Supplementary Appendix

Nivolumab Plus Ipilimumab in Unresectable Malignant Pleural Mesothelioma

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List of CheckMate 743 Investigators

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Yolanda Bautista	Centro Médico Nacional Siglo XXI	Mexico	15
Robin Cornelissen	Erasmus MC University Hospital	The Netherlands	15
Laurent Greillier	Aix Marseille University, APHM, INSERM, CNRS, CRCM, Hôpital Nord, Multidisciplinary Oncology and Therapeutic Innovations Department	France	14
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Dariusz Kowalski	Klinika Nowotworow Pluca i Klatki Piersiowej	Poland	13
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Julien Mazieres	CHU de Toulouse, Hôpital Larrey	France	11
Michele Maio	Azienda Ospedaliera Universitaria Senese	Italy	11
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Amjad Jalil	Allegheny Cancer Center	United States	4
Anthony Linton	Concord Repatriation General Hospital	Australia	3
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Clarisse Audigier-Valette	Hopital Sainte-Musse	France	3
Anne-Elisabeth Quoix	Nouvel Hôpital Civil CHRU de Strasbourg	France	3
Achim Rittmeyer	Lungenfachklinik Immenhausen	Germany	3
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Tatsuro Fukuhara	Miyagi Cancer Center	Japan	3
Satoshi Watanabe	Niigata University Medical & Dental Hospital	Japan	3
Hidetoshi Hayashi	Kindai University Hospital	Japan	3
Oscar Arrieta-Rodriguez	Instituto Nacional De Cancerologia	Mexico	3
Michael Schenker	SF. Nectarie Oncology Center	Romania	3
Solange Peters	Lausanne University Hospital	Switzerland	3
Paul Taylor	Wythenshawe Hospital	United Kingdom	3
Lore Decoster	Universitair Ziekenhuis Brussel	Belgium	2
Shun Lu	Shanghai Chest Hospital	China	2
Yunchao Huang	Yunnan Provincial Tumor Hospital	China	2
Sven Henschke	Universitaetsklinikum d. Saarlandes	Germany	2
Tsuneo Shimokawa	Yokohama Municipal Citizen's Hospital	Japan	2
Yuichi Takiguchi	Chiba University Hospital	Japan	2
Satoshi Oizumi	Hokkaido Cancer Center	Japan	2
Evgeny Levchenko	N.N. Petrov National Medical Research Center of Oncology	Russian Federation	2

Amina Scherz	Inselspital Bern	Switzerland	2
Zeynep Turna	Cerrahpasa Tip Fakultesi	Turkey	2
Katherine Scilla	Univ of Maryland Greenbaum Cancer Center	United States	2
Hirva Mamdani	Barbara Ann Karmanos Cancer Center	United States	2
Yuanbin Chen	Cancer & Hematology Centers of Western Michigan	United States	2
Gongyan Chen	Affiliated Cancer Hospital of Haerbin Medical University	China	1
Ichidai Tanaka	Nagoya University Hospital	Japan	1
Kenichi Gemba	Chugoku Central Hospital	Japan	1
Carlos Alberto Ronquillo	Centro Medico De Occidente	Mexico	1
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Supplementary Methods

Inclusion and Exclusion Criteria

Eligible patients included those with a history of pleurodesis and prior prophylactic radiotherapy to a pleurodesis drainage tract. Patients had to be off corticosteroids, or on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent) for ≥2 weeks prior to first treatment.

Patients with malignant pleural lesions had to have measurable disease by computed tomography scan per an adaptation of the modified Response Evaluation Criteria in Solid Tumors [mRECIST] for pleural mesothelioma[1]; at least 1 lesion was measured in up to 2 positions at 3 different levels on transverse cuts (up to 6 measurements in total). Patients with non-pleural lesions (such as nodal, subcutaneous, and other metastatic malignant pleural mesothelioma [MPM] lesions) had to have measurable disease by computed tomography or magnetic resonance imaging per RECIST version 1.1 in order to be considered for inclusion.

Patients who had received prior treatment with adjuvant or neoadjuvant chemotherapy, prior intraoperative or intracavitary chemotherapy for pleural mesothelioma, radical pleuropneumonectomy with or without intensity modulated radiotherapy, or non-palliative radiation therapy were also excluded. Undetermined epithelioid or non-epithelioid tumour histology was not permitted.

Chemotherapy Regimen

Cisplatin was preferred, but carboplatin could be used at the discretion of the investigator.

Vitamin and Corticosteroid Supplementation

Patients treated with nivolumab plus ipilimumab discontinued pretreatment with folic acid and vitamin B12 after randomization. Patients treated with pemetrexed were given folic acid throughout treatment and for 21 days after the last dose of study drug; vitamin B12 supplementation also continued throughout treatment with pemetrexed per local policy, and dexamethasone (4 mg orally twice daily) was recommended the day before, the day of, and the day following treatment.

Assessments

Confirmation of complete or partial response, determined by blinded independent central review (BICR) (per adapted mRECIST and/or RECIST v1.1 criteria), was required at least 4 weeks after the initial response.

Laboratory assessments

Laboratory tests were performed within 14 days prior to first randomization and within 3 days prior to each dose. Assessments included complete blood count with differential; chemistry panel including albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, blood urea nitrogen or serum urea level, creatinine, calcium, magnesium, sodium, potassium, chloride, lactate dehydrogenase, phosphate, glucose, amylase, and lipase; and thyroid function testing (evaluated every 6 weeks) including thyroid stimulating hormone with reflexive Free T4, and Free T3. Hepatitis C RNA and HIV (where locally mandated) tests were performed at screening only. All tests had to be performed at follow-up visits 1 and 2.

Discontinuation of Ipilimumab and Continuation on Nivolumab Alone

Ipilimumab was permanently discontinued due to: grade ≥2 treatment-related uveitis, eye pain, or blurred vision that did not improve to grade 1 with topical treatment within 2 weeks, or required systemic treatment; any-cause grade ≥3 bronchospasm or other hypersensitivity reaction; grade 3 non-skin treatment-related adverse events with the exceptions of laboratory abnormalities, nausea, vomiting, neutropenia, thrombocytopenia, and symptomatic endocrinopathies which resolved; AST or ALT >8 x upper limit of normal (ULN), total bilirubin >5 x ULN, or concurrent AST or ALT >3 x ULN and total bilirubin >2 x ULN; grade 4 treatment-related adverse events or laboratory abnormalities, except neutropenia lasting ≤7 days, lymphopenia, leukopenia, or grade ≥3 amylase or lipase abnormalities that were not associated with symptoms of pancreatitis; treatment interruption for >12 weeks, except in case of delays due to treatment-related adverse events needing slow steroid tapering off or in case of delays due to non-drug related reasons.

If discontinuation criteria were met for ipilimumab but not for nivolumab, treatment with nivolumab could continue. Ipilimumab could not be continued alone.

Serious Adverse Events

Serious adverse events were defined as any untoward medical occurrence that at any dose was considered life-threatening or an important medical event, caused or prolonged inpatient hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or led to death. Suspected transmission of an infectious agent via the study drug, pregnancy, overdose, and potential drug-induced liver injury were also to be reported as serious adverse events.

Treatment Beyond Progression

Treatment with nivolumab plus ipilimumab beyond initial investigator-assessed and BICR-confirmed progression, as defined by adapted mRECIST for pleural mesothelioma and RECIST 1.1, was permitted if the patient had an investigator-assessed clinical benefit, was tolerating the treatment, showed stable performance, and provided written consent. Continued treatment could not delay an imminent intervention to prevent serious complications of disease progression. If follow-up scans showed further disease progression (defined as an additional 10% increase in tumor burden with ≥5 mm absolute increase in the sum of diameters of all existing and/or new lesions from the time of initial progressive disease), treatment was discontinued permanently.

Detailed Statistical Methodology

For the primary endpoint of overall survival, a sample of approximately 600 randomized patients with 473 deaths at the final analysis would provide 90% power to detect a target hazard ratio of 0·72 with a two-sided type 1 error of 0·05 by means of a log-rank test. This was based on a simulation model incorporating known aspects of immune-oncology, such as delayed separation and long-term benefits. For the chemotherapy arm, an exponential distribution was assumed with a median overall survival of 16 months. For overall survival in the nivolumab plus ipilimumab arm, a piecewise exponential model was used, assuming a delay of treatment effect in the first 6 months, an exponential distribution of overall survival from 6 months to 34 months, and a long-term survival rate plateau starting approximately at 34 months. At the prespecified interim analysis 419 patients had died (89% of the 473 deaths required for final analysis). The boundary for declaring superiority for overall survival was a p-value of <0·0345, based on the Lan–DeMets alpha spending function with O'Brien–Fleming boundaries. No formal statistical testing procedure was used for assessing the secondary objectives of this study. Demographic and efficacy analyses included all randomised patients. Overall survival and progression-free survival were stratified by histology and gender. Hazard ratios and CIs were estimated with a stratified Cox proportional-hazards model with treatment group as a single covariate. The proportional-hazards assumption was checked only for the primary endpoint of overall survival by adding a time-dependent covariate, defined by treatment-by-time interaction, into the stratified Cox regression model of overall survival. Survival curves were estimated using Kaplan–Meier methodology. When specified, medians were reported with 95% CIs using the Brookmeyer and Crowley method[3] with log-log transformation.[4] Survival rate estimates were derived from the Kaplan–Meier estimates and corresponding CIs were derived based on Greenwood[5] formula for variance derivation and on log-log transformation applied on the survivor function.[6] Exact two-sided 95% CIs for objective response and disease control rate estimates were calculated using the Clopper–Pearson method.[7] Pre-specified subgroup analyses were descriptive and summarized using hazard ratios (along with 95% CIs), calculated using an unstratified Cox

proportional-hazards model. Safety analyses included all patients who received at least one dose of study drug.

Tables

Table S1. Exposure summary for all treated patients.

	Nivolumab plus ipilimumab (n=300)	**Chemotherapy* (n=284)**
Duration of therapy, months		
Mean	7·9	3·0
Range	0–26·2	0–4·7
Median	5·6	3·5
IQR	2·0–11·4	2·7–3·7
Number of nivolumab doses		
Mean	16·5	
SD	14·5	Not applicable
Median	12·0	
IQR	5·0–23·5	
Number of ipilimumab doses		
Mean	5·4	
SD	4·6	Not applicable
Median	4·0	
IQR	2·0–7·0	
Number of pemetrexed cycles (n=284)		
Mean		5·1
SD	Not applicable	1·4
Median		6·0
IQR		4·0–6·0
Number of cisplatin cycles (n=104)		
Mean		4·3
SD	Not applicable	1·9
Median		5·0

	Nivolumab plus ipilimumab (n=300)	Chemotherapy* (n=284)
IQR		3·0–6·0
Number of carboplatin cycles (n=209)		
Mean		4·8
SD	Not applicable	1·6
Median		6·0
IQR		4·0–6·0
Treatment discontinuation	295 (98·3%)	284 (100·0%)
Patients receiving therapy		
>3 months	202 (67·3%)	195 (68·7%)
>6 months	144 (48·0%)	0
>9 months	99 (33·0%)	0
>12 months	71 (23·7%)	0
Patients still on treatment	5 (1·7%)	0

Data are n (%) unless indicated otherwise.

* Maximum of 6 cycles

Table S2. Subsequent therapies in all treated patients.

Subsequent therapy	Nivolumab plus ipilimumab (n=303)	Chemotherapy (n=302)
Any	145 (47·9%)	136 (45·0%)
Radiotherapy	23 (7·6%)	28 (9·3%)
Surgery	1 (0·3%)	3 (1·0%)
Systemic therapy	134 (44·2%)	123 (40·7%)
Immunotherapy	10 (3·3%)	61 (20·2%)
Nivolumab	7 (2·3%)	41 (13·6%)
Pembrolizumab	2 (0·7%)	17 (5·6%)
Ipilimumab	2 (0·7%)	3 (1·0%)
Rituximab	1 (0·3%)	0
Atezolizumab	0	1 (0·3%)
Avelumab	0	1 (0·3%)
Epacadostat	0	1 (0·3%)
Unspecified anti–PD-1	0	1 (0·3%)
Chemotherapy	131 (43·2%)	95 (31·5%)
Pemetrexed	121 (39·9%)	48 (15·9%)
Carboplatin	89 (29·4%)	39 (12·9%)
Cisplatin	40 (13·2%)	8 (2·6%)
Gemcitabine	25 (8·3%)	45 (14·9%)
Vinorelbine	15 (5·0%)	25 (8·3%)
Doxorubicin	2 (0·7%)	1 (0·3%)
Antineoplastic	2 (0·7%)	0
Methotrexate	1 (0·3%)	2 (0·7%)
Docetaxel	1 (0·3%)	1 (0·3%)
Carboplatin/Pemetrexed	1 (0·3%)	0
Raltitrexed	1 (0·3%)	0
Irinotecan	0	2 (0·7%)
Paclitaxel	0	2 (0·7%)
Pevonedistat	0	2 (0·7%)
Dicanth/Pyrdx	0	1 (0·3%)
Gimeracil/Oteracil/Tegafur	0	1 (0·3%)
Topotecan	0	1 (0·3%)
Targeted therapy	20 (6·6%)	10 (3·3%)
Experimental drugs	2 (0·7%)	12 (4·0%)

Data are n (%). Patients may have received more than one type of subsequent therapy.

Table S3. All treatment-related adverse events of grade 3 or 4 severity*

	Nivolumab plus ipilimumab (n=300)		Chemotherapy (n=284)	
Treatment-related adverse events	Grade 3	Grade 4	Grade 3	Grade 4
Any	79 (26·3%)	12 (4·0%)	73 (25·7%)	18 (6·3%)
Increased lipase	11 (3·7%)	2 (0·7%)	1 (0·4%)	0
Diarrhoea	10 (3·3%)	0	2 (0·7%)	0
Colitis	7 (2·3%)	0	1 (0·4%)	0
Increased amylase	6 (2·0%)	1 (0·3%)	0	0
Acute kidney injury	4 (1·3%)	0	0	0
Increased alanine aminotransferase	3 (1·0%)	2 (0·7%)	0	0
Abnormal hepatic function	3 (1·0%)	2 (0·7%)	0	0
Fatigue	3 (1·0%)	0	5 (1·8%)	0
Pruritus	3 (1·0%)	0	0	0
Rash	3 (1·0%)	0	0	0
Increased aspartate aminotransferase	3 (1·0%)	0	0	0
Infusion-related reaction	3 (1·0%)	0	0	0
Hypopituitarism	3 (1·0%)	0	0	0
Immune-mediated hepatitis	2 (0·7%)	1 (0·3%)	0	0
Thrombocytopenia	2 (0·7%)	0	4 (1·4%)	6 (2·1%)
Hyponatraemia	2 (0·7%)	0	2 (0·7%)	0
Decreased appetite	2 (0·7%)	0	2 (0·7%)	0
Drug-induced liver injury	2 (0·7%)	0	0	0
Arthritis	2 (0·7%)	0	0	0
Increased gamma glutamyltransferase	2 (0·7%)	0	0	0
Myositis	2 (0·7%)	0	0	0
Anaemia	1 (0·3%)	0	32 (11·3%)	0
Neutropenia	1 (0·3%)	1 (0·3%)	31 (10·9%)	12 (4·2%)
Hepatitis	1 (0·3%)	1 (0·3%)	0	0
Nausea	1 (0·3%)	0	7 (2·5%)	0
Dehydration	1 (0·3%)	0	1 (0·4%)	0
Arthralgia	1 (0·3%)	0	0	0
Maculo-papular rash	1 (0·3%)	0	0	0
Pneumonitis	1 (0·3%)	0	0	0
Hypersensitivity	1 (0·3%)	0	0	0
Increased blood alkaline phosphatase	1 (0·3%)	0	0	0

Adrenal insufficiency	1 (0·3%)	0	0	0
Interstitial lung disease	1 (0·3%)	0	0	0
Erythematous rash	1 (0·3%)	0	0	0
Increased blood bilirubin	1 (0·3%)	0	0	0
Dermatitis acneiform	1 (0·3%)	0	0	0
Musculoskeletal pain	1 (0·3%)	0	0	0
Hyperglycaemia	1 (0·3%)	0	0	0
Hypersensitivity vasculitis	1 (0·3%)	0	0	0
Psoriasis	1 (0·3%)	0	0	0
Toxic skin eruption	1 (0.3%)	0	0	0
Malaise	1 (0·3%)	0	0	0
Hepatotoxicity	1 (0·3%)	0	0	0
Hepatocellular injury	1 (0·3%)	0	0	0
Enterocolitis	1 (0·3%)	0	0	0
Erosive gastritis	1 (0·3%)	0	0	0
Adrenocorticotropic hormone deficiency	1 (0·3%)	0	0	0
Osteoarthritis	1 (0·3%)	0	0	0
Spinal pain	1 (0·3%)	0	0	0
Hyperamylasaemia	1 (0·3%)	0	0	0
Ataxia	1 (0·3%)	0	0	0
Limbic encephalitis	1 (0·3%)	0	0	0
Myasthenic syndrome	1 (0·3%)	0	0	0
Transverse myelitis	1 (0·3%)	0	0	0
Paraplegia	1 (0·3%)	0	0	0
Polyneuropathy	1 (0·3%)	0	0	0
Chronic kidney disease	1 (0·3%)	0	0	0
Iritis	1 (0·3%)	0	0	0
Temporal arteritis	1 (0.3%)	0	0	0
Confusional state	1 (0·3%)	0	0	0
Myocarditis	1 (0·3%)	0	0	0
Pleuropericarditis	1 (0·3%)	0	0	0
Nephrotic syndrome	1 (0.3%)	0	0	0
Myasthenia gravis	0	1 (0·3%)	0	0
Thrombocytopenic purpura	0	1 (0·3%)	0	0
Opsoclonus myoclonus	0	1 (0·3%)	0	0
Renal impairment	0	1 (0·3%)	0	0
Increased blood creatine phosphokinase	0	1 (0.3%)	0	0

Asthenia	0	0	12 (4·2%)	0
Vomiting	0	0	6 (2·1%)	0
Leukopenia	0	0	5 (1·8%)	3 (1·1%)
Febrile neutropenia	0	0	2 (0·7%)	1 (0·4%)
Atrial fibrillation	0	0	2 (0·7%)	0
Decreased neutrophil count	0	0	2 (0·7%)	0
Pancytopenia	0	0	1 (0·4%)	4 (1·4%)
Lymphopenia	0	0	1 (0·4%)	1 (0·4%)
Platelete count decreased	0	0	1 (0·4%)	1 (0·4%)
Mucosal inflammation	0	0	1 (0·4%)	1 (0·4%)
Abdominal pain	0	0	1 (0·4%)	0
Dyspnoea	0	0	1 (0·4%)	0
Urticaria	0	0	1 (0·4%)	0
Renal failure	0	0	1 (0·4%)	0
Hypophosphataemia	0	0	1 (0·4%)	0
Haematotoxicity	0	0	1 (0.4%)	0
Pyrexia	0	0	1 (0·4%)	0
Constipation	0	0	1 (0·4%)	0
Stomatitis	0	0	1 (0·4%)	0
Hypomagnesaemia	0	0	1 (0·4%)	0
Decreased white blood cell count	0	0	1 (0·4%)	0
Pneumonia	0	0	1 (0·4%)	0
Seizure	0	0	1 (0·4%)	0
Syncope	0	0	1 (0·4%)	0
Bacterial pleural infection	0	0	1 (0·4%)	0
Myocardial infarction	0	0	1 (0·4%)	0
Haemorrhagic diarrhoea	0	0	0	1 (0·4%)
Sepsis	0	0	0	1 (0·4%)

Data are n (%). Included events reported between the first dose of study drug and 30 days after the last dose of study drug.

*According to the study sponsor practice, only events that led to death within 24 hours were documented as grade 5 and reported as deaths in this manuscript. Events leading to death >24 hours after onset are reported with the worst grade before death.

Table S4. Treatment-related adverse events leading to discontinuation

	Nivolumab plus ipilimumab (n=300)		Chemotherapy (n=284)	
Event	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Any	69 (23·0%)	45 (15·0%)	45 (15·8%)	21 (7·4%)
Events leading to discontinuation in ≥1% of patients				
Colitis	7 (2·3%)	7 (2·3%)	1 (0·4%)	1 (0·4%)
Diarrhea	7 (2·3%)	4 (1·3%)	0	0
Pneumonitis	5 (1·7%)	1 (0·3%)	0	0
Infusion related reaction	5 (1·7%)	3 (1·0%)	0	0
Abnormal hepatic function	4 (1·3%)	4 (1·3%)	0	0
ALT increased	3 (1·0%)	2 (0·7%)	0	0
Acute kidney injury	3 (1·0%)	1 (0·3%)	0	0
Neutropenia	1 (0·3%)	1 (0·3%)	5 (1·8%)	3 (1·1%)
Fatigue	1 (0·3%)	0	3 (1·1%)	1 (0·4%)
Anemia	0	0	11 (3·9%)	5 (1·8%)
Asthenia	0	0	6 (2·1%)	5 (1·8%)
Thrombocytopenia	0	0	5 (1·8%)	5 (1·8%)
Nausea	0	0	5 (1·8%)	0
Vomiting	0	0	3 (1·1%)	2 (0·7%)
Hypoacusis	0	0	3 (1·1%)	0

Data are n (%). Included events reported between the first dose of study drug and 30 days after the last dose of study drug. Included discontinuations due to any component of the regimen. If criteria for nivolumab discontinuation were met, ipilimumab was also discontinued.
ALT=alanine aminotransferase.

Table S5. Time to onset and resolution of treatment-related select adverse events and the proportion of patients requiring immune-modulating medication and the duration of immune-modulating medication use in the nivolumab plus ipilimumab group.

	Nivolumab plus ipilimumab (n=300)						
Category	**Any grade / grade 3–4 events**	**Median time to onset, weeks**	**Any grade events leading to discontinuation**	**Median time to resolution, weeks**	**Any grade events that resolved**	**Proportion of patients requiring immune-modulating medication***	**Duration of immune-modulating medication, weeks**
Skin	108 (36·0%) / 9 (3·0%)	6·9 (0·1–97·1)	2 (0·7%)	12·1 (0·4–146·4+)	71 (66·4%)	45 (41·7%)	12·1 (0·7–122·0)
Endocrine	52 (17·3%) / 4 (1·3%)	12·1 (2·0–90·3)	1 (0·3%)	NR (0·3–144·1+)	17 (32·7%)	18 (34·6%)	54·8 (5·0–142·9)
Gastrointestinal	66 (22·0%) / 16 (5·3%)	16·9 (0·1–94·3)	15 (5·0%)	3·1 (0·1–100·0+)	62 (93·9%)	24 (36·4%)	6·1 (0·7–50·7)
Hepatic	36 (12·0%) / 16 (5·3%)	7·9 (2·0–88·1)	11 (3·7%)	4·1 (1·0–78·3+)	31 (86·1%)	17 (47·2%)[†]	9·1 (0·1–61·0)
Pulmonary	20 (6·7%) / 2 (0·7%)	7·6 (1·1–90·3)	7 (2·3%)	6·1 (1·1–113·1+)	16 (80·0%)	17 (85·0%)[‡]	12·1 (1·1–30·0)
Renal	15 (5·0%) / 4 (1·3%)	15·7 (2·1–62·6)	4 (1·3%)	6·1 (0·9–126·4+)	12 (80·0%)	8 (53·3%)[¶]	13·7 (2·3–40·4)
Hypersensitivity/ infusion reaction	36 (12·0%) / 4 (1·3%)	2·1 (0·1–51·6)	5 (1·7%)	0·1 (0·1–106·4+)	34 (94·4%)	10 (27·8%)[§]	0·1 (0·1–4·7)

Data are n (%) or median (range). Treatment-related select adverse events are events with potential immunologic aetiology that require frequent monitoring/intervention. Included are any grade events reported between the first dose of study drug and 30 days after the last dose of study drug. Symbol + indicates a censored value. NR=not reported.

* Unless otherwise noted, treatment was with systemic corticosteroids.

[†] 2 patients also received mycophenolic acid.

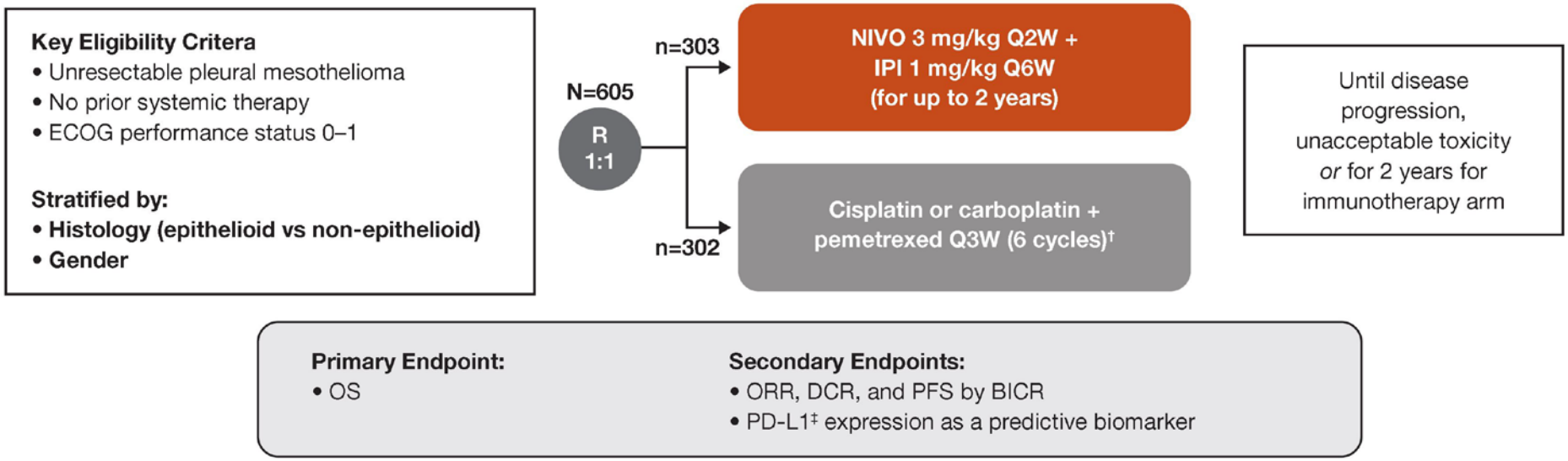
[‡] 1 patient also received infliximab

[¶] 39 patients were treated with dermatological corticosteroids, 1 patients was treated with topical tacrolimus, and 19 patients were treated with systemic corticosteroids.

[§] 1 patient was treated with dermatological corticosteroids and 9 were treated with systemic corticosteroids.

FIGURES

Figure S1. Study design*



Patients were enrolled at 103 hospitals in 21 countries (Australia, Belgium, Brazil, Chile, China, Columbia, France, Germany, Greece, Italy, Japan, Mexico, Netherlands, Poland, Romania, Russia, South Africa, Switzerland, Turkey, United Kingdom, and United States).

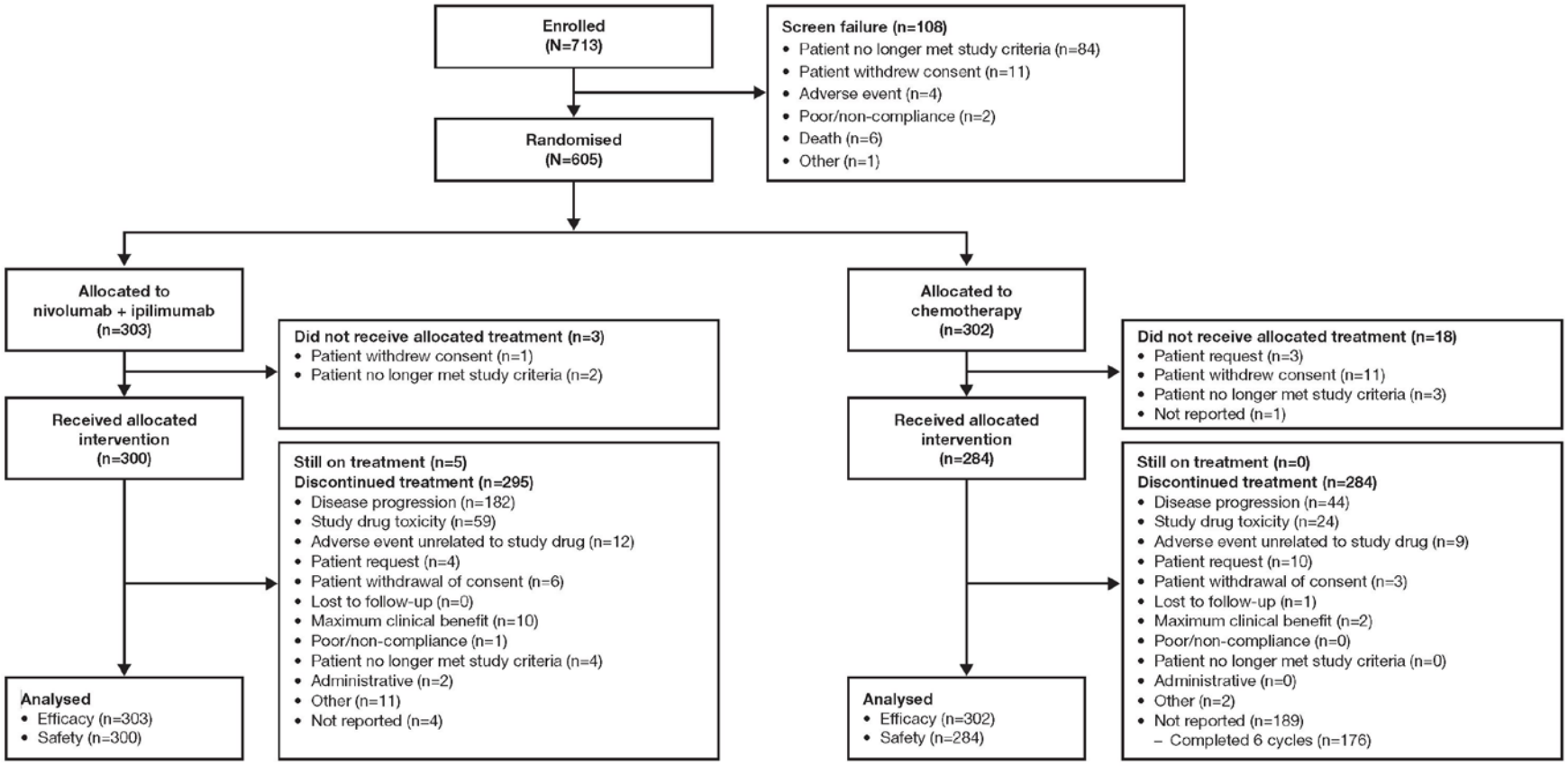
* NCT02899299.

† Cisplatin (75 mg/m^2) or carboplatin (AUC 5 mg/mL/min) plus pemetrexed (500 mg/m^2) Q3W for 6 cycles.

‡ Determined by PD-L1 IHC 28-8 pharmDx assay from Dako.

AUC=area under the curve; BICR=blinded independent central review; DCR=disease control rate; IPI=ipilimumab; NIVO=nivolumab; ORR=objective response rate; PFS=progression-free survival; Q2W=every 2 weeks, Q3W=every 3 weeks, Q6W=every 6 weeks.

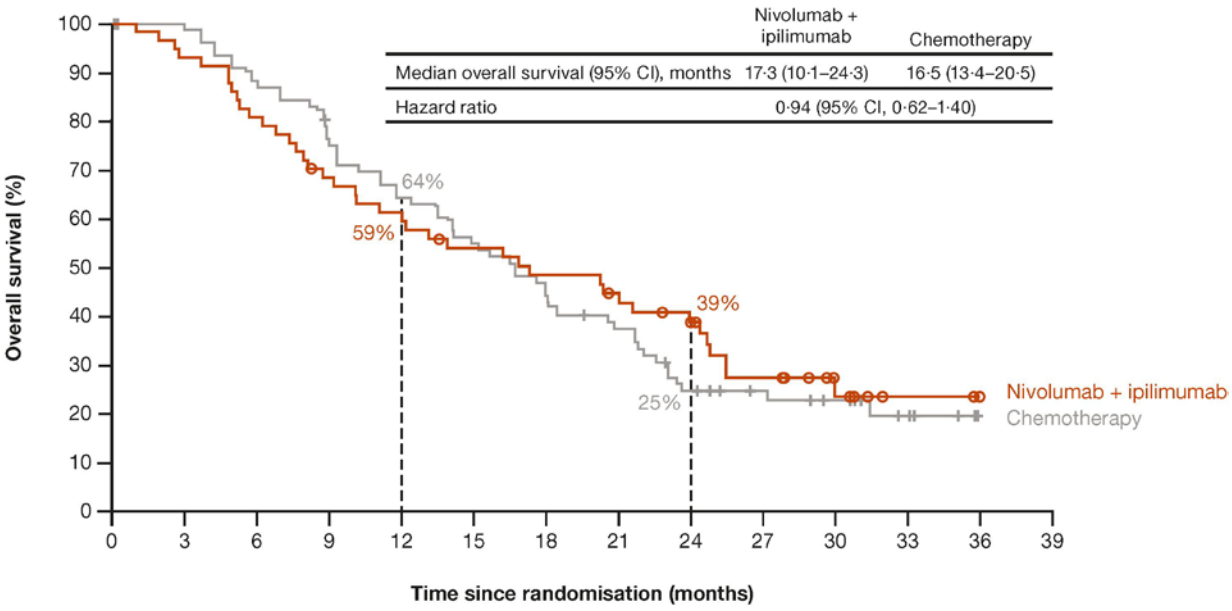
Figure S2. Consolidated Standards of Reporting Trials (CONSORT) flow chart of patient disposition



At database lock, 295 (98·3%) of 300 treated patients in the nivolumab plus ipilimumab group and 284 (100·0%) of 284 patients in the chemotherapy group had discontinued treatment. The main reason for treatment discontinuation in the nivolumab plus ipilimumab group was disease progression (182 of 300 patients; 60·7%) followed by study drug toxicity (59 patients; 19·7%). In the chemotherapy group, the main reason for treatment discontinuation was “not reported” (189 of 284 patients ; 66·5%); of these, the majority (176 patients; 93·1%;) were patients completing chemotherapy (6 cycles).

Figure S3. Overall survival in patients with tumour PD-L1 expression <1% (A) and ≥1% (B). Minimum and median follow-up for overall survival were 22·1 and 29·7 months, respectively.

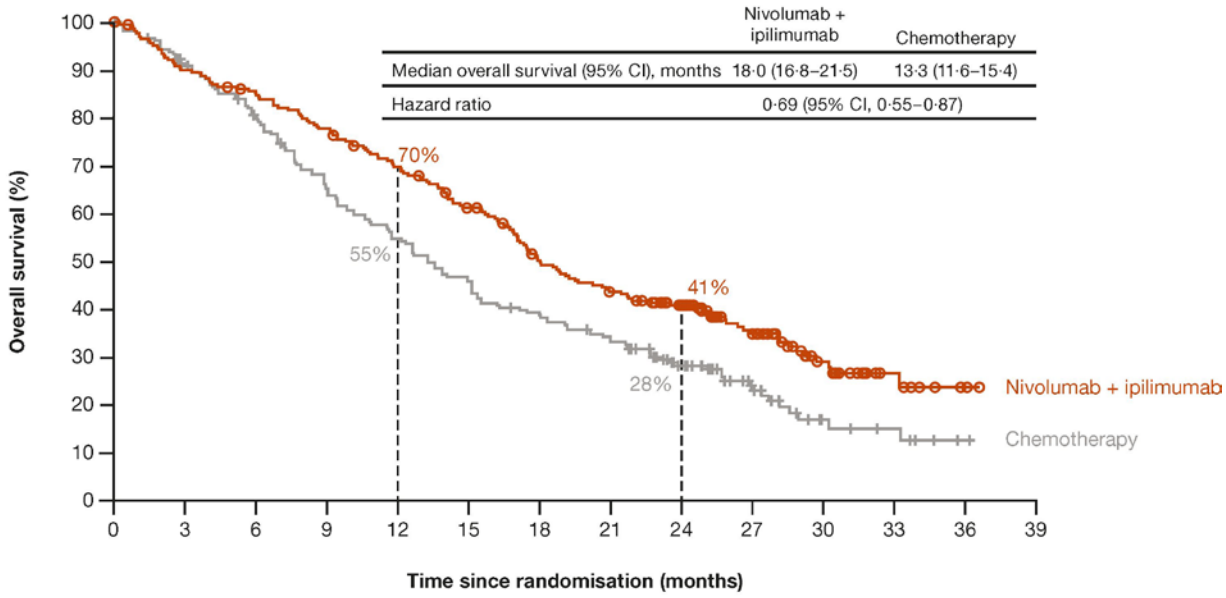
A



Number at risk (censored)

Nivolumab + ipilimumab	57 (0)	53 (0)	46 (0)	38 (1)	33 (1)	29 (2)	26 (2)	22 (3)	18 (5)	12 (6)	6 (11)	2 (15)	0 (17)	0 (17)
Chemotherapy	78 (0)	75 (2)	67 (2)	56 (3)	48 (3)	41 (3)	33 (3)	27 (4)	17 (5)	13 (9)	10 (11)	5 (15)	0 (20)	0 (20)

B



Number at risk (censored)

Nivolumab + ipilimumab	232 (0)	207 (2)	194 (4)	177 (4)	157 (6)	135 (9)	108 (12)	93 (13)	76 (24)	50 (41)	24 (61)	9 (74)	2 (80)	0 (82)
Chemotherapy	219 (0)	188 (13)	162 (16)	131 (17)	111 (17)	92 (17)	78 (18)	66 (19)	44 (31)	24 (46)	9 (55)	6 (57)	1 (61)	0 (62)

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Original and final trial protocol, and original and final statistical analysis plan