2019: Are there new standards of care in head and neck cancer?

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Recent Results

- Locally Advanced HPV-Associated Oropharynx Cancer
  - R1016
  - De-ESCALaTE HPV
  - HN002
- Recurrent/Metastatic Disease
  - First-line IO or IO plus chemotherapy
  - Second line regimens incorporating CTLA-4i
- Ongoing Studies

Randomized Trials Studied Increasingly Intense Therapies

- Studies conducted in predominantly HPV negative populations examined
  - Addition of 9 weeks of induction chemotherapy
  - Altered fractionation schemes
  - Higher radiation dose
  - High dose cisplatin
  - Post-operative combined modality or altered fractionation radiation
- Increased acute and chronic toxicity and increased cost

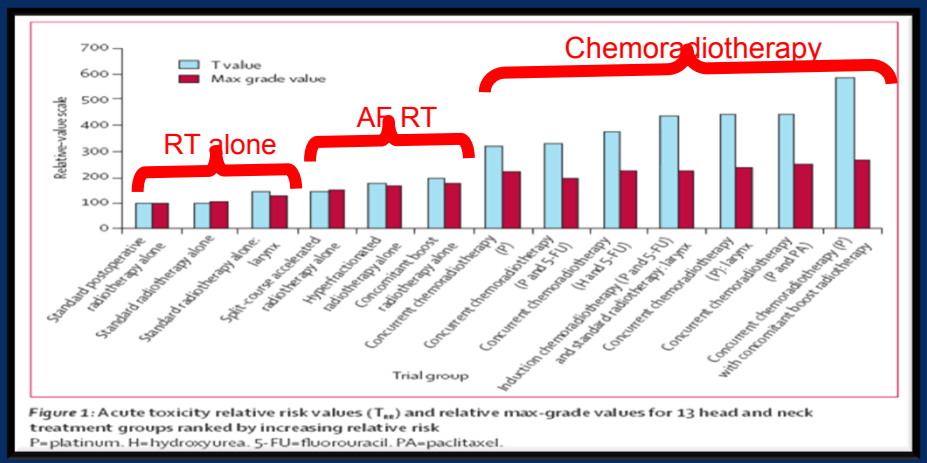
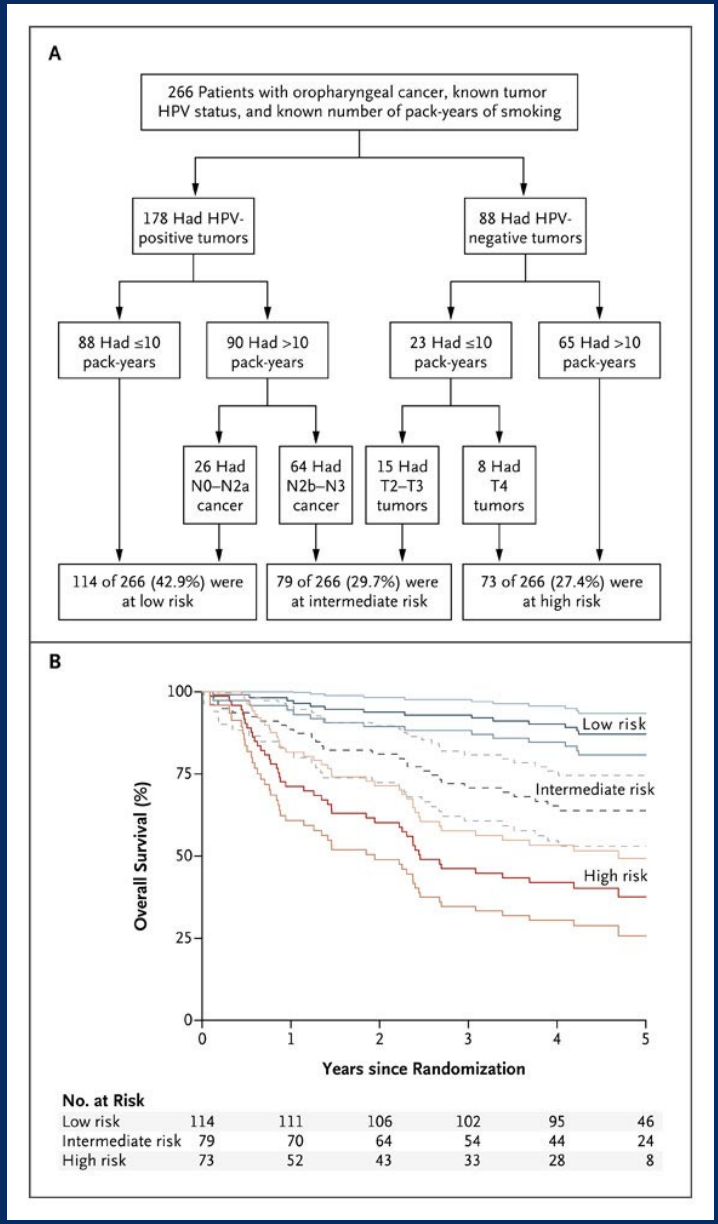


Figure 1: Acute toxicity relative risk values (T_{RR}) and relative max-grade values for 13 head and neck treatment groups ranked by increasing relative risk
P=platinum. H=hydroxyurea. 5-FU=fluorouracil. PA=paclitaxel.

R0129 Classification of the Study Patients into Risk-of-Death Categories and Overall Survival According to Those Categories



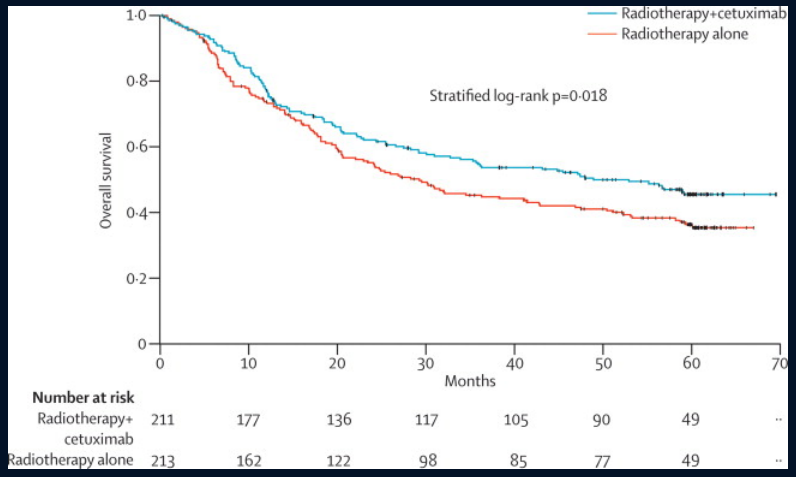
Ang K et al. N Engl J Med 2010;10.1056/NEJMoa0912217

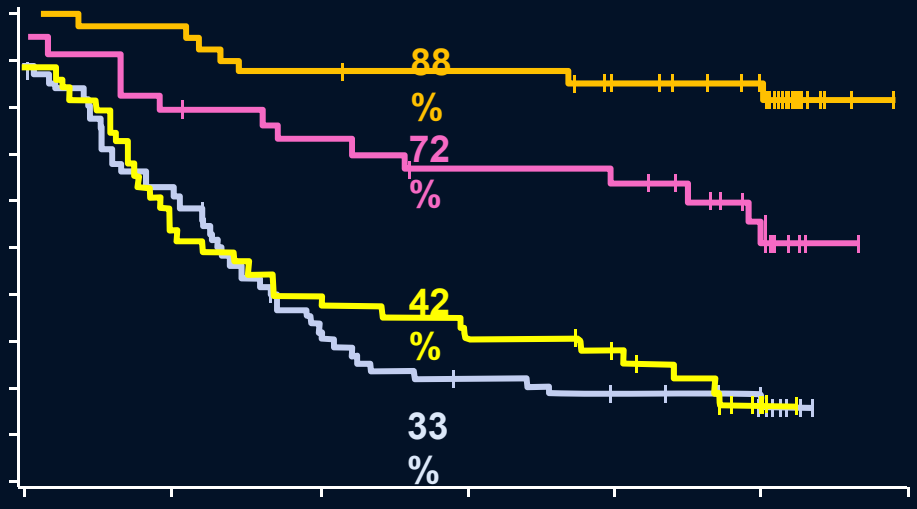
The NEW ENGLAND JOURNAL of MEDICINE

Goals for HPV-Associated Oropharynx Cancer

- Identify patients with near certainty of cure
- Maintain high cure rates while reducing morbidity
  - Acute toxicity grade and duration
  - Late toxicity
    - Speech and swallowing
    - Non-cancer mortality
    - Psychological effects
  - Resource utilization
- Explore novel agents for intermediate risk patients

Radiation with or without Cetuximab: Overall survival median follow-up 60 months





OS interaction test p=NS

RT; p16+ **HR=0.38 [0.15–0.94]**

RT + cet; p16–

RT; p16– **HR=0.85 [0.61–1.19]**

Bonner et al. Lancet Oncol, 2010; 11:21–28

Phase III Trial of Radiotherapy plus Cetuximab versus Chemoradiotherapy in HPV-Related Oropharynx Cancer

REGISTER	Mandatory p16 testing	STRATIFY	T Stage 1. T1-2 2. T3-4 N Stage 1. N0-2a 2. N2b-3 Zubrod Performance Status 1. 0 2. 1 Smoking History 1. ≤ 10 pack-years 2. > 10 pack-years	RANDOMIZE	Arm 1 (Control): Accelerated IMRT, 70 Gy for 6 weeks + high dose DDP (100 mg/m^2) Days 1 and 22 (Total: 200 mg/m^2) Arm 2: Accelerated IMRT, 70 Gy for 6 weeks + cetuximab (400 mg/m^2) loading dose pre-IMRT, then 250 mg/m^2 weekly during IMRT, + 1 week after IMRT for a total of 8 doses of cetuximab

Objectives

Primary objective: To determine whether cetuximab will result in non-inferior 5-year OS

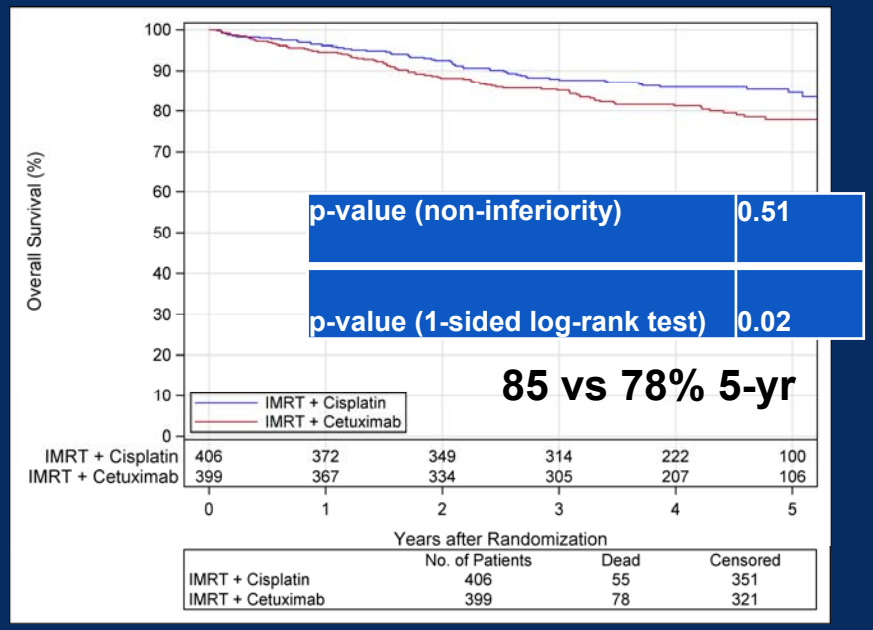
N= 800; 1-sided 95% CI for the HR (cetuximab/cisplatin) is < 1.45

Toxicity and Function
Quality of Life
Acute toxicity burden (T-score)
Swallowing function at 1 year (EORTC swallowing domain)

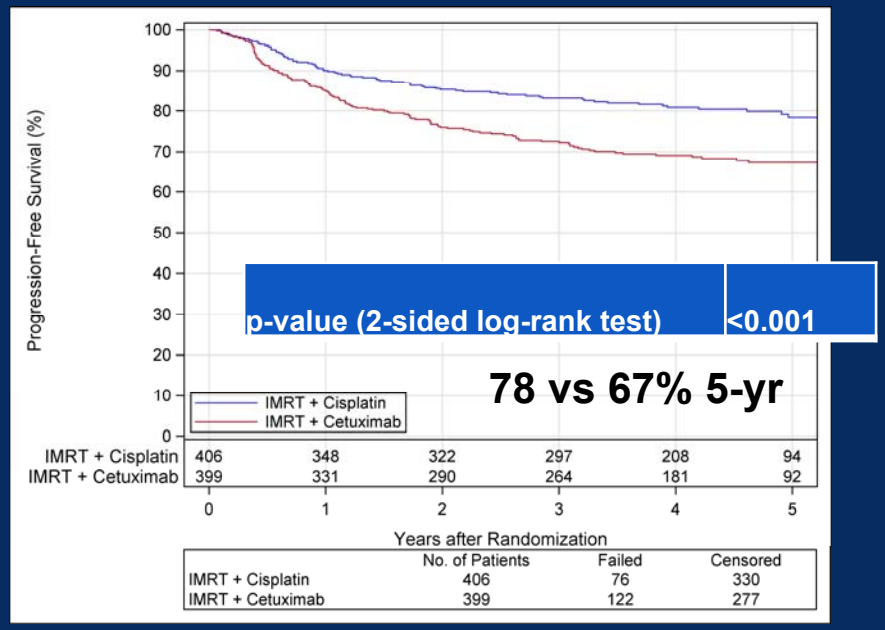
Patient Characteristics

- 805 patients analyzed
- Median age 58
- 90% male; 93% white
- 74%/26% Zubrod 0/1
- 38% >10 pack-years smoking
- T4 disease 12%
- 90% N2-3 (AJCC 7th edition)

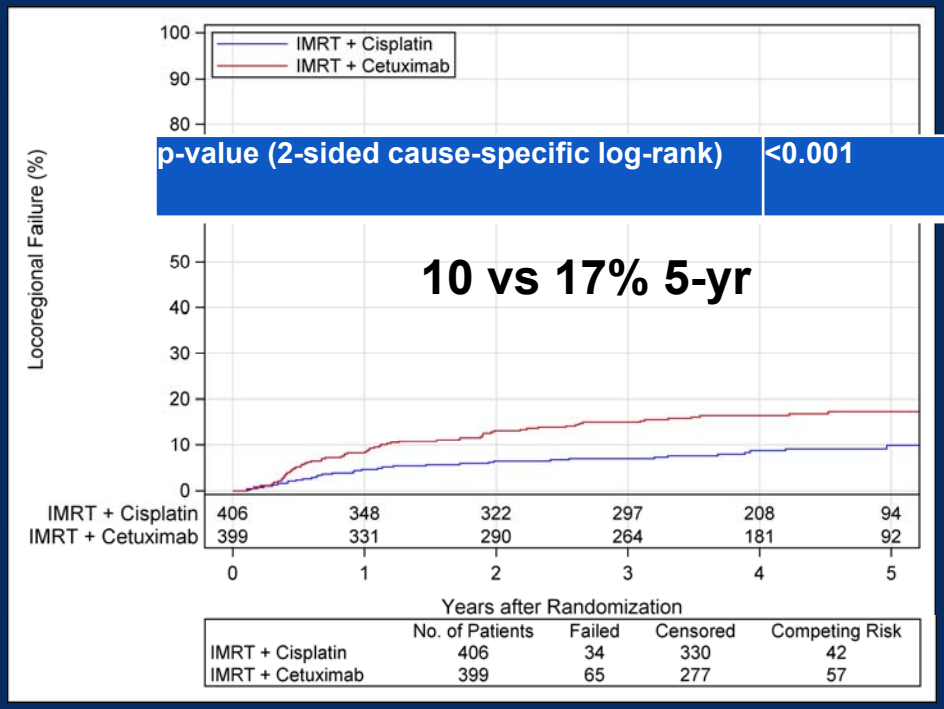
Overall Survival

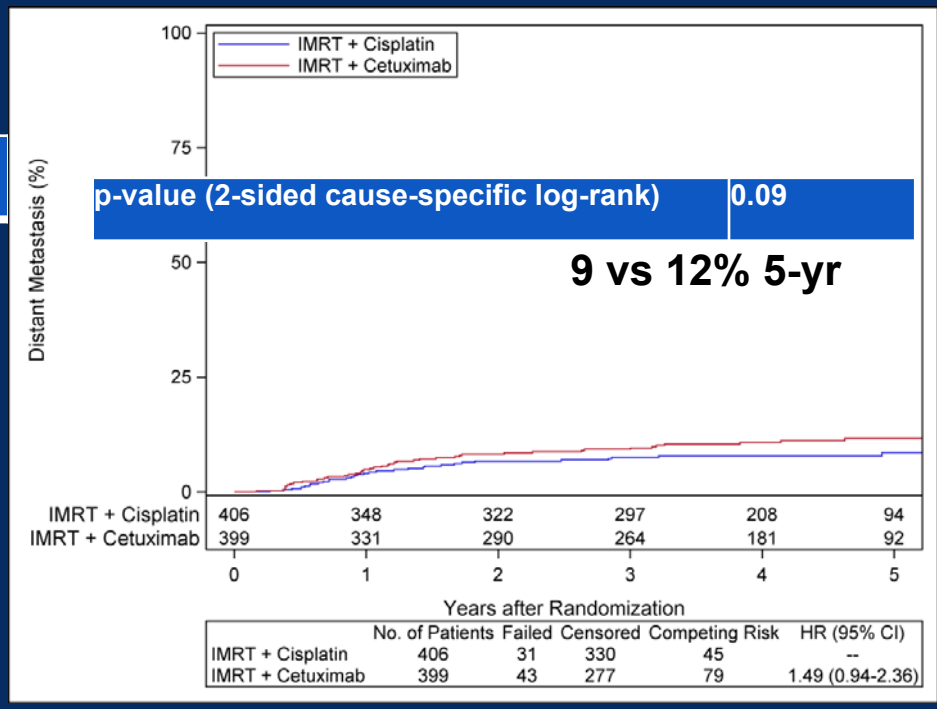


Progression-Free Survival



Locoregional Failure





Acute toxicity: worst grade method

	Cisplatin	Cetuximab	
Acute period, n	398	394	
Early death	1.5%	1.5%	1.00
Grade 3-4 overall	81.7%	77.4%	0.16
Grade 3-4 anemia	2.8%	0.0%	<0.001
Grade 3-4 hearing impaired	3.0%	0.3%	<0.001
Grade 3-4 dysphagia	37.4%	32.0%	0.12
Grade 3-4 mucositis oral	41.5%	46.2%	0.20
Grade 3-4 nausea	19.1%	8.1%	<0.001
Grade 3-4 vomiting	12.1%	4.1%	<0.001
Grade 3-4 fatigue	5.8%	4.3%	0.42
Grade 3-4 dermatitis radiation	8.0%	12.4%	0.05
Grade 3-4 neutrophil count decreased	15.3%	0.5%	<0.001
Grade 3-4 weight loss	7.8%	5.8%	0.32
Grade 3-4 white blood cell decreased	12.1%	0.0%	<0.001
Grade 3-4 acute kidney injury	3.3%	0.3%	0.002
Grade 3-4 rash acneiform	0.3%	9.4%	<0.001
Grade 3-4 pain (all terms)	14.6%	12.7%	0.47

* “worst grade” includes only 1 event per patient

Acute Toxicity Burden:T-score

	Cisplatin	Cetuximab		
Mean raw T-score	**3.19**	**2.35**	**40% increase acute toxicity**	**<0.001**
Grade 3-4 overall (classical)	**81.7%**	**77.4%**	**4 point (N.S.) Difference**	**0.16**

*Acute Toxicity Burden: captures *all Gr 3-4 acute adverse events*

Late Toxicity: Worst Grade

	Cisplatin	Cetuximab	
Late period, n	383	375	
Grade 3-4 overall	**20.4%**	**16.5%**	**0.19**
Grade 3-4 hearing impaired	6.3%	2.1%	0.006
Grade 2-3 dry mouth	32.1%	33.6%	0.70
Grade 3-4 dysphagia	4.4%	6.1%	0.33
Grade 3-4 weight loss	4.4%	2.9%	0.34
Grade 3-4 osteonecrosis of jaw	2.1%	0.8%	0.22
Grade 3-4 pain (all terms)	1.3%	2.1%	0.42

worst grade includes only 1 event per patient

Late Toxicity Burden: A-score

Mean raw A-score	**0.38**	**0.27**	**40% Increased Late Toxicity**	**0.12**
Grade 3-4 overall (classical)	**20.4%**	**16.5%**	**4 point (N.S.) Difference**	**0.19**

Late Toxicity Burden: captures *all late Gr 3-4 adverse events*

Conclusions

- Non-inferiority of cetuximab was NOT demonstrated
- Cisplatin had better OS, PFS, LRC
- Worst Grade Acute Toxicity: no difference
- Acute “Toxicity Burden”: 40% worse with cisplatin
- Late “Toxicity Burden”: 40% worse with cisplatin

De-ESCALaTE HPV

OUTCOMES

Primary outcome:

- Overall (acute+late) severe (CTCAE v4 G3-5) toxicity

Secondary outcomes:

- Acute severe toxicity ≤ 3 mo post-treatment
- Late severe toxicity - –≥ 3 mo post-treatment
- QoL - EORTC QLQC30 and HN35
- Swallowing – MD Anderson Dysphagia Inventory (MDADI)
- Overall survival and recurrence
- Cost effectiveness – EQ-5D

SAMPLE SIZE

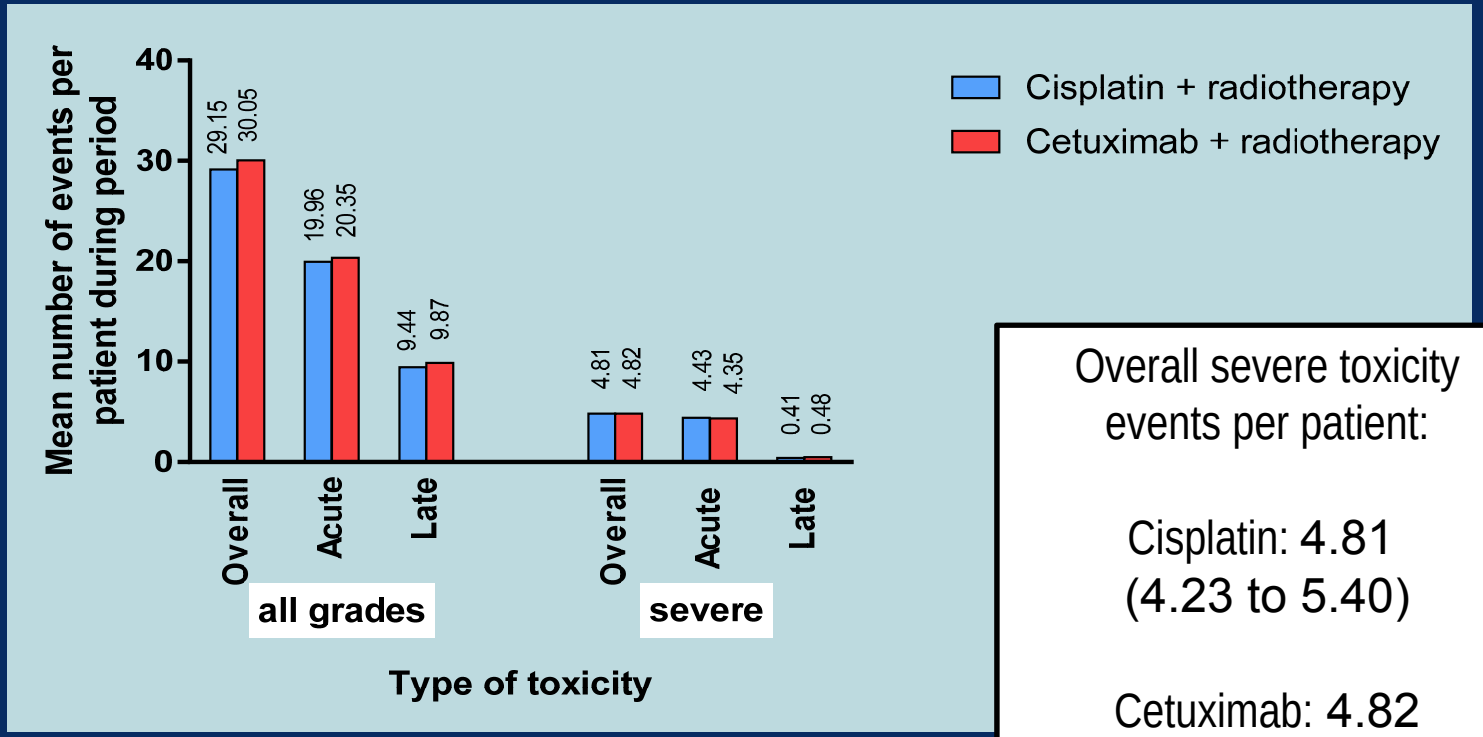
- N=304
- Detection of reductions >25% in overall number of severe (grade 3-5) (acute and late) toxicities
- 2-sided test, 5% significance, >90% power allowing for 10% drop out

CAVEATS

- Not powered for OS
- 2 year follow up inadequate for HPV-related cancer
- 25% of deaths non-cancer
- Multiple comparisons increases type 1 error

PRIMARY OUTCOME: TOXICITY

Same rates of severe (G3-5) and all-grade (G1-5) toxicity between arms



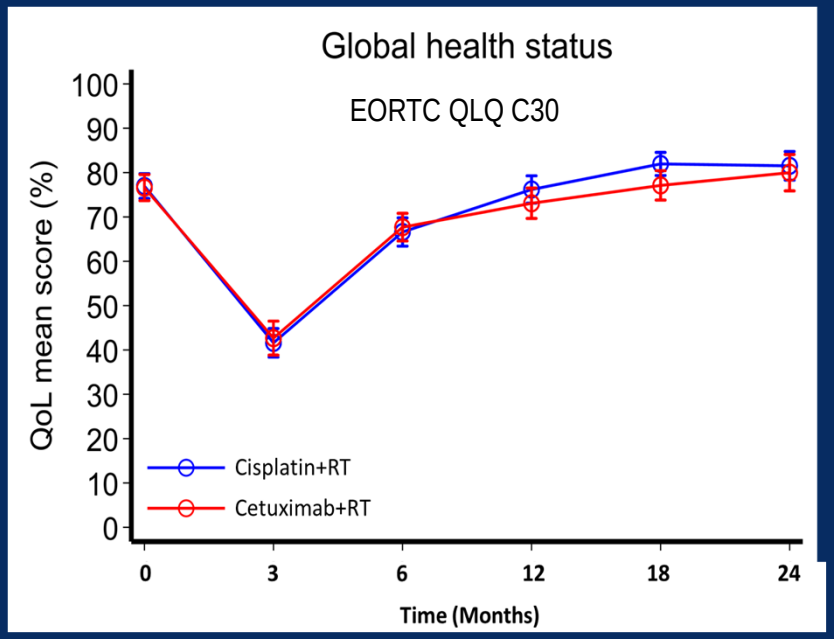
Overall severe toxicity events per patient:

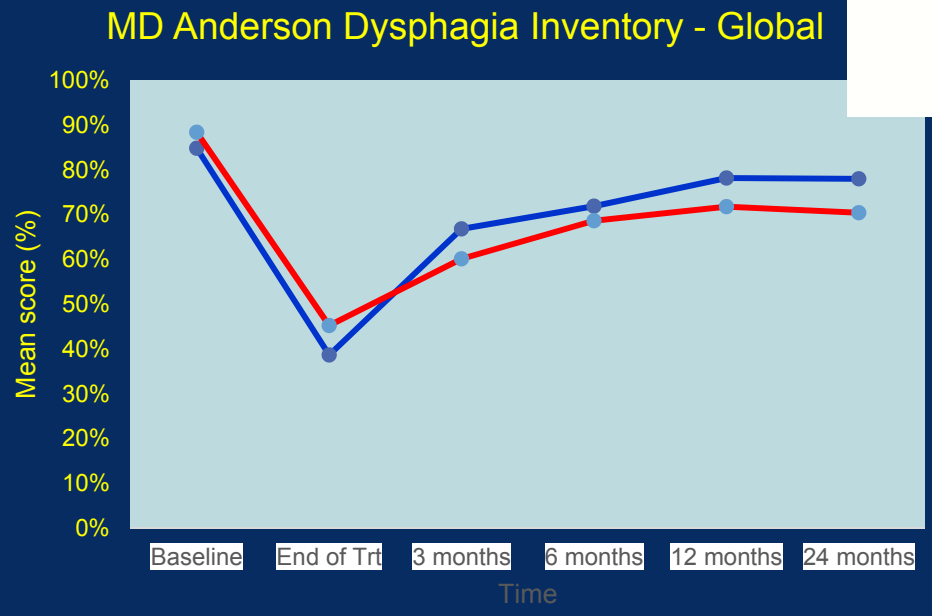
Cisplatin: 4.81 (4.23 to 5.40)

Cetuximab: 4.82 (95%CI = 4.22 to 5.43)

p= 0.98

QUALITY OF LIFE & SWALLOWING DID NOT DIFFER



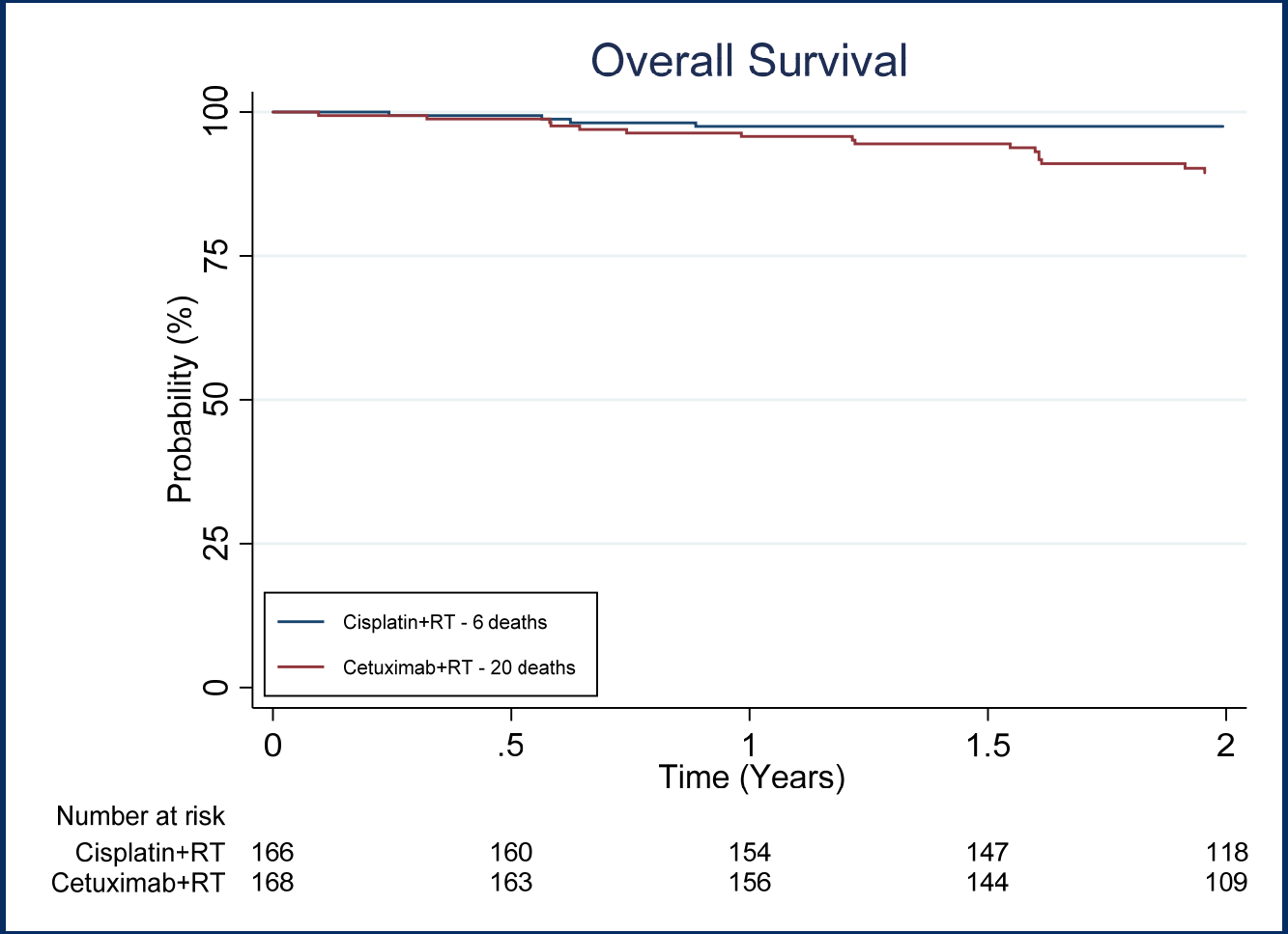


SURVIVAL

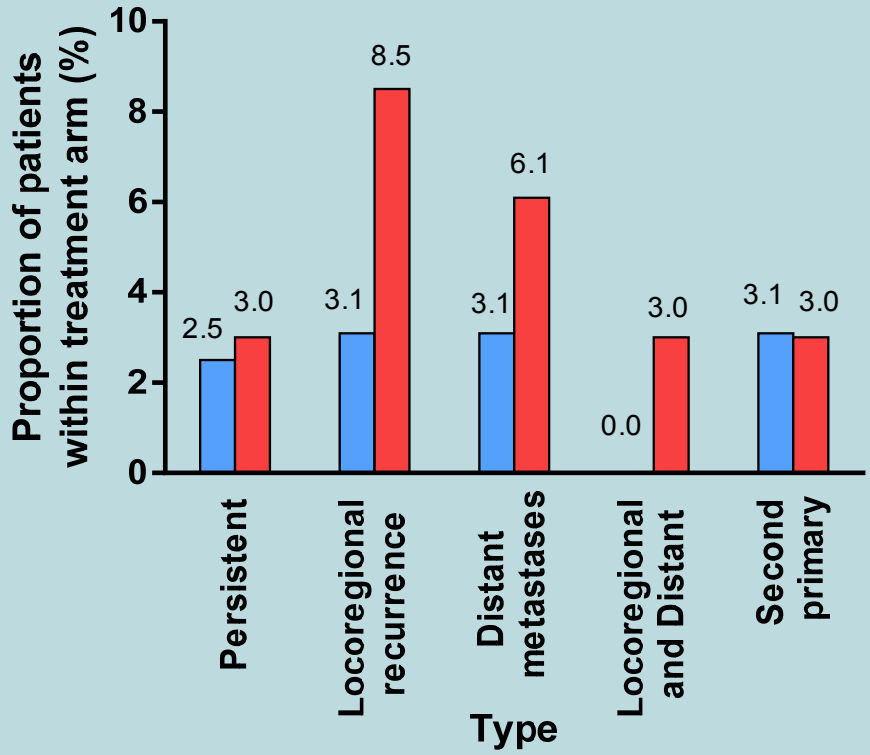
2 yr OS:
97.5% vs 89.4%
p= 0.001

HR=4.99
95% CI: 1.70 to 14.67

Adjusted HR: 5.94,
95% CI: 1.98-17.79, p=0.001



RECURRENCE



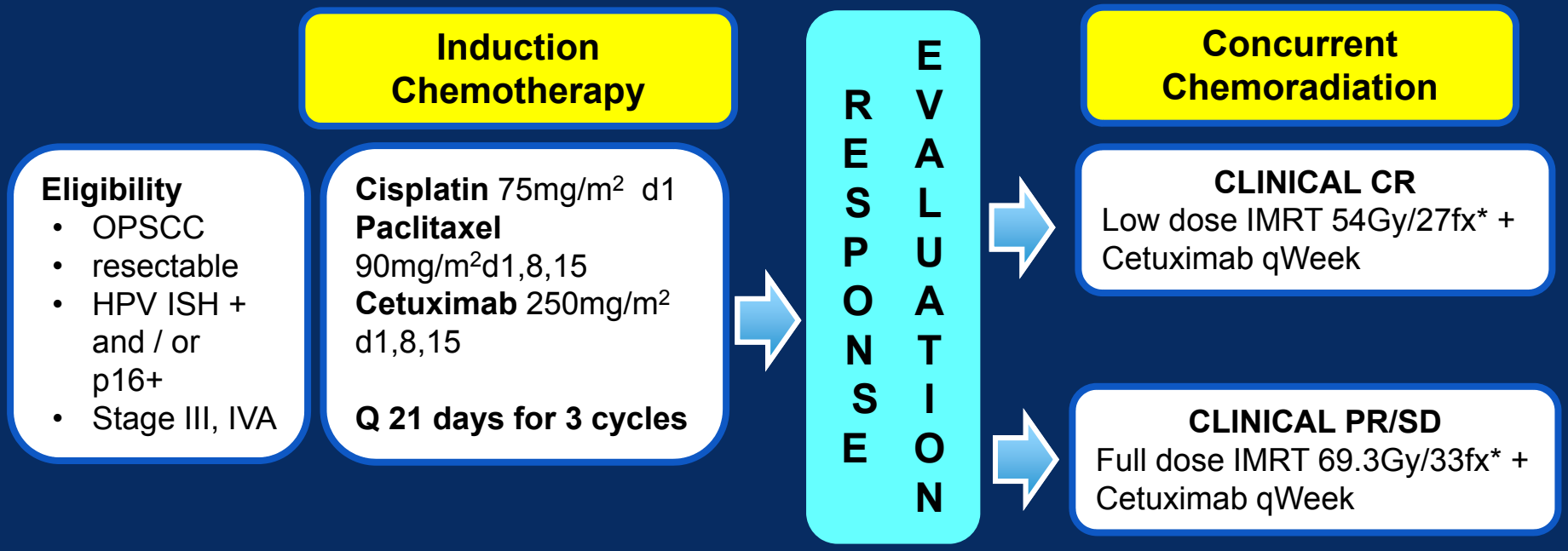
Cisplatin + radiotherapy

Cetuximab + radiotherapy

Loco-regional recurrence
3% vs 12%
(p=0.003)

Distant recurrence
3% vs 9%
(p=0.009)

ECOG 1308: Can Induction Serve as a Dynamic Biomarker of Radiation Sensitivity?



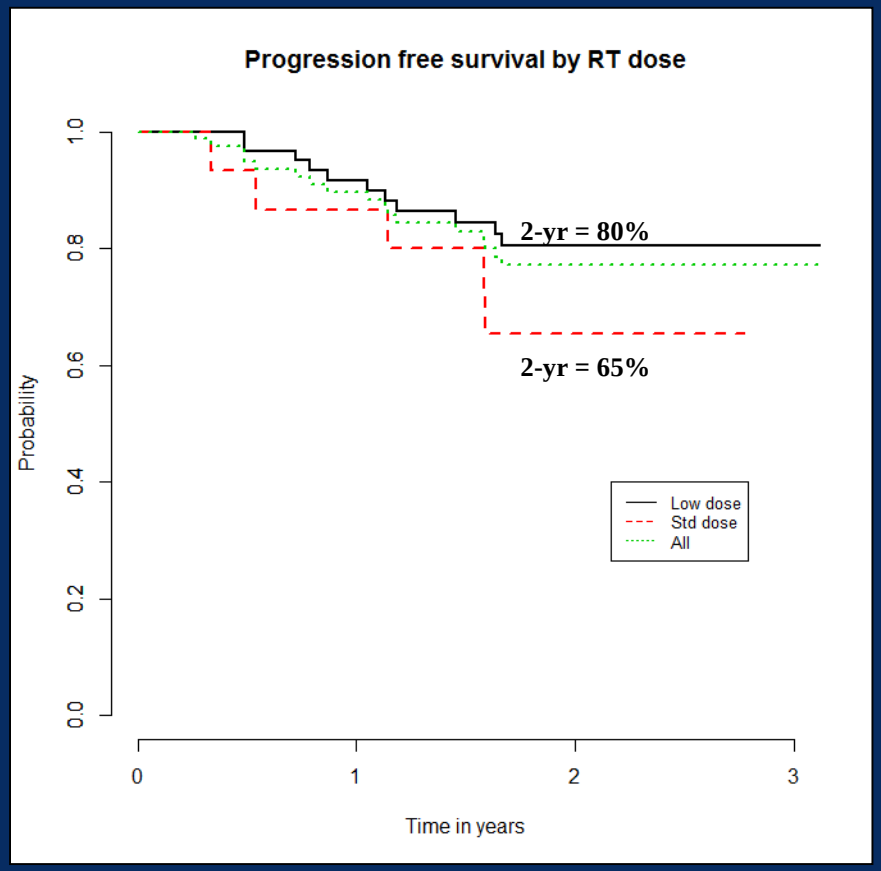
IMRT margins for primary: 1.0 to 1.5cm around gross dz
Nodal margin: 1cm margin minimum

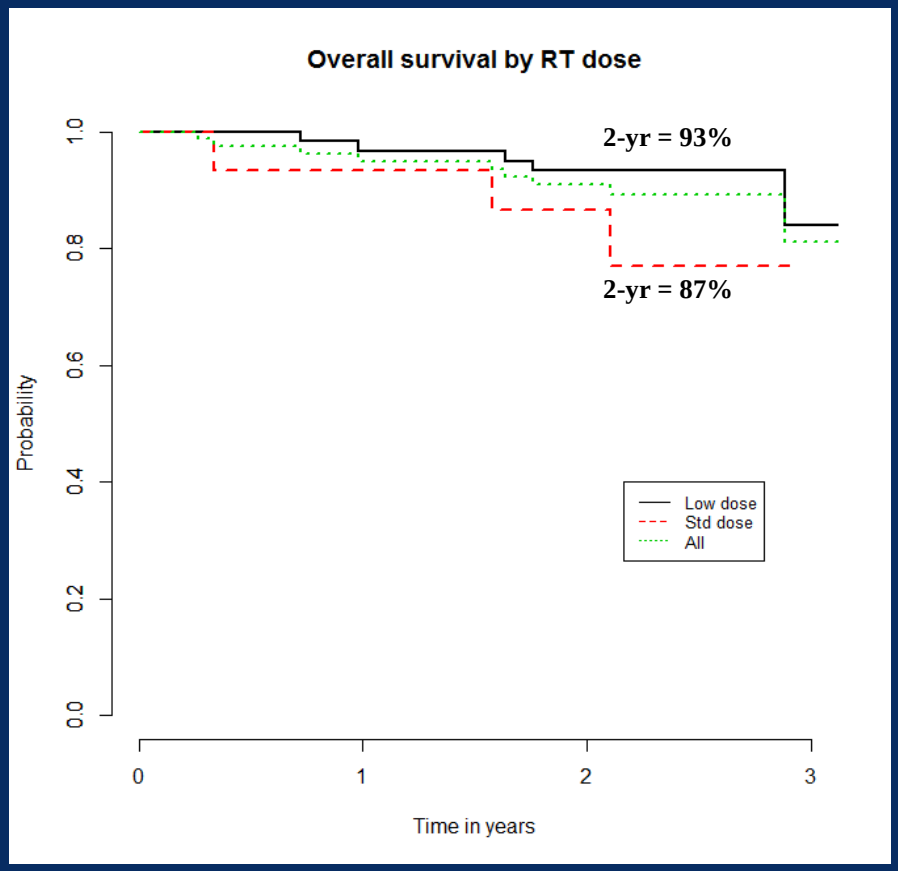
Endpoint: 2yr PFS and OS

Cohort (n)	2 year PFS (90% CI)	2 year OS
All low dose pts (62)	0.80 (0.70, 0.88)	0.93 (0.85, 0.97)
T4a (7)	0.54 (0.19, 0.79)	0.86 (0.45, 0.97)
Non-T4a (55)	0.84 (0.73, 0.91)	0.94 (0.86, 0.98)
N2c (19)	0.77 (0.56, 0.89)	0.95 (0.76, 0.99)
Non-N2c (43)	0.82 (0.69, 0.90)	0.93 (0.82, 0.97)
Smoker >10pk-yrs (22)	0.57 (0.35, 0.73)	0.86 (0.67, 0.94)
Smoker ≤10pk-yrs (40)	0.92 (0.81, 0.97)	0.97 (0.87, 0.995)
Smoker ≤10pk-yrs, <T4, <N2c (27)	0.96 (0.82, 0.99)	0.96 (0.82, 0.99)
All high-dose pts (15)*	0.65 (0.41, 0.82)	0.87 (0.63. 0.96)

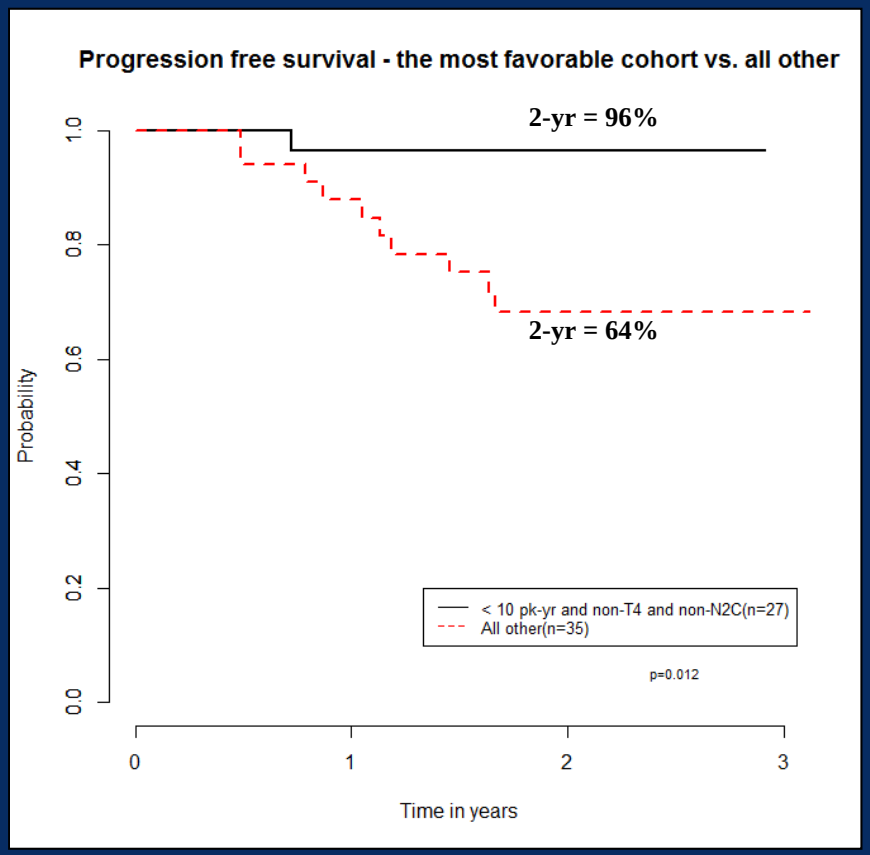
* 3 high-dose pts did not go on to receive RT

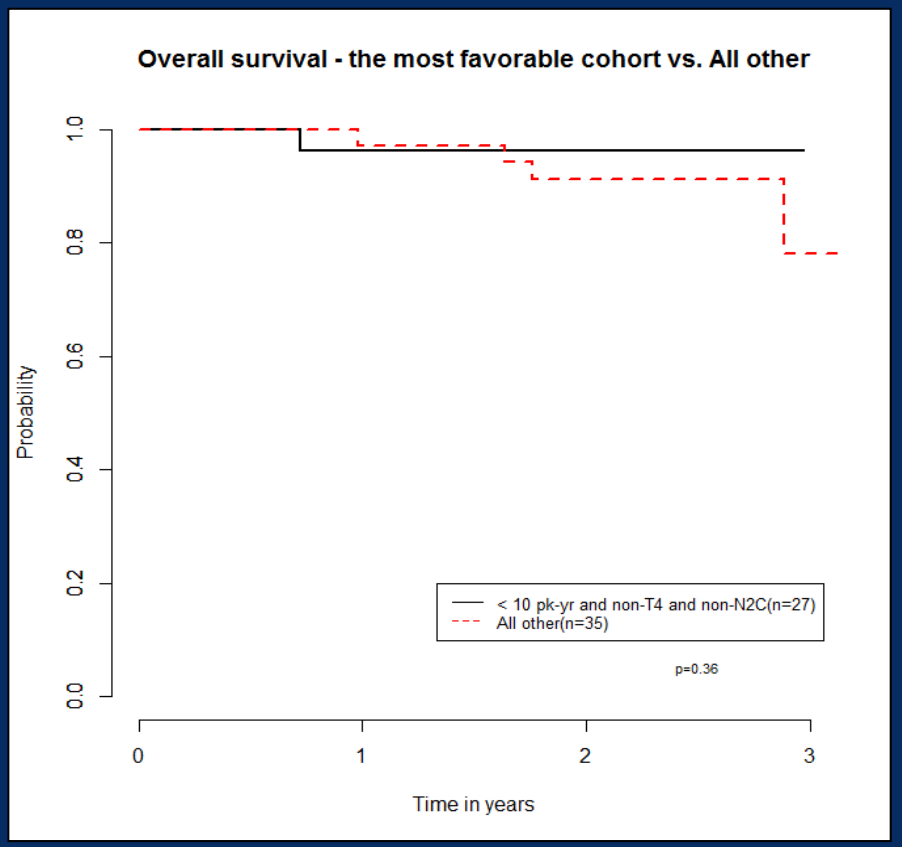
PFS and Survival: Dose



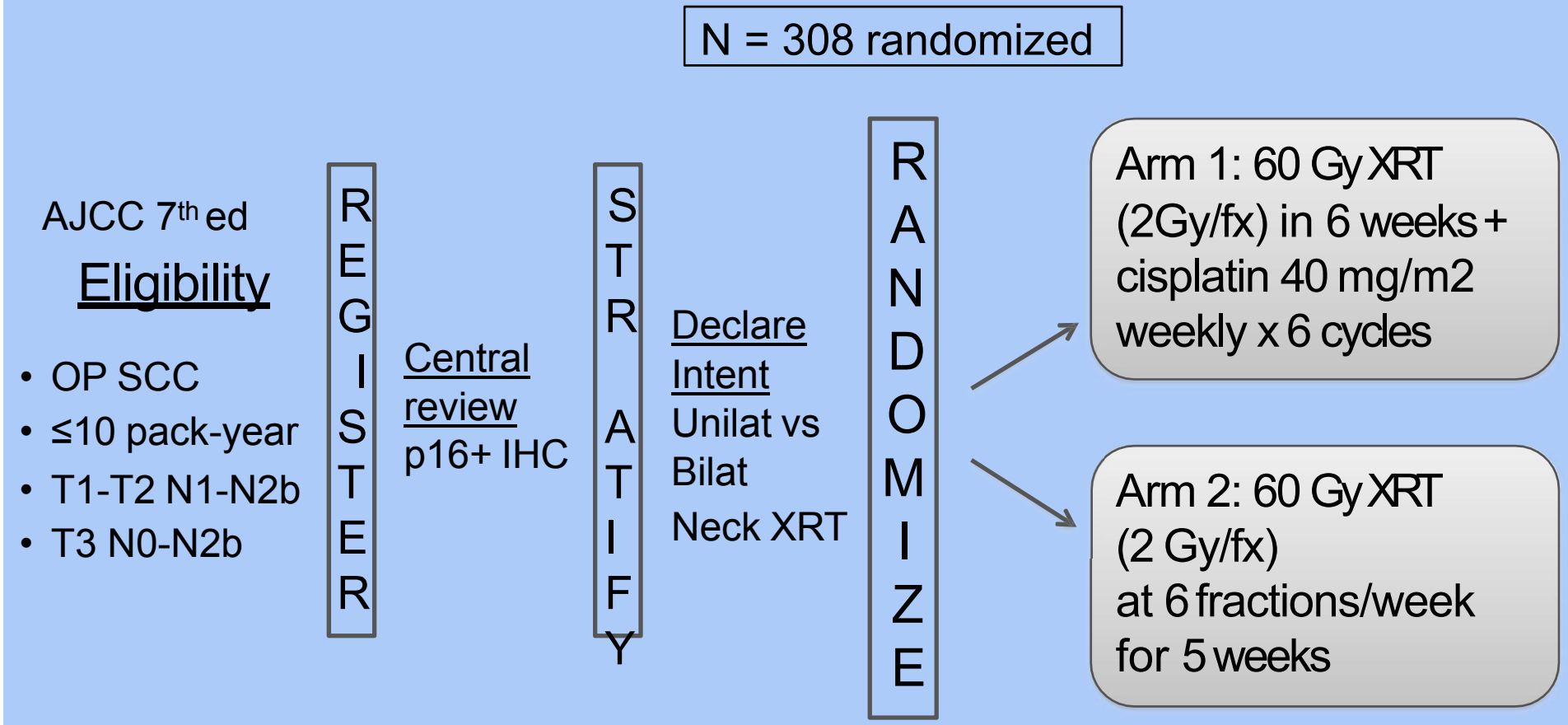


Best Outcome: <T4, T1-N2b, <10 pk-yr





HN002 Schema



Co-primary endpoints: PFS + QOL

- Primary Hypothesis: One or both arms will achieve a 2-year PFS rate of ≥ 85%, without unacceptable swallowing toxicity.
  - Null hypothesis: Neither arm achieves 2-year PFS of ≥ 85%.
  - Alternative hypothesis: One or both arms result in 2-year PFS > 91%.
  - 280 analyzable patients: 1-sided error rate of 10% and 80% power.

- QOL defined as the mean of the MDADI composite score at 1 year
  - If an arm reaches ≥ 85% PFS, the acceptability bound for QOL is MDADI composite score ≥ 60.
  - 80% power to detect a 5-point difference between arms.

Baseline characteristics

	IMRT + C (%)	IMRT (%)	Total (%)
≤ 49 yo	17.8	9.4	13.7
50 to 69 yo	**65**	**77.2**	**70.9**
≥ 70 yo	17.2	13.4	15.4
Male	**84.7**	**83.2**	**84.0**
White	**96.2**	**87.2**	**91.8**
Zubrod score 0	**84.1**	**75.8**	**80.1**
0 pack-years	**71.3**	**67.8**	**69.6**
>0-10 pack-years	28.7	32.2	30.4

	IMRT + C (%)	IMRT (%)	Total (%)
Tonsil	**52.9**	**52.3**	**52.6**
Tongue base	43.3	38.9	41.2
Other	3.8	8.7	6.2
T1	40.8	34.2	37.6
T2	**42.7**	**53.7**	**48.0**
T3	16.6	12.1	14.4
N0	3.8	4.7	4.2
N1	17.8	22.8	20.3
N2a	15.3	12.8	14.1
N2b	**63.1**	**59.7**	**61.4**

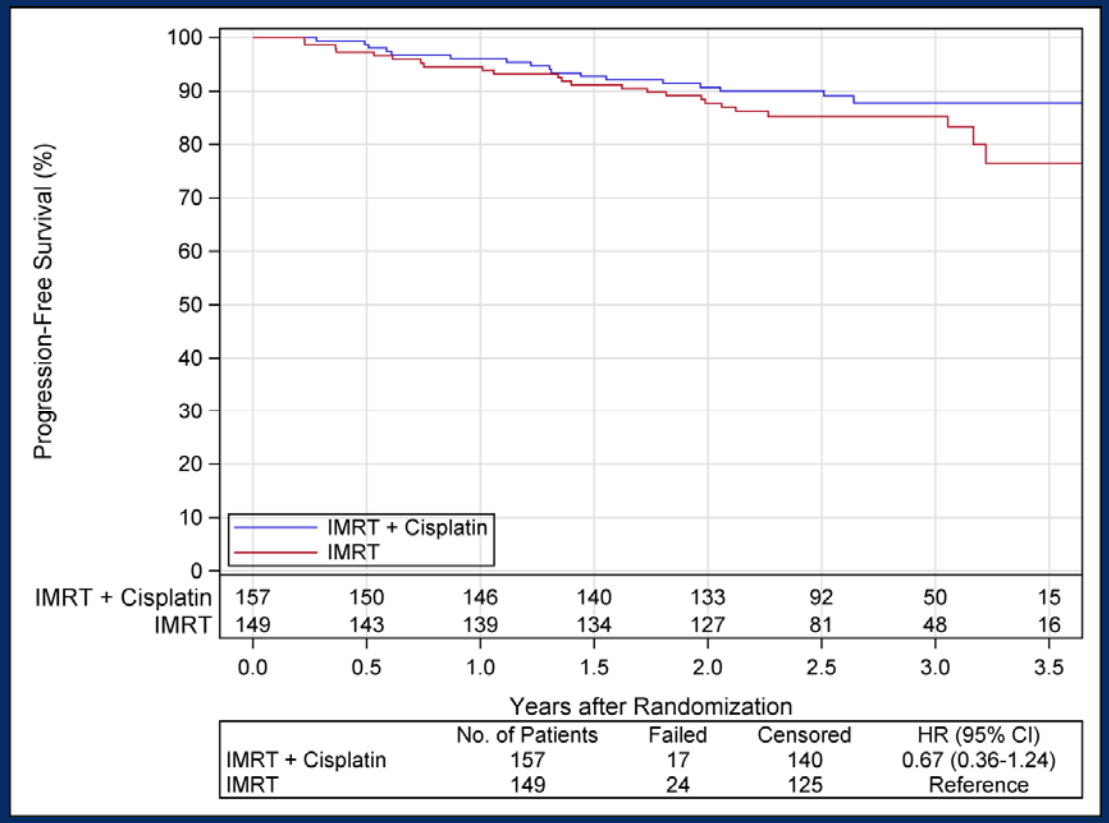
CTCAE Late Gr 3-4 Toxicities (highest grade event at >180 days)

No clear patterns of difference between arms

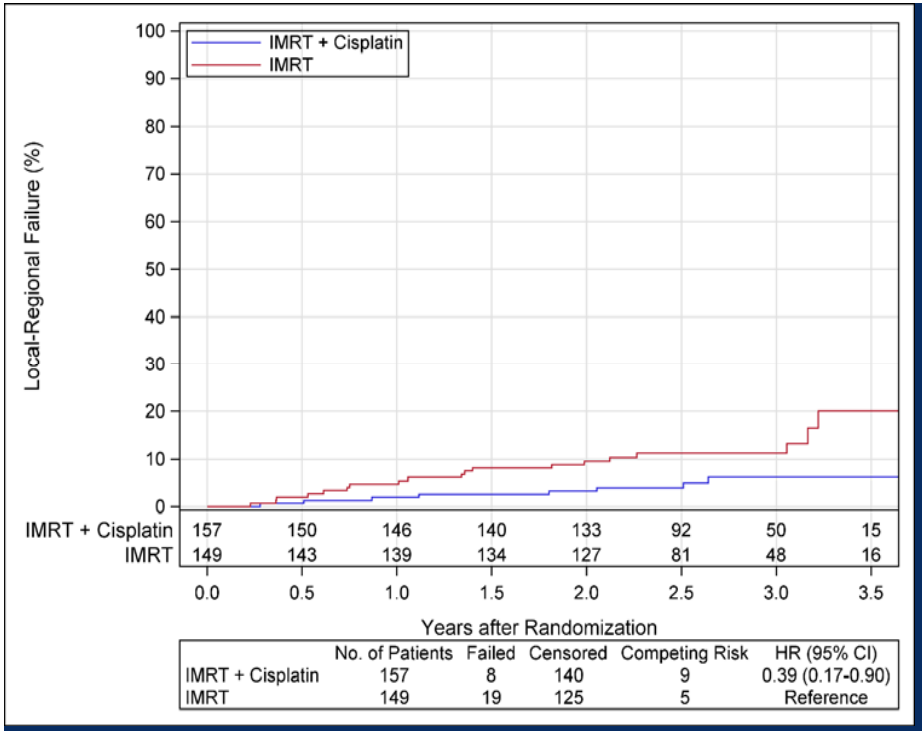
	IMRT+C		IMRT	
	N	**%**	**N**	**%**
Overall	**32**	**21.3**	**26**	**18.1**
Lymphocyte count decreased	16	10.7	7	4.9
Thromboembolic event	1	0.7	0	0
Hearing impaired	5	3.3	7	4.9
Pain	3	2.0	0	0
Hypertension	3	2.0	3	2.1

	IMRT+C		IMRT	
	N	**%**	**N**	**%**
Dysphagia	5	3.3	6	4.2
Weight loss	4	2.7	8	5.6
Pharyngeal mucositis	1	0.7	0	0
Dry mouth	1	0.7	0	0
Dental caries	2	1.3	0	0
Neck soft tissue necrosis	1	0.7	0	0
Trismus	1	0.7	0	0

Results: Primary PFS Endpoint

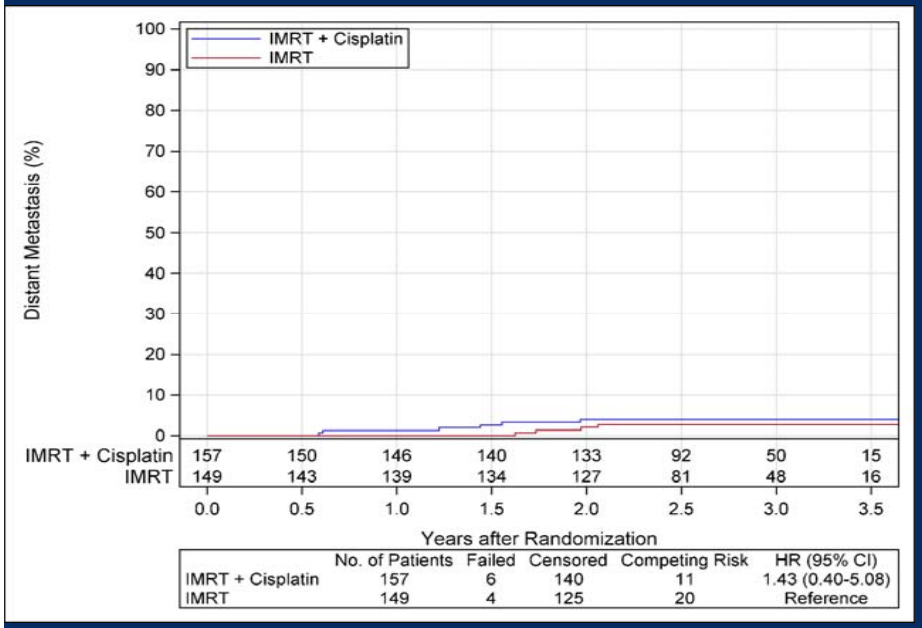


- Median follow-up is 2.6 years.
- **2-year PFS estimate for IMRT + C arm is 90.5%** (95% CI 84.5-94.7%) with p=0.0350 rejecting the null hypothesis.
- **2-year PFS estimate for IMRT arm is 87.6%** (95% CI 81.1-92.5%) with p=0.2284 failing to rejecting the null hypothesis.



2-year LRF rates:

- **3.3%** (95% CI 1.2-7.1%) for IMRT + C
- **9.5%** (95% CI 5.5-15.0%) for IMRT



2-year DM rates:

- **4.0%** (95% CI 1.6-8.0%) for IMRT+ C
- **2.1%** (95% CI 0.6-5.5%) for IMRT

Results: MDADI composite score

Arm	N at baseline	N at 1 year	Mean baseline MDADI score (95%CI)	Mean 1-year MDADI score (95%CI)	Mean change from baseline (95%CI)
IMRT + C	132 (84.1%)	121 (77.1%)	90.82 (89.10, 92.55)	**85.30** (82.53, 88.07)	**-5.62** (-8.64, -2.60)
IMRT	134 (89.9%)	106 (71.1%)	87.94 (85.75, 90.14)	**81.76** (78.98, 84.54)	**-6.22** (-9.34, -3.11)
			p = 0.0424	**p = 0.0755**	p = 0.7838

No difference between arms and both above acceptability boundary

Pembrolizumab and HNSCC

- Pembrolizumab: anti–PD-1 monoclonal antibody with antitumor activity and manageable safety profile in R/M HNSCC

Study	Population	ORR	Median DOR	Median PFS
KEYNOTE-012[1]	PD-L1–positive R/M HNSCC (N = 61)	18%	12.2 months	2 months
KEYNOTE-012 expansion cohort[2]	R/M HNSCC of any PD-L1 expression (N = 132)	Total: 18% PD-L1^{+}: 22% PD-L1^{-}: 4%	Not reached	2 months
KEYNOTE-055[3]	Platinum and cetuximab-refractory HNSCC of any PD-L1 expression (N = 171)	Total: 16% PD-L1^{+}: 18% PD-L1^{-}: 12%	8 months	2.1 months

1. Seiwert TY et al. *Lancet Oncol* 2016;17:956-965. 2. Chow LQM et al. *J Clin Oncol* 2016;34:3838-3845. 3. Bauml J et al. *J Clin Oncol* 2017;35:1542-1549.

MUNICH 2018 ESMO congress

KEYNOTE-048: Phase 3 Study of First-Line Pembrolizumab for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC)

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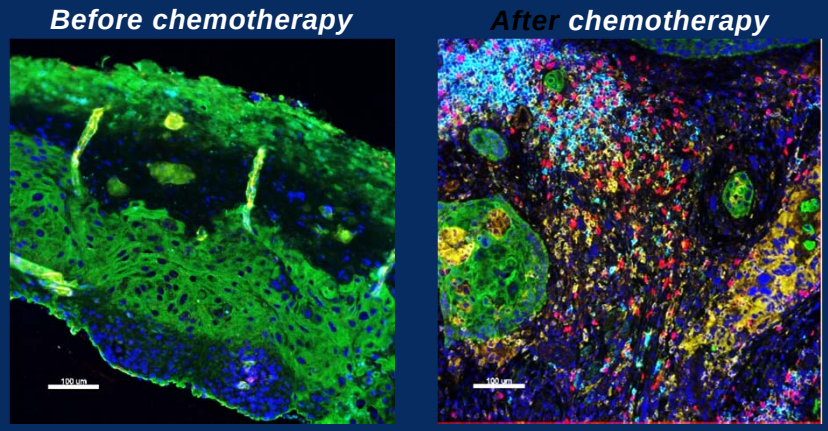
Immunotherapy and HNSCC

- PD-1 inhibitors pembrolizumab and nivolumab are approved for second-line R/M HNSCC treatment[1,2]
- Higher PD-L1 expression is associated with improved response to pembrolizumab[1]
- Chemotherapy is a rational combination partner for anti-PD-1 therapy[3]
  - Disrupts tumor architecture and may overcome immune exclusion
  - Results in antigen shedding
  - Induces rapid disease control

Chemotherapy induces tumor infiltration by lymphocytes

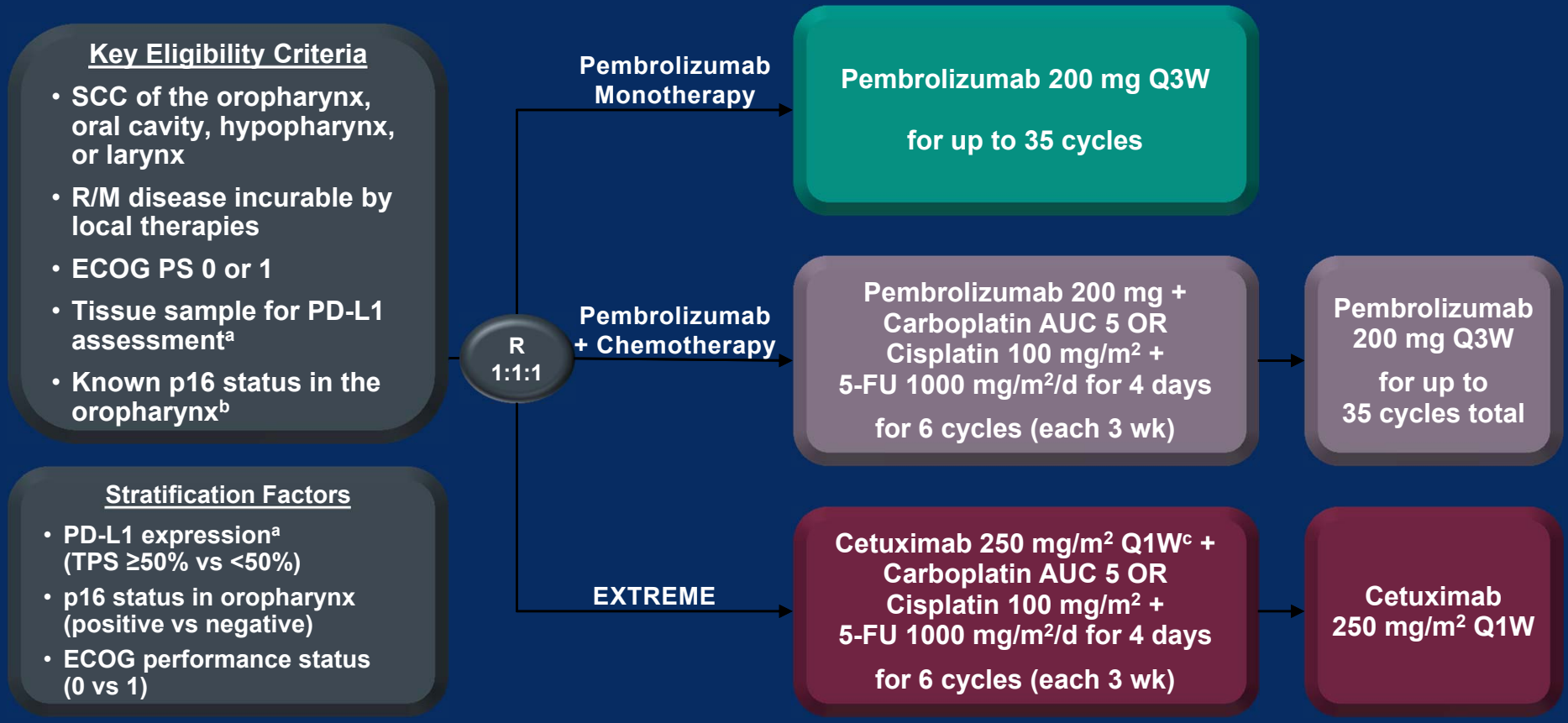


Images courtesy of D Rimm and WG Yarbrough, Yale School of Medicine and Yale Cancer Center.

1. Cohen EA et al. *Ann Oncol* 2017;28(suppl 5): abstr LBA45_PR.
2. Ferris RL et al. *N Engl J Med* 2016;375:1856-67.
3. Economopoulou P et al. *Ann Oncol* 2016;27:1675-85.

KEYNOTE-048 Study Design

(NCT02358031)



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Study End Points: Pembrolizumab vs EXTREME and Pembrolizumab + Chemotherapy vs EXTREME

Primary

- CPS ≥20,[a] CPS ≥1,[a] and total populations
  - OS
  - PFS[b]

Secondary

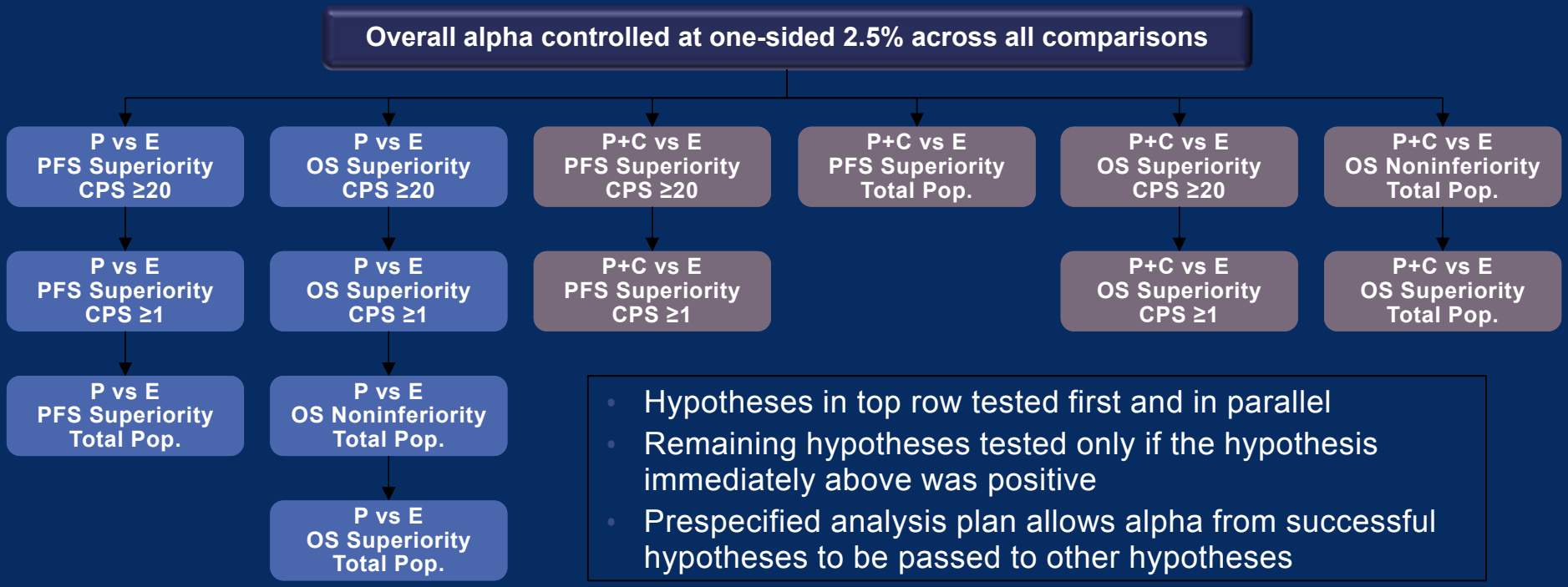
- CPS ≥20,[a] CPS ≥1,[a] and total populations
  - PFS[b] rates at 6 and 12 mo
  - ORR[b]
  - Change from baseline and time to deterioration in quality of life (EORTC QLQ-C30 and H&N-35)[c]
- Total population
  - Safety and tolerability

Key Exploratory

- CPS ≥20,[a] CPS ≥1,[a] and total populations
  - Duration of response[b]

[a]Assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay. CPS = combined positive score = number of PD-L1–positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells × 100.
[b]Assessed per RECIST v1.1 by blinded, independent central review.
[c]To be presented at a later date.

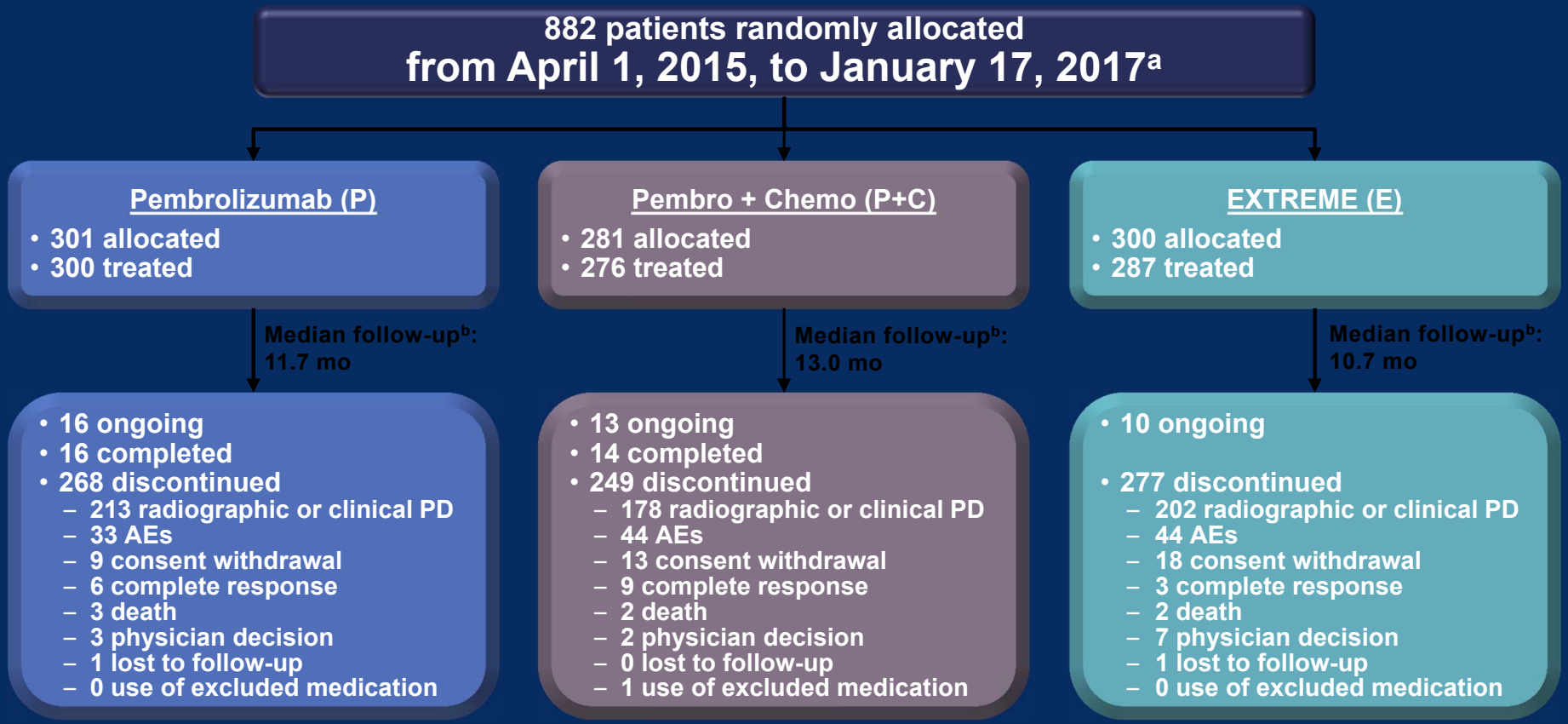
Statistical Considerations



- Hypotheses in top row tested first and in parallel
- Remaining hypotheses tested only if the hypothesis immediately above was positive
- Prespecified analysis plan allows alpha from successful hypotheses to be passed to other hypotheses

- Second interim analysis: per protocol, performed 17 mo after the last patient enrolled
  - Data cutoff date: June 13, 2018

Disposition of All Randomized Patients



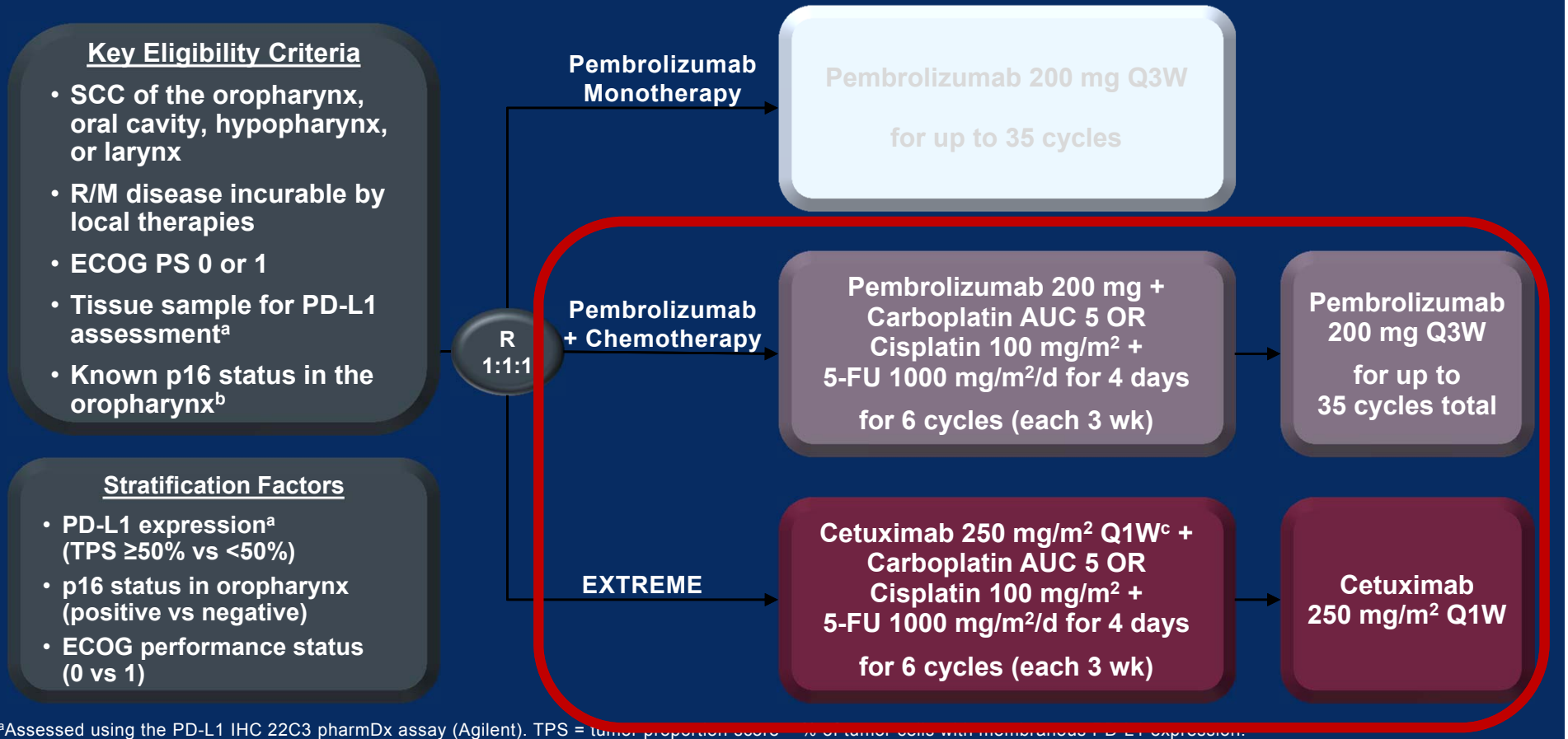
[a]There was an enrollment hold for the pembrolizumab + chemotherapy arm from Aug 13, 2015 to Oct 2, 2015.
[b]Defined as the time from randomization to the date of death or database cutoff date of Jun 13, 2018, if the patient was alive.

Baseline Characteristics, ITT Population

Characteristic, n (%)	Pembro Alone vs EXTREME		Pembro + Chemo vs EXTREME	
	Pembro N = 301	EXTREME N = 300	Pembro + Chemo N = 281	EXTREME N = 278[a]
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[b]				
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)

[a]Patients randomized to EXTREME during the pembro + chemo enrollment hold were excluded from all pembro + chemo vs EXTREME efficacy comparisons.
[b]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).

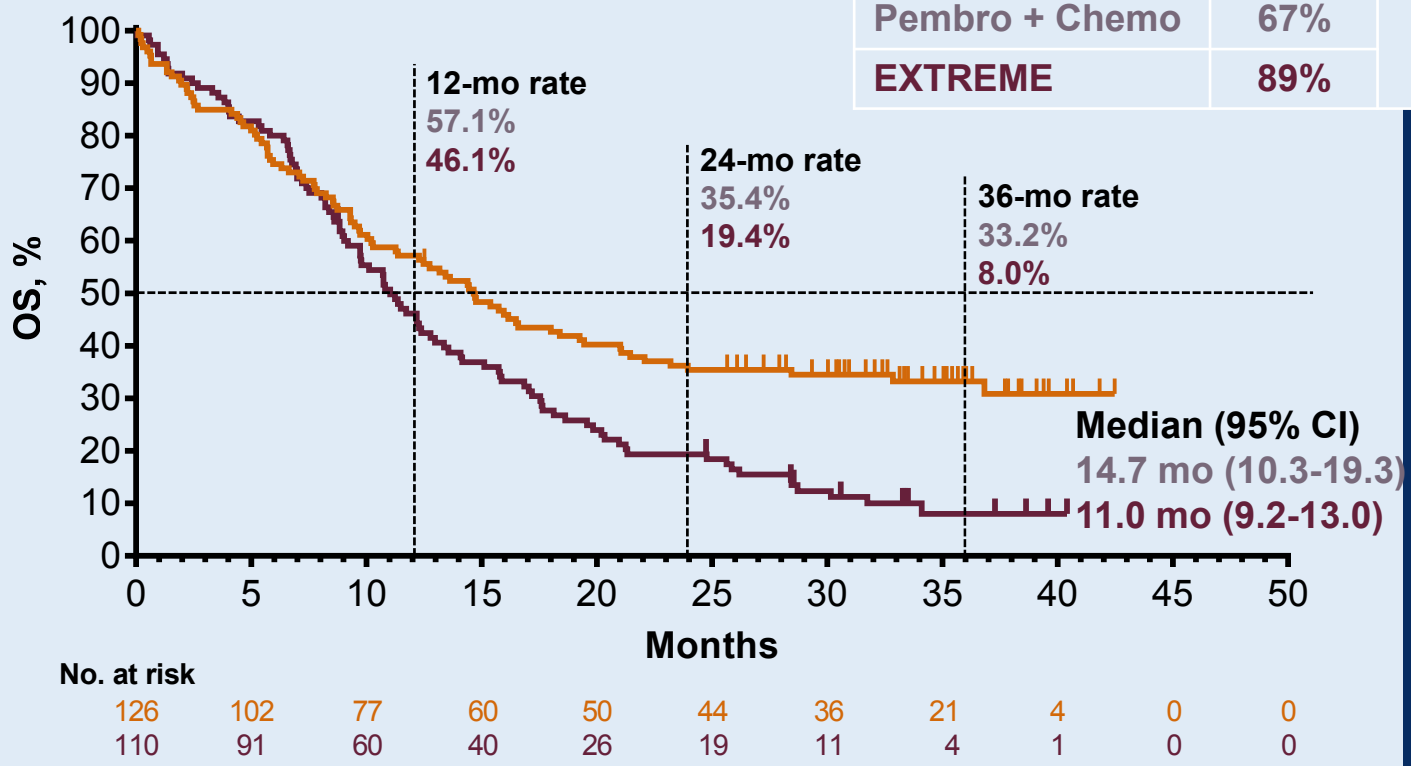
KEYNOTE-048 Study Design (NCT02358031)



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score [illegible]% of tumor cells with membranous PD-L1 expression.
[b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

OS, P+C vs E, CPS ≥20 Population

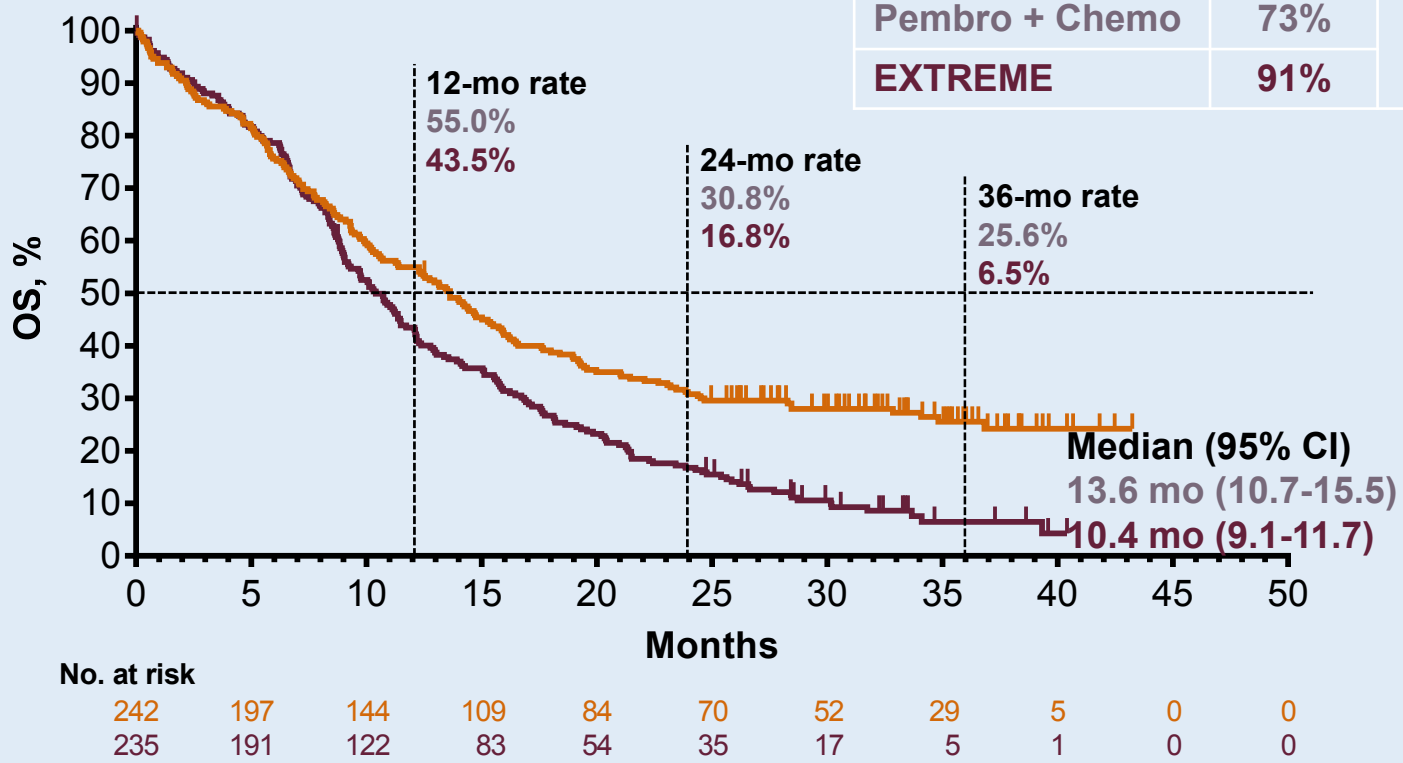
	Events	HR (95% CI)	*P*
Pembro + Chemo	67%	0.60 (0.45-0.82)	0.0004[a]
EXTREME	89%		



[a]Statistically significant at the superiority threshold of *P* = 0.0023.
FA (data cutoff date: Feb 25, 2019).

OS, P+C vs E, CPS ≥1 Population

	Events	HR (95% CI)	*P*
Pembro + Chemo	73%	0.65 (0.53-0.80)	<0.0001[a]
EXTREME	91%		

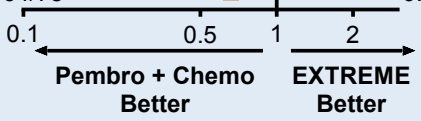


[a]Statistically significant at the superiority threshold of *P* = 0.0026.
FA (data cutoff date: Feb 25, 2019).

OS in Subgroups, P+C vs E

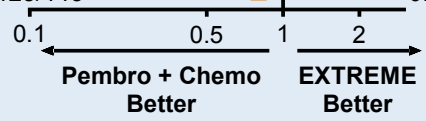
CPS ≥20

Subgroup	No. of Deaths/ No. of Patients	Hazard Ratio (95% CI)
Overall	182/236	0.61 (0.46-0.82)
Age		
<65 yrs	118/154	0.59 (0.41-0.85)
≥65 yrs	64/82	0.67 (0.41-1.10)
Sex		
Male	143/186	0.57 (0.41-0.80)
Female	39/50	0.63 (0.32-1.23)
ECOG PS		
0	61/94	0.55 (0.33-0.92)
1	121/142	0.60 (0.41-0.86)
Region of enrollment		
North America	43/60	0.66 (0.36-1.21)
Europe	55/74	0.49 (0.28-0.84)
Rest of world	84/102	0.63 (0.41-0.98)
Smoking status		
Never	45/58	0.54 (0.30-1.00)
Former	106/138	0.69 (0.47-1.01)
Current	30/39	0.53 (0.26-1.09)
p16 status (oropharynx)		
Positive	28/52	0.39 (0.18-0.84)
Negative	154/184	0.66 (0.48-0.91)
Disease status		
Metastatic	117/156	0.60 (0.42-0.87)
Recurrent	64/78	0.66 (0.40-1.09)



CPS ≥1

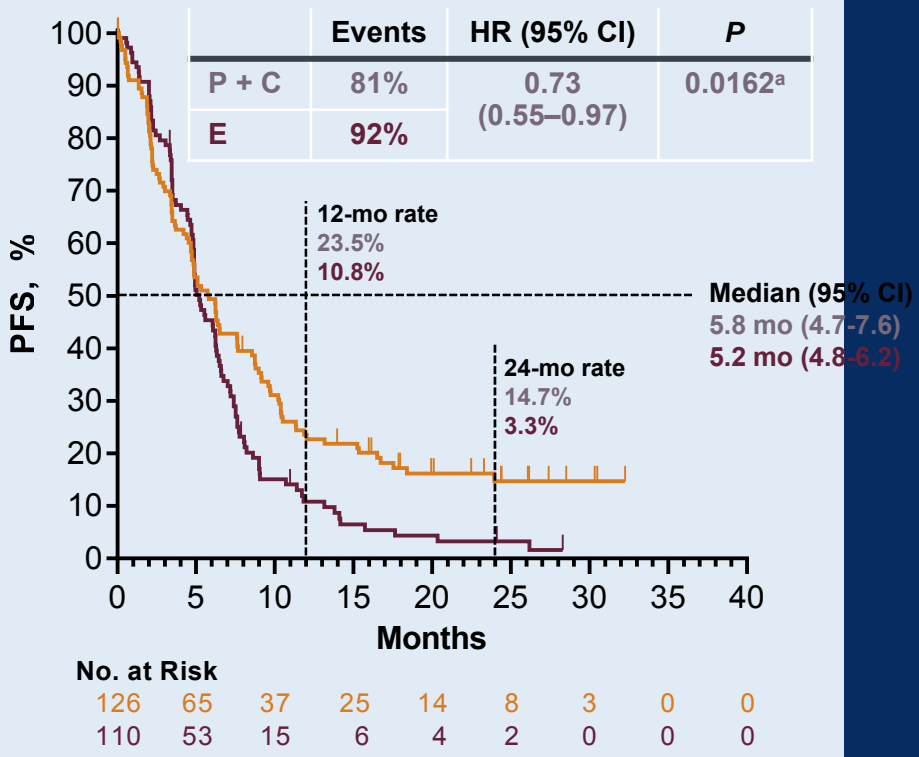
Subgroup	No. of Deaths/ No. of Patients	Hazard Ratio (95% CI)
Overall	390/477	0.66 (0.54-0.80)
Age		
<65 yrs	251/305	0.74 (0.57-0.94)
≥65 yrs	139/172	0.54 (0.39-0.76)
Sex		
Male	321/391	0.66 (0.53-0.83)
Female	69/86	0.59 (0.36-0.96)
ECOG PS		
0	139/186	0.66 (0.47-0.92)
1	251/291	0.64 (0.49-0.82)
Region of enrollment		
North America	79/104	0.62 (0.40-0.98)
Europe	127/158	0.51 (0.36-0.73)
Rest of world	184/215	0.78 (0.58-1.04)
Smoking status		
Never	89/108	0.58 (0.38-0.89)
Former	237/285	0.74 (0.57-0.95)
Current	62/82	0.58 (0.35-0.97)
p16 status (oropharynx)		
Positive	71/103	0.55 (0.34-0.88)
Negative	319/374	0.69 (0.55-0.86)
Disease status		
Metastatic	261/327	0.60 (0.47-0.77)
Recurrent	125/143	0.80 (0.56-1.14)



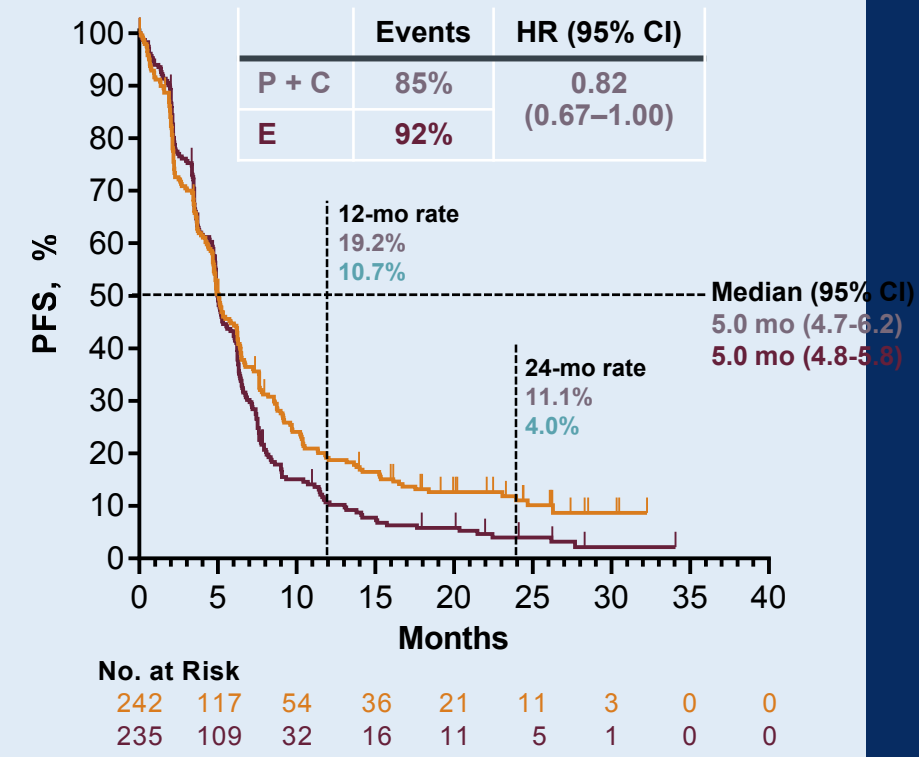
FA (data cutoff date: Feb 25, 2019).

PFS, P+C vs E, CPS ≥20 and ≥1

CPS ≥20



CPS ≥1

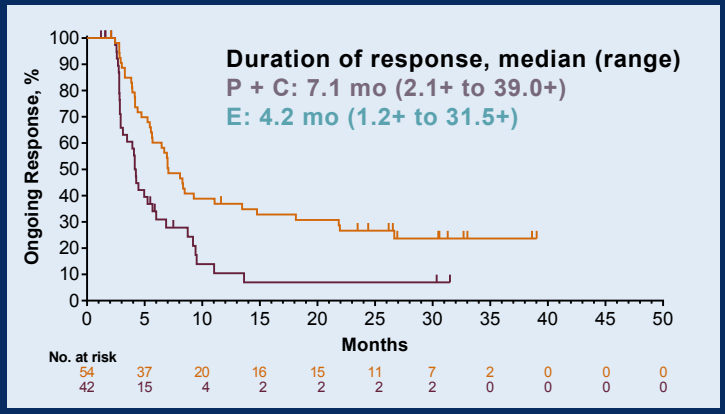


[a]Not statistically significant at the superiority threshold of 0.0017.
IA2 (data cutoff date: Jun 13, 2018). PFS assessed per RECIST v1.1 by blinded, independent central review.

Response Summary, P+C vs E

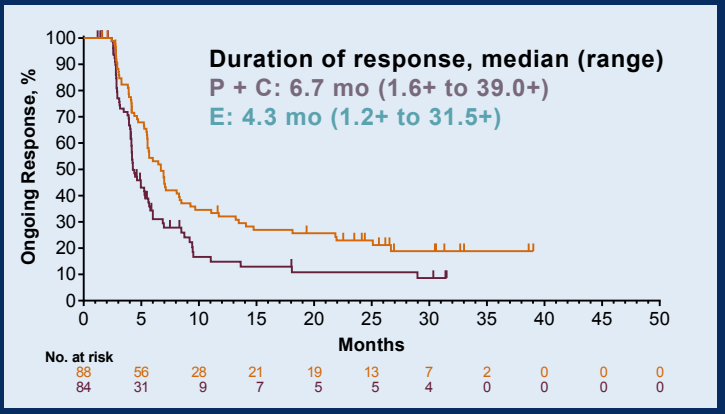
CPS ≥20

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[a]	4 (3.2)	5 (4.5)
Not evaluable or assessed[b]	20 (15.9)	16 (14.5)



CPS ≥1

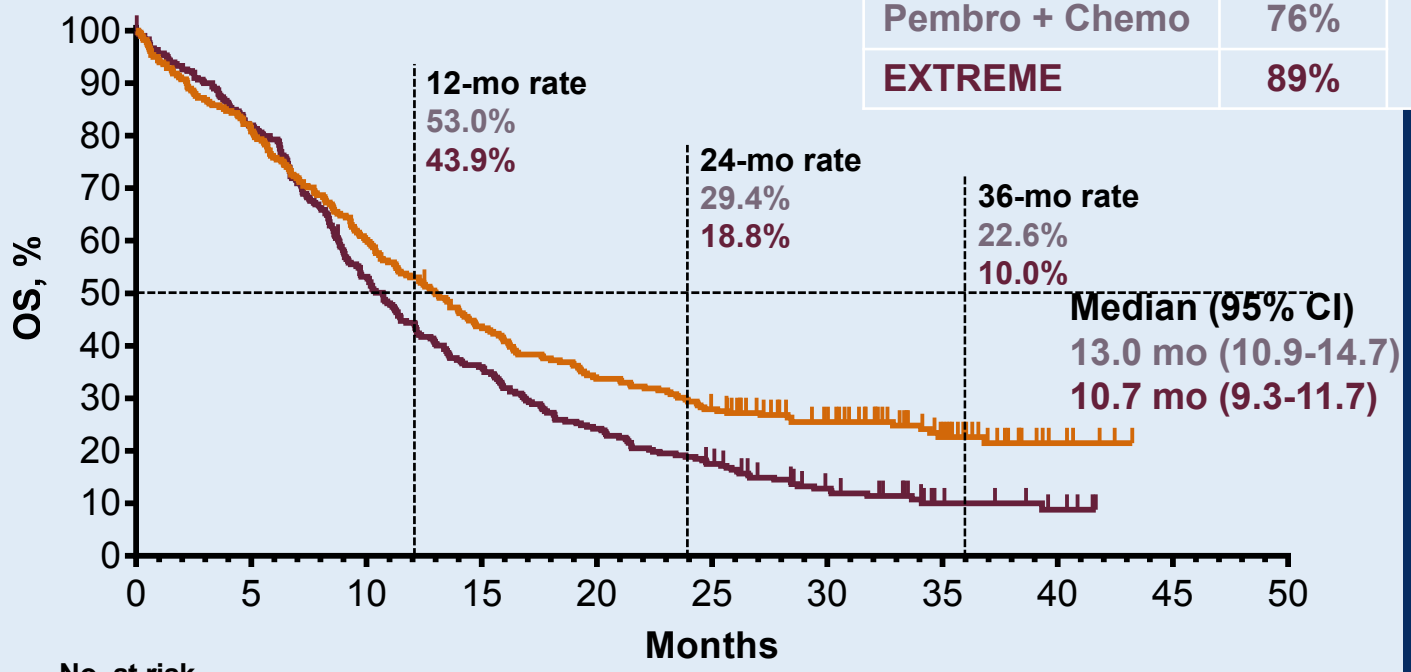
Confirmed Response, n (%)	P + C N = 242	E N = 235
ORR	**88 (36.4)**	**84 (35.7)**
CR	16 (6.6)	7 (3.0)
PR	72 (29.8)	77 (32.8)
SD	64 (26.4)	77 (32.8)
PD	42 (17.4)	29 (12.3)
Non-CR/non-PD[a]	11 (4.5)	9 (3.8)
Not evaluable or assessed[b]	37 (15.3)	36 (15.3)



[a]Patients without measurable disease per central review at baseline who did not have CR or PD. [b]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).

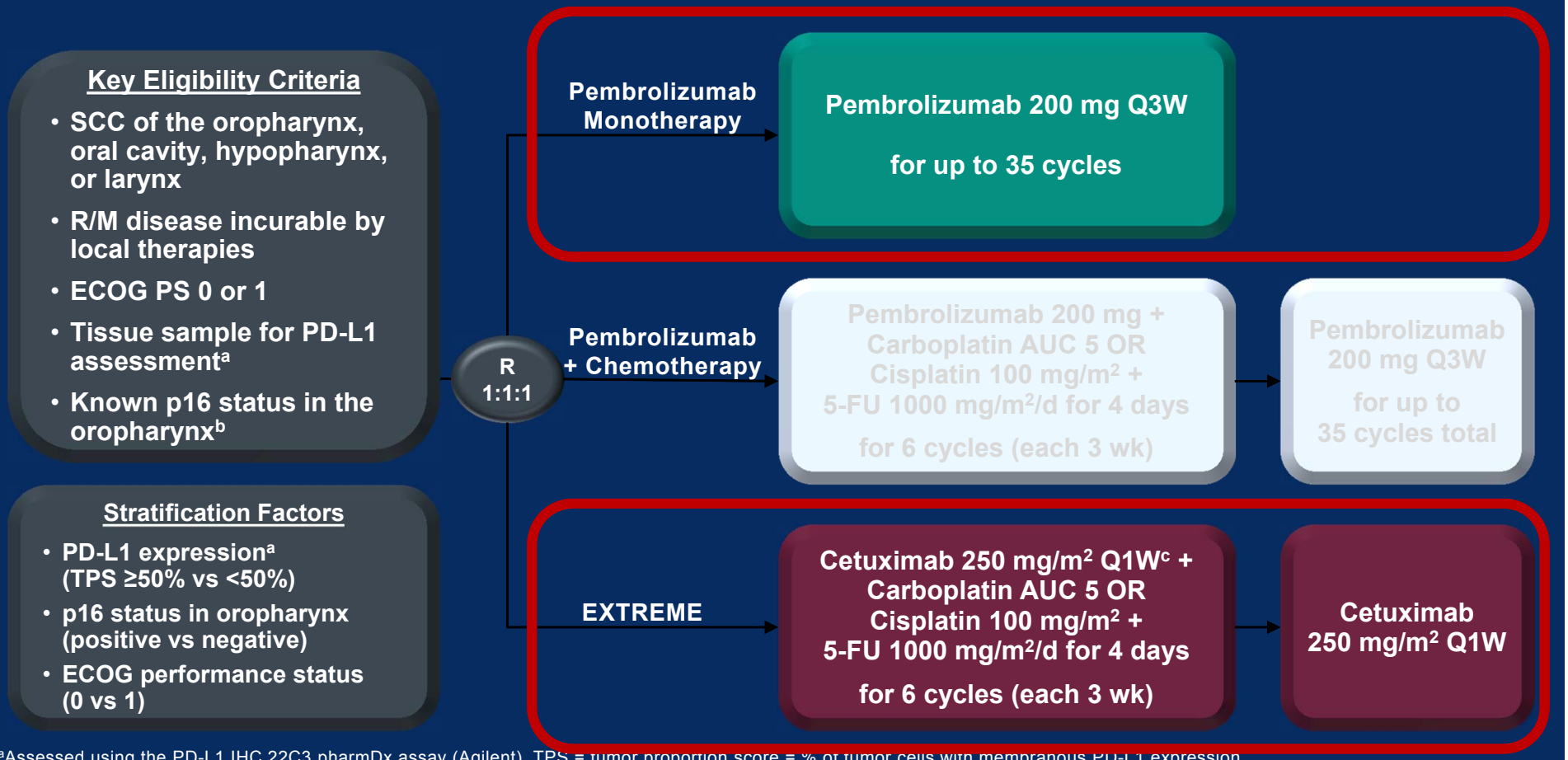
OS, P+C vs E, Total Population

	Events	HR (95% CI)
Pembro + Chemo	76%	0.72[a] (0.60–0.87)
EXTREME	89%	



[a]At IA2 (data cutoff date: Jun 13, 2018): HR 0.77 (95% CI 0.53–0.93).
FA (data cutoff date: Feb 25, 2019).

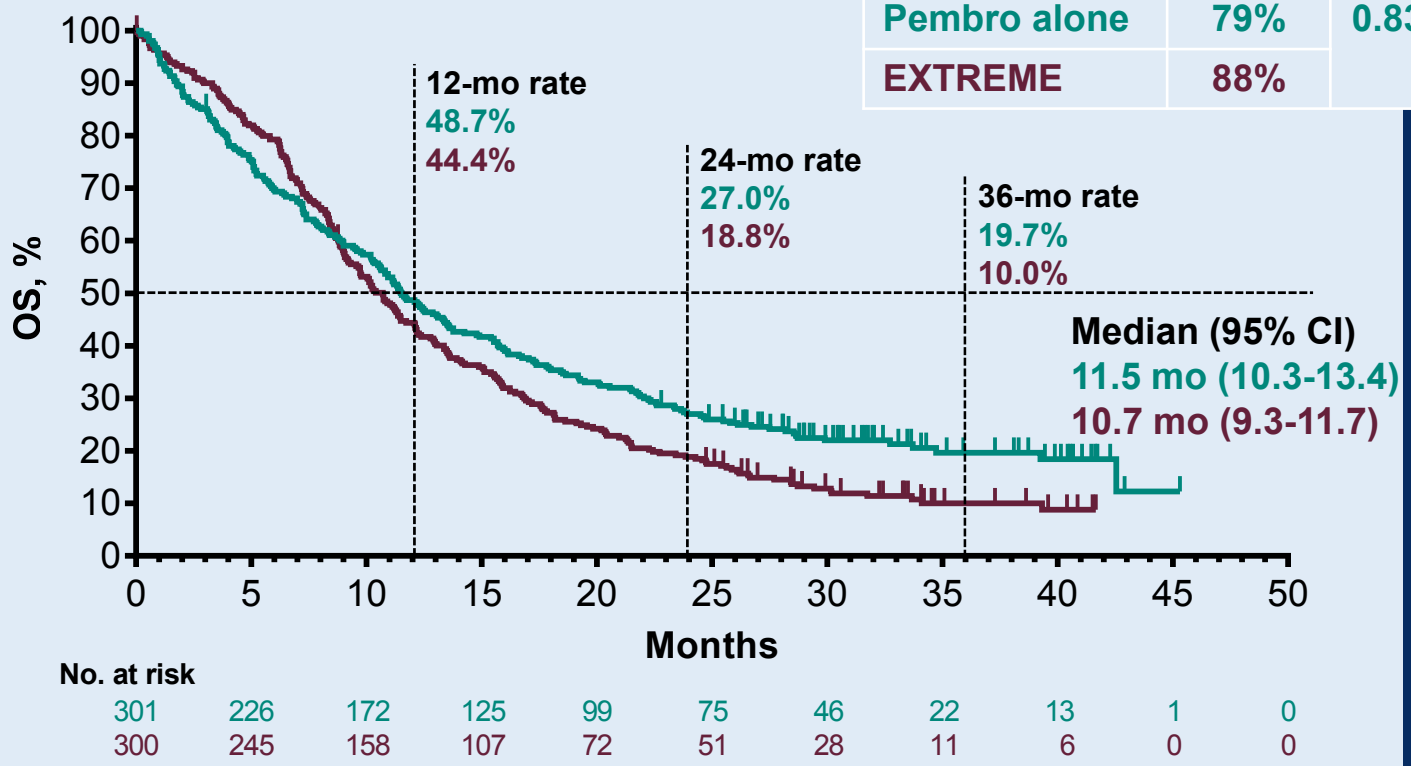
KEYNOTE-048 Study Design (NCT02358031)



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression.
[b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

OS, P vs E, Total Population

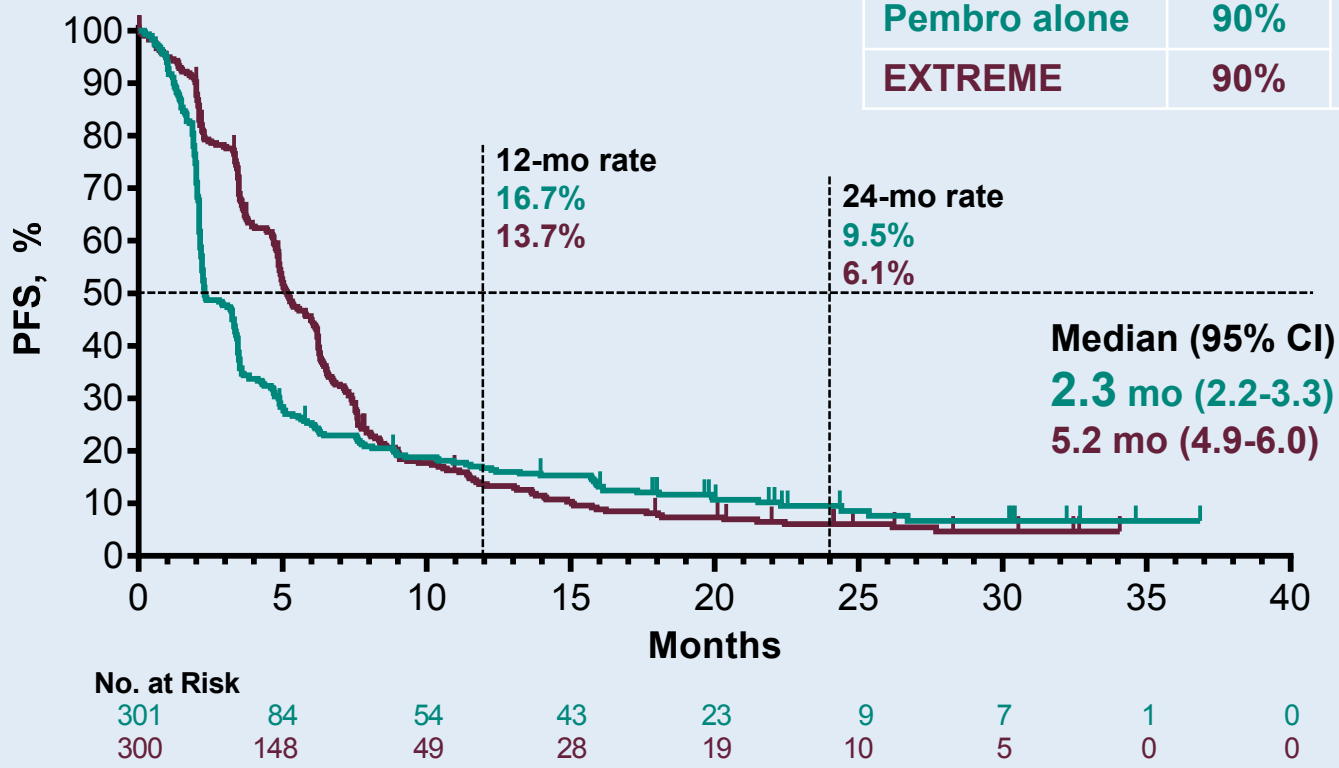
	Events	HR (95% CI)	*P*
Pembro alone	79%	0.83 (0.70-0.99)	0.0199[a]
EXTREME	88%		



[a]Not statistically significant at the superiority threshold of *P* = 0.0059.
FA (data cutoff date: Feb 25, 2019).

PFS, P vs E, Total Population

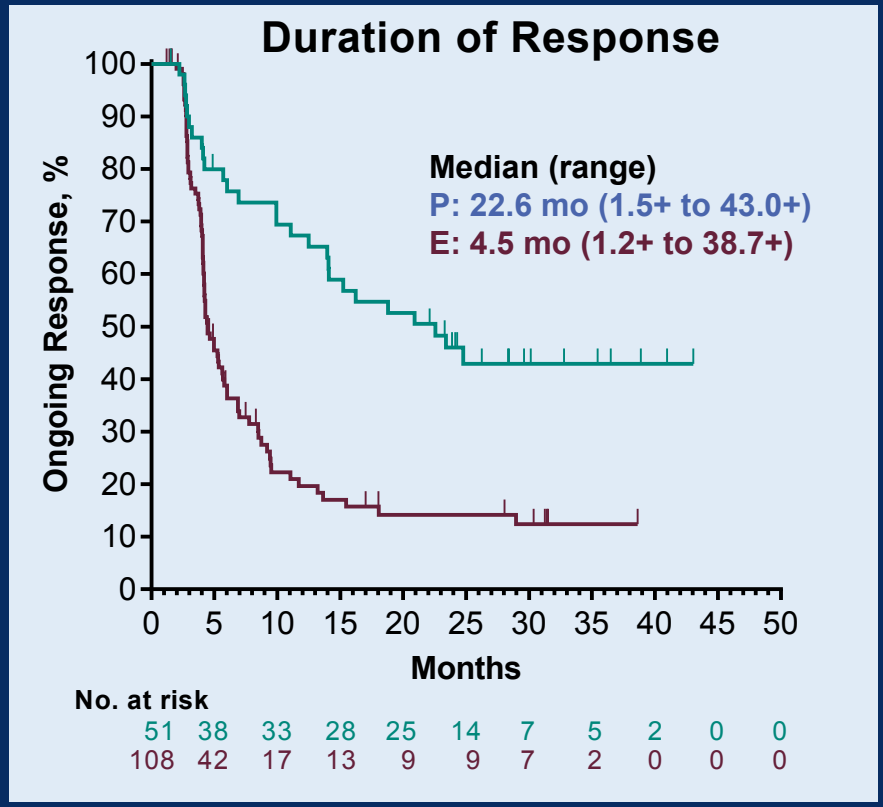
	Events	HR (95% CI)
Pembro alone	90%	1.34 (1.13–1.59)
EXTREME	90%	



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

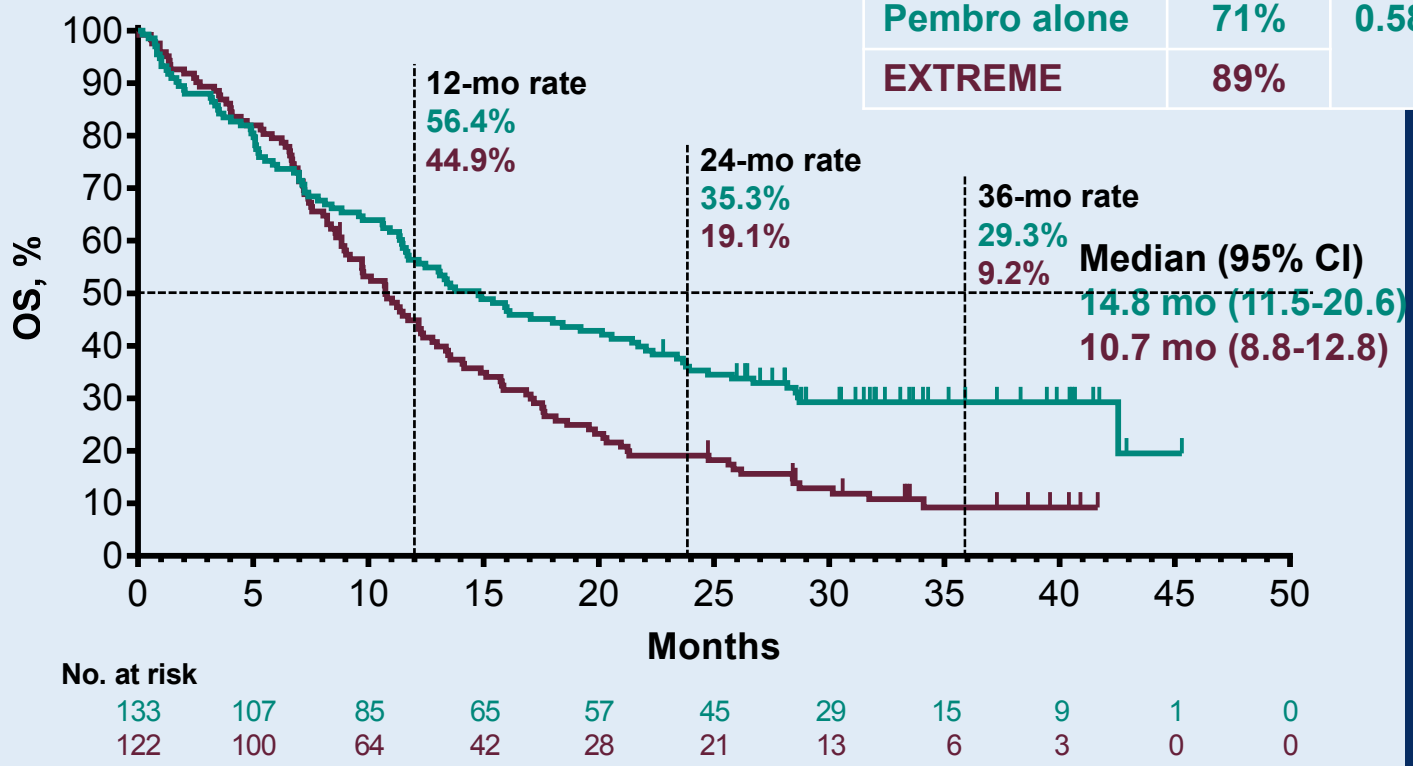
Confirmed Response, n (%)	Pembro N = 301	EXTREME N = 300
ORR	**51 (16.9)**	**108 (36.0)**
CR	14 (4.7)	8 (2.7)
PR	37 (12.3)	100 (33.3)
SD	82 (27.2)	102 (34.0)
PD	122 (40.5)	37 (12.3)
Non-CR/non-PD[a]	14 (4.7)	11 (3.7)
Not evaluable or assessed[b]	32 (10.6)	42 (14.0)



[a]Patients without measurable disease per central review at baseline who did not have CR or PD. [b]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).

OS, P vs E, CPS ≥20 Population

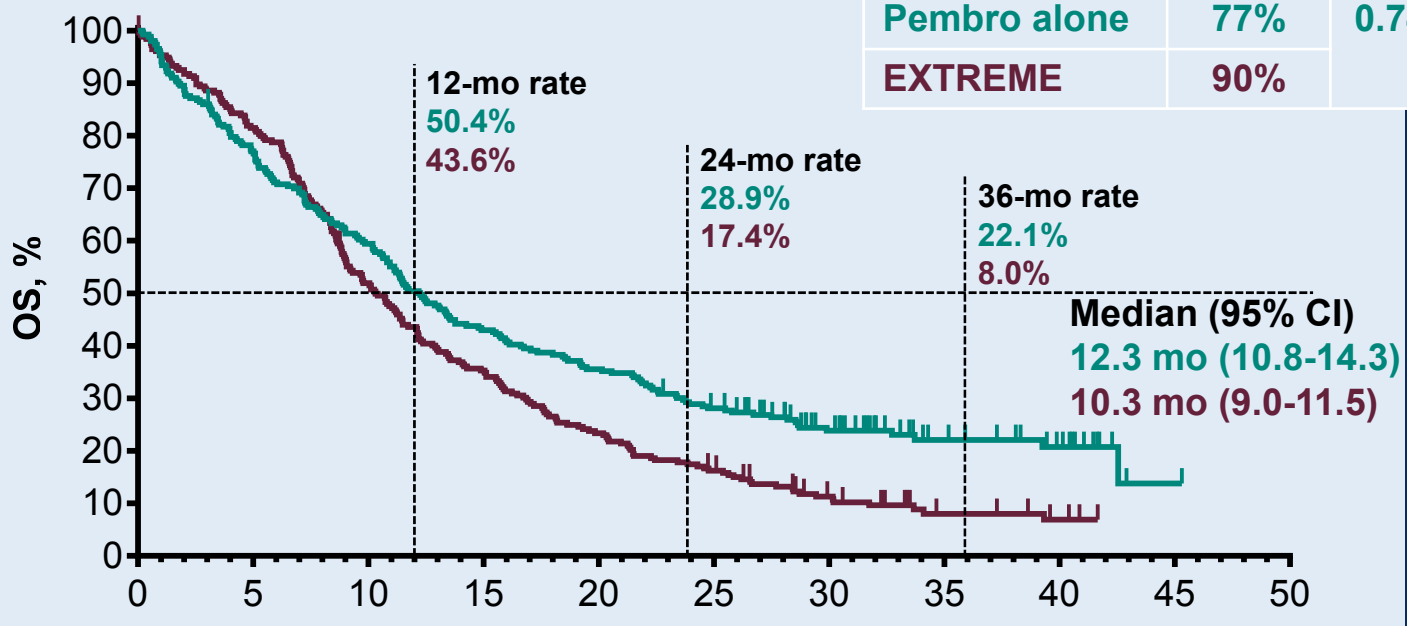
	Events	HR (95% CI)
Pembro alone	71%	0.58 (0.44-0.78)[a]
EXTREME	89%	



[a]At IA2 (data cutoff date: Jun 13, 2018): HR 0.61 (95% CI 0.45–0.83).
FA (data cutoff date: Feb 25, 2019).

OS, P vs E, CPS ≥1 Population

	Events	HR (95% CI)
Pembro alone	77%	0.74 (0.61-0.90)[a]
EXTREME	90%	



[a]At IA2 (data cutoff date: Jun 13, 2018): HR 0.78 (95% CI 0.64–0.96).
FA (data cutoff date: Feb 25, 2019).

Summary of Overall Survival

Population	IA2[1] HR (95% CI)	FA HR (95% CI)
Pembrolizumab monotherapy vs EXTREME		
PD-L1 CPS ≥20	0.61 (0.45–0.83); *P* = 0.0007[a]	0.58 (0.44–0.78)[c]
PD-L1 CPS ≥1	0.78 (0.64–0.96); *P* = 0.0086[a]	0.74 (0.61–0.90)[c]
Total	0.85 (0.71–1.03)[b]	0.83 (0.70–0.99); *P* = 0.0199[d]
Pembrolizumab + chemotherapy vs EXTREME		
PD-L1 CPS ≥20	—	0.60 (0.45–0.82); *P* = 0.0004[a]
PD-L1 CPS ≥1	—	0.65 (0.53–0.80); *P* < 0.0001[a]
Total	0.77 (0.63–0.93); *P* = 0.0034[a,b]	0.72 (0.60–0.87)[c]

[a]Superiority demonstrated. [b]Noninferiority demonstrated (boundary of 1.2). [c]No statistical testing performed. [d]Superiority not demonstrated.

1. Burtness B et al. *Ann Oncol* 2018;29(suppl 8):LBA8_PR.

Summary and Conclusions

- Radiation with cisplatin remains the standard of care for HPV-associated oropharynx cancer
- Treatment de-escalation achieves very high early disease control rates in favorable risk patients
  - <10 pack years
  - Non-T4
  - Non-N3
- Treatment de-escalation by omitting chemotherapy may increase local and distant failures, without significantly reducing late toxicity
- Immune checkpoint inhibition prolongs survival for first-line metastatic-recurrent HNSCC, with or without chemotherapy