



Clinical trial results: MEDI4736 combinations in metastatic renal cell carcinoma Summary

EudraCT number	2015-002042-31
Trial protocol	ES
Global end of trial date	17 July 2024

Results information

Result version number	v1 (current)
This version publication date	29 August 2025
First version publication date	29 August 2025

Trial information

Trial identification

Sponsor protocol code	010580QM
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Queen Mary University of London
Sponsor organisation address	Mile End Road, London, United Kingdom, E1 2EF
Public contact	Mays Jawad, Queen Mary University of London, +44 2078827260, sponsorsrep@bartshealth.nhs.uk
Scientific contact	Mays Jawad, Queen Mary University of London, +44 2078827260, sponsorsrep@bartshealth.nhs.uk

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	17 July 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 July 2024
Global end of trial reached?	Yes
Global end of trial date	17 July 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

De-escalation phase: To determine the recommended dose of MEDI4736 and savolitinib in combination by assessment of dose limiting toxicities.

Expansion phase: To determine how well different combinations of MEDI4736, savolitinib and tremelimumab can reduce tumour sizes in patients with papillary and clear cell renal cell carcinoma.

Protection of trial subjects:

Eligibility criteria for this study were selected to enhance patient safety. A number of exclusion criteria were based on the known safety profiles of the study drug treatments. All enrolled patients were evaluated clinically before and throughout their participation in the study. Safety evaluations consisted of medical interviews, adverse event recording, and laboratory assessments. Patients were monitored for adverse events (all grades), serious adverse events, and any toxicities requiring treatment interruption or discontinuation during the course of the study. Outcomes of pre-specified early safety reviews that affected study conduct were communicated promptly to Investigators for onward reporting to the appropriate ethics committees.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 May 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 96
Country: Number of subjects enrolled	United Kingdom: 83
Worldwide total number of subjects	179
EEA total number of subjects	96

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)	123
From 65 to 84 years	55
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study opened to recruitment on 05 May 2016 with Phase Ib recruiting 7 patients in total. Phase IIa opened to recruitment on 05 January 2017, with total recruitment of 181 patients (RCC/sRCC: 138; PCC 41). The PCC cohort closed in July 2018, and the RCC/sRCC cohort closed in March 2021 after also meeting its target.

Pre-assignment

Screening details:

7 patients were recruited from a single site as part of phase 1b to assess recommended DLT. 179 patients were enrolled into phase II.

Pre-assignment period milestones

Number of subjects started	179
Number of subjects completed	179

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Savolitinib and Durvalumab

Arm description:

Savolitinib (600mg OD) and Durvalumab (1500mg Q4W)

Arm type	Experimental
Investigational medicinal product name	Savolitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients self-administered a 200 mg dose of savolitinib tablets by mouth daily.

Investigational medicinal product name	Durvalumab
Investigational medicinal product code	
Other name	MEDI4736
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

500mg vial solution for infusion after dilution. A starting dose of 1500mg (for patients >30kg in weight) was administered every 4 weeks using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final MEDI4736 concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

Arm title	Savolitinib alone
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Arm description:

savolitinib (600mg OD) only

Arm type	Experimental
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Investigational medicinal product name	Savolitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

600mg once daily. Self administered daily.

Arm title	Durvalumab alone
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Arm description:

MEDI4736 alone (1500mg Q4W)

Arm type	Experimental
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	
Other name	MEDI4736
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

500mg vial solution for infusion after dilution. A starting dose of 1500mg (for patients >30kg in weight) was administered every 4 weeks using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final MEDI4736 concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

Arm title	Tremelimumab plus Durvalumab
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Arm description:

Tremelimumab (75mg Q4W) plus Durvalumab (1500mg Q4W for 4 cycles), followed by Durvalumab alone (1500mg Q4W)

Arm type	Experimental
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	
Other name	MEDI4736
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

500mg vial solution for infusion after dilution. A starting dose of 1500mg (for patients >30kg in weight) was administered every 4 weeks using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final MEDI4736 concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

Investigational medicinal product name	Tremelimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

400mg vial solution for infusion after dilution. A dose of 75mg (for patients >30kg in weight) was administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final tremelimumab concentration ranging from 0.10 to 10mg/mL.

Number of subjects in period 1	Savolitinib and Durvalumab	Savolitinib alone	Durvalumab alone
Started	80	21	39
Completed	80	21	39

Number of subjects in period 1	Tremelimumab plus Durvalumab
Started	39
Completed	39

Baseline characteristics

Reporting groups

Reporting group title	Savolitinib and Durvalumab
Reporting group description: Savolitinib (600mg OD) and Durvalumab (1500mg Q4W)	
Reporting group title	Savolitinib alone
Reporting group description: savolitinib (600mg OD) only	
Reporting group title	Durvalumab alone
Reporting group description: MEDI4736 alone (1500mg Q4W)	
Reporting group title	Tremelimumab plus Durvalumab
Reporting group description: Tremelimumab (75mg Q4W) plus Durvalumab (1500mg Q4W for 4 cycles), followed by Durvalumab alone (1500mg Q4W)	

Reporting group values	Savolitinib and Durvalumab	Savolitinib alone	Durvalumab alone
Number of subjects	80	21	39
Age categorical Units: Subjects			
Adults (18-64 years)	64	10	23
From 65-84 years	15	11	16
85 years and over	1	0	0
Gender categorical Units: Subjects			
Female	16	5	6
Male	64	16	33

Reporting group values	Tremelimumab plus Durvalumab	Total	
Number of subjects	39	179	
Age categorical Units: Subjects			
Adults (18-64 years)	26	123	
From 65-84 years	13	55	
85 years and over	0	1	
Gender categorical Units: Subjects			
Female	9	36	
Male	30	143	

Subject analysis sets

Subject analysis set title	Clear cell cohort
Subject analysis set type	Per protocol
Subject analysis set description: Renal Cell Cohort	
Subject analysis set title	Papillary Cell Cohort

Subject analysis set type		Per protocol	
Subject analysis set description:			
Papillary Cell Cohort			
Reporting group values	Clear cell cohort	Papillary Cell Cohort	
Number of subjects	138	41	
Age categorical			
Units: Subjects			
Adults (18-64 years)	82	41	
From 65-84 years	55	0	
85 years and over	1	0	
Gender categorical			
Units: Subjects			
Female	28	7	
Male	110	34	

End points

End points reporting groups

Reporting group title	Savolitinib and Durvalumab
Reporting group description: Savolitinib (600mg OD) and Durvalumab (1500mg Q4W)	
Reporting group title	Savolitinib alone
Reporting group description: savolitinib (600mg OD) only	
Reporting group title	Durvalumab alone
Reporting group description: MEDI4736 alone (1500mg Q4W)	
Reporting group title	Tremelimumab plus Durvalumab
Reporting group description: Tremelimumab (75mg Q4W) plus Durvalumab (1500mg Q4W for 4 cycles), followed by Durvalumab alone (1500mg Q4W)	
Subject analysis set title	Clear cell cohort
Subject analysis set type	Per protocol
Subject analysis set description: Renal Cell Cohort	
Subject analysis set title	Papillary Cell Cohort
Subject analysis set type	Per protocol
Subject analysis set description: Papillary Cell Cohort	

Primary: Objective Response Rate

End point title	Objective Response Rate
End point description:	
End point type	Primary
End point timeframe:	
ORR based on measurements (Response Evaluation Criteria in Solid Tumours version 1.1 [RECIST v1.1]) taken at baseline, week 4 and every 8 weeks until disease progression.	

End point values	Savolitinib and Durvalumab	Savolitinib alone	Durvalumab alone	Tremelimumab plus Durvalumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	21	39	39
Units: number of patients	17	1	4	13

End point values	Clear cell cohort	Papillary Cell Cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	138	41		
Units: number of patients	21	12		

Statistical analyses

Statistical analysis title	Objective Response Rate
Comparison groups	Savolitinib and Durvalumab v Savolitinib alone v Durvalumab alone v Tremelimumab plus Durvalumab v Clear cell cohort v Papillary Cell Cohort
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Not applicable - response rate only
Point estimate	0
Confidence interval	
level	95 %
sides	1-sided
lower limit	0

Secondary: Progression Free Survival

End point title	Progression Free Survival
End point description:	
End point type	Secondary
End point timeframe:	
PFS defined as the time from the date of enrolment/randomisation to the date of first documented disease progression (RECIST v1.1) or death from any cause, whichever occurs first.	

End point values	Savolitinib and Durvalumab	Savolitinib alone	Durvalumab alone	Tremelimumab plus Durvalumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	21	39	39
Units: months				
number (confidence interval 95%)	3.54 (1.90 to 6.17)	2.95 (2.10 to 11.92)	4.63 (2.66 to 8.60)	4.59 (2.36 to 11.49)

End point values	Clear cell cohort	Papillary Cell Cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	138	41		
Units: months				

number (confidence interval 95%)	4.40 (2.82 to 6.20)	6.47 (2.72 to 11.99)		
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Statistical analyses

Statistical analysis title	Progression Free Survival
Comparison groups	Savolitinib and Durvalumab v Savolitinib alone v Durvalumab alone v Tremelimumab plus Durvalumab v Papillary Cell Cohort v Clear cell cohort
Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	= 0.999 ^[2]
Method	Kaplan-Meier median PFS (no formal compa

Notes:

[1] - Kaplan-Meier medians and 95% CIs were calculated. No hypothesis testing was performed.

[2] - Median progression-free survival (PFS) was estimated using the Kaplan-Meier method. No formal hypothesis testing (e.g., log-rank test or Cox regression) was performed for this secondary endpoint. The above parameter entry is provided solely to meet s

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:

OS defined as the time from enrolment/randomisation to death from any cause. All deaths will be included, whether they occur on study or following treatment discontinuation. For patients who have not died, OS overall survival will be censored at the dat

End point values	Savolitinib and Durvalumab	Savolitinib alone	Durvalumab alone	Tremelimumab plus Durvalumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	21	39	39
Units: month				
median (confidence interval 95%)	16.29 (8.25 to 28.39)	23.69 (20.40 to 39.72)	25.79 (13.89 to 31.97)	24.18 (14.03 to 43.66)

End point values	Clear cell cohort	Papillary Cell Cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	138	41		
Units: month				
median (confidence interval 95%)	22.05 (18.00 to 26.68)	14.1 (7.3 to 30.7)		

Statistical analyses

Statistical analysis title	Survival analysis (Kaplan-Meier)
Statistical analysis description: Kaplan-Meier method used to estimate OS distribution	
Comparison groups	Savolitinib and Durvalumab v Savolitinib alone v Durvalumab alone v Tremelimumab plus Durvalumab v Clear cell cohort v Papillary Cell Cohort
Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	other
P-value	= 999 ^[3]
Method	Hypothesis testing not performed

Notes:

[3] - Median PFS and 95% CI estimated using Kaplan-Meier method. No formal hypothesis test was performed; no p-value calculated.

Secondary: Duration of Response

End point title	Duration of Response
End point description:	
End point type	Secondary
End point timeframe:	
Duration of response defined as the time from first documentation of confirmed CR or PR to disease progression (RECIST v1.1) or death from any cause, whichever occurs first.	

End point values	Savolitinib and Durvalumab	Savolitinib alone	Durvalumab alone	Tremelimumab plus Durvalumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	0 ^[4]	4	13
Units: months	13		9	19

Notes:

[4] - No response seen

End point values	Clear cell cohort	Papillary Cell Cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	12		
Units: months	16	9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs will be collected throughout the study as described in the schedule of assessments, from the time the patient gives informed consent to the safety follow-up visit or PD visit, whichever occurs at a later date.

Adverse event reporting additional description:

Safety reporting is reported for the entire clear cell cohort and papillary cohort. The following was collected: AE term, date of onset, date of resolution, CTCAE grade, seriousness, causality.

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4.03
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Reporting groups

Reporting group title	Papillary Cohort
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Reporting group description:

Papillary Cohort

Reporting group title	Clear Cell Cohort
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Reporting group description: -

Serious adverse events	Papillary Cohort	Clear Cell Cohort	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 41 (39.02%)	9 / 138 (6.52%)	
number of deaths (all causes)	25	103	
number of deaths resulting from adverse events	2	3	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 41 (4.88%)	0 / 138 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 41 (2.44%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Gastrointestinal disorders			
Upper GI Bleeding			
subjects affected / exposed	0 / 41 (0.00%)	3 / 138 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 41 (7.32%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	7 / 41 (17.07%)	4 / 138 (2.90%)	
occurrences causally related to treatment / all	0 / 7	1 / 4	
deaths causally related to treatment / all	0 / 1	1 / 1	

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

Non-serious adverse events	Papillary Cohort	Clear Cell Cohort	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 41 (92.68%)	133 / 138 (96.38%)	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	25 / 41 (60.98%)	36 / 138 (26.09%)	
occurrences (all)	25	36	
Oedema			
subjects affected / exposed	22 / 41 (53.66%)	30 / 138 (21.74%)	
occurrences (all)	22	30	
Anaemia			
subjects affected / exposed	5 / 41 (12.20%)	30 / 138 (21.74%)	
occurrences (all)	5	30	
Asthenia			
subjects affected / exposed	2 / 41 (4.88%)	30 / 138 (21.74%)	
occurrences (all)	2	30	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	7 / 41 (17.07%)	32 / 138 (23.19%)	
occurrences (all)	7	32	
Musculoskeletal and connective tissue disorders			

Musculoskeletal pain subjects affected / exposed occurrences (all)	24 / 41 (58.54%) 24	53 / 138 (38.41%) 53	
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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 March 2016	Summary of changes: protocol updates of: section 6.11 (maximum tolerated dose), section 8.2 (population of analysis to reflect change for maximum tolerated dose), section 6.18 (Contraception advice updated to reflect HMA guidance), section 6.12.1 (Dosing modifications and toxicity management guidelines for Immune Mediated Reactions associated with durvalumab and Tremelimumab) and Section 12 of Patient information sheets to reflect updated safety information re durvalumab.
16 November 2016	Summary of changes: updated protocol and patient information sheets: durvalumab dose changes in all parts of the study, removing a treatment arm from the phase IIa (randomisation/dose expansion), Clinical biochemistry monitoring for potential endocrinopathy, Vital sign monitoring during and after durvalumab and tremelimumab Infusions, PK blood collection and research blood collection, Toxicity guidelines, Statistical considerations. Updates to IMP label templates and updates to IBs, specifically durvalumab IB has been updated to Edition 9 dated 22 Jan 2016 and Tremelimumab IB has been updated to Edition 6 (11th feb 2016) and edition 7 (7th Jun 2016).
07 December 2016	Summary of changes: amendment of protocol section 6.12.2 and patient information sheet to include 'Stevens-Johnson Syndrome' as an AE.
03 March 2017	Summary of changes: addition of 1 UK site
10 March 2017	Summary of changes: addition of 2 UK sites (University Hospital Bristol and Mid Essex Hospital) and change of PI at Western General Hospital
24 April 2017	Summary of changes: amendment of protocol section 6.12.2 and patient information sheet section 12 to include pyrexia as an AE.
20 July 2018	Summary of changes: addition of 1 UK site
24 August 2018	Summary of changes: protocol and patient information sheet updated to include triplicate ECGs weekly during cycle 1 and at each cycle thereafter as an urgent safety measure for potential Savolitinib-induced QTc prolongation.
22 February 2019	Summary of changes: change of PI at one UK site
07 March 2019	Summary of changes: Addition of QMUL Malta as the Legal Representative within the EU in the event the United Kingdom becomes classed as a third country.
20 March 2019	Summary of changes: Change of savolitinib formulation from uncoated to film-coated. Addition of Weil am Rhein Fisher facility in Germany as contingency in case of a no-deal Brexit.
23 August 2019	Summary of changes: removal of savolitinib alone arm; submission of updated IBs for MEDI4736, Savolitinib and Tremelimumab. Submission of new Letter of Access for MEDI4736 and Tremelimumab IMPDs. Updated: GP Letter V2.0, PIS V10.0 for PCC and RCC Cohort and Protocol V7.0. Change of sponsor representative and study statistician. General protocol administrative updates and changes to align with new IBs.
05 November 2019	Summary of changes: change of PI at UK site

16 June 2020	Summary of changes: Submission of updated investigator brochures for MEDI4736 (V15.0 08-Oct-2019), Savolitinib (V6.1 28-Oct-2019) and Tremelimumab (V10.0 08-Oct-2019).
03 August 2020	Summary of changes: Update to IMP labelling: Specifically, update to the MEDI4736 outer box and MEDI4736 vial label to reference that the IMP is a solution for intravenous use. The MEDI4736 outer carton and MEDI4736 vial label has also been updated to state that the protocol should be referenced for directions of use.
24 November 2021	Summary of changes: Savolitinib – updated UK letter of access was submitted in parallel with AstraZeneca submitting an updated Savolitinib IMPD.
17 May 2022	Summary of changes: Updates to IBs including the Reference Safety Information (RSI) for Durvalumab (MEDI4736) and Savolitinib, updated text for the IRAS form and the PIS following Re-review of radiation exposure by HRA Radiation Assurance to ensure these documents accurately reflect the protocol's schedule of assessments and participants' expected radiation exposure.
07 September 2023	Summary of Changes: Updates to IB's for for Durvalumab (MEDI4736) and Savolitinib. There are no updates to the RSI in the Savolitinib IB V9.0, and the changes in the Durvalumab (MEDI4736) IB V18.0 RSI are related to system organ class updates. PIS has also been changed to include new events and study end date has been extended from July 2023 to July 2024.
21 December 2023	Summary of changes: This amendment is related to discontinuation of research blood sample collection. -This was originally sent to be submitted to MHRA on 10/Oct/2023 but was missed in error and was finally sent on 31/Oct/2023 when the error was discovered
23 May 2024	Summary of changes: This amendment is related to the changes to the end of trial definition, changing it from last patient last visit, which included 2 years post treatment survival follow up to last patient last treatment visit alongside updates to all three study IMP IB's. Savolitinib IB V10.2, Tremelimumab V11.0 and Durvalumab (MEDI4736) v19.0

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.

As part of substantial amendment 13, the savolitinib only arm was removed. This was due to changes in the treatment landscape that meant monotherapy should not be explored further.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/36809050>