Dana-Farber Cancer Institute

Immunotherapy in Head & Neck Cancer and What After IO Failure?

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Head and Neck Cancer
Current Landscape in 2022

- HPV major cause of oropharynx cancer in the western world: Young pts with high cure rate . Treatment de-Escalation approaches evolving
- New Staging system for HPV + in AJCC 8
- Cisplatin, Radiation, Surgery are mainstay of therapy for locally advanced disease
- High toxicity seen with combined therapy
- Treatment of recurrent/metastatic disease remains challenging but new treatment options available
- Checkpoint inhibitors are active in recurrent /metastatic disease and improve survival
- Current Standard of Care in first line R/M SCC is Pembrolizumab ± Chemotherapy Role of CPS PDL-1

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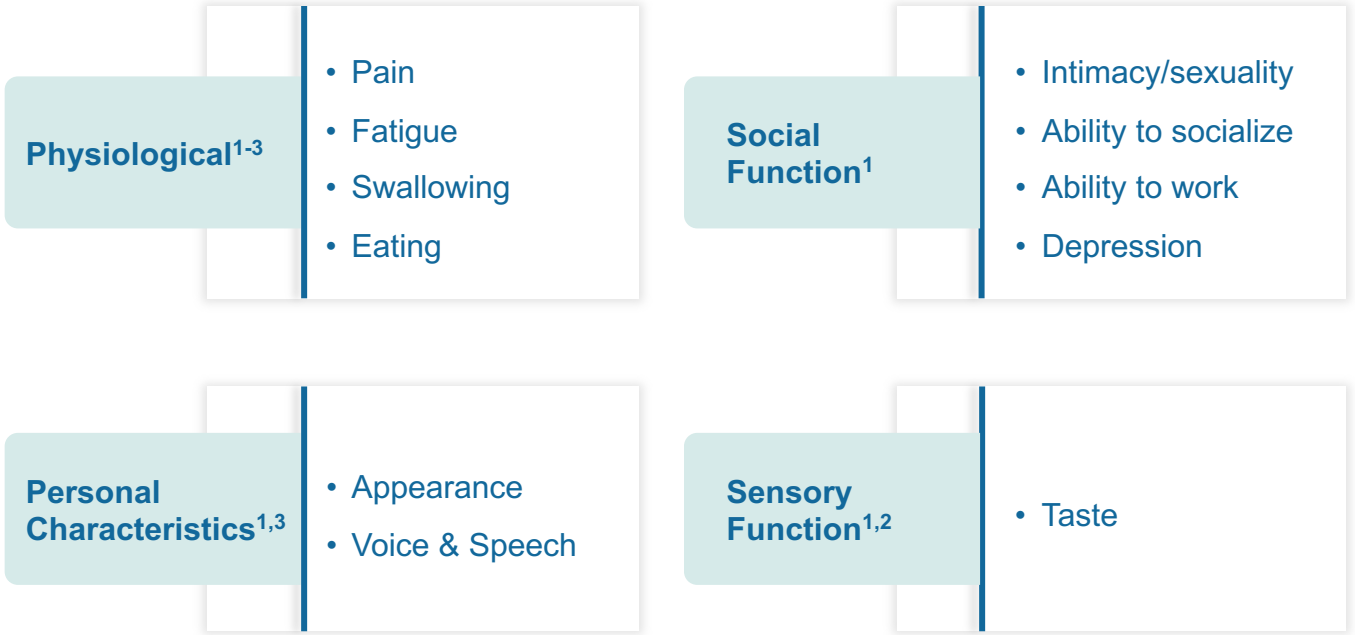
Quality of Life in Head and Neck Cancer



QoL, quality of life; SCCHN, squamous cell carcinoma of the head and neck.

1. Gritz ER et al. *J Clin Oncol*. 1999;17(1):352-360. 2. Curran D et al. *J Clin Oncol*. 2007:25(16): 2191-2197. 3. Rogers SN et al. *Br J Oral Maxillofac Surg*. 2016;54(6):doi: 10.1016/j.bjoms.2016.02.012.

Palliative Systemic Therapy for R/M HNSCC

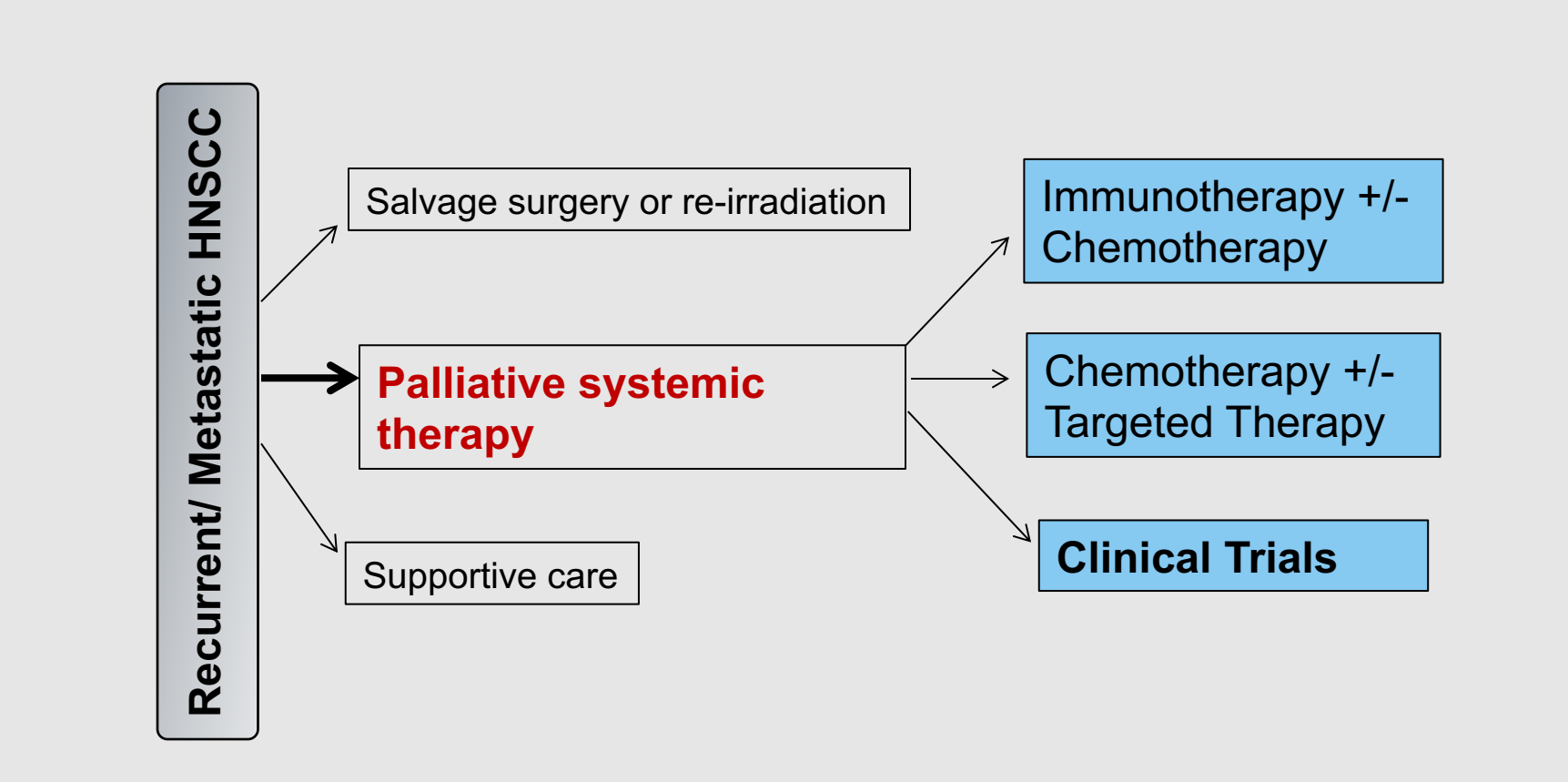
Goals of treatment

- Symptom control, prevention of new cancer-related symptoms
- Improve quality of life
- Disease control
- PFS, OS prolongation

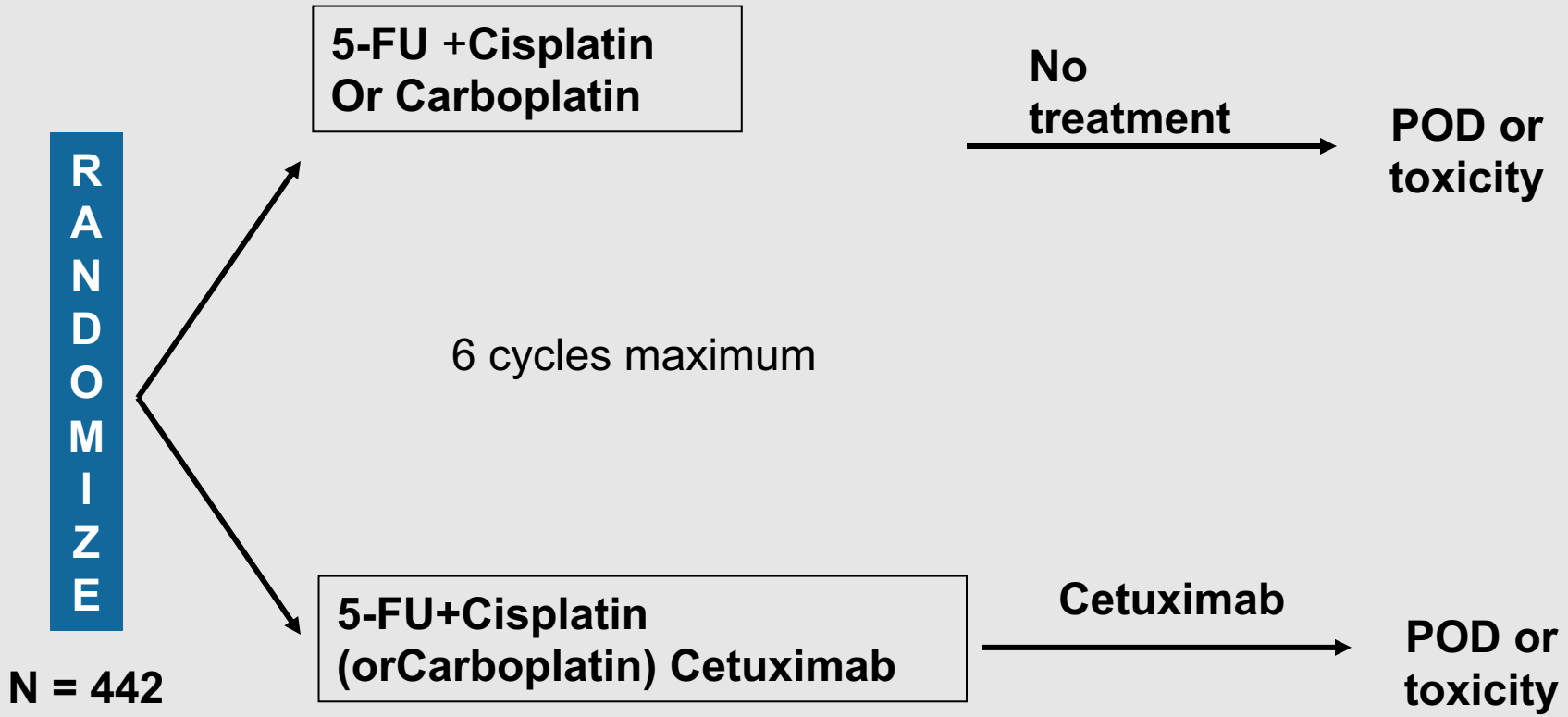
Choice of treatment depends on

- Performance status
- Comorbidities (alcohol or tobacco use, aspiration pneumonia, infection, malnutrition)
- Prior treatment
- Symptoms
- Patient preference & logistics
- Biomarkers

Management Of Recurrent/Metastatic SCCHN



EXTREME: Study Design

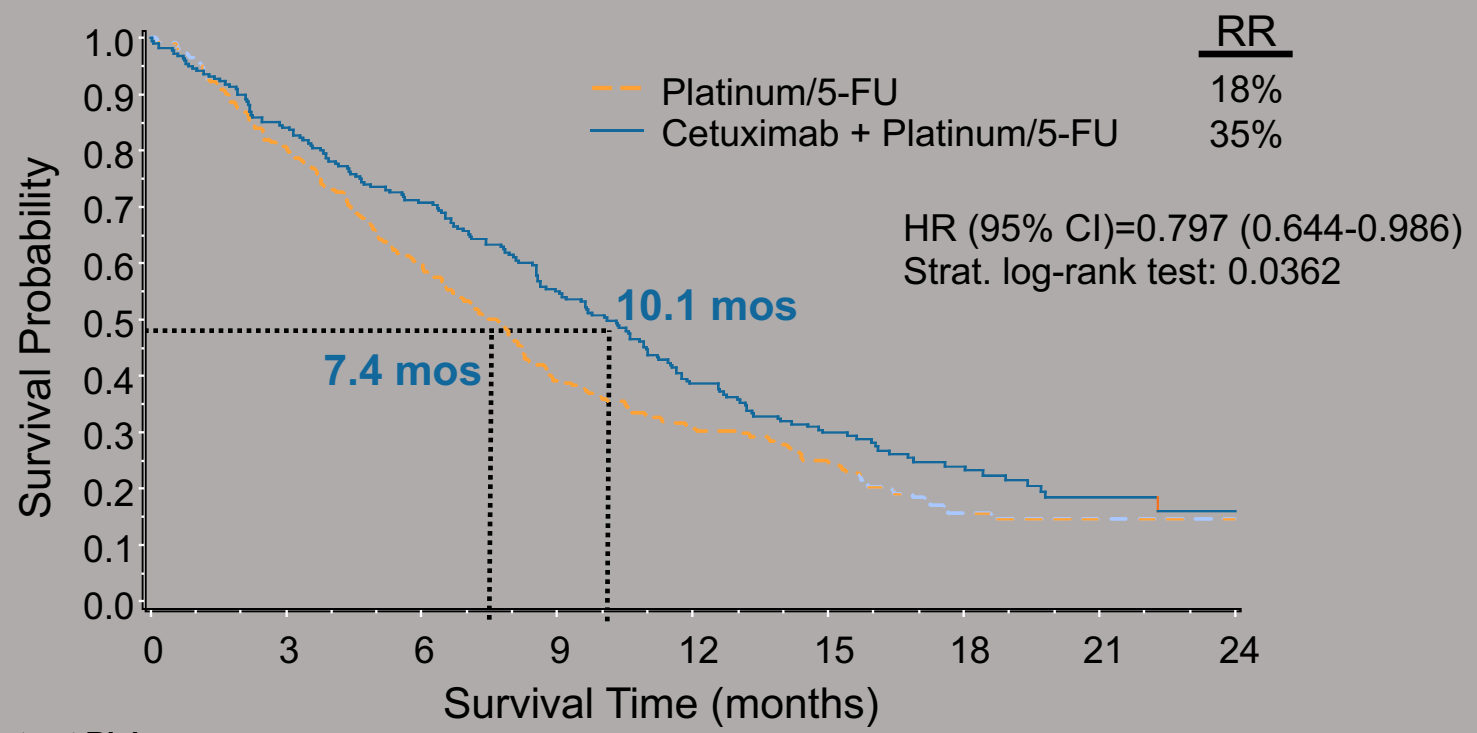


*Loading dose of 400 mg/m^2 on week 1

Vermorken JB, et al. N Engl J Med. 2008;359(11):1116-1127

EXTREME: First-line Platinum/5-FU ± Cetuximab In Recurrent/Metastatic SCC: Survival

OS



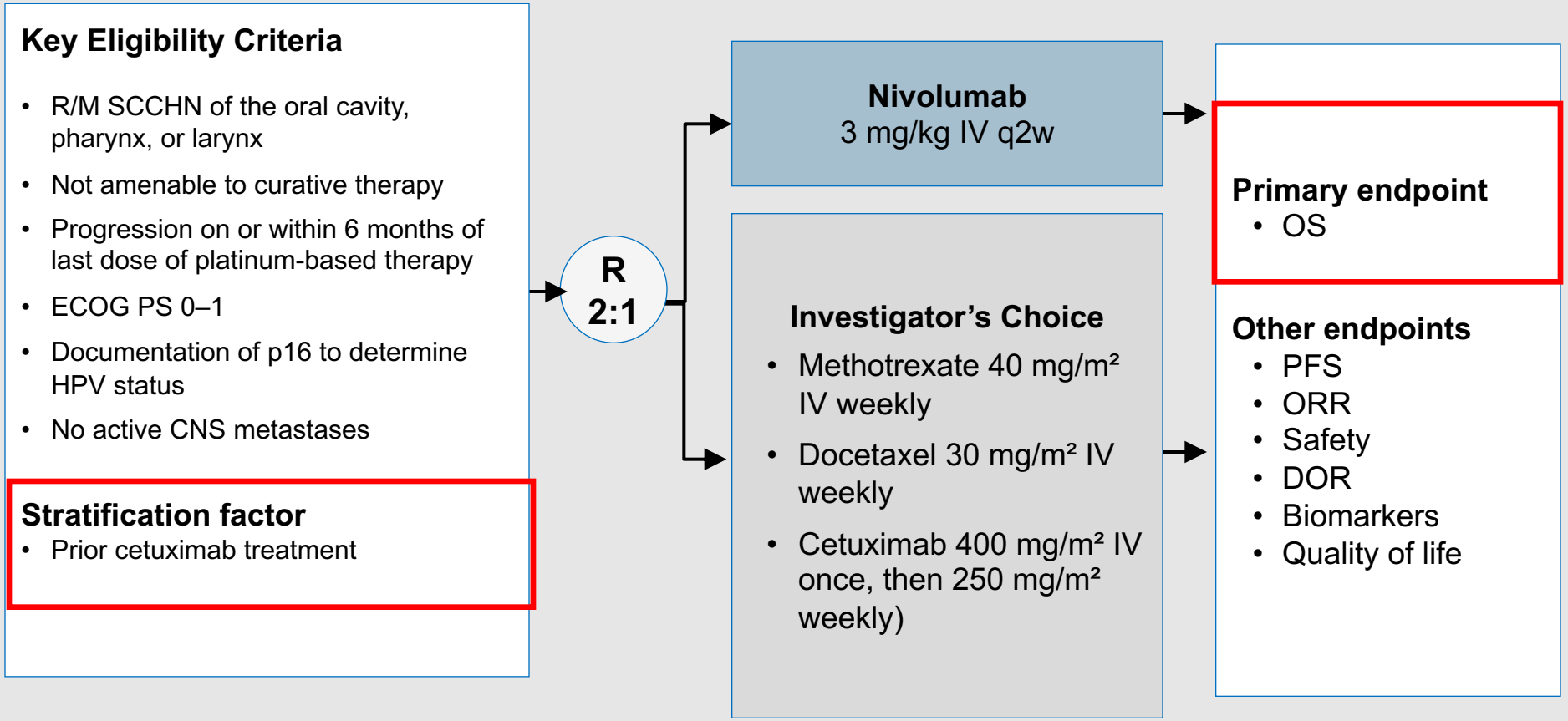
Patients at Risk:

Platinum/5-FU	220	173	127	83	65	47	19	8	1
Cetuximab + Platinum/5-FU	222	184	153	118	82	57	30	15	3

Vermorken JB, et al. N Engl J Med. 2008;359(11):1116-1127

Immunotherapy In Recurrent/Metastatic Head and Neck Cancer

Checkmate 141 Study Design
Nivolumab vs. Chemotherapy

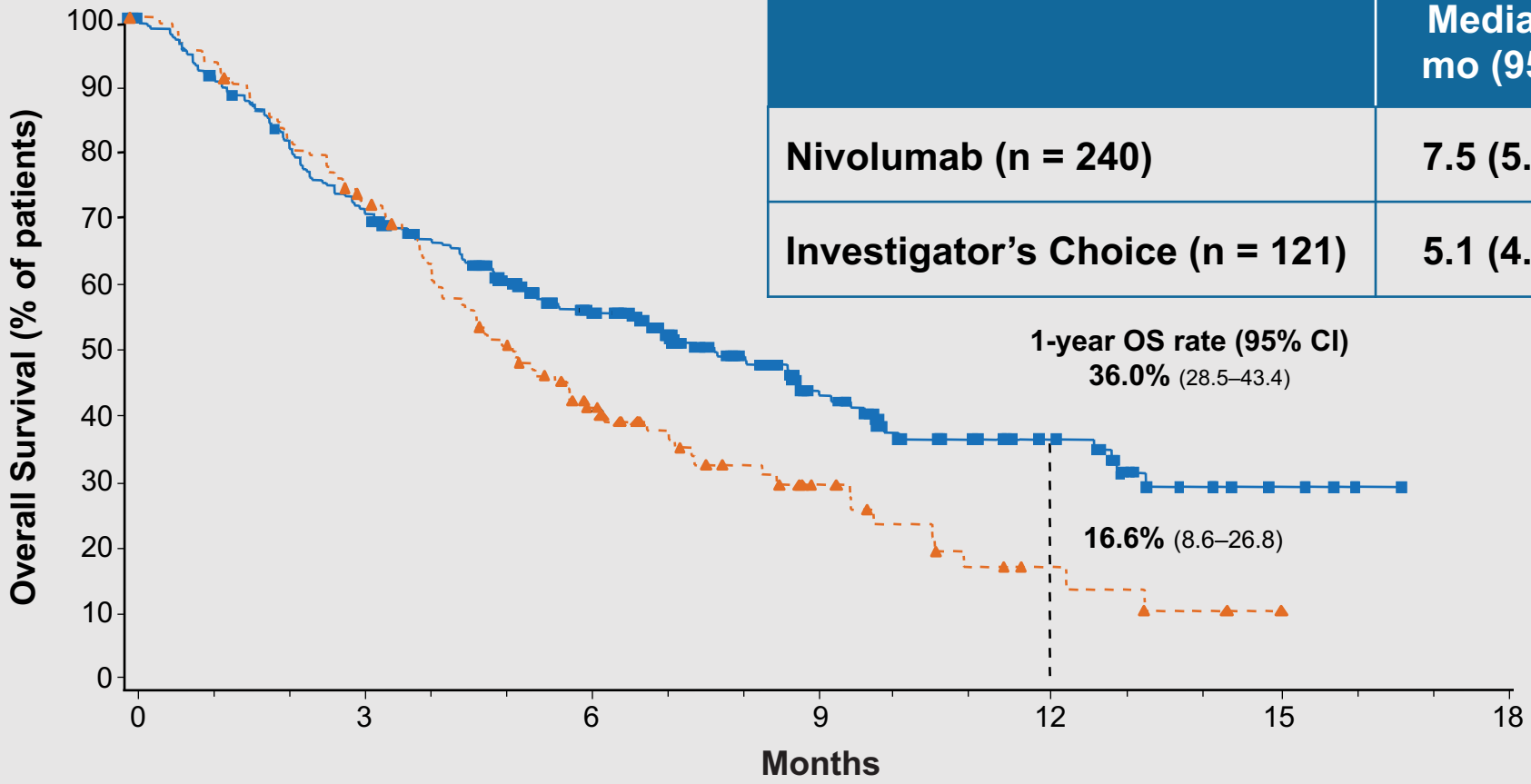


CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papillomavirus; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomized; R/M, recurrent/metastatic; SCCHN, squamous cell carcinoma of the head and neck; Clinicaltrials.gov, NCT02105636.

Ferris et al : NEJM 2016

Checkmate 141: Overall Survival

	Median OS, mo (95% CI)	HR (97.73% CI)	p-value
Nivolumab (n = 240)	7.5 (5.5–9.1)	0.70 (0.51–0.96)	0.0101
Investigator's Choice (n = 121)	5.1 (4.0–6.0)		



No. at Risk

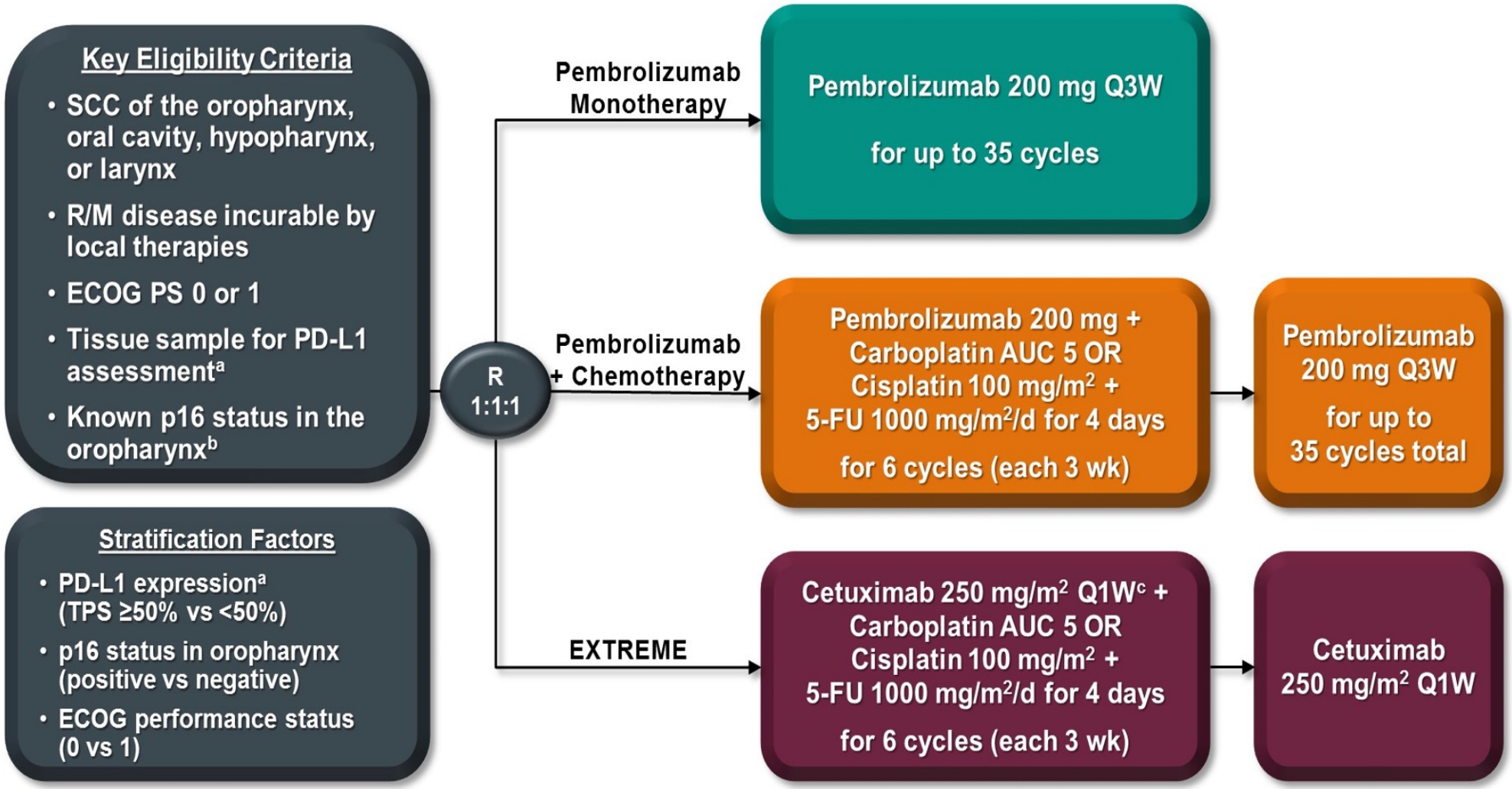
Nivolumab	240	167	109	52	24	7	0
Investigator's Choice	121	87	42	17	5	1	0

KEYNOTE-048

Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study

*Barbara Burtness, Kevin J Harrington, Richard Greil, Denis Soulières, Makoto Tahara, Gilberto de Castro Jr, Amanda Psyrri, Neus Basté, Prakash Neupane, Åse Bratland, Thorsten Fuereder, Brett G M Hughes, Ricard Mesía, Nuttapong Ngamphaiboon, Tamara Rordorf, Wan Zamaniah Wan Ishak, Ruey-Long Hong, René González Mendoza, Ananya Roy, Yayan Zhang, Burak Gumuscu, Jonathan D Cheng, Fan Jin, Danny Rischin, on behalf of the KEYNOTE-048 Investigators**

KEYNOTE-048: Study Design

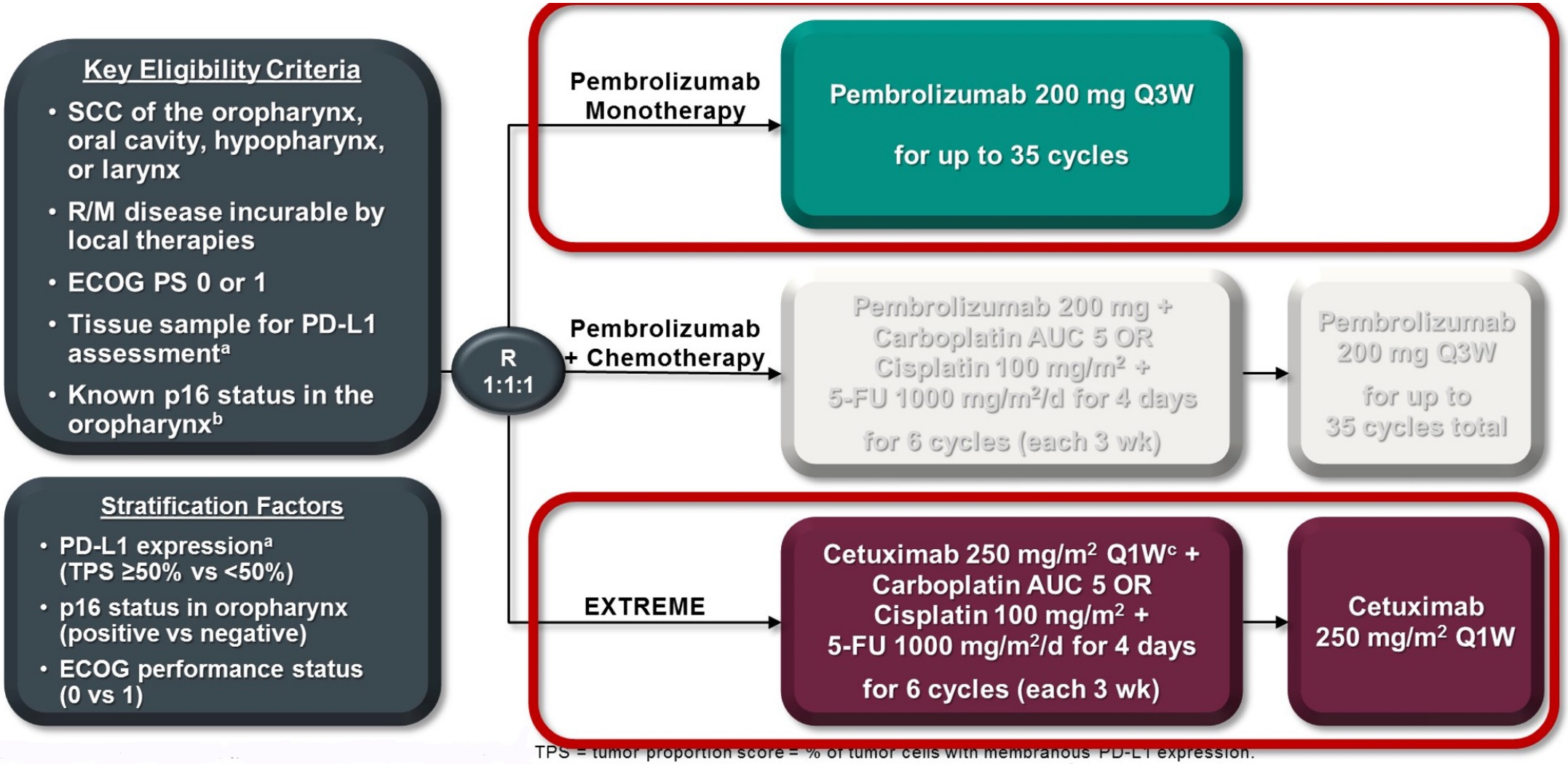


Burtness et al: Lancet 2019

Baseline Characteristics

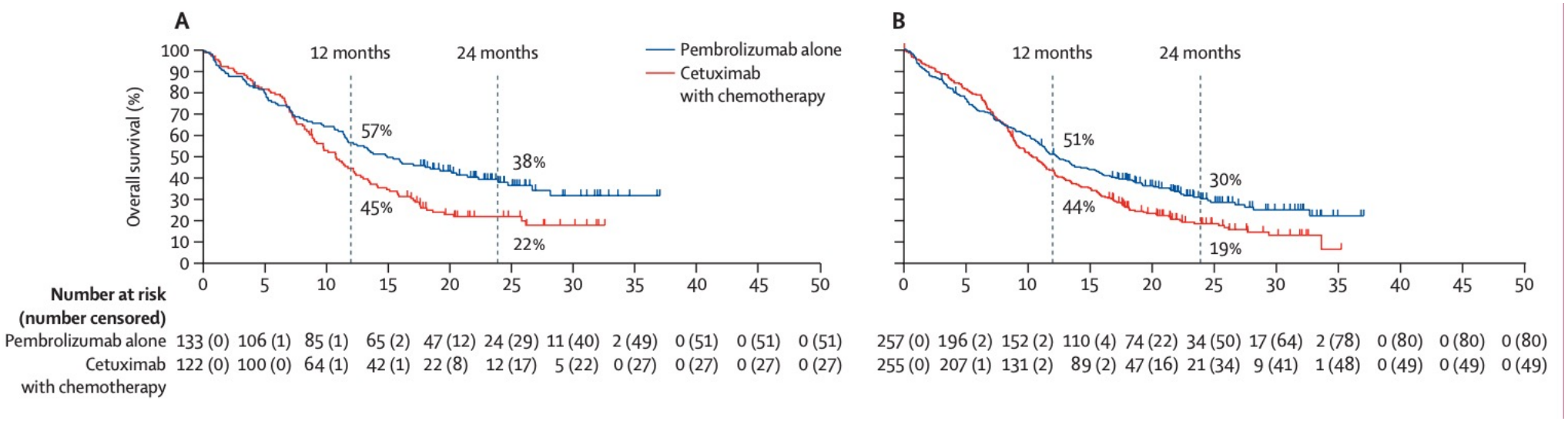
	Pembrolizumab alone vs cetuximab with chemotherapy		Pembrolizumab with chemotherapy vs cetuximab with chemotherapy*	
	Pembrolizumab alone (n=301)	Cetuximab with chemotherapy (n=300)	Pembrolizumab with chemotherapy (n=281)	Cetuximab with chemotherapy (n=278)
PD-L1 CPS				
≥1	257 (85%)	255 (85%)	242 (86%)	235 (85%)
≥20	133 (44%)	122 (41%)	126 (45%)	110 (40%)
Disease status				
Metastatic	216 (72%)	203 (68%)	201 (72%)	187 (67%)
Recurrent only†	82 (27%)	94 (31%)	76 (27%)	88 (32%)
Newly diagnosed, non-metastatic	3 (1%)	3 (1%)	4 (1%)	3 (1%)
Primary tumour location				
Hypopharynx	38 (13%)	39 (13%)	44 (16%)	36 (13%)
Larynx	74 (25%)	61 (20%)	46 (16%)	56 (20%)
Oral cavity	82 (27%)	91 (30%)	82 (29%)	84 (30%)
Oropharynx	113 (38%)	114 (38%)	113 (40%)	107 (38%)
Investigator's choice of platinum for study treatment‡				
Carboplatin	181 (60%)	170 (57%)	160 (57%)	156 (56%)
Cisplatin	120 (40%)	130 (43%)	121 (43%)	122 (44%)

KEYNOTE-048: Study Design



TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression.

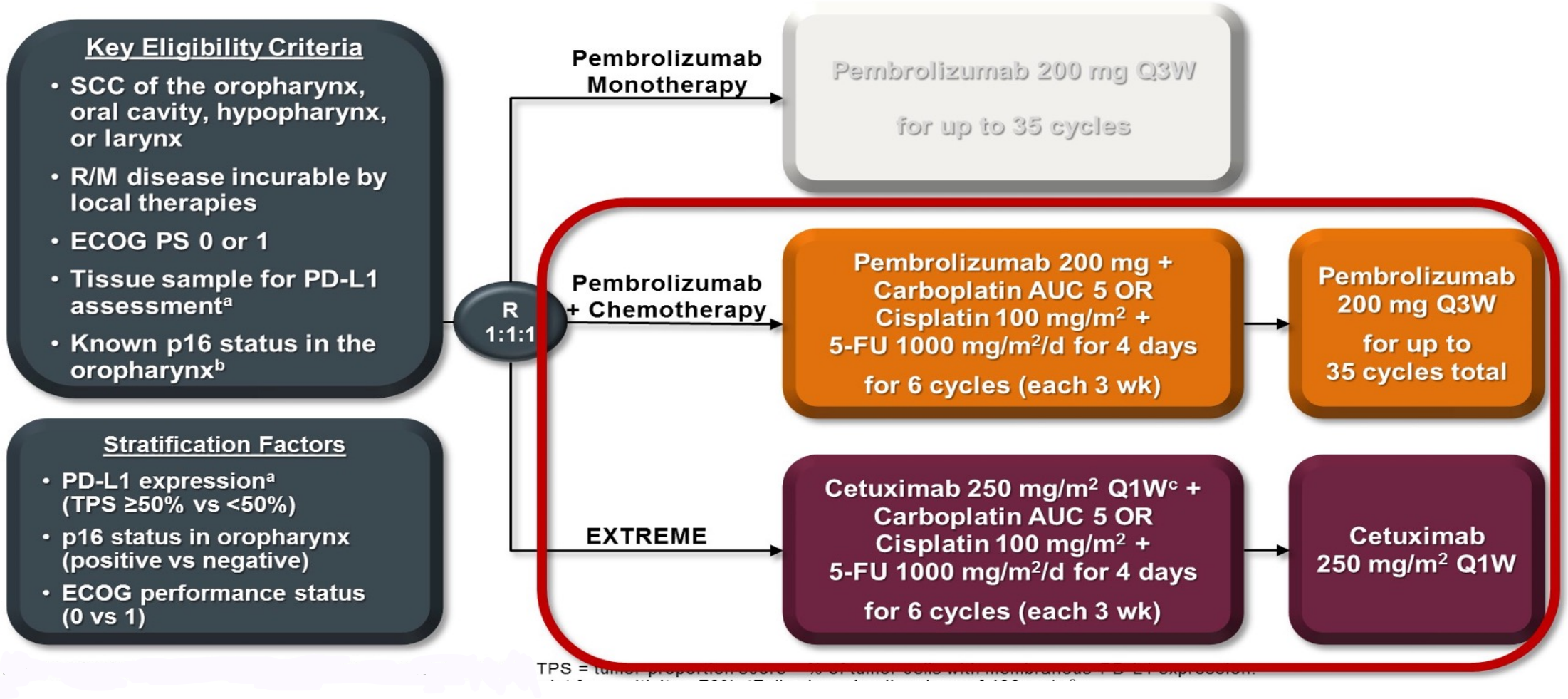
Pembrolizumab vs Extreme



CPS 20

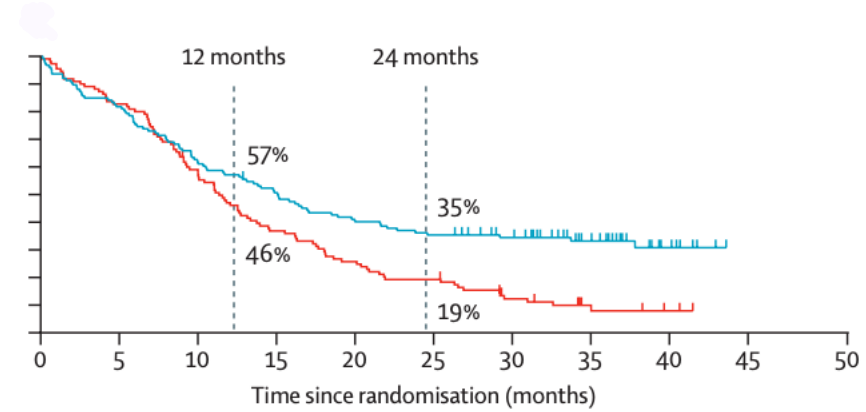
CPS 1

KEYNOTE-048: Study Design



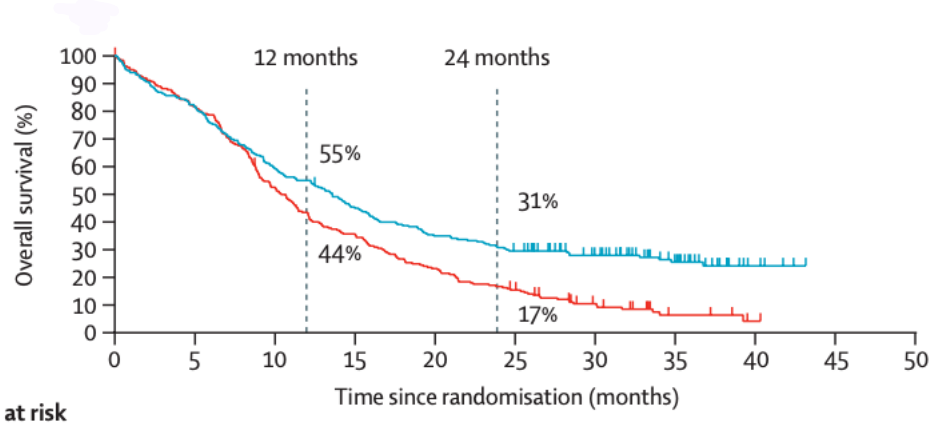
TPS = tumor proportion score

Pembrolizumab/Chemotherapy vs EXTREME



126 (0)	102 (0)	77 (0)	60 (1)	50 (1)	44 (1)	36 (8)	21 (22)	4 (38)	0 (42)	0 (42)
110 (0)	91 (0)	60 (1)	40 (1)	26 (1)	19 (2)	11 (4)	4 (8)	1 (11)	0 (12)	0 (12)

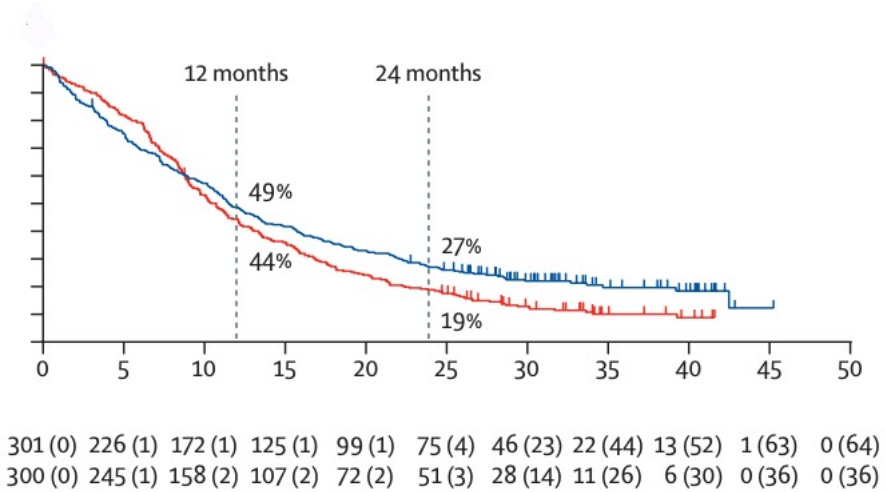
CPS 20



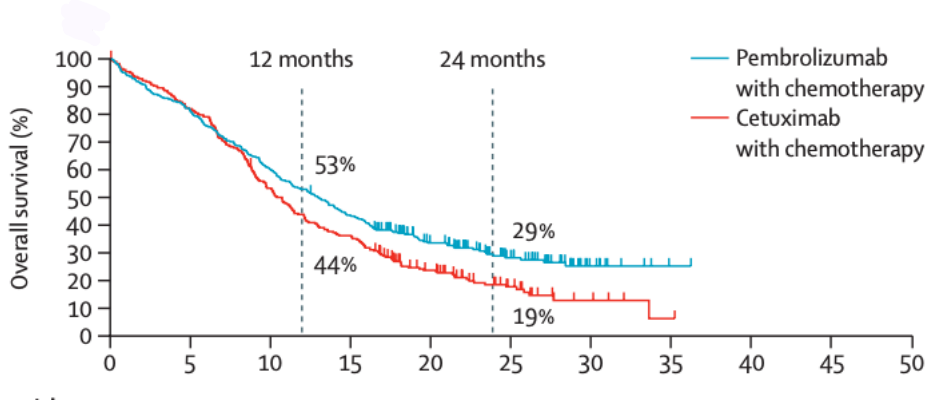
Number at risk (number censored)											
Pembrolizumab with chemotherapy	242 (0)	197 (0)	144 (0)	109 (1)	84 (1)	70 (2)	52 (17)	29 (37)	5 (60)	0 (65)	0 (65)
Cetuximab with chemotherapy	235 (0)	191 (1)	122 (2)	83 (2)	54 (2)	35 (3)	17 (11)	5 (18)	1 (21)	0 (22)	0 (22)

CPS 1

Total Population

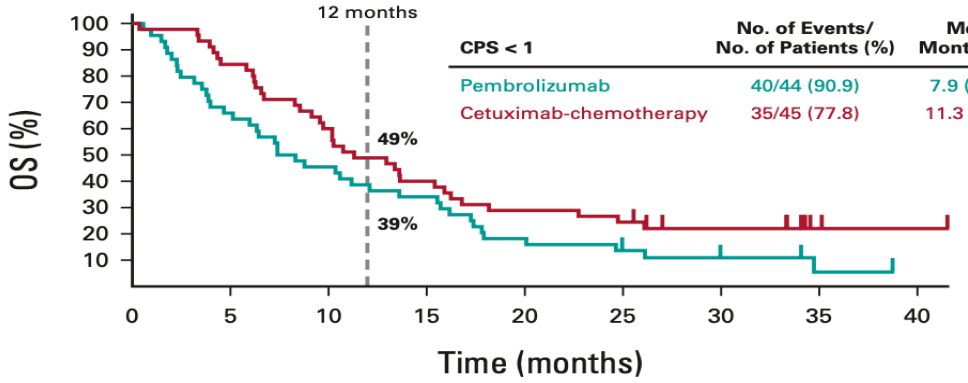


Pembro vs. EXTREME



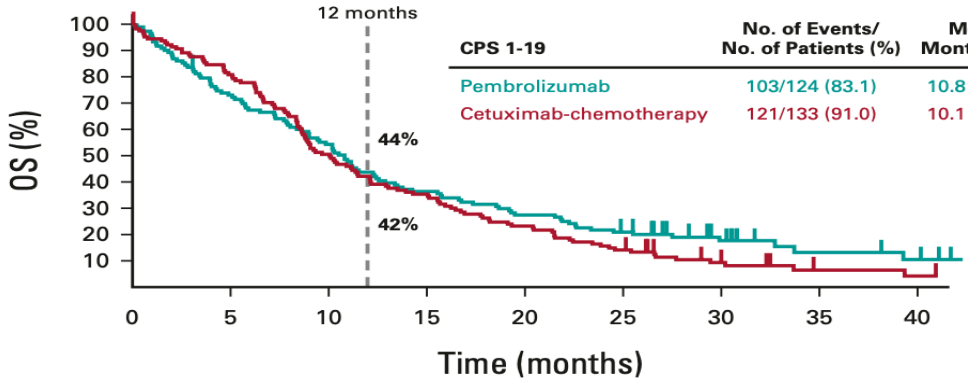
Pembro/Chemo vs. EXTREME

KEYNOTE-048: Subgroup Analysis by CPS



CPS < 1	No. of Events/ No. of Patients (%)	Median OS, Months (95% CI)[a]	HR (95% CI)[b]	Nominal *P*[c]
Pembrolizumab	40/44 (90.9)	7.9 (4.7 to 13.6)	1.51 (0.96 to 2.37)	.96241
Cetuximab-chemotherapy	35/45 (77.8)	11.3 (9.1 to 15.9)		

No. at risk:									
Pembrolizumab	44	29	20	15	8	5	3	1	0
Cetuximab-chemotherapy	45	38	27	18	13	11	7	2	1

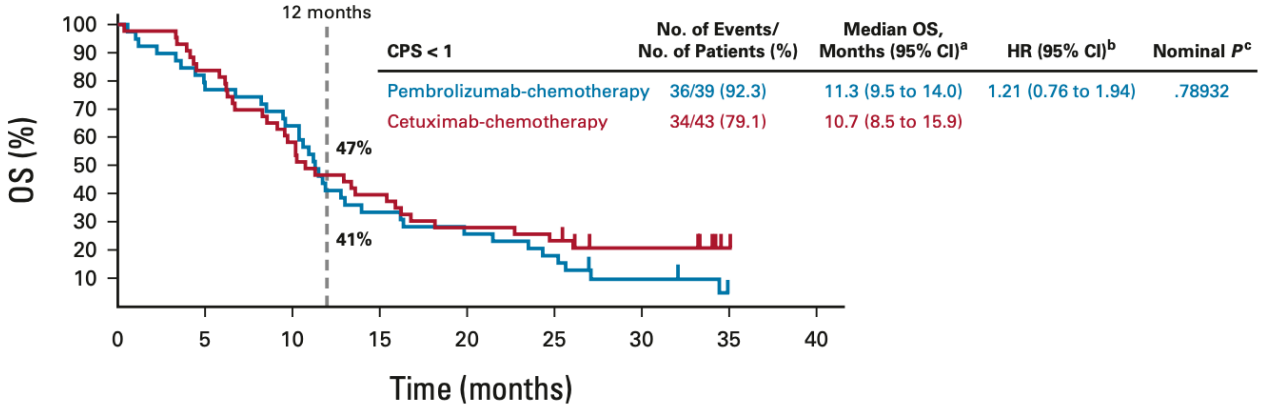


CPS 1-19	No. of Events/ No. of Patients (%)	Median OS, Months (95% CI)[a]	HR (95% CI)[b]	Nominal *P*[c]
Pembrolizumab	103/124 (83.1)	10.8 (9.0 to 12.6)	0.86 (0.66 to 1.12)	.12827
Cetuximab-chemotherapy	121/133 (91.0)	10.1 (8.7 to 12.1)		

No. at risk:									
Pembrolizumab	124	90	67	45	34	25	14	6	4
Cetuximab-chemotherapy	133	107	67	47	31	19	8	3	2

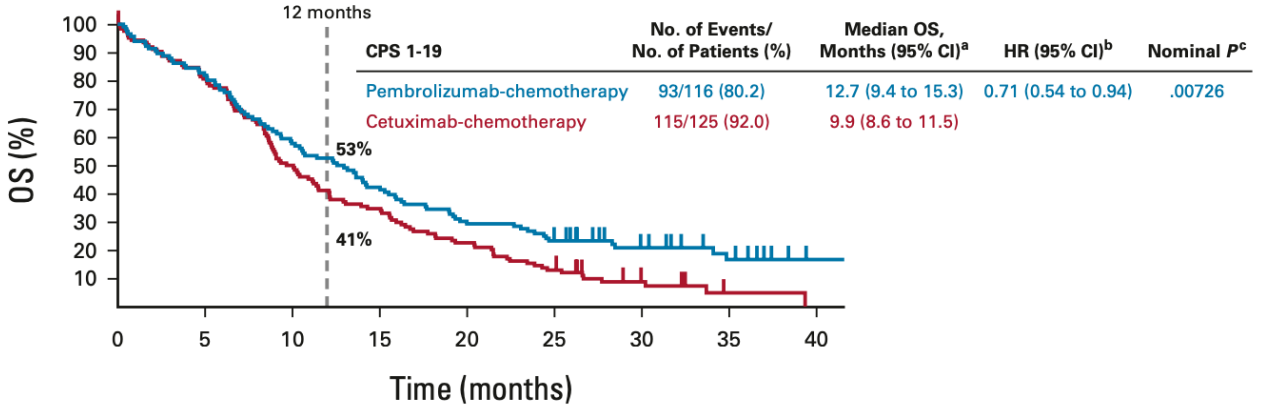
Burtness B et al: J Clin Oncol. 2022

KEYNOTE-048: Subgroup Analysis by CPS



CPS < 1	No. of Events/ No. of Patients (%)	Median OS, Months (95% CI)[a]	HR (95% CI)[b]	Nominal *P*[c]
Pembrolizumab-chemotherapy	36/39 (92.3)	11.3 (9.5 to 14.0)	1.21 (0.76 to 1.94)	.78932
Cetuximab-chemotherapy	34/43 (79.1)	10.7 (8.5 to 15.9)		

No. at risk:									
Pembrolizumab-chemotherapy	39	30	25	13	10	7	3	0	0
Cetuximab-chemotherapy	43	36	25	17	12	10	6	1	0



CPS 1-19	No. of Events/ No. of Patients (%)	Median OS, Months (95% CI)[a]	HR (95% CI)[b]	Nominal *P*[c]
Pembrolizumab-chemotherapy	93/116 (80.2)	12.7 (9.4 to 15.3)	0.71 (0.54 to 0.94)	.00726
Cetuximab-chemotherapy	115/125 (92.0)	9.9 (8.6 to 11.5)		

No. at risk:									
Pembrolizumab-chemotherapy	116	95	67	49	34	26	16	8	1
Cetuximab-chemotherapy	125	100	62	43	28	16	6	1	0

Burtness B et al: J Clin Oncol. 2022

Conclusions: Keynote-048

- Pembrolizumab plus a platinum and 5-FU vs EXTREME
  - Superior OS for pembrolizumab + chemotherapy in the PD-L1 CPS ≥20 and CPS ≥1 and total populations
  - Longer duration of response for pembrolizumab + chemotherapy
  - Comparable safety profiles for pembrolizumab + chemotherapy and EXTREME
- Pembrolizumab monotherapy vs EXTREME
  - Superior OS for pembrolizumab in the CPS ≥20 and CPS ≥1 populations
  - Noninferior OS for pembrolizumab in the total population
  - Substantially longer duration of response for pembrolizumab

2022 ASCO® ANNUAL MEETING

A Phase II trial of Pembrolizumab and Cabozantinib in Patients With Recurrent Metastatic Head and Neck Squamous Cell Carcinoma

Nabil F. Saba, Asari Ekpenyong, Ashley McCook-Veal, Mihir Patel, Nikki Schmitt, Bill Stokes, James Bates, Soumon Rudra, Marin Abousaud, Jameel Muzaffar, Kedar Kirtane, Yong Teng, Conor Steuer, Dong M. Shin, Liu Yuan, Christine H. Chung

Abstract 6008

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Study Design

Phase II, open label, multi-center, single arm trial

Patients with R/M HNSCC

Inclusion criteria

- Inoperable, refractory or metastatic R/M HNSCC
- RECIST v1.1 measurable disease
- ≤1 prior radiation therapy to the HN allowed
- Life expectancy >3 months
- ECOG performance status 0–1

Exclusion criteria

- HPV negative unknown primary disease
- Cavitating lesions or recent bleeding history

→ **Pembrolizumab 200 mg IV Q3W + Cabozantinib 40 mg PO QD**

→ Tumors were assessed by RECIST v1.1 criteria by CT/MRI every 9 weeks

Primary objectives

- Determine the safety and tolerability of pembrolizumab + cabozantinib in this patient population
- Determine the objective response rate ORR per RECIST v1.1

Statistics

- ORR was tested based on the reported ORR for single-agent pembrolizumab of 18%
  - Estimated that ORR will improve to ≥35% with pembrolizumab + cabozantinib, yielding a type 1 error of 0.05 and a power of 80% when the true response rate is 35%
- For single-arm design with null hypothesis of ORR ≤15% vs one-sided alternative, 34 patients with evaluable responses are needed
- If the number of responses is ≤9 out of 34, the trial will be claimed as not promising

ECOG = Eastern Cooperative Oncology Group; HPV = human papillomavirus; RECIST = Response Evaluation Criteria in Solid Tumors

Patient Characteristics

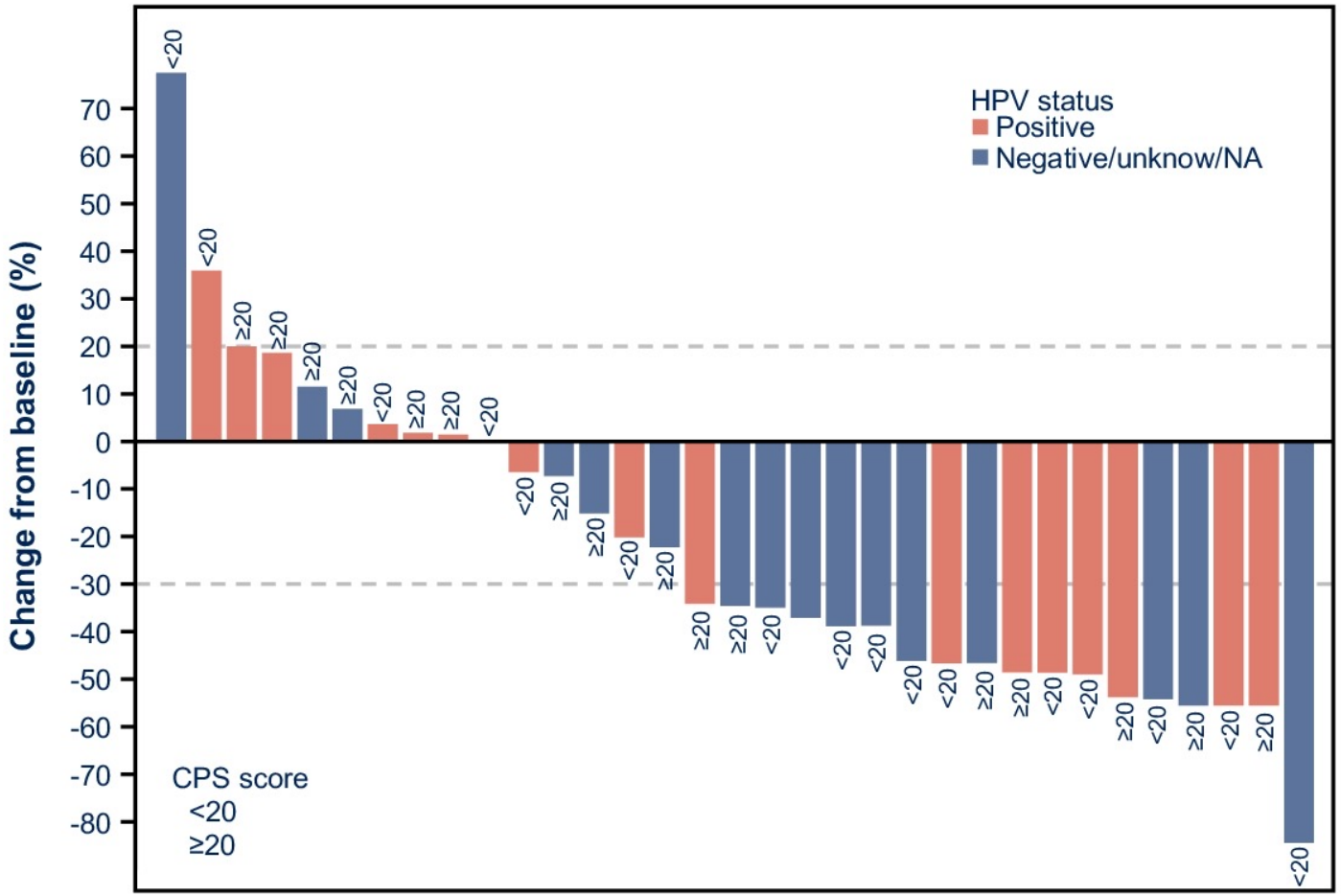
Patient Characteristic		N=36 n (%)
Age, median (range), years		62 (54-67)
Gender	Male Female	30 (83) 6 (17)
ECOG performance status, %	0 1	18 (50) 18 (50)
Primary site	Oropharynx Oral cavity Hypopharynx Larynx Nasopharynx	22 (61) 2 (6) 2 (6) 4 (11) 6 (16)
HPV (p16)	Positive Negative Unknown	17 (47) 12 (33) 7 (20)
Prior therapy	Radiation Cisplatin Cetuximab	31 (89) 36 (100) 3 (8)
PD-L1 CPS score (total of 34)	CPS <1 CPS 1-19 CPS ≥20	2 (6) 15 (44) 17 (50)

Cabozantinib Dose Reductions

	N=36 n (%)
Cabozantinib dose reduction	17 (47.2)
Oral mucositis	4 (23.5)
Hand foot skin reaction	4 (23.5)
Diarrhea	2 (11.7)
Physician's discretion	2 (11.7)
Hyponatremia	1 (5.9)
Hypertension	1 (5.9)
Epistaxis	1 (5.9)
ALT / AST increase	1 (5.9)
Vomiting	1 (5.9)

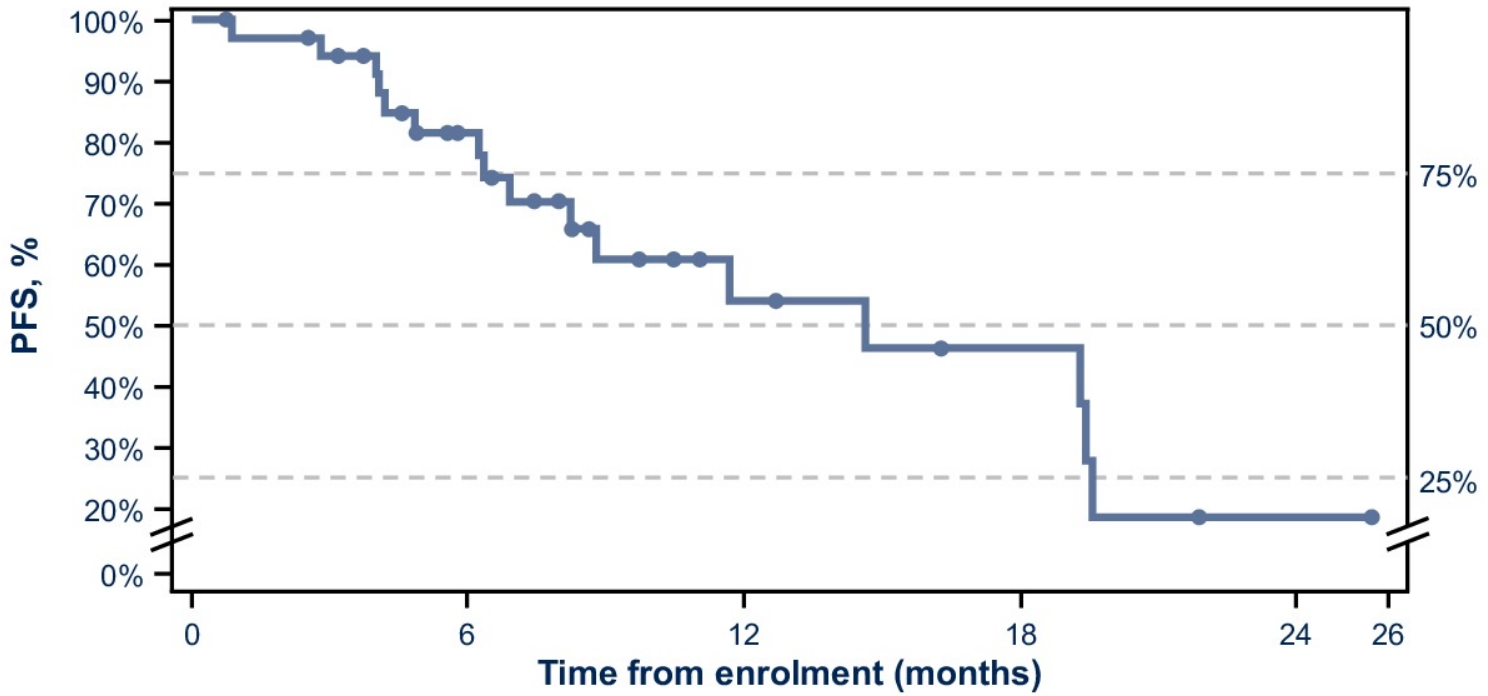
Best Overall Response in Evaluable Patients

	N=33 n (%)
ORR	18 (54)
CR	0 (0)
PR	18(54)
SD	12(36)
PD	3(9)
Clinical benefit	30(91)



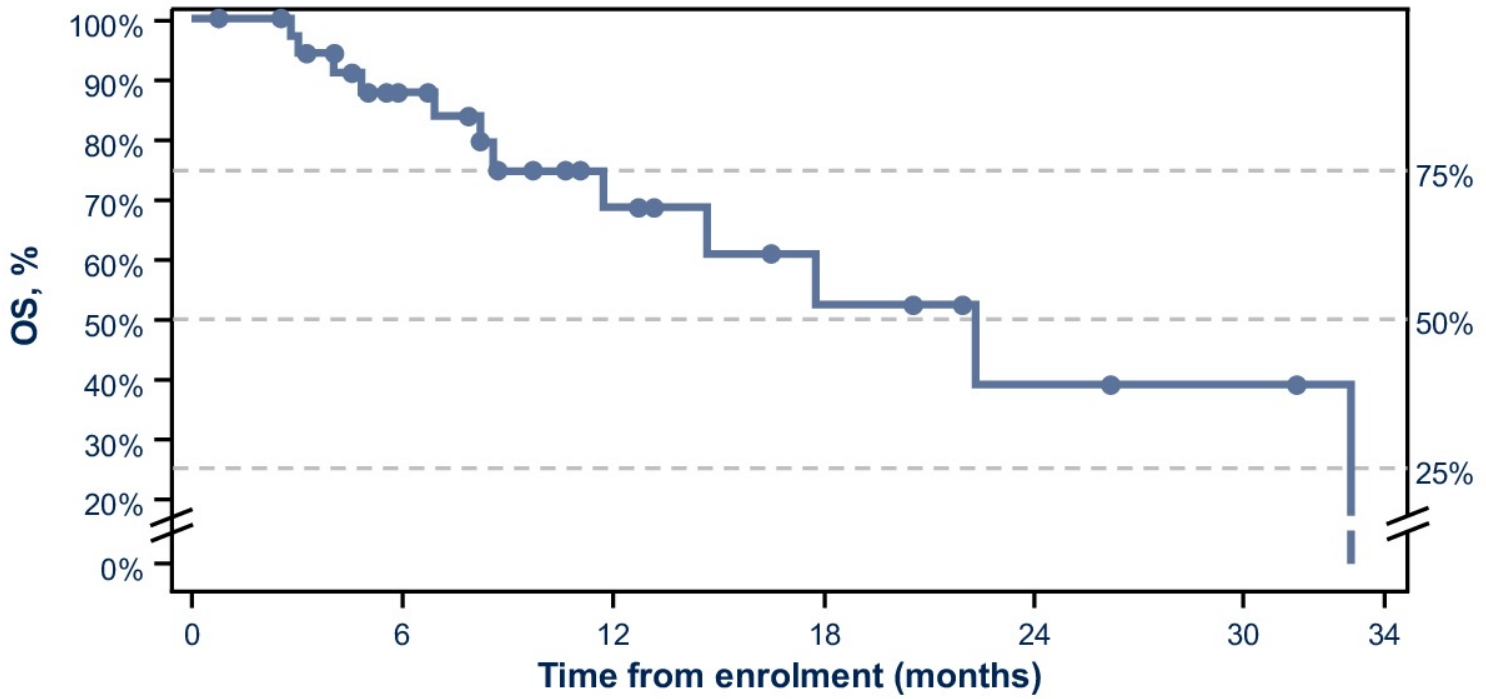
CR = complete response; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease

Progression-Free Survival



N	Event	Censored	mPFS (95% CI), mo	1-yr PFS (95%CI), %	Median follow-up (95% CI), mo
36	16 (44%)	20 (56%)	14.6 (8.2–19.6)	54.0 (31.5–72.0)	10.6 (7.8–16.5)

Overall Survival



N	Event	Censored	mOS (95% CI), mo	1-yr OS (95%CI), %	Median follow-up (95% CI), mo
36	12 (33%)	24 (67%)	22.3 (11.7–32.9)	68.4 (45.1–83.5)	10.6 (7.8–16.5)

Lenvatinib and Pembrolizumab Ongoing Trials

Trial	Patients/Eligibilty	Treatment	Line
LEAP-009, NCT04428151	**Recurrent/metastatic HNSCC** of the oral cavity, oropharynx, hypopharynx, and/or larynx that progressed during/after platinum chemotherapy with/without cetuximab and progressed during/after anti–PD-1/PD-L1 monotherapy or combination therapy	Arm 1: lenvatinib + pembrolizumab Arm 2: SOC chemotherapy	≥ 2L
LEAP-010, NCT04199104	**Recurrent/metastatic HSNCC** of the oral cavity, oropharynx, hypopharynx, or larynx with PD-L1 CPS ≥1	Arm 1: lenvatinib + pembrolizumab Arm 2: pembrolizumab + placebo	1L

Phase 2 trial of Ficlatuzumab ±Cetuximab

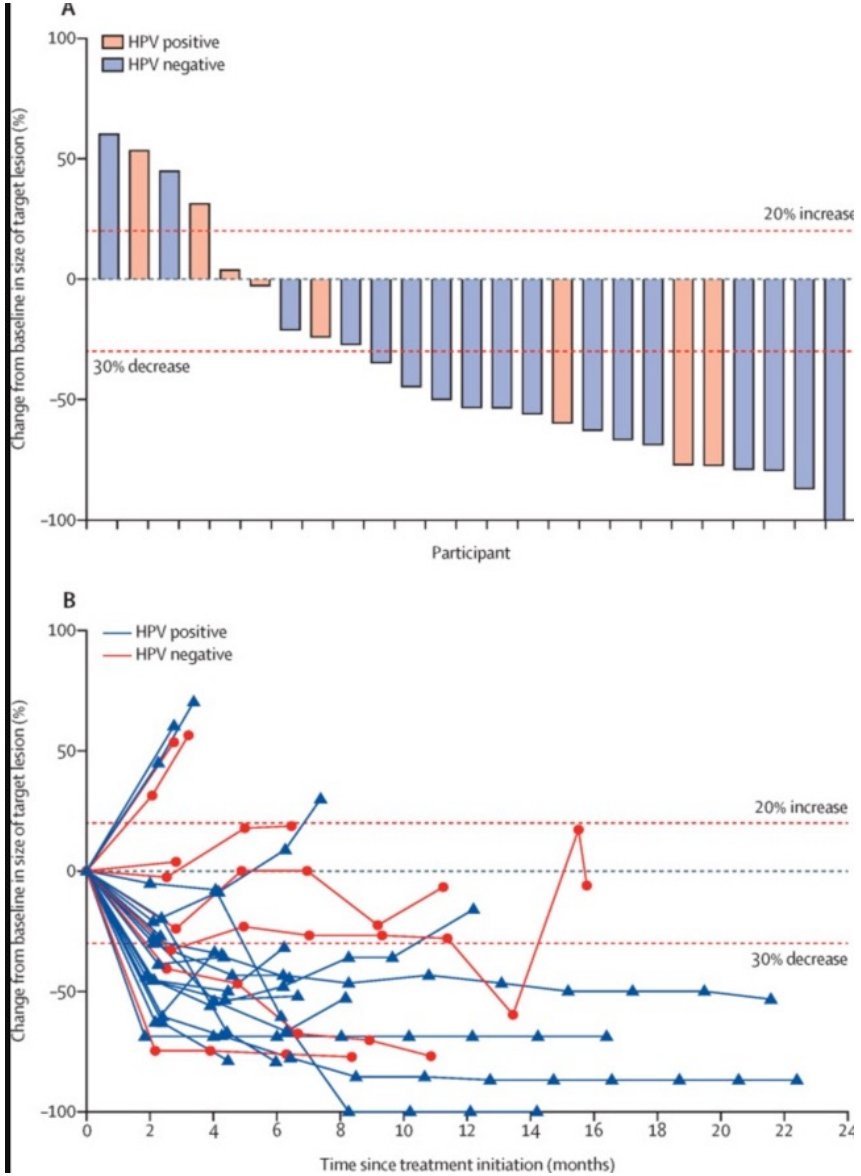
- Ficlatuzumab (F) is an anti-HGF IgG1 monoclonal antibody which has been combined safely with cetuximab (C) in phase 1 studies
- Phase 2: randomized pan refractory SCCHN to F or F+C
- Grade ≥3 adverse events: pneumonitis; edema; diarrhea; LFT elevation; rash; electrolyte abnormality.

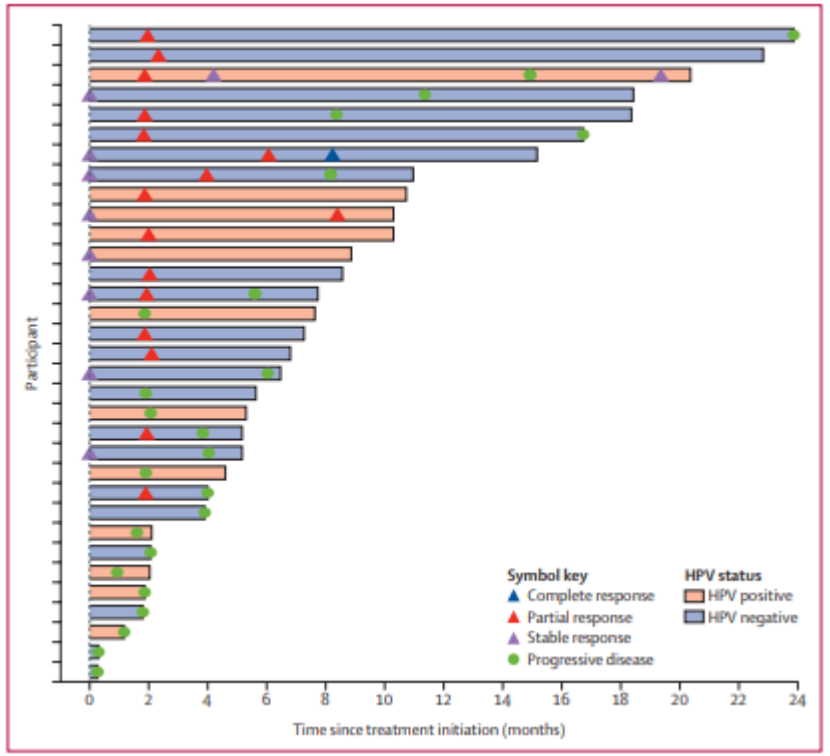
Population	Endpoint	F (n = 26)	FC (n = 32)
Total	ORR	1PR/26 (4%)	2PR + 4CR/32 (19%)
	mPFS	1.8 (1.7)	3.6 (2.3)
HPV+	ORR	0/10 (0%)	0/16 (0%)
	mPFS	NE	2.3 (1.9)
HPV-	ORR	1PR/16 (6%)	2CR + 4PR/16 (38%)
	mPFS	NE	3.8 (2.9)

1. Bauman et al. ASCO 2021 Abstract 6015.

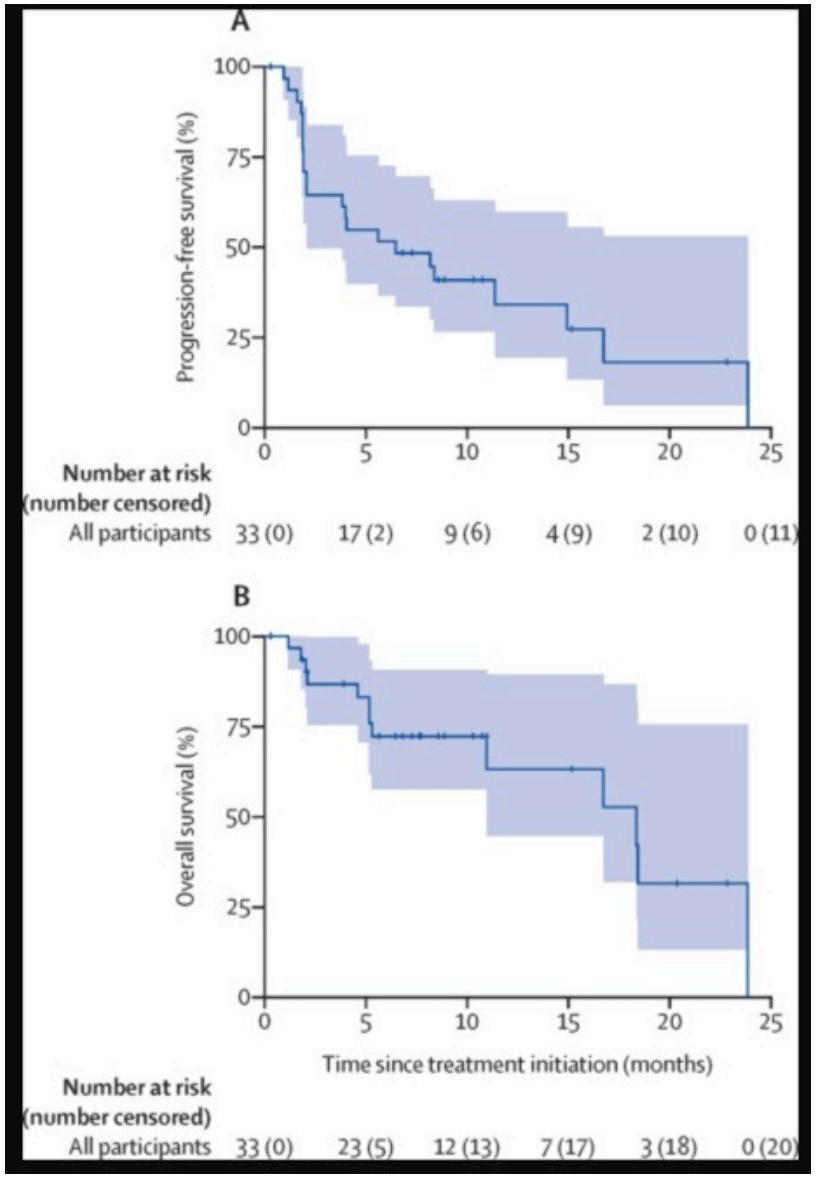
Pembrolizumab+Cetuximab
Recurrent HNC

Sacco et al June 2021 ,
Lancet Oncology





ORR 45 % (15/33 pts)



Sacco et al June 2021 ,
Lancet Oncology

Conclusions

- Pembrolizumab is the current standard of care for first-line RMSCC in CPS-positive HNC
- Response rates are higher with pembrolizumab-chemotherapy
- CPS zero: Neither pembrolizumab nor pembrolizumab-chemotherapy improve survival compared with EXTREME
- CPI+VEGF , CPI+EGFR promising : Need further study
- No Role for CPI in definitive, neoadjuvant, adjuvant therapy outside of a trial