Indication	Locally advanced, metastatic or locally recurrent non-small-cell lung cancer of adenocarcinoma histology that has progressed after first-line chemotherapy.
Treatment Intent	Palliative
Frequency and number of cycles	Combination treatment repeated every 21 days for a minimum of 4 cycles, then nintedanib monotherapy repeated every 28 days Until disease progression or unacceptable toxicity
Monitoring parameters pre-treatment	• Use with caution in patients who may develop QTc prolongation. • Monitor FBC, LFTs and U&Es prior to day 1 of each cycle • If neuts <1.5 or platelets <100 then discuss with consultant • **Hepatic Impairment:** Consider dose reduction of docetaxel in hepatic impairment. If bilirubin >22µmol/L / >ULN +/or ALT/AST >3.5ULN with ALP >6xULN docetaxel not recommended. Treatment of patients with Nintedanib that have moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment is not recommended. If AST/ALT increases to >3 x ULN in conjunction with an increase in bilirubin to ≥2 x ULN and ALKP <2 x ULN then interrupt nintedanib and consider discontinuation if no other cause. • **Renal Impairment:** No dose adjustment of nintedanib is necessary for mild to moderate renal impairment. No information is available where CrCl< 30ml/min. No dose adjustment of docetaxel required in renal impairment. • **Dose adjustment of docetaxel:** One dose reduction of docetaxel to 60mg/m^2 may be considered based on toxicity • **Dose adjustment of nintedanib:** As initial measure for the management of adverse reactions (see Tables 1 and 2 below) 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). On resuming treatment **t**he dose may be reduced to 150mg bd in a first step and then to 100mg bd if needed**.** Only 2 dose reductions are allowed and no dose escalations. • If the start of a new treatment cycle is delayed for more than 14 days the patient may be discontinued at the discretion of the consultant. • **Drug & food interactions:** Co-administration with strong P-gp inducers (e.g rifampicin, carbamazepine, phenytoin, St John's Wort) may decrease exposure to nintedanib. Strong P-gp inhibitors (e.g ketoconazole, erythromycin) may increase exposure to nintedanib, monitor closely. Nintedanib is contra-indicated in patients allergic to peanut or soya. Patients taking concomitant anticoagulation, such as warfarin should be monitored regularly for changes in prothrombin time, international normalized

	ratio (INR), and clinical bleeding episodes. • Nintedanib may impair wound healing. Do not give if patient has undergone major surgery within the previous 28 days. Treatment should be stopped prior to elective surgery. Treatment should therefore only be initiated based on clinical judgement of adequate wound healing. **Ensure Dexamethasone pre-med is prescribed & dispensed to the patient at pre-assessment clinic.**
Reference(s)	SPC accessed on line 15/11/17 KMCC prescribing proformas LUN-029 C1-4v2 and LUN-029 C5 onwards v1

Table 1 : Recommended dose adjustments for Nintedanib (Vargatef®) 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	

Table 2: Recommended dose adjustments for Nintedanib (Vargatef®) 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 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

Combination treatment repeated every 21 days for a minimum of 4 cycles

Day	Drug	Dose	Route	Infusion Time	Administration Details
Day 1	Metoclopramide	20mg	IV		
	Dexamethasone pre-medication must be taken prior to docetaxel administration				
	DOCETAXEL	(75mg/m²)	IV	1 hr	Sodium Chloride 0.9% 250ml
TTO MEDICATION	Drug	Dose	Route	Directions	
Days 2 – 21 NOT TO BE TAKEN ON THE DAY OF DOCETAXEL ADMINISTRATION.	**NINTEDANIB**	200mg	po	**bd swallowed whole, with a full glass of water, with or after food for 20 days.** The first dose of each cycle should be taken on the morning of day 2. The dosing interval is 12 hours and at the same times each day. If a dose is missed, administration should resume at the next scheduled time at the recommended dose. The maximum daily dose of 400mg should not be exceeded. **(available as 100mg and 150mg capsules)**	
	Dexamethasone	8mg	po	bd for 3 days starting the day prior to next cycle of chemotherapy	
	Metoclopramide	10mg	po	up to 3 times a day for 3 days, then 10mg up to 3 times a day as required (max. 30mg per day including 20mg pre-chemo dose). Do not take for more than 5 days continuously.	
	Loperamide	2mg	po	take two initially, then one after each loose stool up to a maximum of 16mg daily To be dispensed if required	
	Filgrastim	300 micrograms **or consider dose of 480 micrograms if patient > 80kg**	sub cutaneous	od starting on day 2 for 7 days	

Monotherapy repeated every 28 days starting after a minimum of 4 cycles of nintedanib and docetaxel

TTO MEDICATION	Drug	Dose	Route	Directions
Days 1 – 28 .	**NINTEDANIB**	200mg	po	**bd swallowed whole, with a full glass of water, with or after food for 28 days.** The first dose of each cycle should be taken on the morning of day 1. The dosing interval is 12 hours and at the same time each day. If a dose is missed, administration should resume at the next scheduled time at the recommended dose. The maximum daily dose of 400mg should not be exceeded. **(available as 100mg and 150mg capsules)** **Supply 30 days treatment**
	Metoclopramide	10mg	po	up to 3 times a day for 3 days, then 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	Loperamide	2mg	po	take two initially, then one after each loose stool up to a maximum of 16mg daily To be dispensed if required