Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Immunotherapy in the Curative Intent Setting – Neoadjuvant

Ravi Uppaluri MD/PhD

BWH Distinguished Chair in Otolaryngology

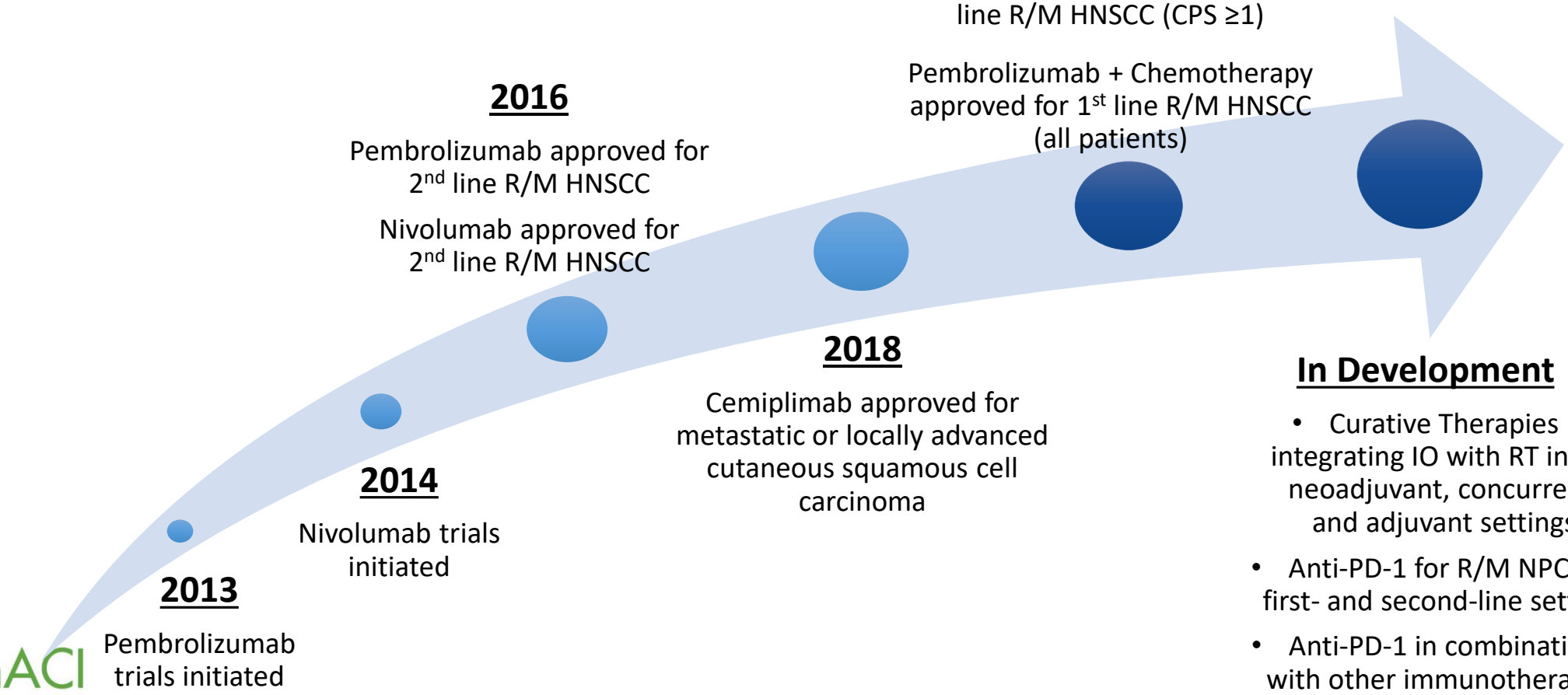
Brigham and Women's Hospital and Dana-Farber Cancer Institute

#LearnACI

Disclosures

- Grant/Research support : NIH/NCI/NIDCR, Merck Inc. and V Foundation
- Advisory Board: Merck, Inc
- Royalties: Washington University, Kerafast, BioLegend
- I will be discussing non-FDA approved indications during my presentation.

Development of checkpoint inhibitors in head and neck cancer



2013

Pembrolizumab trials initiated

2014

Nivolumab trials initiated

2016

Pembrolizumab approved for 2nd line R/M HNSCC

Nivolumab approved for 2nd line R/M HNSCC

2018

Cemiplimab approved for metastatic or locally advanced cutaneous squamous cell carcinoma

2019

Pembrolizumab approved for 1st line R/M HNSCC (CPS ≥1)

Pembrolizumab + Chemotherapy approved for 1st line R/M HNSCC (all patients)

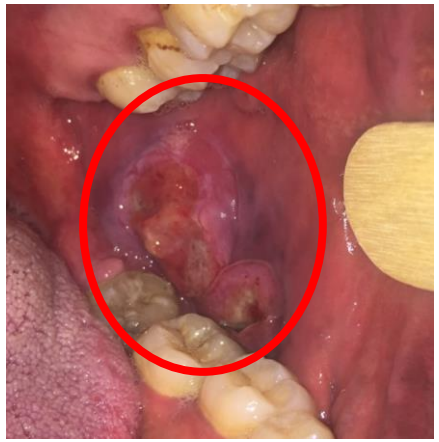
In Development

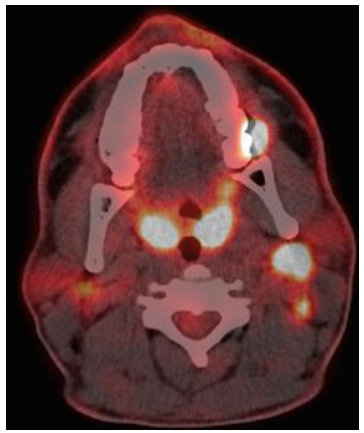
- Curative Therapies integrating IO with RT in the neoadjuvant, concurrent, and adjuvant settings
- Anti-PD-1 for R/M NPC in first- and second-line settings
- Anti-PD-1 in combination with other immunotherapies

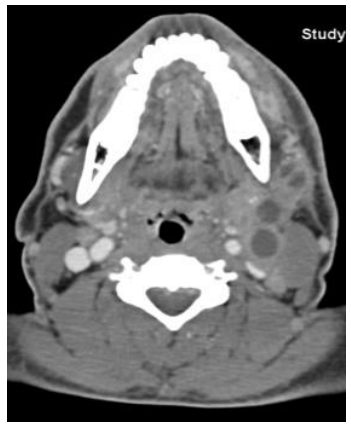
#LearnACI

Standard of Care- Oral cavity SCCA

Buccal SCCA
cT2N2b







1. **Multidisciplinary evaluation**
   a) Metastatic workup
2. **Surgery- ablation/ reconstruction**
3. **Adjuvant treatment based on surgical pathology**
   a) POART- post-operative adjuvant radiation therapy
   b) POACRT- post-operative adjuvant chemo-radiotherapy
4. **Post-op management**
5. **Cancer surveillance**

Why neoadjuvant immunotherapy?

- Improvements needed for high-risk LA-HNSCC
- Neoadjuvant approach may help induce immune response to deliver durable benefit
- “Immuno-reduction”- may alter surgery
- Reduced need for adjuvant approaches

HNSCC trials including Neoadjuvant CPI- published

- CIAO trial- durvalumab/ tremelimumab in OPSCC
  - Ferrarotto et al., CCR, 2019
- Pembrolizumab in LA-HNSCC
  - Uppaluri et al., CCR, 2020
- Nivolumab/ Ipilimumab in OCSCC
  - Schoenfeld et al., JAMA Onc., 2020
- Nivolumab and discordant primary/ LN path responses
  - Merlino et al., Frontiers Oncology, 2020
- Neoadjuvant Nivolumab in HPV+ and HPV- HNSCC
  - Ferris et al., CCR, 2021
- Neoadjuvant Cemiplimab in cutaneous SCCA
  - Ferrarotto et al., CCR, 2021
- Neoadjuvant SBRT+nivolumab in HNSCC
  - Leidner et al., JITC, 2021
- Nivolumab (3-4 doses) in OCSCC
  - Knochelmann et al., Cell Medicine, 2021

Are CPIs safe prior to surgery?

Well tolerated with several anti-PD1/PDL1 agents

- WashU/ DFCI experience
  - Nivolumab/Ipilimumab- in 30 patients, no delays
  - Pembrolizumab- >60 patients to date, no delays
  - Nivolumab/lirilumab- 27 patients, no delays
- Several other reports in HNSCC with no surgical issues

Timing- what is a safe delay in surgery?

Time to surgery and "delay"

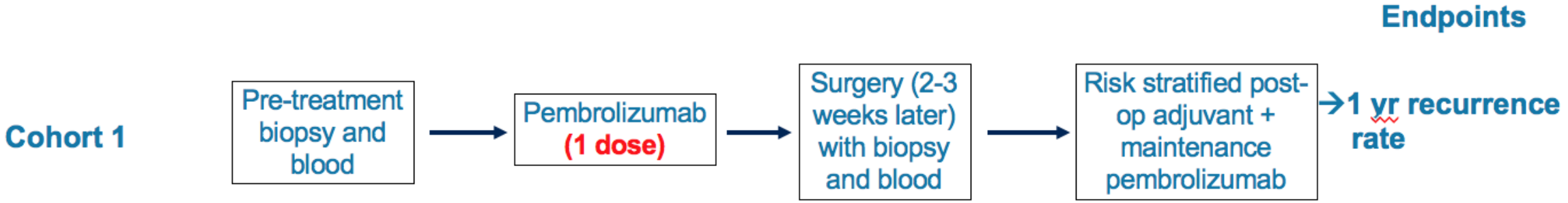
- Not a delay as treatment is being initiated in the "window"

- Several HNSCC studies on time to treatment initiation
  - "TTI of greater than 46 to 52 days introduced an increased risk of death that was most consistently detrimental beyond 60 days", Murphy et al., JCO 2016
  - >67 days associated with increased risk of death (HR, 1.189), Rygalski et al., Ann. Surg Onc, 2021
  - >60 days associated with worse outcomes, Liao et al. JAMA-Oto/HNS, 2019

Six questions and key study findings

- What are characteristics of HNSCC pathologic tumor response?
- What is implication of partial pathologic responses to clinical outcomes?
- What is the data in HPV+ and HPV- disease?
- What is impact of neoadjuvant therapy in the salvage surgical setting?
- How about combinations? Nivolumab and Nivolumab+Ipilimumab
- Does neoadjuvant therapy work in cutaneous SCCA?

Immunotherapy With MK-3475 in Surgically Resectable Head and Neck Squamous Cell



Endpoints

Co-Primary

1. Reduce relapse rate at 1 year—from 35% to 15% in high-risk patients
2. Rate of major pathologic tumor response (PTR>50%) in surgical specimen

Secondary

1. Safety
2. Correlative biomarker and genomic assessment in the pre-/post-treatment blood and tumor tissue

NCT02296684, Uppaluri/ Adkins

Key Clinical Outcomes

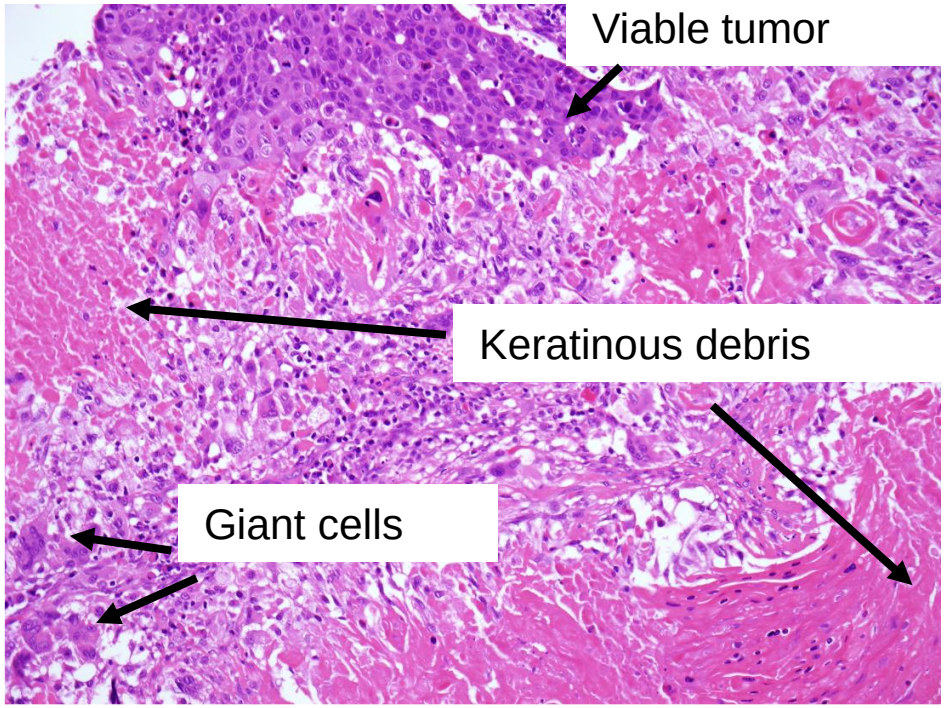
- **Safety:** No serious study drug-related AEs or unexpected surgical delays
- **Relapse rate** of 16.7% for high-risk patients and 9% for overall cohort
- **Pathologic tumor responses**
  - Grading scale→**pTR0**=no or <10% response, **pTR1**= ≥ 10% and <50%, and **pTR2**= ≥50%
  - pTR2 in 22.2% of patients (8/36)
  - Any pTR (>10%) in 44.4% of patients (16/36)

Pathologic tumor response (pTR)

- Tumor cell necrosis and/or
- Giant cell/histiocytic reaction to keratinous debris
- *Distinct* from growing tumor and only seen with therapy
- *→Evidence of activated immune response to tumor*

- All pathology slides reviewed by two independent pathologists
- Consensus review for cases with differing reads (in deciles)

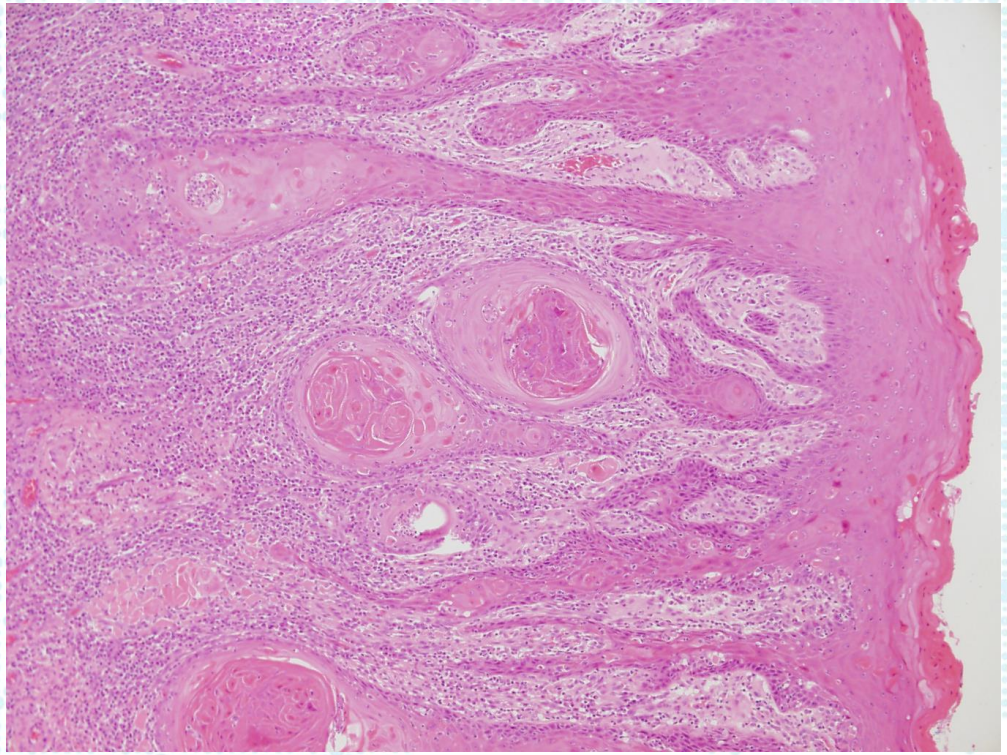
$$\text{Percent pTR} = \frac{\text{area pTR}}{\text{area pTR} + \text{area tumor}}$$



R. Chernock, WUSTL

2021 ASCO ANNUAL MEETING

ENHANCED PATHOLOGIC TUMOR RESPONSE WITH TWO CYCLES OF NEOADJUVANT PEMBROLIZUMAB IN SURGICALLY RESECTABLE, LOCALLY ADVANCED HPV-NEGATIVE HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC)



Ravindra Uppaluri, MD/PhD

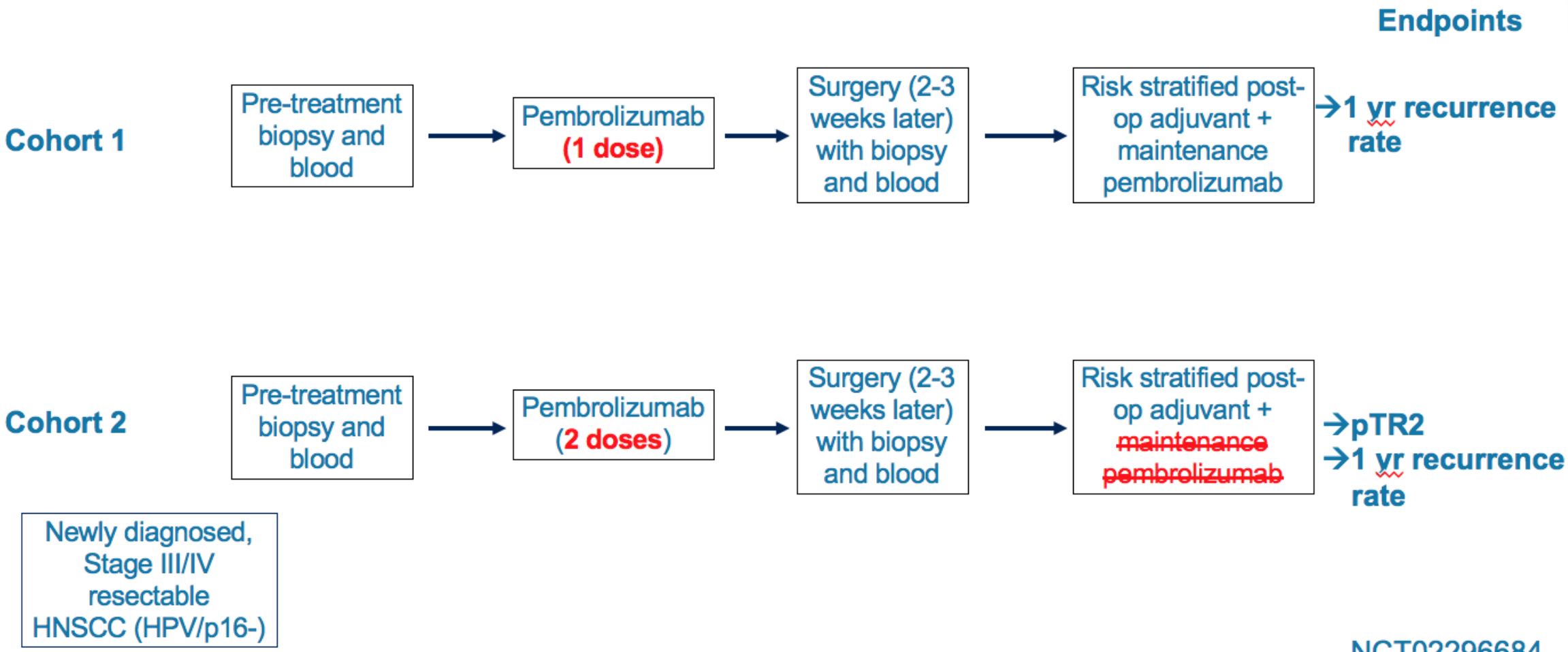
Dana-Farber/ Brigham and Women's Cancer Center

Douglas Adkins, MD

Siteman Cancer Center/ Washington University in St. Louis

June 7, 2021

Schema for Cohort 2



Summary of neoadjuvant pembrolizumab studies

- pTR-2 rates were doubled with two versus one dose of neoadjuvant pembrolizumab
  - Possible explanation includes timing (3 versus 6 weeks) or 2 doses of drug
  - 1-year OS and PFS were excellent

- Further studies are needed to define optimal dosing/timing and relevance of pTR to clinical outcome

Pathologic response and clinical outcomes

- Only a minority of patients achieve a pCR to single-agent neoadjuvant anti-PD1/ PDL1
  - HNSCC shows lower rates of pCR than lung and melanoma

- Emerging data that any pathologic response may be correlated with outcomes

2021 ASCO ANNUAL MEETING

PATHOLOGICAL RESPONSE TO NEOADJUVANT PEMBROLIZUMAB IS ASSOCIATED WITH TUMOR PD-L1 EXPRESSION AND HIGH DISEASE-FREE SURVIVAL (DFS) IN PATIENTS WITH RESECTABLE, LOCAL-REGIONALLY ADVANCED, HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC)

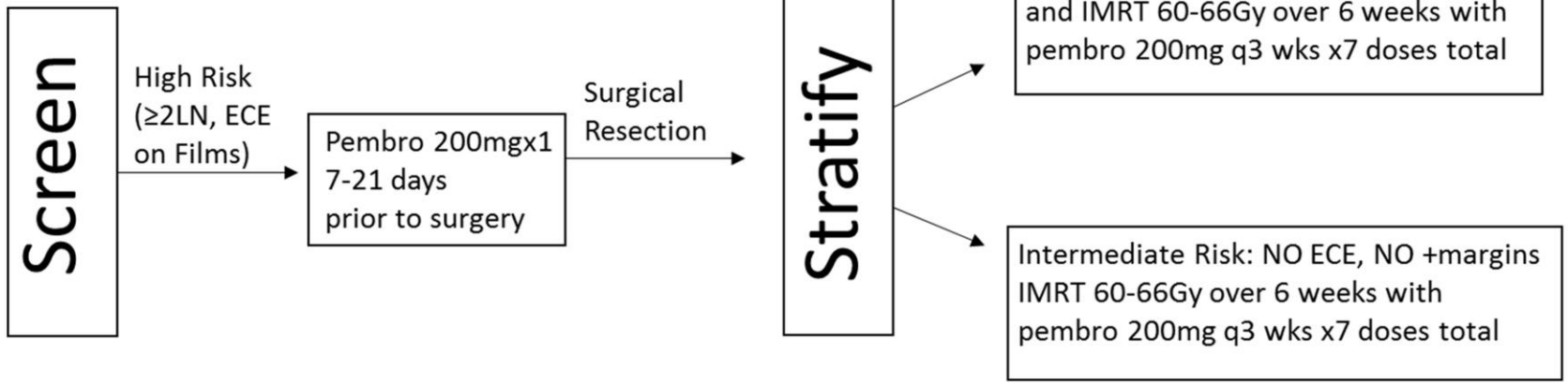
Trisha Wise-Draper MD, PhD, University of Cincinnati

June 7th, 2021

Co-Authors: Vinita Takiar MD, PhD, Michelle Mierzwa MD, Keith Casper MD, Sarah Palackdharry, Francis Worden MD, Matthew Old MD, Neal Dunlap MD, John Kaczmar MD, Yash Patil MD, Muhammad Kashif Riaz MD, Shuchi Gulati MD, Aubrey Hamilton MD, Ann Gillenwater MD, Benjamin Hinrichs MD, Diana Bell MD, Casey L. Allen, Sheena Lanverman, Li Zhang PhD, Nusrat Harun, J. Jack Lee PhD, Maura Gillison MD, PhD

Pembrolizumab in resectable HPV-negative HNSCC

Flow Diagram



- 40 patients in each arm had 80% power and alpha=0.025 (one-sided) to detect an increase of 21% in DFS at 1 year
- 92 patients enrolled; 76 evaluable (Received ≥ 1 dose adjuvant pembrolizumab)
- Sites: UC, UMich, OSU, MUSC, Univ of Louisville, MDA

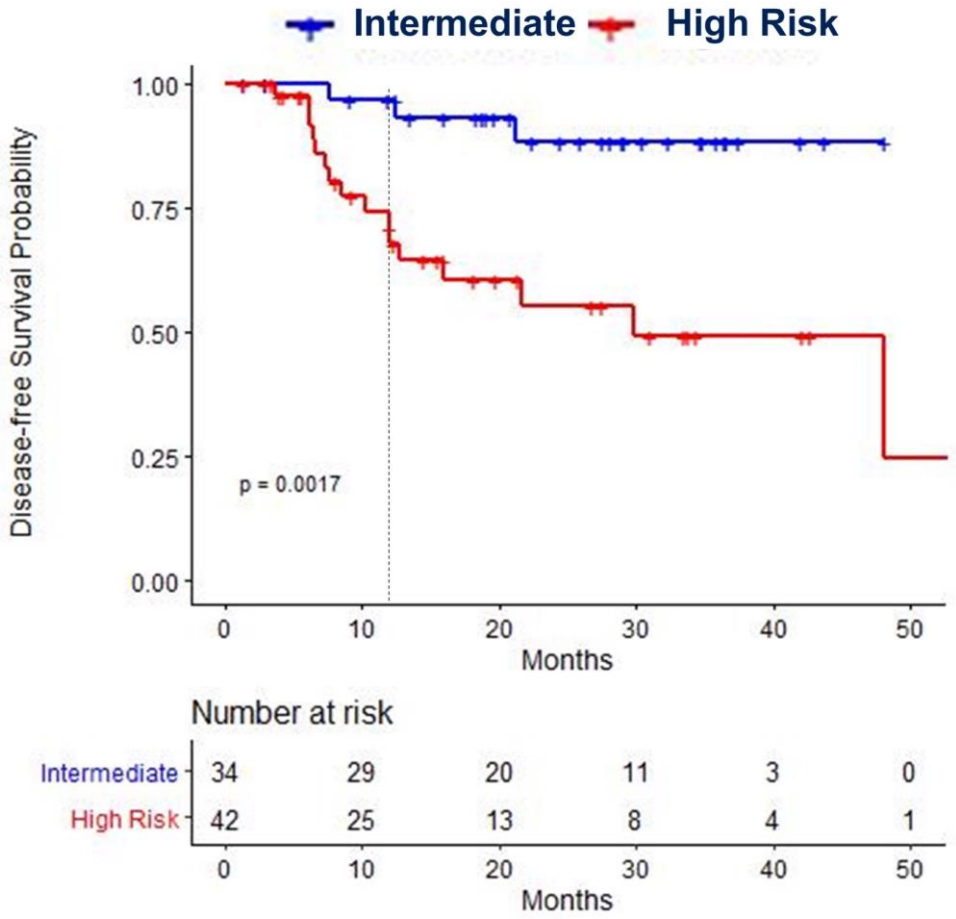
RTOG 9501 analysis showed 1-year DFS of 65 and 69% for high-and intermediate-risk pathology, respectively

Endpoints

1. DFS at 1 year
2. OS and TME changes
3. Safety

Wise-Draper, ASCO2021

Disease Free Survival: High vs. Intermediate risk



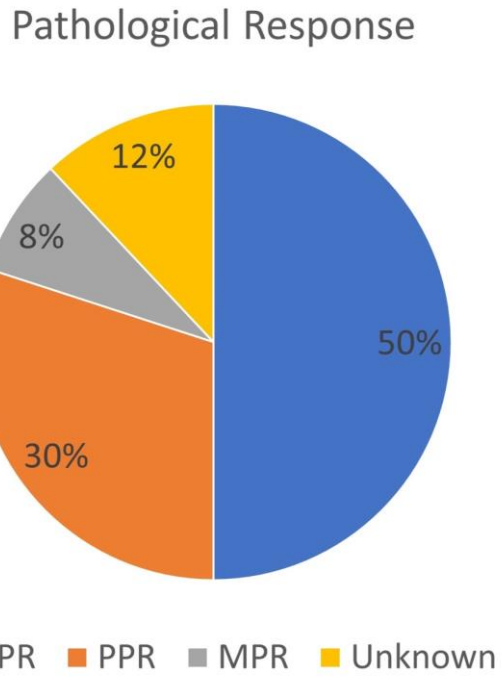
Risk	RTOG 9501 1-yr DFS	95% CI	This study 1-yr DFS	95% CI
High	65%	0.57-0.74	68%	0.54-0.86
Intermediate	69%	0.59-0.78	97%	0.91-1

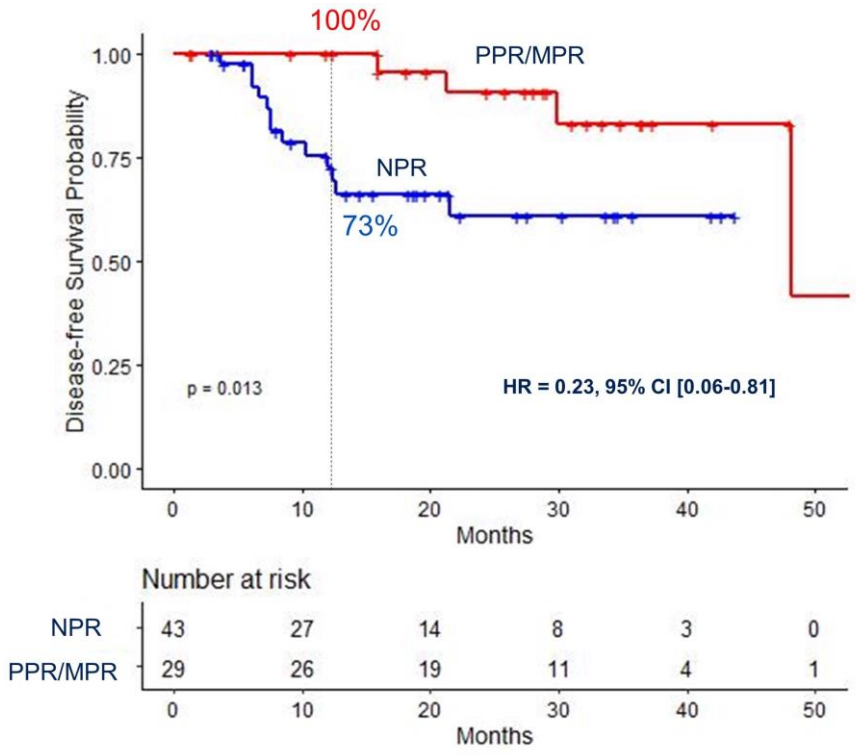
→Endpoint met for the intermediate risk group

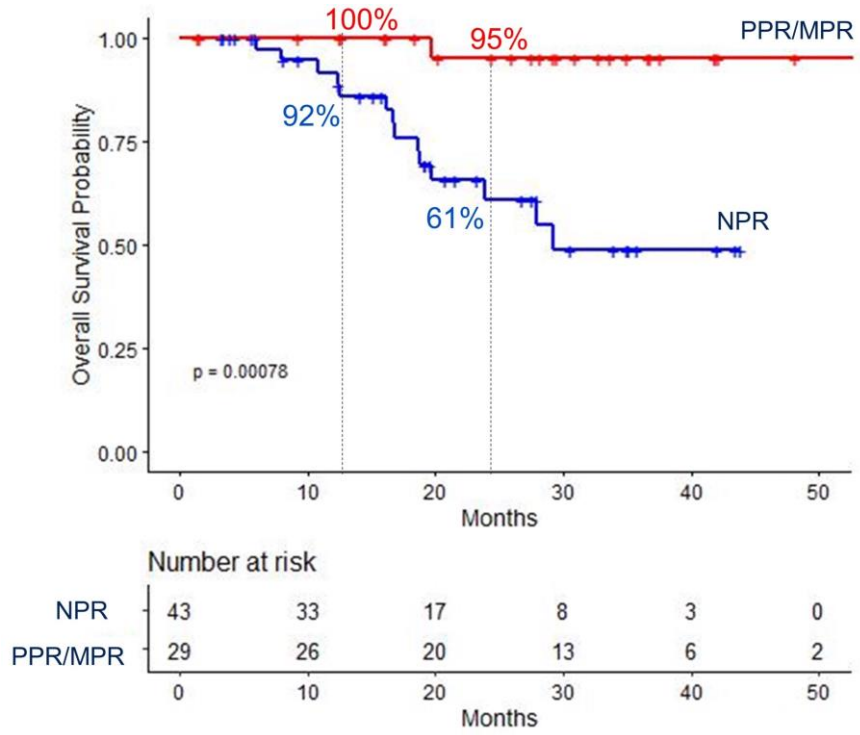
#LearnACI

Wise-Draper, ASCO2021

DFS and OS by pathological response







Non-response (NPR): <20% TE
Partial response (PPR): 20-90% TE
Major response (MPR): ≥ 90% TE

#LearnACI

Wise-Draper, ASCO2021

Summary of results

- DFS was increased compared to historical controls in intermediate risk patients

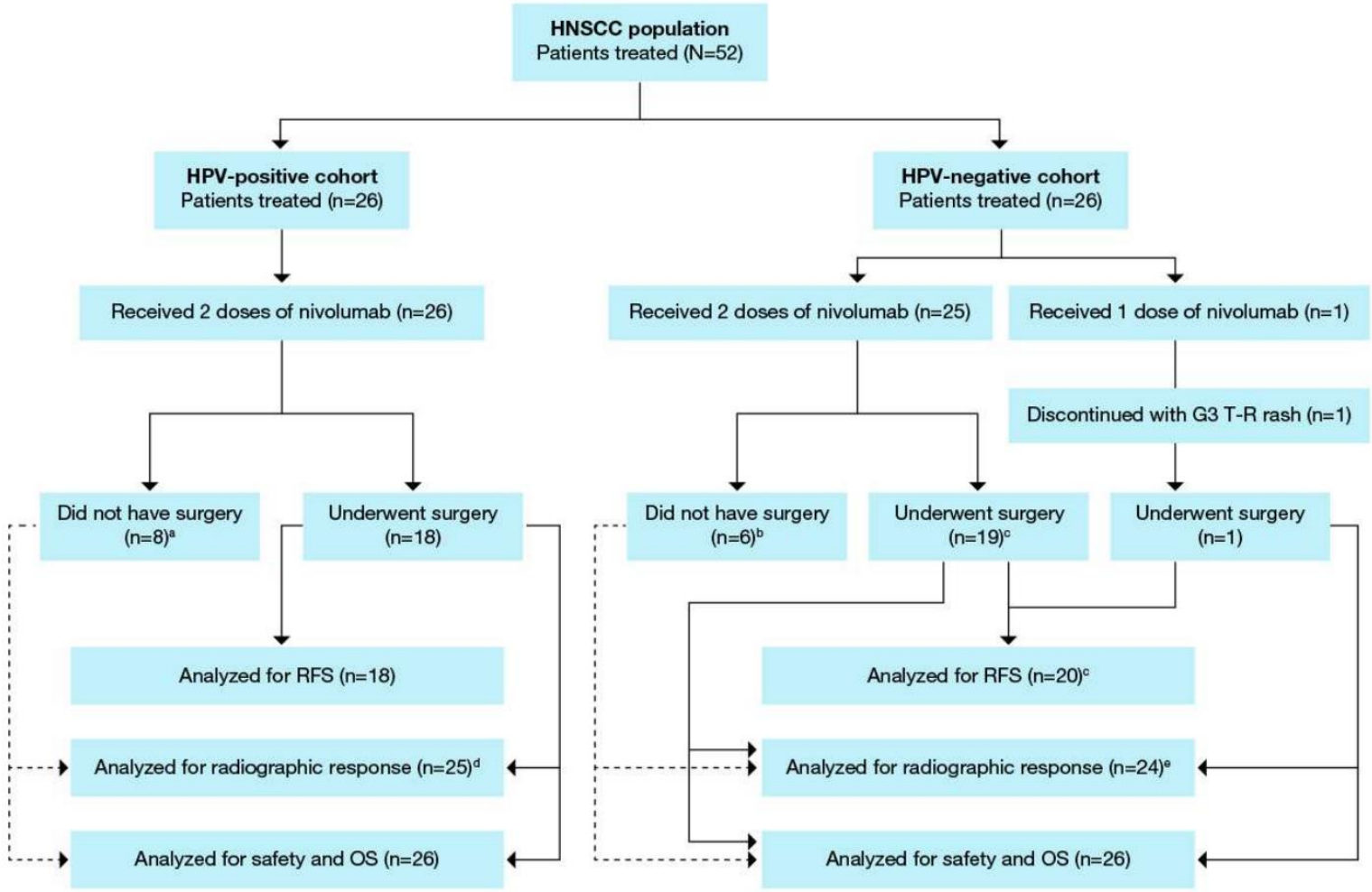
- Pathological responses were associated with improved DFS/OS

Wise-Draper, ASCO2021

Checkmate358- Neoadjuvant nivolumab for HPV+ and HPV- HNSCC

Primary endpoint
-Safety/tolerability of neoadjuvant nivolumab (TRAEs and and surgical delays (>4 weeks from surgery date).

Exploratory endpoints
-Pathologic response
-Radiographic response (RECIST v1.1)
-Recurrence free survival
-Overall survival



Ferris et al., JITC 2021

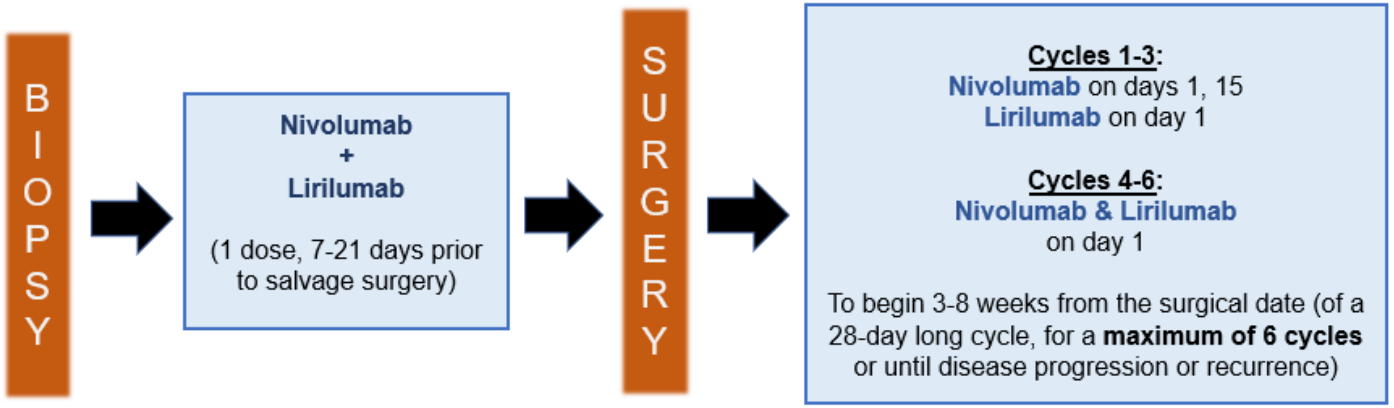
#LearnACI

Summary of results

- Safety
  - No patient discontinued nivolumab due to a TRAE, no treatment-related deaths.
  - No patient had a protocol-defined TRAE-related surgical delay (>4 weeks)
- Pathologic response
  - HPV-positive
    - 1/17 (5.9%) HPV-positive tumors had an MPR
    - 3/17 (17.6%) HPV-positive tumors had a pPR
    - MPR + pPR rate of 23.5%.
  - HPV-negative
    - 1/17 HPV-negative tumors evaluated by central review, one (5.9%) achieved a pPR.
- RECIST
  - 49 evaluable patients-12.0% and 8.3% in the HPV-positive and HPV-negative, respectively

Ferris et al., JITC 2021

Neoadjuvant and adjuvant nivolumab and lirilumab in patients with recurrent, resectable squamous cell carcinoma of the head and neck



Primary endpoint: **1-year disease-free survival (DFS)**

Secondary endpoints:
Overall survival (OS)
Safety and tolerability
Overall response rate (ORR) based on imaging

Exploratory endpoints:
Tumor PD-L1 status
Tumor genomic sequencing parameters
Paired tumor and peripheral blood immune profiling

Hanna et al., CCR, 2021

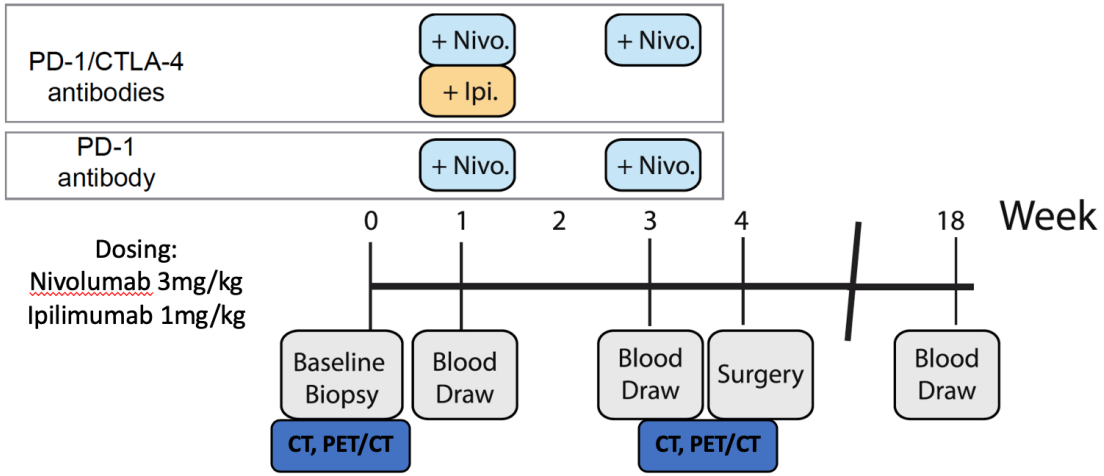
Neoadjuvant and adjuvant nivolumab and lirilumab in patients with recurrent, resectable squamous cell carcinoma of the head and neck

- Most had SD as best radiologic ORR to pre-op immunotherapy, **3 (11%) with tumor regression** (not achieving PR)
- There were **no delays to salvage surgery**; no grade 4+ AEs observed
- **43% rate of pathologic response (partial or major)**
- **1-year DFS: 55.2%; 1-year OS: 85.7%**
- **13 (46%) experienced recurrence**: only 3/13 with prior pathologic response
- Positive margins and *not* completing 6-cycles of adjuvant therapy were associated with failure

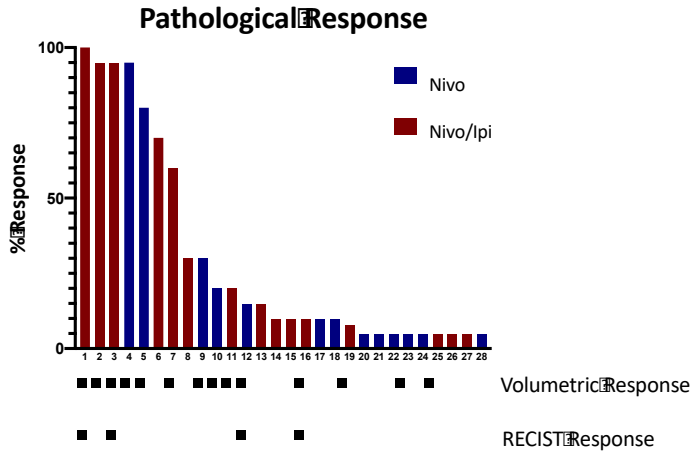
Hanna et al., CCR, 2021

Neoadjuvant Nivolumab +/- Ipilimumab in Patients with Oral Cavity Cancer

Inclusion criteria: SCC of the oral cavity, at least clinically T2 or node positive.



Surgery performed from 72 hours to 1 week following C2 after restaging scans



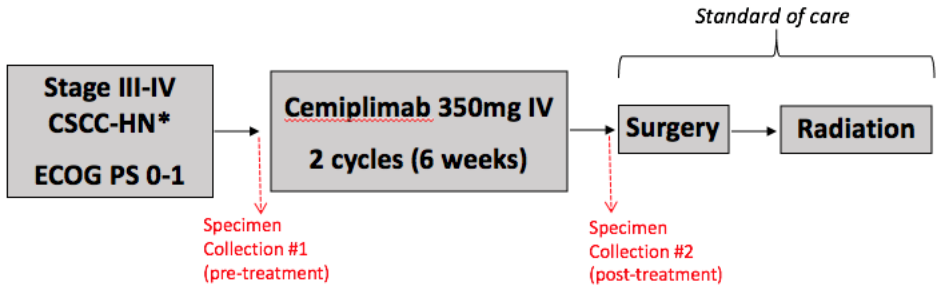
Treatment	N (n=14)	N+I (n=15)
Volumetric response	50% (7)	53% (8)
RECIST response*	13% (1)	38% (3)
Pathologic response >50%	15% (2)	33% (5)
Pathologic response >90%	8% (1)	20% (3)

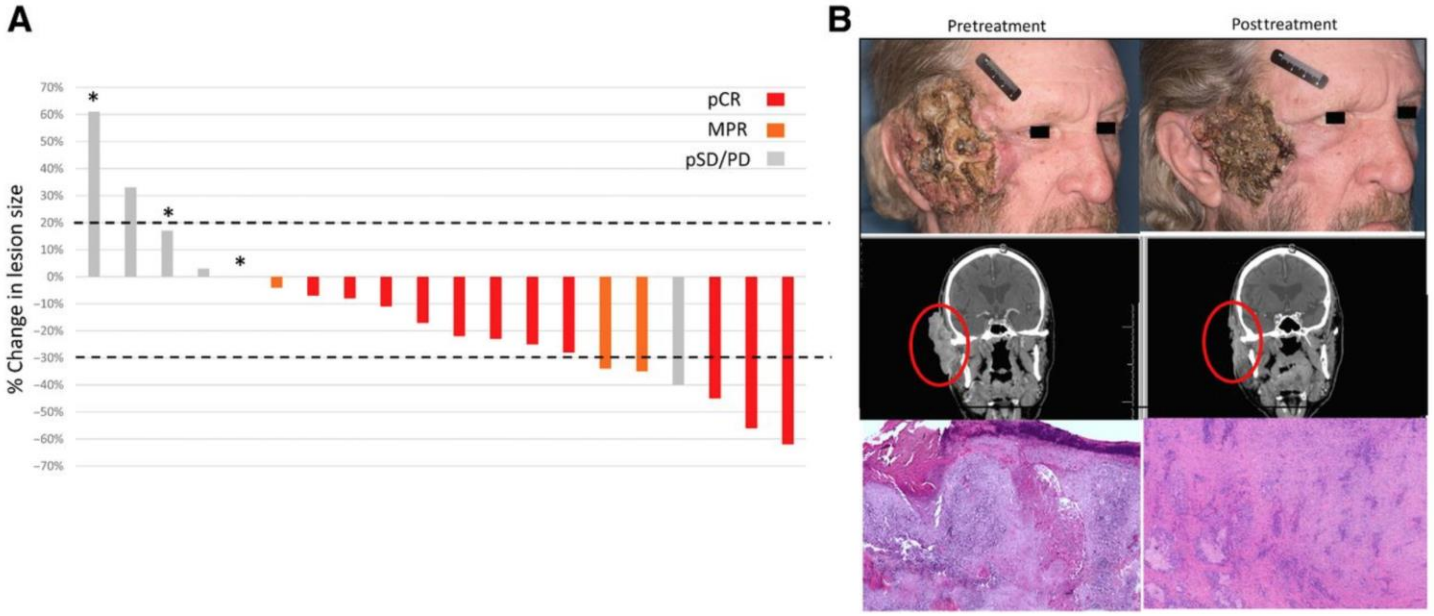
*13 patients without measurable disease on CT and/or PET/CT (6 in N arm, 7 in N+I arm) not assessed for RECIST response.

Schoenfeld et al., JAMA Onc, 2020

#LearnACI

Neoadjuvant Immunotherapy in Locoregionally Advanced, Resectable Cutaneous SCCHN





Key Points

1. 20 patients enrolled (13 new and 7 recurrent)

2. No serious adverse events and all TRAE resolved fully with no surgical delays

3. No association of imaging and pathologic response

4. 70% (14/20; 95% CI, 45.7–88.1) of patients achieved either a pCR (11, 55%) or MPR (3, 15%)

#LearnACI

Ferrarotto et al., CCR, 2021

Six questions and key study findings

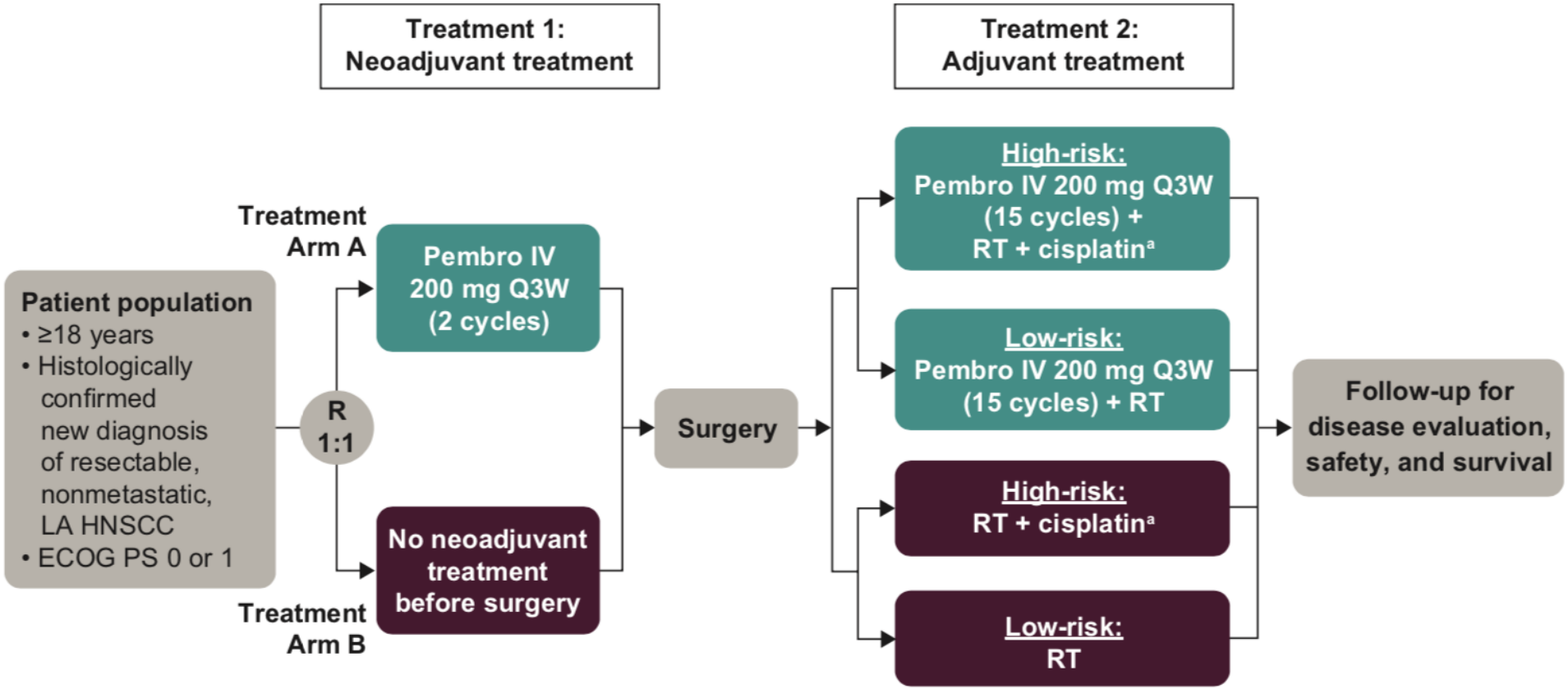
- What are characteristics of HNSCC pathologic tumor response?
- What is implication of partial pathologic responses to clinical outcomes?
- What is the data in HPV+ and HPV- disease?
- What is impact of neoadjuvant therapy in the salvage surgical setting?
- How about combinations? Nivolumab and Nivolumab+Ipilimumab
- Does neoadjuvant therapy work in cutaneous SCCA?

HNSCC Neoadjuvant Approaches- Future Directions

- Multiple ongoing Phase 2 studies with novel combinations/ approaches
  - Study of Safety and Tolerability of Nivolumab Treatment Alone or in Combination With Relatlimab or Ipilimumab in Head and Neck Cancer (Ferris, NCT04080804)
  - Neoadjuvant Immunoradiotherapy in Head & Neck Cancer (NIRT 2-HNC, Bell, NCT04938609)

- Phase III KN689

KEYNOTE-689: Phase 3 Study of Neoadjuvant and Adjuvant Pembrolizumab Combined With Standard of Care in Patients With Resectable, Locally Advanced Head and Neck Squamous Cell Carcinoma



#LearnACI

NCT03765918

Conclusions

- Neoadjuvant immunotherapy
  - Safe with no concerning TRAEs or surgical delays
  - Pathologic responses (partial) across several HNSCC settings
  - Clinical outcomes may be associated with partial pathologic responses

- Clinical implications
  - Can we improve on partial pathologic responses?
  - For HPV-negative disease, what is relevance of adding pembrolizumab for intermediate risk patients ?
  - Salvage surgery setting is ideal area to further evaluate neoadjuvant/ adjuvant therapy
  - Cutaneous SCCAs have high pCR rates and most obvious setting to include neoadjuvant therapy

Acknowledgements

Our patients and their families

DFCI/BWH HNOP: J Schoenfeld, GJ Hanna, J Lorch, R Tishler, D Margalit, N Treister, L Goguen, J Kass, E Rettig, D Annino

DFCI/BWH Lab: AM Egloff, T Mudianto, H Shibata, S Saito, J Webb, N Xu, L Zhou

McDonnnell Genome Institute: OL Griffith, M Griffith, K Campbell

DFCI/BWH Pathology: S Rodig, E Gjini, A Lako, M Stachler, V Jo

WUSTL/Siteman: D Adkins, P Zolkind, R Chernock, J Piccirillo, D Kallogjeri, J Ley, N Beck, B Nussenbaum, R Paniello, J Rich, R Jackson, P Pipkorn, P Oppelt, T Wildes, T Lin, GP Dunn, W Thorstad and I Hagemann

Funding agencies

Merck Investigator Initiated Studies Program
Jimmy V Foundation Translational Research Award
National Comprehensive Cancer Network
NIH/NIDCR R01 DE024403
NIH/NIDCR R01 DE027736
NIH/NCI/NIDCR U01 DE029188