

SUPPLEMENTARY MATERIAL

TABLE S1. Patient Demographics and Disease Characteristics in the Intent-to-Treat and Biomarker-Evaluable Populations

Characteristic	HAWK/CONDOR ^a		EAGLE	
	ITT (N=379)	tTMB evaluable (n=153)	ITT (N=736)	bTMB evaluable (n=247)
Age (years), median	61	60	60	61
Age <65 years, n (%)	259 (68.3)	106 (69.2)	514 (69.8)	173 (70.0)
Sex, male, n (%)	300 (79.2)	114 (74.5)	618 (84.0)	208 (84.2)
Race, n (%)				
White	330 (87.1)	132 (86.3)	591 (80.3)	185 (74.9)
Asian	13 (3.4)	2 (1.3)	113 (15.4)	52 (21.1)
Other	36 (9.5)	19 (12.4)	32 (4.3)	10 (4.0)
ECOG PS, n (%) ^b				
0	115 (30.4)	37 (24.2)	205 (27.9)	79 (32.0)
1	263 (69.6)	116 (75.8)	531 (72.1)	168 (68.0)
Smoking status, n (%)				
Never smoker	86 (22.7)	38 (24.8)	155 (21.1)	52 (21.1)
Ever smoker	293 (77.3)	115 (75.2)	581 (78.9)	195 (78.9)
Primary tumor location, n (%)				
Oral cavity	101 (26.6)	44 (28.8)	190 (25.8)	57 (23.1)
Oropharynx	147 (38.8)	66 (43.1)	274 (37.2)	100 (40.5)
Hypopharynx	52 (13.7)	18 (11.8)	129 (17.5)	47 (19.0)

Larynx	75 (19.8)	24 (15.7)	115 (15.6)	36 (14.6)
PD-L1 high, n (%)	112 (29.6)	50 (32.7)	212 (28.8)	81 (32.8)
HPV status, n (%) ^b				
Positive	116 (32.4)	46 (31.5)	126 (24.6)	45 (19.4)
Negative	242 (67.6)	100 (68.5)	387 (75.4)	187 (80.6)

Abbreviations: bTMB, blood plasma tumor mutational burden; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papillomavirus; IHC, immunohistochemistry; ITT, intent-to-treat; PD-L1, programmed cell death-ligand 1; tTMB, tissue tumor mutational burden.

^aData include the durvalumab monotherapy arms of HAWK and CONDOR and the durvalumab plus tremelimumab arm and tremelimumab monotherapy arm of CONDOR.

^bData not available for all patients. In HAWK and CONDOR, HPV status was collected from historical medical records or tested centrally. In EAGLE, HPV was tested locally by any method or centrally. Central HPV testing was using p16 IHC.

TABLE S2. Baseline Demographic and Disease Characteristics of Patients in the High-tTMB (≥ 10 mut/Mb) and Low-tTMB (< 10 mut/Mb) Subgroups from HAWK/CONDOR

Characteristic	tTMB≥ 10 mut/Mb (n=84)	tTMB < 10 mut/Mb (n=69)	P value
Age (years), median	62	59	0.052
Age < 65 years, n (%)	54 (64.3)	52 (75.4)	0.193
Sex, male, n (%)	68 (81.0)	46 (66.7)	0.067
Race, n (%)			
White	73 (86.9)	59 (85.5)	0.989
Asian	1 (1.2)	1 (1.4)	1.000
Other	10 (11.9)	9 (13.0)	1.000
ECOG PS, n (%)			
0	17 (20.2)	20 (29.0)	0.286
1	67 (79.8)	49 (71.0)	0.286
Smoking status, n (%)			
Never smoker	14 (16.7)	24 (34.8)	0.017
Ever smoker	70 (83.3)	45 (65.2)	0.017
Primary tumor location, n (%)			
Oral cavity	20 (23.8)	24 (34.8)	0.189
Oropharynx	35 (41.7)	31 (44.9)	0.810
Hypopharynx	11 (13.1)	7 (10.1)	0.755
Larynx	17 (20.2)	7 (10.1)	0.138
PD-L1 status, n (%)			
High	23 (27.4)	27 (39.1)	0.171
Low	61 (72.6)	42 (60.9)	0.171

HPV status, n (%)^a

Positive	24 (30.4)	22 (32.8)	0.889
Negative	55 (69.6)	45 (67.2)	0.889

Abbreviations: HPV, human papillomavirus; IHC, immunohistochemistry; mut/Mb, mutations/megabase; PD-L1, programmed cell death-ligand 1; tTMB, tissue tumor mutational burden.

^aData not available for all patients. HPV status was collected from historical medical records or tested centrally.

Central HPV testing was using p16 IHC.

TABLE S3. Baseline Demographic and Disease Characteristics of Patients in the Biomarker-Evaluable Population, High-bTMB (≥ 16 mut/Mb) Subgroup, and Low-bTMB (<16 mut/Mb) Subgroup from EAGLE

Characteristic	bTMB ≥ 16 mut/Mb (n=74)	bTMB <16 mut/Mb (n=173)	<i>P</i> value
Age (years), median	60	61	0.361
Age <65 years, n (%)	54 (73.0)	119 (68.4)	0.613
Sex, male, n (%)	64 (86.5)	144 (83.2)	0.652
Race, n (%)			
White	56 (75.7)	129 (74.6)	0.981
Asian	10 (13.5)	42 (24.3)	0.084
Other	8 (10.8)	2 (1.2)	0.002
ECOG PS, n (%)			
0	21 (28.4)	58 (33.5)	0.519
1	53 (71.6)	115 (66.5)	0.519
Smoking status, n (%)			
Never smoker	12 (16.2)	40 (23.1)	0.294
Ever smoker	62 (83.8)	133 (76.9)	0.294
Primary tumor location, n (%)			
Oral cavity	16 (21.6)	41 (23.7)	0.849
Oropharynx	26 (35.1)	74 (42.8)	0.328
Hypopharynx	18 (24.3)	29 (16.8)	0.226
Larynx	12 (16.2)	24 (13.9)	0.779
PD-L1 status, n (%)			
High	23 (31.1)	58 (33.5)	0.052

Low	51 (68.9)	115 (66.5)	0.052
HPV positive, n (%) ^a			
Positive	12 (17.6)	33 (20.1)	0.801
Negative	56 (82.4)	131 (79.9)	0.801

Abbreviations: bTMB, blood plasma tumor mutational burden; HPV, human papilloma virus; IHC, immunohistochemistry; mut/Mb, mutations/megabase; PD-L1, programmed cell death-ligand 1.

^aData not available for all patients. HPV was tested locally by any method or centrally. Central HPV testing was using p16 IHC.

TABLE S4. OS HRs for Durvalumab and Durvalumab plus Tremelimumab versus SoC in Subgroups of Patients in EAGLE by PD-L1 Expression and bTMB

	Durvalumab				Durvalumab plus tremelimumab			
	bTMB-high		bTMB-low		bTMB-high		bTMB-low	
	n	HR (95% CI)	n	HR (95% CI)	n	HR (95% CI)	n	HR (95% CI)
PD-L1 high	17	0.25 (0.06- 1.03)	34	0.74 (0.32- 1.70)	13	0.21 (0.04- 1.16)	44	1.03 (0.53- 2.02)
PD-L1 low	37	0.50 (0.23- 1.07)	76	0.89 (0.55- 1.44)	34	0.50 (0.23- 1.09)	72	0.77 (0.47-1.27)

Abbreviations: bTMB, blood plasma tumor mutational burden; CI, confidence interval; HR, hazard ratio; OS, overall survival; PD-L1, programmed cell death-ligand 1; SoC, standard of care.

HRs were calculated as durvalumab with/without tremelimumab versus chemotherapy.