Treatment Options for Locoregionally Advanced Head & Neck Cancer Patients with a Contraindication to Cisplatin

OncLive CME Course

April 10, 2024

Where discoveries are delivered.℠

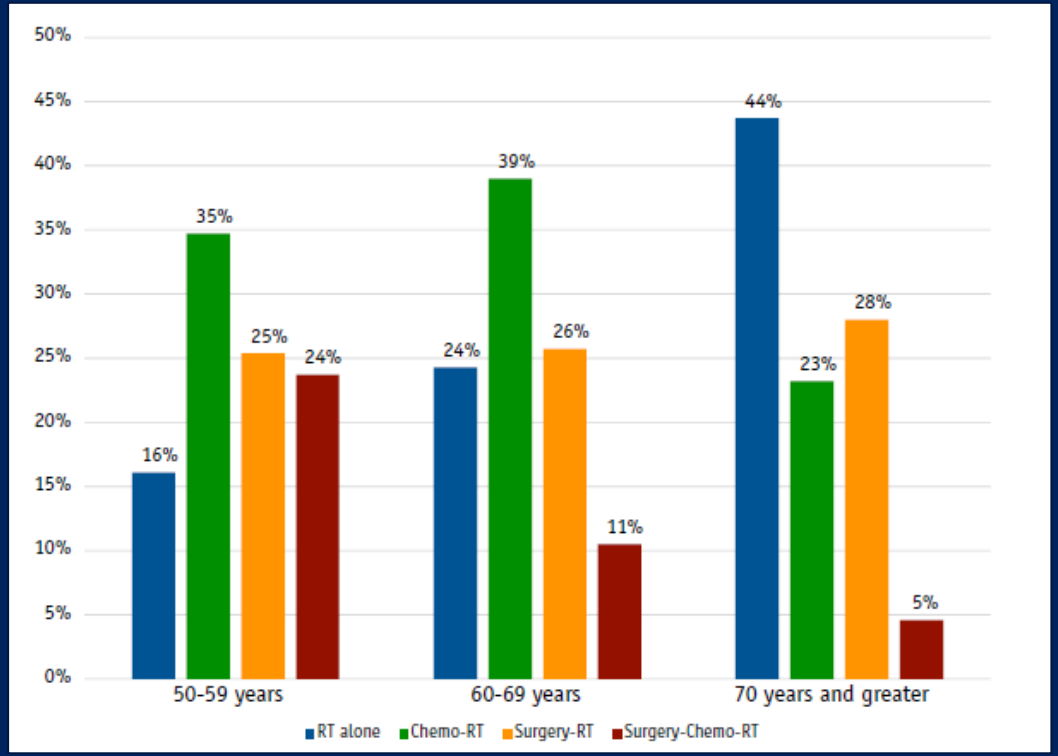
UC San Diego
MOORES CANCER CENTER

Background

- Concurrent RT with cisplatin (40 mg/m^2 weekly or 100 mg/m^2 tri-weekly) is standard of care for locoregionally advanced HNSCC

- However, many HNSCC patients have a contraindication to cisplatin, due to advanced age or comorbidities
  - Poor Performance Status
  - Renal Insufficiency
  - Hearing Loss / Neuropathy

Juarez et al. 2017

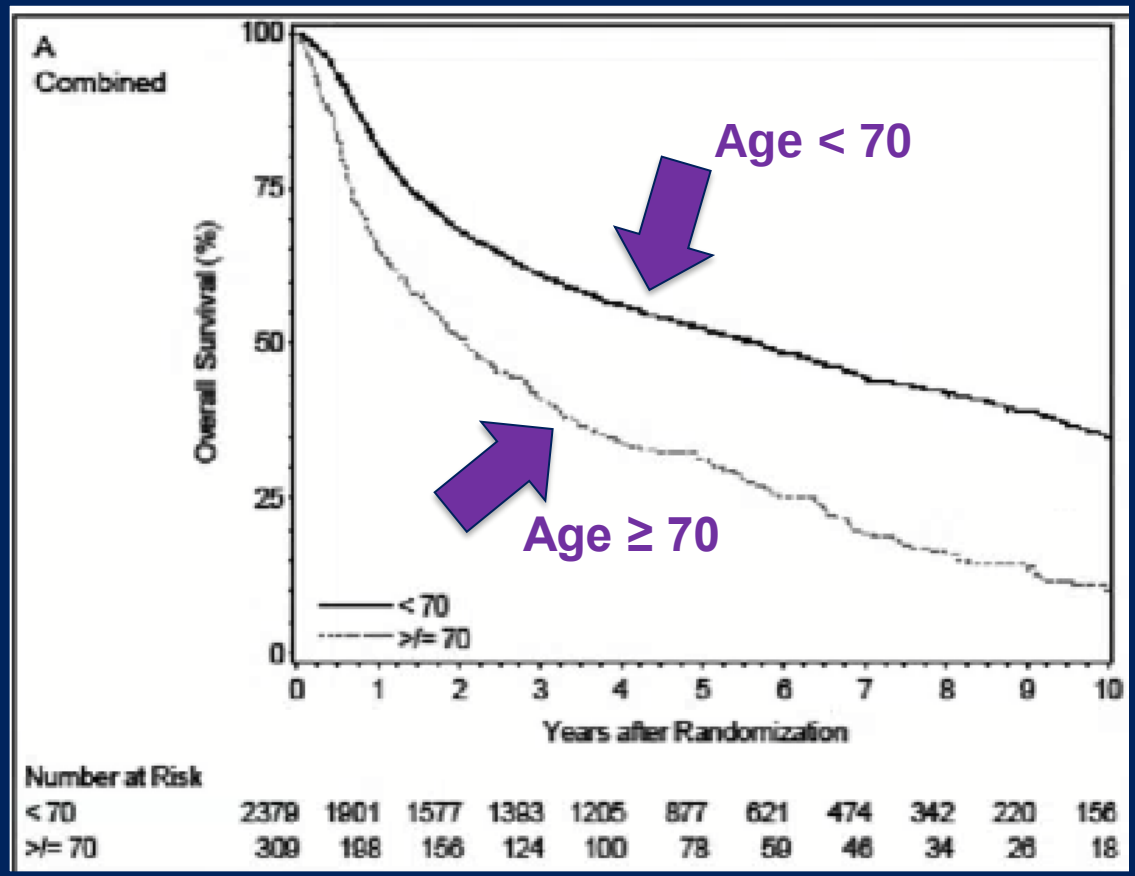


UC San Diego
Moores Cancer Center

Poor Outcomes for Older Patients

- Many studies have documented poor outcomes for older or medically unfit patients (2Y PFS ~40%)
- Poorer fitness for intensive therapy → worse disease control
- Poorer underlying health → increased competing mortality

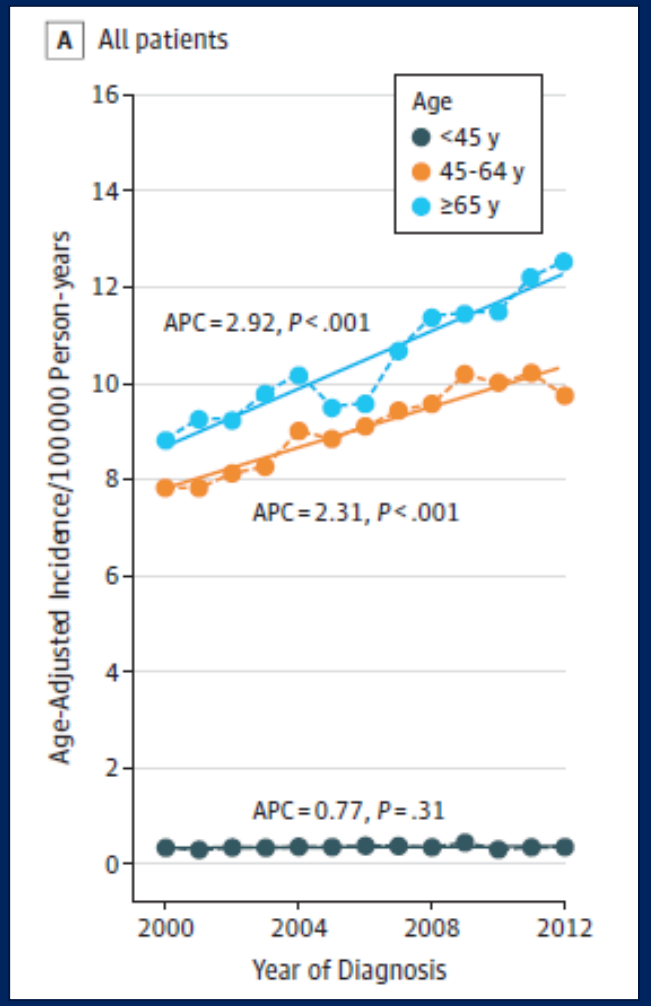
Kish et al. J Geriatr Oncol 2021
RTOG Trial Data



Increasing Prevalence of HNSCC in Older Patients

- Approximately 1/3 of the HNSCC population is > 65
- Incidence of HNSCC rising among older patients
- People living longer with comorbid illnesses (~10-15% of HNSCC patients with severe comorbidity)
- More than 50% of patients > 70 will not receive cisplatin even if otherwise indicated

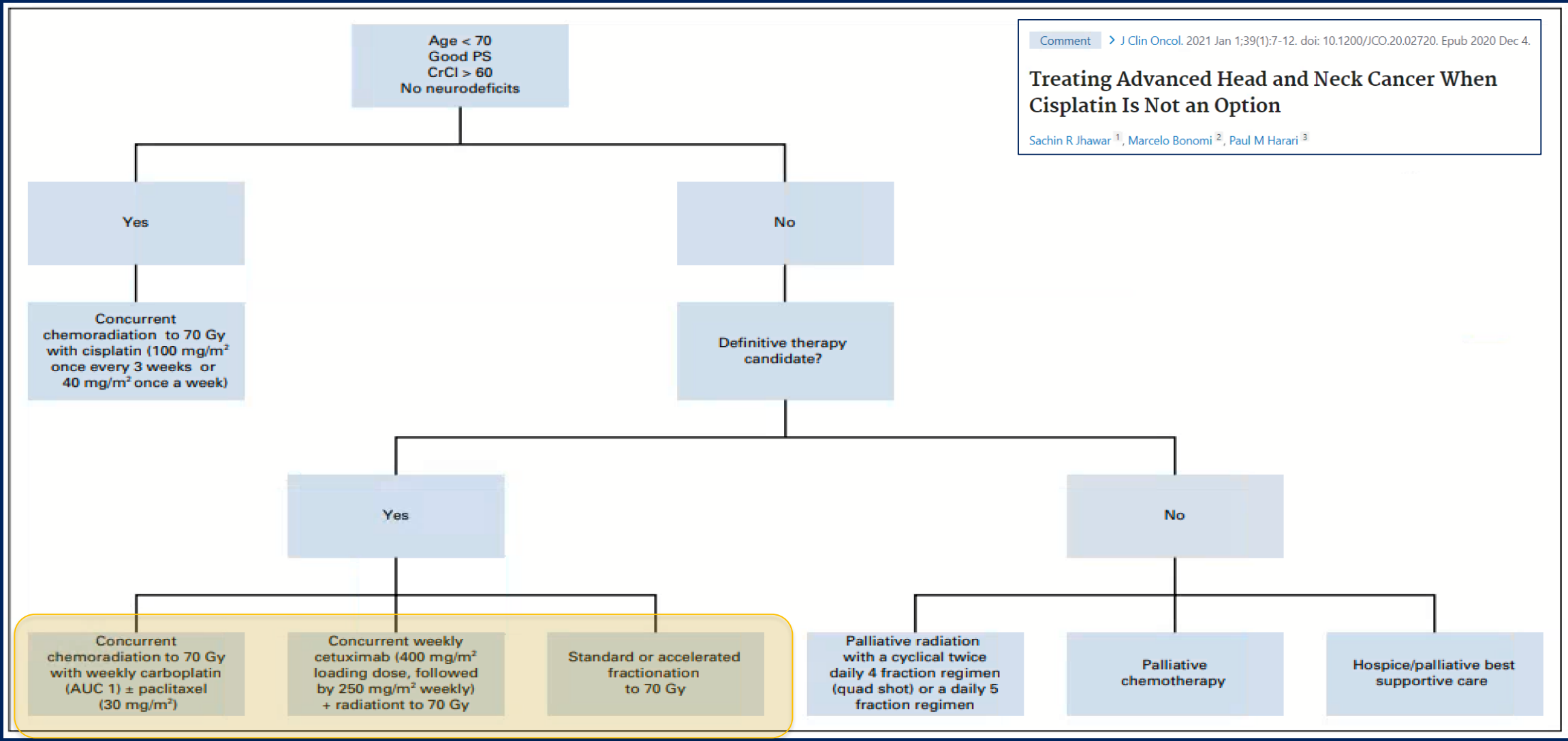
Zumsteg et al. 2016



Challenges with Conducting Trials in This Population

- Older patients / patients with comorbidities under-represented in most trials
- No universally agreed upon standard of care
- Lack of uniform definition of cisplatin ineligibility

Treatment Options in Cisplatin Ineligible Patients



Comment › J Clin Oncol. 2021 Jan 1;39(1):7-12. doi: 10.1200/JCO.20.02720. Epub 2020 Dec 4.

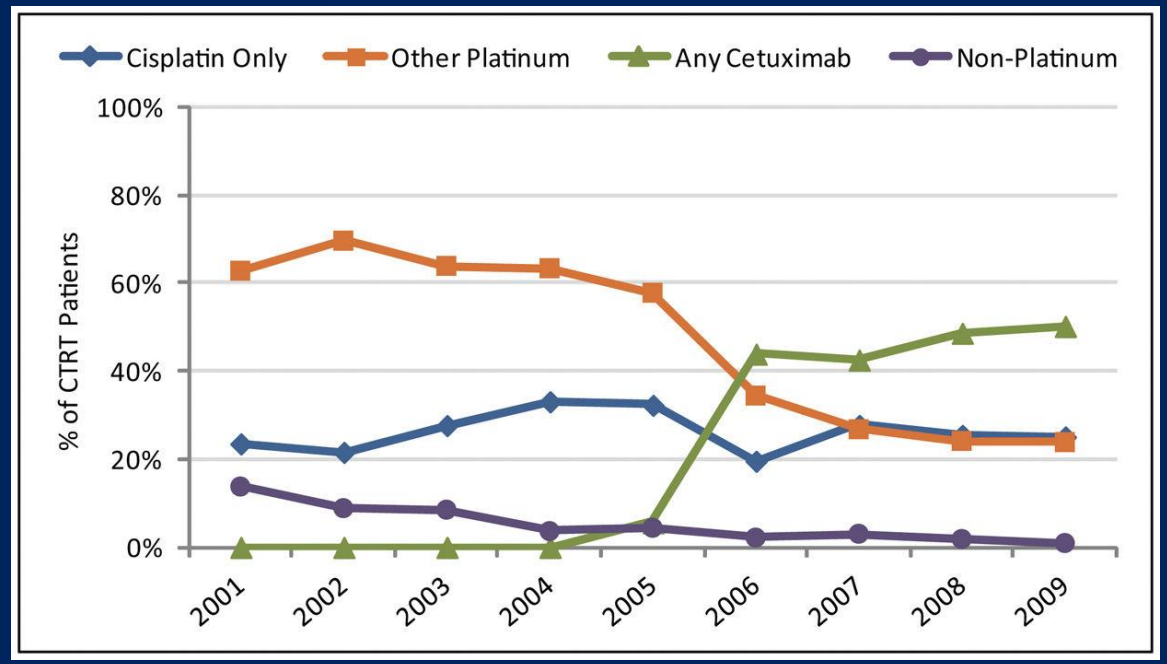
Treating Advanced Head and Neck Cancer When Cisplatin Is Not an Option

Sachin R Jhawar [1], Marcelo Bonomi [2], Paul M Harari [3]

Alternatives to Cisplatin

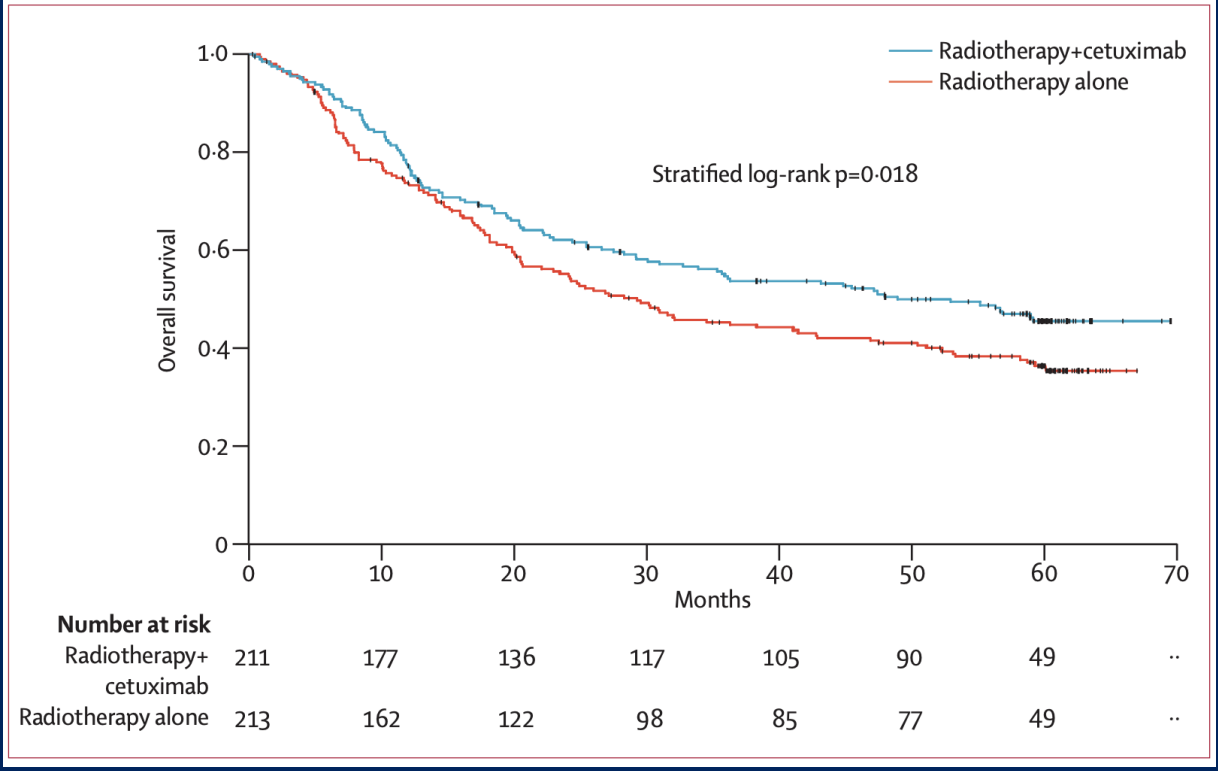
- #1 Cetuximab
  - Most common regimen in U.S./Europe, used in ~2/3 of cases
  - FDA-approved / standard dosing
- #2 Carboplatin and/or Taxane-based Chemotherapy
  - Favored by some institutions
  - Lack of head-to-head data
- #3 RT alone
  - Used primarily in frail populations
  - Likely inferior to RT + radiosensitizer

Baxi et al. 2016
U.S. Medicare / SEER



UC San Diego
Moores Cancer Center

RT+Cetuximab (Bonner et al.)



- Conducted in cisplatin-eligible population
- Did not include patients with medical comorbidities
- Median age was 56
- Trend toward worse outcomes in older patients

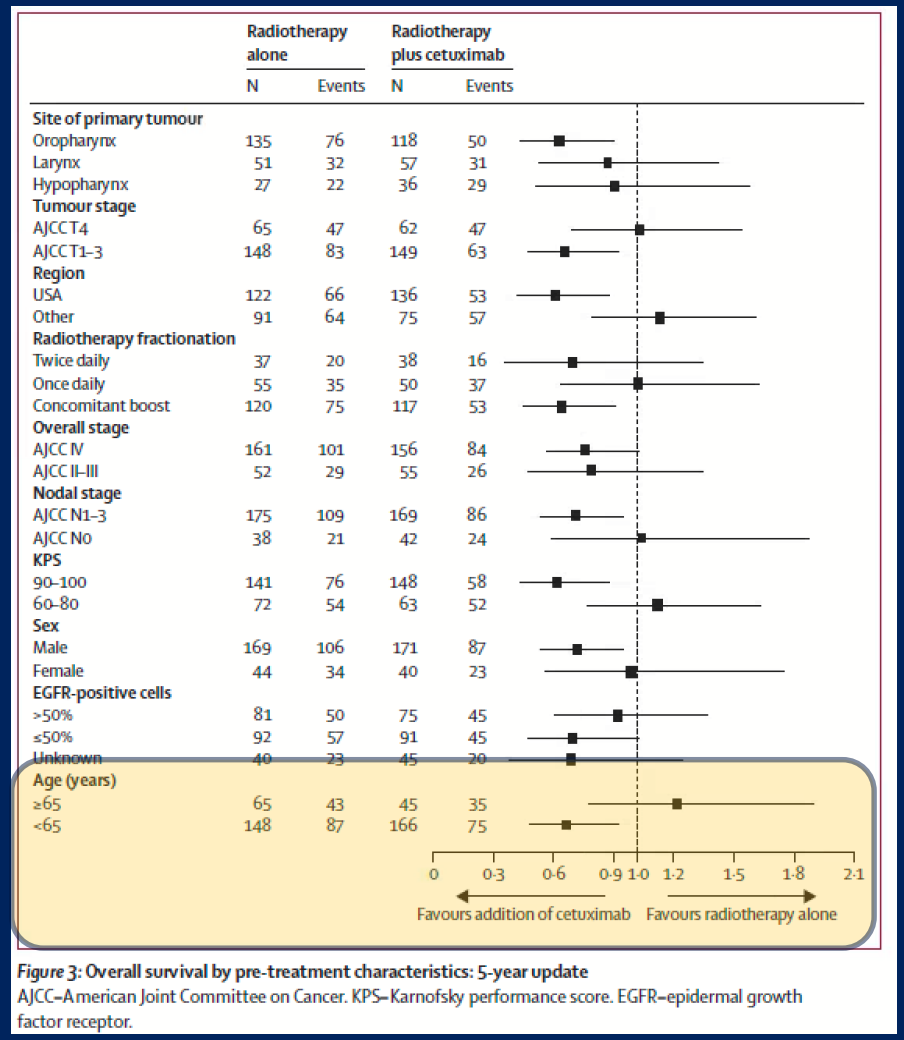
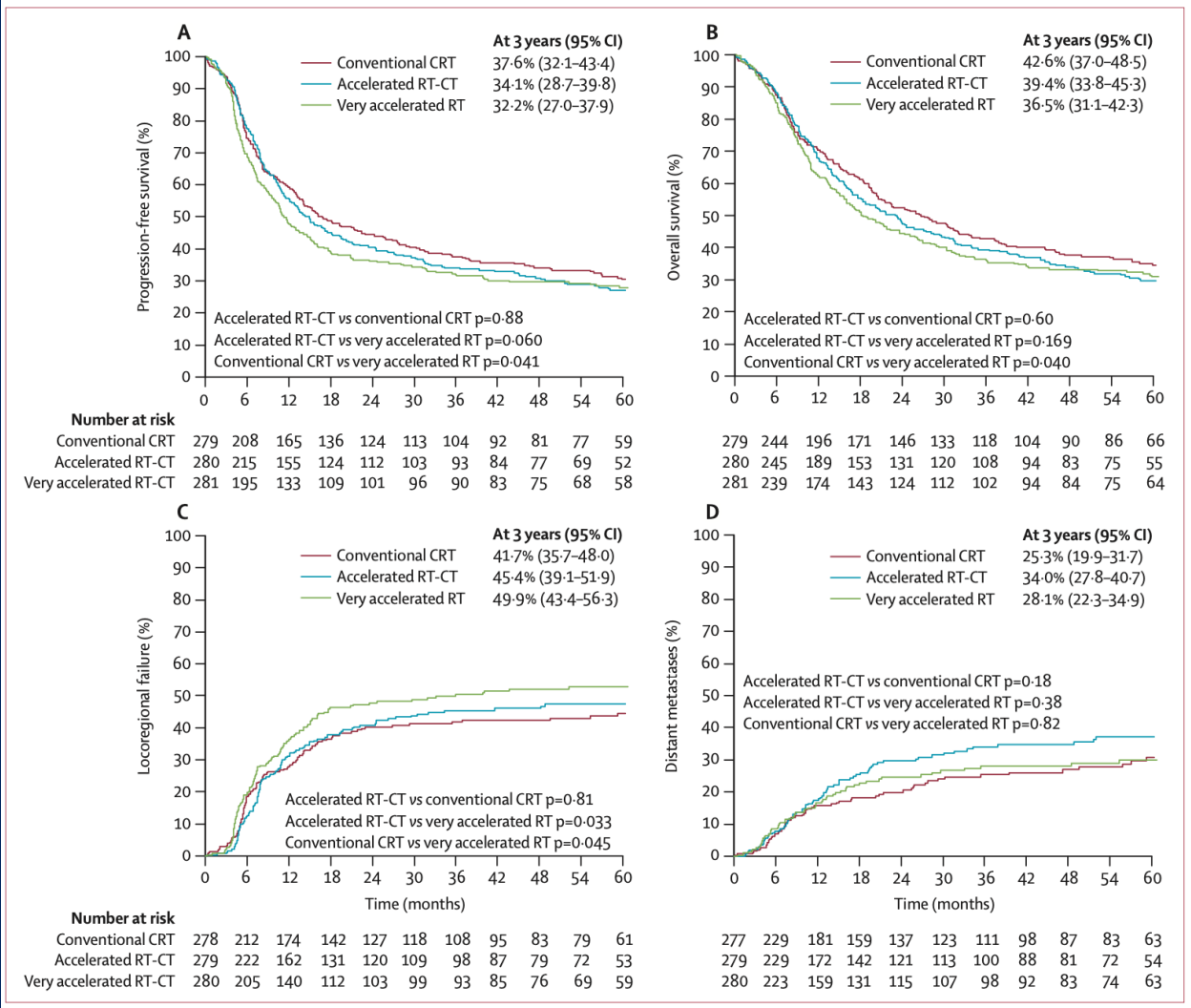


Figure 3: **Overall survival by pre-treatment characteristics: 5-year update**
AJCC=American Joint Committee on Cancer. KPS=Karnofsky performance score. EGFR=epidermal growth factor receptor.

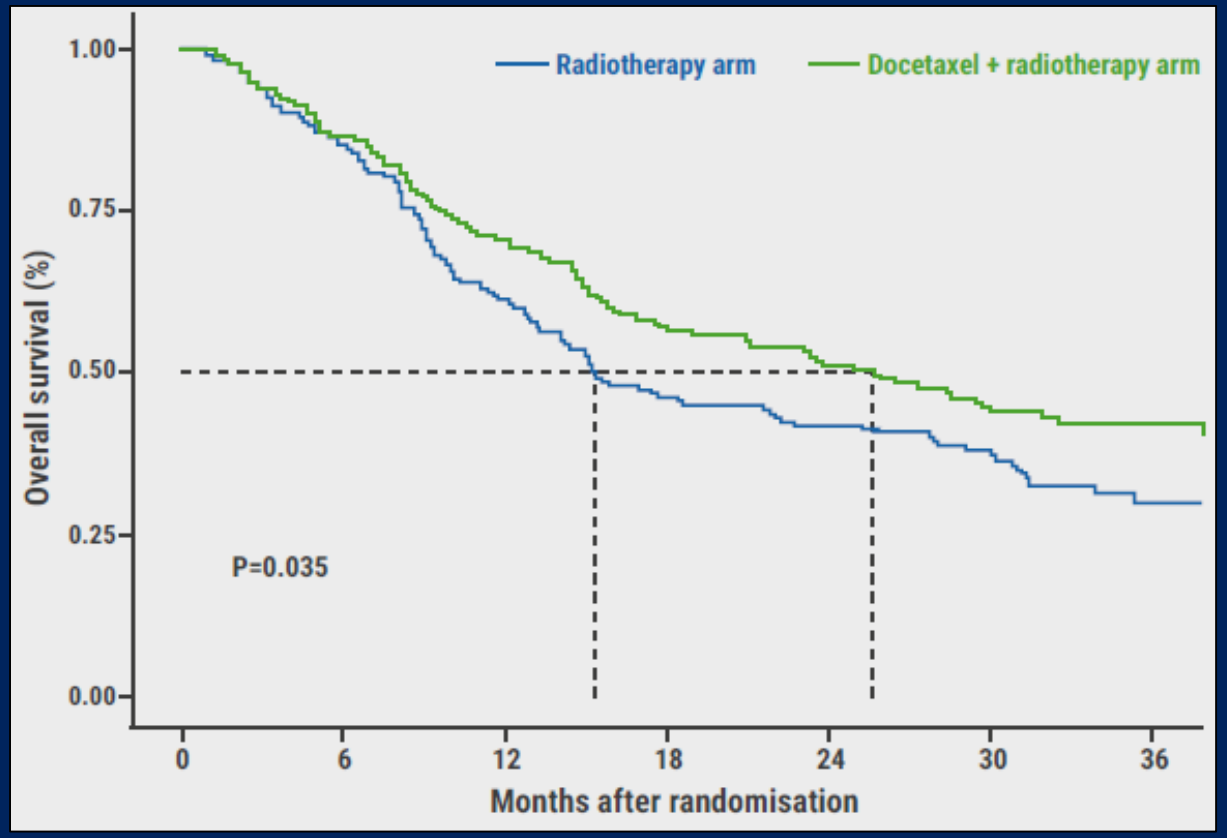
GORTEC 99-02 (Bourhis et al. Lancet Oncol 2012)



Superior Results with Carboplatin (350 mg/m^2) + 5FU (3000 mg/m^2) x two 5-day cycles over RT with Altered Fractionation

UC San Diego
Moores Cancer Center

DHANUSH (Tata) Trial
Patil et al. JCO 2023

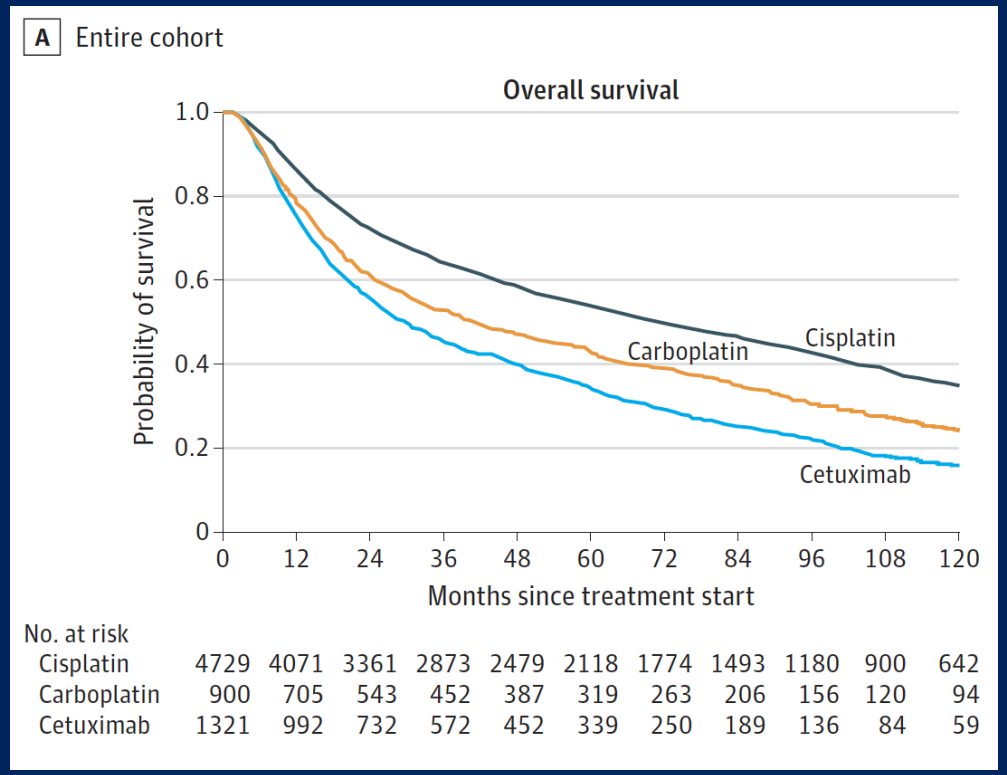


- 356 cisplatin-ineligible patients
- >90% HPV negative
- **2 year DFS 42% for RT/Docetaxel**, 30% for RT Alone
- **2 year OS 51% for RT/Docetaxel**, 42% for RT Alone
- Grade 3+ toxicities in 82% vs. 58% for RT Alone

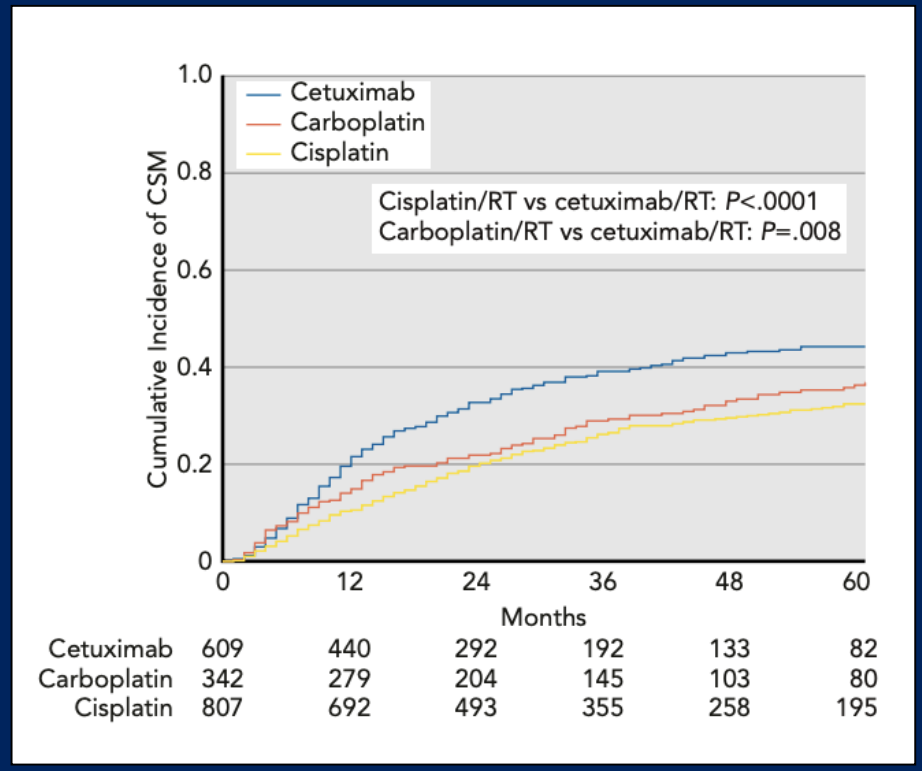
UC San Diego
Moores Cancer Center

Comparative Effectiveness Studies

Sun et al. 2022



Xiang et al. 2019



Selection Bias is a Major Problem in CE Studies

UC San Diego
Moores Cancer Center

What Makes Someone "Ineligible" for Cisplatin?

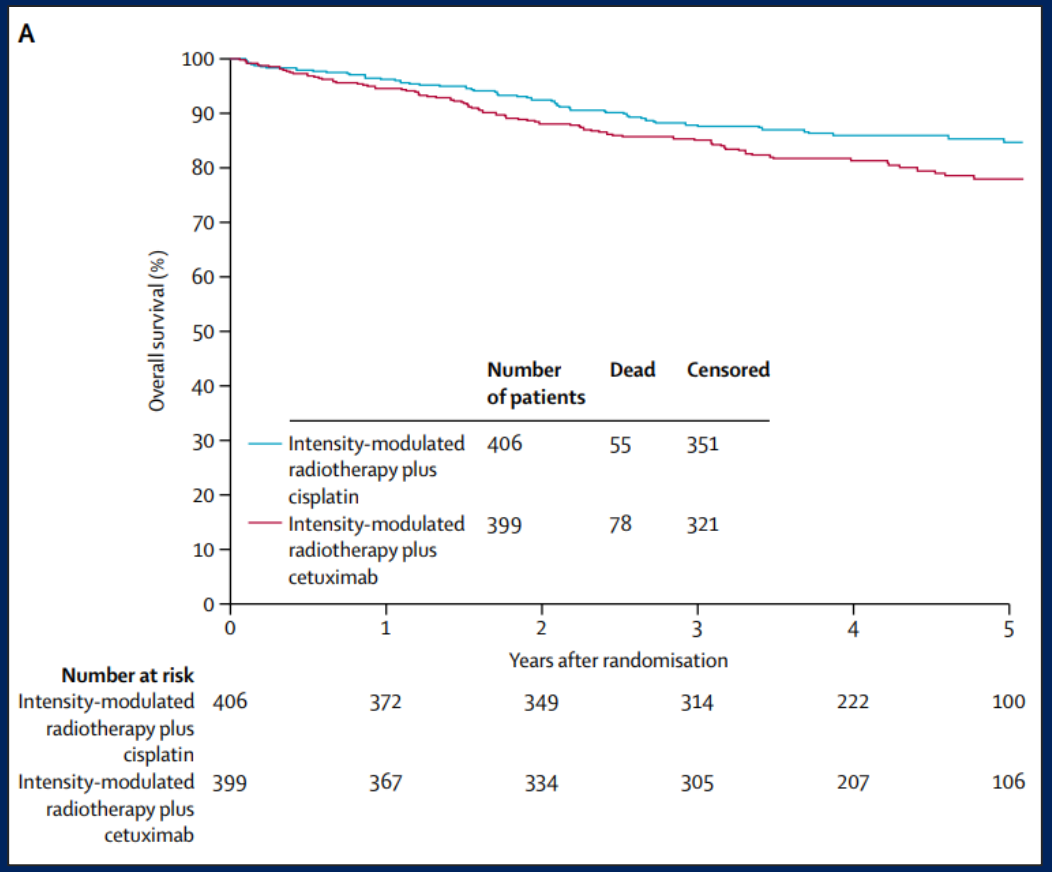
- Absolute Contraindications
  - Renal impairment (CCR < 50)
  - Hearing loss / grade ≥ 2 tinnitus
  - Grade ≥ 2 Neuropathy
  - ECOG ≥ 3
  - Pregnancy, Hypersensitivity
- Relative Contraindications
  - ECOG = 2
  - Significant / Multiple Comorbidities
  - Weight Loss / Low BMI
  - Advanced Age (> 70)
  - ***Frailty Scores***

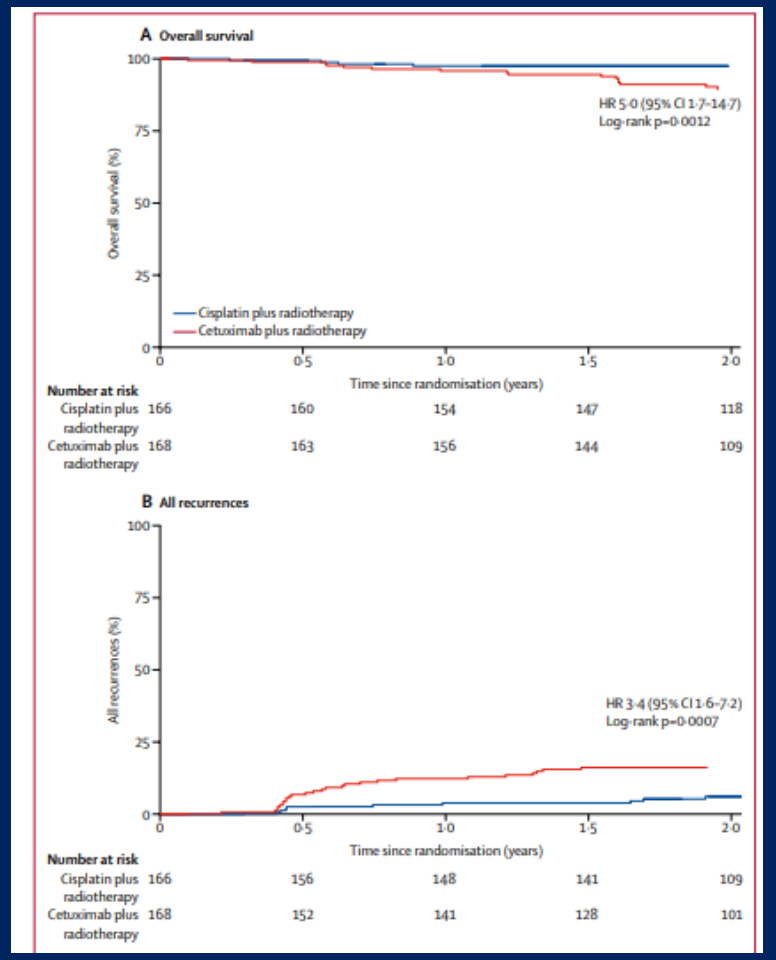
Tata (DHANUSH) Trial Criteria

Population
Nonmetastatic stage III-IV HNSCC (OC, OPX, HPX, LX, CUP) Age ≥ 18 years ECOG PS 0-2 Indication for definitive or adjuvant chemoradiation Definitive: stage III-IV Adjuvant: stage III-IV with either ECE or positive or close (≤ 0.5 mm) margin Cisplatin Ineligible (any of below): ECOG PS 2 Grade ≥ 2 organ dysfunction CCR < 50 mL/min BMI < 16 kg/m^2 > 10% weight loss over 6 months Borderline comorbidities Cisplatin hypersensitivity Concomitant nephrotoxic medications

UC San Diego
MOORES CANCER CENTER

RTOG 1016 & De-Escalate Trials

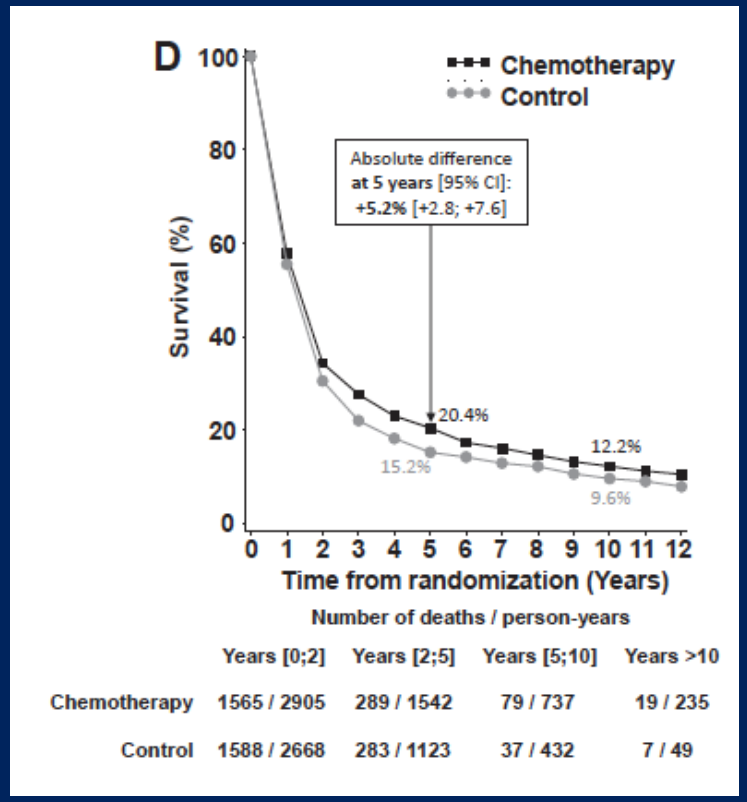


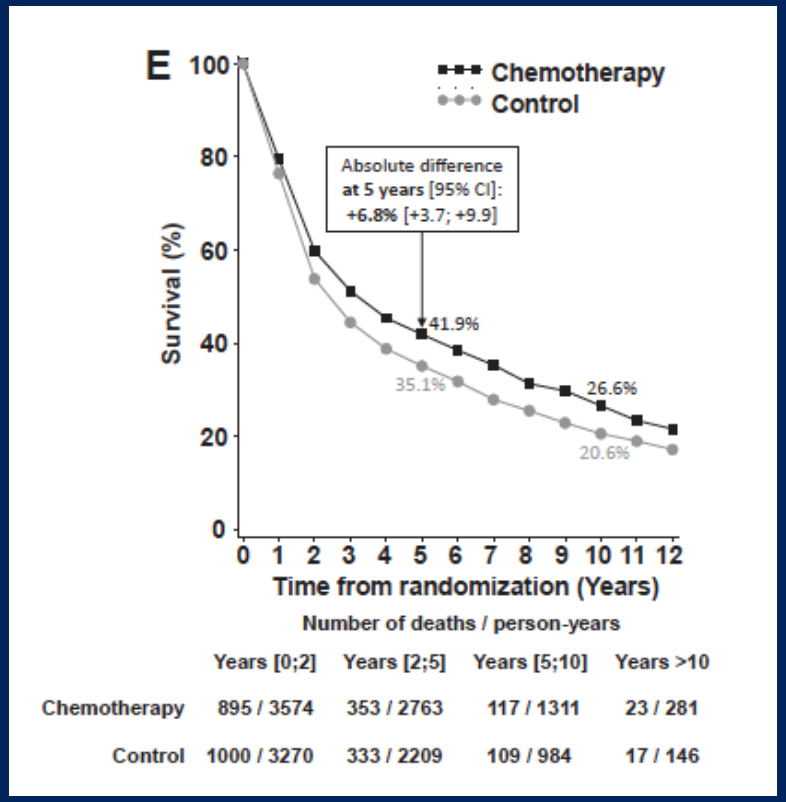


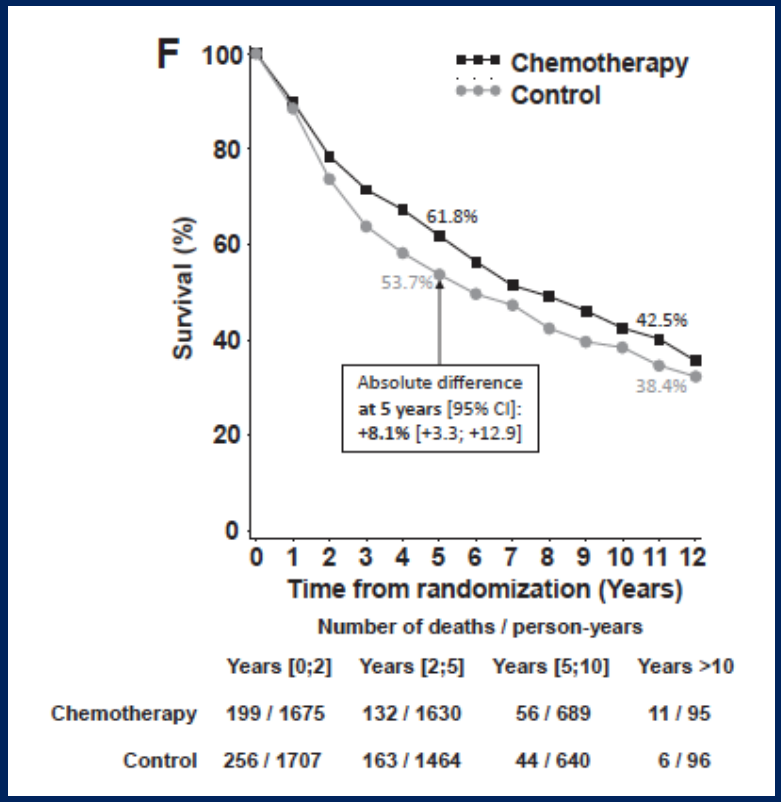
Cetuximab arm had worse OS, PFS, LRF

UC San Diego
MOORES CANCER CENTER

Benefit of Chemotherapy Does Not Vary with Recurrence Risk







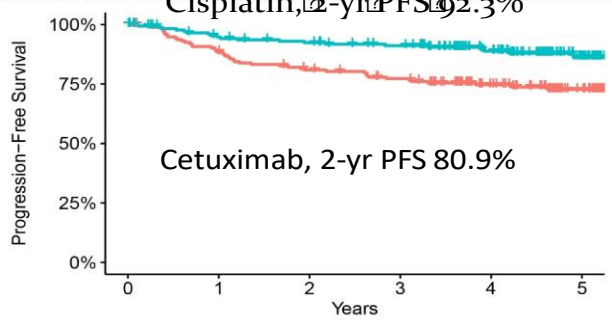
- MACH-NC Meta-Analysis (Zakeri et al.)
- >11,000 HN patients on RCTs

UC San Diego
Moores Cancer Center

Effect of Cisplatin on PFS by Standard Risk Group

Very Low (HN005 Eligible)

Cisplatin, 2-yr PFS 92.3%

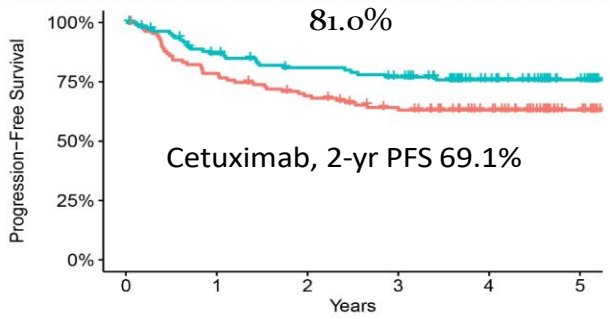


Cetuximab	175	153	137	127	88	46
Cisplatin	179	160	153	144	109	48

HR 0.42 (0.25-0.70)

Low (RTOG 0129)

Cisplatin, 2-yr PFS 81.0%

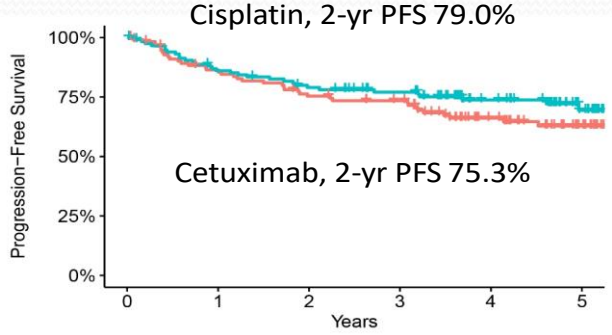


Cetuximab	109	84	72	62	47	24
Cisplatin	110	90	81	75	47	22

HR 0.59 (0.36-0.97)

Intermediate (RTOG 0129)

Cisplatin, 2-yr PFS 79.0%



Cetuximab	115	94	81	75	46	22
Cisplatin	117	98	88	78	52	24

HR 0.76 (0.47-1.22)

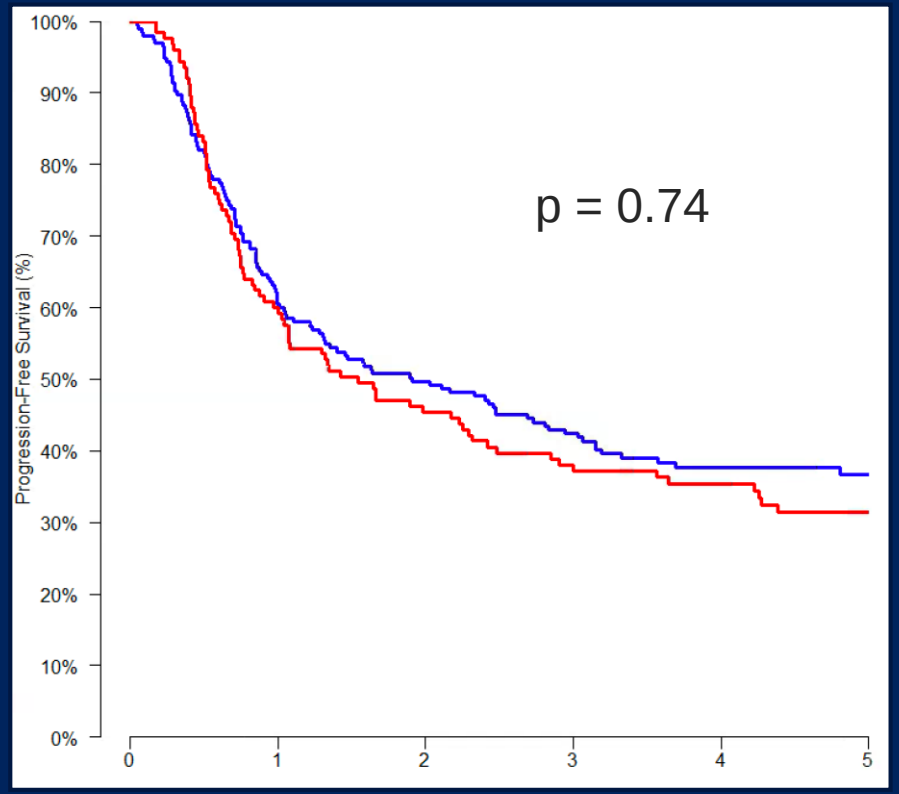
1-sided interaction p=0.94

Cisplatin effectiveness ←

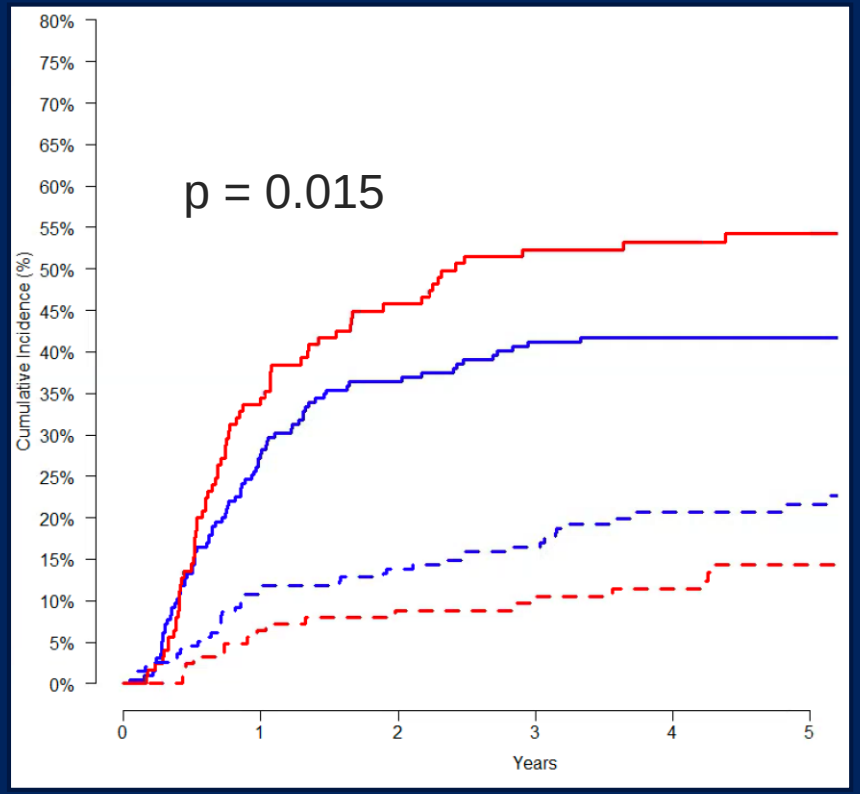
Morse et al. ASTRO 2023

Same PFS, Different Prognosis

Same PFS



Different Relative Risk



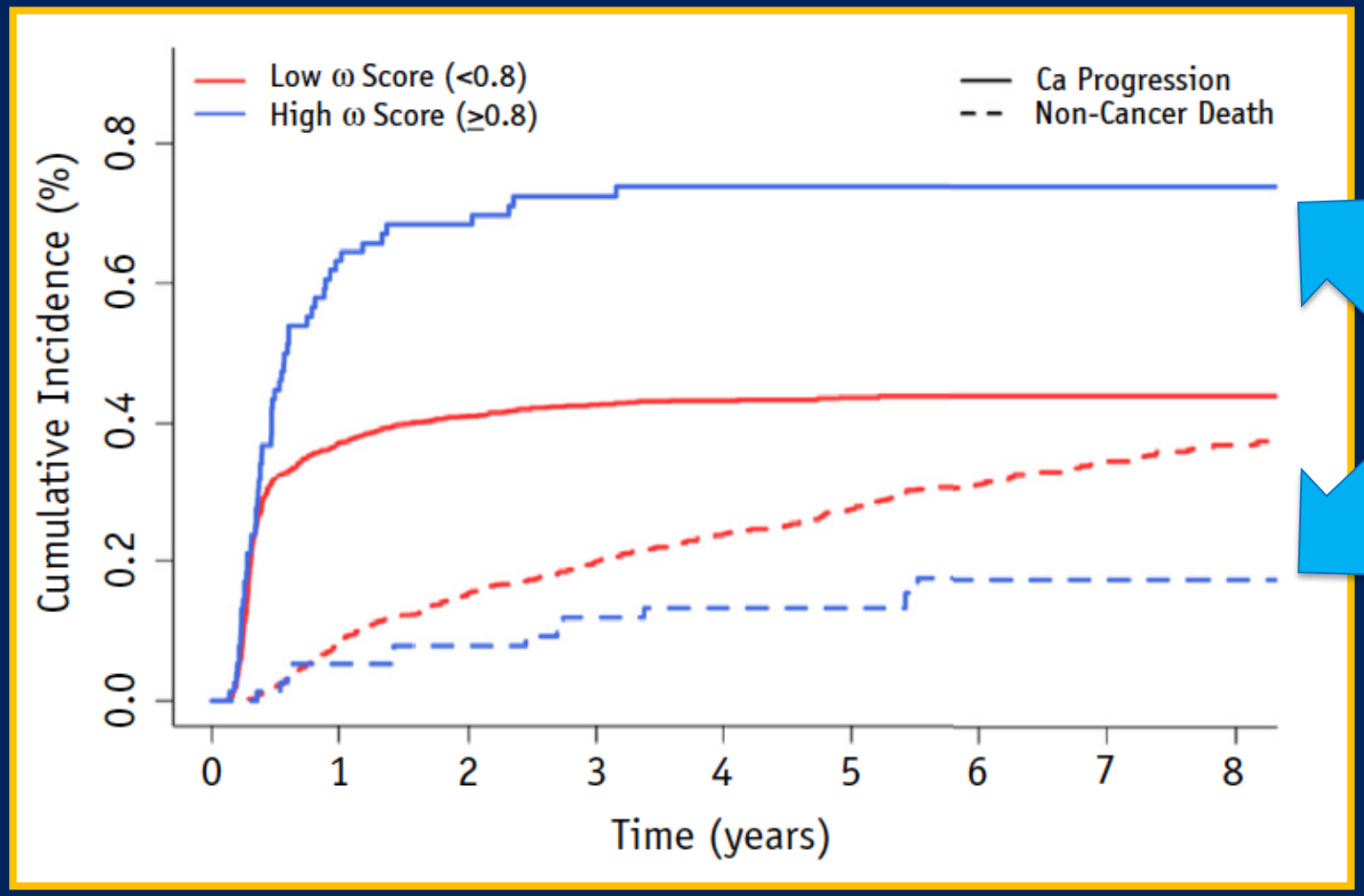
Data courtesy of RTOG (NRG Oncology)

Cancer Event

Competing Event

UC San Diego
Moores Cancer Center

Plotting Relative Risk: Alligator Plots



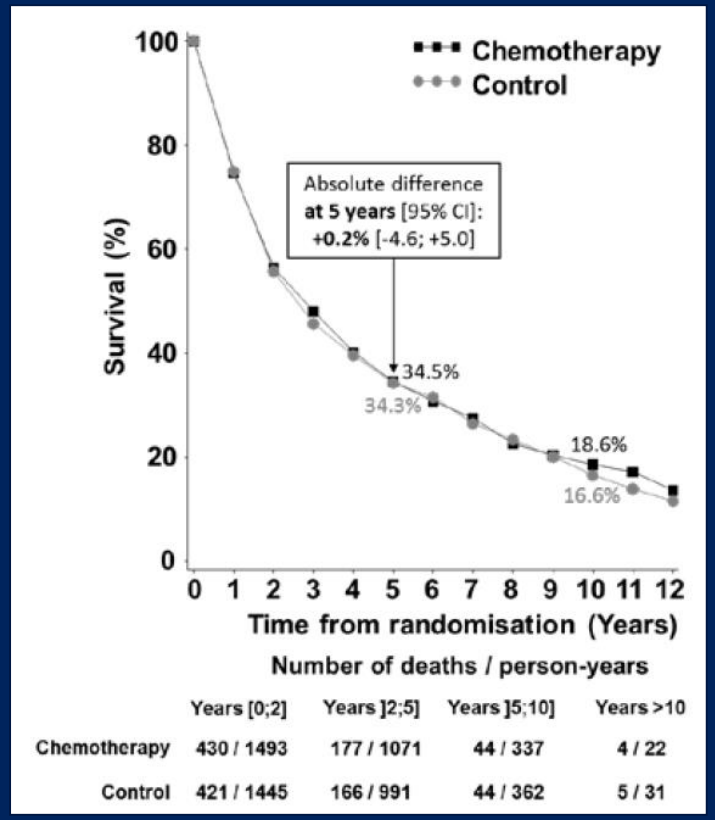
HIGHER RELATIVE RISK FOR CANCER EVENTS

Vitzthum et al. 2020

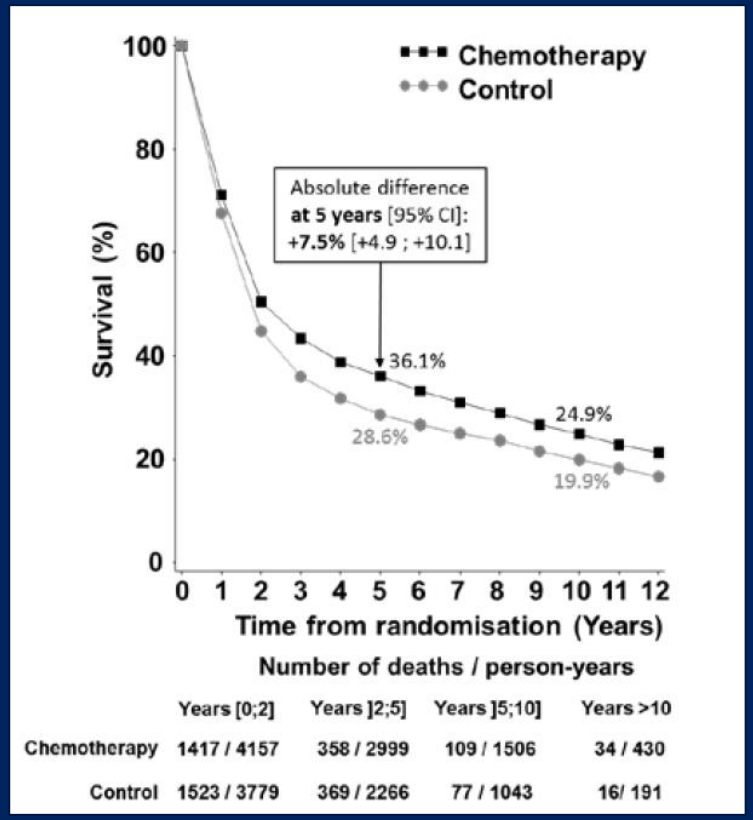
UC San Diego
Moores Cancer Center

Relative Risk Better for Treatment Prediction

ω Score < 0.80



ω Score ≥ 0.80

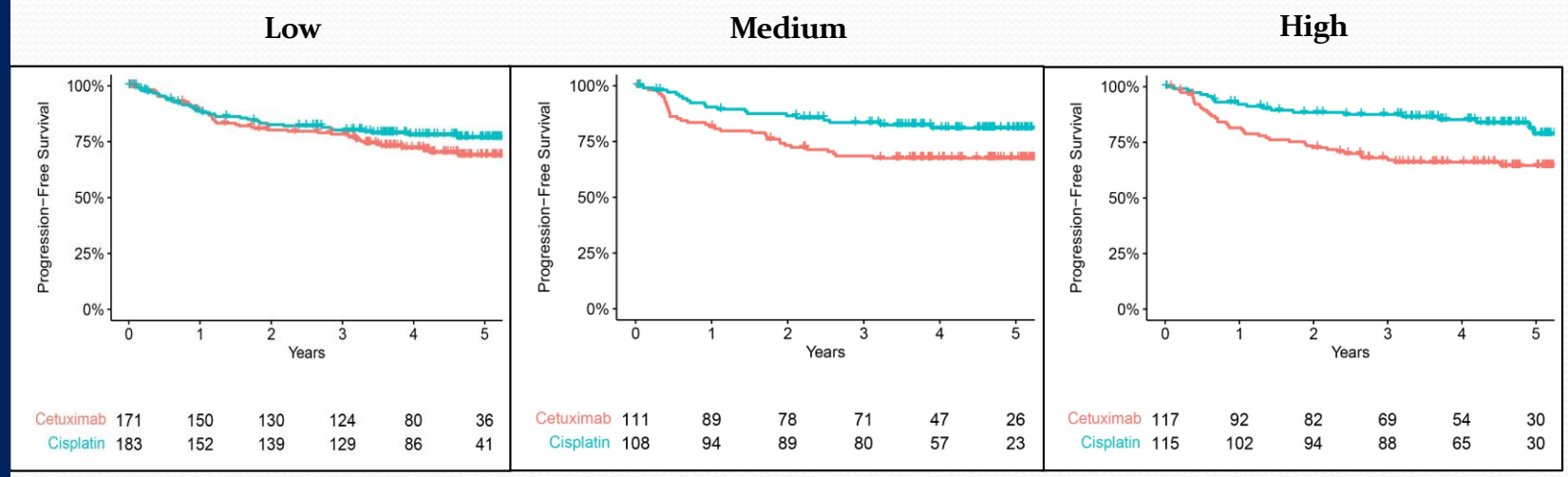


Zakeri et al. Cancer 2020

UC San Diego
Moores Cancer Center

Same Information, Advanced Model

Effect of Cisplatin on PFS by Omega Score (RTOG 1016)



HR 0.75 (0.49-1.15)

HR 0.51 (0.29-0.90)

HR 0.44 (0.25-0.76)

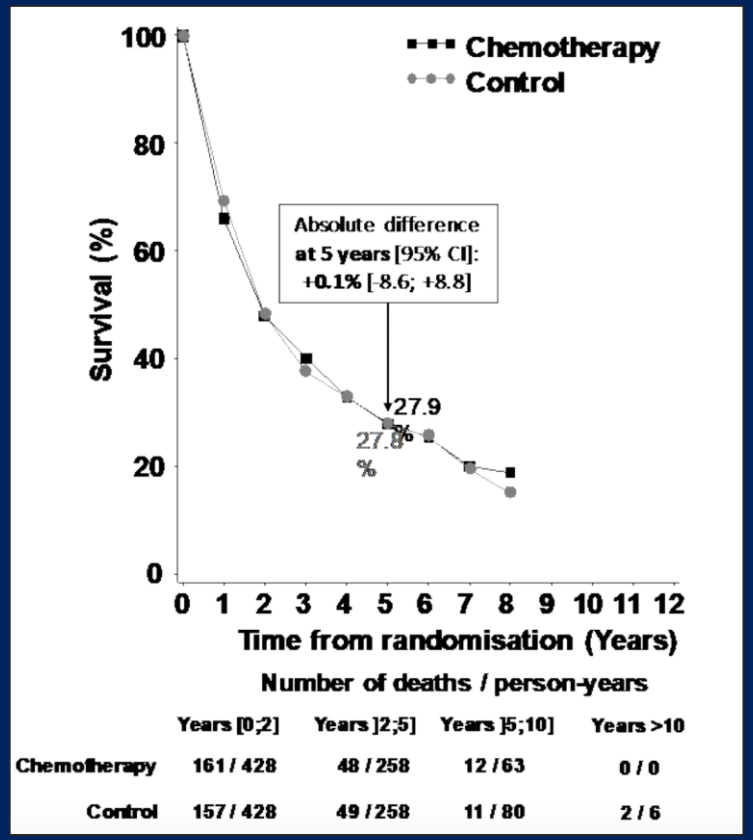
1-sided interaction p=0.055

Cisplatin effectiveness →

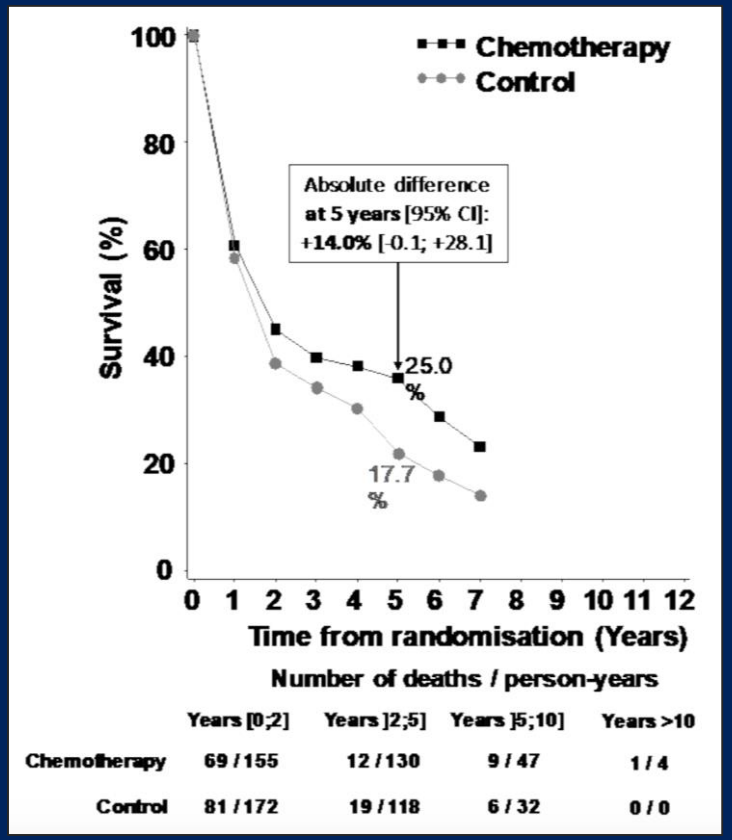
Morse et al. ASTRO 2023

Chemotherapy Effective in Patients > 70 with Higher Relative Risk

ω Score < 0.80



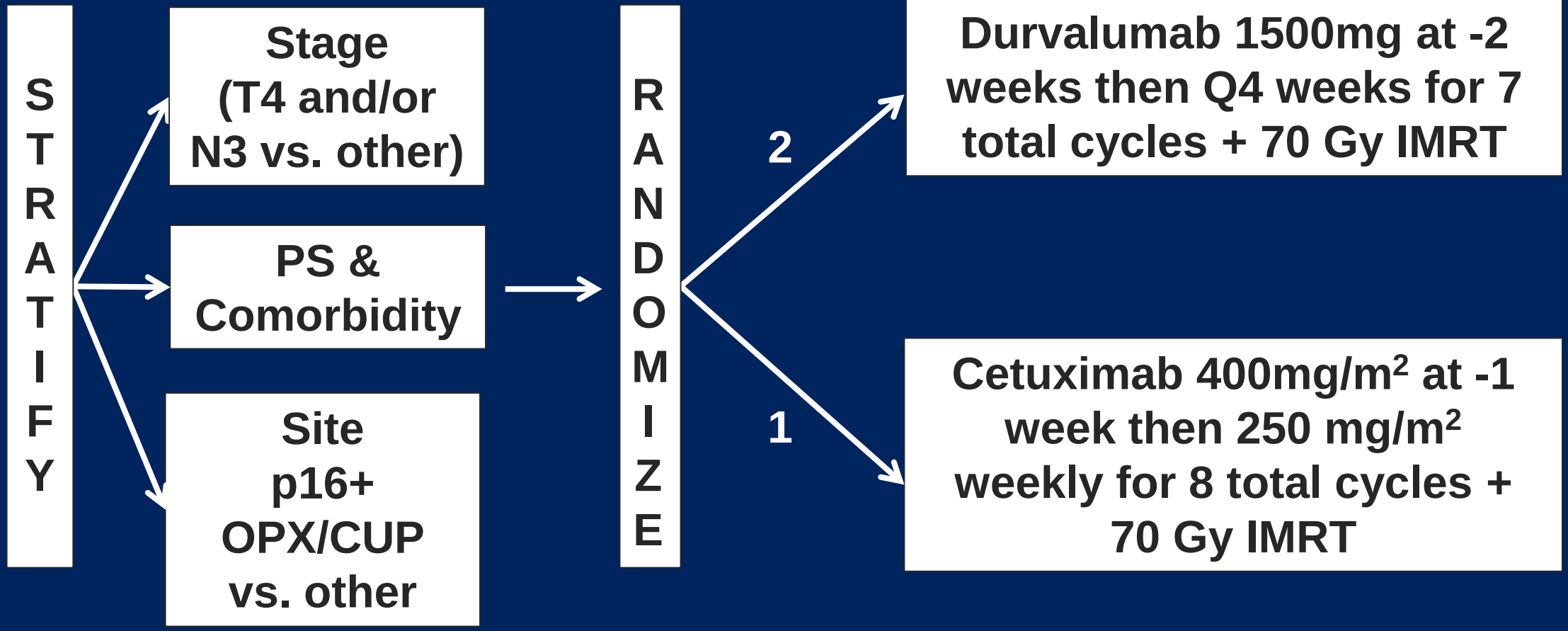
ω Score ≥ 0.80



Zakeri et al. Cancer 2020

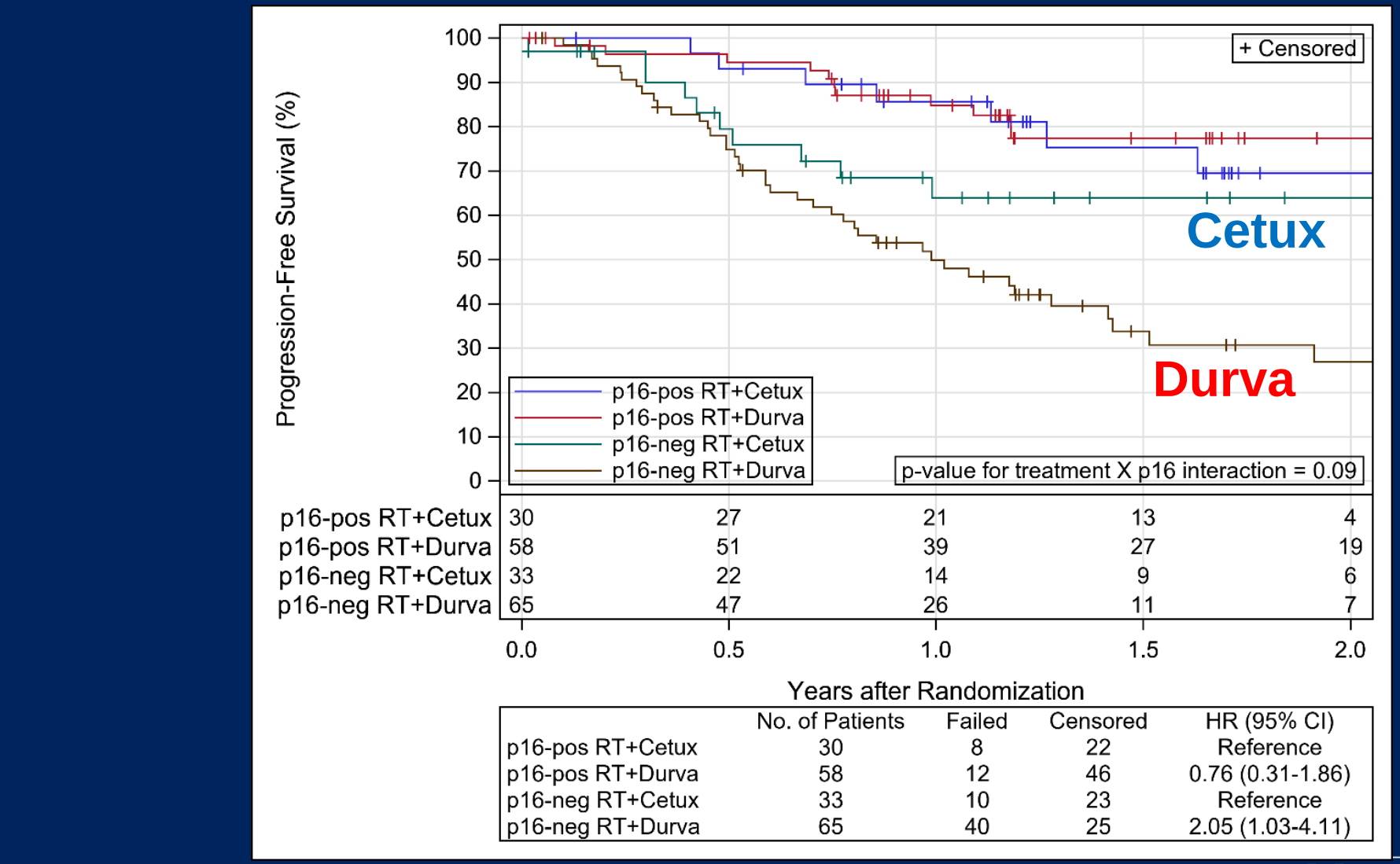
UC San Diego
MOORES CANCER CENTER

NRG HN004 Phase II/III Trial Schema



UC San Diego
Moores Cancer Center

PFS by Treatment & P16 (post-hoc analysis)



	No. of Patients	Failed	Censored	HR (95% CI)
p16-pos RT+Cetux	30	8	22	Reference
p16-pos RT+Durva	58	12	46	0.76 (0.31-1.86)
p16-neg RT+Cetux	33	10	23	Reference
p16-neg RT+Durva	65	40	25	2.05 (1.03-4.11)

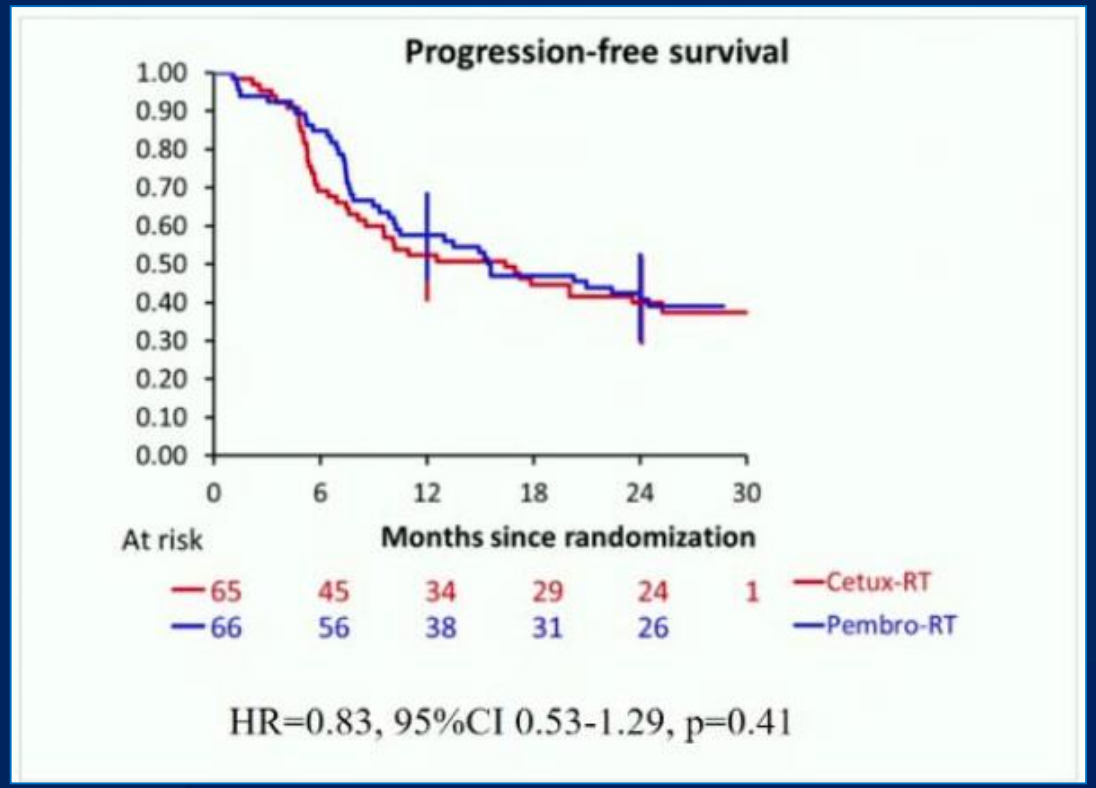
P16+

P16-

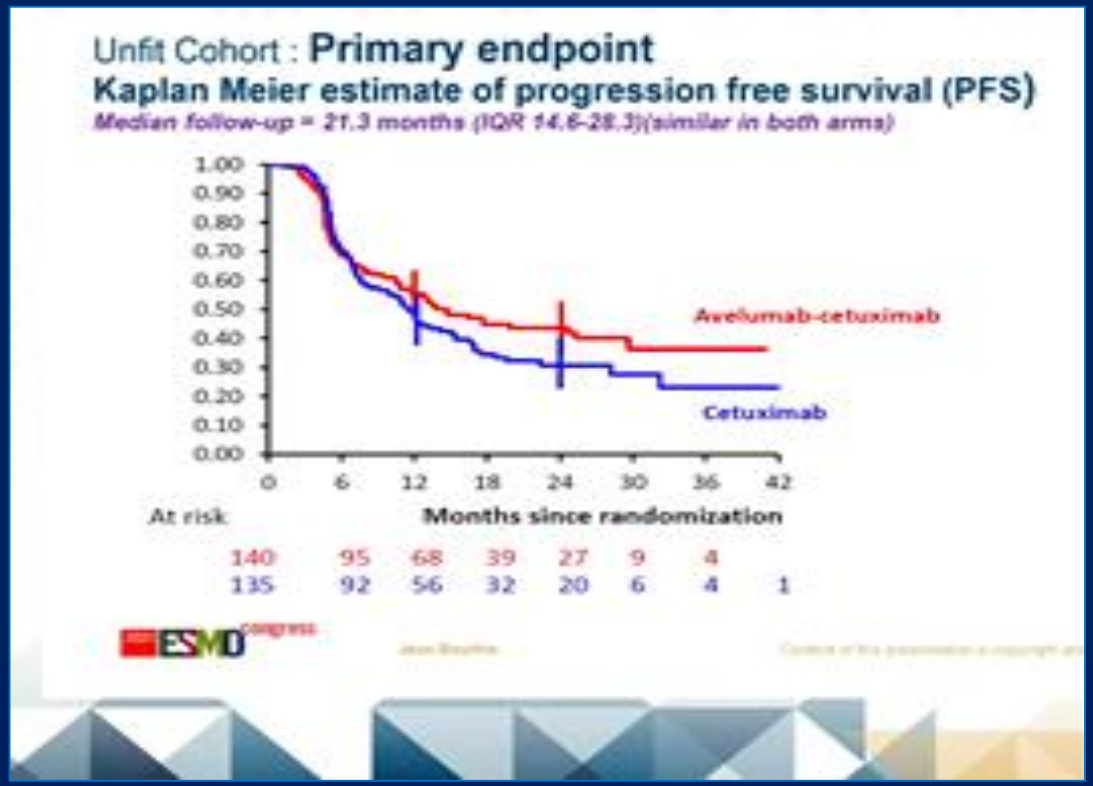
San Diego
Moores Cancer Center

Other Negative Immunotherapy Trials

PembroRad Trial (Tao et al Ann Oncol 2023)



GORTEC-REACH (Bourhis et al. Ann Oncol 2021)



Randomized Trials
Testing Cisplatin Alternatives

NRG HN005

NRG-HN005

PHASE II SCHEMA

- Oropharyngeal squamous cell carcinoma, p16-positive
- ≤ 10 pack-year history of smoking
- 8th ed. clinical stages T1-2N1M0 or T3N0-N1M0 (8th ed. stage I-II excluding T0, T1-2N0, or any N2)

↓

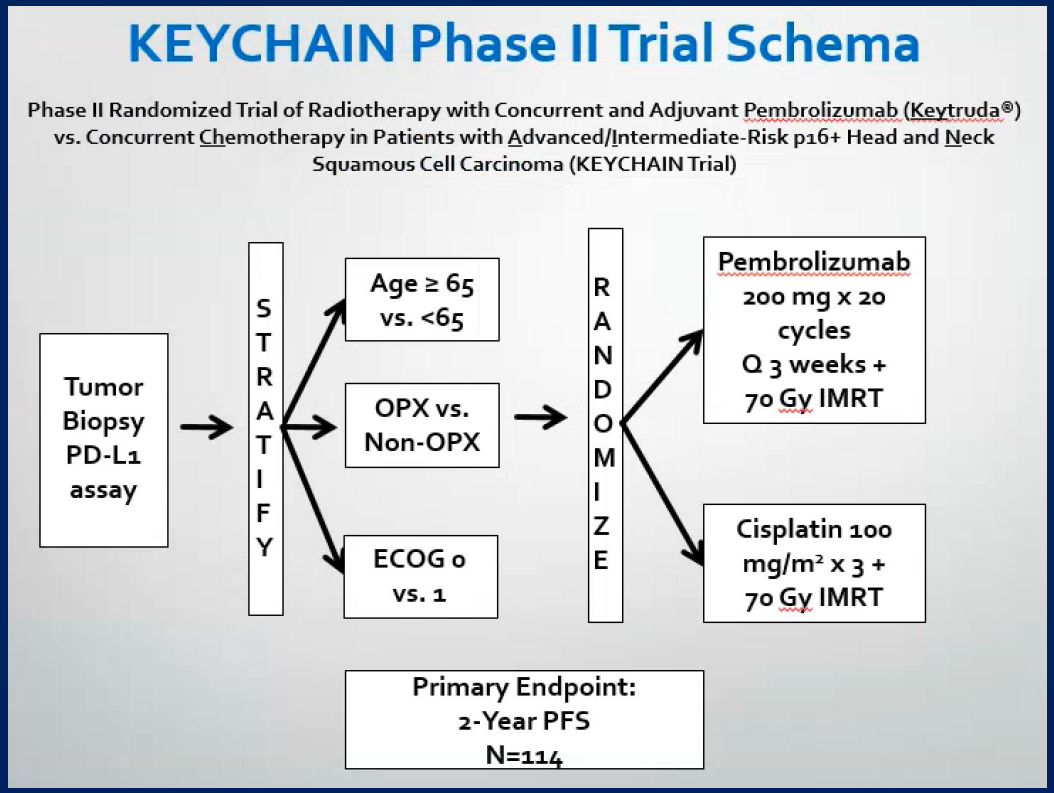
STRATIFICATION
Zubrod Performance Status: 0 vs.1

RANDOMIZE*

Arm 1**	**Arm 2****	**Arm 3****
70 Gy radiation in 6 weeks using 6 fractions per week + Cisplatin	60 Gy radiation in 6 weeks using 5 fractions per week + Cisplatin	60 Gy radiation in 5 weeks using 6 fractions per week + Nivolumab

*Randomization is 1:1:1.
**See Section 5 for radiation and systemic therapy treatment details.

KEYCHAIN



Novel Therapeutics: DNA-PK Inhibition (Peposertib) - NRG HN008 Trial

NRG-HN008

SCHEMA

REGISTRATION
Cisplatin-ineligible patients with stage 3-4 local-regionally advanced head and neck squamous cell carcinoma (HNSCC)

↓

M3814 (peposertib) at assigned dose level
+
Intensity Modulated Radiation Therapy (IMRT)

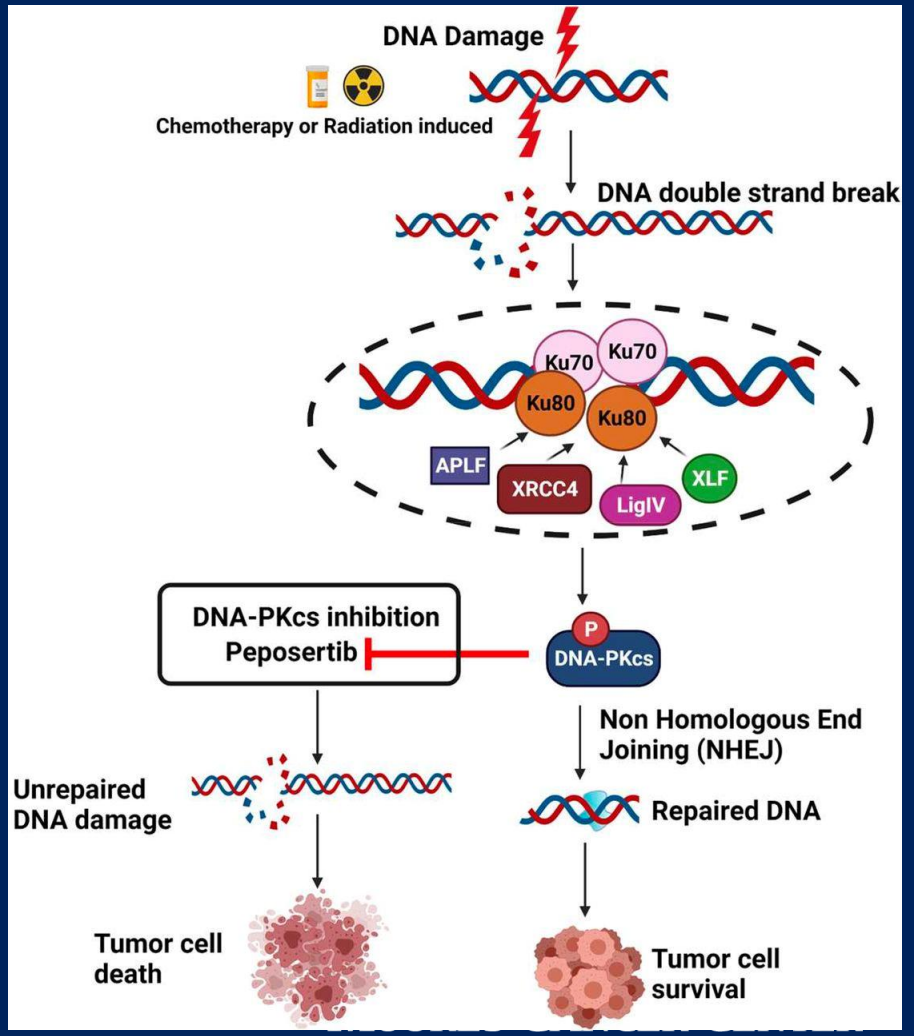
↓

Dose Expansion Cohort, N=12 patients
At a to-be-specified maximum tolerated dose (MTD) for M3814 (peposertib) and IMRT

For more details on treatment plans and the dose expansion cohort (DEC), please refer to Section 5.1 and 14.3.3, respectively.

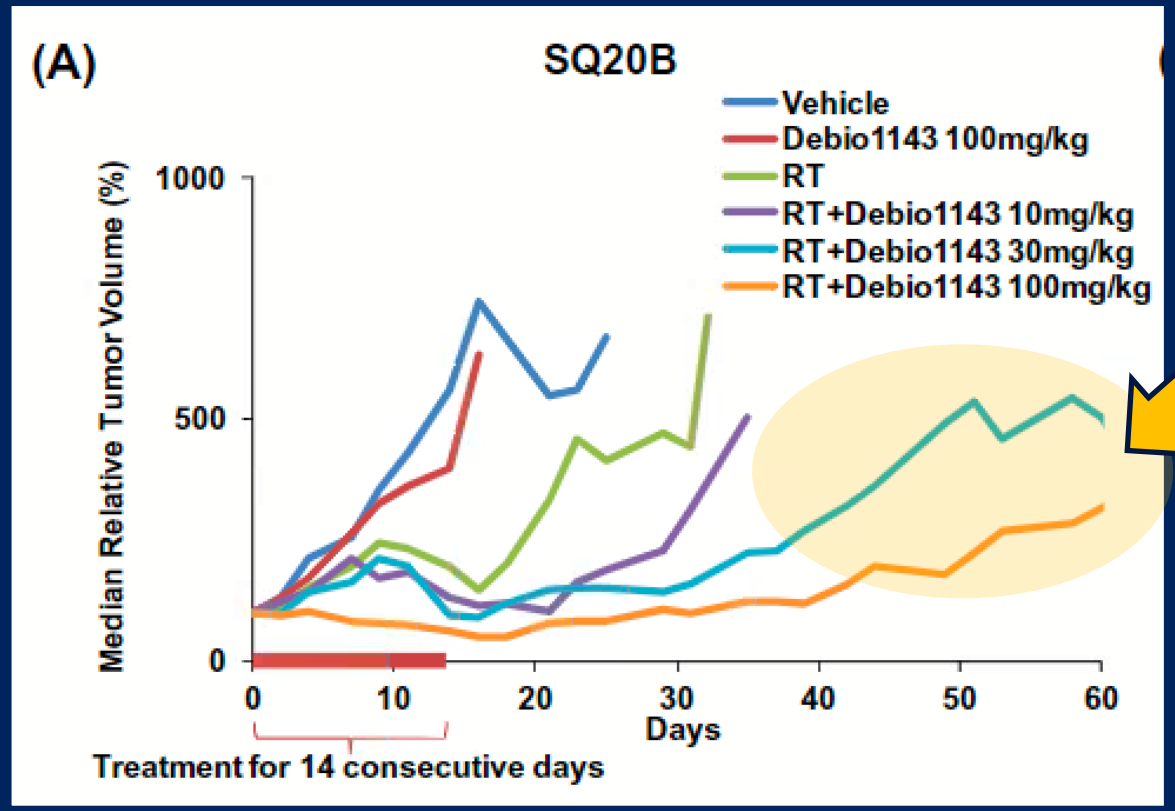
M3814 (peposertib) Dose Escalation/De-escalation Table for Maximum Tolerated Dose/Recommended Phase II Dose Determination*

Dose Level	Dose**
-1	50 mg
1 (starting dose)	100 mg
2	150 mg
3	200 mg
4	250 mg

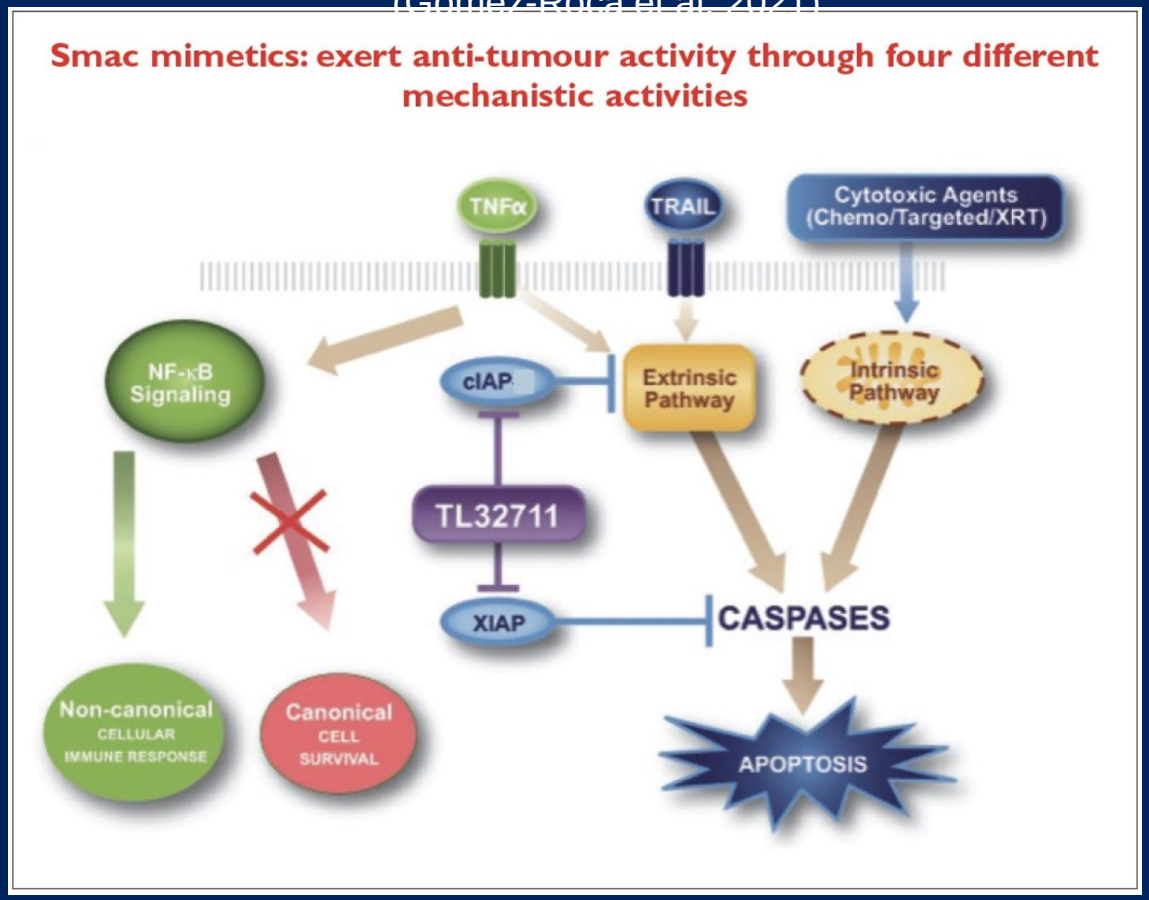


Second mitochondria-derived activator of caspase (SMAC) Mimetics in Head/Neck Cancer

IAPs regulate apoptosis and modulate NF-κB signaling driving expression of genes involved in immune/inflammatory responses. Radiosensitizing effect of xevinapant is mediated by caspases and TNF-α. (Gomez-Roca et al. 2021)

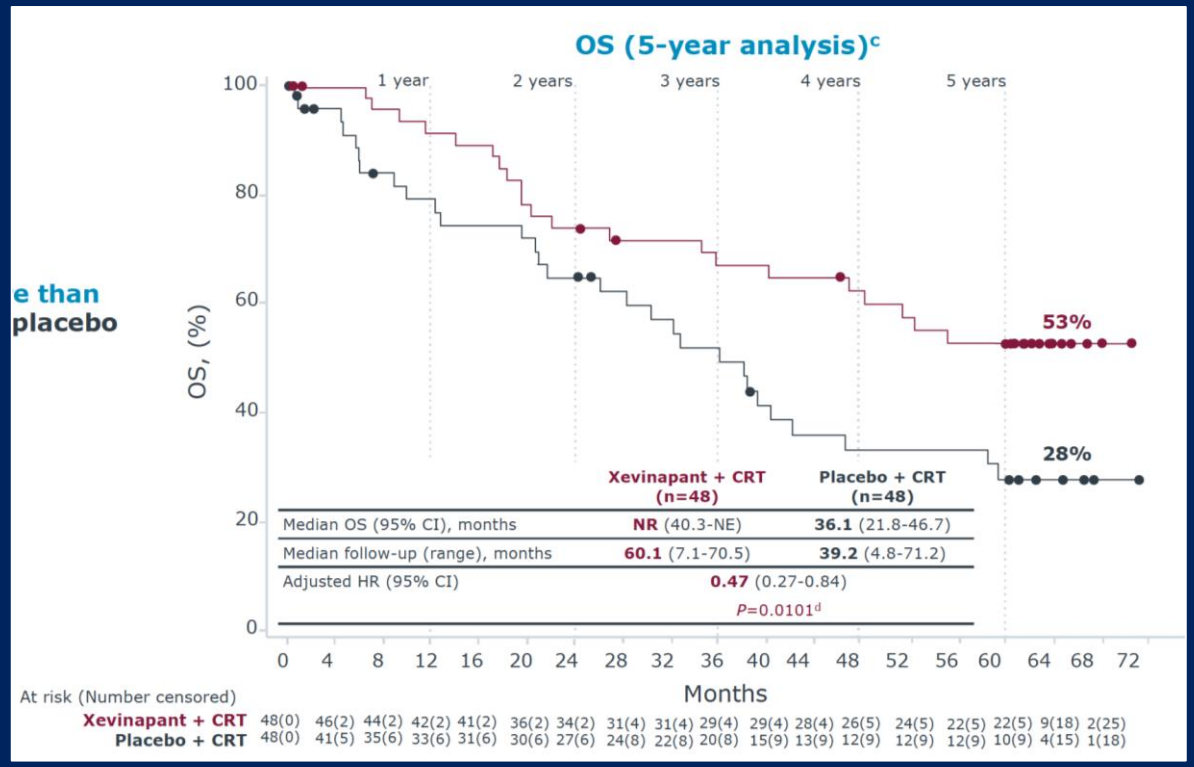


Matzinger et al. Radiother Oncol 2015



Phase 2 Efficacy & Safety of Xevinapant with CRT

- Oral xevinapant 200 mg per day on days 1–14 of 21-day cycles, x 3 cycles was well tolerated with CRT
- Similar overall Grade 3+ toxicity
  - 85% Xevinapant arm
  - 87% Placebo arm
- Grade 3+ Dysphagia (with bolus cisplatin)
  - 50% Xevinapant arm
  - 21% Placebo arm
- Xevinapant improved PFS/OS when added to RT/cisplatin, in contrast to cetuximab (RTOG 0522) and immunotherapy (Javelin, KEYNOTE-412)

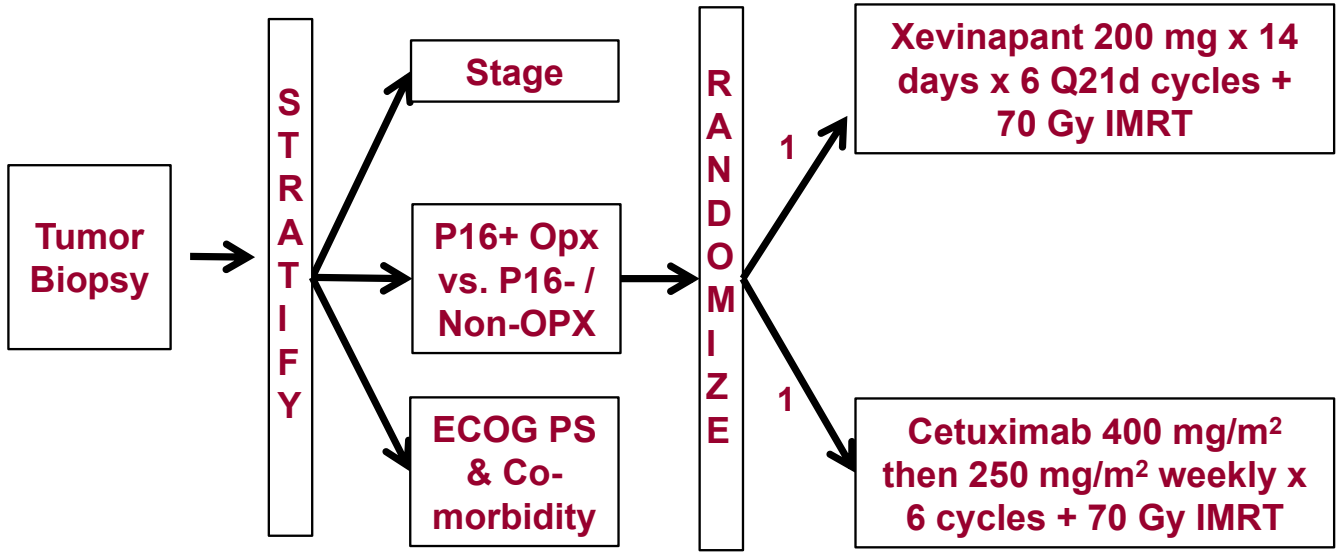


Debio 1143 and high-dose cisplatin chemoradiotherapy in high-risk locoregionally advanced squamous cell carcinoma of the head and neck: a double-blind, multicentre, randomised, phase 2 study

Xu-Shan Sun*, Yungan Tao*, Christophe Le Tourneau, Yoann Pointreau, Christian Sire, Marie-Christine Kaminsky, Alexandre Coutte, Marc Alfonsi, Pierre Baisselier, Laurent Martin, Jessica Miroir, Jean-Francois Ramee, Jean-Pierre Delord, Florian Clatot, Frederic Rolland, Julie Villa, Nicolas Magne, Olgun Elicin, Elisabeta Gherga, France Nguyen, Cedrick Lafond, Guillaume Bera, Valentin Calugaru, Lionnel Geoffrois, Bruno Chauffert, Angela Zubel, Claudio Zanna, Silvano Brienza, Philippa Crompton, Elisabeth Rouits, Kathrin Gollmer, Sergio Szyldergemajn, Jean Bourhis

NRG HN012 (X-CELSIOR) Trial Schema

Randomized Phase II/III Trial of Radiotherapy with Concurrent Xevinapant vs. Radiotherapy with Concurrent Cetuximab in Patients with Stage III-IVB Head and Neck Cancer with a Contraindication to Cisplatin



NRG ONCOLOGY™

Phase II/III, N=260/526

Conclusions

- Standard of Care when Cisplatin Contraindicated Remains Controversial
  - RT + Cetuximab
  - RT + Carbo/Taxol
  - RT + Docetaxel
- Radioimmunotherapy Essentially a Bust
- Relative risk is a critical predictor of treatment effects
- Novel therapeutic strategies under investigation (SMAC mimetics, etc.)

UC San Diego
Moores Cancer Center

Acknowledgments

- Mell Lab
  - Lei Gao
  - Hannah Liu
  - Ryan Morse
  - Jingjing Zou
- Gleiberman H&N Cancer Center
  - Joe Califano
  - Ezra Cohen
  - Liza Blumenfeld
  - Silvio Gutkind
- H&N Cancer Intergroup
  - Jean-Pierre Pignon
  - Benjamin Lacas
  - Quynh Le
- NRG Oncology
  - Stu Wong
  - Sue Yom
  - Pedro Torres-Saavedra

UC San Diego
MOORES CANCER CENTER