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REVIEW **Open Access**

Nanomedicine review: clinical developments in liposomal applications

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Abstract

Background: In recent years, disease treatment has evolved strategies that require increase in pharmaceutical agent's efficacy and selectivity while decreasing their toxicity in normal tissues. These requirements have led to the development of nanoscale liposome systems for drug release. This review focuses on lipid features, pharmacological properties of liposomal formulations and the clinical studies of their application.

Main body: Several lipids are available, but their properties could affect pharmacological or clinical efficiency of drug formulations. Many liposomal formulations have been developed and are currently on the market. Proper selection of lipid is essential for the pharmacological effect to be improved. Most of the formulations use mainly zwitterionic, cationic or anionic lipids, PEG and/or cholesterol, which have different effects on stability, pharmacokinetics and delivery of the drug formulation. Clinical trials have shown that liposomes are pharmacologically and pharmacokinetically more efficient than drug-alone formulations in treating acute myeloid leukemia, hepatitis A, pain management, ovary, gastric breast and lung cancer, among others.

Conclusion: Liposomal formulations are less toxic than drugs alone and have better pharmacological parameters. Although they seem to be the first choice for drug delivery systems for various diseases, further research about dosage regimen regarding dose and time needs to be carried out.

Keywords: Drug delivery systems, Nanoscale, Liposomal nanotechnology, Recent clinical trials

Background

Many conventional drugs exhibit poor pharmacokinetics, limited bioavailability and a high toxicity, all of which restrain their use. To overcome these issues and improve the therapeutic indexes of the drug, the emergent fields of nanotechnology and nanomedicine have made significant progress in detection, diagnosis and treatment of several diseases at clinical level (Li et al. 2014; Yingchoncharoen et al. 2016; Signorell et al. 2018). In fact, thanks to nanoparticles and liposomes, it has been possible to decrease the toxicity and improve the pharmacokinetics parameters, such as distribution, increased circulation time, targeted controlled release, increased intracellular concentration, and enhanced solubility and stability of drugs in the organism (Medina-Alarcón et al. 2017; Ventola 2017). All these advantages have been reached by using drug delivery systems with 1–100 nm diameter nanoparticles, where a large surface leads to an increase in cellular interactions and multiple alterations of surface properties (Ud Din et al. 2017; Senapati et al. 2018; Gonda et al. 2019). Moreover, by co-delivering multiple drugs, treatments with NPs have also facilitated synergistic therapies and avoided drug resistance (Casals et al. 2017). For example, in CPX-351, a liposomal formulation, cytarabine and daunorubicin are packed together at a 5:1 molar ratio within 100-nm-diameter liposomes (Gergis et al. 2013; Cortes et al. 2015; Lancet et al. 2014).

Liposomes were discovered by Alec D. Bangham in 1965 (Allen and Cullis 2013) and were the first approved class of therapeutic NPs for cancer treatment. They still represent a large proportion of clinical-stage nanotherapeutics (Shi et al. 2017; Bourquin et al. 2018) due to their biodegradable, biocompatible, non-toxic, and non-immunogenic composition (Bozzuto and Molinari 2015; Zamani et al. 2018). The amphiphilic phospholipid bilayer of liposomes has close resemblance to the mammalian cell membrane, enabling efficient interactions between liposomes and cell membrane and subsequently effective cellular uptake (Gonda et al. 2019). In addition, liposomes may be added with ligands to increase efficiency and specifically target damaged cells, thus improving liposome pharmacokinetics and their ability to pass through target membranes, reaching high concentrations inside cells while reducing toxicity and enhancing treatment efficacy (Li et al. 2014; Ud Din et al. 2017; Zamani et al. 2018; Hussain et al. 2017; Lombardo et al. 2016; Fouladi et al. 2017; Maranhão et al. 2017; Miller et al. 2016). For instance, MM-302, an antibody–liposomal doxorubicin conjugate, specifically targets HER2 overexpressing cells (Miller et al. 2016). Liposome encapsulation may reduce drug clearance by the immune and renal systems, extending circulation time in the blood and increasing their availability (Bulbake et al. 2017). Another advantage of liposomes in their thermosensitive feature, i.e., an increase of temperature (to 40–41 °C) causes packing changes in the bilayer favoring the release of the encapsulated drug. These thermo-devices favor the specific release of a large amount of the cytotoxic agent to a heat-treated tumor site when using an external heat source, avoiding damage to the surrounding normal tissue (Nardecchia et al. 2019).

The first nanosized liposomal product to obtain regulatory approval in the US was Doxil®, which was approved in 1995 for the treatment of ovarian cancer and AIDS-related Kaposi's sarcoma. Later, in 1996 the US FDA approved DaunoXome®, manufactured by NeXstar Pharmaceuticals, for the delivery of daunorubicin to treat advanced HIV-associated Kaposi sarcoma. Subsequently, more products have become available for the treatment of cancer and different diseases (Bulbake et al. 2017).

The most commonly investigated nanoparticles are phospholipids-based carriers, micelles, polymeric nanoparticles based on poly(lactide-coglycolide) (PLGA), polybutylcyanoacrylate, poly(isohexyl cyanoacrylate), poly(amine-co-ester), chitosan nanoparticles (Chaudhuri and Straubinger 2019; van Rijt et al. 2014), cellulose nanocrystals systems (Mohanta et al. 2019), viral vectors (Gomes et al. 2017), self-assemble proteins (Colton et al. 2014), carbon nanotubes (Kaur et al. 2019), dendrimers (Hudson 2001), core–shell and metallic NPs (Wu et al. 2008), Fig. 1. However, for nanomaterial-based therapeutics, liposomes have been the most successful formulation for clinical application to date (Gonda et al. 2019), and the sterically stabilized liposomal formulations

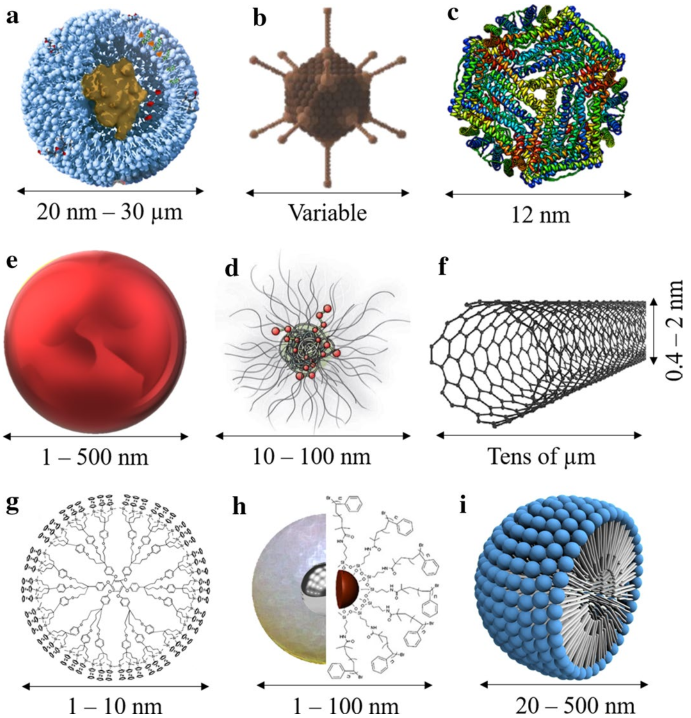

Fig. 1 Nanoparticles commonly used as drug delivery systems. **a** Liposomes: biomimetic structure, encapsulate hydrophobic and hydrophilic drugs. Schematic image done with Adobe® Photoshop® CS6. **b** Viral vector: schematic representation of viral adenovirus. From Gomes et al. (2017). **c** Self-assembled proteins: ribbon diagram representing the structure of the ferritin protein. From Colton et al. (2014). **d** Polymeric nanoparticle [image from van Rijt et al. (2014)]. **e** Metallic nanoparticle: magnetic and non-immunogenic sphere, rod or cage nanoparticles (schematic image done with Paint 3D®). **f** Single-walled carbon nanotube: efficient drug-loading capacity because of ultrahigh surface area. Diameter range from 0.4 to 2 nm for SWCN and 2–100 nm for MWCN. From Kaur et al. (2019). **g** Astruc's 54-ferrocene dendrimer. From Hudson (2001). **h** Polystyrene-coated magnetic NPs with core/shell structure. Modified from Wu et al. (2008). **i** Micelle formulation as drug delivery system. Public domain

currently dominate the clinical landscape with FDA-approved products (Chaudhuri and Straubinger 2019). The success of liposomes in clinics is based on their versatility and their characteristics, such as their structural similarity to mammalian cell membranes and their capability to encapsulate either hydrophobic or hydrophilic drugs (Gonda et al. 2019), among the other features described above.

In recent years, many clinical trials using liposome as a drug delivery system to treat several diseases have been published. This review discusses the emerging research and clinical developments in liposome therapeutics, as well anoverview of the liposome characteristics and the distribution of liposomal clinical trials worldwide.

Liposomes: an overview

Liposomes are bilayer spherical vesicles composed by phospholipids and cholesterol that in water create at least one lipid bilayer surrounding an aqueous core, which may encapsulate both hydrophilic drugs (e.g., Doxil®, encapsulated doxorubicin in the aqueous core) and hydrophobic compounds (e.g., AmBisome®, trapped amphotericin B) immersed in the lamellae by Van der Waals forces (Senapati et al. 2018; Gonda et al. 2019; Gao et al. 2018), see Fig. 2.

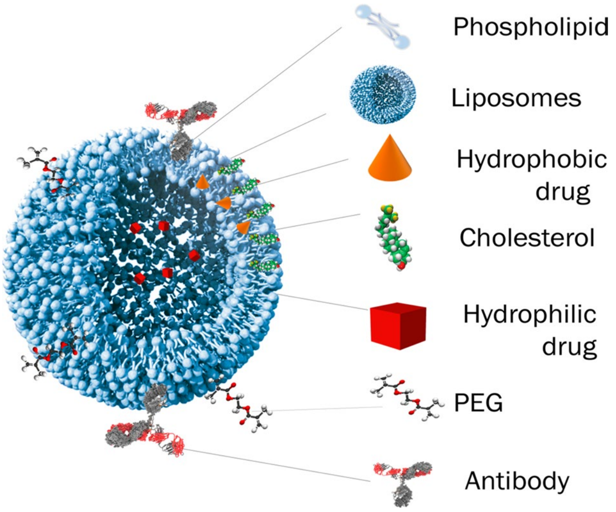

Fig. 2 Schematic structure of a stable antibody–liposome encapsulating hydrophobic and hydrophilic drugs. Hydrophilic drugs like doxorubicin can be encapsulated in the aqueous compartment. Hydrophobic drugs like amphotericin B, paclitaxel, and docetaxel, can be encapsulated in the non-polar compartment. Liposome size varies between 20 nm to several hundred microns. Pharmacokinetics depends directly of the size (schematic image done with Adobe® Photoshop® CS6)

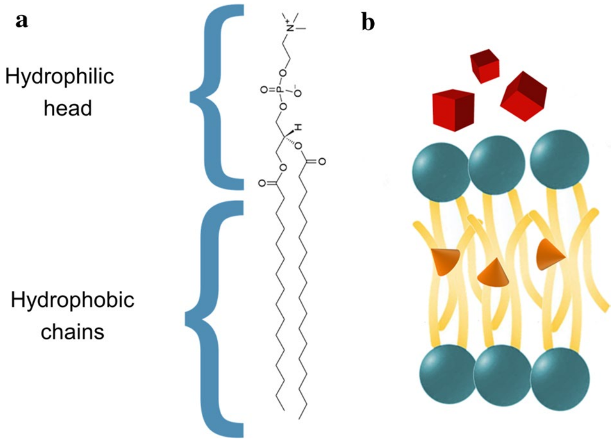

Fig. 3 **a** Chemical structure of hydrogenated soybean phosphatidylcholine (HSPC), a phospholipid used in Doxil®, the first approved liposomal nanoformulation. Brackets indicate the polar and non-polar portions of the phospholipid. **b** Scheme of the membrane permeability of liposomes with unsaturated phospholipids. Blue figures represent charged compounds while orange ones have no charge: the circles represent the polar head of phospholipids; bars, the fatty acid chains; hexagons, hydrophobic drugs; and triangles, the hydrophilic drugs (schematic image done with Adobe® Photoshop® CS6)

Phospholipids are amphiphilic lipids that consist of a glycerol molecule bound to a phosphate group (PO_4^{2-}) and to two fatty acid chains that may be saturated or unsaturated (Pinot et al. 2014). The phosphate has also an ester bound with an organic molecule, e.g., choline or ethanolamine (Monteiro et al. 2014) (Fig. 3). Phospholipids are key components and provide specific characteristics to liposomes, i.e., the way of encapsulating the compounds and the functionalization into the organism (Hussain et al. 2017). Since phospholipids are the main biological cell membrane components, both liposomal and cell membranes can coexist during the release mechanism (Rothfield 1971).

As we seen, liposome properties are affected not only by its composition, but also by size, surface charge, number of lamellae, rigidity of the bilayer, surface modification and method of preparation (Olusanya et al. 2018). For instance, the ammonium sulfate method would render a high concentration of amphipathic drugs, such as doxorubicin, similar to the pH gradient method for vincristine (Senapati et al. 2018). Another important parameter for preparing self-aggregating amphiphiles such as surfactants, lipids and liposomes, is the critical micelle concentration (CMC), i.e., the relatively narrow concentration range over which amphiphile dispersions show an abrupt change in physical properties. At concentrations below the CMC, the phospholipids are in monomeric form; at the CMC, aggregation of the molecules produce micelles, and the physical properties of the dispersion show changes. The CMC values depend on intrinsic factors such as structure of the hydrophobic and hydrophilic parts of the amphiphile molecule and external factors such as medium temperature and composition (ionic strength, dielectric constant, pH) (Priev et al. 2002). For the purpose of this review, only the physicochemical parameters of phospholipids affecting liposomes characteristics will be discussed.

The transition temperature of phospholipids (T_C) (the temperature at which phospholipids shift from gel to liquid crystalline phase), is one of the main parameters in the manufacture of liposomes (Zamani et al. 2018). T_C depends on the length of the fatty acid chains, their degree of saturation, charge and head group species, as shown in Table 1 (Li et al. 2014; Hussain et al. 2017; Monteiro et al. 2014). T_C determines the fluidity and permeability of the liposome bilayer. In fact, at temperatures lower than T_C the phospholipids are in gel phase, which has low fluidity and low permeability. In contrast, at temperatures higher than T_C, phospholipids are in liquid-crystalline phase, having greater fluidity and permeability but low permeability to certain particles. Also, as shown in Table 1, the longer the chain the higher the T_C is. The T_C decreases, the more double bonds. Thus, when compared at certain temperatures, bilayers with long and saturated hydrocarbon chains are more rigid and less permeable than bilayers with shorter and unsaturated chains (Monteiro et al. 2014; Lin and Gu 2014; Murthy et al. 2016; Kraft et al. 2014) (Fig. 2). The transition temperature and lipid composition influence the curvature of liposomes, i.e., a liposome whose diameter varies between 100 and 200 nm can be appreciated as a sphere whose curvature will be defined by a homogeneous surface perimeter. However, the surface of the liposome can actually present a ripple phase depending mainly on the lipid composition and temperature that are directly related to the aggregate state of the liposome. Therefore, the ripple phase can be considered as domains of ordered phases of liquid crystalline phase with the gel phase. Other compound that can also modify the ripple phase is cholesterol, which directly affects the fluidity of the liposome bilayer increasing fluidity in the core of the bilayer, but increasing viscosity close to phospholipid headgroups. Thus, cholesterol produces similar phases to liquid crystalline and gel phases, the so-called disordered and ordered phases. Further studies on membrane fluidity of the liposomal dosage forms and their impact on drug delivery may improve formulations and their efficacy. Therefore, the phase transition behavior of the lipid bilayers has been exploited to improve liposome aggregation, curvature of membrane (ripple phase), lipid transfer and drug release. Proper lipid

Table 1 Phospholipids characteristics

Phospholipid	Abbreviation	C:U	T_C (° C)	Charge[a]	Advantages	Drawbacks
Hydrogenated soy phosphatidylcholine	HSPC	16–18:0	52	Neutral	Important role in membrane fusion, combined cationic lipids	Low cellular incorporation rate Low cytotoxicity (Kolašinac et al. 2018; Zhao and Song Zhuang 2011)
Dilauroyl phosphatidylcholine	DLPC	12:0	− 2			
Dimyristoyl phosphatidylcholine	DMPC	14:0	24			
Dipalmitoyl phosphatidylcholine	DPPC	16:0	41			
Distearoyl phosphatidylcholine	DSPC	18:0	55			
Dioleoyl phosphatidylcholine	DOPC	18:1c9	− 17			
Dilauroyl phosphatidylethanolamine	DLPE	12:0	29			
Dimyristoyl phosphatidylethanolamine	DMPE	14:0	50			
Dipalmitoyl phosphatidylethanolamine	DPPE	16:0	60			
Distearoyl phosphatidylethanolamine	DSPE	18:0	74			
Dioleoyl phosphatidylethanolamine	DOPE	18:1	− 16			
Dilauroyl phosphatidylglycerol	DLPG	12:0	− 3	Negative	Prevent the aggregation of liposomes due to electrostatic repulsion Laterally assemble into nanoclusters and this occurs in a charge-dependent manner Accumulation in tumor Adsorptive endocytosis and enhance stability	Rapidly removed from circulation by the reticuloendothelial system (RES) Negatively charged liposomes do not significantly adsorb protein (Tsermentseli et al. 2018; Ma et al. 2017)
Dimyristoyl phosphatidylglycerol	DMPG	14:0	23			
Dipalmitoyl phosphatidylglycerol	DPPG	16:0	41			
Distearoyl phosphatidylglycerol	DSPG	18:0	55			
Dioleoyl phosphatidylglycerol	DOPG	18:1	− 18			
Dilauroyl phosphatidylserine	DLPS	12:0				
Dimyristoyl phosphatidylserine	DMPS	14:0	35			
Dipalmitoyl phosphatidylserine	DPPS	16:0	51			
Distearoyl phosphatidylserine	DSPS	18:0	68			
Dioleoyl phosphatidylserine	DOPS	18:1	− 11			
Dilauroyl phosphatidic acid	DLPA	12:0	31			
Dimyristoyl phosphatidic acid	DMPA	14:0	52			
Dipalmitoyl phosphatidic acid	DPPA	16:0	65			
Distearoyl phosphatidic acid	DSPA	18:0	75			
Dioleoyl phosphatidic acid	DOPA	18:1	− 4			

Table 1 (continued)

Phospholipid	Abbreviation	C:U	T_C (° C)	Charge[a]	Advantages	Drawbacks
Diacyl dimethylammonium-propane	DAP			Positive	Strong gene transfer ability The head group helps to attract the liposome to the negatively charged cell membrane, thus increasing the cell incorporation rate Good protein adsorption, through adsorptive endocytosis	High cytotoxicity Low efficiency Positively charged lipids are not approved by FDA for clinical use (Li et al. 2019; Honary and Zahir 2013)
Dioleoyl trimethylammonium-propane	DOTAP	18:1	< 5			

C:U number of carbons:number of unsaturation, T_C transition temperature

[a] At pH 7

compositions preserve the bilayer structure, as well as physical properties at body temperature (37 °C), which are key considerations for liposome design (Rühling et al. 2017; Vallejo et al. 2007).

Modifications of polar and non-polar regions of natural phospholipids have allowed researchers to create a wide variety of synthetic phospholipids, which have proved to be more stable (Monteiro et al. 2014; Agassandian and Mallampalli 2013). The surface charge in liposomes depends on the phospholipid headgroup, and it can be negative, neutral or positive. This may alter liposome stability, pharmacokinetics, biodistribution and cellular uptake, see Table 1. Negatively charged phospholipids, such as DMPG or DOPS, are recognized by macrophages and enter the cell via endocytosis at a faster rate than neutral phospholipids, like HSPC and DOPE, resulting in a shorter circulation time. A small negative charge may stabilize neutral liposomes increasing the electrostatic repulsive forces, affecting the aggregation-dependent phagocytic uptake mechanism (Olusanya et al. 2018; Kraft et al. 2014). On the other hand, cationic liposomes interact with plasma proteins enhancing the uptake by the phagocytic system that promotes clearance by the lung, liver or spleen. Moreover, uptake of liposomes with a positive charge appears to be much higher than negative liposomes. Thus, negatively charged lipid liposomes are common to most FDA-approved liposome formulations (Bourquin et al. 2018; Zamani et al. 2018; Kraft et al. 2014; Merino et al. 2018).

Liposomes have a diameter ranging from 20 nm to more than several hundred micrometers, as shown in Table 2. Particle size affects their pharmacokinetics, tissue extravasation, tissue diffusion, hepatic uptake, kidney excretion, and clearance rate from the site of injection (Zamani et al. 2018; Gao et al. 2018; Olusanya et al. 2018; Kraft et al. 2014). Only liposomes of a mean diameter between 100 and 150 nm are able to enter fenestrated vessels in the liver endothelium, secondary lymphoid structures, or tumor microenvironments (Bourquin et al. 2018; Gao et al. 2018; Kraft et al. 2014). Only liposomes with such a diameter can easily escape from blood vessel capillaries that perfuse tissues, such as lung, heart, and kidney. On the other hand, particles less than 10 nm undergo renal filtration through the glomerular capillary wall and are not reabsorbed (Gao et al. 2018; Kraft et al. 2014; Merino et al. 2018). Furthermore, cell uptake is most relevant to liposomes of 100–150 nm diameter. The immune system phagocytosis is also important, since reduction of liposome diameter to 50 nm or below greatly reduces phagocytosis clearance (Kraft et al. 2014; Merino et al. 2018). Thus, liposomes within 50–100 nm, such as DaunoXome, avoid phagocytosis and have long blood circulation time (Olusanya et al. 2018; Kraft et al. 2014). Therefore, the optimal range-size is between 80 and 150 nm (Olusanya et al. 2018; Kraft et al. 2014; Merino et al. 2018; Riaz et al. 2018). It has been demonstrated that larger liposomes can persist longer in the injection site (Bourquin et al. 2018), such as Exparel® and DepoDur™, which are used for pain control.

Cholesterol has an important role in the preparation and chemical properties of liposomes. This molecule accommodates itself along with the phospholipid chain, with its hydroxyl group close to the hydrophilic region and its aromatic rings parallel to the fatty acid chain within the bilayer (Fig. 1) due to hydrophobic interactions. Fluidity and water permeability decrease because of the increase in mechanical rigidity caused by the dense rings (Yingchoncharoen et al. 2016; Monteiro et al. 2014; Sinatra et al. 2014).

Table 2 Liposomal formulation present in clinical trials

LF	Active agent	Composition	Size (nm)	Indication	Status	References
ONPATTRO®	Patisiran (siRNA)	DLin-MC3-DMA, Cholesterol, DSPC, PEG_{2000}-C-DMG	–	Hereditary transthyretin amyloidosis	Approved by FDA in August 2018	(Anselmo and Mitragotri 2019)
CPX-351 (Vyxeos™)	Daunorubicin + cytarabine	DSPC, DSPG, cholesterol (7:2:1) daunorubicin, cytarabine 5:1	100	Acute myeloid leukemia	Approved by FDA in 2017	(Ventola 2017; Lancet et al. 2014; Kaspers et al. 2013; Inman 2017)
Onivyde®	Irinotecan + fluorouracil + folinic acid	PEGylated liposome	80–140	Pancreatic adenocarcinoma	Approved by FDA in 2015	(Pelzer et al. 2017; Tran et al. 2017)
LEP-ETU	Paclitaxel	DOPC, cholesterol, cardiolipin (90:5:5) Lipid, PTX (33:1)	150	Ovarian cancer	Not approved by FDA	(Bozzuto and Molinari 2015; Bulbake et al. 2017; Slingerland et al. 2017)
Marqibo®	Vincristine	Sphingomyelin, Cholesterol (60:40)	100	Non-Hodgkin's lymphoma and leukemia	Approved by FDA in August 2012	(Bozzuto and Molinari 2015; Silverman and Deitcher 2013)
Exparel®	Bupivacaine	DEPC, DPPG, cholesterol, tricaprylin	3000–30,000	Pain management	Approved by FDA in 2011	(Bulbake et al. 2017; Yeung et al. 2018)
Mepact®	Mifamurtide	Non-PEGylated liposome, Muramyl tripeptide PE	–	Osteosarcoma	FDA denied approval 2007. This medicine is authorized for use in the European Union	(Shi et al. 2017; Sinatra et al. 2014)
Inflexal V®	Inactivated hemagglutinin of A or B influenza virus	DOPC, DOPE (75:25)	150	Influenza	Approved by European Medicines Agency (EMEA) in 2008	(Bulbake et al. 2017; Gasparini et al. 2013)
Genexol-PM	Paclitaxel	PEG–PLA polymeric micelle	20–50	Breast, lung and ovarian cancer	Approved in Korea and marketed in Europe in 2007	(Ahn et al. 2014; Tran et al. 2017)
Epaxal®	Inactivated hepatitis A virus (strain RGSB)	DOPC, DOPE (75:25)	150	Hepatitis A	Approved in 2006 and is currently used in Switzerland and Argentina	(Bulbake et al. 2017; Lim et al. 2014)
Lipusu®	Paclitaxel	72 g PC, 10.8 cholesterol in ethanol	400	Gastric, ovarian and lung cancer	Approved by FDA in 2005	(Xu et al. 2013; Ye et al. 2013)
DepoDur™	Morphine sulfate	Cholesterol, triolein, DOPC, DPPG (11:1:7:1)	17,000–23,000	Pain management	Approved by FDA in 2004	(Bulbake et al. 2017; Carvalho et al. 2007)
Lipo-Dox®	Doxorubicin	DSPC, cholesterol, PEG 2000-DSPE (56:39:5)	20	Breast and ovarian cancer	Approved by FDA in 2012	(Bozzuto and Molinari 2015; Smith et al. 2016)
Myocet®	Doxorubicin + cyclophosphamide	EPC, cholesterol (55:45)	190	Metastatic breast cancer	Approved by EMEA in 2000	(Bozzuto and Molinari 2015; Eitan et al. 2014)
Visudyne®	Verteporphin	EPG, DMPC (3:5)	100	Ocular histoplasmosis	Approved by FDA in 2000	(Bozzuto and Molinari 2015; Jain et al. 2016)

Table 2 (continued)

LF	Active agent	Composition	Size (nm)	Indication	Status	References
Depocyt®	Cytarabine	Cholesterol, triolein, DOPC, DPPG (11:1:7:1)	20	Neoplastic meningitis	FDA status: discontinued	(Bozzuto and Molinari 2015; Phuphanich et al. 2006)
Abelcet®	Amphotericin B	DMPC, DMPG (7:3)	600–11,000	Invasive fungal infection	Approval FDA in 1995	(Bozzuto and Molinari 2015; Bulbake et al. 2017)
Amphotec®	Amphotericin B	Cholesteryl sulfate	–		FDA status: discontinued	(Clemons and Stevens 2004)
DaunoXome®	Daunorubicin	DSPC, cholesterol, daunorubicin (10:5:1)	45–80	Leukemia	FDA status: discontinued	(Olusanya et al. 2018; Kraft et al. 2014; Kaspers et al. 2013)
Doxil®	Doxorubicin	HSPC, cholesterol, PEG 2000-DSPE (56:39:5)	100	Kaposi's sarcoma	Approved by FDA in 1995	(Bozzuto and Molinari 2015; Kohli et al. 2014)
AmBisome®	Amphotericin B	HSPC, DSPG, cholesterol, amphotericin B (2:0.8:1:0.4)	45–80	Invasive fungal infection	Approved by FDA in 1997	(Bozzuto and Molinari 2015; Bulbake et al. 2017)
Thermodox®	Doxorubicin	DPPC, MSPC, PEG 2000-DSPE (90:10:14)	175	Hepatocellular carcinoma, solid tumors	Not approved	(Bozzuto and Molinari 2015; Lombardo et al. 2016; Chang and Yeh 2012)
EndoTAG®	Paclitaxel	DOTAP, DOPC, PTX (50:47:3)	180–200	Breast cancer	Not approved	(Bozzuto and Molinari 2015; Bulbake et al. 2017; Strieth et al. 2013)
MM-302	Doxorubicin	DSPE, HER2, PEG	75–110	Breast cancer	Not approved	(Miller et al. 2016)
PTX–LDE	Paclitaxel	135 mg cholesteryl oleate, 333 mg egg PC, 132 mg miglyol 812 N, 6 mg cholesterol, 60 mg PTX	1–1000	Epithelial ovarian carcinoma	Not approved	(Graziani et al. 2017; Jin et al. 2016)
Arikace®	Amikacin	DPPC, cholesterol (2:1)	≈ 300	Lung infections	Not approved	(Rose et al. 2014; Olivier et al. 2017)
MRX34	miR-34a	DOTAP, cholesterol	≈ 110	Advanced solid tumors and hematological malignances	Not approved	(Shi et al. 2017; Beg et al. 2016; Li et al. 2013)
Xemys	Myelin basic proteins	Egg PC, monomannosyl dioleoyl glycerol, α-tocopherol and lactose	–	Multiple sclerosis	Not approved	(Jr et al. 2016)

LF liposomal formulation, *siRNA* small interfering RNA, *DLin-MC3-DMA* (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino)butanoate, *PEG*$_{2000}$*-C-DMG* α-(30-{[1,2-di(myristyloxy)propanoxy] carbonylamino}propyl)-ω-methoxy polyoxyethylene, *DSPC* distearoyl phosphatidylcholine, *DSPG* distearoyl phosphatidylglycerol, *DOPC* dioleoyl phosphatidylcholine, *DPPG* dipalmitoyl phosphatidylglycerol, *DOPE* dioleoyl phosphatidylethanolamine, *PC* phosphatidylcholine, *PEG 2000-DSPE* polyethylene glycol 2000-distearoyl phosphatidylethanolamine, *EPC* ethyl phosphatidylcholine, *EPG* ethyl phosphatidylglycerol, *DMPC* dimyristoyl phosphatidylcholine, *DMPG* dimyristoyl phosphatidylglycerol, *HSPC* hydrogenated soybean phosphatidylcholine, *MSPC* monostearoyl phosphatidylcholine, *DOTAP* dioleoyl trimethylammonium-propane, *HER2* human epidermal growth factor receptor 2, *DPPC* dipalmitoyl phosphatidylcholine, *PTX* paclitaxel, *IU* investigational use

Various clinically approved liposomal formulations incorporating cholesterol are already in the market (Table 2). Cholesterol acts as a cell membrane stabilizer: in its absence, liposomes often interact with proteins, including albumin, transferrin, macroglobulin and high-density lipoproteins. Such interaction destabilizes the structure of the liposomes and consequently decreases their capacity as drug delivery systems (Yingchoncharoen et al. 2016; Maranhão et al. 2017; Lu et al. 2013). Cholesterol is also crucial for the structural stability of liposome membranes against intestinal environment stress (Olusanya et al. 2018; Kraft et al. 2014).

Although their biocompatibility, biodegradability, and ability to encapsulate hydrophilic, hydrophobic, and amphiphilic compounds are important advantages, one of the major drawbacks of conventional liposomes is their rapid clearance from the bloodstream (Senapati et al. 2018; Gangadaran et al. 2018), which shortens the blood circulation time. To overcome this drawback, several approaches have been used. Small fractions of hydrophilic polymers, such as polyethylene glycol (PEG), are used as surface coatings in order to extend blood circulation half-life from few minutes (conventional liposomes) to several hours (stealth liposomes). In fact, PEGylated liposomes with a mean 100–150 nm diameter reduce the interaction of liposomes with plasma proteins such as opsonins (Yingchoncharoen et al. 2016; Senapati et al. 2018; Bourquin et al. 2018; Kraft et al. 2014; Lamichhane et al. 2018). Thus, PEG prevents liposome opsonization and consumption by the reticuloendothelial system (RES) since it entangles 2–3 molecules of water per oxyethylene unit, which may increase 5–10 times the apparent molecular weight. This improves solubility and decreases the aggregation and the immunogenicity of the drug, leading to 10 times longer circulation time and an increase of liposome accumulation in damaged tissues (Yingchoncharoen et al. 2016; Maranhão et al. 2017; Li et al. 2013). This PEG-technology has been successfully proven in Doxil® (Bulbake et al. 2017) and there are various clinically approved stealth and non-stealth liposomal formulations with or without cholesterol in the market (Table 2), as compared in the following section.

In summary, the properties of the membrane and general structure of liposomes depend on (a) the nature of the lipid, either natural or synthetic; (b) the phospholipid polar headgroup and its charge; (c) the length and degree of unsaturation of the fatty acids; (d) the T_C, the temperature before and after the liposome synthesis, and (e) the addition of other compounds to the membrane or surface of the liposome such as cholesterol, PEG, proteins, ligands and/or antibodies (Bozzuto and Molinari 2015; Maranhão et al. 2017; Sercombe et al. 2015). The manipulation and design of all the factors mentioned above make liposomes versatile and capable of a wide range of functions. This has made liposomes one the most explored and used release system to address different functions and specific purposes for the treatment of cancer and other diseases (Yingchoncharoen et al. 2016; Maranhão et al. 2017; Monteiro et al. 2014; Meng et al. 2016; Rose et al. 2014). Currently, there is a wide variety of liposome formulations that are in preclinical and clinical trials, while some others are already being used as approved therapies, as will be discussed in the next section.

Clinical trials: efficacy and toxicity

A literature search regarding clinical studies was carried out in PubMed during April and May 2018 using the search term "liposome". The sort function and the filters were used to show only the most recent clinical trials in the PubMed search.

The inclusion criteria were:

- The study must be a phase I, II or III clinical trial.
- The study must report either the side effects or the efficacy of the liposomal formulation.
- The article publishing date must be after 2013.

Pain management: bupivacaine

Liposomal bupivacaine (Exparel®, Pacira Pharmaceuticals, San Diego, CA) was approved for local surgical site injection for postoperative pain after haemorrhoidectomy and bunionectomy by the US FDA in 2011 (Yeung et al. 2018). Each liposomal bupivacaine particle (DepoFoam®, Pacira Pharmaceuticals, Parsippany, NJ) is composed of a honeycomb-like structure of internal aqueous chambers containing encapsulated bupivacaine (Mazloomdoost et al. 2017). A single dose (266 mg) of encapsulated bupivacaine amide-based local anesthetic is injected directly into the surgical site. A slow-release mechanism involving reorganization of the barrier lipid membranes is sustained for up to 92 h with concomitant pain control for up to 72 h, as compared to 7–12 h with standard bupivacaine. Studies show bupivacaine decreased pain compared to placebo, the use of opioids and the hospital costs (Yeung et al. 2018; Mazloomdoost et al. 2017; Sabesan et al. 2017; Declaire et al. 2017; Smith et al. 2017; Mcgraw-tatum et al. 2017; Abildgaard et al. 2017; Alijanipour et al. 2016; Davidovitch et al. 2017). Although the liposomal bupivacaine is not a nanoparticle (3–30 µm mean diameter), it is mentioned here because it is one of the most recent liposomal formulations approved. Characteristics and efficacy of the last 13 clinical studies with liposomal bupivacaine (LB) for pain management are summarized in Table 3. In 2017, Rice et al. (2017) published the pharmacokinetic and safety profiles of LB. When administered in two doses (266 mg each) immediately, 24, 48, 72 h after the first one, the mean maximum concentration (Cmax) of bupivacaine in plasma was higher than with only one dose, but did not reach the double of the Cmax from a single dose. The highest Cmax was observed in an individual taking the second dose 24 h after the first, but was below toxic levels for central nervous system and cardiac. In general, LB was well tolerated and revealed no clinically relevant unsafety signs (Rice et al. 2017), provided excellent pain scores, lower opioids consumption, and at a lower cost (Mazloomdoost et al. 2017; Sabesan et al. 2017; Mcgraw-tatum et al. 2017; Davidovitch et al. 2017; Johnson et al. 2017; Barron et al. 2016). Thus, liposome formulation of the anesthetic rendered longer therapeutic times with no adverse effects.

Cancer treatment

In this section, the most recent clinical studies using different liposomal drugs for the treatment of various solid cancers are described. The meaning of the endpoints in the clinical trials described here go as follows: complete response (CR): disappearance of

Table 3 Evaluation of liposomal bupivacaine (LB) effect on pain scores and narcotic consumption

References	Years	Surgery	*n*	Efficacy at POD 1		
				VAS score	NRS score	POTO (mg)
Yeung et al. (2018)	2018	Robotic sacrocolpopexy with posterior repair	33	28	–	27.2[a]
Mazloomdoost et al. (2017)	2017	Retropubic sling placement	54	8.25	2	13.56
Davidovitch et al. (2017)	2017	Operative fixation of ankle fracture	37	65	–	3.4
Johnson et al. (2017)	2017	Total hip arthroplasty	54	–	3.5	26.3
McGraw-Tatum et al. (2017)	2017	Total hip arthroplasty	40	107.5[d]	–	60.6
Sabesan et al. (2017)	2017	Shoulder arthroplasty	34	41[b]	2.6	78.6
Abildgaard et al. (2017)	2017	Shoulder arthroplasty	37	40.9[a]	–	103.11
Namdari et al. (2017)	2017	Shoulder arthroplasty	78	39[e]	–	14.4
Amundson et al. (2017)	2017	Total knee arthroplasty	52	–	3.7	45
DeClaire et al. (2017)	2017	Total knee arthroplasty	47	44.4[b]	–	97.7
Smith et al. (2017)	2017	Total knee arthroplasty	104	40[c]	–	10.9
Alijanipour et al. (2016)	2016	Total knee arthroplasty	59	26	–	71.20
Barron et al. (2016)	2016	Laparoscopic hysterectomy	32	–	2.79	360

n number of patients, *POD* postoperative day, *VAS* visual analogue scale pain score in POD 3 (0–100 range, 0 = "no pain" and 100 = "worst pain"), *NRS* numerical rating scale pain score in POD 3 (0–10 range, 0 = "no pain" and 10 = "worst pain"), *POTO* postoperative total opiates consumption

[a] Median consumption of opiates for POD 1–3

[b] At POD 2

[c] Average on POD 0 through 3

[d] Obtained by integrating serial pain assessments over the entire time interval

[e] At POD 1

all clinical evidences of disease or all target lesions; partial response (PR), at least 30% reduction in size of the target lesions; stable disease (SD), a 30% reduction or less than 25% increase in the size of all detectable disease; objective response rate (ORR) refers to the percentage of patients with partial or complete response to therapy (tumor reduction); "effects" refers to those effects that are attributable directly to the drug and not the natural history of the disease; progression-free survival (PFS) means the time between treatment assignments and disease progression or death, not affected by crossover or subsequent therapies and generally based on objective and quantitative assessment; events-free survival (EFS): time from treatment assignments to disease progression, death, or discontinuation of treatment for any reason (e.g., toxicity, patient preference, or initiation of a new treatment without documented progression); overall survival (OS): time from treatment assignments to patient death, irrespective of cause. Patients who are alive or missed to follow-up at the cut-off date are excluded (Fiteni et al. 2014; Villaruz and Socinski 2013; Roever 2016). Table 4 describes the phases of a clinical trial.

Doxorubicin and daunorubicin

Doxil® is the first drug delivery system based on PEGylated liposome technology. It consists of encapsulated doxorubicin hydrochloride, an anticancer drug of the anthracycline family that induces caspase-dependent apoptosis in cancer cells through oxidative DNA

Table 4 Description of clinical trial phases

Phase	No. of patients[b]	Duration[a]	Description[a]
I	< 25	Several months	Safety and dosage
II	25–100	Several months to 2 years	Efficacy and side effects
III	At least several hundred	1–4 years	Efficacy and monitoring of adverse reactions
IV	Several thousand	> 4 years	Safety and efficacy

[a] According to FDA (2018)

[b] According to American Cancer Society (2018)

damage by blocking topoisomerase IIα, an enzyme needed by cancer cells to divide and grow (Table 5). This enzyme also generates free radicals (reactive oxygen species) that can lead to lipid peroxidation and membrane impairment (Yingchoncharoen et al. 2016; Medina-Alarcón et al. 2017; Bozzuto and Molinari 2015; Lombardo et al. 2016). The composition of different liposomal doxorubicin formulations (Doxil, LipoDox, Myocet, Thermodox, and Caelix), as well as their therapeutic indications and other relevant characteristics are presented in Table 2. Characteristics and efficacy of the reviewed studies with liposomal doxorubicin therapy are presented in Table 6. The major toxicities are presented in Table 7.

The major drawback of non-liposomal or conventional anthracyclines, such as doxorubicin and daunorubicin, is their related cardiotoxicity (Kaspers et al. 2013; Thorn et al. 2011).Thisis because cardiac muscle is enriched with mitochondria, which contains a high level of anionic diphosphatidylglycerol (cardiolipin) that interacts strongly with positively charged doxorubicin, and can lead to lipid peroxidation within cardiac tissue (Yingchoncharoen et al. 2016; Chang and Yeh 2012). Therefore, encapsulated doxorubicin in liposomes (PLD) was developed to overcome the challenges associated with the use of free doxorubicin (Miller et al. 2016; Chang et al. 2018; Coltelli et al. 2017; Rocca et al. 2017; Zhao et al. 2017; Luminari et al. 2017; Fridrik et al. 2016). In addition, PLD showed a reduced cardiac toxicity compared to non-liposomal doxorubicin. Few cardiac events were found in most of the clinical trials described in Table 5 (Coltelli et al. 2017; Rocca et al. 2017; Luminari et al. 2017; Fridrik et al. 2016; Tampaki et al. 2018).

As previously described, PEGylation may extend the blood circulation time of liposomes and improve accumulation in tumor tissues, hence reducing related adverse effects (e.g., cardiotoxicity). However, PLD causes specific side effects, such as hand–foot syndrome (HFS), hypersensitivity reaction, stomatitis and mucositis (Bozzuto and Molinari 2015; Chang and Yeh 2012; Zhao et al. 2017; Casadei et al. 2018; Jung et al. 2017; Bun et al. 2018). PLDs are small enough to pass through the vasculature in both tumor and healthy organs, including the skin (Bun et al. 2018). Thus, PLDs are secreted in sweat after intravenous infusion. This causes an oxidant/antioxidant imbalance in the skin, since doxorubicin and the Cu(II) ions that are abundant in skin tissue generate reactive oxygen species, leading to HFS lesions (Jung et al. 2017; Bun et al. 2018). As Table 7 shows, only > 3rd grade stomatitis/mucositis and HFS appeared in the PLD studies, but not in the three studies that used Myocet®, a non-PEGylated version of liposomal doxorubicin formulation (NPLD). In addition, Volgger et al. in 2015 reported no > 3rd grade stomatitis/mucositis, HFS, or cardiac toxicity in a phase II trial ($n = 39$)

Table 5 Efficacy of recent clinical trials with liposomal doxorubicin in mono and combination therapy

References	Years	Phase	Disease	LF	*n*	Dose by cycle	Efficacy	
							ORR (%)	m-PFS (months)
Banerjee et al. (2018)	2018	II	ROC	PLD	48	40 mg/m^2 IV Q4W	15	3.1
Lee et al. (2017)	2017	II	ROC	PLD	40	50 mg/m^2	5	5
Monk et al. (2017)	2017	II	ROC	PLD	149	40 mg/m^2	21.5	5.2
Marth et al. (2017)	2017	III	ROC	PLD	109	50 mg/m^2 Q4W	21	7.2
Lindemann et al. (2017)	2017	III	ROC	PLD	86	40 mg/m^2	16.9	12.7
Herzog et al. (2016)	2016	II	ROC	PLD	15	50 mg/m^2 IV Q4W	–	–
Lee et al. (2017)	2017	II	ROC	PLD + carboplatin	12	50 mg/m^2 + 5 AUC	33.3	13
Sehouli et al. (2016)	2016	III	ROC	PLD + carboplatin	5	30 mg/m^2 + 5 AUC	75.1	11
Nagao et al. (2016)	2016	I	ROC	PLD + carboplatin + paclitaxel	7	30 mg/m^2 + 60 mg/m^2 + 6 AUC	33	12
Landrum et al. (2016)	2016	I	ROC	PLD + carboplatin + veliparib	10	30 mg/m^2 + 5 AUC + 50 mg	50	–
Kim et al. (2015)	2016	I	ROC	PLD + carboplatin + farletuzumab	15	30 mg/m^2 + 5–6 AUC + 2.5 mg/kg	73.2	10.4[b]
Runnebaum et al. (2018)	2018	II	ROC	PLD + trabectedin	77	30 mg/m^2 + 1.1 mg/m^2 IV Q3W	31	6.3
Monk et al. (2017)	2017	II	ROC	PLD + motolimod	148	40 mg/m^2 + 30 mg/m^2	20.9	4.8
Marth et al. (2017)	2017	III	ROC	PLD + trebananib	114	50 mg/m^2 Q4W + 15 mg/kg Q1W	46	7.6
Shoji et al. (2017)	2017	II	ROC	PLD + irinotecan	31	30 mg/m^2	32.3	2
Thaker et al. (2017)	2017	I	ROC	PLD + GEN	7	50 mg/m^2 + 36 mg/m^2	29	4.7
Herzog et al. (2016)	2016	II	ROC	PLD + vintafolide	22	50 mg/m^2 IV Q4W + 7.5 mg IV Q2W	–	–
Jehn et al. (2016)	2016	II	MBC	Caelix®	25	25 mg/m^2	4.5	1.75[a]
Harbeck et al. (2016)	2016	III	MBC	PLD	105	150 mg/m^2	–	6[a]
Chang et al. (2018)	2018	II	MBC	PLD + CPM	21	30 mg/m^2 Q4–6W + 60 mg/m^2 PO daily	21	6.4
Tampaki et al. (2018)	2018	II	BC	PLD + CPM + bevacizumab + paclitaxel	62	30 mg/m^2 + 600 mg/m^2 + 8 mg/kg + 120 mg/m^2 Q2W	95.2	–

Table 5 (continued)

References	Years	Phase	Disease	LF	*n*	Dose by cycle	Efficacy	
							ORR (%)	m-PFS (months)
Basho et al. (2016)	2016	I	TNBC	PLD + bevacizumab + temsirolimus	24	30 mg/m^2 + 15 mg/kg Q3W + 25 mg Q1W IV	21	4
				PLD + bevacizumab + everolimus	9	30 mg/m^2 + 15 mg/kg Q3W IV + 7.5 mg PO daily		
Rocca et al. (2017)	2017	I	BC	PLD + lapatinib	9	30 mg/m^2 Q3W + 1500 mg/day on days 1–21	11	5.75[a]
Coltelli et al. (2017)[b]	2017	II	BC	Myocet® + CPM + paclitaxel	47	60 mg/m^2 + 600 mg/m^2 IV Q3W + 80 mg/m^2 Q1W	–	–
Orlowski et al. (2016)	2016	III	RMM	PLD + bortezomib	324	30 mg/m^2 + 1.3 mg/m^2	–	33.0[c]
Cohen et al. (2018)	2018	II	MM	PLD + pomalidomide + dexamethasone	16	5 mg/m^2 + 40 mg IV days 1, 4, 8 and 11 + 4 mg/day for 21 days, 28-day cycle	31	5
Becker et al. (2016)	2016	II	MM	PLD + bortezomib + CPM + dexamethasone	20	30 mg/m^2 IV Q4W + 1.6 mg/m^2 + 300 mg/m^2 + 40 mg three times by cycle	90	–
Voorhees et al. (2017)	2017	I	RMM	PLD + bortezomib + vorinostat	32	30 mg/m^2 + 1.3 mg/m^2 + escalating dose of vorinostat	65	13.9
Casadei et al. (2018)	2018	I	MHL	PLD	9	60 mg IV Q3W	50	–
Luminari et al. (2017)	2017	II	DLBCL	Myocet® + CPM + vincristine + prednisone + rituximab	49	50 mg/m^2 + 750 mg/m^2 and 1.4 mg/m^2 day 1 + 100 mg days 1–5 + 375 mg/m^2 day 3 of each cycle	72	17
Fridrik et al. (2016)	2016	II	DLBCL	Myocet® + CPM + vincristine + prednisolone + rituximab	40	50 mg/m^2 + 750 mg/m^2 + 1.4 mg/m^2 + 40 mg/m^2/day for 5 days + 375 mg IV QW3	97.5	–

LF liposomal formulation, *ORR* objective response rate, *m-PFS* median progression-free survival, *CPM* cyclophosphamide, *PLD* PEGylated liposomaldoxorubicin,*GEN* an IL-12 plasmid formulated with PEG–PEI–cholesterol lipopolymer; Q4W, Q3W, Q2W, Q1W, every 4, 3, 2 and 1 weeks, respectively, *AUC* areas under curve, *ROC* recurrent ovarian cancer, *MBC* metastatic breast cancer, *BC* breast cancer, *TNBC* triple-negative breast cancer, *RMM* relapse or refractory multiple myeloma, *MM* multiple myeloma, *MHL* multirelapsed Hodgkin's lymphoma, *DLBCL* diffuse large B-cell lymphoma

[a] TTP, time to progression [the event of interest is only disease progression, while patients who die of other causes are not included (Fiteni et al. 2014)]

[b] Median radiologic PFS

[c] Median overall survival. The median follow-up for survival was 103 months (8.6 years)

with NPLD conducted by AGO (Volgger et al. 2015). Also, Baselga et al. reported that 9% of NPLD-treated patients showed > 3 grade stomatitis and a higher heart safety in a phase III clinical trial ($n = 179$) than with doxorubicin (Pharmachemie B.V.) (Baselga et al. 2014). Nevertheless, NPLD exhibits a short half-life compared to PLD, leading to use higher NPLD doses than PLD (50–70 mg/m^2 Q3W, Table 6) (Zhao et al. 2017).

Other liposomal formulations with doxorubicin designed to be more tolerable and more effective than free doxorubicin have been developed, such as MM-302 and

Table 6 Toxicity of the clinical trials with doxorubicin

References	Disease	LF	Toxicity Grade 3–5 (%)										
			Hematological				Non-hematological						
			N	T	L	A	F	Na	D	V	S/M	HFS	R
Banerjee et al. (2018)	ROC	PLD	4				6		2	6	6		
Lee et al. (2017)	ROC	PLD	7	3		4							
Monk et al. (2017)[a]	ROC	PLD					74.1			33.3			4.1
Marth et al. (2017)	ROC	PLD	15			4	5	5	5	6	6	12	2
Lindemann et al. (2017)	ROC	PLD		2		2		7		7			
Herzog et al. (2016)	ROC	PLD	13			13							
Runnebaum et al. (2018)	ROC	PLD + trebananib	18	10	15			5		5			
Lee et al. (2017)	ROC	PLD + carboplatin	26	13		8							
Sehouli et al. (2016)	ROC	PLD + carboplatin	27	15	17	10	2						2
Nagao et al. (2016)	ROC	PLD + paclitaxel + carboplatin	83	33	83	100		17			50	17	
Landrum et al. (2016)	ROC	PLD + carboplatin + bevacizumab + veliparib	30	40	30								
Kim et al. (2015)	ROC	PLD + carboplatin + farletuzumab	40			13	67	33	20	20		33	33
Monk et al. (2017)[a]	ROC	PLD + motolimod					87.8			50.3			10.9
Marth et al. (2017)	ROC	PLD + trebananib	8			4	7	6	3	6	7	20	2
Shoji et al. (2017)	ROC	PLD + irinotecan	55	3	32	10	3	3	3	10			
Thaker et al. (2017)	ROC	PLD + GEN	71		57	28					28		
Herzog et al. (2016)	ROC	PLD + vintafolide	17		5						5		
Jehn et al. (2016)	MBC	Caelix®				4						12	
Harbeck et al. (2016)	MBC	PLD	3	1	4	1	4				6	39	
Chang et al. (2018)	MBC	PLD + cyclophosphamide	42		47	5		10		5	1		
Tampaki et al. (2018)	BC	PLD + cyclophosphamide + bevacizumab + paclitaxel	24	1.6				6.5		1.6	9.7		
Basho et al. (2016)	TNBC	PLD + bevacizumab + temsirolimus	8	4			4				8	13	
		PLD + bevacizumab + everolimus	22	11		22	22				11		

Table 6 (continued)

References	Disease	LF	Toxicity Grade 3–5 (%)										
			Hematological				Non-hematological						
			N	T	L	A	F	Na	D	V	S/M	HFS	R
Rocca et al. (2017)	BC	PLD + lapatinib							11		11	11	
Coltelli et al. (2017)	BC	Myocet® + cyclophosphamide + PTX	25					6	4	6			
Cohen et al. (2018)	MM	PLD + pomalidomide + dexamethasone	51	4	38	31	9						
Orlowski et al. (2016)	RMM	PLD + bortezomib											
Becker et al. (2016)	MM	PLD + bortezomib + cyclophosphamide + dexamethasone	10			5			5		5	10	
Voorhees et al. (2017)	RMM	PLD + bortezomib + vorinostat	37	47			16	9	19	9		9	
Luminari et al. (2017)	DLBCL	Myocet® + cyclophosphamide + vincristine + prednisone	64	8		46		2					
Fridrik et al. (2016)	DLBCL	Myocet® + cyclophosphamide + vincristine + prednisone + rituximab	50		50	85							29

In the blanks, this type of toxicity is not reported

LF liposomal formulation, *N* neutropenia, *T* thrombocytopenia, *L* leukopenia, *A* anemia, *F* fatigue, *Na* nauseas, *D* diarrhea, *V* vomiting, *S/M* stomatitis/mucositis, *HFS* hand–foot syndrome, *R* rash, *PLD* PEGylated liposomal doxorubicin, *GEN* an IL-12 plasmid formulated with PEG–PEI–cholesterol lipopolymer, *ROC* recurrent ovarian cancer, *MBC* metastatic breast cancer, *BC* breast cancer, *TNBC* triple-negative breast cancer, *RMM* relapse or refractory multiple myeloma, *MM* multiple myeloma, *DLBCL* relapse or refractory multiple myeloma

[a] Any serious adverse event = 3.4 and 8.2% in PLD and PLD + motolimod injections, respectively

Table 7 **Efficacy of recent clinical trials with liposomal daunorubicin in mono or combined therapy**

References	Years	Phase	Disease	LF	*n*	Dose	Efficacy			
							CR (%)	M-EFS (months)	OS rate (%)	M-OS (months)
Inman (2017)	2016	III	AML	CPX-351	153	100 units/m^2/day	47.7	2.53	41.5^a	–
Cortes et al. (2015)	2015	II	AML	CPX-351	81	100 units/m^2/day	49.4	4	36^c	8.5
Lancet et al. (2014)	2014	II	AML	CPX-351	85	100 units/m^2/day	66.7	6.5	–	14.7
Gergis et al. (2013)	2013	I	AML	CPX-351	36	Dose escalation^a	72.2	3.2^b	37^c	8.3
Kaspers et al. (2013)	2013	III	AML	DaunoXome® + fludarabine + cytarabine + filgrastim	197	60 mg/m^2/day + 30 mg/m^2/day + 2000 mg/m^2/day + 200 µg/m^2/dose	69	–	40^d	–
Creutzig et al. (2013)	2013	III	AML	Liposomal daunorubicin	257	60 mg/m^2/day	89	59%^{e}	76^e	–

CR or complete remission, was defined as < 5% leukemic blasts in bone marrow with signs of normal hematopoiesis and of regeneration of normal peripheral blood cell production (platelets > 50 × 10^9/L without transfusions, neutrophils > 1.0 × 10^9/L) and no leukemic cells in the peripheral blood or anywhere else (Kaspers et al. 2013)

LF liposomal formulation, *n* number of patients, *AML* acute myeloid leukemia

[a] It is not described here

[b] Leukemia-free survival

[c] At 1 year

[d] At 4 years

[e] At 5 years

ThermoDox®. The MM-302 formulation is a HER2-targeted antibody–liposomal doxorubicin conjugate that specifically targets HER2 overexpressing cells, increasing the delivery of doxorubicin to tumor cells and limiting exposure to healthy cells, such as cardiomyocytes. Lipid compositions are shown in Table 2. In 2016, Miller et al. (2016) used the MM-302 formulation plus trastuzumab (30 mg/m^2 + 14 mg/kg IV Q3W, respectively) in a phase II trial in patients with HER2-positive locally advanced/metastatic breast cancer. ThermoDox® is a specially formulated and long-circulating lyso-thermosensitive liposomal doxorubicin that has been used clinically combined with radiofrequency ablation (RFA) to remove the core of the tumor. In a phase I trial, (Oxford.) Lyon et al. (2017) explored the safety and feasibility of using an extracorporeal ultrasound-guided focus ultrasound (FU), a non-invasive clinical treatment modality, to induce highly localized hyperthermia in liver tumors in order to trigger the release of doxorubicin and enhance the delivery of systemically circulating ThermoDox® (50 mg/m^2). No results have been reported in the study.

DaunoXome® was the first liposomal daunorubicin formulation developed by NeXstar Pharmaceuticals in 1996 for the management of HIV-associated Kaposi's sarcoma (Table 2). Because of their small size (45–80 nm), the reticulo-endothelial system (RES) uptake of DaunoXome is diminished, leading to extensive drug circulation. DaunoXome has a half-life of between 4 and 5.6 h, longer than that of free daunorubicin ≈ 0.77 h (Bulbake et al. 2017). Moreover, as described previously, liposomally entrapped anthracyclines cause less cardiotoxicity than conventional anthracyclines, such as doxorubicin and daunorubicin (Kaspers et al. 2013; Thorn et al. 2011). CPX-351 is also a liposomal daunorubicin formulation encapsulating cytarabine at a 5:1 molar ratio within 100-nm-diameter liposomes, which was found to be maximally synergistic and minimally antagonistic. Each unit of CPX-351 is composed of 0.1 mg of cytarabine and 0.44 mg of daunorubicin. It also increases the plasma's half-life and leads to drug accumulation within the bone marrow (Gergis et al. 2013; Cortes et al. 2015; Lancet et al. 2014).

In a PubMed search covering 2013–2018, only six clinical studies using liposomal daunorubicin were found. The studies' characteristics and toxicity indexes are, respectively, shown in Tables 7 and 8. The study by Creutzig et al. (2013), using liposomal daunorubicin, achieved the larger percentage of patients with a complete response (89%), followed by the study of Gergis et al. (2013), which uses CPX-351 (72.2%) (Cortes et al. 2015), which uses CPX-351 (72.2%) (Gergis et al. 2013). The two studies showed low toxicity levels, as same as the study by Kaspers et al. (2013), as shown in Table 9. However, thanks to a phase III study that demonstrated better overall survival rate (Kraft et al. 2014), FDA recently approved the liposomal combination of daunorubicin and cytarabine, CPX-351 (Vyxeos™), for the treatment of acute myeloid leukemia (AML), as shown in Table 8. In general, liposomal daunorubicin proved to be effective with a low cardiac toxicity profile in an increased anthracycline dose in older patients, children, and adolescents (Gergis et al. 2013; Lancet et al. 2014; Kaspers et al. 2013; Creutzig et al. 2013).

Irinotecan

Irinotecan, also known as CPT-11, is a water-soluble semi-synthetic analogue of the natural alkaloid camptothecin. It prevents DNA from unwinding and replicating by inhibition of topoisomerase-I. It is used as antineoplastic agent to treat various types of cancers, diarrhea, and myelosuppression. Onivyde® (nal-IRI) is a nanoliposomal hydrochloride irinotecan formulation approved by the FDA in the US and the European Medicines Agency for the treatment of metastatic pancreatic adenocarcinoma (mPAC) in combination with 5-FU/LV, a fluoropyrimidine-based agent, in patients previously treated with gemcitabine-based therapy (Pelzer et al. 2017; Clarke et al. 2017; Wang-gillam et al. 2016; Chiang et al. 2016). In 2017, Clarke et al. (2017) published a phase I trial of nal-IRI in patients with recurrent high-grade glioma to assess the safety and pharmacokinetics (PKs) of nal-IRI and to determine the maximum tolerated dose (MTD). Patients homozygous WT for UGT1A1 (a genotype reported as toxicity predictor when heterozygous) were initially dosed at 120 mg/m^2 IV Q3W and with 60 mg/m^2 dose increments, while heterozygous (WT/*28 UGT1A1) patients were started at 60 mg/m^2 with dose increments of 30 mg/m^2. In the WT cohort ($n = 16$), the MTD was 120 mg/m^2; in the HT cohort ($n = 18$), the MTD was 150 mg/m^2. Nal-IRI had no unexpected toxicities. PFS-6 was 2.9%, median PFS was 42 days and median OS was 107 days. The terminal half-life for nal-IRI did not change with dosage. In 2016, Chiang et al. (2016) (PharmaEngine, Inc.) published a phase I dose escalation study of nal-IRI in patients with advanced solid tumors. In this study, the dose-limiting toxicity (DLT), MTD and PKs were investigated. Three individuals were dosed with 60 mg/m^2, six with 80 mg/m^2, five with 100 mg/m^2, and two with 120 mg/m^2 on day 1, followed by 5-FU 2000 mg/m^2 and LV 200 mg/m^2 on days 1 and 8 IV Q3W. Four patients showed DLT: two at the 100 mg/m^2 dosage level, and two at the 120 mg/m^2. The MTD was 80 mg/m^2, which, after the study, has been the recommended dosage. The most common observed adverse effects were nausea (81%), diarrhea (75%), and vomiting (69%). Only four individuals had stable disease, one showed partial response, and the other, a progressive disease. The irinotecan liposome injection increased the bioavailability. Maximum plasma concentration decrease and half-life increased. The area under the plasma concentration–time curve from zero to infinity of SN-38 (the active metabolite of irinotecan) was higher than irinotecan itself at a similar dosage level. Thus, liposomal dosage form improved pharmacokinetic parameters of the chemotherapeutic drug, without adding more adverse effects than the drug itself.

The US FDA approved nal-IRI + 5-FU/LV based on results from the NAPOLI-1 clinical trial (Pelzer et al. 2017). This phase III trial of Wang-Gillam et al. (2016) (Merrimack Pharmaceuticals) was published in 2016 and demonstrated that the combination of nal-IRI + 5-FU/LV (80 mg/m^2 + 2400 mg/m^2 + 400 mg/m^2, respectively) improved median overall survival (6.1 vs. 4.2 months) and median progression-free survival (3.1 vs. 1.5 months) compared with 5-FU/LV therapy alone in metastatic pancreatic cancer after previous gemcitabine-based therapy. The grade 3 or 4 adverse events that most frequently occurred in the 117 patients assigned nanoliposomal irinotecan plus fluorouracil and folinic acid were neutropenia (27%), diarrhea (13%), vomiting (11%), and fatigue (14%). It can be concluded that nanoliposomal irinotecan, in combination with 5-FU/LV, extends survival rates with a manageable safety profile in patients with metastatic pancreatic ductal adenocarcinoma.

Table 8 Toxicity of the clinical trials with daunorubicin

References	Disease	LF	Toxicity Grade 3–5 (%)											
			FN	B	P	H	S	F	ARF	UTI	R	H_t	RF	C
Inman (2017)	AML	CPX-351	68	10	20		9					10	7	
Cortes et al. (2015)	AML	CPX-351	54	30	17	9	9	15	5	6	11	5		
Lancet et al. (2014)	AML	CPX-351	63.5	35	15	15	12	9	9	7	8			
Gergis et al. (2013)	AML	CPX-351												3^a
Karspers et al. (2013)	AML	DaunoXome® + fludarabine + cytarabine + filgrastim												2.7
Creutzig et al. (2013)	AML	Liposomal daunorubicin									3.6		16	2.1

In the blanks, this type of toxicity is not reported

AML acute myeloid leukemia, *LF* liposomal formulation, *FN* febrile neutropenia, *B* bacteremia, *P* pneumonia, *H* hypokalemia, *S* sepsis, *F* fatigue, *ARF* acute renal failure, *UTI* urinary tract infection, *R* rash, H_t hypertension, *RF* respiratory failure, *C* cardiotoxicity

[a] Grade 2

Table 9 Efficacy of recent clinical trials with liposomal paclitaxel in mono or combined therapy

References	Years	Phase	Disease	LF	*n*	Dose	Efficacy		
							ORR (%)	m-PFS (months)	m-OS (months)
Wang and Zhang (2014)	2014	II	NSCLC	LPTX + carboplatin	27	175 mg/m^2	44.4	6	–
Lu et al. (2015)	2015	II	NSCLC	LPTX + gemcitabine + carboplatin	48	3 mg/ml IT + 1000 mg/m^2 IV day 1 and 8 + 5 AUC IV day 1 Q3W	81	16.5	23.2
Ahn et al. (2014)	2014	II	NSCLC	Genexol-PM + gemcitabine		230 mg/m^2 day 1 + 1000 mg/m^2 days 1 and 8 IV Q3W	46.5	4	14.8
Hu et al. (2013)[a]	2013	II	NSCLC	LPTX + cis-platin	63	135 mg PTX/m^2 to 175 mg PTX/m^2	–	–	–
Ignatiadis et al. (2016)	2016	I	BC	EndoTAG-1 + PTX + fluorouracil + epirubicin + cyclophosphamide	15	22 mg/m^2 + 70 mg/m^2 IV Q1W + 500 mg/m^2 + 100 mg/m^2 + 500 mg/m^2 Q3W	33	–	–
Awada et al. (2014)	2014	II	TNBC	EndoTAG-1 + PTX	56	22 mg/m^2 + 70 mg/m^2 Q1W	45	3.7	13.0
				EndoTAG-1	58	88 mg/m^2 Q1W	25	3	11.9
Lu et al. (2016)	2016	II	AGC	LPTX + capecitabine	34	135 mg/m^2 IV day 1 + 2000 mg/m^2 PO days 1–14 Q3W	47	6.9	12.5
Xu et al. (2013)	2013	II	MGC	Lipusu®	30	135 mg/m^2 IV day 1	47	–	–
Haas et al. (2012)	2012	II	PC	EndoTAG-1 + Gem	50	11 mg/m^2	14	4.1	8.1
					50	22 mg/m^2	14	4.6	8.7
					5	44 mg/m^2	16	4.4	9.3
Graziani et al. (2017)	2017	II	EOC	PTX–LCN	14	175 mg/m^2	–	3	–
Strieth et al. (2013)[b]	2013	I	HNC	EndoTAG-1	5	1.1 mg PTX/kg	–	–	–
Slingerland et al. (2017)[b]	2013	II	AC	LEP-ETU	30	175 mg PTX/m^2 Q3W	–	–	–

LF liposomal formulation, *n* number of patients, *ORR* objective response rate, *m-PFS* median progression-free survival, *m-OS* median overall survival, *LPTX* liposomal paclitaxel, *PTX–LCN* paclitaxel lipid core nanoparticle, *PTX* paclitaxel, *Gem* gemcitabine, *LEP-ETU* paclitaxel liposomal; Q4W, Q4W, Q3W, Q2W, Q1W, every 4, 3, 2 and 1 weeks, respectively, *BC* breast cancer, *TNBC* triple-negative breast cancer, *AGC* atypical glandular cells, *MGC* metastatic gastric cancer, *PC* pancreatic cancer, *EOC* epithelial ovarian carcinoma, *HNC* head and neck cancer, *AC* advance cancer, *NSCLC* non-small-cell lung carcinoma

[a] No results have been proportionated

[b] Only the toxicity was mentioned

Paclitaxel and docetaxel

Paclitaxel inhibits tumor endothelial cells growth, through combination with beta microtubules (Qu et al. 2017; Xu et al. 2013; Slingerland et al. 2017). Because of the paclitaxel's (PTX) insolubility in water, polyethoxylated castor oil (Cremophor EL) and dehydrated ethanol in a 1:1 (v/v) ratio are used as formulation vehicles, although it has toxic effects, such as hypersensitivity reactions, hyperlipidemia and neurotoxicity (Bulbake et al. 2017; Xu et al. 2013; Slingerland et al. 2017; Ahn et al. 2014; Graziani et al. 2017; Strieth et al. 2013). To avoid these drawbacks, many Cremophor-free liposomal paclitaxel (LPTX) formulations have been approved by FDA, such as (1) LEP-ETU, a conventional cationic nanosome with a size of about 150 nm (Slingerland et al. 2017); (2) EndoTAG™-1, a cationic liposome formulation of lipid-embedded paclitaxel, which interacts with negatively charged tumor endothelial cells lessening their tumor blood supply (Strieth et al. 2013; Awada et al. 2014; Haas et al. 2012; Ignatiadis et al. 2016); and (3) Lipusu® (Sike Pharmaceutical Co. Ltd., Nanjing, Jiangsu, P.R. China), a formulation approved in China prepared by using film dispersion methods followed by a lyophilization technique (Xu et al. 2013; Slingerland et al. 2017; Ahn et al. 2014; Graziani et al. 2017; Strieth et al. 2013; Awada et al. 2014; Haas et al. 2012; Ignatiadis et al. 2016; Ye et al. 2013). Even Cremophor-free liposome-like formulations, such as Genexol-PM, a polymeric micelle formulation of paclitaxel (Samyang Co., Seoul Korea) (Ahn et al. 2014), and PTX–LDE, a lipid core nanoparticle with encapsulated paclitaxel that binds to low-density lipoprotein receptors of cancer cells and concentrates in the tumor tissues (Graziani et al. 2017). Compositions of liposomal and non-liposomal formulations are shown in Table 2.

Table 10 shows the characteristics of the most recent liposomal PTX formulation, which include clinical trials, liposomal formulation, number of patients, dosage, and treatment efficacy. In Table 11, a toxicity map is provided. As shown in the non-small-cell lung carcinoma (NSCLC) treatment, the study of Lu et al. (2015) had the highest endpoint outputs (ORR 81%, PFS 16.5 months, OS 23.2 months), while the study of Wang and Zhang (2014) had the lowest (ORR 44%, PFS 6 months). This may be caused by the addition of gemcitabine. Ahn's et al. study also combined gemcitabine with paclitaxel encapsulated within a non-liposomal formulation (polymeric micelle). The results were similar to those of Wang et al. (2014) and Hu et al. (2013) used L-PTX plus cisplatin for the treatment of NSCLC but did not report any results. The study of Lu et al. was the most effective in the treatment of NSCLC, but it also showed the highest toxicity levels, as shown in Table 11.

Docetaxel is a semi-synthetic taxane analogue and an antimitotic agent which binds itself to the beta subunit of tubulin and causes stabilization of tubulinpolymerization. This stabilization results in a microtubule disrupting and cell cycle arrests at the G_2/M phase, thus inhibiting mitosis. It is poorly soluble in water, and is commonly used in the treatment of a variety of solid tumors (Mahalingam et al. 2014; Deeken et al. 2013). Due to its insolubility, the currently marketed docetaxel (Taxotere) is formulated in Tween 80 and ethanol. However, this compound has been implicated in infusion-related toxicity, acute hypersensitivity reactions, as well as cumulative fluid retention. To avoid such undesirable side effects, several Tween 80-free and ethanol delivery systems have been developed and clinically tested, such as nanosomes, polymeric micelles, protein, and nanospheres (Deeken et al. 2013; Ahmad et al. 2014). For instance, in the phase I

Table 10 Toxicity of the clinical trials to paclitaxel

References	Disease	LF	Toxicity[a] Grade 3–5 (%)								
			N	A	T	L	Na	D	V	P	Ast
Wang and Zhang (2014)	NSCLC	L-PTX + carboplatin		13		57					
Lu et al. (2015)	NSCLC	L-PTX + gemcitabine + carboplatin	14	4	2		2	4	2		
Ahn et al. (2014)	NSCLC	Genexol-PM + gemcitabine	16					3			7
Ignatiadis et al. (2016)	BC	EndoTAG-1 + paclitaxel + fluorouracil + epirubicin + cyclophosphamide	7								
Awada et al. (2014)	TNBC	EndoTAG-1 + paclitaxel	22	2		7			2	2	6
		EndoTAG-1	5			2		2		4	5
Lu et al. (2016)	AGC	L-PTX + capecitabine		2.9		17.6					
Xu et al. (2013)	MGC	Lipusu®		3		7	3		3		
Haas et al. (2012)	APC	EndoTAG-1 + gemcitabine	12		8	10			2		
			16	4	16	12				6	
			22	8	14	10	6		4	8	
Graziani et al. (2017)[b]	EOC	PTX–LCN									
Strieth et al. (2013)[c]	HNC	EndoTAG-1									
Slingerland et al. (2017)[d]	AC	LEP-ETU	17			3					

In the blanks, this type of toxicity is not reported

LF liposomal formulation, *n* number of patients, *LPTX* liposomal paclitaxel, *PTX–LCN* paclitaxel lipid core nanoparticle, *PTX* paclitaxel, *Gem* gemcitabine, *LEP-ETU* paclitaxel liposomal, *BC* breast cancer, *TNBC* triple-negative breast cancer, *AGC* atypical glandular cells, *MGC* metastatic gastric cancer, *PC* pancreatic cancer, *EOC* epithelial ovarian carcinoma, *HNC* head and neck cancer, *AC* advance cancer, *NSCLC* non-small-cell lung carcinoma, *N* neutropenia, *A* anemia, *T* thrombocytopenia, *L* leukopenia, *Na* nauseas, *D* diarrhea, *V* vomiting, *P* pneumonia, *Ast* asthenia

[a] Toxicity was rounded

[b] No grade > 3 even grade < 2 toxicity was found

[c] No grade > 3 toxicity or severe adverse events occurred

[d] No results have been proportionated

Table 11 Characteristics of recent clinical trials with liposomal amphotericin B in mono or combined therapy

References	Years	Phase	Disease	LF	*n*	Dose
Cornely et al. (2017)	2017	III	IFD	AmBisome®	228	5 mg/kg
Romero et al. (2017)	2017	III	VL	AmBisome®	109	3 mg/kg/day for 7 days
				AmBisome® + MA	112	10 mg/kg single dose + 20 mg Sb^{+5}/kg/day for 10 days
Rahman et al. (2017)	2017	III	VL	AmBisome® + Mil	142	5 mg/kg + 17.5 mg/kg
				AmBisome + Par	159	5 mg/kg + 150 mg/kg
				AmBisome®	158	15 mg/kg
Miyao et al. (2016)	2016	II	RFN	AmBisome®	80	1 mg/kg
Wasunna et al. (2016)	2016	II	VL	AmBisome® + SSG	51	10 mg/kg + 20 mg/kg/day
				AmBisome® + Mil	49	10 mg/kg + 2.5 mg/kg/day

IFD invasive fungal diseases, *VL* visceral leishmaniasis, *RFN* refractory febrile neutropenia, *LF* liposomal formulation

clinical trial of Mahalingam et al. (2014) (University of Texas Health Science Center), 15–110 mg/m^2 of ATI-1123, a liposomal formulation of docetaxel that uses protein-stabilized nanoparticles encapsulating docetaxel in the liposome, was administered Q3W to 29 adult patients with advanced solid tumors (lung, pancreas, prostate, cervix, and ovarian). The partial response and stable disease percentages were 3% and 75%, respectively. The grade > 3 toxicities were as follows: 65% neutropenia, 28% anemia, 7% nausea, 7% vomiting, 3% asthenia, 14% fatigue, and 10% febrile neutropenia. Ahmad et al. (2014) administered 75 mg/m^2 of a nanosomal docetaxel lipid suspension in 49 patients with metastatic breast cancer where no > 3 grade toxicities were reported. The complete and partial responses were 4.2% and 31.3%, respectively. Deeken et al. (2013) used a liposomal docetaxel formulation with a mean diameter of 100 nm composed by DOPC, cholesterol, cardiolipin, and alpha-tocopheryl acid succinate to 24 patients (50–132 mg/m^2 IV Q3W) with advanced solid tumors. The partial response and stable disease percentages were 8% and 33%, respectively. Only a 38% of > 3 grade neutropenia was reported. In conclusion, liposomal docetaxel shows an acceptable tolerance, improves clinical efficacy without any premedication and thus, a beneficial treatment for solid tumors (Mahalingam et al. 2014; Deeken et al. 2013; Ahmad et al. 2014).

Other liposomal formulations for cancer treatment

Mepact® is a liposomal mifamurtide formulation (liposomal muramyl tripeptide phosphatidylethanolamine) approved by European Union, Switzerland, and other countries for the treatment of osteosarcoma (Venkatakrishnan et al. 2013). In the PubMed search for publications on the subject carried out, no recent results were found. In 2014, Venkatakrishnan et al. (2013) published an evaluation of the pharmacokinetics and pharmacodynamics after a single dose of Mepact® (4 mg IV) in adult subjects with hepatic impairment in comparison with healthy subjects. In 2009, Chou et al. (2009) (IDM Pharma) published a phase III trial ($n = 91$) of liposomal mifamurtide addition to chemotherapy (cis-platin, doxorubicin, methotrexate and ifosfamide) for patients with osteosarcoma. The 5-year event-free survival rate for patients who received liposomal mifamurtide ($n = 46$) was 42% vs. the 26% of those who did not ($n = 45$). The 5-year overall survival rate for patients who received Mepact compared to those who did not received Mepact was 53% and 40%, respectively. Moreover, data suggest that liposomal mifamurtide might provide a benefit when added to chemotherapy for the treatment of osteosarcoma.

Vincristine sulfate, a semi-synthetic chemotherapeutic agent, has been encapsulated in sphingomyelin/cholesterol nanoliposomes to overcome the dosing, pharmacokinetic, and pharmacodynamic limitations of non-liposomal vincristine. This vincristine injection dosage form (VSLI, Marqibo®) has been approved by FDA, since it has proved to be safe. It also showed tolerability, enhanced vincristine cell uptake, penetration and concentration in tissues and organs with fenestrated vasculature or involved in the mononuclear phagocyte system, including non-Hodgkin lymphomas. It did not show toxic effects, but high ORR. Thus, it provides encouraging PFS and OS when substituted for standard vincristine in polytherapy (Shah et al. 2016; Kaplan et al. 2014; Hagemeister et al. 2013). In a phase I study carried out in 2016 with 21 patients suffering of refractory solid tumors or leukemias, no subjects experienced dose-limiting toxicity (DLT) at the first dosage level (1.75 mg/m^2/dose). Even though, at 2.25 mg/m^2, one subject had transient dose-limiting grade 4 transaminase elevation, no additional DLT was observed when the dose level was increased. A stable disease was observed in nine patients, although in one subject with leukemia, a minimal residual disease and a negative complete remission was observed. Children were able to tolerate adult dosages (2.25 mg/m^2/dose of weekly VSLI) with no evidence of neurotoxicity (Shah et al. 2016). In a phase II study of Marqibo and rituximab (Therapeutics Inc.), the ORR was 59%: 27% of complete response, and 32% of partial response in 22 patients with relapsed and refractory diffuse large B-cell lymphoma (DLBCL) or mantle cell lymphoma (MCL). Median response duration was 147 days, TTP was 121 days, and overall survival was 322 days. Nevertheless, patients reported adverse effects like Grade 3 peripheral neuropathy, febrile neutropenia, and constipation. Thus, VSLI + rituximab provokes a durable response in those lymphomas. Adverse effects were manageable (Kaplan et al. 2014). In a phase II study, 72 patients with untreated and aggressive non-Hodgkin lymphomas, including 60 with DLBCL, were treated with Marqibo® plus cyclophosphamide, doxorubicin, and prednisone (2 mg/m^2 + 750 mg/m^2 + 50 mg/m^2 IV + 100 mg PO Q3W, respectively), with or without rituximab (375 mg/m^2 IV Q3W). Of them, 96% showed complete response and 3% were unconfirmed. The 5-year and 10-year PFS and OS were 75% and 63%; and 87% and 77%, respectively. Although exposure was up to 35 mg, this multidrug treatment (Marqibo plus cyclophosphamide, doxorubicin, and prednisone ± rituximab) was as safe as the same therapy with non-liposomal vincristine. As for the adverse effects, grade 3 peripheral neuropathy was reported in 3% of the patients and there was no reported Grade 3/4 constipation. All this demonstrates that the encapsulation does not alter the safety properties of the drug. Moreover, Marqibo was well tolerated and showed a higher activity, probably due to the pharmacokinetic optimization and the enhanced delivery (Hagemeister et al. 2013).

Liposomal cytarabine (Depocyt®) is a slow-release dosage form of cytarabine that results in cytotoxic cytarabine concentrations in the cerebrospinal fluid for at least 1 week, while non-liposomal cytarabine is maintained for only 24 h (Levinsen et al. 2016; Ferreri et al. 2015; Peyrl et al. 2014). In 2016, Levinsen et al. (2016) published a phase II trial ($n = 40$) that investigated the efficacy and toxicity of intrathecal liposomal cytarabine in comparison with conventional triple (cytarabine, methotrexate, and hydrocortisone) intrathecal therapy for the treatment of childhood acute lymphoblastic leukemia. Depocyt® showed acceptable toxicity when administered as first-line therapy with concomitant use of dexamethasone, which suggests that it could play a future role in improving outcomes in children with acute lymphoblastic leukemia. Peyrl et al. (2014) studied the pharmacokinetics and toxicity of intrathecal liposomal cytarabine in sixteen children and adolescents with malignant brain tumors. In general, liposomal cytarabine was well tolerated, with relevant but manageable toxicities that showed sufficient drug exposure for at least 1 week (Peyrl et al. 2014).

Molecular therapy

Patisiran (ONPATTRO®) is a siRNA-delivering liposome developed and marketed by Alnylam, for the silencing of a specific gene responsible for expression of transthyretin (TTR), which can cause hereditary transthyretin amyloidosis (Anselmo and Mitragotri 2019). The composition of this liposomal formulation is in Table 2. Actually, ONPATTRO is the newest approved liposomal formulation here described. It is also the first clinicallyapproved example of an RNAi therapy-delivering nanoparticle administered intravenously, and it is actually the first therapeutic RNAi approved by the FDA as well, independent of the nanoparticle delivery vehicle (Anselmo and Mitragotri 2019; Adams et al. 2018), which was the major milestone in the biotech and nanomedicine industry (Anselmo and Mitragotri 2019). RNA interference is a cellular process that controls gene expressions, in which small interfering RNAs (siRNAs) mediate the cleavage of specific messenger RNAs (mRNAs). Patisiran comprises a TTR mRNA-specific siRNA formulated (Anselmo and Mitragotri 2019; Adams et al. 2018; Suhr et al. 2015). Clinical data have shown a potent and sustained knockdown of TTR expression and, while there have been side effects, there has been little evidence of safety concerns about platelets, renal function or liver enzyme elevations. The results were published in July 2018 (Adams et al. 2018) and found that the drug reduced TTR production by about 81%. The following month, patisiran was approved by both the US Food and Drug Administration and the European Medicines Agency (EMA). The efficacy was shown in a clinical trial involving 225 patients, 148 received an patisiran infusion once every 3 weeks for 18 months, The patients who received the RNA had better outcomes on measures of polyneuropathy including muscle strength, sensation (pain, temperature, numbness), reflexes and autonomic symptoms (blood pressure, heart rate, digestion) compared to those receiving the placebo infusions (Minamisawa et al. 2019), additional investigation suggests that patisiran may stop or possibly reverse the progression of hATTR (Solomon et al. 2019).

MRX34 mimics miR-34a, a miRNA suppressor of more than 30 oncogenes. It is the first-in-class drug. It is encapsulated in a liposomal nanoparticle with ≈ 110 nm diameter. The liposomal component contains amphiphilic lipids, which display a positive charge under acidic conditions, ensuring the efficient encapsulation of the negatively charged miR-34a mimic, and a negative charge in vivo at neutral pH to minimize aggregation and electrostatic adherence to the cell membrane of endothelial cells. miR-34a shows interesting pharmacological properties in mice and non-human primates: it has a long residence time in blood, inhibits growth of primary tumors, blocks metastasis, and extends survival (Beg et al. 2016; Li et al. 2013). In a phase I trial with 47 patients showing refractory advanced solid tumors, MRX34 dosage (escalating twice-weekly) showed evidence of antitumor activity. In 2016, a phase I clinical trial of miRNA cancer therapy was carried out, in these study, 47 patients were treated twice a week with escalating doses of MRX34 IV (BAYER®) (Davidovitch et al. 2017). MRX34 treatment with dexamethasone premedication was associated with acceptable safety indexes. Remarkably, it demonstrated that MRX34 has in vivo antitumor activity even in patients with refractory advanced solid tumors, including hepatocellular carcinoma (HCC). The MTD for non-HCC patients was 110 mg/m^2. Two patients experienced DLT of grade 3 hypoxia and enteritis at 124 mg/m^2. A patient with HCC achieved a prolonged confirmed partial response lasting 48 weeks, and four patients experienced stable disease for more than 4 cycles (Beg et al. 2016; Li et al. 2013).

In 2016, a phase I clinical trial was carried out with 20 patients with multiple sclerosis (MS) (Pharmsynthez OJSC). Treatment was performed with myelin basic protein, the structural component of the myelin membrane. It was coencapsulated in CD206-targeted small monolamellar mannosylated liposomes prepared from egg phosphatidylcholine and monomannosyl dioleoyl glycerol with α-tocopherol and lactose (Xemys; Pharmsynthez, St. Petersburg, Russia). Patients were dosed weekly with subcutaneous injections of Xemys at escalating doses of 50, 150, 225, 450 and 900 µg, over 6 weeks (2.675 mg). Dendritic cells uptake was significantly enhanced by mannosylation of liposomes. Administration of Xemys was safe and well tolerated in patients with MS. Mild-to-moderate severe adverse effects were observed mainly after submaximal and maximal doses. Although no concomitant medication was required, no abnormalities in blood or other safety problems were observed (Jr et al. 2016).

Other molecular treatments target the normal human p53 gene, which is a well-known tumor suppressor gene. Over 60% of cancers are related to the loss of p53 suppressor function. Up to 80% of cancer cases show p53 mutations. Moreover, cells lacking p53 are more resistant to chemotherapy. In contrast, p53 restoration enhances sensitivity to standard therapies. SGT-53 has been designed as an immunoliposome nanocomplex designed for systemic, tumor-targeting delivery. This nanodelivery system targets transferrin receptor (TFR), a highly expressed receptor on tumor cells, via a single-chain antibody fragment (termed as TFRscFv). The complex with the receptor is internalized into the tumor cells via endocytosis. In 2016, a trial with 14 patients with advanced cancer was administered with escalating doses of a combination of SGT-53 and docetaxel. The combination was well tolerated. Three of 12 patients showed partial responses with tumor reduction of 47%, 51% and 79%, while the others showed stable disease (Pirollo et al. 2016).

Fungal and bacterial infections

Amphotericin B

Invasive fungal infections (IFI) are considered opportunistic since they occur when the patient is predisposed to medical treatments (Sánchez et al. 2016) because of cancer, malignant hematological neoplasms (cryptococcosis), bone marrow transplants, or hematopoietic progenitors, immunosuppressive treatments (fusarosis), prolonged neutropenia, and immunodeficiencies in cells (zygomycosis or mucormycosis), as well as hepatic dysfunction (invasive candidiasis), injured mucous membranes (invasive aspergillosis), among others (Tacke et al. 2014).

Amphotericin B is used for the treatment of invasive fungal infections (Delattin et al. 2014) and acts by binding itself to sterols in the cell membrane of susceptible fungi, with a resulting change in membrane permeability. The first liposomal formulations were presented as AmBisome® from NeXstar Pharmaceuticals, Inc. (now Astellas Pharma, Inc.); lipid complexes such as Abelcet® from Enzon Pharmaceuticals (now Sigma Tau Pharmaceuticals, Inc. and Amphotec® from InterMune, Inc. (now Kadmon Pharmaceuticals, Inc.) (Table 2). Since the 1970s, more than 353 patents have been registered, some of which protect the formulation of liposomes under specific characteristics, e.g., liposomes and lipid complexes intercalating amphotericin B (Verma et al. 2005).

Table 11 shows the characteristics of recent studies using amphotericin B to treat fungal infections as described below. In the study of Cornely et al. (2017), the primary endpoint was the rate of proven/probable IFI: 7.9% to liposomal amphotericin B (AmBisome) group, and 11.7 to placebo group, suggesting that AmBisome is not as effective as prophylaxis against invasive fungal diseases (IFD) in these patients, which is difficult to explain since AmBisome is effective against IFD. The chosen dose to minimize toxicity represented a major limitation of the study. However, more patients in the AmBisome group than in the placebo group had adverse effects (AE). This resulted in the interruption of treatment with the drug (20.3% versus 7.6%). They also experienced serious AE considered to be related to the drug. Mortality was very similar in both groups (7.2% and 6.8%, respectively). The complete remission rate was 72.8%, which was lower than expected. The low efficacy of AmBisome was attributed to the patients' baseline characteristics and the diagnostic strategy of IFI. Romero et al. (2017) evaluated the efficacy and safety of AmBisome and the combination of AmBisome + meglumine antimoniate (MA). The final analyses showed a CR at 6 months of 87.2% for AmBisome, 83.9% for AmBisome + MA, and 77.5% for MA alone. AmBisome monotherapy was safer than MA, as measured by the frequency of treatment-related adverse events, proportion of patients presenting at least one severe AE, and the proportion of AE resulting in definitive treatment discontinuation. In the study of Rahman et al. (2017), a 35-year-old female patient presented high-grade fever, rash, and swelling of arms and legs in the AmBisome + miltefosine (Milt) group. Treatment wasinterrupted and she was later diagnosed with rickettsial fever with concomitant nutritional edema. Approximately, 34% of AE were related to the treatment. The proportion of patients that experienced any treatment-related side effects was the highest in the AmBisome + Milt group, and the lowest in the AmBisome group (Table 12). None of the other non-fatal AE reported were related to the treatment. No drug-related deaths occurred either in the AmBisome group, or in the combination groups. In the intention-to-treat (ITT) population, the CR at month 6 was 98.1% for the AmBisome group, 99.4% to AmBisome + paromomycin, and 94.4% to AmBisome + Milt. Although not statistically significant, AmBisome + paromomycin was the most effective treatment. In the low-dosage study of Miyao et al. (2016), the most frequent events were electrolyte abnormalities, most of which involved hypokalemia (7.5% of grade 3 and 3.75% grade 4 cases). AE related with AmBisome that necessitated protocol discontinuation occurred in only one case that involved grade 4 glutamate

Table 12 Toxicity of the clinical trials to amphotericin B

References	Disease	LF	Toxicity Grade 3–5 (%)								
			Hk	Ld	C	Na	D	AP	V	P	H
Cornely et al. (2017)	IFD	AmBisome®								28	8
Rahman et al. (2017)	VL	AmBisome® + Mil			2	3	2	2	18	18	
		AmBisome® + Par			0	0	0	1	1	22	
		AmBisome®								23	
Miyao et al. (2016)	RFN	AmBisome®	11.25	2.5							
Wasunna et al. (2016)[a]	VL	AmBisome® + SSG			4[b]				2		
		AmBisome® + Mil			6[b]				12		

In the blanks, this type of toxicity is not reported

IFD invasive fungal diseases, *VL* visceral leishmaniasis, *RFN* refractory febrile neutropenia, *Ld* liver dysfunction, *Hk* hypokalemia, *C* cardiotoxicity, *Na* nauseas, *D* diarrhea, *AP* abdominal pain, *V* vomiting, *P* pneumonia, *H* hypotension, *Mil*, miltefosine, *Par* paromycin, *SSG* sodium stibogluconate, *LF* liposomal formulation

[a] No grade > 3 toxicity was reported

[b] Sinus arrhythmia

pyruvate transaminase elevation. No patient deaths related to the treatment occurred during the study.

In a more recent study by Wasunna et al. (2016), the authors reported the percentage of patients cured in day 210 of the treatment as follows: 87% to the AmBisome + sodium stibogluconate (SSG) group, and 77% to the AmBisome + Milt group. There were two AE related to the studied drug. In the AmBisome + SSG group, severe anemia resulted in death at day 20 (the only death considered drug related), and in the AmBisome + Milt group, renal failure at day 3 was resolved. 73% and 78% of patients in the AmBisome + SSG and AmBisome + Milt had at least one adverse drug reaction. In the AmBisome + SSG and in the AmBisome + Milt groups, all non-serious drug-related events were categorized as mild to moderate. The only group that contained SSG (combined with AmBisome) showed low levels of cardiac disorders (< 5%), which were similar to those of the AmBisome + MF group. The authors concluded that a multiple daily dose of 3 mg/kg AmBisome may be more beneficial to eliminate fungi than a single 10 mg/kg dose at day 1, suggesting that a more frequent administration could result in a higher efficacy of AmBisome.

Amikacin

Pulmonary nontuberculous mycobacterial disease is a chronic infection with necrotizinginflammation, bronchiectasis, and cavitation with irreversible lung damage and increased mortality. To improve efficacy and reduce toxicity, a liposomal amikacin for inhalation (LAI) (Arikace®, ≈ 300 nm), composed of DPPC and cholesterol, has been developed. The liposomes are taken up by lung macrophages, allowing for intracellular delivery of high levels of amikacin into nontuberculous mycobacterial cells (Rose et al. 2014; Olivier et al. 2017). In 2018, Caimmi et al. (2018) reported the effect of LAI (590 mg daily) on five patients with *Mycobacterium abscessus* in cystic fibrosis. None of the five patients showed any side effects related to the treatment, while three patients showed improvement of their pulmonary function test values and their clinical symptoms.

Moreover, LAI showed to be active against both *P. aeruginosa* and *M. abscessus*. In 2017, Olivier et al. (2017) (LAI NTM Study Group) reported the efficacy and safety of LAI (590 mg daily) in 44 patients (phase II study) with refractory pulmonary mycobacterial nontuberculous (*Mycobacterium avium* complex or *Mycobacterium abscessus*). A greater proportion of the LAI group demonstrated at least one negative sputum culture (32% vs. 9%), and improvement in a 6-min-walk test (+ 20.6 m vs. − 25.0 m) with limited systemic toxicity. In 2013, Clancy et al. (2013) published a phase II study of LAI (70, 140, 280, and 560 mg; $n = 7$, 5, 21, and 36) in cystic fibrosis patients chronically infected with *P. aeruginosa*. The adverse event profile was similar among Arikace and placebo subjects, but the lung function was higher in the 560 mg dose group. Also, the sputum *P. aeruginosa* density decreased in the 560 mg group against placebo.

Conclusions

Traditional pharmacological agents have to cross many barriers and hostile environments in the body that degrade them in the way, such as acidic stomach, intestinal wall barrier, liver, proteins, and enzymes in the bloodstream and the blood brain barrier to be able to reach the site where they are needed. Thus, they have to be ingested over and over again to be effective in the body. However, if ingestion exceeds certain doses, the therapeutic agent may become toxic and severely damage one or several organs in the body. Nanomedicine emerges as a potential solution to these problems, where liposomes are one of the most effective, healthy, and safe nanoparticle structures developed thus far. Liposomes can go through the body and function like a vehicle that can reach the specific tissue, organ or receptor of interest. This is achieved by adding molecules on the liposome surface that function like molecular "keys". As described above, the therapeutically benefits of encapsulating anticancer drugs such as daunorubicin, doxorubicin and cytarabine in liposomes have been demonstrated. To achieve that, the liposome formulation should be carefully and properly designed. This may reduce the toxicity while maintaining or improving treatment efficacy. Physicochemical properties and surface composition of liposomes can be easily adjusted and highly personalized, thus dictating the biological destiny of liposomes for each individual or disease. Although this is not a simple task, it may represent a turning point in the application of nano-membrane technology in personalized cancer therapy and other diseases.

Abbreviations

A: anemia; Abelcet®: amphotericin B; AC: advance cancer; AE: adverse effects; AGC: atypical glandular cells; AmBisome®: amphotericin B; AML: acute myeloid leukemia; Amphotec®: amphotericin B; AP: abdominal pain; ARF: acute renal failure; Arikace®: amikacin; Ast: asthenia; AUC: area under curve; B: bacteremia; BC: breast cancer; C: cardiotoxicity; C:U: number of carbons:number of unsaturation; CIATEJ: Centro de Investigación y Asistencia en Tecnología y Diseño del Estado de Jalisco; Cmax: maximum concentration; CPX-351: daunorubicin + cytarabine; CPM: cyclophosphamide; CR: complete response; CR: complete remission; Cyt: cytarabine; D: diarrhea; DAP: diacyldimethylammonium-propane; DaunoXome®: daunorubicin; Depocyt®: cytarabine; DepoDur™: morphine sulfate; DLBCL: diffuse large B-cell lymphoma; DLPA: dilauroyl phosphatidic acid; DLPC: dilauroyl phosphatidylcholine; DLPE: dilauroyl phosphatidylethanolamine; DLPG: dilauroyl phosphatidylglycerol; DLPS: dilauroyl phosphatidylserine; DLT: the dose-limiting toxicity; DLin-MC3-DMA: (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino)butanoate; DMPA: dimyristoyl phosphatidic acid; DMPC: dimyristoyl phosphatidylcholine; DMPE: dimyristoyl phosphatidylethanolamine; DMPG: dimyristoyl phosphatidylglycerol; DMPS: dimyristoyl phosphatidylserine; DNA: deoxyribonucleic acid; DOPA: dioleoyl phosphatidic acid; DOPC: dioleoyl phosphatidylcholine; DOPE: dioleoyl phosphatidylethanolamine; DOPG: dioleoyl phosphatidylglycerol; DOPS: dioleoyl phosphatidylserine; DOTAP: dioleoyl trimethylammonium-propane; Doxil®: doxorubicin; DPPA: dipalmitoyl phosphatidic acid; DPPC: dipalmitoyl phosphatidylcholine; DPPE: dipalmitoyl phosphatidylethanolamine; DPPG: dipalmitoyl phosphatidylglycerol; DPPS: dipalmitoyl phosphatidylserine; DSPA: distearoyl phosphatidic acid; DSPC:

distearoyl phosphatidylcholine; DSPE: distearoyl phosphatidylethanolamine; DSPG: distearoyl phosphatidylglycerol; DSPS: distearoyl phosphatidylserine; EFS: events-free survival; EndoTAG®: paclitaxel; EOC: epithelial ovarian carcinoma; Epaxal®: inactivated hepatitis A virus; EPC: ethylphosphocholine; EPG: esterified propoxylated glycerol; Exparel®: bupivacaine; F: fatigue; FDA: Food and Drug Administration; FN: febrile neutropenia; FU: focus ultrasound; GC: gastric cancer; Gem: gemcitabine; GEN: IL-12 plasmid; Genexol-PM: PEG–PLA polymeric micelle; H: hypotension; HCC: hepatocellular carcinoma; HER2: human epidermal growth factor receptor 2; HFS: hand–foot syndrome; Hk: hypokalemia; HNC: head and neck cancer; HSPC: hydrogenated soy phosphatidylcholine; H_t: hypertension; HT: the heterotype; IFD: invasive fungal diseases; IFI: invasive fungal infections; Inflexal V®: inactivated hemagglutinin, and A or B influenza virus; ITT: the intention-to-treat; IU: investigational use; L: leukopenia; LAI: liposomal amikacin for inhalation; LB: liposomal bupivacaine; Ld: liver dysfunction; LEP-ETU: paclitaxel; LF: liposomal formulation; Lipo-Dox®: doxorubicin; Lipusu®: paclitaxel; LPTX: liposomal paclitaxel; Marqibo®: vincristine; MBC: metastatic breast cancer; MCL: mantle cell lymphoma; Mepact®: mifamurtide; MGC: metastatic gastric cancer; MHL: multirelapsed Hodgkin lymphoma; Mil: miltefosine; Milt: milt; MM: multiple myeloma; MM-302: doxorubicin; mPAC: metastatic pancreatic adenocarcinoma; m-PFS: median progression-free survival; MRX34: Mir-34a; MS: multiple sclerosis; MSPC: monostearoyl phosphatidylcholine; MTD: maximum tolerated dose; Myocet®: doxorubicin + cyclophosphamide; n: number of patients; N: neutropenia; Na: nauseas; nal-IRI: nanoliposomal hydrochloride irinotecan; NPs: nanoparticles; NPLD: liposomal doxorubicin formulation; NRS: numerical rating scale; NSCLC: the non-small-cell lung carcinoma; OC: ovarian cancer; Onivyde®: irinotecan + fluorouracil + folinic acid; ORR: objective response rate; OS: overall survival; P: pneumonia; Par: paromycin; PC: phosphatidylcholine; PDAC: pancreatic cancer; PEG: polyethylene glycol; PEG2000-C-DMG: α-(30-{[1,2-di(myristyloxy)propanoxy]carbonylamino}propyl)-ω-methoxy-polyoxyethylene; PEI: polyethylenimine; PFS: progression-free survival; PFS: median radiologic; PKs: pharmacokinetics; PLA: polylactic acid; PLD: doxorubicin in liposomes; PO_4^{2-}: phosphate group; POD: postoperative day; POTO: postoperative total opiates consumption; PR: partial response; PTX: paclitaxel; PTX–LCN: paclitaxel lipid core nanoparticle; PTX–LDE: paclitaxel a lipid core nanoparticle with encapsulated paclitaxel; Q3W: every 3 weeks; R: rash; RBGB: regulator of G protein signaling rgsb; RES: reticuloendothelial system; RF: respiratory failure; RFA: radiofrequency ablation; RFN: refractory febrile neutropenia; RMM: relapse or refractory multiple myeloma; RNA: ribonucleic acid; ROC: recurrent ovarian cancer; S: sepsis; S/M: stomatitis/mucositis; SD: stable disease; siRNA: small interfering RNA; SSG: sodium stibogluconate; T: thrombocytopenia; T_C: the transition temperature of phospholipids; TFR: targets transferrin receptor; Thermodox®: doxorubicin; TNBC: triple-negative breast cancer; TTP: time to progression; US: United States; UTI: urinary tract infection; V: vomiting; VAS: visual analogue scale; Visudyne®: verteporphin; VL: visceralleishmaniasis; VSLI: vincristine sulfate liposomes injection; Vyxeos™: daunorubicin and cytarabine liposomal; Xemys: myelin basic proteins; WT: the wild-type.

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