Official Title:	**A Phase 2, Open-Label, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib Plus Pembrolizumab Versus Pemigatinib Alone Versus Standard of Care as First-Line Treatment for Metastatic or Unresectable Urothelial Carcinoma in Cisplatin-Ineligible Participants Whose Tumors Express FGFR3 Mutation or Rearrangement (FIGHT-205)**
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Statistical Analysis Plan

INCB 54828-205

A Phase 2, Open-Label, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib Plus Pembrolizumab Versus Pemigatinib Alone Versus Standard of Care as First-Line Treatment for Metastatic or Unresectable Urothelial Carcinoma in Cisplatin-Ineligible Participants Whose Tumors Express FGFR3 Mutation or Rearrangement (FIGHT-205)

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SAP Version:	**Original**
SAP Author:	[redacted] [redacted]**, Biostatistics**
Date of Plan:	**23 FEB 2021**

This study is being conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
AUC	area under the plasma or serum concentration-time curve
BICR	blinded, independent, central review
BMI	body mass index
BOR	best overall response
BSA	body surface area
CI	confidence interval
CPS	combined positive score
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
HR	hazard ratio
ITT	intent to treat
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NE	not evaluable
OS	overall survival
PD	progressive disease
PD-L1	programmed cell death protein 1
PFS	progression-free survival
[redacted]	[redacted]
PO	orally
PP	per protocol
PR	partial response
PS	performance status
PT	preferred term
Q3W	every 3 weeks

Abbreviation	Term
QD	daily
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SD	stable disease
SOC	standard of care
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocytes
TNM	tumor, node, metastasis
UC	urothelial carcinoma
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This is a Phase 2, open-label, randomized, active-controlled study of pemigatinib plus pembrolizumab or pemigatinib alone versus SOC as first-line treatment for metastatic or unresectable UC in cisplatin-ineligible participants whose tumors express FGFR3 mutation or rearrangement. Section 2 of the Protocol provides a detailed description of the investigational product, target patient population, rationale for doses to be examined, and potential risks and benefits of treatment with pemigatinib plus pembrolizumab and pemigatinib alone.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the INCB 54828-205 Protocol. [redacted]

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 54828-205 Protocol Amendment 1 dated 17 APR 2020 and CRFs approved 22 MAY 2020. Unless superseded by an amendment, this SAP will be effective for all subsequent protocol amendments and eCRF versions.

2.2. Study Objectives and Endpoints

The objectives and endpoints apply to a study population of male or female participants at least 18 years of age with a histologically confirmed diagnosis of metastatic or unresectable UC, whose tumors express an FGFR3 mutation or rearrangement and who are medically ineligible to receive cisplatin-based chemotherapy and have not received prior treatment.

This study will be considered to have met its primary objective if pembrolizumab plus pemigatinib or pemigatinib alone is superior to SOC for the primary endpoint.

Table 1 presents the objectives and endpoints.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate and compare PFS in participants treated with pemigatinib in combination with pembrolizumab (Treatment Group A) and pemigatinib alone (Treatment Group B) versus SOC (Treatment Group C). Differences in PFS will be evaluated hierarchically, and the comparison between pemigatinib in combination with pembrolizumab (Treatment Group A) and SOC (Treatment Group C) will be evaluated first, and if significant difference is detected, a second comparison will be made in PFS between pemigatinib alone (Treatment Group B) and SOC (Treatment Group C). Hypothesis: The combination of pembrolizumab plus pemigatinib has superior PFS as compared with SOC. Contribution of pemigatinib alone to combination will be assessed by comparing Treatment Groups A and C and Treatment Groups B and C.	Progression-free survival, defined as the time from randomization date until the date of disease progression (as measured by BICR per RECIST v1.1) or death due to any cause, whichever occurs first.
Secondary	
To evaluate and compare the efficacy of the 3 treatment groups with respect to OS.	Overall survival, defined the time from the date of randomization until death due to any cause.
To evaluate and compare the efficacy of the 3 treatment groups with respect to overall tumor response and DOR.	• Objective response rate, defined as the proportion of participants with BOR of CR or PR determined by BICR per RECIST v1.1. • Duration of response, defined as the time from the date of the first assessment of CR or PR until the date of the first disease progression per BICR per RECIST v1.1 or death, whichever occurs first.
To evaluate the safety of the 3 treatment groups.	Safety and tolerability of pemigatinib with or without pembrolizumab and SOC will be assessed by evaluating the frequency and severity of AEs, physical examination findings, vital sign changes, and clinical laboratory assessments.
To evaluate changes from baseline in patient-reported outcomes.	Patient-reported outcome scales (ie, EORTC QLQ-C30, EQ-5D-5L) at each timepoint and change from baseline to each timepoint.
[redacted]	

3. STUDY DESIGN

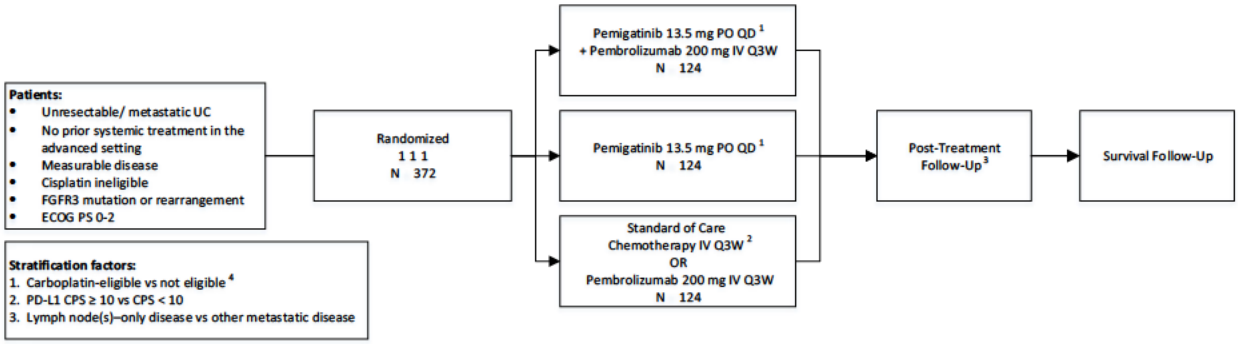
This is a Phase 2, open-label, randomized, and active-controlled study of pemigatinib plus pembrolizumab or pemigatinib alone versus the SOC for participants with metastatic or unresectable UC not eligible to receive cisplatin and harboring FGFR3 mutation or rearrangement and who have not received prior treatment. Randomization will occur after the participant has completed screening. Participants will be stratified by eligible to receive carboplatin versus not eligible to receive carboplatin, PD-L1 CPS $\geq$ 10 versus CPS < 10, and LN-only disease versus other metastatic disease. This is an event-driven clinical study designed to ensure power to detect success of the primary endpoint of PFS. A total of 210 PFS events in the combined treatment groups of pemigatinib plus pembrolizumab and SOC are needed to support the primary objective, where PFS is defined as the time from randomization date until the date of disease progression or death due to any cause, whichever occurs first.

Participant eligibility will be based on genomic testing for FGFR3. Participants can be randomized based on local results, if available, and results will be retrospectively confirmed by the sponsor's central laboratory. Previous therapies may include only neo-adjuvant or adjuvant treatment with platinum-containing chemotherapy if completed at least 12 months before the start of treatment for this study; otherwise, participants should be treatment naive before screening and according criteria outlined in Section 5 of the Protocol.

Treatment will start on Cycle 1 Day 1. Participants will undergo regular safety assessments during treatment, as well as regular efficacy assessments. Participants will be allowed to continue administration in 3-week cycles, as per protocol for each treatment, until disease progression per RECIST v1.1 as assessed by BICR or unacceptable toxicity is reported.

See for Figure 1 the study design.

Figure 1: Study Design Schema



[1] Participants not reaching the target serum phosphate during Cycle 1 will increase the daily dose of pemigatinib to 18 mg.
[2] Gemcitabine 1000 mg/m^2 IV Q3W on Days 1 and 8 + carboplatin AUC 5 (or 4.5) Q3W on Day 1 or 2.
[3] Participants may receive pembrolizumab for up to 2 years, pemigatinib until disease progression, and chemotherapy for 4-6 cycles, or other criteria per protocol.
[4] Carboplatin-eligible participants if randomized to SOC will receive gemcitabine/carboplatin; if not eligible to receive carboplatin, will receive pembrolizumab.
Note: Patients not eligible for carboplatin will not be enrolled in regions where pembrolizumab is not used as SOC in this population.

Full study drug administration information can be found in Section 6 of the Protocol.

3.1. Randomization

Participants who are screened and found to have the FGFR3 mutation or rearrangement will be randomized 1:1:1 into 1 of the 3 treatment groups indicated in Table 2 and stratified by eligible to receive carboplatin versus not eligible to receive carboplatin, PD-L1 CPS ≥ 10 versus CPS < 10, and LN-only disease versus other metastatic disease.

Table 2: Treatment Groups for Randomization

Treatment Group	Regimen
A	Pemigatinib 13.5 mg QD PO[a] until PD + pembrolizumab 200 mg Q3W IV up to 35 cycles (approximately 2 years) or PD, whichever occurs first
B	Pemigatinib 13.5 mg QD PO[a] until PD
C	One of 2 SOC treatment options: 1. Gemcitabine 1000 mg/m^2 Q3W IV on Days 1 and 8 + carboplatin AUC 5 (or AUC 4.5 if required per local guidelines) Q3W on Day 1 or 2 for 4 to 6 cycles. (Participants whose tumors express PD-L1 CPS < 10 who are eligible to receive carboplatin.) OR 2. Pembrolizumab 200 mg Q3W IV up to 35 cycles (approximately 2 years). (Participants whose tumors express PD-L1 CPS ≥ 10 or participants who are not considered eligible to receive any platinum-containing chemotherapy regardless of PD-L1 expression status [only applicable in regions where pembrolizumab is used as SOC for participants who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status].)[b]

[a] Participants not reaching the target serum phosphate during Cycle 1 will increase the daily dose to 18 mg starting at Cycle 2 as described in Section 6.6.2.1 of the Protocol.
[b] Participants can be enrolled if regulatory authorities allow carboplatin-ineligible participants to receive pembrolizumab monotherapy.

3.2. Control of Type I Error

The overall level of significance is strongly controlled for primary and key secondary objectives at 1-sided 0.025 using a fixed sequential testing procedure. The primary and key secondary efficacy endpoints at final analysis will be tested in the following order:

1. PFS comparison for pemigatinib plus pembrolizumab versus SOC at 1-sided 0.025.
2. OS comparison for pemigatinib plus pembrolizumab versus SOC at 1-sided 0.0147 at the time when primary analysis of PFS is conducted; OS comparison for pemigatinib plus pembrolizumab versus SOC at 1-sided 0.0103 at final OS analysis.
3. PFS comparison for pemigatinib only versus SOC at 1-sided 0.025.
4. OS comparison for pemigatinib only versus SOC at 1-sided 0.0147 at the time when primary analysis of PFS is conducted; OS comparison for pemigatinib only versus SOC at 1-sided 0.0103 at final OS analysis.

3.3. Sample Size Considerations

The sample size calculation is based on the primary endpoint of PFS.

The SOC treatment group in this study consists of participants who will receive pembrolizumab or chemotherapy depending on the participant carboplatin eligibility and PD-L1 CPS. In KEYNOTE-052, a large, single-arm, Phase 2 study with pembrolizumab conducted in cisplatin-ineligible participants who had not been previously treated with systemic chemotherapy, the median PFS was 2.1 months (95% CI: 2, 3; Balar et al 2017a). In EORTC 30968, a randomized, Phase 2/3 study comparing gemcitabine and carboplatin versus methotrexate/carboplatin/vinblastine, the median PFS was 5.8 months in the gemcitabine/carboplatin group as compared with 4.2 months in the other group(s) (De Santis et al 2012). Based on available data from KEYNOTE-052 and EORTC 30968 and participants' distribution percentages (see Table 3), it is estimated that the median PFS in the SOC treatment group (pembrolizumab or gemcitabine/carboplatin) is expected to be 5 months based on simulation.

Table 3: Median Progression-Free Survival Assumptions for Standard of Care Treatments

Population	Total (%) (N = 132)	Median PFS Assumption
Carboplatin-ineligible participants who will receive pembrolizumab	26 (20%)	2.1 months
Carboplatin-eligible participants who will receive pembrolizumab (CPS ≥ 10)	16 (12%)	4.9 months
Carboplatin-eligible participants who will receive gemcitabine/carboplatin (CPS < 10)	90 (68%)	5.8 months

It is expected that treatment with pemigatinib plus pembrolizumab will result in an HR of 0.68 for PFS compared to SOC, which corresponds to an increase in median PFS of 2.4 months under the exponential model assumption. It is calculated that a total of 210 PFS events in the combined treatment groups of pemigatinib plus pembrolizumab and SOC need to be observed to ensure 80% power to test the null hypothesis: PFS HR = 1, versus the specific alternative hypothesis: PFS HR = 0.68 for pemigatinib plus pembrolizumab versus SOC. This calculation assumes analysis using a 1-sided log-rank test at a 0.025 overall significance level and participants are randomized to the treatment groups in a 1:1 ratio.

To keep a minimum meaningful hazard ratio of 0.68 for PFS in participants with pemigatinib alone versus SOC, a total of 210 PFS events in the combined treatment groups of pemigatinib alone and SOC need to be observed to achieve 80% power to test the null hypothesis: PFS HR = 1, versus the specific alterative hypothesis: PFS HR = 0.68 for pemigatinib alone versus SOC. This calculation assumes analysis using a 1-sided log-rank test at a 0.025 overall significance level and participants are randomized to the treatment groups in a 1:1 ratio.

Assuming uniform accrual of the participants over a 36-month period, an 8-month follow-up after the last participant is randomized, and a 5% lost to follow-up rate, a total of approximately

372 participants will need to be randomized to observe the targeted PFS events at approximately 44 months after first participant is randomized.

The median OS for the SOC group is about 10 months based on EORTC Study 30968 and KEYNOTE-052. It is calculated that a total of 194 deaths in the combined treatment groups of pemigatinib plus pembrolizumab and SOC need to have been observed to achieve 76% power to detect an HR of 0.68 using a 1-sided log-rank test at a 0.025 overall significant level. Final OS analysis is expected to occur at approximately 52 months after first participant is randomized.

At the time when final PFS analysis is conducted, it is expected that about 169 deaths will be observed in the combined treatment groups of pemigatinib plus pembrolizumab and SOC. Overall survival comparison for pemigatinib plus pembrolizumab versus SOC will be conducted at nominal 1-sided alpha of 0.0147 according to the O'Brien-Fleming spending function. Final OS analysis comparing pemigatinib plus pembrolizumab versus SOC will be conducted at nominal 1-sided alpha of 0.0103 when approximately 194 deaths are observed in the combined treatment groups of pemigatinib plus pembrolizumab and SOC. The actual boundaries will be recalculated from the actual number of deaths at the time when final PFS analysis is conducted using the alpha- and beta-spending functions.

3.4. Schedule of Assessments

Refer to Protocol Amendment 1 dated 17 APR 2020 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

For safety assessments, Day 1 is the date that the first dose of study drug (pemigatinib, pembrolizumab, gemcitabine, or cisplatin) is administered to the participants.

For efficacy assessments, Day 1 is the randomization date.

For randomized participants not treated with any study drug, Day 1 is defined as the date of randomization.

4.1.2. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting date – Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting date – Day 1 date).

A study day of –1 indicates 1 day before Day 1.

4.1.3. Baseline Value

Baseline is the last nonmissing measurement obtained before the first administration of study drug, unless otherwise defined.

For randomized participants not treated with any study drug, baseline is defined as the last nonmissing assessment before randomization for all parameters.

When scheduled assessments and unscheduled assessments occur on the same day and the time of the assessment or time of first dose is not available, use the following convention to determine baseline:

- If both a scheduled and an unscheduled visit are available on the day of the first dose and the time is missing, use the scheduled assessment as baseline.
- If all scheduled assessments are missing on the day of the first dose and an unscheduled assessment is available, use the unscheduled assessment as baseline.

4.1.4. Handling of Missing and Incomplete Dates

In general, values for missing dates will not be handled unless methods for handling missing dates are specified in this section or relevant sections. The original reported dates collected on the eCRF should be used in all relevant listings. The following rules will be used for handling partial dates for analyses requiring dates.

When calculating the time since diagnosis of cancer, a partial cancer diagnosis date will be handled as follows in the calculation:

- If only the day is missing, then the first day of the month will be used.
- If both the month and day are missing, then 01 JAN of the year will be used.
- If the diagnosis date is completely missing, then the time since diagnosis will not be calculated.

When the date of the last dose is used in deriving variables such as duration of treatment or TEAE flag, a missing or partial date of the last dose will be handled as follows:

- If only the day is missing, then the earlier date of the last day of the month or the date that the participant discontinued treatment will be used.
- Otherwise, the date that the participant discontinued treatment will be used as the date of the last dose.

For relevant efficacy endpoints, a partial date of the death date will be handled as follows in the calculation:

- If mmyyyy for the last known alive date = mmyyyy for the death date, then the death date will be set to the day after the last known alive date.
- If mmyyyy for the last known alive date < mmyyyy for the death date, then the death date will be set to the first day of the death month.
- Otherwise, the partial death date will not be imputed.

4.1.5. Cycle Length and Duration

Cycle 1 Day 1 is the day that the first dose of study drug is administered. The scheduled cycle length is 21 days. The actual Day 1 of subsequent cycles will correspond with the first day of administration of pemigatinib, pembrolizumab, or gemcitabine plus cisplatin in that cycle; thus, treatment cycles may become out of sync with the originally planned schedule, and the cycle length may be different from 21 days. The date of the Day 1 of subsequent cycles recorded on the eCRF will be used as the Day 1 of the subsequent cycles.

4.2. Variable Definitions

The following variables will only be calculated if not reported on the eCRF.

4.2.1. Body Mass Index

Body mass index will be calculated as follows:

$$\text{BMI } (kg/m^2) = [\text{weight } (kg)] / [\text{height } (m)]^2.$$

4.2.2. Body Surface Area

Body surface area will be calculated based on the Mosteller (1987) formula as follows:

$$\text{BSA } (m^2) = \{[\text{weight } (kg) \times \text{height } (cm)] / 3600\}^{1/2}.$$

Sites will also record the BSA calculated per institutional standards.

4.2.3. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started before the first dose of pemigatinib, pembrolizumab, or gemcitabine plus cisplatin.

Concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first administration of pemigatinib, pembrolizumab, or gemcitabine plus cisplatin and is ongoing throughout the study or ends on/after the date of first study drug administration.
- On/after the date of first administration of pemigatinib, pembrolizumab, or gemcitabine plus cisplatin and is ongoing or ends during the course of study.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first dose of pemigatinib, pembrolizumab, or gemcitabine plus cisplatin. In the listing, it will be indicated whether a medication is only prior, only concomitant, or both prior and concomitant.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; v9 or later) will be used for the generation of all listings and statistical analyses.

5.2. Treatment Groups

This is a randomized, open-label, parallel treatment group design. Participants will be summarized by treatment group.

5.3. Analysis Populations

5.3.1. Intent-to-Treat Population

All participants who are randomized will constitute the ITT population. Treatment groups for this population will be defined according to the treatment assignment at the time of randomization regardless of the actual study drug the participant might take during his/her participation in the study.

The ITT population will be used for the listings of demographics, baseline characteristics, disease history, participant disposition, and analyses of all efficacy data.

5.3.2. Per Protocol Population

Participants in the ITT population who are considered to be sufficiently compliant with the Protocol will comprise the PP population. This population includes all ITT participants who meet all major inclusion and no major exclusion criteria based on blinded review of clinical data.

The following procedures will be performed to identify those participants who are to be excluded from the PP population:

- Clinical review of Protocol deviations.
- Clinical review of concomitant medications as defined in Section 6.7 of the Protocol.
- Clinical review of the dose administration and drug accountability listing.

The determination of participants being considered for exclusion from the PP population by the clinical team will be prepared and signed before database lock.

The PP population will be used in the supportive sensitivity analyses for primary endpoints.

5.3.3. Safety Population

The safety population includes all randomized participants who received at least 1 dose of study treatment. Treatment groups for this population will be determined according to the actual treatment the participant received regardless of assigned study drug treatment.

All safety analyses will be conducted using the safety population.

6. BASELINE, EXPOSURE, AND DISPOSITION

Appendix A provides a list of data displays.

6.1. Demographics, Baseline Characteristics, and Disease History

6.1.1. Demographics and Baseline Characteristics

The following demographics will be listed for the ITT population: age, sex, race, ethnicity, weight, height, BMI, BSA, eligibility to receive carboplatin, primary disease location, PD-L1 CPS.

6.1.2. Baseline Disease Characteristics

The following baseline disease characteristics will be listed for the ITT population: baseline phosphate, ECOG PS, and tobacco history.

In addition, start date and end date of tobacco consumption, average number of cigarettes consumed, average number of cigars consumed, average number of smokeless (pinches) tobacco consumed, and average number of pipefuls consumed will be listed.

6.1.3. Disease History

Time since initial diagnosis, histology at diagnosis, stage at diagnosis, TNM staging at diagnosis, TIL at diagnosis; time to diagnosis of advanced disease, current stage, current histology, current TNM stage, TIL currently reported, and current sites of disease will be listed for all participants in the ITT population.

Time since diagnosis will be calculated as:

time since diagnosis (years) = (date of randomization – date of diagnosis + 1) / 365.25.

6.1.4. Prior Therapy

Participants who received prior therapy regimens will be listed for the ITT population. The component drugs of prior therapy regimens will be coded using the WHO Drug Dictionary. Regimen name, component drugs, start and stop date, route of the regimen taken, purpose of the regimen, best response, reason for discontinuation, and date of relapse/progression will be listed.

Participants who received prior radiation will be listed for the ITT population, including radiotherapy type, anatomical location of the administration, start and stop date, number of fractions received, total dose, reason for regimen, and best response.

Participants who had prior surgery or surgical procedure for the malignancies under study will be listed for the ITT population, including the date and description of the surgery/procedure.

6.1.5. Medical History

For participants in the ITT population, medical history will be listed.

6.2. Disposition of Participant

Participants who were randomized, who were treated, who were ongoing with study treatment, who discontinued study treatment with a primary reason for discontinuation, who were still in the study, who completed the study, and who withdrew from the study with a primary reason for withdrawal will be listed for the ITT population.

6.3. Protocol Deviations

Protocol deviations recorded on the eCRF will be listed.

6.4. Exposure

For participants in the safety population, exposure to study drug will be listed as the following:

- **Number of cycles**: number of cycles with a nonzero dose of study drug (pemigatinib, pembrolizumab, or gemcitabine plus cisplatin).
- **Duration of treatment with study drug (days)**:

  For participants in Group A who take pemigatinib plus pembrolizumab:

  max (date of last dose of pembrolizumab + 20, date of last dose of pemigatinib) – date of first dose + 1

  For participants in Group B who take pemigatinib:

  date of last dose – date of first dose + 1

  For participants in Group C who take pembrolizumab:

  date of last dose + 20 – date of first dose + 1

  For participants in Group C who take gemcitabine plus cisplatin:

  date of last dose + 6 – date of first dose + 1 if last dose is on Day 1 of a cycle;
  date of last dose + 13 – date of first dose + 1 if last dose is on Day 8 of a cycle.
- **Dose modifications**: participants who had study drug dose reduction and interruption.
- **Average daily dose of pemigatinib (mg/day)**: total actual pemigatinib dose taken (mg) / duration of treatment with pemigatinib (days).

  Total actual dose taken will be calculated based on the information entered on the Drug Accountability eCRF.

For pembrolizumab, gemcitabine, and cisplatin, relative dose intensity will be listed:

- **Relative dose intensity (%):** 100 × [total actual dose] / [total assigned dose]

  Total actual dose (mg) administered is the sum of the dose that has been administered to the participant. Total assigned dose (mg) is the total dose expected if the participant had taken all doses as initially assigned.

6.5. Study Drug Compliance

For participants in the safety population, overall compliance (%) for pemigatinib will be listed and calculated as follows:

compliance (%) = 100 × [total dose actually taken] / [total prescribed dose].

The total prescribed dose is defined as the sum of the doses prescribed by the investigator accounting for dose modifications.

The total actual dose taken will be calculated based on information entered on the Drug Accountability eCRF. If there are dispensed drugs that have not been returned yet, the actual dose taken starting from the dispense date of the unreturned drugs will be imputed by the dose taken as reported on the Dosing eCRF.

6.6. Prior and Concomitant Medication

Prior medications and concomitant medications will be coded using the WHO Drug Dictionary. For participants in the ITT population, each prior and concomitant medication will be listed.

7. EFFICACY

Appendix A provides a list of data displays.

7.1. Efficacy Hypotheses

Not applicable.

7.2. Analysis of the Primary Efficacy Parameter

7.2.1. Primary Efficacy Analysis

The primary endpoint of the study is PFS, defined as the time from the date of randomization to the earlier date of death due to any cause or PD as determined by BICR of objective radiographic disease assessments per RECIST v1.1. Participants without a PFS event at the time of analysis will be censored. Censoring for PFS will follow the algorithm outlined in Table 4, which is based on FDA guidance (2018). Progression-free survival will be listed for each participant in ITT population.

Table 4: Evaluation and Censoring of Progression-Free Survival

Situation	Outcome	Date of Progression or Censoring
No baseline tumor assessments	Censored	Date of randomization
No valid postbaseline response assessments	Censored	Date of randomization
Progression documented between scheduled response assessments	Progressed	Date of first overall response of PD
No progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study withdrawal for undocumented progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study withdrawal for toxicity or other reason	Censored	Date of last valid radiologic assessment (not NE and not missing)
New anticancer treatment started	Censored	Date of last valid radiologic assessment (not NE and not missing) on/before starting a new anticancer treatment
Death before first progressive response assessment	Progressed	Date of death
Death between adequate response assessments	Progressed	Date of death
Death or progression after 2 or more missed assessments	Censored	Date of last valid radiologic assessment (not NE and not missing)

7.2.2. Sensitivity and Supportive Analyses for Primary Endpoint

Not applicable.

7.3. Analysis of the Secondary Efficacy Parameter

Secondary efficacy parameters will be listed for the ITT population.

7.3.1. Overall Survival

Overall survival is defined as the interval between the randomization date and the date of death due to any cause. Date of death will be determined using the Death Report eCRFs. Participants who are lost to follow-up or still alive at the time of analysis will be right-censored at the earlier of the date the participant was last known alive and the clinical data cutoff date for the analysis. Partial death dates will be handled using the rules described in Section 4.1.4.

7.3.2. Best Overall Response and Duration of Response

In general, BOR is the best response recorded postbaseline prior to and including the first PD, in the order of CR, PR, SD, PD and NE. In the case of SD, measurements must meet the SD criteria at least once after randomization date at a minimum interval of 49 days. Participants

who fail to meet this criterion will have a BOR of PD if the next available assessment indicates PD or NE if there is no additional assessment available.

Duration of response is defined as the time from the first assessment of CR or PR until the date of the first PD per RECIST v1.1 or death. Participants who are still responding at the time of analysis will be censored. Censoring of DOR will follow the same algorithm as the censoring of PFS.

7.3.3. Quality-of-Life Questionnaires

7.3.3.1. EORTC QLQ-C30

The EORTC QLQ-C30 score for each of the 5 functional scales, 3 symptom scales, 1 global health status/QoL scale, and 6 single-item scales at each visit where the variable is measured, as well as change from baseline to each visit, will be listed by visit for each participant. The scores for each scale will be calculated based on responses from the 30 questions using the mapping of questions to scales presented in Table 5.

Table 5: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 Scales

Scale	Question(s)
Global health status/QoL	29, 30
Physical functioning	1 to 5
Role functioning	6, 7
Emotional functioning	21 to 24
Cognitive functioning	20, 25
Social functioning	26, 27
Fatigue	10, 12, 18
Nausea and vomiting	14, 15
Pain	9, 19
Dyspnea	8
Insomnia	11
Appetite loss	13
Constipation	16
Diarrhea	17
Financial difficulties	28

The raw score of each scale is the mean of the item values that contribute to the scale, and the standardized score is a linear transformation of the raw score so that the range is from 0 to 100. A higher standardized score represents a higher/better level of functioning/QoL or a higher/worse level of symptoms.

The raw score will be the mean of nonmissing item values if the number of missing item values is less than 50% of the items that contribute to the scale. Otherwise, the raw score will be considered as missing.

Let range be the difference between the possible maximum and minimum of a raw scale, which is 6 for Global Health Status/QoL and 3 for all other scales. The standardized score for functional scale will be calculated by the following:

$$(1-\frac{RawScore-1}{Range})\times 100$$

For all other scales (symptom scales, items and global health status, QoL), the standardized score will be calculated by the following:

$$(\frac{RawScore-1}{Range})\times 100$$

7.3.3.2. EQ-5D-5L

The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ VAS.

The EQ-5D-5L descriptive system is composed of 5 dimensions (mobility, self-case, usual activities, pain/discomfort, and anxiety/depression). Each dimension has 5 response levels, which are coded by single-digit numbers: 1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, 5 = unable to/extreme problems. Answers for each of the 5 dimensions at each visit where the variable is measured will be listed for each participant.

The EQ VAS provides a quantitative measure of the participant's perception of their overall health. The EQ VAS scales will be listed by visit.

[redacted]

8. SAFETY AND TOLERABILITY

Appendix A provides a list of data displays.

8.1. Adverse Events

8.1.1. Adverse Event Definitions

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after the first dose of study drug until 30 days after the last dose of study drug. Analysis of AEs (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study drug administration. For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment-emergent.

Adverse events will be tabulated by MedDRA PT and system organ class. Severity of AEs will be graded using the NCI CTCAE v5.0. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

The subset of AEs considered by the investigator to be related to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, the AE will be considered to be treatment-related.

8.1.2. Adverse Event Listings

The following listings will be produced:

- AEs
- Grade 3 or higher AEs
- Serious AEs
- Treatment-related AEs
- AEs with a fatal outcome
- AEs leading to study drug dose interruption, reduction, or discontinuation

8.2. Clinical Laboratory Tests

8.2.1. Laboratory Value Definitions

Laboratory values will be listed by visit. Baseline will be determined according to Section 4.1.3. If there are multiple values that meet the criteria for baseline, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline.

Any laboratory test results and associated normal ranges from local laboratories will be converted to SI units. Laboratory test values will be assessed for severity based on the numerical component of CTCAE v5.0.

8.2.2. Potential Hy's Law Events

Participants with elevated alanine aminotransferase or aspartate aminotransferase > 3 × ULN range and alkaline phosphatase < 2 × ULN range accompanied by total bilirubin > 2 × ULN range at the same visit will be listed by treatment group.

8.3. Vital Signs

Values at each scheduled visit, change, and percentage change from baseline for vital signs, including systolic blood pressure, diastolic blood pressure, pulse, temperature, respiratory rate, and weight will be listed.

Criteria for clinically notable vital sign abnormalities are defined in Table 6. For participants exhibiting clinically notable vital sign abnormalities, the abnormal values will be listed along with their assigned treatment group. Alert vital signs are defined as an absolute value outside the defined normal range and percentage change greater than 25%. Note that the definition of alert vital signs does not apply for body temperature and weight. The abnormal values for participants exhibiting alert vital sign abnormalities will be listed.

Table 6: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 45 bpm
Temperature	> 38°C	< 35.5°C
Respiratory rate	> 24 breaths/min	< 8 breaths/min

8.4. Electrocardiograms

Twelve-lead ECGs including heart rate, PR, QT, QRS, QTc intervals will be obtained for each participant during the study. Values at each scheduled visit, change, and percentage change from baseline will be listed for each ECG parameter. Baseline will be determined as the average of all nonmissing values before the first administration of pemigatinib or pembrolizumab, gemcitabine plus cisplatin.

Criteria for clinically notable ECG abnormalities are defined in Table 7. Participants exhibiting clinically notable ECG abnormalities will be listed with study visit and assigned treatment group. Alert ECG are defined as an absolute value outside the defined range and percentage change greater than 25% (QRS 30%). The abnormal values for participants exhibiting alert ECG abnormalities will be listed. Outliers of QT and QTc values, defined as absolute values > 450 milliseconds and > 500 milliseconds, or change from baseline > 30 milliseconds, will be summarized.

Table 7: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
PR	> 220 ms	< 75 ms
QT	> 500 ms	< 300 ms
QRS	> 120 ms	< 50 ms
QTc	> 460 ms	< 295 ms
Heart rate	> 100 beats/min	< 45 beats/min

9. INTERIM ANALYSES

Not applicable.

10. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 8.

Table 8: Statistical Analysis Plan Versions

SAP Version	Date
Original	23 FEB 2021

10.1. Changes to Protocol-Defined Analyses

A decision was made to terminate enrollment, and fewer than 10 participants were enrolled into the study. Therefore, an interim futility analysis will not be conducted, and only listings will be provided for the final analysis.

10.2. Changes to the Statistical Analysis Plan

Not applicable.

11. REFERENCES

Balar AV, Castellano D, O'Donnell PH, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. Lancet Oncol 2017;18:1483-1492.

De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol 2012;30:191-199.

Food and Drug Administration. Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2018.

Mosteller RD. Simplified calculation of body surface area. N Engl J Med 1987;317:1098.

APPENDIX A. PLANNED LISTINGS

This appendix provides a list of the planned listings for the Clinical Study Report.

The list of listings is to be used as a guideline. Modifications of the list that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

Listings

Listing No.	Title
2.1.1	Participant Enrollment and Disposition Status
2.1.2	Participant Inclusion and Exclusion Criteria Violations
2.2.1	Protocol Deviations
2.3.1	Analysis Population
2.4.1	Demographic and Baseline Characteristics
2.4.2	Disease History
2.4.3	Tobacco
2.4.4	Prior Radiation Treatment
2.4.5	Prior Systemic Therapy
2.4.6	Prior Surgery or Surgical Procedure
2.4.8	Medical History
2.4.9	Prior and Concomitant Medication
2.4.10	FGF/FGFR Alteration
2.5.1	Study Drug Compliance
2.5.2	Study Drug Administration
2.6.1	Deaths
2.6.2	Best Overall Response, Duration of Response, Progression-Free Survival, and Overall Survival
2.6.3	Overall Response Assessment by Visit
2.6.4	Response Assessment: Target Lesions
2.6.5	Response Assessment: Nontarget Lesions
2.6.6	Response Assessment: New Lesions
2.6.7	EORTC QLQ-C30 Score
2.6.8	EQ-5D-5L Score
2.6.9	Tumor Tissue
2.6.10	ECOG Status
2.7.1	Adverse Events
2.7.2	Serious Adverse Events
2.7.3	Grade 3 and Higher Adverse Events
2.7.4	Fatal Adverse Events
2.7.5	Treatment-Related Adverse Events
2.7.6	Adverse Events Leading to Interruption, Reduction, or Discontinuation of Study Drug
2.8.1	Clinical Laboratory Values - Hematology
2.8.2	Clinical Laboratory Values - Chemistry
2.8.3	Clinical Laboratory Values - Coagulation
2.8.4	Clinical Laboratory Values - Urinalysis
2.8.5	Abnormal Clinical Laboratory Values - Hematology
2.8.6	Abnormal Clinical Laboratory Values - Chemistry

Listing No.	Title
2.8.7	Abnormal Clinical Laboratory Values - Coagulation
2.8.8	Abnormal Clinical Laboratory Values - Urinalysis
2.8.9	Possible Hy's Law Cases
[redacted]	[redacted]
[redacted]	[redacted]
2.9.1	Vital Signs
2.9.2	Abnormal Vital Sign Values
2.9.3	Alert Vital Sign Values
2.10.1	12-Lead ECG Values
2.10.2	Abnormal 12-Lead ECG Values
2.10.3	Alert 12-Lead ECG Values
2.11.1	Eye Examination
2.11.2	Optical Coherence Tomography