# Clinical trial results:
# A PHASE II PROSPECTIVE IMMUNE NEOADJUVANT THERAPY STUDY OF DURVALUMAB (MEDI4736) IN EARLY STAGE NON-SMALL CELL LUNG CANCER

## Summary

| | |
|---|---|
| EudraCT number | 2016-001849-15 |
| Trial protocol | FR |
| Global end of trial date | 28 August 2019 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 11 August 2022 |
| First version publication date | 11 August 2022 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | IFCT-1601 IONESCO |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03030131 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | IFCT |
| Sponsor organisation address | 10 rue de la Grange-Batelière, Paris, France, 75009 |
| Public contact | Contact, IFCT, 33 156811045, contact@ifct.fr |
| Scientific contact | Contact, IFCT, 33 156811045, contact@ifct.fr |

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 | 06 May 2021 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 28 August 2019 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

To assess the impact of neo-adjuvant therapy with durvalumab given by intravenous infusion for one month on the complete resection (R0).

Protection of trial subjects:

Algorithms for management of adverse events were provided in the protocol.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 24 April 2017 |
| 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 | France: 50 |
| Worldwide total number of subjects | 50 |
| EEA total number of subjects | 50 |

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) | 35 |
| From 65 to 84 years | 15 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

A total of 50 patients were recruited from April 2017 to August 2019 in 20 sites, of whom 46 met the eligibility criteria and received durvalumab.

### Pre-assignment

Screening details:

Histologically confirmed NSCLC, classified as stage IB (only ≥4 cm), IIA, IIB, or IIIA non N2. Brain imaging, FDG-PET and a thoraco abdominopelvic CT scan were performed within one month prior to inclusion. Patients ≥18 years old with an ECOG performance status score of 0 1 were eligible. Pre therapeutic tissue was required.

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| **Arm title** | Durvalumab |

Arm description:

Monotherapy arm

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Durvalumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

750 mg at D1, D15 and D29 over 60 minutes

| **Number of subjects in period 1** | Durvalumab |
|---|---|
| Started | 50 |
| Completed | 43 |
| Not completed | 7 |
| Protocol deviation | 4 |
| Lack of efficacy | 3 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Overall trial (overall period) |
|---|---|

Reporting group description: -

| Reporting group values | Overall trial (overall period) | Total | |
|---|---|---|---|
| Number of subjects | 50 | 50 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 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) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous<br>Units: years | | | |
| median | 61.0 | | |
| full range (min-max) | 46.0 to 80.4 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 15 | 15 | |
| Male | 35 | 35 | |
| Smocking status<br>Units: Subjects | | | |
| Smockers | 47 | 47 | |
| Never smockers | 3 | 3 | |
| ECOG performance status<br>Units: Subjects | | | |
| PS 0 | 40 | 40 | |
| PS 1 | 10 | 10 | |
| Histology<br>Units: Subjects | | | |
| Adenocarcinoma | 25 | 25 | |
| Squamous cell carcinoma | 21 | 21 | |
| Other | 4 | 4 | |
| Stage<br>Units: Subjects | | | |
| IB | 5 | 5 | |
| IIA | 14 | 14 | |
| IIB | 29 | 29 | |
| IIIA | 1 | 1 | |
| Other stages | 1 | 1 | |

| | | | |
|---|---|---|---|
| Histological evidence<br>Units: Subjects | | | |
| Yes | 49 | 49 | |
| No | 1 | 1 | |
| Cytological evidence<br>Units: Subjects | | | |
| Yes | 12 | 12 | |
| No | 38 | 38 | |
| Diagnosis<br>Units: Subjects | | | |
| Echoendoscopy | 6 | 6 | |
| Fibroscopy | 24 | 24 | |
| Fibroscopy + Echoendoscopy | 1 | 1 | |
| Transthoracic puncture | 19 | 19 | |
| Smocking details<br>Units: Pack Year | | | |
| median | 40.0 | | |
| full range (min-max) | 2 to 100 | - | |
| Weight<br>Units: kilogram(s) | | | |
| median | 74 | | |
| full range (min-max) | 44 to 101 | - | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Durvalumab |
| Reporting group description: Monotherapy arm | |
| Subject analysis set title | ITT population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All included patients | |
| Subject analysis set title | Safety population - Durvalumab |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All patients who had received at least one dose of durvalumab | |
| Subject analysis set title | Efficacy population - Durvalumab |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Eligible patients without any major deviations from the inclusion/exclusion criteria | |
| Subject analysis set title | Efficacy population - Durvalumab and surgery |
| Subject analysis set type | Per protocol |
| Subject analysis set description: all eligible patients who had received at least one dose of durvalumab and who undergone surgery | |

### Primary: Surgical Resection R0

| | |
|---|---|
| End point title | Surgical Resection R0[1] |
| End point description: Patient percentage of surgical resection R0 after a maximum of 3 cycles of immune therapy | |
| End point type | Primary |
| End point timeframe: 2 months | |

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: Not applicable as the study was single arm

| End point values | Durvalumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 46 | | | |
| Units: % of participants | | | | |
| number (confidence interval 95%) | | | | |
| Complete resection (R0) | 89.1 (80.1 to 98.1) | | | |
| Microscopically incomplete resection (R1) | 4.3 (0.0 to 10.2) | | | |
| Not evaluable/Not done | 6.5 (0.0 to 13.7) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Delay Between Surgery and Start of Treatment

| End point title | Delay Between Surgery and Start of Treatment |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

After 28 days (3 cycles of immune therapy maximum)

| End point values | Durvalumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 43 | | | |
| Units: Days | | | | |
| median (full range (min-max)) | 37.0 (29 to 46) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Response Rate (RECIST 1.1)

| End point title | Response Rate (RECIST 1.1) |
|---|---|

End point description:

Response Rate include patient with complete response (disappearance of all target lesions) or partial response (at least a 30% decrease in the sum of diameters of target lesions since inclusion) as evaluated with Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1).

| End point type | Secondary |
|---|---|

End point timeframe:

After 28 days (3 cycles of immune therapy maximum)

| End point values | Durvalumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 46 | | | |
| Units: % of participants | | | | |
| Partial response | 4 | | | |
| Stable disease | 36 | | | |
| Progressive disease | 6 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Major Pathological Response

| End point title | Major Pathological Response |
|---|---|

End point description:

Major Pathological Response is defined as ≤10% remaining viable tumour cells (RVT).

| End point type | Secondary |
|---|---|

End point timeframe:

2 months

| End point values | Durvalumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 46 | | | |
| Units: % of participants | | | | |
| RVT ≤10% | 8 | | | |
| RVT >10% | 35 | | | |
| Unknown | 3 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Disease-Free Survival (DFS)

| End point title | Disease-Free Survival (DFS) |
|---|---|

End point description:

Time from the date of inclusion to the date of first documented disease relapse or the occurrence of a new invasive primary malignancy or death from any cause

| End point type | Secondary |
|---|---|

End point timeframe:

18 months

| End point values | Durvalumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 46 | | | |
| Units: % of participants | | | | |
| number (confidence interval 95%) | | | | |
| 12-month DFS | 78.3 (63.4 to 87.7) | | | |
| 12-month DFS - RVT ≤10% | 100 (100 to 100) | | | |

| | | | | |
|---|---|---|---|---|
| 12-month DFS - RVT >10% | 77.1 (59.5 to 87.9) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival (OS)

| End point title | Overall Survival (OS) |
|---|---|

End point description:

Time from the inclusion to the date of death of any cause, or censored at their last known alive date

| End point type | Secondary |
|---|---|

End point timeframe:

18 months

| End point values | Durvalumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 46 | | | |
| Units: % of participants | | | | |
| number (confidence interval 95%) | | | | |
| 12-month OS | 89.1 (75.8 to 95.3) | | | |
| 12-month OS - RVT ≤ 10 % | 100 (100 to 100) | | | |
| 12-month OS - RVT > 10 % | 88.6 (72.4 to 95.6) | | | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected for a patient from the date of signature of inform consent form, during treatment period and until 100 days after the last dose of study treatment.
Deaths were collected until data analysis.

Adverse event reporting additional description:

The maximal grade of adverse events was collected by cycle of treatment.

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Safety population |

Reporting group description: -

| Serious adverse events | Safety population | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 19 / 48 (39.58%) | | |
| number of deaths (all causes) | 8 | | |
| number of deaths resulting from adverse events | | | |
| Blood and lymphatic system disorders | | | |
| Haemolytic anaemia | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Chest pain | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 48 (2.08%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Respiratory distress | | | | |
| subjects affected / exposed | 4 / 48 (8.33%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Tracheal stenosis | | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung disorder | | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemoptysis | | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemothorax | | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tracheal fistula | | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| Bronchial fistula | | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Chylothorax | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Subcutaneous emphysema | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | Safety population | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 47 / 48 (97.92%) | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 17 / 48 (35.42%) | | |
| occurrences (all) | 25 | | |
| Chest pain | | | |
| subjects affected / exposed | 12 / 48 (25.00%) | | |
| occurrences (all) | 18 | | |
| Pain | | | |
| subjects affected / exposed | 4 / 48 (8.33%) | | |
| occurrences (all) | 4 | | |
| Ear and labyrinth disorders | | | |

| | | | |
|---|---|---|---|
| Vertigo<br>subjects affected / exposed<br>occurrences (all) | 3 / 48 (6.25%)<br>4 | | |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br>Nausea<br>subjects affected / exposed<br>occurrences (all)<br>Constipation<br>subjects affected / exposed<br>occurrences (all) | <br>6 / 48 (12.50%)<br>7<br><br>6 / 48 (12.50%)<br>7<br><br>3 / 48 (6.25%)<br>3 | | |
| Respiratory, thoracic and mediastinal disorders<br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br>Haemoptysis<br>subjects affected / exposed<br>occurrences (all)<br>Respiratory distress<br>subjects affected / exposed<br>occurrences (all)<br>Pneumothorax<br>subjects affected / exposed<br>occurrences (all)<br>Lung disorder<br>subjects affected / exposed<br>occurrences (all) | <br>14 / 48 (29.17%)<br>23<br><br>12 / 48 (25.00%)<br>26<br><br>6 / 48 (12.50%)<br>9<br><br>5 / 48 (10.42%)<br>6<br><br>4 / 48 (8.33%)<br>4<br><br>3 / 48 (6.25%)<br>3 | | |
| Skin and subcutaneous tissue disorders<br>Pruritus<br>subjects affected / exposed<br>occurrences (all) | <br>3 / 48 (6.25%)<br>5 | | |

| | | | |
|---|---|---|---|
| Rash<br>subjects affected / exposed<br>occurrences (all) | 3 / 48 (6.25%)<br>3 | | |
| Renal and urinary disorders<br>Urinary retention<br>subjects affected / exposed<br>occurrences (all) | 3 / 48 (6.25%)<br>3 | | |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Back pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences (all) | 4 / 48 (8.33%)<br>4<br><br>3 / 48 (6.25%)<br>4<br><br>3 / 48 (6.25%)<br>4 | | |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 5 / 48 (10.42%)<br>9 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 06 June 2017 | A first substantial modification was done in order:<br>• to adapt the protocol to the 8th edition of the UICC TNM classification<br>• to delete "Drug-induced liver injury" from serious adverse events lists<br>• to add a section for the management of myocarditis and similar toxicities |
| 16 May 2018 | A second substantial modification was done in order:<br>• to extent inclusion criteria to stage IIIA non-N2 NSCLC<br>• to make frozen tissue collection optional |
| 08 January 2019 | A third substantial modification was done in order to:<br>• to clarify and update inclusion criteria specifying the size of the tumor<br>• to delete the exclusion criteria about ECG that is no longer required.<br>• to add a central review of all patients before inclusion.<br>• to add a suspension of inclusions after the 57th patients in order to perform a statistical analysis of tolerance data (90-days postoperative).<br>In addition, a definitive discontinuation of the study was planned in case of occurrence of a new death (any cause combined) occurring within 90 days of surgery.<br>• to add collection of feces before starting study treatment. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---|---|---|
| 28 August 2019 | Enrolment was stopped on August 28, 2019 at the request of the independent committee due to excessive 90-day postoperative mortality, with 4 unexpected deaths (8.7% of the 46 eligible patients). | - |

Notes:

## Limitations and caveats

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

The main study limitation was the small sample size, due to the premature ending of the trial. Another limitations were the prevalence of risk factors in the study population and finally, the heterogenity due to the involvement of 20 active centers.

Notes: