



Clinical trial results:

Phase II, Open-label, Study in Patients with anaplastic (ATC) or poorly differentiated thyroid carcinomas (PDTC) to investigate the Clinical Efficacy and Safety of the Combination Therapy of Lenvatinib and Pembrolizumab

Summary

EudraCT number	2017-004570-34
Trial protocol	DE
Global end of trial date	15 September 2024

Results information

Result version number	v1 (current)
This version publication date	14 February 2026
First version publication date	14 February 2026

Trial information

Trial identification

Sponsor protocol code	01045-ATLEP
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Deutsches Register Klinischer Studien: DRKS00013336

Notes:

Sponsors

Sponsor organisation name	Medical Center - University of Freiburg
Sponsor organisation address	Hugstetter Straße 55, Freiburg, Germany, 79106
Public contact	Medical Clinic 1 - ECTU, Medical Center - University of Freiburg, +49 76127071812, christine.dierks@uniklinik-freiburg.de
Scientific contact	Medical Clinic 1 - ECTU, Medical Center - University of Freiburg, +49 76127071812, christine.dierks@uniklinik-freiburg.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 November 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 September 2024
Global end of trial reached?	Yes
Global end of trial date	15 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to obtain first information on the efficacy of combination therapy of lenvatinib and pembrolizumab in patients with ATC or PDTC, measured as Objective Response Rate (ORR) obtained 12 weeks after start of the study treatment.

Protection of trial subjects:

The investigator was responsible for ensuring that the study was performed in accordance with the ethical principles of the Declaration of Helsinki as well as with national law and guidelines for the clinical testing of drugs. The investigations and assessments that were performed throughout the study (see section 9.5.1), mainly include procedures that are performed in patients with this indication on a routine basis in outpatient clinical patient care. Therefore, these procedures are not expected to pose a specific extended risk to the patient above that of routine care. The risks of additional procedures beyond routine patient care such as questionnaires, blood sample collection and imaging (CT/ MRI and PET-CT) investigations are also well balanced and of minor concern. Moreover, the fact that patients included in this trial were closely monitored by an interdisciplinary team in shorter outpatient intervals as in routine care provided a substantial medical benefit by itself.

Background therapy: -

Evidence for comparator:

Currently there are no proven therapies for anaplastic thyroid carcinomas (ATC). No comparative clinical trials have been performed, which would allow to determine a standard chemotherapy regimen for this disease. Therefore, all clinical centers have their own chemotherapy regimen used for this entity. As there are no proven therapies for ATC it is unethical to perform any control interventions.

Actual start date of recruitment	28 May 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 39
Worldwide total number of subjects	39
EEA total number of subjects	39

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	21
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	39
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Number of subjects completed	38
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Pre-assignment subject non-completion reasons

Reason: Number of subjects	Treatment not started: 1
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Period 1

Period 1 title	Overall (overall period)
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Is this the baseline period?	Yes
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Allocation method	Not applicable
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Blinding used	Not blinded
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Blinding implementation details:

Single arm trial

Arms

Arm title	Treatment
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Arm description: -

Arm type	Experimental
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Investigational medicinal product name	Pembrolizumab
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Investigational medicinal product code	
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Other name	Keytruda
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Pharmaceutical forms	Powder for concentrate for solution for infusion
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Routes of administration	Intracavernous use
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Dosage and administration details:

Every 21 days, 200 mg as intravenous infusion about 30 min. Duration: 36 months, or until disease progression, toxicity, death or total end of study (EOS). Patients could continue the treatment if they further profited from the therapy (no CR after 36 months or slow progression without other therapeutic options).

Investigational medicinal product name	Lenvatinib
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Investigational medicinal product code	
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Other name	Lenvatinib mesilate, Lenvima
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Pharmaceutical forms	Capsule, hard
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Routes of administration	Oral use
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Dosage and administration details:

Daily, 20 mg, preferably in the morning but any time is possible (two 10 mg capsules). Duration: 36 months, or until disease progression, toxicity, death or total end of study (EOS). Patients could continue the treatment if they further profited from the therapy (no CR after 36 months or slow progression without other therapeutic options).

Number of subjects in period 1 ^[1]	Treatment
Started	38
Completed	38

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One patient did not start treatment.

Baseline characteristics

Reporting groups

Reporting group title	Treatment
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Reporting group description: -

Reporting group values	Treatment	Total	
Number of subjects	38	38	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	20	20	
From 65-84 years	18	18	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	62.76		
standard deviation	± 11.16	-	
Gender categorical			
Units: Subjects			
Female	16	16	
Male	22	22	

End points

End points reporting groups

Reporting group title	Treatment
Reporting group description: -	

Primary: Objective response rate

End point title	Objective response rate ^[1]
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End point description:

Objective response rate (ORR) was defined in this trial as a rate of patients having achieved complete response (CR) and partial response (PR). For complete response, irRECIST criteria requires the total (100%) remission of all target and non-target lesions. Lymph nodes must be reduced to below 10 mm. For partial response, irRECIST requires a decrease of at least 30% of the tumor burden compared to the baseline.

End point type	Primary
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End point timeframe:

12 weeks after start of the study treatment, i.e. at week 13.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Single arm trial. The primary endpoint was analyzed by estimating the ORR 12 weeks after start of treatment as the number of patients with observed response divided by the number of patients included in the FAS. A two-sided confidence interval at level 80% (in accordance with the specified α) and 95% (for comparability to the literature) was calculated.

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Number of patients				
irCR	0			
irPR	11			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival
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End point description:

End point type	Secondary
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End point timeframe:

Time from the start of study treatment (day 1) to death from any cause or as time to the date the patient was last seen alive (censored observation)

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Rate				
number (confidence interval 95%)				
3 months	0.92 (0.76 to 0.97)			
6 months	0.75 (0.58 to 0.86)			
9 months	0.64 (0.46 to 0.77)			
12 months	0.50 (0.33 to 0.65)			
18 months	0.36 (0.21 to 0.51)			
24 months	0.31 (0.17 to 0.46)			
36 months	0.17 (0.07 to 0.30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival
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End point description:

End point type	Secondary
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End point timeframe:

Time from start of study treatment (day 1) to disease progression or death from any cause, whichever occurred first; or as time to the date the patient was last seen alive without disease progression (censored observation).

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Rate				
number (confidence interval 95%)				
3 months	0.89 (0.73 to 0.96)			
6 months	0.69 (0.52 to 0.82)			
9 months	0.58 (0.41 to 0.72)			
12 months	0.39 (0.23 to 0.54)			
18 months	0.28 (0.15 to 0.43)			

24 months	0.11 (0.04 to 0.24)			
36 months	0.08 (0.02 to 0.20)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate

End point title	Disease control rate
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End point description:

Rate of patients having achieved complete response, partial response or stable disease.

End point type	Secondary
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End point timeframe:

12 weeks after start of study treatment (day 1)

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Number of patients				
Week 7	33			
Week 13	29			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response
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End point description:

End point type	Secondary
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End point timeframe:

Time from first response to the date of first observation of progressive disease.

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Rate				
number (confidence interval 95%)				
3 months	0.85 (0.60 to 0.95)			
6 months	0.60 (0.36 to 0.78)			
9 months	0.50 (0.27 to 0.69)			
12 months	0.40 (0.19 to 0.60)			
18 months	0.20 (0.06 to 0.39)			
24 months	0.15 (0.04 to 0.34)			
36 months	0.10 (0.02 to 0.27)			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient's quality of life (EQ-5D-3L)

End point title	Patient's quality of life (EQ-5D-3L)
End point description: The quality of life (QoL) of the patients was evaluated using the EQ-5D-3L questionnaire.	
End point type	Secondary
End point timeframe: Up to visit 7 (week 13)	

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Mean				
arithmetic mean (standard deviation)				
Screening	66.2 (± 17.8)			
Week 7	64.0 (± 17.3)			
Week 13	62.8 (± 15.7)			
Difference week 13 to screening	-2.2 (± 16.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor burden

End point title	Tumor burden
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End point description:

End point type	Secondary
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End point timeframe:

Week 7

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Target lesions [mm]				
arithmetic mean (standard deviation)				
Screening	86.7 (± 64.2)			
Minimum from week 7 on	52.9 (± 40.2)			
Maximum reduction	-28.8 (± 28.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response

End point title	Best overall response
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End point description:

End point type	Secondary
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End point timeframe:

Until the end of treatment (EOT1).

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Number of patients				
irCR	0			
irPR	20			
irSD	13			
irPD	0			
Death before day 50	1			
Progression/death before day 92	1			
Missing	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Metabolic response

End point title	Metabolic response
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End point description:

Metabolic response assessment was performed according to EORTC criteria.

End point type	Secondary
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End point timeframe:

12 weeks after start of treatment (week 13).

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Number of patients				
CMR	2			
PMR	21			
SMD	2			
PMD	4			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Complete study

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22
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Reporting groups

Reporting group title	Treatment
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Reporting group description:

Lenvatinib/Pembrolizumab

Serious adverse events	Treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 38 (68.42%)		
number of deaths (all causes)	34		
number of deaths resulting from adverse events	14		
Injury, poisoning and procedural complications			
Tracheal haemorrhage			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 2		
Vascular disorders			
Haemorrhage			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Vocal cord paralysis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			

subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pyrexia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Erosive oesophagitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal haemorrhage			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

Nausea			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal perforation			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Autoimmune hepatitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acquired tracheo-oesophageal fistula			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		

Haemoptysis			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fistula			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pathological fracture			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal abscess			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchopulmonary aspergillosis			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Bacterial sepsis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Febrile infection			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infected fistula			

subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pneumonia			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		
Mediastinitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infection			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Sepsis			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 38 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Haemorrhage			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	13 / 38 (34.21%)		
occurrences (all)	16		
Hypotension			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Thrombophlebitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Venous thrombosis			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Vein disorder			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Surgical and medical procedures			
Enteral nutrition			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Parenteral nutrition			

subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Tooth extraction			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	4		
Tracheostomy			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
General disorders and administration site conditions			
Application site haematoma			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Chest pain			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Chills			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	20 / 38 (52.63%)		
occurrences (all)	23		
Feeling cold			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Gait disturbance			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
General physical health deterioration			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Inflammation			

subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Mucosal dryness			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Mucosal inflammation			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	5 / 38 (13.16%)		
occurrences (all)	5		
Oedema			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Peripheral swelling			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	7 / 38 (18.42%)		
occurrences (all)	10		
Scar inflammation			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Swelling face			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Tenderness			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Seasonal allergy			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		

Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	2		
Pelvic pain			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	15 / 38 (39.47%)		
occurrences (all)	18		
Dysphonia			
subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	9		
Dyspnoea			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	6		
Dyspnoea exertional			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Haemoptysis			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Hiccups			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	2		
Increased upper airway secretion			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Nasal inflammation			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Oropharyngeal pain			

subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	7		
Pleural effusion			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Pulmonary oedema			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Pulmonary embolism			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Throat tightness			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Psychiatric disorders			
Apathy			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Depression			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 38 (13.16%)		
occurrences (all)	5		
Aspartate aminotransferase increased			

subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	4		
Aspergillus test positive			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Blood pressure increased			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
C-reactive protein increased			
subjects affected / exposed	11 / 38 (28.95%)		
occurrences (all)	11		
Fibrin D dimer increased			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Hepatic enzyme increased			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Inflammatory marker increased			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Inflammatory marker test			

subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Stenotrophomonas test positive			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Transaminases increased			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Weight decreased			
subjects affected / exposed	17 / 38 (44.74%)		
occurrences (all)	21		
Injury, poisoning and procedural complications			
Burn oral cavity			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Craniofacial fracture			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Limb injury			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Seroma			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Skin wound			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Tooth fracture			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Tongue injury			

subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Wound			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Tracheostomy malfunction			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Nervous system disorders			
Ageusia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	10 / 38 (26.32%)		
occurrences (all)	12		
Hypoaesthesia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Monoplegia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Neuritis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Polyneuropathy			

subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Postictal paralysis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Taste disorder			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Tongue paralysis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Vlth nerve paralysis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Lymphopenia			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	5		
Leukopenia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Leukocytosis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Iron deficiency anaemia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Neutrophilia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		

Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	5 / 38 (13.16%) 5		
Eye disorders Diplopia subjects affected / exposed occurrences (all) Visual acuity reduced subjects affected / exposed occurrences (all) Vision blurred subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1 1 / 38 (2.63%) 1 1 / 38 (2.63%) 1		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Anal eczema subjects affected / exposed occurrences (all) Anal pruritus subjects affected / exposed occurrences (all) Aphthous ulcer subjects affected / exposed occurrences (all) Colitis subjects affected / exposed occurrences (all) Constipation	1 / 38 (2.63%) 1 2 / 38 (5.26%) 2 10 / 38 (26.32%) 10 1 / 38 (2.63%) 1 1 / 38 (2.63%) 1 1 / 38 (2.63%) 1 1 / 38 (2.63%) 1		

subjects affected / exposed	5 / 38 (13.16%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed	21 / 38 (55.26%)		
occurrences (all)	34		
Dyschezia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Dysphagia			
subjects affected / exposed	8 / 38 (21.05%)		
occurrences (all)	11		
Dry mouth			
subjects affected / exposed	9 / 38 (23.68%)		
occurrences (all)	9		
Glossitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Glossodynia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Haematochezia			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Flatulence			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Hyperaesthesia teeth			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Hypoaesthesia oral			

subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Lip haemorrhage			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Lip dry			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Lip blister			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	20 / 38 (52.63%)		
occurrences (all)	24		
Oral discomfort			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Plicated tongue			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Pancreatitis chronic			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Paraesthesia oral			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Periodontal disease			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Rectal polyp			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Retching			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Salivary hypersecretion			

subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Stomatitis			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Tongue discomfort			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	4		
Toothache			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Trichoglossia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	7		
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Alopecia			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Blister			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Dermatitis acneiform			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Dry skin			

subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Erythema			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Hyperkeratosis			
subjects affected / exposed	5 / 38 (13.16%)		
occurrences (all)	5		
Night sweats			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Nail bed inflammation			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Plantar erythema			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Palmar erythema			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	6		
Skin disorder			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	10 / 38 (26.32%)		
occurrences (all)	11		

Rash papular subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Skin haemorrhage subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Vitiligo subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Oliguria subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Proteinuria subjects affected / exposed occurrences (all)	4 / 38 (10.53%) 5		
Urinary retention subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Musculoskeletal and connective tissue disorders			
Bone pain subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Arthralgia subjects affected / exposed occurrences (all)	12 / 38 (31.58%) 17		
Back pain subjects affected / exposed occurrences (all)	7 / 38 (18.42%) 7		
Flank pain subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Exostosis			

subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Muscle tightness			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Musculoskeletal stiffness			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	5 / 38 (13.16%)		
occurrences (all)	5		
Myalgia			
subjects affected / exposed	5 / 38 (13.16%)		
occurrences (all)	8		
Osteonecrosis of jaw			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	6		
Pain in jaw			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Spinal pain			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Infections and infestations			

Abscess neck			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
COVID-19			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Candida infection			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Gastrointestinal infection			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Genital candidiasis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Gingivitis			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Folliculitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Furuncle			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Infection			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Mediastinitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		

Oral herpes			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	3		
Omphalitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Oral candidiasis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Pneumonia fungal			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Pulpitis dental			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Respiratory tract infection			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Pustule			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Tooth abscess			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Tinea pedis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	6		

Viral rash			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Decreased appetite			
subjects affected / exposed	16 / 38 (42.11%)		
occurrences (all)	18		
Dehydration			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Hyperamylasaemia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	3		
Hyperglycaemia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Hyperlipasaemia			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	4		
Hypokalaemia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 March 2019	<ul style="list-style-type: none">• The primary endpoint was changed to ORR to improve comparability with other studies. CBR was now a secondary endpoint.• The number of patients in the study was increased from 10 to 18. This was due, among other things, to a request from the Ethics Committee and a revision of the significance level by our statisticians. To achieve a sufficient number of patients, the recruitment period was increased from 12 to 18 months.• Inclusion criterion 4 was changed from ECOG 0-2 to ECOG 0-1. This corresponds to the inclusion criteria of other clinical trials in anaplastic thyroid carcinoma and increased participant safety.• The lenvatinib dosages were changed as follows: Level 1 from 14 to 16 mg; Level 2 from 10 to 12 mg; Level 3 from 8 to 10 mg. These finer dosing options allowed for better and more individualized dose adjustment per patient.• The definitions of 'response' have been changed. Response criteria should be based on the latest irRECIST criteria for immunotherapies.• Inclusion criterion 13 (life expectancy > 1 month) was removed, as our experience had shown that patients with a life expectancy of less than 1 month without treatment also benefit.• Lenvatinib, one of the two study medications, was provided to us by Eisai as part of the ATLEP study. This allowed for the provision of lenvatinib free of charge to all patients within the study for two years.• Consistent description of the dose reduction of lenvatinib.
26 May 2020	<ul style="list-style-type: none">• Due to the COVID-19 pandemic and the corresponding travel restrictions/ complications we aimed to choose local university hospitals with experience in clinical trials, where our patients could get their 3-weekly pembrolizumab infusions. The 3-monthly study visits still took place in Freiburg. Lenvatinib was surrendered to the patients for the whole 3 months period between two study visits.• Recent clinical data suggested, that the outcome of ATCs (anaplastic thyroid carcinomas) and PDTCs (poorly differentiated thyroid carcinomas) differs regarding response to third-line therapies. Therefore, we aimed to separate the statistical analysis for both entities, and according to our statistical calculations then needed to increase the sample size to 20 ATCs (anaplastic thyroid carcinomas) and 20 PDTCs (poorly differentiated thyroid carcinomas). Enhancement of the recruitment time from 12 to 24 months.• We aimed to change the time point for the PET-CT from 6 months to 3 months and to add another PET-CT at the 12-month time point. Patients suffering from other types of cancer within the last 24 months, which could not be cured by local measures, must be excluded.• In case of hypertension, proteinuria and arterial embolism, it was necessary at first to optimize symptom specific concomitant treatment like antihypertensive medication or anticoagulation; lenvatinib had to be interrupted after outstanding effect of such optimization.• In case of autoimmune hepatitis, pembrolizumab had to be interrupted until transaminases had decreased to CTCAE grade II or below. Pembrolizumab could then be restarted with comedication of budesonide and ursodesoxycholsäure.• Therapy with lenvatinib for a maximum of 4 weeks prior enrolment was permitted.• Duration of the trial was prolonged until 36 months after registration of the last patient.

19 November 2021	<ul style="list-style-type: none"> • Lenvatinib had to be stopped 1 week before and up to 2 weeks after a major surgery • Lenvatinib was shown to induce jaw necrosis as a newly observed side effect, which had to be added • Dr. Cornelius Miething took over the role as Coordinating Investigator (LKP) in Freiburg, Prof. Dr. Christine Dierks is future Scientific Coordinator. <p>Summary of changes to CTP:</p> <ul style="list-style-type: none"> • Adjustments in trial duration and planned dates as well as on funding • Adjustments in Exclusion criteria concerning consistency • Update of contact details of clinical monitoring (CRA) • Update of patient registration times • Inclusion of further information in "Guidelines for management of medical conditions during the study" • Inclusion of further information in section "Permitted prior/ concomitant treatment/ medication" (stop of lenvatinib treatment before major surgery) • Adjustment on monitoring procedure.
22 March 2022	<ul style="list-style-type: none"> • Starting Dose of Lenvatinib was maintained (according to SmPC) at 20mg/day • Pembrolizumab was administered at the Medical Center – University of Freiburg only
22 July 2024	<p>Notification of administrative changes in the conduct of the study:</p> <ul style="list-style-type: none"> • Update of insurance • Follow-up visits had been updated

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported