NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

BYL719

Trial Indication(s)

Recurrent or metastatic head and neck squamous cell carcinoma (RM HNSCC) resistant or intolerant or ineligible to platinum-based chemotherapy

Protocol Number

CBYL719X2104

Protocol Title

A phase Ib dose escalation/randomized phase II, multicenter, open-label study of BYL719 in combination with cetuximab in patients with recurrent or metastatic head and neck squamous cell carcinoma

Clinical Trial Phase

Phase 1/Phase 2

Phase of Drug Development

Phase I

Study Start/End Dates

Study Start Date: November 2012 (Actual)
Primary Completion Date: May 2016 (Actual)
Study Completion Date: May 2016 (Actual)

Reason for Termination (If applicable)

early termination due to Sponsor decision (slow recruitment)

Study Design/Methodology

This is a multicenter, open-label, Phase Ib dose escalation followed by a Phase II study with a randomized part and an additional non-randomized arm. Both, Phase Ib and Phase II were conducted in adult patients who were resistant, ineligible or intolerant to platinum-based chemotherapy.
In the Phase Ib part, various doses of BYL719 combined with standard dose of cetuximab were evaluated in patients with RM HNSCC to determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of the combination and to explore different formulations and routes of administration. The MTD/RP2D was investigated independently for Arm A and Arm B following the recommendation from an adaptive Bayesian logistic regression model (BLRM) incorporating the escalation with overdose control (EWOC) principle. In Arm C, the pharmacokinetics of the new dispersible tablet formulation of BYL719 was planned to be evaluated as compared to the PK of Arm A.
The randomized Phase II part of the study assessed the clinical efficacy of BYL719 in combination with cetuximab vs. cetuximab single-agent in patients resistant or intolerant or ineligible to platinum and naïve to cetuximab. The non-randomized part of the Phase II assessed the clinical efficacy of BYL719 in combination with cetuximab in patients who are resistant or intolerant or ineligible to both platinum and cetuximab.

Centers

30 centers in 9 countries: United States(15), Singapore(1), Hong Kong(1), France(2), Canada(1), Australia(2), Taiwan(3), Korea, Republic of(3), Netherlands(2)

Objectives:

Primary Objectives

Phase Ib

- Arm A and B: To estimate the maximum tolerated dose (MTD(s)) and/or recommended Phase II dose (RP2D) of BYL719 in combination with cetuximab in patients with recurrent or metastatic head and neck squamous cell carcinoma (RM HNSCC) in the following two arms:
    - Arm A: BYL719 administered orally as a film-coated whole tablet in patients able to swallow the tablets.

  - Arm B: BYL719 administered orally as a drinkable suspension prepared from film-coated crushed tablets in patients with swallowing dysfunction.
- Arm C: To compare exposure of BYL719 dispersible tablet via G-tube in combination with cetuximab in RM HNSCC to that of Arm A (film-coated tablets).

Phase II
- Scheme 1: To assess the anti-tumor activity of BYL719 in combination with cetuximab vs. cetuximab as single-agent in RM HNSCC patients naïve to cetuximab.
- Scheme 2: To assess the anti-tumor activity of BYL719 in combination with cetuximab in RM HNSCC cetuximab resistant patients.

Secondary Objectives
Phase Ib
- To characterize the safety and tolerability of BYL719 in combination with cetuximab in Arm A, Arm B and Arm C.
- To determine the single and multiple dose pharmacokinetic (PK) profile of BYL719 in combination with cetuximab in Arm A and Arm B.
- To determine the multiple dose PK profile of BYL719 in combination with cetuximab in Arm C.
- To assess the preliminary anti-tumor activity of BYL719 in combination with cetuximab in Arms A, B and C.

Phase II
- To characterize the safety and tolerability of BYL719 in combination with cetuximab.
- Scheme 1 (Arms 1 and 2): To further assess the anti-tumor activity of the BYL719 in combination with cetuximab vs. cetuximab as single-agent in RM HNSCC patients naïve to cetuximab.
- Scheme 1 (Arm 2B): To further assess the anti-tumor activity of BYL719 + cetuximab in the setting of resistance to single agent cetuximab.
- Scheme 2 (Arm 3): To further assess the anti-tumor activity of the BYL719 in combination with cetuximab in RM HNSCC patients who have progressed following treatment with cetuximab and platinum.

Test Product (s), Dose(s), and Mode(s) of Administration

BYL719 in combination with cetuximab was investigated. In Phase Ib two different formulations of BYL719 were administered using three different methods. In Phase II BYL719 was administered either as whole tablet or drinkable suspension in patients without swallowing dysfunction and patients with swallowing dysfunction, respectively. Cetuximab

was commercially available globally and specifically supplied to France and Netherlands with local regulations. Cetuximab was administered according to the label and institutional guidelines.

Statistical Methods

MTD: The primary endpoint was the incidence of DLTs in Cycle 1. Estimation of the MTD of the combination treatment was based upon the estimation of the probability of DLT rate in Cycle 1 for patients in the dose determining set (DDS). An adaptive BLRM with EWOC principle guided the dose escalation of the combination treatment to its MTD. Summaries of posterior distribution of DLT rates based on the DLT data in Cycle 1 from all patients enrolled in the dose escalation part and included in the DDS were reported separately for each arm (Arm A and Arm B).
Efficacy: PFS by RECIST 1.1 based on the tumor response from central review was the primary efficacy endpoint in the Phase II part of the study**.** In Scheme 1 (Arms 1 and 2), a Bayesian Cox Proportional Hazard (PH) model was used to estimate the hazard ratio of PFS between the combination treatment and cetuximab monotherapy. The combination treatment was considered superior to cetuximab alone if the posterior probability (HR > 1) < 10%, and the posterior median HR < 0.7.
In Scheme 2 (Arm 3), PFS was modelled using Weibull distribution, and the efficacy was concluded if the estimated median PFS was ≥ 4 months, and posterior probability that median PFS is ≥ 2.5 months was at least 80%.
For both Phase Ib and Phase II part, tumor response along with clinical findings was used to calculate the overall response rate (ORR) and disease control rate (DCR). Information about the patients survival status was recorded in the CRF and was used to determine the overall survival (OS).
Pharmacokinetics: PK parameters for the Phase Ib part were determined by a non-compartmental method using Phoenix WinNonlin.
Safety: The assessment of safety was based mainly on the nature, frequency and severity of adverse events and on the number of laboratory values that fell outside of pre-determined ranges. Other safety data (e.g. electrocardiogram, vital signs) were considered as appropriate.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Age ≥ 18 years
- Patients with histologically/cytologically-confirmed HNSCC
- Patients must be resistant to platinum-based chemotherapy, or be ineligible (due to medical comorbidities) or intolerant to platinum-based therapy per medical history

- For Phase Ib, there is no restriction on the number of prior therapies for recurrent or metastatic disease
- For Phase II, patients may have received a maximum of 1 prior line of therapy for recurrent or metastatic disease
- For Phase Ib, prior cetuximab or other EGFR-targeted antibody therapy is allowed regardless of the prior treatment settings.
-For Phase II, Arms 1 and 2, prior cetuximab or other EGFR-targeted antibody therapy is allowed only if administered in the induction setting, or concurrently with radiation in the curative setting, with the last dose of cetuximab administered at least 12 months prior to starting the study treatment. For Arm 3, prior cetuximab must have been administered in the curative, recurrent or metastatic disease setting and disease progression documented within 9 months of the last dose of cetuximab administered in that setting. This regimen (including both platinum and cetuximab) must be the most recent anti-neoplastic treatment regimen administered.
- Patients with swallowing dysfunction who are unable to swallow BYL719 whole tablets and are not using feeding tubes for study drug administration can participate in the Phase Ib Arm B. For the Phase II, these patients with swallowing dysfunction may participate if able to drink the suspension and results of Arm B confirm the use of this method. Patients with swallowing dysfunction requiring G tube (G/PEG tube) for study drug administration may participate in Phase II if Arm C confirms dispersible tablet via G tube administration is permitted if the administration of drinkable suspension of BYL719 is allowed to be used in Phase II.
- Availability of a representative tumor specimen. Patients enrolled in Arm 3 of Phase II must have disease sites amenable to biopsy unless prior agreement between Novartis and the Investigator.
- At least one measurable or non-measurable lesion as per RECIST 1.1 criteria for patients in Phase Ib; Measurable disease as determined by RECIST v1.1 for Phase II patients
- World Health Organization (WHO) Performance Status (PS) ≤ 2
- Adequate organ function
- Negative serum pregnancy test.

Exclusion Criteria:
- Prior treatment with PI3K-inhibitors
- Patients with a prior serious infusion reaction to cetuximab
- Patients with uncontrolled CNS tumor metastatic involvement
- Clinically significant cardiac disease or impaired cardiac function
- Patients with diabetes mellitus
- Impaired GI function or GI disease
- History of another malignancy within 2 years prior to starting study treatment
- Pregnant or nursing (lactating) women

Participant Flow Table

Overall Study

	Arm A - 300mg BYL719+Cetuximab	Arm A - 400mg BYL719+Cetuximab	Arm B - BYL719 + Cetuximab, Oral suspension	Arm C - BYL719+Cetuximab, Dispersible tablets	Arm 1 - BYL719+Cetuximab (randomized)	Arm 2 - Monotherapy Cetuximab (randomized)	Arm 3 - BYL719+Cetuximab (non-randomized)
Started	16	5	18	6	71	35	29
Completed	0	0	0	0	0	0	0
Not Completed	16	5	18	6	71	35	29
Protocol Violation	0	0	0	0	0	1	0
Physician Decision	2	0	0	0	2	1	1
Disease progression	6	3	10	1	41	12	15
Death	1	1	1	1	7	2	2
Withdrawal by Subject	2	0	2	0	6	0	1
Adverse Event	5	1	5	4	15	3	9
Subject/guardian decision	0	0	0	0	0	0	1
Cross-over patients to combo treatment	0	0	0	0	0	16	0

Baseline Characteristics

	Arm A - 300mg BYL719+Cetuximab	Arm A - 400mg BYL719+Cetuximab	Arm B - BYL719 + Cetuximab, Oral	Arm C - BYL719+Cetuxim	Arm 1 - BYL719+Cetuxi	Arm 2 - Monotherapy Cetuximab	Arm 3 - BYL719+Cetuxi	Total

			suspension	ab, Dispersible tablets	mab (randomized)	(randomized)	mab (non-randomized)	
Number of Participants [units: participants]	16	5	18	6	71	35	29	180
Age Continuous (units: years) Mean ± Standard Deviation	52.8±13.40	62.6±7.99	56.7±10.20	60.5±14.10	57.2±9.66	57.1±10.37	56.9±8.25	57.0±10.16
Gender, Male/Female (units: participants)								
Female	7	1	4	2	16	4	10	44
Male	9	4	14	4	55	31	19	136

Summary of Efficacy

Primary Outcome Result(s)

Phase Ib Arms A: Posterior Distribution of Dose Limiting Toxicities (DLTs) at Recommended Phase 2 Dose in Cycle 1 (Cycle 1=28 days)

	0-0.16	0.16-0.35	0.35-1
Number of Participants Analyzed [units: participants]	15	15	15

Phase Ib Arms A: Posterior Distribution of Dose Limiting Toxicities (DLTs) at Recommended Phase 2 Dose in Cycle 1 (Cycle 1=28 days)

(units: Percentages)

200 mg	0.964	0.035	0.001
300 mg	0.764	0.222	0.15
350 mg	0.304	0.543	0.153
400 mg	0.086	0.376	0.538

Phase Ib Arms B: Posterior Distribution of Dose Limiting Toxicities (DLTs) at Recommended Phase 2 Dose in Cycle 1 (Cycle 1=28 days)

	0-0.16	0.16-0.35	0.35-1
Number of Participants Analyzed [units: participants]	15	15	15
Phase Ib Arms B: Posterior Distribution of Dose Limiting Toxicities (DLTs) at Recommended Phase 2 Dose in Cycle 1 (Cycle 1=28 days) (units: Percentages)			
200 mg	0.836	0.160	0.004
300 mg	0.267	0.664	0.069
350 mg	0.054	0.585	0.361
400 mg	0.017	0.346	0.638

For Phase Ib: Incidence of Dose Limiting Toxicities (DLTs) in Cycle 1 (28 days)

	Arm A - 300mg BYL719+Cetuximab	Arm A - 400mg BYL719+Cetuximab	Arm B - BYL719 + Cetuximab, Oral suspension	Arm C - BYL719+Cetuximab, Dispersible tablets	All Patients

Number of Participants Analyzed [units: participants]	11	3	13	3	30
For Phase Ib: Incidence of Dose Limiting Toxicities (DLTs) in Cycle 1 (28 days) (units: Participants)	1	2	4	2	30

Phase II Arms 1 and 2: Progression Free Survival (PFS) as per RECIST v1.1 by central radiology review

	BYL719+ Cetuximab (randomized)	**Monotherapy Cetuximab (randomized)**
Number of Participants Analyzed [units: participants]	71	35
Phase II Arms 1 and 2: Progression Free Survival (PFS) as per RECIST v1.1 by central radiology review (units: participants)		
Number of PFS events	46	27
Progression	33	25
Number of censored	25	8
Death	13	2

Statistical Analysis

Groups	BYL719+ Cetuximab (randomized), Monotherapy Cetuximab (randomized)	The hazard ratio was estimated using the Bayesian Cox proportional

		hazard (PH) model.
Non-Inferiority/Equivalence Test	No	
P Value		
Method		
Other median HR	0.990	
% Confidence Interval	to	

Statistical Analysis

Groups	BYL719+ Cetuximab (randomized), Monotherapy Cetuximab (randomized)
Non-Inferiority/Equivalence Test	No
P Value	0.643
Method	Regression, Cox
Hazard Ratio (HR)	1.12
95 % Confidence Interval 2-Sided	0.69 to 1.82

Statistical Analysis

Groups	BYL719+ Cetuximab (randomized), Monotherapy Cetuximab (randomized)	Adjusted on Covariates: treatment, sum of longest diameters from central data [SLD (C)], Hemaglobin (Hgb) and White Blood Cells (WBC).
Non-Inferiority/Equivalence Test	No	
P Value	0.039	
Method	Regression, Cox	
Hazard Ratio (HR)	0.54	
95 % Confidence Interval 2-Sided	0.30 to 0.97	

Phase II Arm 3: Progression Free Survival (PFS) as per RECIST V1.1

	BYL719+ Cetuximab (non-randomized)
Number of Participants Analyzed [units: participants]	29
Phase II Arm 3: Progression Free Survival (PFS) as per	3.896 (2.868 to 5.241)

RECIST V1.1
(units: months)
Median (95% Confidence Interval)

Phase Ib: Area under curve (AUC) 0-24 for BYL719 by Treatment

	Arm A - 300mg BYL719+Cetuximab	Arm C: BYL719+Cetixumab, Dispersible tablets	Arm A: 400mg BYL719 + Cetuximab
Number of Participants Analyzed [units: participants]	15	6	5
Phase Ib: Area under curve (AUC) 0-24 for BYL719 by Treatment (units: hr*ng/mL) Median (Full Range)			
AUCinf	22600 (16600 to 48500)	24100 (9290 to 33200)	27800 (17200 to 60100)
AUC0_24	18800 (5590 to 43400)	19400 (7580 to 32100)	26300 (16000 to 56100)
AUClast	19200 (5830 to 42700)	22100 (4390 to 31800)	26200 (15800 to 55600)

Secondary Outcome Result(s)

Phase II: Progression Free Survival (PFS) as per RECIST v 1.1

	Arm 2B - BYL719+Cetuximab
Number of Participants Analyzed [units: participants]	16
Phase II: Progression Free Survival (PFS) as per RECIST v 1.1 (units: Participants)	
Number of PFS	12
Progression	9
Death	3
Number of Censored	4

Statistical Analysis

Groups	Arm 2B - BYL719+Cetuximab	
Non-Inferiority/Equivalence Test	No	
P Value		
Method		
Other Kaplan-Meier method (median)	43.0	days
95 % Confidence Interval 2-Sided	27.0 to 88.0	

Phase Ib: Progression Free Survival (PFS) as per RECIST v1.1

	Arm A - 300mg BYL719+Cetuximab	Arm A - 400mg BYL719+Cetuximab	Arm B - BYL719 + Cetuximab, Oral suspension	Arm C - BYL719+Cetuximab, Dispersible tablets
Number of Participants Analyzed [units: participants]	0	0	0	0
Phase Ib: Progression Free Survival (PFS) as per RECIST v1.1 (units: Participants)				

Phase II: Randomized Best overall response as per RECIST v1.1

	Arm 1 - BYL719+Cetuximab (randomized)	Arm 2 - Monotherapy Cetuximab (randomized)	All Patients
Number of Participants Analyzed [units: participants]	71	35	106
Phase II: Randomized Best overall response as per RECIST v1.1 (units: Participants)			
Complete Response	1	0	1
Partial Response	6	2	8
Stable Disease	24	8	32
Progressive Disease	17	12	29
Non-CR/Non-PD (NCRNPD)	6	10	16
Unknown	17	3	20

Phase II: Non-Randomized Best overall response as per RECIST v1.1

	Arm 3 - BYL719+Cetuximab
Number of Participants Analyzed [units: participants]	29
Phase II: Non-Randomized Best overall response as per RECIST v1.1 (units: Participants)	
Complete Response (CR)	1
Partial Response (PR)	2
Stable Disease (SD)	8
Progressive Disease (PD)	5
Non-CR/Non-PD (NCRNPD)	6
Unknown	7

Phase II: Randomized Overall Response Rate (ORR) and Disease Control Rate (DCR) as per RECIST v1.1

	Arm 1 - BYL719+Cetuximab (randomized)	Arm 2 - Monotherapy Cetuximab (randomized)	All Patients (Phase II)
Number of Participants Analyzed [units: participants]	71	35	106
Phase II: Randomized Overall Response Rate (ORR) and Disease Control Rate (DCR) as per RECIST v1.1 (units: Percentages) Number (95% Confidence Interval)			
Overall response rate (ORR) (CR or PR)	9.9 (4.1 to 19.3)	5.7 (0.7 to 19.2)	8.5 (4.0 to 15.5)

Disease control rate 1 (DCR 1) (CR or PR or SD)	43.7 (31.9 to 56.0)	28.6 (14.6 to 46.3)	38.7 (29.4 to 48.6)
DCR 2 (CR or PR or SD or Non-CR/Non-PD)	52.1 (39.9 to 64.1)	57.1 (39.4 to 73.7)	53.8 (43.8 to 63.5)

Phase II: Non-Randomized Overall Response Rate (ORR) and Disease Control Rate (DCR) as per RECIST v1.1

	Arm 3 - BYL719+Cetuximab
Number of Participants Analyzed [units: participants]	29
Phase II: Non-Randomized Overall Response Rate (ORR) and Disease Control Rate (DCR) as per RECIST v1.1 (units: Percentages) Number (95% Confidence Interval)	
Overall response rate (ORR) (CR or PR)	10.3 (2.2 to 27.4)
Disease control rate 1 (DCR 1) (CR or PR or SD)	37.9 (20.7 to 57.7)
DCR 2 (CR or PR or SD or Non-CR/Non-PD)	58.6 (38.9 to 76.5)

Phase II: Randomized Overall Survival (OS) by treatment

	Arm 1 - BYL719+Cetuximab (randomized)	Arm 2 - Monotherapy Cetuximab (randomized)
Number of Participants Analyzed [units: participants]	71	35

Phase II: Randomized Overall Survival (OS) by treatment
(units: Patients)

Number of deaths	51	26
Number of censored	20	9

Statistical Analysis

Groups	Arm 1 - BYL719+Cetuximab (randomized), Arm 2 - Monotherapy Cetuximab (randomized)
Non-Inferiority/Equivalence Test	No
P Value	0.313
Method	Regression, Cox
Hazard Ratio (HR)	1.28
95 % Confidence Interval 2-Sided	0.79 to 2.05

Phase II: Non-Randomized Overall Survival (OS) by treatment

	Arm 3 - BYL719+Cetuximab
Number of Participants Analyzed [units: participants]	29
Phase II: Non-Randomized Overall Survival (OS) by treatment	

(units: Patients)

Number of deaths	13
Number of censored	10

Statistical Analysis

Groups	Arm 3 - BYL719+Cetuximab
Non-Inferiority/Equivalence Test	No
P Value	
Method	
Other Kaplan-Meier (median)	294.0
95 % Confidence Interval 2-Sided	172.0 to 463.0

For Phase Ib: Overall Response Rate (ORR) and Disease Control Rate (DCR) as per RECIST v1.1

	Arm A - 300mg BYL719+Cetuximab	**Arm A - 400mg BYL719+Cetuximab**	**Arm B - BYL719 + Cetuximab, Oral suspension**	**Arm C - BYL719+Cetuximab, Dispersible tablets**	**All Patients**
Number of Participants Analyzed [units: participants]	16	5	18	6	45

For Phase Ib: Overall Response Rate (ORR) and Disease Control Rate (DCR) as per RECIST v1.1
(units: Percentages)
Number (95% Confidence Interval)

ORR (CR) or PR)	25.5 (7.3 to 52.4)	0.0 (0.0 to 52.2)	0.0 (0.0 to 18.5)	0.0 (0.0 to 45.9)	8.9 (2.5 to 21.2)
DCR (CR or PR or Stable Disease or non-CR/Non-PD)	75.0 (47.6 to 92.7)	20.0 (0.5 to 71.6)	50.0 (26.0 to 74.0)	16.7 (0.4 to 64.1)	51.1 (35.8 to 66.3)

Phase II, Scheme 1 (arm 2B): Overall Response Rate (ORR) and Disease Control Rate (DCR) as per RECIST v1.1

	Arm 2B - BYL719+Cetuximab
Number of Participants Analyzed [units: participants]	0
Phase II, Scheme 1 (arm 2B): Overall Response Rate (ORR) and Disease Control Rate (DCR) as per RECIST v1.1 (units: percentages) Number (95% Confidence Interval)	

Phase II, Scheme 2 (Arm 2B): OS from the time of crossing over

	Arm 2B - BYL719+Cetuximab
Number of Participants Analyzed [units: participants]	0
Phase II, Scheme 2 (Arm 2B): OS from the time of crossing over (units: Patients)	

Phase Ib: Primary Plasma Pharmacokinetic Parameters for BYL719 by Treatment

	Arm A - 300mg BYL719+Cetuximab	Arm B: BYL719 + Cetuximab, Oral suspension	Arm C: BYL719+Cetixumab, Dispersible tablets	Arm A: 400mg BYL719 + Cetuximab
Number of Participants Analyzed [units: participants]	15	17	6	5
Phase Ib: Primary Plasma Pharmacokinetic Parameters for BYL719 by Treatment (units: hr*ng/mL) Median (Full Range)				
AUCinf	22600 (16600 to 48500)	27300 (15700 to 47400)	24100 (9290 to 33200)	27800 (17200 to 60100)
AUC0_24	18800 (5590 to 43400)	25600 (14600 to 42100)	19400 (7580 to 32100)	26300 (16000 to 56100)
AUClast	19200 (5830 to 42700)	2370 (1330 to 3710)	22100 (4390 to 31800)	26200 (15800 to 55600)

Phase Ib: Cmax for BYL719 by Treatment

	Arm A - 300mg BYL719+Cetuximab	Arm B: BYL719 + Cetuximab, Oral suspension	Arm C: BYL719+Cetixumab, Dispersible tablets	Arm A: 400mg BYL719 + Cetuximab
Number of Participants Analyzed [units: participants]	15	17	6	5
Phase Ib: Cmax for BYL719 by Treatment (units: ng/mL) Median (Full Range)	2130 (303 to 4280)	2340 (1330 to 3710)	2010 (682 to 2980)	2520 (1800 to 6240)

Phase Ib: Tmax for BYL719 by Treatment

	Arm A - 300mg BYL719+Cetuximab	Arm B: BYL719 + Cetuximab, Oral suspension	Arm C: BYL719+Cetixumab, Dispersible tablets	Arm A: 400mg BYL719 + Cetuximab
Number of Participants Analyzed [units: participants]	15	17	6	5
Phase Ib: Tmax for BYL719 by Treatment (units: hr) Median (Full Range)	2.02 (1 to 24.8)	2.97 (1 to 5.87)	3 (0.767 to 6)	2.23 (1.58 to 3.02)

Phase Ib: Plasma Pharmacokinetic Parameters for BYL719 after continuous dose administration (steady state)

	Arm A - 300mg BYL719+Cetuximab	Arm B: BYL719 + Cetuximab, Oral suspension	Arm C: BYL719+Cetixumab, Dispersible tablets
Number of Participants Analyzed [units: participants]	15	17	6
Phase Ib: Plasma Pharmacokinetic Parameters for BYL719 after continuous dose administration (steady state) (units: hr*ng/mL) Median (Full Range)			
AUC (0-24)	24600 (17900 to 44400)	28500 (12700 to 53900)	30500 (30500 to 30500)
AUClast	24500 (18000 to 76100)	2370 (1330 to 3710)	22100 (4390 to 31800)

Phase Ib: Cmax for BYL719 after continuous dose administration (steady state)

	Arm A - 300mg BYL719+Cetuximab	Arm B: BYL719 + Cetuximab, Oral suspension	Arm C: BYL719+Cetixumab, Dispersible tablets
Number of Participants Analyzed [units: participants]	15	17	6
Phase Ib: Cmax for BYL719 after continuous dose administration (steady state) (units: ng/mL) Median (Full Range)	2200 (1710 to 6520)	2820 (373 to 4710)	2750 (2750 to 2750)

Phase Ib: Tmax for BYL719 after continuous dose administration (steady state)

	Arm A - 300mg BYL719+Cetuximab	Arm B: BYL719 + Cetuximab, Oral suspension	Arm C: BYL719+Cetixumab, Dispersible tablets
Number of Participants Analyzed [units: participants]	15	17	6
Phase Ib: Tmax for BYL719 after continuous dose administration (steady state) (units: hr) Median (Full Range)	3.15 (1.5 to 7.13)	3.15 (1.03 to 8)	1 (1 to 1)

Phase Ib: Notable Abnormal Vital Signs by Treatment

	Arm A - 300mg BYL719+Cetuximab	Arm A - 400mg BYL719+Cetuximab	Arm B - BYL719 + Cetuximab,	Arm C - BYL719+Cetuximab, Dispersible tablets

			Oral suspension	
Number of Participants Analyzed [units: participants]	15	5	18	6
Phase Ib: Notable Abnormal Vital Signs by Treatment (units: Participants)				
Sitting Pulse rate (bpm): High only	0	0	4	4
Sitting Pulse rate (bpm): Low only	0	0	0	0
Sitting Pulse rate (bpm): High and low	0	0	0	0
Sitting systolic B.P. (mmHg): High only	1	0	1	0
Sitting systolic B.P. (mmHg): Low only	1	0	0	1
Sitting systolic B.P. (mmHg): High and low	0	0	1	0
Sitting diastolic B.P. (mmHg): High only	0	0	1	0
Sitting diastolic B.P. (mmHg): Low only	1	0	2	0
Sitting diastolic B.P. (mmHg): High and low	0	0	0	0
Body Temperature (Celsius): High only	0	0	0	1
Body Temperature (Celsius): Low only	0	0	0	0
Body Temperature (Celsius): High and low	0	0	0	0
Weight (kg): High only	0	0	0	0

Weight (kg): Low only	7	1	3	3
Weight (kg): High and low	0	0	0	0
Respiratory Rate (bpm): High only	0	0	2	1
Respiratory Rate (bpm): Low only	0	0	0	0
Respiratory Rate (bpm): High and low	0	0	0	0

Phase Ib: Number of patients with notable Electrocardiogram (ECG) abnormalities

	Arm A - 300mg BYL719+Cetuximab	Arm A - 400mg BYL719+Cetuximab	Arm B - BYL719 + Cetuximab, Oral suspension	Arm C - BYL719+Cetuximab, Dispersible tablets
Number of Participants Analyzed [units: participants]	15	5	18	6
Phase Ib: Number of patients with notable Electrocardiogram (ECG) abnormalities (units: Participants)				
QTcF (msec): Increase from baseline > 30	149	54	1810	61
QTcF (msec): Increase from baseline > 60	142	50	181	60
QTcB (msec): Increase from baseline > 30	1411	54	1812	61
QTcB (msec): Increase from baseline > 60	141	50	181	61
QT (msec): Increase from baseline > 30	1	54	1810	61

QT (msec): Increase from baseline > 60	144	50	183	60
VR (bpm): RR decrease > 25% & to a VR > 100	140	51	181	61
VR (bpm): RR decrease > 25% & to a VR < 50	140	50	180	60
PR (msec): increase > 25% & to a VR > 200	140	50	180	60
QRS (msec): increase > 25% & to a VR > 110	140	50	180	60

For Phase II: Notable Abnormal Vital Signs by Treatment

	Arm 1 - BYL719+Cetuximab (randomized)	Arm 2 - Monotherapy Cetuximab (randomized)	Arm 2B - BYL719+Cetuximab
Number of Participants Analyzed [units: participants]	69	35	29
For Phase II: Notable Abnormal Vital Signs by Treatment (units: Participants)			
Sitting Pulse rate (bpm): High only	4	3	5
Sitting Pulse rate (bpm): Low only	1	0	1
Sitting Pulse rate (bpm): High and low	0	0	0
Sitting systolic B.P. (mmHg): High only	0	1	0
Sitting systolic B.P. (mmHg): Low only	11	3	1

Sitting systolic B.P. (mmHg): High and low	1	0	0
Sitting diastolic B.P. (mmHg): High only	1	2	0
Sitting diastolic B.P. (mmHg): Low only	4	3	2
Sitting diastolic B.P. (mmHg): High and low	1	0	0
Body Temperature (Celsius): High only	1	0	0
Body Temperature (Celsius): Low only	3	1	2
Body Temperature (Celsius): High and low	0	0	0
Weight (kg): High only	1	4	0
Weight (kg): Low only	31	3	9
Weight (kg): High and low	0	0	0
Respiratory Rate (bpm): High only	2	0	1
Respiratory Rate (bpm): Low only	2	1	4
Respiratory Rate (bpm): High and low	0	0	0

For Phase II: Number of patients with notable Electrocardiogram (ECG) abnormalities

	Arm 1 - BYL719+Cetuximab (randomized)	Arm 2 - Monotherapy Cetuximab (randomized)	Arm 2B - BYL719+Cetuximab
Number of Participants Analyzed [units: participants]	69	35	29

For Phase II: Number of patients with notable Electrocardiogram (ECG) abnormalities
(units: Participants)

QTcF (msec): Increase from baseline > 30	6335	324	2815
QTcF (msec): Increase from baseline > 60	686	321	282
QTcB (msec): Increase from baseline > 30	6840	3212	2815
QTcB (msec): Increase from baseline > 60	687	320	282
QT (msec): Increase from baseline > 30	6843	3213	2823
QT (msec): Increase from baseline > 60	6817	322	285
VR (bpm): RR decrease > 25% & to a VR > 100	689	324	283
VR (bpm): RR decrease > 25% & to a VR < 50	681	320	280
PR (msec): increase > 25% & to a VR > 200	680	310	270
QRS (msec): increase > 25% & to a VR > 110	680	320	281

Phase II: Progression Free Survival (PFS) based on Investigator's Assessment with treatment

	BYL719+ Cetuximab (randomized)	Monotherapy Cetuximab (randomized)
Number of Participants Analyzed [units: participants]	71	35
Phase II: Progression Free Survival (PFS)		

based on Investigator's Assessment with treatment
(units: Participants)

Statistical Analysis

Groups	BYL719+ Cetuximab (randomized), Monotherapy Cetuximab (randomized)
Non-Inferiority/Equivalence Test	No
P Value	0.235
Method	Regression, Cox
Hazard Ratio (HR)	0.76
95 % Confidence Interval 2-Sided	0.49 to 1.19

Statistical Analysis

Groups	BYL719+ Cetuximab (randomized), Monotherapy Cetuximab (randomized)	Adjusted on Covariates: treatment, sum of longest diameters from local data [SLD (L)], Hemaglobin (Hgb) and

		White Blood Cells (WBC).
Non-Inferiority/Equivalence Test	No	
P Value	0.062	
Method	Regression, Cox	
Hazard Ratio (HR)	0.64	
95 % Confidence Interval 2-Sided	0.4 to 1.02	

Summary of Safety

Safety Results

Serious Adverse Events by System Organ Class

Time Frame	Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Treatment until Last Patient Last Visit.
Additional Description	Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.
Source Vocabulary for Table Default	MedDRA (18.1)
Assessment Type for Table Default	Systematic Assessment

	Arm A - 300mg BYL719+Cetuximab N = 15	Arm A: 400 mg BYL719 + Cetuximab N = 5	Arm B - BYL719 + Cetuximab Oral suspension N = 18	Arm C - BYL719+Cetuximab Dispersible tablets N = 6	Arm 1 - BYL719+Cetuximab (randomized) N = 69	Arm 2 - Monotherapy Cetuximab (randomized) N = 35	Arm 3 - BYL719+Cetuximab (non-randomized) N = 29	All patients N = 178
Total participants affected	9 (60.00%)	4 (80.00 %)	12 (66.67 %)	4 (66.67%)	40 (57.97%)	15 (42.86%)	15 (51.72%)	99 (55.62 %)
Blood and lymphatic system disorders								
Anaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	1 (3.45%)	2 (1.12%)
Neutropenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Cardiac disorders								
Atrial fibrillation	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Myocardial infarction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Myocardial ischaemia	0 (0.00%)	1 (20.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Pulseless electrical activity	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Gastrointestinal disorders								
Constipation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	1 (3.45%)	2 (1.12%)
Diarrhoea	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	2 (2.90%)	0 (0.00%)	0 (0.00%)	3 (1.69%)
Dysphagia	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	2 (2.90%)	1 (2.86%)	1 (3.45%)	5 (2.81%)
Enterocolitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (0.56%)
Large intestine perforation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	1 (0.56%)

Mouth haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (6.90%)	2 (1.12%)
Nausea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	1 (3.45%)	2 (1.12%)
Oesophageal fistula	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Oesophageal haemorrhage	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Oesophageal ulcer	0 (0.00%)	1 (20.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Oesophagitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Upper gastrointestinal haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.71%)	0 (0.00%)	2 (1.12%)
Vomiting	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
General disorders and administration site conditions								
Asthenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Chills	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Fatigue	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
General physical health deterioration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.90%)	1 (2.86%)	0 (0.00%)	3 (1.69%)
Pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	1 (3.45%)	2 (1.12%)
Pyrexia	1 (6.67%)	0 (0.00%)	1 (5.56%)	1 (16.67%)	4 (5.80%)	1 (2.86%)	0 (0.00%)	8 (4.49%)
Immune system disorders								
Anaphylactic reaction	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)

Drug hypersensitivity	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	1 (3.45%)	2 (1.12%)
Infections and infestations								
Abdominal infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	1 (0.56%)
Brain abscess	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Cellulitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.90%)	1 (2.86%)	0 (0.00%)	3 (1.69%)
Device related infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	1 (0.56%)
Diarrhoea infectious	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	1 (0.56%)
Diverticulitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	1 (0.56%)
Epiglottitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Lower respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	1 (0.56%)
Lung infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (6.90%)	2 (1.12%)
Osteomyelitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Pneumonia	2 (13.33%)	0 (0.00%)	4 (22.22%)	1 (16.67%)	8 (11.59%)	1 (2.86%)	4 (13.79%)	20 (11.24%)
Post procedural infection	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Purulent discharge	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Sepsis	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.80%)	1 (2.86%)	0 (0.00%)	6 (3.37%)
Septic shock	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Superinfection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Upper respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	1 (0.56%)

Urinary tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.71%)	0 (0.00%)	2 (1.12%)
Wound infection	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	2 (2.90%)	0 (0.00%)	0 (0.00%)	3 (1.69%)
Injury, poisoning and procedural complications								
Feeding tube complication	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Pneumocephalus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Spinal fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	1 (0.56%)
Tracheal obstruction	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Wound secretion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Investigations								
Blood creatine phosphokinase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Metabolism and nutrition disorders								
Decreased appetite	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (4.35%)	0 (0.00%)	0 (0.00%)	3 (1.69%)
Dehydration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	1 (3.45%)	2 (1.12%)
Hypercalcaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Hyperglycaemia	1 (6.67%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	7 (10.14%)	0 (0.00%)	5 (17.24%)	15 (8.43%)
Hypernatraemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Hypokalaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Hypophosphataemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	1 (0.56%)

Tumour lysis syndrome	0 (0.00%)	1 (20.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Musculoskeletal and connective tissue disorders								
Back pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Bone pain	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Fistula	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	1 (3.45%)	2 (1.12%)
Muscular weakness	0 (0.00%)	1 (20.00 %)	0 (0.00%)	0 (0.00%)	3 (4.35%)	0 (0.00%)	0 (0.00%)	4 (2.25%)
Musculoskeletal chest pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Neck pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	1 (0.56%)
Trismus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
Tumour haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.90%)	2 (5.71%)	1 (3.45%)	5 (2.81%)
Tumour necrosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (0.56%)
Tumour pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	1 (3.45%)	2 (1.12%)
Nervous system disorders								
Carotid artery perforation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	1 (0.56%)
Cerebrovascular accident	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Embolic cerebral infarction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	1 (0.56%)

Somnolence	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Product issues								
Device dislocation	0 (0.00%)	1 (20.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Renal and urinary disorders								
Acute kidney injury	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Ketonuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (0.56%)
Renal injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	1 (0.56%)
Respiratory, thoracic and mediastinal disorders								
Aspiration	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.90%)	0 (0.00%)	0 (0.00%)	3 (1.69%)
Dyspnoea	0 (0.00%)	1 (20.00 %)	0 (0.00%)	0 (0.00%)	3 (4.35%)	1 (2.86%)	1 (3.45%)	6 (3.37%)
Interstitial lung disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Laryngeal oedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	1 (0.56%)
Lung infiltration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	1 (3.45%)	2 (1.12%)
Oropharyngeal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Pleural effusion	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Pneumonia aspiration	2 (13.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Pneumonitis	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Pneumothorax	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Productive cough	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (0.56%)

Pulmonary air leakage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Pulmonary embolism	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.90%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Pulmonary haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Respiratory distress	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	1 (2.86%)	0 (0.00%)	3 (1.69%)
Respiratory failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	1 (2.86%)	1 (3.45%)	3 (1.69%)
Stridor	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (0.56%)
Skin and subcutaneous tissue disorders								
Erythema nodosum	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Swelling face	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Surgical and medical procedures								
Gastrostomy	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Vascular disorders								
Deep vein thrombosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Embolism	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Hypertension	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	2 (1.12%)
Hypotension	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)

Other Adverse Events by System Organ Class

Time Frame	Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Treatment until Last Patient Last Visit.
Additional Description	Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.
Source Vocabulary for Table Default	MedDRA (18.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Arm A - 300mg BYL719+Cetuximab N = 15	Arm A: 400 mg BYL719 + Cetuximab N = 5	Arm B - BYL719 + Cetuximab Oral suspension N = 18	Arm C - BYL719+Cetuximab Dispersible tablets N = 6	Arm 1 - BYL719+Cetuximab (randomized) N = 69	Arm 2 - Monotherapy Cetuximab (randomized) N = 35	Arm 3 - BYL719+Cetuximab (non-randomized) N = 29	All patients N = 178
Total participants affected	15 (100.00%)	5 (100.00 %)	18 (100.00 %)	6 (100.00%)	69 (100.00%)	35 (100.00 %)	29 (100.00%)	177 (99.44 %)
Blood and lymphatic system disorders								
Anaemia	0 (0.00%)	0 (0.00%)	1 (5.56%)	2 (33.33%)	9 (13.04%)	6 (17.14%)	7 (24.14%)	25 (14.04 %)
Lymph node pain	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Lymphadenopathy	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Thrombocytopenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	2 (1.12%)
Cardiac disorders								
Angina pectoris	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)

Atrial fibrillation	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Cardiac arrest	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Cardiomegaly	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Palpitations	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	2 (1.12%)
Pericardial effusion	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Sinus bradycardia	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Sinus tachycardia	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	2 (1.12%)
Tachycardia	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (16.67%)	0 (0.00%)	1 (2.86%)	2 (6.90%)	5 (2.81%)
Ear and labyrinth disorders								
Tympanic membrane perforation	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Eye disorders								
Conjunctival hyperaemia	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Diplopia	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	2 (1.12%)
Dry eye	3 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.90%)	2 (5.71%)	1 (3.45%)	8 (4.49%)
Eye irritation	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Eye pain	2 (13.33%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (1.69%)
Ocular hyperaemia	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Vision blurred	1 (6.67%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	3 (4.35%)	0 (0.00%)	2 (6.90%)	7 (3.93%)
Gastrointestinal disorders								

Abdominal discomfort	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	2 (2.90%)	1 (2.86%)	1 (3.45%)	5 (2.81%)
Abdominal distension	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (4.35%)	0 (0.00%)	0 (0.00%)	4 (2.25%)
Abdominal pain	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (4.35%)	0 (0.00%)	2 (6.90%)	6 (3.37%)
Abdominal pain upper	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	2 (5.71%)	1 (3.45%)	4 (2.25%)
Anal incontinence	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Ascites	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Constipation	2 (13.33%)	0 (0.00%)	4 (22.22%)	3 (50.00%)	9 (13.04%)	7 (20.00%)	5 (17.24%)	30 (16.85 %)
Dental caries	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	2 (1.12%)
Diarrhoea	7 (46.67%)	2 (40.00%)	10 (55.56 %)	2 (33.33%)	29 (42.03%)	5 (14.29%)	13 (44.83%)	68 (38.20 %)
Dry mouth	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.80%)	3 (8.57%)	3 (10.34%)	11 (6.18%)
Dyspepsia	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (16.67%)	7 (10.14%)	1 (2.86%)	3 (10.34%)	13 (7.30%)
Dysphagia	3 (20.00%)	1 (20.00%)	1 (5.56%)	0 (0.00%)	13 (18.84%)	2 (5.71%)	5 (17.24%)	25 (14.04 %)
Gastritis	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Gastritis erosive	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Gastrooesophage al reflux disease	2 (13.33%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	6 (8.70%)	0 (0.00%)	0 (0.00%)	9 (5.06%)
Glossodynia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	3 (10.34%)	4 (2.25%)
Haemorrhoids	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Melaena	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Mouth haemorrhage	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Mouth ulceration	2 (13.33%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	2 (2.90%)	1 (2.86%)	0 (0.00%)	6 (3.37%)

Nausea	6 (40.00%)	1 (20.00%)	4 (22.22%)	1 (16.67%)	16 (23.19%)	4 (11.43%)	11 (37.93%)	43 (24.16%)
Odynophagia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.80%)	0 (0.00%)	1 (3.45%)	5 (2.81%)
Oesophageal fistula	0 (0.00%)	0 (0.00%)	2 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Oesophageal ulcer	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Oesophagitis	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Oral pain	0 (0.00%)	1 (20.00%)	1 (5.56%)	0 (0.00%)	4 (5.80%)	2 (5.71%)	1 (3.45%)	9 (5.06%)
Salivary gland mucocoele	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Stomatitis	7 (46.67%)	2 (40.00%)	8 (44.44%)	1 (16.67%)	31 (44.93%)	6 (17.14%)	12 (41.38%)	67 (37.64%)
Vomiting	3 (20.00%)	1 (20.00%)	3 (16.67%)	2 (33.33%)	15 (21.74%)	2 (5.71%)	6 (20.69%)	32 (17.98%)
General disorders and administration site conditions								
Asthenia	1 (6.67%)	0 (0.00%)	1 (5.56%)	1 (16.67%)	4 (5.80%)	1 (2.86%)	3 (10.34%)	11 (6.18%)
Chills	1 (6.67%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	3 (4.35%)	4 (11.43%)	1 (3.45%)	10 (5.62%)
Cyst rupture	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Face oedema	1 (6.67%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	3 (4.35%)	1 (2.86%)	1 (3.45%)	7 (3.93%)
Facial pain	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (7.25%)	2 (5.71%)	0 (0.00%)	8 (4.49%)
Fatigue	5 (33.33%)	2 (40.00%)	5 (27.78%)	0 (0.00%)	22 (31.88%)	8 (22.86%)	14 (48.28%)	56 (31.46%)
Gait disturbance	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)

General physical health deterioration	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.90%)	0 (0.00%)	0 (0.00%)	3 (1.69%)
Localised oedema	0 (0.00%)	1 (20.00%)	1 (5.56%)	1 (16.67%)	0 (0.00%)	1 (2.86%)	2 (6.90%)	6 (3.37%)
Malaise	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Mucosal dryness	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Non-cardiac chest pain	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	2 (6.90%)	4 (2.25%)
Oedema peripheral	2 (13.33%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	4 (5.80%)	1 (2.86%)	3 (10.34%)	11 (6.18%)
Pyrexia	3 (20.00%)	0 (0.00%)	5 (27.78%)	2 (33.33%)	6 (8.70%)	3 (8.57%)	3 (10.34%)	22 (12.36%)
Secretion discharge	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	2 (1.12%)
Submandibular mass	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Immune system disorders								
Drug hypersensitivity	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	2 (2.90%)	2 (5.71%)	1 (3.45%)	6 (3.37%)
Infections and infestations								
Candida infection	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (4.35%)	2 (5.71%)	0 (0.00%)	6 (3.37%)
Cellulitis	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.90%)	2 (5.71%)	1 (3.45%)	6 (3.37%)
Conjunctivitis	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Ear infection	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Folliculitis	1 (6.67%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	3 (4.35%)	5 (14.29%)	2 (6.90%)	12 (6.74%)
Herpes virus infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Herpes zoster	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (2.86%)	1 (3.45%)	3 (1.69%)

Klebsiella sepsis	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Lung infection	1 (6.67%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	3 (4.35%)	0 (0.00%)	1 (3.45%)	6 (3.37%)
Nail infection	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	2 (6.90%)	4 (2.25%)
Oral candidiasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.80%)	1 (2.86%)	0 (0.00%)	5 (2.81%)
Paronychia	6 (40.00%)	1 (20.00%)	5 (27.78%)	1 (16.67%)	15 (21.74%)	6 (17.14%)	9 (31.03%)	43 (24.16%)
Rash pustular	1 (6.67%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	3 (4.35%)	1 (2.86%)	0 (0.00%)	6 (3.37%)
Rhinitis	0 (0.00%)	1 (20.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	3 (1.69%)
Sinusitis	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Skin infection	2 (13.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.90%)	0 (0.00%)	0 (0.00%)	4 (2.25%)
Stoma site infection	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	1 (3.45%)	3 (1.69%)
Tooth infection	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Upper respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	1 (2.86%)	2 (6.90%)	4 (2.25%)
Urinary tract infection	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (6.90%)	3 (1.69%)
Viral infection	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Wound infection	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	2 (6.90%)	4 (2.25%)
Injury, poisoning and procedural complications								
Feeding tube complication	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Gastrointestinal stoma complication	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	2 (1.12%)
Infusion related reaction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	2 (5.71%)	0 (0.00%)	3 (1.69%)

Limb injury	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Procedural pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.71%)	0 (0.00%)	2 (1.12%)
Skin abrasion	2 (13.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Stoma site erythema	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Stoma site ulcer	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Tracheal obstruction	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Wound	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Wound secretion	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	2 (2.90%)	0 (0.00%)	0 (0.00%)	4 (2.25%)
Investigations								
Alanine aminotransferase increased	1 (6.67%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	3 (4.35%)	1 (2.86%)	0 (0.00%)	6 (3.37%)
Amylase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (4.35%)	2 (5.71%)	1 (3.45%)	6 (3.37%)
Aspartate aminotransferase increased	2 (13.33%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	3 (4.35%)	1 (2.86%)	0 (0.00%)	7 (3.93%)
Blood alkaline phosphatase increased	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	5 (7.25%)	3 (8.57%)	1 (3.45%)	10 (5.62%)
Blood creatine phosphokinase increased	1 (6.67%)	2 (40.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	2 (5.71%)	1 (3.45%)	7 (3.93%)
Blood creatinine increased	0 (0.00%)	0 (0.00%)	2 (11.11%)	0 (0.00%)	7 (10.14%)	1 (2.86%)	1 (3.45%)	11 (6.18%)
Blood glucose increased	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	2 (1.12%)

Blood testosterone decreased	2 (13.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (6.90%)	4 (2.25%)
Electrocardiogram QT prolonged	1 (6.67%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	4 (5.80%)	1 (2.86%)	0 (0.00%)	7 (3.93%)
Electrocardiogram T wave abnormal	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Electrocardiogram T wave inversion	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Gamma-glutamyltransferase increased	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Glycosylated haemoglobin increased	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.90%)	0 (0.00%)	0 (0.00%)	3 (1.69%)
Lipase increased	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	5 (7.25%)	3 (8.57%)	1 (3.45%)	10 (5.62%)
Lymphocyte count decreased	0 (0.00%)	1 (20.00%)	1 (5.56%)	0 (0.00%)	4 (5.80%)	1 (2.86%)	2 (6.90%)	9 (5.06%)
Troponin increased	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Weight decreased	6 (40.00%)	2 (40.00%)	6 (33.33%)	3 (50.00%)	27 (39.13%)	7 (20.00%)	11 (37.93%)	62 (34.83%)
Weight increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.71%)	0 (0.00%)	2 (1.12%)
Metabolism and nutrition disorders								
Decreased appetite	6 (40.00%)	1 (20.00%)	4 (22.22%)	1 (16.67%)	26 (37.68%)	5 (14.29%)	10 (34.48%)	53 (29.78%)
Dehydration	0 (0.00%)	1 (20.00%)	0 (0.00%)	3 (50.00%)	5 (7.25%)	1 (2.86%)	3 (10.34%)	13 (7.30%)
Glucose tolerance impaired	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)

Hypercalcaemia	1 (6.67%)	1 (20.00%)	3 (16.67%)	1 (16.67%)	4 (5.80%)	1 (2.86%)	1 (3.45%)	12 (6.74%)
Hyperglycaemia	8 (53.33%)	2 (40.00%)	10 (55.56%)	5 (83.33%)	42 (60.87%)	5 (14.29%)	16 (55.17%)	88 (49.44%)
Hyperkalaemia	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	1 (3.45%)	3 (1.69%)
Hypermagnesaemia	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Hypernatraemia	0 (0.00%)	0 (0.00%)	1 (5.56%)	2 (33.33%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	4 (2.25%)
Hyperosmolar state	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Hypertriglyceridaemia	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	2 (1.12%)
Hyperuricaemia	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	2 (1.12%)
Hypoalbuminaemia	2 (13.33%)	1 (20.00%)	1 (5.56%)	0 (0.00%)	5 (7.25%)	4 (11.43%)	2 (6.90%)	15 (8.43%)
Hypocalcaemia	1 (6.67%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	5 (7.25%)	2 (5.71%)	1 (3.45%)	10 (5.62%)
Hypoglycaemia	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Hypokalaemia	5 (33.33%)	0 (0.00%)	4 (22.22%)	1 (16.67%)	13 (18.84%)	3 (8.57%)	8 (27.59%)	34 (19.10%)
Hypomagnesaemia	8 (53.33%)	2 (40.00%)	6 (33.33%)	1 (16.67%)	18 (26.09%)	8 (22.86%)	12 (41.38%)	55 (30.90%)
Hyponatraemia	1 (6.67%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	7 (10.14%)	3 (8.57%)	3 (10.34%)	15 (8.43%)
Hypophagia	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	3 (4.35%)	0 (0.00%)	0 (0.00%)	4 (2.25%)
Hypophosphataemia	2 (13.33%)	1 (20.00%)	4 (22.22%)	1 (16.67%)	5 (7.25%)	5 (14.29%)	2 (6.90%)	20 (11.24%)
Malnutrition	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Musculoskeletal and connective tissue disorders								

Back pain	2 (13.33%)	1 (20.00%)	2 (11.11%)	0 (0.00%)	5 (7.25%)	4 (11.43%)	1 (3.45%)	15 (8.43%)
Bone pain	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.45%)	2 (5.71%)	0 (0.00%)	4 (2.25%)
Muscle spasms	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (2.90%)	0 (0.00%)	1 (3.45%)	4 (2.25%)
Muscular weakness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.80%)	2 (5.71%)	0 (0.00%)	6 (3.37%)
Musculoskeletal chest pain	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (2.90%)	2 (5.71%)	0 (0.00%)	5 (2.81%)
Musculoskeletal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	2 (5.71%)	2 (6.90%)	5 (2.81%)
Musculoskeletal stiffness	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Myalgia	0 (0.00%)	1 (20.00%)	2 (11.11%)	0 (0.00%)	4 (5.80%)	1 (2.86%)	2 (6.90%)	10 (5.62%)
Neck pain	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (16.67%)	6 (8.70%)	4 (11.43%)	3 (10.34%)	15 (8.43%)
Pain in extremity	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.80%)	0 (0.00%)	2 (6.90%)	7 (3.93%)
Trismus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (4.35%)	1 (2.86%)	2 (6.90%)	6 (3.37%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
Cancer pain	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (6.90%)	3 (1.69%)
Tumour haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	2 (1.12%)
Tumour necrosis	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Tumour pain	0 (0.00%)	1 (20.00%)	1 (5.56%)	3 (50.00%)	4 (5.80%)	2 (5.71%)	2 (6.90%)	13 (7.30%)
Nervous system disorders								

Aphasia	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Dizziness	2 (13.33%)	0 (0.00%)	2 (11.11%)	1 (16.67%)	5 (7.25%)	1 (2.86%)	5 (17.24%)	16 (8.99%)
Dysaesthesia	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Dysgeusia	2 (13.33%)	0 (0.00%)	2 (11.11%)	0 (0.00%)	2 (2.90%)	1 (2.86%)	4 (13.79%)	11 (6.18%)
Headache	2 (13.33%)	0 (0.00%)	4 (22.22%)	0 (0.00%)	7 (10.14%)	4 (11.43%)	3 (10.34%)	20 (11.24 %)
Hemiparesis	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Lethargy	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Paraesthesia	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	3 (4.35%)	1 (2.86%)	0 (0.00%)	5 (2.81%)
Parosmia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Peripheral motor neuropathy	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	2 (1.12%)
Peripheral sensory neuropathy	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	3 (4.35%)	1 (2.86%)	3 (10.34%)	8 (4.49%)
Presyncope	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Somnolence	1 (6.67%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	1 (2.86%)	1 (3.45%)	5 (2.81%)
Psychiatric disorders								
Agitation	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	2 (1.12%)
Anxiety	1 (6.67%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	5 (7.25%)	1 (2.86%)	2 (6.90%)	10 (5.62%)
Depression	2 (13.33%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	5 (7.25%)	1 (2.86%)	1 (3.45%)	10 (5.62%)
Insomnia	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (16.67%)	6 (8.70%)	4 (11.43%)	1 (3.45%)	13 (7.30%)
Irritability	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)	2 (6.90%)	4 (2.25%)
Sleep disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (6.90%)	2 (1.12%)
Renal and urinary disorders								

Acute kidney injury	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Dysuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.71%)	0 (0.00%)	2 (1.12%)
Pollakiuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Renal failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Urinary incontinence	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Urinary retention	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	2 (1.12%)
Reproductive system and breast disorders								
Pelvic pain	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Respiratory, thoracic and mediastinal disorders								
Aspiration	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.90%)	0 (0.00%)	0 (0.00%)	3 (1.69%)
Atelectasis	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Cough	2 (13.33%)	1 (20.00%)	4 (22.22%)	1 (16.67%)	15 (21.74%)	7 (20.00%)	6 (20.69%)	36 (20.22%)
Dysphonia	1 (6.67%)	1 (20.00%)	1 (5.56%)	0 (0.00%)	5 (7.25%)	0 (0.00%)	4 (13.79%)	12 (6.74%)
Dyspnoea	1 (6.67%)	2 (40.00%)	3 (16.67%)	1 (16.67%)	11 (15.94%)	5 (14.29%)	3 (10.34%)	26 (14.61%)
Epistaxis	0 (0.00%)	1 (20.00%)	1 (5.56%)	0 (0.00%)	3 (4.35%)	1 (2.86%)	1 (3.45%)	7 (3.93%)
Haemoptysis	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	3 (4.35%)	1 (2.86%)	1 (3.45%)	6 (3.37%)
Hypoxia	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Lung disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (1.45%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Nasal congestion	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)

Nasal dryness	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	2 (1.12%)
Oropharyngeal pain	1 (6.67%)	0 (0.00%)	4 (22.22%)	0 (0.00%)	4 (5.80%)	3 (8.57%)	1 (3.45%)	13 (7.30%)
Pharyngeal inflammation	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Pleural effusion	0 (0.00%)	0 (0.00%)	2 (11.11%)	0 (0.00%)	2 (2.90%)	1 (2.86%)	0 (0.00%)	5 (2.81%)
Pneumonia aspiration	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.12%)
Productive cough	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (16.67%)	5 (7.25%)	2 (5.71%)	1 (3.45%)	10 (5.62%)
Pulmonary mass	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Pulmonary oedema	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Respiratory distress	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Rhinitis allergic	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Rhinorrhoea	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.90%)	3 (8.57%)	0 (0.00%)	6 (3.37%)
Skin and subcutaneous tissue disorders								
Cold sweat	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Decubitus ulcer	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	2 (5.71%)	0 (0.00%)	3 (1.69%)
Dermal cyst	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Dermatitis	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.90%)	0 (0.00%)	0 (0.00%)	3 (1.69%)
Dermatitis acneiform	7 (46.67%)	2 (40.00%)	4 (22.22%)	0 (0.00%)	21 (30.43%)	8 (22.86%)	5 (17.24%)	47 (26.40%)
Dry skin	4 (26.67%)	2 (40.00%)	2 (11.11%)	1 (16.67%)	18 (26.09%)	6 (17.14%)	10 (34.48%)	43 (24.16%)
Erythema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.90%)	2 (5.71%)	4 (13.79%)	8 (4.49%)

Erythema nodosum	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Palmar-plantar erythrodysaesthesia syndrome	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (4.35%)	2 (5.71%)	0 (0.00%)	5 (2.81%)
Papule	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (2.90%)	0 (0.00%)	0 (0.00%)	3 (1.69%)
Pruritus	1 (6.67%)	1 (20.00%)	1 (5.56%)	1 (16.67%)	11 (15.94%)	2 (5.71%)	1 (3.45%)	18 (10.11%)
Rash	7 (46.67%)	0 (0.00%)	4 (22.22%)	2 (33.33%)	26 (37.68%)	14 (40.00%)	7 (24.14%)	60 (33.71%)
Rash maculo-papular	3 (20.00%)	0 (0.00%)	2 (11.11%)	0 (0.00%)	11 (15.94%)	2 (5.71%)	3 (10.34%)	21 (11.80%)
Rash papular	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	2 (2.90%)	0 (0.00%)	1 (3.45%)	4 (2.25%)
Skin discolouration	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Skin fissures	4 (26.67%)	1 (20.00%)	2 (11.11%)	0 (0.00%)	12 (17.39%)	4 (11.43%)	7 (24.14%)	30 (16.85%)
Skin striae	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Skin toxicity	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	4 (5.80%)	3 (8.57%)	2 (6.90%)	10 (5.62%)
Skin ulcer	3 (20.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	5 (7.25%)	0 (0.00%)	2 (6.90%)	11 (6.18%)
Urticaria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.80%)	0 (0.00%)	0 (0.00%)	4 (2.25%)
Vascular disorders								
Deep vein thrombosis	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	2 (1.12%)
Embolism	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Flushing	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	2 (1.12%)
Haematoma	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.56%)
Hypertension	3 (20.00%)	1 (20.00%)	2 (11.11%)	0 (0.00%)	5 (7.25%)	3 (8.57%)	4 (13.79%)	18 (10.11%)

Hypotension	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	4 (5.80%)	3 (8.57%)	1 (3.45%)	9 (5.06%)
Lymphoedema	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	1 (2.86%)	0 (0.00%)	3 (1.69%)

Other Relevant Findings

Conclusion:

- The RP2D of BYL719 was determined to be 300mg qd in combination with cetuximab administered as recommended by the label in patients with RM-HNSCC.
- There was no difference in the PK profile of BYL719 irrespective of two different formulations administered by three different routes (oral as whole tablet or drinkable suspension and intragastric via G tube).
- BYL719 when administered as oral tablets at a dose of 300 mg in combination with cetuximab showed encouraging anti-tumor activity in patients with recurrent or metastatic HNSCC during the Phase Ib, however the addition of BYL719 to cetuximab did not significantly improve the efficacy in cetuximab naïve RM-HNSCC patients and showed moderate activity in RMHNSCC patients who were cetuximab resistant.
- Overall, the safety profile of the combination was consistent with the known safety profiles of BYL719 and cetuximab as single agents in the oncology setting.

Date of Clinical Trial Report

19-Jan-2017