Driving Progress in HNSCC: Integrating Immunotherapy Across the Disease Continuum

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Learning Objectives

- Identify patients with HNSCC most likely to benefit from immunotherapy using predictive and/or prognostic biomarkers
- Design individualized treatment plans leveraging immunotherapy for patients with recurrent or metastatic HNSCC based on approvals, clinical data, guidelines, and patient factors
- Evaluate emerging evidence for novel systemic therapies and their potential application to clinical practice for HNSCC
- Formulate evidence-based strategies for monitoring and managing adverse events related to immunotherapy-based treatments for patients with HNSCC

Leveraging Immunotherapy to Optimize Treatment of Recurrent/Metastatic HNSCC

Systemic Therapy Recommendations for Nonnasopharyngeal HNSCC

- Recurrent unresectable or metastatic disease (with no surgery or RT option)

First Line

- **Pembrolizumab/platinum (cisplatin or carboplatin)/ 5-fluorouracil**
- **Pembrolizumab (for tumors that express PD-L1 with CPS ≥1)**

Subsequent line (if not previously used and if disease progression on or after platinum therapy)

- Nivolumab
- Pembrolizumab

Other Recommendations

Combination regimens

- Cetuximab/platinum/5-fluorouracil
- Cisplatin/cetuximab
- Platinum/taxane
- Cisplatin/5-fluorouracil
- Platinum/taxane/cetuximab
- Pembrolizumab/platinum/taxane

Single agents

- Platinum (cisplatin or carboplatin)
- Taxane (paclitaxel or docetaxel)
- Antimetabolite (5-fluorouracil or methotrexate or capecitabine)
- Cetuximab
- Afatinib (subsequent-line only, if PD on or after platinum therapy)

Certain Circumstances

Squamous cell carcinoma

- Cetuximab/nivolumab
- Cetuximab/pembrolizumab

Select sinus cancers

- Platinum/etoposide
- Cyclophosphamide/doxorubicin/ vincristine

Other recommendations

- Pembrolizumab (for MSI-H, dMMR, TMB-H tumors)
- Taxane/cetuximab
- Cisplatin/pemetrexed (for PS 0-1)
- Gemcitabine/paclitaxel
- Nivolumab/ipilimumab (CPS ≥20 and 1L only)
- Erdafitinib (for *FGFR* mutations or fusions and PD with ≥1 prior line of systemic therapy)
- T-DXd (for HER2+ solid tumors; subsequent line only with no satisfactory alternative treatment options)

NCCN. Clinical practice guidelines in oncology: head and neck cancers. v.2.2025. nccn.org.

KEYNOTE-012: Overall Response by PD-L1 Status

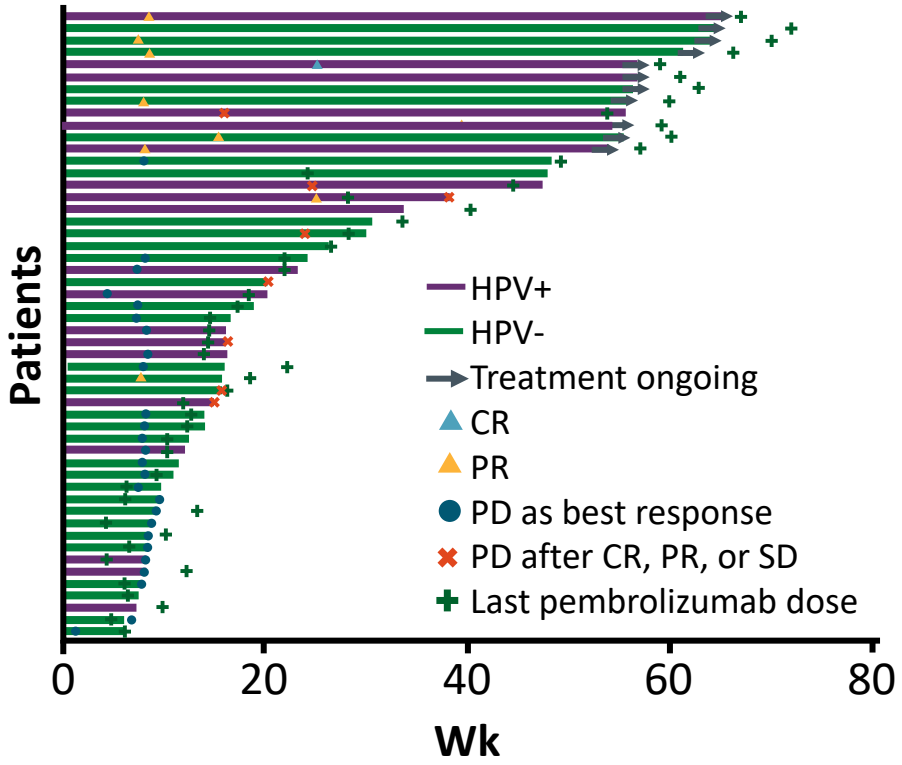
- Phase Ib trial of pembrolizumab in R/M HNSCC: response by PD-L1 expression

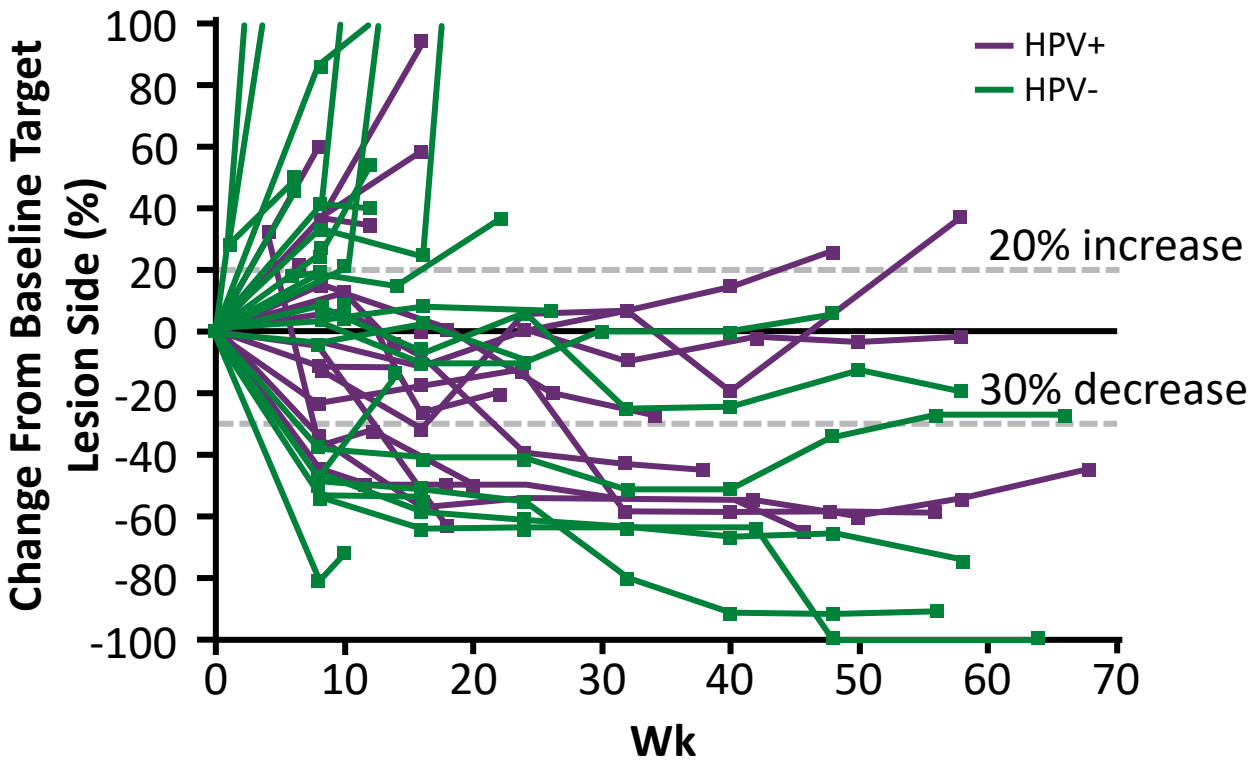
PD-L1 Scoring	PD-L1 Status	Non-Responders, n	Responders, n	ORR, % (95% CI)	*P* Value
TPS (tumor cells)	PD-L1 positive	102	22	18	.461
	PD-L1 negative	53	12	19	
CPS (tumor and inflammatory cells)	PD-L1 positive	120	32	22	.021
	PD-L1 negative	34	2	4	

Chow. JCO. 2016;34:3838.

KEYNOTE-012: Phase Ib Trial of Pembrolizumab in Recurrent or Metastatic HNSCC

- 60 patients with PD-L1–positive HNSCC
  - 23 (38%) HPV positive and 37 (62%) HPV negative

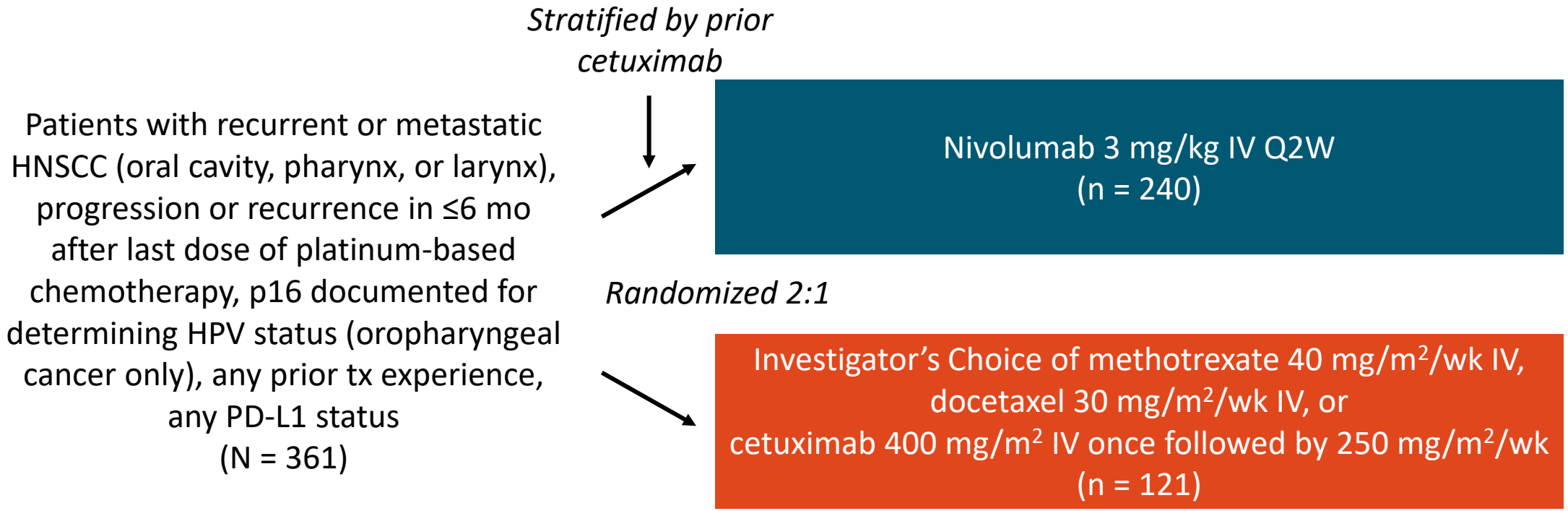




Seiwert. Lancet Oncol. 2016;17:956.

CheckMate 141: Nivolumab in Recurrent/Metastatic HNSCC After Platinum Therapy

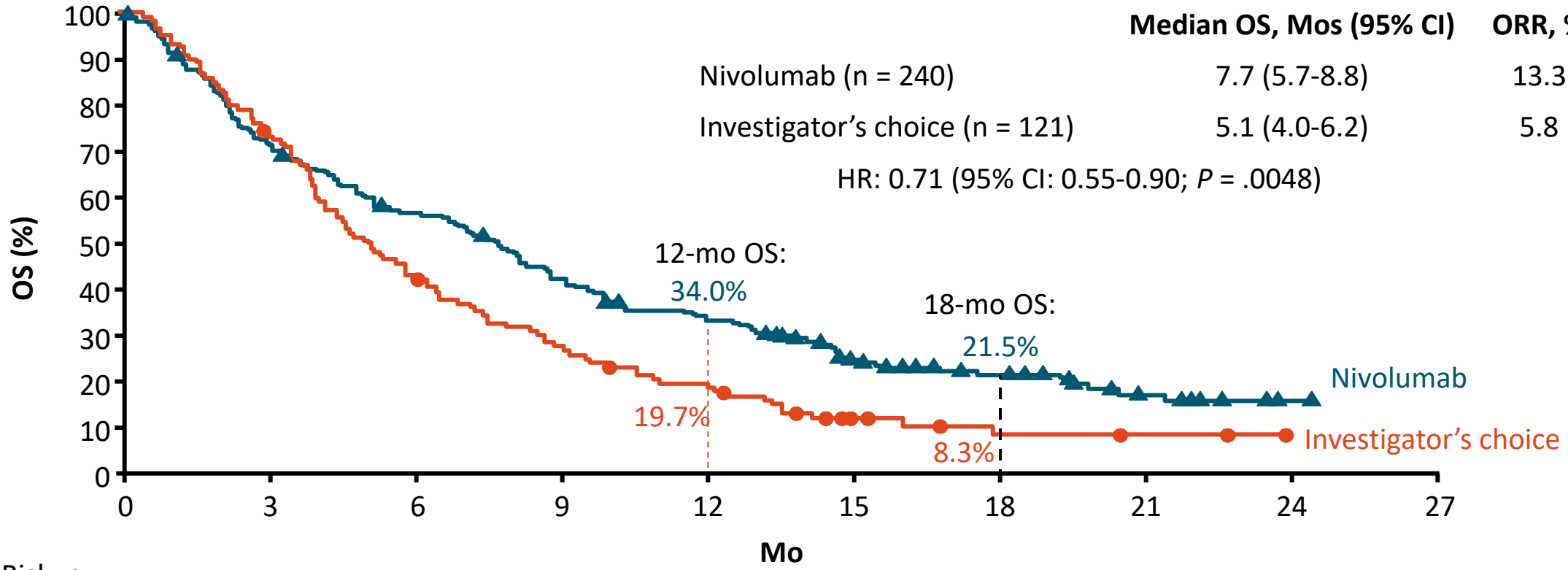
- Randomized, open-label phase III trial



- Primary endpoint: OS
- Other endpoints: PFS, ORR, DoR, safety, biomarkers, QoL

Ferris. NEJM. 2016;375:1856.

CheckMate 141: OS for Nivolumab vs Investigator's Choice in Recurrent/Metastatic HNSCC



	Median OS, Mos (95% CI)	ORR, %
Nivolumab (n = 240)	7.7 (5.7-8.8)	13.3
Investigator's choice (n = 121)	5.1 (4.0-6.2)	5.8

HR: 0.71 (95% CI: 0.55-0.90; *P* = .0048)

Patients at Risk, n

Nivo	240	169	132	98	76	45	27	12	3	0
IC	121	88	51	32	22	9	4	3	0	0

Median follow-up: 11.4 mo

Ferris. Oral Oncol. 2018;81:45.

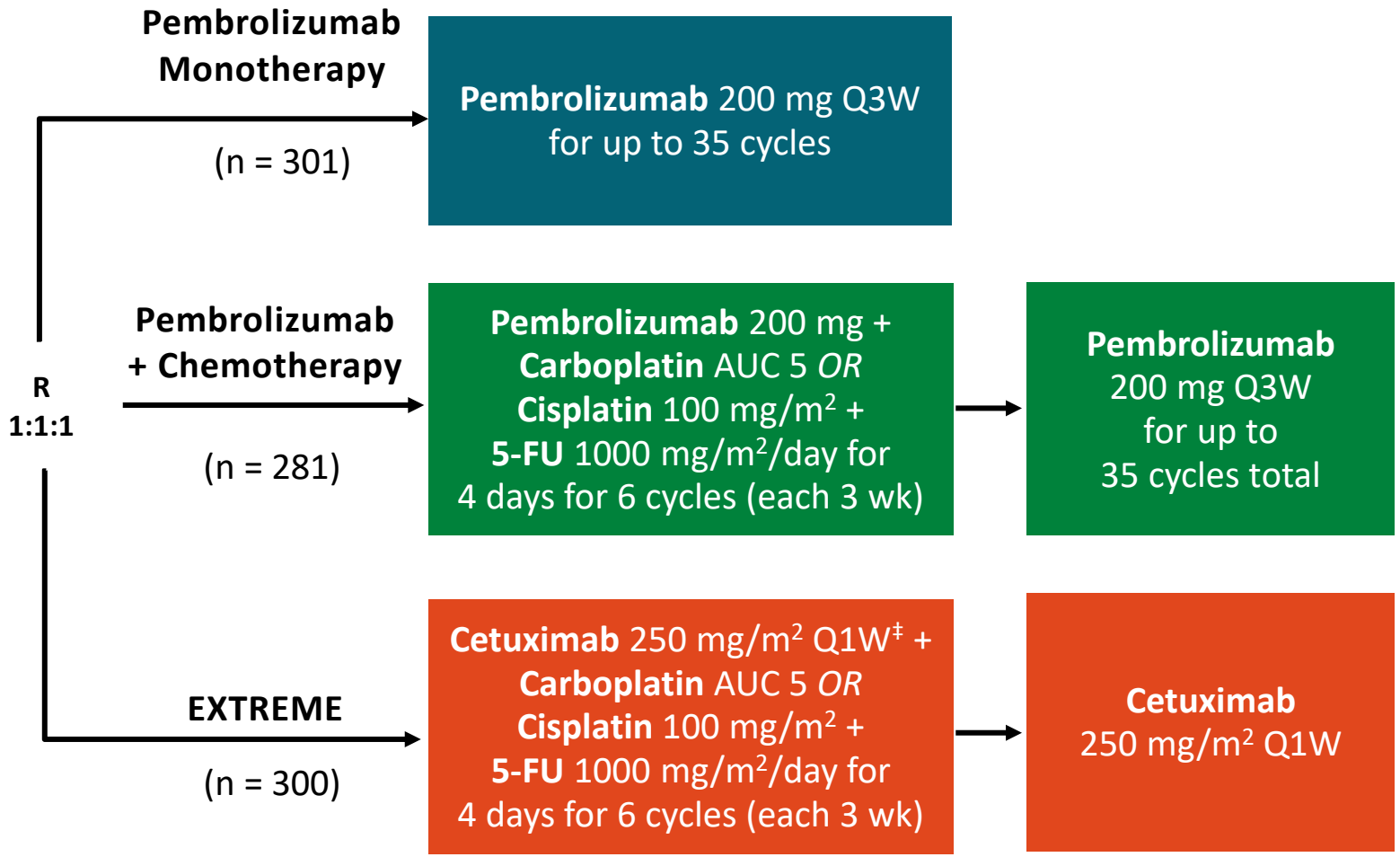
KEYNOTE-048: Pembrolizumab ± Chemotherapy vs EXTREME in R/M HNSCC

Key Eligibility Criteria

- SCC of the oropharynx, oral cavity, hypopharynx, or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment*
- Known p16 status in oropharynx†

Stratification Factors

- PD-L1 expression* (TPS ≥50% vs <50%)
- p16 status in oropharynx (positive vs negative)
- ECOG PS (0 vs 1)



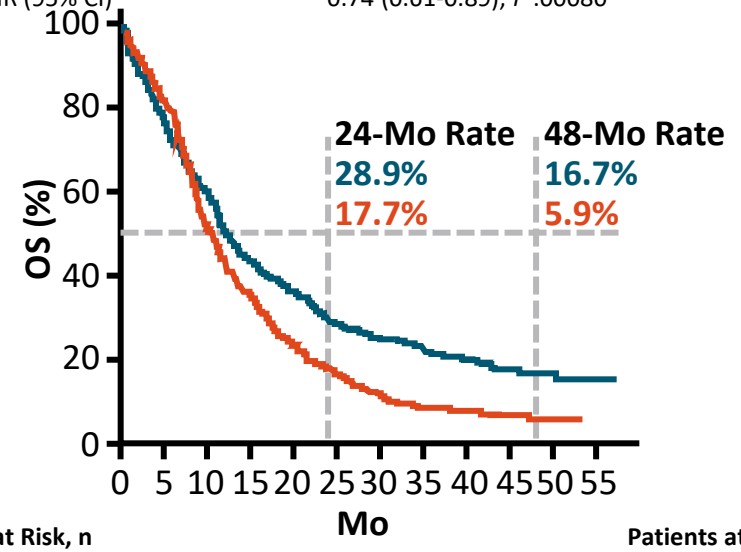
*Assessed using PD-L1 IHC 22C3 *pharmDx* assay (Agilent). †Assessed using *CINtec* p16 histology assay (*Ventana*); cut point for positivity: 70%. ‡Following loading dose of 400 mg/m².

Burtness. Lancet. 2019;394:1915.

KEYNOTE-048: OS for Pembrolizumab Alone vs Cetuximab/Chemotherapy

CPS ≥1

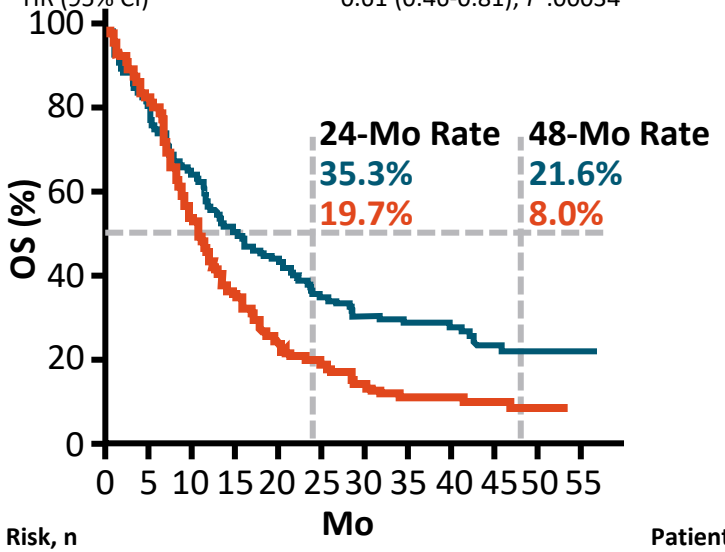
CPS ≥1	Pembrolizumab	Cetuximab/ Chemotherapy
No. of events/ no. of patients (%)	210/257 (81.7)	237/255 (92.9)
Median OS, mo (95% CI)	12.3 (10.8-14.8)	10.4 (9.0-11.7)
HR (95% CI)	0.74 (0.61-0.89); *P* .00080	



Patients at Risk, n												
Pembrolizumab	257	197	152	111	92	71	62	55	40	22	12	2
Cetuximab/chemo	255	207	132	90	60	42	29	22	16	10	6	0

CPS ≥20

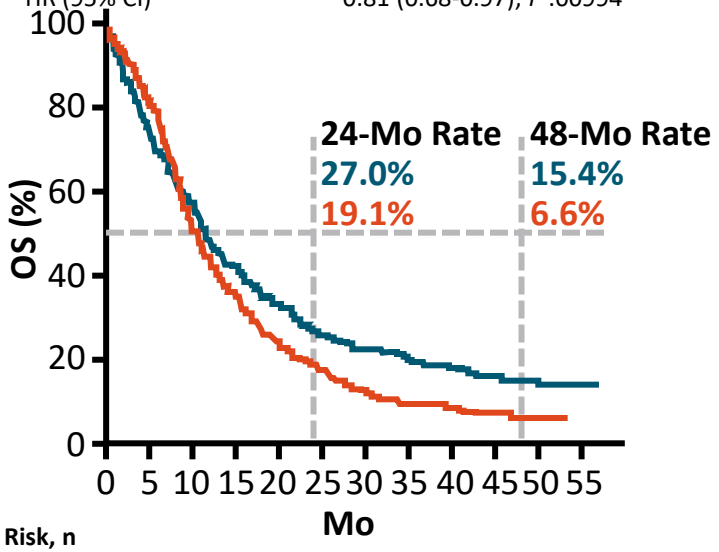
CPS ≥20	Pembrolizumab	Cetuximab/ Chemotherapy
No. of events/ no. of patients (%)	101/133 (75.9)	111/122 (91.0)
Median OS, mo (95% CI)	14.9 (11.5-20.6)	10.8 (8.8-12.8)
HR (95% CI)	0.61 (0.46-0.81); *P* .00034	



Patients at Risk, n												
Pembrolizumab	133	107	85	66	58	45	39	36	30	17	9	2
Cetuximab/chemo	122	100	65	43	29	23	17	13	11	7	4	0

Entire Population

Total	Pembrolizumab	Cetuximab/ Chemotherapy
No. of events/ no. of patients (%)	250/302 (83.1)	276/300 (92.0)
Median OS, mo (95% CI)	11.5 (10.3-13.5)	10.7 (9.3-12.1)
HR (95% CI)	0.81 (0.68-0.97); *P* .00994	



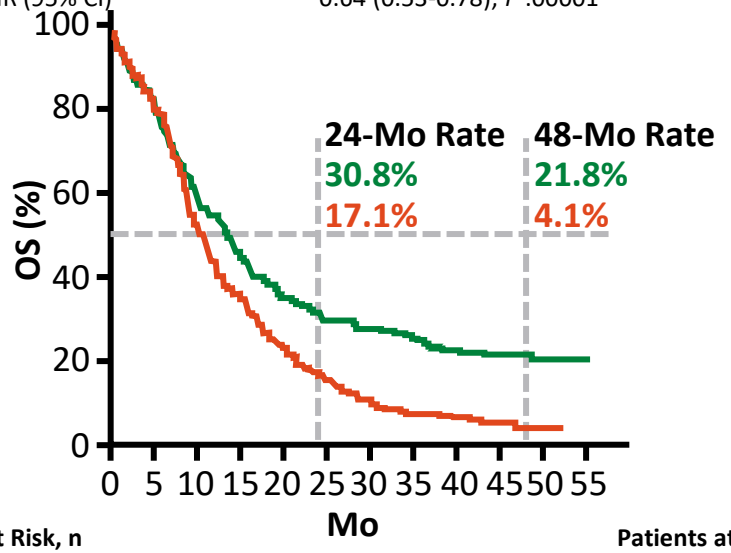
Patients at Risk, n												
Pembrolizumab	301	226	172	126	100	76	66	58	43	24	13	2
Cetuximab/chemo	300	245	159	108	73	53	37	29	22	13	7	0

Harrington. JCO. 2022;41:790.

KEYNOTE-048: OS for Pembrolizumab/Chemotherapy vs Cetuximab/Chemotherapy

CPS ≥1

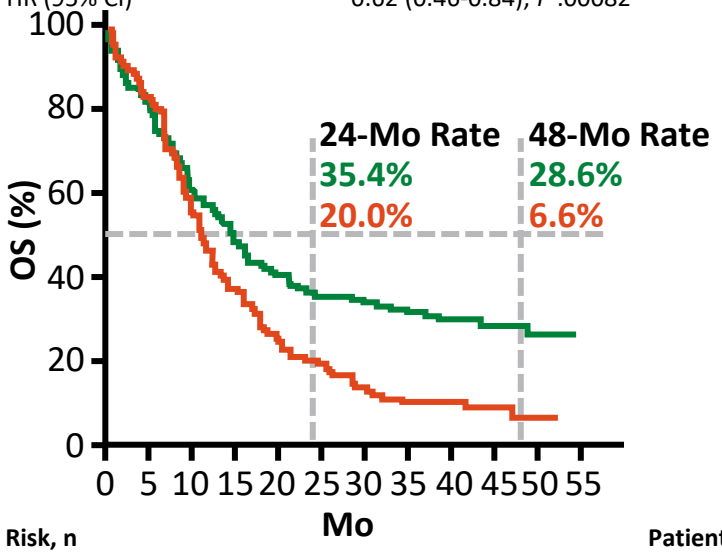
CPS ≥1	Pembrolizumab/ Chemotherapy	Cetuximab/ Chemotherapy
No. of events/ no. of patients (%)	189/242 (78.1)	221/235 (94.0)
Median OS, mo (95% CI)	13.6 (10.7-15.5)	10.6 (9.1-11.7)
HR (95% CI)	0.64 (0.53-0.78); *P* .00001	



Patients at Risk, n												
Pembrolizumab/ chemo	242	197	144	109	84	71	66	61	48	29	9	1
Cetuximab/chemo	235	191	123	84	55	37	25	18	12	6	2	0

CPS ≥20

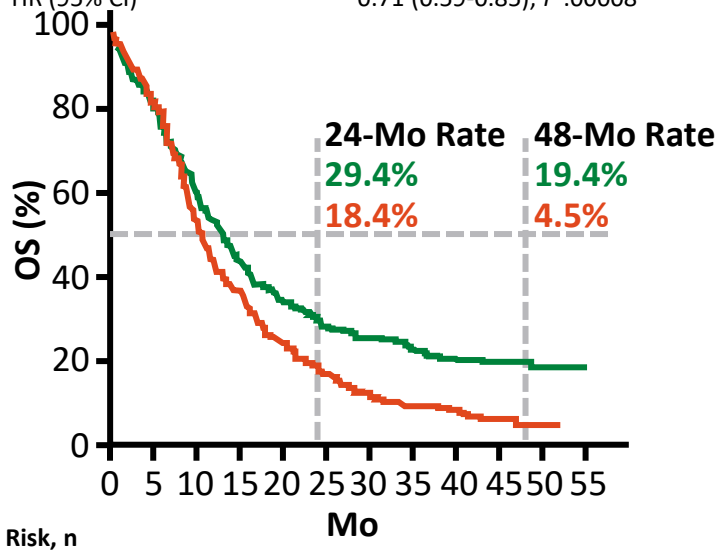
CPS ≥20	Pembrolizumab/ Chemotherapy	Cetuximab/ Chemotherapy
No. of events/ no. of patients (%)	90/126 (71.4)	101/110 (91.8)
Median OS, mo (95% CI)	14.7 (10.3-19.3)	11.1 (9.2-13.0)
HR (95% CI)	0.62 (0.46-0.84); *P* .00082	



Patients at Risk, n												
Pembrolizumab/ chemo	126	102	77	60	50	44	42	39	33	22	7	0
Cetuximab/chemo	110	91	61	41	27	21	15	11	9	5	2	0

Entire Population

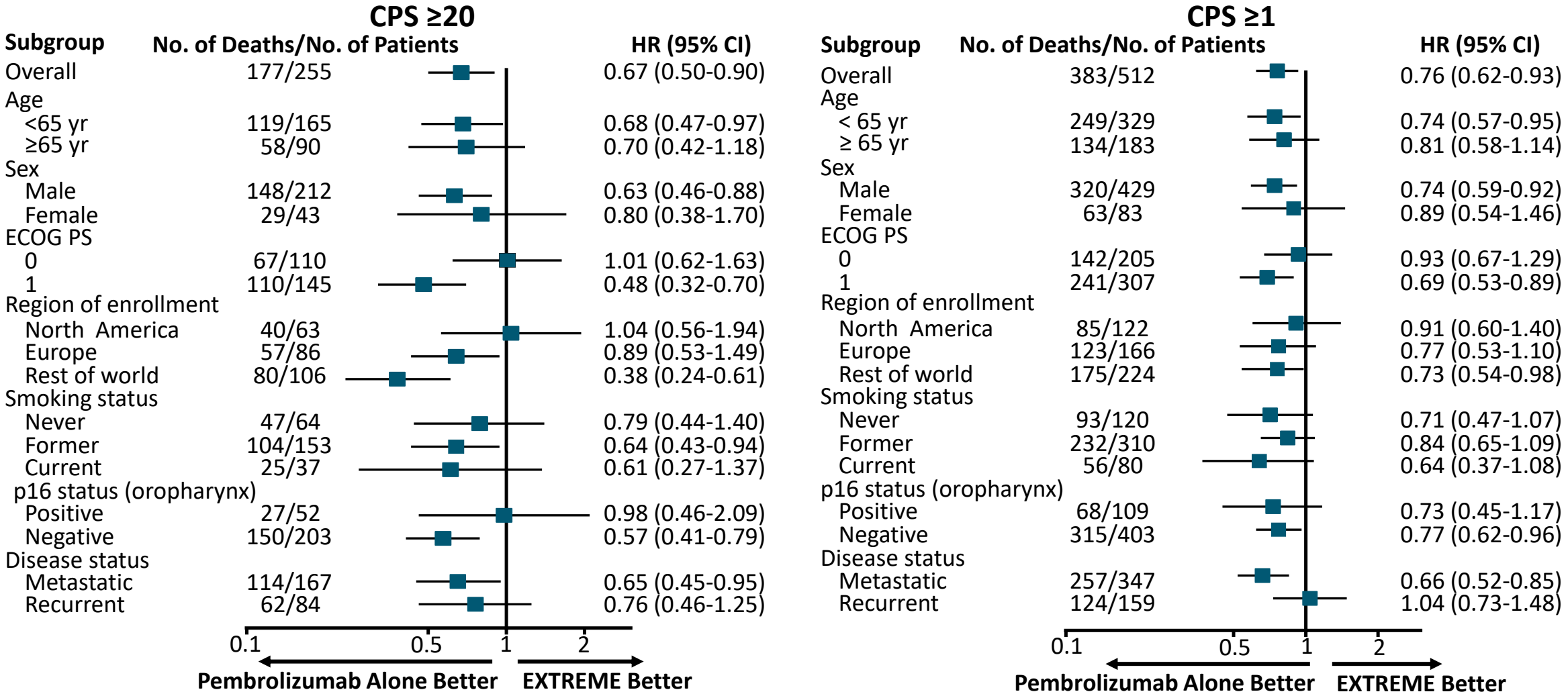
Total	Pembrolizumab/ Chemotherapy	Cetuximab/ Chemotherapy
No. of events/ no. of patients (%)	226/281 (80.4)	259/278 (93.2)
Median OS, mo (95% CI)	13.0 (10.9-14.7)	10.7 (9.3-11.7)
HR (95% CI)	0.71 (0.59-0.85); *P* .00008	



Patients at Risk, n												
Pembrolizumab/ chemo	281	227	169	122	94	78	70	63	49	30	9	1
Cetuximab/chemo	278	227	148	101	67	47	32	24	17	8	2	0

Harrington. JCO. 2022;41:790.

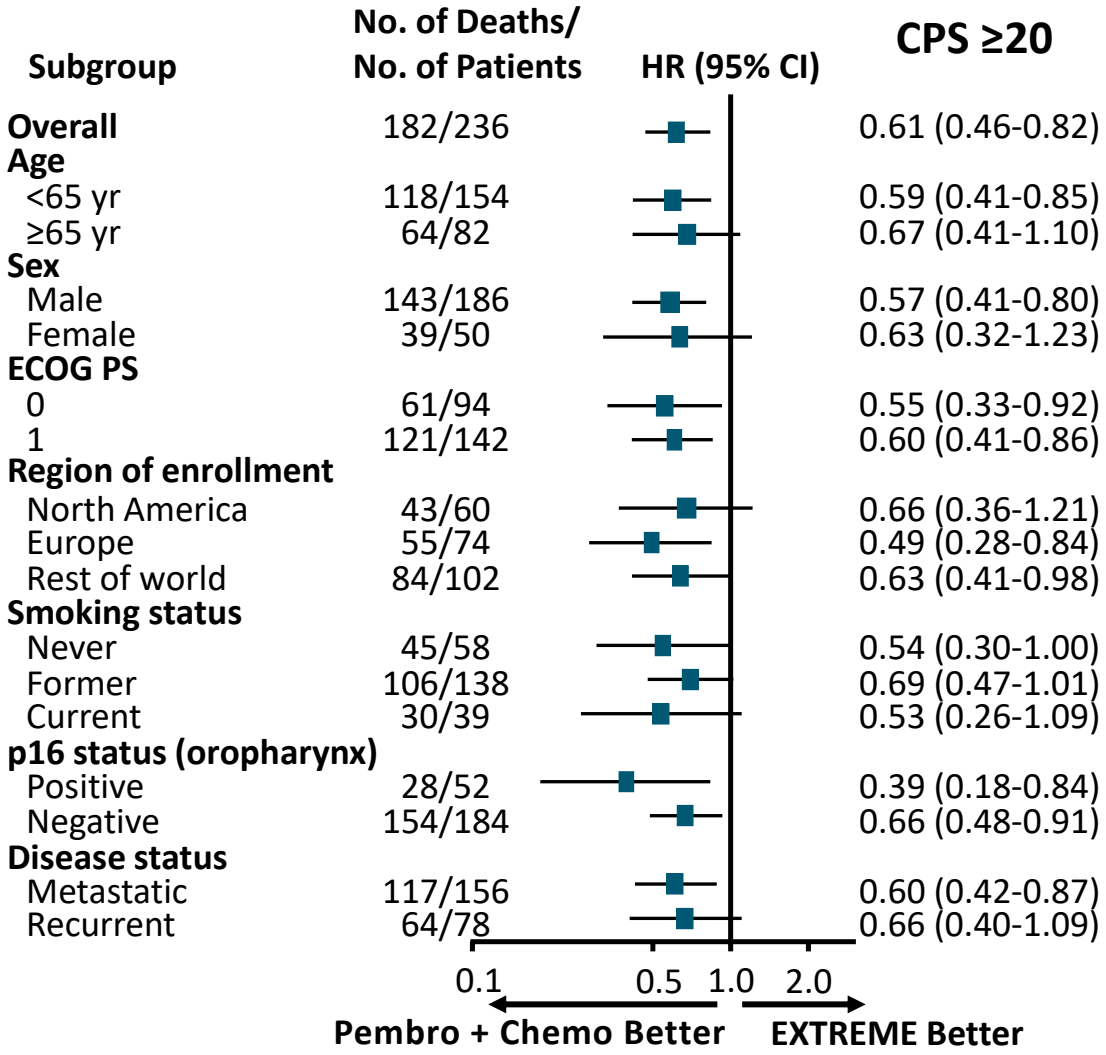
KEYNOTE-048: OS in Subgroups for Pembrolizumab vs EXTREME

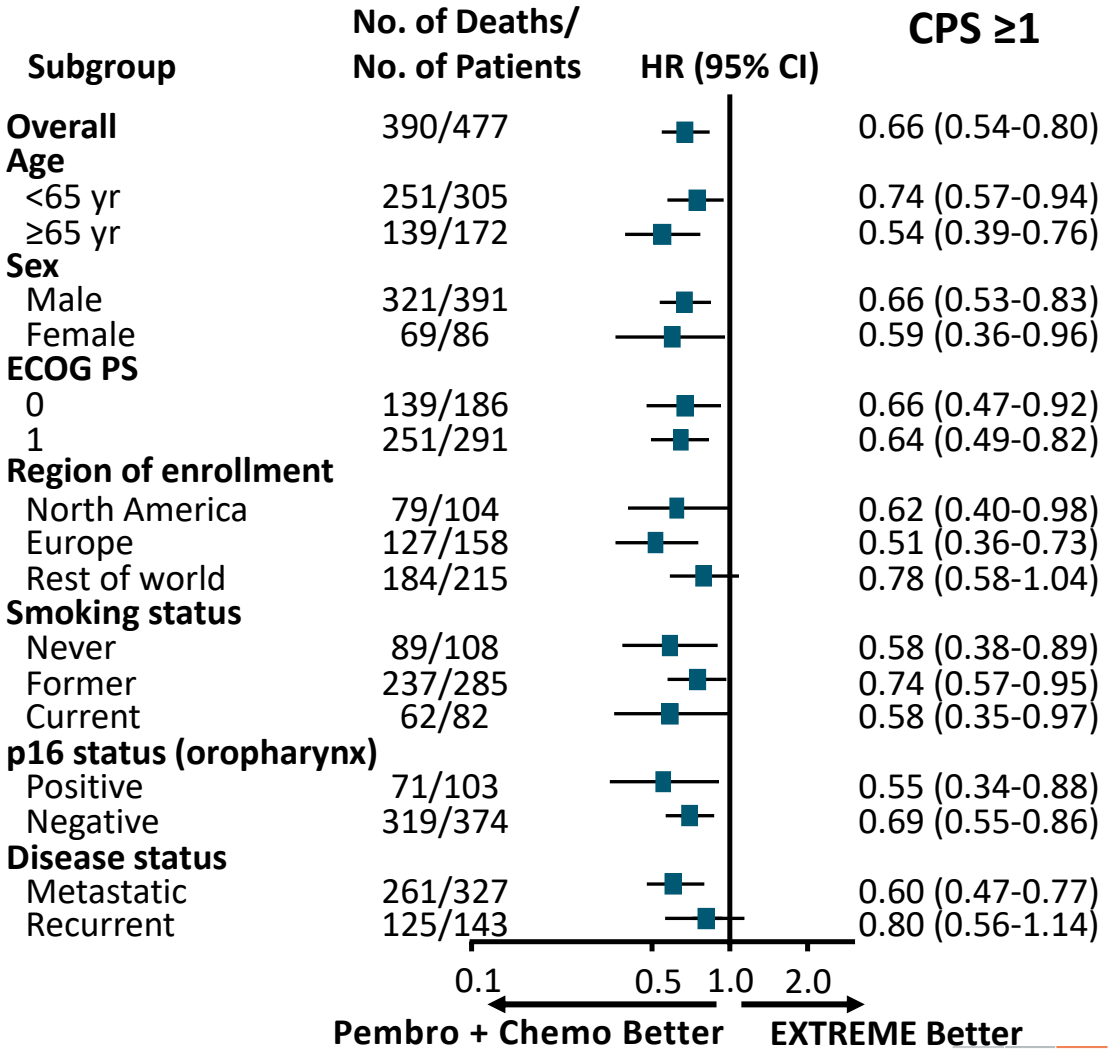


p16-negative subgroup includes participants with non-oropharyngeal tumors. Data cutoff date: Jun 13, 2018.

Burtness. Lancet. 2019;394:1915.

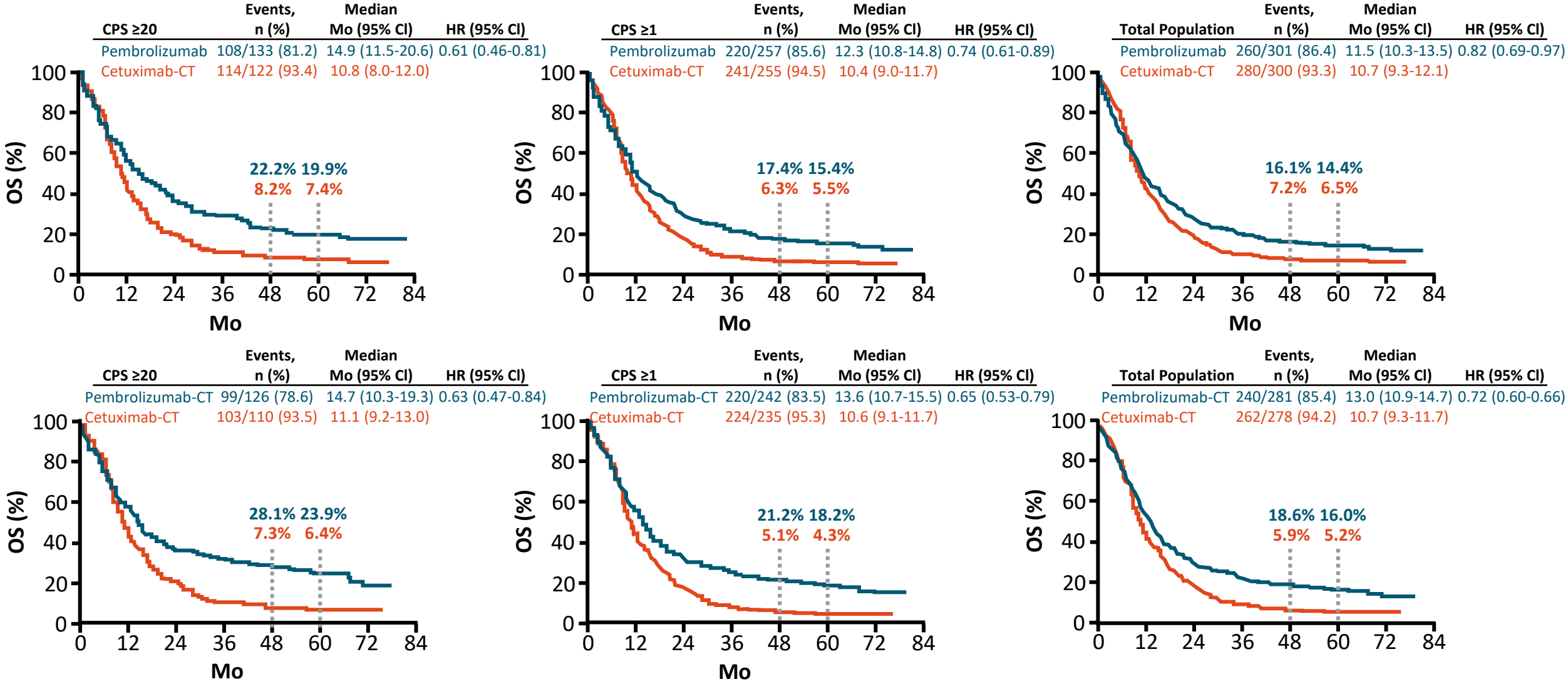
KEYNOTE-048: OS by Subgroups for Pembrolizumab + Chemotherapy vs EXTREME





Burtness. Lancet. 2019;394:1915.

KEYNOTE-048: Long-term OS Results



Tahara. Eur J Cancer. 2025;221:115395.

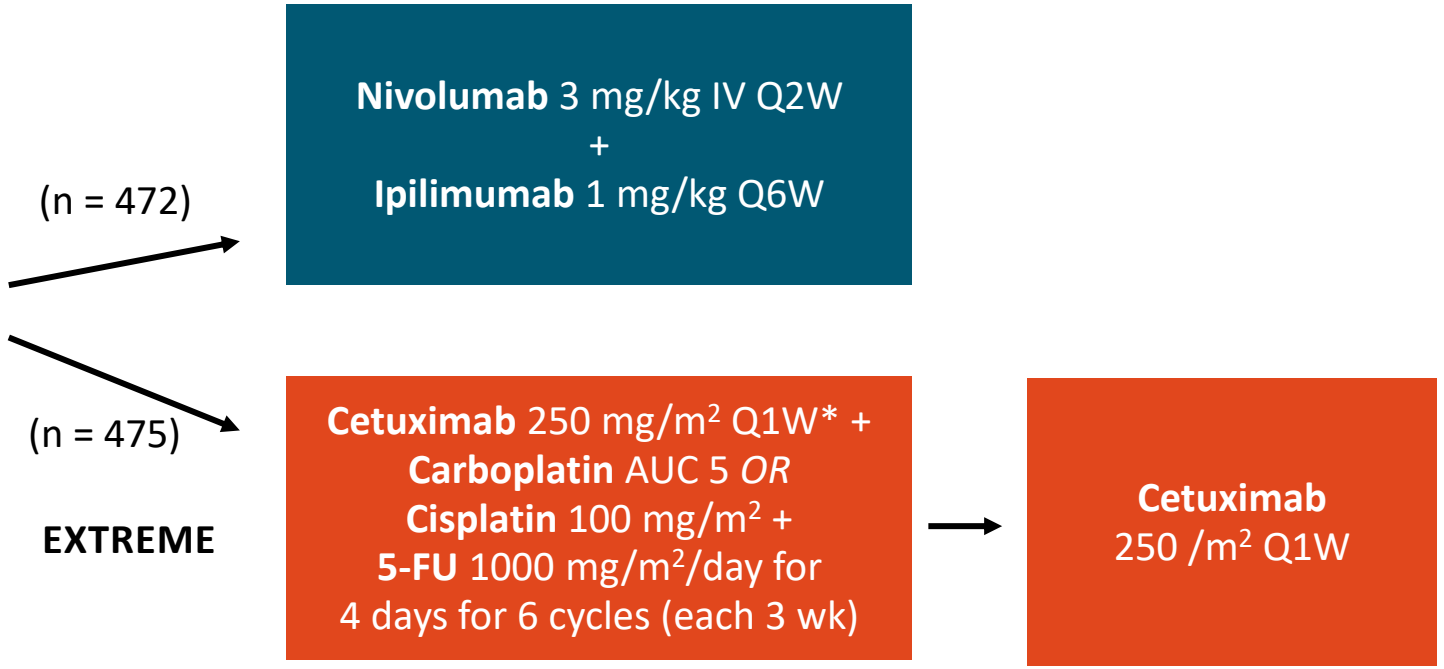
CheckMate-651: Nivolumab + Ipilimumab vs EXTREME as First-line Therapy for R/M HNSCC

- Randomized, open-label phase III trial

Adults with HNSCC of oropharynx, oral cavity, hypopharynx, or larynx not amenable to local curative therapy; documented tumor PD-L1 and HPV; no prior systemic therapy for R/M disease; no prior EGFR inhibitors; recurrence >6 mo after any chemotherapy for locally advanced disease

Stratification Factors

- PD-L1 expression (≥1% vs <1%)
- P16 status (positive or negative)
- Prior chemotherapy for locally advanced disease (yes or no)



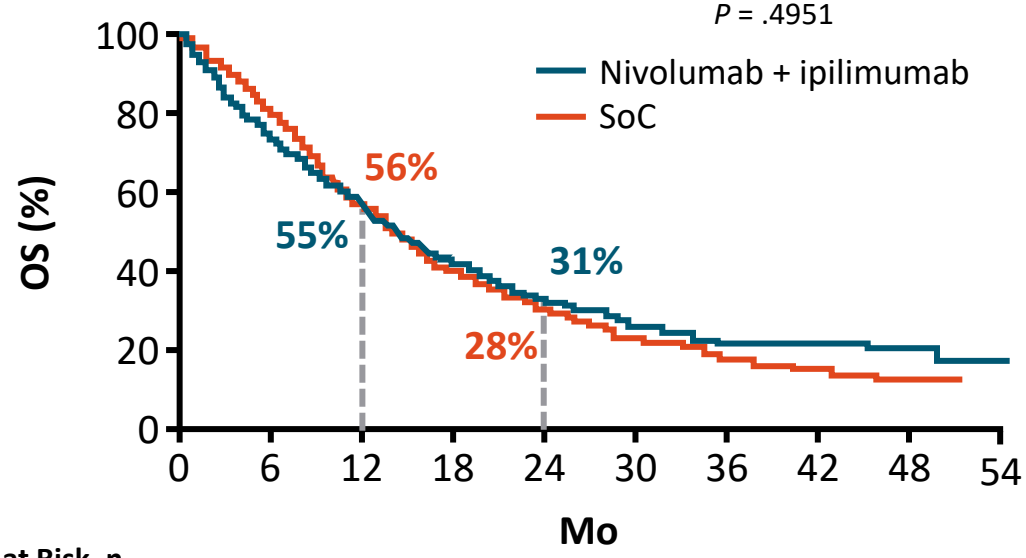
*Following a loading dose of 400 mg/m².

Haddad. JCO. 2022;41:2166.

CheckMate-651: OS With Nivolumab + Ipilimumab vs Cetuximab-Based CT (SoC) in R/M HNSCC

All Randomized Patients

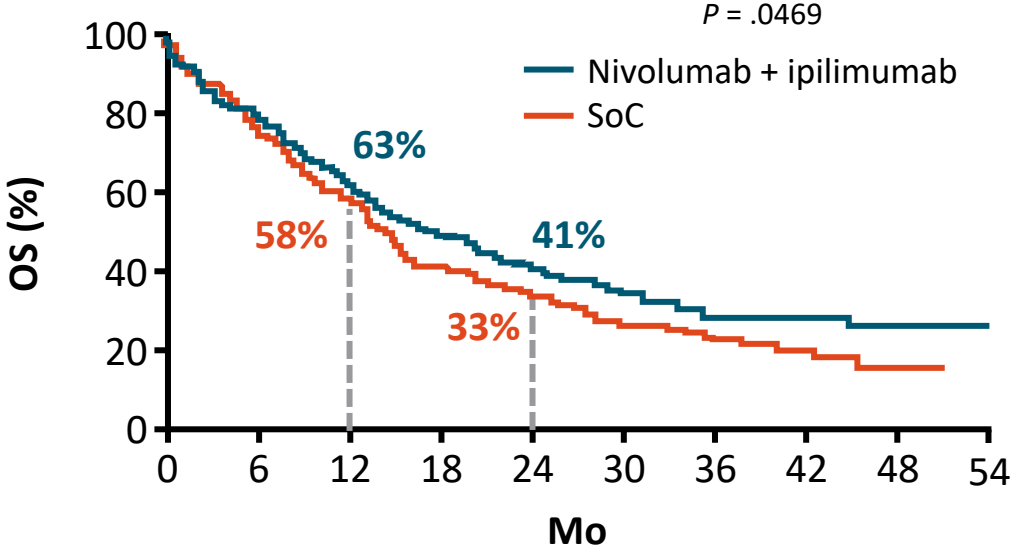
	Nivolumab + Ipilimumab (n = 472)	SoC (n = 475)
Median OS, mo	13.9	13.5
HR (97.9% CI)	0.95 (0.80-1.13)	
P	.4951	



Patients at Risk, n										
Nivolumab + ipilimumab	472	340	254	190	144	108	58	32	8	0
SoC	475	366	255	177	129	88	47	21	8	0

PD-L1 CPS ≥20

	Nivolumab + Ipilimumab (n = 185)	SoC (n = 178)
Median OS, mo	17.6	14.6
HR (97.9% CI)	0.78 (0.59-1.03)	
P	.0469	



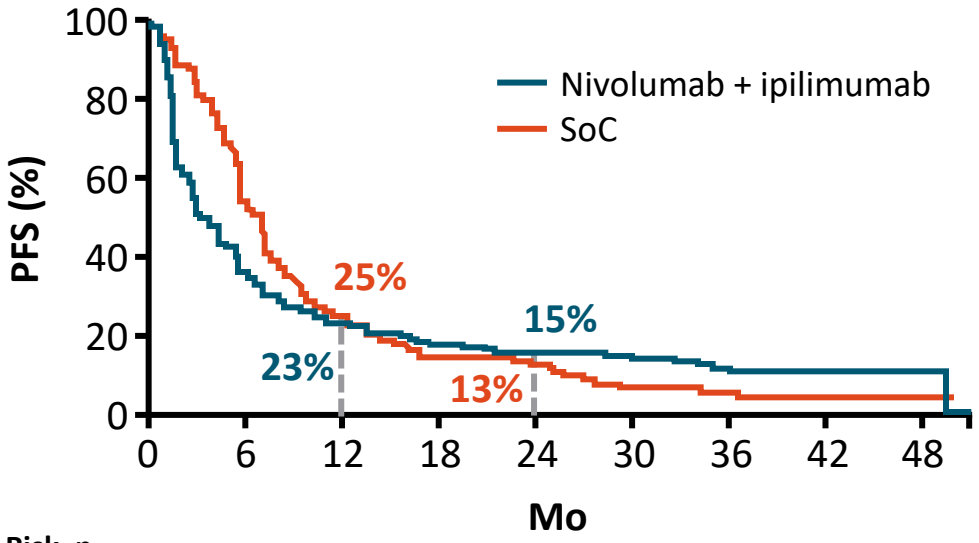
185	147	114	89	74	60	36	21	4	0
178	135	101	70	57	40	26	12	3	0

Haddad. JCO. 2022;41:2166.

CheckMate-651: PFS, DoR With Nivolumab + Ipilimumab vs SoC (All Randomized Patients)

PFS

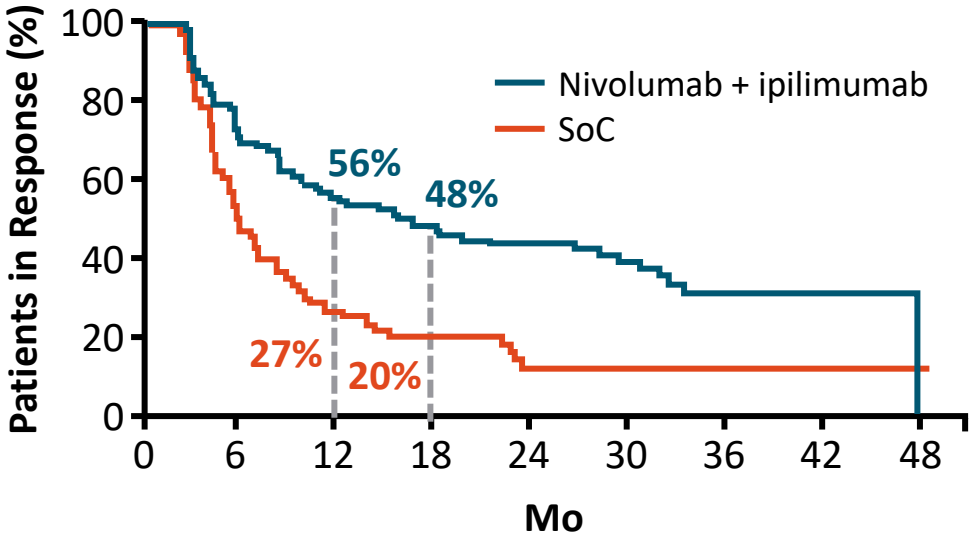
	Nivolumab + Ipilimumab (n = 472)	SoC (n = 475)
Median PFS, mo	3.3	6.7
HR (97.9% CI)	1.41 (1.21-1.65)	



Patients at Risk, n										
Nivolumab + ipilimumab	472	142	76	55	42	35	14	5	1	0
SoC	475	178	59	24	18	8	4	3	2	0

DoR

	Nivolumab + Ipilimumab (n = 472)	SoC (n = 475)
Median DoR, mo	16.6	5.9

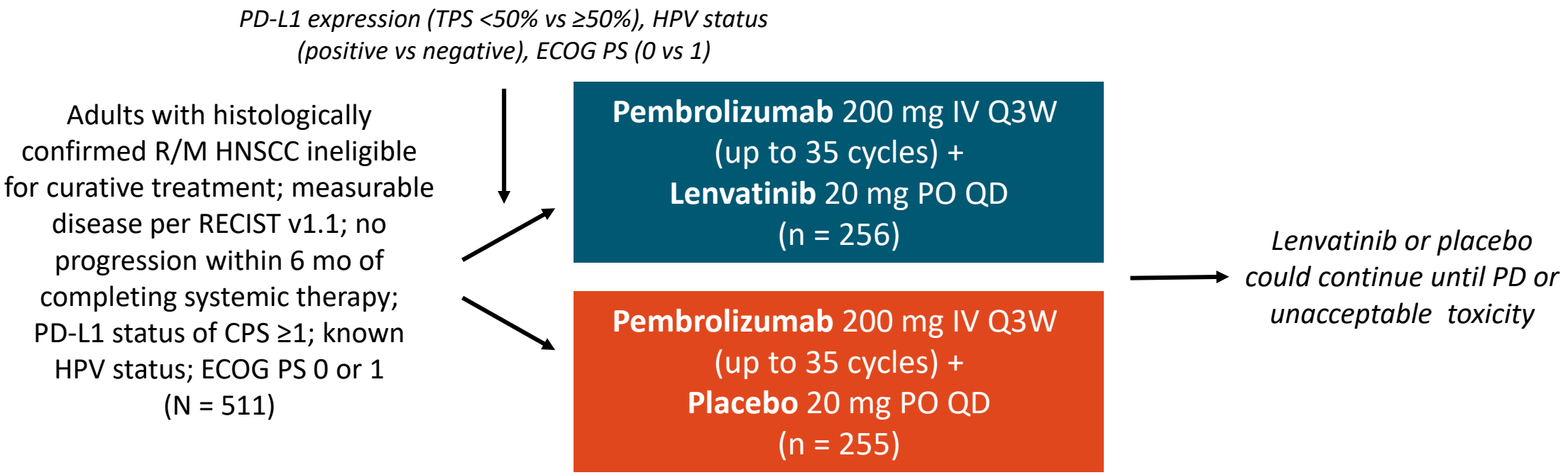


	114	73	54	44	35	26	8	3	0	0
	175	62	26	10	6	3	2	1	1	0

Haddad. JCO. 2022;41:2166.

LEAP-010: First-line Pembrolizumab ± Lenvatinib for R/M HNSCC

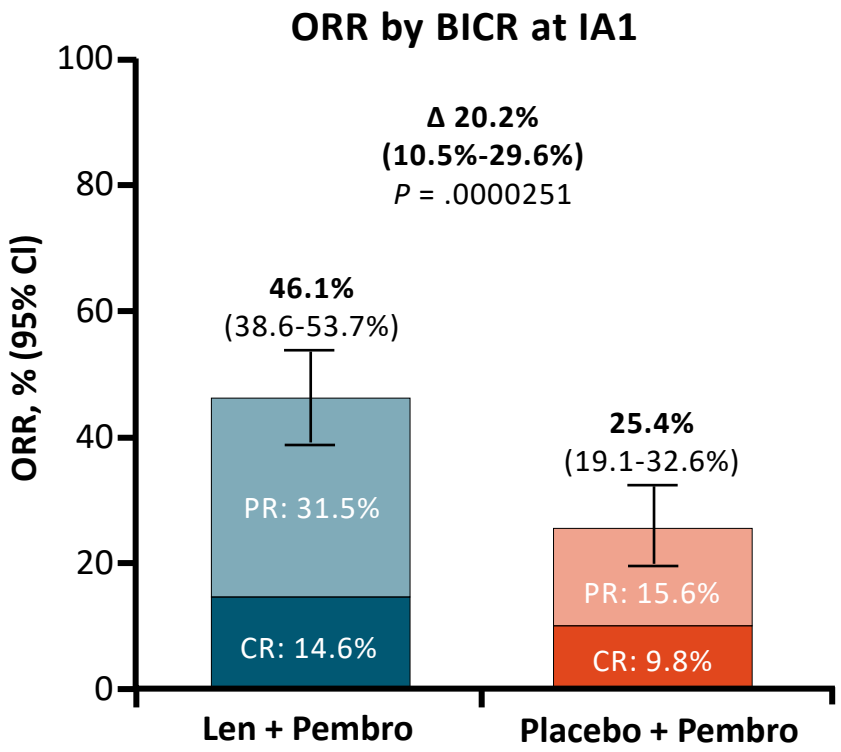
- Randomized, double-blind phase III trial

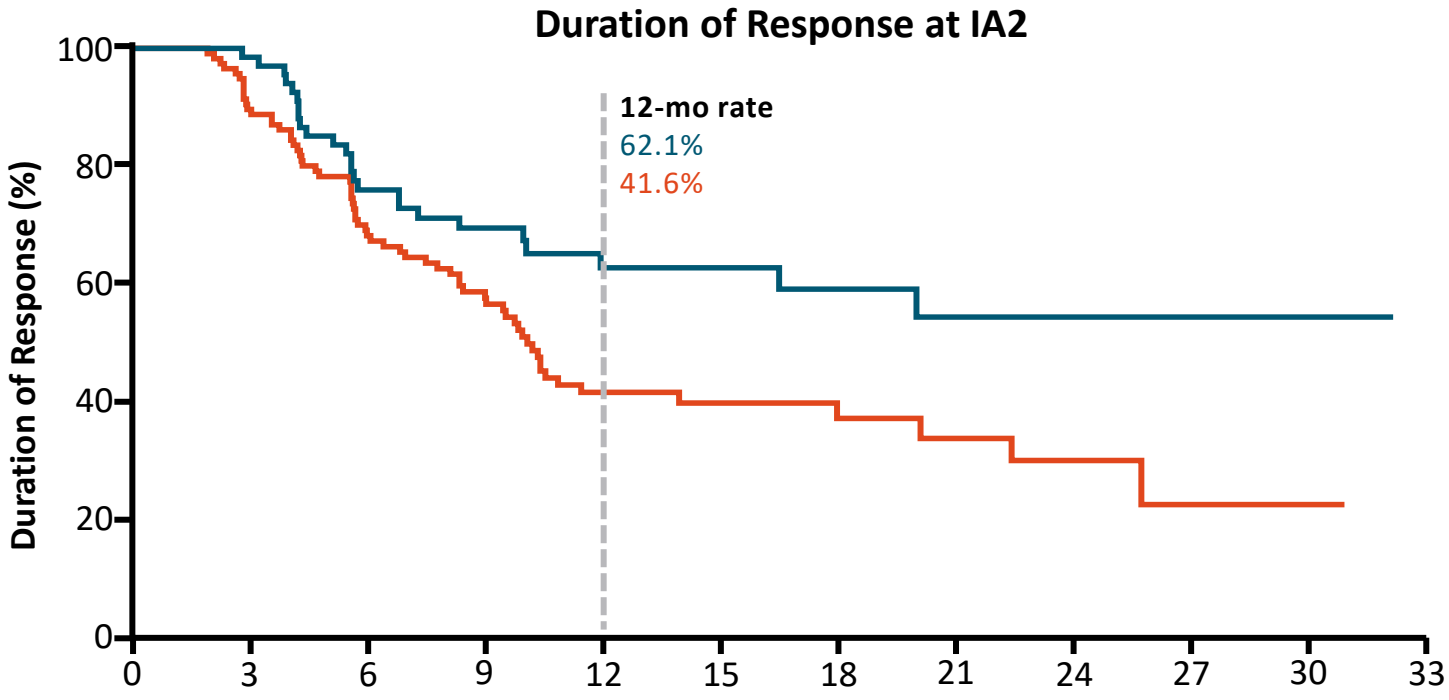


- Primary endpoints: ORR and PFS by BICR per RECIST v1.1, and OS
- Secondary endpoints: DoR by BICR, and safety

Licitra. MHNCS 2024. Abstr 1. NCT04199104.

LEAP-010: Response



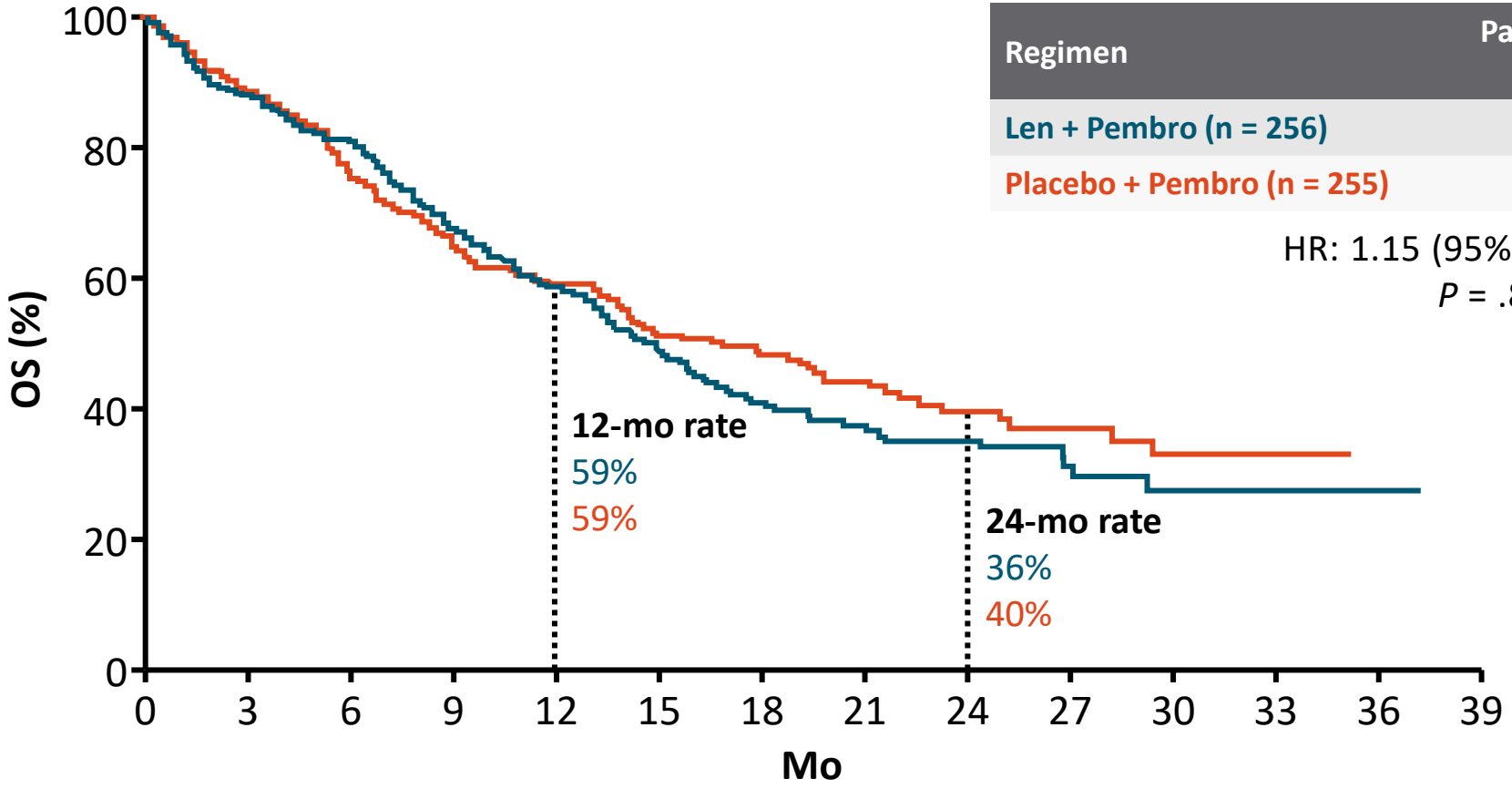


	Len + Pembro	Placebo + Pembro
SD	29.8%	30.1%
PD	11.2%	37.0%
Not Evaluable	3.9%	0.6%
Not Assessed	9.0%	6.9%

	ORR, % (95% CI)	Median Mo (range)
Len + Pembro (n = 120)	46.9% (40.6-53.2)	10.1 (1.3+ to 30.9+)
Placebo + Pembro (n = 70)	27.5% (22.1-33.4)	NR (1.2+ to 32.2+)

Median follow-up 11.5 mo (range 0.0-27.6) for IA1 and 21.3 mo (range 9.0-38.4) for IA2.

LEAP-010: Overall Survival at IA2



Regimen	Patients With Event, %	Median OS, Mo (95% CI)
Len + Pembro (n = 256)	59	15.0 (13.2-17.0)
Placebo + Pembro (n = 255)	54	17.9 (13.8-21.6)

HR: 1.15 (95% CI: 0.91-1.45)
P = .8820

Licitra. MHNCS 2024. Abstr 1.

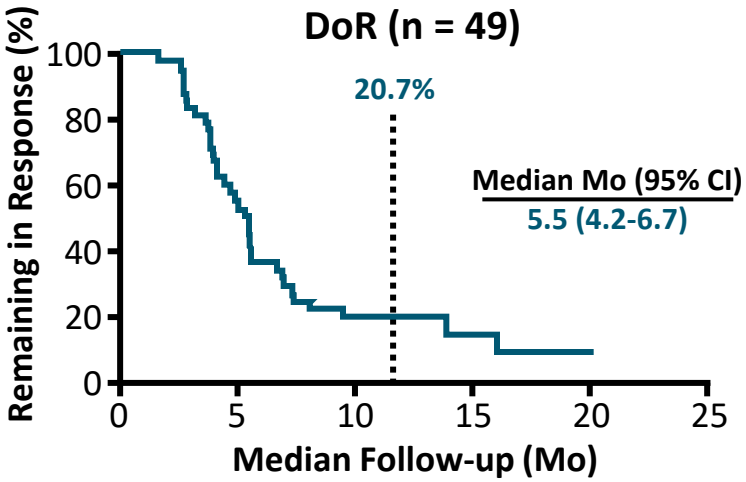
Alternate Approaches

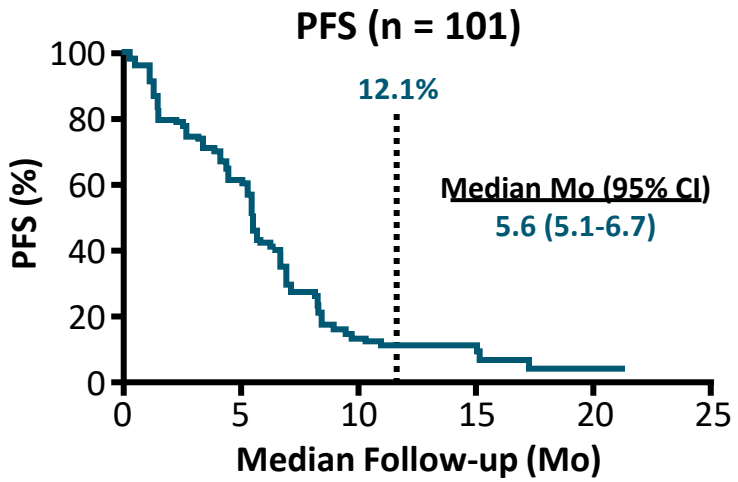
- PD-1 inhibition with pembrolizumab is SoC 1L therapy for R/M HNSCC[1]
  - Monotherapy mOS: 12.3 mo (PD-L1 CPS ≥1)
  - Combined with platinum + 5-FU mOS: 13.6 mo (PD-L1 CPS ≥1)
  - 36% of patients in KEYNOTE-048 were age >65 yr
- PD-L1 inhibition with durvalumab monotherapy was not superior to EXTREME (OS HR: 0.96; *P* = .787)[2]
- Pembrolizumab + platinum + paclitaxel: ORR: 42.7%; mOS: 12.1 mo[3]

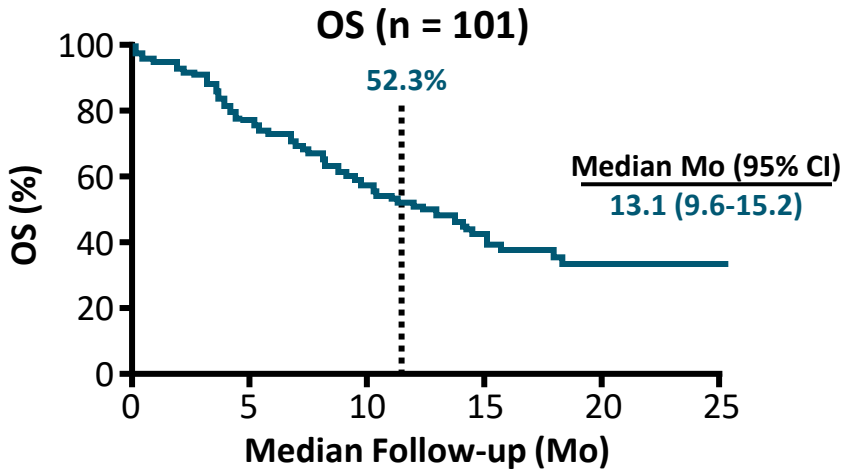
1. Burtness. Lancet. 2019; 394:1915. 2. Psyrri. Ann Oncol. 2023;34:262. 3. Dzienis. ESMO 2022. Abstr 6510.

KEYNOTE-B10: First-line Pembrolizumab + Carboplatin + Paclitaxel for R/M HNSCC

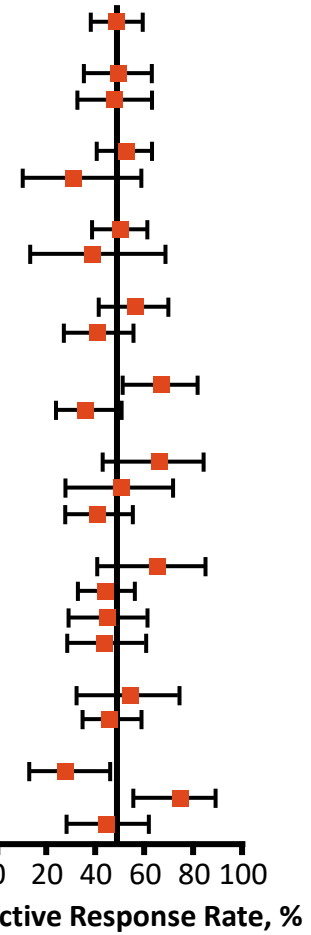
- Single-arm phase IV trial







	N	ORR (95% CI)
Overall	101	49 (38.4-58.7)
Age, yr		
<65	55	49 (35.4-62.9)
≥65	46	48 (32.9-63.1)
Sex		
Male	85	52 (40.7-62.7)
Female	16	31 (11.0-58.7)
Race		
White	88	50 (39.1-60.9)
All others	13	38 (13.9-68.4)
Geographic region		
North America	50	56 (41.3-70.0)
Rest of the world	51	41 (27.6-55.8)
ECOG PS		
0	40	68 (50.9-81.4)
1	61	36 (24.2-49.4)
HPV status		
Positive (oropharynx)	23	65 (42.7-83.6)
Negative (oropharynx)	22	50 (28.2-71.8)
Negative (nonoropharynx)	56	41 (28.1-55.0)
PD-L1 subgroup		
CPS <1	20	65 (40.8-84.6)
CPS ≥1	84	44 (33.4-55.9)
CPS ≥1-19	40	45 (29.3-61.5)
CPS ≥20	41	44 (28.5-60.3)
Choice of paclitaxel dosage		
100 mg/m^2 Q1W	24	54 (32.8-74.4)
175 mg/m^2 Q3W	77	47 (35.3-58.5)
Baseline disease presentation		
Recurrent	32	28 (13.7-46.7)
Metastatic	31	74 (55.4-88.1)
Recurrent and metastatic	38	45 (28.6-61.7)



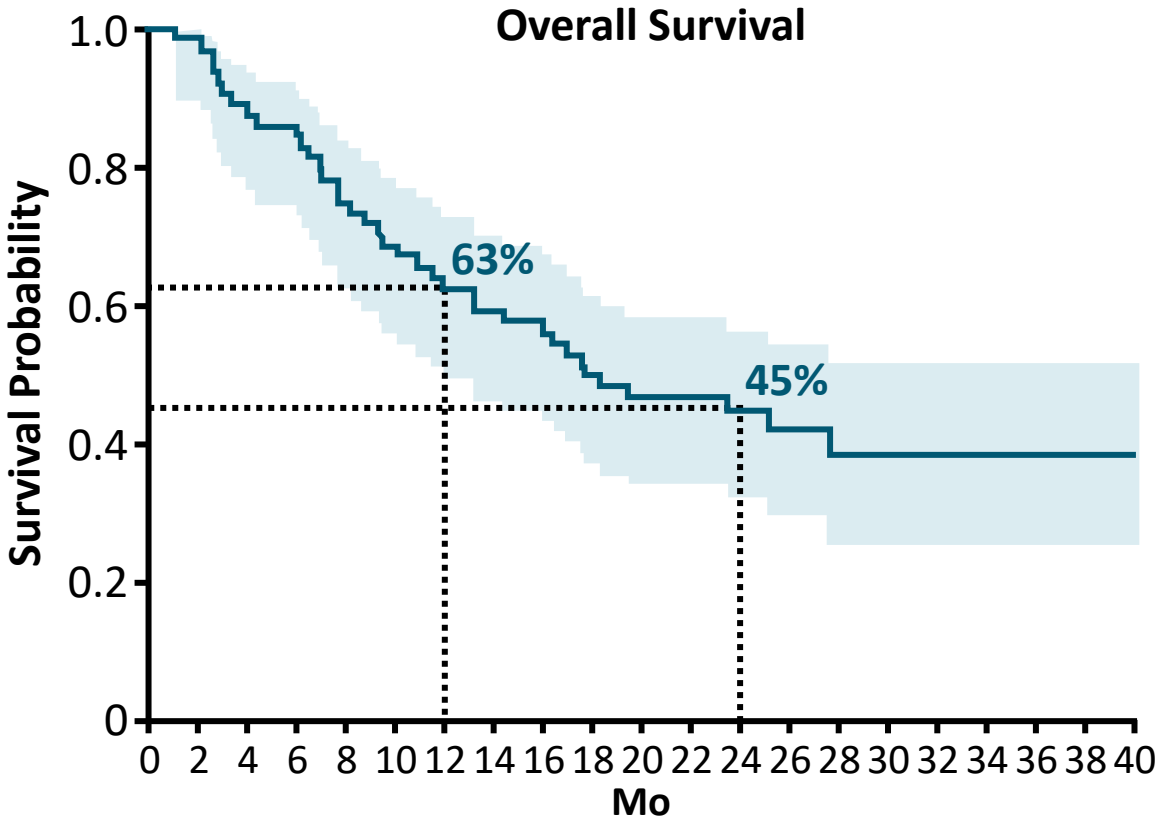
Pembro 200 mg Q3W, carboplatin AUC 5 mg/mL/min Day 1 Q3W, and IC of paclitaxel 100 mg/m^2 on Days 1 and 8 Q3W or 175 mg/m^2 on Day 1 Q3W.

Dzienis. JCO. 2024;42:2989.

Slide credit:

FRAIL-IMMUNE: First-line Durvalumab + Carboplatin + Paclitaxel for R/M HNSCC in Patients Ineligible for Cisplatin

- Single-arm phase II trial; enrolled patients ineligible for standard cisplatin therapy (>70 yr of age [47%], CrCl 40<CrCl<60 mL/min [28%], or severe comorbidities [28%]) (N = 64)



Outcome	N = 64
Median OS, mo (min-max)	18.0 (11.9-NR)
▪ 12-mo OS, % (95% CI)	63 (49-73)
▪ 24-mo OS, % (95% CI)	45 (32-57)
Median PFS, mo (95% CI)	7 (5.4-9.9)
ORR, %	71
Median DoR, mo	5.9
Median follow-up, mo (95% CI)	27.1 (21.5 -40.1)

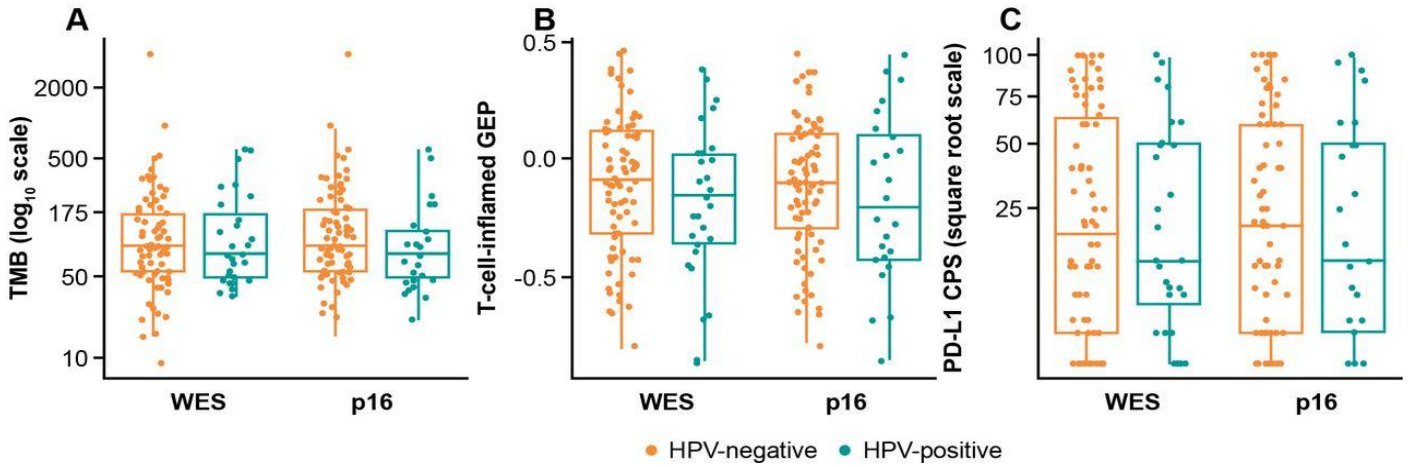
4 cycles of CT (carboplatin AUC2 + paclitaxel 80 mg/m², both at D1, D8, D15) and durvalumab 1500 mg Q4W for a maximum of 12 mo.

Fayette. ASCO 2023. Abstr 6003.

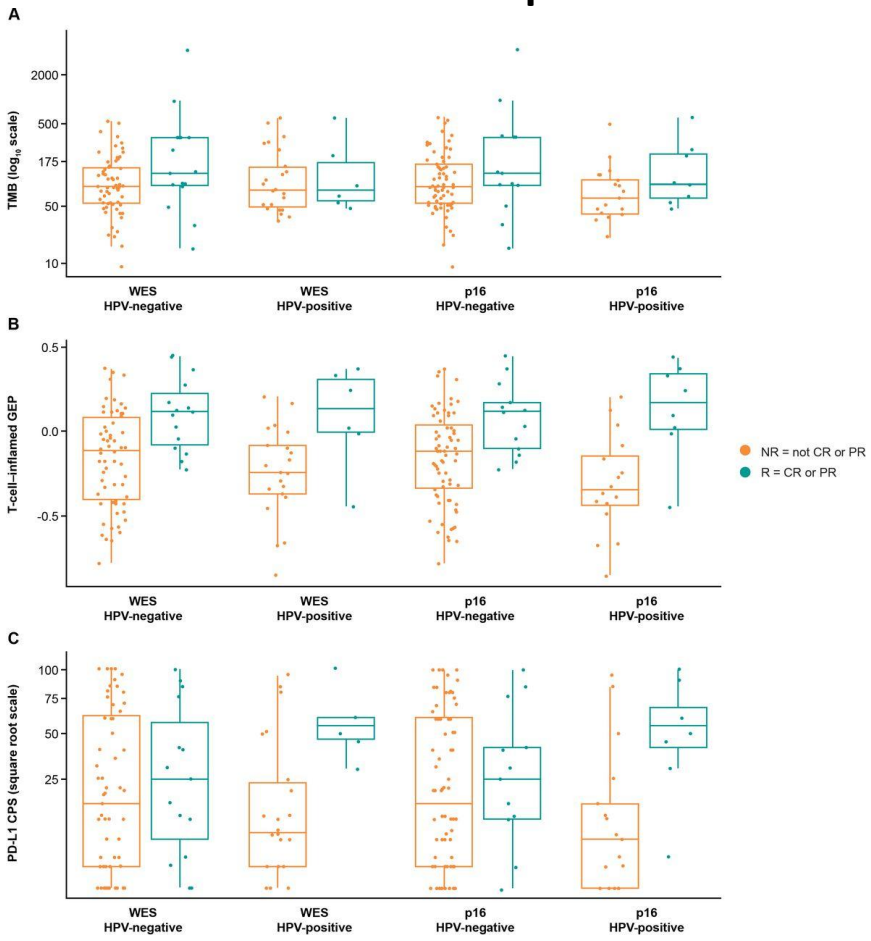
KEYNOTE-012 Phase Ib Trial of Pembrolizumab in R/M HNSCC: Response Biomarkers and HPV Status

- Biomarkers including TMB, T-cell–inflamed GEP, and PD-L1 CPS were evaluated

Biomarkers and HPV/p16 Status



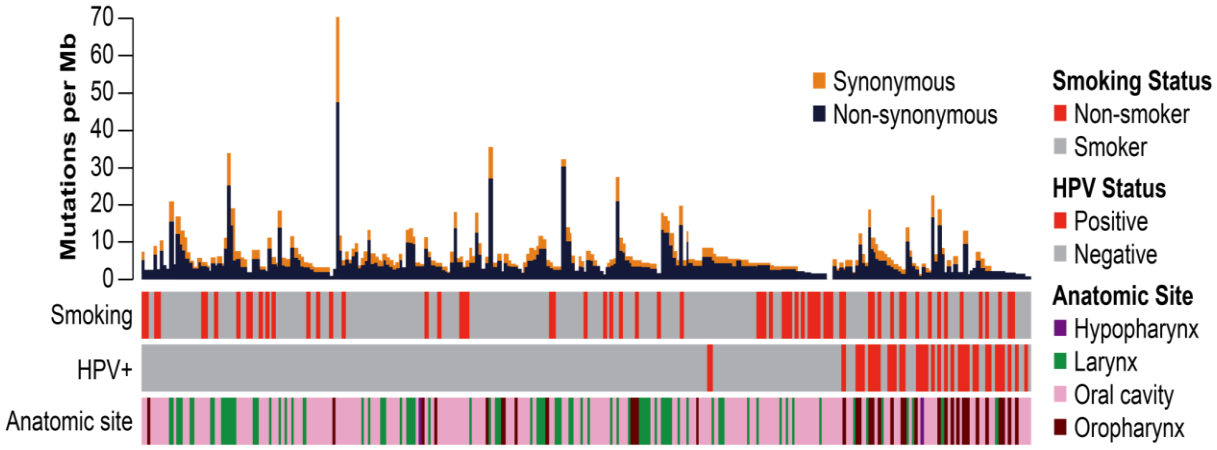
Biomarkers and Response



Haddad. J Immunother Cancer. 2022;10:e003026.

Mutational Load: Genetic Alterations in HNSCC

- Excess nonsynonymous mutations across HNSCC create areas in genome that may be transcribed as tumor neoantigens[1]



- APOBEC signature drives higher mutational load in HPV+ vs HPV- HNSCC[2]
- APOBEC mutations are hydrophobic and more neoantigenic

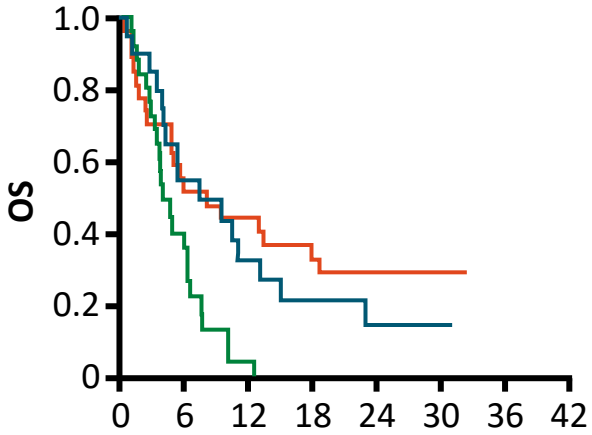
- Phase III trial of durvalumab (D) ± tremelimumab (T) vs CT in R/M HNSCC showed no significant OS difference for D ± T compared with SoC[3]
- TMB potentially may be predictive of outcomes[4]

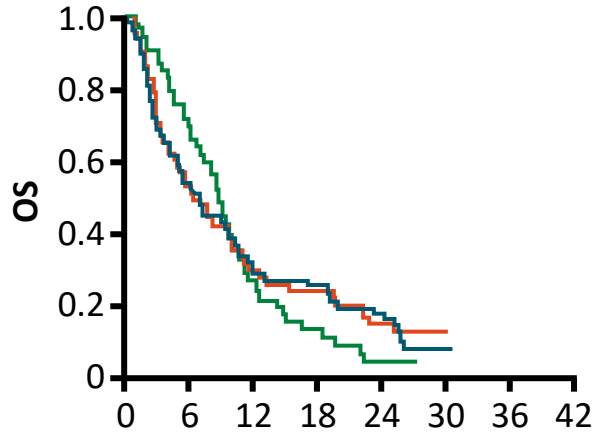
bTMB High (≥16 mut/Mb)

	D + T (n = 20)	D (n = 27)	CT (n = 27)
mOS, mo	7.6	8.1	4.0
HR	0.38	0.39	-
P value	.0061	.0044	-

bTMB Low (<16 mut/Mb)

	D + T (n = 63)	D (n = 57)	CT (n = 53)
mOS, mo	6.8	6.2	8.6
HR	0.92	0.92	-

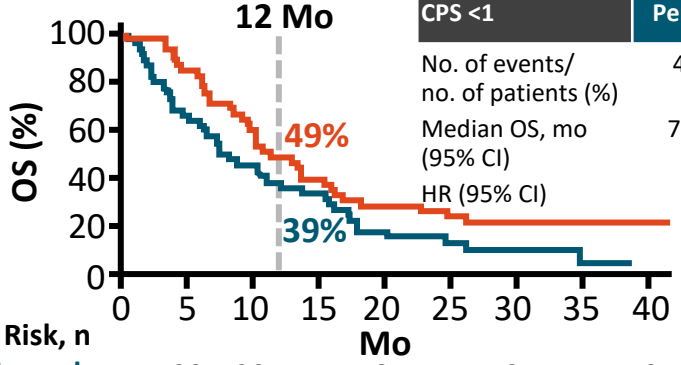




1. Cancer Genome Atlas Network. Nature. 2015;517:576. 2. Cannataro. Oncogene. 2019;38:3475.
3. Ferris. Ann Oncol. 2020;21:942. 4. Li. ASCO 2020. Abstr 6511.

KEYNOTE-048: OS Estimates Pembrolizumab Alone vs Cetuximab/Chemotherapy (CPS <1 and CPS 1-19)

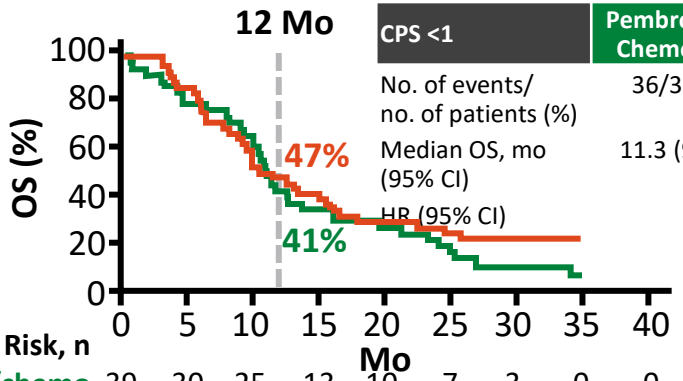
Pembrolizumab Alone



CPS <1	Pembrolizumab	Cetuximab/ Chemotherapy
No. of events/ no. of patients (%)	40/44 (90.9)	35/45 (77.8)
Median OS, mo (95% CI)	7.9 (4.7-13.6)	11.3 (9.1-15.9)
HR (95% CI)	1.51 (0.96-2.37)	

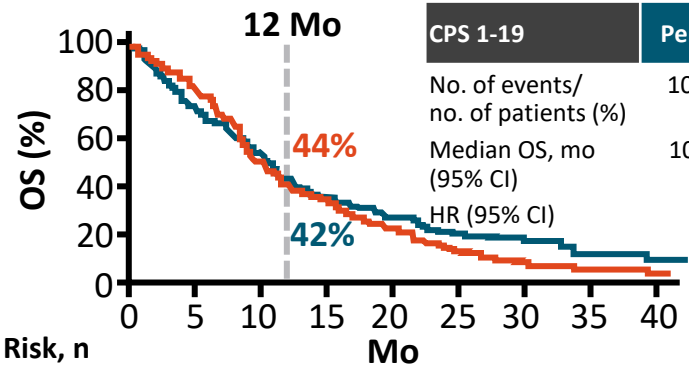
Patients at Risk, n									
Pembrolizumab	44	29	20	15	8	5	3	1	0
Cetuximab/chemo	45	38	27	18	13	11	7	2	1

Pembrolizumab/Chemotherapy



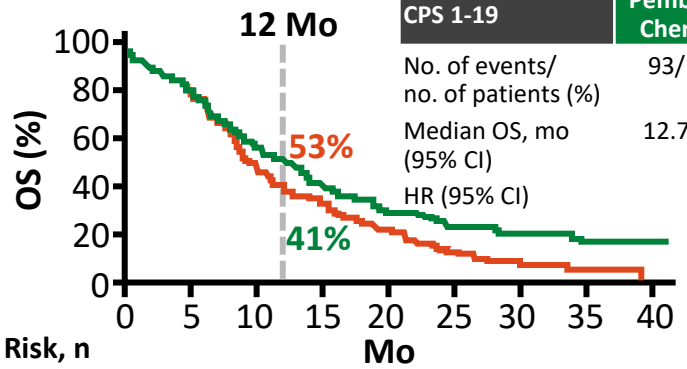
CPS <1	Pembrolizumab/ Chemotherapy	Cetuximab/ Chemotherapy
No. of events/ no. of patients (%)	36/39 (92.3)	34/43 (79.1)
Median OS, mo (95% CI)	11.3 (9.5-14.0)	10.7 (8.5-15.9)
HR (95% CI)	1.21 (0.76-1.94)	

Patients at Risk, n									
Pembrolizumab/chemo	39	30	25	13	10	7	3	0	0
Cetuximab/chemo	43	36	25	17	12	10	6	1	0



CPS 1-19	Pembrolizumab	Cetuximab-Chemotherapy
No. of events/ no. of patients (%)	103/124 (83.1)	121/133 (91.0)
Median OS, mo (95% CI)	10.8 (9.0-12.6)	10.1 (8.7-12.1)
HR (95% CI)	0.86 (0.66-1.12)	

Patients at Risk, n									
Pembrolizumab	124	90	67	45	34	25	14	6	4
Cetuximab/chemo	133	107	67	47	31	19	8	3	2



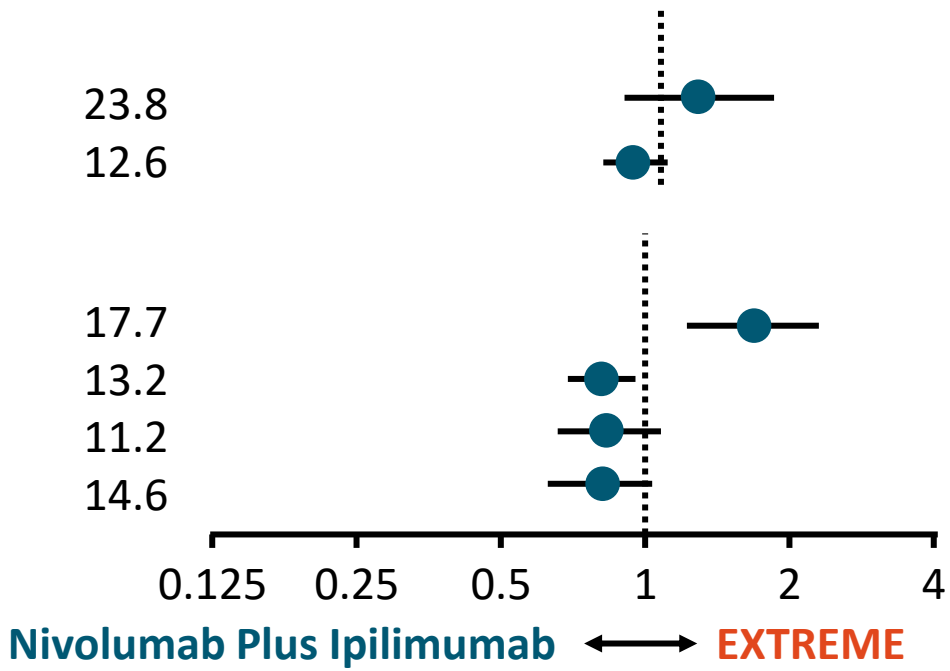
CPS 1-19	Pembrolizumab/ Chemotherapy	Cetuximab/ Chemotherapy
No. of events/ no. of patients (%)	93/116 (80.2)	115/125 (92.0)
Median OS, mo (95% CI)	12.7 (9.4-15.3)	9.9 (8.6-11.5)
HR (95% CI)	0.71 (0.54-0.94)	

Patients at Risk, n									
Pembrolizumab/chemo	116	95	67	49	34	26	16	8	1
Cetuximab/chemo	125	100	62	43	28	16	6	1	0

Burtness. JCO. 2022;40:2321.

CheckMate-651: OS by p16 and PD-L1 Status

Subgroup	Median OS, Mo: Nivolumab Plus Ipilimumab (n = 471)	Median OS, Mo: EXTREME (n = 475)	Unstratified HR (95% CI)
All randomly assigned (N = 947)	13.9	13.5	0.94
p16 status			
OPC p16 positive (n = 186)	19.8	23.8	1.19
OPC p16 negative or non-OPC (n = 761)	13.1	12.6	0.89
PD-L1 CPS			
<1 (n = 178)	7.9	17.7	1.66
≥1 (n = 727)	15.7	13.2	0.81
1-19 (n = 364)	14.5	11.2	0.83
≥20 (n = 363)	17.6	14.6	0.81



Haddad. JCO. 2022;41:2166.

Select Novel Targeted Therapy Approaches for R/M HNSCC

Approach	Select Treatment	Select Ongoing/Recent Trials
TKI + ICI combination therapy	Zanzalintinib (TKI) + pembrolizumab	STELLAR-305 (NCT06082167); ph II/III
Targeting HGF/c-MET	Ficlatuzumab (anti-HGF mAb) + cetuximab	FIERCE-HN (NCT06064877); ph III
Targeting EGFR	Petosemtamab (bispecific EGFR x LGR5 Ab) + pembrolizumab	LiGeR - HN1 (NCT06525220); ph III
	Ficerafusp alfa (bispecific EGFR x TGF-B Ab) + pembrolizumab	FORTIFI-HN01 (NCT06788990); ph II/III
	Amivantimab (bispecific EGFR x MET Ab) ± pembrolizumab ± CT	OrigAMI-4 (NCT06385080); ph I/II
ADCs	Ifinatamab deruxtecan (B7-H3 targeted)	IDeate-PanTumor02 (NCT06330064); ph II
	MRG003 (EGFR targeted)	NCT05751512; ph III
	ABBV-400 (MET targeted)	NCT06084481; ph I
Targeting HPV16+ HNSCC	CUE-101 (novel fusion protein; activates HPV16-specific T cells) ± pembrolizumab	NCT03978689; ph I

The Evolving Role of Neoadjuvant/Adjuvant Immunotherapy for Head and Neck Cancer

Locally Advanced HNSCC: Current Landscape in 2025

- HPV infection is a major cause of oropharyngeal cancer[1]
- Treatment de-escalation approaches are evolving[2,3]
- HPV-unrelated HNSCC (larynx, hypopharynx, oral cavity) remains a therapeutic challenge[4]
- New staging system for HNSCC: HPV+, DOI, unknown primary, ENE[5]
- Surgery, chemotherapy, and RT remain the standard interventions for curative therapy for LA disease; checkpoint inhibitor trials have all been negative to date[4]
  - **This is about to change in 2025**
  - **Two positive trials in LA HNSCC**

1. Argiris. Lancet. 2008;371:1695. 2. Mensour. Front Oncol. 2022;12:1067321. 3. Mehanna. JCO. 2020;38:2552.
4. Chow. NEJM. 2020;382:60. 5. Amin. AJCC Cancer Staging Manual. 8th ed. Springer. 2017.

Summary: Head and Neck Cancer in 2025

Definitive Setting

- Concurrent CRT
- Bolus cisplatin
- Weekly cisplatin

Sequential CRT

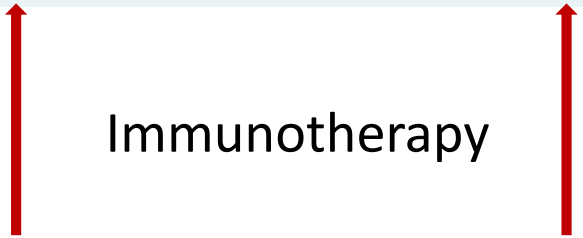
- TPF induction CT
- Organ preservation

Adjuvant Setting

- RT or CRT based on risk
- Bolus cisplatin or weekly cisplatin

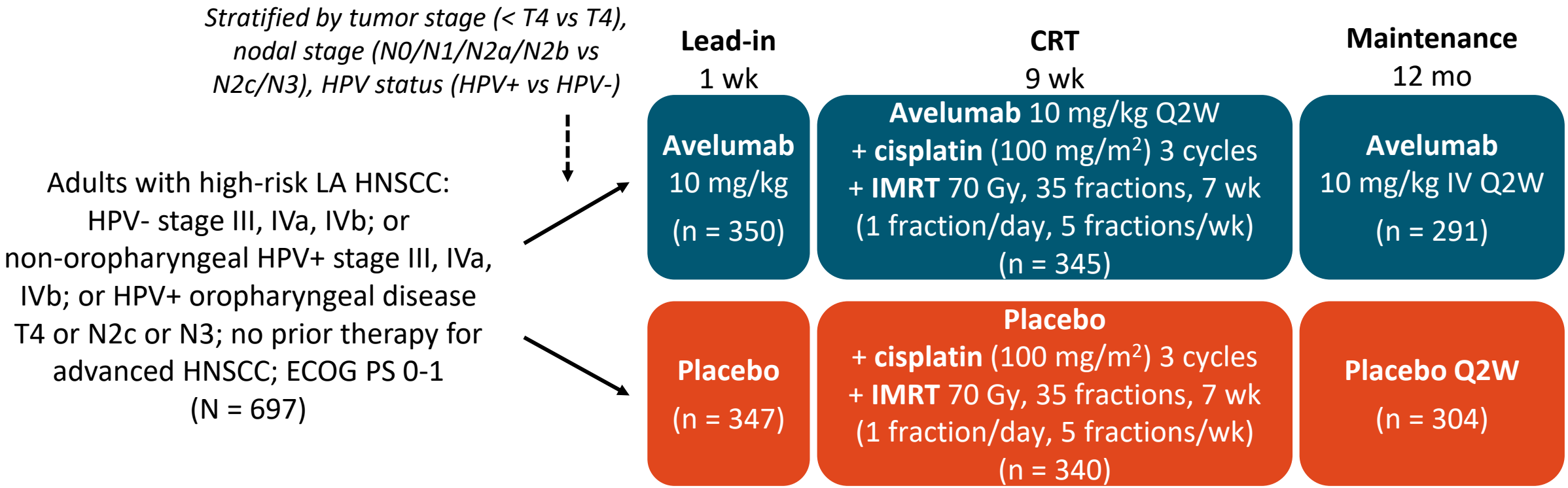
Cisplatin Unsuitable

- RT alone
- RT + docetaxel weekly



Concurrent/Adjuvant Immunotherapy

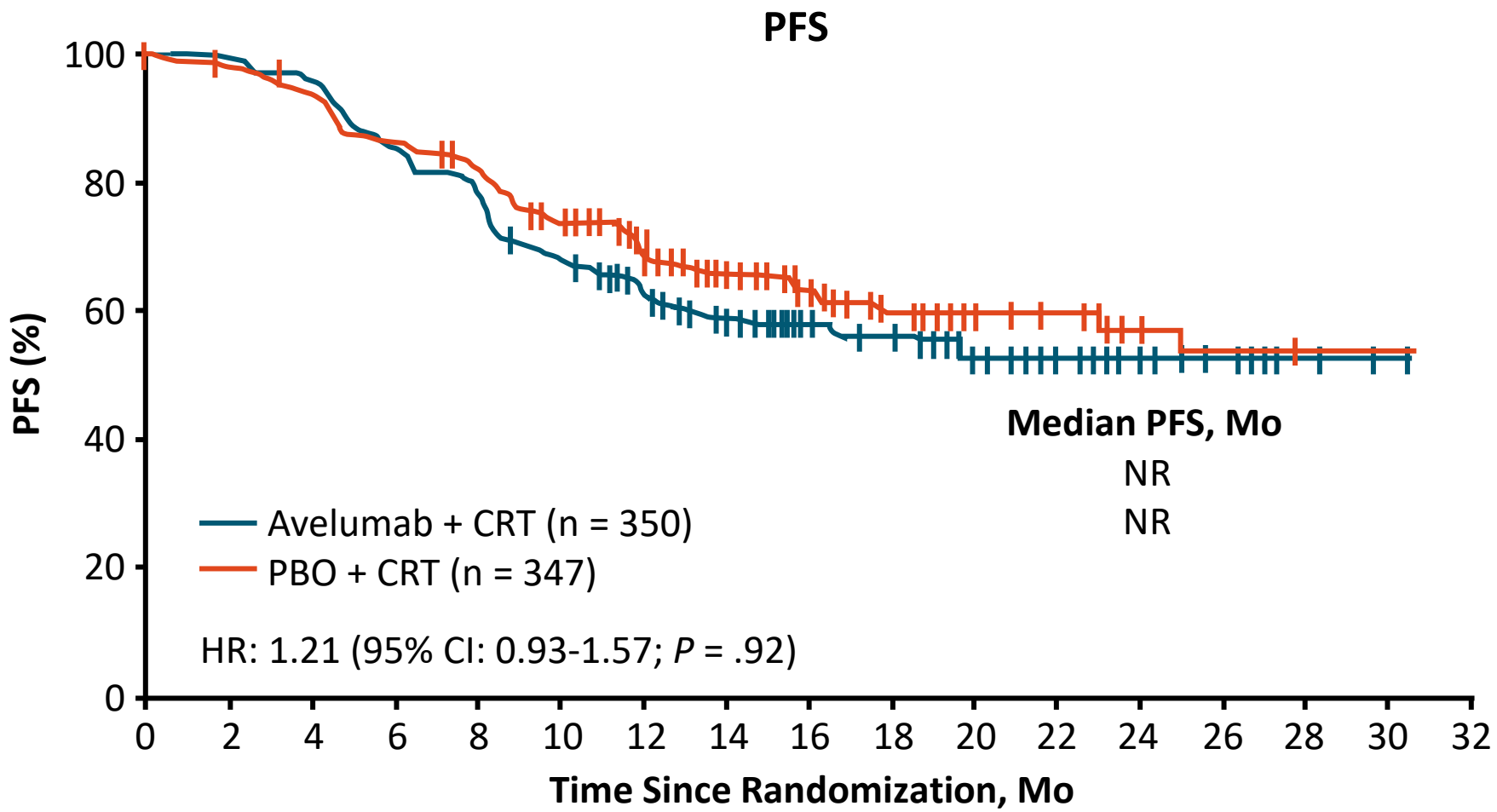
JAVELIN Head and Neck 100: Phase III Trial of Avelumab + CRT vs Placebo + CRT in LA HNSCC



- Primary endpoint: PFS (RECIST v1.1)
- Key secondary endpoints: OS, ORR, DoR, safety

Lee. Lancet Oncol. 2021;22:450.

JAVELIN Head and Neck 100: PFS



Lee. Lancet Oncol. 2021;22:450.

KEYNOTE-412: Phase III Study of Pembrolizumab + CRT vs Placebo + CRT in Locally Advanced HNSCC

Stratified by radiotherapy regimen (AFX vs SFX), tumor site/p16 status (oropharynx [p16+ vs p16-] or larynx/hypopharynx/oral cavity), and disease stage (III vs IV)

Adults with unresected LA HNSCC; T3-T4 (N0-N3) or any N2a-3 (T1-T4) larynx/hypopharynx/oral cavity/p16- oropharynx cancers *or* T4 or N3 p16+ oropharynx cancer; no prior therapy for advanced HNSCC; ECOG PS 0-1 (N = 804)

	CRT	Maintenance
→	**Pembrolizumab** 200 mg Q3W* + **Cisplatin** 100 mg/m^2 Q3W + **AFX or SFX**† 70 Gy	**Pembrolizumab** 200 mg Q3W x 14 cycles
→	**Placebo** 200 mg Q3W* + **Cisplatin** 100 mg/m^2 Q3W + **AFX or SFX**† 70 Gy	**Placebo** Q3W x 14 cycles

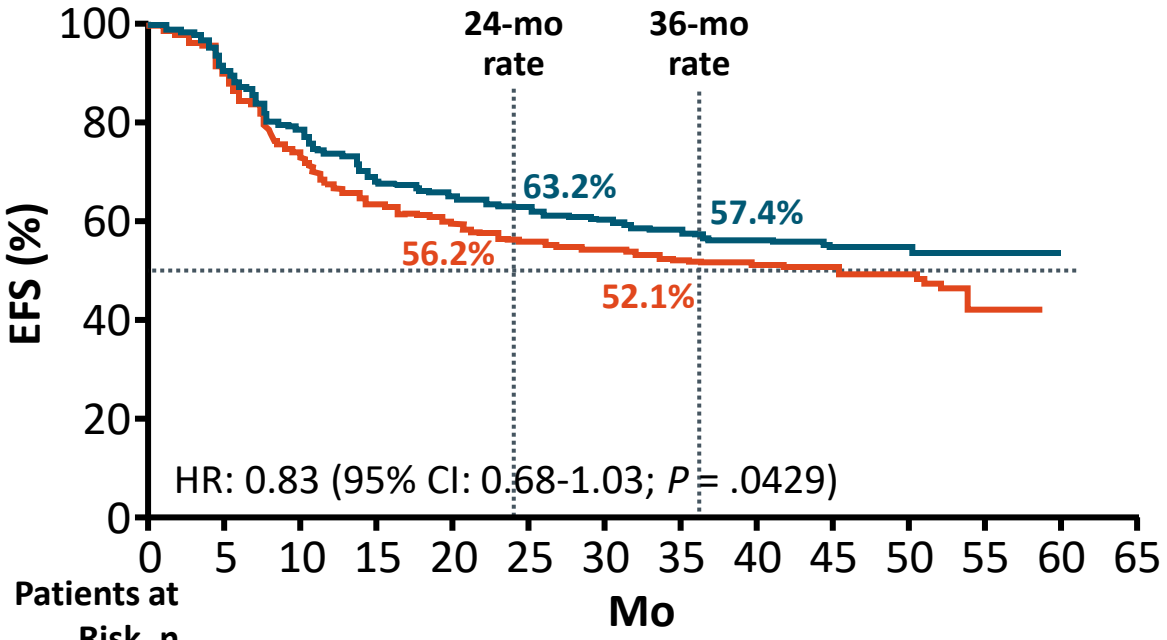
*Priming dose was given 1 wk before CRT, followed by 2 doses during CRT.
†AFX = accelerated fractionation (70 Gy, 35 fractions, 6 fractions/wk for 5 wk, then 5 fractions in Wk 6)
SFX = standard fractionation (70 Gy, 35 fractions, 5 fractions/wk for 7 wk).

- Primary endpoint: EFS
- Key secondary endpoints: OS, safety, QoL

Machiels. ESMO 2022. Abstr LBA5.

KEYNOTE-412: EFS and OS

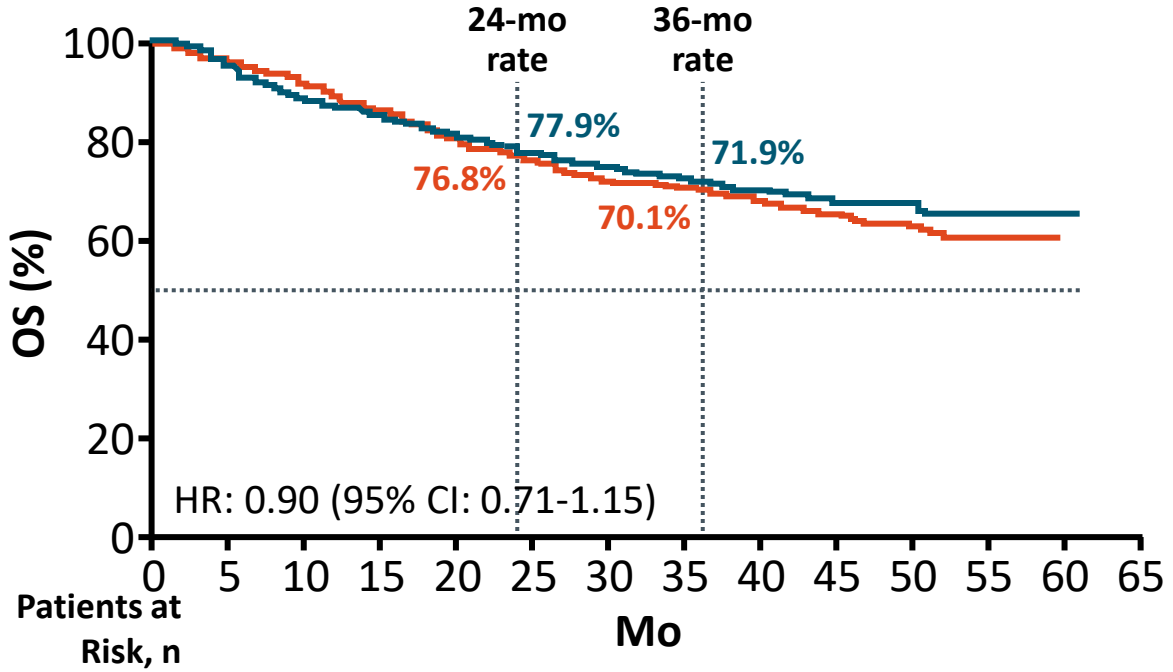
EFS	Events, %	Median, Mo (95% CI)
Pembro + CRT	42.5	NR (44.7-NR)
Placebo + CRT	47.8	46.6 (27.5-NR)



Patients at Risk, n

402	356	306	261	245	235	225	184	176	109	52	10	0	0
402	349	282	240	224	209	200	162	149	99	51	7	0	0

OS	Events, %	Median, Mo (95% CI)
Pembro + CRT	32.1	NR (NR-NR)
Placebo + CRT	35.6	NR (NR-NR)



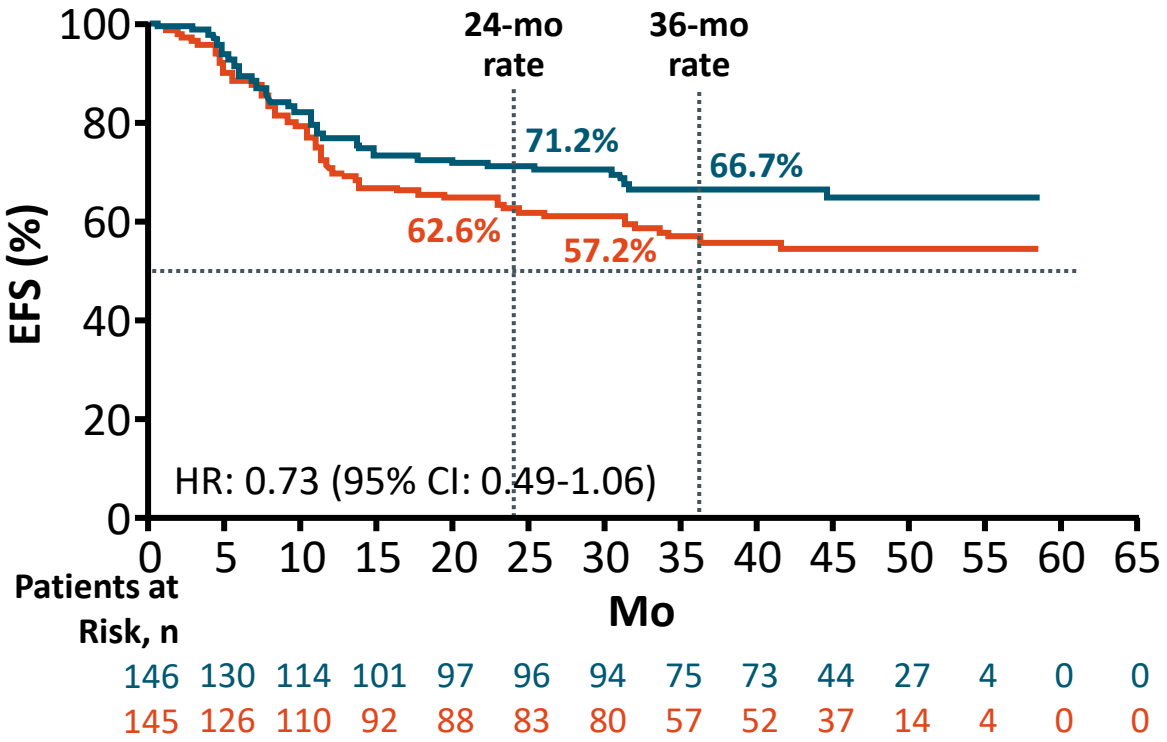
Patients at Risk, n

402	380	351	338	323	310	298	287	243	169	105	30	2	0
402	386	368	345	323	306	288	284	227	159	96	32	0	0

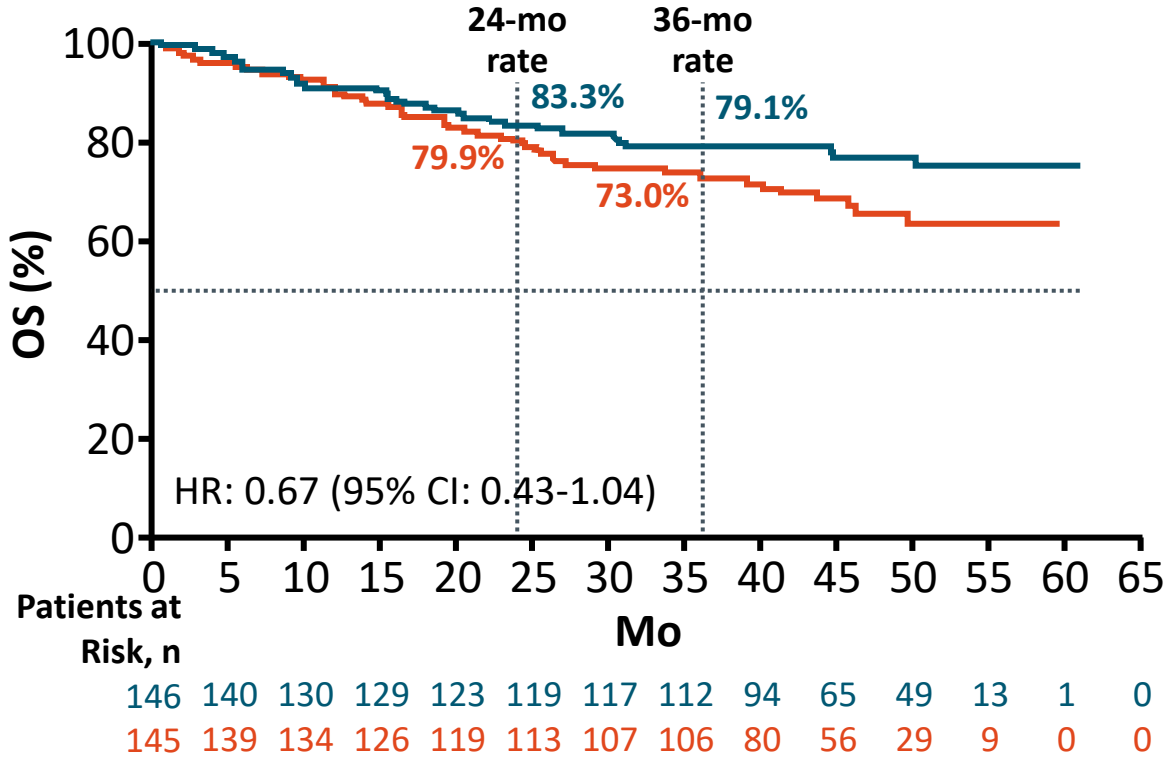
Machiels. ESMO 2022. Abstr LBA5.

KEYNOTE-412: EFS and OS in Patients With PD-L1 CPS ≥20

EFS	Events, %	Median, Mo (95% CI)
Pembro + CRT	32.2	NR (NR-NR)
Placebo + CRT	42.1	NR (33.7-NR)



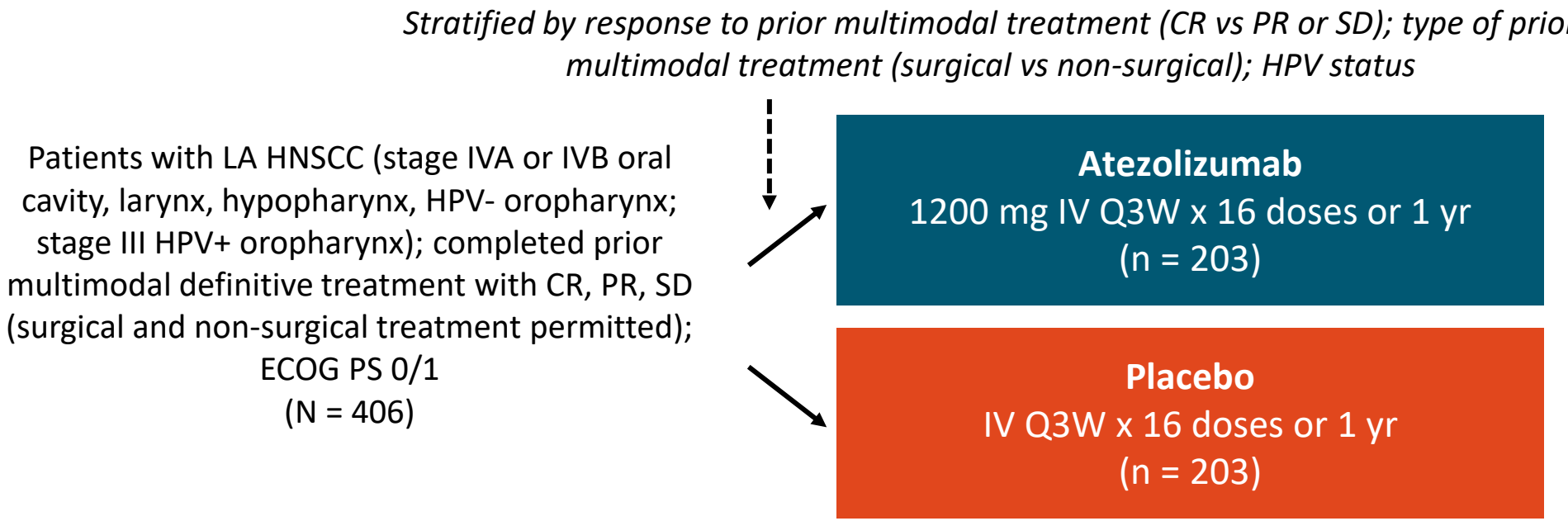
OS	Events, %	Median, Mo (95% CI)
Pembro + CRT	22.6	NR (NR-NR)
Placebo + CRT	32.4	NR (NR-NR)



Machiels. ESMO 2022. Abstr LBA5.

IMvoke010: Atezolizumab After Multimodal Definitive Therapy for High-Risk Locally Advanced HNSCC

- Global, randomized, double-blind phase III study

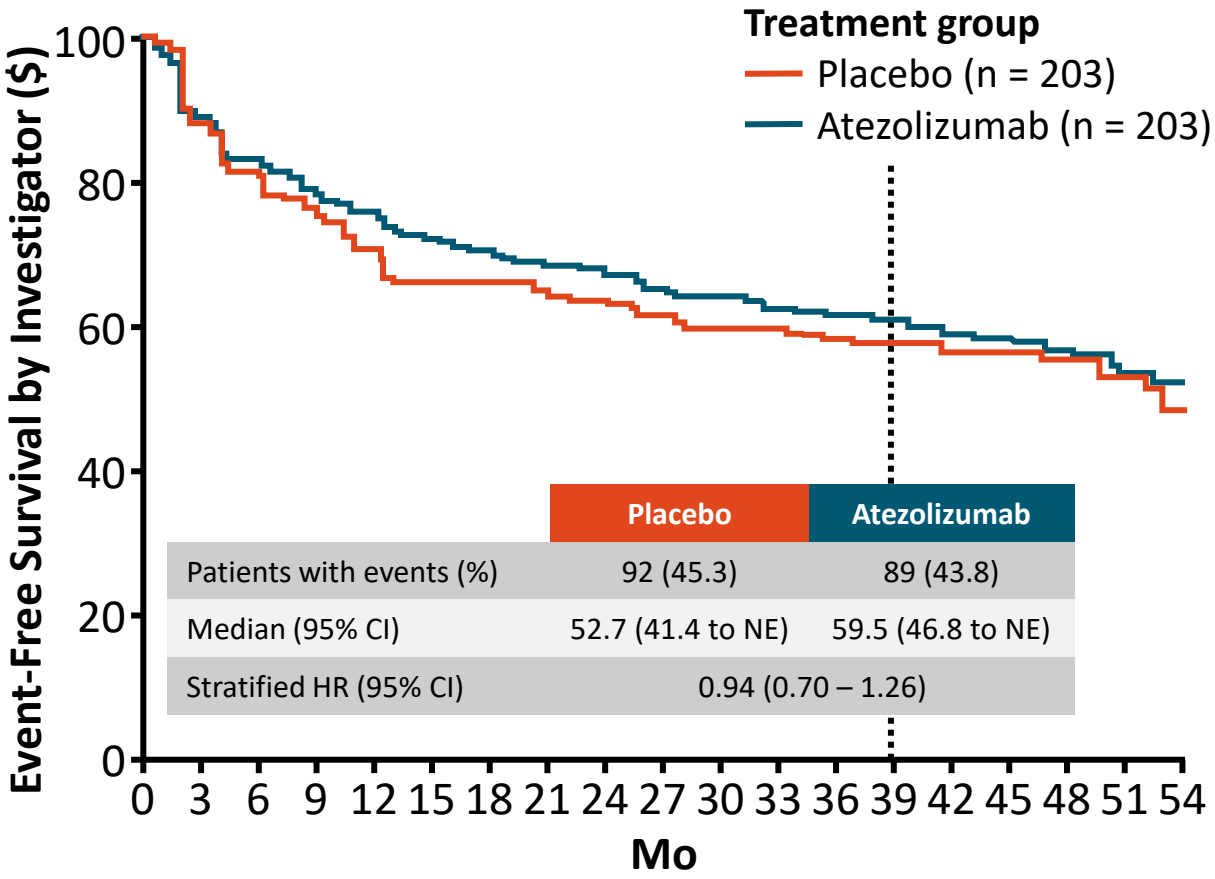


- Primary endpoint: INV-assessed EFS
- Secondary: IRF-assessed EFS, OS, safety

Haddad. JAMA. 2025:e251483.

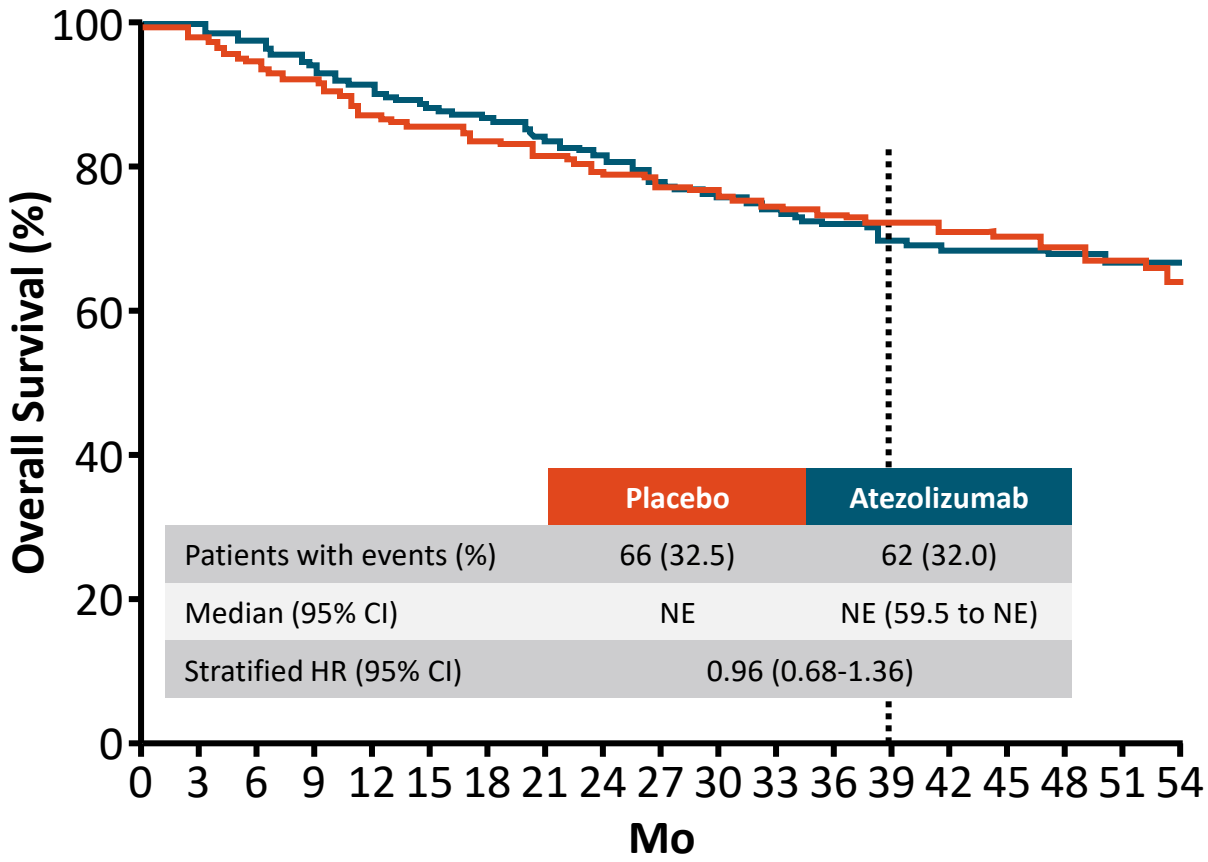
IMvoke010: Outcomes

Investigator-Assessed Event-Free Survival



	Placebo	Atezolizumab
Patients with events (%)	92 (45.3)	89 (43.8)
Median (95% CI)	52.7 (41.4 to NE)	59.5 (46.8 to NE)
Stratified HR (95% CI)	0.94 (0.70 – 1.26)	

Overall Survival



	Placebo	Atezolizumab
Patients with events (%)	66 (32.5)	62 (32.0)
Median (95% CI)	NE	NE (59.5 to NE)
Stratified HR (95% CI)	0.96 (0.68-1.36)	

Haddad. JAMA. 2025:e251483.

Summary: Immunotherapy in Locally Advanced HNSCC

Trial	Phase (N)	Regimen	Primary endpoint
Studies on patients with LA HNSCC eligible for cisplatin 100 mg/m² Q3W + RT			
JAVELIN HN 100[1]	III (697)	Avelumab + cisplatin + RT vs placebo + cisplatin + RT	PFS
KEYNOTE-412[2]	III (804)	Pembrolizumab + cisplatin + RT vs placebo + cisplatin + RT	EFS
REACH[3]	III (eligible cohort) (430)	Avelumab + cetuximab + RT vs cisplatin + RT	PFS
Studies on patients with LA HNSCC ineligible for cisplatin 100 mg/m² Q3W + RT			
REACH[3]	III (ineligible cohort) (277)	Avelumab + cetuximab + RT vs cetuximab + RT	PFS
PEMBRORAD[4]	II (131)	Pembrolizumab + RT vs cetuximab + RT	LRC
NRG-HN004[5]	II/III (190)	Durvalumab + RT vs cetuximab + RT	PFS

1. Lee. Lancet Oncol. 2021;22:450. 2. Machiels. ESMO 2022. Abstr LBA5. 3. Bourhis. ESMO 2021. Abstr LBA35. 4. Tao. Ann Oncol. 2023;34:101. 5. Mell. Lancet Oncol. 2024;25:1576.

What About Neoadjuvant Immunotherapy ?

Rationale for Neoadjuvant Immunotherapy

- Need to improve OS in high-risk SCC (HPV neg, larynx, oral cavity, HP)
- Clear activity in R/M setting
- Neoadjuvant approach may help induce immune response to deliver durable benefit
- Neoadjuvant setting ideal: untreated patients, lower burden of disease, intact tumor to allow for immune response
- “Immuno-reduction” may alter surgery
- Reduced need for adjuvant approaches: less RT, less CRT

Mechanisms of Action: Neoadjuvant Immunotherapy

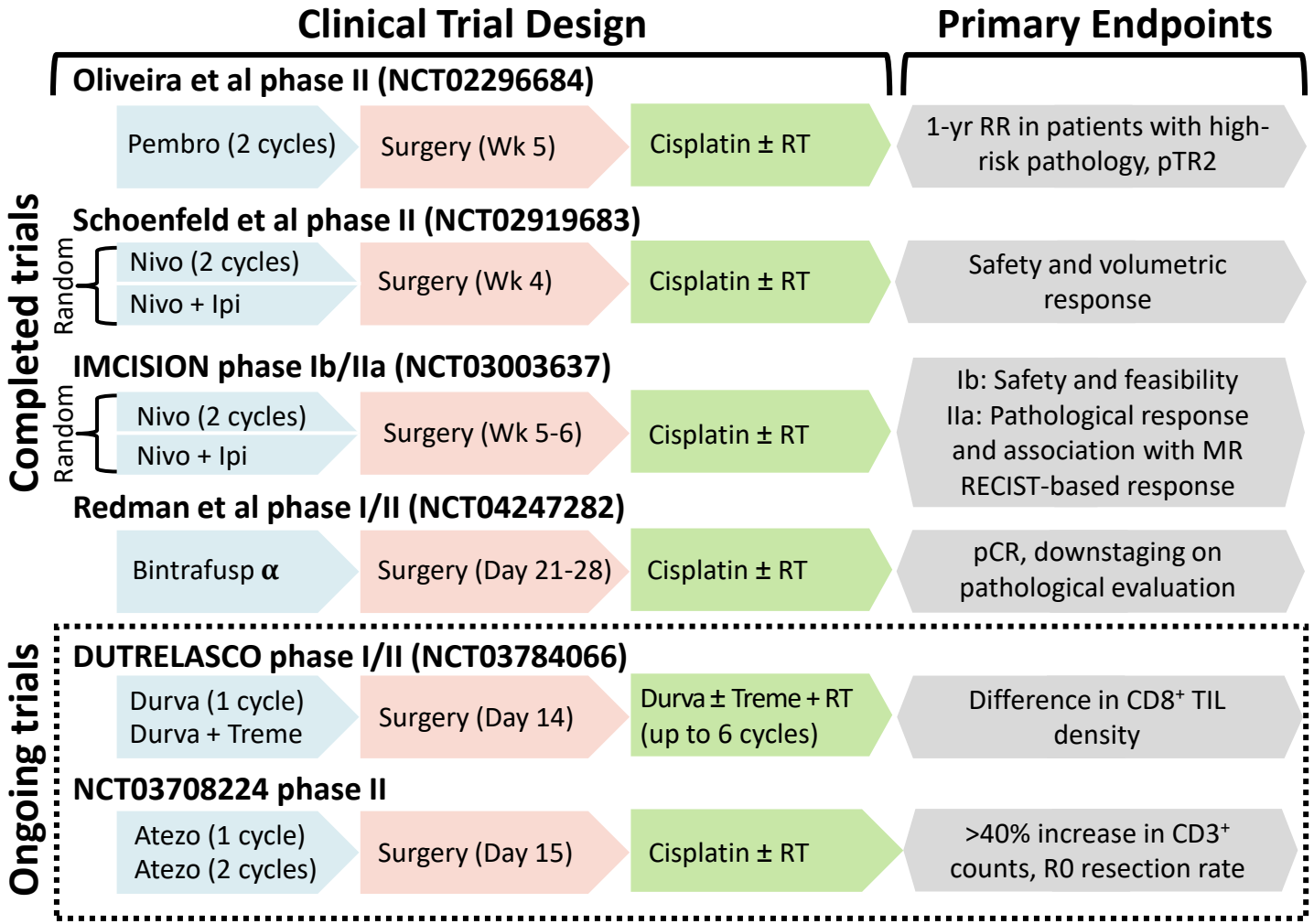
- 2 mechanistic aspects
  - Preexisting antitumor immunity is “unleashed”
  - Direct cytotoxicity → pathologic responses
- Immune checkpoint blockade with tumor antigen burden in place and “functional” lymph nodes provides “vaccination” with enhanced durable immune response

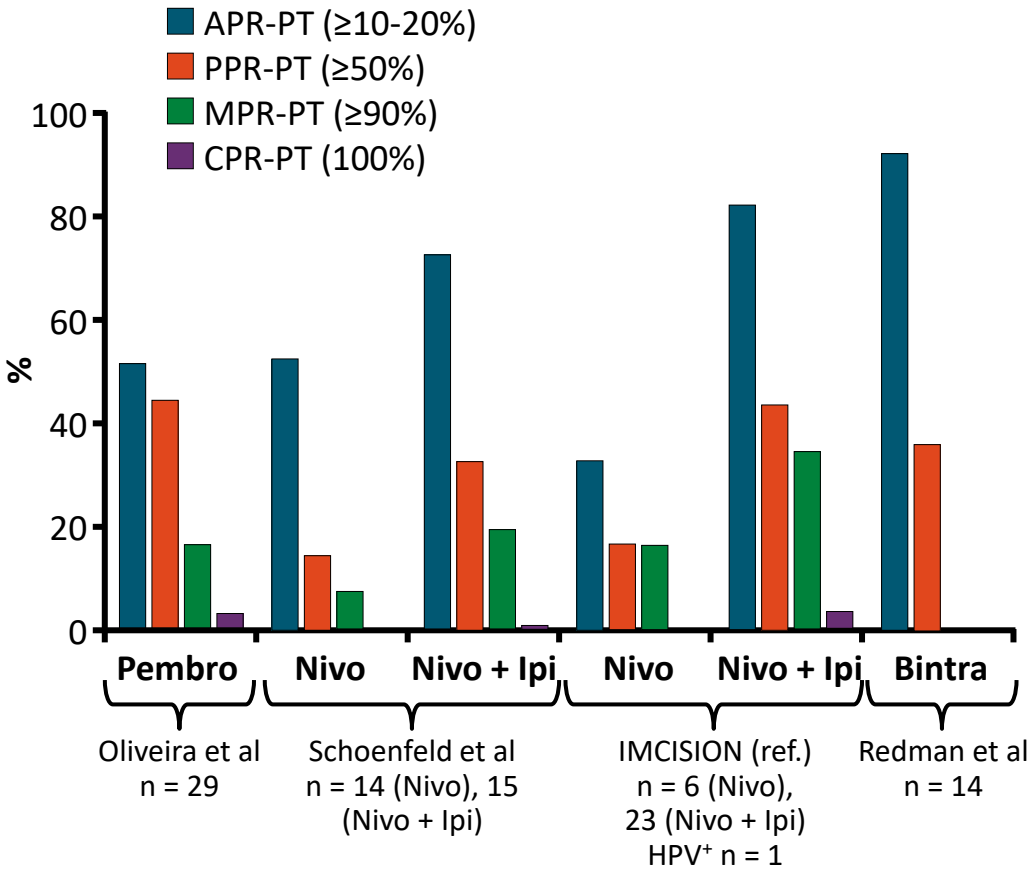
Uppaluri. ASCO 2021. Abstr 6008. Zhao. Nat Rev Clin Oncol. 2025;22:83.

Is Neoadjuvant Immunotherapy Safe Prior to HNSCC Surgery?

- Multiple studies showing no major impact:
  - Planned surgical date
  - Intraoperative and postoperative complications
  - Disease progression during immunotherapy
  - Multidisciplinary collaboration Key

Neoadjuvant Therapy for HNSCC

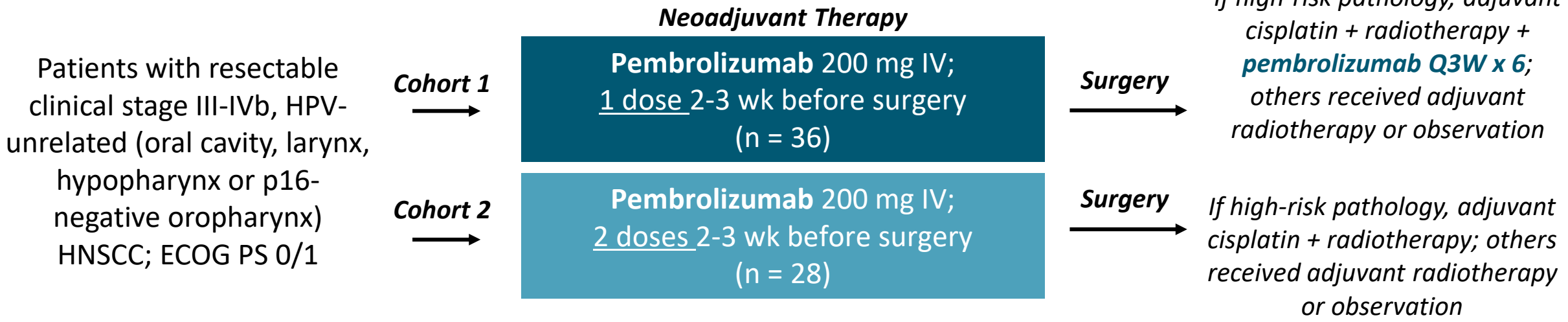




Zhao. Nat Rev Clin Oncol. 2025;22:83.

Neoadjuvant Pembrolizumab for Locally Advanced HNSCC

- Multicenter, nonrandomized 2-group phase II study

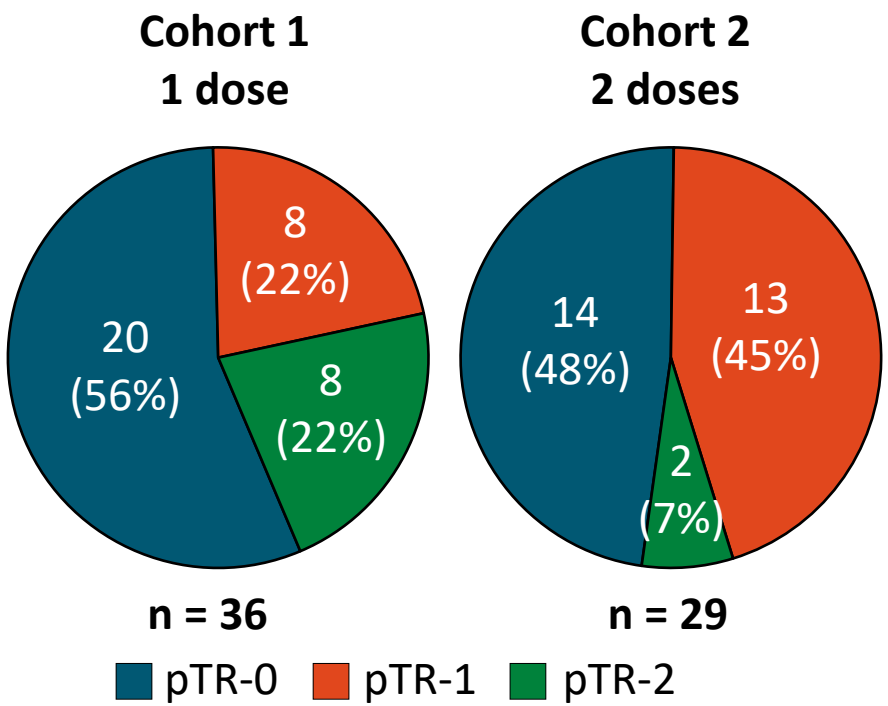


- Primary endpoints: 1-yr recurrence rate in pts with high-risk pathology, pTR-2* in all patients

*Tumor cell necrosis and keratinous debris with giant cell/histiocytic reaction as a percentage of the overall tumor bed; pTR-2 ≥50%.

Uppaluri. Clin Cancer Res. 2020;26:5140. Oliveira. Sci Immunol. 2023;8:eadf4968.

Neoadjuvant Pembrolizumab for Locally Advanced HNSCC: Dose/Timing



- Pathologic response scale
  - **pTR0** <10%
  - **pTR1** ≥10% and <50%
  - **pTR2** ≥50%

Exploratory analysis

- 1 dose pembro before surgery: 22% pTR2
- 2 doses pembro before surgery: 45% pTR2

% patients with any pTR similar cohort 1 and 2

Uppaluri. Clin Cancer Res. 2020;26:5140. Oliveira. Sci Immunol. 2023;8:eadf4968.

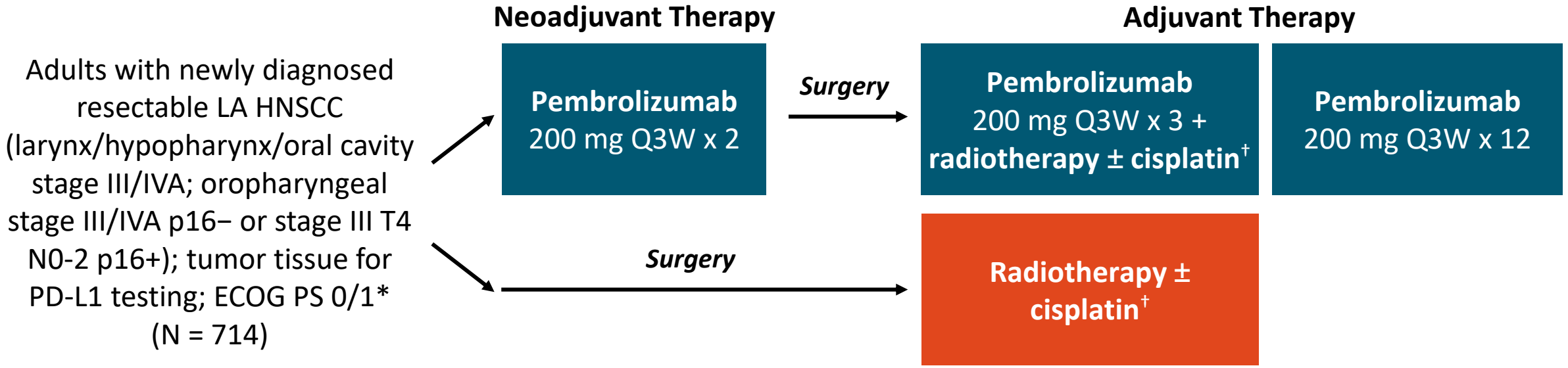
Neoadjuvant Pembrolizumab for Locally Advanced HNSCC: Outcomes

Outcome, n (%)	Cohort 2 (n = 28)	Cohort 1 (n = 36)	*P* Value	Δ (95% CI)
pTR category				
▪ pTR-0	14 (50)	20 (55.6)	.11	-5.6 (-28.4 to 18.0)
▪ pTR-1	2 (7.1)	8 (22.2)		-15.1 (-31.8 to 3.6)
▪ **pTR-2**	**12 (42.9)**	**8 (22.2)**		**20.6 (-2.1 to 41.5)**
Pathologic risk				
▪ **High**	**5 (17.9)**	**18 (50.0)**	**.008**	
▪ **Intermediate/low**	**23 (82.1)**	**18 (50.0)**		**32.1 (8.6 to 50.6)**
Pathologic disease stage				
▪ I-II	5 (17.9)	3 (8.3)	.54	9.5 (-7.3 to 28.1)
▪ III	5 (17.9)	6 (16.7)		1.2 (-17.0 to 21.0)
▪ IVA-IVB	18 (64.3)	27 (75)		-10.7 (-32.3 to 11.3)
Downstaged (clinical > pathologic stage)	**8 (28.6)**	**7 (19.4)**	**.15**	**9.1 (-11.4 to 30.0)**
Upstaged (clinical < pathologic stage)	2 (7.1)	0		7.1 (-3.8 to 22.6)
Stage unchanged	18 (64.3)	29 (80.6)		-16.3 (-37.1 to 5.4)

Uppaluri. ASCO 2021. Abstr 6008. Oliveira. Sci Immunol. 2023;8:eadf4968.

KEYNOTE-689: Perioperative Pembrolizumab + SoC for Locally Advanced HNSCC

- Randomized, open-label phase III trial



*Stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx), tumor stage (III vs IVA), PD-L1 TPS (≥50% vs <50%). †Low risk: RT 60 Gy x 30 fractions; high risk: 66 Gy x 33 fractions + 3 cycles concurrent cisplatin 100 mg/m^2 Q3W; gross residual disease: RT 70 Gy x 35 fractions + cisplatin.

- Primary endpoint: EFS per RECIST 1.1 by BICR
- Key secondary endpoints: mPR, OS, safety

Uppaluri. AACR 2025. Abstr CT001.

KEYNOTE-689: Baseline Characteristics

Characteristic	Pembro + SoC (N = 363)	SoC (N = 351)
Median age, yr (range)	60.0 (29-82)	61.0 (22-87)
Male, n (%)	286 (78.8)	277 (78.9)
Current/former smoker, n (%)*	293 (80.7)	267 (76.1)
Alcohol use, n (%)*	250 (68.9)	238 (67.8)
Primary tumor site, n (%)		
Oral cavity	219 (60.3)	213 (60.7)
Larynx	81 (22.3)	73 (20.8)
Hypopharynx	28 (7.7)	26 (7.4)
Oropharynx	35 (9.6)	38 (10.8)
Missing	0	1 (0.3)
Positive HPV status, n (%)†	12 (3.3)	15 (4.3)
PD-L1 CPS ≥10, n (%)	234 (64.5)	231 (65.8)
PD-L1 CPS ≥1, n (%)	347 (95.6)	335 (95.4)

*Unknown smoking/alcohol use: n = 6 in pembro + SoC group, n = 3 in SoC group. †Unknown HPV status, n = 1 in SoC group.

Uppaluri. AACR 2025. Abstr CT001.

KEYNOTE-689: Treatment Disposition (ITT)

Therapy, n (%)		Pembro + SoC (n = 363)	SoC (n = 351)
Neoadjuvant therapy	Received ≥1 dose of neoadjuvant pembrolizumab	360 (99.2)	2 (0.6)*
	Completed 2 cycles of pembrolizumab	341 (93.9)	1 (0.3)
	Permanently discontinued all study therapy at this phase	30 (8.3)	0
In-study surgery	**Underwent surgery**	**322 (88.7)**	**308 (87.7)**
	▪ **Completed surgery**	**321 (88.4)**	**308 (87.7)**
	▪ **Tumor found to be surgically unresectable**	**1 (0.3)**	**0**
	Permanently discontinued all study therapy at this phase	55 (15.2)	41 (11.7)
	Postoperative risk assessment by BIPR		
	▪ **High-risk features present**	**118 (32.5)**	**156 (44.4)**
	▪ **Low risk (no high-risk features present)**	**196 (54.0)**	**148 (42.2)**
	▪ Missing	49 (13.5)	47 (13.4)
Adjuvant therapy	Received ≥1 dose of adjuvant therapy after surgery	267 (73.6)†	267 (76.1)†
	▪ Started radiotherapy	266 (73.3)	267 (76.1)
	▪ Started pembrolizumab	248 (68.3)	0
	▪ Started cisplatin	100 (27.5)	132 (37.6)
	Permanently discontinued all study therapy at this phase	109 (30.0)	14 (4.0)
All study treatment	Completed all study treatment	155 (42.7)	261 (74.4)
	Treatment ongoing	11 (3.0)	0

*n = 2 received neoadjuvant pembrolizumab (error). †n = 8 in each group received definitive therapy with no surgery.

Uppaluri. AACR 2025. Abstr CT001.

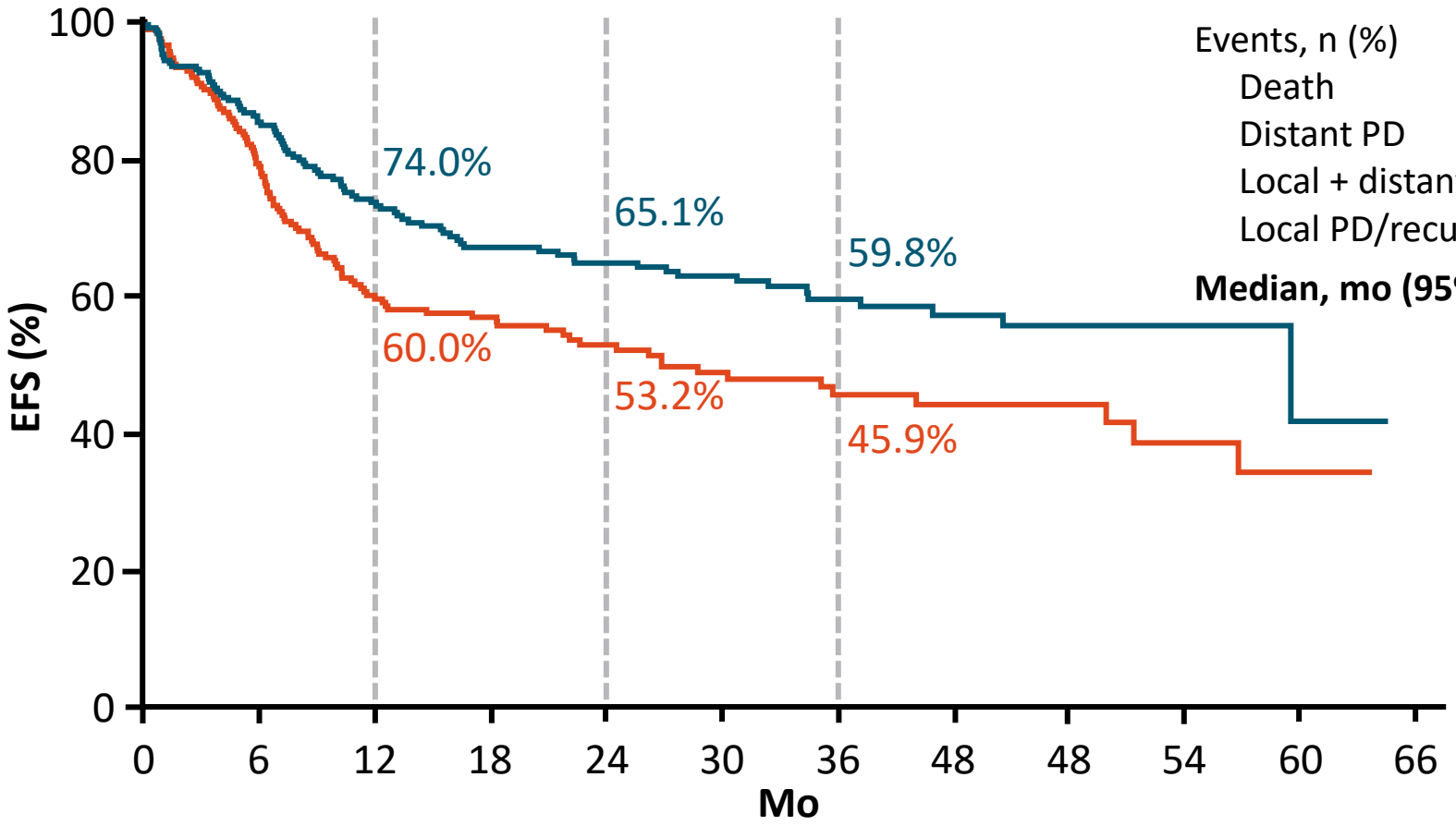
KEYNOTE-689: Treatment Exposure (As-Treated Population)

Parameter	Pembro + SOC	SOC
Total duration on study therapy, including study drugs and in-study surgery/radiotherapy		
n	361	315
Median duration, mo (range)	9.1 (0.03–22.3)	2.9 (0.03–7.2)
Duration of neoadjuvant pembrolizumab		
n	361*	1*
Median duration, mo (range)	0.7 (0.03–1.1)	0.03 (0.03–0.03)
Median cycles, n (range)	2.0 (1.0–2.0)	1.0 (1.0–1.0)
Surgery, n	**323**	**307**
Duration of adjuvant therapy		
Pembrolizumab, N	**255**	**0**
Median duration (range), mo	9.7 (0.03–18.9)	0
Median cycles (range), n	15.0 (1.0–16.0)	0
Radiotherapy, N	**274**	**275**
Median duration (range), days	44.0 (1.0–90.0)	45.0 (3.0–73.0)
Median dose (range), Gy	60.0 (2.0–70.0)	66.0 (6.0–72.0)
Cisplatin, N	**107**	**139**
Median duration (range), mo	1.4 (0.0–1.8)	1.4 (0.0–1.7)
Median cycles (range), n	3.0 (1.0–3.0)	3.0 (1.0–3.0)
Total dose ≥200 mg, n (%)	95 (88.8)	126 (90.6)

*n = 2 in SOC group erroneously received neoadjuvant pembrolizumab (protocol deviations); n = 1 included in the pembro + SOC as-treated population.

Uppaluri. AACR 2025. Abstr CT001.

KEYNOTE-689: EFS in CPS ≥10 Population (Primary Endpoint)



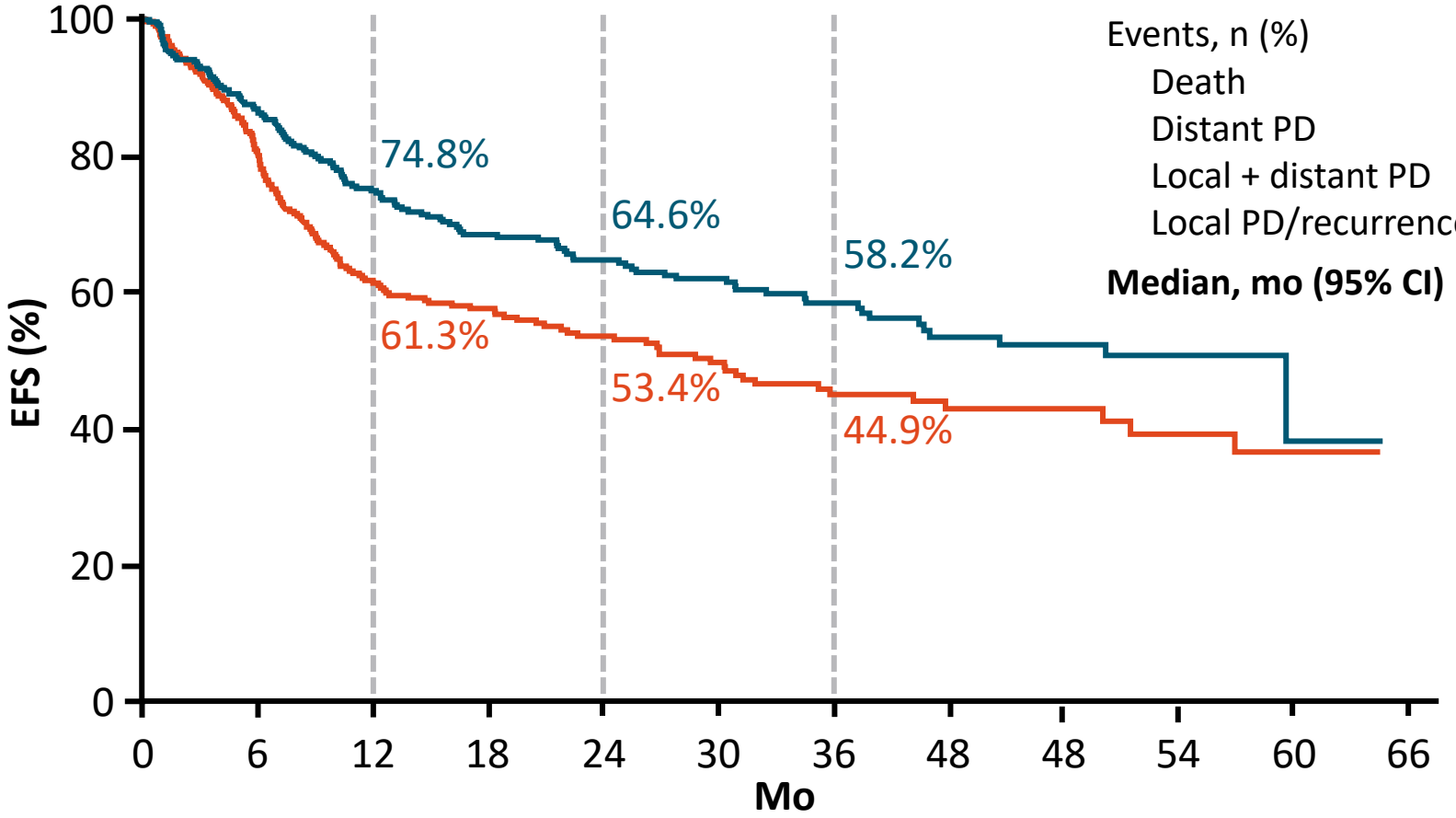
	Pembro + SoC (N = 234)	SoC (N = 231)
Events, n (%)	85 (36.3)	107 (46.3)
Death	43 (18.4)	37 (16.0)
Distant PD	15 (6.4)	39 (16.9)
Local + distant PD	2 (0.9)	2 (0.9)
Local PD/recurrence	25 (10.7)	29 (12.6)
Median, mo (95% CI)	**59.7 (41.1-NR)**	**26.9 (18.3-51.5)**

HR: 0.66 (95% CI: 0.49-0.88)
***P* = .0022**

*Significance boundary was met at IA1.

Uppaluri. AACR 2025. Abstr CT001.

KEYNOTE-689: EFS in CPS ≥1 Population (Primary Endpoint)



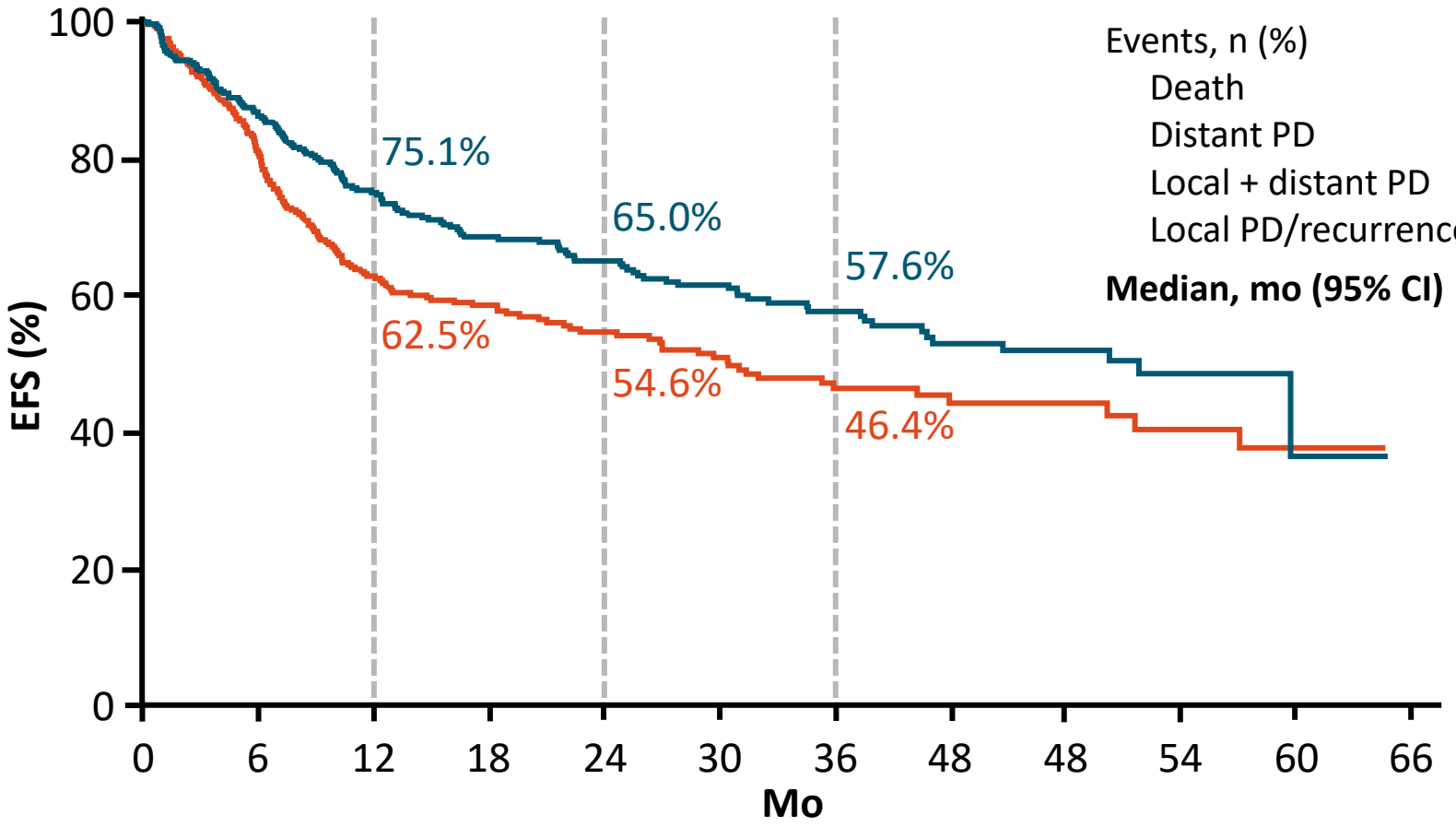
	Pembro + SoC (N = 347)	SoC (N = 335)
Events, n (%)	128 (36.9)	156 (46.6)
Death	63 (18.2)	62 (18.5)
Distant PD	24 (6.9)	51 (15.2)
Local + distant PD	4 (1.2)	6 (1.8)
Local PD/recurrence	37 (10.7)	37 (11.0)
Median, mo (95% CI)	**59.7 (37.9-NR)**	**29.6 (19.5-41.9)**

HR: 0.70 (95% CI: 0.55-0.89)
P* = .0014

*Significance boundary was met at IA1.

Uppaluri. AACR 2025. Abstr CT001.

KEYNOTE-689: EFS in All Participants (Primary Endpoint)



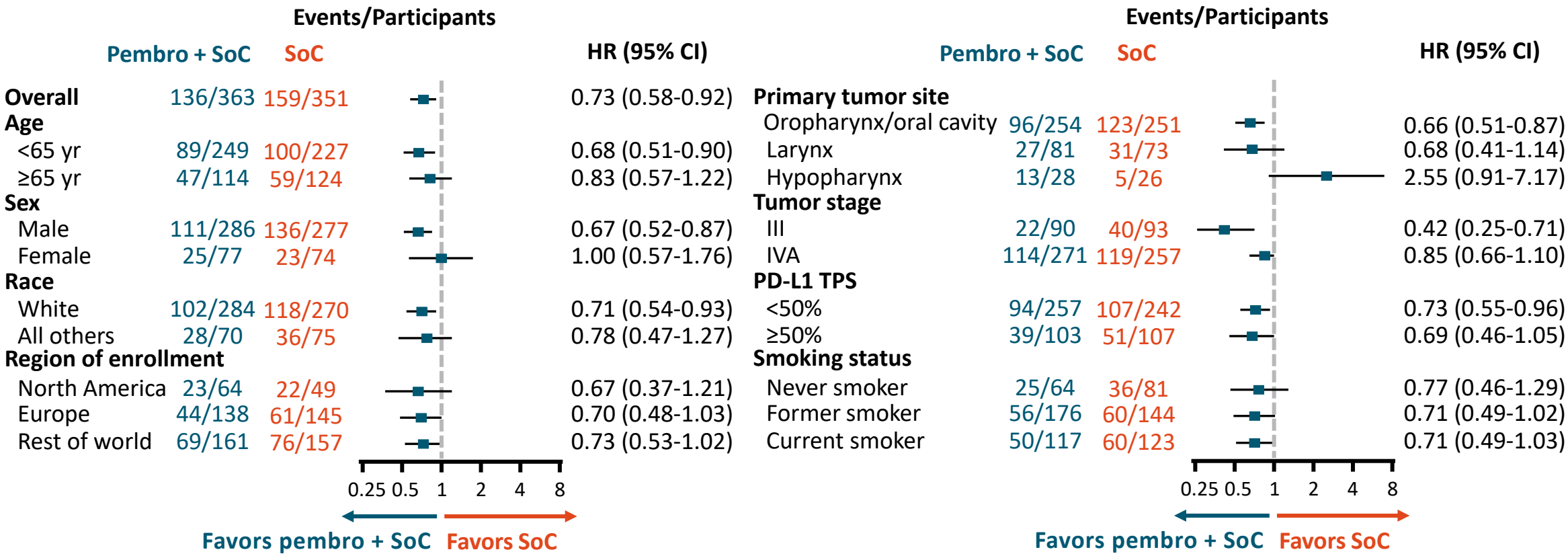
	Pembro + SoC (N = 363)	SoC (N = 351)
Events, n (%)	136 (37.5)	159 (45.3)
Death	67 (18.5)	64 (18.2)
Distant PD	26 (7.2)	51 (14.5)
Local + distant PD	4 (1.1)	7 (2.0)
Local PD/recurrence	39 (10.7)	37 (10.5)
Median, mo (95% CI)	**51.8 (37.5-NR)**	**30.4 (21.8-50.1)**

HR: 0.73 (95% CI: 0.58-0.92)
P* = .0041

*Significance boundary was met at IA1.

Uppaluri. AACR 2025. Abstr CT001.

KEYNOTE-689: EFS by Subgroups in All Participants



Uppaluri. AACR 2025. Abstr CT001.

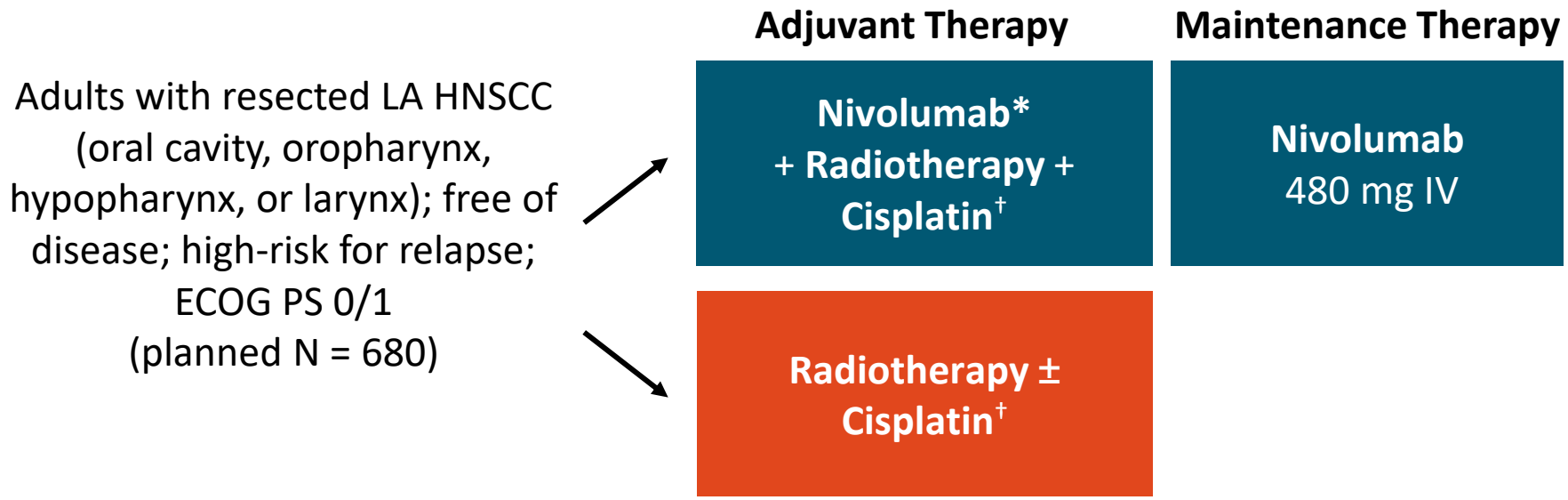
KEYNOTE-689: Conclusions

- In the phase III KEYNOTE-689 study, the addition of neoadjuvant/adjuvant pembrolizumab to SoC for patients with locally advanced HNSCC significantly improved EFS and DMFS in patients with PD-L1 CPS ≥10, CPS ≥1, and in all participants
  - OS benefit not statistically significant at IA1; follow-up ongoing
  - Surgical completion rate not changed by addition of neoadjuvant pembrolizumab
  - Pembrolizumab associated with fewer patients with postoperative high-risk pathologic features
- No new safety signals observed
- Investigators concluded that neoadjuvant pembrolizumab followed by surgery and adjuvant pembrolizumab with and after postoperative radiotherapy ± chemotherapy is a new SoC for patients with resectable locally advanced HNSCC

Uppaluri. AACR 2025. Abstr CT001.

NIVOPOSTOP: Adjuvant Nivolumab + SoC for Locally Advanced HNSCC

- Randomized, open-label phase III trial



*240 mg 3 wk prior to RT + cisplatin; 360 mg on Days 1, 22,43 of RT + cisplatin. †Cisplatin 100 mg/m^2 on Days 1, 22, 43 of RT; IMRT 66 Gy x 6.5 wk.

- Primary endpoint: DFS; key secondary endpoints: OS, acute toxicity, late toxicity
- Per press release, met primary DFS endpoint; data presentation at ASCO 2025 (LBA2)

NCT03576417.

Disease-free survival: (primary endpoint ; ITT)

GORTEC

Analysis based on **252 DFS events**
at the data cutoff of April 30th 2024

Median follow-up: 30.3 months (IQR 16-44.9)

3-years DFS

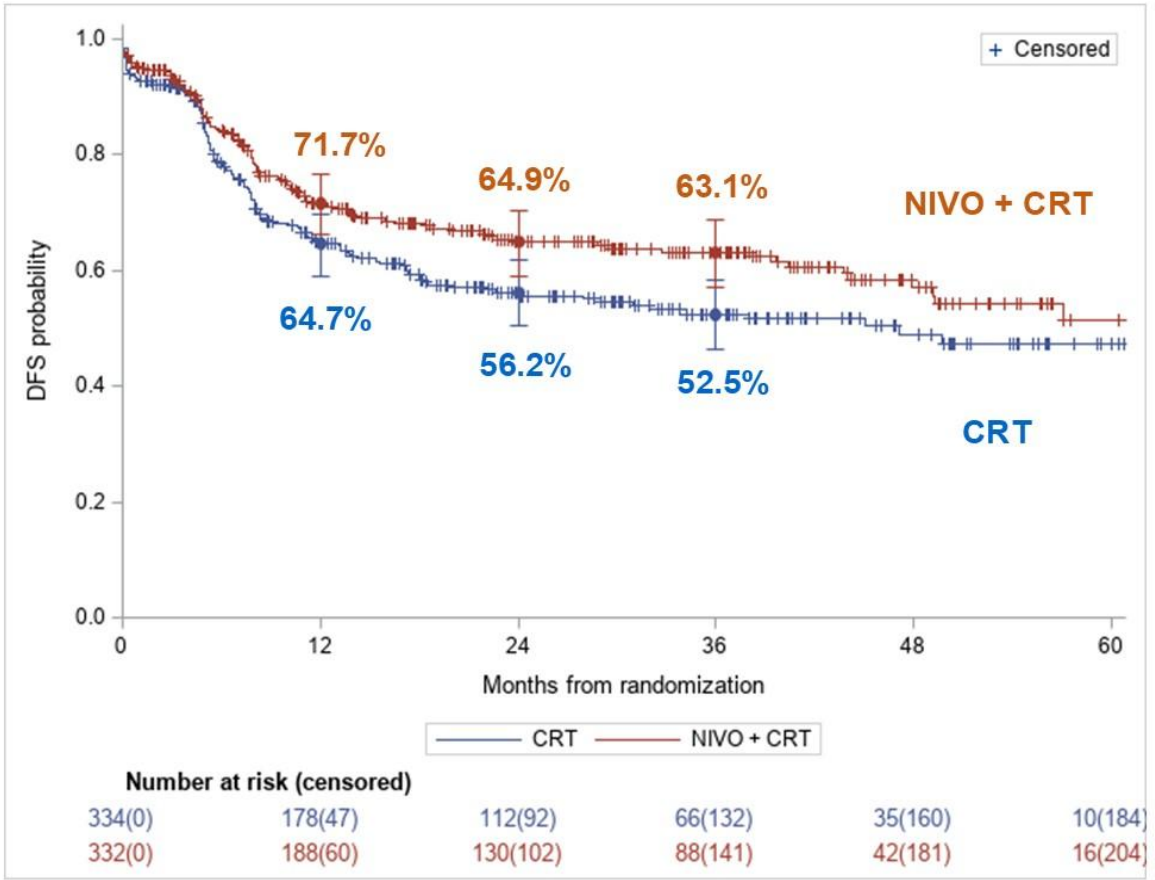
63.1% (95%CI 57.0%; 68.7%)
with NIVO + CRT

versus

52.5% (95%CI 46.2%; 58.4%)
with CRT

Stratified* HR (95%CI) = 0.76 (0.60; 0.98)
Stratified log-rank p-value=0.034

*HR stratified for p16 status (OPC p16 positive *versus* OPC p16 negative and non-OPC) in Cox model



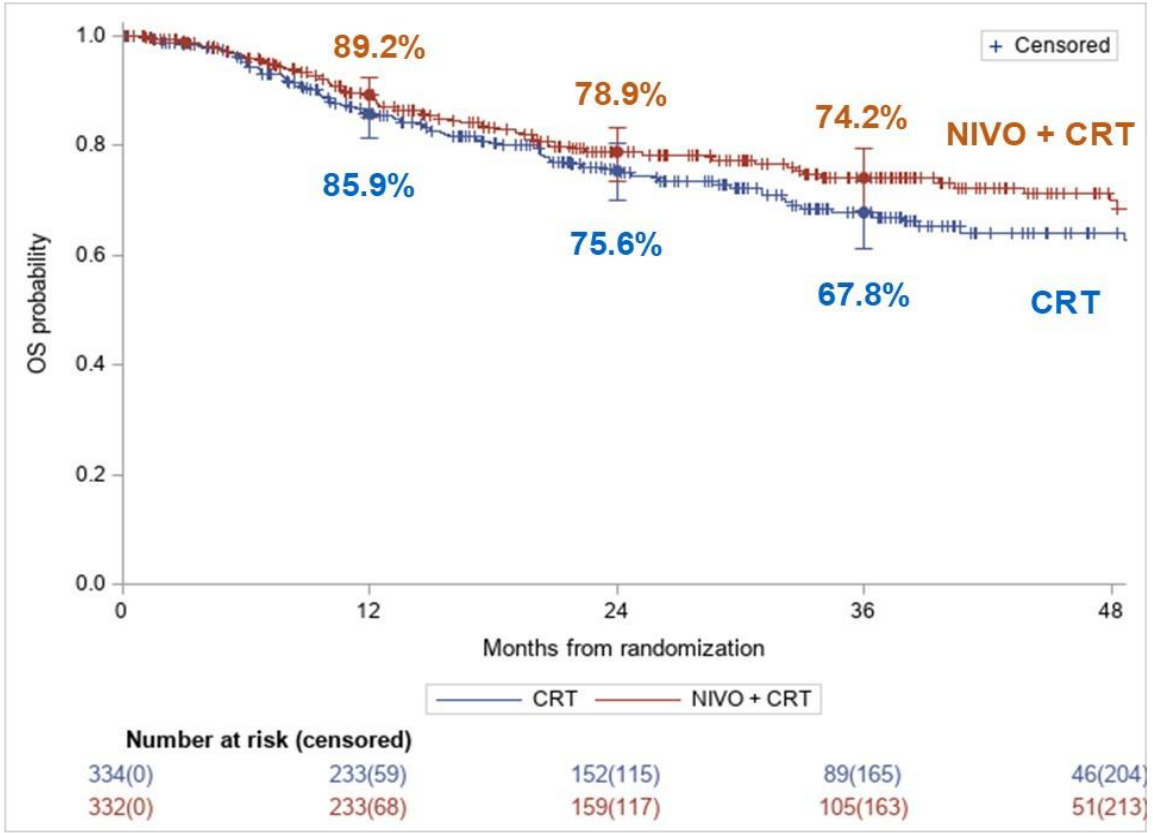
Overall survival (descriptive)

GORTEC

At the data cutoff, 158 patients died.

Results are in favor of NIVO + CRT but **OS could not be formally tested** since the pre-specified number of deaths was not reached.

The statistical analysis of OS requires more mature data according to the statistical plan.



Takeways

- **Background :** for high risk resected head and neck SCC cancers, the SOC cisplatin-radiotherapy did not change in the past decades

- **NIVOPOSTOP** phase III study tested the addition of nivolumab to SOC

- **Outcome :** the primary endpoint of improving DFS was met, with only a moderate increase in toxicity

Summary

GORTEC

The benefit-risk ratio of adding nivolumab appeared favorable :

- The primary endpoint was met : DFS significantly improved (HR 0.76)
- Moderate increased toxicity, without increase in treatment-related deaths

Post-operative nivolumab added to SOC cisplatin-RT improved patient outcomes for resected high-risk LA-SCCHN, that could be proposed as a new standard treatment, … for the first time in two decades…

Select Ongoing Phase III Studies of Sequential Immunotherapy for Unresected Locally Advanced HNSCC

Trial	Population	Treatment	Primary Endpoint
JADE (NCT06256588)	Newly diagnosed, unresected LA HNSCC; completed curative intent cCRT; PD-L1+ (planned N = 864)	Dostarlimab vs placebo; sequentially with CRT	EFS
eVOLVE-HNSCC (NCT06129864)	Unresected LA HNSCC; completed curative intent cCRT without PD (planned N = 1145)	Volrustomig (PD-1/CTLA-4 bispecific mAb) vs observation; sequentially with CRT	PFS in PD-L1 expressing tumors

Conclusions

- The SoC for patients with locally advanced resectable HNSCC has not evolved in many decades: surgery, RT, chemotherapy
  - Checkpoint blockade trials in curatively-treated HNSCC negative to date
  - Poor patient selection, heterogenous populations, no biomarker selection
- New biomarkers for HPV-positive disease and MRD testing possible in all patients
- 2025 could introduce a fundamental change in how surgically treated HNSCC is managed:
  - Multidisciplinary care even more important now
  - Patient selection is key
  - Neoadjuvant and adjuvant trials positive
  - Potential major impact on metastatic disease as immunotherapy moves to frontline therapy

Thank you