Supplementary methods

I. Dose and schedule of study treatment and definition of dose limiting toxicity (DLT) in phase 1b part

(1) Dose and schedule of study treatment in phase 1b part

Study Treatment	Formulation and route of administration	Dose	Schedule
AZD8186 (60mg tablet)	Film-coated tablets for oral administration	60mg-120mg	5 days on (BID)/2 days off
Paclitaxel*	Intravenous	70-80mg/m^2	D1, 8, 15

The treatment cycle was defined as 28 days.
* Paclitaxel 70 mg/m^2 was planned to be evaluated only when paclitaxel dose reduction was necessary

(2) Planned dose level of study treatment in phase 1b part

Level	Paclitaxel (mg/m2) D1, 8, 15 Q 4weeks	AZD8186 (total mg/day) 5 days on/2 days off
1	80	120 (60 mg BID)
2	80	240 (120 mg BID)
-1	70	240 (120 mg BID)
-2	70	120 (60 mg BID)

On the phase 1b stage, 4 dose levels were planned. The traditional 3+3 design was applied to these 4 dose levels. The level -1 was planned to be tested if the dose level 2 was deemed to be intolerable (DLT occurs in more than 2 out of 6 people). The level -2 was planned to be tested if the dose level 1 was deemed to be intolerable (DLT occurs in more than 2 out of 6 people).

(3) Definition of Dose-limiting toxicity (DLT)

DLT assessment (defined as treatment-related adverse events only; DLT did not include adverse events associated with the disease [e.g., symptomatic deterioration due to tumor progression]) was only performed during the first cycle and is based on NCI-CTCAE (version 4.0). The evaluation period of DLT was 28 days (i.e., one cycle treatment period).

In the absence of DLT, subject was considered evaluable for DLT only if paclitaxel was administered all 3 times and AZD8186 was administered more than 80% or more (That is, the completion of taking at least 32 times out of a total of 40 times). Subjects who had been dropped out of the DLT evaluation in the phase 1b part were planned to be replaced with new subjects. DLT was evaluated in subjects who had received at least one dose of the study treatment and when any one of the below developed.

1) Hematological toxicity:

① Grade 3 neutropenia of any duration accompanied with fever ≥ 38.3°C and/or systemic infection

② Grade 4 neutropenia lasting longer than 7 consecutive days [In the first cycle, the use of G-CSF was not allowed. If G-CSF was administered, the subject was considered inevaluable for DLT and should have been

replaced with a new subject]

③ Grade 3 thrombocytopenia lasting longer than 7 consecutive days; Grade 4 thrombocytopenia; Grade 3 thrombocytopenia with bleeding

* During the DLT evaluation period, complete blood counts were checked every week.
* If Grade 4 neutropenia (ANC < 500/mm^3) or Grade 3 thrombocytopenia (platelet < 50,000/m^3) occurs, to determine if the neutropenia and/or thrombocytopenia persists for more than 7 days, a follow-up test should be done on the 8th or later day.
* Paclitaxel (on days 1, 8 and 15) and AZD8186 (on days 1-5, 8-12, 15-19 and 22-26) should be administered when ANC ≥ 1,000/mm^3 and platelet ≥ 75,000 /mm^3.

2) Non-hematological toxicity: ≥Grade 3 including

① Laboratory abnormalities of ≥ Grade 3 (a repeat test may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations, i.e., a suspected spurious value).

② QTc prolongation (> 500 msec) in the presence of normal serum potassium

3) Any other hematologic or non-hematologic toxicity (i.e., greater than at baseline and clinically significant and/or unacceptable) that does not sufficiently respond to supportive care and results in the delay of the dosing schedule of more than 14 days.

4) Any event, including significant dose reductions or omissions, judged to be a DLT by the Safety Review Committee (SRC)

* DLT excluded: Alopecia of any grade; Inadequately managed Grade 3 nausea and/or vomiting and Grade 3 diarrhea (all patients should receive optimal anti-emetic/anti-diarrheal prophylaxis and/or treatment); Short lasting Grade 3 skin rash which can be managed at least to G2 with supportive care within 72 hours (for example, with steroids)

II. Study treatment and dose modification

(1) Study Treatment

AZD8186

AZD8186 is administered at a fixed dose of 60-120 mg (1x60 mg or 2x60 mg tablet) twice daily (BID) depending on the dose level with water. AZD8186 will be taken orally twice daily at approximately the same time (12±1 hour) each day on an empty stomach (water only for at least 2 hours prior and 1 hour after each dose) and approximately 12 hours apart for 5 days on, 2 days off every week.

Paclitaxel

Paclitaxel is administered at a fixed dose on days 1, 8 and 15.

(2) Dose Modification

AZD8186 Dosing delay/Dose modifications

For subjects who are not able to tolerate the 120 mg BID schedule, a single dose reduction to 60 mg BID is allowed to allow the study subjects to continue the study treatment. Dose reduction of less than 60 mg is not permitted (Table II-1); subjects requiring additional dose reduction should stop the study treatment. If the toxicity does not resolve to ≤ CTCAE grade 1 after 21 days of dose interruption, then the subject should be permanently discontinued from AZD8186 and Paclitaxel (withdrawn from the study) and observed until resolution of the toxicity.

Table II-1. AZD8186 Dose Modifications

Dose Modification*		
AZD8186	**Dose level (0)**	**Dose level - 1**
	120 mg BID	60mg BID**

*Dose reduction should be based on the highest AE rating.
** Dose reduction of less than 60 mg bid is not permitted.

Paclitaxel Dosing delay / Dose modifications

For patients who are not able to tolerate the 80mg/m^2 dose schedule, sequential dose reductions to 60mg/m^2 are permitted to allow the subjects to continue to receive study treatment. Dose reduction of less than 60mg/m^2 is not permitted (Table II-2). Subjects requiring additional dose reduction should stop the study treatment. If the toxicity does not resolve to ≤ CTCAE grade 1 after 21 days of dose interruption, then the subject should be permanently discontinued from AZD8186 and Paclitaxel (withdrawn from the study) and observed until resolution of the toxicity. If RP2D is determined to be 70mg/m^2 for paclitaxel (with 60 mg BID or 120 mg BID of AZD8186), the dose level of paclitaxel is set to two levels of 70mg/m^2 and 60mg/m^2, and the dosage adjustment guidelines are the same

Table II-2. Paclitaxel Dose Modifications

Dose Modifications (If PR2P of paclitaxel is 80 mg/m^2)			
Paclitaxel	**Dose level 0**	**Dose level - 1**	**Dose level -2****
	80 mg/m^2	70 mg/m^2	60 mg/m^2

*Dose reduction should be based on the highest AE rating.

** Dose reduction of less than 60mg/m^2 is not permitted.

Dose Modifications (If PR2P of paclitaxel is 70 mg/m^2)		
Paclitaxel	**Dose level 0**	**Dose level -1****
	70 mg/m^2	60 mg/m^2
*Dose reduction should be based on the highest AE rating. ** Dose reduction of less than 60mg/m^2 is not permitted.		

Table II-3. Criteria for administering paclitaxel on day 1 in each cycle

ANC	≥ 1.5 x 10^9/L
Platelet	≥ 100 x 10^9/L
Serum Creatinine	≤ 1 x UNL or calculated creatinine clearance≥ 50mL/min (by Cockcroft-Gault formula, MDRD, CKD-EPI formula or 24-hour urine collection)
Total bilirubin	≤ 1.5 x UNL
AST/ALT	In cases without liver metastases, AST/ALT ≤ 3 x UNL (CTCAE Grade 1) In cases with liver metastases, ≤ 5 x UNL (CTCAE Grade 2)
Paclitaxel related toxicity/adverse events	NCI-CTCAE version 4.02 ≤ Grade 2 or baseline (alopecia excluded)

Table II-4. Criteria for administering paclitaxel on day 8, 15 in each cycle

ANC	≥ 1.0 x 10^9/L
Platelet	≥ 75 x 10^9/L
Total bilirubin	≤ 1.5 x UNL
AST/ALT	In cases without liver metastases, AST/ALT ≤ 3 x UNL (CTCAE Grade 1) In cases with liver metastases, ≤ 5 x UNL (CTCAE Grade 2)
Paclitaxel related toxicity/adverse events	NCI-CTCAE version 4.02 ≤ Grade 2 or baseline (alopecia excluded)

In the first cycle for the DLT evaluation in phase 1b part, dose reduction within the cycle is not allowed, and when the intra-cycle dose reduction is performed without the development of DLT, the subject is deemed inevaluable for DLT and should be replaced with another subject. However, even in the phase 1b part, dose reduction within the cycle can be performed according to an investigator's judgment with the consideration of the safety of subjects from the second cycle. In the phase 2 part, dose reduction within the cycle can be conducted according to an investigator's judgment. If 'an adverse event defined as DLT in phase 1b part' occurs in second or later cycles of phase 1b part or in any cycles of phase 2 part, the study treatment should be reduced by one level even within the cycle.

Decisions on dose reduction/interruption/discontinuation for AZD8186 or paclitaxel should be based on the CTCAE grade of toxicities and guides given below. Generally, dose-reduction or dose-interruption is not performed for Grade 1 toxicity; however, supportive therapy should be administered to control symptoms. All adverse events should be tracked weekly or clinically as appropriate until stabilized or resolved. If a dose reduction has been performed, dose re-escalation is not allowed.

If one or more of the criteria for the administration of next doses of study treatment (in the above table) is not met at the scheduled treatment timepoint, the blood count and serum chemistry test should be repeated at least once a week, and the next dose is delayed until the above criteria are met. Even if study treatment is delayed due to toxicity, the radiological assessment of tumor response should not be postponed and should be done every 8 weeks (± 7 days) during the first 12 months after the first administration of study treatment, and then every 12 weeks (± 7 days) after 12 months until disease progression.

① Hematologic toxicity

Table II-5. Dose modification for neutropenia

ANC count	**AZD8186 Dose modification**	**Paclitaxel Dose modification**
≤ Grade 1 (≥ 1.5 x 10^9/L)	No change in dose	No change in dose
Grade 2 (≥ 1.0 to 1.5 x 10^9/L)	No change in dose	No change in dose
Grade 3	Hold until ≤ Grade 2.	Hold until ≤ Grade 2.

ANC count	AZD8186 Dose modification	Paclitaxel Dose modification
(≥ 0.5 to 1.0 x 10^9/L)	Resume at same dose level	Resume at same dose level (May start the next cycle with one level dose reduction at the discretion of the investigator)*
Grade 4 (<0.5 x 10^9/L)	Hold until ≤ Grade 2. Resume at same dose level (Start the next cycle without AZD8186 dose reduction. If Grade 4 neutropenia redevelops, paclitaxel dose reduction will be preferentially conducted to 60 mg/m^2. If Grade 4 neutropenia redevelops even after paclitaxel dose reduction to 60 mg/m^2, AZD8186 will be reduced to 120 mg/day. If Grade 4 neutropenia redevelops with dosages of AZD8186 120 mg/day plus paclitaxel 60 mg/m^2, the study treatment will be terminated.)	Hold until ≤ Grade 2. Resume paclitaxel with one level dose reduction.
* Dose reduction of within the cycle is not allowed in the first cycle for the DLT evaluation in phase 1b part. However, if DLT has already occurred, dose reduction within the cycle is allowed. When the intra-cycle dose reduction is performed without the development of DLT, the subject is deemed inevaluable for DLT and should be replaced with another subject. ** In the phase 1b part after the completion of first cycle (DLT evaluation period) or phase 2 part, dose reduction of paclitaxel should be done if Grade 3 neutropenia with fever or Grade 4 neutropenia has occurred (Investigators can resume AZD8186 and paclitaxel if neutropenia ≤ Grade 2 within the cycle). Dose reduction of paclitaxel within the cycle is permitted. When Grade 3 neutropenia with fever or Grade 4 neutropenia develops, paclitaxel dose reduction (to 60 mg/m^2) should be preferentially conducted. If Grade 3 neutropenia with fever or Grade 4 neutropenia develops even after the dose reduction of paclitaxel to 60 mg/m^2, then AZD8186 dose reduction will be conducted (to 120 mg/day; if Grade 3 neutropenia with fever or Grade 4 neutropenia develops with AZD8186 120 mg/day plus paclitaxel 60 mg/m^2, the the study treatment must be terminated.) *** If the toxicity does not resolve to ≤ CTCAE grade 1 after 21 days of dose interruption, then the subject should be permanently discontinued from AZD8186 and Paclitaxel.		
During DLT evaluation in the first cycle of phase 1b part, the administration of G-CSF is not permitted. G-CSF may be administered at the discretion of an investigator from the second cycle of phase 1b part or in any cycles of phase 2 part if neutropenia ≥ Grade 3 occurs.		

Table II-6. Dose modification for thrombocytopenia

Thrombocytopenia	AZD8186 Dose modification	Paclitaxel Dose modification
≤ Grade 1 (≥ 75 x 10^9/L)	No change in dose	No change in dose
Grade 2 (≥ 50 to 75 x 10^9/L)	Hold until ≤ Grade 1. Resume at same dose level	Hold until ≤ Grade 1. Resume at same dose level
Grade 3 (≥ 25 to 50 x 10^9/L)	Hold until ≤ Grade 1. Resume at same dose level*	Hold until ≤ Grade 1. Resume paclitaxel with one level dose reduction.*
Grade 4 (<25 x 10^9/L)	Hold until ≤ Grade 1. Resume at same dose level (Start the next cycle without AZD8186 dose reduction. If Grade 4 thrombocytopenia redevelops, then paclitaxel dose reduction will be preferentially conducted to 60 mg/m^2. If Grade 4 thrombocytopenia redevelops even after paclitaxel dose reduction to 60 mg/m^2, AZD8186 will be reduced to 120 mg/day. If Grade 4 thrombocytopenia redevelops with dosages of AZD 8186 120 mg/day plus paclitaxel 60 mg/m^2, the study treatment will be terminated.)	Hold until ≤ Grade 1. Resume paclitaxel with one level dose reduction.**
* Dose reduction of within the cycle is not allowed in the first cycle for the DLT evaluation in phase 1b part. However, if DLT has already occurred, dose reduction within the cycle is allowed. When the intra-cycle dose reduction is performed without the development of DLT, the subject is deemed inevaluable for DLT and should be replaced with another subject. ** In the phase 1b part after the completion of first cycle (DLT evaluation period) or phase 2 part, dose reduction of paclitaxel should be done if ≥ Grade 3 thrombocytopenia has occurred (Investigators can resume AZD8186 and paclitaxel if thrombocytopenia ≤ Grade 1). Dose reduction of paclitaxel within the cycle is permitted. When ≥ Grade 3 thrombocytopenia develops, paclitaxel dose reduction (to 60 mg/m^2) should be preferentially conducted. If ≥ Grade 3 thrombocytopenia develops even after the dose reduction of paclitaxel to 60 mg/m^2, then AZD8186 dose reduction will be		

Thrombocytopenia	AZD8186 Dose modification	Paclitaxel Dose modification
conducted (to 120 mg/day; if ≥ Grade 3 thrombocytopenia develops with AZD8186 120 mg/day plus paclitaxel 60 mg/m^2, the study treatment must be terminated.) *** If the toxicity does not resolve to ≤ CTCAE grade 1 after 21 days of dose interruption, then the subject should be permanently discontinued from AZD8186 and Paclitaxel.		

② **Nausea and vomiting**

Table II-7. Dose modification for nausea

Nausea	AZD8186 Dose modification	Paclitaxel Dose modification
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose May consider holding until ≤ Grade 1. Resume at same dose level with appropriate antiemetics.	No change in dose May consider holding until ≤ Grade 1. Resume at same dose level with appropriate antiemetics.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level with appropriate antiemetics (OR may resume at one level dose reduction at the discretion of the investigator)	Hold until ≤ Grade 1. Resume at same dose level with appropriate antiemetics (OR may resume at one level dose reduction at the discretion of the investigator)
Grade 4	Off protocol therapy	Off protocol therapy
* If the toxicity does not resolve to ≤ CTCAE grade 1 after 21 days of dose interruption, then the subject should be permanently discontinued from AZD8186 and Paclitaxel. ** Subjects requiring dose reductions more than predefined dose levels should go off protocol therapy.		
Recommended treatment: Antiemetics		

Table II-8. Dose modification for vomiting

Vomiting	AZD8186 Dose modification	Paclitaxel Dose modification
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose May consider holding until ≤ Grade 1. Resume at same dose level with appropriate antiemetics.	No change in dose May consider holding until ≤ Grade 1. Resume at same dose level with appropriate antiemetics.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level with appropriate antiemetics (OR may resume at one level dose reduction at the discretion of the investigator)	Hold until ≤ Grade 1. Resume at same dose level with appropriate antiemetics (OR may resume at one level dose reduction at the discretion of the investigator)
Grade 4	Off protocol therapy	Off protocol therapy
* If the toxicity does not resolve to ≤ CTCAE grade 1 after 21 days of dose interruption, then the subject should be permanently discontinued from AZD8186 and Paclitaxel. ** Subjects requiring dose reductions more than predefined dose levels should go off protocol therapy.		
Recommended treatment: Antiemetics		

③ **Diarrhea/colitis**

Patients should be made aware of the risk of diarrhea while receiving treatment with AZD8186. Patients should be advised to drink sufficient fluids and have a supply of loperamide available throughout treatment. However, loperamide should not be administered prophylactically. As soon as the first liquid stool occurs, patients should start loperamide immediately (to be administered per package information and usual clinical practice) and take electrolyte-containing fluids. Patients should inform their attending investigators. Loperamide should not be administered for more than 48 consecutive hours.

Diarrhea must be graded according to CTCAE version 4.03. Uncomplicated Grade 1 or 2 diarrhea does not need dose modification. If Grade ≥3 diarrhea occurs, treatment interruptions and dose modification should be made according to Table II-9.

Table II-9. Dose modification for diarrhea

Diarrhea/colitis	AZD8186 Dose modification	Paclitaxel Dose modification
≤ Grade 1	No change in dose	No change in dose
Grade 2	Initiate best supportive care (BSC) including loperamide and sufficient fluid intake, reassess 24-48 hrs later. If not improved after 48 hours, hold drug. Once ≤ Grade 1 (within 21 days), resume at same dose level.	Hold paclitaxel. Initiate BSC including loperamide and sufficient fluid intake, and then reassess 24-48 hrs later. Once ≤ Grade 1 (within 21 days), resume at same dose level.
Grade 3	Hold, initiate BSC and reassess 24-48 hrs later. If recovered to ≤ Grade 1 (within 21 days), resume at one level dose reduction. If unresolved, hospitalize (if not already) with GI consult	Hold, initiate BSC and reassess 24-48 hrs later. If recovered to ≤ Grade 1 (within 21 days), resume at one level dose reduction if clinically indicated (judged by the investigator)
Grade 4	Off protocol therapy	Off protocol therapy
* If the toxicity does not resolve to ≤ CTCAE grade 1 after 21 days of dose interruption, then the subject should be permanently discontinued from AZD8186 and Paclitaxel. ** Subjects requiring dose reductions more than predefined dose levels should go off protocol therapy.		
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours). Should not be administered for more than 48 consecutive hours. Anti-diarrheal therapies ancillary to loperamide are also permitted.		

④ Rash

During AZD8186 treatment, early identification and intervention is critical for the optimal management of rash. Preliminary clinical evidence suggests that antihistamine drugs may ameliorate occurrence/severity of rash. Therefore, subjects who develop Grade 1 or 2 changes in their skin condition should be treated with the Investigator's choice of antihistamine drugs, over the counter moisturizing cream or ointment, local antihistamines and/or topical or systemic steroids. If bacterial infection is suspected, local and/or systemic antibiotics may be added. Early administration of a short course of oral corticosteroids may be considered in patients with Grade 2 skin rash. For Grade 1 or 2 skin toxicity, no study treatment modifications are required, and every effort should be made to avoid interruptions or discontinuation of study treatment after the onset of rash through early treatment. A short course of systemic steroids (e.g., prednisolone 50 mg Day 1, 25 mg Days 2-5) may be considered as early treatment.

For Grade 3 rash, specifically systemic and not topical steroids should be given. Up to three days of supportive care including high doses of steroids may be given before dose modification of the AZD8186. If bacterial infection is suspected, local and/or systemic antibiotics may be added. Short courses (≤ 14 days) of corticosteroid treatment at doses that do not exceed 100 mg per day of prednisone or equivalent may be given and dermatologic consultation is recommended. Dose reduction of AZD8186 may be determined according to the level of response to systemic steroid treatment (no AZD8186 dose reduction if immediate improvement [= within 3 days] after systemic steroid therapy vs. AZD8186 dose reduction in the cases with no immediate response)

No dose adjustment of paclitaxel is necessary unless the causal relationship between paclitaxel and rash is strongly suggested.

⑤ Hepatic toxicity

Doses of AZD8186 should be adjusted or discontinued according to the following criteria (Table II-10 and II-11). Dose modification criteria are different according to the baseline AST/ALT levels and the presence of liver metastasis before study treatment. However, even in cases baseline AST/ALT levels of >3.0 to ≤5.0 X ULN (with liver metastasis) before the first cycle of study treatment, if AST/ALT levels are improved to grade 1 (≤ 3.0 X ULN) after study treatment, then dose modification should be conducted according to Table II-10.

Table II-10. Dose modification in subjects with baseline AST/ALT ≤ 3.0 x ULN

	Transaminase: SGOT (AST) and/or SGPT (ALT) levels			
	≤3.0 X ULN (Grade 1)	>3.0 to ≤5.0 X ULN (Grade 2)	>5.0 to ≤20.0 X ULN (Grade 3)	>20.0 X ULN (Grade 4)
Total bilirubin ≤1.5 X ULN (Grade 1)	No change in dose	Hold both Paclitaxel and AZD8186. Resume at same dose level if total bilirubin ≤ 1.5 X ULN and AST/ALT level reverts to ≤ CTCAE grade 1.	Hold both Paclitaxel and AZD8186. Resume at one level dose reduction (both Paclitaxel and AZD8186) if total bilirubin ≤ 1.5 X ULN and AST/ALT level reverts to ≤ CTCAE grade 1.	Off protocol therapy
Total bilirubin >1.5 to ≤2.0 X ULN (Grade 2)	Hold both Paclitaxel and AZD8186. Resume at same dose level if total bilirubin ≤ 1.5 X ULN and AST and/or ALT level reverts to ≤ CTCAE grade 1.	Hold both Paclitaxel and AZD8186. Resume paclitaxel with one level dose reduction if total bilirubin ≤ 1.5 X ULN and AST/ALT level reverts to ≤ CTCAE grade 1. Paclitaxel dose reduction (to the level of 60 mg/m^2) will be preferentially conducted and AZD8186 will be administered without dose reduction. If paclitaxel dose is already reduced to 60 mg/m^2, then one level dose reduction of AZD8186 should be conducted.	Hold both Paclitaxel and AZD8186. Resume at one level dose reduction (both Paclitaxel and AZD8186) if total bilirubin ≤ 1.5 X ULN and AST/ALT level reverts to ≤ CTCAE grade 1.	Off protocol therapy
Total bilirubin >2.0 to ≤3.0 X ULN (Grade 2)	Hold both Paclitaxel and AZD8186. Resume paclitaxel with one level dose reduction if total bilirubin ≤ 1.5 X ULN and AST/ALT level reverts to ≤ CTCAE grade 1. Paclitaxel dose reduction (to the level of 60 mg/m^2) will be preferentially conducted and AZD8186 will be administered without dose reduction. If paclitaxel dose is already reduced to 60 mg/m^2, then one level dose reduction of AZD8186 should be conducted.	Hold both Paclitaxel and AZD8186. Resume at one level dose reduction (both Paclitaxel and AZD8186) if total bilirubin ≤ 1.5 X ULN and AST/ALT level reverts to ≤ CTCAE grade 1.	Off protocol therapy	Off protocol therapy
Total bilirubin >3.0 X ULN (≥ Grade 3)	Off protocol therapy	Off protocol therapy	Off protocol therapy	Off protocol therapy)
* Both paclitaxel and AZD8186 should be resumed when total bilirubin ≤ 1.5 X ULN and AST/ALT level reverts to ≤ CTCAE grade 1. If the toxicity does not resolve to ≤ CTCAE grade 1 after 21 days of dose interruption, then the subject should be permanently discontinued from AZD8186 and Paclitaxel. ** Subjects requiring dose reductions more than predefined dose levels should go off protocol therapy.				

Table II-11. Dose modification in subjects with liver metastasis and baseline AST/ALT >3.0 to ≤5.0 X ULN

	Transaminase: SGOT (AST) and/or SGPT (ALT) levels			
	≤3.0 X ULN (Grade 1)	>3.0 to ≤5.0 X ULN (Grade 2)	>5.0 to ≤20.0 X ULN (Grade 3)	>20.0 X ULN (Grade 4)
Total bilirubin ≤1.5 X ULN (Grade 1)	No change in dose	No change in dose	Hold both Paclitaxel and AZD8186. Resume at one level dose reduction (both Paclitaxel and AZD8186) if total bilirubin ≤ 1.5 X ULN and AST/ALT level reverts to ≤ CTCAE grade 2.	Off protocol therapy
Total bilirubin >1.5 to ≤2.0 X ULN (Grade 2)	Hold both Paclitaxel and AZD8186. Resume at same dose level if total bilirubin ≤ 1.5 X ULN.	Hold both Paclitaxel and AZD8186. Resume paclitaxel with one level dose reduction if total bilirubin ≤ 1.5 X ULN and AST/ALT level reverts to ≤ CTCAE grade 2. Paclitaxel dose reduction (to the level of 60 mg/m^2) will be preferentially conducted and AZD8186 will be administered without dose reduction. If paclitaxel dose is already reduced to 60 mg/m^2, then one level dose reduction of AZD8186 should be conducted.	Hold both Paclitaxel and AZD8186. Resume at one level dose reduction (both Paclitaxel and AZD8186) if total bilirubin ≤ 1.5 X ULN and AST/ALT level reverts to ≤ CTCAE grade 2.	Off protocol therapy
Total bilirubin >2.0 to ≤3.0 X ULN Grade 2)	Hold both Paclitaxel and AZD8186. Resume paclitaxel with one level dose reduction if total bilirubin ≤ 1.5 X ULN. Paclitaxel dose reduction (to the level of 60 mg/m^2) will be preferentially conducted and AZD8186 will be administered without dose reduction. If paclitaxel dose is already reduced to 60 mg/m^2, then one level dose reduction of AZD8186 should be conducted.	Hold both Paclitaxel and AZD8186. Resume at one level dose reduction (both Paclitaxel and AZD8186) if total bilirubin ≤ 1.5 X ULN and AST/ALT level reverts to ≤ CTCAE grade 2. .	Off protocol therapy	Off protocol therapy
Total bilirubin >3.0 X ULN (≥ Grade 3)	Off protocol therapy	Off protocol therapy	Off protocol therapy	Off protocol therapy

* Both paclitaxel and AZD8186 should be resumed when total bilirubin ≤ 1.5 X ULN and AST/ALT level reverts to ≤ CTCAE grade 2. If the toxicity does not resolve to the above predefined levels after 21 days of dose interruption, then the subject should be permanently discontinued from AZD8186 and Paclitaxel.
** In cases with baseline AST/ALT levels of >3.0 to ≤5.0 X ULN (with liver metastasis) before the first cycle, if AST/ALT levels are improved to grade 1 (≤ 3.0 X ULN) after study treatment, then dose modification should be conducted according to Table 11.12.
*** Subjects requiring dose reductions more than predefined dose levels should go off protocol therapy.

⑥ **Peripheral neurotoxicity**

Table II-12. Dose modification for peripheral neuropathy

Peripheral Neuropathy	AZD8186 Dose modification	Paclitaxel Dose modification
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose or treatment with one level dose reduction depending on the clinical judgment (may hold the administration of paclitaxel until ≤ Grade 1 at the discretion of the investigator)
Grade 3	No change in dose	Hold until ≤ Grade 2. Resume at one leve dose reduction
Grade 4	Off protocol therapy	Off protocol therapy
* If the toxicity does not resolve to ≤ CTCAE grade 2 after 21 days of dose interruption, then the object should be permanently discontinued from Paclitaxel. ** Subjects requiring dose reductions more than predefined dose levels should go off protocol therapy. If paclitaxel is withdrawn due to peripheral neurotoxicity, AZD8186 monotherapy is allowed.		

⑦ **Mucositis**

For grade 4 mucositis (life-threatening), the participant should be removed from study treatment. For grade 3 mucositis present on Day 1 of a cycle, paclitaxel should be held until toxicity resolves to grade 1. Resume paclitaxel at a dose reduction of one level. If the grade 3 mucositis does not resolve within 3 weeks, the participant should be removed from study treatment.

Table II-13. Dose modification for mucositis

Mucositis	AZD8186 Dose modification	Paclitaxel Dose modification
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	Hold until ≤ Grade 1. Resume at same dose level (May resume at one level dose reduction at the disretion of the investigator)
Grade 3	Hold until ≤ Grade 1. Paclitaxel dose reduction (to the level of 60 mg/m^2) will be preferentially conducted and AZD8186 will be administered without dose reduction. If paclitaxel dose is already reduced to 60 mg/m^2, then one level dose reduction of AZD8186 should be conducted.	Hold until ≤ Grade 1. Resume at one leve dose reduction
Grade 4	Off protocol therapy	Off protocol therapy
*If the toxicity does not resolve to ≤ CTCAE grade 1 after 21 days of dose interruption, then the subject should be permanently discontinued from AZD8186 and Paclitaxel. ** Subjects requiring dose reductions more than predefined dose levels should go off protocol therapy.		

⑧ **Other Non-Hematological Adverse Reactions**

The dosage adjustment guidance for other adverse effects is as follows.

Table II-14. Dose modification for other non-hematologic adverse events

Non-hematologic adverse reactions suspicious of relevance	AZD8186 Dose modification	Paclitaxel Dose modification
≤ Grade 1	No change in dose	No change in dose
Grade 2	Provide symptomatic treatment and best supportive care (BSC). If not improved within 48 hours, hold AZD8186 until ≤ Grade 1. Resume at same dose level (May resume at one level dose reduction at the discretion of the investigator).	Hold until ≤ Grade 1 (May continue paclitaxel administration with BSC). Resume at same dose level (May resume at one level dose reduction at the discretion of the investigator).
Grade 3	Hold until ≤ Grade 1. Resume at one level dose reduction	Hold until ≤ Grade 1. Resume at one level dose reduction
Grade 4	Off protocol therapy	Off protocol therapy
* If the toxicity does not resolve to ≤ CTCAE grade 1 after 21 days of dose interruption, then the subject should be permanently discontinued from AZD8186 and Paclitaxel. ** Subjects requiring dose reductions more than predefined dose levels should go off protocol therapy.		