TREATMENT OF SQUAMOUS CELL CANCER OF THE HEAD AND NECK

Where Are We in 2024?

Biologic Principles, Changing Paradigms, and New Therapies

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Molecular and Biological Events in Head and Neck Cancer

Squamous Cell Cancer of the Head And Neck Cancer can be Divided Into Three Distinct Molecular and Etiologic Subtypes

HPV Cancers

- Caused by High Risk HPV
  - HPV 16 predominantly
  - Driven by Viral Oncogenes
  - Sexual Transmission
- Primarily Oropharyngeal
  - Nasal Cavity and Sinuses
- Responsive, Good Prognosis
- Young, Good General Health

EBV Cancers

- Caused by EBV
  - Driven by Viral Oncogenes
  - Droplet Transmission
- Primarily Nasopharynx
- Racial and Ethnic Predilection
  - Asia, India, Saharan
- Responsive, Good Prognosis

Environmental Cancers

- Caused by Environmental Mutagens
  - Smoking, Alcohol, Vaping
- Throughout The Oral Mucosa
- Distinct Molecular Markers
- "Poor" Prognosis and Co-Morbidities
- Second Cancers
- Suppressor Mutations

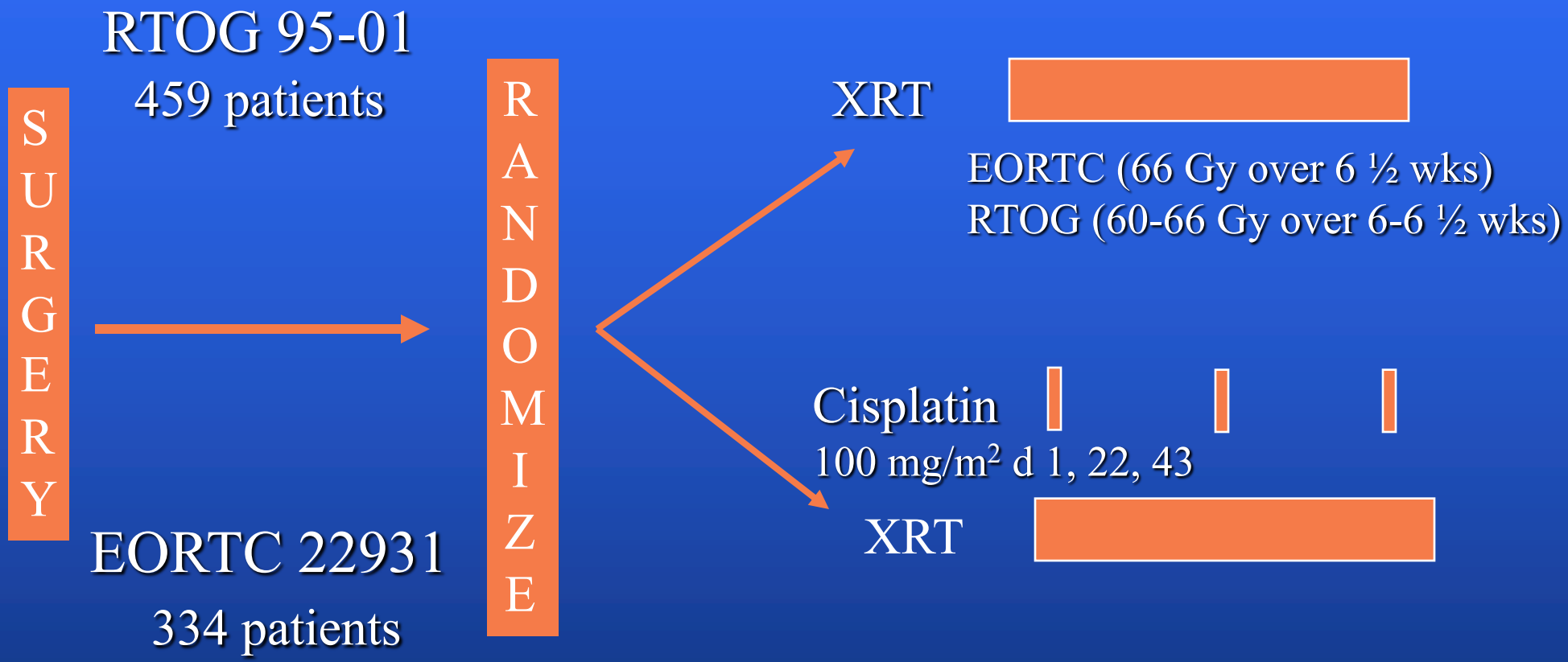
The Current State of The Art For Curative Therapy of HPV and Environmental Cancers

- Surgery – Tors, Microvascular Reconstruction
- Radiotherapy – IMRT, Protons
- Postoperative Chemoradiotherapy
- Concurrent Chemoradiotherapy
- Induction Chemotherapy
- Sequential Therapy
- Immunotherapy (Preliminary Studies Ongoing)

Surgical Technology Has Changed Significantly in the Last 2 Decades

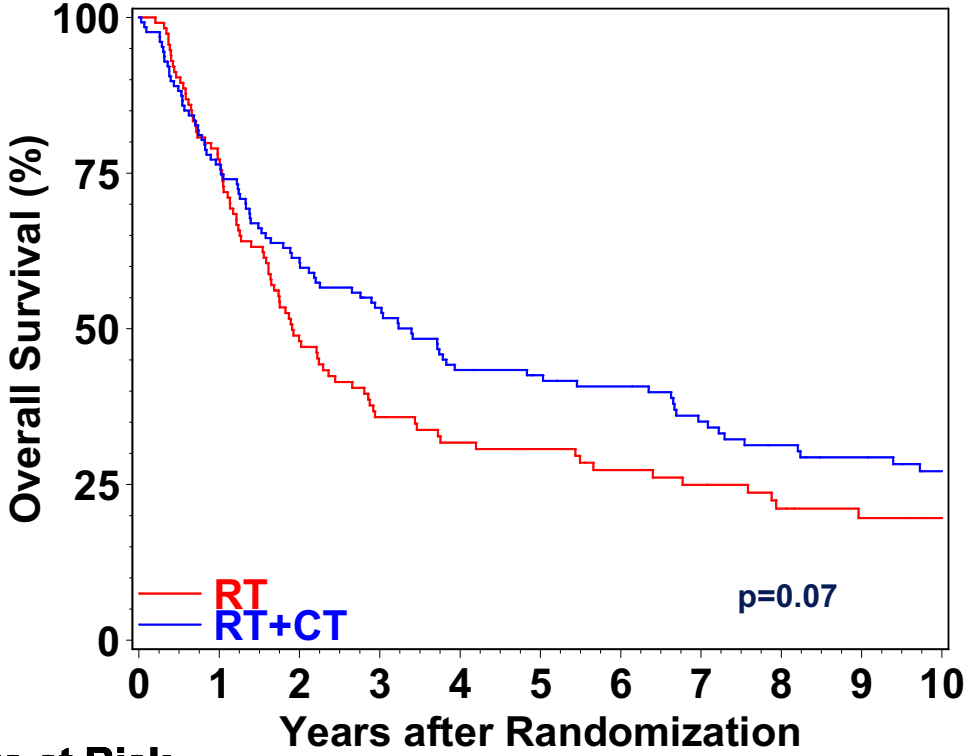
- Transoral Approaches
  - Transoral Laser Microsurgical (TLM) Resection
  - TransOral Robotic Surgery (TORS)
  - Much Better Exposure
- Lessened Morbidity
  - Much Less Bystander Tissue Damage, Trauma
  - Quick Recovery
  - More Tumors Resectable – Oropharynx, Larynx, Pyriform
  - Microvascular Reconstruction
- Preferred Therapy for Resectable, Functionally Acceptable, Non-HPV Tumors and HPV Positive Tumors
  - Pathologically Determined Adjuvant Therapy, Reduced RT
  - Watch for Curative Immunotherapy Trials for Advanced Disease

Postoperative Chemoradiotherapy



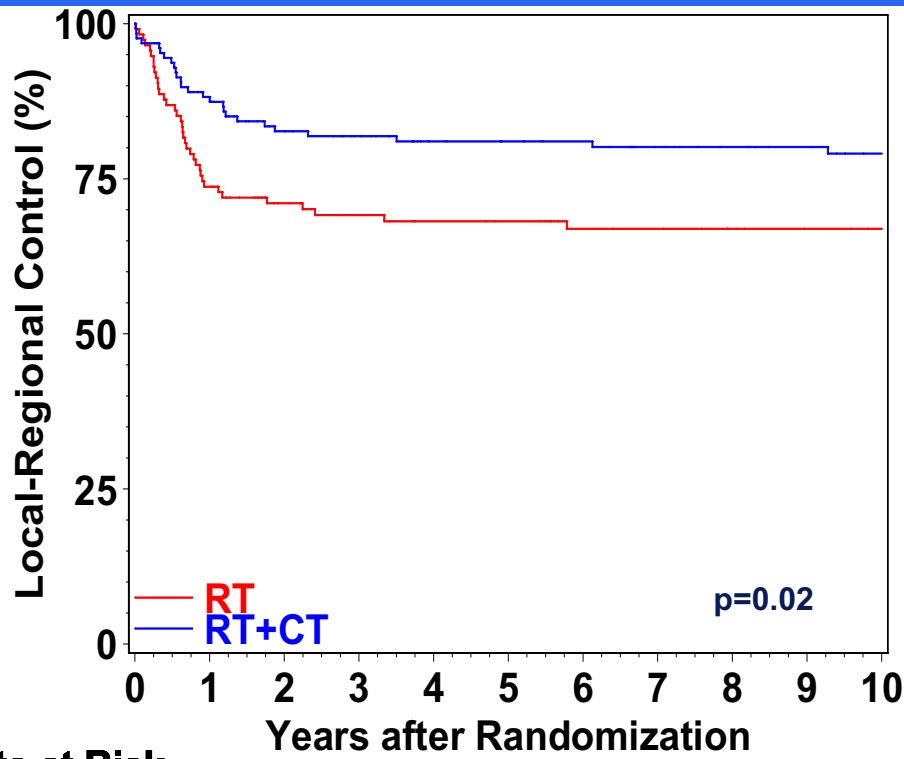
Cooper , NEJM, 2004; 350: 1937 Bernier, NEJM, 2004;350:1945

Survival/Local Regional Control RTOG:95-01
ECE or Positive Margin
Median Follow up 9.4 Years



Patients at Risk

RT	115	88	53	37	31	28	23	21	16	13	11
RT+CT	127	97	77	65	52	48	45	37	32	28	23



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RT+CT	127	93	72	64	50	47	45	37	32	28	23

Jay Cooper, AZ, 2012

Postoperative Chemoradiotherapy

- Indicated for ECE, Positive Margin
  - Relative Indication for LVI, PNI
- Cisplatin High Dose Bolus Therapy
  - Can Replace With Weekly Cisplatin 40 mg/M^2 Based on Data from Randomized and Retrospective Studies
    - » Weekly Carboplatin for Cisplatin Intolerant or Frail Patients
- No Current Indication for Cetuximab or Extended Therapy as Adjuvant
- There Has Been No Improvement on this Recommendation in 20 Years

Multiple Adjuvant Immunotherapy Trials Are Ongoing

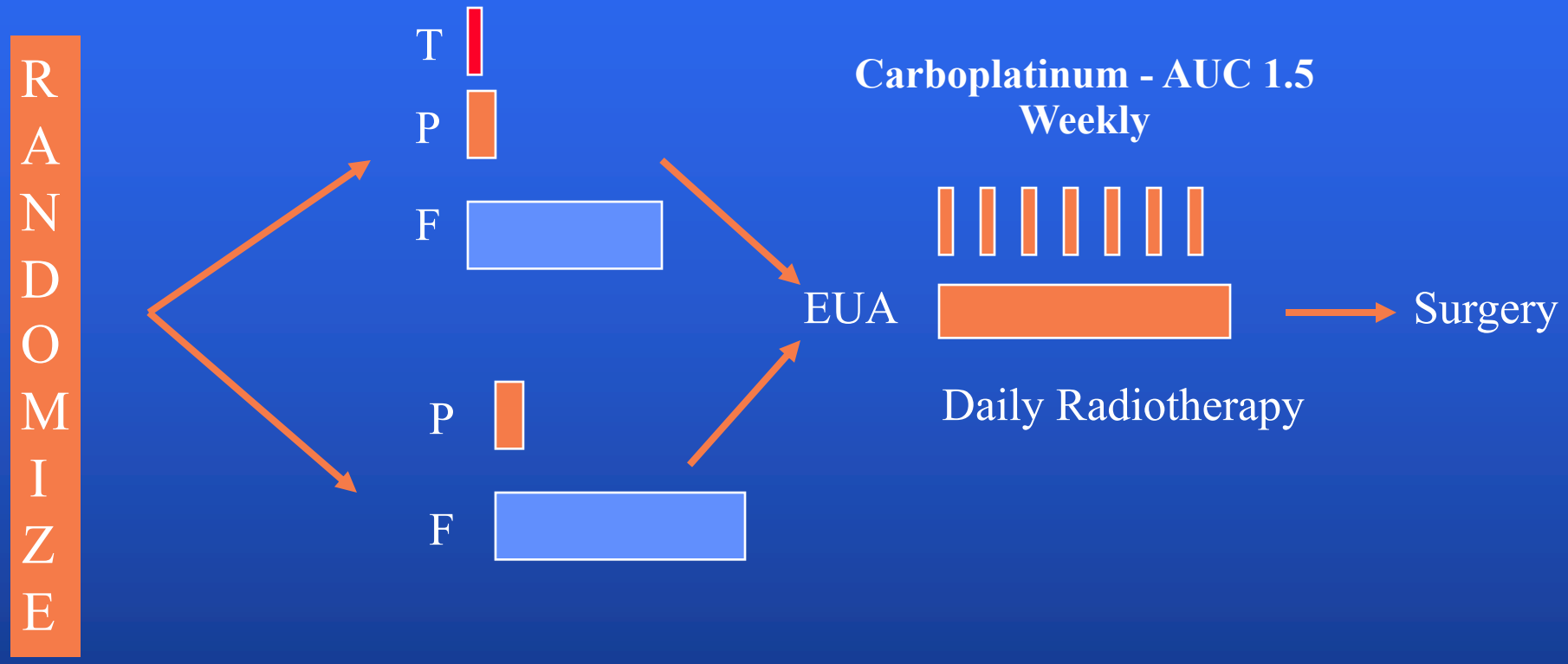
Definitive Chemoradiotherapy for Locally Advanced Head and Neck Cancer

- Chemoradiotherapy Improves Survival Compared To Radiotherapy Alone For Locally Advanced Head And Neck Cancer
- Standard Fraction CRT is Preferred Over ACB CRT With Reduced Chemotherapy
- There Is No Role For Reducing Cisplatin Chemotherapy During CRT
- Platinum Containing Regimens Remains The Standard For CRT – Cisplatin Monotherapy or Platinum plus 5-FU or Taxane
- IMRT and Protons Reduce Toxicity by Reducing Field Size and Require Skilled Radiation Oncologists
- Induction followed by CRT Can be Used for Organ Preservation

Sequential Combined Modality Therapy

A Phase III Study: TAX 324

TPF *vs.* PF Followed by Chemoradiotherapy

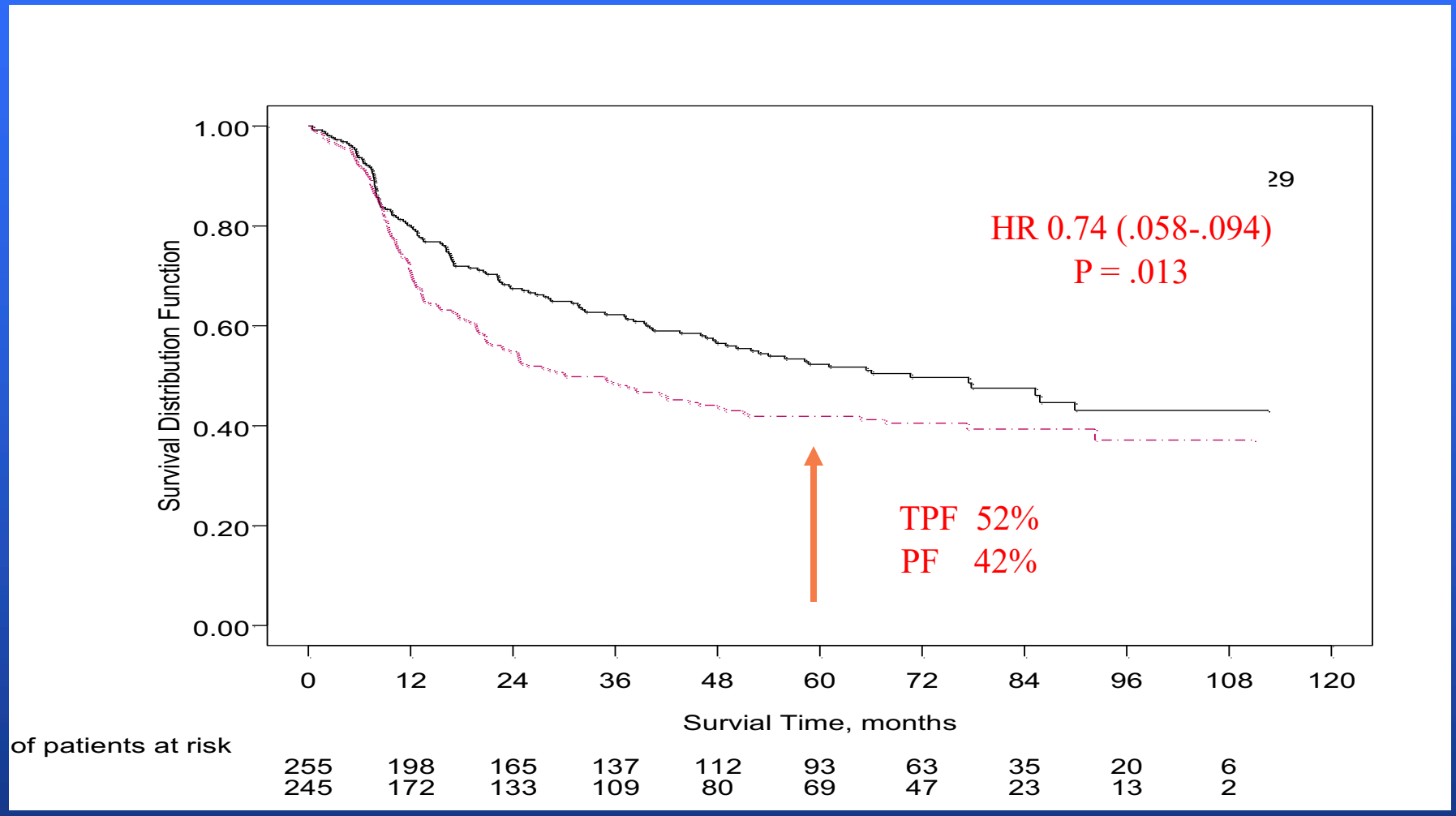


TPF: Docetaxel 75_{D1} + Cisplatin 100_{D1} + 5-FU $1000_{CI\text{-}D1\text{-}4}$ Q 3 weeks x3

PF: Cisplatin 100_{D1} + 5-FU $1000_{CI\text{-}D1\text{-}5}$ Q 3 weeks x 3

Posner, NEJM, 2007

Tax 324 5-year Follow-Up: Overall Survival



Sustained Survival Advantage At 5 Years For Patients Receiving TPF Versus PF: Median Overall Survival 71 Versus 30 Months (HR 0.74, P=0.0129)

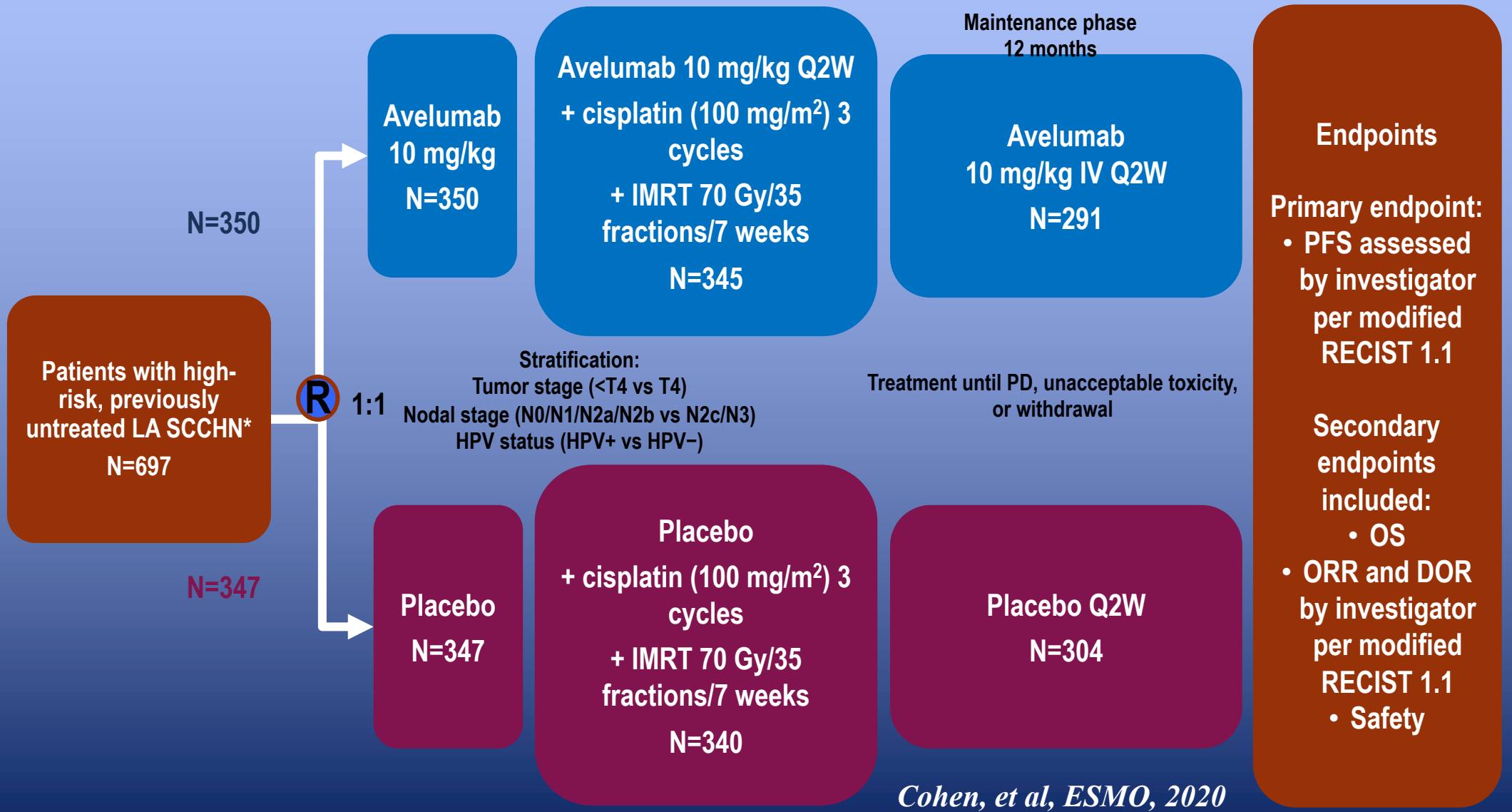
Lorch, Lancet Oncology, 2011

Immunotherapy Containing Regimens Are Not Standard for Primary Therapy with Curative Intent

- IT with Concurrent Radiation May be Biologically Ineffective or Harmful
  - Radiation Eliminates Immune Cells in The Tumor and Draining Lymph Nodes and Is Immunosuppressive (Javelin, Keynote 412)
    - » Scheduling May be Important
- Surgery Prior to/or Followed By IT May Diminish The Efficacy of IT
  - Lymph Node Resection May Eliminate Primed and Activated Immune Cells
    - » Scheduling May Be Important
- Induction IT and Induction Chemotherapy with IT are Undergoing Experimental Evaluation
  - This Approach Has Proven Successful in an RCT in NPC
    - » Induction Chemotherapy is the Standard Approach for Advanced Disease in NPC

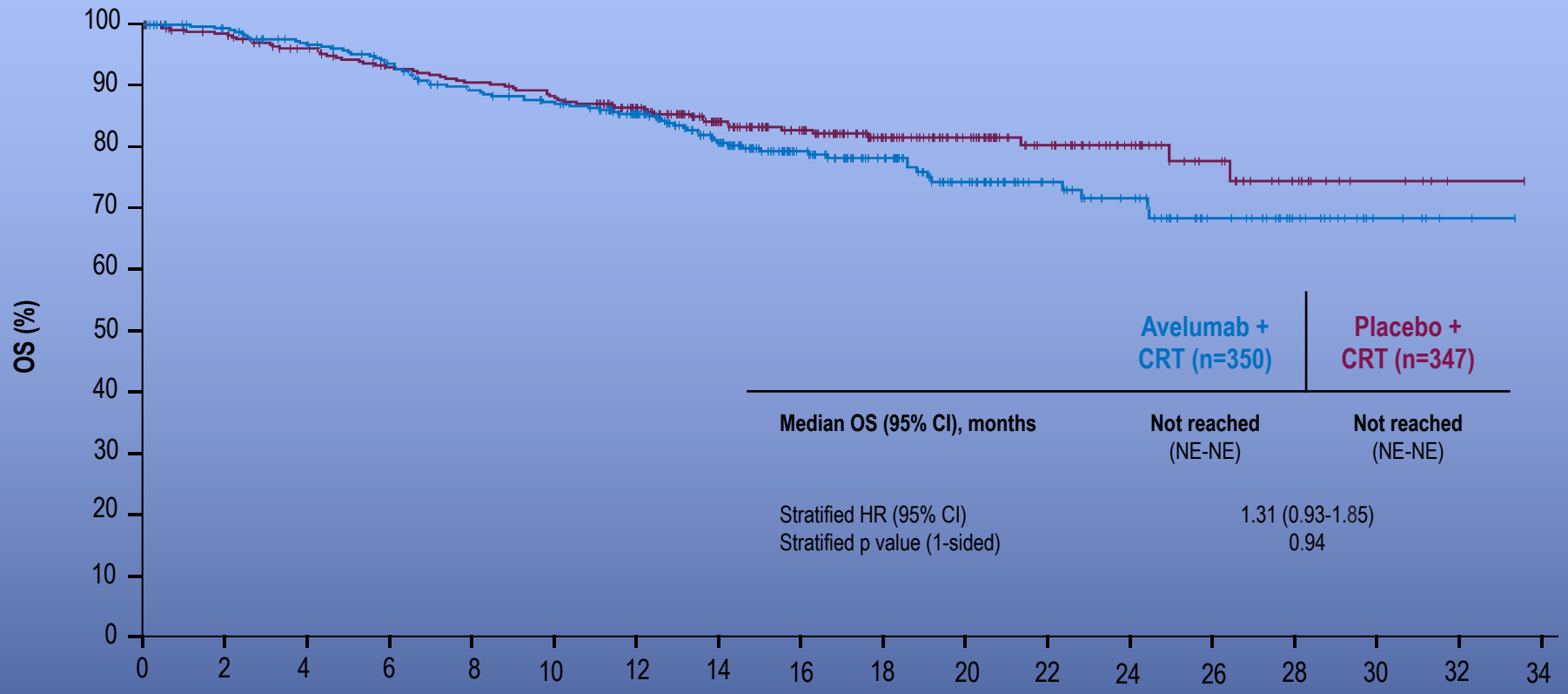
JAVELIN Head & Neck 100: Immunochemoradiotherapy

Randomized, placebo-controlled, double-blind, phase 3 trial



Cohen, et al, ESMO, 2020

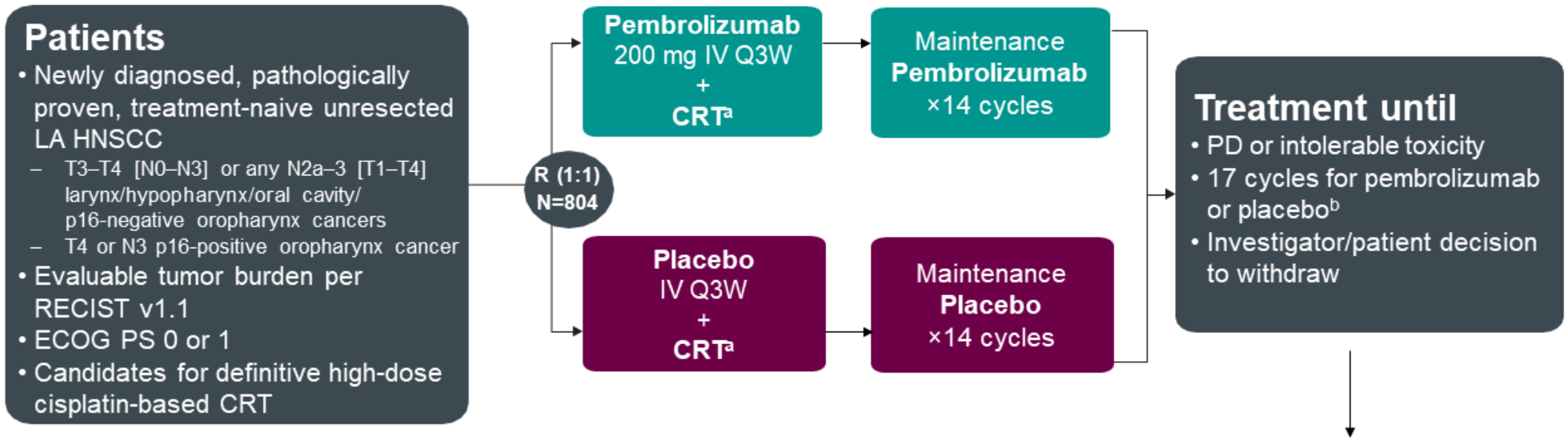
OS: overall patient population



At risk																		
Avelumab + CRT	350	336	319	303	284	273	244	190	148	118	82	59	47	29	18	6	2	0
Placebo + CRT	347	334	315	298	290	282	252	193	160	115	86	58	39	26	13	5	1	0

Cohen, et al, ESMO, 2020; Lee, Lancet, 2021

KEYNOTE-412 Study Design (NCT03040999)



Stratification Factors
- Radiotherapy regimen (AFX vs SFX)
- Tumor site/p16 status (oropharynx [p16+ vs p16-] or larynx/hypopharynx/oral cavity)
- Disease stage (III vs IV)

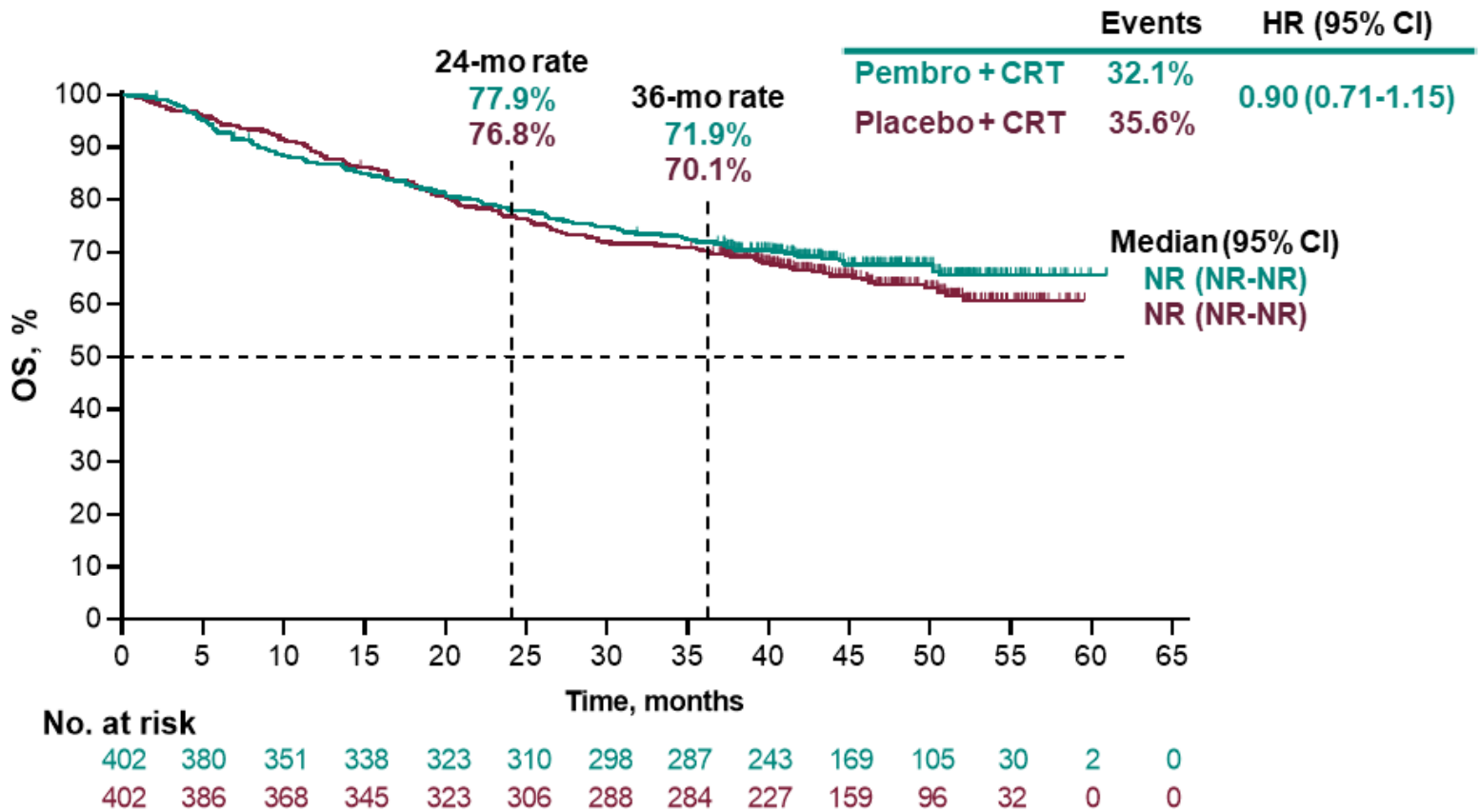
Primary endpoint
- Event-free survival (EFS)

Secondary endpoints included:
- OS
- Safety/tolerability

Post-treatment follow-up to assess
- Safety
- Disease status
- Survival

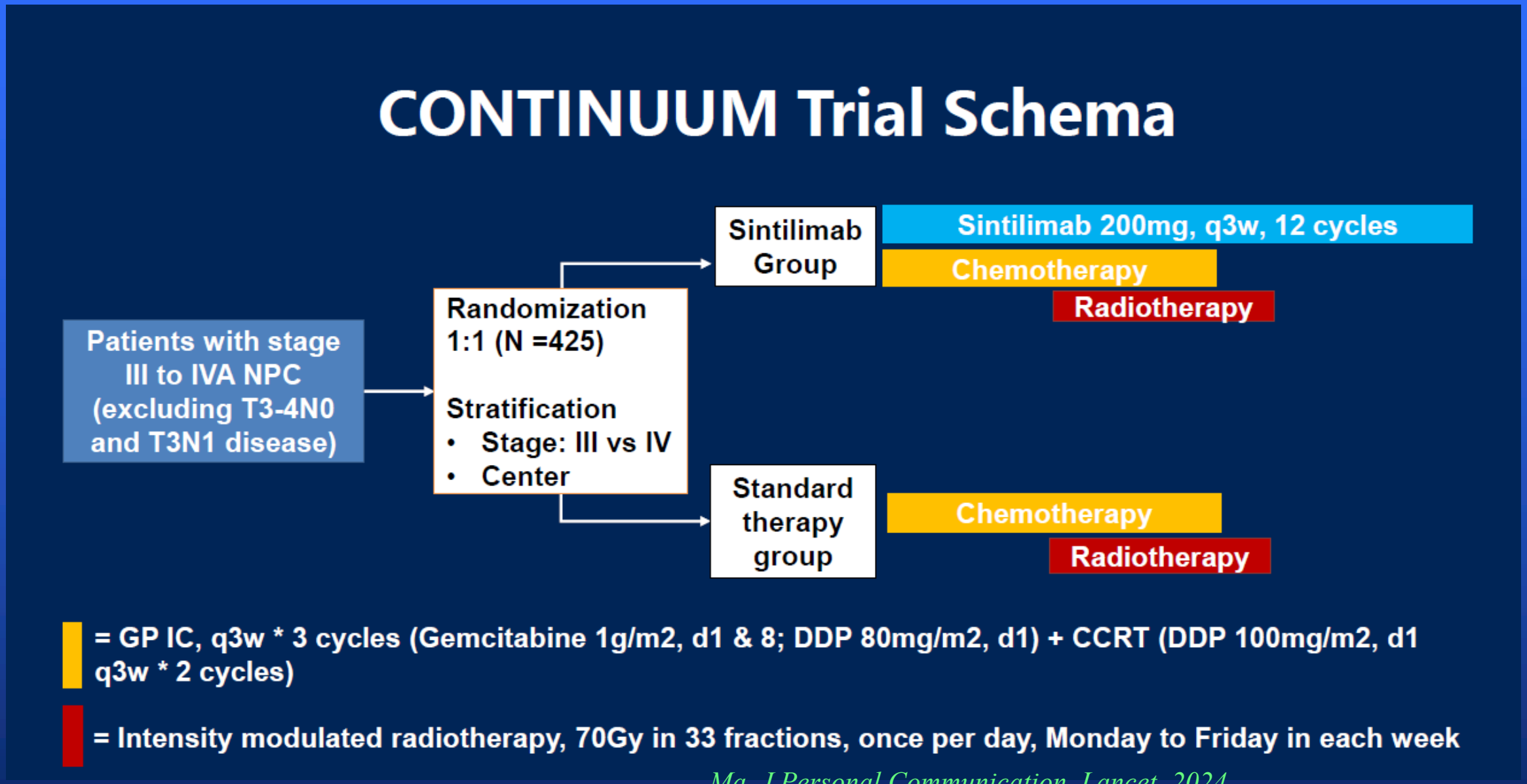
[a]CRT included cisplatin (100 mg/m^2, Q3W) and accelerated fractionation (AFX) (70 Gy, 6 fractions/week for 5 weeks and then 5 fractions for the 6th week, 35 fractions in total) or standard fractionation (SFX) (70 Gy, 5 fractions/week for 7 weeks, 35 fractions in total). [b]A pembrolizumab/placebo priming dose was given 1 week before CRT, followed by 2 doses during CRT and 14 doses of maintenance therapy after CRT, for a total of 17 doses.

Overall Survival, ITT Population



Data cutoff date: May 31, 2022.

Induction Chemoimmunotherapy vs Standard Induction Chemotherapy as Curative Therapy In Locally Advanced Nasopharynx Cancer



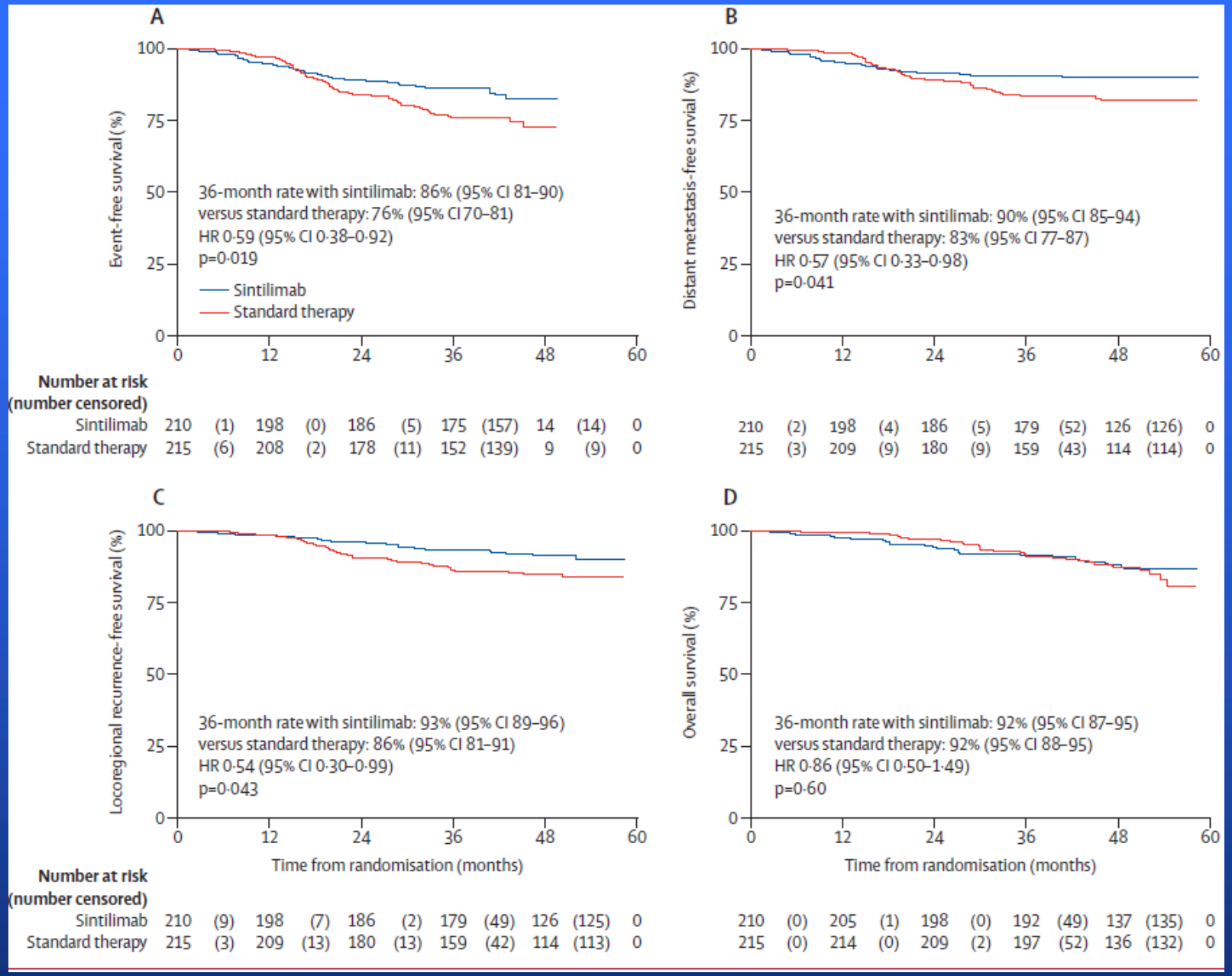
Ma, J Personal Communication, Lancet, 2024

Significant Improvements in 3-year:

EFS (86% vs 76%)
LRRFS (93% vs 86%)
DMFS (90% vs 83%)

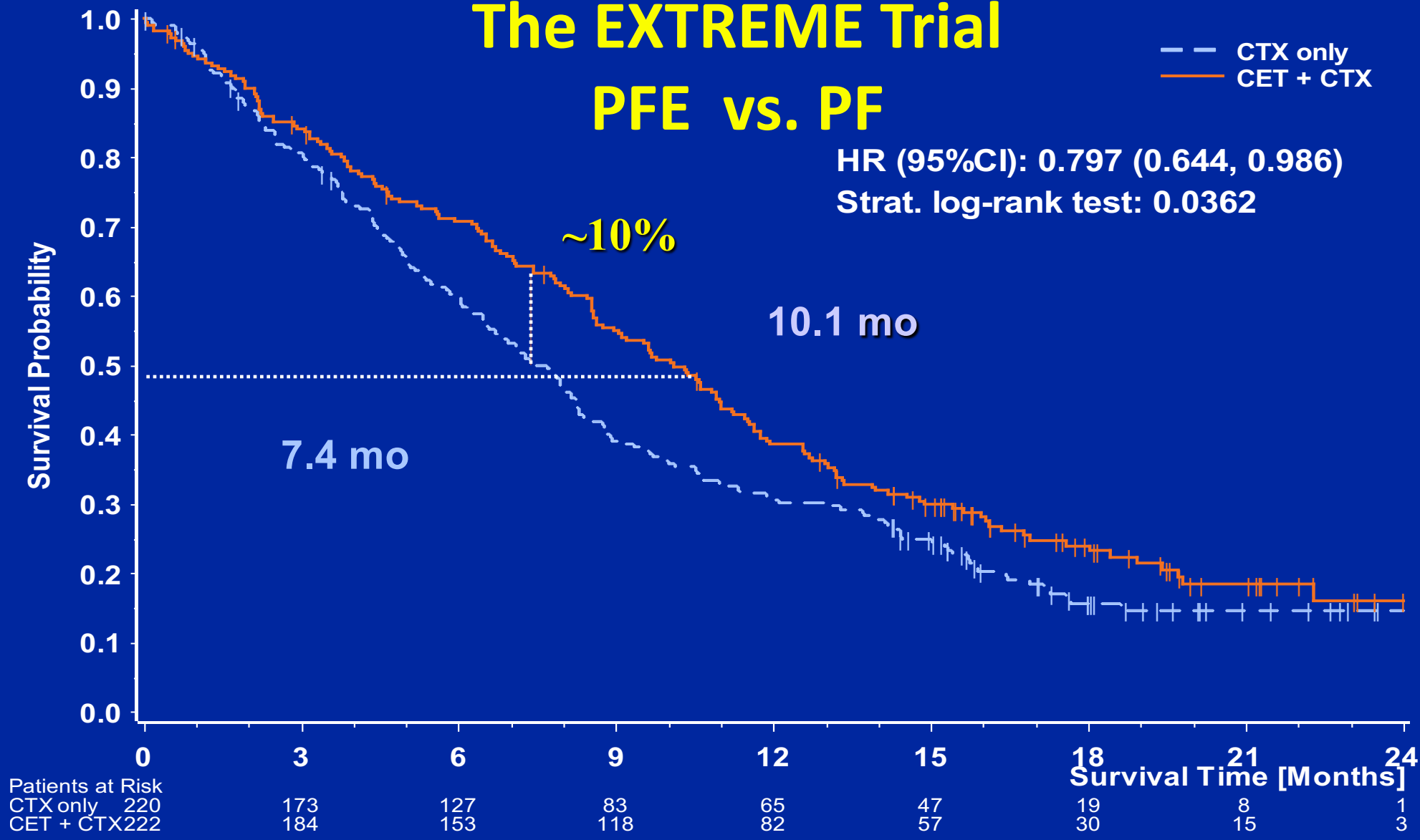
3-Year Overall Survival:
<u>Not Significantly Different</u>

Crossover Allowed



Ma, J Personal Communication, Lancet, 2024

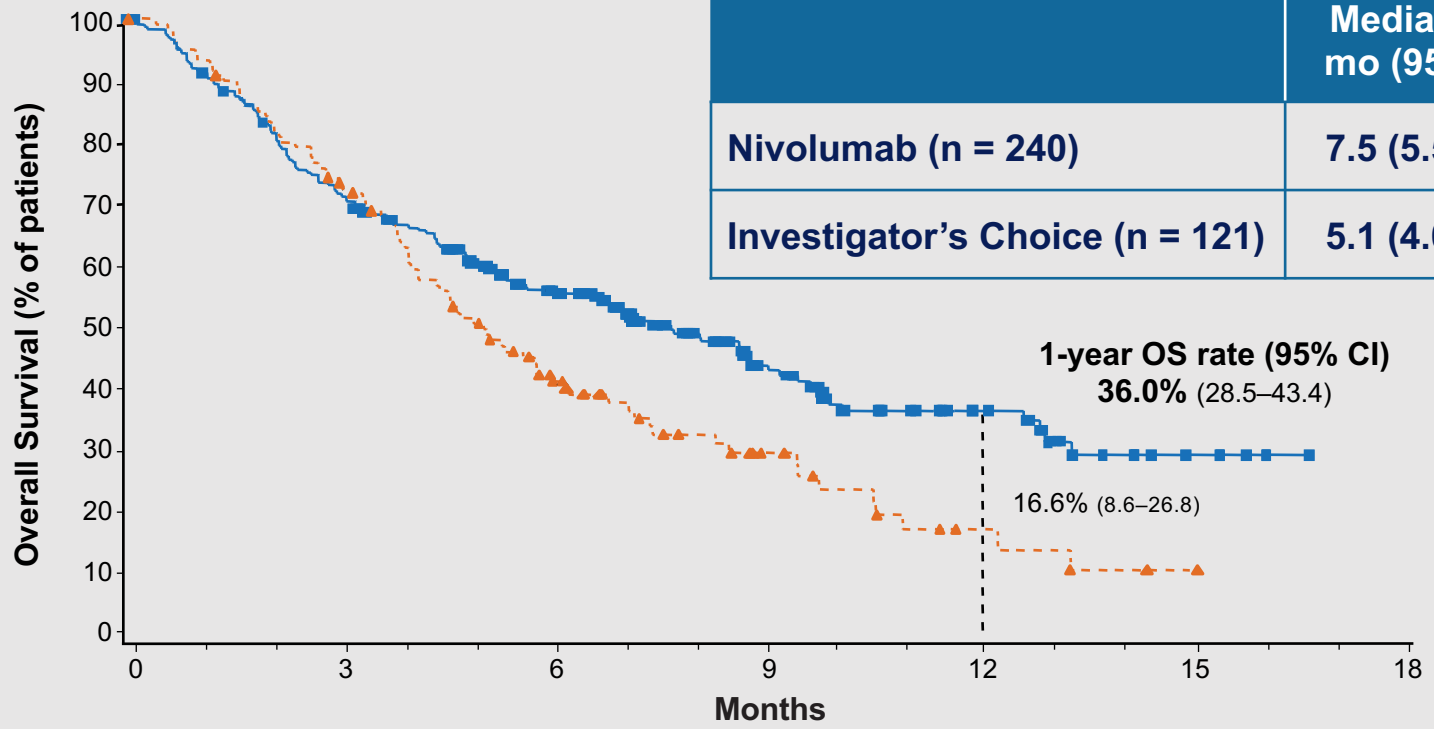
Overall Survival
The EXTREME Trial
PFE vs. PF



Vermorken, et al NEJM, 2008

CHECKMATE 0141 - OVERALL SURVIVAL SECOND LINE THERAPY (PLATINUM RESISTANT)

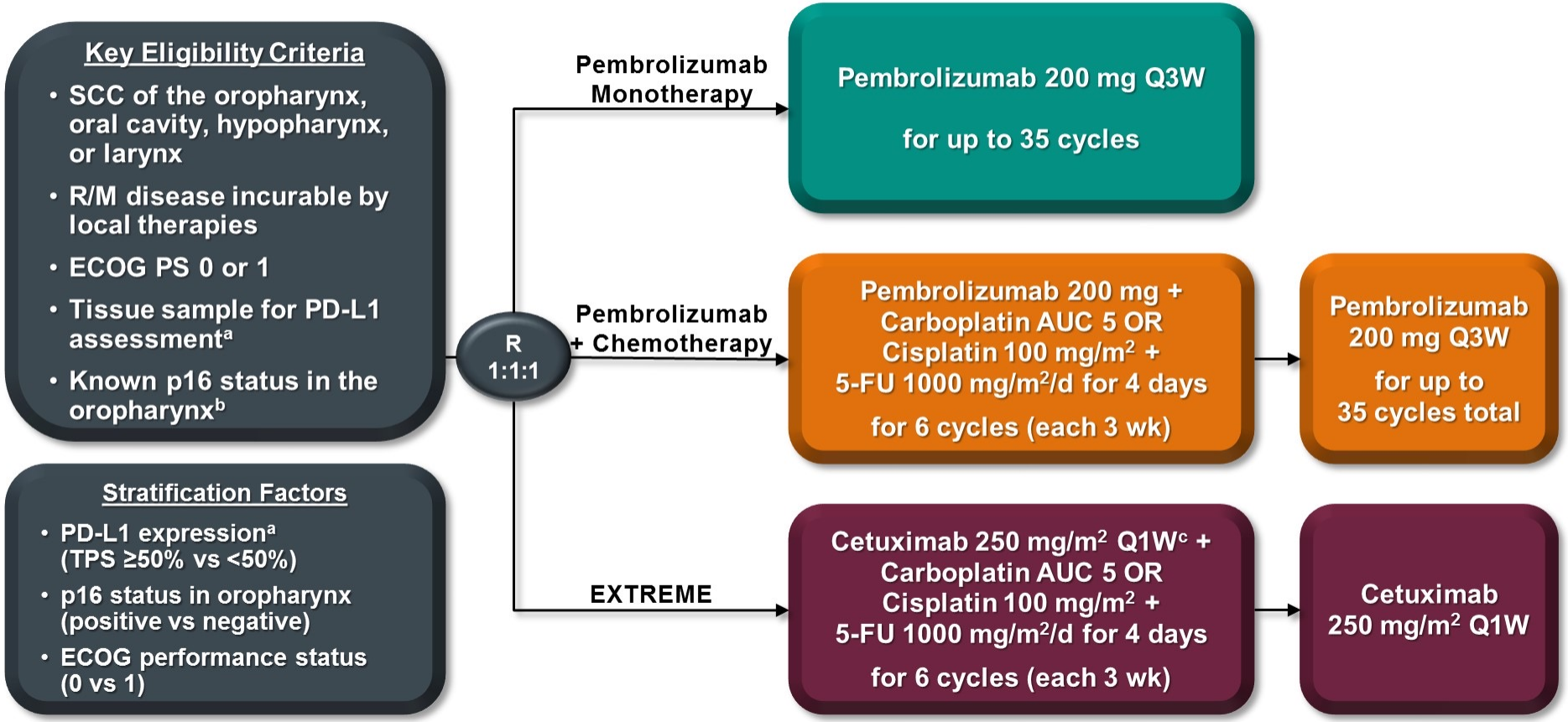
	Median OS, mo (95% CI)	HR (97.73% CI)	p-value
Nivolumab (n = 240)	7.5 (5.5–9.1)	0.70 (0.51–0.96)	0.0101
Investigator's Choice (n = 121)	5.1 (4.0–6.0)		



No. at Risk							
Nivolumab	240	167	109	52	24	7	0
Investigator's Choice	121	87	42	17	5	1	0

Ferris et al : NEJM 2016

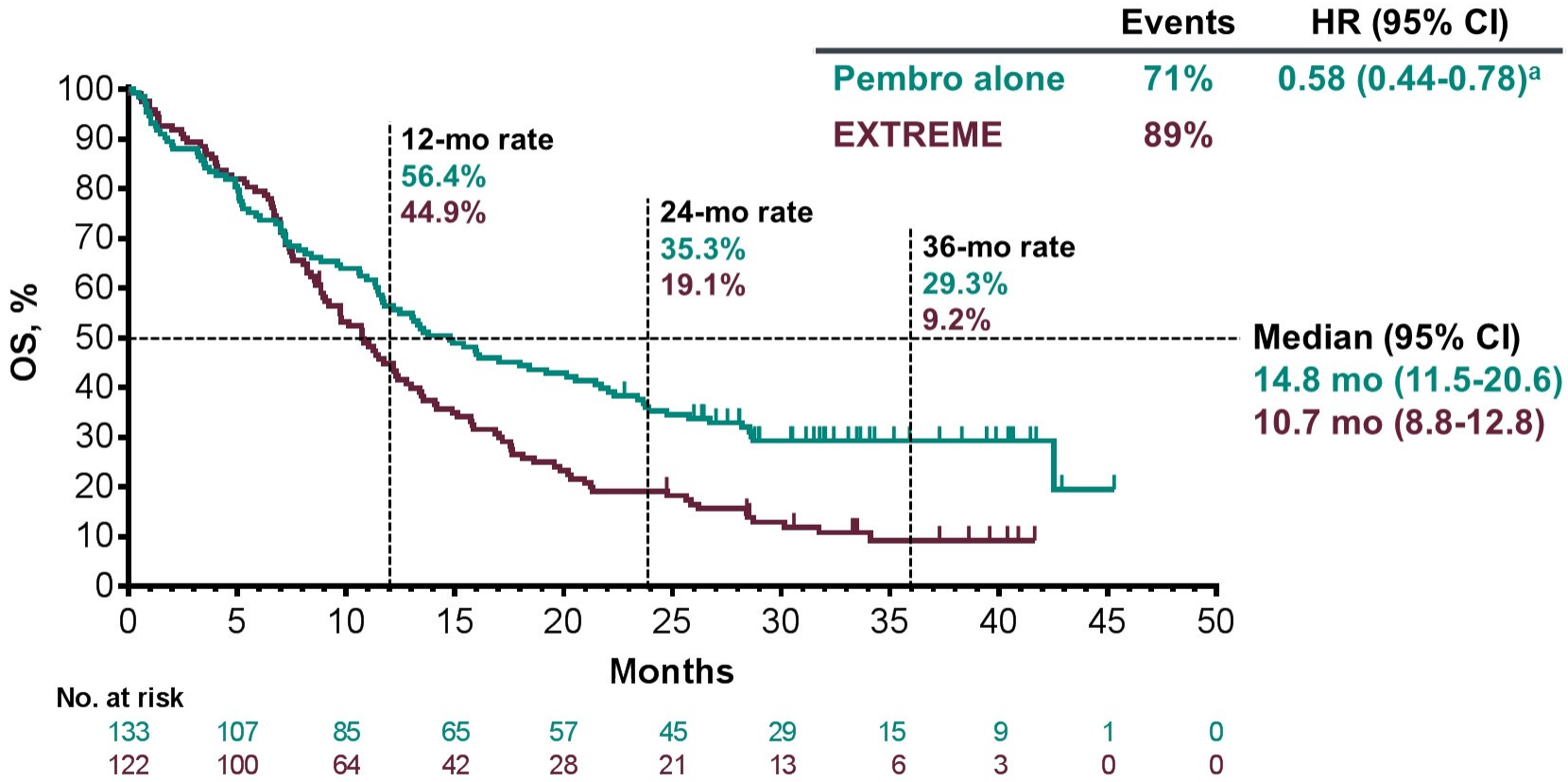
KEYNOTE-048 Study Design (NCT02358031)



[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.

Rischin et al, ASCO 2019

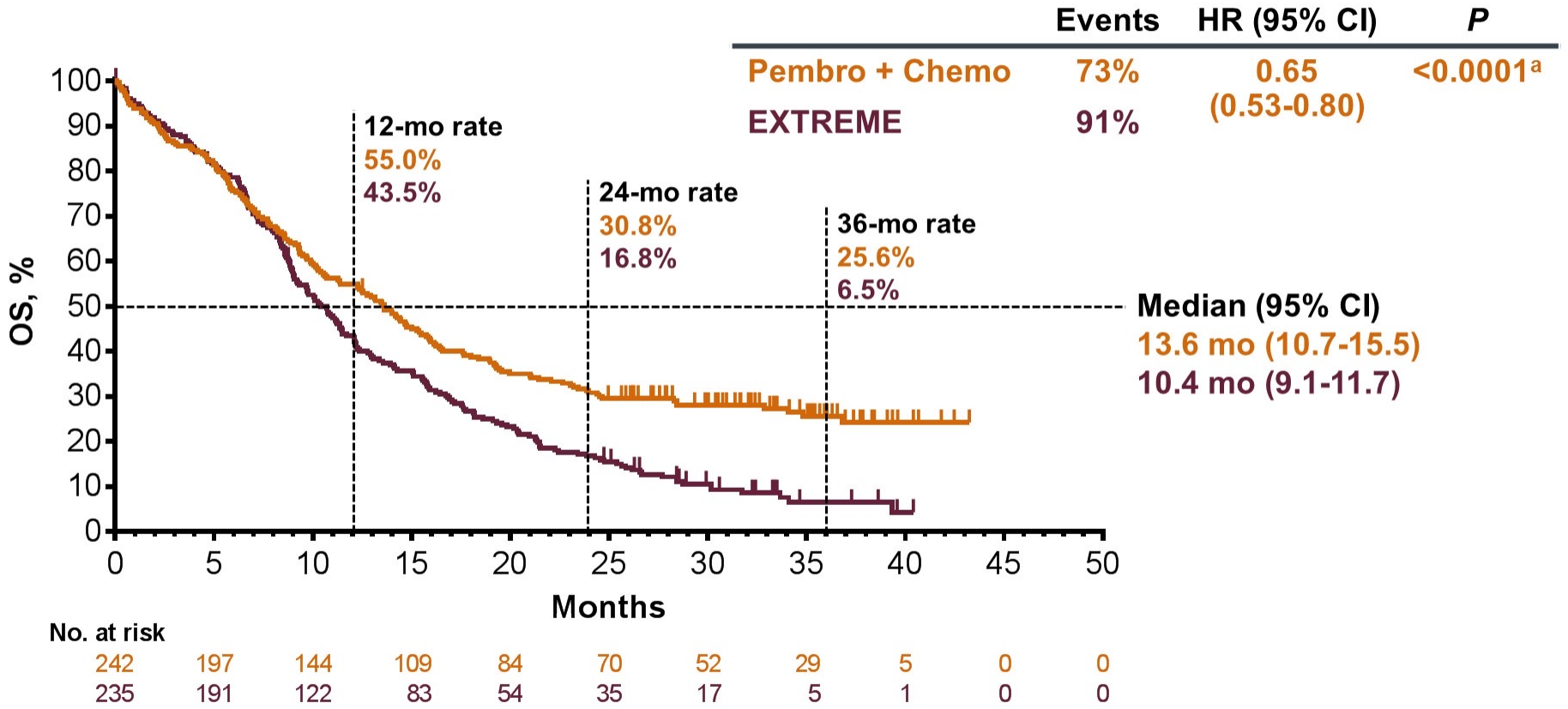
OS, P vs E, CPS ≥20 Population



[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).

Rischin et al, ASCO 2019

OS, P+C vs E, CPS ≥1 Population



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

Rischin et al, ASCO 2019

Immunotherapy in Recurrent and Metastatic Disease

- First-Line Immunotherapy with a PD-1 Inhibitor Only or with Chemotherapy is Indicated for a CPS Score > 20
  - Chemotherapy with a Platinum/5 FU or a Platinum/Taxane Doublet May be Given in this Setting for 3-6 cycles before giving IT only
  - First-line Immunotherapy with Chemotherapy is Indicated for a CPS Score ≥ 1-20 or if a Rapid Response is Needed (Any CPS).
- First or Second Line Immunotherapy With A PD-1 Inhibitor And Chemotherapy Is Indicated Regardless Of CPS Score
- A Clinical Trial is Preferred For Any Patient with Recurrent and Metastatic Disease

Biology and Treatment of Nasopharynx Cancer

- Nasopharynx Cancer Is Endemic In Certain Parts Of The World
  - China, Cambodia, Thailand, Korea, India, Middle East, Northern Africa
- Endemic Nasopharynx Cancer Is Caused By Epstein Barr Virus
  - 99% Of Human Beings Asymptomatically Carry EBV In Their B Cells
  - EBV causes multiple other tumors including lymphomas, Hodgkin's disease, and NKT-cell malignancies
  - Nasopharynx Tumor Cells Have An Episomal Expression Of EBV Which Can Be Detected By An RNA Immunohistochemical Test Known As EBER
  - Nasopharynx Cancers Are Monoclonal Tumors as Identified By A Monoclonal EBV Episome
  - EBV Fragments Can Be Detected In Plasma Of Patients With Nasopharynx Cancer And Can Be Used For Surveillance And Screening

Treatment of NPC in 2024

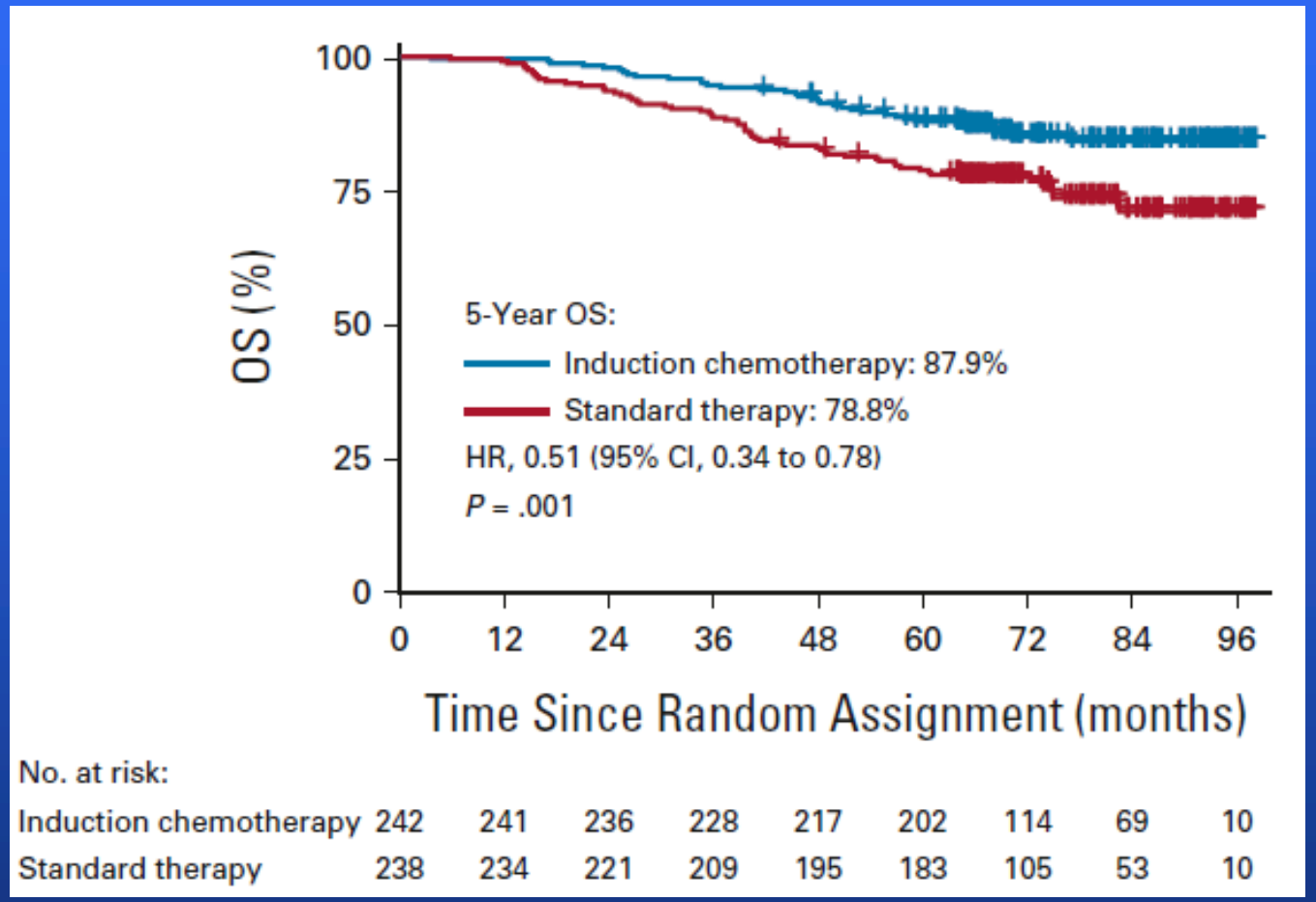
New Diagnosis

- Neoadjuvant Chemotherapy SOC for locally advanced disease
  - T3-4, N1-3 or Any T, N2-3
- Current Paradigm : Sequential Therapy – Induction Chemotherapy followed by ChemoRT
  - Gemcitabine /Cisplatin
  - TPF (Docetaxel, Cisplatin, 5FU)
- ChemoRT or RT alone for earlier disease

Recurrent/Metastatic disease

- Gemcitabine/Cisplatin plus PD-1 Blockade

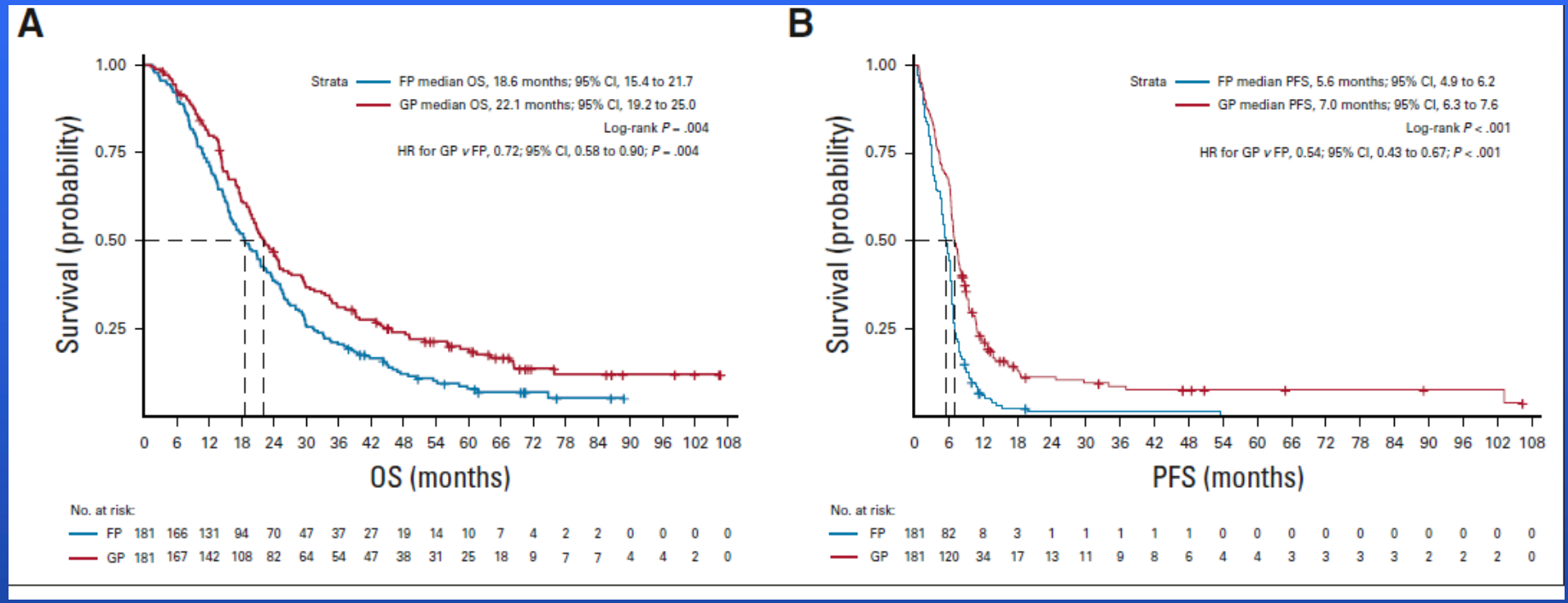
Gemcitabine/Cisplatin Induction Chemotherapy *vs* CRT for NPC



Zhang et al, JCO 2022

Gemcitabine/Cisplatin vs Cisplatin/5-FU for R/M NPC

Survival **PFS**



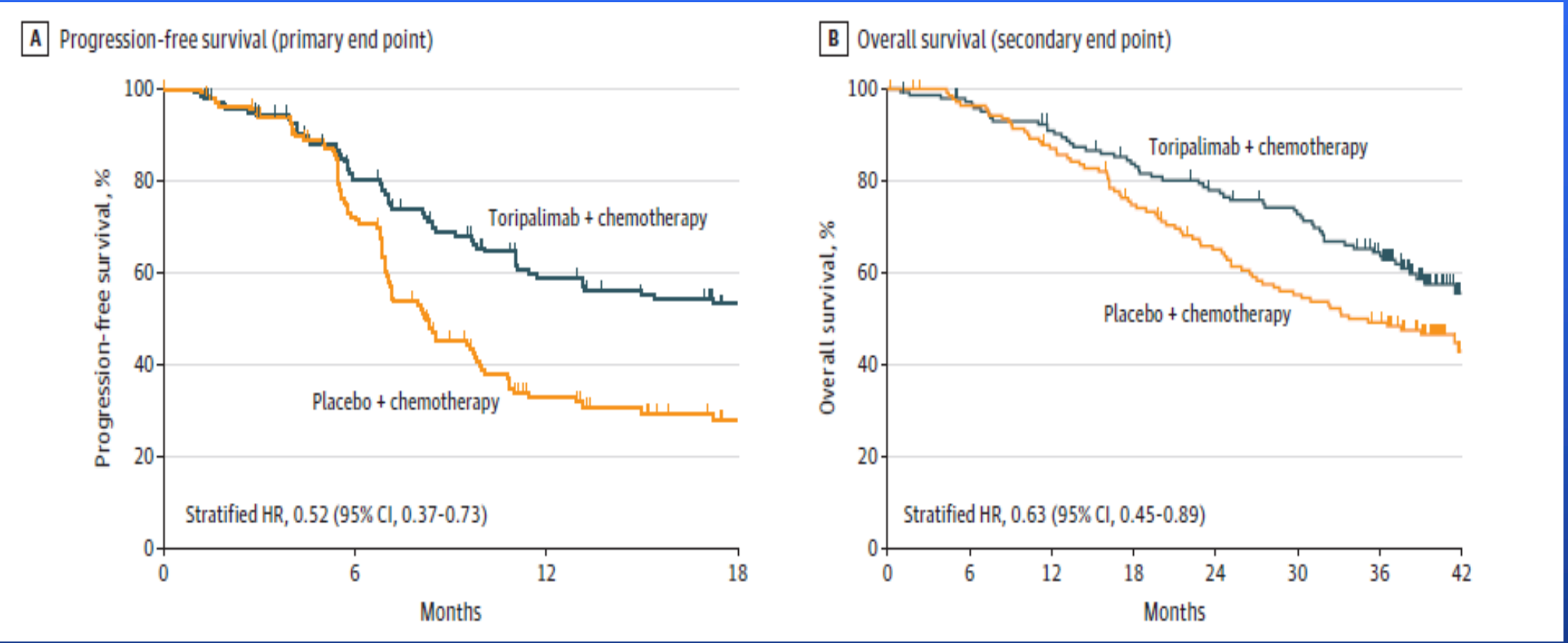
Gemcitabine (1 g/m² on days 1 and 8)
Cisplatin (80 mg/m² on day 1)
Every 3 weeks for a Maximum of 6 Cycles

5-FU (1 g/m² days 1-4)
Cisplatin (80 mg/m² on day 1)
Every 3 weeks for a Maximum of 6 Cycles

30-40% Had No Prior Chemotherapy

Hong et al, JCO, 2021

Jupiter Final Analysis Gem/Cis +/- Toripalimab for First Line R/M NPC



About 70% Had Prior Chemotherapy with Primary Treatment

Mai et al JAMA 2023

HPV+ Oropharynx Cancer: Vaccine and Immune Engagement Approaches

- HB200/201 – Phase 2 Alternating infusions of 2 live viruses carrying modified HPV16 E6 and E7 HPV genes plus PD-1 IT
- ISA1201b – Blinded Randomized Phase 2 HPV16 E6 and E7 long peptides in Adjuvant with a PD-1 IT vs IT alone
- Cue-101 – Phase 1 and 2 Antibody Structure with HLA Presented E6 and E7 Antigens to Engage Antigen Specific T cells with Attached, Affinity Attenuated, IL-2 molecules to Stimulate Restricted/Selective Activation, in combination with PD-1 IT

Ho, Adkins, Even: ASCO Abstracts, 2024

Key Take Away Points

- Surgery is the Mainstay of Therapy for Early Stage Head and Neck Cancer, Excluding NPC
  - The Patient Is Eligible For Surgery, Surgical Resection Supports Functional Preservation, and Surgery Reduces The Application Of Subsequent Radiation Therapy
- Platinum is the Preferred Radiation Sensitizer in the Postoperative and Definitive Setting.
  - Carboplatin or Carboplatin Doublet is an Alternative for Cisplatin Ineligible Patients
- Induction Chemotherapy plus Chemoradiotherapy is Reasonable Treatment for Organ Preservation and is SOC with Gem/Cis for NPC
- IT is First-Line Treatment for R/M Disease, Preferably with a Platinum Doublet, Including NPC
- Early Clinical Trials Suggests That Induction Chemoimmunotherapy May be an Improvement, Especially in NPC