2022 ASCO® ANNUAL MEETING

A Phase II trial of Pembrolizumab and Cabozantinib in Patients With Recurrent Metastatic Head and Neck Squamous Cell Carcinoma

Nabil F. Saba, Asari Ekpenyong, Ashley McCook-Veal, Mihir Patel, Nikki Schmitt, Bill Stokes, James Bates, Soumon Rudra, Marin Abousaud, Jameel Muzaffar, Kedar Kirtane, Yong Teng, Conor Steuer, Dong M. Shin, Liu Yuan, Christine H. Chung

Abstract 6008

PRESENTED BY:
Nabil F. Saba, MD

Introduction

- Patients with recurrent/metastatic squamous cell carcinoma of the head and neck (RM SCCHN) have poor prognosis and suffer from significant morbidity, with deterioration of quality of life[1,2]
- PD-1 inhibitors alone or in combination with chemotherapy increased OS benefit, particularly in patients with PD-L1^{+} expression[3-4]
- R/M SCCHN remains largely a fatal disease with a meager response to therapy and a need for novel and effective therapeutic strategies
- The combination of immune check point inhibitors with receptor tyrosine kinase inhibitors, including VEGFR inhibitors, has emerged as a strategy of interest in R/M SCCHN and other tumor types[5]

OS = overall survival; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1

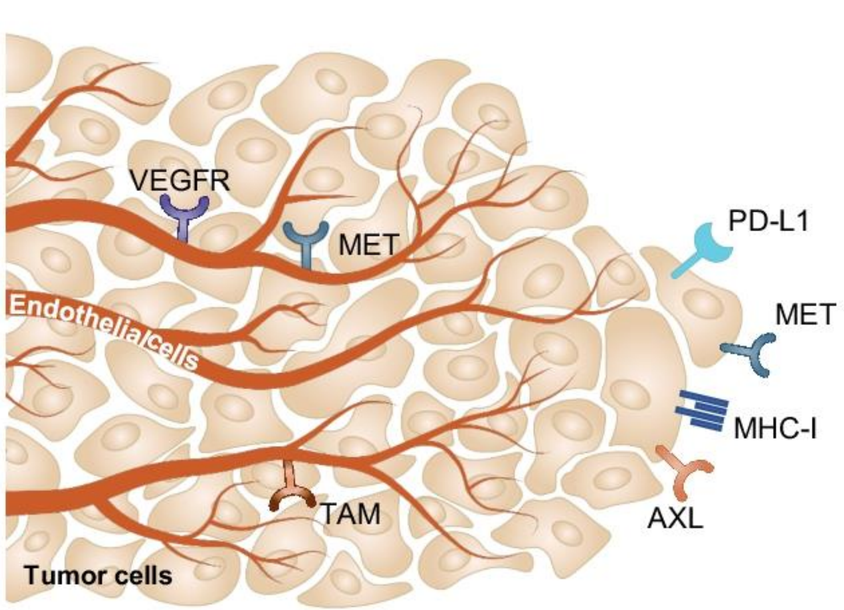
1. Mehta RD, Roth AJ. CA Cancer J Clin. 2015;65:299-314. 2. Machiels JP, et al. F1000 Prime Rep. 2014;6:44. 3. Ferris RL, et al. N Engl J Med. 2016;375:1856-1867. 4. Burtness B, et al. Lancet 2019;394:1915-1928; 5. Saba NF, et al. Cancers. 2022;14(5):1202.

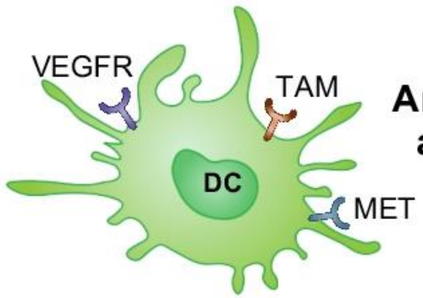
Cabozantinib Indications

- Patients with advanced renal cell carcinoma (RCC)
- Patients with advanced RCC, as a first-line treatment in combination with nivolumab
- Patients with hepatocellular carcinoma who have been previously treated with sorafenib
- Adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible

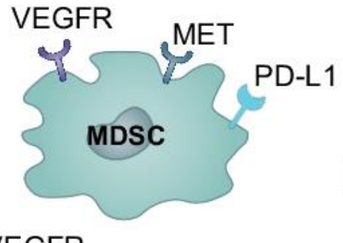
Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

VEGFR, MET, and TAM Family Receptor Tyrosine Kinases Are Expressed on Different Cell Types

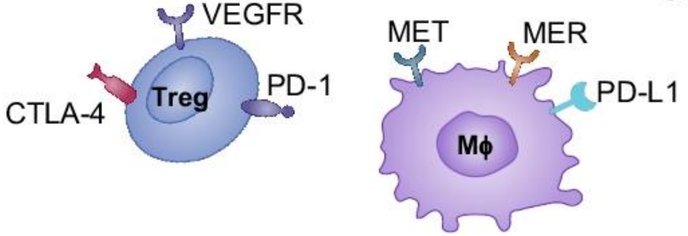


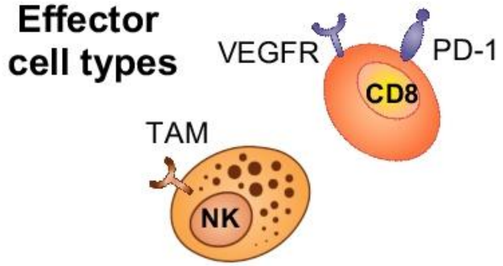


Antigen processing and presentation



Immunosuppressive cell types

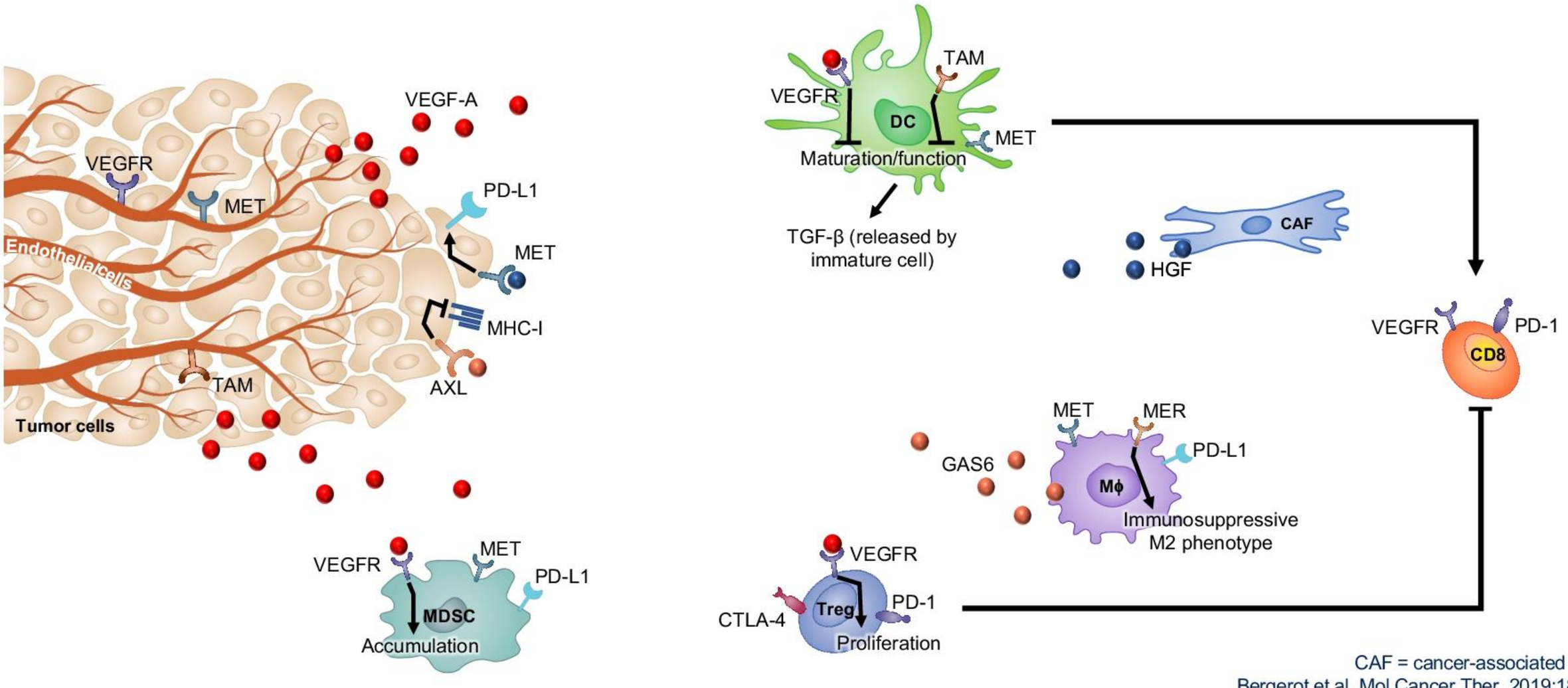




CTLA-4 = cytotoxic-T-lymphocyte associated protein 4; DC = dendritic cell; Mϕ = macrophages; MDSC = myeloid-derived suppressor cells; MHC-I = major histocompatibility complex I; NK = natural killer cells; TAM = Tyro3, AXL, MER receptor family; Treg = T regulatory cells.

1. Li Y, et al. Cancer Biol Med. 2015;13:206-214. 2. Benkoucha M, et al. J Immunol. 2014;193:2743-2752. 3. Peeters MJW, et al. Canc Immunol Immunother. 2020;69:237-244. 4. Qin W, et al. Front Immunol. 2019: Epub. 5. Walker L, et al. Trends Immunol. 2015;36:63-70. Lu C, et al. Oncoimmunology. 2016;5:e1247135; Bergerot et al. Mol Cancer Ther. 2019;18:2185-93.

Immune-Modifying Behavior of Cabozantinib



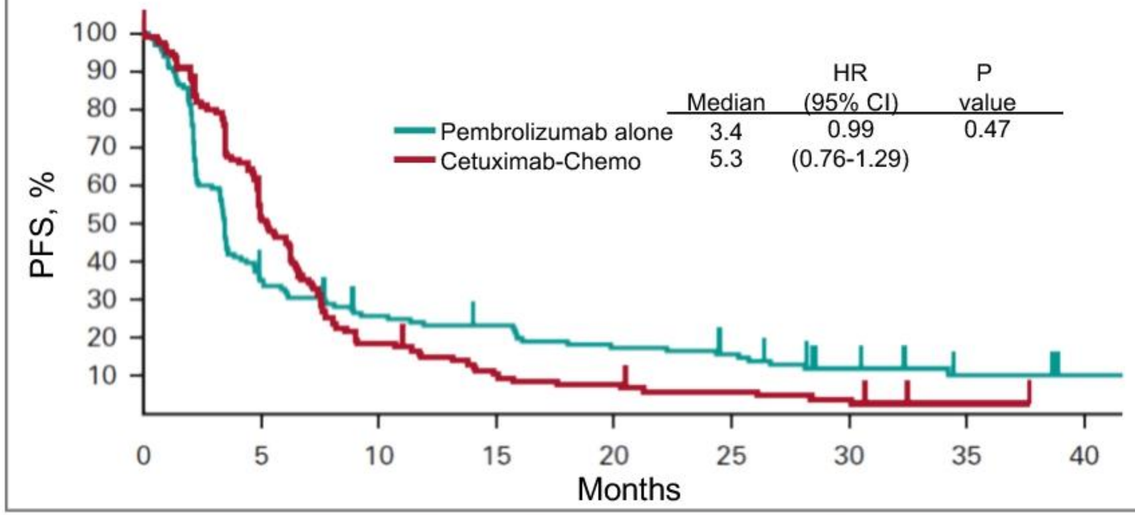
CAF = cancer-associated fibroblasts

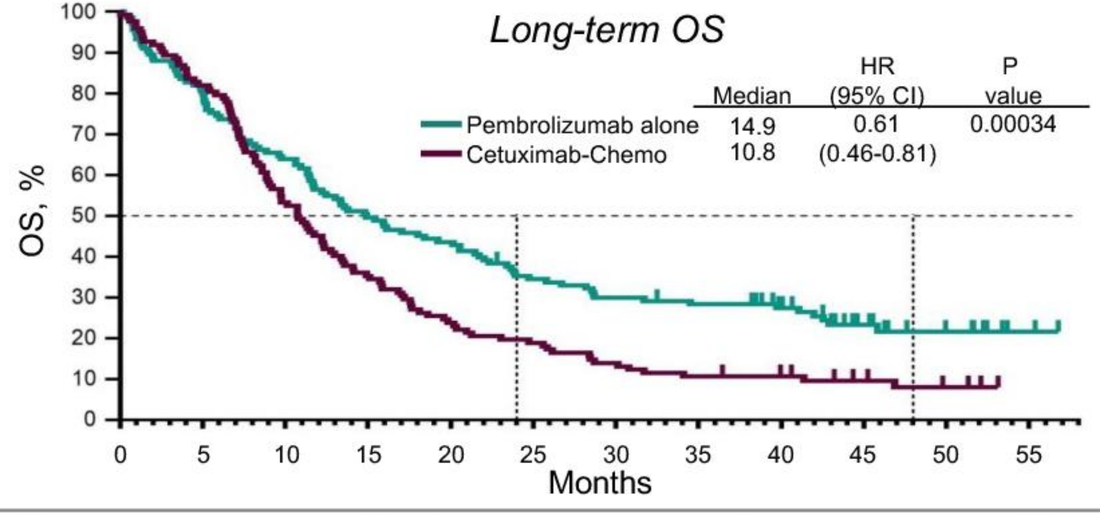
Bergerot et al. Mol Cancer Ther. 2019;18:2185-93.

Clinical Benefit of Single-Agent Pembrolizumab (KN 048)

	PD-L1 CPS <1		PD-L1 CPS 1–19		PD-L1 CPS ≥20	
	Pembrolizumab (n=44)	Cetuximab-Chemo (n=45)	Pembrolizumab (n=124)	Cetuximab-Chemo (n=133)	Pembrolizumab (n=133)	Cetuximab-Chemo (n=122)
mOS (95% CI), mo	7.9 (4.7–13.6)	11.3 (9.1–15.9)	10.8 (9.0–12.6)	10.1 (8.7–12.1)	14.8 (11.5–20.6)	10.7 (8.8–12.8)
HR (95% CI)	1.51 (0.96–2.37)		0.86 (0.66–1.12)		0.58 (0.44–0.78)	
P value	0.96		0.13		0.0001	
12-mo OS rate (95% CI), %	38.6 (24.5–52.6)	48.9 (33.7–62.4)	44.0 (35.1–52.5)	42.4 (33.9–50.7)	56.4 (47.5–64.3)	44.9 (35.9–53.4)
mPFS (95% CI), mo	2.1 (1.9–2.3)	6.2 (5.1–7.6)	2.2 (2.1–2.9)	4.9 (3.8–6.0)	3.4 (3.2–3.8)	5.3 (4.8–6.3)
HR (95% CI)	4.31 (2.63–7.08)		1.25 (0.96–1.61)		0.99 (0.76–1.29)	
P value	1.00		0.95		0.47	

PD-L1 CPS ≥20 Subgroup





CI = confidence interval; CPS = combined positive score; HR = hazard ratio; m = median; PFS = progression-free survival. 1. Burtness B, et al. J Clin Oncol. 2022: Epub. 2. Griel R, et al. Ann Oncol. 2020; 31(suppl 4): Abstract 915MO.

Study Design

Phase II, open label, multi-center, single arm trial

Patients with R/M HNSCC

Inclusion criteria

- Inoperable, refractory or metastatic R/M HNSCC
- RECIST v1.1 measurable disease
- ≤1 prior radiation therapy to the HN allowed
- Life expectancy >3 months
- ECOG performance status 0–1

Exclusion criteria

- HPV negative unknown primary disease
- Cavitating lesions or recent bleeding history

→ **Pembrolizumab 200 mg IV Q3W + Cabozantinib 40 mg PO QD**

→ Tumors were assessed by RECIST v1.1 criteria by CT/MRI every 9 weeks

Primary objectives

- Determine the safety and tolerability of pembrolizumab + cabozantinib in this patient population
- Determine the objective response rate ORR per RECIST v1.1

Statistics

- ORR was tested based on the reported ORR for single-agent pembrolizumab of 18%
  - Estimated that ORR will improve to ≥35% with pembrolizumab + cabozantinib, yielding a type 1 error of 0.05 and a power of 80% when the true response rate is 35%
- For single-arm design with null hypothesis of ORR ≤15% vs one-sided alternative, 34 patients with evaluable responses are needed
- If the number of responses is ≤9 out of 34, the trial will be claimed as not promising

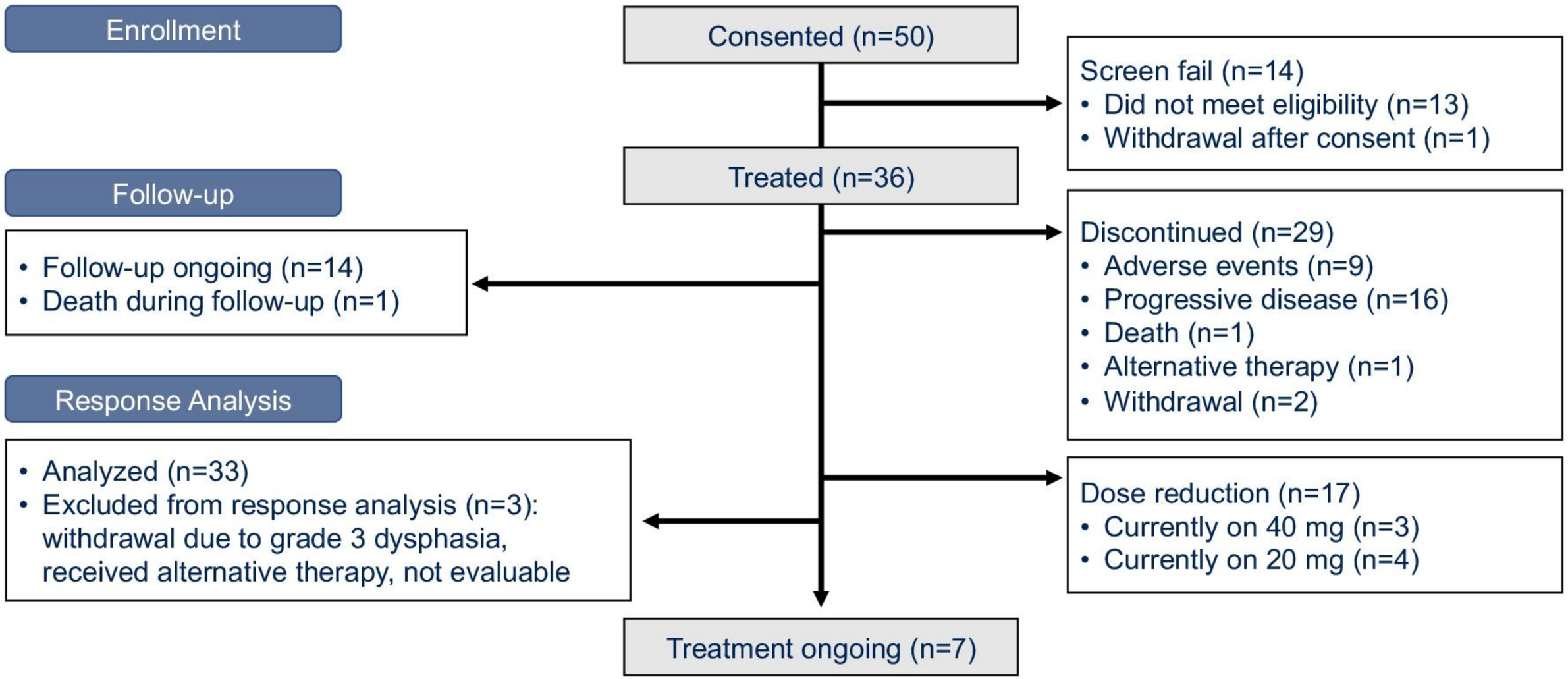
ECOG = Eastern Cooperative Oncology Group; HPV = human papillomavirus; RECIST = Response Evaluation Criteria in Solid Tumors

Patient Characteristics

Patient Characteristic		N=36 n (%)
Age, median (range), years		62 (54-67)
Gender	Male Female	30 (83) 6 (17)
ECOG performance status, %	0 1	18 (50) 18 (50)
Primary site	Oropharynx Oral cavity Hypopharynx Larynx Nasopharynx	22 (61) 2 (6) 2 (6) 4 (11) 6 (16)
HPV (p16)	Positive Negative Unknown	17 (47) 12 (33) 7 (20)
Prior therapy	Radiation Cisplatin Cetuximab	31 (89) 36 (100) 3 (8)
PD-L1 CPS score (total of 34)	CPS <1 CPS 1-19 CPS ≥20	2 (6) 15 (44) 17 (50)

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Patient Disposition



Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Screen Failures – 14 Patients

Screen Failure Reason	n
Cavitating pulmonary lesions	4
Inability to swallow cabozantinib tablets	2
Baseline grade >1 AE	2
Patient decision to withdraw and seek alternative therapy	1
Evidence of GI bleeding within 6 months	1
Significant recent illness	1
Non-measurable disease	1
History of prior malignancy within 1 yr of enrollment	1
Patient on anti-coagulation	1

AE = adverse event; GI = gastrointestinal

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Adverse Events: All Grades

Adverse Event (All Grades)	N=36 n (%)
Fatigue	16 (44.4)
Diarrhea	12 (33.3)
Hypothyroidism	12 (33.3)
Constipation	11 (30.6)
Dry mouth	10 (27.8)
Anorexia	9 (25.0)
Headache	9 (25.0)
Hypertension	9 (25.0)
Hyponatremia	9 (25.0)
Oral mucositis	9 (25.0)

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Most Common Grade ≥3 Adverse Events

Adverse Event (Grade ≥3)	N=36 n (%)
Dysphagia	3 (8.3)
Hypertension	3 (8.3)
Increased AST/ALP	3 (8.3)
Back pain	2 (5.6)
Hypotension	2 (5.6)
Oral mucositis	2 (5.6)
Anemia	1 (2.8)
Anorexia	1 (2.8)

ALP = alkaline phosphatase; AST = aspartate aminotransferase

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Most Common Grade ≥3 Treatment-Related Adverse Events

Treatment-Related Adverse Event (Grade ≥3)	N=36 n (%)
AST increase	3 (8.3)
Hyponatremia	3 (8.3)
GGT increase	2 (5.6)
Lipase increase	2 (5.6)
Oral mucositis	2 (5.6)
ALT/AST increase	1 (2.8)
Bilirubin increase	1 (2.8)
Hypertension	1 (2.8)

There were no grade 5 treatment-related AEs

ALT = alanine aminotransferase; GGT = gamma-glutamyl transferase

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

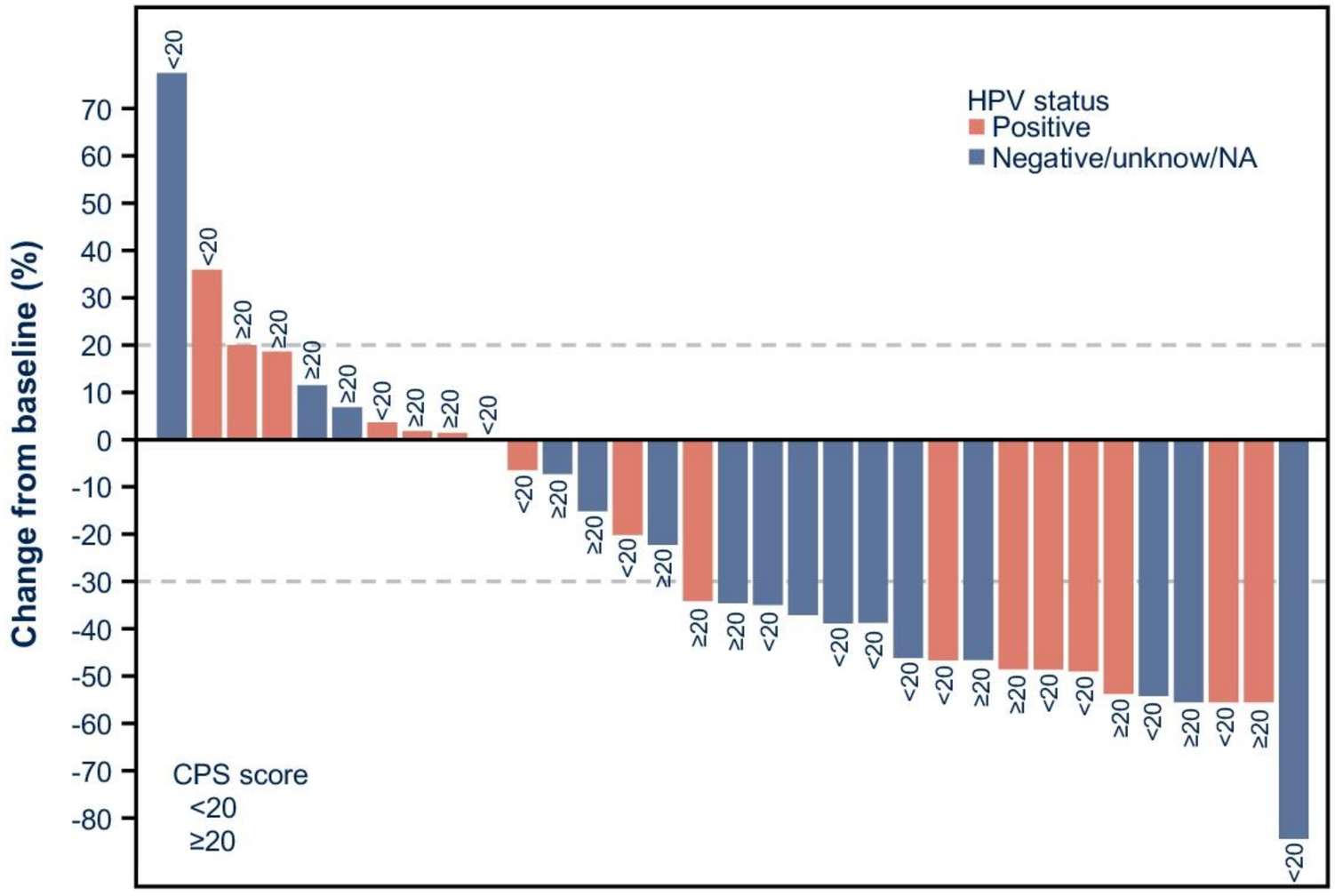
Cabozantinib Dose Reductions

	N=36 n (%)
Cabozantinib dose reduction	17 (47.2)
Oral mucositis	4 (23.5)
Hand foot skin reaction	4 (23.5)
Diarrhea	2 (11.7)
Physician's discretion	2 (11.7)
Hyponatremia	1 (5.9)
Hypertension	1 (5.9)
Epistaxis	1 (5.9)
ALT / AST increase	1 (5.9)
Vomiting	1 (5.9)

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Best Overall Response in Evaluable Patients

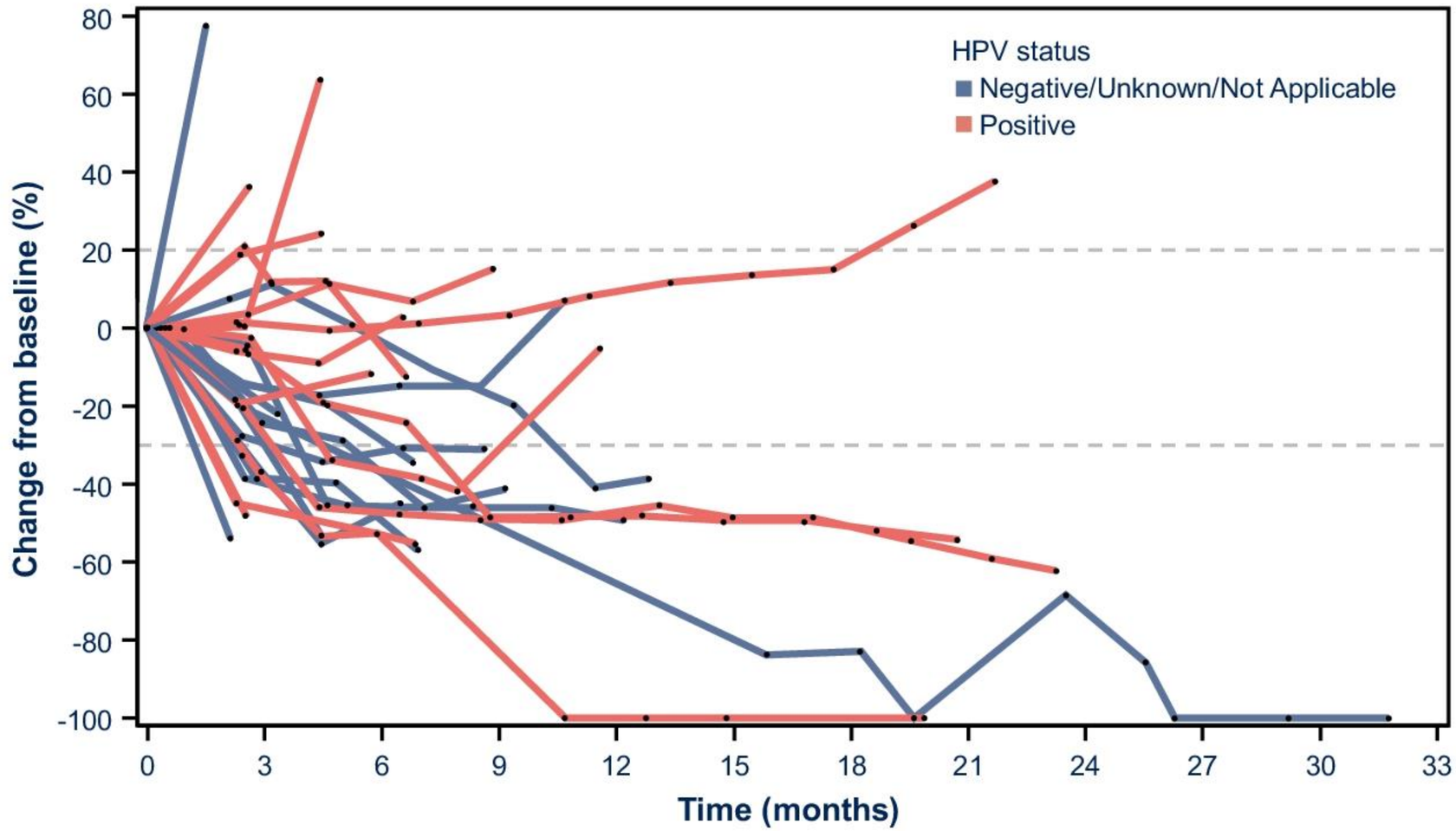
	N=33 n (%)
ORR	18 (54)
CR	0 (0)
PR	18(54)
SD	12(36)
PD	3(9)
Clinical benefit	30(91)



CR = complete response; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease

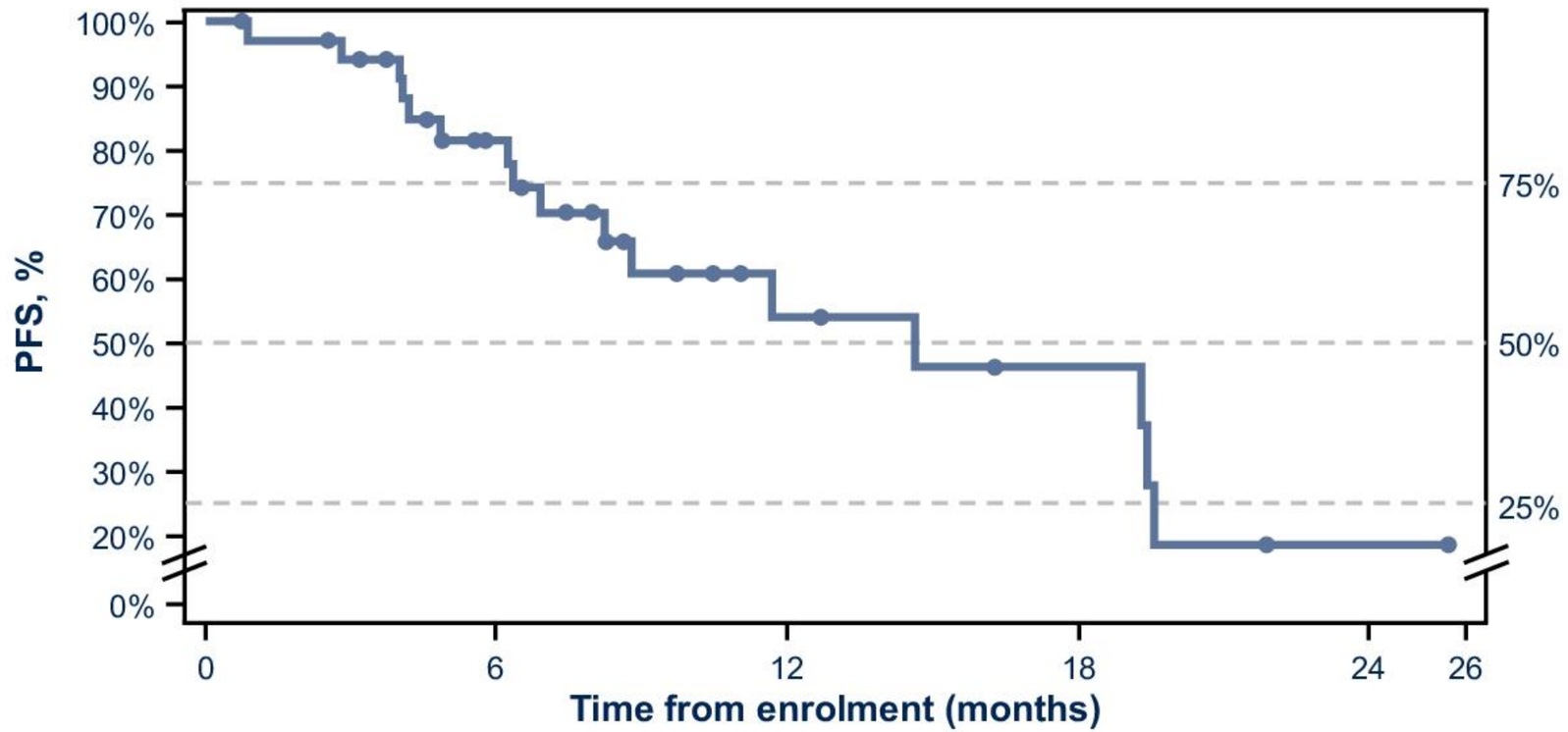
Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Efficacy in Patients Evaluable for Response



Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

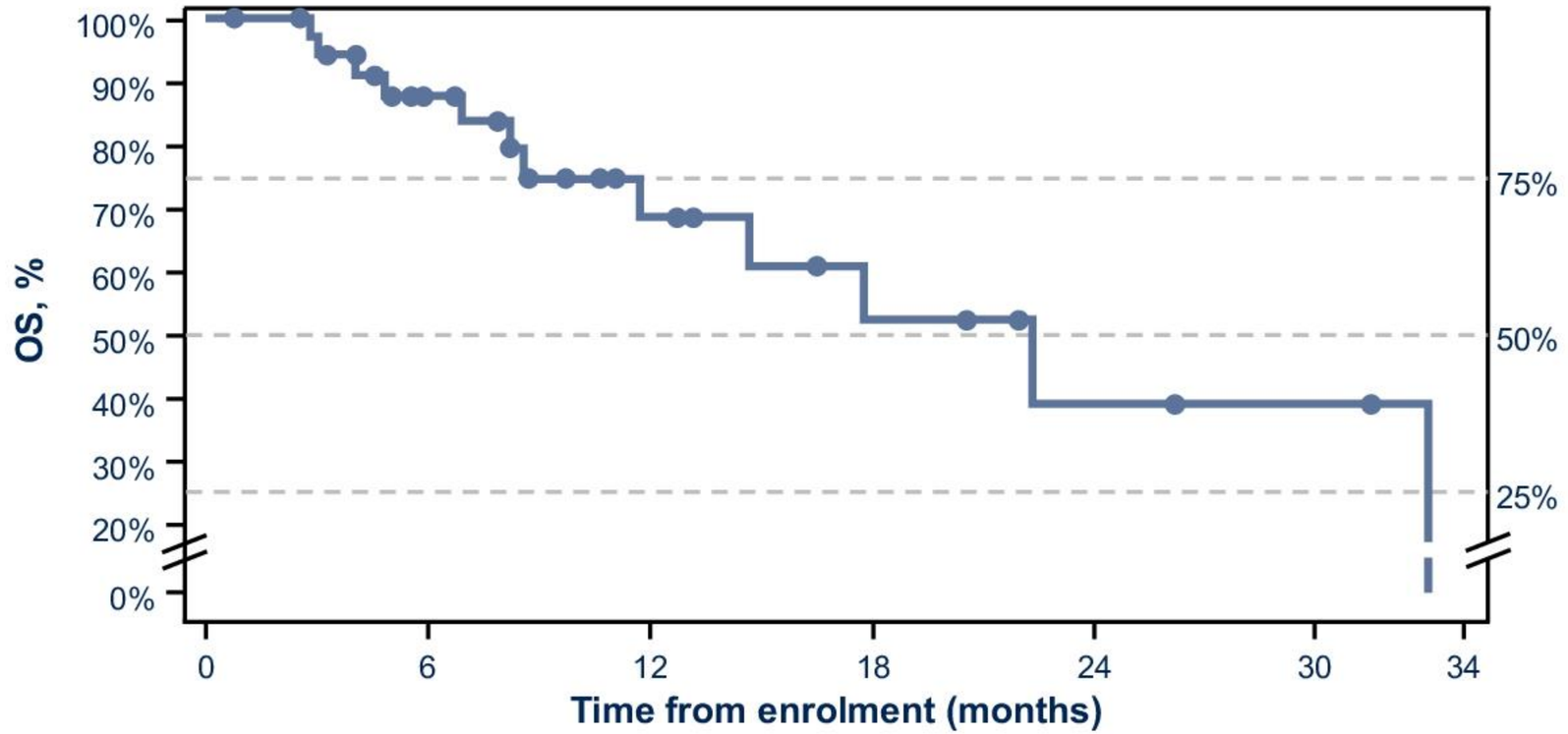
Progression-Free Survival



N	Event	Censored	mPFS (95% CI), mo	1-yr PFS (95%CI), %	Median follow-up (95% CI), mo
36	16 (44%)	20 (56%)	14.6 (8.2–19.6)	54.0 (31.5–72.0)	10.6 (7.8–16.5)

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

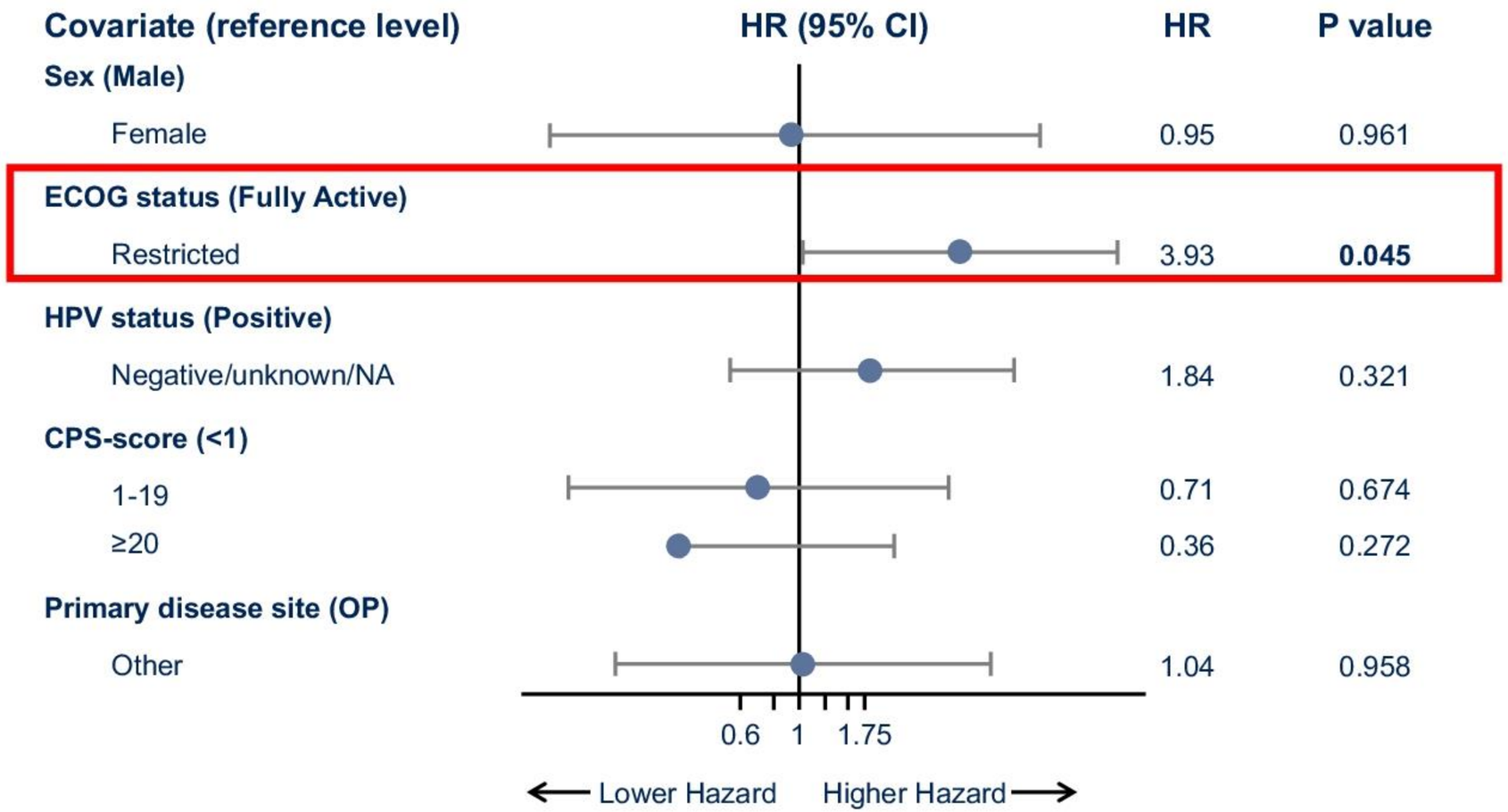
Overall Survival



N	Event	Censored	mOS (95% CI), mo	1-yr OS (95%CI), %	Median follow-up (95% CI), mo
36	12 (33%)	24 (67%)	22.3 (11.7–32.9)	68.4 (45.1–83.5)	10.6 (7.8–16.5)

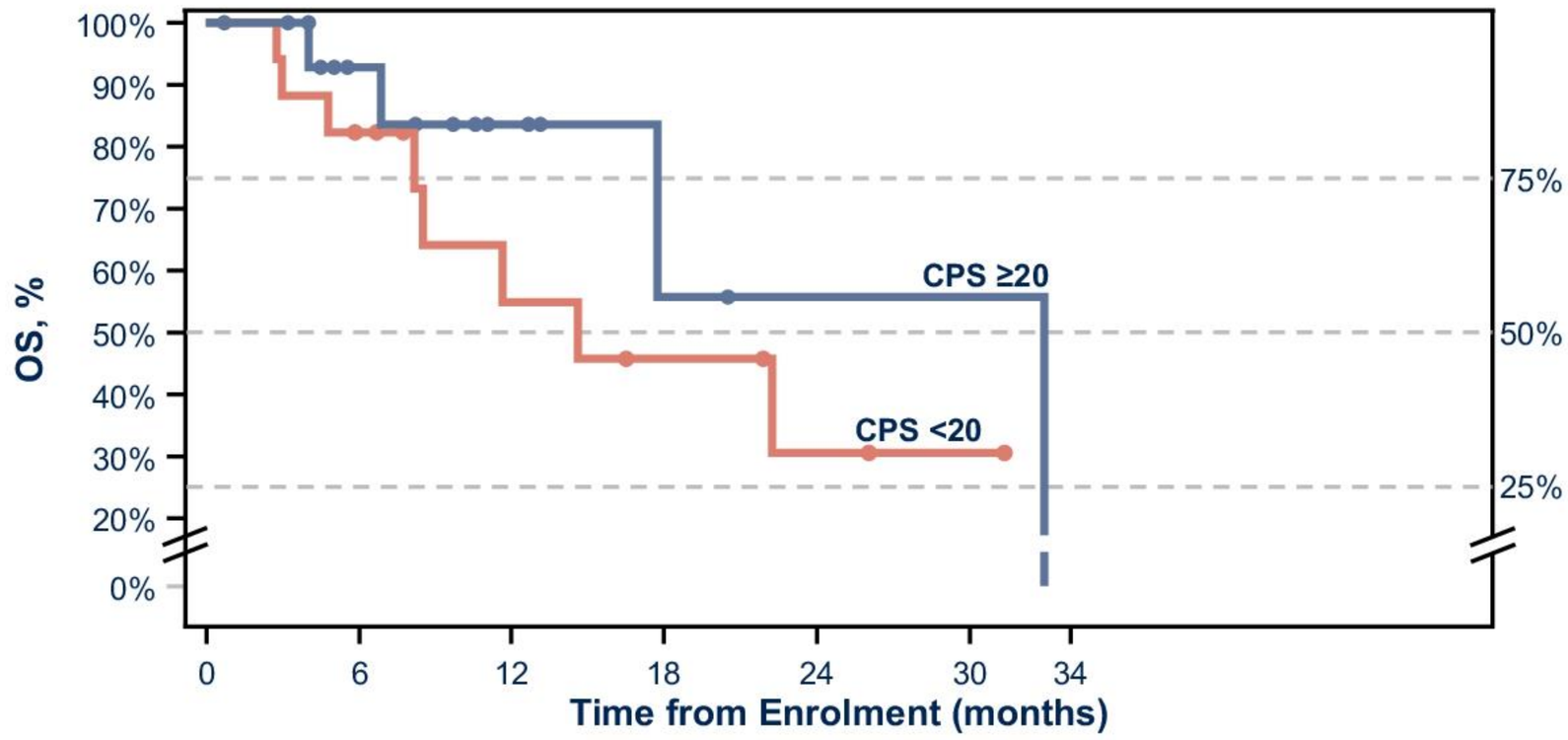
Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Overall Survival- Univariate Association



Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

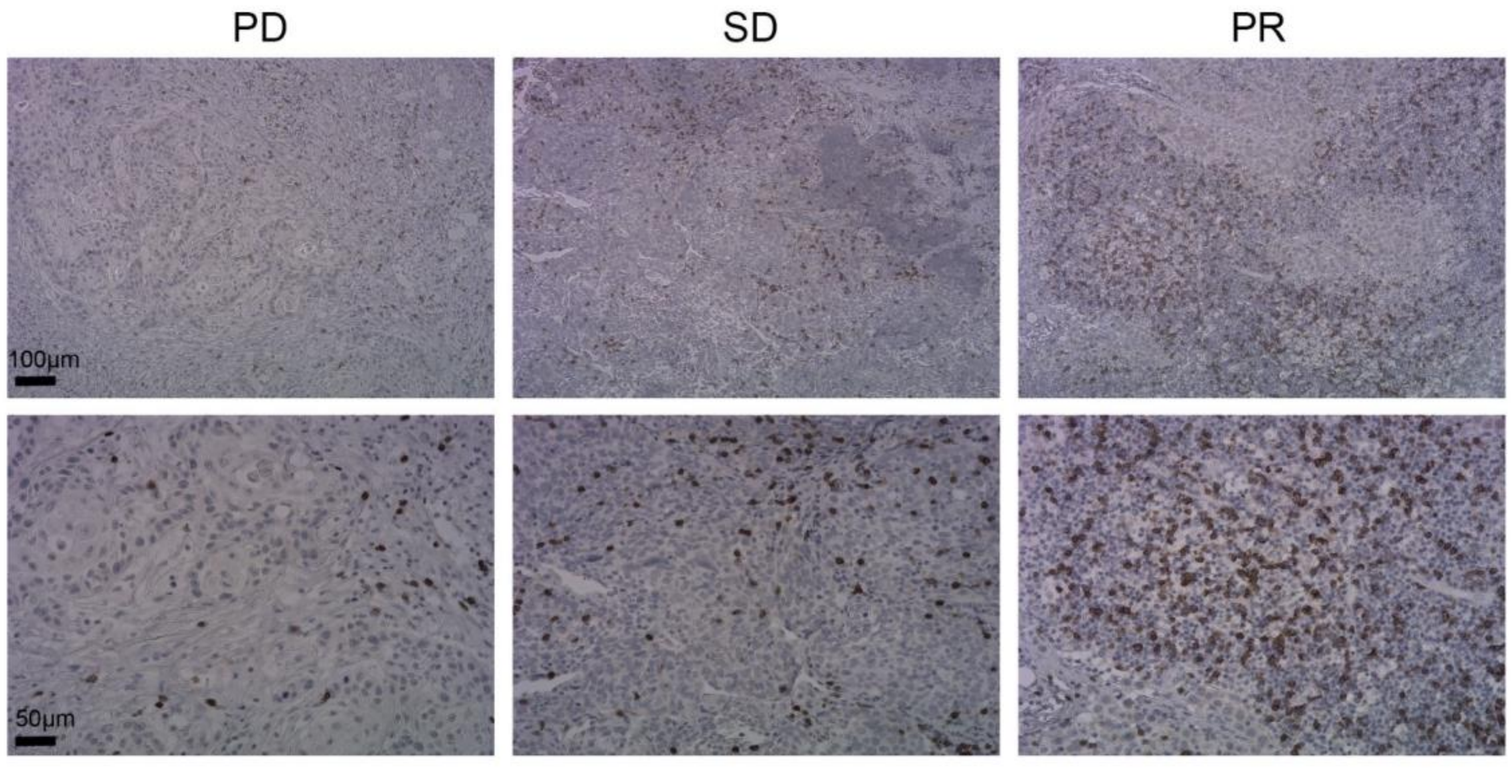
Overall Survival by CPS Score

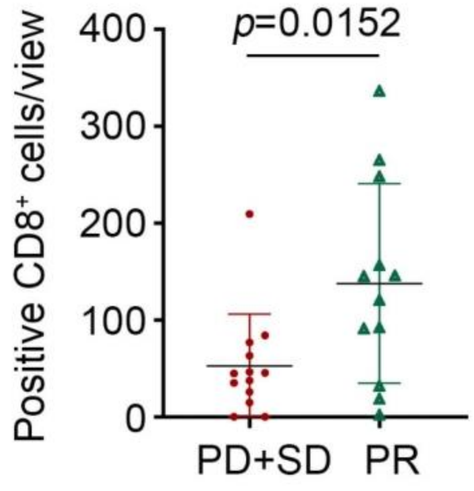


CPS category	N	Event	Censored	mOS (95% CI), mo	1-yr OS (95%CI), %	Median follow-up (95% CI), mo	P value
<20	17	8 (47%)	9 (53%)	14.6 (8.2–NE)	54.9 (24.5–77.5)	21.9 (6.7–31.4)	0.2638
≥20	17	4 (24%)	13 (76%)	32.9 (6.9–32.9)	83.6 (48.0–95.7)	9.7 (4.5–13.1)	

NE = not estimable

Pre-existing CD8+ T-cell Tumor infiltration (26 patients)





Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Safety and Exposure Investigator Observations

- Observed AEs were non-overlapping
- Dose reduction of cabozantinib to 20 mg mitigated the observed toxicities.
- Dose reduction of cabozantinib did not appear to alter clinical benefit
- There were no observed grade 5 treatment-related AEs

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Summary: Pembrolizumab + Cabozantinib in R/M HNSCC

- This phase II trial of pembrolizumab + cabozantinib in R/M HNSCC met its primary endpoint of improved ORR
- Combination resulted in an ORR of 54% and overall clinical benefit of 91%
- 1-yr PFS of 54% and OS of 68% suggests clinical activity that exceeds single agent pembrolizumab in CPS ≥20 group (30% and 56%, respectively, based on KN048)
- Side-effect profile of the combination did not appear to exceed the expected non-competing toxicities of both pembrolizumab and cabozantinib
- Treatment was overall well tolerated, and treatment-related toxicities were generally mitigated by cabozantinib dose reductions to 20mg
- Combination of pembrolizumab + cabozantinib warrants further exploration in R/M HNSCC
- Tissue and blood biomarker analysis will be reported at a later date

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

We would like to thank all study team members, investigators, and in particular, participating patients and their families

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.