

**Clinical trial results:**

**Two-arm randomized phase II trial to assess the feasibility and efficacy of a treatment with Durvalumab a PDL1-Inhibitor plus Tremelimumab a CTLA-4- Inhibitor in combination with radiotherapy and a treatment with Durvalumab in combination with radiotherapy as first-line therapy for patients with non-resectable locally advanced HPV negative HNSCC- A COMPARISON WITH A HISTORICAL CONTROL GROUP-DuTRe-raD.**

**Summary**

EudraCT number	2016-003175-22
Trial protocol	DE
Global end of trial date	14 July 2023

**Results information**

Result version number	v1 (current)
This version publication date	27 January 2024
First version publication date	27 January 2024

**Trial information****Trial identification**

Sponsor protocol code	CCCC-H&N-IRT-1
-----------------------	----------------

**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03624231
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Charité- Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	PD Dr. Konrad Klinghammer, Medizinische Klinik m.S. Hämatologie, Onkologie und Tumورimmunologie, Campus Benjamin Franklin, +49 030 450513525, konrad.klinghammer@charite.de
Scientific contact	Prof . Dr. Ulrich Keilholz, Head of CCCC, Charité Comprehensive Cancer Center CCCC, +49 030 450564621, ulrich.keilholz@charite.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	No

Notes:

**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	27 June 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	14 July 2023
Was the trial ended prematurely?	Yes

Notes:

**General information about the trial**

Main objective of the trial:

The primary objective is to explore the feasibility and efficacy in terms of treatment discontinuation due to toxicity and in terms of 1-year progression free survival of a PDL1-Inhibitor plus a CTLA-4 Inhibitor in combination with radiotherapy vs a PDL1-Inhibitor in combination with radiotherapy as first-line therapy for patients with non-resectable locally advanced HNSCC in the poor prognostic subgroup.

Protection of trial subjects:

Adverse events and serious adverse events were recorded from time of signature of informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of Durvalumab). Safety was assessed on a schedule based on the date of the first dose: Laboratory assessments (Coagulation parameters, pregnancy test, thyroid stimulating hormone, Hepatitis A, B and C virus antibodies, HIV antibodies, hematology tests, clinical chemistry tests, urinalysis test) was performed within 72 h before treatment application.

As the IMP has possible human teratogenicity/fetotoxicity in early pregnancy, pregnancy tests were performed in women of childbearing potential (WOCBP) every 8 weeks. Additionally, the investigators assessed antitumor activity based on radiological assessments and clinical evaluation of patients using modified RECIST v1.1 at baseline and during therapy every 8 weeks. For patients who achieved disease control following 12 months of treatment, or who discontinued the treatment due to toxicity, tumor assessments were performed every 12 weeks relative to the date of first infusion thereafter until confirmed PD by RECIST 1.1 by investigational site review.

Background therapy:

DURTRERAD is a randomized phase II study evaluating feasibility and efficacy of durvalumab (anti-PD-L1) vs. durvalumab and tremelimumab (anti-CTLA-4) in combination with radiotherapy as primary treatment for locally advanced HPV negative HNSCC. (NCT03624231). Concurrent chemo-RT with a platinum-based regimen is considered the standard treatment, although efficacy and long-term toxicity are not satisfactory. Combining immunotherapy with RT might result in improved efficacy with limited long-term toxicity. Methods: The phase II study planned to enroll 120 pts, 60 pts (1:1) in each treatment arm. Treatment with DT (1500mg/75 mg, arm DT), or D (1500mg, arm D) both in combination with RT (70Gy) was considered to be feasible if less than 10% of the patients treated will discontinue treatment due to on-treatment toxicities. A first interim analysis for feasibility and efficacy was planned after randomisation of 20 patients. Results: So far 23 patients have been screened, 16 patients have been randomised and started their allocated treatment, 10 in arm D and 6 in arm DT. Of 10 patients in arm D 1 patient stopped infusional treatment due to immune related toxicity. Out of 6 patients in the DT arm, however, 5 patients stopped treatment due to treatment related AEs, 2 pts due to immune related toxicity with one Grade 5 AE. Three patients stopped due to non-immune related AE. The grade 5 AE prompted the interim analysis, which revealed non-feasibility as well as safety-issues of the DT+radiotherapy combination. As a result, the DT arm was prematurely terminated.

Evidence for comparator: -

Actual start date of recruitment	23 October 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

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)	9
From 65 to 84 years	9
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 3 study centers in Germany, between Date of first enrollment: 23/10/2018 and The last patient on the trial completed maintenance treatment on 01.10.2021.

Date last patient last visit: 24/06/2022

### Pre-assignment

Screening details:

26 patients with Non-resectable locally advanced HPV negative HNSCC were screened, 8 screening failures.

### Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	DT + R

Arm description:

combination arm with Durvalumab and Tremelimumab and radiotherapy

Arm type	Experimental
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	CAS-Code 1428935-60
Other name	MEDI4736, Imfinzi
Pharmaceutical forms	Injection/infusion
Routes of administration	Solution for infusion

Dosage and administration details:

Patients in arm will receive a single dose of durvalumab of 1500 mg administered on day 1, 14 days prior to initiation of the radiotherapy.

Radiotherapy with 35 fractions over 7 weeks (administered as daily fractions of 2 Gy given 5 days every week for 7 weeks) will start on day 14. On week 5, 9, 13 and 17 patients will receive durvalumab (1500 mg) and tremelimumab (75 mg) for up to 4 doses/cycles and then continue 1500 mg durvalumab q4w starting on week 21 to complete a total of 12 months of therapy (overall 9 single doses durvalumab including the initial dose on day 1).

Investigational medicinal product name	Tremelimumab
Investigational medicinal product code	
Other name	Imjudo
Pharmaceutical forms	Injection/infusion
Routes of administration	Solution for infusion

Dosage and administration details:

Patients in arm will receive a single dose of durvalumab of 1500 mg administered on day 1, 14 days prior to initiation of the radiotherapy.

Radiotherapy with 35 fractions over 7 weeks (administered as daily fractions of 2 Gy given 5 days every week for 7 weeks) will start on day 14. On week 5, 9, 13 and 17 patients will receive durvalumab (1500 mg) and tremelimumab (75 mg) for up to 4 doses/cycles and then continue 1500 mg durvalumab q4w starting on week 21 to complete a total of 12 months of therapy (overall 9 single doses durvalumab including the initial dose on day 1).

<b>Arm title</b>	D + R
------------------	-------

Arm description:

Durvalumab and radiotherapy

Arm type	Experimental
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	CAS-Code 1428935-60
Other name	MEDI4736, Imfinzi
Pharmaceutical forms	Injection/infusion
Routes of administration	Solution for infusion

Dosage and administration details:

Patients in arm will receive a single dose of durvalumab of 1500 mg administered on day 1, 14 days prior to initiation of the radiotherapy.  
Radiotherapy with 35 fractions over 7 weeks (administered as daily fractions of 2 Gy given 5 days every week for 7 weeks) will start on day 14.

<b>Number of subjects in period 1</b>	DT + R	D + R
Started	6	12
Completed	6	12

## Baseline characteristics

## End points

### End points reporting groups

Reporting group title	DT + R
-----------------------	--------

Reporting group description:

combination arm with Durvalumab and Tremelimumab and radiotherapy

Reporting group title	D + R
-----------------------	-------

Reporting group description:

Durvalumab and radiotherapy

### Primary: progression-free survival (PFS)

End point title	progression-free survival (PFS) <sup>[1]</sup>
-----------------	--

End point description:

End point type	Primary
----------------	---------

End point timeframe:

teatment + 3 month follow up

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: Based on a failure rate of 10 %, it was planned to include 60 subjects. The analysis was to be conducted when 54 subjects reached follow-up.

However, only 18 subjects were included and analysed. No statistical analyses were carried out.

End point values	DT + R	D + R		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	12		
Units: weeks				
patient 1	0	74		
patient 2	0	146		
patient 3	0	0		
patient 4	0	98		
patient 5	0	10		
patient 6	0	10		
patient 7	0	0		
patient 8	0	23		
patient 9	0	26		
patient 10	0	40		
patient 11	0	26		
patient 12	0	75		
patient 13	25	0		
patient 14	9	0		
patient 15	11	0		
patient 16	43	0		
patient 17	204	0		
patient 18	150	0		

<b>Attachments (see zip file)</b>	safety and efficacy results/Detailed patient information_efficacy
-----------------------------------	---

### Statistical analyses

---

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:  
during treatment and up to 1 year after treatment

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	CTCAE
-----------------	-------

Dictionary version	4.03
--------------------	------

### Reporting groups

Reporting group title	DT+R arm and D+R arm
-----------------------	----------------------

Reporting group description: -

Serious adverse events	DT+R arm and D+R arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 18 (16.67%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Frequency threshold for reporting non-serious adverse events: 1 %

<b>Non-serious adverse events</b>	DT+R arm and D+R arm		
Total subjects affected by non-serious adverse events subjects affected / exposed	18 / 18 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) dysphagia due to oral floor carcinoma subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 4		
Investigations Creatinine increased subjects affected / exposed occurrences (all)  Blood bilirubin increased subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 2  1 / 18 (5.56%) 1		
Cardiac disorders bypass necessary due to high HS-stenosis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Ear and labyrinth disorders Amaurosis fugax subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Gastrointestinal disorders diarrhea subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Respiratory, thoracic and mediastinal disorders Pneumonia aspiration subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Skin and subcutaneous tissue disorders			

<p>papular exanthema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 18 (5.56%)</p> <p>1</p>		
<p>Psychiatric disorders</p> <p>Inner restlessness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 18 (11.11%)</p> <p>2</p>		
<p>Infections and infestations</p> <p>Mucosal oral inflammation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Port infection probably procedural complications</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Herpes Zoster</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 18 (11.11%)</p> <p>3</p> <p>1 / 18 (5.56%)</p> <p>1</p> <p>1 / 18 (5.56%)</p> <p>1</p>		
<p>Metabolism and nutrition disorders</p> <p>due to apply a PEG-system because of malnutrition and loss of weight surgical and medical procedures</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Malnutrition</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Diabetes mellitus</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dehydration</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 18 (5.56%)</p> <p>1</p> <p>1 / 18 (5.56%)</p> <p>1</p> <p>1 / 18 (5.56%)</p> <p>1</p> <p>1 / 18 (5.56%)</p> <p>1</p>		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 July 2016	update protocol Version 4.1
10 January 2020	update protocol Version 5.2
13 August 2020	Amendments to the test plan and investigator's brochure for testing substances MEDI 4736/MEDI 1123

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Enrollment in the trial was slower than expected. After the occurrence of a (SUSAR) in DT+R arm, this arm was terminated as specified in the protocol. The assumption of reaching a 30% PFS rate on D+R arm was judged to be unrealistic.

Notes: