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Primary results of the phase 3 JAVELIN Head & Neck 100 trial: avelumab plus chemoradiotherapy (CRT) followed by avelumab maintenance vs CRT in patients with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN)

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Disclosures for Dr Cohen

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Background

- High-dose cisplatin-based CRT is the current standard-of-care therapy for unresected LA SCCHN[1]
- Anti–PD-1 immune checkpoint inhibitors have proven effective for the treatment of recurrent and/or metastatic SCCHN[2-5]; however, data are limited on the use of immune checkpoint inhibitors in LA SCCHN
- Avelumab, an anti–PD-L1 immune checkpoint inhibitor, has shown antitumor activity and an acceptable safety profile in a range of solid tumors, including recurrent and/or metastatic SCCHN[6-9]
- We hypothesized that the combination of avelumab with CRT may improve outcomes in patients with LA SCCHN

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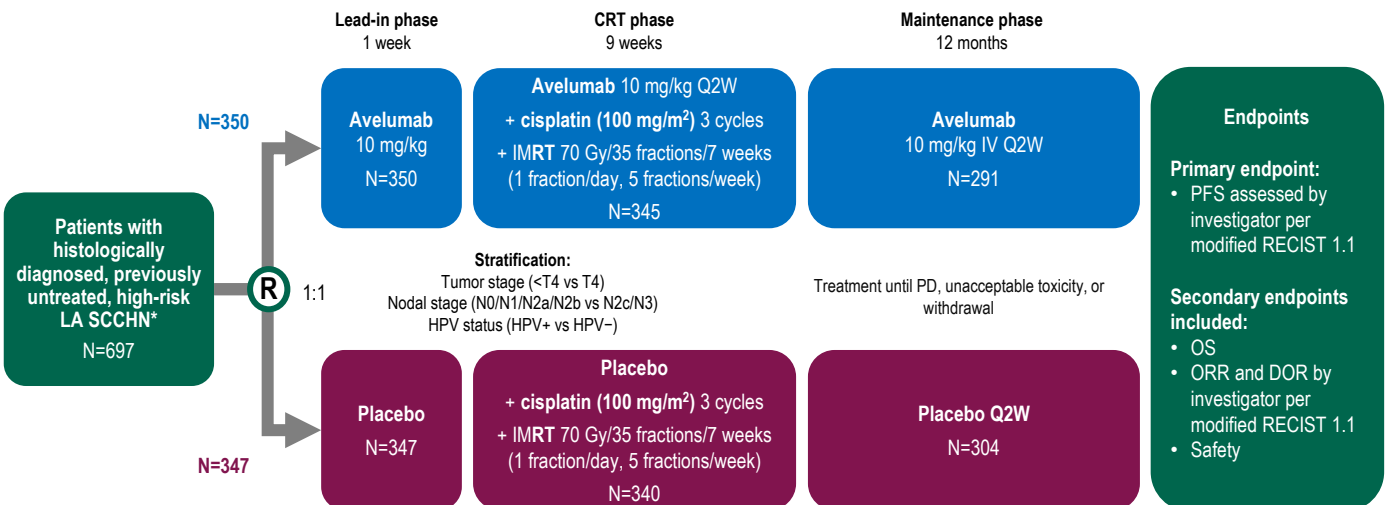
JAVELIN Head & Neck 100: study design

Randomized, placebo-controlled, double-blind, phase 3 trial



DOR, duration of response; **HPV**, human papillomavirus; **IMRT**, intensity-modulated radiation therapy; **IV**, intravenously; **ORR**, objective response rate; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **Q2W**, every 2 weeks; **R**, randomized; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumors version 1.1.

* High-risk LA SCCHN (oral cavity, oropharynx, larynx, or hypopharynx): HPV-negative disease stage III, IVa, IVb; nonoropharyngeal HPV-positive disease stage III, IVa, IVb; HPV-positive oropharyngeal disease T4 or N2c or N3 (TNM staging per AJCC, 7th edition).

Statistical design

- The study had 90% power to detect a HR of 0.68 at 0.025 level of significance (1-sided) based on the assumptions that the median PFS for patients in the placebo arm is 33 months and that avelumab combination treatment is expected to increase the median PFS to ≥48.5 months
- At the time of planned interim analysis, the were 224 PFS events (77% information fraction) observed
- The test statistic crossed the futility boundary, and the study was unblinded

HR, hazard ratio.

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Baseline characteristics

	Avelumab + CRT (n=350)	Placebo + CRT (n=347)
Age, median, years	60	59
Sex, %		
Male	83	82
Female	17	18
ECOG performance status, %		
0	55	62
1	45	38
Geographic region, %		
North America	23	27
Western Europe	30	33
Eastern Europe	15	13
Asia	29	24
Rest of the world	3	4

	Avelumab + CRT (n=350)	Placebo + CRT (n=347)
Site of primary tumor, %		
Oral cavity	13	14
Oropharynx	45	49
Larynx	17	19
Hypopharynx	25	18
HPV status, %*		
Positive	35	34
Negative	65	66
Tumor stage at baseline, %†		
<T4	57	56
T4	43	44
Nodal stage at baseline, %†		
N0/N1/N2a/N2b	53	52
N2c/N3	47	48

ECOG, Eastern Cooperative Oncology Group.
* Determined per institutional standard using p16 immunohistochemistry, based on a randomization system.
† As defined by the American Joint Committee on Cancer, 7th edition, based on a randomization system.

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Treatment exposure and patient disposition

Treatment exposure	Treated patients (N=692)	
	Avelumab + CRT (n=348)	Placebo + CRT (n=344)
Overall duration of avelumab/placebo, median (range), months*	9.8 (0.5-15.2)	12.4 (0.5-16.3)
Cumulative dose of cisplatin, median (range), mg/m^2	259.7 (90.6-316.9)	278.4 (77.5-323.3)
Dose of radiation, median (range), Gy	70.0 (6.0-74.0)	70.0 (2.0-74.0)

Patient disposition	Randomized patients (N=697)	
	Avelumab + CRT (n=350)	Placebo + CRT (n=347)
Entered maintenance phase, %	83	88
Completed maintenance phase, %	31	39
Maintenance ongoing, %	10	14
Reason for discontinuation of maintenance, %		
Progressive disease	17	15
Patient withdrawal	9	7
Adverse event	7	6
Death	5	3
Other†	5	3

* Across all phases.
† Reasons included: global deterioration of health status, physician decision, nonadherence with study drug, lost to follow-up, and other reasons.

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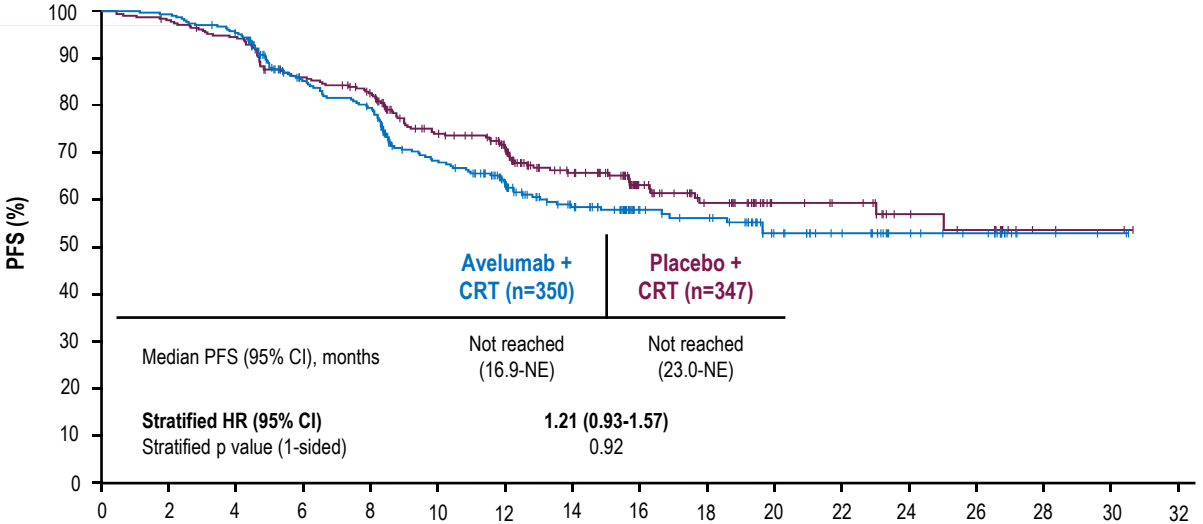
Primary endpoint: PFS by investigator per modified RECIST 1.1



At risk																	
Avelumab + CRT	350	303	289	239	222	176	143	107	69	63	41	33	22	18	4	2	0
Placebo + CRT	347	303	291	257	241	200	172	121	75	56	31	28	18	15	3	2	0

NE, not estimable.

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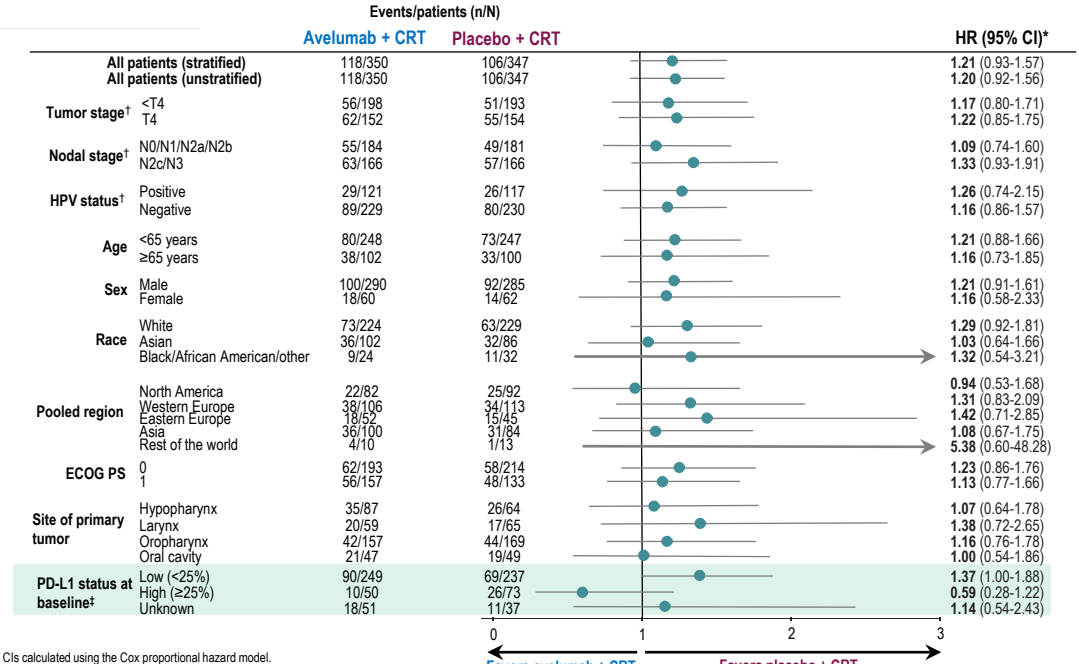
PFS in subgroups



* HR and associated 95% CIs calculated using the Cox proportional hazard model.

† Based on a randomization system.

‡ Exploratory analysis. High PD-L1: tumor samples with ≥25% tumor staining; Low PD-L1: <25% tumor staining. Assessed using the VENTANA PD-L1 (SP263) assay.

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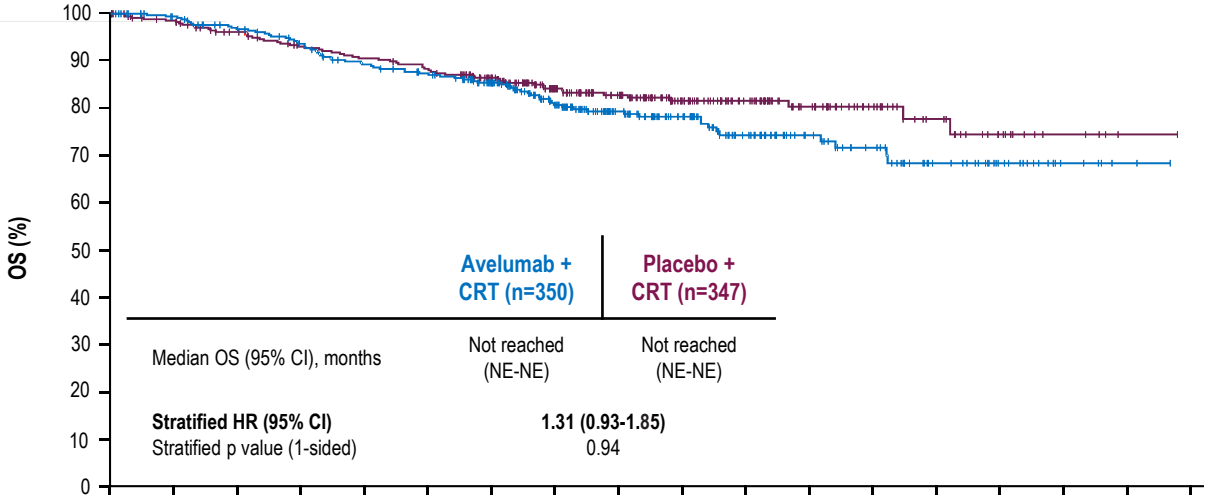
OS: overall patient population



At risk																		
Avelumab + CRT	350	336	319	303	284	273	244	190	148	118	82	59	47	29	18	6	2	0
Placebo + CRT	347	334	315	298	290	282	252	193	160	115	86	58	39	26	13	5	1	0

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Best overall response

	Avelumab + CRT (n=350)	Placebo + CRT (n=347)
Best overall response, %		
Complete response	48	51
Partial response	26	24
Stable disease	5	4
Non–complete response/non-PD	0	1
PD	6	6
Not evaluable*	15	14
ORR, %†	**74**	**75**
Odds ratio (95% CI)‡	0.95 (0.66-1.35)	
p value§	0.62	

- Median duration of response was not reached in either arm

Objective response assessed by investigator per RECIST 1.1.

* No postbaseline assessments due to early death (n=12 and n=16) or other reasons (n=36 and n=25), no adequate baseline assessment (n=1 and n=3), or all postbaseline assessments had overall response of not evaluable (n=3 and n=5) in the avelumab + CRT and placebo + CRT arms, respectively.

† Stratified analysis of proportion of patients with an objective response (complete response or partial response); stratified by tumor stage (<T4 vs T4) and nodal stage (N0/N1/N2a/N2b vs N2c/N3) per American Joint Committee on Cancer, 7th edition, and HPV status (positive vs negative) based on a randomization system. 95% CIs calculated using the Clopper-Pearson method.

‡ Odds ratio estimated using the Mantel-Haenszel method; exact 95% CIs calculated using the Clopper-Pearson method.

§ 1-sided, based on the Cochran-Mantel-Haenszel test.

Treatment-related AEs

	Avelumab + CRT (n=348)		Placebo + CRT (n=344)	
	All grades	Grade 3/4	All grades	Grade 3/4
Any TRAE, %*	**98**	**66/14**	**99**	**63/11**
Nausea	55	6	55	5
Anemia	53	12	50	13
Dry mouth	42	1	43	1
Mucosal inflammation	41	14	37	13
Radiation skin injury	39	5	40	5
Dysphagia	38	14	40	14
Weight decreased	35	4	43	6
Decreased appetite	33	7	33	5
Dysgeusia	30	0	34	1
Neutropenia	30	16	28	15
Fatigue	29	4	34	3
Vomiting	28	5	31	6
Stomatitis	27	7	28	8
Blood creatine increased	22	2	20	1
Hypomagnesemia	22	1	18	1
Neutrophil count decreased	18	11	17	9
Oropharyngeal pain	18	3	23	2
Infusion-related reaction, %	22	2	3	<1

TRAE, treatment-related adverse event.
* TRAEs of any grade occurring in ≥20% of patients or grade 3/4 in ≥10% patients. Two patients died in the avelumab arm (death and vascular rupture; n=1 each) and 1 patient in the placebo arm (acute respiratory failure).

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Safety overview

	Avelumab + CRT (n=348)	Placebo + CRT (n=344)
Serious TRAEs, %	36	32
TRAEs leading to discontinuation of avelumab/placebo, %	7	3
TRAEs leading to discontinuation of cisplatin, %	21	19
TRAEs leading to discontinuation of IMRT, %	<1	<1

Immune-related AEs

	Avelumab + CRT (n=348)		Placebo + CRT (n=344)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any irAE, %	**35**	**5**	**26**	**2**
Thyroid disorders	25	1	17	<1
Rash	10	1	8	<1
Colitis	1	<1	1	1
Hepatitis	1	1	<1	0
Pituitary dysfunction	1	0	<1	0
Pneumonitis	1	1	0	0
Other irAE	1	<1	1	0
Adrenal insufficiency	<1	0	1	<1
Nephritis and renal dysfunction	<1	<1	0	0

irAE, immune-related adverse event.

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Conclusions

- JAVELIN Head & Neck 100 is the first randomized, phase 3 study of an immune checkpoint inhibitor combined with CRT in any tumor type
- The trial was stopped due to futility: avelumab + CRT followed by avelumab maintenance did not significantly improve PFS compared with placebo + CRT followed by placebo maintenance
- CRT exposure was consistent between the avelumab and placebo arms; a higher proportion of grade 3/4 TRAEs occurred in the avelumab arm (80%) vs the placebo arm (74%)
- Based on an exploratory analysis, the observed HR for PFS numerically favored avelumab + CRT in PD-L1–high tumors

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Conclusions (cont'd)

- Given the strong rationale to investigate the addition of immune checkpoint inhibitors to definitive CRT in the LA SCCHN, the lack of improvement in PFS with the addition of avelumab to CRT was unexpected
  - Analysis is ongoing to further understand these results
- These findings will help to inform the design of ongoing and future trials combining immune checkpoint inhibitors and radiotherapy ± chemotherapy
  - Further studies could investigate sequential vs concurrent treatments, fractionated radiotherapy plus anti–PD-1/PD-L1 therapies, or biomarker-determined subgroups

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