Head and Neck Cancer Updates
October 2020
California Cancer Consortium

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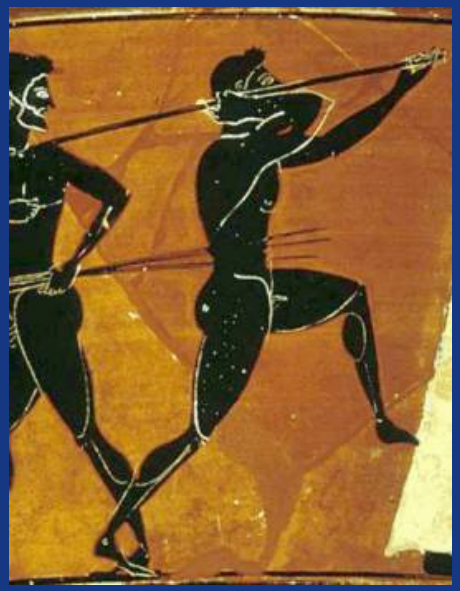
Stanford Cancer Institute

The Anticipated Breakthrough That Fell Short: JAVELIN



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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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* Study co-chairs

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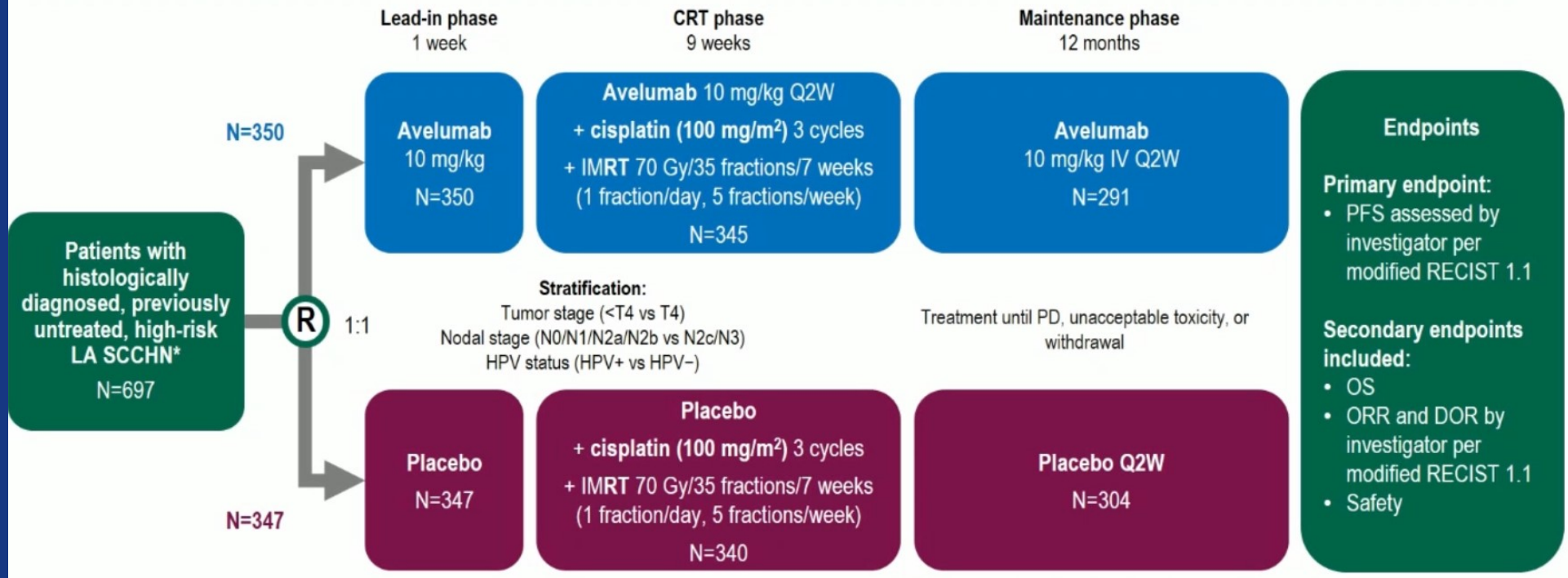
JAVELIN Head & Neck 100: study design

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).

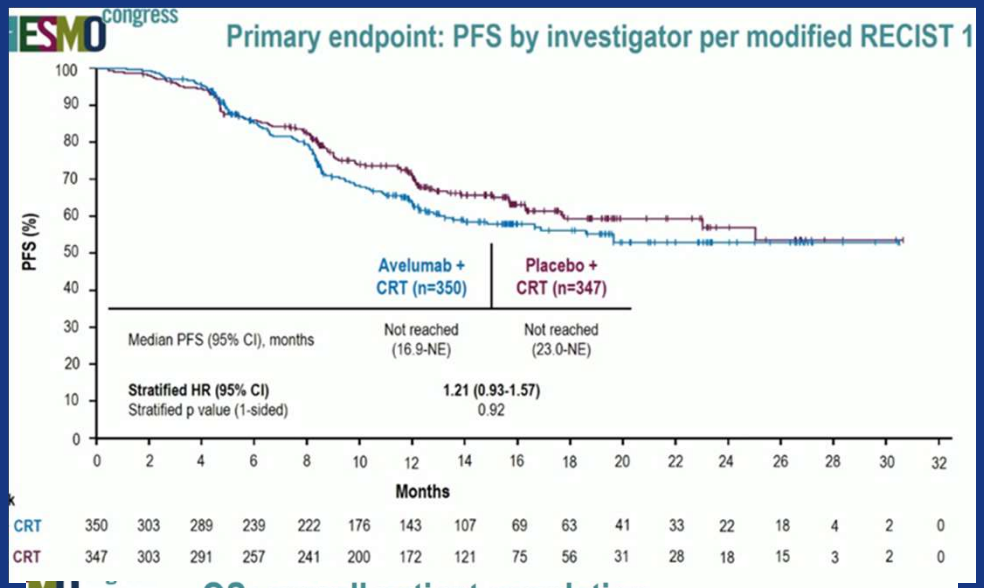
Baseline characteristics

	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

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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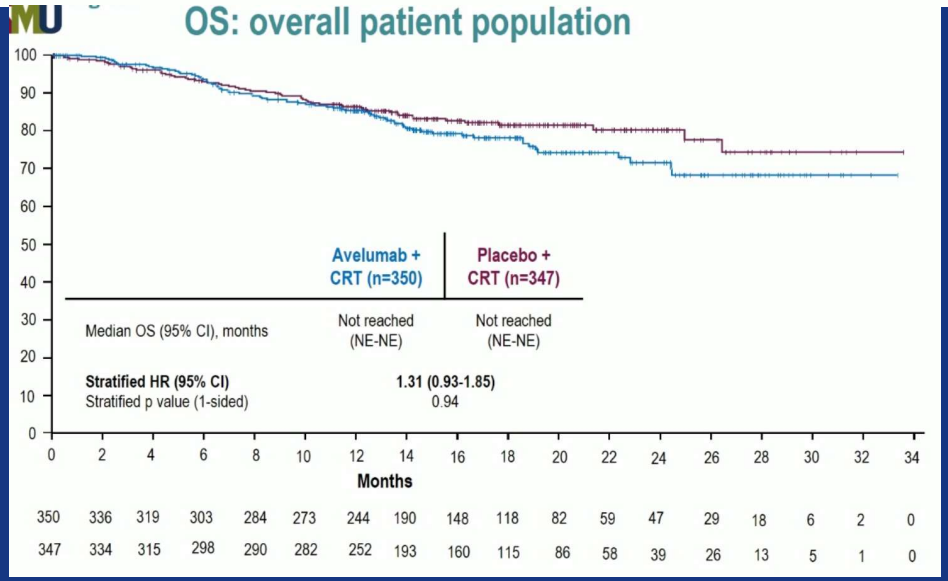
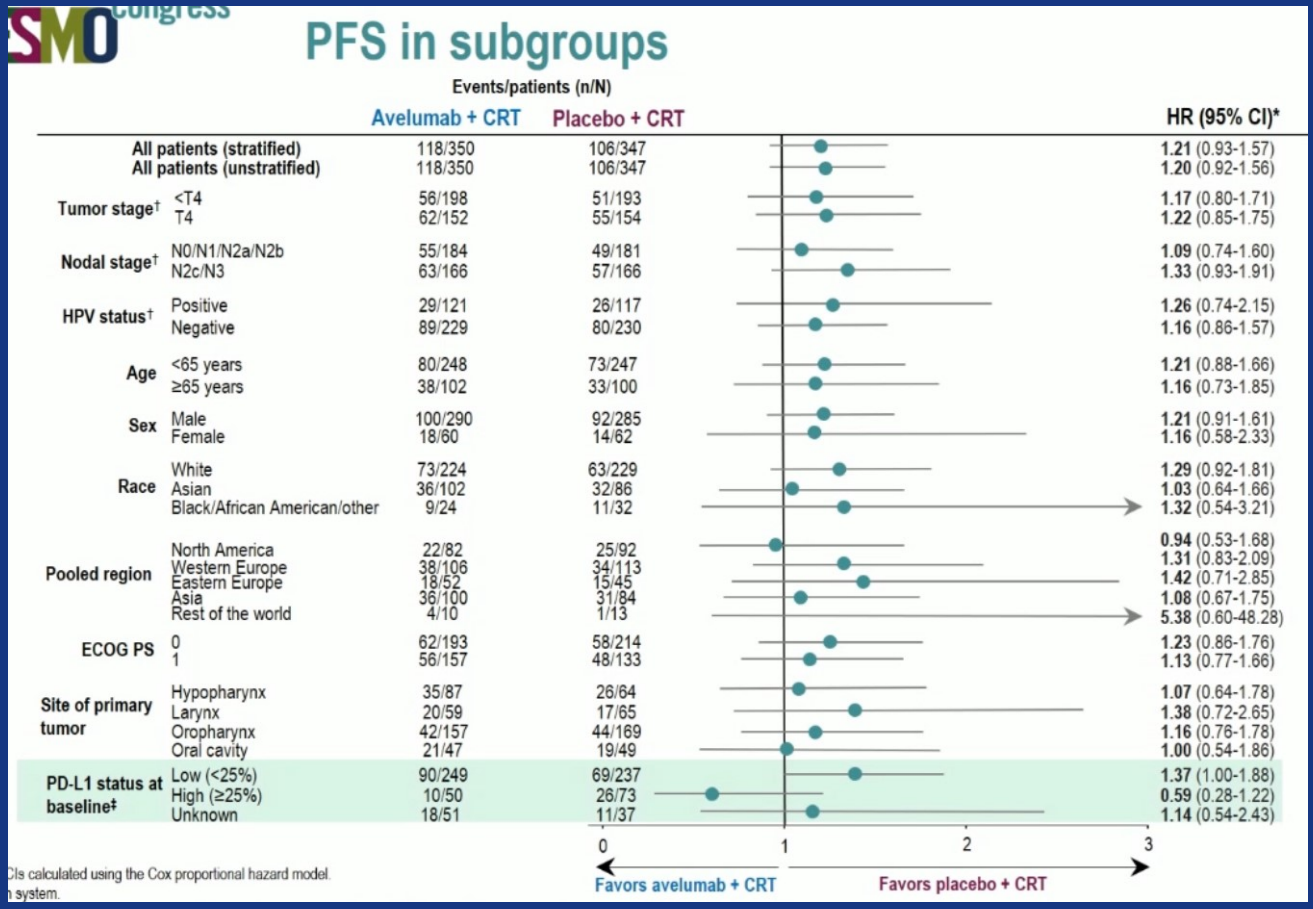
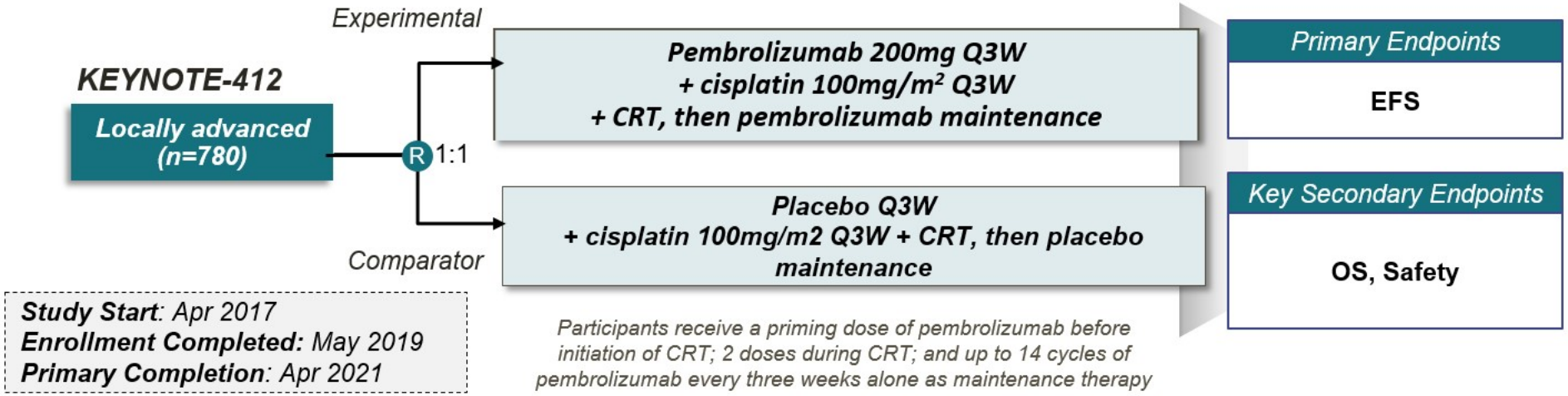
Primary endpoint: PFS by investigator per modified RECIST 1
PFS (%)
Avelumab + CRT (n=350)
Placebo + CRT (n=347)
Median PFS (95% CI), months
Not reached (16.9-NE)
Not reached (23.0-NE)
Stratified HR (95% CI)
1.21 (0.93-1.57)
Stratified p value (1-sided)
0.92
Months
CRT 350 303 289 239 222 176 143 107 69 63 41 33 22 18 4 2 0
CRT 347 303 291 257 241 200 172 121 75 56 31 28 18 15 3 2 0


OS: overall patient population
Avelumab + CRT (n=350)
Placebo + CRT (n=347)
Median OS (95% CI), months
Not reached (NE-NE)
Not reached (NE-NE)
Stratified HR (95% CI)
1.31 (0.93-1.85)
Stratified p value (1-sided)
0.94
Months
350 336 319 303 284 273 244 190 148 118 82 59 47 29 18 6 2 0
347 334 315 298 290 282 252 193 160 115 86 58 39 26 13 5 1 0



My thoughts: SNAP, should have selected for high PD-L1. now we have to do it over in this group. We still search for a therapy with differential outcomes based upon HPV.

Post Javelin Landscape 1



***Study Start**: Apr 2017*
***Enrollment Completed:** May 2019*
***Primary Completion**: Apr 2021*

Participants receive a priming dose of pembrolizumab before initiation of CRT; 2 doses during CRT; and up to 14 cycles of pembrolizumab every three weeks alone as maintenance therapy

Key Inclusion Criteria	Key Exclusion Criteria
• >18 years • new diagnosis of oropharyngeal p16 positive, oropharyngeal p16 negative, or larynx/hypopharynx/oral cavity (independent of p16) squamous cell carcinoma • Participants with oral cavity tumors need to have unresectable disease • Eligible for definitive CRT and not considered for primary surgery based on investigator decision • Tissue evaluable for PD-L1 expression	• Has cancer outside of the oropharynx, larynx, and hypopharynx or oral cavity, such as nasopharyngeal, sinus, other para-nasal, or other unknown primary head and neck cancer • Participants with multiple synchronous tumors are not eligible for the study

Post Javelin Landscape 2

NCT03452137

IMvoke010[1]

LA; Adj (n=400)

R 1:1

Experimental

Atezolizumab 1200mg Q3W, as adjuvant therapy after definitive local therapy

Comparator

Placebo Q3W

***Study Start**: Apr 2018*
***Enrollment Completed:** Sept 2020*
***Primary Completion**: Mar 2021*

- Stratification factors: CR vs. PR or SD; HPV status; type of local therapy received
- Participants receive atezolizumab or placebo for 16 cycles, or up to 1 year (whichever occurs first)

Primary Endpoints

EFS (independent review), OS

Key Secondary Endpoints

EFS (Investigator review), Safety, QoL

Key Inclusion Criteria	Key Exclusion Criteria
• >18 years • Completed definitive local therapy • CR/ PR/ SD to definitive local therapy documented by CT with contrast or MRI with contract to head and neck region done ≥ 8 weeks after completion of definitive local therapy and within 28 days prior to initiation of study drug.	• Patients who have received surgery alone or radiotherapy alone as definitive local therapy • Squamous cell carcinoma of the nasopharynx or paranasal sinuses or non-squamous histology

Most Intriguing/Alarming Data In 2020

Evaluation of the correlation between antibiotic use and survival in patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) treated with immune checkpoint inhibitors (ICIs)

Paz J. Vellanki[1], Shanthi Marur[1], Pradeep Bandaru[2], Pallavi Mishra-Kalyani[1], Kunthel By[1], Andrew Girvin[2], Somak Chatterjee[1], Pourab Roy[1], Harpreet Singh[1], Patricia Keegan[1], Erin A. Larkins[1], Frank Cross[1], Richard Pazdur[1], Marc R. Theoret[1]

[1]U.S. Food and Drug Administration, Silver Spring, MD; [2]Palantir Technologies, Washington, DC

1

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ICI Approvals in R/M HNSCC

Therapy	Indication	Approval Endpoint (Year)
Pembrolizumab	2nd-line platinum-refractory	ORR (2016)* OS (2019)
Nivolumab	2nd-line platinum-refractory	OS (2016)
Pembrolizumab	Untreated R/M HNSCC with CPS ≥1	OS (2019)
Pembrolizumab + Platinum + 5-FU	Untreated R/M HNSCC	OS (2019)

ORR: objective response rate
OS: overall survival
CPS: combined positive score

* Accelerated Approval

- Pooled randomized trial data evaluating treatment of R/M HNSCC submitted to FDA between 2014 – 2019

- 3 randomized trials identified
  - Patients previously untreated for R/M HNSCC, or
  - After disease progression on platinum-based therapy

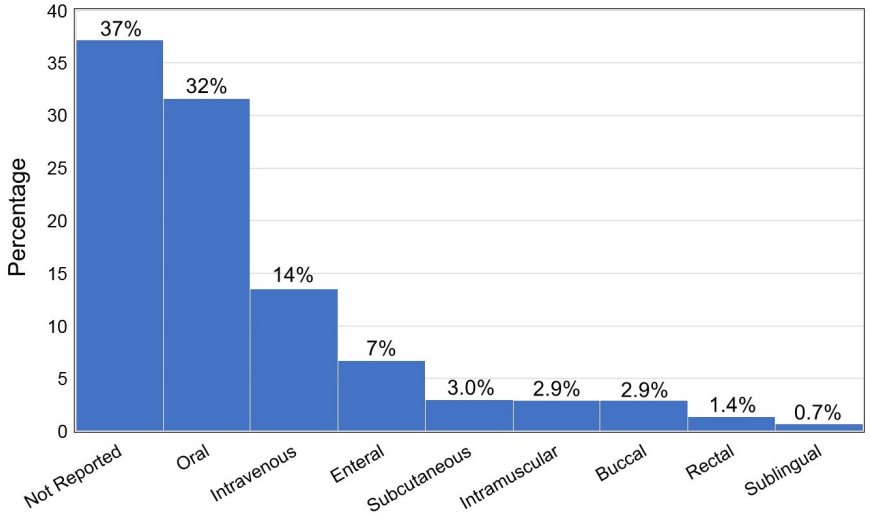
- 1685 total patients:
  - 1037 treated with ICIs (single-agent or with chemotherapy)
  - 648 treated with comparator therapies (chemotherapy and/or cetuximab)

- Identified patients treated with Abx based on review of concomitant medications received during the study period
  - Used ChEMBL chemical database for initial review
  - Manually curated list with second review
  - Non-systemic Abx excluded

- Abx+ cohort: Abx ± 30 days of initiation of anti-cancer therapy

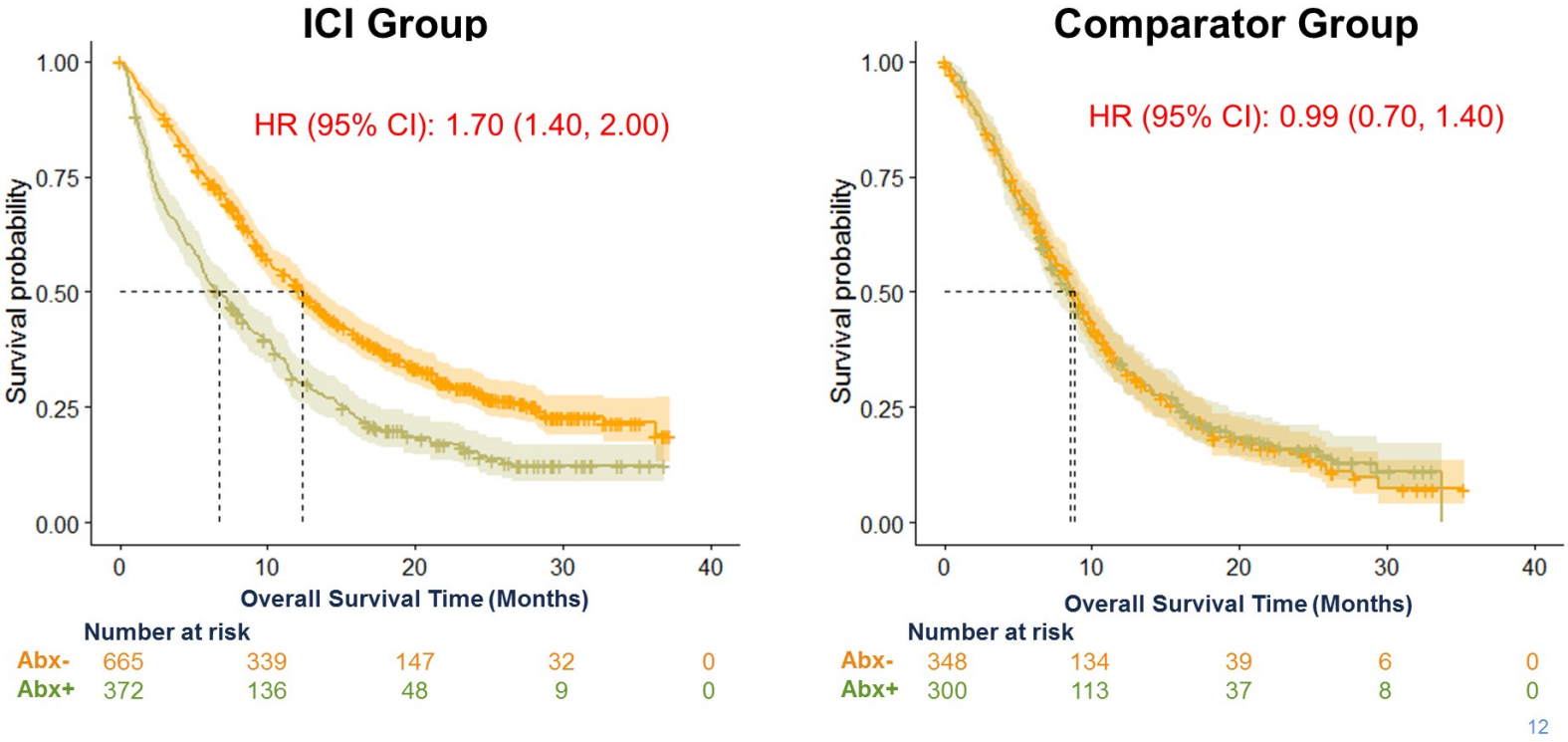
- Abx- cohort: Abx outside 30-day window or no Abx exposure at all

Abx Routes of Administration and Data Completeness



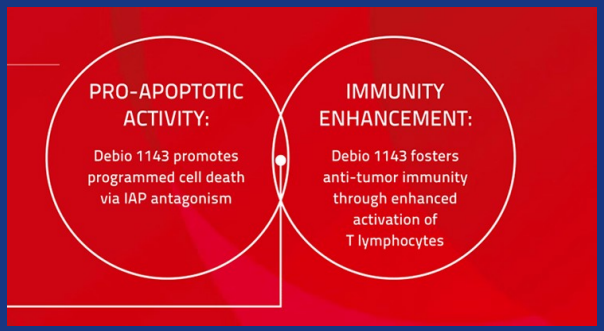
- 37% of Abx with missing routes of administration (Not Reported/ Unknown)
- Topical, ophthalmic, otic, nasal, inhalational, and intra-vaginal Abx excluded

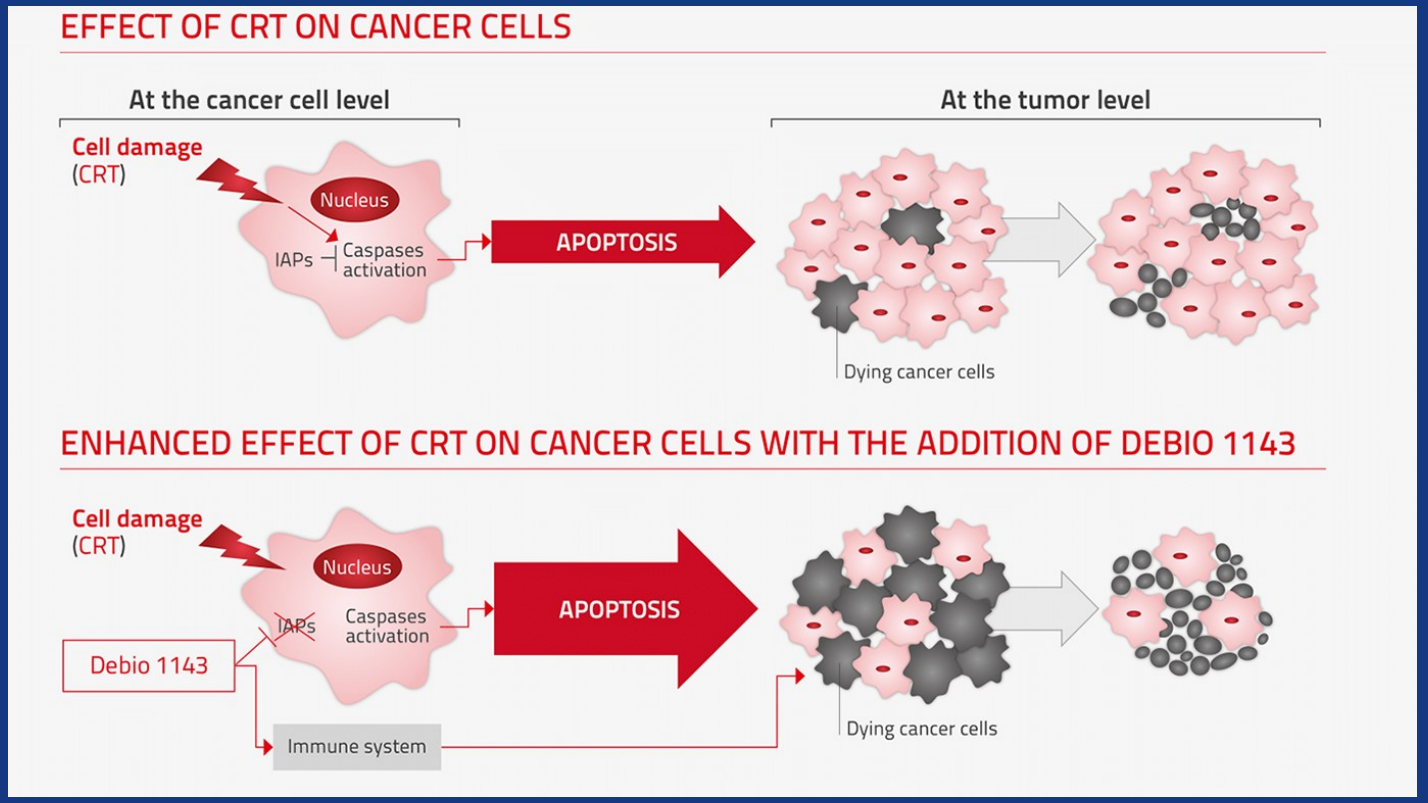
Overall Survival Results



My thoughts: This difference is HUGE.
How will we prospectively test it?
What other datasets to confirm or refute?
RESPECT THE MICROBIOME

Good ‘Ole Small Molecules Win The Year: Debio1143





https://www.debiopharm.com/drug-development/publications/debio-1143-mode-of-action-a-broad-chemo-radio-and-immuno-therapy-sensitizer/

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STUDY DESIGN

Double-blind, placebo-controlled, Randomized Phase II

Part A

N=14

Dose escalation Phase I*

Primary endpoint

Definition of MTD/RP2D

RP2D

200mg QD

Part B

N=96 (ITT)

R

1:1

Xevinapant + CRT n=48

Placebo + CRT n=47

- **Xevinapant/Placebo**
  D1- D14 every 21 days for 3 cycles
- **CDDP**
  100mg/m² every 21 days, for 3 cycles
- **IMRT**
  2Gy 5d/week over 7 weeks (total dose 70Gy)

Stratified by

- N0-N1 vs N2-N3
- Primary tumor site (OPC vs non-OPC)
  - If OPC, by HPV/p16 status

Primary endpoint

- Locoregional control rate at 18 months after CRT (Δ>20% between arms with 0.8 power at 0.2 significance level)

Main secondary endpoints

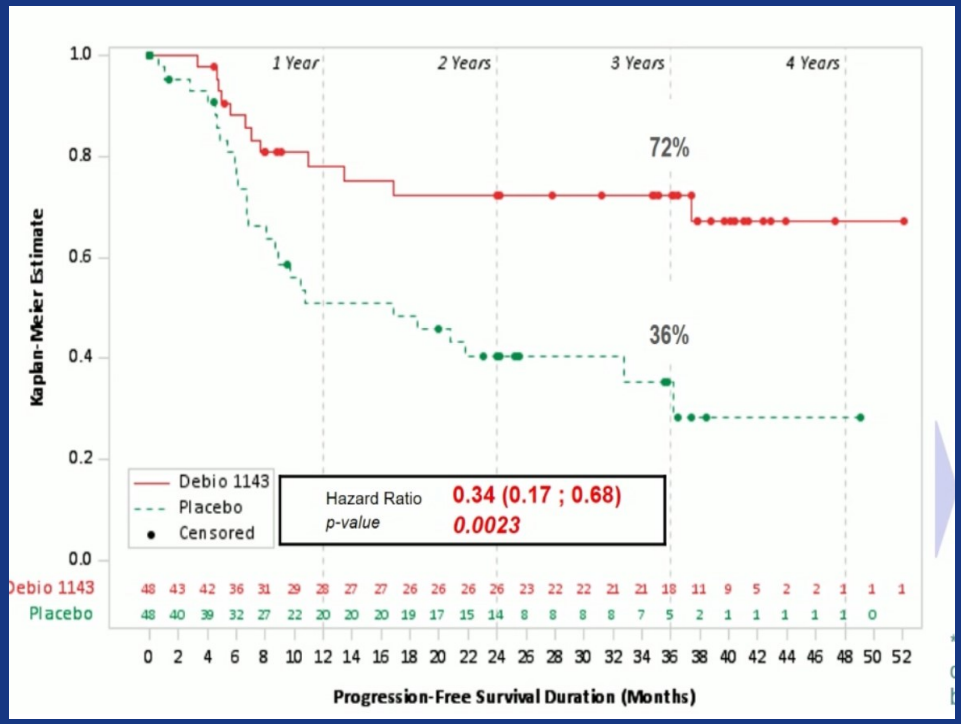
- PFS
- Duration of LRC
- Overall survival

Main inclusion criteria:

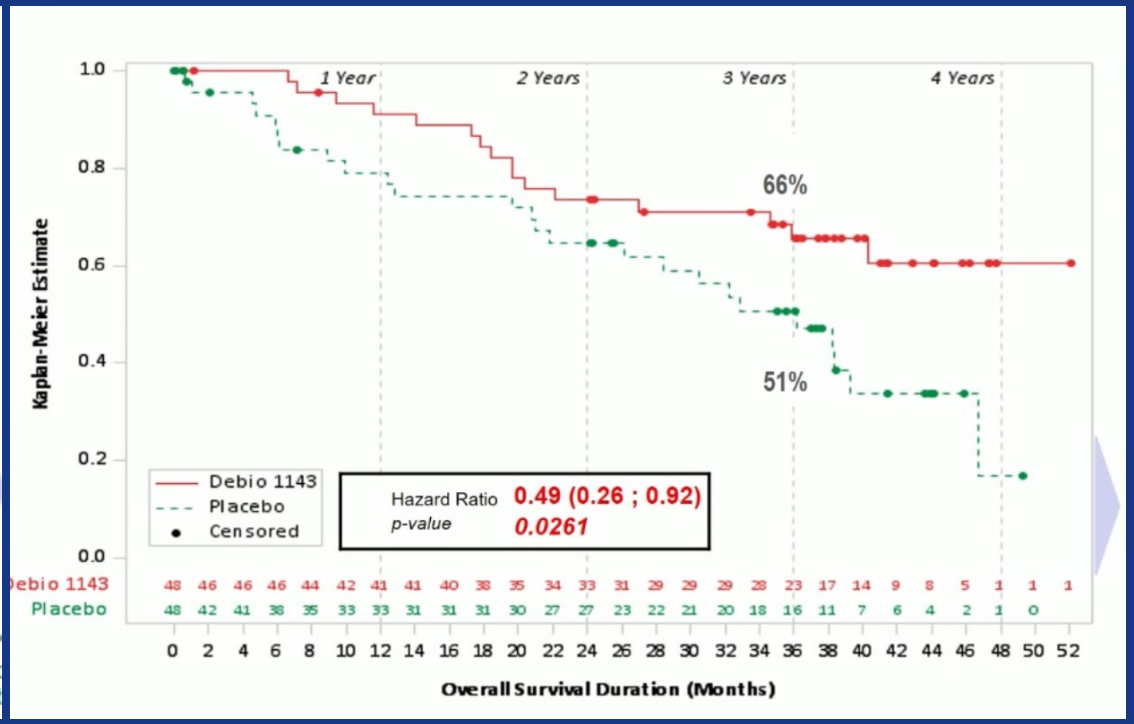
- Previously untreated, unresectable stage III, IVA & IVB LA-SCCHN
- Oral cavity
- Hypopharynx
- Larynx
- Oropharynx-HPV/p16 both negative or positive

ClinicalTrials.gov Identifier: NCT02022098
* Tao et al. ESTRO 2016

PFS


1 Year
2 Years
3 Years
4 Years
72%
36%
Kaplan-Meier Estimate
Debio 1143
Placebo
Censored
Hazard Ratio 0.34 (0.17 ; 0.68)
p-value 0.0023
Progression-Free Survival Duration (Months)

OS


1 Year
2 Years
3 Years
4 Years
66%
51%
Kaplan-Meier Estimate
Debio 1143
Placebo
Censored
Hazard Ratio 0.49 (0.26 ; 0.92)
p-value 0.0261
Overall Survival Duration (Months)

Shall We Stop Talking About Drugs?

JAMA Oncology | Original Investigation

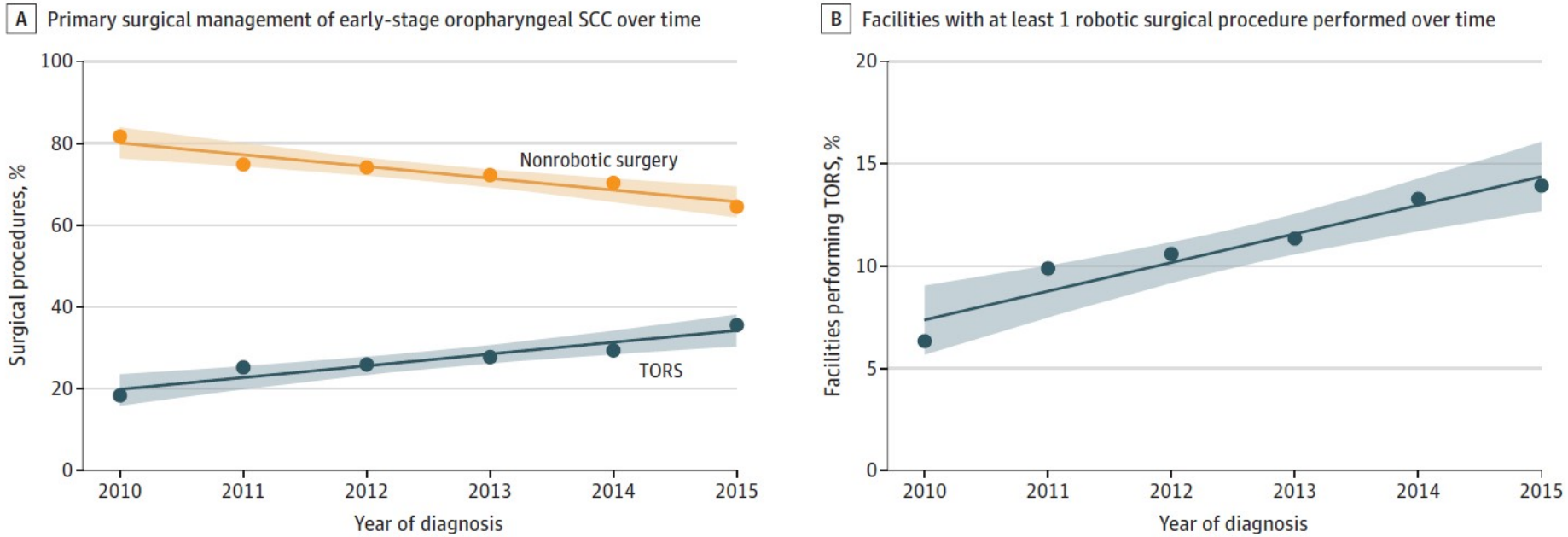
Comparison of Survival After Transoral Robotic Surgery vs Nonrobotic Surgery in Patients With Early-Stage Oropharyngeal Squamous Cell Carcinoma

Anthony T. Nguyen, MD, PhD; Michael Luu, MPH; Jon Mallen-St Clair, MD, PhD; Alain C. Mita, MD; Kevin S. Scher, MD; Diana J. Lu, MD; Stephen L. Shiao, MD, PhD; Allen S. Ho, MD; Zachary S. Zumsteg, MD

JAMA Oncol. 2020;6(10):1555-1562. doi:10.1001/jamaoncol.2020.3172
Published online August 20, 2020.

TORS Continues To Increase

Figure 1. Increasing Use of Transoral Robotic Surgery (TORS) Between 2010 and 2015

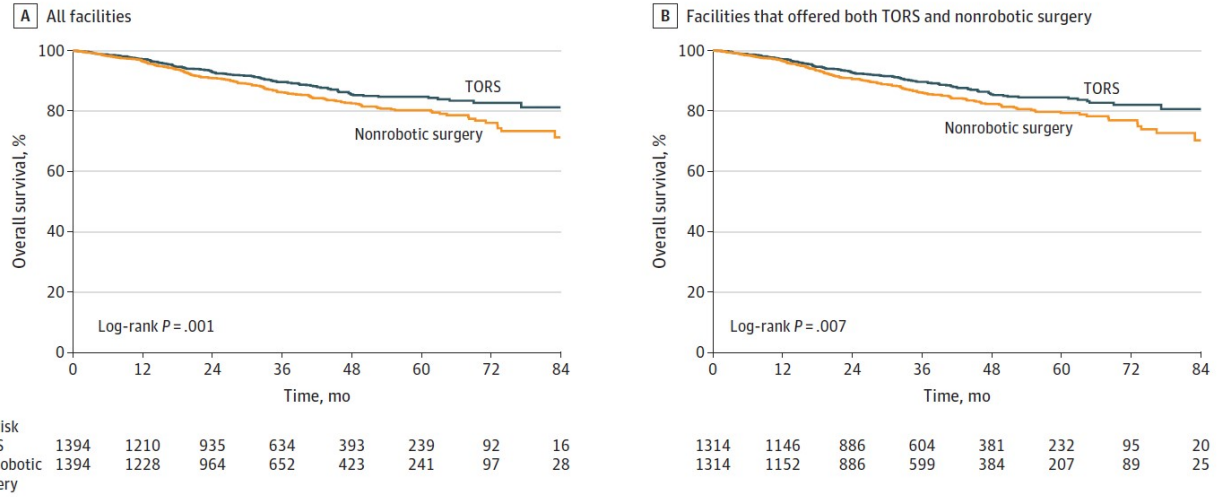


And that is a good thing…

Table 2. Multivariable Cox Proportional Hazards Regression Analysis of Overall Survival in Patients With Early-Stage Oropharyngeal SCC Undergoing Primary Surgery, Using Key Covariates

	Multivariable survival analysis	
Covariate	HR (95% CI)	*P* value
Surgical approach		
Nonrobotic surgery	1.00 [Reference]	NA
TORS	0.74 (0.61-0.90)	.002
Age[a]	1.34 (1.18-1.51)	<.001
Anatomic site		
Base of tongue	1.00 [Reference]	NA
Tonsil	0.85 (0.70-1.03)	.10
Other	0.92 (0.66-1.28)	.62
HPV status		
Negative	1.00 [Reference]	NA
Positive	0.35 (0.29-0.42)	<.001

Figure 2. Overall Survival for Patients With Early-Stage Oropharyngeal SCC Undergoing Either Transoral Robotic Surgery (TORS) or Nonrobotic Surgery in Propensity Score–Matched Cohorts



Kaplan-Meier estimates of overall survival of patients from all facilities (A) and from facilities that offered both TORS and nonrobotic surgery (B). SCC indicates squamous cell carcinoma.

Or is it just that the TORS surgeons are better surgeons?