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# Phase II trial of combination treatment with paclitaxel, carboplatin and cetuximab (PCE) as first-line treatment in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (CSPOR-HN02)


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Comprehensive Support Project

## Abstract


**Background:** The standard of care for first-line treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) is combination treatment with cisplatin, 5-FU and cetuximab (PFE). However, this regimen requires hospitalization to ensure proper hydration and continuous infusion of 5-FU, and causes severe nausea and anorexia. We evaluated the efficacy and safety of paclitaxel, carboplatin and cetuximab (PCE) as first-line treatment in patients with R/M SCCHN.

**Methods:** Eligibility included recurrent and/or metastatic, histologically proven SCC of the oropharynx, oral cavity, hypopharynx or larynx; PS 0-1; adequate organ function; no suitable local therapy for R/M SCCHN; and no prior systemic chemotherapy for R/M SCCHN. Chemotherapy consisted of paclitaxel 100mg/m$^2$ on day 1, 8; carboplatin AUC 2.5 on day 1, 8, repeated every 3 weeks for up to 6 cycles; and cetuximab at an initial dose of 400mg/m$^2$, followed by 250mg/m$^2$ weekly until disease progression or unacceptable toxicities. Primary endpoint was overall response rate (ORR). Secondary endpoints were safety, treatment completion rate, progression-free survival, overall survival, and clinical benefit rate (CBR). Planned sample size was 45 patients.

**Results:** Forty-seven subjects were accrued from July 2013 and Oct 2014. Of 45 evaluable, 40 were male; median age was 63 years; ECOG PS was 0/1 in 23/22 cases; site was the hypopharynx/oropharynx/oral cavity/larynx in 17/11/10/7 cases; and 36/9 cases were smokers/non-smokers, respectively. ORR, the primary end point, was 37.8% (95% CI, 30.9-48.6). Median overall survival was 14.7 months (95% CI, 12.1-Not Reached) and progression-free survival was 5.2 months (95% CI, 3.9-5.6). Grade 3 or 4 adverse events included neutropenia (68%), skin reaction (15%), fatigue (9%) and febrile neutropenia (9%). A potentially treatment-related death occurred in one patient with intestinal pneumonia.

**Conclusions:** The PCE regimen shows promising activity with acceptable toxicity and can be provided in the outpatient clinic. Further studies are needed to compare PCE with PFE in this population.


## Background

- The prognosis for recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) is limited.
- Ideally, the goal of R/M SCCHN is to extend survival while ensuring good quality of life.
- In EXTREME study, adding cetuximab to platinum-based chemotherapy (PF) demonstrated significantly improved survival over platinum-based chemotherapy alone [1].
- Combination treatment with cisplatin, 5-FU and cetuximab (PFE) is now considered to be standard regimen as first-line treatment of R/M SCCHN.
- However, this regimen requires hospitalization to ensure proper hydration and continuous infusion of 5-FU, and causes concerned toxicities including mucositis, anorexia and fatigue, leading to worsen patient's quality of life.
- In the previous study for R/M SCCHN patients who received platinum-derivates, combination with paclitaxel, carboplatin and cetuximab (PCE) demonstrated promising clinical activity with response rate of 56% and median time to progression of 5 month [2].

## Objectives

- To evaluate the efficacy and safety of PCE as first-line treatment in patients with R/M SCCHN.
  - Primary endpoint; overall response rate (ORR)
  - Secondary endpoints; safety, treatment completion rate, progression-free survival, overall survival, and clinical benefit rate (CBR)

## Method

### Patients

Key eligibility criteria:

1) Histologically proven squamous cell carcinoma
2) Primary lesion located larynx, oropharynx, hypopharynx or oral cavity
3) Measurable lesion according to RECIST (ver 1.1)
4) No suitable local therapy for recurrent/metastatic disease
5) ECOG Performance Status (PS) of 0-1
6) Age > 20 years old
7) Adequate organ function
8) Life expectancy of at least 3 months
9) No prior chemotherapy expect > 6 month previous chemotherapy as a curative therapy
10) No prior systemic chemotherapy for recurrent/metastatic disease
11) Written informed consent

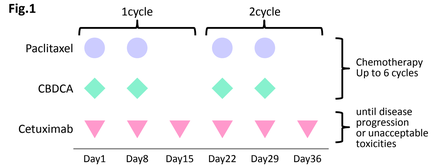
### Study design

This is a single arm, open-label, multicenter, phase 2 study (UMIN000010507)

### Treatment

Chemotherapy consisted of paclitaxel 100mg/m$^2$ on day 1, 8; carboplatin AUC 2.5 on day 1, 8, repeated every 3 weeks for up to 6 cycles; and cetuximab at an initial dose of 400mg/m$^2$, followed by 250mg/m$^2$ weekly until disease progression or unacceptable toxicities (Fig 1).

**Fig.1**




### Assessment

- Tumor responses were assessed by CT or MRI at baseline and at 8-week intervals after the start of treatment until disease progression or treatment discontinuation.
- ORR was assessed by independent central review including two radiologists and evaluated by RECIST version1.1
- Adverse events were monitored weekly throughout the study and evaluated by CTCAE version 4.0.
- After completion of study treatment, disease progression, survival status and any further anticancer treatments were documented at follow-up visits every 6 months.

### Statistical analysis

- The objective of primary analysis is to confirm whether response rate of PCE is non-inferior as compared with that of PFE
  - Assumed the response rate of PFE is 40%
  - Acceptable range of less than 5%
- Targeted accrual: 45 patients in total

## Results

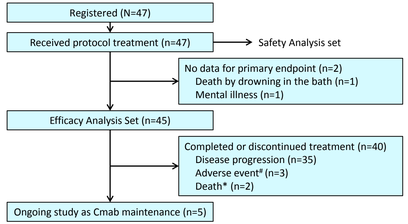
Forty-seven subjects were accrued from July 2013 and Oct 2014.

### Patient Characteristics (n=45)

| Variable | | No. of patients |
|---|---|---|
| Age | Age (yr) - median, range | 63 (41-76) |
| | < 65yr | 25 |
| | ≥ 65yr | 20 |
| Sex | Female | 5 |
| | Male | 40 |
| PS | 0 | 23 |
| | 1 | 22 |
| Primary site | Hypopharynx | 17 |
| | Oropharynx | 11 |
| | Oral cavity | 10 |
| | Larynx | 7 |
| Extent of disease | Only locoregionally recurrent | 8 |
| | Metastatic with or without locoregional recurrence | 37 |
| Previous treatment | Radiation | 28 |
| | Chemotherapy | 13 |
| | Postoperative chemoradiotherapy | 4 |
| Smoking history | smokers | 36 |
| | Brinkman index-median, range | 735 (10-3680) |
| | non-smokers | 9 |

### Patient Flow Diagram

**Fig.2**




# 2pts: skin toxicities, 1pt: hypercalcemia
* 1pt: unspecified death after suffering hematemesis,1pt: intestinal pneumonia grade5

### Compliance

Median cycle of PCE was 6.

| | Median duration-week (range) | Relative dose intensity % |
|---|---|---|
| Paclitaxel | 16.0 (1.0- 27.1) | 82.5 |
| CBDCA | 16.3 (1.0- 27.1) | 82.5 |
| Cetuximab | 22.1 (2.0-155.6) | 93.3 |
| Cetuximab monotherapy* | 11.0 (0.1-155.6) | 87.5 |

*during the maintenance period

| | No. of patients (%) |
|---|---|
| Completion of 6 cycles of PCE | 16 (35.6%) |
| Received cetuximab monotherapy* | 29 (64.4%) |

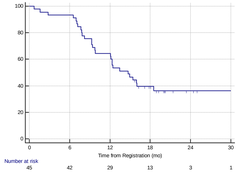
*during the maintenance period

### Analysis of primary endpoint
### Response (N=45) on central review

The primary end point was met with ORR of 40.0% (95% exact CI, 25.7-55.7).

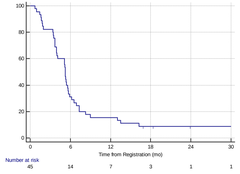
| Response | No. of patients (%) |
|---|---|
| Complete response | 2 (4.4%) |
| Partial response | 16 (35.6%) |
| Stable disease | 9 (20.0%) |
| Progressive disease | 16 (35.6%) |
| Not Evaluable | 2 (4.4%) |

### Overall survival




- Median follow-up was 20.0 months. Median overall survival was 14.7 months (95% CI, 9.8-Not Reached). Number of observed death was 28 (62%).

### Progression-free survival




- Median progression-free survival was 5.2 months (95% CI, 3.9-5.6). 5 patients are still receiving cetuximab maintenance.

### Subsequent treatment

| | No. of patients | | | |
|---|---|---|---|---|
| | 2nd | 3rd | 4th | 5th |
| Total (%) | 32 (68.1%) | 14 | 5 | 2 |
| S-1 | 13 | 1 | 2 | 0 |
| Immunotherapy* | 4 | 5 | 0 | 0 |
| Docetaxel | 3 | 4 | 0 | 0 |
| Cmab | 5 | 0 | 0 | 0 |
| PXL+CBDCA | 1 | 0 | 1 | 0 |
| Others | 2 | 2 | 1 | 2 |
| Palliative RT | 4 | 2 | 1 | 0 |

*anti-PD-1/PDL-1 antibody

### Safety

Adverse events* during PCE (N=47)

| AE | Gr1 | Gr2 | Gr3 | Gr4 | %Gr3-4 |
|---|---|---|---|---|---|
| Neutropenia | 2 | 9 | 19 | 13 | 68% |
| Rash acneiform | 14 | 23 | 2 | 0 | 4% |
| Skin reaction# | 12 | 20 | 7 | 0 | 15% |
| Febrile neutropenia | - | - | 4 | 0 | 9% |
| Anemia | 21 | 22 | 3 | 0 | 6% |
| Anorexia | 13 | 9 | 3 | 0 | 6% |
| Hyponatremia | 16 | 0 | 2 | 0 | 4% |
| Hypomagnesemia | 24 | 3 | 1 | 1 | 4% |
| Diarrhea | 7 | 2 | 1 | 0 | 2% |
| Nausea | 10 | 3 | 1 | 0 | 2% |
| Peripheral neuropathy | 19 | 6 | 1 | 0 | 2% |
| Mucositis | 10 | 8 | 1 | 0 | 2% |
| Hypoalbminemia | 30 | 6 | 1 | 0 | 2% |
| Hypocalcemia | 7 | 2 | 0 | 1 | 2% |
| ALT increased | 13 | 2 | 1 | 0 | 2% |
| Alopecia | 16 | 22 | - | - | 0% |
| Constipation | 17 | 6 | 0 | 0 | 0% |
| Dysgeusia | 8 | 5 | 0 | 0 | 0% |
| Hypokalemia | 10 | 1 | 0 | 0 | 0% |
| Thrombocytopenia | 28 | 1 | 0 | 0 | 0% |
| AST increased | 23 | 0 | 0 | 0 | 0% |
| Tbil increased | 10 | 0 | 0 | 0 | 0% |

*Grade1 or worse adverse events in 20% or more of patients, # Excluded rash acneiform
A potentially treatment-related death occurred in one patient with intestinal pneumonia.

Adverse events* during cetuximab maintenance (N=29)

| AE | Gr1 | Gr2 | Gr3 | Gr4 | %Gr3-4 |
|---|---|---|---|---|---|
| Rash acneiform | 10 | 13 | 3 | 0 | 10 |
| Skin reaction# | 11 | 14 | 3 | 0 | 10 |
| Neutropenia | 5 | 3 | 2 | 0 | 7 |
| Thrombocytopenia | 6 | 1 | 1 | 0 | 3 |
| Anorexia | 10 | 1 | 1 | 0 | 3 |
| Peripheral neuropathy | 14 | 4 | 0 | 0 | 0 |
| Alopecia | 6 | 15 | 0 | 0 | 0 |
| Constipation | 6 | 3 | 0 | 0 | 0 |
| Dysgeusia | 5 | 3 | 0 | 0 | 0 |
| Anemia | 21 | 5 | 0 | 0 | 0 |
| Hypomagnesemia | 13 | 4 | 0 | 0 | 0 |
| Hypoalbminemia | 20 | 2 | 0 | - | 0 |

*Grade1 or worse adverse events in 20% or more of patients, # Excluded rash acneiform

## Summary

- From July 2013 and Oct 2014, 47 participants were accrued and 45 were evaluable.
- The primary end point was met with ORR of 40.0% (95% exact CI, 25.7-55.7) on central review.
- After a median follow-up of 20.0 months,
  - Median progression-free survival: 5.2 months (95% CI, 3.9-5.6)
  - Median overall survival: 14.7 months (95% CI, 9.8-Not Reached)
- Grade 3 or 4 adverse events included neutropenia (68%), skin reaction (15%), fatigue (9%) and febrile neutropenia (9%). A potentially treatment-related death occurred in one patient with intestinal pneumonia.

## Conclusion

- The PCE regimen shows promising activity with acceptable toxicity and can be provided in the outpatient clinic, with weekly adjustment of dosages according to toxicity. Further studies are needed to compare PCE with PFE in this population.


**References**

1. Vermorken JB et al. N Engl J Med 2008; 359: 1116-1127.
2. Buentzel J, et.al. 2007 ASCO Annual Meeting. JCO, 2007; No. 18S (June 20 Suppl) abstr 6077.



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