



COMPREHENSIVE  
CANCER  
CENTER VIENNA

# Kärntner & Steirisches Onkologiesymposium



MEDICAL UNIVERSITY  
OF VIENNA

## Kopf-Hals Tumore

**Assoc.Prof.PD.Dr.Thorsten Füreder**  
**Univ.Klinik für Innere Medizin I &CCC, MUW**



COMPREHENSIVE  
CANCER  
CENTER VIENNA

# Recurrent/met. HNSCC



MEDICAL UNIVERSITY  
OF VIENNA

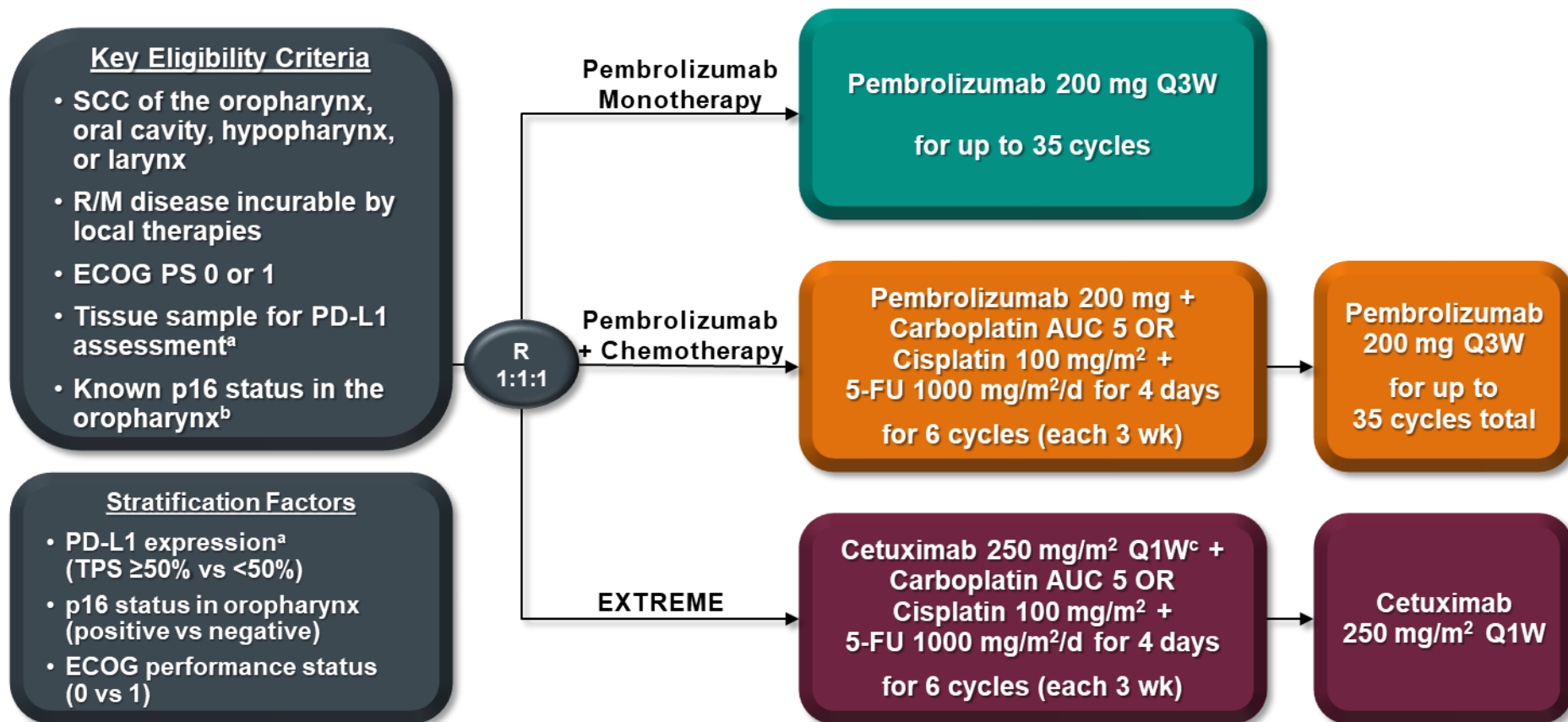


Head & Neck  
Cancer

# Keynote 48

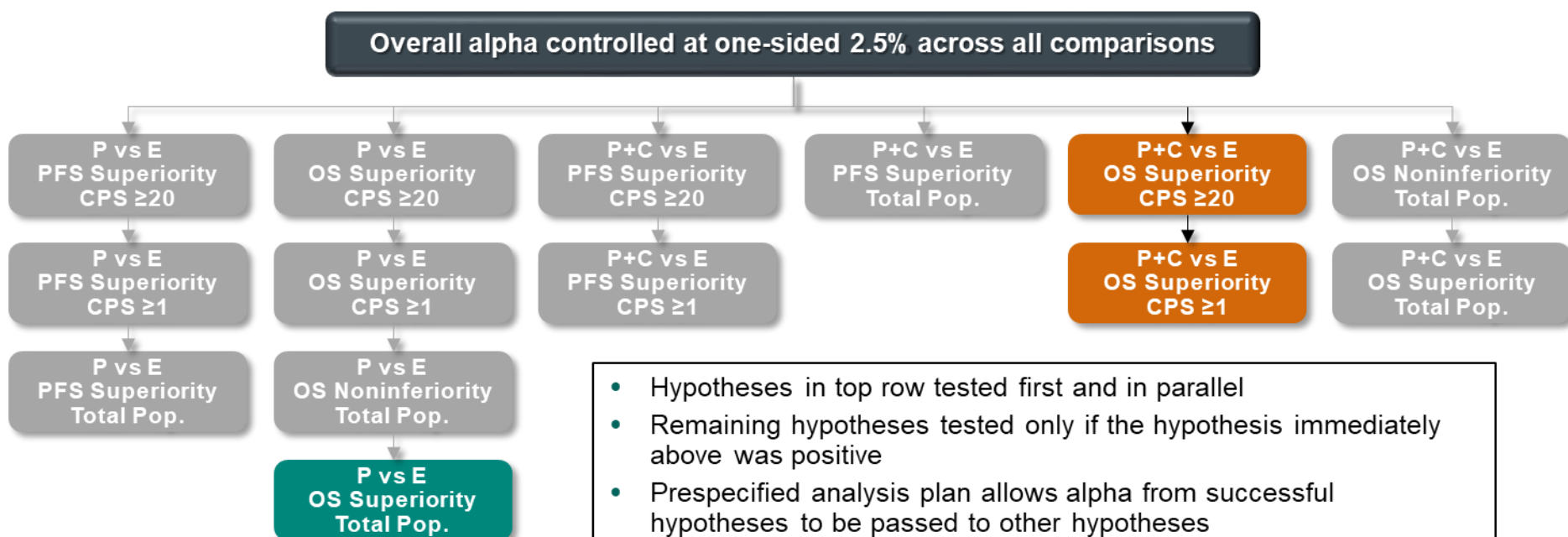
## Studiendesign

### KEYNOTE-048 Study Design (NCT02358031)



<sup>a</sup>Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression.

<sup>b</sup>Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. <sup>c</sup>Following a loading dose of 400 mg/m<sup>2</sup>.



- Teal and orange boxes: available for testing at final analysis (FA)
- Gray boxes: testing completed at IA2<sup>a</sup>
- Final analysis data cutoff date: February 25, 2019 (~25 mo after last patient randomized)

## Throughout this presentation:



First report of the endpoint



Update of an endpoint first reported at ESMO 2018



## Baseline characteristics

Characteristic, n (%)	Pembro Alone vs EXTREME		Pembro + Chemo vs EXTREME	
	Pembro N = 301	EXTREME N = 300	Pembro + Chemo N = 281	EXTREME N = 278 <sup>a</sup>
Age, median (range), yrs	62 (22-94)	61 (24-84)	61 (20-85)	61 (24-84)
Male	250 (83.1)	261 (87.0)	224 (79.7)	242 (87.1)
ECOG PS 1	183 (60.8)	183 (61.0)	171 (60.9)	170 (61.2)
Current/former smoker	239 (79.4)	234 (78.0)	224 (79.7)	215 (77.3)
p16 positive (oropharynx)	63 (20.9)	67 (22.3)	60 (21.4)	61 (21.9)
PD-L1 status				
TPS ≥50%	67 (22.3)	66 (22.0)	66 (23.5)	62 (22.3)
CPS ≥20	133 (44.2)	122 (40.7)	126 (44.8)	110 (39.6)
CPS ≥1	257 (85.4)	255 (85.0)	242 (86.1)	235 (84.5)
Disease status <sup>b</sup>				
Metastatic	216 (71.8)	203 (67.7)	201 (71.5)	187 (67.3)
Locoregional recurrence only	82 (27.2)	94 (31.3)	76 (27.0)	88 (31.7)

<sup>a</sup>Patients randomized to EXTREME during the pembro + chemo enrollment hold were excluded from all pembro + chemo vs EXTREME efficacy comparisons.

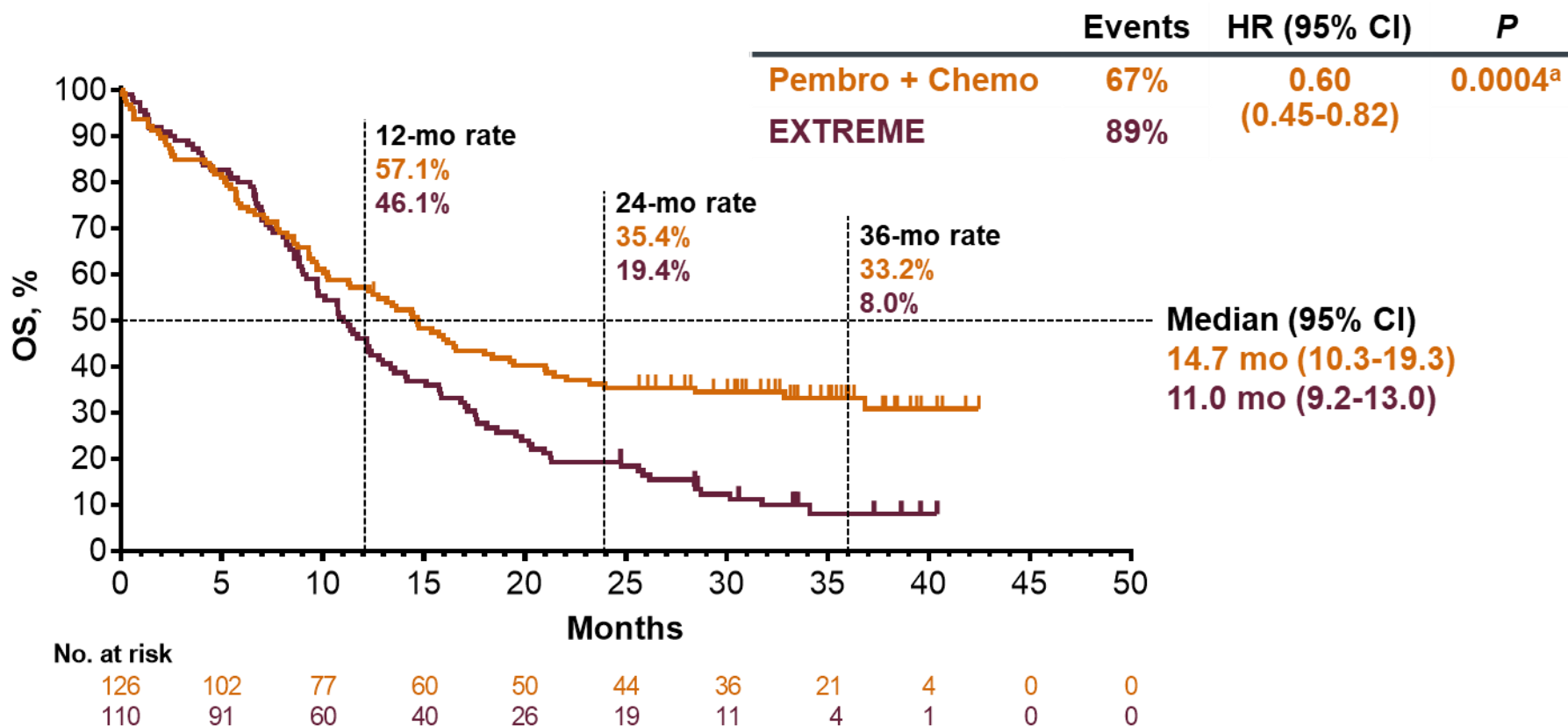
<sup>b</sup>3 patients in the pembro arm, 3 patients in the EXTREME arm, and 4 patients in the pembro + chemo arm had neither metastatic nor recurrent disease.

FA (data cutoff date: Feb 25, 2019).

# Keynote 48 OS

## Pembro+Chemo

### OS, P+C vs E, CPS $\geq 20$ Population

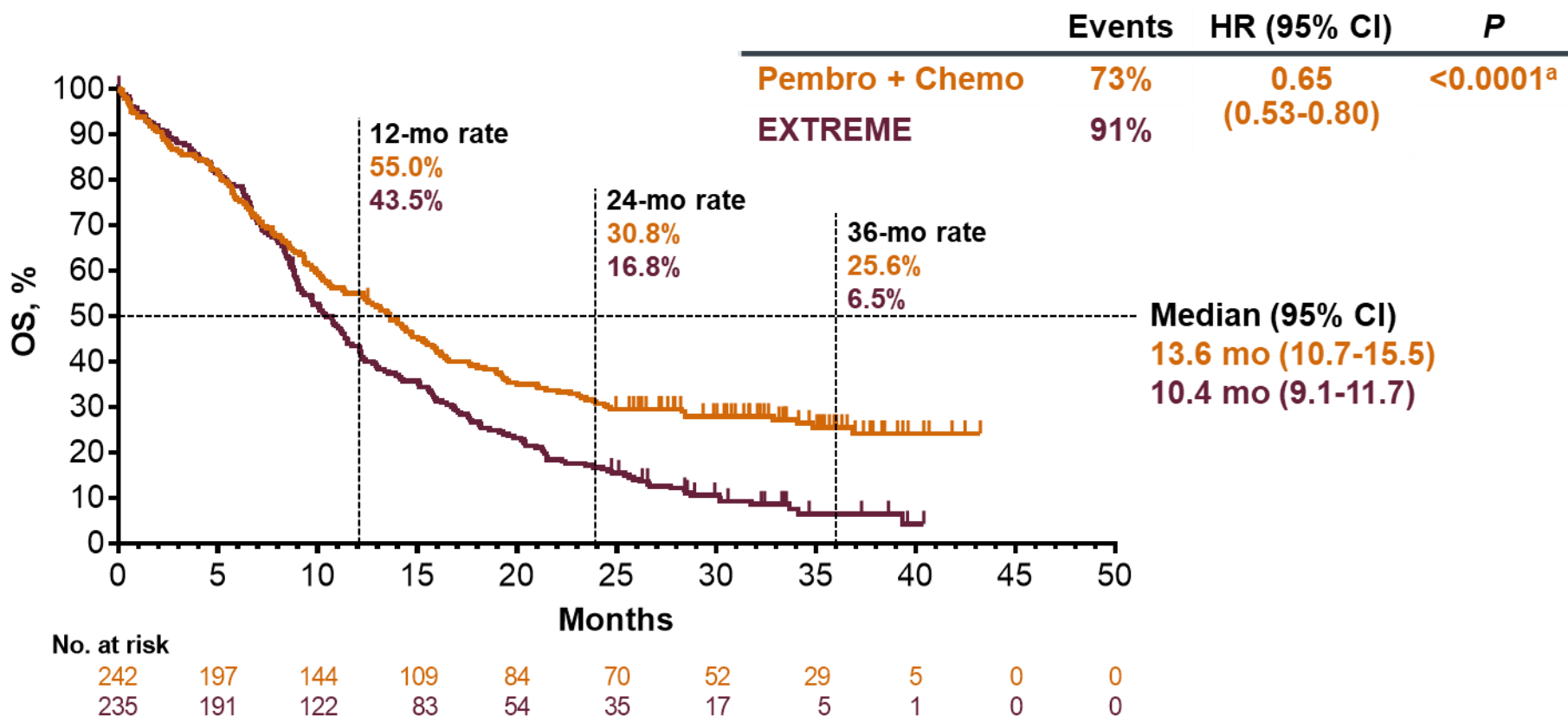


<sup>a</sup>Statistically significant at the superiority threshold of  $P = 0.0023$ .  
FA (data cutoff date: Feb 25, 2019).

# Keynote 48 OS

## Pembro+Chemo

### OS, P+C vs E, CPS $\geq 1$ Population



<sup>a</sup>Statistically significant at the superiority threshold of  $P = 0.0026$ .  
FA (data cutoff date: Feb 25, 2019).

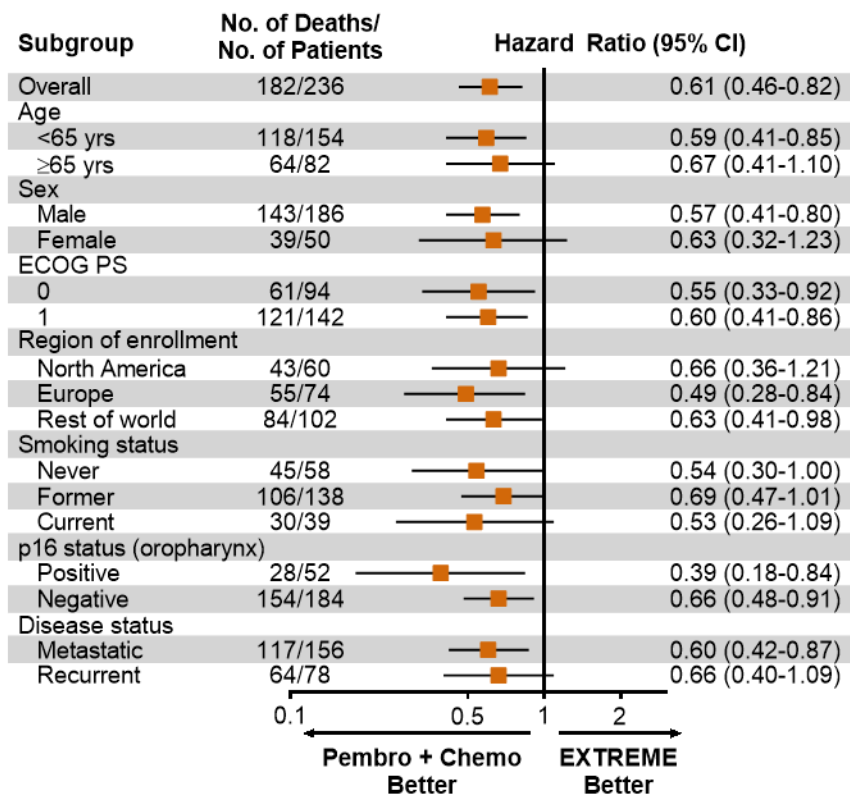


# Keynote 48

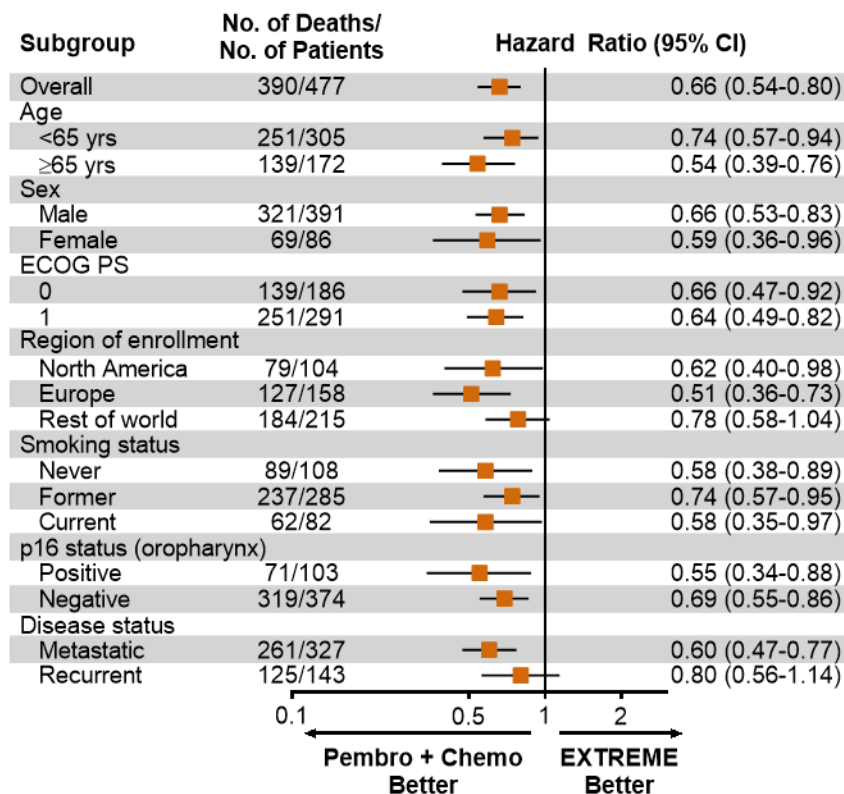
## Subgruppen

### OS in Subgroups, P+C vs E

CPS  $\geq 20$



CPS  $\geq 1$



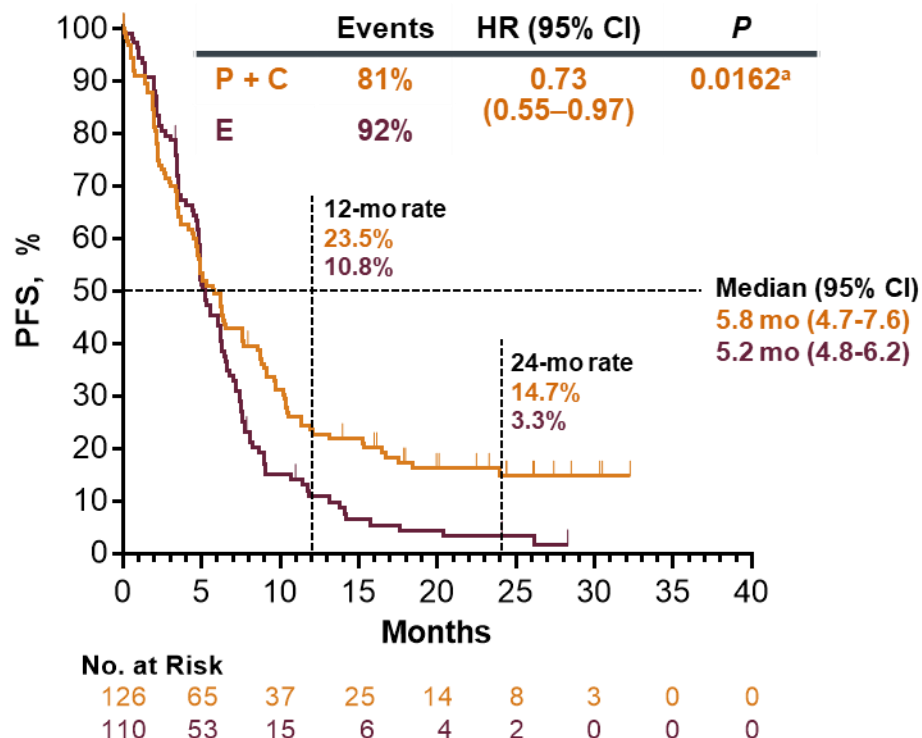


# Keynote 48 PFS

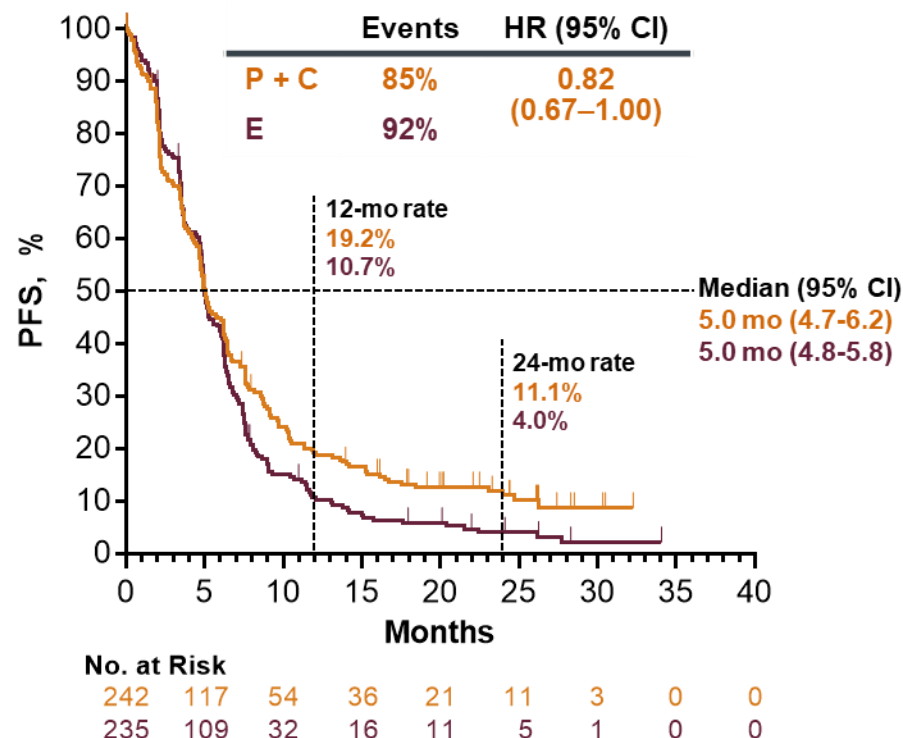
## Pembro+Chemo

### + PFS, P+C vs E, CPS $\geq 20$ and $\geq 1$

#### CPS $\geq 20$



#### CPS $\geq 1$



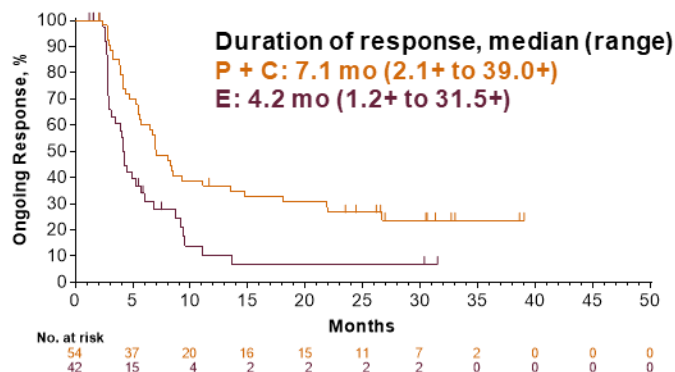
<sup>a</sup>Not statistically significant at the superiority threshold of 0.0017.

IA2 (data cutoff date: Jun 13, 2018). PFS assessed per RECIST v1.1 by blinded, independent central review.

## Response Summary, P+C vs E

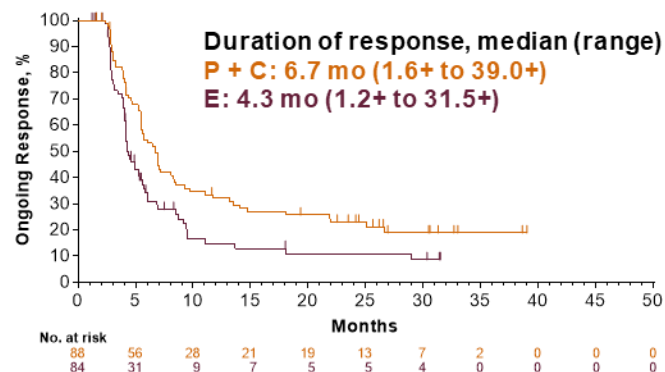
### CPS $\geq 20$

Confirmed Response, n (%)	P + C N = 126	E N = 110
ORR	54 (42.9)	42 (38.2)
CR	12 (9.5)	4 (3.6)
PR	42 (33.3)	38 (34.5)
SD	29 (23.0)	38 (34.5)
PD	19 (15.1)	9 (8.2)
Non-CR/non-PD <sup>a</sup>	4 (3.2)	5 (4.5)
Not evaluable or assessed <sup>b</sup>	20 (15.9)	16 (14.5)



### CPS $\geq 1$

Confirmed Response, n (%)	P + C N = 242	E N = 235
ORR	88 (36.4)	84 (35.7)
CR	16 (6.6)	7 (3.0)
PR	72 (29.8)	77 (32.8)
SD	64 (26.4)	77 (32.8)
PD	42 (17.4)	29 (12.3)
Non-CR/non-PD <sup>a</sup>	11 (4.5)	9 (3.8)
Not evaluable or assessed <sup>b</sup>	37 (15.3)	36 (15.3)



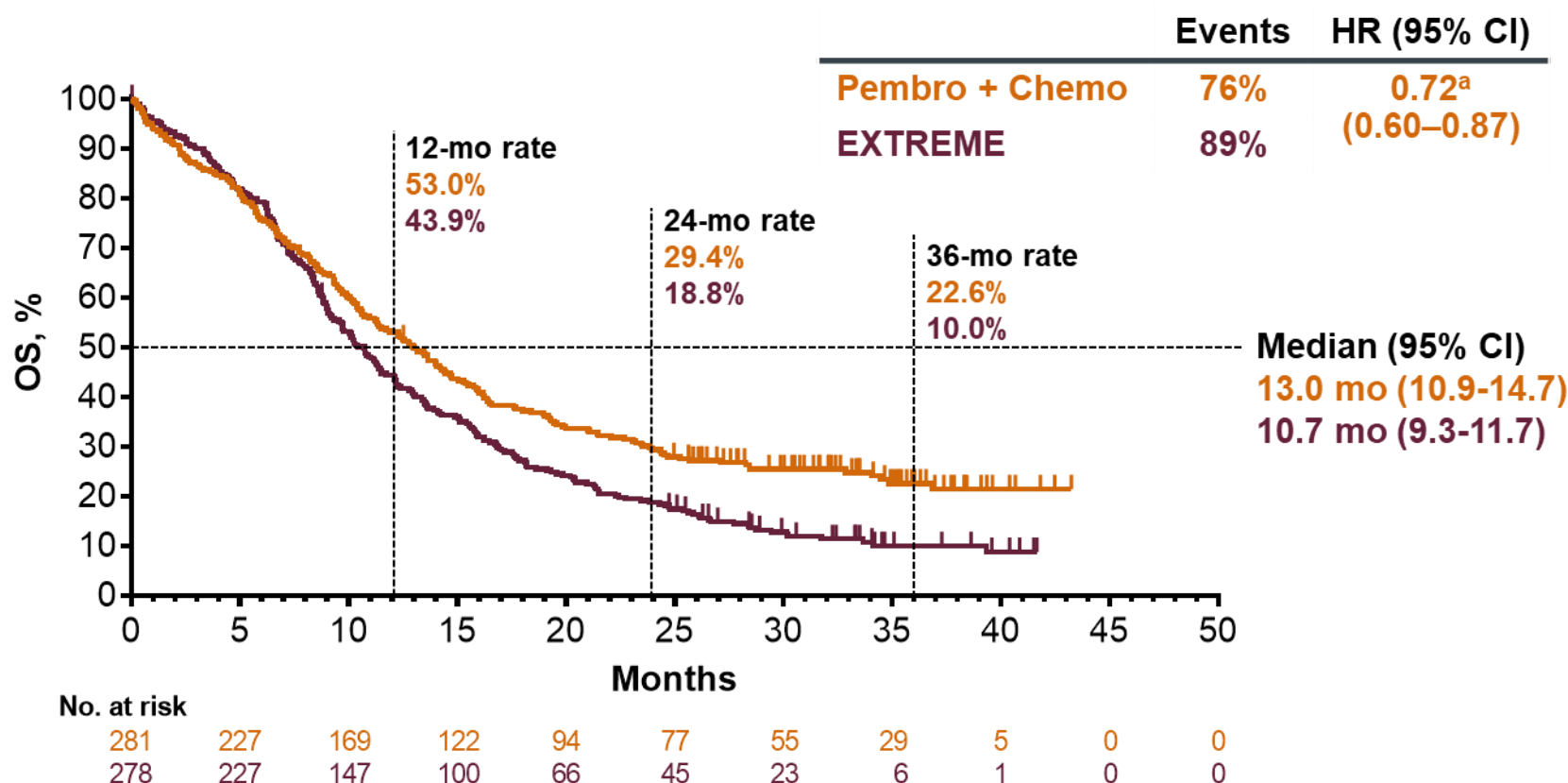
<sup>a</sup>Patients without measurable disease per central review at baseline who did not have CR or PD. <sup>b</sup>Patients who did not have a post-baseline imaging assessment evaluable for response or who did not have post-baseline imaging. Response assessed per RECIST v1.1 by blinded, independent central radiologic review. FA (data cutoff date: Feb 25, 2019).



# Keynote 48 OS Pembro+Chemo



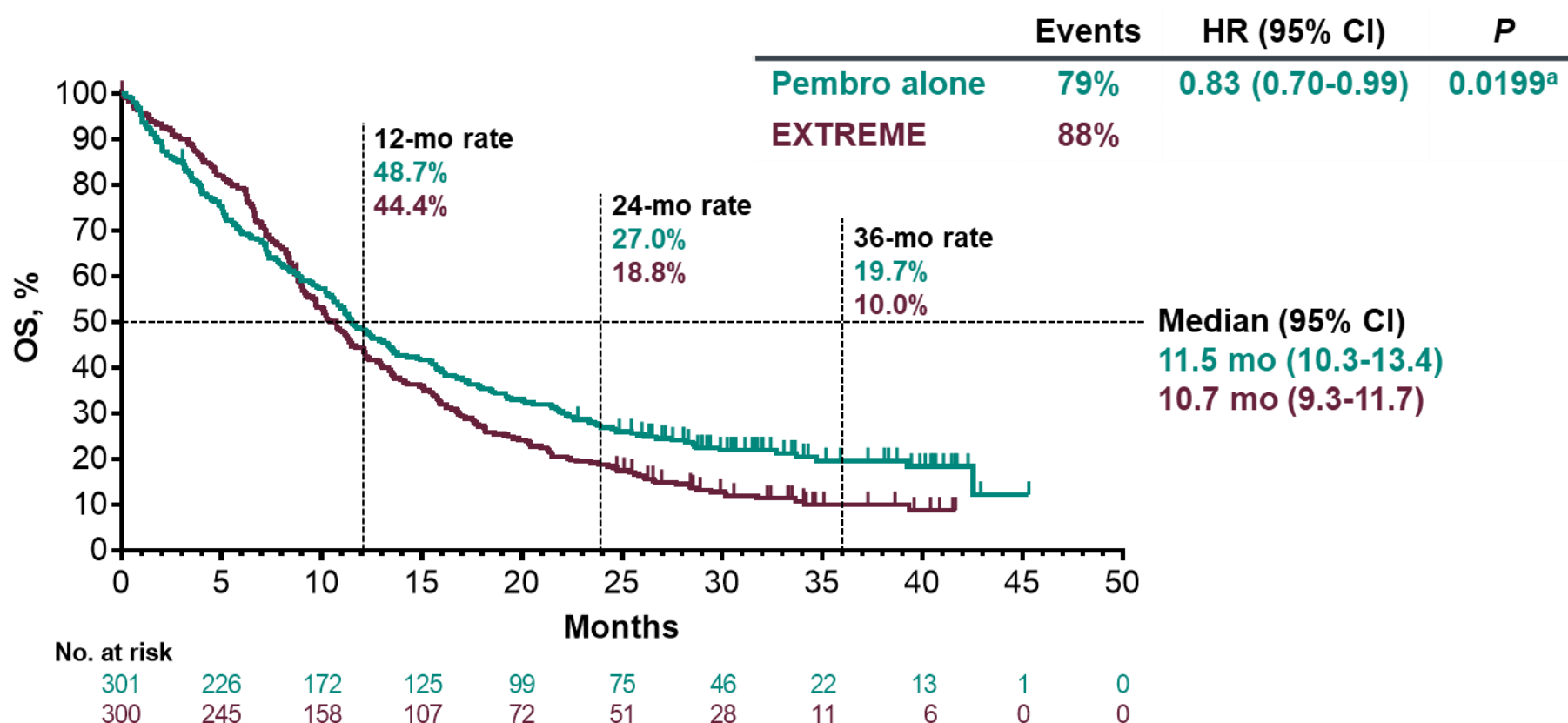
## OS, P+C vs E, Total Population



# Keynote 48 OS

## Pembro Mono

### OS, P vs E, Total Population

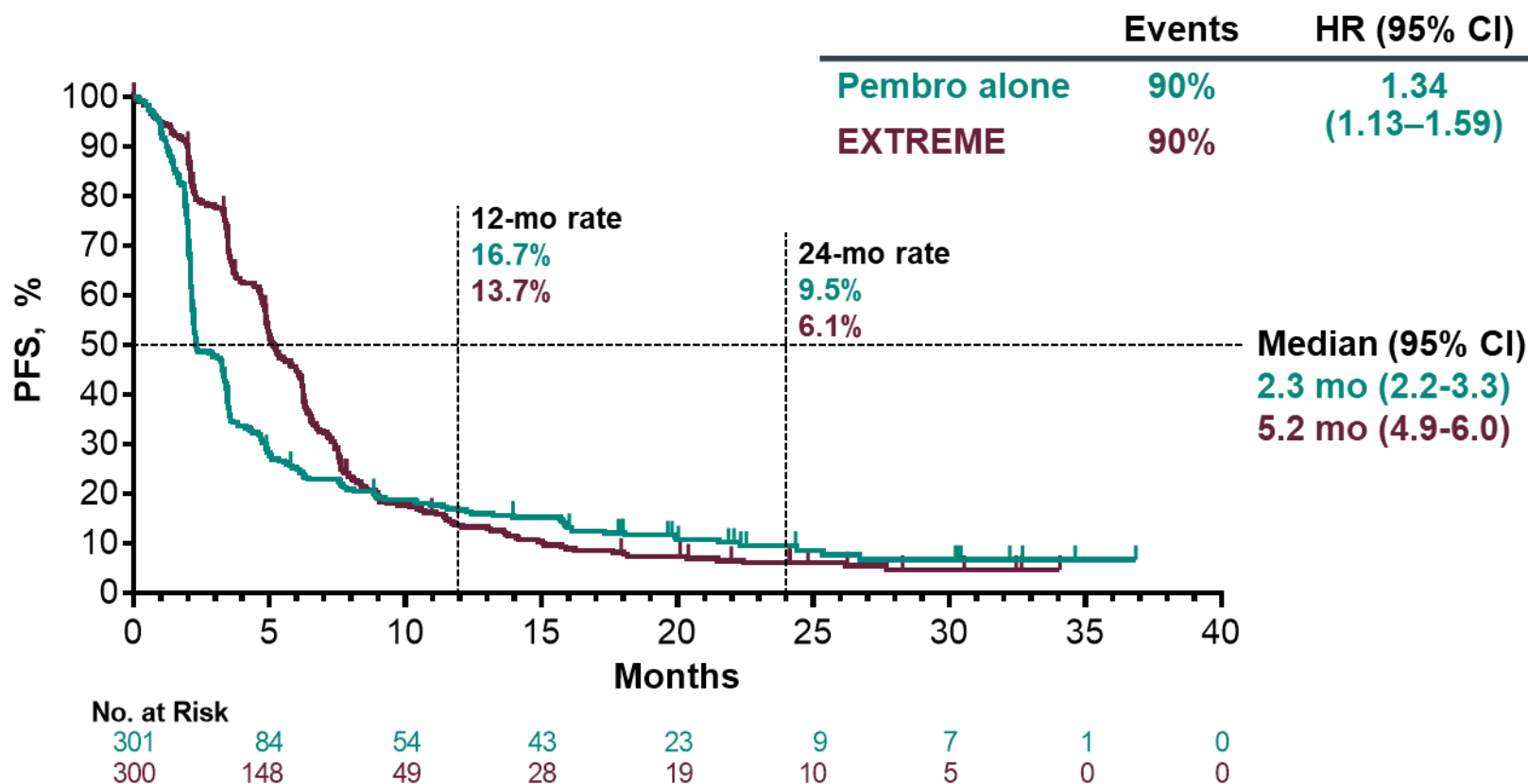


<sup>a</sup>Not statistically significant at the superiority threshold of  $P = 0.0059$ .  
FA (data cutoff date: Feb 25, 2019).

# Keynote 48 PFS

## Pembro Mono

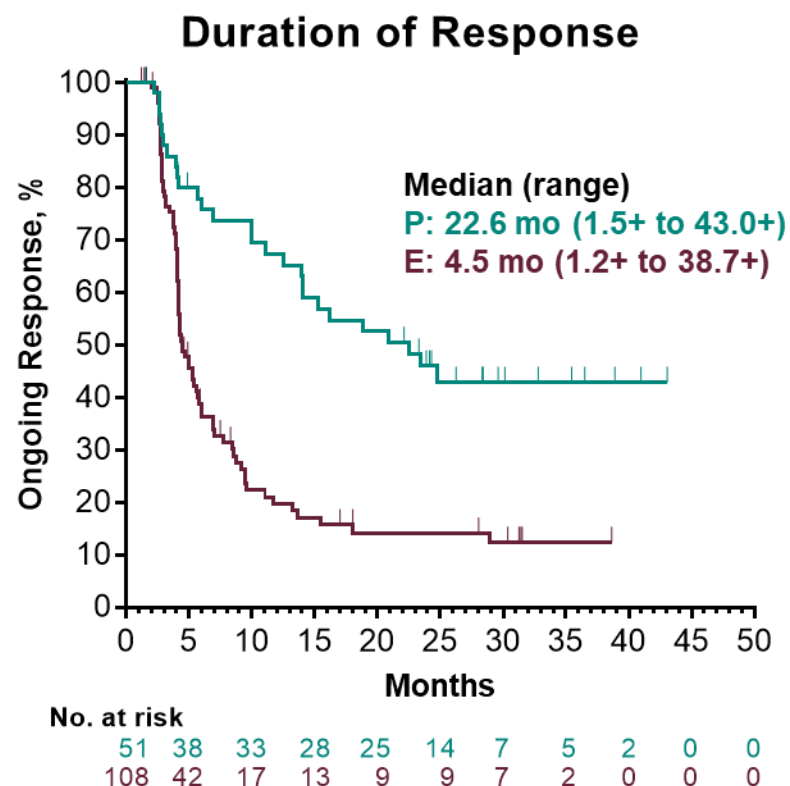
### + PFS, P vs E, Total Population



IA2 (data cutoff date: Jun 13, 2018). PFS was assessed per RECIST v1.1 by blinded, independent central review.

## ⊕ Response Summary, P vs E, Total Population

Confirmed Response, n (%)	Pembro N = 301	EXTREME N = 300
ORR	51 (16.9)	108 (36.0)
CR	14 (4.7)	8 (2.7)
PR	37 (12.3)	100 (33.3)
SD	82 (27.2)	102 (34.0)
PD	122 (40.5)	37 (12.3)
Non-CR/non-PD <sup>a</sup>	14 (4.7)	11 (3.7)
Not evaluable or assessed <sup>b</sup>	32 (10.6)	42 (14.0)

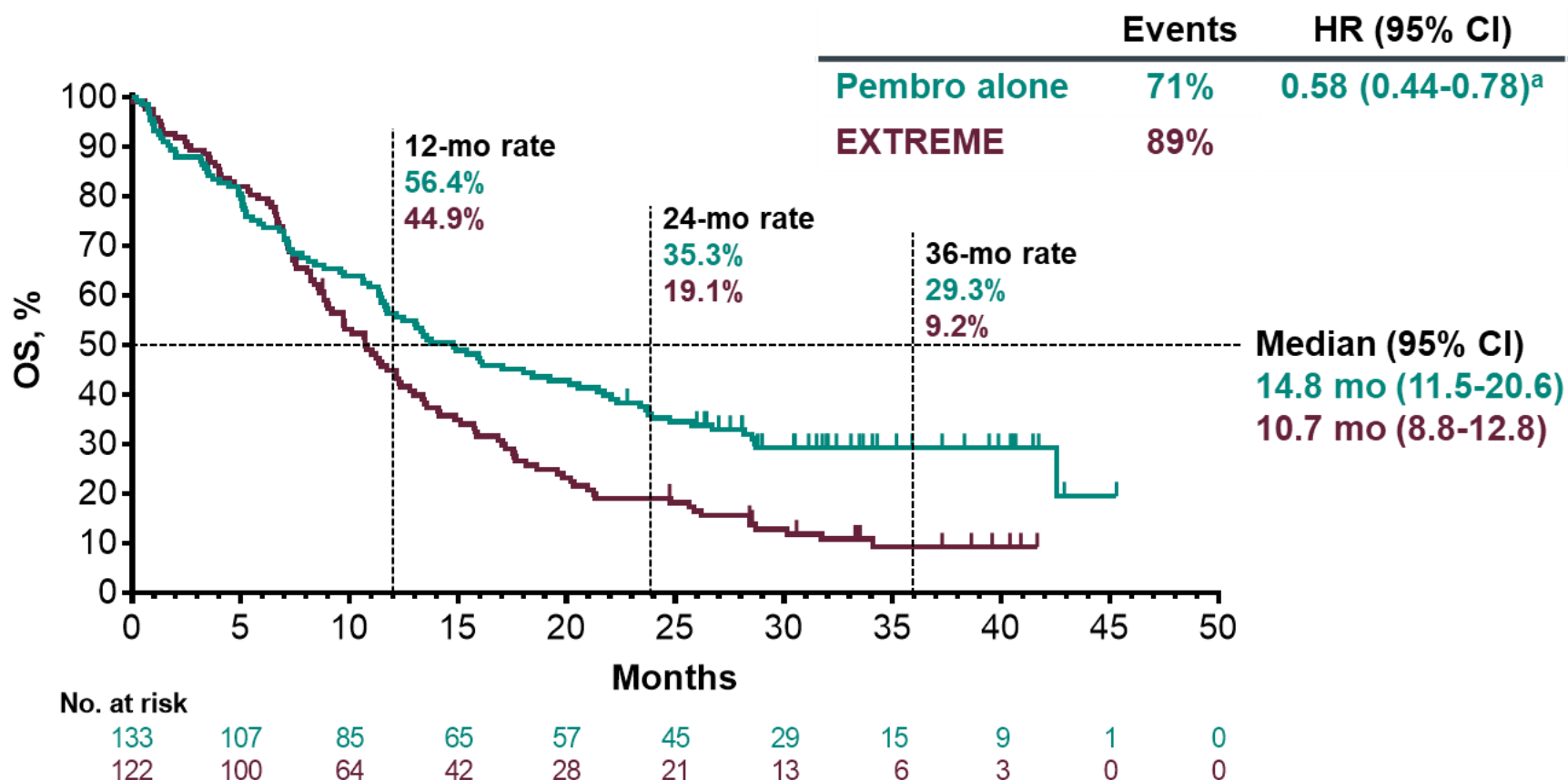


<sup>a</sup>Patients without measurable disease per central review at baseline who did not have CR or PD. <sup>b</sup>Patients who did not have a post-baseline imaging assessment evaluable for response or who did not have post-baseline imaging. Response assessed per RECIST v1.1 by blinded, independent central radiologic review. FA (data cutoff date: Feb 25, 2019).



# Keynote 48 OS Pembro Mono

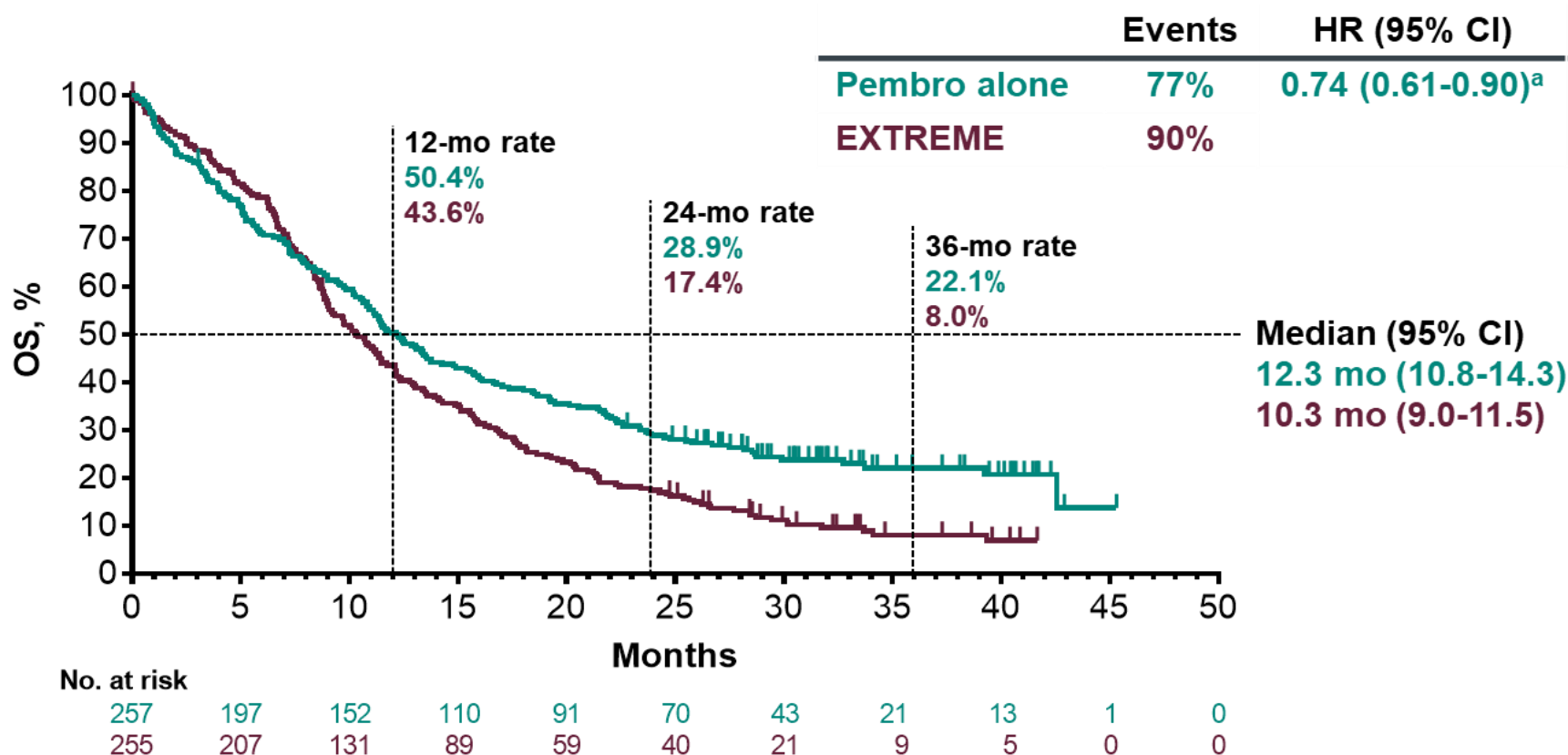
## OS, P vs E, CPS $\geq 20$ Population



# Keynote 48 OS

## Pembro Mono

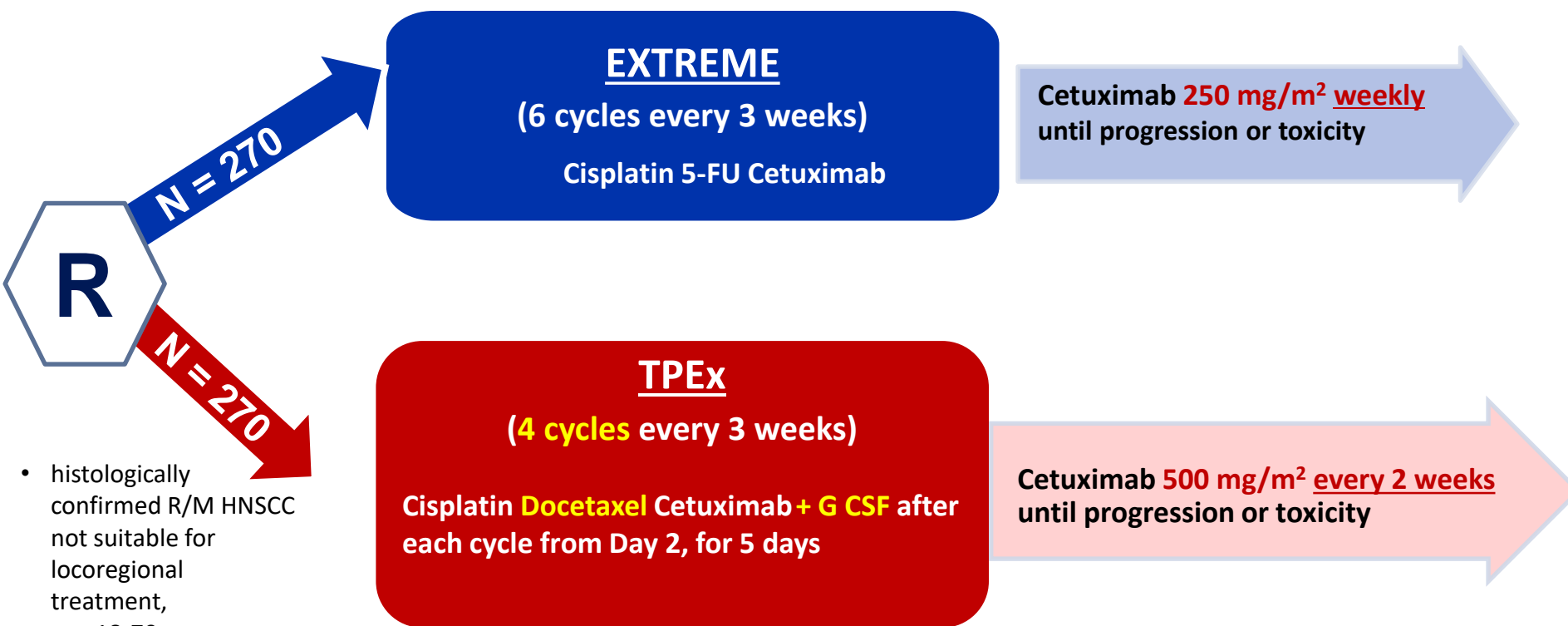
### OS, P vs E, CPS $\geq 1$ Population



# Keynote 48

## Finale Analyse

Arm	P+C	Extreme	P	Extreme
Median OS (mo) in CPS $\geq$ 20	14.7	11.0 HR 0.60, 95% CI 0.45-0.82	14.9	10.7 HR 0.61, 95% CI 0.45-0.83
Median OS (mo) in CPS $\geq$ 1	13.6	10.4 HR 0.65, 95% CI 0.53-0.80	12.3	10.3 HR 0.79, 95% CI 0.64-0.96
Median OS (mo) in total population	13.0	10.7 HR 0.77, 95% CI 0.63-0.93	11.5	10.7 HR 0.83, 95% CI 0.70-0.99
ORR CPS $\geq$ 20	42.9%	38.2%	23.3%	36.1%
ORR CPS $\geq$ 1	36.4%	35.7%	19.1%	34.9%
ORR total population	35.6%	36.3%	16.9%	36.0%

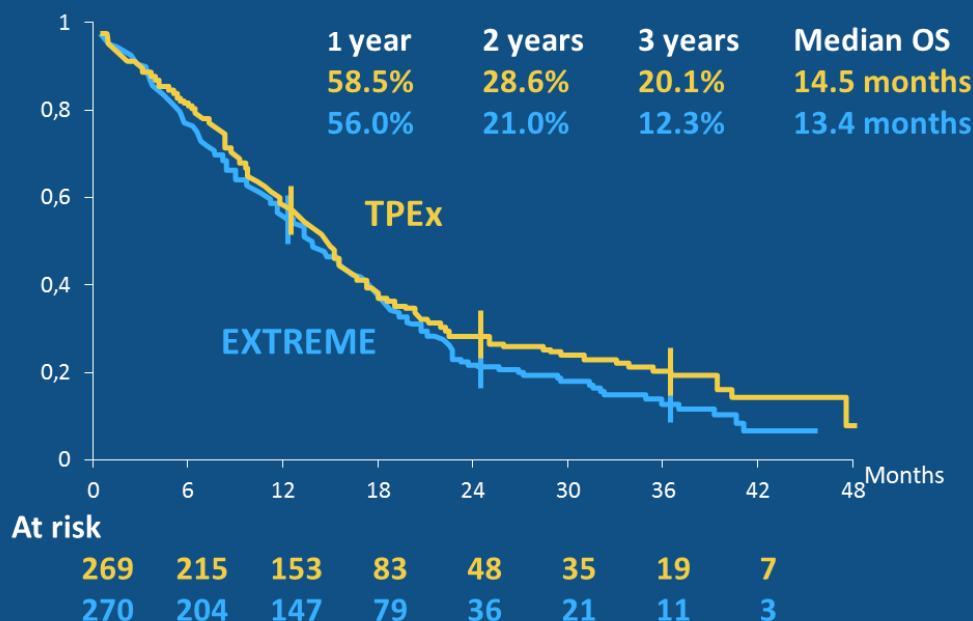


- histologically confirmed R/M HNSCC not suitable for locoregional treatment,
- age 18-70 years,
- PS < 2
- Previous:
- CDDP < 300mg/m<sup>2</sup>
- anti-EGFR > 1y

✓ **Primary objective : OS**



# TPExtreme OS

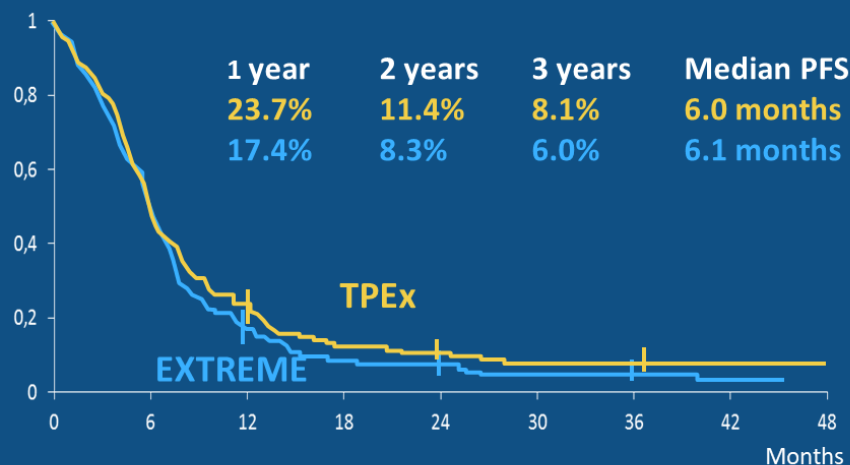


Median OS higher than expected:  
**14.5 months** in **TPEx** arm and  
**13.4 months** in **EXTREME** arm

Hazard ratio **TPEx** vs **EXTREME**:  
HR=0.87 (95% CI: 0.71-1.05)  
p-value=0.15



# TPExtreme PFS



- ORR (CR+PR) at 12 weeks according to local evaluation

→ 46% (123 / 269) in the TPEx arm

→ 40% (109 / 270) in the EXTREME arm

- 486 events, 247 in the EXTREME arm and 239 in the TPEx arm
- HR = 0.88 (95%CI:0.74-1.06), p-value = 0.17





# TPExtreme AEs



Maximal grade of <u>AEs</u>	EXTREME	<u>TPEx</u>
% patients <u>with</u> no AE or AE grade 1-2	8%	19%
% patients <u>with</u> <u>AEs</u> grade 3	41%	45%
% patients <u>with</u> <u>AEs</u> grade 4	44%	30%
% patients <u>with</u> <u>AEs</u> grade 5	7%	6%

**Toxicity was lower in the TPEx arm:**

**36%** pts had grade  $\geq 4$  AEs during CT vs **51%** in **EXTREME** ( $p < 0.001$ )

# Eagle Studiendesign

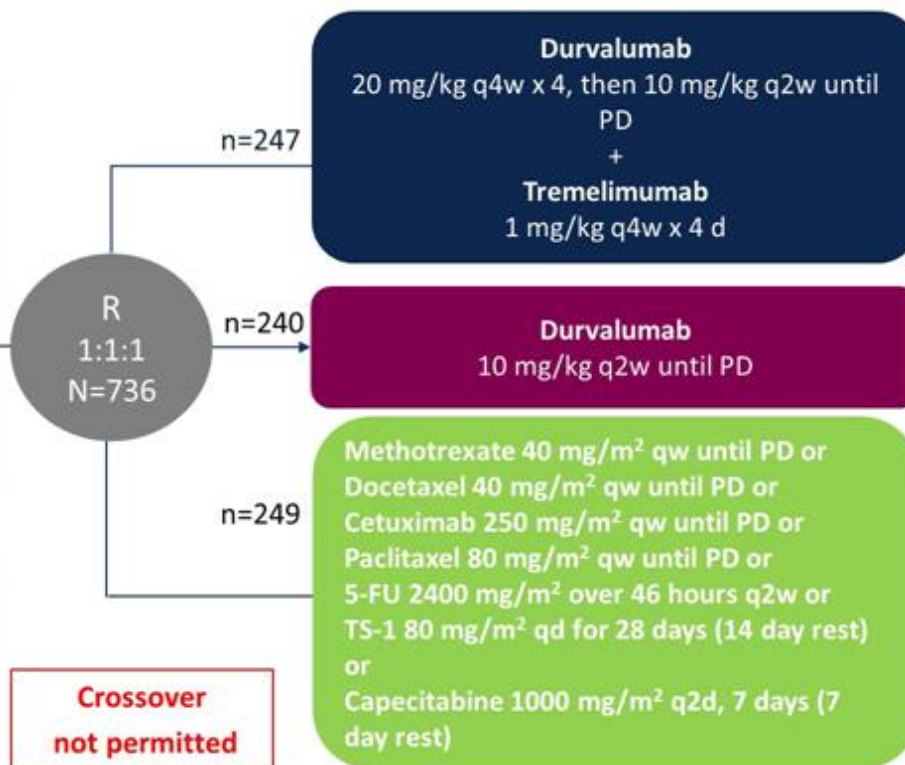
## EAGLE : Phase 3 Trial of Durvalumab alone or Durvalumab + Tremelimumab compared with SOC as 2L Treatment for R/M HNSCC

### Key eligibility criteria

- SCC of the oral cavity, oropharynx, hypopharynx, or larynx
- PD after platinum-containing regimen for R/M HNSCC or recurrence within 6 months of multimodal therapy using platinum with curative intent
- ECOG PS 0 or 1
- Known HPV status (oropharynx)
- Tissue sample for PD-L1 assessment

### Stratification factors

- PD-L1 status (TC  $\geq 25$  vs  $< 25$  %)
- Tumor location/HPV status (OPC HPV- vs HPV+ vs non OPC)
- Smoking history ( $< 10$  pack/y vs  $> 10$ )

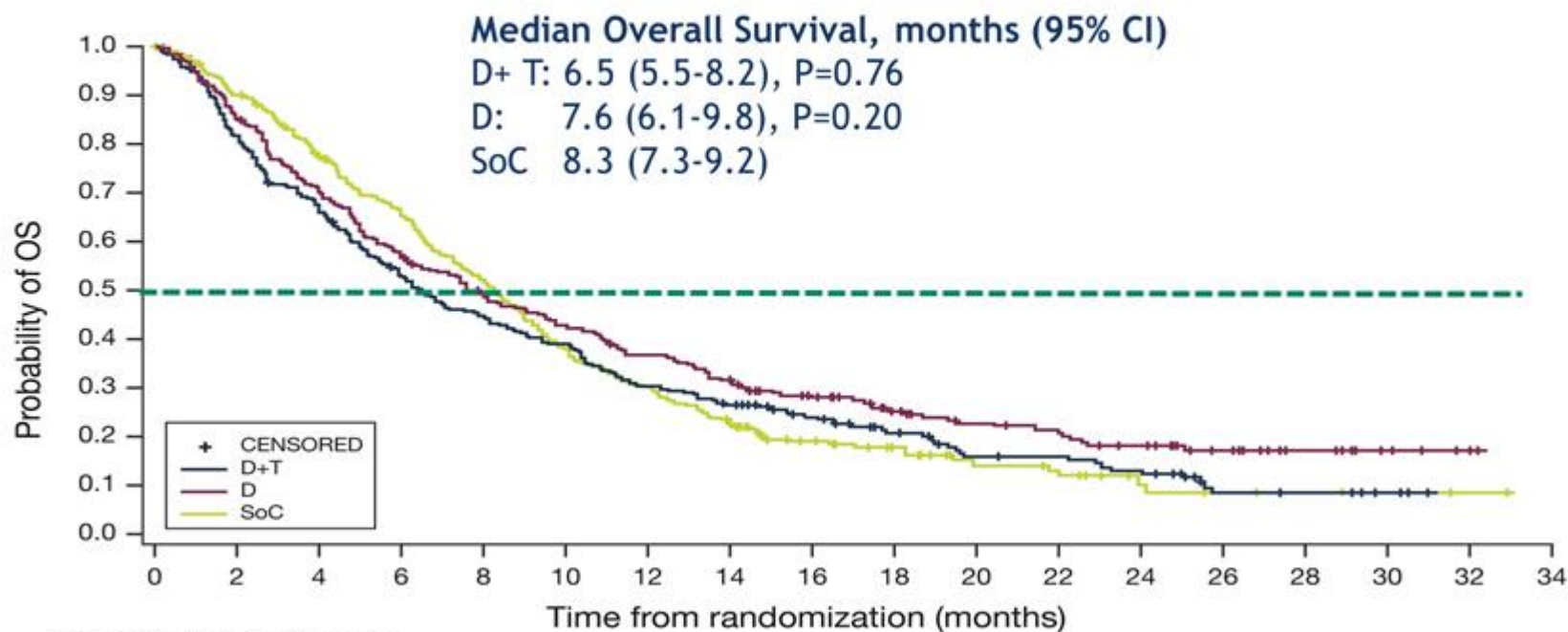


### 1° Endpoints:

- Overall Survival:
  - DT vs SoC
  - D vs SoC



## EAGLE Primary Endpoint: Overall Survival for D+T vs SoC and D vs SOC



Number of patients at risk

D+T	247	200	165	127	108	94	73	63	48	37	25	24	20	8	7	3	0	0
D	240	205	169	138	115	100	85	73	59	44	36	33	26	17	10	5	2	0
SoC	249	219	186	154	122	89	71	53	32	23	14	12	6	4	3	2	0	0

Licitra ASCO 2019



# Take home message

## R/M HNSCC 2019



**R/M HNSCC:Platin  $\geq$  6Monate**



**TEST FOR CPS**



**CPS $\geq$ 20**



**Pembro  
(Pembro+Chemo)**

**CPS $\geq$ 1**



**Pembro+Chemo  
(Pembro)**

**CPS=0**



**Pembro+Chemo  
TPEX  
Chemo Mono bei  
ECOG 2**

**R/M HNSCC:Platin  $\leq$  6Monate**



**Nivolumab  
Pembro bei TPS $\geq$ 50**



# Take home message

## Pseudo-PD ist selten



### Incidence of Pseudoprogression in HNSCC

- Response assessment evaluating PD-1/PD-L1 inhibitors is per RECIST v1.1, not iRECIST
- Inferred incidence of pseudoprogression is low

Study	PD-1/PD-L1 Inhibitor	ORR (platinum-refractory)	Possible Incidence of Pseudoprogression
KEYNOTE-012	Pembrolizumab (phase Ib)	18%	1/45 (2%)
Checkmate 141	Nivolumab (phase III)	13.3%	3/240 (1.25%)
KEYNOTE-040	Pembrolizumab (phase III)	14.6% (confirmed or unconfirmed)	2/247 (0.8%)
	Durvalumab (phase I/II)	6.5% (15% for PD-L1>25%)	1/62 (1.6%)

Seiwert et al. Lancet Oncol 2016;17:956-965.

Ferris et al. Lancet NEJM 2016;375:1856-67.

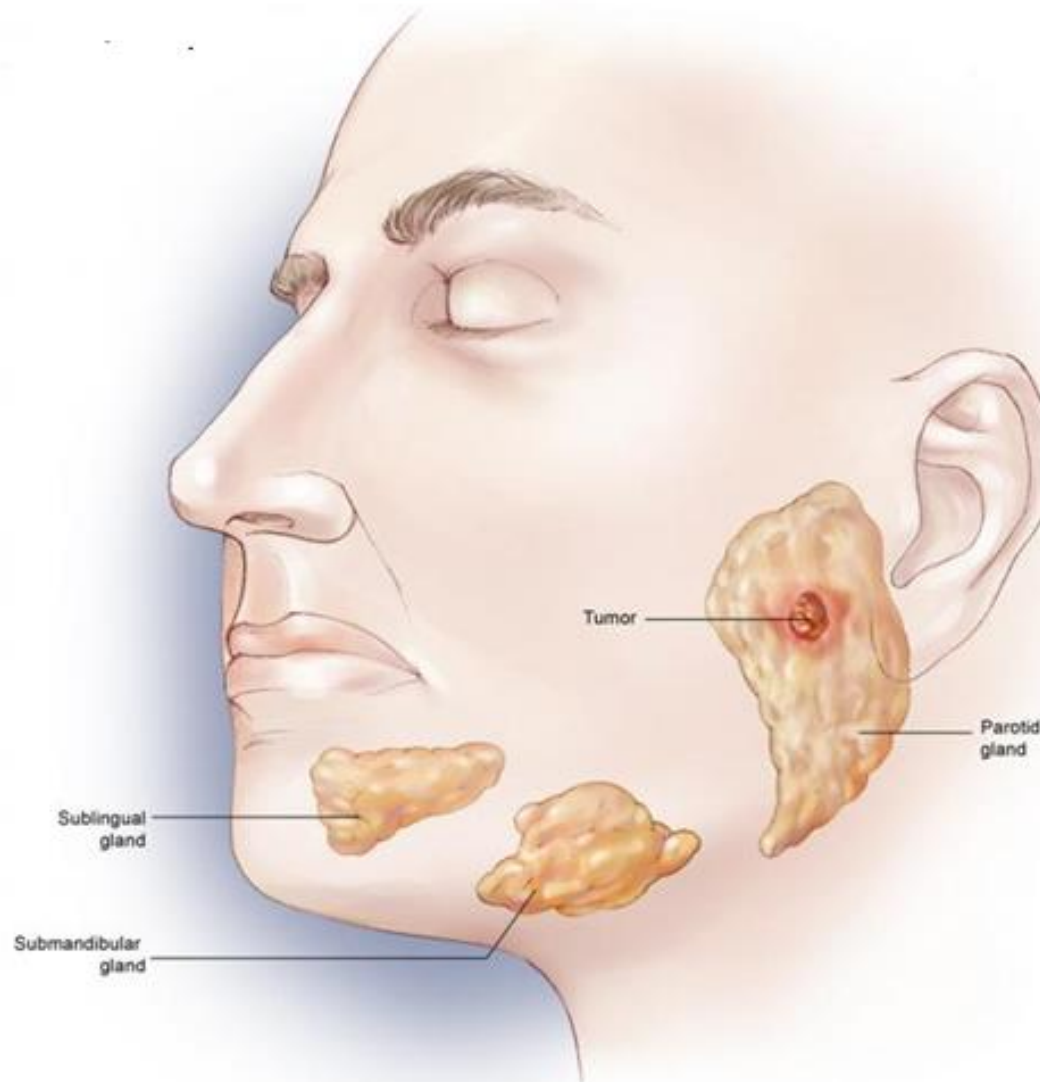
Cohen et al. Lancet 2019;393:156-67.

Segal et al. European Journal of Cancer 2019; 109;154-61.





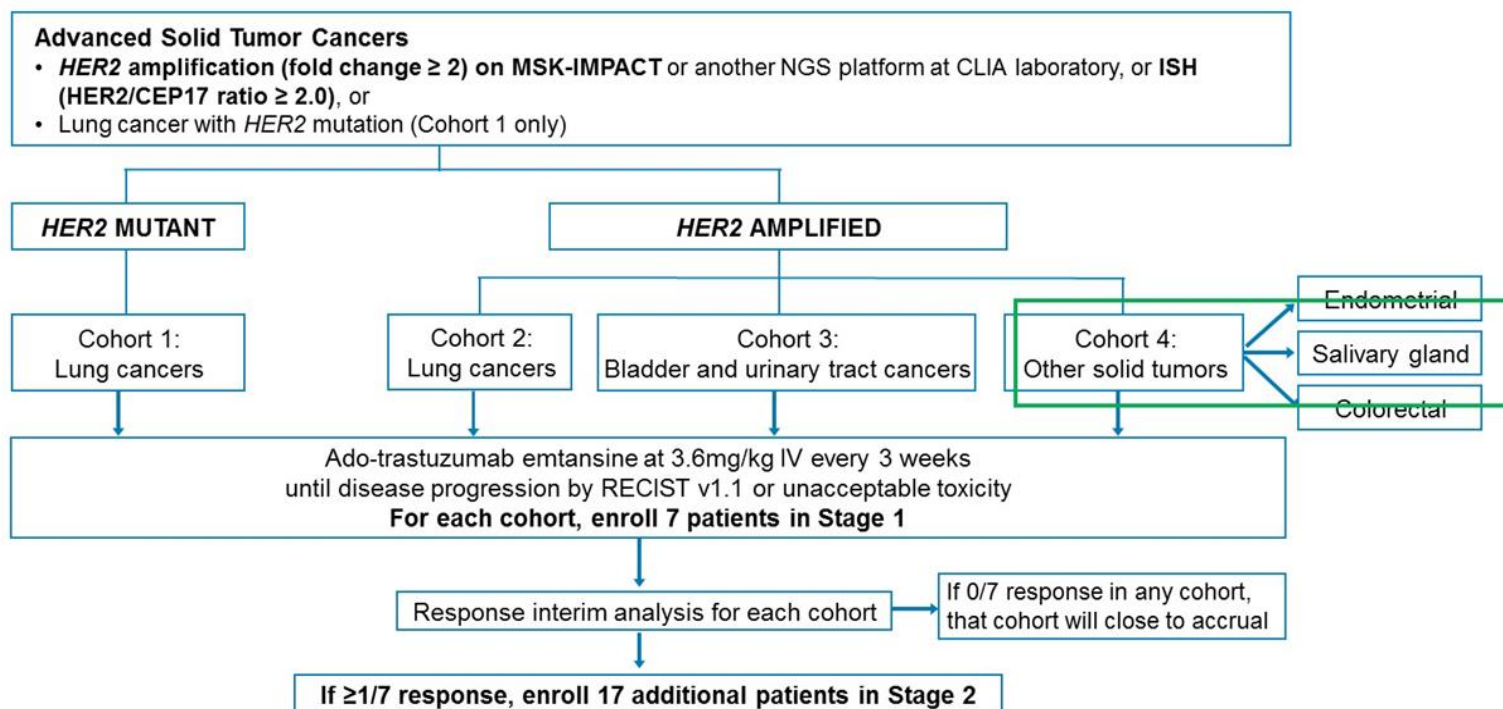
# Speicheldrüsen Ca.







## A phase 2 trial of ado-trastuzumab emtansine for patients with *HER2* amplified or mutant cancers (NCT02675829)



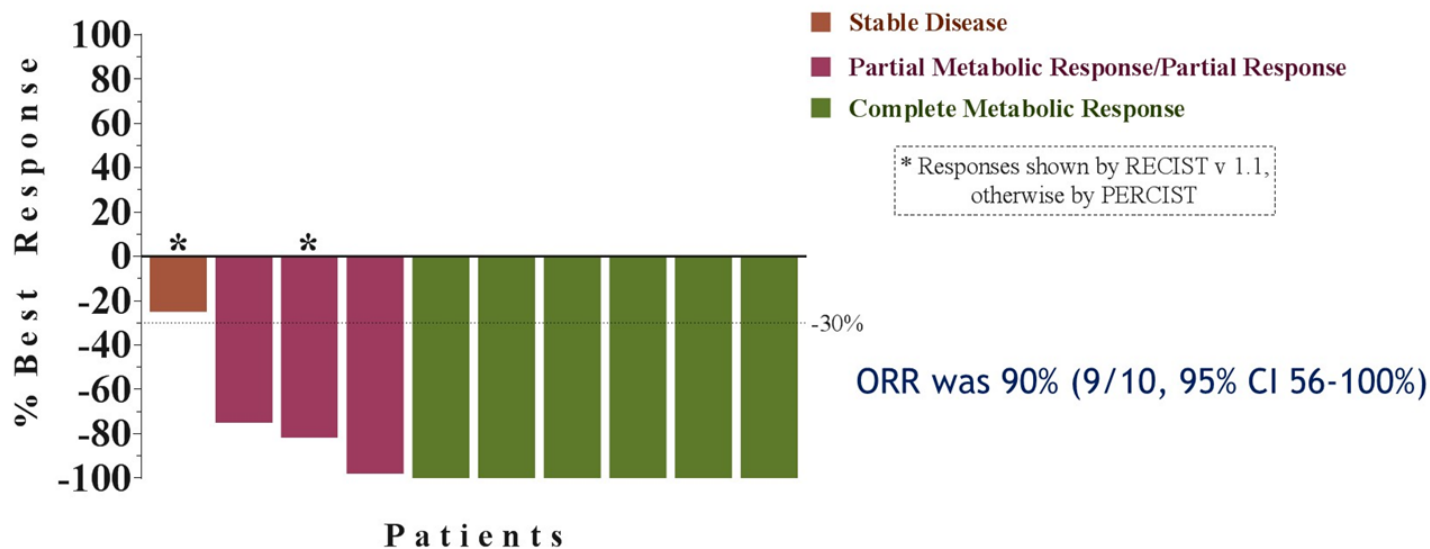


## Patient characteristics

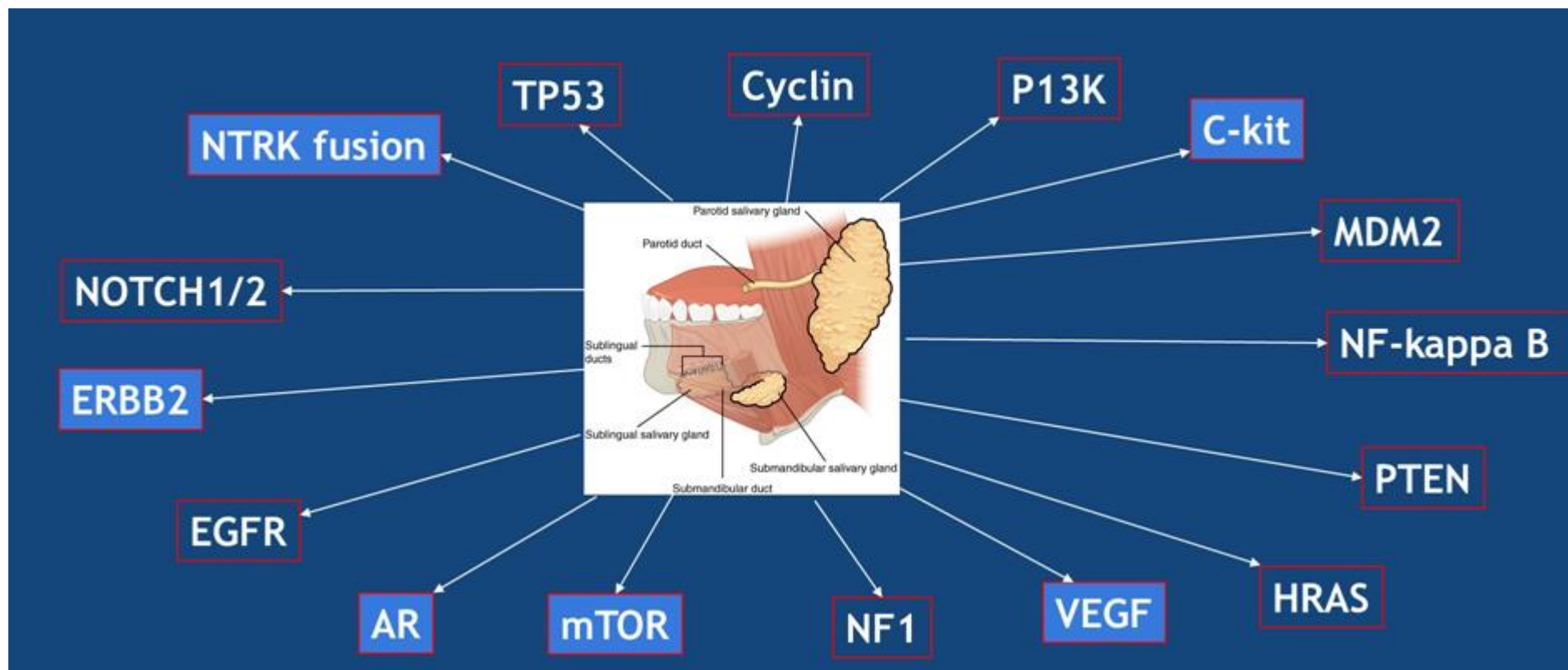
	N
Total patients treated	10
Age, median (range)	65 (36-90)
Sex, Male	90%
Disease histology	
Adenocarcinoma	1
Poorly differentiated carcinoma with apocrine features	3
Carcinoma NOS	6
Median lines of prior systemic therapy (range)	2 (0-3)
Anti-androgen therapy	50%
HER2 targeted therapy	20%

## Best Overall Response

### *HER2* Amplified Salivary Gland Cancers

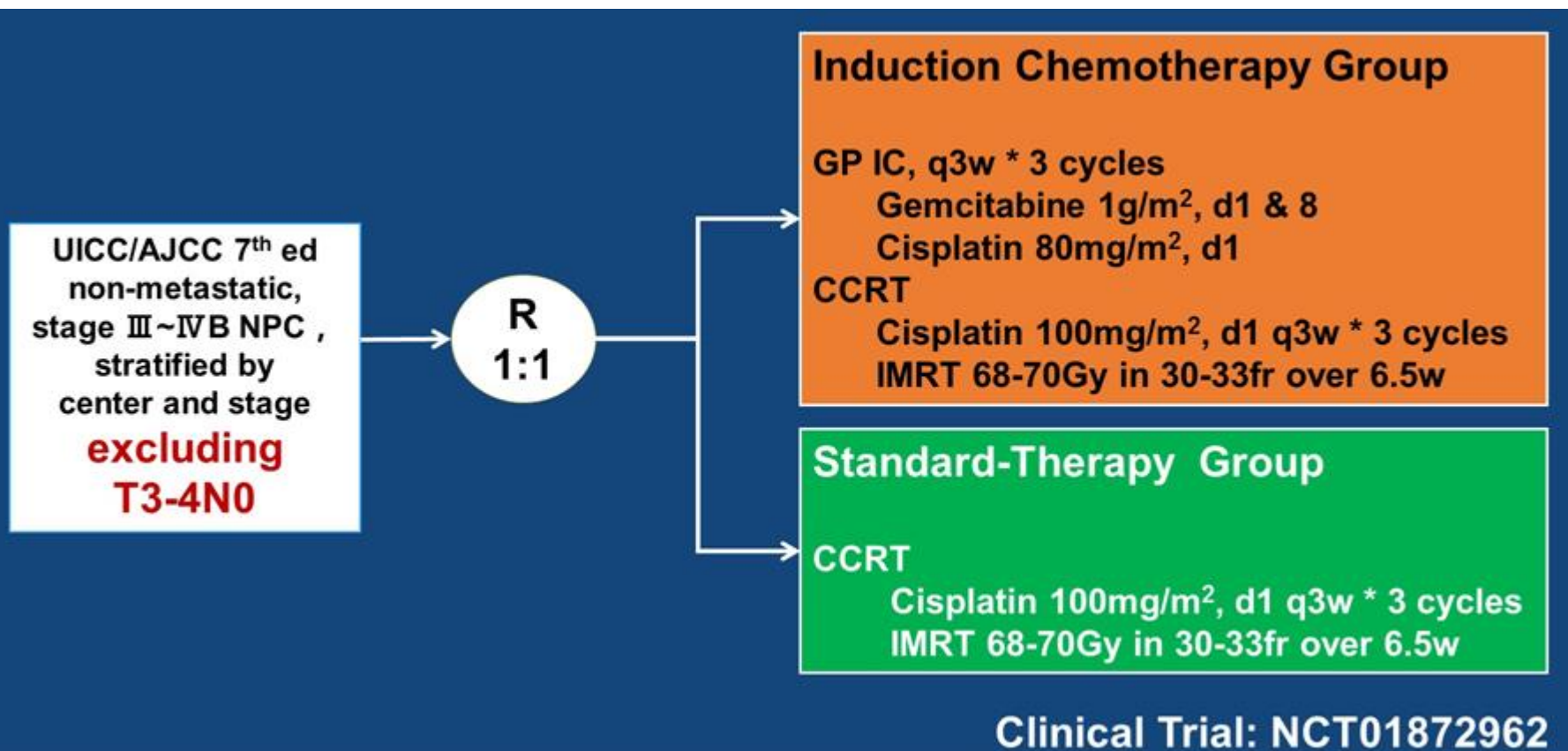


## Molekulare Analyse bei Speicheldrüsencas. notwendig





# NPC: Induktionschemo Studiendesign



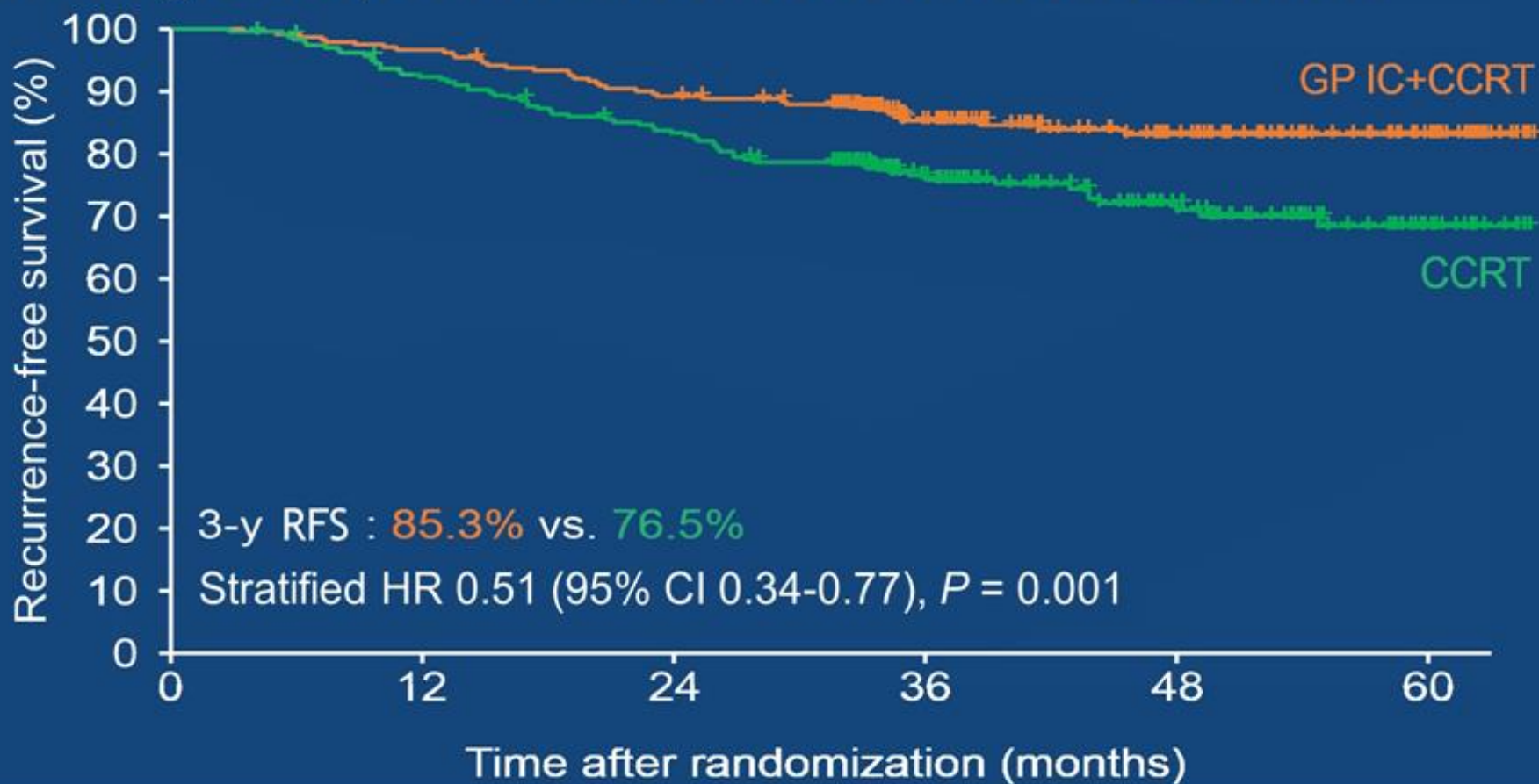




# NPC: Induktionschemo RFS



## Primary endpoint: Recurrence-free survival



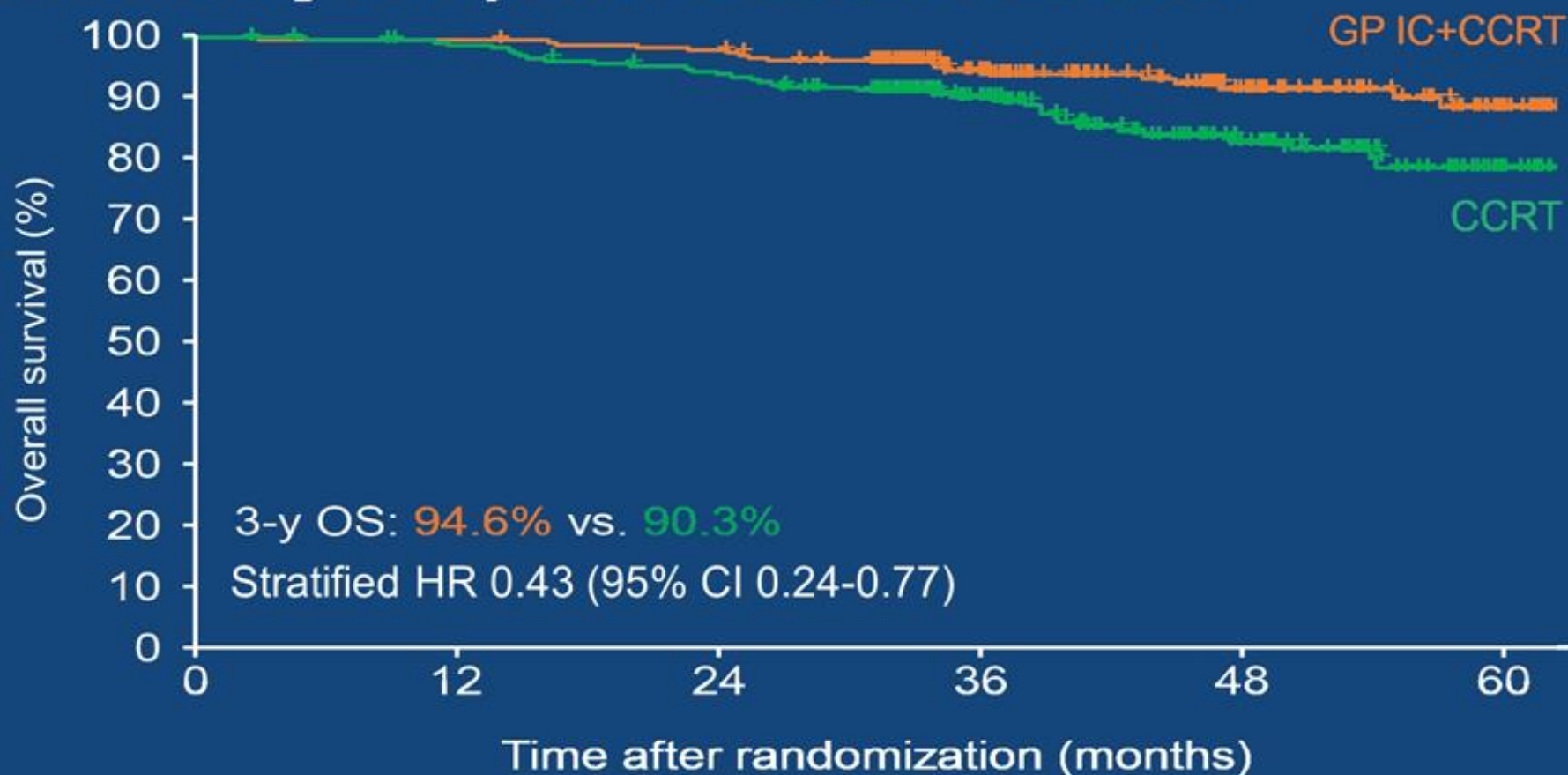




# NPC: Induktionschemo OS



## Secondary endpoint: Overall survival

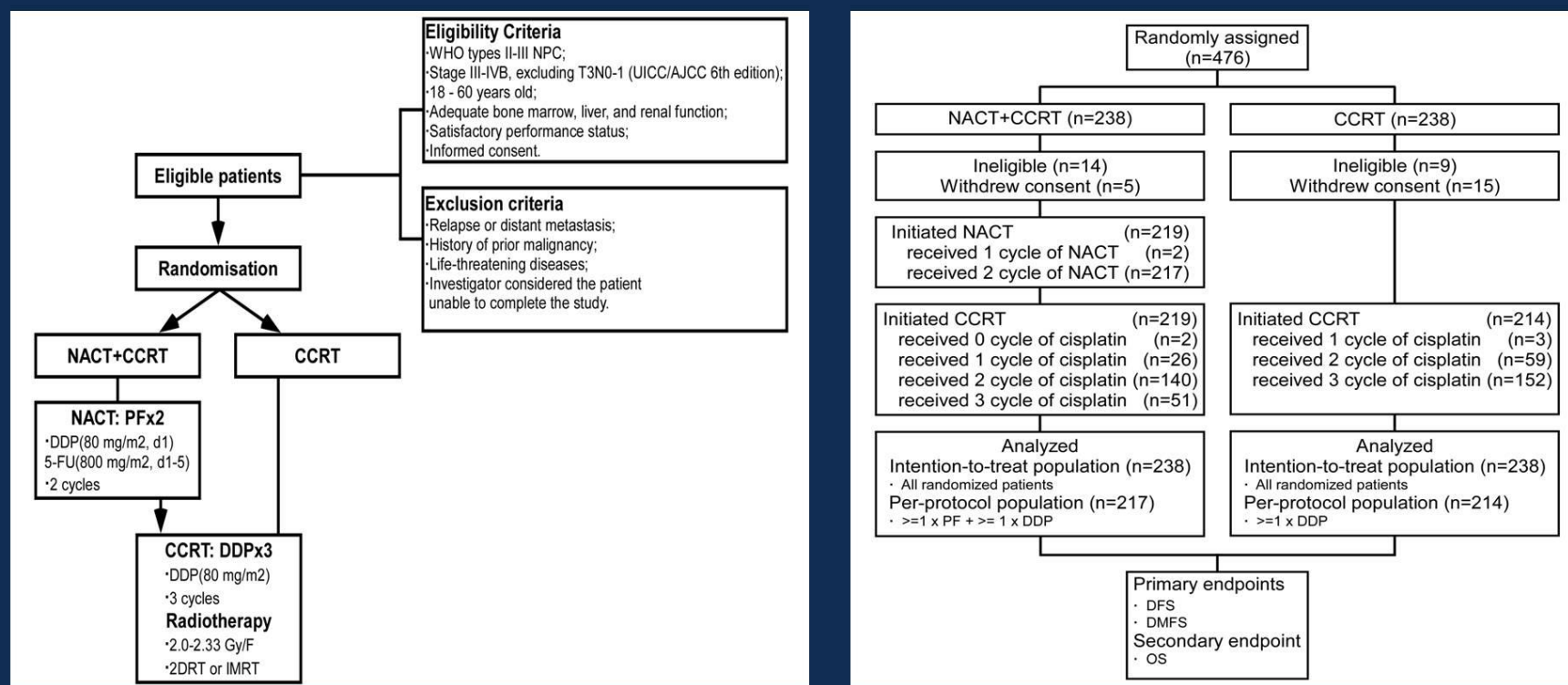




# NPC: Induktionschemo Studiendesign



## Flow and profile of trial participants



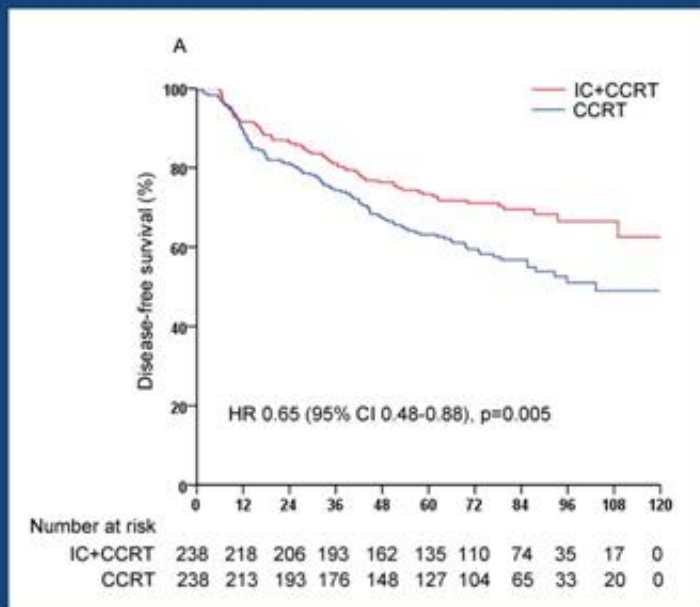


# NPC: Induktionschemo

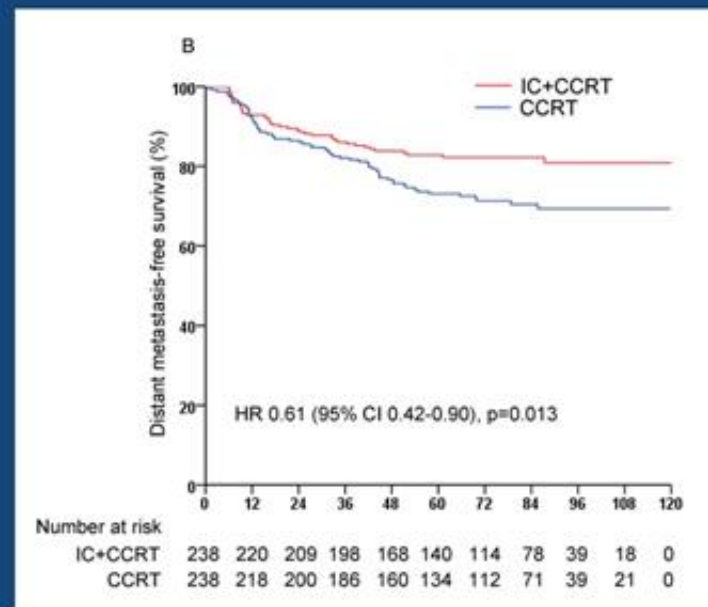
## DFS und DMFS



**5-year DFS ↑ 10%**  
**(63% vs 73%, p=0.005)**



**5-year DMFS ↑ 10%**  
**(73% vs 83%, p=0.013)**

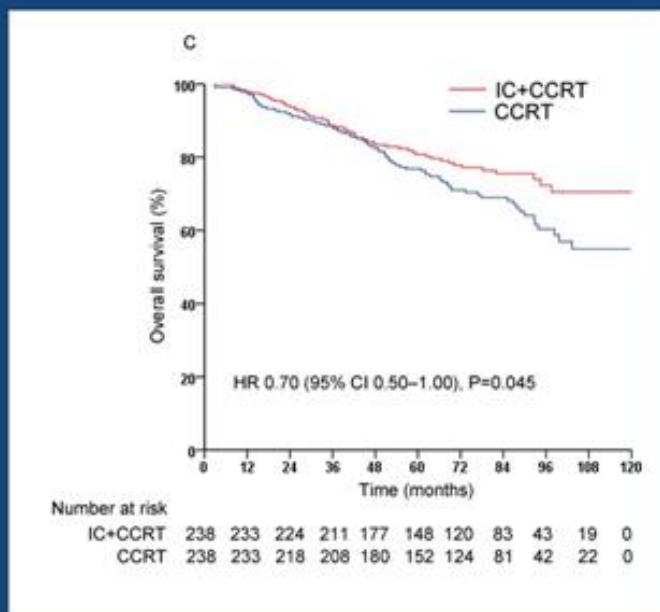




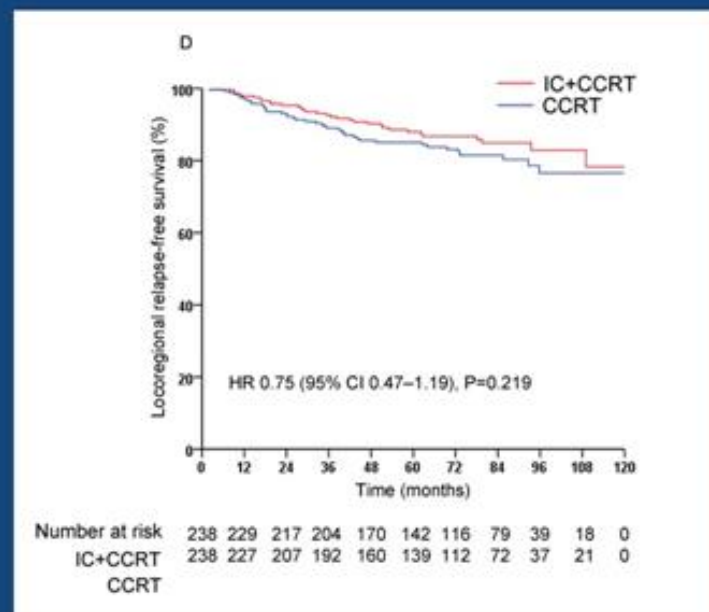
# NPC: Induktionschemo OS und LRRFS

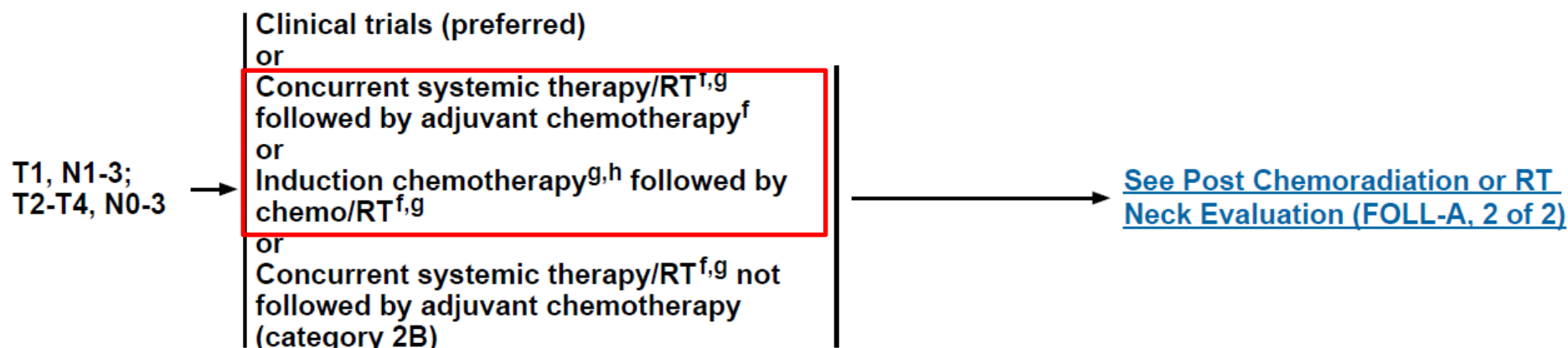


**5-year OS ↑ 4%**  
**(77% vs 81%, p=0.045)**



**5-year LRRFS**  
**(85% vs 88%, p=0.219)**







COMPREHENSIVE  
CANCER  
CENTER VIENNA



MEDICAL UNIVERSITY  
OF VIENNA

