Nintedanib (Vargatef®) and Docetaxel for NSCLC

**DRUG ADMINISTRATION SCHEDULE**

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Daily Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0 to 2</td>
<td>Dexamethasone*</td>
<td>8 mg twice a day</td>
<td>Oral</td>
<td>For 3 days</td>
</tr>
<tr>
<td>Day 1</td>
<td>Sodium Chloride 0.9%</td>
<td>100ml</td>
<td>Infusion</td>
<td>Fast Running</td>
</tr>
<tr>
<td></td>
<td>Ondansetron</td>
<td>8mg</td>
<td>Oral/Slow bolus/15 min infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Docetaxel</td>
<td>75 mg/m²</td>
<td>IV infusion</td>
<td>250mls Normal Saline 1 hour</td>
</tr>
<tr>
<td>Day 2 to 21</td>
<td>Nintedanib</td>
<td>200mg Twice daily</td>
<td>Oral</td>
<td>For 20 days</td>
</tr>
</tbody>
</table>

* Must pre-medicate with dexamethasone because of risk of docetaxel hypersensitivity
**Ondansetron IV must be infused over 15 minutes in patients over 65 years of age.

**Nintedanib Maintenance (following at least 4 cycles of combination)**

<table>
<thead>
<tr>
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<th>Daily Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 to 28</td>
<td>Nintedanib</td>
<td>200mg Twice daily</td>
<td>Oral</td>
<td>Continuous</td>
</tr>
</tbody>
</table>

Nintedanib is supplied as 100mg or 150mg capsules. Two nintedanib containing-products are available, only Vargatef brand is licensed in NSCLC.

**CYCLE LENGTH AND NUMBER OF DAYS**

- 21 Days for 4 cycles (6 cycles if well tolerated):
- Then maintenance with Nintedanib 28 day cycle until progression.
- Patients who discontinue combination therapy because of docetaxel-related adverse events should continue nintedanib monotherapy (given as continuous treatment with no planned breaks) provided they have completed at least four cycles of combination therapy.
- Patients with unacceptable nintedanib-related adverse events are allowed to continue standard-dose docetaxel

**APPROVED INDICATIONS**

Patients with locally advanced or metastatic non-small cell lung cancer (adenocarcinoma only) after failure of first line chemotherapy regimen.

**ELIGIBILITY CRITERIA**

- Locally advanced or metastatic non-small cell lung cancer after failure of one prior chemotherapy regime
- PS 0, 1, 2 and a life expectancy of more than 12 weeks.
- Radiologically or clinically evaluable disease

**EXCLUSION CRITERIA**

- Chemotherapy naïve patients
- Pregnant or lactating women
- Concurrent uncontrolled medical illness
- Severe renal impairment (Serum creatinine > 5 x ULN)
- Impaired hepatic function (Bilirubin > 2 x ULN, ALT > 2.5 x ULN in absence of liver mets and > 5 x ULN with liver mets)
PREMEDICATION
Oral Dexamethasone as above

RECOMMENDED TAKE HOME MEDICATION
Dexamethasone 8mg twice daily for 3 days starting 24 hours prior to chemotherapy
Metoclopramide 10mg three times daily as required
Loperamide 4mg after first loose stool, then 2mg after each loose stool thereafter up to a maximum of 16mg in 24 hours
Suggested antiemetic regimen - may vary with local practice. See CINV policy for more details

INVESTIGATIONS / MONITORING REQUIRED
Pre-treatment
FBC, U&E’s, LFT’s, baseline radiology (CXR/ CT). Repeat radiology after 2 cycles

Prior to each cycle
FBC, U&E’s, LFT’s as required

ASSESSMENT OF RESPONSE
Metastatic: Tumour size and patient symptomatic response

REVIEW BY CLINICIAN
To be reviewed by either a Nurse, Pharmacist or Clinician before every cycle.

NURSE / PHARMACIST LED REVIEW
On cycles where not seen by clinician.

ADMINISTRATION NOTES
• Make sure the patient has taken oral dexamethasone premedication. Docetaxel has been known to produce hypersensitivity reactions; steroid co-medication will also reduce the risk of fluid retention and skin reactions.
• Facilities to treat anaphylaxis MUST be present when the chemotherapy is given.
• Do not need to stop treatment for minor hypersensitivity e.g. reactions, flushing, localised rash.
• Must be stopped for major reactions, e.g. hypotension, bronchospasm and generalised rash.
• The nadir occurs earlier with docetaxel than with other chemotherapy regimens.
• Nintedanib should be taken with food, swallowed whole with water, and must not be chewed or crushed.
• Nintedanib is a substrate of P-gp. If co-administered with nintedanib, potent P-gp inhibitors (e.g. ketoconazole or erythromycin) may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of nintedanib. Management of side effects may require interruption, dose reduction, or discontinuation of therapy with Vargatef.
• Potent P-gp inducers (e.g. rifampicin, carbamazepine, phenytoin, and St. John's Wort) may decrease exposure to nintedanib. Co-administration with nintedanib should be carefully considered.

EXTRAVASATION See NECN/ Local Policy
TOXICITIES
- Diarrhoea (common)
- Anaphylaxis and hypersensitivity reactions
- Fluid retention syndrome
- Nausea and Vomiting,
- Bone Marrow Suppression
- Peripheral Neuropathy
- Deranged LFT’s
- Bleeding Risk
- Mucositis (including stomatitis)
- Rash

DOSE MODIFICATION / TREATMENT DELAYS

Haematological Toxicity:
If the patient has an episode of neutropenic sepsis or fever a reduction docetaxel dose to 60mg/m². If this recurs, treatment with docetaxel should be stopped.
- Delay course 1 week if WBC<3.0, ANC <1.5 Platelets <100
- No dose modification for CTC grade I/II ANC
- Grade III/IV ANC → delay chemotherapy until recovered. On recovery give 20% dose reduction docetaxel

Non- Haematological Toxicity:

Hepatic impairment
- No dose adjustments of nintedanib is needed for mild (Child Pugh A) liver impairment, but it is not recommended for patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment.
- Nintedanib dose must be reduced and or treatment interrupted in case of deranged liver enzymes and /or bilirubin according to table below.

<table>
<thead>
<tr>
<th>ST / ALT and bilirubin elevations</th>
<th>Nintedanib dose adjustment</th>
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<tbody>
<tr>
<td>Elevation of AST and/or ALT values to &gt; 2.5 x ULN in conjunction with total bilirubin elevation to ≥ 1.5 x ULN <strong>OR</strong> Elevation of AST and/or ALT values to &gt; 5x ULN</td>
<td>After treatment interruption and recovery of transaminase-values to ≤ 2.5 x ULN in conjunction with bilirubin to normal, dose reduction from 200 mg twice daily to 150 mg twice daily and - if a 2nd dose reduction is considered necessary - from 150 mg twice daily to 100 mg twice daily.</td>
</tr>
<tr>
<td>Elevation of AST and/or ALT values to &gt; 3 x ULN in conjunction with an increase of total bilirubin to ≥ 2 x ULN and ALKP &lt; 2 x ULN</td>
<td>Unless there is an alternative cause established, nintedanib should be permanently discontinued</td>
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Extreme caution with docetaxel patients with abnormal liver function or patients with evidence of significant replacement of liver parenchyma by tumour. Seek advice if the bilirubin is raised.

<table>
<thead>
<tr>
<th>ALP</th>
<th>ALT</th>
<th>Bilirubin</th>
<th>Docetaxel Dose</th>
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<tbody>
<tr>
<td>&lt; 2.5 x ULN</td>
<td>And</td>
<td>&lt; 1.5 x ULN</td>
<td>And</td>
</tr>
<tr>
<td>2.5 – 6 x ULN</td>
<td>Or</td>
<td>1.5 – 2.5 x ULN</td>
<td>Or</td>
</tr>
<tr>
<td>&gt; 6 x ULN</td>
<td>Or</td>
<td>&gt; 3.5 x ULN</td>
<td>Or</td>
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- If the bilirubin is abnormal, the AST/ALT >3.5x normal and alkaline phosphatase >6x normal take great care when prescribing docetaxel.
- Dose reduction is mandatory in cases of significant hepatic impairment
- If PS deteriorates to 3 or 4 and on assessment patient is more symptomatic withhold treatment and discuss with Oncologist.

Other toxicities
Recommended dose adjustments for nintedanib in case of grade ≥ 2 diarrhoea, vomiting and other non-haematological or haematological adverse reactions is treatment interruption until recovery to grade 1 or baseline, followed by dose reduction from 200mg twice daily to 150 mg twice daily.
If a second dose reduction is considered necessary, reduce from 150 mg twice daily to 100 mg twice daily.

TREATMENT LOCATION
Can be given at Cancer Centre or Cancer Unit

REFERENCES:
1. Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non small cell lung cancer. NICE technology appraisal guidance [TA347] Published date: July 2015.

Document Control

<table>
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<tr>
<td>Reviewer:</td>
<td>Chris Beck Chemotherapy Pharmacist</td>
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<td>Northern Cancer Alliance</td>
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<tr>
<td>Approved by:</td>
<td>Steve Williamson Consultant</td>
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