PEER REVIEWED

Improving Outcomes for Gastric Cancer Patients via a Novel Oral Daily Dose Chemotherapy Formulation, Oncoral

Gastric cancer is the fifth most common cancer, with around one million annual incidences worldwide,[1] and it represents the fourth most common cause of cancer deaths.[2] High incidences of the disease in Asia (Figure 1) mean that screening in countries like Japan have made survival rates better than in Western countries, where the disease is often already advanced by the time of diagnosis. The five-year survival rate in the US and Europe is only 20%, making it a key target for drug development.

The gastric cancer drug market is growing rapidly and is expected to approach USD 4 billion by 2029 according to GlobalData.[3] This growth is fuelled by several factors, including an increase in the overall incidence, as well as higher treatment rates and extended treatment duration.

For patients with recurrent or advanced gastric cancer, the prognosis is poor, which underlines an urgent need for improved treatment options. Today, chemotherapy is a mainstay of treatment, and is associated with toxicity and limiting side-effects. The chemotherapy agent, irinotecan, is proven to be effective in the treatment of several gastrointestinal cancer forms. The injected version is approved for treatment of colorectal and pancreatic cancer in the USA and Europe, and for metastatic gastric cancer in Japan. Although irinotecan is currently not approved for treating gastric cancer in the US and in the EU, there is off-label clinical use. It is also recognised in clinical guidelines (ESMO, ASCO, NCCN) in monotherapeutic or combination treatment regimens for advanced gastric cancer.

Irinotecan has been studied and is being used in clinical settings today in many different solid tumour types. However, it is typically administered every third week via intra-venous (IV) bolus infusion in high doses. With this type of administration, most patients experience gastrointestinal and haematological side-effects, approximately 30% of which are severe or life threatening (grade 3 or 4).[4] A tablet formulation of irinotecan would enable frequent, low dose administration – also called metronomic chemotherapy – a dosing strategy which appears beneficial in a wide range of tumours.

In order to create a better treatment option for patients, Ascelia Pharma is developing a novel patented tablet formulation of irinotecan for daily dosing at home, called Oncoral, which is currently being prepared for Phase 2 clinical development. Daily oral dosing of irinotecan has the potential to play a role in the treatment of various cancer types and, while the initial indication for Oncoral is gastric cancer, it may offer the potential for future use in other types of cancers as well. As gastric cancer is relatively uncommon in the US and Europe, there is the potential for Oncoral to have an orphan drug designation.

Oncoral Mode of Action

Until now, no previously tested oral irinotecan formulations have entered Phase 2 due to issues concerning poor solubility and interpatient variability in bioavailability.

The formulation of Oncoral is based on irinotecan in the free base form being solubilised in a hydrophobic lipid system. The system is formulated into an enteric coated tablet to avoid release in the stomach, as stomach pH may influence the bio-absorption of irinotecan. The tablet releases the irinotecan immediately in the duodenum, avoiding protracted release so that the dosed irinotecan is dispersed before the next dose, to avoid drug accumulation and ensure high bio-absorption with low variability.

After oral administration of Oncoral, conversion of irinotecan takes place in the liver to the active metabolite SN38, which is 100–1,000 more cytotoxic than irinotecan. SN-38 reaches the tumour through systemic circulation and inhibits Topoisomerase 1 to exert its cytotoxic effect via prevention of DNA replication. Following metabolisation, SN-38 is converted to the water-soluble but inactive metabolite SN-38G.

Advantages of Daily Dosing

With Oncoral, researchers are exploring the possibility to give gastric cancer patients irinotecan in daily doses – metronomic chemotherapy – with the potential for better efficacy and an improved safety profile.

Efficacy

After oral administration, approximately five times more irinotecan is converted to the active metabolite SN-38 compared to IV infusion.[6] Several non-clinical and clinical studies provide proof of concept for metronomic dosing, including improved patient outcomes.[7,8] In one study of patients with metastatic refractory breast cancer, overall survival improved from 20% with irinotecan dosing every three weeks, to 32% with weekly dosing (Figure 2).

Frequent dosing may optimise the chance that tumour cells are exposed to SN-38 during the susceptible S-phase of the cell cycle, maximising anti-tumour effect. In the Oncoral Phase 1 study, clinical benefits

	New incidence cases	Cumulative risk 0–74%	Mortality	Cumulative risk 0–74%
East Asia	656,349	2.63	435,211	1.7
Northern America	29,772	0.48	13,391	0.19
Western Europe	28,490	0.66	17,755	0.35

Figure 1: Table showing the numbers of gastric cancer incidence and mortality statistics by region.[5] Data taken from the Global Cancer Observatory, owned by the International Agency for Research on Cancer (IARC)).

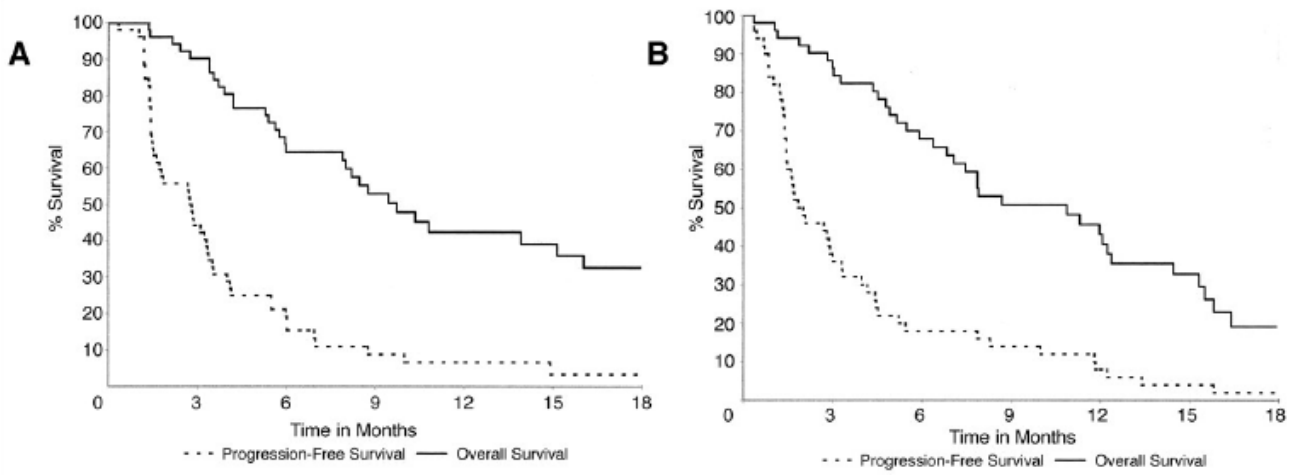


Figure 2: Study comparing irinotecan dosing every third week vs weekly dosing.[8]

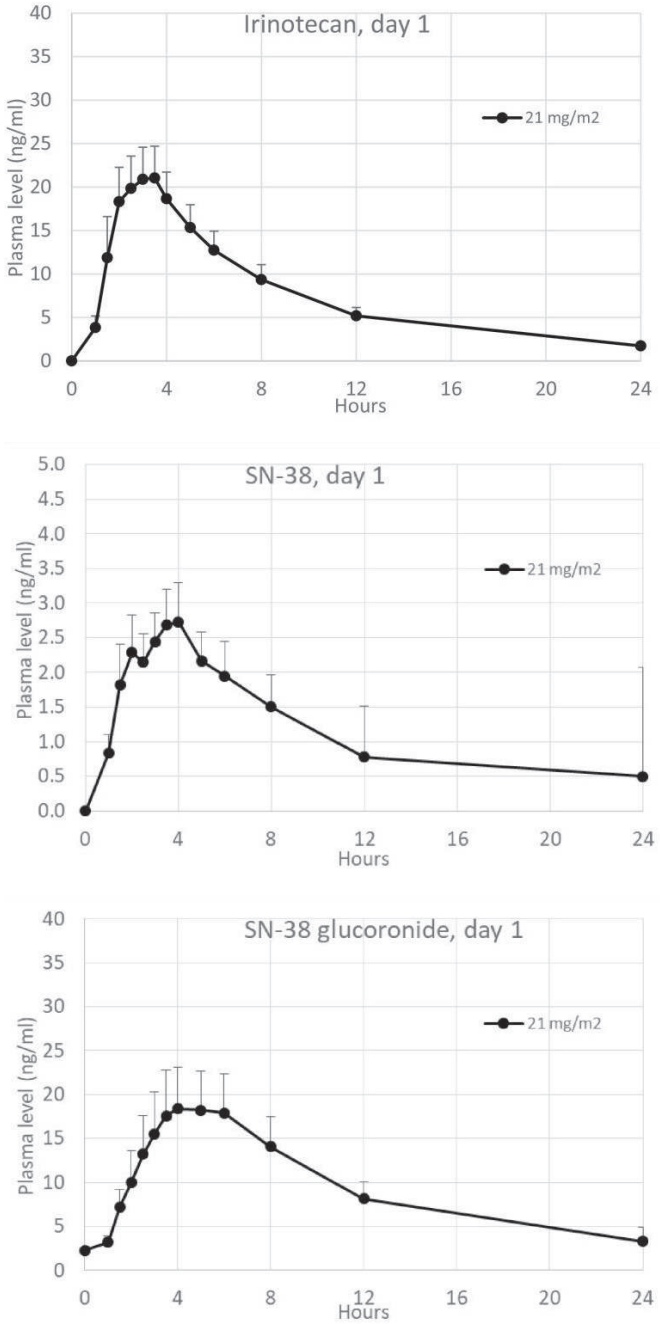


Figure 3: Pharmacokinetic plasma profiles of irinotecan, SN-38 and SN-38G on day 1 (mean values + SEM, n = 15). Graphic used under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).[6]

with stable disease were observed even in patients that previously received IV irinotecan.

Safety/Tolerability/Convenience

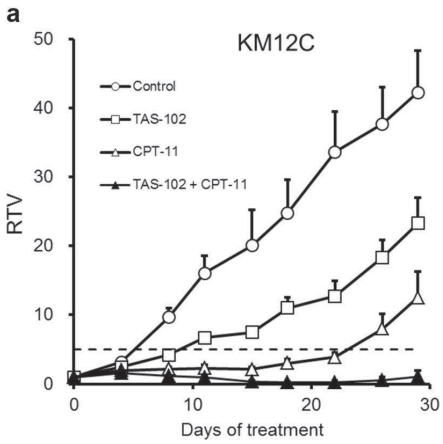
Frequent low dosing, avoiding high peak plasma levels, may reduce toxicity and complications compared to high-dose IV infusions. Oral daily administration also brings the opportunity to adjust dosing quickly in case of acute toxicity, offers convenient administration for patients, and is expected to be a cost-effective treatment alternative. In the Phase 1 single agent study,[6] Oncoral was well-tolerated, and the haematological toxicities were only mild to moderate, grade 1 or grade 2. Pharmacokinetic data showed consistent daily exposures during treatment at days 1 and 14 and no drug accumulation (Figure 3). SN-38 interpatient variability was in the same range as after intravenous administration.

Combination Therapy Shows Promise

Taiho Oncology's LONSURF® is indicated in the EU and US as monotherapy for the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease. LONSURF is an oral compound consisting of a thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase (TP) inhibitor, tipiracil, which increases trifluridine exposure by inhibiting its metabolism by TP. Trifluridine is incorporated into DNA, resulting in DNA dysfunction and inhibition of cell proliferation.

The combination of irinotecan and LONSURF has been tested in animal models which showed that the combination almost stopped the tumour from growing and gave

better results than administering both irinotecan or LONSURF as monotherapies [Figure 4].



TAS-102: LONSURF
CPT-11: IV irinotecan
TAS-102 + CPR-11: LONSURF + IV irinotecan

Figure 4: Efficacy study in an animal model of gastric cancer, Relative tumour volume (RTV) of KM12C human colorectal tumour of KM12C-bearing nude mice. Mice were randomised according to tumour volume on day 0. Mice were treated with the 0.5% hydroxypropyl methylcellulose or TAS-102 (150 mg/kg), administered orally twice daily from days 1 to 14. Irinotecan hydrochloride (CPT-11) (40 mg/kg) was administered intravenously alone or in combination with TAS-102 on days 1 and 8. The tumour volume and body weight were measured twice a week. The values indicate the mean ±SD (n=7). The horizontal dotted line indicates an RTV of 5.9

Oncoral Clinical Development now in Phase 2

The development of Oncoral is supported by a Scientific Advisory Board of leading oncologists, who support the position that a daily tablet formulation of irinotecan could be a valuable additional treatment option for cancer patients, especially in later disease stages.

The Oncoral Phase 2 study, for which the IND was approved in December 2021, is a randomised controlled multicentre all-oral combination study in patients with advanced gastric cancer. Run in collaboration with Otsuka's Taiho Oncology and led by the International Coordinating Investigator, Professor Josep Tabernero, former President of the European Society for Medical Oncology (ESMO), it will compare Oncoral administered in combination with LONSURF (trifluridine and tipiracil) film-coated tablets for oral use, compared to LONSURF alone.

The primary endpoint of the combination study will be progression-free survival, which is standard for an oncology Phase 2 study. Secondary endpoints will include response rate, overall survival, pharmacokinetics, safety, and tolerability.

Patients	• Around 100 patients • Metastatic gastric cancer • Randomized controlled, multicenter, multinational study
Comparator	Oncoral + Lonsurf Vs. Lonsurf
Endpoints	**Primary:** Progression Free Survival **Secondary:** Response rate, PK, Safety and Overall Survival data in a follow up analysis
Study period	Q4 2022–2024

Summary

Gastric cancer patients often face late diagnosis and poor outcomes, due to limited treatment options. The opportunity to introduce metronomic chemotherapy with irinotecan in combination with other effective compounds in an oral tablet, opens up the possibility of better efficacy, and a more convenient and cost-effective treatment regimen with an acceptable safety profile.

REFERENCES

1. World Cancer Research Fund International (www.wcrf.org)
2. World Health Organisation (Cancer (who.int))
3. Gastric and Gastroesophageal Junction Adenocarcinoma – Epidemiology Forecast to 2029' 2020 (https://store.globaldata.com/report/gdhcer248-20--gastric-and-gastroesophageal-junction-adenocarcinoma-epidemiology-forecast-to-2029/)
4. Camptosar prescribing information
5. World Health Organisation https://gco.iarc.fr/today/data/factsheets/cancers/7-Stomach-fact-sheet.pdf (2020)
6. Kümler et al. Cancer Chemother Pharmacol. 2019 Jan;83(1):169-178: Oral administration of irinotecan in patients with solid tumors: an open-label, phase I, dose escalating study evaluating safety, tolerability and pharmacokinetics
7. Furman et al, Direct translation of a protracted irinotecan schedule from a xenograft model to a phase I trial in children,1999 (https://pubmed.ncbi.nlm.nih.gov/10561220/)
8. Perez et al. J Clin Oncol 2004: Randomized Phase II Study of Two Irinotecan Schedules for Patients With Metastatic Breast Cancer Refractory to an Anthracycline, a Taxane, or both
9. Nukatsuka M et al. Efficacy of combination chemotherapy using a novel oral chemotherapeutic agent, TAS-102, with irinotecan hydrochloride on human colorectal and gastric cancer xenografts. Anticancer Res. 2015 Mar;35(3):1437-45. PMID: 25750295.

Carl Bjartmar

Carl Bjartmar, MD, PhD, has been Chief Medical Officer at Ascelia Pharma since 2018 and has a long and solid track record in late-stage orphan drug development. He has previously served in senior roles at large international pharma companies such as Lundbeck, Sanofi and Genzyme, where he gained extensive experience in clinical development, in particular the development of novel therapies for rare diseases. Before joining Ascelia, Carl was most recently Chief Medical Officer for the Swedish biotech company Wilson Therapeutics.