RAMUCIRUMAB IN COMBINATION WITH PEMBROLIZUMAB AS FIRST-LINE TREATMENT FOR RECURRENT OR METASTATIC HEAD AND NECK SQUAMOUS-CELL CARCINOMA: A PHASE 1–2 TRIAL

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Background VEGF, a key mediator of angiogenesis and resistance to immunotherapy, is overexpressed in head and neck squamous-cell carcinoma (HNSCC). The primary aims of this trial were to determine the recommended phase 2 dose (RP2D) of ramucirumab, a potent inhibitor of VEGF receptor-2, given with pembrolizumab, and the objective response rate (ORR) of this combination as first-line treatment for recurrent or metastatic (RM)-HNSCC.

Methods Study participants provided written informed consent. Eligible patients had incurable HNSCC originating in the oral cavity, oropharynx, larynx, or hypopharynx. RM disease within 6 months of curative-intent systemic therapy and programmed death ligand (PD-L1) negative disease were permitted. In a dose de-escalation phase 1 design, patients received ramucirumab (level one: 10 mg/kg; then 8 and 6 mg/kg) and pembrolizumab (200 mg) on day 1 of each 21-day cycle until discontinuation criteria were met. Each dose level included three patients. The RP2D of ramucirumab was defined as the highest dose level at which one or fewer patients experienced a dose-limiting toxicity (DLT) during cycle one. In a Simon two-stage phase 2 design, patients with measurable, previously untreated RM-HNSCC received ramucirumab at the RP2D with pembrolizumab. Tumor response was assessed by RECIST1.1. When the trial was developed, the ORR of pembrolizumab given as first-line treatment wasn't known; however, the ORR for platinum pre-treated disease was 13–18%. Therefore, an ORR of <13% was deemed unacceptable and an ORR of >32% was of clinical interest. In stage one, two or more responses among ten patients were required to enroll to stage two. Eight or more responses among 33 evaluable patients (those with at least one response assessment) was evidence for efficacy (80% power; one-sided $\alpha = 0.05$).

Results Three patients were treated in phase 1 and 37 in phase 2. Eleven patients (28%) had recurrent disease within 6 months of curative-intent systemic therapy. In phase 1, no DLT occurred at the starting dose of ramucirumab. Tumor response occurred in 2 of these 3 patients. In phase 2, tumor response occurred in 19 of 33 evaluable patients (ORR 57.6%, 95%CI: 39.2–74.5). Tumor response by PD-L1 CPS is shown in the table below (table 1). No unexpected safety concerns were identified.

pembrolizumab monotherapy when given as first-line treatment for RM-HNSCC.

Trial Registration This trial is registered with ClinicalTrials.gov (NCT03650764).

Ethics Approval This study was approved by Washington University's Ethics Board; approval number 201809094.

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Abstract 358 Table 1

Best Response (RECIST 1.1)	# Evaluable Patients*	# Patients with PD-L1 CPS Status**		
		≥20 (n=15)	1-19 (n=12)	0 (n=5)
CR + PR	19	9	7	2
Stable	7	2	2	3
Progression	7	4	3	0

CPS, combined positive score; CR, complete response; PR, partial response

* Underwent at least one tumor response assessment.

**PD-L1 status pending for one patient.

Conclusions The RP2D of ramucirumab given with pembrolizumab was 10 mg/kg on day 1 of each 21-day cycle. The primary hypothesis was accepted: the ORR with ramucirumab and pembrolizumab was higher than expected with