IMMUNOTHERAPY IN ADVANCED NECK CANCER – STATE OF THE ART

DDHO, SEA ISLAND, 2026

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National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

POTENTIAL CONFLICT OF INTEREST

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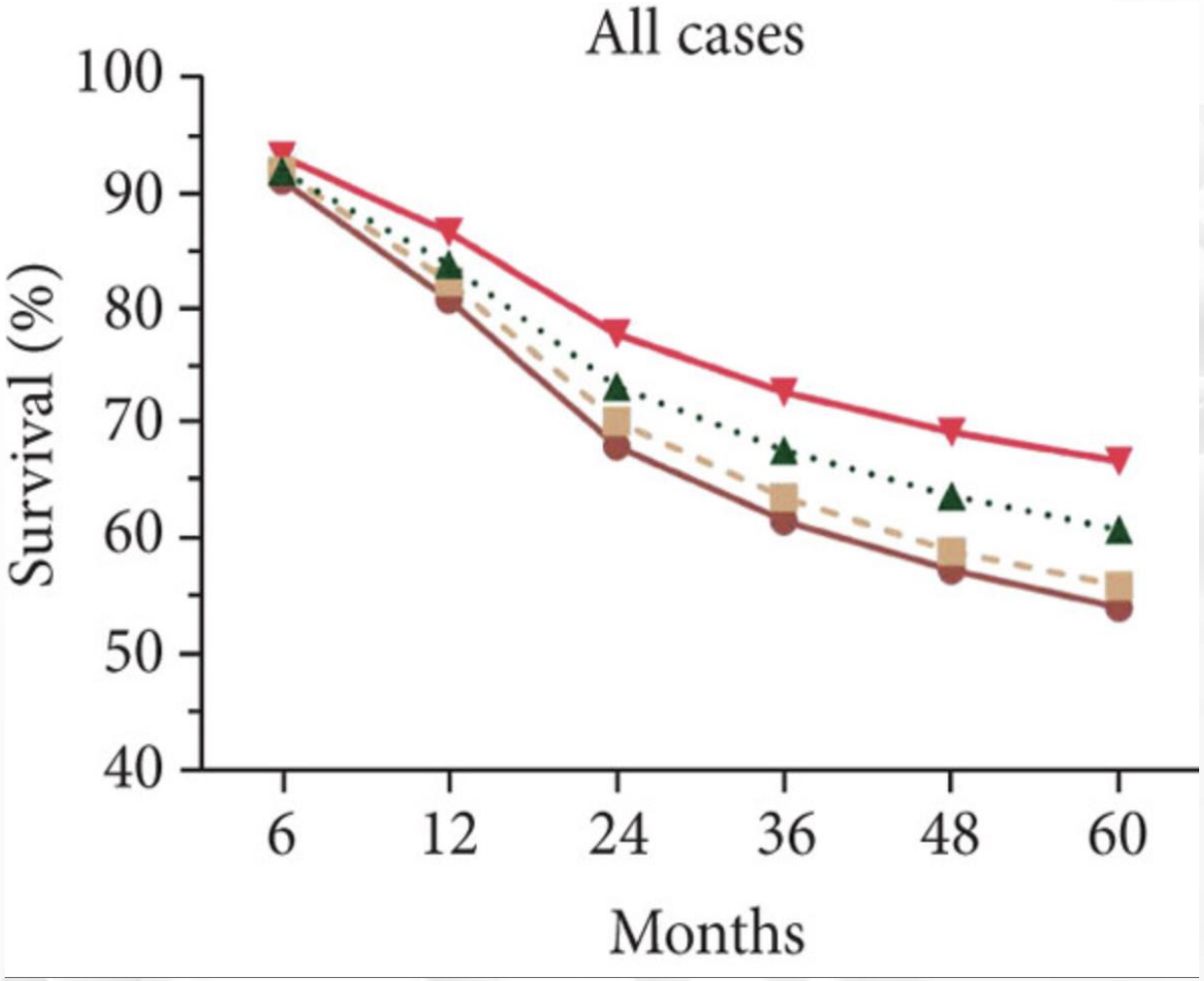
Reports having compensated or non-compensated advisory role with: Astra Zeneca Eisai Medical Exelixis Merck Merck EMD Serono, Pfizer, Kura, Vaccinex, CUE, BionTech, GSK, TOSK, Seagen, Flamingo, Infinity , Inovio, Aveo, Medscape, Onclive, Uptodate, BMS, J&J, JohnsonCornerstone, Celldex, Surface Oncology, Urogen, Summit, Guidepoints,
Astex, Imugene, Faron Pharmaceutical , Coherus, Adagene, Fulgent, Reddy Laboratories, Springer, Nanobiotix, Taiho

HNSCC- THE DISEASE BURDEN



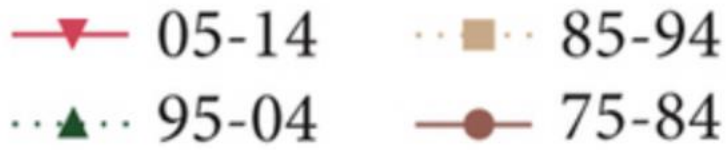
Guo, K, Biomed Search Intern, 2021

Annual new cases (global): up to 950,000

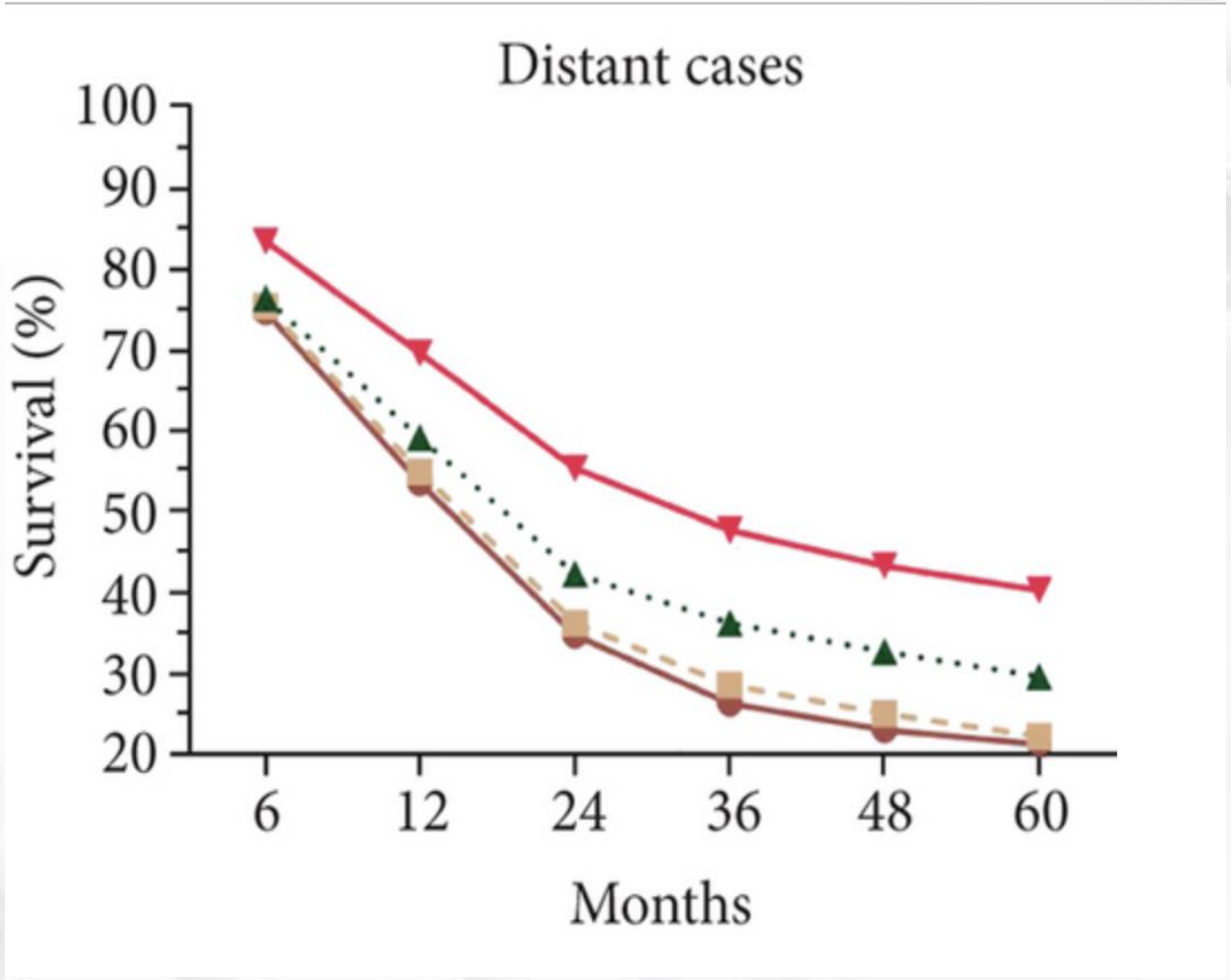
4–5% of all global cancer
Mortality rate (age-standardized):

4.9 per 100,000 worldwide

450,000 deaths/year globally from HNSCC alone



R OR M HNSCC – THE DISEASE BURDEN



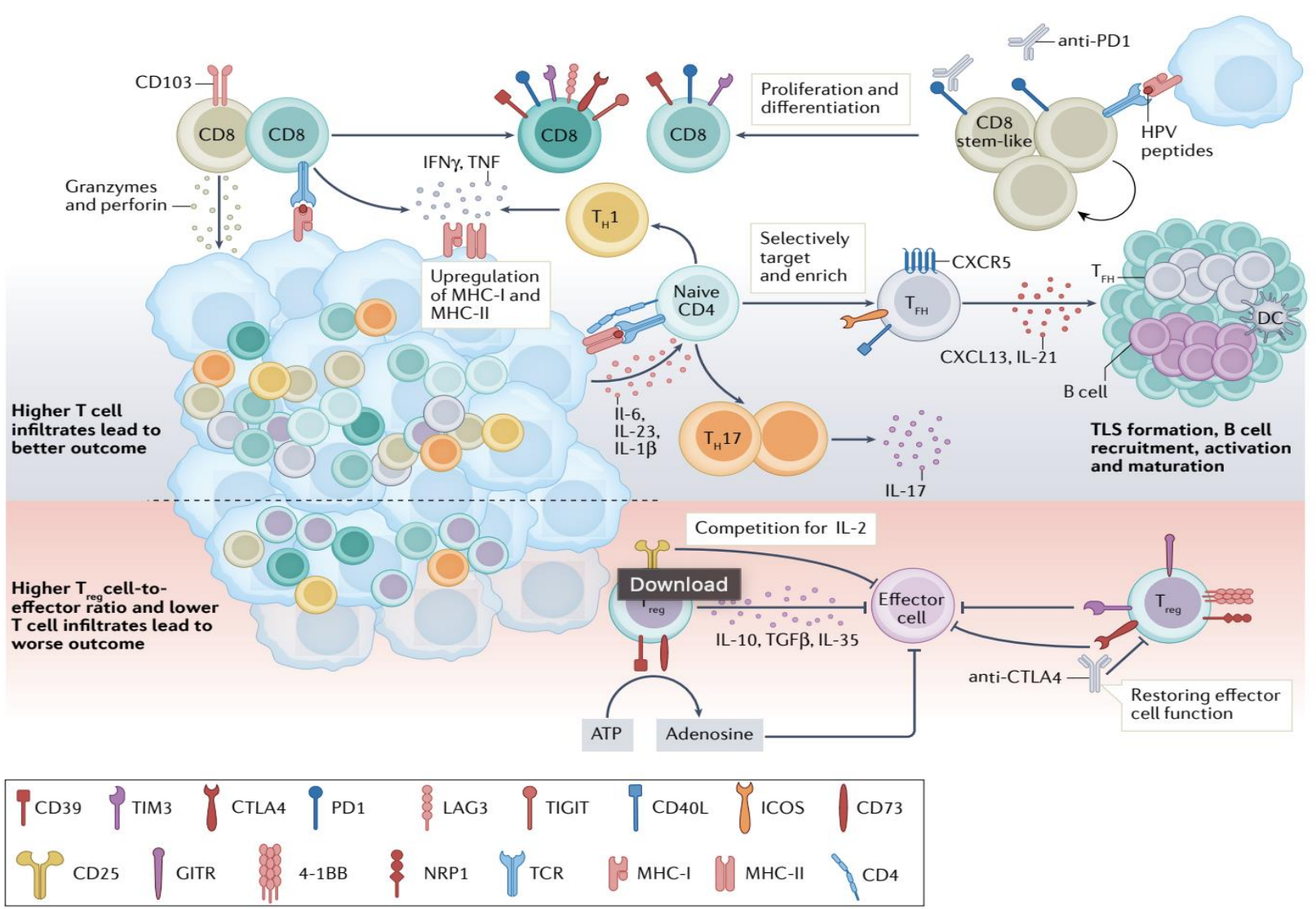
HNSCC is not just a high-incidence cancer—it is a high-failure cancer

40-60 % with LAD develop recurrence.

Even though only 20–30% become R/M, this accounts for a significant proportion of deaths- especially in HPV unrelated disease.

THE RATIONALE OF IMMUNOTHERTAPY

1. Immune microenvironment
2. PD-1/PD-L1 axis
3. T-cell exhaustion
4. Regulatory T cells
5. Myeloid-derived suppressor cells
6. Tumor-associated macrophages
7. HPV-mediated immune modulation
8. Tobacco-associated mutational landscape
9. IFN-γ signaling
10. Antigen presentation loss



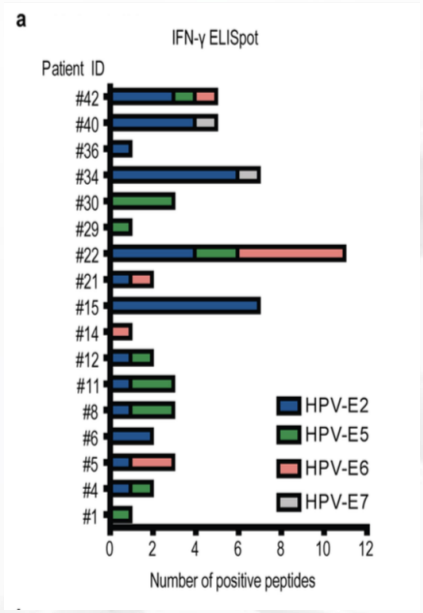
Ruffin AT, Nat Rev Cancer, 2023

Article | Published: 01 September 2021

Functional HPV-specific PD-1$^+$ stem-like CD8 T cells in head and neck cancer

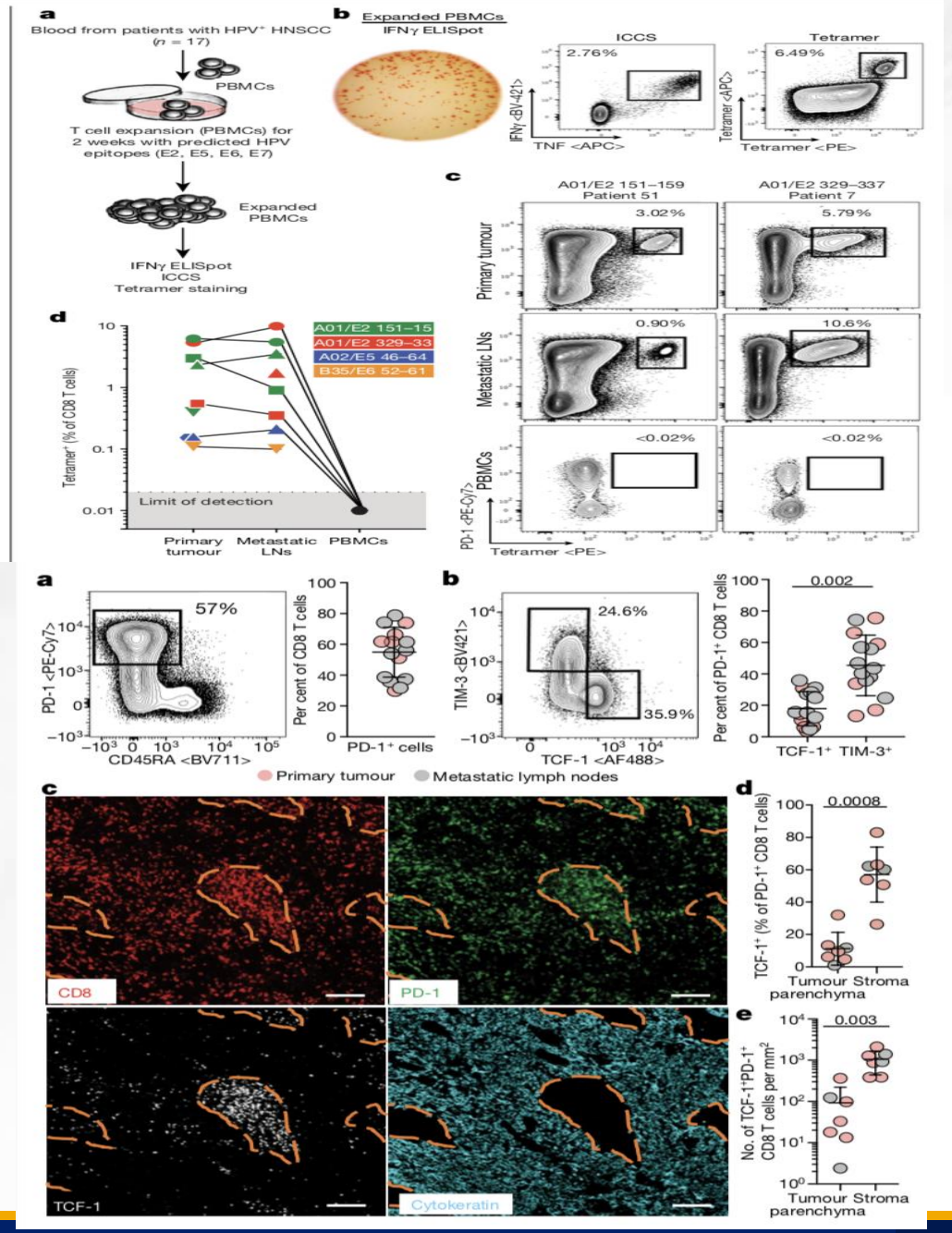
Christiane S. Eberhardt, Haydn T. Kissick, Mihir R. Patel, Maria A. Cardenas, Nataliya Prokhnevska, Rebecca C. Obeng, Tahseen H. Nasti, Christopher C. Griffith, Se Jin Im, Xu Wang, Dong M. Shin, Mary Carrington, Zhuo G. Chen, John Sidney, Alessandro Sette, Nabil F. Saba, Andreas Wieland ✉ & Rafi Ahmed ✉

Nature **597**, 279–284 (2021) | Cite this article



- **Presence of functional HPV-specific PD-1+TCF-1+CD45RO+ stem-like CD8 T cells with proliferative capacity**
- **Differentiation trajectory from stem-like to transitory to terminally differentiated**
- **HPV-specific PD-1+TCF-1+ stem-like TILs proliferated and differentiated into more effector-like cells after in vitro stimulation with the cognate HPV peptide**

Eberhardt CS, et al, Nature 2021



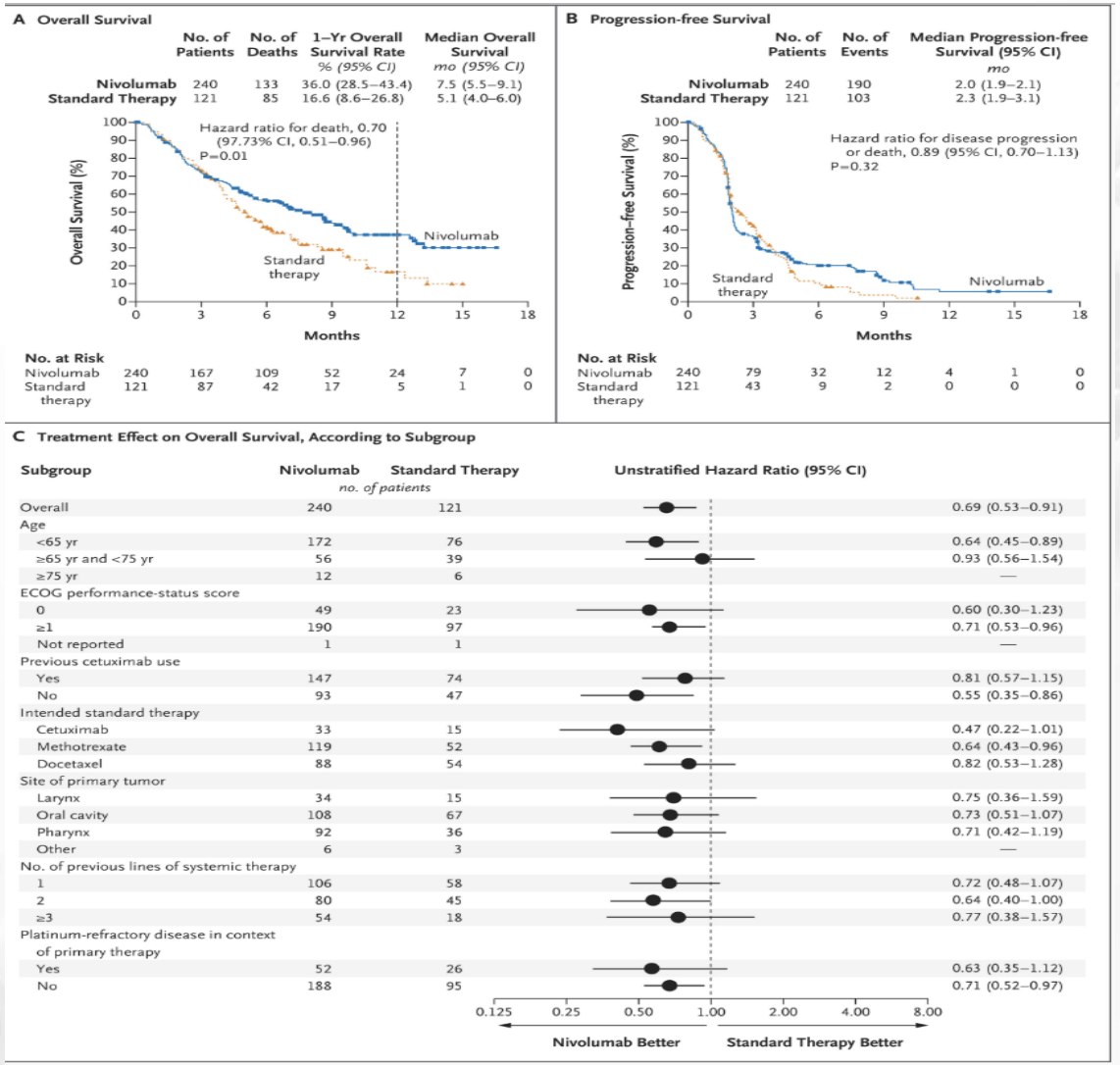
DR MAURA GILLISON
1965-2026

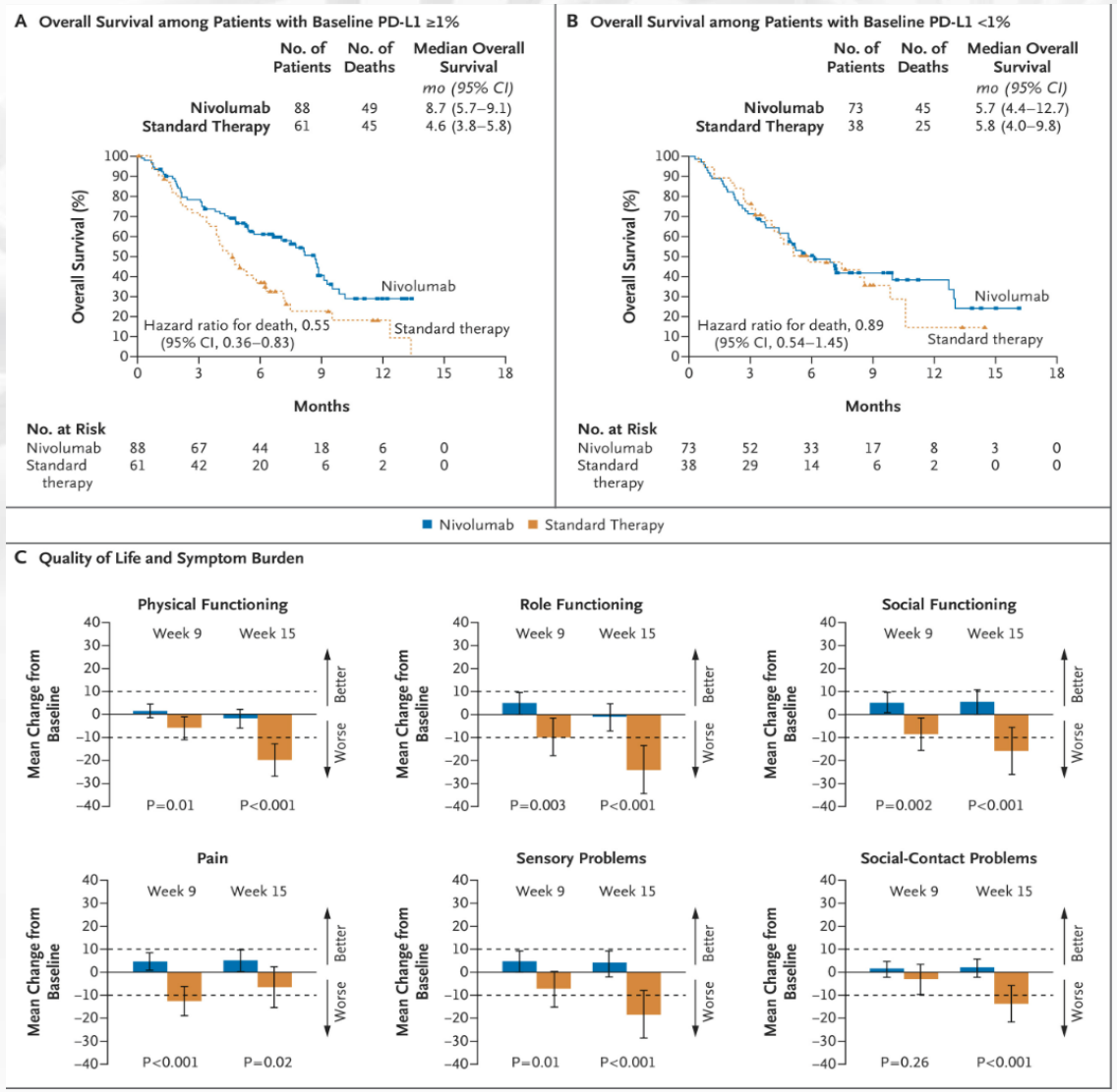
DR GILLISON DEMONSTRATED THAT HPV PARTICULARLY HPV 16 WAS THE CAUSE OF A DISTINCT SUBSET OF OROPHARYNX CANCER

April 2016

September 2024

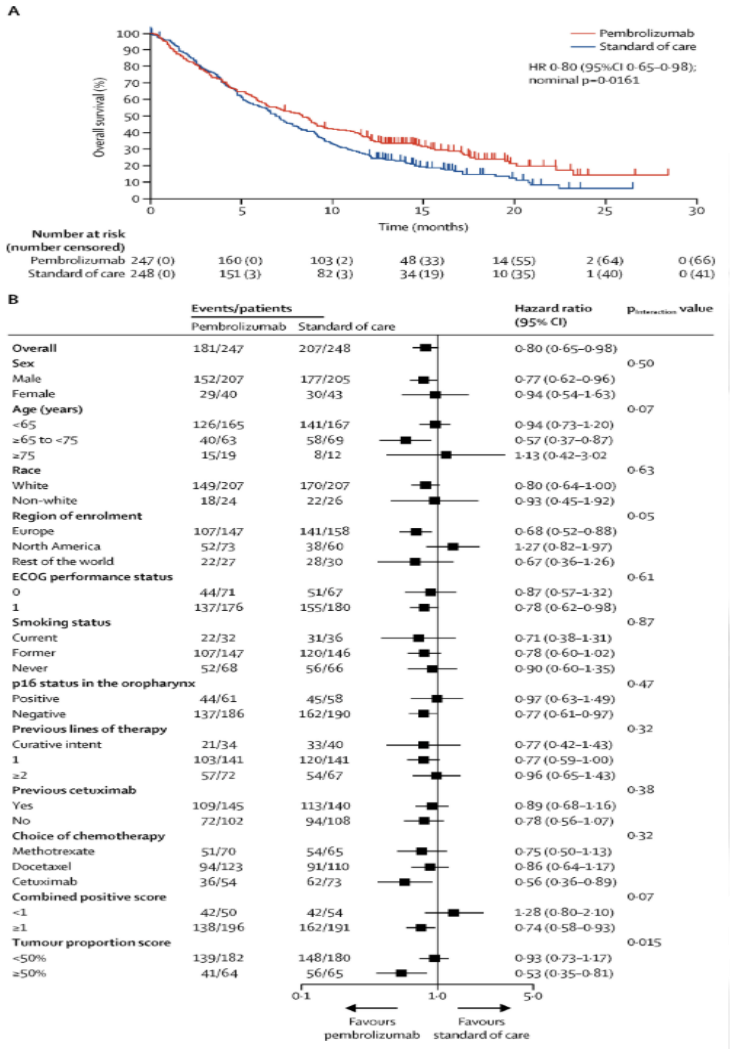
CHECKMATE 141: NIVOLUMAB IN PLATINUM EXPOSED PATIENTS



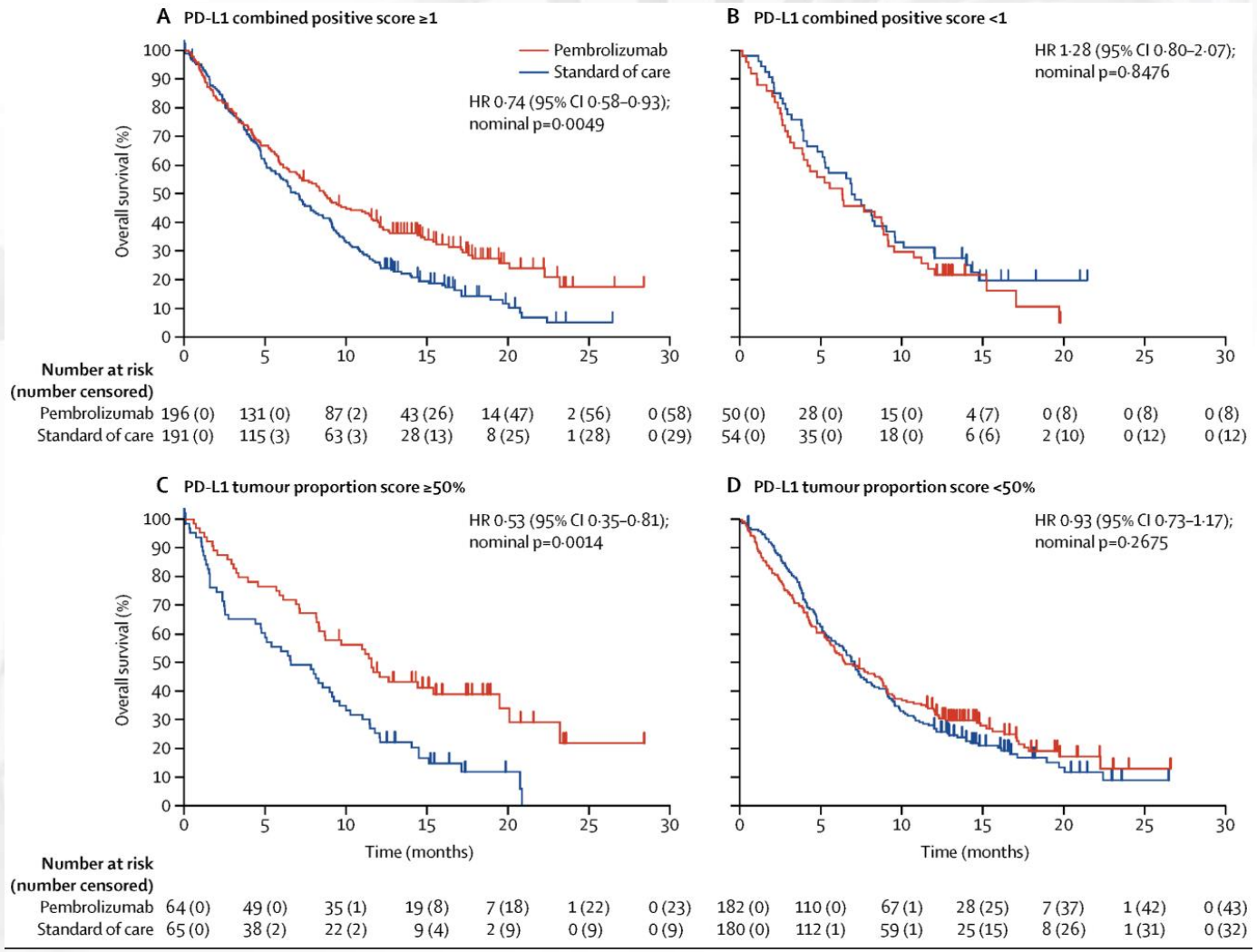


Ferris R, et al, NEJM 2016

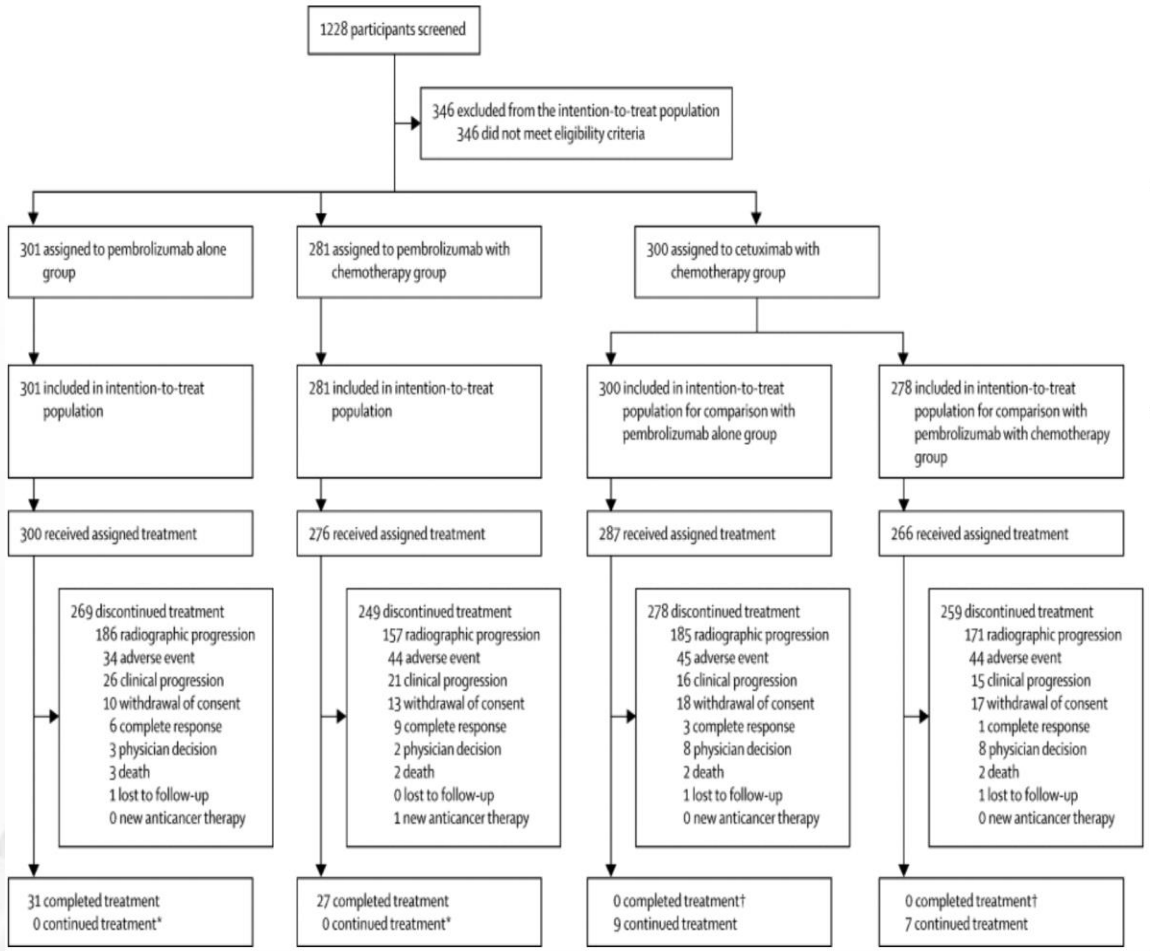
KEYNOTE 040: PEMBROLIZUMAB IN PLATINUM EXPOSED PATIENTS

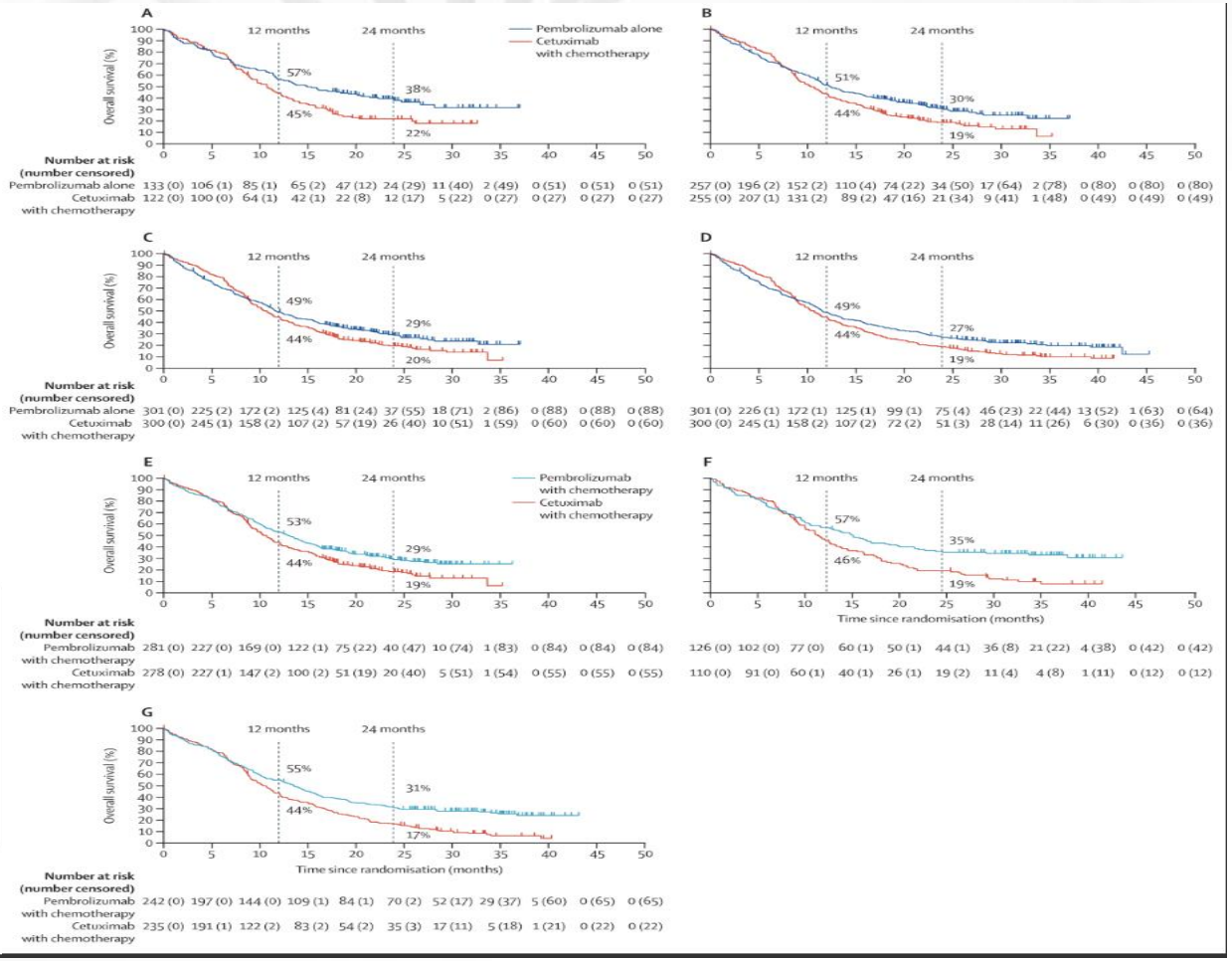


Cohen EEW, Lancet 2019



KEYNOTE 048: PREVIOUSLY UNTREATED RM HNSCC





Burtness B, Lancet 2019

FACTORS THAT AFFECT TREATMENT CHOICE

PD-L1: CPS interpretation (with limitations)

1. CPS ≥20 – more likely to use single agent PD-1 inhibitor
2. CPS 1–19- less likely to use single agent PD-1 inhibitor
3. CPS <1- not recommended to use single agent PD-1 inhibitor

Clinical considerations affecting the use of cytotoxic therapy or cytoreductive therapy + PD-1 inhibitors

1. Symptomatic disease; tumor burden
2. Rapid progression
3. Organ compromise
4. ECOG performance status
5. HPV status
6. Frailty

CASE PRESENTATION

A 60-year-old male with HPV related OPSCC treated with cisplatin and radiation 2 years ago presents with recurrent disease and multiple liver lesions and lung metastatic lesions. His tumor has a CPS score of 60. He is feeling more tired than usual yet is active with a PS of 1

At the time of his presentation, he was not interested in a clinical trial participation.

How would this patient be treated in my clinic ?

1- Single agent Pembrolizumab

2- Platinum /5-FU and Pembrolizumab

3- Paclitaxel Carboplatin and Pembrolizumab

BEYOND PD1 INHIBITORS

VEGF modulation + PD-1 inhibitors, (lenvatinib, cabozantinib, zanzalintinib and others..)

(despite the encouraging clinical activity, there is no practice changing indications)

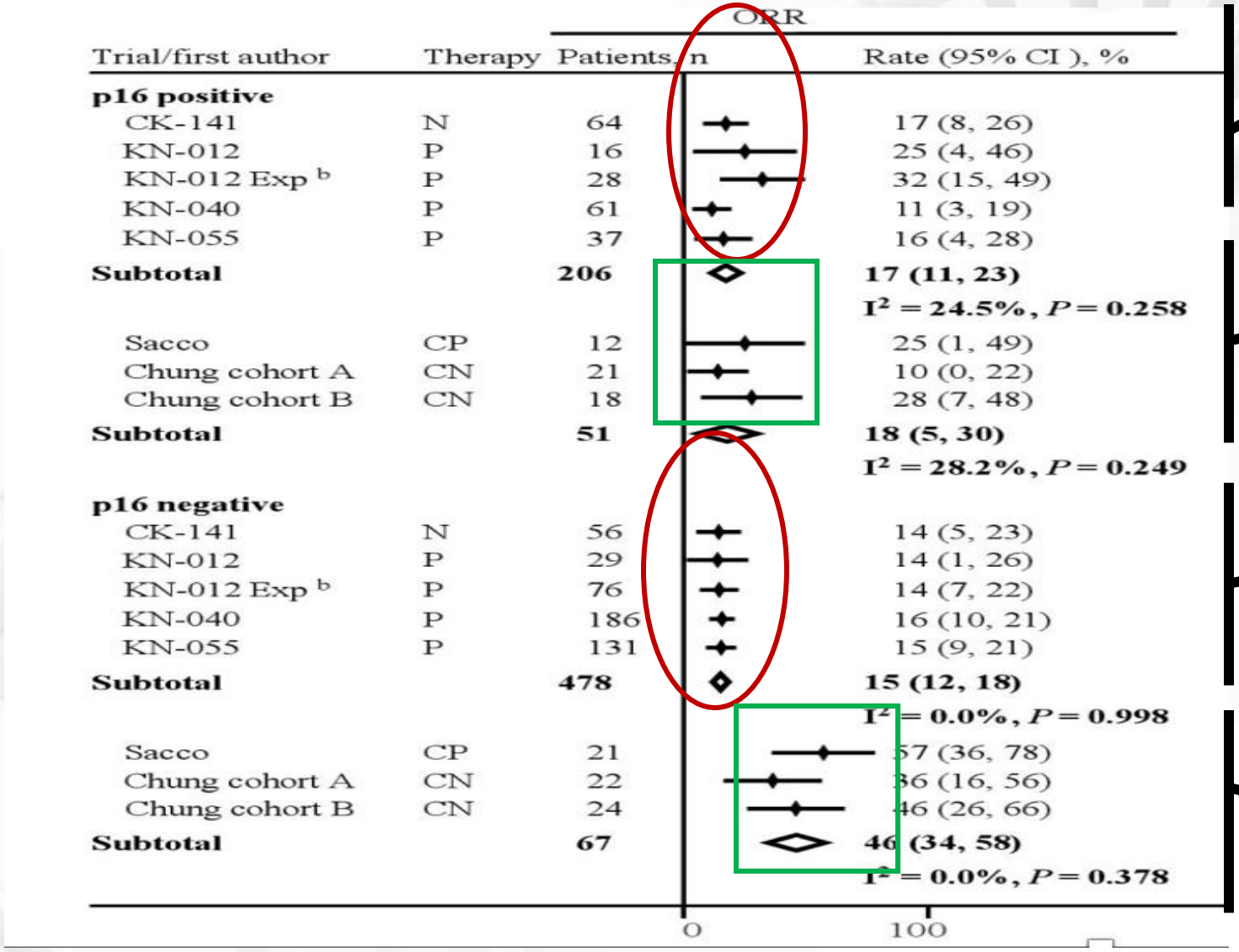
Modulators of EGFR resistance (predominantly in HPV unrelated disease)

Novel checkpoints, TIGIT, LAG-3, TIM-3, CTLA-4 combinations

Cell therapy, Tumor-infiltrating lymphocytes, CAR-T, TCR therapies

Vaccines, HPV therapeutic vaccines (predominantly HPV related)

ORR and OS in HPV pos vs neg HNSCC on different trials using PD-1 inhibitors +/- CETUXIMAB



PD-1 Inhibitors HPV positive

PD-1 Inh + Cetux HPV positive

PD-1 Inhibitors HPV negative

PD-1 Inh + Cetux HPV negative

Zhang JITC, 2022

AMIVANTAMAB - ORIGAMI-4 STUDY DESIGN

Eligibility Criteria for Cohort 1

- Recurrent/metastatic (R/M) head and neck squamous cell carcinoma
- No prior anti-EGFR therapy
- ECOG PS score: 0 or 1
- p16 positive oropharyngeal carcinoma was excluded

***Subcutaneous** amivantamab is administered at 2400 mg (or 3360 mg if ≥80 kg) Q3W[a]*

Cohort 1: Amivantamab monotherapy[b]
Post–PD-(L)1 inhibitor and platinum-based chemotherapy[c]

Cohort 2: Amivantamab plus pembrolizumab[b]
Treatment naïve in the R/M setting

Cohort 3: Amivantamab plus paclitaxel[b]
Post–PD-(L)1 inhibitor

Cohort 4: Amivantamab monotherapy[d]
Post–PD-(L)1 inhibitor and platinum-based chemotherapy[c]

Cohort 5: Amivantamab plus pembrolizumab with carboplatin[d]
Treatment naïve in the R/M setting

Cohort 6: Amivantamab plus pembrolizumab[b]
Treatment naïve in the locally advanced, perioperative setting

Endpoints

- Objective response rate (primary)
- Duration of response
- Clinical benefit rate[e]
- Progression-free survival
- Overall survival
- Safety

Responses were assessed by the investigator per RECIST v1.1 and confirmed via BICR

Treatment beyond progression was permitted for continued clinical benefit per investigator

- A sample size of 80 response-evaluable participants would provide >99% power to reject the null hypothesis (ORR ≤10%) assuming an ORR of 30% with a 2-sided alpha of 5%[f]

OrigAMI-4 (ClinicalTrials.gov Identifier: NCT06385080). Note: All cohorts of OrigAMI-4 will utilize the subcutaneous formulation of amivantamab, which is coformulated with recombinant human hyaluronidase PH20 and manually injected in the abdomen.

[a]Each cycle is 21 days (3 weeks); Cycle 1: 1600 mg (or 2240 mg if ≥80 kg) on Day 1, 2400 mg (or 3360 mg if ≥80 kg) on Day 8 and Day 15; Cycle 2 (and thereafter): 2400 mg (or 3360 mg if ≥80 kg) on Day 1. [b]Participants with HPV+ oropharyngeal squamous cell carcinoma were excluded. [c]Eligible participants must have received an anti–PD-(L)1 and platinum-based chemotherapy in combination or as separate lines of therapy for R/M disease. A participant could have received 1 or both treatments in the locally advanced disease if progression was within 6 months. [d]Participants with HPV+ oropharyngeal squamous cell carcinoma were included. [e]Clinical benefit rate was defined as percentage of confirmed responders or durable stable disease (at the second disease assessment). [f]The INTERLINK-1 data, which showed an ORR of 24% with cetuximab, were not available at the time of protocol/study initiation.[1]

1. Fayette J, et al. Clin Cancer Res. 2025;31(13):2617–2627.

BICR-ASSESSED ORR AND BEST RESPONSE

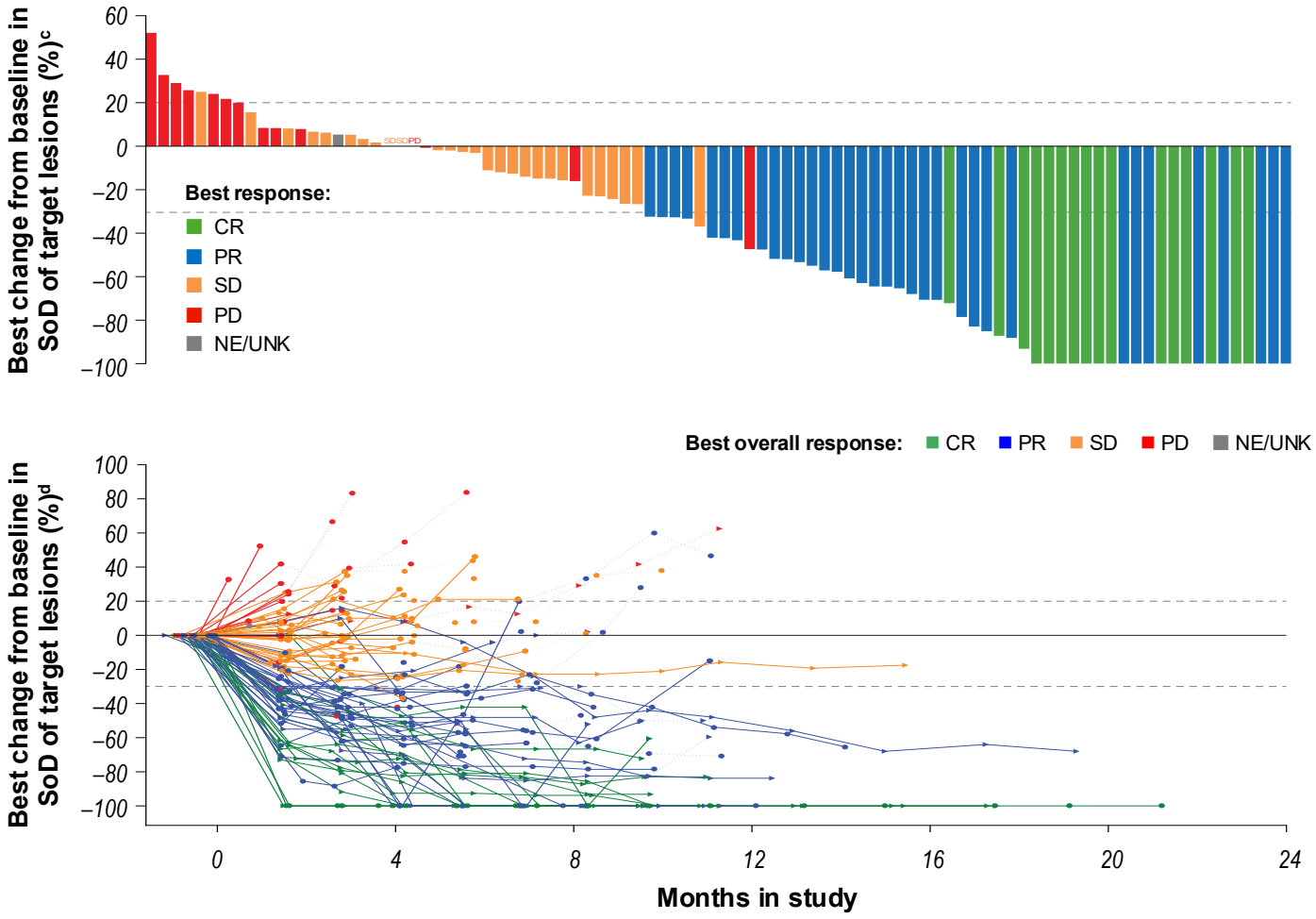
BICR-assessed response	N=102
Confirmed ORR	**42%** (95% CI, 32–52)
Best response, n (%)	
CR	**15 (15)**
PR	28 (27)
SD[a]	36 (35)
PD	16 (16)
NE	7 (7)
Time to first response, weeks	6.6 (range, 5.6–36.9)
Clinical benefit rate[b]	63% (95% CI, 53–72)

Investigator-assessed ORR (**47%**; 95% CI, 37–57) was consistent with the BICR results

- Among participants with ≥1 post-baseline disease assessment, 84% experienced tumor shrinkage of target lesions

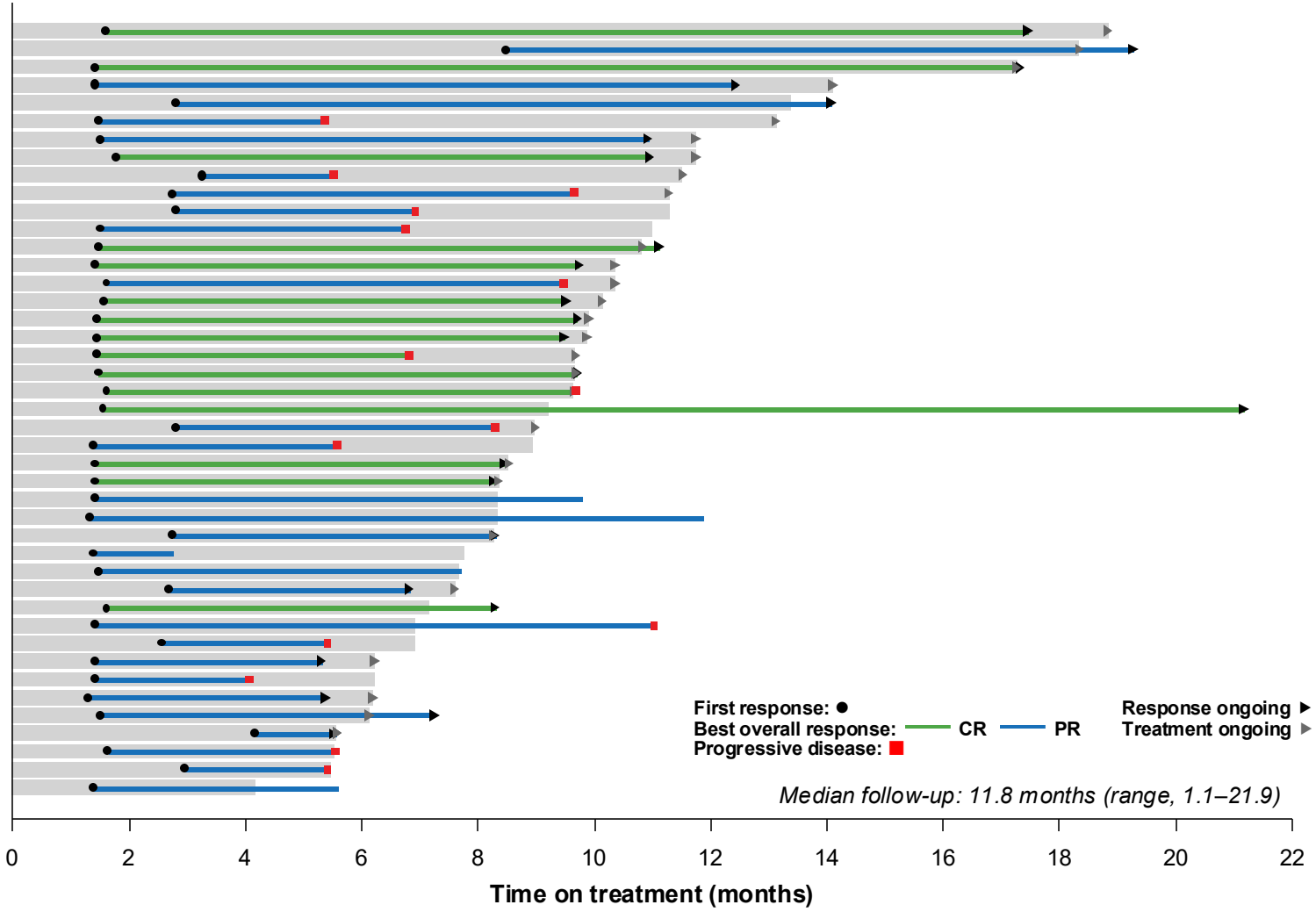
[a]Includes non-CR/non-PD with only non-target lesions at baseline and no evidence of disease with no target or non-target lesions at baseline. [b]Defined as percentage of participants achieving a response or durable SD (at second disease assessment). [c]Ten participants (NE/UNK: n=6; PD: n=2; non-CR/PD: n=1; no evidence of disease: n=1) without postbaseline tumor assessments were not shown; all participants were included in the ORR analysis. [d]Excludes participants without a postbaseline tumor assessment. Triangle indicates ongoing treatment; circle indicates completed/discontinued treatment; solid line indicates before PD; dotted line indicates after PD.

BICR-Assessed Best Response



Burtness B, ASCO 26

DURATION OF RESPONSE



Median DoR was not reached (95% CI, 6.9–NR) in the 43 confirmed responders

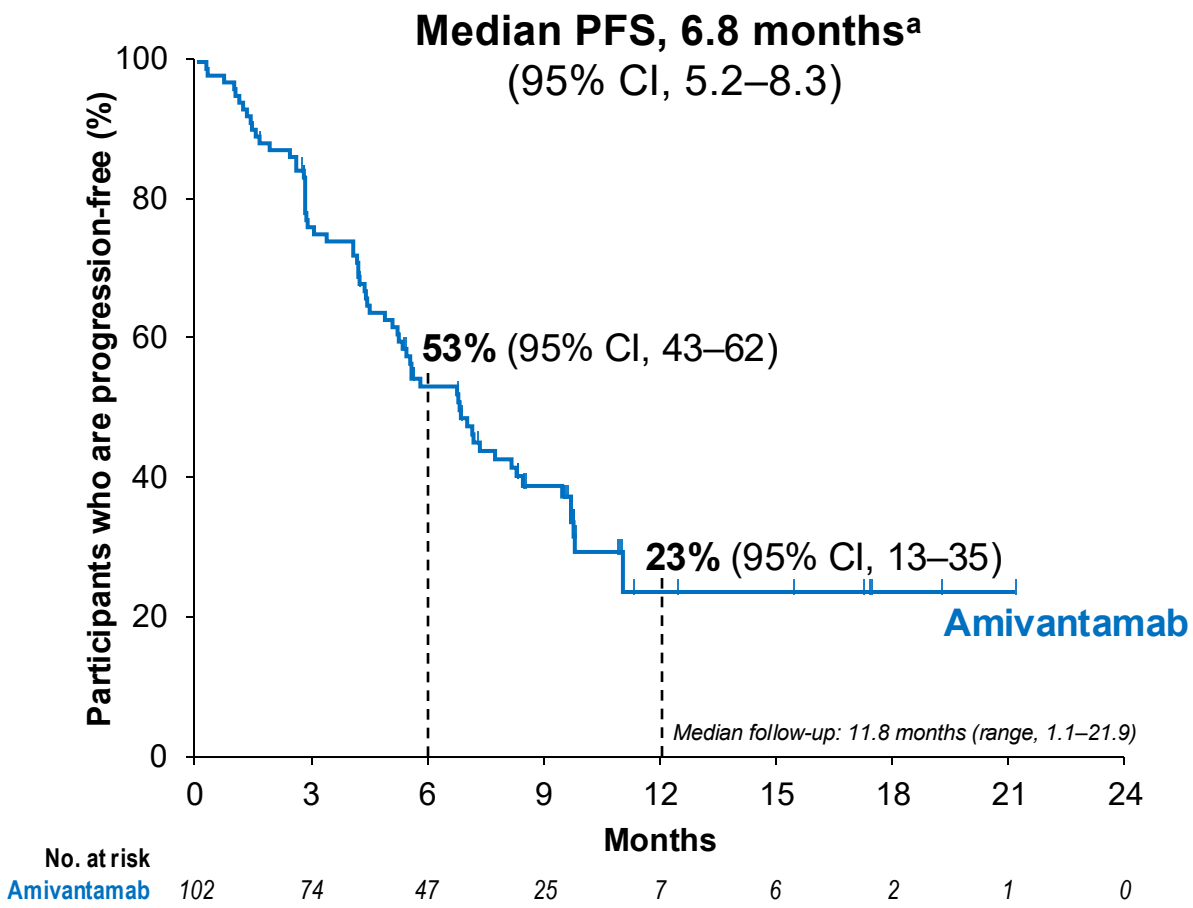
- 56% of responders had a response duration ≥6 months
- 63% of responses are ongoing

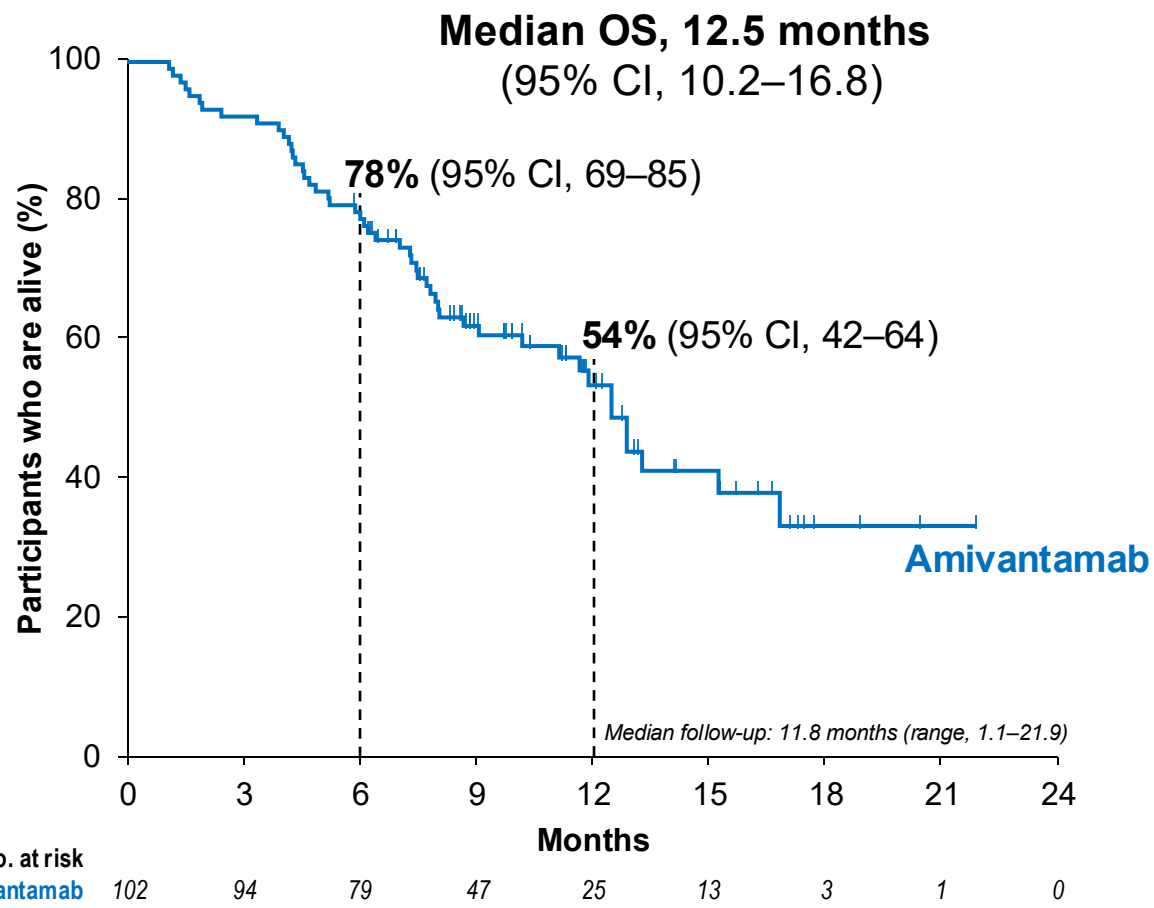
Among the 15 CRs, 13 (87%) are ongoing

Burtness B, ASCO 26

PFS AND OS

54% of participants were alive at 1 year

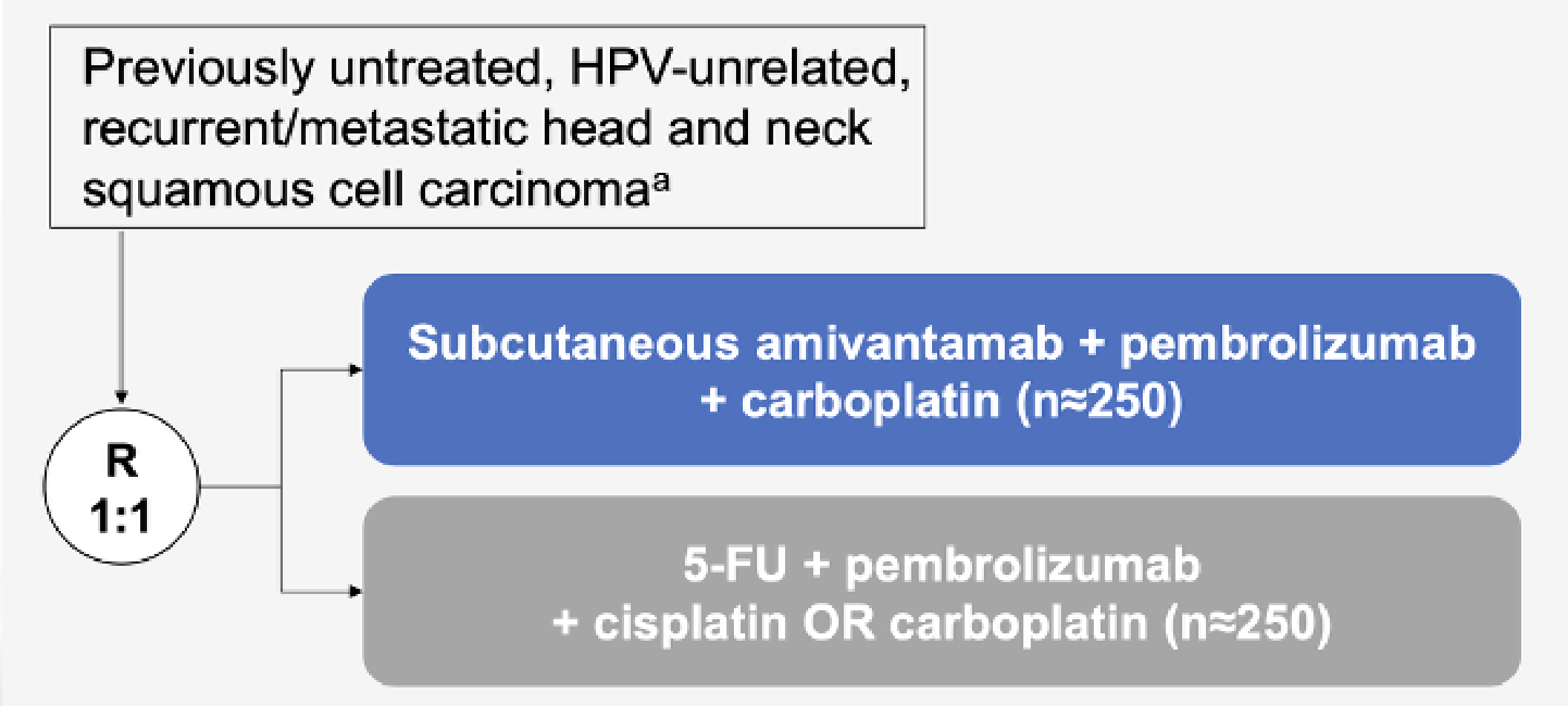




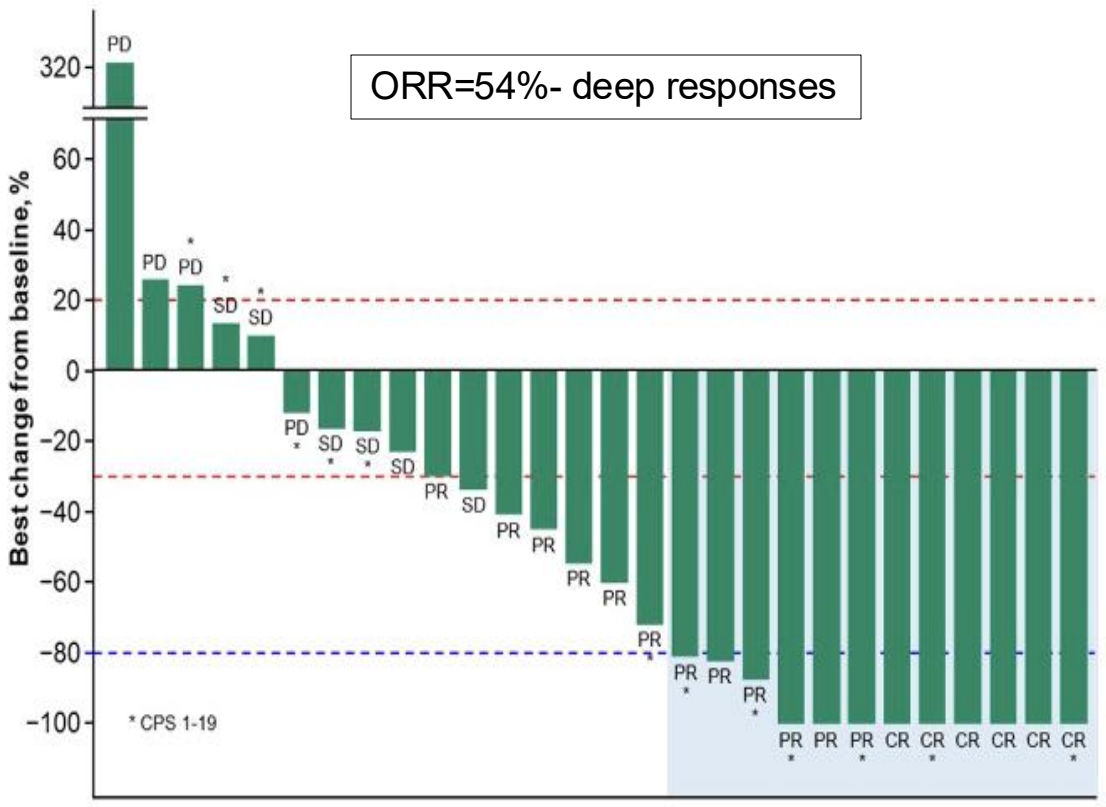
[a]*Assessed by investigator.*

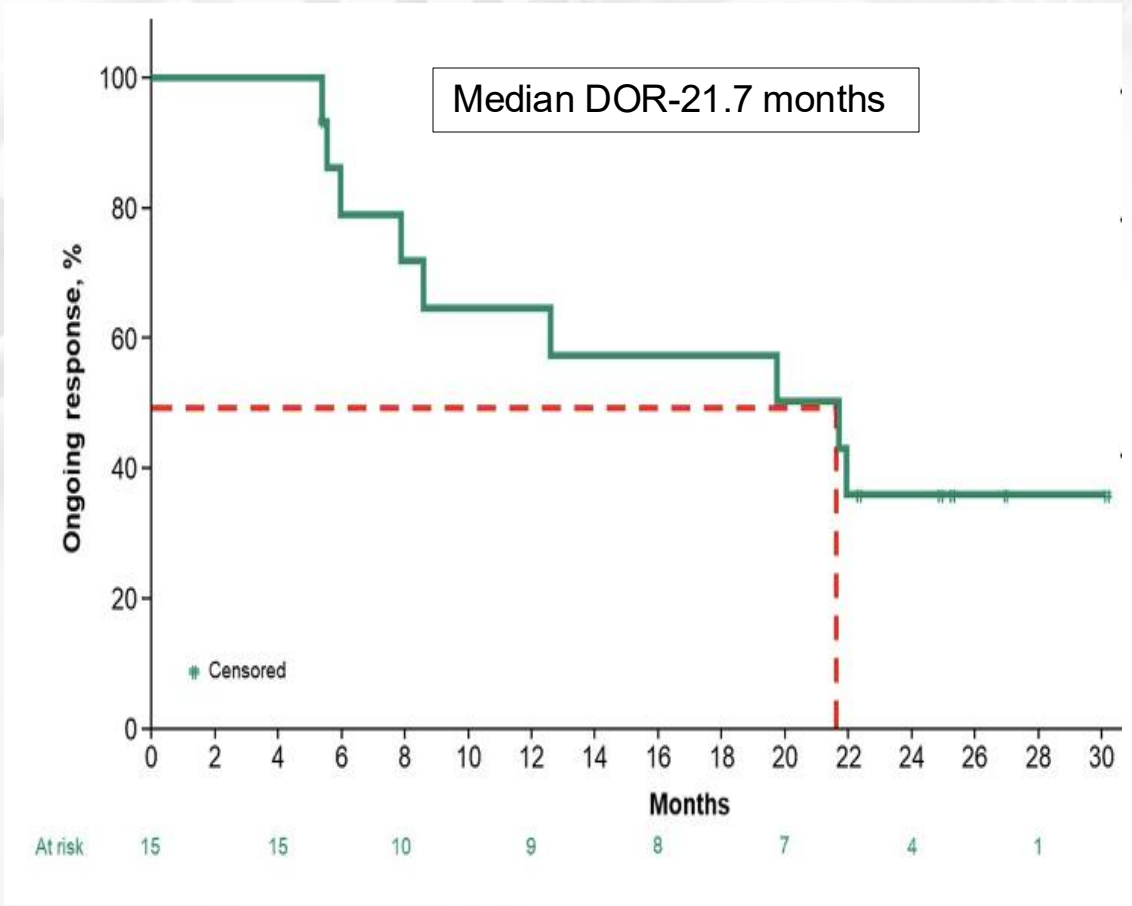
Burtness B, ASCO 26

ORIGAMI -5: PHASE III TRIAL IN HPV- UNRELATED R/M HNSCC



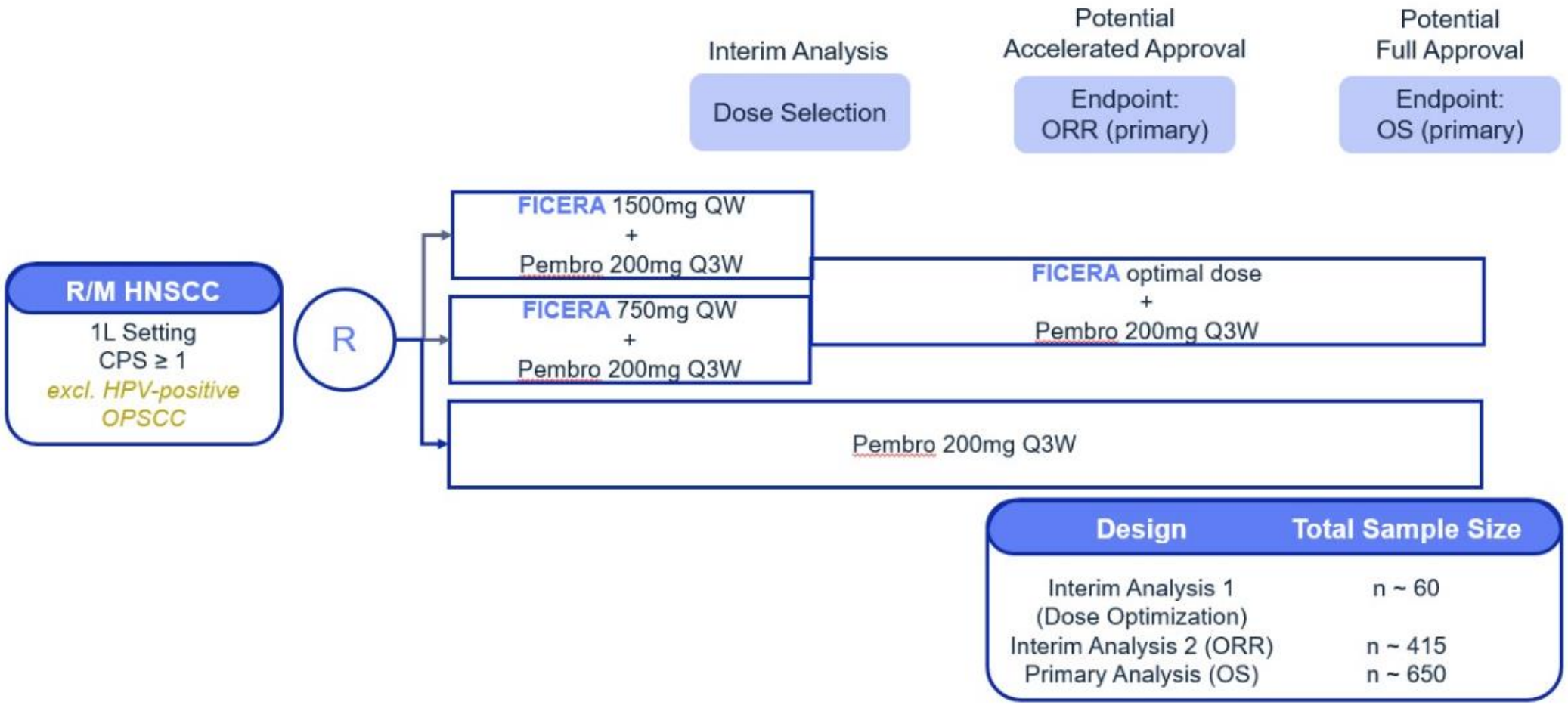
BCA101(FICERAFUSP ALFA) : A BISPECIFIC ANTIBODY TARGETING EGFR AND TGFB[1]





Chung, C ASCO 2025

FORTIFI-HN01: PHASE 2/3 TRIAL OF FICERAFUSP ALFA + PEMBEO IN 1L R/M HNSCC

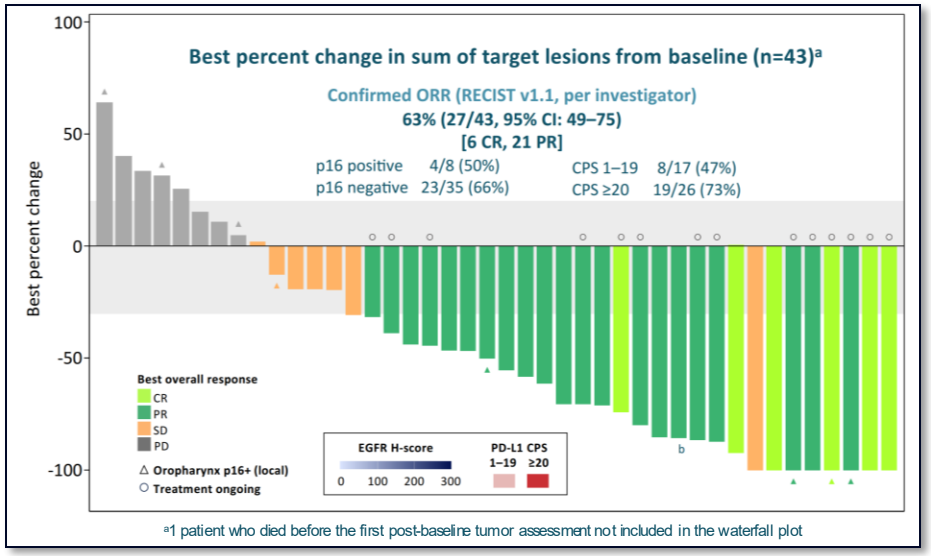


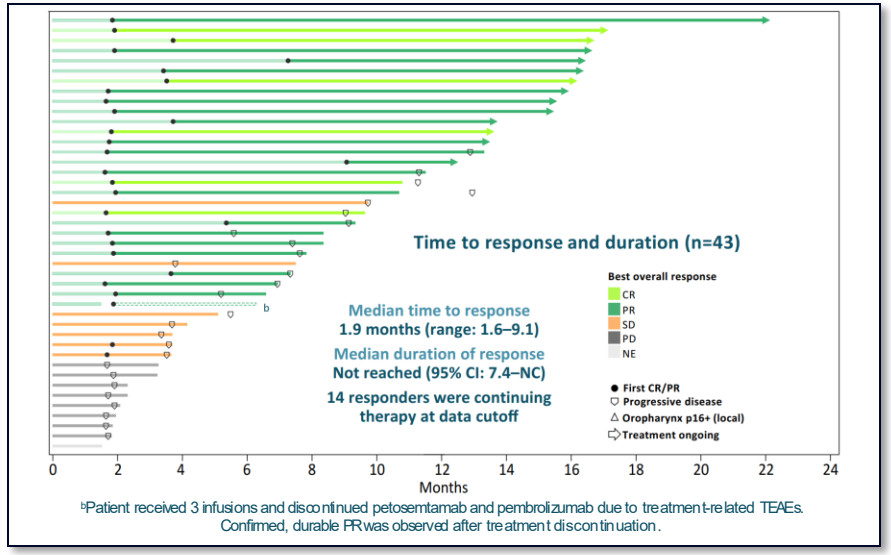
Bicare Therpeutics,
https://www.sec.gov/Archives/edgar/data/2023658/000202365825000012/bcax-20241231.htm

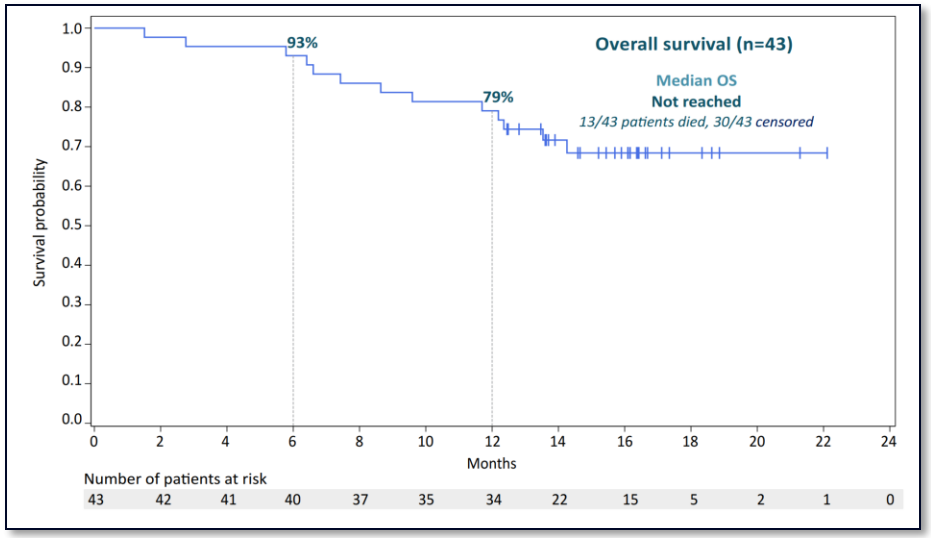
PETOSEMTAMAB + PEMBROLIZUMAB PHASE 2 TRIAL

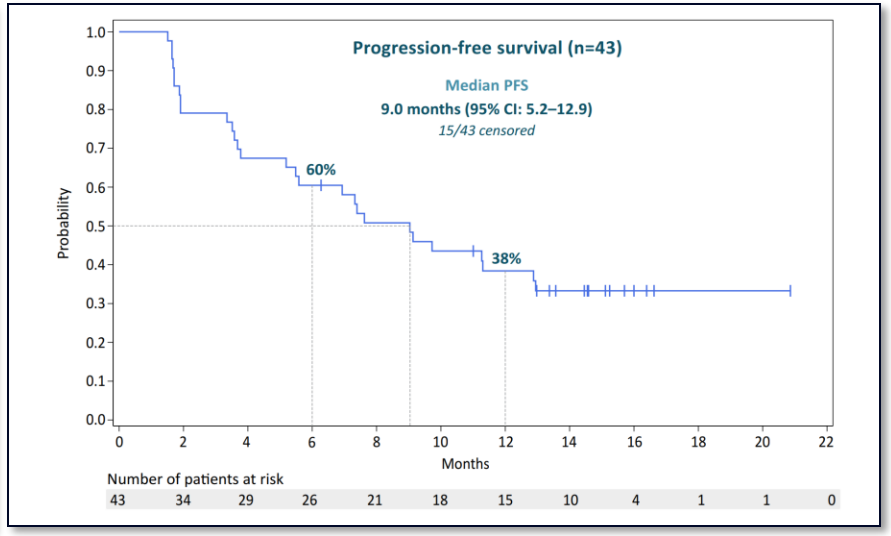
Overall Clinical Efficacy	
ORR	63%
mPFS	9 months
OS	79% at 12 months
mOS	Not reached

KN-048 Benchmark[2] Pembro Monotherapy (PD-L1 CPS ≥1)	
ORR	19%
mPFS	3.2 months
OS	51% at 12 months
mOS	12.3 months





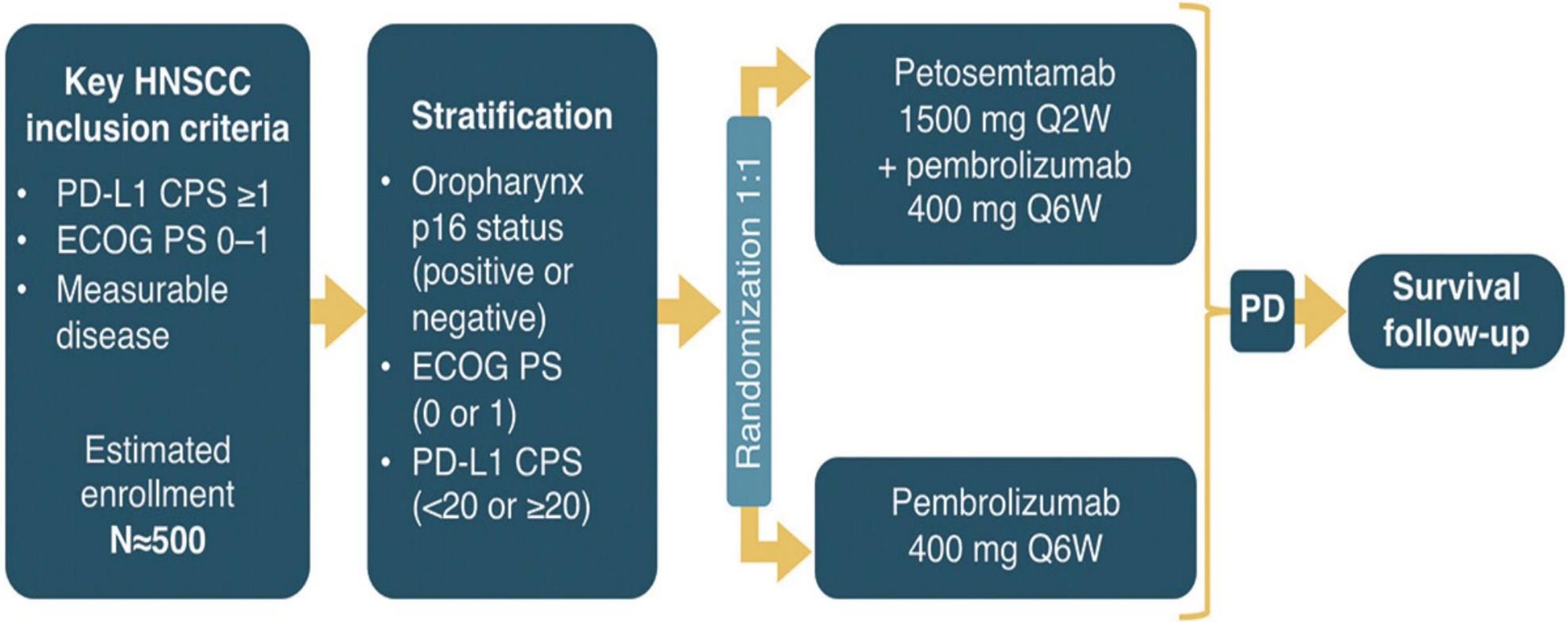




CI: confidence interval; CR: complete response; NA: not available; NC: not calculable; NE: not evaluable; OS: overall survival; PFS: progression-free survival; PR: partial response; SD: stable disease.

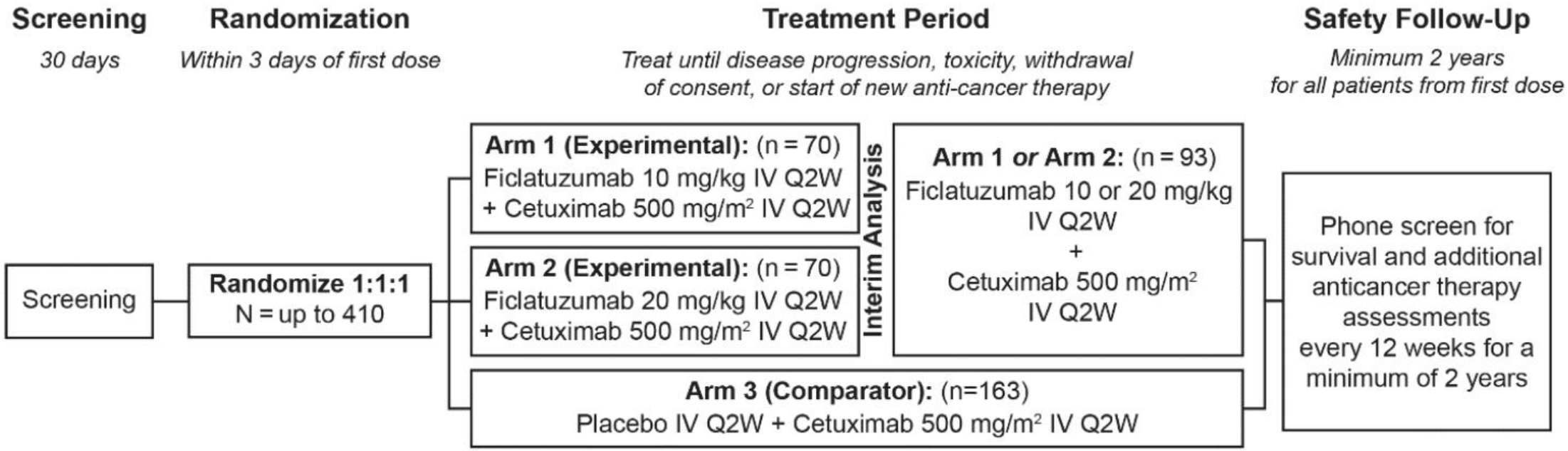
1. Van Herpen C et al. Petosemtamab (MCLA-158) with pembrolizumab as first-line (1L) treatment of PD-L1+ recurrent/metastatic (r/m) head and neck squamous cell carcinoma (HNSCC): Phase 2 study. ASCO 2025;
2. Harrington KJ, et al. *J Clin Oncol* 41, 790-802(2023);

LIGER-HN PHASE III TRIAL OF PETOSEMTAMAB + PEMBROLIZUMAB VS PEMBROLIZUMAB IN FIRST LINE RMHNSCC



Machiels JP, Future Onco 2025

PHASE 3 STUDY OF FICLATUZUMAB IN COMBINATION WITH CETUXIMAB IN RECURRENT OR METASTATIC (R/M) *HPV-NEGATIVE* HEAD AND NECK SQUAMOUS CELL CARCINOMA (FIERCE-HN)



Patient Population:
R/M HNSCC (HPV-neg)
Prior ICI and platinum-chemo required (or intolerant to treatment)

Primary Endpoint: OS
Secondary Endpoint: PFS, ORR, DOR, DCR, Safety, Pk
Exploratory Endpoints: Pd, PRO

Disease Response Assessments:
Day 1 of Cycle 3 (C3), C5, C7, C9, C11, C14, C17, C20, etc. Then every 12 weeks (3 cycles) for years 2 and 3.
Interim Analysis: Arm 1 vs. Arm 2

EVOPARCEPT (blocks CD-47 signal) + PEMBRO vs Pembro

Key Eligibility Criteria
- Metastatic or unresectable, recurrent (R/M) HNSCC
- PD-L1 CPS ≥1
- No prior systemic therapy for advanced disease
- Measurable disease
- ≥18 years old
- ECOG PS 0-1

Minimization Factors
- Geography: Asia Pacific, Europe, North America
- PD-L1 CPS: CPS 1-19, CPS ≥20
- HPV (p16) Status: positive, negative, unknown
- Tobacco Habits: Current, Past, Non-user
- ECOG PS: 0, 1

Safety Lead-In
N=8
Evorpacept + Pembrolizumab

R 2:1

N=121: Evorpacept 45 mg/kg IV + Pembrolizumab 200 mg IV Q3W†

vs.

N=60: Pembrolizumab 200 mg IV Q3W†

†max of 35 cycles (up to 24 months)

Primary Endpoints
- Objective response rate (BICR)

Primary Analysis
- Compare ORR to historical control ORR 20%

Key Secondary Endpoints
- ORR, DCR, DOR, PFS, TTP, OS, 12-month OS rate, Safety

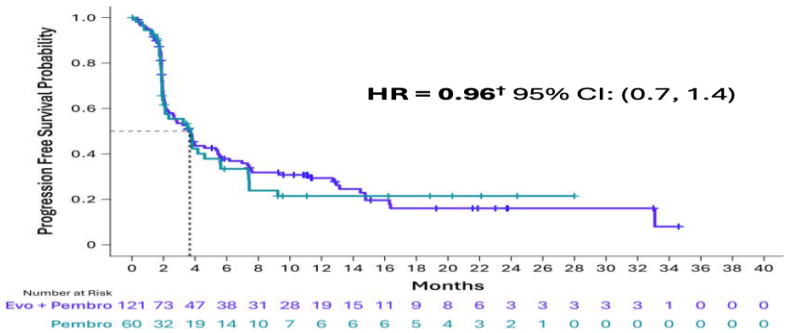
Exploratory Endpoints
- Preplanned biomarker analysis of CD47 vs efficacy endpoints

ORR and DOR by BICR

	Evorpacept + Pembrolizumab (n=121)	Pembrolizumab (n=60)
ORR, % (95% CI)	26.4 (18.8, 35.2)	18.3 (9.5, 30.4)
CR,%	15.7	13.3
PR, %	10.7	5.0
SD, %	21.5	26.7
PD, %	39.7	36.7
Other*, %	12.4	18.3
Median DOR, mo (95% CI)	31.2, (12.6, NE)	NR, (5.7, NE)
Median Follow Up, mo	19.5	17.9

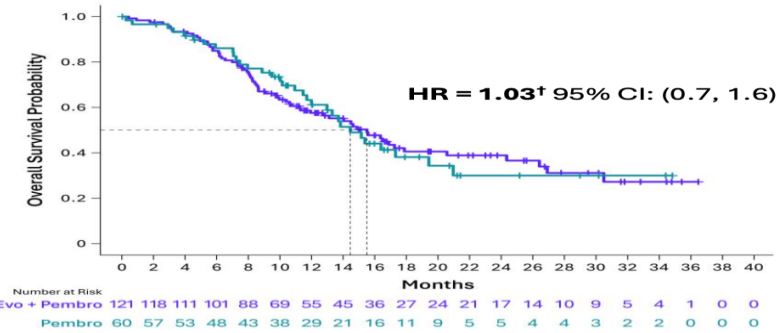
Progression-Free Survival by BICR

	Events	Median, mo
Evo + Pembro	87/121	3.6 (2.2, 5.4)
Pembro	38/60	3.7 (1.9, 5.6)



Overall Survival

	Events	Median, mo
Evo + Pembro	67/121	15.5 (11.3, 20.6)
Pembro	32/60	14.5 (11.7, 19.4)



- ORR for evorpacept + pembrolizumab (26.4%) was not statistically different from ORR for historical control[1] (20%; 1-sided p = 0.038 vs. α = 0.025)
- No evidence of difference in ORR, PFS, or OS between treatment arms

*includes patients without measurable disease at baseline that did not meet criteria for CR or PD, not evaluable, or had no post-baseline assessment available; , †HR (Evo + Pembro vs. Pembro) is from a stratified Cox proportional hazards model stratified by PD-L1 CPS per IRT. **BICR** – Blinded independent central review; **CR** – Complete response; **DOR** – Duration of response; **Evo** – Evorpacept; **mo** – Months; **NR** – Not reached; NE – not estimable; **ORR** – Objective response rate; **OS** – Overall survival; **Pembro** – Pembrolizumab; **PD** – Progressive disease; **PFS** – Progression free survival; **PR** – Partial response; **SD** – Stable disease;

Harrington K, ESMO 2025

SKYSCRAPER 9: TIRAGOLUMAB (ANTI-TIGIT) + ATEZOLIZUMAB IN RM HNSCC

Key eligibility criteria

- 1L R/M SCCHN (oral cavity, larynx, hypopharynx, HPV-negative oropharynx, and HPV-positive oropharynx)
- PD-L1+ (TAP ≥5%) by central SP263 assay
- ECOG PS 0 or 1

R 2:1

- Tiragolumab 600 mg IV Q3W + atezolizumab 1200 mg IV Q3W
- Placebo IV Q3W + atezolizumab 1200 mg IV Q3W

Until progression, loss of clinical benefit or unacceptable toxicity

No crossover

Stratification factors

- HPV-positive oropharynx cancer (yes vs no)
- PD-L1 status (low [TAP 5–19%] vs high [TAP ≥20%])

Primary endpoint

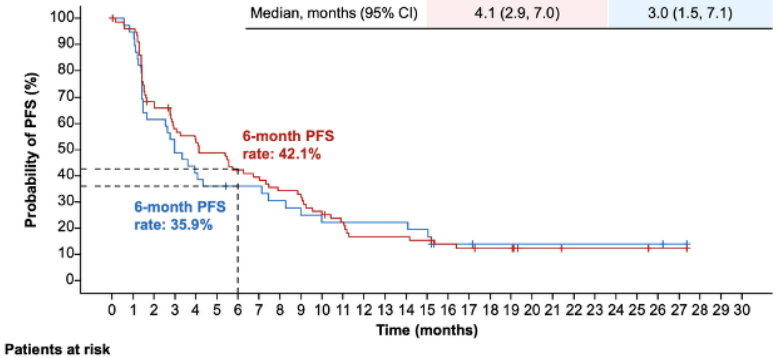
- Confirmed ORR assessed by investigator

Other endpoints

- DOR, PFS, OS, safety

PD-L1+ (TAP ≥5%)

	Tiragolumab + atezolizumab (n=80)	Placebo + atezolizumab (n=39)
Patients with event, n (%)	67 (83.8)	33 (84.6)
Median, months (95% CI)	4.1 (2.9, 7.0)	3.0 (1.5, 7.1)

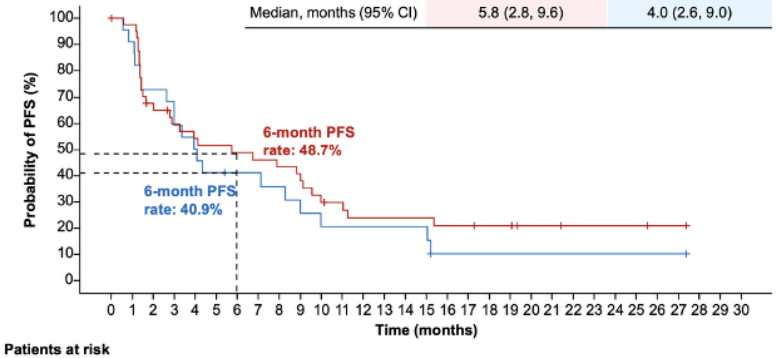


Patients at risk

Tira + atezo	80	76	53	44	41	37	32	29	26	25	19	16	12	12	12	11	9	8	7	7	3	3	2	2	2	2	1	1	0	0	0
Pbo + atezo	39	37	24	19	16	14	13	13	11	10	8	8	8	8	8	7	3	3	2	2	2	2	2	2	2	2	1	0	0	0	0

PD-L1-high (TAP ≥20%)

	Tiragolumab + atezolizumab (n=41)	Placebo + atezolizumab (n=22)
Patients with event, n (%)	30 (73.2)	19 (86.4)
Median, months (95% CI)	5.8 (2.8, 9.6)	4.0 (2.6, 9.0)



Patients at risk

Tira + atezo	41	39	26	22	20	19	18	17	16	15	11	10	8	8	8	8	7	7	6	6	3	3	2	2	2	2	1	1	0	0	0
Pbo + atezo	22	20	16	13	11	9	8	8	7	6	4	4	4	4	4	4	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0

Psyrri A , ESMO 2025

PEMDA-HN TRIAL: RANDOMIZED, OPEN LABEL, PHASE 2 STUDY OF DANVATIRSEN AND PEMBROLIZUMAB IN 1ST LINE HNSCC

PATIENT SELECTION:

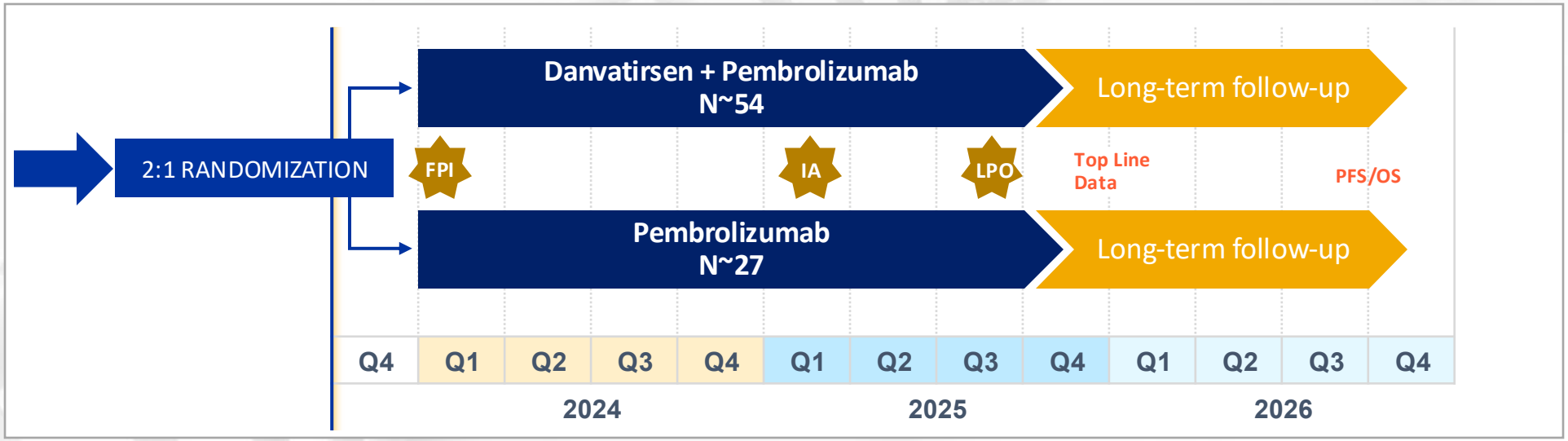
- R/M 1st Line HNSCC (excluding nasopharyngeal)
- CPS ≥ 1
- PD-1/PD-L1 naive
- Measurable disease
- Available Archived Tissue or Biopsy

PRIMARY ENDPOINT:

- ORR per RECIST 1.1 determined by PI

SECONDARY ENDPOINTS:

1. Safety
2. Duration of response
3. CR rate
4. ORR and response duration in CPS ≥ 20 (& CPS ≥ 50)
5. PFS
6. OS
7. PK



EXPLORATORY ENDPOINT:

1. Pharmacodynamic activity of danvatirsen in pre- and on-treatment tumor specimen
2. Correlation between clinical activity and (HPV) and other biomarkers

Sites: 32 | Countries: US, Korea, UK

DESIGN OPERATING CHARACTERISTICS (N=81 WITH INTERIM AT N=39)

- 83% Power (5% 1-sided alpha) to demonstrate an increase of 28% in ORR in Combo vs Mono (15% to 43%)
- In the Combo arm, the 95% CI around a 43% ORR is (30%, 56%)

Saba et al, in press

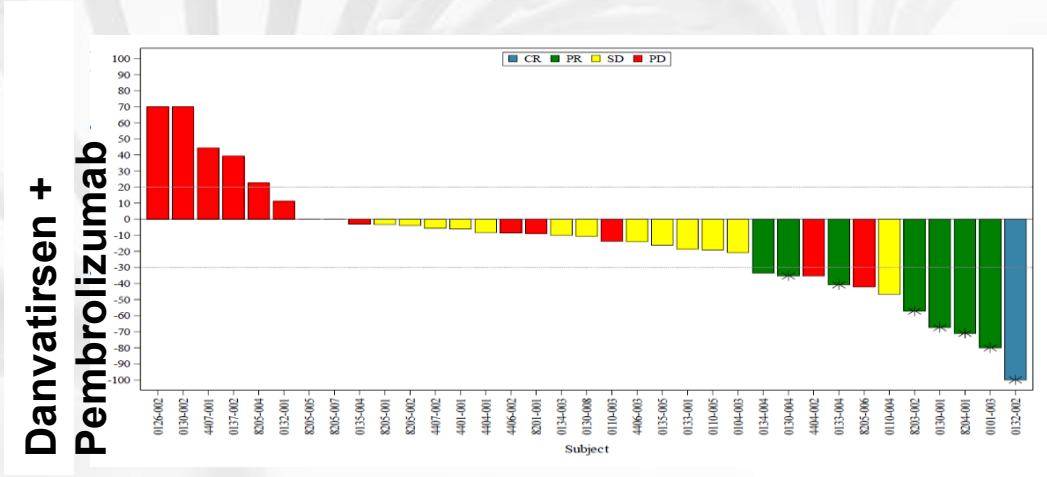
OBJECTIVE RESPONSE RATE

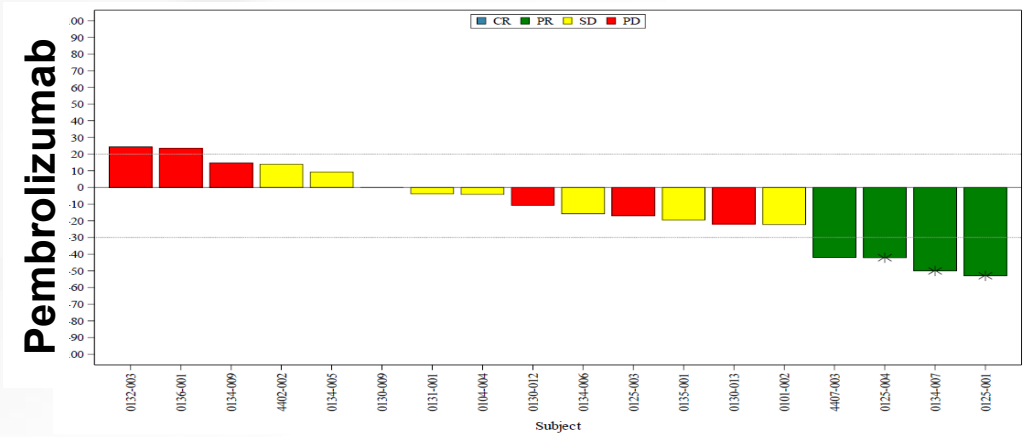
ORR CPS ≥ 1 (N=56pts)		
Tx Arm	N	Response Confirmed
Danva + Pembro	45	**7 (15.6%)** 90% CI 7.5-27.2
Pembro	21	**3 (14.3%)** 90% CI 4-32.9

ORR CPS ≥ 20 (N=37pts)		
Tx Arm	N	Response Confirmed
Danva + Pembro	27	**6 (18.2%)** 90% CI 8.2-32.8
Pembro	10	**3 (21.4%)** 90% CI 6.1-46.6

Median PFS: Danvatirsen + Pembrolizumab: 3.52 mo (95% CI , 1.48-6.83) vs Pembrolizumab: 2.92 mo (95% CI 1.41-)

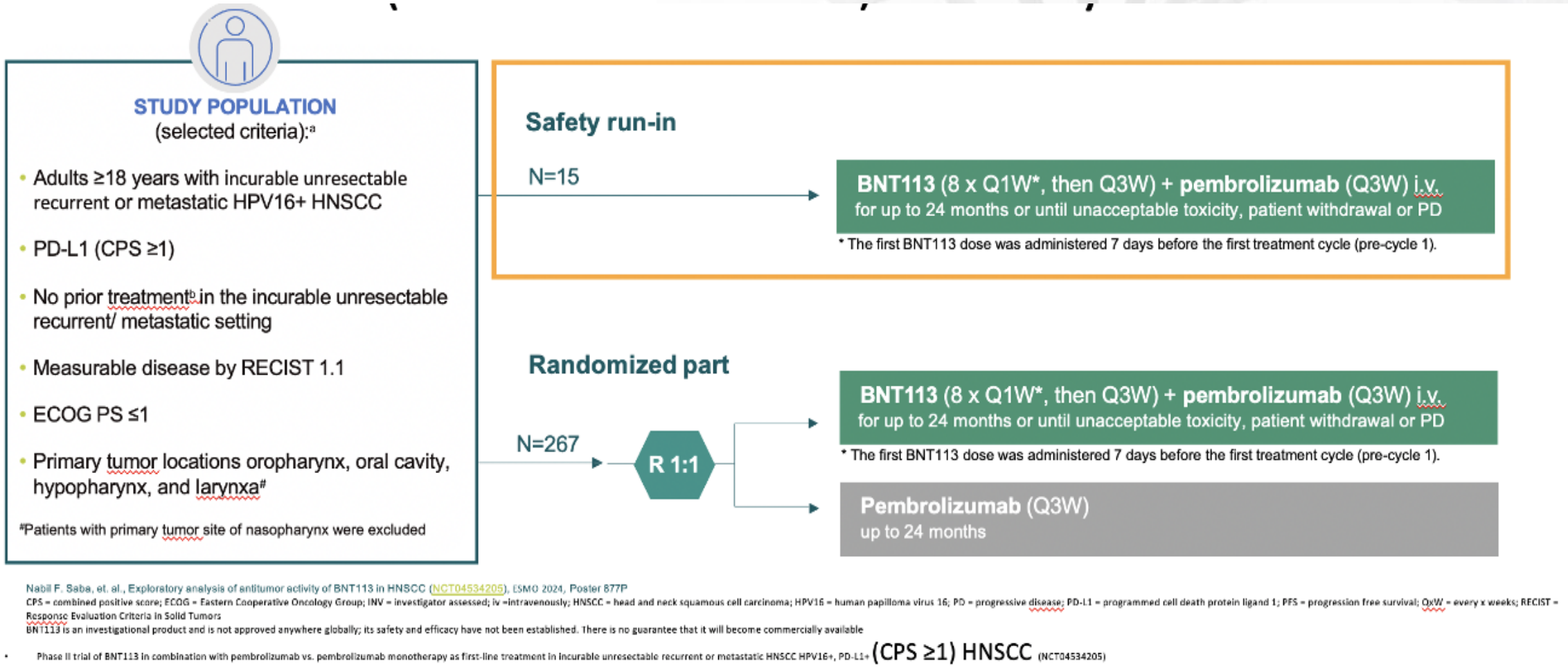
Median Duration of treatment: Danva + Pembro 2.98 mo (0.03-9.36) vs 2.83 mo (0.03-10.38)





Saba et al, in press

RANDOMIZED PHASE III TRIAL OF BNT 113 + PEMBROLIZUMAB VS PEMBROLIZUMAB IN 1ST LINE HPV RELATED RM HNSCC



Nabil F. Saba, et. al., Exploratory analysis of antitumor activity of BNT113 in HNSCC (NCT04534205), ESMO 2024, Poster 877P

CPS = combined positive score; ECOG = Eastern Cooperative Oncology Group; INV = investigator assessed; iv =intravenously; HNSCC = head and neck squamous cell carcinoma; HPV16 = human papilloma virus 16; PD = progressive disease; PD-L1 = programmed cell death protein ligand 1; PFS = progression free survival; QxW = every x weeks; RECIST = Response Evaluation Criteria in Solid Tumors

BNT113 is an investigational product and is not approved anywhere globally; its safety and efficacy have not been established. There is no guarantee that it will become commercially available

- Phase II trial of BNT113 in combination with pembrolizumab vs. pembrolizumab monotherapy as first-line treatment in incurable unresectable recurrent or metastatic HNSCC HPV16+, PD-L1+ (CPS ≥1) HNSCC (NCT04534205)

Saba NF, et al ESMO 2023

Phase II study of Fianlimab and Cemiplimab in HPV positive and Negative HNSCC

Patients

N=120

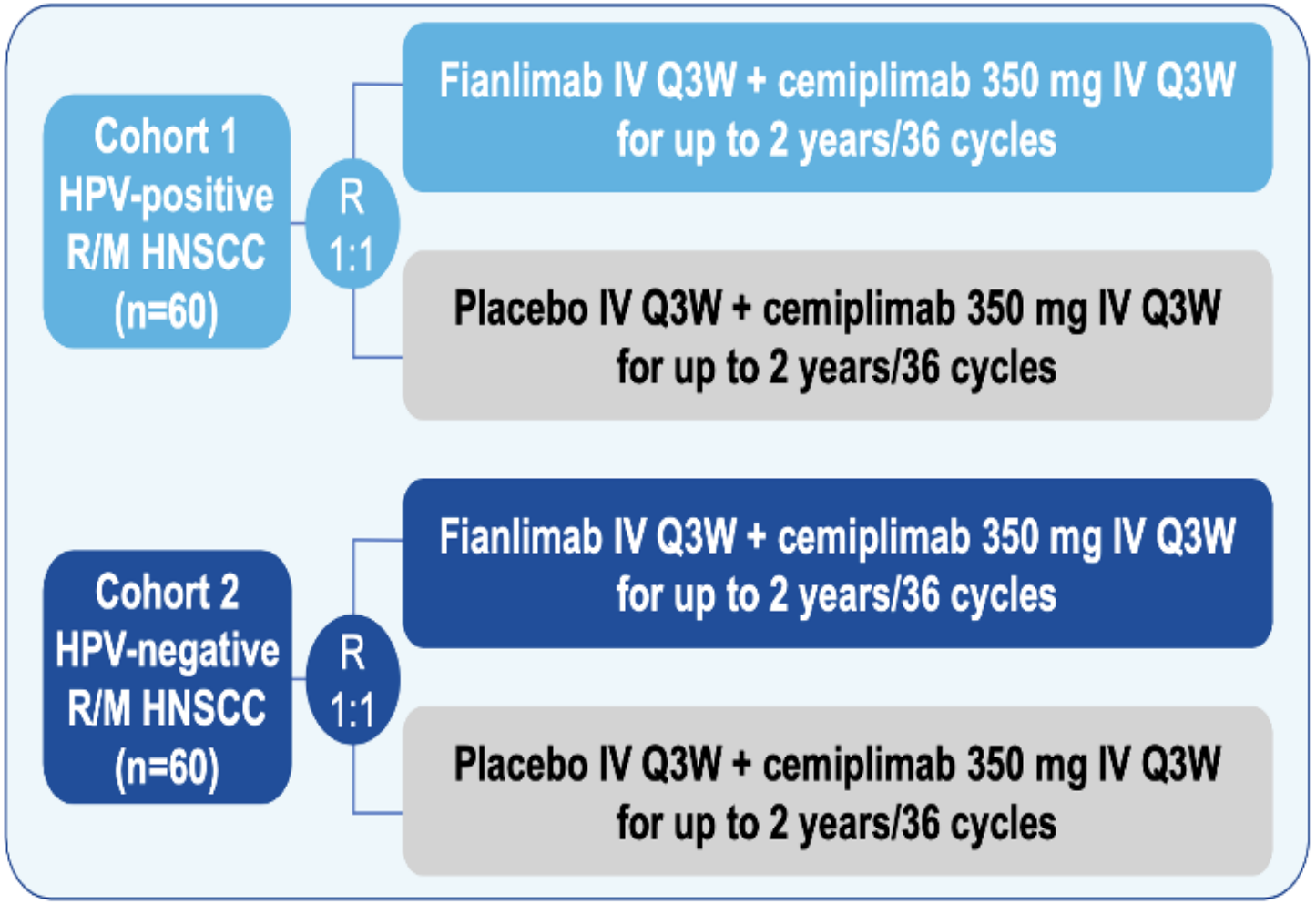
Patient population

- 1L R/M HNSCC
- ECOG PS of 0 or 1
- Anti–PD-1 therapy naïve
- PD-L1 CPS of ≥1

Stratification

- PD-L1 CPS of 1–19 versus ≥20 (within each cohort)

*Key inclusion and exclusion criteria are presented in **Tables 1** and **2**, respectively*



Endpoints

Primary endpoint

- ORR per RECIST v1.1*

Secondary endpoints

- PFS
- DCR
- DOR
- Safety
- Pharmacokinetics

Rischin D, ASCO 25

CASE PRESENTATION – CONTINUED

Following chemo-immunotherapy an excellent response was achieved with a durable CR for 2 years.

Unfortunately, new liver lesions that were confirmed by biopsy appeared on surveillance scans and were consistent with recurrent HPV related disease.

What systemic options are available ?

Need novel agents in HPV related disease…

(approved systemic options are: Taxotere, MTX, Cetuximab).

CONCLUSIONS

1. Immunotherapy has fundamentally changed the treatment landscape of recurrent and metastatic head and neck cancer.

2. Despite this, only a subset of patients derives durable benefit and robust predictive markers beyond PDL1 are lacking.

3. Earlier integration of immunotherapy into curative-intent treatment paradigms represents a major area of ongoing investigation.

4. Novel approaches—including cellular therapies, therapeutic vaccines, and next-generation immune modulators—aim to overcome resistance and improve outcomes.

THANK YOU

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