Improving the Standard in Locally Advanced SCCHN; An Elusive or Delayed Reality ?

EMORY WINSHIP CANCER INSTITUTE
A Cancer Center Designated by the National Cancer Institute

Debates and Didactics in Hematology and Oncology Sea Island, July 25th 2024

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Potential Conflicts of Interest

I received compensation for advisory role or Honoraria from,

-Astra Zeneca,

-Pfizer,

-Merck,

-GSK,

-Novartis,

-Inovio,

-EMD Serono,

-Vaccinex,

-Kura Oncology,

-Celldex Therapeutics,

-Eisai,

-Exelixis,

-CUE Pharma,

-Fulgent

-Akeso

-Seagen

Honoraria from:

-Onclive,

-Reach MD,

-Uptodate,

-WebMD,

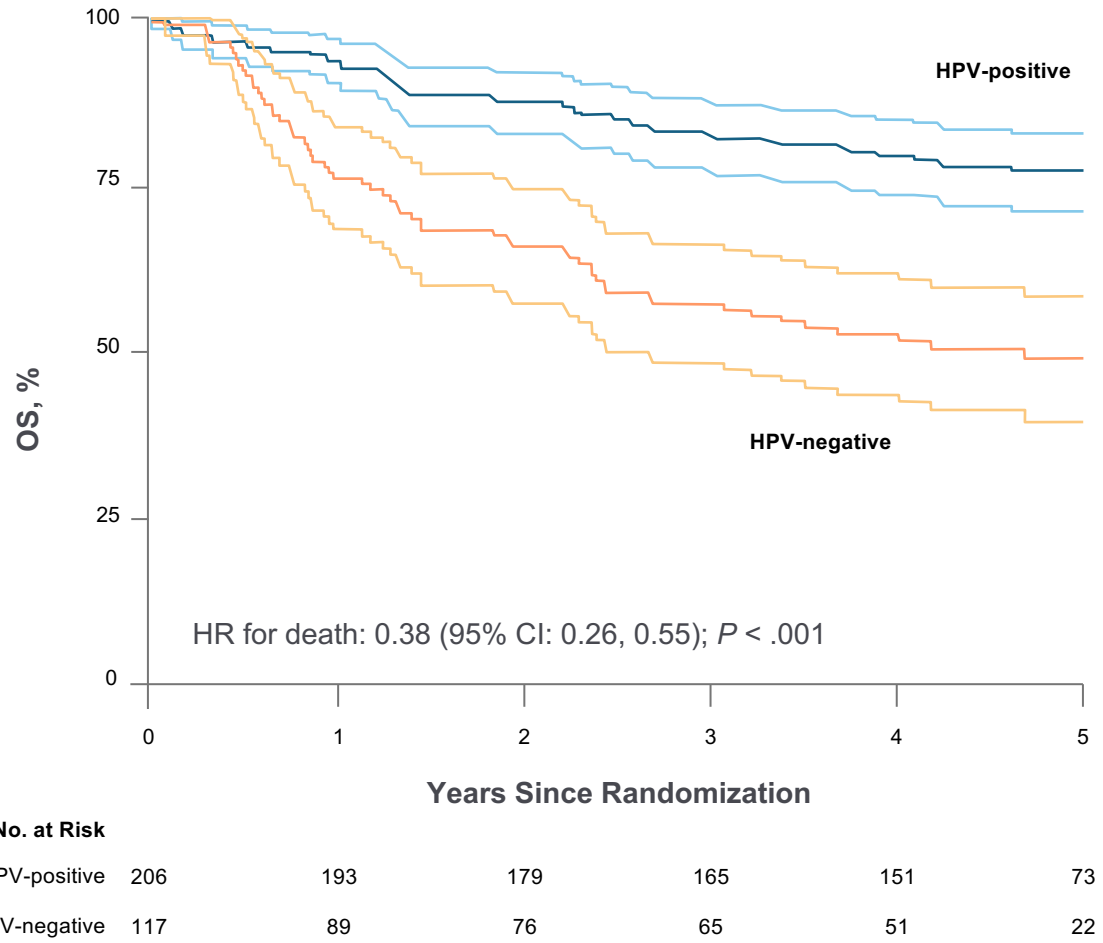
- Springer

I received research funding from:

- BMS, Exelixis, NIH

Locally Advanced SCCHN

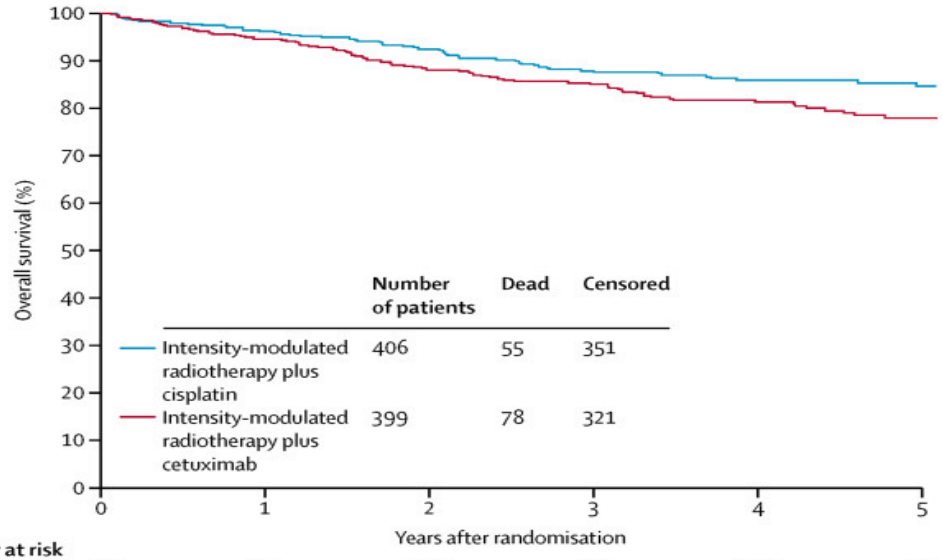
- Survival in locoregionally advanced SCCHN remains inadequate and poor for HPV - disease, [1]
- Standard therapy is associated with acute and late toxicity[2]
- Novel approaches are needed to improve survival while reducing toxicity



1. Ang KK, et al. N Engl J Med. 2010;363:24-
2. Machtay M, et al. J Clin Oncol. 2008;26:3[illegible]

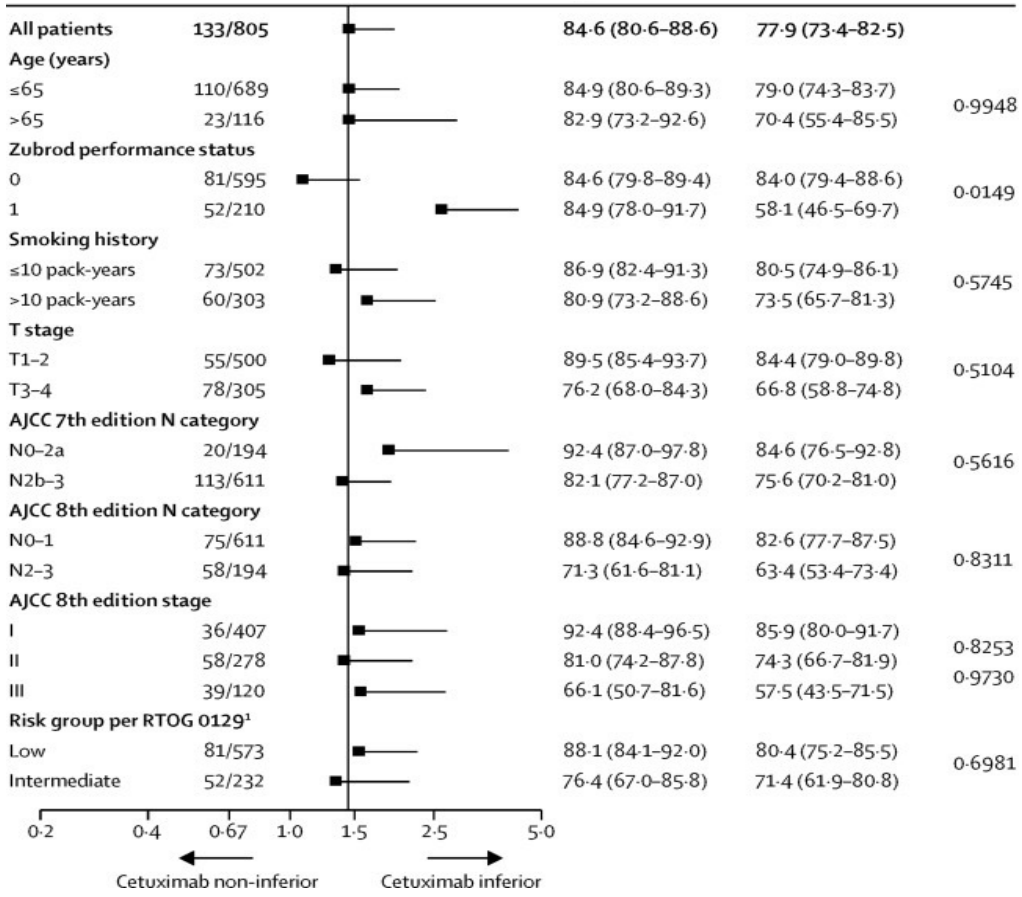
RTOG 1016-Cetux vs Cis in HPV related OPSCC

A



Number at risk						
Intensity-modulated radiotherapy plus cisplatin	406	372	349	314	222	100
Intensity-modulated radiotherapy plus cetuximab	399	367	334	305	207	106

B

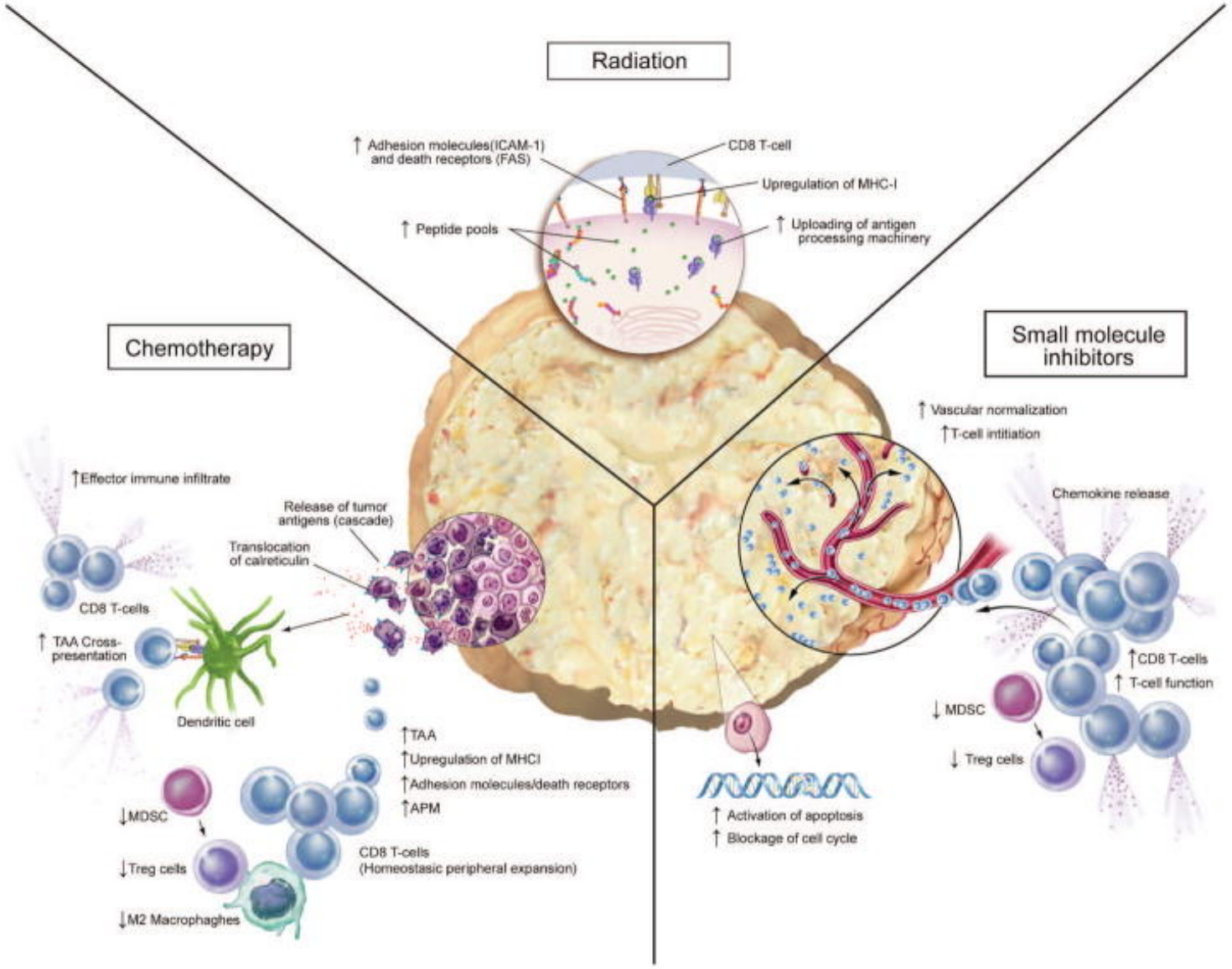


Gillison et al. Lancet 2019

A sobering fact

We have not changed the SOC in LAHNSCC including HPV + disease

Immunogenic Cell Death and Modulation



Hodge JW, et al. *Semin Oncol*. 2012;39(3):323-339.

JAVELIN 100 Trial

Key eligibility criteria:

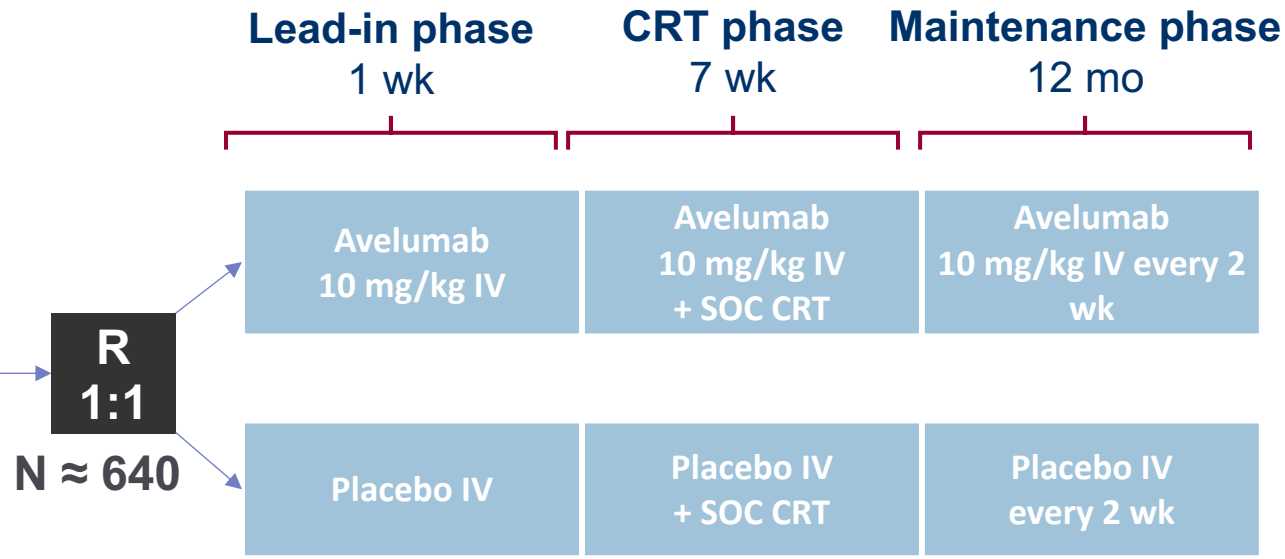
LA SCCHN

High-risk disease

No prior systemic treatment for advanced disease

Candidate for definitive cisplatin-based CRT

HPV positive or negative



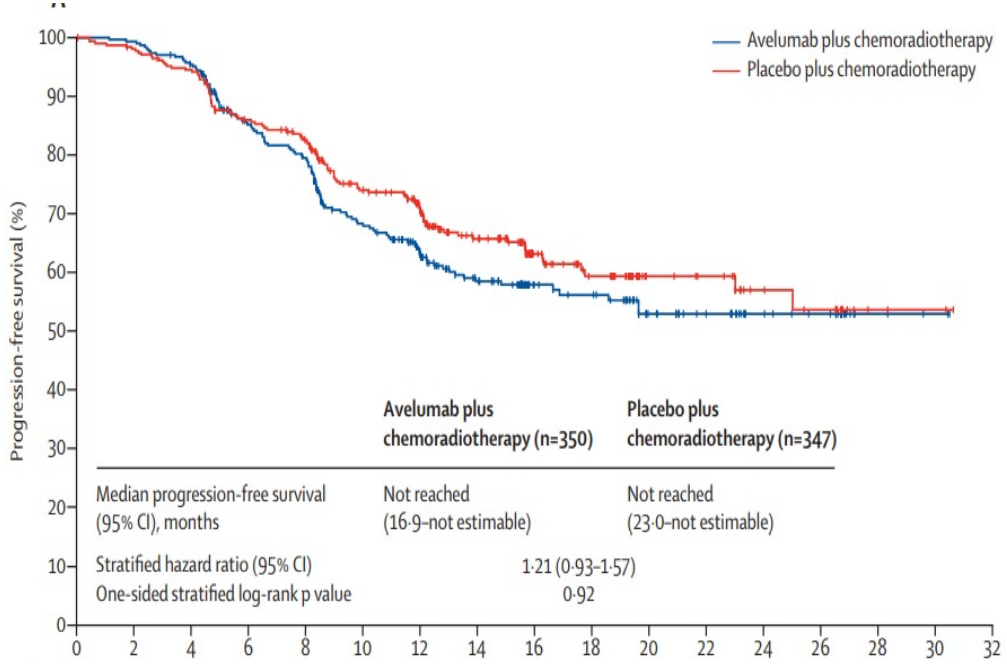
Treatment until:

- Confirmed progression
- Unacceptable toxicity
- Other protocol-specified criterion for withdrawal

- Lee NY, et al. Lancet Oncol. 2021;22:450-462.

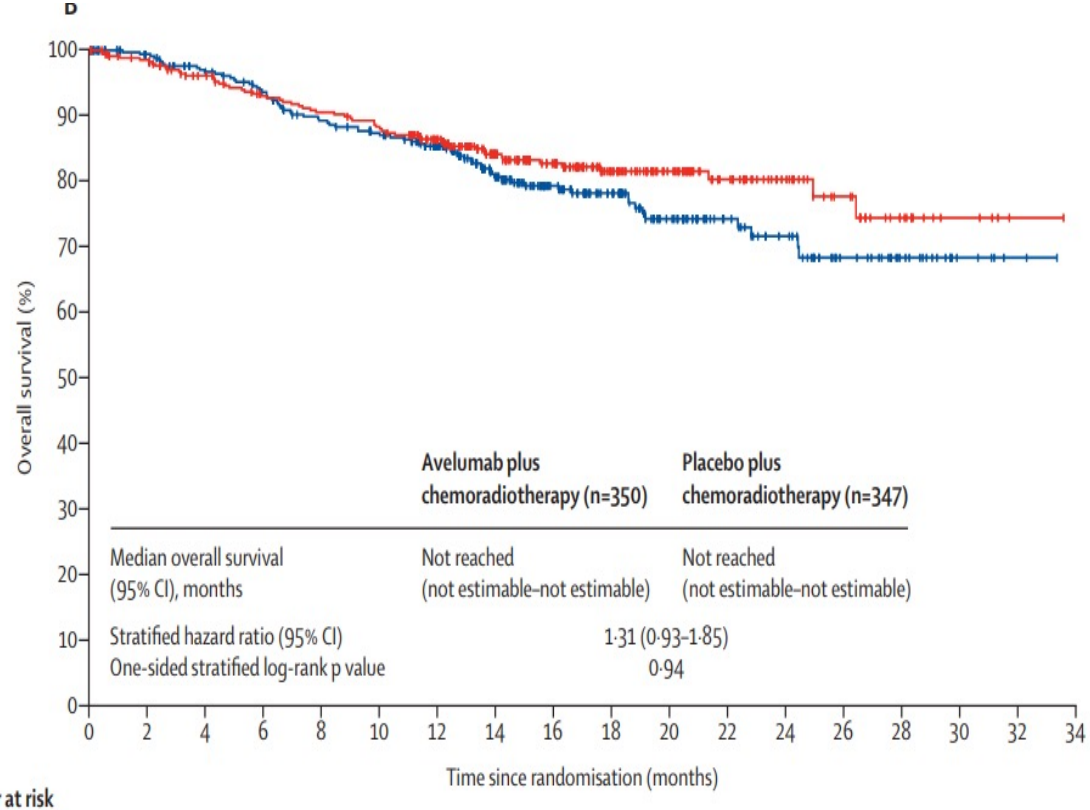
JAVELIN 100: Avelumab + CRT

PFS



Number at risk (number censored)																	
Avelumab plus chemoradiotherapy	350 (0)	303 (45)	289 (47)	239 (67)	222 (68)	176 (84)	143 (105)	107 (131)	69 (168)	63 (172)	41 (191)	33 (199)	22 (210)	18 (214)	4 (228)	2 (230)	0 (232
Placebo plus chemoradiotherapy	347 (0)	303 (38)	291 (39)	257 (47)	241 (53)	200 (70)	172 (90)	121 (130)	75 (172)	56 (187)	31 (212)	28 (215)	18 (224)	15 (226)	3 (238)	2 (239)	0 (241

OS



Number at risk (number censored)																			
Avelumab plus chemoradiotherapy	350 (0)	336 (12)	319 (20)	303 (26)	284 (31)	273 (36)	244 (59)	190 (101)	148 (140)	118 (168)	82 (199)	59 (222)	47 (232)	29 (248)	18 (259)	6 (271)	2 (275)	0 (277)
Placebo plus chemoradiotherapy	347 (0)	334 (8)	315 (19)	298 (26)	290 (26)	282 (27)	252 (51)	193 (104)	160 (134)	115 (177)	86 (206)	58 (233)	39 (252)	26 (264)	13 (276)	5 (284)	1 (288)	0 (289)

- Lee NY, et al. Lancet Oncol. 2021;22:450-46

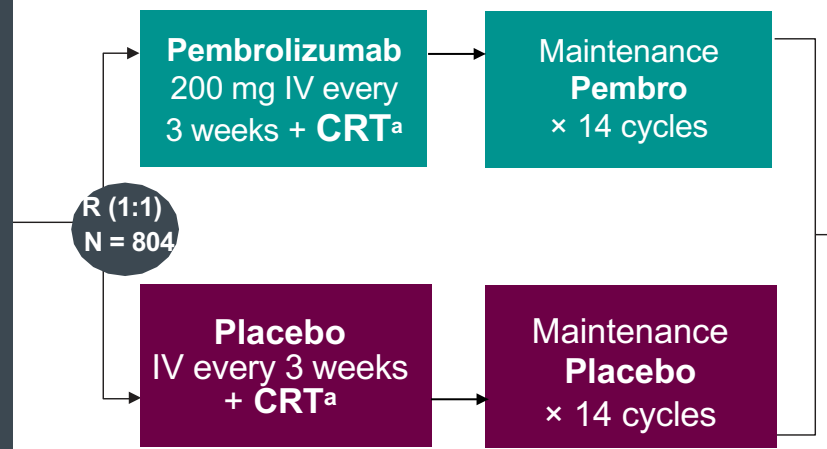
KEYNOTE-412

Patients

- Newly diagnosed, pathologically proven, treatment-naive, unresected LA SCCHN
  - T3-T4 [N0-N3] or any N2a-3 [T1-T4] larynx/hypopharynx/oral cavity/ p16-negative oropharynx cancers
  - T4 or N3 p16-positive oropharynx cancer
- Evaluable tumor burden per RECIST v1.1
- ECOG PS of 0 or 1
- Candidates for definitive high-dose, cisplatin-based CRT

Stratification Factors

- RT regimen (AFX vs SFX)
- Tumor site/p16 status (oropharynx [p16 positive vs p16 negative] or larynx/ hypopharynx/oral cavity)
- Disease stage (III vs IV)



Treatment until

- PD or intolerable toxicity
- 17 cycles of Pembro or placebo[b]
- Investigator's/patient's decision to withdraw

Primary endpoint

- EFS

Secondary endpoints included:

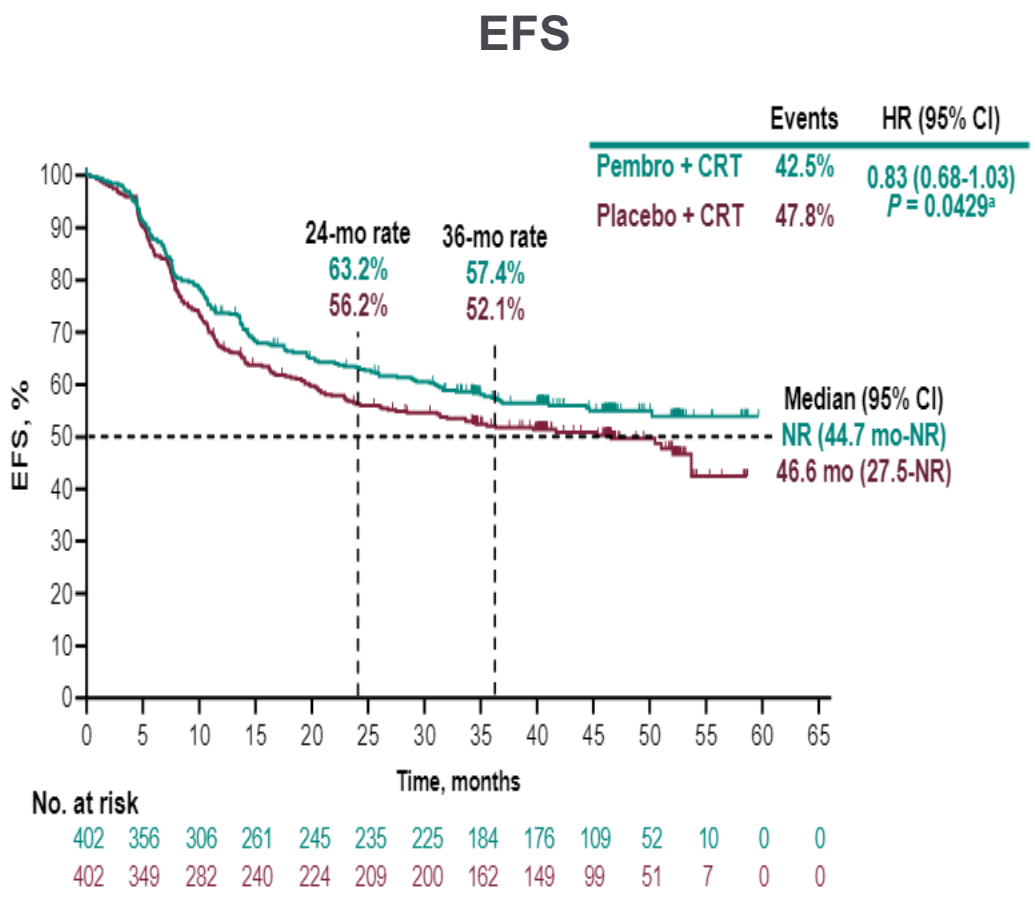
- OS
- Safety/tolerability

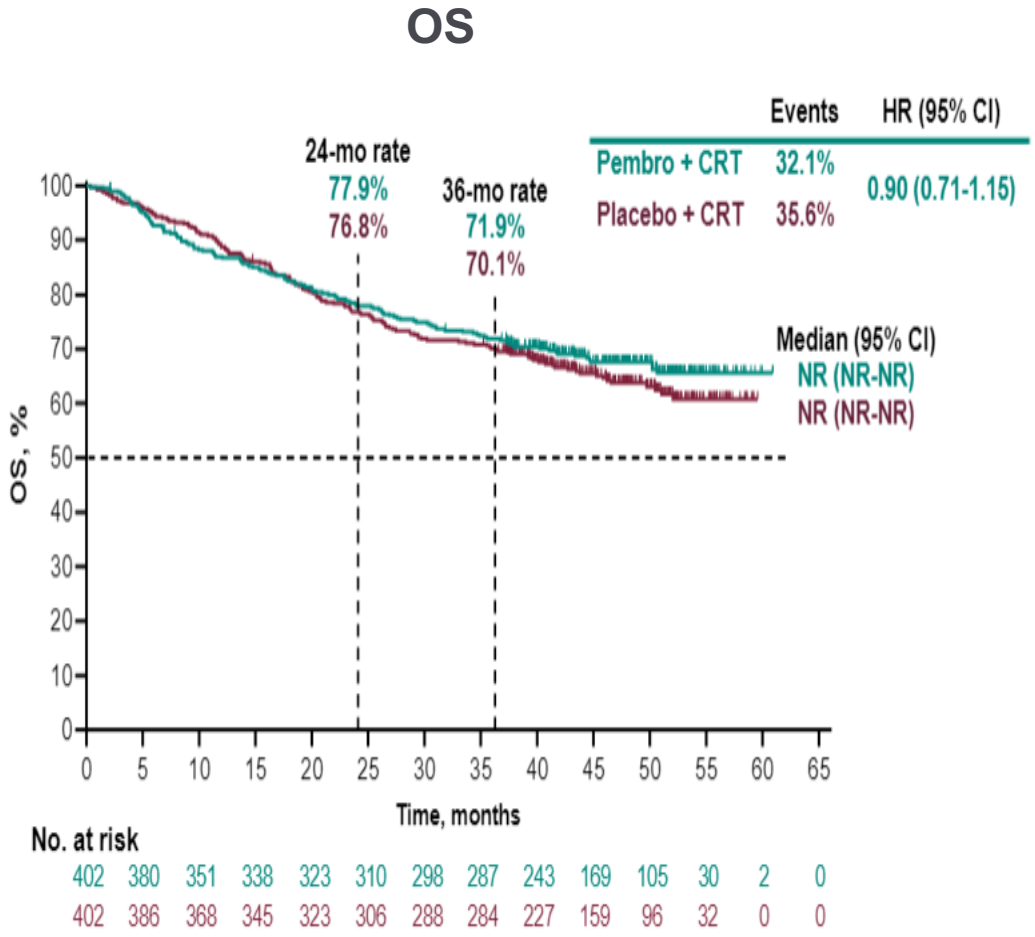
Posttreatment follow-up to assess:

- Safety
- Disease status
- Survival

Machiels JP, Lancet Oncology, 2024

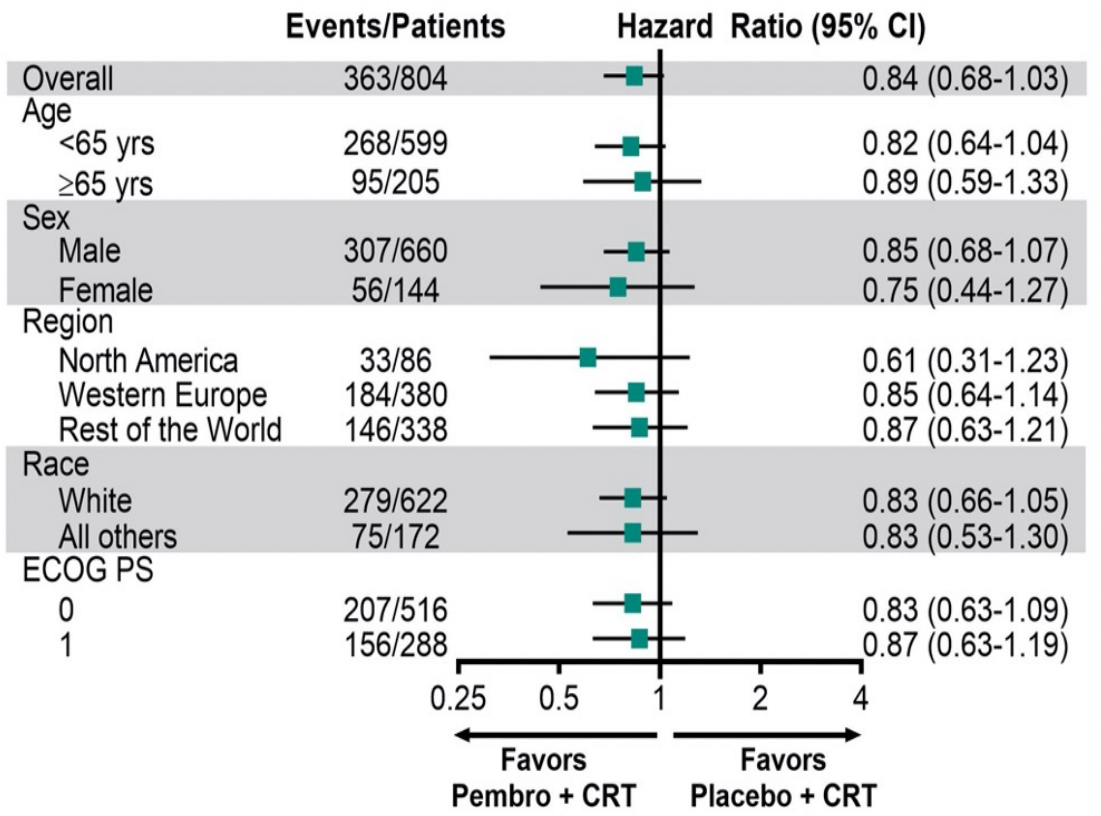
EFS and OS: ITT Population

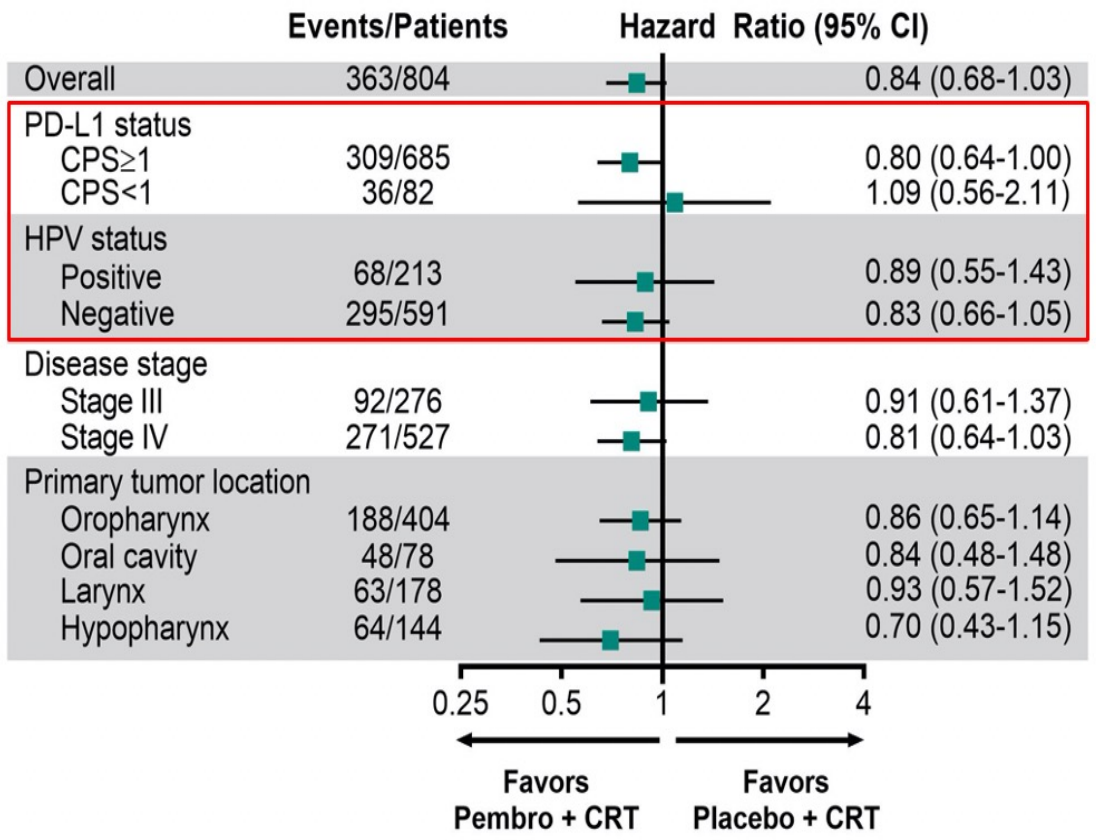




Machiels JP, Lancet Oncology, 2024

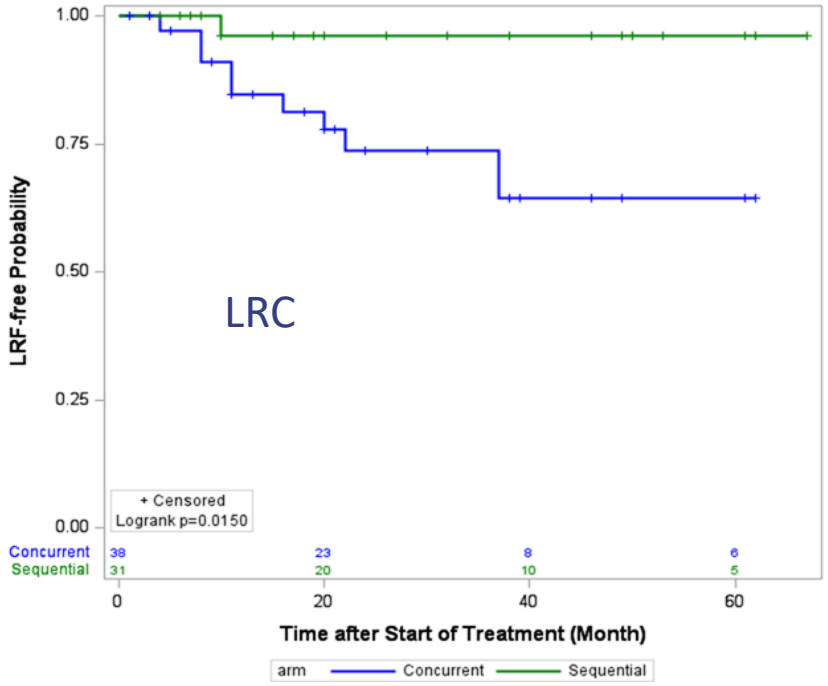
KN-412- EFS, In ITT population

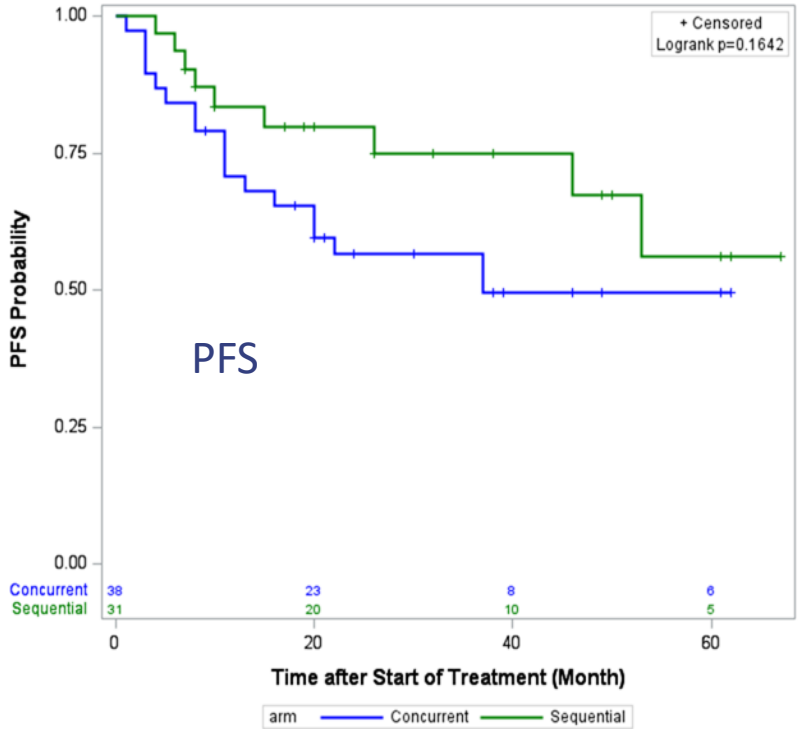


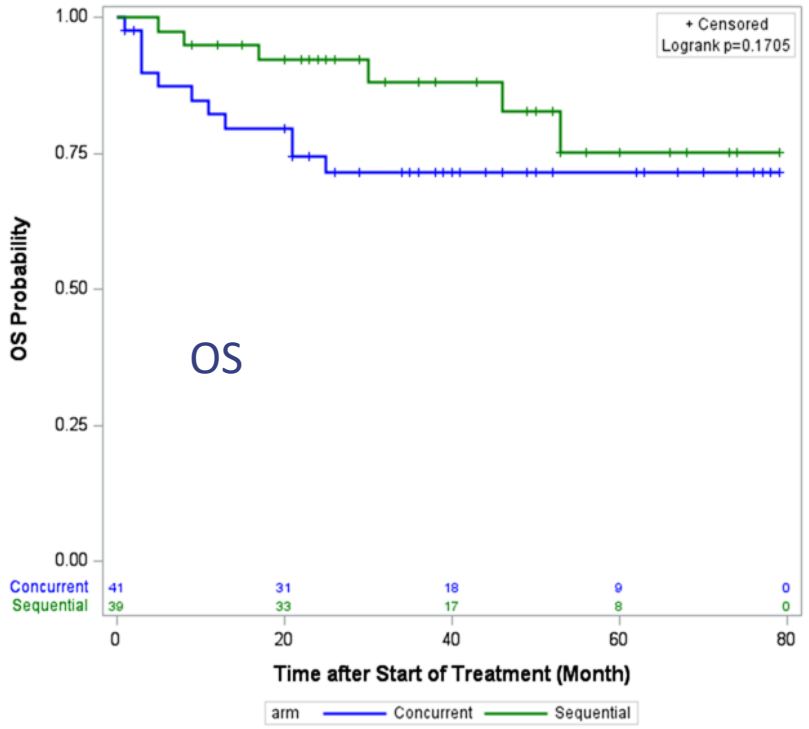


Michaels,JP, ESMO 2022

Concurrent versus Sequential IO ?





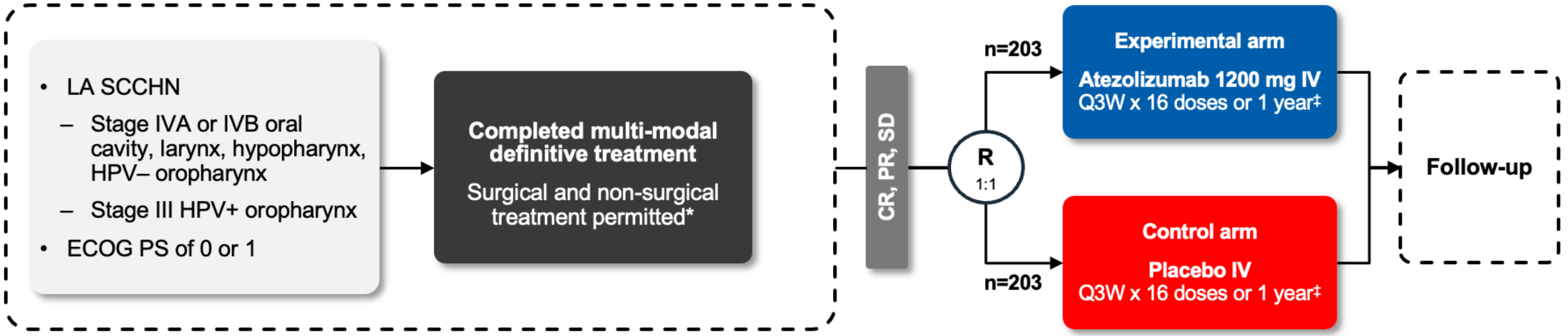


LRC	Concurrent	Sequential	HR (95%CI)	P value
4 Year	64%	95%	0.12 (0.02,0.94)	0.04

		Concurrent	Sequential	HR (95%CI)	P value
PFS	4 Year	49%	67%	0.57 (0.26,1.28)	0.17
OS	4 Year	71%	83%	0.51 (0.19, 1.37)	0.18

Zandberg D, ESMO 23

IMvoke010: a randomized, phase III, global, double-blind, placebo-controlled study



Stratification Factors

- Response to prior multi-modal definitive treatment (CR vs PR or SD)
- Type of prior multi-modal definitive treatment (surgical vs non-surgical)
- HPV status (positive vs negative)

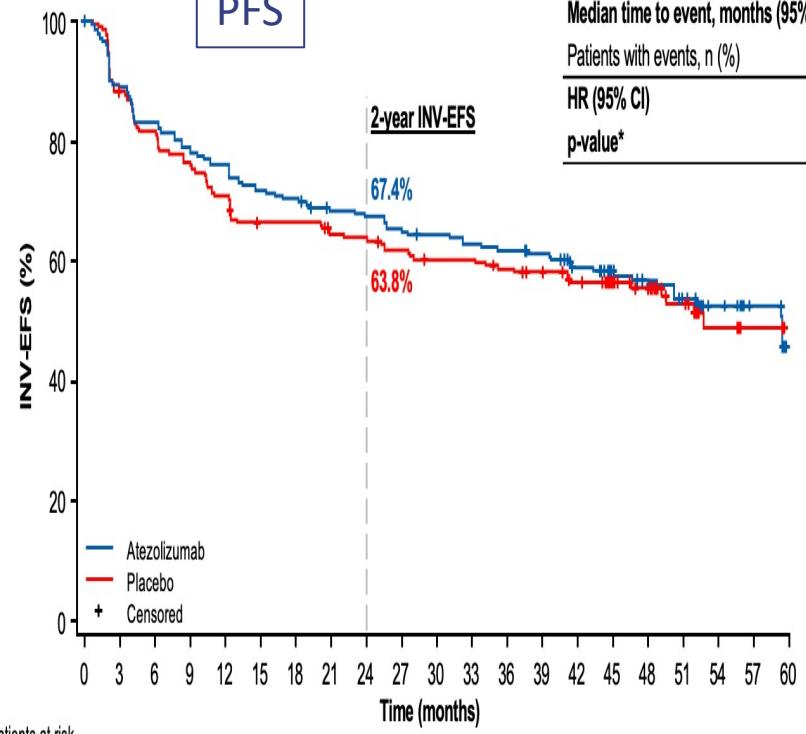
Key Endpoints

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

Wong D, et sl AACR 24

Primary endpoint: investigator assessed PFS

PFS



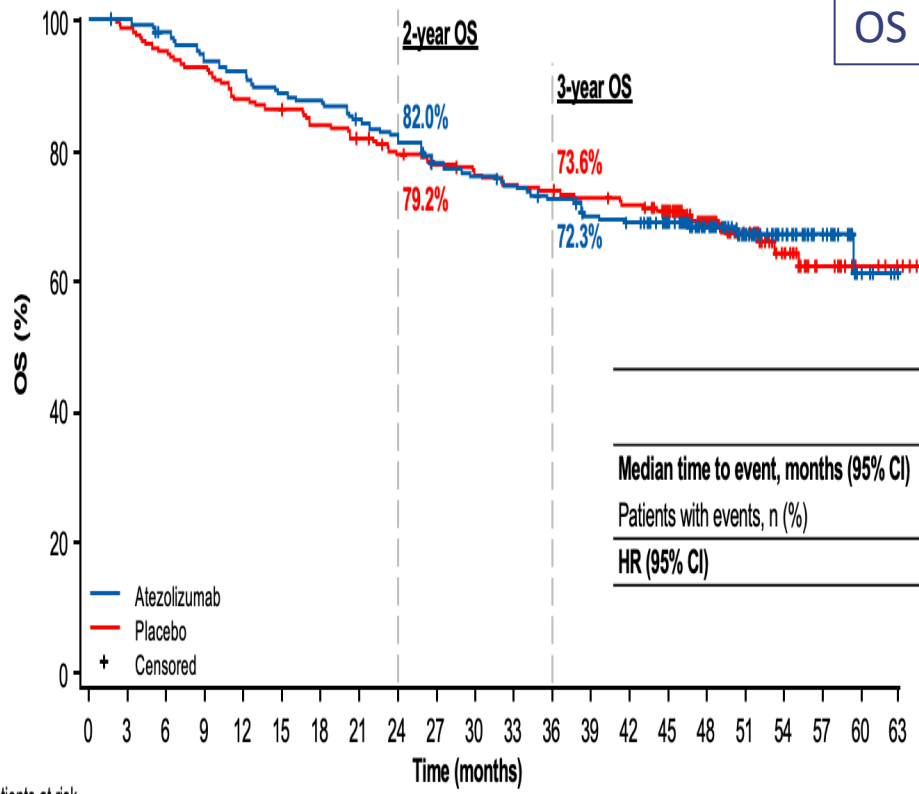
	Atezolizumab (n=203)	Placebo (n=203)
Median time to event, months (95% CI)	59.5 (46.8, NE)	52.7 (41.4, NE)
Patients with events, n (%)	89 (43.8)	92 (45.3)
HR (95% CI)	0.94 (0.70,1.26)	
p-value*	0.680	

No. of patients at risk

Atezolizumab	203	179	165	156	151	143	140	133	131	127	123	120	118	114	101	78	70	45	23	10	0
Placebo	203	178	165	154	143	131	131	125	124	118	114	114	110	107	99	77	64	39	18	7	0

*Alpha boundary: 0.0427
CCOD: 27 Sep 2023. Minimum follow-up: 43 months. Median follow-up: 46.5 months
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; NE, not evaluable

OS



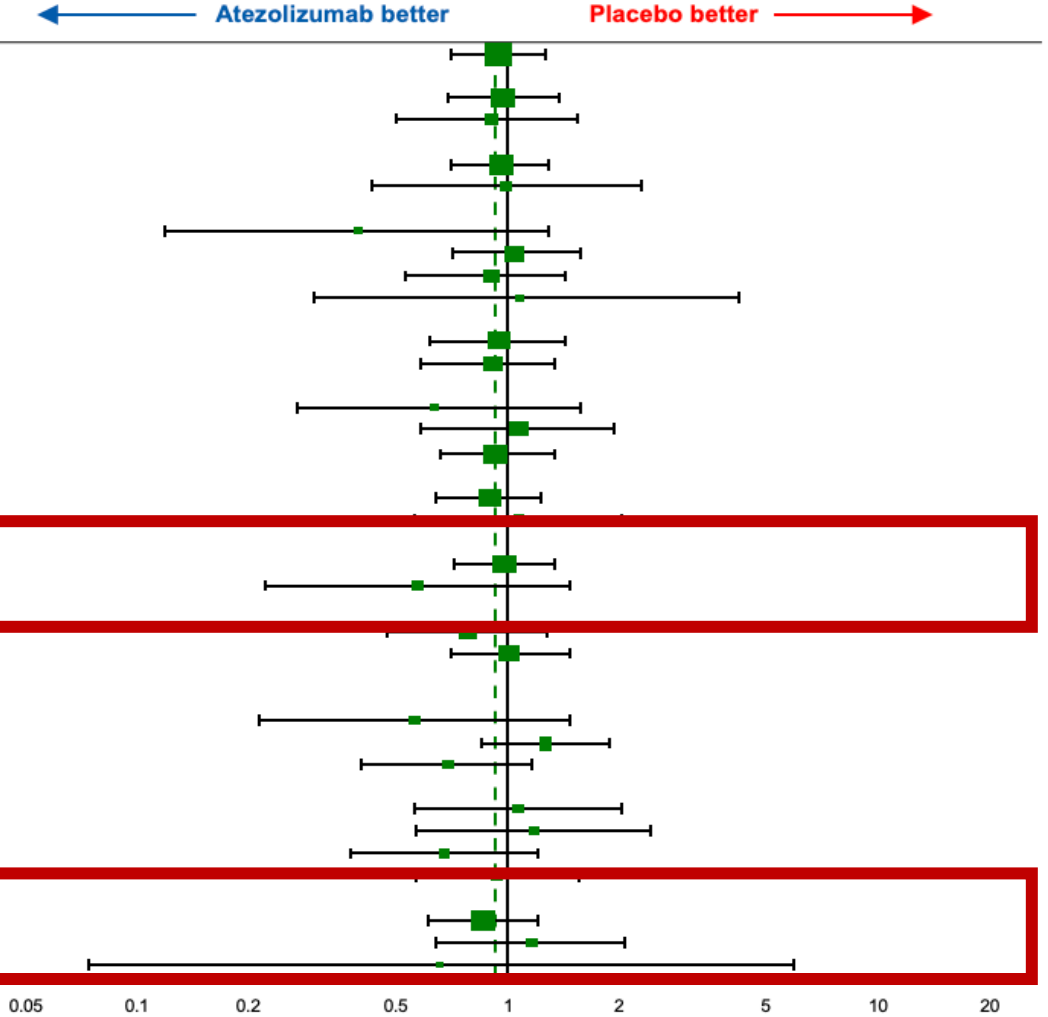
	Atezolizumab (n=203)	Placebo (n=203)
Median time to event, months (95% CI)	NE (59.5, NE)	NE (NE, NE)
Patients with events, n (%)	65 (32.0)	66 (32.5)
HR (95% CI)	0.96 (0.68,1.36)	

No. of patients at risk

Atezolizumab	203	202	196	188	184	177	174	167	163	153	149	145	140	133	130	117	88	65	43	24	6	0
Placebo	203	200	193	188	178	175	169	164	157	152	148	145	143	140	137	124	87	59	38	15	6	3

ImVoke-010 Subgroup analysis

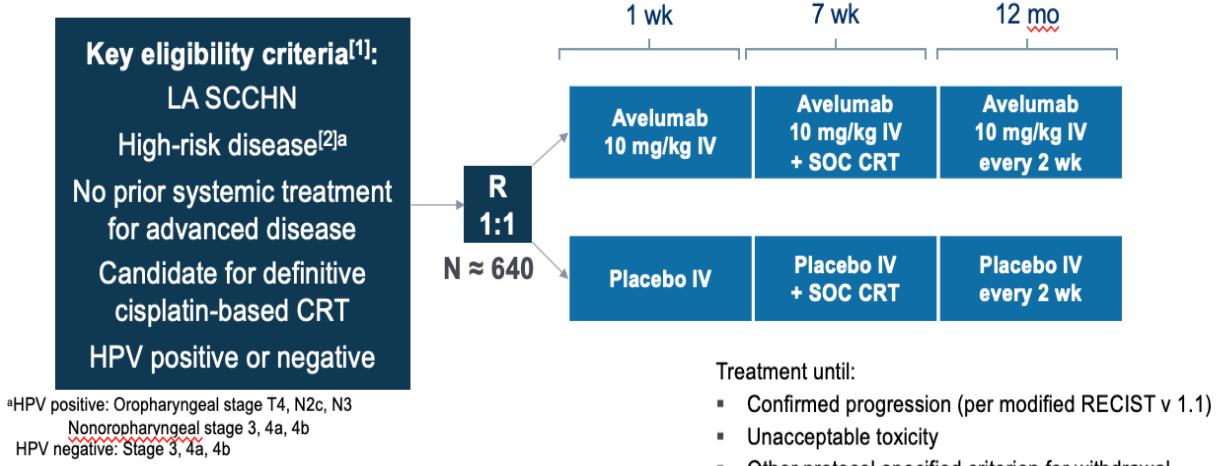
	Total n	Atezolizumab (n=203) n	Events	Median, months	Placebo (n=203) n	Events	Median, months	HR (95%CI)
All patients	406	203	89	59.5	203	92	52.7	0.93 (0.70, 1.25)
Age at randomization								
< 65 years	297	142	62	NE	155	70	52.7	0.96 (0.68, 1.35)
≥ 65 years	109	61	27	59.5	48	22	NE	0.87 (0.49, 1.53)
Sex								
Male	342	168	77	52.2	174	82	52.7	0.94 (0.69, 1.29)
Female	64	35	12	NE	29	10	NE	0.99 (0.43, 2.29)
Region								
North America	31	17	5	NE	14	7	52.7	0.40 (0.12, 1.30)
Europe and Middle East	215	102	48	50.4	113	49	NE	1.07 (0.72, 1.59)
Asia	128	67	31	NE	61	32	41.1	0.89 (0.54, 1.45)
Rest of the world	32	17	5	NE	15	4	NE	1.13 (0.30, 4.20)
Baseline ECOG PS								
0	224	112	45	NE	112	46	NE	0.95 (0.63, 1.44)
1	181	90	43	50.4	91	46	49.5	0.89 (0.59, 1.35)
History of tobacco use (cigarettes and chewing tobacco)								
Never	59	32	10	NE	27	11	NE	0.65 (0.28, 1.54)
Current	80	42	23	41.2	38	20	41.4	1.08 (0.59, 1.96)
Previous	267	129	56	59.5	138	61	NE	0.95 (0.66, 1.37)
Response to prior multi-modal definitive treatment								
CR	342	170	69	59.5	172	74	NE	0.90 (0.64, 1.24)
HPV status								
Negative	335	168	82	50.2	167	81	49.5	0.99 (0.73, 1.35)
Positive	71	35	7	NE	36	11	NE	0.58 (0.22, 1.49)
Type of multi-modal definitive treatment received								
No primary surgery	250	124	60	52.2	126	58	51.9	1.03 (0.72, 1.48)
Staging at diagnosis								
Stage I HPV+ oropharynx	1	0	–	–	1	0	NE	NE (NE, NE)
Stage III HPV+ oropharynx	70	35	7	NE	35	11	NE	0.56 (0.22, 1.46)
Stage IVA oral cavity, larynx, hypopharynx, HPV– oropharynx	231	121	59	52.2	110	44	NE	1.26 (0.85, 1.86)
Stage IVB oral cavity, larynx, hypopharynx, HPV– oropharynx	104	47	23	50.2	57	37	20.2	0.69 (0.41, 1.16)
Site of primary tumor								
Hypopharynx	76	45	23	46.8	31	16	51.9	1.07 (0.56, 2.03)
Larynx	70	33	16	59.5	37	15	NE	1.17 (0.57, 2.39)
Oral cavity	111	54	20	NE	57	29	52.7	0.68 (0.38, 1.20)
PD-L1 status by SP263								
TAP ≥ 5%	315	153	60	59.5	162	71	NE	0.86 (0.61, 1.22)
TAP < 5%	78	39	24	39.7	39	20	36.7	1.16 (0.64, 2.09)
Unknown	13	11	5	52.2	2	1	NE	0.66 (0.07, 6.01)



Wong D, AACR 24

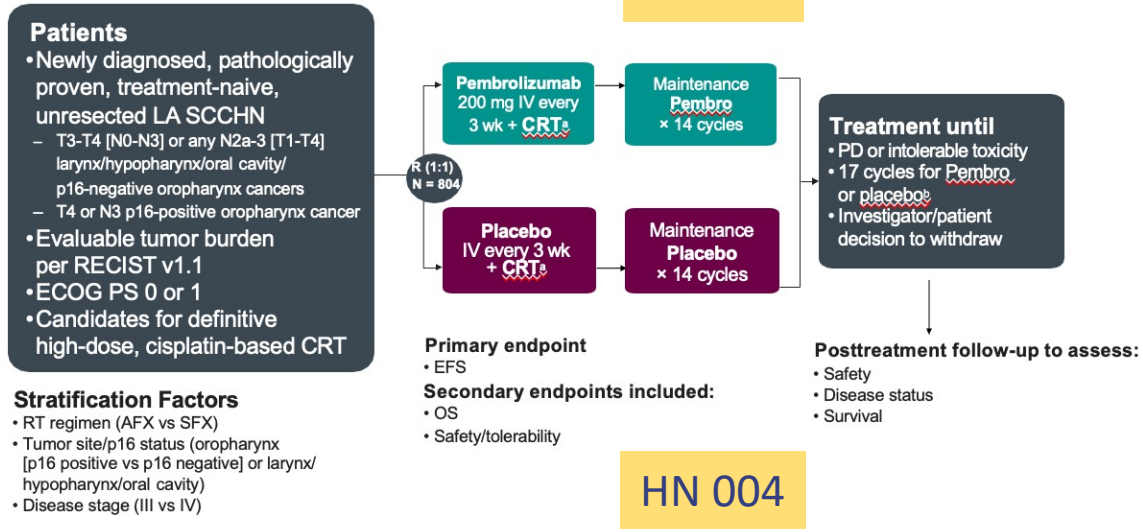
NEGATIVE Randomized Trials of Immunotherapy given in the definitive setting

Javelin

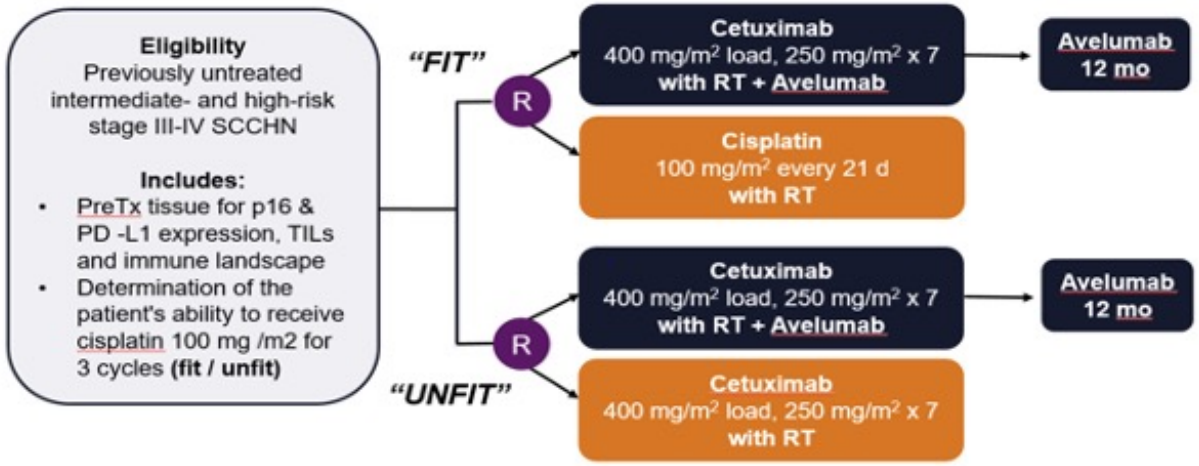


[a]HPV positive: Oropharyngeal stage T4, N2c, N3
Nonoropharyngeal stage 3, 4a, 4b
HPV negative: Stage 3, 4a, 4b

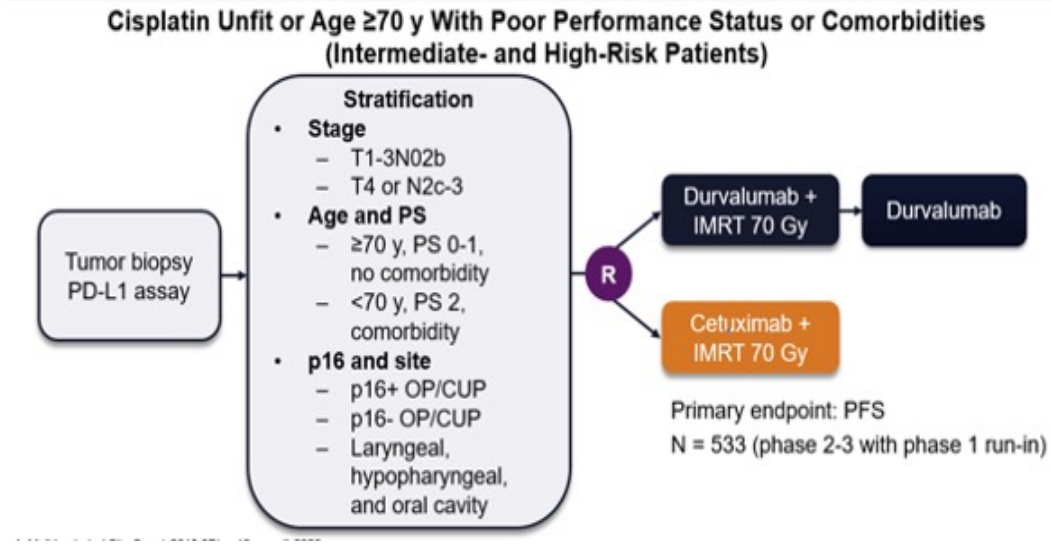
KN412



GORTEC- REACH



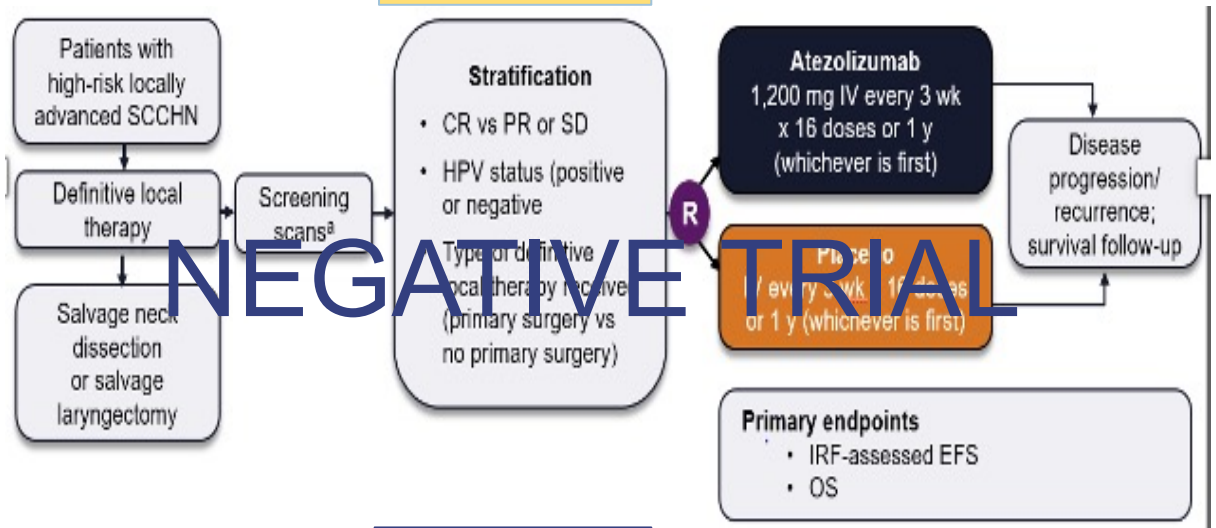
HN 004



1. Bourhis J, et al. ESMO Virtual Congress 2021. LBA35.

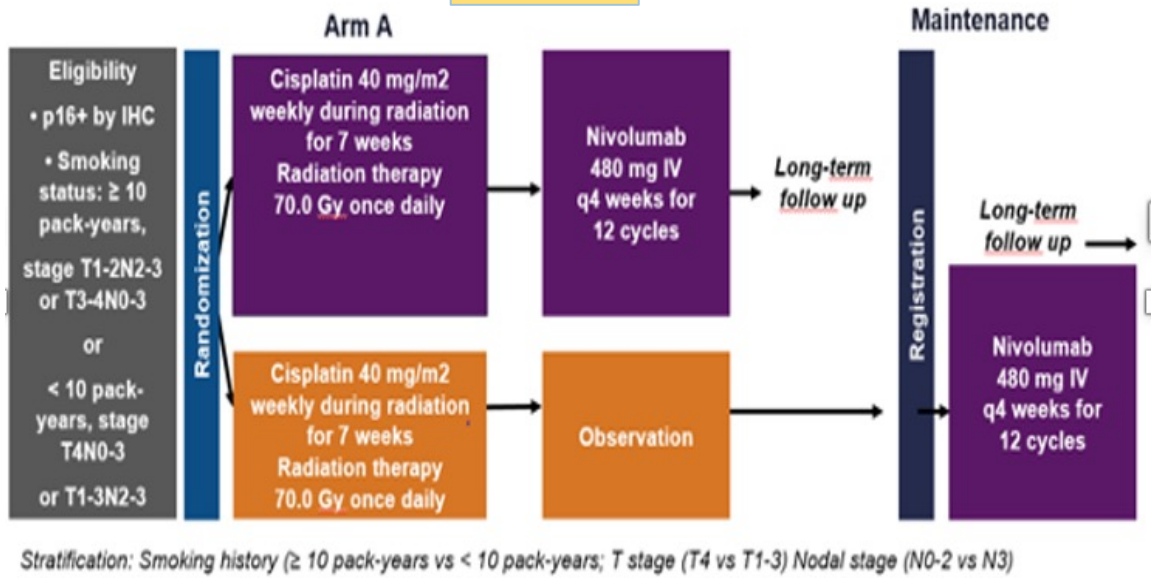
Ongoing Randomized Trials of Immunotherapy given during and/or after CRT or RT

Invoke Trial

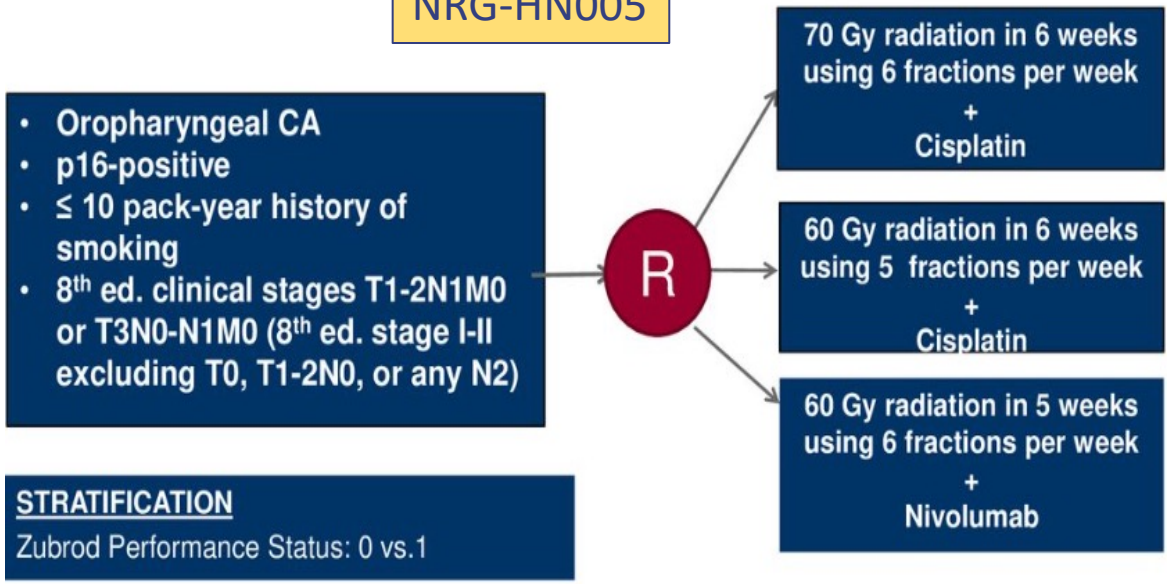


NEGATIVE TRIAL

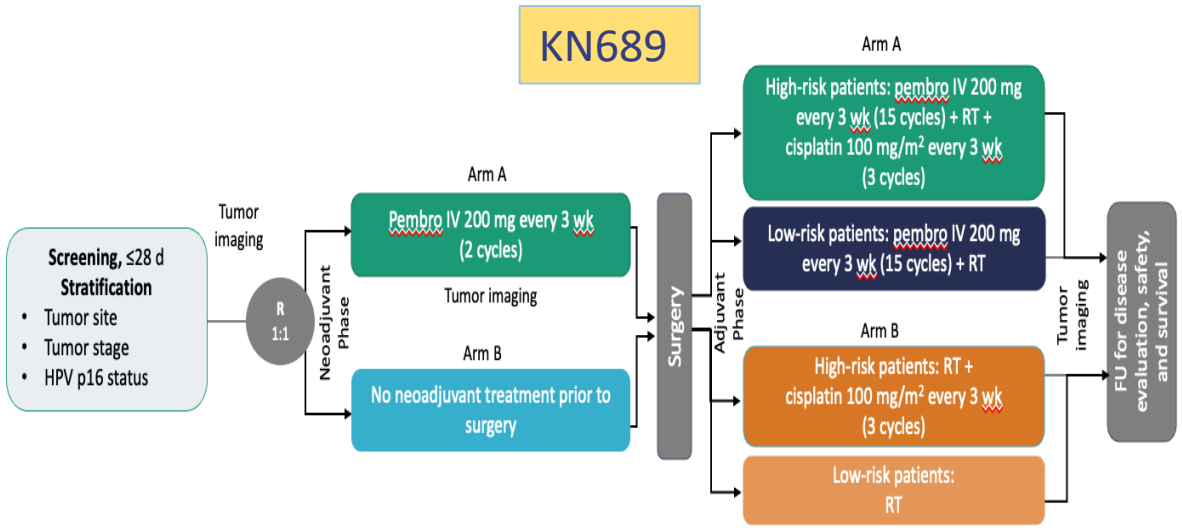
EA3161



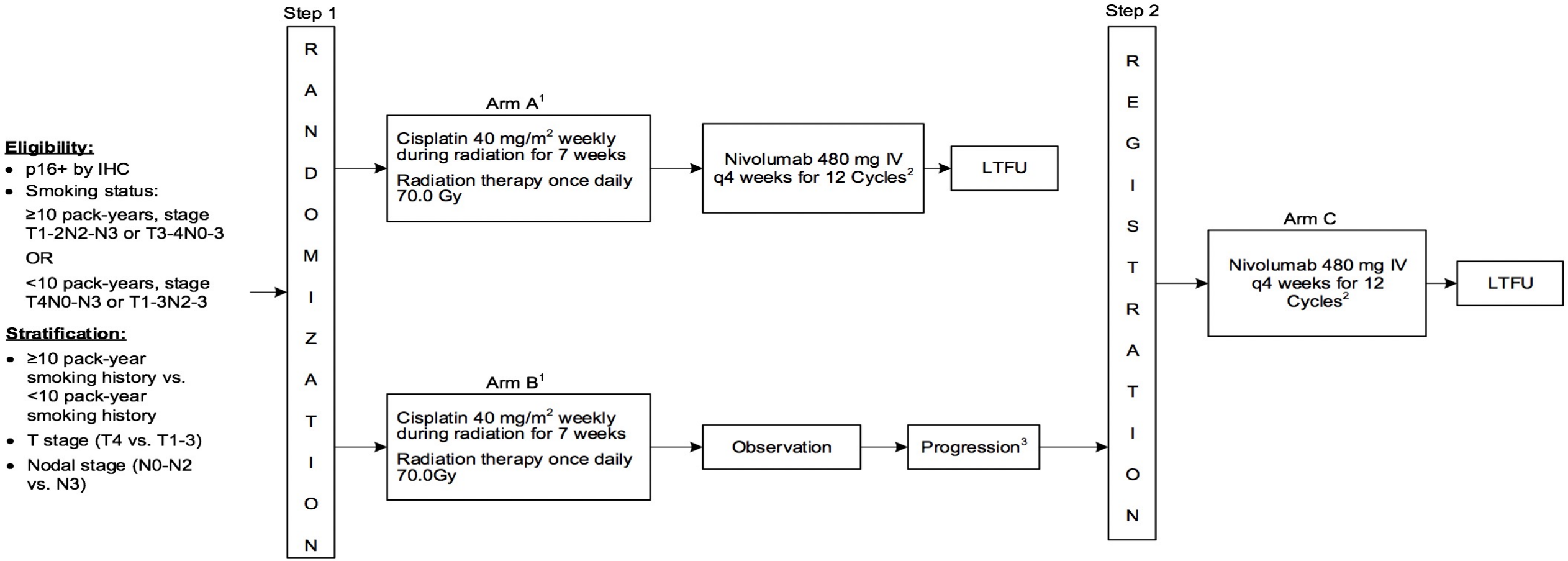
NRG-HN005



KN689



EA3161: Maintenance Nivolumab in HPV related OPSCC with IR group



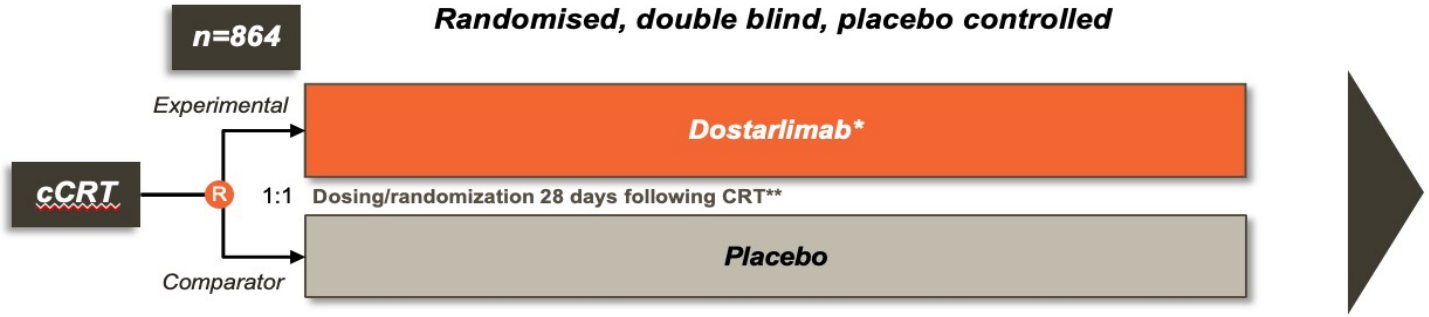
Accrual Goal: 636

1. Submit tissue for PD-L1 testing.
2. Cycle length = 28 days
3. Patients who were randomized to observation will be offered the option to cross over if they have clearly documented progression by the RECIST criteria and tissue-proven progression within 12 months from the end of cisplatin/radiation therapy.

Phase 3 Study of Dostarlimab as Sequential Therapy after Chemoradiation in Locally Advanced Unresected Head and Neck Squamous Cell Carcinoma (JADE)

Population

- Newly diagnosed unresected locally advanced HNSCC
- CPS ≥1 by 22C3
- Treatment naive
- Candidate for definitive cisplatin-based CRT



***Participants receive dostarlimab 500 mg Q3W for 4 cycles, then 1000 mg Q6W or placebo every 6 weeks until PD for approximately 12 months**

****Screening period is 28 days and may be extended to 42 days to allow resolution of CRT-related toxicities following discussion with the Medical Monitor.** Randomization is to occur 28 to 35 days after the end of CRT but may be delayed up to 42 days post-CRT*

Primary Endpoint

EFS per BICR

Key Secondary Endpoint

Overall Survival

Other Secondary Endpoints

EFS per INV, Safety, PK/Immunogenicity

Stratification Factors:

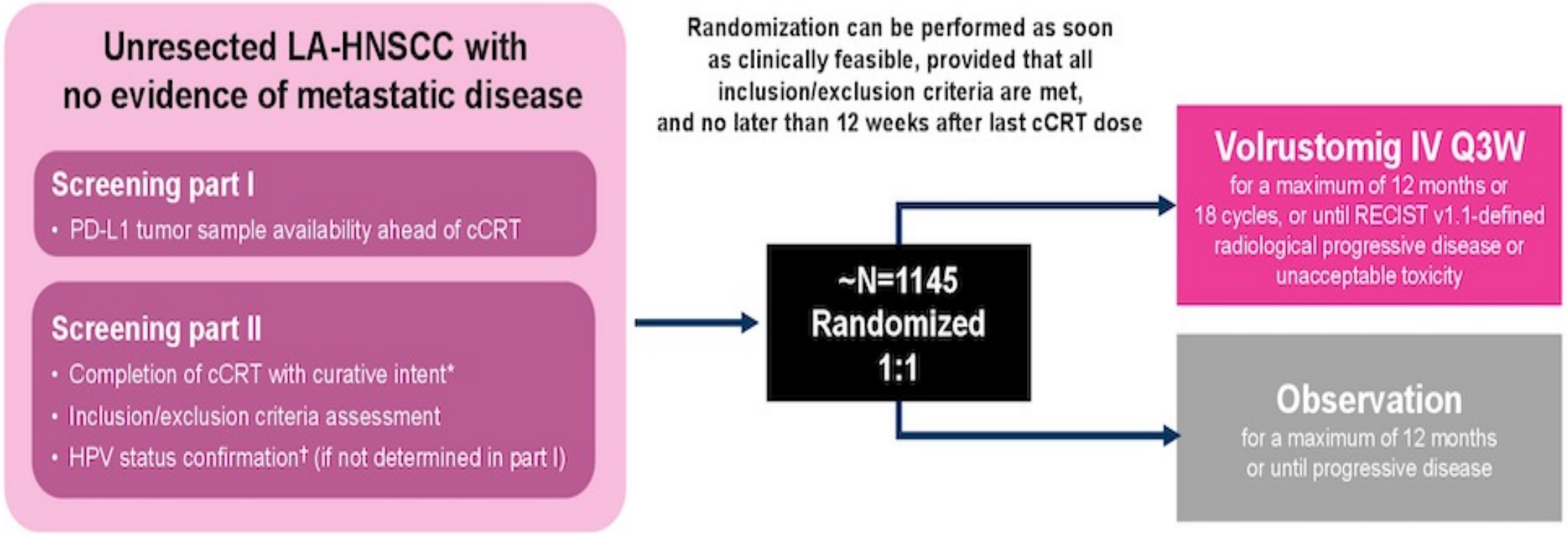
- **Tumor site/p16 status**
- **Cisplatin 40 mg/m² weekly (low dose) vs 100 mg/m² every 3 weeks (high dose)**
- **CPS status (1-19 or ≥20)**

Primary End-Point EFS Definition:

- **First record of locoregional progression or recurrence, or distant metastasis per RECIST 1.1 (BICR)**
- **Salvage surgery at the primary tumour site when invasive cancer is present**
- **Neck dissection performed >20 weeks after completion of CRT when invasive cancer is present**
- **Death due to any cause**

3QW, 3 weekly, 6QW, 6 weekly, BICR, blinded independent central review, CPS, clinical prognostic score, cCRT, concurrent chemoradiotherapy, EFS, event-free survival, HNSCC, head and neck squamous cell carcinoma, INV, investigator, OS, overall survival, PK, pharmacokinetics

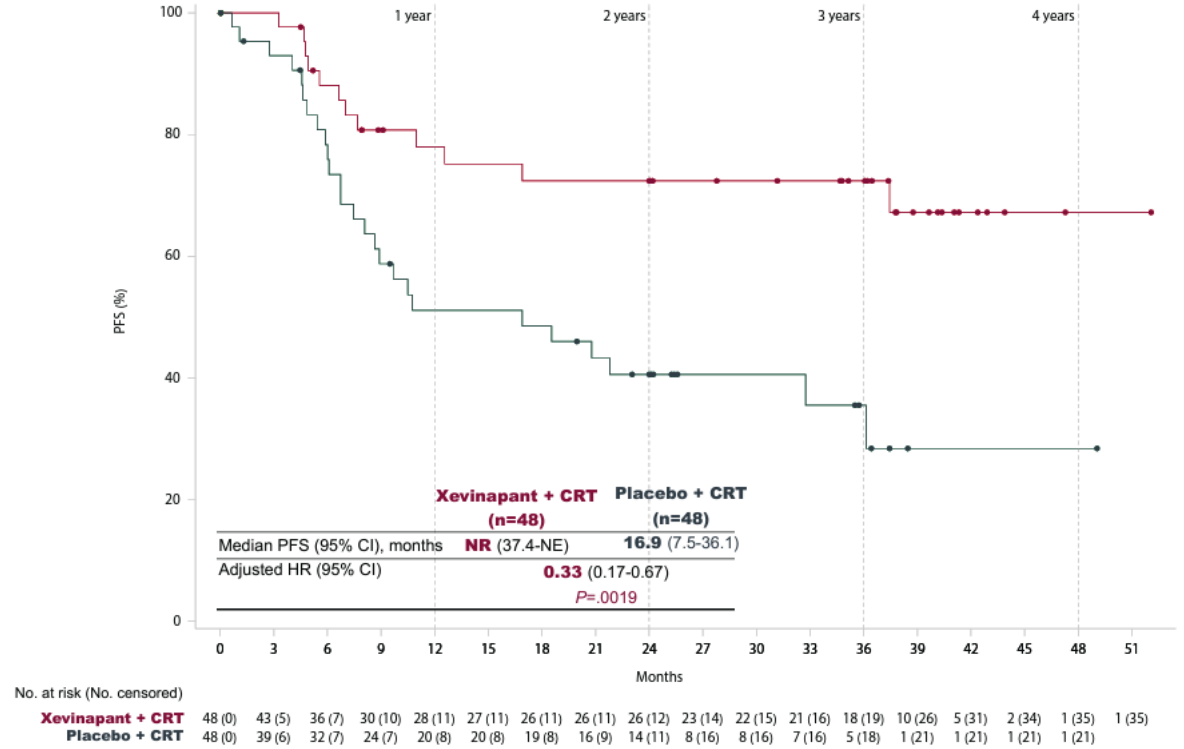
eVOLVE-HNSCC: Phase 3 trial of volrustomig as sequential therapy with LAHNSCC



ASCO 2024, HNCA poster presentation,

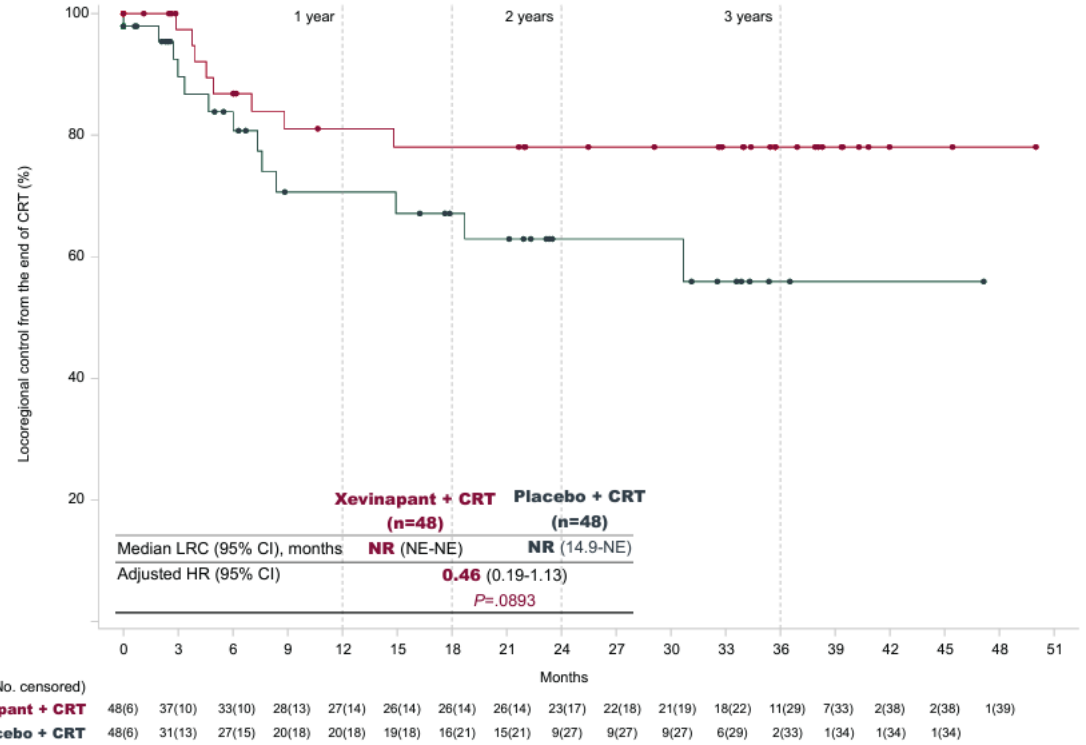
Xevinapant ; Phase II randomized trial

PFS[1]



	Xevinapant + CRT (n = 48)	Placebo + CRT (n = 48)
Median PFS (95% CI), months	NR (37.4, NE)	16.9 (7.5, 36.1)
Adjusted HR (95% CI)	0.33 (0.17, 0.67) *P* = .0019	

LRC

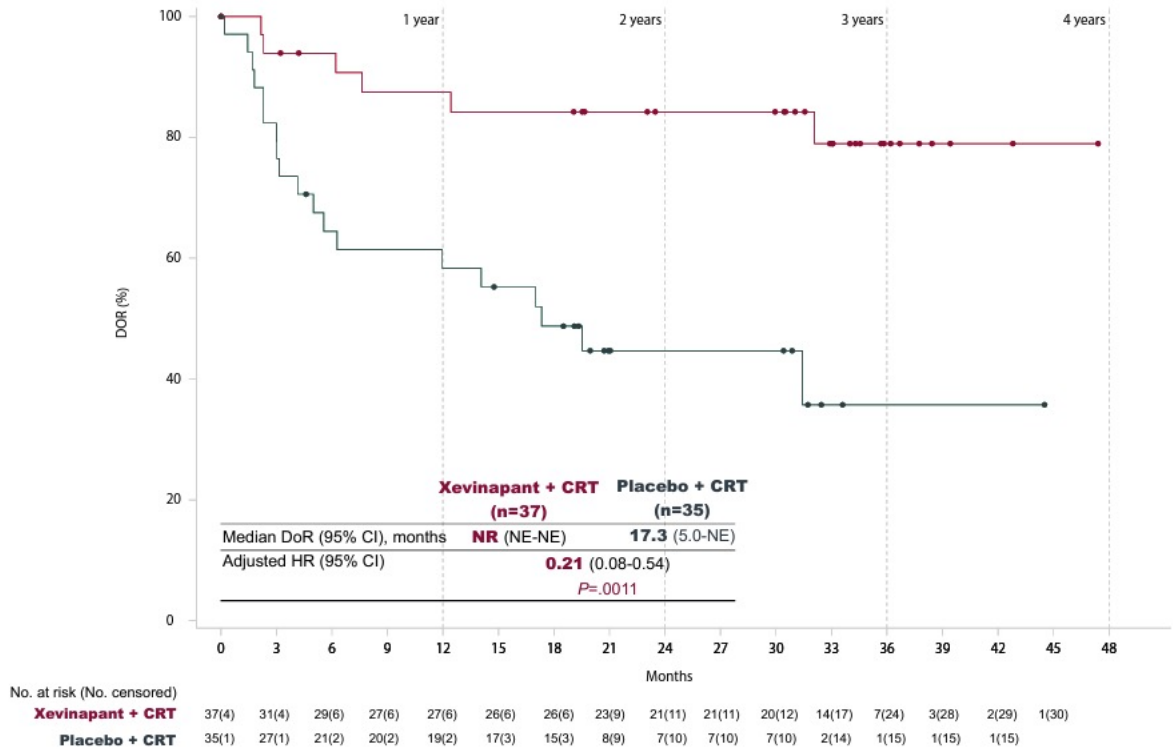


	Xevinapant + CRT (n = 48)	Placebo + CRT (n = 48)
Median LRC (95% CI), months	NR (NE, NE)	NR (14.9, NE)
Adjusted HR (95% CI)	0.46 (0.19, 1.13) *P* = .0893	

- NE, not estimable.
- 1. Bourhis J, et al. Ann Oncol. 2022:3

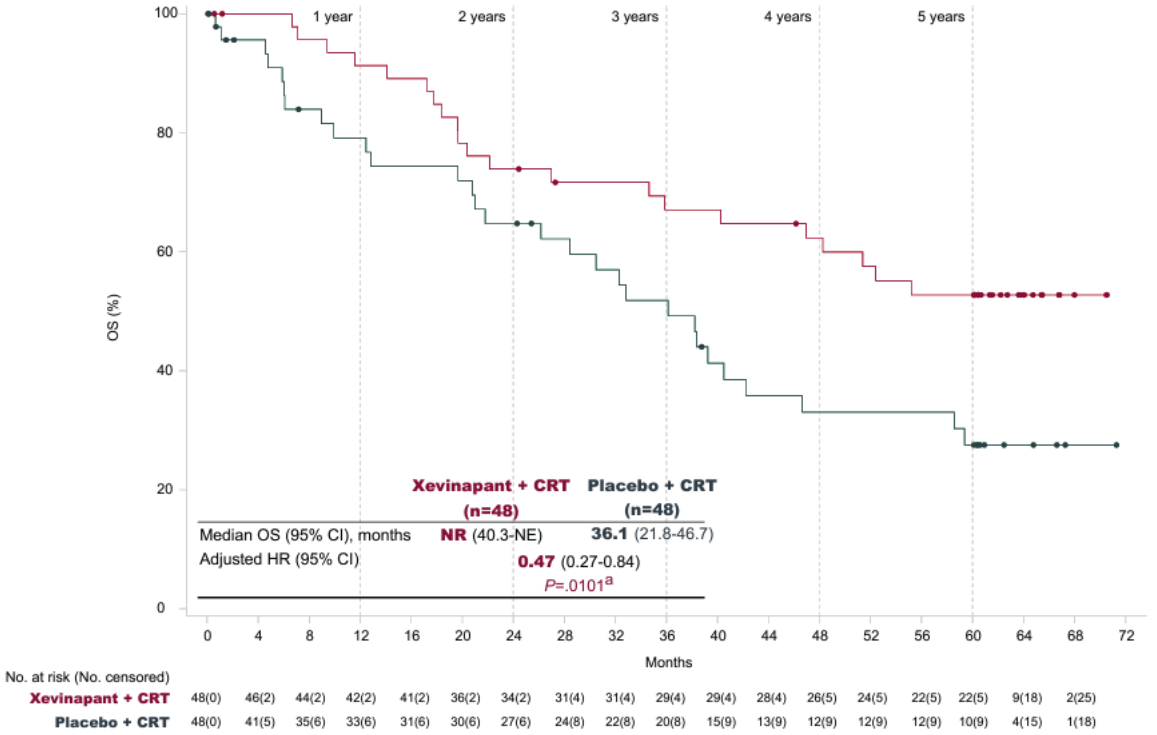
DOR and OS: Phase II trial Xevinapant

DoR



	Xevinapant + CRT (n = 37)	Placebo + CRT (n = 35)
Median DoR (95% CI), months	NR (NE, NE)	17.3 (5.0, NE)
Adjusted HR (95% CI)	0.21 (0.08, 0.54) *P* = .0011	

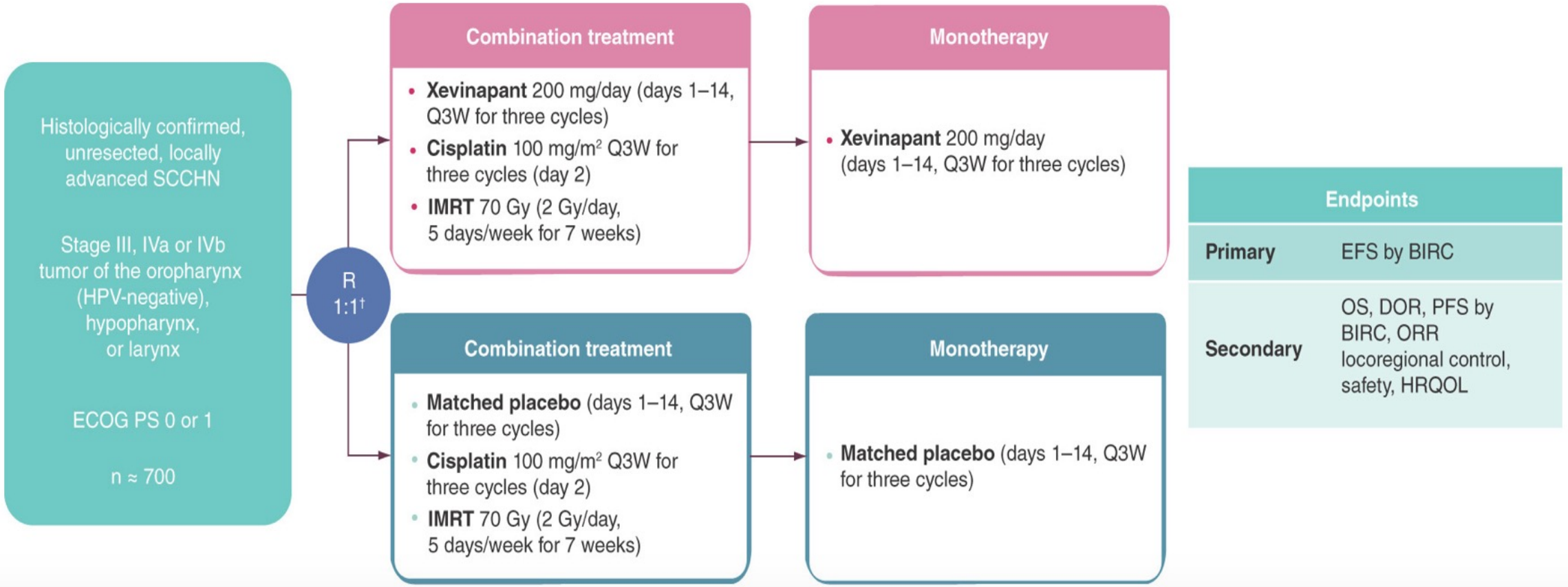
OS



	Xevinapant + CRT (n = 48)	Placebo + CRT (n = 48)
Median OS (95% CI), months	NR (40.3, NE)	36.1 (21.8, 46.7)
Adjusted HR (95% CI)	0.47 (0.27, 0.84) *P* = .0101	

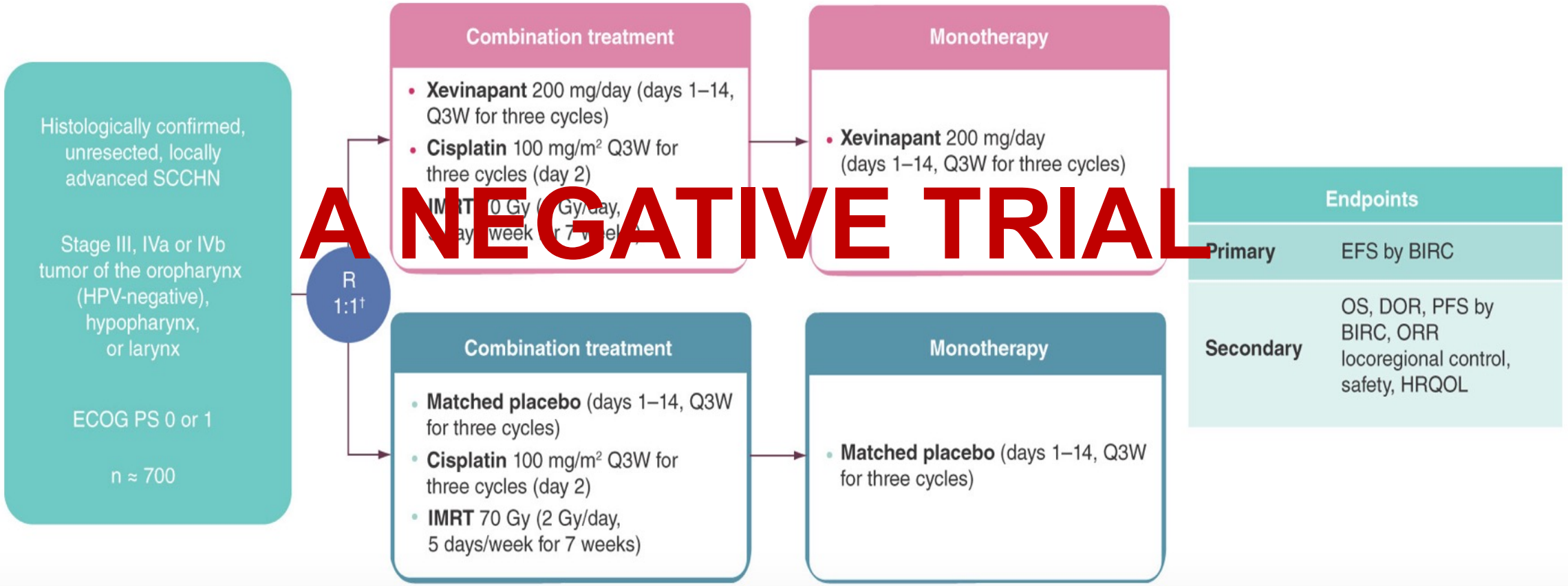
- Bourhis J, et al. Ann Oncol. 2022:3

Xevinapant or placebo plus chemoradiotherapy in locally advanced squamous cell carcinoma of the head and neck: TrilynX phase III study design



https://clinicaltrials.gov/study/NCT04459715

Xevinapant or placebo plus chemoradiotherapy in locally advanced squamous cell carcinoma of the head and neck: TrilynX phase III study design



A NEGATIVE TRIAL

Xevinapant in LA SCCHN

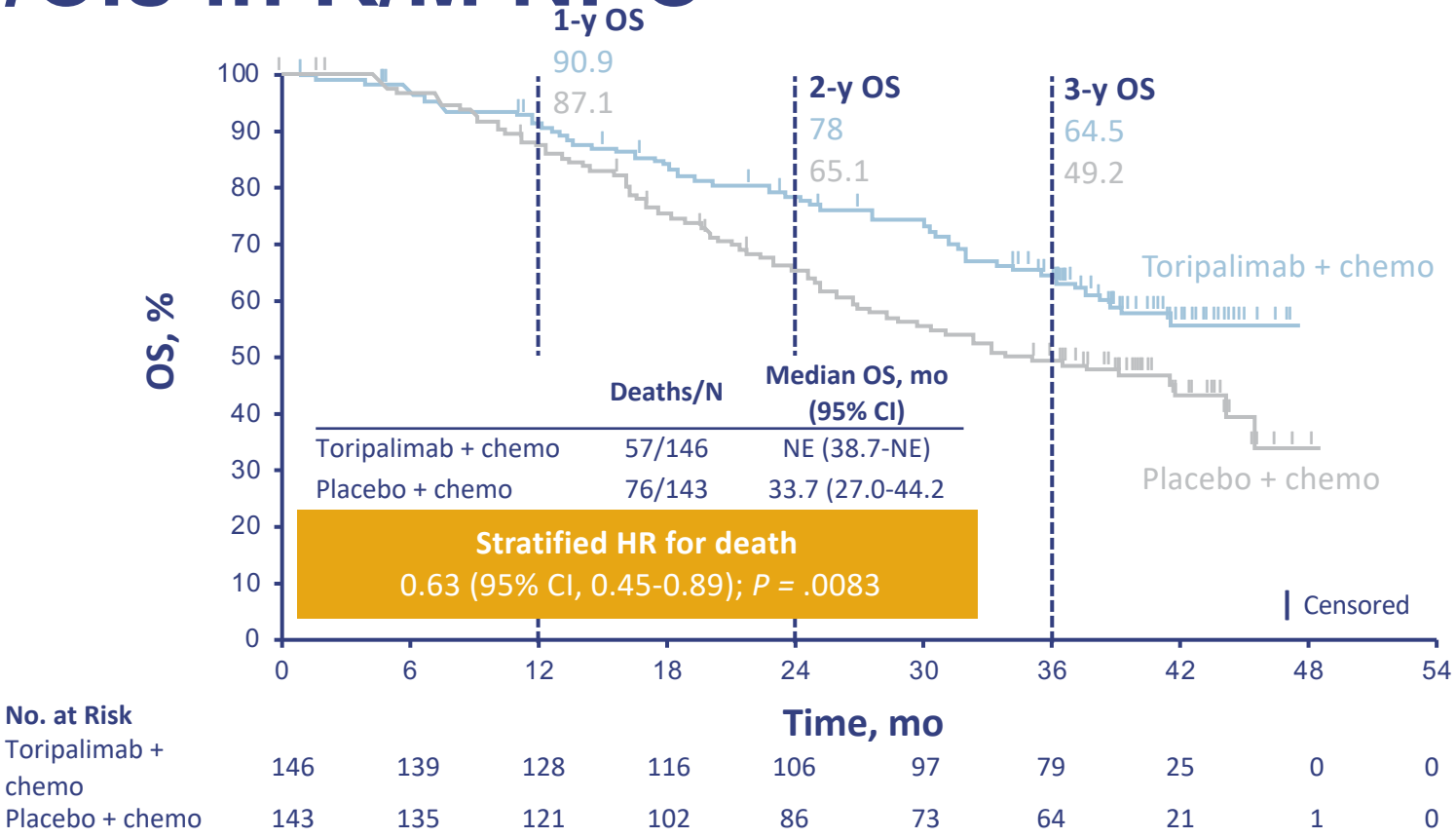
Study Name	Phase	NCT Number	Enrollment	Estimated Completion	Primary Endpoint(s)
Phase 3 Xevinapant and Radiotherapy in Resected LA SCCHN, High-Risk, Cisplatin-Ineligible Participants (XRAY VISION)	3	NCT05386550	700 (Estimated)	12/16/2030	▪ DFS
Phase 1b Safety Study of Xevinapant, Weekly Cisplatin, and RT in Participants With Unresected LA SCCHN (HyperlynX)	1	NCT06056310	40 (Estimated)	4/16/2025	▪ Number of participants with dose-limiting toxicity (DLT)-like events

DISCONTINUED

NPC- A story of Immunotherapy success in LAD

JUPITER-02: OS Analysis Confirms Efficacy of Toripalimab + Gem/Cis in R/M NPC[1]

- Median follow up: 30.1 months
- Significant improvement in OS for the toripalimab arm over the placebo arm
  - HR = 0.63; *P* = .0083
- Median OS was not reached in the toripalimab arm and was 33.7 months in the placebo arm

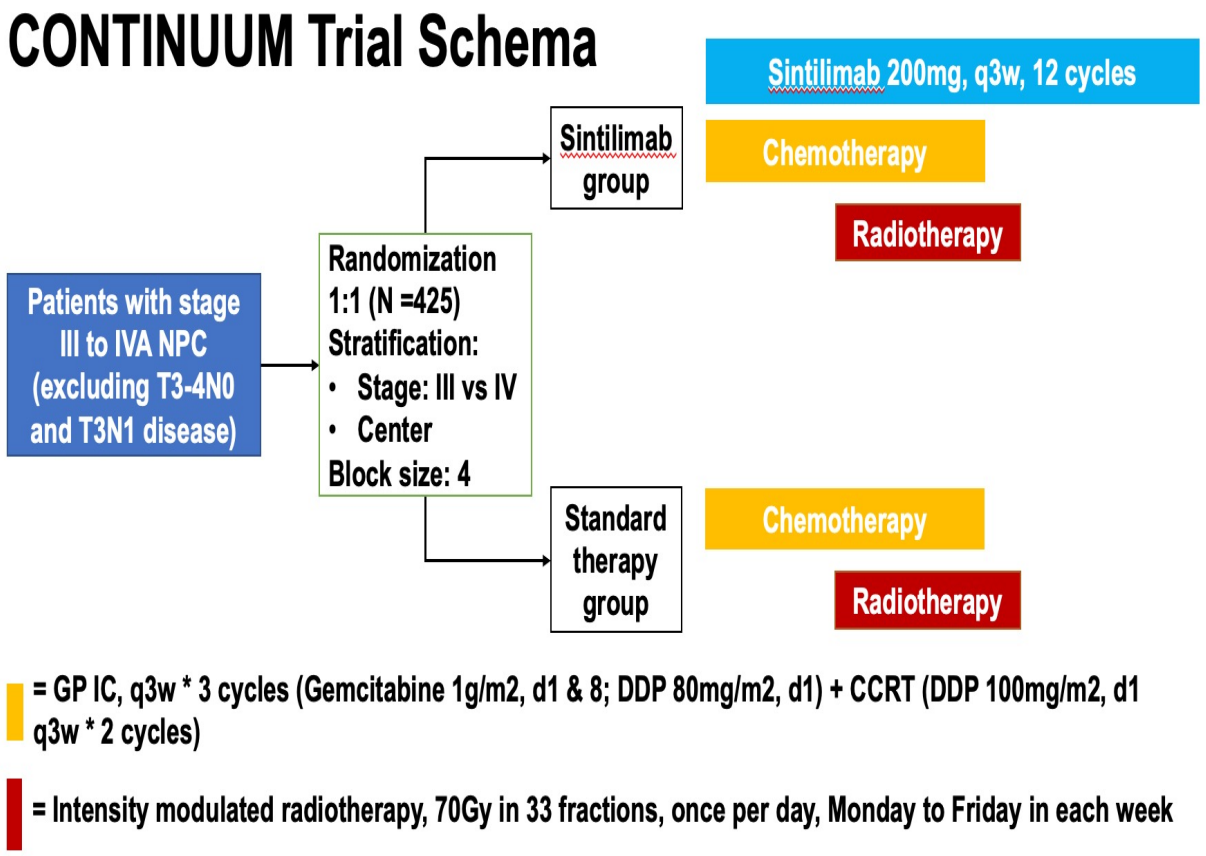


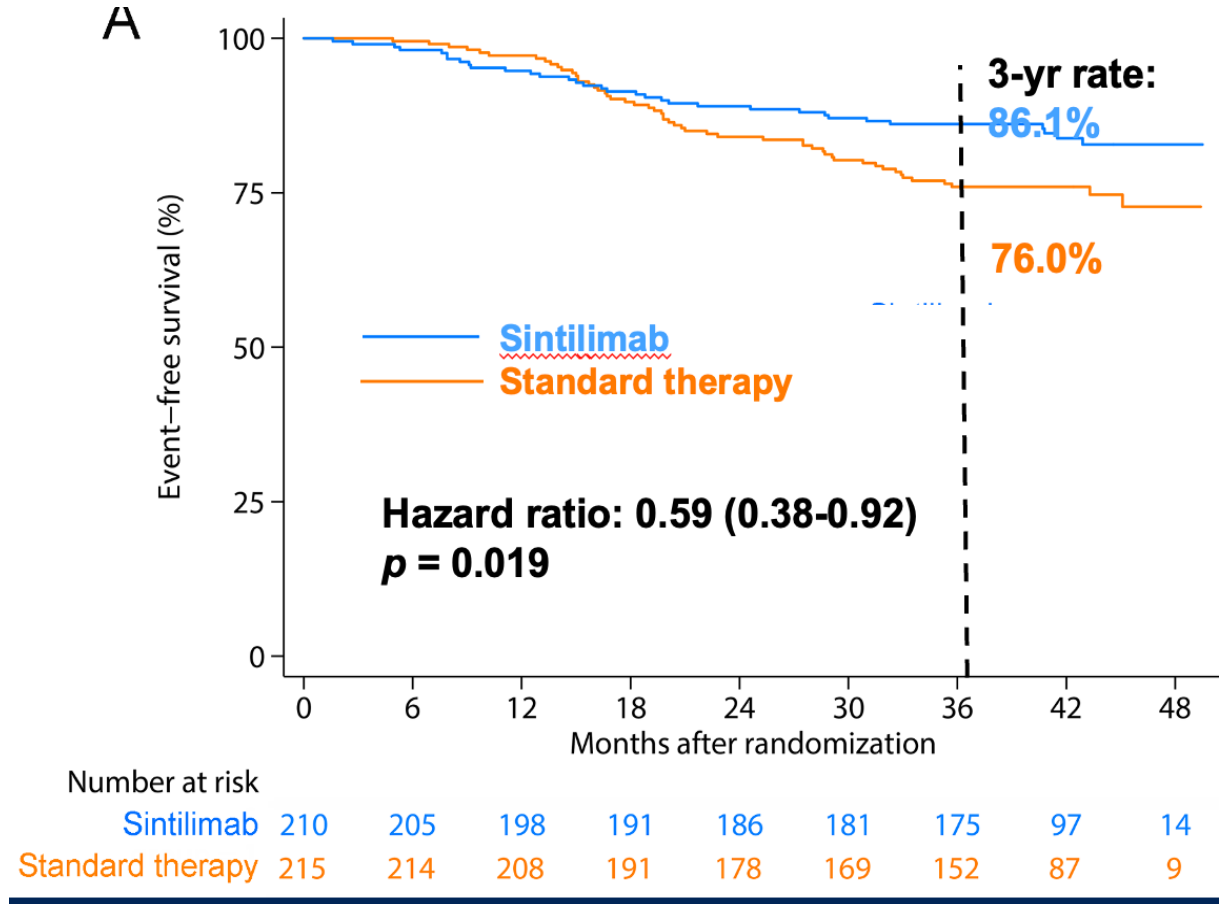
Results led to the FDA approval of **toripalimab in combination with cisplatin and gemcitabine** for the 1L treatment of adults with metastatic or recurrent locally advanced NPC

Single-agent toripalimab is approved for adults with recurrent unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy

1. Mai H-Q et al. ASCO 2023. Abstract 6009.

CONTINUUM; Adding Sintilimab (PD-1 inh) to GC Event-free survival (EFS)





Ma J, Oral presentation, ASCO 2023,

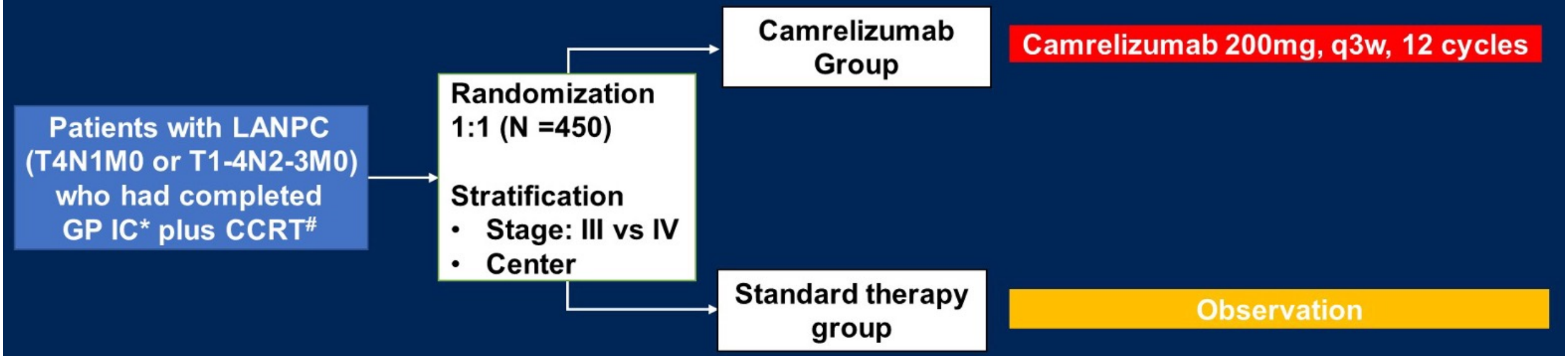
2024 ASCO® ANNUAL MEETING

Adjuvant PD-1 blockade with camrelizumab in locoregionally advanced nasopharyngeal carcinoma (DIPPER): A multicenter, open-label, phase 3, randomized controlled trial.

Jun Ma, Ying Sun, Ye-Lin Liang, Xu Liu, Liang-Fang Shen, Guang-Yuan Hu, Guo-Rong Zou, Ning Zhang, Chuan-Ben Chen, Xiao-Zhong Chen, Xiao-Dong Zhu, Ya-Wei Yuan, Kun-Yu Yang, Feng Jin, Yuan Zhang, Rui Guo

Principal investigator: Prof. Jun Ma
Sun Yat-sen University Cancer Center, Guangzhou, China
majun2@sysu.edu.cn

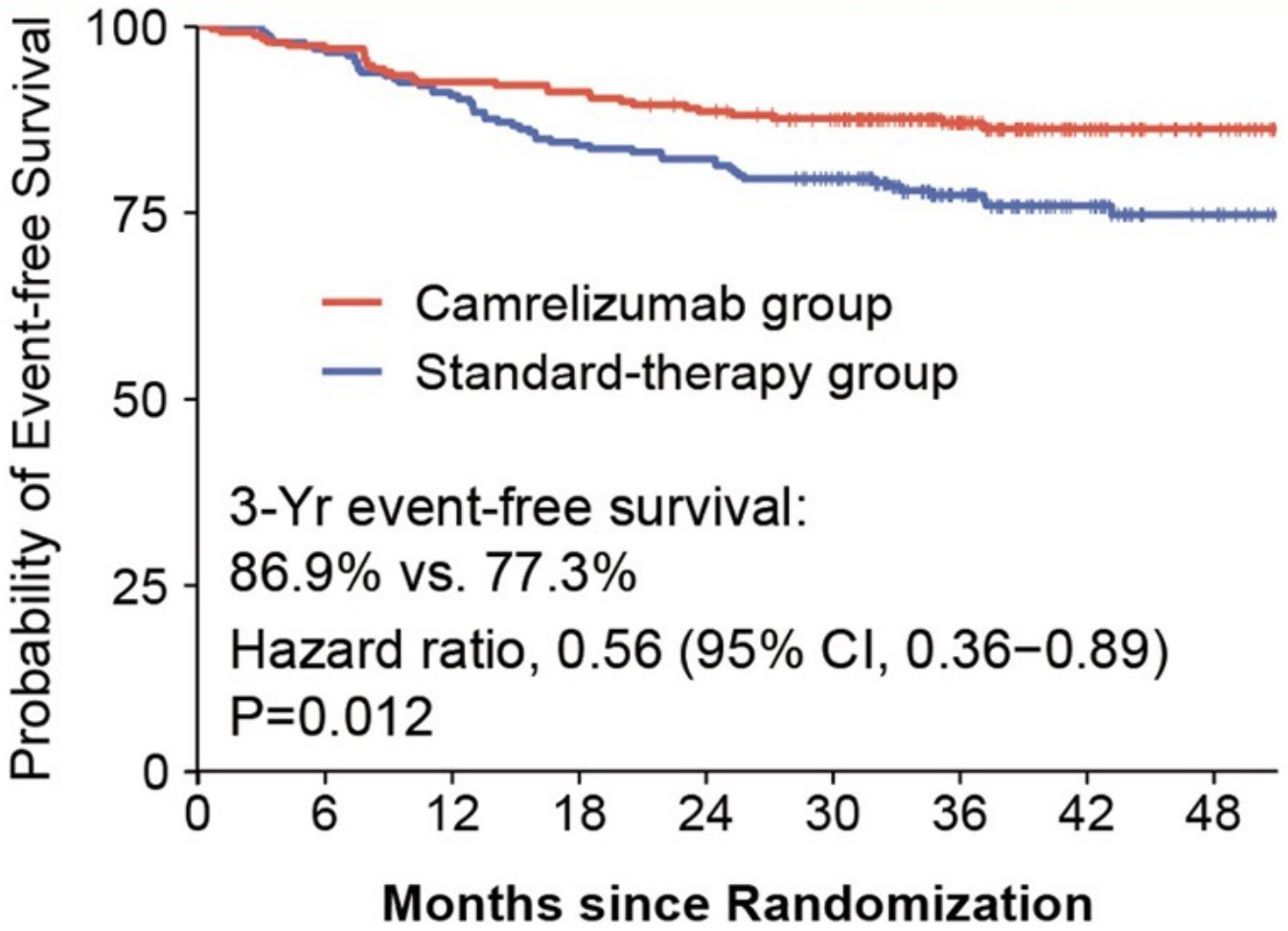
DIPPER Trial Schema



* GP IC, q3w × 3 cycles (Gemcitabine 1g/m2, d1 & 8; DDP 80mg/m2, d1)

\# CCRT (DDP 100mg/m2, d1 q3w * 2 cycles; IMRT, 69.96Gy in 33 fractions, once per day, Monday to Friday in each week)

Primary endpoint: Event-free survival (EFS)

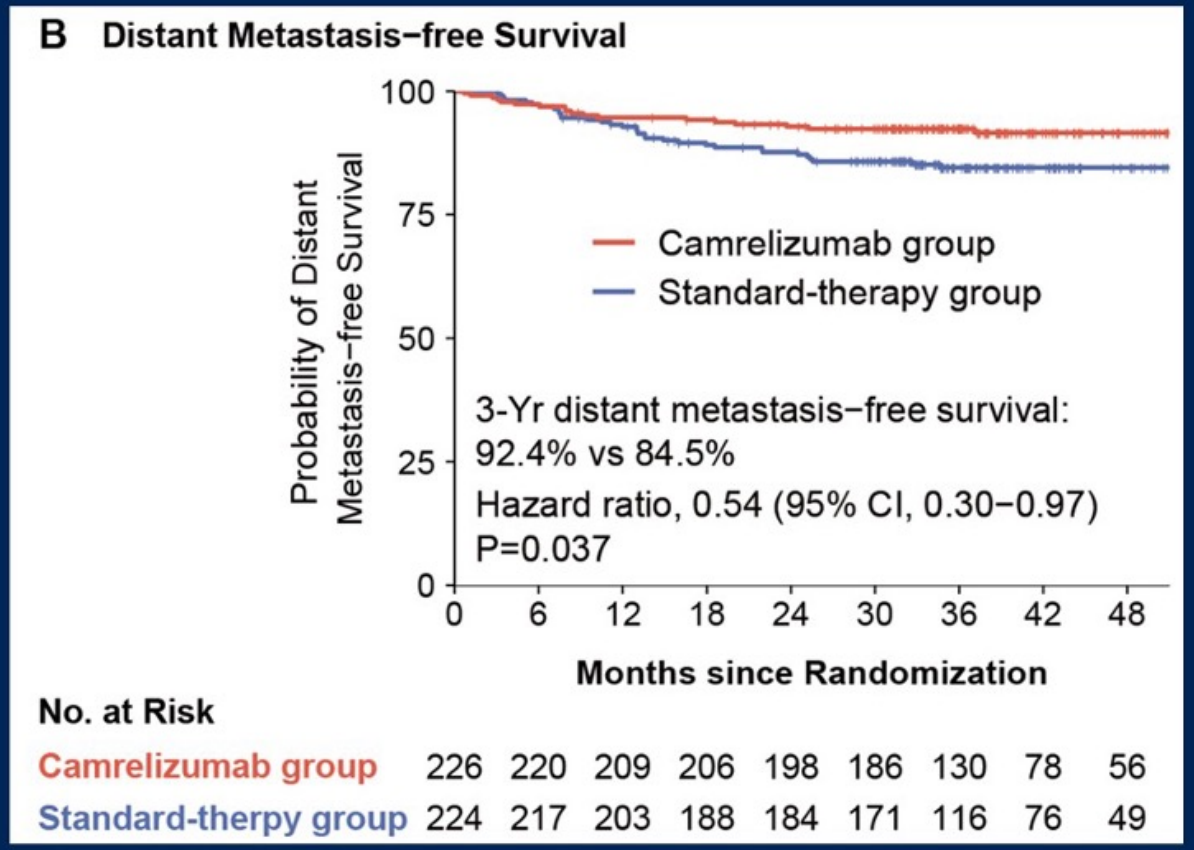


No. at Risk

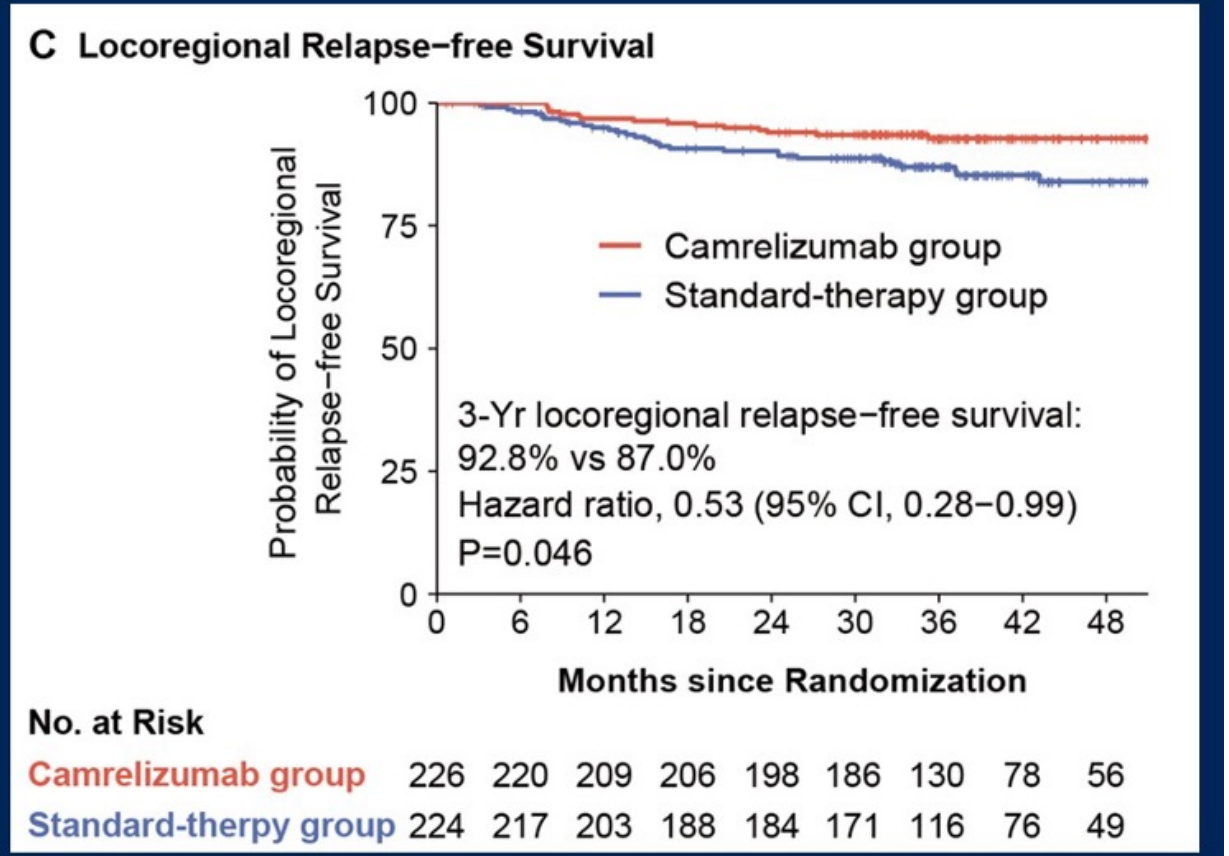
Camrelizumab group	226	220	209	206	198	186	130	78	56
Standard-therpy group	224	217	203	188	184	171	116	76	49

Secondary endpoints: DMFS and LRRFS

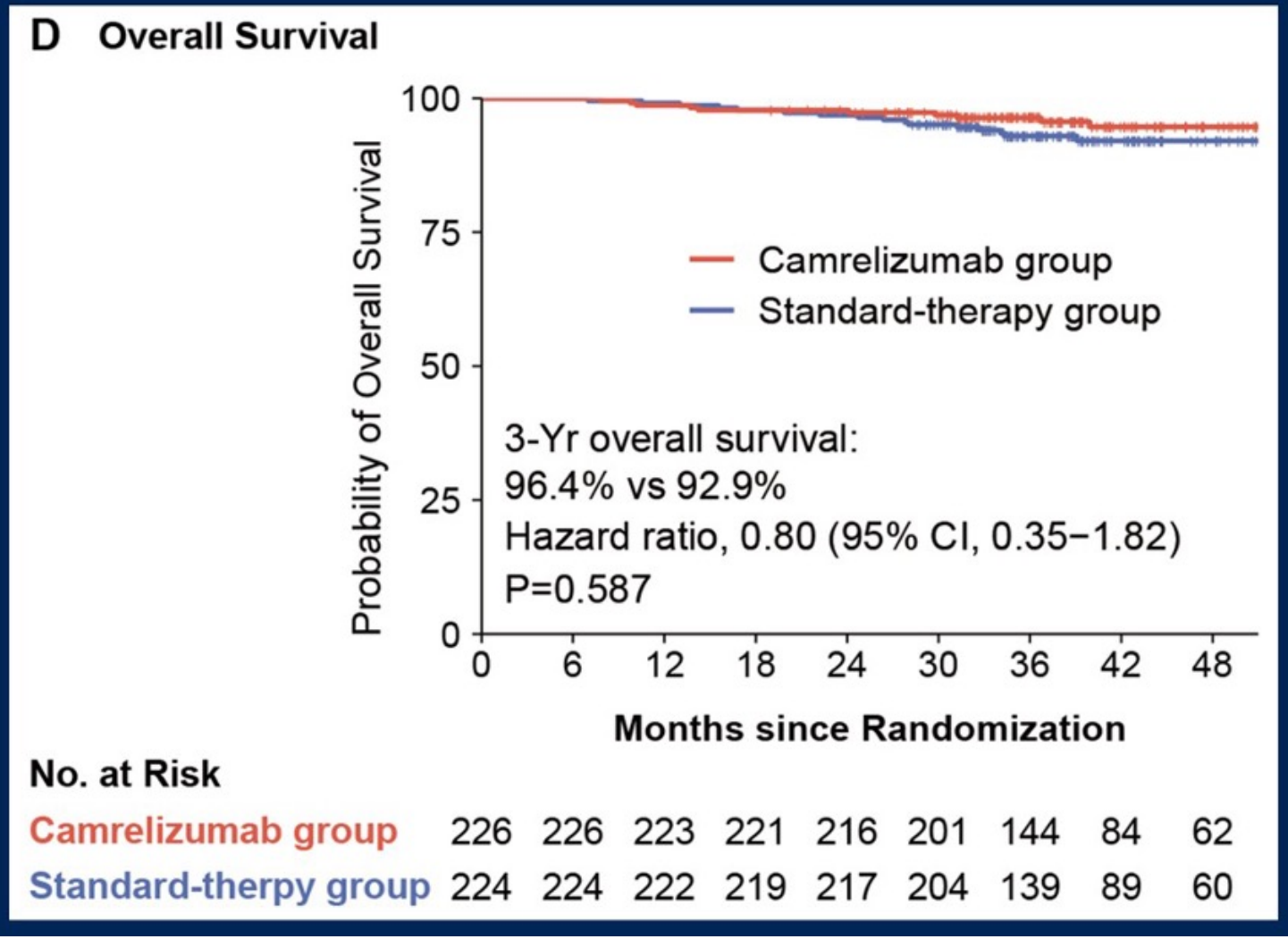
Distant metastasis-free survival: ↑ 7.9%



Locoregional relapse-free survival: ↑ 5.8%



Secondary endpoint: Overall survival



The median follow-up after relapse/metastasis is 23.4 months.

2024 ASCO® ANNUAL MEETING

A randomized, double-blind placebo-controlled phase II study of adjuvant pembrolizumab versus placebo in patients with head and neck squamous cell cancers at high risk for recurrence: the PATHWay Study

Alexander T. Pearson[1]

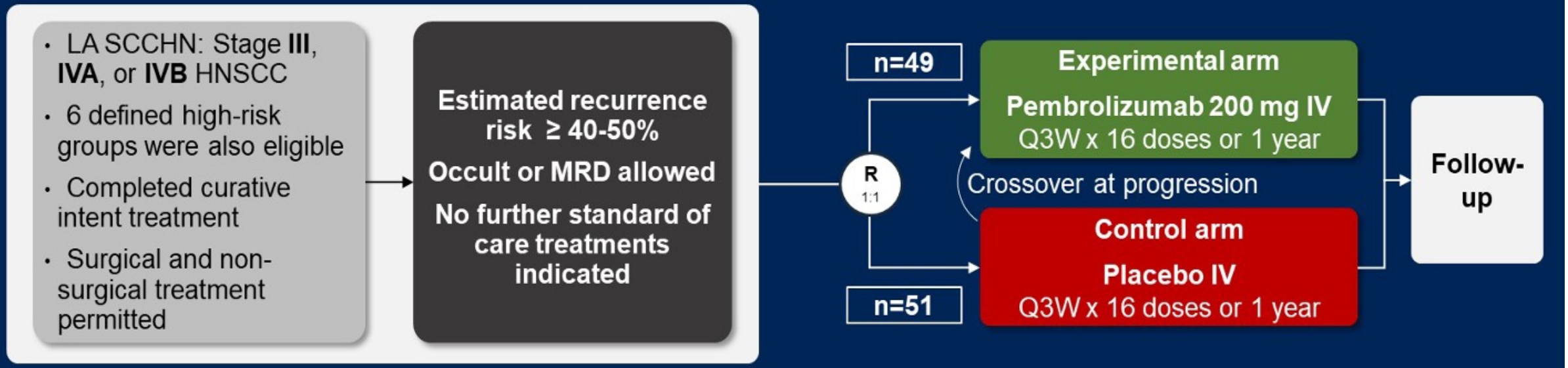
University of Chicago Cancer Center, Chicago, IL

Tanguy Seiwert[2], Roger Cohen[3], Nabil Saba[4], John Kaczmar[5], Mary Fidler[6], James Wade[7], Enrico Castellucci[8], Theodore Karrison[1], Rohan Katipally[1], Aditya Juloori[1], Ari Rosenberg[1], Daniel Haraf[1], Nishant Agrawal[1], Everett Vokes[1]

1. University of Chicago Cancer Center, Chicago IL; 2. Johns Hopkins University Hospital, Baltimore MD; 3. University of Pennsylvania Medical Center, Philadelphia PA; 4. Emory University Medical Center, Atlanta GA; 5. Medical University of South Carolina, Charleston SC; 6. Rush University, Chicago IL; 7. Cancer Care Specialists of Illinois, Decatur IL; 8. Montefiore Medical Center, Bronx NY

Methods
Trial Diagram

- Patients were recruited between May 2017 and December 2021 at 10 potential US Sites



Stratification Factors

- Randomization was stratified by tumor etiology:
  - HPV+/EBV-
  - HPV-/EBV+
  - HPV-/EBV-

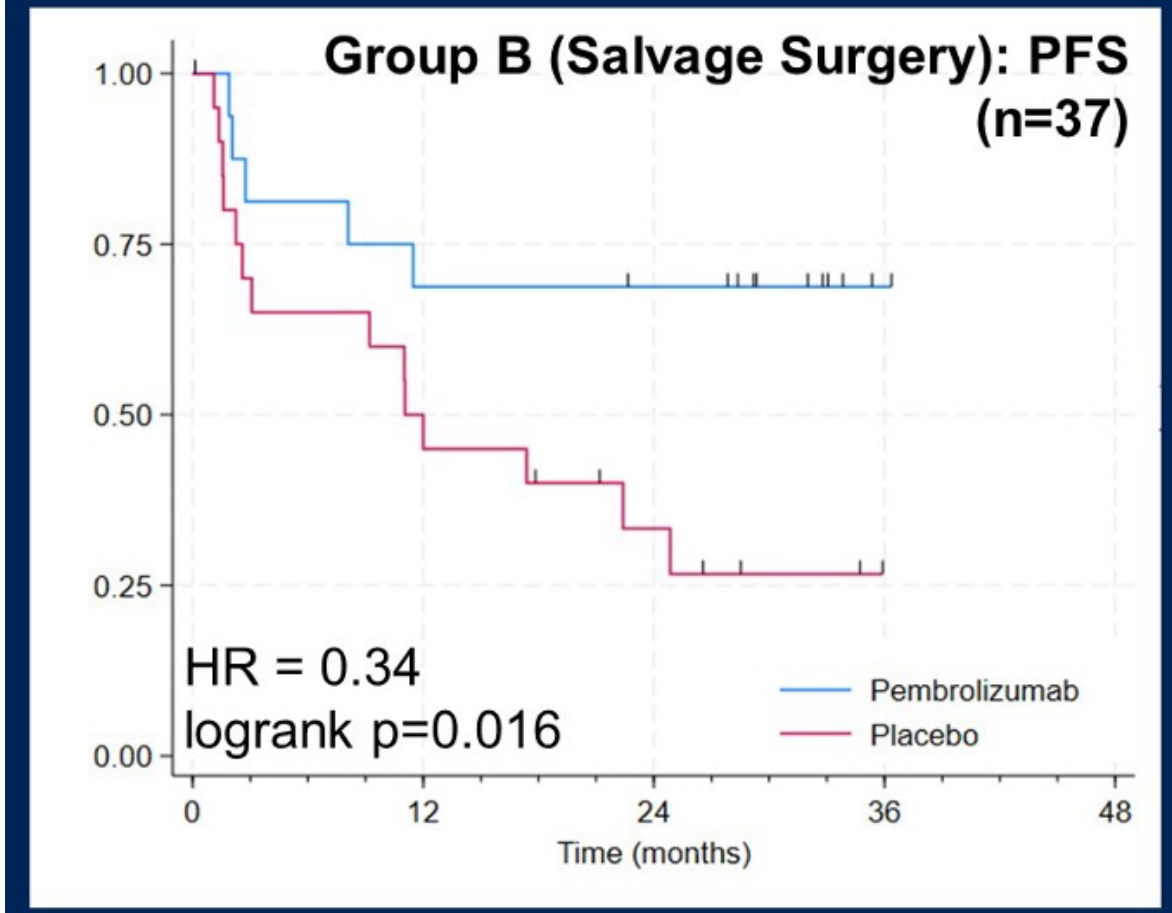
Key Endpoints

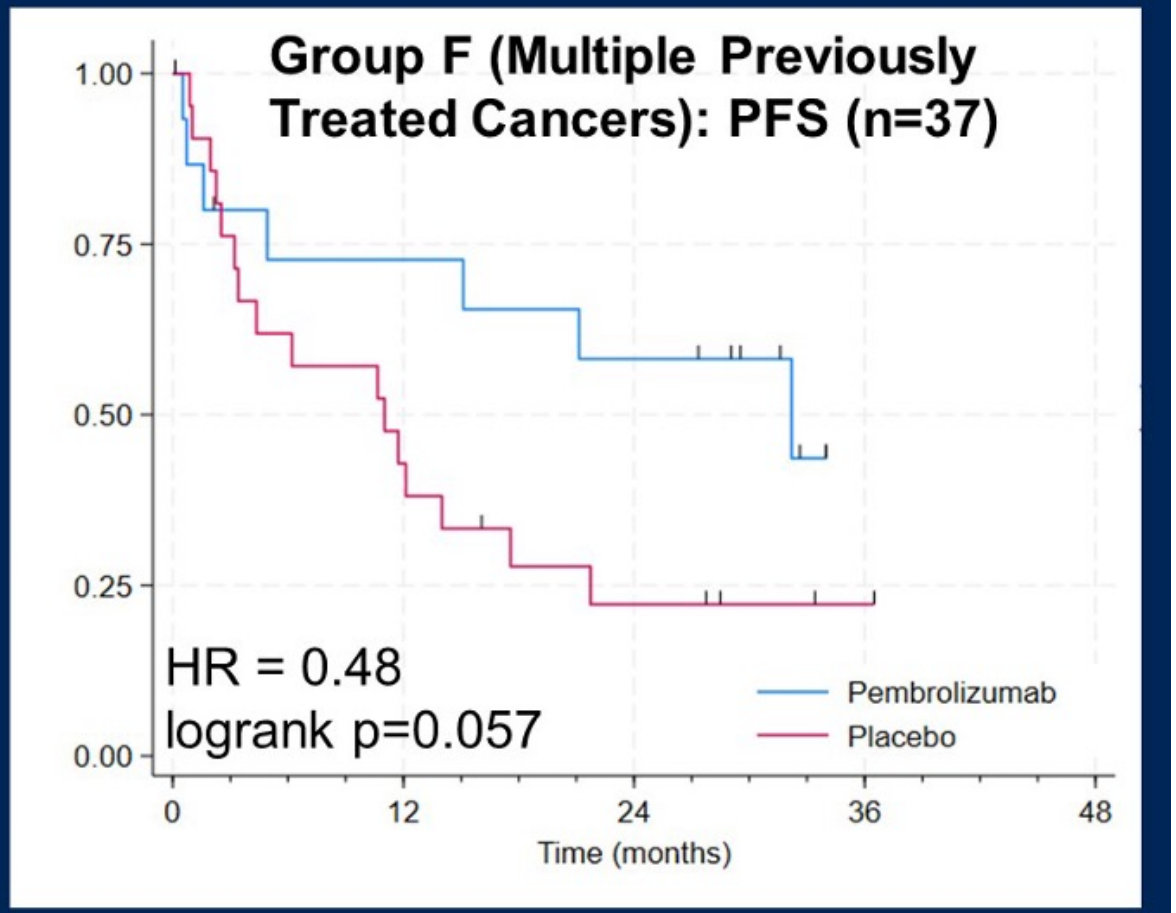
- Primary: Progression-Free Survival (PFS)
- Secondary: PFS in PD-(L)1 ≥ 10; Overall survival (OS) in PD-(L)1 ≥ 10; Influence of gene expression profile

Results

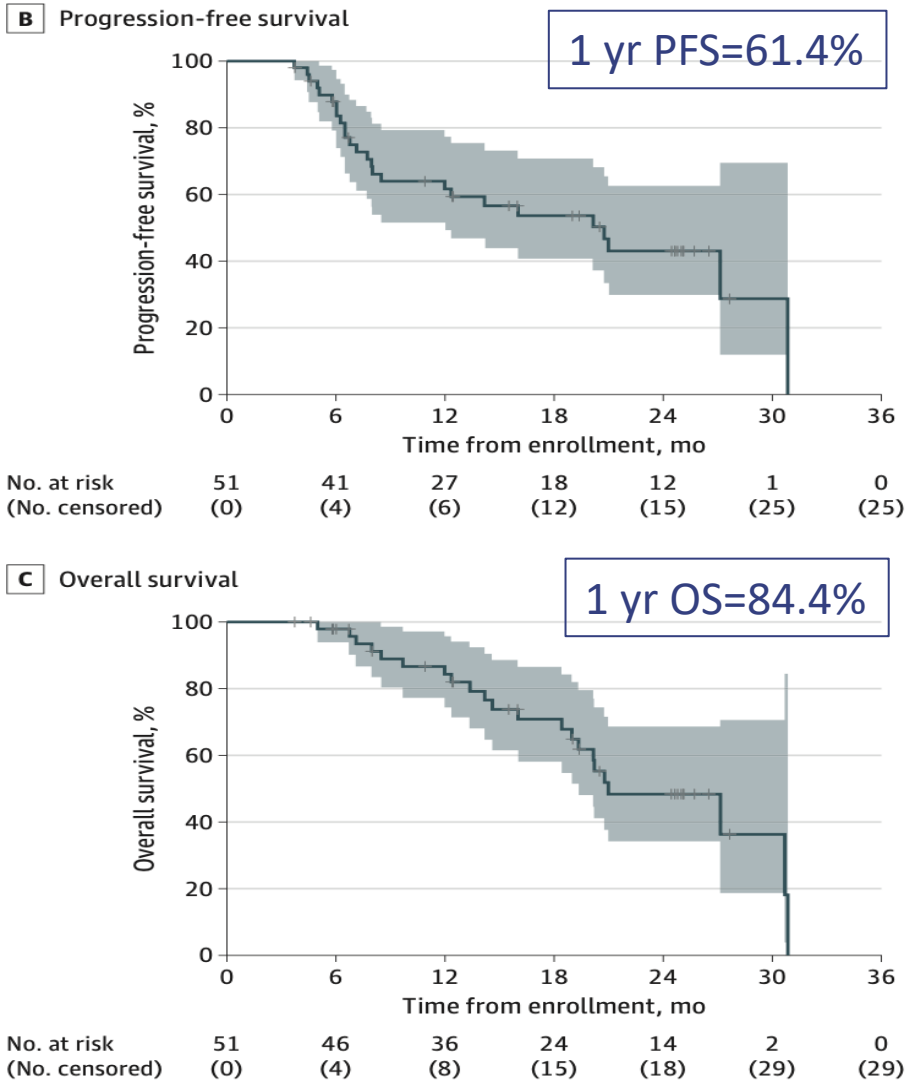
Primary PFS Endpoint Also Evaluated in 2 Large Sub-Cohorts

- Post-hoc analysis





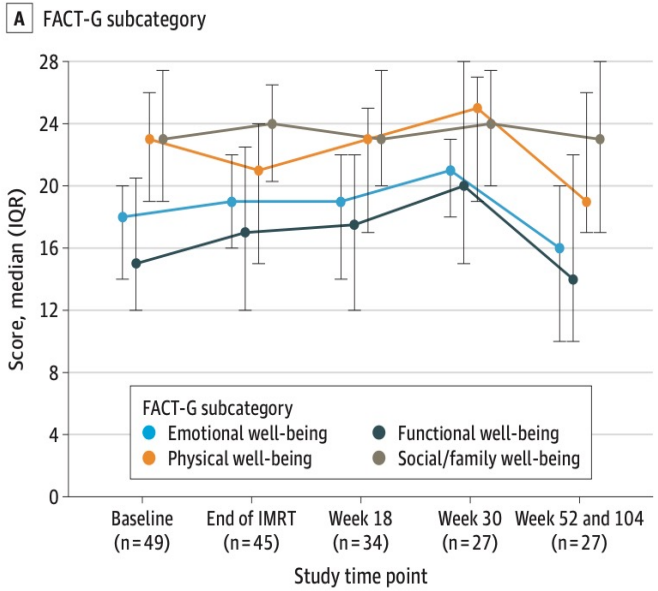
IMRT – Reirradiation with Nivolumab in Recurrent or SP HNSCC

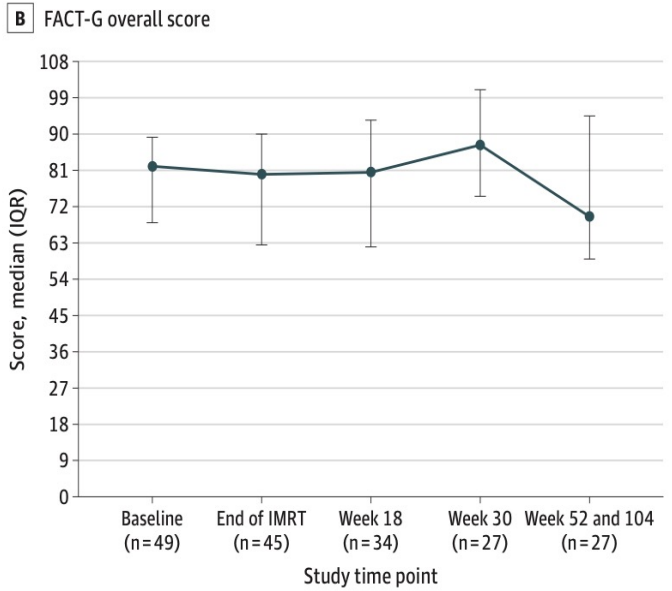


Question Can the addition of nivolumab to IMRT reirradiation improvePFS over historic control

Findings In 51 patients, PFS was improved in patients treated with nivolumab and reirradiation compared with best historical controls. The toxic effect profile was favorable.

Meaning This approach deserves to be tested in a confirmatory larger randomized trial.





Saba NF, JAMA Oncol 2024

Summary and Future Perspectives

Even though progress in the management of LAHNSCC has stagnated

With the advent of novel combinatorial approaches curing a larger proportion of patients with R/M HNSCC is within reach

The proper sequencing of therapy may have paid off in NPC-however sequencing is likely not the only factor determining outcome; ongoing trials with sequential approach include EA3161, JADE and eVOLVE,

In the meantime cisplatin in concurrence with radiation remains the standard for treating LA HNSCC

Despite the current status, improving the standard in LAD is likely to be only a delayed (rather than elusive) reality.

Thank You !