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Immunologic and tumor responses of pegilodecakin with 5-FU/LV and oxaliplatin (FOLFOX) in pancreatic ductal adenocarcinoma (PDAC)

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Declarations

Conflict of Interest

J. Randolph Hecht declares honoraria from ARMO BioSciences a wholly owned subsidiary of Eli Lilly and Company, AstraZeneca, Bristol-Myers Squibb, Gritstone, Halozyme, Ipsen, Merck, Roche; research funding from Abbvie, Advaxis, Amgen, ARMO BioSciences a wholly owned subsidiary of Eli Lilly and Company, Astellas Pharma, Forty Seven, Halozyme, Immunomedics, Eli Lilly and Company, Merck, Novartis; and travel accommodations and expenses from Advaxis, Eli Lilly and Company. **Kyriakos P. Papadopoulos** declares research funding from Abbvie, Amgen, ArQule, ARMO Biosciences a wholly owned subsidiary of Eli Lilly and Company, ADC Therapeutics, Anheart, 3D Medicines, Basilia, Bayer, Calithera Biosciences, Daiichi Sankyo, EMD Serono, F-star, Incyte, Jounce Therapeutics, Linnaeus, Mabspace Biosciences, Merck, Mirati Therapeutics, MedImmune, Mersana, Peloton Therapeutics, Regeneron, Syros Pharmaceuticals and Tempest Therapeutics; advisory board fees from Arqule, Basilia, Bayer. **Gerald S. 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Immunologic and Tumor Responses of Pegilodecakin with 5-FU/LV and Oxaliplatin (FOLFOX) in Pancreatic Ductal Adenocarcinoma (PDAC)

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Ethical Approval

All procedures performed in the study involving human participants were in accordance with Good Clinical Practice Guidelines (GCP), the US Code of Federal Regulations governing the protection of human patients (21 CFR 50), International Conference on Harmonization (ICH) guidelines, local ethical requirements consistent with the current version of the Declaration of Helsinki, and the Institutional Review Board or Independent Ethics Committees (IEC; 21 CFR 56).

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Availability of data and material

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available for request 6 months after the indication studied has been approved in the US and EU 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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Summary

Background—Treatment options for pancreatic ductal adenocarcinoma (PDAC) are limited and checkpoint blockade inhibitors have been disappointing in this disease. Pegilodecakin has demonstrated single agent anti-tumor activity in immune-sensitive tumors. Phase 1 and preclinical data indicate synergy of pegilodecakin with 5-FU and platins. We assessed the safety and activity of pegilodecakin+FOLFOX in patients with PDAC.

Methods—IVY (NCT02009449) was an open-label phase 1b trial in the United States. Here we report on all enrolled patients from cohort C. Heavily pretreated patients were treated with pegilodecakin (self-administered subcutaneously daily at 2.5, 5, or 10μg/kg) + 5-flurouracil/leucovorin/oxaliplatin (FOLFOX), dosed per manufacturers prescribing information, until tumor progression. Eligible patients had measurable disease per immune-related response criteria (irRC), were ≥18 years of age, and had ECOG performance status of 0 or 1. Patients were evaluated for primary(safety) and secondary (tumor response per irRC) endpoints.

Results—From 5 August 2014–12 July 2016, 39 patients enrolled in cohort C. All patients were evaluable for safety. In this advanced population, regimen had manageable toxicities with no immune-related adverse events (irAEs) greater than grade 1. The most common grade 3/4/5 TEAEs were thrombocytopenia (21[53.8%] of 39) and anemia (17[43.6%] of 39). In evaluable PDAC patients, the best overall response of pegilodecakin+FOLFOX was 3(14%) with CRs in 2(9%) patients.

Conclusions—Pegilodecakin+FOLFOX had an acceptable tolerability profile in PDAC, with no substantial irAEs seen, and promising efficacy with the combination yielding a 2-year OS of 24% (95% CI 10–42). These data led to the phase 3 study with pegilodecakin+FOLFOX as second-line therapy of PDAC (SEQUOIA).

Keywords

Metastatic pancreatic adenocarcinoma; Pegilodecakin; FOLFOX; Phase 1; IL-10; pegylated IL-10

Introduction

Pancreatic cancer is the third leading cause of cancer-related death in the United States (US), with a 5-year survival rate of 6%. [1, 2] Most patients with advanced metastatic

pancreatic cancer receive albumin-bound paclitaxel (nab-paclitaxel) plus gemcitabine or FOLFIRINOX (folinic acid, 5-fluorouracil [5-FU], irinotecan, and oxaliplatin) in the first-line setting. [2, 3] However, alternative therapeutic options are needed for patients with PDAC that have progressed after treatment with gemcitabine.[4] FOLFOX has demonstrated acceptable tolerability and clinical activity as second-line therapy in metastatic pancreatic cancer patients who are refractory to first-line gemcitabine chemotherapy.[5] Phase 2 trials with FOLFOX4, FOLFOX6, and mFOLFOX have demonstrated objective response rates of 11.4%, 26.1%, and 7%, respectively.[6] 5-FU/folinic acid or nal-irinotecan + 5-FU/folinic acid therapy after tumor progression on or after first-line therapy with gemcitabine or gemcitabine/nab-paclitaxel achieved a mOS between 4.2 months and 6.1 months in second-line therapy.[7] The 1-year survival in second-line trials is 25%.[7] Meta-analysis of seven pooled studies involving FOLFOX in second line demonstrated a mOS of 6.3 months.[8]

Despite durable benefit in multiple tumor types with new immunotherapy approaches such as immune checkpoint inhibitors (ICI)[9], no objective responses were seen with anti-PD-1 or anti-PD-L1 in pancreatic cancer.[10, 11] Unlike immune-sensitive cancers such as renal cell carcinoma and melanoma, PDAC tumors are immune quiescent tumors, making them immunologically “cold”.[12] Pancreatic tumors have a low number of non-synonymous somatic mutations compared to immune sensitive cancers rendering them less immunogenic.[12] The dense fibrotic stroma and recruitment of immunosuppressive cells by the inflammatory cytokines and chemokines impose a formidable barrier to active T cell infiltration. [12, 13] Furthermore, a vast majority of the tumor-infiltrating CD8+ T cells are ϒδT cells that limit the activation of effector αBT cells. [14] Collectively, the tumor cells, immune milieu, and the stromal components present an unfavorable tumor microenvironment for ICI monotherapies to elicit an effective immune response.

IL-10 has anti-inflammatory properties, however at higher concentrations may stimulate durable tumor immunity.[15, 16] Pegilodecakin is a pegylated human IL-10 (PEG-hIL-10) [17]. In a phase I clinical trial, pegilodecakin monotherapy resulted in immune activation in patients with advanced solid tumors. Durable partial responses were seen in 27% of patients with heavily pretreated advanced renal cell cancer and also in other tumor types [17]. There was strong rationale for combining pegilodecakin with FOLFOX to improve survival in PDAC.

Due to the immune activation observed across tumor types and the encouraging results in advanced pancreatic cancer in the dose escalation phase of this study, pegilodecakin in combination with FOLFOX was further explored in patients with metastatic PDAC as part of this phase I trial.

Patients and methods

Study Design and Participants

Study IVY (NCT02009449) is a multi-institutional, open-label, multiple-cohort, dose-escalation, phase 1b study. Part C was the only cohort with pegilodecakin in combination with FOLFOX. Cohort C enrolled 39 patients (29 PDAC patients, 6 colorectal cancer patients, 2 gastric, and 2 “other” (1 neuroendocrine carcinoma of the colon and 1 liver

adenocarcinoma). Of the 29 PDAC patients, 2 were provided 2.5μg/kg, 2 received 10μg/kg, and 25 patients received 5μg/kg pegilodecakin. Here we will discuss the safety of the entire cohort C, and the activity outcomes for the 25 PDAC patients that received the dose expansion dose of 5μg/kg. Of note, this includes 4 patients who had received prior oxaliplatin therapy. Key eligibility criteria included histologically or cytologically confirmed advanced metastatic PDAC. Male or female patients were ≥ 18 years, Eastern Cooperative Oncology Group performance status 0–1, had at least one measurable lesion per the immune-related response criteria (irRC), and adequate organ function. All patients signed the approved consent forms for this multi-institutional study.

Procedures

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 2mL vials and self-administered subcutaneously daily in combination with modified FOLFOX6 (mFOLFOX6) at a flat dose of 0.2, 0.4, or 0.8 mg for patients with body weight < 80 kg, and 0.25, 0.5, and 1.0 mg for patients ≥ 80 kg. The mFOLFOX6 was administered using standard procedures and doses [18].

Tumor response was determined every 8 weeks by investigator assessment according to irRC [19]. Adverse events (AEs), serious adverse events (SAEs), and laboratory abnormalities were monitored until 30 days after last dose of treatment. Exploratory analysis of serum tumor marker CA19–9 was analyzed at the local lab.

Study endpoints

The primary objectives were to characterize safety and tolerability of pegilodecakin, pharmacokinetics (preliminary pharmacokinetic data was published in the phase 1B paper [17]; full population pharmacokinetic analysis is not yet available), and to determine the maximally tolerated dose (MTD; results previously disclosed)[17] with chemotherapy. Secondary objectives included the determination of anti-tumor activity and tumor response. Exploratory endpoints, prespecified in the protocol, included changes in CA19.9 and immune parameters.

Statistical Methods

IVY was designed to evaluate whether the safety and tolerability 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 tumor measurement. Adverse events were evaluated in the safety population and were coded using Medical Dictionary for Regulatory Activities (MedDRA, version 16.1). Severity grades followed NCI-CTCAE v. 4.02.

Response analyses were performed based on the evaluable population, and overall response rate (ORR) was defined as the percentage of evaluable patients with complete response (CR) and partial response (PR). The disease control rate (DCR) was defined as the percentage of patients with complete responses (CRs), partial responses (PRs) and stable disease (SD). Tumor measurements were assessed by the investigators following irRC. Survival analysis (PFS and OS) was calculated using the intent-to-treat (ITT) population. Progression-free survival was defined as the date from first dose of study drug(s) to the date of tumor progression or patient death, whichever occurred first. Overall survival was defined as the date from first dose of study drug(s) to death. Surviving patients are censored to the last contact date. PFS and OS were analyzed using the Kaplan-Meier method(Kaplan). The reported efficacy and safety data are as of February 19, 2019. 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 (IQR). 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.

Results

From August 5, 2014, to July 12, 2016, 39 patients were enrolled in cohort C. Baseline characteristics are displayed in Table 1. The median age in the PDAC patients was 66 years (IQR 58–70 years). Patients on pegilodecakin+FOLFOX had a median of 2 prior therapies (range 0–7) (Supplemental Table 1).

As of data cut-off on February 19, 2019, the median follow-up was 6.8 months (IQR 3.4–14.6). All 39 patients discontinued. The most common reasons for treatment discontinuation were disease progression (14 [35.9%] of 39 patients), clinical deterioration (13[33.3%] of 39 patients), and adverse events (4[10.3%] of 39 patients). There were deaths in 2(5.1%) of 39 patients, determined to be unrelated to treatment.

Safety results

Toxicity profiles were similar across the cohort. Safety analysis revealed at least one TEAE in all 39 patients. The most common grade ≥3 TEAEs on pegilodecakin with FOLFOX, were anemia (17 [43.6%] of 39), thrombocytopenia (21[53.8%] of 39), and neutropenia (13[33.3%] of 39)(Table 2). In the pegilodecakin+FOLFOX cohort, only grade 1 and 2 neuropathy was observed in 8(20.5%) of 39 patients (Table 2), despite common prior paclitaxel treatment in 26(66.7%) of 39 patients. Grade 1/2 irAEs such as pyrexia and asthenia were infrequent, occurring in 6(15.4%) of 39 and 5(12·8%) of 39 patients, respectively. No patients had grade 3/4/5 pyrexia or asthenia. There was no occurrence of grade ≥3 immune-related adverse events such as pneumonitis, thyroiditis, adrenal insufficiency, optic neuritis, or autoimmune hepatitis. Most common grade ≥3 serious adverse events included sepsis (in 4[10.3%] of 39) and dehydration (in 3[7.7%] of 39) (Supplemental Table 2).

Efficacy results

The 25 PDAC patients with 5μg/kg pegilodecakin in combination with FOLFOX are further described hereafter. Nine (36.0%) patients received at least 16 weeks of therapy (Fig. 1A), a median of 5 cycles (range: 1, 28) of pegilodecakin+FOLFOX treatment, and a median cumulative dose of 365 mg/m^2 oxaliplatin throughout the treatment. Among the 22 evaluable patients who received pegilodecakin+FOLFOX, overall response rate (ORR) was 13.6% with two patients with a complete response (CR) and one patient with a partial response (PR) with 100% reduction in all measurable lesions (Table 3 and Figure 1B). The time to response ranged from 1.4 to 4.5 months, with median time to response of 1.8 months. The responses were all durable for at least 10 months, with a median duration of response of 11.5 months. Median PFS (mPFS) and mOS were 2.6 and 6.8 months, respectively (Table 3). The estimated one and two-year survival rates were 36.0% and 24.0%, respectively (Table 3; Fig. 2A).

Twelve (63.2%) of 19 evaluable patients had an elevated baseline and at least one on-treatment measurement of the tumor marker CA19–9. The combination therapy induced a reduction of the tumor marker CA19–9 in 8 (66.7%) of 12 patients. Five (41.7%) of the 12 patients had a reduction of ≥ 60% in CA19–9 (Fig. 2B).

Discussion

We present data on pegilodecakin in combination with FOLFOX in pancreatic cancer, a tumor type which has been refractory to a variety of immune therapy approaches [20, 21]. Overall, treatment was well-tolerated, and the most common toxicities were anemia and thrombocytopenia. With adjustment of the dosing schedule to administer pegilodecakin SC daily for 5 days and rest for 2 days, further grade 3–4 hematologic toxicities were reduced. No unexpected significant non-hematologic side effects were observed, and in particular, no irAEs were reported greater than grade 1. Low grade peripheral neuropathy was observed in 8(20.5%) of 39 patients on pegilodecakin and FOLFOX. There were no cases of grade ≥3 neuropathy reported. Pancreatic cancer patients on oxaliplatin-based regimens frequently develop neuropathy (51.8%) with grade 3/4 events reported in 7.4% of patients [4]. While the lack of grade ≥3 neuropathy could be related to a relatively small sample size, recombinant IL-10 has been shown to decrease macrophage recruitment, inflammation, and hyperalgesia in a chronic neuropathy model in mice [22]. It is plausible that the apparent reduced incidence of neuropathy may be mediated by the reduction of neuroinflammation by pegilodecakin.

The main limitation of this study was the lack of comparator arm. Other considerations included the relatively small sample size and patient heterogeneity, such as variability in the number and types of prior therapies. In light of these limitations, cross-trial comparisons should be viewed with reservation. Although this is a small and non-randomized trial, the data appear promising when viewed in the context of the very low response rate to oxaliplatin and 5-FU combinations (<2.5%) and the 6 months OS seen in contemporary trials with oxaliplatin or nal-irinotecan based regimen in similar patient populations [4, 7, 23].

Although objective tumor responses were not observed previously with pegilodecakin monotherapy[24], the addition of pegilodecakin to FOLFOX provided CA19–9 declines in 8 (66.7%) of 12 patients, 68.2% DCR, and a 36.0% estimated one-year survival in this heavily pre-treated population. Two patients had complete responses, and one patient had a partial response with 100% tumor reduction.

The combination of immuno-oncology strategies with oxaliplatin showed preclinical efficacy. Oxaliplatin induced immunogenic tumor cell death and decreased Tregs,[25] but oxaliplatin alone may not have been sufficient to lead to a sustained immune response [26]. Therefore, the combination with pegilodecakin may improve tumor immunity and response. Subsequent phase III study SEQUOIA (NCT02923921) followed IVY to assess whether pegilodecakin in combination with FOLFOX improves survival in patients with second-line PDAC. IVY is registered with ClinicalTrials.gov, NCT02009449.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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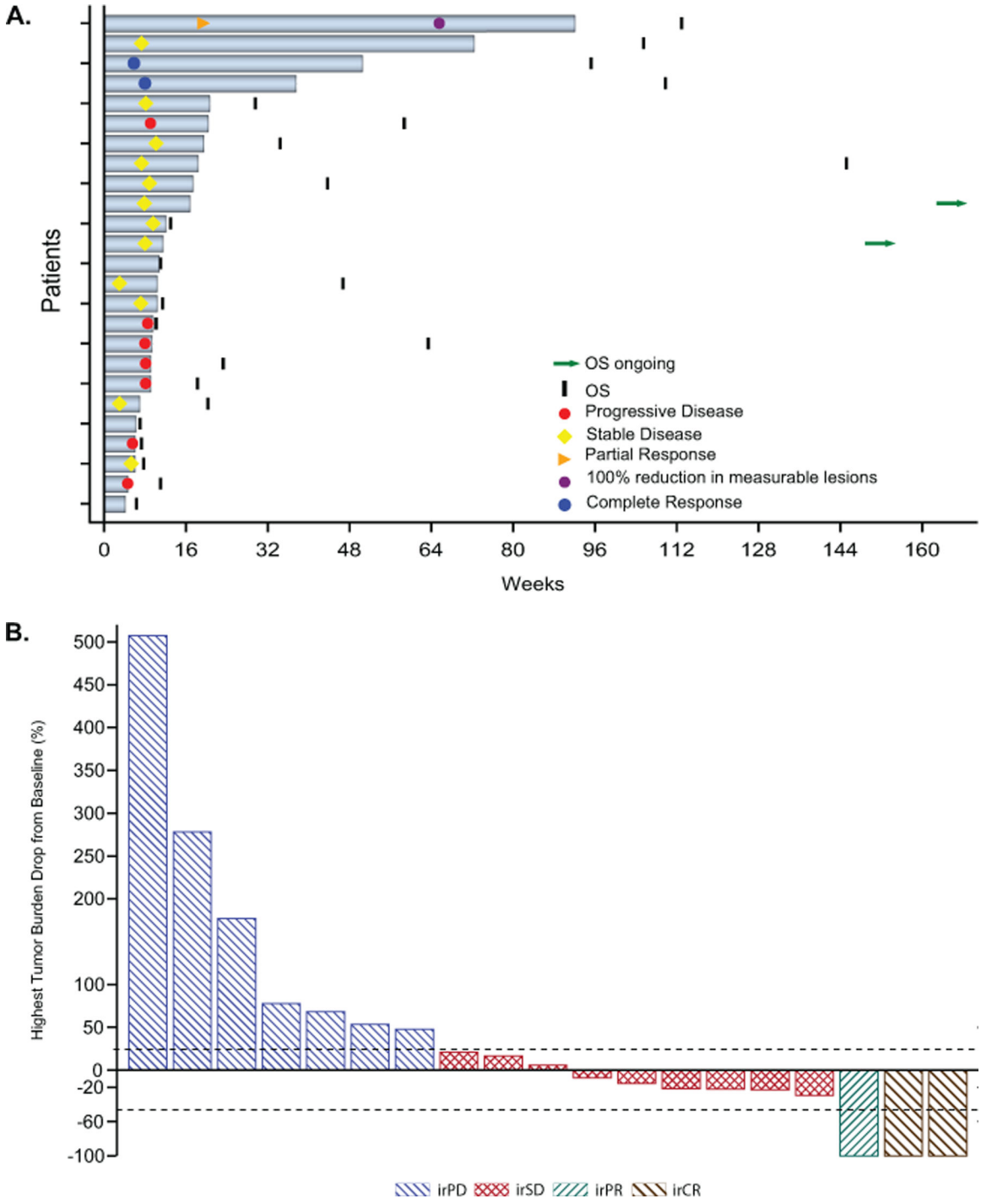

Fig 1.

Treatment duration and change in tumor size A) Tumor burden by irRC in safety population of patients with PDAC receiving pegilodecakin (5μg/kg) and FOLFOX (n=25). Response characteristics, time on therapy, and ongoing overall survival is indicated on the plot. B) Waterfall plot depicts change in tumor size in the evaluable population (n=19). Baseline

tumor burden is normalized to zero (0%). Horizontal line indicates the threshold for defining partial response (-50%) and progressive disease (+25%) according to irRC.

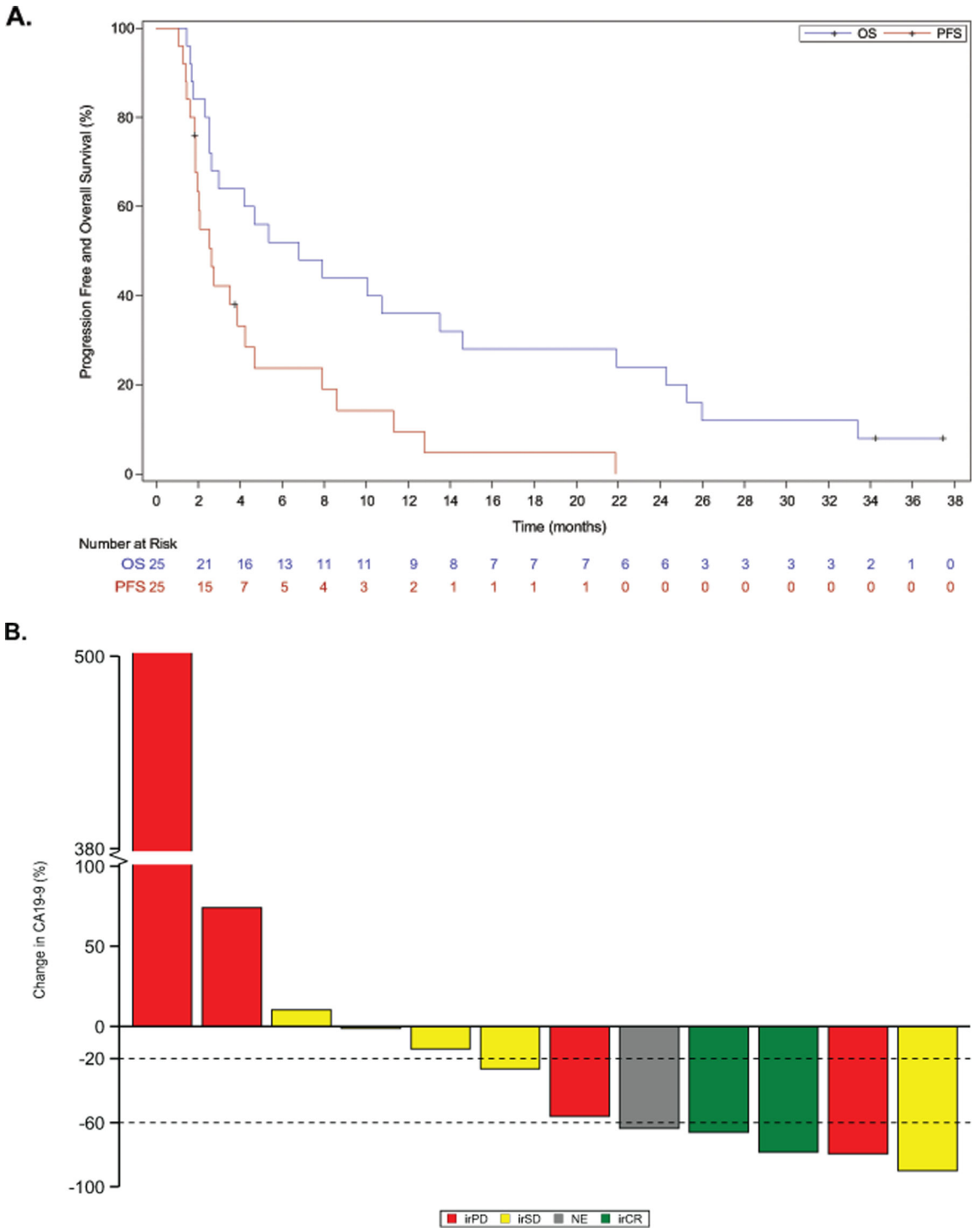

Fig 2.

Clinical activity and tumor marker response of pegilodecakin+FOLFOX A) Kaplan Meier plot of overall survival and progression free survival for PDAC patients on pegilodecakin+FOLFOX (N=25). Censored patients are shown below the graph. B) Tumor marker CA19–9 response in relation to baseline in patients on pegilodecakin+FOLFOX

(N=12). All patients with a baseline and at least one on treatment value were included. Horizontal dotted line indicates a reduction by 20 or 60 percent from baseline.

Table 1.

Baseline Characteristics

	PDAC patients (N=29)	CRC patients (N=6)	Gastric (N=2)	Other[a] (N=2)
Median Age, years [IQR]	66 [58–70]	57.5 [41–59]	51 [50–52]	61.5 [56–67]
Current TNM stage, n (%)				
Stage II	1 (3.5)	0	0	0
Stage III	1 (3.5)	0	0	0
Stage IV	27 (93.1)	6 (100)	2 (100)	2 (100)
Disease site at diagnosis, n (%)				
Bone	1 (3.5)	0	0	0
CNS	0	1 (16.7)	0	0
Colon	1 (3.5)	5 (83.3)	0	1 (50.0)
Distant lymph nodes	9 (31.0)	2 (33.3)	1 (50.0)	0
Kidney	1 (3.5)	0	0	0
Liver	6 (20.7)	4 (66.7)	2 (100)	2 (100)
Lung	6 (20.7)	3 (50.0)	1 (50.0)	0
Other	7 (24.1)	2 (33.3)	2 (100)	1 (50.0)
Pancreas	21 (72.4)	0	0	0
Race, n (%)				
Asian	4 (13.8)	0	0	0
African American	1 (3.5)	2 (33.3)	0	0
Missing	1 (3.5)	0	0	1 (50.0)
White	23 (79.3)	4 (66.7)	2 (100)	1 (50.0)
Sex, n (%)				
Male	20 (69.0)	5 (83.3)	2 (100)	2 (100)
Female	9 (31.0)	1 (16.7)	0	0
ECOG Performance Status, n (%)				
0	11 (38.0)	1 (16.7)	1 (50.0)	2 (100)
1	18 (62.1)	5 (83.3)	1 (50.0)	0
Prior Therapy, n (%)				
0	1 (3.5)	0	0	0
≥1	28 (96.6)	6 (100)	2 (100)	2 (100)

[a]These included 1 liver adenocarcinoma and 1 neuroendocrine carcinoma of the colon.

Abbreviation list: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; PDAC, pancreatic ductal adenocarcinoma; CRC, colorectal carcinoma; IQR, interquartile range; TNM, tumor node and metastasis; N, number of patients in safety population; n, number of patients in subgroup.

Table 2.

Treatment-Emergent Adverse Events

	PDAC (N = 29)		CRC (N=6)		Gastric (N=2)		Other[a] (N=2)	
	G1/2	G3/4/5	G1/2	G3/4/5	G1/2	G3/4/5	G1/2	G3/4/5
Patients with any TEAE, n (%)	3(10.3)	26(89.7)	0	6(100)	0	2(100)	0	2(100)
Blood and lymphatic system disorders								
Anemia	7(24.1)	14(48.3)	1(16.7)	2(33.3)	0	1(50.0)	1(50.0)	0
Thrombocytopenia	6(20.7)	18(62.1)	2(33.3)	1(16.7)	1(50.0)	1(50.0)	0	1(50.0)
Neutropenia	3(10.3)	12(41.4)	2(33.3)	0 (0)	1(50.0)	1(50.0)	1(50.0)	0
Leukopenia	2(6.9)	5(17.2)	0	1(16.7)	1(50.0)	0	0	0
Leukocytosis	1(3.4)	0	0	0	2(100)	0	0	0
Cardiac disorders								
Cardiac failure congestive	0	0	0	1(16.7)	0	0	0	0
Myocardial infarction	0	0	0	1(16.7)	0	0	0	0
Tachycardia	1(3.4)	0	1(16.7)	0	0	0	0	0
Gastrointestinal disorders								
Nausea	14(48.3)	1(3.4)	2(33.3)	0	1(50.0)	0	0	1(50.0)
Vomiting	7(24.1)	2(6.9)	0	0	2(100)	0	0	1(50.0)
Abdominal pain	11(37.9)	0	0	0	0	0	0	0
Abdominal pain upper	4(13.8)	0	0	0	0	0	0	0
Ascites	5(17.2)	0	0	0	0	0	0	0
Constipation	5(17.2)	0	1(16.7)	0	1(50.0)	0	0	0
Diarrhea	5(17.2)	0	0	1(16.7)	0	0	0	0
Dysphagia	1(3.4)	0	0	0	0	1(50.0)	1(50.0)	0
Gastrointestinal reflux disease	3(10.3)	0	1(16.7)	0	0	0	0	0
Hyperaesthesia teeth	0	0	0	0	0	0	1(50.0)	0
Oral disorder	0	0	1(16.7)	0	0	0	0	0
Abdominal distension	3(10.3)	0	0	0	0	0	0	0
General disorders and administration site conditions								
Fatigue	20(69.0)	4(13.8)	2(33.3)	0	1(50.0)	0	2(100)	0
Asthenia	3(10.3)	0	1(16.7)	0	0	0	1(50.0)	0
Cathether site pain	0	0	0	0	1(50.0)	0	0	0
Cathether site rash	0	0	0	0	0	0	1(50.0)	0
Chest pain	1(3.4)	1(3.4)	1(16.7)	0	0	0	0	0
Injection site erythema	2(6.9)	0	1(16.7)	0	0	0	1(50.0)	0
Injection site rash	4(13.8)	0	1(16.7)	0	0	0	0	0
Injection site reaction	1(3.4)	0	0	0	1(50.0)	0	0	0
Injection site urticaria	0	0	0	0	0	0	1(50.0)	0
Edema peripheral	5(17.2)	0	0	0	0	0	1(50.0)	0
Pyrexia	4(13.8)	0	1(16.7)	0	0	0	1(50.0)	0
Temperature intolerance	3(10.3)	0	0	0	1(50.0)	0	1(50.0)	0
Hepatobiliary disorders								

	PDAC (N = 29)		CRC (N=6)		Gastric (N=2)		Other[a] (N=2)	
	G1/2	G3/4/5	G1/2	G3/4/5	G1/2	G3/4/5	G1/2	G3/4/5
Hyperbilirubinemia	0	1(3.4)	1(16.7)	1(16.7)	1(50.0)	0	0	0
Infections and infestations								
Abdominal wall abscess	0	0	0	1(16.7)	0	0	0	0
Pneumonia	2(6.9)	0	1(16.7)	0	0	0	0	1(50.0)
Sepsis	0	4(13.8)	0	0	0	0	0	0
Bacteremia	0	0	0	1(16.7)	0	0	0	0
Oral herpes	1(3.4)	0	1(16.7)	0	0	0	0	0
Pharyngitis streptococcal	0	0	0	0	0	0	1(50.0)	0
Urinary tract infection	6(20.7)	0	1(16.7)	0	1(50.0)	0	1(50.0)	0
Injury, poisoning, and procedural complications								
Skin laceration	0	0	1(16.7)	0	0	0	0	0
Stoma site hemorrhage	0	0	1(16.7)	0	0	0	0	0
Investigations								
Alanine aminotransferase increased	3(10.3)	0	0	0	0	0	0	0
Aspartate aminotransferase increased	4(13.8)	1(3.4)	0	0	0	0	0	0
Blood alkaline phosphatase increased	2(6.9)	2(6.9)	0	0	0	0	0	0
Blood bilirubin increased	2(6.9)	4(13.8)	0	0	0	0	0	0
Blood creatinine increased	0	0	0	0	0	0	1(50.0)	0
Platelet count decreased	0	3(10.3)	0	0	0	0	0	0
Weight decreased	7(24.1)	0	0	0	1(50.0)	0	1(50.0)	0
Metabolism and nutrition disorders								
Decreased appetite	11(37.9)	0	1(16.7)	0	1(50.0)	0	1(50.0)	0
Dehydration	3(10.3)	4(13.8)	1(16.7)	0	0	1(50.0)	2(100)	0
Hyperglycemia	3(10.3)	1(3.4)	0	0	0	0	0	1(50.0)
Hyperlipidemia	0	0	1(16.7)	0	0	0	0	0
Hypertriglyceridemia	4(13.8)	0	1(16.7)	1(16.7)	0	0	0	0
Hypocalcemia	3(10.3)	0	0	0	0	0	0	0
Hypokalemia	4(13.8)	2(6.9)	1(16.7)	0	1(50.0)	0	0	0
Hypomagnesemia	1(3.4)	0	1(16.7)	0	0	0	0	0
Hyponatremia	1(3.4)	2(6.9)	1(16.7)	0	0	0	0	0
Hypophosphatemia	0	1(3.4)	0	1(16.7)	0	0	0	0
Vitamin K deficiency	0	0	1(16.7)	0	0	0	0	0
Musculoskeletal and connective tissue disorders								
Arthralgia	4(13.8)	0	0	0	1(50.0)	0	0	0
Back pain	1(3.4)	1(3.4)	1(16.7)	0	0	0	1(50.0)	0
Muscle spasms	0	0	0	0	0	0	1(50.0)	0
Musculoskeletal chest pain	0	0	1(16.7)	0	0	1(50.0)	1(50.0)	0
Myalgia	3(10.3)	0	0	0	0	0	0	0
Nervous system disorders								
Dizziness	4(13.8)	0	1(16.7)	0	0	0	1(50.0)	0
Dysgeusia	0	0	0	0	0	0	1(50.0)	0

	PDAC (N = 29)		CRC (N=6)		Gastric (N=2)		Other[a] (N=2)	
	G1/2	G3/4/5	G1/2	G3/4/5	G1/2	G3/4/5	G1/2	G3/4/5
Headache	3(10.3)	0	0	0	1(50.0)	0	0	0
Neuropathy peripheral	6(20.7)	0	0	0	1(50.0)	0	1(50.0)	0
Syncope	2(6.9)	1(3.4)	0	0	0	0	0	0
Tunnel vision	0	0	0	0	0	1(50.0)	0	0
Psychiatric disorders								
Anxiety	1(3.4)	0	0	0	0	0	1(50.0)	0
Insomnia	4(13.8)	0	0	0	0	0	1(50.0)	0
Libido decreased	0	0	0	0	0	0	1(50.0)	0
Renal and urinary disorders								
Dysuria	0	0	1(16.7)	0	0	0	1(50.0)	0
Reproductive system and breast disorders								
Erectile dysfunction	0	0	0	0	0	0	1(50.0)	0
Respiratory, thoracic, and mediastinal disorders								
Allergic respiratory symptom	0	0	0	1(16.7)	0	0	0	0
Cough	6(20.7)	0	2(33.3)	0	0	0	1(50.0)	0
Dysphonia	0	0	0	0	0	0	1(50.0)	0
Dyspnea	5(17.2)	0	0	0	1(50.0)	0	1(50.0)	0
Epistaxis	1(3.4)	0	1(16.7)	0	0	0	1(50.0)	0
Hypoxia	0	1(3.4)	0	0	0	0	0	0
Paranasal sinus discomfort	0	0	1(16.7)	0	0	0	0	0
Respiratory tract congestion	0	0	0	0	0	0	1(50.0)	0
Sinus congestion	0	0	1(16.7)	0	0	0	0	0
Skin and subcutaneous tissue disorders								
Dry skin	3(10.3)	0	0	0	0	0	0	0
Hyperhidrosis	0	0	0	0	0	0	1(50.0)	0
Pruritis	2(6.9)	0	0	1(16.7)	0	0	0	0
Rash	2(6.9)	0	0	0	0	0	1(50.0)	0
Rash erythematous	0	0	0	0	1(50.0)	0	0	0
Skin fissures	1(3.4)	0	0	0	0	0	1(50.0)	0
Urticaria	0	0	1(16.7)	0	0	0	0	0
Vascular disorders								
Deep vein thrombosis	1(3.4)	0	1(16.7)	0	0	0	0	0
Flushing	0	0	0	0	0	0	1(50.0)	0
Hypotension	2(6.9)	1(3.4)	1(16.7)	0	0	0	0	0
Peripheral coldness	0	0	0	0	0	0	1(50.0)	0
Thrombosis	0	0	0	0	1(50.0)	0	0	0

All treatment-emergent adverse events are listed that occurred at any grade ≥10% in a subgroup.`

[a]These included 1 liver adenocarcinoma and 1 neuroendocrine carcinoma of the colon.

Abbreviation list: PDAC, pancreatic ductal adenocarcinoma; CRC, colorectal carcinoma; G, grade; TEAE, treatment-emergent adverse event; N, number of patients in safety population; n, number of patients in subgroup.

Table 3.

Clinical Response and Survival

	Pegilodecakin (5μg/kg) + FOLFOX (N = 25)[b]
Evaluable population, n	22
Overall response rate [a], n (%)	3 (13.6)
Disease control rate, n (%)	15 (68.2)
irCR, n (%)	2 (9.1)
irPR, n (%)	1 (4.5)
irSD, n (%)	12 (54.5)
irPD, n (%)	7 (31.8)
Safety population, n	25
mPFS (95% CI)	2.6 (1.9, 4.2)
mOS (95% CI)	6.8 (2.6, 14.6)
1-year OS (%)	36.0
2-year OS (%)	24.0

Data cut 19 February 2019.

[a] Using irRC

[b] Based on evaluable patients (having baseline scan and at least 1 post-baseline scan).

Abbreviations: irCR, immune-related complete response; irPD, immune-related progressive disease; irPR, immune-related partial response; irRC, immune-related response criteria; irSD, immune-related stable disease; N, number of evaluable patients; n, number of patients in subgroup; mPFS, median progression free survival; mOS, median overall survival; CI, confidence interval. Median PFS and mOS are shown in months. Overall response rate= irCR + irPR; Disease control rate = irCR + irPR + irSD.