Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: ASP5878		

SYNOPSIS

Title of Study: An open-label phase 1 study of oral ASP5878 at single and multiple doses in patients with solid tumors

Investigators/Coordinating Investigator:
[redacted], MD, [redacted], [redacted], et al.

Study Center(s): 20 sites in Japan, 4 sites in Korea, 3 sites in Taiwan and 8 sites in the US

Publication Based on the Study: None.

Study Period:
05 November 2013 through 19 July 2017
Study Initiation Date (Date of First Enrollment):
Dose-escalation part: 05 November 2013
Expansion part: 14 December 2015
Study Completion Date (Date of Last Evaluation):
Dose-escalation part: 05 June 2015
Expansion part: 19 July 2017

Phase of Development: Phase 1

Objectives:
Dose-escalation part

The objectives of the dose-escalation part were to determine the tolerability, safety, pharmacokinetics, pharmacodynamics and efficacy of oral ASP5878 at single or multiple doses in patients with a solid tumor.

Primary objectives:

- To determine the tolerability and safety of ASP5878 and decide the dose-limiting toxicity (DLT), maximum tolerated dose (MTD) and recommended dose level of ASP5878 for the expansion part.

Secondary objectives:

- To determine the pharmacokinetics of ASP5878.
- To determine the pharmacodynamics of ASP5878.

Exploratory objective:

- To determine the antitumor activity of ASP5878.

Expansion part

The objectives of the expansion part were to determine the safety, pharmacokinetics, pharmacodynamics and efficacy of oral ASP5878 at multiple doses in patients with urothelial carcinoma, hepatocellular carcinoma or squamous cell lung carcinoma with fibroblast growth factor (FGF) or fibroblast growth factor receptor (FGFR) mutation/overexpression.

Primary objective:

- To determine the safety of ASP5878.

Secondary objectives:

- To determine the pharmacokinetics of ASP5878.
- To determine the pharmacodynamics of ASP5878.
- To determine the antitumor activity of ASP5878.

Methodology: This study was an open-label phase 1 study of oral ASP5878 at single and multiple doses. The study consisted of a dose-escalation part and an expansion part.

Dose-escalation part

The dose-escalation part was to be consisted of 9 cohorts (0.5 mg qd, 1.0 mg qd, 2.0 mg qd, 2.0 mg bid, 4.0 mg bid, 6.0 mg bid, 10 mg bid, 20 mg bid and 40 mg bid). A cohort was to be added to test an intermediate dose as needed. The DLTs were assessed in Cycles 0 and 1 at each dose level. The decision to proceed to the next cohort (the next dose level to enter patients or to end further patient enrollment) was discussed by the sponsor, medical advisor and investigator (or the subinvestigator if delegated by the investigator) by taking the recommended dose level calculated using the Bayesian-continual reassessment method (CRM) [Thall & Lee, 2003; O'Quigley et al, 1990] and the safety data. into consideration. The final decision was made by the Corporate Vice President of Clinical Development (or designee) on the basis of the results of the discussion. In the dose-escalation part, the next cohort was opened after the end of Cycle 1 in each cohort. The sponsor, medical advisor, investigator (or the subinvestigator if delegated by the investigator) and medical statistics advisor comprehensively assessed the data generated in Cycles 0 and 1 of the dose-escalation part, and discussed the MTD and recommended dose for the expansion part. On the basis of the results of the discussion, the Corporate Vice President of Clinical Development (or designee) finally decided the MTD and the recommended dose for the expansion part.

Approximately 30 patients with a solid tumor were to be enrolled in the dose-escalation part (the number of patients to be enrolled was increased or decreased depending on the occurrence of toxicity). Cycle 0 consisted of 3 days and Cycle 1 and subsequent cycles consisted of 28 days each.

The patients who gave consent to participate in the study underwent the tests and assessments specified for the screening visit to confirm their eligibility. The patients enrolled in the dose-escalation part received a single oral dose of ASP5878 once daily at the assigned dose at Cycle 0 Visit 1, followed by 3 days of observation (dosing day inclusive). From Cycle 1 Visit 1, the patients received multiple oral doses of ASP5878 once or twice daily (morning and evening). Following the completion of the 10 mg bid cohort, a dose schedule consisting of 5 days consecutive bid oral dosing followed by 2 days of dose interruption was implemented. This 5-day on/2-day off schedule was implemented on the basis of the review and evaluation of safety and pharmacokinetic data from the completed dose cohorts (0.5 mg qd to 10 mg bid). This schedule enabled the evaluation of the effectiveness of drug holiday in controlling hyperphosphatemia and eliminating the need for

additional intervention, such as phosphate binding agents. The patients continued the study drug dosing until one of the discontinuation criteria was met. Patients who had discontinued the study drug dosing due to adverse events (AEs) underwent the tests and assessments specified at the discontinuation visit within 7 days after the last study drug dosing (when the treatment was discontinued during the interruption of study drug dosing, the tests and assessments were to be performed within 7 days after determining discontinuation). The patients also underwent the tests and assessments specified at the follow-up visit 28 days after the last study drug dosing. When the patients proceeded to another antitumor therapy before 28 days after the last study drug dosing had passed, the patients returned to the site for a follow-up visit to undergo assessments before starting such antitumor therapy.

Expansion part

In the expansion part, all patients began Cycle 1 at a dose and schedule of 16 mg bid for 5 days of consecutive dosing followed by 2 days of interruption. On the basis of the phosphate level at Cycle 1 time points (Cycle 1 Visit 3 [C1V3] and Cycle 1 Visit 7 [C1V7]), the dosing schedule for patients who developed hyperphosphatemia was changed to 16 mg bid for 4 days of consecutive dosing followed by 3 days of interruption of ASP5878. The additional doses and schedules of time on/off drug were explored as needed.

Approximately 20 patients each with urothelial carcinoma, hepatocellular carcinoma or squamous cell lung carcinoma with FGF or FGFR mutation/overexpression were to be enrolled in the expansion part (60 patients in total). To assess safety, tolerability, pharmacokinetics and efficacy in a Western patient population, a minimum of 18 of the approximately 60 patients were to be enrolled in the US. The enrollment could be terminated if the efficacy of ASP5878 was confirmed by the posterior probability of > 80% for a tumor response rate of at least 20%. The patients who gave consent to undergo FGF or FGFR testing underwent the tests. Patients who were positive for FGF or FGFR testing and who gave consent to participate in the study underwent the tests and assessments specified at the screening visit to confirm their eligibility. Each cycle consisted of 28 days. The patients continued the study drug dosing until one of the discontinuation criteria was met. Patients who had discontinued the study drug dosing due to AEs underwent the tests and assessments specified at the discontinuation visit within 7 days after the last study drug dosing (when the treatment was discontinued during the interruption of study drug dosing, the tests and assessments were to be performed within 7 days after determining discontinuation). The patients who discontinued the study drug dosing also underwent the tests and assessments specified at the follow-up visit 28 days after the last study drug dosing. When the patients proceeded to another antitumor therapy before 28 days after the last study drug dosing had passed, the patients returned to the site for a follow-up visit to undergo assessments before starting such antitumor therapy.

Number of Patients (Planned, Enrolled and Analyzed):

Planned

Dose-escalation part: At least 3 patients who were evaluable for DLT at each dose level, a total of approximately 30 patients (the number of patients could be increased or decreased depending on the occurrence of toxicities).

Expansion part: Approximately 60 patients (approximately 20 patients each with urothelial carcinoma, hepatocellular carcinoma and squamous cell lung carcinoma with FGF or FGFR mutation/overexpression. The number of patients could be increased or decreased depending on the status of the response to ASP5878).

Enrolled and Analyzed

Dose-escalation part: A total of 35 patients were enrolled and were included in the full analysis set (FAS),

safety analysis set (SAF), pharmacokinetic analysis set (PKAS) and pharmacodynamics analysis set (PDAS). Among the 35 patients, 33 patients were included in the dose-determine analysis set (DDAS).
Expansion part: A total of 51 patients were enrolled and were included in the FAS, SAF, PKAS and PDAS.

Diagnosis and Main Criteria for Inclusion:
For the dose-escalation part, patients were eligible for inclusion in the study if they were age ≥ 20 years at the time of providing informed consent; had histologically or cytologically confirmed solid tumor; had disease progression despite standard therapies, had progressive disease without any standard therapies established or standard therapies were considered intolerable in the judgment of the investigator or subinvestigator; had Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, and had predicted life expectancy ≥ 12 weeks in the judgment of the investigator or subinvestigator.

For the expansion part, patients were eligible for inclusion in the study if they were at least 18 years old (20 years old in Japan, Korea and Taiwan); had a histologically or cytologically confirmed diagnosis of an urothelial carcinoma, hepatocellular carcinoma or squamous cell lung carcinoma; had disease progression despite standard therapies or standard therapies were considered intolerable in the judgment of the investigator or subinvestigator, and the stage of disease was advanced (unresectable or not eligible for loco-regional therapy), metastatic or recurrent disease; had an ECOG performance status 0 or 1; and had a predicted life expectancy ≥ 12 weeks in the judgment of the investigator or subinvestigator. Patients also had to have evidence of at least one of the following gene mutations or overexpression:

- Urothelial carcinoma: FGFR3-transforming acidic coiled-coil containing protein 3 (TACC3) fusion mutation or FGFR3 point mutation (G372C, K652E, R248C, S249C or Y375C only) based upon local or central analytical laboratory result.
- Hepatocellular carcinoma: FGF19 overexpression based upon central analytical laboratory result.
- Squamous cell lung carcinoma: FGFR1 overexpression based upon central analytical laboratory result.

Patients were not eligible for enrollment if they had ≥ grade 2 (Common Terminology Criteria for Adverse Events [CTCAE: v 4.0-Japan Clinical Oncology Group [JCOG]) persistent symptoms and objective findings due to the toxicity attributable to prior treatment with antitumor effect (except alopecia); received a prior treatment intended for antitumor effect (medication, surgery, radiotherapy, etc.) within 4 weeks prior to the planned first day of study drug dosing (or patient who received mitomycin C or nitrosourea within 6 weeks prior to the planned first day of study drug dosing); had a major surgical procedure within 4 weeks prior to the planned first day of study drug dosing or a surgical procedure was planned during the study period; received blood transfusions, hemopoietic factors, calcium, vitamin D, diuretics or continuous systemic corticosteroids (oral or intravenous) within 2 weeks prior to the planned first day of study drug dosing; were treated with other investigational drug or medical device within 4 weeks prior to the planned first day of study drug dosing; or previously used an investigational drug that selectively inhibits FGFR (including ASP5878).

Test Product, Dose and Mode of Administration, Batch Numbers:
ASP5878 was provided as 0.5 mg capsules, and 2, 10 and 40 mg tablets in bottles containing 30 capsules or 30 tablets each.

The dose-escalation part was to be consisted of 9 cohorts (0.5 mg qd, 1.0 mg qd, 2.0 mg qd, 2.0 mg bid, 4.0 mg bid, 6.0 mg bid, 10 mg bid, 20 mg bid and 40 mg bid). Cycle 0 consisted of 3 days and Cycle 1 and subsequent cycles consisted of 28 days each with consecutive daily dosing. The patients received a single oral dose of

ASP5878 once daily at the assigned dose at the Cycle 0 Visit 1, followed by 3 days of observation (dosing day inclusive). The patients received multiple oral doses of ASP5878 once daily from Cycle 1 Visit 1 onwards and continued the study drug dosing until one of the discontinuation criteria was met. For the treatment at 2.0 mg bid or higher, the patients received a single oral dose of ASP5878 once daily at the assigned dose at the Cycle 0 Visit 1, followed by 3 days of observation (dosing day inclusive). From the Cycle 1 Visit 1, the patients received multiple oral doses of ASP5878 twice daily (morning and evening) or 5 days consecutive bid oral dosing followed by 2 days of dose interruption. The patients continued the study drug dosing until one of the discontinuation criteria was met.

In the expansion part, all patients began Cycle 1 at a dose and schedule of 16 mg bid for 5 days consecutive dosing followed by 2 days of interruption. On the basis of the phosphate level at Cycle 1 time points (C1V3 and C1V7), the dosing schedule for patients who developed hyperphosphatemia was changed to 16 mg bid for 4 days of consecutive dosing followed by 3 days of interruption of ASP5878. Additional doses and schedules of time on/off drug could be explored as needed. Each cycle consisted of 28 days. The patients continued the study drug dosing until one of the discontinuation criteria was met.

Lot numbers for study drugs were [redacted] (0.5 mg capsule), [redacted], [redacted], [redacted], [redacted] (2 mg tablet), [redacted], [redacted] and [redacted] (10 mg tablet) in Japan, Korea and Taiwan, and [redacted] (2 mg tablet) and [redacted] (10 mg tablet) in the US.

Duration of Treatment (or Duration of Study, if applicable):
The patients continued the study drug dosing until one of the discontinuation criteria was met.

Reference Product, Dose and Mode of Administration, Batch Numbers:
Not applicable.

Criteria for Evaluation:
Efficacy

The efficacy of ASP5878 was evaluated on the basis of the antitumor effects of (or antitumor response to) ASP5878 assessed in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). To estimate the antitumor effects of (or antitumor response to) ASP5878 by using the RECIST (version 1.1), tumor lesions were tested with an imaging technique such as X-ray, computed tomography (CT) or magnetic resonance imaging (MRI) at the time points shown in the schedule of assessments in Appendix 13.1.1. The investigator or subinvestigator observed and assessed each tumor lesion (target and nontarget lesions) and estimated the antitumor effects of ASP5878 on each patient.

The best overall response was defined as the best response across all assessment time points. To confirm the best overall response rated as complete response (CR) or partial response (PR), the response had to continue to meet the criteria for CR or PR, respectively, for at least 4 weeks. To confirm the best overall response rated as stable disease (SD), tumor measurements had to meet the criteria for SD at least once during a period of more than 8 weeks after the start of study drug dosing.

Pharmacokinetics

Blood and urine samples were collected to assess plasma and urine concentrations of unchanged ASP5878 at the time points shown in the schedule of assessments in Appendix 13.1.1.

Pharmacodynamics

To evaluate the pharmacodynamic effect of ASP5878 on the serum concentrations of FGF19 (the expansion part only) and FGF23, inorganic phosphorus, calcium (the dose-escalation part only), intact parathyroid hormone (iPTH) and calcitriol were analyzed. FGF21 could be analyzed in any serum remaining after completion of above assays.

Safety

Safety assessment was based on AEs, vital signs, body weight, 12-lead electrocardiogram (ECG), laboratory tests, ophthalmologic examination, bone density measurement, imaging study and echocardiogram.

Statistical Methods:

Efficacy

The following analyses were performed in terms of antitumor activity evaluated based on RECIST (version 1.1).

- The proportion of patients with the best overall response was calculated.
- The proportion of patients with disease control was calculated.

Safety

- The posterior mean of the DLT incidence was calculated for each dose level using Bayesian-CRM.
- AEs and AEs that were related to the study drug were summarized by System Organ Class (SOC) and Preferred Term (PT).
- Descriptive statistics were calculated according to the data characteristics of the following parameters.
    - DLTs
    - Laboratory values
    - Vital signs
    - Body weight
    - 12-lead ECGs (including the evaluation of the QT interval)
    - Ophthalmology
    - Bone density measurement
    - Imaging assessment
    - Echocardiogram

Pharmacokinetics

- PK parameters were calculated and summary statistics were tabulated using the data on plasma (e.g., C_{max} and AUC_{last}) and urine (e.g., Ae and CL_R) concentrations of unchanged ASP5878.
- PK dose proportionality, accumulation, and steady-state profile were determined.
- Possible ethnic differences in PK parameters were assessed.

Pharmacodynamics

- Summary statistics of the actual measured values were calculated for each measured time point for each serum pharmacodynamic parameters
- Possible ethnic differences in PD parameters were assessed.

Summary of Results/Conclusions: The patient disposition and analysis sets in the dose-escalation part and the expansion part can be found in Table 1 and Table 2, respectively. A summary of demographics and baseline characteristics in the dose-escalation part and the expansion part can be found in Table 3 and Table 4, respectively.

Efficacy Results:

Overall Response (Dose-escalation Part)

Overall, 1 patient with urothelial carcinoma (20 mg bid 5-day on/2-day off dosing group) achieved PR, and the response rate (CR + PR) based on the best response rate was 2.9% [Table 5]. The patient who achieved PR was positive for FGFR3 point mutation S249C. No CR was observed. SD was achieved in 12 patients in the 2.0 mg qd and higher dose groups, and the disease control rate (CR + PR + SD) was 37.1%.

Overall Response (Expansion Part)

Overall, 2 patients (both with urothelial carcinoma) achieved PR, and the response rate (CR + PR) based on the best response rate was 3.9% [Table 6]. In the 2 responders, one was positive for FGFR3 point mutation S249C and the other was positive for FGFR3-TACC3 fusion mutation. No CR was observed. SD was achieved in 18 patients, and the disease control rate (CR + PR + SD) was 39.2%. The disease control rate was comparable among the 3 types of carcinoma.

Maximum Shrinkage in Target Lesion (Expansion Part Only)

The maximum shrinkage from baseline in target lesion was ≥ 30% in 4.0% (2/50) of patients, and the 2 patients were both urothelial carcinoma patients [Table 7].

Progression Free Survival (PFS) (Expansion Part Only)

The median PFS was similar among the 3 types of carcinoma, and it was 2.76 months (95% confidence interval [CI]: 2.60, 4.47) in the total population [Table 8]. A total of 70.6% (36/51) of patients had PFS events and 29.4% (15/51) of patients data were censored.

Time to Progression (TTP) (Expansion Part Only)

The median TTP was similar among the 3 types of carcinoma, and it was 2.76 months (95% CI: 2.60, 4.47) in the total population [Table 9]. A total of 70.6% (36/51) of patients had TTP events and 29.4% (15/51) of patients data were censored.

Time to Treatment Failure (TTF) (Expansion Part Only)

The median TTF was 2.60 months (95% CI: 1.64, 2.69) in the total population [Table 10], and it was shorter in patients with squamous cell lung carcinoma (1.77 months) than in those with urothelial carcinoma (2.69 months) and hepatocellular carcinoma (2.66 months). All 51 patients had TTF events.

Overall Survival (OS) (Expansion Part Only)

No deaths were reported for patients enrolled in the expansion part of the study, and the median OS was not reached (Table 12.3.7).

Pharmacokinetic Results:

Dose-escalation Part

After the single-dose administration of ASP5878 on Cycle 0 Day S1 (dose levels 0.5 to 20 mg), the median AUC_{inf} ranged from 16.0 to 600 ng•h/mL, median C_{max} ranged from 6.74 to 142 ng/mL, median t_{max} ranged from 0.975 to 3.05 hours and median $t_{1/2}$ ranged from 2.10 to 9.16 hours [Tables A.12.4.2.1.1.1, A.12.4.2.1.2.1, A.12.4.2.1.3.1, A.12.4.2.2.1.1, A.12.4.2.2.2.1, A.12.4.2.2.3.1, A.12.4.2.2.4.1, A.12.4.2.3.1.1 and A.12.4.2.3.2.1].

After the multiple-dose administration of ASP5878 on Cycle 1 Day 27 for 28 days of multiple dosing (dose levels 0.5 mg qd to 10 mg bid), the median AUC_{tau} ranged from 17.0 to 368 ng•h/mL, median C_{max} ranged from 4.25 to 112 ng/mL and median t_{max} ranged from 0.733 to 2.90 hours [Tables A.12.4.2.1.1.2, A.12.4.2.1.2.2, A.12.4.2.1.3.2, A.12.4.2.2.1.2, A.12.4.2.2.2.2, A.12.4.2.2.3.2 and A.12.4.2.2.4.2]. After the multiple-dose administration of ASP5878 on Cycle 1 Day 5 for 5-day on/2-day off dosing (dose levels 20 and 16 mg bid), the median AUC_{tau} ranged from 701 to 825 ng•h/mL, median C_{max} ranged from 181 to 188 ng/mL and median t_{max} ranged from 1.47 to 2.08 hours [Tables A.12.4.2.3.1.2 and A.12.4.2.3.2.2].

After the single-dose administration of ASP5878 on Cycle 0 Day S1 (dose levels 0.5 to 20 mg), the median Ae_{72h}% ranged from 0.0134% to 0.0423% and median CL_R ranged from 0.00463 to 0.0138 L/h [Tables A.12.4.4.1.1.1, A.12.4.4.1.2.1, A.12.4.4.1.3.1, A.12.4.4.2.1.1, A.12.4.4.2.2.1, A.12.4.4.2.3.1, A.12.4.4.2.4.1, A.12.4.4.3.1.1 and A.12.4.4.3.2.1]. After the multiple-dose administration of ASP5878 on Cycle 1 Day 5 for 5-day on/2-day off dosing (dose levels 20 and 16 mg bid), the median Ae_{tau}% ranged from 0.0313% to 0.0594% and median CL_R ranged from 0.0125 to 0.0176 L/h [A.12.4.4.3.1.2 and A.12.4.4.3.2.2]. After the multiple-dose administration of ASP5878 on Cycle 1 Day 27 (dose levels 0.5 mg qd to 10 mg bid), the median Ae_{tau}% ranged from 0.0167% to 0.0776% and median CL_R ranged from 0.00466 to 0.0152 L/h [Tables A.12.4.4.1.1.2, A.12.4.4.1.2.2, A.12.4.4.1.3.2, A.12.4.4.2.1.2, A.12.4.4.2.2.2, A.12.4.4.2.3.2 and A.12.4.4.2.4.2].

ASP5878 showed linear pharmacokinetics and dose proportionality after the once daily administration of ASP5878 over the dose range evaluated (0.5 to 20 mg).

The steady-state ASP5878 concentrations were assumed to be achieved at least by Day 5 after once or twice daily dosing.

Expansion Part

After the single-dose administration of ASP5878 (16 mg) on Cycle 1 Day 1, the median AUC_{inf} was 557 ng•h/mL, median C_{max} was 142 ng/mL, median t_{max} was 1.00 hour and median $t_{1/2}$ was 2.06 hours [Table B.12.4.2.1.1]. After the multiple-dose administration of ASP5878 (16 mg bid) on Cycle 1 Day 5, the median AUC_{tau} was 650 ng•h/mL, median C_{max} was 171 ng/mL and median t_{max} was 1.03 hours [Table B.12.4.2.1.2].

The steady-state ASP5878 concentrations were achieved at least by Day 5 after twice daily dosing.

No marked differences among ethnicities or types of carcinoma were observed.

Pharmacodynamic Results:

Dose-escalation Part

In the multiple-dose administration of ASP5878, the levels of FGF23, phosphate and calcitriol seemed to be increased dose dependently in each regimen, whereas the level of calcium was not varied by dose. The level of iPTH in multiple doses showed no clear tendency in each regimen.

Expansion Part

Serum FGF19, FGF23, phosphate and calcitriol concentration in the multiple-dose administration of ASP5878 (Cycle 1 Day 5) were higher than those in the single-dose administration of ASP5878 (Cycle 1 Day 1). The levels of iPTH and 7α-hydroxy-4-cholesten-3-one showed no clear tendency in multiple dose. Although the inter-individual variability in the serum concentration–time profile was large, the serum phosphate concentration seemed to be controlled in 16 mg for a 5-day on/2-day off dosing regimen.

Safety Results:

Dose-escalation Part

Among 33 patients in the DDAS, 2 patients in the 20 mg bid 5-day on/2-day off group experienced a DLT during the dose-escalation part. On the basis of the DLT evaluation results and from a medical view point, the recommended dose for the expansion part was determined to be 16 mg administered twice daily for 5 consecutive days followed by 2 days of interruption.

Overall, 94.3% (33/35) of the patients receiving the study drug experienced at least 1 AE and 85.7% (30/35) of the patients experienced a drug-related AE [Table 11]. The common AEs occurring in ≥ 20% of all patients were hyperphosphatemia (62.9%, 22/35), retinal detachment (42.9%, 15/35), diarrhea (42.9%, 15/35), alanine aminotransferase increased (34.3%, 12/35), fatigue (28.6%, 10/35), aspartate aminotransferase increased (28.6%, 10/35), constipation (25.7%, 9/35) and decreased appetite (25.7%, 9/35) [Table 12].

AEs with maximum NCI CTCAE grade 3 or higher were reported in 28.6% (10/35) of all patients, including 50.0% (2/4) of patients in the 1.0 mg qd, 2.0 mg bid and 4.0 mg bid groups; 33.3% (1/3) of patients in the 6.0 mg bid group; 25.0% (1/4) of patients in the 10 mg bid group and 28.6% (2/7) of patients in the 16 mg bid 5-day on/2-day off group. The NCI CTCAE grade 3 or higher AEs reported in ≥ 5% of all patients were lipase increased (8.6%, 3/35), hepatic function abnormal (5.7%, 2/35) and gamma-glutamyltransferase increased (5.7%, 2/35).

One AE of dyspnea leading to death was reported in 1 patient in the 2.0 mg bid group. The investigator did not consider the event to be related to the study drug.

Serious adverse events (SAEs) were reported in 11.4% (4/35) of all patients, including 2 patients in the 2.0 mg bid group and 1 patient each in the 1.0 mg qd and the 16 mg bid 5-day on/2-day off groups [Table 13]. All SAEs were single cases. In 1 of the 4 patients, SAE was considered by the investigator to be related to the study drug.

AEs resulting in permanent discontinuation of the study drug were reported in 11.4% (4/35) of all patients, including 2 patients in the 4.0 mg bid group and 1 patient each in the 2.0 and 10 mg bid groups. All AEs resulting in discontinuation were single cases. All the AEs resulting in discontinuation were considered by the investigator to be related to the study drug.

AEs leading to interruption of the study drug were reported in 65.7% (23/35) of all patients including 33.3% (1/3) of patients in the 2.0 mg qd group; 75.0% (3/4) of patients in the 2.0, 4.0 and 10 mg bid groups; and all patients in the 6.0 mg bid (3/3), 20 mg bid 5-day on/2-day off (3/3) and 16 mg bid 5-day on/2-day off (7/7) groups. The common AEs occurring in ≥ 2 patients were hyperphosphatemia (31.4%, 11/35), retinal detachment (20.0%, 7/35), fatigue (11.4%, 4/35), decreased appetite (11.4%, 4/35), palmar-plantar erythrodysesthesia syndrome (11.4%, 4/35) and vision blurred (8.6%, 3/35). All the AEs leading to interruption of the study drug were considered by the investigator to be related to the study drug.

Two patients (5.7%) experienced a simultaneous increase in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) of greater than 3 times the upper limit of normal (ULN) and an increase in total bilirubin of greater than 2 times ULN.

Postbaseline laboratory values that were NCI CTCAE grade 3 or higher in ≥ 2 patients included triacylglycerol lipase (grade 3: 5.9% [2/34], grade 4: 8.8% [3/34]), leukocytes (grade 3: 17.1% [6/35]), sodium (grade 3: 5.7%

[2/35]), gamma glutamyl transferase (grade 3: 5.7% [2/35]), bilirubin (grade 3: 5.7% [2/35]) and lymphocytes (grade 3: 5.7% [2/35]).

No clinically significant abnormalities were observed in the ECG results at any postbaseline time point.

The maximum postbaseline QT interval corrected for heart rate according to Fridericia's formula (QTcF) of > 450 msec was observed in 11.4% (4/35) of the evaluable patients, including 2 patients in the 4.0 mg bid group and 1 patient each in the 10 mg bid and 16 mg bid 5-day on/2-day off groups. The maximum QTcF change from baseline of > 30 msec was observed in 8.6% (3/35) of the evaluable patients, including 1 patient each in the 10 mg bid, 20 mg bid 5-day on/2-day off and 16 mg bid 5-day on/2-day off groups. No patients experienced a maximum postbaseline QTcF of > 480 msec or a maximum QTcF change from baseline of > 60 msec. The proportion of patients with changes in QTcF interval showed no particular trend with increasing doses.

Clinically significant postbaseline ophthalmologic abnormalities were observed in 17 patients (48.6%), including 1 patient in the 1.0 mg qd group, 3 patients each in the 2.0 and 4.0 mg bid groups, 2 patients each in the 10 mg bid and 20 mg bid 5-day on/2-day off groups, and 6 patients in the 16 mg bid 5-day on/2-day off group.

No clinically significant abnormal results were observed at any time point for CT imaging assessment.

Expansion Part

Overall, all patients receiving the study drug experienced at least 1 AE and 98.0% (50/51) of the patients experienced a drug-related AE [Table 14]. The common AEs occurring in ≥ 20% of all patients were hyperphosphatemia (78.4%, 40/51), diarrhea (70.6%, 36/51), decreased appetite (27.5%, 14/51), alopecia (27.5%, 14/51), retinal detachment (21.6%, 11/51) and nail discoloration (21.6%, 11/51) [Table 15].

AEs with maximum NCI CTCAE grade 3 or higher were reported in 45.1% (23/51) of all patients, including 57.1% (8/14) of patients with squamous cell lung carcinoma, 53.8% (7/13) of patients with urothelial carcinoma and 33.3% (8/24) of patients with hepatocellular carcinoma. The NCI CTCAE grade 3 or higher AEs reported in ≥ 5% of all patients were alanine aminotransferase increased (9.8%, 5/51) and palmar-plantar erythrodysesthesia syndrome (7.8%, 4/51).

No deaths occurred.

SAEs were reported in 21.6% (11/51) of all patients, including 7 patients with squamous cell lung carcinoma and 4 patients with hepatocellular carcinoma [Table 16]. The common SAEs occurring in ≥ 2 patients were alanine aminotransferase increased and aspartate aminotransferase increased, both were reported in 2 patients (3.9%). In 5 of the 11 patients, SAE was considered by the investigator to be related to the study drug.

AEs resulting in permanent discontinuation of the study drug were reported in 15.7% (8/51) of all patients, including 4 patients with squamous cell lung carcinoma and 2 patients each with urothelial carcinoma and hepatocellular carcinoma. The only AE leading to discontinuation reported in ≥ 2 patients was retinal detachment (5.9%, 3/51). All the AEs resulting in discontinuation except for 1 event (metastases to central nervous system) were considered by the investigator to be related to the study drug.

AEs leading to interruption of the study drug were reported in 56.9% (29/51) of all patients including 76.9% (10/13) of patients with urothelial carcinoma, 45.8% (11/24) of patients with hepatocellular carcinoma and 57.1% (8/14) of patients with squamous cell lung carcinoma. The common AEs occurring in ≥ 2 patients were hyperphosphatemia (13.7%, 7/51), palmar-plantar erythrodysesthesia syndrome (7.8%, 4/51), retinal

detachment (5.9%, 3/51), aspartate aminotransferase increased (5.9%, 3/51), diarrhea (3.9%, 2/51), alanine aminotransferase increased (3.9%, 2/51) and onychomadesis (3.9%, 2/51). All the AEs leading to interruption of the study drug except for 3 events (infection, upper respiratory tract infection and vomiting) were considered by the investigator to be related to the study drug.

No patients experienced a simultaneous increase in ALT and/or AST of greater than 3 times ULN and an increase in total bilirubin of greater than 2 times ULN.

Postbaseline laboratory values that were NCI CTCAE grade 3 or higher in ≥ 2 patients included leukocytes (grade 3: 25.5% [13/51]), phosphate (grade 3: 13.7% [7/51]), AST (grade 3: 10.2% [5/49]), triacylglycerol lipase (grade 3: 4.0% [2/50], grade 4: 4.0% [2/50]), lymphocytes (grade 3: 7.8% [4/51]), ALT (grade 3: 7.8% [4/51]), calcium (grade 3: 2.0% [1/51], grade 4: 2.0% [1/51]) and gamma glutamyl transferase (grade 3: 3.9% [2/51]).

No clinically significant abnormalities were observed in the ECG results at any postbaseline time point.

The maximum postbaseline QTcF of > 450 msec was observed in 5.9% (3/51) of the evaluable patients, and all of them were hepatocellular carcinoma patients. The maximum QTcF change from baseline of > 30 msec was observed in 3.9% (2/51) of the evaluable patients, including 1 patient each with urothelial carcinoma and squamous cell lung carcinoma. No patients experienced a maximum postbaseline QTcF of > 480 msec or a maximum QTcF change from baseline of > 60 msec. The proportion of patients with changes in QTcF interval showed no particular trend with the type of carcinoma.

Clinically significant postbaseline ophthalmologic abnormalities were observed in 31 patients (60.8%), including 8 patients (61.5%) with urothelial carcinoma, 14 patients (58.3%) with hepatocellular carcinoma and 9 patients (64.3%) with squamous cell lung carcinoma.

For CT imaging assessment, 2 patients (3.9%) and 3 patients (9.7%) had clinically significant abnormal results at screening and at the discontinuation visit, respectively; however, no clinically significant abnormal results were observed at the follow-up visit.

No patients had abnormal clinically significant echocardiogram results at any time point.

The phosphate level was well managed, and there were no concerns for hyperphosphatemia. On the basis of the safety results of the dose-escalation and the expansion parts, MTD was determined as 16 mg administered twice daily for 5 consecutive days followed by 2 days of interruption.

CONCLUSIONS:

Dose-escalation Part

One patient with urothelial carcinoma (20 mg bid 5-day on/2-day off dosing group) achieved PR, and the response rate based on the best response rate was 2.9%. SD was achieved in 12 patients in the 2.0 mg qd and higher dose groups, and the disease control rate was 37.1%.

ASP5878 showed linear pharmacokinetics and dose proportionality after the once daily administration of ASP5878 over the dose range evaluated (0.5 to 20 mg).

ASP5878 was generally well tolerated at doses up to 20 mg administered twice daily. On the basis of the DLT evaluation results and from a medical view point, the recommended dose for the expansion part was determined to be 16 mg administered twice daily for 5 consecutive days followed by 2 days of interruption.

Expansion Part

Two patients (both with urothelial carcinoma) achieved PR, and the response rate based on the best response rate was 3.9%. SD was achieved in 18 patients, and the disease control rate was 39.2%. The disease control rate was comparable among the 3 types of carcinoma.

No marked differences among ethnicities or types of carcinoma were observed in the pharmacokinetics of ASP5878.

ASP5878 was generally tolerated at 16 mg administered twice daily for 5 consecutive days followed by 2 days of interruption in patients with urothelial carcinoma, hepatocellular carcinoma or squamous cell lung carcinoma. On the basis of the safety results of the dose-escalation and expansion parts, MTD was determined as 16 mg administered twice daily for 5 consecutive days followed by 2 days of interruption.

Date of Report: 10 May 2018

Table 1 Analysis Sets and Study Discontinuation in the Dose-escalation Part

n (%)	0.5 mg qd (n = 3)	1.0 mg qd (n = 4)	2.0 mg qd (n = 3)	2.0 mg bid (n = 4)	4.0 mg bid (n = 4)	6.0 mg bid (n = 3)	10 mg bid (n = 4)	20 mg bid † (N=n = 3)	16 mg bid † (n = 7)	Total (n = 35)
Drug taken	3 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	7 (100.0)	35 (100.0)
Analysis sets										
Full analysis set	3 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	7 (100.0)	35 (100.0)
Safety analysis set	3 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	7 (100.0)	35 (100.0)
Dose-determine analysis set	3 (100.0)	4 (100.0)	3 (100.0)	3 (75.0)	4 (100.0)	3 (100.0)	3 (75.0)	3 (100.0)	7 (100.0)	33 (94.3)
Pharmacokinetics analysis set	3 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	7 (100.0)	35 (100.0)
Pharmacodynamics analysis set	3 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	7 (100.0)	35 (100.0)
Informed consent for pharmacogenomics research	3 (100.0)	2 (50.0)	2 (66.7)	1 (25.0)	2 (50.0)	2 (66.7)	2 (50.0)	1 (33.3)	3 (42.9)	18 (51.4)
Study discontinuation	3 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	3 (100.0)	3 (75.0)	2 (66.7)	5 (71.4)	31 (88.6)
Primary reason for discontinuation										
Adverse event	0	0	0	1 (25.0)	0	1 (33.3)	1 (33.3)	0	0	3 (9.7)
Progressive disease	3 (100.0)	4 (100.0)	3 (100.0)	2 (50.0)	2 (50.0)	1 (33.3)	1 (33.3)	2 (100.0)	5 (100.0)	23 (74.2)
Withdrawal by patient	0	0	0	1 (25.0)	0	1 (33.3)	1 (33.3)	0	0	3 (9.7)
Interruption of the study drug dosing for ≥ 15 consecutive days.	0	0	0	0	2 (50.0)	0	0	0	0	2 (6.5)

† Five consecutive days followed by 2 days of interruption.

Source: Table A.12.1.1.2 and Table A.12.1.1.3.2

Table 2 Analysis Sets and Study Discontinuation in the Expansion Part

n (%)	Urothelial Carcinoma (n = 13)	Hepatocellular Carcinoma (n = 24)	Squamous Cell Lung Carcinoma (n = 14)	Total (n = 51)
Drug taken	13 (100.0)	24 (100.0)	14 (100.0)	51 (100.0)
Analysis sets				
Full analysis set	13 (100.0)	24 (100.0)	14 (100.0)	51 (100.0)
Safety analysis set	13 (100.0)	24 (100.0)	14 (100.0)	51 (100.0)
Pharmacokinetics analysis set	13 (100.0)	24 (100.0)	14 (100.0)	51 (100.0)
Pharmacodynamics analysis set	13 (100.0)	24 (100.0)	14 (100.0)	51 (100.0)
Informed consent for pharmacogenomics research	6 (46.2)	4 (16.7)	2 (14.3)	12 (23.5)
Study discontinuation	13 (100.0)	24 (100.0)	14 (100.0)	51 (100.0)
Primary reason for discontinuation				
Adverse event	3 (23.1)	2 (8.3)	4 (28.6)	9 (17.6)
Progressive disease	10 (76.9)	20 (83.3)	6 (42.9)	36 (70.6)
Withdrawal by patient	0	2 (8.3)	4 (28.6)	6 (11.8)

Source: Table B.12.1.1.2 and Table B.12.1.1.3.2

Table 3 Demographic Characteristics in the Dose-escalation Part (SAF)

Category/Statistic	0.5 mg qd (n = 3)	1.0 mg qd (n = 4)	2.0 mg qd (n = 3)	2.0 mg bid (n = 4)	4.0 mg bid (n = 4)	6.0 mg bid (n = 3)	10 mg bid (n = 4)	20 mg bid † (n = 3)	16 mg bid † (n = 7)	Total (n = 35)
Age (years) (informed consent)										
n	3	4	3	4	4	3	4	3	7	35
Mean (SD)	60.0 (11.3)	56.0 (10.8)	65.7 (4.5)	67.8 (10.1)	54.8 (20.8)	50.0 (26.5)	63.5 (9.7)	68.7 (3.5)	61.4 (9.0)	60.9 (12.7)
Median	66.0	55.0	66.0	67.5	54.5	56.0	65.5	69.0	65.0	65.0
Min, Max	47, 67	44, 70	61, 70	59, 77	34, 76	21, 73	50, 73	65, 72	47, 71	21, 77
Age group (years) (informed consent), n (%)										
< 65	1 (33.3)	3 (75.0)	1 (33.3)	2 (50.0)	2 (50.0)	2 (66.7)	1 (25.0)	0	3 (42.9)	15 (42.9)
≥ 65	2 (66.7)	1 (25.0)	2 (66.7)	2 (50.0)	2 (50.0)	1 (33.3)	3 (75.0)	3 (100.0)	4 (57.1)	20 (57.1)
Sex, n (%)										
Male	3 (100.0)	2 (50.0)	2 (66.7)	3 (75.0)	2 (50.0)	1 (33.3)	2 (50.0)	0	4 (57.1)	19 (54.3)
Female	0	2 (50.0)	1 (33.3)	1 (25.0)	2 (50.0)	2 (66.7)	2 (50.0)	3 (100.0)	3 (42.9)	16 (45.7)
Country, n (%)										
Japan	3 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	7 (100.0)	35 (100.0)
Race, n (%)										
Asian	3 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	7 (100.0)	35 (100.0)
Weight (kg) (baseline)										
n	3	4	3	4	4	3	4	3	7	35
Mean (SD)	59.77 (7.15)	60.73 (15.10)	55.63 (16.57)	62.93 (14.15)	55.83 (11.67)	56.03 (11.25)	55.38 (21.73)	54.23 (5.35)	58.73 (9.67)	57.93 (11.99)
Median	60.00	54.05	64.90	65.60	55.95	50.20	53.00	54.40	55.20	55.20
Min, Max	52.5, 66.8	51.5, 83.3	36.5, 65.5	45.3, 75.2	44.8, 66.6	48.9, 69.0	35.5, 80.0	48.8, 59.5	49.1, 75.3	35.5, 83.3
Height (cm) (screening)										
n	3	4	3	4	4	3	4	3	7	35
Mean (SD)	164.10 (6.35)	165.18 (8.02)	160.77 (9.61)	160.28 (13.44)	164.23 (2.73)	160.93 (6.05)	158.53 (12.43)	160.03 (3.95)	162.49 (10.55)	161.93 (8.42)
Median	165.40	163.30	162.00	163.55	164.70	160.00	160.15	159.00	161.80	163.00
Min, Max	157.2, 169.7	157.6, 176.5	150.6, 169.7	141.3, 172.7	160.5, 167.0	155.4, 167.4	142.8, 171.0	156.7, 164.4	150.9, 180.1	141.3, 180.1
BMI (kg/m^2)										
n	3	4	3	4	4	3	4	3	7	35
Mean (SD)	22.17 (1.96)	22.00 (3.17)	21.20 (4.58)	24.22 (2.46)	20.70 (4.25)	21.49 (2.73)	21.38 (5.44)	21.18 (2.04)	22.21 (2.65)	21.91 (3.16)
Median	21.24	20.62	22.54	23.67	21.02	20.25	20.99	20.13	21.56	21.56
Min, Max	20.8, 24.4	20.0, 26.7	16.1, 25.0	22.0, 27.5	16.1, 24.7	19.6, 24.6	16.2, 27.4	19.9, 23.5	18.8, 27.4	16.1, 27.5

Table continued on next page

Category/Statistic	0.5 mg qd (n = 3)	1.0 mg qd (n = 4)	2.0 mg qd (n = 3)	2.0 mg bid (n = 4)	4.0 mg bid (n = 4)	6.0 mg bid (n = 3)	10 mg bid (n = 4)	20 mg bid † (n = 3)	16 mg bid † (n = 7)	Total (n = 35)
Tobacco history, n (%)										
Never used tobacco	1 (33.3)	2 (50.0)	1 (33.3)	1 (25.0)	2 (50.0)	3 (100.0)	1 (25.0)	1 (33.3)	3 (42.9)	15 (42.9)
Former tobacco user	1 (33.3)	1 (25.0)	2 (66.7)	3 (75.0)	1 (25.0)	0	2 (50.0)	2 (66.7)	4 (57.1)	16 (45.7)
Current tobacco user	1 (33.3)	1 (25.0)	0	0	1 (25.0)	0	1 (25.0)	0	0	4 (11.4)
ECOG performance status, n (%)										
0	2 (66.7)	3 (75.0)	1 (33.3)	2 (50.0)	3 (75.0)	2 (66.7)	1 (25.0)	2 (66.7)	6 (85.7)	22 (62.9)
1	1 (33.3)	1 (25.0)	2 (66.7)	2 (50.0)	1 (25.0)	1 (33.3)	3 (75.0)	1 (33.3)	1 (14.3)	13 (37.1)
2	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
Hepatocellular carcinoma, n (%)										
Yes	0	0	0	1 (25.0)	1 (25.0)	1 (33.3)	0	1 (33.3)	1 (14.3)	5 (14.3)
No	3 (100.0)	4 (100.0)	3 (100.0)	3 (75.0)	3 (75.0)	2 (66.7)	4 (100.0)	2 (66.7)	6 (85.7)	30 (85.7)
Child-Pugh classification (only for patients with hepatocellular carcinoma), n (%)										
A	0	0	0	1 (100.0)	1 (100.0)	1 (100.0)	0	1 (100.0)	1 (100.0)	5 (100.0)
B	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0
Missing	3	4	3	3	3	2	4	2	6	30

BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; Max: maximum; Min: minimum; SAF: safety analysis set.

† Five consecutive days followed by 2 days of interruption.

Source: Table A.12.1.2.2

Table 4 Demographic Characteristics in the Expansion Part (SAF)

Category/Statistic	Urothelial Carcinoma (n = 13)	Hepatocellular Carcinoma (n = 24)	Squamous Cell Lung Carcinoma (n = 14)	Total (n = 51)
Age (years) (informed consent)				
n	13	24	14	51
Mean (SD)	66.5 (7.1)	59.6 (10.1)	60.6 (9.2)	61.6 (9.5)
Median	67.0	60.0	60.5	62.0
Min, Max	52, 74	36, 77	43, 73	36, 77
Age group (years) (informed consent), n (%)				
< 65	4 (30.8)	16 (66.7)	10 (71.4)	30 (58.8)
≥ 65	9 (69.2)	8 (33.3)	4 (28.6)	21 (41.2)
Sex, n (%)				
Male	8 (61.5)	16 (66.7)	12 (85.7)	36 (70.6)
Female	5 (38.5)	8 (33.3)	2 (14.3)	15 (29.4)
Country, n (%)				
Japan	8 (61.5)	6 (25.0)	1 (7.1)	15 (29.4)
Republic of Korea	1 (7.7)	15 (62.5)	9 (64.3)	25 (49.0)
Taiwan, Province of China	0	2 (8.3)	4 (28.6)	6 (11.8)
United States	4 (30.8)	1 (4.2)	0	5 (9.8)
Race, n (%)				
Asian	9 (69.2)	23 (95.8)	14 (100.0)	46 (90.2)
White	4 (30.8)	1 (4.2)	0	5 (9.8)
Weight (kg) (baseline)				
n	12	24	14	50
Mean (SD)	65.97 (17.04)	62.74 (10.72)	59.21 (12.07)	62.53 (12.80)
Median	64.95	63.15	60.70	62.50
Min, Max	41.9, 95.4	44.6, 82.0	36.2, 78.9	36.2, 95.4
Height (cm) (screening)				
n	13	24	14	51
Mean (SD)	166.54 (9.67)	165.00 (7.58)	164.91 (7.39)	165.37 (7.97)
Median	164.70	164.65	164.45	164.70
Min, Max	151.9, 189.4	146.8, 179.0	155.2, 177.3	146.8, 189.4
BMI (kg/m^2)				
n	12	24	14	50
Mean (SD)	23.65 (4.29)	22.93 (2.83)	21.80 (4.38)	22.79 (3.67)
Median	24.16	22.07	20.96	22.02
Min, Max	18.2, 31.2	18.5, 28.2	13.0, 28.4	13.0, 31.2
Tobacco history, n (%)				
Never used tobacco	6 (46.2)	12 (50.0)	1 (7.1)	19 (37.3)
Former tobacco user	6 (46.2)	12 (50.0)	13 (92.9)	31 (60.8)
Current tobacco user	1 (7.7)	0	0	1 (2.0)
ECOG performance status, n (%)				
0	7 (53.8)	18 (75.0)	4 (28.6)	29 (56.9)
1	6 (46.2)	6 (25.0)	10 (71.4)	22 (43.1)
2	0	0	0	0
3	0	0	0	0
4	0	0	0	0
Hepatocellular carcinoma, n (%)				
Yes	0	24 (100.0)	0	24 (47.1)
No	13 (100.0)	0	14 (100.0)	27 (52.9)

Table continued on next page

Category/Statistic	Urothelial Carcinoma (n = 13)	Hepatocellular Carcinoma (n = 24)	Squamous Cell Lung Carcinoma (n = 14)	Total (n = 51)
Child-Pugh classification (only for patients with hepatocellular carcinoma), n (%)				
A	0	24 (100.0)	0	24 (100.0)
B	0	0	0	0
C	0	0	0	0
Missing	13	0	14	27

BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; Max: maximum; Min: minimum; SAF: safety analysis set.

Source: Table B.12.1.2.2

Table 5 Best Overall Response in the Dose-escalation Part (FAS)

Parameter		0.5 mg qd (n = 3)	1.0 mg qd (n = 4)	2.0 mg qd (n = 3)	2.0 mg bid (n = 4)	4.0 mg bid (n = 4)	6.0 mg bid (n = 3)	10 mg bid (n = 4)	20 mg bid † (n = 3)	16 mg bid † (n = 7)	Total (n = 35)
Overall response, n (%)	Complete response	0	0	0	0	0	0	0	0	0	0
	Partial response	0	0	0	0	0	0	0	1 (33.3)	0	1 (2.9)
	Stable disease	0	0	1 (33.3)	3 (75.0)	1 (25.0)	2 (66.7)	1 (25.0)	1 (33.3)	3 (42.9)	12 (34.3)
	Progressive disease	3 (100.0)	4 (100.0)	2 (66.7)	1 (25.0)	3 (75.0)	0	2 (50.0)	1 (33.3)	3 (42.9)	19 (54.3)
	Not evaluated	0	0	0	0	0	1 (33.3)	1 (25.0)	0	1 (14.3)	3 (8.6)
	Total	3	4	3	4	4	3	4	3	7	35
Analysis	Response rate ‡, n (%)	0	0	0	0	0	0	0	1 (33.3)	0	1 (2.9)
	95% CI §	0.0, 70.8	0.0, 60.2	0.0, 70.8	0.0, 60.2	0.0, 60.2	0.0, 70.8	0.0, 60.2	0.8, 90.6	0.0, 41.0	0.1, 14.9
	Disease control rate ¶, n (%)	0	0	1 (33.3)	3 (75.0)	1 (25.0)	2 (66.7)	1 (25.0)	2 (66.7)	3 (42.9)	13 (37.1)
	95% CI §	0.0, 70.8	0.0, 60.2	0.8, 90.6	19.4, 99.4	0.6, 80.6	9.4, 99.2	0.6, 80.6	9.4, 99.2	9.9, 81.6	21.5, 55.1

CI: confidence interval; FAS: full analysis set.

† Five consecutive days followed by 2 days of interruption.

‡ Complete response or partial response.

§ Based on the exact binomial confidence interval (Clopper-Pearson).

¶ Complete response, partial response or stable disease.

Source: Table A.12.3.2

Table 6 Best Overall Response in the Expansion Part (FAS)

Parameter		Urothelial Carcinoma (n = 13)	Hepatocellular Carcinoma (n = 24)	Squamous Cell Lung Carcinoma (n = 14)	Total (n = 51)
Overall Response, n (%)	Complete response	0	0	0	0
	Partial response	2 (15.4)	0	0	2 (3.9)
	Stable disease	3 (23.1)	10 (41.7)	5 (35.7)	18 (35.3)
	Progressive disease	6 (46.2)	12 (50.0)	7 (50.0)	25 (49.0)
	Not evaluated	2 (15.4)	2 (8.3)	2 (14.3)	6 (11.8)
	Total	13	24	14	51
Analysis	Response rate †, n (%)	2 (15.4)	0	0	2 (3.9)
	95% CI ‡	1.9, 45.4	0.0, 14.2	0.0, 23.2	0.5, 13.5
	Disease control rate §, n (%)	5 (38.5)	10 (41.7)	5 (35.7)	20 (39.2)
	95% CI ‡	13.9, 68.4	22.1, 63.4	12.8, 64.9	25.8, 53.9

CI: confidence interval; FAS: full analysis set.

† Complete response or partial response.

‡ Based on the exact binomial confidence interval (Clopper-Pearson).

§ Complete response, partial response or stable disease.

Source: Table B.12.3.2

Table 7 Maximum Shrinkage in Target Lesion in the Expansion Part (FAS)

Parameter	Category/ Statistic	Urothelial Carcinoma (n = 13)	Hepatocellular Carcinoma (n = 24)	Squamous Cell Lung Carcinoma (n = 14)	Total (n = 51)
Maximum change from baseline, n (%) †	≥ -30% ‡	2 (15.4)	0	0	2 (4.0)
	< -30% §	11 (84.6)	23 (100.0)	14 (100.0)	48 (96.0)
	Missing	0	1	0	1

FAS: full analysis set.

† The denominator for percentage calculation is the number of patient who had change in tumor size from baseline.

‡ 30% and more shrunk compared to the baseline.

§ Less than 30% shrunk compared to the baseline.

Source: Table B.12.3.3

Table 8 PFS in the Expansion Part (FAS)

Measure	Urothelial Carcinoma (n = 13)	Hepatocellular Carcinoma (n = 24)	Squamous Cell Lung Carcinoma (n = 14)	Total (n = 51)
Events, n (%)	10 (76.9)	19 (79.2)	7 (50.0)	36 (70.6)
Censored, n (%)	3 (23.1)	5 (20.8)	7 (50.0)	15 (29.4)
PFS, (months)				
Median (95% CI)	2.76 (0.92, 5.45)	2.79 (0.99, 4.53)	2.41 (0.95, 2.79)	2.76 (2.60, 4.47)
PFS rate, % (95% CI)				
At 1 month	83.9 (49.4, 95.7)	68.7 (45.3, 83.8)	75.0 (39.4, 91.5)	74.3 (59.1, 84.6)
At 2 months	83.9 (49.4, 95.7)	68.7 (45.3, 83.8)	62.5 (26.2, 84.8)	71.8 (56.2, 82.6)
At 3 months	46.6 (17.4, 71.7)	42.5 (21.0, 62.6)	Not estimated	38.3 (22.9, 53.6)
At 4 months	46.6 (17.4, 71.7)	36.5 (16.2, 57.2)	Not estimated	34.8 (19.8, 50.4)
At 5 months	23.3 (3.9, 52.0)	18.2 (4.7, 38.8)	Not estimated	17.4 (6.6, 32.4)
At 6 months	11.7 (0.7, 39.6)	18.2 (4.7, 38.8)	Not estimated	13.9 (4.6, 28.4)
At 7 months	11.7 (0.7, 39.6)	6.1 (0.4, 24.0)	Not estimated	7.0 (1.3, 19.7)
At 8 months	11.7 (0.7, 39.6)	6.1 (0.4, 24.0)	Not estimated	7.0 (1.3, 19.7)

CI: confidence interval; FAS: full analysis set; PFS: progression free survival.

Kaplan-Meier estimate with 95% CI of the PFS rate using Greenwood's formula and log-log transformation.

Source: Table B.12.3.4

Table 9 TTP in the Expansion Part (FAS)

Measure	Urothelial Carcinoma (n = 13)	Hepatocellular Carcinoma (n = 24)	Squamous Cell Lung Carcinoma (n = 14)	Total (n = 51)
Events, n (%)	10 (76.9)	19 (79.2)	7 (50.0)	36 (70.6)
Censored, n (%)	3 (23.1)	5 (20.8)	7 (50.0)	15 (29.4)
TTP, (months)				
Median (95% CI)	2.76 (0.92, 5.45)	2.79 (0.99, 4.53)	2.41 (0.95, 2.79)	2.76 (2.60, 4.47)
TTP rate, % (95% CI)				
At 1 month	83.9 (49.4, 95.7)	68.7 (45.3, 83.8)	75.0 (39.4, 91.5)	74.3 (59.1, 84.6)
At 2 months	83.9 (49.4, 95.7)	68.7 (45.3, 83.8)	62.5 (26.2, 84.8)	71.8 (56.2, 82.6)
At 3 months	46.6 (17.4, 71.7)	42.5 (21.0, 62.6)	Not estimated	38.3 (22.9, 53.6)
At 4 months	46.6 (17.4, 71.7)	36.5 (16.2, 57.2)	Not estimated	34.8 (19.8, 50.4)
At 5 months	23.3 (3.9, 52.0)	18.2 (4.7, 38.8)	Not estimated	17.4 (6.6, 32.4)
At 6 months	11.7 (0.7, 39.6)	18.2 (4.7, 38.8)	Not estimated	13.9 (4.6, 28.4)
At 7 months	11.7 (0.7, 39.6)	6.1 (0.4, 24.0)	Not estimated	7.0 (1.3, 19.7)
At 8 months	11.7 (0.7, 39.6)	6.1 (0.4, 24.0)	Not estimated	7.0 (1.3, 19.7)

CI: confidence interval; FAS: full analysis set; TTP: time to progression.

Kaplan-Meier estimate with 95% CI of the TTP rate using Greenwood's formula and log-log transformation.

Source: Table B.12.3.5

Table 10 TTF in the Expansion Part (FAS)

Measure	Urothelial Carcinoma (n = 13)	Hepatocellular Carcinoma (n = 24)	Squamous Cell Lung Carcinoma (n = 14)	Total (n = 51)
Events, n (%)	13 (100.0)	24 (100.0)	14 (100.0)	51 (100.0)
Censored, n (%)	0	0	0	0
TTF, (months)				
Median (95% CI)	2.69 (0.85, 4.53)	2.66 (0.95, 2.89)	1.77 (0.85, 2.60)	2.60 (1.64, 2.69)
TTF rate, % (95% CI)				
At 1 month	76.9 (44.2, 91.9)	66.7 (44.3, 81.7)	71.4 (40.6, 88.2)	70.6 (56.0, 81.1)
At 2 months	69.2 (37.3, 87.2)	62.5 (40.3, 78.4)	35.7 (13.0, 59.4)	56.9 (42.2, 69.1)
At 3 months	38.5 (14.1, 62.8)	29.2 (13.0, 47.6)	7.1 (0.5, 27.5)	25.5 (14.6, 37.9)
At 4 months	30.8 (9.5, 55.4)	20.8 (7.6, 38.5)	Not estimated	17.6 (8.7, 29.2)
At 5 months	15.4 (2.5, 38.8)	12.5 (3.1, 28.7)	Not estimated	9.8 (3.6, 19.7)
At 6 months	7.7 (0.5, 29.2)	12.5 (3.1, 28.7)	Not estimated	7.8 (2.5, 17.2)
At 7 months	7.7 (0.5, 29.2)	4.2 (0.3, 17.6)	Not estimated	3.9 (0.7, 11.9)
At 8 months	7.7 (0.5, 29.2)	4.2 (0.3, 17.6)	Not estimated	3.9 (0.7, 11.9)

CI: confidence interval; FAS: full analysis set; TTF: time to treatment failure.

Kaplan-Meier estimate with 95% CI of the TTF rate using Greenwood's formula and log-log transformation.

Source: Table B.12.3.6

Table 11 Overview of Adverse Events in the Dose-escalation Part (SAF)

n (%)	0.5 mg qd (n = 3)	1.0 mg qd (n = 4)	2.0 mg qd (n = 3)	2.0 mg bid (n = 4)	4.0 mg bid (n = 4)	6.0 mg bid (n = 3)	10 mg bid (n = 4)	20 mg bid † (n = 3)	16 mg bid † (n = 7)	Total (n = 35)
TEAEs	3 (100.0)	3 (75.0)	2 (66.7)	4 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	7 (100.0)	33 (94.3)
Drug-related ‡ TEAEs	1 (33.3)	2 (50.0)	2 (66.7)	4 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	7 (100.0)	30 (85.7)
Deaths	0	0	0	1 (25.0)	0	0	0	0	0	1 (2.9)
Serious TEAEs	0	1 (25.0)	0	2 (50.0)	0	0	0	0	1 (14.3)	4 (11.4)
Drug-related ‡ serious TEAEs	0	0	0	1 (25.0)	0	0	0	0	0	1 (2.9)
NCI CTCAE grade 3 or higher TEAEs	0	2 (50.0)	0	2 (50.0)	2 (50.0)	1 (33.3)	1 (25.0)	0	2 (28.6)	10 (28.6)
Drug-related ‡ NCI CTCAE grade 3 or higher TEAEs	0	0	0	1 (25.0)	2 (50.0)	1 (33.3)	1 (25.0)	0	2 (28.6)	7 (20.0)
TEAEs leading to permanent discontinuation of study drug	0	0	0	1 (25.0)	2 (50.0)	0	1 (25.0)	0	0	4 (11.4)
TEAEs leading to interruption of study drug	0	0	1 (33.3)	3 (75.0)	3 (75.0)	3 (100.0)	3 (75.0)	3 (100.0)	7 (100.0)	23 (65.7)

NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

† Five consecutive days followed by 2 days of interruption.

‡ Possible or probable, as assessed by the investigator.

Source: Table A.12.6.1.1

Table 12 Incidence of Adverse Events Reported in ≥ 2 Patients in Any Group in the Dose-escalation Part (SAF)

MedDRA V16.0 System Organ Class Preferred Term, n (%)	0.5 mg qd (n = 3)	1.0 mg qd (n = 4)	2.0 mg qd (n = 3)	2.0 mg bid (n = 4)	4.0 mg bid (n = 4)	6.0 mg bid (n = 3)	10 mg bid (n = 4)	20 mg bid † (n = 3)	16 mg bid † (n = 7)	Total (n = 35)
Overall	**3 (100.0)**	**3 (75.0)**	**2 (66.7)**	**4 (100.0)**	**4 (100.0)**	**3 (100.0)**	**4 (100.0)**	**3 (100.0)**	**7 (100.0)**	**33 (94.3)**
Eye disorders	**0**	**1 (25.0)**	**0**	**2 (50.0)**	**3 (75.0)**	**0**	**4 (100.0)**	**3 (100.0)**	**6 (85.7)**	**19 (54.3)**
Retinal detachment	0	1 (25.0)	0	2 (50.0)	3 (75.0)	0	2 (50.0)	2 (66.7)	5 (71.4)	15 (42.9)
Vision blurred	0	0	0	0	0	0	1 (25.0)	0	2 (28.6)	3 (8.6)
Gastrointestinal disorders	**1 (33.3)**	**0**	**2 (66.7)**	**2 (50.0)**	**3 (75.0)**	**3 (100.0)**	**3 (75.0)**	**2 (66.7)**	**7 (100.0)**	**23 (65.7)**
Abdominal pain	0	0	0	0	2 (50.0)	0	0	0	0	2 (5.7)
Constipation	0	0	1 (33.3)	0	1 (25.0)	1 (33.3)	2 (50.0)	2 (66.7)	2 (28.6)	9 (25.7)
Diarrhoea	0	0	1 (33.3)	2 (50.0)	1 (25.0)	3 (100.0)	1 (25.0)	2 (66.7)	5 (71.4)	15 (42.9)
Haemorrhoids	0	0	0	0	0	0	0	0	2 (28.6)	2 (5.7)
Stomatitis	0	0	0	1 (25.0)	0	0	2 (50.0)	1 (33.3)	1 (14.3)	5 (14.3)

Table continued on next page

MedDRA V16.0 System Organ Class Preferred Term, n (%)	0.5 mg qd (n = 3)	1.0 mg qd (n = 4)	2.0 mg qd (n = 3)	2.0 mg bid (n = 4)	4.0 mg bid (n = 4)	6.0 mg bid (n = 3)	10 mg bid (n = 4)	20 mg bid † (n = 3)	16 mg bid † (n = 7)	Total (n = 35)
General disorders and administration site conditions	**0**	**2 (50.0)**	**2 (66.7)**	**1 (25.0)**	**1 (25.0)**	**0**	**1 (25.0)**	**1 (33.3)**	**4 (57.1)**	**12 (34.3)**
Fatigue	0	2 (50.0)	2 (66.7)	1 (25.0)	0	0	1 (25.0)	1 (33.3)	3 (42.9)	10 (28.6)
Infections and infestations	**1 (33.3)**	**0**	**0**	**1 (25.0)**	**1 (25.0)**	**0**	**0**	**0**	**3 (42.9)**	**6 (17.1)**
Paronychia	0	0	0	0	0	0	0	0	2 (28.6)	2 (5.7)
Investigations	**2 (66.7)**	**1 (25.0)**	**1 (33.3)**	**4 (100.0)**	**2 (50.0)**	**2 (66.7)**	**1 (25.0)**	**2 (66.7)**	**7 (100.0)**	**22 (62.9)**
Alanine aminotransferase increased	0	1 (25.0)	0	2 (50.0)	1 (25.0)	2 (66.7)	1 (25.0)	2 (66.7)	3 (42.9)	12 (34.3)
Aspartate aminotransferase increased	0	1 (25.0)	0	1 (25.0)	1 (25.0)	1 (33.3)	1 (25.0)	2 (66.7)	3 (42.9)	10 (28.6)
Blood bilirubin increased	0	0	0	2 (50.0)	0	0	0	0	0	2 (5.7)
Blood creatinine increased	0	0	0	0	0	0	0	0	2 (28.6)	2 (5.7)
Lipase increased	0	0	0	0	1 (25.0)	0	0	0	2 (28.6)	3 (8.6)
Liver function test abnormal	2 (66.7)	0	0	0	0	0	0	0	0	2 (5.7)
Weight decreased	0	0	1 (33.3)	0	0	0	0	0	2 (28.6)	3 (8.6)
Metabolism and nutrition disorders	**0**	**2 (50.0)**	**1 (33.3)**	**2 (50.0)**	**4 (100.0)**	**3 (100.0)**	**4 (100.0)**	**3 (100.0)**	**7 (100.0)**	**26 (74.3)**
Decreased appetite	0	1 (25.0)	1 (33.3)	1 (25.0)	0	1 (33.3)	0	1 (33.3)	4 (57.1)	9 (25.7)
Hyperphosphataemia	0	0	0	1 (25.0)	4 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	7 (100.0)	22 (62.9)
Skin and subcutaneous tissue disorders	**0**	**1 (25.0)**	**1 (33.3)**	**1 (25.0)**	**0**	**3 (100.0)**	**3 (75.0)**	**2 (66.7)**	**4 (57.1)**	**15 (42.9)**
Dry skin	0	0	0	0	0	2 (66.7)	1 (25.0)	0	1 (14.3)	4 (11.4)
Palmar-plantar erythrodysaesthesia syndrome	0	0	0	0	0	1 (33.3)	1 (25.0)	2 (66.7)	2 (28.6)	6 (17.1)

SAF: safety analysis set.

† Five consecutive days followed by 2 days of interruption.

Source: Table A.12.6.1.2

Table 13 Incidence of Serious Adverse Events in the Dose-escalation Part (SAF)

MedDRA V16.0 System Organ Class Preferred Term, n (%)	0.5 mg qd (n = 3)	1.0 mg qd (n = 4)	2.0 mg qd (n = 3)	2.0 mg bid (n = 4)	4.0 mg bid (n = 4)	6.0 mg bid (n = 3)	10 mg bid (n = 4)	20 mg bid † (n = 3)	16 mg bid † (n = 7)	Total (n = 35)
Overall	**0**	**1 (25.0)**	**0**	**2 (50.0)**	**0**	**0**	**0**	**0**	**1 (14.3)**	**4 (11.4)**
Hepatobiliary disorders	**0**	**1 (25.0)**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (14.3)**	**2 (5.7)**
Hepatic function abnormal	0	1 (25.0)	0	0	0	0	0	0	0	1 (2.9)
Jaundice cholestatic	0	0	0	0	0	0	0	0	1 (14.3)	1 (2.9)
Infections and infestations	**0**	**0**	**0**	**1 (25.0)**	**0**	**0**	**0**	**0**	**0**	**1 (2.9)**
Urinary tract infection	0	0	0	1 (25.0)	0	0	0	0	0	1 (2.9)
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**0**	**1 (25.0)**	**0**	**0**	**0**	**0**	**0**	**1 (2.9)**
Dyspnoea	0	0	0	1 (25.0)	0	0	0	0	0	1 (2.9)

SAF: safety analysis set.

† Five consecutive days followed by 2 days of interruption.

Source: Table A.12.6.1.7

Table 14 Overview of Adverse Events in the Expansion Part (SAF)

n (%)	Urothelial Carcinoma (n = 13)	Hepatocellular Carcinoma (n = 24)	Squamous Cell Lung Carcinoma (n = 14)	Total (n = 51)
TEAEs	13 (100.0)	24 (100.0)	14 (100.0)	51 (100.0)
Drug-related † TEAEs	13 (100.0)	24 (100.0)	13 (92.9)	50 (98.0)
Deaths	0	0	0	0
Serious TEAEs ‡	0	4 (16.7)	7 (50.0)	11 (21.6)
Drug-related † serious TEAEs ‡	0	2 (8.3)	3 (21.4)	5 (9.8)
NCI CTCAE grade 3 or higher TEAEs	7 (53.8)	8 (33.3)	8 (57.1)	23 (45.1)
Drug-related † NCI CTCAE grade 3 or higher TEAEs	5 (38.5)	5 (20.8)	4 (28.6)	14 (27.5)
TEAEs leading to permanent discontinuation of study drug	2 (15.4)	2 (8.3)	4 (28.6)	8 (15.7)
TEAEs leading to interruption of study drug	10 (76.9)	11 (45.8)	8 (57.1)	29 (56.9)

NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; SAE: serious adverse event; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

† Possible or probable, as assessed by the investigator.

‡ Includes SAEs upgraded by the sponsor based on review of the sponsor's list of always serious terms, if any upgrade was done.

Source: Table B.12.6.1.1

Table 15 Incidence of Adverse Events Reported in ≥ 10% in Any Group in the Expansion Part (SAF)

MedDRA V18.1 System Organ Class Preferred Term, n (%)	Urothelial Carcinoma (n = 13)	Hepatocellular Carcinoma (n = 24)	Squamous Cell Lung Carcinoma (n = 14)	Total (n = 51)
Overall	**13 (100.0)**	**24 (100.0)**	**14 (100.0)**	**51 (100.0)**
Eye disorders	**10 (76.9)**	**14 (58.3)**	**10 (71.4)**	**34 (66.7)**
Chorioretinopathy	0	0	3 (21.4)	3 (5.9)
Corneal opacity	0	4 (16.7)	0	4 (7.8)
Dry eye	4 (30.8)	4 (16.7)	2 (14.3)	10 (19.6)
Keratitis	2 (15.4)	1 (4.2)	0	3 (5.9)
Retinal detachment	6 (46.2)	4 (16.7)	1 (7.1)	11 (21.6)
Retinopathy	0	1 (4.2)	2 (14.3)	3 (5.9)
Vision blurred	3 (23.1)	0	0	3 (5.9)
Gastrointestinal disorders	**13 (100.0)**	**20 (83.3)**	**13 (92.9)**	**46 (90.2)**
Abdominal pain	0	3 (12.5)	0	3 (5.9)
Constipation	1 (7.7)	5 (20.8)	0	6 (11.8)
Diarrhoea	8 (61.5)	16 (66.7)	12 (85.7)	36 (70.6)
Dry mouth	4 (30.8)	1 (4.2)	1 (7.1)	6 (11.8)
Nausea	2 (15.4)	5 (20.8)	1 (7.1)	8 (15.7)
Stomatitis	4 (30.8)	1 (4.2)	1 (7.1)	6 (11.8)
Vomiting	2 (15.4)	2 (8.3)	1 (7.1)	5 (9.8)
General disorders and administration site conditions	**5 (38.5)**	**7 (29.2)**	**4 (28.6)**	**16 (31.4)**
Fatigue	2 (15.4)	4 (16.7)	1 (7.1)	7 (13.7)
Infections and infestations	**7 (53.8)**	**5 (20.8)**	**4 (28.6)**	**16 (31.4)**
Nasopharyngitis	2 (15.4)	2 (8.3)	0	4 (7.8)
Pneumonia	1 (7.7)	0	2 (14.3)	3 (5.9)

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MedDRA V18.1 System Organ Class Preferred Term, n (%)	Urothelial Carcinoma (n = 13)	Hepatocellular Carcinoma (n = 24)	Squamous Cell Lung Carcinoma (n = 14)	Total (n = 51)
Upper respiratory tract infection	2 (15.4)	1 (4.2)	0	3 (5.9)
Investigations	**8 (61.5)**	**5 (20.8)**	**7 (50.0)**	**20 (39.2)**
Alanine aminotransferase increased	1 (7.7)	2 (8.3)	3 (21.4)	6 (11.8)
Aspartate aminotransferase increased	1 (7.7)	4 (16.7)	4 (28.6)	9 (17.6)
Blood creatinine increased	3 (23.1)	0	0	3 (5.9)
Liver function test abnormal	1 (7.7)	0	2 (14.3)	3 (5.9)
Weight decreased	2 (15.4)	0	3 (21.4)	5 (9.8)
Metabolism and nutrition disorders	**12 (92.3)**	**22 (91.7)**	**13 (92.9)**	**47 (92.2)**
Decreased appetite	2 (15.4)	6 (25.0)	6 (42.9)	14 (27.5)
Hypercalcaemia	2 (15.4)	2 (8.3)	3 (21.4)	7 (13.7)
Hyperphosphataemia	11 (84.6)	21 (87.5)	8 (57.1)	40 (78.4)
Hyperuricaemia	2 (15.4)	0	0	2 (3.9)
Hypophosphataemia	2 (15.4)	1 (4.2)	0	3 (5.9)
Musculoskeletal and connective tissue disorders	**5 (38.5)**	**10 (41.7)**	**5 (35.7)**	**20 (39.2)**
Arthralgia	0	3 (12.5)	0	3 (5.9)
Back pain	2 (15.4)	4 (16.7)	0	6 (11.8)
Musculoskeletal pain	0	0	3 (21.4)	3 (5.9)
Pain in extremity	2 (15.4)	2 (8.3)	3 (21.4)	7 (13.7)
Nervous system disorders	**5 (38.5)**	**5 (20.8)**	**2 (14.3)**	**12 (23.5)**
Dysgeusia	3 (23.1)	0	0	3 (5.9)
Peripheral sensory neuropathy	1 (7.7)	3 (12.5)	0	4 (7.8)
Renal and urinary disorders	**3 (23.1)**	**0**	**0**	**3 (5.9)**
Dysuria	2 (15.4)	0	0	2 (3.9)
Respiratory, thoracic and mediastinal disorders	**3 (23.1)**	**2 (8.3)**	**5 (35.7)**	**10 (19.6)**
Dyspnoea	1 (7.7)	0	2 (14.3)	3 (5.9)
Skin and subcutaneous tissue disorders	**11 (84.6)**	**19 (79.2)**	**7 (50.0)**	**37 (72.5)**
Alopecia	4 (30.8)	9 (37.5)	1 (7.1)	14 (27.5)
Dry skin	2 (15.4)	2 (8.3)	0	4 (7.8)
Nail discolouration	3 (23.1)	5 (20.8)	3 (21.4)	11 (21.6)
Nail disorder	1 (7.7)	6 (25.0)	0	7 (13.7)
Onycholysis	3 (23.1)	6 (25.0)	1 (7.1)	10 (19.6)
Onychomadesis	1 (7.7)	2 (8.3)	2 (14.3)	5 (9.8)
Palmar-plantar erythrodysaesthesia syndrome	3 (23.1)	5 (20.8)	1 (7.1)	9 (17.6)
Pruritus	2 (15.4)	1 (4.2)	0	3 (5.9)
Rash	0	2 (8.3)	2 (14.3)	4 (7.8)

SAF: safety analysis set.

Source: Table B.12.6.1.2

Table 16 Incidence of Serious Adverse Events in the Expansion Part (SAF)

MedDRA V18.1 System Organ Class Preferred Term, n (%)	Urothelial Carcinoma (n = 13)	Hepatocellular Carcinoma (n = 24)	Squamous Cell Lung Carcinoma (n = 14)	Total (n = 51)
Overall	**0**	**4 (16.7)**	**7 (50.0)**	**11 (21.6)**
Gastrointestinal disorders	**0**	**1 (4.2)**	**1 (7.1)**	**2 (3.9)**
Ascites	0	1 (4.2)	0	1 (2.0)
Diarrhoea	0	0	1 (7.1)	1 (2.0)
Hepatobiliary disorders	**0**	**1 (4.2)**	**0**	**1 (2.0)**
Hepatic function abnormal	0	1 (4.2)	0	1 (2.0)
Infections and infestations	**0**	**0**	**1 (7.1)**	**1 (2.0)**
Pneumonia	0	0	1 (7.1)	1 (2.0)
Investigations	**0**	**1 (4.2)**	**1 (7.1)**	**2 (3.9)**
Alanine aminotransferase increased	0	1 (4.2)	1 (7.1)	2 (3.9)
Aspartate aminotransferase increased	0	1 (4.2)	1 (7.1)	2 (3.9)
Metabolism and nutrition disorders	**0**	**0**	**1 (7.1)**	**1 (2.0)**
Hypercalcaemia	0	0	1 (7.1)	1 (2.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**1 (4.2)**	**1 (7.1)**	**2 (3.9)**
Metastases to central nervous system	0	0	1 (7.1)	1 (2.0)
Metastases to spine	0	1 (4.2)	0	1 (2.0)
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**3 (21.4)**	**3 (5.9)**
Dyspnoea	0	0	1 (7.1)	1 (2.0)
Pleural effusion	0	0	1 (7.1)	1 (2.0)
Pneumothorax	0	0	1 (7.1)	1 (2.0)
Skin and subcutaneous tissue disorders	**0**	**0**	**1 (7.1)**	**1 (2.0)**
Skin ulcer	0	0	1 (7.1)	1 (2.0)

SAF: safety analysis set.

Source: Table B.12.6.1.7