Trabectedin and Pegylated Liposomal DOXOrubicin (PLD) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of patients with relapsed platinum-sensitive ovarian cancer	C56	00375a	Hospital

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.

Trabectedin is administered as an intravenous infusion over 3 hours once every 21 days immediately after pegylated liposomal DOXOrubicin 30mg/m^2 until disease progression or unacceptable toxicity occurs.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Pegylated Liposomal DOXOrubicin	30 mg/m^2	IV infusion	[a]250 ml glucose 5% at rate of 1mg/min for first cycle	Every 21 days
2	1	Trabectedin	1.1 mg/m^2	IV infusion	[b]1000 ml 0.9% NaCl over 3 hours	Every 21 days

[a]For doses ≥ 90mg, use 500mL infusion bag
Do not use with in-line filters

NOTE: If no infusion reaction observed subsequent infusions may be administered over 60min.

For patients who experience an infusion reaction, the method of infusion should be modified as follows: 5 % of the total dose should be infused slowly over the first 15 minutes. If tolerated without reaction, the infusion rate may then be doubled for the next 15 minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes.

[b]Concentration of trabectedin in the infusion solution being ≤ 0.030 mg/ml.

Intravenous administration through a central venous line is strongly recommended

Table 1: Pre-treatment haematological, renal and liver criteria required before treatment with trabectedin

ANC	≥ 1.5 x10^9/L	Patients should not proceed with treatment with trabectedin unless these pre-treatment criteria are met. If pre-treatment criteria are not met, treatment should be held. Treatment may be held for up to 3 weeks. If criteria are still not met after delay consider discontinuation of treatment or dose reduction (Reference Dose Modifications below)
Platelets	≥ 100 x10^9/L	
Haemoglobin	≥ 9 g/dl	
Albumin	≥ 25 g/L	
Bilirubin	≤ULN	
Alkaline phosphatase	≤2.5 x ULN	
Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)	≤2.5 x ULN	
Creatinine clearance (CrCl) **Or** **Serum Creatinine**	≥60 ml/min ≤1.5 mg/dl (≤132.6 micromol/L)	
Creatine phosphokinase (CPK)	≤2.5 x ULN	

*ULN = Upper limit of normal

ELIGIBILITY:

- Indications as above
- ECOG performance status 0-2
- Adequate haematological, renal and hepatic function (see Table 1 under Treatment)

EXCLUSIONS:

- Hypersensitivity to liposomal pegylated DOXOrubicin, trabectedin or any of the excipients
- Pre-existing cardiac myopathy or congestive heart failure
- Concurrent serious or uncontrolled infection
- Breast-feeding
- Pregnancy

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profiles, CPK
- ECG
- MUGA or ECHO (to determine LVEF)

Regular tests:

- FBC, renal and liver profiles, CPK weekly during first two cycles of therapy and at least once between treatments in subsequent cycles.
- ECG
- MUGA or ECHO (to determine LVEF) prior to each cycle

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.
- The same dose should be given for all cycles provided that no grade 3-4 toxicities are seen and that the patient meets the re-treatment criteria.
- If any of the events listed in table 2 occur at any time between cycles, the dose must be reduced one level, according to table 3 below, for subsequent cycles

Table 2: Dose modification of trabectedin based on adverse events

Adverse event	Dose Modification
ANC < 0.5 x 10^9/L for > 5 days or associated with fever or infection	Reduce dose by one level according to table 2 below, for subsequent cycles. Once dose has been reduced dose escalation in the subsequent cycles is not recommended. If any of these toxicities reappear in subsequent cycles in patient exhibiting clinical benefit, the dose may be further reduced (see Table 3). Colony stimulating factors can be administered for haematologic toxicity **(Refer to local policy)**
Platelets < 25 x 10^9/L	
Increase of bilirubin > ULN and/or alkaline phosphatase > 2.5 x ULN	
Increase of aminotransferases (AST or ALT) > 2.5 x ULN	
Any other grade 3 or 4 adverse reactions	

Table 3: Dose modification table for trabectedin and PLD in ovarian carcinoma

	Trabectedin	PLD
Starting dose	1.1mg/m^2	30mg/m^2
First reduction	0.9mg/m^2	25mg/m^2
Second reduction	0.75mg/m^2	20mg/m^2

Renal and Hepatic Impairment:

Table 4: Dose modifications in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment	
Trabectedin	Considering the pharmacokinetic characteristics of trabectedin, no dose adjustments are warranted in patients with mild or moderate renal impairment.	No studies with the proposed regimen have been conducted in patients with liver dysfunction. Thus, data are not available to recommend a lower starting dose in patients with hepatic impairment. However, special caution is advised and dose adjustments may be necessary in these patients since systemic exposure is probably increased and the risk of hepatotoxicity might be increased. Patients with elevated bilirubin must not be treated with trabectedin.	
Pegylated liposomal DOXOrubicin	No dose reduction necessary	**Bilirubin (micromol/L)**	**Dose**
		20-51	**75%**
		>51	**50%**
		If the patient tolerates the first dose without an increase in serum bilirubin or liver enzymes, the dose for cycle 2 can be increased to the next dose level, i.e., if reduced by 25 % for the first dose, increase to full dose for cycle 2; if reduced by 50 % for the first dose, increase to 75 % of full dose for cycle 2. The dosage can be increased to full dose for subsequent cycles if tolerated. Pegylated liposomal doxorubucin can be administered to patients with liver metastases with concurrent elevation of bilirubin and liver enzymes up to 4 x the upper limit of the normal range	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate (**Refer to local policy).**

PREMEDICATIONS:

All patients must receive corticosteroids e.g. 20 mg of dexamethasone intravenously 30 minutes prior to trabectedin not only as anti-emetic prophylaxis, but also because it appears to provide hepatoprotective effects.

OTHER SUPPORTIVE CARE:

Other strategies to prevent and treat PPE, which may be initiated for 4 to 7 days after treatment with pegylated liposomal DOXOrubicin include keeping hands and feet cool, by exposing them to cool water (soaks, baths, or swimming), avoiding excessive heat/hot water and keeping them unrestricted (no socks, gloves, or shoes that are tight fitting) (Refer to local policy).

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

- **Cardiac Dysfunction:** Patients should be monitored for cardiac-related adverse events or myocardial dysfunction. A thorough cardiac assessment including determination of left ventricular ejection fraction (LVEF) by echocardiogram or multigated acquisition scan (MUGA) should be conducted before initiation of trabectedin and at 2 to 3-month intervals thereafter until trabectedin is discontinued. Patients with LVEF less than the lower limit of normal (LVEF < LLN), prior cumulative anthracycline dose of >300mg/m2, aged > 65 years, or a history of cardiovascular disease (especially in those with cardiac medication) may be at increased risk of cardiac dysfunction at treatment with trabectedin as monotherapy or in combination with doxorubicin. For patients with Grade 3 or 4 cardiac adverse events indicative of cardiomyopathy or for patients with a LVEF that decreases below the LLN (assessed as either an absolute decrease of LVEF of ≥15% or <LLN with an absolute decrease of ≥5%), trabectedin should be discontinued
- **Rhabdomyolosis and severe CPK elevations (> 5 x ULN**): Trabectedin must not be used in patients with CPK > 2.5 x ULN. Rhabdomyolysis has been uncommonly reported, usually in association with myelotoxicity, severe liver function test abnormalities and/or renal or multiorgan failure. Therefore, CPK should be closely monitored whenever a patient may be experiencing any of these toxicities or muscle weakness or muscle pain. If rhabdomyolysis occurs, supportive measures such as parenteral hydration, urine alkalinisation and dialysis should be promptly established, as indicated. Treatment with trabectedin should be discontinued until the patient fully recovers.Caution should be taken if medicinal products associated with rhabdomyolysis (e.g. statins), are administered concomitantly with trabectedin, since the risk of rhabdomyolysis may be increased
- **Injection site reactions:** The use of central venous access is strongly recommended Patients may develop a potentially severe injection site reaction when trabectedin is administered through a peripheral venous line. Trabectedin extravasation may cause tissue necrosis requiring debridement.
- **Allergic Reactions**: During postmarketing experience, hypersensitivity reactions with very rare occurrence of fatal outcome, have been reported in association with trabectedin administration either alone or in combination with pegylated liposomal DOXOrubicin.
- **Acute Infusion Reaction**: Usually seen during the first infusion of DOXOrubicin.
- **Palmar-plantar erythrodysesthesia syndrome (PPE):** Monitor patient for presence of PPE. If present, patient may require an interruption in treatment (see dose modifications).
- **Extravasation:** Pegylated liposomal DOXOrubicin is considered an irritant. (Refer to local guidelines)

DRUG INTERACTIONS:

- Trabectedin is metabolized mainly by CYP3A4. Close monitoring of toxicities is required in patients receiving trabectedin in combination with potent CYP3A4 inhibitors and such combinations should be avoided if possible. If such combinations are needed, appropriate dose adjustments should be applied in the event of toxicities.
- Concomitant use of trabectedin with strong CYP3A4 inducers should be avoided if possible
- Alcohol consumption must be avoided during treatment with trabectedin due to the hepatotoxicity of the medicinal product
- Preclinical data have demonstrated that trabectedin is a substrate to P-gp. Concomitant administration of inhibitors of P-gp, e.g. cyclosporine and verapamil, may alter trabectedin distribution and/or elimination. The relevance of this interaction e.g. central nervous system (CNS) toxicity has not been established. Caution should be taken in such situations.

- Exercise caution in the concomitant use of pegylated liposomal DOXOrubicin with products known to interact with standard DOXOrubicin hydrochloride.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

DOXOrubicin L01DB01
Trabectedin L01CX01

REFERENCES:

1. Monk BJ, Herzog TJ et al. Trabectedin plus Pegylated Liposomal DOXOrubicin in Recurrent Ovarian Cancer. J Clin Oncol 2010;28(19) 3107-3113.
2. Yondelis Summary of Product Characteristics. Accessed Dec 2020. Available at https://www.ema.europa.eu/en/documents/product-information/yondelis-epar-product-information_en.pdf
3. Caelyx ®Summary of product characteristics. Accessed Dec 2020. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Product_Information/human/000089/WC500020180.pdf

Version	Date	Amendment	Approved By
1	11/11/2016		Prof Maccon Keane
2	26/11/2018	Updated with NCCP regimen template. Standardisation of administration fluid and dosing in hepatic impairment	Prof Maccon Keane
3	6/1/2021	Reviewed. Updated adverse events section.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.