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Medicenna Therapeutics Corp. (T.MDNA-TSX)

T.MDNA: Initiating Coverage of Medicenna; Molecular Trojan Horse and Superkines…

Based on our probability adjusted DCF model that takes into account potential future revenues of MDNA55 and MDNA109, MDNA.T is valued at $3.50/share. This model is highly dependent upon continued clinical success of those compounds and will be adjusted accordingly based upon future clinical results.

Current Price (05/14/19)	$0.70
Valuation	**$3.50**

INITIATION

We are initiating coverage of Medicenna, Inc. (MDNA.T) with a $3.50 valuation. Medicenna is developing a diverse group of targeted oncology and immunotherapy products. The company's lead asset, MDNA55, contains an IL-4 receptor binding domain covalently linked to a cytotoxic domain (*Pseudomonas* Exotoxin A) that has completed enrolment in a Phase 2b trial in recurrent glioblastoma (rGBM). We anticipate interim top-line results in June 2019.

Medicenna is also developing a pipeline of 'Superkines' that incorporate the positive attributes of cytokines without the potentially harmful side effects. The lead Superkine is MDNA109, an improved version of IL-2, which should enter clinical testing in 2020.

SUMMARY DATA

52-Week High	**$2.30**
52-Week Low	**$0.64**
One-Year Return (%)	**-57.99**
Beta	**1.78**
Average Daily Volume (sh)	**18,410**
Shares Outstanding (mil)	**29**
Market Capitalization ($mil)	**$20**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**0**
Insider Ownership (%)	**N/A**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2018 Estimate	**N/A**
P/E using 2019 Estimate	**N/A**

Risk Level	**High**
Type of Stock	**Small-Value**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(In millions of $CAD)

	Q1 (Jun)	Q2 (Sep)	Q3 (Dec)	Q4 (Mar)	Year (Mar)
2018	0 A	0 A	0 A	0 A	0 A
2019	0 A	0 A	0 A	0 E	0 E
2020					0 E
2021					0 E

Earnings per Share

	Q1 (Jun)	Q2 (Sep)	Q3 (Dec)	Q4 (Mar)	Year (Mar)
2018	-$0.09 A	- $0.07 A	-$0.09 A	-$0.05 A	-$0.30 A
2019	-$0.04 A	-$0.04 A	-$0.07 A	-$0.08 E	-$0.22 E
2020					-$0.21 E
2021					-$0.20 E

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WHAT'S NEW

Initiating Coverage

We are initiating coverage of Medicenna Therapeutics Corp. (MDNA.T) with a valuation of $3.50. Medicenna is a clinical stage immunotherapy company developing novel versions of the cytokines Interleukin (IL)-2, IL-4, and IL-13, which they term 'Superkines'. The Superkines can be utilized as monotherapies, used in combination with other immune modulating agents (e.g., checkpoint inhibitor antibodies), or fused with toxic agents to generate 'Empowered Cytokines' (EC) that precisely deliver cell-killing moieties to tumors. The company's lead EC is MDNA55, which has completed enrolment in a Phase 2b clinical trial for the treatment of recurrent glioblastoma (rGBM), the most common and deadly form of brain cancer. In addition, the company has a rich pipeline of pre-clinical assets, including its lead Superkine MDNA109, an enhanced version of IL-2.

Targeting a Very Difficult Cancer to Treat

While relatively rare, GBM is the most common form of brain cancer and also the deadliest. Standard of care for an initial diagnosis is surgery, in order to remove as much of the tumor as possible, followed by radiation therapy and chemotherapy with temozolimide. Unfortunately, essentially all patients with GBM suffer recurrence, and there is currently no standard of care for rGBM, although drugs such as Avastin® and lomustine are typically used. The five-year survival rate for GBM is less than 5%, one of the most dismal for any cancer.

Encouraging Early Clinical Data

In Feb. 2019, Medicenna presented encouraging preliminary results from the company's ongoing Phase 2b clinical trial of MDNA55 in patients with rGBM at first or second relapse. Results showed that IL-4 receptor (IL-4R) positive patients had a median overall survival (mOS) of 15.2 months, compared to 8.5 months for patients that were IL-4R negative. In addition, survival rates at 6, 9, and 12 months for IL-4R positive patients were 100%, 67%, and 55%, compared to 73%, 40%, and 30%, respectively, in the IL-4R negative group. These results compare quite favorably to those seen with Avastin® and lomustine (mOS of 8 months for each with 6, 9, and 12-month survival rates of 62%, 38%, 26%, and 65%, 43%, 30%, respectively).

Possibility for Accelerated Approval

MDNA has already been granted Fast Track designation by the FDA and Orphan Drug designation by both the FDA and EMA for the treatment of rGBM and other high-grade gliomas. Based upon the Phase 2b data presented thus far, which shows patients treated with MDNA55 having substantially higher mOS and survival rates compared to other treatments, the company will be conducting an 'end-of-Phase 2' meeting with the FDA in the second half of 2019 to determine if the drug potentially qualifies for accelerated approval, which could allow MDNA55 to reach the market prior to conducting a Phase 3 clinical trial.

Modulating Cytokine Activity an Intense Area of Focus

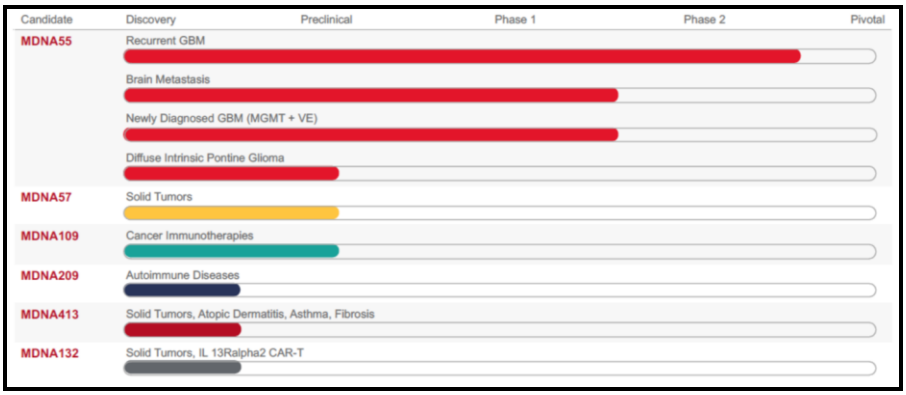
As an example of Big Pharma's interest in modulating cytokine activity, in 2018 Nektar Therapeutics entered into a $3.8 billion collaboration with Bristol-Myers Squibb for its lead development candidate (NKTR-214), which is a long acting version of IL-2 conjugated to polyethylene glycol (PEG) chains and stimulates immune cells through slow release of PEG to generate active IL-2. NKTR-214 is being studied in combination with Opdivo® and/or Yervoy® in more than 20 indications. Medicenna's lead Superkine development product (MDNA109) is an enhanced long acting IL-2 Superkine that has increased affinity for IL-2Rβ for improved selectivity and safety and has shown synergism with both anti-PD-1 and anti-CTLA-4 monoclonal antibodies in pre-clinical studies.

Near-Term Milestones Including Interim Phase 2b Clinical Data in June 2019

The most important near-term milestone for Medicenna will be the release of interim top-line data from the company's Phase 2b rGBM trial, which we anticipate in June 2019. Another important milestone will be the second half, 'end-of-Phase 2' meeting with the FDA to determine the potential for accelerated approval for MDNA55.

INVESTMENT THESIS

Medicenna Therapeutics Corp. (MDNA.T) is a clinical stage biopharmaceutical company developing novel 'Empowered Cytokines' (ECs) and modified versions of the cytokines interleukin (IL)-2, IL-4, and IL-13, known as 'Superkines'. MDNA55 is the company's lead EC asset and consists of an engineered IL-4 with increased affinity to its receptor fused to a fragment of the tumor killing *Pseudomonas* exotoxin as a payload. It recently completed enrollment in a Phase 2b clinical trial in patients with recurrent glioblastoma (rGBM), an aggressive brain cancer with no current standard of care once it recurs. To date MDNA55 has been evaluated in multiple clinical trials in over 130 patients with high grade gliomas and solid tumors including 112 patients with rGBM building a significant database for safety and therapeutic activity. MDNA109 is a modified version of the approved cytokine IL-2 (Proleukin®) that preferentially binds to one of the IL-2 receptors, thus increasing its ability to activate and proliferate effector T cells (which target cancer cells) without promoting the activation of regulatory T-cells (which dampen the immune response). Pre-clinical work shows MDNA109 can enhance the activity of anti-PD-1 and anti-CTLA-4 therapy. Pre-IND work is continuing for a long acting version of MDNA109 and we anticipate it entering the clinic in 2020.



Glioblastoma Multiforme

Glioblastoma multiforme (GBM) is a grade IV brain tumor characterized by a heterogeneous cell population with a number of negative attributes. GBM cells are typically genetically unstable (thus prone to mutation), highly infiltrative, angiogenic, and resistant to chemotherapy (Wen *et al*., 2008). Both activating mutations and loss of tumor suppressor genes give rise to the highly complex and difficult to treat nature of the disease. For example, approximately 50% of GBM tumors have amplification of the epidermal growth factor receptor (EGFR), which can then induce activation of the PI3K signaling pathway (Taylor *et al*., 2012).

GBM is classified into two major subclasses (primary or secondary) depending upon the clinical properties as well as the chromosomal and genetic alterations that are unique to each class. Primary GBM arises *de novo* from normal glial cells and typically occurs in those over the age of 40, while secondary GBM arises from transformation of lower grade tumors and is usually seen in younger patients (Ladha *et al*., 2010). Primary GBM is believed to account for approximately 95% of all GBMs.

While GBM is the most common form of primary brain tumor involving glial cells, it is still relatively rare as approximately 24,000 people in the U.S. were diagnosed with some form of malignant brain cancer in 2018. Gliomas account for approximately 80% of malignant brain cancers, with GBM accounting for approximately 45% of gliomas. The median age of GBM diagnosis is approximately 65 years, with the incidence of GBM in those over 65 increasing rapidly as shown by a doubling in incidence from 5.1 per 100,000 in the 1970's to 10.6 per 100,000 in the 1990's (Chakrabarti *et al*., 2005). Those diagnosed with the disease have a very grim prognosis, with the median survival time of untreated patients being only 4.5 months. Current standard of care treatment only provides 12-14 months of survival time after diagnosis (Johnson *et al*., 2012).

Current Treatments for GBM

Standard of care for GBM tumors always begins with surgical resection of the tumor, unless the tumor is deemed inoperable due to its location near vital centers of the brain. This is performed both to alleviate the symptoms

associated with the disease as well as to facilitate treatment of any residual tumor cells. Even with advances in surgical technique, complete removal of the tumor with clean margins is almost never possible, as the tumors are highly infiltrative and typically extend into the normal brain parenchyma. Due to this, almost all GBM patients have recurrence of the tumor (rGBM), with 90% occurring at the primary site (Wen *et al*., 2008).

Due to the invasive nature of the tumors, surgical resection is followed by radiotherapy coupled with the use of chemotherapeutic agents. Radiotherapy involves the administration of irradiation to the whole brain (Grossman *et al*., 2004). While nitrosoureas were the most common chemotherapeutic agents used for a number of decades, in 1999 temozolomide (TMZ) became available and is now a part of the standard of care. This is due to a clinical trial that showed the addition of TMZ to surgery and radiation increased median survival in newly diagnosed GBM patients to 14.6 months compared to 12.1 months for the surgery and radiation only group (Stupp *et al*., 2005).

Current Treatments for rGBM

In contrast to primary GBM, for which surgery, radiotherapy, and TMZ are standard of care for all patients, there is no consensus regarding the optimal treatment for rGBM. Most chemotherapeutic drugs have a limited ability to cross the blood brain barrier (BBB), thus a strategy to circumvent this was the development of dissolvable chemotherapy wafers (Gliadel®) that could be placed in the tumor bed following surgical resection (Perry *et al*., 2007). Gliadel® contains the nitrosourea chemotherapeutic agent carmustine that is released for several weeks, in contrast to systemically administered carmustine that has a very short half-life. In a Phase 3 clinical trial, 56% of rGBM patients treated with Gliadel® were alive at 6-months compared to only 36% treated with a placebo wafer. In addition, median overall survival for the Gliadel® group was 6.5 months compared to 4.6 in the placebo group.

GBM tumors show increased expression of vascular endothelial growth factor (VEGF) (Bao *et al*., 2006). Bevacizumab (Avastin®) was granted accelerated approved by the FDA for the treatment of rGBM based on a Phase 2 study that found bevacizumab treatment increased six-month progression-free survival from a historical 9-15% to 25% with overall six-month survival of 54% (Raizer *et al*., 2010). However, the confirmatory trials in newly diagnosed GBM patients were not positive (Gilbert *et al*., 2014; Chinot *et al*., 2014), thus bevacizumab was never approved for newly diagnosed GBM patients, however it continues to be approved for rGBM patients.

While the treatment of newly diagnosed GBM is relatively standard for all patients, no such standardization exists for patients with rGBM and there are few treatment options. Since at least 90% of all GBM tumors will recur, there exists a significant unmet medical need for better and more effective treatment options for rGBM patients.

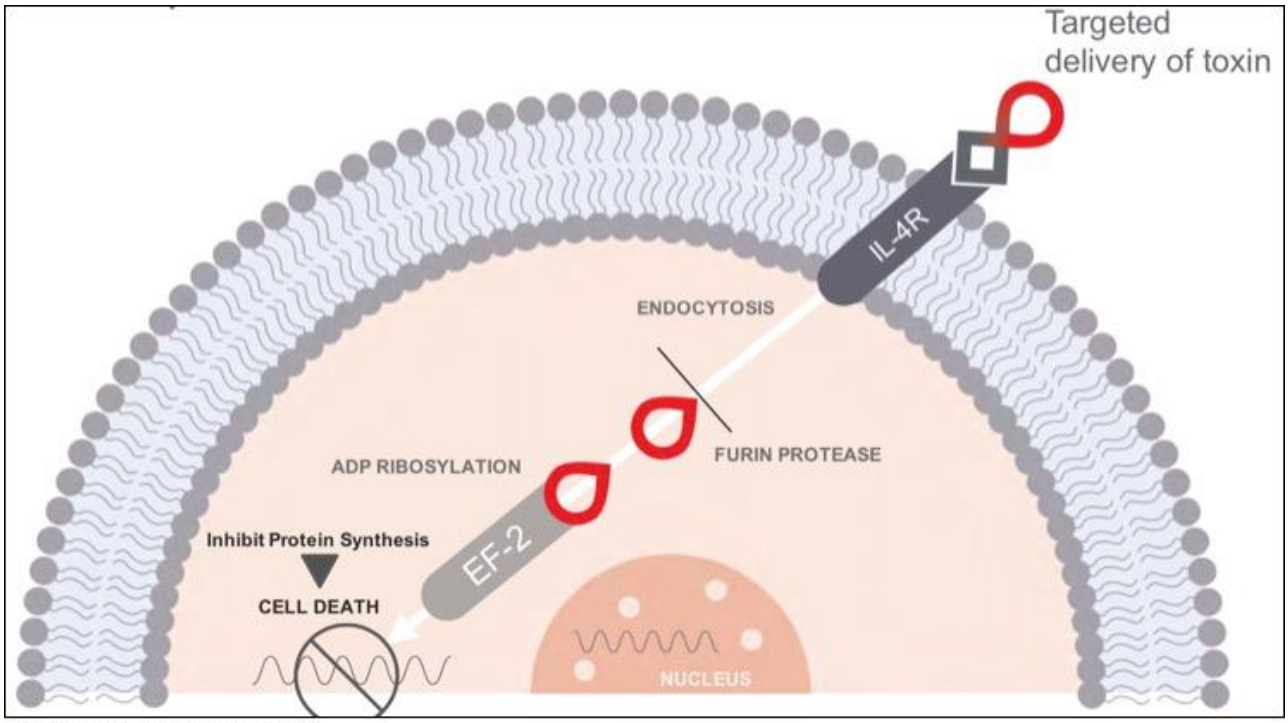
MDNA55

MDNA55 is Medicenna's lead development candidate currently in a Phase 2b clinical trial for the treatment of rGBM. The compound consists of a fusion protein containing a circularly permuted version of IL-4 linked to a fragment of the potent bacterial toxin *Pseudomonas* Exotoxin A (PE). A cartoon representation of the compound is shown in the following figure.



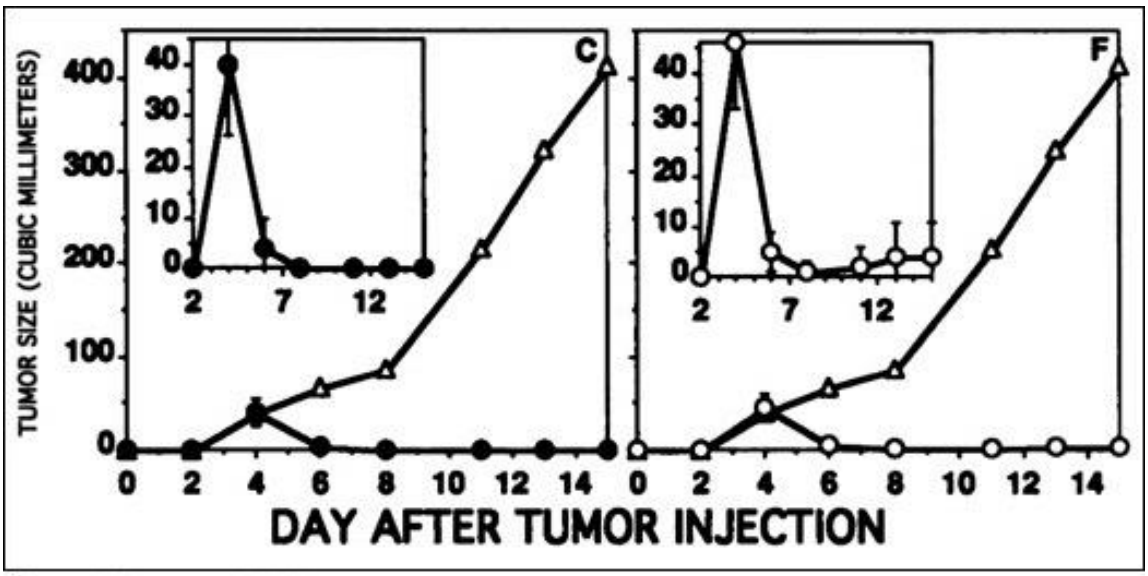
Source: Medicenna Therapeutics Corp.

The mechanism of action for MDNA55 is depicted in the following figure. The entire complex is endocytosed following its binding to the IL-4 receptor (IL-4R). The PE domain is then cleaved from the IL-4 domain through proteolytic cleavage by furin-like proteases. Once liberated in the cytoplasm, PE ADP-ribosylates the eukaryotic elongation factor-2 (eEF-2) on ribosomes (Iglewski *et al*., 1977). This inactivates eEF-2 and effectively shuts down protein biosynthesis in the cell, which leads to apoptosis and cell death. The PE domain in MDNA55 is identical to the PE domain of Lumoxiti™ (Astra Zeneca), which was recently approved by the FDA for the treatment of adult patients with relapsed hairy cell leukemia.



Source: Medicenna Therapeutics Corp.

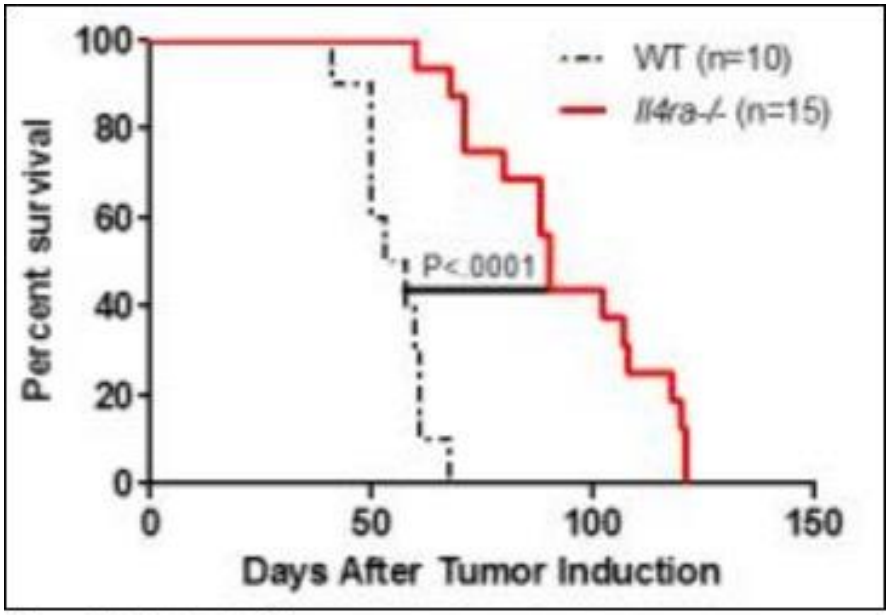
The potential utility of using an IL-4 targeted exotoxin was shown in a preclinical study using mice injected with A431 epidermoid carcinoma cells. The following figure shows that following injection of a regular (panel C, dark circles) or improved (panel F, white circles) circularly permuted IL-4 coupled to PE, there is significant tumor regression, while in mice treated with placebo there is no effect (white triangles). This experiment established the antitumor activity of a circularly permuted IL-4 coupled to PE in tumor cells that express the IL-4R.



Source: Kreitman *et al.*, 1995

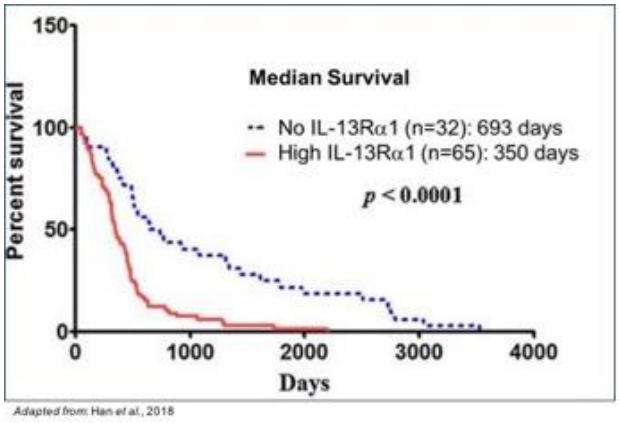
IL-4R Expression in Brain Cancer

Multiple studies have demonstrated that a majority of patient-derived primary glial tumors (including GBM) express the IL-4R, thus making them susceptible to treatment with MDNA55, while there is little to no expression of IL-4R in normal brain tissue (Joshi *et al.*, 2001, Joshi *et al.*, 2002). In addition, expression of IL-4R is correlated with poor survival in both animal models and patients. The following figure shows that in a mouse model of glioma, mice who were deficient in IL-4R ($Il4ra^{-/-}$) showed prolonged survival compared to wildtype mice (Kohanbash *et al.*, 2013).

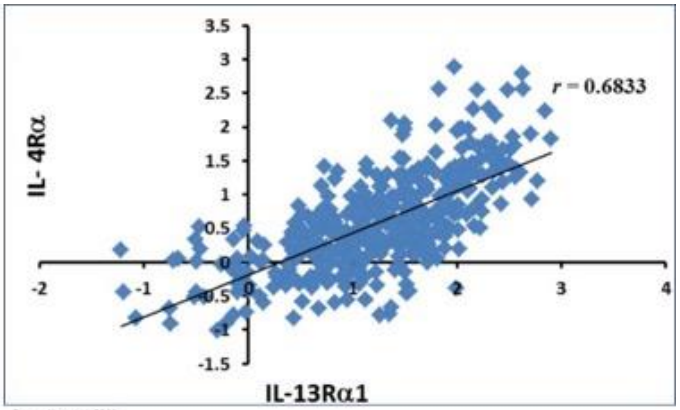


Source: Kohanbash et al., 2013

An analysis of gene expression data and clinical data provided by The Cancer Genome Atlas (TCGA) database revealed that patients with high expression of *IL-13Rα1* mRNA had significantly lower survival rates irrespective of treatment compared to subjects with no *IL-13Rα1* expression and that the expression of *IL-13Rα1* was directly correlated with that of *IL-4Rα* (Han *et al*., 2018), suggesting that IL-13Rα1 and IL-4Rα may form a complex in GBM cells (see this review for an overview of IL-4 and IL-13 receptor biology).

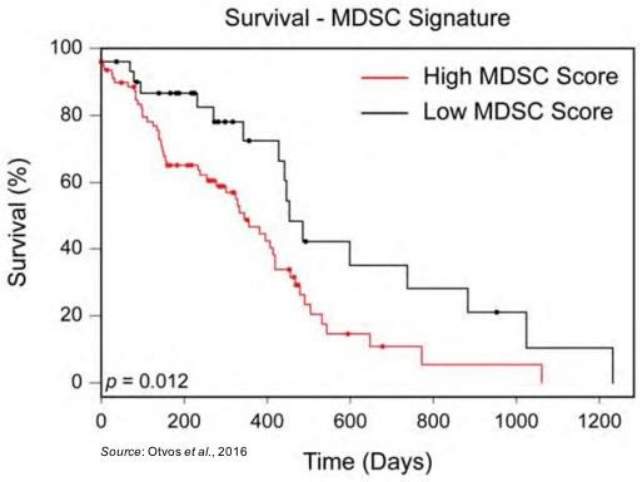


Adapted from Han et al., 2018



Source: Han et al., 2018

In addition to being expressed on the tumor cells, IL-4R is also expressed on myeloid-derived suppressor cells (MDSCs) (Mandruzzato *et al*., 2009; Kamran *et al*., 2017). MDSCs are a heterogeneous population of immature myeloid cells that are prevented from fully differentiating into mature cells (granulocytes, macrophages, dendritic cells) due to the presence of various growth factors and cytokines associated with pathological conditions (e.g., cancer) (Youn *et al*, 2008). MDSCs that are capable of down regulating the immune response are found both in peripheral blood (Raychaudhuri *et al*., 2011) and in the tumor microenvironment (Otvos *et al*., 2016) of GBM patients, where a negative correlation is seen between a high presence of MDSCs and survival, as shown in the following figure. Targeting IL-4R may not only lead to tumor cell death, but could contribute to the depletion of MDSCs, which in turn may eliminate the immunosuppressive environment and allow for long-term disease control brought about by anti-tumor immunity.



Convection-Enhanced Delivery

One of the many difficulties in treating tumors of the central nervous system is getting enough drug into the tumor for a sufficient time to allow for a therapeutic effect. Many drugs do not effectively pass through the blood-brain barrier (such as MDNA55), and for these compounds direct injection into the tumor is commonly used. However, even with direct administration, limited diffusion of drug through the tumor and brain interstitium means only a small volume of tissue surrounding the injection site is effectively treated.

Convection-enhanced delivery (CED) is a method used to deliver drugs into the brain through a pressure gradient in order to saturate the extracellular fluid compartment (Bobo *et al*., 1994). In contrast to diffusion, which depends entirely upon a concentration gradient to distribute the molecules, the use of hydraulic pressure in CED allows for homogenous distribution over large distances by displacing the interstitial fluid. In contrast to first generation CED technology, Medicenna is utilizing novel stepped design catheters to prevent backflow during treatment along with the use of a magnetic resonance imaging (MRI) contrast agent that is administered alongside MDNA55 so that drug distribution can be monitored in real-time to ensure adequate coverage of the tumor bed and margins. The following image shows patient data indicating the size of the tumor as well as the area covered by MDNA55 following CED treatment.



Phase 2b Clinical Trial

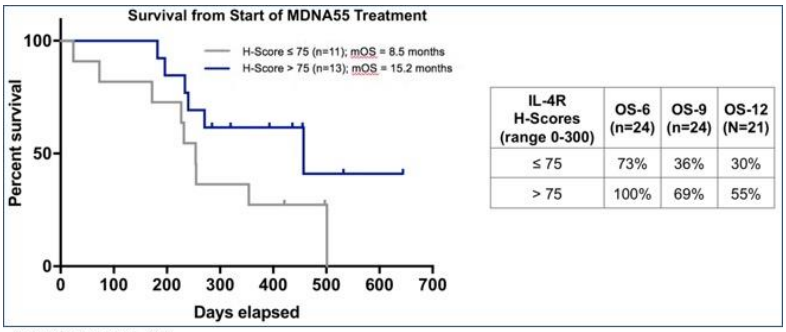
Medicenna has recently completed enrollment in the MDNA55-05 Phase 2b clinical trial in 46 rGBM patients experiencing their first or second relapse (NCT02858895). In this multi-center, open label, single arm study the primary endpoint is median overall survival (mOS) and objective response rate (ORR) is the secondary endpoint following a single intra-tumoral infusion of MDNA55 in adult rGBM subjects. In February 2019, the company reported positive interim data in a podium presentation at the 5th Annual Immuno-Oncology 360 Conference. The preliminary data was based on dosing of 18 – 180 μg of MDNA55 to a total of 27 patients.

The following table gives a comparison between the data seen thus far for MDNA55 and prior clinical trials of approved rGBM therapies. MDNA55 treatment, irrespective of IL4R expression, results in superior median overall survival (mOS = 11.8 months) as well as OS at six, nine, and 12 months when compared to Avastin®, lomustine, and TMZ.

Monotherapy	Population (n)	Survival			
		mOS (mos.)	OS-6	OS-9	OS-12
MDNA55-05 Low Dose Cohorts*	rGBM (n=27)	11.8	89%	59%	46%
Avastin[1]	rGBM (n=50)	8.0	62%	38%	26%
Lomustine[1]	rGBM (n=46)	8.0	65%	43%	30%
Temozolomide[2]	rGBM (n=31)	5.6	NA	NA	NA
Temozolomide[3]	rGBM (n= 792)	NA	65%	NA	36.4%
MDNA55-05 High Dose Cohorts	*Currently enrolling*				

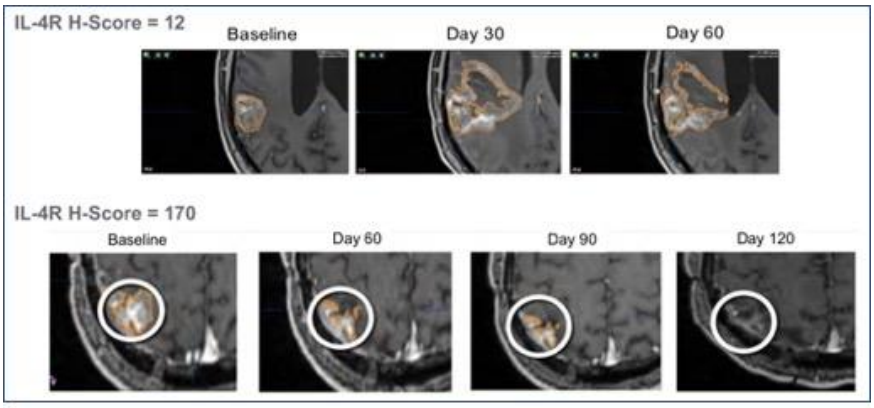
Source: Sampson *et al.*, 2019

Similar encouraging results were seen when the patients were analyzed according to IL-4R expression. The following graph shows that IL-4R+ subjects show better overall survival (15.2 months) following treatment with MDNA55 compared to those patients who have little or no IL-4R expression (8.5 months).



Source: Sampson *et al.*, 2019

This data is supported by serial images taken for an IL-4R- and an IL-4R+ patient. The following figure shows that there is little to no tumor response to MDNA55 treatment in a patient with a low IL-4R H-Score (indicative of very little IL-4R expression) compared to the patient with the high IL-4R H-Score, in which the tumor is almost completely eliminated by Day 120.



Source: Sampson *et al.*, 2019

On April 30, 2019, Medicenna announced that patient enrollment was complete for the Phase 2b trial. We anticipate interim top-line data, which will include response data from 25 patients treated with high dose MDNA55, to be announced in June 2019 and multiple presentations in the second half of the year at relevant scientific conferences. The company will also conduct an 'end-of-Phase 2' meeting with the FDA to determine if MDNA55 is eligible for accelerated approval based on the data that has been presented thus far.

CPRIT Grant

In February 2015, Medicenna was awarded a grant by the Cancer Prevention Research Institute of Texas (CPRIT) in which the company was eligible to receive up to US$14.1 million over a three-year period to support the development of MDNA55. The grant was extended for one year in Oct. 2017 to allow for expenses to be claimed until Feb. 28, 2019 and on Feb. 4, 2019 the company was granted an additional six-month extension allowing expenses to be claimed until Aug. 31, 2019. Of the US$14.1 million approved by CPRIT, Medicenna has received approximately $10 million thus far and can receive the remaining US$4.1 million upon the achievement of certain criteria as determined by CPRIT, which includes the company spending 50% in matching funds on the program.

Additional GBM Therapies Under Development

Given the fact there has been no improvement in the SOC for GBM in nearly two decades and no current SOC for rGBM, there are a number of companies developing a wide range of agents and technologies to treat the condition.

- Northwest Biotherapeutics (DCVax-L): This is an autologous dendritic cell vaccine currently being evaluated in newly diagnosed GBM patients. It is delivered following complete surgical resection and chemoradiation therapy. A Phase 3 clinical trial is currently being conducted.

- Diffusion Pharmaceuticals (Trans sodium crocetinate): This is a small molecule that enhances oxygen delivery to hypoxic tissues. Since GBM is a highly hypoxic tumor, increased oxygenation is thought to enhance standard of care chemoradiation therapy. TSC is currently being investigated in a Phase 3 clinical trial in patients with inoperable GBM.

- Tocagen (Toca 511 & Toca FC): Toca 511 is a retroviral-replicating vector that delivers the gene for cytosine deaminase to tumor cells. Following Toca 511 administration, Toca FC (a novel formulation of flucytosine) is given and the cytosine deaminase in the tumor cells converts Toca FC to the chemotherapeutic agent 5-fluorouracil. A Phase 3 clinical trial has completed enrollment in September 2018 in patients with resectable high grade glioma's, including rGBM and anaplastic astrocytoma.

Market Opportunity in GBM

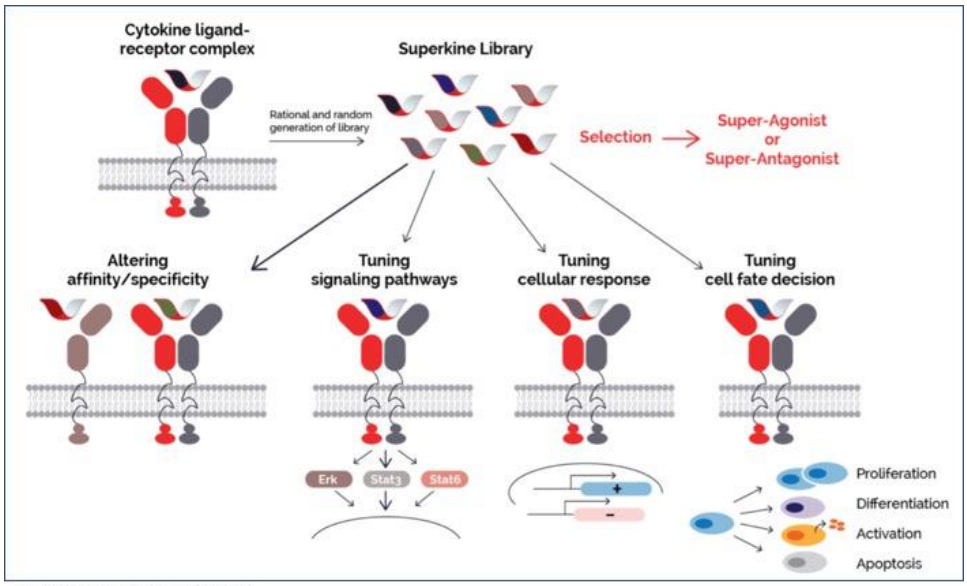
While Medicenna is currently focused on patients with rGBM, we believe that if successful in rGBM the company will likely attempt to expand to newly diagnosed GBM patients and potentially to secondary brain cancer patients, in which the cancer has metastasized to the brain. We estimate there are approximately 30,000 patients diagnosed, with operable GBM each year and that almost all of those patients will relapse. In addition, just based on kidney, colon and breast cancer metastases, there are approximately 90,000 patients diagnosed with secondary brain cancers each year.

The FDA originally approved TMZ in 1999 for the treatment of GBM. Schering-Plough marketed the drug until their 2009 merger with Merck. At the time of the merger, TMZ (sold as Temodar®) was a blockbuster medication, with 2008 revenues of just over $1 billion. Patent exclusivity for Temodar® (marketed as Temodal® outside the US) ended in 2009 in the EU and in 2014 in the US. However, based upon an agreement between Merck and Teva Pharmaceuticals, a generic version of Temodar® was launched in the US in August 2013. Thus, sales have declined from a high of $1.065 billion to in 2010 to $214 million in 2018.

Avastin® is one of the world's top-selling medications, with annual sales of approximately $7 billion. However, given the small patient population associated with GBM, we estimate sales for Avastin® in this indication of only approximately $170 million per year.

MDNA109

MDNA109 is Medicenna's lead development 'Superkine', which are tunable versions of the cytokines IL-2, IL-4, and IL-13. Those cytokines are known to modulate a vast number of different types of human ailments. The Superkines are designed to bind receptors with different specificity and affinity compared to the wild-type cytokine to augment signaling pathways, cellular responses, and cell fate. They are designed through random mutagenesis of the wild-type cytokine and are selected based on the ability to modulate a certain outcome, as depicted in the following figure.



Source: Medicenna Therapeutics Corp.

IL-2 Biology

MDNA109 is an enhanced version of IL-2 designed to increase the ability of T cells to fight cancer. IL-2 (Proleukin®) was one of the first cancer immunotherapies approved by the FDA based on data showing a 16% ORR in patients with metastatic melanoma (Atkins *et al*., 2000). IL-2 activates a wide range of leukocytes, including T cells and natural killer (NK) cells. While effective as an anti-cancer agent, its use has been limited by a range of adverse side effects, including the potentially deadly capillary leak syndrome, as well as its necessity for frequent dosing and ability to stimulate regulatory T cells along with effector T cells (Boyman *et al*., 2012).

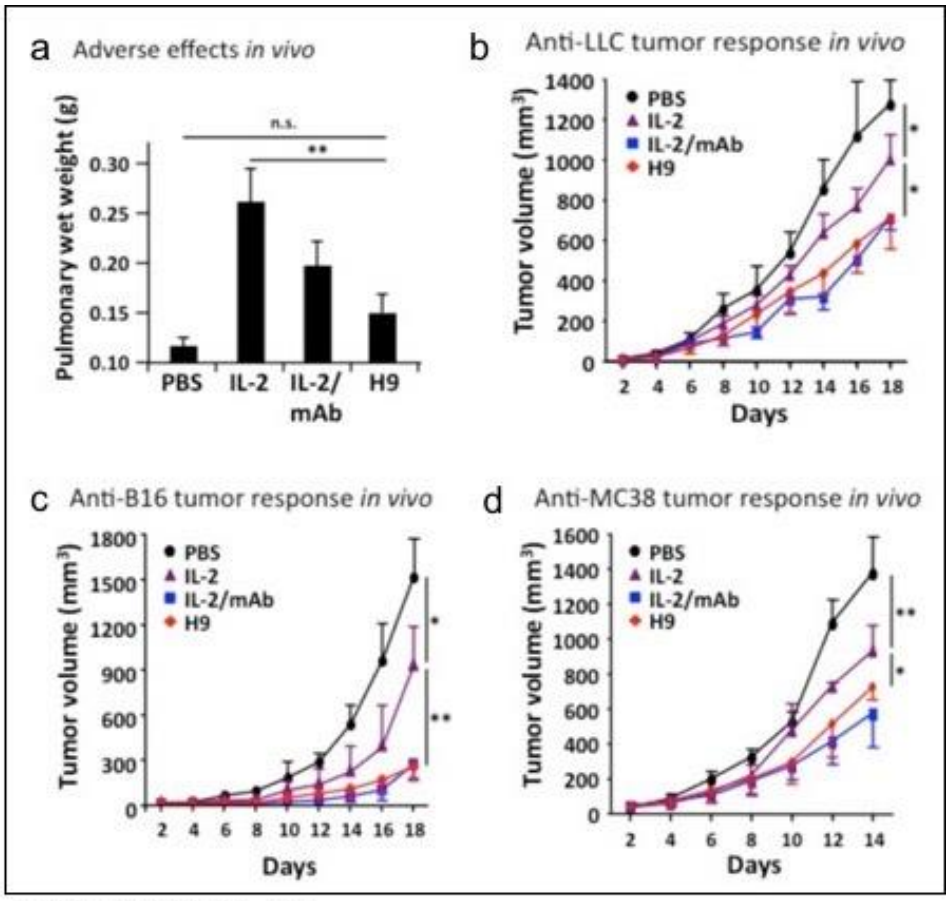
IL-2 is a 16 kDa protein that exerts its effects through binding various IL-2Rs (IL-2Rα, IL-2Rβ, and IL-2Rγ), with the arrangement of these receptors dictating the response seen. Binding of IL-2 to a heterodimer consisting of IL-2Rβ and IL-2Rγ is relatively 'low affinity', whereas a heterotrimer consisting of all three IL-2Rs is a 'high affinity' complex. The heterotrimer is typically found on activated T cells (including regulatory T cells) while naïve T cells only express the heterodimer. Thus, modifying IL-2 signaling to enhance binding to the β–γ complex could enhance T cell activation while diminishing the effect of regulatory T cells.

An enhanced version of IL-2 that exhibited increased affinity to IL-2Rβ was first described in 2012 (Levin *et al*., 2012). The researchers used *in vitro* evolution in which point mutations were randomly created in the IL-2 coding sequence, with each of the mutated versions of IL-2 tested for IL-2Rβ affinity. Following the first round of *in vitro* evolution, a predominant IL-2 variant was identified containing a L85V mutation in the hydrophobic core of the protein, and not a direct IL-2Rβ contact residue. For the second round of *in vitro* evolution, mutations were restricted to six amino acids in the hydrophobic core. The following table shows the consensus sequence that resulted in the identification of MDNA109, which exhibited high affinity binding to IL-2Rβ.

									Affinity for IL-2Rβ		
residue #	**74**	**80**	**81**	**85**	**86**	**89**	**92**	**93**	**K_d(nM)**	**k_{on}(1/ms)**	**k_{off}(1/s)**
WT hIL-2	Q	L	R	L	I	I	I	V	280	$7.9x10^5$	0.22
6-6			I	V					49	$1.2x10^6$	0.061
D10	H	F	D	V	V		F		1.3	$4.1x10^6$	0.0051
H9		F	D	V	V		F		1.4	$4.1x10^6$	0.0056
CONSENSUS		F	D	V	V		F				

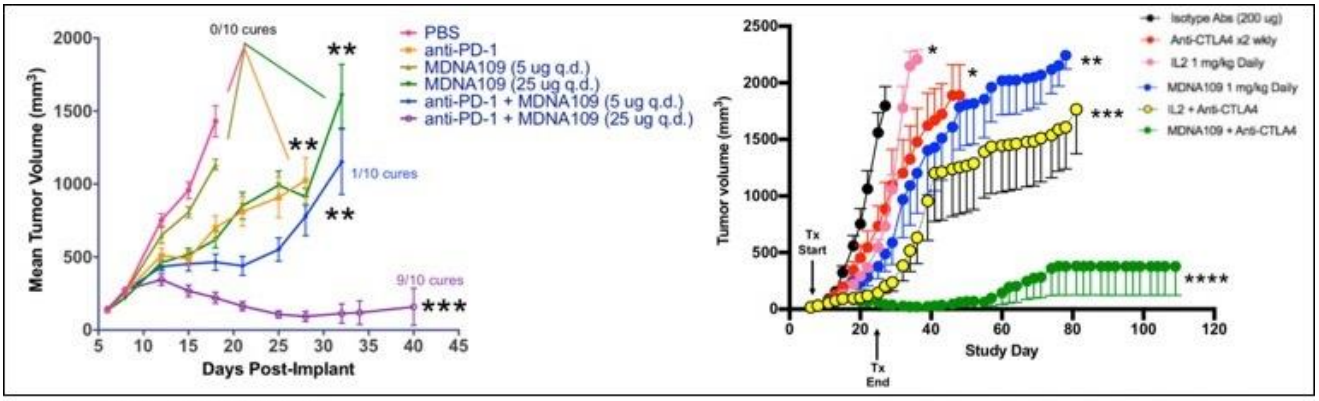
Source: Levin *et al*., 2012

Enhanced IL-2 (denoted as H9 in the above table) was then tested in multiple tumor models *in vivo* to determine its ability to stimulate effector functions of cytotoxic T-cells in comparison to IL-2 and IL-2/anti-IL-2 monoclonal antibody complexes, which exert potent anti-tumor responses with reduced pulmonary edema (Letourneau *et al*., 2010) . The following figure shows that enhanced IL-2 results in substantially less pulmonary edema (panel a) while reducing tumor growth significantly better than wild-type IL-2 and similarly to the IL-2/anti-IL-2 combination (panels b-d).



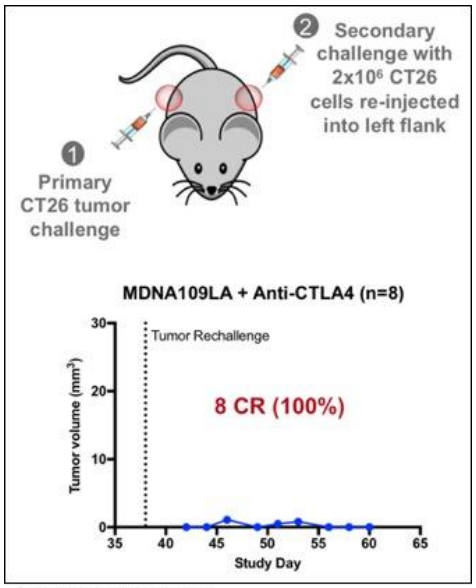
Adapted from: Levin et al., 2012

In addition to showing efficacy as a monotherapy, MDNA109 also shows excellent synergism with the checkpoint inhibitor (CPI) antibodies targeted against PD-1 and CTLA-4. The following figures show enhanced anti-tumor activity upon treatment with a combination of MDNA109 and anti-PD-1 against the M38 murine colon cancer cell line (left panel) as well as the combination of MDNA109 and anti-CTLA-4 against the CT26 colon cancer cell line (right panel).

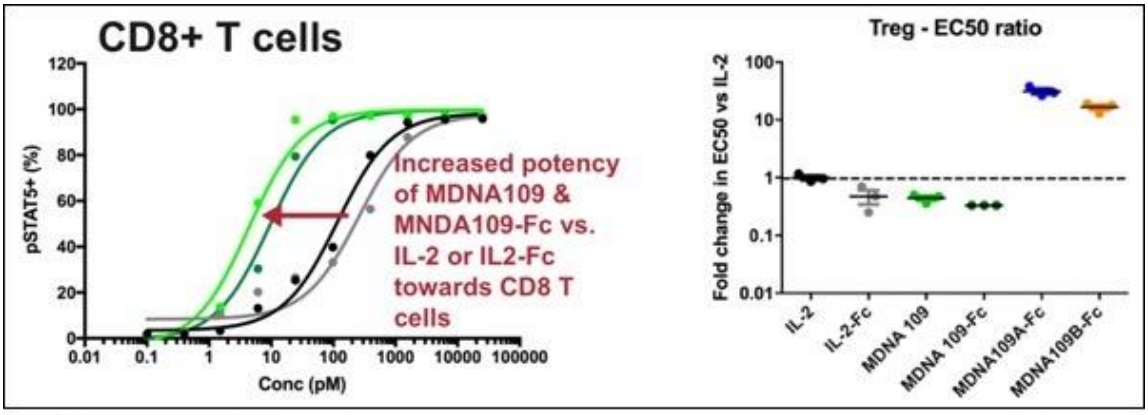


Source: Medicenna Therapeutics Corp.

The enhanced activity of MDNA109 with a CPI is not limited to just the primary tumor, as the following data shows. Following eradication of the primary tumor (which was injected into the right flank of the animal), the same tumor cell line was injected into the left flank of the animals that showed a complete response to treatment with MDNA109 + anti-CTLA-4. There was no tumor growth in any of the eight animals, indicating that immune memory had developed.



One of the drawbacks of IL-2 therapy is the necessity for frequent administration given its short half-life. To overcome this, an Fc-fused version of MDNA109 was engineered (MDNA109-Fc) with a low-effector Fc region to limit immune activation. This compound was shown to activate CD8+ T cells in a manner similar to MDNA109, as shown in the following figure on the left. Variants of MDNA109-Fc (MDNA109A-Fc and MDNA109B-Fc) were also produced that limit regulatory T cell activation in an effort to widen the therapeutic window, as shown in the following figure on the right.



Source: Merchant *et al.*, 2018

While the company is still in the process of selecting the optimal MDNA109 lead candidate, we believe that it will be an enhanced version of IL-2 with improved pharmacodynamic properties and enhanced safety compared to Proleukin® and other IL-2 products currently under development. We anticipate lead selection and pre-IND studies being completed in 2019 such that the drug can enter the clinic in 2020.

Other IL-2 Modulating Products in Development

Cytokine modulation is an area of intense interest for biopharmaceutical companies. An example of this interest is shown by the collaboration agreement signed in 2018 between Nektar Therapeutics (NKTR) and Bristol-Myers Squibb (BMY) for NKTR-214, an IL-2Rβ agonist. The agreement calls for NKTR-214 to be tested in combination with Opdivo® (anti-PD-1) and/or Yervoy® (anti-CTLA-4) in nine different tumor types. Bristol paid Nektar an upfront payment of $1.0 billion in cash and an additional $850 million equity investment.

Synthorx, Inc. (THOR) is a biopharmaceutical company developing cytokine variants, and its lead development product (THOR-707) is an IL-2 with artificial amino acids allowing for site specific pegylation designed to mask IL-2Rα binding. The company had a $120 million IPO in Dec. 2018 and currently has a market cap in excess of $500 million. Clinical testing of THOR-707 is planned to commence in the second half of 2019.

Intellectual Property

MDNA55: Medicenna has multiple patent families that are either licensed or owned by the company and includes issued patents and patent applications with expiry dates ranging from 2023 to 2038.

1. Method for Convection Enhanced Delivery of Therapeutic Agents – U.S Patent No. 7,371,225
2. Targeted Cargo Protein Combination Therapy – U.S. Patent No. 9,629,899
3. Treating Cancer Stem Cells Using Targeted Cargo Proteins – U.S. Patent Application 15/080,038
4. IL-4 Fusion Formulations for Treatment of Central Nervous System Tumors (potential expiry in 2038)

In addition to patent protection, upon approval MDNA55 will also have market exclusivity through Orphan Drug Designation in the U.S. (7 years) and the E.U. (10 years) for the treatment of GBM and biologics data exclusivity in the U.S. (12 years), Europe (10 years), and Canada (8 years).

MDNA109: The Superkine platforms are covered by issued patents and patent applications with expiry dates from 2023 to 2038:

1) Superkines and Synthekines: Repurposed Cytokines with New and Enhanced Signaling Activities (U.S. Patent No. 9.738,696)
2) Superagonists and Antagonists of Interleukin-2 (U.S. Patent No. 9,428,567)
3) Superagonists, Partial Agonists, and Antagonists of Interleukin-2 (U.S. Patent No. 10,150,802)
4) Therapeutic IL-13 Polypeptides (U.S. Patent Nos. 9,512,194 and 9,732,133)
5) Interleukin-4 Receptor-Binding Fusion Proteins and Uses Thereof (Pro-Apoptotic Fusions) (U.S. Patent No. 10,093,708)
6) Interleukin-4 Receptor-Binding Fusion Proteins and Uses Thereof (Anti-Apoptotic Fusions) (U.S. Patent No. 10,106,592)
5. Interleukin-2 Receptor-Binding Fusion Proteins and Uses Thereof (potential expiry in 2034)
6. IL-13 Superkine: Immune Cell Targeting Constructs and Methods of Use Thereof (potential expiry in 2037)
7. IL-2 Superagonists, Agonists and Fusions Thereof (potential expiry in 2038)

Financials and Cap Structure

On Feb. 14, 2019, Medicenna announced financial results for the third quarter of fiscal year 2019 that ended Dec. 31, 2019. The company reported a net loss of $1.7 million, or $0.07 per share, compared to a net loss of $2.2 million, or $0.09 per share, for the three months ended Dec. 31, 2017. R&D expenses for the third quarter of fiscal year 2019 were $1.3 million compared to $1.4 million for the third quarter of fiscal year 2018. The decrease in expenses was primarily due to decreased pre-clinical and clinical trial expenses. G&A expenses for the third quarter of fiscal year 2019 were $0.4 million compared to $0.8 million for the three months ending Dec. 31, 2017. The decrease in G&A expenses was due to lower stock based compensation, reduced legal expenses, and lower salary and benefit expenses.

As of Dec. 31, 2018, Medicenna had cash and cash equivalents of $4.6 million due in part to a public offering in Dec. 2018 in which the company issued 4 million units, with each unit consisting of one common share of stock and one-half warrant to purchase a share of common stock at an exercise price of $1.20 per warrant with an expiration date of Dec. 21, 2023, which resulted in gross proceeds of $4 million. The company's cash total does not include the remainder of the CPRIT grant, of which US$4.1 million is remaining. We anticipate the company currently has sufficient capital to fund operations through to the end of 2019.

As of Dec. 31, 2019, Medicenna had approximately 28.6 million common shares outstanding, and when factoring in the approximately 2.3 million stock options and 5.3 million warrants a fully diluted share count of approximately 36.1 million.

Risks to Consider

Clinical Risk: While early results for MDNA55 in patients with rGBM are encouraging, there is no guarantee that the full data set will continue to show the same efficacy. In addition, it is possible for new safety signals to arise that would preclude the drug's chance of approval. The Superkine development candidates have not been tested in humans, thus there is a risk that the results seen in pre-clinical studies will not be replicated in clinical trials or their use could be associated with serious unforeseen side effects.

Development Risk: Medicenna currently has only one development product (MDNA55) in clinical trials, thus if its development needed to stop the company would be materially harmed. In addition, the biopharmaceutical industry is highly competitive and there are a large number of companies developing treatments for brain cancer, thus even if successful in getting a drug approved, there is no guarantee that it will be accepted by physicians, patients, or payers. In addition, competitors may develop more effective therapies that could render Medicenna's products obsolete.

Financing Risk: Medicenna is not profitable and will require substantial additional capital in order to advance its development products through clinical testing and to approval. We estimate that the company currently has less than 12 months worth of capital and thus will need to raise additional cash in the next year, which could cause significant dilution to current shareholders. The CPRIT grant comes with a number of restrictions and conditions, which if not met could result in the company not receiving any additional tranches of money, which could adversely affect the company's financial condition.

Stock Risk: Medicenna's stock is currently traded on the Toronto stock exchange and the OTC market and has limited liquidity, thus it may be difficult to buy or sell a significant number of shares without affecting the share price. Medicenna is likely a 'passive foreign investment company', which may have adverse U.S. federal income tax consequences for U.S. shareholders. Dr. Fahar Merchant and Ms. Rosemina Merchant collectively own approximately 56% of the company, thus minority shareholders will have no effective voice in the management of the company.

MANAGEMENT PROFILES

Fahar Merchant, PhD – President and Chief Executive Officer

Dr. Merchant is a 25-year biotech veteran, a serial entrepreneur and co-founder of Medicenna. Previously he was President and CEO of Protox Therapeutics (now Sophiris Bio (SPHS), Nasdaq) where he established a late clinical stage urology company. At Protox he raised more than $70M through multiple PIPEs, including a $35M investment by Warburg Pincus. In 1992 he co-founded IntelliGene Expressions, Inc., a biologics CDMO, and built it into one of the fastest growing companies in Canada. In 2000, by strategic in-licensing, he co-founded Avicenna Medica, Inc., a clinical stage oncology company that was sold a year later to KS Biomedix (LSE) for $90M. Dr. Fahar was CTO and Director of KS Biomedix until its acquisition by Xenova (Nasdaq and LSE; now Celtic Pharma). Over his career, Dr. Fahar has closed several transactions valued at more than $300M. He has a PhD in Biochemical Engineering from Western University.

Elizabeth Williams – Chief Financial Officer

Ms. Williams has 15 years of experience in biotech, working with publicly listed entities in both Canada and the United States. She has extensive financing experience, having played an integral role in raising more than $100 million in financing. Prior to joining Medicenna, Ms. Williams was the Vice President of Finance and Administration at Aptose Biosciences Inc. (previously Lorus Therapeutics Inc.), a biotechnology company listed on both the TSX and NASDAQ capital markets. While at Aptose, she held several positions, including Acting Chief Financial Officer during a lengthy transition period, and was responsible for a broad range of activities including financings, financial reporting, and regulatory compliance. She is a CPA and CA and received a BBA from Wilfrid Laurier University.

Rosemina Merchant – Chief Development Officer

Ms. Merchant has 30 years of experience in the development of biopharmaceuticals. Most recently, Ms. Merchant was Senior VP of Development and Regulatory Affairs at Sophiris Bio (formerly, Protox Therapeutics) and responsible for development of PRX302 for prostate cancer and BPH. She transitioned PRX302, a discovery project to a late stage clinical program in less than 6 years. During that time, she executed multiple clinical trials, managed Canadian and US regulatory filings and led all CMC related outsourcing activities in the US and Europe. In 1992, she co-founded IntelliGene Expressions, Inc., a biologics CDMO, where she was VP of Manufacturing and Chief Operating Officer. Ms. Merchant also held a variety of senior level positions at KS Biomedix, Bioniche, GE LifeSciences, Sanof Pasteur, and Alberta Innovates. Her education includes a MESc. in Biochemical Engineering from Western University.

Martin Bexon, MD – Head of Clinical Development

Dr. Bexon has more than 15 years of experience in early and late stage clinical development including medical affairs in various therapeutic areas, particularly in oncology and hematology. He has recently worked as a strategic adviser, study medical expert, and medical monitor in a number of oncology programs (U.S. and E.U.) in both solid tumors and hematological malignancies. While at CSL Behring he led multiple global clinical studies across a range of indications including orphan diseases. As Global Medical Director, Dr. Bexon also led their medical affairs function for immunoglobulin products, generating more than 50% of the company's revenues. At Hoffman-La Roche he designed and implemented multiple global clinical trials enrolling more than 10,000 subjects to support product commercialization. He has also led teams filing numerous regulatory submissions on both sides of the Atlantic and Japan. Prior to joining pharma, he practiced in the clinic as a pediatrician. He obtained his MBBS (MD equivalent) from the University of Newcastle upon Tyne, U.K.

Shafique Fidai, PhD – Head of Discovery and Corporate Development

Dr. Fidai brings nearly 20 years of research and management experience in the biotechnology industry. Most recently, he was VP of Corporate Development at Protox Therapeutics (now Sophiris Bio) where he was part of the executive team and managed the IP portfolio and corporate transactions. Prior to Sophiris, he was at Chromos Molecular Systems and a founding member of the management team at Xenon Pharma. He has experience in strategic planning and corporate development, completing nearly $200M in partnerships, including out-licensing deals with Pfizer, Janssen Biotech, Kissei Pharma, Medimmune, Xencor, Lonza and UniQure. Dr. Fidai has a PhD in Biochemistry from Simon Fraser University.

VALUATION

We are initiating coverage of Medicenna Therapeutics Corp. (MDNA.T) with a valuation of $3.50. Medicenna is a clinical stage immunotherapy company developing novel versions of the cytokines Interleukin (IL)-2, IL-4, and IL-13, which they term 'Superkines'. The Superkines can be utilized as monotherapies, used in combination with other immune modulating agents (e.g., checkpoint inhibitor antibodies), or fused with toxic agents to generate 'Empowered Cytokines' (EC) that precisely deliver cell-killing moieties to tumors. The company's lead EC is MDNA55, which has completed enrolment in a Phase 2b clinical trial for the treatment of recurrent glioblastoma (rGBM), the most common and deadly form of brain cancer. In addition, the company has a rich pipeline of pre-clinical assets, including its lead Superkine MDNA109, an enhanced version of IL-2.

MDNA55

MDNA55 is a fusion protein containing a circularly permuted version of IL-4 linked to a fragment of the potent bacterial toxin *Pseudomonas* Exotoxin A (PE). The entire complex is endocytosed following its binding to the IL-4 receptor (IL-4R). The PE domain is then cleaved from the IL-4 domain through proteolytic cleavage by furin-like proteases. Once liberated in the cytoplasm, PE ADP-ribosylates the eukaryotic elongation factor-2 (eEF-2) on ribosomes. This inactivates eEF-2 and effectively shuts down protein biosynthesis in the cell, which leads to apoptosis and cell death. The PE domain in MDNA55 is identical to the PE domain of Lumoxiti™ (Astra Zeneca), which was recently approved by the FDA for the treatment of adult patients with relapsed hairy cell leukemia.

Multiple data points lend support to the use of MDNA55, including its effectiveness in preclinical cancer models, the fact that a majority of patient-derived primary glial tumors (including GBM) express the IL-4R while there is little to no expression of IL-4R in normal brain tissue, patients with high expression of *IL-13Rα1* mRNA had significantly lower survival rates irrespective of treatment compared to subjects with no *IL-13Rα1* expression and that the expression of *IL-13Rα1* was directly correlated with that of *IL-4Rα*, and IL-4R is expressed on myeloid-derived suppressor cells.

Medicenna has recently completed enrollment in the MDNA55-05 Phase 2b clinical trial in 46 rGBM patients experiencing their first or second relapse. In this multi-center, open label, single arm study the primary endpoint is median overall survival (mOS) and objective response rate (ORR) is the secondary endpoint following a single intra-tumoral infusion of MDNA55 in adult rGBM subjects. We anticipate interim top-line data, which will include response data from 25 patients treated with high dose MDNA55, to be announced in June 2019 and multiple presentations in the second half of the year at relevant scientific conferences. The company will also conduct an 'end-of-Phase 2' meeting with the FDA to determine if MDNA55 is eligible for accelerated approval based on the data that has been presented thus far.

MDNA109

MDNA109 is Medicenna's lead development 'Superkine' and is a tunable version of the cytokine IL-2. The Superkines are designed to bind receptors with different specificity and affinity compared to the wild-type cytokine to augment signaling pathways, cellular responses, and cell fate. MDNA109 is designed to increase the ability of T cells to fight cancer. IL-2 (Proleukin®) was one of the first cancer immunotherapies approved by the FDA based on data showing a 16% ORR in patients with metastatic melanoma. IL-2 activates a wide range of leukocytes, including T cells and natural killer (NK) cells. While effective as an anti-cancer agent, its use has been limited by a range of adverse side effects, including the potentially deadly capillary leak syndrome, as well as its necessity for frequent dosing and ability to stimulate regulatory T cells along with effector T cells.

MDNA109 has increased affinity to IL-2Rβ, one of three IL-2Rs (IL-2Rα, IL-2Rβ, and IL-2Rγ), compared to wild-type IL-2. The modified IL-2 signaling brought about through increased affinity to the IL-2Rβ could enhance T cell activation while diminishing the effect of regulatory T cells and other detrimental side effects. Treatment with MDNA109 results in substantially less pulmonary edema while reducing tumor growth significantly better than wild-type IL-2. In addition to showing efficacy as a monotherapy, MDNA109 also shows excellent synergism with the checkpoint inhibitor (CPI) antibodies targeted against PD-1 and CTLA-4. The company is currently in the process of selecting the optimal MDNA109 lead candidate, and we anticipate lead selection and pre-IND studies being completed in 2019 such that the drug can enter the clinic in 2020.

Valuation

We value Medicenna using a probability adjusted discounted cash flow model that takes into account potential future revenues for MDNA55, MDNA109, and the Superkine platform. We model for Medicenna to partner each of the assets and to receive a 15% royalty on net sales.

For MDNA55, we estimate that following the release of data from the Phase 2b clinical trial in June 2019, the company will need to conduct a Phase 3 clinical trial beginning in 2020, will file an NDA in 2022, and receive approval for rGBM in 2023. We believe the company will eventually go on to receive approval for primary GBM two years later as well as for brain metastases a year after that. Based on approximately 30,000 patients diagnosed with operable GBM each year and approximately 90,000 patients diagnosed with secondary brain cancers each year (from kidney, colon, and breast cancers), we estimate that MDNA55 could have peak sales of over $1 billion. Applying a 60% probability of approval in GBM and a 33% chance of approval in brain metastases along with a 15% discount rate leads to a net present value for MDNA55 of $130 million.

For MDNA109, we believe the drug will be best utilized as an adjunct treatment with CPI antibodies and we initially model for its use in non-small cell lung cancer, since that is a very large market opportunity and CPI therapy is only effective in approximately 25% of patients. We model for a Phase 1 trial to begin in 2020, a Phase 3 trial to initiate in 2024, and approval of the drug in 2027. Based on approximately 225,000 lung cancer cases a year, with 80% of those being NSCLC and 75% resistant to CPIs, we model for a potential market size of approximately 70,000 patients. We estimate that global peak sales would be in excess of $1 billion and applying a 15% discount rate and a 10% probability of approval leads to a net present value of $17 million.

Combining the net present values for each of the company's assets along with a $20 million value for the rest of the Superkine pipeline, the current cash balance, and potential money from exercised warrants leads to a net present value for the company of $180 million. There are approximately 28.6 million common shares outstanding and when factoring in stock options and warrants a fully diluted share count of 36.1 million. We add an additional 15 million shares to account for future financings, which leads to a valuation of $3.50 per share.

PROJECTED FINANCIALS

Medicenna, Inc.
Income Statement

Medicenna Therapeutics Corp. In Canadian Dollars	**FY 2018 A**	**Q1 FY19 A**	**Q2 FY19 A**	**Q3 FY19 A**	**Q4 FY19 E**	**FY 2019 E**	**FY 2020 E**	**FY 2021 E**
MDNA55	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
MDNA109	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
Other Income	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-
Cost of Sales	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-	-
Research & Development	$5.1	$0.6	$0.4	$1.3	$0.3	$2.7	$3.3	$3.8
General & Administrative	$2.3	$0.4	$0.4	$0.4	$1.6	$2.9	$3.0	$3.1
Other (Income) Expense	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($7.4)	($1.0)	($0.9)	($1.7)	($1.9)	($5.6)	($6.3)	($6.9)
Operating Margin	-	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	($0.0)	($0.0)	$0.0	($0.0)	$0.0	($0.0)	$0.0	$0.0
Pre-Tax Income	($7.47)	($1.0)	($0.9)	($1.7)	($1.9)	($5.6)	($6.3)	($6.9)
Income Taxes	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Cumulative translation adjustment	-$0.1	$0.0	$0.0	$0.1	$0.0	$0.1	$0.0	$0.0
Net Income	**($7.5)**	**($1.0)**	**($0.9)**	**($1.7)**	**($1.9)**	**($5.5)**	**($6.3)**	**($6.9)**
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($0.31)**	**($0.04)**	**($0.04)**	**($0.07)**	**($0.08)**	**($0.22)**	**($0.21)**	**($0.20)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	24.6	24.6	24.6	25.0	25.0	24.8	30.0	35.0

Source: Zacks Investment Research, Inc. *David Bautz, PhD*

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