Safety and antitumour activity of durvalumab plus tremelimumab in non-small-cell lung cancer: a multicentre, phase 1b study

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Summary

Background PD-L1 and CTLA-4 immune checkpoints inhibit antitumour T-cell activity. Combination treatment with the anti-PD-L1 antibody durvalumab and the anti-CTLA-4 antibody tremelimumab might provide greater antitumour activity than either drug alone. We aimed to assess durvalumab plus tremelimumab in patients with advanced squamous or non-squamous non-small-cell lung cancer (NSCLC).

Methods We did a multicentre, non-randomised, open-label, phase 1b study at five cancer centres in the USA. We enrolled immunotherapy-naive patients aged 18 years or older with confirmed locally advanced or metastatic NSCLC. We gave patients durvalumab in doses of 3 mg/kg, 10 mg/kg, 15 mg/kg, or 20 mg/kg every 4 weeks, or 10 mg/kg every 2 weeks, and tremelimumab in doses of 1 mg/kg, 3 mg/kg, or 10 mg/kg every 4 weeks for six doses then every 12 weeks for three doses. The primary endpoint of the dose-escalation phase was safety. Safety analyses were based on the as-treated population. The dose-expansion phase of the study is ongoing. This study is registered with ClinicalTrials.gov, number NCT02000947.

Findings Between Oct 28, 2013, and April 1, 2015, 102 patients were enrolled into the dose-escalation phase and received treatment. At the time of this analysis (June 1, 2015), median follow-up was 18·8 weeks (IQR 11–33). The maximum tolerated dose was exceeded in the cohort receiving durvalumab 20 mg/kg every 4 weeks plus tremelimumab 3 mg/kg, with two (30%) of six patients having a dose-limiting toxicity (one grade 3 increased aspartate aminotransferase and alanine aminotransferase and one grade 4 increased lipase). The most frequent treatment-related grade 3 and 4 adverse events were diarrhoea (11 [11%]), colitis (nine [9%]), and increased lipase (eight [8%]). Discontinuations attributable to treatment-related adverse events occurred in 29 (28%) of 102 patients. Treatment-related serious adverse events occurred in 37 (36%) of 102 patients. 22 patients died during the study, and three deaths were related to treatment. The treatment-related deaths were due to complications arising from myasthenia gravis (durvalumab 10 mg/kg every 4 weeks plus tremelimumab 1 mg/kg), pericardial effusion (durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg), and neuromuscular disorder (durvalumab 20 mg/kg every 4 weeks plus tremelimumab 3 mg/kg). Evidence of clinical activity was noted both in patients with PD-L1-positive tumours and in those with PD-L1-negative tumours. Investigator-reported confirmed objective responses were achieved by six (23%, 95% CI 9–44) of 26 patients in the combined tremelimumab 1 mg/kg cohort, comprising two (22%, 95% CI 3–60) of nine patients with PD-L1-positive tumours and four (29%, 95% CI 8–58) of 14 patients with PD-L1-negative tumours, including those with no PD-L1 staining (four [40%, 95% CI 12–74] of ten patients).

Interpretation Durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg showed a manageable tolerability profile, with antitumour activity irrespective of PD-L1 status, and was selected as the dose for phase 3 studies, which are ongoing.

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See Comment page 259

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Introduction

Drugs that block the PD-L1/PD-1 pathway act in the tumour microenvironment and prevent inhibition of T-cell function, whereas drugs that block the CTLA-4 pathway act in the lymphoid compartment to expand the number and repertoire of tumour-reactive T cells.[1,2] Thus, combined blockade of both pathways targets both compartments. The clinical benefit of PD-L1/PD-1 pathway inhibition has been shown in roughly 10–30% of PD-L1 unselected patients with non-small-cell lung cancer (NSCLC).[3] However, fewer than half of NSCLC patients express PD-L1 on their tumour cells,[4] and most patients (including PD-L1-positive and PD-L1-negative) do not respond to PD-1 pathway blockade alone, representing an opportunity for combination treatments. In studies of nivolumab plus ipilimumab for melanoma[5] and NSCLC,[6] durable responses were reported in both PD-L1-positive and PD-L1-negative patients. Tolerability of this treatment combination seemed to be dose-dependent and schedule-dependent, highlighting the need for optimum dose selection to minimise the toxic effects of combination regimens while maintaining clinical activity.

Research in context

Evidence before this study

We searched PubMed between Jan 1, 2005, and Oct 1, 2015, for published preclinical and clinical research on antibody treatments for cancer, with terms including "anti-PD-L1" or "anti-PD-1" and "anti-CTLA-4". Most clinical studies were reported in the past 2 years. Patients with advanced non-small cell lung cancer (NSCLC) progressing after first-line treatment have a pronounced unmet need because current treatments have limited clinical use. Early clinical data suggest that blockade of multiple immune checkpoints might have greater antitumour activity than blockade of one checkpoint in melanoma and other tumour types, including NSCLC, although the incidence of adverse events also seems to be higher than with single drugs. Treatment with the PD-L1 inhibitor durvalumab has produced durable responses in patients with advanced NSCLC, with a manageable tolerability profile. We designed a study to investigate the safety and antitumour activity of durvalumab in combination with the CTLA-4 inhibitor tremelimumab in patients with locally advanced or metastatic NSCLC.

Added value of this study

In the dose-escalation part of the study, the combination of durvalumab 20 mg/kg every 4 weeks and tremelimumab 1 mg/kg had a manageable tolerability profile. Clinical activity was recorded irrespective of PD-L1 expression status, including in patients with no PD-L1 staining in the tumour cell membrane.

Implications of all the available evidence

The clinical activity of durvalumab plus tremelimumab noted in patients with PD-L1-negative tumours is an important advance, because this population is less responsive to treatment with single drugs that block the PD-1 checkpoint pathway. Based on findings of this study and previous investigations, the optimum dose of combination treatment with durvalumab and tremelimumab was selected for phase 3 studies, which are ongoing.

Durvalumab is a selective, high-affinity human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80 but does not bind to PD-L2,[7] avoiding potential immune-related toxic effects due to PD-L2 inhibition, which has been noted in susceptible animal models.[8,9] In an ongoing phase 1/2 study,[10] durvalumab treatment produced durable responses in patients with advanced NSCLC, with a manageable tolerability profile. Furthermore, a maximum tolerated dose was not reached in the dose-escalation phase, and dose-expansion cohorts were initiated with a dose of 10 mg/kg every 2 weeks.[10] Tremelimumab is a selective human IgG2 monoclonal antibody inhibitor of CTLA-4.[11] It promotes T-cell activity through CTLA-4 inhibition but does not seem to deplete regulatory T cells directly.[12] Preclinical data indicate that the PD-L1/PD-1 and CTLA-4 pathways are non-redundant,[13] suggesting that targeting both pathways could have additive or synergistic effects.

We designed a phase 1b study to assess the tolerability and antitumour activity of the combination of durvalumab and tremelimumab in patients with advanced NSCLC, irrespective of PD-L1 expression status. In this report, we present results of the dose-escalation phase; the dose-expansion phase is ongoing.

Methods

Study design and participants

See Online for appendix

We did a non-randomised, open-label, phase 1b study at five cancer centres in the USA (appendix p 27). We judged patients eligible for the study if they were aged 18 years or older and had confirmed locally advanced or metastatic squamous or non-squamous NSCLC with one or more measurable lesions (based on Response Evaluation Criteria In Solid Tumors [RECIST] version 1.1). Patients had to be immunotherapy-naive (with the exception of previous vaccines) but could have received any number of other systemic treatments. Progression at inclusion was investigator-determined using RECIST version 1.1. Further inclusion and exclusion criteria are described in the appendix (p 25).

We undertook the study in accordance with the ethical principles of the Declaration of Helsinki and the International Council on Harmonization guidelines on Good Clinical Practice. The study protocol was reviewed and approved by the Institutional Review Board or Independent Ethics Committee at all participating centres. We obtained written informed consent from all patients.

Procedures

We enrolled patients into the dose-escalation phase of the study according to a standard 3+3 and modified zone-based design,[14] with further expansion of escalation cohorts to allow for safety assessment (appendix pp 17, 18). Zones consist of various dose combinations, which can be assessed for safety in parallel. Dosing arms with excessive toxic effects can be eliminated, permitting more patients to be assigned to combinations with an acceptable toxicity profile.[14] The modified zone-based design allowed for investigation of dose cohorts in lower zones or within a zone. Investigation of higher zones could take place if a lower zone was used as an intermediate. If no more than one of six patients had a dose-limiting toxicity in a given dose cohort then we continued dose escalation until the maximum tolerated dose or the highest protocol-defined dose was reached for each drug. If the maximum tolerated dose was exceeded for two or more cohorts within a zone or for the starting dose cohort for two adjacent zones, then we could not proceed to investigate higher zones, even if a lower intermediate zone was assessed.

We administered study treatment for 12 months or until progressive disease (figure 1). Durvalumab and tremelimumab were given intravenously in the following dose cohorts: durvalumab 3 mg/kg every 4 weeks plus tremelimumab 1 mg/kg; durvalumab 10 mg/kg every 4 weeks plus tremelimumab 1 mg/kg; durvalumab 15 mg/kg every 4 weeks plus tremelimumab 1 mg/kg; durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg; durvalumab 10 mg/kg every 2 weeks plus tremelimumab 1 mg/kg; durvalumab 10 mg/kg every 4 weeks plus tremelimumab 3 mg/kg; durvalumab 15 mg/kg every 4 weeks plus tremelimumab 3 mg/kg; durvalumab 20 mg/kg every 4 weeks plus tremelimumab 3 mg/kg; durvalumab 10 mg/kg every 2 weeks plus tremelimumab 3 mg/kg; and durvalumab 15 mg/kg every 4 weeks plus tremelimumab 10 mg/kg. In all dose cohorts, tremelimumab was given every 4 weeks for six doses followed by every 12 weeks for three doses. We permitted treatment interruptions, but not dose reductions. We offered one round of retreatment 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.

Adverse events, serious adverse events, and laboratory abnormalities were classified and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03) and monitored from the start of the study until 90 days after the last dose of study drugs. Laboratory assessment of haematology, serum chemistry, and thyroid function were done on days 1 and 2, every week through week 13, and then every 4 weeks through week 49. Treatment-related serious adverse events occurring 90 days or more after the last dose of study drugs were reported. Study implementation was overseen by Institutional Review Boards or Independent Ethics Committees at every study site.

Investigator-assessed antitumour activity was based on RECIST (version 1.1). CT or MRI studies were done every 8 weeks during treatment, at the end of treatment, every 3 months after the end of treatment until 12 months after the last dose, then every 6 months thereafter. We measured concentrations of durvalumab in serum with a validated electrochemiluminescence immunoassay, with a lower limit of quantitation of 50 ng/mL. We measured concentrations of tremelimumab in serum with a validated ELISA, with a lower limit of quantitation of 156 ng/mL. We obtained blood samples for pharmacokinetic assessment on weeks 1, 2, 3, and 5, then every 4 or 12 weeks according to the schedule of tremelimumab administration. We detected anti-drug antibodies with validated electrochemiluminescence assays on the Meso Scale Discovery platform (Meso Scale Diagnostics, Rockville, MD, USA). We tested serum samples to detect, confirm, and ascertain titres of antibodies to durvalumab and tremelimumab, using a tiered analysis approach and statistically based cutpoints that were established during method validation. We obtained blood samples for immunogenicity assessment at baseline then every 4 or 12 weeks according to the schedule of tremelimumab administration. Post-hoc analyses of the association of antibodies against durvalumab or tremelimumab with antitumour activity were based on observations of confirmed and unconfirmed partial responses in patients positive for anti-drug antibodies.

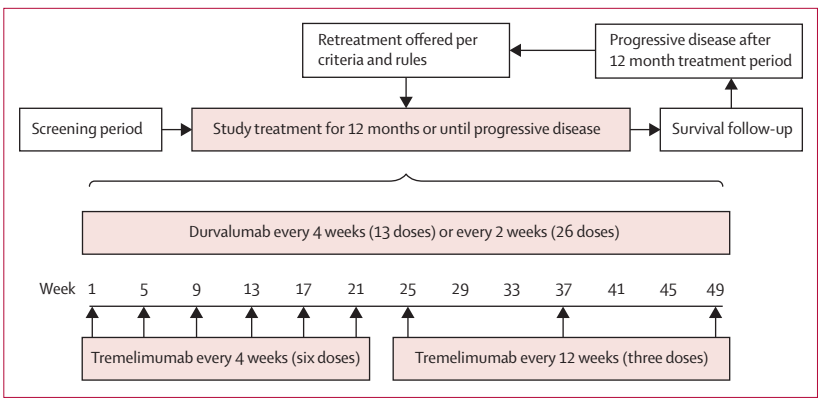

Figure 1: **Dosing schedule**

Target engagement for durvalumab was assessed by suppression of free soluble PD-L1 in serum. We quantified the amount of soluble PD-L1 not bound by durvalumab with a validated electrochemiluminescence method. We monitored circulating quantities of T cells (using CD4 and CD8 cell surface markers) expressing the activation marker HLA-DR or the intracellular proliferation marker Ki67 with validated flow cytometry-based assays.

We assessed archival tumour or fresh tumour biopsy samples obtained at baseline for PD-L1 expression with the validated Ventana SP263 immunohistochemistry assay optimised for use on the automated BenchMark ULTRA platform (Ventana Medical Systems, Tucson, AZ, USA; appendix p 26). Samples were judged positive if 25% or more of tumour cells showed membrane staining for PD-L1.[15] This cutoff was validated clinically based on findings of the durvalumab study in patients with NSCLC or squamous cell carcinoma of the head and neck.[10,16] The only PD-L1 staining variable that correlated with response in that study was PD-L1 expression in the membrane of tumour cells, irrespective of staining intensity. In the current study, if two samples from a patient were tested and one was positive, we judged the patient to be PD-L1-positive. We analysed patients with 0% staining in a separate category from those with less than 25% PD-L1 staining, as they would be more likely to be judged PD-L1-negative irrespective of the assay or PD-L1 expression cutoff used. Local laboratories ascertained *EGFR*, *ALK*, *RAS*, and other mutation status, under study site direction.

	Durvalumab 3 mg/kg every 4 weeks plus tremelimumab 1 mg/kg (n=3)	Durvalumab 10 mg/kg every 4 weeks plus tremelimumab 1 mg/kg (n=3)	Durvalumab 15 mg/kg every 4 weeks plus tremelimumab 1 mg/kg (n=18)	Durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg (n=18)	Durvalumab 10 mg/kg every 2 weeks plus tremelimumab 1 mg/kg (n=17)	Durvalumab 10 mg/kg every 4 weeks plus tremelimumab 3 mg/kg (n=3)	Durvalumab 15 mg/kg every 4 weeks plus tremelimumab 3 mg/kg (n=14)	Durvalumab 20 mg/kg every 4 weeks plus tremelimumab 3 mg/kg (n=6)	Durvalumab 10 mg/kg every 2 weeks plus tremelimumab 3 mg/kg (n=11)	Durvalumab 15 mg/kg every 4 weeks plus tremelimumab 10 mg/kg (n=9)
Age (years)	72·0 (71–78)	67·0 (64–71)	66·5 (53–78)	66·0 (49–78)	70·0 (43–77)	54·0 (54–83)	69·0 (59–76)	70·0 (50–78)	63·0 (22–86)	65·0 (54–77)
Sex										
Male	1 (33%)	2 (67%)	9 (50%)	9 (50%)	8 (47%)	1 (33%)	10 (71%)	3 (50%)	8 (73%)	4 (44%)
Female	2 (67%)	1 (33%)	9 (50%)	9 (50%)	9 (53%)	2 (67%)	4 (29%)	3 (50%)	3 (27%)	5 (56%)
ECOG performance status										
0	0	2 (67%)	5 (28%)	5 (28%)	8 (47%)	2 (67%)	6 (43%)	1 (17%)	1 (9%)	1 (11%)
1	3 (100%)	1 (33%)	13 (72%)	13 (72%)	9 (53%)	1 (33%)	8 (57%)	5 (83%)	10 (91%)	8 (89%)
Histology										
Squamous	1 (33%)	0	1 (6%)	2 (11%)	4 (24%)	0	1 (7%)	0	1 (9%)	0
Non-squamous	2 (67%)	3 (100%)	17 (94%)	16 (89%)	13 (76%)	3 (100%)	13 (93%)	6 (100%)	10 (91%)	9 (100%)
Smoking status										
Never	1 (33%)	0	3 (17%)	0	4 (24%)	1 (33%)	2 (14%)	2 (33%)	3 (27%)	1 (13%)
Current	0	0	0	0	2 (12%)	0	2 (14%)	0	0	0
Former	2 (67%)	3 (100%)	15 (83%)	18 (100%)	11 (65%)	2 (67%)	10 (71%)	4 (67%)	8 (73%)	7 (88%)
Mutation status										
EGFR	0	0	2 (11%)	2 (11%)	4 (24%)	0	1 (7%)	1 (17%)	1 (9%)	2 (22%)
ALK	0	0	0	0	0	0	0	0	1 (9%)	0
KRAS	1 (33%)	1 (33%)	1 (6%)	1 (6%)	2 (12%)	0	2 (14%)	2 (33%)	4 (36%)	3 (33%)
No mutation	0	2 (67%)	14 (78%)	14 (78%)	7 (41%)	3 (100%)	8 (57%)	3 (50%)	5 (45%)	3 (33%)
Other*	0	0	1 (6%)	0	0	0	1 (7%)	0	0	1 (11%)
Unknown	2 (67%)	0	0	1 (6%)	4 (24%)	0	2 (14%)	0	0	0
Lines of previous systemic therapy										
0	0	0	0	1 (6%)	1 (6%)	1 (33%)	1 (7%)	0	2 (18%)	0
1	1 (33%)	0	8 (44%)	9 (50%)	6 (35%)	2 (67%)	5 (36%)	1 (17%)	6 (55%)	2 (22%)
2	0	1 (33%)	7 (39%)	4 (22%)	6 (35%)	0	5 (36%)	1 (17%)	2 (18%)	4 (44%)
3	2 (67%)	1 (33%)	1 (6%)	3 (17%)	2 (12%)	0	1 (7%)	3 (50%)	1 (9%)	2 (22%)
≥4	0	1 (33%)	2 (11%)	1 (6%)	2 (12%)	0	2 (14%)	1 (17%)	0	1 (11%)
PD-L1 status										
Positive	0	0	2 (13%)	6 (43%)	3 (19%)	0	0	3 (50%)	4 (44%)	4 (50%)
Negative	2 (67%)	3 (100%)	12 (75%)	6 (43%)	9 (56%)	3 (100%)	10 (77%)	3 (50%)	4 (44%)	4 (50%)
Unknown	1 (33%)	0	2 (13%)	2 (14%)	4 (25%)	0	3 (23%)	0	1 (11%)	0
Missing	0	0	2	4	1	0	1	0	2	1

Data are number of patients (total %) or median (range). ECOG=Eastern Cooperative Oncology Group. **BRAF* Val600Glu, *EGFR* Asp800Asn and Trp817X (not considered actionable), and *TTF1*.

Table 1: **Baseline characteristics**

Outcomes

The primary endpoint of the dose-escalation phase was safety of durvalumab plus tremelimumab, defined by the maximum tolerated dose or the highest protocol-defined dose in the absence of exceeding the maximum tolerated dose, and tolerability. Secondary endpoints included antitumour activity (defined as an objective response [confirmed complete or partial response]), disease control at 24 weeks (defined as complete or partial response or stable disease for 24 weeks or longer), pharmacokinetic variables (concentration, area under the concentration-time curve, clearance, and half-life of durvalumab and tremelimumab), and immunogenicity (presence of serum antibodies against either drug). Prespecified exploratory endpoints included pharmacodynamic variables—ie, free soluble PD-L1 suppression, and biomarkers assessing the biological activity of durvalumab in combination with tremelimumab. We did a post-hoc analysis of objective response in the *EGFR*/*ALK* wild-type population.

Statistical analysis

The actual number of patients we could enrol was dependent on toxic effects reported as the study progressed.

	Durvalumab 10–20 mg/kg every 2 weeks or 4 weeks plus tremelimumab 1 mg/kg (n=56)*				Durvalumab 10–20 mg/kg every 2 weeks or 4 weeks plus tremelimumab 3 mg/kg (n=34)				Durvalumab 15 mg/kg every 4 weeks plus tremelimumab 10 mg/kg (n=9)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5
Diarrhoea	9 (16%)	4 (7%)	0	0	10 (29%)	6 (18%)	0	0	3 (33%)	1 (11%)	0	0
Colitis	1 (2%)	1 (2%)	0	0	2 (6%)	6 (18%)	0	0	0	1 (11%)	1 (11%)	0
Enteritis	0	1 (2%)	0	0	0	0	0	0	0	0	0	0
Pruritus	11 (20%)	0	0	0	7 (21%)	0	0	0	3 (33%)	0	0	0
Rash	6 (11%)	0	0	0	7 (21%)	0	0	0	2 (22%)	0	0	0
Hypothyroidism	4 (7%)	1 (2%)	0	0	4 (12%)	0	0	0	1 (11%)	0	0	0
Pneumonitis	0	0	0	0	1 (3%)	2 (6%)	0	0	0	2 (22%)	0	0
Rash maculopapular	1 (2%)	0	0	0	2 (6%)	0	0	0	0	1 (11%)	0	0
Amylase increased†	8 (14%)	0	1 (2%)	0	3 (9%)	2 (6%)	0	0	2 (22%)	0	0	0
Lipase increased†	2 (4%)	5 (9%)	0	0	2 (6%)	1 (3%)	1 (3%)	0	0	1 (11%)	0	0
ALT increased	4 (7%)	1 (2%)	1 (2%)	0	3 (9%)	1 (3%)	0	0	0	0	0	0
AST increased	1 (2%)	2 (4%)	1 (2%)	0	2 (6%)	1 (3%)	0	0	0	0	0	0
Blood TSH decreased	2 (4%)	0	0	0	2 (6%)	0	0	0	2 (22%)	0	0	0
Blood creatinine increased	1 (2%)	0	0	0	2 (6%)	0	0	0	1 (11%)	0	0	0
Blood TSH increased	3 (5%)	0	0	0	1 (3%)	0	0	0	1 (11%)	0	0	0
Thyroxine free decreased	2 (4%)	0	0	0	2 (6%)	0	0	0	0	0	0	0

Data are number (%). A patient could be counted under more than one preferred term. Treatment-emergent adverse events occurring in ≥10% of patients and all events of grade 3 or higher are shown in the appendix (pp 3–9). ALT=alanine aminotransferase. AST=aspartate aminotransferase. TSH=thyroid-stimulating hormone. *Three patients who received durvalumab 3 mg/kg every 4 weeks plus tremelimumab 1 mg/kg are excluded because this regimen was judged subtherapeutic. †Amylase and lipase increases were judged adverse events of special interest because they matched criteria for dose-limiting toxicities.

Table 2: **Selected treatment-related adverse events of special interest**

We calculated roughly that up to 118 evaluable patients (78 treated every 4 weeks and 40 treated every 2 weeks) could be enrolled. We based our assessment of maximum tolerated dose on patients who could be assessed for dose-limiting toxicities (appendix p 26). We based our assessment of tolerability on the as-treated population (ie, all patients who received any dose of either study drug). We based our assessment of antitumour activity on the response-evaluable population, who had initiated treatment 24 weeks or more before data cutoff (appendix p 26).

We assessed safety and antitumour activity by individual and combined dose cohorts. Because the safety profile seemed to be driven by the tremelimumab dose (based on the known safety profiles of the single drugs), for clarity, we assessed safety in three combined dose cohorts: durvalumab 10–20 mg/kg every 2 or 4 weeks plus tremelimumab 1 mg/kg; durvalumab 10–20 mg/kg every 2 or 4 weeks plus tremelimumab 3 mg/kg; and durvalumab 15 mg/kg every 4 weeks plus tremelimumab 10 mg/kg. The combined dose cohorts also yielded a larger cohort size compared with the individual cohorts. We excluded the durvalumab 3 mg/kg every 4 weeks plus tremelimumab 1 mg/kg regimen from the combined dose cohort for tremelimumab 1 mg/kg because this regimen was associated with low durvalumab pharmacokinetic exposure and was judged a subtherapeutic durvalumab dose.

We calculated the median duration of response with the Kaplan-Meier method and we calculated 95% CIs with the exact binomial distribution. We estimated objective responses and 95% CIs by PD-L1 status with the exact binomial method. We summarised objective responses and disease control at 24 weeks, including confirmed and unconfirmed complete or partial responses, in a similar way. Immunogenicity results were analysed descriptively by summarising the number and percentage of patients who developed detectable anti-drug antibodies. Pharmacokinetic parameters were estimated by a non-compartmental analysis approach using Phoenix WinNonlin (version 6; Pharsight [Certara], Sunnyvale, CA; appendix p 26). For T-cell proliferation and activation markers measured by flow cytometry, we generated descriptive statistics for each dose group by sample timepoint, and we reported results graphically as mean (SE). We reported free soluble PD-L1 in serum as overlay plots of individual data over time. All other data were analysed with SAS version 9.3.

This study is registered with ClinicalTrials.gov, number NCT02000947.

Role of the funding source

The funder contributed to the design and implementation of the study, data collection, data management, data analysis, data interpretation, and writing of the report. All authors had full access to data used to write the report, and the corresponding author had final responsibility for the decision to submit for publication.

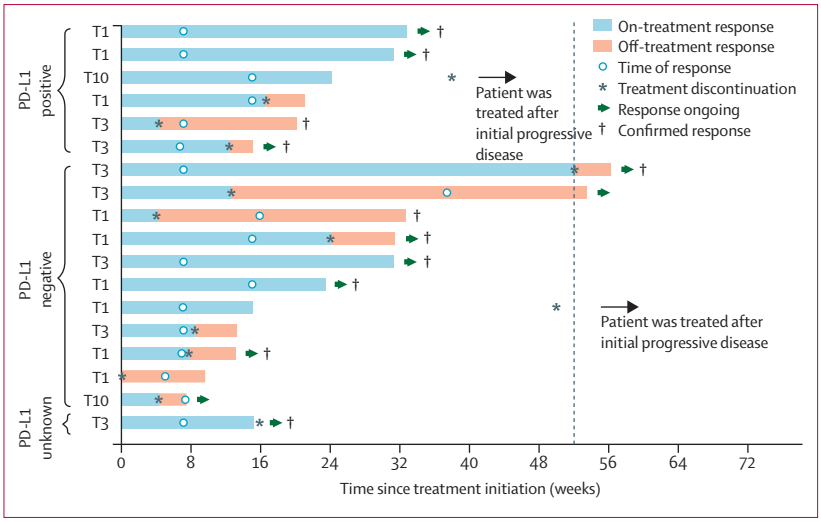

Figure 2: **Time to response and duration of response**
Responses were judged with Response Evaluation Criteria In Solid Tumors, version 1.1. The dotted line represents the maximum duration of treatment (12 months). T1=combined tremelimumab 1 mg/kg cohort. T3=combined tremelimumab 3 mg/kg cohort. T10=tremelimumab 10 mg/kg cohort.

	Durvalumab 10–20 mg/kg every 2 weeks or 4 weeks plus tremelimumab 1 mg/kg*	Durvalumab 10–20 mg/kg every 2 weeks or 4 weeks plus tremelimumab 3 mg/kg	Durvalumab 15 mg/kg every 4 weeks plus tremelimumab 10 mg/kg
All evaluable patients with ≥24 weeks of follow-up			
Objective response	6/26 (23% [9–44])	5/25 (20% [7–41])	0/9 (0% [0–34])
Disease control	9/26 (35% [17–56])	8/25 (32% [15–54])	1/9 (11% [0–48])
PD-L1-positive (≥25%)			
Objective response	2/9 (22% [3–60])	2/5 (40% [5–85])	0/4 (0% [0–60])
Disease control	3/9 (33% [8–70])	2/5 (40% [5–85])	1/4 (25% [1–81])
PD-L1-negative (<25%)			
Objective response	4/14 (29% [8–58])	2/17 (12% [2–36])	0/4 (0% [0–60])
Disease control	6/14 (43% [18–71])	5/17 (29% [10–56])	0/4 (0% [0–60])
PD-L1-negative (0%)			
Objective response	4/10 (40% [12–74])	1/10 (10% [0–45])	0/3 (0% [0–71])
Disease control	5/10 (50% [19–81])	3/10 (30% [7–65])	0/3 (0% [0–71])
PD-L1 status unknown			
Objective response	0/3 (0% [0–71])	1/3 (33% [1–91])	0/1 (0% [0–98])
Disease control	0/3 (0% [0–71])	1/3 (33% [1–91])	0/1 (0% [0–98])

Data are number of patients/total number of patients (% [95% CI]). Objective response includes all confirmed complete and partial responses. Disease control comprises all confirmed complete and partial responses, and stable disease for 24 weeks or longer. Table includes patients with measurable disease at baseline with one or more follow-up scans, and patients who discontinued because of progressive disease or death without any follow-up scan. All patients were treated 24 weeks or more before the cutoff date. *Three patients who received durvalumab 3 mg/kg every 4 weeks and tremelimumab 1 mg/kg are excluded because this regimen was judged subtherapeutic.

Table 3: **Antitumour activity in combined cohorts and by PD-L1 status**

Results

Between Oct 28, 2013, and April 1, 2015, 102 patients from five cancer centres in the USA were recruited into the dose-escalation phase. At data cutoff (June 1, 2015), all patients had received study treatment in the dose-escalation phase and were included in the as-treated population.

Across all dose cohorts, the median duration of follow-up was 18·8 weeks (IQR 11–33) and the median duration of exposure was 11·6 weeks (IQR 7·3–19·0). At data cutoff, four (4%) patients (three with progressive disease before treatment completion and one with an ongoing partial response) had completed 1 year of treatment and were in follow-up and 26 (25%) patients were still on treatment. The primary reasons for ending treatment, as provided by the investigators, were adverse events (27 [26%]), progressive disease (21 [21%]), death (15 [15%]), withdrawal of consent (four [4%]), request by the patient to discontinue (two [2%]), investigator decision (one [1%]), and other reasons (two [2%]). Table 1 shows patients' baseline characteristics.

The maximum tolerated dose was exceeded in the cohort receiving durvalumab 20 mg/kg every 4 weeks plus tremelimumab 3 mg/kg, with two (30%) of six patients having a dose-limiting toxicity (one had grade 3 increased aspartate aminotransferase and alanine aminotransferase and one had grade 4 increased lipase). 82 (80%) of 102 patients had one or more treatment-related adverse events (appendix pp 2–13), the most common of which were diarrhoea (33 [32%]), fatigue (24 [24%]), and pruritus (21 [21%]). One patient in the cohort receiving durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg had a treatment interruption because of an adverse event (grade 2 infusion-related reaction [rigors]). The most common grade 3 or higher treatment-related adverse events were diarrhoea (11 [11%]), colitis (nine [9%]), and increased lipase (eight [8%]; table 2).

Generally, grade 3 or 4 treatment-related adverse events were manageable with standard guidelines; use of immunosuppression drugs in each cohort is shown in the appendix (p 2). 15 (35%) of 43 patients received one or more additional doses of study treatment after the start of the first grade 3 or 4 treatment-related adverse event (adverse events were: increased lipase [n=5]; increased amylase [n=3]; anaemia [n=2]; and increased blood triglycerides, rash maculopapular, lymphocytic hypophysitis, hypothyroidism, diarrhoea, hypotension, and increased blood alkaline phosphatase [each n=1]). Discontinuations attributable wholly or in part to treatment-related adverse events occurred in 29 (28%) of 102 patients (appendix p 10). 37 (36%) of 102 patients had a treatment-related serious adverse event (appendix pp 11, 12).

Based on safety data, in conjunction with available pharmacokinetic, pharmacodynamic, and clinical activity data, durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg was chosen as the expansion phase dose. Of 18 patients in this dose cohort, 11 (61%) had treatment-related adverse events and three (17%) had grade 3 or 4 treatment-related adverse events. The most frequent treatment-related adverse events of any grade in this cohort were pruritus (three [17%]), increased aspartate aminotransferase (two [11%]), diarrhoea (two [11%]), hypothyroidism (two [11%]), and

rash (two [11%]). Six (33%) patients used systemic corticosteroids but none needed additional immunomodulatory agents. Three (17%) patients discontinued because of treatment-related adverse events (grade 4 sepsis, grade 1 pruritus, and grade 5 pericardial effusion; each n=1). 15 (35%) of 43 patients with a grade 3 or 4 treatment-related adverse event received additional study treatment after initial onset of the toxic effect. Two patients received treatment after initial progressive disease, one from the cohort receiving durvalumab 15 mg/kg every 4 weeks plus tremelimumab 10 mg/kg, and one from the cohort receiving durvalumab 15 mg/kg every 4 weeks plus tremelimumab 3 mg/kg (figure 2). Four patients in the cohort receiving durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg had treatment-related serious adverse events: one patient had grade 2 colitis; one patient had grade 4 sepsis, grade 2 depressed level of consciousness, and grade 3 platelet count decreased; one patient had grade 3 asthenia, grade 3 γ-glutamyltransferase increased, grade 3 blood alkaline phosphatase increased, and grade 3 aspartate aminotransferase increased; and one patient had grade 5 pericardial effusion.

22 patients died during the study (appendix p 13) and three deaths were related to treatment (appendix p 2). The treatment-related deaths were due to complications arising from myasthenia gravis (durvalumab 10 mg/kg every 4 weeks plus tremelimumab 1 mg/kg), pericardial effusion (durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg), and neuromuscular disorder (durvalumab 20 mg/kg every 4 weeks plus tremelimumab 3 mg/kg).

63 patients were assessable for tumour response, with 24 weeks or more of follow-up (table 3). 11 (17% [95% CI 9–29]) patients achieved an objective response, and disease control at 24 weeks was achieved in 18 (29% [95% CI 18–41]) patients (figure 2, table 3; appendix pp 14, 15). Among the 11 patients with a confirmed objective response, the median time to response was 7·1 weeks (IQR 7·1–15·0) and the median duration of response was not reached (IQR 16·7–not reached). Response was ongoing in nine of 11 patients at the time of data cutoff; two additional patients with ongoing response were awaiting a confirmatory scan. Of 58 patients in the *EGFR*/*ALK* wild-type population, 11 (19% [95% CI 10–31]) achieved an objective response (post-hoc analysis; appendix p 16).

Objective response and disease control in all cohorts is shown in the appendix (p 14). No responses were reported among patients in the lowest dose cohort (durvalumab 3 mg/kg every 4 weeks plus tremelimumab 1 mg/kg [n=3]), with progression on first scan noted for all patients. Changes from baseline in tumour size in the combined dose cohorts are shown in figure 3.

Prespecified exploratory analyses of antitumour activity seen in subgroups of patients with PD-L1-negative and PD-L1-positive tumours are shown in table 3 and the appendix (pp 14–16, 23, 24).

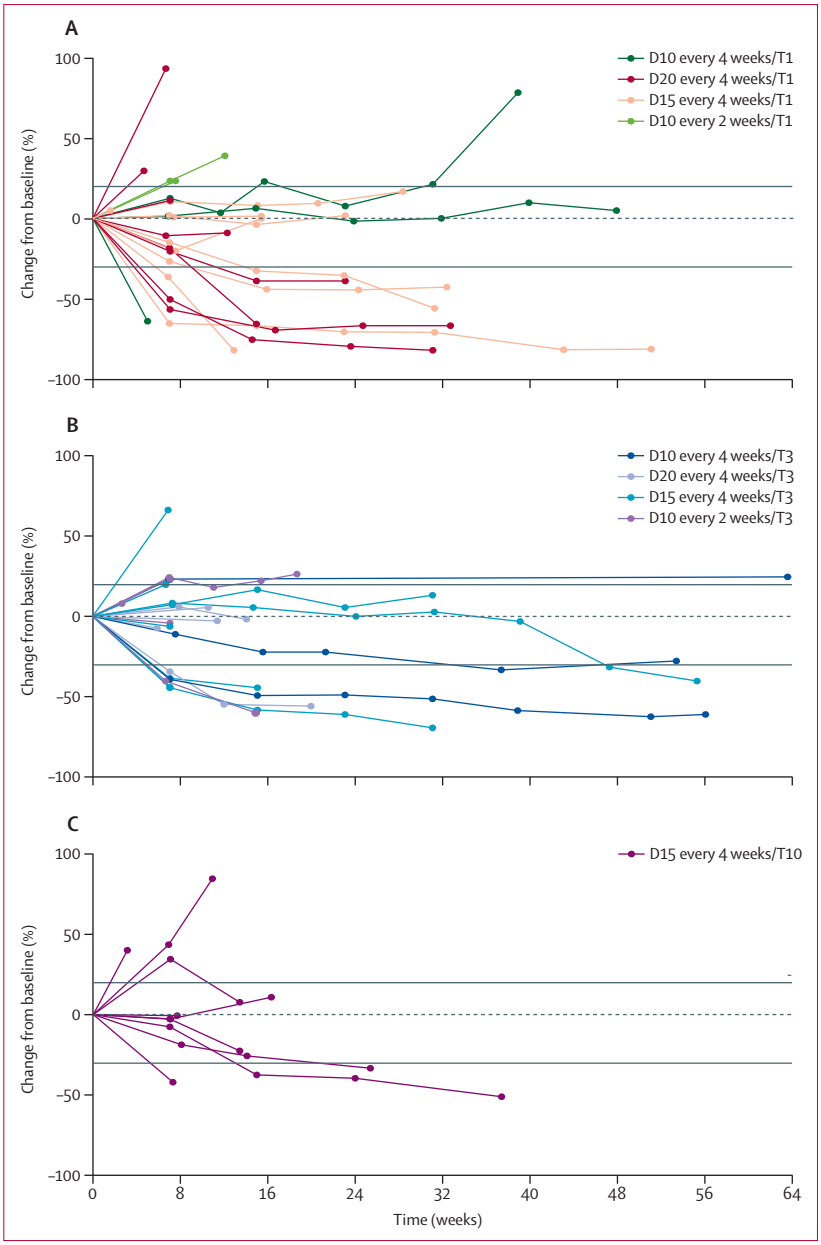

***Figure 3*: Change in tumour size from baseline**
Analysis was done in the response-evaluable population with 24 weeks or longer follow-up. (A) Combined tremelimumab 1 mg/kg cohort. (B) Combined tremelimumab 3 mg/kg cohort. (C) Tremelimumab 10 mg/kg cohort. D10=durvalumab 10 mg/kg. D15=durvalumab 15 mg/kg. D20=durvalumab 20 mg/kg. T1=tremelimumab 1 mg/kg. T3=tremelimumab 3 mg/kg. T10=tremelimumab 10 mg/kg.

The pharmacokinetic profiles of durvalumab and tremelimumab are shown in the appendix (p 19). Durvalumab showed dose-dependent clearance and half-life that are attributed to target-mediated elimination, with saturation of non-linear elimination at doses above 3 mg/kg. The pharmacokinetics of tremelimumab were linear, with an elimination half-life of about 3 weeks and clearance typical of human IgG without target-mediated disposition. Anti-drug

antibodies against durvalumab were noted in four (7%) of 60 patients with available data (two in the cohort receiving durvalumab 15 mg/kg every 4 weeks plus tremelimumab 10 mg/kg; one in the cohort receiving durvalumab 10 mg/kg every 4 weeks plus tremelimumab 3 mg/kg; and one in the cohort receiving durvalumab 15 mg/kg every 4 weeks plus tremelimumab 1 mg/kg) and against tremelimumab in one (2%) of 53 patients with available data (in the cohort receiving durvalumab 15 mg/kg every 4 weeks plus tremelimumab 1 mg/kg). No association was noted between antibodies against either drug and tolerability or antitumour activity (post-hoc analysis; appendix p 27).

Exploratory analysis of free soluble PD-L1 in serum is shown in the appendix (p 20). Exploratory analysis of the association of T cells expressing Ki67 or HLA-DR biomarkers with response is shown in the appendix (pp 21, 22).

Discussion

The findings of our phase 1b study show that the maximum tolerated dose was exceeded with a regimen of durvalumab 20 mg/kg every 4 weeks plus tremelimumab 3 mg/kg. In patients who received treatments containing tremelimumab 1 mg/kg, most adverse events were manageable and did not need treatment discontinuation. Relative to the adverse event profile of the tremelimumab 1 mg/kg combination doses, the tremelimumab 3 mg/kg and tremelimumab 10 mg/kg dose-based combinations had a higher frequency of treatment-related adverse events, grade 3 or 4 adverse events, and serious adverse events, without any increase in clinical activity. Treatment-related adverse events and grade 3 or 4 adverse events were more frequent with durvalumab 10 mg/kg every 2 weeks plus tremelimumab 1 mg/kg than with durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg. The most frequent adverse events were consistent with the known toxicity profiles of durvalumab and tremelimumab. Most adverse events reported were manageable and generally reversible with standard treatment guidelines.

The results of our study are broadly comparable with those of a phase 3 study of nivolumab and ipilimumab in melanoma[5] in terms of the frequency of treatment-related adverse events, the proportion of patients receiving immunomodulatory agents (including topical steroids), and the proportion of patients receiving secondary immunosuppressive agents (eg, infliximab).

Recorded exposures to durvalumab and tremelimumab after concurrent administration were in line with single drug treatment data,[10,12,17,18] and were as predicted by population pharmacokinetic modelling,[19] indicating no pharmacokinetic interaction between the two drugs. Moreover, pharmacokinetic analyses showed that treatment with durvalumab every 4 weeks and every 2 weeks seemed equivalent; the range of concentrations in serum of durvalumab overlapped for 10 mg/kg every 2 weeks and 20 mg/kg every 4 weeks. The overall adverse event profile for durvalumab 20 mg/kg every 4 weeks was previously assessed in a subset of patients in the monotherapy study (NCT01693562)[10] and seemed similar to that for durvalumab 10 mg/kg every 2 weeks. No patient in the durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg cohort developed antibodies against either drug.

Complete suppression of free soluble PD-L1, which is indicative of effective target engagement by durvalumab, was noted in almost all patients. Additionally, combination doses of durvalumab plus tremelimumab showed greater activation and proliferation of peripheral T cells than did durvalumab alone in a separate study,[10] even at the lowest tremelimumab dose (1 mg/kg). Based on the safety profile of the combination of durvalumab plus tremelimumab versus established profiles of the respective single drugs and evidence of enhanced pharmacodynamic activity from exploratory endpoints (eg, enhanced Ki67 indices with the combination versus durvalumab alone), our data suggest that combined CTLA-4 and PD-L1 inhibition is associated with higher biological activity than either drug alone.

Evidence of antitumour activity was seen with the combination of durvalumab plus tremelimumab in our study irrespective of PD-L1 status. An objective response was achieved by 5% of NSCLC patients with PD-L1-negative tumours receiving durvalumab 10 mg/kg every 2 weeks in another trial.[10] Although the number of assessable patients in every subgroup was low, our data suggest that PD-L1 status might not predict response to durvalumab plus tremelimumab to the same extent as has been seen with durvalumab treatment alone. This observation also suggests that additional factors beyond PD-L1 have a role in suppressing an active immune response. It is possible that, in such patients, tremelimumab removes a suppressive effect to drive an antitumour response. A larger study would be needed to confirm that CTLA-4 drives immune escape in this context. The antitumour activity of durvalumab plus tremelimumab seems to be higher than that of treatment with either drug alone,[10,17] most likely because durvalumab and tremelimumab affect distinct targets that act on different aspects of the antitumour immune response. Previous studies in NSCLC and other tumour types have also indicated that combined blockade of PD-1 and CTLA-4 is associated with higher clinical activity than single drug treatment.[5,6,20–22] The present study is currently being expanded to further assess the clinical activity of this drug combination. If confirmed, the combination of durvalumab plus tremelimumab could be a potential novel therapeutic option for patients with PD-L1-negative tumours, a subset who are not expected to derive substantial benefit from current anti-PD-1/PD-L1 drugs.

Although the number of patients in every cohort is small, the results of our study suggest that toxic effects, but not antitumour activity, increase with rising doses of tremelimumab. However, no differences in toxic effects among different durvalumab doses with a constant dose of tremelimumab were noted. Because no pharmacological limitations were evident with dosing every 4 weeks, and the pharmacokinetic profiles recorded with durvalumab 20 mg/kg every 4 weeks and durvalumab 10 mg/kg every 2 weeks were equivalent, dosing every 4 weeks was selected for the phase 3 dose for patients' convenience. Previous data show that durvalumab has non-linear pharmacokinetics at doses less than 3 mg/kg and approaches linearity at doses of 3 mg/kg or higher, indicating full target saturation.[23] Moreover, pharmacokinetic simulations suggest that, after durvalumab 10 mg/kg every 2 weeks or durvalumab 20 mg/kg every 4 weeks, 90% or more of patients achieve target trough concentrations throughout the dosing interval.[19] The durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg regimen has, therefore, been selected for assessment in phase 3 studies. This dose maximises inhibition of free soluble PD-L1, has a manageable safety profile, and incorporates a biologically active dose of tremelimumab that is associated with antitumour activity, including in patients with PD-L1-negative tumours.

A limitation of our study was the heterogeneous population, both overall and within the combined cohorts (eg, the number of previous lines of therapy, tumour mutation status, and smoking history were not equal across cohorts). Moreover, antitumour activity was only assessed in patients who had initiated treatment 24 weeks or more before data cutoff and, thus, activity might have been underestimated because of the short follow-up time. However, in our experience, most patients respond to treatment within this period, which also accords with experience with PD-1/PD-L1-based therapies.[24–26] A longer follow-up period would be needed to establish effects on survival. However, our current data suggest that although adverse events might have been underestimated because of the short follow-up time, most patients who have treatment-related grade 3 or 4 adverse events report them within the first few months after treatment initiation. Because our study did not include treatment with durvalumab or tremelimumab alone, comparisons with single drug data are based on findings of other studies.

In conclusion, the tolerability profile and antitumour activity of the combination of durvalumab plus tremelimumab reported both in PD-L1-positive and PD-L1-negative patients in the dose-escalation phase of this study indicate that 1 mg/kg tremelimumab is sufficient to augment the biological and antitumour activity of durvalumab. Enrolment has begun for the dose-expansion phase of this study to assess the selected combination regimen (durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg). Moreover, phase 2 and 3 studies have been initiated of this dose regimen in patients with NSCLC (NCT02352948, NCT02453282, and NCT02542293), bladder cancer (NCT02516241), and squamous cell carcinoma of the head and neck (NCT02319044, NCT02369874, and NCT02551159).

Contributors

SA, JEC, AG, JJK, KS, and NAR designed the study. SA and NAR were responsible for enrolment and management of patients. SA, SBG, AB, RES, AG, JJK, RN, KS, and YG contributed to data collection and interpretation. SA, SBG, AB, AG, RN, YG, and JJK wrote the report. AG and JJK did the literature search. RN and YG developed the figures.

Declaration of interests

SA has served on advisory boards for MedImmune and AstraZeneca during this study; and has received a grant from the National Institutes of Health (NIH) during this study. SBG has received research funding from AstraZeneca and Boehringer Ingelheim outside the submitted work; and has served on advisory boards for Clovis outside the submitted work. AB has received financial support to run clinical trials from Genentech, Incyte, MedImmune, and Merck during this study; and has received fees for participation in speaker bureaus from Bristol-Myers Squibb and Merck during this study. JEC's institution has received financial clinical trial support from AstraZeneca and MedImmune during this study; and JEC has received personal fees for advisory board membership from Genentech during this study. NAR has received personal fees from AstraZeneca, Bristol-Myers Squibb, Roche, Novartis, and Merck outside the submitted work. AG, KS, YG, JJK, and RN are employees of MedImmune and own stock or options in AstraZeneca. YG was previously an employee of Boehringer Ingelheim. JJK is also an employee of MedStar Montgomery Medical Center and Fauquier Hospital. KS has a provisional patent application related to this work. RES declares no competing interests.

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