

FOLFIRINOX – Modified Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Adjuvant treatment of pancreatic ductal adenocarcinoma	C25	00515a	N/A
Metastatic pancreatic cancer	C25	00515b	N/A

* This is for post 2012 indications

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patient's individual clinical circumstances.

Treatment is administered every 14 days up to a maximum of 12 cycles, unless the patient experiences disease progression or unacceptable toxicity.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

NCCP Regimen FOLFIRINOX Modified Therapy	Published: 10/10/2018 Review: 31/10/2030	Version number: 7
Tumour Group: Gastrointestinal NCCP Regimen Code: 00515	ISMO Contributor: Prof Maccon Keane	Page 1 of 11
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Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Oxaliplatin ^a	85 mg/m ²	IV infusion	500mL glucose 5% over 2 hours immediately followed by:	Repeat every 14 days up to a maximum of 12 cycles
2	1	Folinic acid ^b (Calcium leucovorin)	400mg/m ²	IV infusion	250mL NaCl 0.9% over 2 hours with the addition after 30 minutes of irinotecan as below:	Repeat every 14 days up to a maximum of 12 cycles
3	1	Irinotecan	150mg/m ²	IV infusion	250mL NaCl 0.9% over 90 minutes. This is given through a Y connector placed immediately before the injection site	Repeat every 14 days up to a maximum of 12 cycles
4	1	5-Fluorouracil ^c	2400mg/m ²	Continuous IV infusion	Over 46 hours in NaCl 0.9%	Repeat every 14 days up to a maximum of 12 cycles

^aOxaliplatin is not compatible with NaCl 0.9%. Do not piggyback or flush lines with NaCl 0.9%.

For oxaliplatin doses ≤ 104mg use 250mL glucose 5%.

Increase infusion rate time to 4 – 6 hours in case of laryngopharyngeal dysaesthesia reaction

Oxaliplatin administration must always precede the administration of 5-Fluorouracil.

Oxaliplatin may be given at the same time as Folinic Acid (*Calcium Leucovorin*) using a Y connector.

Acute neurotoxicity is common with oxaliplatin and can be precipitated on exposure to the cold therefore in this regimen patients should NOT suck on ice chips during the bolus injection of 5-Fluorouracil.

^bA dose of 200mg/m² of folinic acid may be considered.

Folinic Acid (*Calcium Leucovorin*) must be administered prior to 5-Fluorouracil. It enhances the effects of 5-Fluorouracil by increasing 5-Fluorouracil binding to the target enzyme thymidylate synthetase

^cSee dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

- Indications as above
- ECOG 0-1
- Adequate haematological, renal and liver status

CAUTION:

- Previous pelvic radiotherapy
- Recent MI, uncontrolled angina, hypertension, cardiac arrhythmias, CHF
- In patients with baseline greater than 3 loose bowel movements (BM) per day (in patients without colostomy or ileostomy)
- Symptomatic peripheral neuropathy
- In patients known to be homozygous for UGT1A1*28, consideration may be given to a reduced irinotecan starting dose
- Severe renal impairment (creatinine clearance < 30mL/minute)
- Gilbert's syndrome increases the risk of irinotecan-induced toxicity. A reduced initial dose should be considered for these patients

NCCP Regimen FOLFIRINOX Modified Therapy	Published: 10/10/2018 Review: 31/10/2030	Version number: 7
Tumour Group: Gastrointestinal NCCP Regimen Code: 00515	ISMO Contributor: Prof Maccon Keane	Page 2 of 11
The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer <i>This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPSACTregimens</i>		

EXCLUSIONS:

- Hypersensitivity to irinotecan, oxaliplatin, 5-Fluorouracil or any of the excipients
- Baseline neutrophils $< 2 \times 10^9/L$ and/or platelet count $< 100 \times 10^9/L$
- Bilirubin $> 3 \times ULN$
- Chronic bowel disease and/or bowel obstruction
- Pregnancy
- Breastfeeding
- CNS metastases
- Known complete DPD deficiency
- Severe bone marrow failure

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, liver and renal profile
- ECG (if patient has compromised cardiac function)
- DPD testing prior to first treatment with 5-Fluorouracil using phenotype and/or genotype testing unless patient has been previously tested
 - In patients with moderate or severe renal impairment, blood uracil levels used for DPD phenotyping should be interpreted with caution, as impaired kidney function can lead to increased uracil blood levels. Consequently, there is an increased risk for incorrect diagnosis of DPD deficiency, which may result in under dosing of 5-Fluorouracil or other fluoropyrimidines, leading to reduced treatment efficacy. Genotype testing for DPD deficiency should be considered for patients with renal impairment.

Regular tests:

- FBC, liver and renal profile prior to each cycle
- Evaluate for peripheral neuropathy every cycle prior to proceeding with treatment
- Assessment of hands and feet for palmar-plantar erythrodysaesthesia (PPE)

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test(s) as directed by the supervising Consultant.

NCCP Regimen FOLFIRINOX Modified Therapy	Published: 10/10/2018 Review: 31/10/2030	Version number: 7
Tumour Group: Gastrointestinal NCCP Regimen Code: 00515	ISMO Contributor: Prof Maccon Keane	Page 3 of 11
The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer <i>This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPSACTregimens</i>		

DOSE MODIFICATIONS:

- Consider a reduced starting dose in patients with identified partial DPD deficiency
 - Initial dose reduction may impact the efficacy of treatment
 - In the absence of serious toxicity, subsequent doses may be increased with careful monitoring
- Any dose modification should be discussed with a Consultant

Haematological

- Treatment is not administered unless ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$
- If levels are below this on Day 1 treatment may be delayed for 1-2 weeks
- If there is no recovery in 2 weeks, consideration should be given to discontinuing the treatment

Table 1: Dose modification of FOLFIRINOX based on Day 1 Absolute Neutrophil Count (ANC)

ANC < $1.5 \times 10^9/L$	Irinotecan	Oxaliplatin	5-Fluorouracil
1 st occurrence	Reduce dose to 120mg/m ²	Maintain full dose	Maintain full dose
2 nd occurrence	Maintain 120mg/m ² dose	Reduce to 60mg/m ²	Maintain full dose
3 rd occurrence	Discontinue treatment		

Table 2: Dose modification of FOLFIRINOX based on Day 1 Platelet Count

Platelets < $75 \times 10^9/L$	Irinotecan	Oxaliplatin	5-Fluorouracil
1 st occurrence	Maintain full dose	Reduce to 60mg/m ²	Reduce to 75% of the original dose
2 nd occurrence	Reduce dose to 120mg/m ²	Maintain at 60mg/m ²	Maintain at 75% of original dose
3 rd occurrence	Discontinue treatment		

NCCP Regimen FOLFIRINOX Modified Therapy	Published: 10/10/2018 Review: 31/10/2030	Version number: 7
Tumour Group: Gastrointestinal NCCP Regimen Code: 00515	ISMO Contributor: Prof Maccon Keane	Page 4 of 11
The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer <i>This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPSACTregimens</i>		

Table 3: Dose modification of FOLFIRINOX based on low nadir blood counts or in case of infection

	Irinotecan	Oxaliplatin	5-Fluorouracil
1st occurrence of • Febrile neutropenia • ANC < 0.5 x 10⁹/L for > 7 days • Infection with concomitant ANC < 1 x 10⁹/L	Maintain full dose	Reduce to 60mg/m ²	Reduce to 75% of the original dose
2nd occurrence of • Febrile neutropenia • ANC < 0.5 x 10⁹/L for > 7 days • Infection with concomitant ANC < 1 x 10⁹/L	Reduce dose to 120mg/m ²	Maintain at 60mg/m ²	Reduce to 50% of the original dose
3rd occurrence • Febrile neutropenia • ANC < 0.5 x 10⁹/L for > 7 days • Infection with concomitant ANC < 1 x 10⁹/L	Discontinue treatment		
Platelets < 50x 10⁹/L 1 st occurrence	Maintain full dose	Reduce to 60mg/m ²	Reduce to 75% of the original dose
2 nd occurrence	Reduce dose to 120mg/m ²	Maintain at 60mg/m ²	Reduce dose by an additional 25%
3 rd occurrence	Discontinue treatment		

***For any febrile neutropenia or a 2nd episode of ANC < 1x10⁹/L, G-SCF prophylaxis should be considered for subsequent cycles.**

NCCP Regimen FOLFIRINOX Modified Therapy	Published: 10/10/2018 Review: 31/10/2030	Version number: 7
Tumour Group: Gastrointestinal NCCP Regimen Code: 00515	ISMO Contributor: Prof Maccon Keane	Page 5 of 11
The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer <i>This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPSACTregimens</i>		

Renal and Hepatic Impairment:

Table 4: Recommended dose modifications for patients with renal or hepatic impairment

Drug	Renal impairment		Hepatic impairment	
Oxaliplatin ^a	CrCl (mL/minute)	Dose	No dose adjustment is needed	
	≥ 30	No need for dose adjustment is expected		
	< 30	Consider 50% of original dose		
	Haemodialysis	Consider 50% of the original dose Haemodialyse within 1.5 hours after administration		
Irinotecan ^b	CrCl (mL/minute)	Dose	Irinotecan is contraindicated in patients with bilirubin levels > 3 x ULN	
	≥ 10	No dose adjustment is expected		
	< 10	Start with 50-66% of the original dose, increase if tolerated		
	Haemodialysis	Start with 50-66% of the original dose, increase if tolerated		
5-Fluorouracil ^c	Renal impairment	No need for dose adjustment is expected	Mild and moderate (without renal impairment)	No need for dose adjustment is expected
	Haemodialysis	No need for dose adjustment is expected	Severe	Not recommended

^{a,c}Oxaliplatin and 5-fluorouracil renal and hepatic impairment dose modification recommendations obtained from Giraud et al. 2023
^bIrinotecan renal impairment dose modification recommendations obtained from Giraud et al. 2023, hepatic impairment dose modification recommendations obtained from SmPC

NCCP Regimen FOLFIRINOX Modified Therapy	Published: 10/10/2018 Review: 31/10/2030	Version number: 7
Tumour Group: Gastrointestinal NCCP Regimen Code: 00515	ISMO Contributor: Prof Maccon Keane	Page 6 of 11
The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer <i>This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPSACTregimens</i>		

Table 5: Dose modification schedule based on non-haematological, non-neurological toxicities

Prior to a Cycle (DAY 1)	Irinotecan dose	Oxaliplatin dose	5-Fluorouracil dose
Diarrhoea			
1st occurrence - Grade 3 or 4 - With fever and/or Grade 3 or 4 neutropenia	Reduce dose to 120mg/m ²	100%	100%
2nd occurrence	Maintain dose at 120mg/m ²	Reduce dose to 60mg/m ²	Reduce to 75% of original dose
3rd occurrence	Discontinue treatment		
Mucositis or hand-foot syndrome Grade 3 or 4	100%	100%	Reduce to 75% of original dose
Other toxicity ≥ Grade 2 (except alopecia and anaemia) - Transient grade 3 paresthesias/dysesthesias or transient grade 2 symptoms lasting > 7 days - Grade 4 or persistent grade 3	Consider dose reduction		
		Decrease oxaliplatin by 25%	
		Discontinue oxaliplatin	
Laryngo-pharyngeal dysaesthesia		Increase infusion time from 2 to 6 hours	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

This regimen poses an overall **high risk of emesis**.

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting [Available on the NCCP website](#)

Oxaliplatin: Moderate (Refer to local policy)

Irinotecan: Moderate (Refer to local policy)

5-Fluorouracil: Low (Refer to local policy)

For information:

Within NCIS regimens, antiemetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - [Available on the NCCP website](#)
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - [Available on the NCCP website](#)

NCCP Regimen FOLFIRINOX Modified Therapy	Published: 10/10/2018 Review: 31/10/2030	Version number: 7
Tumour Group: Gastrointestinal NCCP Regimen Code: 00515	ISMO Contributor: Prof Maccon Keane	Page 7 of 11
The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer <i>This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPSACTregimens</i>		

PREMEDICATIONS:

See other supportive care section below for full details: Prophylactic atropine sulphate 250 micrograms subcutaneously. Atropine should not be used in patients with glaucoma.

OTHER SUPPORTIVE CARE:

- **Acute cholinergic syndrome:** If acute cholinergic syndrome appears (defined as early diarrhoea and various other symptoms such as sweating, abdominal cramping, lacrimation, myosis and salivation) atropine sulphate (250 micrograms subcutaneously) should be administered unless clinically contraindicated. Caution should be exercised in patients with asthma. In patients who experienced an acute and severe cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent doses of irinotecan
- Anti-diarrhoeal treatment (**Refer to local policy**).
 - Patients should be made aware of the risk of delayed diarrhoea occurring more than 24 hours after the administration of irinotecan and at any time before the next cycle.
 - As soon as the first liquid stool occurs, the patient should start drinking large volumes of beverages containing electrolytes and an appropriate anti-diarrhoeal therapy must be initiated immediately
 - The currently recommended anti-diarrhoeal treatment consists of high doses of loperamide (4mg for the first intake and then 2mg every 2 hours)
 - Anti-diarrhoeal treatment should continue for 12 hours after the last liquid stool and should not be modified
 - In no instance should loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours
- Irinotecan induced diarrhoea can be life threatening and requires immediate management
 - Diarrhoea (early onset): see acute cholinergic syndrome above
 - Diarrhoea (late onset):
 - Irinotecan induced diarrhoea can be life threatening and requires immediate management
 - In monotherapy, the median time of onset of the first liquid stool was on day 5 after the infusion of irinotecan
 - Patients with an increased risk of diarrhoea are those who had previous abdominal/pelvic radiotherapy, those with baseline hyperleucocytosis, those with performance status ≥ 2 and women
 - In patients who experience severe diarrhoea, a reduction in dose is recommended for subsequent cycles
- Patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of irinotecan and advised not to drive or operate machinery if these symptoms occur.
- Management of PPE (**Refer to local policy**).

NCCP Regimen FOLFIRINOX Modified Therapy	Published: 10/10/2018 Review: 31/10/2030	Version number: 7
Tumour Group: Gastrointestinal NCCP Regimen Code: 00515	ISMO Contributor: Prof Maccon Keane	Page 8 of 11
The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer <i>This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPSACTregimens</i>		

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for full details

Oxaliplatin

- **Platinum Hypersensitivity:** Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations, the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of oxaliplatin to such patients is contraindicated
- **Laryngopharyngeal dysaesthesia:** An acute syndrome of laryngopharyngeal dysaesthesia occurs in 1% - 2% of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm. Symptoms are often precipitated by exposure to cold. Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome
- **Gastrointestinal toxicity:** It manifests as nausea and vomiting and warrants prophylactic and/or therapeutic anti-emetic therapy. Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining oxaliplatin with 5-Fluorouracil
- **Venous occlusive disease:** A rare but serious complications that has been reported in patients (0.02%) receiving oxaliplatin in combination with 5-Fluorouracil. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Patients should be instructed to report any jaundice, ascites or hematemesis immediately
- **Haemolytic Uraemic Syndrome (HUS):** Oxaliplatin therapy should be interrupted if HUS is suspected: hematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued

Irinotecan

- **Respiratory disorders:** Severe pulmonary toxicity has been reported rarely. Patients with risk factors should be monitored for respiratory symptoms before and during irinotecan therapy

5-Fluorouracil

- **Myocardial ischaemia and angina:** Cardiotoxicity is a serious complication during treatment with 5-Fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with 5-Fluorouracil, should be carefully monitored during therapy
- **DPD deficiency:** DPD is an enzyme encoded by the DPYD gene which is responsible for the breakdown of fluoropyrimidines. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidine-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. Treatment with 5-Fluorouracil, capecitabine or tegafur-containing medicinal products is contraindicated in patients with known complete DPD deficiency. Consider a reduced starting dose in patients with identified partial DPD deficiency. Initial dose reduction may

NCCP Regimen FOLFIRINOX Modified Therapy	Published: 10/10/2018 Review: 31/10/2030	Version number: 7
Tumour Group: Gastrointestinal NCCP Regimen Code: 00515	ISMO Contributor: Prof Maccon Keane	Page 9 of 11
The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer <i>This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPSACTregimens</i>		

impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring. Therapeutic drug monitoring (TDM) of 5-Fluorouracil may improve clinical outcomes in patients receiving continuous 5-Fluorouracil infusions

DRUG INTERACTIONS:

- Current SmPCs and drug interaction databases should be consulted for more information

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Version	Date	Amendment	Approved By
1	10/10/2018		Prof Maccon Keane
2	12/02/2020	Standardisation of treatment table. Updated exclusions and drug interactions. Updated recommended dose modifications for oxaliplatin in renal impairment.	Prof Maccon Keane

NCCP Regimen FOLFIRINOX Modified Therapy	Published: 10/10/2018 Review: 31/10/2030	Version number: 7
Tumour Group: Gastrointestinal NCCP Regimen Code: 00515	ISMO Contributor: Prof Maccon Keane	Page 10 of 11
The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer <i>This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPSACTregimens</i>		

3	02/09/2020	Reviewed. Updated exclusion criteria, baseline testing, dose modifications and adverse events with respect to DPD deficiency as per DHPC from HPRA June 2020 Updated Adverse events regarding palmar-plantar erythrodysesthesia	Prof Maccon Keane
4	17/01/2022	Added caution for patients known to be homozygous for UGT1A1*28 Removed ATC codes. Changed title to FOLFIRINOX modified.	Prof Maccon Keane
5	05/09/2022	Update emetogenic potential	Prof Maccon Keane
5a	23/11/2023	Formatting changes and grammatical corrections.	NCCP
6	17/01/2024	Added metastatic indication 515b	Prof Maccon Keane
6a	13/03/2025	Additional wording added to baseline testing section.	NCCP
7	31/10/2025	Updated regular tests, cautions, exclusions, supportive care, adverse effects, regimen specific complications and dose modifications sections. General NCCP Standardisation updates.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

NCCP Regimen FOLFIRINOX Modified Therapy	Published: 10/10/2018 Review: 31/10/2030	Version number: 7
Tumour Group: Gastrointestinal NCCP Regimen Code: 00515	ISMO Contributor: Prof Maccon Keane	Page 11 of 11
The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer <i>This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPSACTregimens</i>		