Boehringer Ingelheim

EU Risk Management Plan for Vargatef (nintedanib)

RMP version to be assessed as part of this application:

RMP version number:	10.2
Data lock point for this RMP:	31 May 2021
Date of final sign off:	31 May 2022
Rationale for submitting an updated RMP:	Revision of safety concerns in line with GPV Module V, Rev 2
Summary of significant changes in this RMP:	Removal of the following safety concerns (Modules SIV, SVII, SVIII; Parts III, V, VI; Appendix 8):

Important identified risks

- Diarrhoea
- Neutropenia
- Sepsis
- Venous thromboembolism
- Perforation (gastrointestinal and non-gastrointestinal)
- Bleeding
- Hypertension
- Myocardial infarction

Important potential risks

- Arterial thromboembolism excluding myocardial infarction
- Treatment in pregnant women and teratogenicity
- Cardiac failure

Missing information

- Treatment of breastfeeding women
- Treatment of patients with moderate or severe hepatic impairment (Child Pugh B/C)

	– Treatment of patients with healing wounds – Treatment of subpopulations with co-morbid CNS conditions such as dementia, depression, brain metastasis, or with comorbid conditions such as arthritis and osteoporosis Further changes: – The important potential risk 'cardiac failure' will continue to be presented in the following PBRER (update of respective text in Module SVII) – References to SmPC sections corrected (Part V) – Appendix 7: inclusion of all search strategies of current and demoted safety concerns
Other RMP versions under evaluation:	
RMP version number:	Not applicable
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QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.
[redacted]	

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PART I PRODUCT OVERVIEW

PI.Table 1 Product Overview

Active substance (INN or common name)	Nintedanib (nintedanib)
Pharmacotherapeutic group (ATC code)	Other protein kinase inhibitors (L01EX09)
Marketing Authorisation Holder	Boehringer Ingelheim International GmbH
Medicinal product to which this RMP refers	Vargatef
Invented name in the EEA	Vargatef
Marketing authorisation procedure	Centralised
Brief description of the product	*Chemical class* Indolinone derivative
	Summary of mode of action Vargatef is a small molecule tyrosine kinase inhibitor and angiogenesis inhibitor, simultaneously targeting the VEGFR-1, -2, and -3, PDGFR α and ß, and FGFR-1, -2, and -3. All these targets have been shown to promote angiogenesis, a process that enables vascularisation of the tumour and contributes to metastasis.
	Important information about its composition None
Hyperlink to the Product Information	Product information (eCTD module 1.3.1)
Indications in the EEA	*Current* Vargatef is indicated in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first line chemotherapy.
	Proposed None

[redacted]

Dosages in the EEA	*Current* 200 mg twice daily with dose reductions where applicable (orally)
	Proposed None
Pharmaceutical form and strengths	*Current* Soft gelatine capsules, 100 mg and 150 mg
	Proposed None
Is/will the product be subject to additional monitoring in the EU?	No

ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical
EEA	European Economic Area
EU	European Union
FGFR	Fibroblast growth factor receptor
INN	International Non-proprietary Name
NSCLC	Non-small cell lung cancer
PDGFR	Platelet derived growth factor receptor
RMP	Risk Management Plan
VEGFR	Vascular endothelial growth factor receptor

PART II SAFETY SPECIFICATION

MODULE SI EPIDEMIOLOGY OF THE INDICATIONS AND TARGET POPULATIONS

SI.1 NSCLC

The population intended for treatment with Vargatef comprises patients with locally advanced or metastatic NSCLC of adenocarcinomatous histology progressing after first-line chemotherapy. 'Advanced' NSCLC is defined as locally advanced (stage IIIB) or metastatic (stage IV) NSCLC (according to the American Joint Committee on Cancers criteria), or earlier stage disease at diagnosis that has progressed to or relapsed with regional or distant metastases.

Worldwide, NSCLC accounts for a large percentage of all diagnosed lung cancers: from approximately 80% to 90% in Europe and 86.8% in the US [R11-4179, R11-4138]. NSCLC is a heterogeneous group of tumours that are histopathologically subclassified as SCC, adenocarcinoma, large cell undifferentiated carcinoma, and other rarer histology types.

Changes in the histological distribution of NSCLC subtypes over time have been reported. In Europe, among lung cancers diagnosed from 1978 through 1997, there was a general trend of a decline in the incidence of squamous cell cancer among men and an increase in adenocarcinoma among men and women over time [R13-3271 , R09-5782]. Studies from Sweden and the Netherlands covering periods up to 2000 and 2009 have reported changes in the histological distribution of lung cancer cases, with decreases in the proportion of squamous cell cancer cases and increases in adenocarcinoma across genders [R13-3278, R13-3274]. This shift in the histological distribution of lung cancers may be explained by changes in smoking behaviour and the introduction of filter cigarettes in the 1960s [R13-3273].

In Europe, approximately 70% of cases of NSCLC present with stage IIIB or IV at diagnosis, and a similar percentage (62%) is reported for the US [R11-4179, R11-4138]. Patients with advanced NSCLC have a poor prognosis, with median survival times of only 8 to 11 months in randomised clinical trials with platinum-based chemotherapy [R11-4181].

Over the last 10 years, more than 9000 patients have been included worldwide in phase III NSCLC studies performed in the second-line setting. A few studies could demonstrate a prolongation of PFS, (e.g. TAX 317 [R07-1209]; BR.21 [R05-0867, R12-2607]; ZODIAC [R10-5700]; VITAL, BETA [R12-4054]; TAILOR [R13-1419, R13-1420]). Only the BR.21 trial (erlotinib vs. placebo [R05-0867]) and the TAX 317 trial (docetaxel vs. best supportive care [R07-1209]) could demonstrate an OS improvement in unselected NSCLC patients; BR.21 also demonstrated an OS benefit in adenocarcinoma patients.

Pooled analyses of data from phase III trials completed in 2006 or later, of subsequent second- or third-line chemotherapy in patients with advanced NSCLC (N = 6473 patients), reported an average median survival of 8.9 months [R13-3569]. In randomised clinical trials of patients with advanced NSCLC treated with a single agent dual VEGFR and EGFR TK inhibitor (VEGFR-EGFR, vandetanib) or with an EGFR inhibitor (erlotinib) after failure of at

least one prior cytotoxic chemotherapy regimen, the overall median survival ranged from 7 to 8 months [R13-3568, R12-3820]. In trials of a dual VEGFR-EGFR inhibitor (vandetanib) administered in combination with either pemetrexed or docetaxel as second-line treatment of NSCLC (including SCC and adenocarcinoma), median survivals of about 10 months have been reported [R11-2792, R10-5700]. In contrast, in an international trial in which poor-risk patients with NSCLC (i.e. those with progression during or immediately after first-line platinum-based therapy) were randomised to treatment with erlotinib or chemotherapy (docetaxel or pemetrexed at investigator's discretion) for second-line therapy, the median survival in both arms was only approximately 5 months [R12-3824]. This suggests an important effect of patient selection factors (such as response, and duration of response, to first-line therapy) on survival duration after second-line therapy.

SI.1.1 Incidence

In Europe, direct incidence estimates of advanced NSCLC of all histologies are not consistently available at national or regional levels. However, the incidence of all newly diagnosed primary lung cancer cases by tumour stage and histological subtype in Europe in 2012 provides an upper boundary for the incidence of advanced NSCLC. Estimates of the overall and histology-specific incidence of NSCLC in the European region are summarised in the following section.

Incidence of NSCLC

The incidence of NSCLC by histological subtype in European countries during the period from 1993 through 1997 from Janssen-Heijnen and Coebergh [R09-5782] is summarised in SI.Table 1. From this study, the age-standardised incidence rates of NSCLC in Europe for the most recent period available (1993 through 1997) were estimated using 2 different methods:

- By summing-up the rates for the NSCLC histological subtypes (squamous cell cancer, adenocarcinoma, and large cell cancer), which could be considered to depict a conservative lower boundary of the incidence of NSCLC in the registries.
- By subtracting the rate of SCLC from the reported rate of 'all' lung cancer types.

Application of the first, more conservative approach resulted in age-standardised incidence rates of NSCLC ranging from 25.3 to 77.0 per 100 000 males and from 4.5 to 24.8 per 100 000 females. The second approach resulted in age-standardised incidence rates ranging from 26.6 to 93.0 per 100 000 males and from 6.1 to 33.1 per 100 000 females. Since NSCLC comprises the majority of primary lung cancer (among cases classified as either NSCLC or SCLC), it is likely that the true incidence of NSCLC is closer to the upper boundary (i.e. the second estimate) than to the conservative lower boundary (i.e. the first estimate).

SI.Table 1 Age-standardised incidence rates per 100 000 for NSCLC by histological subtype and gender in Europe, 1993 to 1997

	Estimated NSCLC incidence ASR (European standard)[1]							
	All types		Adenocarcinoma		SCC		Large cell carcinoma	
EU country	Male	Female	Male	Female	Male	Female	Male	Female
Denmark[2]	72.0	41.0	17.0	15.0	20.0	6.6	5.0	2.9
England[3]	80.0	34.0	8.5	5.1	23.0	6.7	3.7	1.7
Estonia[3]	104.0	13.0	6.5	2.0	35.0	2.0	3.7	0.7
Finland[3]	66.0	13.0	10.0	4.1	20.0	2.0	0	0
France (north)[4]	66.0	10.0	18.0	4.2	37.0	2.2	7.5	1.0
Germany (Saarland)[3,4]	83.0	17.0	16.0	5.1	27.0	3.1	3.3	0.9
Iceland	52.0	40.0	15.0	15.0	14.0	6.0	5.3	3.8
Italy (Varese)[3, 4]	101.0	14.0	23.0	5.3	32.0	2.0	2.9	0.6
Netherlands (Eindhoven)[4]	109.0	20.0	17.0	5.5	45.0	4.5	15.0	3.2
Norway	51.0	22.0	12.0	7.0	15.0	3.4	3.3	1.4
Poland (Krakow)[3, 4]	101.0	25.0	7.5	2.7	44.0	7.1	1.3	0.8
Scotland[3]	108.0	52.0	14.0	9.0	31.0	10.0	6.6	3.1
Slovenia	94.0	14.0	16.0	5.6	36.0	2.2	9.9	1.3
Spain (Navarra)[4]	71.0	6.3	9.9	3.1	32.0	0.7	6.1	0.7
Sweden	32.0	18.0	8.3	6.8	11.0	3.3	6.0	3.2
Switzerland[4]	73.0	23.0	18.0	9.1	26.0	4.0	4.6	1.4

[1] ASR: age-standardised rate per 100 000 standardised to the European standard population.
[2] 1993 to 1996.
[3] High proportion of tumours 'not otherwise specified'.
[4] <20% coverage of country.
Data source: [R09-5782]

In 2012, there were 309 589 newly diagnosed lung cancer (all types) cases in the 27 EU countries. Of these, 68.3% (211 401 cases) were reported in males, and 31.7% (98 188 cases) were reported in females [R13-3276]. An approximate estimate of the number of newly diagnosed NSCLC patients presenting with advanced stage at diagnosis could be derived from these figures by assuming that 80% to 90% of all lung cancer cases are NSCLC, and 70% of these are diagnosed with stage IIIB–IV. An approximation of the number of patients diagnosed with advanced NSCLC of the adenocarcinoma subtype can be derived by assuming that 36% of all advanced NSCLC patients have adenocarcinoma, based on the

proportion of tumours diagnosed from 2004 through 2009 in the Netherlands and reported by van der Drift et al. [R13-3274]. Based on these calculations, in the 27 EU countries in 2012, about 56% to 63% (i.e. 173 400 to 195 000) of all new lung cancer cases were diagnosed with advanced stage NSCLC. Of these patients, about 62 400 to 70 200 were diagnosed with adenocarcinoma.

SI.1.2 Prevalence

No direct estimates of the total prevalence of advanced NSCLC or advanced NSCLC by histological subtypes are available for any European country. However, the 1-year, 3-year, and 5-year partial prevalence estimates – the estimated proportion of patients alive at a given date who had been diagnosed at any time during the previous 1, 3, and 5 years, respectively – for all patients diagnosed with any lung cancer provide upper boundaries for the corresponding partial prevalences of advanced NSCLC.

In 2012, the estimated 5-year partial prevalence of lung cancer in the 27 EU member states was 79.1 per 100 000 people (ranging from 34.1 to 114.9) [R13-3276]. SI.Table 2 presents the 1, 3, and 5-year partial prevalence proportions per 100 000 people for European countries in 2012.

SI.Table 2 Lung cancer prevalence in European countries in 2012: 1-year, 3-year, and 5-year partial prevalence counts and proportions per 100 000 individuals

	1-Year		3-Year		5-Year	
Country	Count	Proportion	Count	Proportion	Count	Proportion
Europe	184 031	29.4	356 583	57.0	442 811	70.8
European Union (EU-27)	138 061	32.5	269 333	63.4	336 144	79.1
Albania	519	20.5	1 023	40.4	1 283	50.7
Austria	2 094	29.0	4 258	59.0	5 461	75.6
Belarus	1 816	22.5	3 408	42.2	4 135	51.2
Belgium	3 851	43.0	7 954	88.8	10 301	114.9
Bosnia and Herzegovina	835	26.1	1 650	51.5	2 068	64.6
Bulgaria	1 823	28.7	3 420	53.8	4 146	65.2
Croatia	1 463	39.1	2 878	77.0	3 598	96.2
Cyprus	133	14.2	255	27.3	319	34.1
Czech Republic	3 135	34.6	5 723	63.2	6 806	75.1
Denmark	1 598	34.7	2 959	64.3	3 606	78.4
Estonia	278	24.7	520	46.1	626	55.5
Finland	1 191	26.4	2 215	49.1	2 670	59.2
France	21 862	42.2	43 733	84.4	54 812	105.8
FYR Macedonia	631	36.8	1 260	73.4	1 589	92.6
Germany	21 666	30.5	43 554	61.3	55 783	78.5
Greece	3 274	33.6	6 400	65.8	7 974	81.9
Hungary	4 246	50.0	8 014	94.4	9 750	114.9
Iceland	68	26.1	137	52.6	175	67.2
Ireland	722	20.1	1 387	38.6	1 737	48.3
Italy	17 866	34.1	35 159	67.2	43 960	84.0
Latvia	525	27.4	979	51.1	1 185	61.8
Lithuania	688	24.5	1 281	45.7	1 550	55.2
Luxembourg	133	30.8	269	62.3	346	80.1
Malta	68	19.0	128	35.7	158	44.0
Moldova	570	19.4	1 077	36.7	1 312	44.7

Note: Prevalence proportions are per 100 000 population.
Data source: EUCAN website [R13-3276].

SI.Table 3 Lung cancer prevalence in European countries in 2012: 1-year, 3-year, and 5-year partial prevalence counts and proportions per 100 000 individuals

	1-Year		3-Year		5-Year	
Country	Count	Proportion	Count	Proportion	Count	Proportion
Montenegro	176	34.3	346	67.5	431	84.0
Netherlands	5 694	41.2	11 439	82.8	14 544	105.3
Norway	1 119	27.7	2 149	53.2	2 676	66.2
Poland	11 610	35.5	21 944	67.2	26 806	82.1
Portugal	1 865	20.5	3 763	41.3	4 807	52.8
Romania	5 302	29.2	9 929	54.8	12 026	66.3
Russia	25 274	21.0	47 363	39.3	57 403	47.7
Serbia	3 675	45.2	7 241	89.0	9 038	111.1
Slovakia	1 156	24.8	2 151	46.2	2 588	55.5
Slovenia	573	32.7	1 089	62.1	1 341	76.5
Spain	11 551	29.1	22 532	56.9	28 148	71.0
Sweden	1 727	21.8	3 452	43.6	4 396	55.6
Switzerland	2 054	31.2	4 164	63.3	5 320	80.9
UK	13 430	25.9	24 826	47.8	30 298	58.4
Ukraine	7 770	20.2	14 554	37.9	17 639	45.9

Note: Prevalence proportions are per 100 000 population.
Data source: EUCAN website [R13-3276].

SI.1.3 Demographics of the population in the authorised indication – age, gender, and risk factors for the disease

Demographics

Studies in patients with NSCLC indicate that the majority of NSCLC patients diagnosed with advanced disease stage were male and either former or current smokers (SI.Table 4). The median age of these patients was 63 years, ranging from 32 to 85 years at diagnosis. Adenocarcinoma and SCC were the most commonly reported histologies in these studies. However, as the numbers of patients in each subgroup are small, these studies may not be representative of the NSCLC population as a whole.

SI.Table 4 Demographic and histological profile of advanced NSCLC patients from epidemiological studies

	Jacot, 2008[1] (N = 301) France, 2003-2006 [R08-5076]	Girard, 2009[2] (N = 173) France, 2000-2006 [R12-0055]	Blanco et al, 2008[3] (N = 294) Spain, 1997-2006 [R11-4128]
Gender, %			
Female	20	26	16
Male	80	74	84
Age, years	63 (StD 10)	NR	63 (range 33–85)
Smoking history, %			
Former smokers	92	42	NR
Current smokers	-	43	NR
Non-smokers	8	15	NR
COPD history, %			33
Histological subtype, %			
Adenocarcinoma	56	64	32
Bronchioalveolar adenocarcinoma	0	NR	NR
Small cell carcinoma	41	22	46
Large cell carcinoma	12	14	22
Other	1	NR	NR

[1] Patients with histologically confirmed but previously untreated NSCLC; 18% with stage IIIB and 48% with stage IV NSCLC.
[2] Patients who had received at least 3 lines of systemic antineoplastic treatment.
[3] All patients with stage IIIB or IV NSCLC.

Substantial decreases in the incidence of NSCLC among men and increases among women have been reported in European populations since the 1980s [R09-5782, R13-3274]. The decreases in men appear to be driven by decreases in SCC and SCLC. In women, the incidence of lung tumours of all histological subtypes increased; the rates increased from 4.9 to 9.5 per 100 000 for adenocarcinoma, from 3.8 to 5.0 per 100 000 for squamous cell cancer, and from 2.7 to 5.3 per 100 000 for large cell cancer [R13-3270].

Risk factors for NSCLC

Tobacco-induced carcinogenesis is the predominant risk factor for lung cancer [R09-5782]. Other risk factors include passive smoking, air pollution, occupational exposure to carcinogens, and a potential hereditary basis for a subgroup of lung cancer patients [R08-4446].

The role of oestrogens and oestrogen receptors in lung cancer susceptibility have been suggested as a possible explanation for the sex-dependent differences observed in the histological subtype distribution of NSCLC; women are more likely than men to be diagnosed with adenocarcinoma of the lung compared with SCC, and adenocarcinoma has been more frequently reported in never-smokers and in women [R13-3282, R13-3272]. The role of somatic mutations in lung cancer pathogenesis and the identification of other oncogenic alterations involved in the development of NSCLC have also been recent focal points of research [R08-2617, R13-3282].

SI.1.4 The main existing treatment options

In patients with locally advanced or metastatic disease without activating EGFR tumour mutations or ALK translocations, systemic chemotherapy is considered the therapeutic mainstay [R10-0093, R10-0094] and is usually a platinum combination of either cisplatin or carboplatin (for example, including paclitaxel, docetaxel, gemcitabine, bevacizumab, or pemetrexed) for the first-line treatment of most patients. For patients with adenocarcinoma NSCLC, also platinum doublet chemotherapy, e.g. carboplatin/paclitaxel with or without bevacizumab, gemcitabine/cisplatin, or pemetrexed/cisplatin is preferred [R13-0783, P14-05872]. Those patients who only have a stable disease as best response to the first-line therapy may get a maintenance treatment either as switch maintenance or as continuous maintenance treatment. For patients harbouring tumours with activating EGFR mutations or ALK translocations, the preferred option for primary treatment is targeted monotherapy, for example with an EGFR inhibitor such as erlotinib and gefitinib, or ALK inhibitor such as crizotinib. Bevacizumab, a monoclonal antibody against the VEGF, is sometimes used in combination with a platinum-based therapy for treatment of NSCLC. However, bevacizumab is not indicated for the use in patients with NSCLC of squamous histology [R04-4661].

Despite frequent responses to first-line treatment of advanced NSCLC, the tumour will eventually relapse (progress) in almost all patients. Currently, erlotinib, gefitinib, pemetrexed, and docetaxel are approved as monotherapy for the second-line treatment of locally advanced or metastatic NSCLC. Docetaxel is considered equivalent to pemetrexed with respect to efficacy and is registered for all histologies, whereas pemetrexed can only be used in patients with non-squamous tumor cell histology. Gefitinib is approved for the treatment of locally advanced or metastatic NSCLC with activating mutations of EGFR-TK across all lines of therapy.

Pemetrexed is approved as second-line treatment for NSCLC and is also used as first-line treatment (in combination with cisplatin) and as maintenance therapy in patients with advanced NSCLC who have not progressed after 4 cycles of platinum-based standard chemotherapy. Docetaxel is a commonly used second-line treatment in patients who progressed after first-line chemotherapy treatment, and in patients with NSCLC of squamous histology who progressed after other first-line therapies.

Despite the availability of second-line treatment options for patients with locally advanced or metastatic NSCLC, new treatment options are needed to further increase the time until tumour progression, ameliorate signs and symptoms of the disease, and prolong the overall

survival of patients with advanced NSCLC. Thus far, no further survival improvements have been achieved for advanced second-line NSCLC patients.

SI.1.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity

Trends of histology subtype in NSCLC

NSCLC is divided into three major histologic subtypes as SCC, AC, LCC. SCC was the most common type of lung cancer, but in recent years is ranking behind AC constituting approximately 50% of lung cancer [R12-2762, R14-1245, R14-1303]. Histology specific NSCLC data are scarce, therefore histology data derived from total lung cancer are provided.

Temporal analysis of lung cancer (from 1975 to 2002) in 12 populations (11 countries in Europe, North America and Oceania) indicate that age standardised (world) incidence rates of AC in total lung range from 10 to 60 per 100 000 people in men and from 3 to 50 per 100 000 people in women [R14-1245]. Trend analysis shows that adenocarcinoma has risen constantly in the majority of these populations. In men AC surpassed SCC, formerly the most frequent histology subtype, in the mid-1980s.

Mortality rates for all primary lung cancer

No direct data on the mortality of advanced NSCLC are available at the national level for European countries. Country-specific, age-standardised, mortality estimates of lung cancer for all EU countries by gender in the year 2008 are summarised in SI.Table 5.

Since 5-year survival rates for NSCLC are higher than those for SCLC [R11-4179], the proportion of total lung cancer mortality that is due to NSCLC is likely to be somewhat lower than the proportion of total lung cancer incidence that is due to NSCLC.

SI.Table 5 Estimated lung cancer mortality age-standardised rates and number of deaths among European countries by gender, 2008

	Age-standardised mortality rate (world standard)[1]		Number of deaths	
European country/region	Male	Female	Male	Female
European Union (EU-27)	40.5	12.8	182 932	71 099
Austria	32.4	13.6	2 389	1 241
Belgium	50.4	11.8	5190	1341
Bulgaria	45.5	7.4	2877	601
Cyprus	21.3	5.2	144	41
Czech Republic	46.4	13.2	3928	1483
Denmark	40.5	30.0	2097	1790
Estonia	55.6	8.0	559	145
Finland	26.9	9.4	1386	612
France (metropolitan)	38.9	10.8	20 909	6884
Germany	34.7	12.8	29 274	12 521
Greece	47.8	8.5	5321	1081
Hungary	73.5	26.2	5597	2733
Ireland	30.7	18.0	954	670
Italy	38.7	9.0	25 286	7303
Latvia	53.3	5.3	846	161
Lithuania	49.8	5.7	1156	228
Luxembourg	36.5	13.3	143	60
Malta	31.1	5.7	108	21
Poland	61.8	15.5	16 880	5643
Portugal	28.5	5.4	2666	653
Romania	48.8	8.8	7581	1 846
Slovakia	43.4	7.7	1529	396
Slovenia	47.4	13.2	803	293
Spain	44.6	6.2	17 605	2722
Sweden	19.4	16.3	1876	1750
The Netherlands	42.1	22.1	6387	3531

Note: Lung cancer diagnosis coded according to the International Classification of Diseases, 10th Revision (ICD-10), codes C33–C34.
[1] Age-standardised mortality rate per 100 000 people, standardised to the world standard population.
Data source: Estimates of cancer incidence and mortality in Europe in 2008 [R11-4189]

Survival data for NSCLC

Data from the Eindhoven Cancer Registry in the Netherlands indicates that during the period 1970 to 1997, patients with NSCLC had better survival than patients with SCLC. For the most recent period analysed (1993 to 1997), the 1-year relative survival for NSCLC was 47% for patients aged <70 years and 36% for patients aged ≥70 years. Three-year survival was 25% and 20%, and 5-year survival was 19% and 16%, respectively [R09-5782].

Survival rates vary with the stage of the cancer at diagnosis. Relative 1-year and 5-year survival rates for patients diagnosed with localised (stages I or II) NSCLC in the south-eastern part of the Netherlands were 74% and 40%, respectively, whereas these rates for patients with non-localised NSCLC were 27% and 6%, respectively [R09-5782].

SI.1.6 Important co-morbidities

The following section provides a summary of the main co-morbidities in patients with advanced NSCLC. Where few or no epidemiological studies in the target population have been carried out, the section also includes clinical trial results of placebo or chemotherapy control arms. Where information is available, frequently co-prescribed medicinal products are discussed in relation to each co-morbidity.

Lung cancer is associated with advanced age and smoking. These factors are both strongly associated with COPD and cardiovascular disease, which are the two most frequent co-morbidities of lung cancer patients. Due to the relatively short survival of patients with advanced NSCLC, incidence and mortality of other co-morbidities in patients with NSCLC is low, except where treatment has caused AEs.

Elderly patients with advanced NSCLC not only have a higher proportion of comorbidities as compared to the younger patients, but also the frequency of multiple concomitant comorbidities (e.g. COPD, cardiovascular disease and diabetes mellitus) is higher in the elderly population [R11-4128]. Beside these comorbidities, data from observational studies and clinical trials related to the CNS disorders and oestoarticular comorbidities and brain metastases are provided in this section.

SI.1.6.1 Important co-morbidities in the target population

SI.1.6.1.1 Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease has been reported as one of the most common co-morbidities in patients with lung cancer, with some studies suggesting that a prior history of COPD itself confers up to a 6-fold increase in the risk of lung cancer [R11-4188], after adjusting for smoking [R09-0577, R11-4188]. In addition, some researchers have suggested that COPD is a predictor of increased risk of death in patients with lung cancer, with a clear relationship found between the severity of COPD and survival in lung cancer patients [R11-4170].

The prevalence of COPD in lung cancer patients (all types) around the time of cancer diagnosis has been reported to range from 22% to 63% [R11-4177, R11-4169], while the prevalence of COPD in patients with advanced NSCLC ranges from 18% to 48% [R11-4128, R11-4177, R11-4188, R11-4183]. Some studies evaluating the prevalence of COPD in patients with NSCLC by disease stage indicate that the prevalence is higher in patients with early NSCLC stages [R11-4177, R11-4170, R11-4164]. A higher prevalence has also been reported among males and among older patients [R11-4177, R11-4149]. In a large population-based registry of 4072 patients with NSCLC (58% with advanced disease), the prevalence of COPD increased with increasing age, from 15% in patients aged <60 years to 27% among patients aged ≥80 years. Chronic obstructive pulmonary disease was the second most common condition in patients with NSCLC aged 70 years or older, occurring in 29% of males and 20% of females [R11-4149].

A study of 1155 patients with primary lung cancer (NSCLC or SCLC) diagnosed between 1995 and 1998 suggested that among patients with unstaged or stage III–IV disease, patients with COPD had a higher mortality than those without COPD (adjusted HR 1.21; 95% CI 1.01, 1.44) [R11-4183]. Other studies, however, have reported that co-morbidity had no influence on survival, nor did the presence of a specific co-morbidity or combination of diseases [R11-4154, R11-4149, R11-4170].

SI.1.6.1.2 Cardiovascular diseases (heart disease, hypertension) and cerebrovascular disease

Data on the incidence of cardiovascular disease and cerebrovascular disease among NSCLC patients in Europe are not widely available, and so the following section presents data from the US.

In a US population-based cohort study of 1371 patients with newly diagnosed stage IIIB–IV NSCLC (2003 to 2005), 58% of patients received mainly a platinum-based chemotherapy (cisplatin, carboplatin; 76% of patients with chemotherapy). Of these, less than 1% developed congestive heart failure, 1% experienced MI, and 1% experienced cardiac arrest [R11-4155]. A US study of 34 209 patients with NSCLC (without previous diagnoses of cardiac disease) from the Surveillance, Epidemiology and End Results-Medicare database (1991 to 2002, follow-up 2005) found that new cardiac dysfunction was associated with chemotherapy alone, radiotherapy alone, or combined chemo-radiation treatment, and that cardiac risk was higher for patients with left-sided lung tumours [R12-0059]. In 499 patients who underwent resection for NSCLC in Charlottesville, Virginia, in 2002 to 2006, the incidence of MI was 0.8%, of stroke was 1.4%, and of cardiac arrest was 1.2% [R11-4166].

Because of the strong common risk factors of smoking and advanced age, patients with NSCLC are expected to have a worse cardiovascular risk profile than the general population. Cardiovascular co-morbidity is present in an estimated 19% to 36% of patients with advanced NSCLC, depending on the definitions of cardiovascular co-morbidity used [R11-4128, R11-4177, R11-4154, R08-5076]. Studies have generally used a broad definition, including the presence of congestive heart failure and a history of ischaemic heart disease, hypertension, or cerebrovascular disease. SI.Table 6 displays the prevalence of overall cardiovascular disease and specific cardiovascular clinical diagnoses from selected, published, observational studies.

SI.Table 6 Prevalence of cardiovascular disease and specific cardiovascular clinical diagnoses in patients with advanced NSCLC

	Eindhoven Cancer Registry, The Netherlands[1]	OncoLR Health Network, France[2,3]	Germany[4]	Patras, Greece[5]
Study population	N = 1380 NSCLC 100% stage III–IV	N = 301[2], N = 735[3] NSCLC 80%-84% stage III–IV	N = 66 Inoperable NSCLC 88% stage III	N = 331 NSCLC 25.4% stage III; 2.1% stage IV
Time period	1993–1995	2003–2006[2] 1998–2003[3]	1998–2005	1999–2005
Prevalence of co-morbidities				
Cardiovascular disease	20%	36%	—	
Cerebrovascular disease	3%	—	—	1.2%
IHD/CAD	—	—	26%	9.7%
LVEF <50%	—	—	31%	
Hypertension	10%	—	—	22.4%

Data source: 1: [R11-4177], 2: [R08-5076], 3: [R11-4154], 4: [R11-4165], 5: [R11-4178]

There is evidence that cardiovascular disease prevalence increases with increasing age of patients at lung cancer diagnosis. In a Dutch study, prevalence ranged from 11% in patients aged <60 years to 30% among those aged ≥70 years [R11-4149]. In a Spanish study of patients with stage IIIB or IV NSCLC, 15% of those aged <70 years, and 31% of those ≥70 years had prevalent cardiovascular disease at diagnosis [R11-4128]. In a Dutch study of patients with advance NSCLC, hypertension was present in 10% of patients overall, increasing from 8% in patients aged <60 years, to 14% to 15% in patients aged 60 to 79 years, and 11% in those aged ≥80 years [R11-4177].

SI.1.6.1.3 Diabetes mellitus

The prevalence of diabetes mellitus has been evaluated in various subgroups of untreated patients with NSCLC. Direct comparison among studies is difficult due to a lack of clarity or uniformity about how the presence of diabetes was defined (e.g. whether treatment was required or not) and because of different NSCLC stage and age distributions among the study populations. In some studies described here, the prevalence of diabetes appeared to be higher than the 10% expected in the general population of adults in Europe [R10-0752]. Reported prevalences of diabetes are summarised in SI.Table 7.

SI.Table 7 Prevalence of diabetes as reported in observational studies of NSCLC patients

Publication	Country	Period	Diagnosis; stage; histology[1]	Diabetes prevalence
[R11-4160]	Ireland	2004–2006	NSCLC	6%
[R11-4156]	Netherlands	1998–2001	NSCLC; 6 of 433 patients stage IIIB–IV NSCLC	6%
[R11-4128]	Spain	1997–2006	NSCLC; stage IIIB or IV; 46% SCC, 32% adenocarcinoma	11%
[R11-4154]	France	1998–2003	NSCLC; 205 of 735 patients (28%) stage I–IIIA, 521 (71%) stage IIIB or IV; 37% SCC, 47% adenocarcinoma	9%
[R08-5076]	France	2003–2006	NSCLC; 66% advanced stage; 41% SCC, 45% adenocarcinoma	12%
[R11-4177]	Netherlands	1993–1995	Non-localised NSCLC	6%
[R11-4149]	Netherlands	1994–1999	NSCLC, 58% non-localised	8%
[R11-4171]	France	1999–2005	NSCLC; staged N2 after surgery	17%
[R11-4178]	Greece	1999–2005	NSCLC; 25% stage III, 2% stage IV; 54% SCC, 35% adenocarcinoma	6%
[R11-4165]	Germany	1998–2005	NSCLC; 70% stage IIIB; 62% SCC, 26% adenocarcinoma	20%
[R11-4187]	UK	2001–2006	NSCLC; stages I to IIIA	11%
[R11-4166]	US	2002–2006	NSCLC; 64% stage I, 19% stage II, 15% stage III, 2% stage IV	13%
[R11-4185]	US	2000–2005	NSCLC; 82% stage I, 13% stage II, 5% stage III	18%

[1] Where available.

SI.1.6.1.4 Anaemia

Anaemia is common in lung cancer, either due to paraneoplastic effects or related to treatment [R12-2774].

Clinical trials conducted in NSCLC patients receiving second-line therapy may give only limited insight into the incidence of anaemia in the target population, but are presented here as no observational studies were found.

In a predominantly European study of patients with locally advanced or metastatic NSCLC, in which patients were first treated with platinum-based therapies [R08-5614], the incidence of anaemia in 715 patients on docetaxel (after a maximum of 2 platinum-based regimens) was 12% at any CTCAE grade and 2% at CTCAE grades 3 or 4. In the multinational, randomised, Phase III trial ZODIAC in patients with locally advanced or metastatic (stage IIIB to IV) NSCLC after progression following first-line chemotherapy [R10-5700], the incidence of anaemia in the placebo plus docetaxel group was 15% at all CTCAE grades, and 4% at CTCAE grades 3 and higher.

The prevalence of anaemia has been evaluated in various subgroups of untreated patients with NSCLC. Anaemia prevalence in these studies ranged from 7% to 14.7% [R11-4154, R08-5076, R11-4157]. However, direct comparison between studies is not feasible due to the varying definitions of anaemia and different stage distributions of NSCLC among the study populations. The differences among estimates of prevalence of anaemia may reflect a difference in the definitions of anaemia, or the variation among studies in age distributions or co-morbid conditions. There is some evidence for higher prevalence of anaemia in older patients [R11-4159] and those with more advanced lung cancer [R11-4182].

SI.1.6.1.5 Hepatic impairment

The incidence rate of hepatic impairment among patients with NSCLC depends on the NSCLC stage at the time of the assessment of the hepatic function and type of cancer-related therapy. Elevated liver transaminases could also result from toxicity to chemotherapy, e.g. elevations of AST, ALT, alkaline phosphatase, or bilirubin. National or regional statistics on risk of hepatic impairment were not available for the target population.

Any degree of liver enzyme elevation has been reported to occur in as many as 35% of patients with advanced NSCLC receiving chemotherapy (and about 5% of those not receiving chemotherapy). Severe elevations (grade 3 or 4) have been reported in up to approximately 3% of patients receiving chemotherapy, and up to about 1% of those not receiving chemotherapy (SI.Table 8).

SI.Table 8 Incidence of liver enzyme elevations associated with advanced NSCLC

Dataset	Study patients	Previous therapy	Current therapy and number of patients	Event	Incidence of liver enzyme elevations[1]	
					All grades	Grade 3-4
Europe and other regions, RCTs in NSCLC, 2005–2008 [R09-6468]	Stage IIIB–IV NSCLC	First-line therapy	Second line: Placebo, N = 222	Elevation of:		
				ALT	4%	0%
				AST	4%	0%
			Pemetrexed, N = 441	ALT	10%	<1%
				AST	8%	0%
France, GFPC 05–06 Study, 2006–2009 [R12-0235]	Progressive, advanced NSCLC	Cisplatin-based treatment	Second line: Pemetrexed 500 mg/m^2, N = 75	Hepatic toxicity	Not reported	1%
			Docetaxel 75 mg/m^2, N = 75	Hepatic toxicity	Not reported	3%

[1] Grades are classified by the NCI-CTC.

One of 265 patients (0.4%) receiving pemetrexed for NSCLC died of hepatic failure as stated in the ALIMTA (pemetrexed) briefing document [P12-00757]. No data on fatal cases of

hepatic impairment resulting from toxicity of chemotherapy from observational studies have been found.

SI.1.6.1.6 ILD

The term ILD refers to diffuse parenchymal lung disease and is used to describe a heterogeneous group of lung disorders that affect the alveoli [R12-0049, R11-0683, R09-6523]. The most common of these disorders is idiopathic interstitial pneumonia, recently classified into 7 types by the American Thoracic Society [R09-5338]. Other terms for interstitial pneumonias that have been used in different countries are idiopathic pulmonary fibrosis and cryptogenic fibrosing alveolitis [R09-5338].

The association between ILD and lung cancer is well documented [R12-0046, R09-6523]. The co-occurrence of ILD and lung cancer has been found at the time of ILD diagnosis and at autopsy, and lung cancer has been identified in prospective follow-up of ILD patients initially free of lung cancer [R12-0048, R11-0683, R09-6523].

It is difficult to establish the prevalence and incidence of ILD in the general population and in lung cancer patients largely because of non-standard definitions of ILD, common risk factors such as smoking or occupational exposures, and the difficulty in making a definitive diagnosis [R11-0684]. In addition, in patients with advanced NSCLC, often other co-morbidities such as pneumonia or tumour progression with similar symptoms to ILD (dyspnoea, cough, and fever) might be present, and physicians may be reluctant to employ invasive diagnostic procedures such as lung biopsy to make a definitive histological diagnosis [R11-0684, R12-0049].

Estimates of the incidence of ILD in the general population range from 7.6 to 31 per 100 000 person-years [R12-0229, R12-0358, R03-2075]. The wide range of estimates may be partly due to real differences, completeness of case ascertainment, or differences in diagnosis definitions.

The incidence proportion of ILD in placebo arms of clinical trials of NSCLC patients has been reported at <1% to 3% in trials of European, North American, or multi-national populations (SI.Table 9). The incidence was somewhat higher in Asian clinical trial populations, ranging from 1.4% to 4%. The incidence of ILD was slightly higher with erlotinib or gefitinib incidence compared with patients not receiving erlotinib or gefitinib, particularly in Asian populations (SI.Table 10).

SI.Table 9 Incidence of ILD in clinical trials of NSCLC patients

Study setting	Stage and previous treatments	Treatment	Incidence of ILD
Data 2000–2001; 5 European countries and US; Phase III RCT; INTACT-1 [R07-2993]	Advanced NSCLC No previous chemotherapy	6 cycles of cisplatin + gemcitabine	
		+ placebo, N = 355	<1% (N = 3)
		+ gefitinib 500 mg/d, N= 358	<1% (N = 3)
		+ gefitinib 250 mg/d, N= 362	<1% (N = 1)
Data 2000–2001; 80% of patients were in US, others in 5 European countries; Phase III RCT; INTACT-2 [R07-2994]	Advanced NSCLC No previous chemotherapy	Paclitaxel/carboplatin + placebo, N = 341	0.9% (N = 3)
		+ gefitinib 500 mg/d, N = 342	2.0% (N = 7)
		+ gefitinib 250 mg/d, N = 342	1.5% (N = 5)
Data 2001–2002; 27 countries in Europe and other regions; Phase III RCT; TALENT trial in NSCLC [R07-2759]	Advanced NSCLC No previous chemotherapy	Cisplatin and gemcitabine	
		+ placebo, N = 579	N = 2 (not serious)
		+ erlotinib N = 580	N = 1 (death)
Data 2004–2006; Netherlands, UK, Canada, and the US; Phase II RCT; INSTEP trial [R12-0056]	Advanced NSCLC No previous chemotherapy	Best supportive care	
		+ placebo, N = 101	<1% (N = 1, grade 2 pneumonitis)
		+ gefitinib, N = 100	0% (N = 0)
Data 2004–2006; Europe (24 countries) and other regions; Phase III RCT; INTEREST trial [R08-5614]	Advanced NSCLC, progressed or recurred after previous platinum-based chemotherapy	Docetaxel, N = 715	1% (N = 8)
		Gefitinib, N = 729	1% (N = 10)

[redacted] one or more of its affiliated companies

SI.Table 9 (cont'd) Incidence of ILD in clinical trials of NSCLC patients

Study setting	Stage and previous treatments	Treatment	Incidence of ILD
Data cut-off 2004; 28 countries in Europe and other regions; Phase III RCT; ISEL trial [R07-1199]	Advanced NSCLC, refractory after chemotherapy (with initial radiotherapy or surgery)	Best supportive care + placebo N = 562 + gefitinib N = 1129	 1% (4% in Asian subpopulation) 1% (3% in Asian subpopulation)
Data 2001–2003; multinational; Phase III RCT; BR.21 trial, [R05-0867]	Advanced NSCLC After 1st or 2nd line chemotherapy	Placebo, N = 243 Erlotinib, N = 485	Pulmonary fibrosis 3% Pneumonitis or pulmonary infiltrates 3% (any grade) Pulmonary fibrosis 3% Pneumonitis or pulmonary infiltrates 3% (any grade)
Data 2003–2006; Japan; Phase III RCT [R09-0052]	Advanced NSCLC After 1st or 2nd line chemotherapy	Docetaxel, N = 239 Gefitinib, N = 244	3% (N = 7) 6% (N = 14)
Data 2006–2007; East Asia; Phase III RCT; IPASS-Trial [R12-0040]	Advanced NSCLC No previous chemotherapy	Carboplatin + paclitaxel, N = 589 Gefitinib, N = 607	1.4% (N = 8), 1 death 2.6% (N = 16), 3 deaths
Data 2006–2009; Japan; Phase III Trial [R10-0799]	Advanced NSCLC with EGFR mutation No previous chemotherapy	Cisplatin + docetaxel, N = 88 Gefitinib N = 87	0% (N = 0) 2.5% (N = 2) 1 death

SI.Table 10 Incidence of ILD in patients with advanced NSCLC treated with gefitinib or erlotinib: results from published post-marketing surveillance and observational studies

Study	Incidence of ILD[1] (95% CI)	Comments
Post-Marketing Surveillance		
POLARSTAR [R12-2825] N = 3488	Japan: 4.5%	Erlotinib
AstraZeneca Global Drug Safety Database [R06-1603][2] N = 185 000	Global: 0.8% In Japan: 1.6% Outside Japan: 0.3%	Gefitinib
AstraZeneca Global Drug Safety Database [R08-2310][3] N = 215 000	Global: 0.9% In Japan: 3.1% Outside Japan: 0.23% Asia outside Japan: 0.17%	Gefitinib
Expanded Access Programme		
Tsuboi et al. [R11-0683] US: N = 24 227 World other than US: N = 29 329	US: 0.40% Other than US: 0.29%	Gefitinib
Puijenbroek et al. [R12-0124] N = 513	0.4%	Gefitinib Belgium, Caucasian population
Tiseo et al. [R08-5240] N = 609	No events reported	Erlotinib Italy
Observational Studies		
West Japan Thoracic Oncology Group [R12-0045] N = 1976	n (95% CI) Overall: 3.5% (2.8, 4.5) Female non-smokers: 0.4% (0.0, 1.5) Male non-smokers: 1.8% (0.4, 5.3) Female smokers: 3.3% (0.9, 8.2) Male smokers: 6.6% (5.1, 8.4)	Gefitinib Risk factors for ILD: male sex, smoking history, prior interstitial pneumonia

[1] Incidence proportion (number of cases/size of treated population).

[2] As of 01 Sep 2004.

[3] As of January 2006.

SI.Table 10 (cont'd) Incidence of ILD in patients with advanced NSCLC treated with gefitinib or erlotinib: results from published post-marketing surveillance and observational studies

Study	Incidence of ILD[1] (95% CI)	Comments
Observational Studies cont'd		
Japan Thoracic Radiology Group [R11-0686] N = 3166	Overall: 2.8 per 1000 person-weeks[4] Gefitinib sub-cohort: 4.5 per 1000 person-weeks[4] Chemotherapy sub-cohort: 1.7 per 1000 person-weeks[4] Cumulative incidence at 84 days: 4.0% gefitinib, 2.1% chemotherapy	Gefitinib Incidence of ILD highest in the first 4 weeks after starting gefitinib treatment
National Cancer Centre, Japan [R12-0115] N = 112	5.4%	Gefitinib Incidence higher among patients with pulmonary fibrosis (33%) than without (2%)
Okayama Lung Cancer Study Group (West Japan) [R12-0064] N = 330	4.5%	Gefitinib Risk factors: pre-existing pulmonary fibrosis, prior thoracic irradiation
Japan Multi-national Trial Organisation [R12-0113] N = 526	3.2% (95% CI 1.9, 5.1)	Gefitinib

[1] Incidence proportion (number of cases/size of treated population).
[2] As of 01 Sep 2004.
[3] As of January 2006.
[4] 12-week incidence rate.

Drug-associated ILD, a form of hypersensitivity pneumonitis, is a condition that can range in severity from asymptomatic pulmonary interstitial infiltrates to severe dyspnoea and life-threatening acute respiratory distress syndrome. Radiation therapy can cause a similar although usually localised condition (radiation pneumonitis). Radiation-associated pulmonary fibrosis and radiation pneumonitis occur in an estimated 5% to 15% of lung cancer patients [R12-0041, R12-0042]. In a review article, ILD was reported to have occurred in 1% to 50% of patients in clinical trials of chemotherapy and chemo-radiotherapy for lung cancer, with chemotherapy agents including gemcitabine, paclitaxel, vinorelbine, and docetaxel [R11-0683].

Predictors of mortality identified in an observational study of ILD in lung cancer include age >65 years, positive smoking history, pre-existing ILD, and radiological evidence of existing lung damage [R11-0686]. A prospective study of NSCLC patients in Japan reported that 27.9% of chemotherapy-treated ILD cases and 31.6% of gefitinib-treated ILD cases were fatal [R11-0686].

SI.1.6.1.7 Renal disease

There is limited information on renal disease in patients with advanced NSCLC. In 2 small studies from Spain and Germany of selected populations of patients with advanced NSCLC with multiple co-morbidities, the prevalence of renal impairment or insufficiency at baseline was 17% [R11-4162] and 20% [R11-4165]. In an analysis of 301 consecutive patients with NSCLC from the OncoLR database, the reported prevalence of renal insufficiency was 17% [R08-5076]. In the US Henry Ford Health System cohort of lung cancer patients, the prevalence of renal disease in unstaged and stage III–IV disease was 6.2% [R11-4182]. In this study, renal disease was an independent predictor of reduced survival in early stage NSCLC (HR 2.74; 95% CI 1.47, 5.13) and late stage NSCLC (HR 1.42; 95% CI 1.05, 1.93).

SI.1.6.1.8 Dementia

All cancers

Dementia is a term that encompasses several symptoms caused by a number of different disorders that affect the brain. Dementia can alter intellectual function, communication, activities of daily life, social interactions, problem solving, emotional status, memory, and behaviour [R14-1359].

Cognitive function tests are used to assess memory, language, and other mental functioning. There are many interview and self-report test instruments addressing various aspects of cognitive function. Prevalence estimates for dementia can vary depending on the specific instrument used. Various neurological and medical tests are also used in diagnosing dementia [R14-1359].

Studies have found both positive and negative associations of cancer overall with dementia [R14-1482, R14-1346, R14-1372]. Cognitive dysfunction has been reported to be associated with cancer chemotherapy in several studies; patients with breast cancer have been studied most frequently [R14-1346]. However, in 1998-2003 in the large, prospective, population-based Cognition Substudy of the Cardiovascular Health Study (N=3020 aged >65), prevalent cancer of any type at baseline was associated with decreased risk of subsequent Alzheimer disease and vascular dementia (HR: 0.72, 95% CI: 0.52-0.99) [R14-1372]. A follow-up study in the Framingham Heart Disease Study cohort of 1278 subjects >65 from enrolled in 1986-1990 without a history of cancer or dementia at baseline, and followed for a mean of 10 years, showed that those who later developed cancer had a lower risk of developing dementia (HR: 0.67, 95% CI: 0.47-0.97)[R14-1482].

Lung cancer

Ascertaining dementia in patients with lung cancer poses several particular challenges. Lung cancer is known to metastasise to the brain more frequently than several other major cancers [R14-1476]. The cognitive deficits that have been observed in patients with lung cancer are complex and may have multiple causes, such as effects of the neoplasm (e.g., brain metastases, paraneoplastic syndromes), impact of cranial radiation therapy, effects of

chemotherapy, effects of opioid pain medication, comorbid conditions, nutritional status, emotional functioning, activity level, and social support [R14-1369, R14-1346].

In the US, the American Cancer Society, the Centers for Disease Control and Prevention, the National Cancer Institute, and the North American Association of Central Cancer Registries collaborate on annual reports to the nation on the status of cancer [R14-1480]. The 2013 report contains a special section on comorbidities in patients with selected cancers. Using Medicare claims data from 1992 through 2005, and focusing on patients aged 66 years or older (166 053 lung cancers; 1 056 534 total cancers), the estimated prevalence of dementia in patients with lung cancer overall was 1.5% in 1999-2005 This estimate is slightly lower than the 1.8% derived from a large sample of the general population that was matched by calendar year, age, and sex [R14-1480].

A historical cohort study of 1155 patients with lung cancer was carried out in Michigan, using data from the Henry Ford Hospital System and the Josephine Ford Cancer Center, to evaluate the impact of comorbidity and other factors on lung cancer survival. Patients had been diagnosed with primary bronchogenic lung cancer in 1995 through 1998. The overall prevalence of dementia was 2.0% in this cohort, including 0.3% in stage I-II and 2.6% in stage III-IV and unstaged patients. In both early and late stages, dementia was associated with increased risk of death [R14-1482].

The US Medicare programme conducts surveys of beneficiaries at regular intervals, using a nationally representative sample of the Medicare population, which is mostly persons aged 65 years or older [R14-1364]. The beneficiary survey [R14-1355] includes three patient self-report questionnaires: the Katz activities of daily living, the Rosow-Breslau instrumental activities of daily living, and the Nagi physical performance questionnaire [R14-1354]. In 863 patients with lung cancer, the point prevalence of dementia was 4.1% in the year 1991-2009 [R14-1364].

Non–SCLC

There is some evidence that cognitive decline occurs in patients with NSCLC even if radiation to the brain is not part of the treatment plan. In 2002-2007, the US Radiation Therapy Oncology Group trial 0214 studied cognitive impact of prophylactic cranial irradiation compared with observation in NSCLC [R14-1316]. Patients with stage III A/B NSCLC without disease progression after completing therapy were randomly assigned to prophylactic cranial irradiation or to observation, and multiple cognitive assessment instruments were used to determine whether the radiation treatment affected cognitive function. In those without cranial irradiation, 18% had decreased cognitive function from the baseline assessment to the 6-month follow-up evaluation, using the EORTC QLQ-C30, a self-report instrument [R14-1359]. In the same time period (2002-2007) with the same instrument, 35% of those given cranial irradiation had cognitive decline [R14-1316]. On the Mini-Mental State Examination,cognitive deterioration occurred by 6 months in 25% of the observation-only patients and 28% of the patients who had cranial irradiation [R14-1316]. On the Hopkins Verbal Learning Test recall component [R14-1361], at 6 months, recall had

deteriorated in 5% of the observed patients and 19% of the cranial irradiation patients [R14-1316].

In the Netherlands, in 2003-2006, 181 patients aged 70 years or older with stage III-IV NSCLC were randomised to carboplatin and gemcitabine or to carboplatin and paclitaxel [R14-1477]. Assessment of neuropsychiatric toxicity was based on a composite of cognitive disturbances, confusion, delusions, depressed levels of consciousness, hallucinations and insomnia, memory loss, mood alteration-anxiety, agitations, depression, euphoria, and behaviour. In both trial arms, approximately 25% of patients experienced neuropsychiatric toxicity of CTC grade 2 or higher.

Overall, the estimated prevalence of dementia in any lung cancer (1.5% to 4.1%) and in NSCLC (5% to 35%) varies with patient age, tumour stage, type of treatment for cancer, the study setting (clinical, cognitive interview, database, patient self-report), and the specific cognitive domains that are evaluated. Prevalence estimates of dementia specific to NSCLC, adenocarcinoma type, were not found.

SI.1.6.1.9 Depression

All cancers

A meta-analysis of studies published through 2011 on prevalence of depression in cancer patients analysed 211 studies [R14-1349]. Mean prevalence varied from 8% to 24% with the method of ascertainment of depression and cut-off points for categorising numerical scores. SI.Table 10 below shows the prevalence estimates and instruments used to measure them.

SI.Table 11 Survey and Interview Instruments

Name of Survey or Interview Instrument	Acronym and Source	Score Categories and Prevalence of Depression (%)
Hospital Anxiety and Depression Scale—depression subscale	HADS-D [R02-0127]	Score ≥8: 17% Score ≥11: 8%
Center for Epidemiologic Studies	CESD [R14-1398]	Score ≥16: 24%
Semi-structured diagnostic interviews	[R14-1349]	13%

In an Italian study of 363 cancer inpatients aged >65 in 1994-1996, of whom 54 had NSCLC, 39.9% overall had one or more symptoms of depression [R14-1322] on the Geriatric Depression Scale [R14-1360].

The US National Institutes of Health commissioned an evidence review of literature from 1966-2001 on the prevalence of depression in patients with cancer. Major depression and depressive symptoms were estimated to affect 10% to 25% of cancer patients, including all types of cancer [R14-1321].

Distress in cancer patients is a multifactorial condition ranging from normal feelings of vulnerability, sadness, and fears to more disabling problems including depression, anxiety, panic, social isolation, and existential and spiritual crisis [R14-1532]. Therefore, the prevalence of distress may overestimate the prevalence of depression in this population. In the US in a study of 4496 patients with cancer, the Brief Symptom Inventory [R10-0407] was used to assess prevalence of psychological distress. Including all types of cancer in 1987-1993, the prevalence of distress was 35.1% [R14-1313]. In France, 561 consecutive cancer outpatients in two cancer centres were evaluated for psychological distress using three different instruments. Prevalence of psychological distress was 38% [R14-1358]. In the French study population, 31% were receiving professional psychological help, 21% were taking psychotropic drugs, and 8% were using a combination of medical and psychological therapies.

Lung cancer

Using studies with diagnostic interviews, the meta-analysis by Krebber and colleagues [R14-1349] reported a pooled mean prevalence of 3% for depression in respiratory cancer. With self-report instruments, the prevalence was 21%.

In the US Cancer Care Outcomes Research and Surveillance study, 1043 patients with lung cancer (stages I-III) in 2003-2005 were surveyed about symptoms of depression, interest in help for mood, and psychosocial service use [R14-1318]. Symptoms of depression were found in 18.2%.

Adult outpatients treated in 1984-2000 at a tertiary cancer centre in the US were evaluated for symptoms of anxiety and depression with the Brief Symptom Inventory [R14-1546]. In 965 outpatients with lung cancer, 14.4% had a mix of symptoms of anxiety and depression; 7.9% had only symptoms of depression. Among the patients with lung cancer, 66.3% had no symptoms of anxiety or depression.

In the US study of psychological distress in 1987-1993, the prevalence of distress in 629 patients with lung cancer was 43.4% [R14-1313]. This figure was the highest prevalence of distress among the 14 cancer sites studied; brain tumours had the next highest prevalence (42.7%). Prevalence of distress in all the other sites ranged from 29.6% to 37.8%.

NSCLC

In 2008-2010, in a phase 2 trial in Italy, 45 patients with stage IIIB-IV NSCLC (62% adenocarcinomas) received cisplatin, oral etoposide, and bevacizumab [R14-1483]. Using the Hospital Anxiety and Depression Scale, 12 (26.7%) developed cognitive disturbances or depression of grade 2 or higher during the 5 treatment cycles. Three of these patients (6.7% of the total trial subjects) had grade 3-4 depression.

In the UK in the early 1990s, 987 patients with lung cancer in palliative treatment trials were assessed for depression using the Hospital Anxiety and Depression Scale [R14-1366]. Among 461 patients with NSCLC, 9% were probable cases with depression and 13% were

borderline. In patients with SCLC, 25% were probably depressed, and 18% were borderline depressed [R14-1366].

In Norway's Aust-Agder and Vest-Agder counties, in 2002 through 2005, a prospective study of all patients diagnosed with primary lung cancer used the HAD scale to screen for depression [R14-1324]. The screening occurred within a few weeks after the initial diagnosis of lung cancer. Of the total 479 patients studied, 334 (69.7%) had NSCLC. On the HAD scale, 12% of the patients with NSCLC met criteria for clinical depression. In the 102 patients with SCLC, 22% had clinical depression.

Using data from 1995 through 2010 in the US Veterans Affairs-Northwest health network database, treatment and outcomes of depression were studied in a cohort of 3869 patients with primary lung cancer [R14-1317]. Nearly all subjects were men (97%). The prevalence of depression in the cohort was 14%. Of the total cohort, 85% had NSCLC, 26% in stage I, 8% in stage II, 24% in stage III, 36% in stage IV, and 5% with unknown stage. Of 3282 patients with NSCLC, 13.7% were diagnosed as depressed. In 551 patients with SCLC, the prevalence of depression was 17.2%

In 2003-2008, a US study of 980 outpatients with NSCLC at a major cancer centre used symptom data from patient self-reported questionnaires to assess the need for supportive care [R14-1323]. Severe depressed mood was reported by 13% of the study patients. Among all the patients with NSCLC, only 26% were studied during early stages of the disease. Prevalence of severe depressed mood was higher in Hispanic patients (26%) than in Caucasians (14%) or African Americans (11%).

A small US study in 2006-2010 explored a possible relation of tumour EGFR genotype and depression in 53 patients with stage IV NSCLC [R14-1327]. All the patients were newly diagnosed with NSCLC and completed self-reported questionnaires that included items about depression. The percentage of patients who met screening criteria for depression was 0% in the EGFR mutation–positive group and 29.3% in the patients with wild type EGFR.

151 ambulatory patients, no more than 8 weeks after diagnosis of metastatic NSCLC in 2006-2009, participated in a randomised controlled trial of standard oncology care plus early palliative care versus standard oncology care alone [R14-1328]. Baseline prevalence of major depression syndrome was 14%, using the PHQ-9.

It is well established that prevalence estimates for depression are highly sensitive to the particular survey or interview instrument used to screen patients [R14-1334]. In primary lung cancer of any type, studies reported prevalence of depression between 3% and 18.2%. In patients with NSCLC, excluding studies of composites of cognitive disturbances and depression and of probable or borderline depression, most of the prevalence estimates ranged between 12% and 14%.

SI.1.6.1.10 Brain metastases

Lung Cancer

A review article from 2011 reported that brain metastases develop in 17% to 65% of patients with any type of primary lung cancer [R14-1368]. US cancer registry data from Michigan showed that for patients diagnosed in 1973-2001, the cumulative incidence of brain metastases was 19.9% in primary lung cancer of any histology [R14-1476].

Non–SCLC

Approximately 7% to 10% of patients with NSCLC (of any histology) are found to have brain metastases at the time of diagnosis; 20% to 40% develop brain metastases later in the course of NSCLC [R14-1434]. Review articles state that brain metastases are more common in SCLC than in NSCLC, and more common in adenocarcinomas than in SCCs, but numeric details were not reported [R14-1368, P14-05027].

In 2008-2011, in a single-centre clinical trial conducted in France, 15.8% of chemotherapy-naive patients with stage IV NSCLC had brain metastases [R14-1351]. In a tertiary care centre in Canada in 2005 through 2007, all patients (n=878) newly diagnosed with NSCLC were retrospectively studied, and those who developed brain metastases were identified [R14-1434]. Of the total 878 patients, 91 (10.4%) developed brain metastases. Of these 91 patients, 45 (49%) had brain metastases at the time of initial NSCLC diagnosis; 46 (51%) had brain metastases detected later. Of the 91 patients, 47 (52%) had non–small cell adenocarcinoma of the lung. In another study in 1986-1998, cumulative incidence of brain metastases at 5 years was lower in patients aged 70 years or older (8.1%) than in those aged 50-69 (15.6%) or aged 0-49 (17.6%) [R14-1320].

NSCLC (AC)

In the Southwest Oncology Group in the US, a retrospective database study examined the incidence of brain metastases among patients with stage IIIA or IIIB NSCLC [R14-1367]. The trials that were reviewed had been conducted between 1995-2003. A total of 418 patients were followed for at least 4 years. Of 156 patients with NSCLC (AC type), 36 (23.1%) developed metastases of the brain only or of brain plus other sites. The corresponding percentages were 9.8% (14 of 143) for squamous cell histology, 17.3% for large cell NSCLC (13 of 75), and 18.2% for NSCLC not otherwise specified (8 of 44) [R14-1367]. Another US study, using data from Duke University Medical Center from 1995 through 2005, assessed the risk of brain metastases in early stage (I or II) NSCLC [R14-1365]. The overall cumulative incidence of brain metastases was much lower in this patient group (6.2%) than in other studies not restricted to early-stage NSCLC. Among the 975 total patients, the cumulative incidence of brain metastases was 6.6% in the adenocarcinoma subgroup and 5.2% in the squamous or adenosquamous cases [R14-1365].

In summary, primary lung cancers metastasise to the brain commonly. Brain metastases may be present in NSCLC at diagnosis, and 20% to 40% of patients with NSCLC ultimately develop brain metastases. In late-stage NSCLC (AC), the cumulative incidence of brain

metastases is approximately 23%; in earlier stages, the cumulative incidence is approximately 7%.

SI.1.6.1.11 Osteoporosis

All cancers

In a national sample of 12 480 elders (aged 65 or older) from the 2003 US Medicare Current Beneficiary Survey, osteoporosis was defined as reporting a recent history of hip fracture or that a physician described the patient as having soft or fragile bones [R14-1348].

The crude prevalence of osteoporosis among those with cancer was 24.3%, while in those without cancer it was 19.8% [R14-1348] Osteoporosis was negatively associated with prostate cancer but positively associated with cervical or uterine cancer, in accord with its established higher prevalence in women. After adjusting for sex, age, body mass index, race, geographic region, income, marital status, insurance status, and education, those with a history of cancer were more likely to experience osteoporosis (adjusted OR, 1.21; 95% CI, 1.06 to 1.38) than those without a history of cancer. In a study at several Italian centres of 363 consecutive elderly patients with a first cancer diagnosis between 1994 and 1996, 11% had osteoporosis [R14-1322]. Of the 363 patients with cancer, 54 (15%) had lung cancer.

Lung Cancer

Among a cohort of 1155 patients with lung cancer (all stages and histological types included) from the Henry Ford Health System in the US in 1995-1998, the prevalence of osteoporosis overall was 2.2%, and 2.0% among patients with stage III, IV, and unstaged disease [R11-4182].

In Non–SCLC: In 2005-2006, in a multicentre phase II trial of 56 chemotherapy-naive patients with stage IV NSCLC aged 70 years and older, 8.9% had osteoporosis [R14-1319]. This study included 17 patients (30.4%) with adenocarcinoma, 20 patients (35.7%) with SCC, 4 patients (7.1%) with large cell, 1 patient (1.8%) with bronchoalveolar, and 14 (25.0%) with unspecified histology [R14-1319].

SI.1.6.1.12 Arthritis

All cancers

In a national sample of 12 480 elders (aged 65 years or older) from the 2003 US Medicare Current Beneficiary Survey, 18.8% were identified as having cancer. Of those with cancer, 62.2% had arthritis, compared with 57.6% of patients without cancer [R14-1348].

In 1994 through 1996, of 363 consecutive elderly Italian patients with a first cancer diagnosis, 30.9% had arthritis (i.e., osteoarthritis, rheumatoid arthritis, or unspecified arthritis). Of the 363 patients, 54 (15%) had lung cancer [R14-1322].

Comorbidities were assessed among 27 506 newly diagnosed patients treated at one of 8 US cancer centres between 1998 and 2003. Of 13 029 patients aged 65 and older (47%), slightly more than 2% of cancer patients had rheumatologic diseases including various forms of arthritis [R14-1326]. A total of 3793 (13.8% of all cancer diagnoses) were lung cancer.

Non–SCLC

A series of 100 patients with NSCLC who underwent staging between 2004 and 2006 were studied in Ireland; half of the NSCLC cases were adenocarcinomas. Of the 100 patients with NSCLC, 14% had rheumatoid arthritis [R11-4160].

In a study of 237 elderly patients (of which 228 were aged 75 years or older) with stage III NSCLC in the population-based Netherlands Cancer Registry, diagnosed between 2002 and 2008, 0.9% had rheumatoid arthritis at the time of cancer diagnosis [R14-1315]. Of the 237 patients with NSCLC, 16.8% had adenocarcinoma.

SI.1.6.1.13 Treatment for common comorbid conditions in NSCLC

Common comorbid conditions in NSCLC are COPD, dyspnoea and cardiovascular diseases.

Drugs used for COPD and dyspnoea are listed in SI.Table 12. [P13-02399].Cardiovascular drugs likely to be used by patients with NSCLC are also listed [P11-15312, P11-09558].

SI.Table 12 Treatment for common comorbid conditions in NSCLC

Condition	Medications
Dyspnoea	• Bronchodilators
COPD	• Inhaled anticholinergics (ipratropium, tiotropium) • Inhaled beta-agonists (salmeterol, formoterol, indacaterol) • Inhaled corticosteroids • Phosphodiesterase-4 inhibitors
Cardiovascular conditions: • Angina • Hypertension • Peripheral vascular disease • Heart failure • Post-stroke • Dyslipidaemia • Acute MI	• Aldosterone antagonists • Antiarrhythmic agents • Anticoagulants (aspirin, fondaparinux, heparin, bivalirudin) • Antihypertensives (beta-blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, loop, thiazide and other calcium channel blockers) • Digoxin and other inotropic agents • Glyceryl trinitrate, nitroglycerin • Nitroglycerin • Platelet aggregation inhibitors (clopidogrel, prasugrel, ticagrelor, glycoprotein PIIb/IIIa inhibitors) • Statins (HMG CoA-reductase inhibitors), bile acid sequestrants, nicotinic acid, cholesterol absorption inhibitors

SI.1.6.2 Concomitant medications in the target population

Patients with NSCLC may take a variety of medications other than those used specifically to treat the cancer. Some of these concomitant medications are given for comorbidities that result from NSCLC treatment by chemotherapy or radiotherapy, while others are used to treat comorbid conditions not directly related to NSCLC, even though some may be frequently associated with NSCLC (Section SI.1.6). For example, NSCLC patients frequently have co-morbidities such as cardiovascular disease and hypertension, associated with advanced age and a history of smoking; concomitant antihypertensive therapy is therefore common. Patients are often in pain, and are prone to gastric conditions that often require treatment with non-steroidal analgesics, frequently co-administered with medications for e.g. peptic ulcers and gastro-oesophageal reflux disease.

No data on the prevalence of concomitant medication use in patients with NSCLC are available from observational studies. However, information on types of medications used for chemotherapy side effects and for important comorbid conditions associated with NSCLC is available and summarised in sections SI.1.6.2.1 and SI.1.6.1.13.

In the Phase III trials in Vargatef in NSCLC (trials 1199.13 and 1199.14), the majority of patients were on concomitant therapies when they were randomised into the study. The most common classes of medication were analgesics, including anti-inflammatory agents and antirheumatic products, and corticosteroids. Other previous and concomitant medications included angiotensin-converting-enzyme inhibitors and beta blocking agents; hypertension was the most common concurrent baseline condition. Other common concomitant medications included drugs for peptic ulcer and gastro-oesophageal reflux disease, which were often co-administered with non-steroidal anti-inflammatory drugs [U13-1505-01].

SI.1.6.2.1 Medications to treat side effects of cancer therapy

Nausea and vomiting are commonly associated with chemotherapy and radiotherapy.

Several types of medications can be used to prevent or manage nausea and vomiting, which can occur during or after administration of chemotherapy [P13-02404]. Palonosetron and other 5-HT3 receptor antagonists can help prevent nausea and vomiting [R13-0736].

Chemotherapy-induced diarrhoea is a common problem for patients with advanced cancer. GI effects are frequently reported with VEGFR TK inhibitor therapy. Some non-pharmacological treatments can be helpful (e.g. avoiding some foods, oral rehydration). Fatigue is a common side effect of chemotherapy, radiation therapy, or selected biologic response modifiers [R13-0733]. The aetiology of treatment-related fatigue is variable, and managing it may involve a variety of methods. Non-pharmacological approaches are also recommended [R13-0855].

In a Korean observational study including medical records of 113 lung cancer patients who visited an emergency room from 2010 to 2011, gastrointestinal events with the frequency of 12.9% were the third common chief complaints in patients with cancer-related issues. Of

9 gastrointestinal events related to cancer, nausea and vomiting were the most common events [R14-1352].

Pain can be a very burdensome symptom in lung cancer. Opioids are a mainstay of cancer pain management [P13-02602], but can lead to severe constipation that may require prescription drug treatment, or even surgery for bowel obstruction. Non-narcotic analgesics may also be useful [P13-02390]. For neuropathic pain in cancer, antidepressants or anticonvulsants may be helpful [P13-02602].

Constipation can be caused by several chemotherapy agents. For example, the anti-nausea drugs 5- HT3 antagonists increase the risk of constipation. Newer medications for constipation include lubiprostone, alvimopan, and methylnaltrexone [P13-02391].

Oral and GI mucositis occurs in approximately 10% of patients receiving chemotherapy [P13-03581]. A meta meta-analysis reviewing phase II and III clinical trials of different cancer types shows that 1.38% of lung cancer patients presented GI mucositis (95% CI: 1.30-1.99) [P13-03583].

Oral mucositis can be treated with palifermin which stimulates the growth of cells on the surface of the mouth [R13-0737]. Palifermin was approved in the US to reduce the risk and shorten the duration of severe mucositis in patients with cancer who receive high doses of chemotherapy and radiation therapy followed by stem cell rescue [R13-0739]. Although approved for use in patients who received bone marrow transplants for haematopoietic cancers, it has been used in other types of cancer patients [R13-1001]. Coating agents may also be used to protect damaged areas of the mouth [R13-1001].

Mild anaemia in NSCLC patients is commonly treated with iron supplementation. Relevant tumour- and chemotherapy-associated anaemia is commonly treated with red blood cell transfusion.

The treatment for ILD is empiric corticosteroid therapy [P09-08054].

A list of common medications used to treat the side effects of cancer treatment is provided in SI.Table 13.

SI.Table 13 Medications for side effects of cancer treatment

Condition	Medications	References
Nausea and vomiting	Antiemetic agents: • Phenothiazines • Butyrophenones • Dopamine 2 antagonists • 5-HT3 receptor antagonists (dolasetron, granisetron, palonosetron, ondansetron) • Substance P antagonists • Corticosteroids • Cannabis • Benzodiazepines	[P13-02404, R13-0735, R13-0736]
Constipation	• Opioid antagonists, methylnaltrexone • Chloride channel activators • Polyethylene glycol • Stool softeners (docusate, lactulose) • Laxatives	[P13-02392, P13-02391]
Diarrhoea	• Loperamide • Octreotide • Tincture of opium	
Fatigue	• Psychostimulants (methylphenidate, modenafil) • Steroids	[R13-0733, P13-02389]
Pain	• Non-narcotic analgesics including over-the-counter drugs such as ibuprofen, acetaminophen, and aspirin • Weak opioids such as codeine • Strong opioids such as morphine, oxycodone, hydromorphone, fentanyl, methadone • Non-steroidal anti-inflammatory drugs • Antidepressants • Anticonvulsants • Topical analgesics	[P13-02390]
Oral mucositis	• Palifermin • Barrier agents to cover mouth sores	[R13-0737]

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ABBREVIATIONS

AC	Adenocarcinoma
AE	Adverse event
ALT	Alanine aminotransferase
ASR	Age-standardised rate
AST	Aspartate aminotransferase
CAD	Coronary artery disease
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CTC	Common toxicity criteria
CTCAE	Common terminology criteria for adverse events
DLP	Data lock point
EGFR	Endothelial growth factor receptor
EORTC QLQ-C30	European Organisation for the Research and Treatment of Cancer quality-of-life in cancer questionnaire
EU	European Union
EU-27	The 27 countries of the EU as at 2008
FYR	Former Yugoslav republic
GFPC	Groupe Français de Pneumo-Cancérologie
GI	Gastro-intestinal
HAD	Hospital anxiety and depression
HMG CoA	3-hydroxy-3-methylglutaryl-coenzyme
HR	Hazard ratio
IHD	Ischaemic heart disease
ILD	Interstitial lung disease
INSTEP	IRESSA NSCLC Trial Evaluating Poor Performance Status Patients
INTACT	IRESSA NSCLC Trial Assessing Combination Treatment
INTEREST	IRESSA Non-small cell lung cancer Trial Evaluating REsponse and Survival against TAXOTERE
IPASS	IRESSA Pan-Asia Study
ISEL	IRESSA Survival Evaluation in Lung Cancer
LCC	Large cell undifferentiated carcinoma
LVEF	Left ventricular ejection fraction

MAH	Marketing authorisation holder
MI	Myocardial infarction
NCI-CTC	National Cancer Institute Common Toxicity Criteria
NSCLC	Non-small cell lung cancer
NR	Not reported
OncoLR	Cancérologie en Languedoc Roussillon
OR	Odds ratio
OS	Overall survival
PFS	Progression-free survival
PHQ-9	Patient Health Questionnaire-9
POLARSTAR	Postmarketing surveillance study of erlotinib in Japanese patients with NSCLC
RCT	Randomised clinical trial
RMP	Risk management plan
SCC	Squamous cell carcinoma
SCLC	Small-cell lung cancer
StD	Standard deviation
TALENT	TARCEVA Lung Cancer Investigation
TK	Tyrosine kinase
UK	United Kingdom
US	United States
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
ZODIAC	ZACTIMA in cOmbination with Docetaxel In non-smAll cell lung Cancer

MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

SII.1 KEY SAFETY FINDINGS FROM NON-CLINICAL STUDIES AND RELEVANCE TO HUMAN USAGE

Potential adverse reactions of nintedanib that may be expected in humans, based on non-clinical safety data, include gastrointestinal side effects, mild haematological alterations, and increases in liver transaminases (in animals with other severe adverse effects). Non-clinical safety data also indicate that the adverse effects of nintedanib are generally reversible.

The pharmacological, pharmacokinetic, and toxicological characteristics of nintedanib were investigated in an extensive programme of non-clinical studies. The selectivity and potency of nintedanib was tested in a series of *in vitro* assays. Studies on secondary and safety pharmacology were performed to investigate potential neurological, haematological, gastrointestinal, renal, pulmonary, and cardiovascular effects of nintedanib.

The pharmacokinetic evaluation included plasma/blood concentration time-profiles of the parent substance BIBF 1120 and the metabolites BIBF 1202 and BIBF 1202 glucuronide. Whole body autoradiography in albino and pigmented rats, quantitative tissue distribution after repeated dose, plasma protein binding of BIBF 1120, BIBF 1202 and BIBF 1202 glucuronide were also carried out. ADME studies assessed excretion balance and biliary excretion, and investigations on metabolism used plasma, urine, faeces, and bile samples, microsomes, and hepatocytes.

The toxicity of nintedanib was investigated in an extensive programme of non-clinical studies including single-dose toxicity studies in rodents, local tolerance studies in rabbits, repeat-dose toxicity studies in mice (up to 3 months), in rats (up to 6 months), in dogs (up to 2 weeks), in Cynomolgus monkeys (up to 13 weeks) and in Rhesus monkeys (up to 52 weeks). In addition, the complete package of reproductive toxicology studies was conducted in rats and rabbits. The genotoxic potential of nintedanib was assessed in bacterial (Ames-Test) and mammalian systems. 2-year carcinogenicity studies were conducted in mice and rats.

SII.1.1 Toxicity

SII.1.1.1 Single and repeat-dose toxicity

In oral single-dose toxicity studies in mice and rats, the ALDs were above 2000 mg/kg [U04-1066, U02-1491]. Therefore, the acute toxicity of nintedanib after oral administration may be considered to be low. At the maximum dose of 40 mg/kg, no evidence of acute toxicity was observed in mice and rats after intravenous administration [U09-1057-01, U09-1058-01].

Subacute, subchronic, and chronic toxicity of nintedanib were assessed in oral and intravenous repeat-dose toxicity studies in cluster of differentiation 1 mice (up to 13 weeks), Wistar (Han) rat strains (up to 26 weeks), Beagle dogs (up to 2 weeks), Cynomolgus

monkeys (up to 13 weeks), and Rhesus monkeys (up to 52 weeks). Intravenous repeat-dose toxicity studies were carried out in Wistar (Han) rats and Rhesus monkeys (each up to 2 weeks). In all studies, toxicokinetic analyses showed substantial systemic exposure to nintedanib and, when measured, to its main metabolites BIBF 1202 and BIBF 1202 glucuronide. The changes observed during repeat-dose studies of oral nintedanib were either directly (e.g. thickened epiphyseal growth plates) or indirectly related (e.g. changes of red blood cell parameters) to the pharmacological activity of nintedanib.

Adverse effects observed in Cynomolgus and Rhesus monkeys were diarrhoea, vomiting, yellow discolouration of the skin (caused by nintedanib and/or its metabolites, not related to increases in bilirubin), increased salivation, and reduced body weights.

Severe gastrointestinal effects were observed in dogs and mini-pigs, leading to high mortality. Observed effects included severe liquid faeces, vomiting, salivation and paralysis/abnormal motor activity. The intestinal mucosa showed erosions, villous atrophy, and basophilia of crypt epithelium with nuclear crowding and mitoses, i.e. evidence for primary damage to the epithelial cells of the intestine. The high mortality in Beagle dogs was apparently due to a dose-limiting sensitivity for gastrointestinal adverse effects such as diarrhoea and vomiting, to which Beagle dogs were substantially more sensitive than other species. The severity of these side effects in Beagle dogs is not considered representative for the adverse effects observed in patients.

Haematological changes across the studies were generally minimal to mild changes in red blood cell parameters (red blood cell count, haematocrit, haemoglobin, mean corpuscular haemoglobin, mean corpuscular volume, and reticulocytes). Changes in white blood cell, lymphocyte, and platelet count were also observed. Blood chemistry investigations revealed mild increases in alanine ALT, aspartate aminotransferase, alkaline phosphatase, total bilirubin, gamma-glutamyltransferase, and aldolase. However, increases in enzyme activities were not very prominent, were also occasionally observed in control animals, and were often interpreted as incidental, not as unequivocally drug-related.

Histopathological changes related to treatment with nintedanib included dentopathy of the continuously growing incisors of rats and thickening of the growth plates (due to increased number of layers of hypertrophic chondrocytes).

Cellular depletion was observed in the thymus, spleen, and bone marrow. In the kidneys, tubular dilatation and periodic acid-Schiff stain-positive hyaline intracytoplasmic granules in podocytes and glomerular endothelium were noted. An increased number of mature corpora lutea, often reduced in size, and of luteinised follicles was observed in the ovaries. Atrophy considered to be secondary to reduced food consumption was apparent in the exocrine pancreas, submandibular glands, parotis, and serous glands of the tongue. Haemosiderosis (e.g. of Kupffer cells and hepatocytes) and extramedullary haemopoiesis were observed in the spleen and in the liver. In the spleen, lymphoid depletion as well as mineralisation of the capsule and trabecules were seen. Villous atrophy of the small intestine, erosions in the gastrointestinal tract and inflammatory processes adjacent to the extra-hepatic bile ducts probably starting from the Papilla duodeni were also observed.

All treatment-related changes showed complete or partial reversibility within the timescale of the toxicity studies; all changes were recoverable in principle. Growth plate changes recovered quickly.

Several repeat-dose toxicity studies were conducted with nintedanib in combination with other compounds. Combination partners were the ERBb family inhibitor (endothelial growth factor receptor /human epidermal growth factor receptor 2, 3, and 4 inhibitor) afatinib [U06-1624, U06-1606, U06-1196, U06-1605], the serine/threonine-protein kinase 1 inhibitor volasertib [U11-1368-01, U09-1962-01] and an Aurora B-inhibitor, BI 811283 [U11-2658-01, U12-1780-01]. The combination of nintedanib with other agents did not reveal any additional, toxicologically meaningful information with respect to the toxicological profile of nintedanib not already known from non-clinical studies with this compound alone.

SII.1.1.2 Reproductive and developmental toxicity

A complete programme of reproductive toxicology studies was conducted with nintedanib in rats and rabbits [U10-1128-01, U13-2650, U07-1710, U07-1814, U13-1923, U13-1937-01, U13-2641].

In rats, embryofoetal lethality and teratogenic effects were observed at exposure levels below human exposure, at the MRHD of 200 mg b.i.d. [U07-1814, U07-1710]. Effects on the development of the axial skeleton and on the development of the great arteries were also noted at subtherapeutic exposure levels.

In rabbits, embryofoetal lethality was observed at an exposure approximately 8 times higher than at the MRHD [U06-1667, U13-1420-01]. Teratogenic effects on the aortic arches in combination with the heart and the urogenital system were noted at an exposure 4 times higher than at the MRHD and on the embryofoetal development of the axial skeleton at an exposure 3 times higher than at the MRHD.

The induction of similar effects in humans cannot be excluded.

SII.1.1.3 Carcinogenicity

Both 2-year bioassays in mice and rats did not reveal a carcinogenic potential of nintedanib [n00232869-01, n00232871-01].

SII.1.1.4 Genotoxicity

The genotoxic potential of nintedanib was assessed in bacterial and mammalian systems (Ames [U02-1481], mouse lymphoma [U02-1512] and rat bone marrow micronucleus assay [U02-1650]). Test concentrations were selected up to bacterio-/cytotoxic or precipitating concentration levels in *in vitro* assays and up to maximum tolerated/limit doses under *in vivo* conditions. The results of the *in vitro* and *in vivo* mutagenicity studies showed that nintedanib is free from any genotoxic potential up to toxic/limit concentration/dose levels. For the drug substance and drug product, no impurities are individually specified.

SII.1.1.5 Phototoxicity

In accordance with the Organisation for Economic Co-operation and Development Guideline 432, a phototoxicity assay was conducted with Balb/c 3T3 cells [U05-2272]. A phototoxic threshold concentration of approximately 0.5 mcg/mL was estimated. At this concentration, the Photo Effect was around the phototoxicity limit of 0.15. A Photo Irritating Factor of 18.4 and a Mean Photo Effect of 0.554 and 0.560 indicate that nintedanib may have a phototoxic potential.

SII.1.1.6 Immunotoxicity

Immunological investigations (phenotyping of lymphoid subpopulations in blood, spleen, and thymus, as well as determination of spleen natural killer cell activity) were performed in the 4-week toxicity study in rats [U04-1812], in the 13-week toxicity study in Cynomolgus monkeys [U05-2245], and in the 52-week toxicity studies in Rhesus monkeys [U07-1875]. No consistent adverse effects on the immune system of rats, Cynomolgus and Rhesus monkeys were observed.

SII.1.2 Safety pharmacology

Safety pharmacology investigations were conducted for nintedanib, both *in vitro* and *in vivo*. In telemetered conscious male rats, [U02-1398], a dose-dependent increase in systemic blood pressure was observed, whereas in anaesthetised pigs [U02-1674], a dose-dependent decrease in systolic and diastolic blood pressure was noted. Further details are provided in section SII.1.3.1 below. Studies of renal and hepatic function in rats [U02-1260, U04-1416] showed up to 1.6-fold increase in ALT and a comparable increase in serum triglycerides and increases in urine volume, urine sodium, N-acetyl-beta-glucosaminidase and calcium output. Studies on gastric emptying and secretion, gastrointestinal motility and transit [U02-1248, U02-1258, U02-1259] indicated a potential for nintedanib to cause inhibition of both gastric and intestinal functions in a dose-dependent manner. No meaningful effects were observed with respect to central nervous system and respiratory functions [U02-1587, U02-1589].

In safety pharmacology (Good Laboratory Practice Core Battery) studies, there was no evidence for adverse cardiovascular, respiratory or neurological effects of nintedanib. Despite high passive permeability of nintedanib through biomembranes into various cell lines, oral bioavailability was limited in rats by an incomplete absorption followed by first pass metabolism mainly by ester cleavage. Therefore, oral bioavailability was incomplete with 12% in rats and 19% in monkeys. Nintedanib was extensively distributed into all tissues except the central nervous system, in all investigated species (volume >8 L/kg).

SII.1.3 Other toxicity-related information or data

SII.1.3.1 Mechanisms for drug interactions

Oral administration of 5 and 20 mg/kg nintedanib to male Wistar rats once daily for 4 days caused no or only minor and biologically irrelevant changes of the activities of the CYP enzymes 2B,1A, 3A and 2E1 [U04-2195]. There was also no evidence for an *in vitro* induction potential [U09-1731-01] or for inhibitory effects of BIBF 1120, BIBF 1202 and

BIBF 1202-glucuronide [U03-1386, U08-1256-02, U09-1164-02]. Based on these data, metabolic drug-drug interactions of nintedanib resulting from induction or inhibition of CYP enzymes are considered unlikely. Because pronounced inhibition of UGT 1A1 and 2B7 test reactions by BIBF 1202-glucuronide was not observed at concentrations of up to 100 mcM and 200 mcM, respectively, metabolic drug-drug interactions resulting from inhibition of UGT 1A1 and UGT 2B7 are unlikely to occur [n00243909-01].

Non-clinical studies were conducted to assess the metabolism of nintedanib *in vitro*. In human liver microsomes, about 25% of the metabolised BIBF 1120 underwent ester cleavage yielding the carboxylate metabolite BIBF 1202 compared to about 5% for CYP dependent metabolism. CYP 3A4 was the predominant enzyme involved in the formation of hydroxylated and de-methylated metabolites of BIBF 1120 [U03-1355]. Metabolites formed by CYP enzymes were not observed in plasma in the human ADME study and to a low extent only in excreta [U06-1950]. Drug-drug interactions via CYP enzymes are therefore considered unlikely.

Freshly prepared rat and human hepatocytes took up BIBF 1120 base rapidly. Due to a higher rate of BIBF 1202 formation and a lower capacity to form other metabolites, human hepatocytes were exposed to substantially higher concentrations (2.5- to 6-fold) of BIBF 1202 when compared to rat hepatocytes [U05-1001].

Under conditions that enable glucuronidation in microsomal preparations, the carboxylate metabolite BIBF 1202 was glucuronidated. The glucuronidation rate was high in the rat, intermediate in humans and low in dogs [U02-1248, U02-1649]. Of 8 different commercially available human hepatic UGT enzymes, only UGT1A1 was capable of catalysing the formation of the acylglucuronide of BIBF 1202 [U06-1667]. BIBF 1202 is effectively glucuronidated in rat and human intestine. The intestinal tract contributed to the glucuronidation of BIBF 1202 in rats [U10-2910-01]. Human intestinal UGT1A7, UGT1A8 and UGT1A10 catalysed BIBF 1202 glucuronidation with UGT1A8 exhibiting the highest intrinsic clearance. The acylglucuronide was found to be relatively stable and is, therefore, expected to have a low tendency of covalent adduct formation [U03-1296].

The *in vivo* metabolite pattern of nintedanib was investigated in mice, rats, Rhesus monkeys and human subjects [U09-2277-01, U03-1935, U06-2240, U05-2098, U06-1950]. The elimination of BIBF 1120 base was mainly governed by ester cleavage and subsequent glucuronidation. Combining the metabolite patterns of plasma and excreta, the metabolism of BIBF 1120 base can be subdivided into the following principal reactions:

- m1: ester cleavage of the methyl ester BIBF 1120 to yield BIBF 1202
- m2: conjugation of the carboxylate of BIBF 1202 to yield the 1-*O*-acylglucuronide
- m3: oxidative N-demethylation (piperazine moiety) to yield BIBF 1053
- m4: subsequent ester cleavage and oxidative N-demethylation

The principal metabolites in all species investigated, including humans, were m1 to m4. The combination of two or three of these metabolic reactions resulted in the formation of several minor metabolites some of which were present in very small or trace amounts only [U06-

2240]. All principal metabolites that were observed in humans have also been found in animal species (rats, Rhesus monkeys and mice) after oral dosing of [14C]BIBF 1120.

SII.1.3.2 Drug transport

Transport of BIBF 1120 and BIBF 1202 and BIBF 1202-glucuronide: In vitro transporter profiling was performed for BIBF 1120, BIBF 1202, and BIBF 1202 glucuronide [U05-3076, U12-2279-01]. Nintedanib was shown to be a P-gp substrate and clinical drug-drug interaction studies were initiated. BIBF 1202 was a substrate of OATP 1B1 and OATP 2B1; BIBF 1202 glucuronide was a substrate of multidrug resistance-associated protein-2 and BCRP, but was not a substrate of OATP1B1, OATP1B3, OATP2B1 and OCT1.

Inhibition of transporters: Only a weak inhibitory potential on organic cation transporter-1, BCRP, and P-gp was concluded for BIBF 1120.

BIBF 1120 was a weak inhibitor of P-gp and BCRP (72.9% and 36.6% of control activities at concentrations up to 30 mcM). No pronounced inhibition of OATP1B1, OATP1B3, OATP2B1, and OCT2, OAT1 and OAT3 activities by BIBF 1120 was observed, whereas OCT1 activity was dose-dependently inhibited with an IC_{50} value of 0.88 mcM [U05-3076, n00238040-01].

The maximum nintedanib plasma concentrations after administration of 200 mg nintedanib were approximately 40-50 ng/mL, equalling 0.07-0.09 mcM (gCV approx. 70%); the plasma protein binding of nintedanib was 97.8% [U13-1505].

In all cases, half maximal inhibitory concentration values were substantially higher than the therapeutic maximum plasma concentration at steady state and interactions on transporter substrates therefore considered unlikely. Also, the likelihood of relevant drug-drug interactions by nintedanib mediated inhibition of P-gp or BCRP in the intestine is considered to be low.

BIBF 1202 showed dose-dependent inhibition of OATP1B1, OATP1B3, OATP2B1 and OCT1 with IC_{50} values in the range from 14 mcM to 79 mcM, but showed no inhibition of OCT2 up to 100 mcM. BIBF 1202 was also not an inhibitor of P-gp and no pronounced inhibition was observed for BCRP (71.8% of control activity at 30 mcM).

BIBF 1202-glucuronide did not show relevant inhibition up to the highest concentration tested (100 mcM) on any of the transporters investigated (P-gp, BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3 and OCT2) [n00230296-01].

SII.2 CONCLUSIONS ON NON-CLINICAL DATA

The following safety concerns are considered relevant for carrying forward in the risk management plan: diarrhoea, liver enzyme elevations, and teratogenicity (see SVIII. Table 1).

SII.3 ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
ALD	Approximate lethal dose
ALT	Alanine aminotransferase
BCRP	Breast cancer resistance protein
b.i.d.	*bis in die*; twice daily
CYP	Cytochrome P
DLP	Data lock point
EMA	European Medicines Agency
gCV	Geometric coefficent of variation
HEK293	Human embryonic kidney 293
hERG	Human Ether-à-go-go-Related Gene
IC_{50}	Half-maximal inhibitory concentration
MAH	Marketing authorisation holder
mcg	Microgram
mcM	Micromol
MRHD	Maximum recommended human dose
OATP	Organic anion-transporting polypeptide
P-gp	P-glycoprotein
RMP	Risk management plan
UGT	Uridine 5'-diphospho-glucuronosyltransferase

SII.4 REFERENCES

SII.4.1 Published references

Not applicable.

SII.4.2 Unpublished references

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MODULE SIII CLINICAL TRIAL EXPOSURE

The Phase III trial 1199.13 is the pivotal trial on which the safety findings reported in this RMP are predominantly based. This trial aimed to demonstrate the superiority of Vargatef + docetaxel vs placebo + docetaxel in a population of patients with histologically or cytologically confirmed, locally advanced and/or metastatic NSCLC of stage IIIB or IV or recurrent NSCLC after failure of first-line chemotherapy. The data from trial 1199.13 are presented as follows:

- Section SIII.1.1: Vargatef/matching placebo + docetaxel in patients with adenocarcinoma in pivotal phase III study 1199.13 ('target population')
- Section SIII.1.2: Vargatef/matching placebo + docetaxel in all patients in the pivotal phase III study 1199.13 ('overall population')

The treatment groups were patients receiving Vargatef + docetaxel (the 'Vargatef' arm) and patients receiving placebo + docetaxel (the 'placebo' arm). Data for the placebo and the Vargatef arms are presented.

Clinical trial exposure is additionally provided in Section SIII.2 for 2 Phase I/II studies examining HCC patients with hepatic impairment in different countries (1199.37 and 1199.39).

Clinical trial exposure was calculated in total person time (years). It is defined as the sum over all contributing patients of overall treatment time (days) ÷ 365.25. For each patient, overall treatment time (days) = date of last administration of study medication – date of first study medication administration + 1 day. Study medication for combination therapy (investigational drug + backbone chemotherapy) refers to whatever was the first and last drug administered for a patient. The calculation of exposure was based on the treated set of patients, i.e. representing all patients who received at least 1 dose of study medication.

SIII.1 EXPOSURE IN PIVOTAL TRIALS FOR VARGATEF IN SECOND-LINE TREATMENT FOR NSCLC

SIII.1.1 Target population: Vargatef/matching placebo + docetaxel in patients with adenocarcinoma in pivotal phase III trial 1199.13

SIII.Table 1 Cumulative clinical trial exposure – patients with adenocarcinoma in trial 1199.13 / treated set

	Placebo		Vargatef	
Duration of exposure	Number (%)	Person-time [years]	Number (%)	Person-time [years]
Cumulative up to 1 month (30 days)	34 (10.2)	1.66	29 (9.1)	1.57
Cumulative up to 3 months (90 days)	168 (50.5)	21.75	130 (40.6)	17.49
Cumulative up to 6 months (180 days)	255 (76.6)	54.36	212 (66.3)	48.13
Cumulative up to 9 months (270 days)	291 (87.4)	76.43	269 (84.1)	83.08
Cumulative up to 12 months (365 days)	310 (93.1)	92.50	297 (92.8)	107.04
Cumulative up to 24 months (730 days)	328 (98.5)	116.71	315 (98.4)	131.10
Cumulative up to 36 months (1095 days)	331 (99.4)	123.82	317 (99.1)	135.35
Cumulative up to 60 months (1825 days)	333 (100.0)	133.47	318 (99.4)	139.54
Cumulative up to 72 months (2190 days)	333 (100.0)	133.47	319 (99.7)	145.22
Cumulative up to 84 months (2555 days)	333 (100.0)	133.47	320 (100.0	151.27

Source data: data on file:RMP analyses v5.0; Table 5.1.3.1.

SIII.Table 2 Clinical trial exposure by age and gender – patients with adenocarcinoma in trial 1199.13 / treated set

Treatment arm	Number (%)		Person-time [years]	
Age group [years]	Male	Female	Male	Female
Placebo				
<65	139 (67.1)	100 (79.4)	53.42	44.12
≥65	68 (32.9)	26 (20.6)	25.50	10.43
≥65 to ≤74	60 (29.0)	24 (19.0)	23.96	9.95
≥75	8 (3.9)	2 (1.6)	1.55	0.47
Total	207 (100.0)	126 (100.0)	78.92	54.55
Vargatef				
<65	142 (70.6)	88 (73.9)	71.95	37.25
≥65	59 (29.4)	31 (26.1)	25.29	16.78
≥65 to ≤74	47 (23.4)	27 (22.7)	18.98	15.99
≥75	12 (6.0)	4 (3.4)	6.31	0.79
Total	201 (100.0)	119 (100.0)	97.24	54.03

Source data: data on file:RMP analyses version 5.0; Table 5.1.3.2.

SIII.Table 3 Clinical trial exposure by race and special populations – patients with adenocarcinoma in trial 1199.13 / treated set

	Placebo		Vargatef	
Characteristic	Number (%)	Person-time [years]	Number (%)	Person-time [years]
Ethnicity				
White/Caucasian	250 (75.1)	102.90	251 (78.4)	122.30
Black	4 (1.2)	1.17	3 (0.9)	2.08
Asian	79 (23.7)	29.40	66 (20.6)	26.89
Total	333 (100.0)	133.47	320 (100.0)	151.27
Renal function at baseline				
Creatinine <1.5 x ULN	322 (96.7)	129.75	311 (97.2)	147.37
Creatinine ≥1.5 x ULN	1 (0.3)	0.11	0	0
Hepatic function at baseline[1]				
Normal	280 (84.1)	110.90	277 (86.6)	131.58
Mild impairment	42 (12.6)	18.94	32 (10.0)	14.23
Moderate impairment	0	0	2 (0.6)	1.56
Severe impairment	0	0	0	0

[1] Normal: ALT, AST, total bilirubin ≤ULN; Mild impairment: (ULN <ALT/AST ≤2.5 x ULN) or (ULN <total bilirubin ≤1.5 x ULN), Moderate: (2.5 x ULN <AST/ALT ≤5 x ULN) or (1.5 x ULN <total bilirubin ≤3 x ULN), Severe: (5 x ULN <AST/ALT) or (3 x ULN <total bilirubin).

'Missing' data is not shown.

Source data: data on file: RMP analyses v5.0, Table 5.1.3.3; Table 5.1.3.4.

SIII.1.2 Vargatef/matching placebo + docetaxel in all patients in the pivotal phase III study 1199.13

SIII.Table 4 Cumulative clinical trial exposure – all patients in trial 1199.13 / treated set

	Placebo		Vargatef	
Duration of exposure	Number (%)	Person-time [years]	Number (%)	Person-time [years]
Cumulative up to 1 month (30 days)	73 (11.1)	3.54	70 (10.7)	3.35
Cumulative up to 3 months (90 days)	370 (56.5)	49.27	307 (47.1)	40.28
Cumulative up to 6 months (180 days)	535 (81.7)	110.38	483 (74.1)	106.35
Cumulative up to 9 months (270 days)	590 (90.1)	144.19	574 (88.0)	162.22
Cumulative up to 12 months (365 days)	623 (95.1)	172.24	618 (94.8)	200.04
Cumulative up to 24 months (730 days)	647 (98.8)	204.61	643 (98.6)	233.69
Cumulative up to 36 months (1095 days)	652 (99.5)	216.71	647 (99.2)	242.88
Cumulative up to 60 months (1825 days)	654 (99.8)	226.37	648 (99.4)	247.07
Cumulative up to 72 months (2190 days)	655 (100.0	231.95	649 (99.5)	252.75
Cumulative up to 84 months (2555 days)	655 (100.0	231.95	650 (99.7)	258.79
Cumulative up to 96 months (2920 days)	655 (100.0	231.95	652 (100.0)	273.56

Source data: data on file:RMP analyses v5.0; Table 5.1.4.1.

SIII.Table 5 Clinical trial exposure by age and gender – all patients in trial 1199.13 / treated set

Treatment arm	Number (%)		Person-time [years]	
Age group [years]	Male	Female	Male	Female
Placebo				
<65	310 (64.9)	133 (75.1)	108.68	52.47
≥65	168 (35.1)	44 (24.9)	55.43	15.36
≥65 to ≤74	151 (31.6)	40 (22.6)	49.65	14.54
≥75	17 (3.6)	4 (2.3)	5.78	0.82
Total	478 (100.0)	177 (100.0)	164.11	67.83
Vargatef				
<65	322 (68.1)	130 (72.6)	139.43	52.47
≥65	151 (31.9)	49 (27.4)	59.54	22.12
≥65 to ≤74	120 (25.4)	42 (23.5)	40.91	20.59
≥75	31 (6.6)	7 (3.9)	18.64	1.53
Total	473 (100.0)	179 (100.0)	198.97	74.59

Source data: data on file:RMP analyses v5.0; Table 5.1.4.2.

SIII.Table 6 Clinical trial exposure by race and special populations – all patients in trial 1199.13 / treated set

	Placebo		Vargatef	
Characteristic	Number (%)	Person-time [years]	Number (%)	Person-time [years]
Ethnicity				
White/Caucasian	526 (80.3)	190.57	530 (81.3)	229.16
Black	5 (0.8)	1.42	4 (0.6)	2.19
Asian	124 (18.9)	39.95	118 (18.1)	42.21
Total	655 (100.0)	231.95	652 (100.0)	273.56
Renal function at baseline				
Creatinine <1.5 x ULN	635 (96.9)	220.44	639 (98.0)	268.77
Creatinine ≥1.5 x ULN	3 (0.5)	0.37	1 (0.2)	0.01
Hepatic function at baseline[1]				
Normal	548 (83.7)	191.46	572 (87.7)	242.47
Mild impairment	87 (13.3)	29.62	66 (10.1)	24.75
Moderate impairment	3 (0.5)	0.91	2 (0.3)	1.56
Severe impairment	0	0	0	0

[1] Normal: ALT, AST, total bilirubin ≤ULN; Mild impairment: (ULN <ALT/AST ≤2.5 x ULN) or (ULN <total bilirubin ≤1.5 x ULN), Moderate: (2.5 x ULN <AST/ALT ≤5 x ULN) or (1.5 x ULN <total bilirubin ≤3 x ULN), Severe: (5 x ULN <AST/ALT) or (3 x ULN <total bilirubin).

'Missing' data is not shown.

Source data: data on file:RMP analyses v5.0; Table 5.1.3.3; Table 5.1.3.4.

SIII.2 CLINICAL TRIALS 1199.37 AND 1199.39 (PHASE I AND II)

SIII.Table 7 Cumulative clinical trial exposure – all patients in trial 1199.37+39 (phase I and II) / treated set

Duration of exposure	Nintedanib 50 mg b.i.d.		Nintedanib 100 mg b.i.d.		Nintedanib 150 mg b.i.d.	
	Number (%)	Person-time [years]	Number (%)	Person-time [years]	Number (%)	Person-time [years]
Cumulative up to 1 month (30 days)	0	0	7 (33.3)	0.38	2 (15.4)	0.14
Cumulative up to 3 months (90 days)	2 (33.3)	0.33	11 (52.4)	0.96	3 (23.1)	0.34
Cumulative up to 6 months (180 days)	3 (50.0)	0.63	14 (66.7)	2.05	5 (38.5)	1.00
Cumulative up to 9 months (270 days)	5 (83.3)	1.67	14 (66.7)	2.05	7 (53.8)	2.14
Cumulative up to 12 months (365 days)	5 (83.3)	1.67	16 (76.2)	3.92	10 (76.9)	4.68
Cumulative up to 24 months (730 days)	6 (100.0)	2.85	20 (95.2)	10.19	13 (100.0)	8.16
Cumulative up to 36 months (1095 days)	6 (100.0)	2.85	21 (100.0)	12.27	13 (100.0)	8.16
Cumulative up to 48 months (1460 days)	6 (100.0)	2.85	21 (100.0)	12.27	13 (100.0)	8.16

Source data: data on file: RMP analyses – Additional Data for NSCLC v 4.0: Table 2.1.1.1

SIII.Table 8 Cumulative clinical trial exposure – all patients in trial 1199.37+39 (phase I and II) / treated set

Duration of exposure	Nintedanib 200 mg b.i.d.		Nintedanib Total		Sorafenib 400 mg b.i.d.	
	Number (%)	Person-time [years]	Number (%)	Person-time [years]	Number (%)	Person-time [years]
Cumulative up to 1 month (30 days)	27 (17.3)	1.44	36 (18.4)	1.95	9 (14.3)	0.55
Cumulative up to 3 months (90 days)	70 (44.9)	8.57	86 (43.9)	10.20	24 (38.1)	2.96
Cumulative up to 6 months (180 days)	106 (67.9)	21.85	128 (65.3)	25.54	46 (73.0)	11.90
Cumulative up to 9 months (270 days)	121 (77.6)	31.19	147 (75.0)	37.04	53 (84.1)	16.29
Cumulative up to 12 months (365 days)	133 (85.3)	41.46	164 (83.7)	51.72	57 (90.5)	19.72
Cumulative up to 24 months (730 days)	152 (97.4)	69.65	191 (97.4)	90.85	60 (95.2)	23.76
Cumulative up to 36 months (1095 days)	155 (99.4)	76.83	195 (99.5)	100.10	63 (100.0)	30.49
Cumulative up to 48 months (1460 days)	156 (100.0)	80.21	196 (100.0)	103.48	63 (100.0)	30.49

Source data: data on file: RMP analyses – Additional Data for NSCLC v 4.0: Table 2.1.1.1

SIII.Table 9 Clinical trial exposure by age and gender – all patients in trial 1199.37+39 (phase I and II) / treated set

Age group [years]	Nintedanib 50 mg b.i.d.				Nintedanib 100 mg b.i.d.			
	Number (%)		Person-time [years]		Number (%)		Person-time [years]	
Dose	Males	Females	Males	Females	Males	Females	Males	Females
<65	2 (33.3)	0	1.32	0	12 (60.0)	0	3.67	0
≥65	4 (66.7)	0	1.53	0	8 (40.0)	1 (100.0)	8.52	0.08
≥65 to ≤74	2 (33.3)	0	0.68	0	7 (35.0)	1 (100.0)	7.44	0.08
≥75	2 (33.3)	0	0.85	0	1 (5.0)	0	1.08	0
Total	6 (100.0)	0	2.85	0	20 (100.0)	1 (100.0)	12.19	0.08

Source data: data on file: RMP analyses – Additional Data for NSCLC v 4.0: Table 2.1.1.2

SIII.Table 10 Clinical trial exposure by age and gender – all patients in trial 1199.37+39 (phase I and II) / treated set

	Nintedanib 150 mg b.i.d.				Nintedanib 200 mg b.i.d.			
Age group [years]	Number (%)		Person-time [years]		Number (%)		Person-time [years]	
Dose	Males	Females	Males	Females	Males	Females	Males	Females
<65	8 (80.0)	1 (33.3)	4.22	0.27	78 (59.5)	10 (40.0)	39.43	6.10
≥65	2 (20.0)	2 (66.7)	1.85	1.81	53 (40.5)	15 (60.0)	29.94	4.74
≥65 to ≤74	0	2 (66.7)	0	1.81	41 (31.3)	11 (44.0)	25.78	3.92
≥75	2 (20.0)	0	1.85	0	12 (9.2)	4 (16.0)	4.16	0.82
Total	10 (100.0)	3 (100.0)	6.07	2.09	131 (100.0)	25 (100.0)	69.37	10.84

Source data: data on file: RMP analyses – Additional Data for NSCLC v 4.0: Table 2.1.1.2

SIII.Table 11 Clinical trial exposure by age and gender – all patients in trial 1199.37+39 (phase I and II) / treated set

	Nintedanib Total				Sorafenib 400 mg b.i.d.			
Age group [years]	Number (%)		Person-time [years]		Number (%)		Person-time [years]	
Dose	Males	Females	Males	Females	Males	Females	Males	Females
<65	100 (59.9)	11 (37.9)	48.64	6.37	31 (59.6)	5 (45.5)	15.96	0.78
≥65	67 (40.1)	18 (62.1)	41.84	6.63	21 (40.4)	6 (54.5)	8.59	5.16
≥65 to ≤74	50 (29.9)	14 (48.3)	33.91	5.82	14 (26.9)	3 (27.3)	4.41	2.55
≥75	17 (10.2)	4 (13.8)	7.93	0.82	7 (13.5)	3 (27.3)	4.19	2.61
Total	167 (100.0)	29 (100.0)	90.48	13.00	52 (100.0)	11 (100.0)	24.55	5.94

Source data: data on file: RMP analyses – Additional Data for NSCLC v 4.0: Table 2.1.1.2

SIII.Table 12 Clinical trial exposure by race – all patients in trial 1199.37+39 (phase I and II) / treated set

	Nintedanib 50 mg b.i.d.		Nintedanib 100 mg b.i.d.		Nintedanib 150 mg b.i.d.	
Characteristic	Number (%)	Person-time [years]	Number (%)	Person-time [years]	Number (%)	Person-time [years]
Ethnicity						
White/Caucasian	2 (33.3)	0.49	7 (33.3)	5.21	4 (30.8)	2.65
Black	1 (16.7)	1.17	2 (9.5)	0.11	1 (7.7)	0.06
Asian	3 (50.0)	1.19	12 (57.1)	6.95	8 (61.5)	5.45
Total	6 (100.0)	2.85	21 (100.0)	12.27	13 (100.0)	8.16

[1] Normal: ALT, AST, total bilirubin ≤ULN; Mild impairment: (ULN <ALT/AST ≤2.5 x ULN) or (ULN <total bilirubin ≤1.5 x ULN), Moderate: (2.5 x ULN <AST/ALT ≤5 x ULN) or (1.5 x ULN <total bilirubin ≤3 x ULN), Severe: (5 x ULN <AST/ALT) or (3 x ULN <total bilirubin).

'Missing' data is not shown.

Source data: data on file: RMP analyses – Additional Data for NSCLC v 4.0: Table 2.1.1.3

SIII.Table 13 Clinical trial exposure by race – all patients in trial 1199.37+39 (phase I and II) / treated set

	Nintedanib 200 mg b.i.d.		Nintedanib Total		Sorafenib 400 mg b.i.d.	
Characteristic	Number (%)	Person-time [years]	Number (%)	Person-time [years]	Number (%)	Person-time [years]
Ethnicity						
White/Caucasian	68 (43.6)	43.48	81 (41.3)	51.83	24 (38.1)	15.09
Black	1 (0.6)	0.05	5 (2.6)	1.39	1 (1.6)	0.46
Asian	82 (52.6)	34.16	105 (53.6)	47.74	36 (57.1)	14.51
Total	156 (100.0)	80.21	196 (100.0)	103.48	63 (100.0)	30.49

[1] Normal: ALT, AST, total bilirubin ≤ULN; Mild impairment: (ULN <ALT/AST ≤2.5 x ULN) or (ULN <total bilirubin ≤1.5 x ULN), Moderate: (2.5 x ULN <AST/ALT ≤5 x ULN) or (1.5 x ULN <total bilirubin ≤3 x ULN), Severe: (5 x ULN <AST/ALT) or (3 x ULN <total bilirubin).

'Missing' data is not shown.

Source data: data on file: RMP analyses – Additional Data for NSCLC v 4.0: Table 2.1.1.3

SIII.Table 14 Clinical trial exposure by special populations – all patients in trial 1199.37+39 (phase I and II) / treated set

	Nintedanib 50 mg b.i.d.		Nintedanib 100 mg b.i.d.		Nintedanib 150 mg b.i.d.	
Characteristic	Number (%)	Person-time [years]	Number (%)	Person-time [years]	Number (%)	Person-time [years]
Renal function at baseline						
Creatinine <1.5 x ULN	6 (100.0)	2.85	21 (100.0)	12.27	13 (100.0)	8.16
Creatinine ≥1.5 x ULN	0	0	0	0	0	0
Hepatic function at baseline[1]						
Normal	0	0	1 (4.8)	0.13	3 (23.1)	2.72
Mild impairment	1 (16.7)	0.15	14 (66.7)	8.63	4 (30.8)	1.26
Moderate impairment	5 (83.3)	2.70	6 (28.6)	3.51	6 (46.2)	4.18
Severe impairment	0	0	0	0	0	0
Cardiovascular disorder						
Yes	4 (66.7)	2.20	12 (57.1)	5.90	7 (53.8)	4.59
No	2 (33.3)	0.65	9 (42.9)	6.37	6 (46.2)	3.57

[1] Normal: ALT, AST, total bilirubin ≤ULN; Mild impairment: (ULN <ALT/AST ≤2.5 x ULN) or (ULN <total bilirubin ≤1.5 x ULN), Moderate: (2.5 x ULN <AST/ALT ≤5 x ULN) or (1.5 x ULN <total bilirubin ≤3 x ULN), Severe: (5 x ULN <AST/ALT) or (3 x ULN <total bilirubin).

'Missing' data is not shown.

Source data: data on file: RMP analyses – Additional Data for NSCLC v 4.0: Table 2.1.1.4

SIII.Table 15 Clinical trial exposure by special populations – all patients in trial 1199.37+39 (phase I and II) / treated set

	Nintedanib 200 mg b.i.d.		Nintedanib Total		Sorafenib 400 mg b.i.d.	
Characteristic	Number (%)	Person-time [years]	Number (%)	Person-time [years]	Number (%)	Person-time [years]
Renal function at baseline						
Creatinine <1.5 x ULN	153 (98.1)	77.73	193 (98.5)	101.00	62 (98.4)	30.44
Creatinine ≥1.5 x ULN	0	0	0	0	1 (1.6)	0.05
Hepatic function at baseline[1]						
Normal	44 (28.2)	27.37	48 (24.5)	30.21	19 (30.2)	12.43
Mild impairment	90 (57.7)	44.62	109 (55.6)	54.65	42 (66.7)	17.17
Moderate impairment	18 (11.5)	5.74	35 (17.9)	16.13	2 (3.2)	0.89
Severe impairment	1 (0.6)	0.01	1 (0.5)	0.01	0	0

[1] Normal: ALT, AST, total bilirubin ≤ULN; Mild impairment: (ULN <ALT/AST ≤2.5 x ULN) or (ULN <total bilirubin ≤1.5 x ULN), Moderate: (2.5 x ULN <AST/ALT ≤5 x ULN) or (1.5 x ULN <total bilirubin ≤3 x ULN), Severe: (5 x ULN <AST/ALT) or (3 x ULN <total bilirubin).

'Missing' data is not shown.

Source data: data on file: RMP analyses – Additional Data for NSCLC v 4.0: Table 2.1.1.4

SIII.3 REFERENCES

Not applicable

ABBREVIATIONS

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
b.i.d.	*bis in die* (twice daily)
NSCLC	Non-small cell lung cancer
PY	Person-years
RMP	Risk management plan
ULN	Upper limit of normal

MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL TRIALS WITHIN THE DEVELOPMENT PROGRAMME

Patients with known hypersensitivity to Vargatef or any of the excipients	
Reason for exclusion	Vargatef is contraindicated in these patients in order to prevent hypersensitivity reactions.
Is it considered to be included as missing information?	No
Rationale	Hypersensitivity to nintedanib and any excipients of Vargatef is an absolute contraindication.

Pregnant or breast-feeding women	
Reason for exclusion	Following administration of nintedanib to rats, the inhibition of angiogenesis resulted in absorption of foetuses and increased incidence of malformations. These effects occurred at dose levels resulting in plasma drug concentrations comparable to, or lower than, those reached in humans during treatment with Vargatef.
Is it considered to be included as missing information?	No
Rationale	Routine risk minimisation measures are in place and include recommendations on contraception, pregnancy testing before treatment. If the patient becomes pregnant while receiving Vargatef, she should be apprised of the potential hazard to the foetus. Termination of the treatment with Vargatef should be considered.

[redacted]

History of or predisposition to bleeding events (including therapeutic anticoagulation), as covered by several exclusion criteria	
Reason for exclusion	To protect the safety of patients, and maintain the integrity of the trials.
Is it considered to be included as missing information?	No
Rationale	It is not recommended to treat patients with recent pulmonary bleeding (>2.5 ml of red blood), with centrally located tumours with radiographic evidence of local invasion of major blood vessels or radiographic evidence of cavitary or necrotic tumours. In trial 1199.13, in patients on chronic low dose therapy with low molecular weight heparins or acetylsalicylic acid, no increased frequency of bleeding was observed. Patients who developed thromboembolic events during treatment and who required anticoagulant treatment were allowed to continue Vargatef and did not show an increased frequency of bleeding events. Patients taking concomitant anticoagulation, such as warfarin or phenprocoumon should be monitored regularly for changes in prothrombin time, INR, or clinical bleeding episodes.
Significant cardiovascular diseases	
Reason for exclusion	To protect the safety of patients, and maintain the integrity of the trials
Is it considered to be included as missing information?	No
Rationale	In trial 1199.13, there were no imbalances in the frequency of cardiovascular and arterial thromboembolic AEs between the treatment arms. Data from a phase II trial in patients with renal cancer showed that Vargatef did not relevantly prolong QTcF or uncorrected QT interval at the time of each patient's maximum plasma concentrations of Vargatef or its major metabolites after single or repeat dosing.

[redacted]

ECOG performance score ≥2	
Reason for exclusion	To maintain the integrity of the trials
Is it considered to be included as missing information?	No
Rationale	There is no scientific evidence that would suggest that the safety profile of Vargatef in patients with ECOG performance score ≥2 would differ from that in the remaining target population. Therefore, this exclusion criterion is not considered missing information.

Aged <18 years	
Reason for exclusion	According to legal requirements
Is it considered to be included as missing information?	No
Rationale	Vargatef is authorised for treatment of adult patients. NSCLC may occur rarely in adolescent patients <18 years. These patients may benefit from Vargatef treatment in the same way as adult patients (≥18 years) do. However, the safety and efficacy of Vargatef in children aged 0-18 years have not been established.

Renal impairment (including serum creatinine >1.5 x ULN; proteinuria CTCAE grade 2 or greater)	
Reason for exclusion	To protect the safety of patients, and maintain the integrity of the trials
Is it considered to be included as missing information?	Yes
Rationale	The use of Vargatef in patients with renal impairment is considered missing information.

Hepatic impairment (including total bilirubin above ULN; ALT and/or AST >1.5 times ULN; active or chronic hepatitis C and/or B infection)	
Reason for exclusion	To protect the safety of patients, and maintain the integrity of the trials
Is it considered to be included as missing information?	No
Rationale	Treatment with Vargatef is not recommended in patients with moderate and severe hepatic impairment. In patients treated with Vargatef, transaminase, ALKP, and bilirubin levels should be investigated upon initiation of the combination treatment with Vargatef plus docetaxel. The values should be monitored as clinically indicated or periodically during treatment, i.e. in the combination phase with docetaxel at the beginning of each treatment cycle and monthly in case Vargatef is continued as monotherapy after discontinuation of docetaxel. If relevant liver enzyme elevations are measured, interruption, dose reduction or discontinuation of the therapy with Vargatef may be required.

Brain metastasis	
Reason for exclusion	To protect the safety of patients and to maintain the integrity of the trials
Is it considered to be included as missing information?	No
Rationale	Current labeling includes the recommendation not to administer Vargatef in patients with active brain metastasis. Monitoring is recommended in patients with stable brain metastasis as risk factor for bleeding. In case of bleeding, dose adjustment, interruption or discontinuation should be considered based on clinical judgement.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

SIV.Table 1 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Number / Person-time
Pregnant women	Not applicable
Breastfeeding women	Not applicable
Patients with relevant co-morbidities	
• Patients with hepatic impairment	See SIII.Table 3, SIII.Table 6, SIII.Table 14, SIII.Table 15
• Patients with renal impairment	See SIII.Table 3, SIII.Table 6, SIII.Table 14, SIII.Table 15
Population with relevant different ethnic origin	See SIII.Table 3, SIII.Table 6, SIII.Table 12, SIII.Table 13

SIV.4 REFERENCES

Not applicable.

ABBREVIATIONS

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CTCAE	Common terminology criteria for adverse events
ECOG	Eastern Cooperative Oncology Group
INR	International normalised ratio
ULN	Upper limit of normal

MODULE SV POST-AUTHORISATION EXPERIENCE

SV.1 POST-AUTHORISATION EXPOSURE

SV.1.1 Method used to calculate exposure

Ex-factory (commercial) sales numbers for Vargatef as the basis for the estimation of the post-authorisation (non-clinical trial) exposure are only available for complete months, beginning in November 2014 (international birth date).

The method used to estimate patient exposure to the marketed drugs is based on the number of Vargatef capsules sold (ex-factory sales). It is assumed that all capsules were used by the patients. It is also assumed that each patient was treated with four 100 mg capsules per day or two 150 mg capsules in case of a dosage adjustment. The total days of medication is calculated by dividing the total number of capsules sold (ex-factory sales) by the number of capsules taken per day. The total number of days of medication is then divided by 365.25 in order to calculate the total patient exposure in PY.

Exposure data by gender, age and/or indication are not available for Vargatef.

SV.1.2 Exposure

The overall cumulative patient exposure to marketed Vargatef is 7770 PY for the period November 2014 to May 2021. Calculated cumulative exposure by region and by EU/EEA country are presented in tables SV.Table 1 and SV.Table 2 below.

SV.Table 1 Cumulative exposure from marketing experience by region and dose (November 2014 to May 2021)

Strength (dose)	Patient exposure[1] [PY]
EEA	
100 mg	4322
150 mg	1207
Other	
100 mg	1091
150 mg	1150
Total	**7770**

[1] All numbers are rounded to the next integer.

Data source: Data on file, EA-009 Vargatef exposure (2021 05)

[redacted]

SV.Table 2 Cumulative exposure from marketing experience by formulation, dose and EU/EEA country (November 2014 to May 2021)

Country	**Formulation, Strength (dose)**	**Patient exposure [PY]**	**Units sold[1] [bulk unit]**
Germany	Capsules 100mg	[redacted]	
	Capsules 150mg		
Denmark	Capsules 100mg		
	Capsules 150mg		
Norway	Capsules 100mg		
	Capsules 150mg		
Sweden	Capsules 100mg		
	Capsules 150mg		
Malta	Capsules 100mg		
	Capsules 150mg		
Ireland	Capsules 100mg		
	Capsules 150mg		
Netherlands	Capsules 100mg		
	Capsules 150mg		
Belgium	Capsules 100mg		
	Capsules 150mg		
Italy	Capsules 100mg		
	Capsules 150mg		
Croatia	Capsules 100mg		
	Capsules 150mg		
Slovenia	Capsules 100mg		
	Capsules 150mg		
Austria	Capsules 100mg		
	Capsules 150mg		
Spain	Capsules 100mg		
	Capsules 150mg		
Portugal	Capsules 100mg		
	Capsules 150mg		
Bulgaria	Capsules 100mg		
	Capsules 150mg		

[redacted]

SV.Table 2 (cont'd) Cumulative exposure from marketing experience by formulation, dose and EU/EEA country (November 2014 to May 2021)

Country	Formulation, Strength (dose)	Patient exposure [PY]	Units sold[1] [bulk unit]
Poland	Capsules 100mg	[redacted]	
	Capsules 150mg		
Hungary	Capsules 100mg		
	Capsules 150mg		
Czech Republic	Capsules 100mg		
	Capsules 150mg		
Slovak Republic	Capsules 100mg		
	Capsules 150mg		
Greece	Capsules 100mg		
	Capsules 150mg		
Cyprus	Capsules 100mg		
	Capsules 150mg		
Estonia	Capsules 100mg		
	Capsules 150mg		
Lithuania	Capsules 100mg		
	Capsules 150mg		
Total		**5529**	**7 196 580**

[1] All numbers are rounded to the next integer.
Data source: Data on file, EA-009 Vargatef exposure (2021 05)

SV.2 REFERENCES

Not applicable.

ABBREVIATIONS

EEA	European Economic Area
EU	European Union
PY	Patient-years

MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Vargatef is available as a prescription-only medicine. Vargatef has neither psycho-stimulating effects nor any other effects that might lead to dependency. There is no pattern of signals indicative of the potential for illegal misuse. Vargatef is not considered to have the potential for abuse based on its mechanism of action and safety profile. No dependence studies were conducted in humans or animals.

SVI.2 REFERENCES

Not applicable.

MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Since this is not an initial RMP submission, only an overview of the safety concerns identified at the time of first authorisation is provided below.

SVII.Table 1 Summary of safety concerns at the time of first marketing authorisation

Important identified risks	Diarrhoea
	Liver enzyme elevations and hyperbilirubinaemia
	Neutropenia
	Sepsis
	Venous thromboembolism
	Perforation (gastrointestinal and non-gastrointestinal)
	Bleeding
	Hypertension
Important potential risks	Arterial thromboembolism
	Treatment in pregnant women and teratogenicity
	Hepatic failure
	Cardiac failure
	QT prolongation
Missing information	Treatment of breastfeeding women
	Treatment of patients with hepatic impairment
	Treatment of patients with renal impairment
	Treatment of patients with healing wounds
	Treatment of subpopulations with co-morbid CNS conditions such as dementia, depression, brain metastasis, or with co-morbid conditions such as arthritis and osteoporosis
	Treatment of patients weighing <50 kg
	In vitro inhibitory potential on OAT1 and OAT3

Data source: Vargatef RMP v1.4 [s00020173-01], SVIII.Table 1

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

With the EU-RMP version 10.1, the list of safety concerns in the Vargatef EU-RMP has been revised in line with GVP Module V, Rev 2. The following safety concerns are proposed to be removed from the Vargatef EU-RMP:

Important identified risks
- Diarrhoea
- Neutropenia
- Sepsis
- Venous thromboembolism
- Perforation (gastrointestinal and non-gastrointestinal)
- Bleeding
- Hypertension
- Myocardial infarction

Important potential risks
- Arterial thromboembolism excluding myocardial infarction
- Treatment in pregnant women and teratogenicity
- Cardiac failure

Missing information
- Treatment of breastfeeding women
- Treatment of patients with moderate or severe hepatic impairment (Child Pugh B/C)
- Treatment of patients with healing wounds
- Treatment of subpopulations with co-morbid CNS conditions such as dementia, depression, brain metastasis, or with comorbid conditions such as arthritis and osteoporosis

Detailed justifications for removal are provided for each safety concern in the sections below.

SVII.2.1 Important identified risks

SVII.2.1.1 Diarrhoea

In clinical trials, diarrhoea was the most common ADR of Vargatef in co-administration with docetaxel. In the Vargatef pivotal clinical trial, diarrhoea has been reported in the Vargatef+docetaxel arm at an overall frequency of 42.3% vs. 21.8% in the placebo+docetaxel arm (see SVII.Table 2). In the majority of cases diarrhoea events were non-serious and of mild to moderate intensity. In patients treated with Vargatef+docetaxel, serious diarrhoea occurred at low frequencies of up to 2.6% (see SVII.Table 2). Patients on Vargatef+docetaxel had a longer median time to first onset and a longer duration of diarrhoea than patients who received placebo+docetaxel. There appeared to be a temporal association of diarrhoea onset with docetaxel. In patients with adenocarcinoma, 11 patients in the placebo arm and 26 patients in the Vargatef arm had a dose reduction of Vargatef or placebo due to diarrhoea. Diarrhoea led to permanent discontinuation of the study medication in 1 patient in the placebo arm and in 3 patients in the Vargatef arm. Most patients throughout both treatment arms recovered from their diarrhoea.

SVII.Table 2 Diarrhoea in the Vargatef pivotal clinical trial 1199.13

	All patients		Adenocarcinoma	
	Placebo+ docetaxel N=655	Vargatef+ docetaxel N=652	Placebo+ docetaxel N=333	Vargatef+ Docetaxel N=320
Patients with event MedDRA PT Diarrhoea, N (%)	143 (21.8)	276 (42.3)	82 (24.6)	139 (43.4)
Incidence rate per 100 patient years	63.86	145.78	67.13	139.72
Incidence rate ratio (95% CI)*	2.28 (1.87 2.79)[#]		2.08 (1.58, 2.73)[#]	
Incidence rate difference (95% CI)*	81.92 (61.79, 102.05)[##]		72.60 (45.20, 99.99)[##]	
Patients with serious event PT Diarrhoea, N (%)	13 (2.0)	17 (2.6)	7 (2.1)	6 (1.9)
Patients with fatal event PT Diarrhoea, N (%)	0	1 (0.2)	0	0
Patients with CTCAE grade ≥3 event PT Diarrhoea, N (%)	17 (2.6)	44 (6.7)	12 (3.6)	20 (6.3)
Patients with event PT Diarrhoea recovered, N (%)	140 (21.4)	265 (40.6)	80 (24.0)	135 (42.2)

[*] Vargatef+docetaxel vs placebo+docetaxel
[#] IR ratio significantly different from 1.
[##] IR difference significantly different from 0.
Data source: Vargatef EU-RMP v5.1 [s00020173-16], SVII.Table 2 and 3

The cumulative post-marketing experience (MedDRA PT Diarrhoea, MedDRA version 24.0, DLP 31 May 2021, data source BI GSP) is in line with the clinical trial experience. Diarrhoea is also the most frequent post-marketing event; it was non-serious in 88.0% of the 672 reported cases. Serious episodes of diarrhoea, if left untreated, might result in dehydration and electrolyte imbalances that could lead to acute renal function impairment. Serious cases of diarrhoea leading to concurrent dehydration, electrolyte imbalances, or renal function impairment were infrequently reported cumulatively: Dehydration in 5, electrolyte imbalances in 3, and acute renal failure in 2 out of 672 diarrhoea cases (events recovered in the majority of cases). Diarrhoea recovered/ was recovering in 403 (60.0%) of the 672 reported cases. The cumulative diarrhoea reporting rate of 8.6 per 100 patient years has remained relatively stable over more than 5 years.

This important identified risk is considered fully characterised requiring no further evaluation; there are no outstanding additional pharmacovigilance activities.

Diarrhoea associated with docetaxel+Vargatef is well known to oncologists and is manageable/ reversible by routine risk minimisation through labelling. Current labelling includes comprehensive information on the characteristics of diarrhoea, potential complications, as well as management recommendations (adequate hydration, anti-diarrhoeal treatment, dose interruptions, dose reductions, dose discontinuations, electrolyte administration). These allow the specialised physicians prescribing Vargatef, to understand and appropriately manage this risk including the prevention of severe outcomes.

The MAH considers that current routine minimisation activities are appropriate for management of the diarrhoea risk and no additional risk minimisation measures are deemed necessary. Consequently, demotion of this safety concern from the EU-RMP is recommended. The topic will continue to be presented in PBRERs.

SVII.2.1.2 Neutropenia

Relevant clinical outcomes of neutropenia such as febrile neutropenia and sepsis are also discussed under SVII.2.1.3.

For clinical trial and post-marketing analyses, information about neutropenia was analysed using a search based on the non-standardised query (UDAEC) 'Neutropenia' (see Appendix 7A, Table 1 for details). In addition, neutropenia was analysed using laboratory data.
In the Vargatef pivotal clinical trial, decreased neutrophil counts measured as laboratory value of any CTC AE grade were slightly more frequent in patients treated with Vargatef+docetaxel versus placebo+docetaxel (see SVII.Table 4). This was associated with an increased frequency of sepsis in the Vargatef arm (see SVII.2.1.3 Sepsis). Time adjusted incidence rates of neutropenia adverse events were not higher with Vargatef+docetaxel for both all grade as well as for grade ≥3 adverse events (see SVII.Table 4 and SVII.Table 5). Serious neutropenia adverse events were slightly more frequent in the Vargatef arm and mostly required and/or prolonged hospitalisation. One patient in the Vargatef arm (overall population) had a fatal outcome; the patient died due to neutropenic infection. In both treatment arms, the majority of the neutropenia events was of grade 3-4 (see SVII.Table 4 and 5). Whether reported as AEs or as laboratory values, neutropenia had a comparable time to first onset and median duration in the Vargatef and the placebo treatment arms. A slightly longer time to onset was noted for neutrophil count of CTC AE grade 4 in the nintedanib+docetaxel versus placebo+docetaxel (adenocarcinoma patients). The vast majority of patients throughout treatment arms recovered from their neutropenia events (see SVII.Table 4).

SVII.Table 3 Neutrophil counts (laboratory value) in the Vargatef pivotal clinical trial 1199.13

	All patients		**Adenocarcinoma**	
	Placebo+ docetaxel N=655	Vagatef + docetaxel N=652	Placebo+ docetaxel N=333	Vargatef+ Docetaxel N=320
Patients with laboratory value neutrophil counts, N (%)	447 (68.2)	484 (74.2)	240 (72.1)	256 (80.0)
Incidence rate per 100 patient years	578.0	614.2	680.4	722.7
Incidence rate ratio (95% CI)*	1.06 (0.94, 1.21)		1.06 (0.89, 1.26)	
Incidence rate difference (95% CI)*	36.19 (−40.39, 112.77)		42.22 (−81.26, 165.70)	

* Vargatef+docetaxel vs placebo+docetaxel
Data source: Vargatef EU-RMP v5.1 [s00020173-16], SVII.Table 33

SVII.Table 4 Neutropenia AEs (all CTC AE grades) in the Vargatef pivotal clinical trial 1199.13

	All patients		Adenocarcinoma	
	Placebo+ docetaxel N=655	Vargatef+ docetaxel N=652	Placebo+ docetaxel N=333	Vargatef+ Docetaxel N=320
Patients with event*, N (%)	323 (49.3)	326 (50.0)	178 (53.5)	176 (55.0)
Incidence rate per 100 patient years	249.24	196.33	279.03	209.85
Incidence rate ratio (95% CI)**	0.79 (0.68, 0.92)[#]		0.75 (0.61, 0.93)[#]	
Incidence rate difference (95% CI)**	−52.91 (−87.45, −18.37)[##]		−69.19 (−120.58, −17.79)[##]	
Patients with serious event*, N (%)	43 (6.6)	58 (8.9)	18 (5.4)	28 (8.8)
Patients with fatal event*, N (%)	0	1 (0.2)	0	1 (0.3)
Patients with event* recovered, N (%)	316 (48.2)	316 (48.5)	174 (52.3)	171 (53.4)

* UDAEC Neutropenia
** Vargatef+docetaxel vs placebo+docetaxel
[#] IR ratio significantly different from 1.
[##] IR difference significantly different from 0.
Data source: Vargatef EU-RMP v5.1 [s00020173-16], SVII.Table 31 and 33

SVII.Table 5 Neutropenia AEs (CTC AE grade ≥3) in the Vargatef pivotal clinical trial 1199.13

	All patients		**Adenocarcinoma**	
	Placebo+ docetaxel N=655	Vargatef+ docetaxel N=652	Placebo+ docetaxel N=333	Vargatef+ Docetaxel N=320
Patients with event*, N (%)	273 (41.7)	292 (44.8)	155 (46.5)	161 (50.3)
Incidence rate per 100 patient years	171.59	161.76	185.21	173.25
Incidence rate ratio (95% CI)**	0.94 (0.80, 1.11)		0.94 (0.75, 1.17)	
Incidence rate difference (95% CI)**	-9.83 (-37.37, 17.71)		-11.95 (−51.53, 27.6227)	

* UDAEC Neutropenia, CTC AE grade ≥3
** Vargatef+docetaxel vs placebo+docetaxel
Data source: Vargatef EU-RMP v5.1 [s00020173-16], SVII.Table 33

Neutropenia is among the most frequently reported events post-marketing (UDAEC Neutropenia, MedDRA version 24.0, DLP 31 May 2021, data source BI GSP). Cumulatively, neutropenia was serious in 62.0% of the 245 reported post-marketing cases. Most frequent events (both serious and non-serious) were neutropenia (104 cases), febrile neutropenia (64 cases), neutrophil count decreased (60 cases). Most events were reported as recovered/resolved (64.5%). In seven patients, neutropenia events were reported with fatal outcome; these were: Febrile neutropenia (2 cases), (neutropenic) sepsis (3 cases),

neutropenia reported with respiratory failure from lung cancer progression (1 case). One case had very limited information (data source: BI GSP).

The cumulative neutropenia reporting rate of 3.15 per 100 patient years has remained relatively stable over more than 5 years.

Neutropenia is considered fully characterised requiring no further evaluation; there are no outstanding additional pharmacovigilance activities.

The neutropenia risk is well known to oncologists and it is appropriately managed by routine risk minimisation through labelling. Current labelling includes comprehensive information on the characteristics of neutropenia, complications, and management recommendations. These allow the specialised physicians prescribing Vargatef to understand and appropriately manage this risk including the prevention of severe outcomes. The MAH considers that current routine minimisation activities are appropriate for management of the neutropenia risk. No additional risk minimisation measures are deemed necessary. Consequently, demotion of this safety concern from the EU-RMP is recommended. Neutropenia is a laboratory value and thereby does not qualify as an important risk in the RMP. The MAH will continue to monitor neutropenia through routine pharmacovigilance and the established signal detection and evaluation process as applicable. Relevant clinical outcomes of neutropenia, including febrile neutropenia and sepsis will continue to be closely monitored and will be presented under the topic ‘Sepsis’ in PBRERs.

SVII.2.1.3 Sepsis

For the analyses of this risk, the newly available SMQ ‘Sepsis’ (narrow) has been applied. The SMQ sepsis contains by far more terms than the UDAEC that had been used earlier (please see the UDAEC used earlier in Appendix 7a of the Vargatef EU-RMP v9.0 [s00020173-22]). Those few and mostly unspecific terms (Bacterial toxaemia, Bacterial translocation, Bacteroides bacteraemia, Endotoxaemia, Fungaemia, Thrombophlebitis septic, Viraemia) that are missing in the narrow SMQ ‘Sepsis’ had no influence on data presentation. The narrow SMQ ‘Sepsis’ detected the same cases as the UDAEC did from both the pivotal clinical trial and from post-marketing cases. Furthermore, SMQs are standardised and constantly being updated by the MedDRA Maintenance and Support Services Organisation (MSSO).

In the Vargatef pivotal clinical trial, the frequency of patients with sepsis was higher in the Vargatef +docetaxel versus the placebo+docetaxel arm. The IR ratio for Vargatef vs placebo was 1.80 in patients with adenocarcinoma and 2.18 in the overall population (see SVII.Table 6). Sepsis is a serious, frequently life-threatening condition. Most of the sepsis events were serious and required or prolonged hospitalisation. Overall, in 1 patient in the placebo arm and in 7 patients in the Vargatef arm, sepsis had a fatal outcome. The remaining patients recovered from their sepsis events (see SVII.Table 6). Time to onset and duration of sepsis were shorter in the Vargatef arm than in the placebo arm. Among the patients in the overall population who received Vargatef, 3 out of 10 were known to have neutropenia at the time of sepsis. Neutrophil counts at time of sepsis were not reported for the other 7 patients, but many of these patients were neutropenic during chemotherapy cycles before the septic

episode. This suggests that docetaxel-induced neutropenia may have contributed to the incidence of patients with sepsis in the Vargatef arm of trial 1199.13 [P14-02206].

SVII.Table 6 Sepsis AEs in the Vargatef pivotal clinical trial 1199.13

	All patients		Adenocarcinoma	
	Placebo+ docetaxel N=655	Vargatef+ docetaxel N=652	Placebo+ docetaxel N=333	Vargatef+ Docetaxel N=320
Patients with event*, N (%)	4 (0.6)	10 (1.5)	2 (0.6)	4 (1.3)
Incidence rate per 100 patient years	1.42	3.08	1.26	2.27
Incidence rate ratio (95% CI)**	2.18 (0.68, 6.95)		1.80 (0.33, 9.85)	
Incidence rate difference (95% CI)**	1.67 (−0.6933, 4.0286)		1.01 (−1.81, 3.83)	
Patients with serious event*, N (%)	4 (0.6)	9 (1.4)	2 (0.6)	4 (1.3)
Patients with fatal event*, N (%)	1 (0.2)	7 (1.1)	0	3 (0.9)
Patients with CTCAE grade ≥3 event*, N (%)	3 (0.5)	9 (1.4)	2 (0.6)	4 (1.3)
Patients with recovered event*, N (%)	3 (0.5)	3 (0.5)	2 (0.6)	1 (0.3)

* Narrow SMQ ‘Sepsis’
** Vargatef+docetaxel vs placebo+docetaxel
Data source: Vargatef EU-RMP v5.1 [s00020173-16], SVII.Table 39 and 40

Cumulatively during post-marketing (Narrow SMQ ‘Sepsis’, MedDRA version 24.0, DLP 31 May 2021, data source BI GSP), 58 cases concerning this risk were received, all sepsis events were serious. Reporter causality was unrelated to treatment with Vargatef in 27 cases (46.6%) and related in 14 cases (24.1%); it was not reported in 16 cases (27.6%). 1 case reported 2 sepsis events: 1 event was unrelated and the other event was related. In 18 cases (31.0%), the events recovered/resolved. The outcome was unknown in 12 cases (20.7%). 25 cases (43.1%) reported a fatal sepsis event (sepsis in 22 cases and neutropenic sepsis, urosepsis, and septic shock in 1 case each).

Causative factor for both development and fatal outcome of sepsis in many cases was the underlying advanced or progressive lung cancer associated with lower respiratory tract infections leading to sepsis. There was also a contribution of docetaxel to the development of sepsis. The treatment of some patients with palliative care has further contributed to the fatal outcome. The proportion of patients with fatal sepsis during post-marketing (43.1%) was not increased compared to the pivotal clinical trial (70%). By its nature, sepsis is known to have a high mortality rate. The cumulative sepsis reporting rate of 0.75 per 100 patient years has remained relatively stable over more than 5 years. Also cumulatively, the reporting rate of sepsis with fatal outcome has remained relatively stable with 0.36 per 100 patient years.

Routine risk minimisation measures are current for the risk of sepsis. The recommendations for monitoring of blood counts and for dose adjustments of Vargatef due to AEs in the CCDS are appropriate. Furthermore, a cross reference to the product information of docetaxel indicates that the recommendations for docetaxel need to be considered as well.

Febrile neutropenia and sepsis are appropriately managed by routine risk minimisation through labelling. Current labelling includes comprehensive information on the characteristics of neutropenia, subsequent complications such as sepsis and febrile neutropenia (including fatal cases), and management recommendations: Blood counts monitoring, in particular during the combination treatment with docetaxel, i.e. at the beginning of each treatment cycle and around the nadir for patients receiving treatment with Vargatef in combination with docetaxel, and as clinically indicated after the administration of the last combination cycle. A cross-reference to the product information of docetaxel is provided as well. This allows the specialised physicians prescribing Vargatef to fully understand and appropriately manage this risk.

Sepsis is considered fully characterised requiring no further evaluation; there are no outstanding additional pharmacovigilance activities.

The MAH considers that current routine minimisation activities are appropriate for management of sepsis and no additional risk minimisation measures are deemed necessary. Consequently, demotion of this safety concern from the EU-RMP is recommended. Sepsis will continue to be closely monitored and presented in PBRERs.

SVII.2.1.4 Venous thromboembolism (VTE)

Cancer patients are in a hypercoagulable state owing to the procoagulant activity of cancer cells. The medical concept of VTE includes deep and superficial venous thrombotic events and pulmonary embolism (PE) as common complication of deep vein thrombosis. In the Vargatef pivotal clinical trial, VTE events were more frequent in patients treated with Vargatef+docetaxel vs. placebo+docetaxel (overall frequency 2.8% vs. 1.5%; time adjusted incidence rate 5.71 vs. 3.54 per 100 patient years). The frequency of grade ≥3 VTE events was comparable between both treatment arms (see SVII.Table 7). The majority of VTE events in the placebo arm and approximately half of the VTE events in the Vargatef arm were serious (see SVII.Table 7). Most of the serious VTE events required or prolonged hospitalisation. VTE was fatal in 3 patients in the placebo arm (all had PE) and in 2 patients on Vargatef (superior vena cava syndrome and venous thrombosis in 1 patient each) [U13-1504-01]. VTE events recovered in 4 of 10 patients on placebo and in 9 of 18 patients on Vargatef (see SVII.Table 7).

SVII.Table 7 Venous thromboembolism (VTE) events in the Vargatef pivotal clinical trial 1199.13

	All patients		Adenocarcinoma	
	Placebo+ docetaxel N=655	Vargatef+ docetaxel N=652	Placebo+ docetaxel N=333	Vargatef+ docetaxel N=320
Patients with event*, N (%)	10 (1.5)	18 (2.8)	4 (1.2)	9 (2.8)
Patients with event Pulmonary embolism, N (%)	6 (0.9)	5 (0.8)	3 (0.9)	4 (1.3)
Incidence rate per 100 patient years	3.54	5.71	2.51	5.13
Incidence rate ratio (95% CI)**	1.61 (0.74, 3.49)		2.04 (0.63, 6.64)	
Incidence rate difference (95% CI)**	2.17 (−1.26, 5.60)		2.62 (−1.54, 6.78)	
Patients with serious event*, N (%)	7 (1.1)	10 (1.5)	3 (0.9)	4 (1.3)
Patients with fatal event*, N (%)	3 (0.5)	2 (0.3)	0	0
Patients with CTCAE grade ≥3 event*, N (%)	7 (1.1)	8 (1.2)	2 (0.6)	3 (0.9)
Patients with event* recovered, N (%)	4 (0.6)	9 (1.4)	3 (0.9)	4 (1.3)

* Narrow SMQ 'Embolic and thrombotic events, venous'
** Vargatef+docetaxel vs placebo+docetaxel
Data source: Vargatef EU-RMP v5.1 [s00020173-16], SVII.Table 46, 47 and 48

Cumulatively during post-marketing (narrow SMQ 'Embolic and thrombotic events, venous', MedDRA version 24.0, DLP 31 May 2021, data source BI GSP), in 54 of the reported 60 cases with VTE, the events were serious (90.0%). Most frequently reported VTE events were PE and deep vein thrombosis. Most of the events were treated and 16 patients (26.7%) recovered from their events. In 10 cases (16.7%), VTE events had a fatal outcome: Fatal events were PE in 8 cases and superior vena cava syndrome and portal vein thrombosis in 1 case each.

- In 5 of the 10 cases with fatal VTE events (4 PE, 1 superior vena cava syndrome), the underlying malignancy (pericardial effusion with compression of right atrium, tumour-associated retention pneumonia, superior vena cava syndrome, tumour progression) contributed to the fatal VTE events
  - in 3 of the 5 cases Vargatef had been stopped 2 years, 2 months, 26 days before onset of the fatal event respectively
  - Risk factors in 4 of the 5 cases were: coronary artery disease (2 cases), pre-existing polycythemia vera, pre-existing deep vein thrombosis/superior vena cava syndrome
- In 3 of the 10 cases with fatal VTE events (all PE), PE was suspected but not verified by diagnostic tests; in 1 case aspiration pneumonia was an alternative cause of death. In another case pulmonary embolism developed after bilateral pneumonia treated in ICU (immobilisation) in a patient (tobacco user) with lung lobectomy.
- In 2 of the 10 cases with fatal VTE events (1 PE, 1 portal vein thrombosis), the reported information was insufficient to determine the cause of death.

The cumulative reporting rate for VTE events of 0.77 per 100 patient years has remained relatively stable over more than 5 years. Also, the cumulative reporting rate for fatal VTE events of 0.13 per 100 patient years has remained relatively stable over more than 5 years.

This important identified risk is considered fully characterised requiring no further evaluation; there are no outstanding additional pharmacovigilance activities.

This risk is appropriately managed by routine risk minimisation through labelling. Current labelling includes that patients treated with Vargatef 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. Vargatef should be discontinued in patients with life-threatening venous thromboembolic reactions. The MAH considers that current routine minimisation activities are appropriate for management of this risk and no additional risk minimisation measures are deemed necessary. Consequently, demotion of this safety concern from the RMP is recommended. This risk will continue to be closely monitored and will continue to be presented in PBRERs.

SVII.2.1.5 Perforation (gastrointestinal and non-gastrointestinal)

GI perforation has been considered a class effect of VEGF inhibition in cancer patients. In the Vargatef pivotal clinical trial, frequencies of GI perforation events were low and balanced between the treatment arms Vargatef+docetaxel versus placebo+docetaxel. For GI perforation, the IR ratio for Vargatef vs placebo was 0.90 in patients with adenocarcinoma and 0.87 in the overall population (all patients). All but one GI perforation events were serious (see SVII.Table 8). One event (large intestine perforation) was fatal in both treatment arms [U13-1504-01]. The remaining patients recovered from their events.

SVII.Table 8 Gastrointestinal perforation in the Vargatef pivotal clinical trial 1199.13

	All patients		Adenocarcinoma	
	Placebo+ docetaxel N=655	Vargatef+ docetaxel N=652	Placebo+ docetaxel N=333	Vargatef + docetaxel N=320
Patients with event*, N (%)	3 (0.5)	3 (0.5)	1 (0.3)	1 (0.3)
Incidence rate per 100 patient years	1.06	0.92	0.63	0.57
Incidence rate ratio (95% CI)**	0.87 (0.18, 4.32)		0.90 (0.06, 14.43)	
Incidence rate difference (95% CI)**	−0.14 (−1.73, 1.46)		−0.06 (−1.72, 1.59)	
Patients with serious event*, N (%)	3 (0.5)	2 (0.3)	1 (0.3)	1 (0.3)
Patients with fatal event*, N (%)	1 (0.2)	1 (0.2)	0	1 (0.3)
Patients with CTCAE grade ≥3 event*, N (%)	3 (0.5)	1 (0.2)	1 (0.3)	1 (0.3)
Patients with event* recovered, N (%)	2 (0.3)	2 (0.3)	1 (0.3)	0

* Narrow SMQ 'Gastrointestinal perforation'
** Vargatef+docetaxel vs placebo+docetaxel
Data source: Vargatef EU-RMP v5.1 [s00020173-16], SVII.Table 54; Vargatef EU-RMP v6.0 [s00020173-17], SVII.Table 55

Events of non-GI perforation were analysed using the non-standardised query (UDAEC) 'Non-GI hollow organ and tumour perforation' (see Appendix 7A, Table 1 for details). Events of non-GI perforation were only reported in the Vargatef treatment arm; the majority was non-serious (see SVII.Table 9). Lung abscess was reported in 3 of the 6 cases in the Vargatef arm. One event of lung abscess had a fatal outcome [U13-1504-01]; the remaining patients recovered from their events (1 with sequelae).

SVII.Table 9 Non-gastrointestinal perforation in the Vargatef pivotal clinical trial 1199.13

	All patients		Adenocarcinoma	
	Placebo+ docetaxel N=655	Vargatef+ docetaxel N=652	Placebo+ docetaxel N=333	Vargatef+ docetaxel N=320
Patients with event*, N (%)	0	6 (0.9)	0	3 (0.9)
Incidence rate per 100 patient years	0	1.85	0	1.70
Incidence rate ratio (95% CI)**	-		-	
Incidence rate difference (95% CI)**	1.85 (0.37, 3.33)[#]		1.70 (−0.22, 3.62)	
Patients with serious event*, N (%)	0	2 (0.3)	0	1 (0.3)
Patients with fatal event*, N (%)	0	1 (0.2)	0	1 (0.3)
Patients with CTCAE grade ≥3 event*, N (%)	0.	2 (0.3)	0	1 (0.3)
Patients with event* recovered, N (%)	0	4 (0.6)	0	1 (0.3)

* Narrow BIcMQ 'Non-GI hollow organ and tumour perforation'
** Vargatef+docetaxel vs placebo+docetaxel
[#] Incidence rate difference significantly different from 0.
Data source: Vargatef EU-RMP v6.0 [s00020173-17], SVII.Table 54 and 55

During post-marketing, follow-up questionnaires were used to obtain additional information to further characterise both GI and non-GI perforation events. Cumulatively (narrow SMQ 'Gastrointestinal perforation', MedDRA version 24.0, DLP 31 May 2021, data source BI GSP), in 28 of the reported 29 cases with GI perforation, the events were serious (96.6%). Most frequently reported GI perforation events are provided in SVII.Table 10 below:

SVII.Table 10 Most frequently reported GI perforation events* (>2) in 29 post marketing cases

Total patients with events*	29	100.0%
Large intestine perforation	8	27.6%
Intestinal perforation	6	20.7%
Gastrointestinal perforation	4	13.8%

*Narrow SMQ 'Gastrointestinal perforation'
Data source: BI GSP

In 12 cases (41.4%), GI perforation events had a fatal outcome. These fatal events were: Intestinal perforation (4 cases), large intestine perforation (4 cases), GI perforation (2 cases), and 1 case each: Small intestinal perforation/peritonitis, and perforated ulcer. Seven patients (24.1%) recovered from their events. The cumulative reporting rate for GI perforation events of 0.37 per 100 patient years has remained relatively stable over more than 5 years.

No post-marketing cases of non-GI perforation have been reported cumulatively (narrow BIcMQ 'Non-GI hollow organ and tumour perforation', MedDRA version 24.0, DLP 31 May 2021, data source BI GSP). The query identified 3 cases: 1 with serious tracheal fistula, 1 non-serious bronchial fistula, and 1 non-serious abscess oral (recovered); all 3 were per reporter not related to Vargatef. The cumulative reporting rate for non-GI perforation events of 0.04 per 100 patient years has remained relatively stable over more than 5 years.

This important identified risk is considered fully characterised requiring no further evaluation; there are no outstanding additional pharmacovigilance activities. Consequently, the MAH proposes to conclude sending follow-up questionnaires for perforation event cases.

This risk is appropriately managed by routine risk minimisation through labelling. Current labelling includes that cases of GI perforations, some of which were fatal, have been reported in the post-marketing period. Particular caution should be exercised when treating patients with previous abdominal surgery or a recent history of a hollow organ perforation. Vargatef should therefore only be initiated at least 4 weeks after major, including abdominal, surgery. Vargatef should be permanently discontinued in patients who developed GI perforation. The medical concept of non-GI perforation includes abscesses which are a labelled as Vargatef side effect. The MAH considers that current routine minimisation activities are appropriate for management of the perforation risk and no additional risk minimisation measures are deemed necessary. Consequently, demotion of this safety concern from the RMP is recommended. This risk will be further monitored through routine pharmacovigilance activities. GI perforation will continue to be presented in PBRERs.

SVII.2.1.6 Bleeding

Bleeding is a class effect of VEGF inhibition. In the Vargatef pivotal clinical trial, bleeding events were slightly more frequent in patients treated with Vargatef+docetaxel vs. placebo+docetaxel (14.1% vs. 11.8%; time adjusted incidence rate 31.19 vs. 29.84 per 100 patient years, all patients). The imbalance in all patients was driven by patients with squamous NSCLC. In patients with adenocarcinoma, the frequency of bleeding was comparable between both treatment arms. The frequencies of serious bleeding events were comparable between both treatment groups. There were no imbalances of respiratory or fatal bleedings; intracerebral bleeding was not reported. The majority of fatal bleeding events were tumour-associated. Most events of bleeding were of CTCAE grade 1 or 2. Mild to moderate epistaxis represented the most frequent bleeding event. The majority of patients throughout treatment arms recovered from their bleeding events (see SVII.Table 11).

SVII.Table 11 Bleeding in the Vargatef pivotal clinical trial 1199.13

	All patients		Adenocarcinoma	
	Placebo+ docetaxel N=655	Vargatef+ docetaxel N=652	Placebo+ docetaxel N=333	Vargatef+ docetaxel N=320
Patients with event*, N (%)	77 (11.8)	92 (14.1)	38 (11.4)	35 (10.9)
Incidence rate per 100 patient years	29.84	31.19	26.41	21.48
Incidence rate ratio (95% CI)**	1.05 (0.77, 1.41)		0.81 (0.51, 1.29)	
Incidence rate difference (95% CI)**	1.35 (−7.87, 10.57)		−4.93 (−15.94, 6.08)	
Patients with serious event*, N (%)	15 (2.3)	17 (2.6)	5 (1.5)	4 (1.3)
Patients with fatal event*, N (%)	7 (1.1)	9 (1.4)	2 (0.6)	3 (0.9)
Patients with CTCAE grade ≥3 event*, N (%)	12 (1.8)	15 (2.3)	5 (1.5)	4 (1.3)
Patients with event* recovered, N (%)	61 (9.3)	66 (10.1)	31 (9.3)	31 (9.7)

* Narrow SMQ 'Haemorrhage terms, excluding laboratory terms'
** Vargatef+docetaxel vs placebo+docetaxel
Data source: Vargatef EU-RMP v5.1 [s00020173-16], SVII.Table 66 and 67

Cumulatively, during post-marketing (narrow SMQ 'Haemorrhage terms, excluding laboratory terms', MedDRA version 24.0, DLP 31 May 2021, data source BI GSP), the reported bleeding events were non-serious in almost two-thirds (63.3%) of the 109 reported cases. Follow-up questionnaires were used to obtain additional information to further characterise bleeding events. Most frequently reported were bleeding events in the respiratory tract (55.0% of the 109 reported cases) with 27.5% epistaxis and 27.5% haemoptysis (see SVII.Table 12). GI tract bleedings were reported in 21.1% of the 109 reported cases with rectal haemorrhage as most frequent event (5.5%). In 14 cases (12.8%), bleeding events had a fatal outcome. The majority of fatal bleeding events (haemoptysis 4, pulmonary/alveolar haemorrhage 3, tumour haemorrhage 1, epistaxis 1, intracranial haemorrhage 1) were tumour-associated (10 cases). The event outcome was recovered/resolved for more than half (52.3%) of the 109 cases reporting bleeding events. The cumulative reporting rate for bleeding events of 1.40 per 100 patient years has remained relatively stable over more than 5 years.

SVII.Table 12 Most frequently reported bleeding events* (>5) in 109 post marketing cases reporting 111 bleeding events, by seriousness

	All events N (%)		Non-serious N (%)		Serious N (%)	
Total patients with events*	109	100.0%	69	63.3%	42	38.5%
Epistaxis	30	27.5%	28	25.7%	3**	2.8%
Haemoptysis	30	27.5%	21	19.3%	9	8.2%
Haemorrhage	6	5.5%	2	1.8%	4	3.6%
Rectal haemorrhage	6	5.5%	4	3.6%	2	1.8%

*Narrow SMQ 'Haemorrhage terms, excluding laboratory terms'
**1 patient had both a serious and a non-serious epistaxis episode
Data source: BI GSP

This important identified risk is considered fully characterised requiring no further evaluation; there are no outstanding additional pharmacovigilance activities. Consequently, the MAH proposes to conclude sending follow-up questionnaires for bleeding event cases.

This risk is appropriately managed by routine risk minimisation through labelling. Current labelling includes the recommendation not to administer Vargatef in patients with active brain metastasis, recent pulmonary bleeding, centrally located tumours with radiographic evidence of local invasion of major blood vessels or radiographic evidence of cavitary or necrotic tumours. Monitoring is recommended in patients with risk factors including stable brain metastasis or anticoagulative treatment. In case of bleeding, dose adjustment, interruption or discontinuation should be considered based on clinical judgement. The MAH considers that current routine minimisation activities are appropriate for management of the bleeding risk and no additional risk minimisation measures are deemed necessary. Consequently, demotion of this safety concern from the RMP is recommended. This risk will continue to be presented in PBRERs.

SVII.2.1.7 Hypertension

In the pivotal Vargatef clinical trial, hypertension was more frequent in patients treated with Vargatef +docetaxel as compared to treatment with placebo+docetaxel. The time adjusted incidence rate of hypertension was 2.85 times higher with Vargatef+docetaxel (all patients). There were no serious AEs of hypertension in trial 1199.13. In both treatment arms, the vast majority of hypertension events were of CTCAE grades 1 and 2. There were few grade 3 events and no grade 4 or 5 events. Among all treated patients in trial 1199.13, the frequency of patients who started a new antihypertensive medication during the on-treatment period was 0.6% in the placebo arm and 2.1% in the Vargatef arm. Most patients throughout treatment arms recovered from hypertension (see SVII.Table 13).

SVII.Table 13 Hypertension in the Vargatef pivotal clinical trial 1199.13

	All patients		Adenocarcinoma	
	Placebo+ docetaxel N=655	Vargatef+ docetaxel N=652	Placebo+ docetaxel N=333	Vargatef+ Docetaxel N=320
Patients with event*, N (%)	7 (1.1)	23 (3.5)	2 (0.6)	11 (3.4)
Incidence rate per 100 patient years	2.55	7.28	1.28	6.42
Incidence rate ratio (95% CI)**	2.85 (1.22 6.65)#		5.02 (1.11, 22.65)#	
Incidence rate difference (95% CI)**	4.73 (1.21, 8.25)##		5.14 (0.95, 9.33)##	
Patients with serious event*, N (%)	0	0	0	0
Patients with event* recovered, N (%)	5 (0.8)	18 (2.8)	2 0.6)	9 (2.8)

* Narrow SMQ 'Hypertension'
** Vargatef+docetaxel vs placebo+docetaxel
# IR ratio significantly different from 1. ## IR difference significantly different from 0.
Data source: Vargatef EU-RMP v5.1 [s00020173-16], SVII.Table 74 and 75

The post-marketing experience (narrow SMQ 'Hypertension', MedDRA version 24.0, DLP 31 May 2021, data source BI GSP) is in line with the clinical trial experience. Cumulatively, hypertension was non-serious in 91.7% of the 24 reported cases. Hypertension recovered in (58.3%) of cases, there was no fatal outcome. The cumulative hypertension reporting rate of 0.31 per 100 patient years has remained relatively stable over more than 5 years.

This risk is considered fully characterised requiring no further evaluation; there are no outstanding additional pharmacovigilance activities.

Hypertension is appropriately managed by routine risk minimisation through labelling of hypertension as side effect. This allows the specialised physicians prescribing Vargatef to understand and appropriately manage this risk. The MAH considers that current routine minimisation activities are appropriate for management of the hypertension risk and no additional risk minimisation measures are deemed necessary. Consequently, the MAH recommends demotion of this safety concern from the EU-RMP. Hypertension will be further monitored through routine pharmacovigilance activities. This topic will not be presented on a routine basis in PBRERs unless a signal is identified.

SVII.2.1.8 Myocardial infarction (MI)

Cancer patients are in a hypercoagulable state owing to the procoagulant activity of cancer cells. ATE has been associated with VEGF inhibitors in combination treatment with chemotherapy for patients with cancer. Based on this, ATE was selected as an important potential risk for Vargatef. Upon EMA request, myocardial infarction was added as ADR in section 4.8 of the EU-SmPC. Consequently, in version 5.1 of the Vargatef EU-RMP, 'Myocardial infarction' was added as a new important identified risk and the important

potential risk ‘Arterial thromboembolism’ was updated into ‘Arterial thromboembolism excluding myocardial infarction’.

In the Vargatef pivotal clinical trial, adverse events of MI were infrequently reported, both in the Vargatef+docetaxel and in the placebo+docetaxel arm. The number of patients with MI was lower in the Vargatef arm as compared to the placebo arm (1 vs 3 in the adenocarcinoma population; 1 vs 4 in the overall population). The incidence rate ratios and risk ratios for Vargatef vs. placebo showed no substantial differences between the treatment groups. All MI events were serious and most of the events were of CTC AE grade ≥3 (see SVII.Table 14). One patient in the Vargatef arm had a MI with fatal outcome. This 61-year-old male patient suddenly died at home after approximately 3 months of treatment with Vargatef and 4 cycles of docetaxel. The reporter assessed the event MI as not related to the study medication.

SVII.Table 14 Myocardial infarction in the Vargatef pivotal clinical trial 1199.13

	All patients		**Adenocarcinoma**	
	Placebo+ docetaxel N=655	Vargatef+ docetaxel N=652	Placebo+ docetaxel N=333	Vargatef+ Docetaxel N=320
Patients with event*, N (%)	4 (0.6)	1 (0.2)	3 (0.9)	1 (0.3)
Incidence rate per 100 patient years	1.41	0.31	1.88	0.57
Incidence rate ratio (95% CI)**	0.22 (0.02, 1.94)		0.30 (0.03, 2.88)	
Incidence rate difference (95% CI)**	−1.11 (−2.62, 0.40)		−1.32 (-3.72, 1.08)	
Patients with serious event*, N (%)	4 (0.6)	1 (0.2)	3 (0.9)	1 (0.3)
Patients with fatal event*, N (%)	0	1 (0.2)	0	1 (0.3)
Patients with CTCAE grade ≥3 event*, N (%)	3 (0.5)	1 (0.2)	2 (0.6)	1 (0.3)
Patients with event*recovered, N (%)	4 (0.6)	0	3 (0.9)	0

* Narrow SMQ ‘Myocardial infarction’
** Vargatef+docetaxel vs placebo+docetaxel
Data source: Vargatef EU-RMP v5.1 [s00020173-16], SVII.Table 81 and 82

Cumulatively, during post-marketing (narrow SMQ ‘Myocardial infarction’, MedDRA version 24.0, DLP 31 May 2021, data source BI GSP) 8 cases of MI were received, all MI events were serious. Besides the advanced age, in 5 of the 8 cases, at least one cardiovascular risk factor was reported (coronary artery disease, diabetes mellitus, hypercholesterolemia, hypertension, tobacco use, metastasis, past cisplatin treatment). In 4 cases, MI events had a fatal outcome. In 3 cases of the 4 fatal cases, at least 3 risk factors were present (insufficient information received in 1 case). These cases received up to date are consistent with the mortality data in MI patients with multiple comorbidities [R21-1487, R21-1488]. MI recovered with sequelae in 2 of the 8 cases. The cumulative MI reporting rate of 0.10 per 100 patient years has remained relatively stable over more than 5 years.

This important identified risk is considered fully characterised requiring no further evaluation; there are no outstanding additional pharmacovigilance activities.
This risk is appropriately managed by routine risk minimisation through labelling: The population at risk (i.e. with cardiovascular risk factors) and arterial thromboembolism are addressed in labelling. MI is labelled as side effect in the EU-SmPC. This allows the specialised physicians prescribing Vargatef, to understand and appropriately manage this risk. The MAH considers that current routine minimisation activities are appropriate for management of this risk and there is no need for additional risk minimisation activities. Consequently, the MAH recommends demotion of this safety concern from the EU-RMP. The risk will be further monitored through routine pharmacovigilance activities and presented in PBRERs.

SVII.2.2 Important potential risks

SVII.2.2.1 Arterial thromboembolism (ATE) excluding myocardial infarction

Cancer patients are in a hypercoagulable state owing to the procoagulant activity of cancer cells. Arterial thromboembolism (ATE) has been associated with VEGF inhibitors in cancer patients treated with chemotherapy. Based on this, ATE was selected as an important potential risk for Vargatef. Upon EMA request in 2018, myocardial infarction was added as ADR in section 4.8 of the EU-SmPC. Consequently, in version 5.1 of the Vargatef EU-RMP, 'Myocardial infarction' was added as a new important identified risk and the important potential risk 'Arterial thromboembolism' was updated into 'Arterial thromboembolism excluding myocardial infarction'. One possible location of ATE is in the coronary arteries (see SVII.2.1.8 Myocardial infarction).

There was no evidence from the clinical trial programme with Vargatef to suggest that ATE excluding myocardial infarction is an important identified risk in lung cancer patients, as presented below. Of note, the searches used to analyse ATE in the pivotal clinical trial include MI related MedDRA PTs. In the Vargatef pivotal clinical trial, adverse events of ATE were infrequently reported. The frequencies and time adjusted incidence rates of ATE with Vargatef+docetaxel were lower as compared to treatment with placebo+docetaxel. The incidence rate ratio and risk ratio for Vargatef+docetaxel vs. placebo+docetaxel showed no substantial differences between the treatment groups for ATE. Most ATE events were serious and were of CTC AE grade ≥3 (see SVII.Table 15). Two ATE events had a fatal outcome in the Vargatef arm: MI (see Section SVII.2.1.8) and ischaemic stroke: A 60-year-old female patient with a history of hypertension and smoking experienced ischaemic stroke after 4 days of Vargatef+docetaxel administration. The reported ATE events excluding MI in the Vargatef arm (all patients) were (N=1 each) transient ischaemic attack, ischaemic stroke, and pulmonary artery thrombosis. In the placebo arm, the reported ATE events excluding MI were transient ischaemic attack (N=2) and (n=1 each) aortic thrombosis, blindness transient, and subclavian artery thrombosis (Vargatef EU-RMP v5.1 [s00020173-16], Section SVII.3.1.10.3).

SVII.Table 15 ATE in the Vargatef pivotal clinical trial 1199.13

	All patients		Adenocarcinoma	
	Placebo+ docetaxel N=655	Vargatef+ docetaxel N=652	Placebo+ docetaxel N=333	Vargatef+ Docetaxel N=320
Patients with event*, N (%)	9 (1.4)	4 (0.6)	7 (2.1)	3 (0.9)
Incidence rate per 100 patient years	3.24	1.23	4.54	1.70
Incidence rate ratio (95% CI)**	0.38 (0.12, 1.23)		0.37 (0.10, 1.45)	
Incidence rate difference (95% CI)**	−2.01 (−4.45, 0.43)		−2.84 (−6.72, 1.04)	
Patients with serious event*, N (%)	7 (1.1)	3 (0.5)	6 (1.8)	3 (0.9)
Patients with fatal event*, N (%)	0	2 (0.3)	0	2 (0.6)
Patients with CTCAE grade ≥3 event*, N (%)	4 (0.6)	3 (0.5)	3 (0.9)	3 (0.9)
Patients with event* recovered, N (%)	8 (1.2)	2 (0.3)	6 (1.8)	1 (0.3)

* Narrow SMQ 'Embolic and thrombotic events, arterial'
** Vargatef+docetaxel vs placebo+docetaxel
Data source: Vargatef EU-RMP v5.1 [s00020173-16], SVII.Table 88 and 89

Cumulatively, during post-marketing (narrow SMQ 'Embolic and thrombotic events, arterial', MedDRA version 24.0, DLP 31 May 2021, data source BI GSP) 8 cases of ATE (excluding MI: Narrow SMQ 'Embolic and thrombotic events, arterial' minus MedDRA PTs from narrow SMQ 'Myocardial infarction') were received, all ATE events (2 cases ischaemic stroke, 2 cases thrombotic thrombocytopenic purpura, 1 case each: Arterial thrombosis, cerebral artery embolism, ischaemic cerebral infarction, transient ischaemic attack) were serious. Besides the advanced age (3 patients) and male gender (3 patients), 7 of the 8 cases reported at least 1 of the following risk factors: Medical history (pulmonary embolism, deep vein thrombosis, coagulopathy), diabetes mellitus, hypertension, peripheral arterial occlusive disease, extensive intravascular tumour spread, bone metastasis, radiation therapy of collarbone, past cisplatin treatment. 3 cases reported at least 3 of the aforementioned risk factors. In 2 cases, the ATE event was fatal: Arterial thrombosis in 1 patient with extensive intravascular tumour spread and ischaemic stroke in the second case (risk factors high age, male gender, hypertension, diabetes mellitus, bone metastasis, radiation therapy of the collarbone). ATE recovered in 1 of the 8 cases (outcome unknown in 5 cases). The cumulative ATE (excluding MI) reporting rate of 0.10 per 100 patient years has remained relatively stable over more than 5 years.

All currently available data does not provide evidence to support a causal association between Vargatef use and ATE. Based on this, the MAH considers that ATE does not qualify as an important potential risk and recommends removal of this safety concern from the RMP. This risk with a low reporting rate has been a potential risk for more than 5 years with no changes. Consequently, there is no reasonable expectation that any pharmacovigilance activity can further characterise this risk.

This risk is appropriately managed by routine risk minimisation through labelling: The available information (frequency, risk factors, i.e. patients with cardiovascular risk) is adequately addressed in in product labelling. This allows the specialised physicians prescribing Vargatef, to understand and appropriately manage this risk. The MAH considers that current routine minimisation activities are appropriate for management of this risk. Considering the low frequency of events, no additional risk minimisation measures are deemed necessary. Consequently, the MAH recommends demotion of this safety concern from the EU-RMP. The risk will be further monitored through routine pharmacovigilance activities and will be presented in PBRERs.

SVII.2.2.2 Treatment in pregnant women and teratogenicity

Pre-clinical studies in animals have shown reproductive toxicity and teratogenicity of Vargatef. Inhibition of angiogenesis adversely affects foetal development. Following administration of Vargatef to rats, the inhibition of angiogenesis resulted in absorption of foetuses and increased incidence of malformations. These effects occurred at dose levels resulting in plasma drug concentrations comparable to or lower than those reached in humans during treatment with Vargatef. Therefore, teratogenicity has been considered a potential risk for Vargatef.

Routine risk mitigation activities have been established to minimise the risk of use of Vargatef during pregnancy. These include:

- Information about the teratogenic effect observed in pre-clinical studies
- Vargatef should not be used during pregnancy unless the clinical condition requires treatment
- Pregnancy testing at least prior to treatment with Vargatef
- Female patients should be advised to notify their doctor or pharmacist if they become pregnant during therapy with Vargatef
- If the patient becomes pregnant while receiving Vargatef, she should be apprised of the potential hazard to the foetus. Termination of the treatment with Vargatef should be considered.
- Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Vargatef and to use highly effective contraceptive methods at initiation of, during and at least 3 months after the last dose of Vargatef.

Vargatef exposure during pregnancy has not been reported for Vargatef, neither during the clinical trial program nor during the post-marketing period (data source: BI GSP, MedDRA version 24.0, DLP 31 May 2021). Monitoring of pregnancy is a standard topic that has been integrated into the monthly pharmacovigilance activities for Vargatef. Additional pharmacovigilance activities are not considered necessary. The MAH proposes to remove the important potential risk ‘Treatment of pregnant women and teratogenicity’ from the EU-RMP and to continue updating health authorities about the continuous monitoring of pregnancy cases within the PBRER and through the established signal detection and evaluation process as applicable.

SVII.2.2.3 Cardiac failure

Cardiac failure was considered as potential risk for Vargatef based on a potential mechanism and a possible class effect. It was assumed that perturbations of mitochondrial function and inhibition of AMP-activated protein kinase, a serine/threonine kinase, may be possible molecular mechanisms involved in the induction of adverse cardiac effects of tyrosine kinase inhibitors (TKIs) [R13-2035, P14-02206]. However, Vargatef does not show inhibition of serine/threonine kinases [U13-1690-01]. Safety pharmacology studies conducted with nintedanib and the whole non-clinical program (including repeat-dose toxicity studies up to 2 years in mice and rats, up to 13 weeks in Cynomolgus monkeys, and up to 52 weeks in Rhesus monkeys) did not provide evidence for relevant cardiac effects of nintedanib [U13-1690-01]. The systemic exposure levels achieved at the high dose levels were about 3 (rats)/8 (Cynomolgus monkeys)/5 (Rhesus monkeys)-fold higher than the exposure at the maximum recommended human dose.

Some TKIs (e.g. sorafenib, sunitinib) are associated with cardiac failure or decrease in left ventricular ejection fraction. Other TKIs (e.g. axitinib) do not present with such effects [P14-02206]. A large population-based cohort study showed, that out of 13 tyrosine kinase-targeting drugs, 4 TKIs (i.e. trastuzumab, cetuximab, panitumumab, and sunitinib) are associated with an increased risk to develop cardiac failure. In the same study, EGFR inhibition was associated with an increased risk of cardiac failure, whereas VEGFR inhibition was not [R21-2571]. In addition, a meta-analysis of 45 randomised clinical trials with TKI concluded that nintedanib does not exhibit an increased risk of cardiac/cardiotoxic damage [P21-02820].

There was no evidence from the Vargatef clinical trial data to suggest that cardiac failure is an important identified risk in cancer patients. For both clinical trial and post-marketing analyses, the narrow SMQ ‘cardiac failure’ was used. The frequency of AEs in this SMQ was low and balanced between the treatment arms in the Vargatef pivotal clinical trial. The incidence rate ratio and risk ratio for Vargatef vs. placebo showed no substantial differences between the treatment groups (see SVII Table 16, all patients). All events in the placebo arm were serious; 3 of them had a fatal outcome. In the Vargatef arm, 2 patients had a serious event. These events had a fatal outcome. All patients with an event in the narrow SMQ ‘Cardiac failure’ were males (all patients).The fatal events were cardiopulmonary failure (placebo: 2 cases, Vargatef: 1 case) and cardiac failure acute (1 case in each treatment arm). In the Vargatef arm, 1 patient died due to acute cardiac failure due to tumour progression; the second patient experienced cardiorespiratory arrest during sleep. This patient had underlying compensated cardiac ischaemia.

SVII.Table 16 Cardiac failure in the Vargatef pivotal clinical trial 1199.13

	All patients		**Adenocarcinoma**	
	Placebo+ docetaxel N=655	Vargatef+ docetaxel N=652	Placebo+ docetaxel N=333	Vargatef+ docetaxel N=320
Patients with event*, N (%)	5 (0.8)	6 (0.9)	2 (0.6)	1 (0.3)
Incidence rate per 100 patient years	1.77	1.85	1.25	0.57
Incidence rate ratio (95% CI)**	1.05 (0.32, 3.43)		0.45 (0.04, 4.98)	
Incidence rate difference (95% CI)**	0.08 (−2.06, 2.22)		−0.69 (−2.75, 1.38)	
Patients with serious event*, N (%)	5 (0.8)	2 (0.3)	2 (0.6)	0
Patients with fatal event*	3 (0.5)	2 (0.3)	0	0
Patients with CTCAE grade ≥3 event*, N (%)	5 (0.8)	3 (0.5)	2 (0.6)	0
Patients with event*recovered, N (%)	1 (0.2)	1 (0.2)	1 (0.3)	1 (0.3)

* Narrow SMQ ‘Cardiac failure’
** Vargatef+docetaxel vs placebo+docetaxel
Data source: Vargatef EU-RMP v6.0 [s00020173-17], SVII.Table 116 and 117

The cumulative post-marketing experience (narrow SMQ ‘Cardiac failure’, MedDRA version 24.0, DLP 31 May 2021, data source BI GSP) is in line with the clinical trial experience. The low number of 11 post-marketing cases did not provide evidence of causal association between Vargatef and cardiac failure. The event was serious in 9 cases; it was non-serious in 2 cases (event ‘Ejection fraction decreased’ in both cases). The cardiac failure events were unrelated per reporter in 6 of the 11 cases (reasonable possibility in 2 cases, not reported in 3 cases). In 8 of the 11 cases, the following risk factors for cardiac failure were reported: High age, pre-existing cardiac failure, underlying coronary heart disease, hypertension, cardiac arrhythmia, COPD, diabetes mellitus, lung cancer progression (risk factor for right ventricular failure/cor pulmonale). The event was fatal in 6 cases occurring in the terminal phase of the underlying lung cancer disease. The fatal events were: Cardiac failure in 2 cases and, in 1 case each: acute pulmonary oedema, cor pulmonale, pulmonary oedema, and right ventricular failure. In these cases, the underlying advanced lung cancer and or pre-existing cardiac/cardiovascular disorder contributed to / caused the fatal event.

The cumulative reporting rate for cardiac failure events of 0.14 per 100 patient years has been low and decreasing over more than 5 years. There has been not any post-marketing case in patients treated with Vargatef for more than 2 years, since August 2019.

In conclusion, new scientific publications showed that nintedanib and VEGFR inhibition are not associated with an increased risk of cardiac failure. Overall, the currently available data do not provide evidence to support a causal association between Vargatef use and cardiac failure. Based on this, the MAH considers that cardiac failure does not qualify as an important potential risk and recommends removal of this safety concern from the RMP. Cardiac failure will be further monitored through routine pharmacovigilance activities and will continue to be presented in the following PBRER.

Accumulating clinical data, namely the low frequency of events with Vargatef being relatively stable over more than 5 years demonstrates: Impact to the individual has been shown to be less than anticipated. No additional risk minimisation measures are deemed necessary. Considering this risk has been a potential risk for more than 5 years with no changes, there is no reasonable expectation that any PV activity can further characterise this risk. Consequently, the MAH recommends demotion of this safety concern from the EU-RMP. The risk will be further monitored through routine pharmacovigilance activities. Whenever new relevant data become available, the topic will be presented in PBRERs.

SVII.2.3 Missing information

SVII.2.3.1 Treatment of breastfeeding women

Vargatef has not been investigated in pregnant or lactating women. There is no information on the excretion of Vargatef and its metabolites in human milk. Non-clinical studies showed that small amounts of Vargatef and its metabolites (≤0.5% of the administered dose) were secreted into milk of lactating rats. The risk of exposure to Vargatef in new-borns / infants is unknown. Paediatric development has been waived. There is a low likelihood of breastfeeding in women under treatment for lung cancer.

Routine risk minimisation activities through product labelling include:

- Information to prescribers in the EU-SmPC about pre-clinical experience in animals
- Recommendation in the EU-SmPC that breastfeeding should be discontinued during treatment with Vargatef since a risk to the breast-fed child (new-borns/infants) cannot be excluded
- Clear wording in the patient's leaflet: "It is not known if the medicine passes into breast milk and could cause harm to a breast-fed child. Therefore, women should not breast-feed during treatment with Vargatef."

Cumulatively, no cases from breastfeeding women involving Vargatef were reported, neither from clinical trials nor during post-marketing (data source: BI GSP, MedDRA version 24.0, DLP 31 May 2021). For details of the non-standardised query used, see Appendix 7A, Table 1.

Monitoring of exposure via breastfeeding is a standard topic that has been integrated into the routine pharmacovigilance activities for the product. Additional pharmacovigilance activities are not considered necessary. There is no reasonable expectation that existing or future feasible PV activities could further characterise this missing information. Consequently, the MAH proposes to remove the topic 'Treatment of breastfeeding women' from the EU-RMP. The MAH will continue to update health authorities about continuous monitoring of breastfeeding cases within PBRERs and through the established signal detection and evaluation process as applicable.

SVII.2.3.2 Treatment of patients with moderate or severe hepatic impairment (Child Pugh B/C)

Vargatef is predominantly eliminated via biliary/faecal excretion (>90%). A single-dose pharmacokinetic trial in mild or moderately hepatically impaired subjects (trial 1199.200) has been conducted with a stratification based on Child Pugh criteria. In this trial, when compared to healthy subjects, the exposure to Vargatef based on Cmax and AUC were 2.2-fold higher in volunteers with mild hepatic impairment (Child Pugh A; 90% CI for Cmax 1.3, 3.7 and for AUC 1.2, 3.8). In volunteers with moderate hepatic impairment (Child Pugh B), exposure was 7.6-fold higher based on Cmax (90% CI 4.4, 13.2) and 8.7-fold higher based on AUC (90% CI 5.7, 13.1) compared to healthy volunteers. Subjects with severe hepatic impairment (Child Pugh C) have not been studied. Patients with total bilirubin >ULN and AST and/or ALT >1.5x ULN at baseline were excluded from enrolment in the phase III clinical trial in NSCLC.

To identify patients with moderate or severe hepatic impairment at baseline, the safety database was searched for ICSRs from post-marketing sources in patients with past or co-diseases in the SMQ 'Hepatic failure, fibrosis and cirrhosis and other liver-damage-related conditions narrow'. The ICSRs were reviewed with regard to abnormalities of liver enzymes and bilirubin, as well as other symptoms of hepatic impairment (e.g. coagulopathy, hypoalbuminaemia, ascites, and encephalopathy) at baseline. Cumulatively during post-marketing (MedDRA version 24.0, DLP 31 May 2021, data source BI GSP), 19 patients were identified having a history of hepatic impairment (narrow SMQ 'Hepatic failure, fibrosis and cirrhosis and other liver damage related conditions'). In none of the cases, information about the respective Child Pugh score was provided. The characteristics of the events reported in patients with hepatic impairment treated with Vargatef + docetaxel were consistent with the safety profile observed in the overall lung cancer population under treatment: Malignant neoplasm progression (52.6%), diarrhoea (31.6%, non-serious 26.3%), nausea (15.8%), asthenia (15.8%), neoplasm progression (15.8%), decreased appetite (10.5%), fatigue (10.5%), and alopecia (10.5%) were the most frequent adverse events. In all fatal cases, neoplasm progression was the underlying cause of death. In 5 out of the 19 reports, the following hepatic adverse events (most of them non-serious) were reported (1 event each): ALT increased, GGT increased, ALKP increased, liver function test increased, hepatic function abnormal, liver disorder, hepatic steatosis, jaundice, cholestasis, and ascites. This suggests, that the patient's underlying hepatic disease was a predisposing factor for these events. There was no indication that the severity and/or the outcomes of adverse events in these patients were worse under Vargatef treatment.

Routine risk mitigation activities through labelling have been established to minimise the risk of use of Vargatef in patients with hepatic impairment. These include clear recommendations in the EU-SmPC about:

- Warning that the risk of adverse events may be increased in patients with Child Pugh A hepatic impairment
- Management strategy in patients with mild hepatic impairment with treatment interruption, dose reductions, or dose discontinuations

– Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with Vargatef is not recommended

Current risk minimisation activities seem to be effective in reducing the risk of Vargatef use in patients with moderate/severe hepatic impairment. Data collection is limited by the characteristics of post-marketing and real-world data, which do not systematically provide information on the severity/stage of hepatic impairment in many of the cases. A further limitation is the low probability of patients with moderate/severe hepatic impairment to be exposed to Vargatef treatment considering the current recommendations in the EU-SmPC.

Overall, the frequency and pattern of adverse events in patients with pre-existing liver function impairment (all grades of severity) is in line with the safety experience in the lung cancer population treated with Vargatef. Liver events are frequent in this population but there is no increase in severity/worse outcomes. Further characterisation of this safety concern is not considered necessary. There is no reasonable expectation that existing or future feasible PV activities could further characterise this missing information.

The MAH considers that current risk minimisation measures are appropriate to address the safety concern and proposes to remove the missing information topic 'Treatment of patients with moderate or severe hepatic impairment (Child Pugh B/C)' from the EU-RMP. The MAH will continue updating health authorities about the continuous monitoring of use of Vargatef in hepatic impairment within the PBRER as well as through the established signal detection and evaluation process as applicable.

SVII.2.3.3 Treatment of patients with healing wounds

Based on the mechanism of action, Vargatef may impair wound healing. Consequently, patients with major injuries and/or surgery within 10 days prior to trial randomisation, or with incomplete wound healing were excluded from trial 1199.13. No increased frequency of impaired wound healing was observed in the pivotal Vargatef clinical trial 1199.13. No formal studies investigating the effect of Vargatef on wound healing have been performed. Thus, it is difficult to assess the impact of continuing Vargatef treatment in patients with healing wounds and the treatment of patients with healing wounds has been included as missing information.

The search strategy included all MedDRA PTs containing %wound% or %postoperative% (for details of the non-standardised query used, see Appendix 7A, Table 1). Cumulatively during post-marketing (MedDRA version 24.0, DLP 31 May 2021, data source BI GSP), 6 cases were identified that reported the following adverse events: wound infection (3 cases), (post-operative) wound complication (2 cases), and skin wound (1 case). The events were serious in 3 cases and recovered in 4 patients. The available safety information from these patients is limited, there is no concern from the available information.

The risk is appropriately managed by routine risk minimisation through labelling: Warnings & precautions: Vargatef should only be initiated or – in case of perioperative interruption – resumed based on clinical judgement of adequate wound healing. The MAH proposes to remove the missing information topic 'Treatment of patients with healing wounds' from the

EU-RMP. Although the number of reported cases is low, the currently available data does not indicate a specific risk of use in patients with healing wounds beyond the known risks of Vargatef in the overall population. Product labelling advises that treatment with Vargatef should only be initiated or – in case of perioperative interruption – resumed based on clinical judgement of adequate wound healing. No additional risk minimisation or pharmacovigilance activities are considered necessary. Monitoring and presentation of available data in the PBRER will be continued.

SVII.2.3.4 Treatment of subpopulations with co-morbid CNS conditions such as dementia, depression, brain metastasis, or with comorbid conditions such as arthritis and osteoporosis

As described below (see SVII.2.3.4.1 to SVII.2.3.4.5), neither the scientific literature nor the Vargatef product knowledge provided any evidence for anticipating a different safety profile in patients with dementia, depression, arthritis, or osteoporosis treated with Vargatef.

The topic treatment of patients with brain metastasis is considered appropriately managed by routine risk minimisation through labelling. Current labelling includes the recommendation not to administer Vargatef in patients with active brain metastasis. Monitoring is recommended in patients with stable brain metastasis as risk factor for bleeding. In case of bleeding, dose adjustment, interruption or discontinuation should be considered based on clinical judgement.

There is no reasonable expectation that existing or future feasible pharmacovigilance activities could further characterise this missing information topic. Consequently, the MAH proposes to remove the topic ‘Treatment of subpopulations with co-morbid CNS conditions such as dementia, depression, brain metastasis, or with comorbid conditions such as arthritis and osteoporosis’ from the EU-RMP. Although the number of reported cases is low, the currently available data does not indicate a specific risk of use in these patients beyond the known risks of Vargatef in the overall population. The topics will be monitored through routine pharmacovigilance activities and will not be presented on a routine basis in PBRERs unless a signal is identified.

SVII.2.3.4.1 Brain metastases

Active brain metastases are brain metastases that are stable for less than 4 weeks, have not adequately been treated with radiotherapy, are symptomatic, or are requiring treatment with anticonvulsants. Patients with active brain metastases were excluded from the Vargatef pivotal clinical trial 1199.13 because of the possibility of intracranial bleeding and a potential for progression of neurological symptoms. Only patients with brain metastases that were stable for at least 4 weeks were allowed to participate in trial 1199.13; 38 patients in each treatment arm had stable brain metastases. No intracranial haemorrhage has been reported in trial 1199.13.

In post-marketing cases, it is usually not possible to identify whether a patient had active or stable brain metastases. To identify cases in patients with brain metastases, the BI GSP was

searched for post-marketing cases of patients with brain metastases (for details of this non-standardized query used, see Appendix 7A, Table 1). Cumulatively (MedDRA version 24.0, DLP 31 May 2021, data source BI GSP), 46 patients were identified searching for past or concomitant disorders MedDRA PTs brain neoplasm, brain neoplasm malignant, brain cancer metastatic, metastases to central nervous system, central nervous system mass, central nervous system neoplasm. The characteristics of the events in patients with brain metastases treated with Vargatef + docetaxel were consistent with the safety profile observed in the overall population under treatment : Malignant neoplasm progression (28.3%), diarrhoea (19.6%, all events were non-serious), death (13.0%), pneumonia (6.5%). There was 1 case reporting 'Haemorrhage', however, the location was not provided. The reported events (1 case each) of agitation, ataxia, gait disturbance, hemiparesis, craniocerebral injury, hydrocephalus, headache, hallucination, and seizure can be rather explained by the underlying brain metastases. The most frequent fatal event was malignant neoplasm progression. Altogether, the available safety information in patient with brain metastasis is limited, there is no concern from the available information.

SVII.2.3.4.2 Dementia

The safety and efficacy of Vargatef have not been studied in patients with dementia. In the Vargatef pivotal clinical trial 1199.13, there were no patients with dementia at baseline.

Cumulatively (MedDRA version 24.0, DLP 31 May 2021, data source BI GSP), only 1 post-marketing case was received using the narrow SMQ 'Dementia' to search for cases with a medical history of dementia. The patient with a medical history of hippocampal sclerosis died from malignant neoplasm progression. Other reported AEs were back pain, decreased appetite, diarrhoea, immobile, urinary incontinence, dyspnoea. The available safety information in this patient is insufficient to draw any conclusion.

SVII.2.3.4.3 Depression

In the Vargatef pivotal clinical trial 1199.13, the number of patients with depression at baseline (Vargatef: 22 patients; placebo: 17 patients) was too small to allow for a meaningful subgroup analysis.

Cumulatively during post-marketing (MedDRA version 24.0, DLP 31 May 2021, data source BI GSP), 11 patients were identified having a history of depression (narrow SMQ 'Depression and suicide/self-injury'). The characteristics of the events in patients with depression treated with Vargatef + docetaxel were consistent with the safety profile observed in the overall population under treatment: Malignant neoplasm progression (7 cases), diarrhoea (5), transaminases increased (2), nausea (2). The available safety information in patient with depression is limited, there is no concern from the available information.

SVII.2.3.4.4 Arthritis

In the Vargatef pivotal clinical trial 1199.13, the number of patients with arthritis at baseline of 51 patients in each treatment arm was too small to allow for a meaningful subgroup analysis.

During post-marketing (MedDRA version 24.0, DLP 31 May 2021, data source BI GSP), 19 patients were identified having a history of arthritis (narrow SMQ 'Arthritis'). The characteristics of the events in patients with arthritis treated with Vargatef + docetaxel were consistent with the safety profile observed in the overall population under treatment: Diarrhoea (11 cases, mostly non-serious), malignant neoplasm progression (5 cases), metastases (5 cases), vomiting (3), pyrexia (3), death (3 cases), colitis (2), nausea (2), pneumonia (2). The available safety information in patients with arthritis is limited, there is no concern from the available information.

SVII.2.3.4.5 Treatment of patients with osteoporosis

In the Vargatef pivotal clinical trial 1199.13, the number of patients with osteoporosis at baseline (3 on Vargatef and 6 on Placebo) was too small to allow for a meaningful subgroup analysis.

During post-marketing (MedDRA version 24.0, DLP 31 May 2021, data source BI GSP), 9 patients were identified having a history of osteoporosis (narrow SMQ 'osteoporosis'). The characteristics of the events in patients with osteoporosis treated with Vargatef + docetaxel were consistent with the safety profile observed in the overall population under treatment: Diarrhoea (5 cases, all 5 non-serious), malignant neoplasm progression (2 cases). The available safety information in patients with osteoporosis is limited, there is no concern from the available information.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1 Presentation of important identified risks and important potential risks

SVII.3.1.1 Important identified risk: Drug-induced liver injury (DILI)

SVII.3.1.1.1 Potential mechanisms

Although the mechanism has not been elucidated, metabolic pathways in the liver may be implicated. Nintedanib is mainly metabolised by esterases. The by far most frequent metabolites in the human ADME study were BIBF 1202, resulting from ester cleavage of nintedanib, and BIBF 1202-glucuronide, formed by subsequent glucuronidation. The glucuronidation of BIBF 1202 occurs mainly through UGT1A1 (liver and intestine), UGT1A7, UGT1A8, and UGT1A10 (intestine). The major route of elimination of total drug related [14C]-radioactivity after oral administration of [14C]-BIBF 1120 was via faecal/biliary excretion (93.4% of dose) [c01585838-06].

Furthermore, administration of docetaxel is associated with increased blood bilirubin.

SVII.3.1.1.2 Evidence source and strength of evidence

In the Vargatef pivotal clinical trial 1199.13, elevations of liver enzymes and total bilirubin were more frequent in patients treated with nintedanib+docetaxel as compared to patients treated with placebo+docetaxel. DILI was not reported in either treatment arm. Liver enzyme elevations are among the most common reported adverse events in the post-marketing setting; many of the reported hepatic events reflect liver enzyme elevations and/or hepatic events as a consequence of the underlying malignancy. Post-marketing cases of DILI including cases of severe liver injury with fatal outcome have been reported with nintedanib.

SVII.3.1.1.3 Characterisation of the risk

DILI was analysed by using the PT 'Drug-induced liver injury'.

For broader analyses of clinical trial and post-marketing data related to liver enzyme elevations and hyperbilirubinaemia, the UDAEC 'Hepatic events' is used, which consists of the following SMQs:

- Broad SMQ 'Liver related investigations, signs and symptoms'
- Narrow SMQ 'Cholestasis and jaundice of hepatic origin'
- Narrow SMQ 'Hepatitis, non-infectious'

Please refer to the Vargatef EU-RMP v9.0 [s00020173-22, Section SVII.3.1.2.3].

Clinical trial data

In the Vargatef pivotal clinical trial 1199.13, elevations of liver enzymes and total bilirubin were more frequent in patients treated with Vargatef+docetaxel as compared to patients treated with placebo+docetaxel. The incidence rate ratio and risk ratio for Vargatef+docetaxel vs placebo+docetaxel showed substantial differences between the treatment groups. The percentage of patients with serious hepatic events was low and comparable between treatment arms (1.2% with Vargatef+docetaxel, all patients). The majority of patients throughout treatment arms recovered from their hepatic events; no fatal outcome was reported.

In the Vargatef pivotal clinical trial 1199.13, DILI (PT Drug-induced liver injury) was not reported in either treatment arm.

Post-marketing data

Cumulatively (up to 31 May 2021), 1 Vargatef case reported DILI: A patient with progressive liver metastases, progressive paraaortal lymph nodes, and peritoneal carcinosis was treated with Vargatef and 2 subsequent anti-cancer therapies (pembrolizumab and gemcitabine/cisplatin). The patient experienced DILI at a not reported time. Approximately 9-10 months after initiation of the first subsequent anticancer therapy after Vargatef, the patient experienced increased AST, bilirubin and lactate dehydrogenase, jaundice, ascites, and creatinine increase/acute kidney injury as consequences of progressive liver metastases

and peritoneal carcinosis. The patient was treated with permanent ascites drainage and palliative care (data source: BI GSP).

SVII.3.1.1.4 Risk factors and risk groups

A study based on the DILIN in the US assessed the characteristics of DILI patients aged 65 years and above. In this cohort (n = 149), 60% of the patients were female and 85% were White. The highest proportion of patients (58%) took at least 6 medications. Among the DILI patients, antimicrobial agents were the most common class of causative drugs with 57.7% [P15-06939].

Population pharmacokinetics analyses in patients with NSCLC and IPF revealed that female and Asian patients have a higher risk of elevations in liver enzymes upon nintedanib treatment. Nintedanib exposure increased linearly with patients' age and was inversely correlated to weight. The increased nintedanib exposure may result in a higher risk of developing liver enzyme elevations.

Analysis of subgroups (gender, race, age, baseline hepatic or renal function, cardiac impairment) in patients with adenocarcinoma and in the overall patient population for hepatic events of any CTCAE grade and for events of CTCAE grade ≥3 in the overall population confirmed an increased risk to develop hepatic events in females and Asian patients compared to males and white patients. The subgroup analysis of elevated AST and / or ALT of any CTCAE grade and of CTCAE grade ≥3 did not reveal a risk group (data on file: RMP analyses v5.0; Tables 5.2.3.1.1 to 5.2.3.1.6, 5.2.3.1.13 to 5.2.3.1.18, 5.2.4.3.1.1 to 5.2.4.3.1.6, and 5.2.4.3.1.13 to 5.2.4.3.18).

Exposure increased in patients with hepatic impairment (Child Pugh A, Child Pugh B) [c02248479-02, c02705948-01]. Based on increased exposure, the risk for AEs may be increased in patients with mild hepatic impairment (Child Pugh A).

SVII.3.1.1.5 Preventability

Treatment interruption, dose reductions or permanent discontinuation of nintedanib treatment in case of AST, ALT, ALKP, and/or bilirubin elevations are suitable measures to allow recovery of liver enzyme/bilirubin elevations and to prevent more severe outcomes including DILI. Risk groups and risk factors for liver enzyme elevations and hyperbilirubinaemia are female gender, Asian ethnicity, and low body weight. Close monitoring of liver enzymes is recommended in patients with these risk factors treated with nintedanib.

In all patients, liver enzymes should be monitored as clinically indicated or periodically during treatment, i.e. in the combination phase with docetaxel at the beginning of each treatment cycle and monthly in case nintedanib is continued as monotherapy after discontinuation of docetaxel.

SVII.3.1.1.6 Impact on the risk-benefit balance of the product

Administration of Vargatef is associated with elevations of liver enzymes and bilirubin, including DILI. Most hepatic events are of mild or moderate intensity and are reversible. Severe hepatic events are rare and can be the consequence of the underlying malignancy. In the post-marketing period, severe liver injury with fatal outcome has been reported after treatment with nintedanib.

SVII.3.1.1.7 Public health impact

There is no public health impact of liver enzyme and bilirubin elevations resulting in DILI in patients treated with Vargatef.

SVII.3.1.2 Important potential risk: Hepatic failure

SVII.3.1.2.1 Potential mechanisms

Nintedanib is known to be associated with hepatotoxicity.

SVII.3.1.2.2 Evidence source and strength of evidence

Liver enzyme and bilirubin elevations including DILI are identified risks of Vargatef. DILI can be severe and can lead to hepatic failure. In the Vargatef pivotal clinical trial, there was no event of hepatic failure attributable to administration of study medication. In the post-marketing setting, none of the reported events met the medical definition of hepatic failure. Events identified from the SMQ search comprised liver enzyme elevations and/or hepatic events as a consequence of the underlying malignancy.

The potential for further sequelae of liver abnormality is warranted for monitoring ‘hepatic failure’ as a potential risk.

SVII.3.1.2.3 Characterisation of the risk

The safety topic ‘Hepatic failure’ encompasses events coded under the narrow SMQ ‘Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions’. The narrow SMQ was chosen as the broad SMQ terms did not add value and the narrow SMQ ‘Hepatic failure’ detected the same cases as the broad SMQ ‘Hepatic failure’ from both the pivotal clinical trial and from post-marketing cases.

Clinical trial data

In the pivotal Vargatef clinical trial, events in the narrow SMQ ‘Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions’ were infrequently reported. Events were more frequent in patients treated with Vargatef+docetaxel versus placebo+docetaxel (see SVII.Table 17). Most events were non-serious and most patients recovered from their events. The majority of events in the Vargatef arm, namely ascites, hepatocellular injury, hepatotoxicity (n=2 for each event) represented milder conditions than hepatic failure.

Hepatic failure as a MedDRA PT was reported in 2 patients on Vargatef (CTCAE grade 1 and grade 5, respectively). Both did not meet the medical definition of hepatic failure. In the placebo arm, 1 case of hepatic cirrhosis occurred. In depth analysis of all individual cases revealed that these patients had increases of liver enzymes (AST, ALT, Gamma-GT, and ALKP) without elevations of bilirubin. Hepatic failure of CTCAE grade 5 was due to progression of liver metastases.

SVII.Table 17 Hepatic failure in the Vargatef pivotal clinical trial 1199.13

	All patients		**Adenocarcinoma**	
	Placebo+ docetaxel N=655	Vargatef+ docetaxel N=652	Placebo+ docetaxel N=333	Vargatef+ Docetaxel N=320
Patients with event*, N (%)	1 (0.2)	8 (1.2)	1 (0.3)	3 (0.9)
Incidence rate per 100 patient years	0.35	2.47	0.63	1.70
Incidence rate ratio (95% CI)**	7.00 (0.88, 55.96)		2.72 (0.28, 26.14)	
Incidence rate difference (95% CI)**	2.12 (0.27, 3.96)#		1.08 (−1.21, 3.36)	
Patients with serious event*, N (%)	0	1 (0.2)	0	0
Patients with fatal event*, N (%)	0	1 (0.2)***	0	0
Patients with CTCAE grade ≥3 event*, N (%)	0	5 (0.8)	0	3 (0.9)
Patients with event* recovered, N (%)	0	6 (0.9)	0	2 (0.6)

* Narrow SMQ ‘Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions’
** Vargatef+docetaxel vs placebo+docetaxel
*** 1 case with MedDRA PT ‘Hepatic failure’
# IR difference significantly different from 0.
Data source: Vargatef EU-RMP v5.1 [s00020173-16], SVII.Table 95 and 96]

Post-marketing data

The presentation of DILI is included in Section SVII.3.1.1.3 above. The cumulative post-marketing experience (MedDRA version 24.0, DLP 31 May 2021, data source BI GSP) is in line with the clinical trial experience. The narrow SMQ ‘Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions’ retrieved 33 cases cumulatively. In most of the reported cases (57.6%), the events were non-serious and reported unspecific MedDRA PTs (liver disorder, ascites) or PTs covered by the current information in the EU-SmPC (hepatotoxicity, DILI). The MedDRA PT ‘Hepatic failure’ was reported in 3 cases, but none of them matched the clinical definition of hepatic failure (evidence of coagulation abnormality, usually INR ≥1.5, and any degree of mental alteration [encephalopathy] in a patient without pre-existing cirrhosis and with an illness of <26 weeks’ duration).

In summary, 2 cases were reported under the MedDRA PT ‘Hepatic failure’ in clinical trials and 3 during post-marketing, but none of these cases matched the clinical definition of hepatic failure.

SVII.3.1.2.4 Risk factors and risk groups

The low number of patients affected by AEs in the SMQ “Hepatic failure” in trial 1199.13 did not allow for meaningful subgroup analyses. The subgroup analyses of hepatocellular carcinoma patients treated with nintedanib in trials 1199.37 and 1199.39 suggested an increased frequency of hepatic AEs in the SMQ “Hepatic failure” in Asian patients, and in patients with mild and moderate hepatic impairment at baseline. For patients treated with nintedanib 200 mg bid, the frequency of AEs was higher also in the age group ≥65 years.

For risk groups and risk factors for drug-induced liver injury (DILI), please see Section SVII.3.1.1.4.

SVII.3.1.2.5 Preventability

Regular monitoring of liver enzymes and bilirubin, as well as recommendations for treatment interruption and dose reduction of nintedanib in case of abnormalities, are intended to prevent severe hepatotoxicity.

SVII.3.1.2.6 Impact on the risk-benefit balance of the product

Hepatic failure is a severe and life-threatening condition, which is associated with a high mortality rate.

SVII.3.1.2.7 Public health impact

There is no wider public health impact of hepatic failure in patients treated with Vargatef.

SVII.3.2 Presentation of the missing information

SVII.3.2.1 Treatment of patients with renal impairment

SVII.3.2.1.1 Evidence source

The safety, efficacy, and pharmacokinetics of Vargatef have not been explicitly studied in patients with compromised renal function. Patients with serum creatinine >1.5x ULN were excluded from patients enrolled in the pivotal lung cancer trial.

Cumulatively during post-marketing (MedDRA version 24.0, DLP 31 May 2021, data source BI GSP), 36 patients were identified having a history of renal impairment (broad SMQ 'Chronic kidney disease'). The characteristics of the events in patients with renal impairment treated with Vargatef+docetaxel were consistent with the safety profile observed in the overall population under treatment: Diarrhoea (44.4%; non-serious in 36.1%), malignant neoplasm progression (27.8%), nausea (27.8%), vomiting (16.7%), decreased appetite (13.9%), pneumonia (13.9%), dyspnoea (11.1%), fatigue (11.1%). The most frequent fatal event was malignant neoplasm progression.

SVII.3.2.1.2 Anticipated risk/consequence of the missing information

Although the number of reported cases is low, currently available data does not indicate a specific risk/or increased toxicity in patients with renal impairment (including all levels of severity). This is also consistent with the fact that an extremely low amount of the drug is excreted by the kidneys. Routine risk mitigation activities have been established to minimise the risk of use of Vargatef in patients with renal impairment. These include clear recommendations in the EU-SmPC about:

- Management strategy (monitoring, dose adjustments) for patients with risk factors for renal impairment (e.g. dehydration)
- Nintedanib has not been studied in patients with severe renal impairment.

SVII.3.2.2 Treatment of patients weighing <50 kg

SVII.3.2.2.1 Evidence source

Most patients in trial 1199.13 had a body weight above 50 kg. Only a small number of patients weighed less than 50 kg, both in the overall population (Vargatef: 32 patients; placebo: 34 patients) and in the adenocarcinoma population (Vargatef: 17 patients; placebo: 20 patients) ([U13-1504-01], Section 16.1.9.2 Tables 11.12.10 and 12.13.10).

Population PK analyses showed an inverse correlation between body weight and exposure to nintedanib. The AUCτ,ss increased by 25% for a 50 kg patient (5th percentile) and decreased by 19% for a 100 kg patient (95th percentile) relative to a patient with the median weight of 71.5 kg [U13-1506-01].

In study 1199.13, in patients with body weight of <50 kg, there was a higher frequency of SAEs in the Vargatef+docetaxel arm as compared to the placebo+docetaxel arm (Vargatef vs placebo – overall population: 16 [50%] patients vs 11 [32.4%] patients; adenocarcinoma population: 10 [58.8%] patients vs. 6 [30.0%] patients). In patients with a body weight of ≥50 kg, the frequency of SAEs was balanced between the treatment arms in the overall population and in patients with adenocarcinoma ([U13-1504-01], Section 16.1.9.2, Tables 11.12.10 and 12.13.10). The increased frequency of SAEs in the Vargatef arm in patients with body weight of <50 kg was mainly due to a higher frequency of myelosuppression (febrile neutropenia and neutrophil count decreased), GI AEs, and malignant neoplasm progression. However, taking into account the small number of patients with a body weight lower than 50 kg, no definitive conclusions could be made regarding this observation.

During post-marketing (MedDRA version 24.0, DLP 31 May 2021, data source BI GSP), 84 patients were identified having a reported weight <50 kg. Most events (70.0% of cases) were serious. The characteristics of the events in patients weighing <50 kg treated with Vargatef+docetaxel were consistent with the safety profile observed in the pivotal clinical trial 1199.13 under treatment: Malignant neoplasm progression (29.8%), diarrhoea (20.2%), nausea (16.7%), vomiting (9.5%), dyspnoea (8.3%), fatigue (7.1%), general health deterioration (7.1%), and the following events (6.0% each): pneumonia, decreased appetite, neutropenia, stomatitis, WBC decreased. Most (35) of the 46 GI events of diarrhoea,

vomiting, nausea and decreased appetite were non-serious (76.1%). Further, the majority (11) of the 15 myelosuppressive events of neutropenia, neutrophil counts decreased, leukopenia, and WBC decreased were non-serious (73.3%). In approximately half of the 84 patients, the events recovered. A fatal outcome was reported in 31 cases. Most frequent fatal events were malignant neoplasm progression, pneumonia, respiratory failure, and death. The fatal events reflect either tumour progression, pre-existing underlying conditions or are addressed in the EU-SmPC.

In conclusion, taking into account all limitations of real world / post-marketing data, no safety concern could be detected in 84 cumulative post-marketing cases of patients with a body weight <50 kg. Many patients with a weight lower than 50 kg are in the final stage of their tumour disease. In these patients, events reflecting tumour progression or consequences of tumour progression are frequently reported. This explains the high proportion of serious cases and cases with a fatal outcome. The remaining events are consistent with the known safety profile of nintedanib and docetaxel or events that are related to the underlying NSCLC.

SVII.3.2.2.2 Anticipated risk/consequence of the missing information

The safety profile of Vargatef in patients with a body weight lower than 50 kg might differ from that in the remaining patients in the target population. The inverse correlation between nintedanib exposure and weight may result in a higher risk of developing liver enzyme elevations or other AEs. Low body weight may be a sign of terminal cancer.

Although the number of reported cases is relatively low, the currently available data does not indicate a specific risk of use in patients weighing below 50 kg beyond the known risks of Vargatef in the overall population.

This topic is appropriately managed by routine risk minimisation through labelling. Current labelling includes information, that patients with low body weight have a higher risk of elevations in liver enzymes and that close monitoring is recommended in patients weighing <50 kg. An inverse correlation between body weight and exposure to Vargatef was observed. $AUC_{\tau,ss}$ increased by 25% for a 50 kg patient (5th percentile) and decreased by 19% for a 100 kg patient (95th percentile) relative to a patient with the median weight of 71.5 kg. Current labelling also includes information, that in the Vargatef pivotal trial, there was a higher frequency of SAEs in patients treated with Vargatef plus docetaxel with a body weight of less than 50 kg compared to patients with a weight ≥50 kg; however, the number of patients with a body weight of less than 50 kg was small.

SVII.4 REFERENCES

SVII.4.1 Published references

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ABBREVIATIONS

AE	Adverse event
ALKP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATE	Arterial thromboembolism
AUC	Area under the curve
bid	*bis in die*; twice daily
CI	Confidence interval
CNS	Central nervous system
CRCD	Chemotherapy related cardiac dysfunction
cRMP	Core Risk Management Plan
CTCAE	Common terminology criteria for adverse events
CUP	Compassionate use programme
DILI	Drug-induced liver injury
ECG	Electrocardiogram
EGFR	Endothelial growth factor receptor
EU	European Union
FGFR	Fibroblast growth factor receptor
GI	Gastro-intestinal
GSP	Global Safety Platform
HCC	Hepatocellular cancer
hERG	Human ether-a-go-go gene
ICSR	Individual case safety report
HR	Hazard ratio
IPF	Idiopathic pulmonary fibrosis
IR	Incidence rate
MAPK	Mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer

OAT	Organic anion-transporter
OATP	Organic anion-transporting polypeptide
PDGFR	Platelet-derived growth factor receptor
PE	Pulmonary embolism
P-gp	P-glycoprotein
PK	Pharmacokinetic
PSUR	Periodic Safety Update Report
PT	Preferred term
py	Person-years
RAF	Rapidly accelerated fibrosarcoma or rat fibrosarcoma
RMP	Risk Management Plan
SAE	Serious adverse event
SaiL	Safety of avastin in lung
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA query
SOC	System Organ Class
TKI	Tyrosine kinase inhibitor
UDAEC	User defined adverse event categories
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
vs	Versus
VTE	Venous thromboembolism

MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

SVIII.Table 1 Summary of safety concerns

Important identified risks	Drug-induced liver injury (DILI)
Important potential risks	Hepatic failure
Missing information	Treatment of patients with renal impairment Treatment of patients weighing <50 kg

SVIII.1 REFERENCES

Not applicable.

ABBREVIATIONS

DILI	Drug-induced liver injury

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

PART III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for:

Important identified risk

- Drug-induced liver injury (DILI)
  (restricted to serious events of liver enzyme increases, DILI, and hepatic failure)

Important potential risk

- Hepatic failure

PART III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no additional pharmacovigilance activities.

PART III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no ongoing and planned additional pharmacovigilance activities.

PART III.4 REFERENCES

Not applicable.

ABBREVIATIONS

DILI	Drug-induced liver injury

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no planned or ongoing post-authorisation efficacy studies imposed for Vargatef.

The non-interventional study LUME BioNIS (1199.223) has been completed [c27740601-01]. The objective of the study was to examine whether genetic/genomic markers (alone or combined with clinical covariates) could be used to predict overall survival in NSCLC patients eligible for treatment with nintedanib. The results are briefly summarised below.

Despite comprehensive biomarker analyses (30 clinical parameters and >800 molecular markers) using various analytic approaches, no new prognostic marker was identified for the OS outcome. Hence, no possible new predictive marker for OS was identified either. Only known clinical markers with prognostic effect, such as number and sites of metastases were identified, confirming the overall approach of the analysis. The safety profile of Vargatef in combination with docetaxel in LUME-BioNIS was as expected and consistent with the known safety profile of Vargatef in combination with docetaxel.

PART IV.1 REFERENCES

c27740601-01 LUME-BioNIS: A non-interventional biomarker study in patients with Non-Small Cell Lung Cancer (NSCLC) of adenocarcinoma tumour histology eligible for treatment with Vargatef® according to the approved label. 1199.223. 07 Jul 2020.

ABBREVIATIONS

NSCLC	Non-small cell lung cancer
OS	Overall survival

PART V RISK MINIMISATION MEASURES

RISK MINIMISATION PLAN

PART V.1 ROUTINE RISK MINIMISATION MEASURES

PV.Table 1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
Drug-induced liver injury (DILI)	*Routine risk communication* SmPC sections 4.4, 4.8, and 4.9 *Routine risk minimisation activities recommending specific clinical measures to address the risk* Information on dose adjustment / criteria for permanent discontinuation in the context of this risk is provided in the SmPC sections **4.2 Posology and method of administration and 4.4 Special warnings and precautions for use**. Furthermore, the risk of liver enzyme elevations and hyperbilirubinaemia including DILI is addressed in the **Section 4.4 Special warnings and precautions for use**, which includes monitoring of liver enzymes and bilirubin, as well as information on risk groups. *Other routine risk minimisation measures beyond the Product Information* Vargatef is available as a prescription-only medicine. Treatment with Vargatef should be initiated and supervised by a physician experienced in the use of anticancer therapies.
Important potential risks	
Hepatic failure	*Routine risk communication* None *Routine risk minimisation activities recommending specific clinical measures to address the risk* Recommendations for dose adjustment / criteria for permanent discontinuation if elevations of liver enzymes or bilirubin or hepatic AEs occur, are provided in the SmPC sections **4.2 Posology and method of administration** and **4.4 Special warnings and precautions for use**. *Other routine risk minimisation measures beyond the Product Information* Vargatef is available as a prescription-only medicine. Treatment with Vargatef should be initiated and supervised by a physician experienced in the use of anticancer therapies.

PV.Table 1 (cont'd) Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Missing information	
Treatment of patients with renal impairment	*Routine risk communication* SmPC sections 4.2 and 4.4 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None. *Other routine risk minimisation measures beyond the Product Information* Vargatef is available as a prescription-only medicine. Treatment with Vargatef should be initiated and supervised by a physician experienced in the use of anticancer therapies.
Treatment of patients weighing <50 kg	*Routine risk communication* SmPC section 4.4 *Routine risk minimisation activities recommending specific clinical measures to address the risk* Recommendation on close monitoring of patients weighing <50 kg is provided in the SmPC **Section 4.4 Special warnings and precautions for use**. *Other routine risk minimisation measures beyond the Product Information* Vargatef is available as a prescription-only medicine. Treatment with Vargatef should be initiated and supervised by a physician experienced in the use of anticancer therapies.

PART V.2 ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

PART V.3 SUMMARY OF RISK MINIMISATION MEASURES

PV.Table 2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Drug-induced liver injury (DILI)	*Routine risk minimisation measures:* Labelling in SmPC Sections 4.2, 4.4, 4.8, and 4.9. Prescription only medicine. Treatment with Vargatef should be initiated and supervised by a physician experienced in the use of anticancer therapies. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* AE follow-up form *Additional pharmacovigilance activities:* None
Important potential risks		
Hepatic failure	*Routine risk minimisation measures:* Labelling in SmPC Sections 4.2 and 4.4. Prescription only medicine. Treatment with Vargatef should be initiated and supervised by a physician experienced in the use of anticancer therapies. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* AE follow-up form *Additional pharmacovigilance activities:* None
Missing information		
Treatment of patients with renal impairment	*Routine risk minimisation measures:* Labelling in SmPC sections 4.2 and 4.4. Prescription only medicine. Treatment with Vargatef should be initiated and supervised by a physician experienced in the use of anticancer therapies. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* None

PV.Table 2 (cont'd) Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information		
Treatment of patients weighing <50 kg	*Routine risk minimisation measures:* Labelling in SmPC Section 4.4. Prescription only medicine. Treatment with Vargatef should be initiated and supervised by a physician experienced in the use of anticancer therapies. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* None

PART V.4 REFERENCES

Not applicable.

ABBREVIATIONS

AE	Adverse event
DILI	Drug-induced liver injury
SmPC	Summary of Product Characteristics

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR VARGATEF (NINTEDANIB)

This is a summary of the risk management plan (RMP) for Vargatef. The RMP details important risks of Vargatef, how these risks can be minimised, and how more information will be obtained about Vargatef's risks and uncertainties (missing information).

Vargatef's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Vargatef should be used.

This summary of the RMP for Vargatef should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Vargatef's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Vargatef is authorised in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first line chemotherapy (see SmPC for the full indication). It contains nintedanib as the active substance and it is given orally.

Further information about the evaluation of Vargatef's benefits can be found in Vargatef's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/vargatef.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Vargatef, together with measures to minimise such risks and the proposed studies for learning more about Vargatef's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

If important information that may affect the safe use of Vargatef is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Vargatef are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Vargatef. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information

Table 1 Important risks and missing information

Important identified risks	Drug-induced liver injury (DILI)
Important potential risks	Hepatic failure
Missing information	Treatment of patients with renal impairment Treatment of patients weighing <50 kg

II.B Summary of important risks

Important identified risks

Drug-induced liver injury (DILI)	
Evidence for linking the risk to the medicine	In the pivotal clinical trial of Vargatef (trial 1199.13), elevations of liver enzymes and total bilirubin were more frequent in patients treated with nintedanib in combination with docetaxel as compared to patients treated with docetaxel alone. Furthermore, liver enzyme elevations are among the most frequently reported events in the post-marketing setting. Cases of DILI have been observed with nintedanib treatment. In the post-marketing period, severe liver injury with fatal outcome has been reported in a patient with IPF after treatment with Ofev (nintedanib approved in the indication of IPF).
Risk factors and risk groups	Population pharmacokinetics analyses in patients with NSCLC and IPF revealed that female and Asian patients have a higher risk of elevations in liver enzymes upon nintedanib treatment. Nintedanib exposure increased linearly with patients' age and was inversely correlated to weight. The increased nintedanib exposure may result in a higher risk of developing liver enzyme elevations.
Risk minimisation measures	Routine risk minimisation measures: Labelling in SmPC Sections 4.2, 4.4, 4.8, and 4.9. Prescription only medicine. Treatment with Vargatef should be initiated and supervised by a physician experienced in the use of anticancer therapies. Additional risk minimisation measures: None

Important potential risks

Hepatic failure	
Evidence for linking the risk to the medicine	'Drug-induced liver injury (DILI)' is an important identified risk of Vargatef. DILI can be severe and can lead to hepatic failure. In the pivotal clinical trial of Vargatef (trial 1199.13), the majority of the AEs included in the medical concept of 'hepatic failure' (including precursors and symptoms), were liver enzyme elevations which were reversible in the majority of cases. In the post-marketing setting, reported events comprised liver enzyme elevations and/or hepatic events as a consequence of the underlying malignancy. None of the reported events met the medical definition of hepatic failure.
Risk factors and risk groups	Not known in patients with NSCLC.
Risk minimisation measures	Routine risk minimisation measures: Labelling in SmPC Sections 4.2 and 4.4. Prescription only medicine. Treatment with Vargatef should be initiated and supervised by a physician experienced in the use of anticancer therapies. Additional risk minimisation measures: None

Missing information

Treatment of patients with renal impairment	
Evidence for linking the risk to the medicine	The safety, efficacy, and pharmacokinetics of Vargatef have not been studied in patients with compromised renal function. Less than 1% of a single dose of Vargatef is excreted via the kidney. Thus, renal function is not thought to have an impact on elimination and/or Vargatef plasma levels. The reported events from post-marketing in patients with renal impairment are consistent with the known safety profile of nintedanib administered in combination with docetaxel and the advanced tumour disease, with no information to suggest any new safety concern.
Risk minimisation measures	Routine risk minimisation measures: Labelling in SmPC sections 4.2 and 4.4. Prescription only medicine. Treatment with Vargatef should be initiated and supervised by a physician experienced in the use of anticancer therapies. Additional risk minimisation measures: None

[redacted]

Treatment of patients weighing <50 kg	
Evidence for linking the risk to the medicine	In the pivotal clinical trial of Vargatef (trial 1199.13), only a small number of patients weighed less than 50 kg, both in the overall population (Vargatef: 32 patients; placebo: 34 patients) and in the adenocarcinoma population (Vargatef: 17 patients; placebo: 20 patients). Population PK analyses showed an inverse correlation between body weight and exposure to nintedanib. In the post-marketing setting, many patients with a weight lower than 50 kg are experiencing tumour progression or consequences of tumour progression. The remaining events are consistent with the known safety profile of Vargatef, and docetaxel or events that are related to the underlying NSCLC.
Risk minimisation measures	Routine risk minimisation measures: Labelling in SmPC Section 4.4. Prescription only medicine. Treatment with Vargatef should be initiated and supervised by a physician experienced in the use of anticancer therapies. Additional risk minimisation measures: None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Vargatef.

II.C.2 Other studies in post-authorisation development plan

No studies are required for Vargatef.

ABBREVIATIONS

DILI	Drug-induced liver injury
EMA	European Medicines Agency
EPAR	European Public Assessment Report
NSCLC	Non-small-cell lung cancer
RMP	Risk management plan
SmPC	Summary of product characteristics

PART VII APPENDICES

APPENDIX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Appendix 4 Table of Contents

Hepatic Questionnaire Vargatef_Version 7.0

Question ID	BI Questionnaire owner / TA	Questionnaire Name	Question category	Question
Q:HV01	Oncology	Hepatic Event Form (Vargatef)	Questionnaire	Please describe the event including start and end date, clinical course and outcome.
Q:HV02	Oncology	Hepatic Event Form (Vargatef)	Questionnaire	Please provide details on the treatment of the hepatic event(s), including time and dose: - Drug or any other treatment? - Was the treatment interrupted and re-initiated? - Was the drug permanently discontinued? - Was the treatment with a concomitant drug changed? Please specify which drug and whether interruption, permanent discontinuation, dose reduction.

Q:HV03	Oncology	Hepatic Event Form (Vargatef)	Questionnaire	Diagnostic tests, imaging, liver biopsy. Please provide the date and the diagnosis. - Ultrasound - CT/MRI - Liver biopsy - Other
Q:HV04	Oncology	Hepatic Event Form (Vargatef)	Questionnaire	Laboratory liver parameters. Please provide time course of the following laboratory values including value prior to administration, maximum/minimum, and value at time of recovery (with reference range and unit). - AST - ALT
Q:HV05	Oncology	Hepatic Event Form (Vargatef)	Questionnaire	Other laboratoty parameters. Please provide the value, the unit, the date, as well as the reference range. - ASM (anti smooth muscle cell AB) - AMA (anti mitochondrial AB) - Anti-LKM AB (anti liver kidney microsomal AB) - ANA - AFP - CE
Q:HV06	Oncology	Hepatic Event Form (Vargatef)	Questionnaire	Hepatitis serology for Hepatitis A: Please provide the value, the unit, and the date. - Anti Ig M - Anti Ig G - HAV RNA
Q:HV07	Oncology	Hepatic Event Form (Vargatef)	Questionnaire	Hepatitis serology for Hepatitis C: Please provide the value, the unit, and the date. - Anti-HCV

Q:HV08	Oncology	Hepatic Event Form (Vargatef)	Questionnaire	Concomitant medication possibly contributing to the hepatic event(s). Please provide the drug, the indication, the start date, and the end date/ongoing.
Q:HV09	Oncology	Hepatic Event Form (Vargatef)	Questionnaire	Does the patient have a history of any of the following? [Yes/No, start date, if possible specify] - Jaundice (personal or family history) - Hepatic malignancy - Metabolic-induced liver disease, nonalcoholic steatohepatitis (NASH) - Alcohol-induced liver disease - Liver cirrhosis. Please specify cause - Treatment or history of hepatitis B/C

Q:HV10	Oncology	Hepatic Event Form (Vargatef)	Questionnaire	Does the patient have a history of any of the following? [Yes/No, start date, if possible specify] - Extrahepatic manifestations (e.g. gallstones, infestations, pancreatitis) - Hereditary metabolic diseases (e.g. M.Wilson, haemochromatosis) - Extrahepatic malignancy - Any other condition relevant to the Hepatic Event
Q:HV11	Oncology	Hepatic Event Form (Vargatef)	Questionnaire	Does the patient have a history of any of the following? [Yes/No, start date, if possible specify] - History of drug allergy / hypersensitivity reaction - Recent administration of drugs with known hepatic toxicity - Environmental exposure to liver toxins (CCl4, death cap, vinyl chloride, collection of wild mushrooms) - Substance abuse / Intoxications - Blood transfusion
Q:HV12	Oncology	Hepatic Event Form (Vargatef)	Questionnaire	Does the patient have a history of any of the following? [Yes/No, start date, if possible specify] - Infectious diseases (e.g.HIV, EBV, CMV, Cocksackie, malaria, viralhepatitis, schistosomiasis) - Travel to tropical countries or countries where hepatitis is endemic - Autoimmune disorders (e.g. PBC, PSC) - Heart disease (e.g. right heart failure, cardiovascular dysfunction)

Q:HV13	Oncology	Hepatic Event Form (Vargatef)	Questionnaire	Final diagnosis / Cause of the hepatic event(s). Please provide final diagnosis and/or cause of the hepatic event(s) according to your assessment and rationale for it.

APPENDIX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

There are no proposed additional risk minimisation activities for Vargatef.