Protocol Title: A Phase 1/2 open-label, biomarker-defined cohort trial to evaluate the safety, determine the recommended combination dosing, and assess early antitumor activity of tipifarnib and alpelisib for the treatment of adult participants who have HRAS-overexpressing and/or PIK3CA-mutated and/or -amplified recurrent/metastatic head and neck squamous cell carcinoma (the Kurrent trial)

Protocol Number: KO-TIP-013

NCT Number: NCT04997902

Protocol Approval Date: 09 October 2025

CLINICAL TRIAL PROTOCOL

Protocol Title: A Phase 1/2 open-label, biomarker-defined cohort trial to evaluate the safety, determine the recommended combination dosing, and assess early antitumor activity of tipifarnib and alpelisib for the treatment of adult participants who have HRAS-overexpressing and/or PIK3CA-mutated and/or -amplified recurrent/metastatic head and neck squamous cell carcinoma (the Kurrent trial)

Protocol Number: KO-TIP-013

Compounds: Tipifarnib, alpelisib

Brief Title: Phase 1/2 combination trial of tipifarnib and alpelisib to determine the safety and recommended dose and regimen for the treatment of adult HNSCC participants whose tumors are dependent on HRAS protein and/or are PIK3CA-mutated and/or -amplified

Trial Phase: 1/2

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Approval Date:	09 October 2025 Electronic signature appended to end of document

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 1/2 open-label, biomarker-defined cohort trial to evaluate the safety, determine the recommended combination dosing, and assess early antitumor activity of tipifarnib and alpelisib for the treatment of adult participants who have HRAS-overexpressing and/or PIK3CA-mutated and/or -amplified recurrent/metastatic head and neck squamous cell carcinoma (the Kurrent trial)

Brief Title: Phase 1/2 combination trial of tipifarnib and alpelisib to determine the safety and recommended dose and regimen for the treatment of adult HNSCC participants whose tumors are dependent on HRAS protein and/or are PIK3CA-mutated and/or -amplified

Rationale:

Understanding the interdependencies of key cellular pathways may be particularly important in designing combination regimens, an example being the codependency of the Harvey rat sarcoma virus gene homolog (HRAS) and phosphoinositide 3-kinase (PI3K) pathways. HRAS activates PI3K 5-fold more efficiently than Kirsten rat sarcoma virus gene homolog (KRAS), while KRAS is a more efficient activator of RAF (Yan et al, 1998).

Furthermore, mutant HRAS requires PI3K for activity, and is insufficient to be tumorigenic in isolation (Gupta et al, 2007). Similarly, mutant PI3K requires RAS to drive tumor biology (Zhao and Vogt, 2008). Recognition of these interdependencies was the basis for the evaluation of head and neck squamous cell carcinoma (HNSCC) patient-derived xenograft (PDX) models, where the tumor was dependent on HRAS and/or phosphatidylinositol-4,5- bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), as evidenced by the presence of HRAS mutations, HRAS overexpression, PIK3CA amplification, and/or PIK3CA mutations.

Among RAS isoforms, inhibition of the farnesylation of KRAS and neuroblastoma RAS virus oncogene homolog (NRAS) leads to their geranylgeranylation and unchanged membrane localization. HRAS, however, cannot be geranylgeranylated, and its membrane localization and cellular function is suppressed by farnesyltransferase inhibitors (FTIs) (Whyte et al, 1997).

Consequently, HRAS-mutant/-driven tumors are highly sensitive to FTIs. The FTI tipifarnib was therefore selected for PDX experiments to further explore tumors with HRAS and/or PIK3CA dependencies, as was the PI3Kα-selective inhibitor BYL719 (alpelisib).

Each of the PDX models (HRAS-mutant, HRAS wild type-overexpressed, PIK3CA-amplified, and PIK3CA-mutant) was treated with either vehicle, tipifarnib, BYL719, or the tipifarnib-BYL combination. The results across models consistently demonstrated additive or synergistic effects CCI Ultimately, the results confirm the codependency of these pathways, and provide robust rationale for investigating this combination in the clinic.

Objectives and Endpoints:

Each of the objectives and endpoints applies independently to each of the 2 biologically defined cohorts. Each cohort will be treated and assessed separately. Therefore, the objectives will be analyzed in both the PIK3CA-mutated and/or -amplified cohort and the HRAS-overexpressed cohort. Efficacy variables will be assessed by Investigators, based upon local radiology assessments and per RECIST v1.1.

Objectives	Endpoints
Primary	
• To determine the recommended dose and regimen, and evaluate the safety and tolerability of the combination of tipifarnib and alpelisib	• Rate of DLTs per dose level • Descriptive statistics of adverse events per the NCI CTCAE v5.0
Secondary	
• To determine the ORR	• Overall confirmed response rate (CR + PR) ○ Median duration of response
• To determine the disease control rate (DCR)	• Disease control rate (CR + PR + SD) ○ Median duration of disease control • Rate of SD ○ Median duration of SD
• Pharmacokinetics of tipifarnib and alpelisib when administered in combination	• Single dose: C_{max}, T_{max}, $AUC_{(0\text{-}last)}$, $AUC_{(tau)}$, $AUC_{(0\text{-}infinity)}$, CL/F, V_d/F, half-life • Multiple dose: C_{max}, T_{max}, $AUC_{(0\text{-}last)}$, $AUC_{(tau)}$, CL/F, V_d/F, half-life, accumulation ratio
• To determine the antitumor activity in terms of PFS and rate of PFS at 6 months	• Median PFS • Proportion of participants alive and without progression at 6 months
• To estimate the OS and rate of OS at 12 months	• Median OS • Proportion of participants alive at 12 months
Exploratory	
• Evaluate biomarkers related to HNSCC biology and their potential correlation to efficacy, and resistance to study medications.	• Prevalence of genetic alterations in tumor tissue and circulating tumor DNA (ctDNA)

CCI

[redacted]

Abbreviations: $AUC_{(0\text{-}infinity)}$=area under the concentration-time curve from time zero to infinity; $AUC_{(0\text{-}last)}$=area under the concentration-time curve from time zero to time of last measurable concentration; $AUC_{(tau)}$=area under the concentration-time curve during a dosage interval; CL/F=apparent total clearance of the drug after administration; C_{max}=maximum (peak) drug concentration; CR=complete response; CTCAE=Common Terminology Criteria for Adverse Events; DLT=dose-limiting toxicity; NCI=National Cancer Institute; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; SD=stable disease; T_{max}=time to reach maximum (peak) concentration following drug administration; V_d/F=apparent volume of distribution after administration.

Brief Summary:

The purpose of this trial is to evaluate the safety of the combination of tipifarnib and alpelisib, determine the recommended combination dose(s) and regimen, and evaluate preliminary signs of clinical activity in treating participants with HNSCC whose tumors overexpress the HRAS protein and/or are PIK3CA-mutated and/or -amplified.

Trial duration: Approximately 2 years (6 months from Cycle 1 Day 1 dosing of last participant).

Treatment duration: Until a participant experiences an intolerable toxicity, or other criteria for treatment discontinuation are met (treatment may proceed longer than 6 months if clinical benefit continues). If there is disease progression as an overall response at any time during the trial, the Investigator may continue treatment at their discretion if the participant is experiencing clinical benefit. For **Protocol Amendment 3**, participants will be discontinued at the time of disease progression.

Visit Frequency: Approximately Monthly.

Condition/disease: Recurrent/metastatic (R/M) HNSCC that overexpresses the HRAS protein and/or is PIK3CA-mutated and/or -amplified.

Trial hypothesis: The combination of tipifarnib and alpelisib is tolerable, with an optimal biologically active dose (OBAD) that is most likely to result in at least a CCI objective response rate (ORR) while maintaining a DLT rate CCI, as determined using Bayesian logistic regression modeling (BLRM).

Method of Observation: Computed tomography (CT) scans performed at 4, 8, or 12-week intervals (interval dictated by time on trial) and assessed locally according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. For **Protocol Amendment 3**, participants will be assessed according to the treatment facility's local standard of care.

Overall Design:

This is a Phase 1/2, open-label, 2 drug dose escalation trial to evaluate the safety of the combination of tipifarnib and alpelisib and to determine recommended combination dosing regimen of the FTI tipifarnib in combination with the PI3Kα inhibitor alpelisib in adult participants with R/M HNSCC who meet criteria for at least 1 of 2 biomarker-defined cohorts, as follows:

1. Tumors harboring PIK3CA (activating) mutations and/or amplifications as determined by local or central next generation sequencing (NGS) on a tumor tissue biopsy (cohort 1); and
2. Tumors with increased HRAS dependency based on HRAS overexpression as determined using the Sponsor's central laboratory (cohort 2).

The initial dosing cohort will be 600 mg/day of tipifarnib (300 mg twice daily [BID]) and 200 mg of alpelisib once each morning (QAM).

Each biomarker cohort will be conducted in parallel and independent of the other biomarker cohort, though safety information for the combination may influence the dosing of both biomarker cohorts. In the event the biomarker cohorts do not open for enrollment at the same time, dosing levels previously deemed safe by the SMC for one biomarker cohort do not need to be re-evaluated in the other biomarker cohort.

Each biomarker cohort will be analyzed separately. The BLRM approach will be utilized in the trial to characterize safety, tolerability, and clinical activity of the combination of tipifarnib and

alpelisib with the goal of identifying an OBAD (Neuenschwander et al, 2014). This approach uses joint binary toxicity and efficacy endpoint models for each individual agent (tipifarnib and alpelisib) in conjunction with a combination agent modeling approach to provide dose recommendations for both tipifarnib and alpelisib. This strategy will be used in the 2-drug dose escalation/de-escalation design to determine the safest and most effective combination dosing regimen for each biomarker-defined cohort, while minimizing the potential for subtherapeutic dosing. Investigator assessment of the toxicity and efficacy for each participant who receives sufficient trial intervention will be used to inform the models, and the dose escalation/de-escalation recommendations of the safety monitoring committee (SMC). The DLT period for this trial and the initial toxicity and efficacy period to inform the BLRM will be considered the first 28 days following the start of trial intervention (Figure 3).

The modeling is based upon the following endpoints:

- Endpoint 1: Binary endpoint (DLT).
- Endpoint 2: Binary endpoint (efficacy response based on overall response).
- Endpoint 3: Binary endpoint (efficacy response based on stable disease [SD]).

The safe doses will be identified using the dose-toxicity models for endpoint 1. A combination dose will be considered safe if the posterior probability of excessive toxicity at the combination dose does not exceed a pre-defined threshold of 25%. This approach to characterizing the degree of toxicity is similar to the escalation with overdose control (EWOC) principle (Babb et al, 1998; Rogatko et al, 2007) that is commonly applied in dose escalation trials to control the risk of exposing participants to toxic doses.



Number of Participants:

It is recommended that approximately 20 participants per biomarker cohort be enrolled, complete the DLT period, and be evaluable for the model to have reasonable operating characteristics for its OBAD recommendation. To be evaluable, a participant must meet all eligibility criteria, have received at least 75% of the planned dose for each trial intervention, and completed the first efficacy assessment after Cycle 1 Day 28; however, any event meeting DLT criteria experienced prior to the completion of the 28 days will be considered a DLT. If a participant is dosed and experiences a DLT, that participant will not be replaced and will complete associated efficacy scans and assessments to inform the model.

Intervention Groups and Duration:

The total trial duration is estimated to last approximately 2 years (approximately 6 months from cycle 1 Day 1 dosing of last participant), and will consist of the following:

- Prescreening for HRAS overexpression and PIK3CA mutation/amplification (can occur at any timepoint once the prescreening informed consent is signed until enrollment into one of the respective biomarker-defined cohorts).
- Screening to determine eligibility to last up to 28 days. Treatment will continue until a participant experiences intolerable toxicity, or other criteria for treatment discontinuation

are met (treatment may proceed longer than 6 months if clinical benefit continues). If there is disease progression as an overall response at any time during the trial, the Investigator may continue treatment at their discretion if the participant is experiencing clinical benefit. For **Protocol Amendment 3**, participants will be discontinued at the time of disease progression.

- If a participant discontinues treatment for any reason, the remainder of trial participation will involve survival follow-up and collection of subsequent therapy information. This OS follow-up will continue until end of trial or withdrawal of consent. For **Protocol Amendment 3,** end of treatment (EOT) will also be considered as end of trial, and there will be no survival follow-up.

CCI a simultaneous dosing regimen for tipifarnib and alpelisib will be explored (Figure 2). CCI

The simultaneous dosing regimen will involve:

- Tipifarnib dosed BID for 1 week alternating (days 1-7 and 15-21) with 1 week of rest (days 8-14 and 22-28) in a 28-day cycle
- Alpelisib dosed QAM each day of a 28-day cycle

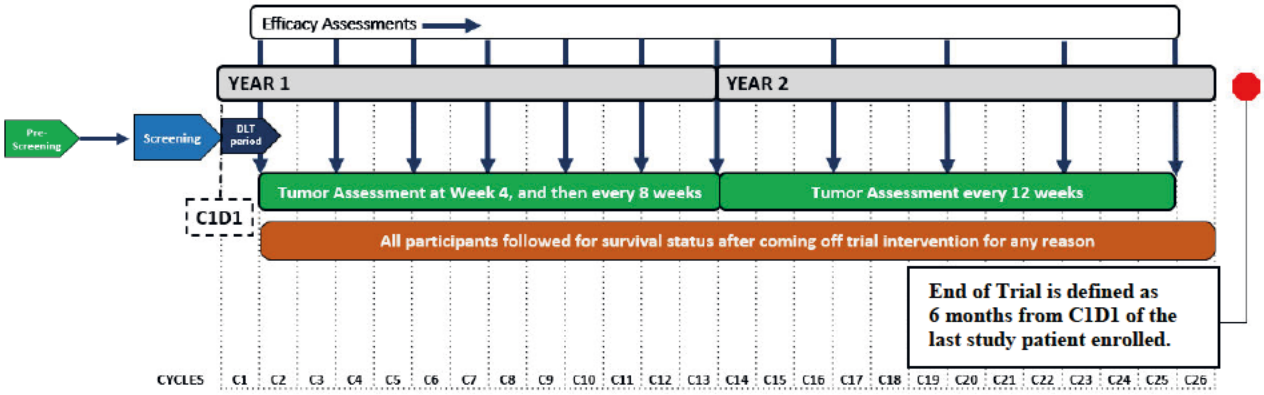
Safety Monitoring Committee:

An SMC composed of Investigators, Sponsor personnel, and independent advisor(s) will review data to assess the safety of the combination and provide recommendations on dose escalation/ de-escalation, expanding current dose, and CCI as clinical data are accumulated for the dose escalation portion of the trial.

At least 2 participants must be enrolled into each dosing cohort and be evaluable (per the DLT period definition) prior to each SMC meeting (unless a DLT occurs that would require the SMC to meet earlier). The SMC members may recommend enrolling more than 2 participants into any given dosing cohort to account for participants who may not be evaluable. Additional details are available in the SMC Charter.

1.2 Schema

Figure 1 Overall Trial Design



Abbreviations: Cx=Cycle x; CxDy=Cycle X Day y; DLT=dose-limiting toxicity

Figure 2 Dose Regimen

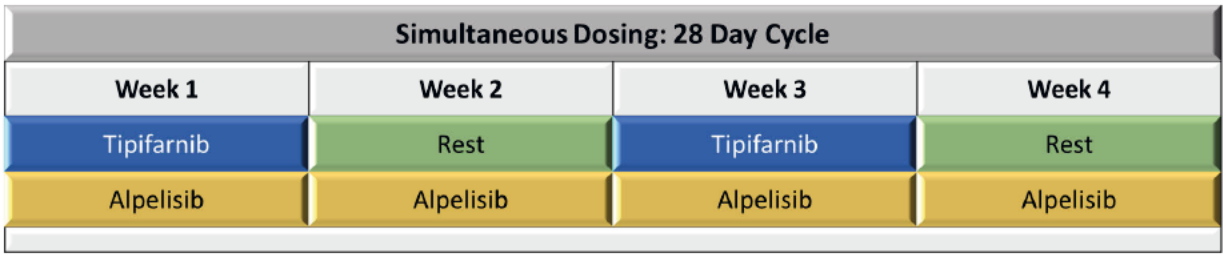
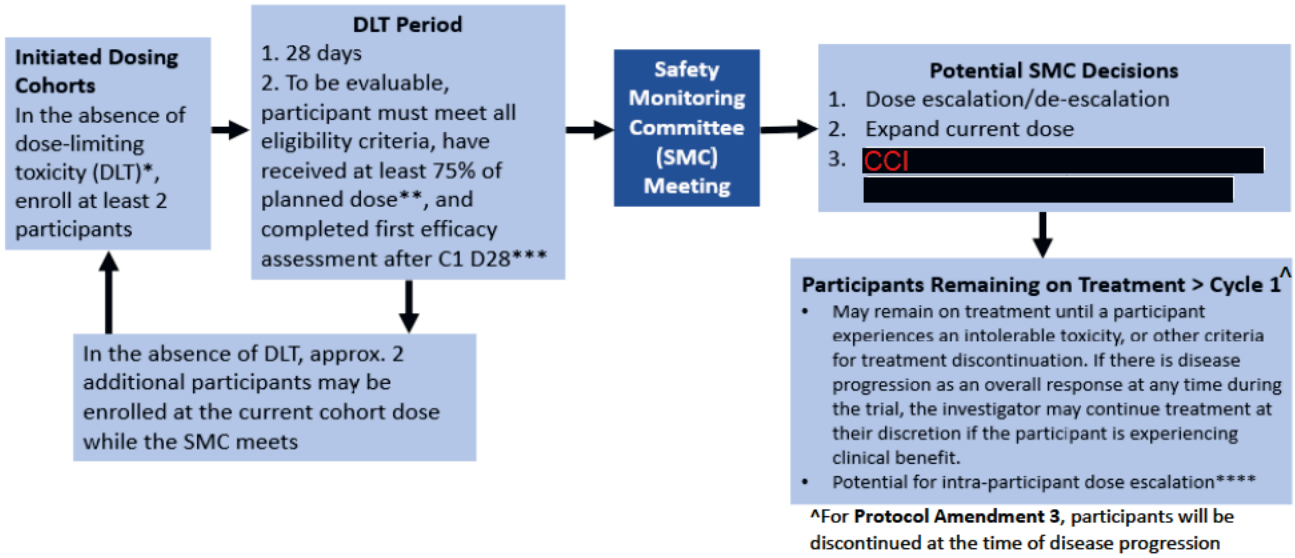


Figure 3 Dose Escalation



* If a DLT occurs, proceed to SMC.
** 75% of planned dose for tipifarnib=10.5/14 days; alpelisib=21/28 days
*** Any event meeting DLT criteria experienced prior to the completion of the 28 days will be considered a DLT. If a participant is dosed and experiences a DLT, that participant will not be replaced and will complete associated efficacy scans and assessments to inform the model.
**** The following criteria may be used to determine if intra-participant dose escalation should occur: Higher proposed dose has been declared safe and demonstrates an increased potential for clinical benefit (compared to lower doses) as assessed by the SMC, participant has not experienced any significant or grade 3 or higher related AEs, has completed a minimum of 12 weeks of starting treatment (3 cycles), and the request for intra-participant dose escalation must be discussed and approved by the medical monitor.

1.3 Schedule of Activities: Prescreening for HRAS Overexpression and PIK3CA Mutation/Amplification

Activity	Pre-Screening[1]
ICF for prescreening for HRAS overexpression and PIK3CA mutation/amplification[2]	X
Tumor tissue for HRAS[3] and PIK3CA testing[4]	X
Disease status at prescreening	X
Demographics[5]	X
Disease-specific history[6]	X
Prior anticancer therapy for HNSCC[7]	X
SAE Assessment[8]	X

Abbreviations: CLIA=Clinical Laboratory Improvement Amendments; HNSCC=head and neck squamous cell carcinoma; HPV=human papillomavirus; HRAS=Harvey rat sarcoma viral oncogene homolog; ICF=informed consent form; PIK3CA=phosphatidylinositol-4,5-biphosphate 3-kinase catalytic subunit alpha; R/M=recurrent/metastatic; SAE=serious adverse event.

If a participant is determined to have PIK3CA mutation and/or amplification and/or HRAS overexpression, the participant will have the option to sign the main ICF for KO-TIP-013 trial and complete all screening procedures (Section 1.4 Schedule of Activities). If eligible, participant will enroll into the respective biomarker-defined cohort.

1. Prescreening for HRAS overexpression and PIK3CA mutation/amplification can be done at any time prior to enrollment into one of the biomarker-defined cohorts. Prescreening should be performed on tumor tissue taken after the most recent progression. However, tumor tissue obtained prior to the most recent progression may be used with sufficient justification (Section 8.1.1).
2. Specimen characteristics for the tumor sample being tested (eg, anatomic biopsy site and collection method) and data on HRAS, PIK3CA, and other genetic alterations will be collected for participants who sign the prescreening ICF.
3. HRAS testing for overexpression will be based on the results of a validated test run in the Sponsor-designated central laboratory. Local testing for HRAS overexpression will not be permitted.
4. PIK3CA testing may occur in the Sponsor-designated CLIA central laboratory or through local PIK3CA testing at a Sponsor-approved CLIA-certified laboratory (or local equivalent). *Note: if local PIK3CA testing report is available from a Sponsor-approved laboratory, additional PIK3CA testing by the central laboratory is not necessary.*
5. Demographic information will be collected from all participants who sign the prescreening ICF regardless of biomarker results.
6. If HRAS overexpression and/or PIK3CA mutation/amplification are identified during prescreening, disease-specific history will be collected which includes primary diagnosis (date of initial diagnosis, stage of disease at diagnosis, anatomical disease site(s) at diagnosis), current stage of disease, date of recurrence/metastasis, smoking and betel nut exposure history, alcohol use, HPV status, and other relevant disease-related medical history, including biopsy reports. Disease status at study entry will also be collected (tumor and anatomical disease site).

7. If HRAS overexpression and/or PIK3CA mutation/amplification are identified during prescreening, prior anticancer therapy for HNSCC will be collected which includes line of anticancer therapy, name, dates (start, end), treatment outcome (response and response criteria), duration of response (if available), and date of progression. Additionally, information will be collected specific to line treatment for R/M HNSCC, including anatomical disease site(s) and performance status at the time of first-line anticancer therapy for R/M disease. Information will also be collected on prior cancer surgery for HNSCC including date(s) of surgery. Information will be collected on prior/current radiological treatments for HNSCC including anatomical site(s) and date(s) of radiation treatment.
8. SAE(s) assessed from signing the prescreening ICF until biomarker status is determined and the participant is either a screen fail at prescreening or signs the main ICF for the KO-TIP-013 trial.

1.4 Schedule of Activities

*Note: Footnotes related to **Protocol Amendment 3** appear in **bold font***

Procedure	Screening (Up To 28 Days Before Day 1)[1]	Within 72 hours of Cycle 1 Day 1[9]	Intervention Period					Treatment Continuation Visit (Protocol Amendment 3) Day 1 (+2d) of Cycle X	EOT Visit[3,4]
			Day 1 (+2d) of Cycle X	Day 2 of Cycle 1 and Cycle 2	Day 7 (±2d) of Cycle 1	Day 15 (±2d) of Cycle 1 and Cycle 2	Tumor Response Assessment Visit[2]		
Informed consent	X								
Inclusion and exclusion criteria	X								
Confirmation of measurable disease per RECIST v1.1 by local radiology	X[5]								
Prior medical illnesses and conditions and prior surgical procedures	X								
Disease status at study entry	X								
Prior and concomitant medications	X	X	X	X	X	X	X	X[8]	X[7]
AE assessment[6,7]	X	X	X	X	X	X	X	X[8]	X[7]
Full physical examination	X								
Symptom-based/focused physical examination		X[9]	X[9]		X			X[9]	
Height	X								
Weight	X	X[9]	X[9]					X[9]	X
Vital signs[10]	X	X[9]	X[9]		X		X	X[10]	X
Triplicate 12-lead ECG[15]	X		X[15]						
ECOG performance status	X	X[9]	X[9]					X	X
Pregnancy test (WOCBP only)[11]	X	X[12]	X[12]						X

Procedure	Screening (Up To 28 Days Before Day 1)[1]	Within 72 hours of Cycle 1 Day 1[9]	Intervention Period					Treatment Continuation Visit (Protocol Amendment 3)	EOT Visit[3,4]
			Day 1 (+2d) of Cycle X	Day 2 of Cycle 1 and Cycle 2	Day 7 (±2d) of Cycle 1	Day 15 (±2d) of Cycle 1 and Cycle 2	Tumor Response Assessment Visit[2]	Day 1 (+2d) of Cycle X	
Laboratory tests (include fasting glucose and other tests specific in APPENDIX 1)[13,14]	X	X[14]	X[9]		X	X	X	X[13,14]	X
Urinalysis	X								
CCI									
CCI									
Blood samples for PK[18,19]			X	X			X[20]		
Radiographic imaging[2]	X						X	X[2,8]	
Tumor tissue for PIK3CA testing[21]	X								
Tumor tissue for central HRAS testing[22]	X								
CCI									
Post-baseline tumor biopsy (optional)[24]							X		
Drug accountability and diary review			X[25]			X		X	X
Collection of survival and subsequent anticancer treatment information[26]									
Photographs (optional)[27]	X		X				X		X
Tipifarnib provision[28]			X					X[9,28]	
Alpelisib provision[28]			X					X[9,28]	

Abbreviations: AE=adverse event; BID=twice daily; CLIA=Clinical Laboratory Improvement Amendments; d=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EOT=end of treatment; HbA1c=hemoglobin A1c; HNSCC=head and neck squamous cell carcinoma; HRAS=Harvey rat sarcoma virus gene homolog; ICF=informed consent form; CCI PIK3CA=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PK=pharmacokinetic; QAM=each morning; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; TEAE=treatment-emergent adverse event; WOCBP=women of childbearing potential.

Note: Assessments may be performed at additional time points if clinically indicated per the discretion of the Investigator.

1. Evaluations performed as part of the standard of care up to 28 days before dosing (prior to trial-specific [main ICF] consent signature) do not need to be repeated. Testing for presence of HRAS overexpression and/or PIK3CA mutations/amplifications may be performed at any time once the prescreening ICF has been signed and prior to enrollment into one of the biomarker-defined cohorts.
2. First tumor response assessment will occur at week 4 (+ 5 days) and subsequently should occur approximately every 8 weeks (± 5 days) for the first 12 months of participation in the trial (through and including cycle 13); thereafter, tumor response assessment should occur approximately every 12 weeks (± 5 days) until disease progression or other criteria for treatment discontinuation are met. If evaluations required at the tumor response assessment are completed within 5 days of the Day 1 visit of the next cycle, it is not necessary to repeat the Day 1 assessments, with the exception of collection of AEs, PK, and concomitant medications. The imaging schedule (week 4 then every 8 weeks or every 12 weeks) should be maintained regardless of dosing delays or additional imaging assessments performed. Imaging performed during the screening period for the purpose of tumor assessment should be reviewed to confirm that there are no relevant pulmonary complications present that might exclude the participant from the trial. **Participants will be managed per the treatment facility's/local standard of care (Protocol Amendment 3).**
3. An EOT visit will be conducted approximately 30 days (± 7 days) after the last dose of tipifarnib/alpelisib or immediately before the initiation of any other anticancer therapy, whichever occurs first **(this may occur as a site visit or a telephone call); EOT will also be considered as end of trial (Protocol Amendment 3).**
4. Survival follow-up should occur approximately every 12 weeks (± 5 days) from EOT visit until death or end of trial. **For participants continuing treatment beyond 6 months intervention period (Protocol Amendment 3), the EOT visit will also be considered the end of trial, and there will be no survival follow-up.**
5. Baseline imaging is preferred to be done within the screening period (up to 28 days before Cycle 1 Day 1), but imaging conducted prior to the screening period (up to 60 days prior to Cycle 1 Day 1) will be accepted if done subsequent to the most recent progression.
6. AE(s) assessed from first dose; SAE(s) assessed from signing the ICF; all S/AE(s) followed through approximately 30 days after treatment discontinuation.
7. Assessments of AEs and concomitant medications may also be conducted if adverse events were not resolved at the time of the EOT visit; **the EOT visit will also be considered the end of trial (Protocol Amendment 3).**
8. **TEAEs, SAEs, response assessments, concomitant medications, and drug administration will be documented in the eCRF. The safety data (TEAEs and SAEs) will continue to be collected until 30 days after the last dose of study drug or until the patient starts a new anticancer therapy, whichever occurs first.**
9. Assessments on Cycle 1 Day 1 are to occur prior to tipifarnib and alpelisib dosing. Note: Assessments that are completed within 72 hours of the Cycle 1 Day 1 visit do not need to be repeated at the Day 1 visit with the exception of concomitant medications and AE assessment. Labs must be reviewed (serum chemistry and hematology) prior to dosing at Cycle 1 Day 1 to confirm participant remains eligible. Thereafter, labs (serum chemistry and hematology) should be drawn within 72 hours and preferably within 24 hours prior to every Cycle X Day 1 to assess if the participant may continue treatment. Efforts should be made to ensure results are available prior to dosing. Note: Participants should not continue on treatment if lab results are not available by Cycle X Day 1. Investigators should notify participants once lab results are available, if drug interruption or modification is necessary.
10. Vital signs to include heart rate, blood pressure, respiratory rate, and temperature.
11. Pregnancy testing will be performed in females of childbearing potential. Testing will be performed in serum at screening and may be performed on urine or serum thereafter. If a positive urine pregnancy test is obtained, a confirmatory serum pregnancy test should be conducted. If confirmatory test is positive, participant must terminate tipifarnib and alpelisib treatment immediately and follow pregnancy reporting guidelines outlined in the protocol. Pregnancy testing will be performed locally at the clinical site or its reference laboratory.
12. Female participants of childbearing potential must have a negative serum pregnancy test within 72 hours prior to start of trial intervention (Cycle 1 Day 1). Pregnancy testing done within 72 hours of dosing may be used for Cycle 1 Day 1.

13. Participants are required to fast for a minimum of 8 hours prior to blood collection for fasting glucose, lipid panel and amylase/lipase levels. Water, coffee or tea (unsweetened and without milk) is allowed during all fasting periods; however, juice is not permitted during the fasting period.
14. Lab investigations (serum chemistry and hematology) should be completed and reviewed within 72 hours of Cycle 1 Day 1 (local laboratory). to confirm participant continues to meet eligibility prior to first dosing. Laboratory tests as listed in APPENDIX 1. Fasting blood glucose required. Note: HbA1c is only required to be obtained during screening.
15. ECGs should be done at screening, prior to first dose on Cycle 1 Day 1, on Cycle 1 Day 1 at approximately CCI and again on Cycle 2 Day 1 at any timepoint. ECGs can be done at any time point if clinically indicated. ECGs should be performed in triplicate no more than 5 minutes apart after the participant has been supine for 10 minutes. ECGs are to be read locally by the Investigator.
16. CCI
17. CCI
18. The time windows for PK blood sample collection are further detailed in Section 8.5. Actual time of sample collection should be recorded. Date, time, and dosage of most recent tipifarnib and alpelisib dose relative to the PK blood sample should also be recorded. Detailed PK blood sample collection, storage and shipping procedures will be provided in a separate lab manual.
19. CCI
20. PK samples are to be collected during the first 2 tumor response assessment visits (approximately 4 weeks and 12 weeks from the start of trial intervention) only and may be collected at any time during these tumor response assessment visits.
21. Eligibility for cohort 1 (PIK3CA mutation/amplification) will be based on the results of a validated NGS test performed by a Sponsor-approved CLIA-certified laboratory or the Sponsor-designated central CLIA-certified laboratory. PIK3CA testing for eligibility will be performed as part of prescreening for the KO-TIP-013 trial unless PIK3CA testing was previously performed as part of the patient's routine clinical care. Participants enrolled in cohort 1 (PIK3CA) should submit archival or fresh tumor tissue within 14 days after starting the first dose for central assessment of HRAS overexpression (see Laboratory Manual for details).
22. Eligibility for cohort 2 (HRAS overexpression) will be based on the results of a validated test run in the Sponsor-designated central CLIA-certified laboratory. HRAS testing for eligibility can be performed as part of prescreening for the KO-TIP-013 trial. Participants enrolled in cohort 2 (HRAS overexpression) should submit archival or fresh tumor tissue within 14 days after starting the first dose for central assessment of PIK3CA status unless PIK3CA status was previously determined by a Sponsor-approved CLIA-certified laboratory and the complete test results are made available to the Sponsor (see Laboratory Manual for details).
23. CCI
24. Effort should be made to collect a tumor biopsy to coincide with tumor assessments and/or at the time of disease progression.
25. Assessment to begin starting at cycle 2.
26. Beginning at the time of the EOT visit, follow-up contact with the participant and/or caregiver(s) (eg, electronic technology-based, telephone or in person) is to occur approximately every 12 weeks (± 1 week) for survival and the use of subsequent anticancer therapy until either death or end of trial. **An EOT visit will be conducted approximately 30 days (± 7 days) after the last dose of tipifarnib/alpelisib or immediately before the initiation of any other anticancer therapy, whichever occurs first (this may occur as a site visit or a telephone call); EOT will also be considered as end of trial, and there will be no survival follow-up (Protocol Amendment 3).** Information on survival and subsequent anticancer therapy for HNSCC will be collected including name, dates (start, end), treatment outcome (response and response criteria), duration of response, date of progression. Information will also be collected on subsequent cancer surgery(ies) for HNSCC including date of surgery. Information will be collected on subsequent radiological treatments for HNSCC including anatomical site(s) and date(s) of radiation treatment.
27. For visible tumors, optional documentation of tumor at regular intervals. Additional photographs may be taken at the judgment of the Investigator.

28. Except for Cycle 1 Day 1 and days on which the site otherwise coordinates on-site dosing with the participant (eg, days on which there are PK assessments [cycle 2, Day 1]), participants will self-administer tipifarnib BID (approximately every 12 hours, at the same time every morning and evening) and alpelisib QAM with a meal as per appropriate dosing schedule. The interval between tipifarnib dosing should not be less than 8 hours. Time of dosing of on-site doses to be recorded.

2 INTRODUCTION

2.1 Trial Rationale

2.1.1 Head and Neck Squamous Cell Carcinoma

Head and neck squamous cell carcinoma (HNSCC) is the 7th most common invasive carcinoma, accounting for more than 830,000 new malignancy diagnoses annually, worldwide (Bray et al, 2018). Carcinogen (tobacco, alcohol) exposure and infection with the human papillomavirus (HPV) are described as the 2 major etiological causes of HNSCC, with the incidence of HPV-positive tumors rapidly on the rise (Chaturvedi et al, 2008).

High cure rates are possible for localized disease, with about 55% of patients surviving at least 5 years (American Cancer Society 2020). Regardless of etiology, once the disease has become advanced, recurrent and/or metastatic (R/M), rates of survival decrease dramatically, with only an estimated 40% of patients surviving at least 5 years (American Cancer Society 2020).

While surgical excision, chemotherapy, and radiotherapy remain mainstays of treatment, in the R/M setting, immunotherapies and targeted therapies are quickly gaining favor, especially with the approvals of pembrolizumab and nivolumab for the treatment of R/M HNSCC (Chow, 2020). Importantly, successful implementation of these therapies requires understanding of the tumor biology, and therefore biopsy and tumor genetic sequencing are increasingly considered standard of care to determine appropriate treatment options.

2.2 Background

Tipifarnib is a selective, potent, nonpeptidomimetic farnesyltransferase inhibitor (FTI) licensed from Janssen. It is well characterized with more than 5,000 participants having been treated in over 70 prior Janssen-sponsored studies. There was sporadic activity seen across indications (advanced breast cancer, metastatic pancreatic cancer, melanoma, small cell lung cancer [SCLC], myelodysplastic syndromes [MDS], multiple myeloma, urothelial tract transitional cell carcinoma, colorectal cancer, and non-small cell lung cancer [NSCLC]) (Adjei et al, 2003; Cohen et al, 2003; Johnston et al, 2003; Alsina et al, 2004; Heymach et al, 2004; Kurzrock et al, 2004; Rao et al, 2004; Rosenberg et al, 2005; Hong et al, 2011; Gajewski et al, 2012). However, methods to predict increased likelihood of response were not apparent, as these trials occurred before the advent of personalized medicine approaches.

Subsequent advances have elucidated the fact that farnesyltransferase is a critical enzyme for the function of dozens of proteins; however, because of multiple redundancies, many remain functional through compensatory mechanisms of activation. Among RAS isoforms, inhibition of the farnesylation of Kirsten rat sarcoma virus gene homolog (KRAS) and neuroblastoma RAS virus oncogene homolog (NRAS) leads to their compensatory geranylgeranylation and unchanged membrane localization (Storck et al, 2019). The Harvey rat sarcoma virus gene homolog (HRAS), however, cannot be geranylgeranylated, and its membrane localization and cellular function is therefore uniquely suppressed by FTIs (Whyte et al, 1997). Consequently, HRAS-driven tumors are highly sensitive to FTIs.

2.2.1 Mechanism of Action of Tipifarnib

Tipifarnib has been shown in vitro and in vivo to be a potent and selective inhibitor of farnesyltransferase. Isoprenylation catalyzed by geranylgeranyltransferase Type 1 is not sensitive to inhibition by tipifarnib. The mechanism of action of tipifarnib is context dependent and appears to include the inhibition of angiogenesis inhibition, induction of apoptosis, and direct antiproliferative effects.

The battery of safety pharmacology studies conducted with tipifarnib indicated no undesirable pharmacodynamic effects on physiological functions in relation to administered dosages in the therapeutic range and above. No functional changes in vital organs or systems which are likely to be of importance in clinical testing of tipifarnib were identified.

Although FTIs prevent more than 140 potential proteins from getting farnesylated, the function of many of these proteins is kept intact due to compensative prenylation through Type 1 geranylgeranyltransferase (Berndt et al, 2011). Among RAS isoforms, HRAS cannot be geranylgeranylated and its membrane localization and cellular function is suppressed by FTIs. FTIs have consistently shown high activity in HRAS-mutated tumor cell lines and in nonclinical animal models of HRAS-driven cancer, including patient-derived xenograft (PDX) models. The activity appears to be mediated by apoptosis, anti-angiogenesis, and direct effects on proliferation, with different findings predominating in different cellular contexts (Table 1). The data suggest that tipifarnib modifies tumor-host interactions important to the malignant process (End et al, 2001).

Table 1: Quantitative Image Analysis of Histological Changes Produced by Tipifarnib Treatment of Human Tumor Xenografts

Tumor (Origin)	Treatment	Apoptosis [a] ISEL	Proliferation [a] BrdU [b]/Ki-67 [c]	Angiogenesis [d] Factor VIII	Angiogenesis [d] VEGF
LoVo (colon) (End et al, 2001)	Vehicle	Tipifarnib: 1.99 ± 0.70	30.3 ± 1.67	3.26 ± 0.41	11.6 ± 1.26
	25 mg/kg	3.10 ± 0.98	25.2 ± 7.68	1.76 ± 0.39 [e]	8.88 ± 2.52
	50 mg/kg	2.90 ± 0.53	22.1 ± 8.10 [e]	1.29 ± 0.29 [e]	7.21 ± 1.54
CAPAN-2 (pancreatic) (End et al, 2001)	Vehicle	Tipifarnib: 5.54 ± 3.00	27.2 ± 2.37	2.16 ± 0.34	41.3 ± 3.90
	50 mg/kg	9.56 ± 4.26	21.9 ± 1.54 [e]	2.94 ± 0.76	41.2 ± 1.80
	100 mg/kg	10.6 ± 3.00 [e]	13.0 ± 0.93 [e]	2.43 ± 0.81	37.2 ± 2.34
C32 (melanoma) (End et al, 2001)	Vehicle	Tipifarnib: 4.38 ± 2.90	30.4 ± 16.1	6.8 ± 0.42	38.1 ± 3.07
	25mg/kg	21.7 ± 19.7 [e]	35.1 ± 14.4	6.09 ± 0.50	39.1 ± 2.88
	50 mg/kg	44.2 ± 23.6 [e]	37.7 ± 6.53	4.98 ± 0.30	36.9 ± 3.12
	100 mg/kg	42.0 ± 26.8 [e]	35.2 ± 7.16	5.13 ± 0.64	43.5 ± 4.05

Abbreviations: BrdU=bromodeoxyuridine; ISEL=in situ end labeling; SE=standard error; VEGF=vascular endothelial growth factor.

[a] Data expressed as the percentage of cells staining positive. Values are means ± standard deviation.
[b] Analysis of LoVo and CAPAN-2 tumors only.
[c] Analysis of C32 melanoma.
[d] Data expressed as the percentage area per slide with a staining signal for VEGF or Factor III. Values are medians ± SE.
[e] Statistically significant ($p<0.05$) from vehicle controls by Wilcoxon-Mann-Whitney U Test.

2.2.2 Mechanism of Action of Alpelisib

Alpelisib is an inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against PI3Kα.

In vivo, alpelisib inhibited the PI3K/Akt-signaling pathway and reduced tumor growth in xenograft models, including models of breast cancer (Fritsch et al, 2014) and HNSCC (Sheng et al, 2013, Novartis AACR 2013 poster).

In HNSCC cell lines, the combination of BYL719 (alpelisib) and cetuximab induced over 50% growth inhibition in 85% of the HNSCC lines tested, regardless of PIK3CA mutation status (Sheng et al, 2013). In mouse xenograft models, antitumor activity was observed with alpelisib, both as a single agent or in combination with cetuximab. These observations support the hypothesis that PI3K inhibition may help overcome cetuximab resistance in HNSCC. Alpelisib has been further studied in preclinical models with HNSCC cell lines and has showed activity against mutated and wild type cells (Sheng et al, 2013; Keam et al, 2015; Ruicci et al, 2019; Meister et al, 2019).

2.2.3 Consideration of Gender Effect

The impact of gender on the pharmacokinetics of alpelisib was evaluated with a population PK approach. Due to the SOLAR-1 study enrolling primarily females (one male was randomized), this assessment was based on the Phase I population PK model. The analysis included 52 (21.2%) males and 193 (78.8%) females from Phase I studies CBYL719X1101 (in participants from Japan with advanced solid tumors) and CBYL719X2101 (as a first-in-human dose escalation and expansion study) single agent and fulvestrant (estrogen receptor antagonist antineoplastic agent) combination data. In the final model, males had a 35% higher clearance (CL) compared to females, leading to a reduction in AUC by ~25% compared to a female with the same covariates. While exposure-response analysis in PIK3CA-mutant, ER (estrogen receptor)-positive, HER2 (human epidermal growth factor receptor)-negative metastatic breast cancer indicated relationships between exposure (PK exposure and dose intensity) and safety (hyperglycemia, rash) and efficacy (PFS), the clinical impact of the difference in males is difficult to assess at present, given the magnitude of the change and the observed intra-subject (intra-CV% ~30%) and inter-subject variability (~20%) in participants with cancer as well as limited data in the male population.

2.2.4 Rationale for Combination Treatment with Tipifarnib and Alpelisib

Numerous genetic mutations are commonly seen in HNSCC. Per the Cancer Genome Atlas (TCGA) Network, some of the most common include TP53 (84%), CDKN2A (cyclin dependent kinase inhibitor 2A) (58%), CCDN1 (cyclin D1 gene) (31%), and PIK3CA (34%) (Cancer Genome Atlas Network, 2015; cBioPortal for Cancer Genomics, 2020). While mutations are important drivers of tumor biology, there are other factors, including overexpression of non-mutated oncogenic signaling proteins and the influence of the tumor microenvironment, that may regulate tumor growth and survival. For instance, TCGA shows the over expression of HRAS in 25%-30% of HNSCC patients, indicating a potential dependence on HRAS that may be analogous to HRAS as a driver mutation, potentially expanding the actionable influence of HRAS as a driver oncogene to a broader population of HNSCCs (cBioPortal for Cancer Genomics, 2020).

Understanding the interdependencies of key cellular pathways may be particularly important in designing combination regimens, an example being the codependency of the HRAS and PI3K

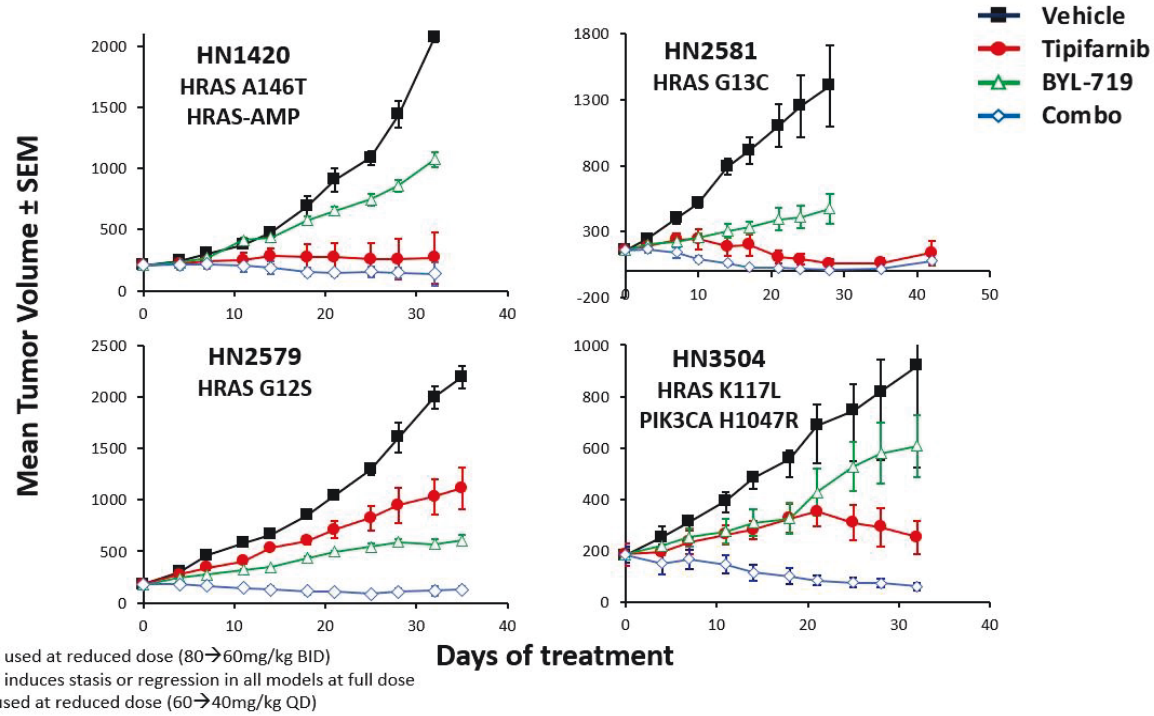
pathways. HRAS activates PI3K five-fold more efficiently than KRAS, while KRAS is a more efficient activator of RAF (Yan et al, 1998).

Furthermore, mutant HRAS requires PI3K for activity, and is insufficient to be tumorigenic in isolation (Gupta et al, 2007). Similarly, mutant PI3K requires RAS in order to drive tumor biology (Zhao and Vogt, 2008). Recognition of these interdependencies was the basis for the evaluation of HNSCC PDX models, where the tumor was dependent on HRAS and/or PIK3CA, as evidenced by the presence of HRAS mutations, HRAS overexpression, PIK3CA amplification, and/or PIK3CA mutations.

Among RAS isoforms, inhibition of the farnesylation of KRAS and NRAS leads to their geranylgeranylation and unchanged membrane localization. HRAS, however, cannot be geranylgeranylated and its membrane localization and cellular function is suppressed by FTIs (Whyte et al, 1997). Consequently, HRAS-mutant/-driven tumors are highly sensitive to FTIs. The FTI tipifarnib was therefore selected for PDX experiments to further explore tumors with HRAS and/or PIK3CA dependencies, as was the PI3Kα-selective inhibitor BYL719.

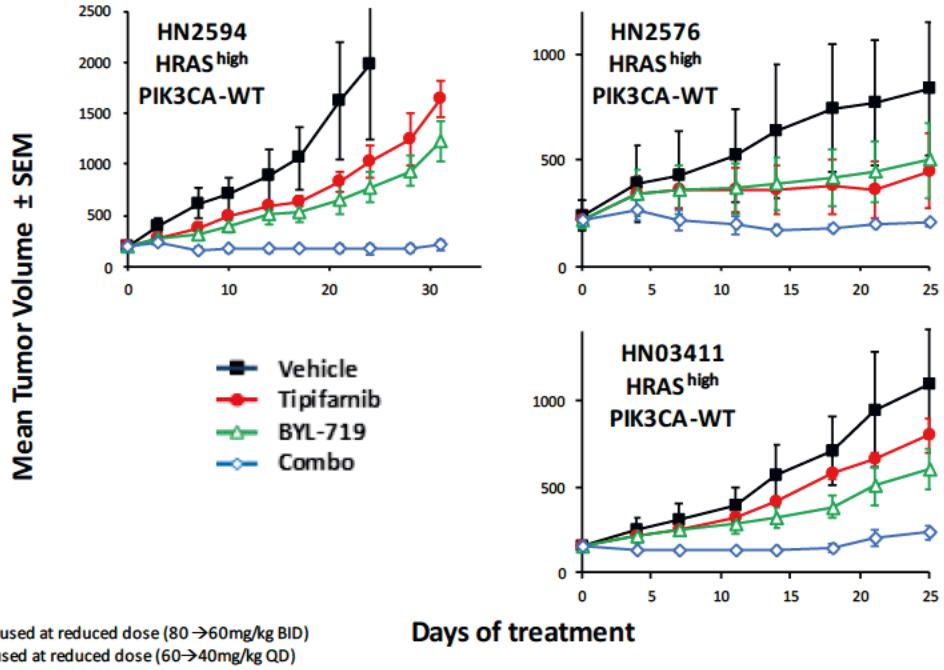
Each of the PDX models (HRAS-mutant [Figure 4], HRAS wild type-overexpressed [Figure 5], PIK3CA-mutant [Figure 6], and PIK3CA-amplified [Figure 7]) was treated with either vehicle, tipifarnib, BYL719, or the tipifarnib-BYL combination. The results across models consistently demonstrated additive or synergistic effects CCI

Figure 4 Combination Activity of Tipifarnib and BYL719 in HRAS-Mutant HNSCC PDX



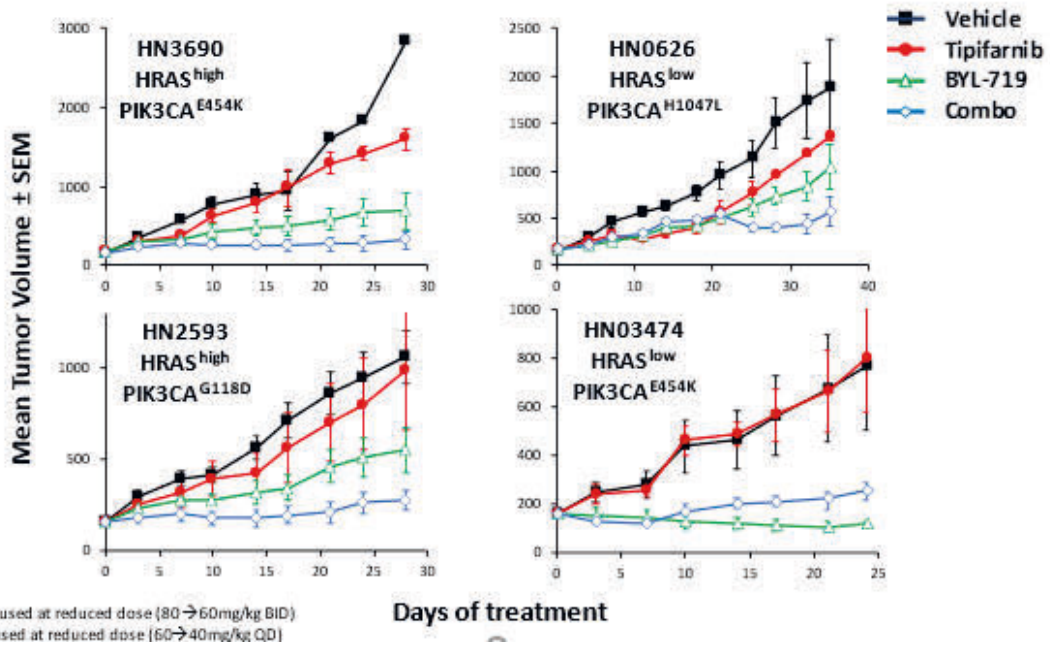
Abbreviations: BID=twice daily; HNSCC=head and neck squamous cell carcinoma; HRAS=Harvey rat sarcoma virus gene homolog; HRAS-AMP=Harvey rat sarcoma virus gene homolog-amplified; PDX=patient-derived xenograft; PIK3CA=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QD=once daily; SEM=standard error of the mean.

Figure 5 Combination Activity of Tipifarnib and BYL719 in HRAS-WT^{high} PIK3CA WT HNSCC PDX



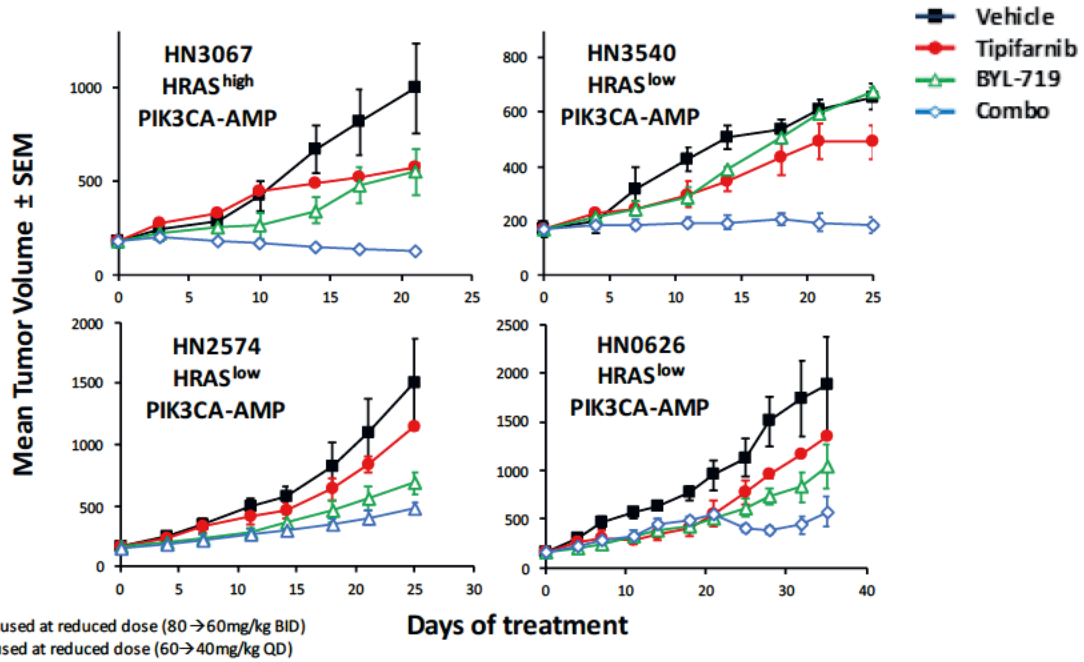
Abbreviations: BID=twice daily; HNSCC=head and neck squamous cell carcinoma; HRAS^{high}=Harvey rat sarcoma virus gene homolog-high; HRAS-WT^{high}=Harvey rat sarcoma virus gene homolog-wild type high; PDX=patient-derived xenograft; PIK3CA-WT=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha-wild type; QD=once daily; SEM=standard error of the mean.

Figure 6 Combination Activity of Tipifarnib and BYL719 in PIK3CA-Mutant HNSCC PDX



Abbreviations: BID=twice daily; HNSCC=head and neck squamous cell carcinoma; HRAS=Harvey rat sarcoma virus gene homolog; $HRAS^{high}$=Harvey rat sarcoma virus gene homolog-high; $HRAS^{low}$=Harvey rat sarcoma virus gene homolog-low; PDX=patient-derived xenograft; PIK3CA=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QD=once daily; SEM=standard error of the mean.

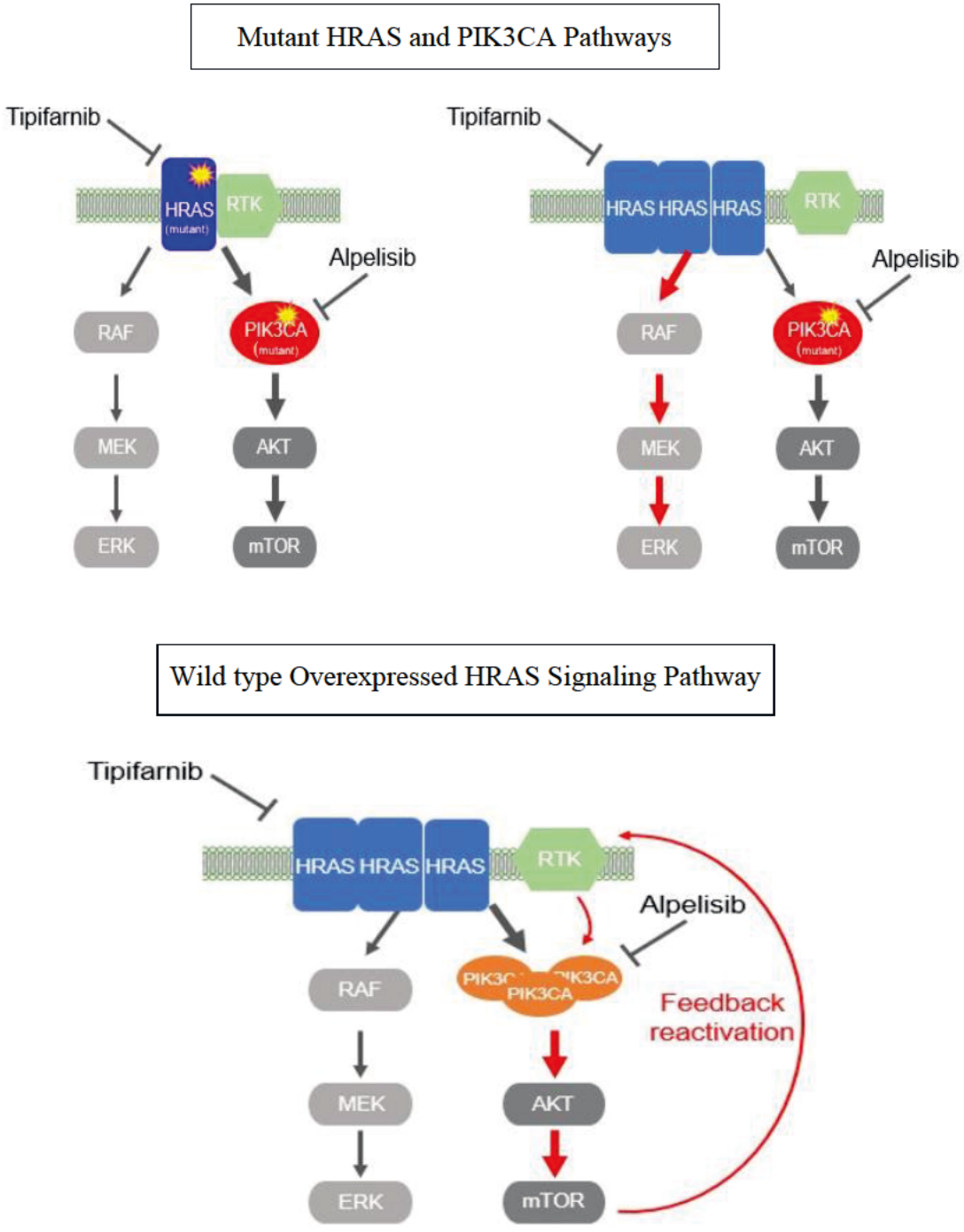
Figure 7 Combination Activity of Tipifarnib and BYL719 in PIK3CA-Amplified HNSCC PDX



Abbreviations: BID=twice daily; HNSCC=head and neck squamous cell carcinoma; HRAS=Harvey rat sarcoma virus gene homolog; HRAS^{high}=Harvey rat sarcoma virus gene homolog-high; HRAS^{low}=Harvey rat sarcoma virus gene homolog – low; PDX=patient-derived xenograft; PIK3CA=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PIK3CA-AMP=PIK3CA-Amplified; QD=once daily; SEM=standard error of the mean.

Ultimately, the results confirm the codependency of these pathways, and provide robust rationale for investigating this combination in the clinic. A summary of the pathways and interactions is provided in Figure 8. These nonclinical data, as well as that described in Section 2.2.1 indicate that additional HNSCC patients, beyond those with HRAS driver mutations, can potentially benefit from a combination treatment of tipifarnib and a PI3Kα inhibitor, and thus the expansion of the clinical development program is warranted beyond HRAS mutants to include HRAS- and PIK3CA-dependent tumors.

Figure 8 Tipifarnib and BYL719 Pathways



Abbreviations: AKT=protein kinase B; ERK=extracellular signal-regulated kinase; HRAS=Harvey rat sarcoma virus gene homolog; MEK=mitogen-activated protein kinase; mTOR=mechanistic target of rapamycin; PIK3CA=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RTK=receptor tyrosine kinase.

2.2.5 Clinical Development

Several efficacy trials of tipifarnib in participants with malignancies have been reported, including those with advanced breast cancer, metastatic pancreatic cancer, melanoma, SCLC, MDS, multiple myeloma, urothelial tract transitional cell carcinoma, colorectal cancer and NSCLC (Adjei et al, 2003; Johnston et al, 2003; Alsina et al, 2004; Heymach et al, 2004; Kurzrock et al, 2004; Rao et al, 2004; Rosenberg et al, 2005; Hong et al, 2011; Gajewski et al, 2012). While sporadic tumor responses were observed in some of these studies, the level of activity in the absence of a molecular selection strategy did not support further development of tipifarnib as a single agent without selection strategies.

Regarding selection strategies in solid tumors, nonclinical data indicated that tumor models carrying HRAS mutations are highly sensitive to FTIs. The reason for this selectivity is potentially the fact that, contrary to KRAS and NRAS, HRAS protein does not undergo geranylgeranylation. Consistent with this hypothesis, the Sponsor initiated a Phase 2 clinical trial in participants with R/M HRAS-mutant solid tumors (KO-TIP-001). Among 20 evaluable participants with HNSCC with high HRAS-mutant variant allele frequency (VAF), the objective response rate (ORR) was 55.0% (95% confidence interval [CI]: 31.5-76.9) based on a best overall response of partial response (PR) in 11 participants, and a best response of stable disease (SD) in the remaining participants (Ho et al, 2021). Median progression-free survival (PFS) was 5.6 months (95% CI: 3.6 to 16.4). Median overall survival (OS) was 15.4 months (95% CI: 7.0 to 29.7). Among the most frequently observed treatment-emergent adverse events (TEAEs) of any Grade observed in >10% of HNSCC participants were hematologic-related events in 50% (anemia [37%], leukopenia [10%], neutropenia [10%], lymphopenia [13%]) and gastrointestinal disturbances in 20% (nausea [10%]). There were no tipifarnib-related deaths. Serious adverse events (SAEs) occurring in ≥10% included dyspnea and anemia (3 participants, or 10% each). Adverse events (AEs) were managed with dose interruption and/or supportive care, including the use of transfusions and growth factors for hematologic events. Tipifarnib is currently being evaluated in an ongoing pivotal trial in HRAS-mutant HNSCC (KO-TIP-007).

PIQRAY® (alpelisib) is approved in the United States (US) and other jurisdictions in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor-positive, human epidermal growth factor receptor 2-negative, advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine-based therapy (PIQRAY® USPI 2020).

Alpelisib has been explored in 2 studies, including in patients with HNSCC, that showed encouraging antitumor activity. CBYL719X2101 was a first-in-human Phase 1 trial of alpelisib in adult participants with advanced solid malignancies (including HNSCC) whose tumors have an alteration of the PIK3CA gene. This trial also included the investigation of alpelisib in combination with fulvestrant in participants with estrogen receptor-positive (ER+) advanced or metastatic breast cancer. Overall, 134 participants were enrolled into the single agent arm of the trial. Nine alpelisib dose levels (30 mg to 450 mg) were tested using a once daily regimen and 3 alpelisib dose levels (120, 150, and 200 mg) were tested using a twice daily regimen. The maximum tolerated dose (MTD) of alpelisib as a single agent was determined to be 400 mg daily and the recommended Phase 2 dose (RP2D) was established at 350 mg daily (Alpelisib [BYL719] Investigator's Brochure).

Nineteen participants (14.2%) had HNSCC and received monotherapy with alpelisib. The overall response rate was 0%; 13 (68.4%) of the 19 participants had stable disease (SD) as the best overall

response. The clinical benefit rate (including CR or PR or SD >24 weeks) was 10.5% (95% CI: 1.3; 33.1) (Trial X2101 CSR).

Trial CBYL719X2104 was a multicenter, open-label, Phase 1b dose escalation trial of alpelisib in combination with cetuximab followed by a Phase 2 trial with a randomized part in cetuximab-naïve participants, and a non-randomized arm in cetuximab-resistant participants. The trial was conducted in participants with recurrent or metastatic HNSCC who were resistant to, ineligible for, or intolerant to platinum-based chemotherapy.

Forty-five participants were enrolled in the Phase 1b trial. The median duration of exposure to the trial intervention was 7.0 weeks. A total of 9 participants reported one or more DLTs after administration of alpelisib. The recommended Phase 2 dose (RP2D) of alpelisib was determined to be 300 mg once daily (QD) in combination with cetuximab (administered as recommended by the label). AEs reported in ≥20% regardless of treatment arm, Grade, causality and alpelisib dose were hyperglycemia (55.6%); diarrhea (46.7%); stomatitis (40.0%); hypomagnesemia and weight decreased (37.8% each); dermatitis acneiform, paronychia and rash (28.9% each); decreased appetite, fatigue and nausea (26.7% each); pyrexia (24.4%); hypokalemia (22.2%); and constipation, dry skin and vomiting (20.0% each). Grade 3 or 4 AEs reported in ≥10%, regardless of causality and alpelisib dose, were hyperglycemia (31.1%); hypokalemia (13.3%); hypophosphatemia and pneumonia (11.1% each). Eight on-treatment deaths occurred (during treatment or up to 30 days after EOT) of which 3 participants died due to underlying disease; 4 participants died due to AEs considered not related to the trial intervention; and 1 participant treated with 400 mg alpelisib QD in combination of cetuximab died due to tumor lysis syndrome (TLS) suspected to be related to the trial intervention. A full review of laboratory and clinical data across alpelisib clinical program concluded that the risk of TLS is mainly associated with the combination of alpelisib with cetuximab and not with single-agent alpelisib nor with other combinations.

During the Phase 1b portion, alpelisib at dose of 300 mg in combination with cetuximab showed encouraging antitumor activity in participants with recurrent or metastatic HNSCC. However, the addition of alpelisib to cetuximab did not significantly improve the efficacy in cetuximab-naïve R/M HNSCC participants and showed moderate activity in R/M HNSCC participants who were cetuximab-resistant. Posterior distribution of PFS based on the Bayesian analysis did not meet the success criteria (estimated posterior median hazard ratio [HR]=0.9 and posterior probability HR >1 = 48.8%), and therefore the combination treatment was not superior to cetuximab monotherapy. There was no statistically significant difference between the combination treatment arm and cetuximab monotherapy arm in terms of PFS (unadjusted HR: 1.12 [95% CI: 0.69, 1.82]). The ORR (95% CI) was 9.9% (4.1%, 19.3%) in the combination treatment arm and 5.7% (0.7, 19.2) in the cetuximab monotherapy arm. The disease control rate (DCR) (95% CI) was 43.7% (31.9%, 56.0%) vs 28.6% (14.6%, 46.3%), respectively.

2.3 Benefit/Risk Assessment

Standard anticancer therapy for HNSCC is multimodal consisting of radiation, chemotherapy, and surgery. For R/M disease, platinum-based chemotherapy (cisplatin or carboplatin plus 5-fluorouracil) with and without cetuximab, remains an important anticancer therapy (Vermorken et al, 2008). Other approved systemic therapies include immunotherapy with pembrolizumab and nivolumab, and their use as single agents and in combination in the front-line setting continue to increase (KEYNOTE-048) (Ferris et al, 2016). However, overall response rates to systemic

anticancer therapy in the second-line setting are <20% with a median OS of 5-8 months (Seiwert et al, 2016; Ferris et al, 2016) emphasizing the significant unmet need for effective therapies for the treatment of R/M HNSCC.

As discussed in Section 2.2.1, understanding the interdependencies of key cellular pathways may be an important factor important to selecting cancer therapies by understanding the key oncogenic drivers. Key nonclinical data and PDX models have indicated potential synergistic effects of the combination of tipifarnib and a PI3K inhibitor in HRAS and/or PIK3CA-dependent tumors, that if clinically translated would mean a significant new therapeutic option for what is estimated to be approximately 50% of R/M HNSCC patients.

Based on its mechanism of action, the results of the preclinical toxicology studies and available clinical safety data, the main known toxicities for alpelisib are hyperglycemia, hypersensitivity/anaphylactic reactions, severe cutaneous reactions, rash/skin toxicities, gastrointestinal toxicities (diarrhea, nausea, and vomiting), pneumonitis/interstitial lung disease, pancreatitis-related events, arterial hypertension, hematologic toxicity and osteonecrosis of the jaw. The expected on-target side effects of PI3K inhibition are insulin resistance and hyperglycemia (Busaidy et al, 2012).

Based on the unmet medical need of the HRAS-mutant HNSCC population and results of PDX models that demonstrated additive and most often synergistic effects with the combination anticancer therapy of tipifarnib and alpelisib, the Sponsor has planned a 2-cohort, open-label trial to determine the recommended combination dose of tipifarnib and alpelisib for the treatment of adult patients with R/M HNSCC whose tumors are dependent on HRAS and/or PIK3CA pathways.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives and Endpoints

The objectives and endpoints apply independently to each of the 2 biologically defined cohorts.

Each cohort will be treated and assessed separately. Therefore, the objectives will be analyzed in both the PIK3CA-mutated and/or -amplified cohort and the HRAS-overexpressed cohort.

Efficacy variables will be assessed by Investigators, based upon local radiology assessments and per RECIST v1.1.

A detailed description of all endpoints is provided in Section 9.4.

Objectives	Endpoints
Primary	
• To determine the recommended dose and regimen, and evaluate the safety and tolerability of the combination of tipifarnib and alpelisib	• Rate of DLT per dose level • Descriptive statistics of AEs per the NCI CTCAE v5.0
Secondary	
• To determine the ORR	• Overall confirmed response rate (CR + PR) ○ Median duration of response
• To determine the disease control rate	• Disease control rate (CR + PR + SD) ○ Median duration of disease control • Rate of SD ○ Median duration of SD
• Pharmacokinetics of tipifarnib and alpelisib when administered in combination	• Single dose: C_{max}, T_{max}, $AUC_{(0\text{-last})}$, $AUC_{(tau)}$, $AUC_{(0\text{-infinity})}$, CL/F, V_d/F, half-life • Multiple dose: C_{max}, T_{max}, $AUC_{(0\text{-last})}$, $AUC_{(tau)}$, CL/F, V_d/F, half-life, accumulation ratio
• To determine the antitumor activity in terms of PFS and rate of PFS at 6 months	• Median PFS • Proportion of participants alive and without progression at 6 months
• To estimate the OS and rate of OS at 12 months	• Median OS • Proportion of participants alive at 12 months
Exploratory	
• Evaluate biomarkers related to HNSCC biology and their potential correlation to efficacy and resistance to study medications.	• Prevalence of genetic alterations in tumor tissue and circulating tumor DNA (ctDNA)
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Abbreviations: AE=adverse event; $AUC_{(0\text{-infinity})}$=area under the concentration-time curve from time zero to infinity; $AUC_{(0\text{-last})}$=area under the concentration-time curve from time zero to time of last measurable concentration;

$AUC_{(tau)}$=area under the concentration-time curve during a dosage interval; CL/F=apparent total clearance of the drug after administration; C_{max}=maximum (peak) drug concentration; CR=complete response; CTCAE=Common Terminology Criteria for Adverse Events; DLT=dose-limiting toxicity; NCI=National Cancer Institute; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; SD=stable disease; T_{max}=time to reach maximum (peak) concentration following drug administration; V_d/F=apparent volume of distribution after administration.

4 TRIAL DESIGN

4.1 Overall Design

KO-TIP-013 is a Phase 1/2, open-label, 2 drug dose escalation trial to evaluate the safety of the combination of tipifarnib and alpelisib and determine recommended combination dosing regimen of the FTI tipifarnib in combination with the PI3Kα inhibitor alpelisib in adult participants with R/M HNSCC who meet criteria for at least 1 of 2 biomarker-defined cohorts (Figure 1):

1. Tumors harboring PIK3CA (activating) mutations and/or amplifications as determined by local or central next generation sequencing (NGS) on a tumor tissue biopsy (cohort 1); and
2. Tumors with increased HRAS dependency based on HRAS overexpression as determined by the Sponsor's central laboratory (cohort 2).

PIK3CA and HRAS status should be determined using tumor tissue obtained at the time of or after the most recent progression; however, tissue obtained prior may be used when this is not possible, and with sufficient justification. If several tissue samples are available, testing should occur on the most recently obtained sample.

Each biomarker cohort will be conducted in parallel and independent of the other biomarker cohort, though safety information for the combination may influence the dosing of both biomarker cohorts.

Each biomarker cohort will be analyzed separately. The BLRM approach will be utilized in the trial to characterize safety, tolerability, and clinical activity of the combination of tipifarnib and alpelisib with the goal of identifying an optimal biologically active combination dose (OBAD) (Neuenschwander et al, 2014). This approach uses joint binary toxicity and efficacy endpoint models for each individual agent (tipifarnib and alpelisib) in conjunction with a combination agent modeling approach to provide dose recommendations for both tipifarnib and alpelisib. This strategy will be used in the 2-drug dose escalation/de-escalation design in order to determine the safest and most effective dosing regimen for each biomarker-defined cohort, while minimizing the potential for subtherapeutic dosing. Investigator assessment of the toxicity and efficacy for each participant who receives sufficient trial intervention will be used to inform the models, and the dose escalation/de-escalation recommendations of the safety monitoring committee (SMC).

The modeling is based upon the following endpoints:

- Endpoint 1: Binary endpoint (DLT).
- Endpoint 2: Binary endpoint (efficacy response based on overall response).
- Endpoint 3: Binary endpoint (efficacy response based on SD).

The safe doses will be identified using the dose-toxicity models for endpoint 1 (APPENDIX 7). A combination dose will be considered safe if the posterior probability of excessive toxicity at the combination dose does not exceed a pre-defined threshold of 25%. This approach to characterizing the degree of toxicity is similar to the escalation with overdose control (EWOC) principle (Babb et al, 1998; Rogatko et al, 2007) that is commonly applied in dose escalation trials to control the risk of exposing participants to toxic doses.

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CCI The DLT period for this trial and the initial toxicity and efficacy period to inform the BLRM will be considered the first 28 days following the start of trial intervention.

The BLRM model will only be run for evaluable participants, however a sensitivity analysis may be run separately to include participants who are not evaluable per the DLT definition. A participant will be evaluable if he/she has received at least 75% of the planned dose for each trial intervention (10.5/14 days for tipifarnib and 21/28 days for alpelisib) and completed the first efficacy assessment after Cycle 1 Day 28; however, any event meeting DLT criteria (see Section 4.1.1) experienced prior to the completion of the 28 days will be considered a DLT (Figure 3).

CCI a simultaneous dosing regimen for tipifarnib and alpelisib will be explored (Figure 2). The simultaneous dosing regimen will involve:

- Tipifarnib dosed BID for 1 week alternating (days 1-7 and 15-21) with 1 week of rest (days 8-14 and 22-28) in a 28-day cycle
- Alpelisib dosed QAM each day of a 28-day cycle

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Safety Monitoring Committee:

An SMC composed of Investigators, Sponsor personnel, and independent advisor(s) will review data to assess the safety of the combination and provide recommendations on dose escalation/ de-escalation, expanding current dose, and CCI as clinical data are accumulated for the dose escalation portion of the trial.

At least 2 participants must be enrolled into each dosing cohort and be evaluable (per the DLT definition) prior to each SMC meeting (unless a DLT occurs that would require the SMC to meet earlier). The SMC members may recommend enrolling more than 2 participants into any given dosing cohort to account for participants who may not be evaluable. Additional details are available in the SMC Charter.

The total trial duration is estimated to last approximately 2 years (approximately 6 months from cycle 1 Day 1 dosing of the last participant), and will consist of the following:

- Prescreening for HRAS overexpression and PIK3CA mutation/amplification (can occur at any timepoint once prescreening informed consent is signed until enrollment into one of the respective biomarker-defined cohorts).
- Screening to determine eligibility to last up to 28 days.
- Treatment will continue until a participant experiences an intolerable toxicity, or other criteria for treatment discontinuation are met (treatment may proceed longer than 6 months if clinical benefit continues). If there is disease progression as an overall response at any time during the trial, the Investigator may continue treatment at their discretion if the participant is experiencing clinical benefit. For **Protocol Amendment 3**, participants will be discontinued at the time of disease progression.
- If a participant discontinues treatment for any reason, the remainder of trial participation will involve survival follow-up and collection of subsequent anticancer therapy information. This overall survival (OS) follow-up will continue until the end of trial or withdrawal of consent. For **Protocol Amendment 3**, survival follow-up will not be conducted; End of Trial will occur at EOT.

The initial dosing cohort will be 600 mg/day of tipifarnib (300 mg BID; Table 2) and 200 mg QAM of alpelisib (Table 3). Dose modifications that may be needed during the conduct of trial due to AEs are discussed in Section 6.6.

In participants with swallowing dysfunction, alpelisib tablets can be administered as a drinkable suspension by crushing the tablets under water with a spoon (the Investigator will instruct the participant according to the crushing instructions in Section 6.1.1). The drinkable suspension prepared from the crushed tablets must not be administered through feeding tubes.

Participants should use the same alpelisib administration method throughout the trial whenever possible. Participants may be allowed to change from alpelisib whole tablets to the drinkable suspension (and vice versa) after discussion with the Sponsor, provided that the change of participant's swallowing function is not due to disease progression.

Tipifarnib tablets may be chewed or crushed if the Investigator deems it necessary (Section 6.1.2). Only tipifarnib may be administered using a percutaneous endoscopic gastronomy tube or nasogastric tube at the judgment of the Investigator.

All changes to tipifarnib and alpelisib administration must be documented in the appropriate electronic case report form (eCRF).

Table 2: Potential Dosing of Tipifarnib

	Tipifarnib (T)
Dose level 3T	1200 mg/day (600 mg BID)
Dose level 2T	900 mg/day (600 mg QAM, 300 mg QPM)***
Dose level 1T*	600 mg/day (300 mg BID)
Dose level -1T	300 mg/day (300 mg QD)**

Abbreviations: BID=twice daily; QAM=each morning; QD=once daily; QPM=each evening; T=tipifarnib.
Initial cohort Starting Dose.
** Single daily dose should be taken at the same time each day with food.
*** 900 mg/day should be divided into 600 mg QAM and 300 mg QPM, though reversal of doses (300 mg QAM and 600 mg QPM) is permitted as long as consistently done throughout the cycle. The specifics of dosing should be recorded in the dosing diary.

Table 3: Potential Dosing of Alpelisib

	Alpelisib (A)**
Dose level 3A	300 mg QAM
Dose level 2A	250 mg QAM
Dose level 1A*	200 mg QAM
Dose level -1A	150 mg QAM

Abbreviations: A=alpelisib; QAM=each morning.
Initial cohort Starting Dose.
** Single daily dose should be taken orally at approximately the same time each day with food (preferably in the morning).

4.1.1 Dose-Limiting Toxicity

A DLT will be defined per the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 as follows:

TOXICITY	DLT CRITERIA
Hematologic	CTCAE Grade 4 neutropenia for more than 7 consecutive days
	CTCAE Grade 4 thrombocytopenia
	CTCAE Grade 3 thrombocytopenia with bleeding
	Febrile neutropenia (decrease in neutrophils associated with fever ≥38.5°C, Absolute neutrophil count (ANC) $<1.0\times10^9$/L)
Metabolism and nutrition disorders	Any CTCAE Grade hyperglycemia leading to diabetic keto-acidosis, hospitalization for intravenous insulin infusion, or non-ketotic coma
	FG >250-500 mg/dL (confirmed with a repeat FPG [fasting plasma glucose] within 24 hours) that does not resolve to ≤250 mg/dL within 7 days (after initiation of oral antidiabetic treatment)
	FG >160-250 mg/dL (confirmed with a repeat FPG within 24 hours) that does not resolve to ≤160 mg/dL within 21 consecutive days (after initiation of oral antidiabetic treatment)
	CTCAE Grade 3 weight loss that does not improve/resolve within 14 days with optimal medical management including nutritional intervention
Hepatic disorders	CTCAE Grade 2 increased bilirubin for more than 7 consecutive days
	CTCAE Grade ≥3 total increased bilirubin
	CTCAE Grade ≥2 increased ALT in conjunction with blood bilirubin Grade ≥2 of any duration in the absence of liver metastases
	CTCAE Grade ≥3 increased ALT for more than 4 consecutive days
	CTCAE Grade ≥4 increased ALT or AST
Gastrointestinal disorders	CTCAE Grade ≥3 diarrhea for 48 hrs or more despite optimal anti-diarrhea treatment
	CTCAE Grade ≥3 nausea that does not improve to < Grade 3 in ≤7 days with optimal medical management
	CTCAE Grade 3 vomiting that does not improve to < Grade 3 in ≤7 days with optimal medical management
	CTCAE Grade 3 stomatitis that does not improve to < Grade 3 in ≤7 days with optimal medical management
Cardiac disorders	CTCAE Grade ≥3 cardiac toxicity
Pulmonary disorders	CTCAE Grade ≥3 pulmonary toxicity as defined by MedDRA SMQ narrow "Interstitial Lung Disease"
Rash	CTCAE Grade 3 rash for more than 7 days despite optimal treatment including systemic steroid use
	CTCAE Grade 4 rash
Renal	CTCAE Grade 3 renal toxicity that cannot be corrected to < Grade 3 with best supportive care within 7 days
Non-hematologic	Any CTCAE Grade 4 non-hematologic toxicity, except for the exclusions noted below in the "Exception for DLT criteria" field
	CTCAE Grade 3 fatigue >5 days

TOXICITY	DLT CRITERIA
	• Any Grade 3 non-hematologic toxicity with >1 week of duration excluding: • Alopecia • Asthenia • Insomnia
Exception for DLT criteria	• CTCAE Grade ≥3 laboratory abnormalities that are responsive to oral supplementation or deemed by the Investigator to be clinically insignificant
	• CTCAE Grade 3 headache that improves to < Grade 3 in ≤7 days with optimal medical management
	• CTCAE Grade 3 Loss of appetite/anorexia
	• CTCAE Grade ≥3 laboratory abnormalities that are responsive to oral supplementation or deemed by the Investigator to be clinically insignificant

Discontinuation of either combination agent **and** continuation on trial with a single agent is not permitted.

4.1.2 DLT Reporting Guidelines

All potential DLTs should be reported within 24 hours of the site's awareness of the occurrence of the event. At a minimum, the site should provide the following information to the Sponsor and CRO: participant ID, date, Grade, and description of potential DLT.

If a participant is dosed and experiences a DLT, that participant will not be replaced and will complete associated efficacy scans and assessments to inform the model.

4.2 Scientific Rationale for Trial Design

Because of the complexity of dosing each of the compounds both as single agents and in combination, the trial will utilize an adaptive dose escalation design which allows for prospectively planned modifications to certain aspects of the design based on accumulated toxicity and efficacy data of both drugs. Advantages of the adaptive approach include:

- statistical efficiency,
- reducing unnecessary exposure to ineffective, subtherapeutic or excessively toxic dose levels,
- improving understanding of the clinical activity/efficacy.

The adaptive design will rely on the BLRM approach to arrive at a safe and effective combination of tipifarnib and alpelisib doses (OBAD) using a minimal number of participants enrolled (at least 2 evaluable participants per dosing cohort).

4.3 Justification for Dose

This trial aims to evaluate the recommended doses of tipifarnib and alpelisib when used in combination to treat participants with R/M HNSCC.

The effect of intermittent schedules of tipifarnib was tested in several Phase 1 studies, including a 5-day BID dosing followed by 9-day rest (5-day schedule) (Zujewski et al, 2000) and 2 trials investigating a 7-day BID dosing followed by 7-day rest (7-day schedule) (Lara et al, 2005; Kirschbaum et al, 2011). In the 5-day schedule Phase 1 trial in participants with nonhematological malignancies, doses from 25 to 1300 mg BID were explored. No MTD was identified.

Dose-limiting toxicity of Grade 3 neuropathy was observed in 1 participant and Grade 2 fatigue in 4 of 6 participants treated with 1300 mg BID. Fatigue, that was not dose-limiting, was observed at the prior dose level (800 mg BID). Of note, myelosuppression which was the most common toxicity in the 21-day schedule (45% at 300 mg BID, Tipifarnib Investigator's Brochure, 2022), was limited with the 5-day schedule and included a Grade 3 neutropenia in a participant with a prior history of myelosuppression treated with 50 mg BID and a Grade 2 thrombocytopenia in a participant treated at the 1300 mg BID dose level. No objective responses were noted.

In the first of the weekly schedule studies (Lara et al, 2005), the starting dose was 300 mg BID with 300 mg dose escalations to a maximum planned dose of 1800 mg BID. Two of 6 participants with nonhematological tumors in dose level 3 (900 mg BID) developed Grade 3 fatigue attributable to trial intervention, and 600 mg BID on alternate weeks was identified as the recommended Phase 2 dose. There were no objective responses but 4 out of 21 participants, 3 of whom had NSCLC, remained on trial for at least 1 year with SD (12, 13, 16 and 17 months). Five Grade 3 events of myelosuppression (out of 21 participants) were described by the authors (doses not indicated) that were not considered DLTs and hematologic toxicity was described as moderate and manageable.

The second weekly schedule trial was conducted in participants with relapsed/refractory acute myeloid leukemia (Kirschbaum et al, 2011). Tipifarnib was administered BID on Days 1–7 and 15–21 of 28-day cycles at doses up to 1600 mg BID. At the 400 mg BID dose level, a Grade 5 hepatorenal failure occurred, ultimately determined to not be due to trial intervention. There were no additional DLTs reported at 600, 800 or 1000 mg BID dose levels. At the 1200 mg BID dose level, a Grade 3 creatinine elevation was seen in 1 participant out of 6 treated. At the 1400 mg BID dose level, 1 participant experienced a Grade 4 hypotension and a rising Grade 2 creatinine that were dose-limiting, and a second participant had a rising Grade 2 creatinine that resulted in treatment discontinuation and was therefore considered dose-limiting. At the 1600 mg dose level, Grade 3 liver function tests and a rising Grade 2 creatinine were dose-limiting, and in a second participant, a rapidly rising creatinine was seen, and treatment stopped. As a result, the 1200 mg BID dose was established as the maximum tolerated dose (MTD) and 7 additional participants were treated.

Sixteen participants were treated at the 1000 and 1200 mg dosing levels, with 3 of them experiencing complete responses (CRs). No formal responses were seen among participants treated at the lower dose levels.

Based on these data, the tipifarnib regimen investigated in KO-TIP-001, a Phase 2 trial of tipifarnib in nonhematological malignancies that carry HRAS mutations was set with a starting dose of 900 mg, orally, BID on Days 1-7 and 15-21 of 28-day treatment cycles. Preliminary data from KO-TIP-001 indicate a tolerability that is broadly similar to the safety profile observed of other tipifarnib regimens in prior clinical studies which administered tipifarnib daily in a 21-day on, 7 days off treatment cycle schedule (Ho et al, 2021). The most common AEs of tipifarnib including hematologic events, gastrointestinal disturbances (nausea, vomiting and diarrhea) and fatigue have been monitorable and manageable with protocol defined assessments and management of toxicity guidance. Dose reduction to a starting dose of 600 mg BID has been able to reduce tipifarnib-related toxicity while preserving efficacy and several participants have maintained their response and continued on treatment for over 1 year. This dose was carried forward into the pivotal trial of single agent tipifarnib in KO-TIP-007.

The recommended dose for alpelisib in combination with fulvestrant is 300 mg QD taken orally with food (PIQRAY® USPI 2020). The MTD for the single agent has been found to be 400 mg per

day (Juric et al, 2018). First signs of tumor suppression were seen at a single agent dose of 180 mg/day with the first objective response seen at 270 mg/day.

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Based on these data, the planned combinations of tipifarnib and alpelisib for this trial are provided in Table 2 and Table 3. The proposed starting dose of this combination is 600 mg/day (300 mg BID) of tipifarnib and 200 mg QAM of alpelisib. The planned dose levels for tipifarnib are generally well tolerated in previous studies and are within the established therapeutic dose range. The maximum dose level for alpelisib that may be tested in this trial is the 300 mg QAM dose level which is currently marketed for combination use.

4.4 End of Trial Definition

For reporting purposes, the end of this clinical trial is defined as the point when all participants have had the opportunity to receive 6 months of treatment. Participants deriving clinical benefit at the end of the trial may continue to receive tipifarnib in combination with alpelisib beyond 6 months at the Investigator's discretion. TEAEs, SAEs, response assessments, drug administration, concomitant medication data collection, date of last drug administration, and reason for discontinuation will be documented in the eCRF. The safety data (TEAEs and SAEs) will continue to be collected until 30 days after the last dose of study drug or until the patient starts a new anticancer therapy, whichever occurs first (Schedule of Activities [SoA] Footnote 8; Section 1.4).

5 TRIAL POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

For inclusion of a participant in the trial, **all** the following inclusion criteria must be fulfilled. If a participant does initially not meet any inclusion criteria, the participant may be re-screened at a later time.

1. At least 18 years of age.
2. Histologically confirmed head and neck cancer (oral cavity, pharynx, larynx, sinonasal, nasopharyngeal, or unknown primary) of squamous histology not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy).
3. Documented treatment failure from at least 1 prior therapy (eg, tumor progression, clinical deterioration, or recurrence) in the R/M setting, with the following exception:
   - Participant is considered not appropriate for treatment with standard of care in this setting, with documented rationale.

   There is no limit on the number of prior lines of therapy a participant may have received.
4. Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (APPENDIX 3) that meets the criteria for selection as a target lesion according to RECIST v1.1. The presence of at least one measurable target lesion per RECIST v1.1 must be confirmed by local radiology prior to participant entry.
5. Has a tumor that per criteria outlined in the protocol, is dependent upon HRAS and/or PIK3CA (Section 8.1).
6. At least 2 weeks or 5 half-lives, whichever is shorter, since the last systemic therapy regimen prior to Cycle 1 Day 1, with the following exception:
   - Last dose of any prior checkpoint inhibitor therapy must have been administered at least 2 weeks prior to Cycle 1 Day 1.
   - Participants must have recovered to NCI CTCAE v5.0 < Grade 2 from all acute toxicities (excluding Grade 2 toxicities that are not considered a safety risk by the Sponsor and Investigator), or toxicity must be deemed irreversible by the Investigator.
7. At least 2 weeks since last radiotherapy to the time of first dose.
   - Participants must have recovered from all acute toxicities from radiotherapy.
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 (APPENDIX 4).
9. Acceptable liver function:
   a) Bilirubin ≤1.5 times upper limit of normal (× ULN).
   b) Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT) (serum glutamic pyruvic transaminase [SGPT]) ≤1.5× ULN.
   - The participant must meet/continue to meet these criteria at the time of first dosing, as confirmed by analysis within 72 hours of Cycle 1 Day 1.

10. Acceptable renal function with either serum creatinine ≤1.5× ULN or a calculated creatinine clearance ≥60 mL/min using the Cockcroft-Gault or Modification of Diet in Renal Disease formulas.
    - The participant must meet/continue to meet these criteria at the time of first dosing, as confirmed by review of analysis performed within 72 hours of Cycle 1 Day 1.
11. Acceptable hematologic status:
    a) Absolute neutrophil count (ANC) ≥ 1000 cells/µL.
    b) Platelet count ≥ 75,000/µL.
    c) Hemoglobin ≥ 8.0 g/dL.
    - The participant must meet/continue to meet these criteria at the time of first dosing, as confirmed by review of analysis performed within 72 hours of Cycle 1 Day 1.
12. Participants who have Type 2 diabetes mellitus must meet criteria for acceptable diabetes control, which includes fasting glucose ≤140 mg/dL (7.7 mmol/L) and HbA1c <6.4% at the time of enrollment.
13. Fasting serum amylase ≤2× ULN.
14. Fasting serum lipase ≤ULN.
15. Must be able to take oral medications with food. Must be able to swallow alpelisib whole tablet or oral suspension containing crushed tablets.
    Note: Feeding tube may not be used for alpelisib administration.
16. Female participants of childbearing potential and male participants with female partners of childbearing potential must follow protocol-specified guidance for avoiding pregnancy (APPENDIX 2) while on treatment and for and at least 28 days after last dose of tipifarnib for females and 90 days for males. Female participants must have a negative serum pregnancy test within 72 hours prior to start of trial intervention.
17. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 Exclusion Criteria

Participants are excluded from the trial if any of the following criteria apply. If a participant initially meets any exclusion criteria, the participant may be re-screened at a later time.

1. Has disease that is suitable for therapy administered with curative intent.
2. Histologically confirmed salivary gland, thyroid, (primary) cutaneous squamous or non-squamous histologies (eg, mucosal melanoma).
3. Ongoing treatment with an anticancer agent (excluding adjuvant hormonal therapy for breast cancer and hormonal treatment for castration sensitive prostate cancer) or any known additional malignancy that is progressing or requires active treatment (excluding non-melanoma skin cancer, adjuvant hormonal therapy for breast cancer and hormonal treatment for castration sensitive prostate cancer).
4. Prior treatment (at least 1 full treatment cycle) with an FTI.
5. Prior treatment (at least 1 full treatment cycle) with a PI3K, mTOR, or AKT inhibitor.

6. Any use of investigational therapy within 2 weeks of Cycle 1 Day 1 or 5 half-lives (whichever is longer).
    - Last dose of any prior checkpoint inhibitor therapy must have been administered at least 2 weeks prior to Cycle 1 Day 1.
7. Received treatment for unstable angina, myocardial infarction, and/or cerebrovascular attack within the prior 6 months.
    - A history of New York Heart Association Grade III or greater congestive heart failure.
    - Current serious cardiac arrhythmia requiring medication, except atrial fibrillation.
8. Non-tolerable Grade 2, or ≥ Grade 3 neuropathy or evidence of unstable neurological symptoms within 4 weeks of Cycle 1 Day 1.
    - Non-tolerable Grade 2 toxicities are defined as those with moderate symptoms that the participant is not able to endure for the conduct of instrumental activities of daily life or that persists ≥7 days.
9. Mean corrected QT interval by Fredericia's formula (QTcF) >480 ms on triplicate electrocardiograms (ECGs) performed within 5 minutes of each other.
10. Major surgery, other than diagnostic surgery, within 2 weeks prior to Cycle 1 Day 1, without complete recovery.
11. Active, uncontrolled bacterial, viral, or fungal infections requiring systemic therapy.
12. Participant with an established diagnosis of diabetes mellitus Type 1 or not controlled Type 2 (based on fasting glucose and HbA1c).
13. Participant has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the trial drugs (eg, ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection) based on Investigator discretion.
14. Participant has currently documented pneumonitis/interstitial lung disease.
15. Participant has a history of acute pancreatitis within 1 year of screening or past medical history of chronic pancreatitis.
16. Participant with unresolved osteonecrosis of the jaw.
17. Participant has a history of severe cutaneous reaction, such as Stevens-Johnson Syndrome (SJS), Erythema Multiforme (EM), Toxic Epidermal Necrolysis (TEN), or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
18. Participant who has history of allergic reactions to tipifarnib (or structural compounds similar to tipifarnib or to its excipients) or alpelisib (or structural compounds similar to alpelisib or to its excipients).
    - This includes hypersensitivity to imidazoles, such as clotrimazole, ketoconazole, miconazole, and others in this drug class.
19. Participant is currently receiving or has received systemic corticosteroids ≤2 weeks prior to starting trial drug, or who have not fully recovered from side effects of such treatment. Note: The following uses of corticosteroids are permitted: single doses, topical applications (eg, for rash), inhaled sprays (eg, for obstructive airways diseases), eye drops or local injections (eg, intra-articular).

20. Required use of concomitant medications classified as the following that cannot be discontinued at least 7 days prior to the start of treatment:
    - strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4, Table 15)
    - strong inhibitors or inducers uridine 5'-diphospho-glucuronosyltransferase (UDP)-glucuronosyltransferase (UGT)
    - inhibitors of breast cancer resistance protein (BCRP)
21. Concomitant disease or condition that could interfere with the conduct of the trial or that would, in the opinion of the Investigator, pose an unacceptable risk to the participant in this trial.
22. Female participant who is pregnant or lactating.
23. Unwillingness or inability to comply with the trial protocol for any reason.

5.3 Lifestyle Considerations

Unless otherwise contraindicated, participants should be advised to remain appropriately hydrated throughout the trial.

Hyperglycemia is a known side effect with alpelisib, and appropriate lifestyle changes in consultation with a healthcare practitioner with expertise in treatment of hyperglycemia may be needed (PIQRAY® USPI 2020).

Considerations related to dosing with food are provided in Section 6.1.

5.4 Screen Failures

Pre-screen failures are defined as participants who consent to participate in the prescreening testing but do not meet the criteria for either biomarker-defined cohort (ie, do not have HRAS overexpression and/or PIK3CA mutation/amplification).

Screen failures are defined as participants who consent to participate in the trial but are not subsequently entered in the trial because of not having met inclusion/exclusion criteria.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants (this applies to participants who screen fail during prescreening and participants who screen fail for the trial) to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities.

Minimal information for prescreening screen failures includes demography, biomarker-defined eligibility criteria, and any SAEs.

Minimal information for screen failures for the trial includes screen failure details, eligibility criteria, and SAE(s).

SAEs that occur during the prescreening and screening Phase of the trial need to be documented on a paper SAE Form and submitted to the Drug Safety Vendor: AEReporting@kuraoncology.com.

6 TRIAL INTERVENTION(S) AND CONCOMITANT THERAPY

Trial intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a trial participant according to the trial protocol.

Participants enrolled in this trial will receive the combination of tipifarnib and alpelisib.

6.1 Trial Interventions Administered

Tipifarnib should be administered orally with a meal, and again with a meal approximately 12 hours later at approximately the same times each treatment day. Participants should be instructed on the importance of taking their tipifarnib doses with a meal as the presence of food has been shown to improve the absorption of tipifarnib, as well as to reduce variability in the pharmacokinetic (PK) profile.

Tipifarnib tablets should be swallowed whole with water (~8 oz. or 250 mL). Tablets may be chewed or crushed if the Investigator deems it necessary (Section 6.1.2). Use of a percutaneous endoscopic gastrostomy tube or nasogastric tube is allowed at the judgment of the Investigator. If a dose is vomited or partially vomited it should not be replaced with a new dose. Dosing should resume at the next scheduled dose time. The interval between tipifarnib dosing should not be less than 8 hours. If a dose of tipifarnib is missed, it can be taken within 4 hours after the time in which the dose should have been taken; after more than 4 hours, that dose should be skipped and the next dose should be taken at the usual time.

Alpelisib tablets should be swallowed whole with water or swallowed after converting into a suspension [see pharmacy manual for additional details] and should be taken with a meal at approximately the same time of the morning each day. If a dose of alpelisib is missed, it can be taken within 8 hours after the time it is usually taken; after more than 8 hours, the dose should be skipped for that day and taken the next day at the usual time. If a dose is vomited or partially vomited it should not be replaced with a new dose. Dosing should resume at the next scheduled dose time. **NOTE: Alpelisib suspension should not be administered via feeding tube.**

With initiation of alpelisib, a non-sedating antihistamine, such as cetirizine once daily on a continuous basis, is recommended to start on Cycle 1 Day 1 for approximately 8 weeks for the prevention of rash associated with PI3K inhibition. For participants benefiting from the antihistamine, treatment can be continued beyond the first 8 weeks, if clinically indicated at the Investigator's discretion (Wang et al, 2020). Refer to Table 9 and Section 6.6 for additional information on antihistamine treatment and incidence/severity of rash based on alpelisib clinical trial experience.

Alpelisib and tipifarnib can be taken at the same time (ie, the AM dose of tipifarnib and alpelisib can be taken together with a morning meal).

The first trial dosing (Cycle 1 Day 1) will take place in the trial clinic. On Cycle 1 Day 1, the Investigator will provide tipifarnib and alpelisib to the participant from bulk supplies.

For Cycle 2 Day 1, participants should be instructed to take their dose(s) at the clinic as necessary to accommodate the 24-hour PK draw. For cycles 3 through 6, Day 1 PK assessments, the timing of the participant's morning dose(s) (tipifarnib and alpelisib) should be recorded but the dose(s) may be taken prior to arrival at the site.

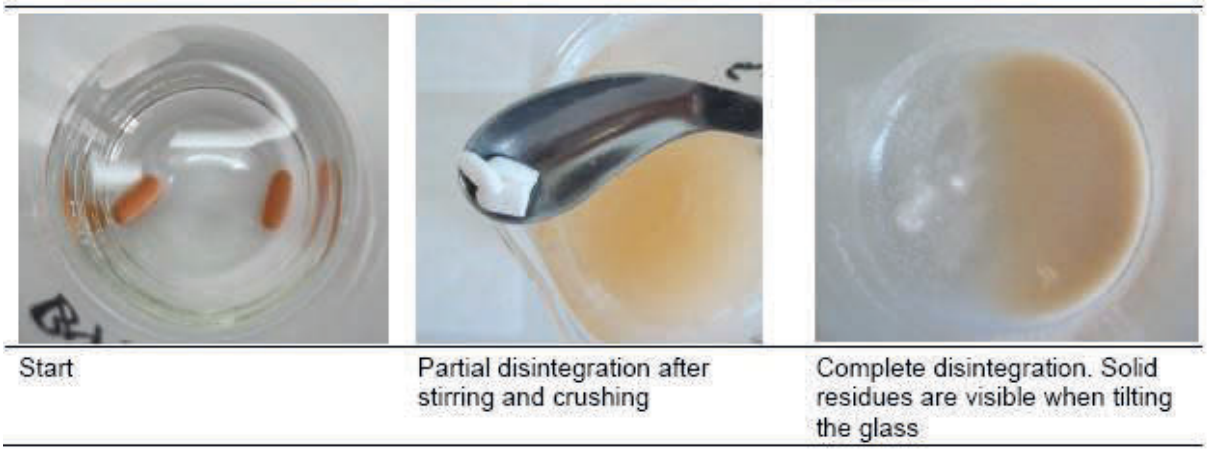
Participants will be provided with diaries with instructions to record the date and time of each dose and asked to bring the diaries and tablet bottles to each clinic visit for compliance and drug accountability review by the site staff.

6.1.1 Alpelisib Medication Crushing Instructions

Alpelisib preparation and administration instructions:

- Wash and dry your hands
- Add the required number of alpelisib film-coated tablet(s) into an appropriately sized glass
- Add approximately 150 mL (2/3 cup) of water
- Let the mixture stand for 5 minutes
- Following the 5 minutes hold time, stir and crush the mixture with a spoon to help the disintegration of the tablet(s)
- Prolong stirring / crushing until the tablet(s) is sufficiently disintegrated for you to be able to drink. It may take up to 30 minutes if you want to reach complete disintegration of the tablet(s)
- Alpelisib film-coated tablet(s) contains excipients that are insoluble in water. Therefore, the final oral suspension will contain solid particulate material (Figure 9). This has no impact on the treatment

Figure 9 Suspension of 2 Film-Coated Tablets of 200 mg Alpelisib



- Gently stir the suspension with the spoon and drink the full amount
- Rinse the glass with approximately 50 mL (1/4 cup) of water and drink the rinse. Ensure that there are no visible solid residues left in the glass
- Clean your hands and the glass

6.1.2 Tipifarnib Medication Crushing Instructions

Tipifarnib preparation and administration instructions:

Prior to preparing the dose: it is recommended to wear a mask and gloves for individuals crushing the tablets (health care professional or participant), especially for individuals of childbearing potential.

- Tablets should be crushed with a commercial tablet crusher (anything that is designed and sold as a pill crusher) and transferred into a dosing cup/glass.
- Crushed tipifarnib tablets might have a bitter flavor profile. The crushed tablets can be mixed with various media according to the table below (Table 4). Participants should be instructed to consume the mixture with a meal. Following consumption, the dosing cup or glass should be rinsed, and each rinse completely swallowed to ensure the entire dose is consumed.
- After dosing the crushed tablets, wash hands, tablet crusher, and dosing cup with soap and water. In addition, thoroughly clean the surface where the tablets were crushed with soap and water and avoid the use of solvents while cleaning.
- Use of crushed tablets and percutaneous endoscopic gastrostomy tube or nasogastric tube for administration of tipifarnib is only allowed at the judgment of the Investigator. After completion of dosing, the cup and tube should be flushed with water twice to ensure that the entire dose is delivered.

Table 4: Tipifarnib Medias

Media	Amount of Media	Rinse	Use Period
Water Ensure® (Protein shake)*	At least 40 mL (~1.4 oz. or ~3 Tbs)	Rinse cup with water twice	2 hours
Orange juice Apple juice Tomato juice	At least 40 mL (~1.4 oz. or ~3 Tbs)	Rinse cup twice with water or juice	2 hours

*Ensure protein shake is the only protein shake that should be used to dissolve tipifarnib. Other protein shakes should not be used.

6.2 Trial Intervention Characteristics

Tipifarnib film-coated tablets for oral administration (300 mg) are supplied in high-density polyethylene (HDPE) bottles. In addition to the active substance, the tablets contain the following inactive ingredients: lactose monohydrate, maize starch, hypromellose, microcrystalline cellulose, crospovidone, colloidal anhydrous silica, and magnesium stearate. The nonfunctional coating contains polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc. Further information can be obtained from the current version of the Tipifarnib Investigator's Brochure.

Alpelisib film-coated tablets for oral administration (50 mg or 200 mg) are supplied in HDPE bottles with induction seal and child-resistant closure with a desiccant. In addition to the active substance, the tablets contain the following commonly used excipients which are referenced in European Pharmacopoeia (Ph Eur) and the United States Pharmacopeia (USP)/National Formulary (NF): Microcrystalline cellulose / cellulose microcrystalline, Mannitol, Sodium starch glycolate (Type A) / Sodium starch glycolate, Hypromellose and Magnesium stearate. The tablet film coat contains the following excipients: Hypromellose, Titanium dioxide, Macrogol 4000/ polyethylene glycol 4000, Talc, Iron oxide red, and Iron oxide black. Further information can be obtained from the current version of the Alpelisib Investigator's Brochure.

6.3 Storage and Labeling

Tipifarnib should be stored at controlled room temperature 15°C to 30°C (59°F to 86°F).

Alpelisib should not be stored above 25°C and should be protected from moisture and light.

All trial supplies must be kept in a restricted access area.

Packaging and labeling will be in accordance with applicable regulatory requirements and current Good Manufacturing Practice guidelines. The information on the medication will be in accordance with regulatory submission documents.

Trial intervention accountability records will be maintained by the pharmacy or designated drug preparation area at the trial sites. Upon receipt of investigational medicinal product (IMP), the pharmacist or designated trial site investigational drug handler will inventory the product (separately for each material and strength, if applicable) and document receipt per pharmacy manual instructions.

6.4 Measures to Minimize Bias: Randomization and Blinding

Not applicable as this is an open-label trial.

6.5 Trial Intervention Compliance

When participants are dosed at the site, they will receive trial intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of trial intervention and trial participant identification will be confirmed at the time of dosing by a member of the trial site staff other than the person administering the trial intervention.

The importance of treatment compliance should be emphasized to the participant. Participants will be given trial intervention and detailed instructions on how to take the trial intervention at home. Participants will be instructed to return all used and unused trial intervention containers at each trial visit. Participant compliance with the dosing schedule will be assessed by reconciliation of the used and unused trial intervention at each clinic visit and review of the dosing diaries. The quantity dispensed, returned, used, lost, etc. must be recorded on the dispensing log provided. In addition, it should be recorded whether the dose was taken with food.

Compliance will be monitored and documented by site personnel on the appropriate form. The site personnel will question the participant regarding adherence to the dosing schedule by reviewing the dosing diaries, recording the number of tablets (and strengths, if applicable) returned, the date returned, and determining treatment compliance (at least 75% of the total assigned dose of each trial intervention) before dispensing new trial intervention to the participant.

During the DLT period, noncompliant participants (those who do not complete at least 75% of dosing due to causes other than a DLT or drug interruption) will be replaced (refer to Section 7.4); following discussion with the Medical Monitor, the participant may continue in the trial, but the participant's data will not contribute to the evaluation of the trial objectives. Beyond the DLT period, participants who are noncompliant may be re-educated on dosing, with confirmation that the participant can continue to meet the dosing requirements of the protocol, at the discretion of the Investigator. Any participant that is noncompliant for more than 28 days (1 cycle) must be removed from trial participation.

6.6 Dose Modification

Dose Modifications Due to Safety Monitoring Committee Recommendations

The initial dosing cohort will begin treatment with simultaneous dosing of tipifarnib at a starting dose of 300 mg BID (600 mg per day on days 1-7, 15-21 of 28-day cycles) and alpelisib 200 mg QAM (continuous, days 1-28 of 28-day cycles). CCI [redacted]

Permanent discontinuation of either combination agent and continuation on trial with a single agent is not permitted.

Based on SMC recommendation, doses of tipifarnib and/or alpelisib may be escalated or de-escalated as mentioned in Table 2 and Table 3, and all determinations will be based on biostatistical modeling and clinical data recommendations.

Dose Modifications Due to AEs and Laboratory Abnormalities

At any time, due to safety events the doses of tipifarnib and/or alpelisib will be modified as outlined below. After the DLT period, in exceptional circumstances, dosing delays or skipping of dosing for reasons other than the management of toxicity will be allowed at the judgment of the Investigator (and in agreement with the Sponsor) as long as 50% of the total dose is maintained in a given cycle, and dose interruptions do not exceed 4 weeks.

Hepatic Impairment

If a participant develops hepatic impairment, the Child-Pugh score should be calculated according to the criteria in Table 5, where encephalopathy is graded according to Table 6. The sum of the points for each Child-Pugh criterion (CPC) used to classify the score (Table 7).

Table 5: Child-Pugh Criteria

CPC Criteria	Points		
	1	2	3
Encephalopathy Grade (see Table 6)	0	1 or 2	3 or 4
Ascites	Absent	Asymptomatic	Requiring intervention
Serum bilirubin, mg/dL	<2	2 to 3	>3
Serum albumin, g/dL	>3.5	2.8 to 3.5	<2.8
Prothrombin time, sec prolonged	<4	4 to 6	>6

Abbreviations: CPC=Child-Pugh criteria.

Table 6: Encephalopathy Grading

Encephalopathy Grade	Definition (EEG required for Grades 2, 3, & 4)
0	Normal consciousness, personality, neurological exam
1	Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting
2	Lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves on EEG
3	Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves on EEG
4	Unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity on EEG

Abbreviations: cps=cycles per second; EEG=electroencephalogram.

Table 7: Classification of Child-Pugh Score

Child-Pugh Classification	Level of Dysfunction	Score
A	Mild	5-6
B	Moderate	7-9
C	Severe	≥10

If the hepatic impairment is mild (Child-Pugh score 5-6), tipifarnib and alpelisib may be administered safely provided there is close monitoring of toxicity, especially hematologic events (see discussion below), with dose reductions for those hematologic events when indicated. The trial intervention combination should be permanently discontinued in participants who develop moderate hepatic impairment (Child-Pugh score 7-9) or higher (severe hepatic impairment; Child-Pugh score ≥10) due to the high incidence of severe hematologic events observed in this patient population associated with tipifarnib therapy.

Non-Hepatic Toxicities

If treatment-related, treatment-emergent AEs are observed meeting criteria for the dose modification detailed further in this section, the dose level reductions summarized in Table 8 will be used, in conjunction with treatment recommendations in Table 9. The dose adjustment should be performed based upon a participant's starting/current dose. Therefore, if a participant is being dosed at tipifarnib 600 mg/day (300 mg BID), the appropriate reduction would be to dose level -3, or 300 mg/day. Alpelisib dose adjustments will also be based upon the starting/current dose of therapy. Each drug can be dose adjusted for toxicity independently as appropriate based upon the nature of the event (Table 8); however, it is not possible to permanently discontinue one drug and continue only on single agent therapy.

Table 8: Dose Level Adjustments for Toxicity

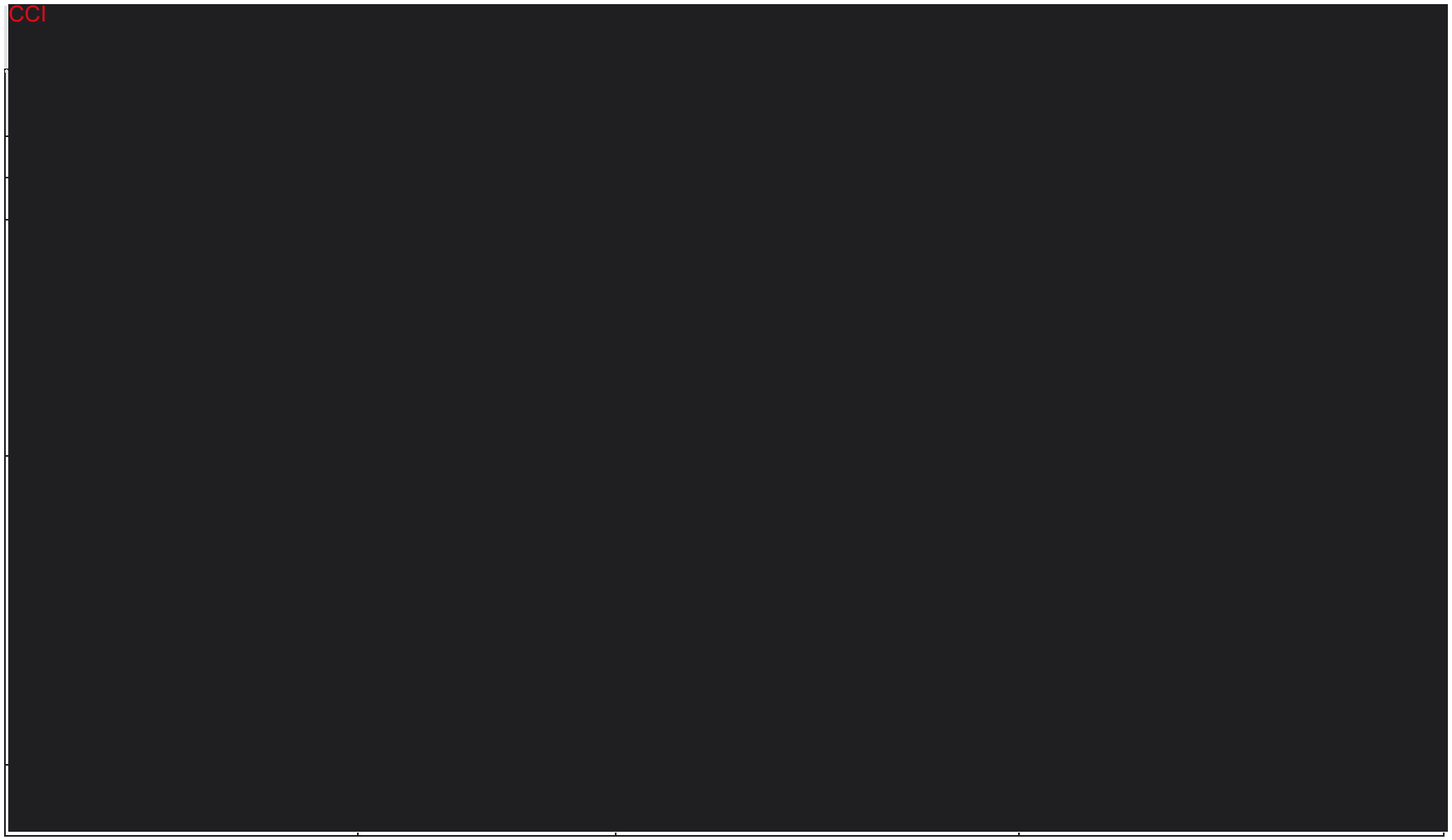
Dose Level	Tipifarnib Doses for AM *and* PM	Alpelisib Doses for AM
Maximum combination dose per protocol	600 mg + 600 mg	300 mg
-1	600 mg* + 300 mg	250 mg
-2	300 mg + 300 mg	200 mg
-3	300 mg*	150 mg

Abbreviations: AM=morning; PM=evening.
*900 mg/day should be divided into 600 mg QAM and 300 mg QPM, though reversal of doses (300 mg QAM and 600 mg QPM) is permitted as long as consistently done throughout the cycle, and total daily dose is administered. Tipifarnib and alpelisib should be taken with a meal.
Note: if the participant experiences toxicity and is already at the lowest dose level (dose level -3), trial intervention may be interrupted for up to 14 days (7/14 days for tipifarnib and 14/28 days for alpelisib). If the toxicity has not resolved or returned to baseline or < Grade 1 within 28 days, the participant should discontinue trial intervention. The 28 days should be considered to include the potential to restart trial intervention even if dosing schedules allow for regular breaks.

Unless otherwise indicated in Table 9 for tipifarnib, reduced doses may be re-escalated to the original dose at the judgment of the Investigator. However, participants who experience SAEs or a recurrence of ≥ Grade 3 toxicity deemed to be related to tipifarnib, will not have their dose re-escalated following dose reduction. In addition, participants experiencing more than one dose delay of ≥14 days will not have their tipifarnib dose re-escalated.

Unless otherwise indicated in Table 9 alpelisib dosing should be restarted at a lower dose. If the same toxicity reoccurs with the same severity, then the next treatment re-initiation must resume at a lower dose irrespective of duration, except if specified in Table 9. Once the alpelisib dose has been reduced by the Investigator, no re-escalation is allowed, even upon resolution of AE.

Asymptomatic laboratory findings (eg, those not requiring corrective actions/therapies) not covered in this section will not be considered dose-limiting, unless otherwise determined by the Investigator. A summary of dose modifications is presented in Table 9.


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Guidelines for the Treatment Alpelisib Related Skin Toxicity

Skin toxicity is a class-effect adverse event observed with PI3Ki agents.

Close monitoring of potential skin reactions will be performed at each planned visit and will be reported as an adverse event. The most frequent skin AEs reported are: maculopapular rash (only a minority present acneiform rash); pruritus and dry skin. The onset is typically within the first 2 months of treatment start and is reversible with adequate co-medication and treatment interruption if needed. Skin reactions may improve over several weeks. Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity at any Grade and mandated if severe cutaneous reaction like SJS, TEN, EM or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected.

Workup for skin toxicity events may include a complete blood count with differential, and a full chemistry panel. It is strongly recommended that a paired skin biopsy is obtained (from both affected and an unaffected skin area) for local histopathology assessment, to further assess the skin toxicity, and to confirm suspected diagnosis of any severe cutaneous reactions. See Table 9 for dose modification guidelines.

In Study BYL719C2301 (SOLAR-1), among the 86 participants who received prophylaxis prior to rash onset, 73% did not develop a rash, while among the 198 participants who did not receive prophylaxis, 36% did not develop a rash. Similar trends were observed in the BYLieve study, where 70% of participants (n=10) who received prophylaxis did not develop a rash compared with 53% of participants (n=117) who did not receive prophylaxis did not develop a rash (Patel and Seminario-Vidal 2020). Additionally, in a single center retrospective analysis of 102 participants receiving alpelisib, prophylaxis with non-sedating antihistamines (n=43) was correlated with a reduction in Grade 1/2 rash events (OR=0.39, p=0.09) (Wang et al, 2020).

Based on these data, prophylactic treatment with non-sedating antihistamines (eg, cetirizine [Zyrtec©], fexofenadine [Allegra], loratadine [Claritin]) can be started on Cycle 1 Day 1 and continued for approximately 8 weeks in all participants, especially in those with a history of atopy such as allergic rhinitis, asthma, atopic dermatitis, or drug allergies, at the discretion of the Investigator. Preventive strategies, including the administration of non-sedating, oral antihistamines (eg, cetirizine [Zyrtec©], fexofenadine [Allegra], loratadine [Claritin]) prior to rash onset and before starting alpelisib, may decrease incidence and severity of rash, in all participants and especially for participants with a history of atopy such as allergic rhinitis, asthma, atopic dermatitis, or drug allergies, based on alpelisib clinical trial experience.

Recommended therapies for skin toxicity events of all grades and as clinically indicated include:

- Consultation with a dermatologist should always be considered.
- Mid to high potency topical steroids: triamcinolone 0.01% or fluocinonide 0.05% twice daily for at least 28 days. Recommend spray, lotion, or cream preparation for ease of application on trunk. For scalp involvement, recommend a foam or solution preparation.
- Gamma-aminobutyric acid (GABA) Agonists: Gabapentin 300 mg every 8 hours, Pregabalin 50-75 mg every 8 hours (to adjust for renal impairment). Depending on participant's clinical condition, be aware of potential and common side effects observed with GABA agonists such as: somnolence, dizziness (both drugs) and peripheral edema (Gabapentin) among others.

For Grade 4 skin events or any Grade of severe cutaneous reactions (including SJS, TEN, EM, DRESS), alpelisib treatment must be permanently discontinued without any re-challenge.

If dry skin is reported, it is recommended that participants with dry skin use mild and fragrance-free soaps and detergents.

Although preclinical experiments demonstrated that alpelisib has no potential phototoxic effect, participants should avoid sun exposure during treatment with alpelisib, especially when they already have experienced rash or other skin toxicities as the increased blood flow of the skin may worsen skin symptoms. Participants should be advised to take measures to protect themselves from direct exposure to sunlight, including the wearing of sunglasses as well as the regular use of sunscreen, hats, long-sleeve shirts, and long pants when outdoors.

Guidelines for the Treatment of Alpelisib-Induced Hyperglycemia

Alpelisib, like other PI3K inhibitors, may affect glucose homeostasis which could result in increases of plasma glucose and insulin resistance (Busaidy et al, 2012). Alpelisib-induced hyperglycemia is generally manageable with adequate antidiabetic treatment. Alpelisib-induced hyperglycemia typically occurs within the first month of treatment. Participants with pre-diabetes (ie, FG 100-125 mg/dl; 5.6-6.9 mmol/L) and those with an established diagnosis of Type 2 diabetes mellitus should be monitored carefully, thus allowing an early detection and prompt management of increases in fasting glucose while on alpelisib treatment. However, all participants, even those with fasting glucose within normal limits at screening, may develop alpelisib-induced hyperglycemia which is an on-target effect seen with PI3K inhibitors. Participants should always be instructed to follow dietary guidelines provided by the American Diabetes Association and/or the European Association for the trial of diabetes, eg, small frequent meals, low carbohydrate content, high fiber, balancing carbohydrates over the course of the day; 3 small meals and 2 small snacks rather than one large meal and exercise, as appropriate.

Hyperglycemic hyperosmolar non-ketotic syndrome (HHNKS) and diabetic ketoacidosis (DKA) are 2 of the most serious metabolic complications associated with hyperglycemia. DKA is characterized by ketoacidosis and a comparatively lower hyperglycemic level (blood glucose 250 mg/dL-600 mg/dL), while HHNKS is characterized by more severe hyperglycemia (blood glucose >600 mg/dL) together with hyperosmolarity and dehydration without significant ketoacidosis. HHNKS is also known as non-ketotic hyperosmolar syndrome, hyperosmolar hyperglycemic state or hyperglycemic hyperosmolar non-ketotic coma. Most patients with HHNKS have a known history of diabetes mellitus Type 2. HHNKS usually develops over a course of many days to weeks, unlike DKA which can develop in a few hours or days.

Detailed guidelines for management of alpelisib-induced hyperglycemia is provided in Table 9. This includes early administration of metformin. Metformin may be titrated to a daily dose of 1000 mg BID (twice a day) or a sodium-glucose cotransporter 2 (SGLT2) inhibitor (alone or in combination with metformin).

Local standard clinical practice may be followed for monitoring and managing hyperglycemia. Fasting glucose testing may be performed both locally and/or centrally for rapid availability for safety evaluation and management guidance. However, it is strongly recommended that dose reduction to be based on FPG only.

Special attention should be paid to the risk of hypoglycemia in participants interrupting alpelisib treatment and concomitantly receiving insulin and/or sulfonylureas. Due to the short half-life of

alpelisib, all glucose lowering medications should be discontinued when alpelisib is stopped/interrupted.

If metformin or an antidiabetic agent is interrupted for radiologic assessments or another reason, then alternative hyperglycemia management should be considered for those days to ensure optimal hyperglycemia management.

Consultation with a diabetologist or healthcare provider experienced in the management of hyperglycemia is highly recommended for better assessment and management of alpelisib-induced hyperglycemia.

Follow-up on Amylase or Lipase Elevation (≥CTCAE Grade 3)

Participants with amylase or lipase elevation ≥CTCAE Grade 3 must be tested weekly (or more frequently if clinically indicated) until ≤ Grade 1 (or baseline). After resumption of dosing, continue to test weekly for one additional cycle. If no reoccurrence of ≥ Grade 2 event, continue monitoring every cycle.

An exception to these follow-up guidelines will be made for cases of isolated amylase elevations in which amylase fractionation demonstrates that pancreatic amylase is ≤ Grade 1. In such cases, total amylase and fractionated amylase should be monitored weekly (or more frequently if clinically indicated) for 4 weeks. If pancreatic amylase remains ≤ Grade 1, subsequent monitoring must be performed at least every 4 weeks (or more frequently if clinically indicated).

Participants who discontinue trial treatment due to pancreatic toxicity must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ Grade 1 or stabilization occurs (no CTCAE v5.0 Grade change over 4 weeks).

If amylase and/or lipase elevations are accompanied by new or progressive unexplained abdominal symptoms such as severe pain or vomiting, withhold trial treatment, then perform diagnostic procedures (eg, abdominal CT scan or ultrasound) to exclude pancreatic pathology.

See also dose modification guidelines described in Table 9.

Follow-up on Potential Drug-Induced Liver Injury (DILI) Cases

Transaminase increase combined with total bilirubin increase may be indicative of potentially severe DILI and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

The threshold for potential DILI may depend on the participant's baseline AST/ALT and total bilirubin value; participants meeting any of the following criteria will require further follow-up as outlined below:

- For participants with normal ALT and AST and total bilirubin value at baseline: AST or ALT >3.0× ULN combined with total bilirubin >2.0× ULN
- For participants with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT >3.0× baseline] OR [ALT or AST >8.0× ULN], whichever occurs first, combined with [total bilirubin >2.0× baseline AND >2.0× ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered, and their role clarified before DILI is assumed as the cause of liver injury.

A detailed history, including relevant information, such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, or history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, gamma glutamyltransferase (GGT), prothrombin time/international normalized ratio (INR), alkaline phosphatase (ALP), albumin, and creatine kinase. If available, testing of glutamate dehydrogenase is additionally recommended.

Evaluate status of liver metastasis (new or exacerbation) or vascular occlusion (eg, using computed tomography [CT], magnetic resonance imaging [MRI], or duplex sonography).

Perform relevant examinations (ultrasound or MRI, endoscopic retrograde cholangiopancreatography) as appropriate to rule out an extrahepatic cause of cholestasis. Cholestasis (is defined as an ALP elevation >2.0× ULN with R value <2 in participants without bone metastasis, or elevation of the liver-specific ALP isoenzyme in participants with bone metastasis).

> Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤2), hepatocellular (R ≥5), or mixed (R >2 and <5) liver injury. In clinical situations in which it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury.

Table 10 provides guidance on specific clinical and diagnostic assessments that can be performed to rule out possible alternative causes of observed liver function test (LFT) abnormalities.

Table 10 Alternative Causes of Liver Disease

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	IgM and IgG anti-CMV, IgM and IgG anti-HSV; IgM and IgG anti-EBV
Autoimmune hepatitis	Antinuclear Antibodies and anti-smooth muscle antibody titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI
Biliary tract disease	Ultrasound or MRI, endoscopic retrograde cholangiopancreatography as appropriate
Wilson disease (if <40 years old)	Ceruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin

Table 10 Alternative Causes of Liver Disease

Disease	Assessment

Abbreviations: CD=carbohydrate deficient; CMV=cytomegalovirus; EBV=Epstein-Barr virus; GGT=gamma glutamyltransferase; HAV=hepatitis A virus; HBc=hepatitis B core antigen; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HEV=hepatitis E virus; HSV=herpes simplex virus; IgA=immunoglobulin A; IgE=immunoglobulin E; IgG=immunoglobulin G; IgM=immunoglobulin M; MCV=mean corpuscular volume; MRI=magnetic resonance imaging.

Other causes should also be considered based upon participants' medical history (hyperthyroidism / thyrotoxic hepatitis – triiodothyronine [T3], thyroxine [T4], thyroid-stimulating hormone [TSH]; cardiovascular disease / ischemic hepatitis – electrocardiogram [ECG], prior hypotensive episodes; Type 1 diabetes / glycogenic hepatitis).

Obtain PK sample to determine drug exposure.

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" ie, >50% likely, if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates *probably caused* by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of SAE and should be reported as SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

Guidelines for Hypersensitivity

Alpelisib and tipifarnib are associated with hypersensitivity reactions, including anaphylaxis and angioedema. These are manifested by symptoms including, but not limited to, dyspnea, flushing, rash, fever, hypotension, dizziness, tachycardia, facial or laryngeal edema. The combination of tipifarnib and alpelisib should be permanently discontinued and should not be re-introduced in participants with serious (Grade 3 and above) hypersensitivity reactions. Appropriate treatment should be promptly initiated.



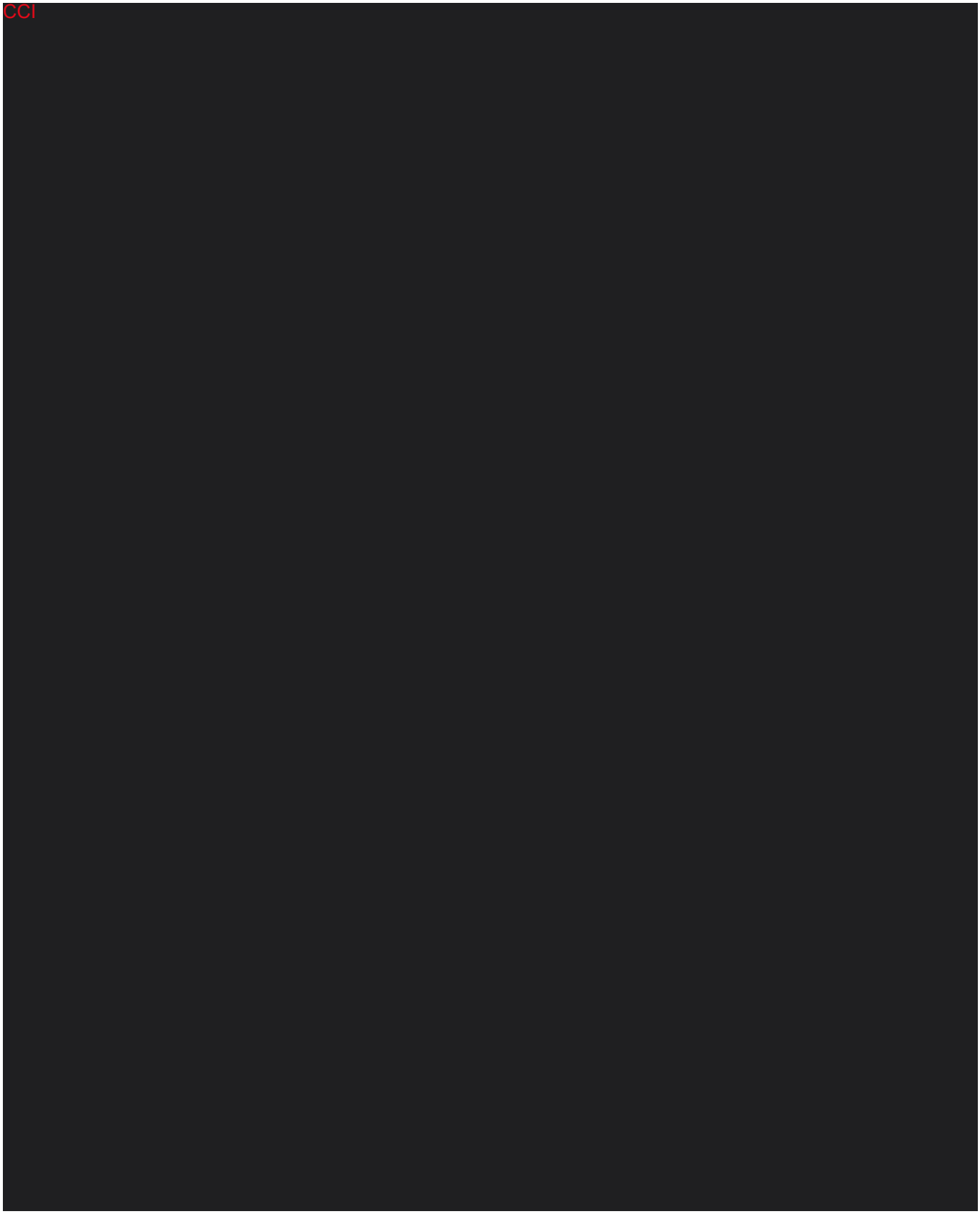
CCI

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[redacted]

CCI



CCI



Radiographic imaging for tumor response must maintain the fixed time schedule and is invariant to the drug exposure of the participant. Radiographic imaging will be performed at least once approximately every 8 weeks (± 5 days) for 12 months, thereafter once approximately every 12 weeks (± 5 days) until disease progression. All other procedures/visits can follow the cycle's drug administration (For **Protocol Amendment 3**, assessments will be conducted per the treatment facility's/local standard of care).

6.6.2 Intra-participant Dose Escalation

After the DLT period, intra-participant escalation from a lower dose level to a dose level at which the SMC has reviewed sufficient data and approved escalation (ie, 1 dose level lower than the dose level being currently evaluated) may be considered.

The following criteria may be used to determine if intra-participant dose escalation should occur:

- Higher proposed dose has been declared safe and demonstrates an increased potential for clinical benefit (compared to lower doses) as assessed by the SMC,
- Participant has not experienced any significant or Grade 3 or higher related AEs,
- Participant has completed a minimum of 12 weeks of on-study treatment (3 cycles),
- The request for intra-participant dose escalation must be discussed and approved with the Medical Monitor.

6.7 Continued Access to Trial Intervention After the End of the Trial

On trial treatment will continue until a participant experiences an intolerable toxicity, or other criteria for treatment discontinuation are met.

Participants deriving clinical benefit at the end of the trial may continue treatment beyond 6 months at the Investigator's discretion. Response assessments will be performed per the treatment facility's/local standard of care (**Protocol Amendment 3** SoA; Section 1.4). TEAEs, SAEs, response assessments, concomitant medications, and drug administration will be documented in the eCRF. The safety data (TEAEs and SAEs) will continue to be collected until 30

days after the last dose of study drug or until the patient starts a new anticancer therapy, whichever occurs first. The EOT visit will occur 30 days (± 7 days) after the last dose of tipifarnib/alpelisib or immediately before the initiation of any other anticancer therapy, whichever occurs first (this may occur as a site visit or a telephone call) after the last dose and will also serve as end of trial.

If there is disease progression as an overall response at any time during treatment, the Investigator may continue treatment at their discretion if the participant is experiencing clinical benefit (Per **Protocol Amendment 3**, participants will be discontinued at the time of disease progression).

6.8 Treatment of Overdose

Any overdose must be recorded in the trial intervention and overdose sections of the eCRF, as well as on the AE section if the overdose is associated with an AE.

For this trial, any dose of tipifarnib greater than 20% of the daily intended will be considered an overdose. There is no known antidote for tipifarnib. In the event of overdose of tipifarnib, participants should receive appropriate advice and supportive medical care by the Investigator or his/her designee and be followed up accordingly.

There is limited experience of overdose with alpelisib in clinical trials, nor has it been defined what constitutes an overdose (PIQRAY® USPI 2020). In the clinical studies, alpelisib was administered at doses up to 450 mg once daily. In cases where accidental overdosage of alpelisib was reported in the clinical studies, the adverse reactions associated with the overdose were consistent with the known safety profile of alpelisib and included hyperglycemia, nausea, asthenia, and rash. Initiate general symptomatic and supportive measures in all cases of overdosage where necessary. There is no known antidote for alpelisib, and there is no clinical experience regarding the effect of hemodialysis on decreasing the plasma levels alpelisib elimination thus far.

For monitoring purposes, any case of overdose of either agent – whether or not associated with an AE (serious or non-serious) – must be reported in an expedited manner.

In the event of an overdose, the Investigator should:

- Contact the Medical Monitor immediately.
- Complete and sign the paper SAE Reporting Form.
    - If the overdose did not have an associated SAE, verbatim term should be documented as ‘overdose with no adverse event’.
    - If the overdose did have an associated SAE, there would be 2 verbatim terms: 1) overdose; 2) SAE verbatim term.
    - All overdoses are to be reported within 24 hours of awareness to: AEReporting@kuraoncology.com
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether trial intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.9 Prior and Concomitant Therapy

All prescription and over-the-counter medications taken by a participant within 14 days before the first trial intervention administration will be recorded in the eCRF. In particular, participants will

be asked about the use of strong inducers of CYP3A4 (eg, rifampin), BCRP inhibitors (eg, cyclosporin A), agents that may affect the mevalonate pathway including statins (eg, atorvastatin, rosuvastatin, pravastatin), bisphosphonates (eg, pamidronate, risedronate, ibandronate, etidronate, alendronate) and nutritional agents (eg, coenzyme Q_{10}, ubiquinone).

Supportive care medications, with the exception of growth factors (eg, G-CSF, GM-CSF) may be given at any time throughout the trial at the discretion of the Investigator. After the initial 28-day DLT period, growth factors may be administered.

BSC will be provided by the clinical trial sites according to local guidelines and standard practices. Any additional concomitant therapy that becomes necessary during the trial and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug.

Furthermore, the following treatments are allowed during the trial:

- Correction of electrolyte deficiency.
- Radiotherapy for pain control against non-target lesions as long as it is not anticipated to influence bone marrow function.
- Total tumor resection in responding participants who have become candidates for curative resection.
- Hematopoietic growth factors and transfusions of blood or blood products in participants who are experiencing hematologic toxicity in accordance with standard institutional practice. However, such supportive care should not be used prior to hematologic findings unless absolutely clinically necessary and after discussion with the Sponsor or designee's Medical Monitor.
- Antiemetic and/or antidiarrheal therapy in a participant experiencing gastrointestinal symptoms in accordance with standard clinical practice. If a participant experiences vomiting or nausea, prophylactic antiemetic medications may be administered with subsequent treatment in accordance with standard clinical practice.
- Concurrent use of adjuvant hormonal therapy for breast cancer or hormonal treatment for castration sensitive prostate cancer.
- Antidiabetic medications (eg, metformin, insulin) for the treatment of hyperglycemia.
- Systemic glucocorticosteriod treatment administration with a daily dose of ≤20 mg prednisone or equivalent.

Medications to be used with caution during combined alpelisib and tipifarnib treatment in this trial are listed below. This list is not comprehensive and is only meant to be used as a guide. The Investigator may contact the Kura Medical Monitor regarding the use of permitted concomitant therapy requiring caution and/or action.

These medications should be excluded from use if possible. If they must be given, based on the Investigator's judgment, then use with caution and consider an alpelisib interruption, as appropriate, if the concomitant medication is only needed for a short time.

Medications to be used with caution include:

CYP2C9 substrates with narrow therapeutic index (NTI) (eg, anticoagulants): In vitro evaluations indicated that pharmacological activity may be reduced by the CYP2C9 induction effects of alpelisib. In the absence of clinical data, caution is recommended with therapeutic doses of warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants as alpelisib may

reduce the clinical activity of such drugs. Alternatively, therapeutic anticoagulation may be accomplished using low-molecular-weight heparin or Direct Thrombin inhibitors and Factor Xa inhibitors.

CYP2B6 sensitive substrates or CYP2B6 substrates with NTI: Based on a static mechanistic assessment with sensitive CYP2B6 substrates such as bupropion, a reduction of exposure by up to 3-fold can be expected when co-administered with alpelisib. In absence of clinical data, sensitive CYP2B6 substrates (eg, bupropion, evafirenz) or CYP2B6 substrates with a narrow therapeutic window should be used with caution in combination with alpelisib, as alpelisib may reduce the clinical activity of such drugs.

Herbal Medications: The use of herbal preparations/medications and dietary supplements are permitted with caution unless explicitly prohibited for being strong inducers of CYP3A such as St. John's Wort (Hypericum perforatum) and avasimibe or BCRP inhibitors such as Curcumin. Medications such as Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, black cohosh and ginseng should be avoided if possible due to their potential for complex interactions. Since cannabinoids have been shown to inhibit BCRP in vitro, medical cannabis should be used with caution. Participants should be closely monitored for increased adverse reactions (as the relevance of this interaction in vivo is currently unknown). In cases of unexpected toxicities, participants should stop using all herbal medications. Use of all such medications (including frequency of administration) should be documented.

Use of bisphosphonates/RANK-ligand inhibitors: The use of bisphosphonates/RANK-ligand inhibitors (eg, denosumab) regardless of indication is allowed provided participants have been on stable doses for at least 2 weeks prior to enrollment. Stable dose should be maintained during the treatment period.

Bisphosphonates may be given according to the local prescribing information and routine clinical practice, at the Investigator's discretion.

Participants taking bisphosphonates prior to entering the trial should continue with the same bisphosphonate treatment, given as per local medical practice.

Participants requiring initiation of bisphosphonate/RANK-ligand inhibitors (eg, denosumab) treatment during the course of the trial should be assessed by appropriate image modalities to exclude disease progression; if disease progression is documented, the participant should discontinue trial treatment. If bisphosphonate/ RANK-ligand inhibitors (eg, denosumab) therapy is to be started after the first dose of trial treatment, the reason for its use must be clearly documented.

Osteonecrosis of the jaw (ONJ) is a known adverse reaction for bisphosphonates/RANK-ligand inhibitors. In SOLAR-1, ONJ was reported in 4.2% of participants (12/284) in the alpelisib plus fulvestrant arm compared to 1.4% participants (4/287) in the placebo plus fulvestrant arm. All participants experiencing ONJ were also exposed to prior or concomitant bisphosphonates (eg, zoledronic acid). Therefore, in participants receiving alpelisib and bisphosphonates, an increased risk of development of ONJ cannot be excluded. For prevention and clinical management of ONJ, prescribing information of bisphosphonates should be followed.

6.10 Non-Permitted Treatments

Use of the following medications and therapies is not allowed during the trial:

- Investigational agents other than tipifarnib and alpelisib.
- Any other anticancer therapy, including radiation or surgery, for the primary disease under trial with the exception of palliative treatment of non-target lesions or treatment of residual disease in trial participants who have experienced a partial response (PR) during the trial.
- Strong inhibitors or inducers of CYP3A4 or UGT beginning at least 14 days prior to cycle 1 Day 1 and during participation in the trial. See Appendix 5 for a list of medications classified as strong inhibitors or inducers of CYP3A4. If continued concomitant therapy is needed, participants should be transitioned to a medicine that is not a strong inhibitor or inducer of CYP3A4 or UGT.
- Sensitive substrates of CYP3A4 beginning Cycle 1 Day 1 and during the participant's participation in the trial. See Appendix 5 for a list of medications classified as sensitive CYP3A4 substrates. If continued concomitant therapy is needed, participants should be transitioned to a medicine that is not a sensitive substrate of CYP3A4.
- Enzyme-inducing anticonvulsants (eg, phenytoin, phenobarbital, and carbamazepine) beginning at Cycle 1 Day 1 and during participation in the treatment portion of this trial. If needed, participants may use non-enzyme-inducing anticonvulsants (eg, gabapentin, topiramate, valproate) while taking tipifarnib.

If the administration of a non-permitted concomitant drug becomes necessary during the trial, eg, because of AEs or disease progression, the participant in question will be withdrawn from the trial, and the participant's data obtained before the withdrawal may be used for safety and efficacy evaluations.

7 DISCONTINUATION OF TRIAL INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Trial Intervention

Participants may withdraw their consent to participate in this trial at any time without prejudice. The Investigator must withdraw from the trial anyone who requests to be withdrawn. A participant's participation in the trial may also be discontinued at any time at the discretion of the Investigator and in accordance with his/her clinical judgment. Every effort should be made to complete, whenever possible, the tests and evaluations listed for the EOT visit. The Sponsor must be notified of all participant withdrawals as soon as possible. The Sponsor also reserves the right to discontinue the trial at any time for either clinical research or administrative reasons and to discontinue participation by an individual Investigator or site for poor enrollment or noncompliance.

In addition to reasons for treatment discontinuation discussed in Section 6.6, other reasons for which the Investigator or Sponsor may withdraw a participant from trial intervention include, but are not limited to, the following:

- Participant experiences disease progression and there is no clinical benefit based upon Investigator assessment (For **Protocol Amendment 3**, participants will be discontinued at the time of disease progression).
- Participant experiences an unacceptable toxicity/adverse event
- Participant requests to withdraw from the trial intervention
- Participant requires medication prohibited by the protocol
- Participant is unwilling or unable to comply with the trial requirements
- Participant withdraws consent to collect future health information
- Participant was erroneously admitted into the trial or does not meet entry criteria
- Participant is lost to follow-up
- Participant becomes pregnant

Participants enrolled in the trial will return for an EOT visit (this may occur as a site visit or a telephone call) approximately 30 days after the last administration of the trial intervention (or sooner if another anticancer therapy is to be initiated). For **Protocol Amendment 3**, EOT will also be considered as end of trial.

7.2 Premature Discontinuation of the Trial

This trial may be discontinued prematurely in the event of any of the following:

- SMC recommendation based on observed safety leading to an unfavorable risk-benefit of tipifarnib and alpelisib combination.
- New information leading to a judgment of unfavorable risk-benefit of tipifarnib, alpelisib and/or combination of tipifarnib and alpelisib becomes available, eg, occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of previously known adverse reactions, or other unfavorable safety findings with use of either individual agent or the combination.
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons.

- Poor enrollment of participants, making completion of the trial within an acceptable time frame unlikely.
- Discontinuation of development of either individual agent.
- Request by a Health Authority.

Health Authorities and IRBs/IECs will be informed about the discontinuation of the trial in accordance with applicable regulations. In the case of premature discontinuation of the trial, the EOT visit should be performed and the appropriate eCRF section should be completed.

7.3 Medical Care of the Participant After End of Trial

Not applicable.

7.4 Replacement of Participants

Replacement of participants will only be allowed for participants who do not complete the DLT evaluation period and/or associated evaluations (Section 4.1).

7.5 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a participant fails to return to the clinic for a required trial visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the trial.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the trial.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants treated with trial intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 TRIAL ASSESSMENTS AND PROCEDURES

Trial procedures and their timing are summarized in the SoA (Section 1.4). Protocol waivers or exemptions are not allowed. Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue trial intervention. Adherence to the trial design requirements, including those specified in the SoA, is essential and required for trial conduct.

8.1 Prescreening for HRAS Overexpression and PIK3CA Mutations/Amplifications

The prescreening activities and data collection for HRAS overexpression and PIK3CA mutations/amplifications are outlined in Section 1.3.

The Sponsor or its designee will assign a participant number identifier for each participant upon completion of informed consent for prescreening. Identification of HRAS overexpression and/or PIK3CA mutation and/or amplification to be performed for eligibility for the KO-TIP-013 trial as outlined in Section 8.1.1 and Section 8.1.2.

If a participant meets criteria for both PIK3CA dependency (PIK3CA mutation and/or amplification) and HRAS dependency (HRAS overexpression), the participant will be enrolled into the PIK3CA cohort (cohort 1) preferentially until the cohort enrollment is complete, after which they would by default be enrolled into the HRAS-dependent cohort (cohort 2).

The tumor tissue obtained at the time of, or after, the most recent progression event is the preferred source for the required PIK3CA and HRAS prescreening, though tumor tissue from an earlier timepoint may be used with sufficient justification. If several tissue samples are available, testing should occur on the most recently obtained sample.

8.1.1 PIK3CA Testing

Participants enrolled in cohort 1 must have PIK3CA mutation/amplification status determined by a Sponsor-approved Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory (local PIK3CA testing) or the Sponsor-designated central CLIA-certified laboratory. PIK3CA dependency is defined as having a PIK3CA mutation and/or amplification based on a next generation sequencing (NGS) test performed in a CLIA-certified laboratory (or locally certified laboratory outside of the US).

Eligible PIK3CA mutations for cohort 1 include known activating mutations in the helicase domain (Exon 7: C420R; Exon 9: E542K, E545A, E545D, E545G, E545K, Q546E, Q546R) and kinase domain: (Exon 20: H1047L, H1047R, H1047Y). PIK3CA mutations that are not listed may be eligible based on approval of the Sponsor.

PIK3CA amplification is defined as PIK3CA gene copy number ≥6 as determined by the local or central laboratory's NGS test.

Options to determine PIK3CA status include:

- Sponsor's central laboratory: NGS testing of tumor tissue by the Sponsor-designated central laboratory if the results from local testing are not available or if local testing is not approved by the Sponsor.
- Local PIK3CA testing: NGS testing of tumor tissue by a Sponsor-approved CLIA-certified (or equivalent) local laboratory that is compliant with local requirements for laboratory-developed tests or in vitro diagnostics (IVD). Local assessment by other non-NGS method

is not permitted. The local laboratory test report (including all pages) documenting the PIK3CA mutation and/or amplification must be made available for Sponsor review and approval for all participants.

Additional data that is routinely generated as part of NGS-based testing, including the following data, will be collected and used for analysis of the exploratory objectives: (1) all genetic alterations identified on local or central laboratory NGS gene panel; (2) pathologic disease stage of the sample tested; (3) information on the method of sample collection (biopsy type or resection) and date of sample collection; (4) anatomic site of tumor collection; (5) HNSCC histology; (6) prior treatment history.

If a participant is enrolled into cohort 1 and additional tumor tissue is available (either archival or new biopsy performed for purposes of clinical care), participants must submit tumor tissue for central assessment of HRAS overexpression CCI [redacted]. If no additional tumor tissue is available, cohort 1 participants are not required to undergo a new tissue biopsy for reciprocal HRAS testing.

See the Laboratory Manual for additional details on submission of tumor samples CCI [redacted].

8.1.2 HRAS Testing

Participants in cohort 2 must have HRAS overexpression in tumor tissue as assessed by the Sponsor-designated central laboratory. Local testing for HRAS overexpression will not be accepted.

For cohort 2, HRAS dependency is defined by high levels of HRAS expression by real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR) of ribonucleic acid (RNA) or immunohistochemistry (IHC) of tumor tissue. The level of RNA expression or protein that defines the cut-point of HRAS dependency will be determined empirically using leftover tumor samples from participants treated with tipifarnib (and for which there is informed consent to use the samples for this purpose) and other HNSCC tumor samples. The qRT-PCR or IHC assay has been validated according to the guidelines of the College of American Pathologists (CAP) and the CLIA and performed in a central CLIA laboratory designated by the Sponsor. See the Laboratory Manual for additional details on the specimen requirements for HRAS testing.

If a participant enrolled into cohort 2 did not have their PIK3CA status previously determined by local or central NGS testing, then available tumor tissue (either archival or new biopsy performed for purposes of clinical care) must be submitted to the Sponsor-designated central laboratory to determine PIK3CA status. Cohort 2 participants are not required to undergo a new tissue biopsy for reciprocal PIK3CA testing. See the Laboratory Manual for additional details on submission of tumor to the central laboratory for PIK3CA testing.

8.1.2.1 Known HRAS Mutation

Participants with known HRAS mutations will be noted and not excluded from the trial but must meet criteria for HRAS overexpression and/or PIK3CA mutation/amplification in order to enroll and be assigned to an appropriate cohort.

8.2 Prescreening Medical History

If a PIK3CA mutation/amplification and/or HRAS overexpression is identified, the following information will be collected at prescreening including, but not limited to:

- Demographics (should be collected for all participants who sign the prescreening ICF even if participant does not have a PIK3CA mutation/amplification and/or HRAS overexpression identified)
- Tumor tissue for HRAS and PIK3CA testing
- Disease-specific history:
    - Primary diagnosis, date of initial diagnosis, stage of disease at diagnosis, anatomical disease site(s) at diagnosis
    - Current stage of disease
    - Smoking and betel nut exposure
    - Alcohol use
    - HPV status
    - Other relevant disease-related medical history including biopsy reports
    - Written documentation of the PIK3CA or HRAS test report including all pages
- Disease status at trial entry:
    - Tumor and anatomical disease site
- All prior anticancer therapy for HNSCC including:
    - Line of therapy
    - Anatomical disease site(s) at the time of first-line therapy for R/M disease
    - Performance status at the time of first-line therapy for R/M disease
    - Name of treatment
    - Dates of treatment (start, end)
    - Treatment outcome (response and response criteria), duration of response (DOR)
    - Date of progression
    - Prior cancer surgery for HNSCC including date(s) of surgery
    - Prior/current radiological treatments for HNSCC including anatomical site(s) and date(s) of radiation treatment
    - Baseline photographs (optional)

8.3 Screening Medical History

The following information will be collected at screening for the KO-TIP-013 study:

- Prior medical illnesses and conditions
- Prior surgical procedures
- Prior and concomitant medications
- Disease status at study entry
    - Tumor and anatomical disease site

A pre-existing condition is one that is present prior to administration of trial intervention. Such conditions should be recorded as medical history. A pre-existing condition should be recorded as a treatment-emergent AE or SAE only if the frequency, intensity, or nature of the condition worsens following the first dose of trial intervention.

8.4 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.4).

8.4.1 Efficacy Assessments

The presence of at least one measurable target lesion per RECIST v1.1 must be confirmed by local radiology prior to enrollment. Participants without at least one measurable target lesion confirmed by local radiology will not be enrolled in the trial. Note: Confirmation of RECIST v1.1 measurable disease by local radiology is required for trial eligibility.

Objective response (CR and PR) as determined by the participant's best tumor response, DOR, and time to progression will be assessed using RECIST v1.1 (APPENDIX 3) by Investigator assessment. Confirmation of response is required according to RECIST v1.1 guidelines.

Tumor response assessments will continue until disease progression, initiation of new anticancer therapy, or trial withdrawal. For **Protocol Amendment 3**, assessments will be conducted per the treatment facility's/local standard of care.

8.4.2 Method and Timing

Radiological assessments of the tumor lesions will be made at screening (within 4 weeks prior to first trial intervention administration on Cycle 1 Day 1, though if not possible scans must have been performed within 60 days of Cycle 1 Day 1), at week 4 (+ 5 days), and at least once approximately every 8 weeks (± 5 days) for the remainder of the first 12 months of trial intervention (through and including cycle 13), and once approximately every 12 weeks (± 5 days) for year 2 and beyond of trial intervention. Additional tumor assessments may be conducted at the judgment of the Investigator but will not substitute for protocol-required assessments. Optional photographs of lesions to coincide with tumor assessments are recommended.

Radiological assessments will be discontinued at the time of trial intervention discontinuation, and completion of EOT procedures (eg, completion of assessments within 4, 8, or 12 weeks before treatment discontinuation or confirmation of response required).

Lesions to be included in the tumor assessments should follow RECIST v1.1 (See APPENDIX 3). CT scan with a contrast agent is the preferred imaging method and the same technique should be used at screening and post-treatment assessments. CT scan coverage at screening should encompass scans of the neck (including the skull base), chest and abdomen (including the liver and adrenals). Any other areas of disease involvement should be scanned based on the participant's signs and symptoms.

Participants with contrast allergy or renal insufficiency may use non-contrast CT or magnetic resonance imaging (MRI), whichever is required to adequately assess all disease. For participants who develop a contraindication to contrast after screening scans are performed with a contrast agent, the decision to use non-contrast CT or MRI (enhanced or non-enhanced) should be based on tumor type, anatomic location of disease and should be optimized to allow for comparison to the prior scans if possible. The one exception where MRI would not be recommended is for the evaluation of parenchymal lung metastases. In this instance, CT would be preferred. If imaging of the brain is indicated, MRI of the brain with and without gadolinium should be performed for optimal evaluation of the brain. If MRI is medically contraindicated, CT of the brain with and without contrast would be suggested.

8.4.3 Survival Follow-up

Beginning at the time of the EOT visit, follow-up contact with the participant and/or caregiver(s) (eg, electronic technology-based, telephone, or in person) is to occur approximately every 12 weeks (± 1 week) for survival and the use of subsequent anticancer therapy until either death or end of trial. Information on survival and subsequent anticancer therapy for HNSCC will be collected including name, dates (start, end), treatment outcome (response and response criteria), DOR, and date of progression. Information will also be collected on subsequent cancer surgery for HNSCC including date of surgery. Information will be collected on subsequent radiological treatments for HNSCC including anatomical site(s) and date(s) of radiation treatment. For **Protocol Amendment 3**, survival follow-up will not be conducted; end of trial will occur at EOT.

8.5 Pharmacokinetics

The blood samples for PK analysis will be collected from participants at the time points described in Table 11.

Table 11 Blood Sampling Timepoints for PK CCI Analysis

Blood Sampling Day	CCI
Cycle 1 Day 1	
Cycle 2 Day 1	
Tumor Response Assessment visits [1]	
Cycle 3 Day 1	
Cycle 4 Day 1	
Cycle 5 Day 1	
Cycle 6 Day 1	

Abbreviations: CCI PK=pharmacokinetics.

1. If the tumor response assessment visit coincides with a Day 1 visit where a blood sample for PK is also scheduled for collection, follow the PK timepoints defined for the respective Day 1 visit.
2. Sample should be collected CCI the PK sample collection.

Window:
CCI

The time and date of blood sample collection will be collected and recorded in the eCRF. Additionally, on trial visit days when a blood sample for PK analysis is collected, the time, date and dosage of the participant's last dose of tipifarnib and alpelisib (most recent dose to the PK blood sample) will be collected and recorded in the eCRF.

Up to 3 additional blood samples for the determination of tipifarnib and/or alpelisib plasma concentration may be collected at the discretion of the SMC and/or Sponsor based on review of ongoing PK and safety data. An additional PK sample may be drawn at Sponsor or Investigator discretion as part of the evaluation of specific AEs.

Samples for the evaluation of tipifarnib and alpelisib concentrations will be collected, processed, and shipped as detailed in the Laboratory Manual.

8.6 Safety Assessments

8.6.1 Adverse Events

An AE is defined as any untoward medical occurrence in a participant who is administered an IMP.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.

For all AEs, the Investigator and/or designee(s) is responsible for obtaining accurate and complete information to determine the following:

- Appropriate descriptive/verbatim term: AEs should be reported using concise medical terminology, preferably referring to the syndrome/diagnosis rather than symptoms, when possible.
- Event severity: AE severity will be primarily assessed using the most current version of NCI CTCAE v5.0 (National Cancer Institute, 2020b; 2020c).
- Onset and resolution dates.
- Outcome.
- Causality: The relationship of each AE to trial intervention will be defined as "not related" or "related" as follows:
    - Not related: There is little or no possibility that the trial intervention caused the reported AE and other factor(s) including: concurrent illnesses, progression and expression of the disease state, concurrent medications, or a reaction to concurrent medications, appear to explain the AE.
    - Related: There exists at least a reasonable possibility that the trial intervention caused or contributed to the AE. An inability to identify an alternate etiology for an AE should not, by itself, justify a "related" attribution.
- Whether it meets the criteria for classification as a SAE.

"Progression of underlying disease" should not be reported as a stand-alone AE or SAE. If the adverse signs or symptoms occur in association with disease progression, then these signs and symptoms should be recorded as the verbatim AEs. If the adverse signs or symptoms meet any of the serious criteria defined in Section 8.6.2, then these events are to be reported on a paper SAE Form and submitted to: AEReporting@kuraoncology.com within 24 hours of awareness. Death due to disease progression occurring during treatment and within 30 days after the end of trial intervention are to be reported on the paper SAE Form within 24 hours of awareness.

8.6.2 Serious Adverse Events

An SAE is any AE that results in one of the following outcomes:

- Death.
- Requires initial or prolonged inpatient hospitalization.

- Any initial admission (24 hours or longer), to a healthcare facility, meets these criteria; initial hospitalization would be selected on the paper SAE Form.
    - Any event occurring while the participant is hospitalized which would otherwise require hospitalization or requires transfer within the hospital to an acute/intensive care unit should also be reported under this criterion; prolonged hospitalization should be selected on the paper SAE Form.
    - This criterion would exclude hospitalization in the absence of a precipitating AE, such as admission for treatment of a pre-existing condition not associated with a new/worsening AE, or admission for elective surgery.
    - This criterion would exclude admission to rehabilitation/hospice/nursing facilities and outpatient admission for same-day surgeries are not considered "hospitalizations" for the purpose of this criterion.
- Is life-threatening (immediate risk of dying).
- Is a persistent or significant disability/incapacity.
- Congenital anomaly/birth defect.
- Other important medical event (IME).
    - Medical and scientific judgment should be exercised in determining whether an event is an IME. An IME may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the participant and/or may require intervention to prevent one of the other outcomes, the IME should be reported as serious.
    - Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.3 Pregnancy and In Utero Drug Exposure

Details of all pregnancies in female participants and, if indicated, female partners of male participants, will be collected after the start of trial intervention and until end of follow-up period (30 days post last dose).

If a female trial participant becomes pregnant, the trial treatment should be stopped, and the trial participant must be asked to read and sign the pregnancy consent form to allow the Trial Doctor to ask about her pregnancy. If a female partner of a male participant becomes pregnant, the outcome should be collected and consent to report information regarding the pregnancy outcome should be obtained from the mother.

To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to AEReporting@kuraoncology.com within 24 hours of learning of its occurrence. Site staff should use the Pregnancy Notification Form followed by the Pregnancy Outcome Form.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the trial treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication (mother or baby) or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. If any of these events, meet any of the criteria defined in Section 8.6.2, a paper SAE Form must be completed and signed and sent to: AEReporting@kuraoncology.com.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The participant / pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant / pregnant female partner and the neonate and the information will be forwarded to the Sponsor. Newborns will be followed up to 12 months.

Any post-trial pregnancy-related SAE(s) considered reasonably related to the trial intervention by the Investigator will be reported to AEReporting@kuraoncology.com as described in Section 8.6.4. While the Investigator is not obligated to actively seek this information in former trial participants/ pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

8.6.4 Adverse Event and Serious Adverse Event Reporting

The Investigator is to record all directly observed AEs and all AEs spontaneously reported by the participant in the eCRF. In addition, each trial participant, will be questioned about AEs throughout the trial.

All AEs will be reported on the AE page(s) of the eCRF.

AEs that are further assessed as SAEs, should be reported in tandem on the paper SAE Form.

The AE eCRF(s) and SAE Report Form must be completed in a consistent manner. For example, the same AE verbatim term, serious criteria, causality, severity, and onset/resolution dates should be used on both forms.

AEs will be recorded and monitored starting at the time of dosing of trial intervention. SAEs will be recorded and monitored starting at the time of signing the informed consent. AE / SAE recording and monitoring, will continue for:

- 30 days after trial completion,
- or 30 days after last dose of trial intervention (applicable to **Protocol Amendment 3**),
- or until the Investigator deems the event(s) as resolved or stable (unchanging),
- or if the participant stops administration of tipifarnib/alpelisib and initiates a new anticancer therapy (applicable to **Protocol Amendment 3**),
- or the participant is considered lost to follow-up.

Any SAE that is assessed as related to trial intervention (tipifarnib or alpelisib) that occurs any time after any of the above, must be promptly reported to Kura Drug Safety (AEReporting@kuraoncology.com).

For AEs/SAEs with a causal relationship to the IMP, follow-up by the Investigator is required until the event or its sequelae resolve to ≤ Grade 1 or stabilize for at least 3 months after the last administration of trial intervention (whichever is sooner).

When reporting an SAE, a paper SAE Report Form must be completed and submitted to AEReporting@kuraoncology.com within 24 hours of the site's awareness of the event, irrespective of the extent of available information. At a minimum, the following should be provided:

- Complete site information
- Complete participant information
- SAE verbatim term
- Serious criteria (with onset date, if available)
- Causal assessment (Not Related or Related; leaving blank will result in a default of related)
- Trial intervention information

SAEs, pregnancy, and/or overdose should be submitted to:

Drug Safety Vendor
E-mail (preferred method of contact): AEReporting@kuraoncology.com
Fax: +1 617 830 0955

This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports. The Investigator is obligated to pursue additional information required for thorough evaluation of each SAE as may be requested by the Sponsor (or designee).

SAE reporting to regulatory authorities and all participating Investigators will be conducted by the Sponsor (or designee) in accordance with 21 CFR 312.32 and international regulations, as appropriate.

8.6.5 Clinical Laboratory Assessments

See APPENDIX 1 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.4) for the timing and frequency.

- Screening and baseline results are required to determine participant eligibility.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the trial as an AE. The laboratory reports must be filed with the source documents. Relevant results essential for participant management decisions (serum chemistry and hematology) must be available and reviewed before administration of trial intervention at Day 1 visits.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the trial or within 30 days after the last dose of trial intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
    - All protocol-required laboratory tests, as defined in APPENDIX 1, must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.4).
    - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE, require trial intervention or dose modification), then the results must be recorded.

8.6.5.1 Urinalysis

Macroscopic assessment of the amount of protein, glucose, white blood cells and blood will be conducted. If abnormalities are noted, these will be recorded, and a microscopic analysis conducted and recorded (APPENDIX 1). If at any time, the participant's serum creatinine is ≥ Grade 2, then a serum chemistry, microscopic urinalysis including the measurement of protein, glucose, blood, white blood cells will be conducted. If abnormalities are noted, then spot urine sodium, protein and creatinine should be performed to assess fractional sodium excretion (plasma creatinine×urine sodium/plasma sodium×urine creatinine) and urine protein/creatinine ratio (urine protein mg/urine creatinine mg ratio).

8.6.5.2 Pregnancy Testing

Pregnancy testing will be performed in females of childbearing potential. Testing will be performed in serum at screening (within 72 hours of Cycle 1 Day 1) and may be performed on urine or serum thereafter. If a positive urine pregnancy test is obtained, a confirmatory serum pregnancy test should be conducted. If confirmatory test is positive, participant must terminate IMP treatment immediately and follow pregnancy reporting guidelines outlined in the protocol. Pregnancy testing will be performed locally at the clinical site or its reference laboratory.

8.6.6 Physical Examinations

- A full physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height (at baseline) and weight will also be measured and recorded.
- A symptom-based/focused physical examination will be symptom- and history-directed.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Significant findings are to be reported in electronic data capture on the Medical History or Adverse Event pages.

8.6.7 Vital Signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 1 blood pressure measurement. Additional readings may be taken if clinically indicated.

8.6.8 Electrocardiograms

- Triplicate 12-lead ECG will be obtained as outlined in the SoA (Section 1.4) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. ECGs should be conducted after a participant has been in the supine position for 10 minutes.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 5 minutes apart.
- Screening results are required to determine participant eligibility.
- ECGs (either triplicate or single, per judgment of the Investigator) should be repeated if clinically indicated at any time during the trial.

8.7 Biomarkers

Due to limited understanding of the biological activities induced by combining tipifarnib and alpelisib in participants who have cancer, in addition to determining the MTD, the trial will serve to evaluate CCI [redacted] investigate CCI [redacted] Participants will be required to submit blood and tumor tissue samples for analysis to carry out the exploratory objectives.

- Baseline (prescreening) tumor tissue for HRAS overexpression and PIK3CA mutation/amplification: Archival tumor tissue obtained at the time of, or after, the most recent progression event or new biopsy performed for purposes of clinical care prior to study treatment.
- CCI [redacted]
- Blood for exploratory biomarkers: Blood collected at baseline, during treatment, and at EOT will be used to isolate ctDNA for genomic analysis.
- CCI [redacted]

CCI [redacted] nalysis of baseline and on treatment samples will be used to investigate CCI [redacted] tipifarnib.

CCI [redacted]

Sponsor-designated lab(s) will be used for processing of all tumor and blood samples collected. The Sponsor will provide kits to collect and ship these samples to Sponsor-designated lab(s) for analysis. Refer to the Laboratory Manual for additional instructions on the collection, handling, storage, and shipment of samples. Sample collection must be captured on the appropriate eCRF and requisition page(s). The samples may be stored under the control of the Sponsor or its authorized agents. Samples may be stored longer if the Sponsor is required to answer questions from a regulatory or governmental agency. The data may be shared with health authorities worldwide, at medical meetings, or in medical publications.

While the goal of the exploratory biomarker objectives is to provide supportive data for the clinical and advance research for HNSCC, there may be circumstances when a decision is made to stop a collection, or not perform or CCI [redacted] (eg, inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis, CCI [redacted] etc.). Therefore, depending on the results obtained during the study, sample collection analysis may be omitted at the discretion of the Sponsor.

Participants will have an opportunity to CCI [redacted] research related to cancer. A participant's consent to the use of any remaining samples for such additional future research shall be optional and shall not affect participation in the current trial.

9 STATISTICAL CONSIDERATIONS

This section provides a summary of key reporting and statistical analytic methods of the trial data. A detailed description of these concepts, including modifications to the methods described below, will be given in the Statistical Analysis Plan (SAP) and will be finalized before the database lock. Any deviations from the SAP will be reported in the clinical trial report.

9.1 Statistical Hypotheses

The hypothesis for this trial is that the combination of tipifarnib and alpelisib is tolerable, with an OBAD that is most likely to result in at least a 20% ORR while maintaining a DLT rate<33%, as determined using BLRM.

9.2 Sample Size Determination

Each initiated dosing level cohort will enroll at least 2 evaluable participants, including at least 6 participants at the OBAD. The trial will utilize an adaptive design based on BLRM models for the toxicity and efficacy outcomes. Multiple dosing level cohorts will be sequentially enrolled to the initial dose or current model-recommended dose level. It is recommended that approximately 20 participants (per biomarker-defined cohort) be enrolled, complete the DLT period, and be evaluable for the model to have reasonable operating characteristics for its OBAD recommendation.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical trial following completion of the informed consent process and determination of having met biomarker-defined and other eligibility criteria. Potential participants who are screened for the purpose of determining eligibility for the trial, but do not participate in the trial, are not considered enrolled.

9.3 Analysis Sets

The following analysis sets will be used in the trial:

- Enrolled Analysis Set: The enrolled analysis set (ENR) will consist of all participants who have met all eligibility criteria and were administered either agent (tipifarnib or alpelisib).
- Full Analysis Set: The full analysis set (FAS) will consist of ENR participants who received at least 1 dose of either agent (tipifarnib or alpelisib) and have at least one valid post-baseline efficacy assessment.
- Safety Analysis Set: The safety analysis set (SAF) will consist of ENR participants who are administered at least 1 dose of either agent (tipifarnib or alpelisib) and have at least one valid safety assessment.
- Dose-Determining Analysis Set: The dose-determining analysis set (DDS) will consist of SAF participants who have completed 1 cycle of trial intervention and experienced an event of interest (DLT, CR, PR, or SD) or completed the observation period without experiencing such an event.
- Per Protocol Analysis Set: The per protocol analysis set consists of SAF participants who do not have major treatment deviations. Participants with major treatment deviations unrelated to safety or tolerability events are not evaluable for the dose escalation assessment and will be replaced as needed.

- Pharmacokinetic Analysis Set: The pharmacokinetic analysis set (PKAS) will consist of SAF participants who provide at least 1 valid concentration value (tipifarnib or alpelisib). The PKAS will be used for the analysis of PK data.

9.4 Statistical Analyses

The trial will utilize an adaptive dose escalation design which allows for prospectively planned modifications to certain aspects of the design based on accumulated toxicity and efficacy data. Advantages of the adaptive approach include:

- statistical efficiency,
- reducing unnecessary exposure to ineffective, subtherapeutic or excessively toxic dose levels,
- improving understanding of the clinical activity/efficacy.

The adaptive design will rely on the BLRM approach to arrive at a safe and effective combination of tipifarnib and alpelisib doses (OBAD) using a minimal number of participants enrolled.

9.4.1 General Considerations

Continuous variables, including baseline characteristics, will be summarized by reporting the number of observations, mean, standard deviation, median, minimum and maximum and categorical variables will be summarized using frequency tables showing the number and percentage of participants within each category. Time-to-event data will be summarized using the Kaplan-Meier method with parameter estimates displayed at pre-defined time points along with the number of censored observations.

The baseline will be defined as the last available observation prior to the first administration of either agent (tipifarnib or alpelisib). Demographic characteristics and baseline clinical characteristics will be summarized by dose level cohort.

9.4.2 Primary Endpoint(s)

- The primary analysis endpoint is the incidence of DLTs. The DLT incidence will be used as a component of the BLRM-based dose recommendation process. DLT and related data will be listed and summarized by dose level cohort and overall in the DDS participants.

9.4.3 Secondary Endpoint(s)

The secondary analysis endpoints include the following efficacy and PK endpoints:

- Efficacy endpoints: ORR (CR + PR), median DOR, DCR (CR + PR + SD), median duration of disease control; rate of SD, median duration of SD), PFS (median PFS and proportion of participants alive and without progression at 6 months), and OS (median OS and proportion of participants alive at 12 months).
- PK parameters:
    - Single dose evaluations:
        - Maximum (peak) drug concentration (C_{max})
        - Time to reach maximum (peak) concentration following drug administration (T_{max})
        - Area under the concentration-time curve from time zero to time of last measurable concentration ($AUC_{(0\text{-last})}$)

- Area under the concentration-time curve during a dosage interval ($AUC_{(tau)}$)
- Area under the concentration-time curve from time zero to infinity ($AUC_{(0\text{-infinity})}$)
- Apparent total clearance of the drug from after administration (CL/F)
- Apparent volume of distribution/F (V_d/F)
- Half-life

o Multiple dose evaluations:

- C_{max}
- T_{max}
- $AUC_{(0\text{-last})}$
- $AUC_{(tau)}$
- CL/F
- V_d/F
- Half-life
- Accumulation ratio

Analyses of efficacy endpoints will be performed using the FAS. The following definitions of the efficacy endpoints will be used:

- Antitumor activity will be categorized as a CR, PR, or SD using local Investigator assessment based on RECIST v1.1. ORR is defined as the proportion of participants who achieved CR or PR, and DCR is defined as the proportion of participants who achieved CR, PR, or SD.
- DOR is defined for participants with confirmed objective response as the time from the first documentation of response to the first documentation of disease progression by RECIST v1.1 or to death due to any cause, whichever occurs first. Duration of SD is defined for participants with a best response of SD as the time from the first documentation of stable disease to the first documentation of disease progression by RECIST v1.1 or to death due to any cause, whichever occurs first.
- PFS is the time from the date of enrollment to the first documentation of disease progression or death due to any cause. For participants with no events, PFS is censored at the date of last tumor assessment.
- OS is the time from the date of enrollment to the date of death due to any cause.

The antitumor activity endpoints (ORR and DCR) will be summarized using descriptive statistics. The DOR data will be summarized by computing the median DOR time with a 2-sided 95% CI. The PFS data will be summarized by computing the Kaplan-Meier curve and the median PFS time with a 2-sided 95% CI, and the proportion of participants alive and without progression at 6 months will be presented. The OS data will be summarized by computing the Kaplan-Meier curve and the median OS time with a 2-sided 95% CI. In addition, the proportion of participants alive at 12 months will be presented.

Participant data listings will include the dose level, disease response at each visit, and best overall response. In addition, the progression date, death date, date of first response and last disease assessment date, and date of last contact will be listed.

9.4.4 Safety Analyses

Analyses of safety endpoints will be performed using the SAF. The following definitions of the safety endpoints will be used:

9.4.4.1 Adverse Events

Treatment-emergent AEs through 30 days after last trial intervention dose will be summarized by system organ class and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The incidences and percentages of participants experiencing each PT will be summarized using descriptive statistics. TEAEs will also be summarized using the NCI CTCAE by Grade and causality. TEAEs resulting in dose modification or treatment discontinuation will be summarized by PT.

9.4.4.2 Laboratory Evaluations

Laboratory values and grading will be listed by laboratory parameter, dose level cohort and cycle. The incidence of lab abnormalities will be shown by parameter, dose level cohort and cycle. In addition, laboratory results will be summarized using Grade shift tables and summary statistics of absolute values and changes from baseline will be presented.

9.4.4.3 Pharmacokinetic Analyses

Descriptive statistics for tipifarnib and alpelisib concentrations and calculated PK parameters will be performed on the PKAS and will include the number of participants, mean, standard deviation, median, minimum, maximum and coefficient of variation. Geometric means will be computed for PK parameters only, and only mean, minimum, and maximum will be reported for T_{max}.

The impact of demographic variables and/or disease state on tipifarnib and alpelisib concentrations will be evaluated graphically or by utilizing population PK analyses. An exploratory exposure-response analysis will also be performed. The SAP will provide more details of such exploratory analyses

9.4.5 Other Analyses

9.4.5.1 Trial Intervention

The actual doses of either agent (tipifarnib or alpelisib) will be listed and summarized, and dose intensity will be calculated.

9.4.5.2 Concomitant Treatments

Concomitant medications and other therapies prior to and after the start of the trial intervention will be listed by participant and summarized by PT.

9.4.5.3 Compliance

Compliance to the protocol will be assessed by the number and proportion of participants with protocol deviations.

9.4.5.4 Biomarker Analysis

CCI

Biomarkers related to HNSCC biology and their potential correlation to efficacy and resistance to study medications will be determined using tumor tissue and blood (for ctDNA). The difference in biomarker results from samples taken before and during treatment may be explored.

CCI

[redacted]

9.4.6 Interim Analysis

No interim efficacy analysis is planned for this trial; however, the model-based dose escalation process entails decisions based on the aggregate toxicity and efficacy data and the observed/available data during each cohort will be evaluated before choosing the combination dose for the next cohort.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This trial will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the trial is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial participants.
- Protocols and any substantial amendments to the protocol will require health authority approval if required per local regulations prior to initiation except for changes necessary to eliminate an immediate hazard to trial participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and Sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

10.1.3 Informed Consent Process

The Investigator or his/her representative will explain the nature of the trial to the participant and/or his/her legally authorized representative and answer all questions regarding the trial.

Participants or their guardians/legal representatives must be informed that trial participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or trial center.

As used in the protocol, the term "informed consent" includes all informed assent given by participants, informed permission by legally authorized representative, or, as applicable, informed consent by the participant during trial participation.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the trial (ie, before any trial-specific screening evaluations are performed) and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

If determined to be necessary by the IRB/IEC, participants must be reconsented to the most current version of the ICF(s) during their participation in the trial.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is re-screened is not required to sign another ICF unless an updated ICF is available.

10.1.4 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor and/or designee will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal trial-related data will be used by the Sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant in order for he or she to give consent for the data to be used as described in the ICF.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Committee Structure

10.1.5.1 Safety Monitoring Committee

An SMC composed of Investigators, Sponsor personnel, and independent advisor(s) will review participant data to assess the safety of the combination and help to determine the dose levels, regimen, further mitigations and ultimately the safest and most efficacious dose of the combination for each biomarker-defined cohort, and will review data to assess the safety of the combination and provide recommendations on, dose escalation/ de-escalation, expanding current dose, CCI [redacted] as clinical data are accumulated for the dose escalation portion of the trial.

At least 2 participants must be enrolled into each dosing cohort and be evaluable prior to each SMC meeting unless a DLT occurs that would require the SMC to meet earlier. The SMC members may

recommend enrolling more than 2 participants to account for participants who may not be evaluable (not having met the definition of DLT period). Additional details are available in the SMC Charter.

- Participant safety will be continuously monitored by the SMC
- In the absence of safety concerns, enrollment into the biomarker-defined cohorts will proceed independently

10.1.6 Dissemination of Clinical Trial Data

Trial-related information and trial results may be posted on the US National Institutes of Health website www.clinicaltrials.gov, the EU website www.clinicaltrialsregister.eu/, or other publicly accessible websites as appropriate and in accordance with local regulations.

10.1.7 Data Quality Assurance

All participant data relating to the trial will be recorded in an eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this trial including quality checking of the data.

Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements. Trial monitors will communicate with investigational sites on a regular basis regarding the trial and all protocol deviations will be appropriately documented by the Investigator or designee, and trial monitors.

Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the Investigator for 5 years after trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Data Quality and Integrity Monitoring

Data quality and integrity will be managed at multiple points throughout the data lifecycle. The specific control mechanisms implemented will be customized to the trial but will include: logical case report form design and corresponding data entry guidelines to promote accurate data reporting at the time of initial entry, implement and maintain data access controls to ensure authorized and appropriate user access, data entry gates and edit checks to evaluate data format and reasonableness, cumulative data review to ensure data conformance; and holistic participant review to ensure data consistency.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigational site.

The Investigator or designee will prepare and maintain adequate and accurate source documents (medical records, ECGs, AE and concomitant medication reporting, and raw data collection forms) designed to record all observations and other pertinent data for each participant.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.

Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10 Trial and Site Start and Closure

The Sponsor or designee reserves the right to close the investigational site or terminate the trial at any time for any reason at their sole discretion. An investigational site is considered closed when all required documents and trial supplies have been collected and an investigational site closure visit has been performed. Portable Document Format versions of data entered in the eCRF will be distributed to the sites at time of trial closure and not during an individual site close-out visit.

The Investigator may initiate investigational site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further tipifarnib and/or alpelisib development.

If the trial is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

10.1.11 Publication Policy

The full terms regarding publication of the results of this trial are outlined in the applicable Clinical Trial Agreement.

- The results of this trial may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before

submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of trial results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Guidelines to Be Applied During Infectious Disease Outbreak – COVID-19

These guidelines only apply during any public health emergency related to coronavirus disease 2019 (COVID-19), declared by government authorities, in the countries where the trial sites are located.

The activities in this guideline include:

- Safety reporting by sites
- Adherence to protocol-specified activities
- Informed consent process
- Provision of trial intervention to participants
- Site monitoring by clinical research associates
- Documentation requirements

10.2.1 Ensuring Continuity of Safety Reporting

Investigators may conduct telemedicine calls via phone/video to identify or to follow-up on AEs.

In the event that participants cannot complete a site visit, they may be directed to utilize local labs/primary care providers to collect labs and conduct participant assessments (eg, vitals, physical exams), and use local imaging facilities where necessary.

If the participant cannot get to an alternative location, then the decision to continue dosing in absence of required safety laboratory assessments is made by the Investigator in consultation with the Sponsor Medical Monitor. These decisions will be made on a case-by-case basis.

For any reports of flu-like symptoms, fevers and/or respiratory problems; the Investigator should determine if the participant has been/should be tested for COVID-19.

10.2.2 Maintaining Protocol Requirements, Including Schedule of Activities

Exposure to or instances of a confirmed positive result for COVID-19 will not mandate early termination of a participant from the trial. Continued participation in the trial will be at the Investigator's discretion.

However, if Investigators have suspected/confirmed positive participants, then they should notify the Sponsor. The Investigator and the Medical Monitor should make a case-by-case assessment of which procedures/samples are appropriate to continue.

10.2.3 Clinic Visits

- If participants cannot travel to the trial site or the Investigator cannot accommodate a visit, but can still receive care via a local provider, efforts should be made to collect data from the local provider in accordance with local privacy/data protection requirements. Data collected may include but is not limited to collection of weight and vital signs (heart rate, respiratory rate, blood pressure, temperature). If possible, the Investigator should prospectively request that data be collected according to good documentation practices (ie, ALCOA+). Alternatively, home nursing visits may be arranged to perform study assessments as necessary. Any forms and records collected during these visits will be confidentially protected and securely kept. Any samples collected during these visits will be labeled with the participant identification number only.
- Where applicable, participant visits may be conducted virtually via telephone or video conference. Data collected during calls may include, but is not limited to adverse event assessment, concomitant medication assessment, ECOG assessments, survival follow-up, and trial intervention compliance assessment. Investigators should ensure:
    - Site staff or Investigators are appropriately trained on how to conduct real-time video conferencing visits (ie, training on use of telemedicine for remote clinical trial visits).
    - Necessary procedures and safeguards are in place to maintain a trial participant's privacy.
    - Both the Investigator and trial participant confirm their respective identities with one another before starting a real-time video conference visit (eg, have the trial participant confirm their date of birth or, if the visit is conducted via videoconference, present a form of government issued photographic identification). Consult with the Sponsor or designee to confirm the specifics of any process implemented.
    - Details about the date and time of the real-time video conference visit, the location of the trial participant, the location of the Investigator or staff conducting the visit should be appropriately documented.
- Radiographic imaging may be collected locally and reviewed by the Investigator or applicable delegated staff member.

10.2.4 Clinical Laboratory Testing

- Clinical laboratory testing may be completed by a certified (eg, College of American Pathologists) local provider and reviewed by the Investigator. Laboratory results should be reviewed prior to either administration or additional shipping of IMP.
- If a local laboratory is utilized, the normal ranges for this lab need to be collected and the source of these values (ie, coming from a local laboratory) needs to be clearly documented.

10.2.5 Disruptions for Shipping to Central Laboratories

If the ability to ship samples to the central laboratory for analysis are impacted, then, if local facilities are available, it is permissible to store samples according to Laboratory Manual guidelines for analysis later when disruptions are resolved. Central laboratories should be consulted to resolve any questions.

Biomarker samples can be frozen and batched shipped later, with the exception of eligibility samples requiring centralized testing.

10.2.6 Informed Consent Process

This trial will utilize the following ICFs: prescreening ICF, main ICF, and a pregnant partner ICF.

When it is not possible to obtain informed consent in a face-to-face consent interview, it is permissible to obtain informed consent virtually. Such virtual consent interviews need to ensure that an adequate exchange of information and documentation occurs. In addition, there needs to be a method to ensure that the person who plans to enroll as a participant (or who is already enrolled as a participant in the case of a revised ICF) is actually the person who signs the ICF. This virtual process can involve, for example, telephone or other videoconference mechanisms, along with the participant providing photographic or facsimile evidence of completing the ICF.

Consult with the Sponsor or designee to confirm the specifics of any process implemented.

10.2.7 Ensuring Continuity of Drug Supply to Participants

Trial Intervention Shipping:

- If site visit restrictions are anticipated but are not yet in effect, additional trial intervention (beyond 1 cycle) may be dispensed during on-site participant visits at the Investigator's discretion.
- If site visit restrictions are implemented between participant visits, trial intervention may be shipped directly from sites to participants under the Investigator's supervision via overnight courier along with instructions for dosing and documentation of dosing. Delivery signature confirmation should be requested whenever possible. Trial intervention should be shipped at ambient temperature using an insulated package/container. Appropriate safeguards should be used to ensure appropriate shipping and receipt, including documentation of receipt (signature of receiver) and condition of package (eg, ensuring no tamper proof seal had been broken).
- The trial intervention may be shipped at ambient temp in credo with no temperature monitoring device.
- Consult with Sponsor, or designee, as needed to assign trial intervention.

10.2.8 Managing Restrictions to Site Monitoring by Clinical Research Associates

Where there are physical access restrictions to clinical sites or country-specific travel limitations, implementation of remote or off-site monitoring visits may be conducted in lieu of on-site visits whenever possible.

Off-site monitoring visits should not place an extra burden on trial sites, and participants must consent to any sharing of their personal information outside the trial site.

10.2.9 Documentation of COVID-19 Related Guidelines or Other Measures

It is important to document the reason for implementing any of these contingency measures. Such documentation should include details on how restrictions related to COVID-19 led to the use of these contingency measures during trial conduct, the duration of those changes, which trial participants were impacted and how those trial participants were impacted. When any non-trial site labs are needed, these should be clearly documented so that the Sponsor can align on usability of the data on a case-by-case basis. When adopting or implementing these guidelines, Investigators should make every effort to minimize any impacts on trial integrity. If any additional changes are required that are not covered in these guidelines, Investigators should act according to local guidelines and

regulations, but above all to assure the safety of trial participants, maintaining compliance with GCP, and minimizing risks to trial integrity. Any changes made should be appropriately documented as protocol deviations.

In advance of any interim analyses/planned database locks, the Sponsor will ensure that the impact from trial visit changes are assessed and will revise the SAP accordingly.

APPENDICES

APPENDIX 1: CLINICAL LABORATORY TESTS

- The tests detailed in Table 12 will be performed by the local laboratory.
- Additional tests may be performed at any time during the trial as determined necessary by the Investigator or required by local regulations.
- Any laboratory result(s) that is abnormal and considered clinically significant (eg, requires intervention) must be reported as an AE/SAE when applicable.

Table 12 Protocol-Required Safety Laboratory Tests

Laboratory Tests	Parameters
Serum chemistry	• Fasting blood glucose, fasting amylase and lipase • Blood urea nitrogen (or urea), creatinine, sodium, potassium, chloride, calcium, magnesium, phosphorus, total protein, albumin, total bilirubin, ALP,[1] ALT, AST, gamma glutamyltransferase, and lactate dehydrogenase. Bicarbonate (or total CO_2) is optional.
Hematology	• White blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count, neutrophils, lymphocytes, monocytes, eosinophils, basophils
Coagulation profile	• APTT, PT/INR
Lipid profile	• Fasting total cholesterol, triglycerides, HDL, and LDL
HbA1c	• HbA1c
Routine urinalysis	• Specific gravity • Macroscopic assessments of the amount of glucose, protein, blood, white blood cells, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal) • If abnormalities are noted, then spot urine sodium, protein and creatinine should be performed to assess fractional sodium excretion (plasma creatinine×urine sodium/plasma sodium×urine creatinine) and urine protein/creatinine ratio (urine protein mg/urine creatinine mg ratio).
Pregnancy testing	• Highly sensitive serum (screening or post-screening) hCG pregnancy test (post-screening only) as needed for women of childbearing potential)[2,3]

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; APTT=activated partial thromboplastin time; AST=aspartate aminotransferase; hCG=human chorionic gonadotropin; IEC=independent ethics committee; IRB=Institutional Review Board; PT/INR=prothrombin time/international normalized ratio.

1. If ALP is elevated, consider fractionating.
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.
3. If a positive urine pregnancy test is obtained, a confirmatory serum pregnancy test should be conducted.

Investigators must document their review of each laboratory safety report.

APPENDIX 2: CONTRACEPTIVE AND BARRIER GUIDANCE

CCI [redacted]
additional details can be found in the Tipifarnib Investigator's Brochure.

Based on findings in animals and its mechanism of action, alpelisib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of alpelisib to pregnant rats and rabbits during organogenesis caused adverse developmental outcomes, including embryo-fetal mortality (post-implantation loss), reduced fetal weights, and increased incidences of fetal malformations at maternal exposures based on area under the curve (AUC) that were ≥0.8 times the exposure in humans at the recommended dose of 300 mg/day. Advise pregnant women and females of reproductive potential of the potential risk to a fetus (PIQRAY® USPI 2020).

In light of the observations in nonclinical testing, both female participants and male participants with female partners of childbearing potential must agree to use a highly effective method of contraception, as defined below and as applicable to local guidelines and regulations, from the first dose of trial intervention, during treatment, and at least 28 days after last dose of trial intervention for females and 90 days for males. Female participants of childbearing potential must have a negative serum pregnancy test within 72 hours prior to start of trial intervention.

CCI [redacted] If the participant in the trial is male, then the following items will be discussed with the participant:

- Prevention of pregnancy in a female partner
- Prevention of exposure of a partner to semen by any means (not just intercourse)
- Prevention of the possible exposure of a pregnant female to the trial intervention from semen
- Informing their partner of the potential for harm to an unborn baby. The partner should know that if pregnancy occurs, she should promptly notify her personal doctor.
- Acceptable methods of birth control for male participants while participating in this trial and for 90 days after the last dose of the study drug:
    - Abstinence (no sex)
    - Condom plus spermicidal agent (foam gel/cream/film/suppository)

Birth Control Methods Considered As Highly Effective:

According to the Clinical Trials Facilitation Group, "Recommendations related to contraception and pregnancy testing in clinical trials" methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. These include:

- Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation[1] (oral, intravaginal, transdermal)
- Progesterone-only hormonal contraception associated with inhibition of ovulation1 (oral, injectable, implantable[2])
- Intrauterine device[2]
- Intrauterine hormone-releasing system[2]
- Bilateral tubal occlusion[2]

- Vasectomized partner[2,3]
- Sexual abstinence[4]

[1] Hormonal contraception may be susceptible to interaction with the trial intervention, which may reduce the efficacy of the contraception method.

[2] Contraception methods in the context of this guidance are considered to have low user dependency.

[3] Vasectomized partner is highly effective birth control method provided that the partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

APPENDIX 3: RECIST V1.1 GUIDELINES

Source: (Eisenhauer et al, 2009)

Table 13: RECIST v1.1 Guidelines

	Definitions
Response criteria – target lesion	*Complete Response (CR)*: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm. *Partial Response (PR)*: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. *Progressive Disease (PD)*: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on trial (this includes the baseline sum if that is the smallest on trial). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression. *Stable Disease (SD)*: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on trial.
Evaluation of non-target lesions	While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol. *Complete Response (CR)*: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size. *Progressive Disease (PD)*: Unequivocal progression of existing non-target lesions.[a] *Non-CR/Non-PD*: Neither CR nor PD *Unknown (UNK)*: Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline.[b]

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below.

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Lesion Response**
CR	CR	No	CR[c]
CR	Non-CR/Non-PD	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[c]
SD	Non-PD and not UNK	No	SD[c, d]
UNK	Non-PD or UNK	No	UNK[c]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; UNK=unknown.

[a] The assignment of PD solely based on change in non-target lesions in light of target lesion response of CR, PR or SD should be exceptional. In such circumstances, the opinion of the Investigator or central reviewer prevails.

[b] It is recommended that the Investigator and/or central reviewer should use expert judgment to assign a Non-UNK response wherever possible (see notes section for more details).

[c] This overall lesion response also applies when there are no non-target lesions identified at baseline.

[d] Once confirmed PR was achieved, all these assessments are considered PR.

Adapted from: https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf

Table 14: Best Overall Response When Confirmation of PR and CR are Required

Best overall response when confirmation of PR and CR are required		
Overall response First time point	**Overall response Subsequent time point**	**BEST overall response**
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

Abbreviations: CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the participant had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Adapted from: https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf

APPENDIX 4: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Source: (Oken et al, 1982)

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house-work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

APPENDIX 5: PROHIBITED MEDICATION LIST

For participants in trial, the following medications may not be taken from at least 14 days prior to the start of tipifarnib treatment and throughout the tipifarnib treatment portion of KO-TIP-013. This list was current as of the finalization of Protocol Version 2. For the most up to date list, this link should be referenced:

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

Table 15 Strong Inhibitors or Inducers of CYP3A4

Strong Inhibitors	Strong Inducers
boceprevir	apalutamide
clarithromycin	carbamazepine
cobicistat	enzalutamide
dasabuvir	mitotane
danoprevir	phenytoin
elvitegravir	rifampin
idelalisib	St. John's wort
indinavir	
itraconazole	
ketoconazole	
lopinavir	
nefazodone	
nelfinavir	
ombitasvir	
paritaprevir	
posaconazole	
ritonavir	
saquinavir	
telaprevir	
telithromycin	
tipranavir	
troleandomycin	
voriconazole	

For participants in trial, the following medications may not be taken during the tipifarnib treatment portion of KO-TIP-013.

Table 16: Sensitive Substrates of CYP3A4

alfentanil	lovastatin
avanafil	lurasidone
budesonide	maraviroc
buspirone	midazolam
conivaptan	naloxegol
darifenacin	nisoldipine
darunavir	quetiapine
dasatinib	saquinavir
dronedarone	sildenafil
ebastine	simvastatin
eletriptan	sirolimus
eplerenone	tacrolimus
everolimus	ticagrelor
felodipine	tipranavir
ibrutinib	tolvaptan
indinavir	triazolam
lomitapide	vardenafil

APPENDIX 6: ABBREVIATIONS

A	alpelisib
ALCOA+	data integrity principles of attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring and available
AE	adverse event
AKT	protein kinase B
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AMP	amplified
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{(tau)}$	area under the concentration-time curve during a dosage interval
$AUC_{(0\text{-infinity})}$	area under the concentration-time curve from time zero to infinity
$AUC_{(0\text{-last})}$	area under the concentration-time curve from time zero to time of last measurable concentration
BCRP	breast cancer resistance protein
BID	twice a day
BIW	twice weekly
BLRM	Bayesian logistic regression modeling
BrdU	bromodeoxyuridine
BSA	body surface area
BSC	best supportive care
CD	carbohydrate deficient
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL/F	apparent total clearance of the drug from after administration
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum (peak) drug concentration
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CPC	Child-Pugh criteria
cps	cycles per second
CR	complete response
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CxDy	Cycle X Day y
CYP	cytochrome P450
CYP2C9	cytochrome P450 2C9
CYP3A4	cytochrome P450 3A4

DCR	disease control rate
DDS	dose-determining analysis set
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DOR	duration of response
DRESS	drug reaction of eosinophilia and systemic symptoms
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EEG	electroencephalogram
ENR	enrolled analysis set
EOT	end of treatment
ERK	extracellular signal-regulated kinase
EWOC	escalation with overdose control
FAS	full analysis set
FDA	Food and Drug Administration
FG	fasting glucose
FPG	fasting plasma glucose
FTI	farnesyltransferase inhibitor
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
HAV	hepatitis A virus
HBc	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDPE	high-density polyethylene
HEV	hepatitis E virus
HIPAA	Health Insurance Portability and Accountability Act
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
HR	hazard ratio
HRAS	Harvey rat sarcoma virus gene homolog
HSV	herpes simplex virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IEC	Independent Ethics Committee

IHC	immunohistochemistry
IME	important medical event
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
ISEL	in situ end labeling
IV	intravenous
IVD	in vitro diagnostics
KRAS	Kirsten rat sarcoma virus gene homolog
LFT	liver function test
MCV	mean corpuscular volume
MDS	myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mechanistic target of rapamycin
NA	not applicable
NCI	National Cancer Institute
NE	not evaluable
NF	National Formulary
NGS	next generation sequencing
NRAS	neuroblastoma RAS virus oncogene homolog
NSCLC	non-small cell lung cancer
OBAD	optimal biologically active combination dose
ORR	objective response rate
OS	overall survival
PD	progressive disease
CCI [redacted]	
PDX	patient-derived xenograft
PFS	progression-free survival
Ph Eur	European Pharmacopoeia
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetic
PKAS	pharmacokinetic analysis set
PR	partial response
PT	preferred term
PT/INR	prothrombin time/international normalized ratio
QAM	each morning
QD	once daily
QPM	each evening
QTcF	QT interval corrected by Fridericia's formula
qRT-PCR	Real-time quantitative reverse transcription Polymerase chain reaction

QW	once weekly
R/M	recurrent/metastatic
RBC	red blood cell
RECIST	Response evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SCAR	severe cutaneous adverse reaction
SCLC	small cell lung cancer
SD	stable disease
SE	standard error
SEM	standard error of the mean
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SMC	safety monitoring committee
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reactions
T	tipifarnib
T3	triiodothyronine
T4	thyroxine
TCGA	The Cancer Genome Atlas
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
T_{max}	time to reach maximum (peak) concentration following drug administration
TSH	thyroid-stimulating hormone
UGT	uridine 5'-diphospho-glucuronosyltransferase - glucuronosyltransferase
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
VEGF	vascular endothelial growth factor
WOCBP	women of childbearing potential
WT	wild type
VAF	variant allele frequency
V_d/F	apparent volume of distribution after non-intravenous administration

APPENDIX 7: DOSE-TOXICITY AND DOSE-EFFICACY MODELING

General Considerations

An adaptive dose escalation design will be applied to evaluate the toxicity and efficacy profiles of the following 2 agents:

- Agent 1: Tipifarnib.
- Agent 2: Alpelisib.

The adaptive design will be utilized to characterize the dose-toxicity or dose-response relationships and identify an OBAD based on the following endpoints:

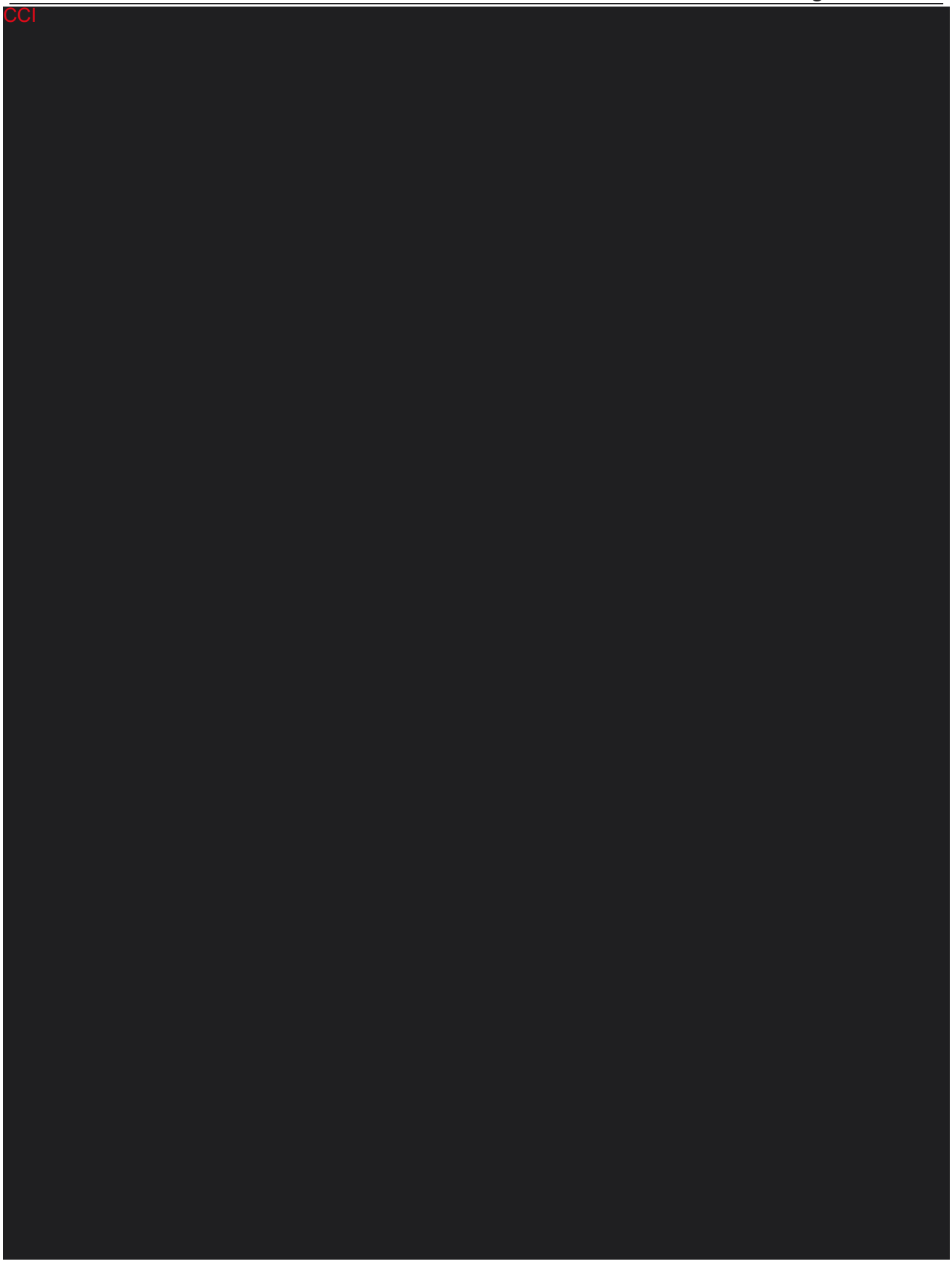
- Endpoint 1: Binary endpoint (DLT).
- Endpoint 2: Binary endpoint (efficacy response based on overall response).
- Endpoint 3: Binary endpoint (efficacy response based on SD).

The adaptive design will rely on a Bayesian modeling approach for a combination of the 2 agents where each marginal dose-toxicity or dose-response relationship is described by a BLRM (Neuenschwander et al, 2014).

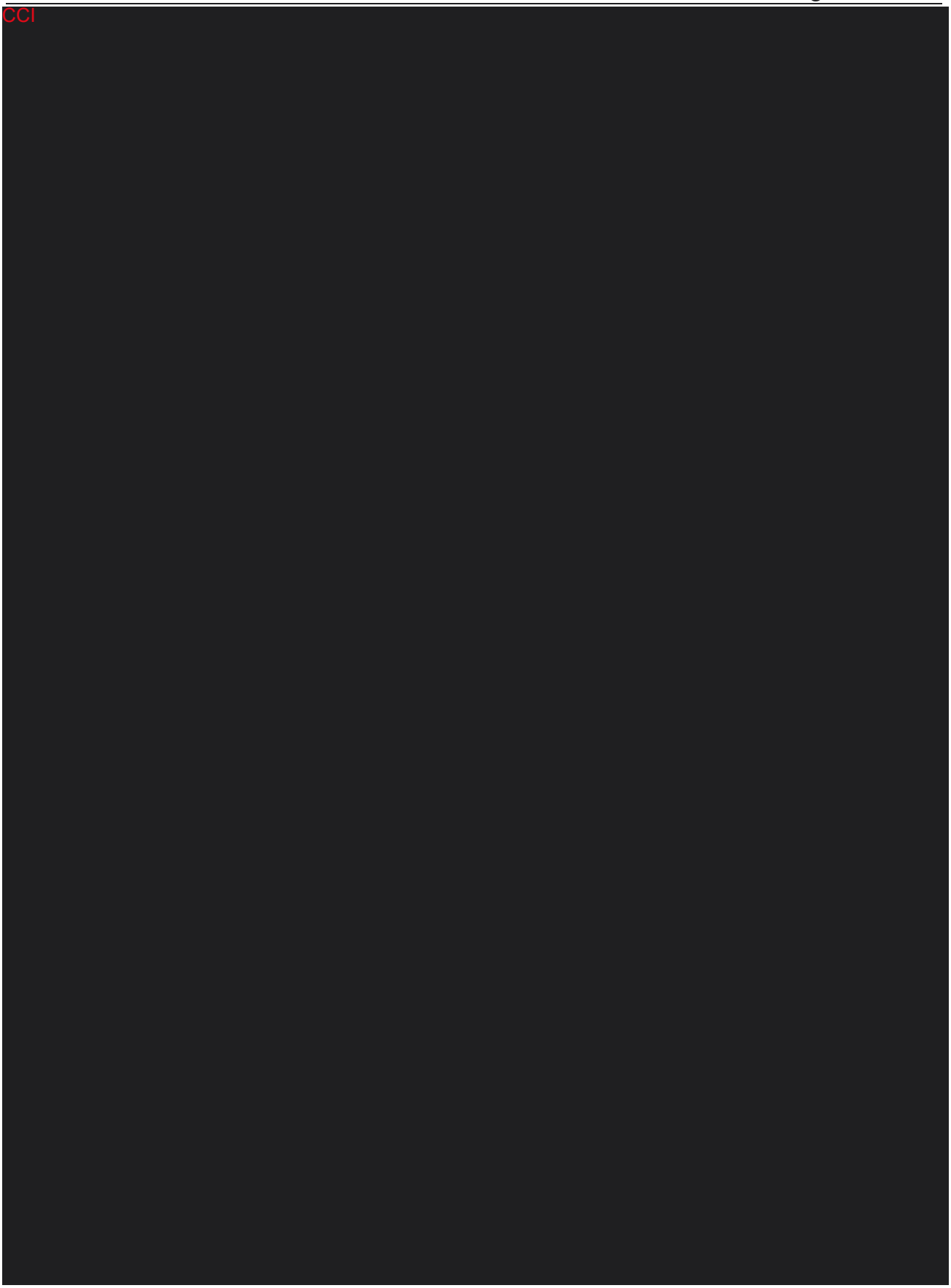
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[redacted]

Dose Selection Rules

The starting dose level will be dose level 1 as defined in Table 2 and Table 3. At the end of each cohort, the eligible dose range for the next cohort of participants is defined as the set of safe combination doses from the combination doses defined in Table 2 and Table 3 (see Safe Combination Doses). If the set of safe combination doses is empty, the trial will be stopped.

The combination dose for the next cohort will be selected from the eligible dose range by maximizing the clinical utility index (see Clinical Utility Index) as well as by using additional relevant information, eg, a global assessment of the safety profile, PK data and other relevant clinical data.

Dose escalation will continue until an OBAD or a suitable lower dose is identified. This will occur when the following conditions are met:

- At least 6 participants have been treated at the selected combination dose.
- The combination dose satisfies 1 of the following conditions:
  - The posterior probability of excessive toxicity at this combination dose does not equal or exceed 25% and the clinical utility index is the highest among the eligible combination doses, or
  - A minimum of 20 participants have already been treated.

BLRM Guidelines

Participants who complete the 28-day DLT period and are evaluable (per protocol) will have their data incorporated into the model.

CCI

[redacted]

CCI [redacted]

BLRM Restrictions

The model requires data from a minimum of 2 evaluable participants.

The model does not provide recommendations on how many participants subsequent cohorts should enroll. This will be up to the SMC members to determine. However, it will be important to consider the potential that not all participants may be evaluable in any given cohort.

Dose of only one agent should be increased at a time.

Doses cannot be increased by more than 100%.

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Section	Summary of Change	Rationale for Change
Synopsis Objectives and Endpoints, Section 3.1 Objectives and Endpoints	CCI [redacted]	
Synopsis Overall Design, Section 4.1 Overall Design	The description of Cohort 2 was modified to reference HRAS overexpression as determined by Sponsor's Central Laboratory.	The text was modified to describe plans more accurately for the HRAS overexpression assay.
Synopsis Figure 3 Dose Escalation	Updated the wording to clarify that in the absence of a DLT, approximately 2 additional participants may be enrolled at the current dose cohort while the SMC meets.	The intent is to allow for the opportunity to enroll 2 additional participants while the SMC meets.
Section 1.3 Schedule of Activities	Triplicate ECG assessments were added at Cycle 1 Day 1 at approximately 3 hours post dose and Cycle 2 Day 1 to provide monitoring at the anticipated maximal tipifarnib concentration and steady state, respectively. Day 1 (± 2d) of every Cycle has been updated to Day 1 (± 2d) of Cycle X.	CCI [redacted] as the QT prolongation risk has not yet been formally assessed.
Section 1.3 Schedule of Activities	CCI [redacted]	
Section 1.3 Schedule of Activities	Tumor tissue and extracts for HRAS expression testing has been updated to Tumor Tissue for Central HRAS testing. Superscript 21 has been updated.	This change was made to reflect that all participants should submit tumor tissue for central assessment of HRAS overexpression.
Section 1.3 Schedule of Activities	Superscript 22 has been updated to: All enrolled participants should have PIK3CA mutation/amplification status determined by a	To clarify that all testing for PIK3CA must be done by a Sponsor approved CLIA lab or a Sponsor designated central laboratory.

	Sponsor-approved CLIA-certified laboratory or the Sponsor-designated central laboratory.	
Section 1.3 Schedule of Activities	CCI [redacted]	
Section 2.2.3 Consideration of Gender Effect	Newly added subsection.	To provide updated information on the effects of alpelisib in male and female patients with PIK3CA inhibition per Novartis's SOLAR-1 study. Due to the magnitude of the gender effect on exposure-response, no dosing modifications are warranted.
Section 5.1 Inclusion Criteria	Current IC #14 should be two separate IC's and therefore they have been separated out to IC #14 and #15.	To correct a formatting error in which two inclusion criteria were included within the same number, these were separated.
Section 5.2 Exclusion Criteria	New exclusion criteria #9 added: Mean corrected QT interval by Fredericia's formula (QTcF) >480 ms on triplicate electrocardiograms (ECGs) performed within 5 minutes of each other.	CCI [redacted] as the QT prolongation risk has not yet been formally assessed.
Section 6.1 Trial Interventions Administered	Guidance for tipifarnib missed dose was added and alpelisib missed dose guidance was updated from within 9 hours to within 8 hours.	To align with tipifarnib missed dose guidance which is 8 hours.
Section 6.1.2 Tipifarnib Medication Crushing Instructions (new), Section 4.1	Inclusion of instructions for the preparation and administration for crushed tipifarnib	To provide guidance to Investigators for the appropriate preparation and administration of crushed tipifarnib tablets.
Section 6.2 Trial Intervention Characteristics	Removed reference to the 100 mg strength tipifarnib tablets.	The trial will only supply 300 mg strength tablets of tipifarnib.
Section 8.1 Screening for HRAS Overexpression and PI3K Mutations/Amplifications	Updated section to provide clarity around eligibility and tumor tissue.	To be less specific for the tumor tissue sample as the most recent tissue may be from a surgical resection and not a biopsy.

		Participants who enroll in the study may be required to submit additional tumor tissue (archival) for the companion diagnostics. This will apply to participants who are part of the primary analysis set.
Section 8.1.1 PIK3CA Testing	Section name has been updated. Additionally, the section includes pre-specifying activating mutations-additional mutations may be eligible based on approval from the Sponsor. Information has been updated to include options for PIK3CA testing as well to allow for the collection of samples to test for HRAS expression.	It is important to pre-specify the PIK3CA mutations that are eligible but to also account for new variants for where there is scientific support that they activate PIK3CA.
Section 8.1.2: HRAS Testing	Section heading has been updated as well as the section to provide additional information on HRAS expression.	To provide information on the type of assays to determine HRAS expression and guidance on identifying potential participants with HRAS overexpression for eligibility into the trial.
Table 11 Blood Sampling Timepoints for PK Analysis	CCI [redacted]	
Section 8.5.3 Pregnancy and In Utero Drug Exposure	Section updated to include guidance for information collection pertaining to any female partner of a male participant who becomes pregnant.	Per guidelines, the collection of this information is required.
Section 8.6 Biomarkers	CCI [redacted]	

Section 9.4.4.3 Pharmacokinetic Analyses	CCI	
Section 9.4.5.4 Biomarker Analysis		
Section 10.2.3 Clinic Visits	Language added to include at home nursing visits.	Adopted the addition of this language in response to COVID and various health authority guidances.
Table 14 Strong Inhibitors or Inducers of CYP3A4	Removed grapefruit juice (high dose or double strength preparations only) from the list.	Grapefruit juice is not a medication (Table 14, Appendices).
General	Editorial and formatting changes made for internal consistency, clarification, and correctness.	

Table 1: Summary of Changes

Section	Summary of Change	Rationale for Change
Pre-screening ICF for HRAS Overexpression and PIK3CA mutation/amplification Section 1.3 SOA, Section 8	Addition of pre-screening ICF for HRAS and PIK3CA testing.	Testing for HRAS and PIK3CA can occur outside of the KO-TIP-013 study with the aim of pre-identifying patients and only consenting patients for CCI and not to the entire study.
Section 1.4 SOA	CCI [redacted]	
6.6.1 Management of Dose Interruptions	Addition of drug interruption management guidelines for tipifarnib, alpelisib, and both drugs.	To ensure drug interruptions are managed appropriately given the different dosing schedules of tipifarnib and alpelisib to maximize the dose intensity within a given cycle.
6.6.2 Intra-participant Dose Escalation	Addition of criteria to be considered for participants who intra-participant dose escalate.	To ensure a participant is appropriate for intra-participant dose escalation.
Table 9 Summary of Dose Modifications for Treatment-Related Toxicities	Aligned management of tipifarnib with alpelisib for overlapping toxicities.	To ensure consistency on the management and re-initiation of study drugs when the same toxicity is experienced at the same grade.
General	Editorial and formatting changes made for internal consistency, clarification, and correctness.	

SUMMARY OF KEY CHANGES: KO-TIP-013 PROTOCOL AMENDMENT 3 (09 OCTOBER 2025) FROM PROTOCOL AMENDMENT 2 (14 APRIL 2022)

This is a high-level overview of key changes from KO-TIP-013 Protocol Amendment 2 to KO-TIP-013 Protocol Amendment 3.

Editorial changes related to grammar and formatting are not listed.

Section	Summary of Change	Rationale for Change
Title Page	The Kura Oncology logo was updated	The Kura Oncology logo was revised to align with updated corporate branding guidelines
Title Page	Legal registered address was updated	Updated legal address to reflect company office relocation; administrative change only, no impact to study
Title Page	The amendment number and approval date have been updated	Updated to reflect the most recent information
Protocol Approval Page	The sponsor signatory was updated	Updated to reflect the most recent information
Table of Contents	Updated	Revised to include accurate sections and corresponding page numbers
Section 1.1	Revisions made to clarify language and make synopsis text consistent with body text	Editorial; Updated to align with revised End of Trial definition and to note that participants will be discontinued at the time of disease progression
Section 1.2	Revisions made to make Figure 1 and Figure 3 consistent with body text	Editorial; Updated to align with revised End of Trial definition and to note that participants will be discontinued at the time of disease progression

Section	Summary of Change	Rationale for Change
Section 1.4	Treatment Continuation Visit column added to align with the updated End of Trial definition, with appropriate assessments indicated as applicable. Footnotes revised to reflect the Treatment Continuation Visit column and the intervention period beyond 6 months. The End of Treatment (EOT) Visit column was updated to align with the updated End of Trial definition, with appropriate assessments indicated as applicable.	Schedule of Activities table updated to align with revised End of Trial definition
Section 4.1	The Trial Design section was updated to incorporate the revised End of Trial definition	Editorial; Updated to align with revised End of Trial definition and to note that participants will be discontinued at the time of disease progression
Section 4.4	End of Trial definition updated (6 months treatment); patients may continue treatment beyond 6 months if clinically beneficial	End of Trial definition updated to allow trial closure while permitting continued treatment beyond 6 months for patients deriving clinical benefit
Sections 5.4, 6.8, and 8.6	Updated safety reporting contact information	Safety reporting contact information updated to reflect current company contacts
Section 6.6.1	Revised to note that radiographic imaging assessments will be conducted per treatment facility's/local standard of care	Aligned with updated End of Trial definition and all other corresponding revisions
Section 6.7	Revised to enable patients benefiting clinically to continue treatment beyond 6 months, updated documentation requirements, updated definition of	Aligned with updated End of Trial definition and all other corresponding revisions

Section	Summary of Change	Rationale for Change
	end of treatment visit/End of Trial, and noted participants will be discontinued at the time of disease progression	
Section 7.1	Discontinuation of trial intervention was updated	Aligned with updated End of Trial definition and all other corresponding revisions
Section 7.3	Text in the Medical Care of the Participant After End of Trial Section was replaced with "Not applicable" since End of Trial definition was revised	No longer relevant with revised End of Trial definition
Section 8.4.3	For participants receiving treatment beyond 6 months, survival follow-up will not be performed	No longer relevant with revised End of Trial definition
Section 8.6.4	Protocol revised to state adverse event/serious adverse event monitoring extends 30 days beyond final dose	Aligned with updated End of Trial definition and all other corresponding revisions