First-in-Human Study of PF-06647020 (Cofetuzumab Pelidotin), an Antibody-Drug Conjugate Targeting Protein Tyrosine Kinase 7 (PTK7), in Advanced Solid Tumors

Michael L. Maitland[1]*, Jasgit C. Sachdev[2]*, Manish R. Sharma[3], Victor Moreno[4], Valentina Boni[5], Shivaani Kummar[6], Erica Stringer-Reasor[7], Nehal Lakhani[8], Allison R. Moreau[9], Dawei Xuan[9], Ray Li[9], Eric L. Powell[9], Amy Jackson-Fisher[9], Michelle Bowers[9], Shilpa Alekar[9], Xiaohua Xin[9], Anthony W. Tolcher[10], and Emiliano Calvo[5]

[1]Inova Schar Cancer Institute and Center for Personalized Health, University of Virginia Cancer Center, Fairfax, Virginia. [2]HonorHealth Research Institute/TGen, Scottsdale, Arizona. [3]University of Chicago, Chicago, Illinois. [4]START Madrid-FJD, Hospital Universitario Fundacion Jimenez Diaz, Madrid, Spain. [5]START Madrid-CIOCC, HM Hospital Sanchinarro, Madrid, Spain. [6]Stanford University School of Medicine, Stanford, California. [7]University of Alabama Comprehensive Cancer Center, Birmingham, Alabama. [8]START Midwest, Grand Rapids, MI, USA. [9]Pfizer, San Diego, California. [10]NEXT Oncology, San Antonio, Texas.

*M. L. Maitland and J. C. Sachdev contributed equally to this work.

Running title: PF-06647020 in patients with advanced solid tumors.

Keywords: PF-06647020, PTK7, ADC, non-small-cell lung cancer, ovarian cancer.

Funding: This study was sponsored by Pfizer.

Corresponding author: Michael L. Maitland, M.D., Ph.D., Inova Schar Cancer Institute and Center for Personalized Health, University of Virginia Cancer Center, 8081 Innovation Park Drive, Third Floor, Fairfax, VA 22031.

Email: michael.maitland@inova.org

Conflict of interest disclosure: M. L. Maitland disclosed institutional research funding to Inova Health System from Pfizer. J. Sachdev disclosed grants/research support from Celgene, Genentech, and Pfizer; advisory board participation for Celgene, Ipsen, Novartis, Pfizer, PUMA, TapImmune, Tempus, and TTC Oncology; honoraria from Celgene, Ipsen, Novartis, Pfizer, PUMA, and Tempus; and travel support from Celgene. M. R. Sharma disclosed institutional research funding to START Midwest from Pfizer, and ownership of Pfizer stock. V. Moreno disclosed consulting honoraria from Bayer, BMS, Janssen, and Pieris; travelling support from Bayer, BMS, and Regeneron/Sanofi; speaker´s bureau honoraria from Bayer, BMS, and Nanobiotix; and an educational grant from Medscape/Bayer. V. Boni disclosed advisory board participation for CytomX, Ideaya, Loxo Therapeutics, and Puma; and consulting for Guidepoints and Oncoart. S. Kummar disclosed consulting for Boehringer Ingelheim, Mundipharma EDO Gmbh, Seattle Genetics, Springworks Therapeutics, and Varian; consulting and advisory board participation for Bayer, Genome & Company, Gilead, and Harbour Biomed; cofounder role/equity in PathomIQ; and spouse role as scientific advisor for Cadilla Pharmaceutical ltd. and founder of Arxeon Inc. E. Stringer-Reasor disclosed consulting for Mylan Biosimilars and Novartis; consulting and speaker honoraria from Lilly; and institutional clinical trial funding from Pfizer. N. Lakhani disclosed clinical trial funding to START Midwest from Alpine Biosciences, ALX Therapeutics, Apexian, Asana, Ascentage, Beigene, Celgene, Constellation Pharmaceuticals, CytomX, Formation Biologics, Forty Seven Inc., Ikena, Incyte, InhibRx, Innovent Biologics, Jounce, Livzon, Loxo Oncology, Macrogenics, Merck, Mersana, Northern Biologics, Odonate Therapeutics, Pfizer, Regeneron, Sapience Therapeutics, Shattuck Labs, Symphogen; and advisory committee honoraria from Innovent Biologics. A. R. Moreau, D. Xuan, R. Li, E. L. Powell, A. Jackson-Fisher, M. Bowers, S. Alekar, and X. Xin were employees of and owned stock in Pfizer Inc. at the time of this study. A. W. Tolcher disclosed consulting for AbbVie, Adagene, Agenus, Aro Biotherapeutics, Ascentage, Aximmune, Bayer, Bioinvent, Birdie, Cello Health, Ellipses, EMD Serono, Five Prime, Forbius, Gilde Healthcare Partners, Immunomet, HBM Partners, Karma Oncology, Mekanistic, Menarini, Mersana, Nanobiotix, Nuvalent, OSI, Partner Therapeutics, Pfizer, Pieris, Pierre Fabre, Ridgeway, Ryvu Therapeutics, Scitemex, Seattle Genetics, Symphogen, Syneos, and TFS Trial Form Support

International; and advisory board membership for Abgenomics, Adagene, ADC Therapeutics, Aro Biotherapeutics, Bioinvent, Eleven Bio, Elucida, Immunome, Jazz Therapeutics, NBE Therapeutics, Pelican, PSI Pharma, Support America, Inc, TFS Trial Form Support International, and Zymeworks. E. Caldo disclosed research support from AstraZeneca, BeiGene, and Novartis; leadership or ownership for START Madrid, Oncoart Associated, International Cancer Consultants, and HM Hospitals Group; consulting for AbbVie, Amcure, Astellas Pharma, AstraZeneca, BMS, Boehringer-Ingelheim, Celgene, Cerulean, EUSA Pharmaceuticals, Gehrman Consulting, Gilead, GLG, Guidepoint, Janssen, Medscape, Merck, Pfizer, Nanobiotix, Novartis, Pierre-Fabre, PsiOxus, Roche/Genentech, Seattle Genetics, and Servier; speaker honoraria from Novartis, Pfizer, and Roche/Genentech; and institutional research funding from AbbVie, ACEA Bio, Amcure, Amgen, Astellas, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Boston Therapeutics, BMS, Cytomx, Daiichi, DebioPharma, Dynavax, Eisai, GSK, H3-Biomedicine, Hospira, Incyte, Innovio, Janssen Oncology, Kura, Lilly, Loxo, Macrogenics, Menarini, Merck, Mersana, Merus, Millennium, MSD, Nanobiotix, Nektar, Novartis, OncoMed, ORCA, Pfizer, PharmaMar, Principia, PsiOxus Therapeutics, Puma Biotechnology, Regeneron, Rigontec, Roche/Genentech, Sanofi, Seattle Genetics, Spectrum Pharmaceuticals, Synthon, Tahio, Takeda, Tesaro, and Transgene.

Journal: *Clinical Cancer Research*
Article type: Original Research Article
Abstract word count: 250
Text word count: ~4408
References: 29
Tables and Figures: 4 Tables / 2 Figures = 6
Supplementary Information: 2 Figures / 4 Tables

Translational Relevance

The transmembrane protein tyrosine kinase 7 (PTK7), involved in Wnt signaling, is overexpressed in multiple tumor types, including advanced non-small-cell lung cancer (NSCLC), ovarian cancer (OvCa), and triple-negative breast cancer (TNBC). Also expressed in tumor-initiating cells (TICs) or cancer stem cells, PTK7 is a tumor-associated target for elimination of cancer cells and TICs.

PF-06647020 (cofetuzumab pelidotin) is a humanized, anti-PTK7 antibody–drug conjugate (ADC), designed to deliver an auristatin microtubule inhibitor payload (Aur0101) into target cells. It was shown to induce prolonged tumor regression in patient-derived, tumor xenograft preclinical models. In this first-in-human, dose-finding study, PF-06647020 administered every 2 or 3 weeks demonstrated a tolerable safety profile and preliminary clinical activity in previously treated patients with locally advanced/metastatic, PTK7-positive NSCLC, TNBC, and platinum-resistant OvCa, suggesting the feasibility of this PTK7-targeting approach. Further clinical investigations are ongoing to assess the therapeutic potential of PF-06647020/cofetuzumab pelidotin in advanced, PTK7-positive cancers.

Abstract

Purpose: We investigated safety, tolerability, pharmacokinetics, and antitumor activity of the protein tyrosine kinase 7 (PTK7)-targeted, auristatin-based antibody–drug conjugate (ADC) PF-06647020/cofetuzumab pelidotin (NCT02222922).

Experimental Design: Patients received PF-06647020 IV every 3 weeks (Q3W) at 0.2–3.7 mg/kg or Q2W at 2.1–3.2 mg/kg, in sequential dose-escalation, following a modified toxicity probability interval method. In dose expansion, pretreated patients with advanced, platinum-resistant ovarian cancer (OvCa), non-small-cell lung cancer (NSCLC) or triple-negative breast cancer (TNBC) received PF-06647020 2.8 mg/kg Q3W.

Results: The most common, treatment-related adverse events (TRAEs) for PF-06647020 administered Q3W were nausea, alopecia, fatigue, headache, neutropenia, and vomiting (45%-25%); 25% of patients had grade ≥ 3 neutropenia. Two patients experienced dose-limiting toxicities (DLTs, grade 3 headache and fatigue) at the highest Q3W dose evaluated. The recommended phase 2 dose was 2.8 mg/kg Q3W. The overall safety profile observed with PF-06647020 administered Q2W was similar to that of the Q3W regimen. Systemic exposure for the ADC and total antibody generally increased in a dose-proportional manner. Antitumor activity was observed in treated patients with overall objective response rates of 27% in OvCa (*n* = 63), 19% in NSCLC (*n* = 31) and 21% in TNBC (*n* = 29). Responders tended to have moderate or high PTK7 tumor expression by immunohistochemistry.

Conclusions: This PTK7-targeted ADC demonstrated therapeutic activity in previously treated patients with OvCa, NSCLC, and TNBC at a dose range of 2.1-3.2

mg/kg, supporting further clinical evaluation to refine dose, schedule, and predictive tissue biomarker testing in patients with advanced malignancies.

Introduction

PTK7 is a highly conserved, catalytically inactive, transmembrane protein tyrosine kinase (PTK), involved in Wnt signaling during development of hematopoietic and somatic progenitor cells as well as stem cells (1, 2). It is overexpressed in multiple tumor types, including advanced non-small-cell lung cancer (NSCLC), ovarian cancer (OvCa), triple-negative breast cancer (TNBC), and colon, gastric, and esophageal cancers (3-8).

PTK7 overexpression has been associated with a poor prognosis and worse overall survival in patients with NSCLC, TNBC, and other solid tumor types (3-8). In addition, immunohistochemical (IHC) analysis of tumor tissue from patients with lung adenocarcinoma indicated that PTK7 expression correlated with the presence of lymph node metastases (8). PTK7 has also been shown to be enriched in tumor-initiating cells (TICs) or cancer stem cells in patient-derived tumor tissues (9-11). Thus, PTK7 is a tumor-associated target that may facilitate elimination of cancer cells as well as the TICs responsible for tumor recurrence and progression.

PF-06647020 (cofetuzumab pelidotin) is an antibody–drug conjugate (ADC) comprising a humanized anti-PTK7 monoclonal antibody (mAb hu6M024, IgG1) joined to a proprietary auristatin microtubule inhibitor payload, auristatin-0101 (Aur0101), by a cleavable valine-citrulline (“vc”) based linker (drug/mAb ratio: 4) (9, 12-15). Following binding and internalization of the ADC PF-06647020 into PTK7-expressing cells, the cleavable linker is processed by endosomal proteases leading to release of the auristatin payload, microtubule disruption, induction of mitotic arrest (G2/M phase), and

apoptotic cell death in target cancer cells (9, 12). Preclinical studies have demonstrated sustained tumor regression in patient-derived xenograft (PDX) models following administration of PF-06647020, with greater antitumor activity than standard chemotherapy (9). In addition, serial transplantation experiments showed that treatment with PF-06647020 reduced the frequency of TICs (9).

Based on these findings, we investigated safety, pharmacokinetics (PK), and preliminary therapeutic activity of PF-06647020 in a first-in-human, phase I study of patients with advanced solid tumors resistant to or with no available standard therapy. Following completion of dose escalation with once every 3 weeks (Q3W) infusion, a range of doses was explored with once every 2 weeks (Q2W) infusion and treatment with single-agent PF-06647020 was further evaluated in expansion cohorts of previously treated patients with advanced NSCLC, TNBC, or platinum-resistant OvCa.

Patients and Methods

Study design and treatment

This was a phase I, open label, multi-center, non-randomized, dose-escalation and dose-expansion study designed to evaluate PF-06647020, administered Q3W or Q2W, in patients with advanced solid tumors.

Primary objectives of dose escalation were to assess safety and tolerability of treatment with PF-06647020, to determine the MTD and select the recommended phase 2 dose (RP2D). Secondary objectives included evaluation of PK profiles (ADC: PF-06647020, total antibody: hu6M024, and unconjugated payload: PF-06380101), immunogenicity, and antitumor activity of PF-06647020 in patients with advanced solid tumors. Dose escalation was guided by the modified toxicity probability interval (mTPI)

method, with a target dose-limiting toxicity (DLT) rate of 25% and an acceptable DLT interval of 20-30%.

Patients received PF-06647020 intravenously (IV) Q3W at doses ranging from 0.2 mg/kg to 3.7 mg/kg or Q2W at 2.1, 2.8, and 3.2 mg/kg, in sequential dose-escalation cohorts (**Supplementary Figure S1**). The duration of the IV drug infusion was approximately 60 minutes for all dose levels. The starting dose of 0.2 mg/kg given as an IV infusion Q3W represented ~1/6th of the highest non-severely toxic dose (HNSTD) assessed in monkeys (based on the human equivalent dose, normalized to body surface area). For Q2W dosing, 2.1 mg/kg represented 75% of the most commonly tolerated dose of 2.8 mg/kg for PF-06647020 administered Q3W in the first part of the study. Pharmacokinetic modeling based on the initial data from the Q3W patients suggested that the cumulative exposure of 6 weeks with 2.1 mg/kg Q2W dosing would be comparable to that achieved with 2.8 mg/kg Q3W dosing with a potentially superior therapeutic index (14).

In dose expansion, patients were treated with PF-06647020 IV at the RP2D of 2.8 mg/kg Q3W. Primary objectives of dose expansion were to further evaluate safety and tolerability of treatment specifically in patients with advanced OvCa, NSCLC, and TNBC. Secondary objectives included evaluation of the clinical antitumor activity, PK, and immunogenicity of PF-06647020 in these patient cohorts.

Biomarker (i.e. PTK7 protein expression level) assessments were an eligibility requirement for the Q3W dose expansion and Q2W dose escalation patients with NSCLC, and a subset of the TNBC Q3W dose expansion patients. Patients continued study treatment until disease progression, unacceptable toxicity, or withdrawal of consent. Administration of granulocyte-colony stimulating factor was allowed after cycle 1 to treat neutropenia; erythropoietin could be used at the investigator's discretion for

the supportive treatment of anemia. Additional supportive care medications, such as prophylactic 5-HT3 receptor antagonists or corticosteroids were administered at the treating physician's discretion.

Patients

Eligible, adult patients (18 years or older) had locally advanced or metastatic solid tumors resistant to standard therapy or with no available standard therapy, and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. Patients had adequate bone marrow function (absolute neutrophil count ≥1,500/mm^3 or ≥1.5 x 10^9/L, platelets ≥100,000/ mm^3 or ≥100 x 10^9/L and hemoglobin ≥9 g/dL), renal function (serum creatinine ≤1.5 x upper limit of normal [ULN] or estimated creatinine clearance ≥60 ml/min), liver function (total serum bilirubin ≤1.5 x ULN [unless patient had documented Gilbert syndrome], aspartate and alanine transaminase ≤3.0 x ULN or ≤5.0 x ULN (if liver metastasis at study entry), alkaline phosphatase ≤2.5 x ULN; [≤5 x ULN if bone and/or hepatic metastasis at study entry]) and adequate cardiac function. With regards to cardiac function, patients were ineligible if any of the following occurred within 12 months of study entry: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism. In addition, eligibility exclusion criteria prohibited patients with any ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, any grade of atrial fibrillation, or QTcF interval >470 msec (with exception of right bundle branch block).

Patients with measurable (by RECIST v1.1) (16) and non-measurable disease were included in Q3W dose escalation. In the Q3W dose-expansion and Q2W dose-

escalation cohorts, measurable disease was required for patients with recurrent NSCLC or TNBC; patients with OvCa had platinum-resistant disease (progression/relapse within 6 months after completion of at least 4 cycles of the most recently administered platinum-containing therapy and a maximum of 3 prior lines of chemotherapy) and disease measurable by RECIST v1.1 or assessable by the Gynecological Cancer Intergroup (GCIG 2011) criteria (17).

Q3W dose-escalation patients with any cancer type were not pre-selected at baseline for PTK7 expression in tumors. In the expansion cohorts, patients with OvCa were not pre-selected for PTK7 baseline expression in tumors; the PTK7 expression rate was assumed to be >80% and confirmed retrospectively by IHC. Q3W dose-expansion and Q2W dose escalation patients with NSCLC were selected pre-treatment for moderate to high tumor PTK7 expression by IHC. For TNBC, after preliminary assessment in dose-expansion of 9 patients initially included without pre-selection, subsequent patients were pre-selected for moderately high to high tumor PTK7 expression, as previously described (15).

Patients were not eligible for this study if they had known, symptomatic brain metastases; an active and clinically significant bacterial, fungal, or viral infection; grade ≥ 2 peripheral neuropathy; or known/suspected hypersensitivity to recombinant human or murine proteins. In addition, patients were excluded if they had received major surgery, radiation therapy or systemic anti-cancer therapy within 3 weeks of starting study treatment.

The study was approved by the institutional review board or independent ethics committee of the participating institutions and followed the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines. The patient informed consent complied with ICH GCP guidelines, local

regulatory requirements, and legal requirements. The study was sponsored by Pfizer and registered at ClinicalTrials.gov (NCT02222922).

Assessments

Safety and DLT

The severity of the reported AEs was graded using the Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03. The monitoring period for DLTs was 28 days.

Any of the following events occurring in the first treatment cycle and deemed related to study treatment was to be considered a DLT: grade 4 neutropenia lasting > 7 days; febrile neutropenia; grade ≥ 3 neutropenic infection; grade 4 anemia or thrombocytopenia; grade ≥ 3 thrombocytopenia with clinically significant bleeding; grade ≥ 3 elevation in serum bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) or alkaline phosphatase; ALT or AST ≥ 3 x upper limit of normal (ULN) concurrent with elevation in bilirubin ≥ 2 x ULN; grade ≥ 3 non-hematologic, non-hepatic toxicities (excluding alopecia of any grade and grade 3 diarrhea, nausea, and vomiting responding to therapy); or a delay > 2 weeks in receiving the next treatment cycle due to persisting, treatment-related toxicities.

Pharmacokinetics

Blood samples for PK analyses were collected from treated patients at protocol-predefined time points: on day 1 in cycle 1 (pre-dose, 1 and 4 hours after start of infusion); day 2 in cycle 1 (24 hours after infusion); days 4, 8, and 15 in cycle 1; day 1 in cycles 2 and 3; days 1, 2, 4, 8, and 15 in cycle 4; then on day 1 of every cycle thereafter, and at the end of treatment. ADC (PF-06647020) and total antibody

(conjugated or unconjugated mAb hu6M024) concentrations were quantified by enzyme-linked immunosorbent assays (ELISAs); the assays had lower limits of quantitation (LLOQ) of 90 ng/mL and 100 ng/mL for the ADC and total antibody, respectively. Unconjugated payload (PF-06380101) concentrations were determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method (18, 19); the assay had a LLOQ of 15 pg/mL for the unconjugated payload. Samples below the LLOQs were set to zero for analysis. PK parameters were determined from the respective concentration-time data by standard, non-compartmental analysis, using an internally validated, electronic, non-compartmental analysis software (eNCA) version 2.2.4.

Immunogenicity

Incidence of anti-drug antibodies (ADA) was assessed by a validated electrochemiluminescent (ECL) method (20, 21) in samples collected from treated patients at protocol-predefined time points: on day 1 and 15 of cycle 1, day 1 of all subsequent cycles, and at the end of treatment. ADA-positive samples were further evaluated for the presence of neutralizing antibodies (NAb) using a validated, competitive ligand-binding ECL method.

Preliminary therapeutic activity

Objective tumor responses were determined by the investigators every 6 weeks or 8 weeks (Q2W cohorts) using RECIST v1.1 (16) and summarized by calculating objective response rates (ORRs). Complete responses (CRs) or partial responses (PRs) were confirmed in the Q3W and Q2W expansion cohorts by repeat assessment at least 4 weeks after the response criteria were first met.

PTK7 protein expression

Tumor-associated PTK7 protein expression levels were assessed by a Clinical Laboratory Improvement Amendments (CLIA) validated IHC assay in formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples collected from patients, as previously described (15 and manuscript in development). Digital tissue analysis was performed using the Flagship Biosciences (Westminster, Colorado) proprietary Image Analysis platform. At least 90% of cells quantified by the algorithm were tumor cells. H-scores were determined from image analysis mark-up (regions of analysis) and quantified based on percentage of positive cells and staining intensity. If a sample failed digital tissue analysis, a visual assessment was performed for non-quantitative plasma membrane staining. All analytical markups were reviewed and accepted by a board-certified MD pathologist. H-scores were rank ordered lowest to highest and divided into tertiles. Tumor H-scores were divided into relatively low, moderate, and high PTK7 expression categories based on tertiles.

Statistical analyses

The prior distribution of DLT for the mTPI was set as a beta (0.75, 0.65) and the threshold probability for early termination and dose exclusion was set to 0.975. The algorithm for dose escalation was to be stopped if the maximum, planned sample size had been reached (~40 patients), at least 9 patients had been treated at a dose level predicted to be at or greater than the MTD, or all doses explored appeared to be too toxic and the MTD could not be determined. The estimated MTD was to be the highest tested dose level with a DLT rate < 0.30 in at least 9 DLT-evaluable patients.

The sample size for the Q3W dose expansion was mainly based on clinical and feasibility considerations. Evaluation of the Q2W regimen in this study ran in parallel

with the Q3W expansion cohorts. The Q2W regimen completed dose escalation and did not proceed to dose expansion.

Results

Patients and treatment

A total of 112 patients received PF-06647020 Q3W in the dose-escalation (0.2 to 3.7 mg/kg) and dose-expansion (2.8 mg/kg) cohorts: 0.2 (*n* = 2), 0.5 (*n* = 2), 1.25 (*n* = 2), 2.1 (*n* = 4), 2.8 (*n* = 96), and 3.7 (*n* = 6) mg/kg (**Supplementary Figure S1**). The 2.8 mg/kg Q3W cohort included 15 patients in dose escalation and 11 patients enrolled in a drug-drug interaction sub-study with multiple-dose fluconazole, the full details of which will be reported separately. In the second part of the study, 25 patients were treated with PF-06647020 Q2W across 3 dose levels: 2.1 (*n* = 3), 2.8 (*n* = 10), and 3.2 mg/kg (*n* = 12). Demographic and baseline characteristics for all patients are presented in **Table 1**. The majority of patients (63% and 60% in the Q3W and Q2W cohorts, respectively) had ECOG performance status 1.

The Q3W cohorts included patients with platinum-resistant OvCa (39%), advanced NSCLC (22%), or advanced TNBC (26%); a minority of patients (13%) had other locally advanced/metastatic solid tumor types. Across the Q3W cohorts, 34% of OvCa patients had high-grade serous carcinoma, 64% of NSCLC patients had adenocarcinoma and 79% of TNBC patients had ductal carcinoma. Patients in the Q2W cohorts had a primary tumor diagnosis of platinum-resistant OvCa (76%) or advanced NSCLC (24%). In these cohorts, 68% of OvCa patients had high-grade serous carcinoma and 83% of NSCLC patients had adenocarcinoma.

All patients had received prior systemic, anticancer therapy; 93% of patients in the Q3W cohorts and 88% in the Q2W cohorts had received 2 or more prior treatment regimens.

DLT and safety

Two DLTs (grade 3 headache and grade 3 fatigue) were reported at the highest dose of PF-06647020 evaluated with the Q3W regimen (3.7 mg/kg, *n* = 6, 33%). Absent further exploration of doses between 3.7 mg/kg and the previously completed dose cohort of 2.8 mg/kg, the protocol specified that the MTD for Q3W administration of PF-06647020 in patients with solid tumors was estimated to be the last completed, lower dose level, 2.8 mg/kg. Overall, 3 DLTs were observed with the Q2W dosing regimen: grade 3 neutropenic infection in 1 patient at 2.8 mg/kg (*n* = 10) and grade 3 abdominal pain in 2 patients at 3.2 mg/kg Q2W (*n* = 12, 17%). Based on the DLT rates observed, the MTD for the Q2W regimen was not reached at the dose levels evaluated in this study.

Treatment-emergent, all-cause AEs were reported in all patients treated with PF-06647020 Q3W or Q2W. Eighty-nine (79.4%) and 18 (72%) patients, respectively, experienced grade ≥ 3 all-cause AEs. Seventeen (15.2%) patients and 4 (16%) patients died on study in the Q3W and Q2W cohorts, respectively, mostly due to disease progression (*n* = 15 and *n* = 4, respectively), or respiratory arrest and urosepsis (*n* = 1 each, Q3W cohorts). None of the patients died due to a treatment-related AE (TRAE).

In the Q3W cohorts, the most common TRAEs were nausea, alopecia, fatigue, headache, neutropenia, and vomiting (45-25% of patients, **Table 2**). Treatment-related peripheral sensory neuropathy was observed in 12.5% of patients (all events were

grade 1 or 2). Forty-four (39.3%) patients had grade ≥ 3 TRAEs. The most frequent grade ≥ 3 TRAE was neutropenia (25%); 3 (2.7%) patients developed febrile neutropenia. The incidence of TRAEs in the Q3W cohorts was highest in patients dosed at 2.8 mg/kg (**Table 3**).

The most common TRAEs observed with Q2W dosing across dose levels also were alopecia, nausea, fatigue, and headache (**Supplementary Table S1**). Thirteen (52%) patients had grade ≥ 3 TRAEs. Treatment-related grade 3-4 neutropenia was reported in 24% of patients; 1 patient developed a grade 3 neutropenic infection (DLT). Grade 1-2 peripheral sensory neuropathy occurred in 20% and grade 3 in 8% of the patients on the Q2W regimen.

Treatment with PF-06647020 Q3W was generally tolerable with a manageable safety profile in the majority of patients. Three (2.7%) patients treated with the Q3W regimen and 1 (4%) of the patients on Q2W dosing discontinued due to a TRAE; 7 (6.3%) and 4 (16%) patients, respectively, had a dose reduction of PF-06647020. Temporary discontinuations due to TRAEs occurred less frequently with the Q3W (14.3%) than the Q2W (44%) dosing regimen (**Supplementary Table S2**). The AE most frequently leading to temporary treatment discontinuation was neutropenia. Forty-six (41%) and 19 (76%) patients in the Q3W and Q2W cohorts, respectively, received concomitant treatment with ondansetron to manage nausea and vomiting. Of all the patients enrolled across the Q3W and Q2W cohorts, 54 reported development of headache at some point during the course of the study. Cumulatively, investigators recorded 29 of these patients to have reported a headache after infusion on cycle 1, day 1 (C1D1) or 2. The first such post-infusion event occurred in a breast cancer patient who was enrolled in the 2.1 mg/kg Q3W dose-escalation cohort. The patient first reported a grade 2 headache, associated with vomiting, on C1D1 of

treatment, approximately 4 hours after the end of the infusion. The patient was treated with analgesics and antiemetics in the clinic but required hospital admission for the management of persistent symptoms. The symptoms resolved within 48 hours of C1D1. She was premedicated for the subsequent cycles with acetaminophen and antiemetics including 5-HT3 antagonists plus dexamethasone. She experienced no recurrent headache or vomiting with further study drug administration. Empirically, as each site managed the care of a few patients, the headaches almost always occurred only after completion of the infusion, and were not associated with fever, chills, or other typical infusion reaction-like symptoms. The collective impression of the investigators was that this headache syndrome (at times accompanied by nausea, photophobia, and/or meningismus-like symptoms) was reminiscent of a transient central nervous system inflammatory syndrome. For all patients, the headaches resolved spontaneously within a maximum of a few days. Analgesics, including opioids, did not seem helpful and anti-inflammatory agents, especially glucocorticoids, seemed most effective. Therefore, although not mandated in the protocol, many investigators ulitmately decided to routinely administer pre-infusion steroids to reduce the likelihood of post-PF-06647020 infusion headache syndrome. Based on these collective observations, the use of steroids warrants further exploration as prophylactic treatment for patients who will receive PF-06647020.

Based on overall clinical and statistical assessments, the actual MTD for PF-06647020 is between 2.8 and 3.7 mg/kg Q3W. By protocol definition, the RP2D is 2.8 mg/kg Q3W, but notably there is variance in clearance and tolerability that could lead investigators to revisit higher doses with steroid prophylaxis in the future.

Pharmacokinetics

PK analyses showed that systemic exposure, based on the observed area under the serum concentration-time curve during the dosing interval (AUC_{tau}) and maximum concentration (C_{max}) values for the ADC (PF-06647020), total antibody (hu6M024), and unconjugated payload, generally increased in a dose-related manner across the 0.2 to 3.7 mg/kg Q3W dose levels (**Figure 1**). Following single IV infusion of PF-06647020 at 2.8 mg/kg Q3W, peak concentrations for the ADC and total antibody were observed at or shortly after the end of the infusion, followed by a multi-phasic decline (Figure 1), with a mean $t_{1/2}$ value in cycle 1 of 3.1 days for the ADC (**Supplementary Table S3**). The AUC ratio between ADC and total antibody was ~0.9. Individual C_{max} for the payload ranged between 1.2 to 24.5 ng/mL and $t_{1/2}$ between 0.7 to 5.3 days, across all Q3W dose levels (cycles 1 and 4).

The PK parameters for Q2W dosing of PF-06647020 are presented in **Supplementary Table S4**. At the 2.8 mg/kg Q2W dose level, the observed C_{max} for the ADC was 99.7 µg/mL in cycle 1 (compared to 79.8 µg/mL with Q3W dosing), with a mean $t_{1/2}$ value of 2.7 days.

The major cytochrome P450 isoform involved in the metabolism of unconjugated payload (PF-06380101) in humans was predicted to be CYP3A4 based on initial reaction phenotyping experiments. To assess potential CYP3A-mediated drug-drug interaction, the effects of multiple doses of fluconazole, a moderate CYP3A4 inhibitor, on the PK of PF-06380101 (unconjugated payload) following single-dose co-administration of PF-06647020 (ADC) was investigated. For the 11 patients enrolled in this drug-drug interaction sub-study, co-administration of PF-06647020 with fluconazole did not have a notable impact on the overall exposure of PF-06380101. Ratios of the adjusted geometric means and (90% CI) for PF-06380101 exposure based on AUCinf(dn) and Cmax(dn) were 91% (45%, 186%), and 102% (51%, 205%),

respectively, when PF-06647020 (ADC) was co-administered with fluconazole in Cycle 2 (test) compared to administration alone in Cycle 1 (reference). In addition, co-administration of PF-06647020 with fluconazole did not have a notable impact on the overall exposure of PF-06647020 (ADC) and hu6M024 mAb (total antibody).

Immunogenicity

Of the 108 patients treated with PF-06647020 Q3W with at least 1 evaluable, post-dose sample, 11 (10.2%) patients tested positive for treatment-induced ADA. Ten of these ADA-positive patients had NAb. One (4%) of the 25 evaluable patients on the Q2W regimen had treatment-induced ADA and Nab. An additional patient (4%) in the Q2W cohorts had ADA at baseline, but they were not boosted by treatment and had resolved by the second ADA assessment. No hypersensitivity or infusion-related reactions (IRRs) were reported in the ADA-positive patients treated Q3W. One ADA-positive patient on the Q2W regimen experienced a grade 2 IRR (day 1, cycle 4), which resolved on the same day.

Antitumor activity and PTK7 biomarker analysis

PF-06647020 demonstrated antitumor activity in the Q3W and Q2W cohorts, with ORRs of 27% and 26%, respectively, in patients with OvCa, 16% and 33% in NSCLC, and 21% in TNBC (Q3W regimen), across the dose levels evaluated (**Table 4**).

In OvCa, 3 (7%) patients treated with PF-06647020 Q3W achieved a CR and 9 (21%) patients a PR (**Figure 2**). All responses, except for 1 CR (2.1 mg/kg), were observed in the 2.8 mg/kg Q3W cohorts. In addition, 2 (11%) patients treated Q2W had a CR and 3 (16%) a PR, in the 2.8 mg/kg (1 CR, 2 PR) or 3.2 mg/kg (1 CR, 1 PR) cohorts. In patients with NSCLC treated with PF-06647020, all responses were

observed in the 2.8 mg/kg Q3W (4 PRs) and the 3.2 mg/kg Q2W cohorts (2 PRs). Median duration of response and median PFS (mPFS) results (data cut-off, Dec 19, 2019) are presented in Table 4, according to dosing regimen and tumor type.

PTK7 protein expression levels and best overall response to treatment with PF-06647020 administered Q3W or Q2W are shown in **Figure 2**. After adjusting for tumor type, patients with High baseline H-score have significantly larger mean percent reduction from baseline in tumor size than that in patients with Low baseline H-score ($p= 0.027$). No significance was observed between H-score High and Moderate, or between Moderate and Low (**Supplementary Figure S2**).

Discussion

In this first-in-human dose-finding study, single-agent treatment with a PTK7-targeted ADC, PF-06647020, demonstrated a manageable safety profile and preliminary antitumor activity in patients with advanced OvCA, NSCLC, or TNBC who had received multiple, prior lines of standard-of-care therapy.

The majority of the TRAEs observed with the Q3W regimen were mild or moderate. None of the patients experienced a grade 5 TRAE. Two DLTs (grade 3 headache and grade 3 fatigue) were observed at the highest Q3W dose level evaluated. Although neutropenia was the most frequent grade 3-4 TRAE reported (25%), it resolved in most cases with supportive care; febrile neutropenia occurred only in 2.7% of treated patients. Peripheral sensory neuropathy observed in 12.5% of patients was limited to grade 1-2. A comparable safety profile has been previously observed following treatment with other ADCs containing an auristatin payload, such as the Notch-3 targeted ADC PF-06650808, in patients with advanced solid malignancies (i.e. BC, OvCa, and NSCLC) (22). Treatment with PF-06647020 Q3W was generally tolerable,

as only 2.7% of patients discontinued and 6.3% had a dose reduction due to a TRAE. PK analyses showed that at 2.8 mg/kg Q3W, the mean terminal half-life for PF-06647020 was ~3 days.

Further evaluation of single-agent PF-06647020 was undertaken with Q2W dosing in patients with advanced, platinum-resistant OvCa or recurrent NSCLC, based on the hypothesis that therapeutic activity could be augmented by sustaining higher trough concentrations of PF-06647020. Overall safety findings in patients treated with PF-06647020 Q2W were similar to those observed with Q3W dosing. However, 2 patients with OvCa on the Q2W regimen experienced grade 3 abdominal pain (DLT) at the highest dose level evaluated (3.2 mg/kg) and 8% of patients developed grade 3 peripheral sensory neuropathy across dose levels. Grade 2-3 abdominal pain of unknown etiology has also been previously reported with the auristatin-based ADC PF-06650808 (22). Notably, a patient with NSCLC who had no known peritoneal metastases experienced treatment-emergent abdominal pain.

Objective tumor responses were observed following treatment with both PF-06647020 Q3W and Q2W regimens, with ORRs of 26%-27% in patients with OvCa, 16%-33% with NSCLC and 21% with TNBC, who had progressed on prior standard therapies. Most of the responses associated with either dosing regimen occurred at the 2.8 mg/kg dose level, which was selected as the RP2D for further single-agent Q3W administration of PF-06647020. Biomarker analysis showed that patients with clinical responses tended to have moderate to high H-scores, suggesting the feasibility of patient selection using the IHC assay.

Other ADCs, including mirvetuximab soravtansine (an anti-folate receptor α–DM4 ADC), sacituzumab govitecan-hziy (an anti-human trophoblast cell-surface antigen 2–SN38 ADC), trastuzumab deruxtecan (an anti-HER2–topoisomerase I inhibitor

ADC), and lifastuzumab vedotin (an anti-NaPi2b–monomethyl auristatin E ADC) are being developed for the treatment of patients with advanced OvCa or NSCLC and other solid malignancies (23-28). Although our study was not powered to demonstrate antitumor efficacy and despite the small sample size in some tumor types, we observed encouraging preliminary antitumor activity with PF-06647020. Hence, our study results with PF-06647020 suggest that treatment with an ADC directed to PTK7 represents a feasible approach for the management of patients with advanced OvCa, NSCLC, and TNBC.

Further clinical development is in progress for PF-06647020/cofetuzumab pelidotin using the Q3W regimen. Safety and efficacy are being evaluated in a phase Ib study in patients with advanced, recurrent PTK7+ NSCLC, who have received prior treatment with chemotherapy and immune checkpoint inhibitors or targeted agents (NCT04189614, primary study endpoint: ORR). In addition, a combination of PF-06647020 with the investigational PI3K/mTOR inhibitor gedatolisib (29) is being explored in a phase I study in patients with chemotherapy-pretreated, metastatic TNBC (NCT03243331).

Acknowledgments

The authors thank the patients, their families/caregivers, the investigators, research nurses, study coordinators, and operations staff who contributed to this study, Qionghua (Barbara) Zhao and Yingzhi Chen for their statistical programming support, and Xiaoying Chen and Shibing Deng for their contributions to this study. This study was sponsored by Pfizer. Medical writing was provided by S. Mariani, MD, PhD, of Engage Scientific Solutions, and funded by Pfizer.

Data Sharing Statement

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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Author Manuscript Published OnlineFirst on June 3, 2021; DOI: 10.1158/1078-0432.CCR-20-3757
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Tables

Table 1. Patient demographics and baseline characteristics.

	Q3W Regimen	**Q2W Regimen**
	***N* = 112**	***N* = 25**
Age, years mean (range)	58.4 (31-80)	65.4 (51-79)
Male: Female, *n* (%)	20 (17.9) : 92 (82.1)	1 (4) : 24 (96)
Race, *n* (%)		
White	103 (92.0)	21 (84)
Black	6 (5.4)	1 (4)
Asian	1 (0.9)	1 (4)
Other	2 (1.8)	2 (8)
Primary tumor diagnosis, *n* (%)		
NSCLC	25 (22.3)	6 (24)
OvCa	44 (39.3)	19 (76)
TNBC	29 (25.9)	0
Other	14 (12.5)	0
ECOG PS, *n* (%)		
0	40 (35.7)	10 (40)
1	71 (63.4)	15 (60)
2	1 (0.9)[a]	0
Prior systemic anticancer therapy, *n* (%)	112 (100)	25 (100)
≥ 2 regimens	104 (92.9)	22 (88)
≥ 3 regimens	84 (75.0)	6 (24)
Prior radiation therapy, *n* (%)		
Yes	54 (48.2)	6 (24)
No	58 (51.8)	19 (76)

[a] Protocol deviation. ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small-cell lung cancer; OvCa, ovarian cancer; Q2W, every 2 weeks; Q3W, every 3 weeks; TNBC, triple-negative breast cancer.

Table 2. Treatment-related adverse events reported in >10% of patients with Q3W dosing of PF-06647020 (all cycles, *N* = 112).

	Grade 1	Grade 2	Grade 3	Grade 4	Total[a]
AE	*n* (%)				
Nausea	28 (25.0)	21 (18.8)	1 (0.9)	0	50 (44.6)
Alopecia	13 (11.6)	33 (29.5)	0	0	46 (41.1)
Fatigue	19 (17.0)	19 (17.0)	3 (2.7)	0	41 (36.6)
Headache	13 (11.6)	19 (17.0)	5 (4.5)	0	37 (33.0)
Neutropenia	0	4 (3.6)	17 (15.2)	11 (9.8)	32 (28.6)
Vomiting	10 (8.9)	14 (12.5)	4 (3.6)	0	28 (25.0)
Arthralgia	16 (14.3)	2 (1.8)	1 (0.9)	0	19 (17.0)
Decreased appetite	11 (9.8)	7 (6.3)	0	0	18 (16.1)
Diarrhea	8 (7.1)	8 (7.1)	1 (0.9)	0	17 (15.2)
Myalgia	11 (9.8)	3 (2.7)	1 (0.9)	0	15 (13.4)
Peripheral sensory neuropathy	7 (6.3)	7 (6.3)	0	0	14 (12.5)

[a] No treatment-related grade 5 AEs were observed with the Q3W regimen. AE, adverse event; Q3W, every 3 weeks.

Table 3. Summary of treatment-related adverse events by dose level with Q3W dosing of PF-06647020 (all cycles, *N* = 112).

	0.2 mg/kg n (%)	**0.5 mg/kg n (%)**	**1.25 mg/kg n (%)**	**2.1 mg/kg n (%)**	**2.8 mg/kg n (%)**	**3.7 mg/kg n (%)**
Evaluable pts	2	2	2	4	96	6
Number of AEs	1	1	6	28	475	27
Pts with AEs	1 (50.0)	1 (50.0)	1 (50.0)	4 (100.0)	84 (87.5)	5 (83.3)
Pts with SAEs	0	0	0	1 (25.0)	9 (9.4)	0
Pts with G3/G4 AEs	1 (50.0)	0	0	0	40 (41.7)	3 (50.0)
Pts discontinued due to AEs	0	0	0	1 (25.0)	2 (2.1)	0
Pts with dose reduction due to AEs	0	0	0	0	7 (7.3)	0
Pts with temporary discontinuation due to AEs	0	0	0	0	16 (16.7)	0
Pts with dose reduction and temporary discontinuation due to AEs	0	0	0	0	3 (3.1)	1 (16.7)

Pts, patients; AE, adverse event; SAE, serious adverse event

Table 4. Antitumor activity of PF-06647020 administered Q3W or Q2W in patients with advanced OvCa, NSCLC, or TNBC.

Regimen and Tumor	***N***	**CR, PR** ***n***	**ORR** **% (95% CI)**	**mDOR** **mo (95% CI)**	**mPFS** **mo (95% CI)**
Q3W					
OvCa	44	3, 9	27 (15, 43)	4.2 (2.8, 8.3)	2.9 (2.3, 5.5)
NSCLC	25	0, 4	16 (5, 36)	5.7 (1.5, 9.9)	2.9 (1.4, 6.1)
TNBC	29	0, 6	21 (8, 40)	4.3 (1.3, 10.2)	1.5 (1.4, 4.3)
Q2W					
OvCa	19	2, 3	26 (9, 51)	6.5 (3.9, 8.3)	3.8 (3.1, 7.4)
NSCLC	6	0, 2	33 (4, 78)	NR (3.7, NR)	2.7 (1.0, NR)

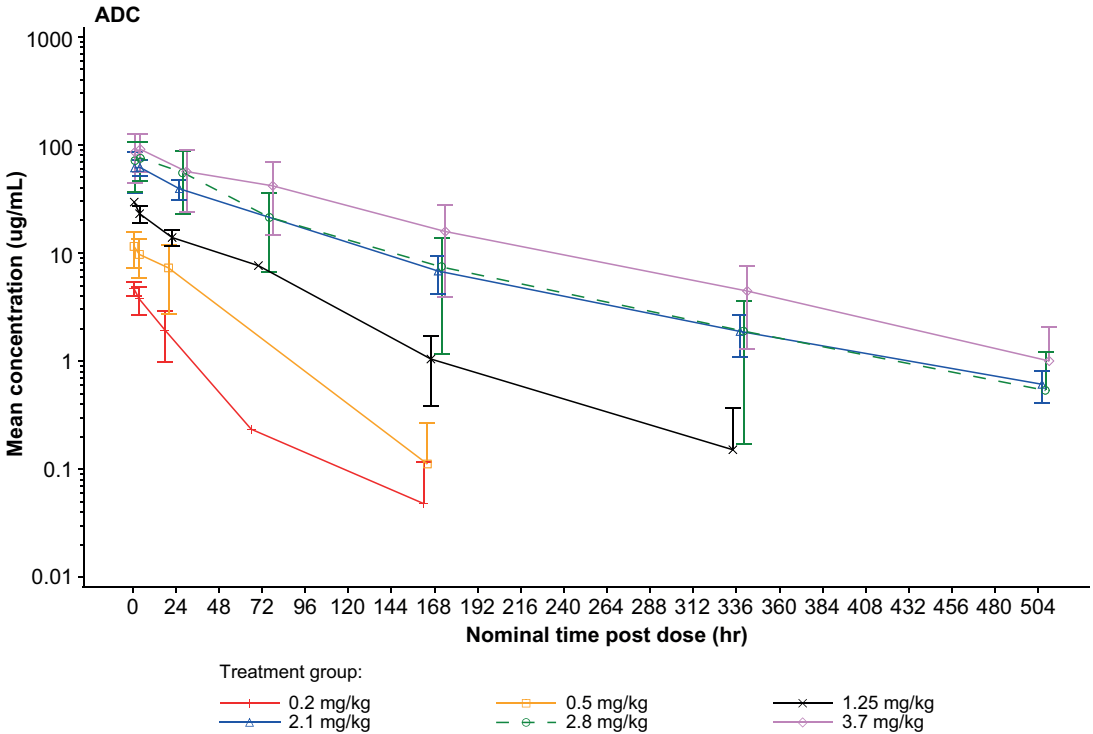
CR, complete response; mDOR, median duration of response; mo, months; mPFS, median progression-free survival; NR, not reached; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OvCa, ovarian cancer; PR, partial response; Q2W, every 2 weeks; Q3W, every 3 weeks; TNBC, triple-negative breast cancer.

Figure Legends

Figure 1. Mean pharmacokinetic profiles for PF-06647020 administered Q3W in patients with solid tumors. Results are shown for the ADC (**A**), total antibody (**B**), and unconjugated payload (**C**). Error bars indicate the standard deviations. ADC, antibody–drug conjugate; Q3W, once every 3 weeks.

Figure 2. PTK7 protein expression and best overall response to treatment with PF-06647020 administered Q3W (**A, B, C**) or Q2W (**D, E**) in patients with advanced OvCa (**A, D**), NSCLC (**B, E**), and TNBC (**C**). A visual assessment of non-quantitative PTK7 membrane staining was performed for samples that failed digital tissue analysis. CR, complete response; NSCLC, non-small-cell lung cancer; OvCa, ovarian cancer; PD, progressive disease; PR, partial response; Q2W, every 2 weeks; Q3W, every 3 weeks; SD, stable disease; TNBC, triple-negative breast cancer.

A.



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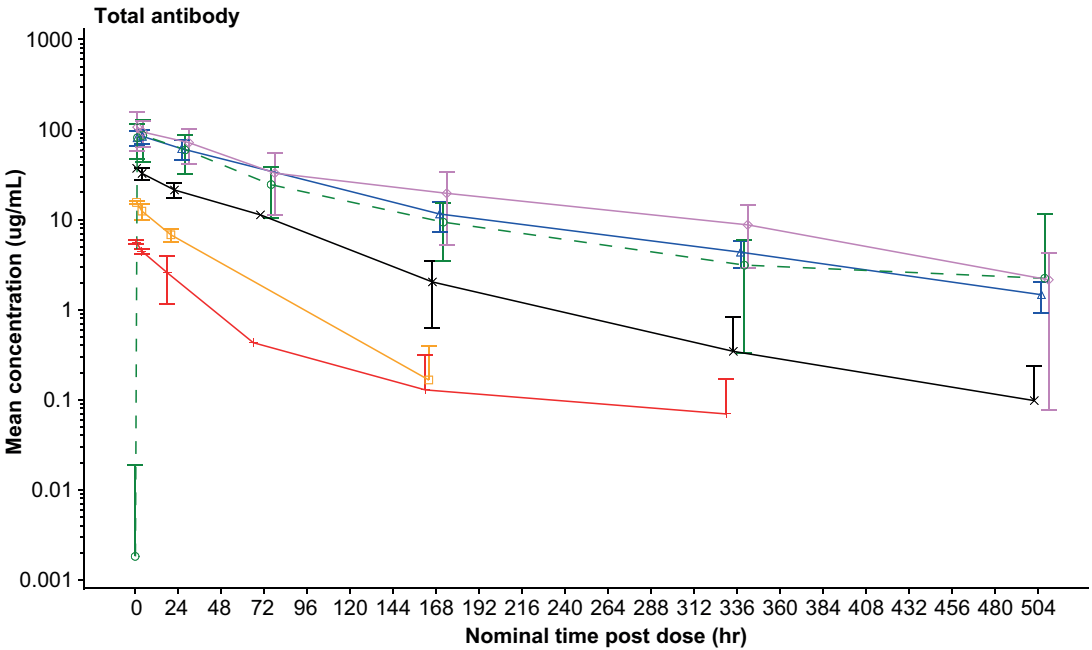

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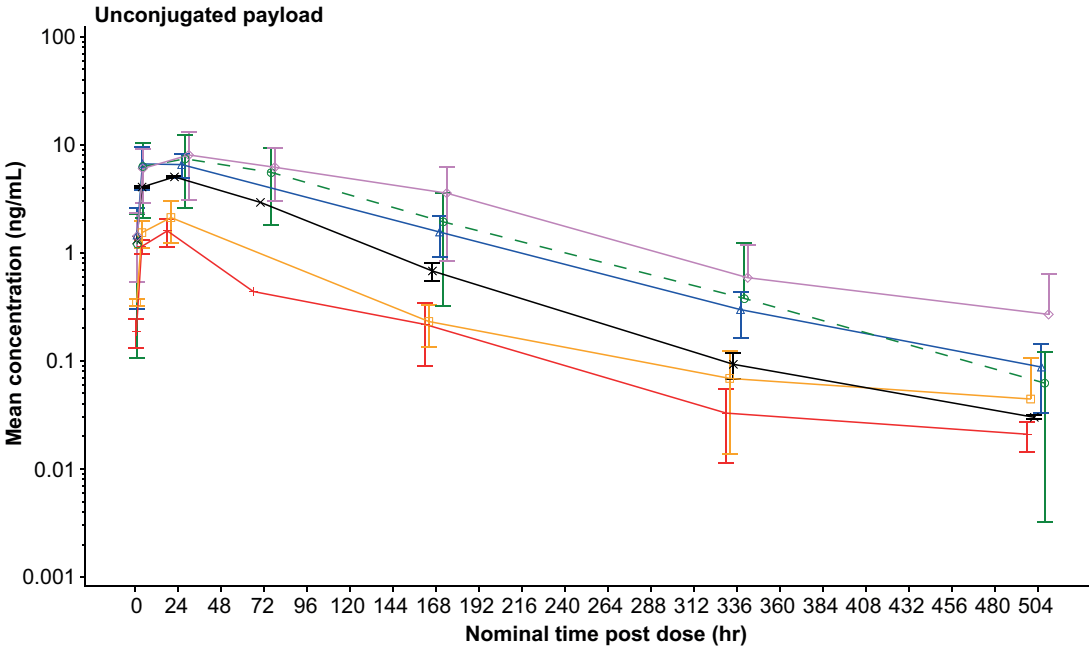

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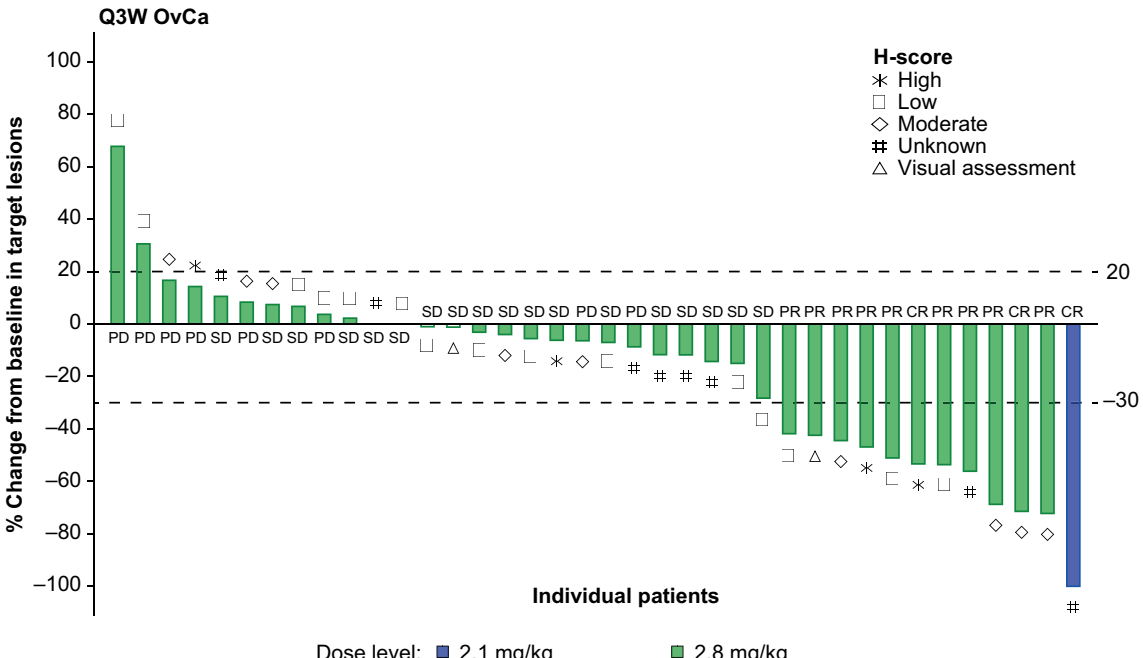

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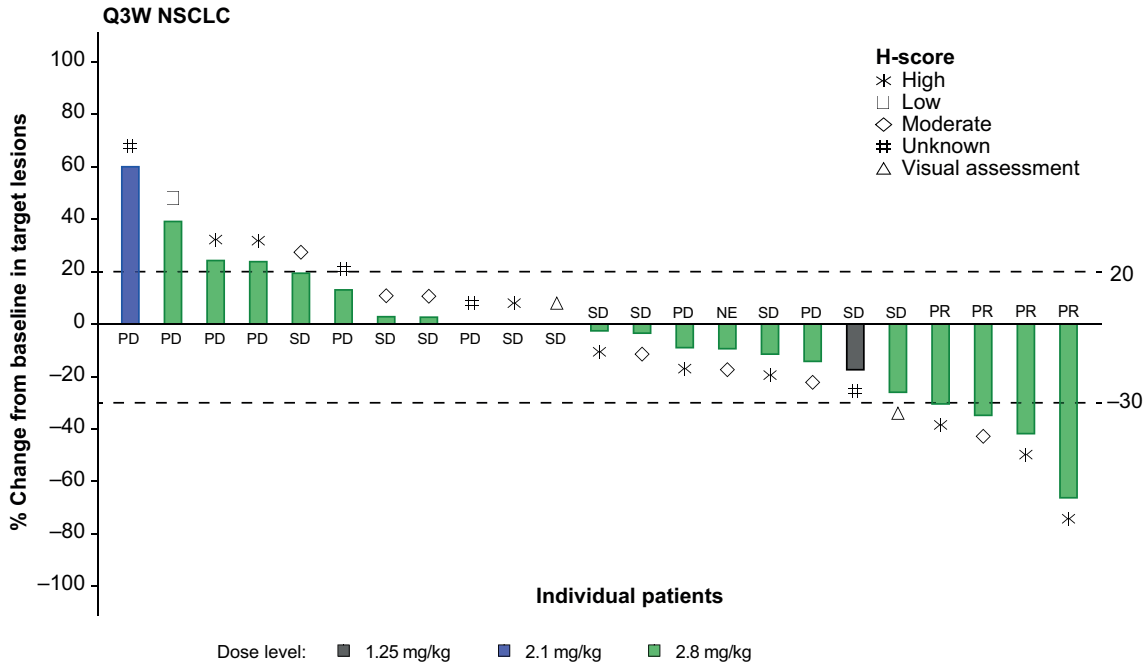
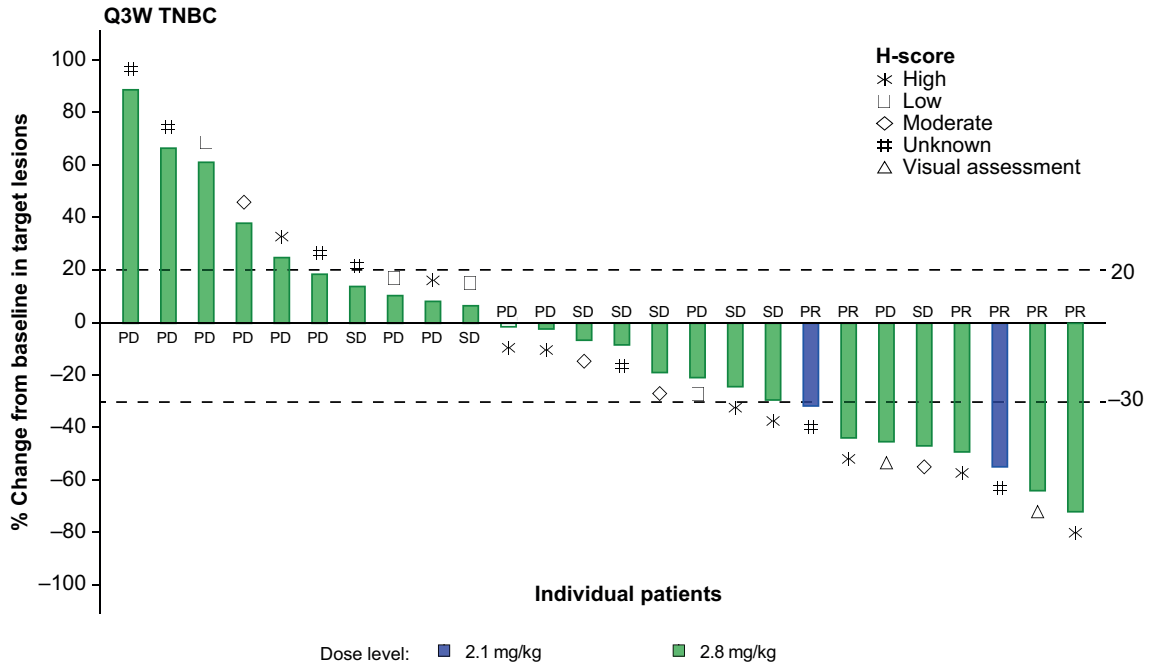
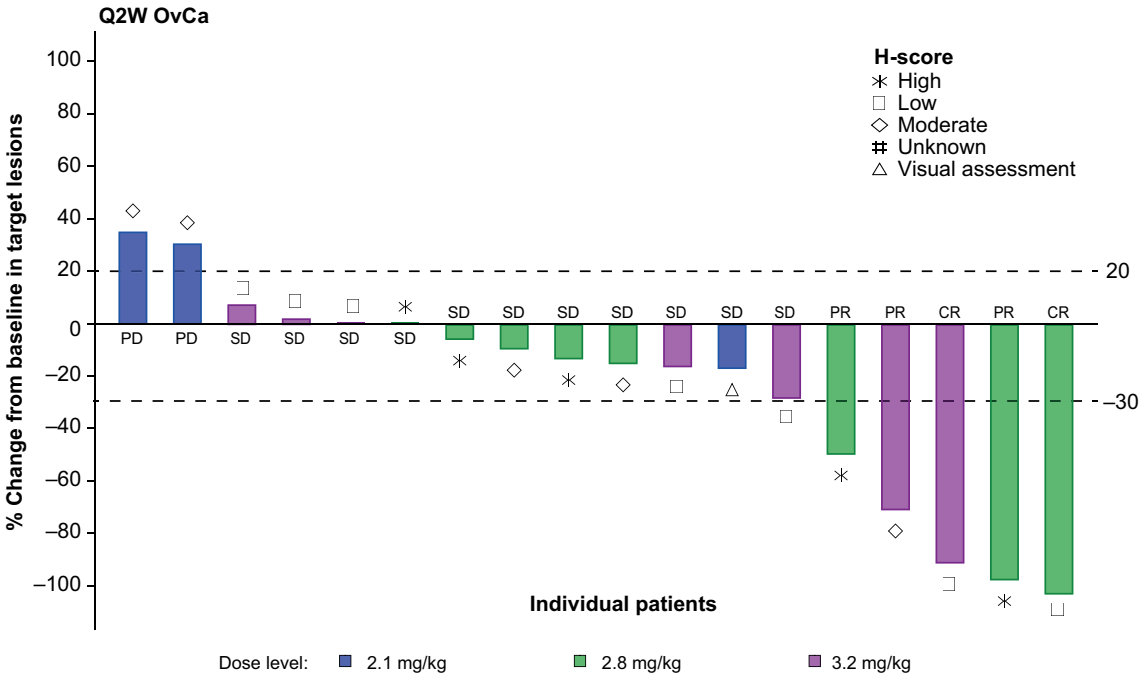


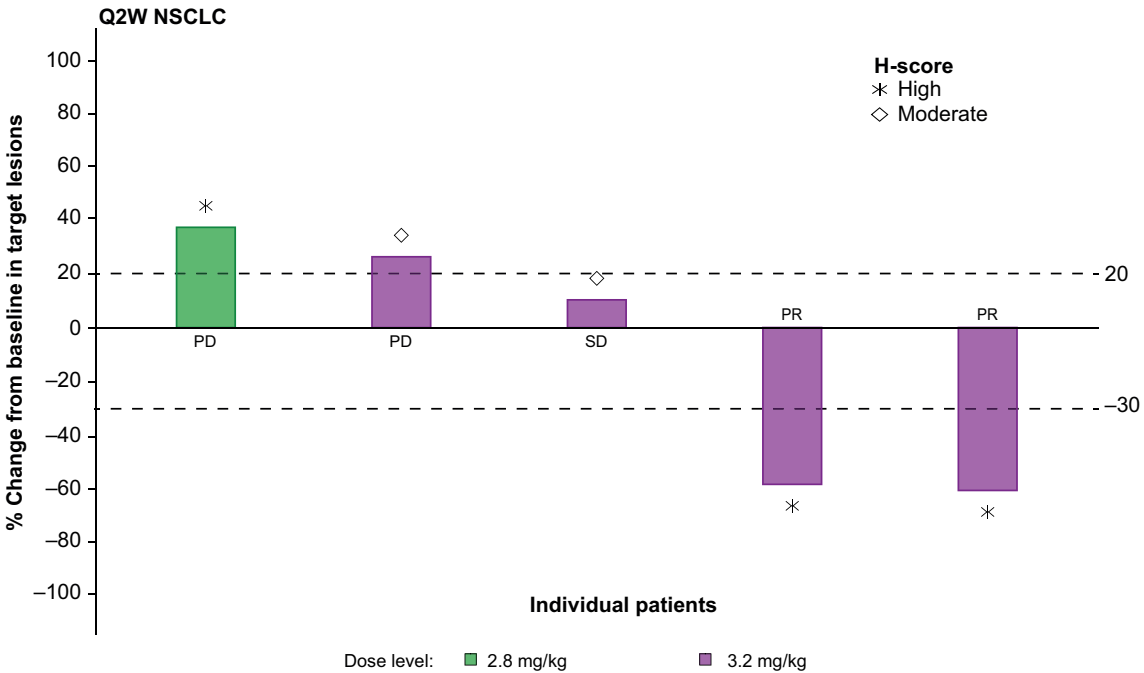
C.



D.



E.



AACR American Association for Cancer Research

Clinical Cancer Research

First-in-Human Study of PF-06647020 (Cofetuzumab Pelidotin), an Antibody-Drug Conjugate Targeting Protein Tyrosine Kinase 7 (PTK7), in Advanced Solid Tumors

Michael L. Maitland, Jasgit C Sachdev, Manish R Sharma, et al.

Clin Cancer Res Published OnlineFirst June 3, 2021.