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**Protocol-specific Sponsor contact information can be found in the Investigator(s) Study File. Laboratory-related information can be found in the Investigator(s) Study File, Section named 'Laboratory Documents'.**

**Investigator Signatory**

I agree to conduct this Clinical Study in accordance with the designed outlined in this protocol and to abide by all provisions of this protocol.

| Name | Signature | Date |
|---|---|---|

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# 1 BACKGROUND

## 1.1 Background of the Study Population

Pancreatic ductal adenocarcinoma (PDA) is a lethal cancer with 5-year survival rate < 5%. [1] Majority of patients presented late when curative resection is impossible. For patients with locally advanced or metastatic disease, gemcitabine-based therapies have been the standard of care for the past two decades. [2] Until recently, two combination regimes, namely FOLFIRINOX (a combination of oxaliplatin, folinic acid, and 5-fluorouracil, 5-FU) and albumin-bound paclitaxel in combination with gemcitabine, have demonstrated their survival advantages over gemcitabine mono-therapy and accepted as front-line treatments. [3-4] Despite these advances, progression is inevitable; there are limited options and no universally accepted standard among patients who progressed after front-line treatment. There is a huge unmet need in this population.

The use of subsequent lines of treatment has been increased over the past decade. Various second-line therapies have been studied and associated with improved survival in patients who have experienced progression on gemcitabine-based regimes. Primarily, fluoropyrimidine (FP) based regime is commonly studied in this setting. In NAPOLI-1, a large randomized phase 3 trial; the combination of 5-FU and nanoliposomal irinotecan (nal-IRI) demonstrated a significant survival advantage compared with 5-FU monotherapy (median overall survival of 6.1 months vs. 4.2 months, hazard ratio 0.67). Based on these results, the US Food and Drug Administration had approved this regime in patients with refractory pancreatic cancer. [5] Similarly, the CONKO-003 trial showed improved survival in patients who received combined oxaliplatin, leucovorin (LV), and 5-FU (OFF) compared with those who received 5-FU/LV. [6] However, results from the PANCREOX study suggested a potential detriment from the addition of oxaliplatin to 5FU/LV. [7] Table 1 summarized the selected randomized studies in evaluating second-line combination chemotherapy in gemcitabine-refractory PDA. The median progression-free survival was ranged from 1.6-3.8 months and overall survival was ranged from 3.3-9.9 months. [5-11]

| Study | N | Treatment | Median PFS (months) | Median OS |
|---|---|---|---|---|
| Loka et al. (8) | 127 | S-1 + Irinotecan vs. S-1 | 3.5 vs. 1.9 months | 6.8 vs. 5.8 months |
| Ueno et al. (9) | 140 | SL vs. S-1 | 3.8 vs. 2.7 months | 6.3 vs. 6.1 months |
| Gill et al. (7) | 108 | mFOLFOX6 vs. 5FU/LV | 3.1 vs. 2.9 months | 6.1 vs. 9.9 months |
| Wang-Gillam et al. (5) | 417 | Nal-IRI + 5FU/LV vs. Nal-IRI vs. 5FU/LV | 3.1 vs. 2.7 vs. 1.6 months | 6.1 vs. 4.9 vs. 4.2 months |
| Ohkawa et al. (10) | 268 | S-1 + Oxaliplatin vs. S-1 | 3.0 vs. 2.8 months | 7.4 vs. 6.9 months |
| Oettle et al. (6) | 160 | OFF vs. FF | 2.9 vs. 2.0 months | 5.9 vs. 3.3 months |
| Ge et al. (11) | 92 | SL vs. S-1 | 3.0 vs. 1.9 months | 6.3 vs. 5.5 months |

Abbreviations: SL, TS-1 and leucovorin; 5FU, 5-fluorouracil; LV, leucovorin; Nal-IRI, nano-liposomal irinotecan

**Table 1. Selected randomized studies of combination chemotherapy in gemcitabine-refractory pancreatic cancer patients**

However, as patient's performance status often rapidly declines when tumor is locally or systemically progressing, it can be difficult to administer second-line combination chemotherapy in some patients. Several small single-arm phase II studies have demonstrated modest activity and favorable toxicity profile of single-agent chemotherapy (Table 2); therefore mono-agent chemotherapy may constitute a feasible treatment option in this setting.

| Study | N | Treatment | Median PFS (months) | Median OS |
|---|---|---|---|---|
| Hosein et al. (12) | 19 | Nab-paclitaxel | 1.7 months | 7.3 months |
| Ko et al. (13) | 40 | Nal-IRI | 2.4 months | 5.2 months |
| Sudo et al. (14) | 21 | S-1 | 4.1 months | 6.3 months |
| Yi et al. (15) | 33 | Irinotecan | 2.0 months | 6.6 months |
| Morizane et al. (16) | 40 | S-1 | 2.0 months | 4.5 months |
| Boeck et al. (17) | 39 | Capecitabine | NA | 7.6 months |
| Boeck et al. (18) | 52 | Pemetrexed | NA | 5 months |
| Androulakis et al. (19) | 18 | Oxaliplatin | NA | 3.5 months |

Abbreviations: Nal-IRI, nano-liposomal irinotecan

**Table 2. Single-armed phase II clinical trials evaluating second-line single-agent chemotherapy in advanced pancreatic cancer**

## 1.2 Introduction of TAS-102

TAS-102, a novel functional antitumor nucleoside, is a combined form of 1M trifluridine (FTD; α,α,α-trifluorothymidine) and 0.5 M tipiracil hydrochloride (TPI; 5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]pyrimidine-2,4-(1H,3H)-dione monohydrochloride). FTD, an antineoplastic antimetabolite, is a thymidylate synthase (TS) inhibitor. [20-25] Based on pre-clinical data, FTD also appears to be incorporated into deoxyribonucleic acid (DNA), thereby providing a second mechanism of action for antitumor activity. [26-27] Preliminary results suggest that when FTD is incubated with cancer cells at a high concentration for short time periods, it is passively incorporated into the DNA fraction of the cell, and that such behavior of FTD is different from the primary cytotoxic mechanism of 5-fluorouracil (5-FU) and 2'-deoxy-5 fluorouridine (FdUrd), i.e., inhibition of TS. [28]

Supportive of this mechanistic differentiation between FTD and fluoropyrimidines are preclinical data showing a markedly greater degree (approximately 700-fold) of incorporation of FTD into DNA compared with that of FdUrd (Study M01-2006-0025). [29] A potential further differentiating feature is that FTD has been shown to induce cell cycle arrest at the G2/M phase, whereas 5-FU appears to induce a G1- and S-phase arrest (Study M01-2006-0016). From an important clinical perspective, TS or dihydropyrimidine dehydrogenase (DPD) overexpression or induction are reported to be involved in resistance to 5-FU and also to 5-FU-based formulations. Due to FTD's mechanisms of cytotoxicity beyond TS inhibition and the lack of DPD effect on FTD metabolism, these mechanisms of resistance for fluoropyrimidines may not affect FTD activity. [30]

FTD, when orally administered, is rapidly degraded to an inactive form, 5-trifluoromethyluracil or 5-trifluoromethyl-2,4 (1H,3H)-pyrimidinedione (FTY) by thymidine phosphorylase (TPase), which is present in gastrointestinal tract, liver, and tumor tissue. Co-administration of TPI, which inhibits TPase, with FTD prevents the rapid degradation of FTD in the body, allowing a twice daily oral administration as well as a potential augmentation of cytotoxicity by FTD. Neither FTD nor TPI inhibited cytochrome P450 (CYP) enzymes in studies using human liver microsomes. The optimum ratio of TPI to FTD was investigated by measuring FTD exposure after oral administration with TPI in rat and monkey. Plasma FTD level reached a maximum at the molar ratio of 1:0.5 for FTD and TPI. Efficacy of FTD also reached a maximum value after oral administration at the molar ratio using mice xenografted with human gastrointestinal cancer cell lines. Based on nonclinical pharmacokinetic (PK)

and efficacy studies, a combination molar ratio of 1:0.5 for FTD and TPI was determined to be optimal. [31]

A mechanistic differentiation of FTD versus fluoropyrimidines is supported by the results of preclinical studies in which the antitumor activity of TAS-102 against 5-FU resistant gastric and colon cancer cell sublines in nude mice xenografts models was compared with that of intravenous bolus 5-FU, continuous intravenous infusion (CIV) of 5-FU, and oral UFT (tegafur + uracil) therapies at toxicologically similar doses. The results indicated that TAS-102 was active and significantly more effective than 5-FU IV bolus, 5-FU CIV, and oral UFT against human cancer cell sublines that had acquired resistance to 5-FU. [28, 32]

## 1.3 Clinical Studies of TAS-102

TAS-102 has been approved for the treatment of (a) refractory metastatic colorectal cancer (mCRC) previously treated with at least 2 prior lines of chemotherapy that included a fluoropyrimidine (FP), oxaliplatin, or irinotecan, and (b) metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least 2 prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.

**Phase 3 Studies in Metastatic Colorectal Cancer (RESOURSE)**
In a double-blinded randomized phase 3 study assigned 800 patients in a 2:1 ratio, in patients refractory colorectal cancer, the median overall survival improved from 5.3 months with placebo to 7.1 months with TAS-102. The median time to worsening of performance status was 5.7 months with TAS-102 versus 4.0 months with placebo. Adverse events of grade 3 or higher occurred more frequently in the TAS-102 group (69% vs. 52%); 38% patients had ≥ grade 3 neutropenia, 4% had neutropenic fever. [33]

**Phase 3 Studies in Gastric or Gastroesophageal Junction Cancer (TAGS)**
In a double-blinded randomized phase 3 study assigned 557 patients in a 2:1 ratio, in patients with FP-refractory gastric cancer, the median overall survival was 5.7 months in the TAS-102 group and 3.6 months in the placebo group (hazard ratio: 0.69). The commonest grade 3 or higher toxicities were neutropenia (34%) and anemia (19%).

Taken together, both pre-clinical and clinical data demonstrated that TAS-102 possesses anti-tumor activity in patients who are refractory to 5-FU resistant cancer. [34]

## 1.4 Rationale of studying TAS-102 in pancreatic cancer

Many chemotherapeutic regimes in the treatment of pancreatic cancer patients are 5-FU based; multiple studies have demonstrated the anti-tumor activity of FP and its derivatives in pancreatic cancer patients. [5-11, 14, 16, 17] Pre-clinical data suggested TAS-102 is effective in pancreatic cell lines (PAN-12 and BxPC-3), while clinical studies showing advantages for TAS-102 over 5-FU and its derivative in 5-FU resistant tumor cells. [32,35] As such, we postulated that as a more potent nucleoside analogue, TAS-102 is an active treatment in patients with refractory pancreatic cancer.

Herein, we conduct a prospective single-arm phase II study to evaluate the clinical outcome of TAS-102 in refractory pancreatic cancer patients.

# 2 STUDY OBJECTIVES

## 2.1 Primary Objective

1. To evaluate the 16-week progression free survival (PFS) rate to TAS-102 in previously treated advanced PC patients per response evaluation criteria of solid tumor (RECIST) version 1.1

## 2.2 Secondary Objectives

1. To assess the median progression-free survival (PFS) per RECIST version 1.1
2. To assess the median overall survival (OS) per RECIST version 1.1
3. To assess the objective response rate (ORR) per RECIST version 1.1
4. To assess the disease control rate (DCR) per RECIST version 1.1
5. To measure the time to deterioration of ECOG performance status
6. To measure the toxicities and tolerability of TAS-102 in previously treated advanced PC patients (CTCAE version 5)
7. To measure the time to deterioration of quality of life (EORTC QLQ-C30)

## 2.3 Study Design

This is a prospective phase II, single arm, single institutional study conducted in Queen Mary Hospital (Hong Kong) assessing the efficacy and safety of TAS-102 in previously treated advanced or metastatic pancreatic cancer patients.

## 2.4 Study Participants

A total of 28 patients will be accrued to assess the potential benefit of TAS-102.

# 3 ELIGIBILITY CRITERIA

## 3.1 Inclusion Criteria

1. Histological or cytological confirmed advanced or metastatic pancreatic cancer
2. Measurable disease according to the RECIST criteria (version 1.1) for the evaluation of measurable disease
3. Documented progression after one or more lines of systemic chemotherapy
   a. For the treatment of advanced or metastatic disease
   b. Within 6 months after completion of neo-adjuvant therapy or adjuvant therapy
4. Age ≥ 18 years
5. Eastern Cooperative Oncology Group (ECOG) performance 0-1
6. Written informed consent obtained for clinical trial participation and providing archival tumor tissue, if available
7. Females of childbearing potential or non-sterilized male who are sexually active must use a highly effective method of contraception

8. Females of childbearing potential must have negative serum or urine pregnancy test
9. Have life expectancy ≥ 3 months
10. Adequate organ function as defined as:
    a. Hemoglobin value of ≥9.0 g/dL.
    b. Absolute neutrophil count of ≥1,500/mm3 (IU: ≥1.5 × $10^9$/L).
    c. Platelet count ≥100,000/mm3 (IU: ≥100 × $10^9$/L).
    d. Total serum bilirubin of ≤1.5 mg/dL (except for Grade 1 hyperbilirubinemia due solely to a medical diagnosis of Gilbert's syndrome).
    e. Aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) ≤3.0 × upper limit of normal (ULN); if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤5 × ULN.
    f. Serum creatinine of ≤1.5 mg/dL.

## 3.2 Exclusion Criteria

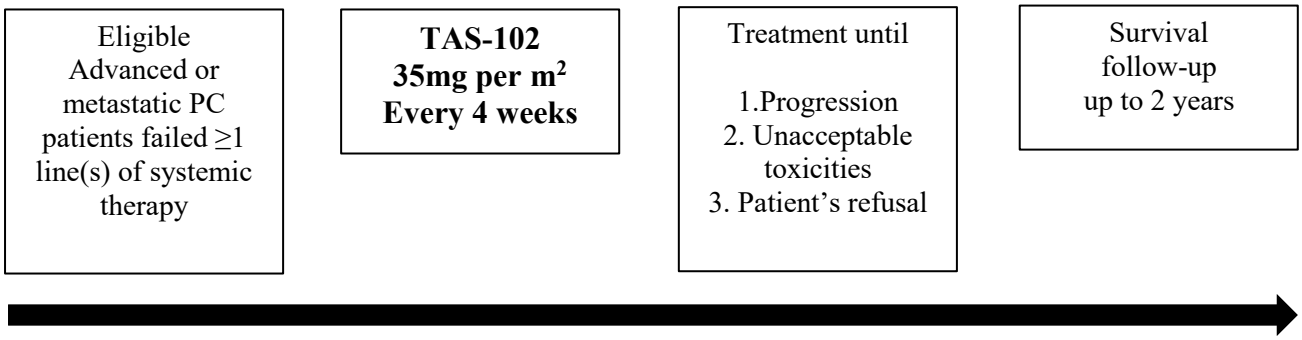
1. Has disease that is suitable for local therapy administrated with curative intent

2. Has a serious illness or medical condition(s) including, but not limited to the following:
    a. Other concurrently active malignancies excluding malignancies that are disease free for more than 5 years or carcinoma-in-situ deemed cured by adequate treatment.
    b. Known brain metastasis or leptomeningeal metastasis.
    c. Active infection (i.e. body temperature ≥38°C due to infection).
    d. Ascites, pleural effusion or pericardial fluid requiring drainage in last 4 weeks.
    e. Intestinal obstruction, pulmonary fibrosis, renal failure, liver failure, or cerebrovascular disorder.
    f. Uncontrolled diabetes.
    g. Myocardial infarction within the last 12 months, severe/unstable angina, symptomatic congestive heart failure New York Heart Association (NYHA) class III or IV
    h. Gastrointestinal hemorrhage.
    i. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or hepatitis B or C.
    j. Patients with autoimmune disorders or history of organ transplantation who require immunosuppressive therapy.
    k. Psychiatric disease that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results.

3. Has had treatment with any of the following within the specified time frame prior to study drug administration:
    a. Major surgery within prior 4 weeks.
    b. Any systemic therapy within prior 2 weeks.
    c. Any radiation within prior 2 weeks.
    d. Any investigational agent received within prior 4 weeks.

4. Untreated active hepatitis B or hepatitis C infections.
5. Has received TAS-102.
6. Has unresolved toxicity of greater than or equal to CTCAE Grade 2 attributed to any prior therapies (excluding anemia, alopecia, skin pigmentation and platinum-induced neurotoxicity).
7. Is a pregnant or lactating female.
8. Is inappropriate for entry into this study in the judgment of the Investigator.

# 4 STUDY SCHEMA




Safety monitoring will begin at the time the Informed Consent Form (ICF) is signed and continue for 30 days after the last dose of study medication or until the initiation of another cancer therapy, whichever comes first.

At the end of treatment, all patients will be followed for survival at scheduled 8-week time intervals until 2 years.

# 5 SCREENING PROCEDURE

## 5.1 Clinical Evaluation / Management

- Document performance status, concomitant medications, and past medical history
- Documentation of prior therapies of PC
- Blood tests including complete blood count, liver function test, renal function test, eGFR, coagulation profile, hepatitis B status within 28 days prior to study assessment
- Urinalysis
- Electrocardiogram (ECG)
- CA 19-9 level within 28 days prior to study entry
- Urine or serum pregnancy test must be performed at baseline while on TAS-102
- 10cc plasma for exploratory biomarker research

## 5.2 Radiological Evaluation

All advanced or metastatic PC patients are required to have a contrast computed-tomography (CT) of thorax, abdomen and pelvis to assess the tumor status within 28 days prior to study entry:

- Site(s) of metastatic disease(s)
- Number of metastatic disease(s)
- Measurable or non-measureable lesion(s)

## 5.3 Informed Consent

The Investigator(s) or person(s) designated by the Investigator(s), and under the Investigator(s)'s responsibility, should fully inform the patient of all pertinent aspects of the clinical study including the written information giving approval/favorable opinion by the Ethics Committee (IRB/EC). All participants shall be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patients' participation in the clinical study, the written Informed Consent Form (Form B) and any other local applicable documents in accordance with local laws and regulations, should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

The Informed Consent Form used by the Investigator(s) for obtaining the patient's informed consent must be reviewed and approved by the appropriate Ethics Committee (IRB/EC) for approval/favorable opinion.

During a patient's participation in the trial, any updates to the consent form and/or any updates to the written information will be provided to the patient.

Further information about the informed consent is available in Section 10.2 and Section 10.3.

## 5.4 Registration Guidelines

- All the patients must be registered with the Investigator(s) prior to initiation of treatment
- Forms A (registration) and B (consent) will be submitted
- The registration desk will confirm all eligibility criteria and obtain essential information (including patient number)

# 6 STUDY INTERVENTION

## 6.1 General Information of Study Intervention TAS-102

TAS-102 contains FTD and TPI as active ingredients with a molar ratio of 1:0.5. TAS-102 drug products are immediate-released film coated tablets, available in 2 strengths (15 mg and 20 mg tablet, expressed as FTD content). The inactive ingredients of the TAS-102 15 mg and 20 mg tablets are lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, polyethylene glycol, titanium dioxide, red ferric oxide (only 20 mg tablet), and magnesium stearate.

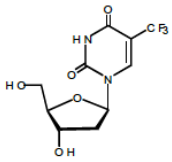
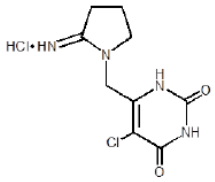
| | FTD | TPI |
|---|---|---|
| Generic name: | Trifluridine | Tipiracil hydrochloride |
| Chemical name: | α,α,α-trifluorothymidine | 5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]pyrimidine-2,4-(1*H*,3*H*)-dione monohydrochloride |
| Structural formula: |  |  |
| Molecular formula: | $C_{10}H_{11}F_3N_2O_5$ | $C_9H_{11}ClN_4O_2 \cdot HCl$ |
| Molecular weight: | 296.20 | 279.12 |

**Table 3. Physical and Chemical Characteristics of Active Ingredients of TAS-102**

## 6.2 Formulation

TAS-102 tablet (15 mg) contains 15 mg FTD and 7.065 mg TPI (corresponding to 6.14 mg tipiracil) as active ingredients. The appearance is white, round, biconvex film coated tablets.

TAS-102 tablet (20 mg) contains 20 mg FTD and 9.42 mg TPI (corresponding to 8.19 mg tipiracil) as active ingredients. The appearance is pale red, round, biconvex film-coated tablets.

Clinical packaging: Blister package with desiccant in aluminum pouch.

Storage condition: All study medication must be stored at room temperature between 59°F and 86°F (15°C–30°C). All study medication must be kept in a locked area with access restricted to specific study personnel.

Stability: TAS-102 tablets (15 mg and 20 mg) are stable at 25°C 60% relative humidity for 36 months and 40°C 75% relative humidity for 6 months in blister packaging with desiccant in aluminum pouch.

## 6.3 Study Medication Regimen, Administration, and Dose Reduction / Modification Procedures

### 6.3.1 Study Medication Regime

Each treatment cycle will be 28 days in duration. One treatment cycle consists of the following:

**Days 1 through 5:** TAS-102 (35 mg/m$^2$/dose) orally 2 times daily with the first dose administered in the morning of Day 1 of each cycle and the last dose administered in the evening of Day 5.
**Days 6 through 7:** Recovery
**Days 8 through 12:** TAS-102 (35 mg/m$^2$/dose) orally 2 times daily with the first dose administered in the morning of Day 8 of each cycle and the last dose administered in the evening of Day 12.
**Days 13 through 28:** Recovery

### 6.3.2 Administration

The study drug tablet calculation is presented in the following table, which shows the number of tablets that are needed per calculated BSA.

| TAS-102 Dose (2x daily) | BSA[a] ($m^2$) | Dosage in mg (2x daily) | Total daily dose (mg) | Tablets per dose | |
|---|---|---|---|---|---|
| | | | | 15 mg | 20 mg |
| 35 $mg/m^2$ | < 1.07 | 35 | 70 | 1 | 1 |
| | 1.07 - 1.22 | 40 | 80 | 0 | 2 |
| | 1.23 - 1.37 | 45 | 90 | 3 | 0 |
| | 1.38 - 1.52 | 50 | 100 | 2 | 1 |
| | 1.53 - 1.68 | 55 | 110 | 1 | 2 |
| | 1.69 - 1.83 | 60 | 120 | 0 | 3 |
| | 1.84 - 1.98 | 65 | 130 | 3 | 1 |
| | 1.99 - 2.14 | 70 | 140 | 2 | 2 |
| | 2.15 - 2.29 | 75 | 150 | 1 | 3 |
| | ≥2.30 | 80 | 160 | 0 | 4 |

[a] Calculate BSA to 2 decimal places.

**Table 4. Number of tablets per TAS-102 dose**

### 6.3.3 Dose reduction or modification

Study medication dose reductions to be applied in case of toxicity and the number of tablets for each calculated BSA are described in following table. Patients are permitted dose reduction(s) to a minimum dose of 20 $mg/m^2$ (40 $mg/m^2$/day) in 5 $mg/m^2$ steps.

If dose modification fails to result in achieving minimal criteria to resume treatment, the Investigator should discontinue study medication.

Should the toxicities that require dose reduction recur after dose reduction to 20 $mg/m^2$, study medication should be discontinued.

| TAS-102 or Placebo Dose (2x daily) | BSA[a] ($m^2$) | Dosage in mg (2x daily) | Total daily dose (mg) | Tablets per dose | |
|---|---|---|---|---|---|
| | | | | 15 mg | 20 mg |
| **Level 1 Dose Reduction: From 35 $mg/m^2$ to 30 $mg/m^2$** | | | | | |
| **30 $mg/m^2$** | < 1.09 | 30 | 60 | 2 | 0 |
| | 1.09 - 1.24 | 35 | 70 | 1 | 1 |
| | 1.25 - 1.39 | 40 | 80 | 0 | 2 |
| | 1.40 - 1.54 | 45 | 90 | 3 | 0 |
| | 1.55 - 1.69 | 50 | 100 | 2 | 1 |
| | 1.70 - 1.94 | 55 | 110 | 1 | 2 |
| | 1.95 - 2.09 | 60 | 120 | 0 | 3 |
| | 2.10 - 2.28 | 65 | 130 | 3 | 1 |
| | ≥ 2.29 | 70 | 140 | 2 | 2 |
| **Level 2 Dose Reduction: From 30 $mg/m^2$ to 25 $mg/m^2$** | | | | | |
| **25 $mg/m^2$** | < 1.10 | 25[b] | 50[b] | 2 (PM)[b] | 1 (AM)[b] |
| | 1.10 - 1.29 | 30 | 60 | 2 | 0 |
| | 1.30 - 1.49 | 35 | 70 | 1 | 1 |
| | 1.50 - 1.69 | 40 | 80 | 0 | 2 |
| | 1.70 - 1.89 | 45 | 90 | 3 | 0 |
| | 1.90 - 2.09 | 50 | 100 | 2 | 1 |
| | 2.10 - 2.29 | 55 | 110 | 1 | 2 |
| | ≥ 2.30 | 60 | 120 | 0 | 3 |
| **Level 3 Dose Reduction: From 25 $mg/m^2$ to 20 $mg/m^2$** | | | | | |
| **20 $mg/m^2$** | < 1.14 | 20 | 40 | 0 | 1 |
| | 1.14 – 1.34 | 25[b] | 50[b] | 2 (PM)[b] | 1 (AM)[b] |
| | 1.35 – 1.59 | 30 | 60 | 2 | 0 |
| | 1.60 – 1.94 | 35 | 70 | 1 | 1 |
| | 1.95 – 2.09 | 40 | 80 | 0 | 2 |
| | 2.10 – 2.34 | 45 | 90 | 3 | 0 |
| | ≥ 2.35 | 50 | 100 | 2 | 1 |

[a] Calculate BSA to 2 decimal places.
[b] At a total daily dose of 50 mg, patients should take 1 x 20-mg tablet in the morning and 2 x 15-mg tablets in the evening.

**Table 5. TAS-102 Dose modification**

### 6.3.4 Dosing Modifications in Response to Non-hematologic Toxicities

Rules for study medication dosing modifications for treatment-related non-hematologic toxicities are provided in the following table:

| Grade[a] | Dose Hold/Resumption within a 28-day Treatment Cycle | Dose Adjustment for Next Cycle |
|---|---|---|
| **Grade 1 or 2** | | |
| Any occurrence | Maintain treatment at the same dose level | None |
| **Grade 3[b] or Higher** | | |
| 1st, 2nd, or 3rd occurrence | Suspend treatment until Grade 0 or 1 | Reduce by 1 dose level from the previous level |
| 4th occurrence | Discontinue treatment | Discontinue treatment |

[a] At the discretion of the Investigator, patients may continue on study medication at the same dose without reduction or interruption for AEs (irrespective of grade) considered unlikely to become serious or life-threatening (including, but not limited to, fatigue, alopecia, changes in libido, and dry skin).
[b] Except for Grade 3 nausea and/or vomiting controlled by aggressive antiemetic therapy or diarrhea responsive to antidiarrheal medication.

**Table 6. TAS-102 dose modification schedule for non-hematologic drug-related toxicities**

### 6.3.5 Dose Hold and Resumption in Response to Hematologic Toxicities

Myelosuppression are described in the following table. Note that for all patients with decreases in neutrophils and/or platelets, the next cycle of study treatment should not be started until the resumption criteria are met even if the decreases do not meet the hold criteria.

Uncomplicated neutropenia or thrombocytopenia ≤ Grade 3 does not require a reduction in dose of study medication. Patients who experience uncomplicated Grade 4 neutropenia or thrombocytopenia that results in a >1 week delay of the start of the next cycle should start the next cycle at one reduced dose level. If the delay is ≤1 week, the patient should start the next cycle at the same dose level.

| Parameter | Hold Criteria | | Resumption Criteria[a] |
|---|---|---|---|
| | Conventional Units | SI Units | |
| Neutrophils | <500/mm$^3$ | <0.5 × 10$^9$/L | ≥1500/mm$^3$ (IU: ≥1.5 × 10$^9$/L) |
| Platelets | <50,000/mm$^3$ | <50 × 10$^9$/L | ≥75,000/mm$^3$ (IU: ≥75 × 10$^9$/L) |

[a] These resumption criteria apply to the start of the next cycle for all patients regardless of whether or not the hold criteria were met.
Both conventional and SI (International System) units are presented in CTCAE v. 4.03.

**Table 7. TAS-102 Dose hold and resumption criteria for hematologic toxicities related to myelosuppression**

If the patient recovers from the toxicities to the resumption criteria defined above during the 2-week treatment period (treatment Days 1 through 5, 8 through 12), and no dose reduction is required, study drug therapy may be resumed during that cycle. If a dose reduction is required, study drug therapy should be resumed at the start of the next cycle at the appropriate dose level. If the study drug dose is reduced, it must not be increased for subsequent cycles.

If the toxicities that are defined above recover during the recovery period (Days 13 through 28), start the next cycle on schedule at the appropriate dose level. If the toxicities that are defined above do not recover during the treatment or rest period, the start of the next cycle can be delayed for a maximum of 28 days from the scheduled start date of the next cycle. If resumption criteria are met by this maximum 28-day delay, start the next cycle at the appropriate dose level according to protocol.

Patients who require more than a 28-day delay in the scheduled start date of the next cycle will have study medication discontinued.

## 6.4 Adverse Events (AE) and AE Management

### 6.4.1 Adverse Events (AEs)

The followings have been considered to be frequent or important AE according to previous studies:

**Blood and lymphatic system disorders:** anemia, neutropenia, thrombocytopenia, and febrile neutropenia
**Gastrointestinal disorders:** diarrhea, nausea, vomiting, abdominal ileus, and stomatitis
**General disorders:** Asthenia, fatigue, decreased appetite, mucosal inflammation, and pyrexia
**Infectious disorders:** Pneumonia, and urinary tract infection
**Others:** Dysgeusia, alopecia, and pulmonary embolism

| | TAS-102 (N=335) n (%) | | Placebo (N=168) n (%) | |
|---|---|---|---|---|
| **MedDRA SOC Preferred Term** | **All Grades** | **Grade ≥3** | **All Grades** | **Grade ≥3** |
| **Blood and lymphatic system disorders** | | | | |
| Anaemia | 149 (44.5) | 63 (18.8) | 32 (19.0) | 13 (7.7) |
| Neutropenia | 129 (38.5) | 78 (23.3) | 6 (3.6) | 0 |
| Leukopenia | 57 (17.0) | 23 (6.9) | 3 (1.8) | 0 |
| Thrombocytopenia | 33 (9.9) | 7 (2.1) | 2 (1.2) | 0 |
| **Gastrointestinal disorders** | | | | |
| Diarrhoea | 76 (22.7) | 9 (2.7) | 24 (14.3) | 3 (1.8) |
| Nausea | 124 (37.0) | 10 (3.0) | 53 (31.5) | 5 (3.0) |
| **General disorders and administration site conditions** | | | | |
| Fatigue | 89 (26.6) | 23 (6.9) | 35 (20.8) | 10 (6.0) |
| **Investigations** | | | | |
| Neutrophil count decreased | 51 (15.2) | 38 (11.3) | 1 (0.6) | 0 |
| White blood cell count decreased | 23 (6.9) | 9 (2.7) | 0 | 0 |

MedDRA = Medical Dictionary for Regulatory Activities; N = total number; n = subset of total; SOC = system organ class

| | Studies J003-10040030 and TPU-TAS-102-301 Combined | | | |
|---|---|---|---|---|
| | TAS-102 (N=646) n (%) | | Placebo (N=322) n (%) | |
| MedDRA SOC Preferred Term | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| **Blood and lymphatic system disorders** | | | | |
| Anemia | 216 (33.4) | 88 (13.6) | 22 (6.8) | 7 (2.2) |
| Neutropenia | 156 (24.1) | 107 (16.6) | 0 | 0 |
| Thrombocytopenia | 37 (5.7) | 11 (1.7) | 1 (0.3) | 1 (0.3) |
| **Gastrointestinal disorders** | | | | |
| Diarrhea | 213 (33.0) | 23 (3.6) | 45 (14.0) | 1 (0.3) |
| Nausea | 331 (51.2) | 15 (2.3) | 79 (24.5) | 3 (0.9) |
| Vomiting | 186 (28.8) | 15 (2.3) | 52 (16.1) | 1 (0.3) |
| **General disorders and administration site conditions** | | | | |
| Asthenia | 97 (15.0) | 18 (2.8) | 30 (9.3) | 8 (2.5) |
| Fatigue | 246 (38.1) | 25 (3.9) | 82 (25.5) | 16 (5.0) |
| **Investigations** | | | | |
| Hemoglobin decreased | 85 (13.2) | 21 (3.3) | 9 (2.8) | 3 (0.9) |
| Hematocrit decreased | 37 (5.7) | 0 | 4 (1.2) | 0 |
| Lymphocyte count decreased | 63 (9.8) | 21 (3.3) | 12 (3.7) | 5 (1.6) |
| Neutrophil count decreased | 229 (35.4) | 142 (22.0) | 2 (0.6) | 0 |
| Platelet count decreased | 125 (19.3) | 18 (2.8) | 7 (2.2) | 0 |
| Red blood cell count decreased | 39 (6.0) | 0 | 2 (0.6) | 0 |
| White blood cell count decreased | 232 (35.9) | 87 (13.5) | 3 (0.9) | 0 |
| **Metabolism and nutrition disorders** | | | | |
| Decreased appetite | 278 (43.0) | 24 (3.7) | 97 (30.1) | 15 (4.7) |
| **Nervous system disorders** | | | | |
| Dysgeusia | 42 (6.5) | 0 | 9 (2.8) | 0 |
| **Skin and subcutaneous tissue disorders** | | | | |
| Alopecia | 38 (5.9) | 0 | 3 (0.9) | 0 |

MedDRA = Medical Dictionary for Regulatory Activities; N = total number; n = subset of total; SOC = system organ class

**Table 8. A summary of most frequently reported adverse events (≥5% in TAS-102 group that occurred twice or ≥5% than placebo group) in previous randomized trials**

### 6.4.2 Serious Adverse Events (SAEs)

Serious adverse drug reactions (SADR) were reported for 177 of 2066 patients (8.6%) with colorectal and gastric cancer who received TAS-102 35 mg/m$^2$/dose monotherapy in unblended studies (see Table 9). The most commonly reported SADRs were febrile neutropenia (1.8%) and anemia (1.5%).

| MedDRA SOC<br>Preferred Term | Baseline[b] (N=2066)<br>n | <br>% |
|---|---|---|
| **Total number of subjects with serious adverse drug reactions** | **177** | **8.6** |
| **Blood and lymphatic system disorders** | **89** | **4.3** |
| Anaemia | 32 | 1.5 |
| Bone marrow failure | 1 | 0.0 |
| Disseminated intravascular coagulation | 1 | 0.0 |
| Febrile neutropenia | 37 | 1.8 |
| Granulocytopenia | 2 | 0.1 |
| Leukopenia | 3 | 0.1 |
| Neutropenia | 19 | 0.9 |
| Pancytopenia | 12 | 0.6 |
| Thrombocytopenia | 3 | 0.1 |
| **Cardiac disorders** | **4** | **0.2** |
| Acute myocardial infarction | 2 | 0.1 |
| Cardiorespiratory arrest | 1 | 0.0 |
| Myocardial infarction | 1 | 0.0 |
| **Eye disorders** | **1** | **0.1** |
| Diplopia | 1 | 0.1 |
| **Gastrointestinal disorders** | **45** | **2.2** |
| Abdominal pain | 4 | 0.2 |
| Anal fistula | 1 | 0.1 |
| Ascites | 1 | 0.1 |
| Colitis | 2 | 0.1 |
| Constipation | 2 | 0.1 |
| Diarrhoea | 4 | 0.2 |
| Enterocolitis haemorrhagic | 1 | 0.0 |
| Gastric haemorrhage | 1 | 0.0 |
| Gastrointestinal haemorrhage | 1 | 0.0 |
| Ileus | 3 | 0.1 |
| Nausea | 11 | 0.5 |
| Pancreatitis acute | 1 | 0.0 |
| Small intestinal obstruction | 3 | 0.1 |
| Subileus | 1 | 0.0 |
| Vomiting | 16 | 0.8 |
| **General disorders and administration site conditions** | 12 | 0.6 |
| Fatigue | 5 | 0.2 |
| General physical health deterioration | 2 | 0.1 |
| Malaise | 1 | 0.0 |
| Pyrexia | 4 | 0.2 |
| **Hepatobiliary disorders** | 3 | 0.2 |
| Cholangitis | 1 | 0.0 |
| Liver disorder | 1 | 0.0 |
| Liver injury | 1 | 0.0 |
| **Infections and infestations** | 34 | 1.6 |
| Atypical pneumonia | 1 | 0.0 |
| Bacteraemia | 3 | 0.1 |
| Biliary tract infection | 1 | 0.0 |
| Cellulitis | 1 | 0.0 |
| Cellulitis staphylococcal | 1 | 0.0 |
| *Clostridium difficile* colitis | 1 | 0.0 |
| Device-related infection | 1 | 0.0 |
| Endophthalmitis | 1 | 0.0 |
| Enteritis infectious | 1 | 0.0 |
| Infection | 2 | 0.1 |

| | | |
|---|---|---|
| Lower respiratory tract infection | 1 | 0.0 |
| Neutropenic sepsis | 4 | 0.2 |
| Pelvic infection | 2 | 0.1 |
| Pneumonia | 8 | 0.4 |
| Pneumonia *Klebsiella* | 1 | 0.0 |
| Sepsis | 2 | 0.1 |
| Septic shock | 3 | 0.1 |
| Urinary tract infection | 3 | 0.1 |
| Urosepsis | 1 | 0.0 |
| **Investigations** | **22** | **1.1** |
| Blood bilirubin increased | 3 | 0.1 |
| Blood lactate dehydrogenase increased | 1 | 0.0 |
| Haemoglobin decreased | 2 | 0.1 |
| Neutrophil count decreased | 8 | 0.4 |
| Platelet count decreased | 4 | 0.2 |
| Weight decreased | 2 | 0.1 |
| White blood cell count decreased | 8 | 0.4 |
| **Metabolism and nutrition disorders** | **12** | **0.6** |
| Alkalosis hypochloraemic | 1 | 0.0 |
| Decreased appetite | 7 | 0.3 |
| Dehydration | 6 | 0.3 |
| Hypokalaemia | 1 | 0.0 |
| Hyponatraemia | 1 | 0.0 |
| **Nervous system disorders** | **3** | **0.1** |
| Cerebral infarction | 1 | 0.0 |
| Cerebrovascular accident | 1 | 0.0 |
| Transient ischaemic attack | 1 | 0.0 |
| **Renal and urinary disorders** | **2** | **0.1** |
| Acute kidney injury | 2 | 0.1 |
| **Respiratory, thoracic and mediastinal disorders** | **1** | **0.0** |
| Pulmonary embolism | 1 | 0.0 |
| **Vascular disorders** | **1** | **0.0** |
| Hypotension | 1 | 0.0 |

MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class

[a] Only includes serious adverse drug reactions from completed monotherapy protocols as of 24 Mar 2019: 10040010, 10040030, 10040040, TAS-102-101, TAS-102-102, TAS-102-103, TAS-102-104, TAS-102-108, TAS-102-301, TAS-102-302, 10040090, 10040100, TAS-102-106, and TAS-102-401.

Note: Includes TAS-102 studies investigating 35 mg/m$^2$/dose monotherapy in patients with colorectal and gastric cancer. Study medication-related adverse drug reactions are those adverse events considered by either the investigator or the sponsor as not denied, possibly related, probably related, and definitely related to TAS-102. Patients are counted at most once for each preferred term and each SOC. Inclusion in this table is subject to medical judgment.

**Table 9. TAS-102 Baseline Frequency Serious Adverse Drug Reactions by System Organ Class and Preferred Term in Patients Receiving TAS-102 Monotherapy (Based on SAE Database) - Data Cutoff 24 Mar 2019**

### 6.4.3 Management of AEs

All TAS-102-related toxicities should be treated with supportive care measures and symptoms managed as clinically indicated or local institutional practice. The criteria in this protocol regarding modifications of TAS-102 (dose interruption, reduction, resumption, and permanent discontinuation) should be followed closely.

#### 6.4.3.1 Hematologic Toxicities

Patients should be informed of the possibility of severe infection related to myelosuppression and advised to promptly report any signs of infection such as fever to the treating physician.

Patients with low WBC counts and low neutrophil counts should be monitored carefully for infection and treated as medically indicated (e.g., with antibiotics, granulocyte-colony stimulating factor). Patients with thrombocytopenia and/or anemia should also be closely monitored for complications and provided treatments as clinically indicated. TAS-102 dose should be modified as recommended in the protocol.

#### 6.4.3.2 Gastrointestinal Toxicities

Patients with nausea, vomiting, diarrhea and other gastrointestinal toxicities should be carefully monitored. Appropriate measures such as antiemetic, antidiarrheal, and/or fluid replacement therapy should be administered as clinically indicated. In addition, dehydration and any associated electrolyte disturbances should be prevented or corrected at onset. TAS-102 dose should be modified as recommended in the protocol.

# 7 FOLLOW UP AND OUTCOME EVALUATION

## 7.1 Follow-Up Schedule

The study assessments are described by procedure in the following sections. The study schedule must be followed with a window of +/-3 days which is allowable for study procedures, as long as the proper order is maintained, and a window of +/-7 days is allowable for CT scans and follow-up visits. During the baseline period, these windows are not applicable. Patients should be followed-up for up to 2 years.

## 7.2 Study Procedures

### 7.2.1 Informed Consent

Obtain signed and dated ICF from the patient prior to the implementation of study procedures required by the protocol. A copy of the signed and dated ICF should be given to the patient.

### 7.2.2 Medical History

Obtain a complete medical history at Baseline within 28 days prior to study medication administration.

### 7.2.3 Diagnostic Confirmation

Obtain histological or cytological confirmation of pancreatic cancer via pathology report at Baseline.

### 7.2.4 Physical Examination

Perform a complete physical examination at the time points listed below:

- Baseline within 7 days prior to study drug administration on Day 1 of Cycle 1.
- Beginning with Cycle 2, obtain within 24 hours prior to study drug administration.
- End of Treatment Visit.
- 30-day Safety Follow-up Visit.

### 7.2.5 Baseline Signs and Symptoms

Baseline signs and symptoms present within 28 days prior to study drug administration on Day 1 of

Cycle 1 should be recorded in the patient's source documents.

### 7.2.6 Electrocardiogram

A 12-lead resting electrocardiogram (ECG) within 28 days prior to study drug administration on Day 1 of Cycle 1 should be obtained and recorded in the patient's source documents.

### 7.2.7 Height, Vital Signs, and Weight

Obtain the patient's height at Baseline within 7 days prior to study drug administration on Day 1 of Cycle 1. Collect the patient's vital signs (blood pressure, heart rate, body temperature, and respiration rate) and body weight at the time points listed below. Obtain all the vital signs in a position that is consistent for all time points for each patient.

- Baseline within 7 days prior to study drug administration on Day 1 of Cycle 1
- Beginning with Cycle 2, obtain within 24 hours prior to study drug administration
- End of Treatment Visit
- 30-day Safety Follow-up Visit

### 7.2.8 Performance Status (ECOG)

Obtain an ECOG performance status score at the following time points:

- Baseline within 28 days prior to study medication administration on Day 1 of Cycle 1
- On Day 1 of Cycle 1
- Beginning with Cycle 2, obtain within 24 hours prior to study drug administration
- End of Treatment Visit
- 30-day Safety Follow-up Visit

### 7.2.9 Hematology, Biochemistry, and CA 19-9

Collect blood for hematological, biochemistry and CA 19-9 assessments at the following time points and when clinically indicated:

- Baseline within 7 days prior to study drug administration on Day 1 of Cycle 1
- On Day 15 of Cycle 1
- Beginning with Cycle 2, obtain within 24 hours prior to Day 1 study drug administration and on Day 15
- End of Treatment Visit
- 30-day Safety Follow-up Visit

### 7.2.10 Urinalysis

Collect urine samples for qualitative (dipstick) analysis, to include tests for protein, glucose, urobilinogen, RBC, and WBC, at the time points listed below:

- Baseline within 7 days prior to study drug administration on Day 1 of Cycle 1
- Or clinically indicated

### 7.2.11 Pregnancy Test

For females of childbearing potential, collect urine samples for qualitative (dipstick) analysis, to include tests for protein, glucose, urobilinogen, RBC, and WBC, at the time points listed below:

- Baseline within 7 days prior to study drug administration on Day 1 of Cycle 1

### 7.2.12 Tumor Measurement

Tumor assessments/imaging studies of the chest, abdomen, and pelvis (as clinically indicated) must be obtained at each time point listed below for all patients.

- Baseline within 28 days prior to Day 1 Cycle 1

- Every 8 weeks from the start of treatment
- Within 2 weeks of the End of Treatment Visit if the patient has discontinued treatment for reasons other than radiologic disease progression. If an End of Treatment visit is not performed, tumor measurements must be obtained at the time the patient is discontinued from treatment.
- For patients that discontinued treatment for reasons other than radiologic progression, every 8 weeks during the follow-up period until the patient develops radiologic progression or the start of new anticancer treatment.

On-site tumor assessments will be performed by the Investigator/local radiologist according to RECIST criteria (version 1.1). Results of these assessments including response for target and non-target lesions and appearance of new lesions will be the basis for the continuation or discontinuation of study medication.

If the Investigator determines that a patient develops clinical progression manifested by symptomatic deterioration but not supported by radiologic evidence of progression, the patient should stop treatment. Symptoms of clinical progression must be documented in the patient's source documents. Every effort should be made to document objective progression even after discontinuation of treatment.

If a patient is withdrawn due to radiologic disease progression, additional CT scans are not required at the End of Treatment Visit. The same method of assessment and the same technique must be used to characterize each identified and reported lesion at Baseline, throughout the study, and during the follow-up period.

All patients' files and radiological assessments must be available for source verification. Results of any unscheduled evaluations should be recorded.

### 7.2.13 Concomitant Medications and Therapies

Collect all therapies and medications, prescription and over-the-counter, from the time of signed ICF through the 30-day Safety Follow-Up Visit, including any medication used to treat AEs or serious AEs (SAEs) during the 30-day follow-up period. In addition, at the 30-day Safety Follow-Up Visit, collect the time of initiation of new anticancer therapy. Use of concomitant medication should be documented. During the survival follow-up period, collect only anticancer therapies.

### 7.2.14 Adverse Event Assessment

Monitor patients for any untoward medical events (AEs or SAEs) from the time of signed ICF through 30 days after last dose of study medication. SAEs should be reported to Taiho Drug Safety or designee. If any medical occurrences outside the 30-day follow-up period are reported to or observed by the Investigator that he/she believes are related to the administration of the study medication, it is the Investigator's responsibility to record those events on the case report form. If any of those events are serious, then the investigator has to report this occurrence to Taiho Drug Safety or designee. See Section 8 for definitions and detailed reporting of AEs and SAEs.

### 7.2.15 Quality of Life Assessment

Quality of life will be assessed by validated EORTC QLQ-C30 questionnaire. As a self-administered survey, it incorporates 30 items comprising five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), as well as a global health and QoL scale. It will be completed by the patient at the time points listed below:

- Within 7 days prior to start of study treatment
- Prior to dose administration on Day 1 of Cycles ≥2

- At the 30-day safety follow-up (if not performed within the prior 4 weeks)

#### 7.2.16 End of Treatment

The end of treatment is defined as the date when the Investigator determines that the patient will stop all study medication. If the decision to discontinue study medication is made within 2 weeks after the patient's last treatment visit, an End of Treatment Visit is not required unless deemed clinically necessary by the Investigator. If the decision to discontinue study medication (due to disease progression or other reasons) is made more than 2 weeks after the last treatment visit, an End of Treatment Visit is required. If this visit occurs within 2 weeks of the 30-day Safety Follow-up Visit, the 2 visits can be combined.

#### 7.2.17 30-Day Safety Follow-up

A Safety Follow-up visit will be conducted 30 days after the last dose of study medication. If the patient starts new anticancer therapy within 30 days after the last dose of study medication, the 30-day Safety Follow-up Visit should be performed prior to the start of new anticancer therapy within the 30-day window. If this visit occurs within 2 weeks of the End of Treatment Visit, the 2 visits can be combined but should not take place less than 30 days after the last dose of study medication.

#### 7.2.18 Survival Follow-up after 30-Day Safety Visit

All patients will be followed for survival status (alive/dead) at scheduled 8-week (+/- 7 days) time intervals until death. Patients will be followed until 12 months after the first dose of study medication for the last patient randomized, even if consent for study participation has been withdrawn. The Investigator should make every effort to contact the patient or primary caregiver to determine his/her survival status. Times and dates of contact must be documented in the patient's records.

#### 7.2.19 By Visit Assessment

Detailed patient visit timetable is specified in Appendix 1**.**

## 7.3 Outcome Measures

### 7.3.1 Primary Outcome:

- **16-week progression-free survival (PFS) rate:** The percentage of study population alive and without progression (according to RECIST 1.1) at 16 weeks from the date of informed consent

### 7.3.2 Secondary Outcomes:

- **Progression-free Survival (PFS):** PFS is measured from the date of informed consent to radiographically documented progression according to RECIST 1.1 or death from any cause (whichever occurs first). Participants alive and without disease progression or lost to follow-up will be censored at the date of their last radiographic assessment

- **Time to progression (TTP):** TTP is measured from the date of informed consent to radiographically documented progression according to RECIST 1.1. Participants death and without disease progression, alive without disease progression, or lost to follow-up will be censored at the date of their last radiographic assessment

- **Overall survival (OS):** OS is measured from date of informed consent to the date of death from any cause. Participants alive or lost to follow-up will be censored at the date of their last radiographic assessment

- **Objective response rate (ORR):** The percentage of patients with radiologically complete or partial response as determined by the Investigator according to RECIST version 1.1.

- **Disease control rate (DCR):** The percentage of patients with radiologically complete response, partial response, or stable disease as determined by the Investigators according to RECIST version 1.1

- **Duration of response (DoR):** DoR is the time from documentation of tumor response to radiographically documented disease progression

- **Time to deterioration of ECOG performance status:** Time from date of informed consent until the first date on which ECOG performance status score of 2 or higher was recorded [36-37]

- **Time to deterioration of quality of life:** Decrease from baseline of 10 points or more on the EORTC QLQ–C30 maintained for two consecutive assessments or a decrease of 10 points or more in one assessment followed by death from any cause within 3 weeks.

- **Safety outcome measures:** Incidence, nature, and severity of adverse events graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE 5)

## 7.4 Criteria for Removal from Protocol Treatment

- RECIST-defined disease progression
- Clinical progression
- Patient experiences an irreversible, treatment-related, Grade 4, clinically relevant, non-hematologic event.
- Inter-current disease that would affect assessments of clinical status to a significant degree, require discontinuation of drug, or both.
- Unacceptable adverse events, or change in underlying condition such that the patient can no longer tolerate therapy, including:
  (a) A maximum dose delay >28 days from the scheduled start date of the next cycle.
  (b) Need for more than 3 dose reductions of study medication
- Physician's decision including need for other anticancer therapy not specified in the protocol or surgery or radiotherapy to the only site(s) of disease being evaluated in this protocol
- Patient's request irrespective of the reason

# 8 SAFETY REPORTING

## 8.1 Adverse Events (AEs)

- According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product,

regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)

- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline

- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug

- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

## 8.2 Serious Adverse Events (SAEs)

- A serious adverse event is any adverse event that meets any of the following criteria:
    - Is fatal (i.e., the adverse event actually causes or leads to death)
    - Is life threatening (i.e., the adverse event, in the view of the Investigator(s), places the patient at immediate risk of death)
    - This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
    - Requires or prolongs inpatient hospitalization
    - Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
    - Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
    - Is a significant medical event in the Investigator(s)'s judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

- The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]; the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

- Severity and seriousness need to be independently assessed for each adverse event recorded in the clinical database.

## 8.3 Pregnancy Reports

- Female patients of childbearing potential will be instructed to immediately inform the Investigator(s) if they become pregnant during the study.

## 8.4 Assessment of Causality of Adverse Events

Investigator(s) should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "Yes" or "No" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction,
- Discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

## 8.5 Methods of Recording Adverse Events

- All AEs must be documented in the appropriate section of the CRF. An SAE report form (initial or follow up) must be completed in case of any of the seriousness criteria is met.

- The following aspects must be recorded for each event in the CRF:
    - A description of the AE in medical terms, not as reported by the subject;
    - The date of onset (start date)
    - The time of onset (start time)
    - The date of recovery (stop date)
    - The time of recovery (stop time)
    - The severity of the sign and/or symptom or clinically significant abnormal laboratory value according to NCI-CTCAE v.5. If no toxicity grade is described for a given sign, symptom or abnormal laboratory value, the Investigator(s) will grade the severity as mid (grade 1), moderate (grade 2), severe (grade 3), or life-threatening or disabling (grade 4).
    - Death (grade 5) as defined by NCI-CTCAE v.5 is mainly regarded as an outcome and will be documented accordingly (see below).

- The causal relationship to TAS-102 as assessed by the Investigator(s); the decisive factor in the documentation is the temporal relation between the AE and the study drug. The following judgments of the causality to study drug or study procedures are to be used:
    - Not Related = not suspected to be reasonably related to the investigational product. AE could not medically (pharmacologically/ clinically) be attributed to the investigational product under study in this protocol
    - Related = suspected to be reasonably related to the investigational product. AE could medically (pharmacologically/ clinically) be attributed to the investigational product under study in this protocol
    - Action taken on TAS-102 (none, medication discontinued, dose reduction, medication delayed, reduction of infusion rate).
    - Other action (none, concomitant medication given, new or prolonged hospitalization,

procedural surgery).

- The outcome according to the following definitions:
  - Recovered without sequelae (AE disappeared)
  - Recovered with sequelae (AE has resulted in permanent disability/incapacity)
  - Not yet recovered
  - Not recovered at death
  - Change in toxicity grade/severity or seriousness (e.g., an AE with no change of toxicity grade but newly classified as an SAE due to hospitalization
  - Fatal (AE resulted in death)

- Concomitant medication given: Yes or No (Note: If this question is answered "Yes" the corresponding serious criteria must be ticked)
  - Subject died
  - Life-threatening
  - New or prolonged hospitalization
  - Persistent/significant disability
  - Congenital abnormality
  - Important medical event
  - Seriousness: Yes or No

- If in any one patient the same AE occurs on several occasions, then the AE in question must be documented and assessed anew each time.

## 8.6 Procedure of Reporting Serious Adverse Events

- The Sponsor-Investigator(s) primary responsibilities for safety reporting are to identify and follow-up on Serious Adverse Events (SAEs) experienced by participants in the study and to forward the information to the local regulatory authorities and Taiho, as required by local regulations (for regulatory reporting) and as required by the Investigator Sponsored Study (ISS) agreement (for reporting to Taiho).

- The following reportable events must be submitted to Taiho within 2 business days or 3 calendar days (whichever comes first) using the applicable safety report form provided. The Principal Investigator(s) will assume responsibility for submitting the reportable event(s) to Taiho as well as ensuring that any local reporting requirements are completed in parallel.

- Serious Adverse Events (see section 6.4.2)
  - Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)
  - Occupational exposure (even if not associated with an adverse event)

## 8.7 Monitoring of subjects with Adverse Events

- Any AE that occurs in the course of a clinical study must be monitored and followed up until the last study visit. It is the responsibility of the Investigator(s) that any necessary additional therapeutic measures and follow-up procedures are performed.

# 9 STATISTICS

## 9.1 Statistical Analysis

The 16-week PFS rate will be estimated by Kaplan-Meier method and expressed based on exact binomial distribution. Other survival outcomes including TTP, PFS, OS and their corresponding 95% confidence interval will be estimated using Kaplan-Meier method.

All of the reported P values will be 2-tailed, and $P<0.05$ will be considered statistically significant. No multiplicity will be considered. The analyses will be performed using statistical software packages SPSS and R.

## 9.2 Procedures for Handling Missing, Unused, and Spurious Data

All available data will be included in the data listings and tabulations. Where appropriate, imputations of values for missing data for primary and secondary efficacy analyses will be performed as specified in the Statistical Analysis Plan. All data recorded on the CRF will be included in the data listings that will accompany the clinical study report.

If, after the study has begun, but prior to the conduct of any analysis, changes made to primary and / or key secondary endpoints, or the statistical methods related to those hypotheses, then the protocol will be amended. Changes to exploratory analyses made after the protocol finalized will be documented and referenced in the final report. Post hoc exploratory analyses will also be identified in the final report.

## 9.3 Sample Size Calculation

H0: The null hypothesis is that the 16-week PFS rate of 10% is similar to historical results.

H1: The alternative hypothesis of treatment efficacy: experimental treatment with TAS-102 would result in 16-week PFS rate of 30%.

To detect a 20% of differences from 10% to 30% in the 16-week PFS rate, with Type I error of 0.05 and 80% power, and assuming 10% drop out rate, the target sample size is 28 patients.

The null hypothesis will be rejected if 6 or more out of first 25 evaluable patients are progression-free and alive at 16 weeks, the treatment will be considered worthy of further investigation. Otherwise, if 5 or fewer patients were progression-free and alive at 16 weeks in the 25 evaluable patients, this regimen would have been considered ineffective in this patient population.

Patients may drop out before their 16-week PFS rate can be assessed. Such patients will be excluded for the primary endpoint assessment and will be replaced by other patients that 16-week PFS rate can be assessed. We assume 50% of screened population will be eligible for the study, thus we plan to screen for 56 patients.

# 10 ETHICAL, REGULATORY & STUDY OVERSIGHT CONSIDERATIONS

## 10.1 Responsibilities of the Investigator(s)

The Investigator(s) undertake(s) to perform the clinical study in accordance with this clinical study protocol, ICH guideline for Good Clinical Practice (GCP) (ICH E6 R2 Step 4) approved on November 9, 2016) and applicable regulatory requirements in Hong Kong. These documents state that the informed consent of the subjects is an essential precondition for participation in the clinical study.

## 10.2 Subject Information

An unconditional prerequisite for a patient participating in the study is his/her written informed consent. Adequate information must therefore be given to the subject by the Investigator(s) before informed consent is obtained. A person designated by the Investigator(s) may give the information, if permitted by local regulations. A subject information sheet in the local language and prepared in accordance with Good Clinical Practice will be provided by the Investigator(s) for the purpose of obtaining informed consent. In addition to this written information, the Investigator(s) or his/her/their designate will inform the subject verbally. In doing so, the wording used will be chosen so that the information can be fully and readily understood by laypersons.

The patient information sheet will be revised whenever important new information becomes available that may be relevant to the consent of patients.

## 10.3 Informed Consent

The consent of the patient to participate in the clinical study has to be given in writing before any study-related activities are carried out. It must be signed and personally dated by the patient and by the Investigator(s)/person designated by the Investigator(s) to conduct the informed consent discussion.

Provision of consent will be confirmed in the case report form (CRF) by the Investigator(s). The signed and dated declaration of informed consent will remain at the Investigator(s)'s site and must be safely archived by the Investigator(s) so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and consent should be provided to the patient prior to participation.

If the patient or legally acceptable representative is unable to read, a reliable, impartial and independent witness should be present during the entire informed consent discussion. The choice of the witness must not breach the subject’s right to confidentiality. A reliable independent witness is defined as one not affiliated with the institution or engaged in the investigation. A family member or acquaintance is an appropriate independent witness. After the subject or legally acceptable representative verbally consents and has signed, if capable, the witness should sign and personally date the consent form attesting that the information is accurate and that the subject or legally acceptable representative has fully understood the content of the informed consent agreement and is giving true informed consent.

## 10.4 Compensation to Subjects

The patients will not receive payment for taking part in the study. Patients who are entitled to discounted or free health care, e.g. civil servants, will receive their entitled free treatment as normal. The study is covered by an insurance policy managed by the Clinical Trial Centre of The University of Hong Kong, in which to cover claim by, or compensation for, patients treated in study.

## 10.5 Ethics Committee or Institutional Review Board

Prior to commencement of the study, the study protocol will be submitted together with its associated documents (patient information, consent form, IB) to the IRB/EC for their favourable opinion. The favourable opinion/approval of the IRB/EC will be filed in the study file. The study will only commence following provision of a written favourable opinion.

Any amendments to the protocol will be submitted to the IRB/EC and they will be informed about SAEs in accordance with national and/or local requirements.

## 10.6 Role of Funding Source

The study drug and partial funding will be provided by Taiho Pharmaceutical Co., Ltd, Japan. The Funder otherwise has no role in study design, data collection, data analysis, data interpretation, or in the writing of the study report. The Funder will review the manuscript before submission for publication.

## 10.7 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results in accordance with standard editorial and ethical practice.

The Sponsor agrees to submit all manuscripts or abstracts to the Funder for review before submission for publication. This allows the Funder to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

# 11 STUDY MANAGEMENT

## 11.1 Data Quality Assurance

The main objective is to obtain those data required by the study protocol in a complete, accurate, legible and timely fashion. The data in the CRF should be consistent with the relevant source documents.

The CRFs must be filled in completely and legibly (with either black or blue ballpoint pen, acceptable for use on official documents). Any amendments and corrections necessary must be undertaken and countersigned by the Investigator(s), stating the date of the amendment/correction. Errors must remain

legible and may not be deleted with correction aids (e.g., Tipp-Ex®). The Investigator(s) must state his/her reasons for the correction of important data. In the case of missing data/remarks, the entry spaces provided in the case report form should be cancelled out so as to avoid unnecessary follow-up inquiries.

CRF entries will be done by the study team and checked against source documents, except for the pre-identified source data directly recorded in the CRF. The Informed Consent Form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB/EC), and the regulatory authorities to have direct access to source data which support the data on the CRF. Such personnel, bound by professional secrecy, must keep confidential all personal identity or personal medical information (according to confidentiality rules).

## 11.2 Direct Access to Source Data/Documents

For the purpose of ensuring compliance with the clinical study protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator(s) shall permit auditing by the Sponsor, the Funder, and inspection by applicable regulatory authority.

The Investigator(s) agree(s) to allow the auditors/inspectors to have direct access to the study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose personal identity or personal medical information.

The Investigator(s) will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator(s) is/are notified of a future inspection by the authority, he will inform the Sponsor and the Funder.

The confidentiality of the data verified, and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authority will be immediately communicated by the Investigator(s) to the Sponsor and the Funder as per timeframe stipulated in the ISS agreement.

The Investigator(s) shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

## 11.3 Study File and Archiving

The Investigator(s) shall maintain a Study File for the study purpose. This file contains all relevant documents necessary for the conduct of the study. This file must be safely archived after termination of the study in accordance with the local relevant regulations.

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## Appendix 1. STUDY SCHEDULE

| | **Baseline Period** | | **On Treatment Period (+/-3 days for procedures; +/-7 days for CT scans & FU)** | | | | | | | | **End of Treatment Period (q8wk)** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cycle 1 | | | | Subsequent Cycles | | | | End of Treatment | 30-day Safety FU | Survival FU |
| | Baseline Day | | Day of Cycle | | | | Day of Cycle | | | | | | |
| | -28 to -1 | -7 to -1 | 1 | 12 | 15 | End of recovery | 1 | 12 | 15 | End of recovery | | | |
| Procedure | x | | | | | | | | | | | | |
| Sign ICF | x | | | | | | | | | | | | |
| Enrolment | x | | | | | | | | | | | | |
| Medical History | x | | | | | | | | | | | | |
| Physical Examination | | x | | | | | x | | | | x | x | |
| Baseline signs and symptoms | x | | | | | | | | | | | | |
| ECG | x | | | | | | | | | | | | |
| Vital signs, height, body weight | | x | | | | | x | | | | x | x | |
| ECOG performance status | x | | x | | | | x | | | | x | x | |
| Hematology | | x | | | x | | x | | x | | x | x | |
| Serum chemistry | | x | | | x | | x | | x | | x | x | |
| CA 19-9 | | x | | | x | | x | | x | | x | x | |
| Urinalysis | | x | | | | | | | | | | | |
| Pregnancy Test | | x | | | | | | | | | | | |
| Tumor measurement | x | | | | | | | | | x | x | | x |
| Concomitant Medications | x | → | → | → | → | → | → | → | → | → | → | → | → |
| AE / SAE assessment | | | x | → | → | → | → | → | → | → | → | → | → |
| Survival status | | | x | → | → | → | → | → | → | → | → | → | → |
| Quality of life assessment | | x | | | | | x | | | | | | |
| TAS-102 treatment | | | x (D1-5) | x (D8-12) | | | x (D1-5) | x (D8-12) | | | | | |

Footnotes:

(1) Sign ICF: Written informed consent should be obtained prior to the performance of any study procedure

(2) Vital Signs: Heart rate, blood pressure, body temperature, respiratory rate; collect at the start of every cycle; collect within 24 hours prior to Day 1 study drug administration.

(3) Blood tests within 28 days prior to study assessment include complete blood count, liver function test, renal function test, eGFR, coagulation profile & hepatitis B status.

(4) Tumor Measurements: Obtain a contrast-enhanced computed tomography (CT) scan of the chest and abdomen (and pelvis, if clinically indicated) within 28 days prior to Day 1 of Cycle 1 and **every 8 weeks thereafter** during study treatment. If a patient discontinues treatment due to radiologic disease progression, additional tumor assessment is not required at the End of Treatment visit. For patients who discontinue treatment for reasons other than radiologic disease progression, every effort should be made to perform an end of treatment tumor assessment prior to the start of new anticancer therapy. Patients that discontinued treatment for reasons other than disease progression should continue to be followed for tumor response every 8 weeks until the patient develops radiologic disease progression (or death) or initiation of new anticancer therapy.

(5) Quality of Life: Patients should complete the EORTC QLQ-C30 questionnaires within 7 days prior to start of study treatment, prior to dose administration on Day 1 of Cycles ≥2, and at the 30-day safety follow-up if not performed within the prior 4 weeks.