Systemic Anti Cancer Treatment Protocol

Docetaxel + Nintendanib

PROCTOCOL REF: MPHALUNDNI
(Version No: 1.0)

Approved for use in:

Non-Small Cell Lung: Second line treatment in patients with locally advanced or metastatic adenocarcinoma lung cacner when relapse has occurred after prior chemotherapy

Patients may continue with nintedanib monotherapy following **at least 4 cycles of docetaxel + nintedanib**, after discontinuation of docetaxel for as long as clinical benefit is observed or until unacceptable toxicity occurs. (See separate protocol)

Dosage:

Drug	Dosage	Route	Frequency
Docetaxel	75mg/m² day 1	IV	21 days
Nintendanib	200mg BD Day 2 to day 21	PO	20 days out of each 21 day cycle

Pre-medication is required before docetaxel-

Dexamethasone 8mg oral twice daily for 3 days, starting 24 hours pre-docetaxel.

Supportive Treatments:

Anti emetic risk – Low

Domperidone 10mg orally three times a day when required

Loperamide 2mg after each loose stool as required

Extravasation risk:

Docetaxel – non vesciant

Administration:

Day	Drug	Dose	Route	Diluent and rate
-1	**Dexamethasone** Commencing 24 hours before docetaxel	8mg BD for three days	PO	
1	Sodium Chloride 0.9%	50ml	IV Infusion	Flush
	Docetaxel	**75mg/m²**	**IV Infusion**	**Sodium chloride 0.9% 250mL over 1 hour**
	Sodium Chloride 0.9%	100ml	IV Infusion	Flush
Days 2 to 21	**Nintendanib**	200mg BD	PO	

- If dexamethasone premedication has not been commenced then administer 16mg intravenously 30 minutes prior to docetaxel, and then continue with the remainder of the oral doses.

- First 2 cycles of docetaxel to be administered using step up feature of the Hospira Plum A infusion pump. The risk of infusion reactions is increased during these first two cycles, therefore administer with caution. Hypersensitivity reactions normally occur within the first few minutes of the initiation of the infusion.

- Facilities to treat anaphylaxis must be present when administering this regimen. If a patient experiences an **infusion-related reaction**, give future does with premedication cover of IV chlorphenamine 10mg and IV hydrocortisone 100mg.

- Nintedanib capsules must be taken orally, preferably with food, swallowed whole with water, and must not be chewed or crushed

- Nintedanib must not be taken on the same day of docetaxel chemotherapy administration (= day 1 of each cycle).

- If a dose of nintedanib is missed, administration should resume at the next scheduled time at the recommended dose.

- The individual daily doses of nintedanib should not be increased beyond the recommended dose to make up for missed doses. The recommended maximum daily dose of 400 mg should not be exceeded

For severe reactions, discuss with Consultant before continuing with treatment.

Medical/Nursing review: as per patient management plan/consent.

Main Toxicities:

Neutropenia, hypersensitivity reactions, flushing, broncospasm, rash, dizziness, headache, nausea, vomiting, diarrhoea, fluid retention, myelosuppresion, alopecia, mucositis, electrolyte imbalance, taste changes, palmer plantar erythema, loss of appetite, fatigue, joint and muscle pain, nail changes, neuropathy, increased LFTs, venous thromboembolism and hypertension

Investigations and treatment plan

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Comments
Medical Assessment	X		X		X	
Nursing Assessment	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	Every cycle
U&E & LFT	X	X	X	X	X	Every cycle
CT scan	X		X		X	At the end of treatment
Informed Consent	X					
Blood pressure measurement	X					Repeat if clinically indicated
PS recorded	X	X	X	X	X	Every cycle
Toxicities documented	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management:

Haematological Toxicity:

Proceed on day 1 if-

WCC ≥ 3.0 x 10^9/L	Plt ≥ 100 x 10^9/L	ANC ≥ 1.0 x 10^9/L

Delay 1 week on day 1 if-

WCC ≤ 2.9 x 10^9/L	Plt ≤ 99 x 10^9/L	ANC ≤ 0.9 x 10^9/L

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

If WCC, platelets or neutrophil count still below required levels for treatment at week 2, delay treatment again and patient will need assessment and chemotherapy dose reduction

If treatment delayed > 1 week or ANC < 0.5 x 10^9/L, or any febrile neutropenia reduce docetaxel to 60mg/m^2 for subsequent cycles

If platelets < 25 x 10^9/L, consider dose reduction to 60mg/m^2 for subsequent cycles upon recovery. (Discuss with consultant)

If persistent toxicity – stop treatment refer to consultant

IF DOCETAXEL ADMINISTRATION IS DEFERRED, NINTEDANIB SHOULD CONTINUE - ONLY WITHOLD NINTEDANIB ON THE DAY OF DOCETAXEL ADMINISTRATION

Non-haematological toxicity

Renal	No dose adjustments needed
Hepatic	If Bilirubin > 22mmol/l or ALT/AST > 3.5 x ULN and ALP> 6x ULN Not recommended – delay treatment and refer to consultant
Cutenaeous	Grade 1 persistent or Grade 2 – delay treatment until resolved to grade 0-1. Restart at same dose Grade 3 restart once recovered at 60mg/m^2
Neuropathy	Grade 1 persistent or Grade 2 – delay treatment until resolved to grade 0-1. Reduce dose to 60mg/m^2 Grade 3 or 4 – stop docetaxel permanently
Other grade 3-4 reactions	Discontinue treatment – discuss with consultant

Nintendanib:

As initial measure for the management of adverse reactions (see Tables 1 and 2) treatment with nintedanib should be temporarily interrupted until the specific adverse reaction has resolved to levels that allow continuation of therapy (to grade 1 or baseline).

Nintedanib treatment may be resumed at a reduced dose. Dose adjustments in 100 mg steps per day (i.e. a 50 mg reduction per dosing) based on individual safety and tolerability are recommended as described in Table 1 and Table 2.

In case of further persistence of the adverse reaction(s), i.e. if a patient does not tolerate 100 mg twice daily, treatment with nintedanib should be permanently discontinued.

In case of specific elevations of aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) values to > 3 x upper limit normal (ULN) in conjunction with an increase of total bilirubin to ≥ 2 x ULN and alkaline phosphatase (ALKP) < 2 x ULN; (see Table 2) treatment with nintedanib should be interrupted. Unless there is an alternative cause established, Nintedanib should be permanently discontinued.

Table 1: Recommended dose adjustments for nintedanib in case of diarrhoea, vomiting and other non-haematological or haematological adverse reactions

CTCAE* Adverse reaction	**Dose adjustment**
Diarrhoea ≥ grade 2 for more than 7 consecutive days despite anti-diarrhoeal treatment ***OR*** Diarrhoea ≥ grade 3 despite anti-diarrhoeal treatment	After treatment interruption and recovery to grade 1 or baseline, 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.
Vomiting ≥ grade 2 ***AND/OR*** Nausea ≥ grade 3 despite anti-emetic treatment	
Other non-haematological or haematological adverse reaction of ≥ grade 3	

* CTCAE: Common Terminology Criteria for Adverse Events

Table 2: Recommended dose adjustments for nintedanib in case of AST and/or ALT and bilirubin elevations

AST / ALT and bilirubin elevations	**Dose adjustment**
Elevation of AST and/or ALT values to > 2.5 x ULN in conjunction with total bilirubin	After treatment interruption and recovery of transaminase-values to ≤ 2.5 x ULN in

elevation to ≥ 1.5 x ULN ***OR*** Elevation of AST and/or ALT values to > 5x ULN	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.
Elevation of AST and/or ALT values to > 3 x ULN in conjunction with an increase of total bilirubin to ≥ 2 x ULN and ALKP < 2 x ULN	Unless there is an alternative cause established, nintendanib should be permanently discontinued

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase

ALKP: Alkaline phosphatase; ULN: Upper limit normal

Renal impairment

Less than 1 % of a single dose of nintedanib is excreted via the kidney. Adjustment of the starting dose in patients with mild to moderate renal impairment is not required.

The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (< 30 ml/min creatinine clearance).

Hepatic impairment

Nintedanib is predominantly eliminated via biliary/faecal excretion (> 90 %).

No adjustment of the starting dose is needed for patients with mild hepatic impairment based on clinical data (Child Pugh A).

The safety, efficacy, and pharmacokinetics of nintedanib have not been investigated in patients with hepatic impairment classified as Child Pugh B and C. Therefore, treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with nintedanib is not recommended.

References:

1. Boehringer Ingelheim Limited Summary of Product Chracteristics; Vargatef 150 mg soft capsules. Last Updated on eMC 18-Mar-2015 (Accessed 10th September 2015)

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

3. http://www.medicines.org.uk/emc/medicine/23925/spc