Clinical trial results:
A Randomized, Double-Blind, Adaptive, Phase II/III Study of GSK3359609 in Combination With Pembrolizumab and 5FU-Platinum Chemotherapy Versus Placebo in Combination With Pembrolizumab Plus 5FU-Platinum Chemotherapy for First-Line Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma

Summary

EudraCT number	2019-003981-42
Trial protocol	FR SE DK DE BE GB HU PL GR IT RO
Global end of trial date	19 September 2023

Results information

Result version number	v2 (current)
This version publication date	03 October 2024
First version publication date	13 May 2022
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	209227

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04428333
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	Rue de l'Institut 89, Rixensart, Belgium, B-1330
Public contact	GSK Response Center, GlaxoSmithKline, 044 2089-904466, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 044 2089-904466, GSKClinicalSupportHD@gsk.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	27 April 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate if the addition of GSK3359609 to pembrolizumab in combination with 5FU-platinum based chemotherapy improves the efficacy of the pembrolizumab combination with 5FU-platinum based chemotherapy in participants with recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC).

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 August 2020
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	Argentina: 5
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Ireland: 6
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Japan: 2
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Romania: 12
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	117
EEA total number of subjects	61

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)	77
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment in the study stopped post interim safety/efficacy data review after a pre-specified futility analysis of the 209229 trial. Participants discontinued feladilimab/placebo, but treatment with pembrolizumab + chemotherapy continued until disease progression, death or unacceptable toxicity.

Pre-assignment

Screening details:

1 subject was incorrectly re-randomized into the study twice & was given a new subject ID. However, the subject was considered only once for the analyses. An additional subject was randomized after the data cut off for primary posting and received only pembrolizumab. Therefore, this subject is included in safety analysis for LSLV posting

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Feladilimab + Pembrolizumab + 5-FU-platinum chemotherapy

Arm description:

Participants were administered feladilimab (humanized anti- ICOS immunoglobulin G4 [IgG4] monoclonal antibody [mAb]) and pembrolizumab (humanized anti-PD-1 IgG4 mAb) as an intravenous (IV) infusion along with 5 Fluorouracil (FU)- platinum chemotherapy (cisplatin OR carboplatin) every 3 weeks (Q3W).

Arm type	Experimental
Investigational medicinal product name	Feladilimab+ Pembrolizumab+ Platinum chemotherapy (cisplatin/carboplatin)+ Fluorouracil (5FU)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants were administered feladilimab first followed by pembrolizumab and thereafter 5FU-platinum chemotherapy intravenously

Arm title	Placebo + Pembrolizumab + 5-FU-platinum chemotherapy

Arm description:

Participants were administered placebo and pembrolizumab as an IV infusion along with 5 FU-platinum chemotherapy (cisplatin OR carboplatin) Q3W.

Arm type	Placebo
Investigational medicinal product name	Placebo+ Pembrolizumab+ Platinum chemotherapy (cisplatin/carboplatin)+ Fluorouracil (5FU)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants were administered placebo first followed by pembrolizumab and thereafter 5FU-platinum chemotherapy intravenously

Number of subjects in period 1	Feladilimab + Pembrolizumab + 5-FU-platinum chemotherapy	Placebo + Pembrolizumab + 5-FU-platinum chemotherapy
Started	57	60
mITT population	52	55
Completed	37	35
Not completed	20	25
Physician decision	5	6
Consent withdrawn by subject	1	3
Study Terminated By Sponsor	14	16

Baseline characteristics

Reporting groups	
Reporting group title	Feladilimab + Pembrolizumab + 5-FU-platinum chemotherapy
Reporting group description:	
Participants were administered feladilimab (humanized anti- ICOS immunoglobulin G4 [IgG4] monoclonal antibody [mAb]) and pembrolizumab (humanized anti-PD-1 IgG4 mAb) as an intravenous (IV) infusion along with 5 Fluorouracil (FU)- platinum chemotherapy (cisplatin OR carboplatin) every 3 weeks (Q3W).	
Reporting group title	Placebo + Pembrolizumab + 5-FU-platinum chemotherapy
Reporting group description:	
Participants were administered placebo and pembrolizumab as an IV infusion along with 5 FU-platinum chemotherapy (cisplatin OR carboplatin) Q3W.	

Reporting group values	Feladilimab + Pembrolizumab + 5-FU-platinum chemotherapy	Placebo + Pembrolizumab + 5-FU-platinum chemotherapy	Total
Number of subjects	57	60	117
Age Categorical Units:			
18-64 years	37	40	77
>=65-84 years	20	20	40
Sex: Female, Male Units: Participants			
Female	10	14	24
Male	47	46	93
Race/Ethnicity, Customized Units: Subjects			
Asian - Central/South Asian Heritage	2	1	3
Asian - East Asian Heritage	5	7	12
Asian - Japanese Heritage	2	0	2
Asian - South East Asian Heritage	2	1	3
Black or African American	1	0	1
Missing	2	1	3
White - White/Caucasian/European Heritage	43	50	93

End points

End points reporting groups

Reporting group title	Feladilimab + Pembrolizumab + 5-FU-platinum chemotherapy

Reporting group description:

Participants were administered feladilimab (humanized anti- ICOS immunoglobulin G4 [IgG4] monoclonal antibody [mAb]) and pembrolizumab (humanized anti-PD-1 IgG4 mAb) as an intravenous (IV) infusion along with 5 Fluorouracil (FU)- platinum chemotherapy (cisplatin OR carboplatin) every 3 weeks (Q3W).

Reporting group title	Placebo + Pembrolizumab + 5-FU-platinum chemotherapy

Reporting group description:

Participants were administered placebo and pembrolizumab as an IV infusion along with 5 FU-platinum chemotherapy (cisplatin OR carboplatin) Q3W.

Subject analysis set title	Feladilimab + pembrolizumab + chemotherapy mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All randomized participants whether or not randomized intervention was administered, excluding those who were first dosed or randomized after the date of DIL requesting immediate discontinuation of feladilimab/placebo. This analysis set was based on the study intervention to which the participants were randomized.

Subject analysis set title	Placebo + pembrolizumab + chemotherapy mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All randomized participants whether or not randomized intervention was administered, excluding those who were first dosed or randomized after the date of DIL requesting immediate discontinuation of feladilimab/placebo. This analysis set was based on the study intervention to which the participants were randomized.

Subject analysis set title	Feladilimab + pembrolizumab + chemotherapy Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomized participants who took at least 1 dose of study intervention. Participants were assigned to the actual study intervention group of feladilimab+pembrolizumab if the participants received any dose of feladilimab. Participants were analyzed according to the actual study intervention received.

Subject analysis set title	Placebo + pembrolizumab + chemotherapy Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomized participants who took at least 1 dose of study intervention. Participants were assigned to the actual study intervention group of feladilimab+pembrolizumab if the participants received any dose of feladilimab. Participants were analyzed according to the actual study intervention received.

Primary: Overall Survival (OS) in mITT population

End point title	Overall Survival (OS) in mITT population

End point description:

OS was defined as the time from the date of randomization until the date of death due to any cause. Kaplan-Meier estimate for the median OS is presented, along with associated 95% confidence interval, estimated using the Brookmeyer-Crowley method. All randomized participants whether or not randomized intervention was administered, excluding those who were first dosed or randomized after the date of DIL requesting immediate discontinuation of feladilimab /placebo were included in the mITT population. 99999 = The median was not reached at the time of data cut off and the upper limit of the 95% CI was not calculable from the available data at the time of data cut off.

End point type	Primary

End point timeframe:

Up to approximately 7 months

End point values	Feladilimab + pembrolizumab + chemotherapy mITT	Placebo + pembrolizumab + chemotherapy mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	55		
Units: Months				
median (confidence interval 95%)	99999 (5.1 to 99999)	99999 (4.1 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The hazard ratio and corresponding 2-sided 95% confidence interval was calculated from the cox regression model with Efron's method of tie handling with treatment as a covariate and stratified by PD-L1 expression (CPS ≥20 vs. 1≤ CPS <20 vs. CPS <1) and Human Papilloma Virus (HPV) status (positive vs. negative). Participants with oropharynx HPV negative/unknown and non-oropharyngeal tumors were combined as the HPV negative group.

Comparison groups	Feladilimab + pembrolizumab + chemotherapy mITT v Placebo + pembrolizumab + chemotherapy mITT
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.74 [1]
Method	Stratified Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	2.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	23.87

Notes:

[1] - Nominal p-value was calculated based on the one sided log-rank test, stratified by stratified by PD-L1 expression (CPS ≥20 vs. 1≤ CPS <20 vs. CPS <1) and HPV status (oropharynx HPV positive vs oropharynx HPV negative/unknown and non-oropharynx).

Primary: OS in programmed death receptor-ligand 1 (PD-L1) combined positive score (CPS) ≥1 population

End point title	OS in programmed death receptor-ligand 1 (PD-L1) combined positive score (CPS) ≥1 population

End point description:

OS was defined as the time from the date of randomization until the date of death due to any cause. CPS was defined as the ratio of the combined number of PD-L1 expressing tumor cells and immune cells (lymphocytes and macrophages) to the total number of viable tumor cells. Kaplan-Meier estimate for the median OS is presented, along with associated 95% confidence interval, estimated using the Brookmeyer-Crowley method in PD-L1 CPS ≥1 subjects from mITT population. 99999 = The median was not reached at the time of data cut off and the upper limit of the 95% CI was not calculable from the available data at the time of data cut off.

End point type	Primary

End point timeframe:

Up to approximately 7 months

End point values	Feladilimab + pembrolizumab + chemotherapy mITT	Placebo + pembrolizumab + chemotherapy mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	52		
Units: Months				
median (confidence interval 95%)	99999 (5.1 to 99999)	99999 (4.1 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The hazard ratio and corresponding 2-sided 95% confidence interval was calculated from the cox regression model with Efron's method of tie handling with treatment as a covariate and stratified by PD-L1 expression (CPS≥20 vs 1≤CPS<20) and HPV status (positive vs. negative). Participants with oropharynx HPV negative/unknown and non-oropharyngeal tumors were combined as the HPV negative group.

Comparison groups	Feladilimab + pembrolizumab + chemotherapy mITT v Placebo + pembrolizumab + chemotherapy mITT
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.74 [2]
Method	Stratified Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	2.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	23.87

Notes:

[2] - Nominal p-value was calculated based on the one sided log-rank test, stratified by stratified by PD-L1 expression (CPS≥20 vs 1≤CPS<20) and HPV status (oropharynx HPV positive vs oropharynx HPV negative/unknown and non-oropharynx).

Primary: Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1 in mITT population

End point title	Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1 in mITT population

End point description:

PFS per RECIST version (v)1.1 was defined as the time from the date of randomization to the date of first documented disease progression or death due to any cause, whichever occurs first. Kaplan-Meier estimate for the median PFS is presented, along with associated 95% confidence interval, estimated

using the Brookmeyer-Crowley method. All participants in the mITT population were analyzed.

End point type	Primary

End point timeframe:

Up to approximately 7 months

End point values	Feladilimab + pembrolizumab + chemotherapy mITT	Placebo + pembrolizumab + chemotherapy mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	55		
Units: Months				
median (confidence interval 95%)	5.5 (3.7 to 5.5)	4.7 (4.7 to 5.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The hazard ratio and corresponding 2-sided 95% confidence interval was calculated from the cox regression model with Efron's method of tie handling with treatment as a covariate and stratified by PD-L1 expression (CPS ≥20 vs. 1≤ CPS <20 vs. CPS <1) and HPV status (positive vs. negative). Participants with oropharynx HPV negative/unknown and non-oropharyngeal tumors were combined as the HPV negative group.

Comparison groups	Feladilimab + pembrolizumab + chemotherapy mITT v Placebo + pembrolizumab + chemotherapy mITT
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.284 [3]
Method	Stratified Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	2.43

Notes:

[3] - Nominal p-value was calculated based on the one-sided log-rank test, stratified by stratified by PD-L1 expression (CPS ≥20 vs. 1≤ CPS <20 vs. CPS <1) and HPV status (oropharynx HPV positive vs oropharynx HPV negative/unknown and non-oropharynx).

Secondary: PFS per RECIST v1.1 in the PD-L1 CPS ≥1 population

End point title	PFS per RECIST v1.1 in the PD-L1 CPS ≥1 population

End point description:

PFS per Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1 was defined as the time from the date of randomization to the date of first documented disease progression or death due to any cause, whichever occurs first. CPS was defined as the ratio of the combined number of PD-L1 expressing tumor cells and immune cells (lymphocytes and macrophages) to the total number of viable tumor cells. Data for participants in the mITT population with PD-L1 CPS ≥1 is presented here. Kaplan-Meier

estimate for the median PFS are presented, along with associated 95% confidence interval, estimated using the Brookmeyer-Crowley method.

End point type	Secondary

End point timeframe:

Up to approximately 7 months

End point values	Feladilimab + pembrolizumab + chemotherapy mITT	Placebo + pembrolizumab + chemotherapy mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	52		
Units: Months				
median (confidence interval 95%)	5.5 (3.7 to 5.5)	4.7 (4.7 to 6.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The hazard ratio and corresponding 2-sided 95% confidence interval was calculated from the cox regression model with Efron's method of tie handling with treatment as a covariate and stratified by PD-L1 expression (CPS≥20 vs 1≤CPS<20) and HPV status (positive vs. negative). Participants with oropharynx HPV negative/unknown and non-oropharyngeal tumors were combined as the HPV negative group.

Comparison groups	Feladilimab + pembrolizumab + chemotherapy mITT v Placebo + pembrolizumab + chemotherapy mITT
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.284 [4]
Method	Stratified Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	2.43

Notes:

[4] - Nominal p-value was calculated based on the one-sided log-rank test, stratified by stratified by PD-L1 expression (CPS ≥20 vs. 1≤ CPS <20) and HPV status (oropharynx HPV positive vs oropharynx HPV negative/unknown and non-oropharynx).

Secondary: Milestone OS rate at 12, 24 and 36 months in PD-L1 CPS ≥1 population

End point title	Milestone OS rate at 12, 24 and 36 months in PD-L1 CPS ≥1 population

End point description:

Milestone OS rate at 12, 24, and 36 months was not evaluated. CPS was defined as the ratio of the combined number of PD-L1 expressing tumor cells and immune cells (lymphocytes and macrophages) to the total number of viable tumor cells.

End point type	Secondary
End point timeframe: Months 12, 24 and 36	

End point values	Feladilimab + pembrolizumab + chemotherapy mITT	Placebo + pembrolizumab + chemotherapy mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[5]	0[6]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[5] - No participant had follow-up duration exceeding 12 months.

[6] - No participant had follow-up duration exceeding 12 months.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) per RECIST v1.1 in mITT population

End point title	Overall Response Rate (ORR) per RECIST v1.1 in mITT population

End point description:

ORR per RECIST v1.1 was defined as the proportion of the participants who have a complete response (CR) or partial response (PR) as the best overall response per RECIST v1.1 based upon investigator assessment. As a randomized double-blind study in which primary endpoints are OS and PFS, the confirmation of CR and PR was not required. Rate and associated 2-sided 95 percent Exact (Clopper-Pearson) Confidence Intervals are provided for each treatment arm which are unadjusted. All participants in the mITT population were analyzed.

End point type	Secondary
End point timeframe: Up to approximately 7 months	

End point values	Feladilimab + pembrolizumab + chemotherapy mITT	Placebo + pembrolizumab + chemotherapy mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	55		
Units: Percentage of participants				
number (confidence interval 95%)	19.2 (9.6 to 32.5)	23.6 (13.2 to 37.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The comparison between treatment groups was based on the stratified Miettinen & Nurminen method with strata weighting by sample size and a single treatment covariate. Stratification factors included PD-L1 expression (CPS ≥20 vs. 1≤ CPS <20 vs. CPS <1) and HPV status (positive vs. negative). Participants with oropharynx HPV negative/unknown and non-oropharyngeal tumors were combined as the HPV negative group.

Comparison groups	Feladilimab + pembrolizumab + chemotherapy mITT v Placebo + pembrolizumab + chemotherapy mITT
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Percentage
Point estimate	-4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.8
upper limit	11.3

Secondary: Milestone OS rate at 12, 24 and 36 months in mITT population

End point title	Milestone OS rate at 12, 24 and 36 months in mITT population

End point description:

Milestone OS rate at 12, 24, and 36 months was not evaluated.

End point type	Secondary

End point timeframe:

Months 12, 24 and 36

End point values	Feladilimab + pembrolizumab + chemotherapy mITT	Placebo + pembrolizumab + chemotherapy mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[7]	0[8]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[7] - No participant had follow-up duration exceeding 12 months.

[8] - No participant had follow-up duration exceeding 12 months.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) per RECIST v1.1 in mITT population

End point title	Disease Control Rate (DCR) per RECIST v1.1 in mITT population

End point description:

DCR per RECIST v1.1 based upon investigator assessment, was defined as the percentage of participants with a best overall response of CR or PR at any time plus stable disease (SD) meeting the minimum time of 15 weeks. A status of SD≥15 weeks will be assigned if the follow-up disease assessment has met the SD criteria at least once after the date of randomization at a minimum of 14 weeks (98 days) considering a one-week visit window. Rate and associated 2-sided 95 percent Exact (Clopper-Pearson) Confidence Intervals are provided for each treatment arm which are unadjusted. All participants in the mITT population were analysed.

End point type	Secondary

End point timeframe:

Up to approximately 7 months

End point values	Feladilimab + pembrolizumab + chemotherapy mITT	Placebo + pembrolizumab + chemotherapy mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	55		
Units: Percentage of participants				
median (confidence interval 95%)	32.7 (20.3 to 47.1)	36.4 (23.8 to 50.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The comparison between treatment groups was based on the stratified Miettinen & Nurminen method with strata weighting by sample size and a single treatment covariate. Stratification factors included PD-L1 expression (CPS ≥20 vs. 1≤ CPS <20 vs. CPS <1) and HPV status (positive vs. negative). Participants with oropharynx HPV negative/unknown and non-oropharyngeal tumors were combined as the HPV negative group.

Comparison groups	Feladilimab + pembrolizumab + chemotherapy mITT v Placebo + pembrolizumab + chemotherapy mITT
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Percentage
Point estimate	-4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.2
upper limit	13.1

Secondary: ORR per RECIST v1.1 in PD-L1 CPS ≥1 population

End point title	ORR per RECIST v1.1 in PD-L1 CPS ≥1 population

End point description:

ORR per RECIST v1.1 was defined as the proportion of the participants who have a CR or PR as the best overall response per RECIST v1.1 based upon investigator assessment. As a randomized double-blind study in which primary endpoints are OS and PFS, the confirmation of CR and PR was not required. Rate and associated 2-sided 95 percent Exact (Clopper-Pearson) Confidence Intervals are provided for each treatment arm which are unadjusted. CPS was defined as the ratio of the combined number of PD-L1 expressing tumor cells and immune cells (lymphocytes and macrophages) to the total number of viable tumor cells. Data for participants in the mITT population with PD-L1 CPS ≥1 are presented here.

End point type	Secondary

End point timeframe:

Up to approximately 7 months

End point values	Feladilimab + pembrolizumab + chemotherapy mITT	Placebo + pembrolizumab + chemotherapy mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	52		
Units: Percentage of participants				
number (confidence interval 95%)	18.4 (8.8 to 32.0)	23.1 (12.5 to 36.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The comparison between treatment groups was based on the stratified Miettinen & Nurminen method with strata weighting by sample size and a single treatment covariate. Stratification factors included PD-L1 expression (CPS≥20 vs 1≤CPS<20) and HPV status (positive vs. negative). Participants with oropharynx HPV negative/unknown and non-oropharyngeal tumors were combined as the HPV negative group.

Comparison groups	Feladilimab + pembrolizumab + chemotherapy mITT v Placebo + pembrolizumab + chemotherapy mITT
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Percentage
Point estimate	-5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.4
upper limit	11.3

Secondary: DCR per RECIST v1.1 in PD-L1 CPS ≥1 population

End point title	DCR per RECIST v1.1 in PD-L1 CPS ≥1 population

End point description:

DCR per RECIST v1.1 based upon investigator assessment, was defined as the percentage of participants with a best overall response of CR or PR at any time plus SD meeting the minimum time of 15 weeks. A status of SD≥15 weeks will be assigned if the follow-up disease assessment has met the SD criteria at least once after the date of randomization at a minimum of 14 weeks (98 days) considering a one-week visit window. Rate and associated 2-sided 95 percent Exact (Clopper-Pearson) Confidence Intervals are provided for each treatment arm which are unadjusted. CPS was defined as the ratio of the combined number of PD-L1 expressing tumor cells and immune cells (lymphocytes and macrophages) to the total number of viable tumor cells. Data for participants in the mITT population with PD-L1 CPS ≥1 are presented here.

End point type	Secondary

End point timeframe:

Up to approximately 7 months

End point values	Feladilimab + pembrolizumab + chemotherapy mITT	Placebo + pembrolizumab + chemotherapy mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	52		
Units: Percentage of participants				
number (confidence interval 95%)	30.6 (18.3 to 45.4)	34.6 (22.0 to 49.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The comparison between treatment groups was based on the stratified Miettinen & Nurminen method with strata weighting by sample size and a single treatment covariate. Stratification factors included PD-L1 expression (CPS≥20 vs 1≤CPS<20) and HPV status (positive vs. negative). Participants with oropharynx HPV negative/unknown and non-oropharyngeal tumors were combined as the HPV negative group.

Comparison groups	Feladilimab + pembrolizumab + chemotherapy mITT v Placebo + pembrolizumab + chemotherapy mITT
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Percentage
Point estimate	-5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.8
upper limit	13.3

Secondary: Duration of Response (DoR) per RECIST v1.1 in mITT population

End point title	Duration of Response (DoR) per RECIST v1.1 in mITT

	population

End point description:

DoR per RECIST v1.1 is defined as the time from first documented evidence of CR or PR until first documented disease progression per RECIST v1.1 based upon investigator assessment or death due to any cause, whichever occurs first, among participants who demonstrated CR or PR as the best overall response per RECIST v1.1. Kaplan-Meier estimate for the median DoR is presented, along with associated 95% confidence interval, estimated using the Brookmeyer-Crowley method. CPS was defined as the ratio of the combined number of PD-L1 expressing tumor cells and immune cells (lymphocytes and macrophages) to the total number of viable tumor cells. Data for participants with a best overall response of CR or PR in mITT population are presented. 99999 = The median was not reached at the time of data cut off, the lower and upper limit of the 95% CI was not calculable from the available data at the time of data cut off.

End point type	Secondary

End point timeframe:

Up to approximately 7 months

End point values	Feladilimab + pembrolizumab + chemotherapy mITT	Placebo + pembrolizumab + chemotherapy mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	13		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	2.8 (1.2 to 2.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: DoR per RECIST v1.1 in PD-L1 CPS ≥1 population

End point title	DoR per RECIST v1.1 in PD-L1 CPS ≥1 population

End point description:

DoR per RECIST v1.1 is defined as the time from first documented evidence of CR or PR until first documented disease progression per RECIST v1.1 based upon investigator assessment or death due to any cause, whichever occurs first, among participants who demonstrated CR or PR as the best overall response per RECIST v1.1. Kaplan-Meier estimate for the median DoR is presented, along with associated 95% confidence interval, estimated using the Brookmeyer-Crowley method. CPS was defined as the ratio of the combined number of PD-L1 expressing tumor cells and immune cells (lymphocytes and macrophages) to the total number of viable tumor cells. Data for participants with a best overall response of CR or PR in mITT population with PD-L1 CPS ≥1 are presented. 99999 = The median was not reached at the time of data cut off, the lower and upper limit of the 95% CI was not calculable from the available data at the time of data cut off.

End point type	Secondary

End point timeframe:

Up to approximately 7 months

End point values	Feladilimab + pembrolizumab + chemotherapy mITT	Placebo + pembrolizumab + chemotherapy mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	12		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	2.8 (1.4 to 2.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Serious Adverse Events (SAEs) in safety population

End point title	Number of participants with Serious Adverse Events (SAEs) in safety population

End point description:

A SAE was defined as any untoward medical occurrence that, at any dose, results in death, was life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, was a congenital anomaly/birth defect and other situations according to medical or scientific judgement. Safety Population. An additional participant was randomized after the data cut off and received pembrolizumab. Therefore, participant was included in safety analysis.

End point type	Secondary

End point timeframe:

Up to approximately 37.2 months

End point values	Feladilimab + pembrolizumab + chemotherapy Safety	Placebo + pembrolizumab + chemotherapy Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	65		
Units: Participants	23	32		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Adverse Events (AEs) in safety population

End point title	Number of participants with Adverse Events (AEs) in safety population

End point description:

An AE was defined as any untoward or unfavorable medical occurrence in a participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease,

temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research. Safety Population: All randomized participants who took at least 1 dose of study intervention. Participants were analyzed according to the actual study intervention received. An additional participant was randomized after the data cut off and received pembrolizumab. Therefore, participant was included in safety analysis.

End point type	Secondary

End point timeframe:

Up to approximately 37.2 months

End point values	Feladilimab + pembrolizumab + chemotherapy Safety	Placebo + pembrolizumab + chemotherapy Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	65		
Units: Participants	51	65		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with AEs in PD-L1 CPS ≥1 population

End point title	Number of participants with AEs in PD-L1 CPS ≥1 population

End point description:

An AE was defined as any untoward or unfavorable medical occurrence in a participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research in PD-L1 CPS ≥1 participants from safety population. CPS was defined as the ratio of the combined number of PD-L1 expressing tumor cells and immune cells (lymphocytes and macrophages) to the total number of viable tumor cells. Data for participants with PD-L1 CPS ≥1 in the safety population are presented. An additional participant was randomized after the data cut off and received pembrolizumab. Therefore, participant was included in safety analysis.

End point type	Secondary

End point timeframe:

Up to approximately 37.2 months

End point values	Feladilimab + pembrolizumab + chemotherapy Safety	Placebo + pembrolizumab + chemotherapy Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	62		
Units: Participants	48	62		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with adverse Events of Special Interest (AESI) in safety population

End point title	Number of participants with adverse Events of Special Interest (AESI) in safety population

End point description:

AESI was defined as events of potential immunologic etiology, including immune-related (ir) AEs. Safety Population. An additional participant was randomized after the data cut off and received pembrolizumab. Therefore, participant was included in safety analysis.

End point type	Secondary

End point timeframe:

Up to approximately 37.2 months

End point values	Feladilimab + pembrolizumab + chemotherapy Safety	Placebo + pembrolizumab + chemotherapy Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	65		
Units: Participants	29	43		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of AEs in safety population

End point title	Severity of AEs in safety population

End point description:

Severity of each AE was reported during the study and was assigned a grade according to the National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE). AEs severity were graded on a 5-point scale as: 1 = mild; discomfort noticed, but no disruption to daily activity, 2 = moderate; discomfort sufficient to reduce or affect normal daily activity, 3 = severe; inability to work or perform normal daily activity, 4 = life-threatening consequences and 5 = death related to AE. Safety Population. An additional participant was randomized after the data cut off and received pembrolizumab. Therefore, participant was included in safety analysis.

End point type	Secondary

End point timeframe:

Up to approximately 37.2 months

End point values	Feladilimab + pembrolizumab + chemotherapy Safety	Placebo + pembrolizumab + chemotherapy Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	65		
Units: Participants				
Grade 1	1	3		
Grade 2	17	15		
Grade 3	23	34		
Grade 4	4	10		
Grade 5	6	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with SAEs in PD-L1 CPS ≥1 population

End point title	Number of participants with SAEs in PD-L1 CPS ≥1 population

End point description:

A SAE was defined as any untoward medical occurrence that, at any dose, results in death, was life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, was a congenital anomaly/birth defect and other situations according to medical or scientific judgement in PD-L1 CPS ≥1 participants from safety population. CPS was defined as the ratio of the combined number of PD-L1 expressing tumor cells and immune cells (lymphocytes and macrophages) to the total number of viable tumor cells. Data for participants with PD-L1 CPS ≥1 in the safety population are presented. An additional participant was randomized after the data cut off and received pembrolizumab. Therefore, participant was included in safety analysis.

End point type	Secondary

End point timeframe:

Up to approximately 37.2 months

End point values	Feladilimab + pembrolizumab + chemotherapy Safety	Placebo + pembrolizumab + chemotherapy Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	62		
Units: Participants	21	32		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with AESIs in PD-L1 CPS ≥1 population

End point title	Number of participants with AESIs in PD-L1 CPS ≥1 population

End point description:

AESI was defined as events of potential immunologic etiology, including irAEs in PD-L1 CPS ≥1 participants from safety population. CPS was defined as the ratio of the combined number of PD-L1 expressing tumor cells and immune cells (lymphocytes and macrophages) to the total number of viable tumor cells. Data for participants with PD-L1 CPS ≥1 in the safety population are presented. An additional participant was randomized after the data cut off and received pembrolizumab. Therefore, participant was included in safety analysis.

End point type	Secondary

End point timeframe:

Up to approximately 37.2 months

End point values	Feladilimab + pembrolizumab + chemotherapy Safety	Placebo + pembrolizumab + chemotherapy Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	62		
Units: Participants	27	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of AESIs in safety population

End point title	Severity of AESIs in safety population

End point description:

Severity of each AESI was reported during the study and was assigned a grade according to the NCI-CTCAE. AESIs severity were graded on a 5-point scale as: 1 = mild; discomfort noticed, but no disruption to daily activity, 2 = moderate; discomfort sufficient to reduce or affect normal daily activity, 3 = severe; inability to work or perform normal daily activity, 4 = life-threatening consequences and 5 = death related to AE. Data of participants experiencing AESIs of Grade >= 3 has been presented. Data of participants experiencing AESIs of Grade >= 3 have been presented. Safety Population. An additional participant was randomized after the data cut off and received pembrolizumab. Therefore, participant was included in safety analysis.

End point type	Secondary

End point timeframe:

Up to approximately 37.2 months

End point values	Feladilimab + pembrolizumab + chemotherapy Safety	Placebo + pembrolizumab + chemotherapy Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	65		
Units: Participants				
Grade >= 3	5	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of SAEs in safety population

End point title	Severity of SAEs in safety population

End point description:

Severity of each SAE was reported during the study and was assigned a grade according to the NCI-CTCAE. SAEs severity were graded on a 5-point scale as: 1 = mild; discomfort noticed, but no disruption to daily activity, 2 = moderate; discomfort sufficient to reduce or affect normal daily activity, 3 = severe; inability to work or perform normal daily activity, 4 = life-threatening consequences and 5 = death related to AE. Data of participants experiencing SAEs of Grade >= 3 have been presented. Safety Population. An additional participant was randomized after the data cut off and received pembrolizumab. Therefore, participant was included in safety analysis.

End point type	Secondary

End point timeframe:

Up to approximately 37.2 months

End point values	Feladilimab + pembrolizumab + chemotherapy Safety	Placebo + pembrolizumab + chemotherapy Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	65		
Units: Participants				
Grade >= 3	17	26		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of SAEs in PD-L1 CPS ≥1 population

End point title	Severity of SAEs in PD-L1 CPS ≥1 population

End point description:

Severity for each SAE was reported during the study and assigned a grade according to the NCI-CTCAE v5.0. CPS was defined as the ratio of the combined number of PD-L1 expressing tumor cells and immune cells (lymphocytes and macrophages) to the total number of viable tumor cells. Data for

participants with PD-L1 CPS ≥1 in the safety population experiencing SAEs of Grade ≥3 have been presented. An additional participant was randomized after the data cut off and received pembrolizumab. Therefore, participant was included in safety analysis.

End point type	Secondary

End point timeframe:

Up to approximately 37.2 months

End point values	Feladilimab + pembrolizumab + chemotherapy Safety	Placebo + pembrolizumab + chemotherapy Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	62		
Units: Participants				
Grade >= 3	15	26		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of AEs in PD-L1 CPS ≥1 population

End point title	Severity of AEs in PD-L1 CPS ≥1 population

End point description:

Severity for each AE was reported during the study and assigned a grade according to the NCI-CTCAE v5.0. CPS was defined as the ratio of the combined number of PD-L1 expressing tumor cells and immune cells (lymphocytes and macrophages) to the total number of viable tumor cells. Data for participants with PD-L1 CPS ≥1 in the safety population experiencing AEs of Grade ≥3 have been presented. An additional participant was randomized after the data cut off and received pembrolizumab. Therefore, participant was included in safety analysis.

End point type	Secondary

End point timeframe:

Up to approximately 37.2 months

End point values	Feladilimab + pembrolizumab + chemotherapy Safety	Placebo + pembrolizumab + chemotherapy Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	62		
Units: Participants				
Grade >= 3	30	45		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of AESI in PD-L1 CPS ≥1 population

End point title	Severity of AESI in PD-L1 CPS ≥1 population

End point description:

Severity for each AESI was reported during the study and assigned a grade according to the NCI-CTCAE v5.0. CPS was defined as the ratio of the combined number of PD-L1 expressing tumor cells and immune cells (lymphocytes and macrophages) to the total number of viable tumor cells. Data for participants with PD-L1 CPS ≥1 in the safety population experiencing AESIs of Grade ≥3 have been presented. An additional participant was randomized after the data cut off and received pembrolizumab. Therefore, participant was included in safety analysis.

End point type	Secondary

End point timeframe:

Up to approximately 37.2 months

End point values	Feladilimab + pembrolizumab + chemotherapy Safety	Placebo + pembrolizumab + chemotherapy Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	62		
Units: Participants				
Grade >= 3	5	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with dose modifications in safety population

End point title	Number of participants with dose modifications in safety population

End point description:

Number of participants with dose modifications (including dose interruptions, dose delays, dose reductions and treatment discontinuations) were reported by each interventional component. All participants in the safety population were analyzed. 99999 = The numbers are reported per component and dose reductions were not permitted for feladilimab/placebo/pembrolizumab. The data presented is based on the primary data cut-off.

End point type	Secondary

End point timeframe:

Up to approximately 7 months

End point values	Feladilimab + pembrolizumab + chemotherapy Safety	Placebo + pembrolizumab + chemotherapy Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	65		
Units: Participants				
Dose Interruption per component-feladilimab	0	99999		
Dose Interruption per component-placebo	99999	0		
Dose Interruption per component-pembrolizumab	0	0		
Dose Interruption component-carboplatin/cisplatin	1	1		
Dose Interruption per component-fluorouracil	0	7		
Dose Delays per component-feladilimab	13	99999		
Dose Delays per component-placebo	99999	12		
Dose Delays per component-pembrolizumab	13	13		
Dose Delays by component-carboplatin/cisplatin	12	9		
Dose Delays per component-fluorouracil	9	10		
Dose Reduction per component-feladilimab	99999	99999		
Dose Reduction per component- placebo	99999	99999		
Dose Reduction per component-pembrolizumab	99999	99999		
Dose Reduction by component-carboplatin/cisplatin	12	19		
Dose Reduction per component-fluorouracil	18	21		
Treatment Discontinuation - feladilimab/placebo	50	56		
Discontinuation per component-pembrolizumab	10	15		
Discontinuation by component-carboplatin/cisplatin	16	18		
Discontinuation per component-fluorouracil	13	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with dose modifications in PD-L1 CPS ≥1 population

End point title	Number of participants with dose modifications in PD-L1 CPS ≥1 population

End point description:

Number of participants with dose modifications (i.e. interruptions, discontinuations) in the PD-L1 CPS ≥1 population was reported. CPS was defined as the ratio of the combined number of PD-L1 expressing tumor cells and immune cells (lymphocytes and macrophages) to the total number of viable tumor cells. 99999 = The numbers are reported per component and dose reductions were not permitted for feladilimab/placebo/pembrolizumab. The data presented is based on the primary data cut-off.

End point type	Secondary

End point timeframe:

Up to approximately 7 months

End point values	Feladilimab + pembrolizumab + chemotherapy Safety	Placebo + pembrolizumab + chemotherapy Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	62		
Units: Participants				
Dose Interruptions per component-feladilimab	0	99999		
Dose Interruptions per component-placebo	99999	0		
Dose Interruptions per component-pembrolizumab	0	0		
Dose Interruptions component-carboplatin/cisplatin	1	1		
Dose Interruptions per component-fluorouracil	0	7		
Dose Delays per component - feladilimab	12	99999		
Dose Delays per component - placebo	99999	11		
Dose Delays per component - pembrolizumab	12	12		
Dose Delays per component-carboplatin/cisplatin	11	9		
Dose Delays per component - fluorouracil	8	9		
Dose Reductions per component-feladilimab	99999	99999		
Dose Reductions per component-placebo	99999	99999		
Dose Reductions per component-pembrolizumab	99999	99999		
Dose Reductions by component-carboplatin/cisplatin	11	16		
Dose Reductions per component-fluorouracil	16	19		
Treatment Discontinuations-feladilimab/placebo	47	53		
Discontinuations per component - pembrolizumab	10	14		
Discontinuation by component-carboplatin/cisplatin	13	16		
Discontinuations per component - fluorouracil	15	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to deterioration in pain in mITT population

End point title	Time to deterioration in pain in mITT population

End point description:

TTD in pain is defined as the time from randomization to the first definitive meaningful deterioration from baseline in the European Organization for Research and Treatment of Cancer Item Library(EORTC IL51) Questionnaire pain domain, i.e. an increase from baseline of at least 8.33 observed at all subsequent non-missing visits. The EORTC Quality of Life Questionnaire 35-Item Head and Neck Module (QLQ-H&N35) is a head and neck specific module with multi-item scales. The questionnaire scores for each scale and single-item measure are averaged and transformed linearly to present a score ranging from 0–100. A high score represents a high/healthy level of functioning. Kaplan-Meier estimate for the median TTD is presented, along with associated 95% confidence interval, estimated using the Brookmeyer-Crowley method. All participants in the mITT population were analysed. 99999 = The upper limit of the 95% CI was not calculable from the available data at the time of data cut off.

End point type	Secondary

End point timeframe:

Up to approximately 7 months

End point values	Feladilimab + pembrolizumab + chemotherapy mITT	Placebo + pembrolizumab + chemotherapy mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	55		
Units: Months				
median (confidence interval 95%)	4.4 (2.1 to 4.4)	2.8 (1.4 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The hazard ratio and corresponding 2-sided 95% confidence interval was calculated from the cox regression model with Efron's method of tie handling with treatment as a covariate and stratified by PD-L1 expression (CPS ≥20 vs. 1≤ CPS <20 vs. CPS <1) and HPV status (positive vs. negative). Participants with oropharynx HPV negative/unknown and non-oropharyngeal tumors were combined as the HPV negative group.

Comparison groups	Feladilimab + pembrolizumab + chemotherapy mITT v Placebo + pembrolizumab + chemotherapy mITT
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.329 [9]
Method	Stratified Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.71

Notes:

[9] - Nominal p-value was calculated based on the one-sided log-rank test, stratified by stratified by PD-L1 expression (CPS ≥20 vs. 1≤ CPS <20 vs. CPS <1) and HPV status (oropharynx HPV positive vs oropharynx HPV negative/unknown and non-oropharynx).

Secondary: Time to deterioration in pain in PD-L1 CPS ≥1 populations

End point title	Time to deterioration in pain in PD-L1 CPS ≥1 populations

End point description:

TTD in pain is defined as the time from randomization to the first definitive meaningful deterioration from baseline in the EORTC IL51 pain domain, i.e. an increase from baseline of at least 8.33 observed at all subsequent non-missing visits. The EORTC QLQ-H&N35 is a head and neck specific module with multi-item scales. The mouth pain, swallowing, speech problems, opening mouth, coughing, feeding tube, and trouble with social eating domains were administered and referred to as the EORTC IL51. The questionnaire scores for each scale and single-item measure are averaged and transformed linearly to present a score ranging from 0–100. A high score represents a high/healthy level of functioning. 99999 = The upper limit of the 95% CI was not calculable from the available data at the time of data cut off. Data for participants with PD-L1 CPS ≥1 in the mITT population are presented.

End point type	Secondary

End point timeframe:

Up to approximately 7 months

End point values	Feladilimab + pembrolizumab + chemotherapy mITT	Placebo + pembrolizumab + chemotherapy mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	55		
Units: Months				
median (confidence interval 95%)	3.4 (1.3 to 4.4)	2.8 (1.4 to 9999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The hazard ratio and corresponding 2-sided 95% confidence interval was calculated from the cox regression model with Efron's method of tie handling with treatment as a covariate and stratified by PD-L1 expression (CPS ≥20 vs. 1≤ CPS <20) and HPV status (positive vs. negative). Participants with oropharynx HPV negative/unknown and non-oropharyngeal tumors were combined as the HPV negative group.

Comparison groups	Feladilimab + pembrolizumab + chemotherapy mITT v Placebo + pembrolizumab + chemotherapy mITT
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.302 [10]
Method	Stratified Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.69

Notes:

[10] - Nominal p-value was calculated based on the one-sided log-rank test, stratified by stratified by PD-L1 expression (CPS ≥20 vs. 1≤ CPS <20) and HPV status (oropharynx HPV positive vs oropharynx HPV negative/unknown and non-oropharynx).

Secondary: Time to deterioration in physical function in mITT population

End point title	Time to deterioration in physical function in mITT population

End point description:

TTD in physical function is defined as the time from randomization to the first definitive meaningful deterioration from baseline in the Physical Function (PF) T-score, i.e. a decrease from baseline of at least 2.4 observed at all subsequent non-missing visits, as measured by the Patient-Reported Outcomes Measurement Information System - Physical Function (PROMIS PF 8c). The PROMIS PF 8c is an 8-item fixed length short form derived from the PROMIS Physical Function item bank. It includes a 5-point scale with three sets of response options. Scores on the PROMIS PF 8c are reported on a T score metric (mean = 50 and SD = 10), with higher scores reflecting better physical functioning. All participants in the mITT population were analyzed. 99999 = The upper limit of the 95% CI was not calculable from the available data at the time of data cut off.

End point type	Secondary

End point timeframe:

Up to approximately 7 months

End point values	Feladilimab + pembrolizumab + chemotherapy mITT	Placebo + pembrolizumab + chemotherapy mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	55		
Units: Months				
median (confidence interval 95%)	2.8 (1.4 to 99999)	4.3 (2.1 to 5.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The hazard ratio and corresponding 2-sided 95% confidence interval was calculated from the cox regression model with Efron's method of tie handling with treatment as a covariate and stratified by PD-L1 expression (CPS ≥20 vs. 1≤ CPS <20 vs. CPS <1) and HPV status (positive vs. negative). Participants with oropharynx HPV negative/unknown and non-oropharyngeal tumors were combined as the HPV negative group.

Comparison groups	Feladilimab + pembrolizumab + chemotherapy mITT v Placebo + pembrolizumab + chemotherapy mITT

Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.472 [11]
Method	Stratified Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	2.11

Notes:

[11] - Nominal p-value was calculated based on the one-sided log-rank test, stratified by stratified by PD-L1 expression (CPS ≥20 vs. 1≤ CPS <20 vs. CPS <1) and HPV status (oropharynx HPV positive vs oropharynx HPV negative/unknown and non-oropharynx).

Secondary: Time to deterioration in physical function in PD-L1 CPS ≥1 population

End point title	Time to deterioration in physical function in PD-L1 CPS ≥1 population

End point description:

TTD in physical function is defined as the time from randomization to the first definitive meaningful deterioration from baseline in the PF T-score, i.e. a decrease from baseline of at least 2.4 observed at all subsequent non-missing visits, as measured by the PROMIS PF 8c. The PROMIS PF 8c is an 8-item fixed length short form derived from the PROMIS Physical Function item bank. It includes a 5-point scale with three sets of response options. Scores on the PROMIS PF 8c are reported on a T score metric (mean = 50 and SD = 10), with higher scores reflecting better physical functioning. Data are presented for the PD-L1 CPS ≥1 participants from mITT population. CPS was defined as the ratio of the combined number of PD-L1 expressing tumor cells and immune cells (lymphocytes and macrophages) to the total number of viable tumor cells. 99999 = The upper limit of the 95% CI was not calculable from the available data at the time of data cut off.

End point type	Secondary

End point timeframe:

Up to approximately 7 months

End point values	Feladilimab + pembrolizumab + chemotherapy mITT	Placebo + pembrolizumab + chemotherapy mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	52		
Units: Months				
median (confidence interval 95%)	4.8 (2.1 to 99999)	4.3 (2.1 to 5.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The hazard ratio and corresponding 2-sided 95% confidence interval was calculated from the cox regression model with Efron's method of tie handling with treatment as a covariate and stratified by PD-

L1 expression (CPS ≥20 vs. 1≤ CPS <20) and HPV status (positive vs. negative). Participants with oropharynx HPV negative/unknown and non-oropharyngeal tumors were combined as the HPV negative group.

Comparison groups	Feladilimab + pembrolizumab + chemotherapy mITT v Placebo + pembrolizumab + chemotherapy mITT
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.335 [12]
Method	Stratified Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1.9

Notes:

[12] - Nominal p-value was calculated based on the one-sided log-rank test, stratified by stratified by PD-L1 expression (CPS ≥20 vs. 1≤ CPS <20) and HPV status (oropharynx HPV positive vs oropharynx HPV negative/unknown and non-oropharynx).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All cause mortality, non-SAEs and SAEs were collected from Day 1 to up to approximately 37.2 months.

Adverse event reporting additional description:

Six participants randomized to feladilimab arm, received first dose after the DIL date were re-assigned to placebo arm.1 participant randomized to feladilimab arm, was never dosed and excluded from the safety population. Safety data for participants who continued to receive Pembrolizumab has been updated after study completion.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Placebo + Pembrolizumab + 5-FU-platinum chemotherapy

Reporting group description:

Participants were administered placebo and pembrolizumab as an IV infusion along with 5FU-platinum chemotherapy (cisplatin OR carboplatin) Q3W.

Reporting group title	Feladilimab + Pembrolizumab + 5-FU-platinum chemotherapy

Reporting group description:

Participants were administered feladilimab (humanized anti- ICOS IgG4 mAb) and pembrolizumab (humanized anti-PD-1 IgG4 mAb) as an IV infusion along with 5 FU-platinum chemotherapy (cisplatin OR carboplatin) Q3W.

Serious adverse events	Placebo + Pembrolizumab + 5-FU-platinum chemotherapy	Feladilimab + Pembrolizumab + 5-FU-platinum chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 65 (27.69%)	19 / 51 (37.25%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	2 / 65 (3.08%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Haemorrhage			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 65 (3.08%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	2 / 65 (3.08%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 65 (3.08%)	2 / 51 (3.92%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Lung disorder			

subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis aspiration			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal fistula			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal fistula			

subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Embedded device			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 65 (1.54%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Tracheal obstruction			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			

subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 65 (3.08%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cervical cord compression			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 65 (1.54%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 65 (3.08%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 65 (3.08%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 65 (1.54%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 65 (3.08%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			

subjects affected / exposed	1 / 65 (1.54%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 65 (3.08%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 65 (3.08%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pemphigoid			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 65 (0.00%)	2 / 51 (3.92%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular disorder			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Synovial cyst			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 65 (1.54%)	2 / 51 (3.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lower respiratory tract infection			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 65 (7.69%)	2 / 51 (3.92%)	
occurrences causally related to treatment / all	1 / 5	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Sepsis			
subjects affected / exposed	1 / 65 (1.54%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumonia aspiration			

subjects affected / exposed	3 / 65 (4.62%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 65 (1.54%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tracheostomy infection			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			

subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 65 (1.54%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 65 (3.08%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperammonaemia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypochloraemia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 65 (1.54%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			

subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic disorder			
subjects affected / exposed	1 / 65 (1.54%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Pembrolizumab + 5-FU-platinum chemotherapy	Feladilimab + Pembrolizumab + 5-FU-platinum chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 65 (84.62%)	44 / 51 (86.27%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 65 (6.15%)	0 / 51 (0.00%)	
occurrences (all)	5	0	
Hypertension			
subjects affected / exposed	1 / 65 (1.54%)	3 / 51 (5.88%)	
occurrences (all)	2	4	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 65 (10.77%)	4 / 51 (7.84%)	
occurrences (all)	11	6	
Mucosal inflammation			
subjects affected / exposed	16 / 65 (24.62%)	6 / 51 (11.76%)	
occurrences (all)	20	6	
Fatigue			

subjects affected / exposed	24 / 65 (36.92%)	17 / 51 (33.33%)	
occurrences (all)	29	20	
Asthenia			
subjects affected / exposed	13 / 65 (20.00%)	8 / 51 (15.69%)	
occurrences (all)	15	12	
Pain			
subjects affected / exposed	3 / 65 (4.62%)	3 / 51 (5.88%)	
occurrences (all)	3	3	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	5 / 65 (7.69%)	4 / 51 (7.84%)	
occurrences (all)	4	5	
Cough			
subjects affected / exposed	5 / 65 (7.69%)	4 / 51 (7.84%)	
occurrences (all)	5	4	
Oropharyngeal pain			
subjects affected / exposed	4 / 65 (6.15%)	2 / 51 (3.92%)	
occurrences (all)	5	2	
Productive cough			
subjects affected / exposed	5 / 65 (7.69%)	1 / 51 (1.96%)	
occurrences (all)	6	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 65 (4.62%)	5 / 51 (9.80%)	
occurrences (all)	3	5	
Investigations			
Blood creatinine increased			
subjects affected / exposed	10 / 65 (15.38%)	3 / 51 (5.88%)	
occurrences (all)	21	3	
Neutrophil count decreased			
subjects affected / exposed	10 / 65 (15.38%)	10 / 51 (19.61%)	
occurrences (all)	16	18	
Platelet count decreased			
subjects affected / exposed	9 / 65 (13.85%)	6 / 51 (11.76%)	
occurrences (all)	11	8	
Weight decreased			

subjects affected / exposed	5 / 65 (7.69%)	8 / 51 (15.69%)	
occurrences (all)	5	8	
White blood cell count decreased			
subjects affected / exposed	6 / 65 (9.23%)	5 / 51 (9.80%)	
occurrences (all)	6	13	
Lymphocyte count decreased			
subjects affected / exposed	2 / 65 (3.08%)	4 / 51 (7.84%)	
occurrences (all)	2	4	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 65 (6.15%)	1 / 51 (1.96%)	
occurrences (all)	7	1	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 65 (9.23%)	5 / 51 (9.80%)	
occurrences (all)	6	5	
Neuropathy peripheral			
subjects affected / exposed	3 / 65 (4.62%)	4 / 51 (7.84%)	
occurrences (all)	4	4	
Dizziness			
subjects affected / exposed	4 / 65 (6.15%)	2 / 51 (3.92%)	
occurrences (all)	4	2	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	21 / 65 (32.31%)	9 / 51 (17.65%)	
occurrences (all)	47	15	
Leukopenia			
subjects affected / exposed	7 / 65 (10.77%)	4 / 51 (7.84%)	
occurrences (all)	14	5	
Anaemia			
subjects affected / exposed	30 / 65 (46.15%)	27 / 51 (52.94%)	
occurrences (all)	53	40	
Thrombocytopenia			
subjects affected / exposed	17 / 65 (26.15%)	6 / 51 (11.76%)	
occurrences (all)	29	8	
Gastrointestinal disorders			

Dyspepsia			
subjects affected / exposed	5 / 65 (7.69%)	2 / 51 (3.92%)	
occurrences (all)	5	2	
Diarrhoea			
subjects affected / exposed	13 / 65 (20.00%)	3 / 51 (5.88%)	
occurrences (all)	18	3	
Constipation			
subjects affected / exposed	13 / 65 (20.00%)	12 / 51 (23.53%)	
occurrences (all)	13	12	
Vomiting			
subjects affected / exposed	8 / 65 (12.31%)	5 / 51 (9.80%)	
occurrences (all)	12	6	
Stomatitis			
subjects affected / exposed	13 / 65 (20.00%)	11 / 51 (21.57%)	
occurrences (all)	14	11	
Nausea			
subjects affected / exposed	25 / 65 (38.46%)	21 / 51 (41.18%)	
occurrences (all)	28	25	
Dysphagia			
subjects affected / exposed	4 / 65 (6.15%)	2 / 51 (3.92%)	
occurrences (all)	4	2	
Abdominal pain			
subjects affected / exposed	4 / 65 (6.15%)	1 / 51 (1.96%)	
occurrences (all)	4	1	
Oral pain			
subjects affected / exposed	3 / 65 (4.62%)	3 / 51 (5.88%)	
occurrences (all)	3	4	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 65 (7.69%)	3 / 51 (5.88%)	
occurrences (all)	5	5	
Pruritus			
subjects affected / exposed	6 / 65 (9.23%)	2 / 51 (3.92%)	
occurrences (all)	6	2	
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	9 / 65 (13.85%)	7 / 51 (13.73%)	
occurrences (all)	9	10	
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	7 / 65 (10.77%)	1 / 51 (1.96%)	
occurrences (all)	7	2	
Arthralgia			
subjects affected / exposed	7 / 65 (10.77%)	1 / 51 (1.96%)	
occurrences (all)	8	1	
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	9 / 65 (13.85%)	2 / 51 (3.92%)	
occurrences (all)	11	2	
COVID-19			
subjects affected / exposed	6 / 65 (9.23%)	2 / 51 (3.92%)	
occurrences (all)	6	2	
Upper respiratory tract infection			
subjects affected / exposed	5 / 65 (7.69%)	1 / 51 (1.96%)	
occurrences (all)	6	1	
Pneumonia			
subjects affected / exposed	4 / 65 (6.15%)	1 / 51 (1.96%)	
occurrences (all)	5	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 65 (12.31%)	8 / 51 (15.69%)	
occurrences (all)	10	8	
Dehydration			
subjects affected / exposed	2 / 65 (3.08%)	3 / 51 (5.88%)	
occurrences (all)	2	3	
Hyperglycaemia			
subjects affected / exposed	3 / 65 (4.62%)	4 / 51 (7.84%)	
occurrences (all)	5	4	
Hypokalaemia			
subjects affected / exposed	4 / 65 (6.15%)	1 / 51 (1.96%)	
occurrences (all)	8	1	

Hypocalcaemia subjects affected / exposed occurrences (all)	5 / 65 (7.69%) 12	2 / 51 (3.92%) 2	
Hyponatraemia subjects affected / exposed occurrences (all)	6 / 65 (9.23%) 8	2 / 51 (3.92%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 April 2021	Amendment 1: The primary rationale for the amendment was to account for a study design update from a Phase III study to an adaptive Phase II/III study which allows for a proper balance of the risk and benefit of a Phase III expansion decision. Additional updates included were: eligibility criteria to address high risk of bleeds that are a feature inherent to the underlying disease of a population with HNSCC and define unstable medical condition; definition of second course of study treatment that was expanded to include participants who complete 35 cycles of study treatment.
30 June 2021	Amendment 2: A DIL dated 13-April-2021 was issued requiring the stopping of further screening and the discontinuation of the administration of GSK3359609 (feladilimab) or placebo for all participants on INDUCE-4, effective immediately. Further to the DIL, since all participants had the option to remain on pembrolizumab alone plus 5FU-platinum as study therapy, GSK issued a Protocol Clarification Letter (PCL) dated 28-April-2021 to reduce any unnecessary burden of on treatment and follow up assessments (the PCL did not alter any screening assessments). This protocol amendment was a follow up to the PCL, with a primary intent to only update the SoA; other impacted, relevant sections were also updated accordingly. Additionally, updates were made to management guidelines to align with pembrolizumab IB update.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Data are reported following the interim analysis decision to stop further accrual into the study and discontinue feladilimab/placebo. The study primary completion analysis results should be interpreted with consideration of the immature data

Notes: