REPORTS FROM ASCO 2019 Head and neck cancer

Paolo Bossi
Medical Oncology Unit
University of Brescia

NEWS FROM HEAD AND NECK

- HNSCC: Curative
- HNSCC: Recurrent/metastatic disease
- Immunotherapy arena
- Nasopharyngeal cancer
- Salivary gland cancer
- Thyroid cancer
- Cutaneous sCC

CURATIVE APPROACHES

- **Surgery or RT for early stage oropharyngeal cancer?**

CURATIVE APPROACHES

A Randomized Trial of Radiotherapy versus Trans-Oral Robotic Surgery and Neck Dissection for Oropharyngeal Squamous Cell Carcinoma (ORATOR)

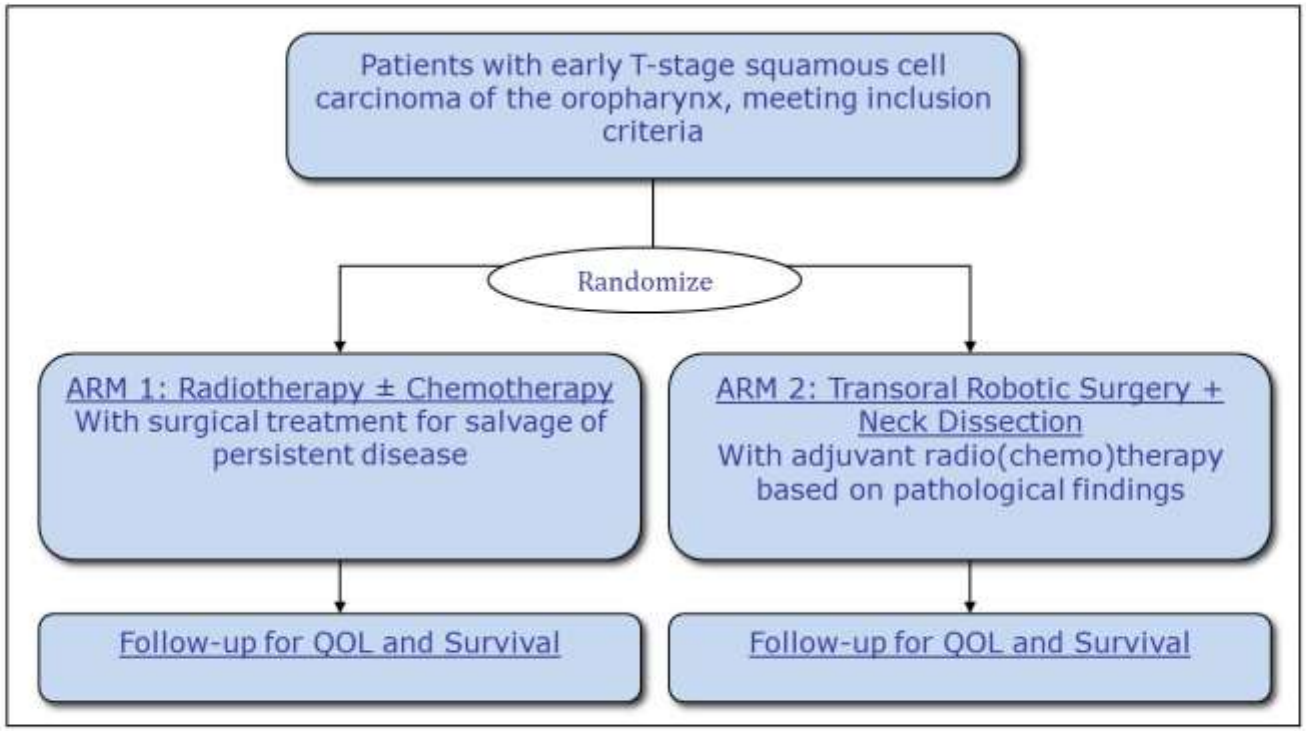
A. Nichols, J. Theurer, E. Prisman, N. Read, E. Berthelet, E. Tran, K. Fung, J. de Almeida, A. Bayley, D. Goldstein, M. Hier, K. Sultanem, K. Richardson, A. Mlynarek, S. Krishnan, H. Le, J. Yoo, S.D. MacNeil, E. Winquist, J. A. Hammond, V. Venkatesan, S. Kuruvilla, A. Warner, S. Mitchell, J. Chen, M. Corsten, S. Johnson-Obaseki, L. Eapen, M. Odell, C. Parker, B. Wehrli, K. Kwan, **D. Palma**

Western UNIVERSITY · CANADA

Canadian Cancer Society / Société canadienne du cancer

OICR Ontario Institute for Cancer Research

ORATOR Schema



Baseline Characteristics

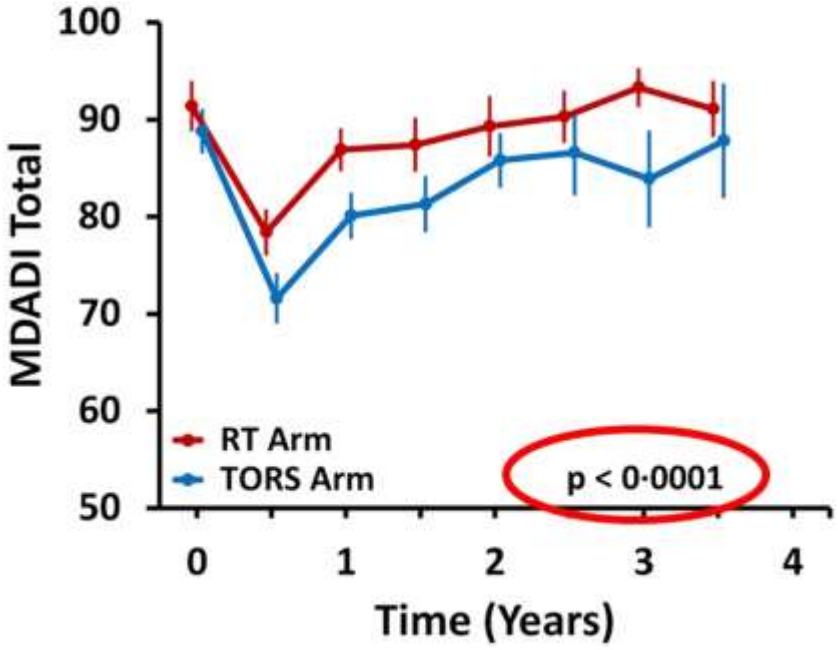
Characteristic	All Patients (n=68)	RT Arm (n=34)	TORS + ND Arm (n=34)	p-value
Dropout after randomization	2 (2.9)	2 (5.9)	0 (0)	0.49
Primary Treatment		RT: 9 (28.1) CRT: 23 (71.9)	Surgery: 10 (29.4) S + RT: 16 (47.0) S + CRT: 8 (23.5)	

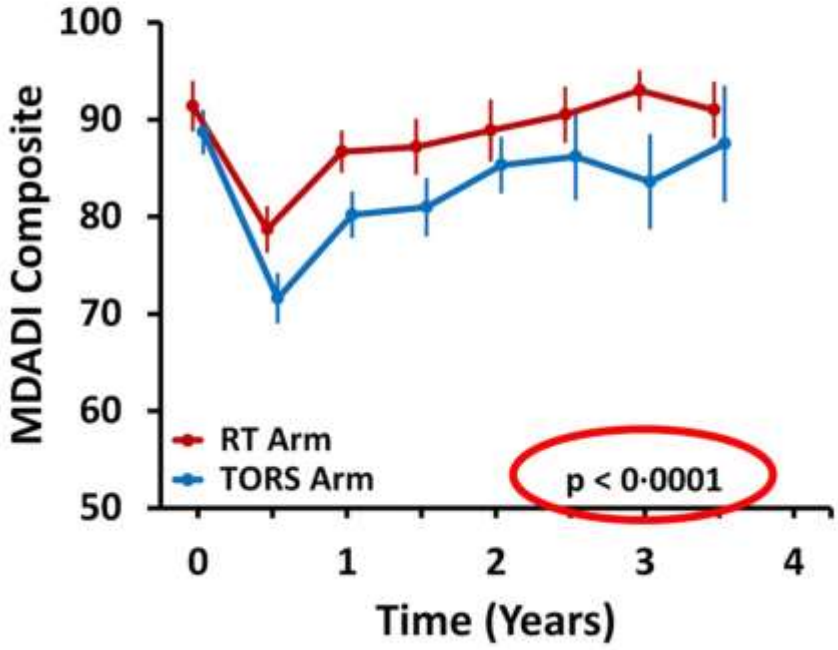
90% HPV positive

N0 31%; N1 18%; N2 51%

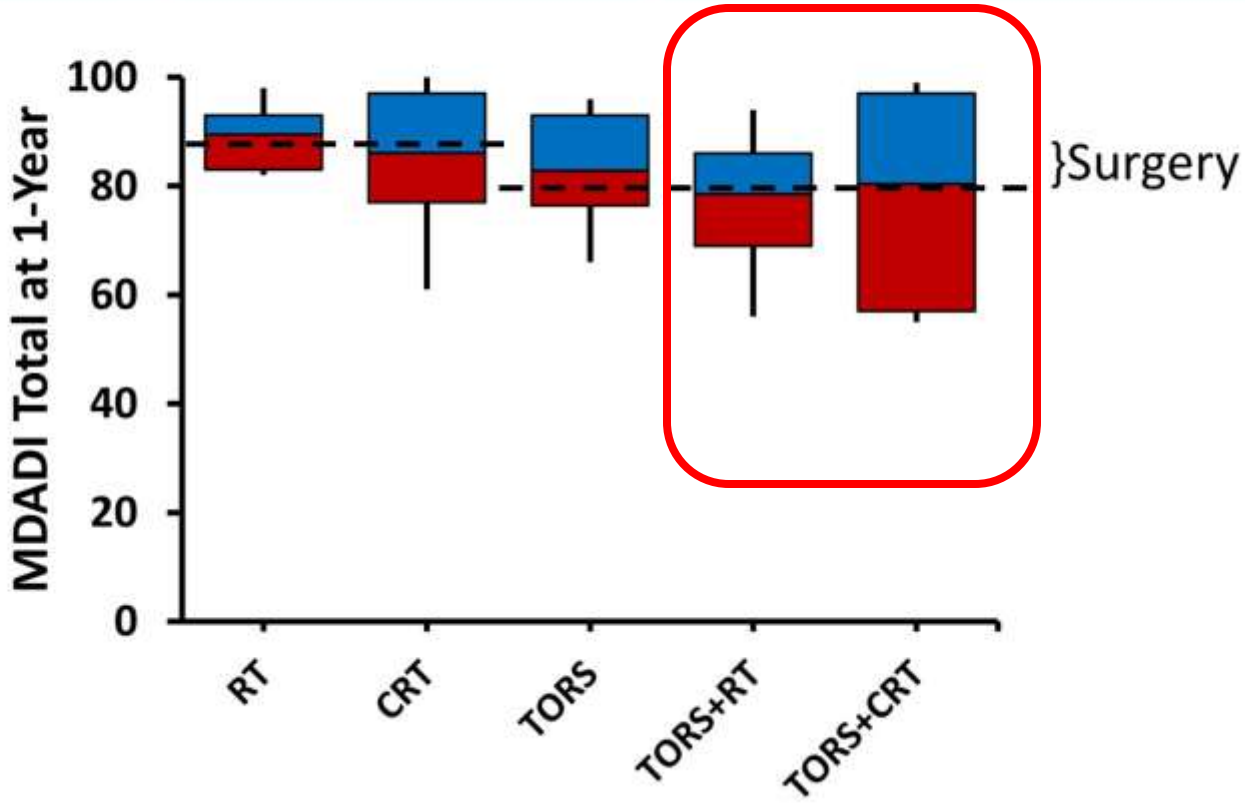
CURATIVE APPROACHES

Longitudinal MDADI Scores





Post-Hoc Analyses: MDADI by Treatment Intensity



CURATIVE APPROACHES

THM

- Better swallowing with RT (+CT)
- In early stages, surgery +RT(CT) highly toxic (less is more!)

Open questions

- Deescalation with reduced RT (HN002) or with surgery + reduced RT(CT)?

RECURRENT-METASTATIC

- **TPEx vs Extreme in first line?**

RECURRENT-METASTATIC

TPExtreme study design (NCT 02268695)

KEY ELIGIBILITY CRITERIA

- → R/M HNSCC not suitable for locoregional treatment
- → Age 18-70 years
- → PS 0-1
- → Creatinine clearance >60 mL/min
- → Prior cisplatin ≤300 mg/m²
- → No Anti-EGFR for 1 year

MINIMIZATION FACTORS

- → PS
- → Metastatic status
- → Previous cetuximab
- → Country

R 1:1

N = 270

EXTREME
(Reference arm)

6 cycles Q3W CT

CISPLATIN → 100 mg/m² IV
5FU → 4000 mg/m² 96h continuous infusion
CETUXIMAB → 400 mg/m² (loading dose), then 250 mg/m² IV weekly

– Maintenance cetuximab 250 mg/m²
– WEEKLY
– until progression or unacceptable toxicity

N = 269

TPEx
(Experimental arm)

4 cycles Q3W CT

CISPLATIN → 75 mg/m² IV
DOCETAXEL → 75 mg/m² IV
CETUXIMAB → 400 mg/m² (loading dose), then 250 mg/m² IV weekly
+ G CSF after each cycle

– Maintenance cetuximab 500 mg/m²
– EVERY 2 WEEKS
– until progression or unacceptable toxicity

RECURRENT-METASTATIC

Overall Survival

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

RECURRENT-METASTATIC

Adverse events (AEs) during chemotherapy phase

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

Toxicity was lower in the TPEx arm:

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

THM

- TPEx not superior to Extreme
- 4 cycles TPEx + Cet Every other week maintenance better tolerated than Extreme

Open questions

- Paclitaxel instead of Docetaxel?

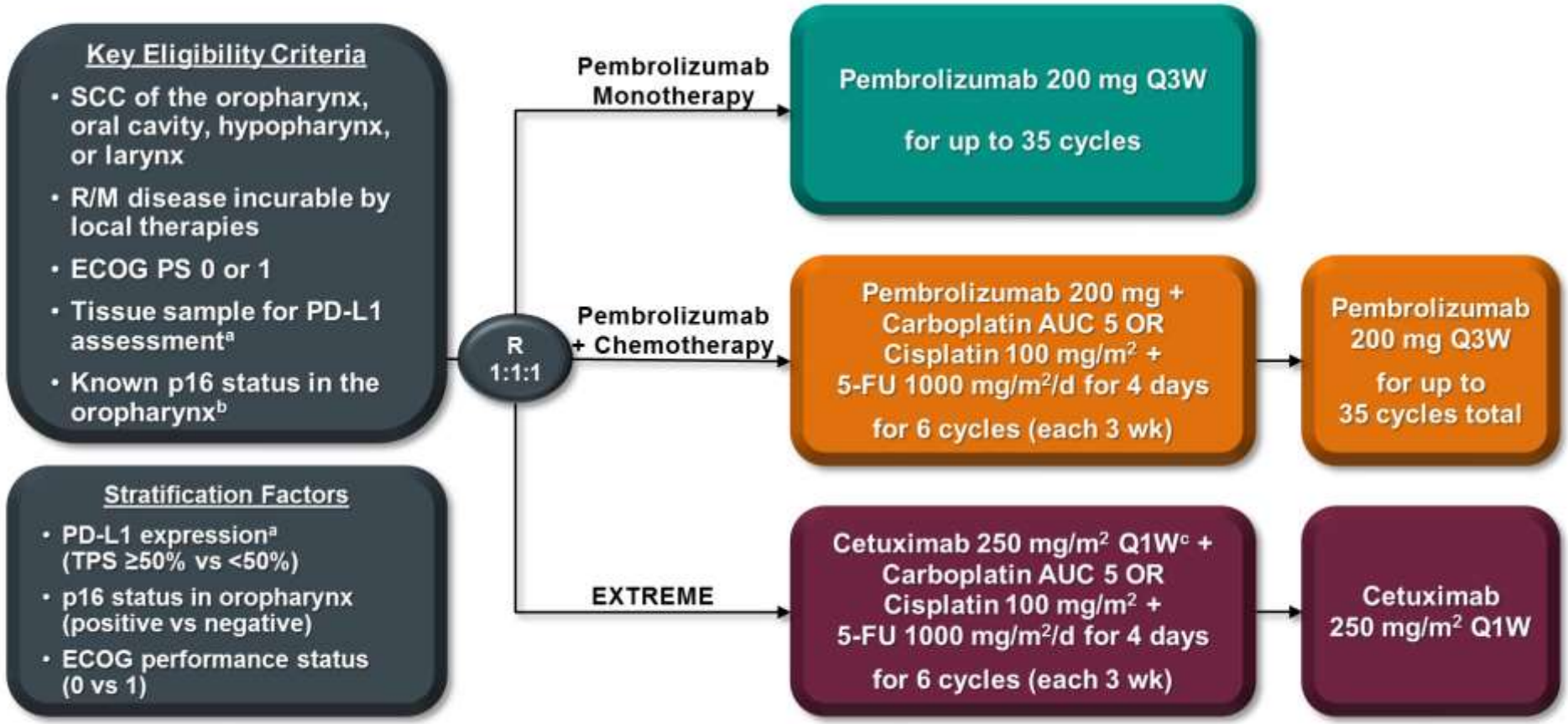
IMMUNOTHERAPY ARENA

- **Update Keynote 048**
- **Clinical predictive factors?**

Protocol-Specified Final Results of the KEYNOTE-048 Trial of Pembrolizumab as First-Line Therapy for Recurrent/ Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC)

Danny Rischin[1], Kevin Harrington,[2] Richard Greil,[3] Denis Soulières,[4] Makoto Tahara,[5]

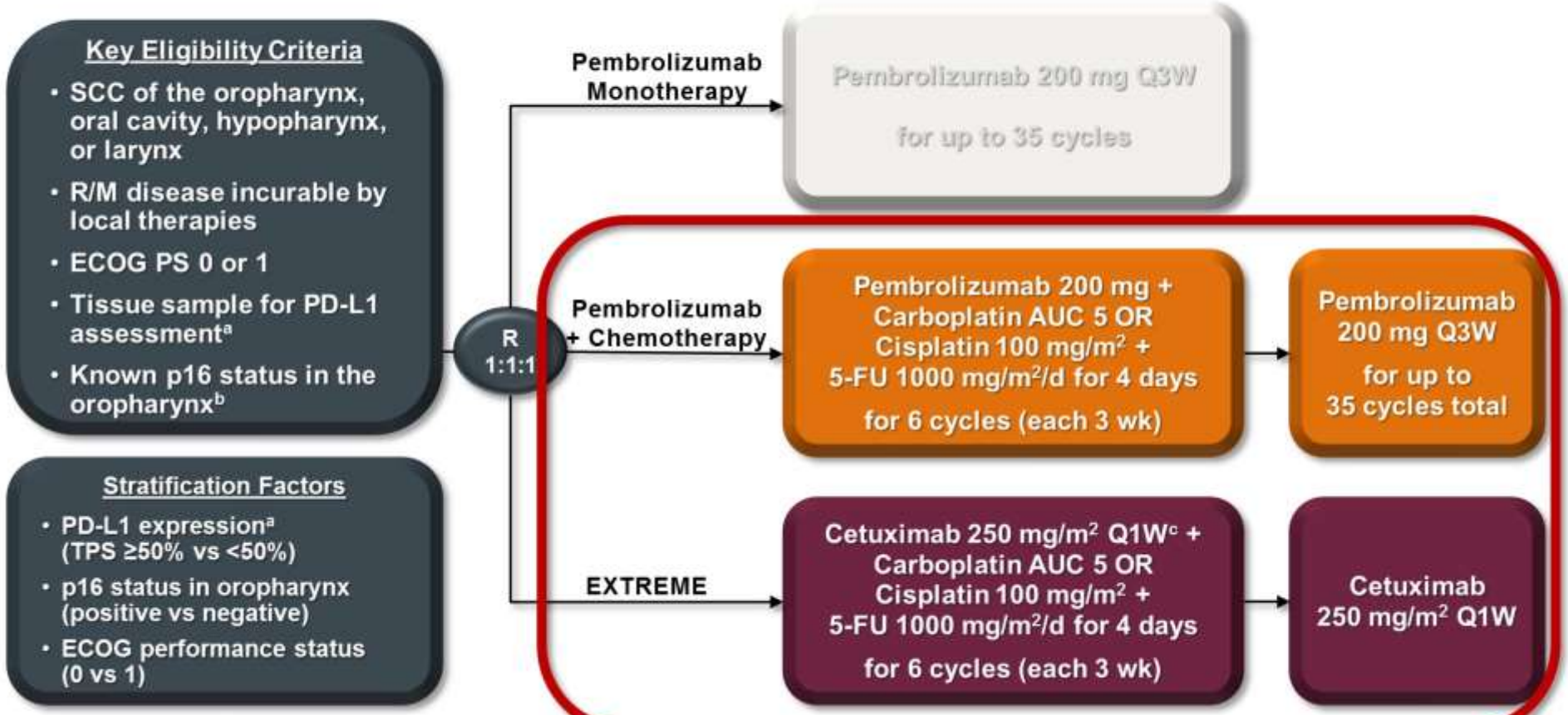
KEYNOTE-048 Study Design (NCT02358031)



[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.

IMMUNOTHERAPY ARENA

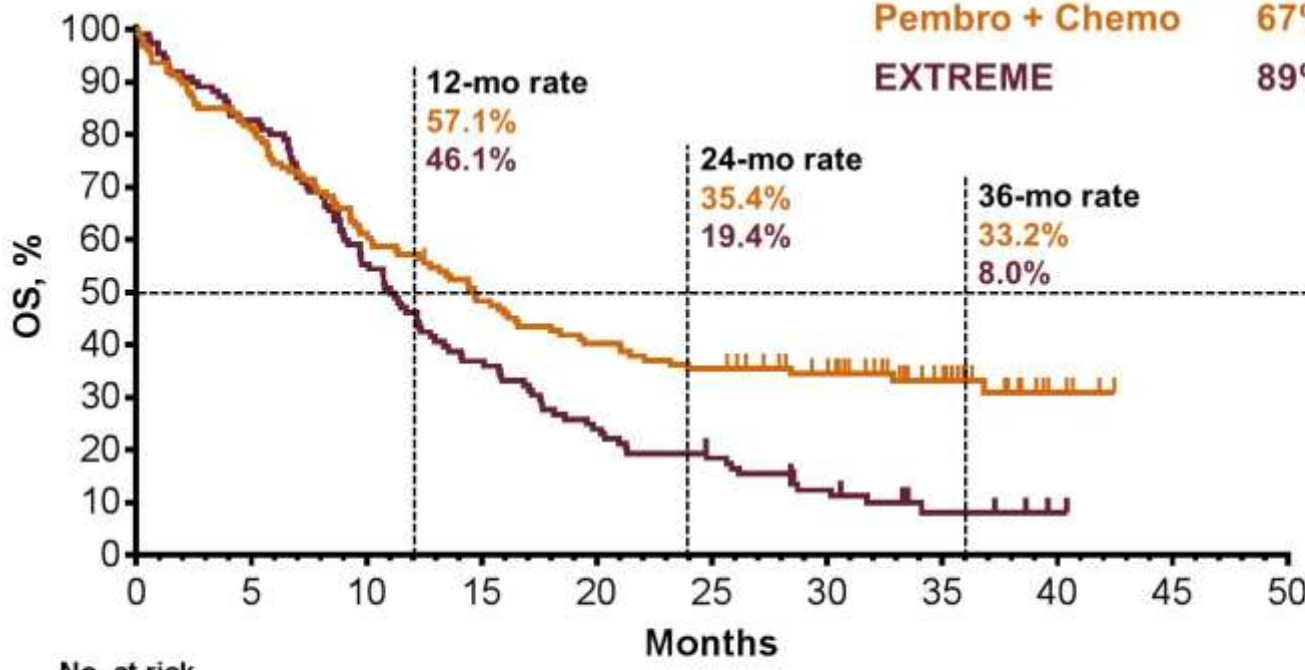
KEYNOTE-048 Study Design (NCT02358031)



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

IMMUNOTHERAPY ARENA

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%		

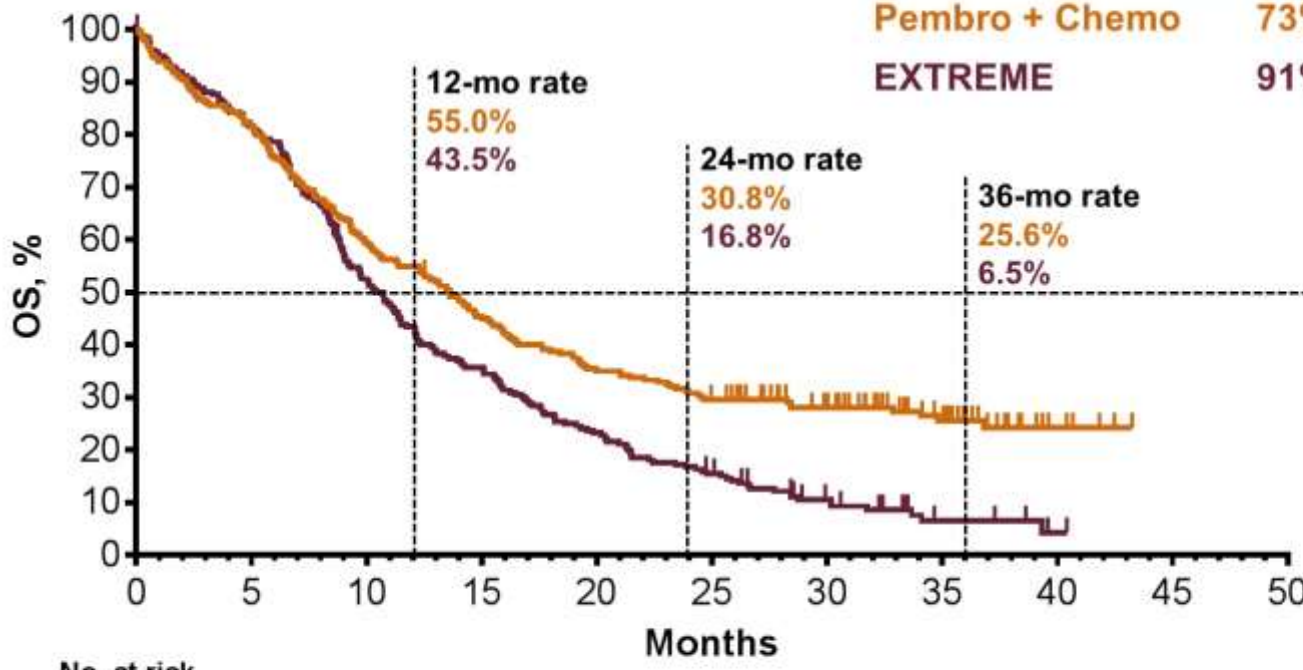
Median (95% CI)
14.7 mo (10.3-19.3)
11.0 mo (9.2-13.0)

No. at risk

126	102	77	60	50	44	36	21	4	0	0
110	91	60	40	26	19	11	4	1	0	0

[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%		

Median (95% CI)
13.6 mo (10.7-15.5)
10.4 mo (9.1-11.7)

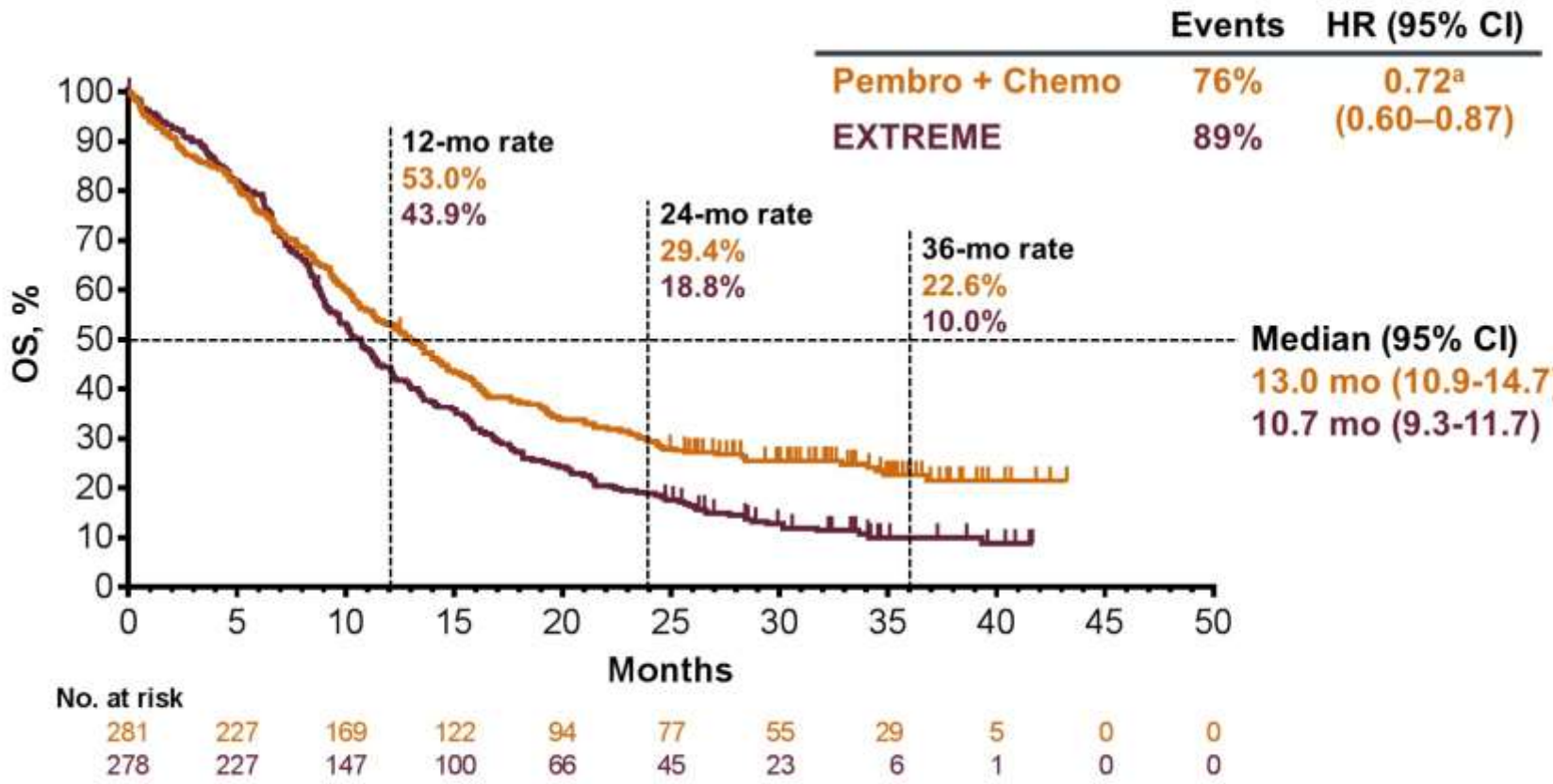
No. at risk

242	197	144	109	84	70	52	29	5	0	0
235	191	122	83	54	35	17	5	1	0	0

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

IMMUNOTHERAPY ARENA

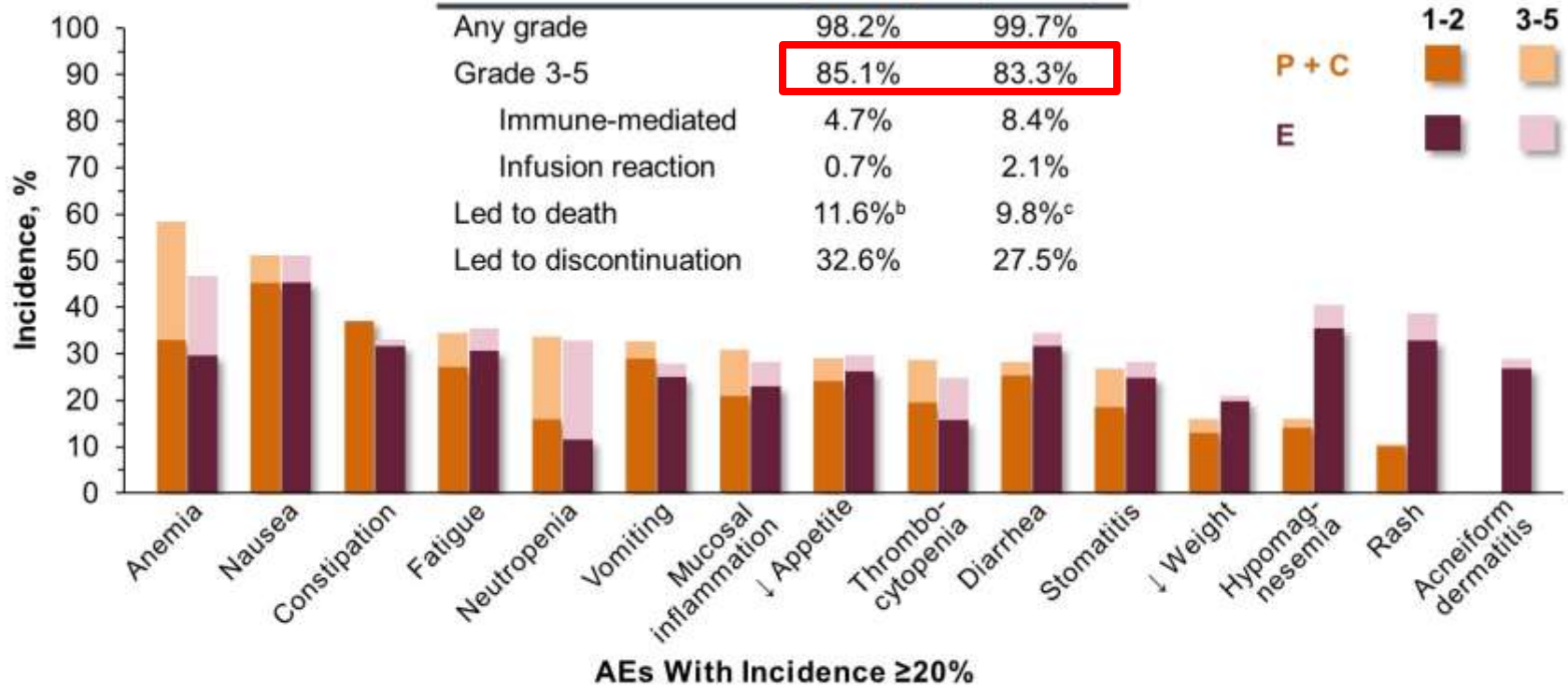
OS, P+C vs E, Total Population



[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).

All-Cause AEs,[a] P + C vs E, Total Population

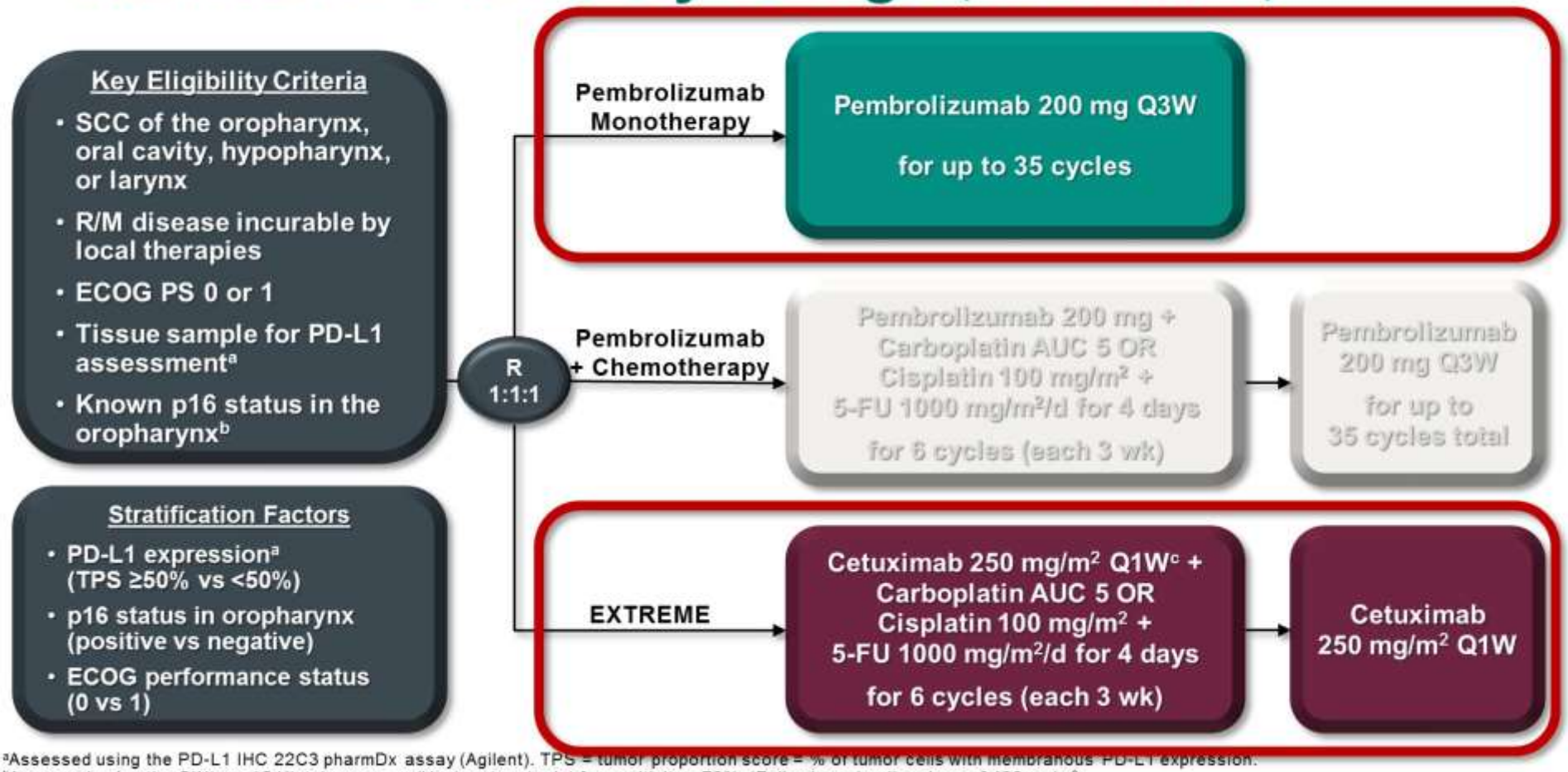
All AEs	P + C (n = 276)	E (n = 287)
Any grade	98.2%	99.7%
Grade 3-5	85.1%	83.3%
Immune-mediated	4.7%	8.4%
Infusion reaction	0.7%	2.1%
Led to death	11.6%[b]	9.8%[c]
Led to discontinuation	32.6%	27.5%



[a]Data for treatment-related AEs were presented at ESMO 2018. [b]Events were considered treatment related in 4.0%. [c]Events were considered treatment related in 2.8%.
FA (data cutoff date: Feb 25, 2019).

IMMUNOTHERAPY ARENA

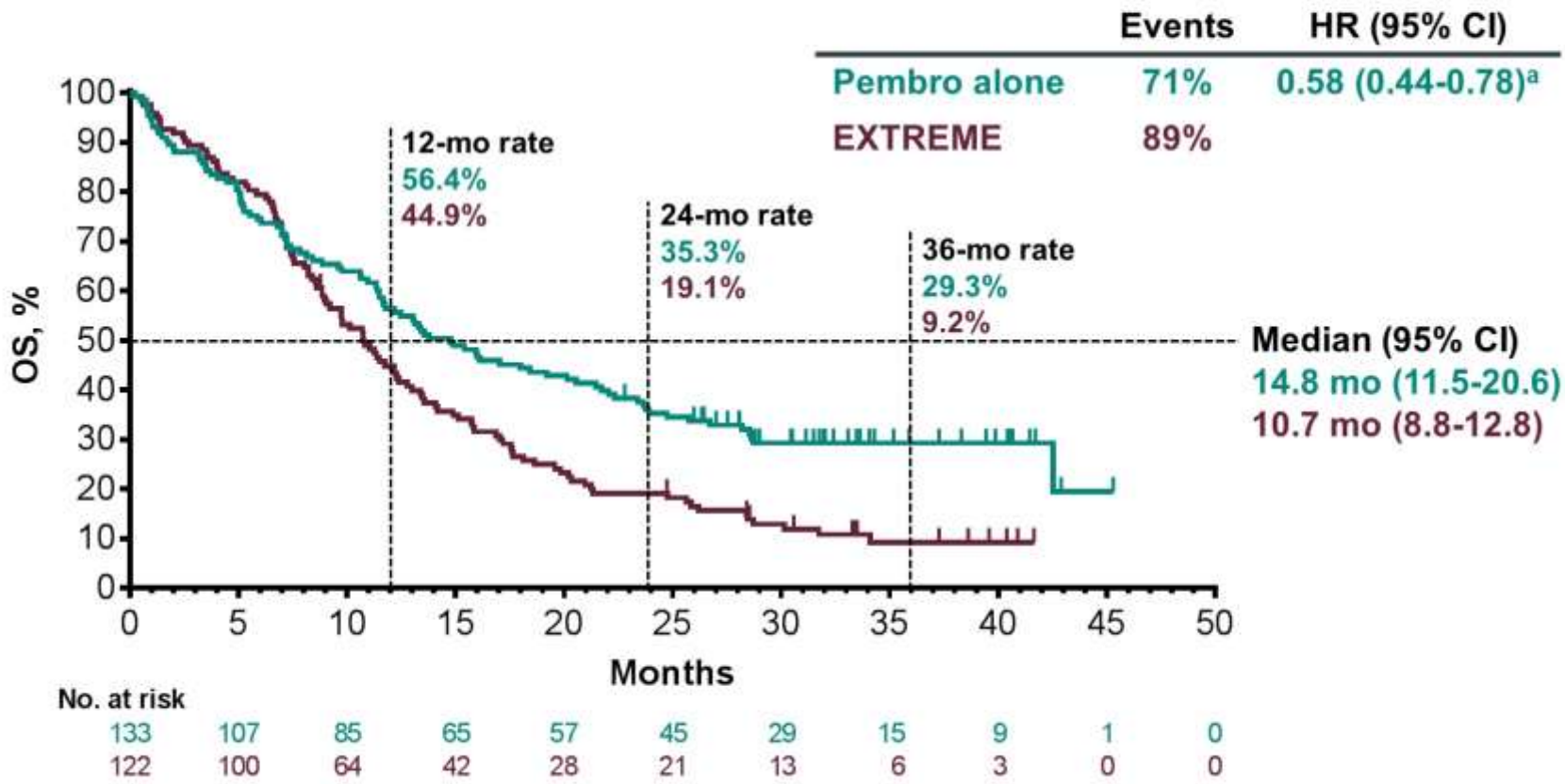
KEYNOTE-048 Study Design (NCT02358031)



[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.

IMMUNOTHERAPY ARENA

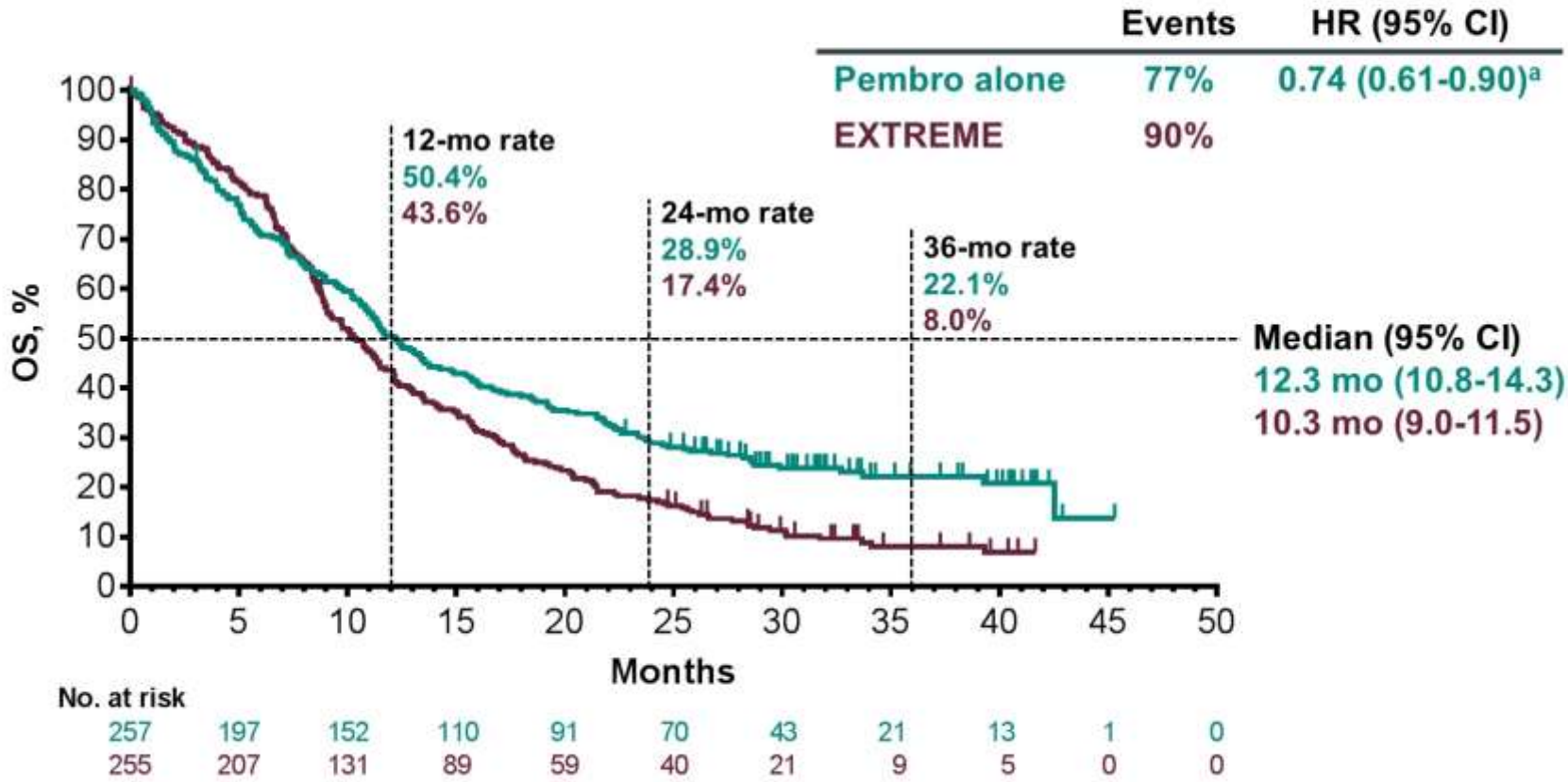
OS, P vs E, CPS ≥20 Population



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

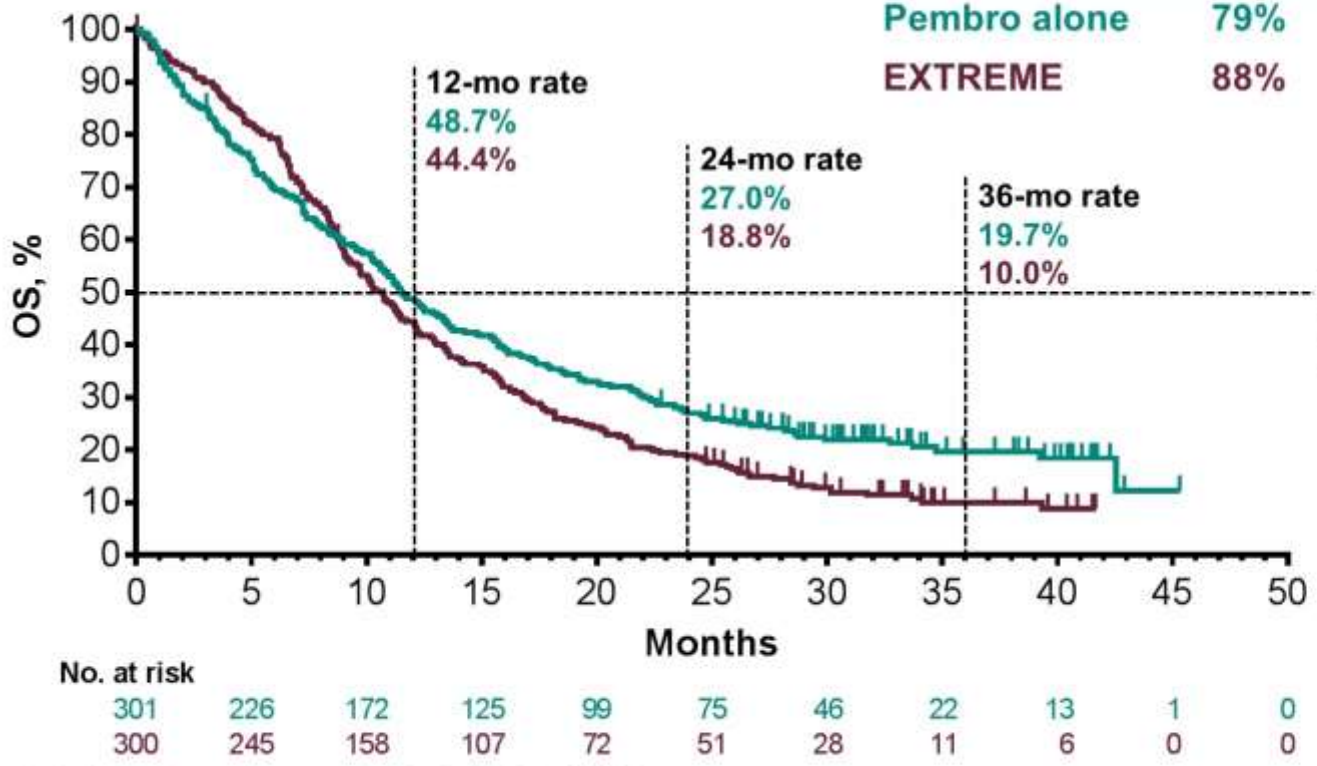
IMMUNOTHERAPY ARENA

OS, P vs E, CPS ≥1 Population



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

OS, P vs E, Total Population



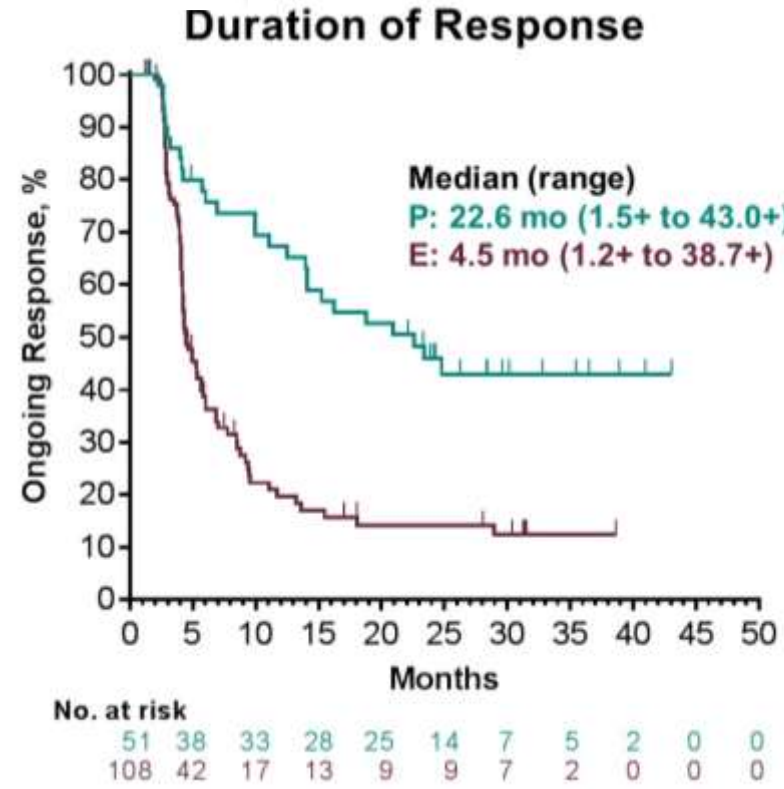
	Events	HR (95% CI)	*P*
Pembro alone	79%	0.83 (0.70-0.99)	0.0199[a]
EXTREME	88%		

Median (95% CI)
11.5 mo (10.3-13.4)
10.7 mo (9.3-11.7)

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

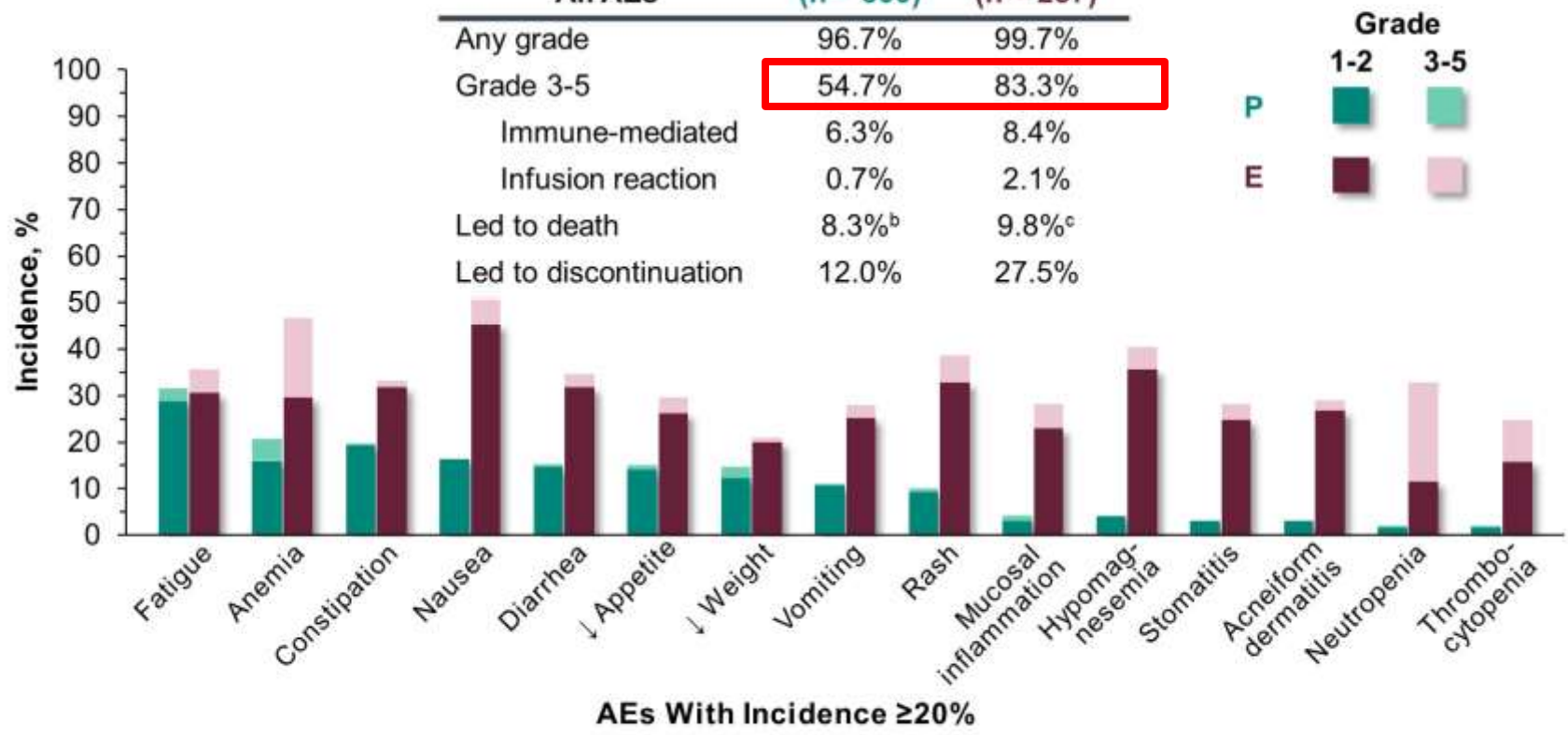
Response Summary, P vs E, Total Population

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)



All-Cause AEs,[a] P vs E, Total Population

All AEs	P (n = 300)	E (n = 287)
Any grade	96.7%	99.7%
Grade 3-5	54.7%	83.3%
Immune-mediated	6.3%	8.4%
Infusion reaction	0.7%	2.1%
Led to death	8.3%[b]	9.8%[c]
Led to discontinuation	12.0%	27.5%



[a]Data for treatment-related AEs were presented at ESMO 2018. [b]Events were considered treatment related in 1.0%. [c]Events were considered treatment related in 2.8%.
FA (data cutoff date: Feb 25, 2019).

IMMUNOTHERAPY ARENA

THM

- Prepare to test CPS
- Tailor treatment according to pt's need
- Chemo + Pembro better than Extreme
- Pembro alone in CPS > 20 if pt does not need a quick response (>1?)
- Waiting for EMA and AIFA approval….

IMMUNOTHERAPY ARENA

Open questions

- What about CPS 1-19?
- Who is the pt needing a quick response?
- Is chemo + pembro feasible for all the pts?
- Which second line after immuno?

IMMUNOTHERAPY ARENA

PROGNOSTIC FACTORS IN 2nd LINE

Abs 6026-6032-6035-6041-6044

Better outcome for:

- **Metastatic only** vs LR recurrence
- If metastatic: distant **nodes** best outcome, liver worst
- HPV positive contradictory data
- No impact for previous RT
- No impact of age

- **(almost) Definitively Induction Chemotherapy Wins!**

NASOPHARYNGEAL CANCER

Gemcitabine and cisplatin (GP) induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma: primary analysis of a phase 3 RCT

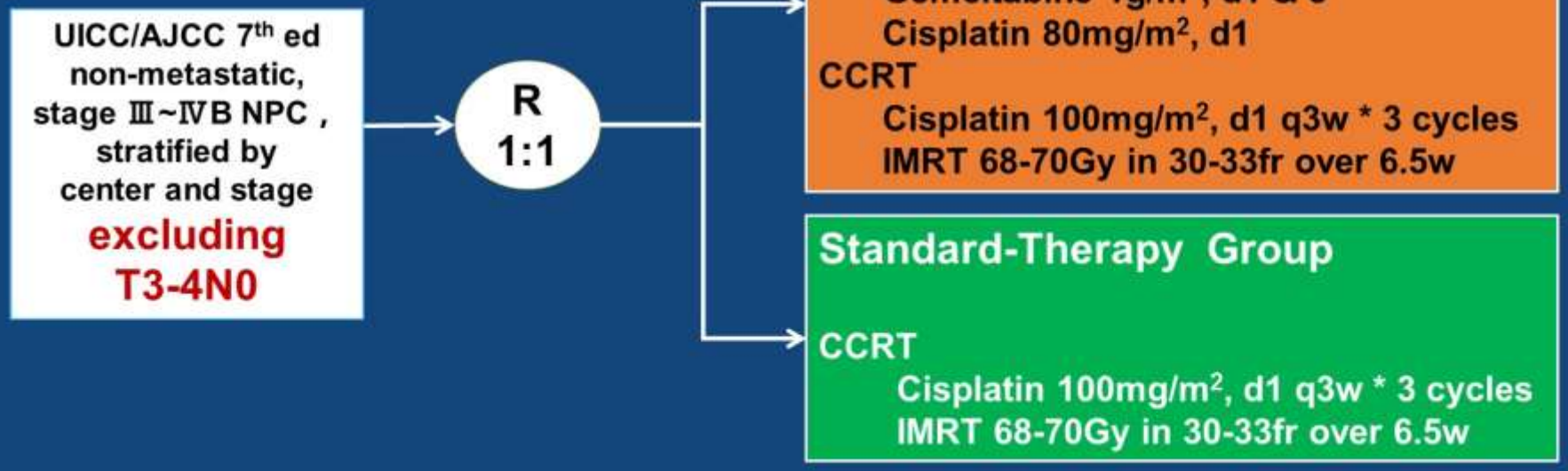
Jun Ma,[1] Yuan Zhang,[1] Lei Chen,[1] Guo-Qing Hu,[2] Ning Zhang,[3] Xiao-Dong Zhu,[4] Kun-Yu Yang,[5] Feng Jin,[6] Mei Shi,[7] Yu-Pei Chen,[1] Wei-Han Hu,[1] Zhi-Bin Cheng,[8] Si-Yang Wang,[8] Ye Tian,[9] Xi-Cheng Wang,[10] Yan Sun,[11] Jin-Gao Li,[12] Wen-Fei Li,[1] Yu-Hong Li,[1] Ling-Long Tang,[1] Yan-Ping Mao,[1] Guan-Qun Zhou,[1] Rui Sun,[1] Xu Liu,[1] Rui Guo,[1] Guo-Xian Long,[2] Shao-Qiang Liang,[3] Ling Li,[4] Jing Huang[5] Jin-Hua Long,[6] Jian Zang,[7] Qiao-Dan Liu,[8] Li Zou,[9] Qiong-Fei Su,[10] Bao-Min Zheng,[11] Yun Xiao,[12] Ying Guo,[1] Fei Han,[1] Hao-Yuan Mo,[1] Jia-Wei Lv,[1] Xiao-Jing Du,[1] Cheng Xu,[1] Na Liu,[1] Ying-Qin Li,[1] Melvin L K Chua,[13] Fang-Yun Xie,[1] and Ying Sun.[1]

[1]Sun Yat-sen University Cancer Center; [2]Tongji Hospital and [5]Union Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology; [3]The First People's Hospital of Foshan; [4]The Affiliated Cancer Hospital of Guangxi Medical University; [6]Guizhou Cancer Hospital; [7]XiJing Hospital of Forth Military Medical University; [8]The Fifth Affiliated Hospital of Sun Yat-sen University; [9]The Second Affiliated Hospital of Soochow University; [10]The First Affiliated Hospital of Guangdong Pharmaceutical University; [11]Peking University Cancer Hospital; [12]Jiangxi Cancer Hospital; all in China & [13]National Cancer Center Singapore

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

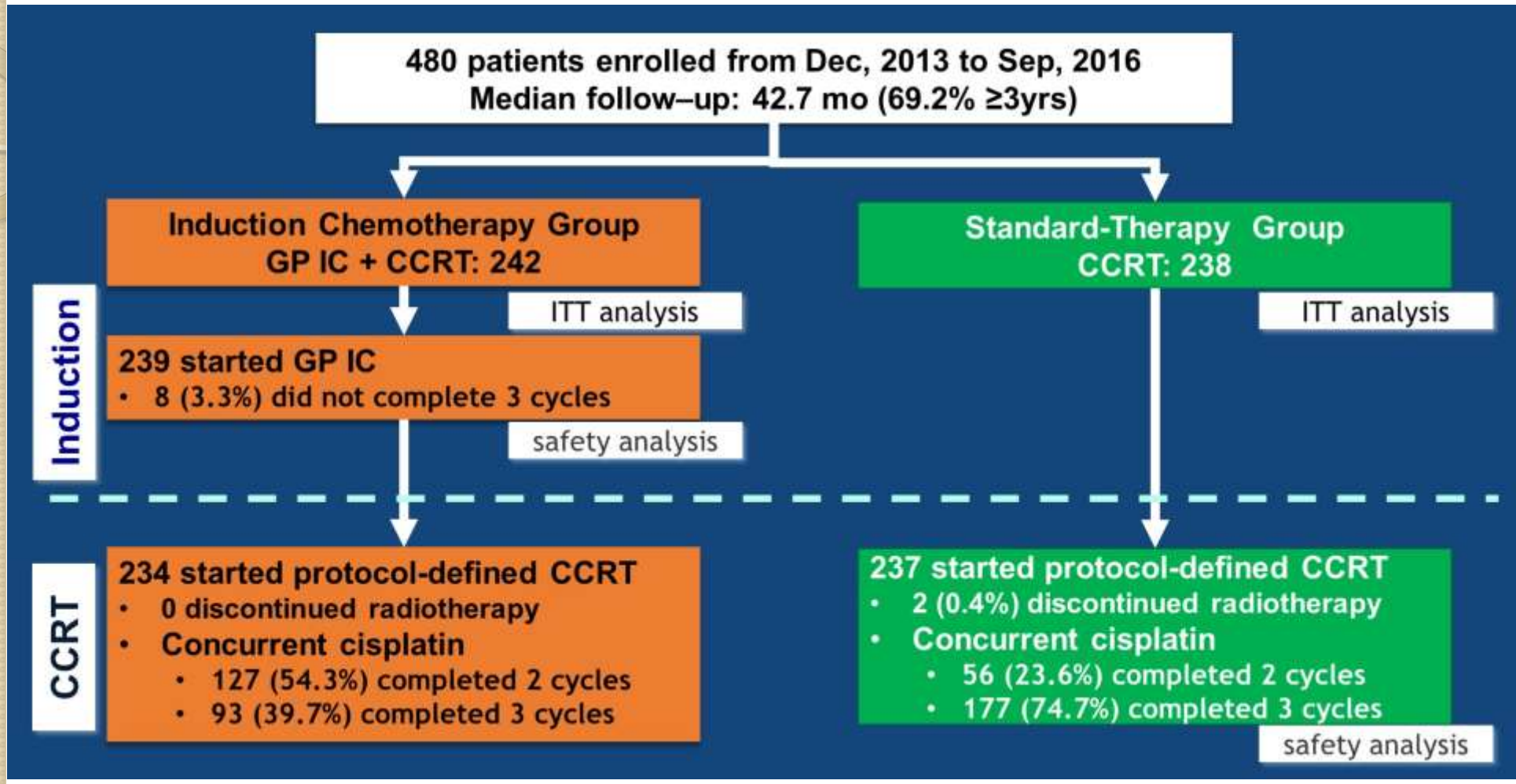
PRESENTED BY: Dr. Jun Ma (ORCID: 0000-0002-1137-93)

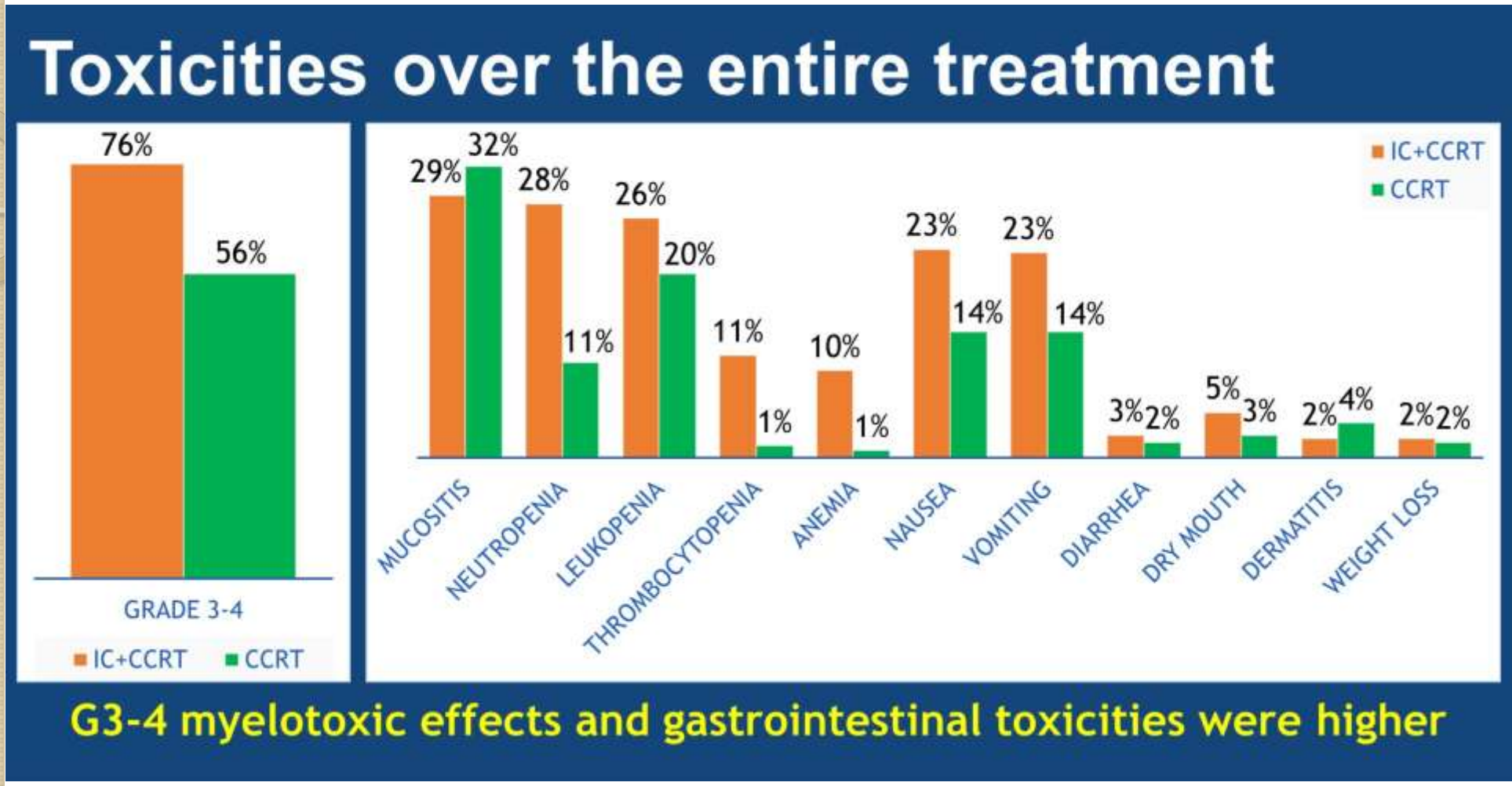
Trial Schema



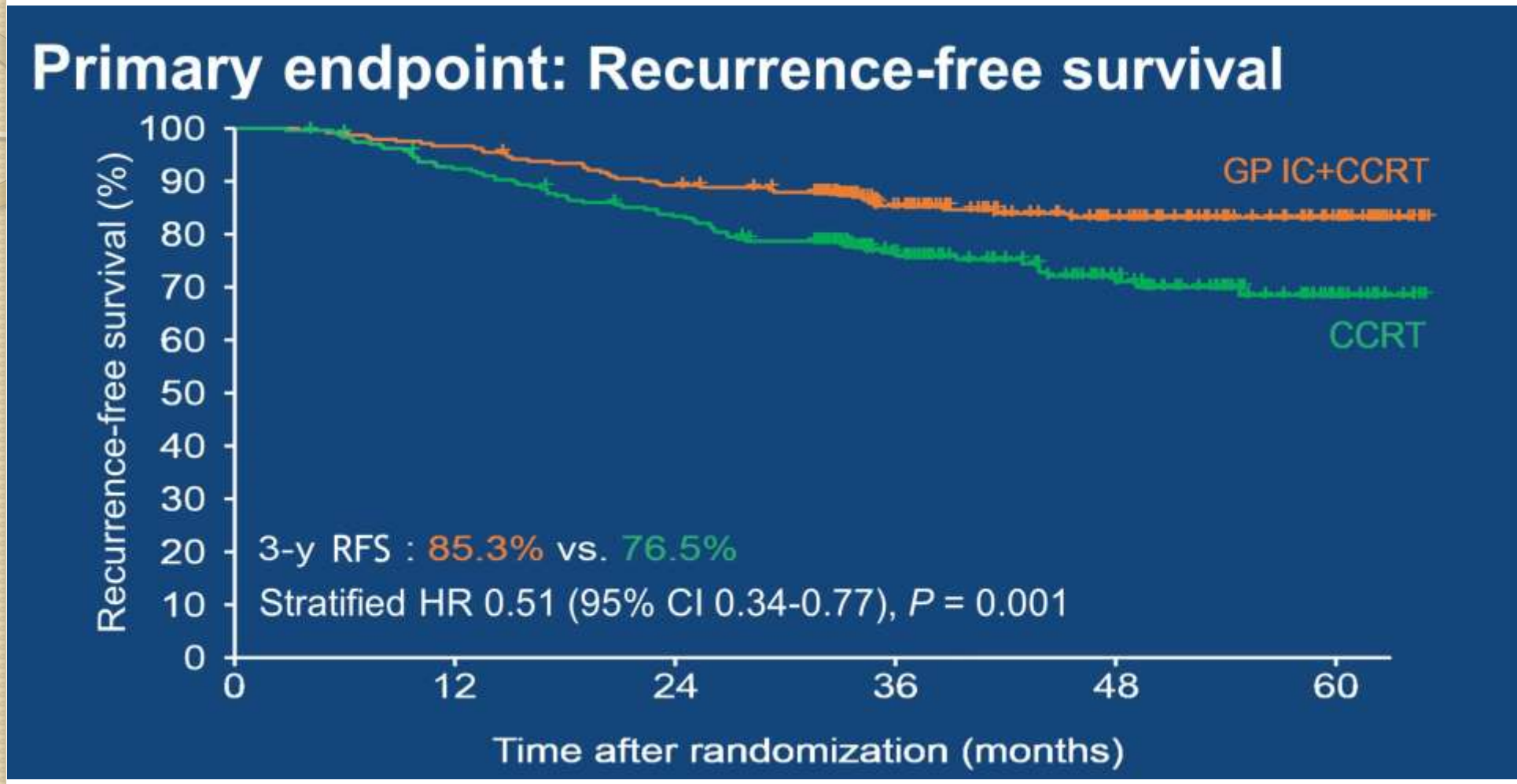
Clinical Trial: NCT01872962

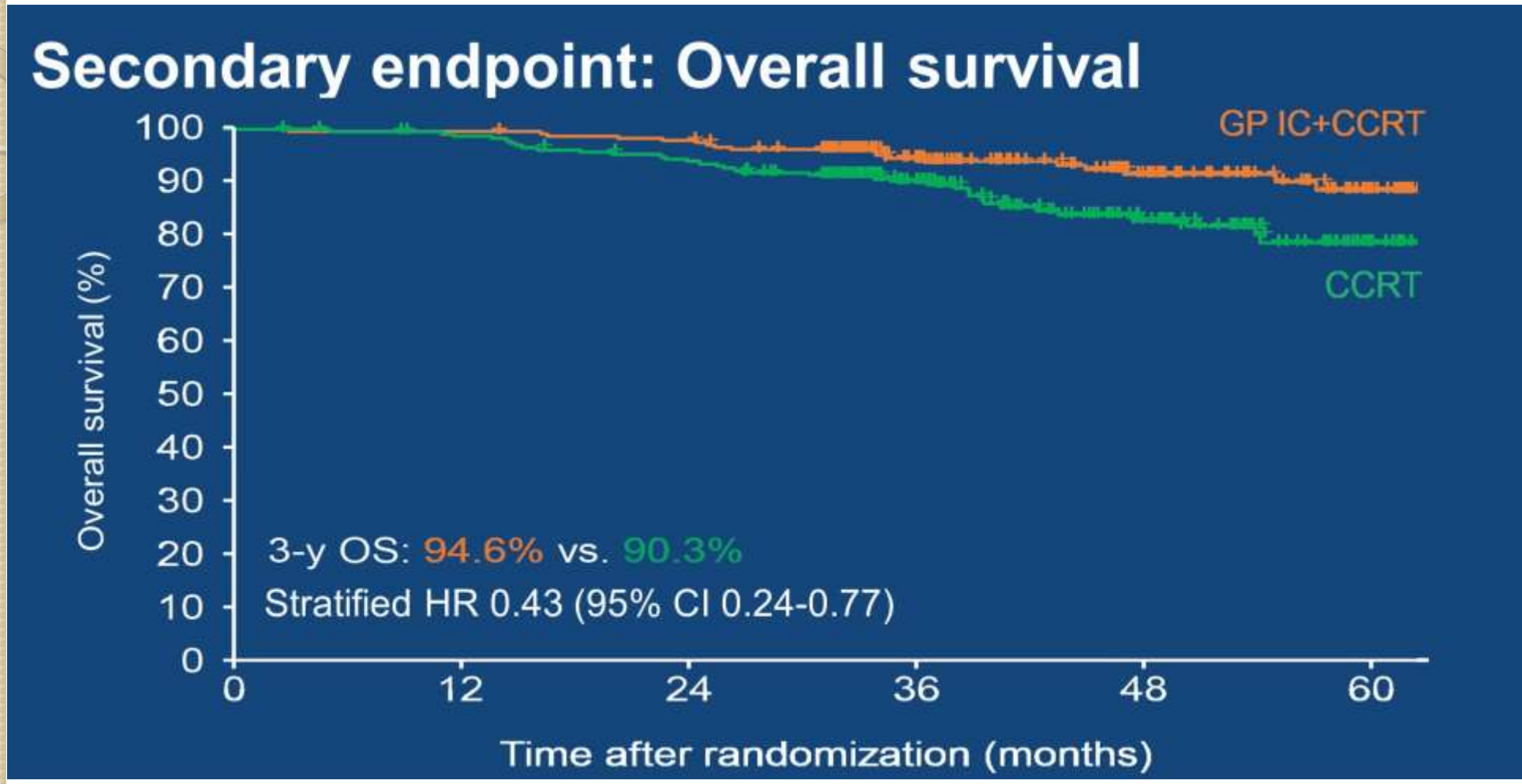
NASOPHARYNGEAL CANCER





But no difference in late Toxicities!


Primary endpoint: Recurrence-free survival
Recurrence-free survival (%)
100
90
80
70
60
50
40
30
20
10
0
GP IC+CCRT
CCRT
3-y RFS : 85.3% vs. 76.5%
Stratified HR 0.51 (95% CI 0.34-0.77), P = 0.001
0
12
24
36
48
60
Time after randomization (months)


Secondary endpoint: Overall survival
GP IC+CCRT
CCRT
Overall survival (%)
100
90
80
70
60
50
40
30
20
10
0
3-y OS: 94.6% vs. 90.3%
Stratified HR 0.43 (95% CI 0.24-0.77)
0
12
24
36
48
60
Time after randomization (months)

THM

- Induction chemotherapy (GC or TPF) + chemoradiation should become state of the art in locally advanced (N+?) NPC

New hope for salivary gland cancer

Ado-trastuzumab emtansine in patients with *HER2* amplified salivary gland cancers: Results from a phase 2 basket trial

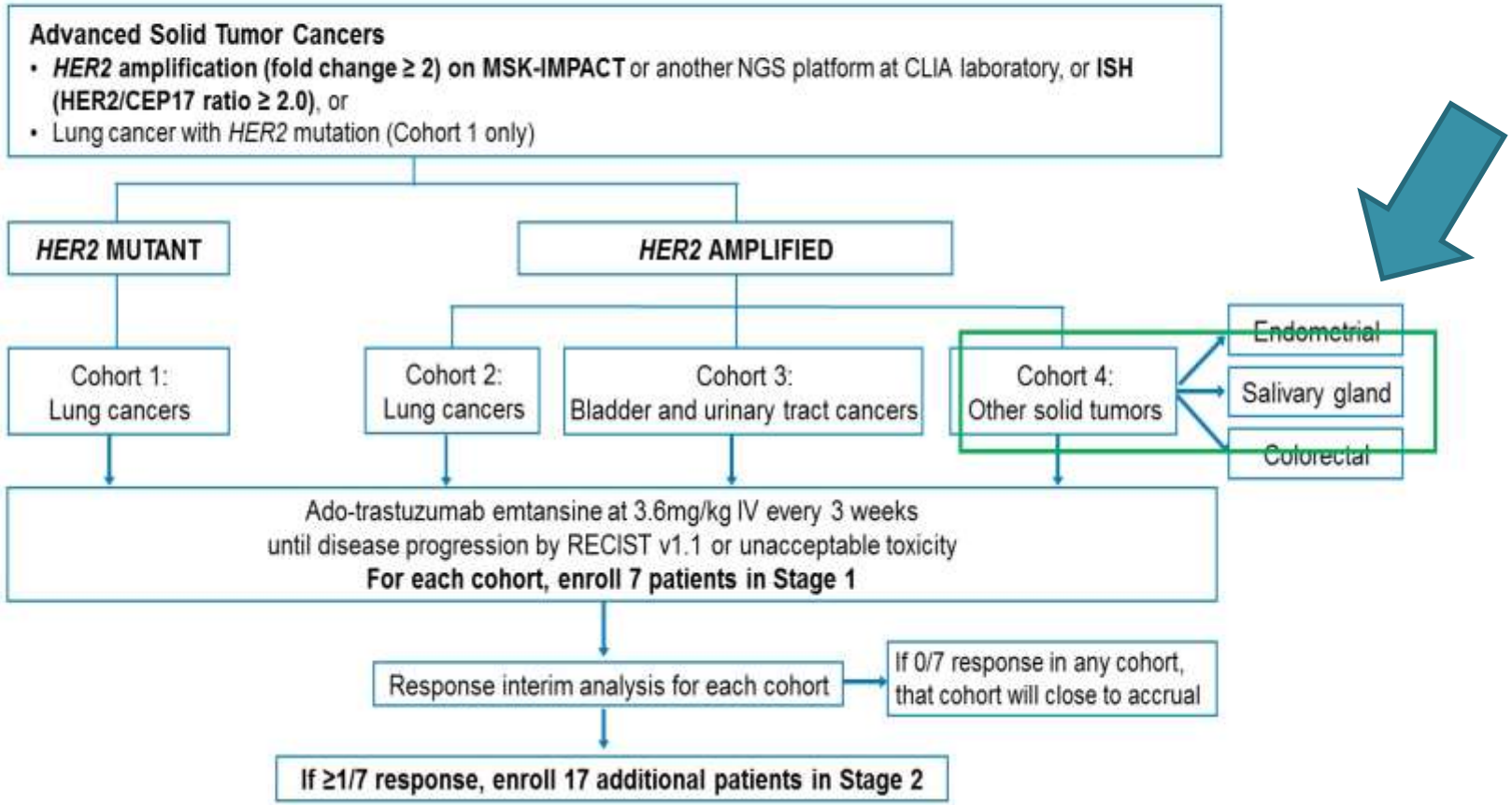
Bob T. Li, Ronglai Shen, Michael Offin, Darren Buonocore, Mackenzie L. Myers, Aishwarya Venkatesh, Pedram Razavi, Michelle S. Ginsberg, Gary A. Ulaner, David B. Solit, David M. Hyman, Charles M. Rudin, Erika Gedvilaite, Dana Tsui, Maria E. Arcila, Mark G. Kris, Gregory Weitsman, Tony Ng, Maurizio Scaltriti, Alan L. Ho

Memorial Sloan Kettering Cancer Center, New York, NY, USA

King's College London, London, UK

SALIVARY GLAND CANCER

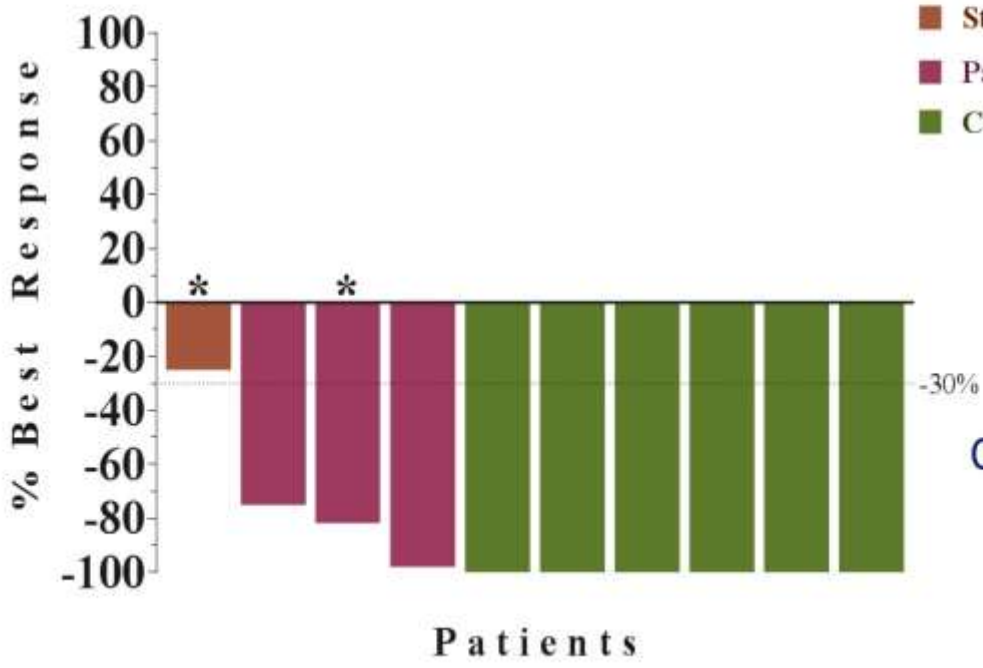
A phase 2 trial of ado-trastuzumab emtansine for patients with *HER2* amplified or mutant cancers (NCT02675829)



SALIVARY GLAND CANCER

Best Overall Response

HER2 Amplified Salivary Gland Cancers



ORR was 90% (9/10, 95% CI 56-100%)

THM

- Test salivary gland cancer (adenoca, apocrine, ductal carcinoma and carcinoma NOS) for HER2 (and AR)

- Anti HER2 treatment + chemo works!

THYROID CANCER

- **More targeted available in thyroid cancer!**

THYROID CANCER

Activity and Tolerability of BLU-667, a Highly Potent and Selective RET Inhibitor, in Patients with Advanced RET-altered Thyroid Cancers

- Matthew H. Taylor[1], Justin F. Gainor[2], Mimi I-Nan Hu[3], Viola Weijia Zhu[4], Gilberto Lopes[5], Sophie Leboulleux[6], Marcia S. Brose[7], Martin H. Schuler[8], Daniel W. Bowles[9], Dong-Wan Kim[10], Christina S. Baik[11], Elena Garralda[12], Chia-Chi Lin[13], Douglas Adkins[14], Debashis Sarker[15], Giuseppe Curigliano[16], Hui Zhang[17], Corinne Clifford[17], Michael R. Palmer[17], Christopher D. Turner[17], Vivek Subbiah[3]

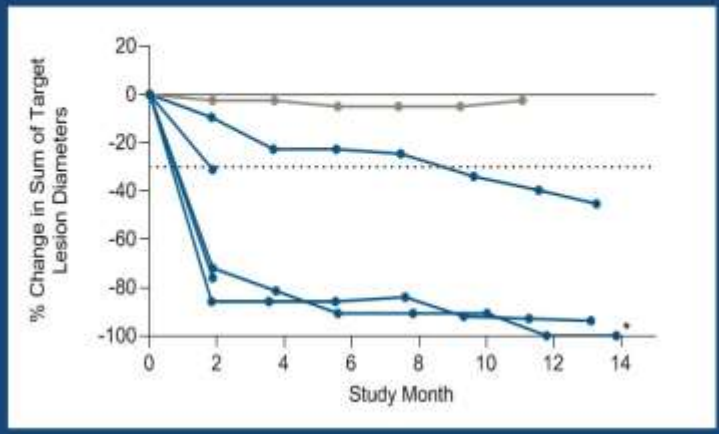
- [1]Oregon Health & Science University, Portland, OR; [2]Massachusetts General Hospital, Boston, MA; [3]The University of Texas MD Anderson Cancer Center, Houston, TX; [4]Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, Orange, CA; [5]Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL; [6]Institut Gustave Roussy, Villejuif, France; [7]Department of Otorhinolaryngology: Head and Neck Surgery, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; [8]West German Cancer Center, University Hospital Essen, Essen, Germany; [9]University of Colorado, Aurora, CO; [10]Seoul National University Hospital, Seoul, Korea, Republic of (South); [11]Fred Hutchinson Cancer Research Center, Seattle, WA; [12]Hospital Universitari Vall d'Hebron, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [13]Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan; [14]Washington University School of Medicine, St. Louis, MO; [15]King's College Hospital, Institute of Liver Studies, London, United Kingdom; [16]University of Milano, European Institute of Oncology, Division of Early Drug Development, Milan, Italy; [17]Blueprint Medicines Inc, Cambridge, MA

THYROID CANCER

BLU-667 in MTC: Results

- N=64, 48 cases in current analysis
- Included 43 cases with prior MTKI, 16 in current analysis
- Overall response rate (ORR) 56%,
- ORR 63% with prior MTKI
- DCR 97% vs 94%
- Overall disease control rate DCR 97% and 94%, respectively
- In RET fusion differentiated thyroid cancer 5/6 cases analyzed to date with 4 PR

	All MTC (n=32)	Prior Cabo or Vand (n=16)
ORR (95% CI)	56% (38–74)	63% (35–85)
Best response:		
CR	1	-
PR[b]	17	10
SD	13	5
PD	1	1
DCR (95% CI)	97% (84–100)	94% (70–100)
Tumor shrinkage	94%	100%



THM

- New class of drug for thyroid cancer
- RET mutation and fusion!

Open question

- How to position in respect to multikinase inh?

cSCC

- **Immunotherapy in cutaneous squamous cell carcinoma gains a role!**

cSCC

Abstract 6015: Primary Analysis of Phase 2 Results of Cemiplimab, a Human Monoclonal Anti–PD-1, in Patients with Locally Advanced Cutaneous Squamous Cell Carcinoma

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cSCC

Tumour response assessment by independent central review: Locally advanced compared with metastatic CSCC

	Locally advanced CSCC (N = 78)	Metastatic CSCC (N=59)[1]
Best overall response, n (%)		
Complete response	10 (12.8)	4 (7)
Partial response	24 (30.8)	24 (41)
Stable disease	28 (35.9)	9 (15)
Progressive disease	9 (11.5)	11 (19)
Not evaluable†	7 (9.0)	7 (12)
Objective response rate, % (95% CI)‡	**43.6 (32.4-55.3)**	**47 (34-61)**
Disease control rate, % (95% CI)	**79.5 (68.8-87.8)**	**N/R**
Durable disease control rate, % (95% CI)§	**62.8 (51.1-73.5)**	**61 (47-74)**
Median observed time to response, months (range)¶	1.9 (1.8-8.8)	1.9 (1.7-6.0)

[1]Migden et al., *NEJM* 2018;379:341-51.

cSCC

THM

- New opportunity for advanced cSCC (LocoRegional and/or Metastatic)
- Decrease of response after >2 surgical procedures

Open question

- Immunosuppressed and transplant pts?

JUST AN OVERVIEW…

SETTING	NEWS
EARLY STAGE OROPHARYNX CANCER	RT: BETTER SWALLOWING THAN SURGERY
FIRST LINE REC MET	4 CYCLES TPEx better tolerated than EXTREME
PREDICTIVE FACTORS TO IMMUNO?	MET vs LOCOREG; NODE vs LIVER MET; HPV?
IMMUNOTHERAPY 1ST LINE	TEST CPS (benefit >20?); PEMBRO+CT better than EXTREME; PEMBRO ALONE LESS RESPONSE but LESS TOXIC
NASOPHARYNGEAL CANCER	INDUCTION CHEMO IN STAGE III-IV
SALIVARY GLAND CANCER	ADO-TRAST ETAMSINE HIGH RESPONSE RATE
THYROID CANCER	NEW HOPE FROM RET-TARGETING DRUGS
CUTANEOUS SCC	CEMIPLIMAB HIGH RESPONSE AND DURABLE

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