Gemcitabine (1000mg/m^2) and CARBOplatin (AUC 5) Therapy - 21 day

Please refer to NCCP Regimen 00849 Nivolumab 360mg and Chemotherapy for relevant information when used in combination with nivolumab

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of patients with locally advanced or metastatic transitional cell carcinoma (TCC) of the urothelium where CISplatin is contraindicated[i]	C67	00310a	N/A
Treatment of patients with locally advanced, recurrent or metastatic non-small cell lung cancer (NSCLC)[i]	C34	00310b	N/A
In combination with nivolumab for the neoadjuvant treatment of resectable NSCLC at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1% **(3 cycles only)** **(This combination is available in NCIS (00849.2))**	C34	00310c	Nivolumab: ODMS 01/05/2024 Chemotherapy: N/A

*For post 2012 indications only

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 patients individual clinical circumstances.

Gemcitabine is administered on day 1 and day 8 and CARBOplatin on day 1 of a 21 day cycle for 4-6 cycles or until disease progression or unacceptable toxicity develops.

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

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1 and 8	Gemcitabine	1000mg/m^2	IV infusion	250mL NaCl 0.9% over 30 minutes	Every 21 days
2	1	CARBOplatin	AUC5	IV infusion	500mL glucose 5% over 30 minutes	Every 21 days

CARBOplatin dose:

The dose in mg of CARBOplatin to be administered is calculated as follows:

Dose (mg) = target AUC (mg/mL x min) x (GFR mL/min +25)

- **Measured GFR** (e.g. nuclear renogram) is preferred whenever feasible
- Estimation of GFR may be performed using the Wright formula or the Cockcroft and Gault formula to measure creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125mL/min

- For obese patients and those with a low serum creatinine, for example, due to low body weight and post-operative asthenia, estimation using formulae may not give accurate results; measured GFR is recommended
  - Where obesity (body mass index [BMI] ≥ 30 kg/m^2) or overweight (BMI 25-29.9) is likely to lead to an overestimate of GFR and isotope GFR is not available, the use of the adjusted ideal body weight for Cockcroft and Gault may be considered
  - Where serum creatinine is less than 63 micromol/L, the use of a creatinine value of 62 micromol/L or a steady pre-operative creatinine value may be considered
- These comments do not substitute for the clinical judgement of a physician experienced in prescription of CARBOplatin

WRIGHT FORMULA

There are two versions of the formula depending on how serum creatinine values are obtained, by the kinetic Jaffe method or the enzymatic method. The formula can be further adapted if covariant creatine kinase (CK) values are available (not shown).

1. *SCr measured using enzymatic assay.*

$$\text{GFR (mL/min)} = \frac{(6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr (micromol/min)}}$$

2. *SCr measured using Jaffe assay*

$$\text{GFR (mL/min)} = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \textit{Sex})}{\text{SCr (micromol/min)}}$$

Key: Sex = 1 if female, 0 if male; Age in years; BSA= DuBois BSA

COCKCROFT-GAULT FORMULA

$$\text{GFR (mL/min)} = \frac{S \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

S= 1.04 for females and 1.23 for males

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- Adequate marrow reserve (ANC > 1.5 x 10^9/L, platelets > 100x10^9/L)

EXCLUSIONS:

- Hypersensitivity to gemcitabine, CARBOplatin* or any of the excipients
- Pregnancy or Breastfeeding

*If it is felt that the patient may have a major clinical benefit from CARBOplatin, it may in exceptional circumstances be feasible to rechallenge a patient with a prior mild hypersensitivity reaction e.g. using a desensitisation protocol, but only with immunology advice, premedication as advised, and a desensitisation protocol under carefully controlled conditions with resuscitation facilities available and medical and/or ITU/ HDU supervision

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Isotope GFR measurement (preferred) or GFR / Cr Clearance estimation
- Audiometry and creatinine clearance as clinically indicated

Regular tests:

- Day 1: FBC, renal and liver profile
- Day 8: FBC, renal profile

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.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant

Haematological:

Prior to commencing a new treatment cycle (i.e. day 1), ANC must be >1x10^9/L and platelets >100x10^9/L

Dose modifications for **gemcitabine within a cycle (i.e. day 8)**

Table 1: Dose modifications for gemcitabine within a cycle (i.e. day 8)

ANC (x 10^9 /L)		Platelet count (x 10^9 /L)		Other toxicity	Recommended dose of Gemcitabine
>1	And	> 100			100 %
0.5- 1	Or	50-100			75%
< 0.5	or	<50			Omit. Do not restart treatment until ANC > 0.5 and platelets > 50
ANC < 0.5 for > 5 days **or** ANC < 0.1 for > 3 days **or** Any incidence of febrile neutropenia	**Or**	< 25	**Or**	cycle delay of >1 week due to any toxicity	Reduce dose to 75% of the original cycle initiation dose for all subsequent cycles.

Renal and Hepatic Impairment:

Table 2: Dose modification of CARBOplatin and Gemcitabine in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment
CARBOplatin	• See note below[a]		No dose modification required
Gemcitabine	**CrCl (mL/min)**	**Dose**	**Hepatic Impairment**
	≥30	100%	Total bilirubin < 27 micromol/L: no dose adjustment is needed Total bilirubin ≥ 27 micromol/L: either start at 80% of the original dose and increase the dose if tolerated or start with full dose with active monitoring
	<30	No need for dose adjustment is expected	
	Haemodialysis	No need for dose adjustment is expected. Start haemodialysis 6-12 hrs after administration	

[a]Renal dysfunction and CARBOplatin:

- Patients with creatinine clearance values of <60mL/min are at greater risk of developing myelosuppression
- If GFR between 20 to ≤ 30mL/min, CARBOplatin should be administered with extreme caution
- If GFR ≤ 20mL/min, CARBOplatin should not be administered at all
- If Cockcroft & Gault or Wright formula are used, the dose should be calculated as required per cycle based on a serum creatinine obtained within 48 hrs of drug administration. If isotope GFR is used, the dose can remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine increases, consideration should be given to remeasuring the GFR or to estimating it using Cockcroft & Gault or Wright formulae.

Management of adverse events:

Table 3: Dose Modification schedule for Adverse Events

Adverse reactions	Recommended dose modification
Grade ≥ 3 non-haematological toxicity (except nausea/vomiting)	Therapy with gemcitabine and CARBOplatin should be withheld (until toxicity has resolved to grade ≤ 1) and may be resumed with dose reduction at discretion of prescribing consultant.
Grade ≥ 2 pneumonitis	Discontinue gemcitabine

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Gemcitabine: Low **(Refer to local policy).**

CARBOplatin: High **(Refer to local policy).**

PREMEDICATIONS: None usually required

OTHER SUPPORTIVE CARE: No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.

Gemcitabine:

- **Renal Toxicity**: Irreversible renal failure associated with hemolytic uremic syndrome may occur (rare) with gemcitabine. Use caution with pre-existing renal dysfunction.
- **Pulmonary Toxicity**: Acute shortness of breath may occur with gemcitabine. Discontinue treatment with gemcitabine if drug-induced pneumonitis is suspected.
- **Cardiovascular:** Due to the risk of cardiac and/or vascular disorders with gemcitabine, particular caution must be exercised with patients presenting a history of cardiovascular events.
- **Infusion time:** Infusion time prolonged beyond 60 minutes has been shown to increase volume of distribution and has been associated with an increase in toxicity. However, given in the context of a fixed dose rate (FDR) regimen, prolonged infusions have also been reported to produce a higher response rate than standard regimens in association with a higher intracellular accumulation of its active metabolite (dFdCTP).

CARBOplatin:

- **Hypersensitivity:** Reactions to CARBOplatin may develop in patients who have been previously exposed to platinum therapy. However allergic reactions have been observed upon initial exposure to CARBOplatin.
- **Neurotoxicity and ototoxicity:** Neurological evaluation and an assessment of hearing should be performed on a regular basis, especially in patients receiving high dose CARBOplatin. Neurotoxicity,

such as parasthesia, decreased deep tendon reflexes, and ototoxicity are more likely seen in patients previously treated with CISplatin, other platinum treatments and other ototoxic agents. Frequency of neurologic toxicity is also increased in patients older than 65 years.

DRUG INTERACTIONS:

- Avoid concurrent use with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Avoid concurrent use with ototoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS). If necessary perform regular audiometric testing.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Nogué-Aliguer M, Carles J et al. Gemcitabine and Carboplatin in Advanced Transitional Cell Carcinoma of the Urinary Tract. An Alternative Therapy. Cancer 2003;97 (9); 2180-2186.
2. Zatloukal P, et al. Gemcitabine plus CISplatin vs. gemcitabine plus carboplatin in stage IIIb and IV non- small cell lung cancer: a phase III randomized trial. Lung Cancer 2003;41(3):321-31.
3. Veltkamp SA, Beijnen JH, Schellens JHM. Prolonged versus standard gemcitabine infusion: translation of molecular pharmacology to new treatment strategy
4. Pollera CF, Ceribelli A, Crecco M, et al. Prolonged infusion gemcitabine: a clinical phase I study at low- (300 mg/m2) and high-dose (875mg/m2) levels. Invest New Drugs 1997; 15 (2):115-121.
5. Kwan P, Mukhopadhyay P, Rastogi A, et al. A novel administration of gemcitabine (via constant dose rate) in combination with docetaxel in advanced non-small cell lung cancer. Proceedings of the American Society of Clinical Oncology 2000; 19:507a (abstract 1985).
6. Dragovich T, Ramanathan RK, Remick S, et al. Phase II trial of a weekly 150-minute gemcitabine infusion in patients with biliary tree carcinomas. Proceedings of the American Society of Clinical Oncology 2000;19:296a (abstract 1159
7. Forde PM et al; CheckMate 816 Investigators. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med. 2022 May 26;386(21):1973-1985. doi: 10.1056/NEJMoa2202170. Epub 2022 Apr 11. PMID: 35403841; PMCID: PMC9844511
8. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2012; 30 (13) 1553-1561.
9. Ekhart C, Rodenhuis S et al. Carboplatin dosing in overweight and obese patients with normal renal function, does weight matter? Cancer Chemother Pharmacol 2009;64:115-122.
10. NCCN CARBOplatin dosing in adults https://www.nccn.org/docs/default-source/clinical/order-templates/appendix_b.pdf?sfvrsn=6286822e_6
11. Wright JG, Boddy AV, et al, Estimation of glomerular filtration rate in cancer patients. British Journal of Cancer 2001; 84(4):452-459
12. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Onco/2019; 20:e201-08. https://doi.org/10.1016/S1470-2045(19)30145-7
13. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

14. Gemcitabine 38mg/mL Concentrate for Solution for Infusion Summary of Product Characteristics. Accessed July 2023. Available at: http://www.hpra.ie/img/uploaded/swedocuments/2195981.PA0437_063_001.a35ac87a-bb27-486b-af29-5033b52ac588.000001PIL.180731.pdf
15. CARBOplatin Summary of Product Characteristics HPRA. Accessed July 2023. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-032-001_08022024123309.pdf

Version	Date	Amendment	Approved By
1			Prof Maccon Keane
2	15/11/2017	Updated title and dosing in renal and hepatic impairment. Emetogenic status of CARBOplatin amended from moderate to moderate to high Applied new NCCP regimen template	Prof Maccon Keane
3	06/11/2019	Reviewed. Treatment table standardised, updated emetogenic potential and management of adverse events	Prof Maccon Keane
4	18/11/2021	Reviewed. Updated Carboplatin Dose wording. Updated Dose modification in hepatic impairment, Adverse effects and Drug interactions.	Prof Maccon Keane
5	22/09/2023	Updated CARBOplatin infusion time. Updated standard wording for CARBOplatin dosing and creatinine value. Updated baseline tests and dose modifications sections.	Prof Maccon Keane
6	01/05/2024	New indication for nivolumab in the neoadjuvant setting and reference to relevant nivolumab regimen added.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This regimen is outside its licensed indication in Ireland. Patients should be informed of the unlicensed nature of this indication and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be aware of their responsibility in communicating any relevant information to the patient and also in ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.