Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors. Supplement to: Antonia S, Goldberg S, Balmanoukian A, et al. Safety and antitumour activity in a phase 1b study of combined checkpoint blockade with anti-PD-L1 (durvalumab) and anti-CTLA4 (tremelimumab) in non-small cell lung cancer. Lancet Oncol 2015; published online

Supplementary Table 1. Safety summary and immunosuppression use – all dose cohorts

n (%)	D3 q4w T1 n=3	D10 q4w T1 n=3	D15 q4w T1 n=18	D20 q4w T1 n=18	D10 q2w T1 n=17	D10 q4w T3 n=3	D15 q4w T3 n=14	D20 q4w T3 n=6	D10 q2w T3 n=11	D15 q4w T10 n=9	All cohorts N=102
Safety summary											
Any AE	3 (100)	3 (100)	18 (100)	18 (100)	16 (94)	3 (100)	14 (100)	6 (100)	11 (100)	9 (100)	101 (99)
Any Grade 3/4 AE	0 (0)	2 (67)	13 (72)	11 (61)	9 (53)	3 (100)	11 (79)	6 (100)	9 (82)	8 (89)	72 (71)
Any deaths	0 (0)	1 (33)	6 (33)	6 (33)	2 (12)	0 (0)	3 (21)	2 (33)	1 (9)	1 (11)	22 (22)
SAE	1 (33)	2 (67)	13 (72)	10 (56)	6 (35)	2 (67)	10 (71)	6 (100)	8 (73)	8 (89)	66 (65)
AE leading to D/C	1 (33)	1 (33)	8 (44)	4 (22)	3 (18)	2 (67)	6 (43)	5 (83)	5 (45)	5 (56)	40 (39)
Related AE	1 (33)	3 (100)	13 (72)	11 (61)	14 (82)	3 (100)	13 (93)	5 (83)	11 (100)	8 (89)	82 (80)
Related Grade 3/4 AE	0 (0)	2 (67)	8 (44)	3 (17)	4 (24)	2 (67)	7 (50)	5 (83)	5 (45)	7 (78)	43 (42)
Related deaths	0 (0)	1 (33)[*]	0 (0)	1 (6)[†]	0 (0)	0 (0)	0 (0)	1 (17)[‡]	0 (0)	0 (0)	3 (3)
Related SAE	0 (0)	1 (33)	5 (28)	4 (22)	2 (12)	2 (67)	6 (43)	5 (83)	5 (45)	7 (78)	37 (36)
Related AE leading to D/C	0 (0)	1 (33)	3 (17)	3 (17)	2 (12)	2 (67)	4 (29)	4 (67)	5 (45)	5 (56)	29 (28)

Immunosuppression use											
Corticosteroids	1 (33)	3 (100)	6 (33)	6 (33)	8 (47)	3 (100)	8 (57)	3 (50)	6 (55)	7 (78)	51 (50)
Adalimumab	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	1 (1)
Infliximab	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	1 (9)	2 (22)	4 (4)

[*]Related death due to polymyositis (complications arising from drug-related myasthenia gravis); [†]Related death due to pericardial effusion; [‡]Related death due to neuromuscular disorder. AE=adverse event; D=durvalumab; D/C=discontinuation; q=every; SAE=serious AE; T=Tremelimumab; w=weeks; doses are mg/kg.

Supplementary Table 2. Treatment-related AEs of interest – combined cohorts

n (%)	D10–20 q4/2w T1* n=56		D10–20 q4/2w T3 n=34		D15 q4w T10 n=9		All cohorts N=102	
Clinical conditions	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Adrenal insufficiency								
Adrenal insufficiency	1 (2)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)
Colitis								
Colitis	2 (4)	1 (2)	8 (24)	6 (18)	2 (22)	2 (22)	12 (12)	9 (9)
Enteritis	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)
Dermatitis								
Pruritus	11 (20)	0 (0)	7 (21)	0 (0)	3 (33)	0 (0)	21 (21)	0 (0)
Rash	6 (11)	0 (0)	7 (21)	0 (0)	2 (22)	0 (0)	15 (15)	0 (0)
Rash maculopapular	1 (2)	0 (0)	2 (6)	0 (0)	1 (11)	1 (11)	4 (4)	1 (1)
Rash pruritic	2 (4)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	3 (3)	0 (0)
Skin exfoliation	0 (0)	0 (0)	1 (3)	0 (0)	1 (11)	0 (0)	2 (2)	0 (0)
Eczema	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Erythema	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Rash generalised	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Rash papular	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)

Diarrhoea								
Diarrhoea	13 (23)	4 (7)	16 (47)	6 (18)	4 (44)	1 (11)	33 (32)	11 (11)
Hyperthyroidism								
Blood TSH decreased	2 (4)	0 (0)	2 (6)	0 (0)	2 (22)	0 (0)	6 (6)	0 (0)
Hyperthyroidism	2 (4)	0 (0)	2 (6)	0 (0)	0 (0)	0 (0)	4 (4)	0 (0)
Thyroiditis	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Thyroxine free increased	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	0 (0)	1 (1)	0 (0)
Tri-iodothyronine free increased	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	0 (0)	1 (1)	0 (0)
Hypophysitis								
Hypophysitis	0 (0)	0 (0)	2 (6)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)
Hypopituitarism	1 (2)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)
Lymphocytic hypophysitis	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)
Hypothyroidism								
Hypothyroidism	5 (9)	1(2)	4 (12)	0 (0)	1 (11)	0 (0)	10 (10)	1 (1)
Blood TSH increased	3 (5)	0 (0)	1 (3)	0 (0)	1 (11)	0 (0)	5 (5)	0 (0)
Thyroxine free decreased	2 (4)	0 (0)	2 (6)	0 (0)	0 (0)	0 (0)	4 (4)	0 (0)
Tri-iodothyronine free decreased	0 (0)	0 (0)	2 (6)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)
Tri-iodothyronine decreased	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Infusion-related/hypersensitivity/ anaphylaxis reactions								

Infusion-related reaction	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Nephritis/acute renal failure								
Blood creatinine increased	1 (2)	0 (0)	2 (6)	0 (0)	1 (11)	0 (0)	4 (4)	0 (0)
Glomerular filtration rate decreased	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Neuropathy								
Myasthenia gravis	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)
Neuromyopathy	0 (0)	0 (0)	1 (3)	1 (3)	0 (0)	0 (0)	1 (1)	1 (1)
Pancreatitis								
Amylase increased[†]	9 (16)	1 (2)	5 (15)	2 (6)	2 (22)	0 (0)	17 (17)	3 (3)
Lipase increased[†]	7 (13)	5 (9)	4 (12)	2 (6)	1 (11)	1 (11)	12 (12)	8 (8)
Pancreatitis	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)
Pneumonitis								
Pneumonitis	0 (0)	0 (0)	3 (9)	2 (6)	2 (22)	2 (22)	5 (5)	4 (4)
Select hepatic events								
ALT increased	6 (11)	2 (4)	4 (12)	1 (3)	0 (0)	0 (0)	10 (10)	3 (3)
GGT increased	4 (7)	1 (2)	4 (12)	1 (3)	1 (11)	1 (11)	9 (9)	3 (3)
AST increased	4 (7)	3 (5)	3 (9)	1 (3)	0 (0)	0 (0)	7 (7)	4 (4)

Note: A patient may be counted in multiple preferred terms.

*Excludes D3 q4w T1 cohort (n=3).

[†]Amylase/Lipase increase was added to Adverse Events of Significant Interest list because it matched the DLT criteria.

AE=adverse event; ALT=alanine transaminase; AST=aspartate transaminase; D=durvalumab; GGT=gamma-glutamyl transferase; q=every; SAE=serious AE; T=tremelimumab; TSH=thyroid-stimulating hormone; w=weeks.

Supplementary Table 3. Antitumour activity summary by dose level, in combined cohorts, and by PD-L1 status (confirmed and unconfirmed responses)*

Antitumour activity by dose level											
n (%)	**D3 q4w T1 n=3**	**D10 q4w T1 n=3**	**D15 q4w T1 n=12**	**D20 q4w T1 n=8**	**D10 q2w T1 n=3**	**D10 q4w T3 n=3**	**D15 q4w T3 n=10**	**D20 q4w T3 n=6**	**D10 q2w T3 n=6**	**D15 q4w T10 n=9**	**All cohorts N=63**
All evaluable patients with ≥24 weeks follow-up											
ORR	0 (0)	1 (33)	4 (33)	4 (50)	0 (0)	2 (67)	3 (30)	1 (17)	1 (17)	2 (22)	18 (29)
DCR (CR, PR, SD ≥24 weeks)	0 (0)	2 (67)	8 (67)	4 (50)	0 (0)	2 (67)	5 (50)	2 (33)	1 (17)	2 (22)	26 (41)

Antitumour activity – combined cohorts				
n (%; 95% CI)	**D10–20 q4/2w T1[†] n=26**	**D10–20 q4/2w T3 n=25**	**D15 q4w T10 n=9**	**All cohorts N=63**
All evaluable patients with ≥24 weeks follow-up				
ORR	9 (35; 17–56)	7 (28; 12–49)	2 (22; 3–60)	18 (29; 18–41)
DCR (CR, PR, SD ≥24 weeks)	14 (54; 33–73)	10 (40; 21–61)	2 (22; 3–60)	26 (41; 29–54)
PD-L1^{+} (≥25%)	**n=9**	**n=5**	**n=4**	**n=18**
ORR	3 (33; 7–70)	2 (40; 5–85)	1 (25; 1–81)	6 (33; 13–59)
DCR (CR, PR, SD ≥24 weeks)	4 (44; 14–79)	2 (40; 5–85)	1 (25; 1–81)	7 (39; 17–64)
PD-L1^{-} (<25%)	**n=14**	**n=17**	**n=4**	**n=37**
ORR	6 (43; 18–71)	4 (24; 7–50)	1 (25; 1–81)	11 (30; 16–47)
DCR (CR, PR, SD ≥24 weeks)	9 (64; 35–87)	7 (41; 18–67)	1 (25; 1–81)	17 (46; 29–63)

PD-L1⁻ (0%)	**n=10**	**n=10**	**n=3**	**n=24**
ORR	6 (60; 26–88)	2 (20; 3–56)	1 (33; 1–91)	9 (38; 19–59)
DCR (CR, PR, SD ≥24 weeks)	7 (70; 35–93)	5 (50; 19–81)	1 (33; 1–91)	13 (54; 33–74)
PD-L1 unknown	**n=3**	**n=3**	**n=1**	**n=8**
ORR	0 (0; 0–71)	1 (33; 1–91)	0 (0; 0–98)	1 (13; 0–53)
DCR (CR, PR, SD ≥24 weeks)	1 (33; 1–91)	1 (33; 1–91)	0 (0; 0–98)	2 (25; 3–65)

*Includes confirmed and unconfirmed CR or PR. In patients with measurable disease at baseline, ≥1 follow-up scan includes those that discontinued due to PD or death without any follow-up scan. All patients were dosed ≥24 weeks prior to the cutoff date.

†Excludes D3 q4w T1 cohort (n=3).

CI=confidence interval; CR=complete response; D=durvalumab; DCR=disease control rate; ORR=objective response rate; PR=partial response; q=every; SD=stable disease; T=tremelimumab; w=weeks.

Supplementary Table 4. Response rates by PD-L1 status (confirmed with ≥24 weeks follow-up)

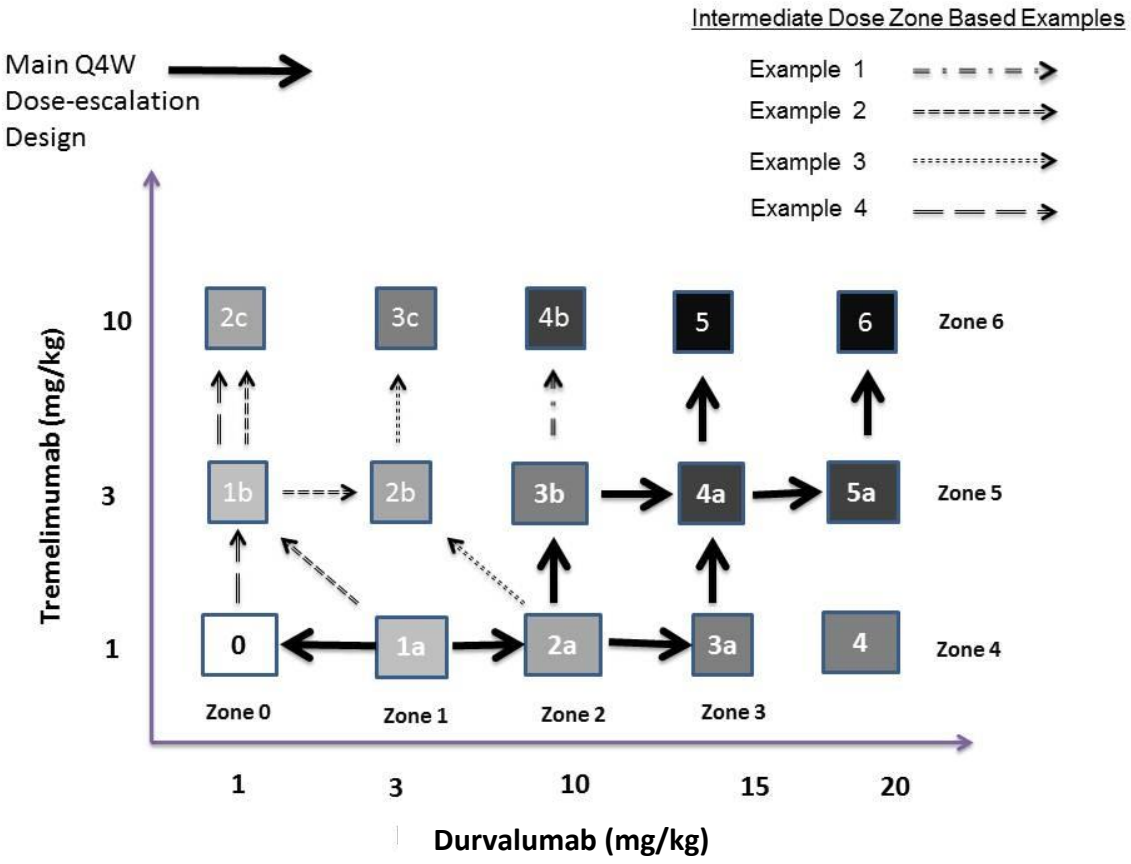
	Overall population				EGFR/ALK wild-type population			
	All cohorts		Combined T1 cohort D10–20 q4/2w T1*		All cohorts		Combined T1 cohort D10–20 q4/2w T1*	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
All patients	11/63 (17)	9–29	6/26 (23)	9–44	11/58 (19)	10–31	6/25 (24)	9–45
PD-L1^{+} (≥25%)	4/18 (22)	6–48	2/9 (22)	3–60	4/15 (27)	8–55	2/9 (22)	3–60
PD-L1^{-}								
<25%	6/37 (16)	6–32	4/14 (29)	8–58	6/36 (17)	6–33	4/13 (31)	9–61
0%	5/24 (21)	7–42	4/10 (40)	12–74	5/24 (21)	7–42	4/10 (40)	12–74
All 2L patients	9/22 (41)	21–64	5/10 (50)	19–81	9/22 (41)	21–64	5/10 (50)	19–81
PD-L1^{+} (≥25%)	3/6 (50)	12–88	1/3 (33)	1–91	3/6 (50)	12–88	1/3 (33)	1–91
PD-L1^{-}								
<25%	5/12 (42)	15–72	4/6 (67)	22–96	5/12 (42)	15–72	4/6 (67)	22–96
0%	4/7(57)	18–90	4/4 (100)	40–100	4/7 (57)	18–90	4/4 (100)	40–100

2L, second line: 1 prior line of therapy, receiving study treatment in second line.

*Excludes D3 q4w T1 cohort (n=3). ALK= anaplastic lymphoma kinase; CI=confidence interval; D= durvalumab; EGFR=epidermal growth factor receptor; q=every; T=tremelimumab; w=weeks.

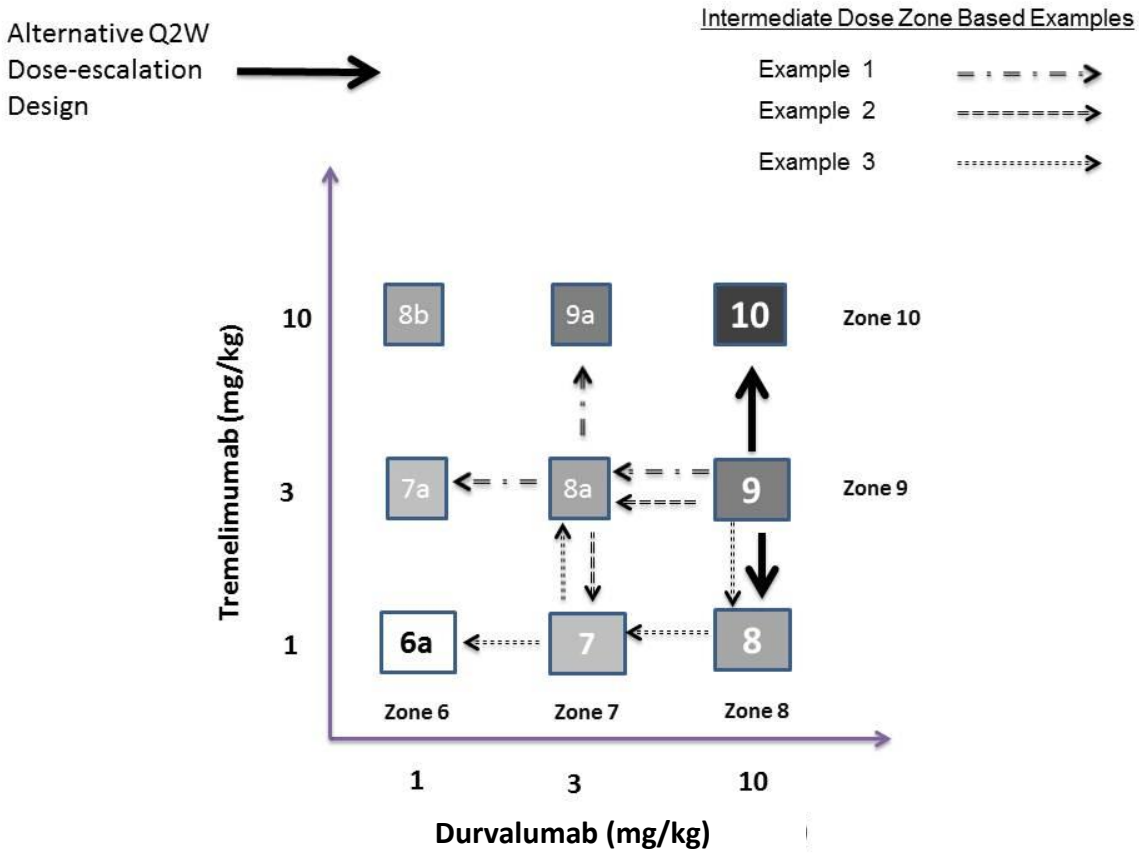
Supplementary Figure 1. Modified zone-based design for intermediate dosing for (A) main Q4W and (B) alternative Q2W dose-escalation schedule. Doses evaluated in this study are indicated.

A



1a: Durvalumab 3 mg/kg + tremelimumab 1 mg/kg
2a: Durvalumab 10 mg/kg + tremelimumab 1 mg/kg
3a: Durvalumab 15 mg/kg + tremelimumab 1 mg/kg
4: Durvalumab 20 mg/kg + tremelimumab 1 mg/kg
3b: Durvalumab 10 mg/kg + tremelimumab 3 mg/kg
4a: Durvalumab 15 mg/kg + tremelimumab 3 mg/kg
5a: Durvalumab 20 mg/kg + tremelimumab 3 mg/kg
5: Durvalumab 15 mg/kg + tremelimumab 10 mg/kg

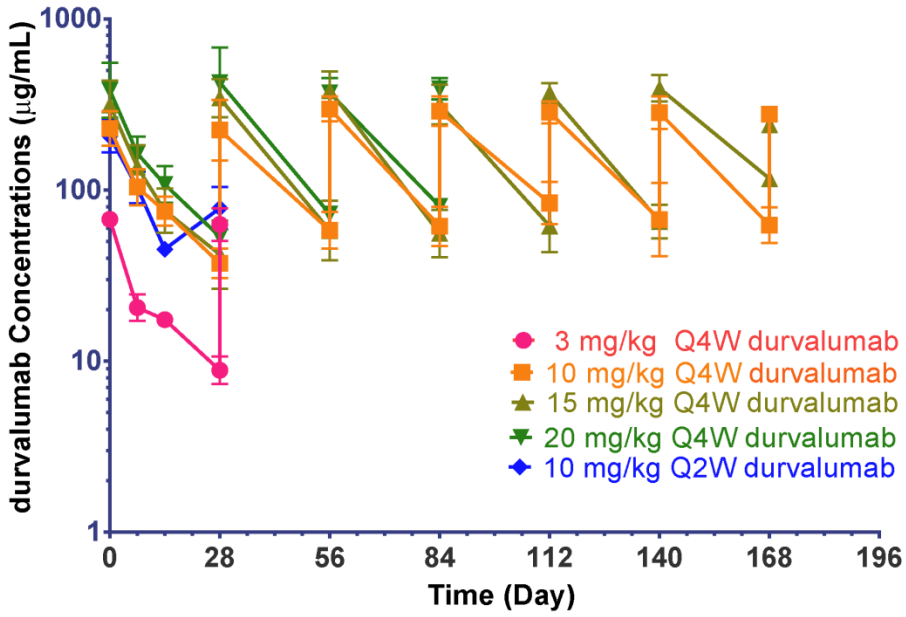
B



8: Durvalumab 10 mg/kg + tremelimumab 1 mg/kg
9: Durvalumab 10 mg/kg + tremelimumab 3 mg/kg

Supplementary Figure 2. Serum concentrations of (A) durvalumab and (B) tremelimumab in combination.

A



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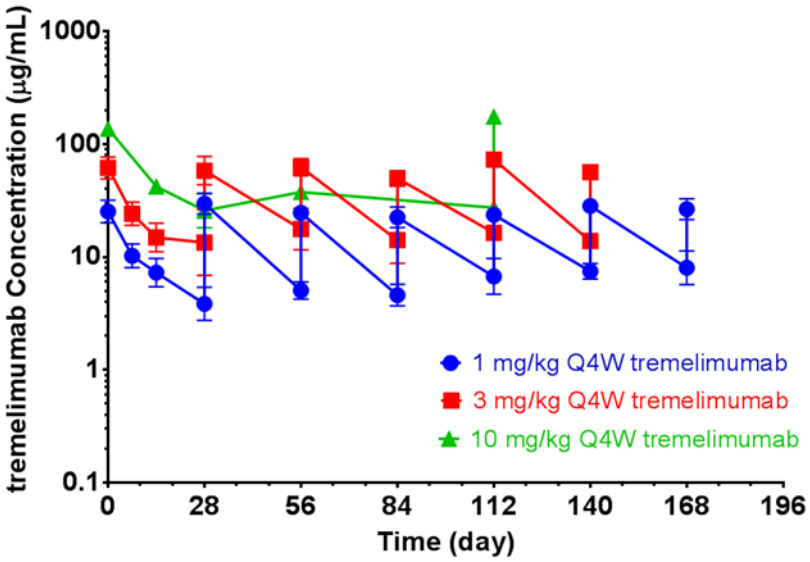
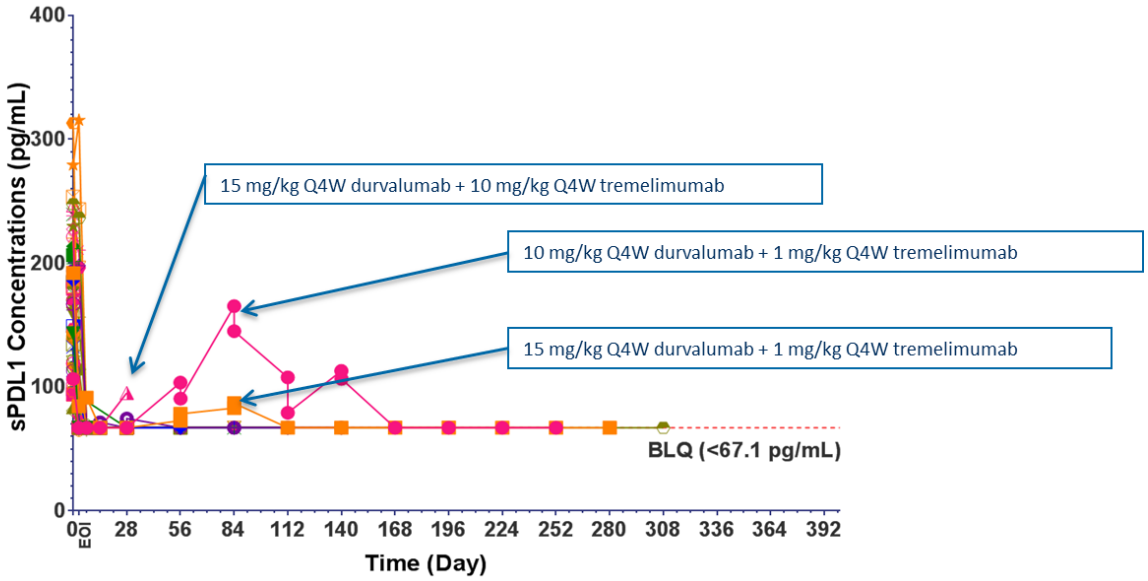


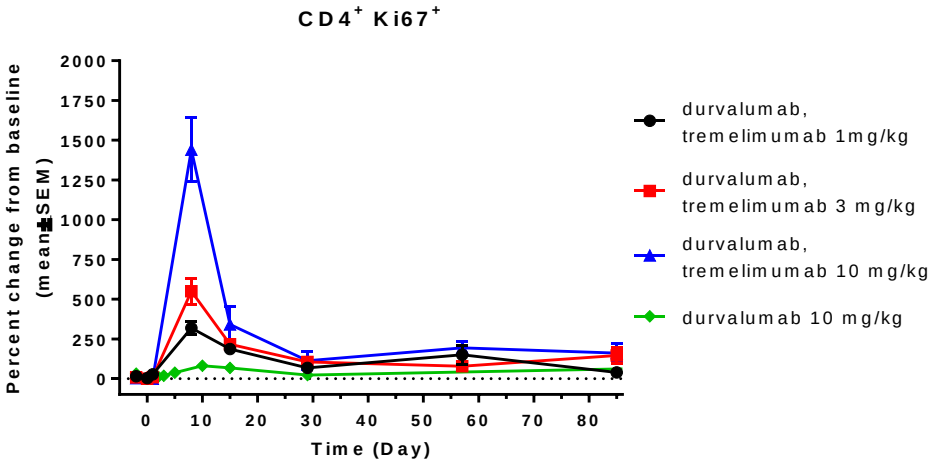
Q=every; W=weeks

Supplementary Figure 3. Suppression of serum free sPD-L1 observed in patients treated with durvalumab and tremelimumab in combination (n=69). Two patients (D10 q4w/T1, PD due to non-target lesion from first disease assessment, treated after PD; D15 q4w/T1, unconfirmed response and treated after PD) showed partial free sPD-L1 suppression at some visits followed by complete suppression after repeated dosing. One patient (D15 q4w/T10, with one disease assessment and best overall response of PD) who was ADA positive with an impact on PK showed partial free sPD-L1 suppression on Day 29. Each line represents one patient. BLQ=below the limit of quantitation; EOI=end of infusion.



Supplementary Figure 4. T-cell proliferation and activation by flow cytometry. All durvalumab doses combined, with durvalumab monotherapy data[8] shown in comparison: (A) $CD4^+Ki67^+$, (B) $CD8^+Ki67^+$ and (C) $CD4^+HLR\text{-}DR^+$ proliferating cells. (D) $CD4^+Ki67^+$ proliferating cells by durvalumab dose, at 1 mg/kg tremelimumab. SEM=standard error of the mean.

A



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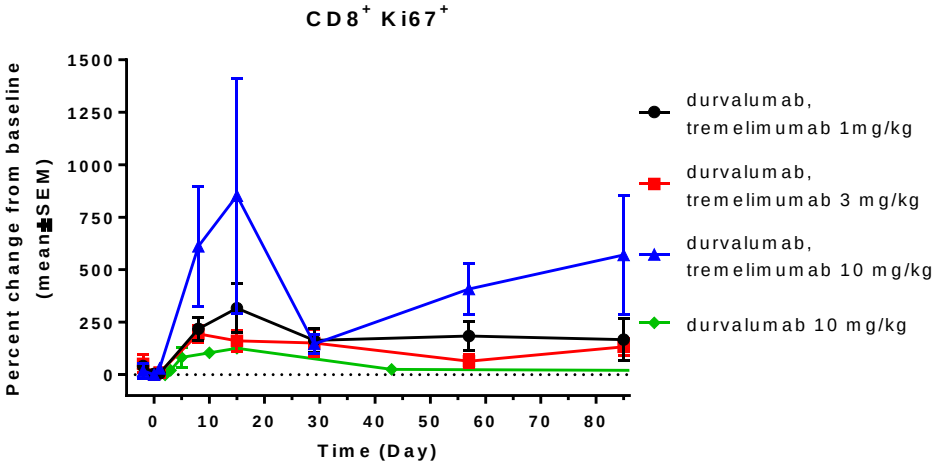
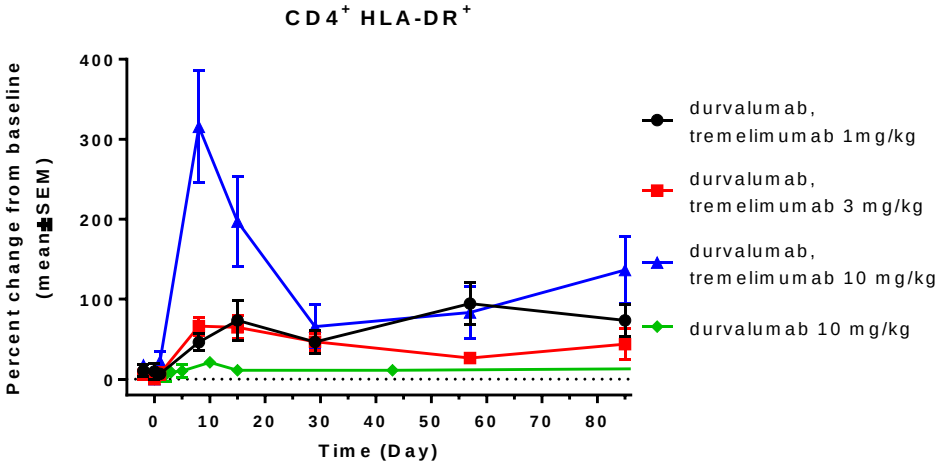
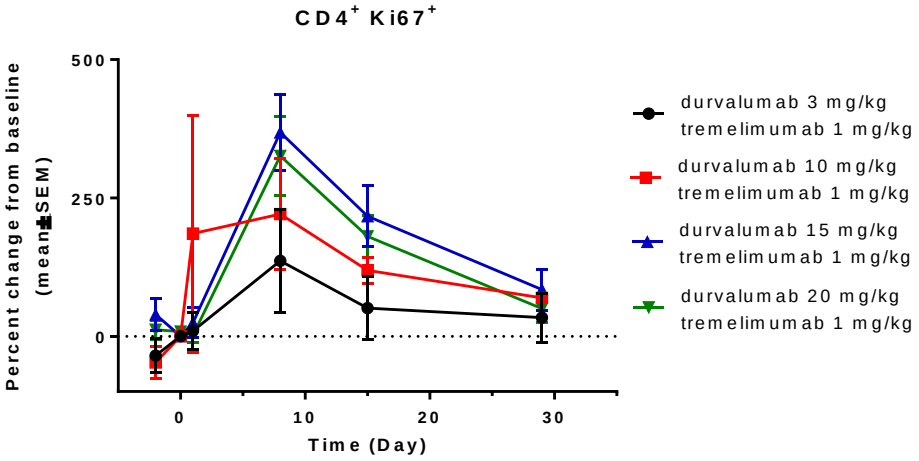


C

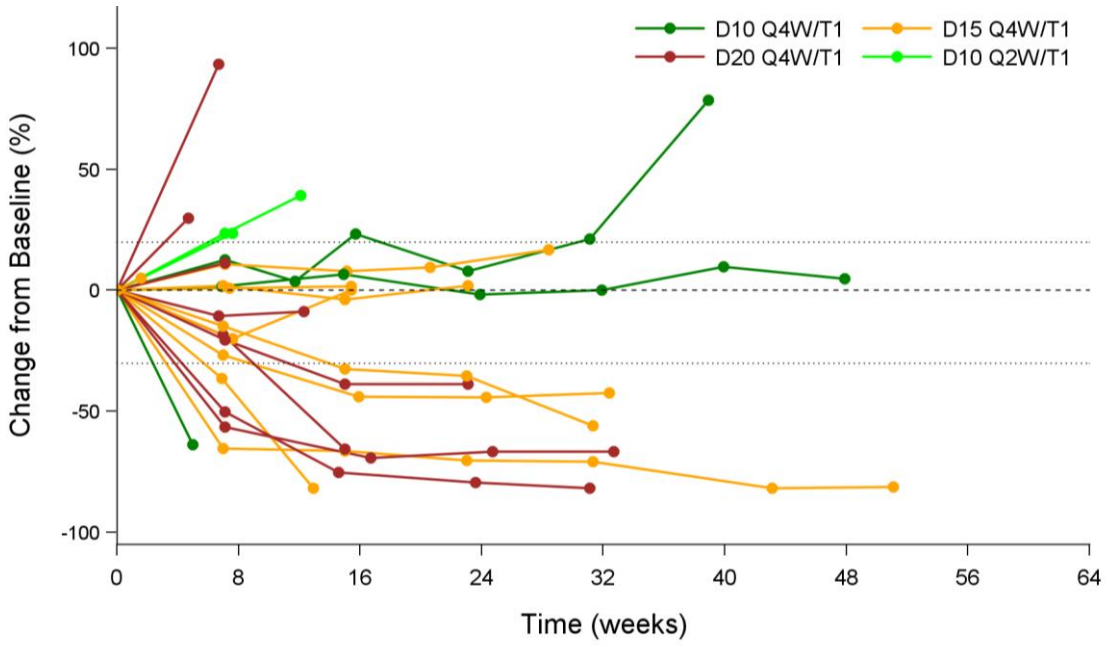

CD4+ HLA-DR+
Percent change from baseline (mean±SEM)
400
300
200
100
0
0
10
20
30
40
50
60
70
80
Time (Day)
durvalumab, tremelimumab 1mg/kg
durvalumab, tremelimumab 3 mg/kg
durvalumab, tremelimumab 10 mg/kg
durvalumab 10 mg/kg

D


CD4+ Ki67+
Percent change from baseline (mean±SEM)
500
250
0
0
10
20
30
Time (Day)
durvalumab 3 mg/kg tremelimumab 1 mg/kg
durvalumab 10 mg/kg tremelimumab 1 mg/kg
durvalumab 15 mg/kg tremelimumab 1 mg/kg
durvalumab 20 mg/kg tremelimumab 1 mg/kg

Supplementary Figure 5. Change from baseline in tumour size (response evaluable population with ≥24 weeks follow-up). (A) Combined T1 cohort; (B) combined T3 cohort; (C) T10 cohort.

A



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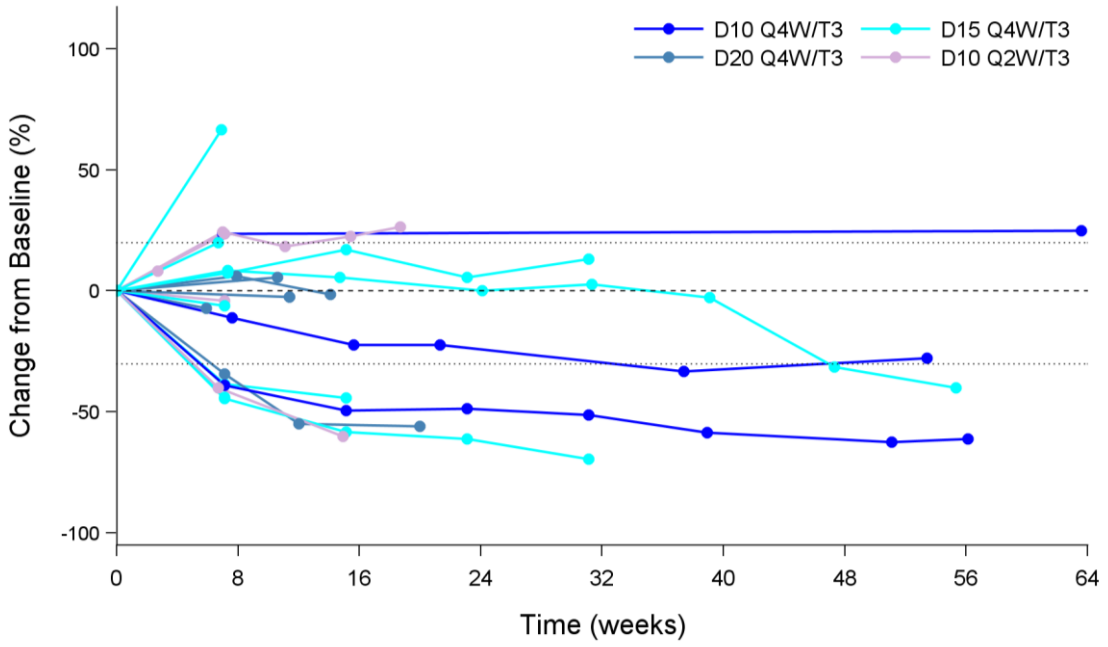

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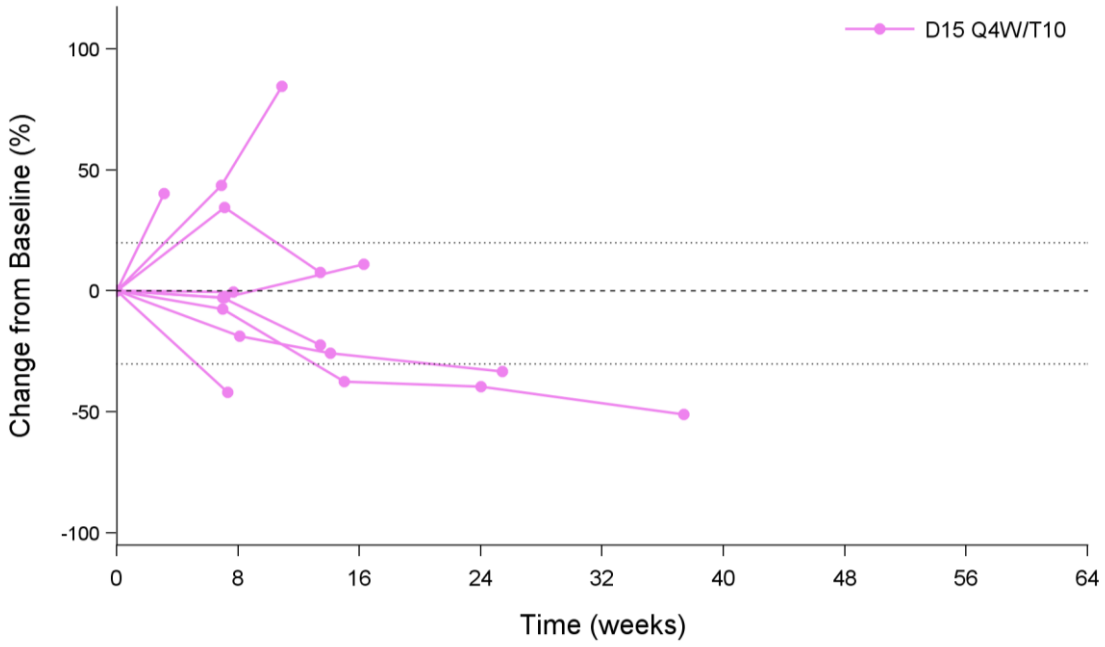
D15 Q4W/T10
Change from Baseline (%)
100
50
0
-50
-100
0
8
16
24
32
40
48
56
64
Time (weeks)

Supplementary Appendix

Methods

Patients

Eligible patients were aged ≥18 years and had confirmed locally advanced or metastatic squamous or non-squamous NSCLC with one or more measurable lesions based on RECIST Version 1·1.[14] Patients had to be immunotherapy-naïve (with the exception of prior vaccines) but may have received any number of other systemic therapies. Patients entering the dose-escalation phase had not responded to, relapsed after, were unable to tolerate, or were not eligible for standard treatment. Other inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1 and adequate organ and marrow function, defined as hemoglobin ≥ 9 g/dL, absolute neutrophil count ≥ 1,500/mm^3, platelet count ≥ 100,000/mm^3, total bilirubin ≤ 1.5 × upper limit of normal (ULN) except subjects with documented Gilbert's syndrome (> 3 × ULN) or liver metastasis, who must have a baseline total bilirubin ≤ 3.0 mg/dL, ALT and AST ≤ 2.5 × ULN (for subjects with hepatic metastases, ALT and AST ≤ 5 × ULN), and serum creatinine ≤ 2.0 mg/dL. Patients with central nervous system (CNS) metastases were required to be asymptomatic without concurrent treatment and to have had ≥28 days of non-progression of CNS metastases (except for those with leptomeningeal disease or cord compression, who were excluded). Study exclusion criteria included concurrent anticancer therapy (except localised palliative treatment); any investigational anticancer therapy or live attenuated vaccine ≤28 days before first doses of study drugs; prior severe or persistent immune-related adverse events (AEs); persistent AEs from prior anticancer therapy (except those judged unlikely to be exacerbated by study drugs); current or prior use (≤14 days before first doses of study drugs) of immunosuppressive medication (except intranasal/inhaled corticosteroids or systemic corticosteroids ≤10 mg prednisone equivalent); history of primary immunodeficiency; and human immunodeficiency virus or hepatitis A, B, or C.

Study Oversight

The study has been conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Council on Harmonization guidelines on Good Clinical Practice, all applicable laws and regulatory requirements, and all conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC). The study protocol was reviewed and approved by the IRB/IEC of participating centres. Written informed consent was obtained from all patients.

Study Design

STUDY TREATMENT

Study treatment continued for 12 months or until progressive disease, dose limiting toxicities (DLTs) or other unacceptable toxicity, withdrawn consent, or discontinuation for other reasons. Patients who achieved and maintained disease control (i.e., complete response [CR], partial response [PR], or stable disease [SD]) through to the end of the 12-month treatment period entered follow-up. One round of re-treatment was offered if progressive disease was noted during follow-up and the patient had not received other treatments for their disease and still met the study eligibility criteria.

DOSE-LIMITING TOXICITIES (DLTS) AND DLT EVALUATION PERIOD

A DLT was defined as any Grade 3 or higher drug-related toxicity that occurred from the first dose until administration of: (i) the third dose of durvalumab + tremelimumab (for the cohort receiving D3 q4w/T1); (ii) the second dose of durvalumab + tremelimumab (for all other cohorts receiving durvalumab q4w); or (iii) the third dose of durvalumab and second dose of tremelimumab (for cohorts receiving durvalumab q2w).

SECONDARY ENDPOINTS AND ASSESSMENTS

Pharmacokinetic (PK) parameters were estimated by a non-compartmental analysis approach using Phoenix WinNonlin (version 6; Pharsight [Certara], Sunnyvale, CA). Peak (maximum) concentration (C_{max}), trough serum concentration (C_{trough}), area under the concentration–time curve over the dosing interval (AUC_{τ}), dose-normalised C_{max}, dose-normalised C_{trough}, and dose-normalised AUC_{τ} were determined after the first dose. Steady state PK parameters, including peak concentration ($C_{max,ss}$) and trough concentration ($C_{trough,ss}$), were also estimated, as were accumulation ratios for C_{max} and C_{trough}.

Immunogenicity results were analysed descriptively by summarising the number and percentage of patients who developed detectable anti-drug antibodies (ADAs). ADAs were measured using validated electrochemiluminescence (ECL) assays performed on the Meso Scale Discovery platform.

EXPLORATORY ENDPOINTS

PD-L1 immunohistochemical staining of formalin-fixed, paraffin-embedded samples was performed on an automated BenchMark ULTRA® platform using the Ventana PD-L1 SP263 rabbit monoclonal antibody (mAb) assay.[15]

Target engagement for durvalumab was assessed using suppression of free soluble PD-L1 in serum (sPD-L1). sPD-L1 that is not bound by durvalumab was quantified using a validated ECL method. Briefly, sPD-L1 was captured by biotinylated anti-PD-L1 antibody clone 2·7A4 (MedImmune) that competes with durvalumab for PD-L1 binding, and detected by anti-PD-L1 antibody clone 130021 (R&D Systems) plus ruthenium-labeled goat anti-mouse IgG. The ECL signal is measured by a Sector Imager 2400 or 6000 (MSD) and is proportional to serum concentration of sPD-L1. Serum sPD-L1 concentration was quantified by interpolating from sPD-L1 standard curves. Quantities of activated (HLA-DR+) or proliferating (Ki67+) T cells were assessed using qualified flow cytometry-based assays. In brief, whole blood specimens were incubated with optimised quantities of fluorochrome-labeled antibodies with specificities for T cell-associated proteins CD3, CD4 and CD8 (clone UCHT1, RPA-T4 and SK1, respectively) and HLA-DR (clone L243) or Ki67 (clone B56), with the latter being added following a cell-permeabilisation step. Antibody-labeled cells were subsequently analysed on a FACSCanto II flow cytometer (BD Biosciences), and absolute counts of each population were calculated from total T-cell counts derived from the BD Multitest™ 6-color TBNK reagent (BD Biosciences) performed according to the manufacturer's protocol. Data for durvalumab monotherapy were reported previously.[9] Pharmacodynamic data were summarised using descriptive and graphical approaches in Phoenix WinNonlin (Certara) and Prism (version 6·03 GraphPad Software).

PATIENT POPULATIONS

MTD evaluation was based on the DLT evaluable population (received protocol-assigned treatment and completed the DLT evaluation period or experienced a DLT during the DLT evaluation period). Non-evaluable patients in the dose-escalation phase could be replaced. Tolerability was based on the as-treated population (all patients receiving any dose of either study drug). Antitumour activity was based on the response evaluable population dosed ≥24 weeks prior to data cutoff. The response evaluable population included treated patients with measurable disease at baseline who had ≥1 follow-up scan or discontinued treatment due to disease progression or death without any follow-up scan.

Results

Immunogenicity

Post-treatment, 4/60 patients (6·6%: two patients in the D15 q4w/T10 cohort, one with best overall response [BOR] of unconfirmed PR, the other with PD; one patient in the D10 q4w/T3 cohort with BOR of confirmed PR; one patient in the D15 q4w/T1 cohort with no evaluable response) were positive for anti-durvalumab antibodies and 1/53 (1·8%: in the D15 q4w/T1 cohort, BOR of SD) was positive for anti-tremelimumab antibodies. No clear relationship between ADAs and dose of either durvalumab or tremelimumab was observed, nor was there an association between ADAs and tolerability or antitumour activity. One patient (D15 q4w/T10, BOR of PD) was ADA positive on d29 with an impact on PK (decreased durvalumab serum PK concentrations and increased sPD-1 values around d29).

Clinical research sites

Location	Principal investigators	Number of patients recruited
All sites		102 (100%)
H Lee Moffitt Cancer Center, Tampa, FL, USA	Scott Antonia	38 (37%)
Yale University, Yale Cancer Center, New Haven, CT, USA	Sarah Goldberg	26 (25%)
Memorial Sloan Kettering Cancer Center, New York, NY, USA	Naiyer Rizvi Jamie Chaft	18 (18%)
The Angeles Clinic and Research Institute, Los Angeles, CA, USA	Ani Balmanoukian	15 (15%)
Earle A. Chiles Research Institute, Providence Cancer Center, Portland, OR, USA	Rachel Sanborn	5 (5%)