A Phase I Study of the CDK4/6 Inhibitor, Palbociclib in combination with Cetuximab and Intensity Modulated Radiation Therapy (IMRT) for Locally Advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN); An Expansion Cohort

Nuttapong Ngamphaiboon[1], Teerada Siripoon[1], Somthawin Lukerak[1], Artit Jinawath[2], Lalida Arsa[2], Prapimporn Ch. Shantavasinkul[1], Naphat Taonam[1], Natini Jinawath[3], Arpakorn Kositwattanarerk[4], Thiparom Sananmuang[4], Poompis Pattaranutaporn[4], Chuleeporn Jiarpinitnun[4]

[1]Department of Medicine; [2]Department of Pathology; [3]Program in Translational Medicine; [4]Department of Radiology; Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

Mahidol University
Faculty of Medicine Ramathibodi Hospital

677P

INTRODUCTION

Loss of p16 expression is a poor prognostic marker in SCCHN. Palbociclib is a selective inhibitor of CDK4/6 by blocking Rb phosphorylation and has radiosensitizing activity in preclinical studies. Addition of palbociclib to cetuximab and radiotherapy provides a strong rationale to improve efficacy of treatment in locally advanced SCCHN, especially in p16-negative SCCHN.

METHODS

- Using a classical 3+3 design **(NCT03024489)**.
- The study included locally advanced SCCHN of oral cavity, oropharynx, larynx, and hypopharynx.
- In the expansion cohort, we accrued 14 locally advanced p16-negative SCCHN patients to confirm safety and preliminary efficacy.

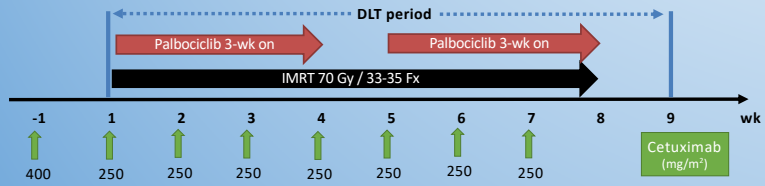
CONCLUSION

This is the first prospective study evaluated a CDK 4/6 inhibitor in combination with radiotherapy. The recommended phase 2 dose of palbociclib was 125 mg/d. The combination was well tolerated with promising preliminary efficacy. Molecular biomarkers involving the Rb/CDK4/6 pathways are being explored.

RESULTS

Patient characteristics	N = 27 (%)
Median age (range)	57 (32 - 82)
Sex	
Male	24 (89)
Female	3 (11)
ECOG	
0	17 (63)
1	10 (37)
Smoking status	
Never	5 (18)
Active	14 (52)
Former	8 (30)
Mean pack-year (range)	25.1 (3 - 60)
Primary Site	
Oropharynx	12 (44)
Oral cavity	1 (4)
Larynx	7 (26)
Hypopharynx	7 (26)
Pathologic differentiation	
Well differentiation	1 (4)
Moderately differentiation	17 (63)
Poorly differentiation	4 (15)
Non-specific	5 (18)
T stage	
2	8 (30)
3	13 (48)
4a	2 (7)
4b	4 (15)
N Stage	
0	2 (7)
1	8 (30)
2	13 (48)
3	4 (15)
The 7th AJCC Stage	
III	9 (33)
IVa	9 (33)
IVb	9 (33)

STUDY SCHEMA



DOSE LEVEL AND NUMER OF PATIENT

Dose level	IMRT (Gy)	Cetuximab (mg/m²)	Palbociclib (mg/day)	N=27
(starting) 1	70	400/250	75	3
2	70	400/250	100	3
3	70	400/250	125	21

- Two patients had febrile neutropenia at the DL3 (1 patient in the dose escalation cohort and anther one in the expansion cohort).
- MTD was not achieved.

TREATMENT COMPLIANCE

Treatment	N=27
Mean Actual dose RT (Gy)	69.96
Median Duration of RT (days)	48 (43 - 55)
RT completion (%)	100%
RT interruption (%)	2 (7.4)
Cetuximab	
• Interruption	4 (15%)
• Dose reduction	2 (7%)
• Mean total cumulative dose (mg/m²)	2,089 (1,400 – 2,150)
• RDI (%)	94%
Palbociclib	
• Interruption	7 (26%)
• Dose reduction	3 (11%)
• Mean Compliance of palbociclib (%)	97.1% (61.9 – 100%)
• RDI (%)	95%

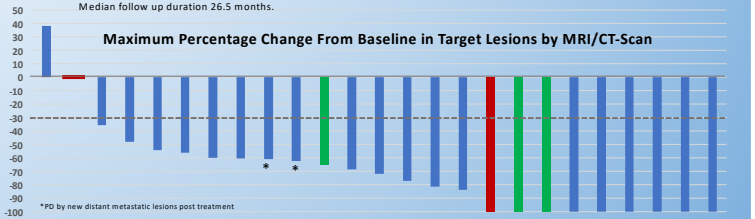
ADVERSE EVENT BY CTCAE V.1.1

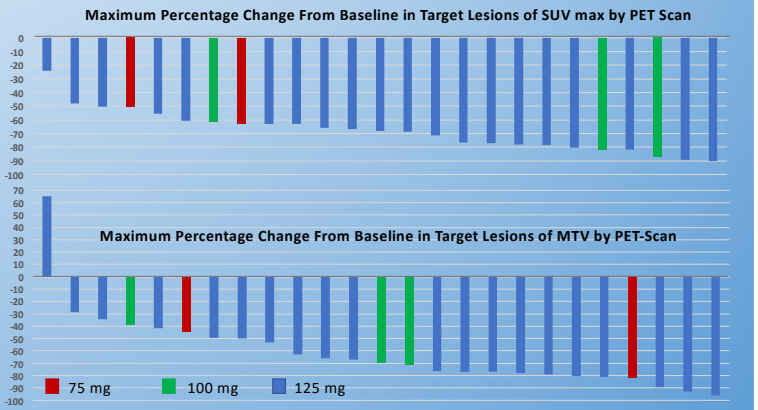
AE Term	Gr 1-2 (%)	Gr 3-4 (%)
Hematologic toxicity		
Neutropenia	13 (48)	6 (22)
Anemia	3 (11)	3 (11)
Thrombocytopenia	8 (30)	1 (4)
Febrile neutropenia	0	2 (7)
Non- Hematologic toxicity		
Mucositis oral	12 (44)	16 (59)
Dermatitis radiation	19 (70)	6 (22)
AST	8 (30)	2 (7)
Rash acneiform	25 (93)	1 (4)
ALT	9 (33)	1 (4)
Diarrhea	7 (26)	1 (4)
Hyponatremia	7 (26)	1 (4)
Fever	6 (22)	1 (4)
Hyperglycemia	0	1 (4)
Fatigue	15 (56)	0
Constipation	14 (52)	0
Cough	14 (52)	0
Insomnia	14 (52)	0
Xerostomia	12 (44)	0
Dry skin	5 (19)	0
Dyspepsia	4 (15)	0
Lymphedema Neck	4 (15)	0
Nausea	4 (15)	0
Hyperkalemia	3 (11)	0
Hypomagnesemia	3 (11)	0
Hypothyroidism	3 (11)	0
Infusion related reaction	3 (11)	0
Trismus	3 (11)	0
Voice alteration	3 (11)	0
Vomiting	3 (11)	0
Eczematous rash	2 (7)	0
GERD	2 (7)	0
Hearing impaired	2 (7)	0
Hiccups	2 (7)	0
Hypoalbuminemia	2 (7)	0
Oral candidiasis	2 (7)	0
PEG-tube infection	2 (7)	0
Soft tissue infection	2 (7)	0

PRELIMINARY EFFICACY

Preliminary Efficacy	N (%)
Objective response by RECIST 1.1 (n=25)	
CR	10 (40)
PR	11 (44)
SD	1 (4)
PD	3 (12)
ORR	21 (84)
Mean percent changes of PET scan (n=25)	
SUV max	-68%
MTV	-61%
TLG	-80%
Pattern of first recurrence (n=27)	
Overall recurrent rate	14 (52)
Locoregional	9 (33)
Distant	7 (26)
Median survival (months)	
LRFS	26.3 months
1-yr LRFS rate	77%
2-yr LRFS rate	53%
DisFS	42.2 months
1-yr DFS rate	70%
2-yr DFS rate	57%
DFS	19.4 months
1-yr DFS rate	58%
2-yr DFS rate	46%
OS	43.2 months
1-yr OS rate	89%
2-yr OS rate	72%

Median follow up duration 26.5 months.





Acknowledgements: The study is sponsored by Ramathibodi hospital, Mahidol university. The funding and palbociclib are supported by Pfizer.

Corresponding Author: Nuttapong Ngamphaiboon, MD [Email: nuttapong.nga@mahidol.ac.th]