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Contributors

AN, NMT, PVV, NR, ADiab, and RV contributed to study design/conception. AN, JRI, DJW, WMK, RA, KPP, KAA, SP, TMB, AD, NGD, ADiab, and NMT were involved in the provision of patients. AN, JRI, DJW, WMK, RA, KPP, KAA, SP, TMB, AD, NGD, NMT, AH, PVV, RV, NR, SM, DF, EBG, ADiab, and MO contributed to data acquisition, analysis, and/or interpretation. AN, DF, NMT, KAA, TMB, NGD, AD, WMK, SP, KPP, RA, PVV, DJW, NR, SM, EBG, ADiab, and RV assisted in drafting and/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. All authors contributed to the writing of the report, reviewed it for intellectual content, and approved the submitted version.

Declaration of Interests

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Pegilodecakin Combined With Pembrolizumab or Nivolumab for Patients With Advanced Solid Tumours (IVY): A Multicentre, Open-Label, Phase 1b Trial

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Abstract

Background—Interleukin (IL)-10 has anti-inflammatory and CD8+ T-cell–stimulating activities. Pegilodecakin (pegylated IL-10) induces oligoclonal T-cell expansion and has single-agent activity in advanced solid tumours. We assessed safety and activity of pegilodecakin with anti-programmed cell death receptor (PD)-1 inhibitors in patients with advanced solid tumours.

Methods—IVY was a multicenter, open-label, phase 1b trial at 12 cancer research centres in the United States. Here, we report on all enrolled patients from the only two cohorts in which patients were treated with pegilodecakin (subcutaneous daily at 10 or 20 μg/kg) combined with anti-PD-1 inhibitors (3 mg/kg nivolumab every 2 weeks or 2 mg/kg pembrolizumab every 3 weeks). Eligible patients had histologically or cytologically confirmed advanced malignant solid

tumour refractory to prior therapies, were ≥18 years of age, and had ECOG performance status of 0 or 1. Pegilodecakin was self-administered subcutaneously at 10 or 20 μg/kg in combination with pembrolizumab (2 mg/kg every 3 weeks) or nivolumab (3 mg/kg every 2 weeks). The primary endpoints were safety and tolerability. The secondary endpoints were clinical activity and tumour response, measured by immune-related response criteria. The study is active but no longer recruiting and is registered with ClinicalTrials.gov, number NCT02009449.

Findings—From 13 February 2015 to 12 September 2017, 111 patients enrolled in Cohorts H and I of IVY. All patients were evaluable for safety. Grade 3/4 treatment-related adverse events were observed in 74 (67%) of 111 patients, including but not limited to anaemia (28 [25%] of 111), thrombocytopenia (26 [23%] of 111), fatigue (17 [15%] of 111, and hypertriglyceridemia (11 [10%] of 111). There were no fatal adverse events (Grade 5) determined to be related to the study treatments. Of the patients evaluable for response, objective responses were 12 (43%) of 28 (NSCLC), 3 (10%) of 31 (melanoma), and 14 (40%) of 35 (RCC). All patients were PD-1 inhibitor naïve except 1 patient with RCC and 25 patients with melanoma.

Interpretation—Pegilodecakin is a first-in-class, long-acting IL-10 receptor agonist. In this patient population, pegilodecakin with anti-PD-1 monoclonal antibodies had a manageable toxicity profile and promising antitumour activity. Pegilodecakin with pembrolizumab or nivolumab may provide a new therapeutic opportunity for heavily pretreated patients with RCC and NSCLC.

Keywords

Pegilodecakin; Nivolumab; Pembrolizumab; phase 1; IL-10; pegylated IL-10

INTRODUCTION

Immune checkpoint inhibitors (ICI) have demonstrated promise in treating patients with advanced malignancies.[1] One example of an effective ICI therapy utilizes the programmed cell death receptor (PD)-1 expressed on activated T-cells. This receptor downregulates excessive immune responses through binding to the ligands PD-L1 and PD-L2.[2, 3] Anti-PD-1 therapeutic antibodies have demonstrated clinical activity in advanced solid tumours, such as non-small cell lung cancer (NSCLC), melanoma, and renal cell carcinoma (RCC).[4, 5] Between December 2014 and November 2015, the anti-PD-1 monoclonal antibody nivolumab received approvals from the US Food and Drug Administration (FDA) to treat patients with advanced melanoma, lung cancer, and metastatic RCC. Pembrolizumab is also an anti-PD-1 antibody that has been approved and exhibited a manageable safety profile as well as 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 NSCLC, melanoma, and RCC, respectively.[8–10] However, despite recent progress there still remains substantial unmet need in the treatment of advanced solid tumours.[11, 12]

Human interleukin (IL)-10 is produced by a variety of immune cells and plays a significant role in reducing inflammation. Recent studies suggest therapeutic opportunities for targeting IL-10 receptors.[13] IL-10 has a very short half-life *in vivo*.[14] Pegilodecakin, a

pegylated recombinant human IL-10 and first-in-class long-acting IL-10 receptor agonist, retains agonism at the IL-10 receptor. 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 induces amplification of intratumoural CD8+ T-cells resulting in cures and long-term immune memory against rechallenge with the same tumour.[16]

Pegilodecakin has demonstrated single-agent activity in patients with advanced solid tumours.[15] 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] In view of the substantial unmet clinical need, we explored the combination of pegilodecakin with anti-PD-1 monoclonal antibodies with the primary objective of examining safety and activity.

METHODS

Study Design and Participants

IVY (NCT02009449) is a multi-institutional, open-label, multiple-cohort, dose-escalation, phase 1b study (see Appendix p 13 for additional details for all cohorts of IVY). Patients were recruited from 12 cancer research centres throughout the United States. Cohorts H and I were the only cohorts of IVY with anti-PD-1 inhibitors. Cohort H patients received pembrolizumab with pegilodecakin, and Cohort I patients received nivolumab with pegilodecakin. All treatments were given in an outpatient setting and responses evaluated by immune-related response criteria (irRC) method.[18] All patients who were enrolled in the study were included in the safety evaluation. Two patients (one patient with triple negative breast cancer and one patient with bladder cancer) were excluded from the outcomes analyses (Appendix p. 2). Study inclusion criteria included histologically or cytologically confirmed advanced malignant solid tumor. Male or female patients were ≥18 years of age, had Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1, had at least one measurable lesion per the irRC, and had adequate organ function. Patients with immune-mediated inflammatory diseases were not excluded, except patients with prior Guillain-Barré syndrome or neuroinflammatory conditions. Patients with uncontrolled infectious diseases were excluded. The study protocol was reviewed and approved by the Institutional Review Board at participating sites and was conducted in accordance with the Declaration of Helsinki and other Good Practice Guidelines. All patients signed the approved consent forms for the study.

Procedures

Patients were assigned sequentially into cohorts. At baseline, all patients underwent baseline investigations, including physical examination, ECOG performance status, electrocardiogram, computed tomography or magnetic resonance imaging of sites of disease, laboratory assessments, serum and pharmacokinetic samples for analysis, and listing of concomitant medications. Pegilodecakin (manufactured by Cytovance biologics [Oklahoma City, Oklahoma, USA], on behalf of ARMO BioSciences, a wholly owned subsidiary of Eli Lilly and Company [Redwood City, California, USA]) was provided in single-use 3mL vials

and self-administered subcutaneously daily. In the dose escalation phase of the study, two doses of pegilodecakin, 10 μg/kg (n=6) and 20 μg/kg (n=32), were explored in combination with pembrolizumab (2 mg/kg intravenously [IV] every 3 weeks) or with nivolumab (3 mg/kg IV every 2 weeks). Per the evolved 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 originally dosed at 3 mg/kg every 2 weeks, which was later changed to flat dosing of 240 mg every 2 weeks. Published pharmacokinetic/pharmacodynamic data indicate that both dosing schedules achieved serum concentrations close to target saturation; therefore, the dosing regimen was not changed in the IVY study. Patients received pembrolizumab or nivolumab with pegilodecakin until disease progression (irPD), toxicity necessitating treatment discontinuation, patient withdrawal of consent, or study end. Patients continued to receive combination therapy or pegilodecakin monotherapy after confirmed irPD in the absence of clinical deterioration and if the investigator considered that the patient continued to receive benefit from the treatment. Dose interruptions were allowed, but dose reduction was allowed only for pegilodecakin. Interruptions lasting >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 >6 weeks that occurred due to nondrug-related reasons if approved by the study's medical monitor. If the anti-PD-1 therapy was interrupted or discontinued due to toxicities, treatment continuation of pegilodecakin was allowed.

Throughout the study, performance status, complete blood counts, and chemistries were recorded. Tumour assessment 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 evaluated according to irRC. Adverse events, serious adverse events (SAEs), and laboratory abnormalities were graded and recorded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4·03 and were monitored until 30 days after last dose of treatment. In the case of toxicities, subsequent treatment cycles were delayed until toxicities were ≤G1. Immunological assessment included blood T-cell receptor (TCR) sequencing for T-cell clonality assessment (performed by Adaptive Biotechnologies).[17] The assay quantifies individual (clonal) TCR 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 NSCLC samples were performed by PhenoPath, PLLC (Seattle, Washington, USA). Scoring reflected pharm DX/22C3 assay results. For RCC samples, PD-L1 expression was analysed with ARMO BioSciences (Redwood City, CA, USA) immunohistochemical assay utilising anti-PD-1 antibody clone SP142, with a cutoff of >1% infiltrating cells (the majority of patients had a PD-L1 score below 1%; 12 (32%) of 38 patients) (data not shown). PD-L1 correlative analyses were performed by ARMO BioSciences. Tumour mutational burden analyses were performed by Translational Bioscience (Sunnyvale, California, USA) and analysed by ARMO BioSciences.

Outcomes

The primary endpoints of the study was to characterise the safety, tolerability, maximal tolerated dose (MTD; results previously disclosed),[15] and pharmacokinetic

(preliminary pharmacokinetic data was published in the phase 1B paper[15]; full population pharmacokinetic analysis is not yet available)) of pegilodecakin in patients after daily subcutaneous administrations in combination with pembrolizumab or nivolumab. Secondary endpoints were to measure tumour responses by irRC and to evaluate the formation of anti-pegilodecakin antibodies (results not available; data is being collected and to be analysed in due course). Exploratory analyses, prespecified in the protocol, were to investigate biomarkers for patient stratification and treatment response including evaluation of T-cell responses as surrogates for anti-tumor activity of pegilodecakin.

Statistical Analysis

IVY was designed to evaluate and characterize the safety, tolerability, and pharmacokinetics of pegilodecakin that was established in preclinical species can be transferrable to humans, and pegilodecakin would decrease disease-associated biomarkers. No formal sample size calculation was performed, the cohort size was agreed upon by the regulators, and investigators observed clinically meaningful activities. Safety analyses were based on the Safety Population which included all patients who received any amount of study medication. The Response Population, or evaluable population, was composed of all patients who were treated and had an adequate baseline and at least one adequate postbaseline tumour measurement. The protocol did not prespecify that the cohorts be reported together or separately. Adverse events were evaluated in the safety population and included toxicity grade rating, concomitant medications, electrocardiogram (ECG), hematology, physical examination, serum chemistry, urinalysis, and vital signs. CTCAE 4·03 was used to grade and report treatment-related adverse events (TRAEs). Number and percentage of patients experienced TRAEs were tabulated by system organ class and preferred name and at highest grade. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16·1.

Response analyses were performed based on the evaluable population, and the proportion of patients who achieved an objective response was defined as the percentage of patients with complete response (CR) and partial response (PR). The disease control rate (DCR) was defined as the percentage of patients with CR, PR, and stable disease. Based on the safety population, OS was defined as the time from first dose of study drug to the date of death due to any cause, and progression-free survival was calculated from the date of first dose of study drug to the date of progression or death due to any cause. These estimates were determined using the Kaplan Meier method [(Kaplan)]. Exploratory endpoints included changes in immune parameters, including serum chemokines and T-cell responses. Data reported are as of July 1, 2018.

The results for all endpoints were reported descriptively. No statistical hypothesis testing or inferential analysis was performed for this study. Categorical variables were reported as counts and percentages, and continuous variables were reported as median (range or IQR) or mean, as appropriate. Analyses were performed using SAS version 9·4 or higher (SAS Institute Inc., Cary, NC, USA).

This study is registered with ClinicalTrials.gov, number NCT02009449.

Role of the Funding Source

AH, RV, NR, SM, PV, and MO were employed by ARMO and played a significant part in study design, data collection, data analysis, data interpretation, and writing of the report (see Contributors for details). The sponsor (ARMO) provided the study drug and worked with the investigators. As of June 2018, ARMO became a fully owned affiliate of Eli Lilly and Company, who is now the sponsor of the IVY trial. The report was prepared by the corresponding author with input and approval from all coauthors. The corresponding author (AN) had full access to all data in the study and had final responsibility for the decision to submit for publication, design the study, collect the data, run the analysis, and interpret the results.

RESULTS

Between 13 February 2015 and 12 September 2017, 111 patients were enrolled and treated with pegilodecakin combined with either pembrolizumab (Cohort H; N=53) or nivolumab (Cohort I; N=58). Cohort H was composed of 9 RCC patients, 5 NSCLC patients, 1 bladder cancer patient, 1 triple negative breast cancer (TNBC) patient, and 37 melanoma patients. Cohort I included 29 NSCLC patients and 29 RCC patients (Figure 1). The 34 NSCLC patients, 37 melanoma patients, and 38 RCC patients are further described hereafter. Information on the patients with TNBC (n=1) and bladder cancer (n=1) is provided in the Appendix p. 2. Baseline characteristics are provided in Table 1. Most patients had at least one prior therapy (Appendix pp. 3–5). Of the patients with melanoma, 25 (68%) of 37 were refractory to prior anti-PD-1 and anti-cytotoxic T-lymphocyte antigen-4 therapy, and 12 (32%) of 37 were anti-PD-1 naïve. No patients with NSCLC had received prior PD-1 therapy. No patients with NSCLC or melanoma had prior pegilodecakin therapy. Two (5%) of 38 patients with RCC had received prior pegilodecakin monotherapy (response in one and stable disease for 19 weeks in the other) in an earlier cohort of the trial.

As of data cutoff on July 1, 2018, the median follow-up was 26·9 months (IQR 22·3–31·5) in NSCLC patients, 33·0 months (IQR 29·2–35·1) in melanoma patients, and 22·7 months (IQR 20·9–27·0) in RCC patients. Ninety-five (85·6%) of 111 patients discontinued (Figure 1). The most common reasons for treatment discontinuation were progressive disease in 42 (37·8%) of 111 patients, adverse events in 11 (9·9%) of 111 patients, clinical deterioration in 18 (16·2%) of 111 patients, and consent withdrawal in 12 (10·8%) of 111 patients (Figure 1). There were 6 deaths (2 from Cohort H and 4 from Cohort I) and all were determined to be unrelated to treatment. Causes included sepsis (n=1), disease progression (n=2), cancer (n=1), pneumonia (n=1), and respiratory failure (n=1).

Safety analysis revealed presence of at least one TRAE in 103 (93%) of 111 patients. Toxicity profiles were similar between Cohort H and Cohort I (Appendix pp. 6–7). Grade 3/4 TRAEs were observed in 73 (66%) of 111 patients. Grade 3/4 TRAEs experienced by ≥10% of patients who received pegilodecakin plus anti-PD-1 included anaemia (28 [25%] of 111), thrombocytopaenia (26 [23%] of 111), fatigue (17 [15%] of 111), and hypertriglyceridaemia (11 [10%] of 111) (Table 2 and Appendix pp. 6–7). Aside from these four TRAEs, incidence of Grade 3/4 TRAEs was very low (≤9%) across all patients. Serious adverse events related to treatment (Grade 3/4) were infrequent (5 [9%] of 53 patients in

Cohort H, and 4 [7%] of 58 patients in Cohort I), with the highest incidence of Grade 3/4 SAEs of anaemia (5 [5%] of 111 patients) and thrombocytopaenia (4 [4%] of 111 patients) (see Appendix p. 11). There were no fatal adverse events (Grade 5) determined related to the study treatments. Gastrointestinal disorders, such as nausea (11 [30%] of 37), diarrhea (5[14%] of 37), and vomiting (7 [19%] of 37), appeared more frequently in melanoma patients, but these events were low-grade. Grade 3/4 blood or lymphatic system disorders were more evident in RCC patients, but frequency was still ≤8% (with the exception of the previously discussed anaemia and thrombocytopaenia). Grade 1/2 immune-mediated red-blood-cell phagocytosis (haemophagocytic lymphohistiocytosis [HLH]) was observed in 1 (3%) of 37 patients with melanoma and 1 (3%) of 38 patients with RCC, and Grade 4 HLH was experienced by 1 (3%) of 38 patients with RCC. Although these three patients met the HLH-2004 diagnostic criteria,[19] the course was more benign than routinely seen in adult HLH, with full recovery and no HLH recurrence. Additional information on HLH in these patients is provided in the Appendix p. 1. Dose reduction of pegilodecakin occurred in 27 (51%) of 53 patients in Cohort H, and 34 (59%) of 58 patients in Cohort I (data not shown).

Of the 111 patients, 96 were evaluable for response (adequate tumour assessments at baseline and at least one postbaseline). The proportion of patients who achieved an objective response by irRC was recorded as 12 (42·9%) of 28 in NSCLC, 3 (9·7%) of 31 in melanoma, and 14 (40·0%) of 35 in RCC (Table 3). One (1%) of 96 evaluable patients achieved CR. This was a NSCLC patient with high PD-L1 expression and low tumour mutational burden (TMB; ≤243 mut/exome) that had been treated with pegilodecakin + nivolumab. Also, 1 (4%) of 28 NSCLC and 3 (9%) of 35 RCC patients had a best overall response of PR, as confirmed by the investigator, even though they exhibited 100% measurable target lesion reduction with residual nonmeasurable, lesion-consistent with tumour scars (Figure 2 and Appendix pp. 14–15). For NSCLC, response was most favourable in patients with high PD-L1 expression (PD-L1≥50%; n=6) (objective response in 5 [83·3%] of 6 patients). For melanoma, patients who were not PD-1 refractory (n=11) had the best response (objective response in 3 [27·3%] of 11 patients). The proportion of patients with objective response was the highest in RCC patients with prior therapy (excluding prior pegilodecakin) (objective response 12 [44·4%] of 27 patients). In two (5%) of 38 RCC patients with prior pegilodecakin therapy, both achieved stable disease upon the addition of pembrolizumab to pegilodecakin (Figure 2). The proportion of patients with objective response for papillary renal cancer was 3 (50%) of 6 patients (Appendix p. 14). Activity outcomes are also shown by cohort, see Appendix p. 12.

Although PD-L1 expression demonstrated no significant correlation with objective response in RCC patients (data not shown), there was improved survival in NSCLC patients with high PD-L1 expression (Table 3). The TMB was assessed in a RCC patient subset, and was revealed to be low (data not shown) and in line with the expected TMB.[20] When TMB was analysed in a subset of NSCLC patients, it showed a possible correlation between high PD-L1 expression and low TMB (Appendix pp. 16). However, previous work has demonstrated TMB may not demonstrate a strong association with survival in RCC, and is therefore uninformative.[20]

Exploratory analysis of clonal T-cell expansion was assessed by comparing the T-cell repertoire by TCR-deep sequencing the peripheral blood samples taken from RCC (n=1), NSCLC (n=2), and melanoma (n=4) patients before and during treatment. This revealed an expansion of a distinct subset of previously undetectable or under-represented T-cell clones in the blood of the patient on combination therapy (pegilodecakin with anti-PD-1), while the majority of T-cells did not change (Appendix p. 17). Similarly in melanoma, the clonal T-cell expansion appeared to increase with slight improvements in OS (Appendix p. 17). In order to further understand the clonal T-cell response, we assessed the number of T-cell clones that changed more than 10-times the baseline value (as a percentage of all T-cells in the blood). Analysis of 16 NSCLC and 21 RCC patients' blood before and after combination treatment revealed an expansion after treatment of T-cell clones (Appendix p. 17). Furthermore, the sum of T-cells derived from expanding T-cell clones in the blood of patients appeared to have a possible correlation with OS in RCC (p=0·02) but not in the NSCLC patient analyzed (p=0.59) (Appendix p. 17).

DISCUSSION

Anaemia and thrombocytopaenia have been previously observed with pegilodecakin monotherapy related to on-target pegilodecakin-induced immune activation.[15] Our results show that the combination of pegilodecakin plus anti-PD-1 antibodies had manageable toxicity of anaemia and thrombocytopaenia in advanced solid tumours. Pegilodecakin in combination with anti-PD-1 therapy demonstrated favourable response in second line NSCLC and RCC patients compared to previous studies with anti-PD-1 inhibitor monotherapy.[21, 22] Although median OS and median progression-free survival were more favourable in melanoma patients that were not PD-1 refractory compared to the PD-1 refractory melanoma patients (Appendix p. 18), the best overall response in these treated melanoma patients was disappointing (Table 3). Therefore, this combination therapy in melanoma was not promising enough to develop further. This may be explained in part by observations that melanoma can demonstrate aberrant Notch signaling, which increases TGFB1 and PD-1 expression, and inhibits CD8+ cytotoxic T lymphocytes.[23] Activity was more promising in NSCLC and RCC; thus, pegilodecakin in combination with anti-PD-1 will be further investigated in these indications.

Expansion of novel T-cell clones was observed in RCC, NSCLC, and melanoma. However, the correlation of T-cell expansion with OS was most clearly seen in RCC, which is possibly due to the small sample size analysed. Although exploratory, these findings may be directly related to the proposed mechanism of action of pegilodecakin. Pegilodecakin demonstrates a novel mechanism of action for intratumoural CD8+ T-cell activation and expansion, interferon (IFN)-γ-dependent tumour rejection, and subsequent tumour-immune memory.[17] Patients treated with pegilodecakin have previously demonstrated a durable increase in T helper (Th)1 (IFN-γ, IL-18) and Th2 (IL-4) cytokines and a reduction in transforming growth factor (TGF)-β.[17] The increased IL-18 may directly stimulate memory CD8+ T-cell proliferation in the tissue. Pegilodecakin's increase of both IFN-γ and IL-18 may be crucial for the clinical activity that is observed in these mRCC patients.[15, 17]

The overall toxicity seen in our study is manageable and primarily included anaemia, thrombocytopaenia, hypertriglyceridaemia, and fatigue. Thrombocytopaenia has previously been observed in correlation with IL-10 administration. Healthy volunteers provided with recombinant human IL-10 exhibited a significant reduction in platelets compared to those who received placebo.[24] A large decrease in splenic sequestration of platelets and decreased megakaryocyte colony-forming units was observed only in those treated with IL-10 but not placebo.[24] Increased IL-10 levels have also been observed in patients with chronic autoimmune thrombocytopaenic purpura.[25] More recent studies of polymorphisms in the IL-10 promoter have also supported the potential role of IL-10 in thrombocytopaenia.[26] Haplotypes containing a short IL-10 allele were less frequent in patients with heparin-induced thrombocytopaenia, suggesting IL-10 may play a role in heparin-induced thrombocytopaenia pathogenesis through heparin-modified PF4 antibody production.

Previously, dose-dependent recombinant human (rHu)IL-10 induced anaemia was reported in patients treated with the recombinant unmodified IL-10.[27] The mechanism of rHuIL-10 therapy-induced anaemia correlated with 3-times the elevation of serum ferritin. Serum transferrin was elevated, and it appeared that iron restriction was in part 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] The 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 the patients' provided dose escalation of pegilodecakin monotherapy.[15] The mechanism of pegilodecakin anaemia is under active investigation.

In addition, erythrophagocytosis contributes to the turnover of red blood cells.[32] Erythrophagocytosis can be increased by the macrophage checkpoint inhibitor CD47, the "don't eat me" signal. Anaemia has been observed in clinical trials of monoclonals targeting CD47.[33] In one patient with melanoma and two patients with RCC in the current study treated with the combination of pegilodecakin and anti-PD-1, a haemophagocytic condition was diagnosed called acquired HLH. In adults, this is generally associated with malignancy,[34] but immunosuppression can also cause HLH.[35] Epstein-Barr virus can also be associated with HLH, and these patients have very high ferritin levels.[36] For the patients investigated in this cohort, it is plausible to assume that the HLH may be associated with the T-cell activation by pegilodecakin. These cases of HLH were manageable and reversible (see Appendix p. 1 for additional patient information).

Although the regulation and role of IL-10 in hypertriglyceridaemia is not well understood, it has been found to act as an important modulator of lipoprotein metabolism.[37] It is of note that pegilodecakin leads to decreased cholesterol,[38] and there were no cardiovascular adverse events. In a previous clinical trial, patients with psoriatic arthritis were administered recombinant IL-10, resulting in a 2-times increase in triglycerides within a week. Levels of high-density lipoprotein and low-density lipoprotein decreased in the same patient population.[39, 40] Similar lipoprotein profiles have been seen in patients with visceral leishmaniasis,[41] sepsis, and rheumatoid arthritis.[42] Additionally, IL-10 levels have been shown to be higher in patients with hypertriglyceridaemia. IL-10 levels were statistically

different between individuals depending on whether they had normal triglycerides or hypertriglyceridaemia. However, there was not a significant difference in serum IL-10 levels in relationship to the lipid profile.[43] Therefore, further investigation of the possible association between IL-10 and hypertriglyceridaemia may help to shed light on this phenomenon.

The main limitation of this study was the single-arm cohorts with lack of comparator arms. Other considerations are the relatively small sample sizes of the cohorts as well as the patient heterogeneity. Variability in the prior therapies of the patients is provided in Supplemental Tables 2–4 (Appendix pp. 3–5). Similarly, the exploratory translational data require verification in a larger cohort study. In light of all of these limitations, cross-trial comparisons should be viewed with reservation.

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 to the treatment of advanced solid tumours. Future randomised trials will determine the tolerability and efficacy of pegilodecakin as a single agent and in combinations in a range of oncology indications.

Data-Sharing Statement

Eli Lilly provides access, after anonymisation, to all individual participant data collected during the trial, except for pharmacokinetic and genetic data. Data can be requested 6 months after the indication studied has been approved in the USA and EU or after primary publication acceptance, whichever is later. No expiration date for data requests is set once the 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, and blank or annotated case report forms, will be provided in a secure data-sharing environment for up to 2 years per proposal. Further details about submitting a data request are available online.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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RESEARCH IN CONTEXT

Evidence Before This Study

We searched PubMed with the terms “phase 1” [All fields] AND “cancer” [All fields] AND “IL-10” [All fields] with no restriction on language. The search refined to clinical trials revealed six results. Three of these publications were within the last 5 years. Of these, one publication discussed nivolumab in patients with advanced melanoma, in which pretreatment serum interleukin (IL)-10 levels were significantly higher in patients with objective tumour responses than in those with tumour progression. A second publication discussing relapsed lymphoma of the central nervous system revealed that the change in cerebrospinal fluid IL-10 correlated with clinical benefit and response duration. When we searched PubMed with the terms “IL-10 receptor” [All fields] AND “anti-PD-1” [All fields] with no restriction on language, the search revealed 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 anti- programmed cell death receptor (PD)-1. The rationale was that complement-mediated inhibition of antitumor immunity is not impacted by PD-1 pathway. Therefore, incorporating IL-10 with the tumour-infiltrating lymphocytes would improve their antitumour activity.

Added Value of This Study

IVY is the first clinical study to report results in patients with advanced solid tumours who have been treated with this first-in-class, pegylated IL-10 cytokine (pegilodecakin), which was safely combined with anti-PD-1 drugs (nivolumab or pembrolizumab) in a variety of cancers, such as renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), and melanoma. The novel mechanism of action which leads to the clonal T-cell expansion is associated with durable responses, especially in patients with NSCLC who demonstrated an objective response of 12 (43%) of 28, and RCC patients who demonstrated an objective response of 14 (40%) of 35. In Charych et al. 2016, NKTR-214 (a pegylated cytokine which binds to the IL-2 receptor) demonstrated preclinical activity in solid tumours. However, to our knowledge, there are currently no other clinical stage IL-10 analogues in development. Pegilodecakin has a unique target and mechanism of action by intratumoural CD8+ T-cell activation and expansion, interferon (IFN)-γ-dependent tumour rejection, and subsequent tumour-immune memory. In Naing et al. 2016, patients treated with pegilodecakin demonstrated a durable increase in T helper (Th)1 (IFN-γ, IL-18) and Th2 (IL-4) cytokines and a reduction in transforming growth factor (TGF)-β. This increased IL-18 may directly stimulate memory CD8+ T-cell proliferation in the tissue.

Implications of All the Available Evidence

This phase 1b study shows the safety and activity profile of the combination of pegilodecakin plus anti-PD-1 for patients with advanced solid tumours. Overall, these data support further investigation of pegilodecakin and anti-PD-1 as therapy in patients with metastatic RCC and NSCLC.

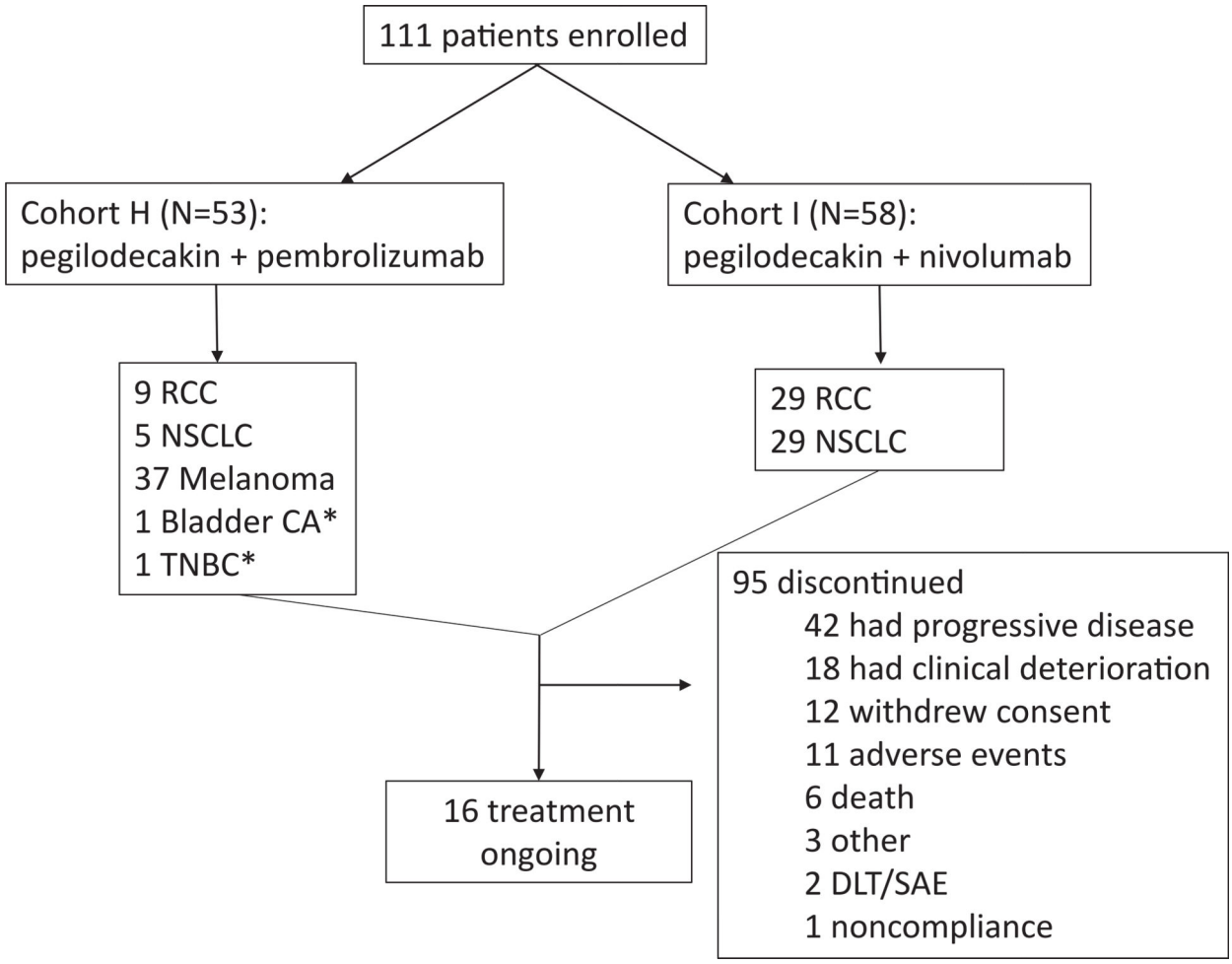

Figure 1.

IVY Trial Profile of Cohorts H and I. The CONSORT diagram depicts the composition of Cohorts H and I. Patient disposition and reasons for discontinuation as well as the number of patients still on treatment are indicated. CA=cancer; DLT =dose-limiting treatment; NSCLC= non-small cell lung cancer; RCC=renal cell carcinoma; SAE=serious adverse event; TNBC=triple negative breast cancer. * Only 1 bladder cancer patient and 1 triple negative breast cancer (TNBC) patient enrolled, such that the breast and bladder cancer subcohorts were not further recruited. Therefore, these two patients were excluded from the manuscript discussion.

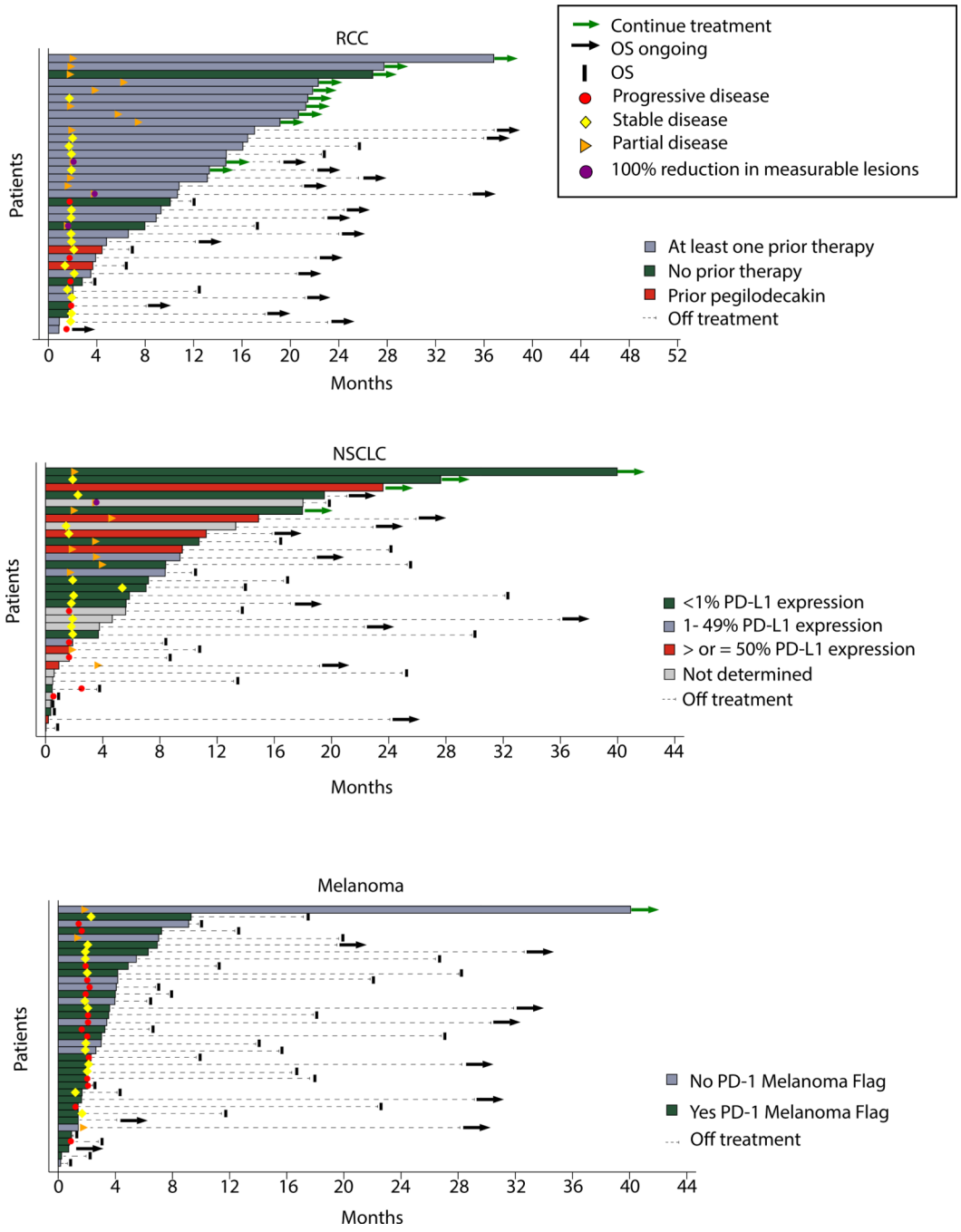

Figure 2.

Patient response. Swimmer plot depicting best overall response, duration of therapy, and overall survival from pegilodecakin (AM0010) + anti-PD-1 therapy in renal cell cancer (RCC), non-small cell lung cancer (NSCLC), and melanoma patients. OS=overall survival.

Table 1.

Baseline Characteristics

	RCC PATIENTS (N=38)	NSCLC PATIENTS (N=34)	MELANOMA PATIENTS (N=37)	TNBC PATIENT (N=1)	BLADDER CANCER PATIENT (N=1)
Pembrolizumab/nivolumab, n	9/29	5/29	37/0	1/0	1/0
Median age, years	66	67	59	68	74
Range	32–77	40–84	26–85	NA	NA
Sex, n (%)					
Male	27 (71)	18 (53)	18 (49)	0	1
Female	11 (29)	16 (47)	19 (51)	1	0
ECOG PS, n (%)					
0	12 (32)	8 (24)	25 (68)	0	0
1	26 (68)	26 (77)	12 (32)	1	1
Histology, n (%)					
Squamous (NSCLC)	NA	6 (18)	NA	NA	NA
Non-squamous (NSCLC)	NA	27 (79)	NA	NA	NA
Unknown (NSCLC)	NA	1 (3)	NA	NA	NA
Clear cell	30 (79)	NA	NA	NA	NA
Papillary	6 (16)	NA	NA	NA	NA
Invasive ductal carcinoma	NA	NA	NA	1	NA
Poorly differentiated invasive urothelial carcinoma of the bladder	NA	NA	NA	NA	1
Not reported	1 (3)	NA	NA	NA	NA
Translocation	1 (3)	NA	NA	NA	NA
Current TNM stage, n (%)					
Stage III	1 (3)	0	0	0	0
Stage IV	37 (97)	34 (100)	36 (97)	1	1
Other	0	0	1 (3)	0	0
Prior cancer therapies, n (%)					
0	5 (13)[a]	3 (9)	3 (8)		
≥1	32 (84)[b]	31 (91)	34 (92)	1	1
NA	1 (3)	0	0		
No prior PD-1 therapy	37 (97)	34 (100)	12 (32)	0	0
Race, n (%)					
White	31 (82)	27 (79)	36 (97)	1	1
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, n (%)					
Bone	8 (21)	6 (18)	2 (5)	0	0
CNS	1 (3)	2 (6)	0	0	0

	RCC PATIENTS (N=38)	NSCLC PATIENTS (N=34)	MELANOMA PATIENTS (N=37)	TNBC PATIENT (N=1)	BLADDER CANCER PATIENT (N=1)
Distant lymph nodes	8 (21)	9 (27)	6 (16)	1	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
IMDC risk category, n (%)					
Favourable	6 (16)	NA	NA	NA	NA
Intermediate	29 (76)	NA	NA	NA	NA
Poor	3 (8)	NA	NA	NA	NA

[a] Six patients did not have prior antiangiogenic therapy and are excluded from the outcome analysis but included in the safety analysis.

[b] Two patients with prior pegilodecakin monotherapy included in safety but not in outcome analysis.

CNS=central nervous system. ECOG PS=Eastern Cooperative Oncology Group performance status. IMDC=International Metastatic Renal Cell Carcinoma Database Consortium Criteria.[44] NA=not available. RCC=renal cell cancer. TNBC=triple negative breast cancer; TNM=tumour, node, metastases.

Table 2.

Treatment-related adverse events

	RCC		NSCLC		Melanoma	
	Grade 1/2	**Grade 3/4**	**Grade 1/2**	**Grade 3/4**	**Grade 1/2**	**Grade 3/4**
System Organ Class	N=38	N=38	N=34	N=34	N=37	
Preferred term						
ALL	37 (97)	26 (68)	28 (82)	23 (68)	36 (97)	23 (62)
Blood and lymphatic system disorders						
Anaemia	11 (20)	10 (26)	6 (18)	9 (27)	12 (32)	9 (24)
Histiocytosis haematophagic	1 (3)	1 (3)	-	-	1 (3)	0
Leukopenia	0	1 (3)	0	0	3 (8)	0
Neutropenia	0	3 (8)	1 (3)	0	1 (3)	0
Splenomegaly	2 (5)	1 (3)	-	-	-	-
Thrombocytopenia	8 (21)	8 (21)	5 (15)	8 (24)	9 (24)	9 (24)
Gastrointestinal disorders						
Autoimmune hepatitis	0	1 (3)	0	1 (3)	-	-
Nausea	5 (13)	0	1 (3)	0	10 (27)	1 (3)
Vomiting	5 (13)	0	1 (3)	0	7 (19)	0
Colitis	-	-	-	-	0	1 (3)
Diarrhoea	3 (8)	0	1 (3)	2 (6)	5 (14)	0
General disorders and administration-site conditions						
Chills	5 (13)	0	3 (9)	0	6 (16)	0
Fatigue	14 (37)	1 (3)	8 (24)	6 (18)	18 (49)	10 (27)
Malaise	2 (6)	1 (3)	-	-	-	-
Oedema peripheral	1 (3)	1 (3)	0	0	3 (8)	1 (3)
Pyrexia	13 (34)	0	8 (24)	2 (6)	9 (24)	0
Hypothyroidism	2 (6)	1 (3)	2 (6)	0	1 (3)	0
Influenza-like illness	1 (3)	0	0	0	6 (16)	0
Injection-site reaction	1 (3)	0	3 (9)	0	7 (19)	0
Asthenia	-	-	1 (3)	0	4 (11)	0
Investigations						
Amylase increased	0	3 (8)	-	-	1 (3)	0
Alanine aminotransferase increased	5 (13)	2 (5)	0	1 (3)	4 (11)	1 (3)
Aspartate aminotransferase increased	7 (18)	2 (5)	0	1 (3)	3 (8)	2 (5)
Gamma-glutamyltransferase increased	0	1 (3)	1 (3)	0	3 (8)	0
Lipase increased	3 (8)	2 (5)	0	1 (3)	1 (3)	1 (3)
Serum ferritin increased	4 (11)	0	-	-	-	-
Weight decreased	3 (8)	0	-	-	2 (5)	0
Blood bilirubin increased	1 (3)	0	1 (3)	0	3 (8)	1 (3)
Lipids decreased	-	-	-	-	0	1 (3)
Platelet count decreased	11 (29)	2 (5)	5 (15)	1 (3)	4 (11)	2 (5)
Metabolism and nutrition disorders						

	RCC		NSCLC		Melanoma	
	Grade 1/2	**Grade 3/4**	**Grade 1/2**	**Grade 3/4**	**Grade 1/2**	**Grade 3/4**
Hypertriglyceridaemia	8 (21)	6 (16)	4 (12)	3 (9)	11 (30)	2 (5)
Hyperuricaemia	0	1 (3)	-	-	-	-
Decreased appetite	4 (11)	0	7 (21)	0	13 (35)	1 (3)
Hypolipidaemia	-	-	-	-	0	1 (3)
Hyperglycaemia	3 (8)	0	-	-	4 (11)	0
Musculoskeletal and connective tissue disorders						
Arthralgia	5 (13)	0	3 (9)	0	-	-
Muscular weakness	0	1 (3)	1 (3)	0	1 (3)	0
Myalgia	7 (18)	0	4 (12)	0	3 (8)	0
Vasculitis	0	1 (3)	-	-	-	-
Nervous system disorders						
Headache	6 (16)	0	2 (6)	0	8 (22)	0
Renal and urinary disorders						
Renal failure	0	1 (3)	0	1 (3)	-	-
Respiratory, thoracic, and mediastinal disorders						
Cough	2 (5)	0	-	-	7 (19)	0
Dyspnoea	3 (8)	0	3 (9)	0	6 (16)	0
Skin and subcutaneous tissue disorders						
Pruritus	8 (21)	2 (5)	5 (15)	0	8 (22)	0
Rash	9 (24)	0	6 (18)	1 (3)	3 (8)	0
Rash maculopapular	8 (21)	1 (3)	7 (21)	2 (6)	6 (16)	0
Night sweats	4 (11)	0	-	-	4 (11)	0
Eczema	0	1 (2.6)	-	-	-	-

All treatment-related adverse events are listed that occurred at any grade ≥10% in a subgroup or ≥1 patient for Grade 3/4. There were no Grade 5 events.

Table 3.

Best Overall Response

	All RCC	RCC ≥1 Prior n=29	RCC ≥ 1 Prior Peg Naive n=27	All NSCLC	NSCLC PD-L1 High n=6	NSCLC PD-L1 Low n=3	NSCLC PD-L1 negative n=12	All Melanoma	Melanoma PD-1 refractory n=20	Melanoma Not PD-1 refractory n=11
Evaluable	**N=35** [a]			**N=28** [b]				**N=31** [c]		
DCR, No. (%)	30 (85.7)	27 (93·1)	25 (92·6)	23 (82·1)	6 (100·0)	2 (66·7)	11 (91·7)	16 (51·6)	9 (45·0)	7 (63·6)
PR, No.	14	12	12	11	4	2	4	3	0	3
ORR, %	40·0	41·4	44·4	42·9	83·3	66·7	33·3	9·7	0	27·3
PR (−100%) *	3 (8·6)	2 (6·9)	2 (7·4)	1 (3·6)[d]	0	0	0	0	0	0
CR, No.	0	0	0	1	1	0	0	0	0	0
DoR, median, months	15·1	15·1	15·1	10·3	10·3	6·5	14·8	NA	NA	NA
Safety	**N=38**			**N=34**				**N=37**		
mPFS, months	12·5	15·4	16·7	9·4	10·7	8·9	11·0	2·2	2·1	4·0
1-year OS, %	86·2	86·9	93·1	73·5	85·7	33·3	84·6	64·5	60·0	72·7
mOS	NR	NR	NR	24·1	NR	10·4	25·4	16·7	16·7	17·8

[a] Median follow-up (range: Q1–Q3) for RCC was 22·7 months (20·9–27·0)Two RCC patients had partial responses with 100% reduction in measurable disease.

[b] Median follow-up for NSCLC was 26·9 months (22·3–31·5).

[c] Median follow-up for melanoma was 33·0 months (29·2–35·1).

[d] PD-L1 expression status was not determined.

* These patients had 100% reduction in target lesions, but response was confirmed by the investigator as partial response. Patients had remaining residual non-target lesions. Abbreviations: DCR=disease control rate. DOR=duration of response. mPFS=median progression-free survival. NR=not reached. ORR=objective response rate. OS=overall survival. PR=partial response. mOS=median overall survival. PD-L1 High=(≥50%). PD-L1 Low=(1–49%). PD-L1 negative=(<1%). Prior=prior treatment. Peg Naïve=no prior pegilodecakin. Study in progress. Numbers as of July 1, 2018.