The International Federation of Head and Neck Oncologic Societies

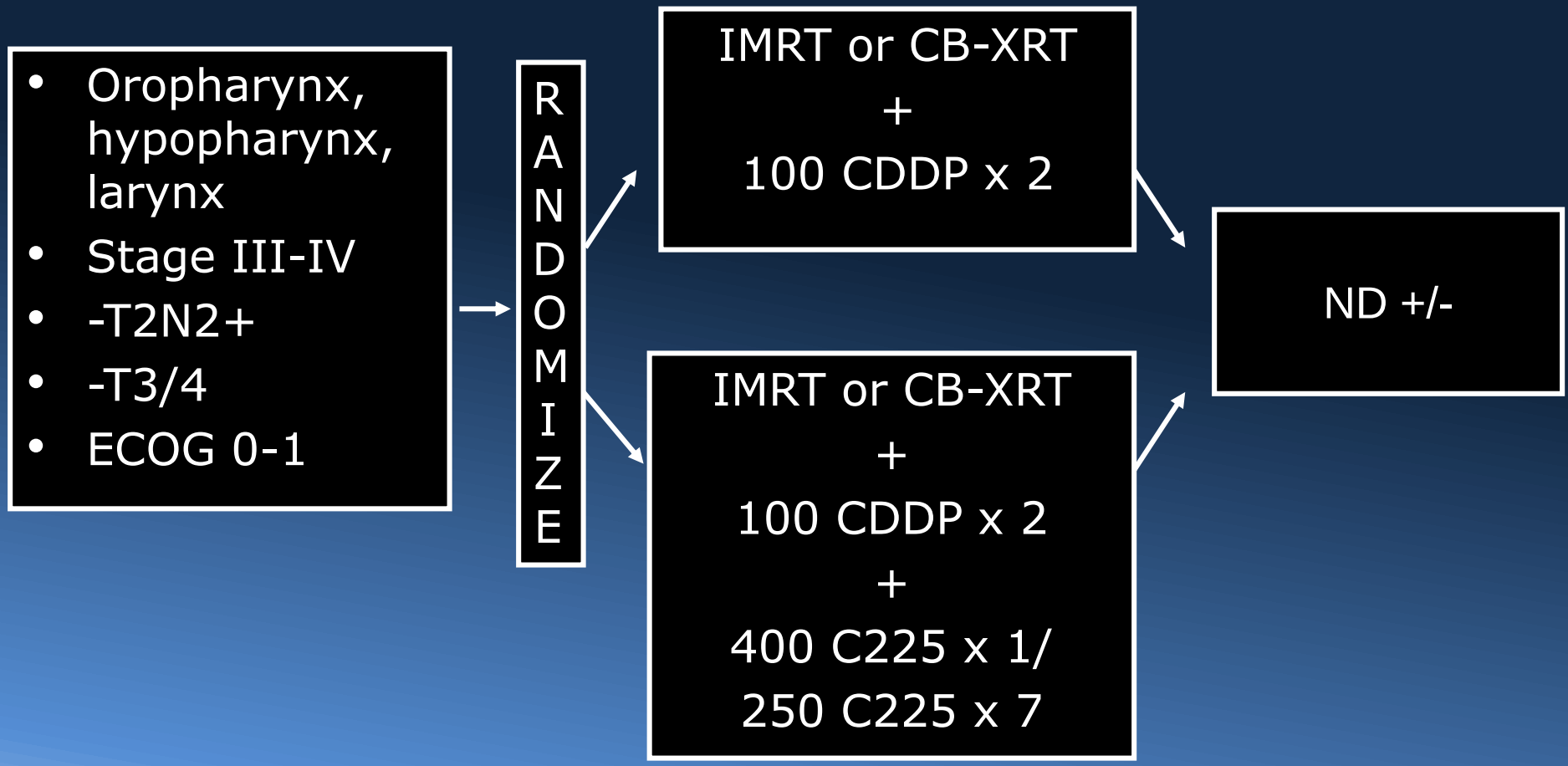
Current Concepts in Head and Neck Surgery and Oncology 2017

www.ifhnos.net

SCCHN: Multimodal Therapy

Merrill S. Kies

RTOG 0522 Phase III: CB-XRT +/- C225 Chemoradiotherapy for Locally Advanced Disease



Ang KK et al, JCO 2014

EGFR-Based Bioradiotherapy with Panitumumab (P)

	N	2-yr LRC %
Concert 1		
CT – RT	63	68
CT – RT + P	87	61
Concert 2		
CT – RT	61	61
P – RT	90	51

Mesia et al, Lancet Oncol 2015
Giralt et al, Lancet Oncol 2015

MACH-NC Update
Concomitant vs Induction CT

- Concomitant superior in LRC and event-free survival; trend for OS (p=0.15)
- Induction superior for reduction in distant failure.
  - Induction: HR 0.73 (0.61-0.88), p=0.001
  - Concomitant: HR 0.88 (0.77-1.00), p=0.04
- Authors suggest the potential for sequencing the two approaches, with concern re adverse impact on compliance/ toxicities

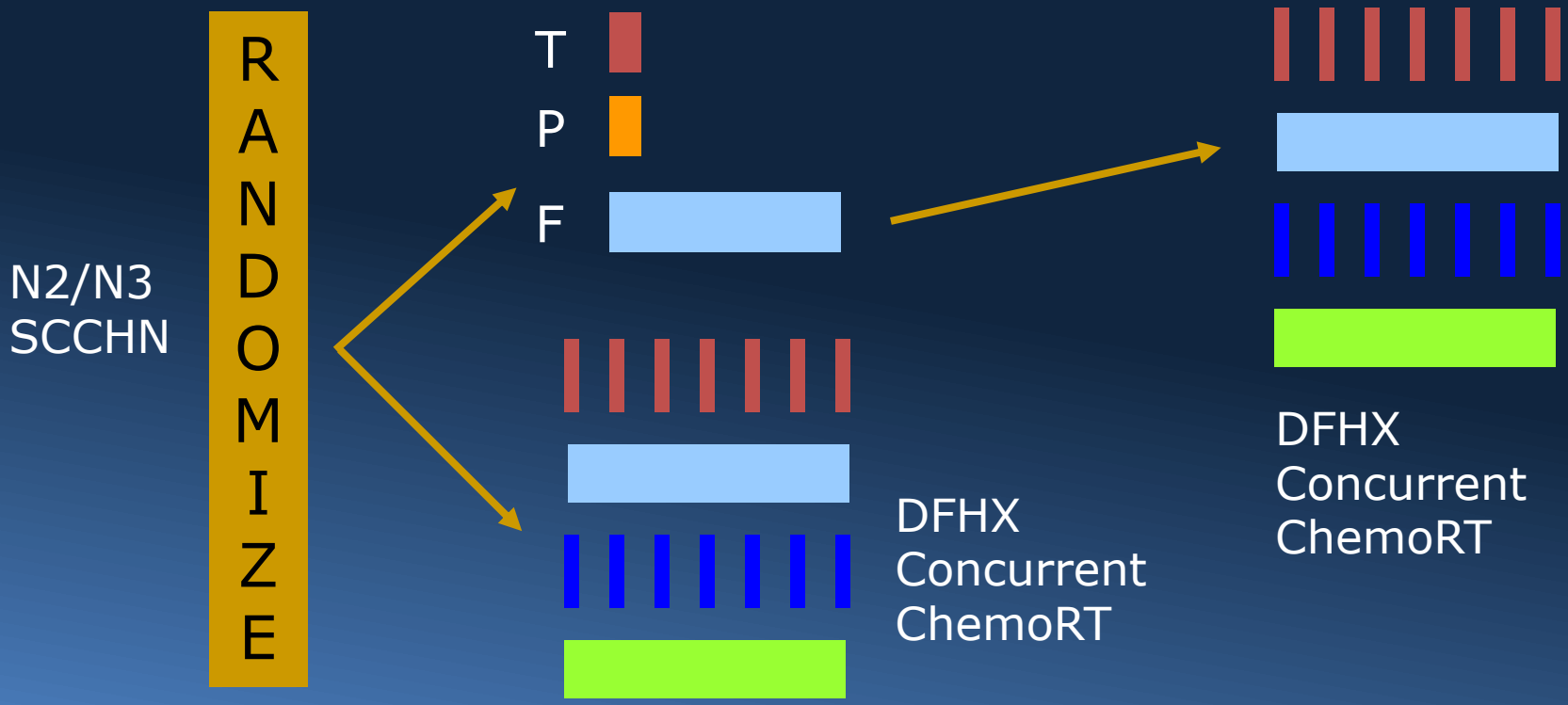
Pignon JP et al, Radiotherapy Oncology 2009

TAX 323 and TAX 324: Summary

- Response rates are higher with TPF compared to PF
- Induction TPF improves survival compared to PF, possibly due to increased LRC
- Rate of distant failure is low
- There was no comparison with accepted CT-RT

Posner M et al, NEJM 2007
Vermorken J et al, NEJM 2007

DECIDE Phase III Trial: TPF Followed by ChemoRT Versus Concurrent ChemoRT



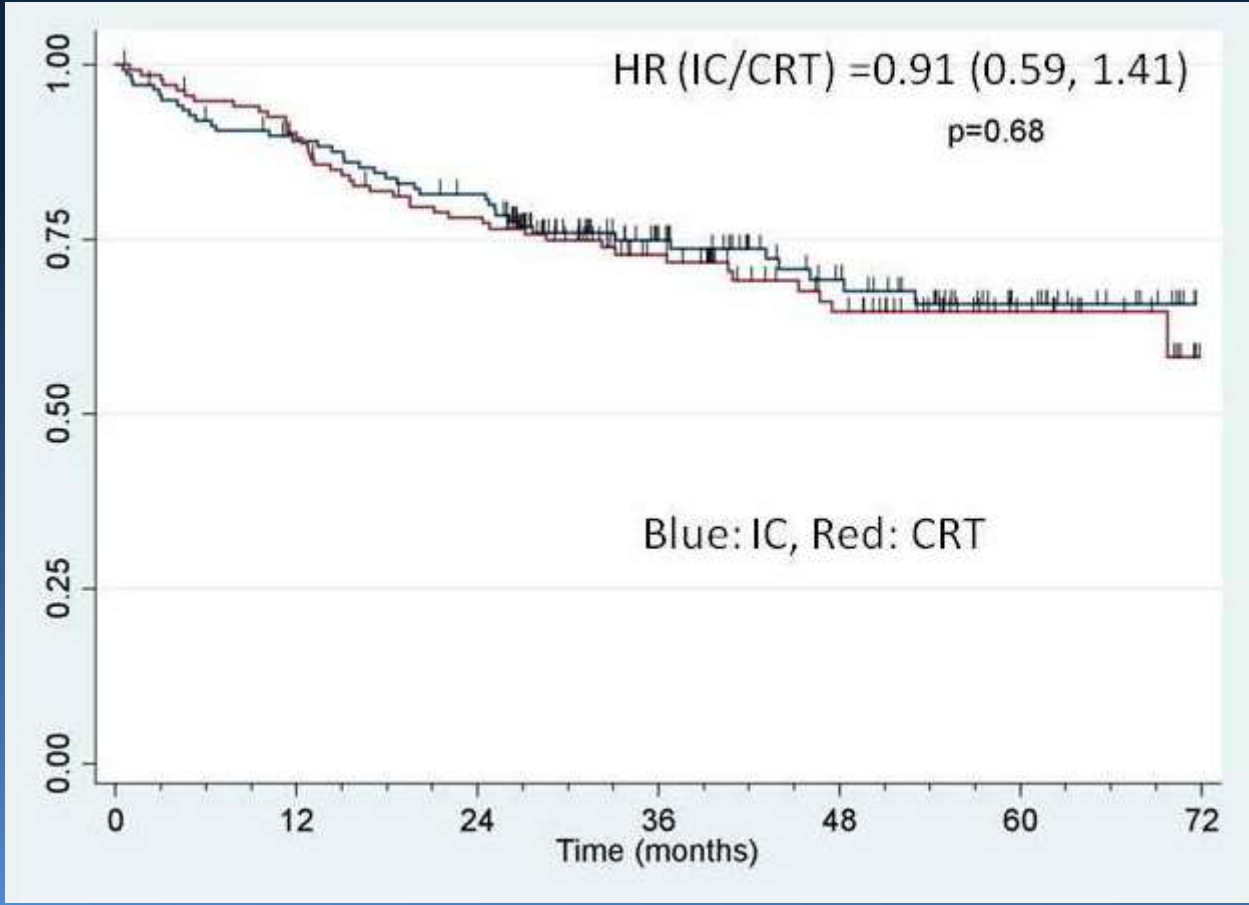
TPF: docetaxel + cisplatin + 5-FU q 3 wk x 2

DFHX: docetaxel + hydroxyurea + FU + hyperfractionated RT

2017

PI: Ezra Cohen

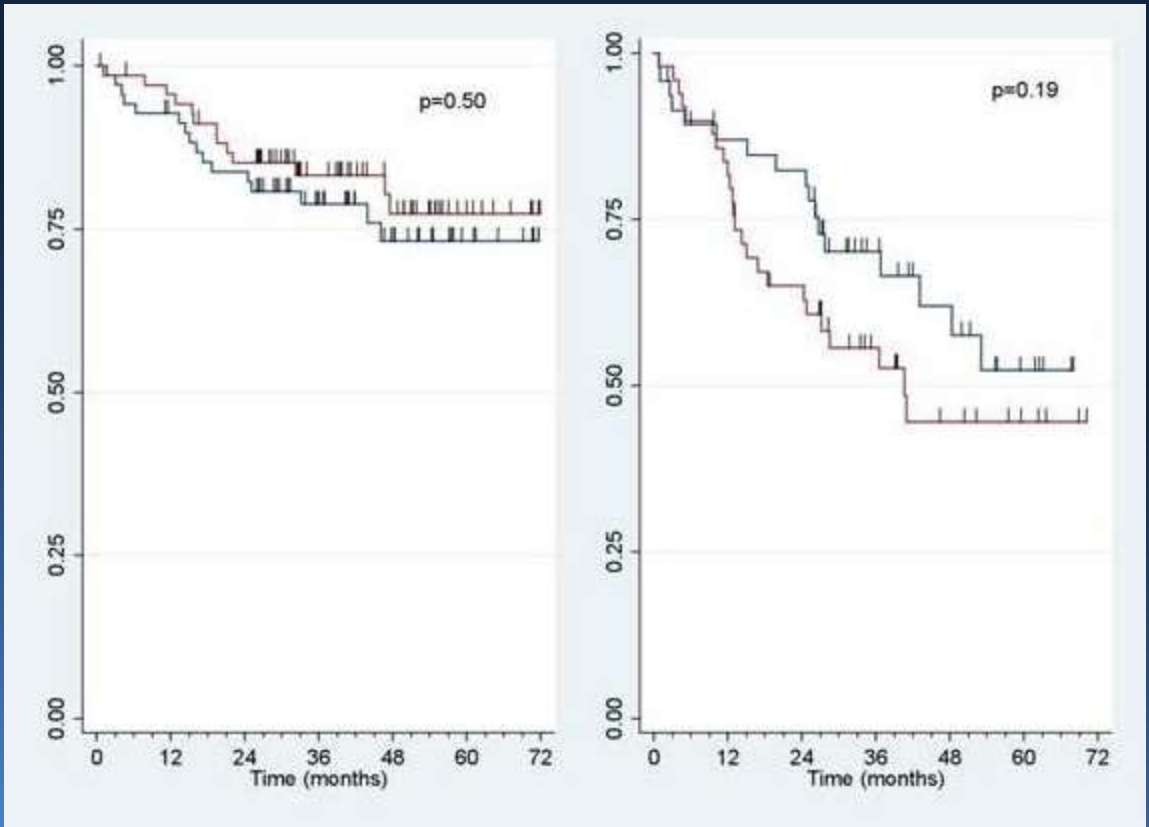
Overall Survival by Treatment Arm
Primary Endpoint



Cohen E et al, JCO 2014

Overall Survival by Nodal Stage

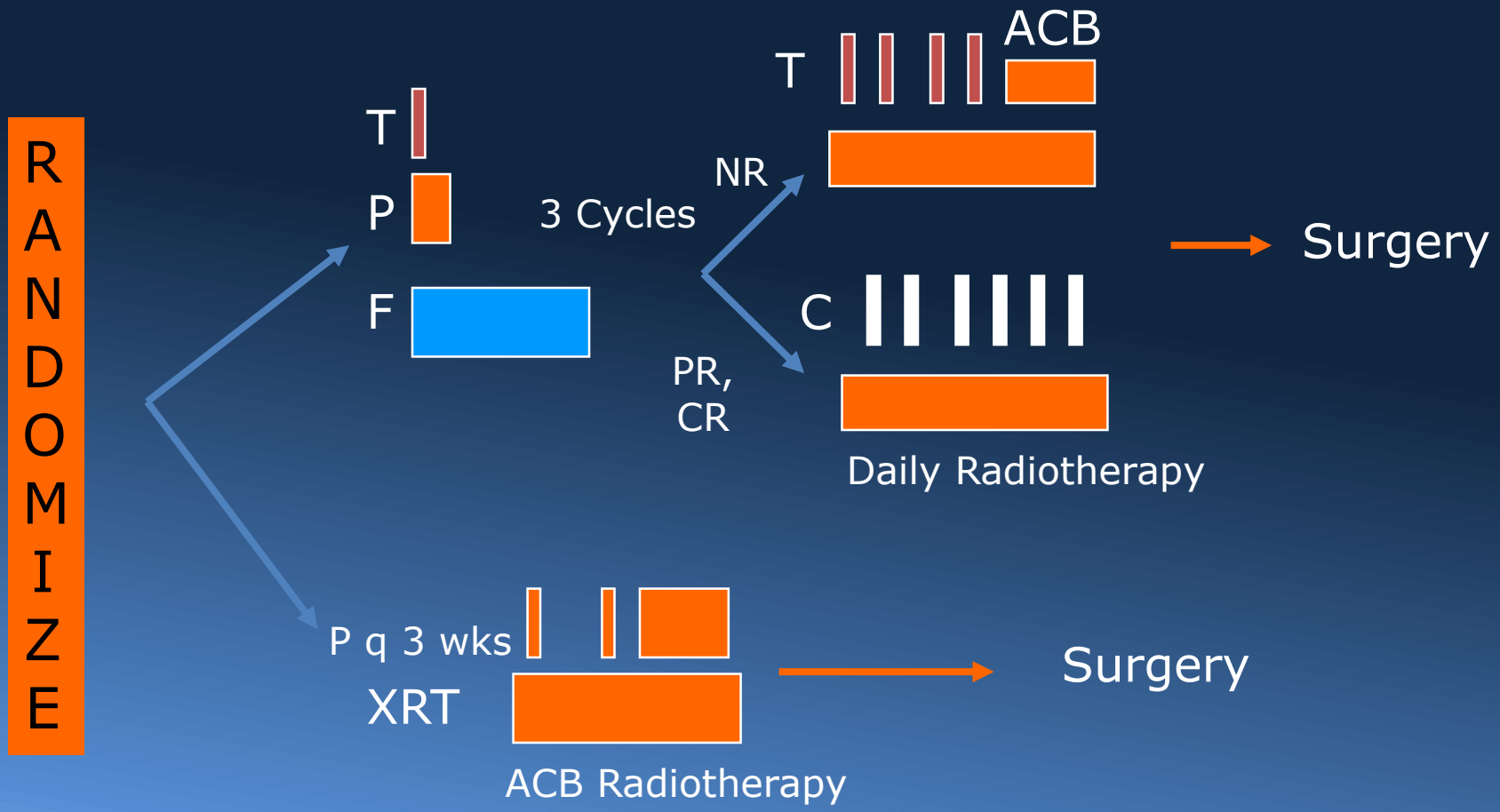
N2A/N2B (n=139) N2C/N3 (n=96)



Blue: IC, Red: CRT

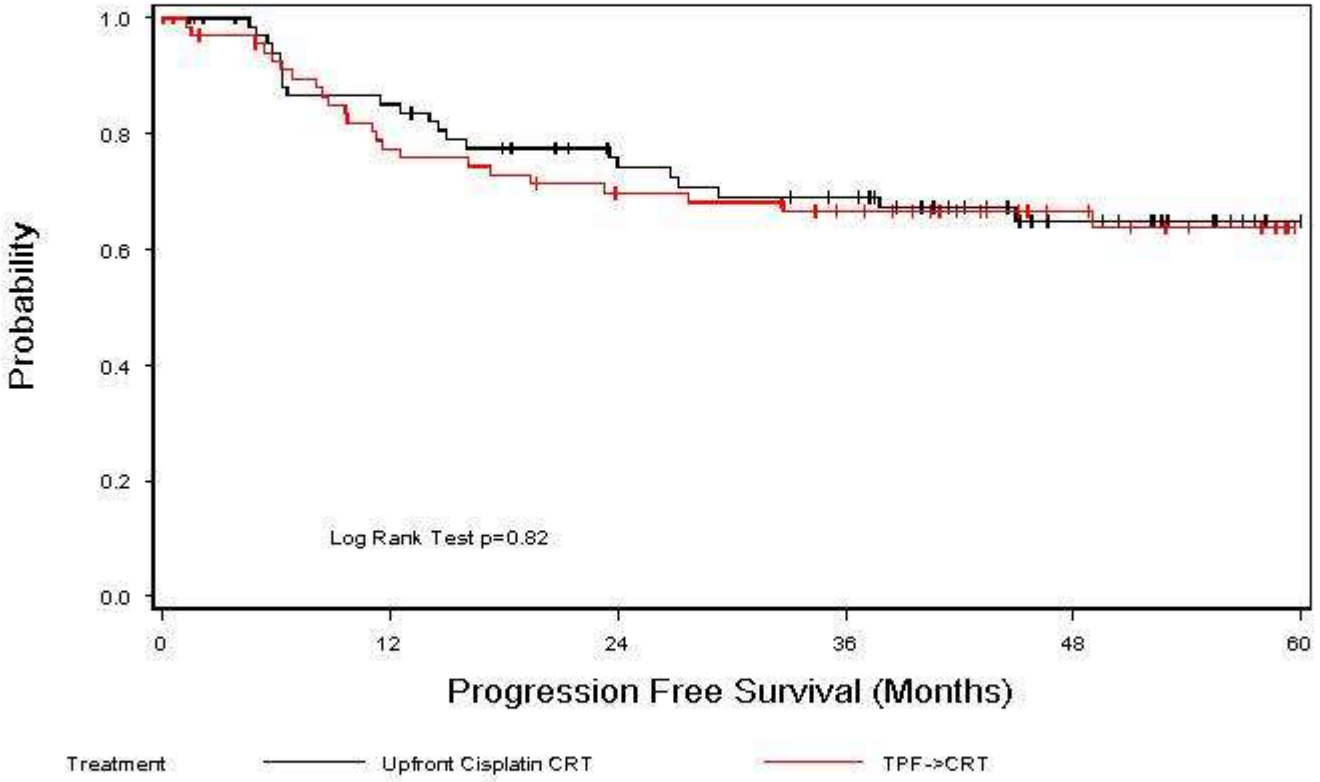
Cohen E et al, JCO 2014

The PARADIGM Study: Sequential Therapy *vs* Chemoradiotherapy A Phase III Study of TPF/C-XRT *vs* P-ACBXRT



PI: Robert Haddad

PARADIGM: Progression Free Survival



Is There Still a Role for Induction Chemotherapy for Head and Neck Cancer?

Adam S. Garden, *The University of Texas MD Anderson Cancer Center, Houston, TX*

J Clin Oncol 23(6):1059-60, 2015. Editorial

Phase II Study of TPF Followed by Cisplatin/5-FU/XRT

Stage III/IV M0 HNSCC

Unresectable disease

PS 0-1

N=103 patients

RANDOMIZE

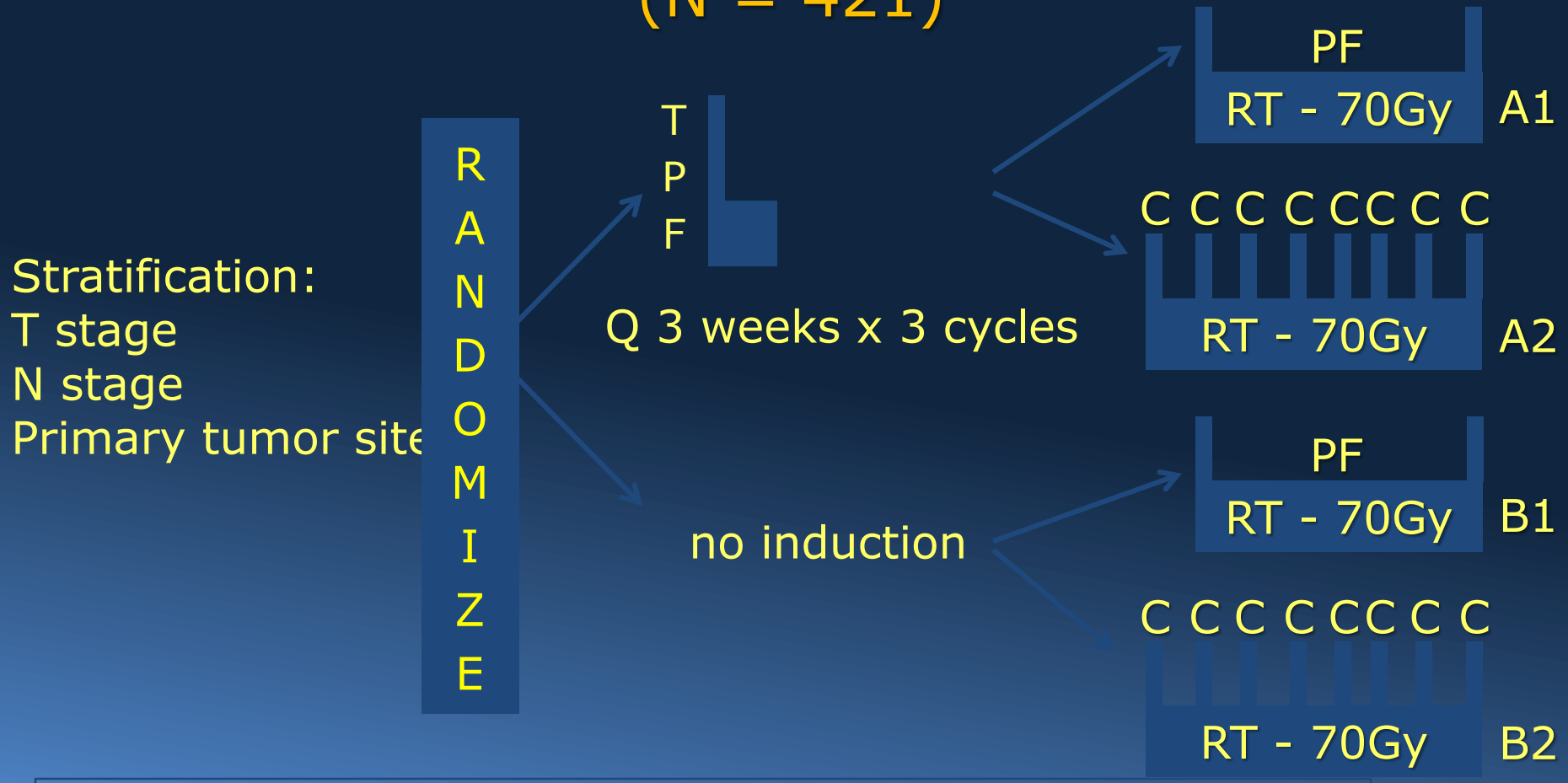
ChemoXRT
Cisplatin 20 mg/m2/day s 1 to 4
5-FU 800 mg/m2/day 96 h
(weeks 1+6 of RT)

TPF x 3 → ChemoXRT
Docetaxel 75 mg/m^2 day 1
Cisplatin 80 mg/m^2 day 1
5-FU 800 mg/m^2/day 96 h
(q 21 days)

Primary endpoint: radiologic CR after chemoXRT

Paccagnella A et al, Ann Oncol 2010

Phase III: 2 X 2 Factorial Design (N = 421)



Primary endpoints:

1) 3y OS Induction vs no induction: A1 + A2 vs B1 + B2

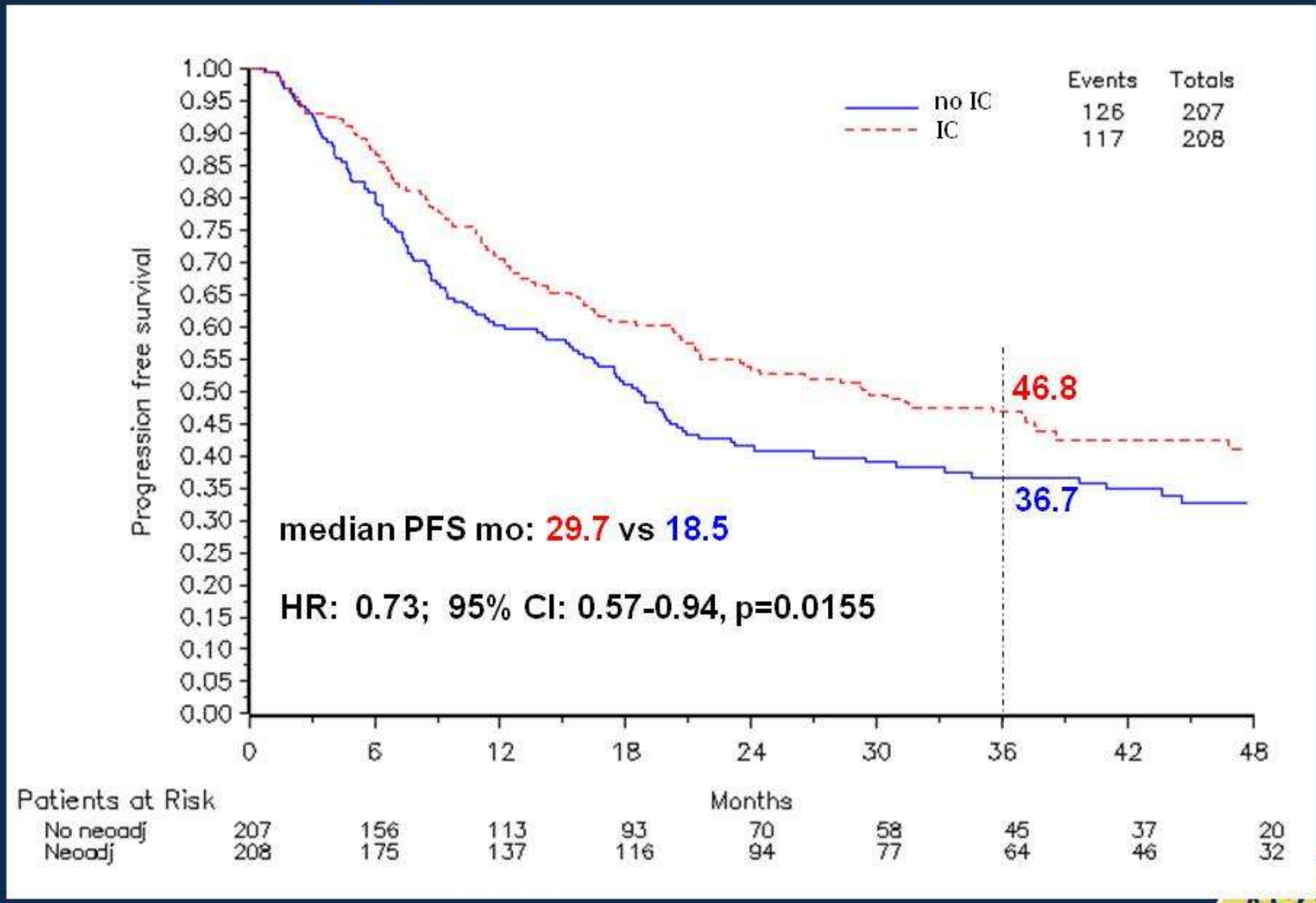
2) 2) G3-4 in field toxicity: A1 + B1 vs A2 + B2

MG Ghi et al, ASCO 2014

Compliance with Concomitant Treatments

	TPF + concomitant n=185	Concomitant n= 199	p value
PF 2 cy/cetuximab 7 wks - no modifications	86% 56%	88% 59%	0.772
RT completion - no modifications	93% 61.5%	93% 64.5%	0.820
Median RT dose, Gy (range)	70 (8-73)	70 (18-70)	0.199
Median RT duration, weeks (range)	7.3 (1-13)	7.4 (3-11)	0.674
Pts with RT interruption > 3 consecutive days (%)	51 (27.5%)	59 (30%)	0.607
Death from any cause within 30 days after treatments	6 (3%)	7 (3.5.%)	0.772

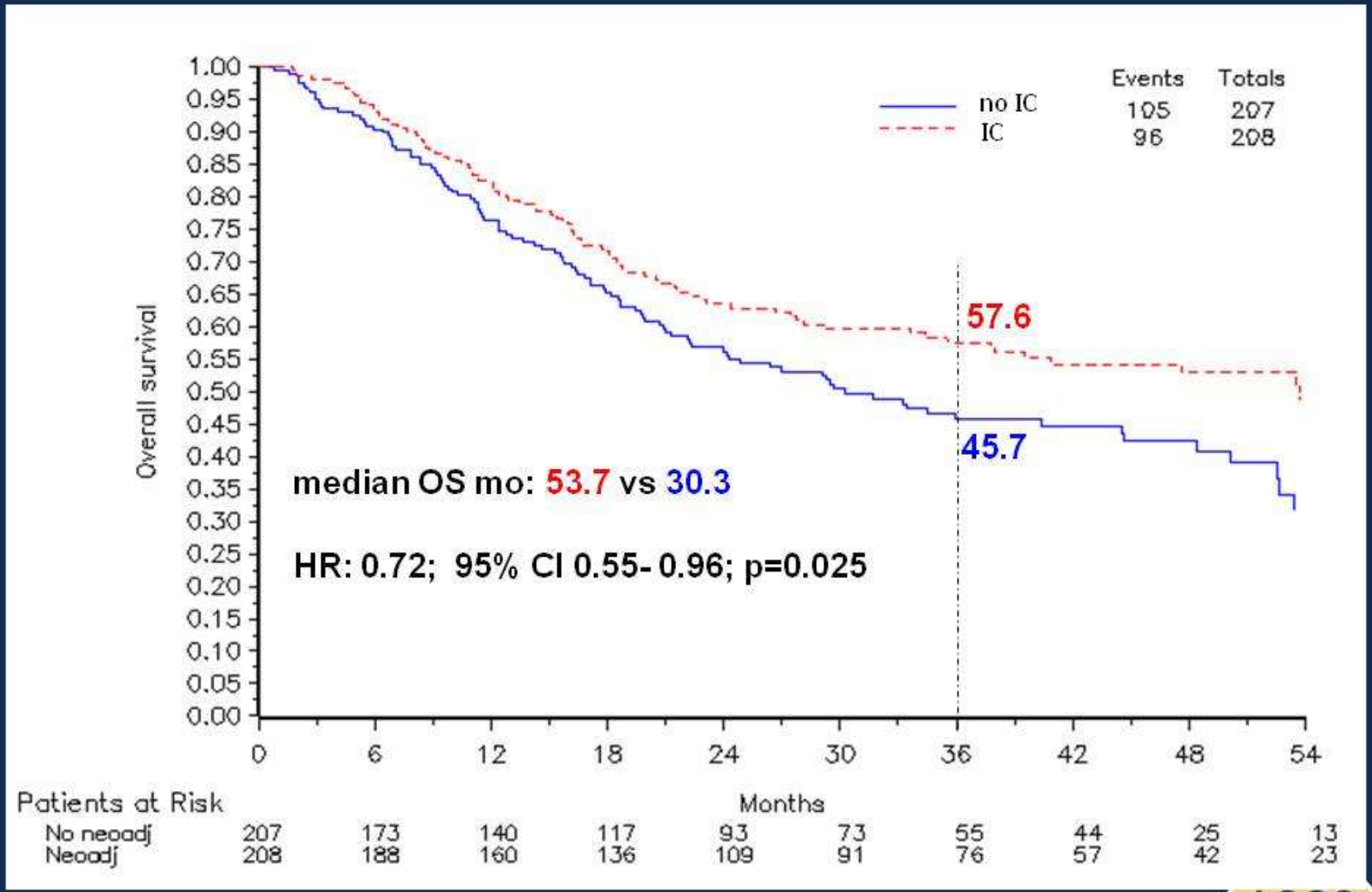
Progression Free Survival



Presented by: MG Ghi, MD

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Overall Survival



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Induction CT Trial Outcomes

		N	3yr % PFS	3yr % OS
Paradigm	ICT	70	67	73
	CT – RT	75	69	78
DeCIDE	ICT	142	67	75
	CT – RT	138	60	74
Ghi, et al.	ICT	199	47	58
	CT – RT	185	37	46

HPV-positive and negative cancers

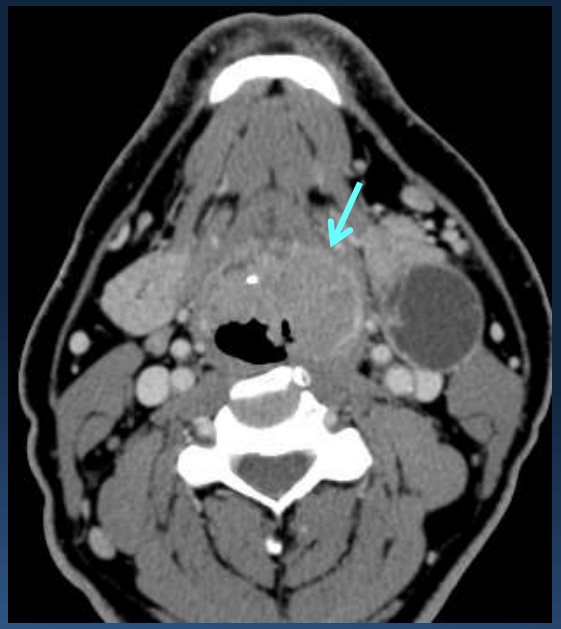
HPV-related cancers

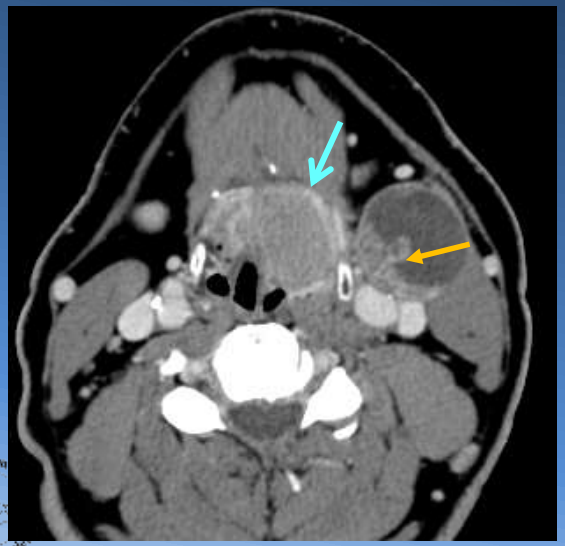
- Caused by HPV
  - HPV 16 is high-risk subtype
  - Driven by viral oncogenes
- Concentrated in oropharynx
- E6 and E7 oncogenes
- Young, favorable health
- Cured in 80%

SCC related to substance abuse

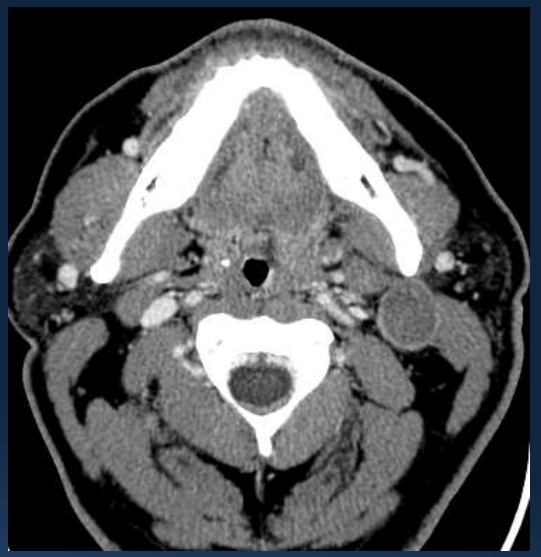
- Caused by toxic exposures
  - Tobacco and alcohol
- Throughout HN mucosa
- P53 mutations
- “Poor” prognosis, comorbidities
- Second primary cancers

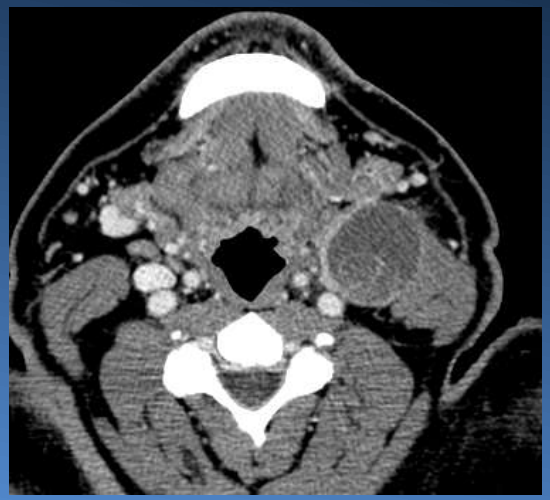
50-y/o man, HPV+, mostly cystic nodes,





59-y/o man, HPV+, cystic nodes, occult primary





Integrating Accelerated Fractionation & Cisplatin Phase III Trial RTOG 0129, PI: K. Ang

Stage III & IV SCC of:

- Oral cavity
- Oropharynx
- Larynx
- Hypopharynx

Stratify:

- Lx vs Non-Lx
- N0 vs N+
- KPS
  60-80 VS 90-100

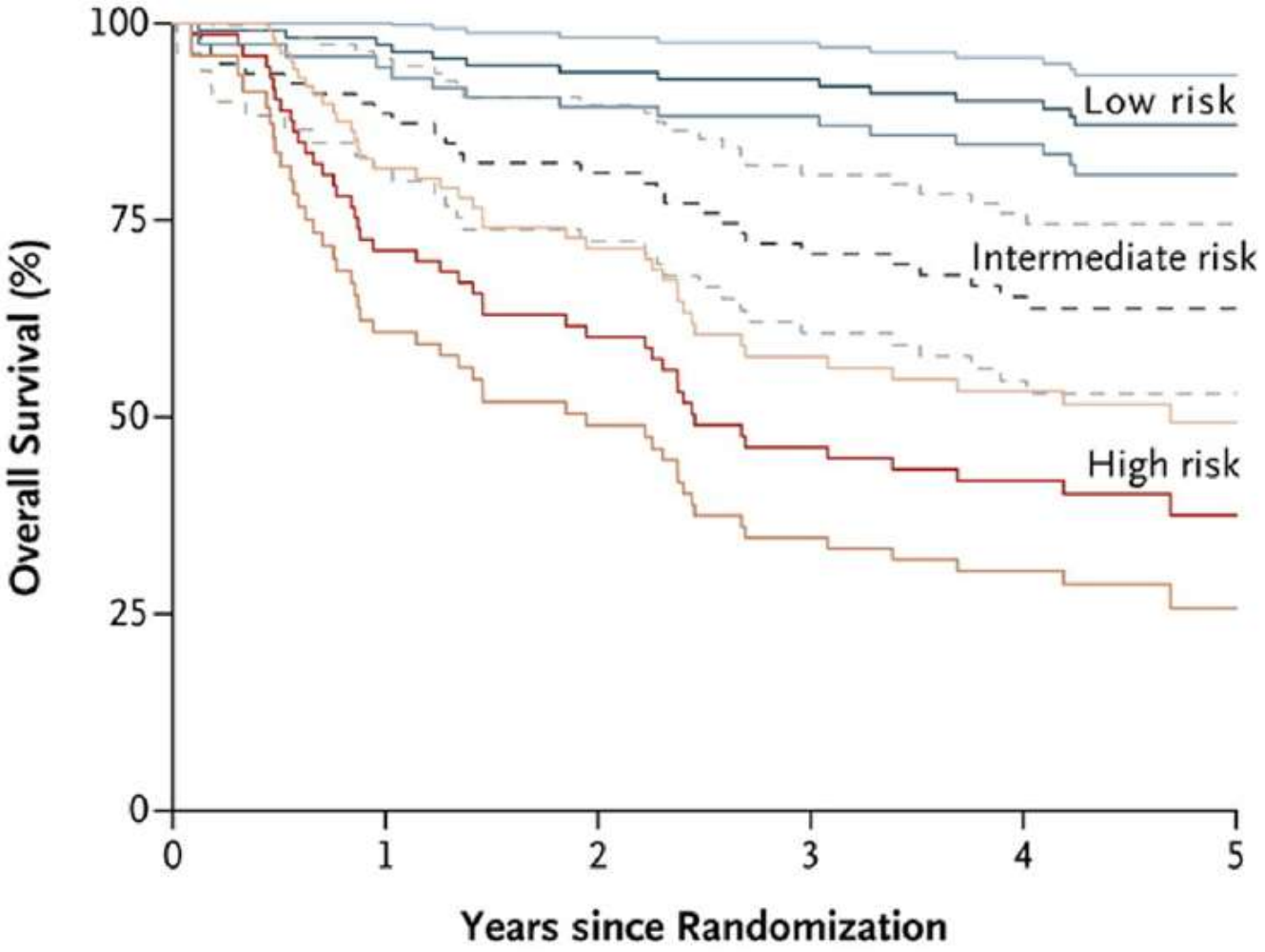
RANDOMIZE

1. SFX: 70 Gy/35 F/7 W + CDDP: 100 mg/m^2 (d 1, 22, 43)
2. AFX-CB: 72 Gy/42 F/6 W + CDDP: 100 mg/m^2 (d 1, 22)

Accrued 743 patients
Collected 596 tumor specimens

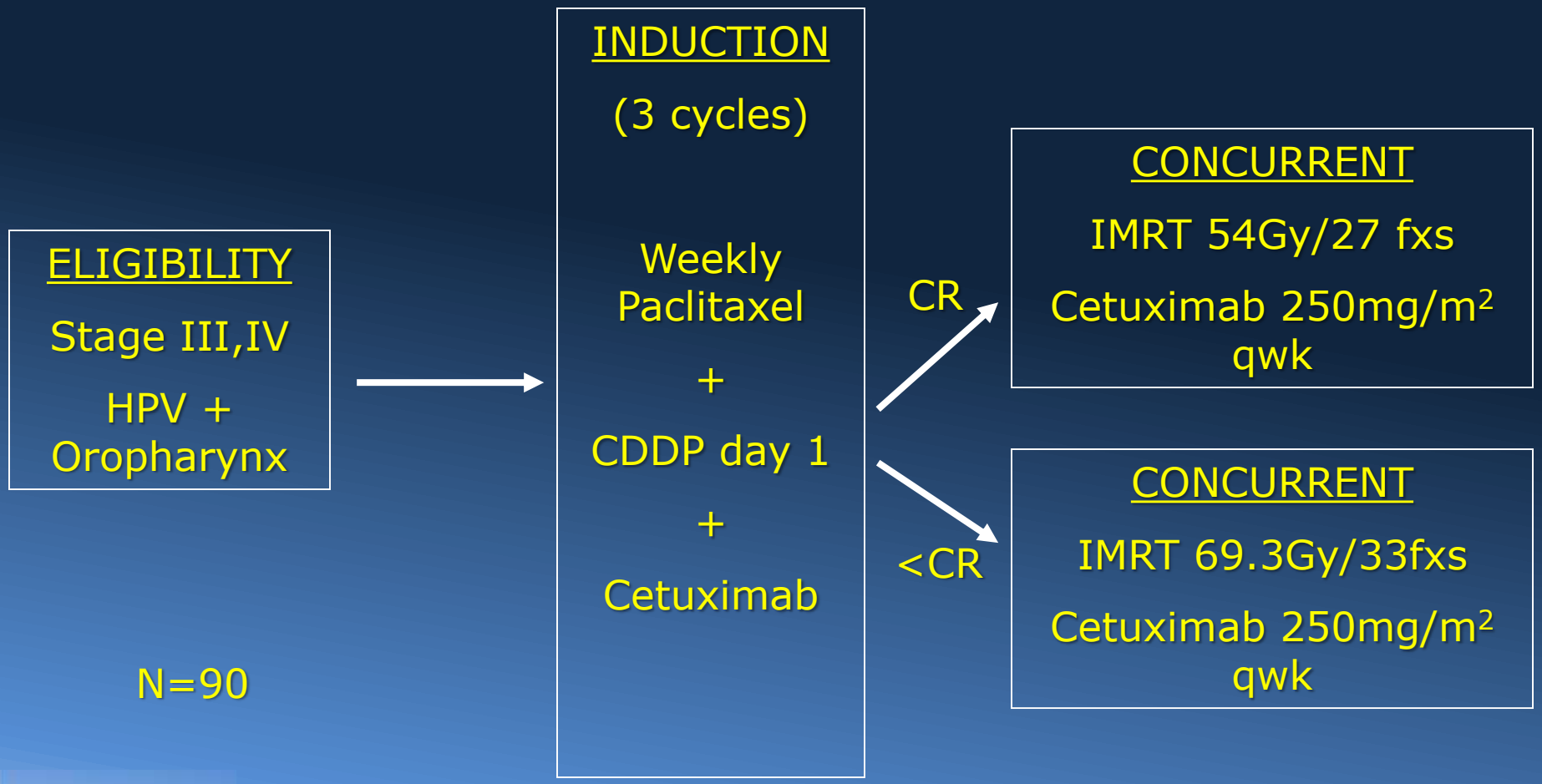
Oropharyngeal Cancer
Enrolled: 433 - Specimens: 317

Excluded T1-2N1



Ang KK et al, NEJM 2010

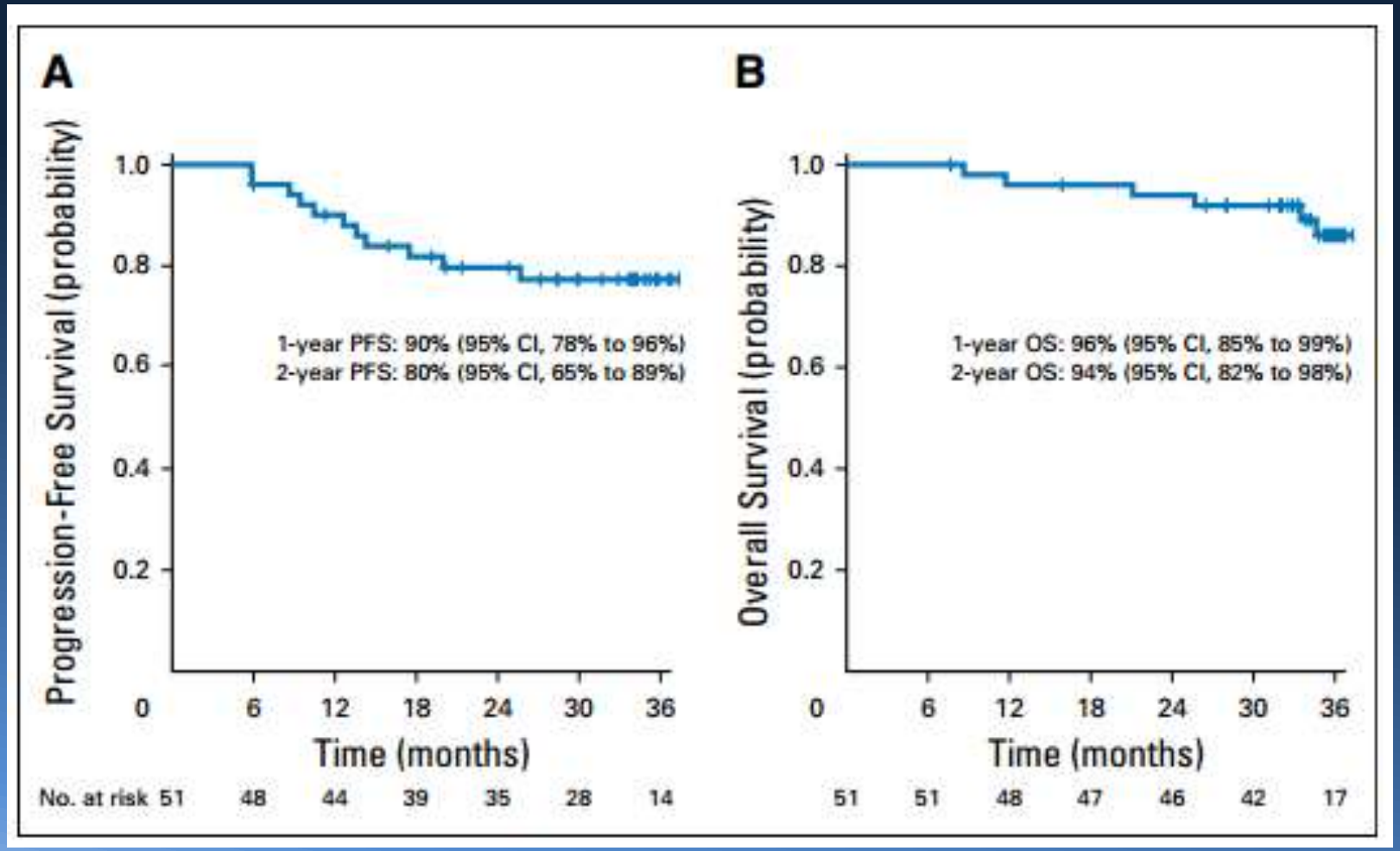
E1308: Reduced Dose IMRT for HPV+ Stage III/IV OPSCC Patients Achieving cCR to ICT



N=90

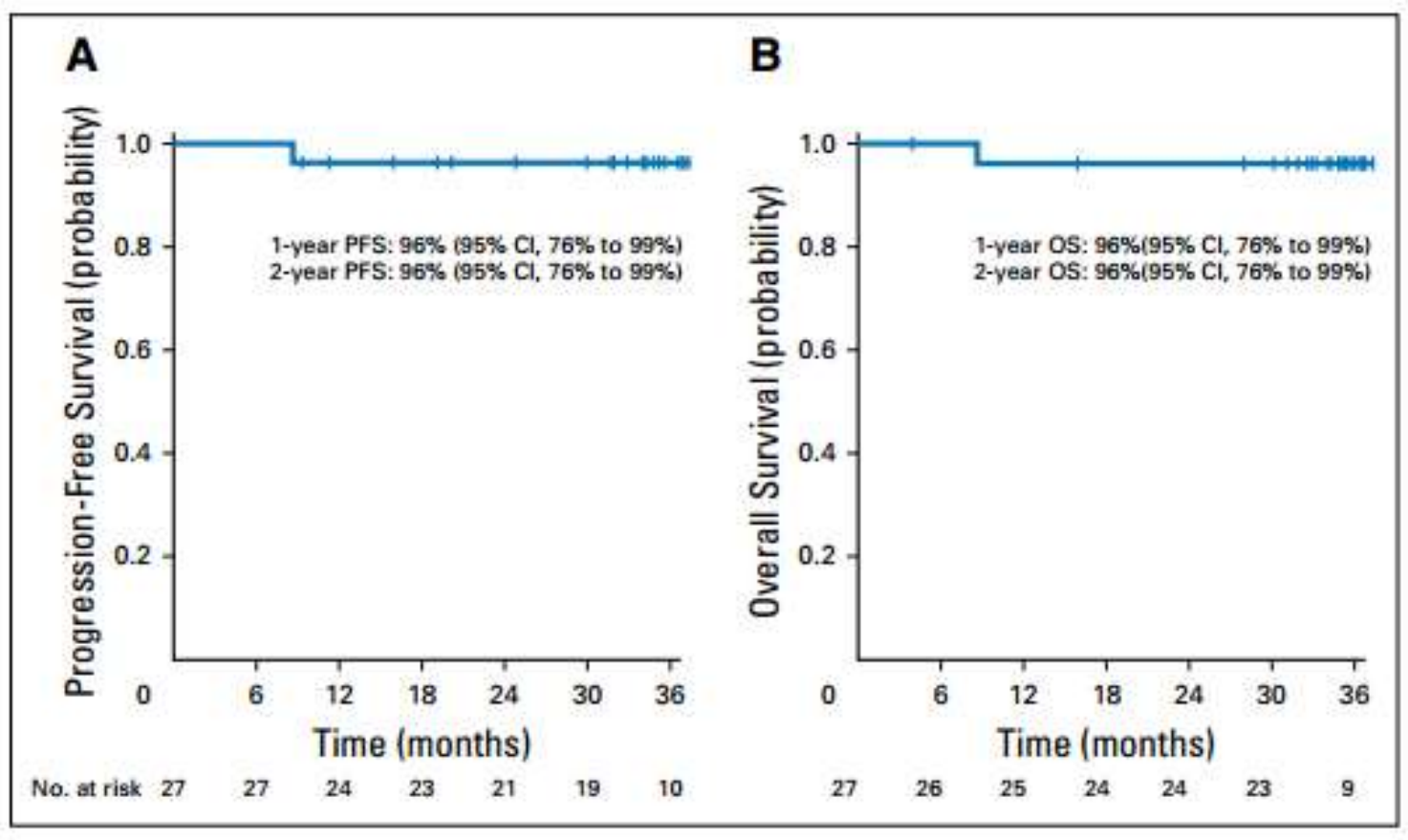
Cetuximab loading dose = 400mg/m^2 on Day1 of Cycle 1 with Induction

Progression Free and Overall Survival in Clinical CRs



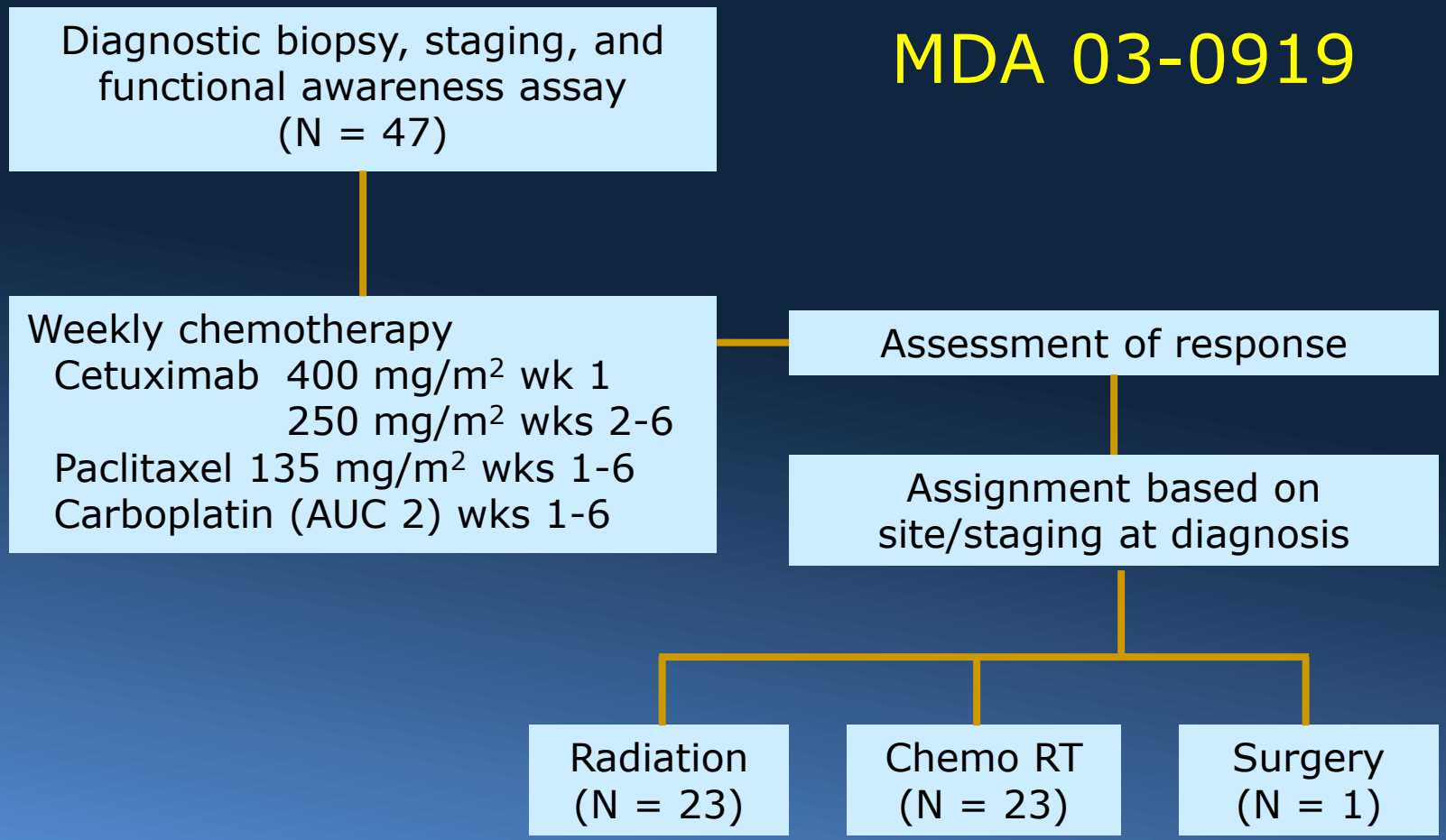
Marur S et al, JCO 2017

PFS and OS in Favorable Cohort



Marur S et al, JCO 2017

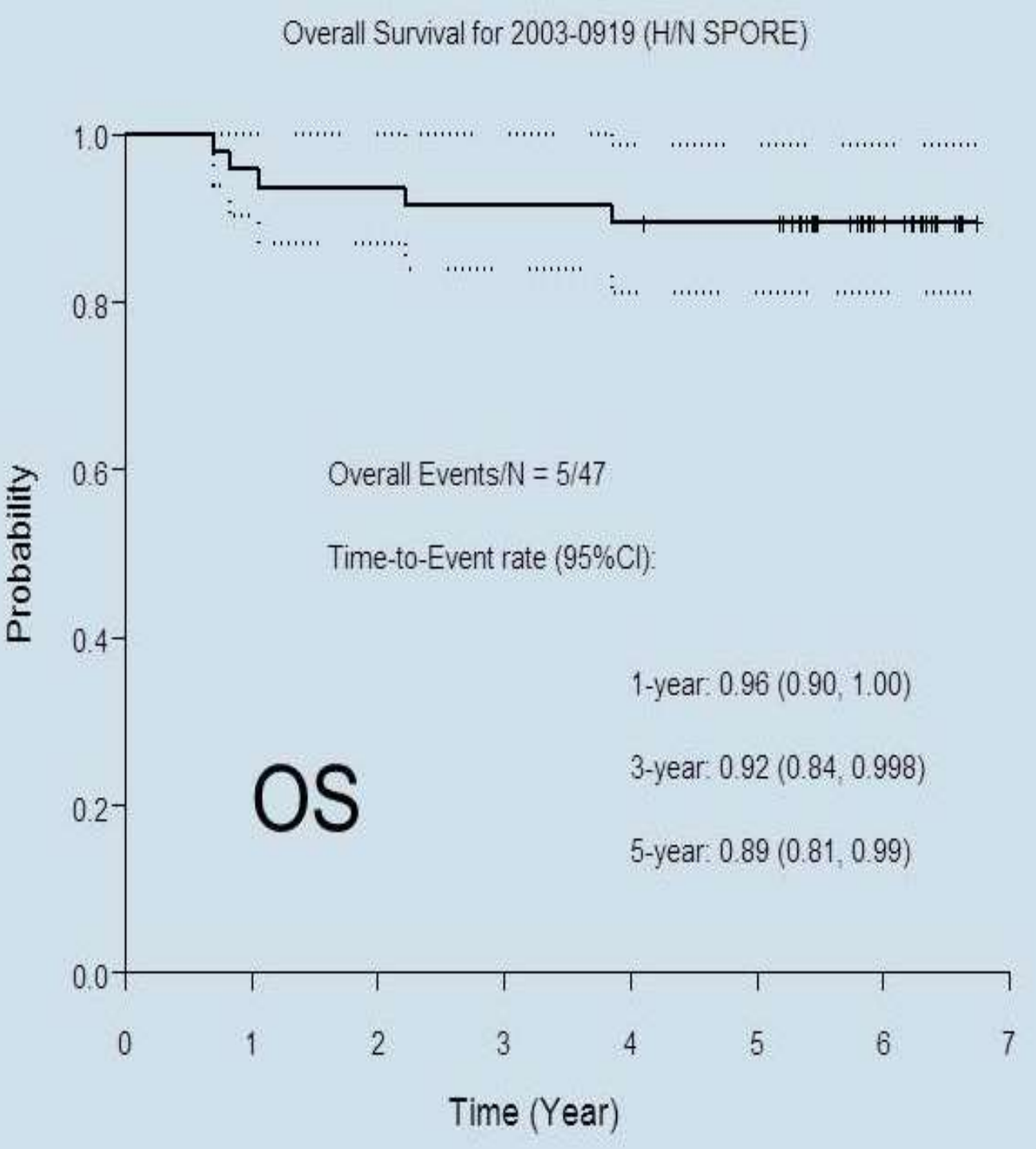
MDA 03-0919



Kies M et al, JCO 2010

5-year survival

- No new LR recurrence
- 1 new SPM (spindle cell scalp)
- Overall survival: 89%



2017

5-year Functional Outcomes

- n=42 long-term survivors
- Most OP survivors (39)
- Chronic dysphagia rare

	All sites (n=42)	OroPh (n=39)
Diet		
NPO	1 (2%)	1 (3%)
Tube + PO	1 (2%)	0 (0%)
Liquid only	1 (2%)	1 (3%)
Soft	5 (12%)	5 (13%)
Regular/full	34 (81%)	32 (82%)
Feeding-tube	2 (5%)	1 (3%)
Laryngectomy	1 (2%)	1 (3%)
Tracheostomy	0 (0%)	0 (0%)
Pneumonia	2 (5%)	1 (3%)
Stricture	0 (0%)	0 (0%)
Chronic dysphagia*	3 (7%)	1 (3%)
Total	**42**	**39**

*composite endpoint of chronic dysphagia defined by chronic aspiration or stricture per MBS and/or permanent gastrostomy dependence

Hutcheson K et al,
Head and Neck 2013

MDA 2009-0885 Schema

Diagnosis & Staging + Biopsies

After stratification for HPV status, positive patients with N2b/c/3 disease are eligible and randomized to PCC v TPF-C

Response Assessment + Biopsies

Patients with staging at diagnosis T 0-3

Patients with staging, at diagnosis T4 or unresectable N+

Radiation Therapy

Chemoradiotherapy

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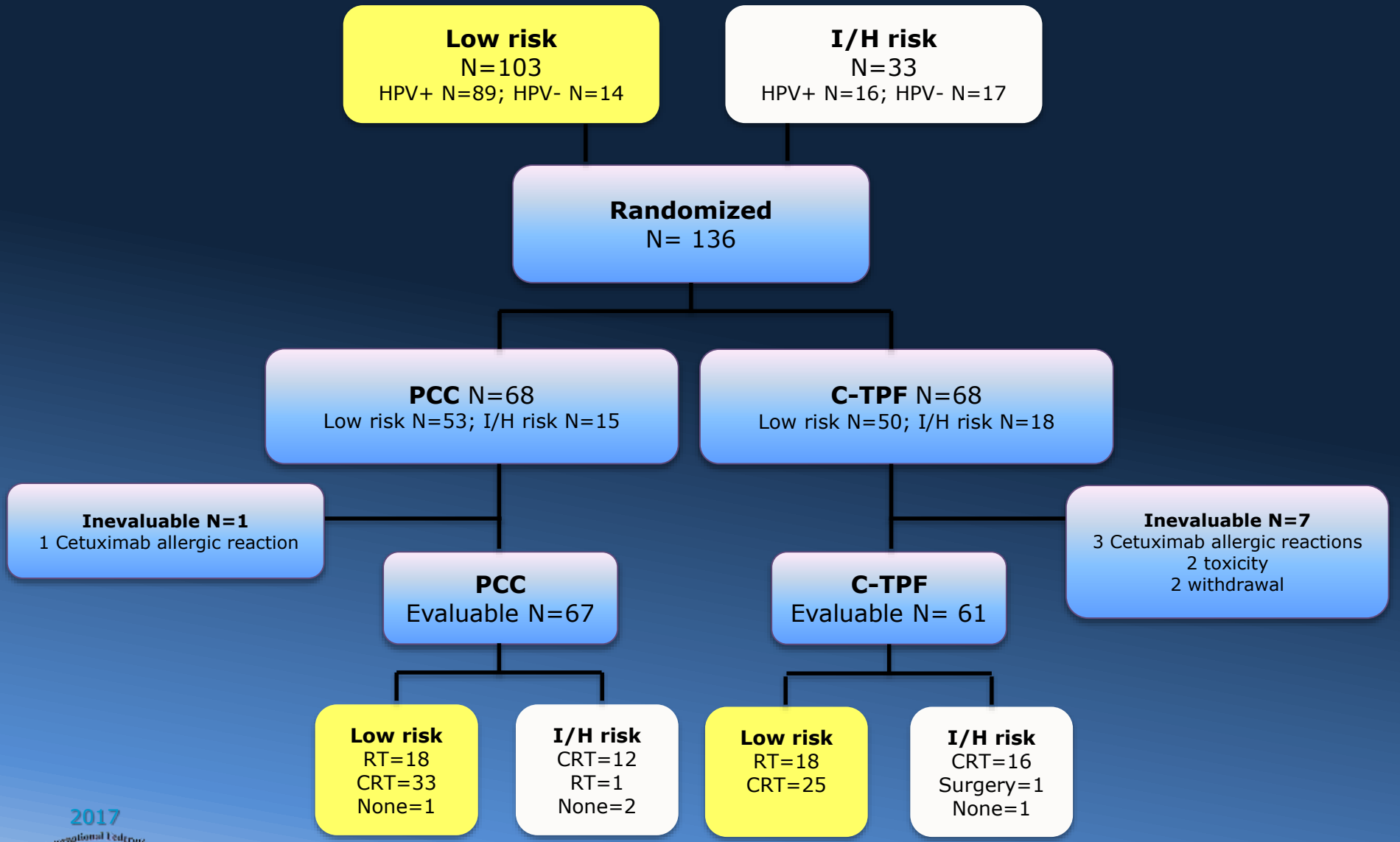
V Papadimitrakopoulou, PI

MDA 2009-0885 / Biomarker Correlates

- Immunoprofiling – CD3, DC4, LD8, RO, FOXp3, CD68, LD 113, PD-L1
- Blood flow cytometry for T cells
- Tumor mutation panel

Study Population

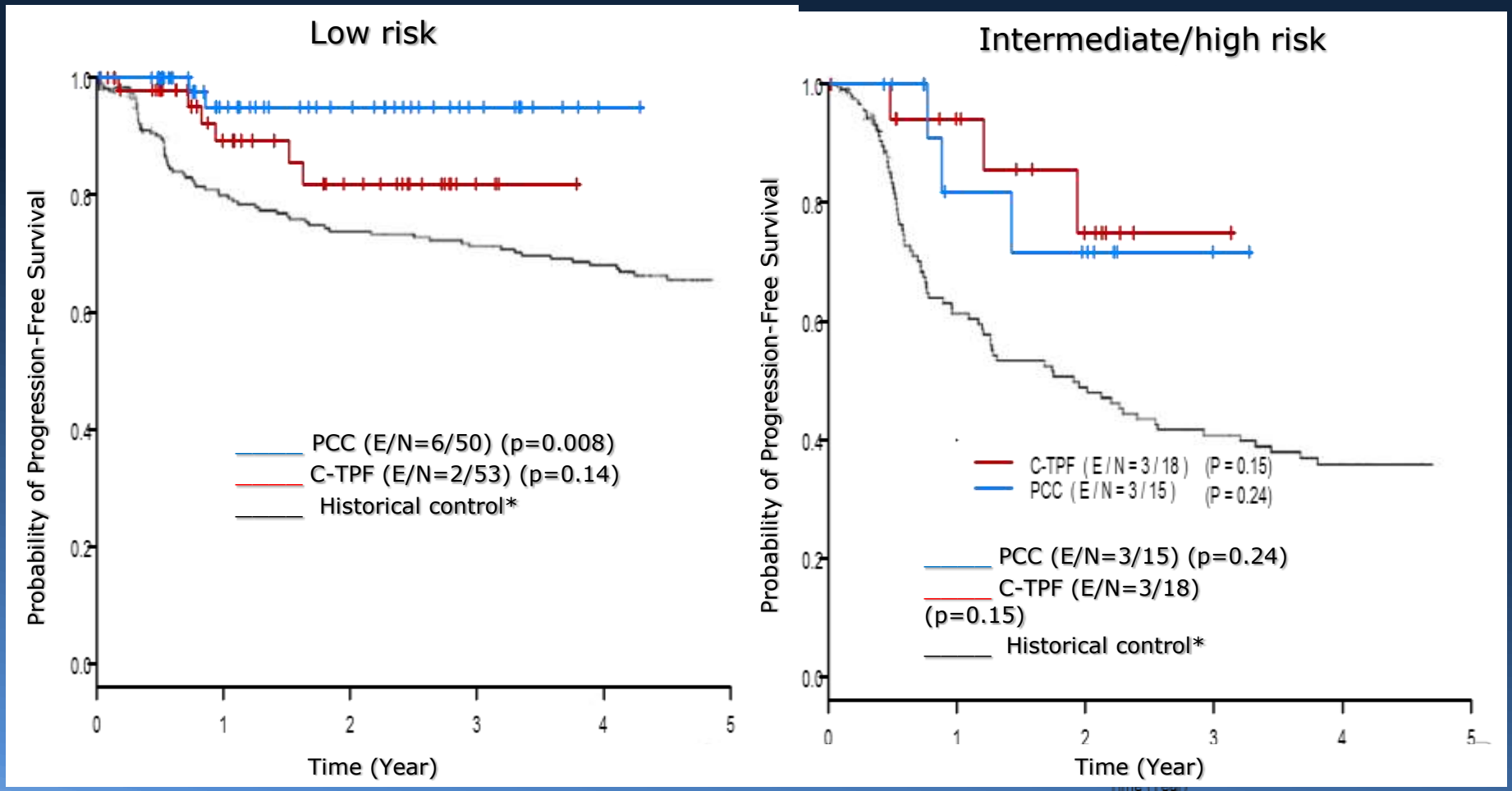


2017

Primary objective:
Estimated 2-year Progression free survival rate

	All patients % (CI)	**PCC % (CI)**	**C-TPF % (CI)**
Overall		89 (81, 99)	80 (68, 93)
Low risk	89 (81, 97)	95 (88, 100)	82 (69, 97)
I/H risk	74 (58, 95)	72 (49, 100)	75 (53, 100)

Primary objective: Progression free survival by risk group



*Historical control curves based on Ang KK et al. N Engl J Med 2010; 363:24-35

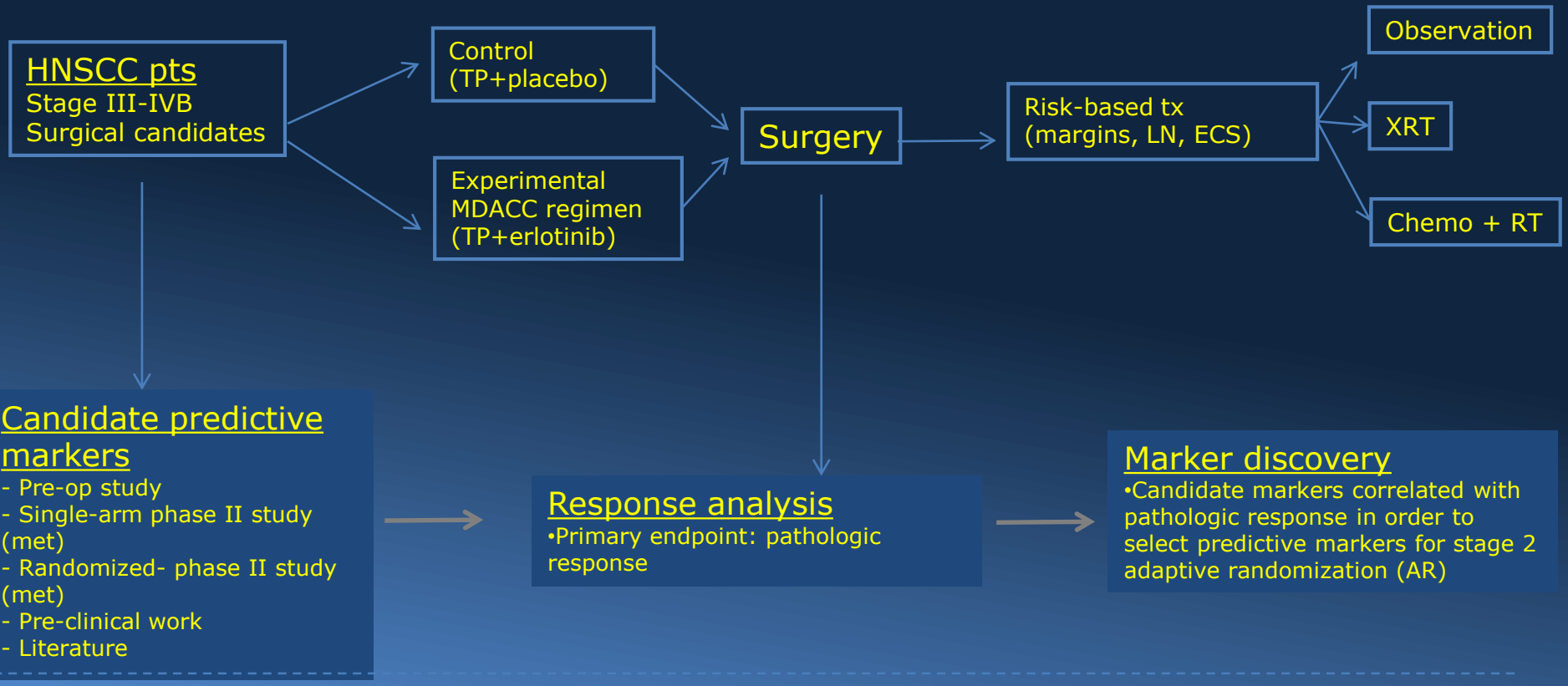
Estimated 2 year Progression free survival: subgroup analysis

	PCC % (CI)	C-TPF % (CI)
HPV-positive/never smokers	100 (100, 100)	86 (70, 100)
HPV-positive/<=10 pack years	100 (100, 100)	88 (67, 100)
HPV-positive/>10 pack years	87 (71, 100)	65 (44, 97)
HPV-negative	76 (55, 100)	83 (58, 100)
N2c-N3	83 (67, 100)	82 (67, 100)
N0-N2b	93 (85, 100)	78 (62, 98)

Trial Design (MDA 2013-0179)

Stage I (biomarker discovery/validation)

adaptive randomization based on pathologic response



Stage II (personalized biomarker-driven therapy)

2017

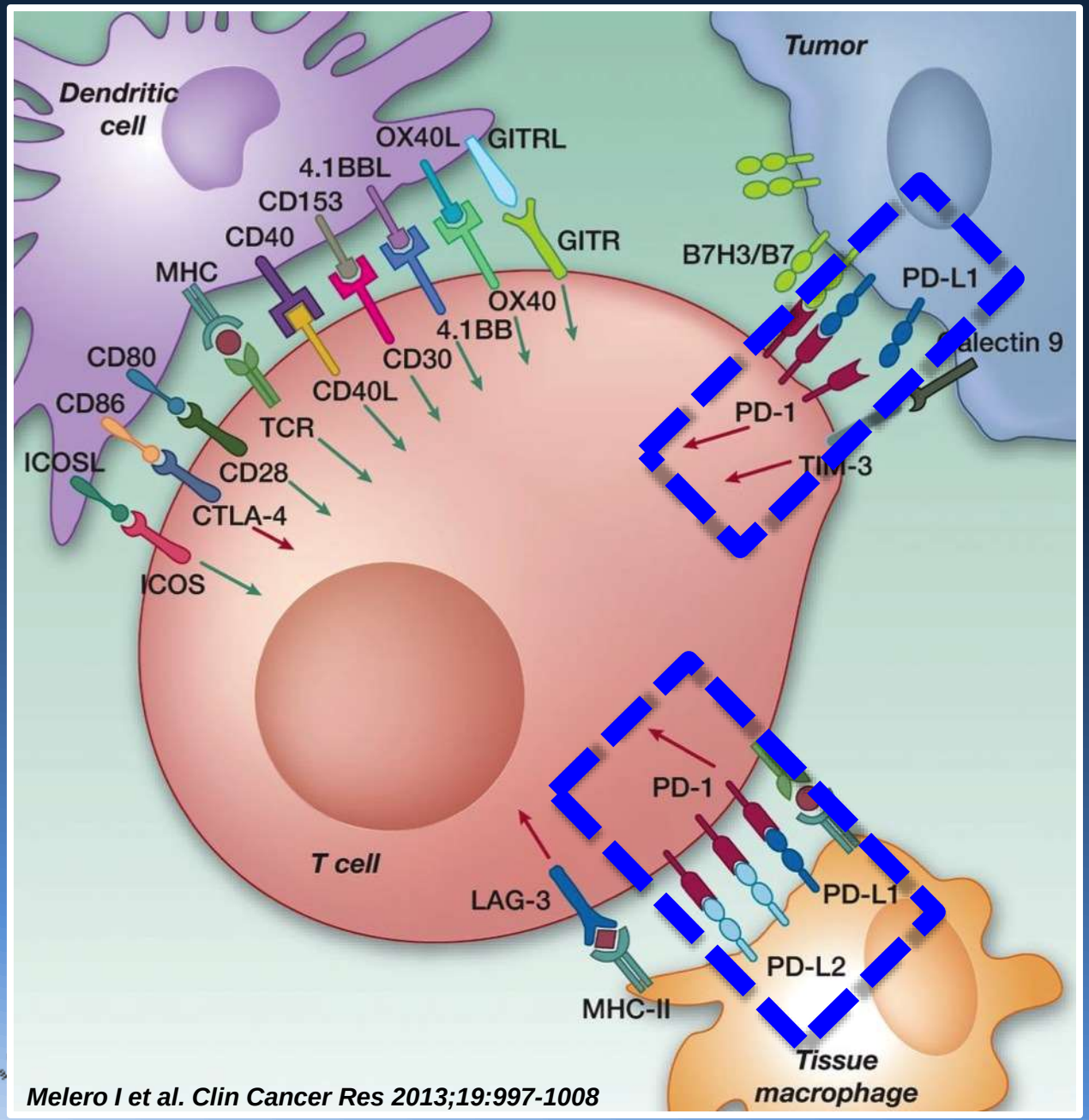
HNSCC pts
Stage III-IVB
Surgical candidates

adaptive randomization based on stage 1 markers

THE SEQUENTIAL CT AND RT PLATFORM FOR LOCALLY ADVANCED SCCHN

Systemic Rx → RT (+/- CT) → S

Basis for Immune therapy – Immune Escape



Melero I et al. Clin Cancer Res 2013;19:997-1008

- Expression of PD-L1 on
  a) tumor cells &
  b) macrophages
  can suppress immune surveillance.
- In mouse models antibodies ***blocking PD-1 / PD-L1 interaction*** lead to tumor rejection
- **Clinical prognosis** correlates with presence of **TILs** and **PD-L1** expression in multiple cancers.

CT - Observations

- Individualization of therapy continues to be based on site, stage, HPV status, PS, and tobacco consumption history
- CT – RT remains the fundamental consideration for non-surgical rx of locally advanced ds
- Pts with bulky N2b/c, N3, N level 4 are candidates for systemic rx and study
- Modification of combined treatment regimens in HPV+ ds is under investigation
- Efficacy relates to the entire treatment sequence
- Induction therapy is an investigational vehicle for the study of clinical and molecular endpoints

Old Texas Longhorn

Twin Creek Ranch of Cat Spring, Texas

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