**NANOENABLED SYSTEM FOR THE DELIVERY OF IRINOTECAN AS ANTICANCER**

**INTRODUCTION**

Irinotecan is a recently discovered semisynthetic analog of camptothecin drug. Nowadays it will becomes commercially available and continues to under-go wide-ranging clinical assessments. Irinotecan is additionally recognized as Camptosar and CPT-11. This medication determine its anticancer efficacy in many solid tumors. CPT-11 is widely used to treat of lung cancer, colorectal and pancreatic. Irinotecan is a pro-drug for SN-38 that inhibits topoisomerase-I, an enzyme that is concerned in the replication of DNA. SN-38 is 100- to 1000 times greater cytotoxic than irinotecan, and is definitely inconstant with its exposure. SN-38 is deactivated through prior enzymatic conversion to SN-38 glucuronide (SN-38G). The unique mechanism of action concerning this agent, linked with preclinical studies assessing its efficacy and toxicological profile, suggested the possibility of schedule-dependent antitumor and toxicological effects. Irinotecan was first approved for the cancer treatment in 1994. Till now, it remains the world’s leading anticancer drug. Nowadays, this wonderful drug has contributed either for cancer patient’s treatment or to the advancement of chemical and biological health sciences. Treatment of Irinotecan is generally related to the “hematological and gastrointestinal toxicity, neutropenia and simple delayed diarrhea as the major dose-limiting toxicity”. Irinotecan also increases the body of indication, which shows a relationship between growth of steatohepatitis and treatment with irinotecan. Steatohepatitis is pathologically described as “fat accumulation (steatosis), inflammation, ballooning of hepatocytes, and fibrosis”. Mainly 20% of patients affected by steatohepatitis through metastatic colorectal cancer getting irinotecan chemotherapy. Steatohepatitis growth increased 10 folds in 90-day postoperative mortality, specifically liver failure’s death.

This chapter highlights the impressive of Irinotecan and its mechanisms of irinotecan as anticancer, nano-formulations of irinotecan, pharmacokinetic properties (Table no. 1) and toxicities. This evidence helps to enhance the therapeutic activity of Irinotecan. Irinotecan first launched January 1994 by “Yakult Honsha Company in Japan” (then in 1984 it is formulated by an “alliance with Daiichi Pharmaceuticals”), in France in May 1995 and in US in June 1996 (based on initial research performed), then used by many other countries. In 1987 the first research paper of irinotecan was published by Japanese author.



**Fig 1: pH-dependent equilibrium of irinotecan and SN-38 isoforms**

Advanced use of irinotecan is in colon cancers and other solid tumors like “non-small cell lung cancer, biliary tract cancers, gastric cancer and cervical cancer”. It is either used for adult person or pediatric in different types of tumors. It can be used as mono-therapy but it is most commonly joint with other cytotoxic agents, like “5-fluorouracil and oxaliplatin”, as well as by monoclonal antibodies, like “Cetuximab and bevacizumab”. According to experimental and clinical studies irinotecan can be joint by kinase inhibitors, which is “Fruquintinib, Apatinib, Dasatinib, Regorafenib and Sunitinib or with cell-cycle checkpoint inhibitors”. Irinotecan-based combinations can be very prolonged; irinotecan can be efficiently combined with inhibitors of DNA repair, epigenetic modifications, signaling modulators and immunotherapy. This drug was plays very important role for about 15 years (1994–2008) in the treatment of colon cancer and then approved by about 100 countries and sold in 88 countries.

In 2008 the first generic version or irinotecan was entered in the world of pharmaceutical and health science and till now, remains for the different solid tumor’s treatment, as ordinary injectable drug. Recently, the oral use of irinotecan was established. Its outcomes look capable and well tolerated and established activity in a seriously pre-treated patient population with solid tumors. According to recent preclinical data liposomal Irinotecan may also be useful for advanced and metastatic triple negative breast cancer. There are many camptothecin derivatives was established in past years, such as “rubitecan, lurtotecan, diflomotecan, silatecan, exatecan, elomotecan, namitecan, gimatecan etc”, but in clinical trials they all failed to show a best therapeutic activity as compared to irinotecan or to the average of care chemotherapy for a specified tumor type.

**TABLE 1: Pharmacokinetic properties of Irinotecan.**

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| --- |
| **IRINOTECAN**  |
| **SYNONYM** | “Irinotecan hydrochloride tri-hydrate, CPT-11” |
| **COMMON TRADE NAME** | “CAMPTOSAR®” |
| **CLASSIFICATION**  | “Topoisomerase I inhibitor” |
| **PHARMACOKINETIC** |
| Inter-patient variability | “In pharmacokinetics of irinotecan and SN-38 high inter-patient variability” |
| Oral Absorption | “Quickly absorbed” |
| time to peak plasma concentration | “In 1-2 hour”  |
| Distribution | “Detected in pleural fluid with maximum concentration of 37% for irinotecan” |
| Volume of distribution | “125 mg/m dose: 110 ± 48.5 L/m ; 340 mg/m dose: 234 ± 69.6 L/m” |
| Plasma protein binding | “Irinotecan: 30-68%; SN-38: 95%” |
| Metabolism | “Hepatic metabolism” |
| Active metabolite | “SN-38” |
| Inactive metabolite | “SN-38 glucuronide, amino pentane carboxylic acid” |
| Excretion | “Biliary and urinary excretion” |
| Clearance | “13.3 ± 6.1 L/h/m” |
| Terminal half life | “340 mg/m dose: irinotecan 11.7 ± 1.0 h; SN-38 21 ± 4.3 h half-life increases with dose but this does not affect the linear relationship between dose and AUC” |
| Feces | “63.7 ± 6.8%”  |
| Urine | “11-20% as irinotecan; < 1% as SN-38” |
| Bile | “25% as irinotecan; 1% as SN-38” |
| Gender | “No clinically significant difference” |
| Elderly | “No clinically significant difference” |
| Children | “Greater inter-patient variability than in adults, with comparable clearance but shorter half-lives” |
| **USES** | “Cervical cancer, Colorectal cancer, Esophageal cancer, Gastric cancer, Lung cancer, Glioma, Mesothelioma, Pancreatic cancer”.  |
| **SIDE EFFECTS** | “Sudden chest pain or discomfort, wheezing, dry cough, feeling short of breath, nausea and vomiting.Redness, numbness and peeling skin on your hands or feet.Loss of appetite, weakness, coma, fever, abnormal liver functions tests, temporary hair loss and changing in skin colour”. |

**ADVANTAGE OF NANOTECHNOLOGY IN UTILIZING THE IRINOTECAN**

* Increase solubility
* Enhance the bioavailability of drug
* Decrease Toxicity
* Enhance Permeability
* Reduce side effects
* Enhance the therapeutic activity of drug
* Target on specific site of disease

**LIMITATION OF IRINOTECAN**

* Use of Irinotecan could harm the pregnant women and unborn baby by passing into breast milk and they can’t breast feed to new born baby while taking this drug.
* Irinotecan can cause diarrhea, which can be dangerous if it leads to dehydration.
* IV infusion of Irinotecan cause burning sensation, pain, or swelling around the IV needle.
* Low blood cell counts: fever, chills, flu-like symptoms, swollen gums, mouth sores, skin sores, rapid heart rate, pale skin, easy bruising, unusual bleeding, feeling light-headed.

**MECHANISM BY WHICH IRINOTECAN ACT AS ANTICANCER AGENT:**

Irinotecan interacts with Topo I–DNA cellular developments and has S-phase-specific cytotoxicity. Topoisomerases decrease DNAtwisting and supercoiling thathappen in particular DNA states as a result of important cellular methods like “transcription, replication and repair recombination”. They bind and reseal the phosphodiester backbone of DNA, and form a covalent enzyme–DNA linkage that permits another single- or double-stranded DNA to pass via misappropriated DNA. **“**Irinotecan (CPT-11) acts as a pro-drug that is activated to 7-ethyl10-hydroxycamptothecin (SN-38) by carboxyl esterase 2 in the blood and liver, and then SN-38 is detoxified in the liver by uridine diphosphate-glucuronosyl-transferase 1A1 to form a β-glucuronide conjugate, SN-38G. SN-38 is a strong inhibitor of DNA topoisomerase I, an important enzyme that controls DNA structural changes by relaxing DNA supercoil and religating cleaved DNA strands during DNA replication and transcription. SN-38 can bind with DNA-topoisomerase I complex to form a constant ternary complex that avoids religation of DNA strands and interferes with the moving replication fork, thus inducing replication arrest and lethal double-strand DNA breaks and ultimately cell death. Inhibition of DNA topoisomerase I is the essential mechanism for the antitumor activity of irinotecan, although it may cause DNA damage and cell death in fast-proliferating normal cells like, bone marrow cells and intestinal basal cells”. Mechanism of Irinotecan is shown in fig 2.



**Fig 2:** **Irinotecan targets on cancer cells and its anticancer activities.**

Different metabolomics skills allow high amount charge of a large amount of endogenous metabolites, which offer influential tools for mapping biochemical pathways implicated in disease and in response to drug treatment. To define the metabolic signature of drug exposure the Pharmaco-metabolomics is an emerging field, thus allowing the identification of biochemical pathways implicated in drug efficacy and adverse drug reactions.

**NANOENABLED TARGATING STRATEGIES FOR IRINOTECAN**

Targeted delivery of anticancer CPT-11 irinotecan faces the problems in bioavailability due to ADME (Absorption, distribution, metabolism and excretion). To overcome these problems and to enhance efficacy and bioavailability of the anticancer CPT-11s, targeted strategies is employed and also called as smart CPT-11 delivery. Target CPT-11 delivery systems are used for target specific action and enhance the stay of CPT-11 in tumor tissue. Advantages of targeted CPT-11 delivery systems over conventional CPT-11 delivery systems are:

* CPT-11 administration frequency is decreased and also decrease in CPT-11 side effects.
* Targeted CPT-11 delivery systems delivers the optimum amount of CPT-11 for optimum period of time at the site of action by which the plasma and tissue CPT-11 levels is maintained and reduction in fluctuation in circulating CPT-11 levels. Targeted CPT-11 delivery systems does not affect the healthy tissues so, reduction in side effects. Some formulations or irinotecan is described in Table 2.

**TABLE 2: Formulations of Irinotecan.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **S No.** | **Title** | **Formulation** | **Year** | **Reference** |
| 1 | “Liposomal Irinotecan: Formulation Development and Therapeutic Assessment in Murine Xenograft Models of Colorectal Cancer” | Liposome | 2004 | Corrie Lynn Messerer et al. |
| 2 | “Irinophore C: A Liposome Formulation of Irinotecan with Substantially Improved Therapeutic Efficacy against a Panel of Human Xenograft Tumors” | Liposome | 2008 | Euan C. Ramsay et al. |
| 3 | “Preparation of pegylated nano-liposomal formulation containing SN-38: In vitro characterization and in vivo bio-distribution in mice” | nano-liposomal | 2009 | Atyabi F et al. |
| 4 | “Lipid-based nano-formulation of irinotecan: dual mechanism of action allows for combination chemo/angiogenic therapy” | Liposome | 2011 | Dawn N Waterhouse et al. |
| 5 | “Formulation optimization and characterization of irinotecan nanoparticles” | Nanoparticles | 2012 | Trivedi et al. |
| 6 | “Development and Targeting Efficiency of Irinotecan Engineered Pro-niosomes” | Pro-niosomes | 2012 | Prakash S Goudanavar et al. |
| 7 | “Treatment of Colorectal Cancer Using a Combination of Liposomal Irinotecan (Irinophore CTM) and 5-Fluorouracil” | Liposome | 2013 | Jennifer I. Hare et al. |
| 8 | “Active loading liposomal irinotecan hydrochloride: Preparation, in vitro and in vivo evaluation” | Liposome | 2013 | Hongyan Wei et al. |
| 9 | “Formulation and Evaluation of Irinotecan Suppository for Rectal Administration” | suppository | 2014 | Haiyang Feng et al. |
| 10 | “Biodegradable peg nanoparticles for colorectal cancer using irinotecan as anticancer agent” | Nanoparticles | 2014 | J.Balasubramanian et al. |
| 11 | “Liposomal Irinotecan in the Treatment of Refractory Pancreatic Cancer” | Liposome | 2016 | Harold Bien et al. |
| 12 | “Preparation and Characterization of Irinotecan Loaded Cross-Linked Bovine Serum Albumin Beads for Liver Cancer Chemoembolization Therapy” | Beads | 2016 | Jin Yan et al. |
| 13 | “Formulation and in-vitro evaluation of irinotecan loaded mucoadhesive microspheres made of chitosan-alginate mixture by using inotropic gelation technique” | Microsphere | 2016 | Champak Kalita et al. |
| 14 | “Development and characterization of Irinotecan loaded colloidal drug delivery system” | Nanoparticles | 2018 | Prakash Goudanavar et al |
| 15 | “The development of a method to quantify total and free irinotecan and 7-ethyl-10-hydroxycamptothecin (SN-38) for pharmacokinetic and bio-distribution studies after administration of irinotecan liposomal formulation” | Liposome | 2018 | Wenqian Yang et al. |
| 16 | “Oral administration of irinotecan in patients with solid tumors: an open-label, phase I, dose escalating study evaluating safety, tolerability and pharmacokinetics” | Enteric coated immediate release tablet | 2019 | Kumler I et al. |
| 17 | “Liposomal Irinotecan for Treatment of Colorectal Cancer in a Preclinical Model” | Liposome | 2019 | Jiao-Ren Huang et al. |

There are two types of targeted CPT-11 delivery such as:

**Passive Targeting:** Angiogenesis is a phenomena in which two tasks are performed, first is, when the solid tumor start to grow at surrounding vasculature it becomes deficient to fuel for its production and second is, when the cells start dying they hide the growth factors for maintaining the development of new blood vessels. The size range of these blood vessels is 200-2000 nm and these are irregular in shape. As compare to chemotherapeutic soluble CPT-11 the polymeric nano vehicles are large in size and they cannot permeate through tight endothelial junctions. This tight junction is the basic structure of normal blood vessels, but can extravagate the tumor vasculature and remain surrounded inside it. With due sequence of time, the concentration of tumor reaches some times higher in the comparison of plasma and because of the deficiency of effective lymphatic drainage, it forms the origin for the application for EPR based selective anticancer irinotecan delivery.

The plasma concentration of the CPT-11 should be effectively high, which is measured by the area under time-concentration curve for the effective EPR effect and the polymeric nano therapeutics should have a high molecular weight as compare to renal threshold, so they cannot cleared by renal clearance and accumulate in tumor tissues following intravenous (I.V) injection to give a desired therapeutic response. Higher concentration of drug is achieved as long as irinotecan remains in the circulation. Sometimes the EPR effect is overestimated resulting in differences between quickly increasing rodent tumors, slowly growing rodent tumors and human tumors. It is a highly heterogeneous phenomenon which is varies from a tumor (do not have a structured architecture) model to human model.

There are some areas in which endothelial cells are not permeable, the interstitial fluid pressure is high, or tumor cell density is high, which results controlled penetration of small-sized molecules in the interstitium, while in some other parts large particles are capable to extravagate. To improve the solubility and stability of drug there are some approaches are used, nanoparticulates delivery systems for irinotecan delivery have been investigated for their tumor-targeting ability, drug-loading capacity, and controlled release.

**Active Targeting:** Active targeting is attained by both simple absorption process or by conjugating a specific ligand for the receptors on tumor surface and nan-delivery of irinotecan make it more target specific by enhancing the efficacy of drug. Active targeting enhances the efficacy of the drug loaded in Nano systems and makes it more specific to target site and this active targeting is achieved by simple absorption process or by conjugating a specific ligand for the overexpressed receptors on the tumor surface. The ligand conveys the receptor-mediated endocytosis in the cell membrane, which leads to increase the uptake of SN38 molecule in the tumor cells. There are number of studies are reported for effective functionalization of ligands onto the surface of Nano systems, which established the enhanced therapeutic efficacy by comparing with CPT-11 or passively targeted systems. In the synthesis of camptothecin derivatives, the lactone ring was reserved together to be measured for anticancer activity.

For the nano-delivery system Polyethylene glycol was selected as a carrier, while the synthetic peptides were selected for increasing the antitumor activity and for suppression of anti-apoptotic defense of CPT-11 in conjugate form. BCL-2 homology 3 peptide bound to anti-apoptotic BCL-2 family proteins helps in decreasing resistance in ovarian cancer cells to different chemotherapeutic agents. Luteinizing receptors released from luteinizing hormone are overexpressed in ovarian and some other cancer cells and are not found in healthy tissues. So, luteinizing hormone-releasing hormone was a potential target to deliver the irinotecan to cancer cells and the cellular uptake was also increased. When a target ligand (e.g., antibodies, aptamers and peptides) is conjugated to acoustic droplets, ADV occurs selectively near the target cell. This phenomenon causes membrane damage or increase in permeation by a process of mechanical stretching. High concentration of folic acid is necessary for deoxyribonucleic acid replication in malignant cells; hence, folate receptors are overexpressed in Pancreatic and lung cancers. These receptors are present at very low density in normal healthy cells.

**REPORT ON CLINICAL TRIALS AND PATENTS OF IRINOTECAN** Research studies which are performed in people that focused on evaluating a surgical, medical or behavioral intervention called as clinical trials. These researches are used to find out if a new treatment, like a new diet, drug or medical device is safe and effective for people. For drug development clinical trials are performed and described by phases which are defined by FDA (Food and Drug Administration).

Clinical trial has 5 phases and phases are described below using example of new drug treatment:

* **Phase 0:** This phase is the first clinical trials done among people. The aim of this phase is to study how the drug is processed in body and how drug may affect the body. In this phase very minute dose of drug is administrated or given to 10-15 healthy people.
* **Phase I:** The aim of this phase is to find optimum dose of the new drug with least side effects. This study is performed on small group of 15-30 patients. This phase is used to find drug safety.
* **Phase II:** This phase is also used to find safety of the drug but performed for specific type of cancer. This phase is performed on large group of patients with new combination of drugs. If the drug works as expectedly than testing is passed for phase III.
* **Phase III:** The aim of this phase is to compare the new drug to standard of care drug and to find out the side effects if each drug and which works better. This study is performed on more than 100 patients.
* **Phase IV:** In this phase the new drug is tested in 1000 or more than 1000 patients. The aim of this testing is to find out the short time and longtime side effects of the drug, adverse effects and safety of drug.

Irinotecan is camptothecin derived drug and was first approved in 1994 for the treatment of cancer. Irinotecan has used for the treatment of advanced colon cancers and other solid tumors including non-small cell lung cancer, pancreatic and biliary tract cancers, advanced gastric and cervical cancer. Many studies are conducted for the treatment of various cancers. Lot of clinical trials of irinotecan are in process like in phase I, II, III, IV. There are few studies which completed the phase IV of clinical trials especially for the treatment of malignant neoplasm of colon cancer, colorectal cancer, metastatic colorectal cancer, solid tumors, upper gastrointestinal tumors and adenocarcinoma of esophagus. There are lot of studies which completed the phase III, phase II and phase I of clinical trials for the treatment of rectal adenocarcinoma, colon cancer, adenocarcinoma of stomach, colorectal cancer, esophageal carcinoma, lung cancer, pancreatic cancer, solid tumor, biliary tract cancer, central nervous system tumors, cancer of gall , breast cancer, liver cancer, cervix cancer etc. Some of them are shown in table no. 3

**TABLE 3: Report on clinical trials of Irinotecan.**

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| --- | --- | --- | --- | --- |
| **S No.** | **Indication** | **Title** | **Phase** | **Purpose** |
| **1** | Malignant Neoplasm of Colon  | “Resection vs no Resection of the Primary in Colorectal Cancer With Unresectable Metastases” | 4 | Health Services Research |
| **2** | Malignant Neoplasm of Stomach / Stage IV Colorectal Cancer | “Investigation of Association Between UGT1A1 Polymorphisms and Irinotecan Toxicity in Korean Patients” | 4 | Treatment |
| **3** | Colorectal Cancers | “Study of Biomarkers in Patients Undergoing Chemotherapy for Metastatic Colorectal Cancer” | 4 | Treatment |
| **4** | Colorectal (Metastatic ) Cancer  | “Toxicity/Benefit Ratio Optimization of Chemotherapy in Colorectal Cancer (CRC) Patients by Determination of Individual Genotypic Determinants” | 4 | Treatment |
| **5** | Neoplasms, Colorectal | “A Translational Study of Bevacizumab in Participants With Metastatic Colorectal Cancer” | 4 | Treatment |
| **6** | Tumors, Solid | “Pharmacokinetic Study of CPT-11, Raltegravir and Midazolam With Characterization of UGT1A1 Genotype” | 4 | Treatment |
| **7** | Upper Gastrointestinal Tumours | “Phase II Trial Evaluating Irinotecan and Capecitabine Relapsed/Refractory Upper GI Tumours” | 4 | Treatment |
| **8** | Adenocarcinoma Of Esophagus / Gastric Adenocarcinoma / Stage IIB Gastric Cancer / Stage IIIA Esophageal Adenocarcinoma / Stage IIIA Gastric Cancer / Stage IIIB Esophageal Adenocarcinoma / Stage IIIB Gastric Cancer / Stage IIIC Esophageal Adenocarcinoma / Stage IIIC Gastric Cancer | “Genetic Analysis-Guided Irinotecan Hydrochloride Dosing of mFOLFIRINOX in Treating Patients With Locally Advanced Gastro esophageal or Stomach Cancer” | 4 | Treatment |
| **9** | Neoplasms Metastasis / Stomach Neoplasms | “Irinotecan Versus Only Best Supportive Care for Gastric Cancer” | 3 | Not Available |
| **10** | Rectal Adenocarcinoma | “GRECCAR 8: Primary Tumor Resection in Rectal Cancer With Unresectable Metastasis” | 3 | Other |
| **11** | Adenocarcinoma of the Colon / Stage III Colon Cancer | “Comparison of Combination Chemotherapy Regimens With or Without Cetuximab in Treating Patients Who Have Undergone Surgery For Stage III Colon Cancer” | 3 | Treatment |
| **12** | Adenocarcinoma of the Stomach and Gastro esophageal Junction | “Intergroup Trial of Adjuvant Chemotherapy in Adenocarcinoma of the Stomach” | 3 | Treatment |
| **13** | Colorectal Cancer | “Sequential Versus Combination Chemotherapy in Advanced Colorectal Carcinoma” | 3 | Treatment |
| **14** | Antineoplastic Agents | “Erbitux Metastatic Colorectal Cancer Strategy Study” | 3 | Treatment |
| **15** | Chemotherapy / Colorectal Cancers / Metastatic Cancers | “Combination Chemotherapy in Treating Patients With Colorectal Cancer and Resectable Metastases” | 3 | Treatment |
| **16** | Colorectal Cancers | “Irinotecan With or Without Oxaliplatin in Treating Patients With Metastatic Colorectal Cancer” | 3 | Treatment |
| **17** | Colorectal Cancers / Metastasis | “Trial Comparing Two Strategies of Chemotherapy for Metastatic Colorectal Cancer” | 3 | Treatment |
| **18** | Digestive System Neoplasms / Intestinal Neoplasms / Neoplasms Metastasis / Neoplasms, Colorectal / Neoplasms, Gastrointestinal | “Phase III Study of 2nd-line XELIRI ± Bevacizumab vs. FOLFIRI ± Bevacizumab in mCRC” | 3 | Treatment |
| **19** | Epidermal Growth Factor Receptor (EGFR) Expressing Metastatic Colorectal Cancer | “Cetuximab Combined With Irinotecan in First-line Therapy for Metastatic Colorectal Cancer (CRYSTAL)” | 3 | Treatment |
| **20** | Esophageal Carcinoma | “Study of SHR-1210 Versus Investigator's Choice Standard Therapy for Participants With Advanced Esophageal Cancer” | 3 | Treatment |
| **21** | Gastric Cancer Third Line / Unresectable, Recurrent, Locally Advanced or Metastatic Gastric or Gastro esophageal Junction Adenocarcinoma | “Avelumab in Third-Line Gastric Cancer (JAVELIN Gastric 300)” | 3 | Treatment |
| **22** | Hepatic Metastases / Neoplasm Recurrence, Local / Neoplasms Metastasis / Neoplasms, Colorectal | “Phase 3 Trial of Litx™ Plus Chemotherapy vs. Chemotherapy Only Treating Colorectal Cancer Patients With Recurrent Liver Metastases” | 3 | Treatment |
| **23** | Inoperable Gastric Cancer | “FOLFIRI Versus Docetaxel and Cisplatin as a Second-line Chemotherapy After Failure of First-line Chemotherapy in Advanced Gastric Cancer” | 3 | Treatment |
| **24** | Lung Cancers | “A Phase Ⅲ Randomized Study of Mitomycin/Vindesine/Cisplatin Versus Irinotecan/Carboplatin Versus Paclitaxel/Carboplatin With Concurrent Thoracic Radiotherapy for Unresectable Stage Ⅲ Non-Small-Cell Lung Cancer” | 3 | Treatment |
| **25** | Malignant Neoplasm of Stomach | “Prospective Randomized Trial Comparing Gastrectomy, Metastasectomy Plus Systemic Therapy Versus Systemic Therapy Alone: GYMSSA Trial” | 3 | Treatment |
| **26** | Metastatic Colorectal Cancer (MCRC) | “Trial Comparing Two sequences of Therapy in Colorectal Metastatic Patients” | 3 | Treatment |
| **27** | Neoplasms Metastasis / Neoplasms, Colorectal | “Aflibercept Versus Placebo in Combination With Irinotecan and 5-FU in the Treatment of Patients With Metastatic Colorectal Cancer After Failure of an Oxaliplatin Based Regimen” | 3 | Treatment |
| **28** | Neoplasms, Colorectal / Neoplasms, Hepatic | “Comparing Irinotecan and 5 FU/FA To 5-FU/FA After Resection Of Liver Metastases For Colorectal Cancer” | 3 | Treatment |
| **29** | Pancreatic Cancer Metastatic | “Study of MM-398 With or Without 5-FU/LV, Versus 5-FU/LV in Patients With Metastatic Pancreatic Cancer” | 3 | Treatment |
| **30** | Sarcomas | “High-Dose Combination Chemotherapy and Radiation Therapy in Treating Patients With Newly Diagnosed Metastatic Rhabdomyosarcoma or Ectomesenchymoma” | 3 | Treatment |
| **31** | Small Cell Lung Cancer (SCLC) | “Study Of Irinotecan Hydrochloride (Campto(R)) And Cisplatin Versus Etoposide And Cisplatin In Small Cell Lung Cancer” | 3 | Treatment |
| **32** | Tumors, Solid | “Treatment Extension Study for Patients Who Have Previously Participated and Have Benefited From Iniparib in a Clinical Trial” | 3 | Treatment |
| **33** | Unknown Primary Neoplasms | “Gemcitabine/Irinotecan/ZD1839 vs Paclitaxel/Carboplatin/Etoposide/ZD1839 in Carcinoma of Unknown Primary Site” | 3 | Treatment |
| **34** | Glioma, Malignant | “Cetuximab, Bevacizumab and Irinotecan for Patients With Malignant Glioblastomas” | 2 | Not Available |
| **35** | Metastatic Colorectal Cancer (MCRC) | “Nordic 8 - A Phase II Trial” | 2 | Basic Science  |
| **36** | Upper Gastrointestinal Tumours | “A Phase II Trial Evaluating Irinotecan Plus 5FU/LV in Patients With Relapsed/Refractory Upper GI Tumours” | 2 | Diagnostic |
| **37** | Metastatic Colorectal Adenocarcinoma | “Evaluation of Bevacizumab in Combination With First-Line Chemotherapy in Patients Aged 75 Years of Older With Metastatic Colorectal Adenocarcinoma (Prodige20)” | 2 | Other |
| **38** | Colorectal Cancers | “Study Evaluating Biomarkers in Patients With Colorectal Cancer and Native KRAS Treated With Chemotherapy + Cetuximab” | 2 | Screening |
| **39** | Colorectal Cancers | “G-CSF in Preventing Neutropenia During First-Line Treatment With Chemotherapy and Bevacizumab in Patients With Metastatic Colorectal Cancer” | 2 | Supportive Care |
| **40** | Colorectal Cancers / Nausea and vomiting | “Phase II Trial of Aprepitant & Palonosetron for CINV Prevention w FOLFOX” | 2 | Supportive Care |
| **41** | Adenocarcinoma of the Pancreas | “Second Line Chemotherapy for Advanced Pancreatic Cancer” | 2 | Treatment |
| **42** | Adult Glioblastoma / Adult Gliosarcoma / Recurrent Adult Brain Neoplasm | “Bevacizumab and Irinotecan or Temozolomide in Treating Patients With Recurrent or Refractory Glioblastoma Multi-forme or Gliosarcoma” | 2 | Treatment |
| **43** | Advanced Pancreatic Carcinoma | “Study of Individualized Selection of Chemotherapy in Patients With Advanced Pancreatic Carcinoma According to Therapeutic Targets” | 2 | Treatment |
| **44** | Astrocytoma’s / Glioblastomas | “A Study to Evaluate the Efficacy of Bevacizumab Plus Irinotecan in Recurrent Gliomas” | 2 | Treatment |
| **45** | Basal Cell Carcinoma (BCC) / Metastatic Colorectal Cancer (MCRC) / Ovarian Cancer | “A Study of Vismodegib (GDC-0449) in Patients Treated With Vismodegib in a Previous Genentech-sponsored Phase I or II Cancer Study” | 2 | Treatment |
| **46** | Biliary Cancer / Cholangio-carcinomas | “Study of Gemcitabine, Irinotecan and Panitumumab in Patients With Advanced and Metastatic Biliary Tract Adenocarcinoma” | 2 | Treatment |
| **47** | Biliary Tract Cancer | “Irinotecan, Gemcitabine, Chemotherapy for Biliary Tract Cancer” | 2 | Treatment |
| **48** | Brain and Central Nervous System Tumors | “Thalidomide and Irinotecan in Treating Patients With Glioblastoma Multiforme Who Have Undergone Radiation Therapy” | 2 | Treatment |
| **49** | Breast Cancer | “Irinotecan and Etoposide in Treating Patients With Recurrent, Locally Advanced, or Metastatic Breast Cancer” | 2 | Treatment |
| **50** | Cancer of the Gallbladder | “Irinotecan in Treating Patients With Advanced Gallbladder or Bile Duct Cancer” | 2 | Treatment |
| **51** | Cancer, Bladder / Transitional Cell Cancer of the Renal Pelvis and Ureter / Urethral Cancer | “Irinotecan in Treating Patients With Recurrent or Refractory Advanced Transitional Cell Cancer of the Urothelium Previously Treated With Chemotherapy” | 2 | Treatment |
| **52** | Liver Cancer | “Irinotecan in Treating Young Patients With Refractory or Recurrent Hepatoblastoma” | 2 | Treatment |
| **53** | Cervix Cancer | “CAmpto-CISplatine Plus Radiotherapy in Advanced Cervix Cancer : Search of Tolerated Maximum Dose of Campto” | 1 | Treatment |

**Report on patents:** Patents are rights given to inventor which allows them to exclude others to manufacture, use or selling their invention for 20 years. Government agencies are handle and approve the applications for patents.

There are three types of patents:

* **Utility patents:** This patent cover the new or useful process.
* **Design patents**: This cover new, unique and original design for manufacture of product.
* **Plant patents:** This cover anyone who discover, invents and produce unique kind of plant which is capable of reproduction.

Irinotecan has many patents during 2005 to 2020 which gives new hike to the irinotecan studies and for better treatment using the irinotecan drug. Patents are shown in the table no. 4

**TABLE 4: Report on patents of Irinotecan**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **S No.** | **Patent no.** | **Patent Name** | **Country** | **Approved year** | **Estimate Expires** |
| **1** | CA2202531 | “Lyophilizate of lipid complex of water insoluble camptothecin” | Canada | 2005 | 2015 |
| **2** | CA2294031 | “Self-emulsifying formulation for lipophilic compounds” | Canada | 2005 | 2018 |
| **3** | US10722508 | “Liposomes useful for drug delivery” | United States | 2005 | 2025 |
| **4** | US8329213 | “Liposomes useful for drug delivery” | United States | 2012 | 2025 |
| **5** | US8147867 | “Liposomes useful for drug delivery” | United States | 2012 | 2028 |
| **6** | US8703181 | “Liposomes useful for drug delivery” | United States | 2014 | 2025 |
| **7** | US8992970 | “Liposomes useful for drug delivery” | United States | 2015 | 2025 |
| **8** | US9339497 | “Methods for treating pancreatic cancer using combination therapies comprising liposomal irinotecan” | United States | 2016 | 2033 |
| **9** | US9364473 | “Methods for treating pancreatic cancer using combination therapies comprising liposomal irinotecan” | United States | 2016 | 2033 |
| **10** | US9452162 | “Methods for treating pancreatic cancer using combination therapies comprising liposomal irinotecan” | United States | 2016 | 2033 |
| **11** | US9492442 | “Methods for treating pancreatic cancer using combination therapies comprising liposomal irinotecan” | United States | 2016 | 2033 |
| **12** | US9717724 | “Methods for treating pancreatic cancer using combination therapies” | United States | 2017 | 2033 |
| **13** | US9730891 | “Liposomes useful for drug delivery” | United States | 2017 | 2025 |
| **14** | US9724303 | “Liposomes useful for drug delivery” | United States | 2017 | 2025 |
| **15** | US9782349 | “Liposomes useful for drug delivery” | United States | 2017 | 2025 |
| **16** | US10456360 | “Stabilizing camptothecin pharmaceutical compositions” | United States | 2019 | 2036 |

**CONCLUSION AND FUTURE PERSPECTIVE**

For improving the solubility and therapeutic effects of drug, decreasing the side effects and also for overcoming drug resistance the nano-delivery system for SN38 is very helpful or advantageous and there is no doubt in this. Though, there are quiet enormous space among current development and clinical application, also for the SN38-based nano-medicines under clinical trials. For instance, “the liposomal SN38 (LE-SN38) presents a burst drug release, while the polymeric micelle carrying SN38 (NK012) is poorly stable under physiological conditions, and EZN-2208 has a drug loading content of only 3.6%”. For developing the translational SN38 nano-delivery system there are numerous designs and biological concerns shows some critical difficulties, like enhance the stability, effective preparation and controlled release formulation etc.

SN38 is poorly stable in their active form and stability of this agent throughout the research of nano-formulation and after in-vivo administration is remains as a difficult task or challenging. So here, the first concern for nano-delivery if irinotecan is improving the stability.

Second concern is, “a more effective and reproducible preparation process”. The great difficulty in the formulation design is, the low efficacy of chemistry, and the poor reproducibility among different groups are some difficulties require to be resolved.

Third is, requirement of better-controlled released formulation. Premature release of the drug may reduce the therapeutic window and increase the toxicity. So, minimization of premature release of irinotecan is necessary for developing the nano formulation with controllable biological identity. Active tumor-targeting ability and tumor microenvironment-responsiveness could also allow the more favorable release of drug, which is attained by rational design.

Fourth concern is, decrease the unwanted toxicity of irinotecan. Assumed that, UGT1A1 is responsible for the metabolism of irinotecan in vivo, polymorphisms in the UGT1A1 gene is essential be taken into concern for the dose adjustment of irinotecan nano-medicines specially when applied in patients. Otherwise, the high-level accumulation of SN38 cause severe toxicities, including diarrhea and neutropenia.

Finally, more extrapolative animal models and more translational treatment strategies for pre-clinical evaluation. It is necessary to select an in-vivo model that preferably mimics the cancer patients, but, numerous in-vivo studies were only performed using “xenograft human tumor models” in Immuno-deficient mice, which may essentially look like a little of the real scenario.

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