Novel Systemic Therapy for Head and Neck Cancer

EMORY WINSHIP CANCER INSTITUTE
A Cancer Center Designated by the National Cancer Institute

Debates and Didactics in Hematology and Medical Oncology, The Cloister in Sea Island
July 20th , 2023

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Potential Conflicts of Interest

I received compensation for advisory role or Honoraria from,

-Astra Zeneca,

-Pfizer,

-Merck,

-GSK,

-Novartis,

-Inovio,

-EMD Serono,

-Vaccinex,

-Kura Oncology,

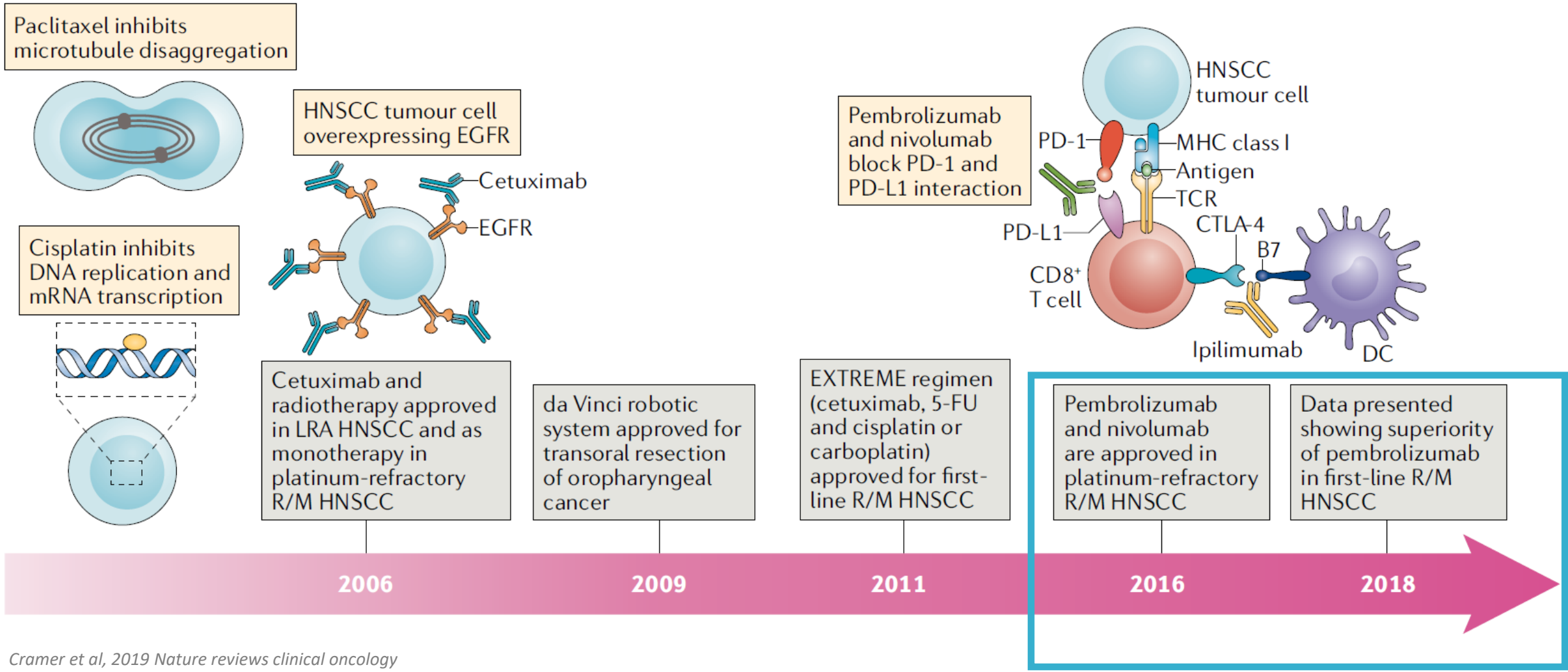
-Celldex Therapeutics,
-Eisai,
-Exelixis,
-CUE Pharma,
-Fulgent
-Akeso
-Seagen

Honoraria from:
-Onclive,
-Reach MD,
-Uptodate,
-WebMD,
- Springer

I received research funding from:

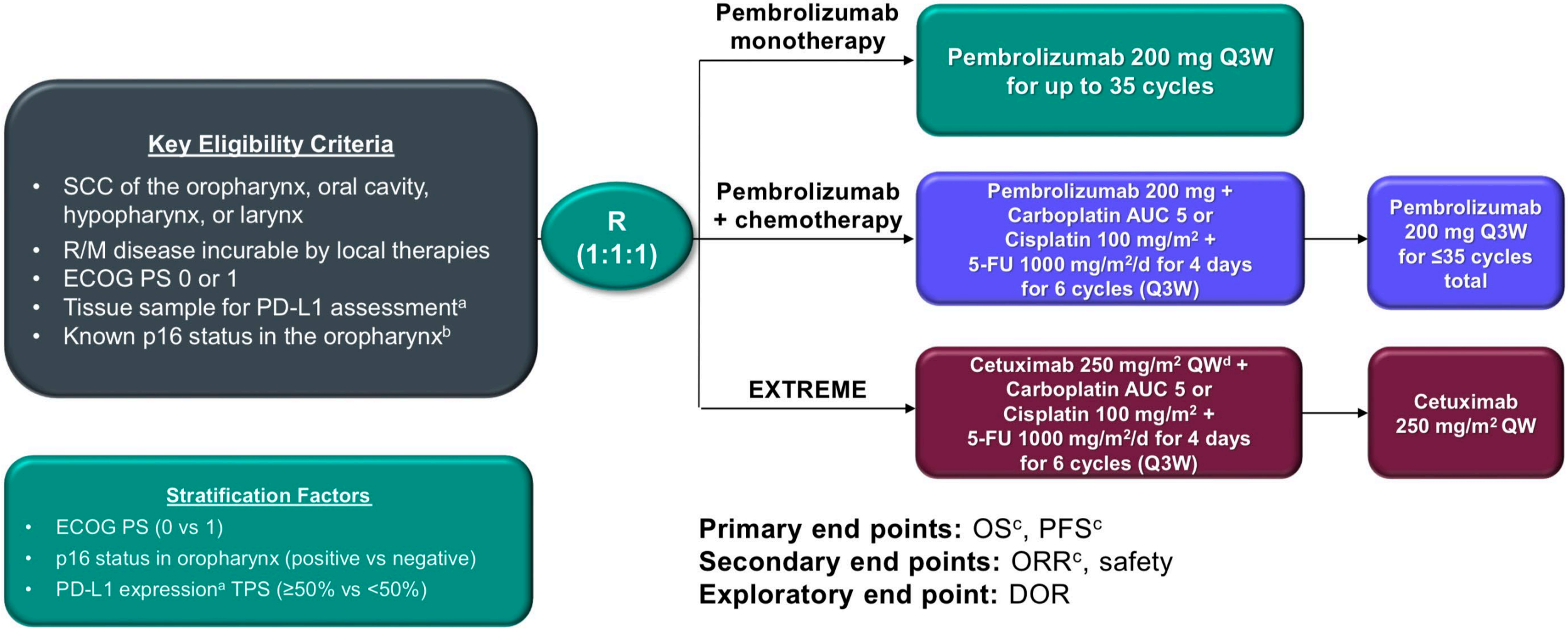
- BMS, Exelixis, NIH

Immunotherapy Advances Treatment



Cramer et al, 2019 Nature reviews clinical oncology

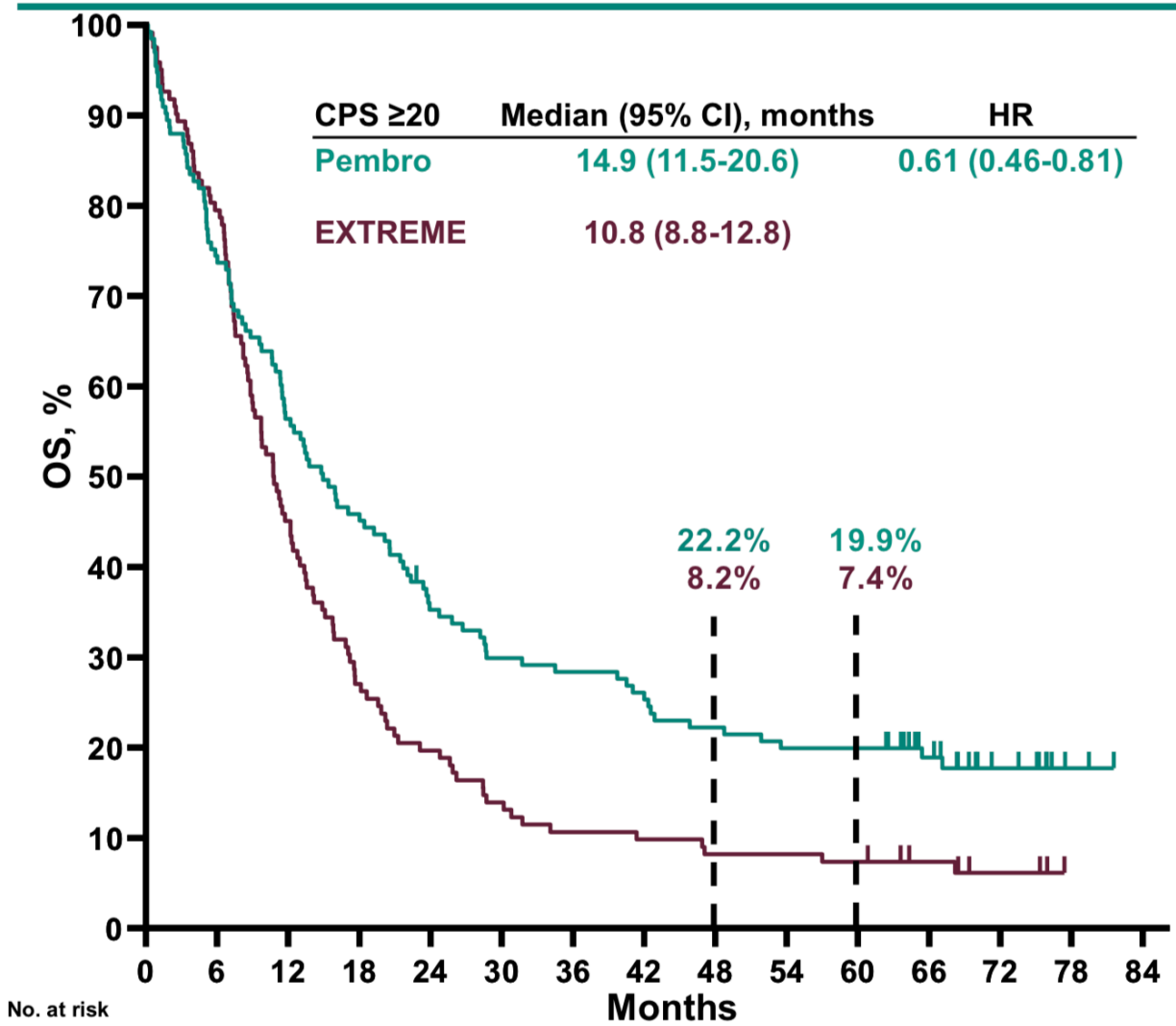
Study Design of KEYNOTE-048 (NCT02358031)

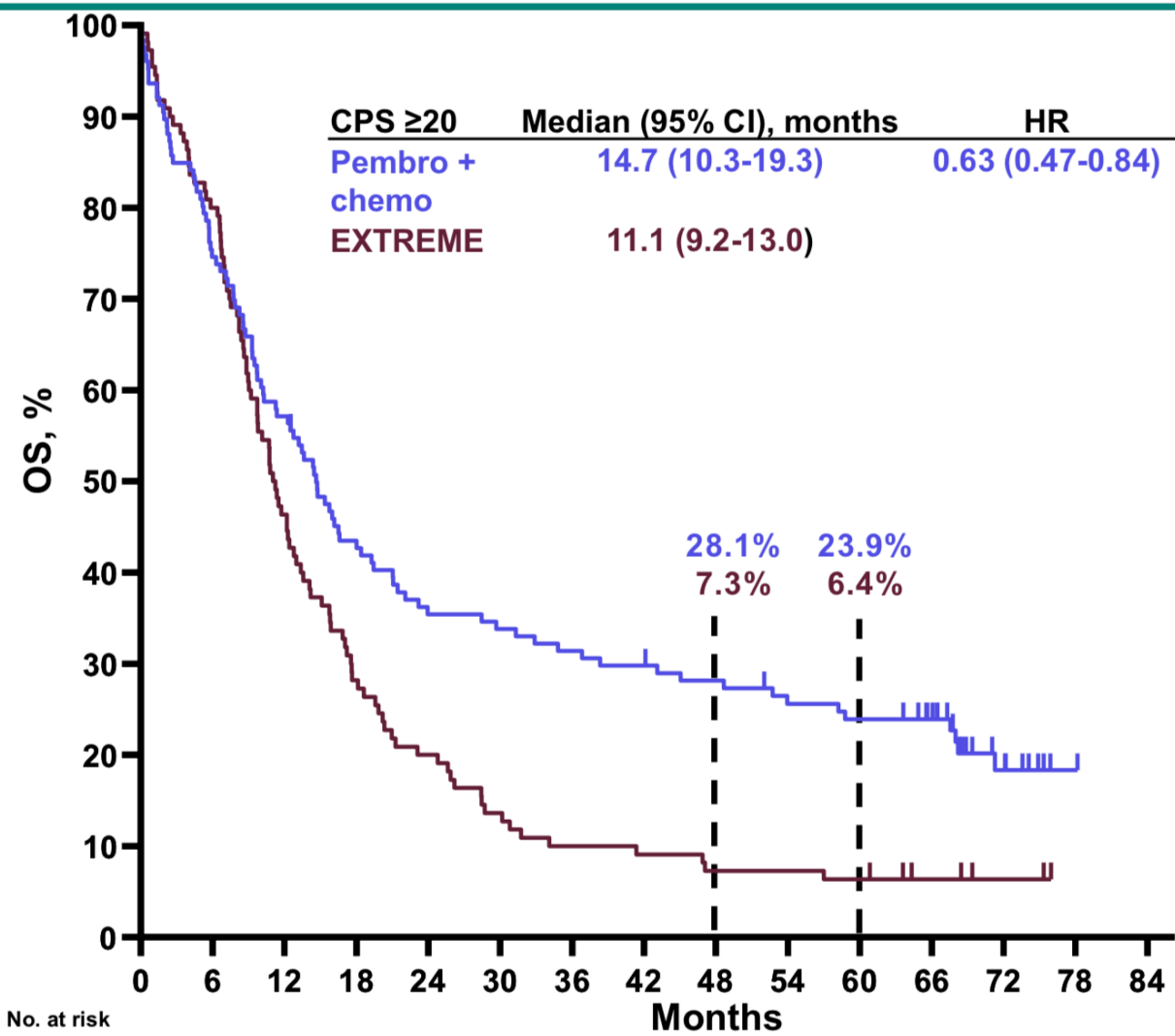


Median follow-up was 69.2 mo (range, 61.2-81.6) for pembrolizumab versus EXTREME and 68.6 mo (range, 61.2-82.1) for pembrolizumab + chemotherapy versus EXTREME.
[a]Assessed using PD-L1 IHC 22C3 pharmDx (Agilent Technologies). TPS = percentage of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 histology assay (Ventana); cut point for positivity = 70%. [c]Analyzed in PD-L1 CPS ≥1, PD-L1 CPS ≥20, and total populations. [d]After a loading dose of 400 mg/m². Data cutoff date February 21, 2022.
Burtness B et al. *Lancet*. 2019;394:1915-1928.

Tahara M, ESMO 2022

Overall Survival in the CPS ≥20 Population





Data cutoff date: February 21, 2022.

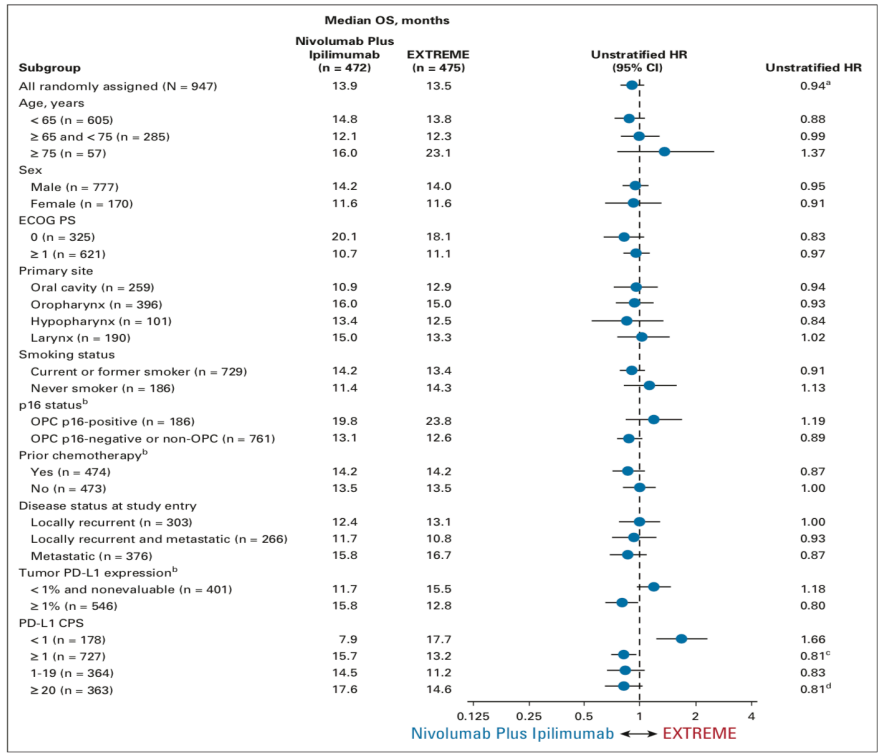
Checkmate 651- Nivolumab Plus Ipilimumab Versus EXTREME Regimen as First-Line Treatment for Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck: The Final Results of

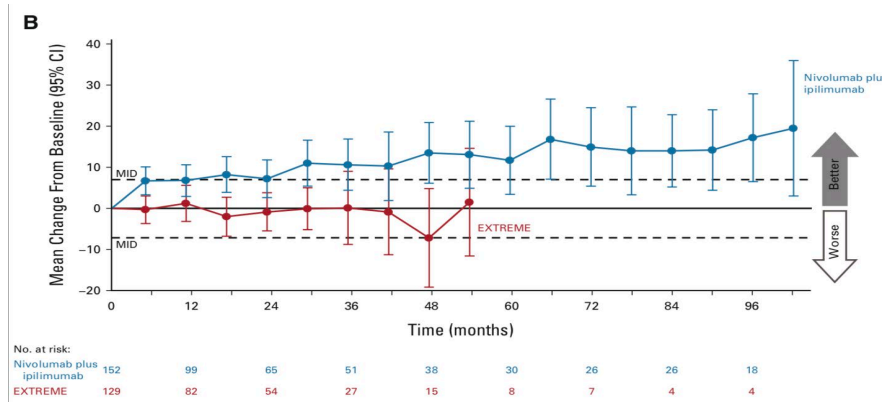
-Study did not meet its primary end points of OS in the all randomly assigned or CPS more than 20 populations.

-Nivo/Ipi was well tolerated with lower frequency of grade ¾ TRAE

-Nivo/Ipi improved Health related QOL with delayed symptom deterioration compared to EXTREME

Haddad R et al, JCO 2022





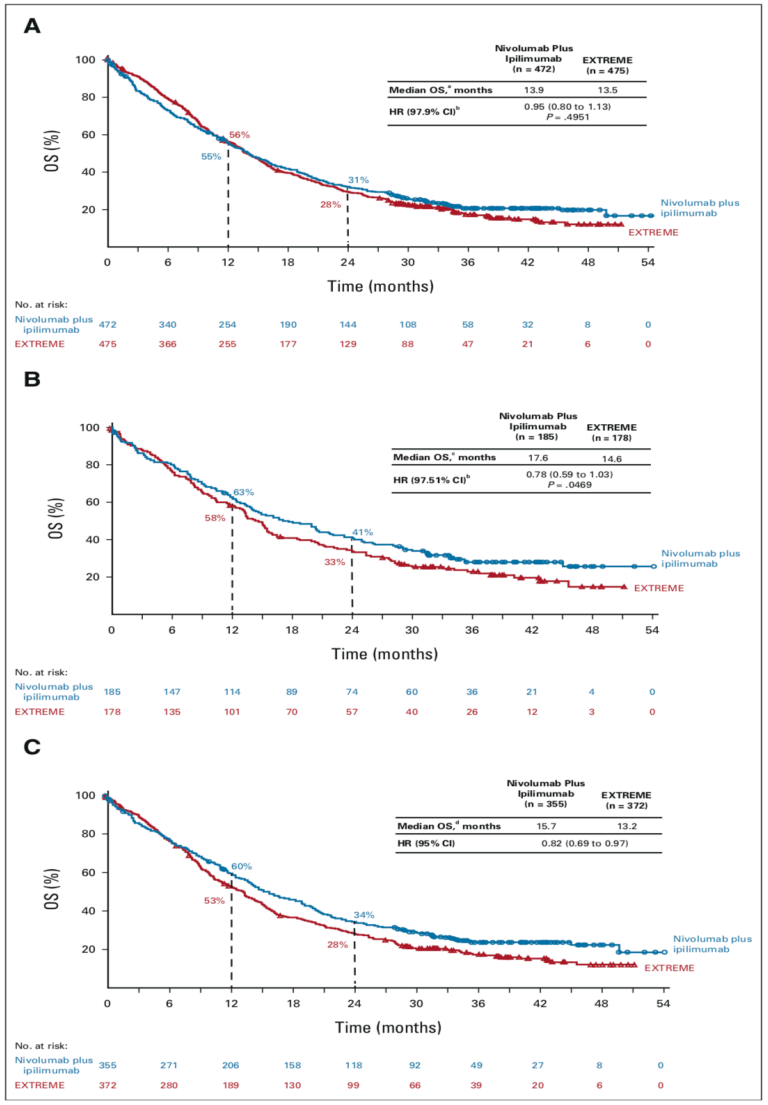
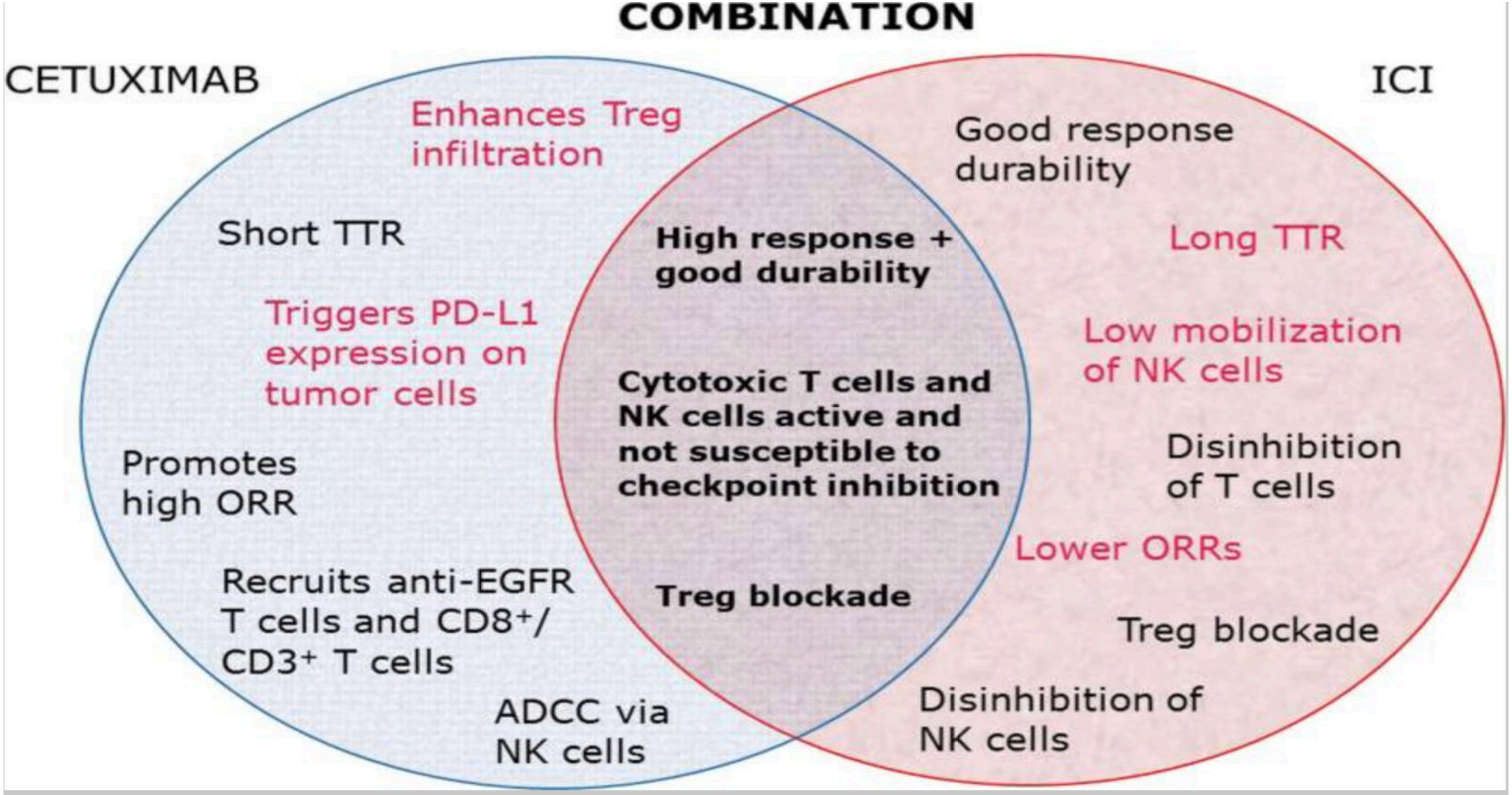


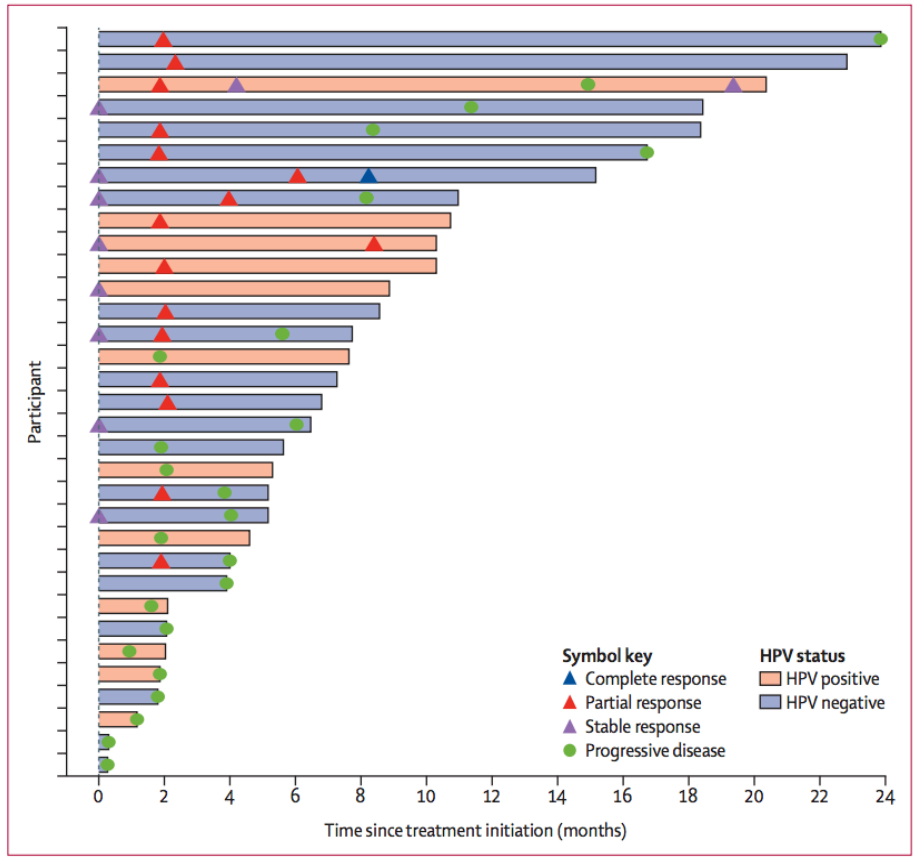
FIG 2. OS in the (A) all randomly assigned population, (B) PD-L1 CPS ≥ 20 population, and (C) PD-L1 CPS ≥ 1 population. Minimum follow-up: 27.3 months. [a]95% CI, 12.1 to 15.8 (continued on following page)

Rationale For Combining EGFR MoAb with ICI

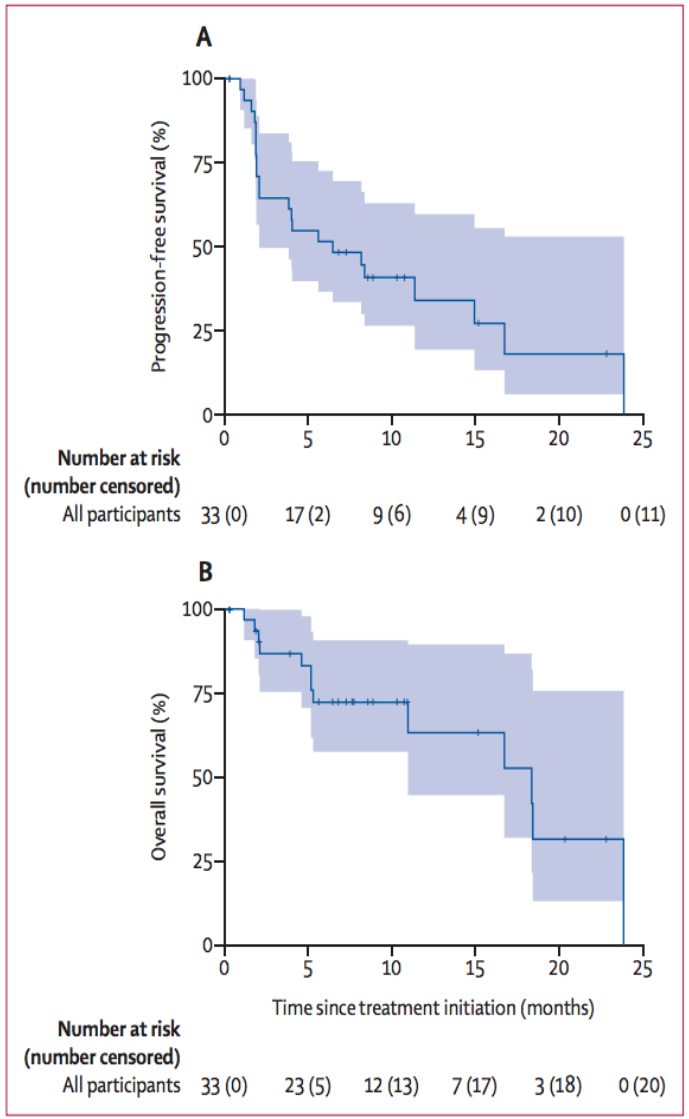


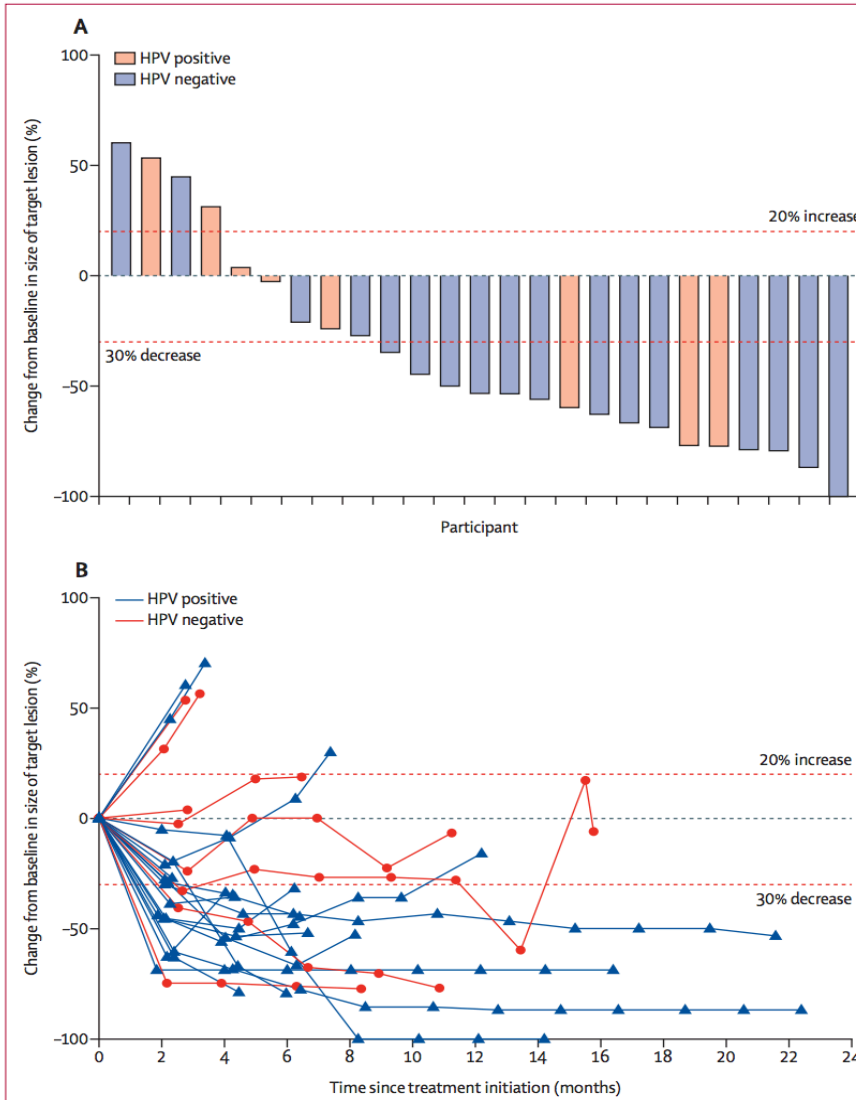
Ferris, *et al.* Cancer Treatment Reviews, 2018

Pembrolizumab + Cetuximab



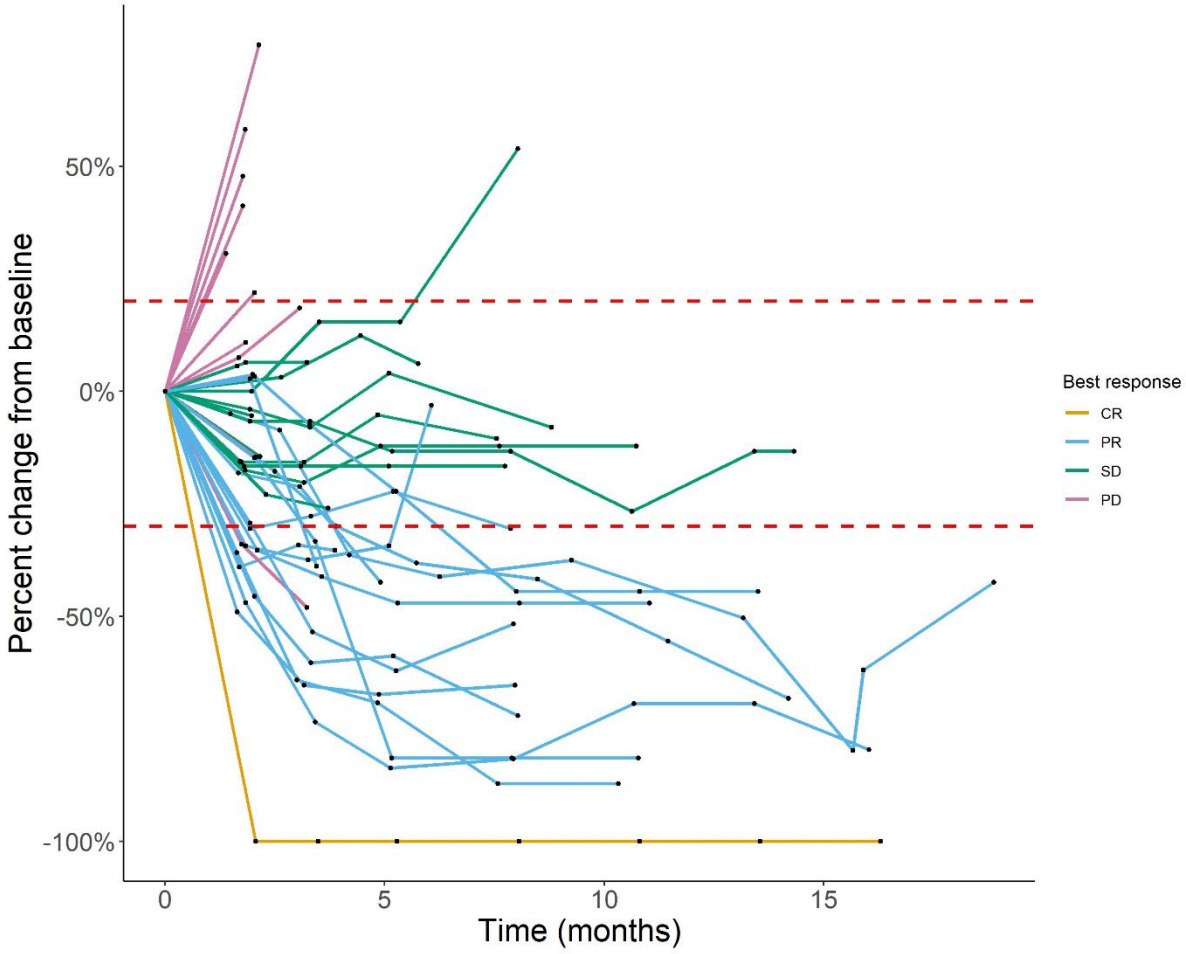
Sacco AG, Lancet Oncology 2021

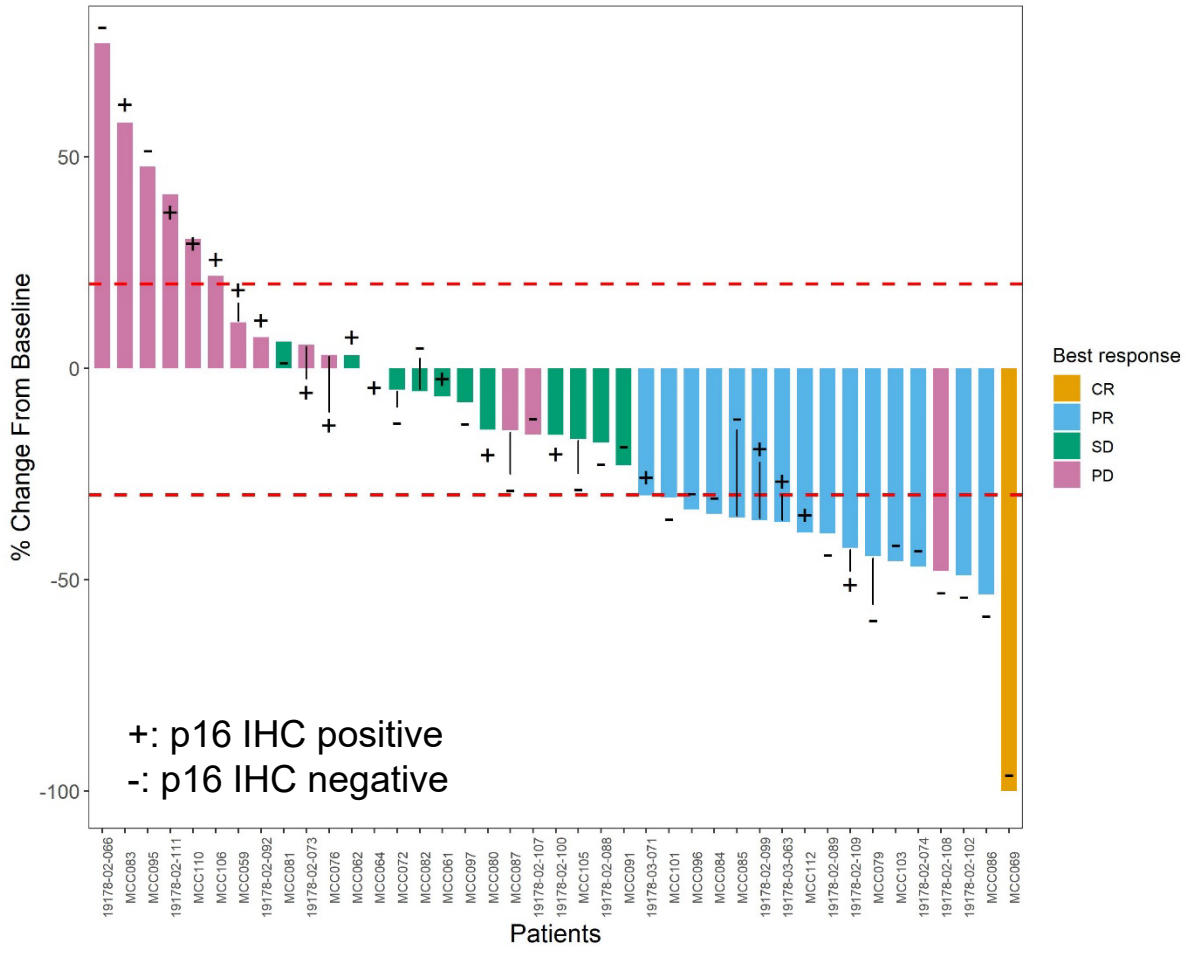




Phase I/II clinical trial: concurrent cetuximab and nivolumab in patients with recurrent and/or metastatic HNSCC

Overall response rate: 37% (16/43)





Chung C, et al, Cancers 2021CCR 2022

A Phase II trial of Pembrolizumab and Cabozantinib in Patients With Recurrent Metastatic Head and Neck Squamous Cell Carcinoma

Patients with R/M HNSCC

Inclusion criteria

- Inoperable, refractory or metastatic R/M HNSCC
- RECIST v1.1 measurable disease
- ≤1 prior radiation therapy to the HN allowed
- Life expectancy >3 months
- ECOG performance status 0–1

Exclusion criteria

- HPV negative unknown primary disease
- Cavitating lesions or recent bleeding history

→ **Pembrolizumab 200 mg IV Q3W**
+
Cabozantinib 40 mg PO QD

→ Tumors were assessed by RECIST v1.1 criteria by CT/MRI every 9 weeks

Primary objectives

- Determine the safety and tolerability of pembrolizumab + cabozantinib in this patient population
- Determine the objective response rate ORR per RECIST v1.1

Statistics

- ORR was tested based on the reported ORR for single-agent pembrolizumab of 18%
  - Estimated that ORR will improve to ≥35% with pembrolizumab + cabozantinib, yielding a type 1 error of 0.05 and a power of 80% when the true response rate is 35%
- For single-arm design with null hypothesis of ORR ≤15% vs one-sided alternative, 34 patients with evaluable responses are needed
- If the number of responses is ≤9 out of 34, the trial will be claimed as not promising

ECOG = Eastern Cooperative Oncology Group; HPV = human papillomavirus; RECIST = Response Evaluation Criteria in Solid Tumors

Pembrolizumab and cabozantinib in recurrent metastatic head and neck squamous cell carcinoma: a phase 2 trial

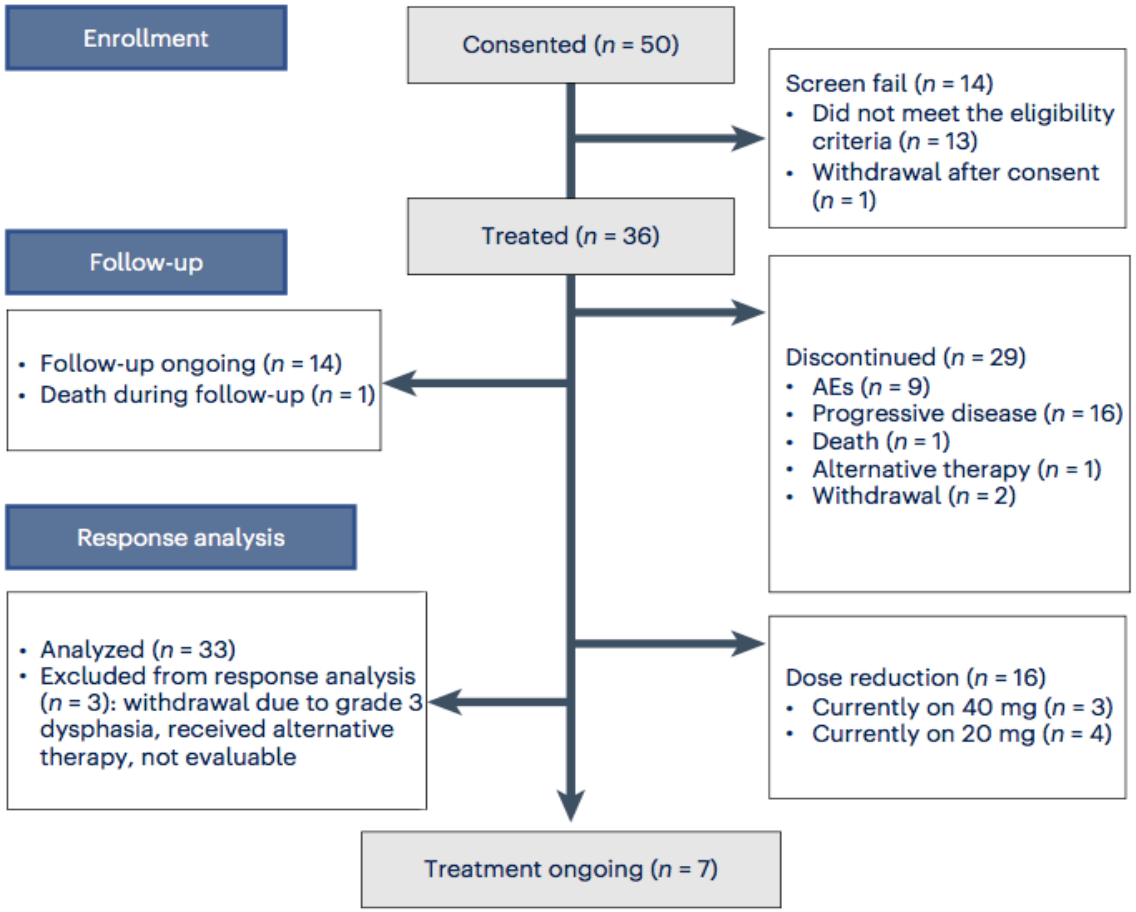


Fig. 1 | CONSORT diagram. Study CONSORT diagram.

Table 1 | Characteristics of the patients treated

Variable	n = 36[a]
Race	
Asian	5 (14%)
Black or African American	4 (11%)
White	27 (75%)
Ethnicity	
Hispanic or Latino	1 (2.8%)
Non-Hispanic	34 (94%)
Unknown	1 (2.8%)
Sex	
Male	30 (83%)
Female	6 (17%)
Age at enrollment, years	62 (54–67)
Smoking status	
Current	9 (25%)
Former	8 (22%)
Never	19 (53%)
Distant metastasis	35 (97%)
Stage at initial diagnosis	
0	1 (2.8%)
I	4 (11.1%)
II	8 (22.2%)
III	6 (16.7%)
IV	16 (44.4%)
Unknown	1 (2.8%)
Previous treatment	
Radiation	33 (91.6%)
Platinum-based chemotherapy	26 (72.2%)
No chemotherapy	2 (5.6%)
Cetuximab	3 (8.3%)
Primary disease site	
Oropharynx	22 (61%)
Oral cavity	2 (6%)
Hypopharynx	2 (6%)
Larynx	4 (11%)
Nasopharynx	6 (16%)
Dose reduction	16 (44%)
HPV/P16 status	
Negative	12 (33%)
Positive	17 (47%)
Not applicable/unknown	7 (19%)
PD-L1-CPS	
<20	17 (50%)
≥20	17 (50%)
TMB	
<6.71	8 (50%)
≥6.71	8 (50%)
ECOG status	
0	18 (50%)
1	18 (50%)

Saba N, et al, Nat Med 2023

Pembrolizumab and Cabozantinib in RMHNSCC Phase 2 trial

	N=33 n (%)
ORR	17 (52)
CR	0 (0)
PR	17(52)
SD	13(39)
PD	3(9)
Clinical benefit	30(91)

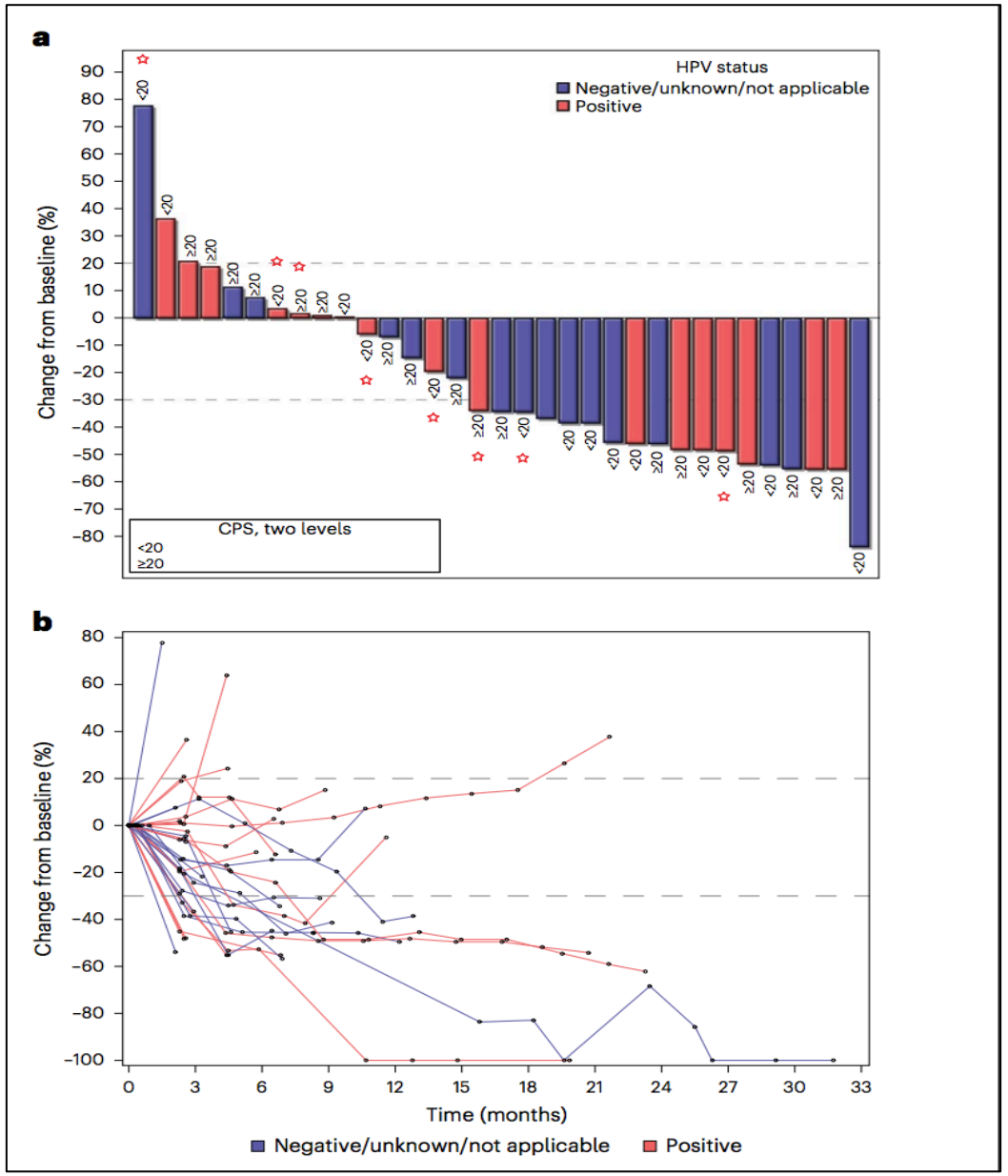


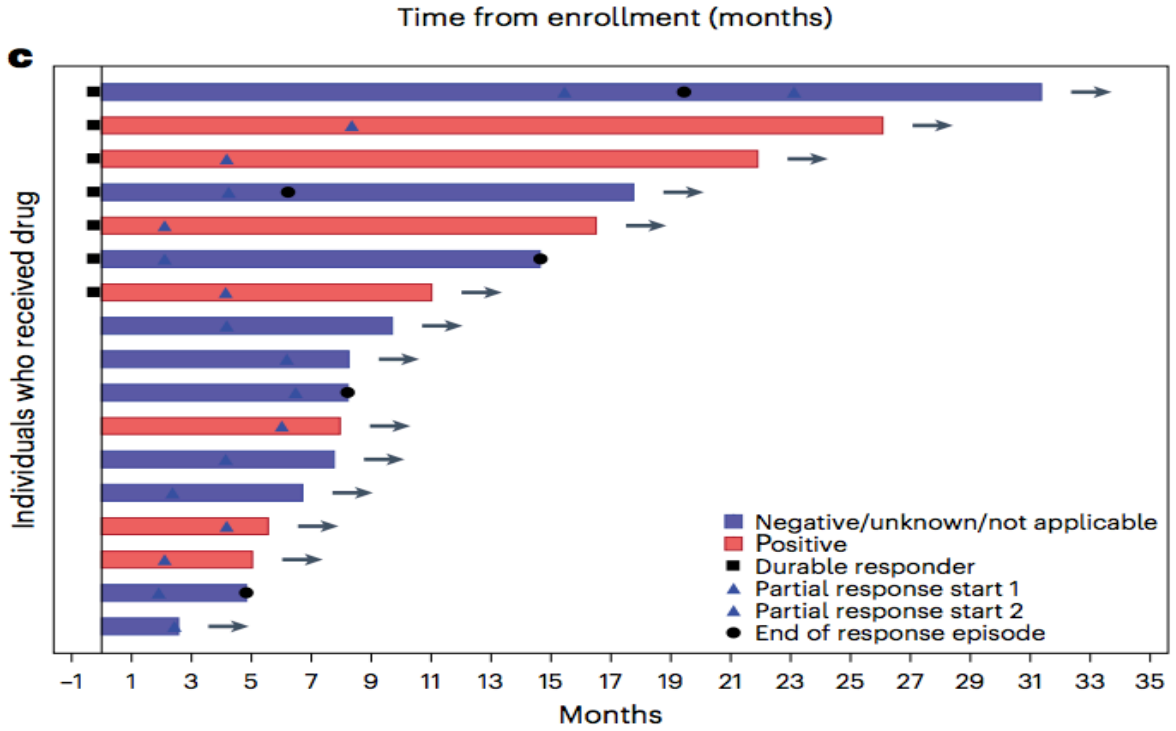
Table 2 | (continued) Frequency of AEs: all grades, grade 3 or higher and treatment-related grade 3 or higher

Most common AEs with any-grade toxicity	*n* (%)=36
Oral pain	1 (2.8)
Pain	1 (2.8)
Pancreatitis	1 (2.8)
Decreased platelet count	1 (2.8)
Sore throat	1 (2.8)
Vomiting	1 (2.8)
All AEs with grade 3 and 4 toxicity attributed to treatment	***n* (%)**=36
Overall	*6 (17%)*
Increased AST	2 (5.6)
Increased alanine aminotransferase	1 (2.8)
Increased alkaline phosphatase	1 (2.8)
Increased blood bilirubin	1 (2.8)
Increased gamma-glutamyl transferase	1 (2.8)
Hypertension	1 (2.8)
Hyponatremia	1 (2.8)
Increased lipase	1 (2.8)
Oral mucositis	1 (2.8)

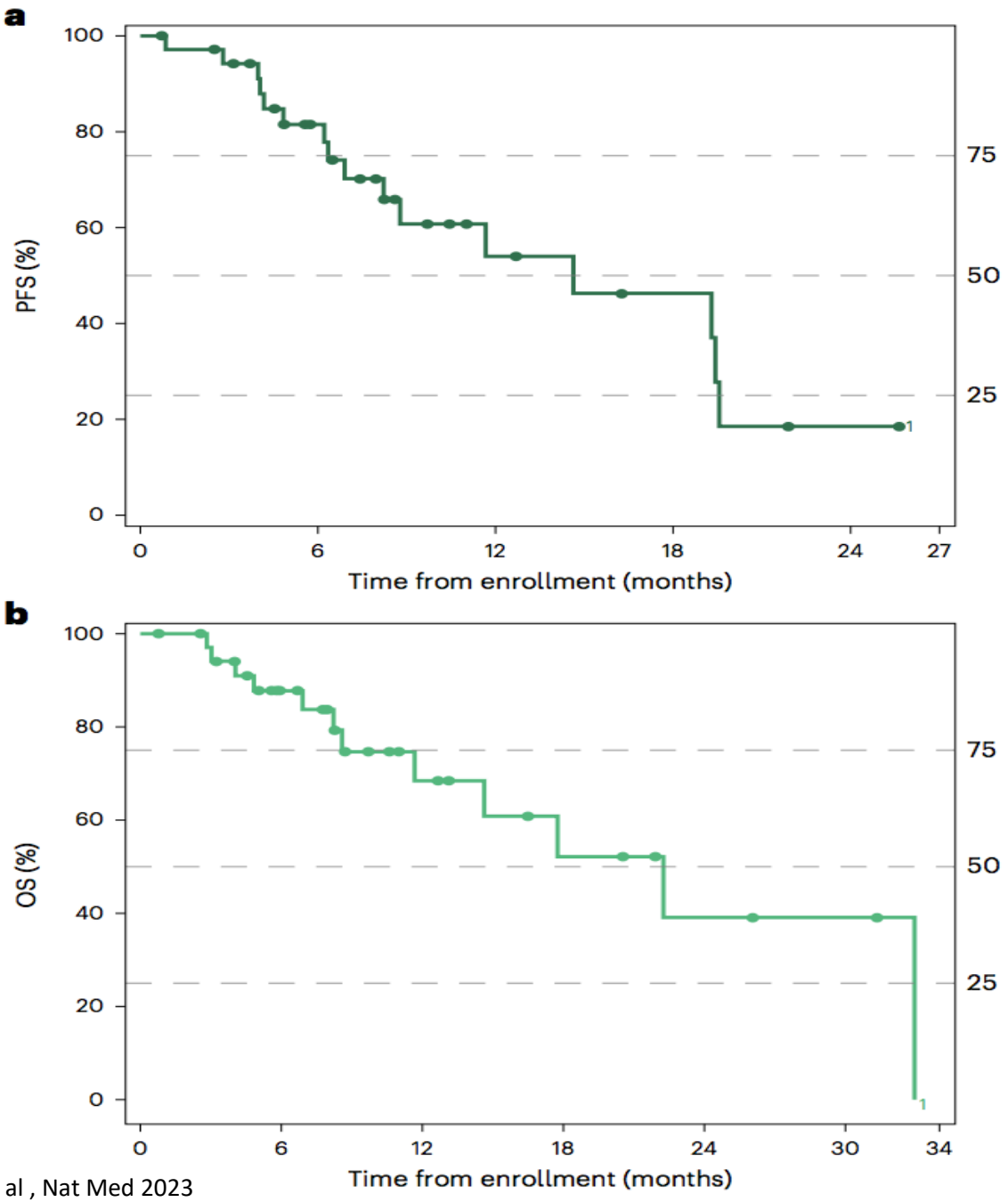
Thirty-six patients were accounted for in the AE count. Patients may have more than one AE reported.

Saba N, et al , Nat Med 2023

Pembrolizumab and cabozantinib in recurrent metastatic head and neck squamous cell carcinoma: a phase 2 trial

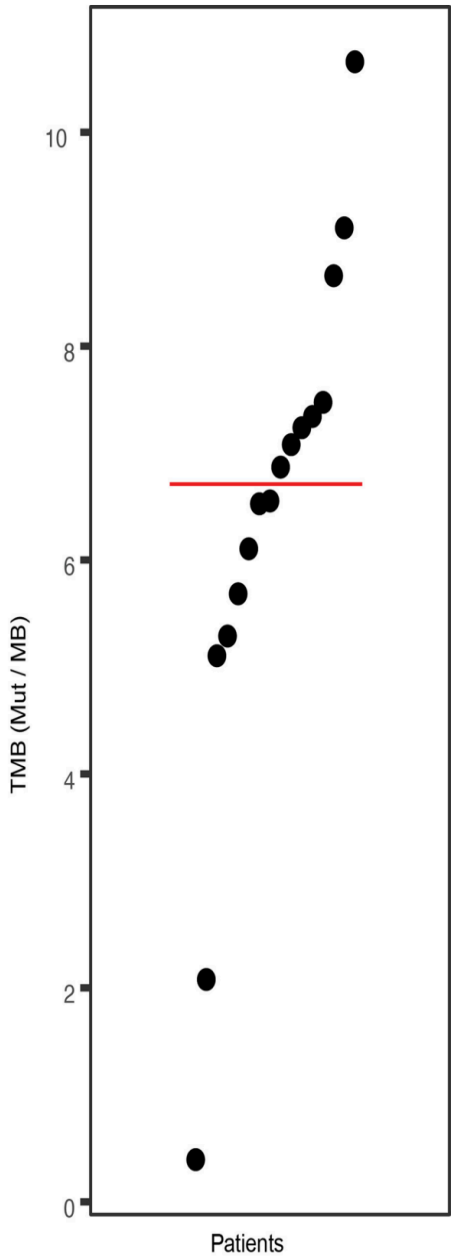


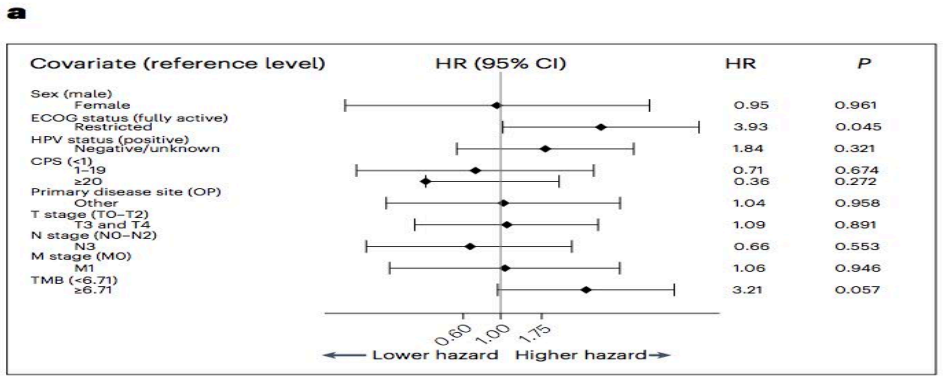
N	Event	Censored	mPFS (95% CI), mo	1-yr PFS (95%CI), %	Median follow-up (95% CI), mo
36	16 (44%)	20 (56%)	14.6 (8.2–19.6)	54.0 (31.5–72.0)	10.6 (7.8–16.5)

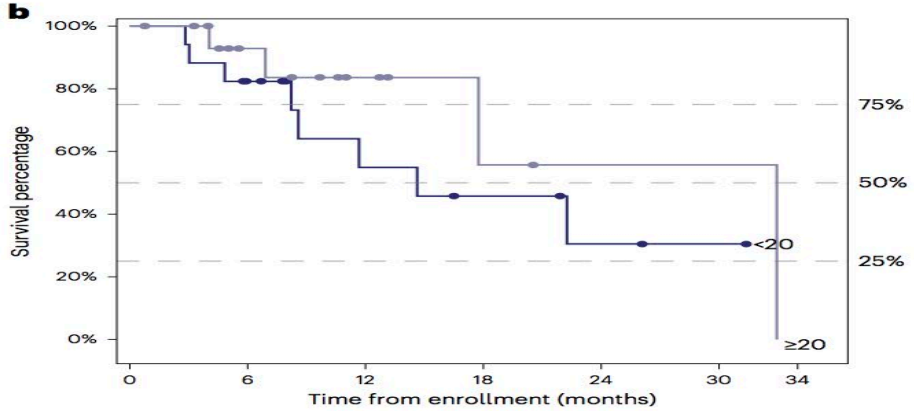


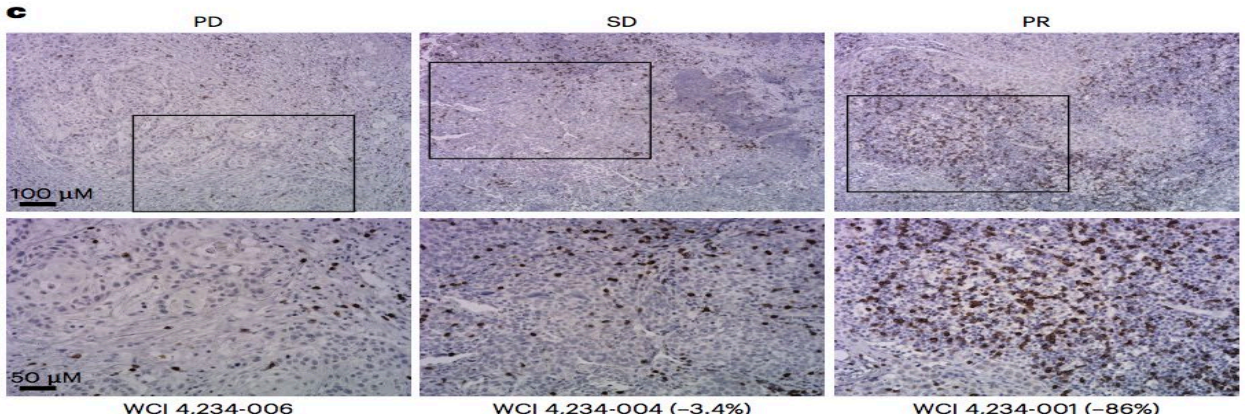
Saba N, et al , Nat Med 2023

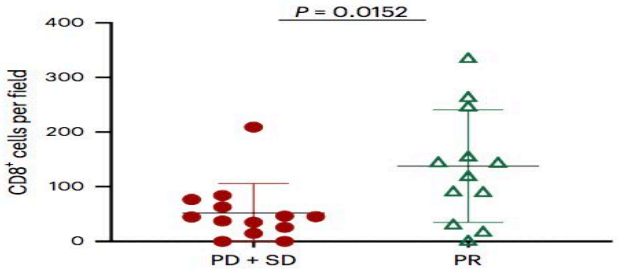
Pembrolizumab and Cabozantinib in RMHNSCC Phase 2 trial











CPS category	N	Event	Censored	mOS (95% CI), mo	1-yr OS (95%CI), %	Median follow-up (95% CI), mo	P value
<20	17	8 (47%)	9 (53%)	14.6 (8.2–NE)	54.9 (24.5–77.5)	21.9 (6.7–31.4)	0.2638
≥20	17	4 (24%)	13 (76%)	32.9 (6.9–32.9)	83.6 (48.0–95.7)	9.7 (4.5–13.1)	

Saba N, et al , Nat Med 2023

Randomized Phase II Trial of Ficlatuzumab With or Without Cetuximab in Pan-Refractory, Recurrent/Metastatic HNCA

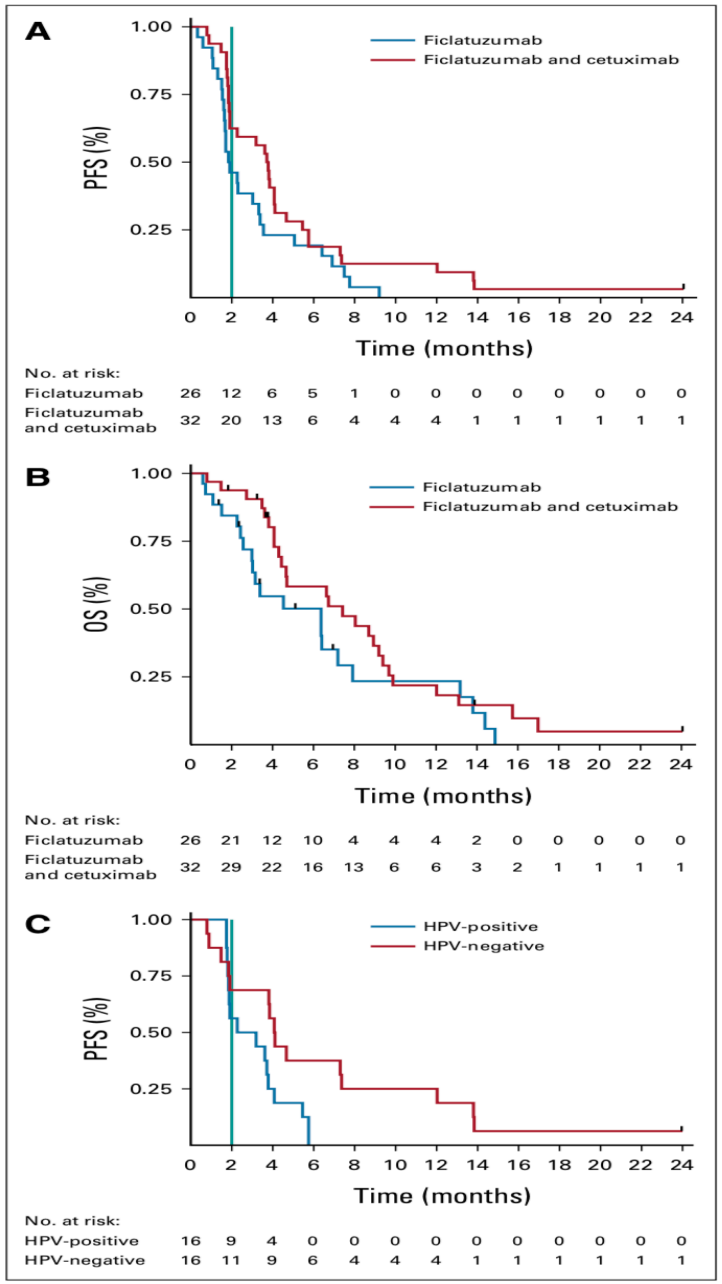


FIG 2. Kaplan-Meier estimates of progression-free (PFS) and overall survival (OS). (A) PFS in both treatment arms. (B) OS in both treatment arms. (C) PFS in the HPV-stratified subgroups on the combination arm. The green vertical line depicts the historical control for PFS of 2 months in both (A) and (C). HPV, human papillomavirus.

TABLE 2. HPV Subgroup Analysis on the Combination Arm

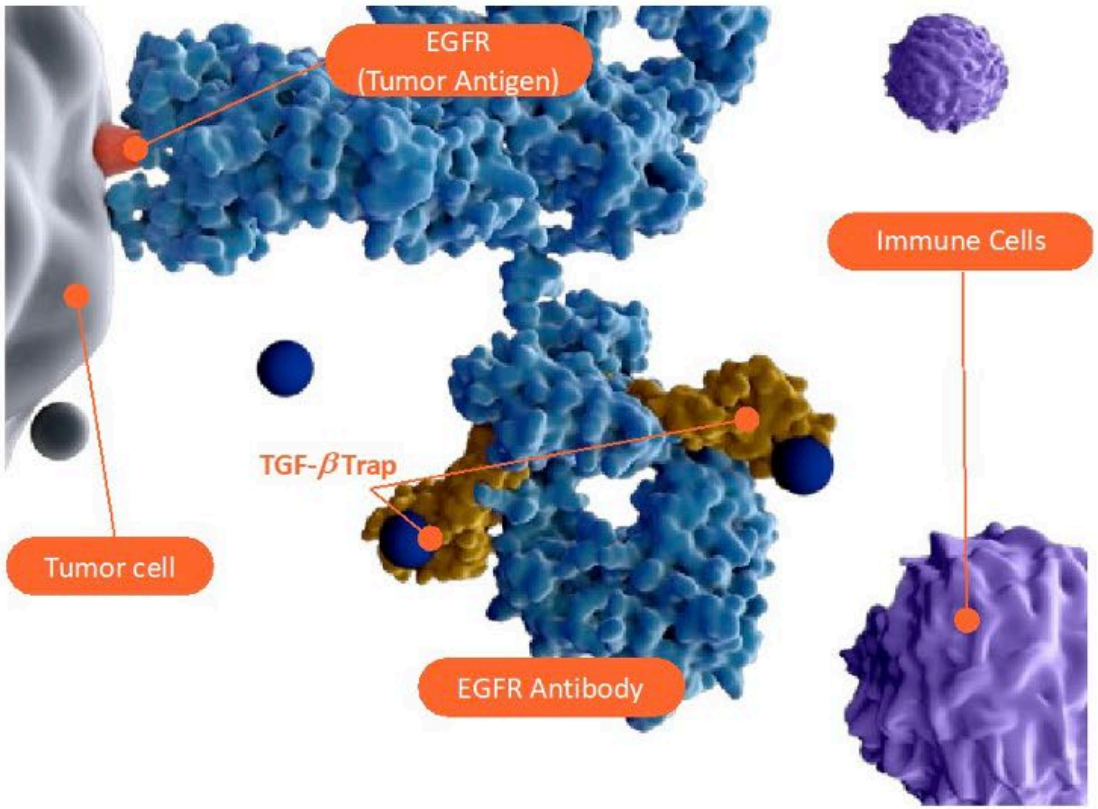
ORR and PFS	Ficlatuzumab + Cetuximab (n = 32)	P
ORR[a]		.02
HPV-positive	0/16 (0%)	
HPV-negative	2 CR + 4 PR/16 (38%)	
Median PFS[b]		.03
HPV-positive	2.3 (1.9)	
HPV-negative	4.1 (2.9)	

TABLE 4. cMet and HGF Classification and Progression-Free Survival on the Combination Arm

Type of Variable	HPV Status	HR for Progression	95% CI	P
cMet	All cases (n = 26)	0.3	0.1 to 0.8	.02
	HPV-positive (n = 13)	3.2	0.6 to 17.5	.20
	HPV-negative (n = 13)	0.1	0.03 to 0.8	.03
HGF	All cases (n = 26)	1.4	0.9 to 2.0	.10
	HPV-positive (n = 13)	3.4	0.9 to 13.1	.07
	HPV-negative (n = 13)	1.4	0.4 to 4.7	.60

Bauman JE, JCO, 2023

BCA101: Targeting a TGF-β trap to EGFR expressing tumors



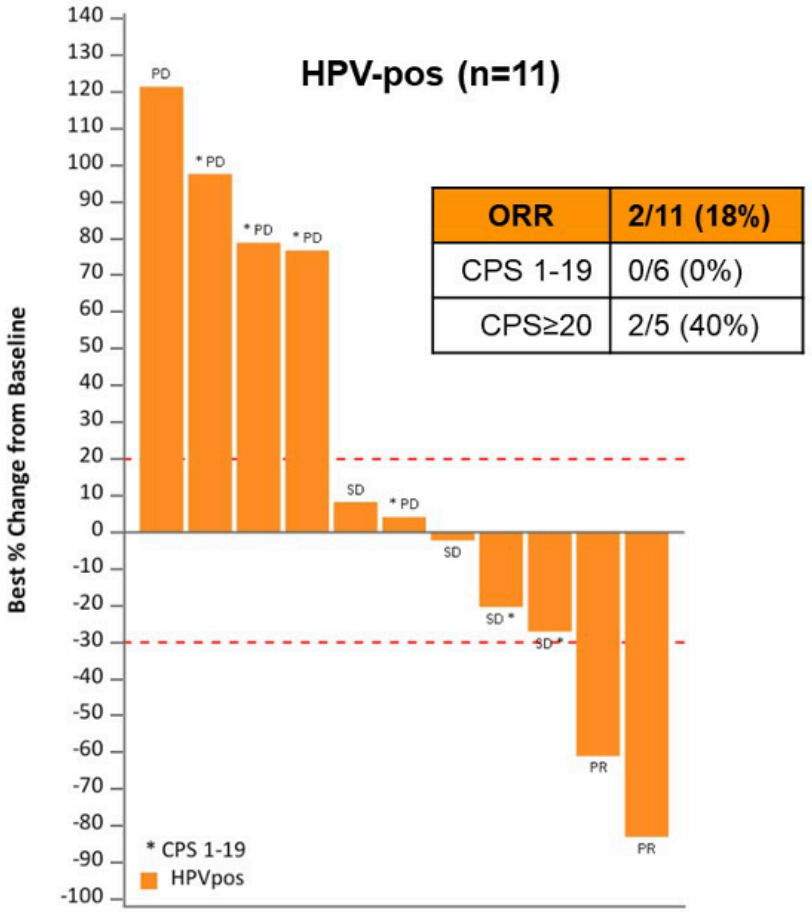
Proposed mechanisms of action

1. Localizes TGF-β inhibition to the TME through an EGFR-directed approach
2. Aims to increase anti-tumor activity via enhanced ADCC and increased NK cell activation
3. Dual inhibition of EGFR and TGF-β prevents epithelial-mesenchymal transition (EMT) and metastasis

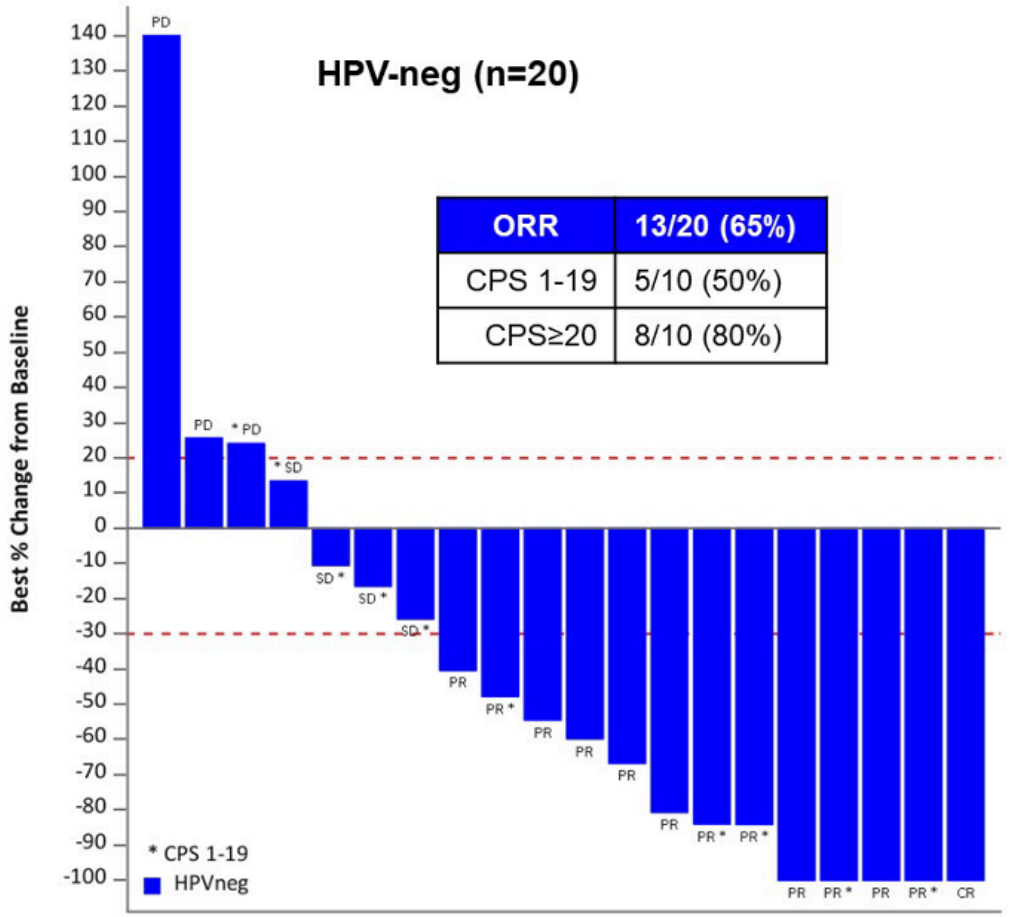
Hanna G, ASCO 2023

BCA101 + pembrolizumab in CPS≥1 R/M HNSCC (1L)

Preliminary Efficacy – by HPV status



ORR	2/11 (18%)
CPS 1-19	0/6 (0%)
CPS≥20	2/5 (40%)



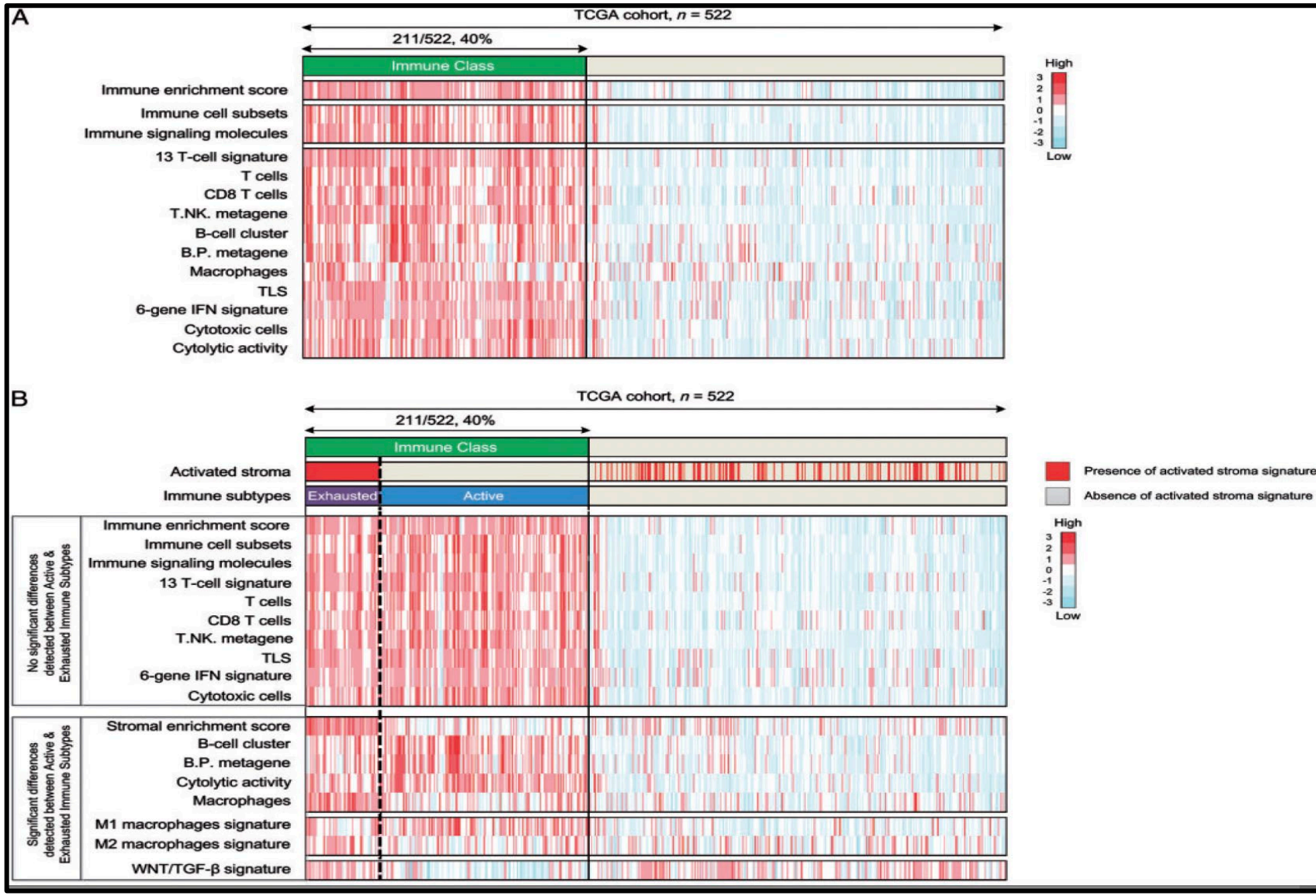
ORR	13/20 (65%)
CPS 1-19	5/10 (50%)
CPS≥20	8/10 (80%)

- ORR 65% in HPV-neg subjects with responses observed in both CPS subgroups

Hanna G, ASCO 2023

Presence of an immune phenotype does not absolutely predict immunotherapy response.

Separation of molecular signatures of tissue compartments from measurements of bulk tumor samples.

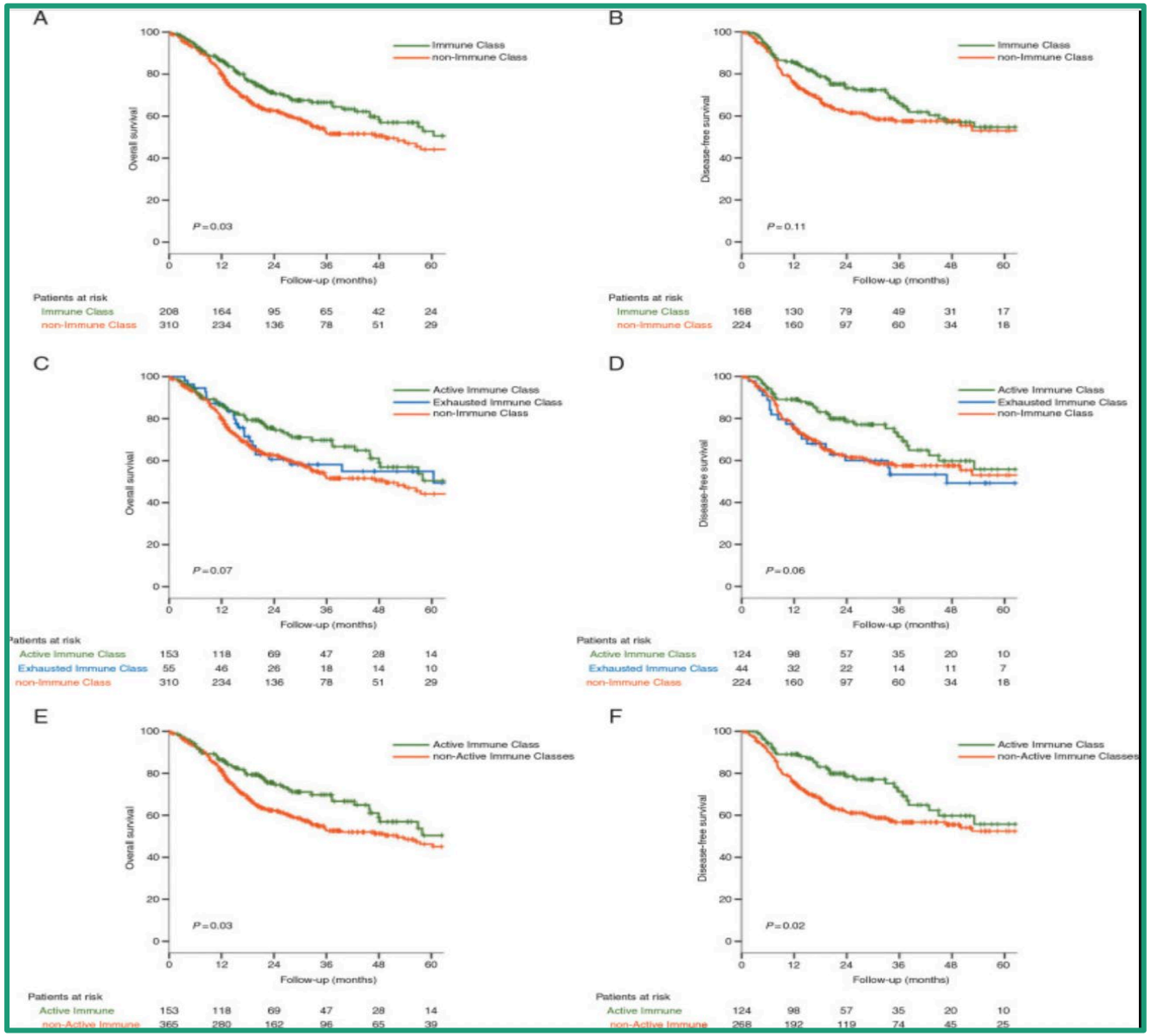


Chen YP, Annal of Oncology , 2019

Active Immune Class had a significantly favorable prognosis.

While T-cell-related immune signatures did not differ between the two subtypes, the Active Immune Class showed enrichment of *B-cell-related* immune signatures

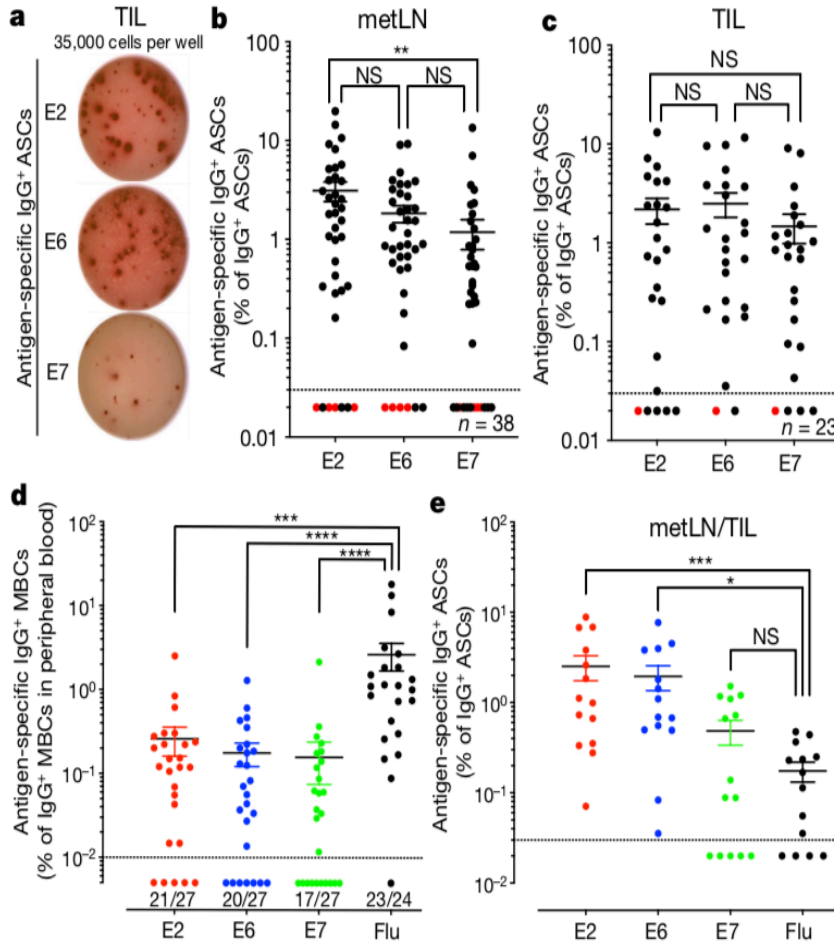
More HPV-positive tumors in the Active Immune Class.



Chen YP, Annal of Oncology , 2019

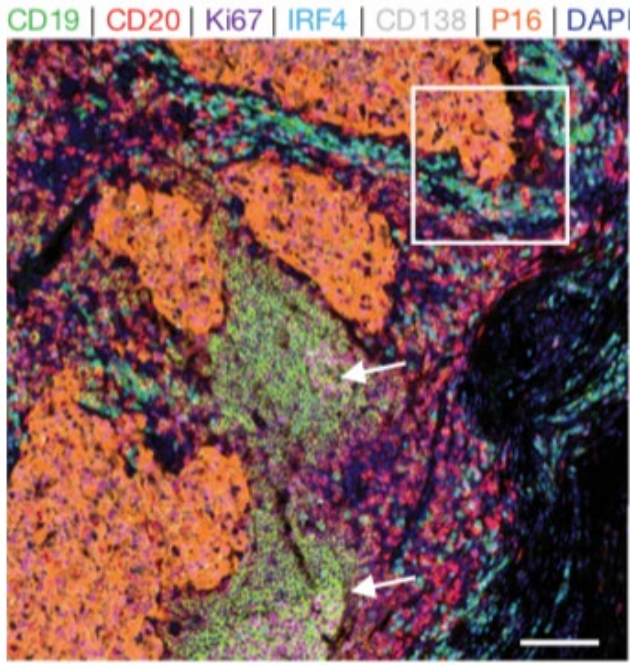
Defining HPV-specific B cell responses in patients with head and neck cancer

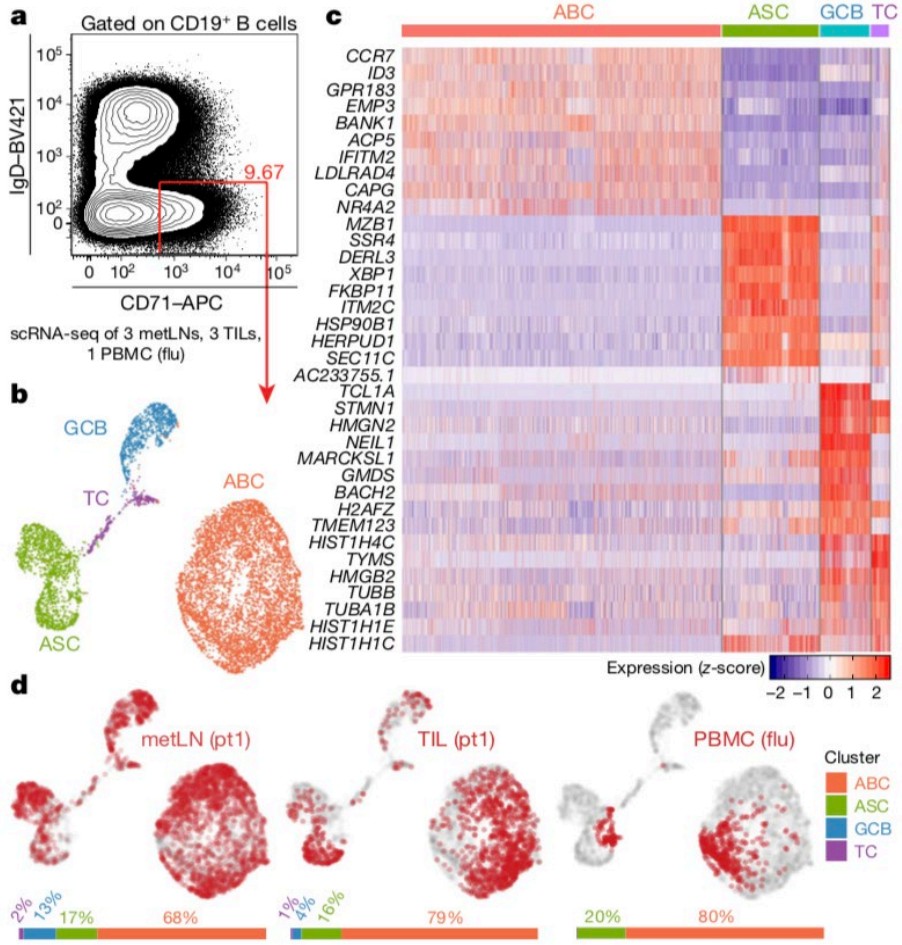
HPV-specific ASCs are present in the TME



Correlation between ASC and HPV antibody

Transcriptomic and spatial characterization of B cells and plasma cells in the TME





The TME contains activated B cells, germinal centre B cells and ASCs.

Wieland et al, Nature 2021

Methods and Limitations

VERSATILE-002 (NCT04260126) is a Phase 2, open-label, non-randomized, adaptive design study evaluating the combination of PDS0101 and pembrolizumab

Key Entry Criteria for ICI Naïve Subjects

- Recurrent and/or metastatic HNSCC based on RECIST 1.1
- ≥18 years of age
- HPV16-positive tumor
- Combined positive score (CPS) ≥1

Study Treatment

- Pembrolizumab 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)

Population and Treatment Exposure

Intent-to-treat (ITT) Population (n=48)

- Received at least 1 cycle of combination treatment
- Median age 62.5 (range 45–83)
- 93.8% male
- 93.8% White
- 62.5% ECOG 0
- 41.7% CPS ≥20

Modified ITT (mITT) Population (n=34)*

- ITT Population who had imaging assessment following treatment
- Median age 63.5 (range 44–83)
- 94.1% male
- 97.1% White
- 58.8% ECOG 0
- 50.0% CPS ≥20

Treatment Exposure (ITT Population)

- Median Treatment Duration: 3.5 months (range 0.0–19.5)
- Median number of PDS0101 doses: 4 (range 1–5)
  - 56.3% received 4 doses; 22.9% received 5 doses
- Median number of pembrolizumab doses: 5 (range 1–29)
  - 27.1% received ≥10 doses

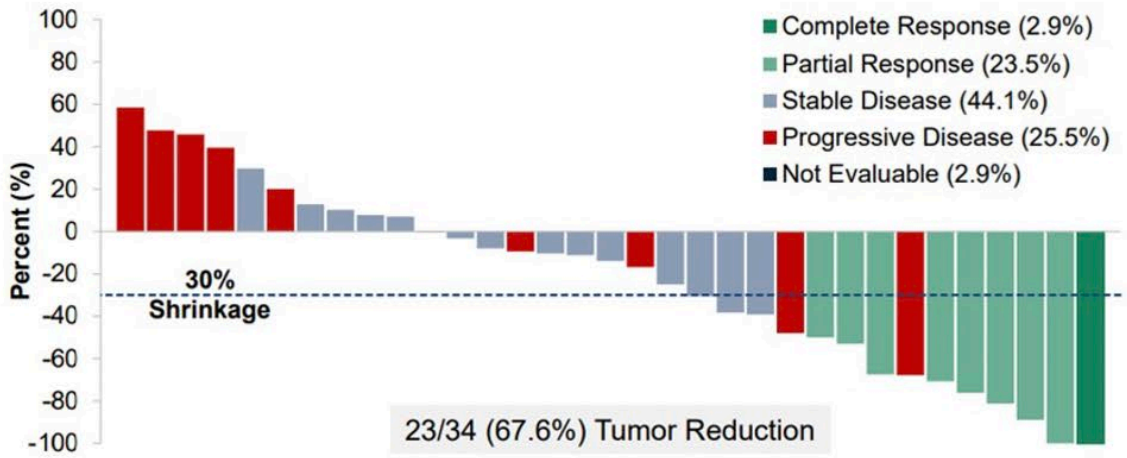
* As of this data cut, 14 subjects were enrolled but had not yet been followed long enough to have an imaging assessment.

Limitations: This study presents data from a snapshot of an ongoing study. Final results may differ for reasons including: outcomes from additional subjects enrolled in the study, new outcomes from existing subjects, delays in data entry at the research site, ongoing monitoring and clarification of data queries.

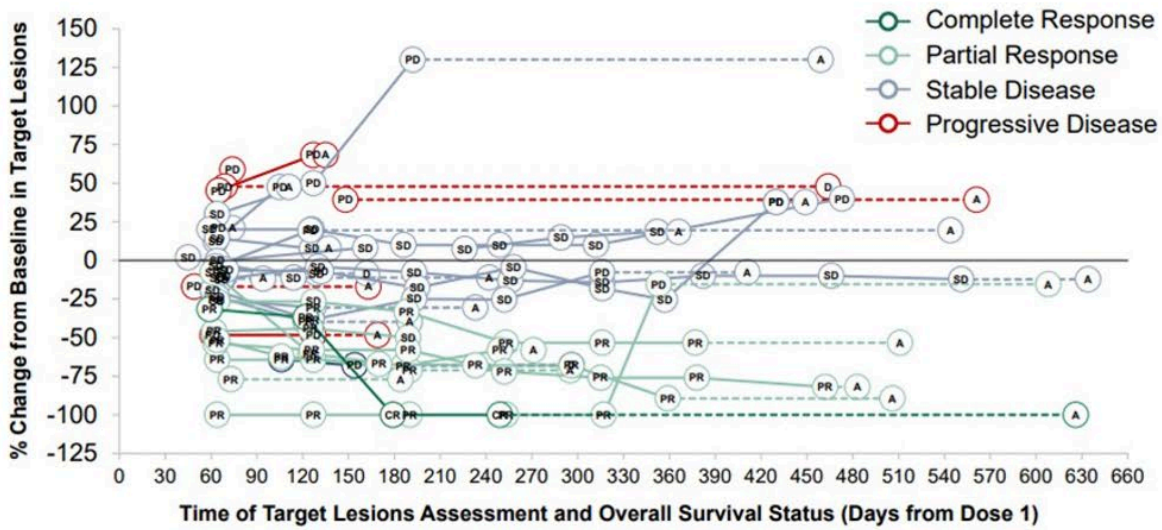
Price et al, ASCO 2023

#6012: Change from Baseline in Target Lesions

Waterfall Plot of Maximum % Change from Baseline in Target Lesions*



Spider Plot of % Change from Baseline in Target Lesions and Overall Survival Status*

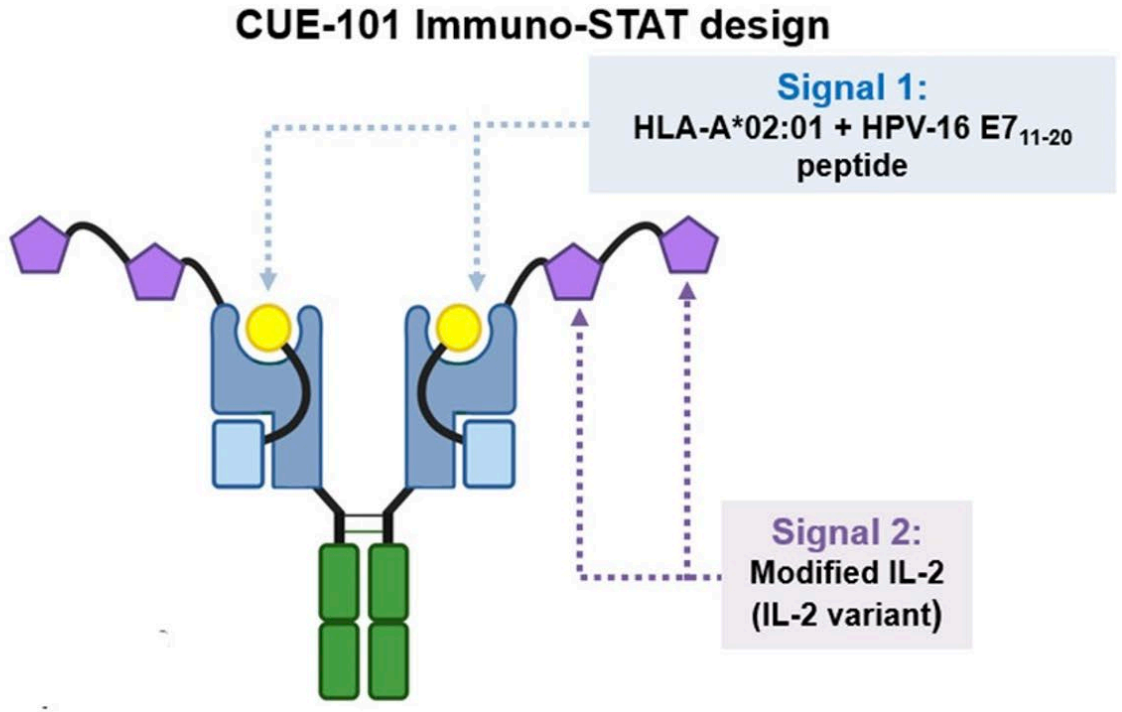


N=34
Median age of 63.5 (range 46–83)
Male= 94.1%
White= 97.1%
ECOG 0=58.8%
CPS ≥20= 50%

Price KAR et al. ASCO 2023

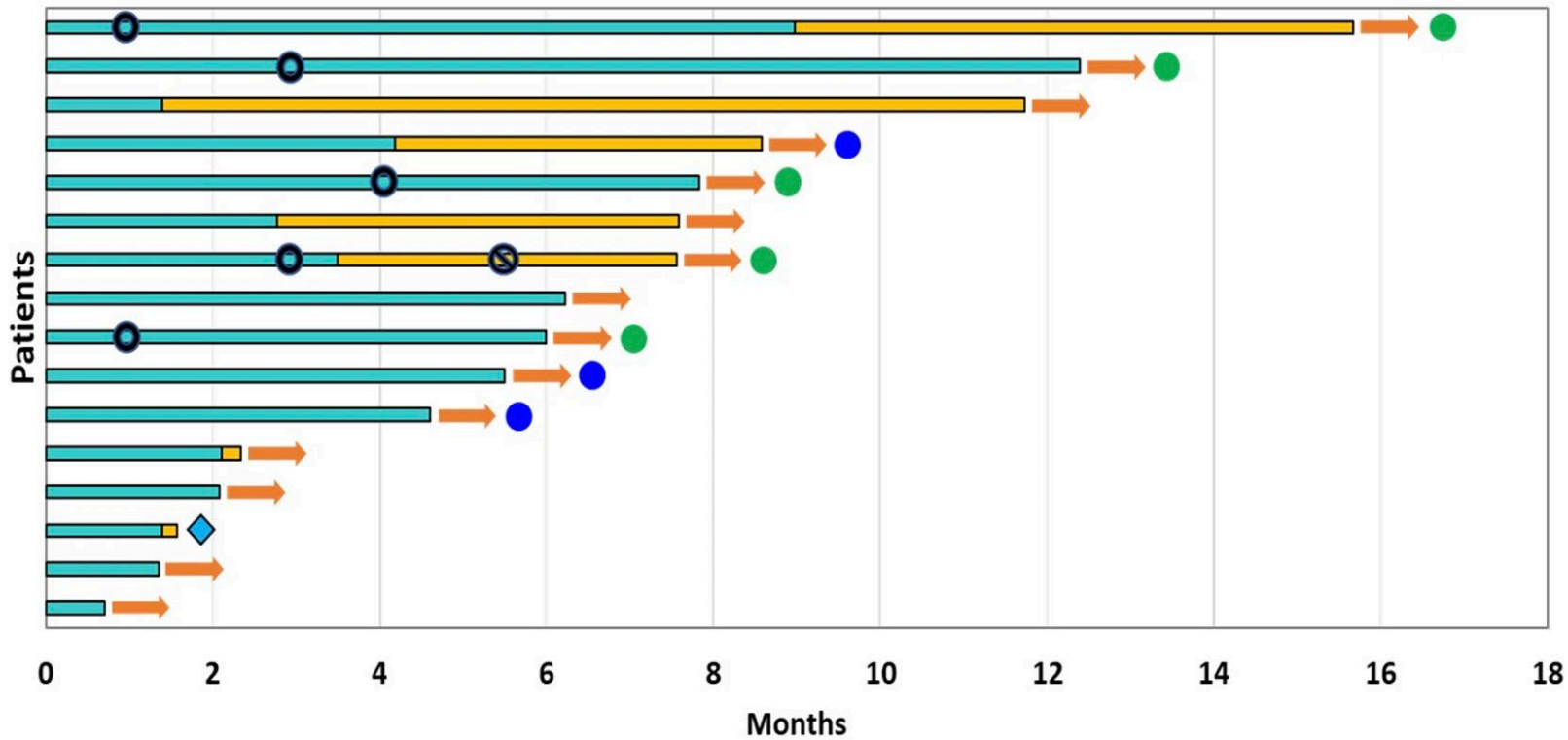
#6013: Phase 1 Study of CUE-101, a Novel HPV16 E7-pHLA-IL2-Fc Fusion Protein, as Monotherapy/In Combination with Pembrolizumab in Recurrent/Metastatic HPV16+ HSNCC

- Immuno-STATs (ISTs) are TCR-selective engager biologics comprised of a bivalent peptide-MHC complex and multivalent co-stimulatory molecules built on an Fc framework to enable stability, valency, favorable PK and manufacturability
- The CUE-100 series ISTs are designed to deliver attenuated IL-2 selectively to tumor-specific CD8+T cells
- Trial eligibility includes HLA-A*0201 genotype and HPV16+ HNSCC, determined by p16 IHC and HPV16 mRNA in-situ hybridization. Pembrolizumab combination patients are also required to have a CPS ≥ 1



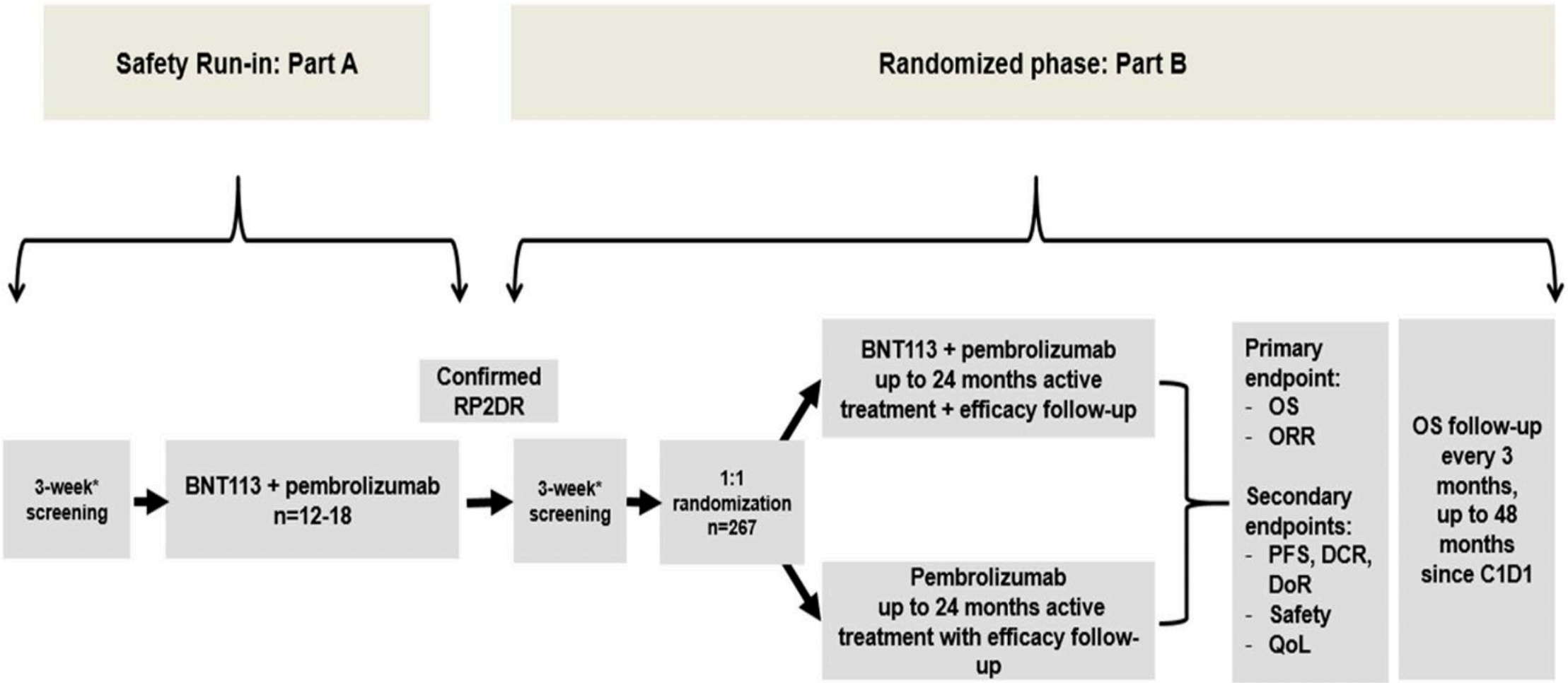
#6013: Survival in Combination Patients at the RP2D

MTD not established
ORR 36%
DCR 57%
mDOR 35.1 weeks
mPFS 4.9 months



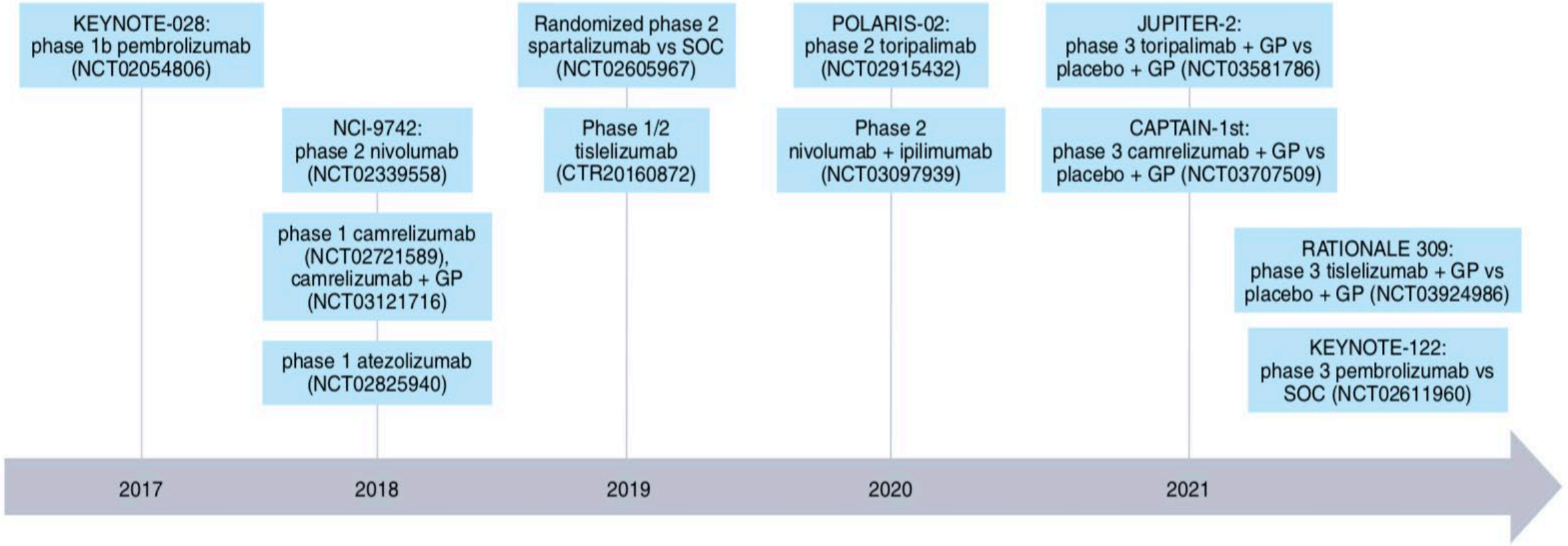
Chung CH et al. ASCO 2023

BNT-113 -01 clinical trial – AN open label randomized phase II study of E7 RNA vaccine with pembrolizumab vs pembrolizumab



Schema curtesy of BioNtech

Journey of Immune Checkpoint applications in NPC



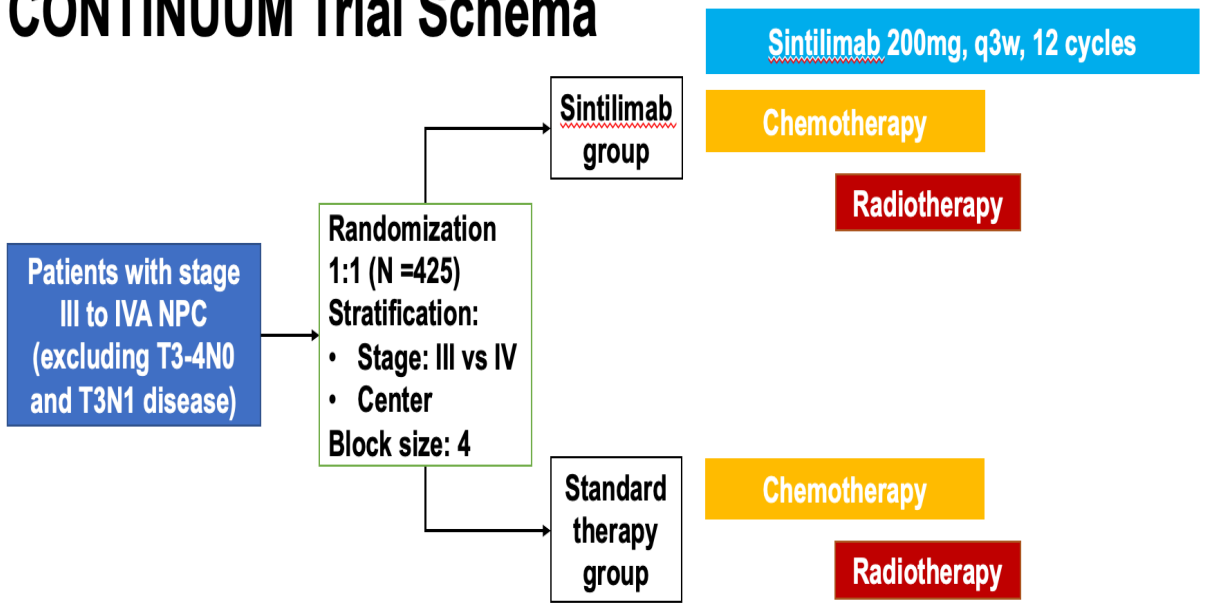
Ma BBY, Nature Med 2021

Different PD-1 inhibitors with GC improve PFS

JUPITER-2 Toripalimab	CAPTAIN-1st Camrelizumab	RATIONALE 309 Tislelizumab
N= 289	N= 263	N= 263
Median PFS (95% CI) 11.7, vs 8.0 mos HR=0.52, p=0.0003	Median PFS (95% CI) 9.7 vs 6.9 mos HR = 0.54, p=0·0002	Median PFS (95% CI) 9.2 vs 7.4 mos HR=0.52, P <0.0001
ORR: 77.0 vs 66.4%	ORR: 88.1 vs 80.6%	ORR: 69.5 vs 55.3%

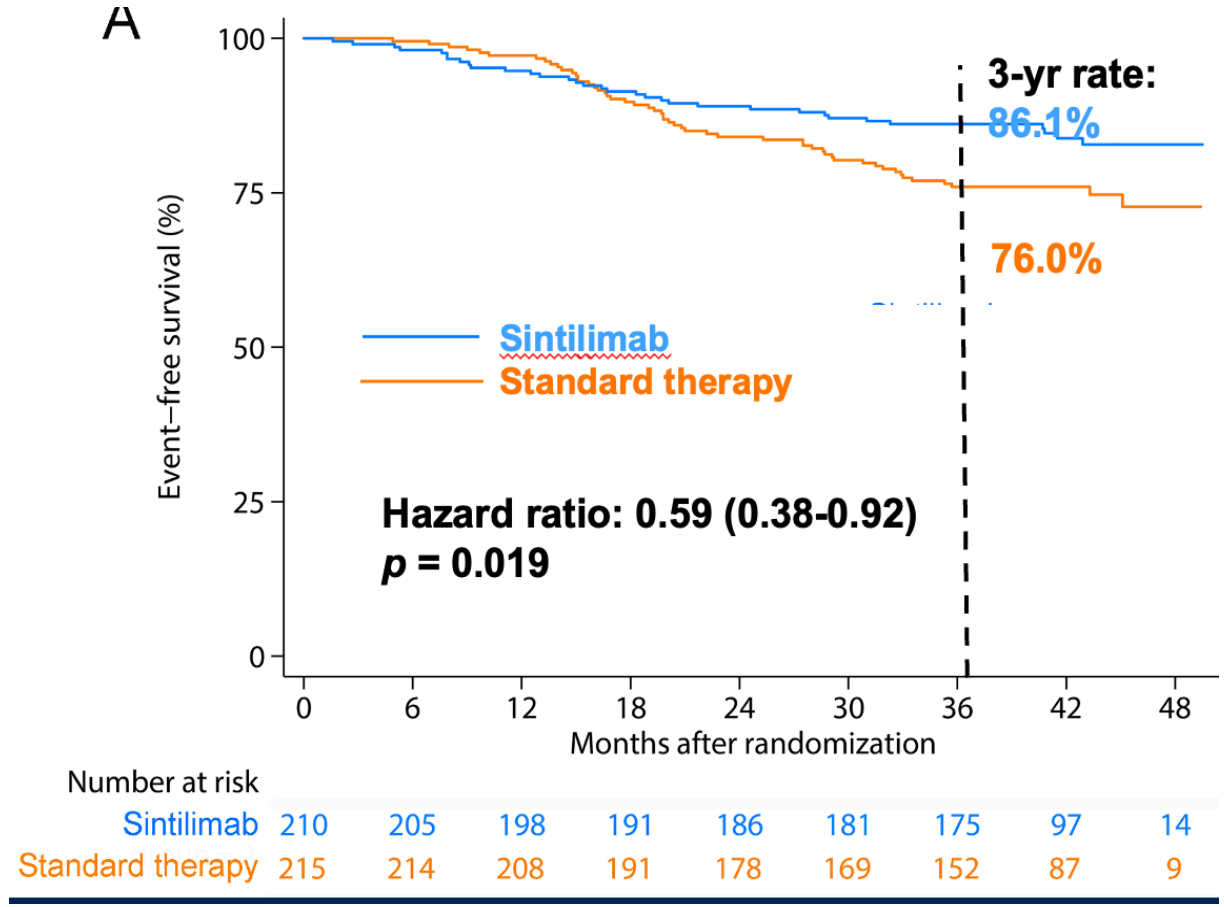
CONTINUUM; Adding Sintilimab (PD-1 inh) to GC

CONTINUUM Trial Schema



= GP IC, q3w * 3 cycles (Gemcitabine 1g/m2, d1 & 8; DDP 80mg/m2, d1) + CCRT (DDP 100mg/m2, d1 q3w * 2 cycles)

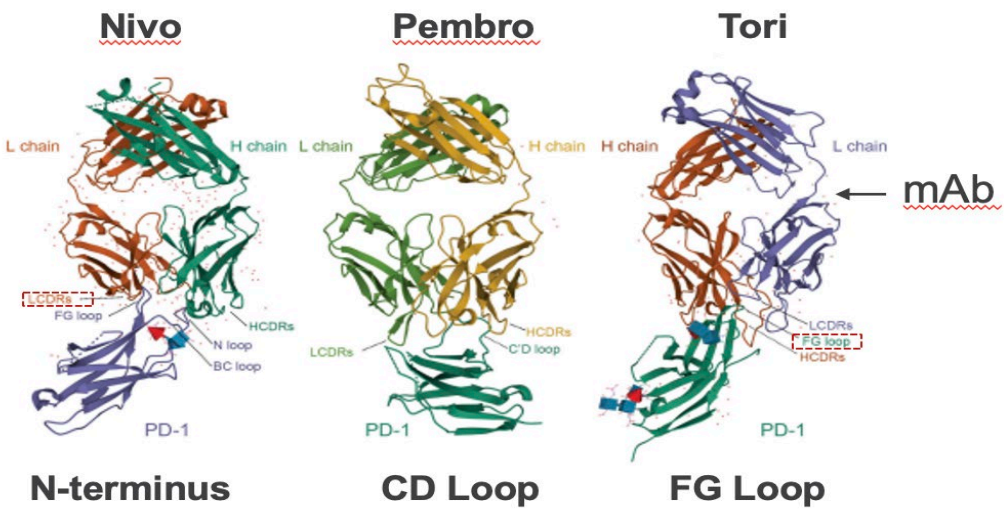
= Intensity modulated radiotherapy, 70Gy in 33 fractions, once per day, Monday to Friday in each week



The elephant in the room
PD-1 inhibitors are not created equal

- **Epitope is crucial for reducing on-target side effects.**
- **Positive and negative regulators of T cell activation may differ**
- **Cannot assume that differences in trial results are linked to clinical parameters only**
- **Interchangeability** of agents ought to be discouraged

Antibody	K_D (nM)	Epitope
Toripalimab	0.3	FG loop
Pembrolizumab	7.0	CD loop
Nivolumab	10.5	N-terminus



Lin et al. Frontiers in Immunology, Volume 12. 2022. https://www.frontiersin.org/article/10.3389/fimmu.2021.730666

Summary and Future Perspectives

- Novel combinations with PD-1 inh could lead to several new standards in RMD
- VEGF TKIs in combination with PD-1 inhibitors is a promising approach in treating HNSCC.
- Novel immunotherapeutic combination approaches (vaccines /fusion proteins+ PD-1) are promising in HPV related disease
- Pursuing EGFR targeting with or without immunotherapy agents with PD-1 inh is promising in HPV negative disease
- The landscape of immunotherapy in NPC is rapidly changing and new standards in LAD are expected.

Thank You !