ASOCIACIÓN DE ONCÓLOGOS CLÍNICOS DE CÓRDOBA

Durvalumab with or without tremelimumab in patients with recurrent or metastatic head and neck squamous cell carcinoma: EAGLE, a randomized,open-label phase III study

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Introduction

- Head and neck squamous cell carcinoma (HNSCC) is among the 10 most common cancers worldwide
- Approximately 10% of patients with HNSCC will be diagnosed with metastatic disease (1, 2)
- Around half will have disease recurrence
- The platinum-based doublet chemotherapy with cetuximab regimen has been the most widely-used therapy and considered standard of care (SoC) since 2007 (3, 4)
- The available options in second-line have delivered limited survival benefits (3)

Principles of systemic therapies

Preferred Regimens (First-Line)

- Cetuximab/platinum (cisplatin or carboplatin)/5-FU[c,29] (category 1)
- Immunotherapy
  - Pembrolizumab/platinum (cisplatin or carboplatin)/5-FU[c,30] (category 1)
  - Pembrolizumab (for tumors that express PD-L1 with CPS ≥1)[30,31] (category 1 if CPS ≥ 20)

Preferred Regimens (Subsequent-Line)

- Immunotherapy (if not previously used)
  - Nivolumab[32] if disease progression on or after platinum therapy (category 1)
  - Pembrolizumab[33-35] if disease progression on or after platinum therapy (category 1)

Other Recommended Regimens (First-Line)

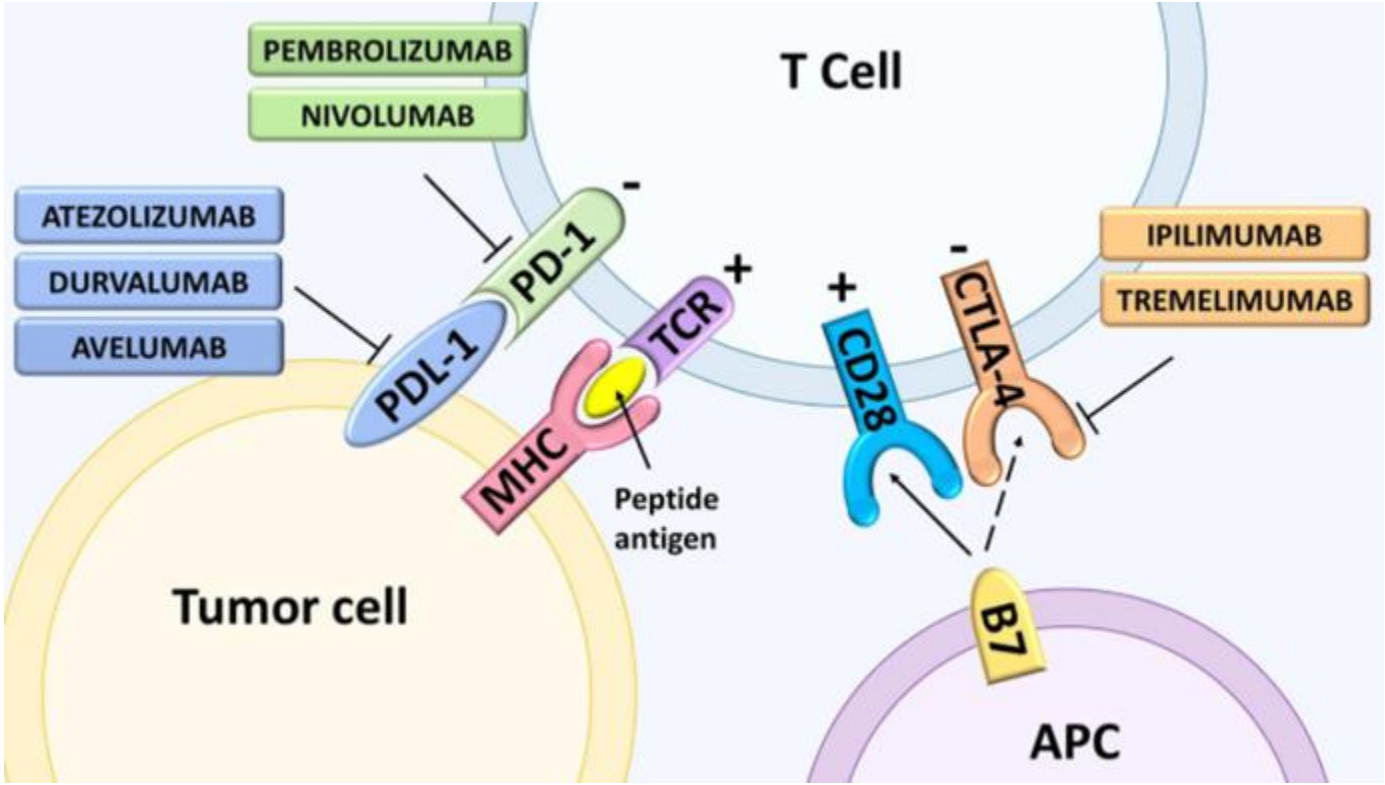
Combination Therapy
- Cisplatin/cetuximab[36]
- Cisplatin or carboplatin/ docetaxel[37] or paclitaxel[38]
- Cisplatin/5-FU[38,39]
- Cisplatin or carboplatin/ docetaxel/cetuximab[40]
- Cisplatin or carboplatin/ paclitaxel/cetuximab[41]

Single Agents
- Cisplatin[36,42]
- Carboplatin[43]
- Paclitaxel[44]
- Docetaxel[45,46]
- 5-FU[42]
- Methotrexate[39,47]
- Cetuximab[48]
- Capecitabine[49]

Other Recommended Regimens (Subsequent-Line)

- Combination Therapy or Single Agents
  - See preferred and other recommended first-line therapy options above
- Targeted Therapy
  - Afatinib[50] if disease progression on or after platinum therapy (category 2B)

Mechanism of action



Study design

Phase III trial, randomly 1:1, >18 years old, PE 1 first- line
The study was conducted at 156 sites globally
Stratified to: PD-L1 expression (V= SP263 AZ), tumor location, HPV and smoking status

Endpoints: 1° - OS
2° - PFS, ORR, DoR and Safety

Doses
A- Durvalumab 10 mg/Kg q2w
B- Durvalumab 20 mg/Kg plus Tremelimumab 1 mg/Kg q4w x4 → Durv. 10mg/Kg q2w
C- SoC single- agent (cetuximab,docetaxel, paclitaxel, methotrexate, 5-fluorouracil, TS-1, or capecitabine)

* dosed and administered according to local regulations

Study design

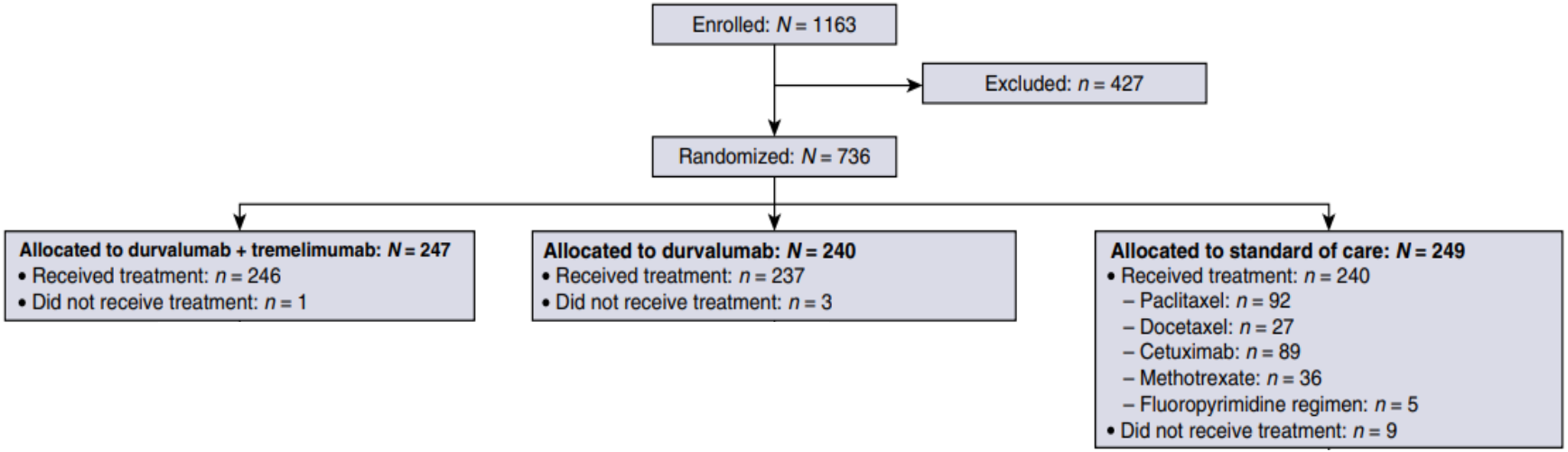


Table 1. Baseline demographics and clinical characteristics in the full analysis set

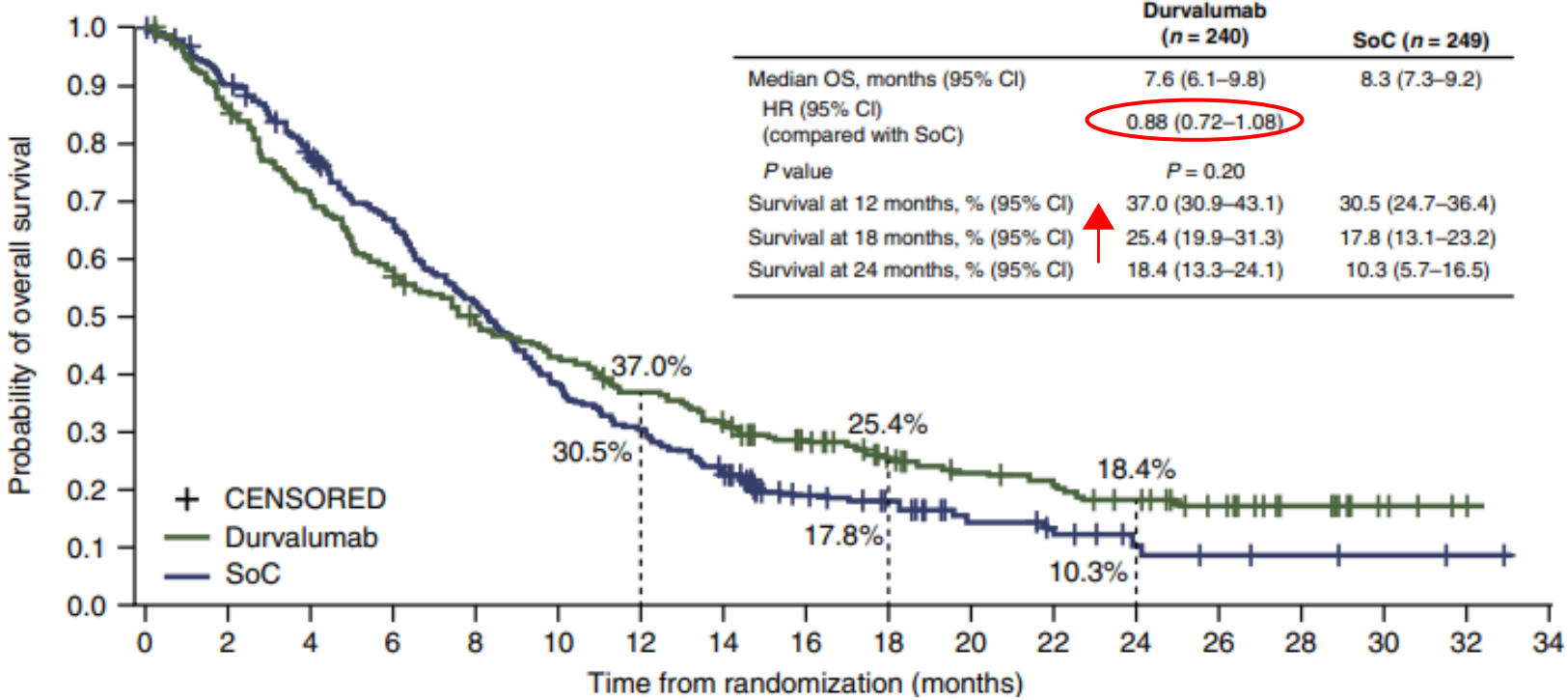
	Durvalumab (n = 240)	Durvalumab + tremelimumab (n = 247)	Standard of care (n = 249)
Median age, years (range)	59.0 (24–84)	61.0 (23–81)	61.0 (22–82)
Male, *n* (%)	202 (84.2)	209 (84.6)	207 (83.1)
Race, *n* (%)	n = 238	n = 242	n = 240
White	198 (83.2)	204 (84.3)	189 (78.8)
Asian	35 (14.7)	33 (13.6)	45 (18.8)
Other (including black or African American)	5 (2.1)	5 (2.0)	6 (2.4)
Ethnicity, *n* (%)			
Hispanic or Latino	15 (6.3)	16 (6.6)	13 (5.4)
Nicotine use, *n* (%)			
Current smoker	41 (17.1)	45 (18.2)	56 (22.5)
Former smoker	153 (63.8)	146 (59.1)	140 (56.2)
Never	46 (19.2)	56 (22.7)	53 (21.3)
Other nicotine use[a]	3 (1.3)	0	2 (0.8)
Primary tumor location, *n* (%)			
Oral cavity	64 (26.7)	65 (26.3)	61 (24.5)
Oropharynx	92 (38.3)	91 (36.8)	91 (36.5)
Hypopharynx	41 (17.1)	51 (20.6)	37 (14.9)
Larynx	37 (15.4)	33 (13.4)	45 (18.1)
Other	6 (2.5)	7 (2.8)	15 (6.0)
Time from last platinum therapy, *n* (%)	n = 227	n = 234	n = 237
≤6 months	185 (81.5)	195 (83.3)	208 (87.8)
>6 months	42 (18.5)	39 (16.7)	29 (12.2)
ECOG PS, *n* (%)			
0	62 (25.8)	64 (25.9)	79 (31.7)
1	178 (74.2)	183 (74.1)	170 (68.3)
Median number of prior treatments (range)	1.0 (1–4)	1.0 (1–4)	1.0 (1–4)
Tumor location/HPV status, *n* (%)	n = 240	n = 246	n = 249
OPC/positive	30 (12.5)	30 (12.2)	31 (12.4)
OPC/negative	60 (25.0)	58 (23.6)	60 (24.1)
Non-OPC/any HPV	150 (62.5)	158 (64.2)	158 (63.5)
PD-L1 status, *n* (%)			
TC ≥ 25%	68 (28.3)	72 (29.1)	72 (28.9)
TC < 25%	172 (71.7)	175 (70.9)	177 (71.1)
Disease extent at baseline, *n* (%)			
Local/regional recurrence ± distant metastases	221 (92.1)	224 (90.7)	214 (85.9)
Distant metastases only	19 (7.9)	23 (9.3)	35 (14.1)

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papilloma virus; OPC, oropharyngeal cancer; PD-L1, programmed death ligand 1; TC, tumor cell.

[a] Including chewing tobacco/oral snuff/sublingual nicotine.

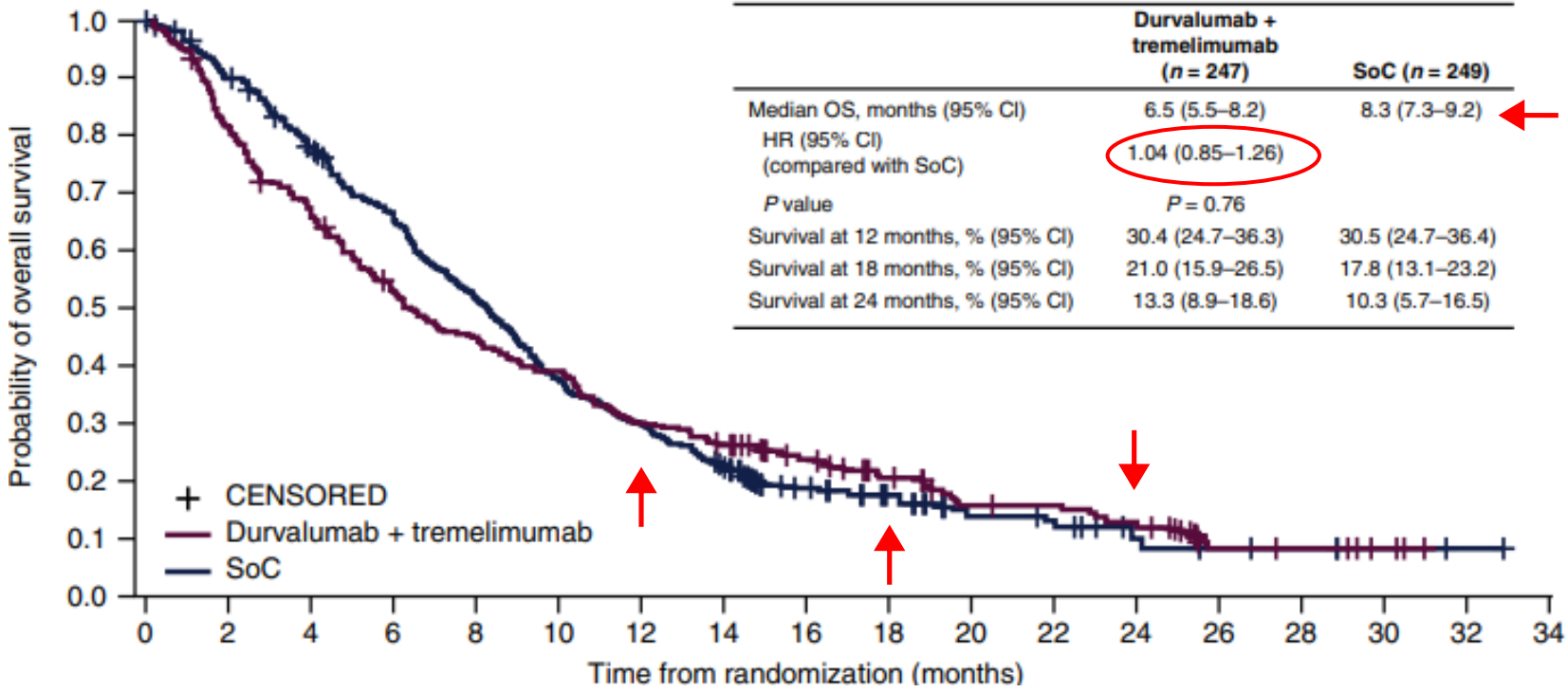
Median OS for durvalumab versus SoC

	Durvalumab (n = 240)	SoC (n = 249)
Median OS, months (95% CI)	7.6 (6.1–9.8)	8.3 (7.3–9.2)
HR (95% CI) (compared with SoC)	0.88 (0.72–1.08)	
P value	P = 0.20	
Survival at 12 months, % (95% CI)	37.0 (30.9–43.1)	30.5 (24.7–36.4)
Survival at 18 months, % (95% CI)	25.4 (19.9–31.3)	17.8 (13.1–23.2)
Survival at 24 months, % (95% CI)	18.4 (13.3–24.1)	10.3 (5.7–16.5)



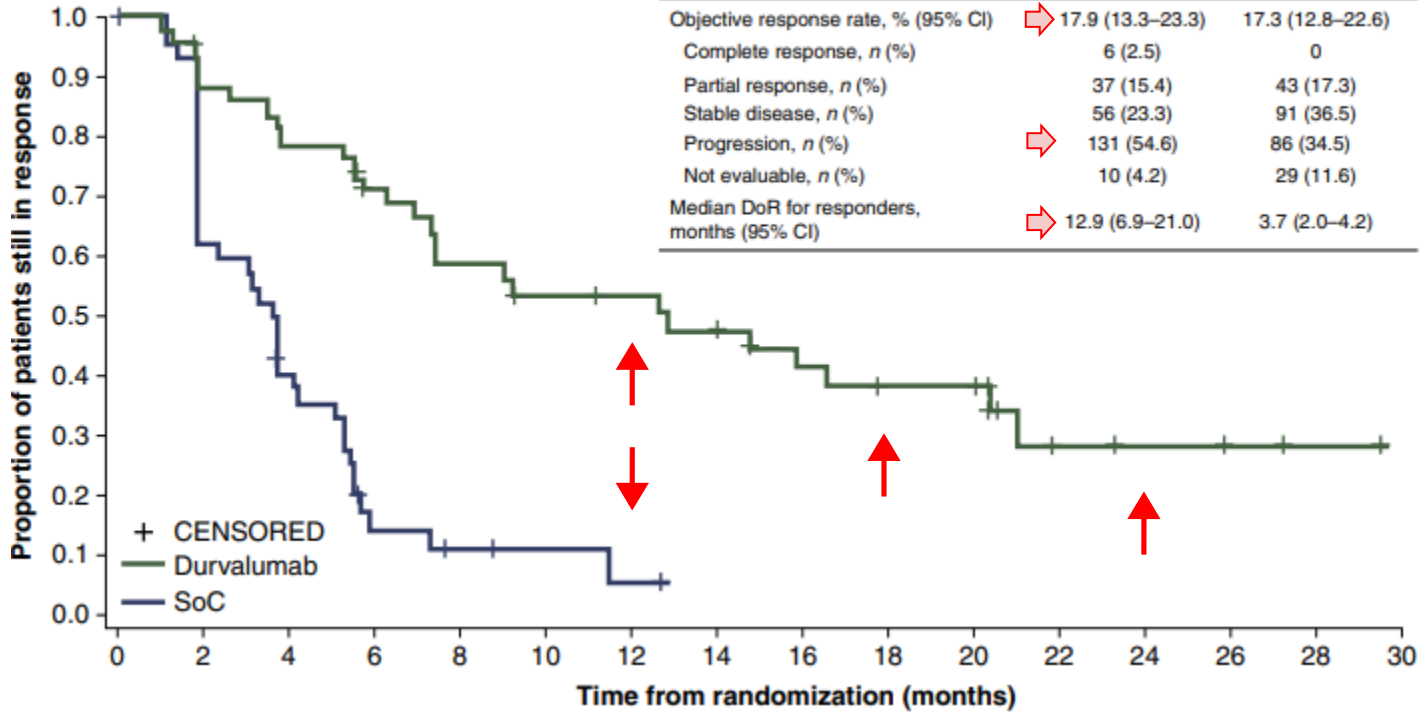
Median OS for durvalumab plus tremelimumab vs SoC

	Durvalumab + tremelimumab (*n* = 247)	SoC (*n* = 249)
Median OS, months (95% CI)	6.5 (5.5–8.2)	8.3 (7.3–9.2)
HR (95% CI) (compared with SoC)	1.04 (0.85–1.26)	
P value	*P* = 0.76	
Survival at 12 months, % (95% CI)	30.4 (24.7–36.3)	30.5 (24.7–36.4)
Survival at 18 months, % (95% CI)	21.0 (15.9–26.5)	17.8 (13.1–23.2)
Survival at 24 months, % (95% CI)	13.3 (8.9–18.6)	10.3 (5.7–16.5)

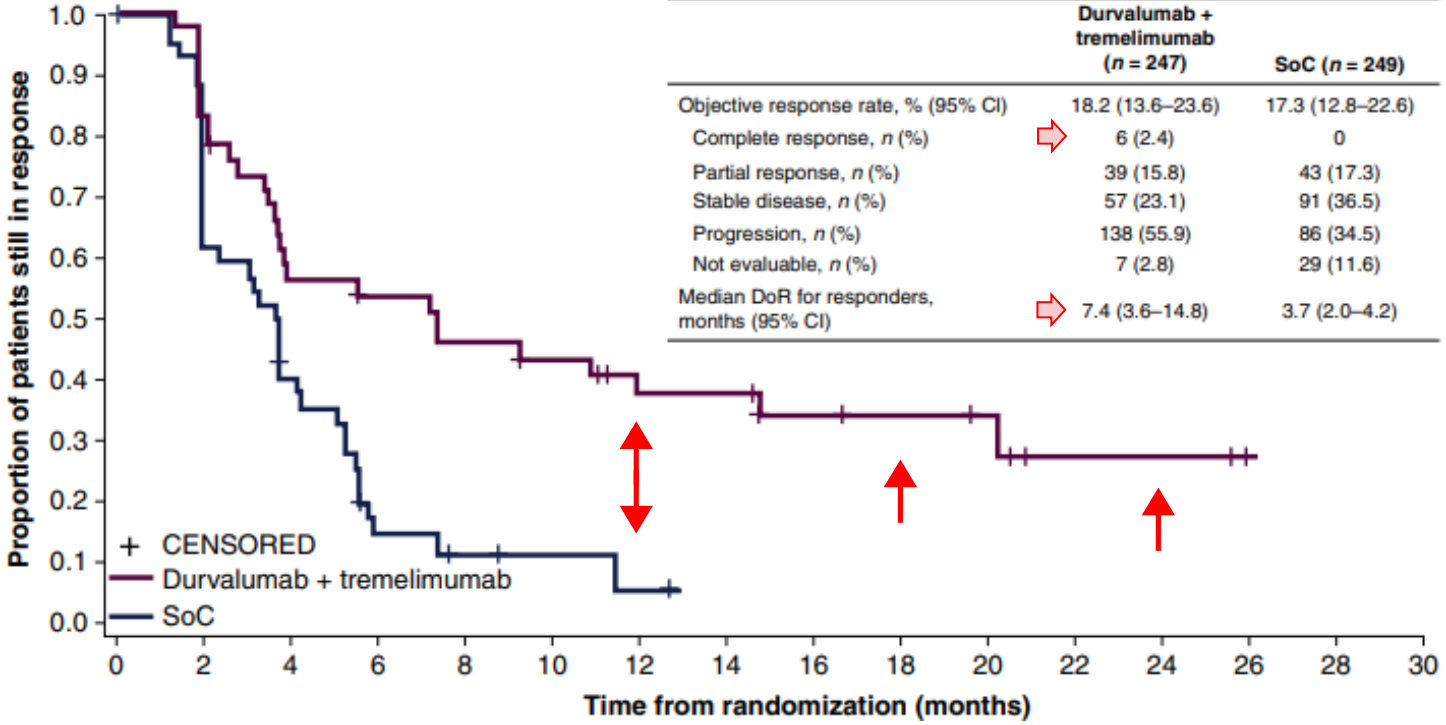


Duration of response for who responded to durvalumab vs SoC

	Durvalumab (n = 240)	SoC (n = 249)
Objective response rate, % (95% CI)	17.9 (13.3–23.3)	17.3 (12.8–22.6)
Complete response, n (%)	6 (2.5)	0
Partial response, n (%)	37 (15.4)	43 (17.3)
Stable disease, n (%)	56 (23.3)	91 (36.5)
Progression, n (%)	131 (54.6)	86 (34.5)
Not evaluable, n (%)	10 (4.2)	29 (11.6)
Median DoR for responders, months (95% CI)	12.9 (6.9–21.0)	3.7 (2.0–4.2)



Duration of response for who responded to durvalumab plus tremelimumab vs SoC



	Durvalumab + tremelimumab (*n* = 247)	SoC (*n* = 249)
Objective response rate, % (95% CI)	18.2 (13.6–23.6)	17.3 (12.8–22.6)
Complete response, *n* (%)	6 (2.4)	0
Partial response, *n* (%)	39 (15.8)	43 (17.3)
Stable disease, *n* (%)	57 (23.1)	91 (36.5)
Progression, *n* (%)	138 (55.9)	86 (34.5)
Not evaluable, *n* (%)	7 (2.8)	29 (11.6)
Median DoR for responders, months (95% CI)	7.4 (3.6–14.8)	3.7 (2.0–4.2)

Safety

Table 2. Incidence of trAEs (≥5% for any grade, ≥2% for grade 3–4 in any arm) in the safety analysis set

	Durvalumab (n = 237)		Durvalumab + tremelimumab (n = 246)		Standard of care (n = 240)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Patients with any trAE, n (%)	**136 (57.4)**	**24 (10.1)**	**150 (61.0)**	**40 (16.3)**	**197 (82.1)**	**58 (24.2)**
Alopecia	0	0	0	0	28 (11.7)	0
Anemia	12 (5.1)	0	20 (8.1)	4 (1.6)	42 (17.5)	11 (4.6)
Asthenia	15 (6.3)	1 (0.4)	20 (8.1)	5 (2.0)	32 (13.3)	2 (0.8)
Decreased appetite	12 (5.1)	0	14 (5.7)	2 (0.8)	28 (11.7)	3 (1.3)
Dermatitis acneiform	2 (0.8)	0	2 (0.8)	0	16 (6.7)	0
Diarrhea	14 (5.9)	0	20 (8.1)	2 (0.8)	17 (7.1)	3 (1.3)
Elevated ALT	7 (3.0)	1 (0.4)	10 (4.1)	0	14 (5.8)	1 (0.4)
Elevated GGT	8 (3.4)	1 (0.4)	10 (4.1)	2 (0.8)	12 (5.0)	1 (0.4)
Fatigue	16 (6.8)	2 (0.8)	18 (7.3)	3 (1.1)	26 (10.8)	2 (0.8)
Hypothyroidism	27 (11.4)	0	30 (12.2)	0	0	0
Leukopenia	2 (0.8)	0	9 (3.7)	0	12 (5.0)	4 (1.7)
Mucosal inflammation	0	0	1 (0.4)	0	12 (5.0)	1 (0.4)
Nausea	12 (5.1)	1 (0.4)	10 (4.1)	0	33 (13.8)	0
Neuropathy peripheral	3 (1.3)	1 (0.4)	3 (1.2)	0	20 (8.3)	2 (0.8)
Neutropenia	3 (1.3)	0	11 (4.5)	1 (0.4)	31 (12.9)	12 (5.0)
Pruritus	8 (3.4)	0	20 (8.1)	0	6 (2.5)	0
Rash	15 (6.3)	0	11 (4.5)	0	33 (13.8)	0
Stomatitis	4 (1.7)	1 (0.4)	3 (1.2)	0	23 (9.6)	0
Thrombocytopenia	5 (2.1)	1 (0.4)	11 (4.5)	2 (0.8)	16 (6.7)	1 (0.4)

Conclusions

- Not demonstrate a statistically significant survival benefit for immunotherapy over single-agent SoC as second-line treatment of patients with HNSCC R / M

- Combining durvalumab with tremelimumab did not show improvement over durvalumab activity

- Cross- trial comparison,12-month survival rates for all three were similar (durvalumab, 37.0%; nivolumab, 36.0%; pembrolizumab,37.0%)

- There were examples of activity in favor of durvalumab, including complete responders and longer DoR vs SoC, suggesting that the benefit from durvalumab was more durable than from SoC

Discussion

- Unexpectedly high OS for the SoC arm with a median of 8.3 months.

- Patients who received an immunotherapy after discontinuation of treatment in the EAGLE study had longer OS

- Imbalances in characteristics between groups, specifically ECOG PS and patients with metastatic disease

- Crossover phenomenon of Kaplan- Meier OS curves