Nintedanib and 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.

(NICE TA347)

ICD-10 codes

Codes with a prefix C34

Regimen details

Patients must receive at least 4 cycles of nintedanib in combination with docetaxel before continuing with nintedanib monotherapy.

Docetaxel and nintedanib

Day	Drug	Dose	Route
1	Docetaxel	75mg/m^2	IV infusion
2-21	Nintedanib	200mg BD	PO

Nintedanib monotherapy

Day	Drug	Dose	Route
1-28 (continuously)	Nintedanib	200mg BD	PO

Cycle frequency

21 days – combination therapy
28 days – monotherapy (for supply purposes)

Number of cycles

4-6 cycles (depending on response)
Nintedanib may continue as monotherapy after at least 4 cycles of docetaxel and nintedanib until disease progression or unacceptable toxicity.

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.

Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel and therefore facilities for the treatment of hypotension and bronchospasm must be available.

If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy. The infusion may be temporarily interrupted and when symptoms improve re-started at a slower infusion rate. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel and appropriate therapy.

Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel.

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.

Nintedanib must not be taken on the same day as docetaxel administration.

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).
In the case where 3 doses have not been taken, dexamethasone 16-20mg IV should be administered 30-60 minutes prior to chemotherapy and the remaining 3 oral doses should be taken as normal.

Emetogenicity

This regimen has mild - moderate emetic potential

Additional supportive medication

Mouthwashes as per local policy
H_2 antagonist or proton-pump inhibitor if required
Loperamide if required.
Emollients as required.

Extravasation

Docetaxel is an exfoliant (Group 4)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local practice)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Blood pressure	Baseline

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local practice)
FBC	96 hours (monthly for nintedanib monotherapy)
U+E (including creatinine)	7 days (monthly for nintedanib monotherapy)
LFTs	7 days (monthly for nintedanib monotherapy)
Blood pressure	Each cycle

Standard limits for administration to go ahead

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

Investigation	**Limit**
Neutrophils	$\geq 1.5 \times 10^9$/L
Platelets	$\geq 100 \times 10^9$/L
Bilirubin	≤ ULN
AST/ALT	≤ 1.5 x ULN
Alkaline Phosphatase	≤ 2.5 x ULN

Dose modifications

Nintedanib doses should be reduced in 50mg BD increments. If a patient does not tolerate a dose of 100mg BD, nintedanib should be permanently discontinued.

- **Haematological toxicity**

If neutrophils <1.5 x 10^9/L and/or platelets <100 x 10^9/L delay 1 week or until recovery.

If febrile neutropenia or neutrophils < 0.5 x 10^9/L for more than 1 week reduce docetaxel dose to 60mg/m^2 for all subsequent cycles. Reduce nintedanib dose in 50mg BD increments.

If platelets <25 x 10^9/L consider dose reduction to 60mg/m^2 after recovery (discuss with consultant). Reduce nintedanib dose in 50mg BD increments.

Nintedanib monotherapy phase:
If neutrophils <1.0 x 10^9/L and/or platelets <50 x 10^9/L interrupt treatment until recovery and then continue with reduced nintedanib dose.

- **Renal impairment**

There is no data available on the use of docetaxel in severe renal impairment. No modifications required.

Nintedanib has not been studied in severe renal impairment (CrCl < 30mL/min) – use with caution, discuss with consultant.

- **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 (x ULN)		**Bilirubin** (x ULN)		**Alkaline phosphatase** (x ULN)	**Nintedanib dose**
≤ 2.5	and	≤ 1.5	and	< 2.0	100%
> 2.5 (or > 5 irrespective of bilirubin)	and	> 1.5			Withhold until AST/ALT ≤ 2.5 x ULN and bilirubin ≤ x ULN. Reduce dose by 50mg BD increments If a 2nd dose reduction is considered necessary reduce by a further 50mg BD increment
> 3.0	and	> 2			Discontinue - unless an alternative cause is established.

If AST/ALT > 3 x ULN and bilirubin > 2 x ULN treatment with nintedanib should be discontinued (unless an alternative cause is established).

- **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	
Other	Grade 3-4	Discontinue or discuss with consultant.	Withhold until ≤ grade 1 Resume with 50mg BD dose reduction.

Venous thromboembolism: patients should be closely monitored and nintedanib discontinued if venous thrombotic event occurs.

Impaired wound healing: nintedanib may impair would healing. Nintedanib must only be initiated at least 4 weeks after surgery.

GI perforation: nintedanib should be discontinued in patients who develop GI perforation.

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 Johns Wort): may decrease exposure to nintedanib.

Additional comments

Nintedanib should be supplied as the brand Vargatef ®.

References

- National Institute for Health and Clinical Excellence. TA 347 accessed 29 June 2016 via www.nice.org.uk
- Summary of Product Characteristics Docetaxel (Sanofi Aventis) accessed 29 June 2016 via www.medicines.org.uk
- Summary of Product Characteristics Nintedanib (Boheringer Ingelheim) accessed 29 June 2016 via www.medicines.org.uk
- Reck. M, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small cell lung cancer (LUME-LUNG 1): a phase 3, double-blind, randomised controlled trial. (2014) The Lancet. Volume 15, No. 2, p143–155.

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