Thames Valley
Chemotherapy Regimens
Urological Cancer
Notes from the editor

All chemotherapy regimens, and associated guidelines eg antiemetics and dose bands are available on the Network website www.tvscn.nhs.uk/networks/cancer-topics/chemotherapy/

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**Thames Valley Chemotherapy Regimens**

**Urological Cancer**

Network Chemotherapy regimens approved for use within the Thames Valley Cancer Network by the Urology PODG

**Date published: November 2018**

**Date of review: November 2020**

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List of amendments in this version

Regimen type: Urology Tumours
Date due for review: November 2020
Previous Version number: 3.9
This version number: 4.0

Table 1 Amendments

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Table 2 New regimens to be approved and or checked by PODG included in this version

<table>
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</tbody>
</table>

For anti-emetic guidelines: http://tvscn.nhs.uk/networks/cancer/cancer-topics/chemotherapy/
For dose banded chemotherapy standardized product specifications:
www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b02/dose-banded-chemotherapy-standardised-productSpecifications/
Abiraterone (Prostate)

Indications:
Advanced or metastatic castration resistant prostate cancer, previously treated with docetaxel, with PSA and / or radiographic evidence of disease progression (NICE TA259)

Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated
The patient has documented castration-resistant metastatic prostate cancer
The patient has no or mild symptoms after androgen deprivation therapy has failed
Chemotherapy is not yet indicated.
ONE of the following applies to this patient:
OPTION 1 - The patient has not previously received treatment with enzalutamide.
OPTION 2 - The patient has previously received enzalutamide but it was stopped within 3 months of starting due to dose limiting toxicity and there is clear absence of disease progression.
To be given in combination with prednisolone.
Licensed dose and frequency of abiraterone will be used. (NICE TA387)

Abiraterone in the above indication is not routinely commissioned in England in patients who have received prior enzalutamide therapy. An exception will be where enzalutamide has had to be stopped within 3 months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression.

Ensure individual funding has been obtained prior to prescribing for non-NICE approved indications
Blueteq form needs to be completed for all patients for all funding streams

DRUG REGIMEN
Day 1  Abiraterone 1000mg orally once daily
Prednisolone 5mg orally twice daily

Cycle Frequency: Daily until progression
DOSE MODIFICATIONS

*Abiraterone:*
Any dose modifications should be discussed with a Consultant.
Renal impairment
No dose adjustment necessary. Caution advised in patients with severe renal impairment.

Hepatic impairment
For patients who develop hepatotoxicity during treatment, suspension of treatment and dose adjustment may be required.
No dose adjustment is required in pre-existing mild hepatic impairment.
Moderate (Child-Pugh class B) give 250mg daily. Elevations in ALT or AST >5xULN or bilirubin >3xULN in patients with moderate hepatic impairment discontinue abiraterone.
Abiraterone should be avoided in severe hepatic impairment.

INVESTIGATIONS
Routine Blood test
1) Blood results required before drug administration

<table>
<thead>
<tr>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10 &lt; 10</td>
</tr>
<tr>
<td>Plt x 10^9/L</td>
<td>≥100 &lt; 100</td>
</tr>
<tr>
<td>Neutrophils x 10^9/L</td>
<td>≥1.5 &lt; 1.5</td>
</tr>
</tbody>
</table>

Blood tests should initially be performed 2 weekly for first 3 months of treatment, then monthly.
Creatinine
Liver function tests (LFT)
2) Non urgent tests
Tests relating to disease response/progression

CONCURRENT MEDICATION
Check drug interactions, particularly cytochrome inducers and inhibitors and adjust doses accordingly.

ANTIEMETIC POLICY
Minimal emetic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Hypertension, hypokalaemia and fluid retention use with caution
Adrenocortical insufficency
Hepatotoxicity

REFERENCES
SPC September 2011
Cabazitaxel (Prostate)

**Indication:** 2\textsuperscript{nd} line treatment of castrate resistant metastatic prostate cancer following docetaxel based therapy

NICE TA 391 Cabazitaxel in combination with prednisolone is recommended as an option for treating metastatic hormone-relapsed prostate cancer in people whose disease has progressed during or after docetaxel chemotherapy, only if:

- the person has an eastern cooperative oncology group (ECOG) performance status of 0 or 1
- the person has had 225 mg/m\textsuperscript{2} or more of docetaxel
- to be prescribed in combination with prednisone or prednisolone.
- treatment with cabazitaxel is stopped when the disease progresses or after a maximum of 10 cycles (whichever happens first).

Blueteq form needs to be completed for all patients for all funding streams

**DRUG REGIMEN**

**Day 1**
- **Cabazitaxel** 25mg/m\textsuperscript{2} in 250ml sodium chloride 0.9% IV infusion over 1 hour
- **Prednisolone** 10mg orally daily

**Cycle Frequency:** Every 21 days for 6 (maximum 10) cycles

**DOSE MODIFICATIONS**

**Cabazitaxel:**

**Hepatic impairment**

Cabazitaxel is extensively metabolised by the liver.

As a precautionary measure, cabazitaxel should not be given to patients with hepatic impairment (bilirubin $\geq 1 \times$ ULN, or AST and/or ALT $\geq 1.5 \times$ ULN).

**Renal impairment**

- **Mild renal impairment** (creatinine clearance (CL\textsubscript{CR}): 50 to 80 ml/min) no dose adjustment necessary.
- **Moderate** (CL\textsubscript{CR}: 30 to 50 ml/min) limited data available
- **Severe renal impairment** (CL\textsubscript{CR} <30 ml/min) or end stage renal disease treat with caution and monitor carefully during treatment.

Dose modifications should be made if patients experience the following adverse reactions:

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Dose modification</th>
</tr>
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<tbody>
<tr>
<td>Prolonged grade $\geq 3$ neutropenia (longer than 1 week) despite appropriate treatment including G-CSF</td>
<td>Delay treatment until neutrophil count is $&gt;1.5\times10^9$/L, then reduce cabazitaxel dose from 25 mg/m\textsuperscript{2} to 20mg/m\textsuperscript{2}.</td>
</tr>
<tr>
<td>Febrile neutropenia or neutropenic infection</td>
<td>Delay treatment until improvement or resolution, and until neutrophil count is $&gt;1.5\times10^9$/L, then reduce cabazitaxel</td>
</tr>
</tbody>
</table>
Grade >= 3 diarrhoea or persisting diarrhoea
Despite appropriate treatment, including fluid and electrolytes replacement
dose from 25 mg/m² to 20 mg/m².
Delay treatment until improvement or resolution, then reduce cabazitaxel dose from 25 mg/m² to 20 mg/m².

Grade >= 2 peripheral neuropathy
Delay treatment until improvement, then reduce cabazitaxel dose from 25 mg/m² to 20 mg/m².

The treatment should be discontinued if a patient continues to experience any of these reactions at 20 mg/m².

INVESTIGATIONS
Routine Blood test
1) Blood results required before drug administration

Give Discuss
Hb x g/dL ≥10 < 10
Plt x 10⁹/L ≥100 < 100
Neutrophils x 10⁹/L ≥1.5 < 1.5

Creatinine
Liver function tests (LFT)

2) Non urgent tests
Tests relating to disease response/progression

CONCURRENT MEDICATION

ANTIEMETIC POLICY
Low emetic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Hypersensitivity reactions
Peripheral neuropathy

REFERENCES
SPC September 2011
Enzalutamide (Prostate)

**Indications:**
Metastatic castration resistant prostate cancer, with progressive disease following docetaxel chemotherapy (NICE TA316)
The treatment of chemotherapy naïve castrate-resistant Metastatic adenocarcinoma Prostate Cancer

Ensure individual funding has been obtained prior to prescribing for non-NICE approved indications
Blueteq form needs to be completed for all patients for all funding streams

Enzalutamide in the above indication is not routinely commissioned in patients who have received prior abiraterone therapy. An exception will be where abiraterone has had to be stopped within 3 months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression.

**DRUG REGIMEN**
Day 1  Enzalutamide 160mg orally once daily

*Cycle Frequency: Daily until progression*

**DOSE MODIFICATIONS**
*Enzalutamide:*
Any dose modifications should be discussed with a Consultant.

If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to ≤ Grade 2, then resumed at the same or a reduced dose (120mg or 80mg) if warranted.

Renal impairment
No dose adjustment necessary. Caution advised in patients with severe renal impairment.

Hepatic impairment
No dose adjustment is necessary for patients with mild hepatic impairment (Child Pugh Class A). Caution is advised in patients with moderate hepatic impairment (Child Pugh Class B). It is not recommended in patients with severe hepatic impairment (Child-Pugh Class C).
INVESTIGATIONS
Routine Blood test
1) Blood results required before drug administration
   
   **Give Discuss**

   - Hb x g/dL ≥10 < 10
   - Plt x 10⁹/L ≥100 < 100
   - Neutrophils x 10⁹/L ≥1.5 < 1.5

   FBC, U&Es LFTs (including AST or ALT)
   Restaging - clinical decision, PSA as a surrogate marker

2) Non urgent tests
   Tests relating to disease response/progression
   Ask GP to monitor blood pressure on a regular basis

CONCURRENT MEDICATION
Check drug interactions, particularly cytochrome inducers and inhibitors and adjust doses accordingly.

ANTIEMETIC POLICY
Minimal emetic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
- Fatigue
- Diarrhoea
- Hot flush
- Musculoskeletal pain
- Headache
- Insomnia
- Hypertension
- Risk of seizures (<1%)

REFERENCES
AFFIRM Phase III study. Lead author Professor De Bono, ICR Royal Marsden Hospital. 
Prevail Study: A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-Naïve Patients with Progressive Metastatic Prostate Cancer Who Have Failed Androgen Deprivation Therapy

Enzalutamide Urology PODG Chair Authorisation: Date: Page 2 of 2 Published: November 2018 Review: November 2020 Version 4.0

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MITOXANTRONE (Prostate)

*Indication: Hormone refractory metastatic prostate cancer*

**DRUG REGIMEN**
Day 1 MITOXANTRONE 12mg/m² IV in 100ml sodium chloride 0.9% infusion over 15 minutes

*Cycle Frequency: Every 21 days maximum 9 cycles*

**DOSE MODIFICATIONS**
*Mitoxantrone:*
- Bilirubin >60micromol/L and good performance status give 60% dose
- Bilirubin >60micromol/L and poor performance status omit
- Maximum cumulative dose = 110 mg/m²

**INVESTIGATIONS**
Routine Blood test 1) Blood results required before chemotherapy administration

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10 &lt; 10</td>
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<tr>
<td>Plt x 10⁹/L</td>
<td>≥100 &lt; 100</td>
</tr>
<tr>
<td>Neutrophils x 10⁹/L</td>
<td>≥1.5 &lt; 1.5</td>
</tr>
</tbody>
</table>

Cardiac function if required.

2) Non-urgent tests
Tests relating to disease response/progression

**CONCURRENT MEDICATION**
Prednisolone 5mg bd (or 10mg od) orally continuously

**ANTI-EMETIC POLICY**
Low emetogenic risk

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**
Cardiotoxicity – monitor cardiac function. Mitoxantrone may be stopped in future cycles if signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue.

**REFERENCES**
DOCETAXEL

**Indications:**

*Castrate resistant metastatic prostate cancer*

*Hormone naïve metastatic prostate cancer in men either commencing, or who have commenced within 12 weeks, long-term ADT for metastatic disease for the first time; and men of sufficient performance status to be treated with 6 cycles of docetaxel chemotherapy.*

(Unlicensed indication)

NICE recommend docetaxel as a possible treatment for men with hormone-refractory metastatic prostate cancer.

**DRUG REGIMEN**

*Day 1*  
PREMEDICATION: DEXAMETHASONE  
DOCETAXEL 75mg/m² in 250ml sodium chloride 0.9% infusion over 1 hour

**Cycle Frequency:** Every 21 days

*Castrate resistant metastatic prostate cancer maximum 10 cycles*  
*Hormone naïve metastatic prostate cancer maximum 6 cycles*

**DOSE MODIFICATIONS**

Discuss if severe cutaneous reactions, peripheral neuropathy or fluid retention after previous course.  
Hepatic impairment:

Patients who have both elevations of transaminases (ALT and/or AST) > 1.5 x ULN and ALP > 2.5 x ULN: give 75% dose

Patients with serum bilirubin > ULN and/or ALT and AST > 3.5 x ULN associated with ALP > 6 x ULN: docetaxel should not be used unless strictly indicated.

**INVESTIGATIONS**

Routine Blood test

1) Blood results required before chemotherapy administration

<table>
<thead>
<tr>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10</td>
</tr>
<tr>
<td>Plt x 10⁹/L</td>
<td>≥100</td>
</tr>
<tr>
<td>Neutrophils x 10⁹/L</td>
<td>≥1.5</td>
</tr>
</tbody>
</table>

2) Non urgent tests. Tests relating to disease response/progression

**CONCURRENT MEDICATION**

Prednisolone 5mg bd po continuously.

**ANTIEMETIC POLICY**

Low emetogenic risk

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**

Ensure pre-medication is given  
Dermatology – hand-foot syndrome
**DOCETAXEL** weekly

**Indications:** Advanced prostate cancer

*NICE recommend docetaxel as a possible treatment for men with hormone-refractory (castrate resistant) metastatic prostate cancer.*

**DRUG REGIMEN**

**Day 1**  
PREMEDICATION: DEXAMETHASONE  
**DOCETAXEL** 30mg/m² in 250ml sodium chloride 0.9% infusion over 1 hour

**Day 8**  
PREMEDICATION: DEXAMETHASONE  
**DOCETAXEL** 30mg/m² in 250ml sodium chloride 0.9% infusion over 1 hour

**Day 15**  
PREMEDICATION: DEXAMETHASONE  
**DOCETAXEL** 30mg/m² in 250ml sodium chloride 0.9% infusion over 1 hour

**Day 22**  
PREMEDICATION: DEXAMETHASONE  
**DOCETAXEL** 30mg/m² in 250ml sodium chloride 0.9% infusion over 1 hour

**Day 29**  
PREMEDICATION: DEXAMETHASONE  
**DOCETAXEL** 30mg/m² in 250ml sodium chloride 0.9% infusion over 1 hour

*Cycle Frequency: Every 42 days for 2 cycles*

**DOSE MODIFICATIONS**

Discuss if severe cutaneous reactions, peripheral neuropathy or fluid retention after previous course.

Hepatic impairment: Patients who have both elevations of transaminases (ALT and/or AST) > 1.5 x ULN and ALP > 2.5 x ULN: Give 75% dose.

Patients with serum bilirubin > ULN and/or ALT and AST > 3.5 x ULN associated with ALP > 6 x ULN: docetaxel should not be used unless strictly indicated.

**INVESTIGATIONS**

Routine Blood test  
1) Blood results required before chemotherapy administration

*Give*  
*Discuss*

- Hb x g/dL  
  ≥10  < 10
- Plt x 10⁹/L  
  ≥100  < 100
- Neutrophils x 10⁹/L  
  ≥1.5  < 1.5

2) Non urgent tests. Tests relating to disease response/progression

**CONCURRENT MEDICATION**

Prednisolone 5mg bd po continuously.
ANTIEMETIC POLICY
Low emetogenic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Ensure pre-medication is given
Dermatology – hand-foot syndrome

REFERENCES
9. Petrioli et al. Weekly low dose docetaxel in advanced hormone resistant prostate cancer patients previously exposed to chemotherapy. 2003, Oncology, 64 (4): 300-305.
ATEZOLIZUMAB

Indications:
The first line treatment of locally advanced or metastatic urothelial cancer in patients who are ineligible for cisplatin-based chemotherapy.
Histologically or cytologically documented transitional cell carcinoma of the urothelial tract, that is either locally advanced (ie T4b any N or any T N2-3 disease) or metastatic (any T any N M1 disease). ECOG PS of 0, 1 or 2
The patient has not received previous chemotherapy for inoperable locally advanced or metastatic urothelial cancer
The patient has either: not received previous adjuvant chemotherapy, neoadjuvant chemotherapy or chemo-radiotherapy, or if previously treated with platinum-based chemotherapy whether as adjuvant chemotherapy or as neoadjuvant chemotherapy or with chemo-radiotherapy, has relapsed more than 12 months since completing the platinum-based chemotherapy** Patients meeting this criterion are eligible to be considered as treatment naïve for locally advanced/ metastatic disease but must satisfy all other criteria. The patient is ineligible for platinum-based chemotherapy, due to one or more of the following:* impaired renal function (EDTA-assessed glomerular filtration rate >30 and <60mls/min)* hearing loss of 25dB as assessed by formal audiometry * NCI CTCAE grade 2 or worse peripheral neuropathy * ECOG PS 2
The patient has not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody

Locally advanced or metastatic urothelial cancer previously treated with platinum-based chemo. Histologically or cytologically documented transitional cell carcinoma of the urothelial tract. The patient’s disease is either locally advanced (i.e. T4b any N or any T N2-3 disease) or metastatic (any T any N M1 disease). ECOG PS score of 0 or 1.
Either not received previous adjuvant chemotherapy, neoadjuvant chemotherapy or chemo-RT, or if previously treated with platinum-based chemotherapy whether as adjuvant chemotherapy or as neoadjuvant chemotherapy or with chemo-radiotherapy, has relapsed ≤ 12 months since completing the platinum-based chemotherapy (Patients meeting this criterion are eligible to be considered as previously treated for locally advanced/ metastatic disease (and can answer “Yes” to next criteria) but must satisfy all other criteria).
There has been disease progression during or following previous platinum-based combination chemotherapy for inoperable locally advanced or metastatic urothelial cancer. The patient has not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PDL2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody unless it was received as part of the atezolizumab compassionate use programme for this indication and the patient meets all other criteria.

Atezolizumab monotherapy and will commence at a fixed dose of 1200mg per infusion
A formal medical review as to whether treatment with atezolizumab should continue or not will be scheduled to occur at least by the end of the third cycle of treatment
The patient is to be treated until disease progression, maximum treatment duration 2 years
The patient has no symptomatically active brain metastases or leptomeningeal metastases
DRUG REGIMEN

Day 1  Atezolizumab  1200mg in 250ml sodium chloride 0.9% IV infusion

Cycle Frequency: every 3 weeks until disease progression (maximum 2 years if previously treated with platinum based therapy)
Treatment breaks of up to 12 weeks beyond the expected cycle length are allowed but solely to allow immune toxicities to settle (treatment break form to be completed).

DOSE MODIFICATIONS

Dose modification advice for specified adverse drug reactions

Pneumonitis
- Grade 2: Withhold Atezolizumab
  - Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
- ≤ Grade 3 or 4: Permanently discontinue Atezolizumab

Hepatitis
- Grade 2: Withhold Atezolizumab
  - Treatment may be resumed when the event improves to Grade 0 or 5 x [ULN] x Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ or blood bilirubin > 1.5 to 3 x ULN
- Grade 3 or 4: Permanently discontinue Atezolizumab
  - (ALT or AST > 5 x ULN or blood bilirubin > 3 x ULN)

Colitis
- Grade 2 or 3 Diarrhoea
  - Withhold Atezolizumab
  - Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone equivalent per day
- or Symptomatic Colitis
- Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated)
  - Permanently discontinue Atezolizumab
Hypothyroidism or hyperthyroidism
Symptomatic Withhold Atezolizumab
Hypothyroidism:
Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing
Hyperthyroidism:
Treatment may be resumed when symptoms are controlled by antithyroid medicinal product and thyroid function is improving

Adrenal insufficiency
Symptomatic Withhold Atezolizumab
Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy

Hypophysitis
Grade 2 or 3 Withhold Atezolizumab
Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy

Grade 4 Permanently discontinue Atezolizumab

Type 1 diabetes mellitus
Grade 3 or 4 Withhold Atezolizumab
hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L) Treatment may be resumed when metabolic control is achieved on insulin replacement therapy

Infusion-related reactions
Grade 1 or 2 Reduce infusion rate or interrupt. Treatment may be resumed when the event is resolved

Grade 3 or 4 Permanently discontinue Atezolizumab

Rash
Grade 3 Withhold Atezolizumab
Treatment may be resumed when rash is resolved and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day

Grade 4 Permanently discontinue Atezolizumab
Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis

All Grades Permanently discontinue Atezolizumab

Pancreatitis

Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN) or Grade 2 or 3 pancreatitis

Withhold Atezolizumab

Treatment may be resumed when serum amylase and lipase levels improve to Grade 0 or Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day

Grade 4 or any grade of recurrent pancreatitis

Permanently discontinue Atezolizumab

Atezolizumab should be permanently discontinued:

• For Grade 4 toxicities except for endocrinopathies that are controlled with replacement hormones
• For any recurrent event at Grade ≥ 3 severity
• If a treatment-related toxicity does not resolve to Grade 0 or Grade 1 within 12 weeks after adverse reaction onset date
• If a corticosteroid dose of > 10 mg prednisone or equivalent per day is required for treatment-related toxicity beyond 12 weeks after adverse reaction onset date.

INVESTIGATIONS

Routine Blood test

1) Blood results required before chemotherapy administration

Give Discuss

<table>
<thead>
<tr>
<th>Test</th>
<th>Grade 1</th>
<th>Grade 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Plt x 10^9/L</td>
<td>≥100</td>
<td>&lt; 100</td>
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<tr>
<td>Neutrophils x 10^9/L</td>
<td>≥1.5</td>
<td>&lt; 1.5</td>
</tr>
</tbody>
</table>

Creatinine clearance (GFR) calculated or EDTA at the Consultants discretion (Cisplatin)

2) Non-urgent tests
Tests relating to disease response/progression

CONCURRENT MEDICATION

None required

ANTI-EMETIC POLICY

Low emetic risk
ADVERSE EFFECTS / REGIMENT SPECIFIC COMPLICATIONS

Inflammation of the lung (pneumonitis): symptoms may include new or worsening cough, shortness of breath, and chest pain

• Inflammation of the liver (hepatitis): symptoms may include yellowing of skin or eyes, nausea, vomiting, bleeding or bruising, dark urine, and stomach pain

• Inflammation of the intestines (colitis): symptoms may include diarrhoea (watery, loose or soft stools), blood in stools, and stomach pain

• Inflammation of the thyroid and adrenal glands (hypothyroidism, hyperthyroidism, or adrenal insufficiency): symptoms may include tiredness, weight loss, weight gain, change in mood, hair loss, constipation, and dizziness

• Type 1 diabetes mellitus, including acid in the blood produced from diabetes (diabetic ketoacidosis): symptoms may include feeling more hungry or thirsty than usual, need to urinate more often, weight loss, and feeling tired

• Inflammation of the brain (encephalitis) or inflammation of the membrane around the spinal cord and brain (meningitis): symptoms may include neck stiffness, headache, fever, chills, vomiting, eye sensitivity to light, confusion and sleepiness

• Inflammation or problems of the nerves (neuropathy): symptoms may include muscle weakness and numbness, tingling in hands and feet

• Inflammation of the pancreas (pancreatitis): symptoms may include abdominal pain, nausea and vomiting

• Severe reactions associated with infusion (events occurring during or within one day of having the infusion) may include fever, chills, shortness of breath and flushing.

REFERENCES

SPC
PEMBROLIZUMAB

Indications:

Pembrolizumab for locally advanced or metastatic urothelial cancer previously treated with platinum-based chemotherapy

2. The prescribing clinician is fully aware of the management of and the treatment modifications that may be required for the immune-related adverse reactions due to anti-PD-L1 treatments including pneumonitis, colitis, nephritis, endocrinopathies and hepatitis

3. The patient has histologically or cytologically documented transitional cell carcinoma of the urothelial tract

4. The patient’s disease is either locally advanced (ie T4b any N or any T N2-3 disease) or metastatic (any T any N M1 disease)

5. There has been disease progression during or following previous platinum-based combination chemotherapy for inoperable locally advanced or metastatic urothelial cancer

6. The patient has either: not received previous adjuvant chemotherapy, neoadjuvant chemotherapy or chemo-radiotherapy, or if previously treated with platinum-based chemotherapy whether as adjuvant chemotherapy or as neoadjuvant chemotherapy or with chemo-radiotherapy, has relapsed <= 12 months since completing the platinum-based chemotherapy** Patients meeting this criterion are eligible to be considered as previously treated for locally advanced/ metastatic disease but must satisfy all other criteria

7. The patient has an ECOG performance status (PS) score of 0 or 1 or 2 Note: treatment of patients with performance status 2 should only proceed with caution as there is limited safety data on PS 2 patients with urothelial carcinoma treated with pembrolizumab

8. The patient has not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PDL2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody unless it was received as part of the pembrolizumab compassionate use programme for this indication and the patient meets all other criteria listed here

9. Pembrolizumab is being given as monotherapy and will commence at a fixed dose of 200mg per infusion

10. A formal medical review as to whether treatment with pembrolizumab should continue or not will be scheduled to occur at least by the end of the third cycle of treatment

11. The patient is to be treated until disease progression and loss of clinical benefit or excessive toxicity or patient choice, whichever is the sooner

12. The patient will receive a maximum treatment duration of 2 years

13. Treatment breaks of up to 12 weeks beyond the expected cycle length are allowed but solely to allow immune toxicities to settle

14. The patient has no symptomatically active brain metastases or leptomeningeal metastases

15. Pembrolizumab will otherwise be used as set out in its SPC

Pembrolizumab as first line treatment of locally advanced or metastatic urothelial cancer in patients who are ineligible for cisplatin-based chemotherapy

2. I confirm that as the prescribing clinician I am fully aware of the management of and the treatment modifications that may be required for immune-related adverse reactions due to anti-PD-L1 treatments including pneumonitis, colitis, nephritis, endocrinopathies and hepatitis.
3. I confirm that the patient has histologically or cytologically documented transitional cell carcinoma of the urothelial tract.

4. I confirm that the patient has disease that is either locally advanced (ie T4b any N or any T N2-3 disease) or metastatic (any T any N M1 disease).

5. I confirm that the patient has not received previous chemotherapy for inoperable locally advanced or metastatic urothelial cancer.

6. I confirm that the patient has EITHER not received previous adjuvant chemotherapy, neoadjuvant chemotherapy or chemo-radiotherapy for localised urothelial cancer OR, if previously treated with platinum-based chemotherapy whether as adjuvant chemotherapy or as neoadjuvant chemotherapy or with chemo-radiotherapy for localised urothelial cancer, has relapsed more than 12 months since completing the platinum-based chemotherapy.

Patients meeting this criterion are eligible to be considered as treatment naïve for locally advanced/metastatic disease but must satisfy all other criteria.

I confirm that the patient has an ECOG performance status (PS) of 0-2. Note: treatment of patients with performance status 2 with pembrolizumab should only proceed with caution as there is limited safety data on PS 2 patients with urothelial carcinoma treated with pembrolizumab.

8. The patient is ineligible for platinum-based chemotherapy, due to one or more of the following: impaired renal function (EDTA-assessed glomerular filtration rate >30 and <60mls/min) * hearing loss of 25dB or more as assessed by formal audiometry * NCI CTCAE grade 2 or worse peripheral neuropathy * ECOG PS 2.

9. I confirm that the patient has not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody unless it was received as part of the pembrolizumab compassionate access scheme for this indication and the patient meets all other criteria listed here.

10. I confirm that the patient has no symptomatically active brain metastases or leptomeningeal metastases.

11. I confirm that pembrolizumab is being given as monotherapy and will commence at a fixed dose of 200mg per infusion.

12. I confirm that a formal medical review as to whether treatment with pembrolizumab should continue or not will be scheduled to occur at least by the end of the third cycle of treatment.

13. I confirm that the patient will be treated until loss of clinical benefit or excessive toxicity or patient choice to discontinue treatment, whichever is the sooner.

14. I confirm that the patient will receive a maximum treatment duration with pembrolizumab of 2 years.

15. I confirm that treatment breaks of up to 12 weeks beyond the expected cycle length are allowed but solely to allow immune toxicities to settle.

16. I confirm that pembrolizumab will otherwise be used as set out in its Summary of Product Characteristics (SPC).
DRUG REGIMEN

Day 1  PEMBROLIZUMAB 200mg in sodium chloride 0.9% infusion over 30 minutes

*Cycle Frequency: Every 21 days until disease progression for a maximum of 2 years uninterrupted treatment*

DOSE MODIFICATIONS

Pembrolizumab
See Immuno-oncology adverse event management guidelines

INVESTIGATIONS

Routine Blood test
1) Blood results required before chemotherapy administration
   FBC,U&Es including magnesium, ,Cr, LFTs Every cycle
   TFT Every other cycle
   ECG
   Non urgent blood tests - Tests relating to disease response/progression

CONCURRENT MEDICATION

None required.

ANTiemetic POLICY

Low emetogenic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Immune-mediated pneumonitis
Immune-mediated colitis
Immune-mediated hepatitis
Immune-mediated endocrinopathies

REFERENCES

SPC July 2015
CDF May 2017
CMV (Bladder)

*Indications Metastatic bladder cancer and adjuvant bladder cancer - should only rarely be used for bladder cancer*

**DRUG REGIMEN**

**Day 1** Pre-hydration regimen

- METHOTREXATE 30mg/m$^2$ IV bolus
- VINBLASTINE 4mg/m$^2$ (Max. 10mg) in 50ml sodium chloride 0.9% IV infusion over 10 minutes
- CISPLATIN 100mg/m$^2$ in 1000ml sodium chloride infusion over 2 hours (daypatient) or 4 hours (inpatient)

Post-hydration regimen

**Day 8** METHOTREXATE 30mg/m$^2$ IV bolus

- VINBLASTINE 4mg/m$^2$ (Max. 10mg) in 20ml sodium chloride 0.9% IV over 10 minutes

*Cycle Frequency: Every 21 days maximum 6 cycles*

**DOSE MODIFICATIONS**

* **Cisplatin:**
  - GFR > 60ml/min give 100% dose
  - GFR 45-60ml/min give 75% dose
  - GFR < 45ml/min consider carboplatin
  - If patient complains of tinnitus, tingling of fingers and/or toes discuss with Consultant or Registrar before administration

* **Methotrexate:**
  - GFR 60ml/min give 65% dose
  - GFR 45ml/min give 50% dose
  - GFR <30 ml/min omit

  - Bilirubin 51-85micromol/L or AST>180 give 75% dose
  - Bilirubin >85micromol/L omit

* **Vinblastine:**
  - Bilirubin 26-51 micromol/L or AST/ALT>60-80 give 50% dose
  - Bilirubin >51 micromol/L and AST/ALT normal give 50% dose
  - Bilirubin >51 micromol/L and AST/ALT >180 omit
INVESTIGATIONS
Routine Blood test
1) Blood results required before chemotherapy administration

\[
\begin{align*}
\text{Hb} & \quad \text{g/dL} & \geq 10 & < 10 \\
\text{Plt} & \quad \times 10^9/L & \geq 100 & < 100 \\
\text{Neutrophils} & \quad \times 10^9/L & \geq 1.5 & < 1.5 \\
\text{Creatinine clearance (GFR)} & \text{calculated or EDTA at the Consultants discretion (Cisplatin)}
\end{align*}
\]

Give  Discuss

2) Non-urgent tests
Tests relating to disease response/progression

CONCURRENT MEDICATION
Ensure adequate pre- and post-hydration prescribed as per TVCN regimens.
Daypatient: If urine output is < 100ml/hour or if patient gains > 2kg weight during IV administration post Cisplatin give 20 - 40mg Furosemide PO/IV or 200ml Mannitol 10% IV
Inpatient: If fluid balance is > 2L positive after 8 hours post hydration OR urine output is < 100ml/hour during IV administration post Cisplatin give 20 - 40 mg Furosemide PO/IV OR 200ml Mannitol 10% IV

For patient requiring Folinic acid support the dose is Folinic acid 15mg PO/IV every 6 hours for 6 doses starting 24 hours after Methotrexate especially if:
- Pleural effusions/ascites
- Previous mucositis
- Serum creatinine > 120micromols/L

ANTI-EMETIC POLICY
Highly emetogenic day 1
Minimal emetogenic risk day 8

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Methotrexate induced mucositis - folinic acid (calcium folinate) rescue (see concurrent medication)
Nephrotoxicity – ensure adequate pre and post hydration is prescribed. Caution with furosemide.
Ototoxicity – assess patient for tinnitus or hearing abnormalities.

REFERENCES
CISPLATIN / GEMCITABINE (Bladder)

Indications: Metastatic bladder cancer and neoadjuvant or adjuvant bladder cancer

DRUG REGIMEN
Day 1 Pre-hydration regimen
GEMCITABINE 1000mg/m² in 250ml sodium chloride 0.9% infusion over 30 minutes
CISPLATIN 70mg/m² in 1000ml sodium chloride 0.9% infusion over 2 hours (daypatient) or 4 hours (inpatient)
Post-hydration regimen

Day 8 GEMCITABINE 1000mg/m² in 250ml sodium chloride 0.9% infusion over 30 minutes

Cycle Frequency: Every 21 days (6 cycles for metastatic disease, 4 cycles for adjuvant)

DOSE MODIFICATIONS
Cisplatin:
GFR > 60ml/min give 100% dose
GFR 45-60ml/min give 75% dose
GFR < 45ml/min consider carboplatin

If patient complains of tinnitus, tingling of fingers and/or toes discuss with SpR or Consultant before administration

Gemcitabine:
CrCl <30ml/min consider dose reduction (Clinical decision)

Neutrophils >1.0x10⁹/L and platelets >100x10⁹/L give 100% dose
Neutrophils 0.5-1.0x10⁹/L or platelets 50-100x10⁹/L give 75% dose or delay based on clinical assessment
Neutrophils <0.5x10⁹/L or platelets <50x10⁹/L delay treatment

Diarrhoea and/or mucositis
Grade 2 toxicity – omit until toxicity resolved then restart at 100% dose
Grade 3 toxicity – omit until toxicity resolved then restart at 75% dose
Grade 4 toxicity – omit until toxicity resolved then restart at 50% dose

Omit if treatment is delayed for more than 4 weeks but continue with Cisplatin
INVESTIGATIONS
Routine Blood test
1) Blood results required before chemotherapy administration

<table>
<thead>
<tr>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10</td>
</tr>
<tr>
<td>Plt x 10^9/L</td>
<td>≥100</td>
</tr>
<tr>
<td>Neutrophils x 10^9/L</td>
<td>≥1.5</td>
</tr>
</tbody>
</table>

Creatinine clearance (GFR) calculated or EDTA at the Consultants discretion. (Cisplatin)

2) Non-urgent tests
Tests relating to disease response/progression

CONCURRENT MEDICATION
Ensure adequate pre-and post-hydration prescribed as per TVCN regimens.
Daypatient: If urine output is < 100ml/hour or if patient gains >2kg weight during IV administration post Cisplatin give 20 - 40mg Furosemide PO/IV or 200ml Mannitol 10% IV
Inpatient: If fluid balance is > 2L positive after 8 hours post hydration OR urine output is < 100ml/hour during IV administration post Cisplatin give 20 – 40 mg Furosemide PO/IV OR 200ml Mannitol 10% IV

ANTI-EMETIC POLICY
Highly emetogenic day 1
Low emetogenic risk days 8, 15

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Diarrhoea – see dose modifications
Mucositis – see dose modifications
Nephrotoxicity – ensure adequate pre and post hydration is prescribed.
Ototoxicity – assess patient for tinnitus or hearing abnormalities.

REFERENCES
GEMCITABINE / CARBOPLATIN (Bladder)

*Indications: Metastatic bladder cancer when cisplatin is contra-indicated or unsuitable*

**DRUG REGIMEN**

**Day 1**  
GEMCITABINE 1000mg/m² in 250ml sodium chloride 0.9% infusion over 30 minutes  
CARBOPLATIN (AUC= 4.5) in 500ml glucose 5% infusion over 1 hour  
Dose = (25 + GFR) x AUC

**Day 8**  
GEMCITABINE 1000mg/m² in 250ml sodium chloride 0.9% infusion over 30 minutes

*Cycle Frequency: Every 21 days for 6 cycles*

**NB** Ideally GFR should be measured using EDTA  
If not it *may be* calculated

**DOSE MODIFICATIONS**

*Carboplatin:*
Contraindicated if CrCl<20ml/min

*Gemcitabine:*
If CrCl <30ml/min consider dose reduction (Clinical decision)  
Neutrophils >1.0x10⁹/L and platelets >100x10⁹/L give 100% dose  
Neutrophils 0.5-1.0x10⁹/L or platelets 50-100x10⁹/L give 75% dose or delay based on clinical assessment  
Neutrophils <0.5x10⁹/L or platelets <50x10⁹/L delay treatment

Diarrhoea and/or mucositis  
Grade 2 toxicity – omit until toxicity resolved then restart at 100% dose  
Grade 3 toxicity – omit until toxicity resolved then restart at 75% dose  
Grade 4 toxicity – omit until toxicity resolved then restart at 50% dose

Omit if treatment is delayed for more than 4 weeks but continue with Cisplatin
INVESTIGATIONS
Routine Blood test 1) Blood results required before chemotherapy administration

\[
\begin{array}{ll}
\text{Give} & \text{Discuss} \\
\hline
\text{Hb x g/dL} & \geq 10 \quad < 10 \\
\text{Plt x 10^9/L} & \geq 100 \quad < 100 \\
\text{Neutrophils x 10^9/L} & \geq 1.5 \quad < 1.5 \\
\end{array}
\]

Liver function tests (LFT)

Creatinine clearance (GFR) ideally measured by \(^{51}\text{Cr-EDTA}\) or calculated at the Consultants discretion (Carboplatin).

2) Non-urgent tests

Tests relating to disease response/progression

CONCURRENT MEDICATION
Carboplatin- Anaphylaxis treatment should be prescribed if the patient has had an anaphylactic episode previously.

DEXAMETHASONE 20mg IV bolus
CHLORPHENAMINE 10mg IV bolus
RANITIDINE 50mg IV bolus

Carboplatin should be given at a slower rate e.g. 2-4 hours.

ANTI-EMETIC POLICY
Moderately emetogenic day 1
Low emetic risk day 8

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Diarrhoea – see dose modifications
Mucositis – see dose modifications

REFERENCES
GEMCITABINE and RT (Bladder)

*Indications: Bladder cancer with concurrent radiotherapy*

**DRUG REGIMEN**
Days 1, 8, 15 and 22

GEMCITABINE 100mg/m² in 250ml sodium chloride 0.9% infusion over 30 minutes

*Cycle Frequency: Every 28 days with radiotherapy*

NB Dose may be amended to 75mg/m2 weekly for 6 weeks

**DOSE MODIFICATIONS**

*Gemcitabine:*
if there is any toxicity \( \geq \) RTOG grade 3, then gemcitabine should be stopped and the radiotherapy should continue to a full course

**INVESTIGATIONS**

Routine Blood test 1) Blood results required before chemotherapy administration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Requirement</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>( \geq 10 )</td>
<td>( &lt; 10 )</td>
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<td>Plt x 10⁹/L</td>
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<td>( &lt; 100 )</td>
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<tr>
<td>Neutrophils x 10⁹/L</td>
<td>( \geq 1.0 )</td>
<td>( &lt; 1.0 )</td>
</tr>
</tbody>
</table>

Liver function tests (LFT)
Creatinine clearance (GFR) ideally measured by \(^{51}\text{Cr-EDTA}\) or calculated at the Consultants discretion (Carboplatin).

2) Non-urgent tests
Tests relating to disease response/progression

**CONCURRENT MEDICATION**

**ANTI-EMETIC POLICY**
Mildly emetogenic

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**

Diarrhoea – see dose modifications
Mucositis – see dose modifications
Urinary symptoms

**REFERENCES**

Mitomycin and Fluorouracil (MF) with concurrent RT

Indications: Bladder cancer with concurrent RT

DRUG REGIMEN
Day 1 MITOMYCIN 12mg/m² IV bolus. Max 20 mg
Days 1 and 22 FLUOROURACIL 2500mg/m² over 5 days via an infusor

Cycle Frequency: 1 cycle with concurrent radiotherapy

DOSE MODIFICATIONS
Symptoms including diarrhoea, mucositis and leucopenia, discuss with Registrar or Consultant.

Fluoruracil:
Consider dose reductions in severe renal impairment only
Bilirubin > 85micromol/L or AST >180 omit

Mitomycin:
GFR > 10ml/min give 100% dose
GFR < 10ml/min give 75% dose
Consider a dose reduction for high doses of Mitomycin when GFR 10-60ml/min
AST >2xULN Clinical decision

INVESTIGATIONS
Routine Blood test 1) Blood results required before chemotherapy administration

<table>
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<td>Neutrophils x 10⁹/L</td>
<td>≥1.5</td>
</tr>
</tbody>
</table>
2) Non urgent blood tests
Tests relating to disease response/progression

CONCURRENT MEDICATION
Prophylactic antibiotics ciprofloxacin 250mg bd for 6 weeks during chemoradiotherapy

ANTIEMETIC POLICY
Low emetogenic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Palmar plantar (hand foot syndrome) causing red palms and soles – treat with pyridoxine 50mg tds
Mucositis – use routine mouth care
Diarrhoea – treat with loperamide or codeine
Cardiotoxicity - special attention is advisable in treating patients with a history of heart disease or those who develop chest pain during treatment with fluorouracil.
MVAC ACCELERATED (Bladder)

Indications: Neoadjuvant bladder cancer pre surgery and metastatic bladder cancer

DRUG REGIMEN
Day 1  Pre-hydration regimen
METHOTREXATE 30mg/m² IV bolus
VINBLASTINE 3mg/m² in 50ml sodium chloride 0.9% IV infusion over 10 minutes
DOXORUBICIN 30mg/m² IV bolus
CISPLATIN 70mg/m² in 1000ml sodium chloride 0.9% infusion over 2 hours
(daypatient) or 4 hours (inpatient)
Post-hydration regimen
Days 2 to 8 GCSF as per local policy

Cycle Frequency: Every 14 days for 3 cycles pre-surgery neoadjuvant, 6 cycles for metastatic disease

DOSE MODIFICATIONS
Doxorubicin:
Dose reduce in severe renal impairment.
Bilirubin 20-50micromol/L give 50% dose
Bilirubin 51-85micromol/L give 25% dose
Bilirubin >85micromol/L omit
If ALT/AST is 2-3 x ULN give 75% dose
If ALT/AST is >3 x ULN give 50% dose

Maximum cumulative dose = 450-550 mg/m² (in normal cardiac function)
= 400 mg/m² (in patients with cardiac dysfunction or exposed to mediastinal irradiation)

Cisplatin:
GFR > 60ml/min give 100% dose
GFR 45-60ml/min give 75% dose
GFR < 45ml/min consider carboplatin

If patient complains of tinnitus, tingling of fingers and/or toes discuss with Consultant or Registrar before administration

Vinblastine:
Bilirubin 26-51 micromol/L or AST/ALT>60-80 give 50% dose
Bilirubin >51 micromol/L and AST/ALT normal give 50% dose
Bilirubin >51 micromol/L and AST/ALT >180 omit
**Methotrexate:**
GFR 60ml/min give 65% dose  
GFR 45ml/min give 50% dose  
GFR < 30 ml/min omit  
Bilirubin 51-85micromol/L or AST>180 give 75% dose  
Bilirubin >85micromol/L omit

**INVESTIGATIONS**
Routine Blood test
1) Blood results required before chemotherapy administration
   
   *Give Discuss*

   Hb x g/dL  
   ≥10 < 10  
   Plt x 10⁹/L  
   ≥100 < 100  
   Neutrophils x 10⁹/L  
   ≥1.5 < 1.5  

   Creatinine clearance (GFR) calculated or EDTA at the Consultants discretion (Cisplatin)
   
   2) Non-urgent tests; tests relating to disease response/progression

**CONCURRENT MEDICATION**
For patient requiring Folinic acid support the dose is Folinic acid 15mg PO/IV every 6 hours for 6 doses starting 24 hours after Methotrexate especially if:

- Pleural effusions/ascites
- Previous mucositis
- Serum creatinine >120 micromols/L

Ensure adequate pre-and post-hydration prescribed as per TVCN regimens.

Daypatient: If urine output is < 100ml/hour or if patient gains >2kg weight during IV administration post Cisplatin give 20 - 40mg Furosemide PO/IV or 200ml Mannitol 10% IV

Inpatient: If fluid balance is > 2L positive after 8 hours post hydration OR urine output is < 100ml/hour during IV administration post Cisplatin give 20 ¬ 40 mg Furosemide PO/IV OR 200ml Mannitol 10% IV

**ANTI-EMETIC POLICY**
Highly emetogenic day 1

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**
Methotrexate induced mucositis - folinic acid (calcium folinate) rescue (see concurrent medication)
Nephrotoxicity – ensure adequate pre and post hydration is prescribed.
Ototoxicity – assess patient for tinnitus or hearing abnormalities.
Cardiotoxicity – monitor cardiac function

**REFERENCES**
PACLITAXEL CARBOPLATIN 21 day

Indications: Second line incurable locally advanced or metastatic urothelial bladder cancer, when cisplatin-based chemotherapy is unsuitable.

DRUG REGIMEN
Day 1 PRE-MEDICATION 30 mins prior to paclitaxel

- DEXAMETHASONE 20mg IV bolus
- RANITIDINE 50mg IV bolus
- CHLORPHENAMINE 10mg IV bolus
- PACLITAXEL 175mg/m² in 500ml* sodium chloride 0.9% infusion over 3 hours (PVC free)
- CARBOPLATIN AUC 5 in 500ml Glucose 5% infusion over 60 mins

Dose (mg) = (GFR + 25) x AUC

Cycle Frequency: Every 21 days for maximum 8 cycles

* doses 84mg to 144mg in 250ml sodium chloride 0.9%
NB Ideally GFR is measured using ⁵¹Cr-EDTA

DOSE MODIFICATIONS
Previous neutropenic sepsis, discuss with Consultant or Registrar.

Carboplatin:
If GFR/CrCl = or < 20ml/min discuss with consultant.

Paclitaxel:
If patient complains of tinnitus, tingling of fingers and/or toes or motor weakness discuss with Consultant or Registrar before administration. If grade II or > neuropathy, consider using paclitaxel 135mg/m².
Bilirubin <1.25xULN and AST/ALT <10xULN dose at 175mg/m²
Bilirubin <26micromol/L give 135mg/m²
Bilirubin 27-51micromol/L give 75mg/m²
Bilirubin >51micromol/L give 50mg/m²[3]

If GFR/CrCl = or < 20ml/min discuss with consultant.
INVESTIGATIONS
Routine Blood test
1) Blood results required before chemotherapy administration
   | Give | Discuss |
   | Hb x g/dL | ≥10 | <10 |
   | Plt x 10^9/L | ≥100 | <100 |
   | Neutrophils x 10^9/L | ≥1.5 | <1.5 |
   a. Liver function tests (LFTs)
   b. GFR assessed using \(^{51}\)Cr-EDTA result or calculated creatinine clearance at the Consultant’s discretion. (Carboplatin)
   c. Patients with hydronephrosis or serum creatinine ≥ 100 micromol/L need a serum creatinine checked every cycle. All patients have serum creatinine checked 1st and 4th cycle - Carboplatin.

2) Non-urgent blood tests
   Tests relating to disease response/progression

CONCURRENT MEDICATIONS
Paclitaxel – ensure pre medication is given
Carboplatin - Anaphylaxis treatment should be prescribed if the patient has had an anaphylactic episode previously. Carboplatin should be given at a slower rate e.g. 2-4 hours.

ANTI-EMETIC POLICY
Moderately emetogenic (routinely dexamethasone and metoclopramide is adequate but 5HT\(_3\) antagonist may be required if there is inadequate control).

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
2% risk of severe hypersensitivity. Reactions to paclitaxel range from mild hypotension (light-headedness) to full cardiac collapse (anaphylactic shock). Discontinue infusion and resuscitate appropriate to reaction. If reaction is mild and settles promptly (i.e. within 5-10mins), cautiously restart at a slower rate under close supervision. If further reactions occur stop treatment.
Ototoxicity - monitor
Neurotoxicity – monitor

REFERENCES
**BEP (3 day) adjuvant (NSGCT)**

*Indications: Adjuvant treatment for non-metastatic non-seminomatous germ cell tumour (stage 1 only) in patients with vascular or lymphatic invasion (risk of relapse up to 40% without treatment). Consider for patients who are unable to attend for intensive outpatient surveillance.*

**DRUG REGIMEN**

**Day 1**  
Pre-hydration regimen  
ETOPOSIDE 120mg/m² in 1000ml* sodium chloride 0.9% infusion over 2 hours  
CISPLATIN 50mg/m² in 1000ml sodium chloride 0.9% infusion over 2 hours  
(daypatient) or 4 hours (inpatient)  
Post-hydration regimen

**Day 2**  
Pre-hydration regimen  
ETOPOSIDE 120mg/m² in 1000ml* sodium chloride 0.9% infusion over 2 hours  
CISPLATIN 50mg/m² in 1000ml sodium chloride 0.9% infusion over 2 hours  
(daypatient) or 4 hours (inpatient)  
BLEOMYCIN 30,000units in 3ml Lidocaine 1% IM injection (daypatient) or in 1000ml sodium chloride 0.9% IV infusion over 12 hours (inpatient)  
Post-hydration regimen

**Day 3**  
ETOPOSIDE 120mg/m² in 1000ml* sodium chloride 0.9% infusion over 2 hours

**Day 9**  
HYDROCORTISONE 100mg IM  
BLEOMYCIN 30,000units in 3ml 1% lidocaine IM

**Day 16**  
HYDROCORTISONE 100mg IM  
BLEOMYCIN 30,000units in 3ml 1% lidocaine IM

* doses 48mg to 88mg in 250ml, 96mg to 180mg in 500ml sodium chloride 0.9%

**Cycle Frequency: Every 21 days for TWO cycles ONLY**

**DOSE MODIFICATIONS**  
Any delays with/without dose modification may cause treatment failure.  
Discuss with Consultant before delaying treatment or reducing doses of any drug

**Cisplatin:**  
GFR > 60ml/min give 100% dose  
GFR 50-60ml/min give 75% dose (to be discussed with consultant, consider full dose)  
GFR 40-50ml/min give 50% dose  
GFR < 40ml/min omit dose  
If patient complains of tinnitus, tingling of fingers and/or toes discuss Consultant before administration

**Bleomycin:**  
GFR > 50ml/min give 100% dose  
GFR 10-50ml/min give 75% dose  
GFR <10ml/min give 50% dose
**Etoposide:**
CrCl > 50ml/min give 100% dose  
CrCl 15-50ml/min give 75% dose  
CrCl <15ml/min give 50% dose  
Bilirubin 26-51micromol/L or AST 60-180u/L 50% give dose  
Bilirubin >51micromol/L or AST >180u/L Clinical decision

**INVESTIGATIONS**
Check patient has had sperm-banking prior to starting first treatment  
Routine Blood test  
1) Blood results required before chemotherapy administration  
   Give Discuss  
   Hb x g/dL ≥10 < 10  
   Plt x 10⁹/L ≥100 < 100  
   Neutrophils x 10⁹/L ≥1.5 < 1.5  
   Creatinine clearance (GFR) calculated or EDTA at the Consultants discretion (Cisplatin)  
2) Non-urgent tests relating to disease response/progression

**CONCURRENT MEDICATION**
Ensure adequate pre-and post-hydration prescribed as per TVCN regimens.  
Daypatient: If urine output is < 100ml/hour or if patient gains >2kg weight during IV administration post Cisplatin give 200ml Mannitol 10% IV or consider 20 - 40mg Furosemide PO/IV  
Inpatient: If fluid balance is > 2L positive after 8 hours post hydration OR urine output is < 100ml/hour during IV administration post Cisplatin give 200ml Mannitol 10% IV or consider 20 ¬ 40 mg Furosemide PO/IV

**ANTI-EMETIC POLICY**
Highly emetogenic. days 1, 2  
Low emetogenic risk day 3  
Minimal emetogenic risk days 8, 15

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**
Pulmonary function tests (including transfer factor) prior to commencement of BEP. If breathlessness or infiltrates appear not attributable to tumour or co-existence of lung disease bleomycin must be stopped immediately. Consider treatment with corticosteroids and a broad spectrum antibiotic and / referral to chest team. Investigation of choice high resolution CT chest.  
Nephrotoxicity – ensure adequate pre and post hydration is prescribed.  
Ototoxicity – assess patient for tinnitus or hearing abnormalities.

**REFERENCES**
BEP (3 day) metastatic (NSGCT)

**Indications:** Good prognosis metastatic non-seminomatous germ cell tumour (3 cycles only)

**DRUG REGIMEN**

**Day 1**
- Pre-hydration regimen
  - **ETOPOSIDE** 166mg/m² in 1000ml* sodium chloride 0.9% infusion over 2 hours
  - **CISPLATIN** 50mg/m² in 1000ml sodium chloride 0.9% infusion over 2 hours (daypatient) or 4 hours (inpatient)
  - Post-hydration regimen

**Day 2**
- Pre-hydration regimen
  - **ETOPOSIDE** 166mg/m² in 1000ml* sodium chloride 0.9% infusion over 2 hours
  - **CISPLATIN** 50mg/m² in 1000ml sodium chloride 0.9% infusion over 2 hours (daypatient) or 4 hours (inpatient)
  - **BLEOMYCIN** 30,000units in 3ml Lidocaine 1% IM injection (daypatient) or in 1000ml sodium chloride 0.9% IV infusion over 12 hours (inpatient)
  - Post-hydration regimen

**Day 3**
- **ETOPOSIDE** 166mg/m² in 1000ml* sodium chloride 0.9% infusion over 2 hours

**Day 9**
- **HYDROCORTISONE** 100mg IM
- **BLEOMYCIN** 30,000units in 3ml 1% lidocaine IM

**Day 16**
- **HYDROCORTISONE** 100mg IM
- **BLEOMYCIN** 30,000units in 3ml 1% lidocaine IM

* doses 48mg to 88mg in 250ml, 96mg to 180mg in 500ml sodium chloride 0.9%

NB Day 9 may be given on day 8 instead. Day 16 may be given on day 15 instead (RBFT).
NB Day 9 and 16 are given as outpatient treatments

**Cycle Frequency:** Every 21 days for THREE cycles ONLY

can give 4 cycles (good prognosis metastatic germ cell tumour, 4th cycle excluding bleomycin)

**DOSE MODIFICATIONS**

Any delays with/without dose modification may cause treatment failure.
Discuss with Consultant before delaying treatment or reducing doses of any drug.

**Cisplatin:**
- GFR > 60ml/min give 100% dose
- GFR 50-60ml/min give 75% dose (to be discussed with consultant, consider full dose)
- GFR 40-50ml/min give 50% dose
- GFR < 40ml/min omit dose

If patient complains of tinnitus, tingling of fingers and/or toes discuss with Consultant before administration

**Bleomycin:**
- GFR > 50ml/min give 100% dose
- GFR 10-50ml/min give 75% dose
- GFR <10ml/min give 50% dose
**Etoposide:**
CrCl > 50 ml/min give 100% dose
CrCl 15-50ml/min give 75% dose
CrCl<15 ml/min give 50% dose Confirm with Consultant
Bilirubin 26-51 micromol/L or ALT/AST 60-180 u/L give 50% dose
Bilirubin >51 micromol/L or ALT/AST >180 u/L Clinical decision

**INVESTIGATIONS**
Check patient has had sperm banking prior to first treatment.
Routine Blood test
1) Blood results required before chemotherapy administration
   
<table>
<thead>
<tr>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10</td>
</tr>
<tr>
<td>Plt x 10⁹/L</td>
<td>≥100</td>
</tr>
<tr>
<td>Neutrophils x 10⁹/L</td>
<td>≥1.5</td>
</tr>
</tbody>
</table>

   EDTA or Creatinine clearance (GFR) calculated at the Consultants discretion (Cisplatin)

2) Non-urgent tests
Tests relating to disease response/progression

**CONCURRENT MEDICATION**
Ensure adequate pre-and post-hydration prescribed as per TVCN regimen.
Daypatient: If urine output is < 100ml/hour or if patient gains >2kg weight during IV administration post Cisplatin give 200ml Mannitol 10% IV or consider 20 - 40mg Furosemide PO/IV
Inpatient: If fluid balance is > 2L positive after 8 hours post hydration OR urine output is < 100ml/hour during IV administration post Cisplatin give 200ml Mannitol 10% IV or consider 20 - 40mg Furosemide PO/IV

**ANTI-EMETIC POLICY**
Highly emetogenic days 1, 2
Low emetogenic risk day 3
Minimal emetogenic risk days 9, 16

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**
Pulmonary function tests (including transfer factor) prior to commencement of BEP. If breathlessness or infiltrates appear not attributable to tumour or coexistence of lung disease bleomycin must be stopped immediately. Consider treatment with corticosteroids and a broad spectrum antibiotic and / referral to chest team. Investigation of choice high resolution CT chest. Nephrotoxicity – ensure adequate pre and post hydration is prescribed. Ototoxicity – assess patient for tinnitus or hearing abnormalities.

**REFERENCES**
**BEP (5 day) metastatic (NSGCT)**

*Indication: Intermediate or poor prognosis non-seminomatous germ cell tumour*

**DRUG REGIMEN**

**Day 1**  
Pre-hydration regimen  
ETOPOSIDE 100mg/m² in 500ml* sodium chloride 0.9% infusion over 2 hours  
CISPLATIN 20mg/m² in 1000ml sodium chloride 0.9% infusion over 2 hours (daypatient) or 4 hours (inpatient)

Post-hydration regimen

**Day 2**  
Pre-hydration regimen  
ETOPOSIDE 100mg/m² in 500ml* sodium chloride 0.9% infusion over 2 hours  
CISPLATIN 20mg/m² in 1000ml sodium chloride 0.9% infusion over 2 hours (daypatient) or 4 hours (inpatient)  
BLEOMYCIN 30,000 units in 3ml Lidocaine 1% IM injection (daypatient) or in 1000ml sodium chloride 0.9% IV infusion over 12 hours (inpatient)

Post-hydration regimen

**Day 3**  
Pre-hydration regimen  
ETOPOSIDE 100mg/m² in 500ml* sodium chloride 0.9% infusion over 2 hours  
CISPLATIN 20mg/m² in 1000ml sodium chloride 0.9% infusion over 2 hours (daypatient) or 4 hours (inpatient)

Post-hydration regimen

**Day 4**  
Pre-hydration regimen  
ETOPOSIDE 100mg/m² in 500ml* sodium chloride 0.9% infusion over 2 hours  
CISPLATIN 20mg/m² in 1000ml sodium chloride 0.9% infusion over 2 hours (daypatient) or 4 hours (inpatient)

Post-hydration regimen

**Day 5**  
Pre-hydration regimen  
ETOPOSIDE 100mg/m² in 500ml* sodium chloride infusion over 2 hours  
CISPLATIN 20mg/m² in 1000ml sodium chloride 0.9% infusion over 2 hours (daypatient) or 4 hours (inpatient)

Post-hydration regimen

**Day 9**  
HYDROCORTISONE 100mg in 2ml water for injection IM  
BLEOMYCIN 30,000 units in 3ml Lidocaine 1% IM

**Day 16**  
HYDROCORTISONE 100mg in 2ml water for injection IM  
BLEOMYCIN 30,000 units in 3ml Lidocaine 1% IM

NB Day 9 may be given on day 8 instead. Day 16 may be given on day 15 instead (RBFT)  
NB Day 9 and 16 are given as daypatient treatments

* doses 48mg to 88mg in 250ml, 200mg to 360mg in 1000ml sodium chloride 0.9%

**Cycle Frequency: Every 21 days for FOUR cycles ONLY**
DOSE MODIFICATIONS
Any delays with/without dose modification may cause treatment failure.
Discuss with Consultant before delaying treatment or reducing doses of any drug

Cisplatin:
GFR > 60ml/min give 100% dose
GFR 45 - 59 mL/min give 75% dose
GFR < 45ml/min consider carboplatin
If patient complains of tinnitus, tingling of fingers and/or toes, discuss.

Bleomycin:
GFR > 50ml/min give 100% dose
GFR 10-50 ml/min give 75% dose
GFR < 10 ml/min give 50% dose
Confirm with SpR or Consultant
If patient is breathless discuss with Consultant

Etoposide:
CrCl > 50 ml/min give 100% dose
CrCl 15-50 ml/min give 75% dose
CrCl <15ml/min give 50% dose
Bilirubin 26-51 micromol/L or ALT/AST 60-180 u/L give 50% dose
Bilirubin >51 micromol/L or ALT/AST >180 u/L omit dose

INVESTIGATIONS
Check patient has had sperm-banking prior to first cycle of chemotherapy

Routine Blood test
1) Blood results required before chemotherapy administration

<table>
<thead>
<tr>
<th></th>
<th>Give</th>
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<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Plt x 10^9/L</td>
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</tr>
<tr>
<td>Neutrophils x 10^9/L</td>
<td>≥1.5</td>
<td>&lt; 1.5</td>
</tr>
</tbody>
</table>

Creatinine clearance (GFR) calculated or EDTA at the Consultants discretion (Cisplatin)

2) Non-urgent tests
Tests relating to disease response/progression
CONCURRENT MEDICATION
Ensure adequate pre-and post-hydration prescribed as per TVCN regimens.
Daypatient: If urine output is < 100ml/hour or if patient gains >2kg weight during IV administration post Cisplatin give 20 - 40mg Furosemide PO/IV or 200ml Mannitol 10% IV
Inpatient: If fluid balance is > 2L positive after 8 hours post hydration OR urine output is < 100ml/hour during IV administration post Cisplatin give 20 ¬ 40 mg Furosemide PO/IV OR 200ml Mannitol 10% IV
Consider GCSF for next cycle if patient experiences an episode of neutropenic sepsis

ANTI-EMETIC POLICY
Highly emetogenic days 1, 2, 3, 4, 5
Minimal emetogenic risk days 9, 16

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Pulmonary function tests (including transfer factor) prior to commencement of BEP. If breathlessness or infiltrates appear not attributable to tumour or co-existence of lung disease bleomycin must be stopped immediately. Consider treatment with corticosteroids and a broad spectrum antibiotic and / referral to chest team. Investigation of choice high resolution CT chest.
Nephrotoxicity – ensure adequate pre and post hydration is prescribed.
Ototoxicity – assess patient for tinnitus or hearing abnormalities.

REFERENCES
CARBOPLATIN (Seminoma)

**Indication:** Seminoma stage 1 (adjuvant single dose) IFR required.

**DRUG REGIMEN**  
**Day 1** CARBOPLATIN (AUC = 7) in 500ml glucose 5% infusion over 60 minutes  
Dose = (25 + GFR) x AUC  

*Cycle Frequency: ONCE only*

**DOSE MODIFICATIONS**  
Contraindicated if CrCl<20ml/min

**INVESTIGATIONS**  
Routine Blood test  
1) Blood results required before chemotherapy administration  
   Give Discuss  
   - Hb x g/dL \[ \geq 10 < 10 \]  
   - Plt x \[10^9\]/L \[ \geq 100 < 100 \]  
   - Neutrophils x \[10^9\]/L \[ \geq 1.5 < 1.5 \]  
Creatinine clearance (GFR) ideally measured by \(^{51}\)Cr-EDTA (or calculated) at the Consultants discretion (Carboplatin).

2) Non-urgent tests  
Tests relating to disease response/progression

**CONCURRENT MEDICATION**  
Anaphylaxis treatment should be prescribed if the patient has had an anaphylactic episode previously.  
DEXAMETHASONE 20mg IV bolus  
CHLORPHENAMINE 10mg IV bolus  
RANITIDINE 50mg IV bolus  
Carboplatin should be given at a slower rate e.g. 2-4 hours.

**ANTI-EMETIC POLICY**  
Moderately emetogenic

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**

**REFERENCES**  
IRINOTECAN / PACLITAXEL / OXALIPLATIN (IPO)

**Indications:** Treatment of relapsed germ-cell tumours

**DRUG REGIMEN**

**Days 1**
- **OXALIPLATIN** 200mg/m^2 in 500ml* glucose 5% IV infusion over 2 hours
- ATROPINE 300mcg subcutaneously
- **IRINOTECAN** 200mg/m^2 in 250ml glucose 5% IV infusion over 1 hour
- PRE-MEDICATION 30 minutes prior to infusion:
  - DEXAMETHASONE 8mg IV bolus
  - RANITIDINE 50mg IV bolus
  - CHLORPHENAMINE 10mg IV bolus
  - **PACLITAXEL** 80mg/m^2 in 250ml sodium chloride 0.9% infusion over 1 hour (PVC free)

**Days 8 & 15**
- PRE-MEDICATION 30 minutes prior to infusion:
  - DEXAMETHASONE 8mg IV bolus
  - RANITIDINE 50mg IV bolus
  - CHLORPHENAMINE 10mg IV bolus
  - **PACLITAXEL** 80mg/m^2 in 250ml sodium chloride 0.9% infusion over 1 hour (PVC free)

GCSF subcutaneously on alternate days from day 1 to 15

* doses 55mg to 200mg in 250ml sodium chloride 0.9%
^ doses 162mg to 600mg in 500ml sodium chloride 0.9%

**Cycle Frequency:** Every 21 days for 4 cycles

**DOSE MODIFICATIONS**

**Oxaliplatin**
- If persistent sensory symptoms occur, withdraw treatment
- GFR > 30ml/min give 100% dose and adjust according to toxicity
- Omit if GFR <30ml/mi
- If bilirubin >50 micromol/L give 50% dose
- If patients develop acute laryngopharyngeal dysaesthesia infuse the next cycle over 6 hours. If symptoms persist give 80% dose.

**Irinotecan**
- If Bilirubin 25 - 50 micromol/L give 50% dose
- Omit if bilirubin > 3xULN
- Omit if GFR < 30 ml/min.
- If patients suffer from severe diarrhoea, which required IV rehydration or neutropenic fever, dose should be reduced in subsequent cycles, discuss with SpR or Consultant.

**Paclitaxel**
- Bilirubin <1.25xULN and AST <10xULN dose at 175mg/m^2
- Bilirubin <26micromol/L give 135mg/m^2
- Bilirubin 27-51micromol/L give 75mg/m^2
- Bilirubin >51micromol/L give 50mg/m^2
If patient complains of tinnitus, tingling of fingers and/or toes or motor weakness discuss with Consultant or Registrar before administration. If grade II or > neuropathy, consider using reducing dose of paclitaxel.

Delay 1 week if day 1 neutrophil count < 1.5 X 10^9/L and / or platelet count is < 100 x 10^9/L.

Myelosuppression is reasonably common consider dose reduction from 80 to 60 mg/m2

In the absence of Gilbert’s syndrome: Bilirubin >51 micromol/L, stop treatment.

INVESTIGATIONS
Routine Blood test
1) Blood results required before chemotherapy administration

<table>
<thead>
<tr>
<th></th>
<th>Give</th>
<th>Discuss</th>
</tr>
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<tbody>
<tr>
<td>Hb x  g/dL</td>
<td>≥10</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Plt x 10^9/L</td>
<td>≥100</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Neutrophils x 10^9/L</td>
<td>≥1.5</td>
<td>&lt; 1.5</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>≥25</td>
<td>&lt;25</td>
</tr>
</tbody>
</table>

2) Liver function tests
3) Serum creatinine- GFR should be calculated
4) Assess response after 2 cycles with scan

CONCURRENT MEDICATION
Ensure Pre medication given with paclitaxel

ANTIEMETIC POLICY
High emetogenic risk day 1
Low emetic risk days 8 and 15

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Paclitaxel: 2% risk of severe hypersensitivity. Reactions range from mild hypotension (light-headedness) to full cardiac collapse (anaphylactic shock). Discontinue infusion and resuscitate appropriate to reaction. If reaction is mild and settles promptly (i.e. within 5-10 minutes) cautiously restart at a slower rate under close supervision. If further reactions occur stop treatment.

Oxaliplatin: Peripheral sensory neuropathy and laryngeal spasm – avoid cold drinks and touching cold items

Irinotecan: Diarrhoea – delayed diarrhea occurring more than 24 hours after administration. Drink large volumes of fluid containing electrolytes and an appropriate antidiarrhoeal therapy e.g. loperamide 4mg initially then 2mg every 2 hours, continuing for 12 hours after the last liquid stool (maximum of 48 hours in total). Take prophylactic broad spectrum antibiotics.

REFERENCES
PACLITAXEL / IFOSFAMIDE / CISPLATIN (TIP)

**Indications:** Salvage for metastatic germ cell, metastatic seminoma

**DRUG REGIMEN**

**Days 1**
PRE-MEDICATION 30 minutes prior to infusion:
- **DEXAMETHASONE** 20mg IV bolus
- **RANITIDINE** 50mg IV bolus
- **CHLORPHENAMINE** 10mg IV bolus
- **PACLITAXEL** 175mg/m² in 500ml* sodium chloride 0.9% infusion over 3 hours (PVC free)

**Days 1 to 5**
Pre-hydration
- **CISPLATIN** 20mg/m² IV in 1000ml sodium chloride 0.9% infusion over 2 hours
- **MESNA** 200mg/m² in 250ml sodium chloride 0.9% infusion over 30 minutes
- **IFOSFAMIDE** 1g/m² with **MESNA** 1g/m² in 1L sodium chloride 0.9% infusion over 1 hour
- **MESNA** 600mg/m² in 500ml sodium chloride 0.9% over 12 hours

* doses 84mg to 144mg in 250ml sodium chloride 0.9%

**Cycle Frequency:** Every 21 days for 4 to 6 cycles

**DOSE MODIFICATIONS**

If patient complains of tinnitus, tingling of fingers and/or toes or motor weakness or has/had previous neutropenic sepsis, discuss with Consultant or Registrar before administration.

**Cisplatin**
- GFR > 60ml/min give 100% dose
- GFR 45 - 59 mL/min give 75% dose
- GFR < 45ml/min consider carboplatin

**Ifosfamide**
- GFR >60ml/min give 100% dose
- GFR 40-59ml/min give 70% dose
- GFR <40ml/min clinical decision.
- Creatinine >120micromol/L ifosfamide not recommended
- Discuss if *Bilirubin >17 micromol/L
  - *AST and Alk Phos > 2.5 x upper limit of normal

**Paclitaxel**
- Bilirubin <1.25xULN and AST <10xULN dose at 175mg/m²
- Bilirubin <26micromol/L give 135mg/m²
- Bilirubin 27-51micromol/L give 75mg/m²
- Bilirubin >51micromol/L give 50mg/m²
INVESTIGATIONS
Routine Blood test
1) Blood results required before chemotherapy administration
   
   **Give**  **Discuss**
   
   Hb x g/dL  ≥9  < 9  
   Plt x 10^9/L  ≥100  < 100  
   WBC x 10^9/L  ≥3.0  < 3.0  
   Bilirubin  ≥25  <25  
   
   Creatinine clearance (GFR) ideally measured by \(^{51}\text{Cr-EDTA}\) or calculated at the Consultants discretion
   
   Neurological assessment and neurological toxicity
   
2) Non urgent tests.
   
   Tests relating to disease response/progression

CONCURRENT MEDICATION
Ensure Pre medication given with paclitaxel

Ensure adequate pre-and post-hydration prescribed as per inpatient schedule at the end of the TVCN regimens. If fluid balance is > 2L positive after 8 hours post hydration OR if patient gains >2kg in weight or urine output <100ml/hour during IV administration post Cisplatin give 20 - 40 mg Furosemide PO/IV OR 200ml Mannitol 10% IV

ANTIEMETIC POLICY
High emetic risk all days

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Cisplatin Nephrotoxicity – ensure adequate pre and post hydration is prescribed.
Ototoxicity – assess patient for tinnitus or hearing abnormalities.

**Paclitaxel- (2% risk of severe hypersensitivity)**
Reactions range from mild hypotension (lightheadedness) to full cardiac collapse (anaphylactic shock). Discontinue infusion and resuscitate appropriate to reaction. If reaction is mild and settles promptly (i.e. within 5 10mins), cautiously restart at a slower rate under close supervision.

If further reactions occur stop treatment. Ensure pre-medication is given.

Ifosfamide encephalopathy - methylene blue and supportive therapy

**Methylothioninium chloride (methylene blue)**
Methylothioninium chloride (methylene blue) can be given as prophylaxis against, or treatment of, ifosfamide-induced encephalopathy (See specific neural toxicity grade and nomogram below). This should be started on the day of ifosfamide administration and continued for 24 hours after administration or until neurotoxic symptoms subside.

Other risk factors include cisplatin, brain irradiation, hepatic failure and advancing age.

**Dose:** 50mg tds IV or orally. (NB. 50mg = 5ml of 1% solution.)
**Administration**

**IV:** administer 50mg in 50 to 100ml sodium chloride 0.9% or glucose 5%, over 15 to 30 minutes  
**Orally:** use injection for oral administration. Dilute one ampoule in 100ml water before taking orally to minimise GI effects. Drink through a straw to avoid staining teeth. 53-97% oral absorption

**Nephrotoxicity:** Irreversible renal failure and tubular damage can occur, and this is more frequent with cumulative doses over 25 – 50g/m$^2$ of Ifosfamide. Dose reductions should be instituted for GFR and changes in fractional phosphate clearance (Tm$_p$/GFR mmol/l).

**Neural toxicity grade**

Classify toxicity as grade 0-1, 2 or 3-4 and adjust ifosfamide treatment as indicated if either GFR or Tp/C$_{crea}$ (Tm$_p$/GFR) or HCO$_3$ is reduced.

<table>
<thead>
<tr>
<th>Toxicity Grade*</th>
<th>GFR (ml/min/1.73m$^2$)</th>
<th>Tp/C$_{crea}$ (Tm$_p$/GFR) (mmol/l)</th>
<th>HCO$_3$** (mmol/l)</th>
<th>Action (apply worst grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0/1</td>
<td>≥60</td>
<td>≥1.00</td>
<td>≥17.0</td>
<td>Ifos dose 100%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>40-59</td>
<td>0.8-0.99</td>
<td>14.0-16.9</td>
<td>Ifos dose 70% of total</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>≤40</td>
<td>≤0.8</td>
<td>≤14.0</td>
<td>***Switch to Cyclophosphamide</td>
</tr>
</tbody>
</table>

*Toxicity is scored from 0-4, analogous to the CTC system, but for the purpose of modifying treatment grades 0-1 and 3-4 are considered together.

** Low values of HCO$_3$ should be re-checked when the patient is clinically stable (to rule out infection as a cause, etc) before modifying treatment

***Discuss with consultant before and to confirm substitution of ifosfamide with cyclophosphamide 1500mg/m$^2$/day

Fractional phosphate clearance calculated as below

$$\text{Tp/C}_{crea} = \frac{\text{Phosphate}_{serum} - \frac{\text{Phosphate}_{urine} \times \text{creatinine}_{serum}}{\text{Creatinine}_{urine}}}{\text{mmol/ml}}$$
Neural toxicity nomogram

![Nomogram diagram]

Fig. 1. Nomogram to determine probability of not developing grade 3–4 clinical CNS toxicity with ifosfamide/mesna 36 hr infusion. The probability that a patient will NOT develop severe CNS toxicity falls on the intersection of a straight line joining their serum albumin and serum creatinine concentrations on the appropriate pelvic disease scale.

REFERENCES
1. ASWCS Chemotherapy handbook Jan 2005
2. Mead G et al. on behalf of the MRC Testicular tumour working party. A phase 2 trial of TIP given as second line (post BEP)
**POMB / ACE (Germ cell)**

*Indication: Metastatic germ cell*

**DRUG REGIMEN**

**POMB**

Day 1  **VINCRISTINE** 1mg/m² (max 2mg) IV infusion in 50ml sodium chloride 0.9%

**METHOTREXATE** 300mg/m² in 500ml sodium chloride 0.9% over 12 hours
1000ml sodium chloride 0.9% + 20mmol KCl over 4 hours

Day 2  **BLEOMYCIN** 30,000iu in 2000ml sodium chloride 0.9% infusion over 24 hours

FOLINIC ACID 15mg qds PO for 6 doses starting 24 hours after methotrexate

Day 3  Pre-hydration regimen

**CISPLATIN** 60mg/m² in 500ml sodium chloride 0.9% infusion over 4 hours

**CISPLATIN** 60mg/m² in 500ml sodium chloride 0.9% infusion over 4 hours

Post-hydration regimen

*Cycle Frequency: Every 14 days alternating with ACE (see regimen sequence below)*

**ACE**

Day 1  **DACTINOMYCIN** 500micrograms IV bolus

**ETOPOSIDE** 100mg/m² in 1000ml* sodium chloride 0.9% infusion over 2 hours

Day 2  **DACTINOMYCIN** 500micrograms IV bolus

**ETOPOSIDE** 100mg/m² in 1000ml* sodium chloride 0.9% infusion over 2 hours

Day 3  **CYCLOPHOSPHAMIDE** 500mg/m² IV bolus

**DACTINOMYCIN** 500micrograms IV bolus

**ETOPOSIDE** 100mg/m² in 1000ml* sodium chloride 0.9% infusion over 2 hours

* doses 48mg to 88mg in 250ml, 96mg to 180mg in 500ml sodium chloride 0.9%

*Cycle frequency: Every 14 days alternating with POMB (see regimen sequence below)*

*Regimen sequence: POMB POMB ACE POMB ACE POMB ACE*
DOSE MODIFICATIONS

POMB

Bleomycin:
- GFR > 50ml/min give 100% dose
- GFR 10-50 ml/min give 75% dose
- GFR < 10 ml/min give 50% dose

Vincristine:
- Bilirubin 25-51 or AST 60-180u/L give 50% dose
- Bilirubin >51 micromol/L and normal AST give 50% dose
- Bilirubin >51 micromol/L and AST >180u/L omit

Methotrexate:
- CrCl 60 mL/min give 65% dose
- CrCl 45 mL/min give 50% dose
- CrCl < 30 mL/min omit dose
- Bilirubin 51-85 micromol/L or AST >180 u/L give 75% dose
- Bilirubin >85micromol/L omit

Cisplatin:
- GFR > 60ml/min give 100% dose
- GFR 45 - 59 mL/min give 75% dose
- GFR < 45ml/min consider carboplatin

ACE

Etoposide:
- CrCl > 50ml/min give 100% dose
- CrCl 15-50 ml/min give 75% dose
- CrCl < 15 ml/min give 50% dose
- Bilirubin 26-51 micromol/L or AST 60-180 u/L give 50% dose
- Bilirubin >51micromol/L or AST >180u/L Clinical decision

Cyclophosphamide:
- GFR >20ml/min give 100% dose
- GFR 10 - 20 mL/min give 75% dose
- GFR < 10 mL/min give 50% dose

Dactinomycin:
Consider dose reduction in severe hepatic disease.
INVESTIGATIONS
Routine Blood test
1) Blood results required before chemotherapy administration

\[
\begin{array}{lll}
\text{Give} & \text{Discuss} \\
\text{Hb x g/dL} & \geq 10 & < 10 \\
\text{Plt x } 10^9/L & \geq 100 & < 100 \\
\text{Neutrophils x } 10^9/L & \geq 1.5 & < 1.5
\end{array}
\]

Creatinine clearance (GFR) ideally measured by $^{51}\text{Cr-EDTA}$ or calculated at the Consultants discretion.

2) Non-urgent tests
Tests relating to disease response/progression

CONCURRENT MEDICATION
Ensure adequate pre-and post-hydration prescribed as per inpatient schedule at the end of the TVCN regimens. If fluid balance is $> 2L$ positive after 8 hours post hydration OR if patient gains $>2kg$ in weight or urine output $<100ml//hour$ during IV administration post Cisplatin give 20 - 40 mg Furosemide PO/IV OR 200ml Mannitol 10% IV

ANTI-EMETIC POLICY
Moderately emetogenic for POMB day 1
Minimal emetogenic for POMB day 2
Highly emetogenic for POMB day 3
Moderately emetogenic risk for ACE

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Pulmonary function tests (including transfer factor) prior to each cycle of BEP. If breathlessness or infiltrates appear not attributable to tumour or co-existence of lung disease bleomycin must be stopped immediately. Treat patients with corticosteroids and a broad spectrum antibiotic. Cyclophosphamide may irritate bladder, drink copious volumes of water. Nephrotoxicity – ensure adequate pre and post hydration is prescribed. Ototoxicity – assess patient for tinnitus or hearing abnormalities. Methotrexate induced mucositis - folinic acid (calcium folinate) rescue (see drug regimen).

REFERENCES
PEC (Germ cell)

Indication: relapsed germ cell tumour

Drug Regimen

Day 1  
PRE-MEDICATION 30 mins prior to infusion:
- DEXAMETHASONE 20mg IV bolus
- RANITIDINE 50mg IV bolus
- CHLORPHENAMINE 10mg IV bolus
- PACLITAXEL 90mg/m² in 500ml* sodium chloride 0.9% infusion over 3 hours
- ETOPOSIDE 150mg/m² in 1000ml^ sodium chloride 0.9% infusion over 2 hours

Day 15  
PRE-MEDICATION 30 mins prior to infusion:
- DEXAMETHASONE 20mg IV bolus
- RANITIDINE 50mg IV bolus
- CHLORPHENAMINE 10mg IV bolus
- PACLITAXEL 90mg/m² in 500ml* sodium chloride 0.9% infusion over 3 hours

Pre-hydration regimen
- CISPLATIN 60mg/m² in 1000ml sodium chloride 0.9% infusion over 4 hours

Post-hydration regimen

* doses 84mg to 144mg in 250ml sodium chloride 0.9%
^ doses 48mg to 88mg in 250ml, 96mg to 180mg in 500ml sodium chloride 0.9%

Cycle Frequency: Every 28 days for 6 cycles

Dose Modifications

If patient complains of tinnitus, tingling of fingers and/or toes or motor weakness discuss with Consultant or Registrar before administration.

**Paclitaxel:**
- Bilirubin <1.25xULN and AST <10xULN dose at 100%
- Bilirubin >17micromol/L dose reduction required
- AST and Alk phos > 3x normal dose reduction required

**Cisplatin:**
- GFR > 60ml/min give 100% dose
- GFR 45 - 59 mL/min give 75% dose
- GFR < 40ml/min consider carboplatin

**Etoposide:**
- CrCl > 50ml/min give 100% dose
- CrCl 15-50 mL/min give 75% dose
- CrCl <15ml/min give 50% dose
- Bilirubin 26-51micromol/L or AST 60-180u/L give 50% dose
- Bilirubin >51micromol/L or AST >180u/L Clinical decision
INVESTIGATIONS
Routine Blood test 1) Blood results required before chemotherapy administration

\[\begin{align*}
& \text{Give} \quad \text{Discuss} \\
& \text{Hb} \times 10^9/L \quad \geq 10 \quad < 10 \\
& \text{Plt} \times 10^9/L \quad \geq 100 \quad < 100 \\
& \text{Neutrophils} \times 10^9/L \quad \geq 1.5 \quad < 1.5
\end{align*}\]

Liver function tests (LFT)
Creatinine clearance (GFR) ideally measured by $^{51}$Cr-EDTA or calculated at the Consultants discretion

2) Non urgent tests Tests relating to disease response/progression

CONCURRENT MEDICATION
Ensure pre medication given
Ensure adequate pre-and post-hydration prescribed as per inpatient schedule at the end of the TVCN regimens. If fluid balance is > 2L positive after 8 hours post hydration, or weight gain of >2kg, OR urine output is < 100ml/hour during IV administration post Cisplatin give 20 - 40 mg Furosemide PO/IV OR 200ml Mannitol 10% IV

ANTIEMETIC POLICY
Moderately emetogenic day 1
Highly emetogenic day 15

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

\textit{Paclitaxel (2\% risk of severe hypersensitivity)}
Reactions range from mild hypotension (light-headedness) to full cardiac collapse (anaphylactic shock). Discontinue infusion and resuscitate appropriate to reaction. If reaction is mild and settles promptly (i.e. within 5-10 minutes), cautiously restart at a slower rate under close supervision. If further reactions occur stop treatment.
Nephrotoxicity – ensure adequate pre and post hydration is prescribed.
Ototoxicity – assess patient for tinnitus or hearing abnormalities.

REFERENCES
### EP (Seminoma)

**Indication:** First line for metastatic seminoma

#### DRUG REGIMEN

**Day 1**
- Pre-hydration regimen
  - **ETOPOSIDE** 166mg/m² in 1000ml* sodium chloride 0.9% infusion over 2 hours
  - **CISPLATIN** 50mg/m² in 1000ml sodium chloride 0.9% infusion over 2 hours (daypatient) or 4 hours (inpatient)
- Post-hydration regimen

**Day 2**
- Pre-hydration regimen
  - **ETOPOSIDE** 166mg/m² in 1000ml* sodium chloride 0.9% infusion over 2 hours
  - **CISPLATIN** 50mg/m² in 1000ml sodium chloride 0.9% infusion over 2 hours (daypatient) or 4 hours (inpatient)
- Post-hydration regimen

**Day 3**
- **ETOPOSIDE** 166mg/m² in 1000ml* sodium chloride 0.9% infusion over 2 hours

* doses 48mg to 88mg in 250ml, 96mg to 180mg in 500ml sodium chloride 0.9%

#### Cycle Frequency: Every 21 Days for FOUR cycles ONLY

#### DOSE MODIFICATIONS

Any delays with/without dose modification may cause treatment failure. Discuss with Consultant before delaying treatment or reducing doses of any drug if patient has had neutropenic sepsis.

**Cisplatin:**
- GFR > 60ml/min give 100% dose
- GFR 45 - 59 ml/min give 75% dose
- GFR < 45ml/min consider carboplatin

If patient complains of tinnitus, tingling of fingers and/or toes discuss with Consultant before administration

**Etoposide:**
- CrCl > 50ml/min give 100% dose
- GFR 15 - 50 ml/min give 75% dose
- GFR < 15 ml/min give 50% dose
- Bilirubin 26-51micromol/L or AST 60-180u/L give 50% dose
- Bilirubin >51micromol/L or AST >180u/L clinical decision
INVESTIGATIONS
Check patient has had sperm-banking prior to starting first treatment

Routine Blood test
1) Blood results required before chemotherapy administration

<table>
<thead>
<tr>
<th>Test</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Plt x 10⁹/L</td>
<td>≥100</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Neutrophils x 10⁹/L</td>
<td>≥1.5</td>
<td>&lt; 1.5</td>
</tr>
</tbody>
</table>

Creatinine clearance (GFR) calculated or EDTA at the Consultant’s discretion (Cisplatin)

2) Non-urgent tests
Tests relating to disease response/progression

CONCURRENT MEDICATION
Ensure adequate pre- and post-hydration prescribed as per TVCN regimens.
Daypatient: If urine output is < 100ml/hour or if patient gains > 2kg weight during IV administration post Cisplatin give 20 - 40mg Furosemide PO/IV or 200ml Mannitol 10% IV
Inpatient: If fluid balance is > 2L positive after 8 hours post hydration OR urine output is < 100ml/hour during IV administration post Cisplatin give 20 → 40 mg Furosemide PO/IV OR 200ml Mannitol 10% IV

ANTI-EMETIC POLICY
Highly emetogenic. days 1, 2
Low emetic risk day 3

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Nephrotoxicity – ensure adequate pre and post hydration is prescribed.
Ototoxicity – assess patient for tinnitus or hearing abnormalities.

REFERENCES
**BEP (3 day) (Unknown primary adenocarcinoma)**

*Indications: Adenocarcinoma of unknown primary*

**DRUG REGIMEN**

**Day 1**  
Pre-hydration regimen  
**ETOPOSIDE** 166mg/m² in 1000ml* sodium chloride 0.9% infusion over 2 hours  
**CISPLATIN** 50mg/m² in 1000ml sodium chloride 0.9% infusion over 2 hours (daypatient) or 4 hours (inpatient)  
Post-hydration regimen  

**Day 2**  
Pre-hydration regimen  
**ETOPOSIDE** 166mg/m² in 1000ml* sodium chloride 0.9% infusion over 2 hours  
**CISPLATIN** 50mg/m² in 1000ml sodium chloride 0.9% infusion over 2 hours (daypatient) or 4 hours (inpatient)  
**BLEOMYCIN** 30,000units in 3ml Lidocaine 1% IM injection (daypatient) or in 1000ml sodium chloride 0.9% IV infusion over 12 hours (inpatient)  
Post-hydration regimen  

**Day 3**  
**ETOPOSIDE** 166mg/m² in 1000ml* sodium chloride 0.9% infusion over 2 hours

* doses 48mg to 88mg in 250ml, 96mg to 180mg in 500ml sodium chloride 0.9%

**Cycle Frequency: Every 21 days for up to 6 cycles**

**DOSE MODIFICATIONS**

Any delays with/without dose modification may cause treatment failure. Discuss with Consultant before delaying treatment or reducing doses of any drug.

**Cisplatin:**  
GFR > 60ml/min give 100% dose  
GFR 45-59ml/min give 75% dose  
GFR < 45ml/min consider carboplatin

If patient complains of tinnitus, tingling of fingers and/or toes discuss with Consultant before administration

**Bleomycin:**  
CrCl > 50ml/min give 100% dose  
CrCl 10-50 ml/min give 75% dose  
CrCl < 10 ml/min give 50% dose
**Etoposide:**
CrCl > 50ml/min give 100% dose  
CrCl 15-50ml/min give 75% dose  
CrCl <15ml/min give 50% dose  
Bilirubin 26-51micromol/L or ALT/AST 60-180u/L give 50% dose  
Bilirubin >51micromol/L or AST >180u/L clinical decision

**INVESTIGATIONS**
Check patient has had sperm banking prior to first treatment.  
Routine Blood test  
1) Blood results required before chemotherapy administration
   
<table>
<thead>
<tr>
<th>Blood Result</th>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Plt x 10⁹/L</td>
<td>≥100</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Neutrophils x 10⁹/L</td>
<td>≥1.5</td>
<td>&lt; 1.5</td>
</tr>
<tr>
<td>Creatinine clearance (GFR) calculated using or EDTA at the Consultant's discretion (Cisplatin)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2) Non-urgent tests- Tests relating to disease response/progression

**CONCURRENT MEDICATION**
Ensure adequate pre- and post-hydration prescribed as per TVCN regimens.  
Daypatient: If urine output is < 100ml/hour or if patient gains >2kg weight during IV administration post Cisplatin give 20 - 40mg Furosemide PO/IV or 200ml Mannitol 10% IV  
Inpatient: If fluid balance is > 2L positive after 8 hours post hydration OR urine output is < 100ml/hour during IV administration post Cisplatin give 20 - 40 mg Furosemide PO/IV OR 200ml Mannitol 10% IV  
Hydrocortisone administered prior to bleomycin doses.

**ANTI-EMETIC POLICY**
Highly emetogenic days 1, 2  
Low emetogenic risk day 3

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**
Pulmonary function tests (including transfer factor) prior to each cycle of BEP. If breathlessness or infiltrates appear not attributable to tumour or co-existence of lung disease bleomycin must be stopped immediately. Treat patients with corticosteroids and a broad spectrum antibiotic.  
Nephrotoxicity – ensure adequate pre and post hydration is prescribed.  
Ototoxicity – assess patient for tinnitus or hearing abnormalities.

**REFERENCES**
Axitinib (Renal cell carcinoma)

*Indication: Treatment of advanced renal cell carcinoma, after first line treatment with a cytokine or a tyrosine kinase inhibitor.*

NICE: Axitinib is recommended as an option for treating adults with advanced renal cell carcinoma after failure of treatment with a TKI

Ensure funding is available for patient prior to prescribing / NICE / NHS England circular SSC1508 Blueteq form needs to be completed for all patients for all funding streams

**DRUG REGIMEN**

**Day 1**  
**Axitinib** 5mg orally twice daily

Patients who tolerate the axitinib starting dose of 5mg twice daily with no adverse reactions > Grade 2 (i.e. without severe adverse reactions according to the CTCAE] for two consecutive weeks may have their dose increased to 7mg twice daily unless the patient’s blood pressure is > 150/90 mmHg or the patient is receiving antihypertensive treatment. Subsequently, using the same criteria, patients who tolerate an axitinib dose of 7mg twice daily may have their dose increased to a maximum of 10 mg twice daily.

*Cycle Frequency: Daily for 4 weeks continuously until progression*

**DOSE MODIFICATIONS**

**Axitinib:**  
Any dose modifications should be discussed with a Consultant.

Management of some adverse reactions may require temporary or permanent discontinuation and/or dose reduction of axitinib therapy. When dose reduction is necessary, the axitinib dose may be reduced to 3mg twice daily and further to 2mg twice daily.

Hepatic impairment  
A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B). Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population.
INVESTIGATIONS
Routine Blood test
1) Blood results required before drug administration

Give Discuss

Hb x g/dL ≥10 < 10
Plt x 10^9/L ≥100 < 100
Neutrophils x 10^9/L ≥1.5 < 1.5
Creatinine
Liver function tests (LFT)
Thyroid function tests

Blood tests should initially be performed 4 weekly, but later in the treatment course can be done less often in stable patients.
Ask GP to monitor blood pressure on a regular basis, weekly initially.

2) Non urgent tests
Tests relating to disease response/progression

CONCURRENT MEDICATION
Check drug interactions, particularly cytochrome inducers and inhibitors and adjust doses accordingly.

ANTIEMETIC POLICY
None required

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Skin - skin discolouration and depigmentation of the hair and skin may occur.
Haemorrhage – an increased risk of bleeding may occur.
Hypertension – treatment induced hypertension. Axitinib dose should be reduced if persistent hypertension despite use of anti-hypertensives.
Gastrointestinal – gastrointestinal complications including gastrointestinal perforation or fistula should be monitored for throughout treatment.
Hypothyroidism / hyperthyroidism

REFERENCES
SPC October 2012
**Cabozantinib (Renal cell carcinoma)**

**Indication:** The treatment of renal cell carcinoma:

Histological diagnosis of renal cell carcinoma with a clear cell component

The patient has either metastatic disease or inoperable locally advanced disease

The patient has previously received at least 1 vascular endothelial growth factor (VEGF)-targeted systemic therapy for renal cancer

The patient has progressed on previous treatment or within 6 months of most recent dose of VEGF inhibitor

The patient has a performance status of 0 or 1

If the patient has brain metastases then these have been treated and are stable

Cabozantinib is to be continued until disease progression or unacceptable toxicity or the patient’s choice to stop treatment

No planned treatment breaks of more than 4 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve).**Requests for continuation of treatment after unplanned treatment breaks over this duration should be made via the treatment break approval process.

Cabozantinib will otherwise be used as set out in its SPC. NICE: TA436

The treatment of treatment-naïve intermediate or poor risk advanced renal cell carcinoma:

Histological diagnosis of renal cell carcinoma (RCC) with a clear cell component

The patient has either metastatic disease or inoperable locally advanced disease

The patient is treatment naïve to systemic therapy and in particular has previously received neither any vascular endothelial growth factor (VEGF)-targeted systemic therapy nor mTOR pathway inhibitor-targeted treatment unless prior treatment with pazopanib or sunitinib or tivozanib has had to be stopped solely as a consequence of dose-limiting toxicity and in the clear absence of progressive disease

The patient has intermediate risk OR poor risk advanced renal cell carcinoma as defined by the International Metastatic Renal Cell Carcinoma Database Consortium. Good risk patients are not eligible for cabozantinib therapy. Intermediate risk is defined as having 1 or 2 risk factors and poor risk as having ≥3 factors, these factors being:- Time from diagnosis of RCC to need for systemic therapy of <1 year- Haemoglobin < lower limit of normal- Corrected calcium > upper limit of normal- Karnofsky performance status <80%- Neutrophils > upper limit of normal- Platelet count > upper limit of normal. ECOG performance status of either 0 or 1 or 2

If the patient has brain metastases, then these have been treated and are stable

No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve)**Requests for continuation of treatment after unplanned treatment breaks over this duration should be made via the treatment break approval process. Cabozantinib is to be otherwise used as set out in its SPC

Blueteq form needs to be completed for all patients for all funding streams
DRUG REGIMEN
Day 1  Cabozantinib 60mg orally daily

_Cycle Frequency:_ Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. A formal medical review as to whether treatment with cabozantinib should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment

DOSE MODIFICATIONS
_Cabozantinib:_
Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of cabozantinib therapy. When dose reduction is necessary, it is recommended to reduce to 40 mg daily, and then to 20 mg daily. Dose interruptions are recommended for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities. Dose reductions are recommended for events that, if persistent, could become serious or intolerable.

If a patient misses a dose, the missed dose should not be taken if it is less than 12 hours before the next dose

<table>
<thead>
<tr>
<th>Adverse reaction and severity</th>
<th>Treatment Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 and Grade 2 adverse reactions which are tolerable and easily manageable</td>
<td>Dose adjustment is usually not required. Consider adding supportive care as indicated.</td>
</tr>
<tr>
<td>Grade 2 adverse reactions which are intolerable and cannot be managed with a dose reduction or supportive care</td>
<td>Interrupt treatment until the adverse reaction resolves to Grade ≤1. Add supportive care as indicated. Consider re-initiating at a reduced dose.</td>
</tr>
<tr>
<td>Grade 3 adverse reactions (except clinically nonrelevant laboratory abnormalities)</td>
<td>Interrupt treatment until the adverse reaction resolves to Grade ≤1. Add supportive care as indicated. Re-initiate at a reduced dose.</td>
</tr>
<tr>
<td>Grade 4 adverse reactions (except clinically nonrelevant laboratory abnormalities)</td>
<td>Interrupt treatment. Institute appropriate medical care. If adverse reaction resolves to Grade ≤1, re-initiate at a reduced dose. If adverse reaction does not resolve, permanently discontinue cabozantinib.</td>
</tr>
</tbody>
</table>

Renal impairment
Cabozantinib should be used with caution in patients with renal impairment. Cabozantinib is not recommended for use in patients with severe renal impairment since there is limited data in patients with severe renal impairment, and safety and efficacy have not been established.
Hepatic Impairment
In patients with mild or moderate hepatic impairment the recommended dose is 40mg once daily. cabozantinib is not recommended for use in patients with severe hepatic impairment

INVESTIGATIONS
Routine Blood test
1) Blood results required before drug administration

Give  Discuss
Hb x g/dL  ≥10   < 10
Platelets x 10⁹/L  ≥100  < 100
Neutrophils x 10⁹/L  ≥1.5  < 1.5
Creatinine
Liver function tests (LFT)
Thyroid function tests

Blood tests should initially be performed 4 weekly, but later in the treatment course can be done less often in stable patients.
Ask GP to monitor blood pressure on a regular basis, weekly initially.

2) Non urgent tests
Tests relating to disease response/progression

CONCURRENT MEDICATION

ANTIEMETIC POLICY
None required

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Perforations and fistulas
Haemorrhage
Thrombotic events
Wound complications
Hypertension
Osteonecrosis jaw

REFERENCES
1. US prescribing information 2012
2. EU SPC
Everolimus (Renal cell carcinoma)

*Indication: Treatment of metastatic renal cell carcinoma, previously treated with or had intolerance to only 1 TKI (the patient has progressed during or after treatment with vascular endothelial growth factor targeted therapy)*

Blueteq form needs to be completed for all patients for all funding streams

**DRUG REGIMEN**

Day 1  
*Everolimus* 10mg orally daily

*Cycle Frequency: Daily for 4 weeks continuously until progression*

**DOSE MODIFICATIONS**

*Everolimus:*

Any dose modifications should be discussed with a Consultant.

Renal impairment

No dose adjustment is required in patients with renal impairment.

Hepatic impairment

For patients with moderate hepatic impairment (Child-Pugh class B), the dose should be reduced to 5 mg daily. Everolimus has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C) and is not recommended for use in this patient population.

**INVESTIGATIONS**

Routine Blood test

1) Blood results required before drug administration

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10 &lt; 10</td>
</tr>
<tr>
<td>Plt x 10⁹/L</td>
<td>≥100 &lt; 100</td>
</tr>
<tr>
<td>Neutrophils x 10⁹/L</td>
<td>≥1.5 &lt; 1.5</td>
</tr>
</tbody>
</table>

Routine bloods: FBC, renal function, liver function.
Random blood sugar, lipid profile; if elevated to repeat on fasting blood
Baseline imaging: CT and/or MRI at baseline and every three months.

2) Non urgent tests

Tests relating to disease response/progression

**CONCURRENT MEDICATION**

Check drug interactions, particularly cytochrome inducers and inhibitors and adjust doses accordingly.
ANTIEMETIC POLICY
Minimal emetic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Increased glucose, lipids and triglycerides
Decreased haemoglobin, lymphocytes, neutrophils and platelets
Hypersensitivity reactions
Pneumonitis, Infections
Oral ulceration

REFERENCES
1. SPC May 2010
   Long-term response with everolimus for metastatic renal cell carcinoma refractory to sunitinib. Molina AM, Ginsberg MS, Motzer RJ.
Everolimus Lenvatinib (Renal cell carcinoma)

**Indication:** The treatment of previously treated advanced renal cell carcinoma

1. The patient has a confirmed histological diagnosis of renal cell carcinoma with a clear cell component
2. The patient has either metastatic disease or inoperable locally advanced disease
3. The patient has received only 1 vascular endothelial growth factor (VEGF)-targeted systemic therapy for advanced/metastatic renal cancer**Patients treated with more than 1 line of VEGF-targeted therapy for advanced/metastatic disease are not eligible for treatment using lenvatinib with everolimus
4. The patient has progressed on previous treatment or within 6 months of discontinuing previous treatment
5. The patient has an ECOG performance status of either 0 or 1**Patients with a performance status of 2 or more are not eligible for lenvatinib with everolimus
6. The patient has received no previous treatment with either lenvatinib or everolimus
7. The patient either has no brain metastases or, if the patient has brain metastases, then these have been treated and are symptomatically stable
8. Lenvatinib with everolimus will be continued until loss of clinical benefit or unacceptable toxicity or patient choice to stop treatment
9. If unacceptable toxicity occurs, the daily doses of lenvatinib and, if necessary, everolimus are to be modified as needed according to the dose/management plan as set out in section 4.2 of the Summary of Product Characteristics for lenvatinib (Kisplyx)
10. All treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve)
11. Lenvatinib (Kisplyx) and everolimus are to be otherwise used as set out in their Summaries of Product Characteristics

Blueteq form needs to be completed for all patients for all funding streams

**DRUG REGIMEN**

**Day 1**

<table>
<thead>
<tr>
<th></th>
<th>Everolimus 5mg orally daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lenvatinib 18mg orally daily</td>
</tr>
</tbody>
</table>

**Cycle Frequency:** Daily for 4 weeks continuously until progression

**DOSE MODIFICATIONS**

Any dose modifications should be discussed with a Consultant.

**Everolimus:**

Renal impairment
No dose adjustment is required in patients with renal impairment.

Hepatic impairment
For patients with moderate hepatic impairment (Child-Pugh class B), the dose should be reduced to 5 mg daily. Everolimus has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C) and is not recommended for use in this patient population.
Lenvatinib
Renal impairment
No adjustment of starting dose is required on the basis of renal function in patients with mild or moderate renal impairment. In patients with severe renal impairment, the recommended starting dose is 14 mg taken once daily. Further dose adjustments November be necessary based on individual tolerability. The use of lenvatinib in these patients is not recommended in end-stage renal disease.

Hepatic impairment
No adjustment of starting dose is required on the basis of hepatic function in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. In patients with severe (Child-Pugh C) hepatic impairment, the recommended starting dose is 14 mg taken once daily. Further dose adjustments may be necessary on the basis of individual tolerability.

See Lenvima SPC for specific adverse reaction related dose modifications.
http://www.medicines.org.uk/emc/medicine/30412

INVESTIGATIONS
Routine Blood test
1) Blood results required before drug administration
   Give  Discuss
   Hb x g/dL  ≥10  < 10
   Plt x 10⁹/L  ≥100  < 100
   Neutrophils x 10⁹/L  ≥1.5  < 1.5
   Routine bloods: FBC, renal function, liver function.
   Random blood sugar, lipid profile; if elevated to repeat on fasting blood
   Baseline imaging: CT and/or MRI at baseline and every three months.
   2) Non urgent tests
   Tests relating to disease response/progression

CONCURRENT MEDICATION
Check drug interactions, particularly cytochrome inducers and inhibitors and adjust doses accordingly.

ANTIEMETIC POLICY
Minimal emetic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Increased glucose, lipids and triglycerides
Decreased haemoglobin, lymphocytes, neutrophils and platelets
Hypersensitivity reactions
Pneumonitis, Infections
Oral ulceration

REFERENCES
1. SPC

Everolimus
Lenvatinib
Urology PODG Chair Authorisation:
Date:
Page 2 of 2
Published: November 2018
Review: November 2020
Version 4.0
Thames Valley Cancer Network
INTERFERON (Roferon-A®) (Renal)

*Indication: Advanced renal cell cancer*

**DRUG REGIMEN**

**Week 1 ONLY**

**Dose 1 & 2**  
INTERFERON 2α (Roferon) 4.5 million Units subcutaneous for the first TWO doses  
ONLY either Mon, Wed or Fri in the evening

**Dose 3**  
INTERFERON 2α (Roferon®) 9 million Units subcutaneous either Mon, Wed or Fri in the evening

**Week 2 onwards**

**Doses 1 - 3**  
INTERFERON 2α (Roferon®) 9 million Units subcutaneous 
THREE times per week. Mon, Wed and Fri in the evening

*Cycle Frequency: Continuous treatment dependent on tolerance and response with reviews every 2 - 3 months*

**DOSE MODIFICATIONS**

Reduce according to toxicity, discuss with Consultant or Registrar

**INVESTIGATIONS**

Routine Blood test

1) Blood results required before chemotherapy administration  

*Give Discuss*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hb x g/dL</th>
<th>Plt x 10⁹/L</th>
<th>Neutrophils x 10⁹/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥10</td>
<td>≥100</td>
<td>≥1.5</td>
</tr>
<tr>
<td></td>
<td>&lt; 10</td>
<td>&lt; 100</td>
<td>&lt; 1.5</td>
</tr>
</tbody>
</table>

2) Non-urgent tests

Tests relating to disease response/progression

**CONCURRENT MEDICATION**

Paracetamol should be administered 1 hour prior to treatment

**ANTI-EMETIC POLICY**

Non emetogenic

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**
Nivolumab (Renal cell carcinoma)

**Indication:** The treatment of previously treated advanced renal cell carcinoma where all the following criteria are met:
Advanced or metastatic histologically proven renal cell carcinoma with clear cell component, previously treated with only 1 or 2 previous lines of antiangiogenic therapy for advanced or metastatic disease, Karnofsky performance status (KPS) is 70 or more.

Blueteq form needs to be completed for all patients for all funding streams

**DRUG REGIMEN**

**Day 1**  NIVOLUMAB 480mg in 100ml sodium chloride 0.9% infusion over 60 minutes

*Cycle Frequency: every 28 days until progression or intolerance*

Or

**Day 1**  NIVOLUMAB 240mg in 100ml sodium chloride 0.9% infusion over 30 minutes

*Cycle Frequency: every 14 days until progression or intolerance*

Treatment breaks of up to 12 weeks beyond the expected cycle length are allowed but solely to allow immune toxicities to settle (treatment break form to be completed).

**DOSE MODIFICATIONS**

*Nivolumab:*

See Immuno-oncology adverse event management guidelines

**INVESTIGATIONS**

Routine Blood test

1) Blood results required before drug administration

<table>
<thead>
<tr>
<th></th>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Plt x 10⁹/L</td>
<td>≥100</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Neutrophils x 10⁹/L</td>
<td>≥1.5</td>
<td>&lt; 1.5</td>
</tr>
</tbody>
</table>

2) Non urgent tests

Tests relating to disease response/progression

**CONCURRENT MEDICATION**

**ANTIEMETIC POLICY**

None required
ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Immune-mediated adverse reactions: Administer corticosteroids based on the severity of the reaction.
- Immune-mediated pneumonitis: Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis.
- Immune-mediated colitis: Withhold for moderate or severe and permanently discontinue for life-threatening colitis.
- Immune-mediated hepatitis: Monitor for changes in liver function. Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation.
- Immune-mediated nephritis and renal dysfunction: Monitor for changes in renal function. Withhold for moderate and permanently discontinue for severe or life-threatening serum creatinine elevation.
- Immune-mediated hypothyroidism and hyperthyroidism: Monitor for changes in thyroid function. Initiate thyroid hormone replacement as needed.
- Embryofetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception.

REFERENCES
1. SPC Nivolumab SPC April 2018
2. CDF October 2016
Thames Valley Cancer Network

Pazopanib (Renal cell carcinoma)

*Indication: Treatment of advanced and/or metastatic renal cell carcinoma.*

Nice guidance: Pazopanib is recommended as a first-line treatment option for people with advanced renal cell carcinoma: who have not received prior cytokine therapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and if the manufacturer provides pazopanib with a 12.5% discount on the list price in the patient access scheme.

**DRUG REGIMEN**

Day 1  Pazopanib 800mg orally daily for 4 weeks

*Cycle Frequency: Daily for 4 weeks continuously until progression*

**DOSE MODIFICATIONS**

*Pazopanib:*
Any dose modifications should be discussed with a Consultant.

Renal impairment
No dose adjustment is required in patients with creatinine clearance above 30 ml/min. Caution is advised in patients with creatinine clearance below 30 ml/min as there is no experience of pazopanib in this patient population.

Hepatic impairment
Administration of pazopanib to patients with mild or moderate hepatic impairment should be undertaken with caution and close monitoring due to potentially increased exposure to the medicinal product.
Insufficient data are available in patients with mild hepatic impairment to provide a dose adjustment recommendation but a reduced pazopanib dose of 200 mg once daily is recommended in patients with moderate hepatic impairment.
Pazopanib is contraindicated in patients with severe hepatic impairment.

**INVESTIGATIONS**

Routine Blood test
1) Blood results required before drug administration

*Give  Discuss*

<table>
<thead>
<tr>
<th>Hb x g/dL</th>
<th>≥10</th>
<th>&lt; 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plt x 10⁹/L</td>
<td>≥100</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Neutrophils x 10⁹/L</td>
<td>≥1.5</td>
<td>&lt; 1.5</td>
</tr>
</tbody>
</table>
Liver function tests (LFT) - Serum liver tests should be monitored before initiation of treatment with pazopanib and at weeks 3, 5, 7 and 9. Thereafter, monitored at month 3 and at month 4, and as clinically indicated. Periodic monitoring should then continue after month 4. Other blood tests should initially be performed 4 weekly, but later in the treatment course can be done less often in stable patients.
Creatinine
Thyroid function tests
Ask GP to monitor blood pressure on a regular basis, weekly initially

2) Non urgent tests
Tests relating to disease response/progression

CONCURRENT MEDICATION
Check drug interactions, particularly cytochrome inducers and inhibitors and adjust doses accordingly.

ANTIEMETIC POLICY
Minimal emetic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

REFERENCES
3. SPC December 2014
4. NICE guidance May 2011
**Sunitinib (Renal cell carcinoma)**

*Indication: Treatment of advanced and/or metastatic renal cell carcinoma.*

Nice guidance: Sunitinib is recommended as a first-line treatment option for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

**DRUG REGIMEN**

Day 1  **Sunitinib** 50mg orally daily for 4 weeks

*Cycle Frequency: Daily for 4 weeks then a 2 week rest period (6 week cycle)*

**DOSE MODIFICATIONS**

**Sunitinib:**

Any dose modifications should be discussed with a Consultant.

Renal impairment

No data available for use in impaired renal function

Hepatic impairment

No dose adjustment is required in mild or moderate hepatic impairment.

No data available for severe hepatic impairment

**INVESTIGATIONS**

Routine Blood test

1) Blood results required before drug administration

<table>
<thead>
<tr>
<th>Test</th>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Plt x 10⁹/L</td>
<td>≥100</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Neutrophils x 10⁹/L</td>
<td>≥1.5</td>
<td>&lt; 1.5</td>
</tr>
</tbody>
</table>

Blood tests should initially be performed 4 weekly, but later in the treatment course can be done less often in stable patients.

Creatinine

Liver function tests (LFT)

Thyroid function tests

Ask GP to monitor blood pressure on a regular basis, weekly initially

2) Non urgent tests

Tests relating to disease response/progression
CONCURRENT MEDICATION
Check drug interactions, particularly cytochrome inducers and inhibitors and adjust doses accordingly.

ANTIEMETIC POLICY
Minimal emetic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Skin - skin discoloration and depigmentation of the hair and skin may occur.
Palmar / plantar syndrome
Neutropenia
Mouth pain / irritation / sensitivity may occur
Haemorrhage – an increased risk of bleeding may occur.
Hypertension – treatment induced hypertension. Sunitinib treatment should temporarily be suspended until hypertension is controlled.
Gastrointestinal – serious gastrointestinal complications including gastrointestinal perforation have occurred rarely.
Hypothyroidism

REFERENCES
1. SPC September 2008
2. NICE guidance November 2009
TEMSIROLIMUS (Renal Cell)

Indication: Advanced, poor risk, renal cell cancer first line.

Ensure funding is available for each patient before prescribing.

DRUG REGIMEN
Day 1 Pre-medication
TEMSIROLIMUS 25mg in 250ml sodium chloride 0.9% IV infusion over 30-60 minutes

Cycle Frequency: Every 7 days

DOSE MODIFICATIONS
Temsirolimus:

Hepatic impairment
Temsirolimus is largely excreted by the liver and the drug should not be administered to patients with moderate or severe liver impairment defined as Bilirubin >1.5 x upper limit of normal.

Renal impairment
Studies have not been conducted. No dose adjustment of temsirolimus is recommended in patients with renal impairment. Temsirolimus should be used with caution in patients with severe renal impairment.

INVESTIGATIONS
Routine Blood test
1) Blood results required before drug administration

   | Give | Discuss |
---|---|---|
Hb x g/dL | ≥10 < 10 |
Plt x 10^9/L | ≥100 < 100 |
Neutrophils x 10^9/L | ≥1.5 < 1.5 |

Blood tests should initially be performed 4 weekly, but later in the treatment course can be done less often in stable patients.

Creatinine
Liver function tests (LFT)
U&Es, glucose, Mg^{2+}, Ca^{2+} and PO_4

2) Non urgent tests
Tests relating to disease response/progression
CONCURRENT MEDICATION
Check drug interactions, particularly cytochrome inducers and inhibitors and adjust doses accordingly.

ANTIEMETIC POLICY
Minimal emetic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
1. Thrombocytopenia is the most commonly reported side effect and may lead to delays.
2. Neutropenia is also common
3. There was one report of interstitial pneumonitis in phase III trial of temsirolimus in relapsed mantle cell lymphoma

REFERENCES
SPC August 2014
**TIVOZANIB (Renal Cell)**

Indication: The treatment of advanced renal cell carcinoma where all the following are met:
2. This patient has a confirmed histological diagnosis of renal cell carcinoma with a clear cell component
3. The patient has either metastatic disease or inoperable locally advanced disease
4. The patient is treatment naïve to systemic therapy and in particular has previously received neither any vascular endothelial growth factor (VEGF)-targeted systemic therapy nor mTOR pathway inhibitor-targeted treatment unless prior treatment with pazopanib or sunitinib has had to be stopped solely as a consequence of dose-limiting toxicity and in the clear absence of progression (see criteria 10).
5. The patient has an ECOG performance status of either 0 or 1. A patient with a performance status of 2 is not eligible for tivozanib
6. If the patient has brain metastases, then these have been treated and are stable
7. Tivozanib is to be continued until loss of clinical benefit or unacceptable toxicity or patient choice to stop treatment
8. A formal medical review as to whether treatment with tivozanib should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment
9. No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve)
10. I confirm that the patient has had no prior treatment either with pazopanib or sunitinib unless such prior treatment has had to be stopped solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression.* *Patients treated with tivozanib may switch to pazopanib or sunitinib where treatment has had to be stopped early under the same circumstances.
11. Tivozanib is to be otherwise used as set out in its Summary of Product Characteristics

Blueteq registration required for all patients for all funding streams

**DRUG REGIMEN**
Days 1 to 21 TIVOZANIB 1340mcg orally once daily (followed by 7 day rest period)

*Cycle Frequency: Every 28 days*

**DOSE MODIFICATIONS**
The occurrence of undesirable effects may require temporary interruption and/or dose reduction of tivozanib therapy. In the pivotal study, the dose was reduced for grade 3 events and interrupted for grade 4 events.
When dose reduction is necessary, the tivozanib dose can be reduced to 890 microgram once daily with the normal treatment schedule of 21 days of dosing, followed by a 7-day rest period.

<table>
<thead>
<tr>
<th>Tivozanib</th>
<th>Urology PODG Chair Authorisation:</th>
<th>Page 1 of 2</th>
<th>Published: November 2018</th>
<th>Review: November 2020</th>
<th>Version 4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date:</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Network Chemotherapy Protocols – Urological Cancer 77
Renal impairment
No dose adjustment is required in patients with mild or moderate renal impairment. Caution is advised in patients with severe renal impairment due to limited experience and in patients undergoing dialysis as there is no experience of tivozanib in this patient population.

Hepatic impairment
All patients should have liver function tests evaluated, including ALT, AST, bilirubin, and alkaline phosphatase, to determine hepatic function before starting and during treatment with tivozanib. Tivozanib is not recommended in patients with severe hepatic impairment. Patients with moderate hepatic impairment should only be treated with one tivozanib 1340 microgram capsule every other day as they may be at an increased risk of adverse reactions due to increased exposure with the dose of 1340 microgram every day. No dose adjustment is required when administering tivozanib to patients with mild hepatic impairment. Tivozanib should be used with caution in patients with mild and moderate hepatic impairment with close monitoring of tolerability.

INVESTIGATIONS
Routine Blood test
Blood tests should initially be performed regularly
Creatinine, proteinuria monitoring
Liver function tests (LFT)
U&Es, glucose, Mg²⁺, Ca²⁺ and PO₄

CONCURRENT MEDICATION
Check drug interactions, particularly cytochrome inducers and inhibitors and adjust doses accordingly.

ANTIEMETIC POLICY
None required

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Palmar / plantar syndrome
Neutropenia
Mouth pain / irritation / sensitivity may occur
Hepatotoxicity
Posterior reversible encaphalopathy syndrome
Haemorrhage – an increased risk of bleeding may occur.
QT prolongation, VTE, cardiac failure, arterial thromboembolic events
Hypertension –
Gastrointestinal – serious gastrointestinal complications including gastrointestinal perforation have occurred rarely.
Hypothyroidism

REFERENCES
SPC
CDF
MITOMYCIN C bladder installation weekly (Bladder)

Indications: Superficial bladder tumours

DRUG REGIMEN
Day 1 MITOMYCIN C 40mg in 40-50ml water or sodium chloride 0.9% intravesically

Cycle frequency: Every 7 days for 6 cycles

DOSE MODIFICATIONS
Urine dipsticks – if positive for nitrates, leucocytes, blood or protein then delay by 1 week.

INVESTIGATIONS
Urine dipsticks

CONCURRENT MEDICATION

ANTI-EMETIC POLICY
Non emetogenic

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
MITOMYCIN C bladder installation 14 day (Bladder)

Indication: Superficial bladder tumours

DRUG REGIMEN
Day 1 MITOMYCIN C 40mg in 40-50ml water or sodium chloride 0.9% intravesically

Cycle frequency: Every 14 days for 6 cycles

DOSE MODIFICATIONS
Urine dipsticks – if positive for nitrites, leucocytes, blood or protein then delay by 1 week.

INVESTIGATIONS
Urine dipsticks

CONCURRENT MEDICATION

ANTI-EMETIC POLICY
Non emetogenic

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
MITOMYCIN C bladder installation post-op (Bladder)

*Indication: Superficial bladder tumours post operatively*

**DRUG REGIMEN**
Day 1 MITOMYCIN C 40mg in 40-50ml water or sodium chloride 0.9% intravesically

*Cycle frequency: Once only*

**DOSE MODIFICATIONS**
Urine dipsticks – if positive for nitrites send MSU. Recomence on completion of antibiotics.

**INVESTIGATIONS**
Urine dipsticks

**CONCURRENT MEDICATION**

**ANTI-EMETIC POLICY**
Non emetogenic

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**
BCG bladder installation (Bladder)

**Indication:** Superficial bladder tumours

**DRUG REGIMEN**

Day 1 BCG 1 vial (12.5mg) in 50ml sodium chloride 0.9% intravesically

Cycle frequency: Every 7 days for 6 cycles

Followed by maintenance

BCG 1 vial in 50ml sodium chloride 0.9% intravesically

Day 1 each week for 1 to 3 weeks at 6, 12, 18, 24, 30 and 36 months following the initiation of induction treatment.

**DOSE MODIFICATIONS**

Urine dipsticks – if positive for nitrites or urine visibly blood stained or bleeding on catheterisation.

**INVESTIGATIONS**

Urine dipsticks

**CONCURRENT MEDICATION**

**ANTI-EMETIC POLICY**

Non emetogenic

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**
Pre-hydration and post-hydration regimens

Ensure adequate diuresis is obtained prior to administration and maintained during and after administration.

1. **Inpatient**
   - **Pre**
     - 1L sodium chloride 0.9% + 20mmol KCl + 8mmol MgSO$_4$ infusion over 4 hours
   - Give cisplatin in **1000ml volume over 4 hours**
   - **Post**
     - 1L sodium chloride 0.9% + 20mmol KCl + 8mmol MgSO$_4$ infusion over 4 hours
     - 1L sodium chloride 0.9% + 20mmol KCl + 8mmol MgSO$_4$ infusion over 4 hours
   - NB 1L sodium chloride 0.9% + 20mmol KCl + 8mmol MgSO$_4$ infusion over 6 hours if oral intake is inadequate

2. **Day case / Outpatient**
   - **Pre**
     - 1L sodium chloride 0.9% + 20 mmol KCl + 8mmol MgSO$_4$ infusion over 2 hours
     - 100ml mannitol 20% infusion over 30 minutes
   - Give cisplatin in **1000ml volume over 2 hours**
   - **Post**
     - 1L sodium chloride 0.9% + 20 mmol KCl + 8mmol MgSO$_4$ infusion over 2 hours

   NB Furosemide 40mg may be added if required