PDS0101 in HPV16+ Head and Neck Cancer KOL Roundtable

NASDAQ: PDSB

PDS Biotechnology

Precision Designed Science For Immunotherapy

October 3, 2023

Forward Looking Statements

Certain information in this presentation may include forward-looking statements (including within the meaning of Section 21E of the United States Securities Exchange Act of 1934, as amended, and Section 27A of the United States Securities Act of 1933, as amended) concerning PDS Biotechnology Corporation (the "Company") and other matters. These statements may discuss goals, intentions and expectations as to future plans, trends, events, results of operations or financial condition, or otherwise, based on current beliefs of the Company's management, as well as assumptions made by, and information currently available to, management. Forward-looking statements generally include statements that are predictive in nature and depend upon or refer to future events or conditions, and include words such as "may," "will," "should," "would," "expect," "anticipate," "plan," "likely," "believe," "estimate," "project," "intend," "forecast," "guidance", "outlook" and other similar expressions. Forward-looking statements are based on current beliefs and assumptions that are subject to risks and uncertainties and are not guarantees of future performance. Actual results could differ materially from those contained in any forward-looking statement as a result of various factors, including, without limitation: the Company's ability to protect its intellectual property rights; the Company's anticipated capital requirements, including the Company's anticipated cash runway and the Company's current expectations regarding its plans for future equity financings; the Company's dependence on additional financing to fund its operations and complete the development and commercialization of its product candidates, and the risks that raising such additional capital may restrict the Company's operations or require the Company to relinquish rights to the Company's technologies or product candidates; the Company's limited operating history in the Company's current line of business, which makes it difficult to evaluate the Company's prospects, the Company's business plan or the likelihood of the Company's successful implementation of such business plan; the timing for the Company or its partners to initiate the planned clinical trials for PDS0101, PDS0203 and other Versamune® and Infectimune® based product candidates; the future success of such trials; the successful implementation of the Company's research and development programs and collaborations, including any collaboration studies concerning PDS0101, PDS0203 and other Versamune® and Infectimune® based product candidates and the Company's interpretation of the results and findings of such programs and collaborations and whether such results are sufficient to support the future success of the Company's product candidates; the success, timing and cost of the Company's ongoing clinical trials and anticipated clinical trials for the Company's current product candidates, including statements regarding the timing of initiation, pace of enrollment and completion of the trials (including the Company's ability to fully fund its disclosed clinical trials, which assumes no material changes to our currently projected expenses), futility analyses, presentations at conferences and data reported in an abstract, and receipt of interim or preliminary results (including, without limitation, any preclinical results or data), which are not necessarily indicative of the final results of the Company's ongoing clinical trials; the timing of and the Company's ability to obtain and maintain U.S. Food and Drug Administration or other regulatory authority approval of, or other action with respect to, PDS0101, PDS0203 and other Versamune® and Infectimune® based product candidates; any Company statements about its understanding of product candidates mechanisms of action and interpretation of preclinical and early clinical results from its clinical development programs and any collaboration studies; and other factors, including legislative, regulatory, political and economic developments not within the Company's control, including unforeseen circumstances or other disruptions to normal business operations arising from or related to COVID-19. The foregoing review of important factors that could cause actual events to differ from expectations should not be construed as exhaustive and should be read in conjunction with statements that are included herein and elsewhere, including the risk factors included in the Company's annual and periodic reports filed with the SEC. The forward-looking statements are made only as of the date of this press release and, except as required by applicable law, the Company undertakes no obligation to revise or update any forward-looking statement, or to make any other forward-looking statements, whether as a result of new information, future events or otherwise.

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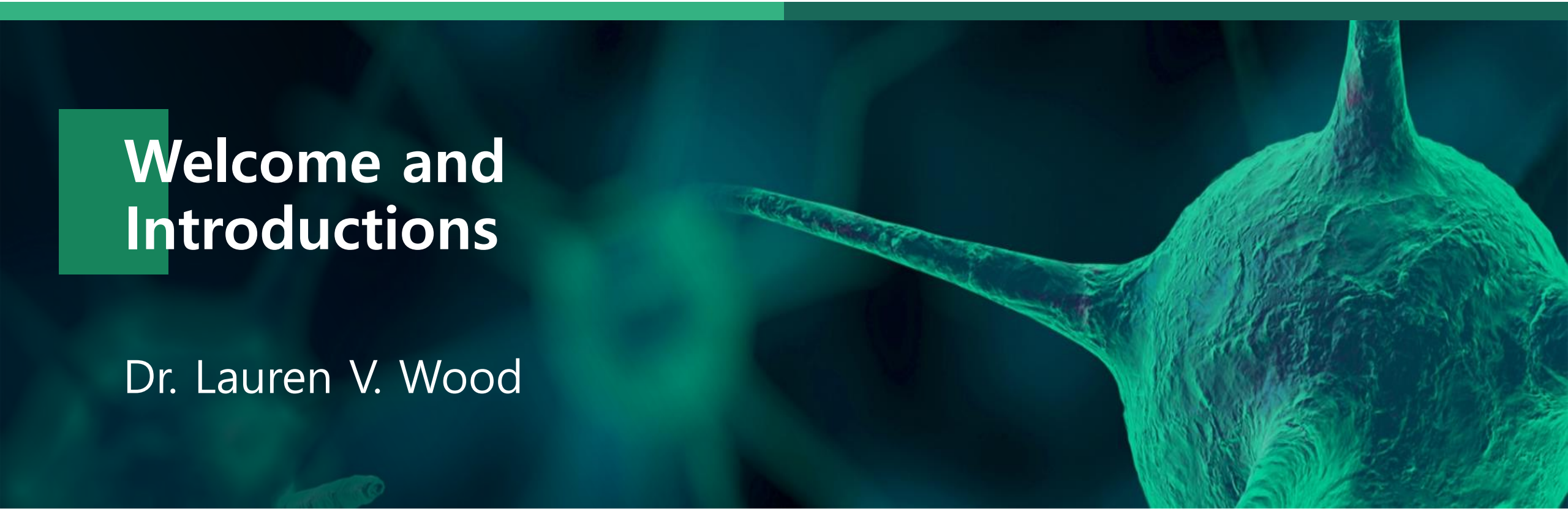
- Each panelist is speaking on behalf of PDS Biotech under the terms of a consulting agreement
- Information presented is consistent with FDA regulations and guidelines

Welcome and Introductions

Dr. Lauren V. Wood



Introducing Our Panel

Dr. Ricard Mesía
Head of Medical Oncology
Catalan Institute of Oncology

Dr. John Kaczmar
Associate Professor Medical
University of South Carolina

Dr. Katharine Price
Associate Professor
Mayo Clinic Comprehensive
Cancer Center

Dr. Glenn Hanna
Assistant Professor, Harvard
University and Medical
Oncologist, Dana-Farber
Cancer Institute

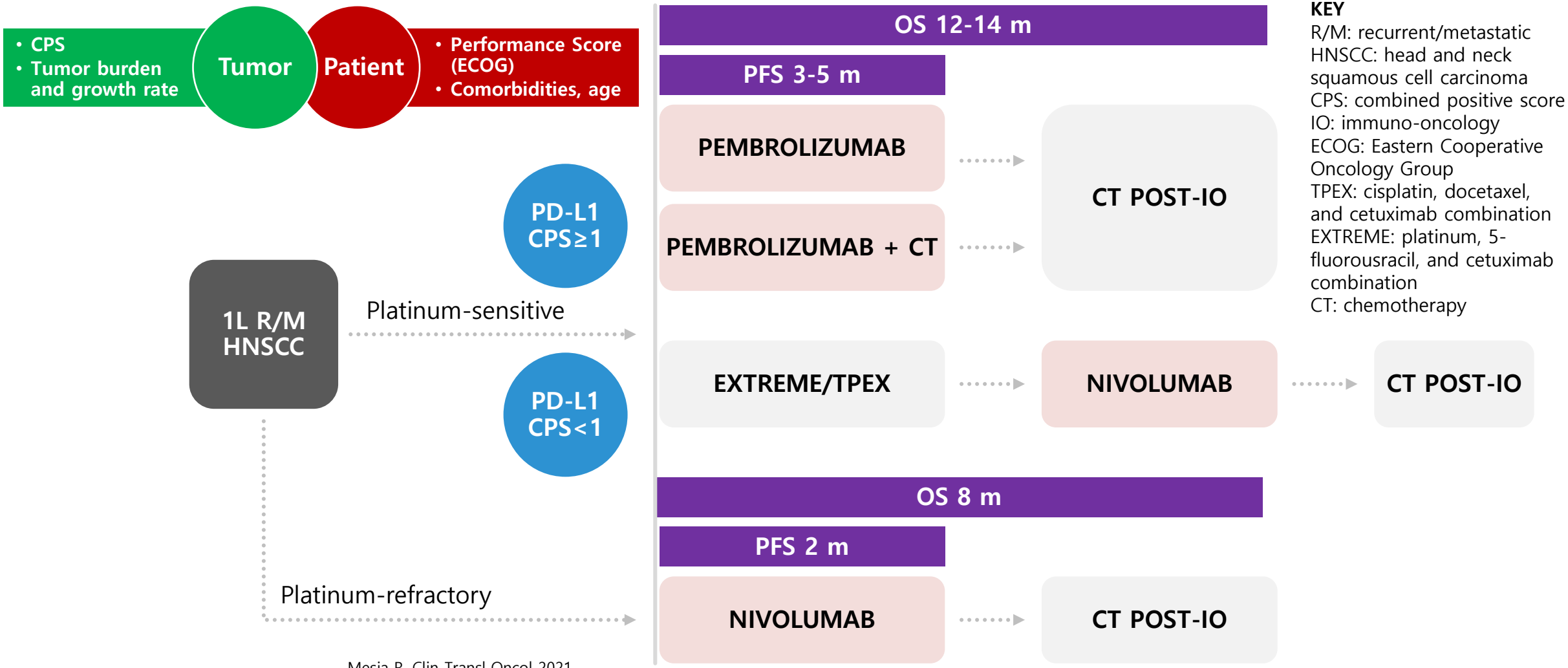
Today's Agenda

Welcome and Introductions	Dr. Lauren V. Wood
Current Treatment of HPV16+ HNSCC and Unmet Needs	Dr. Ricard Mesía
PDS0101 for the Treatment of HPV16+ HNSCC Data to Date	Dr. John Kaczmar
Plans for Phase 3 Study	Dr. Katharine Price
Emerging Use of ctDNA in Treatment of HPV+ HNSCC	Dr. Glenn Hanna
PDS0101 + KEYTRUDA® in ICI Refractory Subjects	Dr. Lauren V. Wood
Panel Discussion (including Q&A from audience)	Moderator: Dr. Lauren V. Wood
Closing Remarks	Dr. Lauren V. Wood

Current Treatment of HPV16+ HNSCC and Unmet Needs

Dr. Ricard Mesía

Standard-of-Care in Recurrent/Metastatic HNSCC: ECOG 0-1

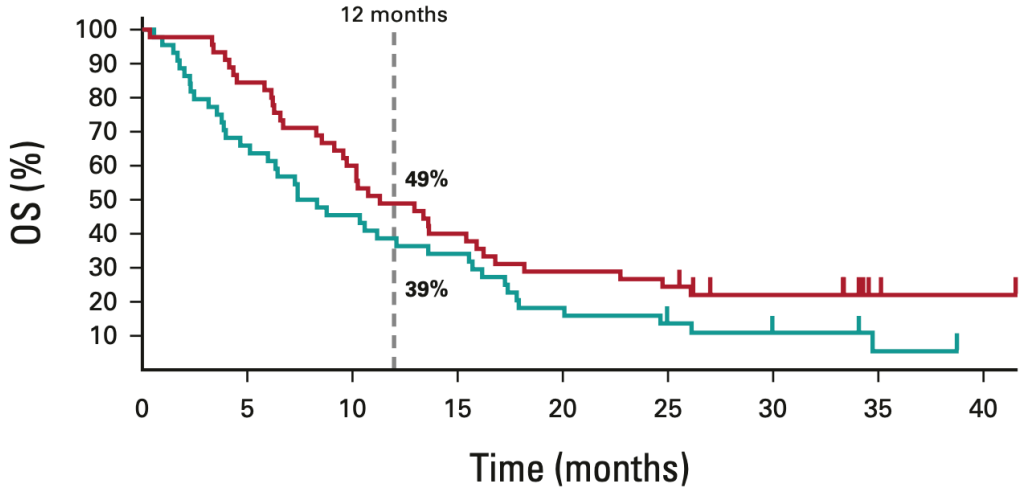


KEY
R/M: recurrent/metastatic
HNSCC: head and neck squamous cell carcinoma
CPS: combined positive score
IO: immuno-oncology
ECOG: Eastern Cooperative Oncology Group
TPEX: cisplatin, docetaxel, and cetuximab combination
EXTREME: platinum, 5-fluorousracil, and cetuximab combination
CT: chemotherapy

Mesia R, Clin Transl Oncol 2021
Ferris RL, et al. *NEJM*. 2016;375:1856-67
Burtness B et al., *Lancet*. 2019; 394:1915-1928

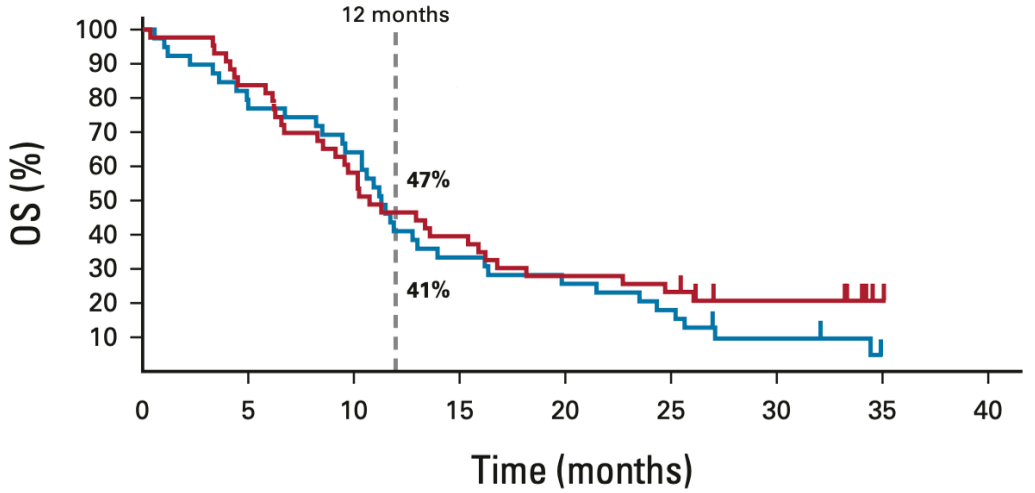
What Happened with CPS<1?

Pembrolizumab vs EXTREME



CPS < 1	No. of Events/ No. of Patients (%)	Median OS, Months (95% CI)[a]	HR (95% CI)[b]	Nominal *P*[c]
Pembrolizumab	40/44 (90.9)	7.9 (4.7 to 13.6)	1.51 (0.96 to 2.37)	.96241
Cetuximab-chemotherapy	35/45 (77.8)	11.3 (9.1 to 15.9)		

Pembrolizumab + CT vs EXTREME



CPS < 1	No. of Events/ No. of Patients (%)	Median OS, Months (95% CI)[a]	HR (95% CI)[b]	Nominal *P*[c]
Pembrolizumab-chemotherapy	36/39 (92.3)	11.3 (9.5 to 14.0)	1.21 (0.76 to 1.94)	.78932
Cetuximab-chemotherapy	34/43 (79.1)	10.7 (8.5 to 15.9)		

CPS < 1: pembrolizumab alone is detrimental and pembrolizumab + CT is not superior

CT: chemotherapy

Burtness B, et al. *J Clin Oncol.* 2022.

Baseline Characteristics, KEYNOTE-048

Characteristic, n (%)	Pembrolizumab Alone vs EXTREME		Pembrolizumab + Chemo vs EXTREME	
	Pembro N = 301	EXTREME N = 300	Pembro + Chemo N = 281	EXTREME N = 278[a]
Age, median (range), years	62 (22-94)	61 (24-84)	61 (20-85)	61 (24-84)
Male	250 (83.1)	261 (87.0)	224 (79.7)	242 (87.1)
ECOG PS 1	183 (60.8)	183 (61.0)	171 (60.9)	170 (61.2)
Current/former smoker	239 (79.4)	234 (78.0)	224 (79.7)	215 (77.3)
p16 positive (oropharynx)	63 (20.9)	67 (22.3)	60 (21.4)	61 (21.9)
Sum of target lesions, median (range), mm	54.1 (10-430)	58.7 (10-419)	67.3 (12-385)	58.7 (10-419)
PD-L1 status				
TPS ≥50%	67 (22.3)	66 (22.0)	66 (23.5)	62 (22.3)
CPS ≥20	133 (44.2)	122 (40.7)	126 (44.8)	110 (39.6)
CPS ≥1	257 (85.4)	255 (85.0)	242 (86.1)	235 (84.5)
Disease status[b]				
Metastatic	261 (71.8)	203 (67.7)	201 (71.5)	187 (67.3)
Recurrent only	82 (27.2)	94 (31.3)	76 (27.0)	88 (31.7)

Burtness B et al., *Lancet*. 2019; 394:1915-1928

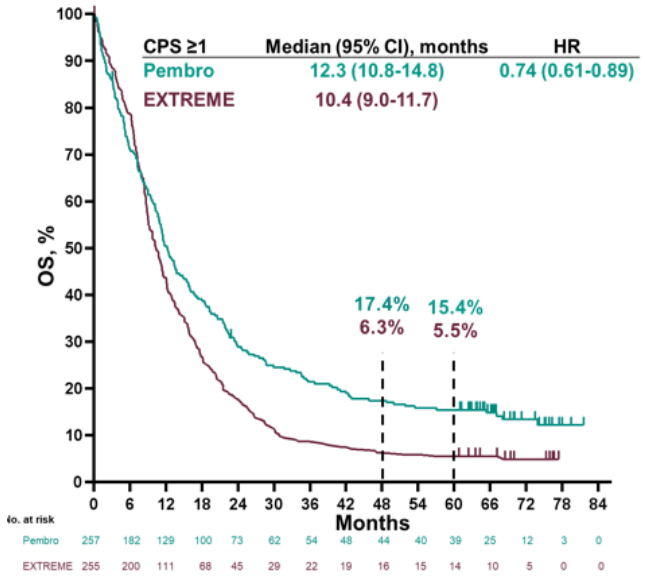
The Actual Goals of Therapy in Recurrent/Metastatic Disease

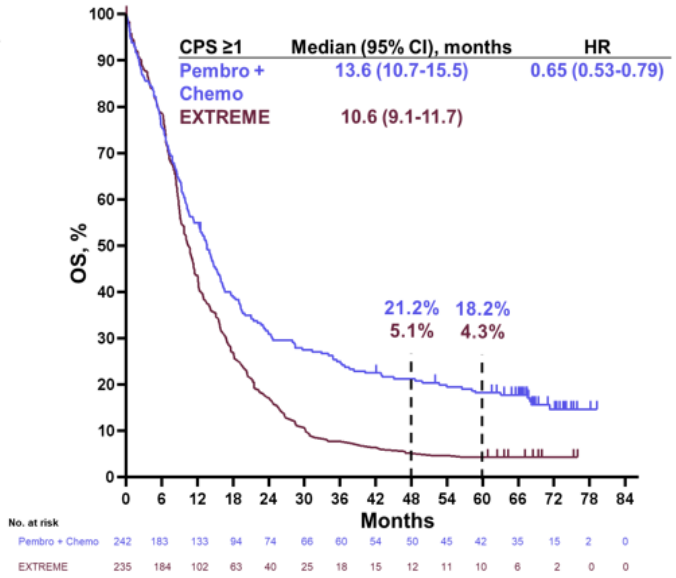
Recurrent/Metastatic

Treatment Goal

Palliative intent = Only???

- ↑ Survival
- ↑ Response rates
- ↑ Symptom control
- ↑ QoL





5-yr OS: 15-18% with IOsin CPS≥1

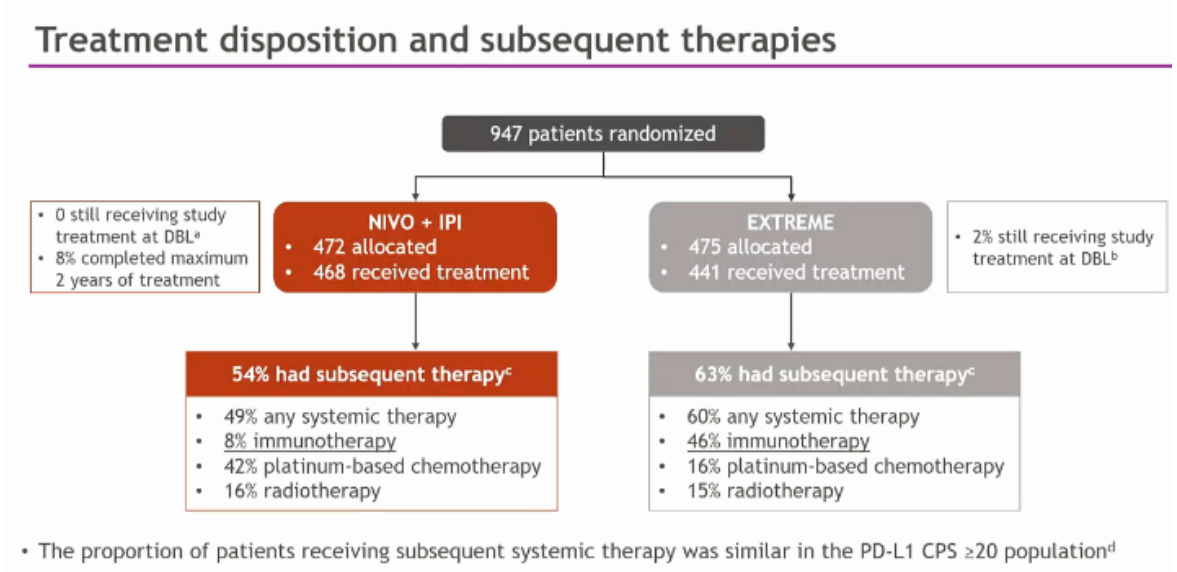
Improve long-survivors rate
The complete cure of the recurrent/metastatic patient?

IO: immuno-oncology therapy

1. Tahara M ESMO 2022

Treatment After 1st Line Recurrent/Metastatic: Expectations

n (%)	Pembro Monotherapy n = 301	Pembro + Chemotherapy n = 281	EXTREME n = 300
Any new anticancer treatment[a]	148 (49.2)	115 (40.9)	159 (53.0)
Chemotherapy	135 (44.9)	88 (31.3)	102 (34.0)
EGFR inhibitor	59 (19.6)	37 (13.2)	19 (6.3)
Immune checkpoint inhibitor	6 (2.0)	12 (4.3)	50 (16.7)
Other immunotherapy	1 (0.3)	0 (0.0)	6 (2.0)
Kinase inhibitor	1 (0.3)	7 (2.5)	1 (0.3)
Other	2 (0.7)	1 (0.4)	2 (0.7)

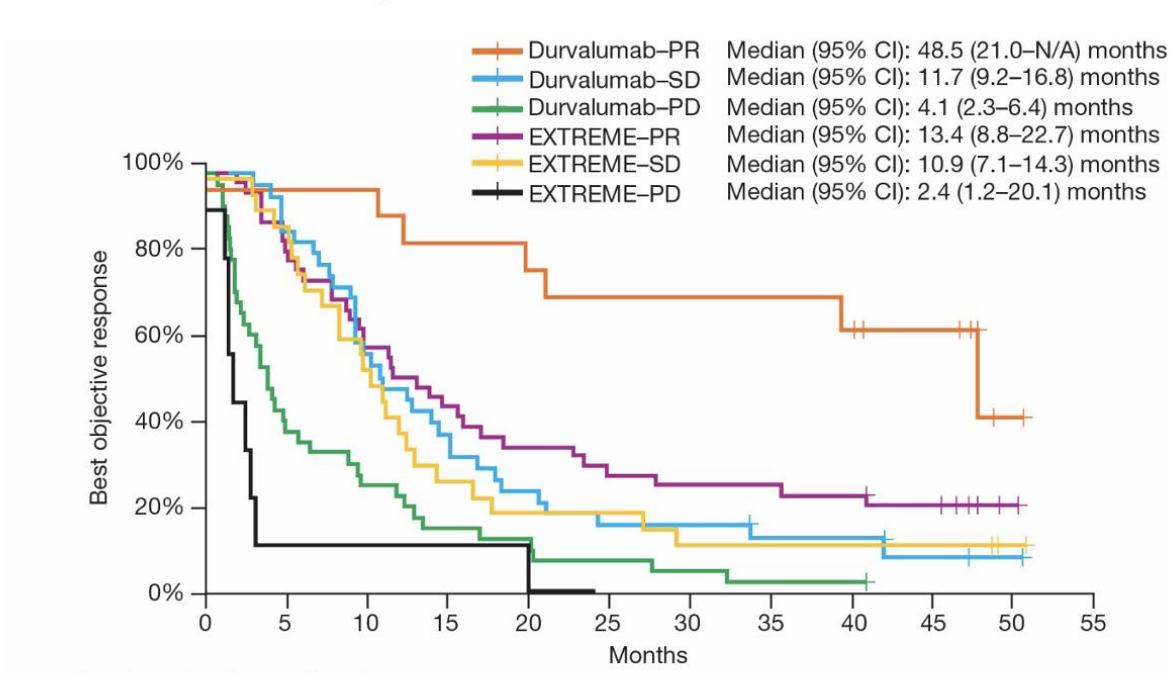


Only 50 to 60% will receive a second line therapy based on what, they received first

Harrington K. et al. ASCO Annual meeting 2020
Haddad *J Clin Oncol* 2023

Treatment After 1st Line Recurrent/Metastatic: Expectations

mOS Can Be Predicted by Response to First Line

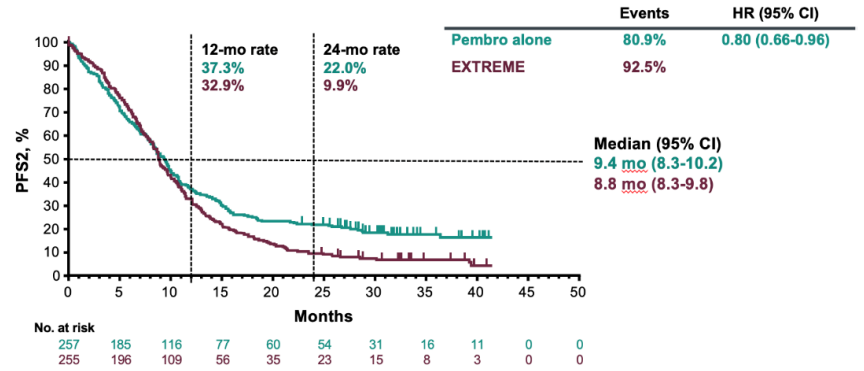


Number of patients still at risk

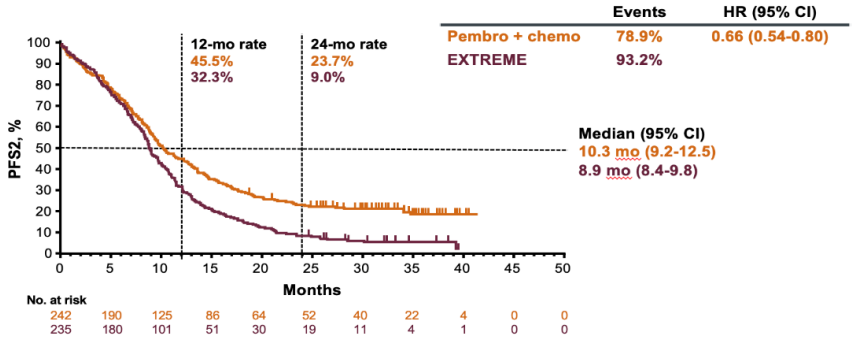
Durvalumab–PR	16	16	16	14	13	12	12	11	8	6	1	0
Durvalumab–SD	38	35	22	15	10	6	6	5	5	2	1	0
Durvalumab–PD	40	16	11	7	6	4	3	2	1	0	0	0
EXTREME–PR	44	36	26	20	16	13	12	12	10	8	1	0
EXTREME–SD	27	24	15	8	6	6	4	3	3	3	1	0
EXTREME–PD	9	2	2	2	2	0	0	0	0	0	0	0

mPFS to 2L May Range Between 3-6m

PFS2: Initially Randomized, Pembro vs EXTREME, CPS ≥1 Population



PFS2: Initially Randomized, Pembro + Chemotherapy vs EXTREME, CPS ≥1 Population



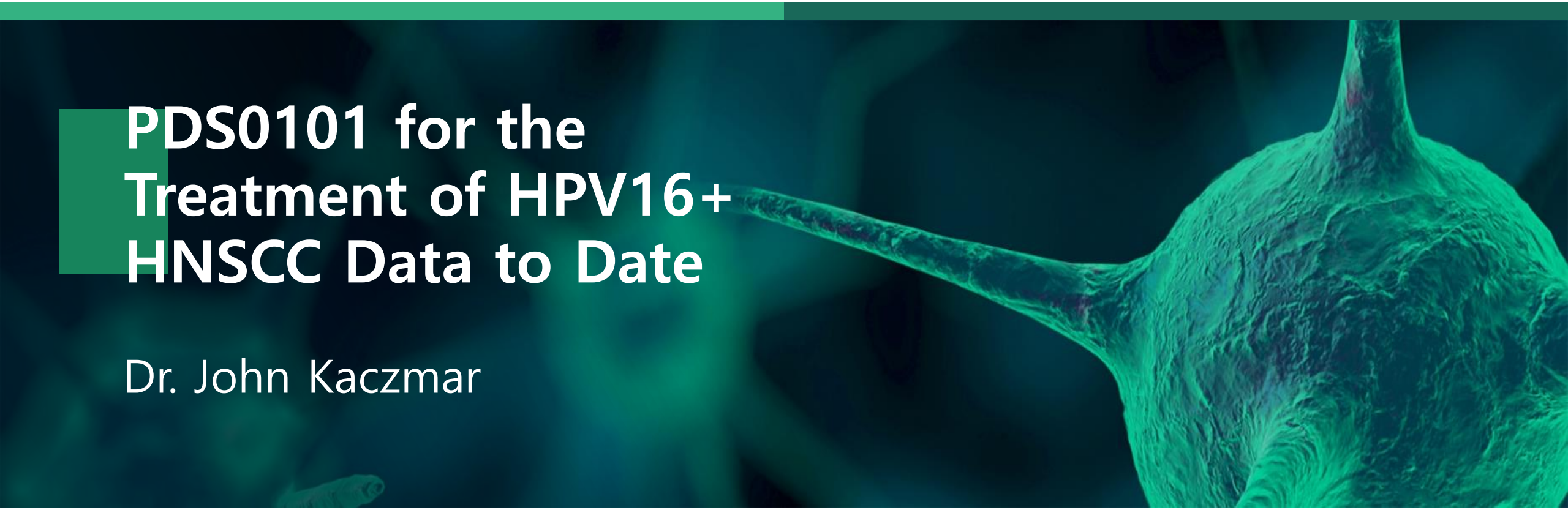
Psyrri A. et al. Annals of Oncology, 2023, Harrington K. et al. ASCO Annual meeting 2020

Unmet Needs in 1st Line Recurrent/Metastatic – HPV16+

- To improve the rate of long-term survival
- To reduce the toxicity of the actual treatments, to improve QoL
- To define the best sequence of treatment for specific HPV-related patients with recurrent/metastatic disease. The best option of treatment should be administered in 1st line, because up to 50% may not receive a 2nd line
- To date standard of care chemotherapy or IOs alone is not enough in most of HPV-related HNSCC

HNSCC: Head and neck squamous cell carcinoma
IO: Immuno-oncology therapy

PDS0101 for the Treatment of HPV16+ HNSCC Data to Date



Dr. John Kaczmar

VERSATILE-002 Key Goal: Improve Survival with PDS0101 Targeted Immunotherapy

- Overall Survival with KEYTRUDA® or KEYTRUDA® + chemo is only 12–14 months in KEYNOTE-048
  - 24-month survival rate with KEYTRUDA® or KEYTRUDA® + chemo is only 29% - 31% in KEYNOTE-048
- No difference in survival between HPV-positive and -negative patients in the recurrent/metastatic setting
- There is no specific therapy targeting the type of HPV which represents a majority of head and neck cancers
- Goal of PDS0101 is to target HPV16 to treat the disease and improve overall survival and enhance quality of life, while maintaining safety

Limitations: This presentation shows data from a snapshot of an ongoing study as of August 2, 2023. Final results may differ for reasons including: new outcomes from existing subjects, delays in data entry at the research site, ongoing monitoring and clarification of data queries.

Burtness B et al., *Lancet*. 2019; 394:1915-1928
Mehra R et al., *Br J Cancer* 2018; 119:153-159

VERSATILE-002 Phase 2 Clinical Trial

Objective: To Assess the Combination of PDS0101 and KEYTRUDA® in ICI Naïve Subjects with Recurrent or Metastatic HPV-positive HNSCC

Partner	FDA Approved Standard of Care	Study Design	Key Entry Criteria for ICI Naïve Subjects	Study Treatment	Endpoints
MERCK ***Fast Track Designation***	KEYTRUDA® (pembrolizumab)	Open-label, non-randomized, adaptive design study N=54 ***Enrollment complete***	Recurrent or metastatic HNSCC ≥18 years of age HPV16-Positive tumor Combined positive score (CPS) ≥1	Pembrolizumab 200mg IV Q3W up to 35 Cycles (2 years) PDS0101 1 mL subcutaneous injection at Cycles 1, 2, 3, 4 and 12	**Primary:** Best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR) per RECIST 1.1 **Key Secondary:** Progression Free Survival (PFS) per RECIST 1.1 Overall Survival (OS) Safety and tolerability ***Achievement of Statistical Threshold for efficacy***

VERSATILE-002 ICI Naïve
Key Demographics and Treatment Exposure

Majority of Patients Are CPS 1-19

Demographic	ITT Population (N=55)	mITT Population (N=52)
Age, Median (Min, Max)	64.0 (46, 83)	64.0 (46, 83)
Sex, n (%)		
Male	51 (92.7)	48 (92.3)
Female	4 (7.3)	4 (7.7)
Race, n (%)		
American Indian or Alaska Native	0	0
Asian	1 (1.8)	1 (1.9)
Black or African American	1 (1.8)	1 (1.9)
Pacific Islander	0	0
White	52 (94.5)	49 (94.2)
Other	1 (1.8)	1 (1.9)
ECOG, n (%)		
0	32 (58.2)	29 (55.8)
1	23 (41.8)	23 (44.2)
CPS, n (%)*		
<1	0	0
1–19	33 (60.0)	31 (59.6)
≥20	22 (40.0)	21 (40.4)

Treatment Exposure (ITT Population)

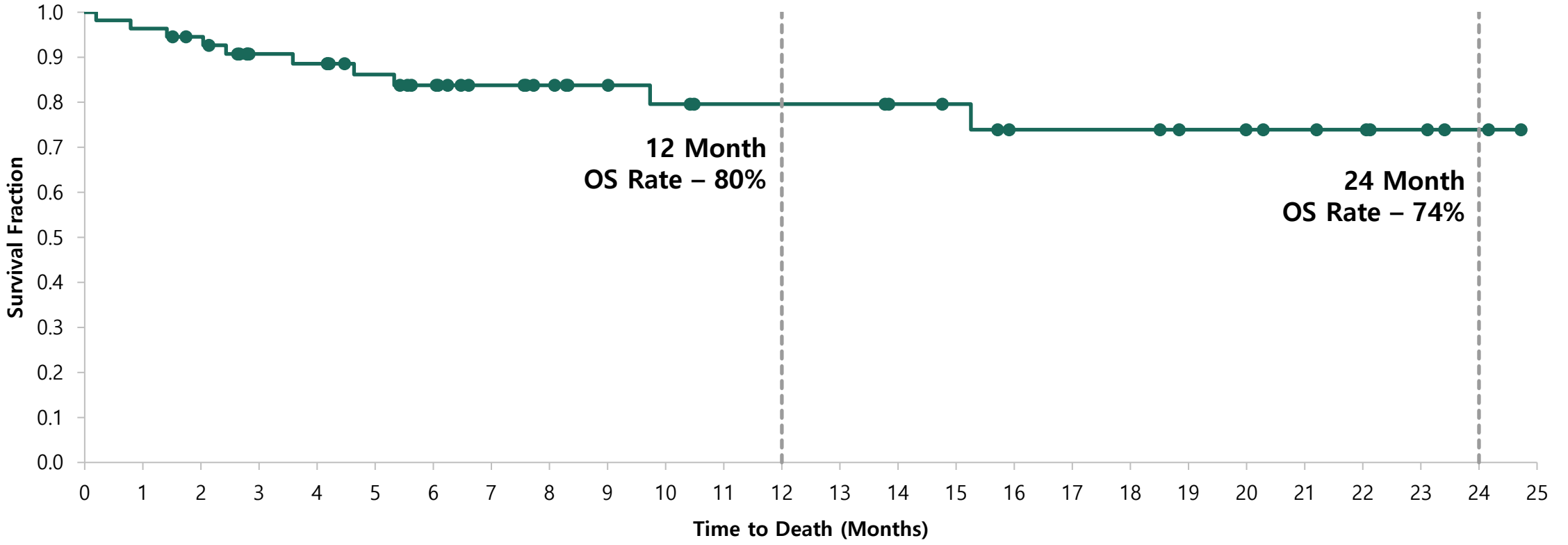
- Median number of PDS0101 doses: 4 (range 1–5)
  - 72.7% received ≥4 doses
    25.5% received 5 doses (5th dose is 6 months after dose 4)
- Median number of KEYTRUDA® doses: 7 (range 1–33)
  - 32.7% received ≥10 doses

Data on File. 08/02/23 Data Cut.

PDS0101 and KEYTRUDA® Combination in ICI Naïve HNSCC Demonstrates Promising Patient Survival to Date

Median OS Not Yet Estimable

Kaplan-Meier Estimates of Overall Survival (OS) (Intent-to-Treat Population)

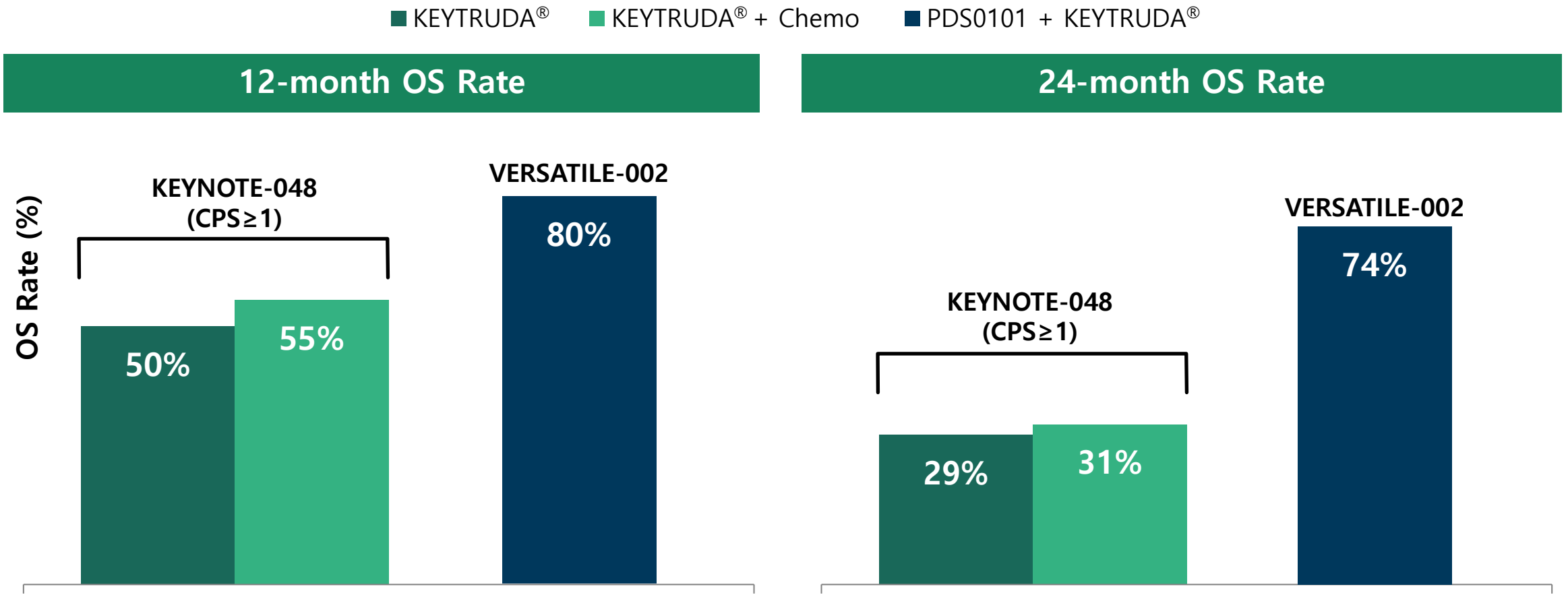


No. of Subjects at Risk (Events)	55 (0)	53 (2)	50 (3)	42 (5)	41 (6)	36 (7)	32 (8)	27 (8)	24 (8)	21 (8)	19 (9)	17 (9)	17 (9)	17 (9)	15 (9)	14 (9)	11 (10)	11 (10)	11 (10)	9 (10)	8 (10)	7 (10)	6 (10)	4 (10)	2 (10)	0 (10)

Data on File. 08/02/23 Data Cut.

PDS0101 and KEYTRUDA® Combination in ICI Naïve HNSCC Demonstrates Promising Patient Survival to Date

Overall Survival is Primary Endpoint in Planned Phase 3 Study VERSATILE-003

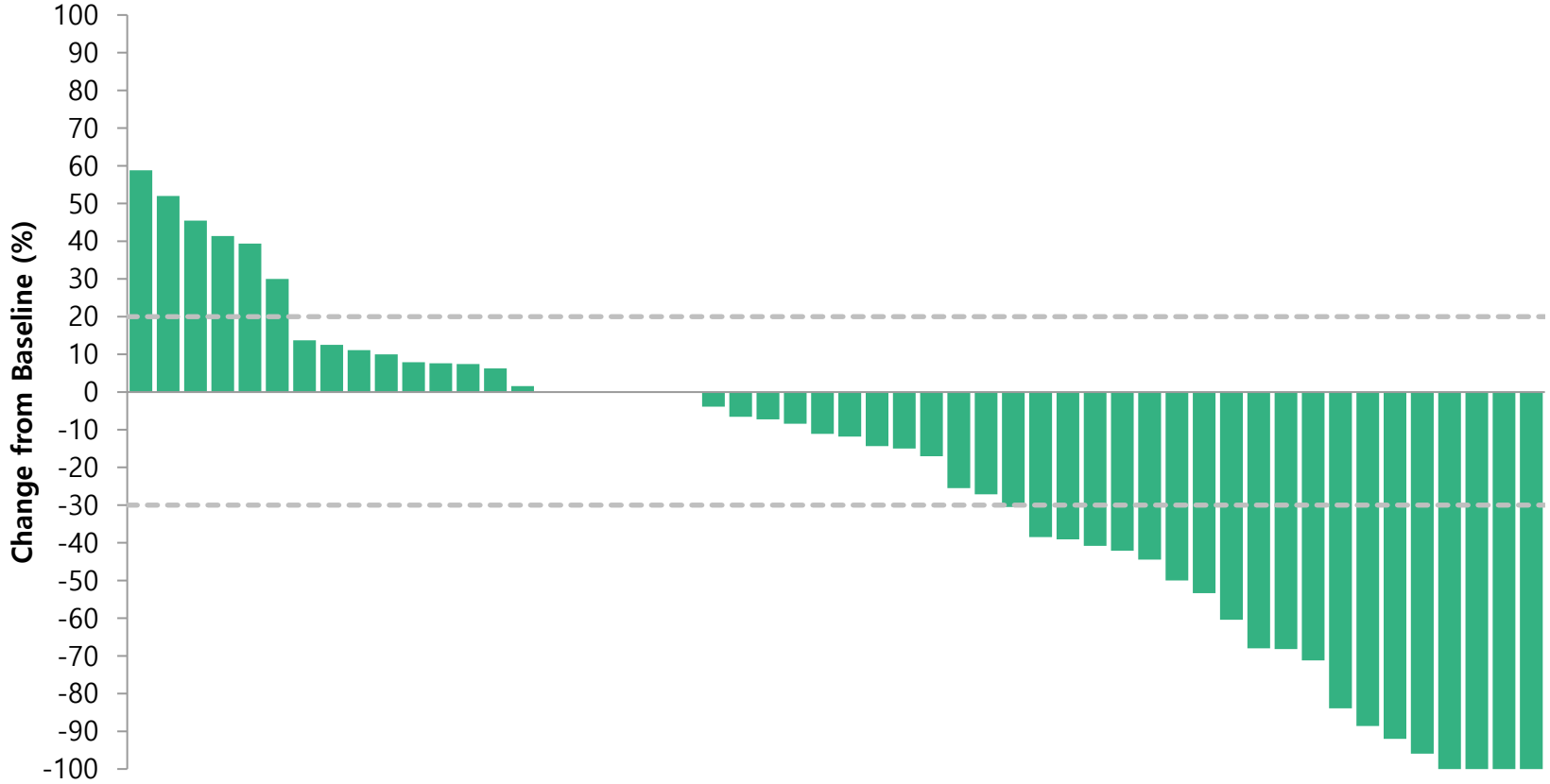


* No controlled or comparative studies have been conducted between checkpoint inhibitors and PDS0101
Data on File. 08/02/23 Data Cut
Burtness B et al., *Lancet.* 2019; 394:1915-1928

Disease Stabilization or Tumor Reduction in 81% of Patients

Tumor Shrinkage in 60% (31/52) with Confirmed Objective Response in 27% (14/52) to Date

Best Percentage Change from Baseline in Target Lesions (mITT population)



Progression Free Survival

VERSATILE-002	Months (95% CI)
PDS0101+KEYTRUDA®	8.1

KEYNOTE-048 (CPS≥1)	Months (95% CI)
KEYTRUDA® Monotherapy	3.2
KEYTRUDA® + Chemo	5.0
EXTREME Chemo	5.0

Assessments based on Investigator assessment per RECIST 1.1
Data on File. 08/02/23 Data Cut.
Burtness B et al., *Lancet*. 2019; 394:1915-1928.

No ICI Naïve Subjects Have Grade 4 or 5 Combination Treatment Related Adverse Events (N=62)

13% (8/62) Subjects have Grade 3 Combination Treatment Related Adverse Events

Injection Site Specific AEs

Preferred Term	n (%)
Any Combination-TRAE	49 (79.0)
Injection site pain	32 (51.6)
Injection site swelling	17 (27.4)
Injection site erythema	11 (17.7)
Injection site discoloration	9 (14.5)
Injection site warmth	9 (14.5)
Injection site inflammation	7 (11.3)
Injection site pruritus	7 (11.3)
Injection site reaction	4 (6.5)

No Grade 3-5 Injection Site Specific AEs

Other AEs

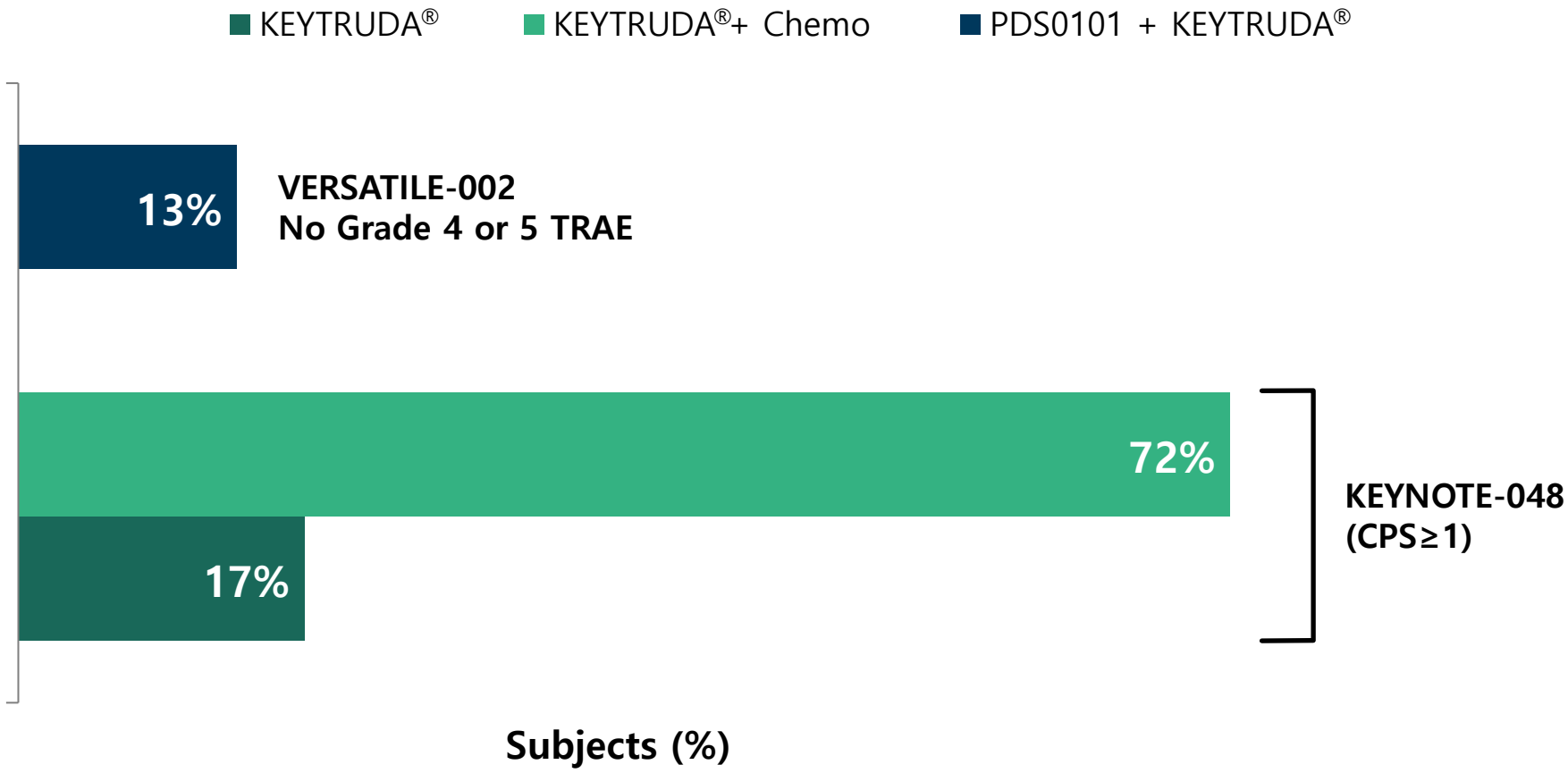
Preferred Term	n (%)
Fatigue	23 (37.1)
Headache	9 (14.5)
Pruritis	7 (11.3)
Pain	5 (8.1)
Diarrhea	5 (8.1)
Rash	5 (8.1)
Alanine aminotransferase increased	5 (8.1)
Aspartate aminotransferase increased	4 (6.5)
Cough	4 (6.5)
Arthralgia	4 (6.5)

Safety Population: All enrolled subjects who received at least 1 dose of pembrolizumab or PDS0101. Includes subjects who became ineligible, for example due to lack of central confirmation of HPV16-positivity. Used for all safety analyses

Data on File. 08/02/23 Data Cut.

PDS0101 with KEYTRUDA® Well Tolerated in VERSATILE-002 to Date

Grade 3–5 Treatment Related Adverse Events



*No controlled or comparative studies have been conducted between checkpoint inhibitors and PDS0101
Data on File. 08/02/23 Data Cut
Burtness B et al. *Lancet*. 2019;394:1915-1928

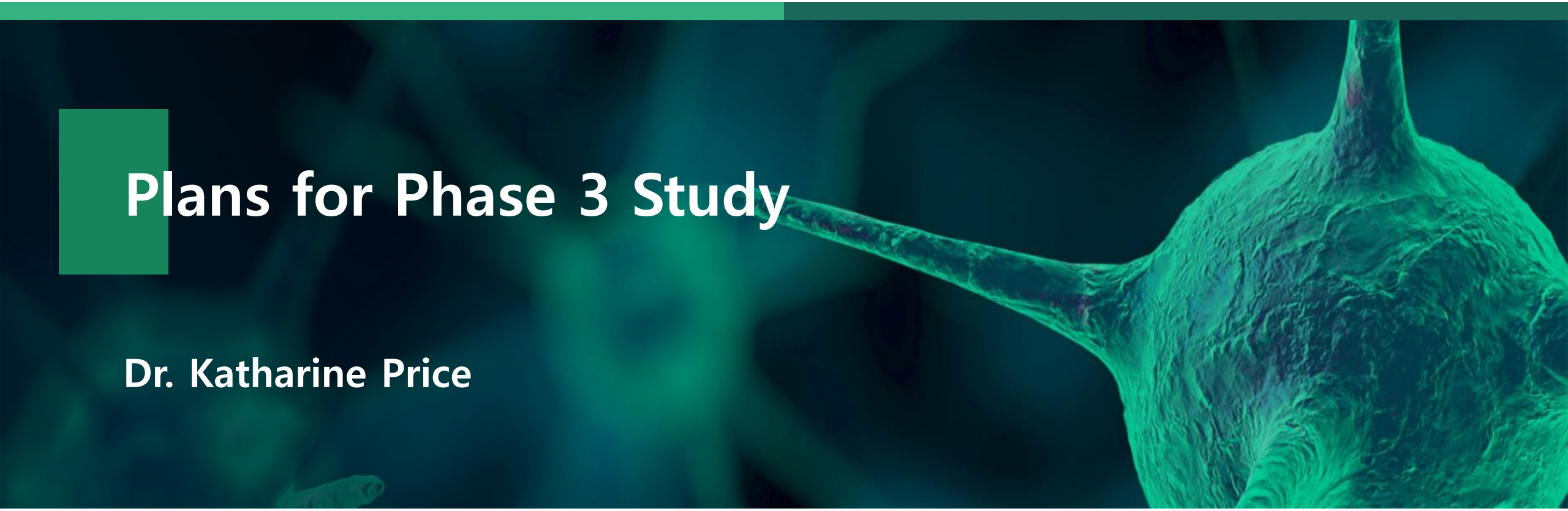
Combination of PDS0101 & KEYTRUDA® Continues to Show Promising Survival Outcomes in ICI Naïve subjects

PDS0101 with KEYTRUDA® Combination Data Shows Potential Of PDS0101 to Safely Modify the Tumor Microenvironment and Target HPV16-positive HNSCC to Promote Survival

- **The 24-month OS rate in the ICI naïve cohort is 74%;** published results of 29% in KEYNOTE-048
- **The 12-month OS rate in the ICI naïve cohort is 80%;** published results of 50% in KEYNOTE-048
- The addition of PDS0101 to KEYTRUDA® does not appear to compound toxicity in ICI naïve patients
  - 13% (8/62) Grade 3 and 0% Grade 4 & 5 Treatment Related Adverse Events

* No controlled or comparative studies have been conducted between checkpoint inhibitors and PDS0101
Data on File. 08/02/23 Data Cut.
Burtness B, et al. *Lancet.* 2019;394:1915-28.

Plans for Phase 3 Study



Dr. Katharine Price

VERSATILE-003

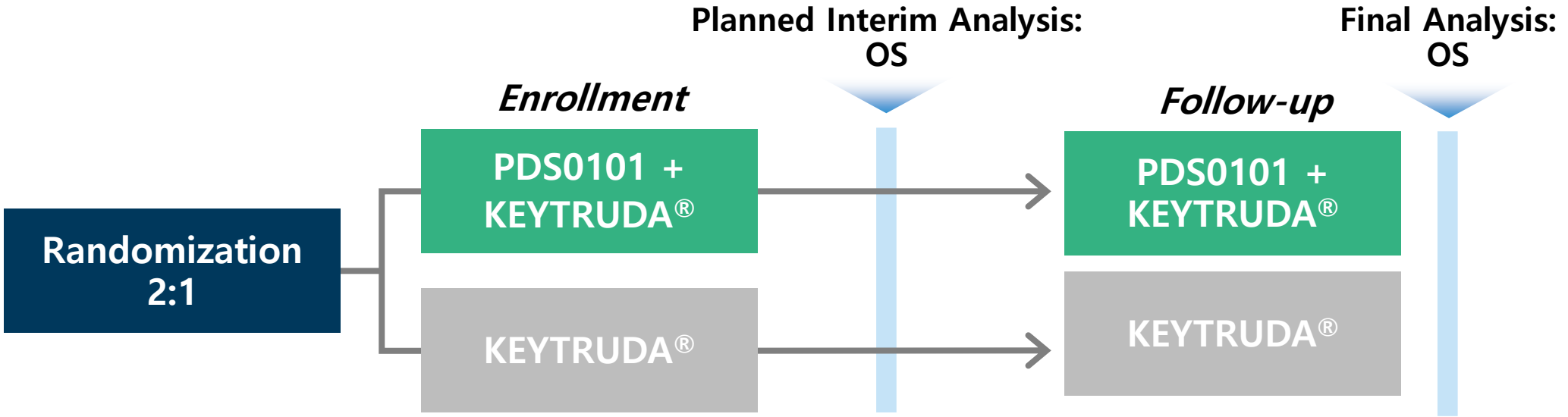
Designed to Be Confirmatory Trial for ICI Naïve Cohort of Phase 2 VERSATILE-002 Study with Overall Survival as Primary Endpoint

A Phase 3 Open-Label, Randomized Study of PDS0101 Plus Pembrolizumab vs Pembrolizumab Alone in First Line Treatment of Immune Checkpoint Inhibitor (ICI) Naïve Subjects with Recurrent and/or Metastatic (R/M) Human Papillomavirus 16 (HPV16)-Positive Head and Neck Squamous Cell Carcinoma (HNSCC)

VERSATILE-003 Phase 3 Study Design

Global Randomized, Controlled Clinical Study with Estimated 90–100 Sites

Targeted Indication	For the treatment of recurrent or metastatic HPV16-positive HNSCC
Primary Endpoint	Overall survival (OS)



Primary and Secondary Objectives

Primary Objective

- Overall survival (OS) between investigational arm (PDS0101 + KEYTRUDA®) vs. control arm (KEYTRUDA®)

Secondary Objectives

- Progression-free survival (PFS) between the investigational arm vs. control arm per RECIST1.1, BICR
- Objective response rate (ORR) between the investigational arm vs. control arm per RECIST1.1, BICR
- Duration of response (DOR) between the investigational arm vs. control arm per RECIST1.1, BICR
- Changes in patient reported outcomes (PRO) using: EQ-5D-3L, EORTC QLQ-C30, and EORTC QLQ-H&N35
- Time to deterioration in PRO scores

Safety and Exploratory Objectives

Safety Objective

- Overall safety between the investigational arm vs control arm

Exploratory Objectives

- Disease Control Rate (DCR) between the investigational arm vs control arm
- PFS2 between the investigational arm vs control arm
- iORR, iPFS, and iDOR between the investigational arm and control arm by iRECIST
- Changes in ctHPVDNA (substudy)
- Correlation between ctHPVDNA with tumor HPV-specific genotype (substudy)
- Changes in HPV16-specific immune responses (substudy)
- Healthcare utilization between the investigational arm and control arm (substudy)

Study Treatment Schedule

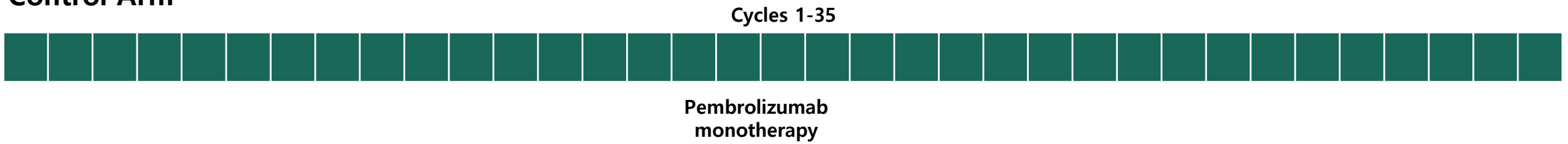
Study Treatments

- PDS0101 1mL subcutaneous every 3 weeks
- Pembrolizumab 200mg intravenous every 3 weeks

Treatment Schedule

Investigational Arm

Control Arm



Key Inclusion Criteria

1. Subject is ≥18 years of age
2. History of histologically- or cytologically-confirmed diagnosis of squamous cell cancer of the head and neck (HNSCC)
3. Unresectable recurrent and/or metastatic measurable disease with confirmation of at least 1 lesion that is considered a target lesion per RECIST 1.1 criteria as assessed by BICR
4. HPV16 tumor positivity (central testing)
5. Tumor PD-L1 expression defined as a CPS ≥ 1 using the FDA/EMA-approved assay (local testing)
6. No prior receipt of any immune checkpoint inhibitor (ICI) therapy
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Key Exclusion Criteria

1. Prior therapy with HPV-specific immunotherapy including therapeutic cancer vaccines and cellular immunotherapy. **Note:** subjects who have received prophylactic HPV vaccines are eligible for enrollment
2. Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T cell receptor (e.g., CTLA-4, OX40, CD137)
3. Prior systemic anticancer therapy within 30 days prior to randomization
4. Major surgery, including surgical resection of tumor, within 30 days prior to randomization
5. Radiotherapy prior to randomization outside minimum washout periods
6. Live vaccine within 30 days prior to randomization
7. Has known carcinomatous meningitis and/or active central nervous system (CNS) metastases **Note:** Subjects with previously treated brain metastases are eligible if all the specific criteria are met

Timeline to Registrational Trial Initiation

Worldwide Randomized, Controlled Clinical Study to Be Initiated Q4 2023

PDS0101 + KEYTRUDA® in Recurrent or Metastatic HPV16-Positive HNSCC

2Q 2022

- **FDA *Fast Track designation*** for PDS0101 + KEYTRUDA®

3Q 2022

- Successful EOP2 meeting with FDA
- Initiated PDS0101 tech-transfer, scale up at selected Phase 3 clinical/ commercial manufacture

1Q 2023

- Completed Phase 3 clinical manufacturing of PDS0101
- Obtained visibility to potential OS and PFS information for VERSATILE-002 trial needed to finalize VERSATILE-003 trial design

2Q 2023

- Completed CMC-related activities for PDS0101
- Obtained feedback from EU regulatory agencies on protocol

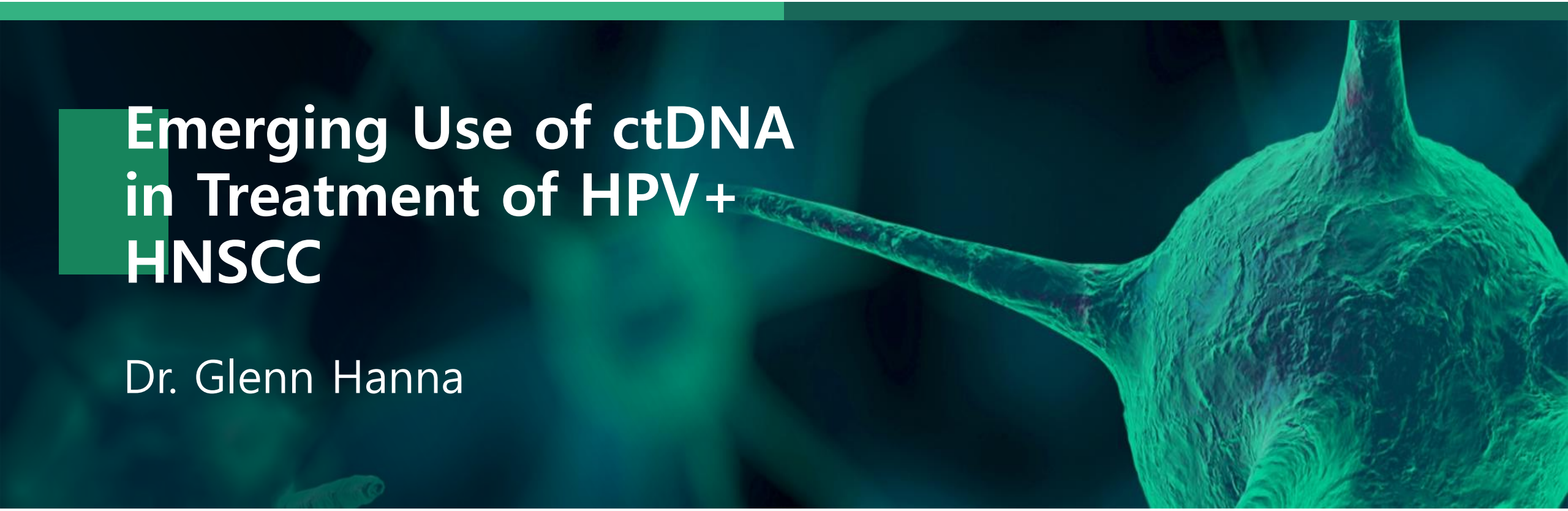
3Q 2023

- Received feedback from FDA allowing for initiation of VERSATILE-003
- Initiate site activation and related clinical, operational activities (4- to 6-month process)

4Q 2023

Initiate VERSATILE-003 Phase 3 Trial

Emerging Use of ctDNA in Treatment of HPV+ HNSCC



Dr. Glenn Hanna

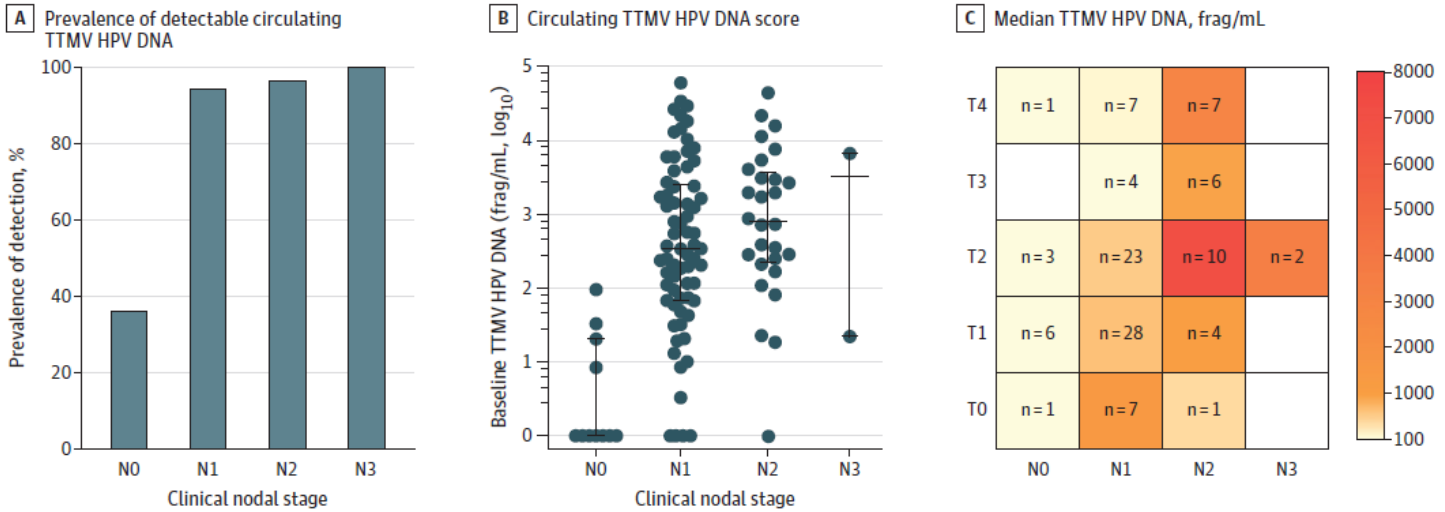
Pre-treatment HPV ctDNA Detection

JAMA Otolaryngology–Head & Neck Surgery | Original Investigation | FROM THE AMERICAN HEAD AND NECK SOCIETY

Association of Pretreatment Circulating Tumor Tissue–Modified Viral HPV DNA With Clinicopathologic Factors in HPV-Positive Oropharyngeal Cancer

Eleni M. Rettig, MD; Annette A. Wang, BS; Ngoc-Anh Tran, MD; Evan Carey, BS; Tanujit Dey, PhD; Jonathan D. Schoenfeld, MD, MPH; Kartik Sehgal, MD; Jeffrey P. Guenette, MD; Danielle N. Margalit, MD, MPH; Rosh Sethi, MD, MPH; Ravindra Uppaluri, MD, PhD; Roy B. Tishler, MD, PhD; Donald J. Annino, MD, DMD; Laura A. Goguen, MD; Vickie Y. Jo, MD; Robert I. Haddad, MD; Glenn J. Hanna, MD

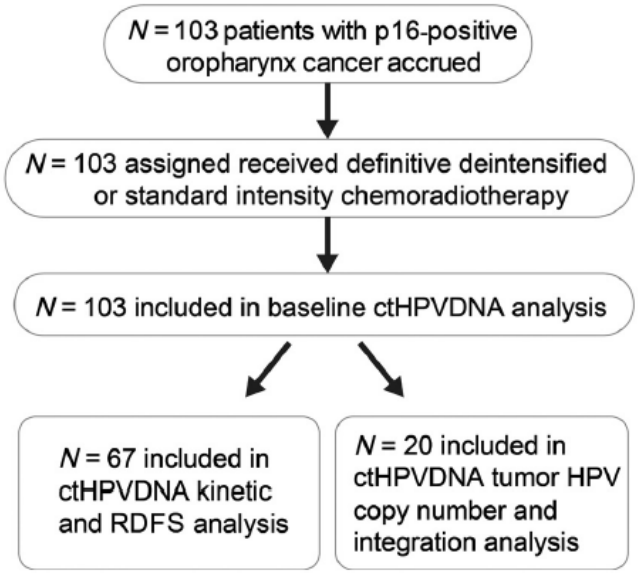
Figure 1. Circulating Tumor Tissue–Modified Viral (TTMV) Human Papillomavirus (HPV) DNA and Clinical Staging



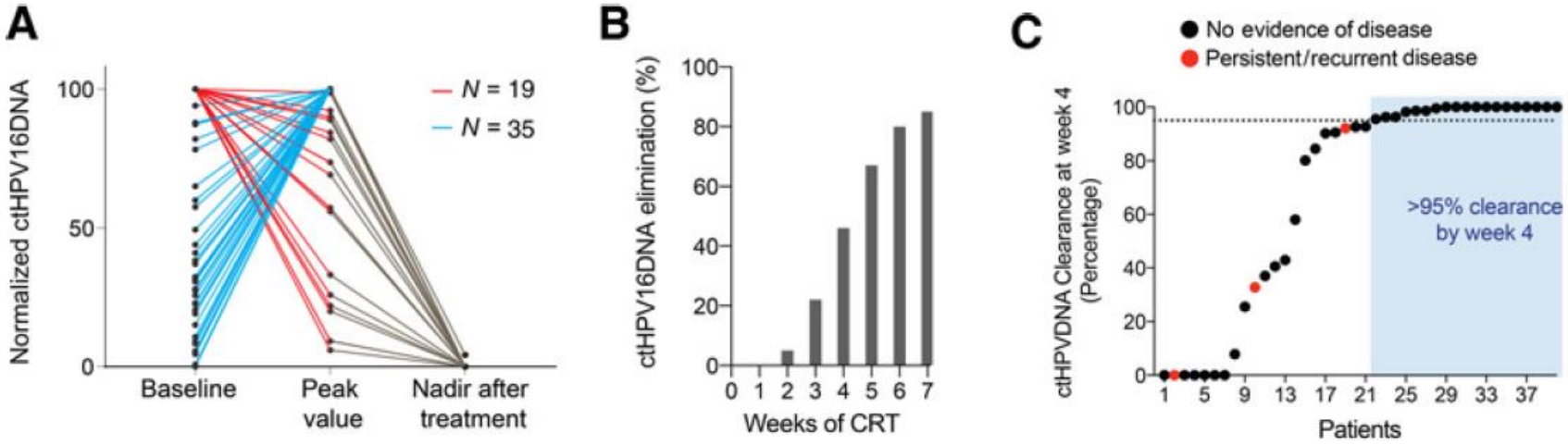
A, Prevalence of detectable circulating TTMV HPV DNA by clinical nodal stage. B, Circulating TTMV HPV DNA score by clinical nodal stage (log scale). Dark horizontal lines and error whiskers indicate medians and interquartile ranges, respectively. Median TTMV HPV DNA score for N0 is 0. C, Heat map of circulating TTMV HPV DNA score by clinical tumor and nodal stages. Blank boxes indicate no values represented. Numbers denote the number of patients in each group. All stages are based on the American Joint Committee on Cancer staging manual, 8th edition. Frag/mL indicates fragment per milliliter.

Rettig EM, et al. *JAMA* Otolaryngol Head Neck Surg 2022

HPV ctDNA Clearance During Treatment



* N=87 (84%) received deintensified CRT on a clinical trial (60 Gy)



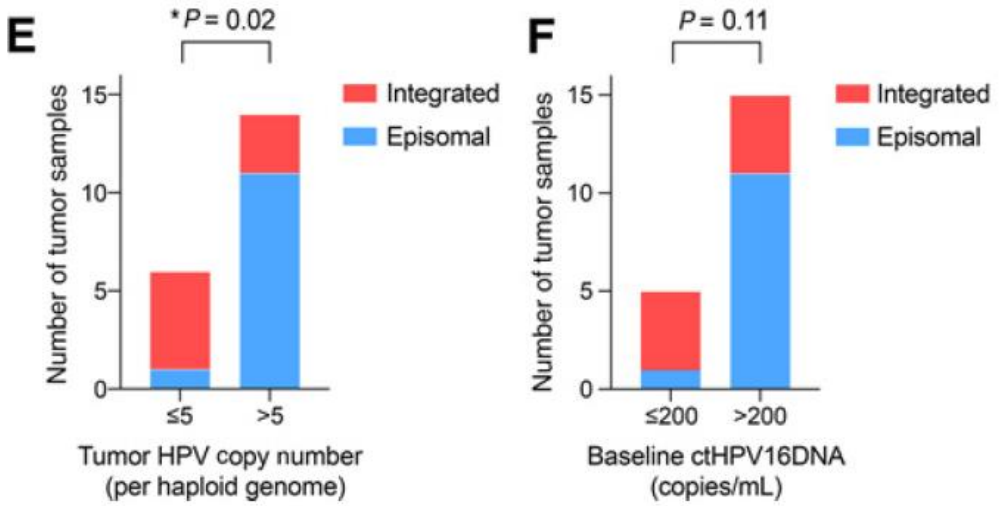
ctHPV16DNA levels increased after starting CRT and later declined

80% of patients had no detectable ctHPV16DNA by the end of CRT

No patients with >95% viral clearance (from baseline) by week 4 demonstrated recurrence

Chera BS, et al. *Clin Cancer Res* 2019

HPV ctDNA Clearance During Treatment



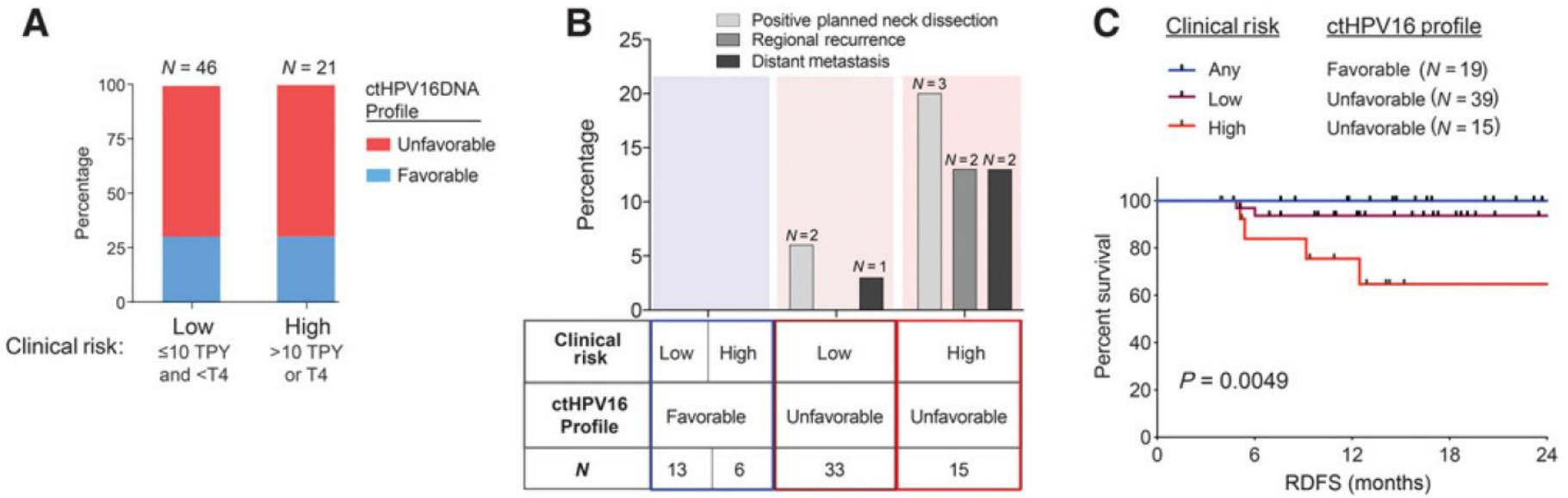
Low baseline ctHPV16DNA (≤200 copies/mL) had lower tumor HPV copy number

Those with low tumor HPV copy number (≤5 copies/haploid genome) had HPV integration

Low baseline ctHPV16DNA → HPV integration → adverse tumor genomics

Chera BS, et al. *Clin Cancer Res* 2019

HPV ctDNA Clearance During Treatment

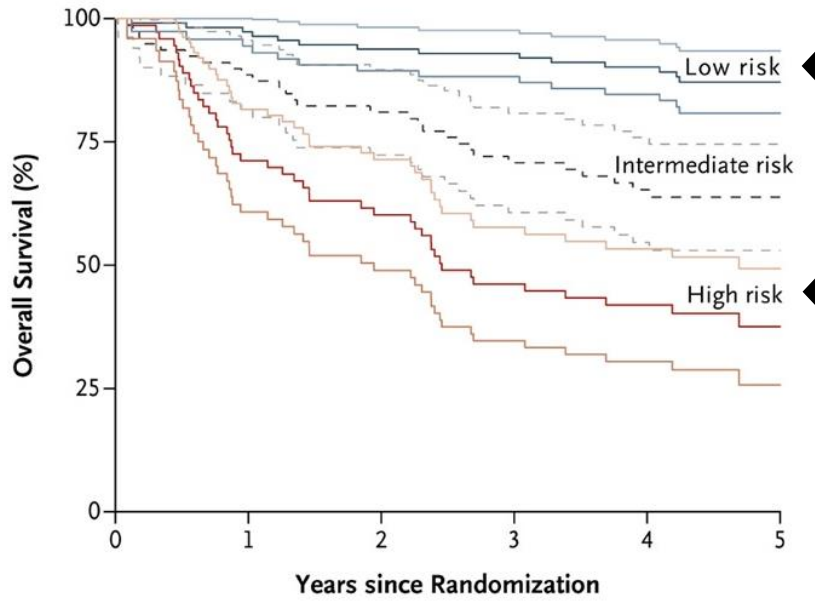


Favorable ctHPV16DNA profile: >200 copies/mL baseline and >95% viral clearance by week 4

Chera BS, et al. *Clin Cancer Res* 2019

Risk Stratifying HPV+ Oropharyngeal Cancer

B



No. at Risk						
Low risk	114	111	106	102	95	46
Intermediate risk	79	70	64	54	44	24
High risk	73	52	43	33	28	8

HPV+, ≤10 pack-year smoker
0-1 lymph node

HPV-, >10 pack-year smoker,
T4 tumors, multiple and large
lymph nodes

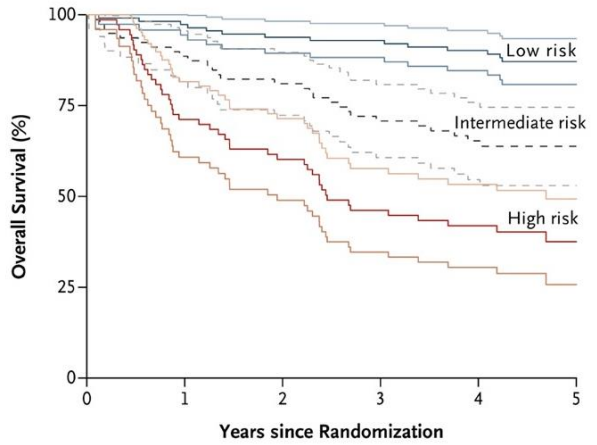
Trend towards de-intensification

TORS + Radiation (60 Gy), or lower dose chemoradiation, or induction chemotherapy followed by lower dose radiation

Standard chemoradiation in 35 fractions (70 Gy) with bolus cisplatin

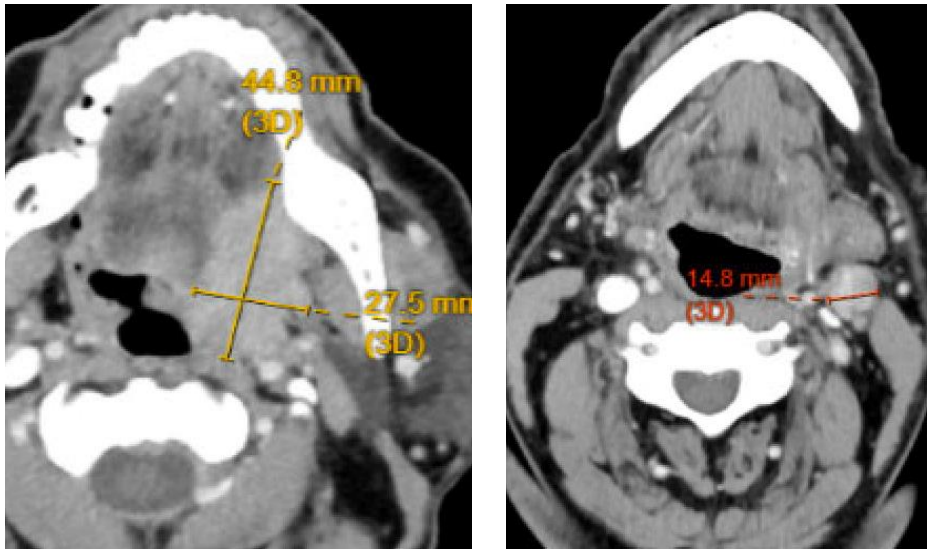
Ang KK, et al. *N Engl J Med* 2010

Risk Stratifying HPV+ Oropharyngeal Cancer



No. at Risk

Low risk	114	111	106	102	95	46
Intermediate risk	79	70	64	54	44	24
High risk	73	52	43	33	28	8



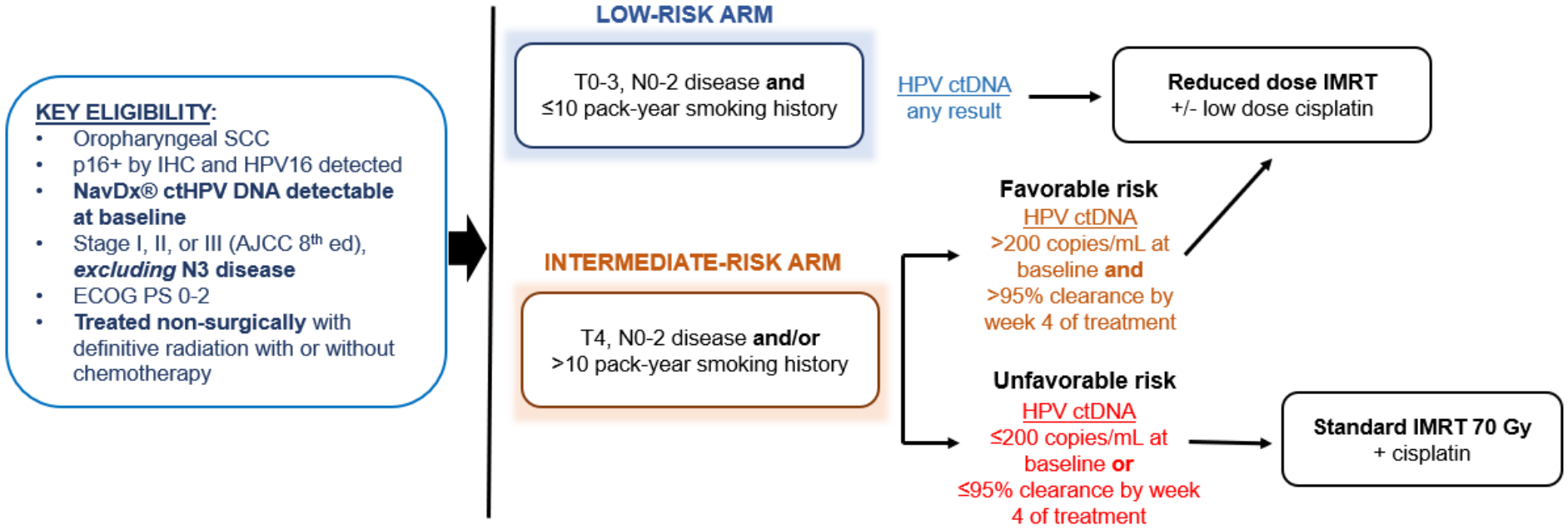
What do we do for the <u>intermediate risk group</u>?

63M (former smoker) with **HPV+** left tonsil SCC with cT4N1 (stage III, AJCC 2017 8th ed) disease?

Standard bolus cisplatin with chemoradiation <u>or</u> can we de-intensify at all?

What can we use to risk stratify him *beyond* clinical factors?

Risk-adapted Therapy in HPV+ Oropharyngeal Cancer Using Circulating Tumor (ct)HPV DNA Profile ReACT Study



Phase II, non-randomized, exploratory study

2-year PFS of 75% from RTOG 1016 for the favorable intermediate-risk group
N=45 evaluable pts provides 80% power to improve **PFS to 86%** at 2-years (0.56 HR, alpha=0.1)

N=75 total cohort size (80% intermediate risk, 75% of which will be favorable risk)

Hanna GJ, Schoenfeld JD, et al. Accruing 2022

Risk-adapted Therapy in HPV+ Oropharyngeal Cancer Using Circulating Tumor (ct)HPV DNA Profile ReACT Study

Patient Disease Status

Diagnosis: HPV-driven SCC arising from the right base of tongue

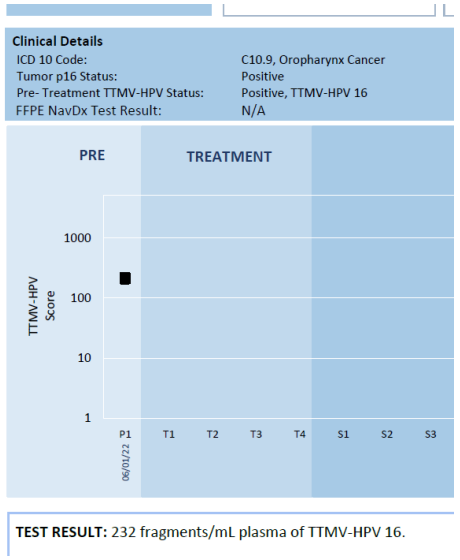
Molecular: p16(+)

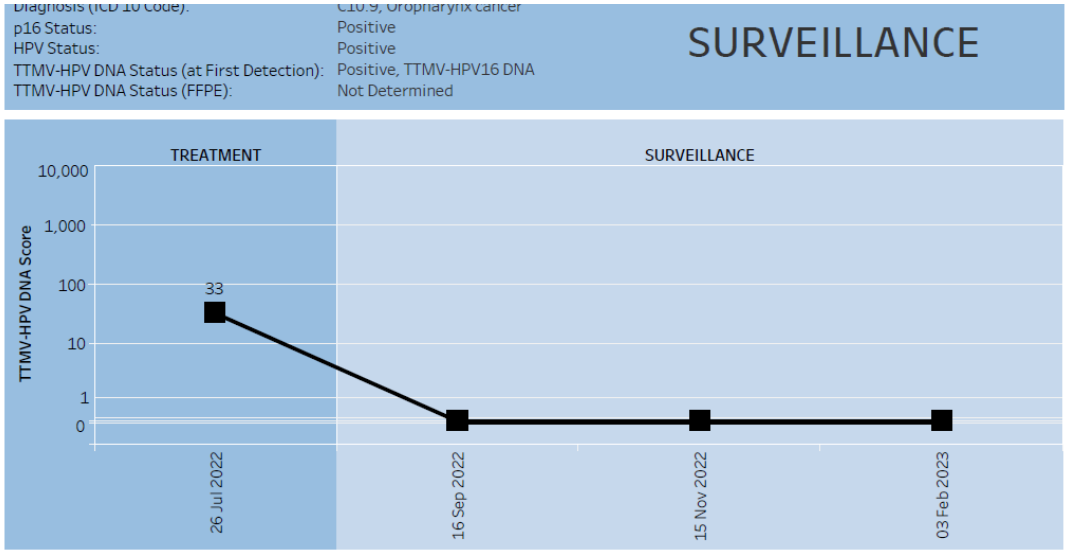
Staging: cT3-4N1M0 (stage II-III, AJCC 2017 8th ed)

Treatment Summary: definitive chemoradiotherapy

Protocol: 21-191/ReACT
Radiation: IMRT (35/35 fractions, total dose: 70 Gy) to the oropharynx and bilateral necks, elapsed over 50 days (TTMV-HPV DNA failed to clear at week 4, not de-intensified)
Systemic therapy: bolus cisplatin to a total dose of: 200 mg/m2
Toxicity: moderate
Complications: none
Completion date: 8/15/22

Failure to clear TTMV-HPV DNA by 95% at week 4-5, no de-escalation (higher risk?)

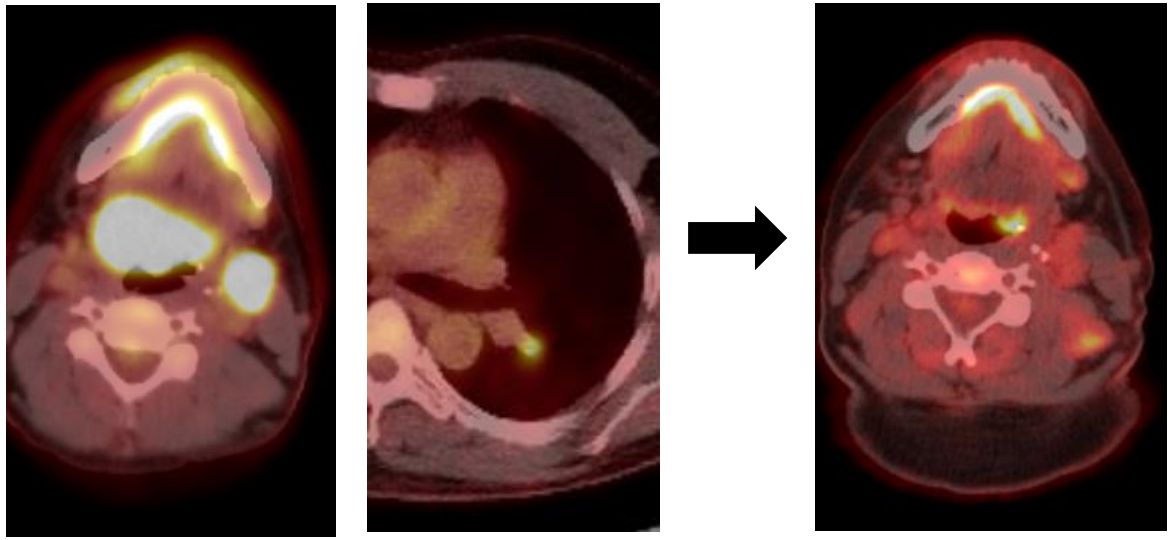




Hanna GJ, Schoenfeld JD, et al. Accruing 2022

HPV ctDNA and Response to Induction

39M (Never Smoker) with de novo Metastatic HPV+ BOT SCC with Lung Metastases, After 1-Cycle of Chemoimmunotherapy TTMV-HPV DNA Nearly Clears…Completed 3-cycles, Now on to Consolidative CRT…



Tumor Tissue Modified Viral (TTMV)®-HPV DNA Score

Indeterminate

2

Report Details

Sample Type:	Blood
Collection Date:	20 Apr 2023
Receipt Date:	21 Apr 2023
Report Date:	03 May 2023

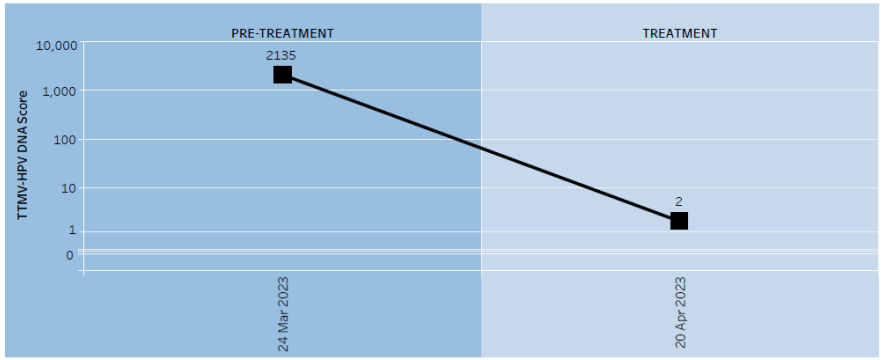
Contact Details

Physician:	Glenn J Hanna
Facility:	Dana Farber Cancer Institute
Address:	450 Brookline Ave Boston, MA 2215
Additional Recipients:	

Clinical Details

Diagnosis (ICD 10 Code):	C10.9, Malignant neoplasm of oropharynx, unspecified
p16 Status:	Positive
HPV Status:	Positive
TTMV-HPV DNA Status (at First Detection):	Positive, TTMV-HPV16 DNA
TTMV-HPV DNA Status (FFPE):	Not Determined

TREATMENT



Hanna GJ, patient example

HPV ctDNA and Response to Surgery

CLINICAL INVESTIGATION

Detectable Postoperative Circulating Tumor Human Papillomavirus DNA and Association with Recurrence in Patients With HPV-Associated Oropharyngeal Squamous Cell Carcinoma

David M. Routman, MD,* Sunil Kumar, PhD,†,‡ Bisham S. Chera, MD,†,‡ Krishan R. Jethwa, MD,*,§ Kathryn M. Van Abel, MD,‖ Kelsey Frechette, MD,* Todd DeWees, PhD,¶ Michael Golafshar, MS,¶ Joaquin J. Garcia, MD,# Daniel L. Price, MD,‖ Jan L. Kasperbauer, MD,‖ Samil H. Patel, MD,** Michelle A. Neben-Wittich, MD,* Nadia L. Laack, MD,* Ashish V. Chintakuntlawar, MBBS, PhD,†† Katharine A. Price, MD,†† Minetta C. Liu, MD,†,†† Robert L. Foote, MD,* Eric J. Moore, MD,‖ Gaorav P. Gupta, MD, PhD,†,‡ and Daniel J. Ma, MD*

Table 2 Factors associated with detectable postoperative ctHPVDNA

	Univariate Analysis		Multivariate Analysis	
Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Sex	1.25 (0.39-4.02)	*P* = .714		
Age	1.06 (1.01-1.10)	*P* = .015	1.06 (1.01-1.10)	*P* = .025
Smoking Status	0.76 (0.34-1.73)	*P* = .519		
T1/T2 vs T3/T4	2.96 (1.20-7.28)	*P* = .018		
N1 vs N2	3.19 (1.36-7.48)	*P* = .008		
ENE	6.5 (2.39- 17.7)	*P* <.001	5.67 (2.02-15.91)	*P* = .001
LVSI	2.66 (1.21-5.88)	*P* = .015	3.17 (1.30-7.68)	*P* = .011
PNI	1.12 (0.45-2.77)	*P* = .806		
Largest node	1.14 (0.87-1.48)	*P* = .341		

Abbreviations: CI = confidence interval; ctHPVDNA = circulating tumor human papillomavirus DNA; ENE = extranodal extension; LVSI = lymphovascular space invasion; OR = odds ratio; PNI = perineural invasion.

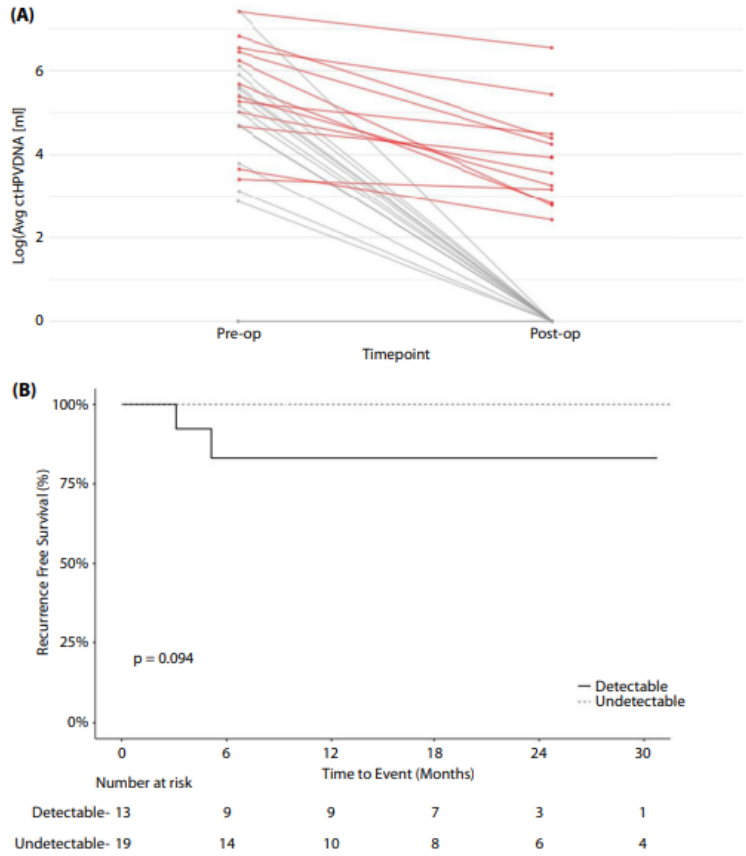
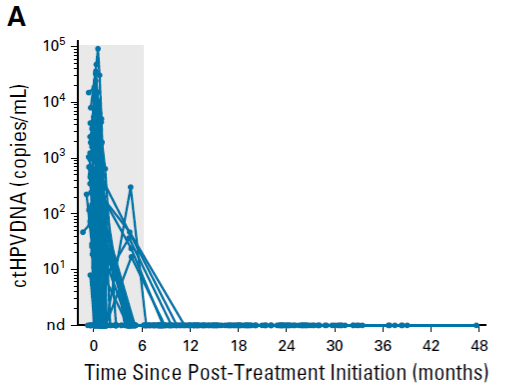
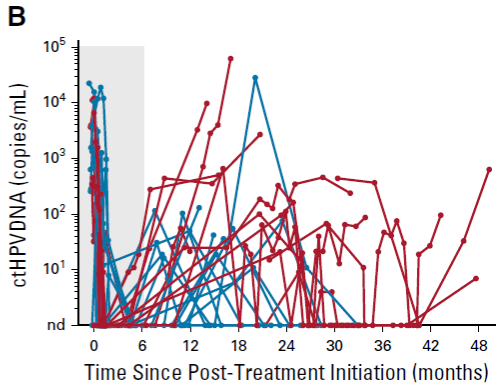


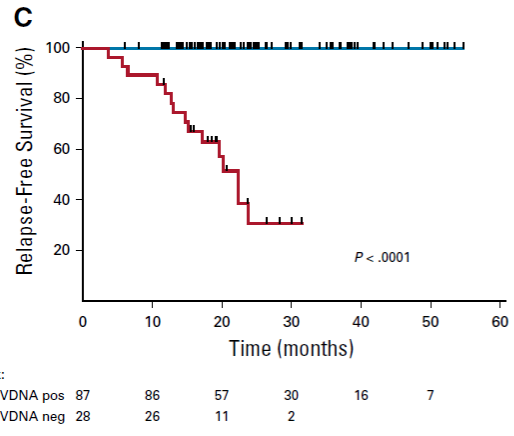
Fig. 2. (A) Change in quantity of preop to postop human papillomavirus–associated oropharyngeal squamous cell carcinoma within 32 patients with both timepoints available. (B) Recurrence-free survival by circulating tumor tDNA detectability in the 32 patients in the primary analysis.

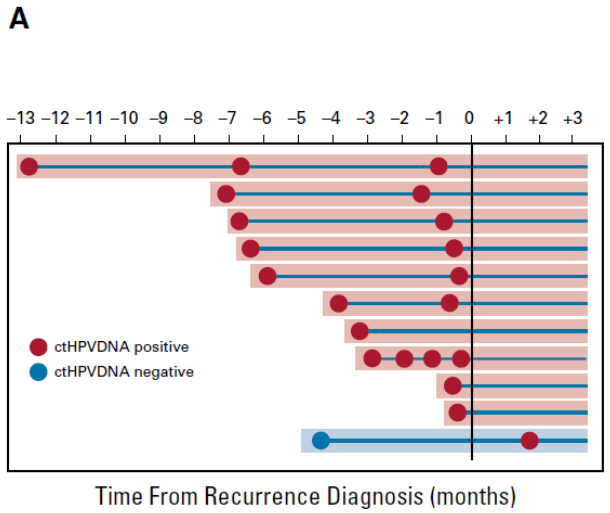
Routman DM, et al. *Int J Radiat Oncol Biol Phys* 2022

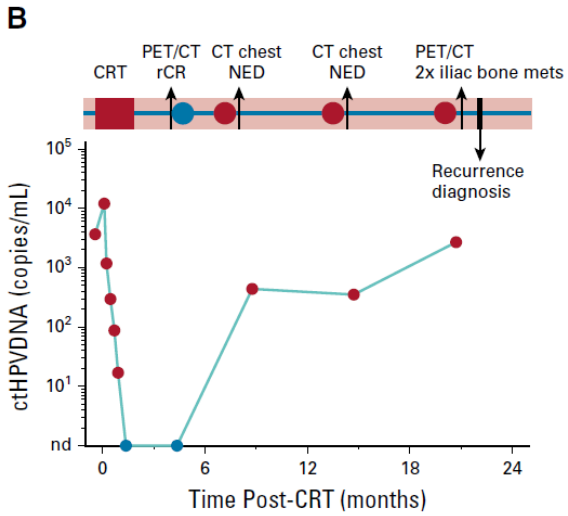
HPV ctDNA During Surveillance











Worse outcomes for those with **two consecutively positive** ctHPVDNA results post-treatment

Among patients with recurrence, ctHPVDNA positivity often **predated detection of recurrence** on imaging or biopsy

Chera BS, et al. *J Clin Oncol* 2020

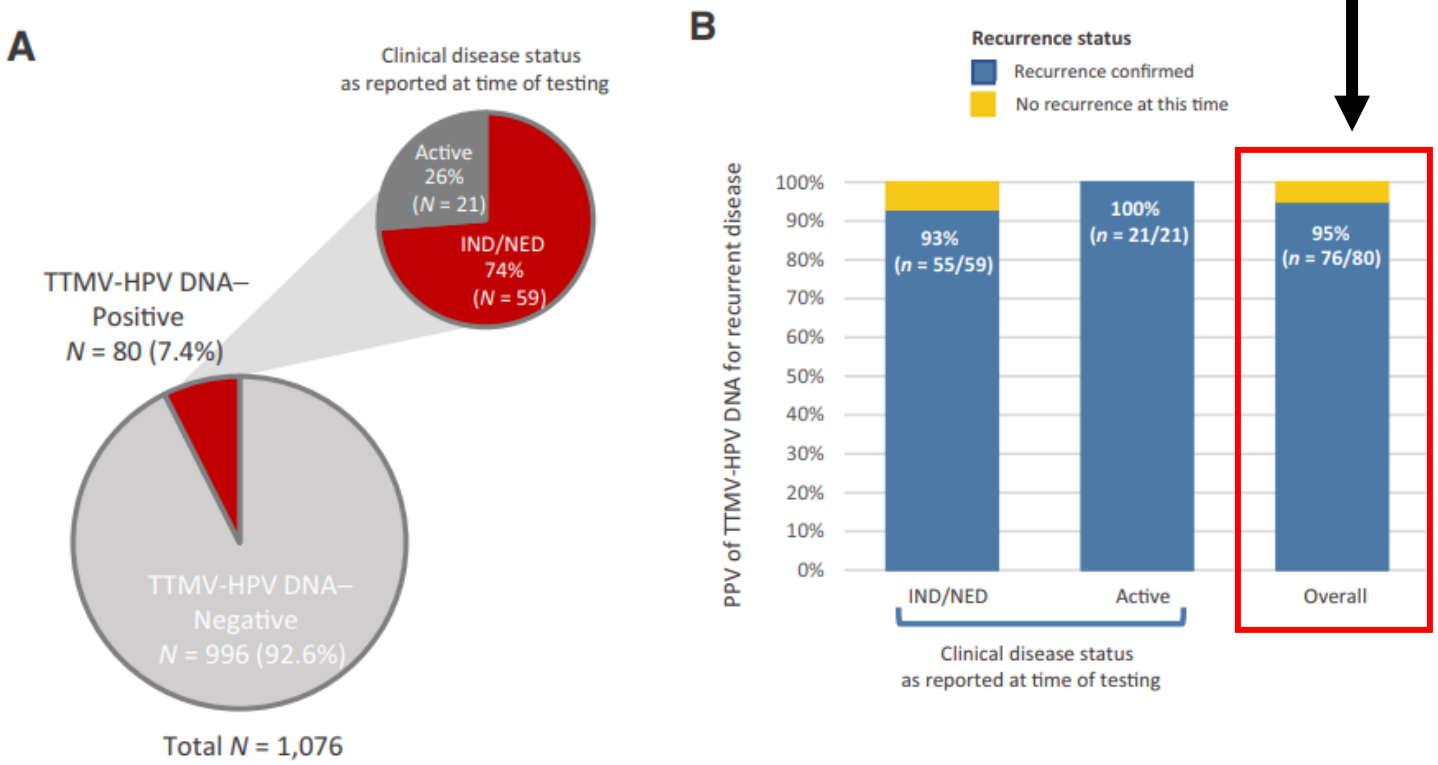
HPV ctDNA During Surveillance

CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

Detection of Occult Recurrence Using Circulating Tumor Tissue Modified Viral HPV DNA among Patients Treated for HPV-Driven Oropharyngeal Carcinoma

Barry M. Berger[1], Glenn J. Hanna[2], Marshall R. Posner[3,4], Eric M. Genden[3,5], Julio Lautersztain[6], Stephen P. Naber[1], Catherine Del Vecchio Fitz[1], and Charlotte Kuperwasser[1]

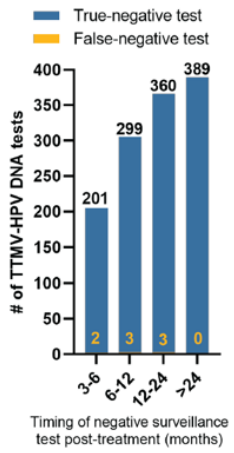
In follow-up, **PPV is 97%** with further cancer events identified



Berger B, Hanna GJ, et al. *Clin Cancer Res* 2021

HPV ctDNA During Surveillance

A



B

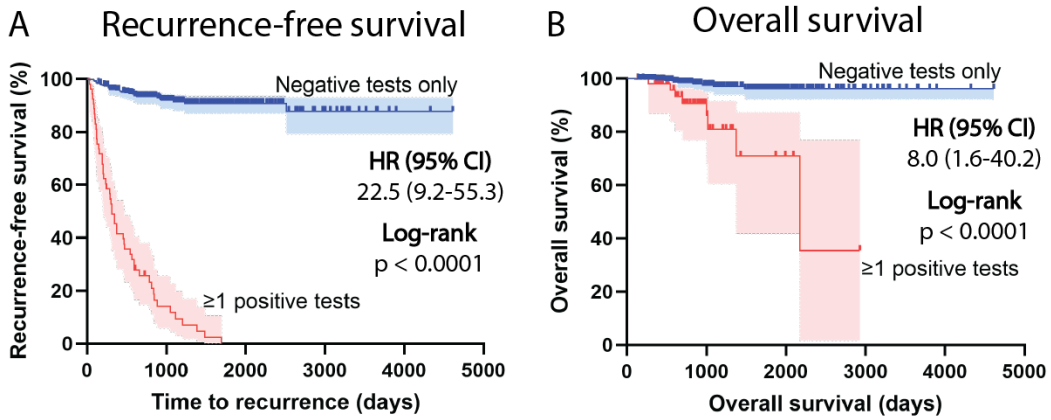
	Per-test accuracy measures		
	Disease "+"	Disease "-"	Predictive value[A]
Test "+"	99	5	PPV = 95.2% (91.1-99.3)
Test "-"	8	1247	NPV = 99.4% (98.9-99.8)
Sensitivity and-Specificity	Sn=92.5% (87.5-97.5	Sp=99.6% (99.3-99.9	
	Per-patient accuracy measures		
Test "+"	55	3	PPV=94.8% (89.1-100)
Test "-"	8[B]	495	NPV=98.4% (97.3-99.5)
Sensitivity and-Specificity	Sn=87.3% (79.1-95.5)	Sp=99.4% (98.7-100)	

[A]One patient was censored from the PPV calculation as they were non-compliant with follow-up despite a TTMV-HPV DNA score >800 and subsequently died.

[B]Only 2 of 8 patients with a false negative had baseline testing results.

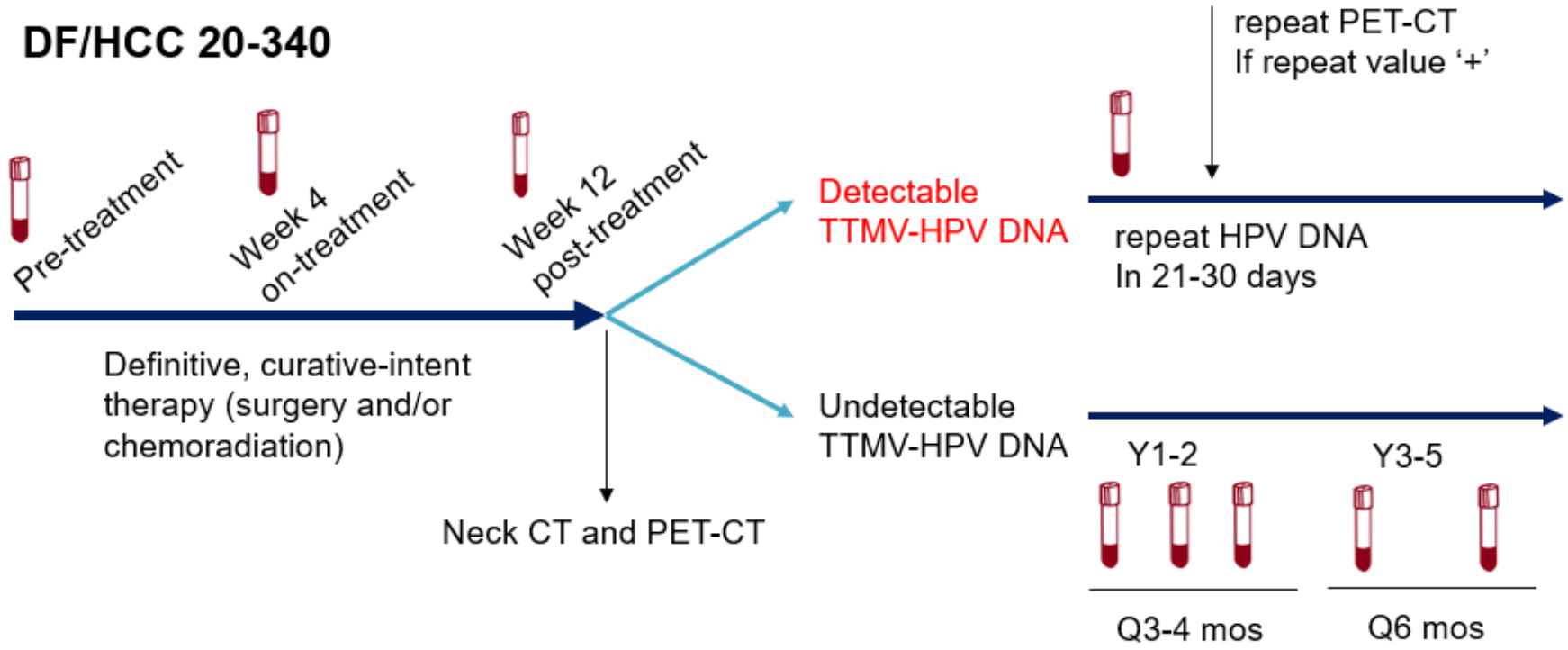
Sn=Sensitivity;
Sp=Specificity;
PPV=Positive predictive value
NPV=Negative predictive value

Figure 4. TTMV-HPV DNA test metrics. (A) There were a total of 8 false negative test results across the various surveillance stages. (B) A summary of TTMV-HPV DNA test metrics at per-test and per-patient levels demonstrates excellent performance.



Hanna GJ, et al. *Clin Cancer Res* 2023

HPV ctDNA During Surveillance



Sample size: 150 evaluable

Primary endpoint: time to detection of recurrence (TTDR) among definitively treated HPV positive oropharyngeal cancer patients monitored with HPV ctDNA as part of surveillance

Rettig EM, Hanna GJ, et al. Accrual completed in 2022

HPV ctDNA Conclusions (or More Questions)…

Should HPV ctDNA be incorporated into routine surveillance for all HPV-positive oropharyngeal cancer patients? **Is this ready for inclusion in the NCCN® guidelines?**

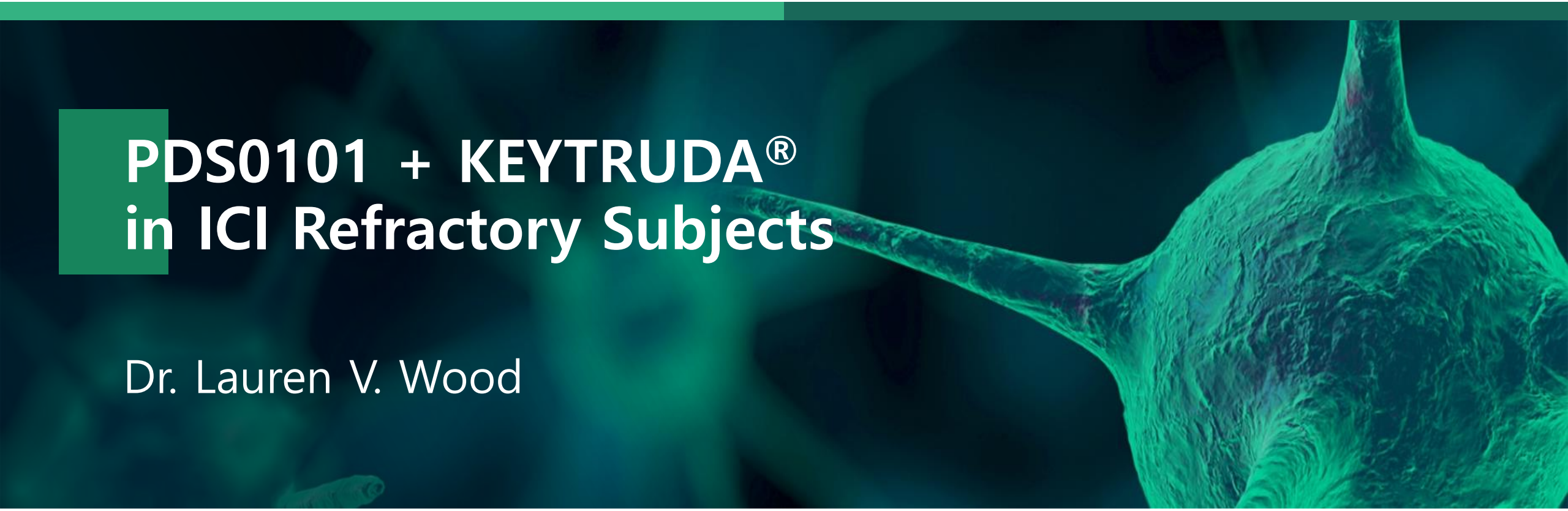
Can HPV ctDNA results **guide the choice of whether to pursue additional surveillance imaging** beyond the 12-week post-treatment scan review?

Can HPV ctDNA metrics **inform (de-)intensification strategies** even among intermediate-risk patients (T4, smokers)?

In the future, could we **screen high-risk patients** for HPV ctDNA and then pursue imaging/endoscopy exam if detectable? Would this impact disease outcomes (cost) and survival?

Rettig EM, Hanna GJ, et al. Accrual completed in 2022

PDS0101 + KEYTRUDA® in ICI Refractory Subjects



Dr. Lauren V. Wood

Assessing the Role of PDS0101 in Extending Survival in the Absence of a VERSATILE-002 KEYTRUDA® Control Arm

Evaluation of PDS0101 + KEYTRUDA® in HPV16-positive head and neck patients who have failed/progressed on KEYTRUDA® therapy (ICI Refractory)

- Evaluation of the combination of PDS0101 and KEYTRUDA in patients who have failed KEYTRUDA therapy provides an "internal control"
- **Important Consideration:** ICI refractory patients have more advanced disease than ICI naïve patients and are much more difficult to treat with immunotherapy
  - Presents a higher treatment bar than ICI naïve patients
- On alternative ICI therapy, historical overall survival rates in HPV-positive ICI refractory cancer is reported to be approximately only 3-4 months
- Results provide useful information regarding
  - Role of PDS0101 targeted immunotherapy in promising VERSATILE-002 survival rates
  - OS endpoint in potential triple combination study with ICI, PDS0101 & PDS0301(NHS-IL12)

Strauss J, et al. *Journal for ImmunoTherapy of Cancer*. 2020;8:e001395.

VERSATILE-002 ICI Refractory Cohort

Phase 2, Open-Label, Non-Randomized, Adaptive Design Study Evaluating the Combination of PDS0101 and KEYTRUDA®

Methods and Limitations

Key Entry Criteria for ICI Refractory Subjects

- Recurrent and/or metastatic HNSCC based on RECIST 1.1
- ≥18 years of age
- HPV16-positive tumor
- No CPS criteria
- ICI Refractory

Study Treatment

- KEYTRUDA® 200mg IV Q3W up to 35 Cycles (2 years)
- PDS0101 SC in two 0.5 mL injections during Cycles 1, 2, 3, 4, and 12 (max 5 doses)

Limitations: This study presents data from a snapshot of an ongoing study. Final results may differ for additional survival follow up of ongoing subjects

Population, Treatment Exposure, and Primary Endpoint

ITT and mITT Population (N=21)

- Received at least 1 cycle of combination treatment
- Median age 64.0 (range 49–78)
- 100% Male
- 90.5% White
- 57.1% ECOG 0
- 33.3% CPS ≥20, 28.6% CPS<1

Treatment Exposure (ITT Population)

- Median number of PDS0101 doses: 3 (range 1–4)
  - 47.6% received 4 doses
- Median number of KEYTRUDA® doses: 3 (range 1–7)
  - 47.6% received ≥ 4 doses; 33.1% received ≥5 doses

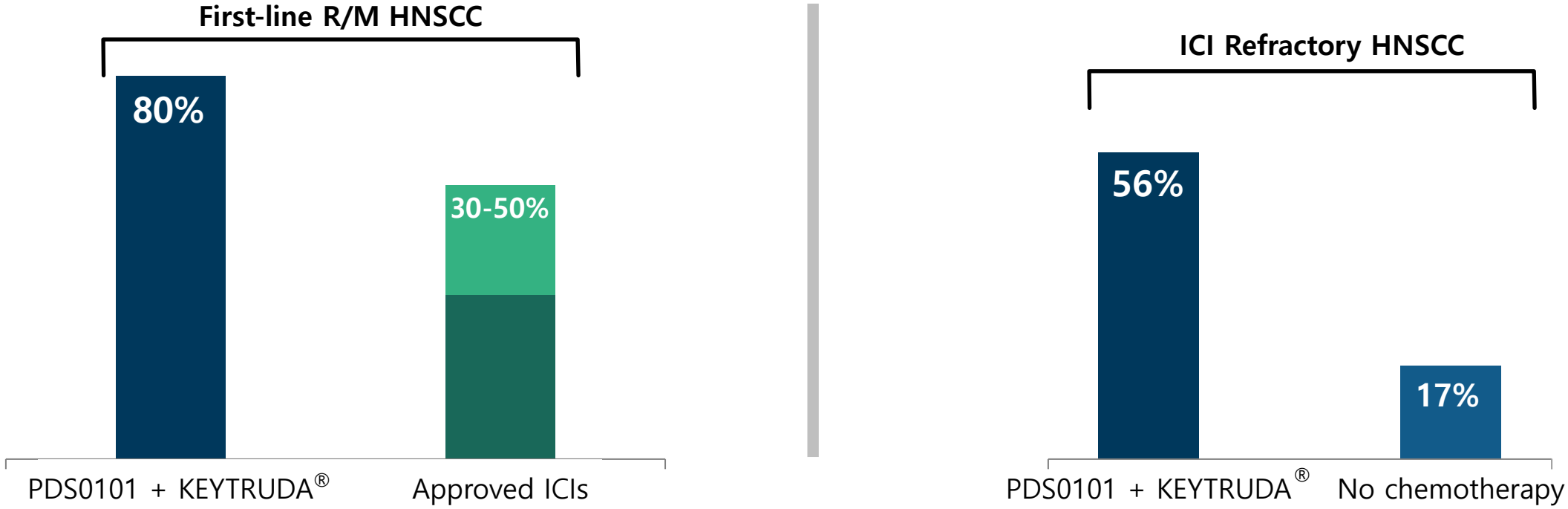
Primary Endpoint

- No confirmed objective responses
- Cohort will not proceed to Stage 2
- **Study goal achieved suggesting role of PDS0101 on survival in ICI refractory patients**

Survival Rates Demonstrate Potential Contribution of PDS0101 to Survival in Advanced Head and Neck Cancer

PDS0101 + KEYTRUDA Shows Promising Survival Benefit even in ICI Refractory Patients

12-month Overall Survival Rate | **Progression** | **12-month Overall Survival Rate**



* No controlled or comparative studies have been conducted between checkpoint inhibitors and PDS0101

Data on File. 08/02/23 Data Cut
Burtness B et al., *Lancet*. 2019;394:1915-1928
Ferris RL, et al. *NEJM*. 2016;375:1856-67.
Bila M, et al. *Frontiers in Oncology*. Jan 2022;12:761428.

No ICI Refractory Subjects Have Grade 4 or 5 Combination Treatment Related Adverse Events (N=25)

4% (1/25) Subjects Have Grade 3 Combination Treatment Related Adverse Events

Injection Site Specific AEs

Preferred Term	n (%)
Any Combination-TRAE	21 (84.0)
Injection site pain	12 (48.0)
Injection site swelling	8 (32.0)
Injection site discolouration	7 (28.0)
Injection site pruritus	5 (20.0)
Injection site warmth	3 (12.0)
Injection site inflammation	3 (12.0)
Injection site inflammation	3 (12.0)
Injection site reaction	3 (12.0)

No Grade 3-5 Injection Site Specific AEs

Other AEs

Preferred Term	n (%): Events
Fatigue	7 (28.0)
Pyrexia	3 (12.0)
Diarrhoea	2 (8.0)
Malaise	2 (8.0)
Chills	2 (8.0)
Pneumonitis	2 (8.0)
Hyponatremia	2 (8.0)
Hyponatremia	2 (8.0)

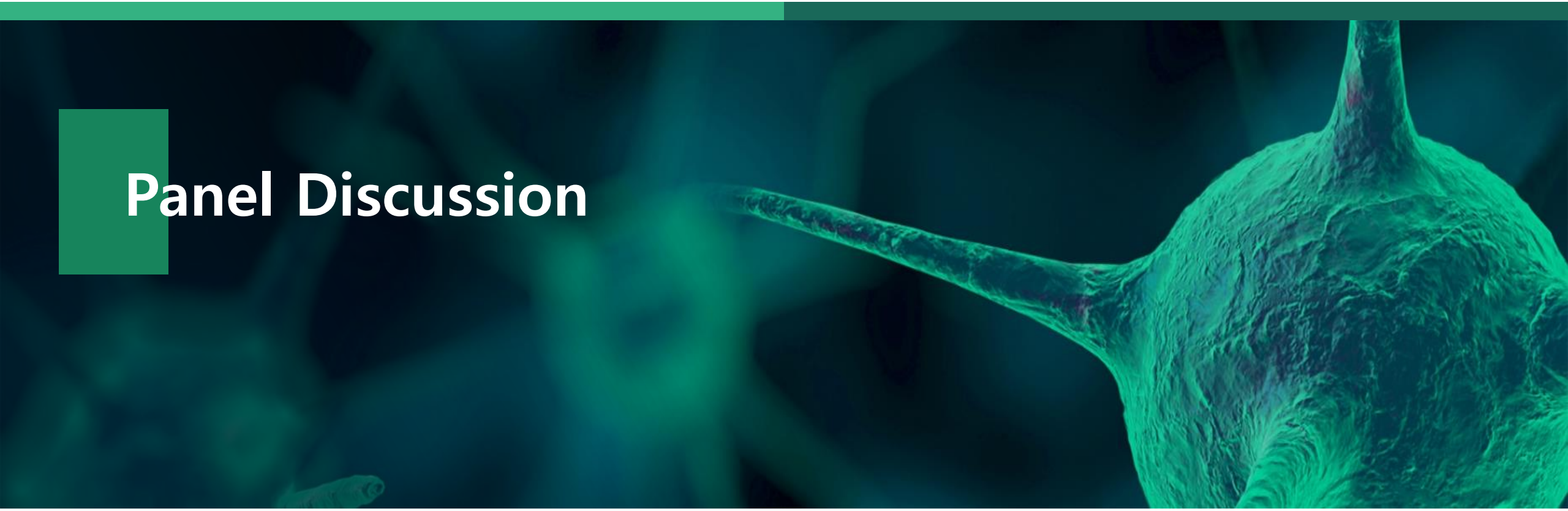
Data on File. 08/02/23 Data Cut

VERSATILE-002 Study Results To-Date Support Initiation of Phase 3 Clinical Trial in ICI Naïve R/M HNSCC

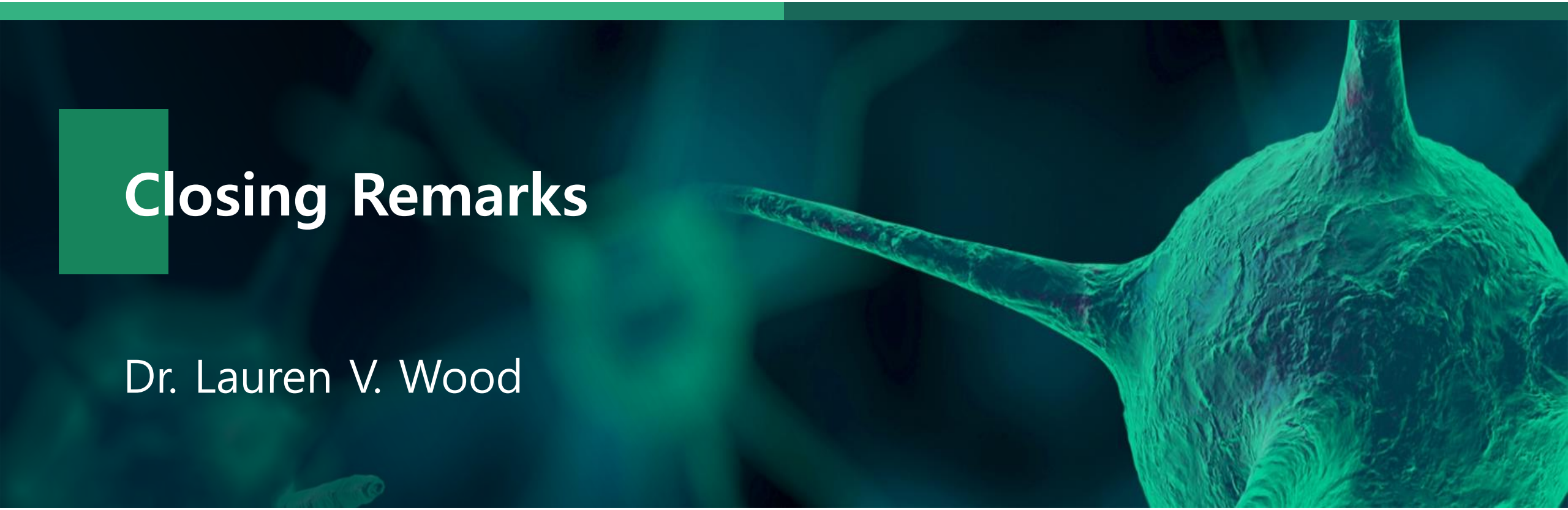
- Promising survival data in target population for phase 3 study
  - 24-month survival rate of 74% in HPV16-positive ICI naïve head and neck cancer patients; published results of 29% with ICI therapy alone
- Supportive survival and safety data in difficult-to-treat ICI refractory population
- Combination of PDS0101 and KEYTRUDA® well tolerated in both ICI naïve and ICI refractory populations
- VERSATILE-002 data supports VERSATILE-003 Phase 3 study design in ICI naïve HNSCC

Data on File. 08/02/23 Data Cut
Burtness B et al., *Lancet.* 2019;394:1915-1928

Panel Discussion



Closing Remarks



Dr. Lauren V. Wood