De-intensification for HPV-OPSCC: Why is it NOT Standard of Care Yet?

39th Annual F. Johnson Putney
Lectureship in Head and Neck Cancer

Bhisham Chera, MD, FASTRO
Department of Radiation Oncology

MUSC
Medical University
of South Carolina

Hollings Cancer Center
An NCI-Designated Cancer Center

Disclosures

Medical University of South Carolina

- **Employment**

Co-inventor of intellectual property held by University of North Carolina regarding the ctHPVDNA detection methodology (US Patent 11,168,373)

Scientific advisor with ownership interest in Naveris, Inc, a company that has licensed ctHPVDNA technology from University of North Carolina for commercialization

The presenter has no relevant nonfinancial relationship to disclose

Objective

To discuss why de-intensification is not yet standard of care.

UNC/UF Paradigm (1st generation, LCCC 1120)

Phase 2 Trial of De-intensified Chemoradiation Therapy for Favorable-Risk Human Papillomavirus–Associated Oropharyngeal Squamous Cell Carcinoma

Bhishamjit S. Chera, MD,[*,†] Robert J. Amdur, MD,[‡,§] Joel Tepper, MD,[*,†] Bahjat Qaqish, PhD,[†,||] Rebecca Green, MSW,[*] Shannon L. Aumer, MA,[#] Neil Hayes, MD, MPH,[†,¶] Jared Weiss, MD,[†,¶] Juneko Grilley-Olson, MD,[†,¶] Adam Zanation, MD,[#] Trevor Hackman, MD,[#] William Funkhouser, MD,[**] Nathan Sheets, MD,[††] Mark Weissler, MD,[#] and William Mendenhall, MD[‡,§]

N=44
Median f/u = 34 months (88% ≥ 2 years)

Primary endpoint (IJROBP 2015):
- pCR rate = 86%

Secondary endpoints (Cancer 2018):
- 3 year PFS = 100%
- 3 year OS = 95%
- Global QoL returned to baseline
- Swallowing returned to baseline
- Dry mouth continues to improve > 1 year

- **De-intensified Chemoradiotherapy**
  - 60 Gy at 2 Gy/fx, daily, 6 weeks (IMRT)
  - Cisplatin 30mg/m^2, 6 weekly doses

All patients had biopsy of primary site and supraselective neck dissection

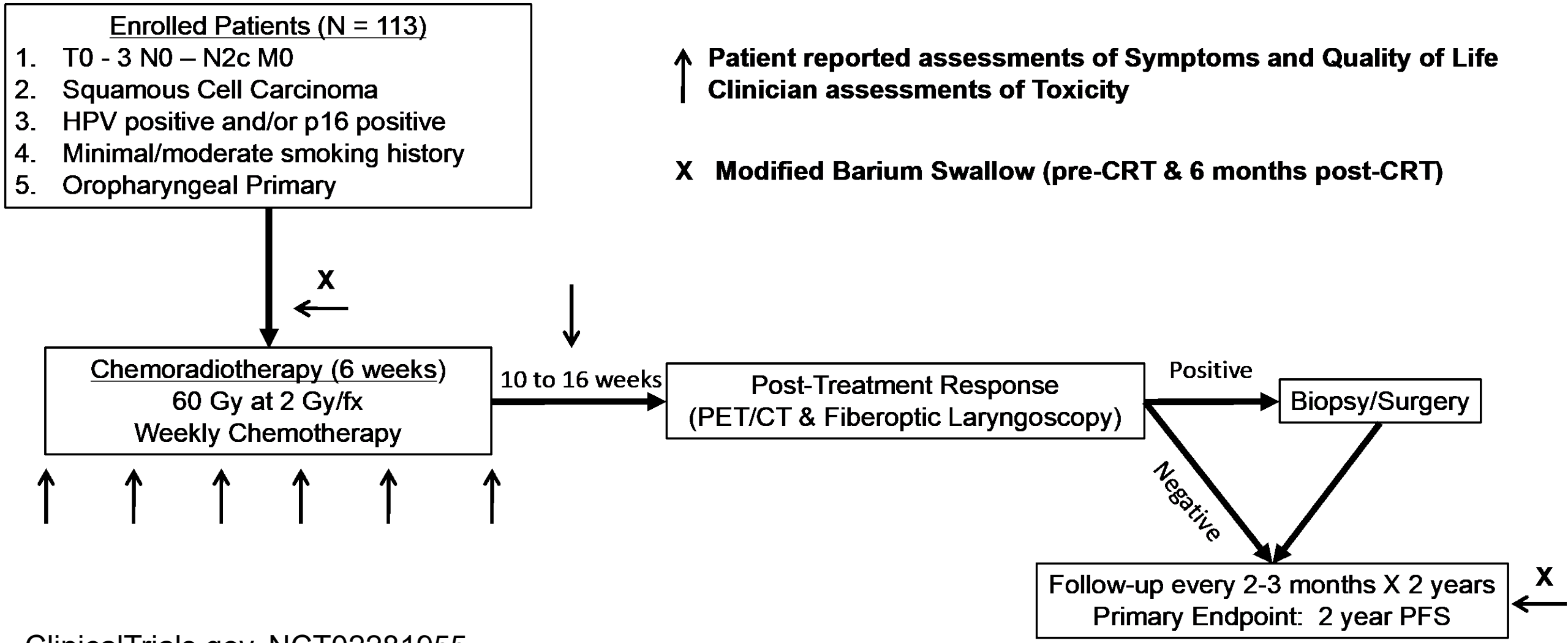
Int J Radiation Oncol Biol Phys, Vol. 93, No. 5, pp. 976–985, 2015

Phase II Trial of De-Intensified Chemoradiotherapy for Human Papillomavirus–Associated Oropharyngeal Squamous Cell Carcinoma

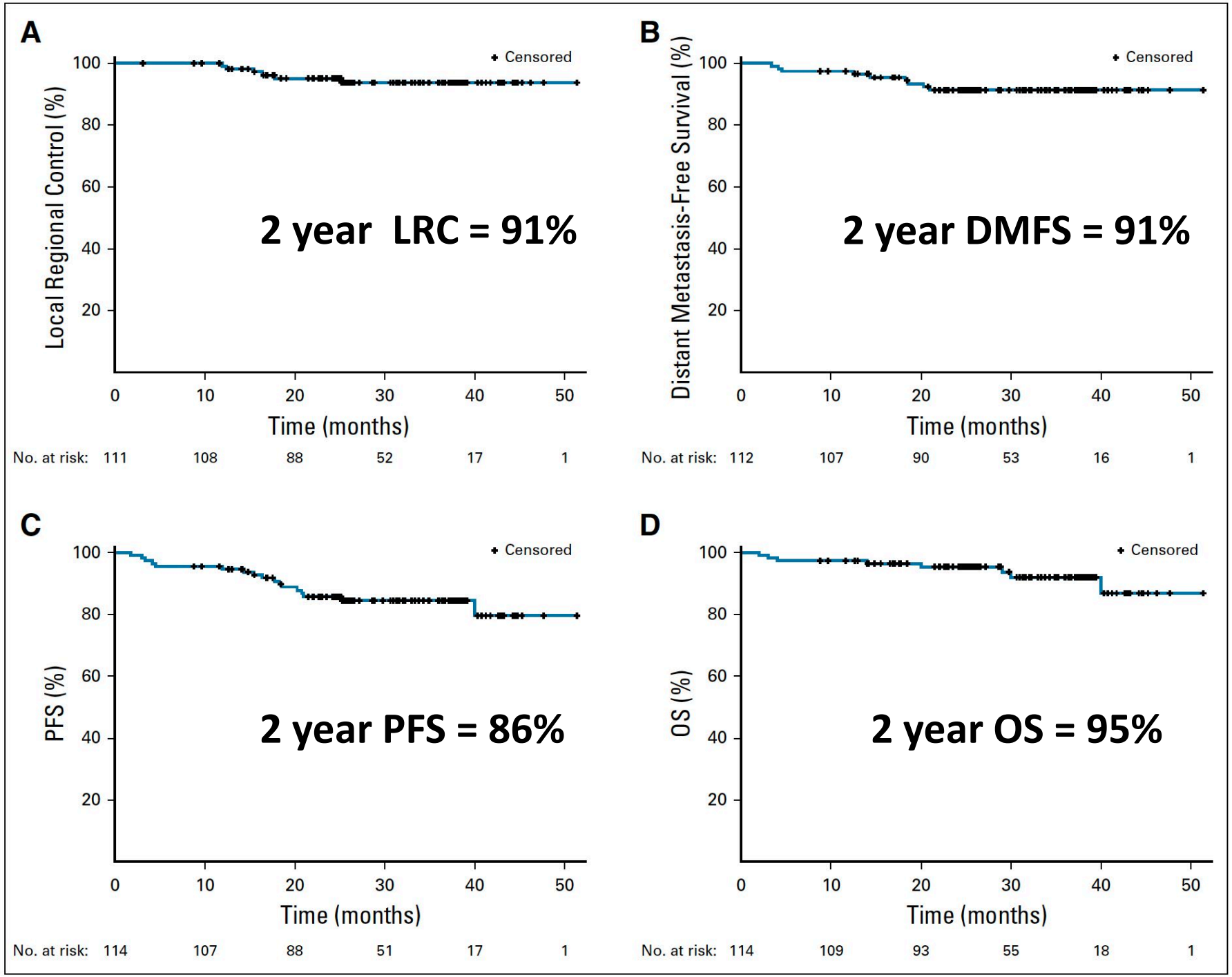
Bhishamjit S. Chera, MD[1,2]; Robert J. Amdur, MD[3]; Rebecca Green, MSW[1]; Colette Shen, MD, PhD[1,2]; Gaorav Gupta, MD, PhD[1,2]; Xianming Tan, PhD[2]; Mary Knowles, ANP[1]; David Fried, PhD[1]; Neil Hayes, MPH, MD[4]; Jared Weiss, MD[1,2]; Juneko Grilley-Olson, MD[1,2]; Shetal Patel, MD, PhD[1,2]; Adam Zanation, MD[1]; Trevor Hackman, MD[1]; Jose Zevallos, MPH, MD[5]; Jeffrey Blumberg, MD[1]; Samip Patel, MD[1]; Mohit Kasibhatla, MD[6]; Nathan Sheets, MD[7]; Mark Weissler, MD[1]; Wendell Yarbrough, MMHC, MD[1,2]; and William Mendenhall, MD[3]

Journal of Clinical Oncology®

Schema LCCC 1413 (De-intensification #2)



ClinicalTrials.gov, NCT02281955


A
Censored
Local Regional Control (%)
100
80
60
40
20
2 year LRC = 91%
0
10
20
30
40
50
Time (months)
No. at risk: 111 108 88 52 17 1
B
Censored
Distant Metastasis-Free Survival (%)
2 year DMFS = 91%
No. at risk: 112 107 90 53 16 1
C
Censored
PFS (%)
2 year PFS = 86%
No. at risk: 114 107 88 51 17 1
D
Censored
OS (%)
2 year OS = 95%
No. at risk: 114 109 93 55 18 1

NRG ONCOLOGY

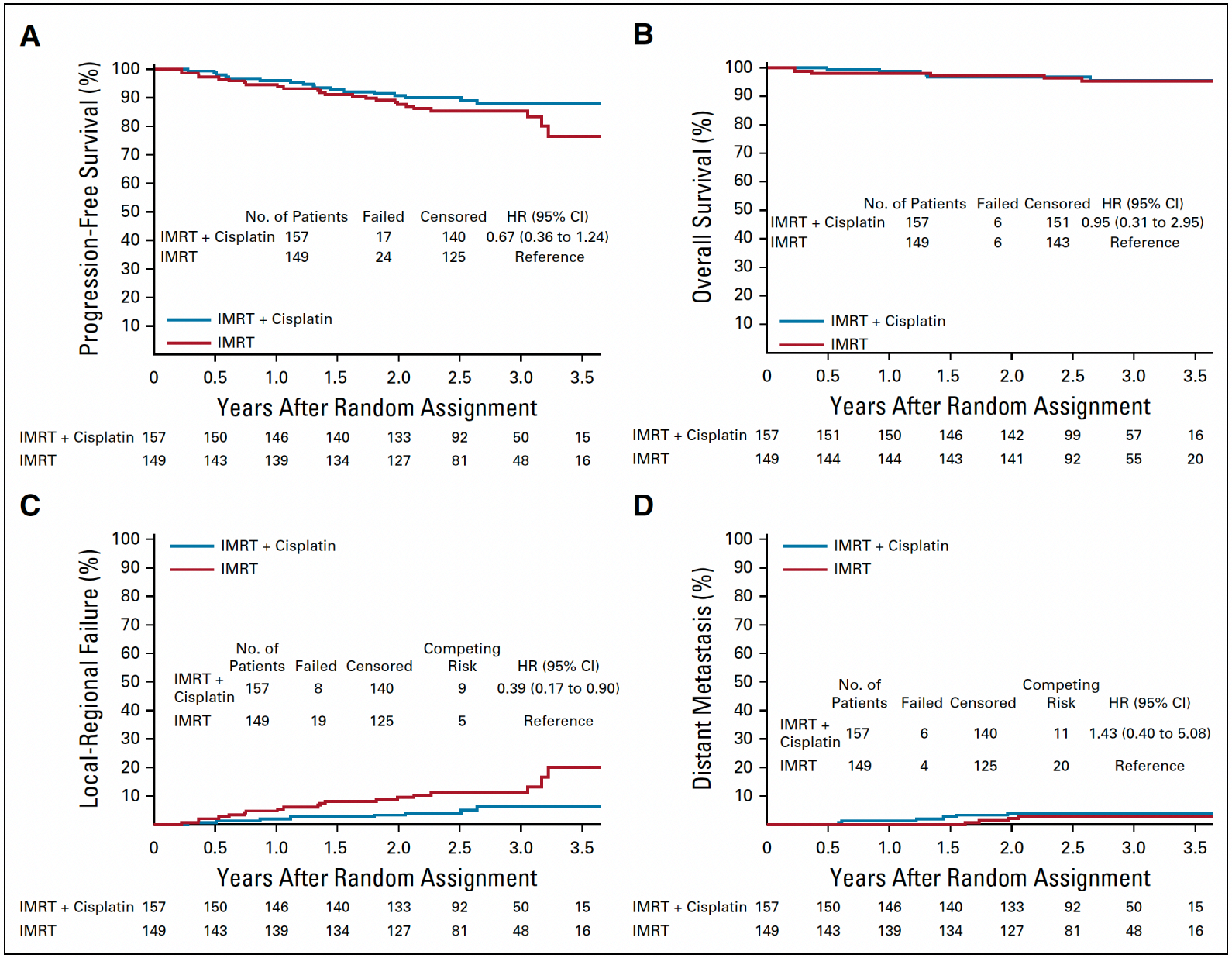
Advancing Research. Improving Lives.™

NRG-HN002: A Randomized Phase II Trial for Patients with p16-Positive, Non-Smoking-Associated, Locoregionally Advanced Oropharyngeal Cancer

Sue S Yom[1], Pedro Torres-Saavedra[2], Jimmy J Caudell[3], John N Waldron[4], Maura L Gillison[5], Minh T Truong[6], Richard Jordan[1], Rathan M Subramaniam[7], Min Yao[8], Christine H Chung[3], Jessica L Geiger[9], Jason W Chan[1], Brian O'Sullivan[4], Dukagjin M Blakaj[10], Loren K Mell[11], Wade L Thorstad[12], Christopher U Jones[13], Robyn N Banerjee[14], Christopher Lominska[15], Quynh-Thu Le[16]

[1]University of California – San Francisco, [2]NRG Oncology, [3]Moffitt Cancer Center, [4]Princess Margaret Hospital, [5]M D Anderson Cancer Center, [6]Boston Medical Center, [7]University of Texas – Southwestern, [8]Case Comprehensive Cancer Center, [9]Cleveland Clinic, [10]The Ohio State University, [11]University of California - San Diego, [12] Washington University School of Medicine, [13]Sutter Cancer Research Consortium, [14] Tom Baker Cancer Centre, [15] University of Kansas, [16] Stanford University

Annual Meeting of American Society for Radiation Oncology
Plenary Session - September 16, 2019



Primary endpoint = PFS

- Median follow-up is 2.6 years.
- **2-year PFS estimate for IMRT + C arm is 90.5%** (95% CI 84.5-94.7%) with p=0.0350 rejecting the null hypothesis.
- **2-year PFS estimate for IMRT arm is 87.6%** (95% CI 81.1-92.5%) with p=0.2284 failing to rejecting the null hypothesis.

E1308: Phase II Trial of Induction Chemotherapy Followed by Reduced-Dose Radiation and Weekly Cetuximab in Patients With HPV-Associated Resectable Squamous Cell Carcinoma of the Oropharynx— ECOG-ACRIN Cancer Research Group

original reports

Phase II Randomized Trial of Transoral Surgery and Low-Dose Intensity Modulated Radiation Therapy in Resectable p16+ Locally Advanced Oropharynx Cancer: An ECOG-ACRIN Cancer Research Group Trial (E3311)

Clinical Investigation

A Phase 2 Trial of Alternative Volumes of Oropharyngeal Irradiation for De-intensification (AVOID): Omission of the Resected Primary Tumor Bed After Transoral Robotic Surgery for Human Papilloma Virus–Related Squamous Cell Carcinoma of the Oropharynx

OPTIMA: a phase II dose and volume de-escalation trial for human papillomavirus-positive oropharyngeal cancer ***U Chicago***

Phase II Evaluation of Aggressive Dose De-Escalation for Adjuvant Chemoradiotherapy in Human Papillomavirus–Associated Oropharynx Squamous Cell Carcinoma ***Mayo Clinic***

Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial

JAMA Oncology | Original Investigation

Assessment of Toxic Effects and Survival in Treatment Deescalation With Radiotherapy vs Transoral Surgery for HPV-Associated Oropharyngeal Squamous Cell Carcinoma
The ORATOR2 Phase 2 Randomized Clinical Trial

TORS vs. CRT

Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial

Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial

70Gy
Cisplatin vs.
Cetuximab

The next NRG Oncology phase II study with two new experimental arms:

NRG-HN005: A Randomized Phase II/III Trial of De-intensified Radiation Therapy for Patients with Early Stage, p16-Positive, Non-Smoking-Associated Oropharyngeal Cancer

Eligibility

- Oropharynx SCCA
- p16+
- ≤10 pack-yr
- T1-2N1 or T3 N0-1

Randomized Phase

N = 399
PFS then MDADI futility analysis

RANDOMIZE

- 70 Gy in 6 weeks + cisplatin 100 mg/m2 q21 days x 2 cycles
- 60 Gy in 6 weeks + cisplatin 100 mg/m2 q21 days x 2 cycles
- 60 Gy in 5 weeks + nivolumab 240 mg q14 days x 6 cycles

Phase III Continuation

N = 104 additional pts PER ARM
Nested co-primary endpoints:
PFS and MDADI

RANDOMIZE

- 70 Gy in 6 weeks + cisplatin 100 mg/m2 q21 days x 2 cycles
- *1 or 2 experimental arms*

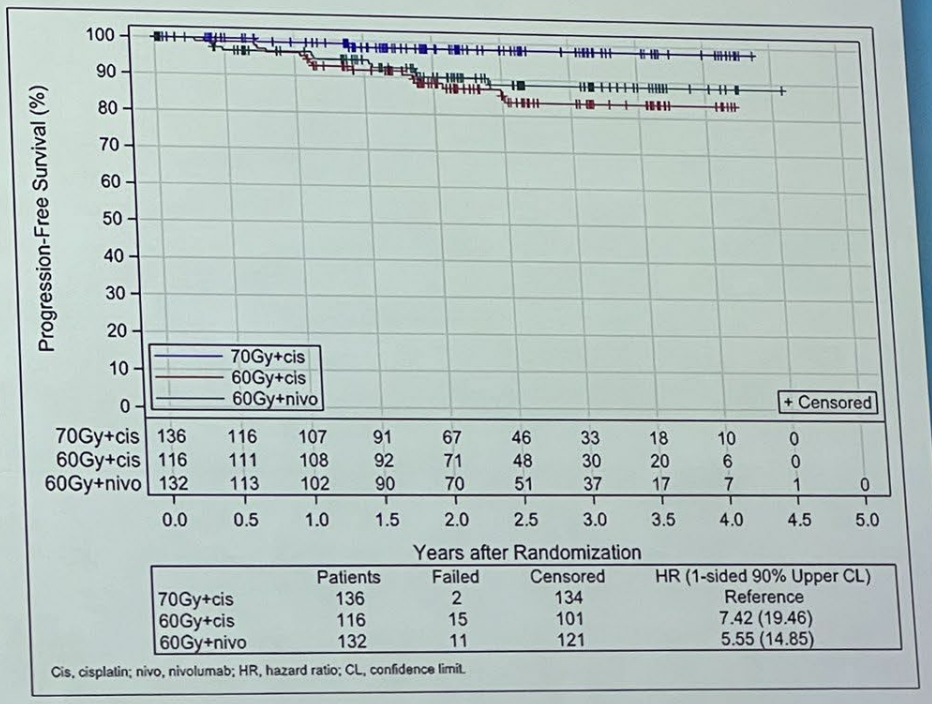
NRG ONCOLOGY™

PROs: MDADI, HHIA-S, EORTC QLQ-C30, EQ-5D-5L Toxicity: CTCAE, PRO-CTCAE

2-Year Progression-Free Survival

At median follow-up of 2.2 years,
2-year PFS estimates are:

- Arm 1: 98.1% (95%CI 95.4, 100)
- Arm 2: 88.6% (95%CI 82.4, 94.7)
- Arm 3: 90.3% (95%CI 84.5, 96.1)



	Patients	Failed	Censored	HR (1-sided 90% Upper CL)
70Gy+cis	136	2	134	Reference
60Gy+cis	116	15	101	7.42 (19.46)
60Gy+nivo	132	11	121	5.55 (14.85)

Cis, cisplatin; nivo, nivolumab; HR, hazard ratio; CL, confidence limit.

NRG ONCOLOGY™

ASTRO 2024

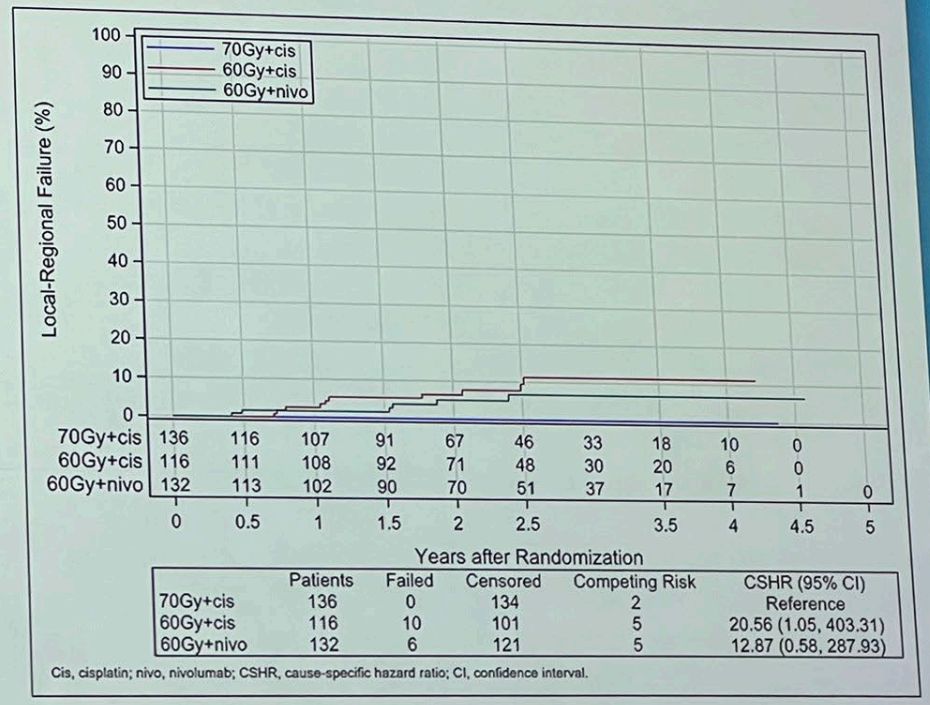
2 year OS:

70Gy + cis = 99%
60Gy + cis = 98%
60Gy + nivo = 96%

2-Year Locoregional Failure

2-year LRF estimates are:

- Arm 1: 0%
- Arm 2: 6.5% (95%CI 2.8, 12.2)
- Arm 3: 5.0% (95%CI 1.8, 10.6)



	Patients	Failed	Censored	Competing Risk	CSHR (95% CI)
70Gy+cis	136	0	134	2	Reference
60Gy+cis	116	10	101	5	20.56 (1.05, 403.31)
60Gy+nivo	132	6	121	5	12.87 (0.58, 287.93)

Cis, cisplatin; nivo, nivolumab; CSHR, cause-specific hazard ratio; CI, confidence interval.

NRG ONCOLOGY™

ASTRO 2024

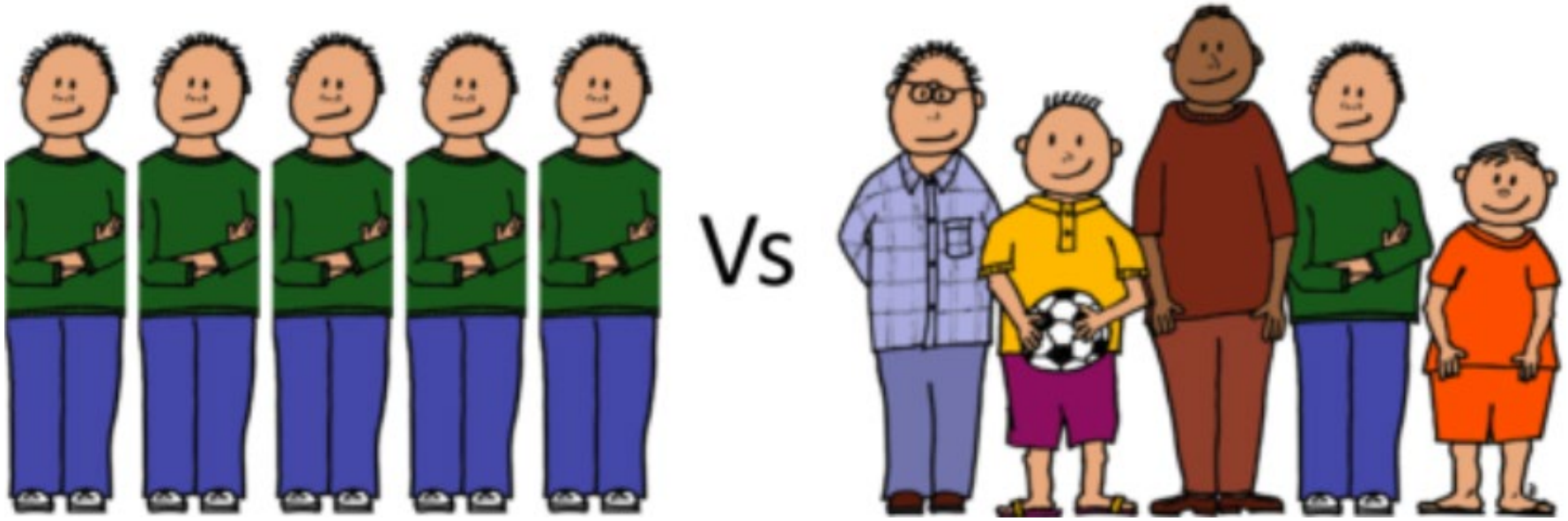
Efficacy → **Effectiveness**

Does it work in clinical trials?

Under ideal situations

Does it work in clinical practice?

Under usual situations



Efficacy does not imply Effectiveness

Prognostic implications of p16 and HPV discordance in oropharyngeal cancer (HNCIG-EPIC-OPC): a multicentre, multinational, individual patient data analysis

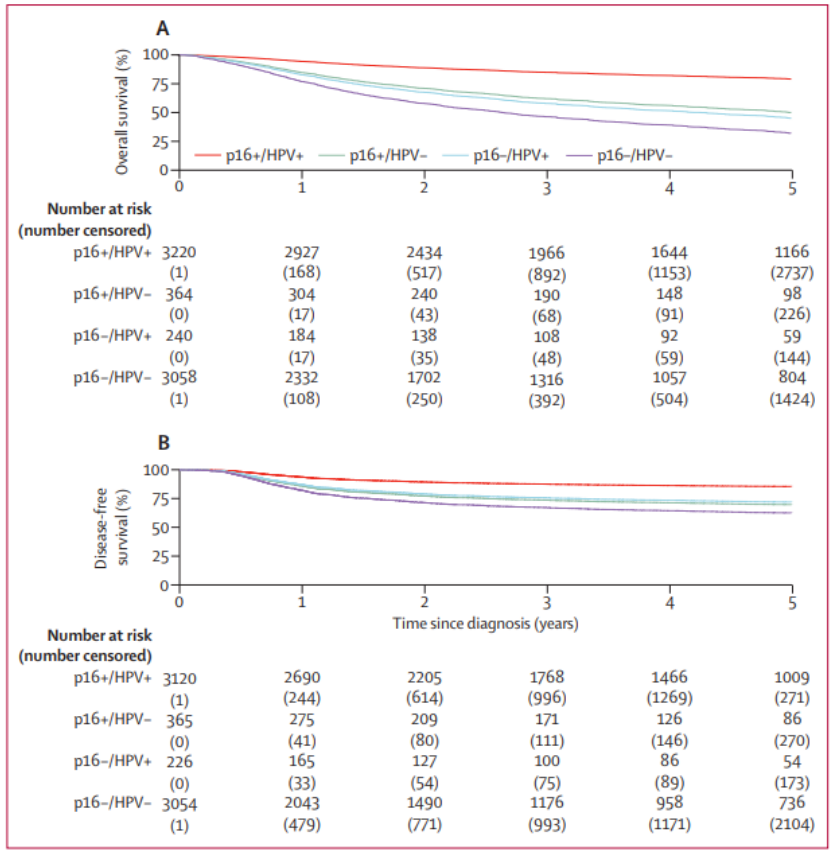
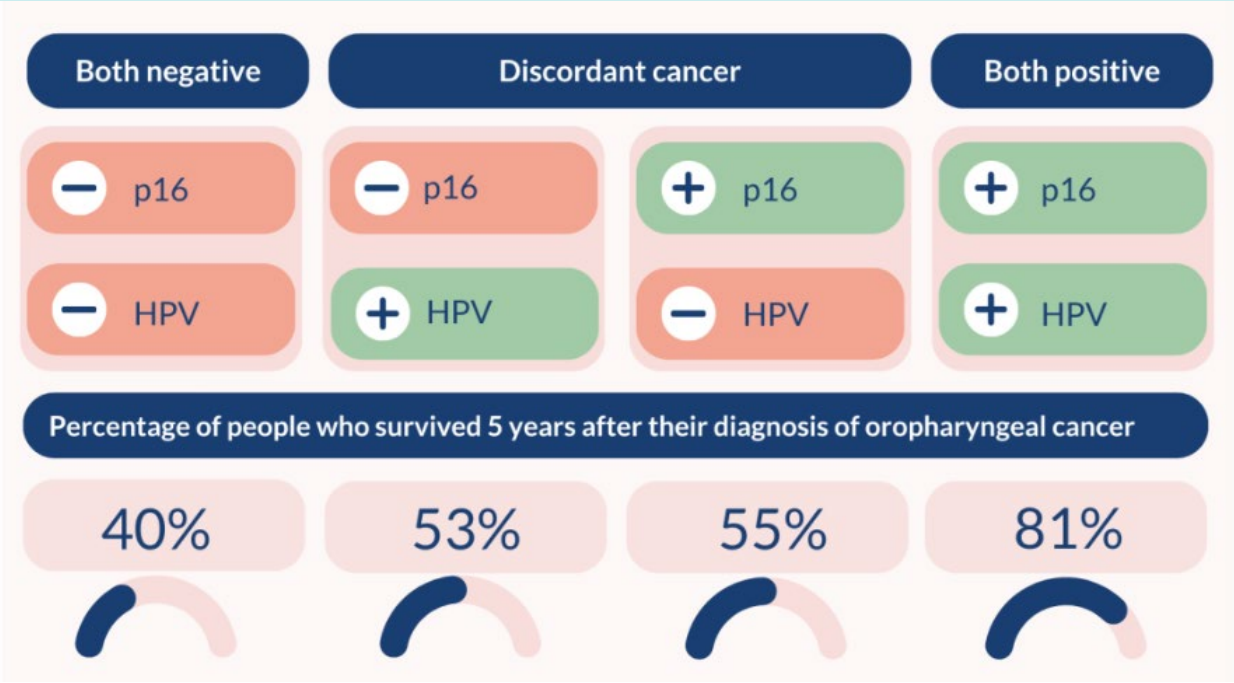


Figure 3: **5-year adjusted overall survival and 5-year adjusted disease-free survival for patients with oropharyngeal cancer by HPV biomarker positivity**
(A) Overall survival curve adjusted by biomarker combinations, sex, and cohort and stratified by treatment, stage (TNM 7th edition), age, smoking status, and year of diagnosis. (B) Disease-free survival curve adjusted by biomarker combinations, stage (TNM 7th edition), sex, year of diagnosis, and smoking status, and stratified by cohort and treatment. HPV=human papillomavirus.

Mehanna Lancet 2023

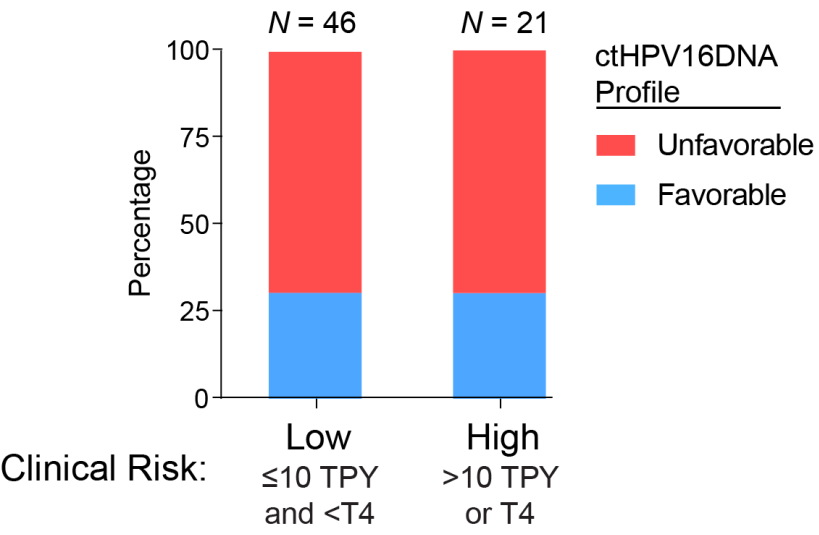


evidence.nihr.ac.uk

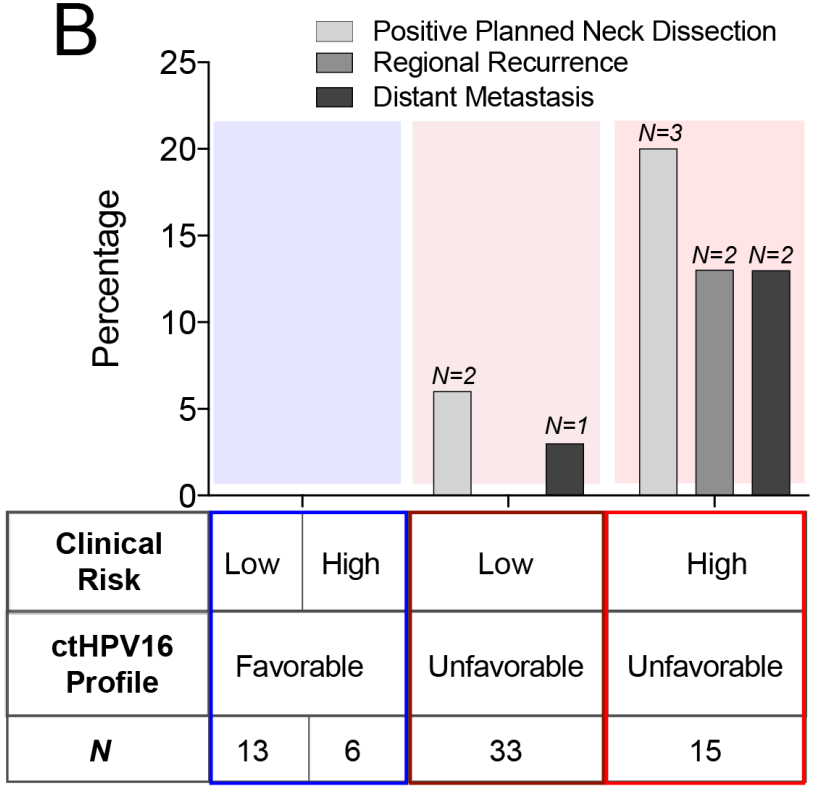
Do we need better biomarkers?

Favorable ctHPV16DNA clearance profile correlates with disease control

A

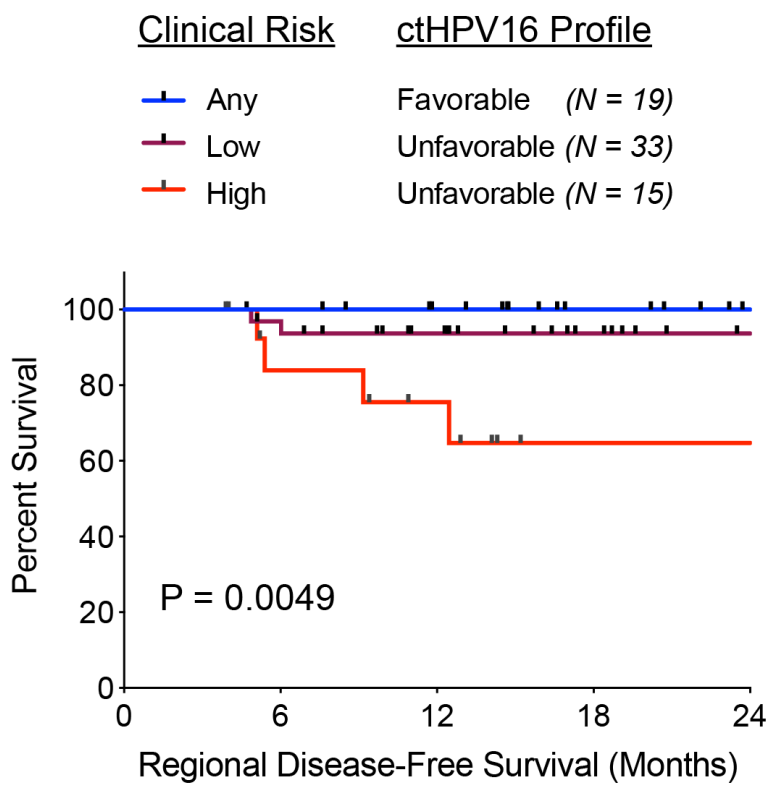


B



Clinical Risk	Low	High	Low	High
ctHPV16 Profile	Favorable		Unfavorable	Unfavorable
N	13	6	33	15

C



Favorable ctHPV16DNA clearance profile = high baseline copy number (>200 copies/mL) and >95% clearance of ctHPV16DNA by day 28 of CRT.

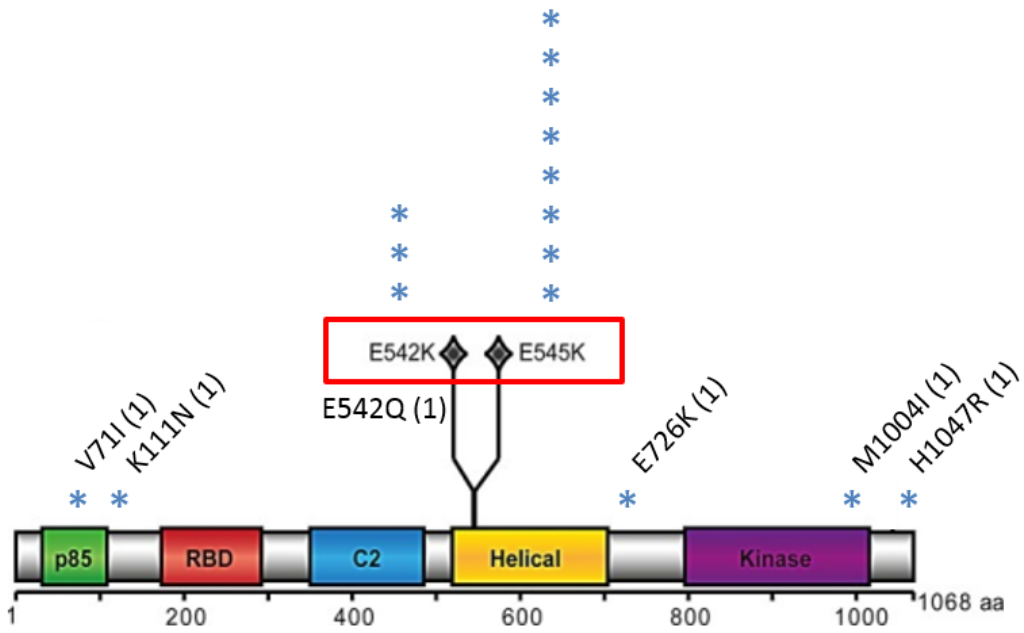
Chera et al. CCR 2019

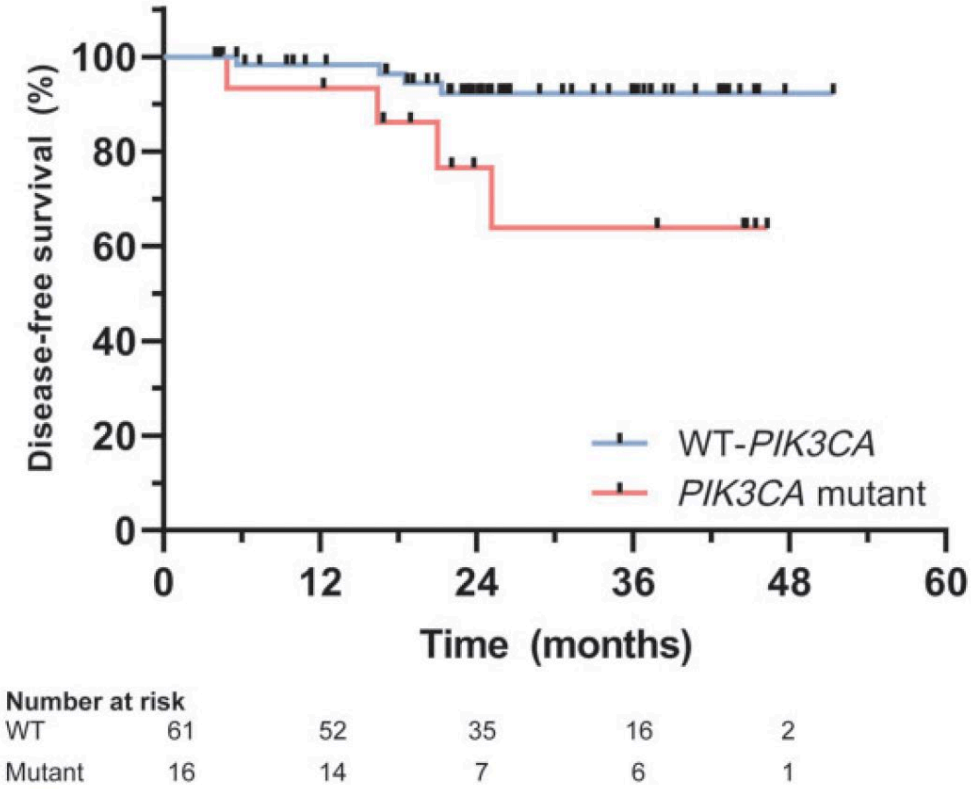
BRIEF COMMUNICATION

PIK3CA Mutation in HPV-Associated OPSCC Patients Receiving Deintensified Chemoradiation

Brian T. Beaty , Dominic H. Moon, Colette J. Shen, Robert J. Amdur, Jared Weiss, Juneko Grilley-Olson, Shetal Patel, Adam Zanation, Trevor G. Hackman, Brian Thorp, Jeffrey M. Blumberg, Samip N. Patel, Mark C. Weissler, Wendell G. Yarbrough, Nathan C. Sheets, Joel S. Parker, D. Neil Hayes, Karen E. Weck, Lori A. Ramkissoon, William M. Mendenhall, Roi Dagan, Xianming Tan, Gaorav P. Gupta, Bhishamjit S. Chera

JNCI J Natl Cancer Inst (2020) 112(8): djz224



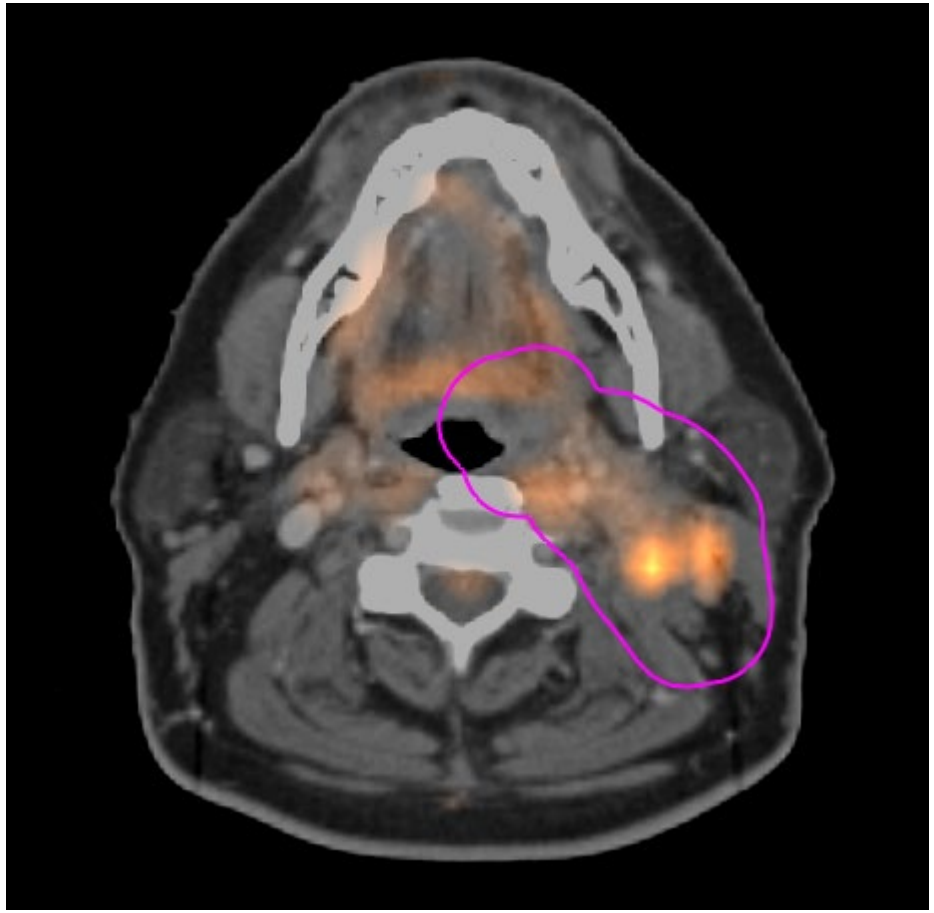


Common sites of *PIK3CA* mutation (16 patients total)

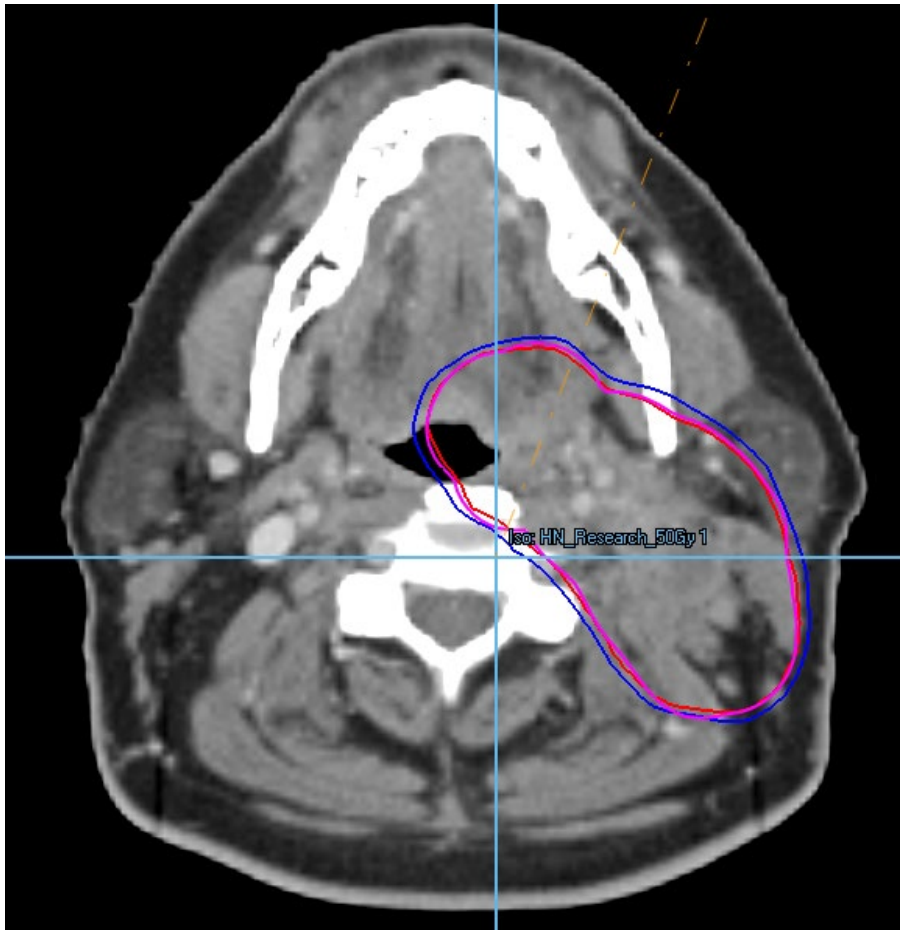
- E545K – 8
- E542K – 2

N=77 patients
Enrolled on De-escalation CRT trials (60Gy)

3 month post-treatment PET fused to CT sim



PTV 60 got 50Gy per protocol



PTV 60 (magenta), 100% IDL (red), 95% IDL (blue)

Pathology and NGS from 2/21/25 salvage neck surgery

Final Diagnosis

A. LYMPH NODE, LABELED AS "LEFT LEVEL 4 NECK DISSECTION", REGIONAL RESECTION:

- THREE BENIGN LYMPH NODES (0/3)

B. LYMPH NODE, LABELED AS "LEFT LEVEL 3 NECK DISSECTION", REGIONAL RESECTION:

- FIVE BENIGN LYMPH NODES
- BENIGN NERVE
- CHANGES SUGGESTIVE OF PRIOR SURGICAL SITE WITH DYSTROPHIC CALCIFICATIONS

C. LYMPH NODE, LABELED AS "LEFT LEVEL 2 NECK DISSECTION", BIOPSY:

- METASTATIC SQUAMOUS CARCINOMA INVOLVING (1/4)
- SIZE OF LARGEST METASTATIC DEPOSIT: AT LEAST 1.6 CM
- EXTRANODAL EXTENSION: PRESENT, INCLUDING DIRECT EXTENSION
    - DISTANCE OF EXTENSION: 0.2 CM
- LYMPHOVASCULAR INVASION: ABSENT
- PERINEURAL INVASION: PRESENT
- DYSTROPHIC CALCIFICATIONS

IMMUNOHISTOCHEMICAL STAIN:

- CK5/6: POSITIVE
- HPV HR: POSITIVE

Results with Therapy Associations

BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
PD-L1 (22c3)	IHC	Protein	Positive, CPS: 90	BENEFIT	pembrolizumab	Level 1

* Biomarker reporting classification - Level 1 – MI Cancer Seek™ or other companion diagnostic (CDx) performed as part of professional services; Level 2 – Strong evidence of clinical significance or is endorsed by standard clinical guidelines; Level 3 – Potential clinical significance. Bolded benefit therapies, if present, highlight the most clinically significant findings.

Important Note

This content is provided as part of the professional services. For MI Cancer Seek™ results, see CDx Associated Findings.

This patient has a potential NCI-ComboMATCH Trial-eligible result. Please see the clinical trials section on *Page 5*.

This tumor is positive for HPV 16*. Please see the additional results page for more details.

This patient's PD-L1 CPS is sufficient for the use of pembrolizumab monotherapy for first-line treatment of metastatic or unresectable, recurrent HNSCC. Pembrolizumab combination therapy with platinum and 5-FU is approved for first-line treatment in metastatic or unresectable, recurrent HNSCC regardless of PD-L1 status. Pembrolizumab monotherapy is also approved for second-line use regardless of PD-L1 status.

For information on Caris GPSai™, please refer to relevant section of the report (Additional Results Page 1).

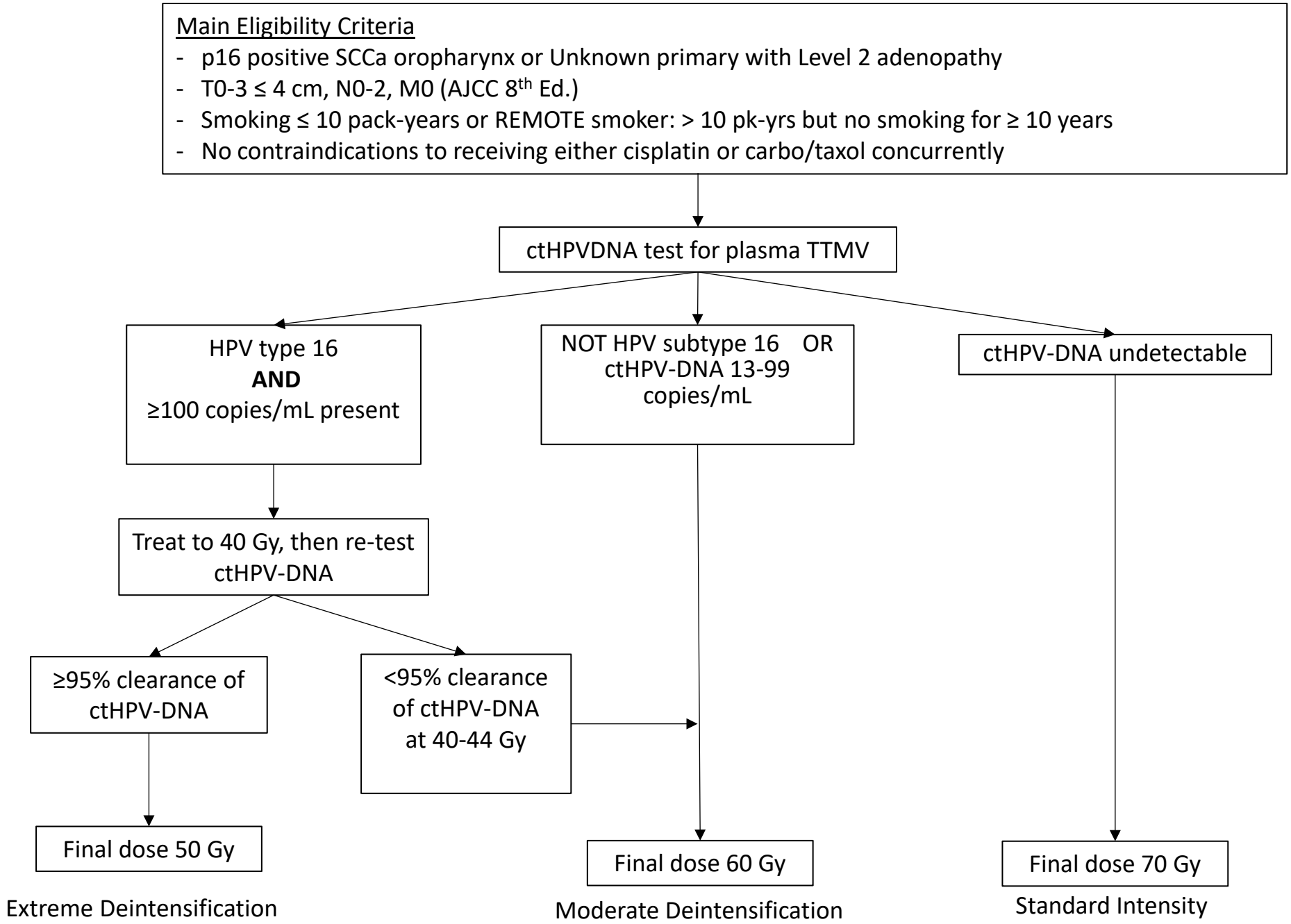
Cancer-Type Relevant Biomarkers

Biomarker	Method	Analyte	Result
PIK3CA	**Seq**	**DNA-Tumor**	**Pathogenic Variant Exon 10 | p.E542K**
p16	**IHC**	**Protein**	**Positive | 2+, 70%**
BRAF	Seq	DNA-Tumor	Mutation Not Detected
MSI	Seq	DNA-Tumor	Stable
NTRK1/2/3	Seq	RNA-Tumor	Fusion Not Detected
RET	Seq	RNA-Tumor	Fusion Not Detected

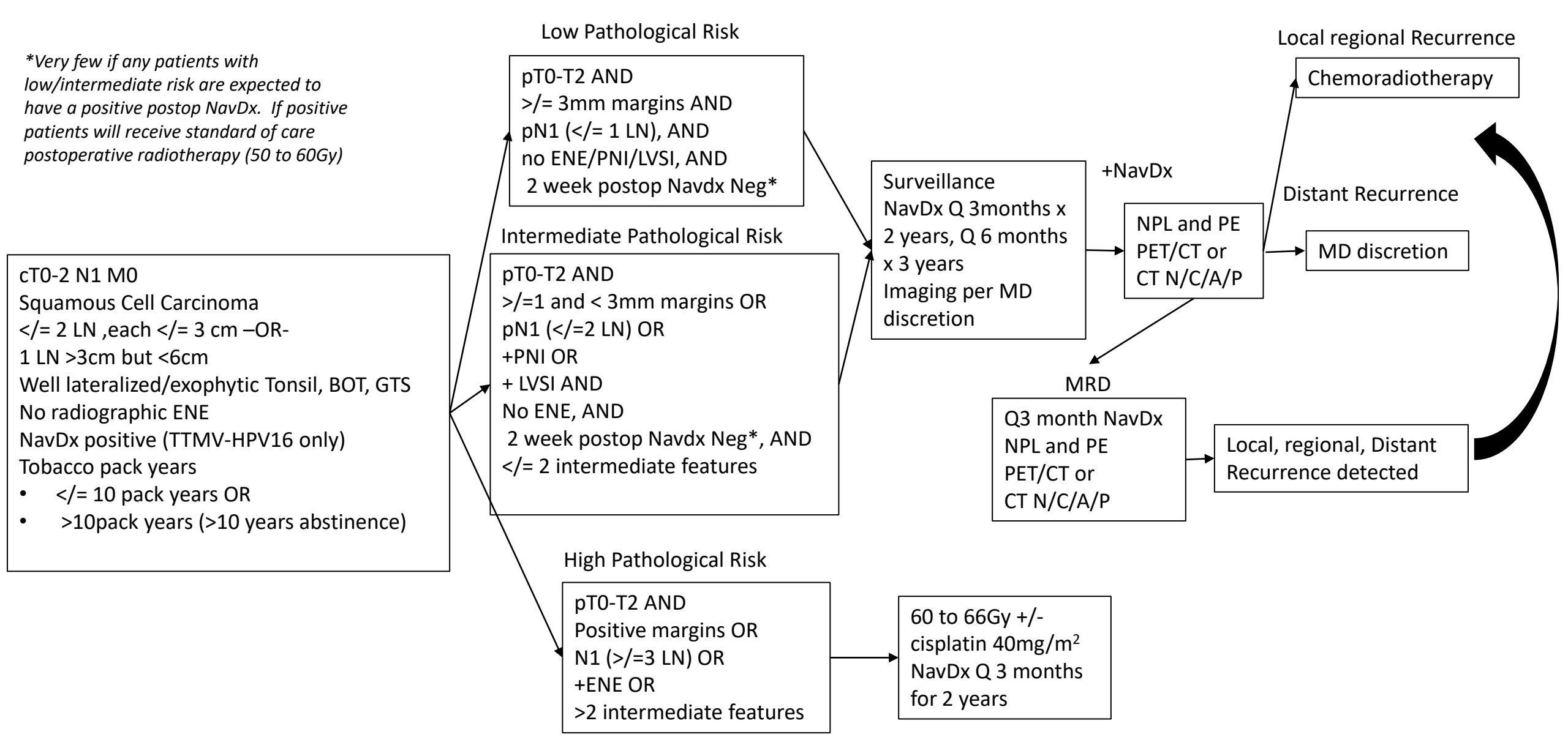
Biomarker	Method	Analyte	Result
Tumor Mutational Burden	Seq	DNA-Tumor	Low, 3 mut/Mb
CCND1	CNA-Seq	DNA-Tumor	Amplification Not Detected
CD274 (PD-L1)	CNA-Seq	DNA-Tumor	Amplification Not Detected
		DNA-Tumor	Deletion Not Detected
CDKN2A	Seq	DNA-Tumor	Mutation Not Detected

University of Florida:

ctHPV16DNA as an integral biomarker to guide intensity of treatment



UF UNIVERSITY of FLORIDA



Primary endpoint is 2 year local regional control (control above the clavicles), should it be salvage rate, negative NavDx at 2 years?

Secondary endpoints: 2 year PFS, DMFS, OS

Exploratory: QOL, anxiety, swallow

Conclusions and Final Thoughts

- I personally do not have equipoise → I think we should be de-intensifying
- Maybe PFS is the wrong endpoint since OS is >95%
  - Salvage treatment more efficacious?
  - Would patients accept a lower cancer control in favor of less toxicity?
- ctHPVDNA →
  - Better “window” into tumor biology
  - Is it a better biomarker that can be used for more precise patient selection?