZVex



Source: Immune Design

The NY-ESO-1 Tumor-Associated Antigen

For some time, NY-ESO-1 has been considered to be among the most attractive cancer-associated antigens. It was first identified in the serum of patient with esophageal cancer in the late 1990s. NY-ESO-1 is part of a family of cancer testis antigens that includes the often targeted MAGE-A3 and has been shown to be expressed in numerous tumor types, with expression limited to the testis in normal adult tissue. It is found in a large fraction of melanomas, breast, lung, bladder, prostate, thyroid, ovarian, head and neck cancers, as well as sarcomas and multiple myeloma. Not surprisingly, NY-ESO-1 represents an ideal therapeutic target given its known immunogenicity and prevalence in cancer. IMDZ is developing its NY-ESO-1 assets in melanoma, sarcoma, lung and ovarian cancer. Several other strategies to exploit the wide-spread expression of NY-ESO-1 in cancer are currently in development and will be detailed below.

Immune Design is currently targeting four indications that express NY-ESO-1 to varying degrees with their '305 platform:

US Incidence of NY-ESO-1 Positivity In IMDZ Target Indications

	# New Cases in 2015	% NY-ESO-1+	# NY-ESO-1+ in 2015
Lung Cancer	221,200	20%	44,240
Ovarian Cancer	21,290	20%	4,258
Melanoma	73,870	30%	22,161
Soft Tissue Sarcoma	11,930	-	-
Myxoid Liposarcoma	671	90%	604
Synovial Sarcoma	895	65%	582

Source: Cowen and Company

Lung Cancer: Several studies have observed NY-ESO-1 to be expressed in NSCLC, in both adenocarcinomas and squamous cell carcinomas subtypes. Some data has suggested NY-ESO-1 positivity to be a poor prognostic marker, correlating with lymph node involvement and shorter survival times. The majority of studies though, have found no link between the presence of NY-ESO-1 and clinical outcome. Across all studies, we estimate ~20% of all NSCLC patients to express the NY-ESO-1 antigen, which translates to ~45K US patients.

Ovarian Cancer: NY-ESO-1 has also been observed in ovarian cancer, with a similar incidence of expression as lung cancer, though positivity may vary between different subtypes. For serous ovarian cancer (SOC), the most common type of ovarian cancer, NY-ESO-1 positivity is estimated to be ~20%. Highlighting NY-ESO-1's immunogenicity, one study has shown expression of NY-ESO-1 in ovarian cancer to positively correlate with the extent of circulating anti-NY-ESO-1 antibodies. Moreover, the presence of NY-ESO-1 reactive antibodies coincided with increased numbers of tumor infiltrating lymphocytes. Approximately 20K new cases of ovarian cancer are expected to be diagnosed in 2015, which translates to ~4K NY-ESO-1+ patients.

Melanoma: NY-ESO-1 is probably most well-associated with metastatic melanoma. Studies evaluating both vaccination strategies and T-cell therapies targeting NY-ESO-1 in melanoma have demonstrated encouraging efficacy to date (discussed below). Approximately 30% of metastatic melanomas have been found to be NY-ESO-1 positive, which is a considerably higher rate of incidence than primary melanoma (~13%). Within metastatic melanomas, NY-ESO-1 is associated with a ~2-year reduction in overall survival. Even within early-stage melanoma, NY-ESO-1 positivity has been associated with poor prognostic factors including tumor thickness and disease stage at time of diagnosis. In 2015, ~74K new cases of melanoma are expected to be diagnosed, though the majority will present as early-stage disease. In total, ~22,000 new cases of NY-ESO-1+ melanoma are projected for 2015.

Soft Tissue Sarcoma (STS): Sarcomas represent a diverse group of tumors that originate from cells of mesenchymal origin. Using its NY-ESO-1 targeting platform, IMDZ is targeting synovial sarcomas (5-10% of STS) and myxoid liposarcomas (liposarcomas represent 15-20% of STS and myxoid/round cell represent 40% of liposarcomas). Of all STS, myxoid liposarcomas have shown the highest incidence of NY-ESO-1 positivity, with some studies seeing 100% NY-ESO-1 positivity; IMDZ puts this number at around 80%. For synovial sarcomas, approximately 65% express the NY-ESO-1 antigen.

Highlighting NY-ESO-1 as an immunotherapeutic target, early in the development of the anti-CTLA-4 antibody ipilimumab, investigators noted that responders often had an antibody response against NY-ESO-1. In five of the eight patients who demonstrated a clinical benefit when treated with ipilimumab, anti-NY-ESO-1 antibodies were detectable in the serum and coincided with the presence of CD4+ and CD8+ NY-ESO-1-specific T-cells. Moreover, one responder who was considered NY-ESO-1 antibody-negative, had a NY-ESO-1-specific T-cell response that the investigators attributed to prior vaccination. In stark contrast, all seven non-responders had undetectable levels of NY-ESO-1-specific antibodies. With these data, the investigators posited that NY-ESO-1 vaccination may compliment immune checkpoint blockade.

In hopes of covering every possible antigenic component of NY-ESO-1, G305 contains the full-length NY-ESO-1 peptide. Both full-length and peptide fragments of NY-ESO-1 have been tested in clinical trials with varying success. A more detailed discussion will follow.

NY-ESO-1: A Tried & True Antigen Waiting For The Right Approach

Since the identification of NY-ESO-1 and the revelation that it harbors strong immunogenicity, multiple approaches have been undertaken to exploit NY-ESO-1 as a target of anti-tumor immunity. Throughout the literature, we find that while many vaccines have been able to elicit a cellular or humoral response against NY-ESO-1, clinical efficacy remains poor with only a limited number of true responders.

Peptide-Based Vaccines

By the far the most studied vaccine strategies targeting NY-ESO-1 have been peptide-based therapies. Like IMDZ's G305, many of the initial trials attempting to therapeutically vaccinate against NY-ESO-1 utilized the full-length peptide. We will highlight just a few peptide-based vaccine trials. An early trial combined full-length NY-ESO-1 with ISCOMATRIX as an adjuvant and evaluated the immune response at various dose levels. As seen with many other vaccine strategies, the combination was generally well-tolerated with no DLTs. The most commonly reported AE was pain at the injection site. All 20 patients (mostly melanoma patients) who received a full course of treatment developed an antibody response against NY-ESO-1, with levels of antibody correlating directly with peptide dose. This study did not have efficacy endpoints, but the investigators noted that many patients who relapsed were those with poor immune responses.

Similarly, full-length NY-ESO-1 peptide was evaluated in combination with TLR7 agonist adjuvant imiquimod. This small trial enrolled 9 patients who had resected melanoma and were all disease free at the time of enrollment. Patients received topical imiquimod on days 1-5, with recombinant NY-ESO-1 protein injected intradermally on day 3 at the site imiquimod treatment. Patients received treatment once every 3 weeks for a total of 4 cycles. Again, the study treatment was well-tolerated with most AEs being transient injection site reactions. Following vaccination 4/9 patients had generated NY-ESO-1-specific antibody responses. While CD4+ T-cell responses were evident after weeklong peptide stimulation in some patients, no patient generated at CD8+ T-cell response.

Viral Delivery Of Antigen

Recently, the results from an early-stage trial that delivered NY-ESO-1 antigen via vaccinia/fowlpox virus were published in PNAS. The study enrolled 25 patients with advanced NY-ESO-1+ melanoma and 22 patients with NY-ESO-1+ ovarian cancer

who had completed surgery and adjuvant chemotherapy. Those enrolled received a prime-boost regimen, whereby patients received NY-ESO-1 antigen via vaccinia virus followed by NY-ESO-1 antigen via fowlpox virus. In the 21 melanoma patients evaluable for response, 2 CRs and 1 PR were observed for a 14% ORR. An additional 11 patients experienced stable disease (71.5% DCR). For the ovarian cohort, all patients had no measurable disease at the time enrollment, but the study reported a median RFS of 21 months and mOS of 48 months (historical data suggests mPFS of 16 months and a mOS of 44.1 in this patient population). The investigators demonstrated that vaccination was capable of driving an NY-ESO-1-specific antibody and T-cell response. Those with pre-existing antibodies and CD8+ T-cells appeared to benefit the most from vaccination.

Antigen-Specific T-Cell Infusion

In June 2008, a case study utilizing NY-ESO-1 specific T-cell in a patient with metastatic melanoma was published in NEJM. The single patient presented with recurrent melanoma with pulmonary and lymph node metastases. Autologous T-cells were harvested and selected for CD4 positivity and reactivity to an NY-ESO-1 peptide derived epitope. Double-positive cells were expanded and reinfused as a single treatment. Following infusion, NY-ESO-1-specific T-cells represented ~2% of all PBMCs and were detectable for more than 80 days following infusion. Two months after infusion the patient had no evidence of disease and remained this way up until the last follow which was >2 years after infusion. Interestingly, infusion of the NY-ESO-1-specific T-cells resulted in a broad immune response. T-cells responsive to other melanoma-specific antigens that were undetectable prior to infusion were now present following infusion. Engineered T-cells designed to target NY-ESO-1 are in development at both Kite and Adaptimmune and will be discussed below.

Competing NY-ESO-1 Targeting Therapies

Celldex's CDX-1401: CDX-1401 is a fusion protein consisting of a monoclonal antibody against the dendritic cell receptor DEC-205 fused to the full coding sequence of NY-ESO-1. The fusion protein directly binds to dendritic cells and elicits a NY-ESO-1 specific T cell response. CDX-1401 is licensed from the Ludwig Institute for Cancer Research and is currently beginning Phase II trials. Phase I study results were published in Science: Translational Medicine in April 2014. The open-label, dose-escalation trial evaluated the safety, MTD, immune response and anti-tumor efficacy of CDX-1401 administered with TLR agonist (resiquimod and/or poly-ICLC) in patients with advanced malignancies. No dose-limiting toxicities were observed and toxicity was limited to grade 1-2 injection site reaction, fatigue, nausea, and chills. CDX-1401 effectively elicited a NY-ESO-1-specific immune response, with 81% of treated patients exhibiting an increase in NY-ESO-1 IgG levels. In the 31 patients that completed at least one cycle of CDX-1401, 13 had stable disease (median=6.7 months) and two had tumor regression. Long-term follow up of patients that received CDX-1401 found that 6 of 8 patients who went on to receive immune-checkpoint inhibitor therapy exhibited tumor shrinkage. Based on this finding, Celldex is enrolling a Phase I/II study of varlilumab, Yervoy, and CDX-1401 in NY-ESO-1-positive patients. They have also begun enrollment in a NCI sponsored Phase II study of CDX-1401 and CDX-301 in metastatic melanoma patients.

NY-ESO-1 Engineered T-Cells: Both Kite and Adaptimmune are developing NY-ESO-1-targeting engineered T-cells. Kite and NCI have collaborated on developing a murine derived TCR construct which recognizes NY-ESO-1 when presented within the context of the MHC molecule. Kite is funding a Phase II trial which will administer autologous T cells expressing the murine NY-ESO-1 TCR along with IL-2 to

approximately 43 HLA-A2 positive patients with NY-ESO-1 positive metastatic cancers. Initial data is expected in 2015, perhaps at ASCO. In November 2014, Kite management stated that responses have been seen within this trial. NCI has granted Kite an exclusive license for the use of this construct in any NY-ESO-1 expressing cancer.

Adaptimmune is using Immunocore's "ImmTAC" TCR affinity selection methods to develop engineered TCRs with high affinity for antigens of interest. Adaptimmune's lead candidate is a human TCR specific for NY-ESO-1 which has been developed under a non-exclusive license from NCI. In 2011, a study out of the NCI using Adaptimmune's product in synovial sarcoma and melanoma was published. At that time, the NCI observed objective responses in 4 out of 6 synovial sarcoma and 5 out of 11 melanoma patients. No treatment related adverse events were observed. At AACR 2014, updated results from this trial were presented. In this larger data set, objective responses were seen in 10 out of 15 (67%) synovial sarcoma patients as well as in 10 out of 19 (53%) metastatic melanoma patients. Adaptimmune is currently conducting proof of concept trials of the human NY-ESO-1 TCR in multiple myeloma, melanoma, sarcoma and ovarian cancer.

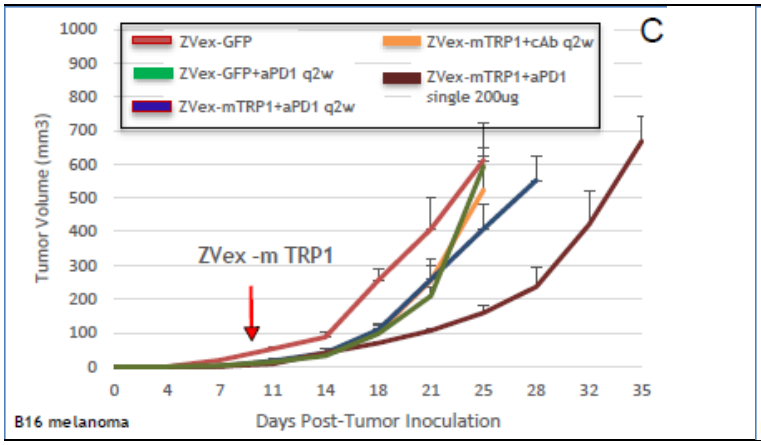
At the 2014 annual meeting of the Connective Tissue Oncology Society, Adaptimmune presented interim data from its Phase I trial in synovial sarcoma. This trial is designed to enroll 10 patients. At the time of the data update eight patients had been treated. Cytokine release syndrome (CRS) was observed in two patients. However, the observed CRS was mild and limited to grade 1 or 2 symptoms. Five patients had passed the 60-day post-infusion time point and were eligible for evaluation. Among these five patients, one complete response (9+ months) and three partial responses (4, 6, and 9 months) were observed. All three partial responders experienced significant enough shrinkage to allow for resection of the remaining detectable lesion. Based on these results, Adaptimmune has begun enrolling an expansion cohort of 30 patients.

Aduro's LADD Vaccine: Aduro's LADD is probably the most similar to IMDZ's approach to antigen delivery. LADD (live, attenuated, double-deleted) utilizes genetically engineered listeria bacteria to deliver tumor-specific antigens. Listeria naturally infects numerous cell types including dendritic cells and is designed so that antigen is secreted upon ingestion. Antigens secreted by the bacteria are targeted to both MHC class I and class II molecules and stimulate both a CD4+ and CD8+ T-cell response. The bacteria itself acts as a natural adjuvant and is a potent activator of the innate immune system. It has also been shown to induce expression of co-stimulatory molecules. While Aduro is developing several vaccines with this platform, ADU-623 is engineered to express both NY-ESO-1 and EGFRvIII. They are currently conducting a Phase I trial in high-grade glioma evaluating ADU-623 as a monotherapy.

Evaluate '305 Platform In Combination With CPIs

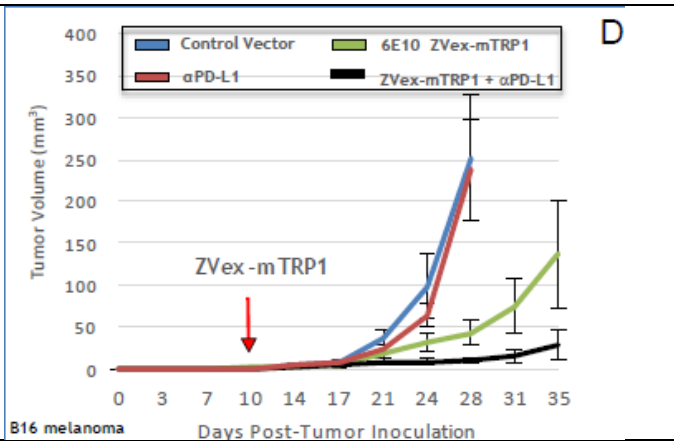
Given the mechanism of action of the '305 platform, it comes as no surprise that IMDZ expects to initiate trials in combination with an immune checkpoint inhibitor. As seen in the figures below, the ZVex platform synergizes with both anti-PD-1 and anti-PD-L1 agents. Using the B16 melanoma model and a ZVex virus to deliver the TRP1 antigen, IMDZ has demonstrated that CPIs can enhance vaccine anti-tumor activity. Trials evaluating both LV305 and CMB305 in combination with a CPI are expected to begin enrolling in 2015.

ZVex Synergizes With Anti-PD-1



Source: Immune Design

ZVex Synergizes With Anti-PD-L1



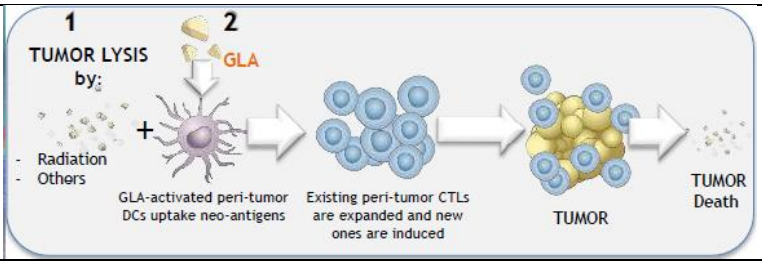
Source: Immune Design

A recent study evaluating vaccine strategies in metastatic melanoma has highlighted the rationale for combining vaccines with immune checkpoint inhibitors. The investigators noted that while therapeutic vaccines, including NY-ESO-1 peptides, are capable of eliciting tumor antigen-specific CD8+ T-cells, responses are rarely observed. They found that the pool of antigen-specific T-cells that expand upon vaccination, up-regulate the PD-1 inhibitory molecule and that this up-regulation dampens T-cell expansion. Ex vivo blockade of PD-1 upon antigen re-stimulation, improved both proliferation and frequency of polyfunctional T-cells.

G100 Adjuvant: Immune Activation Through Endogenous Antigen Release

Unlike the '305 platform which requires selection of a tumor-specific antigen, the G100 adjuvant utilizes endogenous tumor antigens to promote anti-tumor immunity. Like the GLA adjuvant used in G305, G100 is designed to promote antigen uptake and activation of dendritic cells, as well as stimulate pre-existing anti-tumor T-cells. While IMDZ is evaluating G100 as a single-agent in Merkel Cell Carcinoma (MCC), G100 is likely to have the greatest efficacy when used in conjunction with radiation or chemotherapy. The idea being that as tumor cells are killed by radiation, they release tumor antigens in the microenvironment. Tumor localized dendritic cells that have been primed by GLA are now more adept at taking up antigen and activating. Once fully mature and active, APCs can now present antigen to T-cells to trigger anti-tumor immunity.

G100 Mechanism Of Action



Source: Immune Design

Developmental Strategy:

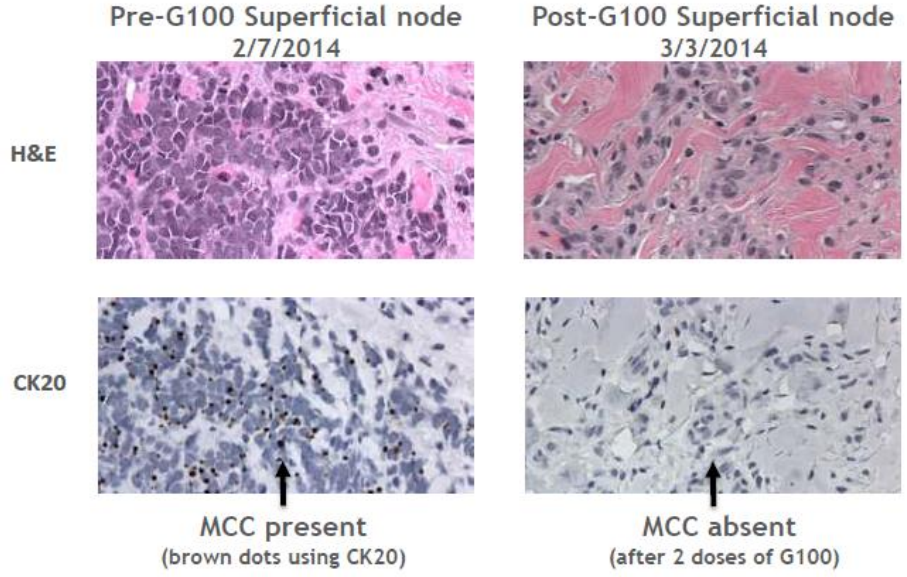
1. **Phase I in MCC (NCT02035657) – ONGOING:** This is a single-arm, open-label evaluating the safety, tolerability, clinical activity and immunogenicity of G100 in 10 patients with loco-regional or metastatic MCC. Data are expected at ASCO 2015.

2. **Phase I w/XRT in Sarcoma (IST; NCT02180698) – ONGOING:** This is a single-arm, open-label trial evaluating G100 in combination with radiation in patients with metastatic sarcoma. It is expected to complete by YE15.

3. **Phase I in combination w/XRT in NHL – EXPECTED 2Q15.**

G100 is currently involved in two ongoing Phase I trials, with an additional trial expected to open for enrollment in 2Q15. IMDZ has previously reported that one patient in the Phase I MCC trial achieved a complete response, with additional clinical activity observed in other patients. Ahead of ASCO 2015, IMDZ provided an update to the MCC trial in the ASCO abstract. As was the case with LV305 and G305, G100 appears to be well-tolerated with only grade 1 and 2 AEs observed in the first eight patients treated. As a single agent, G100 demonstrated a pathologic CR in one patient with loco-regional disease and a 28% reduction in tumor burden in a patient with metastatic disease. An ORR of 50% was reported in the eight patients who received G100 followed by radiation and/or surgery. **Additional data from the Phase I MCC trial are expected to be presented at ASCO 2015.**

Early G100 Activity In MCC



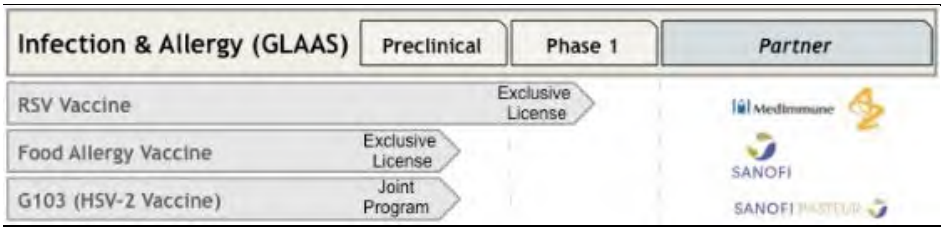
Source: Immune Design

Leveraging Platforms Outside Of Oncology

The ability of the IMDZ's platforms to potentiate immune responses offers a unique opportunity for them to extend application into non-oncology indications. They have formed collaborations with MedImmune and Sanofi to utilize the GLA adjuvant in

infectious disease and food allergy vaccine development and have suggested that the ZVex platform can be used to induce tolerance in autoimmune indications.

Partnerships To Develop GLAAS In Infection & Allergy



Source: Immune Design

Infectious Disease

In 2010, IMDZ entered into three licensing agreements with MedImmune to utilize the GLA adjuvant to develop and commercialize vaccines for three infectious disease indications. One license was later returned to IMDZ. To date, IMDZ has received $5.5MM in payments, with the potential for an additional ~$138MM based on achievement of milestones. IMDZ will also receive a mid-single digit royalty on net sales. In October 2014, IMDZ announced that it would be jointly developing a herpes simplex vaccine with Sanofi Pasteur through Phase II development. Sanofi will continue development beyond Phase II and will be responsible for commercialization. The vaccine includes Sanofi's HSV-529 vaccine and IMDZ's G103 which consists of peptides and a special formulation of GLA.

Food Allergy

In August 2014, IMDZ licensed Sanofi exclusive use of the GLA platform to develop and commercialize products to treat select food allergies. IMDZ received an upfront payment that was not disclosed, but can potentially earn up to $168MM in milestones, as well as tiered royalties on sales.

Autoimmune Disease

While IMDZ has not formally announced an autoimmune program, they believe the ZVex platform can be utilized in such indications. Specifically, they have indicated that ZVex can be designed to induce antigen-specific tolerance, perhaps through lack of co-stimulation.

Ongoing Litigation

IMDZ is involved in ongoing litigation surrounding their manufacturing and patents related to their ZVex platform and GLA adjuvant. TheraVectys, a French biotech, has filed two separate lawsuits against IMDZ. The first alleges that IMDZ is utilizing a contract manufacturer (Henogen) to produce lentivirus, which TVS claims to have had an exclusivity contract with to produce lentiviral-based vaccines. The second lawsuit involves a European patent directed at improvements to the lentiviral vector. IMDZ believes TVS is not using the technology protected by the patent and that the validity of this patent will not have an impact on the scope of their patent protection in Europe. Lastly, a third party has filed opposition to a European patent (owned by IRDI and licensed to IMDZ) directed to GLA formulations and use. IMDZ has acknowledged that this patent is important to protection of the GLA platform in Europe, but like the other ongoing litigation, the resolution timeline is uncertain.

Immune Design Management

Carlos Paya, M.D., Ph.D.; President & CEO: Joined Immune Design in May 2011 as President, Chief Executive Officer and director. He previously served as President of Elan Corporation, which was acquired by Perrigo Company, from November 2008 to April 2011. Before joining Elan Corporation, Dr. Paya was at Eli Lilly & Company from September 2001 to November 2008, as Vice President, Lilly Research Laboratories. From January 1991 to August 2001, Dr. Paya was Professor of Medicine, Immunology, and Pathology, and Vice Dean of the Clinical Investigation Program at the Mayo Clinic in Rochester, Minnesota. He received his M.D. and Ph.D. degrees from the University of Madrid and underwent postdoctoral training at the Institute Pasteur, Paris, France.

Stephen R. Brady, JD, LLM; Chief Business Officer: Joined Immune Design in September 2013 as Chief Business Officer. He previously served as Chief Business Officer for 3-V Biosciences, Inc., from February 2011 to August 2013, and prior to that, he served as 3-V Bioscience, Inc.'s Vice President, Corporate Development, Strategy and Operations, from February 2010 to February 2011. From April 2007 to March 2010, he was at Proteolox, Inc., most recently serving as Vice President, Corporate Development. Prior to Proteolix, Inc., Mr. Brady served as Senior Corporate Counsel at Lexicon Pharmaceuticals, Inc. from 2001 to 2007. Mr. Brady was also a Vice President with Lazard Venture Advisors from 2000 to 2001, and an associate at Morrison & Foerster LLP from 1996 to 2000. Mr. Brady received a B.A. in English from the University of Oregon, a J.D. from the University of the Pacific and an LL.M. from New York University School of Law.

Wayne Gombotz, Ph.D; Chief Development Officer: Joined Immune Design in December 2011 as Chief Development Officer. He previously served as Vice President Pharmaceutical Operations at Omeros Corporation from May 2005 to October 2011. Before joining Omeros Corporation, Dr. Gombotz held several executive management positions including Vice President, Process Science & Pharmaceutical Development at Corixa Corporation from September 2002 to March 2005 and Sr. Director, Analytical Chemistry and Formulation at Immunex Corporation from April 1993 to September 2002. He was also a staff scientist at Bristol-Myers Squibb and Enzytech Inc. Dr. Gombotz also currently serves as an Advisory Board Chair of the Center for Intracellular Delivery of Biologics and an Advisory Board Member for the University of Washington's Department of Bioengineering. Dr. Gombotz received an M.S. and Ph.D. degree in Bioengineering from the University of Washington where he is an Affiliate Assistant Professor.

Richard T. Kenney, M.D.; Chief Medical Officer: Joined Immune Design in September 2013 as Chief Medical Officer. He previously served as Chief Medical Officer for Crucell Holland BV, from July 2012 to August 2013. From December 2009 to June 2012 he was at Vical Incorporated in various key positions, and last served as Senior Vice President, Clinical Development. Dr. Kenney held key positions in vaccine development at GSK Biologicals from December 2005 to November 2009, and he most recently served as Senior Director of Global Clinical R&D. From April 2005 to December 2005 he served as Vice President, Clinical Development of ID Biomedical until it was acquired by GSK Biologicals. Prior to that, Dr. Kenney had various positions at Iomai Corporation from March 2001 to April 2005, where he most recently served as Vice President, Medical and Regulatory Affairs. Dr. Kenney served in the Public Health Service as a Lead Research Investigator at the FDA, Center for Biologics Evaluation and Research, Office of Vaccine Research and Review from July 1995 to February 2001. Dr. Kenney completed his residency in internal medicine at Duke University Medical Center, and received his postdoctoral training at the National Institutes of

Health, National Institute of Allergy and Infectious Diseases, completing a fellowship in infectious diseases, and then post-doctoral training in molecular parasitology and tropical medicine. He received board certifications in Internal Medicine and Infectious Diseases. He earned his M.D. degree at Harvard Medical School and graduated with special honors from George Washington University.

Jan Henrik ter Meulen, M.D.; Chief Scientific Officer: Joined Immune Design in October 2013 as Chief Scientific Officer. He previously served as Executive Director of Vaccine Research and Head of Department of Vaccine Basic Research at Merck Research Laboratories from April 2008 to September 2013. Prior to Merck, from March 2003 to April 2008, Dr. ter Meulen served as Executive Director Infectious Diseases at Crucell Holland and, from September 2006 to April 2008, as Chief Scientific Officer at Etna Biotech S.r.l. Dr. ter Meulen has an M.D. from Albert Ludwigs University Freiburg im Breisgau, a medical doctorate from Julius Maximilians University Wuerzburg, a higher doctorate from Philipps University Marburg, a Diploma in Tropical Medicine and Hygiene from the London School, and is a board certified in Clinical Microbiology by the Chambers of Physicians, Hamburg Germany.

Frank J. Hsu, M.D.; Vice President, Head of Oncology: Joined Immune Design in October 2013 as Vice President, Head of Oncology. Dr. Hsu recently served as Chief Medical Officer for Zyngenia, Inc., where he was responsible for strategic planning and clinical development of multi-specific, multi-valent agents for the company's lead programs in immune-mediated diseases and oncology. Prior to that, Dr. Hsu was Senior Medical Director at Genzyme in the Transplant and Oncology Division, where for more than nine years he was responsible for the clinical development of products in the areas of hematology, oncology, and stem cell transplant, and supported medical affairs and corporate development. From 1996-2003 he served as an Assistant Professor of Medicine in the Section of Oncology and as co-Director of the Immunology Research Program of the Yale Cancer Center. Dr. Hsu received his B.S. from Stanford University, his M.D. from Harvard Medical School, and his residency training in Internal Medicine at UCSF. He was a clinical and research fellow in Oncology at Stanford University from 1990-1996.

Paul Rickey; Vice President, Finance and Administration: Joined Immune Design in July 2009 as Vice President, Finance and Administration, Secretary and Treasurer. Prior to joining Immune Design, he served in various positions, most recently Corporate Controller of Northstar Neuroscience from July 2006 to June 2009. Prior to that, he served as the Accounting Manager at Mobliss Inc. from 2004 to 2006 and was an employee of Ernst & Young LLP from 2001 to 2004. Mr. Rickey has a B.A. in Business Administration, Accounting, and Masters in Professional Accounting from the University of Washington. He currently serves on the board of the Northwest Association of Bioscience Financial Officers and received his Certified Public Accountant Certification from the state of Washington and currently holds an active license.

Immune Design Quarterly P&L

Income Statement ($MMs)	1Q15A	2Q15E	3Q15E	3Q15E	2015E	1Q16E	2Q16E	3Q16E	4Q16E	2016E
Licensing revenues	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Product sales	0.09	0.09	0.09	0.09	0.36	0.09	0.09	0.09	0.09	0.36
Other, net	1.85	1.85	1.85	1.85	7.40	1.85	1.85	1.85	1.85	7.40
Total Revenues	**1.94**	**1.94**	**1.94**	**1.94**	**7.75**	**1.94**	**1.94**	**1.94**	**1.94**	**7.75**
COGS	0.08	0.01	0.01	0.01	0.11	0.01	0.01	0.01	0.01	0.04
Research and development	7.46	7.50	8.00	9.04	32.00	8.24	8.24	8.40	9.67	33.00
General and administrative	3.80	3.70	3.75	3.75	15.00	3.86	3.86	3.94	4.53	17.00
Total Operating Expenses	**11.34**	**11.21**	**11.76**	**12.79**	**47.11**	**12.11**	**12.11**	**12.35**	**14.21**	**50.04**
Loss from operations	(9.41)	(9.27)	(9.82)	(10.86)	(39.35)	(10.17)	(10.17)	(10.42)	(12.27)	(43.03)
Interest and other income	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Change in fair value of convertible preferred stock warrant l	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Net Income	**(9.41)**	**(9.27)**	**(9.82)**	**(10.86)**	**(39.35)**	**(10.17)**	**(10.17)**	**(10.42)**	**(12.27)**	**(43.03)**
EPS	**($0.56)**	**($0.47)**	**($0.49)**	**($0.54)**	**($2.05)**	**($0.51)**	**($0.51)**	**($0.52)**	**($0.61)**	**($2.15)**
Basic shares outstanding	16.94	19.91	19.93	19.94	19.18	19.96	19.97	19.98	20.00	19.98
Diluted shares outsanding	21.42	24.39	24.41	24.42	23.66	24.44	24.45	24.46	24.48	24.46

Source: Company data, Cowen and Company

Immune Design Annual P&L

Income Statement ($MMs)	2014A	2015E	2016E	2017E	2018E	2019E	2020E
Licensing revenues	4.50	0.00	0.00	0.00	0.00	0.00	0.00
Product sales	0.88	0.36	0.36	0.09	25.09	4.27	21.31
Other, net	1.05	7.40	7.40	7.40	7.40	7.40	7.40
Total Revenues	**6.43**	**7.75**	**7.75**	**7.49**	**32.49**	**11.67**	**28.71**
COGS	0.64	0.11	0.04	0.04	0.04	0.50	1.27
Research and development	22.75	32.00	33.00	37.00	40.00	45.00	35.00
General and administrative	12.93	15.00	17.00	19.00	25.00	25.00	25.00
Total Operating Expenses	**36.31**	**47.11**	**50.04**	**56.04**	**65.04**	**70.50**	**61.27**
Loss from operations	(29.88)	(39.35)	(43.03)	(48.55)	(32.55)	(58.83)	(32.56)
Interest and other income	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Change in fair value of convertible preferred stock warrant l	(4.28)	0.00	0.00	0.00	0.00	0.00	0.00
Net Income	**(34.15)**	**(39.35)**	**(43.03)**	**(48.55)**	**(32.55)**	**(58.83)**	**(32.56)**
EPS	**($4.56)**	**($2.05)**	**($2.15)**	**($2.26)**	**($1.41)**	**($2.38)**	**($1.23)**
Basic shares outstanding	7.49	19.18	19.98	21.49	23.01	24.73	26.44
Diluted shares outsanding	11.97	23.66	24.46	25.97	27.49	29.21	30.92

Source: Company data, Cowen and Company

Valuation Methodology And Risks

Valuation Methodology

Biotechnology:

In calculating our 12-month target price, we employ one or more valuation methodologies, which include a discounted earnings analysis, discounted cash flow analysis, net present value analysis and/or a comparable company analysis. These analyses may or may not require the use of objective measures such as price-to-earnings or price-to-sales multiples as well as subjective measures such as discount rates.

We make investment recommendations on early stage (pre-commercial) biotechnology companies based upon an assessment of their technology, the probability of pipeline success, and the potential market opportunity in the event of success. However, because these companies lack traditional financial metrics, we do not believe there are any good methodologies for assigning a specific target price to such stocks.

Investment Risks

Biotechnology:

There are multiple risks that are inherent with an investment in the biotechnology sector. Beyond systemic risk, there is also clinical, regulatory, and commercial risk. Additionally, biotechnology companies require significant amounts of capital in order to develop their clinical programs. The capital-raising environment is always changing and there is risk that necessary capital to complete development may not be readily available.

Risks To The Price Target

There are multiple risks and uncertainties associated with investment in clinical stage biotechnology companies. The key risks are:

Clinical Trial Risk: Immune Design will require FDA approval to market its products in the US and EMEA in Europe. Failure to gain such approvals would significantly impact the value of the company.

Competitive Risk: There are multiple competing agents in development, for indications in which IMDZ's products are being studied. The success of such agents could significantly affect market share of IMDZ's product should they be approved.

Addendum

Stocks Mentioned In Important Disclosures

Ticker	Company Name
CLDX	Celldex Therapeutics
IMDZ	Immune Design
STML	Stemline Therapeutics

Analyst Certification

Each author of this research report hereby certifies that (i) the views expressed in the research report accurately reflect his or her personal views about any and all of the subject securities or issuers, and (ii) no part of his or her compensation was, is, or will be related, directly or indirectly, to the specific recommendations or views expressed in this report.

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Cowen and Company Rating System effective May 25, 2013

Outperform (1): The stock is expected to achieve a total positive return of at least 15% over the next 12 months

Market Perform (2): The stock is expected to have a total return that falls between the parameters of an Outperform and Underperform over the next 12 months

Underperform (3): Stock is expected to achieve a total negative return of at least 10% over the next 12 months

Assumption: The expected total return calculation includes anticipated dividend yield

Cowen and Company Rating System until May 25, 2013

Outperform (1): Stock expected to outperform the S&P 500

Neutral (2): Stock expected to perform in line with the S&P 500

Underperform (3): Stock expected to underperform the S&P 500

Assumptions: Time horizon is 12 months; S&P 500 is flat over forecast period

Cowen Securities, formerly known as Dahlman Rose & Company, Rating System until May 25, 2013

Buy – The fundamentals/valuations of the subject company are improving and the investment return is expected to be 5 to 15 percentage points higher than the general market return

Sell – The fundamentals/valuations of the subject company are deteriorating and the investment return is expected to be 5 to 15 percentage points lower than the general market return

Hold – The fundamentals/valuations of the subject company are neither improving nor deteriorating and the investment return is expected to be in line with the general market return

Cowen And Company Rating Definitions

Distribution of Ratings/Investment Banking Services (IB) as of 03/31/15

Rating	Count	Ratings Distribution	Count	IB Services/Past 12 Months
Buy (a)	450	58.67%	103	22.89%
Hold (b)	302	39.37%	8	2.65%
Sell (c)	15	1.96%	0	0.00%

(a) Corresponds to "Outperform" rated stocks as defined in Cowen and Company, LLC's rating definitions. (b) Corresponds to "Market Perform" as defined in Cowen and Company, LLC's ratings definitions. (c) Corresponds to "Underperform" as defined in Cowen and Company, LLC's ratings definitions.

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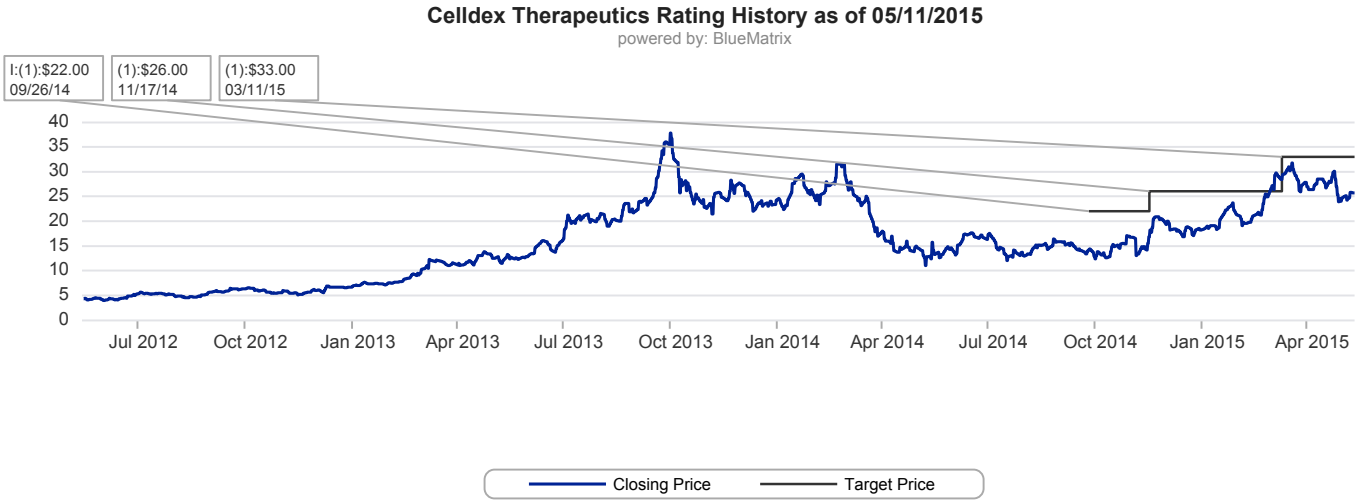

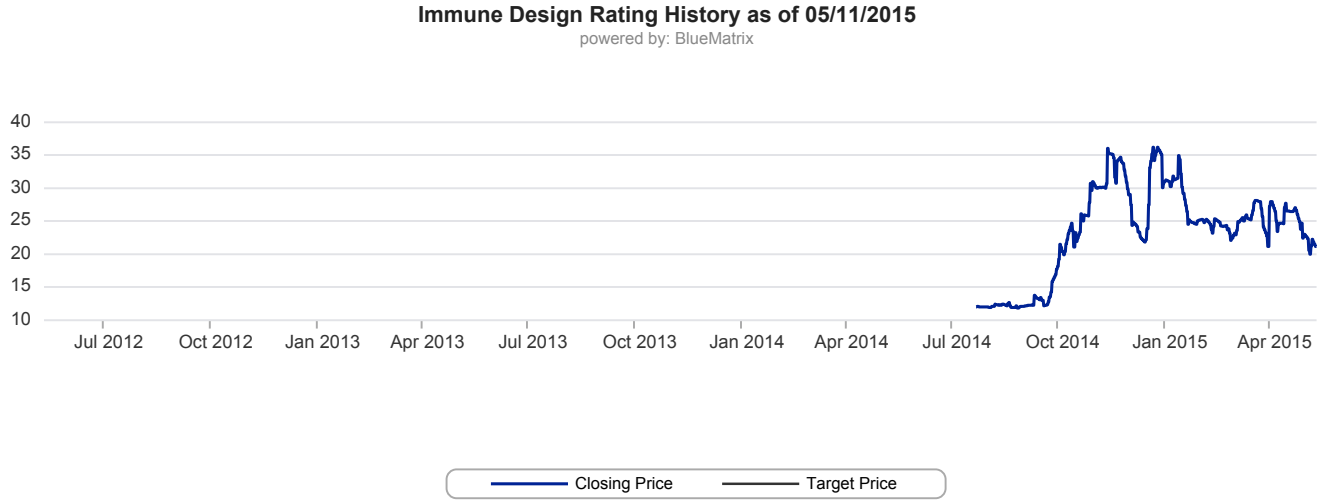

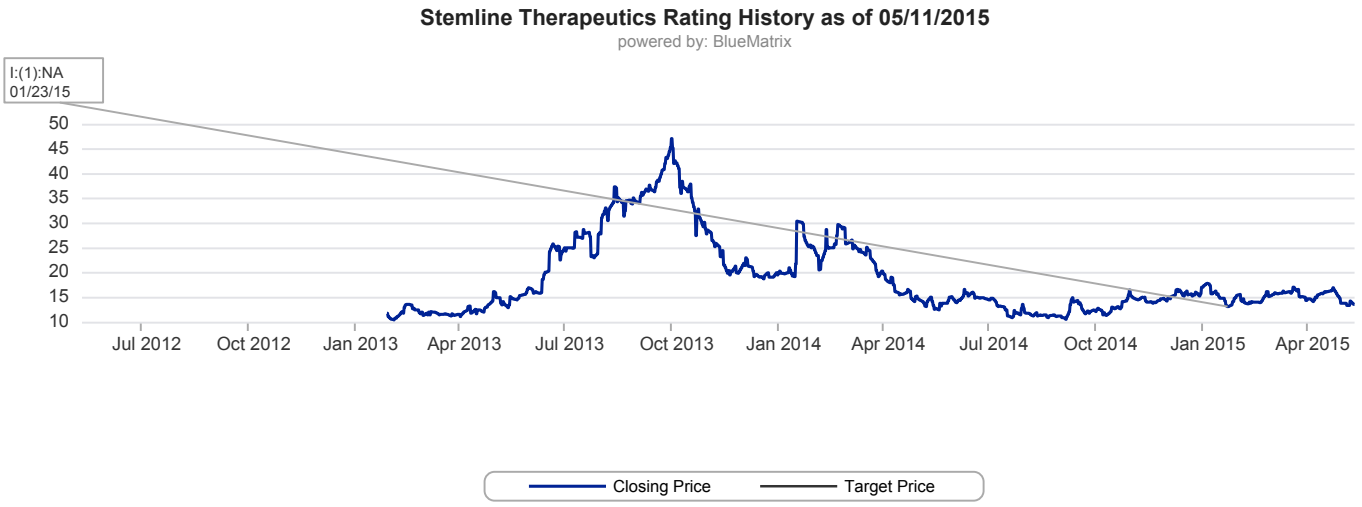

Legend for Price Chart:

I = Initiation | 1 = Outperform | 2 = Market Perform | 3 = Underperform | UR = Price Target Under Review | T = Terminated Coverage | $xx = Price Target | NA = Not Available | S=Suspended

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