DOCETAXEL +/- NINTEDANIB

Docetaxel is an option for patients with locally advanced or metastatic NSCLC which has relapsed after previous chemotherapy (NICE approved 2005)
May be used in the above setting, in combination with nintedanib, if locally advanced or metastatic **adenocarcinoma** NSCLC (NICE approved 2015)

Drug / Dosage:	Docetaxel	75mg/m^2	IV	Day 1
	plus, for adenocarcinoma NSCLC only;			
	Nintedanib	200mg	PO	twice daily on Day 2 to Day 21 (do not take on the same day as docetaxel)

Other Drugs: Docetaxel pre-medication (to prevent hypersensitivity reactions and fluid retention):
Dexamethasone 8mg po bd for 3 days, commencing the morning of the day prior to docetaxel

Primary G-CSF prophylaxis s/c once daily for 5 days, starting on Day 3

Administration: Docetaxel in 250ml 0.9% sodium chloride over 1 hour
Nintedanib available as 100mg and 150mg capsules, to be swallowed whole with water, with or after food.
N.B. Nintedanib is contra-indicated in patients allergic to peanut or soya.

Frequency: 3 weekly cycle for 4 – 6 cycles of docetaxel, according to response
CT scan after cycle 2
Nintedanib to continue after docetaxel course completed, *only if the patient has completed at least 4 cycles of docetaxel,* for as long as clinical benefit is observed or until unacceptable toxicity occurs.

Main Toxicities: hypersensitivity to docetaxel (infusion-related & ↑ risk with 1st/ 2nd treatment); myelosuppression (higher frequency than docetaxel alone); fluid retention; cutaneous reactions and nail changes; alopecia; peripheral neurotoxicity; stomatitis; diarrhoea; ovarian failure/infertility

common nintedanib side-effects: diarrhoea; raised LFTs; nausea

Anti-emetics: docetaxel - moderately emetogenic nintedanib - mildly emetogenic

Extravasation: docetaxel is a non-vesicant

Regular Investigations:	FBC	Day 1
	LFTs	Day 1
	U&Es	Day 1
	CT scan	after cycle 2

Comments: Ensure patients receiving nintedanib have a supply of loperamide.

If the patient has not taken the oral dexamethasone pre-med for any reason, intravenous dexamethasone is not recommended and can only be substituted if prescribed by a Consultant.

Reason for Update: removal of restriction to 2nd line setting only; merged Docetaxel protocol with Docetaxel + nintedanib protocol	Approved by Consultant: Dt A Mehta
Version: 3	Approved by Lead Chemotherapy Nurse: S Wills-Percy
Supersedes: Version 2	Date: 7.9.17
Prepared by: S Taylor	Checked by: C Tucker

Offer scalp cooling.

Nintedanib should only be initiated at least 4 weeks after major surgery.
Nintedanib should be permanently discontinued in patients who develop gastrointestinal perforation.

Dose Modifications

Haematological Toxicity:	Neutrophils 1.0 – 1.49 x 10^9/l or Platelets 50 - 99 x10^9/l	Delay docetaxel for 1 week and repeat FBC. Consultant decision as to whether to interrupt nintedanib therapy.
	Neutrophils < 1.0 x 10^9/l or Platelets < 50 x10^9/l	Delay both docetaxel and nintedanib for 1 week, and then repeat FBC.

In the event of febrile neutropenia or neutrophils < 0.5 x 10^9/l for more than 1 week, give docetaxel 60mg/m^2 for all further cycles, and see table below for nintedanib advice.
If platelets < 25 x 10^9/l, consider docetaxel dose reduction to 60mg/m^2 after recovery - discuss with Consultant - and see table below for nintedanib advice.
If the patient continues to experience these side effects at the lower docetaxel dose, docetaxel should be discontinued.

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

Adverse reaction	Nintedanib dose adjustment
Diarrhoea ≥ grade 2 for more than 7 consecutive days despite anti-diarrhoeal treatment **or** Diarrhoea ≥ grade 3 despite anti-diarrhoeal treatment	Interrupt treatment with nintedanib until recovery to grade 1 or baseline. Then reduce nintedanib dose from 200mg bd to 150mg bd. If a 2nd dose reduction is considered necessary, reduce from 150mg bd to 100mg bd.
Vomiting ≥ grade 2 ***and/or*** Nausea ≥ grade 3 despite anti-emetic treatment	
Other non-haematological or haematological adverse reaction of ≥ grade 3	

Non- Haematological Toxicities:	Grade 3 cutaneous reactions:	once patient recovered, reduce docetaxel dose to 60mg/m^2. If symptoms return, stop docetaxel.
	Grade 2 neuropathy:	once patient recovered reduce docetaxel dose to 60mg/m^2. If symptoms return, stop docetaxel.
	Grade 3 or 4 neuropathy:	discontinue docetaxel permanently.

Any other Grade 3 / 4 toxicities
thought to be docetaxel-related: discontinue docetaxel after discussion with Consultant

Hepatic Impairment:

Bilirubin > 22 μmol/l or ALT/AST > 3.5 x ULN with ALP > 6 x ULN	Docetaxel not recommended - docetaxel should only be administered with consultant approval

Nintedanib is predominantly eliminated via biliary/faecal excretion.
No adjustment of the start dose is needed for patients with mild hepatic impairment (Child Pugh A).
Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with nintedanib is not recommended, due to lack of data in this patient group.

Hepatic Toxicity: Recommended dose adjustments for nintedanib in case of AST and/or ALT and bilirubin elevations after treatment started:

AST / ALT and bilirubin elevations	Nintedanib dose adjustment
AST and/or ALT increased to > 2.5 x ULN in conjunction with total bilirubin increased to ≥ 1.5 x ULN **or** AST and/or ALT increased to > 5 x ULN	Interrupt treatment with nintedanib until recovery of ALT/AST to ≤ 2.5 x ULN in conjunction with bilirubin to normal. Then reduce the dose from 200mg bd to 150mg bd. If a 2nd dose reduction is considered necessary, reduce from 150mg bd to 100mg bd.
AST and/or ALT increased to > 3 x ULN in conjunction with bilirubin ≥ 2 x ULN and ALP < 2 x ULN	Unless there is an alternative cause established, nintedanib should be permanently discontinued

Renal Impairment: Adjustment of the nintedanib start 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 CrCl < 30 ml/min.

References:
Shepherd, FA et al, JCO, 2000; 18 (10): 2095 – 2103
Fosella, FV et al, JCO, 2000; 18: 2354 – 2362
Reck, M et al; Lancet 2014; 15 (2): 143 – 155