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NATIONAL HARBOR, MARYLAND

sitc

Society for Immunotherapy of Cancer

HPV+ Cancers of the H&N and Cervix

Robert L. Ferris, MD, PhD

UPMC Hillman Cancer Center

Pittsburgh, PA

HPV+ Oropharynx Cancer – role for immunotherapy

Robert L. Ferris, MD, PhD

UPMC | HILLMAN CANCER CENTER

NCI Designated Comprehensive Cancer Center

NCI National Clinical Trials Network
a National Cancer Institute program

- Amgen: Advisory Board
- Astra-Zeneca: Advisory Board, Clinical Trial, Research Funding
- Bain Capital Life Sciences: Consulting
- Bristol-Myers Squibb: Advisory Board, Clinical Trial, Research Funding
- EMD Serono: Advisory Board
- Iovance Biotherapeutics, Inc.: Consulting
- Oncorus, Inc.: Advisory Board
- PPD: Advisory Board (Benitec, Immunicum)
- Lilly: Advisory Board
- Merck: Advisory Board, Clinical Trial
- Ono Pharmaceutical Co. Ltd: Consulting
- Pfizer: Advisory Board
- Regeneron Pharmaceuticals, Inc: Advisory Board
- Tesaro: Advisory Board, Research Funding
- TTMS: Founder, Consultant
- VentiRx Pharmaceuticals: Research Funding

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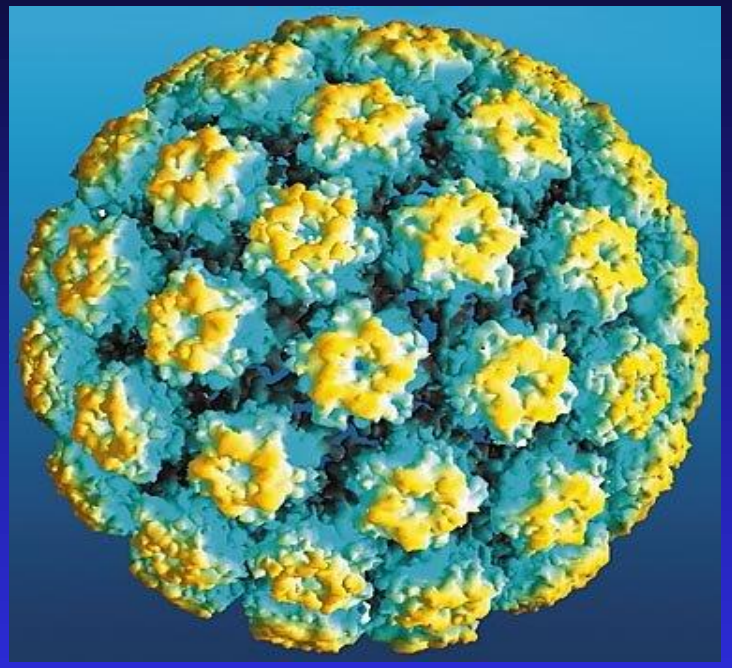
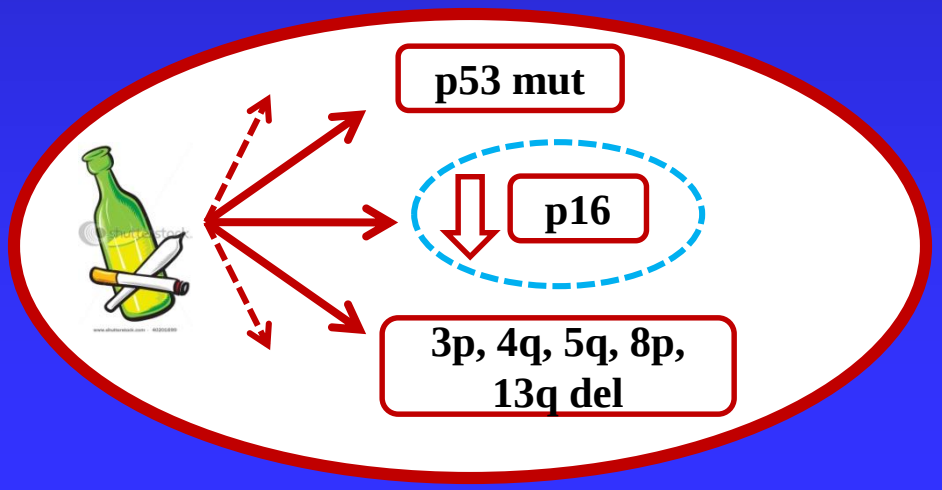
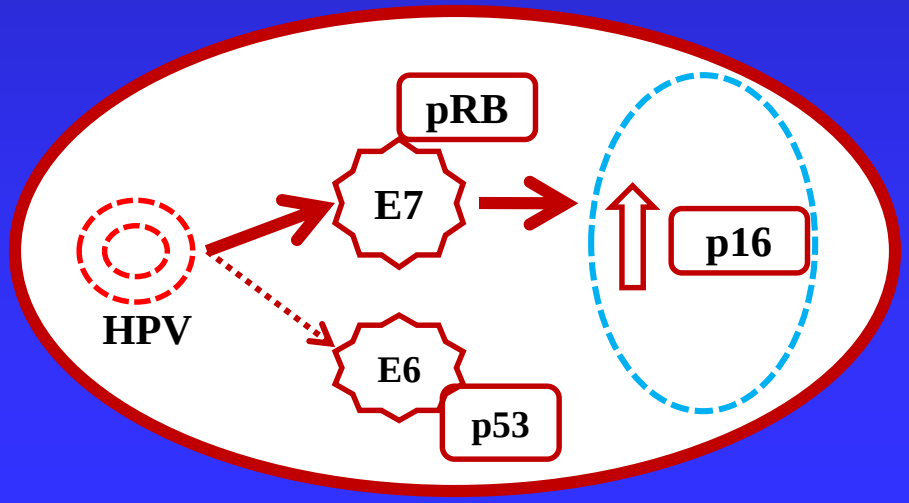
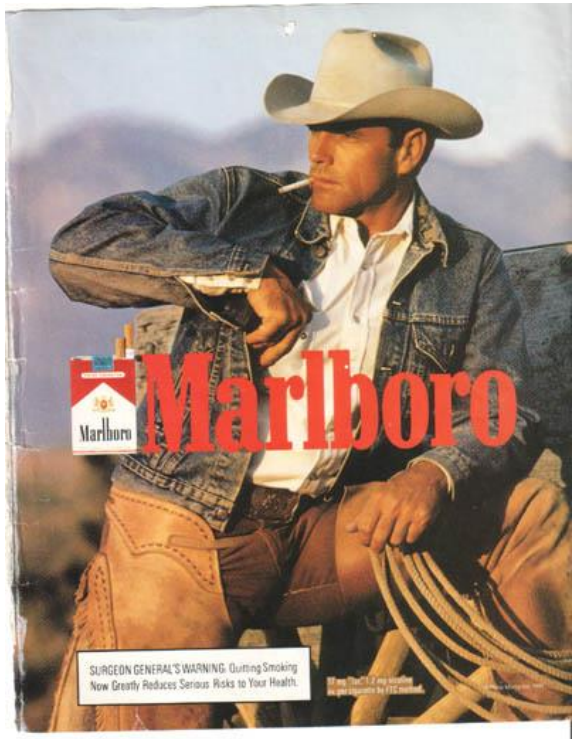
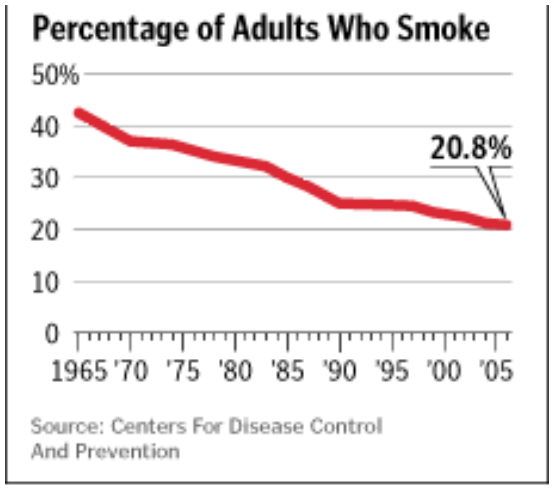
Two distinct diseases comprise OPSCC





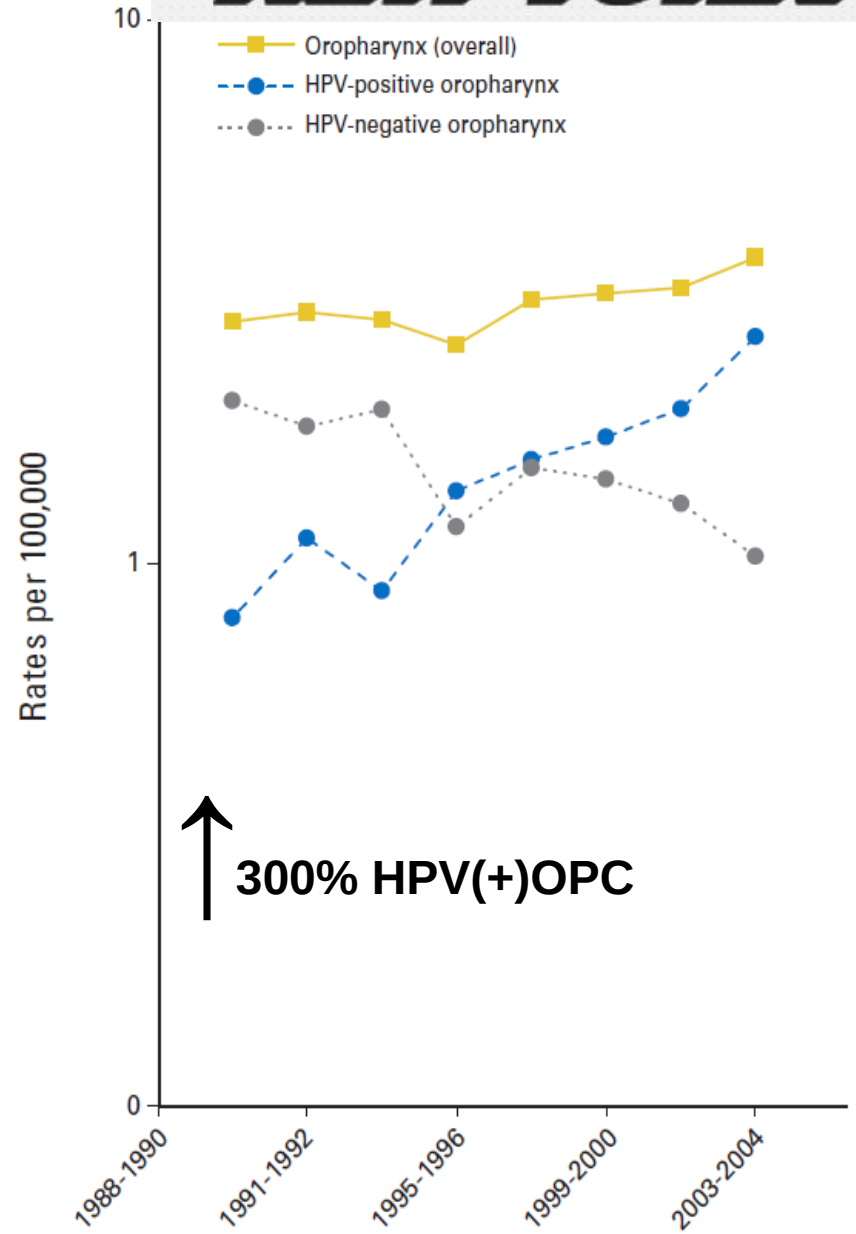


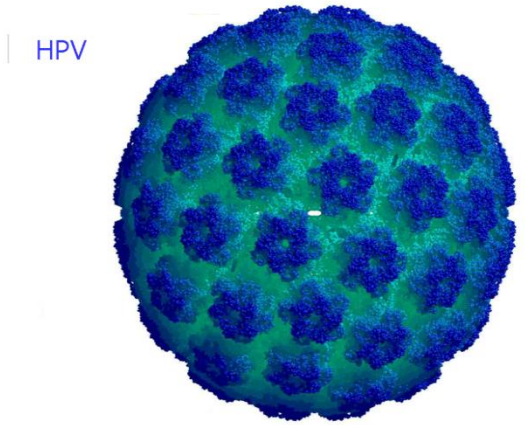




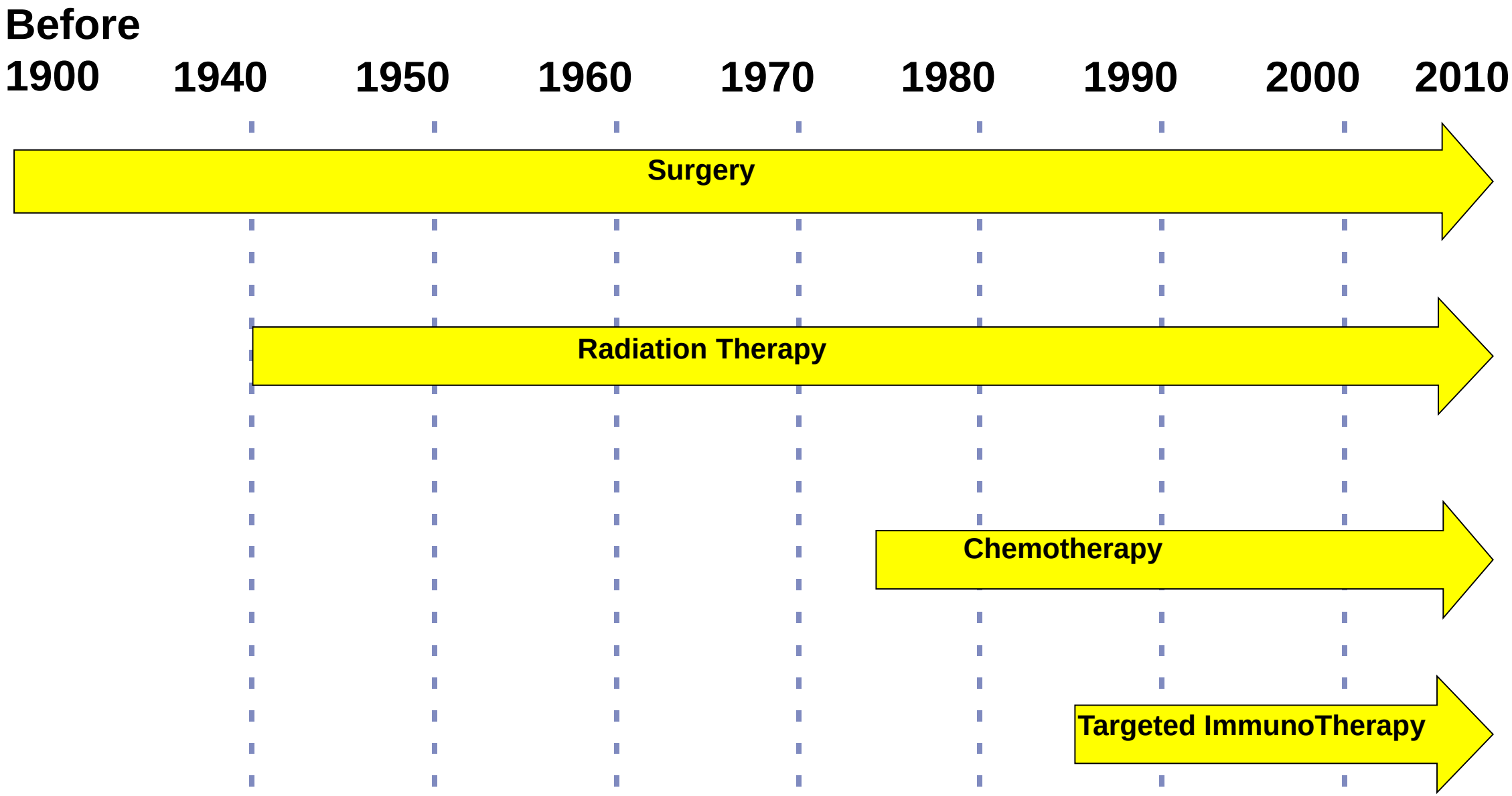
Chaturvedi, *JCO*,2013

NEW YORK POST

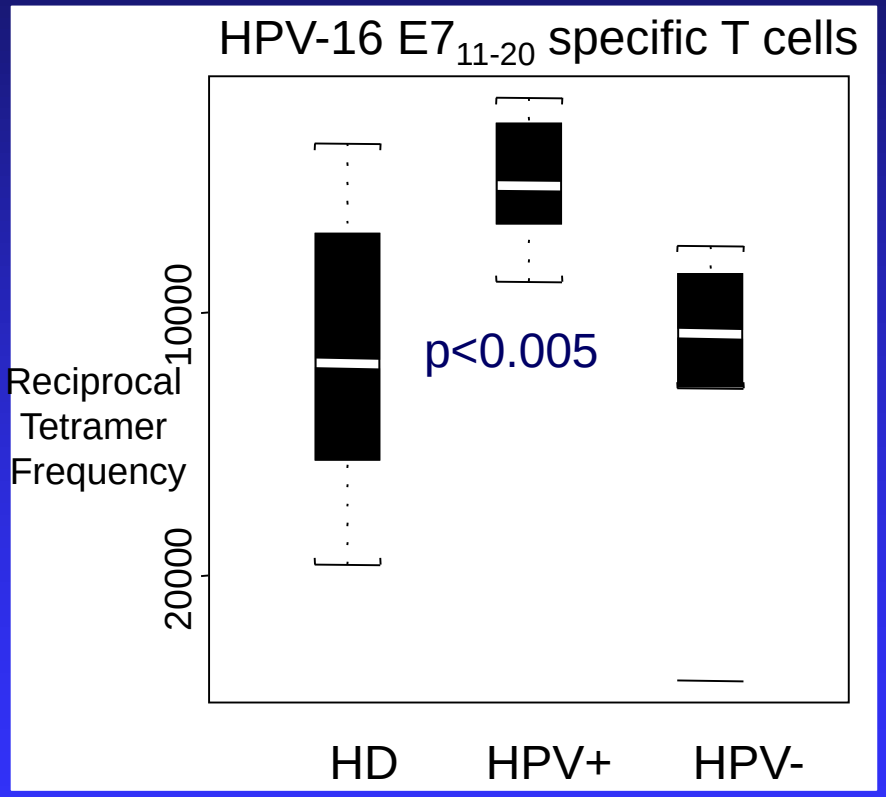




The Evolution of Treatment for Cancer



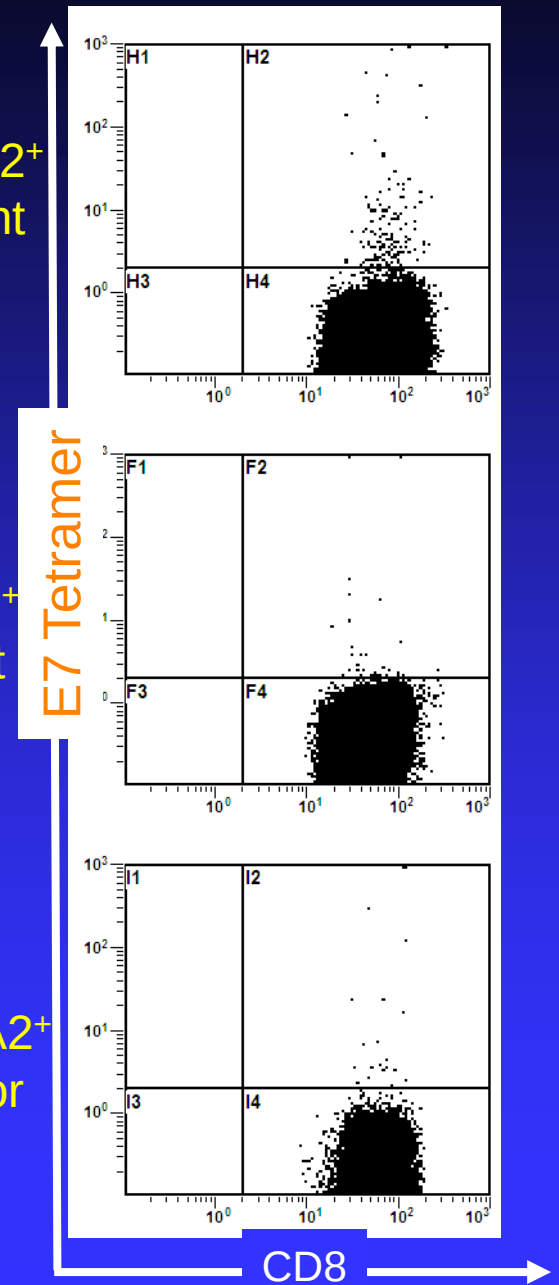
Endogenous HPV E7-specific Immunity



HPV-16^{+} HLA-A2^{+} SCCHN Patient

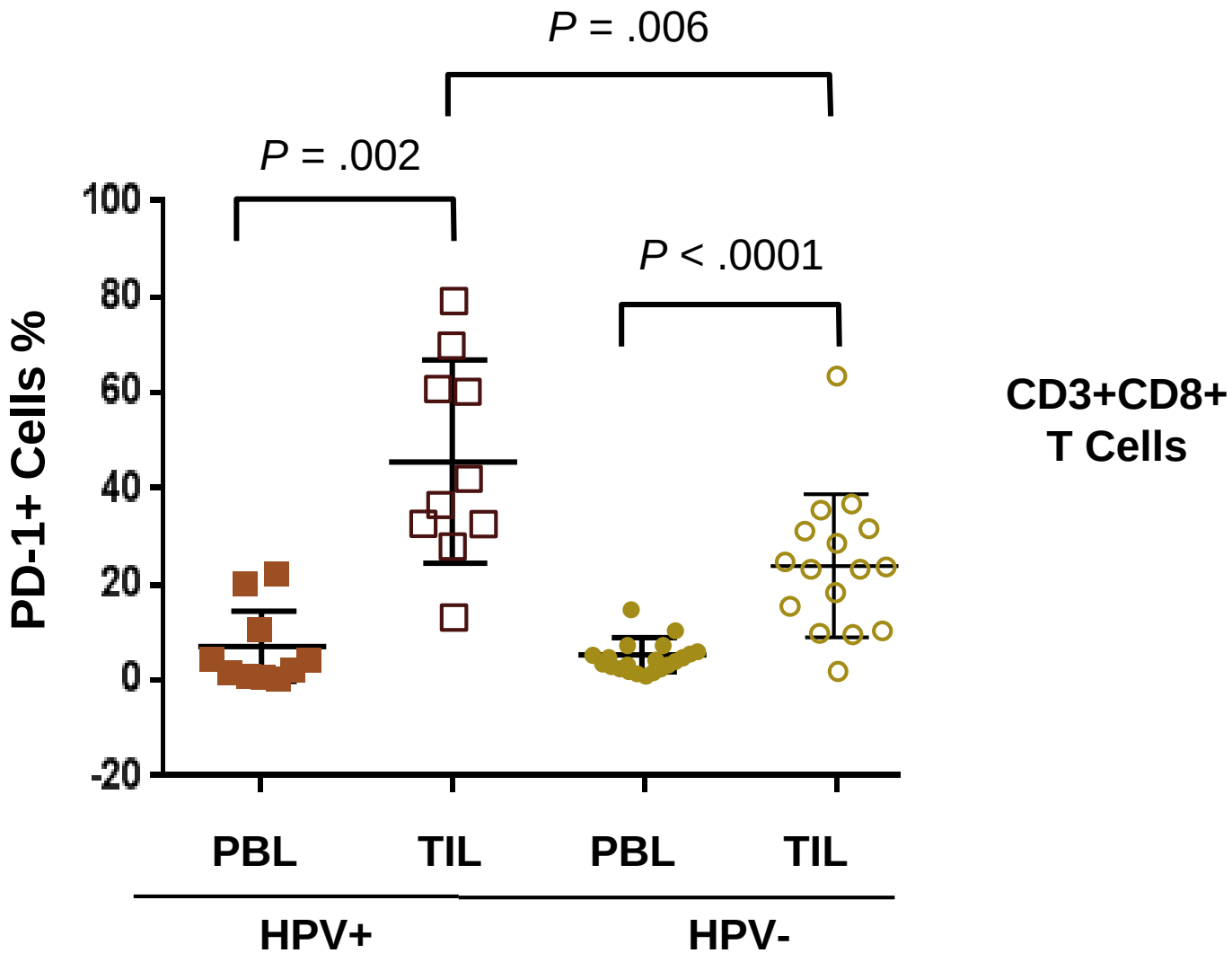
HPV-16^{-} HLA-A2^{+} SCCHN Patient

HPV-16^{-} HLA-A2^{+} Healthy Donor

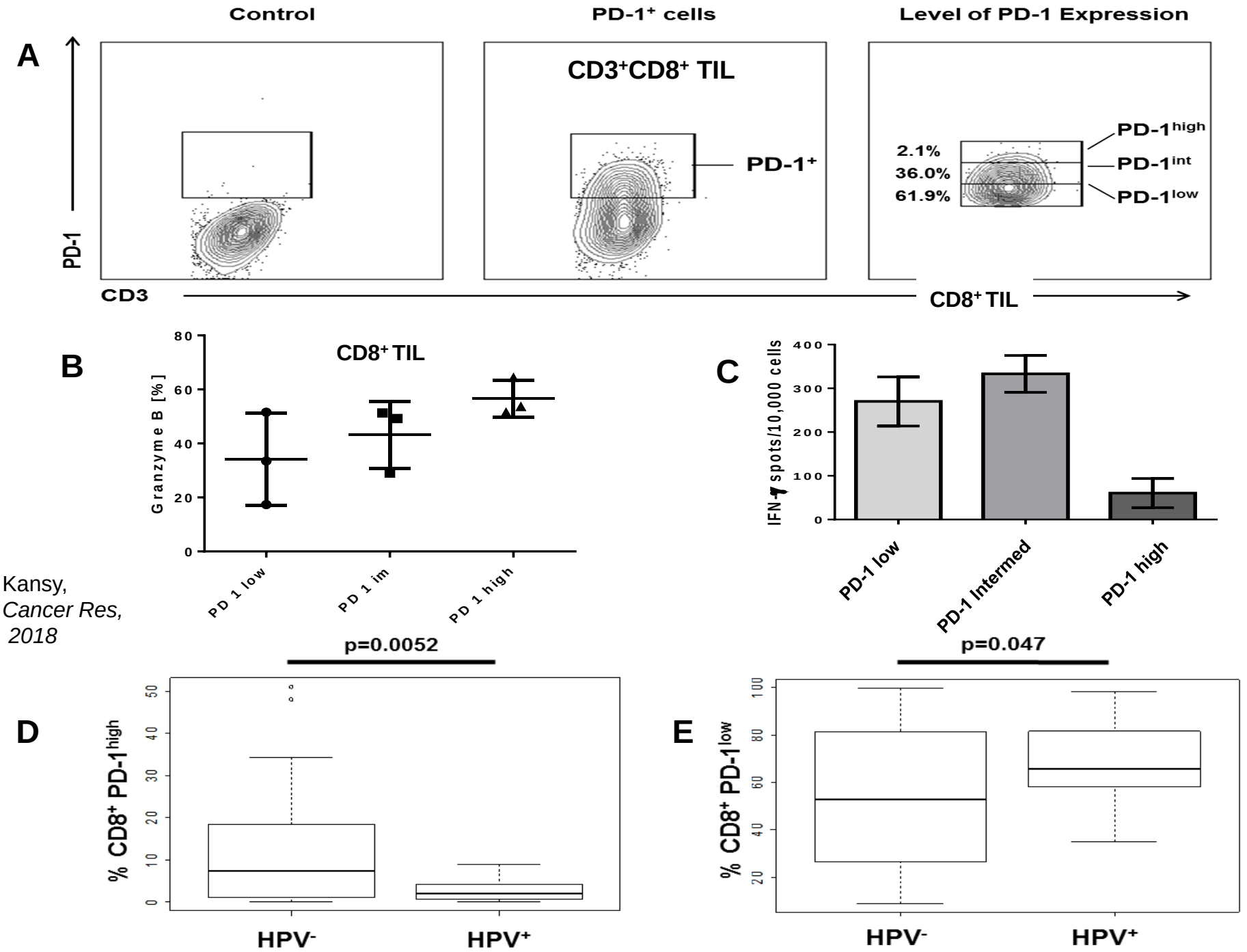


Albers, *Cancer Research* 2005

Enrichment of PD-1+ CD8+ T Cells in the HPV+ Tumor Microenvironment



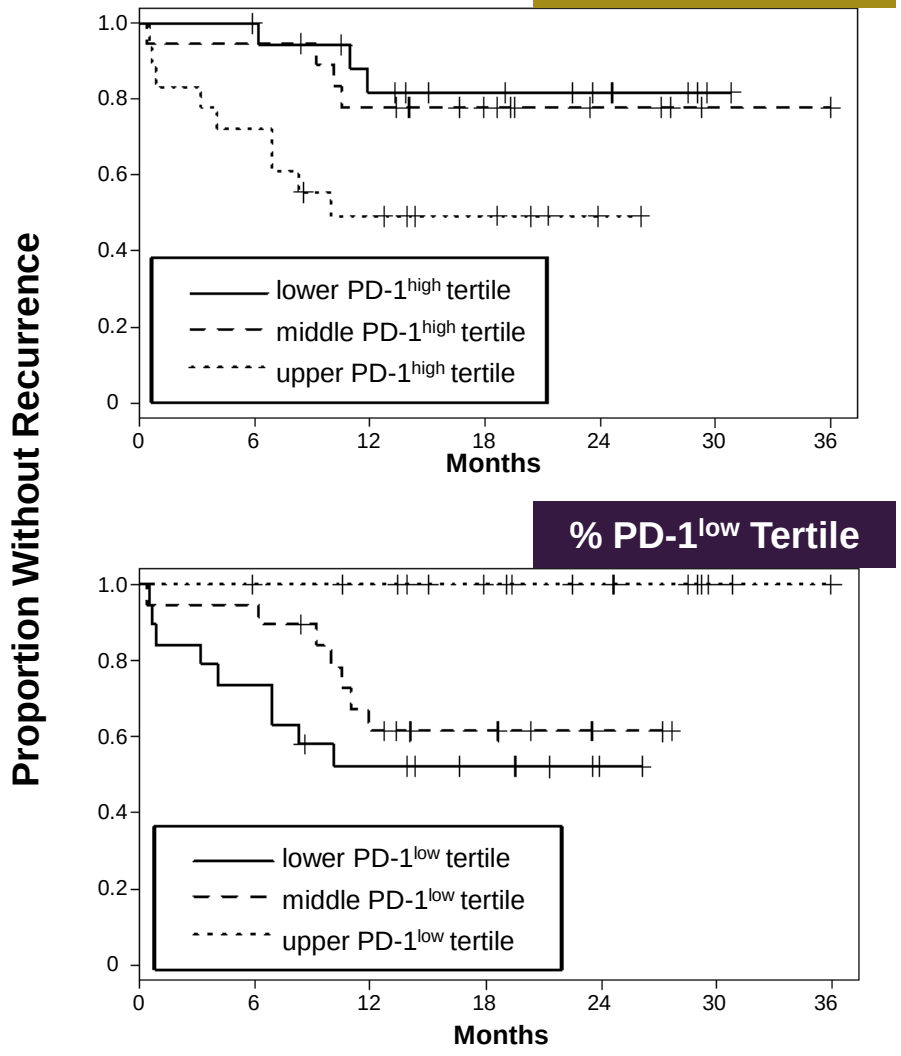
Concha-Benavente F et al. *Cancer Res*. 2016;76:1031-1043.



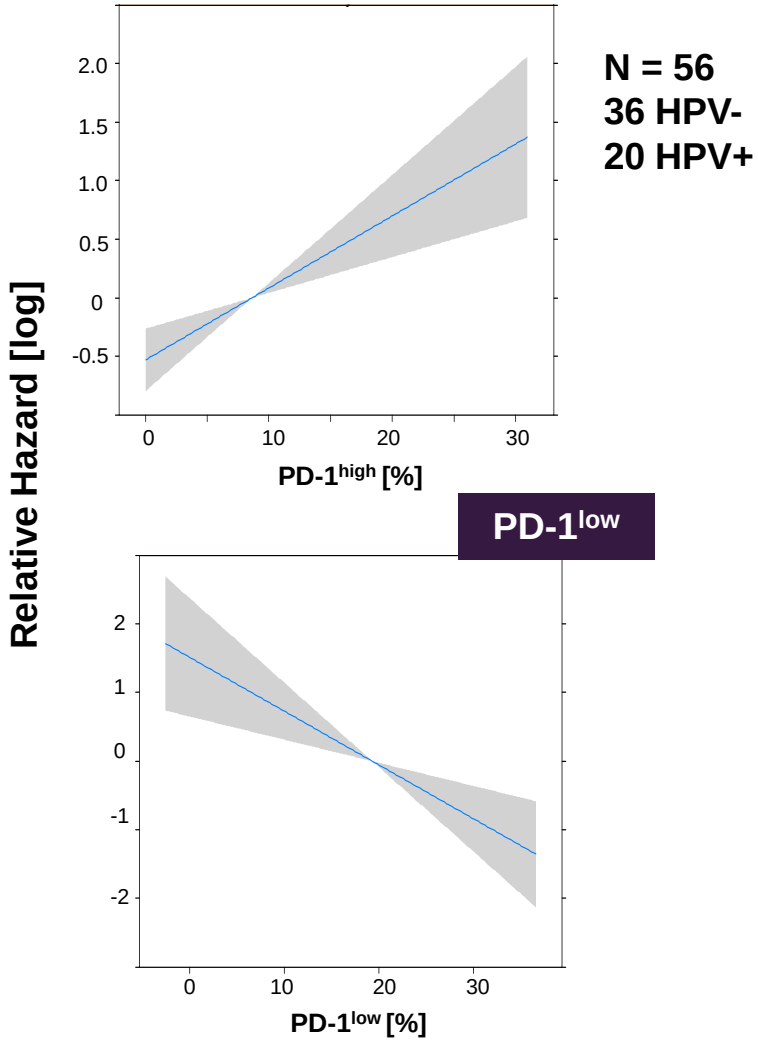
Kansy, *Cancer Res, 2018*

Risk of Recurrence by PD-1 *Intensity*

Disease-Free Survival by: **% PD-1^{high} Tertile**



Relative Risk of Recurrence in Dependence of: **PD-1^{high}**

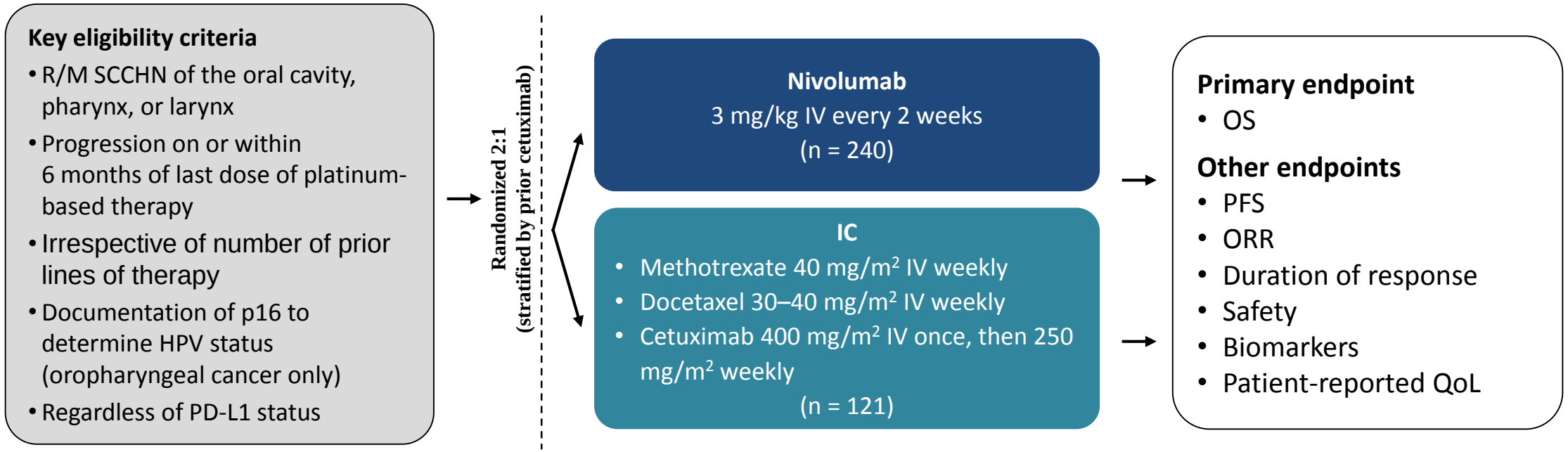


N = 56
36 HPV-
20 HPV+

CheckMate 141 study design

Study design

- CheckMate 141 (NCT02105636) was a randomized, open-label, phase 3 trial in patients with R/M SCCHN who had progressed on or within 6 months after platinum-based therapy (**Figure 1**)



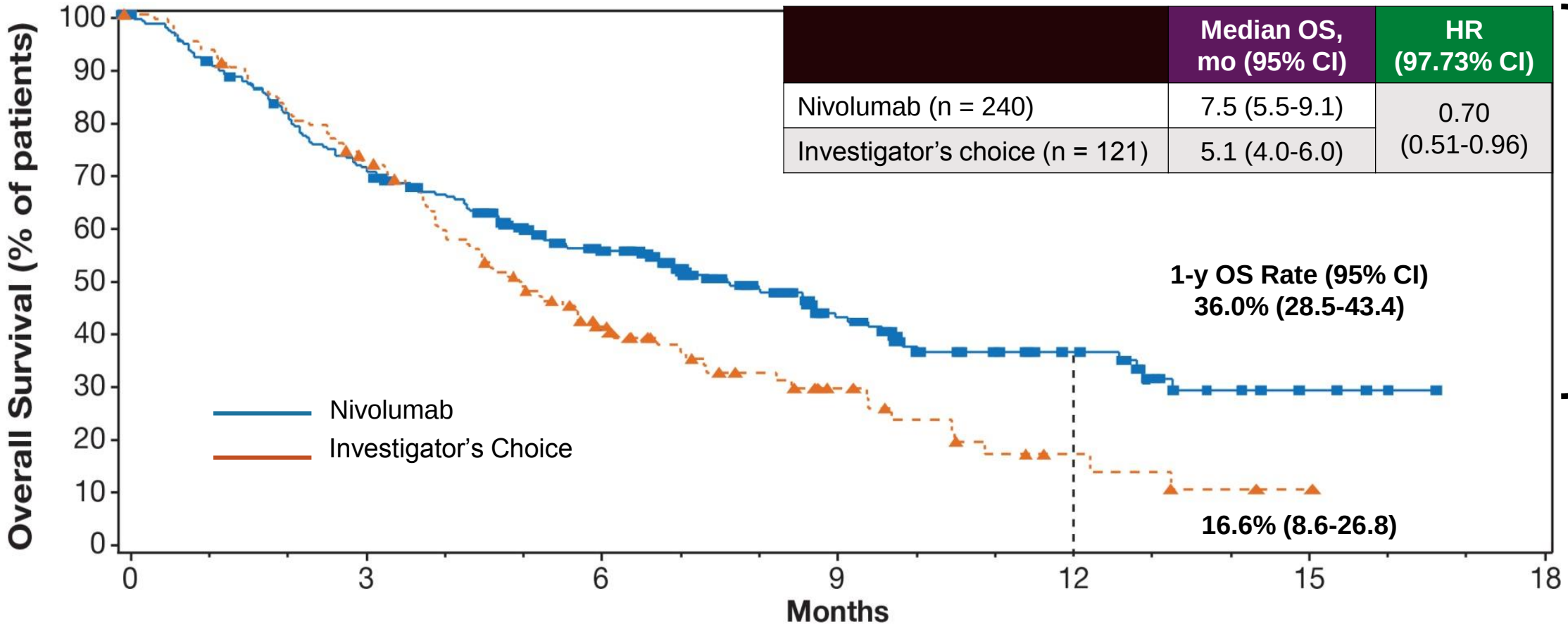
HPV = human papillomavirus; IC = investigator's choice; IV = intravenous; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; QoL = quality of life

Ferris and Gillison, *NEJM* 2016

Overall Survival

So why don't ALL patients benefit?

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



No. at Risk

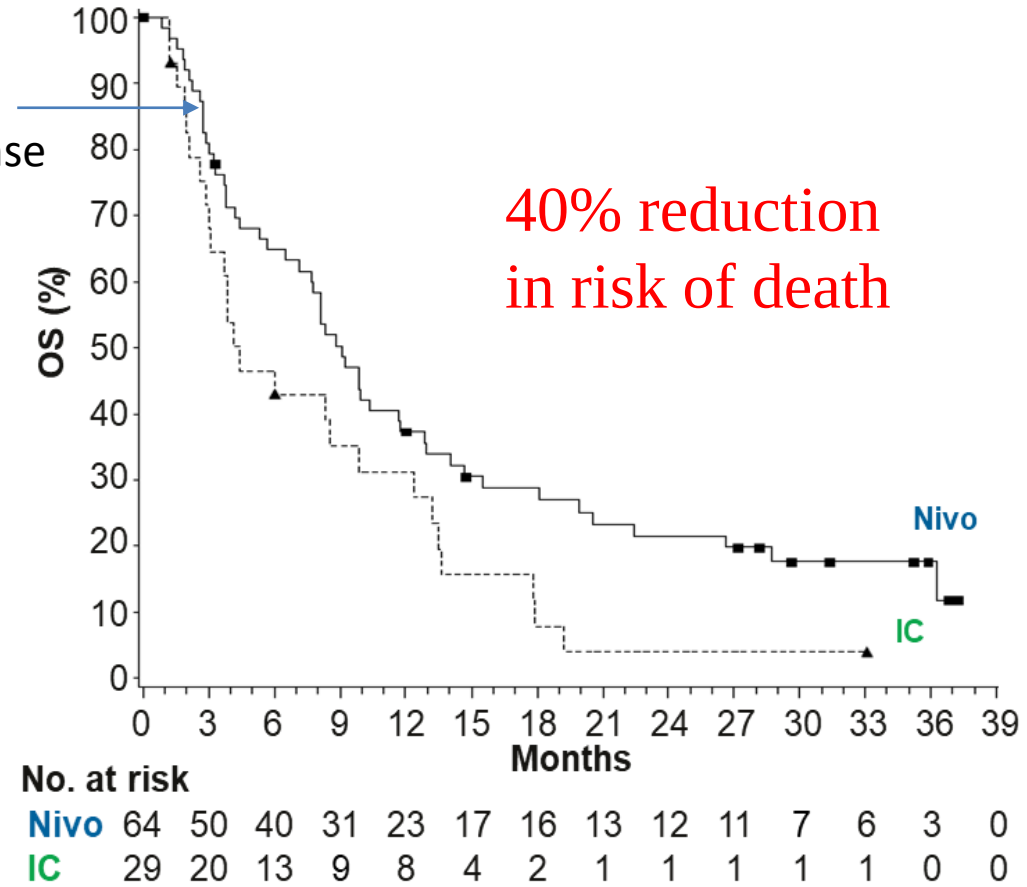
Nivolumab	240	167	109	52	24	7	0
Investigator's Choice	121	87	42	17	5	1	0

Ferris and Gillison et al. *NEJM* 2016

Overall survival by tumor HPV status

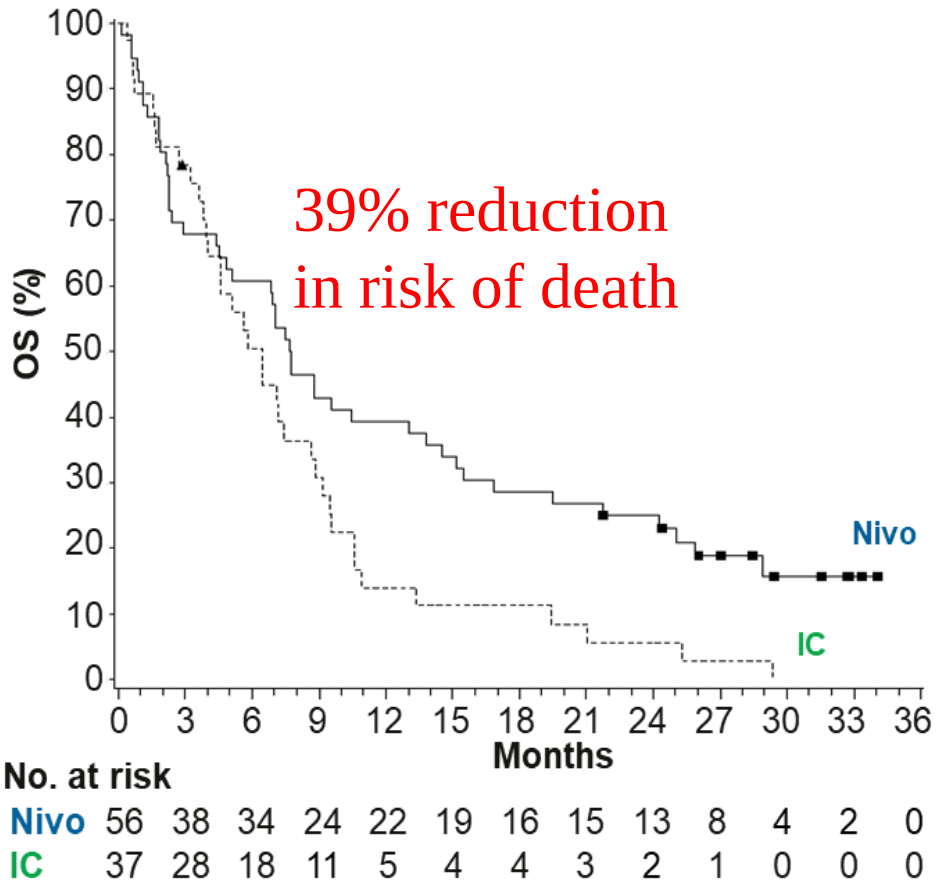
A. HPV positive

Earlier response



HPV positive	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 64)	9.1 (6.5, 11.8)	0.60 (0.37, 0.97)
IC (n = 29)	4.4 (3.0, 9.8)	

B. HPV negative



HPV negative	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 56)	7.7 (4.8, 13.0)	0.59 (0.38, 0.92)
IC (n = 37)	6.5 (3.9, 8.7)	

HCC 18-034

Phase II Trial of Adjuvant De-Escalated Radiation + Concurrent Nivolumab for Intermediate-Risk P16+ Oropharynx Cancer

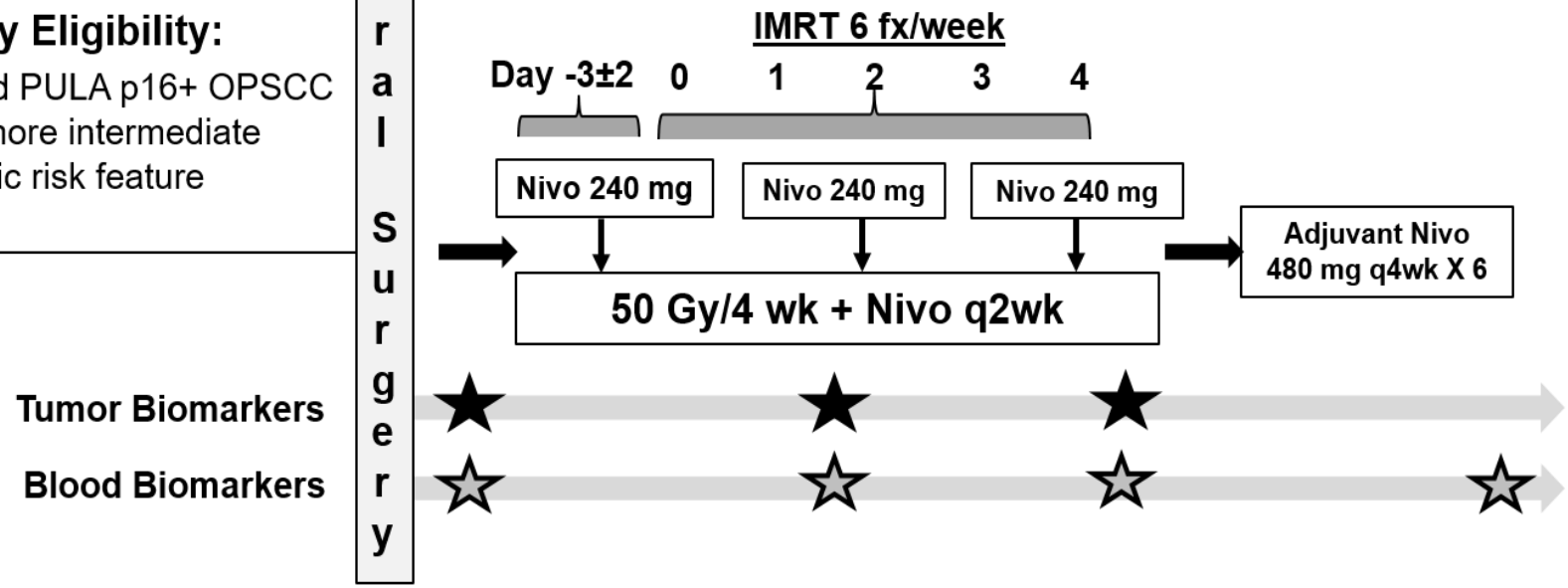
Key Eligibility:

- Resected PULA p16+ OPSCC
- One or more intermediate pathologic risk feature
- M0

Transoral Surgery

Intermediate risk features:

- Tobacco <10 pk-yr: T0-3 plus any one of the following: ≥ 5+ LN's, N2c/N3, +ENE >1 mm, or + margin (approval by surgical chair)
- Tobacco >10 pk-yr: T0-3 plus any one of the following: any N2, N3, +ENE >1 mm, or + margin (approval by surgical chair)

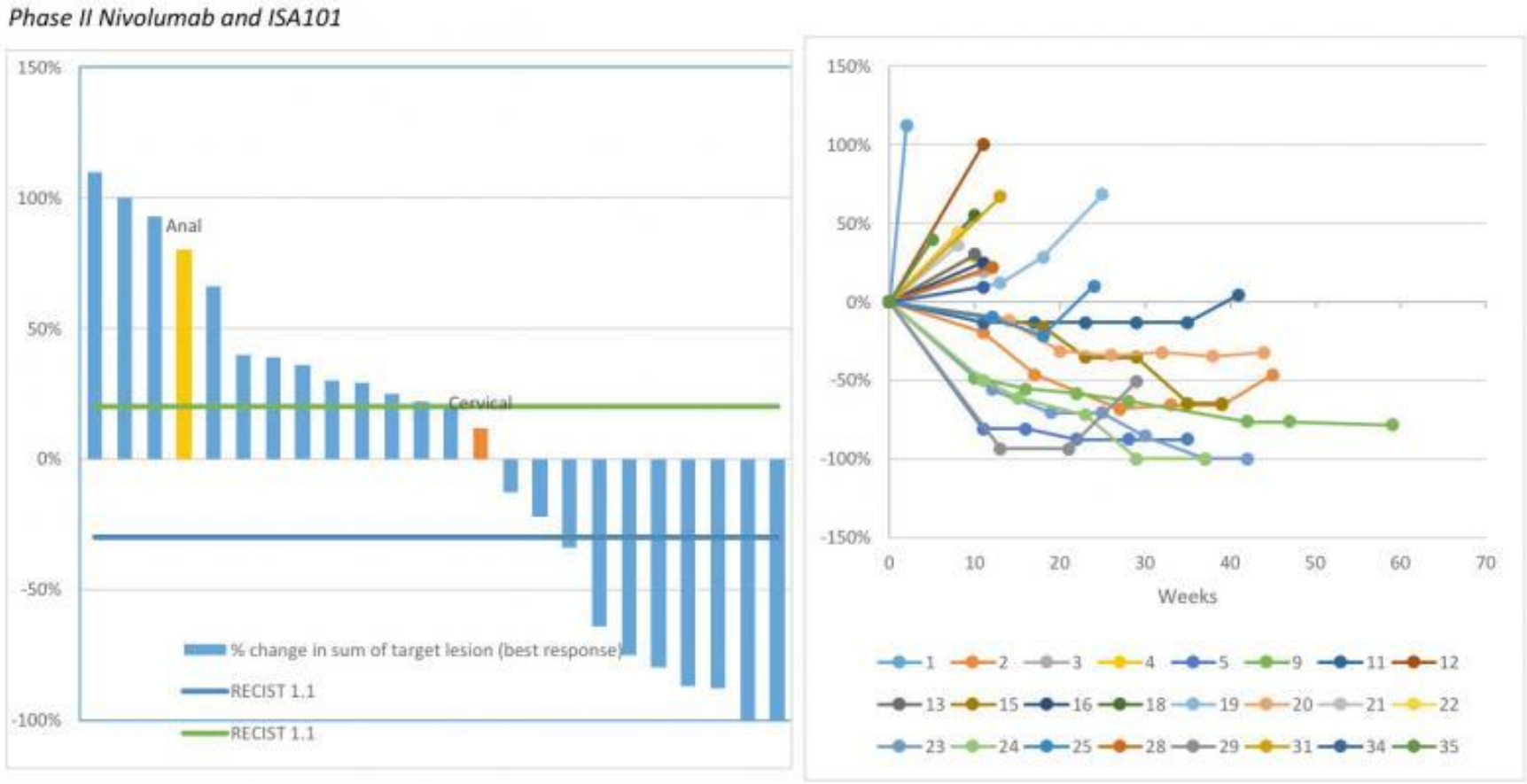


Primary endpoint: 2-year Disease-free survival
Secondary endpoints: QOL/Swallowing function, Distant metastasis, locoregional control, overall survival
Paired tumor/TME/blood biomarkers

Reference

N=15/135

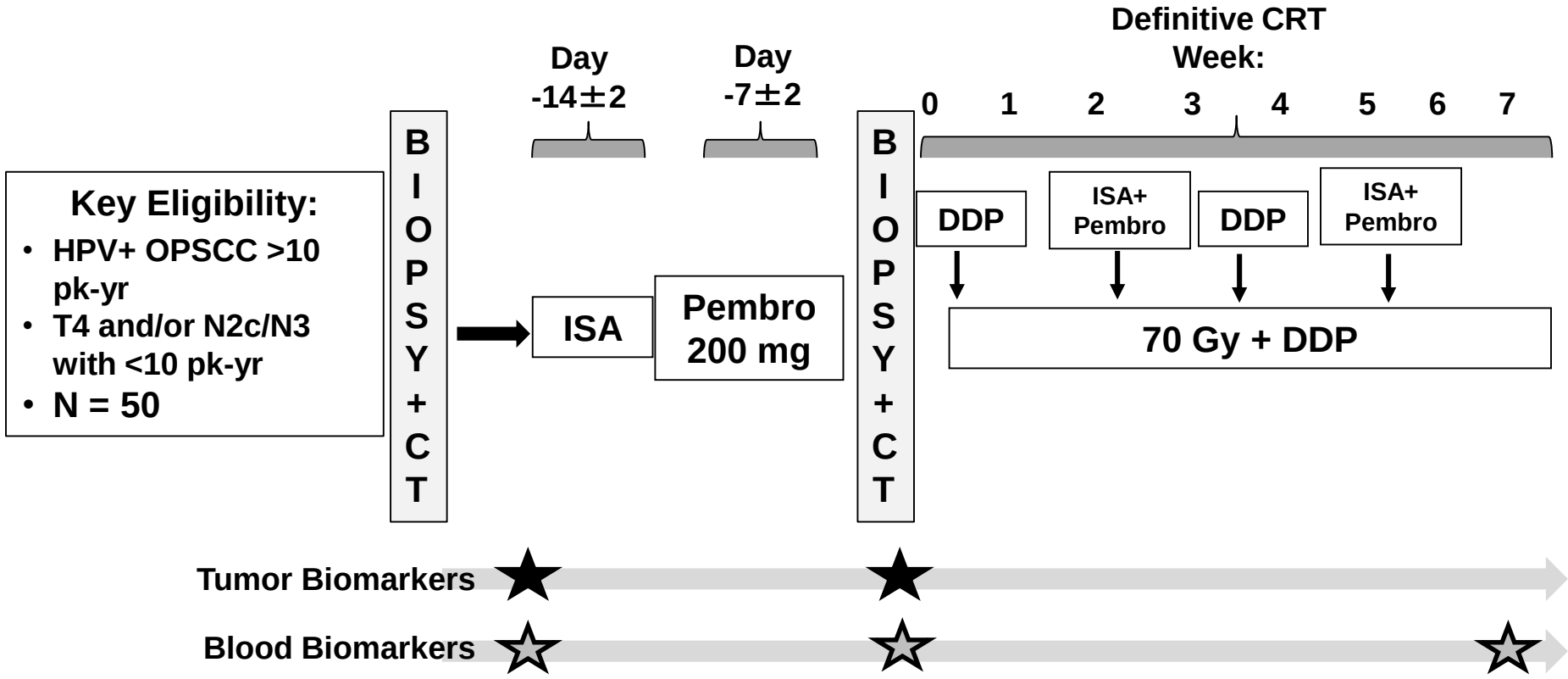
Combined Therapy with Nivolumab and ISA 101 Vaccine Results in Promising Efficacy in HPV-positive Oropharyngeal Cancer (Glisson, *ESMO*, 2017)



HCC 19-082

Phase II trial of CRT+HPV vaccine + pembrolizumab

Intermediate Risk, Locally Advanced, HPV+ H&N cancer patients



Primary endpoint: 3-year Disease-free survival
Secondary endpoints: Distant metastatic control, locoregional control, overall survival
Paired tumor/TME biomarkers, serial peripheral biomarkers

Garcia-Bates, *J Immunol*, 2016 Genter, *NEJM* 2010

N = 50

An Open-label, Multicohort, Phase 1/2 Study in Patients With Virus-Associated Cancers (CheckMate 358): Safety and Efficacy of Neoadjuvant Nivolumab in Squamous Cell Carcinoma of the Head and Neck

Robert L. Ferris,[1] Anthony Gonçalves,[2] Shrujal S Baxi,[3] Uwe M. Martens,[4] Hélène Gauthier,[5] Marlies Langenberg,[6] William C. Spanos,[7] Rom S. Leidner,[8] Hyunseok Kang,[9] Jeffery Russell,[10] Simion Chiosea,[11] Ibrahima Soumaoro,[12] Shangbang Rao,[12] Z. Alexander Cao,[12] Suzanne L. Topalian[9]

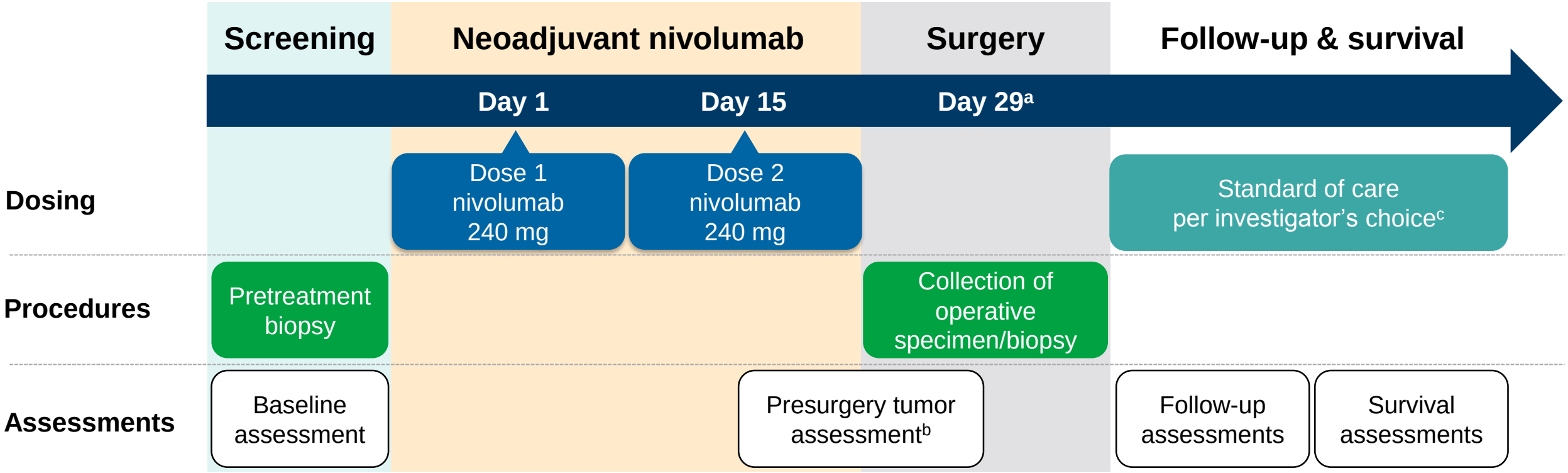
[1]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [2]Institut Paoli-Calmettes, Marseille, France; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]SLK-Clinics, MOLIT Institute, Heilbronn, Germany; [5]APHP CIC and Dermatology Department INSERM 976, University Paris Diderot Hôpital Saint-Louis, Paris, France; [6]UMC Utrecht Cancer Center, Utrecht, The Netherlands; [7]Sanford Health, USD Sanford School of Medicine, Sioux Falls, SD, USA; [8]Earle A. Chiles Research Institute at Providence Cancer Center, Portland, OR, USA; [9]The Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; [10]Moffitt Cancer Center, Tampa, FL, USA; [11]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [12]Bristol-Myers Squibb, Princeton, NJ, USA

ESMO 2017

Background

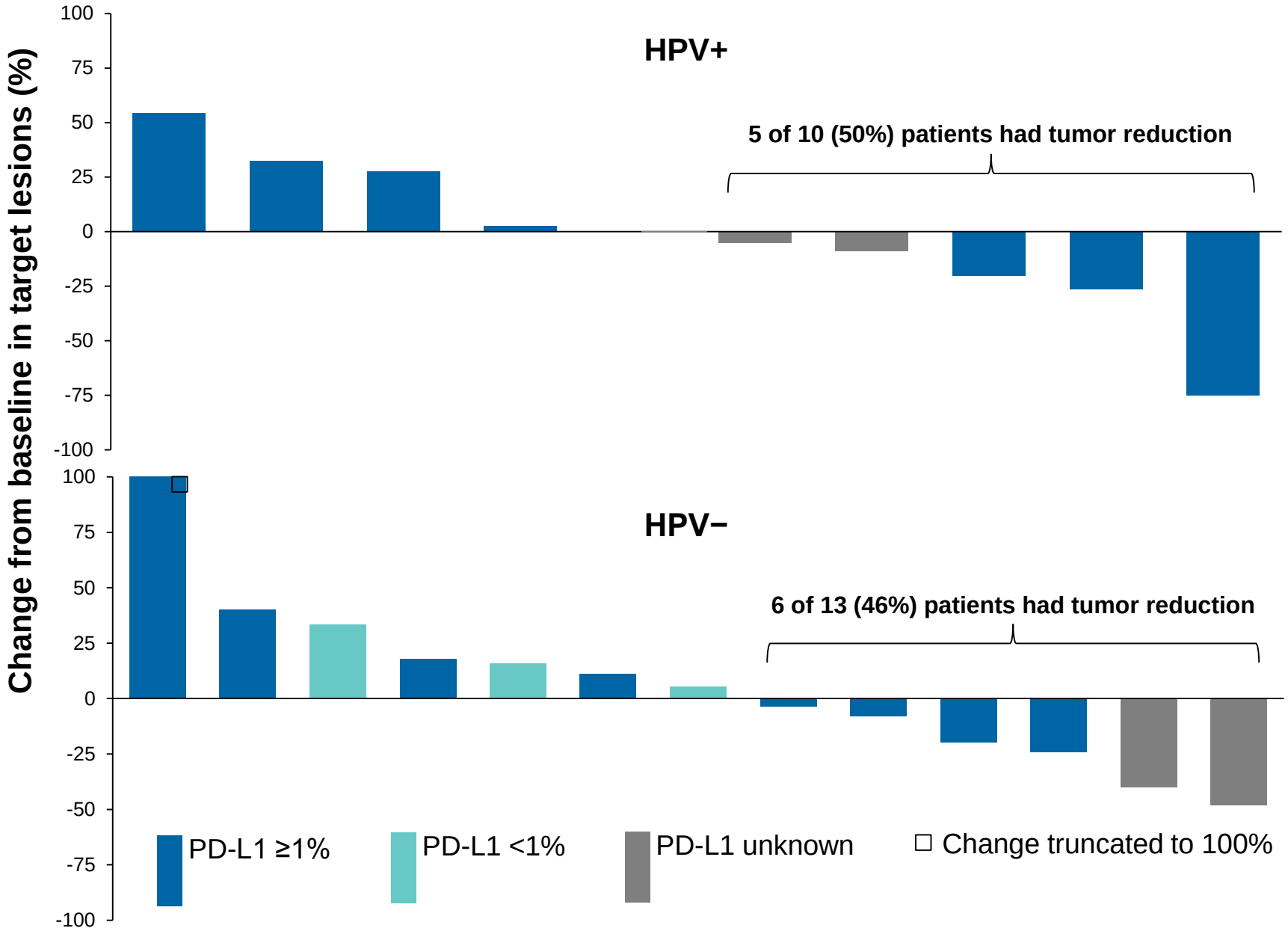
- Worldwide, ~600,000 new cases of squamous cell carcinoma of the head and neck (SCCHN) are diagnosed each year[1]
  - An estimated 70% of oropharyngeal cancers are caused by human papillomavirus (HPV) infection[2]
  - Patients with HPV+ tumors have better survival rates than those with HPV− tumors[3]
- Surgery is a standard therapeutic approach for patients presenting with early-stage or localized SCCHN tumors that can be resected without causing unacceptable morbidity[4,5]
- SCCHN expresses the immune suppressive molecule programmed death ligand 1 (PD-L1), and infiltrating lymphocytes express the inhibitory PD-1 receptor[7]
- Nivolumab is the only PD-1 inhibitor that has reported improved overall survival in a phase 3 trial in platinum-refractory recurrent or metastatic SCCHN[8,9]
- Immune checkpoint inhibitors in the presurgical (neoadjuvant) setting may enhance systemic immunity to prevent tumor recurrence and metastasis
- CheckMate 358 study explored the safety and feasibility of neoadjuvant nivolumab in patients with resectable HPV+ or HPV− SCCHN

CheckMate 358 neoadjuvant cohort assessments and procedures

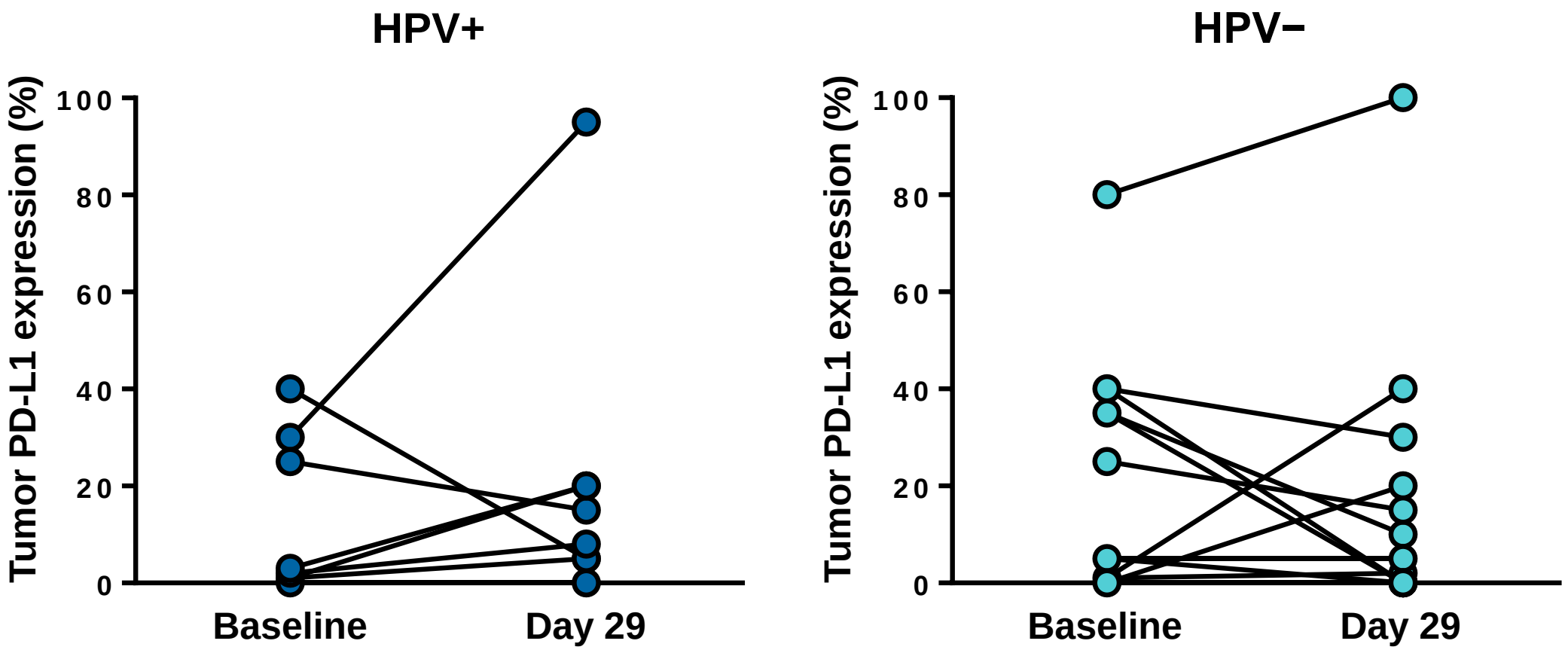


[a]±7 days
[b]Up to 7 days prior to surgery
[c]Observation or chemotherapy (with or without radiotherapy)

Tumor reduction after 2 doses of nivolumab



PD-L1 change from baseline to day 29 in individual patients



BARCELONA 2019 ESMO congress

Efficacy and Safety of Nivolumab + Ipilimumab in Patients With Recurrent/Metastatic Cervical Cancer: Results From CheckMate 358

R. Wendel Naumann[1*], Ana Oaknin[2*], Timothy Meyer[3], Jose Maria Lopez-Picazo[4], Christopher Lao[5], Yung-Jue Bang[6], Valentina Boni[7], William H. Sharfman[8], Jong Chul Park[9], Lot. A. Devriese[10], Kenichi Harano[11], Christine H. Chung[12], Suzanne L. Topalian[8], Kamarul Zaki[3], Tian Chen[13], Junchen Gu[13], Bin Li[13], Adam Barrows[13], Andrea Horvath[13], Kathleen N. Moore[14]

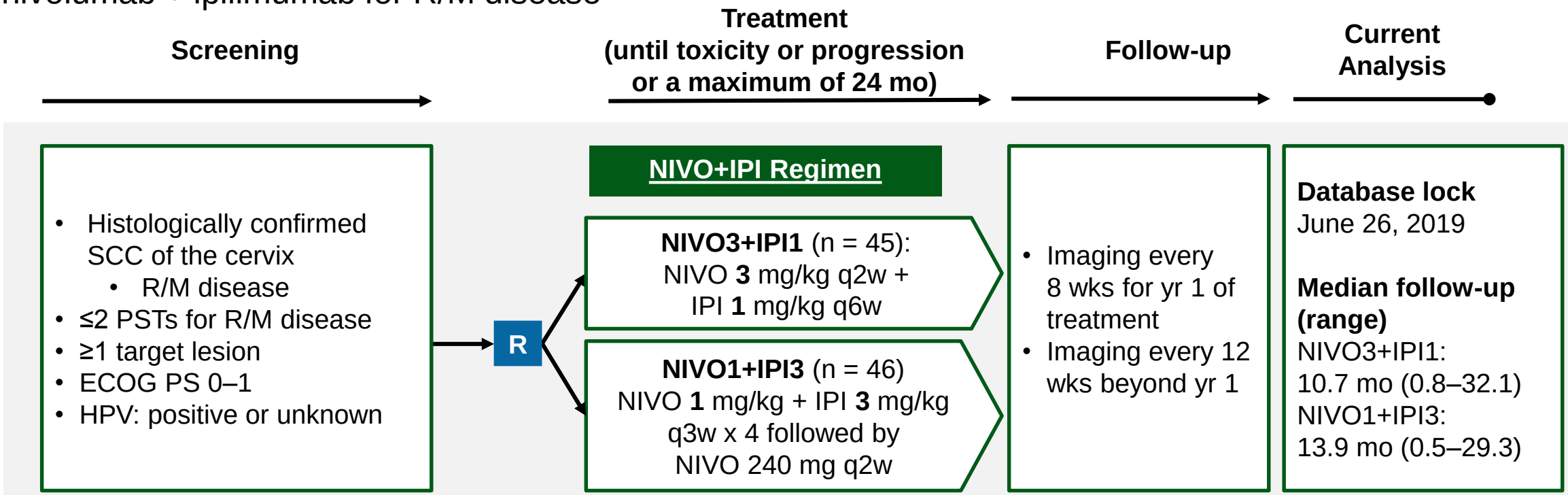
[1]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [2]Vall d´Hebron University Hospital, Vall d´Hebron Institute of Oncology, Barcelona, Spain; [3]University College London, London, UK; [4]Clinica Universidad de Navarra, Navarra, Spain; [5]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA; [6]Seoul National University Hospital, Seoul, South Korea; [7]START Madrid CIOCC Hospital Madrid Norte Sanchinarro, Madrid, Spain; [8]Johns Hopkins Bloomberg-Kimmel Institute for Cancer Immunotherapy and Kimmel Cancer Center, Baltimore, MD, USA; [9]Dana Farber Cancer Institute, Beth Israel Deaconess Medical Center and Massachusetts General Hospital, Boston, MA, USA; [10]Universitair Medisch Centrum Utrecht, Utrecht, The Netherlands; [11]National Cancer Center Hospital East, Kashiwa, Japan; [12]H. Lee Moffitt Cancer Center, Tampa, FL, USA; [13]Bristol-Myers Squibb, Lawrence, NJ, USA; [14]Stephenson Cancer Center at the University of Oklahoma, Oklahoma City, OK, USA and Sarah Cannon Research Institute, Nashville, TN, USA

* Colead authors

Abstract Number 5630

Study Design and Current Analysis

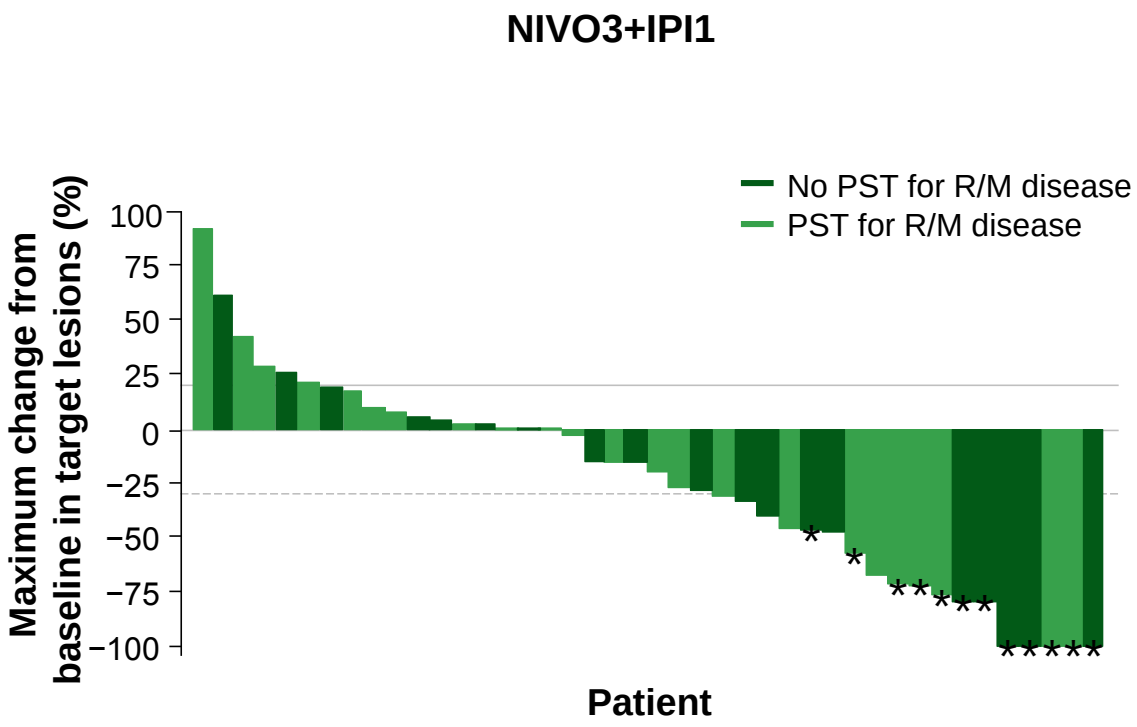
Randomized cervical cancer cohorts of CheckMate 358 (NCT02488759) testing 2 combination regimens of nivolumab + ipilimumab for R/M disease

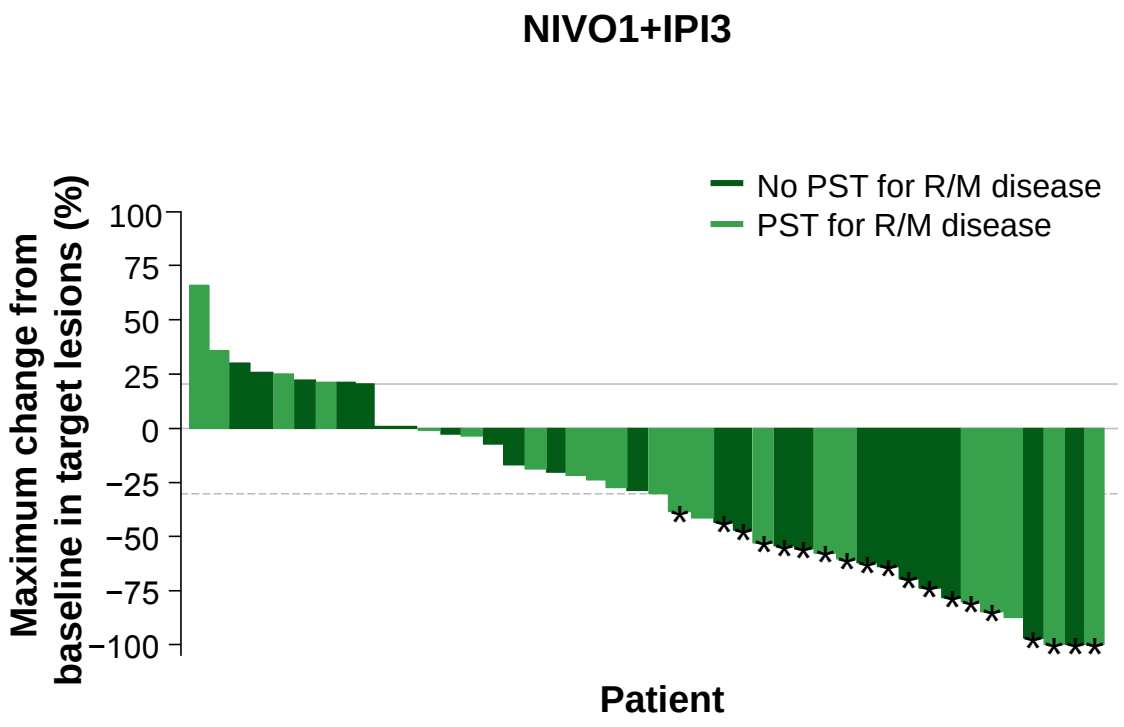


- **Study start date:** October 2015
- **Estimated completion date:** December 2019
- **Primary endpoint:** Investigator-assessed ORR by RECIST 1.1
- **Secondary endpoints:** OS, PFS, duration of response

ECOG, Eastern Cooperative Oncology Group; IPI, ipilimumab; NIVO, nivolumab; ORR, objective response rate; PFS, progression-free survival; PS, performance status; PST, prior systemic therapy; q2w, every 2 weeks; q3w, every 3 weeks; RECIST, response evaluation criteria in solid tumors; SCC, squamous cell carcinoma.

Change From Baseline in Target Lesion Size





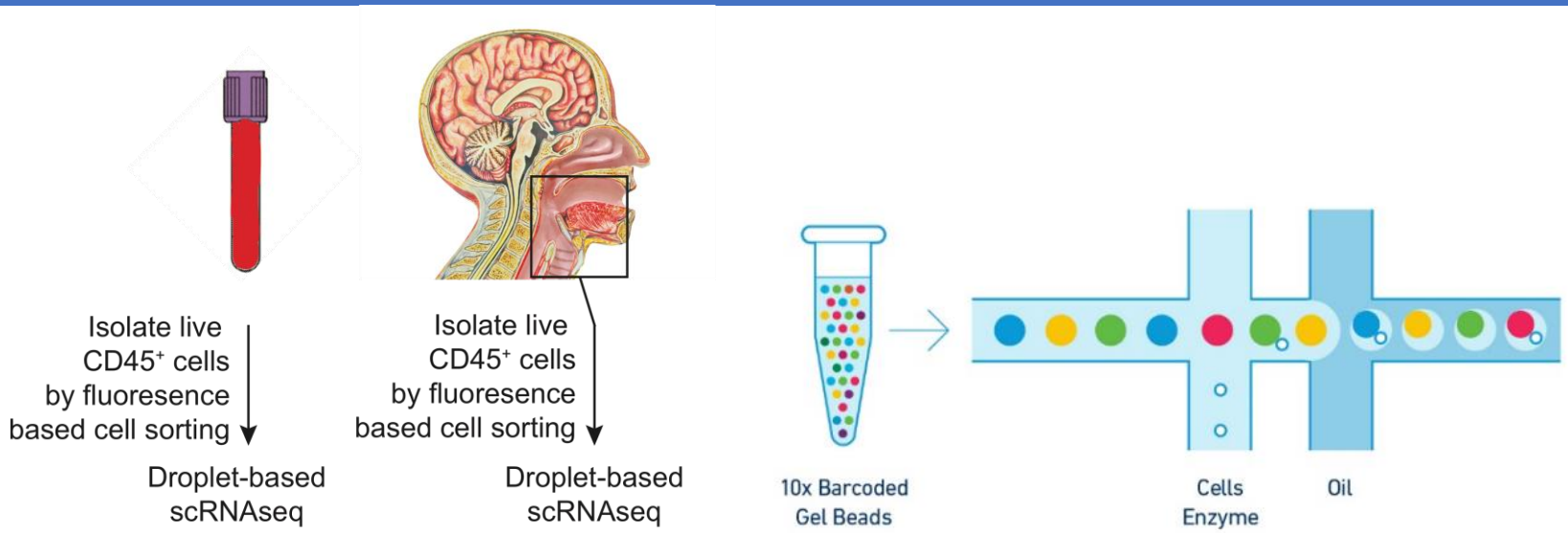
Bars with asterisks represent confirmed responses (complete or partial response).
PST, prior systemic therapy.

Tumor Response

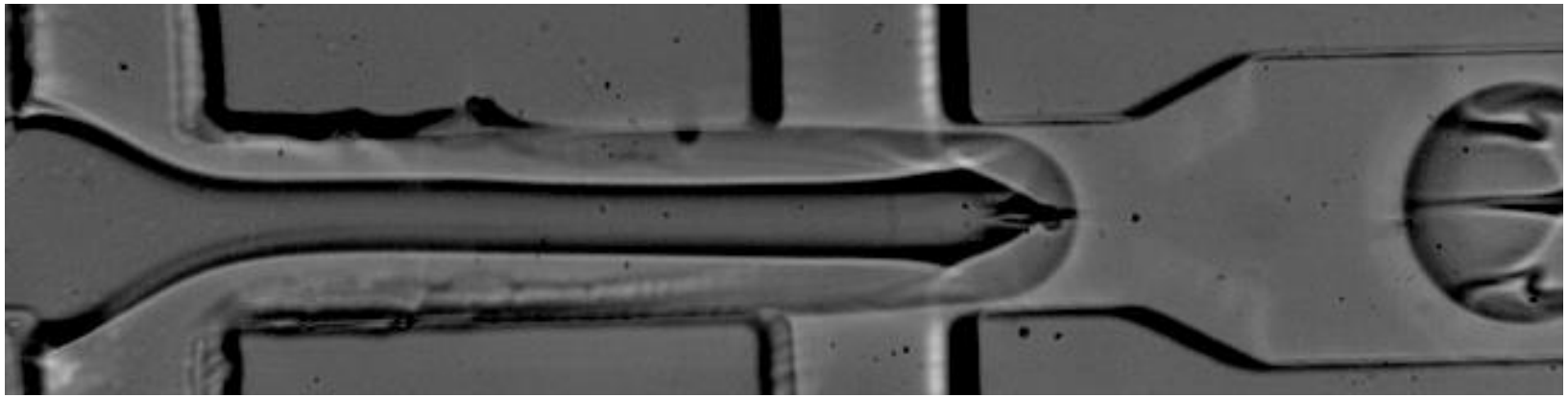
Response in all treated patients	NIVO3+IPI1		NIVO1+IPI3	
	No PST for R/M disease, n = 19	PST for R/M disease, n = 26	No PST for R/M disease, n = 24	PST for R/M disease, n = 22
ORR,* % (95% CI)	31.6 (12.6–56.6)	23.1 (9.0–43.6)	45.8 (25.6–67.2)	36.4 (17.2–59.3)
Clinical benefit rate,*† % (95% CI)	63.2 (38.4–83.7)	53.8 (33.4–73.4)	70.8 (48.9–87.4)	72.7 (49.8–89.3)
Best overall response*				
Complete response	3 (15.8)	1 (3.8)	1 (4.2)	3 (13.6)
Partial response	3 (15.8)	5 (19.2)	10 (41.7)	5 (22.7)
Stable disease	6 (31.6)	8 (30.8)	6 (25.0)	8 (36.4)
Progressive disease	7 (36.8)	11 (42.3)	6 (25.0)	5 (22.7)
Duration of response, median, mo (95% CI)	NR (6.6–NR)	14.6 (7.5–NR)	NR (4.6–NR)	9.5 (1.9–NR)
ORR by tumor cell PD-L1 expression,‡				
PD-L1 ≥1%, # responders/# treated (%) [95% CI]	4/13 (30.8) [9.1–61.4]	4/10 (40.0) [12.2–73.8]	4/11 (36.4) [10.9–69.2]	2/12 (16.7) [2.1–48.4]
PD-L1 <1%, # responders/# treated (%) [95% CI]	1/3 (33.3) [0.8–90.6]	1/11 (9.1) [0.2–41.3]	0/4 (0) [0.0–60.2]	4/7 (57.1) [18.4–90.1]

* Responses could not be determined in 1 patient with PST in NIVO3+IPI1 and in 1 patient each with and without PST in NIVO1+IPI3. † Proportion of patients with a complete response, a partial response, or stable disease. ‡ Tumor cell PD-L1 expression was defined as the percentage of tumor cells exhibiting plasma membrane staining at any intensity.
CI, confidence interval; NR, not reached; PST, prior systemic therapy.

Single-cell RNAseq to assess the immune landscape of HNSCC



- Paired PBMC and TIL from…
  - 18 patients with HPV⁻ disease
  - 7 patients with HPV⁺ disease
- 5 tonsils (sleep apnea patients)
- 6 healthy donor PBMC



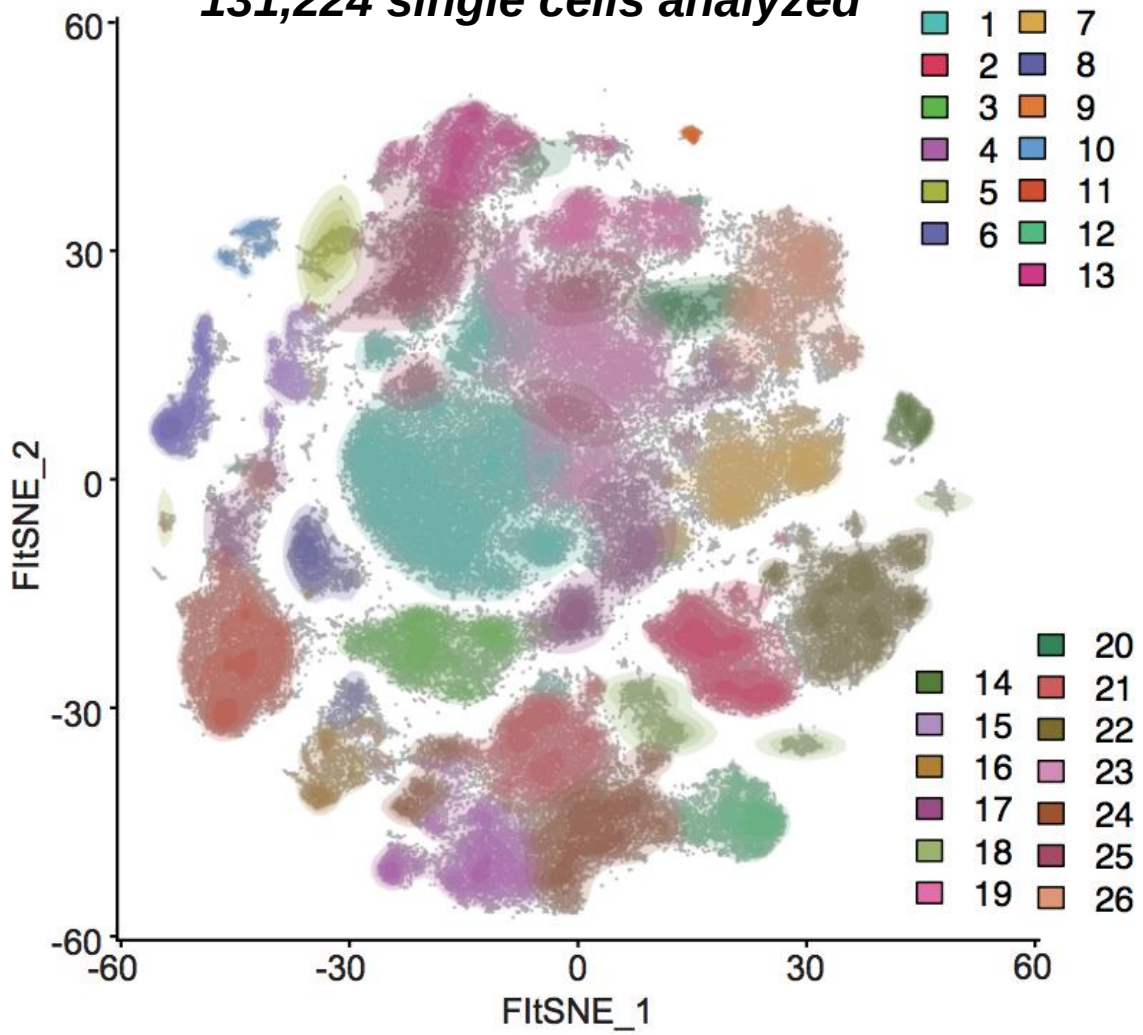
Patrick Stumpf, Matthew Rose-Zerilli, Rosanna Smith, Martin Fischlechner & Jonathan West Centre for Hybrid Biodevices & Cancer Sciences Unit University of Southampton

Overall visualization and clustering of all cells

scRNAseq Bioinformatics pipeline

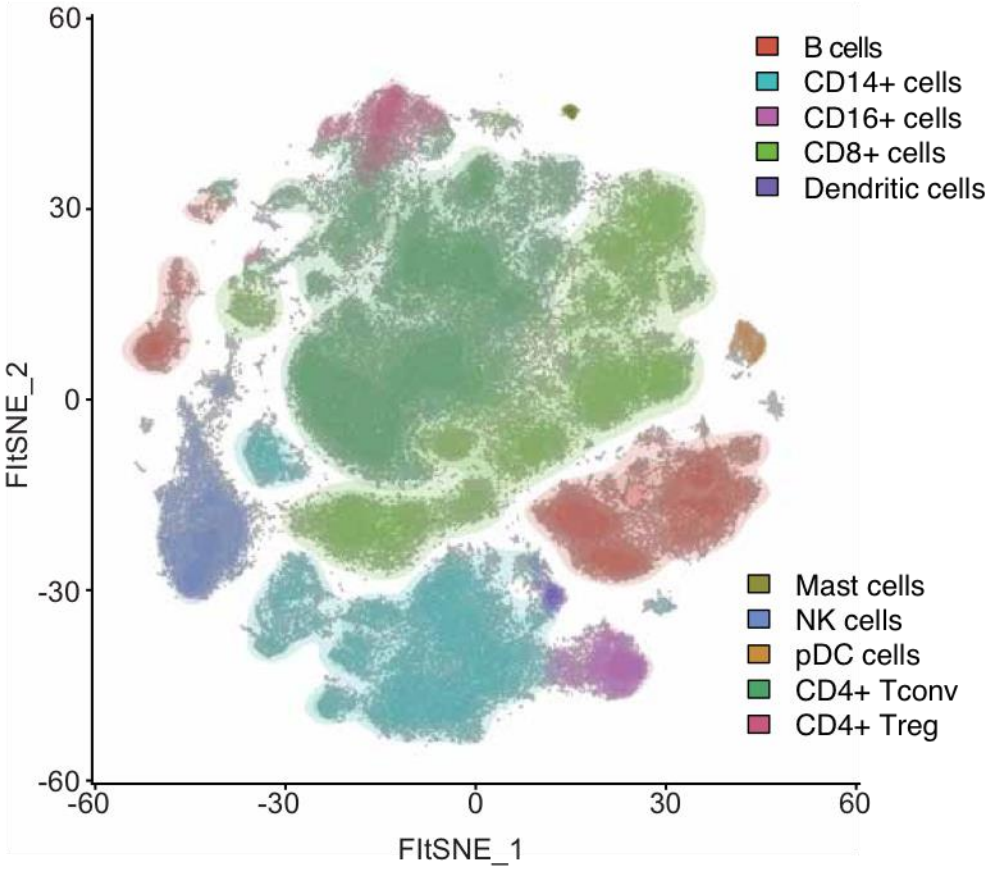
- Dimensionality reduction
  - Normalize expression for library size and regress out technical variables
  - Principal component analysis
- Visualization
  - Fast Fourier transform- accelerated interpolation-based tSNE (FItSNE)
- Clustering
  - DeteRministic Annealing Gaussian mixture mOdel for clusteriNg (**DRAGON**)
  - Check out the algorithm on github: https://github.com/arc85/dragonsc
- Biological inference
  - Differential gene expression
  - Gene set enrichment analysis
  - Diffusion pseudotime analysis
  - Cell-cell communication

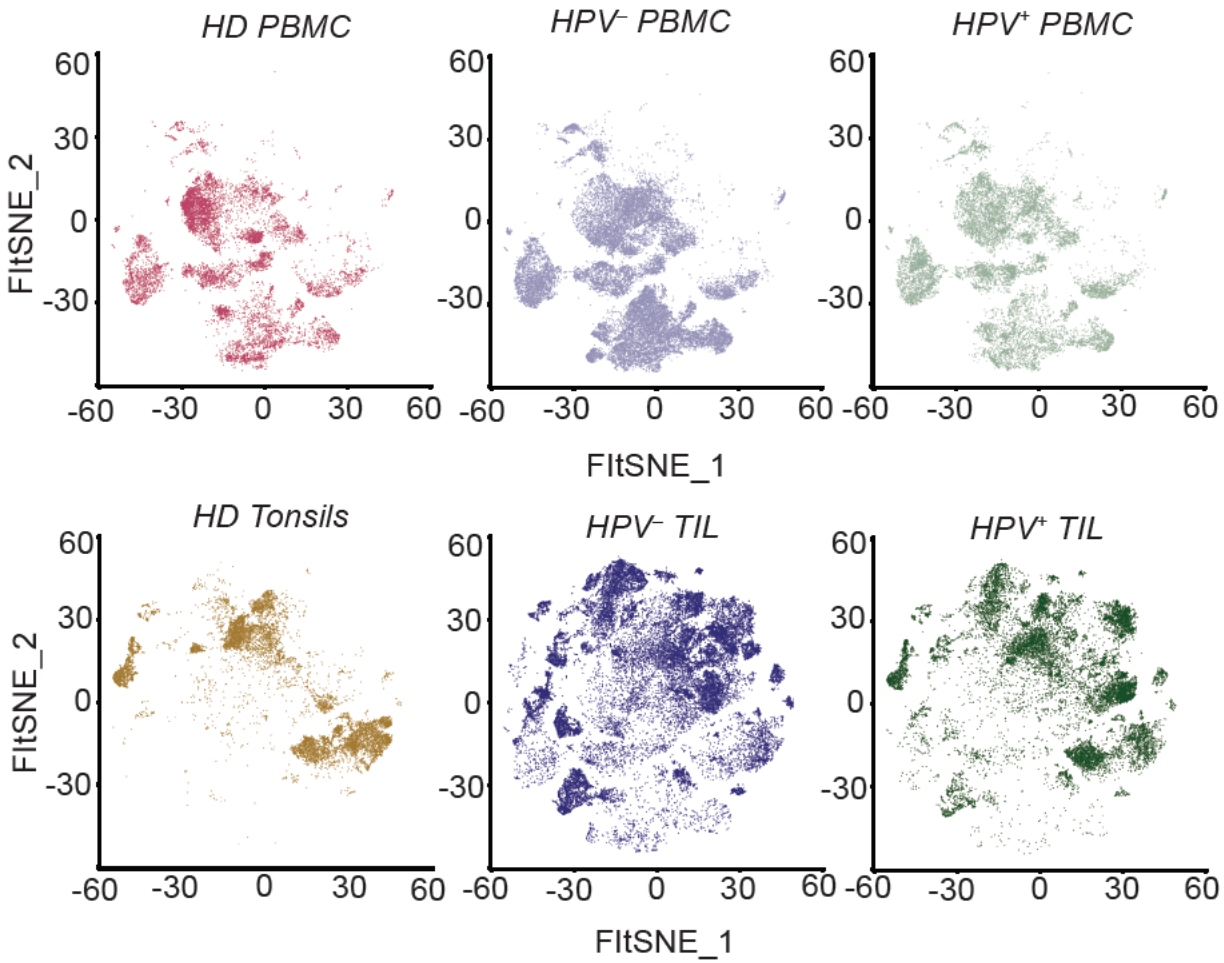
26 clusters by DRAGON
131,224 single cells analyzed



Cillo, *Immunity*, 2019

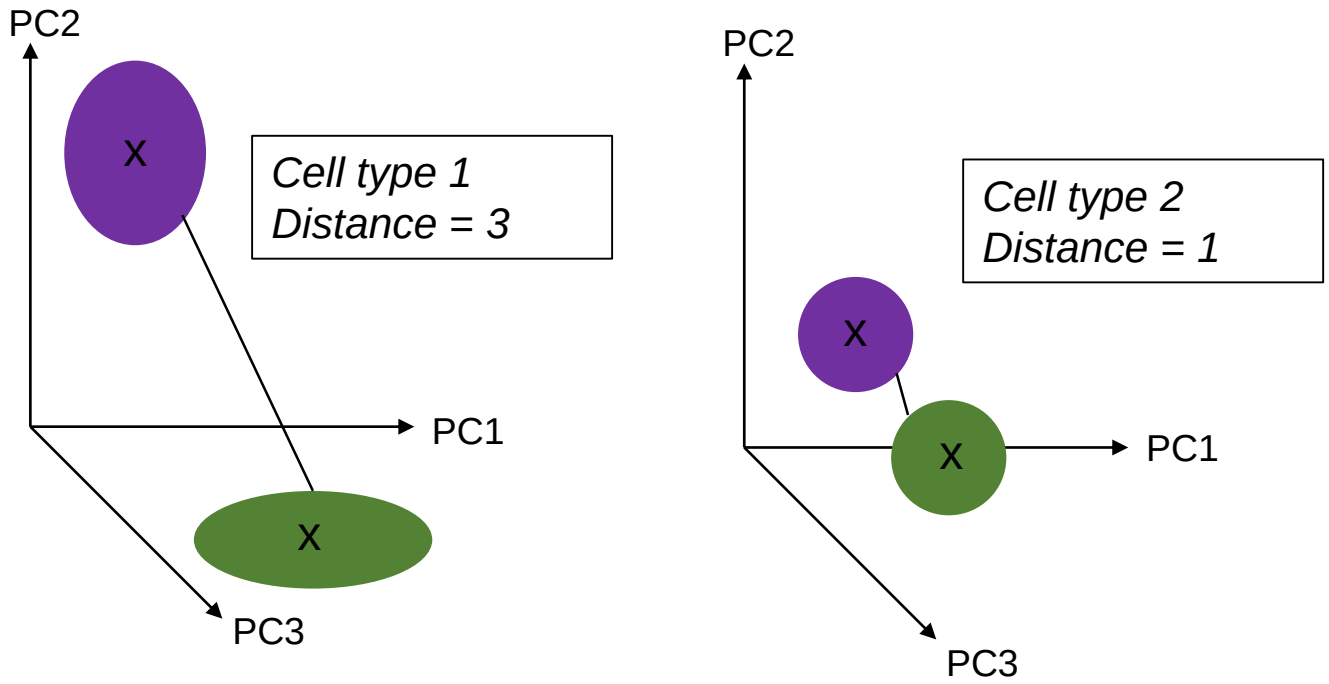
Identification of major immune lineages and distribution across sample types





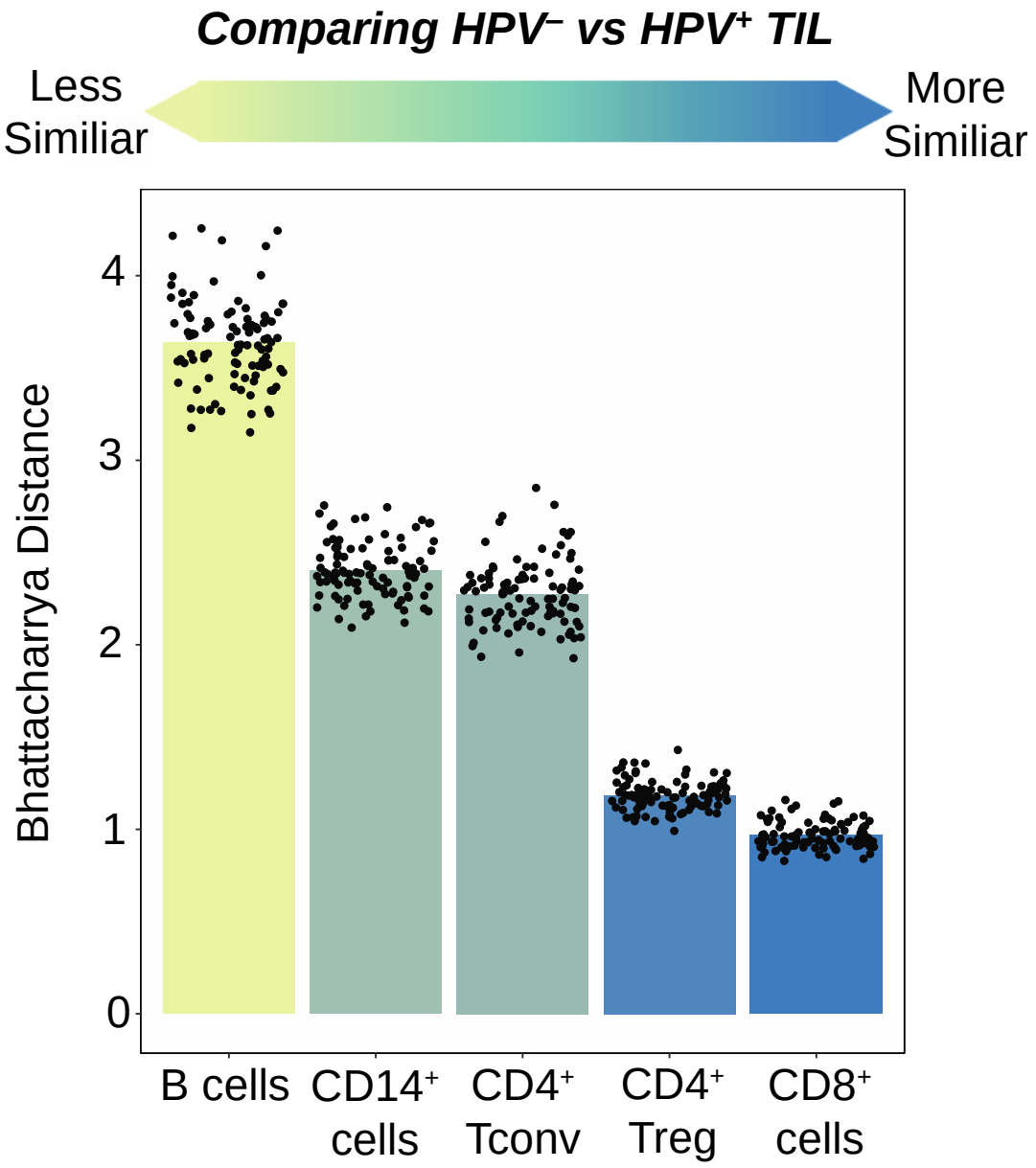
Cillo, *Immunity*, 2019

Quantifying differences in immune lineages between HPV⁻ and HPV⁺ HNSCC

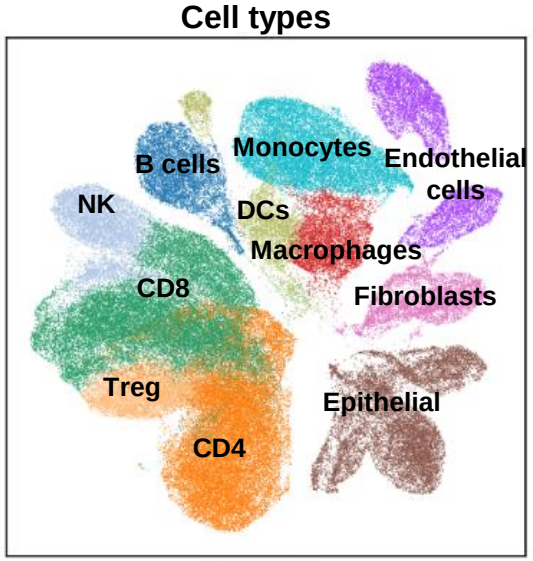


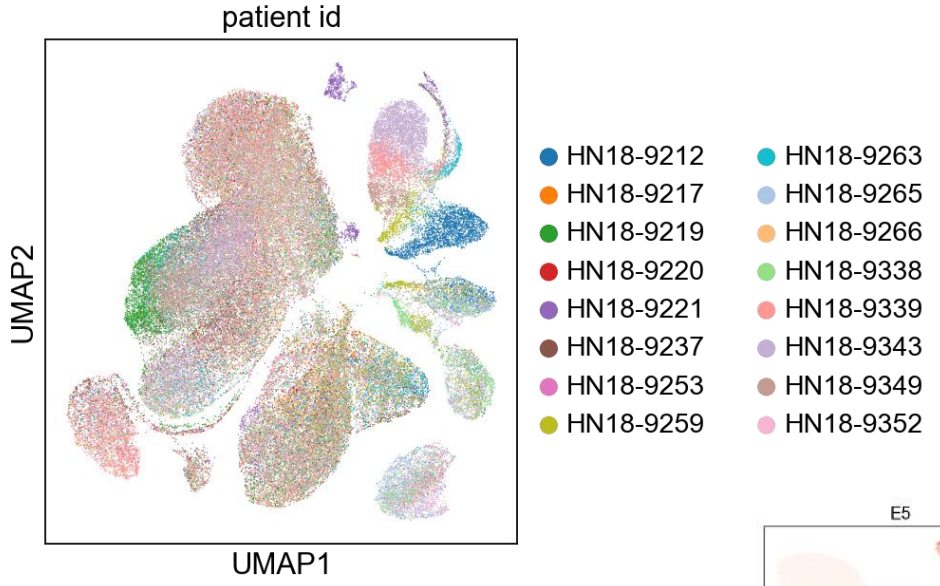
- Distance between distributions is known as the Bhattacharrya Distance (BD)
- Sub-sampled 500 cells from both HPV⁻ and HPV⁺ HNSCC 100 times to estimate distribution of the BD
- Greater BD = greater difference between populations

Cillo, *Immunity*, 2019



Cell type identification using scRNAseq

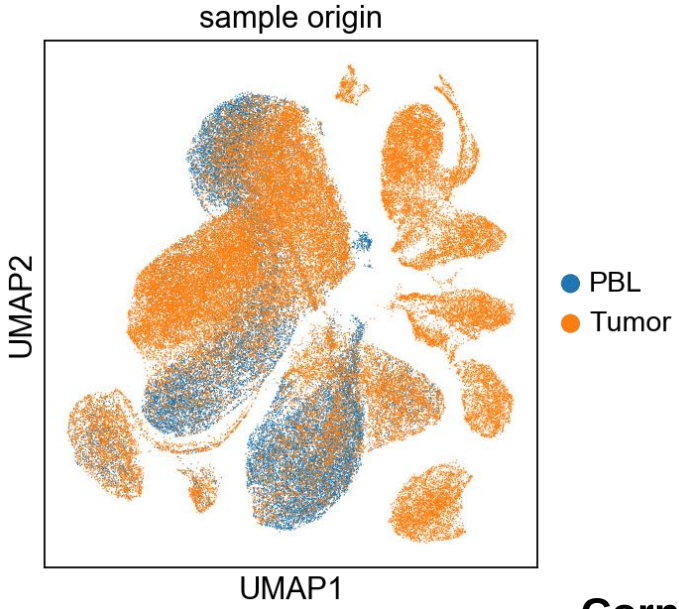


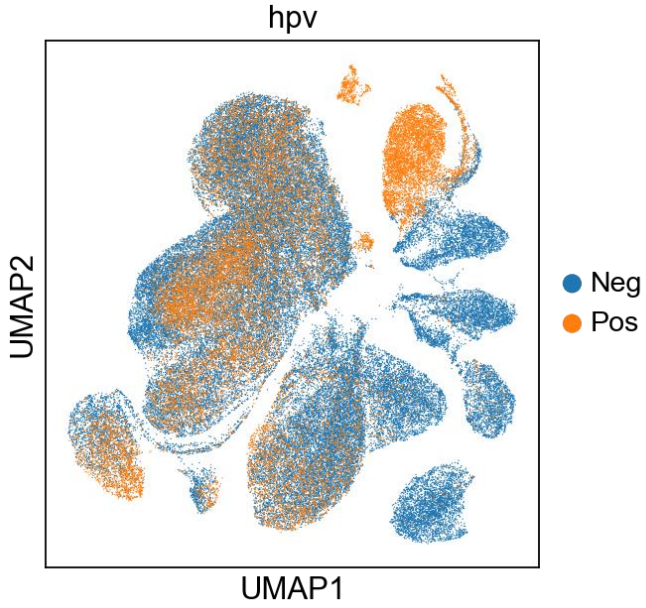


Paired PBMC and TIL from…

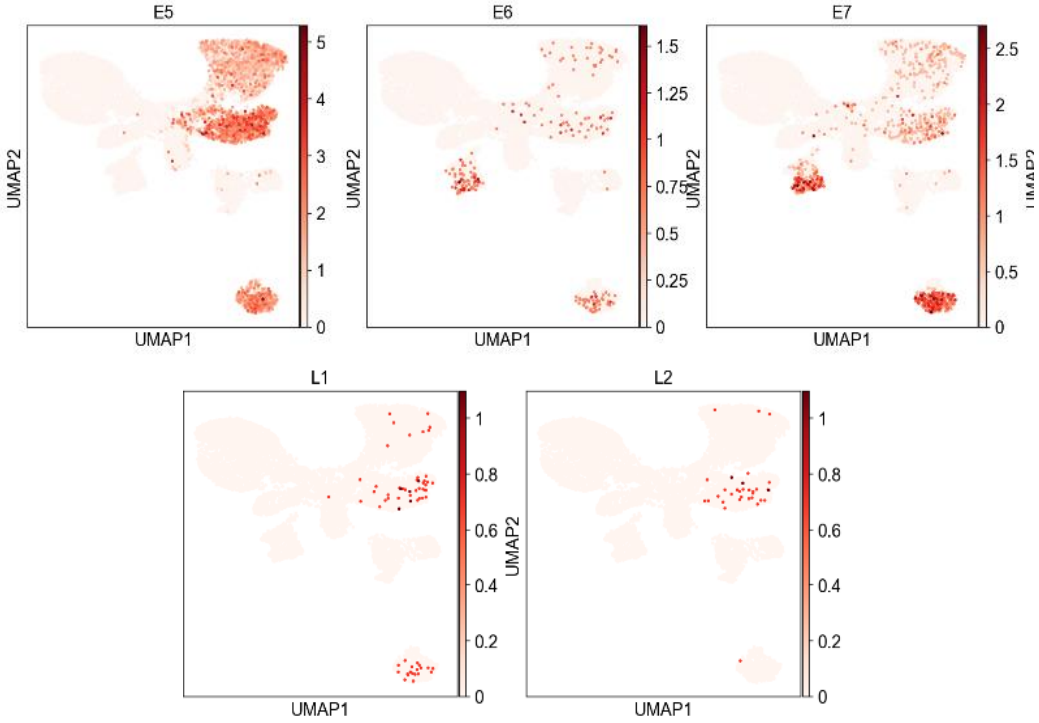
17 patients with HPV⁻ disease

5 patients with HPV⁺ disease



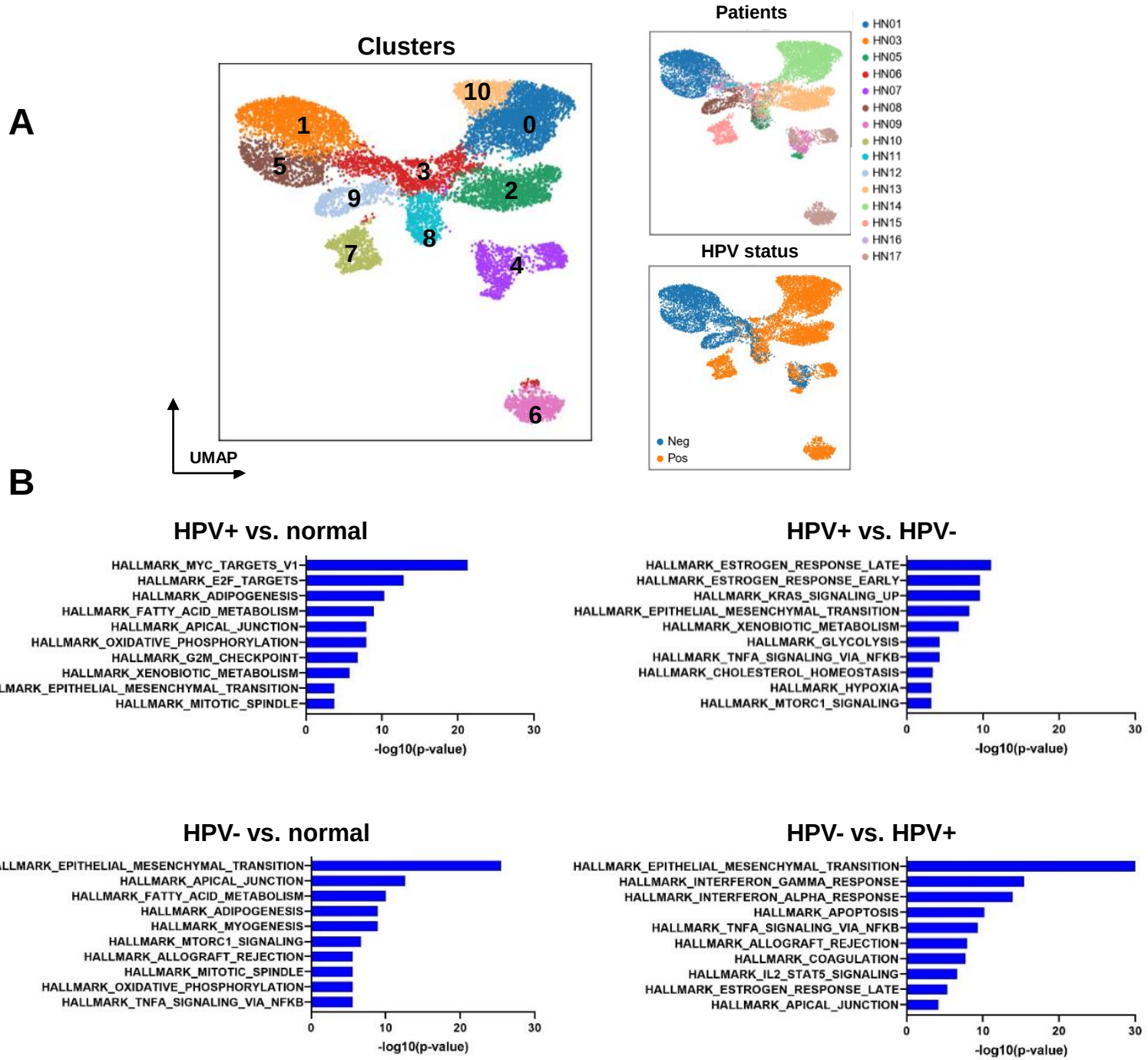


Mapping HPV gene expression



Cornelius Kurten, Aditi Kulkarni, Lazar Vujanovic

Cellular subsets and expression patterns in the HPV+ TME



Summary

- HPV+ Oropharyngeal cancer rising 300% over past 30 yr
- Acute and long-term toxicity in a younger HPV+ group warrants re-evaluation of traditional therapeutic approach
- Immunotherapy of HPV+/- HNSCC is clinically effective and will transform our standard modalities
- Global single cell profiling may provide insights into responders and nonresponders

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