UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

Landscape of Current and Emerging Biomarkers for Head and Neck Cancer

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Disclosure

Ranee Mehra, MD

Has a financial disclosures: Advisory Board with Janssen*/Merck*/Merus*/Summit Therapeutics*/Coherus* and Travel Investigator Meeting with Bicara Therapeutics*

Does not have any relevant non-financial disclosures.

*Indicates the relationship has ended

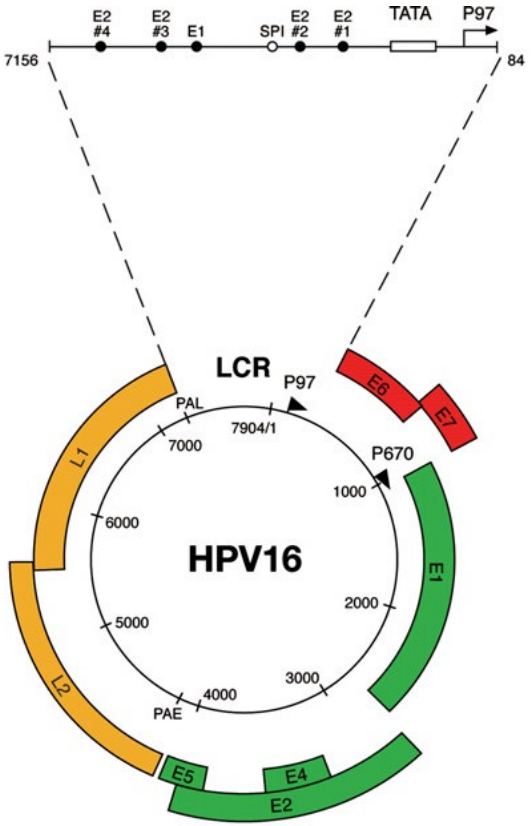
Outline

- p16
- PDL1 CPS
- Potentially actionable somatic alterations
- Future biomarkers

Challenge

- The clinical care of SCCHN has largely not been influenced by clinical biomarkers until recently
- p16 – prognostic with some efforts related to de-intensification (E3311)
- Paucity of driver oncogenic mutations
- PDL1 CPS is an imperfect biomarker but has proven to help guide treatment selection
- Locally advanced disease – still need more robust biomarker to drive treatment discussions.
- GOAL – to better identify treatment paradigms based on biomarker selection to improve the outcome for our patients.

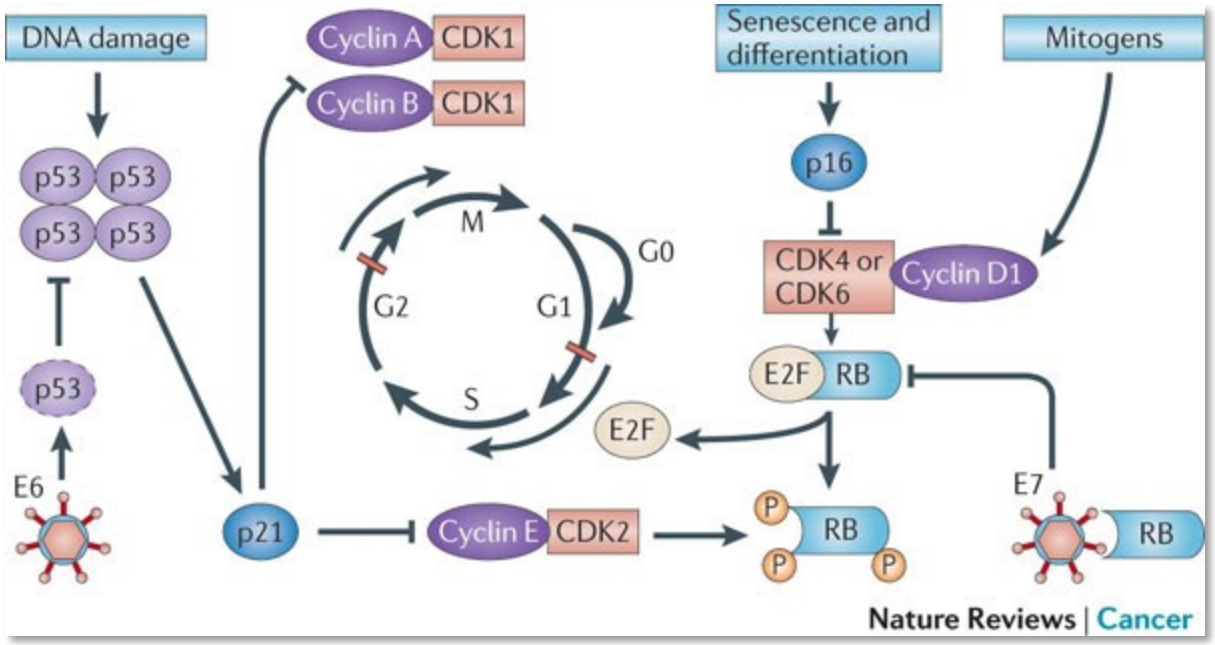
HPV



- Viral genes are encoded on one strand of the double-stranded circular DNA genome and enclosed in capsid (L1, L2)
- Infection – Stable episome
- E6/E7 – stimulate cell cycle progression for viral replication

Doorbar. Clinical Science (2006) **110**, 525–541

Model of HPV+ HNSCC Development

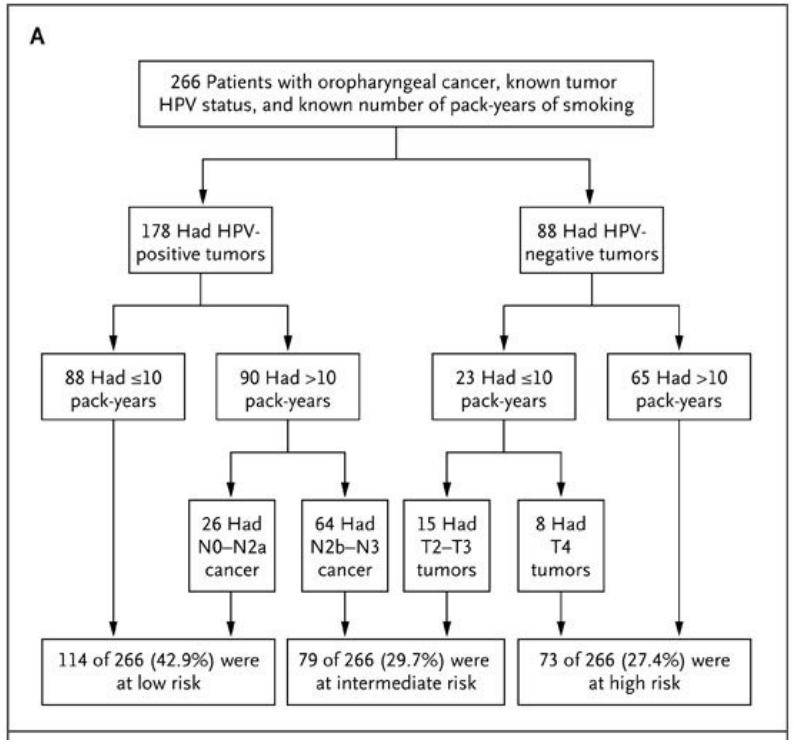


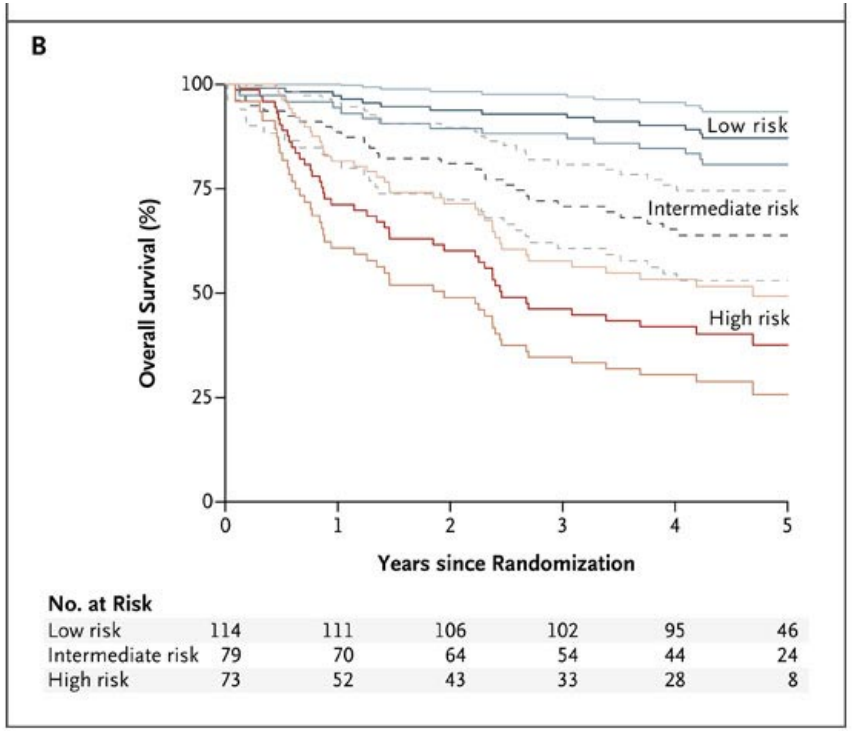
HPV-E6 downregulates the p53 pathway, followed by sequential upregulation of p16 (Au Yeung et al., 2010)

HPV-E7 inactivates tumor suppressor Rb (Wang et al., 2001)

Leemans et al., 2011

Overall Survival - clinical categories





3-year OS:

Low – 93%, intermediate – 70.8%, high – 46%

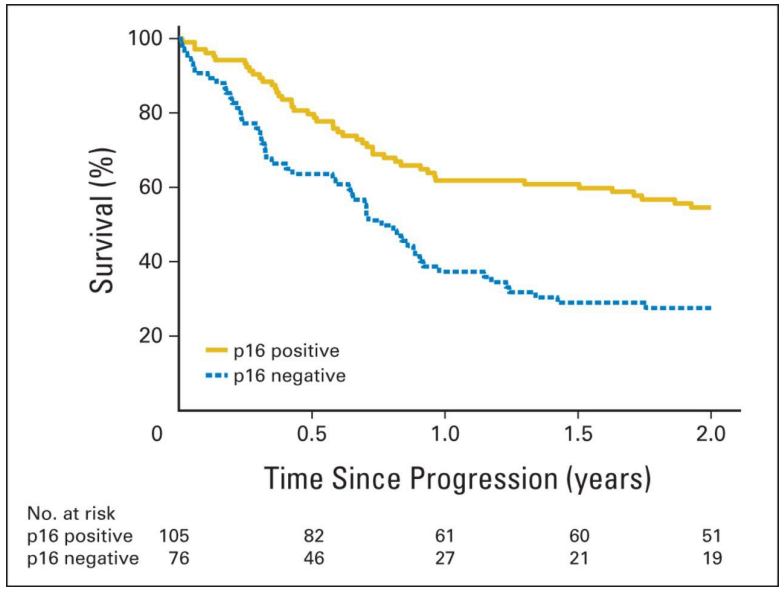
Ang KK et al. N Engl J Med 2010;363:24-35

The NEW ENGLAND JOURNAL of MEDICINE

Recurrent/Metastatic Disease

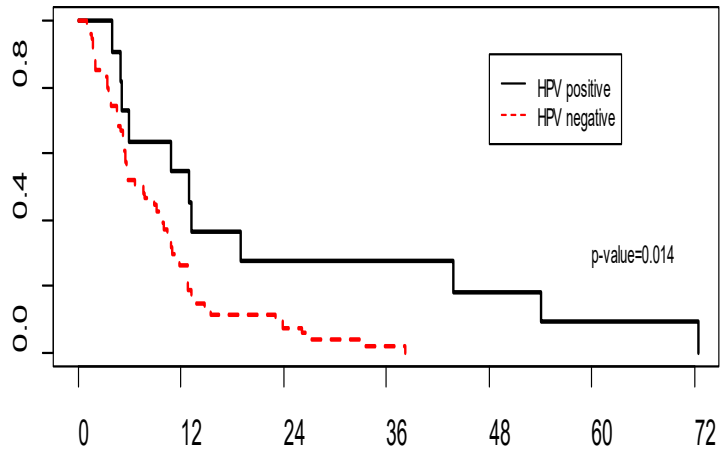
- HPV is also a prognostic factor for R/M disease

RTOG Analysis



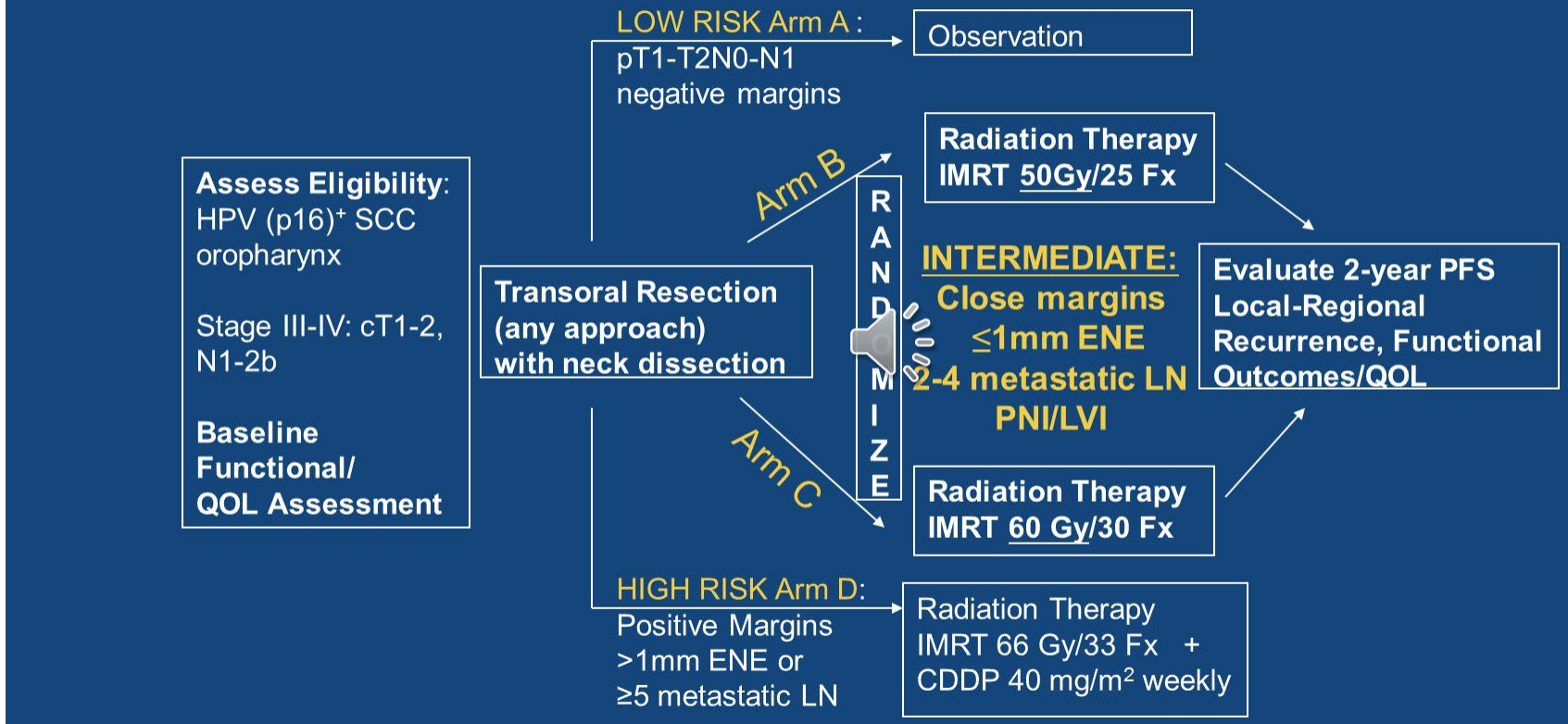
Carole Fakhry et al. JCO 2014;32:3365-3373

ECOG Analysis n=64 (p=0.02)



Ann Oncol. 2014 Jul;25(7)
Prognostic significance of human papillomavirus in recurrent or metastatic head and neck cancer: an analysis of Eastern Cooperative Oncology Group trials.Argiris A, Li S, Ghebremichael M, Egloff AM, Wang L, Forastiere AA, Burtness B, **Mehra R.**

ECOG-ACRIN E3311 schema



PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Robert L. Ferris, MD, PhD

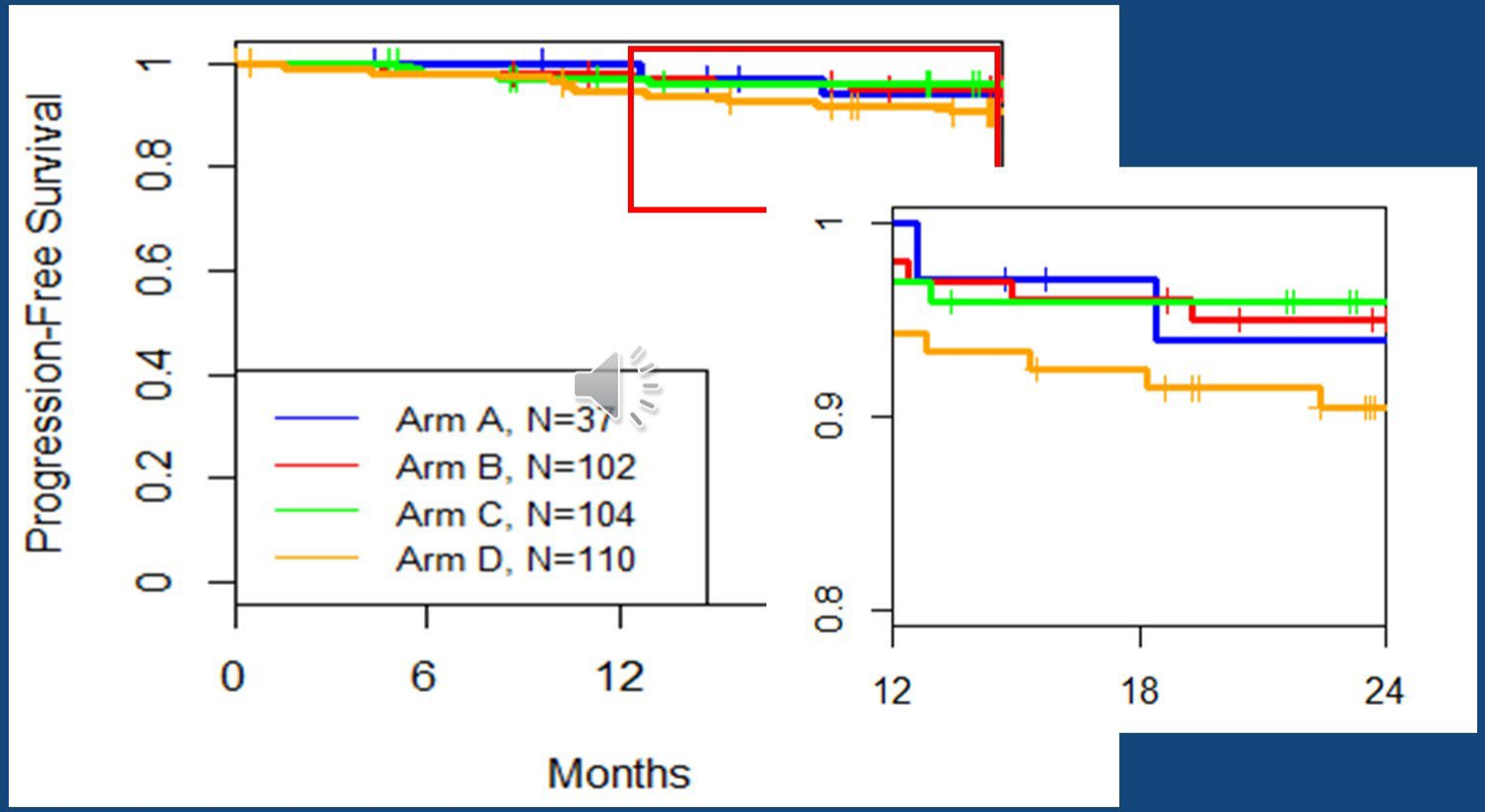
Presented By Robert Ferris at TBD

Results

	N	2-year PFS	90% CI	Deaths (without recurrence)	Recurrences	LRF	DM
Arm A	37	93.9%	87.3, 100	0	2	1	1
Arm B	102	95.0%	91.4, 98.6	1	4	2	2
Arm C	104	95.9%	92.6, 99.3	0	4	0	4
Arm D	110	90.5%	85.9, 95.3	3	7	4	3

- There were 2 treatment-related deaths (one surgical and one Arm D)
- TOS + low-dose radiation is worthy of further study, since the primary endpoint of the upper bound of the 90% CI (in the intermediate risk group) exceeding 85% was met

Kaplan-Meier estimates of 2-year PFS



CtDNA - HPV

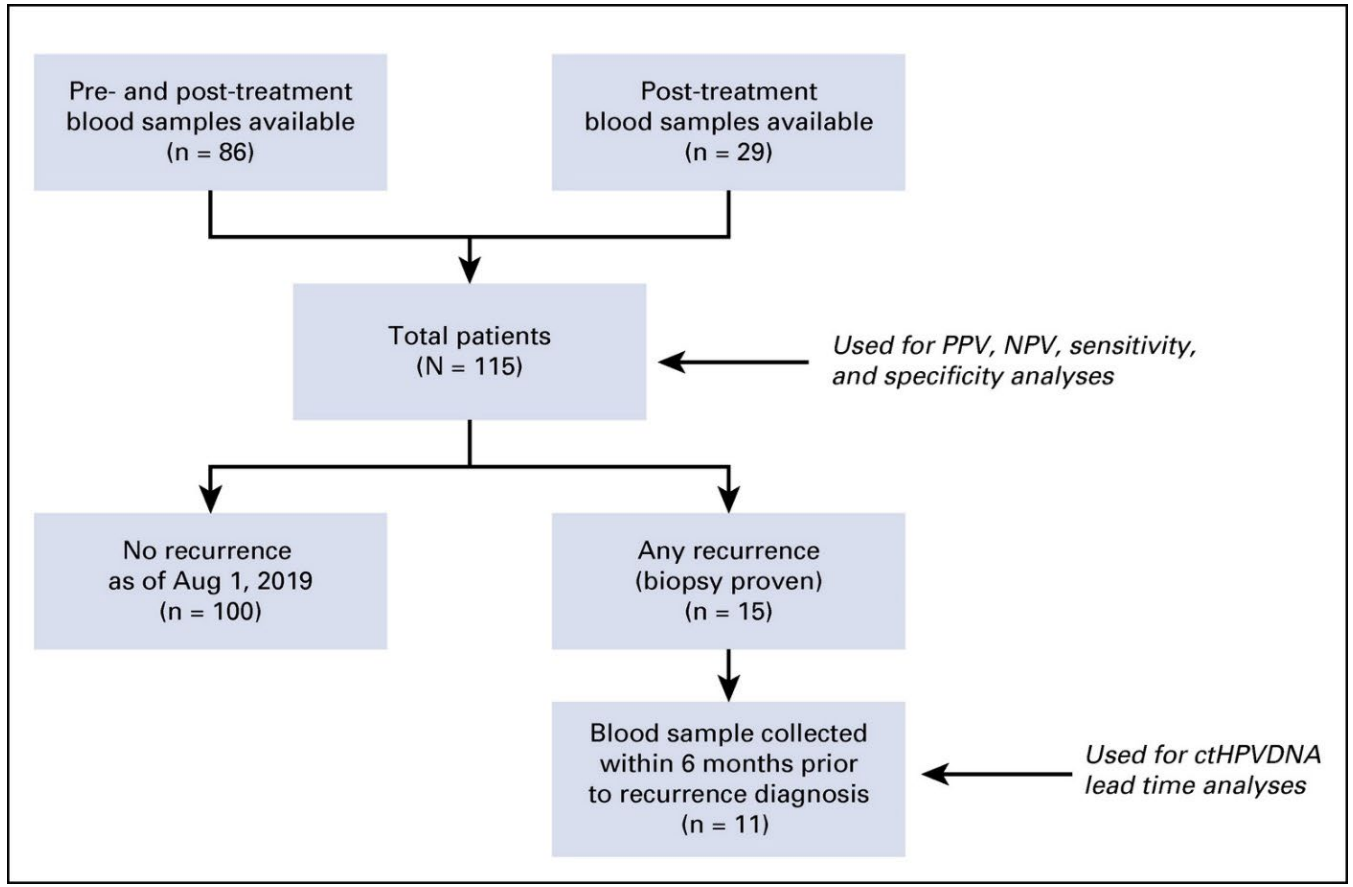
TABLE 1. Patient Characteristics

Characteristic	No Detectable Surveillance ctHPVDNA (n = 87)	At Least 1 Detectable Surveillance ctHPVDNA (n = 28)	All Patients (N = 115)
Mean age, years (range)	59 (33-84)	60 (39-84)	59 (33-84)
Sex			
Female	12 (14)	2 (7)	14 (12)
Male	75 (86)	26 (93)	101 (88)
Tobacco use			
Never smoker	57 (66)	18 (64)	75 (65)
≤ 10 pack-years	20 (23)	5 (18)	25 (22)
> 10 pack-years	10 (11)	5 (18)	15 (13)
Stage (AJCC 8th edition)			
1	65 (75)	21 (75)	86 (75)
2	16 (18)	2 (7)	18 (16)
3	6 (7)	5 (18)	11 (9)
Radiation dose, Gy			
60	75 (86)	22 (79)	97 (84)
70	12 (12)	6 (21)	18 (16)
Chemotherapy			
Yes	72 (83)	21 (75)	93 (81)
No	15 (17)	7 (25)	22 (19)

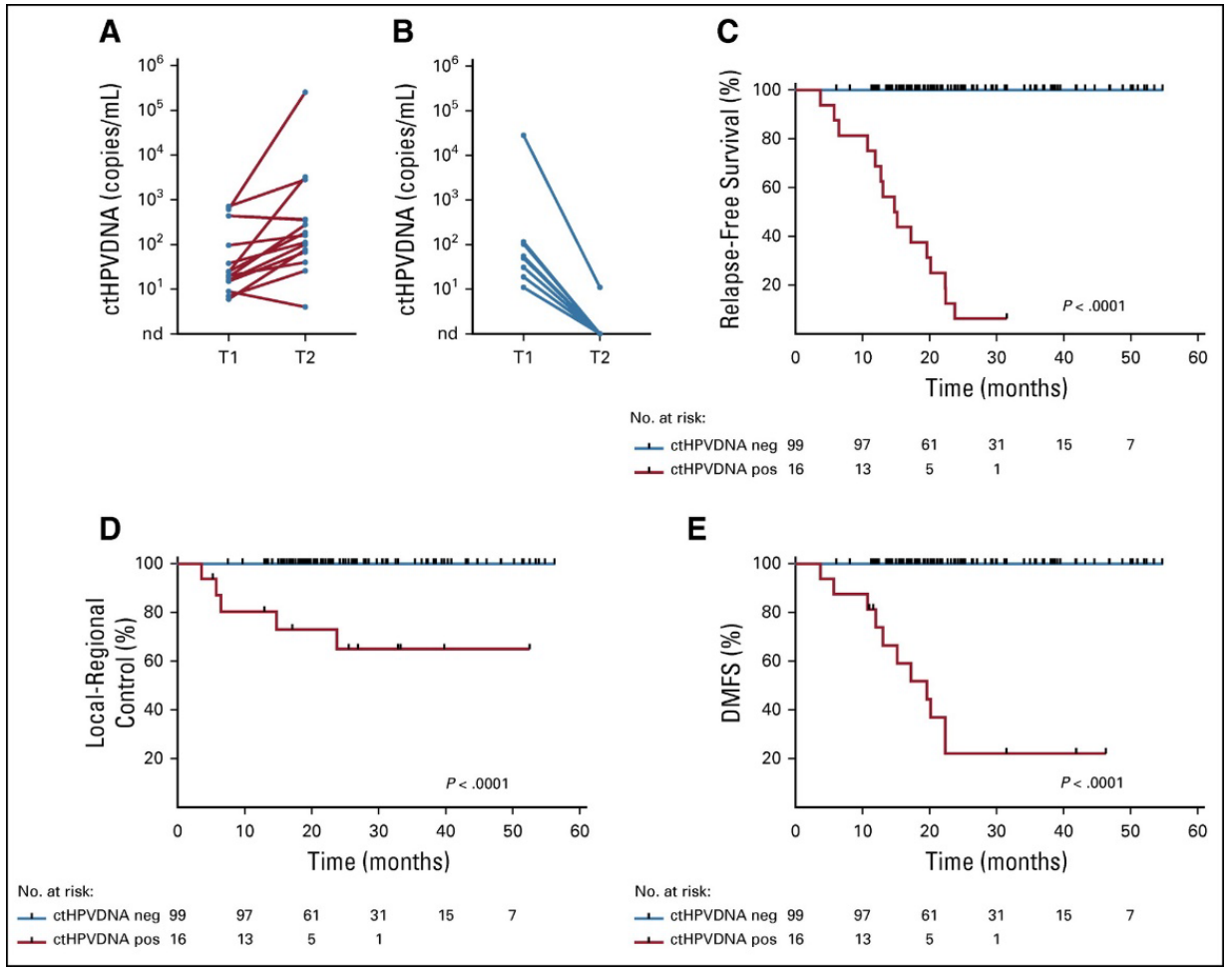
NOTE. Data presented as No. (%) unless otherwise indicated.
Abbreviations: AJCC, American Joint Commission on Cancer; ctHPVDNA, circulating tumor human papillomavirus DNA.

Chera et al. JCO 2020

Schema

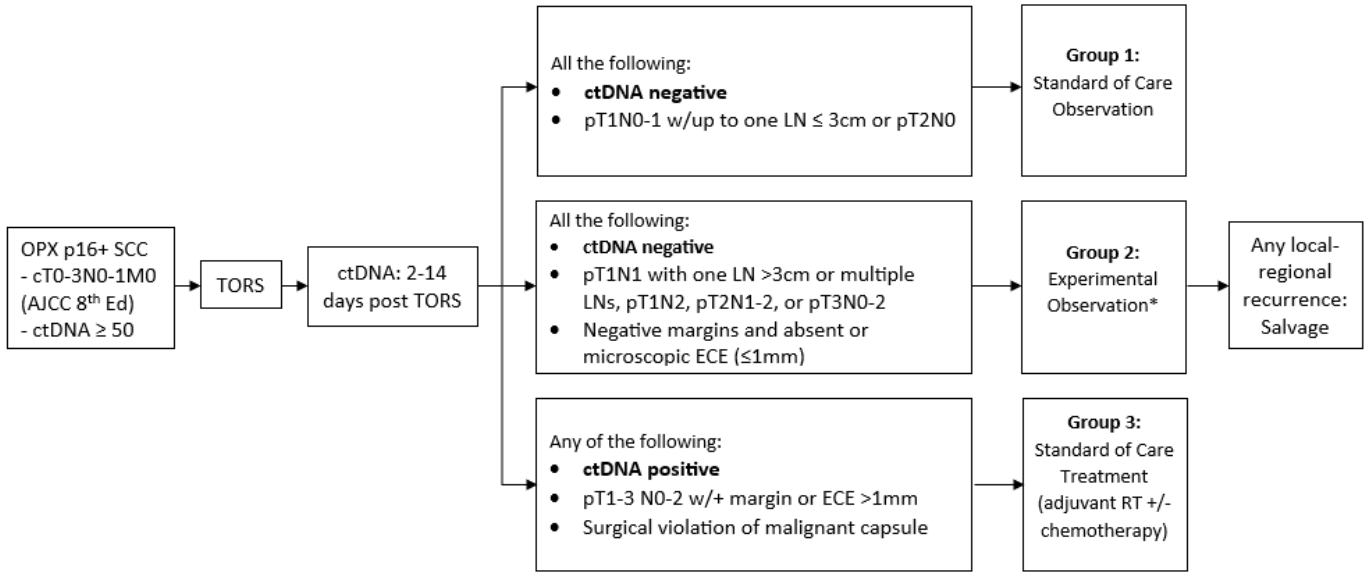

Pre- and post-treatment blood samples available (n = 86)
Post-treatment blood samples available (n = 29)
Total patients (N = 115)
Used for PPV, NPV, sensitivity, and specificity analyses
No recurrence as of Aug 1, 2019 (n = 100)
Any recurrence (biopsy proven) (n = 15)
Blood sample collected within 6 months prior to recurrence diagnosis (n = 11)
Used for ctHPVDNA lead time analyses

Prognostic for recurrence



Study Schema

A Single Arm Phase II Trial Evaluating Selective Adjuvant Therapy for HPV-mediated Oropharynx SCCs based on Residual Circulating Tumor DNA Levels (SAVAL)



*Experimental Observation Group:
- Patients will be monitored with Physical Exam, Anatomical Imaging, and ctDNA levels
- Any suspicious recurrence will be biopsied
- Biopsy confirmed LRR will be treated for Salvage
- Patients will be followed for two year PFS after salvage

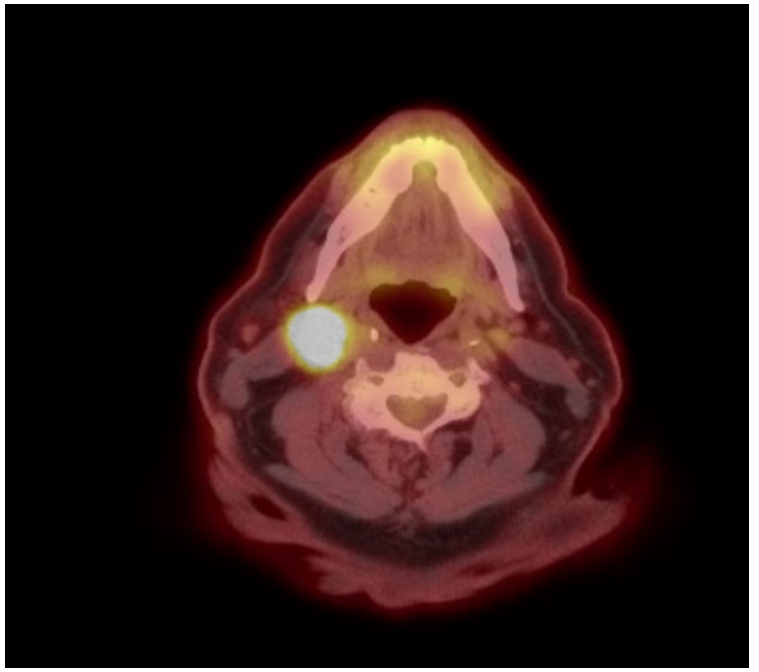
Endpoint:
- 93% two year PFS post TORS or salvage for LRR

Interim Analysis:
- After enrollment of half subjects, ensure less than 31% rate of recurrence post TORS

Main Inclusion Criteria

- ✓ Pathologically (histologically or cytologically) proven diagnosis of p16+ SCC of the oropharynx or p16+ SCC of unknown primary
- ✓ Clinical stage T0-3, N0-N1, and M0 disease (AJCC 8th edition) with appropriate imaging within 60 days prior to enrollment (PET/CT preferred, CT neck w/contrast with CT chest w/o contrast as recommended alternative)
- ✓ TORS candidate based on evaluation by ENT and review at multi-disciplinary tumor board
- ✓ Positive (>50) ctDNA levels prior to surgery

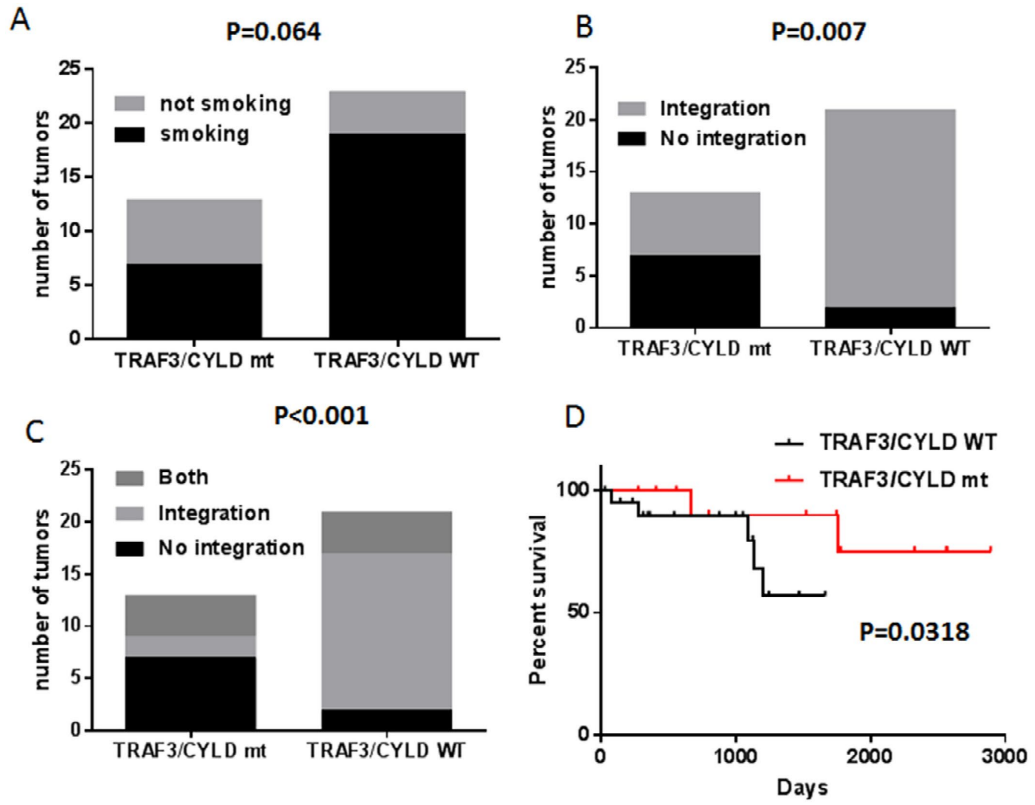
Case

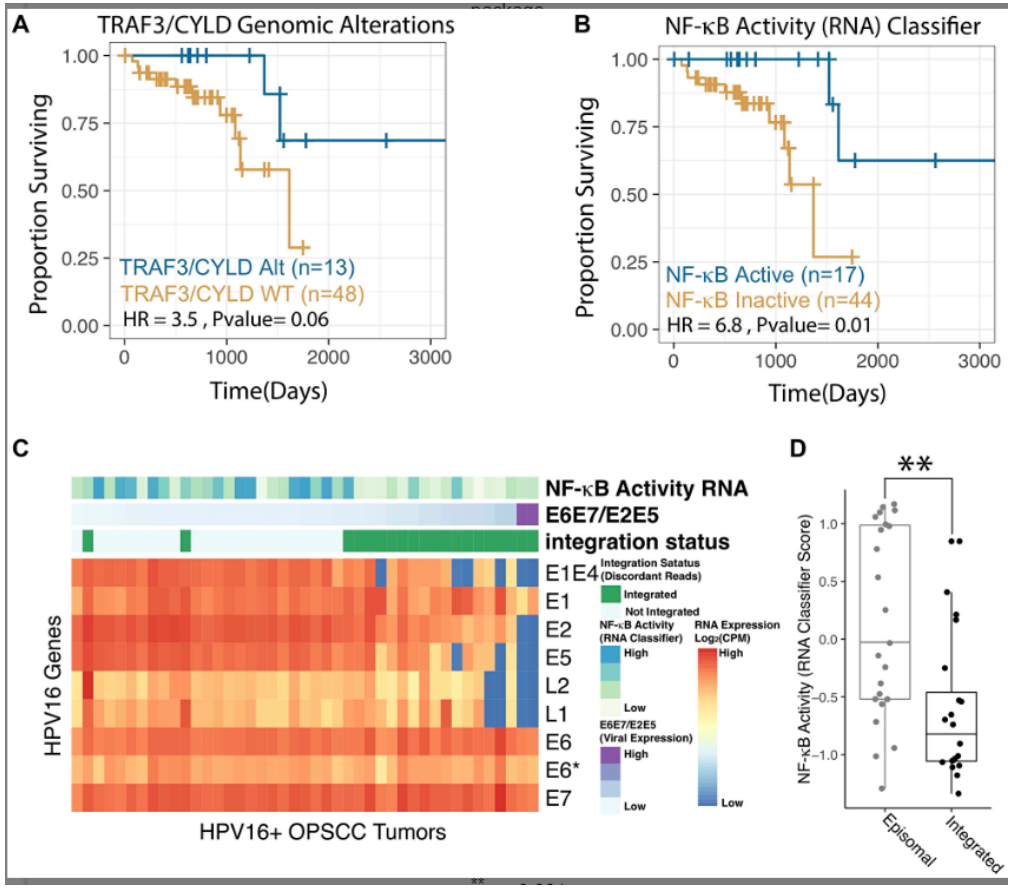


- 68 yo M : squamous cell carcinoma of unknown primary metastatic to R sided cervical lymph node(s).
- NavDx pre op 13428
- underwent TORS hemi-glossectomy of R BOT, R selective neck dissection levels II-Ivm. Final surgical pathology confirms T1N1 HPV+ SCC of the R tongue.
- Post op Nav Dx negative – 5 months

HPV+ OPC genomic variation

TRAF3/CYLD mutations and an NFκb signature identifies a distinct subset of human papillomavirus-associated head and neck squamous cell carcinoma





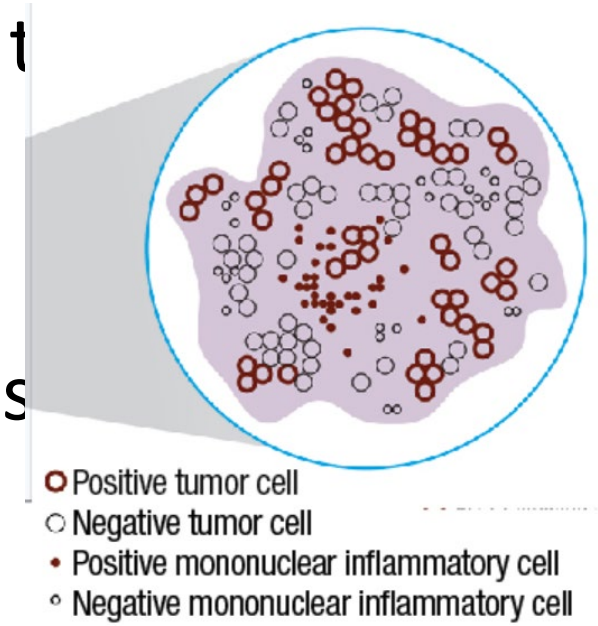
Cancer, Volume: 123, Issue: 10, Pages: 1778-1790, First published: 13 March 2017, DOI: (10.1002/cncr.30570)
Shrank et al. Oncotarget 2022

Outline

- P16
- PDL1 CPS
- Potentially actionable somatic alterations
- Future biomarkers

TPS vs. CPS

- TPS – the percentage of tumour cells with membranous PD-L1 expression.
- CPS - the number of PD-L1-positive cells [tumor cells, lymphocytes, and macrophages] divided by the t number of tumor cells times 100.
- scores ranged from 0 to 100
- a cut-off of ≥1 is used to define the PD-L1 expres



PDL1 and ORR in KN012

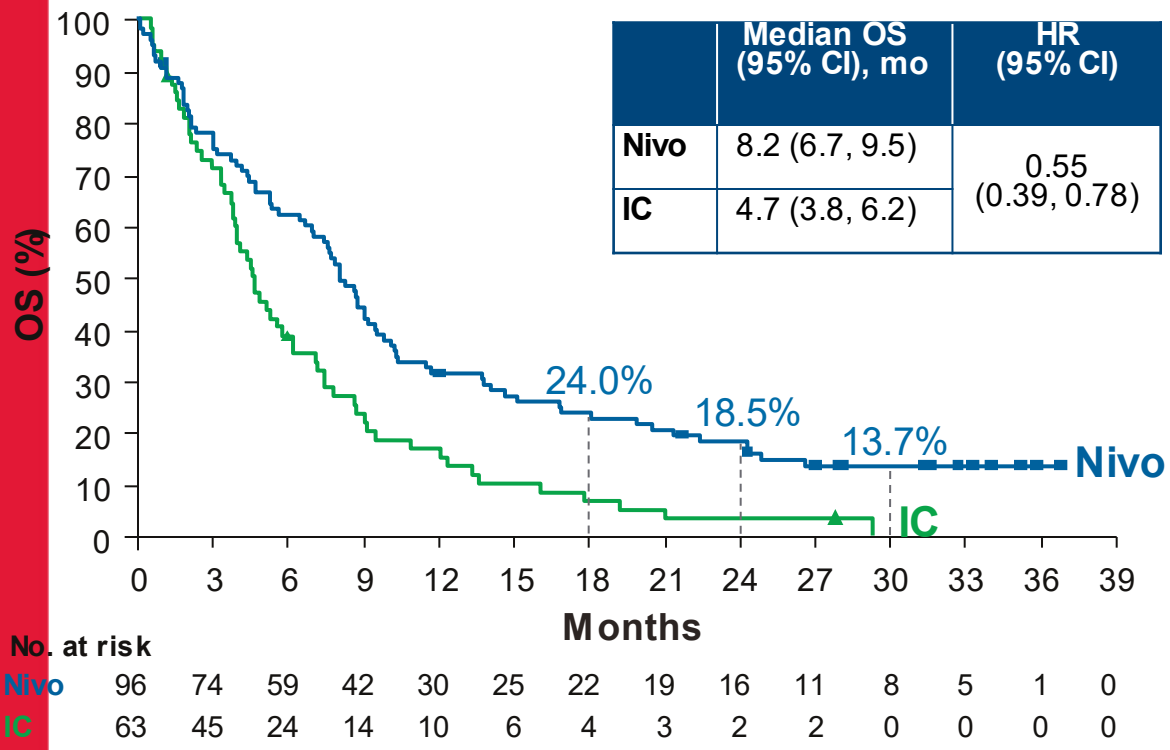
Scoring Method	Expression Status	Number (%) positive	Responders/total n	ORR (%)	P value
TPS	PDL1 +	123 (65%)	22/123	18	0.461
TPS	PDL1-	65 (35%)	12/65	19	
CPS	PDL1 +	152 (81%)	32/152	21	0.023
CPS	PDL1 -	36 (19%)	2/36	6	

Mehra et al. Br J Cancer. 2018 Jul 17; 119(2): 153–159

OS Benefit Across PD-L1 Expressors and Non-Expressors

- OS rates at 18, 24, and 30 months were similar in both groups
  - PD-L1 expressors: nivolumab continued to provide OS benefit, with 45% reduction in risk of death vs IC
  - PD-L1 non-expressors: nivolumab resulted in 27% reduction in risk of death vs IC

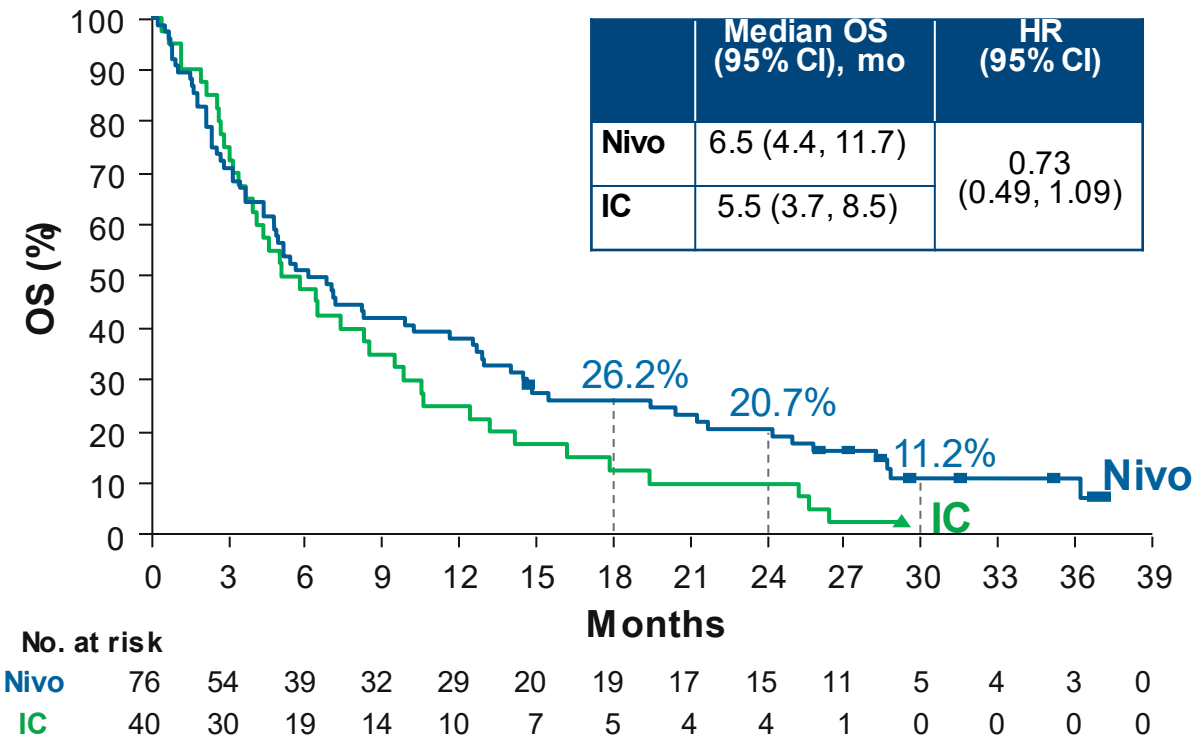
PD-L1 Expressors (≥1%)



	Median OS (95% CI), mo	HR (95% CI)
Nivo	8.2 (6.7, 9.5)	0.55 (0.39, 0.78)
IC	4.7 (3.8, 6.2)	

No. at risk														
Nivo	96	74	59	42	30	25	22	19	16	11	8	5	1	0
IC	63	45	24	14	10	6	4	3	2	2	0	0	0	0

PD-L1 Non-Expressors (<1%)

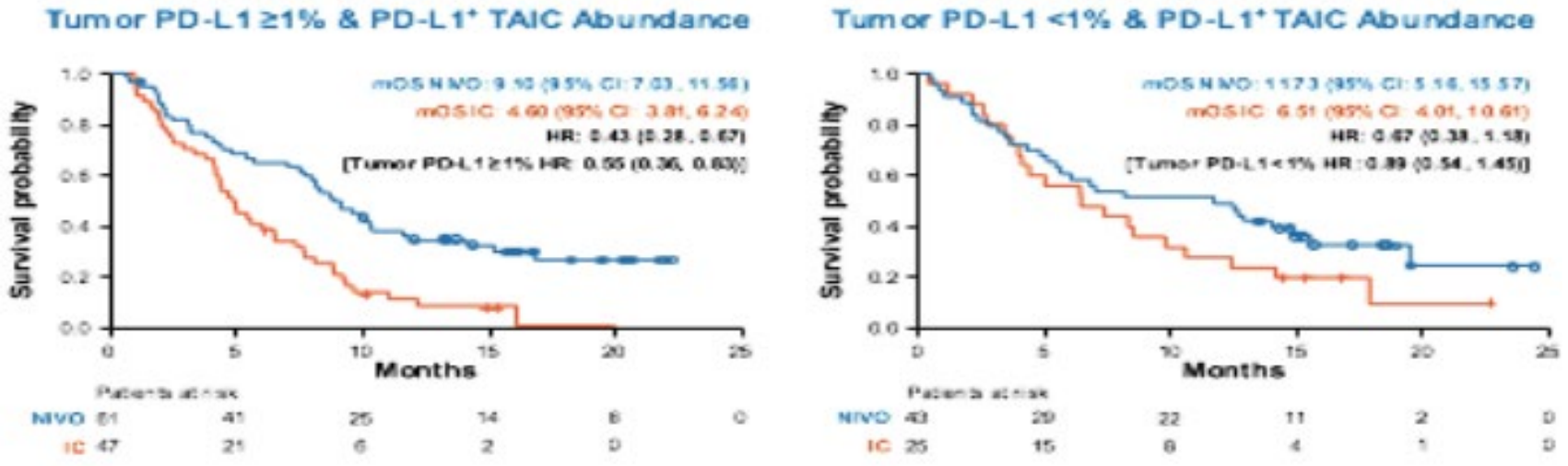


	Median OS (95% CI), mo	HR (95% CI)
Nivo	6.5 (4.4, 11.7)	0.73 (0.49, 1.09)
IC	5.5 (3.7, 8.5)	

No. at risk														
Nivo	76	54	39	32	29	20	19	17	15	11	5	4	3	0
IC	40	30	19	14	10	7	5	4	4	1	0	0	0	0

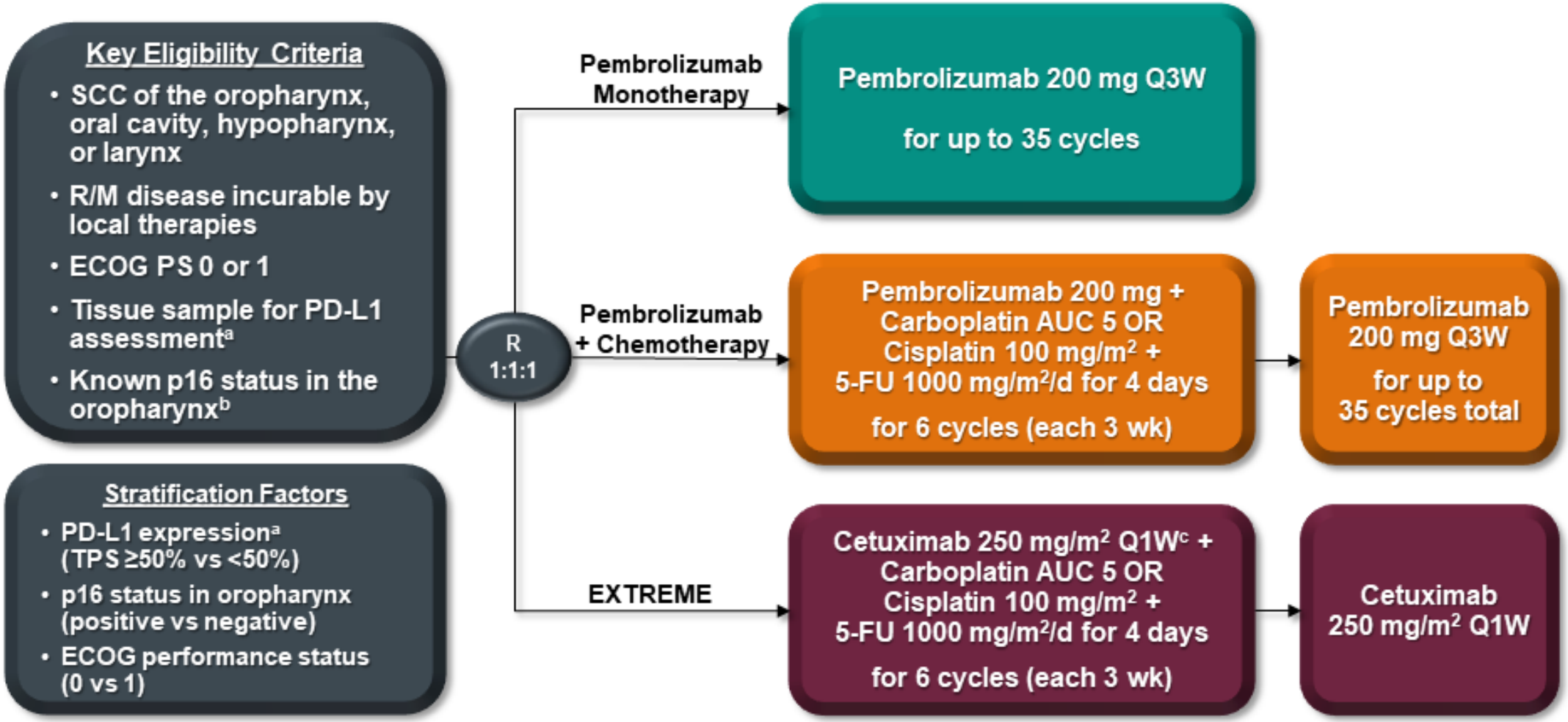
Symbols represent censored observations

CM141 – Tumor and Immune cells



Ferris et al AACR 2017

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.

Response by PDL1 expression

	PD-L1 CPS <1[1]				PD-L1 CPS 1-19[1]			
	Pembrolizumab vs Cetuximab-Chemotherapy		Pembrolizumab-Chemotherapy vs Cetuximab-Chemotherapy[c]		Pembrolizumab vs Cetuximab-Chemotherapy		Pembrolizumab-Chemotherapy vs Cetuximab-Chemotherapy[c]	
	Pembrolizumab n=44	Cetuximab-Chemotherapy n=45	Pembrolizumab-Chemotherapy n=39	Cetuximab-Chemotherapy n=43	Pembrolizumab n=124	Cetuximab-Chemotherapy n=133	Pembrolizumab-Chemotherapy n=116	Cetuximab-Chemotherapy n=125
Objective response[b], No. (%) (95% CI)	2 (4.5) (0.6 to 15.5)	19 (42.2) (27.7 to 57.8)	12 (30.8) (17.0 to 47.6)	17 (39.5) (25.0 to 55.6)	18 (14.5) (8.8 to 22.0)	45 (33.8) (25.9 to 42.5)	34 (29.3) (21.2 to 38.5)	42 (33.6) (25.4 to 42.6)
Complete response, No. (%)	0	1 (2.2)	1 (2.6)	1 (2.3)	4 (3.2)	3 (2.3)	4 (3.4)	3 (2.4)
Partial response, No. (%)	2 (4.5)	18 (40.0)	11 (28.2)	16 (37.2)	14 (11.3)	42 (31.6)	30 (25.9)	39 (31.2)
Stable disease, No. (%)	10 (22.7)	18 (40.0)	14 (35.9)	18 (41.9)	32 (25.8)	41 (30.8)	35 (30.2)	39 (31.2)
Progressive disease, No. (%)	22 (50.0)	4 (8.9)	6 (15.4)	4 (9.3)	58 (46.8)	21 (15.8)	23 (19.8)	20 (16.0)
Non-CR/non-PD, No. (%)	3 (6.8)	0	2 (5.1)	0	3 (2.4)	5 (3.8)	7 (6.0)	4 (3.2)
Not evaluable or assessed, No. (%)	7 (15.9)	4 (8.9)	5 (12.8)	4 (9.3)	13 (10.5)	21 (15.8)	17 (14.7)	20 (16.0)

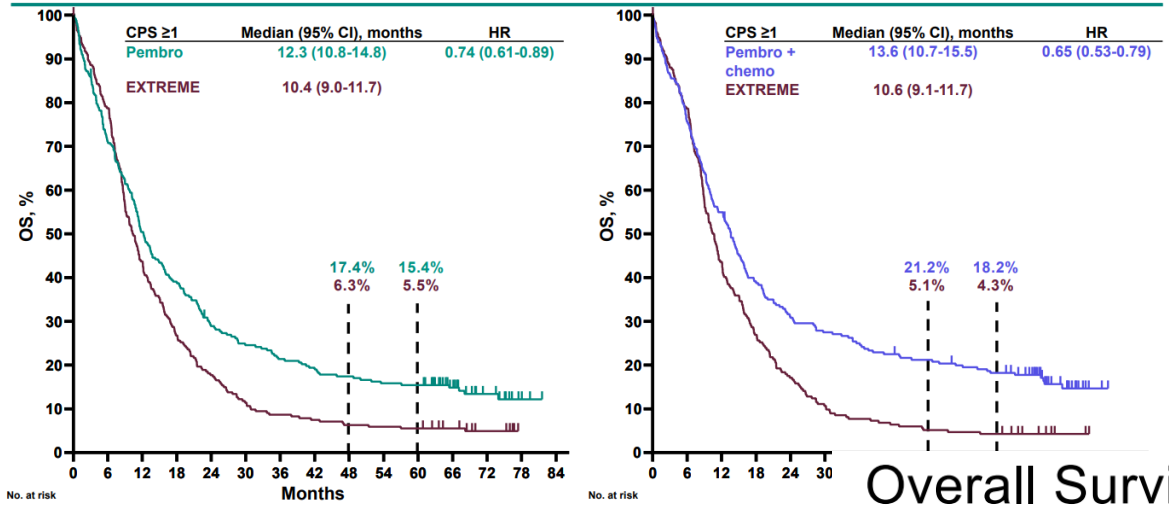
1. Burtness B, et al. *J Clin Oncol.* 2022;JCO2102198. doi:10.1200/JCO.21.02198. Online ahead of print. 2. Burtness B, et al. *Lancet.* 2019;394:1915-1928.

Efficacy based on PDL1

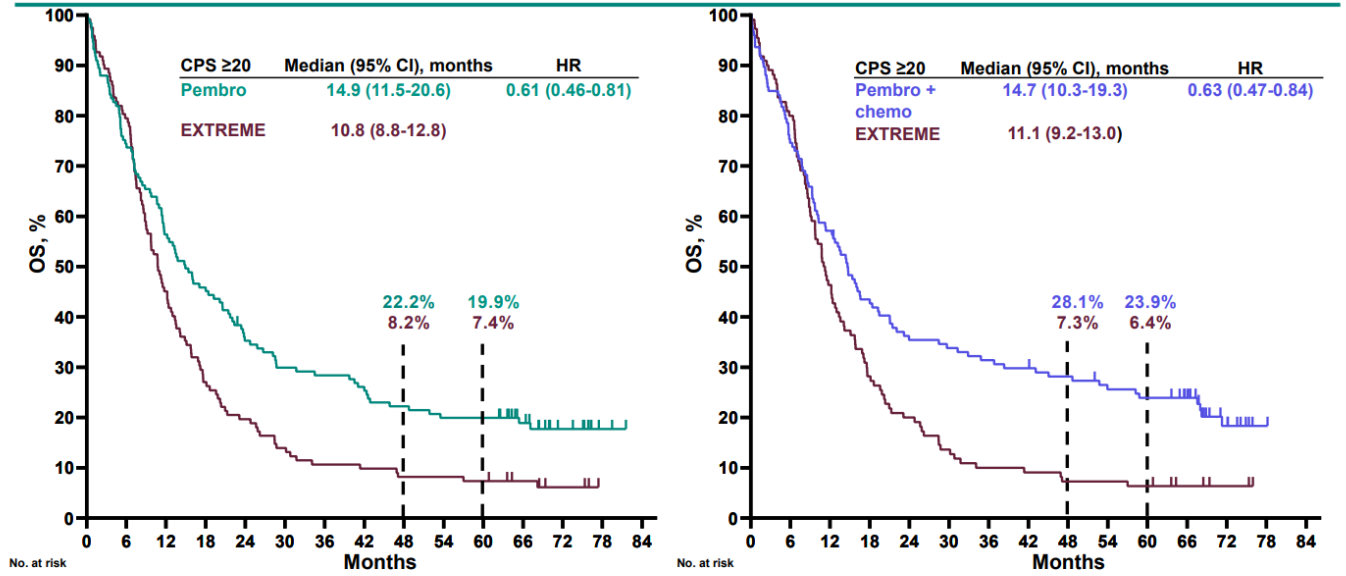
	Pembrolizumab alone vs EXTREME[1-3]		Pembrolizumab + Chemotherapy vs EXTREME[1-3]	
Population	**Pembrolizumab**	**Cetuximab-Chemotherapy**	**Pembrolizumab + Chemo**	**Cetuximab-Chemotherapy**
PD-L1 CPS <1[1,2]				
Median OS, mo	7.9	11.3	11.3	10.7
HR (95% CI)	1.51 (0.96–2.37)		1.21 (0.76–1.94)	
Median DOR (range), mo	2.6 (2.2–3.0)	7.8 (2.0–38.6+)	5.7 (2.6–20.6+)	4.3 (2.0–31.2+)
PD-L1 CPS 1-19[1,2]				
Median OS, mo	10.8	10.1	12.7	9.9
HR (95% CI)	0.86 (0.66–1.12)		0.71 (0.54–0.94)	
Median DOR (range), mo	NR (1.5+–38.9+)	5.0 (1.4+–38.7+)	5.6 (1.6+–25.6+)	4.6 (1.4+–31.4+)
Total Study[3]				
Median OS, mo	11.5	10.7	13.0	10.7
HR (95% CI)	0.83 (0.70–0.99)		0.72 (0.60–0.87)	
Median DOR (95% CI), mo	22.6 (14.0–NR)	4.5 (4.1–5.7)	6.7 (5.6–8.2)	4.3 (4.1–5.6)

Long term data – 5 years

Overall Survival in the CPS ≥1 Population

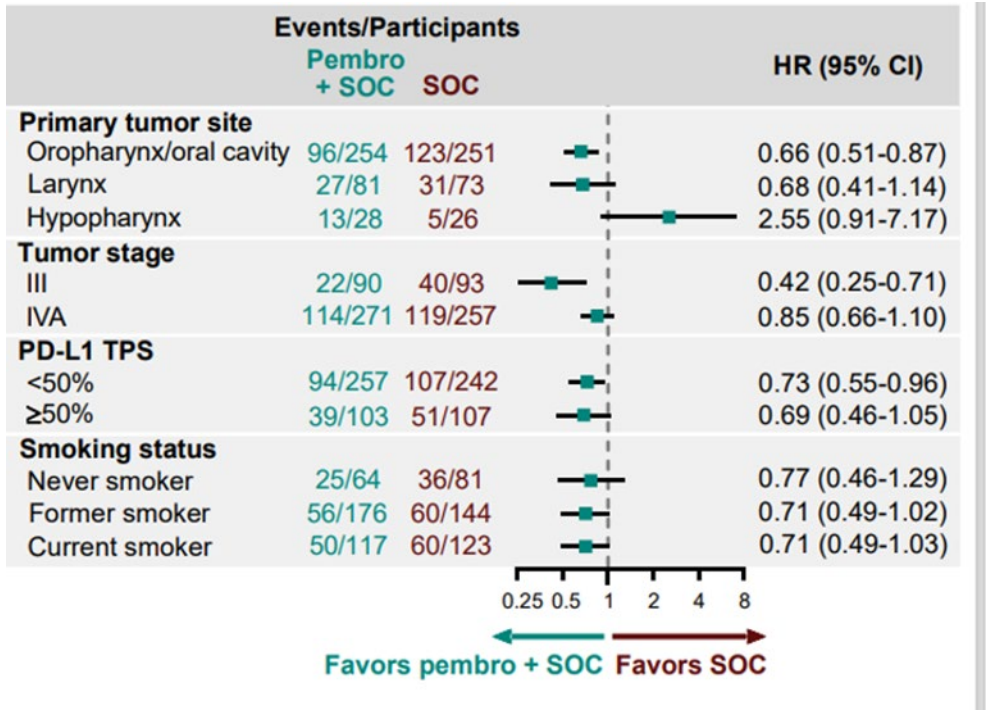


Overall Survival in the CPS ≥20 Population



Tahara et al, ESMO 2022

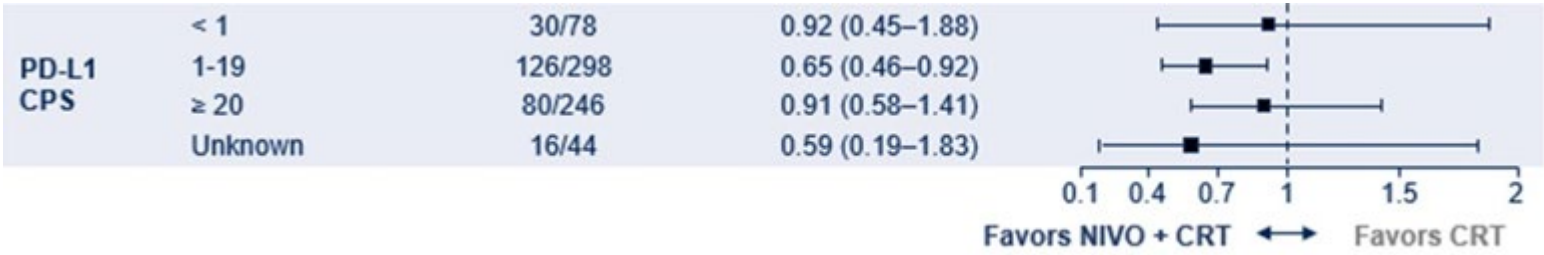
Javelin and KN412 PDL1 subsets



1) No selection based on CPS/PDL1

2) Benefit of nivolumab observed in all comers

3) CPS not strongly correlated with DFS



Centrally assessed PD-L1 IHC 28–8 pharmDx assay (Labcorp)

Case

- T4N2M0 p16+ SCC left tonsil, L>R BOT - treated with chemoRT with 35 fractions protons and concurrent weekly cisplatin - C5 dose reduced die to neutropenia. C7 held - completed 8/20/24
- 9/2/25 - had CT imaging which is concerning for metastatic pulmonary disease and multiple liver mets
- PDL1 CPS 5

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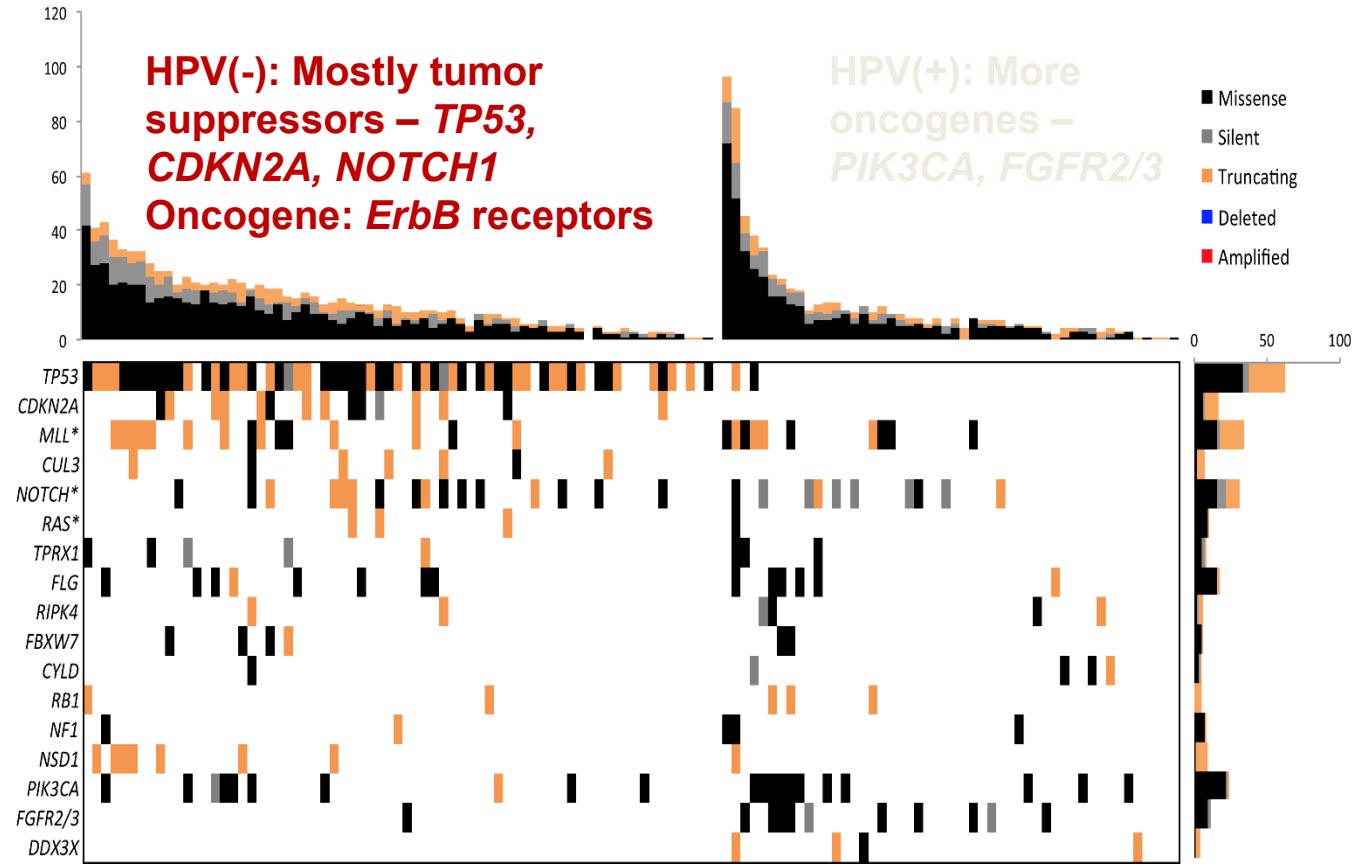
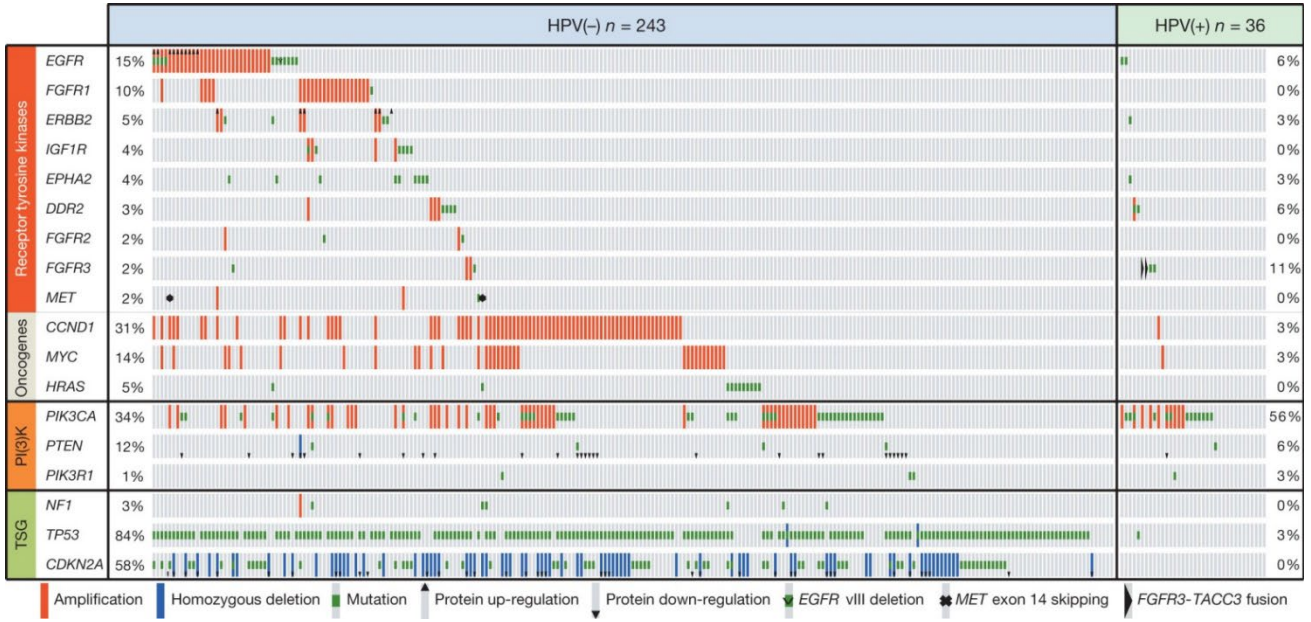
Mutational Spectrum in HPV(-) vs HPV(+)



Seiwert, et al. CCR 2014

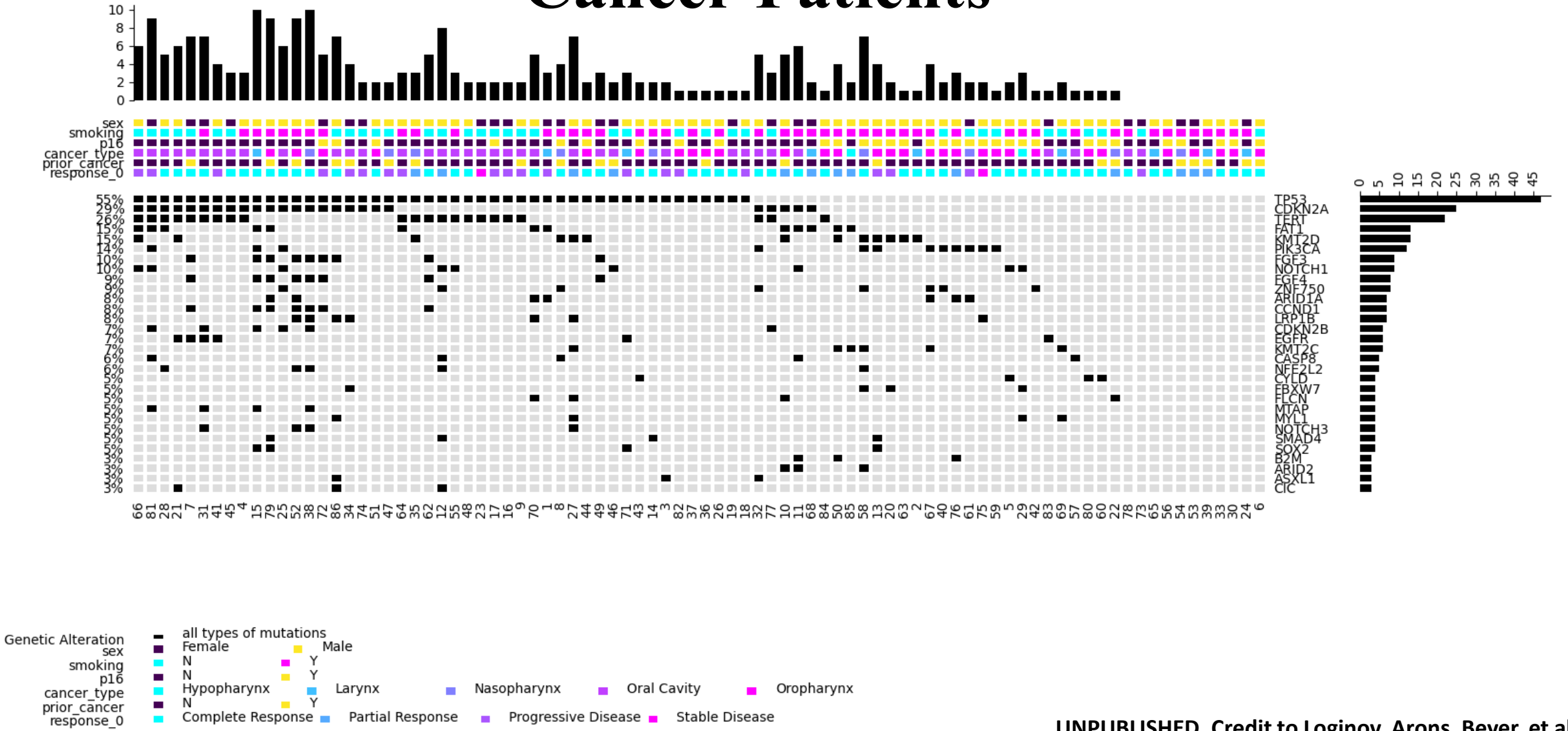
TCGA

- HPV+ disease is distinct from tobacco/alcohol associated cancer



MS Lawrence *et al. TCGA Nature* **517**, 576-582 (2015)

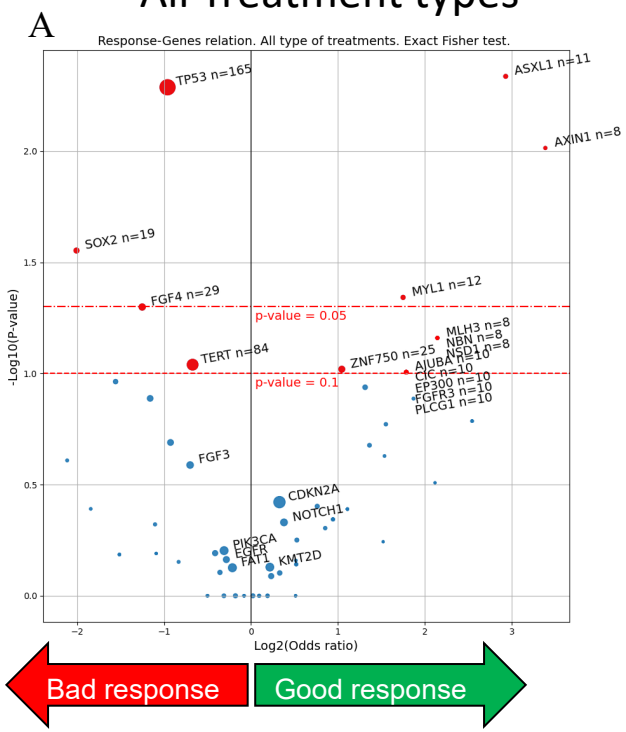
Tumor Genomics In Recurrent Head and Neck Cancer Patients



UNPUBLISHED. Credit to Loginov, Arons, Beyer, et al

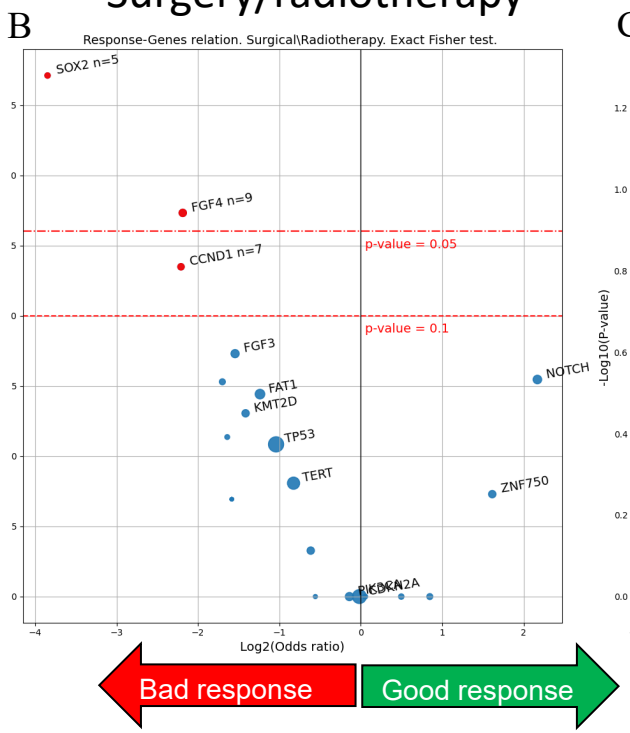
The Relation Between Mutations and Response

All Treatment types



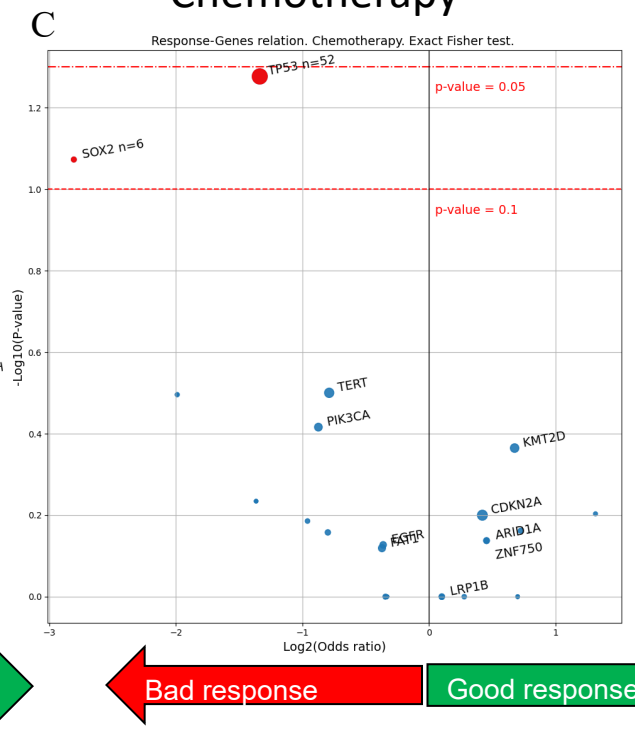
Bad response | Good response

Surgery/radiotherapy



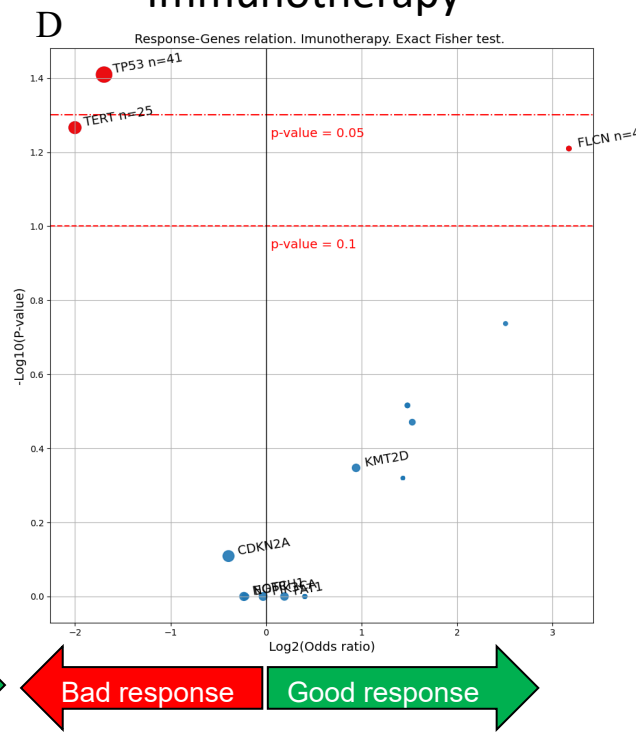
Bad response | Good response

Chemotherapy



Bad response | Good response

Immunotherapy



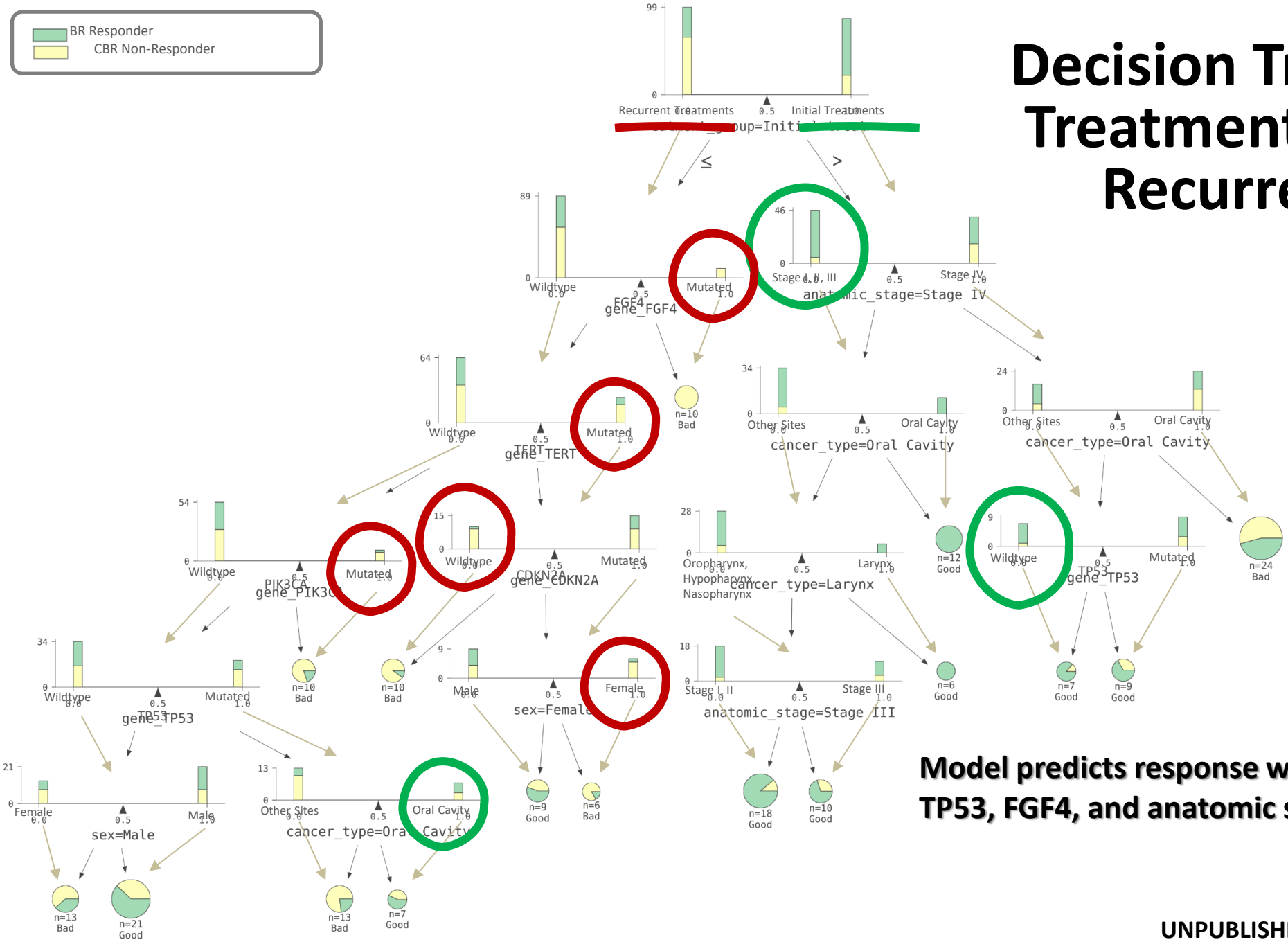
Bad response | Good response

- **TP53, SOX2, FGF4, and TERT mutations linked to poor treatment response**
- **MYL1, AXIN1, ASXL1, and FLCN mutations are associated with better outcomes**

P-values were calculated by the Fisher's exact test

UNPUBLISHED. Credit to Loginov, Arons, Beyer, et al

Decision Tree Predicting Treatment Response in Recurrent HNSCC



Model predicts response with 74% accuracy, highlighting TP53, FGF4, and anatomic stage as key factors.

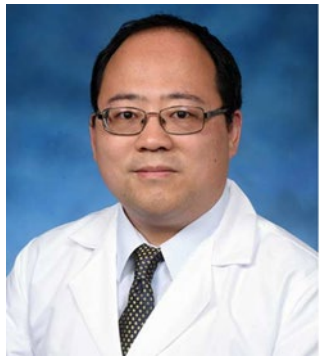
UNPUBLISHED. Credit to Loginov, Arons, Beyer, et al

Outline

- P16
- PDL1 CPS
- Potentially actionable somatic alterations
- Future biomarkers

Leveraging CT-Based Radiomics for Personalized Treatment Selection in Oral cavity Squamous Cell

Lei Ren, PhD, DABR, FAAPM
Professor and Associate Chief of Physics Research
Department of Radiation Oncology
University of Maryland



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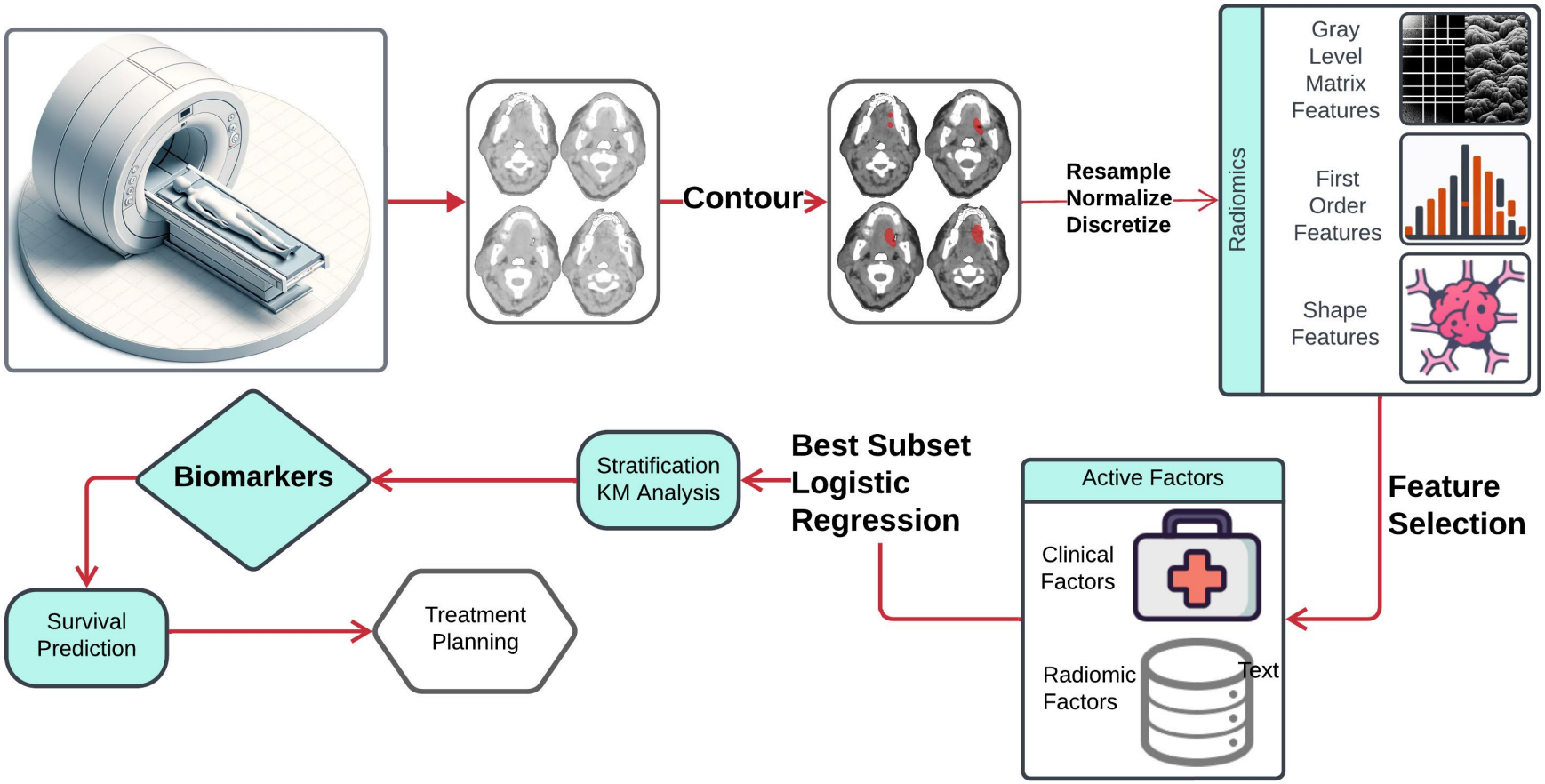
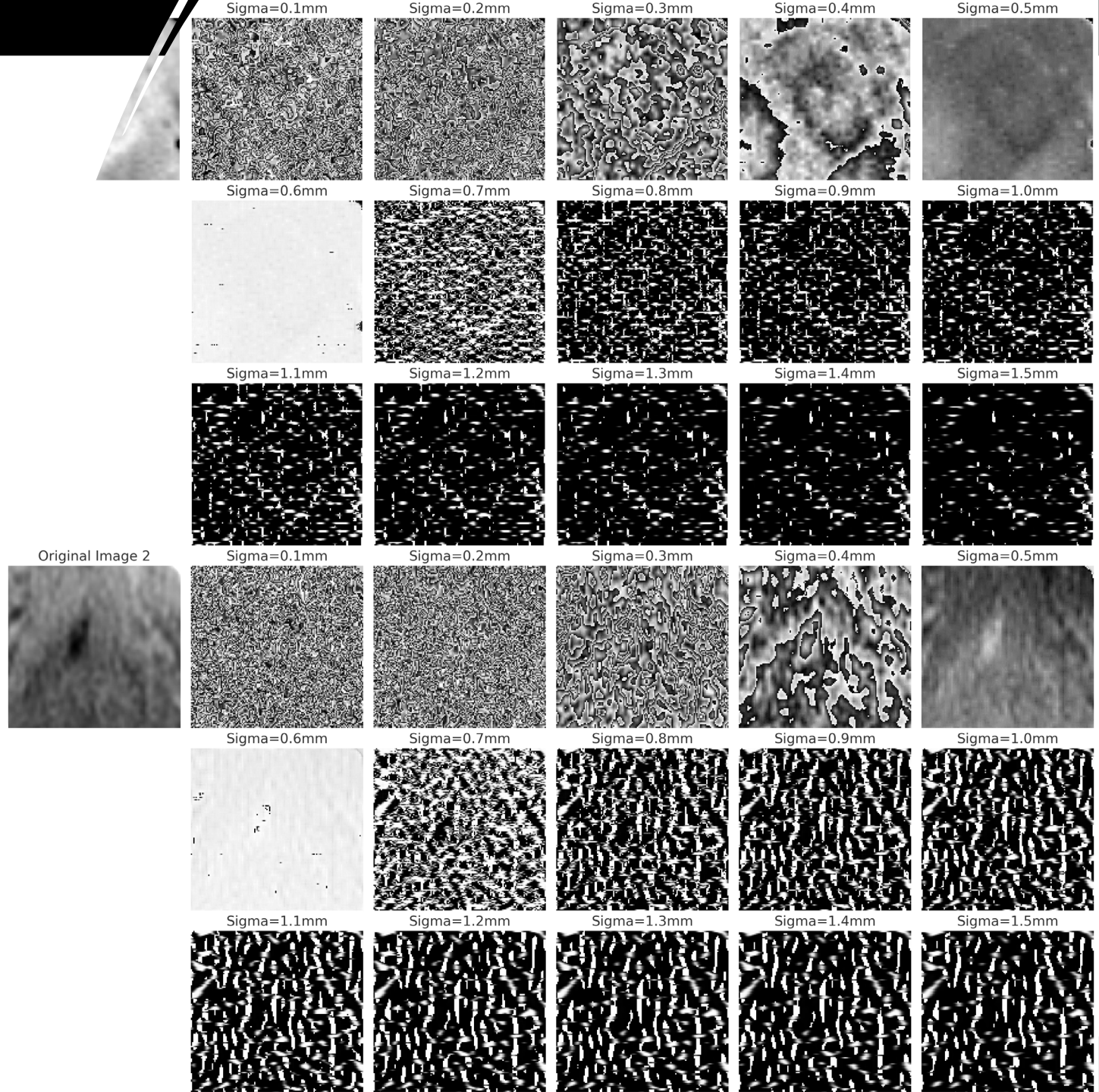
Outcome prediction workflow

Classification Endpoint



LoG Filtered OSCC vs. Normal Tongue Textures Across Sigma Values

The figure displays two sets of LoG filtered images. The first three rows show OSCC images in the tongue region at varying sigma values, illustrating changes in the primary ROI. The last three rows depict normal tissue in the same region, also filtered at corresponding sigma values, to highlight contrasts between OSCC and normal textures.



Material and Method

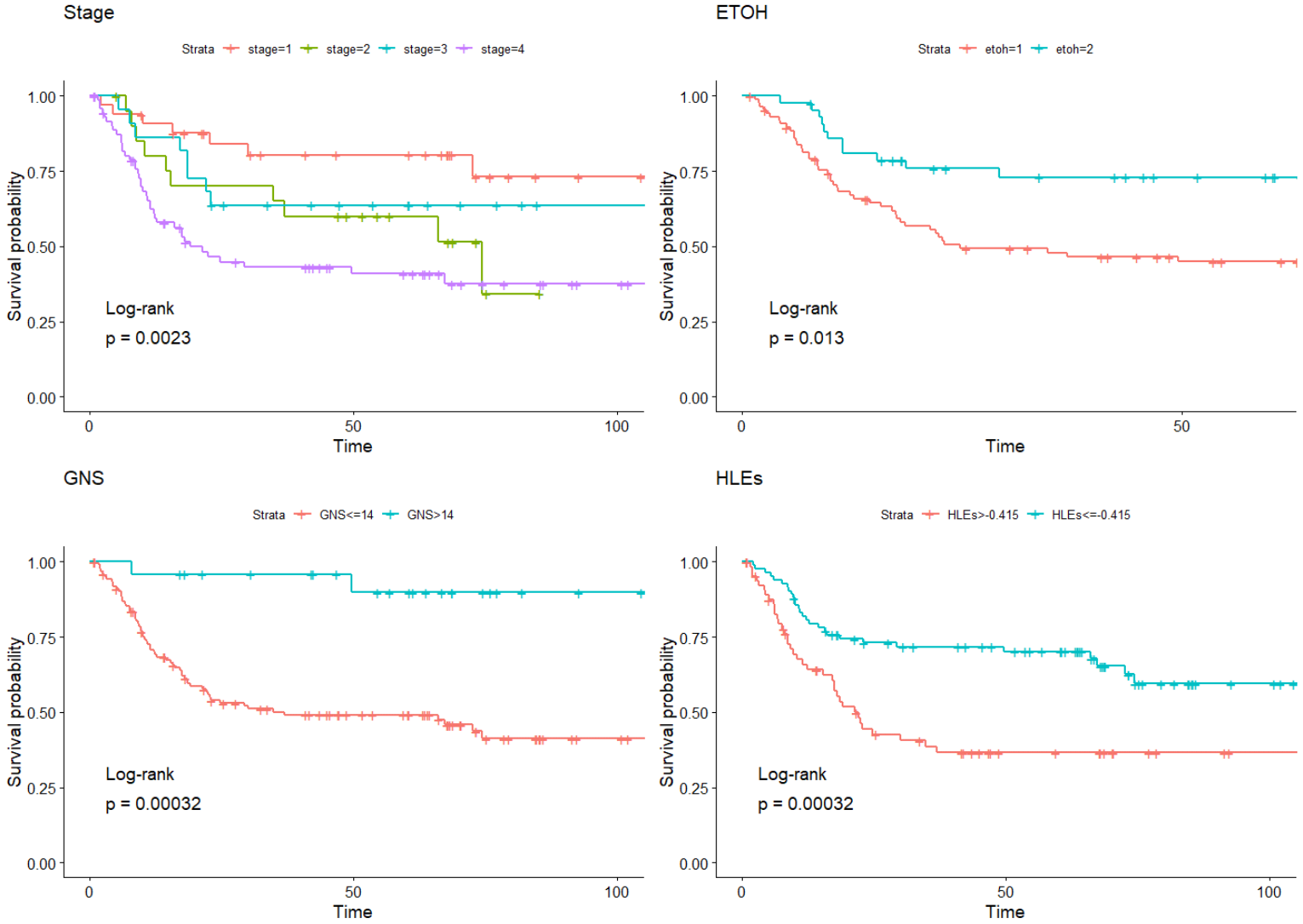
- A locoregional recurrence was defined as a positive biopsy in the primary site or the cervical lymphatic region
- 2-years locoregional recurrence status (LR), defined as that whether a locoregional recurrence happened within 2 years

Frequency of demographic and clinicopathological characteristics.

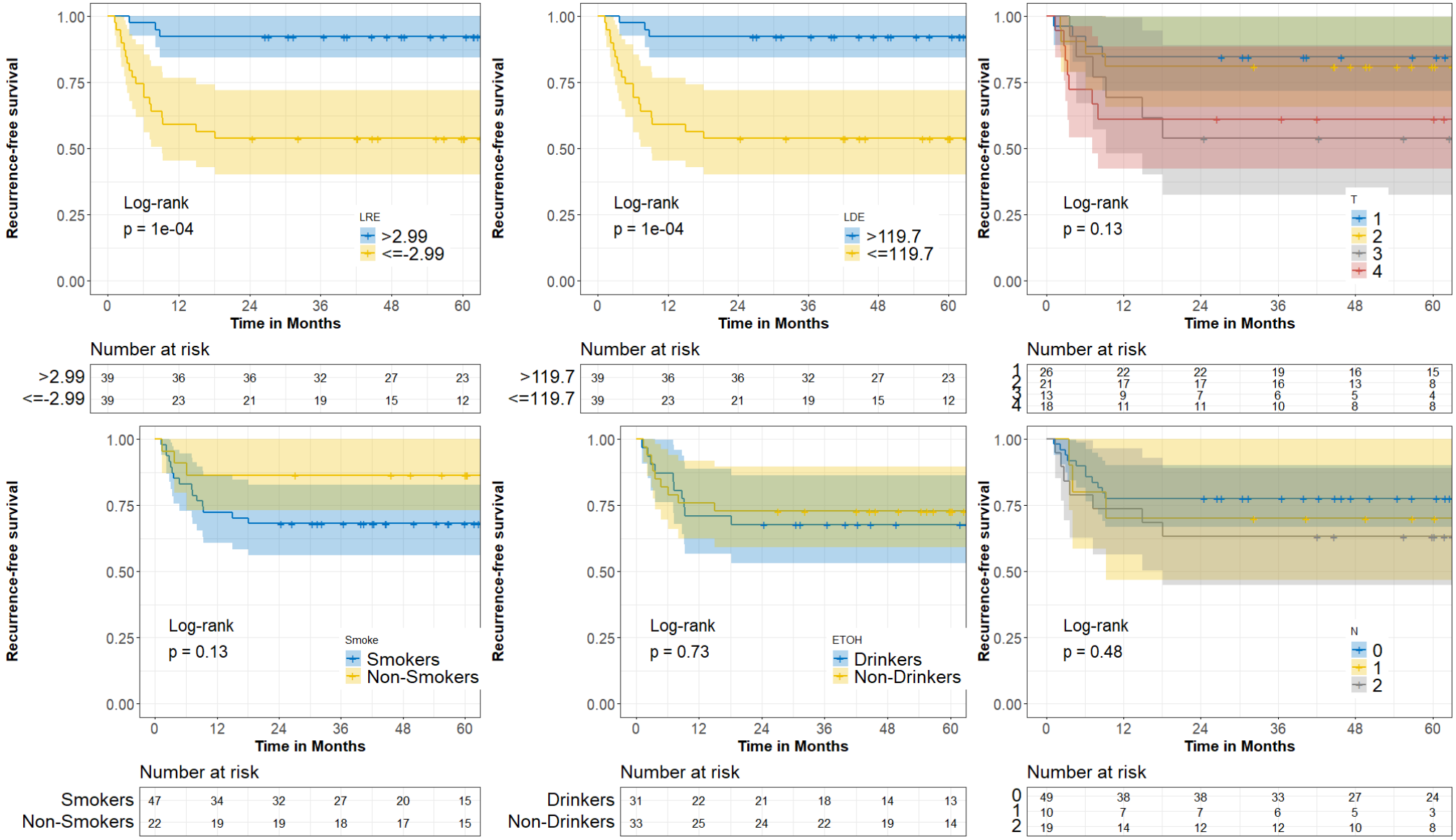
	Total (%)	LR (%)
Gender		
Male	45(58%)	14(67%)
Female	33(42%)	7(33%)
Race		
EA	69(88%)	17(81%)
AA	9(12%)	4(19%)
Smoking		
Yes	47(60%)	15(72%)
No	22(28%)	3(14%)
Unknown	9(12%)	3(14%)
Alcohol		
Yes	31(40%)	10(48%)
No	33(42%)	9(43%)
Unknown	14(18%)	2(9%)
T stage		
T1	26(33%)	4(19%)
T2	21(27%)	4(19%)
T3	13(17%)	6(29%)
T4	18(23%)	7(33%)
N stage		
N0	49(63%)	11(52%)
N1	10(13%)	3(14%)
N2	19(24%)	7(34%)
Treatment		
Sx	45(58%)	8(38%)
Sx + RT	18(23%)	5(24%)
Sx + CRT	15(19%)	8(38%)
Registry Sites		
Buccal Mucosa	11(14%)	1(5%)
Floor of Mouth	6(8%)	2(10%)
Gingiva	13(17%)	2(10%)
Retromolar trigone	1(1%)	0(0%)
Tongue	47(60%)	16(75%)

Overall survival Model Summary

Final Cox model fitting on the sample data.						
	Coef.	coef.	H.ratio	se	95% CI	p-value
Radiomics	HLE_s	0.259	1.29	0.103	[1.05, 1.58]	0.014
	GNS	-0.062	0.94	0.024	[0.90, 0.98]	0.009
Clinical	Stage	0.313	1.37	0.121	[1.08, 1.73]	0.009
	ETOH:2	-0.611	0.54	0.319	[0.29, 1.01]	0.055
	ETOH:3	-0.280	0.76	0.443	[0.32, 1.80]	0.527

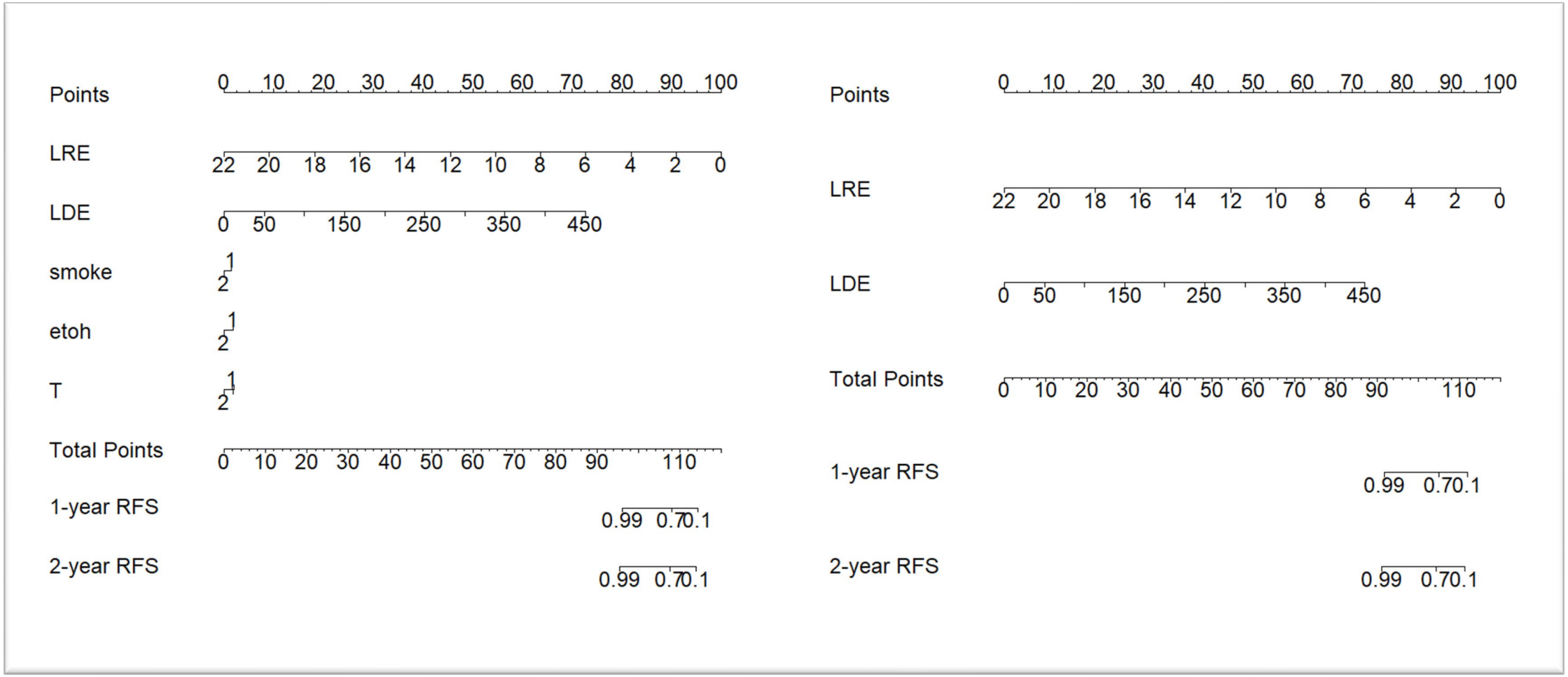


Overall survival rates stratified by significant factor



Radiomic Risk and Recurrence-Free Survival: Kaplan-Meier Analysis

RFS Nomograms



Conclusions

- p16 and PDL1 CPS are currently clinically validated biomarkers
- Future trials with immunotherapy, especially in the locally advanced setting should incorporate PDL1 CPS
- Future directions include incorporating genomic and radionomic biomarkers in patient treatment selection especially in the locally advanced curative setting.
- ctDNA will be a useful biomarker to utilize in future studies

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