EudraCT Clinical Trial Results: Secondary Endpoint (Tumour Response)

EudraCT number	2014-004388-20
Protocol number	CRUKD/15/004
Protocol title	A Cancer Research UK randomised, double-blind, placebo-controlled Phase IIa trial of AMG 319 given orally as a neoadjuvant therapy in patients with human papillomavirus (HPV) positive and negative head and neck squamous cell carcinoma (HNSCC)
Sponsor	Cancer Research UK, Centre for Drug Development 407 St John Street, London, United Kingdom, EC1V 4AD
End of Trial date	03 May 2018

For the purpose of posting clinical trial results for the Cancer Research UK clinical trial CRUKD/15/004 to the European Clinical Trials Database (EudraCT), the following text and table summarising the tumour response data from the trial has been extracted from the approved Clinical Study Report (Version 1.0, dated 09 April 2019):

Secondary endpoint: Tumour Response

In this trial, of the 32 patients in the Intention to Treat (ITT) population, 23 were evaluable for tumour response. Assessment of tumour response was made prior to resection surgery and compared to baseline. The timings of the baseline tumour assessments (within six weeks prior to first dose of IMP) were variable in relation to the timing of the pre-treatment biopsy. Where a tumour assessment was performed after the biopsy procedure, the procedure itself may have given rise to oedema or inflammation as well as removing some of the tumour volume, however where a tumour assessment was performed before the biopsy procedure tumour tissue would have been removed by the biopsy which could then result in a reduced tumour volume for measurement at the subsequent scan. Of the 32 patients who underwent baseline biopsy for this trial, seven patients underwent their scan before their biopsy, three underwent a scan on the same day as their biopsy (and the timing in relation to the biopsy is unknown) and 22 patients underwent a baseline scan after their biopsy. A summary of tumour responses in the ITT and Per Protocol (PP) population is provided in Table 1.

One patient underwent pre-treatment and pre-surgery scans but was not evaluable for radiological tumour response. No primary lesion was visible on the baseline scan for this patient and the reassessment scan showed a lesion that was too small to be adequately assessed radiologically. The patient was therefore considered radiologically not evaluable. However, as there was no tumour tissue in the sample removed at resection for this patient, they were considered to have had a pathological complete response. Of note, however, the baseline scan for this patient was performed one day before the baseline biopsy.

Two patients (one patient who received AMG 319 400 mg and one patient who received AMG 319 300 mg), had a best response of partial response (irPR). However, the patient who received AMG 319 400 mg only received 64% of the scheduled doses of AMG 319 and stopped treatment early due to AMG 319 related toxicity. The patient who received 300 mg completed their AMG 319 dosing

prior to their initial reassessment scan (where overall response was assessed as irPR) and had surgery delayed due to SAEs and an AE. A subsequent additional scan performed prior to their delayed resection surgery showed unequivocal progression.

Sixteen patients had a best response of stable disease (irSD); six of these patients received placebo, nine received AMG 319 400 mg and one received AMG 319 300 mg.

Tumour response was not evaluable for four patients. These patients underwent both pre-treatment and pre-surgery scans, but it was subsequently confirmed that the tumour was not measurable and so these patients were considered not evaluable for tumour response.

An assessment of tumour response was not performed in five patients.

Table 1 Summary of Best Radiological Tumour Response to AMG 319 or Placebo in ITT and PP populations

			Active		
Best Tumour Response	**Number. of patients**	**Placebo**	**All AMG 319**	**AMG 319 400 mg**	**AMG 319 300mg**
ITT population					
Number of patients	**32**	**9**	**23**	**17**	**6**
irPR	2 (6.3%)	0	2 (8.7%)	1 (5.9%)	1 (16.7%)
irSD	16 (50.0%)	6 (66.7%)	10 (43.5%)	9 (52.9%)	1 (16.7%)
irPD	5 (15.6%)	2 (22.2%)	3 (13.0%)	1 (5.9%)	2 (33.3%)
NE	4 (12.5%)	1 (11.1%)	3 (13.0%)	1 (5.9%)	2 (33.3%)
Not Done	5 (15.6%)	0	5 (21.7%)	5 (29.4%)	0
PP population					
Number of patients	**19**	**9**	**10**	**7**	**3**
irPR	1 (5.3%)	0	1 (10.0%)	0	1 (33.3%)
irSD	14 (73.7%)	6 (66.7%)	8 (80.0%)	7 (100%)	1 (33.3%)
irPD	2 (10.5%)	2 (22.2%)	0	0	0
NE	2 (10.5%)	1 (11.1%)	1 (10.0%)	0	1 (33.3%)
Not Done	0	0	0	0	0

Abbreviations: irPR = partial response, irSD = stable disease, irPD = progressive disease, ITT = intention to treat, NE = not evaluable, PP = per protocol.

In the PP population of 19 patients, one patient had a best response of irPR (subsequently assessed as having progressive disease [as discussed above]), 14 patients had a best response of irSD, two had a best response of progressive disease (irPD), and two patients had a best response that that could not be evaluated.

Of the nine patients who received placebo in the PP population, six had a best response of irSD, two had a best response of irPD and of the 10 patients who received AMG 319 in the PP population, one patient had a best response of irPR (subsequently assessed as having progressive disease [as discussed previously]), eight had a best response of irSD and one had a best response that could not be evaluated.

The difference in total tumour size between treatment arms was compared using a non-parametric Mann-Whitney test as there was evidence of non-normality in the distribution of the change in total tumour size. The test compared the differences in total tumour size between the AMG 319 and placebo populations (p=0.64), AMG 319 400 mg and placebo populations (p=0.58) and the AMG 319 300 mg and placebo populations (p=0.92).

A Fisher's exact test was performed to compare the number and percentage of patients with overall irPR and irCR between the placebo and AMG 319 treatment arms; for all patients randomised p=0.54 and for the PP population p=0.53.