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Pembrolizumab in Combination with Chemoradiotherapy (CRT) in Human Papilloma Virus (HPV)-associated Head and Neck Squamous Cell Carcinoma (HNSCC)

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Presenter Disclosure Information

Steven F. Powell

The following relationships exist related to this presentation:

BMS, Consultant

PD-1 inhibitors in HNSCC

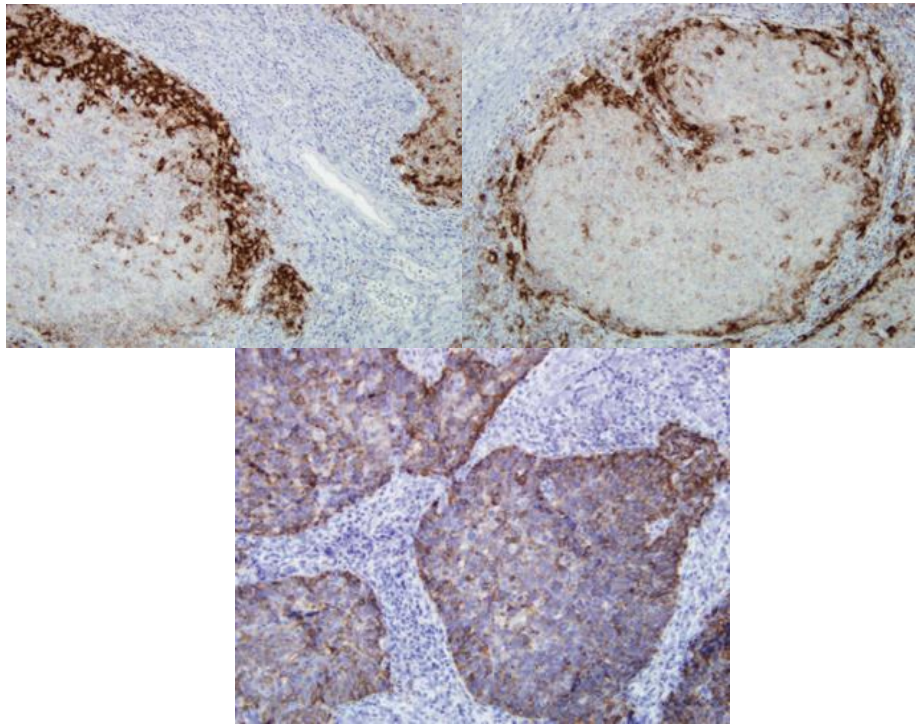
The interaction of programmed death-1 (PD-1) and its ligands (PD-L1/2) are important in immune evasion in HNSCC

Both HPV+ and HPV- disease express PD-L1, making it an appealing target for therapy[1]

PD-1 inhibitors have activity in recurrent/metastatic (R/M) HNSCC and are approved in platinum-refractory disease:

- Pembrolizumab - Keynote-055[2] – ORR 16% (95% CI 11-23%)
- Nivolumab – Checkmate 141[3] – ORR 13.3% (95% CI 9.3-18.3%)

Role in curative-intent therapies, including CRT, is currently unclear

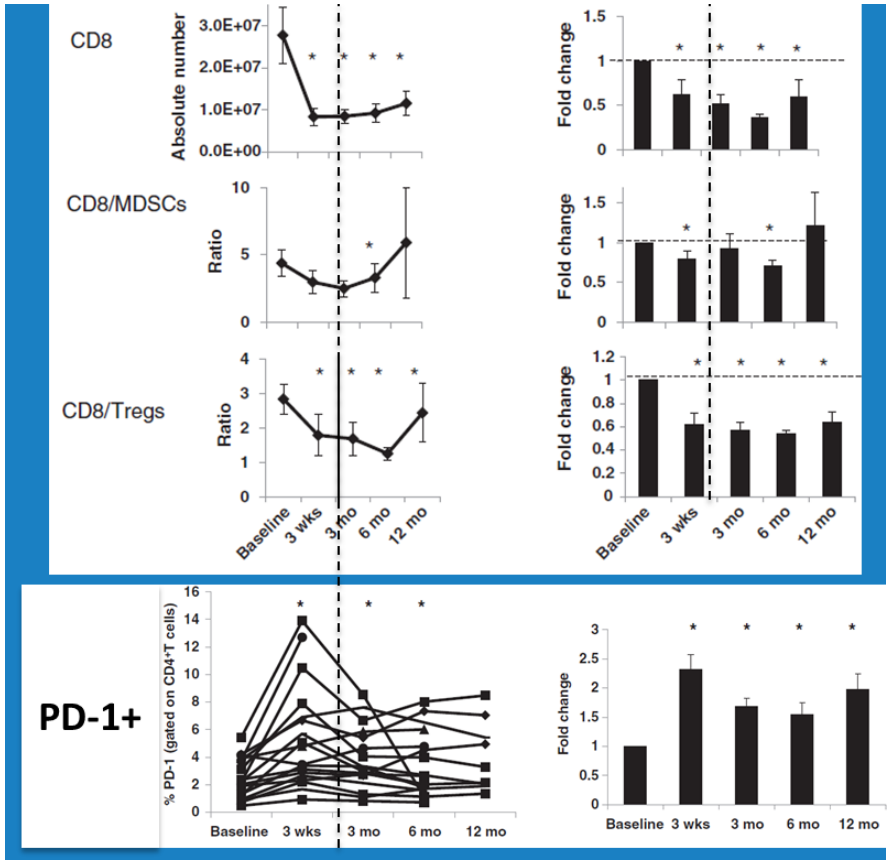


70% HPV + HNSSC PD-L1 + (>5% IHC)
30% HPV – HNSCC PD-L1 + (>5% IHC)

1- Lyford-Pike et al. *Cancer Res.* 2013 doi: 10.1158/0008-5472.
2- Bauml J et al. *J Clin Oncol.* 2017; doi: 10.1200/JCO.2016.70.1524
3 -Ferris RL et al. *N Engl J Med* 2016; DOI: 10.1056/NEJMoa1602252

Rationale for PD-1:PD-L1 inhibition during CRT

Peripheral Blood[1]



Tumor

Radiation[2]

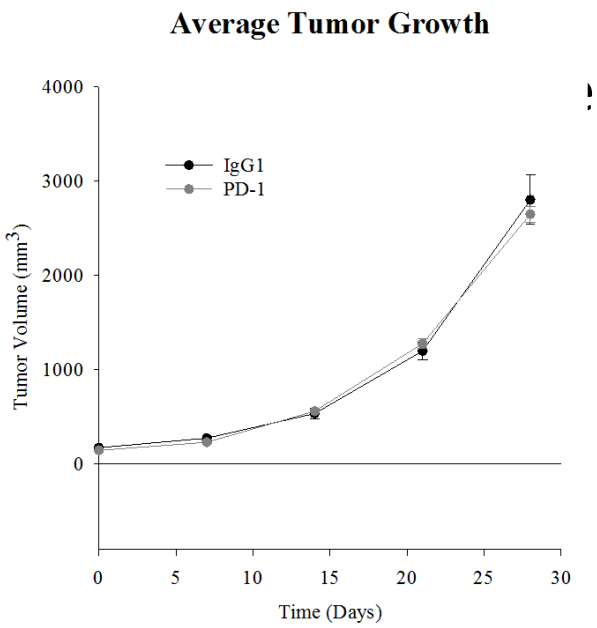
Increased expression of PD-L1 in tumors and microenvironment

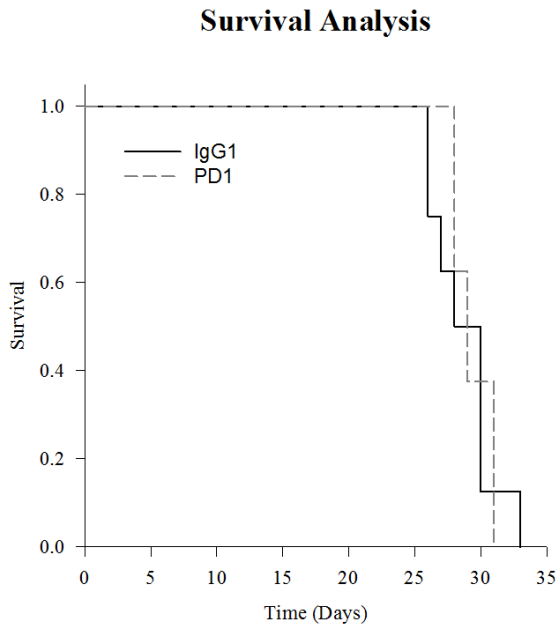
Cisplatin[3]

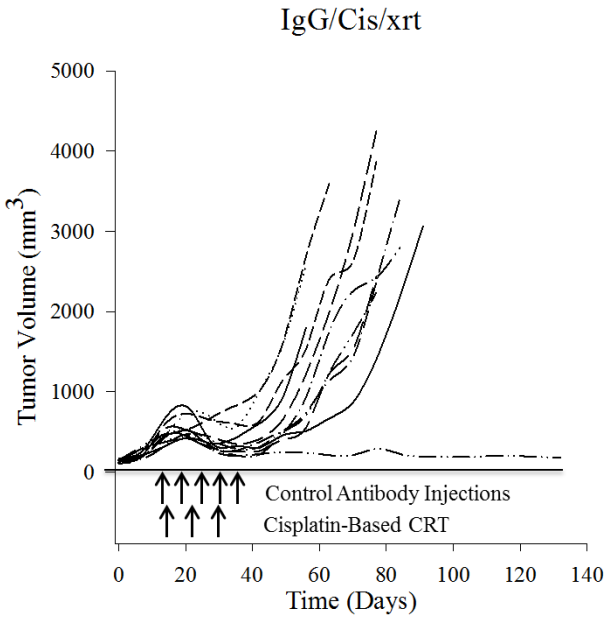
Increased tumor expression of PD-L1

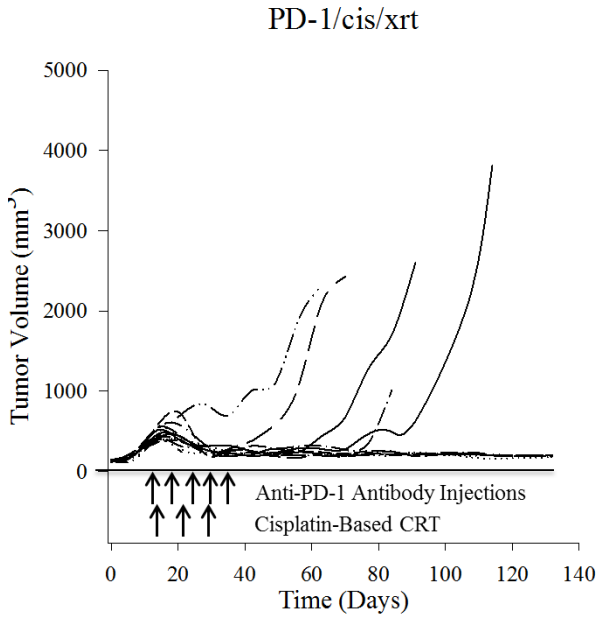
1- Parikh F. Cancer Res. 2014;74(24):7205-16
2- Deng L. J Clin Invest. 2014 Feb;124(2):687-95.
3- Qin X. Cellular and molecular biology. 2010;56 Suppl:OL1366-72

Anti-PD-1 therapy synergizes with CRT in a preclinical mouse model









Activity of anti-PD-1 therapy alone and with CRT in a C57BL/6 mouse with mouse tonsil epithelial cells expressing HPV16 E6, E7, Ras and luciferace (mEERL)[1]

1- Vermeer DW, et al. AHNS Translational Research Meeting 2015. abstract #S004

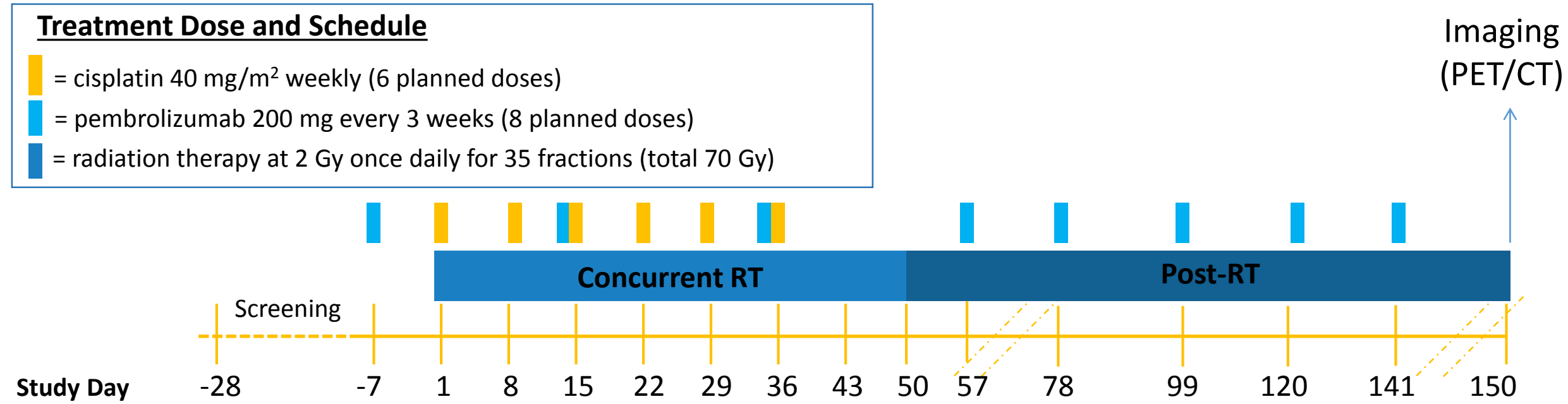
Phase IB Study of Pembrolizumab plus CRT in patients with Locally-Advanced HNSCC

Treatment Dose and Schedule

= cisplatin 40 mg/m^2 weekly (6 planned doses)

= pembrolizumab 200 mg every 3 weeks (8 planned doses)

= radiation therapy at 2 Gy once daily for 35 fractions (total 70 Gy)



Primary end points:

- Safety - dose-limiting adverse events (AEs) and immune-related AEs (irAEs)
- Efficacy - complete response (CR) rate on imaging or salvage surgery at day 150

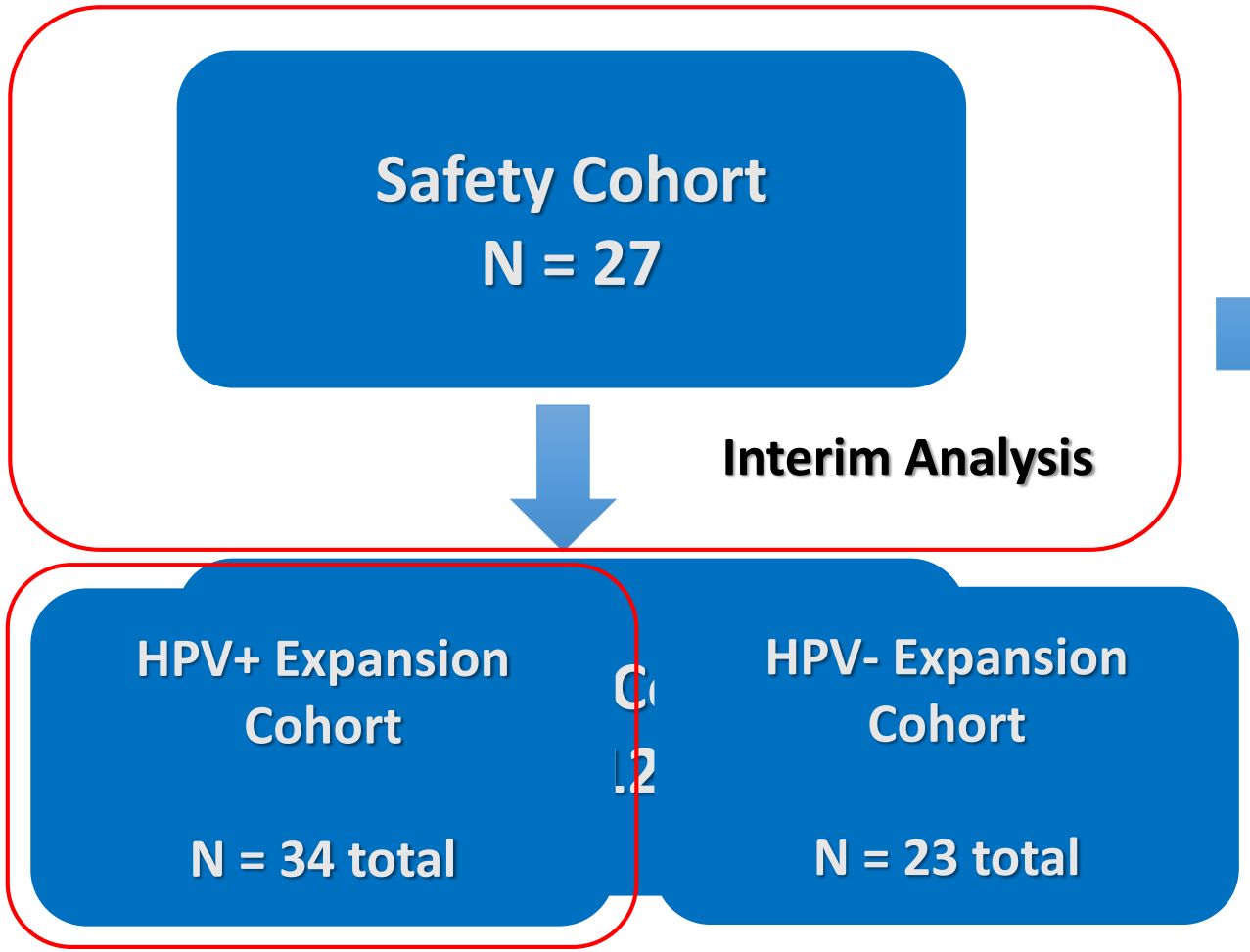
Secondary end points: PFS, OS, locoregional control, distant metastasis rate, quality-of-life (FACT H&N)

Inclusion/Exclusion Criteria

INCLUSION	EXCLUSION
Squamous cell carcinoma of the oral cavity (excluding lip), oropharynx, hypopharynx, or larynx	Prior chemotherapy, radiotherapy, or immunotherapy for SCCHN
Stage III, IVA, or IVB (AJCC 7th ed)	Stage IVC (distant metastases)
HPV + or HPV - (by p16 IHC*)	Concurrent active malignancy (excluding skin basal cell and squamous cell carcinomas)
Age ≥18	Active infections
ECOG PS 0-1	Active autoimmune disease
RECIST 1.1 measurable disease	History of HIV or active Hepatitis B or C
cisplatin eligible	

*HPV DNA testing for indeterminate IHC

Study Cohorts



*Based on Simon 2-stage MiniMax Design: CR rate of 60%

- **Interim Analysis – 27 enrolled**
  - **Study Opened Nov. 13, 2015**
  - **Stopped for IA on Aug. 8th, 2016**
  - **Safety data presented at ASCO 2017**
  - **Decision to expand to HPV+ and HPV- expansion cohorts to further explore efficacy**
- **Efficacy and Safety data for HPV + Cohort presented today**
  - **Efficacy – End of Treatment response**
  - **Safety – AEs and irAEs based on CTCAE v4.0**

*Sample size based on expected CR rate of 90% ($\alpha = 0.05$ and power of 80%) based on a historical control CR rate of 74% in HPV + cohort (NCT01386632)

Efficacy Endpoint Definition – Overall Complete Response at Day 150

RECIST 1.1[1]

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Hopkins Criteria[2]

Score	18F-FDG uptake pattern
1	18F-FDG uptake at the primary site and nodes less than IJV (internal jugular vein)
2	Focal 18F-FDG uptake at the primary site and nodes greater than IJV but less than liver.
3	Diffuse 18F-FDG uptake at the primary site or nodes is greater than IJV or liver.

Surgical

If no CR by CT or PET imaging, biopsy and/or salvage resection with no viable tumor cells

1- Eisenhauer EA, et a. *Eur J Cancer*. 2009 Jan;45(2):228-47.
2- Marcus C, et al. *J Nucl Med*. 2014 Sep;55(9):1411-6.

Demographics and Disease Characteristics

HPV + Patients n = 34	
Age (median, range)	59 yrs (36-81 yrs)
Sex (% male)	32 (94%)
(% female)	2 (6%)
Caucasian	34 (100%)
Non-Hispanic	33 (97%)
Hispanic	1 (3%)

27 pts (79%) had Intermediate-Risk disease with at least 1 high risk factors:

- T4, N2c or N3 disease
- tobacco use ≥10 pack year history (PYH)

HPV + Patients n = 34		
Primary site:		
	Oropharynx	31 (91.2%)
	Larynx	2 (5.9%)
	Hypopharynx	1 (2.9%)
Stage (AJCC 7th ed.)		
	III	3 (8.8%)
	IVA	31 (91.2%)
	IVB	0 (0%)
T stage		
	T0-3	23 (68%)
	T4	11 (32%)
N Stage		
	N0-1	7 (20.6%)
	N2a-b	19 (55.9%)
	N2c	8 (23.5%)
	N3	0 (0%)
Tobacco use (≥10 PYH)		19 (55.9%)

Results: Efficacy on Post-Treatment Imaging

RECIST 1.1 Response	HPV+ (n = 34)	95% CI
CR*	21 (62%)	45-78
PR	11 (32%)	17-48
SD	-	
PD	2(6%)	0-14

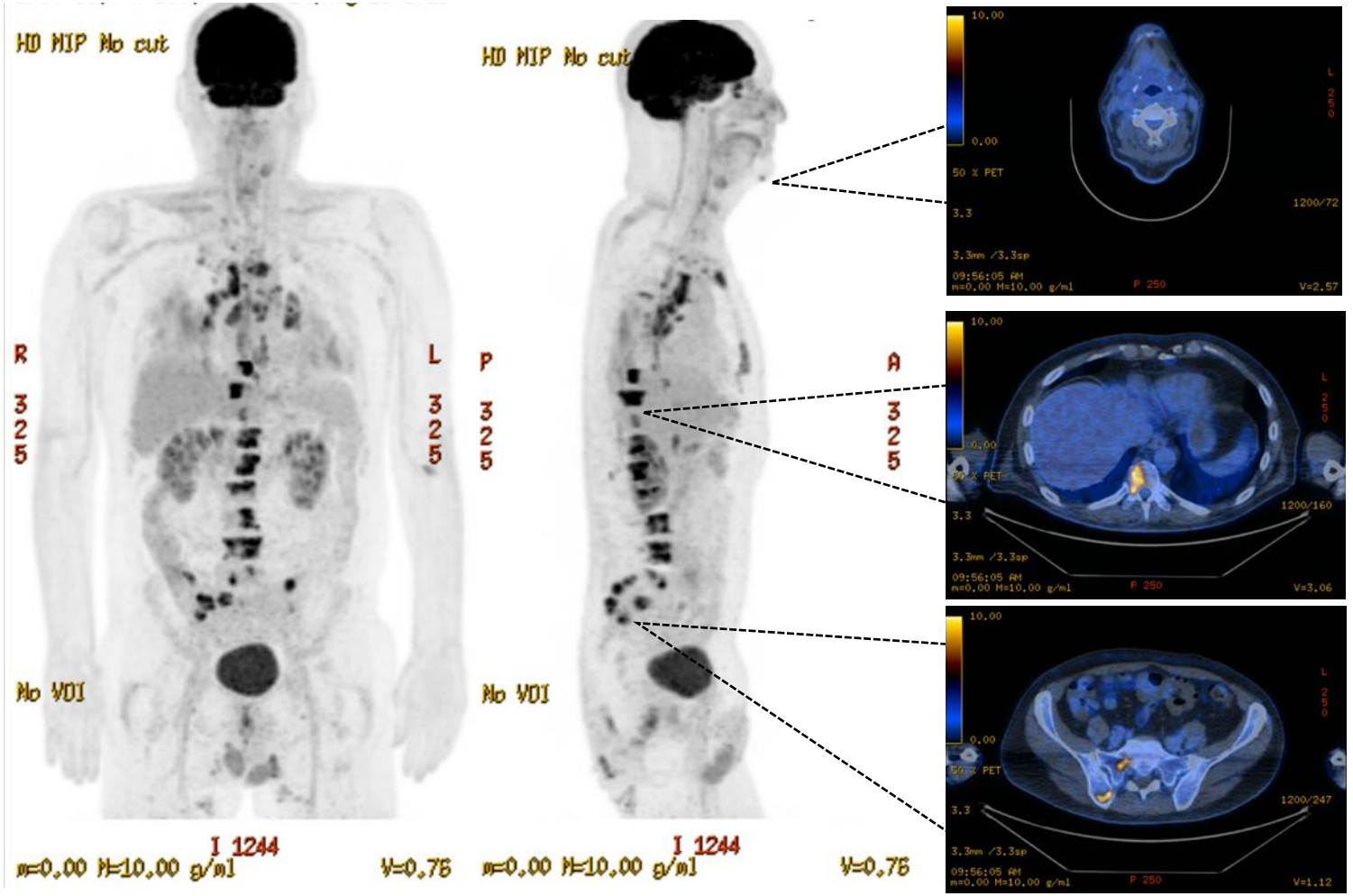
Hopkins PET Response	HPV+ (n = 32)*	95% CI
Negative (CR)	25 (78%)	64-92
Positive	7 (22%)	8-36

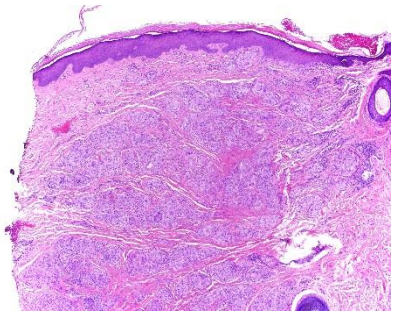
PET → Surgical Response	
RECIST PR (n = 11)	
Hopkins –	6
Hopkins + →Path CR	1
RECIST PD (n =2)	
Hopkins + → Path CR	1

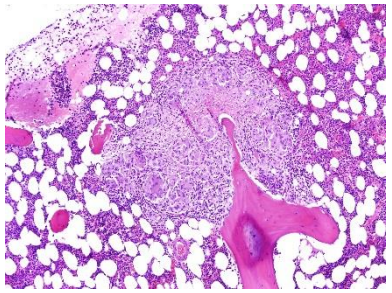
Final Overall Response	HPV+ (n = 34)	95% CI
CR	**29 (85%)**	**73-97**
PR	4 (12%)*	1-23
SD	-	
PD	1 (3%)	

***2 with no clinically evaluable disease, 2 with locoregional failure (1 primary site, 1 nodal)**

Challenges with PET imaging







Biopsies

Granulomatous disease consistent with Sarcoidosis

Resolved over 1 year

PET imaging may be difficult to interpret in this setting

3-month post-treatment PET – Concern for Progression

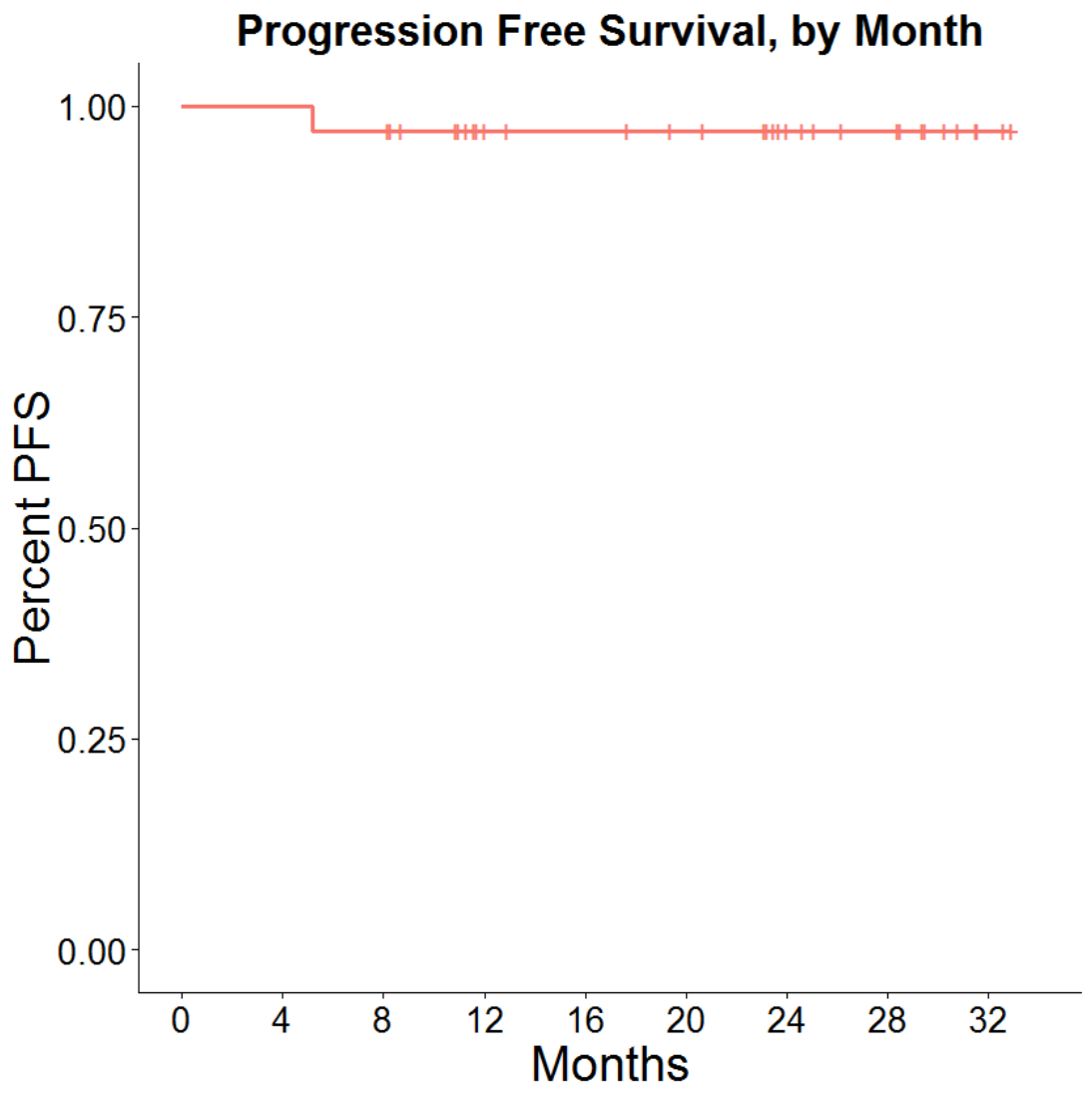
Early Survival Data

Median follow up: 23 months (range 8-33 months)

The estimated probability of PFS at
- 1 years = 97.1% (95% CI 80.9% - 99.6%)

At this point, OS data mirrors PFS data

1 patient death due to disease progression – distant metastases



Pembrolizumab – Discontinuations and irAEs

Pembrolizumab (8 planned doses)	N (%)
<3 doses (CRT)	1 (3%)
>3 but <8 doses (post-CRT)	3 (9%)
All 8 doses	30 (88%)

- **2 discontinuations due to irAEs (6%)**
  - **Grade 2 peripheral motor neuropathy**
  - **Grade 1 Lhermitte-like syndrome**
  - **No other irAEs requiring discontinuation or treatment**
- **2 discontinuations due to protocol reasons (6%)**
  - **Early neck dissection**
  - **Prolonged hospitalization**

Treatment Compliance - CRT

Cisplatin (40 mg/m² x 6 weekly doses)	
Dose reduction (N,%)	4 (12%)
Dose omission (N,%)	9 (26%)
Completed ≥ 200 mg/m² (N,%)	30 (88%)
Median Cumulative Dose (SD)	227 mg/m² (SD - 25)

- Reasons for discontinuation
  - neutropenia (n = 4)
  - thrombocytopenia (n = 3)
  - elevated creatinine (n = 1)
  - allergic reaction (n=1)

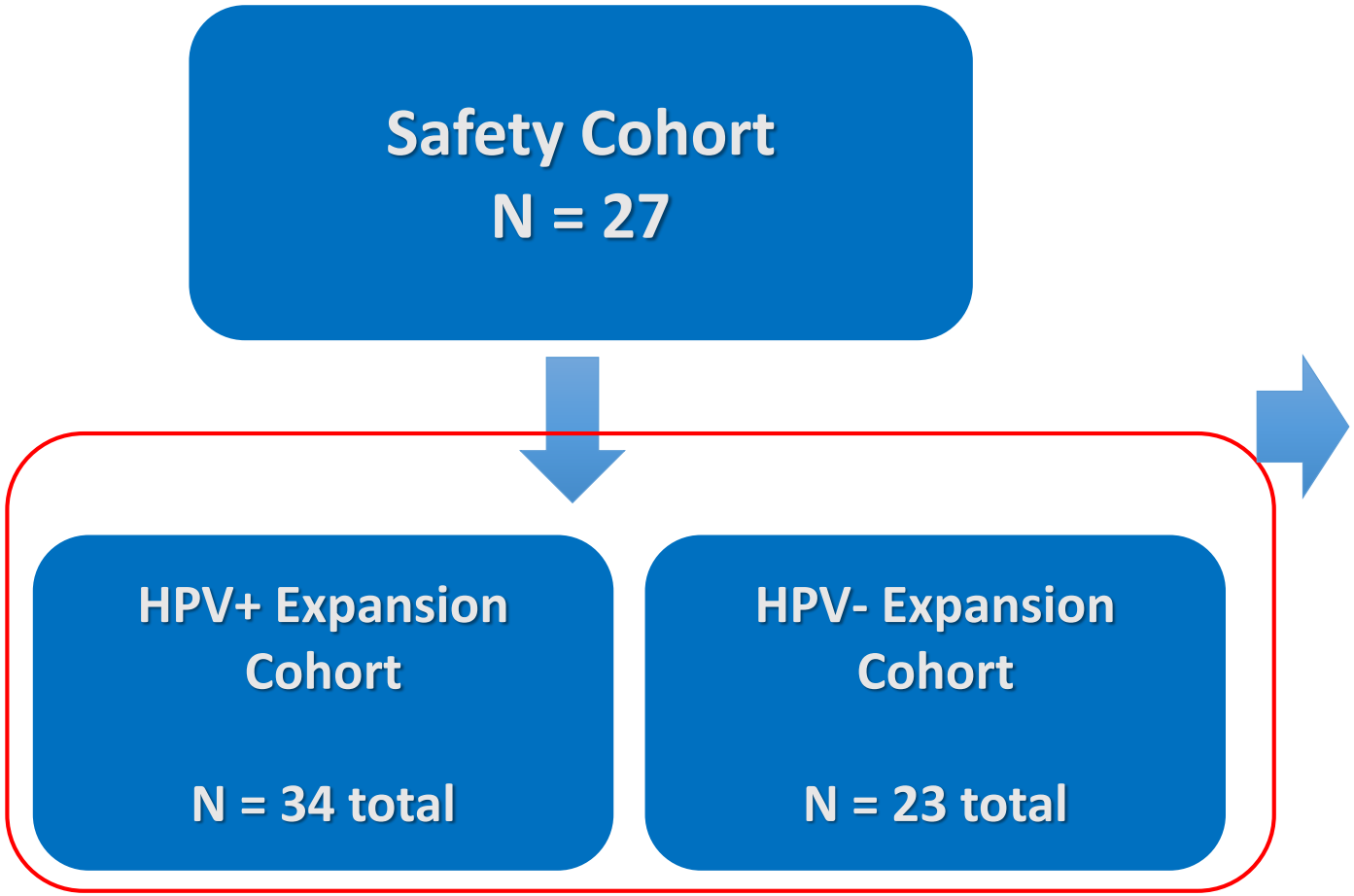
Radiation Therapy (70 Gy planned)	
Treatment Delay > 5 days (N,%)	0 (0%)
Treatment Delay ≤ 5 days (N,%)	2 (7.4%)
Mean Days Duration (SD)	49.5 (2.4)
70 Gy RT Completed (N,%)	34 (100%)

- Reasons for delay (<5 days)
  - Hospitalization (n =1)
  - Equipment Malfunction (n =1)

Selected Adverse Events

AE	ALL Grades	Grade 3	Grade 4
Dysphagia	32 (94%)	21 (62%)	None
Weight loss	32 (94%)	12 (35%)	
Mucositis oral	32 (94%)	12 (35%)	
Dermatitis radiation	28 (82%)	2 (6%)	
Lymphocyte count decreased	34 (100%)	18 (53%)	14 (41%)
Anemia	34 (100%)	4 (12%)	None
White blood cell decreased	32 (94%)	16 (47%)	2 (6%)
Hyponatremia	24 (71%)	5 (15%)	None
Neutrophil count decreased	21 (62%)	6 (18%)	3 (9%)

Current Study Status



- **Expansion Cohorts – Efficacy**
  - **HPV+ disease – Early response data presented here**
  - **HPV- disease – Completed enrollment in August 2018**
- **Correlative Research**
  - **Peripheral Blood T-cell Analysis**
    - **SITC 2018 Poster P465**
  - **Baseline tumor PD-L1 Expression (22c3 assay)**
  - **Tumor DNA, RNA, Proteomic Analysis – NantOmics and CHOC**

Lessons and Take Home Messages

- Pembrolizumab plus weekly cisplatin and radiation is showing promising early response and survival data in locally-advanced HPV-associated HNSCC
  - 85% (29/34) with CR based on imaging/surgery (additional 2 with no clinical evidence of disease)
  - Majority (79%) with Intermediate-Risk Disease
- PET imaging may pose challenges as immunotherapy moves into curative intent approaches
- No new safety signals seen
  - **Pembrolizumab –** Discontinuations due to irAEs in 2 patients (6%) – in line with monotherapy
  - **Radiation –**Definitive dose delivered in all patients without significant delays
  - **Cisplatin –** 88% of participants received **≥200 mg/m²**
- Early efficacy data supports ongoing investigation of this approach
  - Numerous Phase III trials currently enrolling participants with intermediate/high-risk disease
- **Ongoing correlative research is critical to understand timing of IO therapy and potential combinations**

Acknowledgements

Our patients and their families

Participating Centers and Study Team

- *Sanford Cancer Center Sioux Falls*: Chad Spanos, John Lee, Steve McGraw, Michele Lohr, Ryan Nowak, Paul Thompson, Christie Ellison, Lora Black, Christopher Fischer
- *Sanford Cancer Center Bismarck*: John Reynolds
- *Sanford Roger Maris Cancer Center Fargo*: Mark Gitau, Ash Jensen, Miran Blanchard, Andrew Terrell
- *UCSD Moores Cancer Center*: Katherine Gold, Ezra Cohen, Julie Bykowski

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