

First-In-Human Phase I Study of a Next-Generation, Oral, Transforming Growth Factor-Beta Receptor 1 Inhibitor, LY3200882 in Patients with Advanced Cancer

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TRANSLATIONAL RELEVANCE ABSTRACT:

This phase I multicenter trial provides novel insights into the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of LY3200882 as monotherapy and with standard therapies as combination therapy across cancer types. The results indicate that LY3200882, a novel, potent and selective, next-generation, small molecule inhibitor of transforming growth factor-beta receptor 1, is safe and well tolerated, has a robust pharmacokinetic-pharmacodynamic profile, and is associated with early signals of monotherapy antitumor activity in grade 4 glioma. Interestingly, LY3200882 demonstrated promising antitumor activity when given with gemcitabine and nab-paclitaxel chemotherapy in treatment-naïve patients with advanced pancreatic cancer. This study provides supporting clinical evidence to further investigate the efficacy of LY3200882 with gemcitabine and nab-paclitaxel in patients with advanced pancreatic cancer, an area of urgent clinical need.

ABSTRACT

Background. A novel, selective, next-generation transforming growth factor-beta receptor type 1 small molecule inhibitor, LY3200882, demonstrated promising preclinical data. This first-in-human trial evaluated safety, tolerability, recommended phase 2 dose (RP2D), pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of LY3200882 as monotherapy or with other anticancer agents in patients with advanced cancer.

Methods. This phase I multicenter study of oral LY3200882 (NCT02937272) comprised dose escalation, monotherapy expansion in grade 4 glioma, and combination therapy in solid tumors (LY3200882 and PD-L1 inhibitor LY3300054), pancreatic cancer (PC; LY3200882, gemcitabine and nab-paclitaxel), and head and neck squamous cell cancer (LY3200882, cisplatin and radiation).

Results. Overall, 139 patients with advanced cancer were treated. Majority (93.5%) of patients experienced ≥ 1 treatment-emergent adverse events (TEAEs), with 39.6% LY3200882-related. Grade 3 LY3200882-related toxicities were only observed in combination therapy arms. One patient in the PC arm experienced cardiovascular toxicity. The LY3200882 monotherapy RP2Ds were established in 2 schedules: 50 mg BID 2-weeks-on/2-weeks-off and 35 mg BID 3-weeks-on/1-week-off. Four patients with grade 4 glioma had durable RANO partial responses (PR) with LY3200882 monotherapy (n=3) or LY3200882-LY3300054 combination therapy (n=1). In treatment-naïve patients with advanced PC, 6/12 patients achieved RECIST v1.1 PR and 3/12 patients demonstrated stable disease, for an overall 75% disease control rate with the combination of LY3200882, gemcitabine and nab-paclitaxel.

Conclusion. LY3200882 as monotherapy and combination therapy was safe and well tolerated with preliminary antitumor activity observed in PC. Further studies to evaluate the efficacy of LY3200882 with gemcitabine and nab-paclitaxel in advanced PC are warranted.

INTRODUCTION

Transforming growth factor-beta (TGF- β) is a multifunctional cytokine involved in cell growth, differentiation, migration, and survival. It is pivotal for embryogenesis and maintaining tissue homeostasis (1-3). Nonetheless, TGF- β demonstrates paradoxical activity in cancer (2). During early stages of cancer, TGF- β inhibits tumor progression through increased apoptosis, decreased cell proliferation, and reduced expression of growth factors; whereas, during late stages, TGF- β enhances tumor progression by promoting epithelial-mesenchymal transition and tumor angiogenesis, invasion, and metastasis (4,5). Moreover, during tumor progression, TGF- β suppresses immune surveillance by either diminishing the antitumor functions of CD8⁺, CD4⁺, and dendritic cells, or by inhibiting natural killer cells from producing interferon- γ (6), which suggests potential for immunomodulatory therapeutic options. Additionally, cancer associated fibroblasts (CAF) express high levels of TGF- β that suppresses and prevents infiltration of CD8⁺ T-cells into the tumor (7,8). The CAFs are involved in the remodelling of the extracellular matrix during tumorigenesis and causes a stromal rich immunosuppressive environment, a common feature of cold tumors such as pancreatic cancer and CRC (7,8). Combining TGF- β blockade with immune potentiators such as checkpoint inhibitors may induce antitumor killing in stromal rich tumors generally not responsive to checkpoint inhibitors alone (9).

Deregulation of TGF- β signaling is observed in multiple cancers, including pancreatic cancer, grade 4 glioma, and squamous cell carcinoma of the head and neck (SCCHN) (10-13). In glioma, TGF- β is overexpressed compared with normal brain tissue, indicating a role in the development of these tumors. TGF- β enhances the production of platelet-derived cell growth factor, thereby inducing cell proliferation (14). Further, TGF- β type 1 produced by glioma-infiltrating macrophages enhances the invasive properties of cancer cells (14). Among several tumor types, TGF- β has a particularly relevant role in pancreatic cancer with the signal transduction pathway commonly mutated in this disease, as confirmed in a recent whole-genome or exome sequencing analyses (15). In SCCHN, increased expression

promotes cell proliferation and inhibits apoptosis (16). Apart from enhancing tumorigenesis, abnormal TGF- β signaling may promote radioresistance and immune evasion, thereby leading to poor prognosis and cancer recurrence (10,12). Moreover, preclinical studies have demonstrated reduced DNA damage, increased clonogenic cell death and tumor growth delay when TGF- β was inhibited before radiotherapy (17).

The therapeutic efficacy of the pharmacologic inhibition of the TGF- β canonical Smad-dependent pathway in preclinical models of pancreatic cancer was demonstrated by using galunisertib (LY2109761, Lilly, Indianapolis, USA), a selective small molecule inhibitor of TGF- β receptor type-1 (TGF- β R1) (18). The results of the preclinical studies prompted the clinical investigation of the inhibition of TGF- β signaling in combination with chemo- or immunotherapeutic agents as a treatment strategy for patients with pancreatic cancer, and indicated an improvement in overall survival (OS) in combination with gemcitabine in this subset of patients (18-20).

This study introduces, for the first time, LY3200882, a novel, selective, next-generation small molecule inhibitor of TGF- β R1. LY3200882 is an adenosine triphosphate-competitive inhibitor of the serine-threonine kinase domain of TGF- β R1. It has a different chemical structure than galunisertib and was designed to be more potent and selective for TGF- β R1 (21). Preclinical studies demonstrated LY3200882 to be superior to galunisertib from pharmacokinetic (PK), pharmacodynamic (PD), and toxicology perspectives (**Data on file**). LY3200882 induced durable tumor regression in orthotopic syngenic 4T1-luciferase positive preclinical tumor models of triple negative breast cancer *in vitro* and *in vivo* (17). LY3200882 also demonstrated immunomodulatory effects through the induction of T-cell proliferation (21). Furthermore, the combination of the anti-programmed death ligand-1 (PD-L1) inhibitor LY3300054 and LY3200882 demonstrated antitumor activity in syngeneic CT26 models (21). Given these immunomodulatory effects observed in preclinical studies, we hypothesized that LY3200882 induces antitumor killing as monotherapy or with the PD-L1 inhibitor LY3300054 in indications such as gliomas that have been generally refractory to immune checkpoint

blockade. Additionally, considering the pleiotropic role TGF- β exhibits in cell signaling, we set out to test whether combination treatment with standard cytotoxic chemotherapy agents in pancreatic cancer and SCCHN will improve response rates. This first-in-human phase I trial was conducted to determine the safety, tolerability, recommended phase 2 dose (RP2D), PK, PD, and preliminary antitumor activity of LY3200882 as monotherapy or with other anticancer agents as combination therapy for the treatment of patients with advanced cancer.

MATERIALS AND METHODS

Study design

The study was a first-in-human, multicenter, nonrandomized, open-label, phase I study of oral LY3200882 (NCT02937272). The primary objectives of the study were to assess the safety and tolerability and to establish a RP2D of LY3200882 monotherapy and with other anticancer agents as combination therapy in patients with advanced or metastatic cancers. The secondary objectives included evaluation of PK (5 to 50 mg range), PD, and preliminary antitumor activity of LY3200882 as monotherapy or in combination with other anticancer agents. The study was comprised of 3 parts: LY3200882 monotherapy dose escalation in patients with advanced or metastatic cancer (part A), monotherapy dose expansion in patients with grade 4 glioma (part B), and LY3200882 combination therapies in advanced cancers including grade 4 glioma, pancreatic cancer, and SCCHN (part C) (**Supplementary Figure 1**).

Dose escalation was assessed using 2 dosing schedules. In schedule A, LY3200882 was administered orally twice daily (BID) for 2 weeks followed by a treatment break for 2 weeks with a 2 weeks on, 2 weeks off dose schedule (2w/2w). In schedule B, LY3200882 was administered orally BID for 3 weeks followed by a treatment break for 1 week with a 3 weeks on, 1 week off dose schedule (3w/1w). During dose escalation, each treatment arm and dose level group comprised at least 3 patients who were evaluable for dose-limiting toxicity assessment. A 3+3 dose escalation trial design was utilized and guided by safety,

tolerability, and PK data (22). In the dose expansion monotherapy arm, safety, tolerability, PD, and preliminary efficacy of the RP2D of LY3200882 were evaluated in patients with isocitrate dehydrogenase (IDH) 1- or 2-mutant or IDH wild-type grade 4 glioma.

In the combination dose escalation arm, the safety, tolerability, PD, and preliminary antitumor activity of the RP2D of LY3200882 were determined in combination with the PD-L1 inhibitor LY3300054 in patients with advanced solid tumors (Combination arm C1), in combination with gemcitabine and nab-paclitaxel in treatment-naïve patients with pancreatic cancer (Combination arm C2), and in combination with cisplatin and radiation therapy in treatment-naïve patients with SCCHN (Combination arm C3). Details of each dose-schedule regimen and route of administration are provided in **Supplementary Table S1**. After completing the monotherapy arm of the trial, the study was terminated early due to a lack of substantial efficacy in patients with advanced glioblastoma. Hence the subsequent combination arms of the trial were not fully enrolled and evaluated.

Patients

Inclusion criteria

Patients at least 18 years of age, with adequate organ function, an estimated life expectancy of ≥ 12 weeks, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (23) were eligible for the study. In the monotherapy dose escalation arm, patients with histological or cytological evidence of advanced or metastatic cancer who failed to benefit from standard therapies were included. In the monotherapy dose expansion arm, eligible patients had a known histologically-confirmed diagnosis of either recurrent IDH mutant or IDH wild-type grade 4 glioma (24,25). In the combination arms, patients were required to have a confirmed diagnosis of advanced cancers (arm C1), metastatic pancreatic cancer (arm C2), or locoregionally advanced SCCHN (arm C3). Patients enrolled in arms C2 and C3 were treatment-naïve.

Exclusion criteria

All patients with elevated cardiac enzymes, moderate or severe cardiovascular disease, secondary malignancy, diffuse leptomeningeal disease, esophageal or gastric varices with high bleeding risk, acute leukemia, or a history of hypersensitivity to study drug components were excluded. Patients who had received radiotherapy within 2 weeks of enrollment or any systemic treatment within the past 28 days were also excluded from the study. Further, patients with active or suspected autoimmune disease and those receiving systemic steroids were excluded from receiving the combination of LY3200882 and LY3300054.

This study was conducted in accordance with the International Conference on Harmonisation requirements for Good Clinical Practice and with the consensus ethics principles derived from the International Ethics Guidelines, outlined in the Declaration of Helsinki and Council for International Organizations of Medical Sciences (26). All patients provided written informed consent before study enrollment.

Study assessments

Patients who received at least 1 dose of LY3200882 or any of the combination drugs were evaluated for safety, tolerability, PK, PD, and preliminary efficacy profiles. Safety was determined by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v 4.03 (27). Additionally, investigators assessed whether adverse events (AEs) were study treatment-related or caused by other factors. Plasma samples for PK analyses were assayed using a validated liquid chromatography with tandem mass spectrometry method (Covance Bioanalytical Service, Indianapolis, IN, USA). Maximum observed concentration (C_{max}), time of C_{max} (t_{max}), area under the curve (AUC), apparent clearance (CL/F), and volume of distribution (V/F) were estimated. Langerhans cell (LC; langerin-specific clone 12D6) quantification was performed using an immunohistochemistry assay using skin biopsy samples collected at baseline and on treatment as a PD surrogate marker for the TGF- β pathway (NeoGenomics Laboratories Inc, Aliso Viejo, CA, USA). Overall response rate (ORR; complete response [CR]/ partial response [PR]), OS, and

progression-free survival (PFS) were assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 for solid tumors and RANO criteria for gliomas (24). Disease assessment was performed using computed tomography or magnetic resonance imaging at baseline and between days 22 to 28 of every other cycle until confirmed progressive disease or patient withdrawal from the study.

Statistical analyses

All patients who received any dose of the study treatment were included in the safety and efficacy analyses. Clinical data including demographics, baseline characteristics, safety, and efficacy was analyzed using SAS[®] 9.4 software (SAS Institute Inc., Cary, NC, USA). For safety analyses, the frequency and percentage of patients with AEs were presented for each arm of the study. PK parameter estimates were analyzed using noncompartmental procedures with Phoenix WinNolin v64 build 8.1 software (Certara, Princeton, NJ, USA) and log transformed C_{max} and AUC estimates were assessed using a power model with dose as a fixed effect. Best overall response per RECIST v1.1 with confirmation on CR and PR were represented by frequency. PFS and OS were analyzed using the Kaplan-Meier method. PFS was defined as the time from the date of first study treatment to the first date of documented progression or death due to any cause. For patients who were not known to have died or progressed as of the cut-off dates, PFS times were censored at the date of the last progression-free disease assessment before the date of any subsequent anticancer therapy. OS was defined as the time from the date of first study treatment to the date of death from any cause. For each patient who was not known to have died as of the cut-off date, OS data were censored for that analysis at the date of last contact before the data inclusion cut-off date.

RESULTS

Patient disposition and demographic characteristics

Overall, 180 patients were enrolled, of which 139 (77.2%) patients were nonrandomly assigned to study treatment and received at least 1 dose of the study drug. At the time of data cut-off (March 2020), 131 (94.2%) patients had discontinued trial treatment with most patients discontinuing the study because of progressive disease. A total of 62 patients received escalating doses of LY3200882 as monotherapy for 2w/2w (n=30) and 3w/1w (n=32) over a 28-day cycle in the dose escalation arm. In the dose expansion arm, 40 patients with grade 4 glioma (IDH wild-type grade 4 glioma or glioblastoma, n=25; IDH mutant n=15) were treated with the RP2D selected, 50 mg BID for the 2w/2w schedule. A total of 28 patients with advanced cancer, pancreatic cancer, or SCCHN in the combination arms were treated with the RP2D and other anticancer agents. Patient disposition is summarised in **Supplementary Figure S1**.

Most patients enrolled in the dose escalation arm were heavily pretreated with a median of 3 (0–8) prior systemic lines, whereas patients in the expansion arm with grade 4 glioma were treated with a median of 1 (1–5) prior systemic therapy. Patients in the combination arms were treated with a median of 1 (0–7) prior systemic therapy (**Table 1**). Patients with advanced cancer treated in combination with LY3300054 were treated with a median of 2 (1–7) prior systemic therapy. Patients with PC treated in combination with gemcitabine and nab-paclitaxel and patients with SCCHN treated in combination with cisplatin and radiation therapy were treatment-naïve.

Safety outcomes

Overall, 130 (93.5%) patients experienced ≥ 1 treatment-emergent adverse event (TEAE), with 49 (35.3%) patients experiencing grade 3 or greater TEAEs (all causality). Most AEs were either grade 1 or 2 (64.7%) with grade 3 myelosuppression only observed in combination with cytotoxic chemotherapy in patients with pancreatic cancer or SCCHN (**Table 2**). The most common TEAEs experienced by $\geq 15\%$ patients included headache,

nausea, anemia, and fatigue (**Supplementary Table S2**). A total of 55 (39.6%) patients experienced TEAEs that were study treatment-related. The most frequent study-related TEAEs included headache, fatigue, and increased alanine aminotransferase. No LY3200882-related cardiovascular AEs and dose-limiting toxicities were observed with LY3200882 monotherapy.

One patient with pancreatic cancer receiving LY3200882 (35 mg BID with the 3w/1w schedule) with gemcitabine and nab-paclitaxel experienced stage C (ACC/AHA) cardiac insufficiency. At screening, the patient had a left ventricular ejection fraction (LVEF) of 70% with an unremarkable ECHO showing no kinetic or morphologic abnormalities. Patient had a history of hypertension, which was well controlled with angiotensin-converting enzyme inhibitors and beta blockers. The patient's third month on study ECHO showed that LVEF decreased to 57%, but the patient remained asymptomatic with no elevation in cardiac enzymes and the study treatment was continued. On cycle 7, day 1 patient presented with bilateral edema and dyspnea with elevated blood levels of brain natriuretic peptide (BNP; 212 pg/mL), and evidence of subclavian vein thrombosis. A subsequent ECHO revealed LVEF at 50% with total hypokinesia of the apex and the interventricular septum. Study treatment was discontinued, high-dose diuretics and anticoagulants started. Within a week, bilateral edema was completely resolved, and dyspnea improved with BNP levels reduced to 48 pg/mL. Cardiac imaging around this time revealed myocardial inflammation. Patient was not rechallenged with gemcitabine/abraxane or other cytotoxic chemotherapy regimen. PK analysis from blood samples taken during study treatment did not reveal higher exposure levels of LY3200882 than the population median.

A total of 24 (17.3%) patients experienced at least 1 serious AE (SAE), with 3 (2.2%) patients experiencing SAEs related to study drug. The study-drug related SAEs comprised grade 2 diarrhea, grade 4 neutropenia, and grade 2 weight loss, which were observed only in the combination expansion arms. A total of 63 (45.3%) deaths were reported in the study; none were deemed to be related to study treatment.

Pharmacokinetics

The PK profile of LY3200882 was linear with dose and time, and peak concentration was reached at 2 hours after administration (**Figure 1**). The AUC increased in a dose-dependent manner in the 5- to 50-mg dose range investigated (**Supplementary Figure S2, Panel A**). Furthermore, PK parameters such as CL/F, V/F, and half-life ($t_{1/2}$) were constant over time (**Supplementary Figure S2, Panel B**), indicating that the LY3200882 PK was independent of the schedule of administration. After reaching maximum LY3200882 concentration, the PK disposition was characterized by a mean CL/F, V/F, and associated $t_{1/2}$ of 57.3 L/hour, 559 L and 6.7 hours, respectively. The highest RP2D selected was 50 mg BID 2w/2w (schedule A), which achieved the highest exposure among doses tested, and was below the no-observed-adverse-effect level (NOAEL) for cardiotoxicity (3.4 mg*hr/L) determined from nonclinical toxicology studies. Based on the short $t_{1/2}$, steady state of the drug would be achieved after 2 doses with a 1.4-fold accumulation ratio. These data suggest that LY3200882 is neither an inhibitor nor an inducer of its own metabolism.

Pharmacodynamics

Skin LC density was used as a novel surrogate pharmacodynamic biomarker for TGF- β pathway inhibition in this study. Skin biopsies were collected from a subset of patients at baseline before initiating treatment and at day 14 or day 21 for the 2w/2w or 3w/1w dose schedules, respectively. Skin LCs decreased significantly in skin biopsies with LY3200882 monotherapy at 35 mg for 3w/1w (N=5; p=0.02), but not in patients treated with LY3200882 monotherapy at 25 mg 3w/1w (N=7; p=0.82) (**Supplementary Figure S3**) or 50 mg 2w/2w (N=18; p=0.21) (**Figure 1**).

Antitumor outcomes

Assessment of the tumor response of LY3200882 indicated that 41 of 139 (29.5%) patients demonstrated either RECIST v1.1 or RANO CR, PR, or stable disease (SD).

LY3200882 Monotherapy

Dose escalation arm (n=62)

Two patients with grade 4 glioma, of which 1 with IDH wild-type treated on the 2w/2w schedule and 1 patient with IDH 1-mutant on the 3w/1w schedule, achieved PR according to RANO criteria. The duration of response for the 2 patients was 19 months and 3.9 months on the 2w/2w and 3w/1w schedule, respectively.

The ORR of LY3200882 monotherapy was 3% (2/62) for both schedules combined. The disease control rate (DCR; CR/PR/SD) was 23% (7/30) with the 2w/2w schedule and 25% (8/32) with the 3w/1w schedule (**Table 3**). The median PFS for patients with advanced cancers treated with the 50 mg BID 2w/2w (n=17) was 1.8 months (95% CI: 0.9 – 2.0) and for patients on the 35 mg BID 3w/1w dose-schedule (n=8) was 1.7 months (95% CI: 0.8 – 2.6). The median OS for the 17 patients treated with LY3200882 50 mg BID 2w/2w schedule was 6.1 (95% confidence interval [CI]: 1.2 – 11.4) months, while the median OS of 8 patients treated with 35 mg BID 3w/1w schedule of LY3200882 was 4.0 months (95% CI 2.6 – NE).

Although no objective response was observed in patients in either groups, individual patients showed exceptional clinical benefit. A 53-year-old male diagnosed with IDH wild-type grade 4 glioma with *EGFR P772_V774dupPHV* mutation, *CDK4* amplification, and methylated *MGMT* promoter gene enrolled to this study after multiple tumor resections and no clinical benefit with concurrent radiotherapy and chemotherapy, including temozolomide and lomustine. He had a 94% tumor reduction by RANO assessment on LY3200882 monotherapy at 50 mg BID (2w/2w schedule), with no clinical toxicities and remained on trial 30.4 months (**Figure 2A**). A second patient with IDH 1-mutant grade 4 glioma with *EGFRVIII* mutation, *EGFR* amplification, *TERT* mutation, homozygous deletions of *CDKN2A* and *B*, *PIK3CA* mutation and *CCND2* duplication achieved a RANO PR while on study treatment. The magnetic resonance image (MRI) showed a decline in the sum of the perpendicular products of the target lesions from 130 mm² to 30 mm² from baseline MRI in December 2018 to follow up in April 2019. The patient remained in PR until October 2019 when study

treatment was discontinued due to new brain lesions. The patient received subsequent treatment with an investigational treatment of a bispecific T-cell engager targeting *EGFRVIII*, followed by tumor resection, radiotherapy (30 Gy in 10 fractions) and restart of temozolomide; however, no clinical benefit was observed with these therapies. Considering their prior response to treatment, the patient was granted compassionate access use in August 2020 to LY3200882 which was administered as 50 mg BID 2w/2w monotherapy, with disease stabilization and patient benefit, and treatment is still ongoing.

Recurrent IDH mutant and IDH wild-type grade 4 glioma dose expansion arm (n=40)

One patient with IDH wild-type grade 4 glioma treated with 50 mg BID 2w/2w achieved PR according to RANO criteria. The duration of response for this patient was 5.6 months. The ORR and DCR for the dose expansion arm were 3% (1/40) and 18% (7/40), respectively (**Table 3**). The median PFS was also similar between both groups of patients; IDH wild-type glioblastoma 1.6 months (95% CI: 0.9 – 5.5) and IDH mutant 1.7 months (95% CI: 1.3 – 1.8). The median OS of 15 patients with recurrent IDH mutant and 25 patients with IDH wild-type grade 4 glioma was 10.6 months (95% CI: 7.3 – NE) and 8.2 months (95% CI: 4.6 – 9.7), respectively.

LY3200882 in combination with other anticancer agents

LY3200882 and PD-L1 inhibitor LY3300054 (n=13)

A total of 13 patients with advanced cancer were treated with the combination of LY3200882 and PD-L1 inhibitor LY3300054. One patient with IDH wild-type grade 4 glioma achieved a PR per RANO for 5.6 months (**Table 3**). ORR and DCR for the combination therapy arm were 7.7% (1/13) and 39% (5/13), respectively. OS or PFS were not calculated due to the small sample size for this group.

LY3200882, gemcitabine and nab-paclitaxel (n=12)

Six (50%) of 12 patients with treatment-naïve advanced pancreatic cancer achieved confirmed RECIST v1.1 PRs, with all but 1 patient demonstrating tumor target lesion

shrinkage, when treated with the combination of LY3200882, gemcitabine, and nab-paclitaxel. One additional patient had an unconfirmed PR. Notably, the ORR and DCR was 50% (6/12) and 75% (9/12), respectively (**Table 3 and Figure 3**). The median duration of response for patients with pancreatic cancer treated with LY3200882+gemcitabine+nab-paclitaxel was 4.0 months. CA19-9 levels decreased by greater than 50% in 8 of the 12 patients.

An exceptional response was observed in a 36-year-old woman diagnosed with an adenocarcinoma of the tail of the pancreas with multiple and diffuse secondary liver lesions and an ECOG performance status of 1. Molecular profiling was not performed on tumor tissue obtained at diagnosis in this patient and therefore the presence of any oncogenic drivers or other genetic aberrations is unknown. The patient had an early RECIST v1.1 response of PR of both the primary pancreatic and secondary liver lesions; however, because of grade 3 myelotoxicity, the doses of gemcitabine and nab-paclitaxel were reduced. The patient had to be switched to a biweekly schedule for chemotherapy administration, while keeping LY3200882 dose and schedule unchanged. After 18 months of starting study treatment, the patient continues to have a RECIST v1.1 PR, with no cumulative toxicities and an ECOG PS of 0 (**Figure 2B**).

LY3200882, cisplatin and radiation therapy (n=3)

One patient achieved a RECIST v1.1 CR. The other 2 patients in this group achieved RECIST v1.1 SD. ORR and DCR for the combination therapy arm were 33.3% (1/3) and 100% (3/3), respectively. Because of the small patient sample size, PFS and OS data were not calculated.

DISCUSSION

This first-in-human phase I study demonstrated the safety and potential efficacy of LY3200882, a next-generation oral TGF- β R1 small molecule inhibitor as monotherapy for the treatment of recurrent grade 4 glioma and in combination with other anticancer agents for the treatment of advanced solid tumors, including pancreatic cancer. In the present study, treatment with LY3200882 as both monotherapy and in combination with other antitumor agents was well tolerated with mainly mild to moderate TEAEs. The RP2Ds selected were 50 mg BID for the 2w/2w schedule and 35 mg BID for the 3w/1w schedule, respectively. In the overall study population that was comprised of a large proportion of patients with relapsed grade 4 glioma, a DCR of 28.1% was observed. Durable RANO PRs were observed in 3 patients treated with LY3200882 monotherapy (2 patients with IDH wild-type and 1 patient with IDH mutant grade 4 glioma) at 50 mg BID 2w/2w and 35 mg BID 3w/1w, respectively and 1 patient with IDH wild-type grade 4 glioma treated with LY3200882 and PD-L1 inhibitor LY3300054 combination. Six of 12 patients with pancreatic cancer treated with LY3200882, gemcitabine and nab-paclitaxel and 1 patient with SCCHN treated with LY3200882, cisplatin and radiation therapy had RECIST v1.1 PRs and CR, respectively. The majority of TEAEs observed with LY3200882 were not considered related to study treatment; TEAEs considered to be treatment-related were mild or moderate in severity, manageable with supportive care, and reversible. Of note, a key concern with the development of TGF- β inhibitors has been the potential for cardiotoxicity based on preclinical toxicology studies (6). Overall, no cardiovascular AEs were observed in patients receiving LY3200882 as monotherapy. We only observed one case of treatment related cardiac toxicity in a patient with pancreatic cancer receiving LY3200882 in combination with gemcitabine and nab-paclitaxel chemotherapy in the form of decreased ejection fraction, hypokinesia of the interventricular septum, and myocardial inflammation leading to discontinuation after 7 cycles. However, it was not clear if the toxicity were related to LY3200882 or to gemcitabine and nab-paclitaxel chemotherapy treatment. Overall, the lack

of observed cardiovascular toxicity and general tolerability either as single agent or in combination therapy of LY3200882 is similar to the small molecule TGF- β R1 inhibitor galunisertib (19,28-30). The NOAEL daily AUC threshold values for cardiotoxicity established preclinically in rats and dogs for 2w/2w and 3w/1w schedules were 3.4 and 1.56 mg*h/L, respectively. The AUC achieved following the LY3200882 RP2D of 50 mg BID in 2w/2w and 35 mg BID in 3w/1w were within the planned daily AUC range and remained below the established NOAEL daily AUC threshold for cardiotoxicity.

Several biomarkers were evaluated in this study to interrogate if we were able to modulate the TGF- β pathway. TGF- β is an important immune regulator and highly expressed in skin LCs (31), and therefore LC assessment was performed as a novel surrogate PD marker in this study since inhibition of TGF- β signaling leads to LC migration out of the epidermis (32). Our study demonstrated a significant decrease in LC cells with the 35 mg 3w/1w dose-schedule regimen of LY3200882, while no significant difference was observed for the 50 mg 2w/2w and 25 mg 3w/1w dose-schedules, although general trends downwards were observed. The difference of LC migration between the 2w/2w and 3w/1w schedules may suggest that a more sustained inhibition of TGF- β may be required to achieve a more complete targeted inhibition of the pathway. Alternatively, because of the different dosing interval, the on-treatment skin biopsy for the 2w/2w schedule was performed at 2 weeks and the 3w/1w at 3 weeks. Hence, the observed difference in PD effects may be associated with the time needed for LCs to migrate out of the skin. This temporal difference likely explains the lack of change in cell density observed with the 50 mg BID 2w/2w dose-schedule despite being treated with a higher dose of LY3200882 compared to the 35 mg BID 3w/1w dose-schedule. However, the difference between the 35 mg 3w/1w and the 25 mg 3w/1w dose-schedules on LC migration suggests a dose-dependent response with a higher dose more effectively blocking the TGF- β pathway. Additionally, pSMAD levels were assessed from 9 dose escalation paired tumor biopsies collected 1 or 2 weeks after the last treatment of cycle 1; however, as these samples represent multiple treatment dose levels, collection time post

last treatment (1 or 2 weeks), and tumor histology, we were not able to collect sufficient data to draw any conclusions.

Of a total of 139 patients, 11 patients achieved radiological CR/PR and 28 patients had SD with LY3200882-based therapies. A subset of patients with grade 4 glioma (n=2) had tumor reduction that did not meet response criteria for RANO response but showed SD for durable disease stabilization of over 6 months.

Interestingly, 6 (50%) of 12 patients with treatment-naïve advanced pancreatic cancer demonstrated confirmed RECIST PRs, with all but 1 patient demonstrating tumor target lesion shrinkage, and an overall DCR of 75% with LY3200882 in combination with gemcitabine and nab-paclitaxel. In addition, 8 of these 12 patients had significant declines in their CA19-9 levels. Although observed in a small sample size (n=12), these early clinical data compare favorably to the ORR of 23% determined in the registered trial of gemcitabine plus nab-paclitaxel or 31.6% with FOLFIRINOX in patients with treatment-naïve advanced pancreatic cancer (33,34). The ORR observed with LY3200882 with gemcitabine and nab-paclitaxel in our study were similar to that observed with the ongoing trial evaluating gemcitabine and nab-paclitaxel in combination with a CD40 agonist and nivolumab, also given in first line pancreatic cancer (35). These data may suggest that targeting the immune axis with T-cell boosters or mechanisms that reverse immune suppression in pancreatic cancer may result in tumor T-cell infiltration and antitumor activity. Unfortunately, because our trial lacked paired biopsies, we were unable to evaluate immune cell population changes in the tumor. Earlier studies with the first-generation TGF- β R1 inhibitor galunisertib with gemcitabine also showed improved ORR (10.8% vs. 3.8%) and DCR (58.7% vs. 51.9%) when compared to single-agent gemcitabine (19,30).

Early-onset (<50 years) pancreatic cancer accounts for nearly 5% of the total patients with this malignancy. A 2019 transcriptomic analysis comparing the molecular landscape of early-onset and average-age onset pancreatic cancer revealed increased activation of the TGF- β pathway in younger patients who do not respond well to combination chemotherapy

regimens. Given these recent data, efforts were made to enrich our patient population with younger patients. The median age of patients with pancreatic cancer in our trial was 56 years, lower than the expected median age for pancreatic cancer, which is around 70 years in the United States and the Western world.

In conclusion, LY3200882 was safe as monotherapy and well tolerated in combination with the PD-L1 inhibitor LY3300054, chemotherapy, and radiotherapy, with most TEAEs considered to be mild, manageable, and reversible. The selected RP2D using the 2w/2w and 3w/1w schedules were identified as 50 mg and 35 mg BID, respectively. Dose-limiting toxicities were not observed with either schedules, and the exposure levels of the selected doses were within the planned daily AUC range and below the established NOAEL daily AUC threshold for cardiotoxicity. Notably, promising antitumor activity was observed in patients with treatment-naïve advanced pancreatic cancer with LY3200882 in combination with gemcitabine and nab-paclitaxel. The patients enrolled to this study with pancreatic cancer were younger with a median age of 56 years; it is plausible that this hard-to-treat patient population may benefit from combination treatment including TGF- β inhibitors, warranting further studies to evaluate the efficacy of this combination.

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Table 1. Baseline demographics and participant characteristics

Parameter	LY3200882 in a 2 w/2w schedule	LY3200882 in a 3w/1w schedule	Grade 4 glioma treated with RP2D dose from Dose expansion arm in a 2w/2w schedule	Advanced cancer treated with LY3200882 +PD-L1 inhibitor LY3300054	Pancreatic cancer with LY3200882 +gemcitabine +nab-paclitaxel	SCCHN treated with LY3200882 +cisplatin +radiation therapy	Japanese cohort
	Dose escalation arm; Schedule A (N=30)	Dose escalation arm; Schedule B (N=32)	Dose expansion arm (N=40)	Combination arm C1 (N=13)	Combination arm C2 (N=12)	Combination arm C3 (N=3)	(N=9)
Sex, n (%)							
Male	19 (63.3)	26 (81.3)	24 (60.0)	8 (61.5)	10 (58.3)	3 (100.0)	5 (55.6)
Female	11 (36.7)	6 (18.8)	16 (40.0)	5 (38.5)	5 (41.7)	0 (0.0)	4 (44.4)
Age, years							
Mean (SD)	49.8 (11.5)	49.8 (13.9)	48.3 (12.8)	53.2 (16.7)	54.7 (12.6)	51.7 (7.6)	56.8 (12.1)
Baseline ECOG performance status^a, n (%)							
0	8 (26.7)	4 (12.5)	15 (37.5)	3 (23.1)	7 (58.3)	1 (33.3)	9 (100.0)
1	22 (73.3)	27 (84.4)	25 (62.5)	10 (76.9)	5 (41.7)	2 (66.7)	0 (0.0)
Initial pathological diagnosis							
Grade 4 glioma ^b	6 (20.0)	7 (21.9)	25 (62.5)	2 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatic cancer	3 (10.0)	3 (9.4)	0 (0.0)	0 (0.0)	12 (100.0)	0 (0.0)	1 (11.1)
SCCHN ^c	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (66.7)	0 (0.0)
Prior lines of therapy, n (%)							
≥1 prior surgery	25 (83.3)	27 (84.4)	37 (92.5)	10 (76.9)	5 (41.7)	0 (0.0)	4 (44.4)
≥1 prior radiotherapy	25 (83.3)	25 (78.1)	40 (100.0)	10 (76.9)	0 (0.0)	1 (33.3)	3 (33.3)
≥1 prior systemic therapy	29 (96.7)	31 (96.9)	40 (100.0)	13 (100.0)	2 (16.7)	0 (0.0)	9 (100.0)
Patients with >2 regimens	6 (20.0)	6 (18.8)	7 (17.5)	4 (30.8)	0 (0.0)	0 (0.0)	1 (11.1)
Patients with ≥3	22 (73.3)	20 (62.5)	9 (22.5)	6 (46.2)	0 (0.0)	0 (0.0)	7 (77.8)

regimens							
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^aECOG: 0 = fully active, able to carry on all pre-disease performance without restriction; 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work; ^bGrade glioma included patients with glioblastoma, glioblastoma multiforme, IDH wild-type, and IDH mutant; ^cOne patient from this arm had supraglottis edidermoid carcinoma.

Abbreviations: 2w/2w, 2 week on/2 week off schedule; 3w/1w, 3 week on/1 week off schedule; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; N, total population; n, total number of patients in the subset; RP2D, recommended phase 2 dose; SCCHN, squamous cell cancer of head and neck; SD, standard deviation; US, United States

Table 2. Summary of study treatment-related adverse events with >5% frequency

Preferred term	LY3200882 in a 2 w/2w schedule		LY3200882 in a 3w/1w schedule		Grade 4 glioma treated with RP2D dose from Dose expansion arm in a 2w/2w schedule		Advanced cancer treated with LY3200882 +PD-L1 inhibitor LY3300054		Pancreatic cancer with LY3200882 +gemcitabine +nab-paclitaxel		SCCHN treated with LY3200882 +cisplatin +radiation therapy		Japanese cohort	
	Dose escalation arm; Schedule A (N=30)		Dose escalation arm; Schedule B (N=32)		Dose expansion arm (N=40)		Combination arm C1 (N=13)		Combination arm C2 (N=12)		Combination arm C3 (N=3)		(N=9)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any Grade	Grade ≥3
Subjects with ≥1 TEAEs related to study treatment, n (%)	10 (33)	0 (0)	10 (31)	0 (0)	10 (25)	0 (0)	7 (54)	0 (0)	12 (100)	6 (50)	3 (100)	2 (67)	3 (33)	0 (0)
Fatigue	0 (0)	0 (0)	1 (3)	0 (0)	4 (10)	0 (0)	1 (8)	0 (0)	5 (42)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)
Anemia	1 (3)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (50)	1 (8)	3 (100)	0 (0)	1 (11)	0 (0)
ALT increased	0 (0)	0 (0)	2 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (33)	1 (8)	0 (0)	0 (0)	1 (11)	0 (0)
Nausea	1 (3)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (17)	0 (0)	2 (67)	1 (33)	1 (11)	0 (0)

Abbreviations: 2w/2w, 2 week on/2 week off schedule; 3w/1w, 3 week on/1 week off schedule; ALT, alanine aminotransferase; N, total population; n, total number of patients in the subset; RP2D, recommended phase 2 dose; SCCHN, squamous cell cancer of head and neck TEAE, treatment-emergent adverse event

Table 3. Summary of confirmed best overall response

Radiological efficacy parameters*	LY3200882 in a 2 w/2w schedule	LY3200882 in a 3w/1w schedule	Grade 4 glioma treated with RP2D dose from Dose expansion arm in a 2w/2w schedule	Advanced cancer treated with LY3200882 +PD-L1 inhibitor LY3300054	Pancreatic cancer with LY3200882 +gemcitabine +nab-paclitaxel	SCCHN treated with LY3200882 +cisplatin +radiation therapy	Japanese cohort
	Dose escalation arm; Schedule A (N=30) n (%)	Dose escalation arm; Schedule B (N=32) n (%)	Dose expansion arm (N=40) n (%)	Combination arm C1 (N=13) n (%)	Combination arm C2 (N=12) n (%)	Combination arm C3 (N=3) n (%)	(N=9) n (%)
Best overall response							
CR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	0 (0)
PR	1 (3)	1 (3)	1 (3)	1 (8)	6 (50)	0 (0)	0 (0)
SD	6 (20)	7 (22)	6 (15)	4 (31)	3 (25)	2 (67)	0 (0)
Progressive disease	15 (50)	20 (63)	26 (65)	7 (54)	3 (25)	0 (0)	8 (89)
Nonevaluable	8 (27)	4 (13)	7 (18)	1 (8)	0 (0)	0 (0)	1 (11)
Overall response rate (CR/PR)	1 (3)	1 (3)	1 (3)	1 (8)	6 (50)	1 (33)	0 (0)
Disease control rate (CR/PR/SD)	7 (23)	8 (25)	7 (18)	5 (39)	9 (75)	3 (100)	0 (0)

*Radiological assessment using RECIST v1.1 or RANO criteria depending on respective tumor type

Abbreviations – 2w/2w, 2 week on/2 week off dose schedule; 3w/1w, 3 week on/1 week off dose schedule; CR, complete response; N, total population; n, total number of patients in the subset; PR, partial response; RANO, Revised Assessment in Neuro Oncology; RECIST, Response Evaluation Criteria in Solid Tumors v 1.1; RP2D, recommended phase 2 dose; SD, stable disease

Figure legends

Figure 1. LY3200882 pharmacokinetic concentration versus time profiles at steady state (ss) for the different dosing regimen (panels A and C) and corresponding Langerhans cell (LC) density skin biopsy data posttreatment (panels B and D). A. Pharmacokinetic profiles for arms treated by 50 mg 2 weeks on/2 weeks off dose schedule; B. Positive LC count at day 1 and day 14 of patients in the dose escalation arm treated using the 50 mg 2 week on/2 week off regime; C. Pharmacokinetic profiles for arms treated with 3 weeks on/1 week off dose schedule; D. Positive LC count at day 1 and day 21 of patients in dose escalation arm treated with 35 mg 3 week on/1 week off regime

Abbreviations: BID, twice daily; h, hour; LC, Langerhans cell; ss, steady state

Figure 2 A. MRI images of a 53-year-old male diagnosed with IDH wild-type grade 4 glioma with *EGFR P772_V774dupPHV* mutation, *CDK4* amplification, and methylated *MGMT* promoter gene enrolled to this study after multiple tumor resections and no clinical benefit with concurrent radiotherapy and chemotherapy, including temozolomide and lomustine. He had a 94% tumor reduction by RANO assessment on LY3200882 monotherapy at 50 mg BID (2w/2w schedule), with no clinical toxicities and remained on trial ~2 years ;

2 B. Computed tomography scans of patient with pancreatic cancer, after 18 months of treatment with LY3200882+gemcitabine+nab-paclitaxel. A complete response of liver metastases in S6, S4 and 7 and, S3-6 was achieved. Primary pancreatic tumor obtained a 40% reduction of its longest diameter. Liver metastasis in S8 achieved a 58% reduction of its longest diameter.

Abbreviation: IDH, isocitrate dehydrogenase; MRI, magnetic resonance imaging

Figure 3. Best overall response of patients with treatment-naïve advanced pancreatic cancer

JECA Schedule A Mean linear Plasma ss Plots

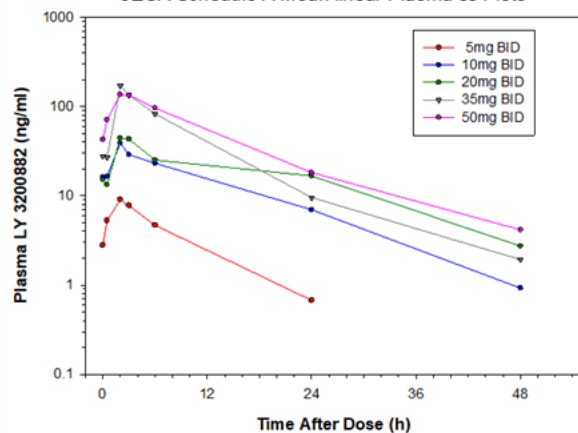


Figure 1A

Figure 1B

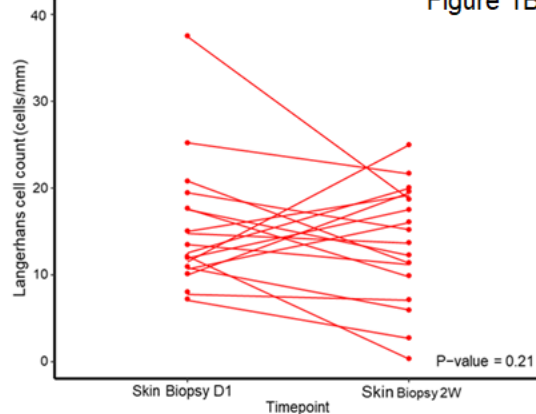
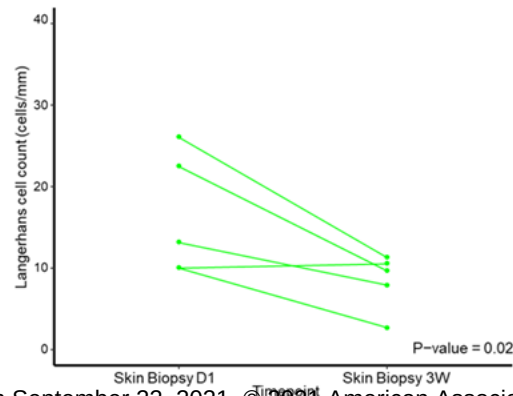
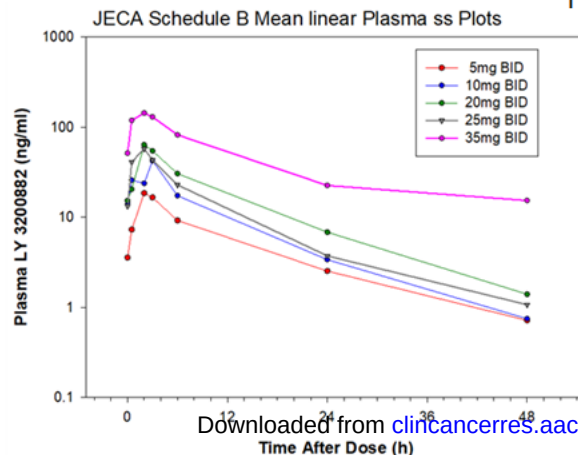
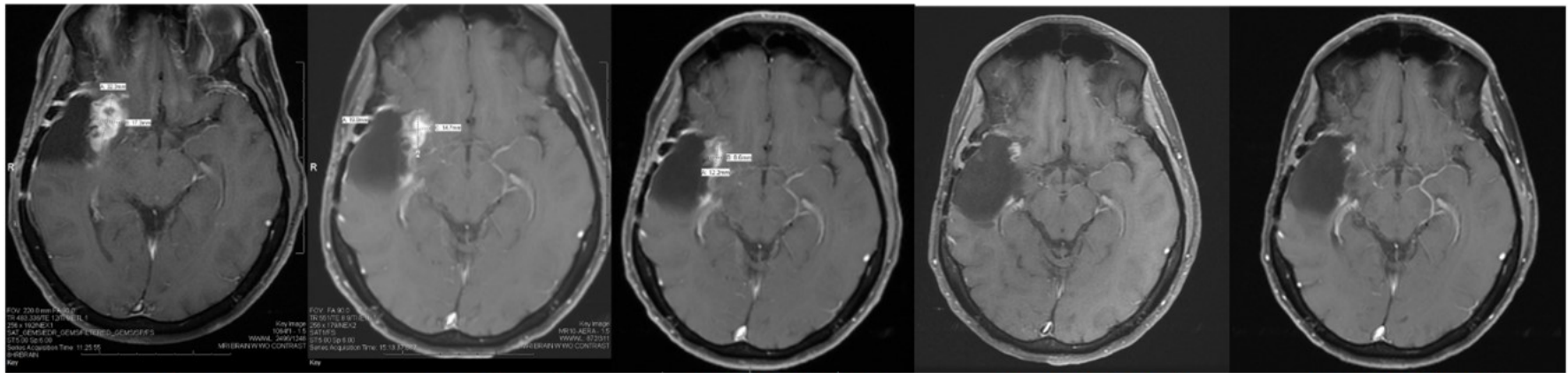


Figure 1C

Figure 1D





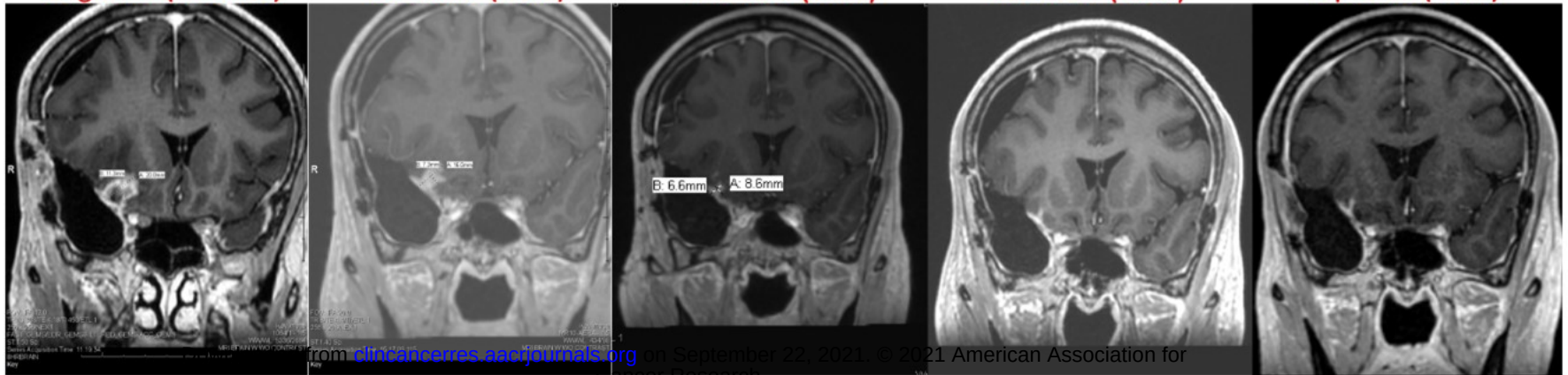
Aug 2017 (baseline)

Oct 2017 (-39%)

Dec 2017 (-69%)

Jan 2018 (-86%)

Sep 2018 (-94%)



Aug 2017 (baseline)

Oct 2017 (-39%)

Dec 2017 (-69%)

Jan 2018 (-86%)

Sep 2018 (-94%)

Figure 2B

Pancreatic primary tumor +
liver metastases S6

Liver metastases S8

Liver metastases S4 + S7

Liver metastases S3-6

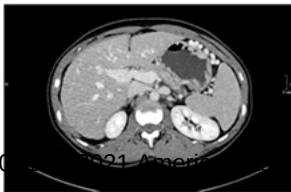
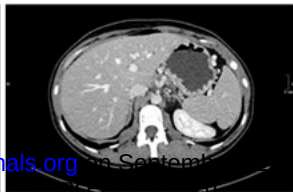
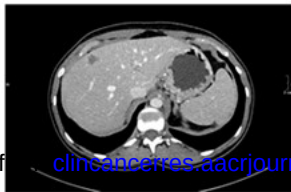
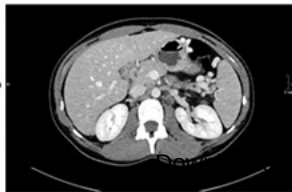
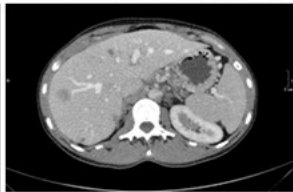
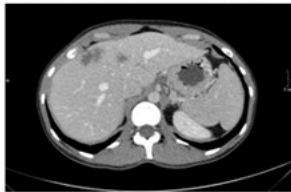
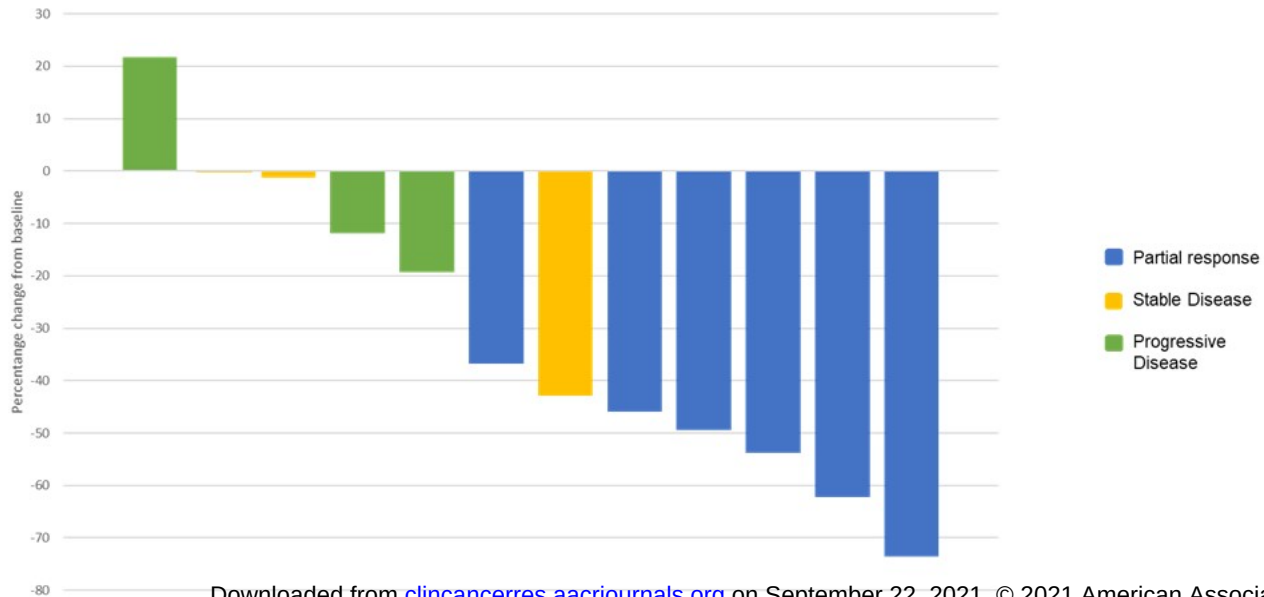


Figure 3

Best Overall Response of Patients with Pancreatic Cancer



Clinical Cancer Research

First-In-Human Phase I Study of a Next-Generation, Oral, Transforming Growth Factor-Beta Receptor 1 Inhibitor, LY3200882 in Patients with Advanced Cancer

Timothy A. Yap, María Vieito, Capucine Baldini, et al.

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