Pegilodecakin combined with pembrolizumab or nivolumab for patients with advanced solid tumours (IVY): a multicentre, multicohort, open-label, phase 1b trial

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Summary

Background IL-10 has anti-inflammatory and CD8+ T-cell stimulating activities. Pegilodecakin (pegylated IL-10) is a first-in-class, long-acting IL-10 receptor agonist that induces oligoclonal T-cell expansion and has single-agent activity in advanced solid tumours. We assessed the safety and activity of pegilodecakin with anti-PD-1 monoclonal antibody inhibitors in patients with advanced solid tumours.

Methods We did a multicentre, multicohort, open-label, phase 1b trial (IVY) at 12 cancer research centres in the USA. Patients were assigned sequentially into cohorts. Here, we report on all enrolled patients from two cohorts treated with pegilodecakin combined with anti-PD-1 inhibitors. Eligible patients were aged at least 18 years with histologically or cytologically confirmed advanced malignant solid tumours refractory to previous therapies, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients with uncontrolled infectious diseases were excluded. Pegilodecakin was provided in single-use 3 mL vials and was self-administered subcutaneously by injection at home at 10 µg/kg or 20 µg/kg once per day in combination with pembrolizumab (2 mg/kg every 3 weeks or 200 mg every 3 weeks) or nivolumab (3 mg/kg every 2 weeks or 240 mg every 2 weeks or 480 mg every 4 weeks at the approved dosing), both of which were given intravenously at the study site. Patients received pembrolizumab or nivolumab with pegilodecakin until disease progression, toxicity necessitating treatment discontinuation, patient withdrawal of consent, or study end. The primary endpoints were safety and tolerability, assessed in all patients enrolled in the study who received any amount of study medication including at least one dose of pegilodecakin, and pharmacokinetics (previously published). Secondary endpoints included objective response by immune-related response criteria in all patients who were treated and had evaluable measurements. The study is active but no longer recruiting, and is registered with ClinicalTrials.gov, NCT02009449.

Findings Between Feb 13, 2015, and Sept 12, 2017, 111 patients were enrolled in the two cohorts. 53 received pegilodecakin plus pembrolizumab, and 58 received pegilodecakin plus nivolumab. 34 (31%) of 111 patients had non-small-cell lung cancer, 37 (33%) had melanoma, and 38 (34%) had renal cell carcinoma; one (<1%) patient had triple-negative breast cancer and one (<1%) had bladder cancer. Data cutoff was July 1, 2018. Median follow-up was 26·9 months (IQR 22·3–31·5) for patients with non-small-cell lung cancer, 33·0 months (29·2–35·1) for those with melanoma, and 22·7 months (20·9–27·0) for those with renal cell carcinoma. At least one treatment-related adverse event occurred in 103 (93%) of 111 patients. Grade 3 or 4 events occurred in 73 (66%) of 111 patients (35 [66%] of 53 in the pembrolizumab group and 38 [66%] of 58 in the nivolumab group), the most common of which were anaemia (12 [23%] in the pembrolizumab group and 16 [28%] in the nivolumab group), thrombocytopenia (14 [26%] in the pembrolizumab group and 12 [21%] in the nivolumab group), fatigue (11 [21%] in the pembrolizumab group and 6 [10%] in the nivolumab group) and hypertriglyceridaemia (three [6%] in the pembrolizumab group and eight [14%] in the nivolumab group). There were no fatal adverse events determined to be related to the study treatments. Of the patients evaluable for response, objective responses were 12 (43%) of 28 (non-small-cell lung cancer), three (10%) of 31 (melanoma), and 14 (40%) of 35 (renal cell carcinoma).

Interpretation In this patient population, pegilodecakin with anti-PD-1 monoclonal antibodies had a manageable toxicity profile and preliminary antitumour activity. Pegilodecakin with pembrolizumab or nivolumab could provide a new therapeutic opportunity for previously treated patients with renal cell carcinoma and non-small-cell carcinoma.

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Research in context

Evidence before this study

We searched PubMed on April 9, 2019, without any date restrictions for studies with the terms "phase 1" [All fields] AND "cancer" [All fields] AND "IL-10" [All fields] with no restriction on language. 19 studies were identified from this search. We then restricted the search to clinical trials; six were identified. After further restriction of the search to clinical trials published within the previous 5 years, three were identified published between 2014 and 2019. Of these, one publication discussed nivolumab in patients with advanced melanoma, in which pretreatment serum IL-10 concentrations were higher in patients with objective tumour responses than in those with tumour progression. A second publication discussing relapsed lymphoma of the central nervous system showed that the change in cerebrospinal fluid IL-10 correlated with clinical benefit and response duration. We then searched PubMed with the terms "IL-10 receptor" [All fields] AND "anti-PD-1" [All fields] between the same dates with no restriction on language, and identified three results. One of these publications was within the last 5 years and discussed the novel strategy of enhanced immunotherapy by a combining IL-10 and PD-1. The rationale was that complement-mediated inhibition of antitumour immunity is not affected by the PD-1 pathway. Therefore, incorporating IL-10 with the tumour-infiltrating lymphocytes was hypothesised to improve their antitumour activity. NKTR-214 (a pegylated cytokine that binds to the IL-2 receptor) showed preclinical activity in solid tumours. However, to our knowledge, there are no other clinical stage-IL-10 analogues in development.

Added value of this study

This is the first clinical study to our knowledge to report results in patients with advanced solid tumours given the first-in-class, pegylated IL-10 cytokine (pegilodecakin) in combination with the anti-PD-1 drugs nivolumab or pembrolizumab in patients with renal cell carcinoma, non-small-cell lung cancer, and melanoma. The novel mechanism of action that leads to the clonal T-cell expansion is associated with durable responses, especially in patients with non-small-cell lung cancer and renal cell carcinoma.

Implications of all the available evidence

This phase 1b study presented the safety and activity profile of the combination of pegilodecakin plus anti-PD-1 antibodies for patients with advanced solid tumours. Overall, these data support further investigation of pegilodecakin and anti-PD-1 as therapy in patients with metastatic renal cell carcinoma and non-small-cell lung cancer, but not in melanoma.

Introduction

Immune checkpoint inhibitors have shown promise in the treatment of patients with advanced malignancies.[1] One class of immune checkpoint inhibitors targets PD-1 expressed on activated T cells, which downregulates excessive immune responses through binding to the ligands PD-L1 and PD-L2.[2,3] Anti-PD-1 therapeutic antibodies have shown clinical activity in advanced solid tumours, such as non-small-cell lung cancer, melanoma, and renal cell carcinoma.[4,5] Between December, 2014, and November, 2015, the anti-PD-1 monoclonal antibody nivolumab has been approved by the US Food and Drug Administration for the treatment of patients with advanced melanoma, lung cancer, and metastatic renal cell carcinoma. Pembrolizumab is another approved anti-PD-1 antibody that has a manageable safety profile and showed antitumour activity in solid tumour malignancies.[6,7] In the KEYNOTE-001, KEYNOTE-002, and KEYNOTE-029 studies, pembrolizumab was well tolerated and had promising clinical activity in previously treated patients with non-small-cell lung cancer, melanoma, and renal cell carcinoma, respectively.[8-10] However, despite progress there still remains substantial unmet need in the treatment of advanced solid tumours.[11,12]

Human IL-10 is produced by several immune cells and has a substantial role in reducing inflammation. Some study findings have suggested therapeutic opportunities for targeting IL-10 receptors.[13] However, IL-10 has a short half-life in vivo.[14] Pegylation of IL-10 leads to the product pegilodecakin, which retains agonism at the IL-10 receptor.[15] N-terminal pegylation provides an increased serum half-life, allowing for once-daily subcutaneous administration of pegilodecakin and sustained systemic exposure.[15] In animal models, pegilodecakin induced amplification of intratumoural CD8+ T cells, resulting in cures and long-term immune memory against rechallenge with the same tumour.[16]

Pegilodecakin has single-agent activity in patients with advanced solid tumours,[15] and pegilodecakin monotherapy or in combination with anti-PD-1 leads to reinvigoration, proliferation, and expansion of antigen-experienced PD-1+ Lag-3+ CD8+ cytotoxic T cells and expansion of novel CD8+ T-cell clones.[17] We explored the combination of pegilodecakin with anti-PD-1 monoclonal antibodies with the primary objective of examining safety and activity. This study was designed to assess and characterise the safety, tolerability, and pharmacokinetics of pegilodecakin that were established in preclinical animal studies, whether they can be transferrable to humans, and whether pegilodecakin would decrease disease-associated biomarkers.

Methods

Study design and participants

We did a multicentre, multicohort, open-label, dose-escalation, phase 1b study at 12 cancer research centres in the USA (IVY; details of all cohorts are in the appendix p 13). Study inclusion criteria were male or female

See Online for appendix

patients aged at least 18 years, with histologically or cytologically confirmed advanced malignant solid tumours refractory to previous therapies; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; at least one measurable lesion per the immune-related response criteria method;[18] life expectancy of more than 16 weeks per investigator opinion; women of childbearing age must have a negative pregnancy test at study entry and bi-weekly or monthly tests thereafter; willingness and ability to comply with study requirements; and adequate organ function. Patients with immune-mediated inflammatory diseases were not excluded, except patients with previous Guillain-Barré syndrome or neuroinflammatory conditions. Patients with uncontrolled infectious diseases were excluded. Investigators at the centres with ethical approval of the protocol approached potential study candidates for consent for screening and subsequent patients were treated per protocol. The study protocol (in appendix) was reviewed and approved by the Institutional Review Board at participating sites (appendix p 229). All patients gave written informed consent for the study.

Procedures

Patients in IVY were assigned sequentially into cohorts. This report discusses results from two patient cohorts who received anti-PD-1 inhibitors. Patients in one cohort received pembrolizumab with pegilodecakin, and patients in the second cohort received nivolumab with pegilodecakin. All treatments were given in an outpatient setting. At baseline, all patients underwent baseline investigations, including physical examination, ECOG performance status, electrocardiogram (ECG), CT or MRI of sites of disease, laboratory assessments, serum and pharmacokinetic samples for analysis, and listing of concomitant medications. Pegilodecakin (manufactured by Cytovance Biologics, Oklahoma City, OK, USA, on behalf of ARMO BioSciences, a wholly owned subsidiary of Eli Lilly and Company) was provided in single-use 3 mL vials and self-administered subcutaneously once per day via injection at home. Adherence was monitored via patient diary. In the dose-escalation phase of the study, pegilodecakin 10 µg/kg and 20 µg/kg were explored in combination with either pembrolizumab (2 mg/kg every 3 weeks) or with nivolumab (3 mg/kg every 2 weeks), pembrolizumab and nivolumab were both given intravenously at the study site. In this study, six patients received pegilodecakin 10 µg/kg and 32 patients received 20 µg/kg. The monotherapy phase 2 dose was 20 µg/kg per day, some patient cohorts were initially treated at 10 µg/kg/day then escalated to 20 µg/kg per day, which was used for the expansion cohorts.

Per the amended guidelines, pembrolizumab was originally dosed at 2 mg/kg every 3 weeks, which was later changed to flat dosing of 200 mg every 3 weeks, and nivolumab was used at the dose approved in the product label, initially 3 mg/kg up until September, 2016, and thereafter at the pharmacokinetically equivalent dose of 240 mg flat dose every 2 weeks or 480 mg every 4 weeks at the approved dosing. Pembrolizumab and nivolumab were dosed according to FDA guidelines. For nivolumab, the FDA introduced modification to 240 mg intravenously per week on Sept 13, 2016.

Published pharmacokinetic and pharmacodynamic data[15,17] suggest that both dosing schedules achieved serum concentrations close to target saturation; therefore, the dosing regimen was not changed in this study. Patients received pembrolizumab or nivolumab with pegilodecakin until disease progression (ie, immune-related progressive disease), toxicity necessitating treatment discontinuation, patient withdrawal of consent, or study end. Patients continued to receive combination therapy or pegilodecakin monotherapy after confirmed immune-related progressive disease in the absence of clinical deterioration and if the investigator judged that the patient continued to receive benefit from the treatment. Dose interruptions were allowed, but dose reductions were allowed only for pegilodecakin. Interruptions lasting more than 6 weeks resulted in discontinuation from the study, except dose interruptions to allow for prolonged steroid tapers to manage drug-related adverse events or dose interruptions for more than 6 weeks that occurred because of non-drug-related reasons if approved by the study's medical monitor. If the anti-PD-1 therapy was interrupted or discontinued because of toxicities, treatment continuation of pegilodecakin was allowed.

Throughout the study, performance status, complete blood counts, and clinical laboratory chemistry tests were recorded every 8 weeks. Tumour assessment by CT, MRI, and CT with contrast occurred every 8 weeks in the nivolumab cohort and every 8 weeks in the pembrolizumab cohort, following the recommended dosing schedule, as assessed by the investigator. Responses were assessed according to the immune-related response criteria method.[18] Adverse events, serious adverse events, and laboratory abnormalities were graded and recorded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03; included toxicity grade rating, concomitant medications, ECG, haematology, physical examination, serum chemistry, urinalysis, and vital signs; and were monitored until 30 days after the last dose of treatment. In the case of toxicities, subsequent treatment cycles were delayed until toxicities were less than grade 1. NCI CTCAE version 4.03 was used to grade and report treatment-related adverse events. Number and percentage of patients who had treatment-related adverse events were reported by system organ class and preferred name and at highest grade. Adverse events were coded using the Medical Dictionary for Regulatory Activities version 16.1. Immunological assessment included blood T-cell receptor sequencing for T-cell clonality assessment (done by

Adaptive Biotechnologies, Seattle, WA, USA).[17] The assay quantified individual (clonal) T-cell receptor sequences in the blood of patients, comparing the frequency of each T-cell clone in the blood of a patient before study day 1 and during therapy. PD-L1 staining and scoring for non-small-cell lung cancer samples were done by PhenoPath (Seattle, WA, USA). Scoring reflected pharm DX/22C3 assay results. For renal cell carcinoma samples, PD-L1 expression was analysed with ARMO BioSciences (Redwood City, CA, USA) immunohistochemical assay using anti-PD-1 antibody clone SP142, with a cutoff of more than 1% infiltrating cells. PD-L1 correlative analyses were done by ARMO BioSciences.

Outcomes

The primary outcome of the study was to characterise the safety, tolerability, maximal tolerated dose, and pharmacokinetics of pegilodecakin in patients after daily subcutaneous administrations in combination with pembrolizumab or nivolumab. The maximal tolerated dose and preliminary pharmacokinetic data has previously been published;[15] full population pharmacokinetic analysis is not yet available. Secondary endpoints were to measure tumour responses by immune-related response criteria (the proportion of patients who achieved an objective response was defined as the percentage of patients with a complete response and a partial response) and to assess the formation of anti-pegilodecakin antibodies (results not available; data are being collected and will be analysed in due course). Exploratory objectives, prespecified in the protocol, were to investigate biomarkers (ie, genetic analysis, serum chemokines, and tumor antigen specific immune responses) for patient stratification and treatment response including evaluation of T-cell responses as surrogates for antitumour activity of pegilodecakin.

Statistical analysis

No formal sample size calculation was done for this study; the cohort size was agreed upon by the FDA, and investigators assessed clinically meaningful activities. Safety analyses were based on the safety population, which included all patients enrolled in the study who received any amount of study medication, including at least one dose of pegilodecakin. The response population (or evaluable population), consisted of all patients who were treated and had an adequate baseline tumour measurement and at least one adequate postbaseline measurement. The protocol did not prespecify that findings from the cohorts be reported together or separately. Adverse events were assessed in the safety population.

Response analyses were done based on the evaluable population. The disease control rate was defined as the percentage of patients with a complete response, partial response, and stable disease. Based on the safety population, overall survival was defined as the time from

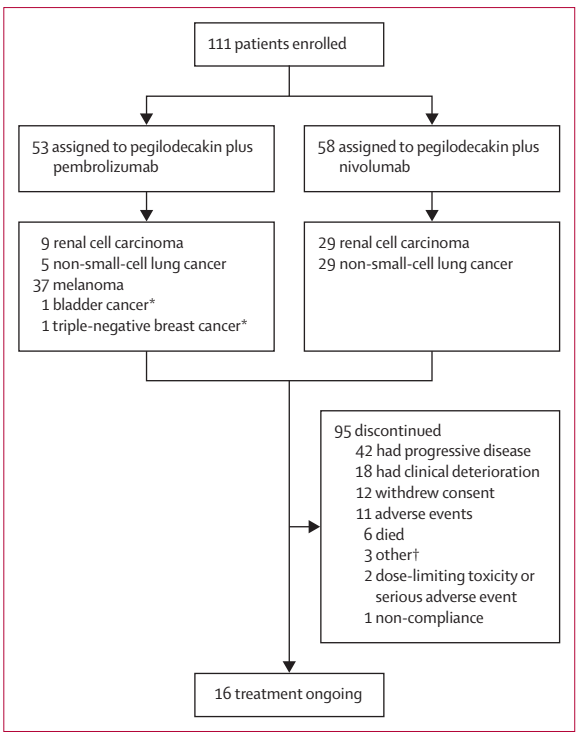

Figure 1: **Trial profile**
irRC=immune-related response criteria. *Only one patient with bladder cancer and one patient with triple-negative breast cancer enrolled, therefore recruitment to the breast and bladder cancer subcohorts were stopped. †One each of maximum benefit received. Treating physician/co-investigator noted progression of pulmonary metastasis, although overall irRC evaluation was stable, and took the patient off study due to progressing lesions; disease progression, anaemia, generalised deconditioning.

	Renal cell carcinoma (n=38)	Non-small-cell lung cancer (n=34)	Melanoma (n=37)	Triple-negative breast cancer (n=1)	Bladder cancer (n=1)
Pembrolizumab	9 (24%)	5 (15%)	37 (100%)	1 (100%)	1 (100%)
Nivolumab	29 (76%)	29 (85%)	0	0	0
Age, years	66 (51–69)	67 (56–74)	59 (50–68)	68 (NA)	74 (NA)
Sex					
Male	27 (71%)	18 (53%)	18 (49%)	0	1 (100%)
Female	11 (29%)	16 (47%)	19 (51%)	1 (100%)	0
ECOG performance status					
0	12 (32%)	8 (24%)	25 (68%)	0	0
1	26 (68%)	26 (77%)	12 (32%)	1 (100%)	1 (100%)
Histology					
Squamous (non-small-cell lung cancer)	NA	6 (18%)	NA	NA	NA
Non-squamous (non-small-cell lung cancer)	NA	27 (79%)	NA	NA	NA
Unknown (non-small-cell lung cancer)	NA	1 (3%)	NA	NA	NA
Clear cell	30 (79%)	NA	NA	NA	NA

(Table 1 continues on next page)

	Renal cell carcinoma (n=38)	Non-small-cell lung cancer (n=34)	Melanoma (n=37)	Triple-negative breast cancer (n=1)	Bladder cancer (n=1)
(Continued from previous page)					
Papillary	6 (16%)	NA	NA	NA	NA
Invasive ductal carcinoma	NA	NA	NA	1 (100%)	NA
Poorly differentiated invasive urothelial carcinoma of the bladder	NA	NA	NA	NA	1 (100%)
Not reported	1 (3%)	NA	NA	NA	NA
Translocation	1 (3%)	NA	NA	NA	NA
Current TNM stage					
III	1 (3%)	0	0	0	0
IV	37 (97%)	34 (100%)	36 (97%)	1 (100%)	1 (100%)
Other	0	0	1 (3%)	0	0
Previous cancer therapies					
0	5 (13%)*	3 (9%)	3 (8%)	0	0
≥1	32 (84%)†	31 (91%)	34 (92%)	1 (100%)	1 (100%)
NA	1 (3%)	0	0	0	0
No previous PD-1 therapy	37 (97%)	34 (100%)	12 (32%)	0	0
Race					
White	31 (82%)	27 (79%)	36 (97%)	1 (100%)	1 (100%)
Black	2 (5%)	1 (3%)	1 (3%)	0	0
Asian	1 (3%)	5 (15%)	0	0	0
Other	4 (11%)	1 (3%)	0	0	0
Disease site at diagnosis					
Bone	8 (21%)	6 (18%)	2 (5%)	0	0
CNS	1 (3%)	2 (6%)	0	0	0
Distant lymph nodes	8 (21%)	9 (27%)	6 (16%)	1 (100%)	0
Kidney	33 (87%)	1 (3%)	1 (3%)	0	0
Liver	2 (5%)	6 (18%)	4 (11%)	0	0
Lung	12 (32%)	33 (97%)	8 (22%)	0	0
Pancreas	0	0	1 (3%)	0	0
Skin	0	0	19 (51%)	0	0
Peritoneum	0	1 (3%)	0	0	0
Other	7 (18%)	5 (15%)	14 (38%)	0	1 (100%)
IMDC risk category					
Favourable	6 (16%)	NA	NA	NA	NA
Intermediate	29 (76%)	NA	NA	NA	NA
Poor	3 (8%)	NA	NA	NA	NA

Data are median (IQR) or n (%). NA=not applicable. ECOG=Eastern Cooperative Oncology Group. TNM=tumour, node, metastases. IMDC=International Metastatic Renal Cell Carcinoma Database Consortium Criteria. *Six patients did not have previous antiangiogenic therapy and were excluded from the outcome analysis but included in the safety analysis. †Two patients with previous pegilodecakin monotherapy included in the safety analysis but not the outcome analysis.

Table 1: **Baseline characteristics**

the first dose of study drug to the date of death from any cause, and progression-free survival was calculated from the date of the first dose of study drug to the date of progression or death from any cause. These estimates were done post-hoc and determined using the Kaplan-Meier method. Exploratory endpoints included changes in immune parameters, including serum chemokines, and T-cell responses as surrogates for anti-tumour activity of pegilodecakin. Pre-specified exploratory analysis of clonal T-cell expansion was assessed by comparing the T-cell repertoire by deep sequencing the peripheral blood samples taken from patients before and during treatment. To further understand the clonal T-cell response, we assessed the number of T-cell clones that changed more than ten times from the baseline value (as a percentage of all T cells in the blood). Post-hoc tumour mutational burden analyses were done by Translational Bioscience (Sunnyvale, California, USA) and analysed by ARMO BioSciences. Exploratory biomarker and disease group statistical analyses were done post-hoc by previous therapy (renal cell carcinoma), PD-L1 expression (non-small cell lung cancer), and whether or not PD-1 refractory (melanoma). The relationship between T-cell clonal expansion and overall survival by Pearson correlation was a post-hoc exploratory analysis.

The results for all endpoints were reported descriptively. No statistical hypothesis testing or inferential analysis were done for this study. Categorical variables were reported as counts and percentages, and continuous variables were reported as median (range or IQR) or mean (SD), as appropriate. Analyses were done using SAS (version 9.4) or a more recent version. This study is registered with ClinicalTrials.gov, NCT02009449.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Feb 13, 2015, and Sept 12, 2017, 111 patients were enrolled and treated with pegilodecakin combined with either pembrolizumab (53 patients) or nivolumab (58 patients). The cohort that received pegilodecakin plus pembrolizumab comprised nine patients with renal cell carcinoma, five with non-small-cell lung cancer, 37 with melanoma, one with bladder cancer, and one with triple-negative breast cancer. The cohort that received pegilodecakin plus nivolumab comprised 29 patients with non-small-cell lung cancer and 29 with renal cell carcinoma (figure 1). The 34 patients with non-small-cell lung cancer, 37 with melanoma, and 38 with renal cell carcinoma are further described in this report. Information on the one patient with triple-negative breast cancer and one with bladder cancer is in the appendix (p 2). Most patients had at least one previous therapy (table 1; details on previous therapies are in the appendix pp 3–5). Of 37 patients with melanoma, 25 (68%) were refractory to previous anti-PD-1 and anti-CTLA-4 therapy. No patients with non-small-cell lung cancer had received previous anti-PD-1 therapy. No patients with non-small-cell lung cancer or melanoma had previous pegilodecakin therapy. Two (5%) of

38 patients with renal cell carcinoma had received previous pegilodecakin monotherapy (one patient had a partial response, and one patient had stable disease for 19 weeks) in an earlier cohort of the trial.[15] 12 (32%) of 38 patients with renal cell carcinoma had a PD-L1 score of less than 1% (data not shown).

	Renal cell carcinoma (n=38)			Non-small-cell lung cancer (n=34)			Melanoma (n=37)		
	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4
All	11 (29%)	20 (53%)	6 (16%)	5 (15%)	20 (59%)	3 (9%)	13 (35%)	19 (51%)	4 (11%)
Blood and lymphatic system disorders									
Anaemia	11 (29%)	10 (26%)	0	6 (18%)	9 (27%)	0	12 (32%)	8 (22%)	1 (3%)
Histiocytosis haematophagic	1 (3%)	0	1 (3%)	0	0	0	1 (3%)	0	0
Leukopenia	0	1 (3%)	0	0	0	0	3 (8%)	0	0
Neutropenia	0	3 (8%)	0	1 (3%)	0	0	1 (3%)	0	0
Splenomegaly	2 (5%)	0	1 (3%)	0	0	0	0	0	0
Thrombocytopenia	8 (21%)	6 (16%)	2 (5%)	5 (15%)	7 (21%)	1 (3%)	9 (24%)	7 (19%)	2 (5%)
Gastrointestinal disorders									
Autoimmune hepatitis	0	1 (3%)	0	0	1 (3%)	0	0	0	0
Nausea	5 (13%)	0	0	1 (3%)	0	0	10 (27%)	1 (3%)	0
Vomiting	5 (13%)	0	0	1 (3%)	0	0	7 (19%)	0	0
Colitis	0	0	0	0	0	0	0	1 (3%)	0
Diarrhoea	3 (8%)	0	0	1 (3%)	2 (6%)	0	5 (14%)	0	0
General disorders and administration site conditions									
Chills	5 (13%)	0	0	3 (9%)	0	0	7 (19%)	0	0
Fatigue	14 (37%)	1 (3%)	0	8 (24%)	6 (18%)	0	18 (49%)	10 (27%)	0
Malaise	2 (6%)	0	1 (3%)	0	0	0	0	0	0
Oedema peripheral	1 (3%)	1 (3%)	0	0	0	0	3 (8%)	1 (3%)	0
Pyrexia	13 (34%)	0	0	8 (24%)	1 (3%)	1 (3%)	9 (24%)	0	0
Hypothyroidism	2 (6%)	1 (3%)	0	2 (6%)	0	0	1 (3%)	0	0
Influenza-like illness	1 (3%)	0	0	0	0	0	6 (16%)	0	0
Injection-site reaction	1 (3%)	0	0	3 (9%)	0	0	7 (19%)	0	0
Asthenia	0	0	0	1 (3%)	0	0	4 (11%)	0	0
Investigations									
Amylase increased	0	2 (5%)	1 (3%)	0	0	0	1 (3%)	0	0
Alanine aminotransferase increased	5 (13%)	2 (5%)	0	0	1 (3%)	0	4 (11%)	1 (3%)	0
Aspartate aminotransferase increased	7 (18%)	2 (5%)	0	0	1 (3%)	0	3 (8%)	2 (5%)	0
γ-glutamyltransferase increased	0	1 (3%)	0	1 (3%)	0	0	3 (8%)	0	0
Lipase increased	3 (8%)	1 (3%)	1 (3%)	0	0	1 (3%)	1 (3%)	0	1 (3%)
Serum ferritin increased	4 (11%)	0	0	0	0	0	0	0	0
Weight decreased	3 (8%)	0	0	0	0	0	2 (5%)	0	0
Blood bilirubin increased	1 (3%)	0	0	1 (3%)	0	0	3 (8%)	1 (3%)	0
Lipids decreased	0	0	0	0	0	0	0	1 (3%)	0
Platelet count decreased	11 (29%)	2 (5%)	0	5 (15%)	1 (3%)	0	4 (8%)	3 (8%)	0
Metabolism and nutrition disorders									
Hypertriglyceridaemia	8 (21%)	5 (13%)	1 (3%)	4 (12%)	3 (9%)	0	11 (30%)	2 (5%)	0
Hyperuricaemia	0	0	1 (3%)	0	0	0	0	0	0
Decreased appetite	4 (11%)	0	0	7 (21%)	0	0	13 (35%)	1 (3%)	0
Hypolipidaemia	0	0	0	0	0	0	0	1 (3%)	0
Hyperglycaemia	3 (8%)	0	0	0	0	0	4 (11%)	0	0
Musculoskeletal and connective tissue disorders									
Arthralgia	5 (13%)	0	0	3 (9%)	0	0	0	0	0
Muscular weakness	0	1 (3%)	0	1 (3%)	0	0	1 (3%)	0	0
Myalgia	7 (18%)	0	0	4 (12%)	0	0	3 (8%)	0	0
Vasculitis	0	1 (3%)	0	0	0	0	0	0	0

(Table 2 continues on next page)

	Renal cell carcinoma (n=38)			Non-small-cell lung cancer (n=34)			Melanoma (n=37)		
	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4
(Continued from previous page)									
Nervous system disorders									
Headache	6 (16%)	0	0	2 (6%)	0	0	8 (22%)	0	0
Renal and urinary disorders									
Renal failure chronic	0	0	1 (3%)	0	1 (3%)	0	0	0	0
Respiratory, thoracic, and mediastinal disorders									
Cough	2 (5%)	0	0	0	0	0	8 (22%)	0	0
Dyspnoea	3 (8%)	0	0	3 (9%)	0	0	6 (16%)	0	0
Skin and subcutaneous tissue disorders									
Pruritus	8 (21%)	2 (5%)	0	5 (15%)	0	0	8 (22%)	0	0
Rash	9 (24%)	0	0	6 (18%)	1 (3%)	0	3 (8%)	0	0
Rash maculopapular	8 (21%)	1 (3%)	0	7 (21%)	2 (6%)	0	6 (16%)	0	0
Night sweats	4 (11%)	0	0	0	0	0	4 (11%)	0	0
Eczema	0	1 (3%)	0	0	0	0	0	0	0

All treatment-related adverse events are listed by System Organ Class preferred term that occurred at any grade in ≥10% of a subgroup or ≥1 patient for grade 3 or 4. There were no deaths due to adverse events. Patients who had a particular adverse event (preferred term) more than once were counted only once by preferred term and at the highest severity.

Table 2: **Treatment-related adverse events**

As of data cutoff on July 1, 2018, the median follow-up was 26·9 months (IQR 22·3–31·5) in patients with non-small-cell lung cancer, 33·0 months (29·2–35·1) in patients with melanoma, and 22·7 months (20·9–27·0) in patients with renal cell carcinoma. Most patients discontinued (figure 1); the most common reasons for treatment discontinuation were progressive disease, adverse events, clinical deterioration, and consent withdrawal (figure 1). Six patients died (two who received pegilodecakin plus pembrolizumab and four who received pegilodecakin plus nivolumab); all deaths were determined to be unrelated to treatment. Causes of death were sepsis (n=1), disease progression (n=2), cancer (n=1), pneumonia (n=1), and respiratory failure (n=1).

In the safety analysis, 103 (93%) of 111 patients were found to have had at least one treatment-related adverse event. Toxicity profiles were similar between the two cohorts (appendix pp 6–10). Grade 3 or 4 treatment-related adverse events occurred in 73 (66%) of 111 patients (35 [66%] of 53 in the pembrolizumab group and 38 [66%] of 58 in the nivolumab group), the most common of which (occurring in at least 10% of patients who received pegilodecakin plus anti-PD-1 therapy) were anaemia (12 [23%] in the pembrolizumab group and 16 [28%] in the nivolumab group), thrombocytopenia (14 [26%] in the pembrolizumab group and 12 [21%] in the nivolumab group), fatigue (11 [21%] in the pembrolizumab group and 6 [10%] in the nivolumab group) and hypertriglyceridaemia (three [6%] in the pembrolizumab group and eight [14%] in the nivolumab group; table 2; appendix pp 6–7). Serious adverse events related to treatment of grade 3 or 4 occurred in five (9%) of 53 patients who received pegilodecakin plus pembrolizumab and four (7%) of 58 patients who received pegilodecakin plus nivolumab; the highest incidence of grade 3 or worse serious adverse events were anaemia (in five [5%] of 111 patients) and thrombocytopenia (four [4%] of 111 patients; appendix p 11). There were no fatal adverse events determined to be related to the study treatments. Gastrointestinal disorders such as nausea, diarrhoea, and vomiting were numerically more frequent in patients with melanoma than in patients with other cancer types, but these events were low-grade. Numerically more grade 3 or 4 blood or lymphatic system disorders occurred in patients with renal cell carcinoma, but the frequency was still in 8% or less of patients (with the exception of anaemia and thrombocytopenia). Grade 1 or 2 immune-mediated red-blood-cell phagocytosis (haemophagocytic lymphohistiocytosis) occurred in one (3%) of 37 patients with melanoma and one (3%) of 38 patients with renal cell carcinoma; grade 4 haemophagocytic lymphohistiocytosis occurred in one (3%) of 38 patients with renal cell carcinoma. Although these three patients met the haemophagocytic lymphohistiocytosis-2004 diagnostic criteria,[19] all three patients fully recovered with no recurrence. Additional information on haemophagocytic lymphohistiocytosis in these patients is in the appendix (p 1). Dose reduction of pegilodecakin occurred in 27 (51%) of 53 patients who received pegilodecakin plus pembrolizumab, and 34 (59%) of 58 patients who received pegilodecakin plus nivolumab. Safety outcomes for the patients with triple-negative breast cancer and bladder cancer are in the appendix (p 2).

96 of 111 patients were evaluable for response (adequate tumour assessments at baseline and at least one post-baseline). The proportion of patients who achieved an objective response by immune-related response criteria

	All renal cell carcinoma	Renal cell carcinoma, ≥1 previous cancer therapy	Renal cell carcinoma, ≥1 previous cancer therapy, no previous pegilodecakin	All non-small-cell lung cancer	Non-small-cell lung cancer, PD-L1 expression ≥50%	Non-small-cell lung cancer, PD-L1 expression 1–49%	Non-small-cell lung cancer, PD-L1 expression <1%	All melanoma	Melanoma, PD-1 refractory	Melanoma, not PD-1 refractory
Evaluable patients (n)	35*	29	27	28†	6	3	12	31‡	20	11
Disease control	30 (86%)	27 (93%)	25 (93%)	23 (82%)	6 (100%)	2 (67%)	11 (92%)	16 (52%)	9 (45%)	7 (64%)
Partial response	14 (40%)	12 (41%)	12 (44%)	11 (39%)	4 (67%)	2 (67%)	4 (33%)	3 (10%)	0	3 (27%)
Objective response	14 (40%)	12 (41%)	12 (44%)	12 (43%)	5 (83%)	2 (67%)	4 (33%)	3 (10%)	0	3 (27%)
Partial response (100% reduction)§	3 (9%)	2 (7%)	2 (7%)	1 (4%)¶	0	0	0	0	0	0
Complete response	0	0	0	1 (4%)	1 (17%)	0	0	0	0	0
Duration of response, months	15·1 (11·3–NR)	15·1 (11·3–NR)	15·1 (11·3–NR)	10·3 (5·8–NR)	10·3 (7·7–NR)	6·5 (5·8–7·1)	14·8 (8·6–NR)	NR (8·4–NR)	NR (NR–NR)	NR (8·4–NR)
Safety population (n)	38	29	27	34	6	3	12	37	20	11
Progression-free survival, months	12·5 (4·5–17·1)	15·4 (5·6–17·1)	16·7 (5·6–21·3)	9·4 (3·8–12·1)	10·7 (9·4–NR)	8·9 (1·7–9·4)	11·0 (3·8–25·4)	2·2 (2·0–4·0)	2·1 (1·9–3·2)	2·9 (1·4–9·8)
1-year overall survival	86% (70–94)	87% (69–95)	93% (75–98)	74% (55–85)	86% (33–98)	33% (1–77)	85% (51–96)	60% (42–74)	57% (35–74)	67% (34–86)
Overall survival, months	NR (25·7–NR)	NR (25·7–NR)	NR (25·7–NR)	24·1 (13·7–29·9)	NR (10·7–NR)	10·4 (8·3–NR)	25·4 (13·9–32·2)	16·7 (10·0–22·1)	16·7 (7·9–22·6)	17·8 (6·5–NR)

Data are n (%) or median (95% CI). Study in progress. Numbers as of July 1, 2018. 1-year survival was estimated by the Kaplan-Meier method. NR=not reached. *Median follow-up (IQR) for patients with renal cell carcinoma was 22·7 months (20·9–27·0). Two patients with renal cell carcinoma had partial responses with 100% reduction in measurable disease. †Median follow-up for non-small-cell lung cancer was 26·9 months (22·3–31·5). ‡Median follow-up for melanoma was 33·0 months (29·2–35·1). §These patients had 100% reduction in target lesions, but response was confirmed by the investigator as a partial response, because patients had remaining residual non-target lesions. ¶PD-L1 expression status was not determined.

Table 3: **Best overall response, progression-free survival, and overall survival**

was 12 (43%) of all 28 patients with non-small-cell lung cancer, three (10%) of all 31 with melanoma, and 14 (40%) of all 35 with renal cell carcinoma (table 3). One (1%) of 96 evaluable patients achieved a complete response; a patient with non-small-cell lung cancer, high PD-L1 expression, and low tumour mutational burden (≤243 mut/exome) who had been treated with pegilodecakin plus nivolumab. Additionally, one patient with non-small-cell lung cancer and three with renal cell carcinoma had a best overall response of partial response confirmed by the investigator, even though they had 100% measurable target lesion reduction with residual non-measurable lesion consistent with tumour scars (figure 2; appendix pp 14–15).

For patients with non-small-cell lung cancer, five (83%) of six patients with at least 50% PD-L1 expression had an objective response, while two (67%) of three patients with less than 50% PD-L1 expression achieved an objective response (table 3). For patients with melanoma, three (27%) of 11 patients who were not PD-1 refractory had an objective response. The proportion of patients with an objective response was highest in patients with renal cell carcinoma who had previous therapy (excluding previous pegilodecakin; in 12 [44%] of 27 patients). Two patients (5%) of 38 with renal cell carcinoma who had received previous pegilodecakin therapy achieved stable disease upon the addition of pembrolizumab to pegilodecakin (figure 2). The proportion of patients with objective response for papillary renal cancer was three (50%) of six patients (appendix p 14). Activity outcomes are also shown by cohort (appendix p 12).

PD-L1 expression had no significant correlation with objective response in patients with renal cell carcinoma (data not shown). Survival was numerically higher in patients with non-small-cell lung cancer and high PD-L1 expression than those with low PD-L1 expression (table 3). However, the number of patients treated were small; therefore, it is difficult to draw conclusions about the level of PD-1 expression and the response to pegilodecakin treatment. Tumour mutational burden was assessed post hoc in a subset of patients with renal cell carcinoma, and was low (data not shown) and in line with expected values.[20] Analysis of a subset of patients with non-small-cell lung cancer showed a possible correlation between high PD-L1 expression and low tumour mutational burden (appendix p 16).

Pre-specified exploratory analysis of clonal T-cell expansion was assessed from blood samples taken from one patient with renal cell carcinoma, two with non-small-cell lung cancer, and four with melanoma. The analysis showed an expansion of a distinct subset of previously undetectable or under-represented T-cell clones in the blood of the patients on combination therapy (pegilodecakin with anti-PD-1), while most T cells did not change (appendix p 17). Similarly for patients with melanoma, clonal T-cell expansion appeared to increase with slight numerical improvements in overall survival (appendix p 17). Analysis of blood from 16 patients with non-small-cell lung

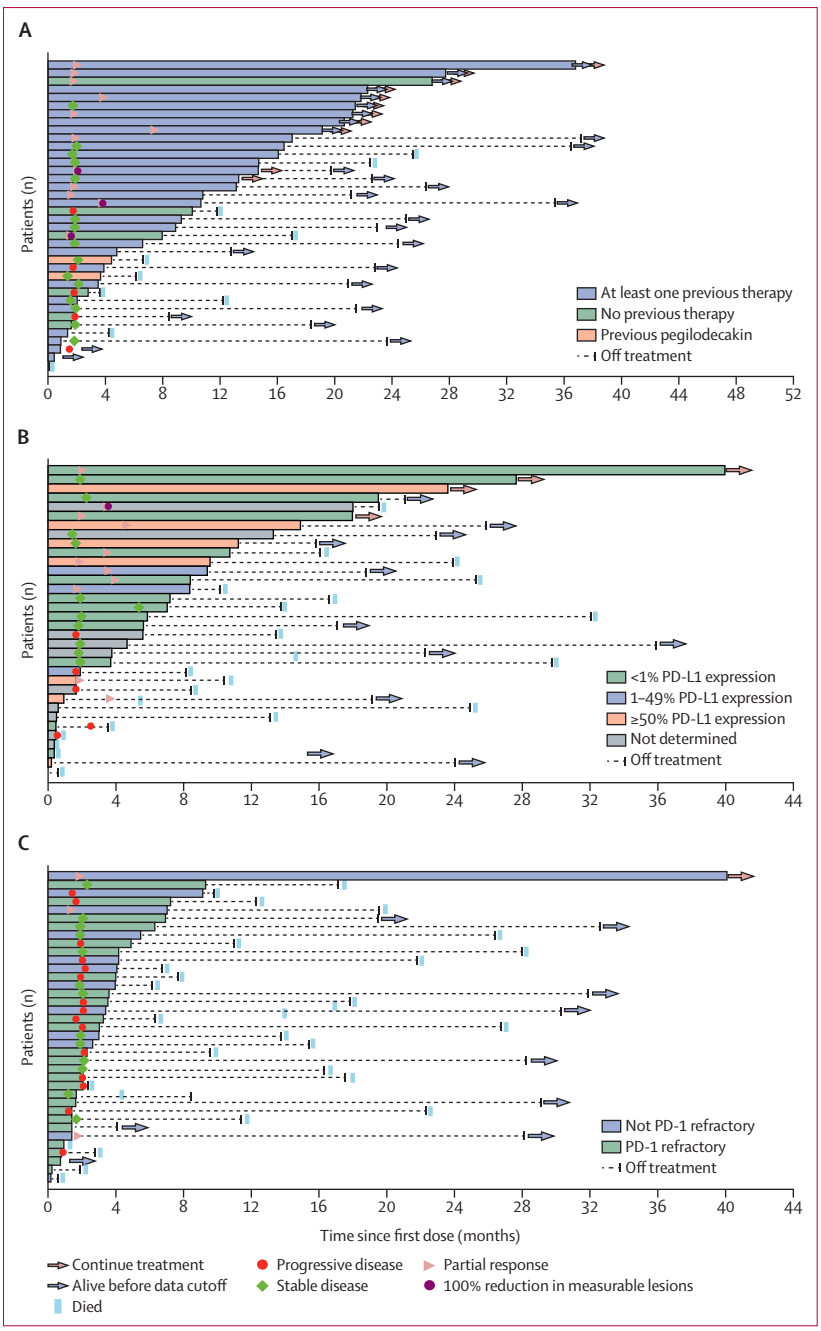

Figure 2: **Overall response**
Swimmer plot depicting best overall response, and duration of therapy, after treatment with pegilodecakin plus anti-PD-1 therapy (nivolumab or pembrolizumab) in patients with (A) renal cell carcinoma, (B) non-small-cell lung cancer, and (C) melanoma.

cancer and 21 with renal cell carcinoma before and after combination treatment revealed an expansion of T-cell clones after treatment (appendix p 17). Furthermore, in post-hoc analyses the sum of T cells derived from expanding T-cell clones in the blood of patients appeared to have a possible correlation with overall survival in patients with renal cell carcinoma (p=0·02) but not in the one patient with non-small cell lung cancer analysed (p=0·59; appendix p 17).

Discussion

Anaemia and thrombocytopenia have been previously observed with pegilodecakin monotherapy related to on-target pegilodecakin-induced immune activation.[15] Our results showed that the combination of pegilodecakin plus anti-PD-1 antibodies had manageable adverse effects of anaemia and thrombocytopaenia in patients with advanced solid tumours. Pegilodecakin in combination with anti-PD-1 therapy showed favourable response as second-line therapy in patients with non-small-cell lung cancer and renal cell carcinoma compared with previous studies with anti-PD-1 inhibitor monotherapy.[21,22] Median overall survival and median progression-free survival were more favourable in patients with melanoma who were not PD-1 refractory compared with those who were PD-1 refractory (appendix p 18). Furthermore, no patients with PD-1 refractory melanoma achieved a complete or partial response as their best overall response. Therefore, this combination therapy in patients with melanoma was not promising enough to develop further. This result might be partly because aberrant Notch signalling can develop in patients with melanoma, which increases transforming growth factor β1 and PD-1 expression, and inhibits CD8+ cytotoxic T lymphocytes.[23] Activity was more promising in patients with non-small-cell lung cancer and renal cell carcinoma; thus, pegilodecakin in combination with anti-PD-1 will be further investigated in these indications. A previous study showed that tumour mutational burden might not show a strong association with survival in renal cell carcinoma, and is therefore uninformative.[20]

Expansion of novel T-cell clones occurred in patients with non-small-cell lung cancer, renal cell carcinoma, and melanoma. However, the correlation of T-cell expansion with overall survival was most clearly seen in patients with renal cell carcinoma; however, as the sample size was small, interpretations should be viewed with caution. Although exploratory, these findings might be related to the proposed novel mechanism of action of pegilodecakin—ie, intratumoural CD8+ T-cell activation and expansion, IFN-γ-dependent tumour rejection, and subsequent tumour-immune memory.[17] Patients treated with pegilodecakin have previously shown a durable increase in T-helper 1 (IFN-γ, IL-18) and T-helper 2 (IL-4) cytokines and a reduction in transforming growth factor β.[17] The increased IL-18 might directly stimulate memory CD8+ T-cell proliferation in the tissue. The increase of both IFN-γ and IL-18 with pegilodecakin might be crucial for the clinical activity in patients with metastatic renal cell carcinoma.[15,17]

The overall toxicity in our study was manageable and primarily included anaemia, thrombocytopenia, hypertriglyceridaemia, and fatigue. Thrombocytopenia has

previously been observed in correlation with IL-10 administration.[24] Healthy adults given recombinant human IL-10 showed a significant reduction in platelets compared with those who received placebo.[24] A large decrease in splenic sequestration of platelets and decreased megakaryocyte colony-forming units occurred only in individuals given IL-10, but not in those given placebo.[24] Increased IL-10 concentrations have also occurred in patients with chronic autoimmune thrombocytopenic purpura.[25] Findings from other studies[26] of polymorphisms in the IL-10 promoter have also supported the potential role of IL-10 in thrombocytopenia. Haplotypes containing a short IL-10 allele were less frequent in patients with heparin-induced thrombocytopenia, suggesting IL-10 might play a role in heparin-induced thrombocytopenia pathogenesis through heparin-modified platelet factor 4 antibody production.

Previously, dose-dependent recombinant human IL-10 induced anaemia was reported in patients treated with the recombinant unmodified IL-10.[27] The mechanism of recombinant human IL-10 therapy-induced anaemia correlated with three times the increase in serum ferritin. Serum transferrin was increased, and iron restriction appeared to be partly the cause of the anaemia. In 2004, hepcidin was discovered following the report of two patients with iron-refractory anaemia.[28] This 25 amino-acid hormone blocks ferroportin in liver and macrophages.[29,30] This result is similar to the anaemia of chronic disease, and indeed IL-10 directly stimulates hepcidin production from macrophages.[31] The degree of anaemia was similar to our study patients' provided dose escalation of pegilodecakin monotherapy.[15] The mechanism of pegilodecakin-associated anaemia is under investigation.

Additionally, erythrophagocytosis contributes to the turnover of red blood cells,[32] and can be increased by the macrophage checkpoint inhibitor CD47 (the so-called don't eat me signal). Anaemia has occurred in clinical trials of monoclonals targeting CD47.[33] In our study in one patient with melanoma and two patients with renal cell carcinoma treated with the combination of pegilodecakin and anti-PD-1, the haemophagocytic condition haemophagocytic lymphohistiocytosis was diagnosed. In adults, this is generally associated with malignancy,[34] but immunosuppression can also cause haemophagocytic lymphohistiocytosis.[35] Epstein-Barr virus can also be associated with this condition, and such patients have very high ferritin concentrations.[36] For the patients investigated in this cohort, it is plausible to assume that the haemophagocytic lymphohistiocytosis might be associated with the T-cell activation by pegilodecakin, but this requires further investigation. These cases of haemophagocytic lymphohistiocytosis were found to be manageable and reversible.

Although the regulation and role of IL-10 in hypertriglyceridaemia is not well understood, it acts as an important modulator of lipoprotein metabolism.[37] Pegilodecakin leads to decreased cholesterol,[38] and there were no cardiovascular adverse events. In a previous clinical trial,[39] patients with psoriatic arthritis were administered recombinant IL-10, resulting in a doubling of triglycerides within a week. Concentrations of HDL and LDL decreased in the same patient population.[39,40] Similar lipoprotein profiles have been noted in patients with visceral leishmaniasis,[41] sepsis, and rheumatoid arthritis.[42] Additionally, IL-10 concentrations have been shown to be higher[43] in patients with hypertriglyceridaemia compared with individuals with normal concentrations of triglycerides. However, there was not a significant difference in serum IL-10 in relationship to the lipid profile,[43] and further investigation of a possible association is therefore needed.

The main limitation of this study was the single-arm cohorts with an absence of comparator groups. Other considerations were the small sample sizes of the cohorts as well as the patient heterogeneity. Similarly, the exploratory translational data require verification in a larger cohort study. In light of these limitations, cross-trial comparisons should be viewed with caution.

In summary, pegilodecakin is a first-in-class IL-10 receptor agonist that leads to proliferation and expansion of antigen-experienced PD-1+ Lag3+ CD8+ cytotoxic T cells.[17] The activity of pegilodecakin as a single agent and in combination with anti-PD-1 monoclonal antibodies introduces a new class of drugs that could be used in the treatment of advanced solid tumours. Future randomised trials are needed to establish the tolerability and efficacy of pegilodecakin as monotherapy and in combinations in a range of oncology indications.

Contributors

AN, NMT, PVV, NR, ADi, and RV contributed to study design or conception. AN, JRI, DJW, WMK, RA, KPP, KAA, SP, TMB, ADr, NGD, ADi, and NMT were involved in the provision of patients. AN, JRI, DJW, WMK, RA, KPP, KAA, SP, TMB, ADr, NGD, NMT, AH, PVV, RV, NR, SM, DF, EBG, ADi, and MO contributed to data acquisition and data analysis or interpretation. AN, DF, NMT, KAA, TMB, NGD, ADr, WMK, SP, KPP, RA, PVV, DJW, NR, SM, EBG, ADi, and RV assisted in drafting or critical revision of the work. AH and MO provided the analysis, including figures and tables. MO was responsible for operational execution and data clean-up as the medical monitor of the sponsor. AN had final responsibility for the design of the study, collection of the data, running the analysis, and interpretation of the results. The report was prepared by AN with input and approval from all coauthors. All authors contributed to the writing of the report, reviewed it for intellectual content, and approved the submitted version.

Declaration of interests

AN received research funding from the National Cancer Institute, EMD Serono, MedImmune, Healios Onc. Nutrition, Atterocor, Amplimmune, ARMO BioSciences (a wholly owned subsidiary of Eli Lilly and Company), Karyopharm Therapeutics, Incyte, Novartis, Regeneron, Merck, Bristol-Meyers Squibb (BMS), Pfizer, CytomX Therapeutics, Neon Therapeutics, Calithera BioSciences, TopAlliance BioSciences, PsiOxus, and Immune Deficiency Foundation (spouse); and is on the advisory board for CytomX Therapeutics and Novartis and received reimbursement for travel and accommodation from ARMO BioSciences. JRI reports consultancy fees from BioMed Valley and ARMO Biosciences; and is an employee of Janssen. RA reports grants from Alliance Foundation Trials, Boston Biomedical, Syneos Health, Array BioPharma, BMS, Huntsman Cancer Institute, Merck,

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Data sharing

Lilly provides access to all individual participant data collected during the trial, after anonymisation, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data-sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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