SYNOPSIS OF RESEARCH REPORT 1084733 (PROTOCOL JO29424)

COMPANY: NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	(FOR NATIONAL AUTHORITY USE ONLY)
TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	**Final CSR Study JO29424,** Survival Follow Up of JO25567, a Randomized Phase 2 Study Comparing Erlotinib and Bevacizumab Combination with Erlotinib Alone in NSCLC Patients Harboring EGFR Mutation. Report No. 1084733 June, 2018
INVESTIGATORS / CENTERS AND COUNTRIES	24 centers participated in the study and all centers were in Japan.
PUBLICATION (REFERENCE)	Not applicable
PERIOD OF TRIAL	First Patient Enrolled: 13-June-2014 Last patient, last visit (Last patient to complete survival follow-up): 31-October-2017 Data cut-off (Final analysis): 31-October-2017
CLINICAL PHASE	IV
OBJECTIVES	The primary objective of Study JO29424 was to follow up on subjects from the JO25567 study that compared combination therapy with bevacizumab plus erlotinib (Erl+Bv arm) and erlotinib (Erl) monotherapy and to make a comparative study of overall survival in both groups. There were no secondary or exploratory objectives for the study.
STUDY DESIGN	Open-label study to follow up survival in patients who participated in the parent study, JO25567. Study JO25567 was a Phase II clinical study conducted to compare bevacizumab (Avastin®) in combination with erlotinib (Tarceva®) with erlotinib alone in the first-line treatment of patients with treatment-naïve, advanced, metastatic, or postoperative recurrent non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations (Exon 19 deletion or Exon 21 L858R substitution).
NUMBER OF SUBJECTS	Planned: 121 patients (maximum) Total enrolled: 75 patients Erl+Bv: 35 patients Erl: 40 patients
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Patients had to meet all the following criteria in order to be eligible for study enrolment: • Enrolled and received investigational medicinal product at least once in the parent study JO25567, "A randomized Phase 2 Study comparing erlotinib and bevacizumab combination with erlotinib alone in NSCLC patients harboring EGFR mutation". • Provided written informed consent after having received

	a detailed explanation of the study by the investigator.
TRIAL DRUG / STROKE (BATCH) No.	Not applicable- No treatment administered
DOSE / ROUTE / REGIMEN / DURATION	Not applicable- No treatment administered
REFERENCE DRUG / STROKE (BATCH) No.	Not applicable- No treatment administered
DOSE / ROUTE / REGIMEN / DURATION	Not applicable- No treatment administered
CRITERIA FOR EVALUATION	
EFFICACY:	The primary efficacy endpoint in this study was OS, defined as the time from the date of randomization to the date of death irrespective of the cause. Patients who had not died at the time of the final analysis were censored at the date the patient was last known to be alive.
PHARMACODYNAMICS:	Not evaluated for this study
PHARMACOKINETICS:	Not evaluated for this study
SAFETY:	Not evaluated for this study

STATISTICAL METHODS

No formal statistical hypotheses were generated. There was no formal sample size calculation. Overall survival (OS) was estimated by the Kaplan Meier (KM) method and the 2 treatment groups were compared using a log-rank test. Median OS and the corresponding 95% confidence interval (CI) were calculated based on Greenwood's formula. The hazard ratio for OS in the Erl+Bv arm vs the Erl arm was determined using a Cox proportional hazards model. Descriptive analysis of the use of anti-cancer treatment for NSCLC including the type of treatment administered and date of initiation of the treatment (i.e., during the period from completion of Study JO25567 to any time during Study JO29424) was performed for the two treatment groups.

METHODOLOGY

The JO29424 study included those patients who had received investigational medicinal product at least once in the parent Study JO25567 and had re-consented to participation in Study JO29424. The JO29424 study was designed to follow patient's survival status and collect treatment history data for subsequent anti-cancer therapy for NSCLC only, without investigational medicinal product being administered or any tests being performed on patients. For each patient, participation in the JO29424 study extended from the date of informed consent to death or lost to follow-up (including withdrawal of consent).

Overall survival analysis was performed on the Full Analysis Set (FAS) population included in the parent study, JO25567 (total FAS population=152 patients; with 75 patients in the Erl+Bv treatment arm and 77 patients in the Erl treatment arm), as well as for subgroups of patients from the FAS based upon their EGFR mutation status (i.e., Exon 19 deletion and Exon 21 L858R). Additional subgroup analyses were performed based on patient characteristics of age, gender, smoking status, Brinkman index, histopathological classification, disease stage at screening, pre-operative/post-operative adjuvant chemotherapy, EGFR gene mutation status, and T790M status. Interim analyses of OS were performed on an annual basis. The final OS analysis was performed when the median OS and its 95% confidence interval for each group could be estimated.

This CSR presents the results from the final analysis of OS up to the clinical cut-off date (CCoD) of 31 October 2017, when the last patient had completed survival follow-up in the JO29424 study.

EFFICACY RESULTS

The final analysis of OS with data cut-off of 31 October 2017 resulted in the following:

- In the FAS, 89 deaths had occurred in total (58.6% of the overall population), with 40 deaths (53.3%) in the Erl+Bv arm and 49 deaths (63.6%) in the Erl arm (Hazard Ratio [HR] was 0.81 (95% CI [0.53; 1.23]). The KM- estimated median duration of OS was 47 months in the Erl+Bv arm compared to 47.4 months in the Erl arm (see Table 1 below).
- The 4- , 5- and 6-year survival rates for patients in the Erl+Bv arm were 50.0%, 41% and 37%, respectively compared with 49%, 35% and 28%, respectively for patients in the Erl arm.
- In the FAS, of the patients that died, the majority of deaths were due to progressive disease (39 deaths [52.0%] in the Erl+Bv arm and 47 [61.0%] in the Erl arm). Three patients died due to causes other than progressive disease, including pneumocystis pneumonia (1 patient in the Erl+Bv arm), thrombosis (1 patient in the Erl arm) and drowning (1 patient in the Erl arm).
- Results from the final OS analysis based upon EGFR gene mutation status (i.e., Exon 19 deletion and Exon 21 L858R substitution) were generally consistent with the results from the final OS analysis for the FAS (see Table 2 and Table 3 below).
- The final OS results of subgroup analysis for the FAS based upon patient demographic and baseline characteristics of age, gender, smoking status, Brinkman index, histopathological classification, disease stage at screening, pre-operative /post-operative adjuvant chemotherapy, EGFR gene mutation status, and T790M status, were in general consistent with the FAS population. However, the small sample size of the subgroups limits the interpretation of the results.

Table 1: Duration of OS- FAS

	AT group N=75	T group N=77
Number of patients with event	40 (53.3%)	49 (63.6%)
Number of patients without event (censored)[1]	35 (46.7%)	28 (36.4%)
Time to event (months)		
Kaplan-Meier estimate of the median	47.0	47.4
95% confidence interval	[35.3; 67.9]	[40.2; 54.9]
P value (log-rank test)[2]	0.3267[2]	
Hazard ratio	0.81	
95% confidence interval	[0.53; 1.23]	

AT=Erl+Bv arm; T=Erl arm

[1] Patients without confirmed death at the cut-off date (i.e., 31 October 2017) were censored at the date they were last confirmed to be alive.

[2] Reported for descriptive purposes

Table 2: Duration of OS- Exon 19 Deletion

	AT group N=40	T group N=40
Number of patients with event	20 (50.0%)	24 (60.0%)
Number of patients without event (censored)[1]	20 (50.0%)	16 (40.0%)
Time to event (months)		
Kaplan-Meier estimate of the median	53.2	50.3
95% confidence interval	[35.3; NR]	[30.9; 73.4]
P value (log-rank test)[2]	0.4438[2]	
Hazard ratio	0.79	
95% confidence interval	[0.44; 1.44]	

AT=Erl+Bv arm; T=Erl arm

[1] Patients without confirmed death at the cut-off date (i.e., 31 October 2017) were censored at the date they were last confirmed to be alive.

[2] Reported for descriptive purposes

Table 3: Duration of OS- Exon 21 L858R Substitution

	AT group N=35	T group N=37
Number of patients with event	20 (57.1%)	25 (67.6%)
Number of patients without event (censored)[1]	15 (42.9%)	12 (32.4%)
Time to event (months)		
Kaplan-Meier estimate of the median	43.6	42.1
95% confidence interval	[25.1; NR]	[28.4; 54.9]
P value (log-rank test)[2]	0.5328[2]	
Hazard ratio	0.83	
95% confidence interval	[0.46; 1.49]	

AT=Erl+Bv arm; T=Erl arm

[1] Patients without confirmed death at the cut-off date (i.e., 31 October 2017) were censored at the date they were last confirmed to be alive.

[2] Reported for descriptive purposes

CONCLUSIONS

In Study JO25567, the addition of bevacizumab to erlotinib demonstrated a statistically significant and clinically relevant PFS benefit in patients with EGFR mutated NSCLC (16.0 months vs 9.7 months; HR: 0.54;[95% CI: 0.36 to 0.79]; p-value=0.0015). The addition of bevacizumab to erlotinib was associated with a OS HR of 0.81 (95% CI: 0.53; 1.23; log-rank p-value 0.3267). These results are in line with what was previously observed at the time of the interim OS analyses. Considering the overall efficacy results as well as the safety profile of this combination shown in Study JO25567, the benefit/risk of Erl+Bv in the first-line treatment of patients with EGFR mut+ non-squamous NSCLC remains positive.