

PLGA Polymers and Doxorubicin for the Treatment of Malignant Gliomas in Adults: An Overview



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Abstract:

Malignant brain tumors, such as glioblastoma and astrocytoma, are the most aggressive diffuse gliomas with a high grade (4) of malignancy in adults, leading to high mortality. The development of pharmacological approaches to drug delivery systems has led to increased effectiveness and reduced systemic toxicity of anticancer therapy. Delivery systems, such as implants, plates, gels, and micro- and nanoparticles, are used as carriers for anticancer substances, improving their solubility and biodistribution. These delivery systems affect the mechanism of drug action, reduce toxicity. Micro- and nanoparticles can penetrate physiological barriers of the body, including the blood-brain barrier (BBB). Due to changes in the microvascular system, they linger and accumulate in the area of pathology. Despite extensive data on delivery systems, only a few have undergone clinical trials and been adopted into clinical practice. For over 20 years, polymeric plates containing carmustine have been clinically used to treat malignant brain tumors. The search for safer and more effective forms of drug anti-tumor agents continues, as glioblastoma remains an incurable disease. Doxorubicin is a primary chemotherapy agent with proven efficacy, which is included in standard therapy for almost all tumor types. However, it is not used to treat central nervous system tumors, as it is believed that it does not cross the BBB. The polymers of lactic acid and glycolic acid (PLGA or PLG) are biocompatible and biodegradable. Standards for different tumor types where doxorubicin is used. We describe the mechanisms of action of polymeric and nanoparticle forms of chemotherapy drugs, the prospects of using PLGA polymers, and assess possible ways to deliver doxorubicin and other medications for brain tumors effectively.

Keywords: Glioblastoma, Astrocytoma, Brain tumors, Doxorubicin, Delivery systems, Polymers, Nanoparticles, PLGA.

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1. INTRODUCTION

Doxorubicin is one of the most effective anti-tumor chemotherapy drugs used in the treatment of nearly all types of cancer [1], both in its standard form and with liposomal delivery systems. However, it is not used for brain tumors because it does not penetrate the BBB [2, 3]. Doxorubicin is administered by rapid intravenous infusion

over 15-20 minutes. It has been found that cardiotoxicity decreases with prolonged infusion over 6 hours or more. A meta-analysis revealed that prolonged infusion reduces cardiotoxic effects with no differences in clinical response [4]. However, prolonged infusions may cause discomfort to the patient. The use of liposomal delivery may facilitate long-term drug administration. Moreover, the effective-

ness of doxorubicin has been demonstrated in glioblastoma patients and human glioma cells *in vitro* [5]. Delivery systems based on PLGA polymers are capable of increasing the anti-tumor efficacy of drugs, such as doxorubicin [6], by avoiding peak concentrations and reducing toxicity. This is due to changes in pharmacokinetics [7, 8], increased solubility [9], the ability to penetrate the BBB, and accumulation in tumors due to the enhanced permeability and retention effect [10]. Liposomes with doxorubicin (Doxil[®], Caelyx[®], and Myocet[®]) have been approved by the FDA and are allowed for increased delivery to tumor tissues, while reducing accumulation in internal organs. However, their therapeutic efficacy increases only slightly [11, 12]. The half-life of liposomal doxorubicin is up to 72 hours compared to 10 minutes for the standard form [13]. Liposomal formulations are also associated with dose-dependent toxicity, which can lead to severe mucositis and hand-foot syndrome [14, 15]. The effectiveness of Gliadel[®] polymeric plates as a delivery system for the chemotherapeutic agent carmustine has been proven in the treatment of malignant brain tumors. The plates were placed in the cavity after tumor resection. In combination with temozolomide and radiation therapy, Gliadel[®] significantly improved the median survival duration of patients. Among different forms of delivery systems, biocompatible and biodegradable nanoparticles, including PLGA, are promising. PLGA is a lipophilic polymer that is approved by the FDA and European Medicines Agency and is used as a delivery vehicle for chemotherapeutics, anti-inflammatories, antibiotics, and other drugs. The complete biodegradability, simple synthesis, and controlled release of PLGA make it a promising delivery agent for these drugs. In experimental therapy of rats with glioblastoma, poloxamer-coated PLGA nanoparticles containing doxorubicin overcame the BBB, penetrated, and accumulated in tumors, thereby increasing the antitumor efficacy of doxorubicin [9]. The PLGA nanoparticle degrades into lactate and glycolate, which are metabolized in the Krebs cycle. The acid ratio determines the hydrophobicity and rate of degradation of PLGA [16]. However, one of the challenges of using PLGA for therapeutic purposes is low drug loading and rapid drug release from nanoparticles [7], which may be due to the predominant adsorption of the drug on the nanoparticle surface, leading to lower levels of drug reaching the target cells or tissues than expected after loading. According to the results of clinical studies, a recommended dose of PLGA nanoparticles containing doxorubicin with a satisfactory safety profile is 90 mg/m² [17], while for liposomal doxorubicin (Caelyx[®]), it is only 50 mg / m², and for the standard form of doxorubicin, *i.e.*, 75 mg / m². The use of delivery systems based on biodegradable polymers and the anti-tumor drug doxorubicin may be promising in the therapy of malignant gliomas. This work aimed to review research and clinical recommendations for the treatment of malignant brain tumors using doxorubicin and polymers. We used the PubMed and eLIBRARY.RU databases, as well as the Google Scholar search engine, to

conduct a search for 70 guidelines based on evidence-based medicine for glioblastoma, astrocytoma, other types of brain tumors and tumors of other localizations from the National Comprehensive Cancer Network (NCCN[®]). The keywords used were: "glioblastoma," "astrocytoma," "doxorubicin," "polymers," "nanoparticles," "PLGA," "therapy," and "toxicity". The works reviewed were published between 1995 and 2024. A total of 218 literary sources were analyzed in preparing the review.

2. CHARACTERISTICS OF GLIOBLASTOMA AND ASTROCYTOMA: A STANDARD THERAPY FOR THEM

It is assumed that glioblastoma may arise from neural stem cells, neuroglial precursor cells, oligodendroglia and astrocytes, mesenchymal stroma cells, *etc* [18, 19]. Astrocytoma, on the other hand, arises from astrocytes [20]. The WHO revision of central nervous system (CNS) tumor classification in 2016 and 2021 changed the structure of glioma classification by incorporating molecular-genetic features of tumors in addition to histological features [21]. For glioblastoma, it was recommended to determine the *IDH1/2* mutation status, which led to the separation of glioblastomas with *IDH1/2* wild type (grade 4) and astrocytoma with mutant *IDH1/2* (grade 4) in adults into separate diseases that belong to a general subgroup of diffuse high-grade gliomas in adults (Table 1). Pediatric-type diffuse gliomas were also systematized based on molecular genetic profiles, and key aberrations were included in their names. They are now no longer called "glioblastomas". In diffuse *IDH1/2* wild-type gliomas occurring in patient age groups younger than 65 (75-84) [18], the possibility of a patient having diffuse pediatric-type glioma should be considered [21]. The collective term "multiform glioblastoma" is no longer used [21].

Table 1. Characteristics of *IDH1/2* wild-type glioblastoma and *IDH1/2* mutant astrocytoma (grade 4).

Type of Tumor	Glioblastoma <i>IDH1/2</i> -wild-type	Astrocytoma <i>IDH1/2</i> -mutant/Refs
Source of origin	Develops <i>de novo</i>	Diffuse astrocytomas <i>IDH1/2</i> mutants (grade 2-3)
Incidence, %	~ 90	~ 10
Median and peak age at diagnosis, years	65(75-84) [22]	38(40-50) [23]
Localization	Supratentorial	Predominantly frontal
Microvascular proliferation	+/-	+/-
Necrosis	+/-	+/-
Molecular-genetic characteristics	<i>IDH1</i> , <i>IDH2</i> - wild-type; <i>TERT</i> promoter mutation; <i>EGFR</i> amplification/mutation; chromosome copy number changes: +7/-10	<i>IDH1</i> or <i>IDH2</i> mutation; <i>CDKN2A/B</i> deletion; <i>TP53</i> mutation; <i>ATRX</i> mutation

Morphologically, *IDH1/2* wild-type glioblastoma are highly cellular tumors that infiltrate brain parenchyma. Tumour cells

are polymorphic with pronounced cell and nuclear atypia. The cellular composition may vary and include small, granular, multinuclear, giant cells, and gemistocytes. Different types of cells with pronounced histological diversity may be present in the same tumour. Mitotic activity is high. Necrosis in glioblastomas often has a pseudopalisading type [24]. However, the histopathological criteria for necrosis and vascular proliferation in the classification of high-grade diffuse gliomas have lost their prognostic value, and prognostic markers have now been identified as *IDH1/2* mutations and homozygous deletions of *CDKN2A/B* [25]. Additionally, these tumors are characterized by point mutations in the *TERT* promoter region (74-83%), homozygosity deletion of *CDKN2A* (37-58%), and amplification/mutation of *EGFR* (25-50%). These genetic features correlate with a negative prognosis for glioblastoma [24]. The methylation status of the *MGMT* promoter is one of the prognostic biomarkers for this type of cancer. With *MGMT*

gene methylation, the response to alkylating agents, such as temozolomide, is better. The frequency of *TP53* mutations is lower in glioblastomas (25-37%) compared to *IDH1/2* mutant astrocytoma (about 80%). Mutations in *ATRX* are rare in glioblastoma with wild-type *IDH1* and *IDH2* but common in astrocytoma with *IDH1* or *IDH2* mutations [24].

Morphologically, cases of *IDH1/2* mutant astrocytoma are indistinguishable from wild-type *IDH1/2* glioblastoma. The classification of CNS tumors is no longer strictly histological, as the presence of a homozygous deletion in *CDKN2A* or *CDKN2B* classifies a tumor as grade 4, the highest grade of malignancy, even if there is no microvascular proliferation or necrosis. Therefore, glioblastomas should be diagnosed in diffuse astrocytic gliomas with *IDH1* or *IDH2* wild type in adults if they have microvascular proliferation, necrosis, *TERT* promoter mutation, *EGFR* gene amplification, or changes in the number of chromosomes (+7/-10) [24]. For *IDH1/2* mutant

Table 2. Standard of therapy for *IDH1/2*-wild-type glioblastoma and *IDH1/2*-mutant astrocytoma (NCCN Guidelines Version 3.2024, 2024) [28-53].

Type of Tumor/Therapy Method	Glioblastoma <i>IDH1/2</i> wild type	Astrocytoma <i>IDH1/2</i> mutant	Advantages of the Method/Refs	Disadvantages of the Method/Refs
Surgical resection	Subtotal/Total		High survival rate with 90% tumor resection, biopsy (diagnosis), palliative care	The low survival rate with less than 90% tumor resection, post-operative edema, infection, risk of metastasis outside the CNS up to 2%
Laser interstitial thermotherapy	-		Minimally invasive method in patients with inoperable craniotomy [26, 27]	Additional research needed; for transient aphasia, temporary hemiparesis, and dysphagia [28]
Radiotherapy	3D, targeted, hypofractionated [29]		Reactivation of the anti-tumor immune response [31]	Nausea, vomiting, oral ulceration, alopecia, skin pigmentation [32]; development of resistance [33]; risk of severe myelotoxicity [34]; development of myelodysplastic syndrome [35]; decrease in hematopoiesis, especially granulocyte and thrombopoiesis; cardiotoxicity; nephrotoxicity - glomerular atrophy and increased permeability of glomerular capillary endothelium [36]; progression [38]
Chemotherapy	Temozolomide; polymer wafers with carmustine (BCNU) in the resection cavity [30]			Patients receiving carmustine wafers are at higher risk of seizures and postoperative infections [40]
(Local/Systemic) At recurrence or disease progression	Combination of lomustine and temozolomide [37]	-	Increase in radiosensitivity [39] Increase in survival, palliative care	Cardiovascular toxicity [41], gastrointestinal perforation, pancreatitis, arterial thromboembolism, hypertension, palmarplantar syndrome [42], toxicity to the nervous system [43], neutropenia, infections, nephrotic syndrome, liver damage, bleeding, thrombocytopenia, anemia, leukopenia, visual impairment, diarrhea, nausea, vomiting, stomatitis, malignant basal cell tumor, cutaneous squamous cell carcinoma, keratoacanthoma, melanoma, dermatitis, pneumonitis, rhabdomyolysis, facial nerve paralysis, arthritis, fever, peripheral edema, asthenia, hypersensitivity reactions, progression of previous chronic myelomonocytic leukemia, pancreatic adenocarcinoma, suppression of bone marrow function and pulmonary fibrosis [49-51], pseudo-response, and progression [52]
If the preferred or other recommended regimens are ineffective or intolerable	Temozolomide, a combination of procarbazine, carmustine/lomustine, and vincristine, polymer wafers (implants) with carmustine (BCNU) in the resection cavity Etoposide, platinum drugs		Increase in survival, overcoming resistance	
Antibodies/Inhibitors (Systemic)	Bevacizumab, regorafenib (VEGF A, VEGFR); Tumors with <i>NTRK</i> gene fusion (Larotrectinib; Entrectinib); BRAF/MEK inhibitors (For <i>BRAF V600E</i> Mutation): Dabrafenib/trametinib; Vemurafenib/cobimetinib	Ivosidenib [44]	Increase in radiosensitivity [45] and chemosensitivity [46] Increase in survival [47], overcoming resistance	
Tumor-treating fields therapy	-		Increase in survival, palliative care [48]	Inconvenience of use; additional studies on effectiveness needed [53]

Table 3. Doxorubicin, polymers, and nanoparticles in the modern standard of therapy for tumors of different types (NCCN Guidelines Version 1.2024- 2.2025, 2024) [64-115].

Drug	Drug Formulation/ Route of Administration	Tumor Type
Doxorubicin	Standard form (Systemic)	Malignant tumors: bladder, breast HER2+/-, cervical, salivary glands, kidney [64], Merkel cell carcinoma, neuroendocrine, adrenal, prostate, colorectal, small cell lung [65], thymus, thyroid [66], endometrial, uterine [67]; Richter's transformation in Hodgkin's lymphoma [68]; mesothelioma, peritoneal, multiple myeloma, neuroblastoma, intermediate-risk nonseminomas, Wilms' tumor (nephroblastoma); cholangiocarcinoma [69]; macroglobulin anemia; soft tissue sarcomas; lymphomas/leukemias: Burkitt's, marginal zone, classic follicular, B-cell, including pediatric, HIV-associated, mantle cell, diffuse large B-cell, post-transplant, Waldenström's/macroglobulinemia, Hodgkin's, including pediatric, anaplastic large cell associated with breast implant [70], T-cell [71], hepatosplenic; pediatric and adult acute lymphoblastic, hairy cell; blastic plasmacytoid dendritic cell neoplasms, vaginal cancer
	Liposomes (Systemic) [72]	Malignant tumors: invasive breast, ovarian, fallopian tube, peritoneal, uterine, endometrial, cervical; mycosis fungoides/Sézary syndrome; lymphomas/leukemia: primary cutaneous, adult T-cell [73], Castleman's disease, Hodgkin's [74, 75]; Kaposi's sarcoma [76], multiple myeloma [77], soft tissue sarcomas [78], prostate [79]
	Microspheres (Local/Chemoembolization)	Uveal melanoma, liver metastases [80]; cholangiocarcinoma, hepatocellular carcinoma [24, 81-83]
Daunorubicin	Liposomes (Systemic)	Chronic lymphocytic leukemia/small lymphocytic lymphoma histologic transformation (Richter) [84]; Kaposi sarcoma [76].
Vincristine	Liposomes (Systemic)	Uveal melanoma [85]
Irinotecan	Liposomes (Systemic)	Malignant tumors of the biliary tract [86, 24]; adenocarcinoma of the pancreas [87, 88]
Carmustine	Biodegradable polymeric wafers (Local)	Glioblastoma IDH1/2 wild-type and astrocytoma IDH1/2 mutant, grade 4 [89, 90]
Aspargase	PEGylated form of engineered protein	Acute lymphoblastic leukemia, pediatric acute lymphoblastic leukemia, extranodal NK/T-cell lymphomas [91-93]
Paclitaxel	Albumin nanoparticles	Breast cancer, non-small cell lung cancer, pancreatic cancer, melanoma, biliary tract cancers [94-98]
Interferon alpha subtype 2b	PEGylated form	Polycythemia vera, adult T-cell leukemia/lymphoma, systemic mastocytosis, mycosis fungoides/sezary syndrome, melanoma, B-cell lymphomas, bone cancer, histiocytic neoplasms [99-107]
Cytarabine and daunorubicin	Liposomes	Acute myeloid leukemia [108]
Rapamycin/sirolimus	Albumin nanoparticles	Perivascular epithelioid cell tumors, soft tissue sarcoma [109, 110]
Lanreotide acetate	Microparticle or Autogel	Gastroenteropancreatic neuroendocrine tumors
Cytosine arabinoside	Liposomes (CSF)	Leptomeningeal metastases (lymphoma, breast cancer), acute lymphoblastic leukemia [111-113]
Filgrastim	PEGylated form (Subcutaneous)	Bladder cancer, gestational trophoblastic neoplasia, hairy cell leukemia [114, 115]

astrocytoma compared to *IDH1/2* wild-type cases, there is an increased frequency of *MGMT* methylation, a decreased frequency of *TERT* mutations (5-28%), and no *EGFR* amplification or *PTEN* mutation [24].

The genome and epigenome of glioblastomas are well described, and biological subtypes have been identified. These subtypes are defined by their gene expression profiles: proneural, classical, and mesenchymal. Although this has not influenced patient survival or the treatment approach, it is likely due to intratumoral heterogeneity in glioblastomas [18]. Despite significant molecular genetic research on malignant gliomas, which has improved the classification of CNS tumors and increased treatment efficacy and prognosis, long-term patient survival remains low [24]. Standard therapy for patients with diffuse malignant glioma includes surgical resection, radiation therapy, chemotherapy (temozolomide), and alternating electric current therapy (Table 2). However, these treatments do not have a long-lasting anti-tumor effect

[25]. Without treatment, the median overall survival for patients with glioblastoma from the time of diagnosis is no more than 3-4 months. After standard therapy, it can be up to 13-16 months [25]. One of the main mechanisms of anti-tumor activity of chemotherapeutics is the inhibition of DNA and protein synthesis, as well as alkylation, methylation, and DNA damage caused by free radicals [191].

The median overall survival of patients with *IDH1/2*-mutant astrocytoma after treatment is higher and amounts to 54 months [25]. Total resection of glioma, regardless of the molecular status of the tumor, increases life expectancy for patients [23], but due to the diffuse growth of the tumor, complete resection is not always possible. The treatment of malignant diffuse gliomas is also complicated by the heterogeneity of genetic drivers [54] and innate or acquired resistance of tumor cells to known therapy [55, 56], which also have pronounced toxic side effects [57, 58].

Thus, malignant diffuse gliomas in adults are currently incurable. The modern standard of therapy helps to prolong life and alleviate the symptoms of the disease, but it does not affect long-term survival. Therefore, the search for more effective treatment methods continues.

3. DOXORUBICIN, AS A PART OF THE MODERN STANDARD THERAPY FOR ONCOLOGICAL DISEASES: MECHANISMS OF ITS ANTITUMOR AND TOXIC EFFECTS

Doxorubicin is one of the main drugs included in the standard therapy for most types of tumors (Table 3). In accordance with the treatment protocol, doxorubicin can be administered systemically as a single agent or in combination with other drugs, either in standard form or as liposomes, both for initial treatment and for recurrent or progressive cancers that have developed resistance to standard therapies, as well as for supportive and palliative care [1]. Doxorubicin is part of a group of essential medications available in the form of concentrate for preparing solutions for infusion, intra-arterial administration, and intravenous injection. Despite its strong antitumor activity, the low permeability of doxorubicin through the BBB has limited its use in tumors of the central nervous system [2, 3].

The mechanisms of toxic and anti-tumor action of doxorubicin are complex and not fully understood. Doxorubicin inhibits topoisomerase II [59], which is associated with its anti-tumor activity. Its toxic effects are also associated with the formation of reactive oxygen species and their impact on cell membranes and organelles [60, 61]. The high affinity of doxorubicin for cardiolipin enables it to accumulate in mitochondria, leading to mitochondrial dysfunction due to oxidative stress [62].

4. POLYMERS AND NANOPARTICLES USED IN MODERN STANDARDS OF THERAPY FOR CANCER: MECHANISMS OF THEIR ANTITUMOR ACTION

Despite numerous preclinical and clinical studies on different delivery systems, such as devices, gels, plates, films, micro- and nanoparticles, which have been conducted since 1958 [63], only a few of them have entered the modern standards for the treatment of some types of cancer (Table 3).

Polymer plates with carmustine (1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), better known as Gliadel® plates, are a part of the evidence-based standard of therapy for malignant gliomas, glioblastoma and astrocytoma [1]. The plates consist of a polyanhydride polymer, which is formed by the polymerization of a carboxylic acid with anhydride bonds and is the most studied, proven biocompatible, and biodegradable polymer for tumor therapy [89]. The plates are biodegradable implants approved by the FDA in 1996 for patients with recurrent glioblastomas as an adjunct surgery. Gliadel® plates were the first FDA-approved method for conducting local prolonged-action chemotherapy for brain tumors. This significantly improved the median survival of patients

[89]. In a 2022 observational study on 506 patients with malignant glioma who received adjuvant treatment with Gliadel® plates, an increase in median overall survival to 18 months was found. Of these, 39.8% of patients survived for two years and 31.5% for three years. These encouraging results open up possibilities for the development of new approaches to treating malignant brain tumors using biocompatible polymers as drug carriers, including nanoparticles [90].

One of the main tasks in the development of new polymeric materials is to achieve controlled and prolonged delivery of drugs to brain tumors. Polymeric nanoparticles, nanofibers, and gels allow for an increased residence time of drugs in the tumor, which contributes to their increased effectiveness. In immunotherapy, PLGA nanoparticles can protect antigens from degradation, increase the likelihood that they will be presented to immune cells, and reduce side toxic effects [116].

During tumor growth, morphological and molecular changes occur in tumor tissues. These changes have divergent effects; some contribute to the efficacy of therapy with micro- and nano-sized forms of drugs, such as the EPR (enhanced permeability and retention) effect, hemorrhages, edema, and microleaks from vessels, all of which contribute to systemic therapy. However, other changes hinder treatment. Due to the heterogeneous BBB during tumor growth [117], thromboses [118], and impaired lymphatic drainage, which contributes to edema and increased intracranial pressure [119, 120], many drugs may poorly penetrate tumor tissues, and their concentrations may be insufficient for a pronounced antitumor response. It has been shown that only about 20% of temozolomide, a first-line drug used in the treatment of glioblastoma and grade 4 astrocytoma, penetrates tumors when it is introduced into the systemic circulation [121].

Upon intravenous injection of nanoparticles, circulating serum proteins attach to the surface of the nanoparticles, forming a “protein corona” [122]. The antitumor action of PLGA nanoparticles with doxorubicin may be facilitated by the adsorption of apolipoprotein E (APO-E) on the surface of nanoparticles, followed by their interaction with APO-E receptors on the surface of endothelial cells in brain vessels, overcoming the BBB due to extravasation through receptor-mediated transcytosis [123, 124]. These effects, along with the “passive” extravasation of nanoparticles caused by tumor-specific leakage from blood capillaries with incompletely formed walls and ineffective lymphatic drainage in tumors (EPR effect), contribute to the accumulation of nanoparticles in tumor tissues [123, 124].

It is known that lactate receptors are overexpressed in glioblastoma cells [125]. It has been found that PLGA nanoparticles enter glioma cells through clathrin-dependent endocytosis [126]. The pH inside PLGA nanoparticles can reach 2 [127]. The acidic microenvironment can affect the effectiveness of the administered drug. The formation of acids during the degradation of PLGA may destabilize acid-sensitive drugs

contained in the nanoparticles and reduce their efficacy [90]. However, some data suggest that acidification within a tumor cell can increase the antitumor efficacy of chemotherapeutic drugs, such as doxorubicin [128, 129] and paclitaxel [128]. Under conditions of high acidity ($\text{pH} < 4$) or high alkalinity ($\text{pH} > 11$), active oxygen species and enzymes, such as hyaluronidases, destroy the intercellular matrix of tumor tissues and areas of invasive tumor growth more efficiently. This promotes the release of antitumor substances in these areas [147]. Alkaline intracellular pH (pHi) promotes DNA synthesis and tumor cell proliferation, increasing their number and tumor volume [129]. Also, the existing pHi threshold, around 7.1-7.2, is the limit below which enzymes lose their activity, and growth factors cannot stimulate the progression of the G1 phase of cell division and entry into the cell cycle [130]. It has been shown that the activity and expression of the Na^+/H^+ antiporters, involved in maintaining pHi, increases in doxorubicin-resistant tumor cells, and a decrease in pHi in the cell contributes to the intracellular accumulation of doxorubicin, reducing its level of resistance [128]. It has been noted that pHi in drug-resistant cells is higher, and an acidic environment increases DNA binding with the alkylating agents, such as cisplatin, which increases its antitumor efficacy. The use of bafilomycin, a hydrogen pump inhibitor, contributes to the reduction in pH of tumor cells, increasing the cytotoxicity of cisplatin. An increase in pH promotes the transition of tumor cells to G2/M [131-148], thus stimulating cell proliferation. It is assumed that a decrease in pHi is an early signal for the activation of caspases during apoptosis. Cytochrome-mediated caspase activation requires cytosolic acidification, with the highest caspase activity at a pHi of 6.3-6.8 [149]. With an increase in alkaline pHi, the activity of glycolysis increases, which is necessary for energy production in rapidly growing tumor cells [150, 151].

One of the mechanisms of action of polymers in the treatment of brain tumors is the enhancement of the effect of radiotherapy. Radiosensitive polymers can exacerbate tumor cell damage, which can be used in glioblastoma using surgical access [152].

Thus, the formation of acids as a result of the degradation of PLGA can contribute to the antitumor effect both by increasing the antitumor activity of doxorubicin and by stopping the cell cycle, inhibiting the activity of the enzyme system and ion channels of tumor cells. Whereas, due to increased expression of lactate receptors on tumor cells, PLGA nanoparticles can selectively accumulate in them.

PLGA nanoparticles, upon intravenous administration, predominantly accumulate in the liver and spleen. Capture and absorption of nanoparticles by macrophages occur after their opsonization by Fc fragments of immunoglobulins. Surface modification of particles reduces the capture opsonization of nanoparticles by macrophages in the liver, spleen, and other tissues, increase the effectiveness of targeted delivery of nanoparticles to tumor cells [152, 153].

The kidneys play an important role in the clearance of nanoparticles. Their excretion depends on the size, shape, surface modification, and charge. Individual studies have reported that both an increase in the accumulation of polyethylene glycol-coated nanoparticles in the kidneys [154-156] and the prevention of their accumulation [157, 158] can occur. There is also evidence that the polyethylene glycol coating does not affect the clearance of these nanoparticles [159, 160]. Presumably, this is due to the fact that these coated nanoparticles are less likely to be captured by cells in the reticuloendothelial system. The size and charge of the nanoparticles are important factors in determining their pharmacokinetics and distribution in the body. Particles smaller than 6 nm undergo rapid renal clearance, while particles larger than 200 nm are metabolized in the liver and spleen. The half-life of nanoparticles and macromolecules in the blood and body increases with their diameter [161, 162]. However, there have been reports on the detection of nanoparticles in urine in an unchanged form after injection into laboratory mice [122]. Nanoparticles can enter through the outflow renal arteriole (Arteriola glomerularis efferens) into the capillaries surrounding the tubules of the nephron, enter its lumen, and then are excreted in the urine.

Systemically administered nanoparticles with a diameter of <5 nm are excreted through renal filtration. Larger nanoparticles (> 200 nm in diameter) cannot effectively reach the BBB due to sequestration in the spleen. PLGA nanoparticles coated with polyethylene glycol, with a size of 100 nm, have a longer circulation time and better accumulation in brain parenchyma compared to particles with sizes of 200 nm and 800 nm for mice with traumatic brain injury. However, Nowak *et al.* (2020) found that polystyrene nanoparticles with a diameter of 200 nm penetrate the BBB more effectively than those with diameters of 100 nm and 500 nm. Other studies reported that the size of the nanoparticles has a limited impact or does not affect their ability to penetrate the BBB at all. These contradictory results highlight the challenges in developing treatments for brain tumors, as the BBB, extracellular space, and physiology differ significantly between *in vivo* and *in vitro* models and humans.

5. CHARACTERISTICS OF PLGA-BASED POLYMERIC DELIVERY SYSTEMS AND THERAPEUTIC PROSPECTS FOR THEIR APPLICATION

Due to the distinctive characteristics of PLGA polymers, they have significant potential for brain tumor treatments. These polymers are completely biodegradable and exhibit mechanical stability [163]. They are relatively straightforward to produce and widely accessible commercially. They ensure stable drug release and offer modifiable properties. They are also biocompatible [90]. The PLGA polymer is used in various medical devices, such as screws, plates, stents, wound dressings, and tissue adhesives. It is also used as a material for surgical meshes, drug carriers, and tissue engineering (Fig. 1) [63]. Depending on the required effect, the degradation rate can be changed from a few days to a few years. RESOMER® is the most commonly used brand of PLGA.

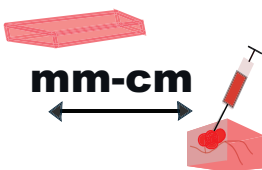
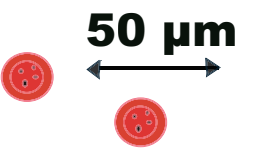
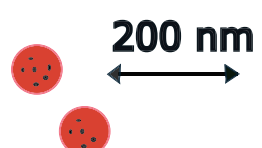
Implant Implant <i>in situ</i>	 mm-cm
Microcapsules Microparticles	 50 μm
Nanocapsules Nanoparticle	 200 nm

Fig. (1). Most commonly used forms and sizes of PLGA polymers for drug delivery systems with controlled release [16, 164].

In the body, polymer degradation occurs due to hydrolysis and the action of the esterase enzyme [165]. PLGA degradation is heterogeneous; it occurs faster in the central part of the delivery system. When water is present, PLGA undergoes hydrolysis, where water first wets the surface and then diffuses into the polymer. Hydrolysis of the ester bond then occurs, splitting the polymer chain into shorter chains that gradually dissolve, leading to erosion of the polymer. The resulting monomers and oligomers are excreted by the kidneys or metabolized into carbon dioxide and water [16]. PLGA polymers are negatively charged, limiting their cellular uptake via negatively charged cell membranes. It is assumed that the specific targeting unit for PLGA nanoparticles and other particles are all pathological conditions of the body associated with damage to the vascular wall.

Peptide-loaded PLGA implants are widely used as drug carriers with a duration of action from 1 to 6 months for the treatment of hormone-sensitive malignant tumors of the prostate or breast [166]. The implant is administered subcutaneously or intramuscularly, and the drug is released in a controlled manner over an extended period of time. Small-sized intravitreal PLGA implants loaded with dexamethasone are used to treat macular edema of the eye [167]. One approach is the formation of *in situ* implants. For this, the PLGA polymer PLGA is dissolved in a biocompatible organic solvent and administered to the patient. This is easier to use, requires less expense, and uses smaller needles. PLGA microspheres (1 μm to 1000 μm micrometers in size) are typically used for parenteral delivery of hydrophilic or hydrophobic drugs. Inside the microsphere, drugs are either solubilized or dispersed. The release profile depends on the size distribution and porosity of microspheres, the characteristics and concentration of drugs, and release conditions. There are several phases in the drug release profile: initially rapid release followed by a slower phase, and finally, an

accelerated release phase. This accelerated final release is caused by acidic pH inside particles due to the autocatalytic degradation of polymers [168]. Nanoparticles and nanocapsules with sizes between 20 and 200 nanometers can be made from PLGA polymers. The main mode of administration for these nanosized delivery systems is through intravenous injections, but other routes, such as oral, dermal, pulmonary, or ocular administration, are also possible [16]. Thus, PLGA polymer in the form of microspheres is used intramuscularly and subcutaneously with leuprolide acetate (Eligard®, Leuprolide acetate®, Durin®) for prostate tumors and Alzheimer's disease [169]. Subcutaneously, octreotide acetate is administered to patients with acromegaly and oncological patients with intestinal tumors and neuroendocrine carcinoid tumors. Microspheres containing goserelin acetate are used for hormone-sensitive breast and prostate tumors [170]. Gels containing doxycycline hyclate are used to treat periodontitis and cancer pain. An implant-pump is used for prolonged intrathecal infusion of ziconotide acetate for cancer treatment [166, 171]. PLGA Trelstar LA microspheres with the hormone triptorelin pamoate are used to treat breast and prostatic tumors [172]. PLGA gel Oncogel® with paclitaxel is used in anticancer therapy [173].

In glioblastoma, inhibition of AKT/mTORC1/GPRs and PI3K/AKT signaling pathways, targeting the glioma microenvironment, and modifying PLGA nanoparticles will be attempted. It is possible that the complex targeting of the main targets is related to glioma, including activation of the growth factor pathway, cell destruction, cycle checkpoints that control cell division, and abnormal telomere maintenance, which may improve patient survival and stimulate the immune system to treat glioblastoma. PLGA-temozolomide and IL-15 nanoparticles

with NK cell membrane-decorated try to elicit the immunostimulatory microenvironment for glioblastoma chemo-immunotherapy.

6. PRECLINICAL AND CLINICAL STUDIES ON DRUG DELIVERY SYSTEMS USING POLYMERS AND DOXORUBICIN

The main polymers used in the development of drug delivery systems for tumor therapy include doxorubicin, which is divided into natural and synthetic categories. Natural polymers, such as gelatin, albumin, collagen, alginate, hyaluronic acid, dextran, cellulose, chitosan, mannan, and pullulan, and synthetic polymers, such as polyglycolic acid, polyglutamic acid, polylactide, poly(lactide-co-glycolide) and poly(lactic acid) as well as polyvinyl alcohol, polylysine and pluronic are also used for

developing new anticancer drugs (Fig. 2).

Due to their unique characteristics, PLGA polymers have great potential for brain tumor treatment. They are exhibit mechanical stability. They are relatively easy to produce and widely available commercially. They ensure stable drug release and offer modifiable properties.

The use of existing, well-studied drugs, which are used for other types of tumors, is one of the alternatives in research. The development of new drugs often takes a long time and costs a lot of money. Most new molecules fail to be effective. Drug repurposing, with proven efficacy, is possible through the use of new forms of drugs, for example as part of delivery systems. Repurposing existing drugs is also cheaper and faster than developing new ones [174].

Polymer forms of doxorubicin	Therapy/Research/References	Local/Systemic	Degradation	Natural/Syntetic
Device/Implant	Research [131]	Local	+/-	Natural/Syntetic
Film	Research [132; 133]	Local	+	Natural/Syntetic
Sponge	Research [134]	Local	+	Natural/Syntetic
Gel	Research [135-140]	Local	+	Natural/Syntetic
Fibers	Research [141]	Local	+	Natural/Syntetic
Microparticles	Therapy [142; 143]	Local	+/-	Natural/Syntetic
Nanoparticles	Research [138; 144; 145]	Local/Systemic	+/-	Natural/Syntetic
Micelles	Research [146]	Local/Systemic	+	Natural/Syntetic
Vesicles	Research [147]	Local/Systemic	+	Natural/Syntetic

Fig. (2). Polymeric forms of doxorubicin used in the clinic and preclinical/clinical trials in oncology.

Table 4. Polymer PLGA with doxorubicin in clinical/preclinical trials for treating and diagnostic malignant gliomas.

Form	Route of Administration	References
Preclinical trials		
Nanoparticle	Systemic	[6, 10]
Nanoparticle	Intranasal	[189]
Nanoparticle/theranostics	Systemic	[190]
Nanoparticle/ multicomponent/modification	Systemic	[191]
Scaffold/ multicomponent/modification	Systemic	[192]
Nanoparticle/ multicomponent	Systemic	[193]
Clinical trial		
Nanoparticle	Systemic	[17]

Maksimenko O. *et al.* (2019) and Kudelkina V. *et al.* (2021) used PLGA nanoparticles with doxorubicin to treat rat glioblastoma 101.8 and found that the nanoparticles penetrate through the BBB into intracranial tumors, increasing the antitumor efficacy of doxorubicin *in vivo* (Table 4).

Anti-tumor effects *in vitro* were also observed against two human glioma cell lines using PLGA-loaded nanoparticles containing the chemotherapeutic agent morusin and conjugated to chlorotoxin, a peptide specific for certain chloride channels expressed on glioma cells. These effects were statistically significant [175]. Similar results were also obtained *in vitro* with PLGA nanoparticles [176-178] and *in vivo* with rodent models of brain tumors [178], opening up the possibility of their clinical application [90]. To improve the delivery of carboplatin as a chemotherapeutic, PLGA conjugates with folic acid receptors, overexpressed on tumor cell membranes, including those of glioblastomas, were developed [179].

To increase the accumulation of anti-tumor drugs in the tumor, a method of convection drug delivery under pressure is used. This method is introduced through a catheter placed in glioblastoma tissues. This leads to an increased volume of distribution compared to diffusion, allowing drugs to spread through brain tissues more efficiently [180]. The effectiveness of doxorubicin has been found in humans with intratumoral administration [181, 5]. Focused ultrasound can increase the permeability of the BBB and penetration of drugs into tumor tissue [90]. Nanoparticles can also be delivered into the brain tissue using phagocytic cells, such as monocytes, neutrophils, and stem cells. Immune cells like monocytes and neutrophils are particularly attractive vectors for nanoparticle delivery because they easily penetrate the BBB to sites of injury, inflammation, and tumors [90]. Clinical trials of PLGA membranes with anti-tumor substances are currently underway [182]. After the surgical removal of soft tissue tumors, PLGA membranes containing drugs are placed in the surgical cavity. In clinical studies on malignant esophageal tumors, nanoparticles of PLGA [183] were used as carriers for an immunomodulating agent consisting of trehalose-6, 6-dimycolate, an invariant activator of natural killer T cells. An oral form of the PLGA tablet [184] was used as a vaccine for patients with melanoma containing tumor proteins and granulocyte-macrophage colony-stimulating factor, oligodeoxynucleotide, and lysates. PLGA nanoparticles protect antigens from degradation, increase their presentation to immune cells, and reduce toxic side effects [116]. Thus, the implant Ozurdex™, containing dexamethasone, slowly decomposes in the polymer PLGA delivery system Novadur® [185], releasing the drug. Currently, this medicinal form of dexamethasone is undergoing clinical trials for its efficacy in patients with retinal detachment due to uveal melanoma.

In addition to its anti-tumor activity, a reduction in drug toxicity in nanoparticles has been demonstrated.

Thus, statistically significant reductions in hematological toxicities, as well as normal levels of erythrocytes, platelets, and hemoglobin, along with cardiotoxicity and testicular toxicity from doxorubicin, were observed in PLGA nanoparticle formulations [186]. Nephrotoxicity was also described in another study [187].

Targeting polymeric drug delivery systems that take advantage of the overexpression of specific molecules and proteins in tumor cells, as well as the microenvironment and extracellular components of the intercellular matrix, may be more effective for anti-cancer therapy [188-204]. Antitumor effectiveness can be increased by targeting multiple targets at once. Compared with single-ligand targeting of PLGA-docetaxel to human U87-MG glioblastoma cells, targeting two ligands at once, the EGFR and PD-L1, is more effective [199].

PLGA nanoparticles are targeted with folic or hyaluronic acid, transferrin for breast cancer treatment [200, 202] and glioblastoma [206], conjugated with antibodies to neuronal cell adhesion molecules in lung cancer [201], and used for targeting artesunate and chloroquine to colorectal cancer [198]. PLGA nanoparticles modified with PEG, biotin, or EpCAM aptamer were used to enhance cellular uptake and cytotoxicity of doxorubicin in breast cancer, non-small cell lung cancer, and prostate cancer [203, 205].

Chemotherapy for malignant gliomas is often given systemically, either through intravenous or oral routes. However, the toxicity of these treatments limits the dose that can be administered. To reduce this toxicity and improve the targeted delivery of antitumor drugs, researchers are exploring alternative routes of administration, such as intraarterial and intranasal routes, which limit systemic toxicity [206-209].

Intranasal administration of polymeric nanoparticles loaded with antitumor drugs into the brain is a non-invasive and painless method that helps to bypass the BBB, increasing the bioavailability and effectiveness of therapy due to enhanced penetration and residence time of the drug in the brain. This approach has been shown to enhance the anti-angiogenic effects of bevacizumab in the treatment of glioblastoma [210].

Intranasal-administered nanoparticles allow for rapid absorption, reduced systemic toxicity, decreased enzymatic degradation, and increased bioavailability of the active agent, leading to a more prolonged and effective pharmacological response. This method allows drug delivery from the nasal cavity directly to the brain through the trigeminal and olfactory nerves, but it is limited by the small surface area of exposure, low epithelial permeability, and the small volume of drug that can be delivered. Additionally, the drug can be removed from the absorption site by nasal secretions [211, 212].

Intracerebroventricular infusion and convection-enhanced delivery are effective treatment options for brain tumors, including using doxorubicin. However, these methods are invasive and require precise injections into the tumor [213].

Additionally, in clinical trials, PLGA implants loaded with high-dose carmustine have been placed into the cavity after glioblastoma resection in patients. This treatment was evaluated and showed good safety results [214].

Moreover, an alternative direct method for drug delivery to the brain could be convection-enhanced delivery, which does not depend on diffusion and allows for precise control of the infusion rate. In this method, drugs are evenly distributed over a large area of the brain, regardless of the size of the molecule administered. However, due to the absence of specific drug targeting, neurotoxicity may occur [215].

CONCLUSION

Glioblastoma and astrocytoma (grade 4) are two rare but deadly brain tumors that affect adults. Unfortunately, there is no cure for them, and the main driver mutations that could potentially be targeted in clinical practice have not been identified in most cases. A total of 9,386 mutations have been detected, including 199 genes that affect patient survival [194]. Standard systemic and local chemotherapy for glioblastoma and astrocytoma has increased the lifespan of patients, but long-term survival of up to 5 years remains extremely low. Tumor cells are resistant to anti-tumor treatments, and the BBB prevents the accumulation of many drugs. Moreover, no driver mutations have been found in glioblastoma or astrocytoma, whose signaling pathways can be targeted. Currently, the treatment of glioblastoma patients is mainly focused on palliative care and therapies that increase life expectancy. Despite this, glioblastomas recur in almost 100% of cases. Therefore, research on new anti-cancer substances and methods for treating glioblastomas continues.

The use of doxorubicin for brain tumors is justified due to its high anti-tumor activity in most types of malignant tumors. Different polymeric forms of doxorubicin, methods of administration, and their combinations can help to overcome the BBB and resistance, increase the anti-tumor efficacy, and reduce toxicity. Conjugation or encapsulation of micro and nanoparticles in PLGA improves the delivery of doxorubicin to malignant gliomas and increases its antitumor activity. This can occur due to the selective accumulation of particles in tumor tissues, the EPR effect, acidification of the extra- and intracellular environment of the tumor, and the acidic composition of the PLGA polymer.

Safe, biocompatible polymers are promising materials for the development of delivery systems for local and systemic administration, such as implantable devices, plates, gels, and nanoparticles for controlled and prolonged targeted delivery of anti-tumor drugs, allowing them to overcome BBB and drug resistance. The development of local therapy using postoperative access is especially relevant because almost all patients undergo surgical treatment. Polymeric carriers are used locally, with plates that actively release drugs directly into the tumor growth site placed in the surgical bed. Combining

local and systemic drug delivery may be an effective strategy in fighting the tumor. PLGA is a promising polymer for delivering anti-tumor agents because it completely decomposes into water and carbon dioxide, contributing to increasing effectiveness and reducing toxicity of anticancer drugs.

AUTHORS' CONTRIBUTION

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

LIST OF ABBREVIATIONS

APO-E	= Apolipoprotein E
ATRX	= Alpha-thalassemia mental retardation syndrome
BBB	= The blood-brain barrier
BCNU	= 1,3-Bis(2-chloroethyl)-1-nitrosourea
CDKN2A	= Cyclin-dependent kinase inhibitor 2A
CNS	= The central nervous system
EGFR	= The epidermal growth factor receptor
EpCAM	= Epithelial cell adhesion molecule
Fc	= Fragment crystallizable
IDH	= The isocitrate dehydrogenase
MEK	= Mitogen-activated protein kinase
MGMT	= Methylguanine methyltransferase
NCCN	= The national comprehensive cancer network
NK	= Natural killer
NTRK	= Neurotrophic receptor tyrosine kinase
PD-L1	= Programmed death-ligand 1
PEG	= Polyethylene glycol
pHi	= Intracellular pH
PTEN	= Phosphatase and tensin homolog
VEGFR	= Vascular endothelial growth factor

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

- [1] The national comprehensive cancer network **2024**. https://www.nccn.org/guidelines/category_1
- [2] Zhou, Y.S.; Wang, W.; Chen, N.; Wang, L.C.; Huang, J.B. Research progress of anti-glioma chemotherapeutic drugs (Review). *Oncol. Rep.*, **2022**, 47(5), 101. <http://dx.doi.org/10.3892/or.2022.8312> PMID: 35362540
- [3] Dhungel, L.; Rowsey, ME; Harris, C; Raucher, D Synergistic effects of temozolomide and doxorubicin in the treatment of glioblastoma multiforme: Enhancing efficacy through combination therapy. *molecules*, **2024**, 29(4), 840.
- [4] Hoeger, C.W.; Turissini, C.; Asnani, A. Doxorubicin cardiotoxicity: Pathophysiology updates. *Curr. Treat. Options Cardiovasc. Med.*, **2020**, 22(11), 52. <http://dx.doi.org/10.1007/s11936-020-00842-w>
- [5] Matcovschii, V.; Lisii, D.; Gudumac, V.; Dorosenko, S. Selective interstitial doxorubicin for recurrent glioblastoma. *Clin. Case Rep.*, **2019**, 7(12), 2520-2525. <http://dx.doi.org/10.1002/ccr3.2546> PMID: 31893093
- [6] Kudelkina, VV; Khalanskiy, AS; Makarova, OV Comparative morphological and biochemical characteristics of the toxic effects of doxorubicin and nanosomal PLGA-doxorubicin form in the experimental glioblastoma treatment. *Clin. exp. morphology*, **2021**, 10(1), 58-65.
- [7] Kovshova, T.; Osipova, N.; Alekseeva, A.; Malinovskaya, J.; Belov, A.; Budko, A.; Pavlova, G.; Maksimenko, O.; Nagpal, S.; Braner, S.; Modh, H.; Balabanyan, V.; Wacker, M.G.; Gelperina, S. Exploring the interplay between drug release and targeting of lipid-like polymer nanoparticles loaded with doxorubicin. *Molecules*, **2021**, 26(4), 831. <http://dx.doi.org/10.3390/molecules26040831> PMID: 33562687
- [8] He, P.; Xu, S.; Guo, Z.; Yuan, P.; Liu, Y.; Chen, Y.; Zhang, T.; Que, Y.; Hu, Y. Pharmacodynamics and pharmacokinetics of PLGA-based doxorubicin-loaded implants for tumor therapy. *Drug Deliv.*, **2022**, 29(1), 478-488. <http://dx.doi.org/10.1080/10717544.2022.2032878> PMID: 35147071
- [9] Liu, W.Y.; Hsieh, Y.S.; Wu, Y.T. Poly (lactic-co-glycolic) acid-poly (vinyl pyrrolidone) hybrid nanoparticles to improve the efficiency of oral delivery of β -carotene. *Pharmaceutics*, **2022**, 14(3), 637. <http://dx.doi.org/10.3390/pharmaceutics14030637> PMID: 35336010
- [10] Maksimenko, O.; Malinovskaya, J.; Shipulo, E.; Osipova, N.; Razzhivina, V.; Arantseva, D.; Yarovaya, O.; Mostovaya, U.; Khalansky, A.; Fedoseeva, V.; Alekseeva, A.; Vanchugova, L.; Gorshkova, M.; Kovalenko, E.; Balabanyan, V.; Melnikov, P.; Baklaushev, V.; Chekhonin, V.; Kreuter, J.; Gelperina, S. Doxorubicin-loaded PLGA nanoparticles for the chemotherapy of glioblastoma: Towards the pharmaceutical development. *Int. J. Pharm.*, **2019**, 572, 118733. <http://dx.doi.org/10.1016/j.ijpharm.2019.118733> PMID: 31689481
- [11] Jain, R.K.; Stylianopoulos, T. Delivering nanomedicine to solid tumors. *Nat. Rev. Clin. Oncol.*, **2010**, 7(11), 653-664. <http://dx.doi.org/10.1038/nrclinonc.2010.139> PMID: 20838415
- [12] Anchordoquy, T.J.; Simberg, D. Watching the gorilla and questioning delivery dogma. *J. Control. Release*, **2017**, 262, 87-90. <http://dx.doi.org/10.1016/j.jconrel.2017.07.021> PMID: 28713040
- [13] Symon, Z.; Peyser, A.; Tzemach, D.; Lyass, O.; Sucher, E.; Shezen, E.; Gabizon, A. Selective delivery of doxorubicin to patients with breast carcinoma metastases by stealth liposomes. *Cancer*, **1999**, 86(1), 72-78. [http://dx.doi.org/10.1002/\(SICI\)1097-0142\(19990701\)86:1<72::AID-CNCR12>3.0.CO;2-1](http://dx.doi.org/10.1002/(SICI)1097-0142(19990701)86:1<72::AID-CNCR12>3.0.CO;2-1) PMID: 10391566
- [14] O'Brien, M.E.R.; Wigler, N.; Inbar, M.; Rosso, R.; Grischke, E.; Santoro, A.; Catane, R.; Kieback, D.G.; Tomczak, P.; Ackland, S.P.; Orlandi, F.; Mellars, L.; Alland, L.; Tendler, C. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX™/Doxil®) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. *Ann. Oncol.*, **2004**, 15(3), 440-449. <http://dx.doi.org/10.1093/annonc/mdh097> PMID: 14998846
- [15] Zhu, Y.; Wang, F.; Zhao, Y.; Zheng, X. Pegylated liposomal doxorubicin-related palmar-plantar erythrodysesthesia: A literature review of pharmaceutical and clinical aspects. *Eur. J. Hosp. Pharm. Sci. Pract.*, **2021**, 28(3), 124-128. <http://dx.doi.org/10.1136/ejhp-2020-002311> PMID: 32591480
- [16] RESOMER® biodegradable polymers for medical device applications research <https://www.sigmaaldrich.com/RU/en/technical-documents/technical-article/materials-science-and-engineering/drug-delivery/resomer>
- [17] Filon, O.; Krivorotko, P.; Kobayakov, G.; Razjivina, V.; Maximenko, O.; Gelperina, S.; Kreuter, J. A phase I study of safety and pharmacokinetics of NanoBB-1-Dox in patients with advanced solid tumors. *J. Clin. Oncol.*, **2017**, 35(15, suppl), e13537-e13537. http://dx.doi.org/10.1200/JCO.2017.35.15_suppl.e13537
- [18] Ah-Pine, F.; Khettab, M.; Bedoui, Y. On the origin and development of glioblastoma: Multifaceted role of perivascular mesenchymal stromal cells. *Acta Neuropathol Commun.*, **2021**, 11, 104. <http://dx.doi.org/10.1186/s40478-023-01605-x>
- [19] Zeng, A.; Wei, Z.; Rabinovsky, R.; Jun, H.J.; El Fatimy, R.; Deforzh, E.; Arora, R.; Yao, Y.; Yao, S.; Yan, W.; Uhlmann, E.J.; Charest, A.; You, Y.; Krichevsky, A.M. Glioblastoma-derived extracellular vesicles facilitate transformation of astrocytes via reprogramming oncogenic metabolism. *iScience*, **2020**, 23(8), 101420. <http://dx.doi.org/10.1016/j.isci.2020.101420> PMID: 32795915
- [20] Kapoor, M.; Gupta, V. Astrocytoma. 2023. In: *StatPearls Internet*; StatPearls Publishing: Treasure Island, FL, **2024**.
- [21] Louis, D.N.; Perry, A.; Wesseling, P.; Brat, D.J.; Cree, I.A.; Figarella-Branger, D.; Hawkins, C.; Ng, H.K.; Pfister, S.M.; Reifenberger, G.; Soffietti, R.; von Deimling, A.; Ellison, D.W. The 2021 WHO classification of tumors of the central nervous system: A summary. *Neuro-oncol.*, **2021**, 23(8), 1231-1251. <http://dx.doi.org/10.1093/neuonc/noab106> PMID: 34185076
- [22] Tan, A.C.; Ashley, D.M.; López, G.Y.; Malinzak, M.; Friedman, H.S.; Khasraw, M. Management of glioblastoma: State of the art and future directions. *CA Cancer J. Clin.*, **2020**, 70(4), 299-312. <http://dx.doi.org/10.3322/caac.21613> PMID: 32478924
- [23] Molinaro, A.M.; Hervey-Jumper, S.; Morshed, R.A.; Young, J.; Han, S.J.; Chunduru, P.; Zhang, Y.; Phillips, J.J.; Shai, A.; Lafontaine, M.; Crane, J.; Chandra, A.; Flanagan, P.; Jahangiri, A.; Cioffi, G.; Ostrom, Q.; Anderson, J.E.; Badve, C.; Barnholtz-Sloan, J.; Sloan, A.E.; Erickson, B.J.; Decker, P.A.; Kosel, M.L.; LaChance, D.; Eckel-Passow, J.; Jenkins, R.; Villanueva-Meyer, J.; Rice, T.; Wrensch, M.; Wiencke, J.K.; Oberheim Bush, N.A.; Taylor, J.; Butowski, N.; Prados, M.; Clarke, J.; Chang, S.; Chang, E.; Agbi, M.; Theodosopoulos, P.; McDermott, M.; Berger, M.S. Association of maximal extent of resection of contrast-enhanced and non-contrast-enhanced tumor with survival within molecular subgroups of patients with newly diagnosed glioblastoma published correction appears. *JAMA Oncol.*, **2020**, 6(4), 495-503. <http://dx.doi.org/10.1001/jamaoncol.2019.6143> PMID: 32027343
- [24] Mallick, S.; Giridhar, P.; Rath, G.K. *Evidence based practice in Neuro-oncology*; Springer, **2021**. <http://dx.doi.org/10.1007/978-981-16-2659-3>
- [25] Christians, A.; Adel-Horowski, A.; Banan, R.; Lehmann, U.; Bartels, S.; Behling, F.; Barrantes-Freer, A.; Stadelmann, C.; Rohde, V.; Stockhammer, F.; Hartmann, C. The prognostic role of IDH mutations in homogeneously treated patients with anaplastic

- astrocytomas and glioblastomas. *Acta Neuropathol. Commun.*, **2019**, 7(1), 156.
<http://dx.doi.org/10.1186/s40478-019-0817-0> PMID: 31623667
- [26] Sujjantarat, N.; Hong, C.S.; Owusu, K.A.; Elsamadicy, A.A.; Antonios, J.P.; Koo, A.B.; Baehring, J.M.; Chiang, V.L. Laser interstitial thermal therapy (LITT) vs. bevacizumab for radiation necrosis in previously irradiated brain metastases. *J. Neurooncol.*, **2020**, 148(3), 641-649.
<http://dx.doi.org/10.1007/s11060-020-03570-0> PMID: 32602021
- [27] Morello, A.; Bianconi, A.; Rizzo, F.; Bellomo, J.; Meyer, A.C.; Garbossa, D.; Regli, L.; Cofano, F. Laser interstitial thermotherapy (LITT) in recurrent glioblastoma: What window of opportunity for this treatment? *Technol. Cancer Res. Treat.*, **2024**, 23, 15330338241249026.
<http://dx.doi.org/10.1177/15330338241249026> PMID: 38693845
- [28] Vetkas, A.; Germann, J.; Boutet, A.; Samuel, N.; Sarica, C.; Yamamoto, K.; Santyr, B.; Cheyuo, C.; Conner, C.R.; Lang, S.M.; Lozano, A.M.; Ibrahim, G.M.; Valiante, T.; Kongkham, P.N.; Kalia, S.K. Laser interstitial thermal therapy for the treatment of insular lesions: A systematic review. *Front. Neurol.*, **2023**, 13, 1024075.
<http://dx.doi.org/10.3389/fneur.2022.1024075> PMID: 36686528
- [29] Matsui, J.K.; Perlow, H.K.; Facer, B.D.; McCalla, A.; Marrazzo, L.; Detti, B.; Scorsetti, M.; Clerici, E.; Scoccianti, S.; Navarria, P.; Trifiletti, D.M.; Gondi, V.; Bovi, J.; Huang, J.; Brown, P.D.; Palmer, J.D. Radiotherapy for elderly patients with glioblastoma: An assessment of hypofractionation and modern treatment techniques. *Chin. Clin. Oncol.*, **2022**, 11(5), 38.
<http://dx.doi.org/10.21037/cco-22-76> PMID: 36336897
- [30] Dragojevic, S.; Turner, L.; Pal, P.; Janorkar, A.V.; Raucher, D. Elastin-like Polypeptide hydrogels for tunable, sustained local chemotherapy in malignant glioma. *Pharmaceutics*, **2022**, 14(10), 2072.
<http://dx.doi.org/10.3390/pharmaceutics14102072> PMID: 36297507
- [31] Gao, Z.; Zhao, Q.; Xu, Y.; Wang, L. Improving the efficacy of combined radiotherapy and immunotherapy: focusing on the effects of radiosensitivity. *Radiat. Oncol.*, **2023**, 18(1), 89.
<http://dx.doi.org/10.1186/s13014-023-02278-5> PMID: 37226275
- [32] Razvi, Y.; Chan, S.; McFarlane, T.; McKenzie, E.; Zaki, P.; DeAngelis, C.; Pidduck, W.; Bushehri, A.; Chow, E.; Jerzak, K.J. ASCO, NCCN, MASCC/ESMO: A comparison of antiemetic guidelines for the treatment of chemotherapy-induced nausea and vomiting in adult patients. *Support. Care Cancer*, **2019**, 27(1), 87-95.
<http://dx.doi.org/10.1007/s00520-018-4464-y> PMID: 30284039
- [33] Bahar, E.; Kim, J.Y.; Yoon, H. Chemotherapy resistance explained through endoplasmic reticulum stress-dependent signaling. *Cancers*, **2019**, 11(3), 338.
<http://dx.doi.org/10.3390/cancers11030338> PMID: 30857233
- [34] Said, M.M.; Broen, M.P.G.; Swart, E.L.; Bartelink, I.H.; Kouwenhoven, M.C.M. Myelotoxicity of temozolomide treatment in patients with glioblastoma is it time for a more mechanistic approach? *Cancers*, **2023**, 15(5), 1561.
<http://dx.doi.org/10.3390/cancers15051561> PMID: 36900352
- [35] Park, R.; Amin, M.; Trikalinos, N.A. Temozolomide duration and secondary hematological neoplasms: A literature review and implications for patients with neuroendocrine neoplasms. *J. Neuroendocrinol.*, **2022**, 34(7), e13178.
<http://dx.doi.org/10.1111/jne.13178> PMID: 35854663
- [36] Garzio, K.; McElroy, K.; Grossman, S.; Holdhoff, M.; Ozer, B.; Yankulina, O. Temozolomide in renal dysfunction. *Neuro-oncol.*, **2020**, 22(2)(Suppl. 2), ii122.
<http://dx.doi.org/10.1093/neuonc/noaa215.511>
- [37] Weller, J.; Tzaridis, T.; Mack, F.; Steinbach, J.P.; Schlegel, U.; Hau, P.; Krex, D.; Grauer, O.; Goldbrunner, R.; Bähr, O.; Uhl, M.; Seidel, C.; Tabatabai, G.; Brehmer, S.; Bullinger, L.; Galldiks, N.; Schaub, C.; Kebir, S.; Stummer, W.; Simon, M.; Fimmers, R.; Coch, C.; Glas, M.; Herrlinger, U.; Schäfer, N. Health-related quality of life and neurocognitive functioning with lomustine-temozolomide versus temozolomide in patients with newly diagnosed, MGMT-methylated glioblastoma (CeTeG/NOA-09): A randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol.*, **2019**, 20(10), 1444-1453.
[http://dx.doi.org/10.1016/S1470-2045\(19\)30502-9](http://dx.doi.org/10.1016/S1470-2045(19)30502-9) PMID: 31488360
- [38] Yoo, K.C.; Kang, J.H.; Choi, M.Y.; Suh, Y.; Zhao, Y.; Kim, M.J.; Chang, J.H.; Shim, J.K.; Yoon, S.J.; Kang, S.G.; Lee, S.J. Soluble ICAM-1 a Pivotal Communicator between tumors and macrophages, promotes mesenchymal shift of glioblastoma. *Adv. Sci. (Weinh.)*, **2022**, 9(2), 2102768.
<http://dx.doi.org/10.1002/adv.202102768> PMID: 34813169
- [39] Minea, R.O.; Duc, T.C.; Swenson, S.D.; Cho, H.Y.; Huang, M.; Hartman, H.; Hofman, F.M.; Schöenthal, A.H.; Chen, T.C. Developing a clinically relevant radiosensitizer for temozolomide-resistant gliomas. *PLoS One*, **2020**, 15(9), e0238238.
<http://dx.doi.org/10.1371/journal.pone.0238238> PMID: 32881880
- [40] Ewend, M.G.; Brem, S.; Gilbert, M.; Goodkin, R.; Penar, P.L.; Varia, M.; Cush, S.; Carey, L.A. Treatment of single brain metastasis with resection, intracavitary carmustine polymer wafers, and radiation therapy is safe and provides excellent local control. *Clin. Cancer Res.*, **2007**, 13(12), 3637-3641.
<http://dx.doi.org/10.1158/1078-0432.CCR-06-2095> PMID: 17575228
- [41] Valdiserra, G.; Mores, N.; Rocchi, R.E.; Sottosanti, L.; Felicetti, P.; Marchione, P.; Laurenti, L.; Fresa, A.; Bucaneve, G.; Cappello, E.; Bonaso, M.; Ferraro, S.; Convertino, I.; Tuccori, M. Signal management and risk minimization strategy: A case study on obinituzumab and non-overt disseminated intravascular coagulation. *Front. drug saf. regul.*, **2023**, 3, 1194683.
<http://dx.doi.org/10.3389/fdsfr.2023.1194683>
- [42] Matsumoto, T.; Ikoma, T.; Yamamura, S.; Miura, K.; Tsuduki, T.; Watanabe, T.; Nagai, H.; Takatani, M.; Yasui, H. Regorafenib is suitable for advanced colorectal cancer patients who have previously received trifluridine/tipiracil plus bevacizumab. *Sci. Rep.*, **2023**, 13(1), 2433.
<http://dx.doi.org/10.1038/s41598-023-29706-6> PMID: 36765099
- [43] Li, W.; Wen, K.; Zhu, W.; Luo, S. A real-world analysis of tyrosine receptor kinase inhibitor-related toxicities in cancer treatment. *Per. Med.*, **2023**, 20(6), 485-491.
<http://dx.doi.org/10.2217/pme-2023-0072> PMID: 37909303
- [44] Mellinghoff, I.K.; Ellingson, B.M.; Touat, M.; Maher, E.; De La Fuente, M.I.; Holdhoff, M.; Cote, G.M.; Burris, H.; Janku, F.; Young, R.J.; Huang, R.; Jiang, L.; Choe, S.; Fan, B.; Yen, K.; Lu, M.; Bowden, C.; Steelman, L.; Pandya, S.S.; Cloughesy, T.F.; Wen, P.Y. Ivosidenib in isocitrate dehydrogenase 1-mutated advanced glioma. *J. Clin. Oncol.*, **2020**, 38(29), 3398-3406.
<http://dx.doi.org/10.1200/JCO.19.03327> PMID: 32530764
- [45] Jost, T.; Schuster, B.; Heinzerling, L.; Weissmann, T.; Fietkau, R.; Distel, L.V.; Hecht, M. Kinase inhibitors increase individual radiation sensitivity in normal cells of cancer patients. *Strahlenther. Onkol.*, **2022**, 198(9), 838-848.
<http://dx.doi.org/10.1007/s00066-022-01945-y> PMID: 35471558
- [46] Heiland, D.H.; Masalha, W.; Franco, P.; Machein, M.R.; Weyerbrock, A. Progression-free and overall survival in patients with recurrent Glioblastoma multiforme treated with last-line bevacizumab versus bevacizumab/lomustine. *J. Neurooncol.*, **2016**, 126(3), 567-575.
<http://dx.doi.org/10.1007/s11060-015-2002-z> PMID: 26614518
- [47] Jahnke, K.; Muldoon, L.L.; Varallyay, C.G.; Lewin, S.J.; Kraemer, D.F.; Neuwelt, E.A. Bevacizumab and carboplatin increase survival and asymptomatic tumor volume in a glioma model. *Neuro-oncol.*, **2009**, 11(2), 142-150.
<http://dx.doi.org/10.1215/15228517-2008-077> PMID: 18772353
- [48] Stupp, R.; Taillibert, S.; Kanner, A.; Read, W.; Steinberg, D.M.; Lhermitte, B.; Toms, S.; Idhah, A.; Ahluwalia, M.S.; Fink, K.; Di Meco, F.; Lieberman, F.; Zhu, J.J.; Straghiotto, G.; Tran, D.D.; Brem, S.; Hottinger, A.F.; Kirson, E.D.; Lavy-Shahaf, G.; Weinberg, U.; Kim, C.Y.; Paek, S.H.; Nicholas, G.; Bruna, J.; Hirte,

- H.; Weller, M.; Palti, Y.; Hegi, M.E.; Ram, Z. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: A randomized clinical trial. *JAMA*, **2017**, *318*(23), 2306-2316. <http://dx.doi.org/10.1001/jama.2017.18718> PMID: 29260225
- [49] Understanding side effects Tafenlar + Mekinist **2024**. <https://www.us.tafinlarmekinist.com/advanced-melanoma/side-effects/understanding-side-effects/>
- [50] Garutti, M.; Bergnach, M.; Polesel, J.; Palmero, L.; Pizzichetta, M.A.; Puglisi, F. BRAF and MEK Inhibitors and their toxicities: A meta-analysis. *Cancers*, **2022**, *15*(1), 141. <http://dx.doi.org/10.3390/cancers15010141> PMID: 36612138
- [51] Poulikakos, P.I.; Sullivan, R.J.; Yaeger, R. Molecular pathways and mechanisms of BRAF in cancer therapy. *Clin. Cancer Res.*, **2022**, *28*(21), 4618-4628. <http://dx.doi.org/10.1158/1078-0432.CCR-21-2138> PMID: 35486097
- [52] Gatto, L.; Franceschi, E.; Tosoni, A.; Di Nunno, V.; Maggio, I.; Tonon, C.; Lodi, R.; Agati, R.; Bartolini, S.; Brandes, A.A. Distinct MRI pattern of "pseudoresponse" in recurrent glioblastoma multiforme treated with regorafenib: Case report and literature review. *Clin. Case Rep.*, **2021**, *9*(8), e04604. <http://dx.doi.org/10.1002/ccr3.4604> PMID: 34457284
- [53] Tumour Treating Fields (TTF) or Optune® for brain tumours. **2024**. <https://www.thebraintumourcharity.org/brain-tumour-diagnosis-treatment/treating-brain-tumours/emerging-treatments/ttf-tumour-treating-fields/>
- [54] Wen, P.Y.; Weller, M.; Lee, E.Q.; Alexander, B.M.; Barnholtz-Sloan, J.S.; Barthel, F.P.; Batchelor, T.T.; Bindra, R.S.; Chang, S.M.; Chiocca, E.A.; Cloughesy, T.F.; DeGroot, J.F.; Galanis, E.; Gilbert, M.R.; Hegi, M.E.; Horbinski, C.; Huang, R.Y.; Lassman, A.B.; Le Rhun, E.; Lim, M.; Mehta, M.P.; Mellinger, I.K.; Minniti, G.; Nathanson, D.; Platten, M.; Preusser, M.; Roth, P.; Sanson, M.; Schiff, D.; Short, S.C.; Taphoorn, M.J.B.; Tonn, J.C.; Tsang, J.; Verhaak, R.G.W.; von Deimling, A.; Wick, W.; Zadeh, G.; Reardon, D.A.; Aldape, K.D.; van den Bent, M.J. Glioblastoma in adults: A society for neuro-oncology (SNO) and European society of neuro-oncology (EANO) consensus review on current management and future directions. *Neuro-oncol.*, **2020**, *22*(8), 1073-1113. <http://dx.doi.org/10.1093/neuonc/noaa106> PMID: 32328653
- [55] Goenka, A.; Tiek, D.; Song, X.; Huang, T.; Hu, B.; Cheng, S.Y. The many facets of therapy resistance and tumor recurrence in glioblastoma. *Cells*, **2021**, *10*(3), 484. <http://dx.doi.org/10.3390/cells10030484> PMID: 33668200
- [56] Yin, D.; Jin, G.; He, H.; Zhou, W.; Fan, Z.; Gong, C.; Zhao, J.; Xiong, H. Celecoxib reverses the glioblastoma chemo-resistance to temozolomide through mitochondrial metabolism. *Aging (Albany NY)*, **2021**, *13*(17), 21268-21282. <http://dx.doi.org/10.18632/aging.203443> PMID: 34497154
- [57] Lu, G.; Zhu, P.; Rao, M.; Linendoll, N.; Buja, L.M.; Bhattacharjee, M.B.; Brown, R.E.; Ballester, L.Y.; Tian, X.; Pilichowska, M.; Wu, J.K.; Hergenroeder, G.W.; Glass, W.F.; Chen, L.; Zhang, R.; Pillai, A.K.; Hunter, R.L.; Zhu, J.J. Postmortem study of organ-specific toxicity in glioblastoma patients treated with a combination of temozolomide, irinotecan and bevacizumab. *J. Neurooncol.*, **2022**, *160*(1), 221-231. <http://dx.doi.org/10.1007/s11060-022-04144-y> PMID: 36203027
- [58] Angom, R.S.; Nakka, N.M.R.; Bhattacharya, S. Advances in glioblastoma therapy: An update on current approaches. *Brain Sci.*, **2023**, *13*(11), 1536. <http://dx.doi.org/10.3390/brainsci13111536> PMID: 38002496
- [59] van der Zanden, S.Y.; Qiao, X.; Neefjes, J. New insights into the activities and toxicities of the old anticancer drug doxorubicin. *FEBS J.*, **2021**, *288*(21), 6095-6111. <http://dx.doi.org/10.1111/febs.15583> PMID: 33022843
- [60] Smuder, A.J. Exercise stimulates beneficial adaptations to diminish doxorubicin-induced cellular toxicity. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, **2019**, *317*(5), R662-R672. <http://dx.doi.org/10.1152/ajpregu.00161.2019> PMID: 31461307
- [61] Wallace, K.B.; Sardão, V.A.; Oliveira, P.J. Mitochondrial determinants of doxorubicin induced cardiomyopathy. *Circ. Res.*, **2020**, *126*(7), 926-941. <http://dx.doi.org/10.1161/CIRCRESAHA.119.314681> PMID: 32213135
- [62] Shi, S.; Chen, Y.; Luo, Z.; Nie, G.; Dai, Y. Role of oxidative stress and inflammation-related signaling pathways in doxorubicin-induced cardiomyopathy. *Cell Commun. Signal.*, **2023**, *21*(1), 61. <http://dx.doi.org/10.1186/s12964-023-01077-5> PMID: 36918950
- [63] Darie-Niță, R.N.; Răpă, M.; Frackowiak, S. Special features of polyester-based materials for medical applications. *Polymers*, **2022**, *14*(5), 951. <http://dx.doi.org/10.3390/polym14050951> PMID: 35267774
- [64] Wilson, N.R.; Wiele, A.J.; Surasi, D.S.; Rao, P.; Sircar, K.; Tamboli, P.; Shah, A.Y.; Genovesi, G.; Karam, J.A.; Wood, C.G.; Tannir, N.M.; Msaouel, P. Efficacy and safety of gemcitabine plus doxorubicin in patients with renal medullary carcinoma. *Clin. Genitourin. Cancer*, **2021**, *19*(6), e401-e408. <http://dx.doi.org/10.1016/j.clgc.2021.08.007> PMID: 34625389
- [65] Aix, S.P.; Ciuleanu, T.E.; Navarro, A.; Cousin, S.; Bonanno, L.; Smit, E.F.; Chiappori, A.; Olmedo, M.E.; Horvath, I.; Grohé, C.; Farago, A.F.; López-Vilariño, J.A.; Cullell-Young, M.; Nieto, A.; Vasco, N.; Gómez, J.; Kahatt, C.; Zeaiter, A.; Carcereny, E.; Roubec, J.; Syrigos, K.; Lo, G.; Barneto, I.; Pope, A.; Sánchez, A.; Kattan, J.; Zarogoulidis, K.; Waller, C.F.; Bischoff, H.; Juan-Vidal, O.; Reinmuth, N.; Dómine, M.; Paz-Ares, L. Combination lurbinectedin and doxorubicin versus physician's choice of chemotherapy in patients with relapsed small-cell lung cancer (ATLANTIS): A multicentre, randomised, open-label, phase 3 trial. *Lancet Respir. Med.*, **2023**, *11*(1), 74-86. [http://dx.doi.org/10.1016/S2213-2600\(22\)00309-5](http://dx.doi.org/10.1016/S2213-2600(22)00309-5) PMID: 36252599
- [66] Romesser, P.B.; Sherman, E.J.; Whiting, K.; Ho, M.L.; Shaha, A.R.; Sabra, M.M.; Riaz, N.; Waldenberg, T.E.; Sabol, C.R.; Ganly, I.; McBride, S.M.; Fagin, J.A.; Zhang, Z.; Tuttle, R.M.; Wong, R.J.; Lee, N.Y. Intensity-modulated radiation therapy and doxorubicin in thyroid cancer: A prospective phase 2 trial. *Cancer*, **2021**, *127*(22), 4161-4170. <http://dx.doi.org/10.1002/cnrc.33804> PMID: 34293201
- [67] Spirtos, N.M.; Enserro, D.; Homesley, H.D.; Gibbons, S.K.; Cella, D.; Morris, R.T.; DeGeest, K.; Lee, R.B.; Miller, D.S. The addition of paclitaxel to doxorubicin and cisplatin and volume-directed radiation does not improve overall survival (OS) or long-term recurrence-free survival (RFS) in advanced endometrial cancer (EC): A randomized phase III NRG/Gynecologic Oncology Group (GOG) study. *Gynecol. Oncol.*, **2019**, *154*(1), 13-21. <http://dx.doi.org/10.1016/j.ygyno.2019.03.240> PMID: 31053405
- [68] Lugtenburg, P.; Avivi, I.; Berenschot, H.; Ilhan, O.; Marolleau, J.P.; Nagler, A.; Rueda, A.; Tani, M.; Turgut, M.; Osborne, S.; Smith, R.; Pfreundschuh, M. Efficacy and safety of subcutaneous and intravenous rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in first-line diffuse large B-cell lymphoma: The randomized MabEase study. *Haematologica*, **2017**, *102*(11), 1913-1922. <http://dx.doi.org/10.3324/haematol.2017.173583> PMID: 28935843
- [69] Kiefer, M.V.; Albert, M.; McNally, M.; Robertson, M.; Sun, W.; Fraker, D.; Olthoff, K.; Christians, K.; Pappas, S.; Rilling, W.; Soulen, M.C. Chemoembolization of intrahepatic cholangiocarcinoma with cisplatin, doxorubicin, mitomycin C, ethiodol, and polyvinyl alcohol. *Cancer*, **2011**, *117*(7), 1498-1505. <http://dx.doi.org/10.1002/cnrc.25625> PMID: 21425151
- [70] Wang, H.; Wuxiao, Z.J.; Zhu, J.; Wang, Z.; Wang, K.F.; Li, S.; Chen, X.; Lu, Y.; Xia, Z.J. Comparison of gemcitabine, oxaliplatin and L-asparaginase and etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone as first-line chemotherapy in patients with stage IE to IIE extranodal natural killer/T-cell lymphoma: a multicenter retrospective study. *Leuk. Lymphoma*, **2015**, *56*(4), 971-977.

- <http://dx.doi.org/10.3109/10428194.2014.939964> PMID: 24991715
- [71] Qian, Z.; Song, Z.; Zhang, H.; Wang, X.; Zhao, J.; Wang, H. Gemcitabine, navelbine, and doxorubicin as treatment for patients with refractory or relapsed T-cell lymphoma. *BioMed Res. Int.*, **2015**, *2015*, 1-7.
<http://dx.doi.org/10.1155/2015/606752> PMID: 25866797
- [72] Horsham, PA Doxorubicin hydrochloride liposome injection, for intravenous use. **2019**. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203263lbl.pdf
- [73] Sutton, G.; Blessing, J.; Hanjani, P.; Kramer, P. Phase II evaluation of liposomal doxorubicin (Doxil) in recurrent or advanced leiomyosarcoma of the uterus: A Gynecologic oncology group study. *Gynecol. Oncol.*, **2005**, *96*(3), 749-752.
<http://dx.doi.org/10.1016/j.ygyno.2004.11.036> PMID: 15721421
- [74] Bartlett, N.L.; Niedzwiecki, D.; Johnson, J.L.; Friedberg, J.W.; Johnson, K.B.; van Besien, K.; Zelenetz, A.D.; Cheson, B.D.; Canellos, G.P. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. *Ann. Oncol.*, **2007**, *18*(6), 1071-1079.
<http://dx.doi.org/10.1093/annonc/mdm090> PMID: 17426059
- [75] Moskowitz, A.J.; Shah, G.; Schöder, H.; Ganesan, N.; Drill, E.; Hancock, H.; Davey, T.; Perez, L.; Ryu, S.; Sohail, S.; Santarosa, A.; Galasso, N.; Neuman, R.; Liotta, B.; Blouin, W.; Kumar, A.; Lahoud, O.; Batlevi, C.L.; Hamlin, P.; Straus, D.J.; Rodriguez-Rivera, I.; Owens, C.; Caron, P.; Intlekofer, A.M.; Hamilton, A.; Horwitz, S.M.; Falchi, L.; Joffe, E.; Johnson, W.; Lee, C.; Palomba, M.L.; Noy, A.; Matasar, M.J.; Pongas, G.; Salles, G.; Vardhana, S.; Sanin, B.W.; von Keudell, G.; Yahalom, J.; Dogan, A.; Zelenetz, A.D.; Moskowitz, C.H. Phase II trial of pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin as second-line therapy for relapsed or refractory classical Hodgkin lymphoma. *J. Clin. Oncol.*, **2021**, *39*(28), 3109-3117.
<http://dx.doi.org/10.1200/JCO.21.01056> PMID: 34170745
- [76] Gbabe, O.F.; Okwundu, C.I.; Dedicoat, M.; Freeman, E.E. Treatment of severe or progressive Kaposi's sarcoma in HIV-infected adults. *Cochrane Libr.*, **2014**, *2014*(9), CD003256.
<http://dx.doi.org/10.1002/14651858.CD003256.pub2>
- [77] Orlowski, R.Z.; Nagler, A.; Sonneveld, P.; Bladé, J.; Hajek, R.; Spencer, A.; San Miguel, J.; Robak, T.; Dmoszynska, A.; Horvath, N.; Spicka, I.; Sutherland, H.J.; Suvorov, A.N.; Zhuang, S.H.; Parekh, T.; Xiu, L.; Yuan, Z.; Rackoff, W.; Harousseau, J.L. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: Combination therapy improves time to progression. *J. Clin. Oncol.*, **2007**, *25*(25), 3892-3901.
<http://dx.doi.org/10.1200/JCO.2006.10.5460> PMID: 17679727
- [78] Constantinidou, A.; Jones, R.L.; Scurr, M.; Al-Muderis, O.; Judson, I. Pegylated liposomal doxorubicin, an effective, well-tolerated treatment for refractory aggressive fibromatosis. *Eur. J. Cancer*, **2009**, *45*(17), 2930-2934.
<http://dx.doi.org/10.1016/j.ejca.2009.08.016> PMID: 19767198
- [79] Harris, K.A.; Harney, E.; Small, E.J. Liposomal doxorubicin for the treatment of hormone-refractory prostate cancer. *Clin. Prostate Cancer*, **2002**, *1*(1), 37-41.
<http://dx.doi.org/10.3816/CGC.2002.n.005> PMID: 15046711
- [80] Rostas, J.W.; Tam, A.L.; Sato, T.; Scoggins, C.R.; McMasters, K.M.; Martin, R.C.G., II Health-related quality of life during transarterial chemoembolization with drug-eluting beads loaded with doxorubicin (DEBDOX) for unresectable hepatic metastases from ocular melanoma. *Am. J. Surg.*, **2017**, *214*(5), 884-890.
<http://dx.doi.org/10.1016/j.amjsurg.2017.07.007> PMID: 28754534
- [81] Lammer, J.; Malagari, K.; Vogl, T.; Pilleul, F.; Denys, A.; Watkinson, A.; Pitton, M.; Sergent, G.; Pfammatter, T.; Terraz, S.; Benhamou, Y.; Avajon, Y.; Gruenberger, T.; Pomoni, M.; Langenberger, H.; Schuchmann, M.; Dumortier, J.; Mueller, C.; Chevallier, P.; Lencioni, R. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: Results of the precision V study. *Cardiovasc. Intervent. Radiol.*, **2010**, *33*(1), 41-52.
<http://dx.doi.org/10.1007/s00270-009-9711-7> PMID: 19908093
- [82] Kaprin, A.D.; Ivanov, S.A.; Petrov, L.O.; Kuchero, V.V.; Pobedintseva, Y.A.; Filimonov, E.V.; Kruglov, E.A.; Petrosyan, A.P.; Nazarova, V.V.; Unguryan, V.M. Transarterial chemoembolization and isolated liver chemoperfusion in the treatment of uveal melanoma in patients with liver metastases (a systematic review). *Med. Technol., Assess. Choice.*, **2022**, *44*(2), 72-79.
<http://dx.doi.org/10.17116/medtech20224402172>
- [83] Brown, K.T.; Do, R.K.; Gonen, M.; Covey, A.M.; Getrajdman, G.I.; Sofocleous, C.T.; Jarnagin, W.R.; D'Angelica, M.I.; Allen, P.J.; Erinjeri, J.P.; Brody, L.A.; O'Neill, G.P.; Johnson, K.N.; Garcia, A.R.; Beattie, C.; Zhao, B.; Solomon, S.B.; Schwartz, L.H.; DeMatteo, R.; Abou-Alfa, G.K. Randomized trial of hepatic artery embolization for hepatocellular carcinoma using doxorubicin-eluting microspheres compared with embolization with microspheres alone. *J. Clin. Oncol.*, **2016**, *34*(17), 2046-2053.
<http://dx.doi.org/10.1200/JCO.2015.64.0821> PMID: 26834067
- [84] Tsimberidou, A.M.; Kantarjian, H.M.; Cortes, J.; Thomas, D.A.; Faderl, S.; Garcia-Manero, G.; Verstovsek, S.; Ferrajoli, A.; Wierda, W.; Alvarado, Y.; O'Brien, S.M.; Albitar, M.; Keating, M.J.; Giles, F.J. Fractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone plus rituximab and granulocyte-macrophage-colony stimulating factor (GM-CSF) alternating with methotrexate and cytarabine plus rituximab and GM-CSF in patients with Richter syndrome or fludarabine-refractory chronic lymphocytic leukemia. *Cancer*, **2003**, *97*(7), 1711-1720.
<http://dx.doi.org/10.1002/cncr.11238> PMID: 12655528
- [85] Bedikian, A.Y.; Papadopoulos, N.E.; Kim, K.B.; Vardeleon, A.; Smith, T.; Lu, B.; Deitcher, S.R. A pilot study with vincristine sulfate liposome infusion in patients with metastatic melanoma. *Melanoma Res.*, **2008**, *18*(6), 400-404.
<http://dx.doi.org/10.1097/CMR.0b013e328311aaa1> PMID: 19011511
- [86] Kobayashi, K.; Tsuji, A.; Morita, S.; Horimi, T.; Shirasaka, T.; Kanematsu, T. A phase II study of LFP therapy (5-FU (5-fluorouracil) continuous infusion (CVI) and Low-dose consecutive (Cisplatin) CDDP) in advanced biliary tract carcinoma. *BMC Cancer*, **2006**, *6*(1), 121.
<http://dx.doi.org/10.1186/1471-2407-6-121> PMID: 16677397
- [87] Wang-Gillam, A.; Hubner, R.A.; Siveke, J.T.; Von Hoff, D.D.; Belanger, B.; de Jong, F.A.; Mirakhor, B.; Chen, L.T. NAPOLI-1 phase 3 study of liposomal irinotecan in metastatic pancreatic cancer: Final overall survival analysis and characteristics of long-term survivors. *Eur. J. Cancer*, **2019**, *108*, 78-87.
<http://dx.doi.org/10.1016/j.ejca.2018.12.007> PMID: 30654298
- [88] Hyung, J.; Kim, I.; Kim, K.; Ryoo, B.Y.; Jeong, J.H.; Kang, M.J.; Cheon, J.; Kang, B.W.; Ryu, H.; Lee, J.S.; Kim, K.W.; Abou-Alfa, G.K.; Yoo, C. Treatment with liposomal irinotecan plus fluorouracil and leucovorin for patients with previously treated metastatic biliary tract cancer: the phase 2b NIFTY randomized clinical trial. *JAMA Oncol.*, **2023**, *9*(5), 692-699.
<http://dx.doi.org/10.1001/jamaoncol.2023.0016> PMID: 36951834
- [89] Brem, H.; Piantadosi, S.; Burger, P.C.; Walker, M.; Selker, R.; Vick, N.A.; Black, K.; Sisti, M.; Brem, S.; Mohr, G.; Muller, P.; Morawetz, R.; Schold, S.C. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. *Lancet*, **1995**, *345*(8956), 1008-1012.
[http://dx.doi.org/10.1016/S0140-6736\(95\)90755-6](http://dx.doi.org/10.1016/S0140-6736(95)90755-6) PMID: 7723496
- [90] Caraway, C.A.; Gaitsch, H.; Wicks, E.E.; Kalluri, A.; Kunadi, N.; Tyler, B.M. Polymeric nanoparticles in brain cancer therapy: A review of current approaches. *Polymers*, **2022**, *14*(14), 2963.
<http://dx.doi.org/10.3390/polym14142963> PMID: 35890738
- [91] Van Trimpont, M.; Peeters, E.; De Visser, Y.; Schalk, A.M.; Mondelaers, V.; De Moerloose, B.; Lavie, A.; Lammens, T.;

- Goossens, S.; Van Vlierberghe, P. Novel insights on the use of L-Asparaginase as an efficient and safe anti-cancer therapy. *Cancers*, **2022**, *14*(4), 902. <http://dx.doi.org/10.3390/cancers14040902> PMID: 35205650
- [92] Wang, J.H.; Wang, H.; Wang, Y.J. Extranodal NK/T-Cell lymphomas analysis of the efficacy and safety of a combined gemcitabine, oxaliplatin and pegaspargase regimen for NK/T-cell lymphoma. *Oncotarget*, **2018**, *7*, 35412-35422. <http://dx.doi.org/10.18632/oncotarget.8643> PMID: 27072578
- [93] Prescribing information for calaspargase pegol-mknl injection, for intravenous use **2023**. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761102s000lbl.pdf
- [94] Teneriello, M.G.; Tseng, P.C.; Crozier, M.; Encarnacion, C.; Hancock, K.; Messing, M.J.; Boehm, K.A.; Williams, A.; Asmar, L. Phase II evaluation of nanoparticle albumin-bound paclitaxel in platinum-sensitive patients with recurrent ovarian, peritoneal, or fallopian tube cancer. *J. Clin. Oncol.*, **2009**, *27*(9), 1426-1431. <http://dx.doi.org/10.1200/JCO.2008.18.9548> PMID: 19224848
- [95] Rugo, H.S.; Barry, W.T.; Moreno-Aspitia, A.; Lyss, A.P.; Cirrincione, C.; Leung, E.; Mayer, E.L.; Naughton, M.; Toppmeyer, D.; Carey, L.A. Randomized Phase III trial of paclitaxel once per week compared with nanoparticle albumin-bound nab-paclitaxel once per week or ixabepilone with bevacizumab as first-line chemotherapy for locally recurrent or metastatic breast cancer: CALGB 40502/NCCTG N063H (Alliance). *J. Clin. Oncol.*, **2015**, *33*(21), 2361.
- [96] Jameson, G.S.; Borazanci, E.; Babiker, H.M.; Poplin, E.; Niewiarowska, A.A.; Gordon, M.S.; Barrett, M.T.; Rosenthal, A.; Stoll-D'Astice, A.; Crowley, J.; Shemanski, L.; Korn, R.L.; Ansaldi, K.; Lebron, L.; Ramanathan, R.K.; Von Hoff, D.D. Response rate following albuminbound paclitaxel plus gemcitabine plus cisplatin treatment among patients with advanced pancreatic cancer: A phase 1b/2 pilot clinical trial. *JAMA Oncol.*, **2020**, *6*(1), 125-132. <http://dx.doi.org/10.1001/jamaoncol.2019.3394> PMID: 31580386
- [97] Kottschade, L.A.; Suman, V.J.; Amatruda, T., III; McWilliams, R.R.; Mattar, B.I.; Nikcevich, D.A.; Behrens, R.; Fitch, T.R.; Jaslowski, A.J.; Markovic, S.N. A phase II trial of nab-paclitaxel (ABI-007) and carboplatin in patients with unresectable stage IV melanoma. *Cancer*, **2011**, *117*(8), 1704-1710. <http://dx.doi.org/10.1002/cncr.25659> PMID: 21472717
- [98] Sahai, V.; Catalano, P.J.; Zalupski, M.M.; Lubner, S.J.; Menge, M.R.; Nimeiri, H.S.; Munshi, H.G.; Benson, A.B., III; O'Dwyer, P.J. Nab-paclitaxel and gemcitabine as first-line treatment of advanced or metastatic cholangiocarcinoma: a phase 2 clinical trial. *JAMA Oncol.*, **2018**, *4*(12), 1707-1712. <http://dx.doi.org/10.1001/jamaoncol.2018.3277> PMID: 30178032
- [99] Crisà, E.; Cerrano, M.; Beggiato, E.; Benevolo, G.; Lanzarone, G.; Manzini, P.M.; Borchellini, A.; Riera, L.; Boccadoro, M.; Ferrero, D. Can pegylated interferon improve the outcome of polycythemia vera patients? *J. Hematol. Oncol.*, **2017**, *10*(1), 15. <http://dx.doi.org/10.1186/s13045-017-0395-1> PMID: 28086927
- [100] Osman, S.; Chia, J.; Street, L. Transitioning to pegylated interferon for the treatment of cutaneous T-Cell lymphoma: Meeting the challenge of therapy discontinuation and a proposed algorithm. *2023111Dermatol. Ther.*, <http://dx.doi.org/10.1155/2023/7171937>
- [101] Beauverd, Y.; Radia, D.; Cargo, C.; Knapper, S.; Drummond, M.; Pillai, A.; Harrison, C.; Robinson, S. Pegylated interferon alpha-2a for essential thrombocythemia during pregnancy: Outcome and safety. A case series. *Haematologica*, **2016**, *101*(5), e182-e184. <http://dx.doi.org/10.3324/haematol.2015.139691> PMID: 26819057
- [102] Schiller, M.; Tsianakas, A.; Sterry, W.; Dummer, R.; Hinke, A.; Nashan, D. Peginterferon alfa-2a may be substituted for other alpha interferon preparations. *J. Eur. Acad. Dermatol. Venereol.*, **2017**, *31*, 1841-1847. <http://dx.doi.org/10.1111/jdv.14366> PMID: 28557110
- [103] Patsatsi, A.; Papadavid, E.; Kyriakou, A.; Georgiou, E.; Koletsa, T.; Avgeros, C.; Koumourtzis, M.; Lampadaki, K.; Tsamaldoupis, A.; Lazaridou, E.; Stratigos, A.; Nikolaou, V. The use of pegylated interferon α -2a in a cohort of Greek patients with mycosis fungoides. *J. Eur. Acad. Dermatol. Venereol.*, **2022**, *36*(4), e291-e293. <http://dx.doi.org/10.1111/jdv.17795> PMID: 34753217
- [104] Eggermont, A.M.M.; Suciu, S.; Testori, A.; Santinami, M.; Kruit, W.H.J.; Marsden, J.; Punt, C.J.A.; Salès, F.; Dummer, R.; Robert, C.; Schadendorf, D.; Patel, P.M.; de Schaetzen, G.; Spatz, A.; Keilholz, U. Long-term results of the randomized phase III trial EORTC 18991 of adjuvant therapy with pegylated interferon alfa-2b versus observation in resected stage III melanoma. *J. Clin. Oncol.*, **2012**, *30*(31), 3810-3818. <http://dx.doi.org/10.1200/JCO.2011.41.3799> PMID: 23008300
- [105] McHutchison, J.G.; Everson, G.T.; Gordon, S.C.; Jacobson, I.M.; Sulkowski, M.; Kauffman, R.; McNair, L.; Alam, J.; Muir, A.J. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N. Engl. J. Med.*, **2009**, *360*(18), 1827-1838. <http://dx.doi.org/10.1056/NEJMoa0806104> PMID: 19403902
- [106] Bielack, S.S.; Smeland, S.; Whelan, J.S.; Marina, N.; Jovic, G.; Hook, J.M.; Krailo, M.D.; Gebhardt, M.; Pápai, Z.; Meyer, J.; Nadel, H.; Randall, R.L.; Deffenbaugh, C.; Nagarajan, R.; Brennan, B.; Letson, G.D.; Teot, L.A.; Goorin, A.; Baumhoer, D.; Kager, L.; Werner, M.; Lau, C.C.; Sundby Hall, K.; Gelderblom, H.; Meyers, P.; Gorlick, R.; Windhager, R.; Helmke, K.; Eriksson, M.; Hoogerbrugge, P.M.; Schomberg, P.; Tunn, P.U.; Kühne, T.; Jürgens, H.; van den Berg, H.; Böhling, T.; Picton, S.; Renard, M.; Reichardt, P.; Gerss, J.; Butterfass-Bahloul, T.; Morris, C.; Hogendoorn, P.C.W.; Seddon, B.; Calaminus, G.; Michelagnoli, M.; Dhooze, C.; Sydes, M.R.; Bernstein, M. Methotrexate, doxorubicin, and cisplatin (MAP) plus maintenance pegylated interferon alfa-2b versus MAP alone in patients with resectable high-grade osteosarcoma and good histologic response to preoperative MAP: First results of the EURAMOS-1 good response randomized controlled trial. *J. Clin. Oncol.*, **2015**, *33*(20), 2279-2287. <http://dx.doi.org/10.1200/JCO.2014.60.0734> PMID: 26033801
- [107] Arnaud, L.; Hervier, B.; Néel, A.; Hamidou, M.A.; Kahn, J.E.; Wechsler, B.; Pérez-Pastor, G.; Blomberg, B.; Fuzibet, J.G.; Dubourguet, F.; Marinho, A.; Magnette, C.; Noel, V.; Pavic, M.; Casper, J.; Beucher, A.B.; Costedoat-Chalumeau, N.; Aaron, L.; Salvatierra, J.; Graux, C.; Cacoub, P.; Delcey, V.; Dechant, C.; Bindl, P.; Herbaut, C.; Graziani, G.; Amoura, Z.; Haroche, J. CNS involvement and treatment with interferon- α are independent prognostic factors in Erdheim-Chester disease: A multicenter survival analysis of 53 patients. *Blood*, **2011**, *117*(10), 2778-2782. <http://dx.doi.org/10.1182/blood-2010-06-294108> PMID: 21239701
- [108] Lancet, J.E.; Uy, G.L.; Cortes, J.E.; Newell, L.F.; Lin, T.L.; Ritchie, E.K.; Stuart, R.K.; Strickland, S.A.; Hogge, D.; Solomon, S.R.; Stone, R.M.; Bixby, D.L.; Kolitz, J.E.; Schiller, G.J.; Wieduwilt, M.J.; Ryan, D.H.; Hoering, A.; Banerjee, K.; Chiarella, M.; Louie, A.C.; Medeiros, B.C. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients With newly diagnosed secondary acute myeloid leukemia. *J. Clin. Oncol.*, **2018**, *36*(26), 2684-2692. <http://dx.doi.org/10.1200/JCO.2017.77.6112> PMID: 30024784
- [109] Wagner, A.J.; Ravi, V.; Riedel, R.F.; Cranmer, L.; Gordon, E.M.; Desai, N.P. nab-sirolimus for patients with malignant perivascular epithelioid cell tumors. *J. Clin. Oncol.*, **2023**, *41*(35), 5477.
- [110] Wagner, A.J.; Ravi, V.; Riedel, R.F.; Ganjoo, K.N.; Van Tine, B.A.; Chugh, R.; Cranmer, L.D.; Gordon, E.M.; Hornick, J.L.; Kwiatkowski, D.J.; Du, H.; Grigorian, B.; Schmid, A.N.; Hou, S.; Harris, K.; Desai, N.; Dickson, M.A. Long-term follow-up for duration of response (DoR) after weekly nab-sirolimus in patients with advanced malignant perivascular epithelioid cell tumors (PEComa): Results from a registrational open-label phase II trial, AMPECT. *J. Clin. Oncol.*, **2020**, *38*(15 suppl), 11516. http://dx.doi.org/10.1200/JCO.2020.38.15_suppl.11516
- [111] Chamberlain, M.C.; Johnston, S.K.; Van Horn, A.; Glantz, M.J.

- Recurrent lymphomatous meningitis treated with intra-CSF rituximab and liposomal ara-C. *J. Neurooncol.*, **2009**, *91*(3), 271-277.
<http://dx.doi.org/10.1007/s11060-008-9707-1> PMID: 18820836
- [112] Mrugala, M.M.; Kim, B.; Sharma, A.; Johnson, N.; Graham, C.; Kurland, B.F.; Gralow, J. Phase II study of systemic highdose methotrexate and intrathecal liposomal cytarabine for treatment of leptomeningeal carcinomatosis from breast cancer. *Clin. Breast Cancer*, **2019**, *19*(5), 311-316.
<http://dx.doi.org/10.1016/j.clbc.2019.04.004> PMID: 31175053
- [113] Wieduwilt, M.J.; Jonas, B.A.; Schiller, G.J.; Liu, L.; Mulrone, C.; Mannis, G.N.; Tzachanis, D.; Castro, J.E.; Ball, E.D.; Curtin, P.T.; Andreadis, C.; Logan, A.C.; Reiner, J.; Damon, L.E. A phase II study of pegylated asparaginase, cyclophosphamide, rituximab, and dasatinib added to the UCSF 8707 (Linker 4-drug) regimen with liposomal cytarabine CNS prophylaxis for adults with newly diagnosed acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL): University of California Hematologic Malignancies Consortium Study (UCHMC) 1401. *Blood*, **2018**, *132*(Suppl. 1), 4018-4018.
<http://dx.doi.org/10.1182/blood-2018-99-117469>
- [114] Choueiri, T.K.; Jacobus, S.; Bellmunt, J.; Qu, A.; Appleman, L.J.; Tretter, C.; Bubley, G.J.; Stack, E.C.; Signoretti, S.; Walsh, M.; Steele, G.; Hirsch, M.; Sweeney, C.J.; Taplin, M.E.; Kibel, A.S.; Krajewski, K.M.; Kantoff, P.W.; Ross, R.W.; Rosenberg, J.E. Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with pegfilgrastim support in muscle-invasive urothelial cancer: Pathologic, radiologic, and biomarker correlates. *J. Clin. Oncol.*, **2014**, *32*(18), 1889-1894.
<http://dx.doi.org/10.1200/JCO.2013.52.4785> PMID: 24821883
- [115] Tadmor, T.; Levy, I.; Herishanu, Y.; Goldschmidt, N.; Bairey, O.; Yukea, M.; Shvidel, L.; Fineman, R.; Aviv, A.; Ruchlemer, R.; Braester, A.; Dally, N.; Rouvio, O.; Shaulov, A.; Greenbaum, U.; Inbar, M.; Polliack, A. Primary peg-filgrastim prophylaxis versus filgrastim given "on demand" for neutropenia during therapy with cladribine for hairy cell leukemia. *Leuk. Res.*, **2019**, *82*, 24-28.
<http://dx.doi.org/10.1016/j.leukres.2019.05.006> PMID: 31152919
- [116] Gu, P.; Liu, Z.; Sun, Y.; Ou, N.; Hu, Y.; Liu, J.; Wu, Y.; Wang, D. Angelica sinensis polysaccharide encapsulated into PLGA nanoparticles as a vaccine delivery and adjuvant system for ovalbumin to promote immune responses. *Int. J. Pharm.*, **2019**, *554*, 72-80.
<http://dx.doi.org/10.1016/j.ijpharm.2018.11.008> PMID: 30399435
- [117] Zhang, L.; Dimberg, A.; Rasouli, J. Editorial: The blood-brain barrier in brain tumors: Molecular mechanisms and therapeutic strategies. *Front. Neurol.*, **2023**, *14*, 1225594.
<http://dx.doi.org/10.3389/fneur.2023.1225594> PMID: 37521282
- [118] Wilhelmy, F.; Gaier, M.; Planitzer, U.; Kasper, J.; Prasse, G.; Frydrychowicz, C.; Oesemann, R.; Meixensberger, J.; Lindner, D. Venous thromboembolism and intracranial hemorrhage in patients undergoing glioblastoma surgery. *Sci. Rep.*, **2023**, *13*(1), 21679.
<http://dx.doi.org/10.1038/s41598-023-48542-2> PMID: 38066037
- [119] Sorribes, IC; Moore, MNJ; Byrne, HM; Jain, HV A biomechanical model of tumor-induced intracranial pressure and edema in brain tissue. *Biophys J.*, **2019**, *116*(8), 1560.
<http://dx.doi.org/10.1016/j.bpj.2019.02.030>
- [120] Chen, F.; Xie, X.; Wang, L. Research progress on intracranial lymphatic circulation and its involvement in disorders. *Front Neurol*, **2022**, *13*, 865714.
<http://dx.doi.org/10.3389/fneur.2022.865714>
- [121] Stepanenko, A.A.; Chekhonin, V.P. On the critical issues in temozolomide research in glioblastoma: Clinically relevant concentrations and mgmt-independent resistance. *Biomedicines*, **2019**, *7*(4), 92.
<http://dx.doi.org/10.3390/biomedicines7040092> PMID: 31783653
- [122] Adhipandito, CF; Cheung, SH; Lin, YH; Wu, SH Atypical renal clearance of nanoparticles larger than the kidney filtration threshold. *Int. J. Mol. Sci.*, **2021**, *22*(20), 11182.
<http://dx.doi.org/10.3390/ijms222011182> PMID: 34681853
- [123] Kreuter, J.; Alyautdin, R.N.; Kharkevich, D.A.; Ivanov, A.A. Passage of peptides through the blood-brain barrier with colloidal polymer particles (nanoparticles). *Brain Res.*, **1995**, *674*(1), 171-174.
[http://dx.doi.org/10.1016/0006-8993\(95\)00023-J](http://dx.doi.org/10.1016/0006-8993(95)00023-J) PMID: 7773690
- [124] Ljubimova, J.Y.; Holler, E. Biocompatible nanopolymers: The next generation of breast cancer treatment? *Nanomedicine (Lond.)*, **2012**, *7*(10), 1467-1470.
<http://dx.doi.org/10.2217/nnm.12.115> PMID: 23148535
- [125] Longhitano, L.; Vicario, N.; Tibullo, D.; Giallongo, C.; Broggi, G.; Caltabiano, R.; Giordano, A.; Parenti, R.; Di Rosa, M.; Baghini, M. Lactate metabolism regulates tumour growth and progression in glioblastoma. *Research Square*, **2021**.
<http://dx.doi.org/10.21203/rs.3.rs-965025/v1>
- [126] Malinovskaya, Y.; Melnikov, P.; Baklaushchev, V.; Gabashvili, A.; Osipova, N.; Mantrov, S.; Ermolenko, Y.; Maksimenko, O.; Gorshkova, M.; Balabanyan, V.; Kreuter, J.; Gelperina, S. Delivery of doxorubicin-loaded PLGA nanoparticles into U87 human glioblastoma cells. *Int. J. Pharm.*, **2017**, *524*(1-2), 77-90.
<http://dx.doi.org/10.1016/j.ijpharm.2017.03.049> PMID: 28359811
- [127] Washington, M.A.; Balmert, S.C.; Fedorchak, M.V.; Little, S.R.; Watkins, S.C.; Meyer, T.Y. Monomer sequence in PLGA microparticles: Effects on acidic microclimates and *in vivo* inflammatory response. *Acta Biomater.*, **2018**, *65*, 259-271.
<http://dx.doi.org/10.1016/j.actbio.2017.10.043> PMID: 29101019
- [128] Miraglia, E.; Viarisio, D.; Riganti, C.; Costamagna, C.; Ghigo, D.; Bosia, A. Na⁺/H⁺ exchanger activity is increased in doxorubicin-resistant human colon cancer cells and its modulation modifies the sensitivity of the cells to doxorubicin. *Int. J. Cancer*, **2005**, *115*(6), 924-929.
<http://dx.doi.org/10.1002/ijc.20959> PMID: 15729714
- [129] Ward, C.; Meehan, J.; Gray, M.E.; Murray, A.F.; Argyle, D.J.; Kunkler, I.H.; Langdon, S.P. The impact of tumour pH on cancer progression: Strategies for clinical intervention. *Explor. target. anti-tumor ther.*, **2020**, *1*(2), 71-100.
<http://dx.doi.org/10.37349/etat.2020.00005> PMID: 36046070
- [130] Lee, J.; Cho, H.R.; Cha, G.D.; Seo, H.; Lee, S.; Park, C.K.; Kim, J.W.; Qiao, S.; Wang, L.; Kang, D.; Kang, T.; Ichikawa, T.; Kim, J.; Lee, H.; Lee, W.; Kim, S.; Lee, S.T.; Lu, N.; Hyeon, T.; Choi, S.H.; Kim, D.H. Flexible, sticky, and biodegradable wireless device for drug delivery to brain tumors. *Nat. Commun.*, **2019**, *10*(1), 5205.
<http://dx.doi.org/10.1038/s41467-019-13198-y> PMID: 31729383
- [131] Seib, F.P.; Coburn, J.; Konrad, I.; Klebanov, N.; Jones, G.T.; Blackwood, B.; Charest, A.; Kaplan, D.L.; Chiu, B. Focal therapy of neuroblastoma using silk films to deliver kinase and chemotherapeutic agents *in vivo*. *Acta Biomater.*, **2015**, *20*, 32-38.
<http://dx.doi.org/10.1016/j.actbio.2015.04.003> PMID: 25861948
- [132] Erthal, L.C.S.; Gobbo, O.L.; Ruiz-Hernandez, E. Biocompatible copolymer formulations to treat glioblastoma multiforme. *Acta Biomater.*, **2021**, *121*, 89-102.
<http://dx.doi.org/10.1016/j.actbio.2020.11.030> PMID: 33227487
- [133] Hayashi, K.; Tokuda, A.; Nakamura, J.; Sugawara-Narutaki, A.; Ohtsuki, C. Tearable and fillable composite sponges capable of heat generation and drug release in response to alternating magnetic field. *Materials*, **2020**, *13*(16), 3637.
<http://dx.doi.org/10.3390/ma13163637> PMID: 32824485
- [134] Umesh Sarkar, S.; Bera, S.; Moitra, P.; Bhattacharya, S. A self-healable and injectable hydrogel for pH-responsive doxorubicin drug delivery *in vitro* and *in vivo*. for colon cancer treatment. *Mater. Today Chem.*, **2023**, *30*, 101554.
<http://dx.doi.org/10.1016/j.mtchem.2023.101554>
- [135] Chung, C.K.; García-Couce, J.; Campos, Y.; Kralisch, D.; Bierau, K.; Chan, A.; Ossendorp, F.; Cruz, L.J. Doxorubicin loaded poloxamer thermosensitive hydrogels: Chemical, pharmacological and biological evaluation. *Molecules*, **2020**, *25*(9), 2219.
<http://dx.doi.org/10.3390/molecules25092219> PMID: 32397328
- [136] Bai, X.; Tirella, A. Injectable multifunctional natural polymer-based

- hy-drogels for the local delivery of therapeutic agents. *Int. J. Drug. Discov. Pharmacol.*, **2022**, 1(1), 10.
<http://dx.doi.org/10.53941/ijddp.v1i1.203>
- [137] Wang, M.; Bergès, R.; Malfanti, A.; Pr  at, V.; Bastiancich, C. Local delivery of doxorubicin prodrug via lipid nanocapsule-based hydrogel for the treatment of glioblastoma. *Drug Deliv. Transl. Res.*, **2023**. PMID: 37889402
- [138] Yang, Z.; Liu, J.; Lu, Y. Doxorubicin and CD-CUR inclusion complex co-loaded in thermosensitive hydrogel PLGA-PEG-PLGA localized administration for osteosarcoma. *Int. J. Oncol.*, **2020**, 57(2), 433-444.
<http://dx.doi.org/10.3892/ijo.2020.5067> PMID: 32468050
- [139] Gherardini, L.; Vetri Buratti, V.; Maturi, M.; Inzalaco, G.; Locatelli, E.; Sambri, L.; Gargiulo, S.; Barone, V.; Bonente, D.; Bertelli, E.; Tortorella, S.; Franci, L.; Fioravanti, A.; Comes Franchini, M.; Chiariello, M. Loco-regional treatment with temozolomide-loaded thermogels prevents glioblastoma recurrences in orthotopic human xenograft models. *Sci. Rep.*, **2023**, 13(1), 4630.
<http://dx.doi.org/10.1038/s41598-023-31811-5> PMID: 36944737
- [140] Yuan, Y.; Choi, K.; Choi, S.O.; Kim, J. Early stage release control of an anticancer drug by drug-polymer miscibility in a hydrophobic fiber-based drug delivery system. *RSC Advances*, **2018**, 8(35), 19791-19803.
<http://dx.doi.org/10.1039/C8RA01467A> PMID: 35540999
- [141] Welling, M.M.; Duzenko, N.; van Meerbeek, M.P.; Molenaar, T.J.M.; Buckle, T.; van Leeuwen, F.W.B.; Rietbergen, D.D.D. Microspheres as a carrier system for therapeutic embolization procedures: Achievements and advances. *J. Clin. Med.*, **2023**, 12(3), 918.
<http://dx.doi.org/10.3390/jcm12030918> PMID: 36769566
- [142] Lewis, A.L.; Adams, C.; Busby, W.; Jones, S.A.; Wolfenden, L.C.; Leppard, S.W.; Palmer, R.R.; Small, S. Comparative *in vitro* evaluation of microspherical embolisation agents. *J. Mater. Sci. Mater. Med.*, **2006**, 17(12), 1193-1204.
<http://dx.doi.org/10.1007/s10856-006-0592-x> PMID: 17143749
- [143] Farheen, M.; Akhter, M.H.; Chitme, H.; Suliman, M.; Jaremko, M.; Emwas, A.H. Surface-modified biobased polymeric nanoparticles for dual delivery of doxorubicin and gefitinib in glioma cell lines. *ACS Omega*, **2023**, 8(31), 28165-28184.
<http://dx.doi.org/10.1021/acsomega.3c01375> PMID: 37576633
- [144] Ordonez, E.; Laken, L. Formaldehyde-doxorubicin dual polymeric drug delivery system for higher efficacy and limited cardiotoxicity of anthracyclines. *Eur. Polym. J.*, **2021**, 143, 110210.
<http://dx.doi.org/10.1016/j.eurpolymj.2020.110210>
- [145] Cavalcante, C.H.; Fernandes, R.S.; de Oliveira Silva, J.; Ramos Oda, C.M.; Leite, E.A.; Cassali, G.D.; Charlie-Silva, I.; Ventura Fernandes, B.H.; Miranda Ferreira, L.A.; de Barros, A.L.B. Doxorubicin-loaded pH-sensitive micelles: A promising alternative to enhance antitumor activity and reduce toxicity. *Biomed. Pharmacother.*, **2021**, 134, 111076.
<http://dx.doi.org/10.1016/j.biopha.2020.111076> PMID: 33341054
- [146] Samanta, P.; Kapat, K.; Maiti, S.; Biswas, G.; Dhara, S.; Dhara, D. pH-labile and photochemically cross-linkable polymer vesicles from coumarin based random copolymer for cancer therapy. *J. Colloid Interface Sci.*, **2019**, 555, 132-144.
<http://dx.doi.org/10.1016/j.jcis.2019.07.069> PMID: 31377639
- [147] Bhattacharyya, M.; Jariyal, H.; Srivastava, A. Hyaluronic acid: More than a carrier, having an overpowering extracellular and intracellular impact on cancer. *Carbohydr. Polym.*, **2023**, 317, 121081.
<http://dx.doi.org/10.1016/j.carbpol.2023.121081> PMID: 37364954
- [148] Putney, L.K.; Barber, D.L. Na-H exchange-dependent increase in intracellular pH times G2/M entry and transition. *J. Biol. Chem.*, **2003**, 278(45), 44645-44649.
<http://dx.doi.org/10.1074/jbc.M308099200> PMID: 12947095
- [149] Matsuyama, S.; Llopis, J.; Deveraux, Q.L.; Tsien, R.Y.; Reed, J.C. Changes in intramitochondrial and cytosolic pH: Early events that modulate caspase activation during apoptosis. *Nat. Cell Biol.*, **2000**, 2(6), 318-325.
<http://dx.doi.org/10.1038/35014006> PMID: 10854321
- [150] Miccoli, L.; Oudard, S.; Sureau, F.; Poirson, F.; Dutrillaux, B.; Poupon, M.F. Intracellular pH governs the subcellular distribution of hexokinase in a glioma cell line. *Biochem. J.*, **1996**, 313(3), 957-962.
<http://dx.doi.org/10.1042/bj3130957> PMID: 8611181
- [151] Dechant, R.; Binda, M.; Lee, S.S.; Pelet, S.; Winderickx, J.; Peter, M. Cytosolic pH is a second messenger for glucose and regulates the PKA pathway through V-ATPase. *EMBO J.*, **2010**, 29(15), 2515-2526.
<http://dx.doi.org/10.1038/emboj.2010.138> PMID: 20581803
- [152] Baboci, L.; Capolla, S.; Di Cintio, F.; Colombo, F.; Mauro, P.; Dal Bo, M.; Argenziano, M.; Cavalli, R.; Toffoli, G.; Macor, P. The dual role of the liver in nanomedicine as an actor in the elimination of nanostructures or a therapeutic target. *J. Oncol.*, **2020**, 2020, 1-15.
<http://dx.doi.org/10.1155/2020/4638192> PMID: 32184825
- [153] Sudheesh, M.S.; Pavithran, K.; M, S. Revisiting the outstanding questions in cancer nanomedicine with a future outlook. *Nanoscale Adv.*, **2022**, 4(3), 634-653.
<http://dx.doi.org/10.1039/D1NA00810B> PMID: 36131837
- [154] Liu, Y.; Hu, Y.; Huang, L. Influence of polyethylene glycol density and surface lipid on pharmacokinetics and biodistribution of lipid-calcium-phosphate nanoparticles. *Biomaterials*, **2014**, 35(9), 3027-3034.
<http://dx.doi.org/10.1016/j.biomaterials.2013.12.022> PMID: 24388798
- [155] Yusoff, A.H.M.; Salimi, M.N. Superparamagnetic nanoparticles for drug delivery. In: *Applications of Nanocomposite Materials in Drug Delivery*; Woodhead Publishing, **2018**; 1, pp. 843-859.
<http://dx.doi.org/10.1016/B978-0-12-813741-3.00037-6>
- [156] Williams, R.M.; Shah, J.; Tian, H.S.; Chen, X.; Geissmann, F.; Jaimes, E.A.; Heller, D.A. Selective nanoparticle targeting of the renal tubules. *Hypertension*, **2018**, 71(1), 87-94.
<http://dx.doi.org/10.1161/HYPERTENSIONAHA.117.09843> PMID: 29133360
- [157] Kojima, C.; Regino, C.; Umeda, Y.; Kobayashi, H.; Kono, K. Influence of dendrimer generation and polyethylene glycol length on the biodistribution of PEGylated dendrimers. *Int. J. Pharm.*, **2010**, 383(1-2), 293-296.
<http://dx.doi.org/10.1016/j.ijpharm.2009.09.015> PMID: 19761822
- [158] Kojima, C.; Turkbey, B.; Ogawa, M.; Bernardo, M.; Regino, C.A.S.; Bryant, L.H., Jr; Choyke, P.L.; Kono, K.; Kobayashi, H. Dendrimer-based MRI contrast agents: The effects of PEGylation on relaxivity and pharmacokinetics. *Nanomedicine*, **2011**, 7(6), 1001-1008.
<http://dx.doi.org/10.1016/j.nano.2011.03.007> PMID: 21515406
- [159] Chatterjee, K.; Sarkar, S.; Jagajjani Rao, K.; Paria, S. Core/shell nanoparticles in biomedical applications. *Adv. Colloid Interface Sci.*, **2014**, 209, 8-39.
<http://dx.doi.org/10.1016/j.cis.2013.12.008> PMID: 24491963
- [160] Xue, W.; Liu, Y.; Zhang, N.; Yao, Y.; Ma, P.; Wen, H.; Huang, S.; Luo, Y.E.; Fan, H. Effects of core size and PEG coating layer of iron oxide nanoparticles on the distribution and metabolism in mice. *Int. J. Nanomedicine*, **2018**, 13, 5719-5731.
<http://dx.doi.org/10.2147/IJN.S165451> PMID: 30310275
- [161] Jiang, Y.; Huo, S.; Mizuhara, T.; Das, R.; Lee, Y.W.; Hou, S.; Moyano, D.F.; Duncan, B.; Liang, X.J.; Rotello, V.M. The interplay of size and surface functionality on the cellular uptake of sub-10 nm gold nanoparticles. *ACS Nano*, **2015**, 9(10), 9986-9993.
<http://dx.doi.org/10.1021/acs.nano.5b03521> PMID: 26435075
- [162] Cabral, H.; Matsumoto, Y.; Mizuno, K.; Chen, Q.; Murakami, M.; Kimura, M.; Terada, Y.; Kano, M.R.; Miyazono, K.; Uesaka, M.; Nishiyama, N.; Kataoka, K. Accumulation of sub-100 nm polymeric micelles in poorly permeable tumours depends on size. *Nat. Nanotechnol.*, **2011**, 6(12), 815-823.
<http://dx.doi.org/10.1038/nnano.2011.166> PMID: 22020122

- [163] Ratner, B.; Hoffman, A.; Schoen, F.; Lemons, J. *Biomaterials Science*; Elsevier: London, **2004**.
- [164] Hamoudi-Ben Yelles, M.C.; Tran Tan, V.; Danede, F.; Willart, J.F.; Siepmann, J. PLGA implants: How Poloxamer/PEO addition slows down or accelerates polymer degradation and drug release. *J. Control. Release*, **2017**, 253, 19-29.
<http://dx.doi.org/10.1016/j.jconrel.2017.03.009> PMID: 28284831
- [165] Elmowafy, E.M.; Tiboni, M.; Soliman, M.E. Biocompatibility, biodegradation and biomedical applications of poly(lactic acid)/poly(lactic-co-glycolic acid) micro and nanoparticles. *J. Pharm. Investig.*, **2019**, 49(4), 347-380.
<http://dx.doi.org/10.1007/s40005-019-00439-x>
- [166] Surya, N.; Bhattacharyya, S. PLGA - The smart polymer for drug delivery. *Pharm. Pharmacol.*, **2021**, 9(5), 334-345.
<http://dx.doi.org/10.19163/2307-9266-2021-9-5-334-345>
- [167] Iovino, C.; Mastropasqua, R.; Lupidi, M.; Bernabei, F.; Borrelli, E.; Cerquaglia, A.; Giannaccare, G.; Pellegrini, M.; Govetto, A.; Finocchio, L. Intravitreal dexamethasone implant as a sustained release drug delivery device for the treatment of ocular diseases: A comprehensive review of the literature. *Pharmaceutics*, **2020**, 12(8), 703.
<http://dx.doi.org/10.3390/pharmaceutics12080703>.
- [168] Fu, K.; Pack, D.W.; Klibanov, A.M.; Langer, R. Visual evidence of acidic environment within degrading poly(lactic-co-glycolic acid) (PLGA) microspheres. *Pharm. Res.*, **2000**, 17(1), 100-106.
<http://dx.doi.org/10.1023/A:1007582911958> PMID: 10714616
- [169] Abulateefeh, SR Long-acting injectable PLGA/PLA depots for leuprolide acetate: Successful translation from bench to clinic. *Drug Deliv Transl Res.*, **2023**, 13(2), 520-530.
- [170] Bradley, R.; Braybrooke, J.; Gray, R.; Hills, R.K.; Liu, Z.; Pan, H.; Peto, R.; Dodwell, D.; McGale, P.; Taylor, C.; Francis, P.A.; Gnant, M.; Perrone, F.; Regan, M.M.; Berry, R.; Boddington, C.; Clarke, M.; Davies, C.; Davies, L.; Duane, F.; Evans, V.; Gay, J.; Gettings, L.; Godwin, J.; James, S.; Liu, H.; MacKinnon, E.; Mannu, G.; McHugh, T.; Morris, P.; Read, S.; Straiton, E.; Jakesz, R.; Fesl, C.; Pagani, O.; Gelber, R.; De Laurentiis, M.; De Placido, S.; Gallo, C.; Albain, K.; Anderson, S.; Arriagada, R.; Bartlett, J.; Bergsten-Nordström, E.; Bliss, J.; Brain, E.; Carey, L.; Coleman, R.; Cuzick, J.; Davidson, N.; Del Mastro, L.; Di Leo, A.; Dignam, J.; Dowsett, M.; Ejlersten, B.; Goetz, M.; Goodwin, P.; Halpin-Murphy, P.; Hayes, D.; Hill, C.; Jaggi, R.; Janni, W.; Loibl, S.; Mamounas, E.P.; Martin, M.; Mukai, H.; Nekljudova, V.; Norton, L.; Ohashi, Y.; Pierce, L.; Poortmans, P.; Pritchard, K.I.; Raina, V.; Rea, D.; Robertson, J.; Rutgers, E.; Spanic, T.; Sparano, J.; Steger, G.; Tang, G.; Toi, M.; Tutt, A.; Viale, G.; Wang, X.; Whelan, T.; Wilcken, N.; Wolmark, N.; Cameron, D.; Bergh, J.; Swain, S.M. Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: A patient-level meta-analysis of 7030 women from four randomised trials. *Lancet Oncol.*, **2022**, 23(3), 382-392.
[http://dx.doi.org/10.1016/S1470-2045\(21\)00758-0](http://dx.doi.org/10.1016/S1470-2045(21)00758-0) PMID: 35123662
- [171] Rubiu, E.; Restelli, F.; Nazzi, V.; Mazzapicchi, E.; Bonomo, G.; Veiceschi, P.; Alfiero, T.; Agresta, G.; Locatelli, D.; Dario, A. Benefit/risk assessment of intrathecal ziconotide in chronic pain: A narrative review. *J. Clin. Med.*, **2024**, 13(6), 1644.
<http://dx.doi.org/10.3390/jcm13061644> PMID: 38541869
- [172] Dieci, M.V.; Griguolo, G.; Bottosso, M.; Tsvetkova, V.; Giorgi, C.A.; Vernaci, G.; Michieletto, S.; Angelini, S.; Marchet, A.; Tasca, G.; Genovesi, E.; Cumerlato, E.; Lo Mele, M.; Conte, P.; Guarneri, V. Impact of estrogen receptor levels on outcome in non-metastatic triple negative breast cancer patients treated with neoadjuvant/adjuvant chemotherapy. *NPJ Breast Cancer*, **2021**, 7(1), 101.
<http://dx.doi.org/10.1038/s41523-021-00308-7> PMID: 34341356
- [173] Constantinou, A.P.; Georgiou, T.K. Pre-clinical and clinical applications of thermoreversible hydrogels in biomedical engineering: A review. *Polym. Int.*, **2021**, 70(10), 1433-1448.
<http://dx.doi.org/10.1002/pi.6266>
- [174] Carlos-Escalante, J.A.; de Jesús-Sánchez, M.; Rivas-Castro, A.; Pichardo-Rojas, P.S.; Arce, C.; Wegman-Ostrosky, T. The use of antihypertensive drugs as adjuvant therapy in cancer. *Front. Oncol.*, **2021**, 11, 660943.
<http://dx.doi.org/10.3389/fonc.2021.660943> PMID: 34094953
- [175] Agarwal, S.; Mohamed, M.S.; Mizuki, T.; Maekawa, T.; Sakthi Kumar, D. Chlorotoxin modified morusin-PLGA nanoparticles for targeted glioblastoma therapy. *J. Mater. Chem. B Mater. Biol. Med.*, **2019**, 7(39), 5896-5919.
<http://dx.doi.org/10.1039/C9TB01131E> PMID: 31423502
- [176] Banstola, A.; Duwa, R.; Emami, F.; Jeong, J.H.; Yook, S. Enhanced caspase-mediated abrogation of autophagy by temozolomide-loaded and panitumumab-conjugated poly(lactic-co-glycolic acid) nanoparticles in epidermal growth factor receptor overexpressing glioblastoma cells. *Mol. Pharm.*, **2020**, 17(11), 4386-4400.
<http://dx.doi.org/10.1021/acs.molpharmaceut.0c00856> PMID: 33079558
- [177] Eivazi, N.; Rahmani, R.; Paknejad, M. Specific cellular internalization and pH-responsive behavior of doxorubicin loaded PLGA-PEG nanoparticles targeted with anti EGFRvIII antibody. *Life Sci.*, **2020**, 261, 118361.
<http://dx.doi.org/10.1016/j.lfs.2020.118361> PMID: 32861796
- [178] Younis, M.; Faming, W.; Hongyan, Z.; Mengmeng, T.; Hang, S.; Liudi, Y. Igaratimod encapsulated PLGA-NPs improves therapeutic outcome in glioma, glioma stem-like cells and temozolomide resistant glioma cells. *Nanomedicine*, **2019**, 22, 102101.
<http://dx.doi.org/10.1016/j.nano.2019.102101> PMID: 31654739
- [179] Feldman, D. Polymers and polymer nanocomposites for cancer therapy. *Appl. Sci.*, **2019**, 9(18), 3899.
<http://dx.doi.org/10.3390/app9183899>
- [180] D'Amico, R.S.; Aghi, M.K.; Vogelbaum, M.A.; Bruce, J.N. Convection-enhanced drug delivery for glioblastoma: A review. *J. Neurooncol.*, **2021**, 151(3), 415-427.
<http://dx.doi.org/10.1007/s11060-020-03408-9> PMID: 33611708
- [181] Walter, K.A.; Tamargo, R.J.; Olivi, A.; Burger, P.C.; Brem, H. Intratumoral chemotherapy. *Neurosurgery*, **1995**, 37(6), 1129-1145.
<http://dx.doi.org/10.1227/00006123-199512000-00013> PMID: 8584154
- [182] First-in-man clinical trial of CEB-01 PLGA membrane in recurrent or locally advanced retroperitoneal soft tissue sarcoma. NC Patent T04619056, **2024**.
- [183] . Escalation study of immunomodulatory nanoparticles (PRECIUS-01) NC Patent T04751786, **2024**.
- [184] Dendritic cell activating scaffold in melanoma. NC Patent T01753089, **2024**.
- [185] Dexamethasone implant for retinal detachment in uveal melanoma. >NC Patent T04082962, **2024**.
- [186] Pereverzeva, E.; Treschalin, I.; Treschalin, M.; Arantseva, D.; Ermolenko, Y.; Kumskova, N.; Maksimenko, O.; Balabanyan, V.; Kreuter, J.; Gelperina, S. Toxicological study of doxorubicin-loaded PLGA nanoparticles for the treatment of glioblastoma. *Int. J. Pharm.*, **2019**, 554, 161-178.
<http://dx.doi.org/10.1016/j.ijpharm.2018.11.014> PMID: 30414476
- [187] Tsvetkov, IS; Zolotova, NA; Kosyreva, AM; Dzhalilova, D.S. Morphological characteristics of nephrotoxicity of dox-orubicin and doxorubicin PLGA-nanoparticles. *Clin. exp. morphology.*, **2021**, 10(s4), 77-86.
- [188] Palko, N.N.; Potemkin, V.A.; Grishina, M.A. Decision tree for mechanism of antitumor drugs action prediction. *Bulletin. South Ural State Univ. Series. Chem.*, **2019**, 11(1), 8-24.
- [189] Chung, K.; Ullah, I.; Kim, N.; Lim, J.; Shin, J.; Lee, S.C.; Jeon, S.; Kim, S.H.; Kumar, P.; Lee, S.K. Intranasal delivery of cancer-targeting doxorubicin-loaded PLGA nanoparticles arrests glioblastoma growth. *J. Drug Target.*, **2020**, 28(6), 617-626.
<http://dx.doi.org/10.1080/1061186X.2019.1706095> PMID: 31852284

- [190] Luque-Michel, E.; Sebastian, V.; Larrea, A.; Marquina, C.; Blanco-Prieto, M.J. Co-encapsulation of superparamagnetic nanoparticles and doxorubicin in PLGA nanocarriers: Development, characterization and *in vitro* antitumor efficacy in glioma cells. *Eur. J. Pharm. Biopharm.*, **2019**, *145*, 65-75. <http://dx.doi.org/10.1016/j.ejpb.2019.10.004> PMID: 31628997
- [191] Cui, Y.; Xu, Q.; Chow, P.K.H.; Wang, D.; Wang, C.H. Transferrin-conjugated magnetic silica PLGA nanoparticles loaded with doxorubicin and paclitaxel for brain glioma treatment. *Biomaterials*, **2013**, *34*(33), 8511-8520. <http://dx.doi.org/10.1016/j.biomaterials.2013.07.075> PMID: 23932498
- [192] Lakkadwala, S.; Singh, J. Co-delivery of doxorubicin and erlotinib through liposomal nanoparticles for glioblastoma tumor regression using an *in vitro* brain tumor model. *Colloids Surf. B Biointerfaces*, **2019**, *173*, 27-35. <http://dx.doi.org/10.1016/j.colsurfb.2018.09.047> PMID: 30261346
- [193] Meng, X.; Xu, Y.; Lu, Q. Ultrasound-responsive alkaline nanorobots for the treatment of lactic acidosis-mediated doxorubicin resistance. *Nanoscale*, **2020**, *12*(25), 13801. <http://dx.doi.org/10.1039/D0NR03726E>
- [194] Pandey, M.; Anoosha, P.; Yesudhas, D.; Gromiha, M.M. Identification of potential driver mutations in glioblastoma using machine learning. *Brief. Bioinform.*, **2022**, *23*(6), bbac451. <http://dx.doi.org/10.1093/bib/bbac451> PMID: 36266243
- [195] Zhang, L.; Zhang, Y.; Wang, X.; Zhou, Y.; Qi, J.; Gu, L.; Zhao, Q.; Yu, R.; Zhou, X. A trojan-horse-like biomimetic nano-NK to elicit an immunostimulatory tumor microenvironment for enhanced GBM chemo-immunotherapy. *Small*, **2023**, *19*(44), 2301439. <http://dx.doi.org/10.1002/sml.202301439> PMID: 37420326
- [196] Akter, F.; Emptage, N.; Berger, M.S.; Engert, F. *Neuroscience for Neurosurgeons*; Cambridge University Press, **2024**, p. 187. <http://dx.doi.org/10.1017/9781108917339>
- [197] Chen, Z.; Soni, N.; Pinero, G.; Giotti, B.; Eddins, D.J.; Lindblad, K.E.; Lujambio, A.; Angione, A.; Vallcorba, M.P. Monocyte depletion enhances neutrophil influx and proneural to mesenchymal transition in glioblastoma. *Nat Commun.*, **2019**, *10*(1), 1839. <http://dx.doi.org/10.1038/s41467-023-37361-8>
- [198] Peng, J.; Zhou, J.; Sun, R.; Chen, Y.; Pan, D.; Wang, Q.; Chen, Y.; Gong, Z.; Du, Q. Dual-targeting of artesunate and chloroquine to tumor cells and tumor-associated macrophages by a biomimetic PLGA nanoparticle for colorectal cancer treatment. *Int. J. Biol. Macromol.*, **2023**, *244*, 125163. <http://dx.doi.org/10.1016/j.ijbiomac.2023.125163> PMID: 37270126
- [199] Emami, F.; Duwa, R.; Banstola, A.; Woo, S.M.; Kwon, T.K.; Yook, S. Dual receptor specific nanoparticles targeting EGFR and PD-L1 for enhanced delivery of docetaxel in cancer therapy. *Biomed. Pharmacother.*, **2023**, *165*, 115023. <http://dx.doi.org/10.1016/j.biopha.2023.115023> PMID: 37329708
- [200] Maddiboyina, B.; Roy, H.; Nakkala, R.K.; Gandhi, S.; Kavisri, M.; Moovendhan, M. Formulation, optimization and characterization of raloxifene hydrochloride loaded PLGA nanoparticles by using Taguchi design for breast cancer application. *Chem. Biol. Drug Des.*, **2023**, *102*(3), 457-470. <http://dx.doi.org/10.1111/cbdd.14222> PMID: 36856306
- [201] Arslan, F.B.; Öztürk, K.; Tavukçuoğlu, E.; Öztürk, S.C.; Esendağlı, G.; Çalı, S. A novel combination for the treatment of small cell lung cancer: Active targeted irinotecan and statin co-loaded PLGA nanoparticles. *Int. J. Pharm.*, **2023**, *632*, 122573. <http://dx.doi.org/10.1016/j.ijpharm.2022.122573> PMID: 36592892
- [202] Al-Nemrawi, N.K.; Altawabeyeh, R.M.; Darweesh, R.S. Preparation and characterization of docetaxel-PLGA nanoparticles coated with folic acid-chitosan conjugate for cancer treatment. *J. Pharm. Sci.*, **2022**, *111*(2), 485-494. <http://dx.doi.org/10.1016/j.xphs.2021.10.034> PMID: 34728172
- [203] Zhang, D.; Liu, L.; Wang, J.; Zhang, H.; Zhang, Z.; Xing, G.; Wang, X.; Liu, M. Drug-loaded PEG-PLGA nanoparticles for cancer treatment. *Front. Pharmacol.*, **2022**, *13*, 990505. <http://dx.doi.org/10.3389/fphar.2022.990505> PMID: 36059964
- [204] Hoover, E.C.; Ruggiero, O.M.; Swingler, R.N.; Day, E.S. FZD7-targeted nanoparticles to enhance doxorubicin treatment of triple-negative breast cancer. *ACS Omega*, **2024**, *9*(12), 14323-14335. <http://dx.doi.org/10.1021/acsomega.3c10275> PMID: 38559981
- [205] Panda, P.K.; Jain, S.K. Doxorubicin bearing peptide anchored PEGylated PLGA nanoparticles for the effective delivery to prostate cancer cells. *J. Drug Deliv. Sci. Technol.*, **2023**, *86*(104667), 104667. <http://dx.doi.org/10.1016/j.jddst.2023.104667>
- [206] Fang, X.; Chen, Z.; Zhou, W.; Li, T.; Wang, M.; Gao, Y.; Ma, S.; Feng, Y.; Du, S.; Lan, P.; Chen, H.; Wei, J.; Zhang, S.; Li, Z.; Liu, X.; Zhang, H.; Guo, X.; Luo, J. Boosting glioblastoma therapy with targeted pyroptosis induction. *Small*, **2023**, *19*(30), 2207604. <http://dx.doi.org/10.1002/sml.202207604> PMID: 37066699
- [207] Cai, J.; Ye, Z.; Hu, Y.; Ye, L.; Gao, L.; Wang, Y.; Sun, Q.; Tong, S.; Zhang, S.; Wu, L.; Yang, J.; Chen, Q. Fatostatin induces ferroptosis through inhibition of the AKT/mTORC1/GPX4 signaling pathway in glioblastoma. *Cell Death Dis.*, **2023**, *14*(3), 211. <http://dx.doi.org/10.1038/s41419-023-05738-8> PMID: 36966152
- [208] Younis, M.; Shaikh, S.; Shahzad, K.A.; Tan, F.; Wang, Z.; Lashari, M.H. Amrubicin encapsulated PLGA NPs inhibits the PI3K/AKT signaling pathway by activating PTEN and inducing apoptosis in TMZ-resistant Glioma. *Biomed. Mater.*, **2024**, *19*(2), 025003. <http://dx.doi.org/10.1088/1748-605X/ad1bb2> PMID: 38181444
- [209] Ma, J.; Dai, L.; Yu, J.; Cao, H.; Bao, Y.; Hu, J.; Zhou, L.; Yang, J.; Sofia, A.; Chen, H.; Wu, F.; Xie, Z.; Qian, W.; Zhan, R. Tumor microenvironment targeting system for glioma treatment via fusion cell membrane coating nanotechnology. *Biomaterials*, **2023**, *295*, 122026. <http://dx.doi.org/10.1016/j.biomaterials.2023.122026> PMID: 36731366
- [210] Sousa, F.; Dhaliwal, H.K.; Gattacceca, F.; Sarmiento, B.; Amiji, M.M. Enhanced anti-angiogenic effects of bevacizumab in glioblastoma treatment upon intranasal administration in polymeric nanoparticles. *J. Control. Release*, **2019**, *309*, 37-47. <http://dx.doi.org/10.1016/j.jconrel.2019.07.033> PMID: 31344424
- [211] Handa, M.; Sanap, S.N.; Bhatta, R.S.; Patil, G.P.; Ghose, S.; Singh, D.P.; Shukla, R. Combining donepezil and memantine via mannoseylated PLGA nanoparticles for intranasal delivery: Characterization and preclinical studies. *Biomaterials Advances*, **2023**, *154*, 213663. <http://dx.doi.org/10.1016/j.bioadv.2023.213663> PMID: 37865027
- [212] Zhao, X.; Ni, S.; Song, Y.; Hu, K. Intranasal delivery of Borneol/R8dGR peptide modified PLGA nanoparticles co-loaded with curcumin and cisplatin alleviate hypoxia in pediatric brainstem glioma which improves the synergistic therapy. *J. Control. Release*, **2023**, *362*, 121-137. <http://dx.doi.org/10.1016/j.jconrel.2023.08.048> PMID: 37633362
- [213] Byeon, H.J.; Thao, L.Q.; Lee, S.; Min, S.Y.; Lee, E.S.; Shin, B.S.; Choi, H.G.; Youn, Y.S. Doxorubicin-loaded nanoparticles consisted of cationic- and mannose-modified-albumins for dual-targeting in brain tumors. *J. Control. Release*, **2016**, *225*, 301-313. <http://dx.doi.org/10.1016/j.jconrel.2016.01.046> PMID: 26826308
- [214] Sai, K.; Zhong, M.; Wang, J.; Chen, Y.; Mou, Y.; Ke, C.; Zhang, X.; Yang, Q.; Lin, F.; Guo, C.; Chen, Z.; Zeng, J.; Lv, Y.; Li, X.; Gao, W.; Chen, Z. Safety evaluation of high-dose BCNU-loaded biodegradable implants in Chinese patients with recurrent malignant gliomas. *J. Neurol. Sci.*, **2014**, *343*(1-2), 60-65. <http://dx.doi.org/10.1016/j.jns.2014.05.022> PMID: 24874252
- [215] Arshad, A.; Yang, B.; Bienemann, A.S.; Barua, N.U.; Wyatt, M.J.; Woolley, M.; Johnson, D.E.; Edler, K.J.; Gill, S.S. Convection-enhanced delivery of carboplatin PLGA Nanoparticles for the treatment of glioblastoma. *PLoS One*, **2015**, *10*(7), e0132266. <http://dx.doi.org/10.1371/journal.pone.0132266> PMID: 26186224