EU Clinical Trials Register

Clinical trial results:

The AIM-HN and SEQ-HN Study: A 2 Cohort, Non-comparative, Pivotal Study Evaluating the Efficacy of Tipifarnib in Patients with Head and Neck Squamous Cell Carcinoma (HNSCC) with HRAS Mutations (AIM-HN) and the Impact of HRAS Mutations on Response to First Line Systemic Therapies for HNSCC (SEQ-HN)

Summary

EudraCT number	2018-001437-40
Trial protocol	ES DE GB NO BE AT NL GR DK IT
Global end of trial date	02 May 2023

Results information

Result version number	v1 (current)
This version publication date	04 May 2024
First version publication date	04 May 2024

Trial information

Trial identification

Sponsor protocol code	KO-TIP-007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03719690
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Kura Oncology, Inc.
Sponsor organisation address	12730 High Bluff Drive, Suite 400, San Diego, United States, CA 92130
Public contact	Clinical Operations, Kura Oncology, Inc., KO-TIP-007@kuraoncology.com
Scientific contact	Clinical Operations, Kura Oncology, Inc., KO-TIP-007@kuraoncology.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 May 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 May 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to determine the objective response rate (ORR) of tipifarnib in participants with Head and Neck Squamous Cell Carcinoma (HNSCC) with Harvey rat sarcoma virus gene homolog (HRAS) mutations with a variant allele frequency (VAF) ≥20% (High VAF population), as assessed by Independent Review Facility (IRF).

Protection of trial subjects:

This study was conducted in accordance with the Note for Guidance on Good Clinical Practice International Council for Harmonisation, Harmonised Tripartite Guideline E6 (R1)/Integrated Addendum E6 (R2); United States Food and Drug Administration Code of Federal Regulations (Title 21 Parts 50, 56, 312), requirements for the conduct of clinical studies as provided in the European Union Directive 2011/20/EC; the general guidelines indicated in the Declaration of Helsinki; and all applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 131
Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Spain: 56
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Thailand: 13
Country: Number of subjects enrolled	Korea, Republic of: 18
Country: Number of subjects enrolled	Taiwan: 16
Country: Number of subjects enrolled	Denmark: 10
Country: Number of subjects enrolled	Malaysia: 5
Country: Number of subjects enrolled	Australia: 3
Worldwide total number of subjects	296
EEA total number of subjects	105

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	175
From 65 to 84 years	118
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

A total of 296 participants were enrolled (59 participants in AIM-HN and 237 participants in SEQ-HN) in 14 countries between March 2019 and May 2023.

Pre-assignment

Screening details:

This study consisted of 2 non-comparative sub-studies: (1) an interventional open-label, single-arm, pivotal study evaluating the efficacy of tipifarnib in mHRAS HNSCC (AIM-HN) and (2) an observational study to evaluate the impact of HRAS mutations on response to first line systemic therapies for HNSCC (SEQ-HN).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Tipifarnib Treatment Cohort: AIM-HN

Arm description:

Participants enrolled as part of AIM-HN received tipifarnib administered with food at a starting dose of 600 mg, orally, twice a day (bid) on Days 1-7 and 15-21 of 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Tipifarnib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tablet for oral administration.

Arm title	Observational Cohort: SEQ-HN

Arm description:

Participants with HNSCC in whom HRAS mutations were not identified (wild type HRAS HNSCC) and who consented to provide first line outcome data and additional follow-up.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Tipifarnib Treatment Cohort: AIM-HN	Observational Cohort: SEQ-HN
Started	59	237
Safety Analysis Set (SAS)	59	0
Modified Intent-to-Treat Analysis Set	59	0
Completed	0	0
Not completed	59	237
Consent withdrawn by subject	5	10

Death	40	149
Miscellaneous	12	56
Lost to follow-up	2	18
Unwilling or unable to comply with requirements	-	4

Baseline characteristics

Reporting groups

Reporting group title	Tipifarnib Treatment Cohort: AIM-HN
Reporting group description:	

Participants enrolled as part of AIM-HN received tipifarnib administered with food at a starting dose of 600 mg, orally, twice a day (bid) on Days 1-7 and 15-21 of 28-day cycles.

Reporting group title	Observational Cohort: SEQ-HN
Reporting group description:	

Participants with HNSCC in whom HRAS mutations were not identified (wild type HRAS HNSCC) and who consented to provide first line outcome data and additional follow-up.

Reporting group values	Tipifarnib Treatment Cohort: AIM-HN	Observational Cohort: SEQ-HN	Total
Number of subjects	59	237	296
Age categorical			
Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	31	144	175
>=65 years	28	93	121
Gender categorical			
Units: Subjects			
Female	15	59	74
Male	44	178	222
Race			
Units: Subjects			
White	33	180	213
Black or African American	1	10	11
Asian	23	37	60
American Indian or Alaska Native	0	2	2
Other	2	7	9
Missing	0	1	1
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	8	8
Not Hispanic or Latino	55	217	272
Not Reported	3	9	12
Unknown	1	3	4
Variant Allele Frequency (VAF) Status			

Genetic testing was done for tumor tissue to confirm mutant (variant) allele frequency at Baseline. Data collection and analysis of VAF status for participants in the Observational SEQ-HN Cohort was not pre-specified.

Units: Subjects			
Participants with low VAF (< 20%)	9	0	9
Participants with high VAF (>= 20%)	50	0	50
Not Applicable	0	237	237

End points

End points reporting groups

Reporting group title	Tipifarnib Treatment Cohort: AIM-HN
Reporting group description:	
Participants enrolled as part of AIM-HN received tipifarnib administered with food at a starting dose of 600 mg, orally, twice a day (bid) on Days 1-7 and 15-21 of 28-day cycles.	
Reporting group title	Observational Cohort: SEQ-HN
Reporting group description:	
Participants with HNSCC in whom HRAS mutations were not identified (wild type HRAS HNSCC) and who consented to provide first line outcome data and additional follow-up.	

Primary: Objective Response Rate (ORR) in High Variable Allele Frequency (VAF) Population, as Assessed by Independent Review Facility (IRF)

End point title	Objective Response Rate (ORR) in High Variable Allele Frequency (VAF) Population, as Assessed by Independent Review Facility (IRF)[1][2]

End point description:

ORR was defined as the percentage of participants who experienced a best overall response (BOR) of complete response (CR; disappearance of all target lesions) or partial response (PR; at least a 30% decrease in the sum of diameters of target lesions) and was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by IRF. 95% confidence interval (CI) was calculated by the exact binomial (Clopper-Pearson) method.

Modified Intent-to-Treat (mITT) Analysis Set: consisted of all participants who received at least one dose of tipifarnib. Analysis was pre-specified for participants with high VAF only. Data collection and analysis of ORR for participants in the Observational SEQ-HN Cohort was not pre-specified.

End point type	Primary
End point timeframe:	
Up to approximately 28 months	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No additional statistical analyses were pre-specified for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive statistics were only pre-specified for the AIM-HN arm.

End point values	Tipifarnib Treatment Cohort: AIM-HN			
Subject group type	Reporting group			
Number of subjects analysed	50[3]			
Units: percentage of participants				
number (confidence interval 95%)	20.0 (10.03 to 33.72)			

Notes:

[3] - High VAF Population (mITT Analysis Set)

Statistical analyses

No statistical analyses for this end point

Secondary: ORR in All VAF Population, as Assessed by IRF

End point title	ORR in All VAF Population, as Assessed by IRF[4]

End point description:

ORR was defined as the percentage of participants who experienced a BOR of CR or PR and was assessed using RECIST v1.1 by IRF. 95% CI was calculated by the exact binomial (Clopper-Pearson) method.

mITT Analysis Set: consisted of all participants who received at least one dose of tipifarnib. Analysis was pre-specified for all VAF participants. Data collection and analysis of ORR for participants in the Observational SEQ-HN Cohort was not pre-specified.

End point type	Secondary

End point timeframe:

Up to approximately 28 months

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Descriptive statistics were only pre-specified for the AIM-HN arm.

End point values	Tipifarnib Treatment Cohort: AIM-HN			
Subject group type	Reporting group			
Number of subjects analysed	59[5]			
Units: percentage of participants				
number (confidence interval 95%)	18.6 (9.69 to 30.91)			

Notes:

[5] - All VAF Population (mITT Analysis Set)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) in High VAF Population, as Assessed by IRF

End point title	Duration of Response (DoR) in High VAF Population, as Assessed by IRF[6]

End point description:

DoR was defined as the time from the date of first response (CR or PR [whichever occurred first]) to the date of progression of disease or death of any cause, whichever occurred first, in participants with a confirmed CR or PR and was assessed using RECIST v1.1 by IRF. Median was calculated using the Kaplan-Meier method. 95% CI was based on Brookmeyer and Crowley method with log-log transformation. Values of "99999" indicate the upper CI was not reached due to lack of events.

mITT Analysis Set: consisted of all participants who received at least one dose of tipifarnib. Analysis was pre-specified for participants with high VAF and available data only. Data collection and analysis of DoR for participants in the Observational SEQ-HN Cohort was not pre-specified.

End point type	Secondary

End point timeframe:

Up to approximately 28 months

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Descriptive statistics were only pre-specified for the AIM-HN arm.

End point values	Tipifarnib Treatment Cohort: AIM-HN			
Subject group type	Reporting group			
Number of subjects analysed	10[7]			
Units: months				
median (confidence interval 95%)	6.51 (3.877 to 99999)			

Notes:

[7] - High VAF Population (mITT Analysis Set) with CR or PR

Statistical analyses

No statistical analyses for this end point

Secondary: DoR in All VAF Population, as Assessed by IRF

End point title	DoR in All VAF Population, as Assessed by IRF[8]

End point description:

DoR was defined as the time from the date of first response (CR or PR [whichever occurred first]) to the date of progression of disease or death of any cause, whichever occurred first, in participants with a confirmed CR or PR and was assessed using RECIST v1.1 by IRF. Median was calculated using the Kaplan-Meier method. 95% CI was based on Brookmeyer and Crowley method with log-log transformation. Values of "99999" indicate the upper CI was not reached due to lack of events.

mITT Analysis Set: consisted of all participants who received at least one dose of tipifarnib. Analysis was pre-specified for all VAF participants with available data. Data collection and analysis of DoR for participants in the Observational SEQ-HN Cohort was not pre-specified.

End point type	Secondary

End point timeframe:

Up to approximately 28 months

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Descriptive statistics were only pre-specified for the AIM-HN arm.

End point values	Tipifarnib Treatment Cohort: AIM-HN			
Subject group type	Reporting group			
Number of subjects analysed	11[9]			
Units: months				
median (confidence interval 95%)	6.51 (3.877 to 99999)			

Notes:

[9] - All VAF Population (mITT Analysis Set) with CR or PR

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) in High VAF Population, as Assessed by IRF

End point title	Progression Free Survival (PFS) in High VAF Population, as Assessed by IRF[10]

End point description:

PFS was defined as months from the first dose of the study drug to the first documented progressive disease (PD, appearance of one or more new lesions or at least a 20% increase in the sum of the diameters of target lesions) or death, whichever came first and was assessed using RECIST v1.1 by IRF. Median was calculated using the Kaplan-Meier method. 95% CI was based on Brookmeyer and Crowley method with log-log transformation.

mITT Analysis Set: consisted of all participants who received at least one dose of tipifarnib. Analysis was pre-specified for participants with high VAF and available data only. Data collection and analysis of PFS for participants in the Observational SEQ-HN Cohort was not pre-specified.

End point type	Secondary

End point timeframe:

Up to approximately 28 months

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive statistics were only pre-specified for the AIM-HN arm.

End point values	Tipifarnib Treatment Cohort: AIM-HN			
Subject group type	Reporting group			
Number of subjects analysed	50[11]			
Units: months				
median (confidence interval 95%)	2.60 (1.873 to 4.402)			

Notes:

[11] - High VAF Population (mITT Analysis Set)

Statistical analyses

No statistical analyses for this end point

Secondary: PFS in All VAF Population, as Assessed by IRF

End point title	PFS in All VAF Population, as Assessed by IRF[12]

End point description:

PFS was defined as months from the first dose of the study drug to the first documented PD or death, whichever came first and was assessed using RECIST v1.1 by IRF. Median was calculated using the Kaplan-Meier method. 95% CI was based on Brookmeyer and Crowley method with log-log transformation.

mITT Analysis Set: consisted of all participants who received at least one dose of tipifarnib. Analysis was pre-specified for all VAF participants with available data. Data collection and analysis of PFS for participants in the Observational SEQ-HN Cohort was not pre-specified.

End point type	Secondary

End point timeframe:

Up to 28 approximately months

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive statistics were only pre-specified for the AIM-HN arm.

End point values	Tipifarnib Treatment Cohort: AIM-HN			
Subject group type	Reporting group			
Number of subjects analysed	59[13]			
Units: months				
median (confidence interval 95%)	2.23 (1.873 to 3.548)			

Notes:

[13] - All VAF Population (mITT Analysis Set)

Statistical analyses

No statistical analyses for this end point

Secondary: PFS Rate in High VAF Population, as Assessed by IRF

End point title	PFS Rate in High VAF Population, as Assessed by IRF[14]

End point description:

PFS rate was defined as the percentage of participants who had not experienced documented PD or death, whichever came first and was assessed using RECIST v1.1 by IRF at 6 and 9 month timepoints. Percentage of participants was calculated using the Kaplan-Meier method. 95% CI was calculated using normal approximation to the log transformed cumulative hazard rate.

mITT Analysis Set: consisted of all participants who received at least one dose of tipifarnib. Analysis was pre-specified for participants with high VAF and available data only. Data collection and analysis of PFS for participants in the Observational SEQ-HN Cohort was not pre-specified.

End point type	Secondary

End point timeframe:

6 months and 9 months

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive statistics were only pre-specified for the AIM-HN arm.

End point values	Tipifarnib Treatment Cohort: AIM-HN			
Subject group type	Reporting group			
Number of subjects analysed	50[15]			
Units: percentage of participants				
number (confidence interval 95%)				
6 months	29 (16.2 to 42.9)			
9 months	20 (8.9 to 33.6)			

Notes:

[15] - High VAF Population (mITT Analysis Set)

Statistical analyses

No statistical analyses for this end point

Secondary: PFS Rate in All VAF Population, as Assessed by IRF

End point title	PFS Rate in All VAF Population, as Assessed by IRF[16]

End point description:

PFS rate was defined as the percentage of participants who had not experienced documented PD or death, whichever came first and was assessed using RECIST v1.1 by IRF at 6 and 9 month timepoints. Percentage of participants was calculated using the Kaplan-Meier method. 95% CI was calculated using normal approximation to the log transformed cumulative hazard rate.

mITT Analysis Set: consisted of all participants who received at least one dose of tipifarnib. Analysis was pre-specified for all VAF participants with available data. Data collection and analysis of PFS for participants in the Observational SEQ-HN Cohort was not pre-specified.

End point type	Secondary

End point timeframe:

6 months and 9 months

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive statistics were only pre-specified for the AIM-HN arm.

End point values	Tipifarnib Treatment Cohort: AIM-HN			
Subject group type	Reporting group			
Number of subjects analysed	59[17]			
Units: percentage of participants				
number (confidence interval 95%)				
6 months	26 (14.9 to 38.4)			
9 months	18 (8.9 to 30.8)			

Notes:

[17] - All VAF Population (mITT Analysis Set)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in High VAF Population

End point title	Overall Survival (OS) in High VAF Population[18]

End point description:

OS was defined as months from first dose date until death from any cause. Median was calculated using the Kaplan-Meier method. 95% CI was based on Brookmeyer and Crowley method with log-log transformation.

mITT Analysis Set: consisted of all participants who received at least one dose of tipifarnib. Analysis was pre-specified for participants with high VAF. Data collection and analysis of OS for participants in the Observational SEQ-HN Cohort was not pre-specified.

End point type	Secondary

End point timeframe:

Up to approximately 28 months

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive statistics were only pre-specified for the AIM-HN arm.

End point values	Tipifarnib Treatment Cohort: AIM-HN			
Subject group type	Reporting group			
Number of subjects analysed	50[19]			
Units: months				
median (confidence interval 95%)	6.97 (4.895 to 11.466)			

Notes:

[19] - High VAF Population (mITT Analysis Set)

Statistical analyses

No statistical analyses for this end point

Secondary: OS in All VAF Population

End point title	OS in All VAF Population[20]

End point description:

OS was defined as months from first dose date until death from any cause. Median was calculated using the Kaplan-Meier method. 95% CI was based on Brookmeyer and Crowley method with log-log transformation.

mITT Analysis Set: consisted of all participants who received at least one dose of tipifarnib. Analysis was pre-specified for all VAF participants. Data collection and analysis of OS for participants in the Observational SEQ-HN Cohort was not pre-specified.

End point type	Secondary

End point timeframe:

Up to approximately 28 months

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive statistics were only pre-specified for the AIM-HN arm.

End point values	Tipifarnib Treatment Cohort: AIM-HN			
Subject group type	Reporting group			
Number of subjects analysed	59[21]			
Units: months				
median (confidence interval 95%)	6.21 (4.370 to 9.035)			

Notes:

[21] - All VAF Population (mITT Analysis Set)

Statistical analyses

No statistical analyses for this end point

Secondary: OS Rate at 12 Months in High VAF Population

End point title	OS Rate at 12 Months in High VAF Population[22]

End point description:

OS rate was defined as the percentage of participants who had not experienced or death and was assessed at 12 months. Percentage of participants was calculated using the Kaplan-Meier method. 95%

CI was calculated using normal approximation to the log transformed cumulative hazard rate.

mITT Analysis Set: consisted of all participants who received at least one dose of tipifarnib. Analysis was pre-specified for participants with high VAF only. Data collection and analysis of OS for participants in the Observational SEQ-HN Cohort was not pre-specified.

End point type	Secondary
End point timeframe:	
12 months	

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive statistics were only pre-specified for the AIM-HN arm.

End point values	Tipifarnib Treatment Cohort: AIM-HN			
Subject group type	Reporting group			
Number of subjects analysed	50[23]			
Units: percentage of participants				
number (confidence interval 95%)	31 (17.2 to 46.6)			

Notes:

[23] - High VAF Population (mITT Analysis Set)

Statistical analyses

No statistical analyses for this end point

Secondary: OS Rate at 12 Months in All VAF Population

End point title	OS Rate at 12 Months in All VAF Population[24]

End point description:

OS rate was defined as the percentage of participants who had not experienced or death and was assessed at 12 months. Percentage of participants was calculated using the Kaplan-Meier method. 95% CI was calculated using normal approximation to the log transformed cumulative hazard rate.

mITT Analysis Set: consisted of all participants who received at least one dose of tipifarnib. Analysis was pre-specified for all VAF participants. Data collection and analysis of OS for participants in the Observational SEQ-HN Cohort was not pre-specified.

End point type	Secondary
End point timeframe:	
12 months	

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive statistics were only pre-specified for the AIM-HN arm.

End point values	Tipifarnib Treatment Cohort: AIM-HN			
Subject group type	Reporting group			
Number of subjects analysed	59[25]			
Units: percentage of participants				
number (confidence interval 95%)	30 (17.2 to			

	43.7)

Notes:

[25] - All VAF Population (mITT Analysis Set)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR) in High VAF Population, as Assessed by IRF

End point title	Time to Response (TTR) in High VAF Population, as Assessed by IRF[26]

End point description:

TTR was defined as months from treatment start to first CR or PR (whichever was first recorded) in participants with confirmed CR or PR and was assessed using RECIST v1.1 by IRF. TTR was summarized descriptively by summary statistics.

mITT Analysis Set: consisted of all participants who received at least one dose of tipifarnib. Analysis was pre-specified for participants with high VAF and available data only. Data collection and analysis of TTR for participants in the Observational SEQ-HN Cohort was not pre-specified.

End point type	Secondary

End point timeframe:

Up to approximately 28 months

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive statistics were only pre-specified for the AIM-HN arm.

End point values	Tipifarnib Treatment Cohort: AIM-HN			
Subject group type	Reporting group			
Number of subjects analysed	10[27]			
Units: months				
median (full range (min-max))	1.9 (1.7 to 3.8)			

Notes:

[27] - High VAF Population (mITT Analysis Set) with confirmed CR or PR by IRF

Statistical analyses

No statistical analyses for this end point

Secondary: TTR in All VAF Population, as Assessed by IRF

End point title	TTR in All VAF Population, as Assessed by IRF[28]

End point description:

TTR was defined as months from treatment start to first CR or PR (whichever was first recorded) in participants with confirmed CR or PR and was assessed using RECIST v1.1 by IRF. TTR was summarized descriptively by summary statistics.

mITT Analysis Set: consisted of all participants who received at least one dose of tipifarnib. Analysis was pre-specified for all VAF participants with available data. Data collection and analysis of TTR for participants in the Observational SEQ-HN Cohort was not pre-specified.

End point type	Secondary

End point timeframe:
Up to approximately 28 months

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Descriptive statistics were only pre-specified for the AIM-HN arm.

End point values	Tipifarnib Treatment Cohort: AIM-HN			
Subject group type	Reporting group			
Number of subjects analysed	11[29]			
Units: months				
median (full range (min-max))	1.9 (1.7 to 18.4)			

Notes:

[29] - All VAF Population (mITT Analysis Set) with confirmed CR or PR by IRF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Experienced Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Participants who Experienced Treatment-Emergent Adverse Events (TEAEs)[30]

End point description:

TEAEs were defined as adverse events (AEs) that started on or after the first dose of the study drug and within 30 days of the last administration of the study drug. Common Terminology Criteria for Adverse Events (CTCAE) v5.0 was used for toxicity grading (Grade 3: severe or disabling; Grade 4: life-threatening; Grade 5: death related to AE). Clinically significant changes in laboratory tests, vital signs, and electrocardiogram results were reported as AEs.

Safety Analysis Set (SAS): consisted of all participants in the AIM-HN who received at least one dose of tipifarnib. Analysis was pre-specified for participants in the AIM-HN Cohort only. Data collection and analysis of safety for participants in the Observational SEQ-HN Cohort was not pre-specified.

End point type	Secondary

End point timeframe:
Up to approximately 28 months

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Descriptive statistics were only pre-specified for the AIM-HN arm.

End point values	Tipifarnib Treatment Cohort: AIM-HN			
Subject group type	Reporting group			
Number of subjects analysed	59[31]			
Units: participants				
Any TEAEs	58			
Any Grade 3 or Higher TEAEs	43			

Notes:

[31] - SAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module 35 (EORTC QLQ-H&N35) Subscales

End point title	Change From Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module 35 (EORTC QLQ-H&N35) Subscales[32]

End point description:

Change from Baseline score in pain, swallowing, speech problems, and senses problems subscales of EORTC QLQ-H&N35 are summarized individually. Raw scores for each subscale were linear transformations and standardized to range (0 - 100), with higher scores representing worse levels of symptoms. Change from Baseline was calculated as End of Treatment Observed - Baseline with a negative change representing a reduction in symptoms.

mITT Analysis Set: consisted of all participants who received at least one dose of tipifarnib. Analysis was pre-specified for participants in the AIM-HN Cohort with available data. Data collection and analysis of EORTC QLQ-H&N35 for participants in the Observational SEQ-HN Cohort was not pre-specified.

End point type	Secondary

End point timeframe:

Baseline and End of Treatment Visit (up to approximately 28 months)

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive statistics were only pre-specified for the AIM-HN arm.

End point values	Tipifarnib Treatment Cohort: AIM-HN			
Subject group type	Reporting group			
Number of subjects analysed	27[33]			
Units: score on a scale				
median (full range (min-max))				
Pain (n = 27)	0.0 (-41.7 to 58.3)			
Swallowing (n = 26)	8.3 (-58.3 to 75.0)			
Senses problems (n = 27)	0.0 (-50.0 to 66.7)			
Speech problems (n = 26)	0.0 (-44.4 to 66.7)			

Notes:

[33] - mITT Analysis Set with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the EuroQol-Visual Analog Scale (EQ-VAS) Score

End point title	Change From Baseline in the EuroQol-Visual Analog Scale (EQ-VAS) Score[34]

End point description:

The EQ-VAS forms part of the EQ-5D-5L and collects the self-rating health status from 0 (the worst imaginable health) to 100 (the best imaginable health). Change from Baseline was calculated as End of Treatment Observed - Baseline with a negative change representing an increase in symptoms.

mITT Analysis Set: consisted of all participants who received at least one dose of tipifarnib. Analysis was pre-specified for participants in the AIM-HN Cohort with available data. Data collection and analysis of EQ-VAS for participants in the Observational SEQ-HN Cohort was not pre-specified.

End point type	Secondary

End point timeframe:

Baseline and End of Treatment Visit (up to approximately 28 months)

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Descriptive statistics were only pre-specified for the AIM-HN arm.

End point values	Tipifarnib Treatment Cohort: AIM-HN			
Subject group type	Reporting group			
Number of subjects analysed	26[35]			
Units: score on a scale				
median (full range (min-max))	3.5 (-30.0 to 60.0)			

Notes:

[35] - mITT Analysis Set with available data

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 28 months

Adverse event reporting additional description:

SAS: consisted of all participants in the AIM-HN who received at least one dose of tipifarnib. Analysis was pre-specified for participants in the AIM-HN Cohort only. Data collection and analysis of safety for participants in the Observational SEQ-HN Cohort was not pre-specified.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Tipifarnib Treatment Cohort: AIM-HN

Reporting group description:

Participants enrolled as part of AIM-HN received tipifarnib administered with food at a starting dose of 600 mg, orally, bid on Days 1-7 and 15-21 of 28-day cycles.

Serious adverse events	Tipifarnib Treatment Cohort: AIM-HN		
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 59 (47.46%)		
number of deaths (all causes)	41		
number of deaths resulting from adverse events	9		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Infected neoplasm			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sudden death			

subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Acute respiratory failure			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Laryngeal stenosis			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Head injury			

subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		

Thrombocytopenia				
subjects affected / exposed	2 / 59 (3.39%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Dysphagia				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal stenosis				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				

subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal prolapse			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	9 / 59 (15.25%)		
occurrences causally related to treatment / all	1 / 10		
deaths causally related to treatment / all	0 / 3		
Sepsis			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	1 / 1		
Septic shock			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Bacteraemia			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Corona virus infection			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia escherichia			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Soft tissue infection			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			

	Tipifarnib Treatment Cohort: AIM-HN		
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Tipifarnib Treatment Cohort: AIM-HN		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 59 (94.92%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	5		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	19 / 59 (32.20%)		
occurrences (all)	29		
Asthenia			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	7		
Mucosal inflammation			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	6		
Pyrexia			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal			

disorders			
Dyspnoea			
subjects affected / exposed	8 / 59 (13.56%)		
occurrences (all)	13		
Cough			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	7		
Productive cough			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Haemoptysis			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	4		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	8 / 59 (13.56%)		
occurrences (all)	8		
Anxiety			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Confusional state			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Investigations			
Blood creatinine increased			
subjects affected / exposed	10 / 59 (16.95%)		
occurrences (all)	17		
Weight decreased			
subjects affected / exposed	7 / 59 (11.86%)		
occurrences (all)	9		
Alanine aminotransferase increased			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	5		
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		

Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	5		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	5		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	7		
Dizziness			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	29 / 59 (49.15%)		
occurrences (all)	56		
Neutropenia			
subjects affected / exposed	20 / 59 (33.90%)		
occurrences (all)	45		
Leukopenia			
subjects affected / exposed	13 / 59 (22.03%)		
occurrences (all)	26		
Thrombocytopenia			
subjects affected / exposed	11 / 59 (18.64%)		
occurrences (all)	27		
Lymphopenia			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	10		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	16 / 59 (27.12%)		
occurrences (all)	26		
Vomiting			
subjects affected / exposed	13 / 59 (22.03%)		
occurrences (all)	16		

Constipation			
subjects affected / exposed	11 / 59 (18.64%)		
occurrences (all)	11		
Diarrhoea			
subjects affected / exposed	10 / 59 (16.95%)		
occurrences (all)	16		
Dysphagia			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	9		
Abdominal pain			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	7		
Abdominal distension			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	6		
Abdominal pain upper			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Dry mouth			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Musculoskeletal pain			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Infections and infestations			

Corona virus infection			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	12 / 59 (20.34%)		
occurrences (all)	18		
Hypokalaemia			
subjects affected / exposed	9 / 59 (15.25%)		
occurrences (all)	17		
Hypercalcaemia			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	6		
Hyponatraemia			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	9		
Hypophosphataemia			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	5		
Hypoalbuminaemia			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Hypocalcaemia			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	5		
Hypomagnesaemia			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 July 2018	The protocol was amended for the following reasons: • The starting dose of tipifarnib was reduced. • AIM-HN inclusion criteria 9b was modified. • AIM-HN exclusion criteria 11 was added.
15 November 2018	The protocol was amended for the following reasons: • AIM-HN inclusion criteria 4 was modified. • AIM-HN inclusion criteria 8 was modified. • AIM-HN inclusion criteria 12 was added. • AIM-HN inclusion criteria 14 was clarified. • AIM-HN exclusion criteria 11 was modified. • SEQ-HN inclusion criteria 3 was further clarified. • SEQ-HN inclusion criteria 5 was clarified. • Provided additional guidance on the management of Grade 2 and 3 renal toxicity. • Adjusted the blood chemistry panel.
09 June 2020	The protocol was amended for the following reasons: • The primary objective was clarified. • Secondary objectives and endpoints were revised. • Other secondary objectives and endpoints for the SEQ-HN study and mHRAS population were revised. • Exploratory objectives were moved to other secondary objectives. • The total number of participants for enrollment into AIM and SEQ was increased. • Determination of HRAS status was further defined. • Circumstances of ineligibility for prior platinum therapy were revised. • Inclusion criteria number 4 was clarified/revised. • Inclusion criteria number 6 was clarified. • Exclusion criteria were updated to include female subjects who were pregnant or lactating. • Populations for analysis were defined. • Detailed RECIST v1.1 criteria was included. • Sensitivity analyses were revised.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported