Short summary

A PHASE II MULTICENTER, UNBLINDED, RANDOMISED STUDY WITH PACLITAXEL AND CAPECITABINE VERSUS PACLITAXEL, CAPECITABINE AND CETUXIMAB AS FIRST-LINE TREATMENT FOR RECURRENT AND/OR METASTATIC SQUAMOUS CELL CARCINOMA Of THE HEAD AND NECK (rmHNSCC).

Ethical Committee, Region Midt: 1-10-72-390-14

EudraCT Number: 2014-001023-80

Background:

Incurable recurrence of Head and Neck cancer is a serious disease in which half will die between 7 and 10 months after diagnosis even if treated with chemotherapy. The disease produces many symptoms, typically from the head-neck area and patients experience pain, smell, change in appearance and have problems with breathing, eating and senses. Chemotherapy is the standard palliative treatment in Denmark typically paclitaxel in combination with capecitabine.

Cetuximab is an antibody that acts on epidermal growth factor receptor molecules on the surface of cells and has relatively few side effects. Cetuximab increases the effect of chemotherapy with cisplatin and 5FU but the effect of combining cetuximab with paclitaxel and capecitabine is unknown.

Aim:

The aim was to investigate whether cetuximab can also increase the effect of paclitaxel and capecitabine, which the vast majority of patients in Denmark receive compared to paclitaxel and capecitabine alone.

Primary endpoint:

To compare the reduction of the tumors (response rate) with standard treatment with paclitaxel and capecitabine vs. combination therapy with paclitaxel, capecitabine and cetuximab.

Secondary endpoints:

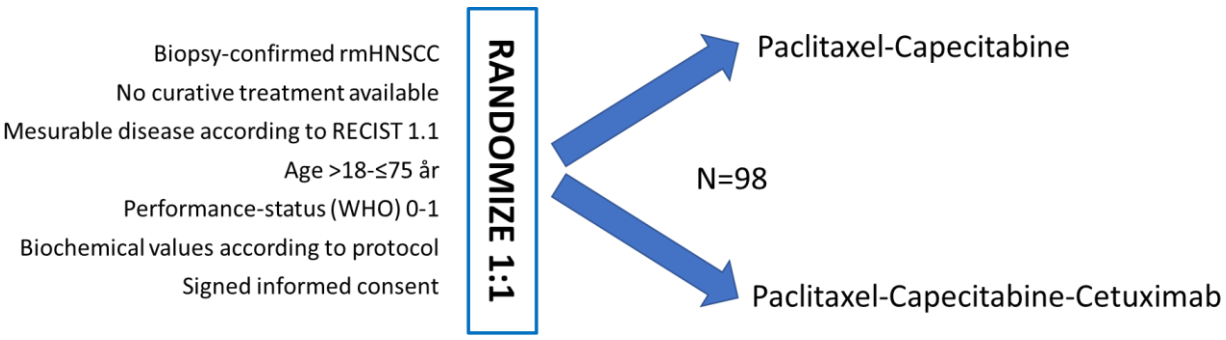
Progression-free survival, Overall survival and side effects.

Why was the study stopped prematurely?

The first patient was randomized February 2nd 2016 and the last patient January 29th 2020. In total 30 patients were randomized over a period of four years leaving less than 8 patients a year on a national basis. The study originally aimed at 98 participants – thus it is estimated to take another 8-9 years to finalize the study. The main reason for this turned out to be the fact that with standard treatment, patients only had to visit the hospital once every three weeks whereas weekly visits were necessary within the experimental arm. In 2020 immunotherapy as a palliative alternative were an option in all centers in Denmark and that decreased the interest for the experimental treatment with paclitaxel-capecitabine-cetuximab even more and the DAHANCA group decided to close the study. This was announced to the authorities in Denmark (Danish Medicines Agency and the Ethical committee on October 14th 2020 when the last patient went off-study).

Methods:

Patients were randomized 1:1 by a central independent office (DAHANCA trial office using a computer-based randomization tool).



Results:

Characteristics	All patients (N=30)	Standard PC (N=16)	Experimental PCC (N=14)
Males	23 (77%)	12 (75%)	11 (79%)
Median age in years	61 [49-72]	61 [53-69]	62 [49-72]
Oral cavity	2 (6%)	2 (13%)	0
Oropharynx	11 (37%)	6 (38%)	5 (36%)
Oropharynx - frequency of p16+	8 (73%)	5 (83%)	3 (60%)
Hypopharynx	8 (27%)	5 (31%)	3 (21%)
Larynx	6 (20%)	1 (6%)	5 (36%)
other	3 (10%)	2 (12%)	1 (7%)
Performance PS=0	14 (47%)	7 (44%)	7 (50%)
PS=1	16 (53%)	9 (56%)	7 (50%)
Median series of treatment	6 [2-12]	6 (3-12)	5 (2-9)
Best response CR	7 (23%)	3 (18%)	4 (29%)
PR	11 (37%)	6 (38%)	5 (35%)
NC	7 (23%)	4 (25%)	3 (21%)
PD	4 (13%)	2 (13%)	2 (14%)
Not evaluable	1 (3%)	1 (6%)	0

Table 1: Selected patient, tumor and treatment characteristics

The to arms seemed o be well-balanced.

Primary endpoint was response rate (RR) defined by best response (CR or PR) vs. all types of response. Overall response rate (RR) was 60% For the standard arm the RR is 56% and for the experimental arm the RR is 64%

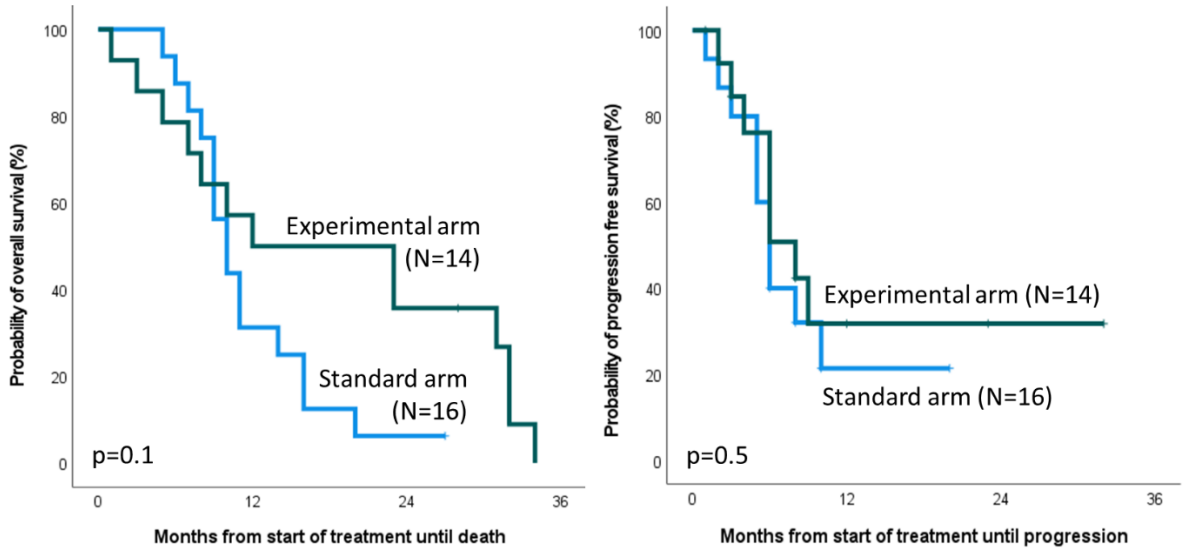


Figure 1

Figure 1, on the left side, shows the overall survival with no significant difference between the two arms. It seems that overall survival is better in the experimental arm, which can be related to this group having better success with 2nd and eventually 3rd line treatments. This difference is not related to a difference of effect between arms in the present study and progression-free survival, presented in the right side of figure 1 is without any difference between the two arms in the study.

Median overall survival is 10 months in the standard arm and 17 months in the experimental arm. Nevertheless, the median progression-free survival is 6 months in both arms.

Toxicity:

The majority of patients goes off-study due to progression of disease.

In the standard arm, 11 of 16 patients (69%) goes off study due to progression, 1 due to weight loss, 1 due to life-threatening infection, 1 due to severe brachycardia and 1 due to poor general condition. 1 goes off-study in complete remission.

In the experimental arm, 8 of 14 goes off study due to progression, 1 due to endocarditis, 1 due to severe neuropathy and 4 due to poor general condition.

It is not possible to deduct any clear differences between the two arms regarding toxicity.

Conclusion:

Based on the available data it is not possible to deduct any relevant differences between the standard treatment with paclitaxel-capecitabine and the experimental arm paclitaxel-capecitabine-cetuximab in terms of response rate, progression-free survival and toxicity. There is a non-significant trend towards a better overall survival for the patients in the experimental arm, but as the progression-free survival is the same in both arms, it is expected that the difference in overall survival is related to either uncertainties due to the very low number of patients in the trial or is due to 2nd or 3rd line treatments given.

In the DAHANCA group we have learnt never to set up a trial again where the difference in the number of visits needed to the hospital is so different between arms. This is for sure the main reason for this trial to ail and face premature closing.