Use these links to rapidly review the document
TABLE OF CONTENTS
TABLE OF CONTENTS

Table of Contents

Filed pursuant to Rule 424(b)(5)
Registration No. 333-238140

The information in this preliminary prospectus supplement is not complete and may be changed. A registration statement relating to these securities has become effective by rule of the Securities and Exchange Commission. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities, and we are not soliciting offers to buy these securities, in any state or other jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED MAY 28, 2020

PRELIMINARY PROSPECTUS SUPPLEMENT
(To Prospectus dated May 15, 2020)

5,000,000 Shares

Common Stock

We are offering 5,000,000 shares of our common stock. Our common stock is listed on The Nasdaq Global Select Market under the symbol "MRSN." On May 27, 2020, the last reported sale price for our common stock on The Nasdaq Global Select Market was $18.19 per share.

We are an "emerging growth company" under applicable Securities and Exchange Commission rules and are subject to reduced public company reporting requirements.

Investing in our common stock involves a high degree of risk. Please read "Risk Factors" on page S-11 of this prospectus supplement and the documents incorporated by reference into this prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved these securities or determined if this prospectus supplement or the accompanying prospectus is accurate or complete. Any representation to the contrary is a criminal offense.

	Per Share	Total
Public offering price	$	$
Underwriting discounts and commissions(1)	$	$
Proceeds, before expenses, to us	$	$

(1) We have agreed to reimburse the underwriters for certain expenses. See "Underwriting."

We have granted the underwriters an option for 30 days from the date of this prospectus supplement to purchase up to 750,000 additional shares of our common stock. See "Underwriting" for more information.

The underwriters expect to deliver the shares to the investors on or about , 2020.

Joint Bookrunning Managers

Cowen **SVB Leerink**

, 2020

TABLE OF CONTENTS

ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is the prospectus supplement, which describes the specific terms of this offering and certain other matters relating to us and our business. The second part, the accompanying prospectus, contains and incorporates by reference important business and financial information about us, a description of our common stock and certain other information about us and this offering. This prospectus supplement and the accompanying prospectus are part of a registration statement that we filed with the Securities and Exchange Commission, or the SEC, using a "shelf" registration process. Under the shelf registration process, we may offer shares of our common stock having an aggregate offering price of up to $250,000,000. Both this prospectus supplement and the accompanying prospectus include or incorporate by reference important information about us, our common stock and other information you should know before investing. You should read both this prospectus supplement and the accompanying prospectus, including all documents incorporated herein and therein by reference, together with the additional information described under "Where You Can Find More Information" below and in the accompanying prospectus before making an investment decision.

You should rely only on the information contained or incorporated by reference in this prospectus supplement, the accompanying prospectus and in any free writing prospectuses we may provide to you in connection with this offering. We have not, and the underwriters have not, authorized any other person to provide you with any information that is different. If anyone provides you with different or inconsistent information, you should not rely on it. We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the accompanying prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement and the accompanying prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus outside the United States. This prospectus supplement and the accompanying prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

This prospectus supplement may add to, update or change the information in the accompanying prospectus or the documents incorporated by reference herein. If information in this prospectus supplement is inconsistent with information in the accompanying prospectus or the documents incorporated by reference herein, this prospectus supplement will apply and will supersede that information in the accompanying prospectus or the documents incorporated by reference herein.

"Mersana Therapeutics," "Mersana," the "Company," "we," "us," "our" and similar names refer to Mersana Therapeutics, Inc. and its consolidated subsidiary, unless we state otherwise or the context otherwise requires.

SUMMARY

This summary highlights selected information contained elsewhere or incorporated by reference in this prospectus supplement and the accompanying prospectus. The summary may not contain all the information that you should consider before investing in our common stock. You should read this entire prospectus supplement and the accompanying prospectus carefully, including "Risk Factors" contained in this prospectus supplement and the documents incorporated by reference herein, before making an investment decision.

Overview

We are a clinical-stage biopharmaceutical company focused on developing antibody drug conjugates, or ADCs, that offer a clinically meaningful benefit for cancer patients with significant unmet need. We have leveraged 20 years of industry learning in the ADC field to develop proprietary and differentiated technology platforms that enable us to design ADCs to have improved efficacy, safety and tolerability relative to existing ADC therapies.

Our innovative platforms, which include Dolaflexin and Dolasynthen, delivering our DolaLock payload, as well as Immunosynthen, delivering a novel stimulator of interferon genes, or STING, agonist, provide a highly efficient product engine that has enabled a robust discovery pipeline for us and our partners. Our ADCs in preclinical and clinical studies are first-in-class molecules that target multiple tumor types with high unmet medical need and have exhibited improved safety and efficacy compared to ADCs developed using first-generation technology.

We have assembled a management team with extensive and relevant experience, including specific ADC experience, from prior work at leading pharmaceutical companies such as Millennium Pharmaceuticals, Inc., Takeda, Biogen, Inc., Merck KGaA, MedImmune, Inc., Bayer AG, Genzyme, Tesaro, Roche and Bristol-Myers Squibb. We are supported by our board of directors and scientific advisory board, who offer complementary experience in drug discovery and development, as well as expertise in building public companies, management and business development. We believe that our highly differentiated platforms, together with the team we have assembled, position us well to generate best-in-class ADCs with the potential to transform the lives of cancer patients.

Strategy

Our goal is to become a leading oncology company by leveraging the potential of our innovative and differentiated ADC technologies and the experience and competencies of our management team to discover and develop promising ADC product candidates and to commercialize cancer therapeutics that address unmet medical needs or provide significant benefit to patients. Key components of our strategy to achieve this goal are as follows:

- **Rapidly advance XMT-1536.** Our lead product candidate, XMT-1536, is a first-in-class Dolaflexin ADC in a Phase 1 proof-of-concept clinical study in patients with tumors likely to express NaPi2b, an antigen broadly expressed in ovarian cancer and non-small cell lung cancer, or NSCLC, adenocarcinoma. We reported data from the dose escalation portion of the Phase I study on March 30, 2020, and data from the expansion portion of the Phase I study on May 27, 2020. We expect a disclosure of more mature data as we advance our proof-of-concept studies and prepare to initiate potential registration-enabling studies.

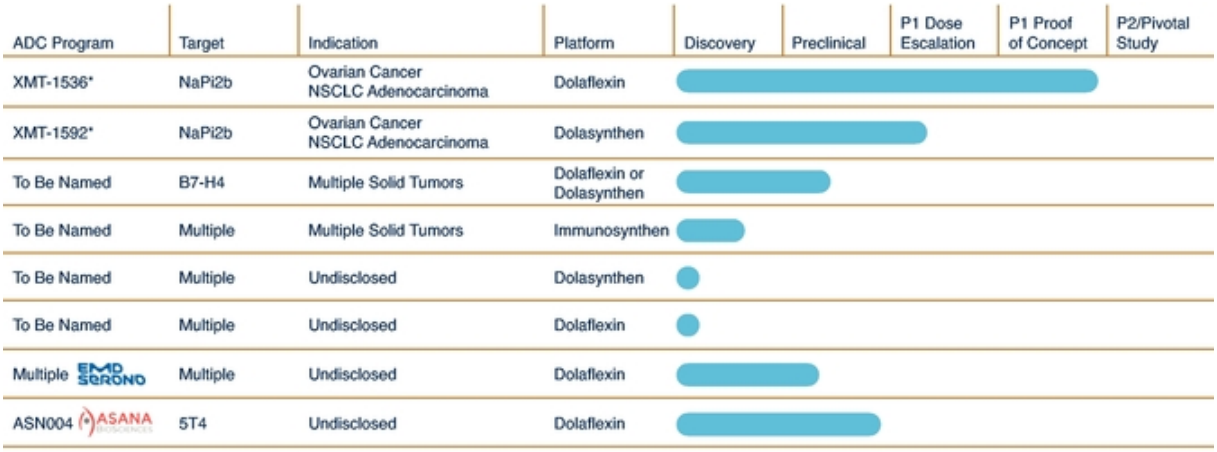
- **Rapidly advance XMT-1592.** Our second product candidate targeting NaPi2b-expressing tumors, XMT-1592, is an ADC created using our Dolasynthen platform. We filed an Investigational New Drug, or IND, application and we initiated our Phase 1 dose escalation study of XMT-1592 in patients with tumors likely to express NaPi2b in May 2020. We believe that we have a path to advance XMT-1592 through rapid dose escalation and clinical validation.

- **Expand our ADC pipeline.** We intend to establish a leading position in the field of ADCs by continuing to advance platform innovations that further broaden the potential of our ADCs to deliver clinically meaningful benefit for cancer patients, by focusing on first-in-class targets and payloads, and by pursuing fast-to-market opportunities. We are advancing a new, potentially first-in-class ADC targeting B7-H4, which leverages our DolaLock payload in IND-enabling studies. We have taken ADCs beyond cytotoxics by developing the Immunosynthen platform, an approach that may allow activation of the innate immune system in a targeted way. We aim to disclose the development data packages for our B7-H4 targeted DolaLock ADC candidate and our Immunosynthen candidate in the second half of 2020.

- **Attract and retain talented and experienced people.** In addition to our team's deep experience with ADC science, drug development and operational management, we believe that our accomplishments are a testament to the talent and commitment of our people. Our team is driven by a shared passion to advance therapies that make a significant difference in the lives of cancer patients. We will continue to cultivate the collaborative and passionate workplace culture that has allowed us to advance this mission.

- **Build strategic partnerships to maximize the value of our programs and platforms.** Our platform technologies, and product discovery and development capabilities, drive the potential for multiple clinically meaningful opportunities for cancer patients. In order to preserve a disciplined drug development and commercialization focus, we may choose to enter into strategic partnerships that facilitate our ability to bring differentiated product candidates to more patients. Our current partnerships with Merck KGaA and Asana Biosciences exemplify different aspects of this strategy.

Figure 1. Product Pipeline



*NaPi2b antibody used XMT-1536 and XMT-1592 is in-licensed from Recepta Biopharma. Recepta has rights to commercialize XMT-1536 and XMT-1592 in Brazil

Our product candidates

We are leveraging our platforms to develop a robust pipeline of clinically meaningful cancer therapies. Our pipeline strategy focuses on targets that have been biologically validated (either as ADCs or through another modality), where the advantages of our platforms may lead to clinically superior therapeutic benefits, where we have the potential to achieve first-in-class status, and where fast-to-market opportunities are available. Our lead product candidate, XMT-1536, a first-in-class Dolaflexin ADC, is in a Phase 1 proof-of-concept study in ovarian cancer and NSCLC adenocarcinoma. Our next product candidate, XMT-1592, a Dolasynthen ADC targeting NaPi2b expressing tumors, is currently in the dose escalation portion of a Phase 1 study in patients with ovarian cancer and NSCLC

adenocarcinoma. We are also advancing a potentially first-in-class DolaLock ADC targeting B7-H4 in IND-enabling studies and are progressing towards nomination of an Immunosynthen development candidate. In addition, our partners have multiple ADC product candidates leveraging our Dolaflexin technology in development.

XMT-1536: our NaPi2b-targeted Dolaflexin ADC

XMT-1536, a first-in-class ADC targeting the sodium-dependent phosphate transport protein NaPi2b, utilizes the Dolaflexin platform to deliver an average of 10-12 DolaLock payload molecules per antibody. The NaPi2b antigen is broadly expressed in NSCLC adenocarcinoma and ovarian cancer with limited expression in normal tissue. We are actively recruiting and dosing patients with ovarian cancer and NSCLC adenocarcinoma, where a majority of patients express NaPi2b in a Phase 1 clinical study. We have also developed a proprietary biomarker assay for patient selection and entered into a collaboration with a partner with expertise in the development of companion diagnostics.

On March 30, 2020, we presented updated data from the dose escalation portion of XMT-1536 Phase I study from an abstract accepted for a late-breaking oral presentation at the Society of Gynecology Oncology (SGO) 2020 Annual Meeting on Women's Cancer, which was cancelled due to the COVID19 pandemic. Updated and new data as of February 3, 2020 included 59 patients enrolled, tumor types included 37 ovarian cancer, 11 NSCLC adenocarcinoma, and 11 other tumor types previously disclosed at lower dose levels. Patients were heavily pre-treated, with a median of five prior lines of treatment (range 1-10). The majority of the ovarian cancer patients had received prior bevacizumab or PARP inhibitors. All NSCLC adenocarcinoma patients had received prior platinum and immunotherapy.

The presented data demonstrated the following:

- Safety profile consistent with previously reported data at lower doses.
  - XMT-1536 was well-tolerated at doses up to 43 mg/m^2 without the severe toxicities commonly seen with other ADCs, such as neutropenia, ocular toxicities, or peripheral neuropathy.
  - The most common treatment-related adverse events, or TRAEs, were Grade 1-2 nausea, fatigue, and headache.
  - The most frequent Grade 3 TRAE was transient AST elevation without associated changes in bilirubin or cases of Hy's law.
  - There were no dose limiting toxicities observed in the 43 mg/m^2 cohort.
  - Evaluation of the 52 mg/m^2 dose cohort is still ongoing, but the first two patients dosed required dose reductions to 43 mg/m^2. 43 mg/m^2 has been declared as the maximum tolerated dose and the dose escalation portion of the study is now closed to new enrollment.
- Additional confirmed responses in heavily pretreated patients and favorable biomarker-response trend observed.
  - First confirmed partial response seen in a NSCLC adenocarcinoma patient with prior treatments including carboplatin, pemetrexed, paclitaxel and nivolumab.
  - For the subset of evaluable patients treated at or above 30 mg/m^2 who had higher NaPi2b expression, 5/15 (33%) achieved PR and 6/15 (40%) achieved SD for a Disease Control Rate, or DCR, of 11/15 (73%).

- In contrast, for the subset of evaluable patients treated at or above 30 mg/m^2 who had lower NaPi2b expression, 0/9 (0%) achieved PR and 5/9 (55%) achieved SD for a DCR of 5/9 (55%).

- Longer treatment duration was observed for patients with tumors having higher NaPi2b expression: 39% remained on treatment for more than 16 weeks on study, compared to 15% remaining on treatment at 16 weeks for patients with tumors having lower NaPi2b expression.

Figure 2. Response Data

		N (%)			
Response—Ovarian Cancer and NSCLC adenocarcinoma N=39*		**All**	**Higher NaPi2b°**	**Lower NaPi2b°°**	**Indeterminate NaPi2b****
20 mg/m^2	N	10	7	2	1
	PR	**1 (10%)**	**0 (0%)**	**0 (0%)**	**1 (100%)**
	SD	6 (60%)	4 (57%)	2 (100%)	0 (0%)
	DCR (PR+SD)	**7 (70%)**	**4 (57%)**	**2 (100%)**	**1 (100%)**
30, 36, 40 mg/m^2	N	22	12	7	3
	PR	**3 (14%)**	**3 (25%)**	**0 (0%)**	**0 (0%)**
	SD	10 (45%)	6 (50%)	3 (43%)	1 (33%)
	DCR (PR+SD)	**13 (59%)**	**9 (75%)**	**3 (43%)**	**1 (33%)**
43 mg/m^2	N	7	3	2	2
	PR	**2 (29%)**	**2 (67%)**	**0 (0%)**	**0 (0%)**
	SD	4 (57%)	0 (0%)	2 (100%)	2 (100%)
	DCR (PR+SD)	**6 (86%)**	**2 (67%)**	**2 (100%)**	**2 (100%)**

* Excludes 3 patients discontinued due to investigator/patient choice and 1 without RECIST scan

** Hypocellular specimen/indeterminate for H-score or not determined yet

° Higher NaPi2b Expression: at / above lowest H-score at which response observed (³110)

°° Lower NaPi2b Expression: below the lowest H-score at which response observed (<110)

The patients treated in the dose escalation study had a median of 5 prior lines. The patients with ovarian cancer had become platinum resistant and had already progressed on standard of care chemotherapies as well as in many cases on experimental therapy. Longitudinal studies have shown that as ovarian cancer patients progress, the potential for a response decreases rapidly with lines of therapy. Triangulating across sources in the literature shows that the expected response rate is close to zero for ovarian cancer patients similar to those enrolled in the dose escalation study with a median of five prior lines (Figure 3).

Figure 3. Standard of Care

Representative Lines of Therapy for OC Patients in the Dose Escalation Portion of the XMT-1536 Phase I Study

Source	2nd Line	3rd Line	4th Line	5th Line	6th Line	Notes
Griffiths 2011 N=274	ORR:16% DCR:37%	ORR:8% DCR:31%	ORR:3% DCR:18%	ORR:2% DCR:18%	ORR:0% DCR:3%	2004 – 2008 UK dataset Platinum Resistant and Refractory. Assume 1 prior lines before PROC
Hoskins 2005 N=120	ORR:20% DCR:45%	ORR:20% DCR:41%	ORR:11% DCR:44%	ORR:8% DCR:23%	ORR:0% DCR:20%	Pre-1999 Canada dataset Not limited to platinum resistant
Bruchim 2013 N=156	ORR:26%	ORR:12%	ORR:3%	ORR:5%	ORR:0%	1995 – 2003 Israel dataset. Platinum status not specified after 2L

In parallel with dose escalation, we initiated proof-of-concept expansion cohorts in still heavily pretreated but more homogeneous patient populations with ovarian cancer and NSCLC adenocarcinoma. Expansion cohorts were initiated in August 2019 at a 36 mg/m^2 once-every-four-week dose regimen, and the dose regimen was amended to 43 mg/m^2 once-every-four-weeks for newly dosed patients in December 2019. The expansion portion of the Phase 1 study is enrolling patients with platinum-resistant ovarian cancer, fallopian tube or primary peritoneal cancer with up to three lines of prior therapy, and in some cases four prior lines of therapy regardless of platinum status, as well as patients with NSCLC adenocarcinoma who had received prior treatment with platinum-based therapy and immunotherapy or targeted agents if their tumors harbor oncogenic driver mutations.

On May 27, 2020, we reported interim data from the expansion portion of the XMT-1536 Phase I study planned for poster presentation at the American Society of Clinical Oncology (ASCO) 2020 Virtual Scientific Program on Friday, May 29, 2020. With a data cutoff of May 1, 2020, these data include 34 patients total, consisting of 27 with ovarian cancer and seven with NSCLC adenocarcinoma. Patients with ovarian cancer had a median of three prior lines of treatment (ranging from 1-5) and patients with NSCLC adenocarcinoma had median two lines of therapy (ranging from 1-3). The majority of ovarian cancer patients had received prior bevacizumab and/or PARP inhibitors. All patients with NSCLC adenocarcinoma had received prior platinum, pemetrexed, and immune checkpoint inhibitors. Fifteen of the patients were dosed at 36 mg/m^2 and 19 patients were dosed at 43 mg/m^2 every four weeks. Patients were not selected for NaPi2b expression; however, archived tissue and fresh tissue biopsies, when feasible, were collected for retrospective assessment of NaPi2b expression.

- Safety profile consistent with previously reported dose escalation data and no new safety signals observed.

  - The most frequently (³20%) reported treatment-related adverse events (TRAEs) were Grade 1-2 fatigue, nausea, vomiting, pyrexia, decreased appetite, diarrhea and fever and transient AST elevation without associated changes in bilirubin or cases of Hy's law. Transient AST elevations are easily monitorable with standard lab tests, peaking on day 8 and self-resolving by the next dose.

  - There were no reported cases of severe neutropenia, peripheral neuropathy or ocular toxicity.

  - Of the 34 patients, 7 (21%) had a dose delay, reduction, and/or discontinuation due to a TRAE, including 4 (12%) discontinuation due to TRAE.

- 18 SAEs have been reported in 10 (29%) patients, of which 2 (6%) were deemed by the investigator to be treatment-related: cerebrovascular accident and pneumonitis (both Grade 2).

- Promising antitumor activity observed in platinum-resistant ovarian cancer.
  - Of the 20 patients that were evaluable for response, 2/20 (10%) achieved confirmed complete responses (CRs) and 5/20 (25%) achieved confirmed partial responses (PRs) for an objective response rate (ORR) of 35%. Additionally, 1/20 (5%) patients achieved an unconfirmed partial response with confirmatory scan pending at the time of the data cutoff and 8/20 (40%) patients achieved stable disease (SD) for a disease control rate (DCR) of 16/20 (80%).
  - The majority of responders had prior treatment with bevacizumab, PARP inhibitors, or both. Both patients with confirmed complete responses had prior treatment with bevacizumab and PARP inhibitors.
  - Some of the responders achieved or deepened their response while on a reduced dose of 30 mg/m^2.

- Patient selection strategy based on NaPi2b biomarker continues to emerge.
  - An emerging biomarker-response relationship continues to be observed. For consistency, these data were bifurcated using the same expression level as used in the dose escalation portion of the study. More data are needed to define the patient selection strategy.
    - Among those patients with higher NaPi2b expression, two (2/14) patients achieved a CR, and two (2/14) achieved a PR.
    - Two (2/2) patients with NaPi2b expression not yet determined at the time of data cutoff achieved confirmed PRs.
    - One (1/4) patient with lower NaPi2b expression (H-score of 90) achieved a confirmed PR.
    - We expect to define the patient selection strategy based on the total data set from patients treated with XMT-1536.

Figure 4. Ovarian Cancer Response Rates, Evaluable Patients

Response—Ovarian Cancer N=20*	All	Higher NaPi2b°	Lower NaPi2b°°	NaPi2b Not Yet Determined
N	20	14	4	2
CR	2 (10%)	2 (14%)	0 (0%)	0 (0%)
PR	5 (25%)	2 (14%)	1 (25%)	2 (100%)
uPR**	1 (5%)	1 (7%)	0 (0%)	0 (0%)
SD	8 (40%)	7 (50%)	1 (25%)	0 (0%)
PD	4 (20%)	2 (14%)	2 (50%)	0 (0%)

* 7 patients not evaluable: 1 withdrew consent (Lower NaPi2b Expression); 1 with unrelated SAE leading to discontinuation and death (Lower NaPi2b Expression); 5 had not yet received a scan as of May 1, 2020

** uPR=1 patient with unconfirmed PR; confirmatory scan pending at the time of data cut

- Higher NaPi2b Expression: defined in dose escalation as at / above lowest H-score at which response observed (³110)
- Lower NaPi2b Expression: defined in dose escalation as below the lowest H-score at which response observed (<110)

- More data are needed to assess antitumor activity of XMT-1536 in NSCLC adenocarcinoma patients.

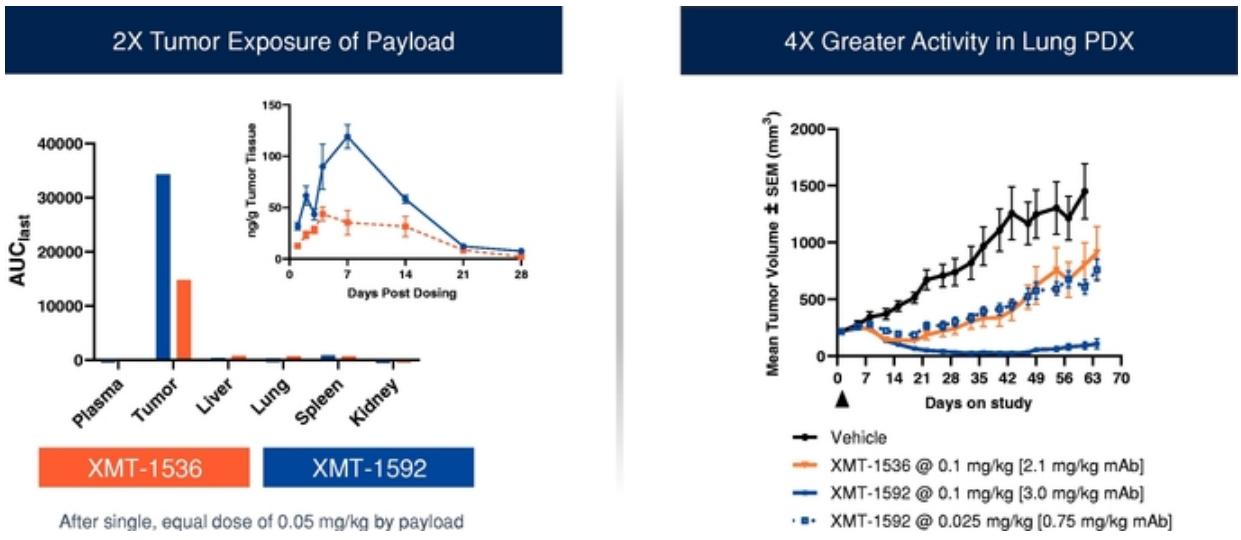
- At the time of data cutoff, four out of seven NSCLC adenocarcinoma patients were evaluable for response with 2/4 (50%) patients achieving SD as best response.

Moving forward, our objective is to enroll approximately 40-45 patients in the ovarian cancer expansion portion of the study over the course of 2020. The ongoing expansion study is designed to generate a robust data set to support a conversation with the U.S. Food and Drug Administration, or FDA, about our plan to initiate a single-arm registration enabling study meant to support an accelerated approval path. Our objective is to be able to provide a more mature look at data in ovarian cancer from the expansion study in the second half of the year. We remain on track to deliver on that goal. Recruitment in lung adenocarcinoma lags behind ovarian cancer but we aim to complete the recruitment of this expansion cohort by year end.

XMT-1592: our NaPi2b targeted Dolasynthen ADC

Our second clinical product candidate, XMT-1592, was created using our Dolasynthen platform and also targets NaPi2b. XMT-1592 comprises the same proprietary NaPi2b antibody and potent auristatin DolaLock payload with controlled bystander effect as XMT-1536, with the additional features of homogeneous, site-specific bioconjugation and precise DAR. Preclinically, XMT-1592 has shown a differentiated profile particularly in NSCLC adenocarcinoma, where it was four times more efficacious than XMT-1536, consistent with higher tumor penetration, as described in below in Figure 5. Based on these preclinical data, we believe that XMT-1592 has the potential to provide us with a second opportunity to treat NSCLC adenocarcinoma patients. We plan to evaluate the clinical differentiation of Dolasynthen by leveraging our experience in NaPi2b to progress XMT-1592 through dose escalation. In May 2020, we initiated a Phase 1 dose escalation trial of XMT-1592 in patients with tumors likely to express NaPi2b.

Figure 5. XMT-1592 Shows Four-Fold Greater Efficacy in Lung Tumor Model



Our B7-H4 targeted ADC candidate

Our early stage programs include a potentially first-in-class B7-H4-targeted DolaLock ADC candidate addressing areas of high unmet medical need. The expression profile of B7-H4 is well suited for our unique DolaLock payload. B7-H4 can be expressed in two places: on tumor cells and on immunosuppressive tumor associated macrophages, or TAMs, which may lead to additional processing of the ADC and more payload in the tumor environment. The DolaLock payload's dual mechanisms of action with a direct cytotoxic effect as well as an immunostimulatory effect through dendritic cell activation and immunogenic cell death are well suited to the biology of the B7-H4 target. We have favorable efficacy and non-human primate tolerability data with both Dolaflexin and Dolasynthen ADCs targeting B7-H4. Our objective is to rapidly progress through IND-enabling studies and scale up manufacturing activities with third parties. B7-H4 provides significant opportunities for development in areas of high unmet need such as breast cancer, NSCLC and ovarian cancer. We anticipate potential fast-to-market clinical development opportunities because expression of B7-H4 and PD-L1 are mutually exclusive, creating an opportunity for high unmet need tumors where patients are ineligible for immune checkpoint inhibitors.

Impact of COVID-19 on Our Business

The ongoing COVID-19 pandemic continues to evolve rapidly. We are monitoring the impact of the pandemic on our operations and ongoing clinical and preclinical development, as well as discovery efforts. Mitigation activities to minimize COVID-19-related operation disruptions are ongoing and include:

- In line with guidance from the U.S. Centers for Disease Control and Prevention and the Commonwealth of Massachusetts, we have implemented work from home measures for all non-laboratory employees and have suspended all business travel. We have also prioritized laboratory activities and implemented staggered schedules in the interest of safety and efficiency for any laboratory-based employees.

- We are currently working with over 20 investigational sites in different geographic areas across the United States that are enrolling patients in the XMT-1536 Phase 1 study. Consistent with FDA guidance, we issued an administrative letter to allow for remote patient monitoring and remote testing, when possible. Most of the study sites continue to enroll patients in the study. At this time and subject to further COVID-19-related implications to patient enrollment, we expect to be able to present more mature data from the expansion portion of the study in the second half of 2020.

- We believe we have sufficient inventory of XMT-1536 and XMT-1592 to support our ongoing and planned clinical studies, as well as sufficient inventory of advanced intermediates stockpiled in the United States to support more than two years of manufacturing of drug substance and product. At this time, and subject to further COVID-19-related implications, we do not anticipate any disruptions to its clinical supply.

The ultimate impact of the COVID-19 pandemic on our business operations is highly uncertain and subject to change and will depend on future developments, which cannot be accurately predicted. While the pandemic did not materially affect our financial results and business operations in the first quarter ended March 31, 2020, we are unable to predict the impact that COVID-19 will have on our financial position and operating results in future periods due to numerous uncertainties. Management is actively monitoring this situation and the possible effects on our financial condition, operations, suppliers, industry, and our employees.

Implications of Being an Emerging Growth Company

We are an "emerging growth company," as defined in the Jumpstart Our Business Act of 2012. We will remain an emerging growth company until the earlier of (1) the last day of the fiscal year following the fifth anniversary of our initial public offering, (2) the last day of the fiscal year in which we have total annual gross revenue of at least $1.07 billion, (3) the last day of the fiscal year in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds $700 million as of the prior June 30th, and (4) the date on which we have issued more than $1.07 billion in non-convertible debt during the prior three-year period. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure and other requirements that are applicable to other public companies that are not emerging growth companies. Accordingly, the information contained or incorporated by reference herein may be different than the information you receive from other public companies in which you hold stock.

Corporate Information

We were incorporated in the state of Delaware in February 2002 as Nanopharma Corp., and we changed our name to Mersana Therapeutics, Inc. in November 2005. Our principal executive offices are located at 840 Memorial Drive, Cambridge, Massachusetts 02139, and our telephone number is (617) 498-0020. Our Internet website is www.mersana.com. The information found on our website, or that may be accessed by links on our website, is not part of this prospectus supplement or the accompanying prospectus.

THE OFFERING

Common stock offered by us	5,000,000 shares.
Option to purchase additional shares	We have granted the underwriters an option for a period of 30 days from the date of this prospectus supplement to purchase up to 750,000 additional shares of our common stock.
Common stock to be outstanding after this offering	63,949,470 shares (or 64,699,470 shares, if the underwriters exercise in full their option to purchase additional shares).
Use of proceeds	We intend to use the net proceeds from this offering to support clinical development of XMT-1536 and XMT-1592, to progress our next ADC product candidates into Phase 1 clinical development, to progress our early platform development and the balance to fund working capital, capital expenditures and other general corporate purposes. See "Use of Proceeds" on page S-14.
Risk factors	See "Risk Factors" beginning on page S-11 of this prospectus supplement for a discussion of factors that you should read and consider before investing in our securities.
Nasdaq Global Select Market ticker symbol	"MRSN"

The number of shares of our common stock that will be outstanding immediately after this offering as shown above is based on 58,949,470 shares outstanding as of April 30, 2020, and excludes, each as of April 30, 2020:

- 39,474 shares of common stock issuable upon the exercise of warrants at a weighted-average exercise price of $0.05 per share;
- 6,031,467 shares of common stock issuable upon the exercise of outstanding stock options at a weighted-average exercise price of $5.43 per share;
- 755,263 shares of common stock issuable upon the vesting of outstanding restricted stock units;
- 1,622,608 shares of common stock reserved for future issuance under our 2017 Stock Incentive Plan; and
- 725,085 shares of common stock reserved for future issuance under our 2017 Employee Stock Purchase Plan.

RISK FACTORS

Investing in our securities involves a high degree of risk. See "Part I, Item 1A—Risk Factors" in our most recent Annual Report on Form 10-K for the fiscal year ended December 31, 2019, as filed with the SEC on February 28, 2020, and "Part II, Item 1A—Risk Factors" in our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2020, as filed with the SEC on May 8, 2020, and any other subsequent Quarterly Report on Form 10-Q, each incorporated by reference in this prospectus supplement and the accompanying prospectus and the "Risk Factors" section in this prospectus supplement for a discussion of the factors you should carefully consider before deciding to purchase our securities. Before you invest in our securities, you should carefully consider these risks as well as other information we include or incorporate by reference into this prospectus supplement and the accompanying prospectus. The risks and uncertainties we have described are not the only ones facing our company. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our business operations. The occurrence of any of these risks might cause you to lose all or part of your investment in the offered securities. The discussion of risks includes or refers to forward-looking statements; you should read the explanation of the qualifications and limitations on such forward-looking statements discussed elsewhere in this prospectus supplement and the accompanying prospectus.

Risks related to this offering

We may allocate the net proceeds from this offering in ways that you or other stockholders may not approve.

We currently intend to use the net proceeds of this offering, if any, to support clinical development of XMT-1536 and XMT-1592, to progress our next ADC product candidates into Phase 1 clinical development, to progress our early platform development and the balance to fund working capital, capital expenditures and other general corporate purposes. This expected use of the net proceeds from this offering represents our intentions based upon our current plans and business conditions. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development efforts, the status of and results from clinical trials, as well as any third party intellectual property or other assets that we may opportunistically identify and seek to license or acquire or any collaborations that we may enter into with third parties for our product candidates, and any unforeseen cash needs. Because the number and variability of factors that will determine our use of the proceeds from this offering, their ultimate use may vary substantially from their currently intended use. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering and could spend the proceeds in ways that do not necessarily improve our operating results or enhance the value of our common stock. See "Use of Proceeds."

You will experience immediate and substantial dilution in the book value per share of the common stock you purchase.

Because the price per share at which shares of our common stock are sold in this offering is substantially higher than the book value per share of our common stock, you will suffer immediate and substantial dilution in the net tangible book value of the common stock you purchase in this offering. After giving effect to the sale of 5,000,000 shares of our common stock in this offering at an assumed public offering price of $18.19 per share, the closing price of our common stock on the Nasdaq Global Select Market on May 27, 2020, and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us, our net tangible book value as of March 31, 2020 would have been $148.3 million, or $2.80 per share of common stock. This represents an immediate increase in the net tangible book value of $1.49 per share to our existing stockholders and an immediate and substantial dilution in net tangible book value of $15.39 per share to new investors who purchase our common stock in the offering. See "Dilution" for a more detailed discussion of the dilution you may incur in connection with this offering.

FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the other documents we have filed with the SEC that are incorporated herein by reference, contain forward-looking statements. Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our clinical results and other future conditions. The words "aim," "anticipate," "believe," "contemplate," "continue," "could," "estimate," "expect," "goal," "intend," "may," "on track," "plan," "possible," "potential," "predict," "project," "seek," "should," "target," "will," "would," or the negative of these terms or other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

These forward-looking statements include, among other things, statements about:

- the initiation, cost, timing, progress and results of our current and future research and development activities, preclinical studies and clinical trials;
- the timing of, and our ability to obtain and maintain, regulatory approvals for our product candidates;
- the unmeet need of ovarian cancer and non-small cell lung cancer;
- our ability to quickly and efficiently identify and develop additional product candidates;
- our ability to advance any product candidate into, and successfully complete, clinical studies;
- our intellectual property position, including with respect to our trade secrets;
- the potential benefits of strategic partnership agreements and our ability to enter into selective strategic partnership arrangements;
- our estimates regarding expenses, future revenues, capital requirements, the sufficiency of our current and expected cash resources and our need for additional financing; and
- the potential impact of the ongoing COVID-19 pandemic.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included herein and in our Annual Report on Form 10-K for the fiscal year ended December 31, 2019, as filed with the SEC on February 28, 2020, in our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2020, as filed with the SEC on May 8, 2020, and any subsequent Quarterly Reports on Form 10-Q, each incorporated by reference in this prospectus supplement and the accompanying prospectus, particularly in the "Risk Factors" sections, that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

In addition, while we expect that the COVID-19 pandemic might adversely affect our preclinical and clinical development efforts, business operations and financial results, the extent of the impact and the value of and market for our common stock will depend on future developments that are highly uncertain and cannot be predicted with confidence at this time, such as the ultimate duration of the pandemic, travel restrictions, quarantines, physical distancing and business closure requirements in the U.S. and in other countries, and the effectiveness of actions taken globally to contain and treat the disease.

We cannot guarantee future results, level of activity, performance or achievements. You should not rely upon forward-looking statements as predictions of future events. Unless required by law, we will not undertake and we specifically disclaim any obligation to release publicly the result of any revisions which may be made to any forward-looking statements to reflect events or circumstances after the date of such statements or to reflect the occurrence of events, whether or not anticipated. In that respect, we wish to caution readers not to place undue reliance on any such forward-looking statements, which speak only as of the date they are made.

USE OF PROCEEDS

We estimate that the net proceeds we will receive from this offering will be approximately $ million, after deducting underwriting discounts and commissions and estimated offering expenses payable by us. If the underwriters exercise their option to purchase additional shares in full, we estimate that the net proceeds from this offering will be approximately $ million.

We intend to use the net proceeds from this offering:

- to support clinical development of XMT-1536 and XMT-1592;
- to progress our next ADC product candidates into Phase 1 clinical development;
- to progress our early platform development; and
- the balance to fund working capital, capital expenditures and other general corporate purposes.

This expected use of the net proceeds from this offering represents our intentions based upon our current plans and business conditions. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development efforts, the status of and results from clinical trials, as well as any third party intellectual property or other assets that we may opportunistically identify and seek to license or acquire or any collaborations that we may enter into with third parties for our product candidates, and any unforeseen cash needs. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering.

Pending our use of the net proceeds from this offering described above, we intend to invest the net proceeds in a variety of capital preservation investments, including short-term, investment grade, interest bearing instruments and U.S. government securities.

DIVIDEND POLICY

We have not declared or paid any cash dividends on our common stock. We do not intend to pay any dividends on our common stock for the foreseeable future.

DILUTION

Our net tangible book value as of March 31, 2020, was approximately $63.1 million, or $1.31 per share of common stock. Net tangible book value per share is calculated by subtracting our total liabilities from our total tangible assets, which is total assets less intangible assets, and dividing this amount by the number of shares of common stock outstanding.

After giving effect to the sale by us of 5,000,000 shares of common stock in this offering at an assumed public offering price of $18.19 per share, the closing price of our common stock on the Nasdaq Global Select Market on May 27, 2020, and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us, our as-adjusted net tangible book value as of March 31, 2020, would have been approximately $148.3 million, or $2.80 per share of common stock. This represents an immediate increase in the net tangible book value of $1.49 per share to our existing stockholders and an immediate and substantial dilution in net tangible book value of $15.39 per share to new investors. The following table illustrates this hypothetical per share dilution:

Assumed public offering price per share		$ 18.19
Net tangible book value per share as of March 31, 2020	$ 1.31	
Increase per share attributable to new investors	1.49	
As-adjusted net tangible book value per share after this offering		2.80
Net dilution per share to new investors		$ 15.39

The foregoing table is based on 48,006,049 shares of our common stock outstanding and excludes the following, each as of March 31, 2020:

- 39,474 shares of common stock issuable upon the exercise of warrants at a weighted-average exercise price of $0.05 per share;
- 6,049,288 shares of common stock issuable upon the exercise of outstanding stock options at a weighted-average exercise price of $5.44 per share;
- 760,193 shares of common stock issuable upon the vesting of outstanding restricted stock units;
- 1,642,679 shares of common stock reserved for future issuance under our 2017 Stock Incentive Plan; and
- 725,085 shares of common stock reserved for future issuance under our 2017 Employee Stock Purchase Plan.

UNDERWRITING

Cowen and Company, LLC and SVB Leerink LLC are acting as representatives of each of the underwriters named below and as joint bookrunning managers for this offering. Subject to the terms and conditions set forth in the underwriting agreement among us and the underwriters, we have agreed to sell to the underwriters, and each of the underwriters has agreed, severally and not jointly, to purchase from us, the number of shares of common stock set forth opposite its name below.

Underwriter	Number of Shares
Cowen and Company, LLC	
SVB Leerink LLC	
Total	5,000,000

Subject to the terms and conditions set forth in the underwriting agreement, the underwriters have agreed, severally and not jointly, to purchase all of the shares sold under the underwriting agreement if any of the shares are purchased. If an underwriter defaults, the underwriting agreement provides that the purchase commitments of the non-defaulting underwriters may be increased or the underwriting agreement may be terminated.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act, or to contribute to payments the underwriters may be required to make in respect of those liabilities.

The underwriters are offering the shares, subject to prior sale, when, as and if issued to and accepted by them, subject to approval of legal matters by their counsel, including the validity of the shares, and subject to other conditions contained in the underwriting agreement, such as the receipt by the underwriters of officers' certificates and legal opinions. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part.

Commissions and Discounts

The representatives have advised us that the underwriters propose initially to offer the shares to the public at the initial public offering price set forth on the cover page of this prospectus supplement and to dealers at that price less a concession not in excess of $ per share. After the initial offering of the shares, the public offering price, concession or any other term of this offering may be changed by the representatives.

The following table shows the initial public offering price, underwriting discounts and commissions and proceeds, before expenses, to us. The information assumes either no exercise or full exercise by the underwriters of their option to purchase additional shares of our common stock.

	Per Share	Total	
		Without Option	With Option
Initial public offering price	$	$	$
Underwriting discounts and commissions	$	$	$
Proceeds, before expenses, to us	$	$	$

We estimate expenses payable by us in connection with this offering, other than the underwriting discounts and commissions referred to above, will be approximately $300,000. We also have agreed to reimburse the underwriters for up to $10,000 for their FINRA counsel fee. In accordance with FINRA Rule 5110, this reimbursed fee is deemed underwriting compensation for this offering.

Option to Purchase Additional Shares

We have granted an option to the underwriters, exercisable for 30 days after the date of this prospectus supplement, to purchase up to 750,000 additional shares at the initial public offering price, less underwriting discounts and commissions. If the underwriters exercise this option, each underwriter will be obligated, subject to the conditions contained in the underwriting agreement, to purchase a number of additional shares proportionate to that underwriter's initial amount reflected in the above table.

No Sales of Similar Securities

We have agreed, for a period of 75 days after the date of this prospectus supplement, that we will not (i) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, or otherwise transfer or dispose of, directly or indirectly, or file with the SEC a registration statement under the Securities Act relating to, any shares of our common stock or any securities convertible into or exercisable or exchangeable for common stock, or publicly disclose the intention to make any offer, sale, pledge, disposition or filing, or (ii) enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of our common stock or any such other securities, without the prior written consent of Cowen and Company, LLC and SVB Leerink LLC on behalf of the underwriters, subject to certain limited exceptions.

Our executive officers and directors have agreed not to sell or transfer any common stock or securities convertible into or exchangeable or exercisable for common stock, for 75 days after the date of this prospectus supplement without first obtaining the written consent of Cowen and Company, LLC and SVB Leerink LLC on behalf of the underwriters. Specifically, we and these other persons have agreed, with certain limited exceptions, not to directly or indirectly:

- offer, pledge, sell or contract to sell any shares of common stock;
- sell any option or contract to purchase any shares of common stock;
- purchase any option or contract to sell any shares of common stock;
- grant any option, right or warrant to purchase any shares of common stock;
- otherwise transfer or dispose of, directly or indirectly, any shares of common stock or any securities convertible into or exercisable or exchangeable for common stock;
- publicly disclose the intention to make any offer, sale, pledge or disposition;
- enter into any swap or other agreement or any transaction that transfers, in whole or in part, any economic consequence of ownership of any common stock, whether any such swap, agreement or transaction is to be settled by delivery of shares or other securities, in cash or otherwise; or
- make any demand for or exercise any right with respect to the registration of any shares of common stock or any security convertible into or exercisable or exchangeable for common stock.

The lock-up provisions apply to common stock and to securities convertible into or exchangeable or exercisable for common stock. They also apply to common stock owned now or acquired later by the person executing the lock-up agreement or for which the person executing the lock-up agreement later acquires the power of disposition.

Nasdaq Global Select Market Listing

Our common stock is listed on The Nasdaq Global Select Market under the symbol "MRSN."

Price Stabilization, Short Positions and Penalty Bids

Until the distribution of the shares is completed, SEC rules may limit underwriters and selling group members from bidding for and purchasing our common stock. However, the representatives may engage in transactions that stabilize the price of the common stock, such as bids or purchases to peg, fix or maintain that price.

In connection with this offering, the underwriters may purchase and sell our common stock in the open market. These transactions may include short sales, purchases on the open market to cover positions created by short sales and stabilizing transactions. Short sales involve the sale by the underwriters of a greater number of shares than they are required to purchase in this offering. "Covered" short sales are sales made in an amount not greater than the underwriters' option to purchase additional shares described above. The underwriters may close out any covered short position by either exercising their option to purchase additional shares or purchasing shares in the open market. In determining the source of shares to close out the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the option to purchase additional shares granted to them under the underwriting agreement described above. "Naked" short sales are sales in excess of such option. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of our common stock in the open market after pricing that could adversely affect investors who purchase in this offering. Stabilizing transactions consist of various bids for or purchases of shares of common stock made by the underwriters in the open market prior to the closing of this offering.

The underwriters may also impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it because the representatives have repurchased shares sold by or for the account of such underwriter in stabilizing or short covering transactions.

Similar to other purchase transactions, the underwriters' purchases to cover the syndicate short sales may have the effect of raising or maintaining the market price of our common stock or preventing or retarding a decline in the market price of our common stock. As a result, the price of our common stock may be higher than the price that might otherwise exist in the open market. The underwriters may conduct these transactions on The Nasdaq Global Select Market, in the over-the-counter market or otherwise.

Neither we nor any of the underwriters make any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of our common stock. In addition, neither we nor any of the underwriters make any representation that the representatives will engage in these transactions or that these transactions, once commenced, will not be discontinued without notice.

The underwriters may also engage in passive market making transactions in our common stock on The Nasdaq Select Global Market in accordance with Rule 103 of Regulation M during a period before the commencement of offers or sales of shares of our common stock in this offering and extending through the completion of distribution. A passive market maker must display its bid at a price not in excess of the highest independent bid of that security. However, if all independent bids are lowered below the passive market maker's bid, that bid must then be lowered when specified purchase limits are exceeded.

Electronic Distribution

In connection with this offering, certain of the underwriters or securities dealers may distribute prospectuses by electronic means, such as e-mail.

Other Relationships

The underwriters and certain of their affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. Some of the underwriters and certain of their affiliates may in the future engage in investment banking and other commercial dealings in the ordinary course of business with us and our affiliates, for which they may in the future receive customary fees, commissions and expenses.

In addition, in the ordinary course of their business activities, the underwriters and their affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers. Such investments and securities activities may involve securities and/or instruments of ours or our affiliates. The underwriters and their affiliates may also make investment recommendations and/or publish or express independent research views in respect of such securities or financial instruments and may hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

Selling Restrictions

Notice to Prospective Investors in the European Economic Area

In relation to each Member State of the European Economic Area and the United Kingdom (each, a "Relevant State"), no shares have been offered or will be offered pursuant to the offering to the public in that Relevant State prior to the publication of a prospectus in relation to the shares that has been approved by the competent authority in that Relevant State or, where appropriate, approved in another Relevant State and notified to the competent authority in that Relevant State, all in accordance with the Prospectus Regulation, except that offers of shares may be made to the public in that Relevant State at any time under the following exemptions under the Prospectus Regulation:

A. to any legal entity that is a qualified investor as defined under the Prospectus Regulation;

B. to fewer than 150 natural or legal persons (other than qualified investors as defined under the Prospectus Regulation), subject to obtaining the prior consent of the representatives; or

C. in any other circumstances falling within Article 1(4) of the Prospectus Regulation;

provided that no such offer of shares shall require the Company or the representatives to publish a prospectus pursuant to Article 3 of the Prospectus Regulation or supplement a prospectus pursuant to Article 23 of the Prospectus Regulation and each person who initially acquires any shares or to whom any offer is made will be deemed to have represented, acknowledged and agreed to and with each of the underwriters and the Company that it is a "qualified investor" within the meaning of Article 2(e) of the Prospectus Regulation. In the case of any shares being offered to a financial intermediary as that term is used in the Prospectus Regulation, each such financial intermediary will be deemed to have represented, acknowledged and agreed that the shares acquired by it in the offering have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in circumstances that may give rise to an offer of any shares to the public other than their offer or resale in a Relevant State to qualified investors as so defined or in circumstances in which the prior consent of the representatives has been obtained to each such proposed offer or resale.

For the purpose of the above provision, the expression an "offer to the public" in relation to any shares in any Relevant State means the communication in any form and by any means of sufficient information on the terms of the offer and any shares to be offered so as to enable an investor to decide to purchase or subscribe for any shares, and the expression "Prospectus Regulation" means Regulation (EU) 2017/1129.

MiFID II Product Governance

Any person offering, selling or recommending the shares (a "distributor") should take into consideration the manufacturers' target market assessment; however, a distributor subject to MiFID II is responsible for undertaking its own target market assessment in respect of the shares (by either adopting or refining the manufacturers' target market assessment) and determining appropriate distribution channels.

Notice to Prospective Investors in the United Kingdom

In addition, in the United Kingdom, this document is being distributed only to, and is directed only at, and any offer subsequently made may only be directed at persons who are "qualified investors" (as defined in the Prospectus Regulation) (i) who have professional experience in matters relating to investments falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended (the "Order"), and/or (ii) who are high net worth companies (or persons to whom it may otherwise be lawfully communicated) falling within Article 49(2)(a) to (d) of the Order (all such persons together being referred to as "relevant persons") or otherwise in circumstances that have not resulted and will not result in an offer to the public of the shares in the United Kingdom within the meaning of the Financial Services and Markets Act 2000, as amended.

Any person in the United Kingdom that is not a relevant person should not act or rely on the information included in this document or use it as basis for taking any action. In the United Kingdom, any investment or investment activity that this document relates to may be made or taken exclusively by relevant persons.

Notice to Prospective Investors in Canada

The shares may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of the Securities Act (Ontario), and are permitted clients, as defined in National Instrument 31-103 Registration Requirements, Exemptions and Ongoing Registrant Obligations. Any resale of the shares must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus supplement (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

WHERE YOU CAN FIND MORE INFORMATION

We have filed a registration statement on Form S-3 with the SEC for the securities offered by this prospectus supplement and the accompanying prospectus. This prospectus supplement and the accompanying prospectus do not include all of the information contained in the registration statement. You should refer to the registration statement and its exhibits for additional information.

We are required to file annual and quarterly reports, current reports, proxy statements, and other information with the SEC. We make these documents publicly available, free of charge, on our website at www.mersana.com as soon as reasonably practicable after filing such documents with the SEC. The information contained on our website is not part of this prospectus supplement or the accompanying prospectus. You can read our SEC filings, including the registration statement, on the SEC's website at http://www.sec.gov.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" into this prospectus supplement and the accompanying prospectus the information we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus supplement and the accompanying prospectus, and information in documents that we file later with the SEC will automatically update and supersede information in this prospectus supplement and the accompanying prospectus. We incorporate by reference into this prospectus supplement and the accompanying prospectus the documents listed below and any future filings made by us with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Exchange Act, except for information "furnished" under Items 2.02, 7.01 or 9.01 on Form 8-K or other information "furnished" to the SEC which is not deemed filed and not incorporated in this prospectus supplement or the accompanying prospectus, until the termination of the offering of securities described in this prospectus supplement. We hereby incorporate by reference the following documents:

- Our Annual Report on Form 10-K for the fiscal year ended December 31, 2019, as filed with the SEC on February 28, 2020;
- The information specifically incorporated by reference into our Annual Report on Form 10-K for the fiscal year ended December 31, 2019 from our definitive proxy statement on Schedule 14A, as filed with the SEC on April 20, 2020;
- Our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2020, as filed with the SEC on May 8, 2020;
- Our Current Reports on Form 8-K filed with the SEC on January 10, 2020, March 16, 2020, March 20, 2020, March 30, 2020, April 8, 2020, April 15, 2020, May 14, 2020 and May 27, 2020; and
- Description of our common stock contained in our Registration Statement on Form 8-A, as filed with the SEC on June 23, 2017, including any amendment or report filed for the purpose of updating such description.

Any statement contained in a document incorporated or deemed to be incorporated by reference in this prospectus supplement or the accompanying prospectus will be deemed modified, superseded or replaced for purposes of this prospectus supplement and the accompanying prospectus to the extent that a statement contained in this prospectus supplement or the accompanying prospectus modifies, supersedes or replaces such statement.

You may request a copy of these filings, at no cost, by writing or telephoning us at the following address:

Investor Relations
Mersana Therapeutics, Inc.
840 Memorial Drive
Cambridge, Massachusetts 02139
(617) 498-0020

Copies of these filings are also available, without charge, on the SEC's website at www.sec.gov and on our website at www.mersana.com as soon as reasonably practicable after they are filed electronically with the SEC. The information contained on our website is not a part of this prospectus supplement or the accompanying prospectus.

LEGAL MATTERS

The validity of the issuance of the securities offered pursuant to this prospectus supplement will be passed upon for us by Ropes & Gray LLP, Boston, Massachusetts. The underwriters are being represented in connection with this offering by Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., Boston, Massachusetts.

EXPERTS

The consolidated financial statements of Mersana Therapeutics, Inc. appearing in Mersana Therapeutics, Inc.'s Annual Report on Form 10-K for the year ended December 31, 2019, have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon, included therein, and incorporated herein by reference. Such financial statements are, and audited financial statements to be included in subsequently filed documents will be, incorporated herein in reliance upon the report of Ernst & Young LLP pertaining to such financial statements (to the extent covered by consents filed with the Securities and Exchange Commission) given on the authority of such firm as experts in accounting and auditing.

Table of Contents

PROSPECTUS

$250,000,000

Common Stock

Preferred Stock

Warrants

Units

We may offer and sell from time to time, in one or more series or issuances and on terms that we will determine at the time of the offering, any combination of the securities described in this prospectus, up to an aggregate amount of $250,000,000.

We will provide specific terms of any offering in a supplement to this prospectus. Any prospectus supplement may also add, update, or change information contained in this prospectus. You should carefully read this prospectus and the applicable prospectus supplement as well as the documents incorporated or deemed to be incorporated by reference in this prospectus before you purchase any of the securities offered hereby.

These securities may be offered and sold in the same offering or in separate offerings; to or through underwriters, dealers, and agents; or directly to purchasers. The names of any underwriters, dealers, or agents involved in the sale of our securities and their compensation will be described in the applicable prospectus supplement.

Our common stock is traded on The Nasdaq Global Select Market under the symbol "MRSN." On May 7, 2020, the closing price of our common stock was $10.02.

Investing in our securities involves risks. See "Risk Factors" on page 3, and any applicable prospectus supplement, and under similar headings in the other documents that are incorporated by reference into this prospectus.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

Prospectus dated May 15, 2020

TABLE OF CONTENTS

You should rely only on the information contained in, or incorporated by reference into, this prospectus. We have not authorized anyone to give you information different from that contained in this prospectus. We are not making an offer to sell these securities in any jurisdiction where the offer is not permitted. The information contained in this prospectus is accurate only as of the date on the front cover of this prospectus, regardless of when this prospectus is delivered or when any sale of our securities occurs. Our business, financial condition, results of operations and prospects may have changed since that date.

ABOUT THIS PROSPECTUS

This prospectus is a part of a registration statement that we filed with the Securities and Exchange Commission, or the SEC, using a "shelf" registration process. Under this shelf registration process, we may offer to sell any combination of the securities described in this prospectus in one or more offerings up to a total dollar amount of $250,000,000. Each time we sell securities under this shelf registration, we will provide a prospectus supplement that will contain specific information about the terms of that offering. The prospectus supplement may also add, update or change information contained in this prospectus. You should read both this prospectus and the applicable prospectus supplement, including all documents incorporated herein by reference, together with additional information described under "Where You Can Find More Information" below.

This prospectus does not include all of the information that is in the registration statement. We omitted certain parts of the registration statement from this prospectus as permitted by the SEC. We refer you to the registration statement and its exhibits for additional information about us and the securities that may be sold under this prospectus.

We have not authorized any dealer, agent or other person to give any information or to make any representation other than those contained or incorporated by reference in this prospectus and any accompanying prospectus supplement. You must not rely upon any information or representation not contained or incorporated by reference in this prospectus or an accompanying prospectus supplement. This prospectus and the accompanying prospectus supplement, if any, do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the registered securities to which they relate, nor do this prospectus and the accompanying prospectus supplement constitute an offer to sell or the solicitation of an offer to buy securities in any jurisdiction to any person to whom it is unlawful to make such offer or solicitation in such jurisdiction. You should not assume that the information contained in this prospectus and the accompanying prospectus supplement, if any, is accurate on any date subsequent to the date set forth on the front of the document or that any information we have incorporated by reference is correct on any date subsequent to the date of the document incorporated by reference, even though this prospectus and any accompanying prospectus supplement is delivered or securities are sold on a later date.

"Mersana Therapeutics," "Mersana," the "Company," "we," "us," "our" and similar names refer to Mersana Therapeutics, Inc. and its consolidated subsidiary, unless we state otherwise or the context otherwise requires.

SUMMARY

This summary highlights selected information contained elsewhere or incorporated by reference in this prospectus. The summary may not contain all the information that you should consider before investing in our common stock. You should read the entire prospectus carefully, including "Risk Factors" contained in this prospectus and the documents incorporated by reference herein, before making an investment decision.

Overview

We are a clinical-stage biopharmaceutical company focused on developing antibody drug conjugates, or ADCs, that offer a clinically meaningful benefit for cancer patients with significant unmet need. We have leveraged 20 years of industry learning in the ADC field to develop proprietary and differentiated technology platforms that enable us to design ADCs to have improved efficacy, safety and tolerability relative to existing ADC therapies.

We believe that our innovative platforms which include Dolaflexin and Dolasynthen, each delivering our DolaLock payload, as well as Immunosynthen, delivering a novel stimulator of interferon genes, or STING, agonist, provide a highly efficient product engine that has enabled a robust discovery pipeline for us and our partners. Our ADCs in preclinical and clinical studies are first-in-class molecules that target multiple tumor types with high unmet medical need and have exhibited improved safety and efficacy compared to ADCs developed using first-generation technology.

Our lead product candidate is XMT-1536, a first-in-class ADC targeting the sodium-dependent phosphate transport protein NaPi2b, utilizing the Dolaflexin platform to deliver an average of 10 to 12 DolaLock payload molecules per antibody. We are actively recruiting and dosing patients with ovarian cancer and NSCLC adenocarcinoma, where a majority of patients express NaPi2b in a Phase 1 clinical trial. Our next clinical product candidate, XMT-1592, uses one of our new platforms, Dolasynthen, and also targets NaPi2b. XMT-1592 comprises the same proprietary NaPi2b antibody and potent auristatin DolaLock payload with controlled bystander effect as XMT-1536, with the additional features of homogeneous, site-specific bioconjugation and precise drug-to-antibody ratio, or DAR. We filed an Investigational New Drug (IND) application in the first quarter of 2020, which was approved by the U.S. Food and Drug Administration (FDA). We remain on track to initiate the Phase 1 dose escalation study of XMT-1592 in the second quarter of 2020.

Our goal is to become a leading oncology company by leveraging the potential of our innovative and differentiated ADC technologies, and the experience and competencies of our management team to identify, acquire and develop promising ADC product candidates and to commercialize cancer therapeutics that are improvements over existing treatments.

We were incorporated in the state of Delaware in February 2002 as Nanopharma Corp., and we changed our name to Mersana Therapeutics, Inc. in November 2005. Our principal executive offices are located at 840 Memorial Drive, Cambridge, Massachusetts 02139, and our telephone number is (617) 498-0020. Our Internet website is www.mersana.com.

RISK FACTORS

Investing in our securities involves a high degree of risk. See "Part I, Item 1A—Risk Factors" in our most recent Annual Report on Form 10-K and "Part II, Item 1A—Risk Factors" in our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2020, as filed with the SEC on May 8, 2020, and any subsequent Quarterly Report on Form 10-Q incorporated by reference in this prospectus, in any other documents we file with the SEC that are deemed incorporated by reference into this prospectus and the "Risk Factors" section in the applicable prospectus supplement for a discussion of the factors you should carefully consider before deciding to purchase our securities. Before you invest in our securities, you should carefully consider these risks as well as other information we include or incorporate by reference into this prospectus and the applicable prospectus supplement. The risks and uncertainties we have described are not the only ones facing our company. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our business operations. The occurrence of any of these risks might cause you to lose all or part of your investment in the offered securities. The discussion of risks includes or refers to forward-looking statements; you should read the explanation of the qualifications and limitations on such forward-looking statements discussed elsewhere in this prospectus.

FORWARD-LOOKING STATEMENTS

This prospectus, any prospectus supplement and the other documents we have filed with the SEC that are incorporated herein by reference, contain forward-looking statements. Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our clinical results and other future conditions. The words "aim," "anticipate," "believe," "contemplate," "continue," "could," "estimate," "expect," "goal," "intend," "may," "on track," "seek," "plan," "possible," "potential," "predict," "project," "seek," "should," "target," "will," "would," or the negative of these terms or other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

These forward-looking statements include, among other things, statements about:

- the initiation, cost, timing, progress and results of our current and future research and development activities and preclinical and clinical studies;
- the timing of, and our ability to obtain and maintain, regulatory approvals for our product candidates;
- unmet need of ovarian cancer and non-small cell lung cancer;
- our ability to quickly and efficiently identify and develop additional product candidates;
- our ability to advance any product candidate into, and successfully complete, clinical studies;
- our intellectual property position, including with respect to our trade secrets;
- the potential benefits of strategic partnership agreements and our ability to enter into selective strategic partnerships;
- our estimates regarding expenses, future revenues, capital requirements, the sufficiency of our current and expected cash resources and our need for additional financing; and
- the potential impact of the ongoing COVID-19 pandemic.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. In particular, you should consider the numerous risks described in our Annual Report on Form 10-K for the year ended December 31, 2019 and our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2020, as filed with the SEC on May 8, 2020, and any subsequent Quarterly Reports on Form 10-Q, each incorporated by reference in this prospectus, and in the "Risk Factors" section in the applicable prospectus supplement. See "Where You Can Find More Information." Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we make.

In addition, while we expect that the COVID-19 pandemic might adversely affect our preclinical and clinical development efforts, business operations and financial results, the extent of the impact and the value of and market for our common stock will depend on future developments that are highly uncertain and cannot be predicted with confidence at this time, such as the ultimate duration of the pandemic, travel restrictions, quarantines, physical distancing and business closure requirements in the U.S. and in other countries, and the effectiveness of actions taken globally to contain and treat the disease.

We cannot guarantee future results, level of activity, performance or achievements. You should not rely upon forward-looking statements as predictions of future events. Unless required by law, we will not undertake and we specifically disclaim any obligation to release publicly the result of any revisions which may be made to any forward-looking statements to reflect events or circumstances after the date of such statements or to reflect the occurrence of events, whether or not anticipated. In that respect, we wish to caution readers not to place undue reliance on any such forward-looking statements, which speak only as of the date they are made.

USE OF PROCEEDS

Except as otherwise provided in an applicable prospectus supplement, we intend to use any net proceeds we receive from our sale of the securities covered by this prospectus primarily for general corporate purposes unless otherwise indicated in the applicable prospectus supplement. General corporate purposes may include, without limitation, research and development expenditures, preclinical and clinical development and commercialization of our product candidates, the acquisition or in-licensing of products or product candidates, business or technologies, collaborations, working capital and capital expenditures. We have not determined the amount of net proceeds to be used specifically for such purposes. As a result, management will retain broad discretion over the allocation of net proceeds. Additional information on the use of net proceeds we receive from the sale of securities covered by this prospectus may be set forth in the prospectus supplement relating to the specific offering.

PLAN OF DISTRIBUTION

We may sell securities in any of the ways described below or in any combination:

- to or through underwriters or dealers;
- through one or more agents;
- directly to purchasers or to a single purchaser; or
- in "at the market offerings," within the meaning of Rule 415(a)(4) of the Securities Act of 1933, as amended, or the Securities Act, to or through a market maker or into an existing trading market, or an exchange or otherwise.

The distribution of the securities by us may be effected from time to time in one or more transactions:

- at a fixed price, or prices, which may be changed from time to time;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

Each prospectus supplement will describe the method of distribution of the securities and any applicable restrictions.

The prospectus supplement will describe the terms of the offering of the securities, including the following:

- name or names of any underwriters, dealers or agents and the amounts of securities underwritten or purchased by each of them;
- the public offering price of the securities and the proceeds to us and any discounts, commissions or concessions allowed or reallowed or paid to dealers; and
- any securities exchanges on which the securities may be listed.

Any offering price and any discounts or concessions allowed or reallowed or paid to dealers will be specified in the applicable prospectus supplement and may be changed from time to time.

Only the agents or underwriters named in each prospectus supplement are agents or underwriters in connection with the securities being offered thereby.

We may authorize underwriters, dealers or other persons acting as our agents to solicit offers by certain institutions to purchase securities from us pursuant to delayed delivery contracts providing for payment and delivery on the date stated in each applicable prospectus supplement. Each contract will be for an amount not less than, and the aggregate amount of securities sold pursuant to such contracts shall not be less nor more than, the respective amounts stated in each applicable prospectus supplement. Institutions with whom the contracts, when authorized, may be made include commercial and savings banks, insurance companies, pension funds, investment companies, educational and charitable institutions and other institutions, but shall in all cases be subject to our approval. Delayed delivery contracts will be subject only to those conditions set forth in each applicable prospectus supplement, and each prospectus supplement will set forth any commissions we pay for solicitation of these contracts.

Agents, underwriters and other third parties described above may be entitled to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, or to contribution from us with respect to payments which the agents, underwriters or other third parties may be required to

make in respect thereof. Agents, underwriters and such other third parties may be customers of, engage in transactions with, or perform services for us in the ordinary course of business. We may also use underwriters or such other third parties with whom we have a material relationship. We will describe the nature of any such relationship in the applicable prospectus supplement.

One or more firms, referred to as "remarketing firms," may also offer or sell the securities, if a prospectus supplement so indicates, in connection with a remarketing arrangement upon their purchase. Remarketing firms will act as principals for their own accounts or as our agents. These remarketing firms will offer or sell the securities in accordance with the terms of the securities. Each prospectus supplement will identify and describe any remarketing firm and the terms of its agreement, if any, with us and will describe the remarketing firm's compensation. Remarketing firms may be deemed to be underwriters in connection with the securities they remarket. Remarketing firms may be entitled under agreements that may be entered into with us to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, and may be customers of, engage in transactions with or perform services for us in the ordinary course of business.

Certain underwriters may use this prospectus and any accompanying prospectus supplement for offers and sales related to market-making transactions in the securities. These underwriters may act as principal or agent in these transactions, and the sales will be made at prices related to prevailing market prices at the time of sale. Any underwriters involved in the sale of the securities may qualify as "underwriters" within the meaning of Section 2(a)(11) of the Securities Act. In addition, the underwriters' commissions, discounts or concessions may qualify as underwriters' compensation under the Securities Act and the rules of the Financial Industry Regulatory Authority.

Our common stock is listed on The Nasdaq Global Select Market. Underwriters may make a market in our common stock, but will not be obligated to do so and may discontinue any market making at any time without notice. We can make no assurance as to the development, maintenance or liquidity of any trading market for the securities.

Certain persons participating in an offering may engage in overallotment, stabilizing transactions, short covering transactions and penalty bids in accordance with rules and regulations under the Securities Exchange Act of 1934, as amended, or the Exchange Act. Overallotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum. Short covering transactions involve purchases of the securities in the open market after the distribution is completed to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the securities originally sold by the dealer are purchased in a short covering transaction to cover short positions. Those activities may cause the price of the securities to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of the activities at any time.

DESCRIPTION OF COMMON STOCK

The following summary of the terms of our common stock does not purport to be complete and is qualified in its entirety by reference to our fifth amended and restated certificate of incorporation and amended and restated by-laws, both of which are on file with the SEC as exhibits to previous filings, and the applicable provisions of the Delaware General Corporation Law, or the DGCL. We refer in this section to our fifth amended and restated certificate of incorporation as our certificate of incorporation, and we refer to our amended and restated by-laws as our by-laws.

General

Our authorized capital stock consists of 175,000,000 shares of our common stock, par value $0.0001 per share. As of April 30, 2020, we had 58,949,470 shares of common stock outstanding.

Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. A contested election of directors by our stockholders shall be determined by a plurality of the votes cast by the stockholders entitled to vote on the election; otherwise, a nominee is elected if the votes properly cast for such nominee exceed the votes properly cast against such nominee. Holders of common stock are entitled to receive any dividends as may be declared by our board of directors, subject to any preferential dividend rights of outstanding preferred stock.

In the event of our liquidation, dissolution or winding up, whether voluntary or involuntary, the holders of common stock are entitled to receive proportionately all assets available for distribution to stockholders after the payment of all debts and other liabilities and subject to the prior rights of any outstanding preferred stock. Holders of common stock have no preemptive, subscription, redemption or conversion rights. The rights, preferences and privileges of holders of common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future.

Delaware Anti-Takeover Law and Certain Charter and Bylaw Provisions

Section 203 of the Delaware General Corporation Law

We are subject to the provisions of Section 203 of the Delaware General Corporation Law. In general, Section 203 prohibits a publicly-held Delaware corporation from engaging in a "business combination" with an "interested stockholder" for a three-year period following the time that this stockholder becomes an interested stockholder, unless the business combination is approved in a prescribed manner. A "business combination" includes, among other things, a merger, asset or stock sale or other transaction resulting in a financial benefit to the interested stockholder. An "interested stockholder" is a person who, together with affiliates and associates, owns, or did own within three years prior to the determination of interested stockholder status, 15% or more of the corporation's voting stock.

Under Section 203, a business combination between a corporation and an interested stockholder is prohibited unless it satisfies one of the following conditions: before the stockholder became interested, the board of directors approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder; upon consummation of the transaction which resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the voting stock outstanding, shares owned by persons who are directors and also officers, and employee stock plans, in some instances; or at or after the time the stockholder became interested, the business combination was approved by the board of directors of the

corporation and authorized at an annual or special meeting of the stockholders by the affirmative vote of at least two-thirds of the outstanding voting stock which is not owned by the interested stockholder.

A Delaware corporation may "opt out" of these provisions with an express provision in its original certificate of incorporation or an express provision in its certificate of incorporation or by-laws resulting from a stockholders' amendment approved by at least a majority of the outstanding voting shares. We have not opted out of these provisions. As a result, mergers or other takeover or change in control attempts of us may be discouraged or prevented.

Anti-Takeover Effects of Our Certificate of Incorporation and Our By-Laws

Our certificate of incorporation and by-laws contain certain provisions that are intended to enhance the likelihood of continuity and stability in the composition of the board of directors and which may have the effect of delaying, deferring or preventing a future takeover or change in control of the company unless such takeover or change in control is approved by the board of directors.

These provisions include:

Classified Board. Our certificate of incorporation provides that our board of directors is divided into three classes of directors, with the classes as nearly equal in number as possible. As a result, approximately one-third of our board of directors will be elected each year. The classification of directors will have the effect of making it more difficult for stockholders to change the composition of our board. Our certificate of incorporation also provides that, subject to any rights of holders of preferred stock to elect additional directors under specified circumstances, the number of directors will be fixed exclusively pursuant to a resolution adopted by our board of directors. Our board of directors currently consists of six members.

Action by Written Consent; Special Meetings of Stockholders. Our certificate of incorporation provides that stockholder action can be taken only at an annual or special meeting of stockholders and cannot be taken by written consent in lieu of a meeting. Our certificate of incorporation and by-laws also provide that, except as otherwise required by law, special meetings of the stockholders can only be called pursuant to a resolution adopted by a majority of our board of directors. Except as described above, stockholders are not permitted to call a special meeting or to require the board of directors to call a special meeting.

Removal of Directors. Our certificate of incorporation provides that our directors may be removed only for cause by the affirmative vote of at least 75% of the voting power of our outstanding shares of capital stock, voting together as a single class. This requirement of a supermajority vote to remove directors could enable a minority of our stockholders to prevent a change in the composition of our board.

Advance Notice Procedures. Our by-laws establish an advance notice procedure for stockholder proposals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to the board of directors. Stockholders at an annual meeting are only able to consider proposals or nominations specified in the notice of meeting or brought before the meeting by or at the direction of the board of directors or by a stockholder who was a stockholder of record on the record date for the meeting, who is entitled to vote at the meeting and who has given our Secretary timely written notice, in proper form, of the stockholder's intention to bring that business before the meeting. Although the by-laws do not give the board of directors the power to approve or disapprove stockholder nominations of candidates or proposals regarding other business to be conducted at a special or annual meeting, the by-laws may have the effect of precluding the conduct of certain business at a meeting if the proper procedures are not followed or may discourage or deter a potential acquirer from conducting a solicitation of proxies to elect its own slate of directors or otherwise attempting to obtain control of the company.

Super Majority Approval Requirements. The DGCL generally provides that the affirmative vote of a majority of the shares entitled to vote on any matter is required to amend a corporation's certificate of incorporation or by-laws, unless either a corporation's certificate of incorporation or by-laws requires a greater percentage. Our certificate of incorporation and by-laws provide that the affirmative vote of holders of at least 75% of the total votes eligible to be cast in the election of directors is required to amend, alter, change or repeal specified provisions. This requirement of a supermajority vote to approve amendments to our certificate of incorporation and by-laws could enable a minority of our stockholders to exercise veto power over any such amendments.

Authorized but Unissued Shares. Our authorized but unissued shares of common stock and preferred stock are available for future issuance without stockholder approval. These additional shares may be utilized for a variety of corporate purposes, including future public offerings to raise additional capital, corporate acquisitions and employee benefit plans. The existence of authorized but unissued shares of common stock and preferred stock could render more difficult or discourage an attempt to obtain control of a majority of our common stock by means of a proxy contest, tender offer, merger or otherwise.

Exclusive Forum. Our certificate of incorporation requires, to the fullest extent permitted by law, that derivative actions brought in the name of the Company, actions against directors, officers and employees for breach of a fiduciary duty and other similar actions may be brought only in specified courts in the State of Delaware. Although we believe this provision benefits us by providing increased consistency in the application of Delaware law in the types of lawsuits to which it applies, the provision may have the effect of discouraging lawsuits against our directors and officers.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, N.A. The transfer agent and registrar's address is 150 Royall Street, Canton, Massachusetts 02021.

Listing

Our common stock is listed on The Nasdaq Global Select Market under the symbol "MRSN."

DESCRIPTION OF PREFERRED STOCK

Under the terms of our certificate of incorporation, our board of directors is authorized to issue up to 25,000,000 shares of our preferred stock, par value $0.0001 per share, in one or more series without stockholder approval. As of April 30, 2020, we had no shares of preferred stock outstanding. Our board of directors has the discretion to determine the rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences, of each series of preferred stock. It is not possible to state the actual effect of the issuance of any shares of preferred stock upon the rights of the holders of common stock until the board of directors determines the specific rights of the holders of preferred stock. However, effects of the issuance of preferred stock include restricting dividends on common stock, diluting the voting power of common stock, impairing the liquidation rights of common stock, and making it more difficult for a third party to acquire us, which could have the effect of discouraging a third party from acquiring, or deterring a third party from paying a premium to acquire, a majority of our outstanding voting stock.

If we offer a specific class or series of preferred stock under this prospectus, we will describe the terms of the preferred stock in the prospectus supplement for such offering and will file a copy of the certificate establishing the terms of the preferred stock with the SEC. To the extent required, this description will include:

- the title and stated value;
- the number of shares offered, the liquidation preference per share and the purchase price;
- the dividend rate(s), period(s) and/or payment date(s), or method(s) of calculation for such dividends;
- whether dividends will be cumulative or non-cumulative and, if cumulative, the date from which dividends will accumulate;
- the procedures for any auction and remarketing, if any;
- the provisions for a sinking fund, if any;
- the provisions for redemption, if applicable;
- any listing of the preferred stock on any securities exchange or market;
- whether the preferred stock will be convertible into our common stock, and, if applicable, the conversion price (or how it will be calculated) and conversion period;
- voting rights, if any, of the preferred stock;
- a discussion of any material U.S. federal income tax considerations applicable to the preferred stock;
- the relative ranking and preferences of the preferred stock as to dividend rights and rights upon liquidation, dissolution or winding up of the affairs of the Company; and
- any material limitations on issuance of any class or series of preferred stock ranking senior to or on a parity with the series of preferred stock as to dividend rights and rights upon liquidation, dissolution or winding up of the Company.

The preferred stock offered by this prospectus, when issued, will not have, or be subject to, any preemptive or similar rights.

Transfer Agent and Registrar

The transfer agent and registrar for any series or class of preferred stock will be set forth in each applicable prospectus supplement.

DESCRIPTION OF WARRANTS

We may issue warrants to purchase shares of our common stock or preferred stock in one or more series together with other securities or separately, as described in each applicable prospectus supplement. Below is a description of certain general terms and provisions of the warrants that we may offer. Particular terms of the warrants will be described in the applicable warrant agreements and the applicable prospectus supplement for the warrants.

As of April 30, 2020, we had warrants outstanding that represent the right to acquire 39,474 shares of common stock.

The applicable prospectus supplement will contain, where applicable, the following terms of and other information relating to the warrants:

- the specific designation and aggregate number of, and the price at which we will issue, the warrants;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;
- if applicable, the exercise price for shares of our common stock and the number of shares of common stock to be received upon exercise of the warrants;
- if applicable, the exercise price for shares of our preferred stock, the number of shares of preferred stock to be received upon exercise, and a description of that class or series of our preferred stock;
- the date on which the right to exercise the warrants will begin and the date on which that right will expire or, if the warrants may not be continuously exercised throughout that period, the specific date or dates on which the warrants may be exercised;
- whether the warrants will be issued in fully registered form or bearer form, in definitive or global form or in any combination of these forms, although, in any case, the form of a warrant included in a unit will correspond to the form of the unit and of any security included in that unit;
- any applicable material U.S. federal income tax consequences;
- the identity of the warrant agent for the warrants and of any other depositaries, execution or paying agents, transfer agents, registrars or other agents;
- the proposed listing, if any, of the warrants or any securities purchasable upon exercise of the warrants on any securities exchange;
- if applicable, the date from and after which the warrants and the common stock and/or preferred stock will be separately transferable;
- if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;
- information with respect to book-entry procedures, if any;
- the anti-dilution provisions of the warrants, if any;
- any redemption or call provisions;
- whether the warrants are to be sold separately or with other securities as parts of units; and
- any additional terms of the warrants, including terms, procedures and limitations relating to the exchange and exercise of the warrants.

Transfer Agent and Registrar

The transfer agent and registrar for any warrants will be set forth in the applicable prospectus supplement.

DESCRIPTION OF UNITS

We may issue units consisting of any combination of the other types of securities offered under this prospectus in one or more series. We may evidence each series of units by unit certificates that we will issue under a separate agreement. We may enter into unit agreements with a unit agent. Each unit agent will be a bank or trust company that we select. We will indicate the name and address of the unit agent in the applicable prospectus supplement relating to a particular series of units.

The following description, together with the additional information included in any applicable prospectus supplement, summarizes the general features of the units that we may offer under this prospectus. You should read any prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the series of units being offered, as well as the complete unit agreements that contain the terms of the units. Specific unit agreements will contain additional important terms and provisions and we will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from another report that we file with the SEC, the form of each unit agreement relating to units offered under this prospectus.

If we offer any units, certain terms of that series of units will be described in the applicable prospectus supplement, including, without limitation, the following, as applicable:

- the title of the series of units;
- identification and description of the separate constituent securities comprising the units;
- the price or prices at which the units will be issued;
- the date, if any, on and after which the constituent securities comprising the units will be separately transferable;
- a discussion of certain United States federal income tax considerations applicable to the units; and
- any other terms of the units and their constituent securities.

WHERE YOU CAN FIND MORE INFORMATION

We have filed a registration statement on Form S-3 with the SEC for the securities offered by this prospectus. This prospectus does not include all of the information contained in the registration statement. You should refer to the registration statement and its exhibits for additional information.

We are required to file annual and quarterly reports, current reports, proxy statements, and other information with the SEC. We make these documents publicly available, free of charge, on our website at www.mersana.com as soon as reasonably practicable after filing such documents with the SEC. The information contained on our website is not part of this prospectus. You can read our SEC filings, including the registration statement, on the SEC's website at http://www.sec.gov.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" into this prospectus the information we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus, and information in documents that we file later with the SEC will automatically update and supersede information in this prospectus. We incorporate by reference into this prospectus the documents listed below and any future filings, including all filings made after the date of the filing of the registration statement of which this prospectus is a part and prior to the effectiveness of such registration statement, made by us with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Exchange Act, except for information "furnished" under Items 2.02, 7.01 or 9.01 on Form 8-K or other information "furnished" to the SEC which is not deemed filed and not incorporated in this prospectus, until the termination of the offering of securities described in the applicable prospectus supplement. We hereby incorporate by reference the following documents:

- Our Annual Report on Form 10-K for the year ended December 31, 2019, as filed with the SEC on February 28, 2020;
- The information specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2019 from our definitive proxy statement on Schedule 14A, as filed with the SEC on April 20, 2020;
- Our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2020, as filed with the SEC on May 8, 2020;
- Our Current Reports on Form 8-K filed with the SEC on January 10, 2020, March 16, 2020, March 30, 2020, April 8, 2020 and April 15, 2020; and
- Description of our common stock contained in our Registration Statement on Form 8-A, as filed with the SEC on June 23, 2017, including any amendment or report filed for the purpose of updating such description.

Any statement contained in a document incorporated or deemed to be incorporated by reference in this prospectus will be deemed modified, superseded or replaced for purposes of this prospectus to the extent that a statement contained in this prospectus modifies, supersedes or replaces such statement.

You may request a copy of these filings, at no cost, by writing or telephoning us at the following address:

Investor Relations
Mersana Therapeutics, Inc.
840 Memorial Drive
Cambridge, Massachusetts 02139
(617) 498-0020

Copies of these filings are also available, without charge, on the SEC's website at www.sec.gov and on our website at www.mersana.com as soon as reasonably practicable after they are filed electronically with the SEC. The information contained on our website is not a part of this prospectus.

LEGAL MATTERS

The validity of the issuance of the securities offered pursuant to this prospectus will be passed upon for us by Ropes & Gray LLP, Boston, Massachusetts. The validity of any securities will be passed upon for any underwriters or agents by counsel that we will name in the applicable prospectus supplement.

EXPERTS

The consolidated financial statements of Mersana Therapeutics, Inc. appearing in Mersana Therapeutics, Inc.'s Annual Report on Form 10-K for the year ended December 31, 2019, have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon, included therein, and incorporated herein by reference. Such financial statements are, and audited financial statements to be included in subsequently filed documents will be, incorporated herein in reliance upon the report of Ernst & Young LLP pertaining to such financial statements (to the extent covered by consents filed with the Securities and Exchange Commission) given on the authority of such firm as experts in accounting and auditing.

5,000,000 Shares

Common Stock

PROSPECTUS SUPPLEMENT

Joint Bookrunning Managers

Cowen **SVB Leerink**

, 2020