Nintedanib & docetaxel

Indication

Second line treatment of locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma histology in patients who have progressed after previous chemotherapy

Regimen details

Docetaxel 75mg/m^2 IV in 250ml sodium chloride 0.9% over 1 hour day 1
Nintedanib 200mg orally twice daily continuous (omit on day of docetaxel)

Cycle frequency

Every 3 weeks during treatment with docetaxel
Monthly when on nintedanib alone

Number of cycles

Until disease progression or unacceptable toxicity (docetaxel may be stopped after 4 cycles)

Administration

Docetaxel is administered as an IV infusion in 250mL or 500mL (concentration dependent) PVC free sodium chloride 0.9% over 60 minutes

Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions

Nintedanib is available as 100mg and 150mg capsules. Capsules must be swallowed whole, preferably with or after food, 12 hours apart. The must not be chewed or crushed. If a dose is missed, it should be omitted and the next dose taken as scheduled

Pre-medication

Dexamethasone 8 mg BD (morning and lunchtime) for 3 days starting 24 hours prior to chemotherapy
(Note: Patients must receive 3 doses of dexamethasone prior to treatment)

Emetogenicity

Minimal (give ondansetron pre-med and metoclopramide as required)

Additional supportive medication

See above

Extravasation

Irritant

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
Blood pressure	Baseline

Nintedanib is contraindicated in peanut or soya allergy

Aneurysm and/or Artery Dissection

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating nintedanib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm

Perforation

Particular caution should be exercised when treating patients with previous abdominal surgery or a recent history of a hollow organ perforation. Nintedanib should therefore only be initiated at least 4 weeks after major surgery. Therapy with nintedanib should be permanently discontinued in patients who develop gastrointestinal perforation

Wound healing

Based on the mechanism of action nintedanib may impair wound healing. No increased frequency of impaired wound healing was observed in the LUME-Lung 1 trial. No dedicated trials investigating the effect of nintedanib on wound healing were performed. Treatment with nintedanib should therefore only be initiated or - in case of perioperative interruption - resumed based on clinical judgement of adequate wound healing

Thromboembolic Events

An increased frequency of arterial thromboembolic events was observed in patients with idiopathic pulmonary fibrosis (IPF) when treated with nintedanib monotherapy. Use caution when treating patients with a higher cardiovascular risk including known coronary artery disease. Treatment interruption should be considered in patients who develop signs or symptoms of acute myocardial ischaemia

Haemorrhage

VEGF inhibitors may be associated with an increased risk of bleeding. It is not recommended to treat with nintedanib, patients with recent pulmonary bleeding as well as patients with centrally located tumours with radiographic evidence of local invasion of major blood vessels or radiographic evidence of cavitary or necrotic tumours

Anticoagulation

Patients taking concomitant anticoagulation, such as warfarin or phenprocoumon should be monitored regularly for changes in prothrombin time, international normalised ratio (INR), and clinical bleeding episodes

Brain metastasis

Stable brain metastasis

No increased frequency of cerebral bleeding in patients with adequately pre-treated brain metastases which were stable for ≥ 4 weeks before start of treatment with nintedanib was observed. However, such patients should be closely monitored for signs and symptoms of cerebral bleeding.

Active brain metastasis

Patients with active brain metastasis were excluded from clinical trials and are not recommended for treatment with nintedanib.

Venous thromboembolism

Patients treated with nintedanib have an increased risk of venous thromboembolism including pulmonary embolism and deep vein thrombosis. Patients should be closely monitored for thromboembolic events. Caution should be used especially in patients with additional risk factors for thromboembolic events. Nintedanib should be discontinued in patients with life-threatening venous thromboembolic reactions.

Arterial thromboembolic events

The frequency of arterial thromboembolic events was comparable between the two treatment arms in the phase 3 trial 1199.13 (LUME-Lung 1). Patients with a recent history of myocardial infarction or stroke were excluded from this trial. However, an increased frequency of arterial thromboembolic events was observed in patients with idiopathic pulmonary fibrosis (IPF) when treated with nintedanib monotherapy. Use caution when treating patients with a higher cardiovascular risk including known coronary artery disease. Treatment interruption should be considered in patients who develop signs or symptoms of acute myocardial ischaemia

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST), blood pressure

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophil count	≥ 1.5 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 45 mL/min
Bilirubin	≤ ULN
AST	< 1.5 x ULN (if known liver mets then < 2.5x ULN)
Alkaline phosphatase	< 2.5 x ULN

Dose modifications

Reduction of nintedanib dose below 100mg BD is not recommended

Nintedanib can be continued as monotherapy if patients have intolerable toxicity to docetaxel

Hepatic Impairment

Docetaxel

AST/ALT (x ULN)		Alkaline phosphatase* (x ULN)	Docetaxel dose
≤ 1.5	And	< 2.5	100%
> 1.5	Or	≥ 2.5 - 6	60mg/m^2
> 3.0	Or	≥ 6	Discuss with consultant

*Unless due to bone metastases only
If bilirubin > 1.0 x ULN withhold docetaxel (or consultant decision to treat)

Nintedanib

AST / ALT and bilirubin elevations	Dose adjustment
Elevation of AST and/or ALT values to > 2.5 x ULN in conjunction with total bilirubin elevation to ≥ 1.5 x ULN ***OR*** Elevation of AST and/or ALT values to > 5x ULN	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.
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, nintedanib should be permanently discontinued

Other toxicities

Toxicity	Grade	Docetaxel dose	Nintedanib dose
Cutaneous reactions	Grade 1 - persistent or Grade 2	Withhold until ≤ grade 1. Resume at same dose	Withhold until ≤ grade 1. Resume at same dose. If recurs reduce dose by 50mg BD.
	Grade 3	Withhold until ≤ grade 1. Resume at 60mg/m^2	Withhold until ≤ grade 1. Resume at same

			dose. If recurs reduce dose by 50mg BD.
	Grade 4	Discontinue	Discontinue
Diarrhoea	Grade 2 for > 7 days or ≥ grade 3 (despite antidiarrhoeals)	Withhold until ≤ grade 1 Resume at 60mg/m^2	Withhold until ≤ grade 1. Resume with 50mg BD dose Reduction
Nausea and vomiting	≥ grade 2 vomiting or ≥ grade 3 nausea (despite antiemetics)	Withhold until ≤ grade 1. Resume at 60mg/m^2	Withhold until ≤ grade 1. Resume with 50mg BD dose reduction
Neuropathy	Grade 1 - persistent or Grade 2	Withhold until ≤ grade 1. Resume at 60mg/m^2 If recurs discontinue.	Continue
	Grade 3-4	Discontinue	

Adverse effects –

for full details consult product literature/ reference texts

- **Serious side effects**

Secondary malignancy
Myelosuppression
Infusion related reactions
Anaphylaxis
Interstitial pneumonitis
Teratogenicity
Infertility
Cardiotoxicity
Peripheral neuropathy
GI perforation
Venous thrombotic events

- **Frequently occurring side effects**

Diarrhoea
Constipation
Fatigue
Nausea and vomiting
Myelosuppression
Stomatitis and mucositis
Arthralgia and myalgia
Hypertension
Impaired wound healing

- **Other side effects**

Alopecia
Fluid retention
Deranged liver function
Phlebitis
Skin toxicity
Nail changes

Rash
Dizziness
Headache
Electrolyte imbalance
Taste changes

Significant drug interactions

– for full details consult product literature/ reference texts

Docetaxel:

CYP3A4 Enzyme inducers/inhibitors: in vitro studies suggest that CYP3A inhibitors (such as ketoconazole, ritonavir, clarithromycin and erythromycin) may raise docetaxel levels, whereas CYP3A inducers (such as rifampicin and barbiturates) may reduce docetaxel levels.

Nintedanib:

P-gp inhibitors (e.g. ketoconazole, erythromycin): co-administration may increase exposure to nintedanib. Patients should be closely monitored.
P-gp inducers (e.g. rifampicin, carbamazepine, phenytoin, St John's Wort): may decrease exposure to nintedanib

Additional comments

Concomitant use of radiotherapy is not recommended, however, patients could receive palliative radiotherapy whilst nintedanib treatment is interrupted

References

Nintedanib SPC: https://www.medicines.org.uk/emc/product/7704/smpc

SWCN protocol: http://www.swscn.org.uk/guidance-protocols/cancer-protocols/

This protocol has been reviewed by the Lancashire & South Cumbria Lung Oncology Consultants' Group and responsibility for the template lies with the Head of Service

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