REVIEW

Nanoparticles in the clinic: An update

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Abstract
Nanoparticle drug delivery systems have been used in the clinic since the early 1990’s. Since that time, the field of nanomedicine has evolved alongside growing technological needs to improve the delivery of various therapeutic functions. Over these past decades, newer generations of nanoparticles have emerged that are capable of performing additional delivery functions that can enable treatment via new therapeutic modalities. In the current clinical landscape, many of these new generation nanoparticles have reached clinical trials and have been approved for various indications. In the first issue of Bioengineering & Translational Medicine in 2016, we reviewed the history, current clinical landscape, and clinical challenges of nanoparticle delivery systems. Here, we provide a 3 year update on the current clinical landscape of nanoparticle drug delivery systems and highlight newly approved nanomedicines, provide a status update on previous clinical trials, and highlight new technologies that have recently entered the clinic.

KEYWORDS
clinic, clinical translation, clinical trials, drug delivery, nanomedicine, nanoparticles, translational medicine

1 | INTRODUCTION

The nanomedicine landscape continues to rapidly evolve driven by newly developed delivery strategies, new technologies, new treatment modalities, new drug approvals, and even clinical failures of current drugs. In 2016, we published a review article on the current clinical landscape of therapeutic nanoparticles, which highlighted over 25 Food and Drug Administration (FDA) or European Medicines Agency (EMA) approved nanomedicines and over 45 other nanoparticle technologies that were not FDA/EMA approved but were currently being evaluated in ongoing clinical trials. That article also featured discussions on different nanoparticle types, their applications, their advantages as compared to free drugs, and their potential. We also discussed many of the biological issues (i.e., biodistribution, biological barrier breaching, and treating heterogeneous diseases), technological issues (i.e., scale-up limitations, parameter optimization, and predicting efficacy), and clinical challenges that have limited the translation of nanoparticles. In these past 3 years, since that article was published, two intravenously administered nanoparticles have been FDA and EMA approved, one intratumoral administered nanoparticle received European market approval (CE Mark), over 75 new trials have begun for the previously highlighted nonapproved nanoparticles, and over 15 new nanoparticle technologies have entered clinical trials. In this 3-year update, we highlight these new clinical approvals, trials, and technologies to provide an updated snapshot on the current clinical landscape of nanoparticles in 2019.

2 | NEW APPROVALS

Since our previous article, three nanomedicines have been approved: Patisiran/ONPATTRO, VYXEOS, and NBTXR3/Hensify. VYXEOS is a
combination chemotherapy nanoparticle, developed and marketed by Jazz Pharmaceuticals, that encapsulates a synergistic molar ratio of cytarabine to daunorubicin of 5:1 and received FDA approval for the treatment of acute myeloid leukemia in August of 2017.\textsuperscript{2,3} VYXEOS are 100 nm bilamellar liposomes where the lipid membrane consists of desaturated phosphatidylcholine:distearylphosphatidylglycerol:cholesterol (72:21:7 ratio)\textsuperscript{5}. In the pivotal efficacy study (NCT01696084), VYXEOS provided a significant (p value = 0.005) improvement in overall survival of 9.6 months as compared to 5.9 months in the free drug control.\textsuperscript{2,3} Importantly, this trial also showed that VYXEOS provided improved efficacy at a lower cumulative daunorubicin and cytarabine dose as compared to free drug counterparts.\textsuperscript{6} Since 2016, the number of clinical trials of VYXEOS has increased from 7 to 21 with the most recent trials investigating the use of VYXEOS in additional patient populations (e.g., children; NCT03826992) and leukemias (e.g., lymphoblastic leukemias; NCT03575325). Unlike other approved nanoparticles for cancer treatment, VYXEOS delivers two drugs in a synergistic ratio. Delivery of the synergistic combination of daunorubicin and cytarabine is enabled by the nanoparticle platform since the encapsulated ratio of drugs is able to both interact with target cells upon release. In the contrasting case of free drugs, each drug exhibits distinct pharmacokinetic profiles and are metabolized at different rates; as such, delivery of synergistic combinations of free drugs to target cells must also consider and counteract these biological processes. Product sales for VYXEOS were $100.8 million in 2018.\textsuperscript{7} As the first clinically approved nanoparticle to deliver a synergistic combination of free drugs, VYXEOS can pave the way for new combination nanoparticle formulations that leverage widely-utilized combination chemotherapy regimens from the clinic.\textsuperscript{8,9}

Patisiran/ONPATTRO is an siRNA-delivering lipid-based nanoparticle developed and marketed by Alnylam, for the silencing of a specific gene responsible for expression of transthyretin, which can cause hereditary transthyretin amyloidosis.\textsuperscript{10} Patisiran/ONPATTRO lipid nanoparticles consist of (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino) butanoate (DLin-MC3-DMA) plus cholesterol, 1,2-distearyl-sn-glycero-3-phosphocholine and \(\alpha\)-(3-{[1,2-di(myristyloxy)propanoxy]-carbonylamino}propyl)-\(\alpha\)-methoxy polyoxyethylene (PEG\textsubscript{2000}-C-DMG).\textsuperscript{11} Patisiran/ONPATTRO was approved by the FDA in August of 2018\textsuperscript{12} and was the first clinically approved example of an RNAi therapy-delivering nanoparticle administered intravenously. Importantly, Patisiran/ONPATTRO is also the first FDA approved RNAi therapeutic in general,\textsuperscript{12} independent of the nanoparticle delivery vehicle. Approval of the first RNAi therapeutic was a major milestone in the biotech industry and considering that the delivery vehicle was a nanoparticle, approval of Patisiran/ONPATTRO was also a major milestone for nanomedicines. In the Phase III efficacy study (NCT01960348), 56% of patients receiving Patisiran/ONPATTRO exhibited improvements in modified Neuropathy Impairment Score\textsuperscript{-7} as compared to 4% receiving the placebo.\textsuperscript{10} Moreover, serum transthyretin decreased by over 70% in patients receiving Patisiran/ONPATTRO as compared to less than 20% in patients receiving the placebo.\textsuperscript{10} Global net revenues for Patisiran/ONPATTRO were $121.1 million in 2018 with over 200 patients in Europe and the United States receiving treatment.\textsuperscript{13}

As the first clinically approved siRNA/RNAi therapeutic, Patisiran/ONPATTRO demonstrates how nanoparticles can be used to enable the delivery, and in this case approval, of highly challenging therapeutics to humans.

NBTXR3/Hensify is a 50 nm crystalline hafnium oxide nanoparticle with negatively charged phosphate coating, developed and marketed by Nanobiotix.\textsuperscript{14} NBTXR3/Hensify enhances external radiotherapy via a physical mode of action that relies on hafnium's natural radioenhancing properties.\textsuperscript{14,15} Specifically, the interaction between ionizing radiation and hafnium facilitates a higher energy deposit as compared to ionizing radiation without hafnium interaction; this results in the generation of significantly more electrons and increases radiation-mediated cell death from standard radiation oncology procedures.\textsuperscript{14,15} NBTXR3/Hensify received CE Mark approval in April of 2019 for the treatment of locally advanced soft tissue sarcoma.\textsuperscript{16} Since our previous article, the number of clinical trials of NBTXR3/Hensify has increased from 1 to 8. While NBTXR3/Hensify is approved for intratumoral administration, clinical trials had investigated it for intra-arterial administration (NCT01946867). The newest trials are only investigating NBTXR3/Hensify for intratumoral injections, but have expanded their indications to include treatment of prostate cancer (NCT02805894) and lung cancer with combined immunotherapy (NCT03589339). The reasoning for including immunotherapy with NBTXR3/Hensify treatment builds on preclinical data that demonstrated improved efficacy of immunotherapies following NBTXR3/Hensify treatment, stemming from an increased antitumor immune response.\textsuperscript{17,18} Since the mechanism of action of NBTXR3/Hensify is unique and unlike other approved nanoparticles or therapeutics, NBTXR3/Hensify may represent the next-generation of nanoparticle therapeutics; specifically, nanoparticle therapeutics that can provide therapeutic benefits in a complementary and possibly synergistic way to standard therapeutic modalities. Table 1, which previously listed FDA/EMA approved nanomedicines as of 2016, is now updated to include these recently approved nanoparticles.

### 3 | UPDATE ON PREVIOUS TRIALS

In our previous article, over 45 different nonapproved nanoparticles (liposomes, polymeric, micelles, albumin-bound nanoparticles, and inorganic nanoparticles) were listed as active in a total of over 80 different clinical trials (mostly for the treatment of various cancers but also radiation exposure, arthritis, pneumonia, amyloidosis, hepatitis, and fibrosis). Of these 80 trials, 28 have since been completed with 12 being terminated early. Of the 45 different nanoparticles, seven possessed targeting functionality, and six offered stimuli-responsive functions (e.g., thermal ablation in response to near-infrared light, thermosensitive liposomes). Three of these nanoparticles, as mentioned above, have received FDA, EMA, or CE Mark approval. Here, we have updated our previous table to reflect the current status of each of these technologies to include new clinical trials and updates on previous trials. Seventy-five new trials exist for the previously highlighted nanoparticles. Of these 75 new trials, 14 are for VYXEOS, 8 are for Patisiran/ONPATTRO, and 6 are for NBTXR3/
### Table 1: Updated clinically approved nanoparticle therapies and diagnostics, grouped by their broad indication

| Name                      | Particle type/drug                                                                 | Approved application/indication                                                                 | Approval (year) | Investigated application/indication | Updates on number of studies on ClinicalTrials.gov identifier |
|---------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-----------------|-------------------------------------|---------------------------------------------------------------|
| **New approvals since 2016** |                                                                                  |                                                                                                |                 |                                     |                                                               |
| VYXEOS                    | Liposomal formulation of cytarabine:daunorubicin (5:1M ratio)                    | Acute myeloid leukemia                                                                            | FDA (2017)      | Various leukemias                    | 2016: VYXEOS: 7, 2019: VYXEOS: 21                             |
| CPX-351 (Jazz Pharmaceuticals) |                                                                                  |                                                                                                | EMA (2018)      |                                     |                                                               |
| ONPATTRO Patisiran ALN-TTR02 (Alnylam Pharmaceuticals) | Lipid nanoparticle RNAi for the knockdown of disease-causing TTR protein | Transthyretin (TTR)-mediated amyloidosis                                                            | FDA (2018)      | Transthyretin (TTR)-mediated amyloidosis | 2016: 3, 2019: 11                                              |
| NBTXR3 Hensify (Nanobiotic) | Hafnium oxide nanoparticles stimulated with external radiation to enhance tumor cell death via electron production | Locally advanced squamous cell carcinoma                                                             | CE Mark (2019) | Locally advanced soft tissue sarcoma | 2016: 1 (an additional trial was listed as completed at the time), 2019: 8 |
| **Cancer nanoparticle medicines** |                                                                                  |                                                                                                |                 |                                     |                                                               |
| Doxil Caelyx (Janssen)     | Liposomal doxorubicin (PEGylated)                                                | Ovarian cancer (secondary to platinum based therapies), HIV-associated Kaposi’s sarcoma (secondary to chemotherapy), Multiple myeloma (secondary) | FDA (1995)      | Various cancers including: solid malignancies, ovarian, breast, leukemia, lymphomas, prostate, metastatic, or liver | 2016: Doxil: 166, CAELYX: 90, 2019: Doxil: 182, CAELYX: 109 |
| DaunoXome (Galen)          | Liposomal daunorubicin (non-PEGylated)                                           | HIV-associated Kaposi’s sarcoma (primary)                                                            | FDA (1996)      | Various leukemias                    | 2016: DaunoXome: 32, 2019: DaunoXome: 15                       |
| Myocet (Teva UK)           | Liposomal doxorubicin (non-PEGylated)                                           | Treatment of metastatic breast cancer (primary)                                                      | EMA (2000)      | Various cancers including: breast, lymphoma, or ovarian | 2016: Myocet: 32, 2019: Myocet: 35                             |
| Abraxane (Celgene)         | Albumin-particle bound paclitaxel                                                 | Advanced non-small cell lung cancer (surgery or radiation is not an option), Metastatic breast cancer (secondary), Metastatic pancreatic cancer (primary) | FDA (2005)      | Various cancers including: solid malignancies, breast, lymphomas, bladder, lung, pancreatic, head and neck, prostate, melanoma, or liver | 2016: Abraxane: 295, 2019: Abraxane: 432                       |

(Continues)
| Name               | Particle type/drug                                      | Approved application/indication                                                                 | Approval (year) | Investigated application/indication                                                                 | Updates on number of studies on ClinicalTrials.gov identifier |
|--------------------|--------------------------------------------------------|--------------------------------------------------------------------------------------------------|-----------------|---------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| Marqibo (Spectrum) | Liposomal vincristine (non-PEGylated)                  | Philadelphia chromosome-negative acute lymphoblastic leukemia (tertiary)                        | FDA (2012)      | Various cancers including: lymphoma, brain, leukemia, or melanoma                                  | 2016: Marqibo: 23, 2019: Marqibo: 28                         |
| MEPACT (Millennium)| Liposomal mifamurtide (non-PEGylated)                 | Treatment for osteosarcoma (primary following surgery)                                         | EMA (2009)      | Osteosarcomas                                                                                     | 2016: MEPACT: 4 (3 active/recruiting), 2019: MEPACT: 9 (3 active/recruiting) |
| Onivyde MM-398 (Merrimack) | Liposomal irinotecan (PEGylated) | Metastatic pancreatic cancer (secondary)                                                        | FDA (2015)      | Various cancers including: solid malignancies, breast, pancreatic, sarcomas, or brain             | 2016: MM-398/Onivyde: 7 (6 active/recruiting), 2019: MM-398/Onivyde: 38 (26 active/recruiting) |

**Iron-replacement nanoparticle therapies**

| Name               | Particle type/drug                                      | Approved application/indication                                                                 | Approval (year) | Investigated application/indication                                                                 | Updates on number of studies on ClinicalTrials.gov identifier |
|--------------------|--------------------------------------------------------|--------------------------------------------------------------------------------------------------|-----------------|---------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| CosmoFer INFeD Ferrisat (Pharmacosmos) | Iron dextran colloid                                  | Iron deficient anemia                                                                            | FDA (1992) Some of Europe | Iron deficient anemia                                                                             | 2016: INFeD: 6 (1 recruiting), 2019: INFeD: 9               |
| DexFerrum DexIron (American Regent)     | Iron dextran colloid                                  | Iron deficient anemia                                                                            | FDA (1996)      | Iron deficient anemia                                                                            | 2016: DexFerrum: 6, 2019: DexFerrum: 9                     |
| Ferrlecit (Sanofi)                    | Iron gluconate colloid                                | Iron replacement for anemia treatment in patients with chronic kidney disease                    | FDA (1999)      | Iron deficient anemia                                                                            | 2016: Ferrlecit: 13 (2 recruiting), 2019: Ferrlecit: 20 (0 recruiting) |
| Venofer (American Regent)             | Iron sucrose colloid                                  | Iron replacement for anemia treatment in patients with chronic kidney disease                    | FDA (2000)      | Iron deficient anemia Following autologous stem cell transplantation                               | 2016: Venofer: 44, 2019: Venofer: 60                       |
| Feraheme Ferumoxytol (AMAG Rienso Takeda) | Iron polyglucose sorbitol carboxymethylether colloid | Iron deficiency in patients with chronic kidney disease                                           | FDA (2009)      | Iron deficient anemia Imaging: brain metastases, lymph node metastases, neuroinflammation in epilepsy, head and neck cancer, myocardial infarction, or multiple sclerosis | 2016: Ferumoxytol: 57 (6 recruiting/active for anemia treatment; 22 recruiting/active for imaging applications), 2019: Ferumoxytol: 84 (6 recruiting/active for anemia treatment; 22 recruiting/active for imaging applications) |

(Continues)
| Name             | Particle type/drug                        | Approved application/indication                      | Approval (year) | Investigated application/indication | Updates on number of studies on ClinicalTrials.gov identifier |
|------------------|------------------------------------------|-----------------------------------------------------|-----------------|-------------------------------------|----------------------------------------------------------------|
| Injectafer       | Iron carboxymaltose colloid              | Iron deficient anemia                               | FDA (2013)      | Iron deficient anemia               | 2016: Ferinject: 70, Injectafer: 8, 2019: Ferinject: 79, Injectafer: 24 |
| Ferinject (Vifor) |                                          |                                                     |                 |                                     |                                                                  |
| Monofer (Pharmacosmos) | 10% iron isomaltoside 1,000 colloid | Treating iron deficiency and anemia when oral methods do not work or when iron delivery is required immediately | Some of Europe  | Iron deficient anemia               | 2016: Monofer: 22 (3 active/recruiting), 2019: Monofer: 22 (11 active/recruiting) |
| Diafer (Pharmacosmos) | 5% iron isomaltoside 1,000 colloid | Iron deficient anemia                               | Some of Europe  | Iron deficient anemia               | 2016: Diafer: 1 recruiting, 2019: Diafer: 1 completed |
| Nano/microparticle imaging agents | | | | | |
| Definity (Lantheus Medical Imaging) | Perflutren lipid microspheres | Ultrasound contrast agent                          | FDA (2001)      | Ultrasound enhancement for: liver or breast or intraocular or pancreatic tumors, pulmonary diseases, heart function, transcranial injuries, strokes, or liver cirrhosis | 2016: Definity: 58, 2019: Definity: 87 |
| Feridex I.V. (AMAG) | Iron dextran colloid | Imaging of liver lesions                          | FDA (1996)      | N/A: No current studies             | 2016: Endorem: 4, Feridex: 2, No current active or recruiting studies, 2019: Endorem: 4, Feridex: 2, No current active or recruiting studies |
| Endorem          |                                          |                                                     | Discontinued (2008) |                                     |                                                                  |
| Optison (GE Healthcare) | Human serum albumin stabilized perflutren microspheres | Ultrasound contrast agent                          | FDA (1997)      | Ultrasound enhancement for: lymph node, renal cell carcinoma, myocardial infarction, pulmonary transit times, or heart transplant rejections | 2016: Optison: 11 currently active or recruiting studies, 2019: Optison: 30 (6 active) |
| SonoVue (Bracco Imaging) | Phospholipid stabilized microbubble | Ultrasound contrast agent                          | EMA (2001)      | Ultrasound enhancement for: liver neoplasms, prostate or breast or pancreatic cancer, or coronary/pulmonary disease | 2016: SonoVue: 43, 2019: SonoVue: 72 |

(Continues)
| Name                     | Particle type/drug                  | Approved application/indication                  | Approval (year)                        | Investigated application/indication | Updates on number of studies on ClinicalTrials.gov identifier |
|--------------------------|-------------------------------------|-------------------------------------------------|----------------------------------------|-------------------------------------|---------------------------------------------------------------|
| **Resovist**<br>(Bayer Schering Pharma)<br>Cliavist | Iron carboxydextran colloid        | Imaging of liver lesions                       | Some of Europe Discontinued (2009)    | N/A No current studies               | 2016: 2 studies mention Resovist: No current active or recruiting studies 2019: 2 studies mention Resovist: No current active or recruiting studies |
| Ferumoxtran-10 Combidx<br>Sinerem (AMAG) | Iron dextran colloid                | Imaging lymph node metastases                  | Only available in Holland              | Imaging lymph node metastases       | 2016: Ferumoxtran-10:11 (1 active) 2019: Ferumoxtran-10:24 (1 active; 6 recruiting) |
| Nanoparticle vaccines    |                                     |                                                 |                                        |                                     |                                               |
| Epaxal<br>(Crucell)      | Liposome with hepatitis A virus     | Hepatitis A vaccine                             | Some of Europe (discontinued)          | Safety and immunogenicity of hepatitis A vaccine | 2016: Epaxal: 6 (1 recruiting) 2019: Epaxal: 6 (0 recruiting) |
| Inflexal V<br>(Crucell)  | Liposome with trivalent-influenza   | Influenza vaccine                              | Some of Europe (discontinued)          | Safety and immunogenicity of influenza vaccine | 2016: Inflexal V: 14 (all completed) 2019: Inflexal V: 14 (all completed) |
| Particle anesthetics     |                                     |                                                 |                                        |                                     |                                               |
| Diprivan                 | Liposomal propofol                 | Induction and maintenance of sedation or anesthesia | FDA (1989)                              | General anesthesia in specific situations: morbidly obese patients, open heart surgery, or spinal surgery | 2016: Diprivan: 110 2016: Diprivan: 162 |
| Nanoparticles for fungal treatments |                                     |                                                 |                                        |                                     |                                               |
| AmBisome<br>(Gilead Sciences) | Liposomal amphotericin B       | Cryptococcal meningitis in HIV-infected patients<br>Aspergillus, Candida and/or Cryptococcus species infections (secondary)<br>Visceral leishmaniasis parasite in immunocompromised patients | FDA (1997)<br>Most of Europe | Preventing or treating invasive fungal infections | 2016: AmBisome: 50 2019: AmBisome: 57 |
| Nanoparticles for macular degeneration |                                     |                                                 |                                        |                                     |                                               |
| Visudyne<br>(Bausch and Lomb) | Liposomal verteporfin            | Treatment of subfoveal choroidal neovascularization from age-related macular degeneration, pathologic, or ocular histoplasmosis | FDA (2000)<br>EMA (2000) | Macular degeneration | 2016: Visudyne: 52 2016: Visudyne: 60 |

Note: Newly approved nanoparticles are separately listed in the first rows. Modified with permission from Reference 1. Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration.
| Name (company) | Particle type/drug | Investigated application/indication | ClinicalTrials.gov identifiers (phase) | Updates since 2016 |
|----------------|-------------------|-------------------------------------|--------------------------------------|------------------|
| **Liposomes (cancer)** | | | | |
| PROMITIL (Lipomedix Pharmaceuticals) | PEGylated liposomal mitomycin-C | Solid tumors | 2016: NCT01705002 (Ph I): Completed 2019 additions: NCT03823989 (Ph Ib): Recruiting | 1 new trial 1 trial completed |
| ThermoDox® (Celsion) | Lyso-thermosensitive liposomal doxorubicin | Temperature-triggered doxorubicin release: Breast cancer recurrence at chest wall (microwave hyperthermia) Hepatocellular carcinoma (radiofrequency ablation) Liver tumors (mild hyperthermia) Refractory solid tumors (magnetic resonance high intensity focused ultrasound) | 2016: NCT02536183 (Ph I): Recruiting NCT00826085 (Ph I/II): Completed NCT02112656 (Ph III): Completed NCT02181075 (Ph I): Completed 2019 additions: NCT03749850 (Ph I): Not yet recruiting | 1 new trial 3 trials completed NCT02181075 (Ph I): Published results highlight how ThermoDox in combination with externally induced mild hyperthermia increase intratumoral concentration of dox by 3.7 times as compared to ThermoDox without hyperthermia induction. |
| VYXEOS CPX-351 (Celator Pharmaceuticals) | Liposomal formulation of cytarabine: daunorubicin (5:1M ratio) | Leukemias | 2016: NCT01804101 (not provided) NCT02286726 (Ph II) NCT02019069 (Ph II) NCT01943682 (Ph I) NCT02269579 (Ph II) NCT02533115 (Ph IV) NCT01696084 (Ph III) 2019 additions: 21 Total studies | Received FDA approval in 2017 and EMA approval in 2018 13 new trials |
| Oncoprex (Genprex) | FUS1 (TUSC2) encapsulated liposome | Lung cancer | 2016: NCT01455389 (Ph I/II): Active, not recruiting | 0 new trials |
| Halaven E7389-LF (Eisai) | Liposomal eribulin mesylate | Solid tumors | 2016: NCT01945710 (Ph I): Completed 2019 additions: NCT03207627 (Ph I): Recruiting | 1 new trial 1 trial completed |
| Mitoxantrone hydrochloride liposome (CSPC ZhongQi Pharmaceutical Technology) | Mitoxantrone liposome | Lymphoma and breast cancer | 2016: NCT02131688 (Ph I): Unknown NCT02596373 (Ph II): Recruiting NCT02597387 (Ph II): Recruiting NCT02595242 (Ph I): Withdrawn | 1 new trial 1 trial withdrawn 1 trial terminated |

(Continues)
| Name (company)          | Particle type/drug                                                                 | Investigated application/indication       | ClinicalTrials.gov identifiers (phase)                                                                 | Updates since 2016 |
|------------------------|----------------------------------------------------------------------------------|------------------------------------------|-------------------------------------------------------------------------------------------------------|-------------------|
| JVRS-100 (Ph I): Terminated (only one subject enrolled in 1.5 years) | Cationic liposome incorporating plasmid DNA complex for immune system stimulation | Leukemia                                 | NCT02597153 (Ph II): Completed                                                                       | 0 new trials      |
|                        |                                                                                  |                                           | NCT03776279 (Ph I): Recruiting                                                                  | 1 trial completed |
| Lipocurc (SignPath Pharma) | Liposomal curcumin                                                              | Solid tumors                             | NCT00860522 (Ph I): Completed                                                                       | 0 new trials      |
|                        |                                                                                  |                                           | NCT02138955 (Ph I/II): Unknown                                                                  | 1 trial changed to unknown status |
| LiPlaCis (LiPlasome Pharma) | Liposomal formulated cisplatin with specific degradation-controlled drug release via phospholipase A2 (PLA2) | Advanced or refractory tumors             | NCT01861496 (Ph I): Recruiting                                                                  | 0 new trials      |
| MM-302 (Merrimack Pharmaceuticals) | HER2-targeted liposomal doxorubicin (PEGylated)                               | Breast cancer                            | NCT01304797 (Ph I): Unknown                                                                      | 1 new trial that was withdrawn |
|                        |                                                                                  |                                           | NCT02213744 (Ph II/III): Terminated (felt not to show benefit over control over DMC and confirmed via futility analysis) | 1 trial terminated |
|                        |                                                                                  |                                           | NCT02735798 (Ph I): Withdrawn (the study was not started due to the sponsor choosing to not fund the trial) | 1 trial changed to unknown status |
|                        |                                                                                  |                                           |                                                                                                     | Merrimack halted the phase II study of MM-302 (NCT02213744) due to it being unlikely that MM-302 would demonstrate benefits over the control comparison. |
|                        |                                                                                  |                                           | Merrimack published results for NCT01304797 where data suggested that a tracer nanoparticle could be used to select for patients that exhibit enhanced EPR effect as a means to screen for patients who would likely respond favorably to nanomedicines. |
| LIPUSU® (Nanjing Luye Sike Pharmaceutical Co., Ltd.) | Paclitaxel liposome                                                          | Advanced solid tumors, or gastric, breast cancer           | NCT01994031 (Ph IV): Unknown                                                                      | 1 new trial       |
|                        |                                                                                  |                                           | NCT02142790 (Ph IV): Unknown                                                                       |                  |
|                        |                                                                                  |                                           | NCT02163291 (Ph II): Unknown                                                                       |                  |
|                        |                                                                                  |                                           | NCT02142010 (not provided): Unknown                                                                |                  |
|                        |                                                                                  |                                           | NCT02996214 (Ph IV): Not yet recruiting                                                           |                  |

**Liposomes (gene therapy: Cancer)**

| Name (company)          | Particle type/drug                                                                 | Investigated application/indication       | ClinicalTrials.gov identifiers (phase)                                                                 | Updates since 2016 |
|------------------------|----------------------------------------------------------------------------------|------------------------------------------|-------------------------------------------------------------------------------------------------------|-------------------|
| TKM-080301 (Arbutus Biopharma) | Lipid particle targeting polo-like kinase 1 (PLK1) for delivery of siRNA         | Hepatocellular carcinoma                | NCT02191878 (Ph I/II): Completed                                                                    | 0 new trials      |
|                        |                                                                                  |                                           |                                                                                                     | 1 trial completed |
| siRNA-EphA2-DOPC       | siRNA liposome for EphA2 knockdown                                                | Solid tumors                             | NCT01591356 (Ph I): Recruiting                                                                    | 0 new trials      |

(Continues)
| Name (company) | Particle type/drug | Investigated application/indication | ClinicalTrials.gov identifiers (phase) | Updates since 2016 |
|---------------|-------------------|-------------------------------------|----------------------------------------|-------------------|
| PNT2258 (ProNAi Therapeutics) | Proprietary single-stranded DNAi (PNT100) encapsulated in lipid nanoparticles | Lymphomas | 2016: NCT02378038 (Ph II): Terminated | 0 new trials |
| | | | NCT02226965 (Ph II): Unknown | 1 trial completed |
| | | | NCT01733238 (Ph II): Completed | 1 trial terminated |
| | | | 2016: NCT02378038 (Ph II): Terminated | 1 trial changed to unknown status |
| | | | NCT02226965 (Ph II): Unknown | |
| | | | NCT01733238 (Ph II): Completed | |
| BP1001 (Bio-Path Holdings) | Growth factor receptor bound protein-2 (Grb-2) antisense oligonucleotide encapsulated in neutral liposomes | Leukemias | 2016: NCT01159028 (Ph I): Active, not recruiting | 2 new trials |
| | | | 2019 additions: NCT02923986 (Ph I): Recruiting | |
| | | | NCT02781883 (Ph II): Recruiting | |
| DCR-MYC (Dicerna Pharmaceuticals) | DsiRNA lipid nanoparticle for NYC oncogene silencing | Solid tumors, multiple myeloma, lymphoma, or hepatocellular carcinoma | 2016: NCT02110563 (Ph I): Terminated (sponsor decision) | 0 new trials |
| | | | NCT02314052 (Ph I/II) terminated (sponsor decision) | 2 trials terminated |
| | | | DCR-MYC development discontinued. | |
| Atu027 (Silence Therapeutics GmbH) | AtuRNAi liposomal formulation for PKN3 knockdown in vascular endothelium | Pancreatic cancer | 2016: NCT01808638 (Ph I/II): Completed | 0 new trials |
| | | | 2016: NCT01808638 (Ph I/II): Completed | 1 trial completed |
| SGT-53 (SynerGene Therapeutics) | Cationic liposome with anti-transferrin receptor antibody, encapsulating wildtype p53 sequence | Glioblastoma, solid tumors, or pancreatic cancer | 2016: NCT02354547 (Ph I): Recruiting | 1 new trial |
| | | | NCT02354547 (Ph I): Recruiting | 1 trial completed |
| | | | NCT02340156 (Ph II): Recruiting | |
| | | | NCT00470613 (Ph I): Completed | |
| | | | 2019 additions: NCT03554707 (Ph I): Not yet recruiting | |
| SGT-94 (SynerGene Therapeutics) | RB94 plasmid DNA in a liposome with anti-transferrin receptor antibody | Solid tumors | 2016: NCT01517464 (Ph I): Completed | 0 new trials |
| | | | 2016: NCT01517464 (Ph I): Completed | 1 trial completed |
| MRX34 (Mirna Therapeutics) | Double-stranded RNA mimic of miR-34 encapsulated in liposomes | Liver cancer | 2016: NCT01829971 (Ph I): Terminated (five immune related serious adverse events) | 1 new trial that was withdrawn |
| | | | 2019 additions: NCT02862145 (Ph I): Withdrawn (5 immune related serious adverse events in phase 1 study) | 1 trial terminated |
| | | | 2016: NCT01829971 (Ph I): Terminated (five immune related serious adverse events) | |
| | | | 2019 additions: NCT02862145 (Ph I): Withdrawn (5 immune related serious adverse events in phase 1 study) | |
| TargomiRs (EnGeneIC) | Anti-EGFR bispecific antibody minicells (bacteria derived nanoparticles) with a miR-16 based microRNA payload | Mesothelioma and non-small cell lung cancer | 2016: NCT02369198 (Ph I): Completed | 0 new trials |
| | | | 2016: NCT02369198 (Ph I): Completed | 1 trial completed |
| | | | NCT02369198 (Ph I): Published study demonstrates that TargomiRs were well-tolerated by refractory malignant pleural mesothelioma patients. | |

(Continues)
| Name (company) | Particle type/drug | Investigated application/indication | ClinicalTrials.gov identifiers (phase) | Updates since 2016 |
|----------------|-------------------|-------------------------------------|----------------------------------------|-------------------|
| Liposomes (gene therapy: Other) | | | |
| ND-L02-s0201 (Nitto Denko) | siRNA lipid nanoparticle conjugated to vitamin A | Hepatic fibrosis and pulmonary fibrosis | 2016: NCT02272459 (Ph I): Completed | 3 new trials (2 completed) |
| | | | 2019 additions: NCT01858935 (Ph I): Completed | 1 trial completed |
| | | | NCT03241264 (Ph I): Completed | |
| | | | NCT03538301 (Ph II): Recruiting | |
| | | | | |
| ARB-001467 TKM-HBV (Arbutus Biopharma) | Lipid particle containing three RNAi therapeutics that target three sites on the HBV genome | Hepatitis B | 2016: NCT02631096 (Ph II): Completed | 0 new trials |
| | | | 2019 additions: | 1 trial completed |
| | | | | |
| ONPATTRO Patisiran ALN-TTR02 (Alnylam Pharmaceuticals) | Lipid nanoparticle RNAi for the knockdown of disease-causing TTR protein | Transthyretin (TTR)-mediated amyloidosis | 2016: NCT02510261 (Ph III) | Received FDA and EMA approval in 2018 |
| | | | NCT01961921 (Ph II) NCT01960348 (Ph III) | |
| | | | 2019 additions: | |
| | | | 11 total studies | |
| Liposomes (other) | | | |
| CAL02 (Combioxin SA) | Sphingomyelin and cholesterol liposomes for toxin neutralization | Pneumonia | 2016: NCT02583373 (Ph I): Completed | 0 new trials |
| | | | 2019 additions: | 1 trial completed |
| | | | | |
| Nanocort (Enceladus in collaboration with sun pharma global) | Liposomal prednisolone (PEGylated) | Rheumatoid arthritis and hemodialysis fistula maturation | 2016: NCT02495662 (Ph II): Terminated (slow inclusion) NCT02534896 (Ph III): Terminated | 0 new trials |
| | | | 2019 additions: | 2 trials terminated |
| | | | | |
| RGI-2001 (Regimmune) | Liposomal formulation of α-GalCer | Mitigating graft versus host disease following stem cell transplant | 2016: NCT01379209 (Ph I/II): Unknown NCT04014790 (Ph II): Not yet recruiting | 1 new trial |
| | | | 2019 additions: | |
| | | | | |
| Sonazoid | F-butane encapsulated in a lipid shell | Contrast enhanced ultrasound for imaging hepatocellular carcinoma, skeletal muscle perfusion, or for estimating portal hypertension | 2016: NCT00822991 (not provided): Recruiting NCT02398266 (Ph II): Unknown NCT02188901 (not provided): Completed NCT02489045 (Ph IV): Recruiting | 0 new trials |
| | | | 2019 additions: | |
| | | | | |
| Polymeric and micelles (cancer) | | | |
| AZD2811 (AstraZeneca with BIND Therapeutics) | Aurora B kinase inhibitor in BIND therapeutics polymer particle accurin platform | Advanced solid tumors | 2016: NCT02579226 (Ph I): Recruiting NCT03366675 (Ph II): Terminated (early detection of the purpose of the study) NCT03217838 (Ph I): New, recruiting | 2 new trials (1 terminated) |

(Continues)
| Name (company) | Particle type/drug | Investigated application/indication | ClinicalTrials.gov identifiers (phase) | Updates since 2016 |
|----------------|--------------------|-------------------------------------|----------------------------------------|-------------------|
| BIND-014 (BIND Therapeutics) | PSMA targeted (via ACUPA) docetaxel PEG-PLGA or PLA–PEG particle | Prostate, metastatic, non-small cell lung, cervical, head and neck, or KRAS positive lung cancers | 2016: NCT02479178 (Ph II): Terminated NCT02283320 (Ph II): Completed NCT01812746 (Ph II): Completed NCT021792479 (Ph II): Completed NCT01300533 (Ph I): Completed | 0 new trials 4 trials completed Pfizer purchased BIND Therapeutics' bankruptcy assets July 2016.  
31 |
| Cynviloq IG-001 (Sorrento) | Paclitaxel polymeric micelle nanoparticle | Breast cancer | 2016: NCT02064829 (not provided): Completed | 0 new trials 1 trial completed |
| Genexol-PM (Samyang Biopharmaceuticals) | Paclitaxel polymeric micelle nanoparticle | Head and neck or breast cancer | 2016: NCT01689194 (Ph II): Unknown NCT02263495 (Ph II): Completed NCT00912639 (Ph IV): Unknown 2019 additions: NCT02739633 (Ph II): Recruiting NCT03008512 (Ph I): Recruiting | 2 new trials 1 trial completed 1 trial changed to unknown status |
| NC-6004 Nanoplatin (Nanocarrier) | Polyamino acid, PEG, and cisplatin derivative micellar nanoparticle | Advanced solid tumors, lung, biliary, bladder, or pancreatic cancers | 2016: NCT02240238 (Ph I/II): Active, not recruiting NCT02043288 (Ph III): Unknown 2019 additions: NCT03771820 (Ph II): Not yet recruiting NCT03109158 (Ph I): Completed NCT02817113 (Ph I): Unknown | 3 new trials 1 trial changed to unknown status |
| NC-4016 DACH-Platin micelle (Nanocarrier) | Polyamino acid, PEG, and oxaliplatin micellar nanoparticle | Advanced solid tumors or lymphomas | 2016: NCT01999491 (Ph I): Completed | 0 new trials |
| NK105 (Nippon Kayaku) | Paclitaxel micelle | Breast cancer | 2016: NCT01644890 (Ph III): Completed | 0 new trials 1 trial completed |
| Docetaxel-PM DOPNP201 (Samyang Biopharmaceuticals) | Docetaxel micelle | Head and neck cancer and advanced solid tumors | 2016: NCT02639858 (Ph II): Recruiting NCT02274610 (Ph I): Completed 2019 additions: NCT03585673 (Ph II): Recruiting | 1 new trial 1 trial completed |
| CriPec (Cristal Therapeutics) | Docetaxel micelles | Solid tumors, ovarian cancer | 2016: NCT02442531 (Ph I): Completed 2019 additions: NCT03712423 (Ph I): Recruiting NCT03742713 (Ph II): Recruiting | 2 new trials 1 trial completed |
| CRLX101 (Cerulean) | Cycloexstrin-based nanoparticle-camptothecin conjugate | Ovarian, renal cell, small cell lung, or rectal cancers | 2016: NCT02187302 (Ph II): Completed | 9 new trials (1 terminated, 1 withdrawn, 5 completed) 2 previous trials completed |
TABLE 2 (Continued)

| Name (company) | Particle type/drug | Investigated application/indication | ClinicalTrials.gov identifiers (phase) | Updates since 2016 |
|----------------|-------------------|-------------------------------------|----------------------------------------|-------------------|
| CRLX301 (Cerulan) | Cyclodextrin based nanoparticle-docetaxel conjugate | Dose escalation study in advanced solid tumors | NCT02010567 (Ph I/II): Active, not recruiting | 2 previous trials terminated |
| | | | NCT02389985 (Ph I): Terminated (company decision) | NCT01803269 (Ph II): Terminated (due to lack of activity and slow accrual) |
| | | | NCT01652079 (Ph II): Completed 2019 additions: | |
| | | | NCT02769962 (Ph I): Recruiting NCT03531827 (Ph II): Recruiting | |
| | | | NCT02648711 (Ph I): Terminated (company decision) | |
| | | | NCT01380769 (Ph II): Completed NCT01612546 (Ph II): Completed NCT00333502 (Ph II): Completed NCT01625936 (Ph I): Completed NCT00753740 (Ph II): Withdrawn (poor trial recruitment) NCT00163319 (Ph III): Completed | |
| | | | 2016: NCT02380677 (Ph I/II): Terminated (company decision) | 0 new trials |
| | | | | 1 trial terminated |
| Polymeric and micelles (other) | RadProtect (Original BioMedicals) | PEG, iron, and amifostine micelle | Dose escalation and safety for acute radiation syndrome | 0 new trials |
| | | Transferrin-mediated chelation for amifostine release | NCT02587442 (Ph I): Unknown | |
| Albumin-bound (cancer) | ABI-009 (Aadi with Celgene) | Albumin bound rapamycin | Bladder cancer, PEComa, or pulmonary arterial hypertension | 12 new trials (2 completed) |
| | | | NCT0209332 (Ph I/II): Recruiting NCT02587325 (Ph I): Recruiting NCT02494570 (Ph II): Active not recruiting 2019 additions: NCT03747328 (Ph II): Not yet recruiting NCT03657420 (Ph I): Not yet recruiting NCT03670030 (Ph II): Recruiting NCT03646240 (Ph I): Recruiting NCT03190174 (Ph I): Recruiting NCT00635284 (Ph I): Completed NCT03817515: Expanded access status: Available | |
| | | | NCT03439462 (Ph II): Recruiting NCT03463265 (Ph II): Recruiting | |

(Continues)
**TABLE 2 (Continued)**

| Name (company) | Particle type/drug | Investigated application/indication | ClinicalTrials.gov identifiers (phase) | Updates since 2016 |
|----------------|--------------------|-------------------------------------|----------------------------------------|-------------------|
| ABI-011 (NantBioScience) | Albumin bound thiocolchicine analog (IDN 5405) | Solid tumors or lymphomas | 2016: NCT02582827 (Ph I): Recruiting | 0 new trials |
| Inorganic (cancer) | | | | |
| AuroLase (Nanospectra Biosciences) | PEG-coated silica-gold nanoshells for near infrared light facilitated thermal ablation | Thermal ablation of solid primary and/or metastatic lung tumors | 2016: NCT1679470 (not provided): Terminated 2019 additions: NCT02680535 (not provided): Recruiting NCT00848042 (not provided): Completed | 2 new trials (1 completed) 1 trial terminated |
| NBTXR3 PEP503 (Nanobiotix) | Hafnium oxide nanoparticles stimulated with external radiation to enhance tumor cell death via electron production | Locally advanced squamous cell carcinoma | 2016: NCT01946867 (Ph I): Unknown 2019 additions: NCT02771076 (Ph II): Unknown NCT02805894 (Ph III): Recruiting NCT03589393 (Ph III): Not yet recruiting NCT02379845 (Ph III): Active not recruiting NCT02901483 (Ph I): Recruiting NCT02465593 (Ph I): Recruiting | Received CE mark approval in 2019 6 new trials 1 trial changed to unknown status |
| Cornell Dots | Silica nanoparticles with a NIR fluorophore, PEG coating, and a $^{124}$I radiolabeled cRGDY targeting peptide | Imaging of melanoma and malignant brain tumors | 2016: NCT01266096 (not provided): Active, not recruiting 2019 additions: NCT03456518 (Ph I): Recruiting NCT02106598 (Ph II): Recruiting | 2 new trials |
| Magnablate | Iron nanoparticles | Thermal ablation for prostate cancer | 2016: NCT02033447 (Ph I): Completed | 0 new trials 1 trial completed |

Note: These trials are grouped by particle type and indication. Modified with permission from Reference 1. Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration.
| Name (company) | Particle type/drug | Investigated application/indication | Current ClinicalTrials.gov identifiers (phase) |
|----------------|--------------------|-------------------------------------|-----------------------------------------------|
| **Liposomes (cancer)** | | | |
| MM-310 (Merrimack Pharmaceuticals) | Nanoliposomal encapsulated docetaxel and functionalized with antibodies targeted to the EphA2 receptor | Solid tumors | NCT03076372 (Ph I): Recruiting |
| EGFR(V)-EDV-Dox (EnGeneIC) | Bacterially derived minicell encapsulating doxorubicin | Recurrent glioblastoma | NCT02766699 (Ph I): Recruiting |
| Alprostadil liposome (CSPC ZhongQi Pharmaceutical Technology) | Alprostadil liposome | Safety and tolerability | NCT03669562 (Ph I): Recruiting |
| Liposomal Annamycin (Moleculin Biotech) | Liposomal Annamycin | Acute myeloid leukemia | NCT03388749 (Ph II): Recruiting; NCT03415039 (Ph II): Recruiting |
| FF-10831 (Fujifilm Pharmaceuticals) | Liposomal Gemcitabine | Advanced solid tumors | NCT03440450 (Ph I): Recruiting |
| Anti-EGFR-IL-dox (Swiss Group for Clinical Cancer Research; University Hospital, Basel, Switzerland) | Doxorubicin-loaded anti-EGFR immunoliposomes | Advanced triple negative EGFR positive breast cancer High grade gliomas | NCT02833766 (Ph II): Recruiting; NCT03603379 (Ph I): Recruiting |
| TLD-1/Talidox (InnoMedica) | A new formulation of liposomal doxorubicin | Advanced solid tumors | NCT03387917 (Ph I): Recruiting |
| NC-6300 (NanoCarrier) | Micelle encapsulated epirubicin | Advanced solid tumors or soft tissue sarcoma | NCT03168061 (Ph II): Recruiting |
| **Liposomes (gene therapy: Cancer)** | | | |
| MRT5201 (Translate Bio) | mRNA encapsulated in PEGylated liposomes | Ornithine transcarbamylase deficiency | NCT03767270 (Ph I): Not yet recruiting |
| Lipo-MERIT (Biontech RNA Pharmaceuticals) | Four naked ribonucleic acid (RNA)-drug products formulated with liposomes | Cancer vaccine for advanced melanoma | NCT02410733 (Ph I): Recruiting |
| **Liposomes (immunotherapy: Cancer)** | | | |
| IVAC_W_bre1_uID | Patient-specific liposome (specificity for antigen-expression on a patient’s tumor) complexed RNA | Triple negative breast cancer | NCT02316457 (Ph I): Recruiting |
| **Liposomes (gene therapy: Vaccine)** | | | |
| mRNA-1944 (Moderna) | Two mRNAs that encode heavy and light chains of anti-Chikungunya antibody formulated in Moderna’s proprietary lipid nanoparticle technology | Safety, tolerability, pharmacokinetics and pharmacodynamics towards the prevention of Chikungunya virus infection | NCT03829384 (Ph I): Recruiting |
| **Micelles (cancer)** | | | |
| MTL-CEBPA (Mina alpha) | Double stranded RNA formulated into SMARTICLES amphoteric liposomes | Advanced liver cancer | NCT02716012 (Ph I): Recruiting |

(Continues)
Of particular note, CRLX101, a cyclodextrin-based nanoparticle-camptothecin conjugate, began nine new trials and ABI-009, albumin bound rapamycin, began 12 new trials. Table 2 summarizes these findings and additionally provides technical and clinical updates, when publicly available, for these clinically investigated nanoparticles.

### NEW NANOPARTICLE TRIALS

Since 2016, our search revealed 18 new nanoparticles to have entered clinical trials. Of these 18 nanoparticles, 12 are liposomes and 17 are indicated for cancer (15 being for treatment and 2 for imaging). The lone non-cancer indication is mRNA-1944, which are two mRNAs encoding heavy and light chains of anti-Chikungunya antibody formulated in lipid nanoparticles, toward the prevention of Chikungunya virus infection. Table 3 summarizes these findings. It should be noted that other clinical trials investigating nanoparticles for the delivery of mRNA exist but since they are predominately delivered through intradermal or other routes of administration they will not be covered here. We point the reader to a recent review on mRNA delivery strategies where current clinical trials and delivery vehicles are a primary focus.19

### CONCLUSIONS

Nanoparticle drug delivery systems offer many advantages over their free drug counterparts, can fundamentally change how therapeutics are delivered, and also enable the development of novel treatment modalities. This is demonstrated by the recent approvals of Patisiran/ONPATTRO (the first FDA approved RNAi therapeutic), VYXEOS (a nanoparticle capable of delivering synergistic ratios of two drugs), and NBTXR3/Hensify (a radio-enhancing nanoparticle that synergizes with standard of care radiation oncology treatments). On the other hand, nanoparticles also face unique challenges related to their biological, technological, and clinical limitations that must be addressed to achieve consistent clinical impact. These advantages and challenges were discussed in-depth in the 2016 review1 and in many other reviews.20-25 With the increasing numbers of nanoparticle clinical trials, including nanoparticle technologies that were in trials at the time of our previous article (Table 2) and those that have entered the clinic since then (Table 3), the interest and pursuit of successful nanoparticle technologies continues. Taken together with these recent approvals, the field of nanoparticle drug delivery continues to make breakthroughs that improve human health.

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