Updates on EGFR targeted therapies and immunotherapies in SCCHN

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

The Cloister
Debates and Didactics
Symposium,
Sea Island,
July 21st, 2022

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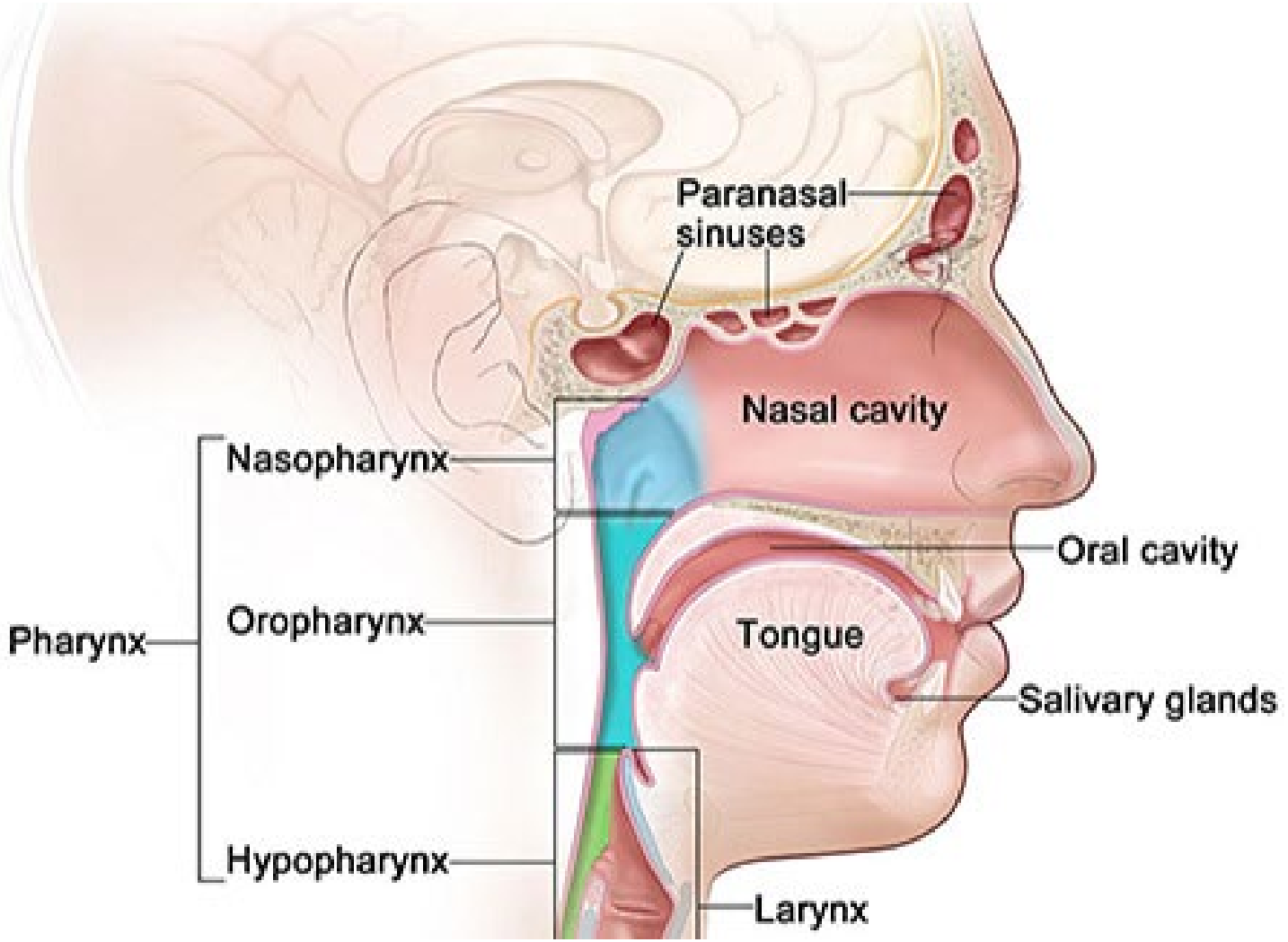
Conflict of Interest

- I received compensation for consulting work from, Pfizer, Merck, GSK, Vaccinex, Kura Oncology, Celldex Therapeutics, Biontech,

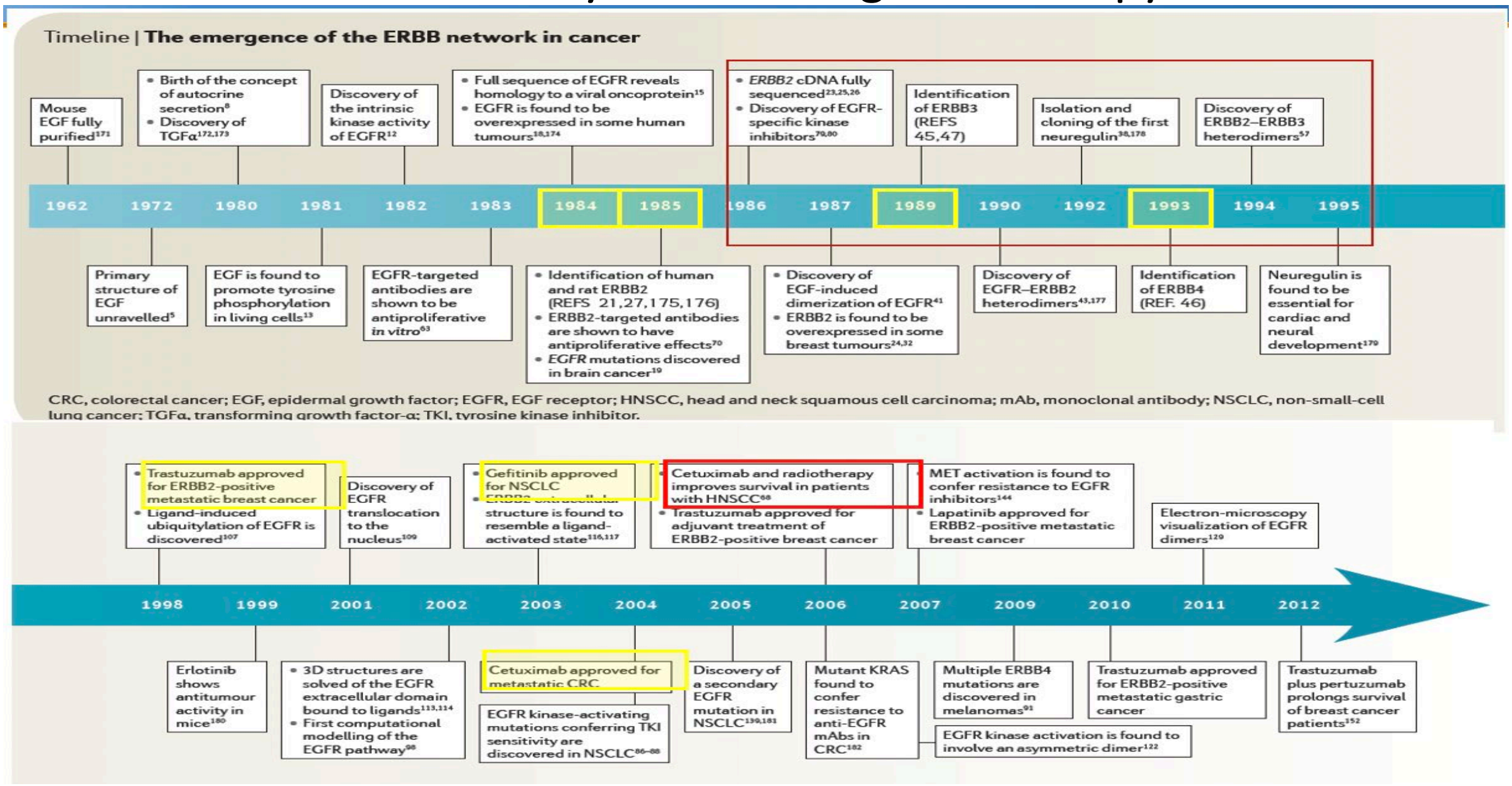
- I received funding for research from:
  - BMS
  - Exelixis
  - NIH

HNSCC is Multiple Diseases



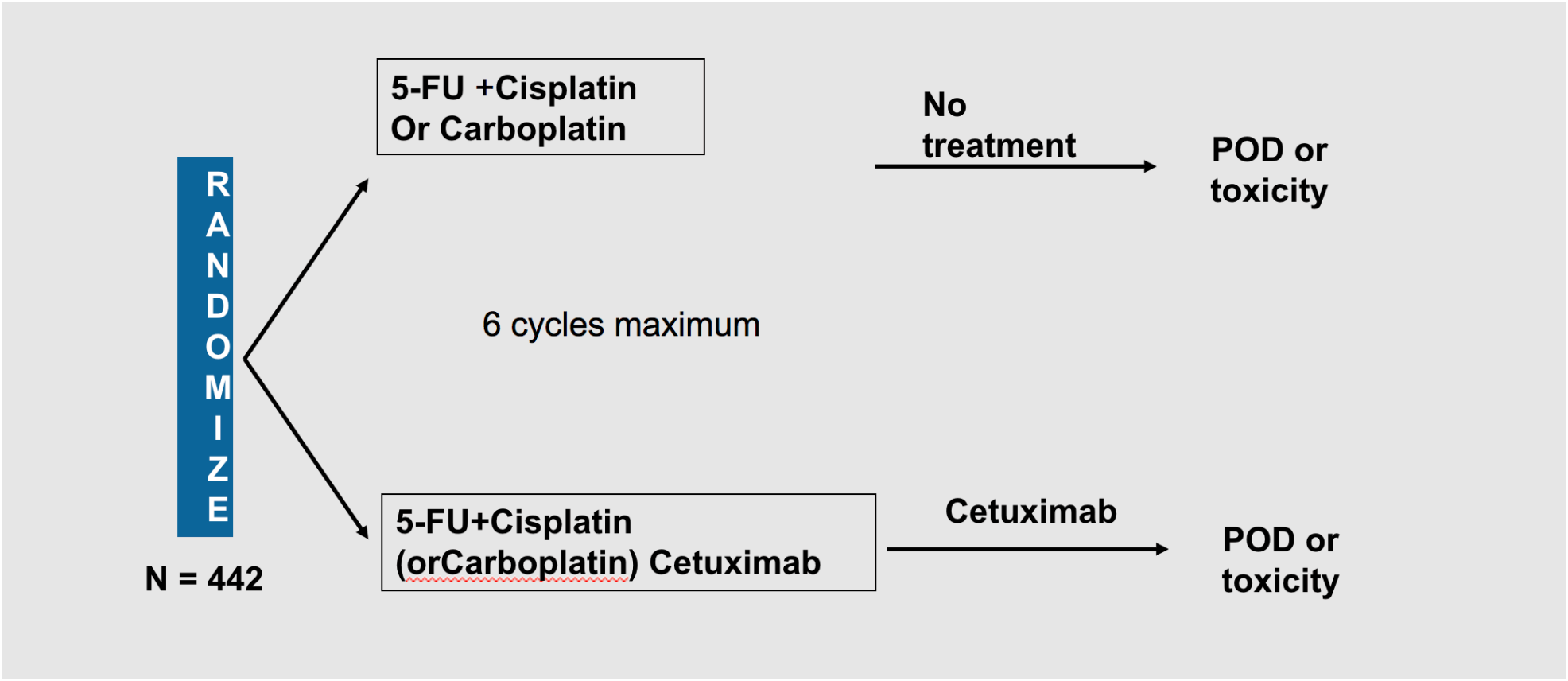
https://www.cancer.gov/types/head-and-neck

The Journey of EGFR Targeted Therapy



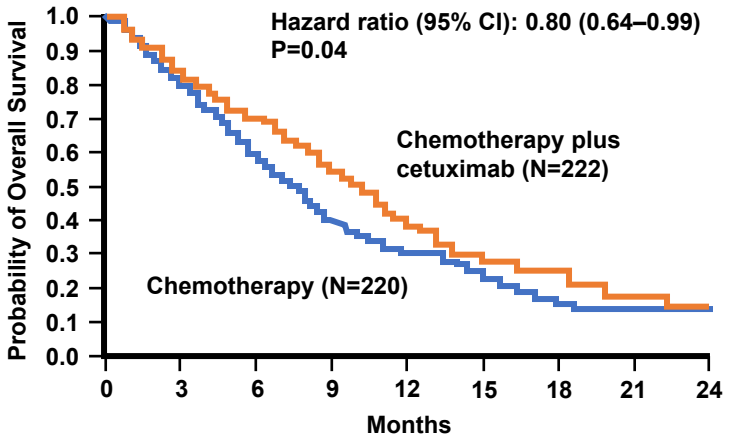
Yarden et al, Nature Reviews, 2012

Extreme Trial- the standard between 2008 -2019



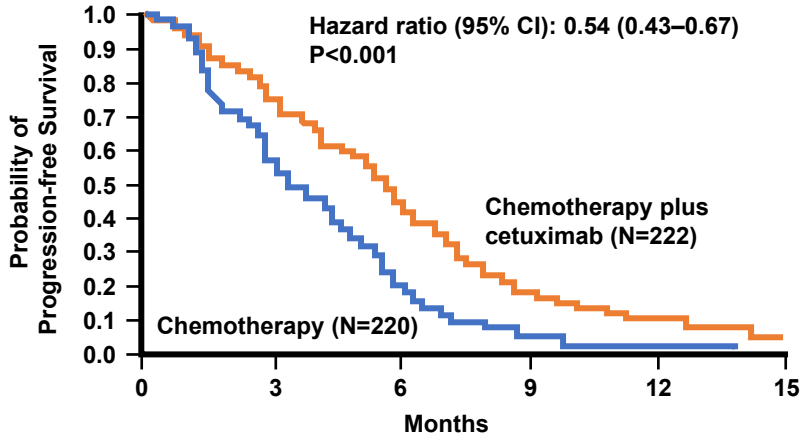
SIGNIFICANT BENEFIT REPORTED WITH EXTREME REGIMEN

Overall Survival



No. at Risk									
Chemotherapy	220	173	127	83	65	47	19	8	1
Chemotherapy plus cetuximab	222	184	153	118	82	57	30	15	3

Progression-Free Survival



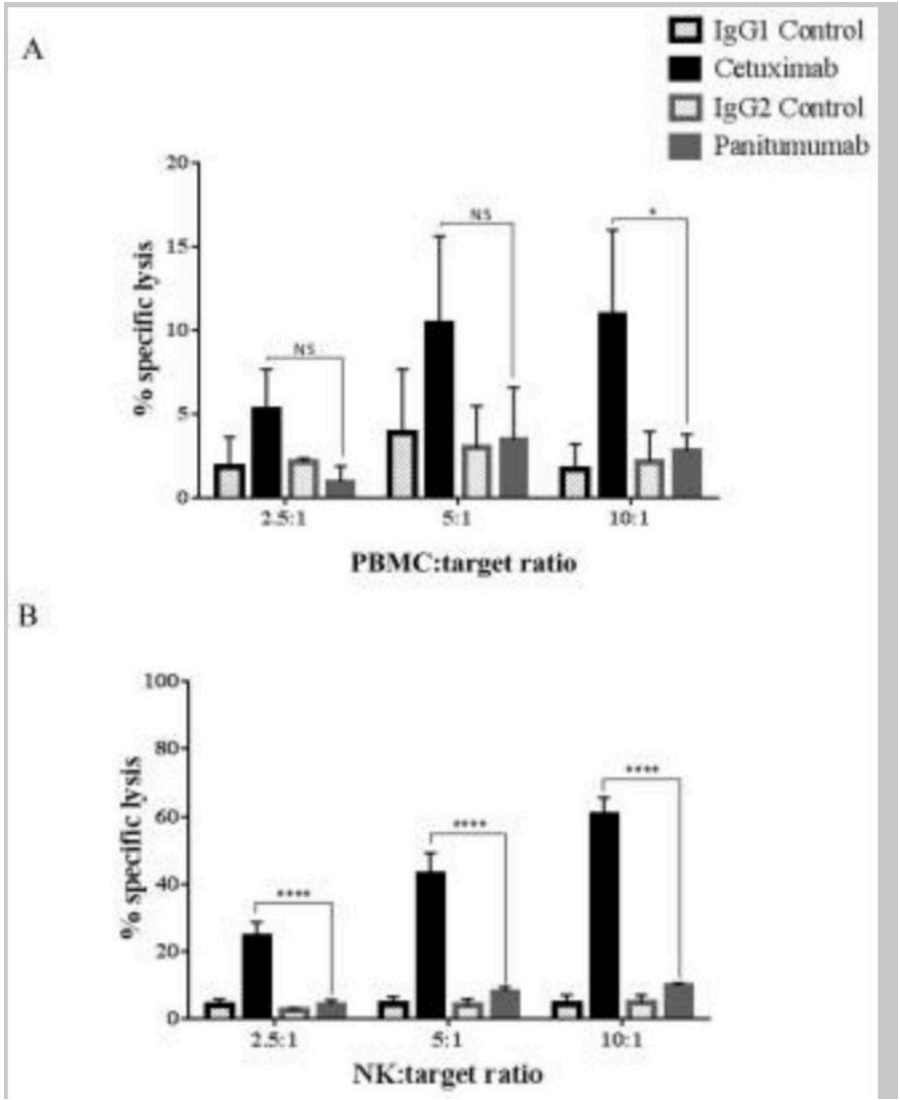
No. at Risk						
Chemotherapy	220	103	29	8	3	1
Chemotherapy plus cetuximab	222	138	72	29	12	7

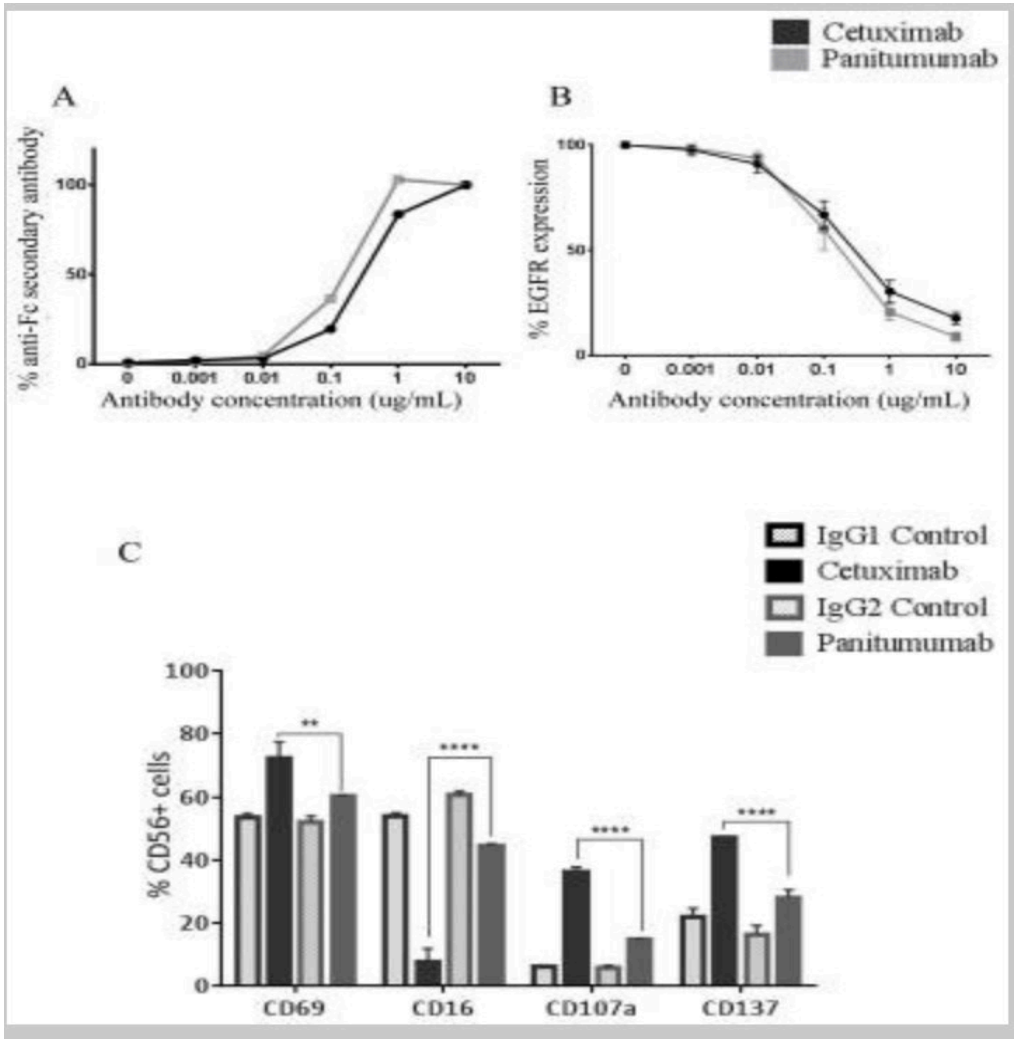
NEJM 2008:359:1116

Cetuximab activates PBMC to a greater extent than panitumumab

Cetuximab treated PBMC express significantly higher activation markers CD69, CD16, CD107a and CD137 compared to panitumumab

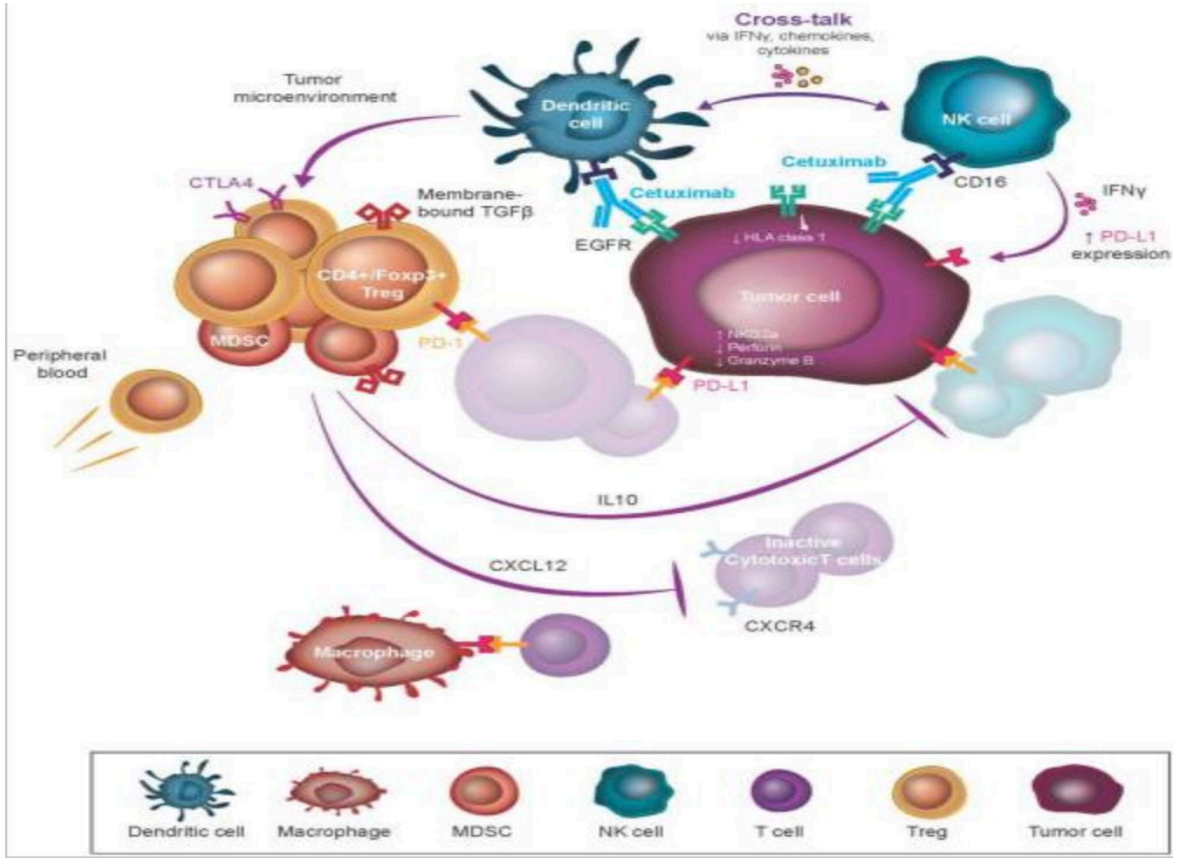
Cetuximab significantly enhanced ADCC compared to panitumumab

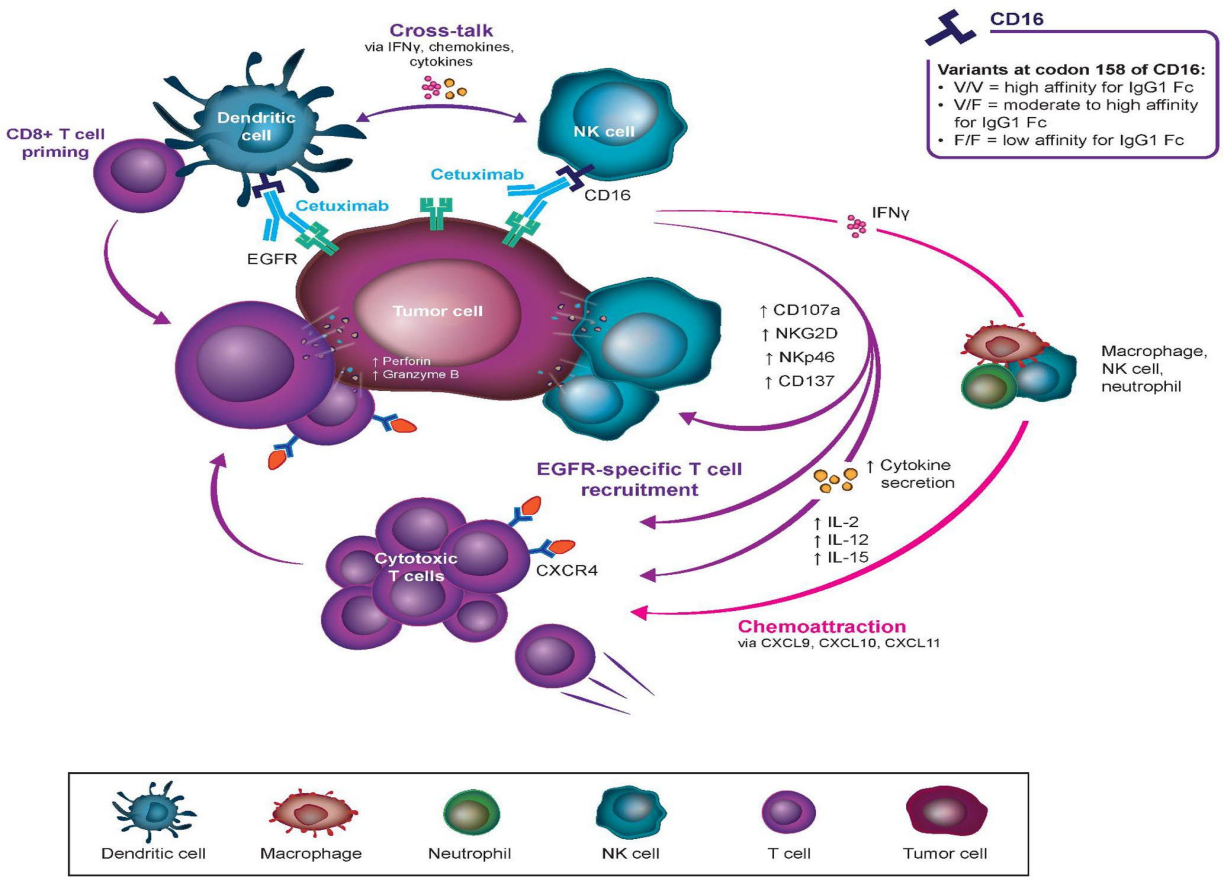




Trivedi S , CCR 2016

Mechanism of cetuximab-mediated immune activity.





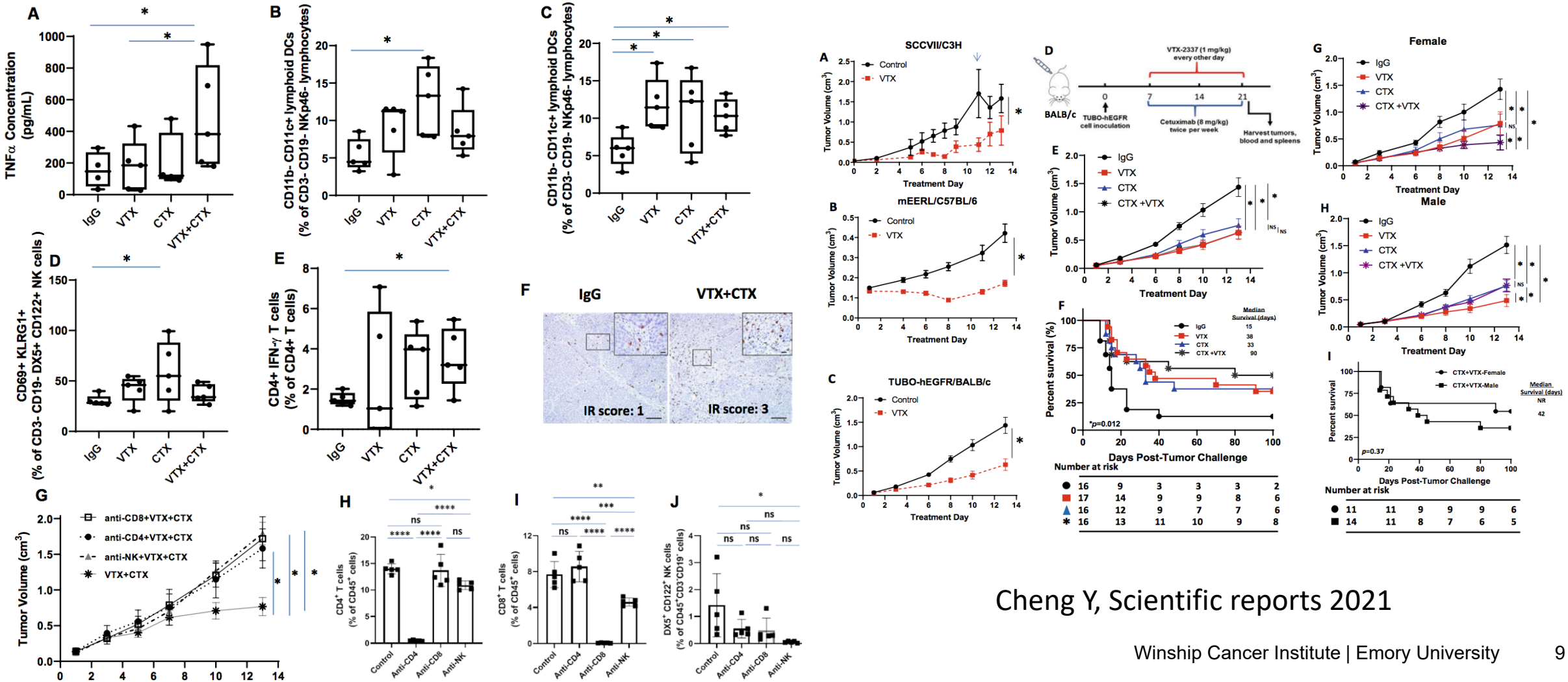
1- Binds to to EGFR and CD16 receptor on NK and dendritic cells

2- Leads to tumor death, through ADCC (innate immunity) and T cell priming (adaptive immunity)

3- Can also set off feedback immunosuppressive mechanisms through Treg, and expression of immune checkpoints

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

TLR 8 agonist augments anti-tumor effect of cetuximab and increase T cell infiltration



Cheng Y, Scientific reports 2021

The Active 8 Randomized Study

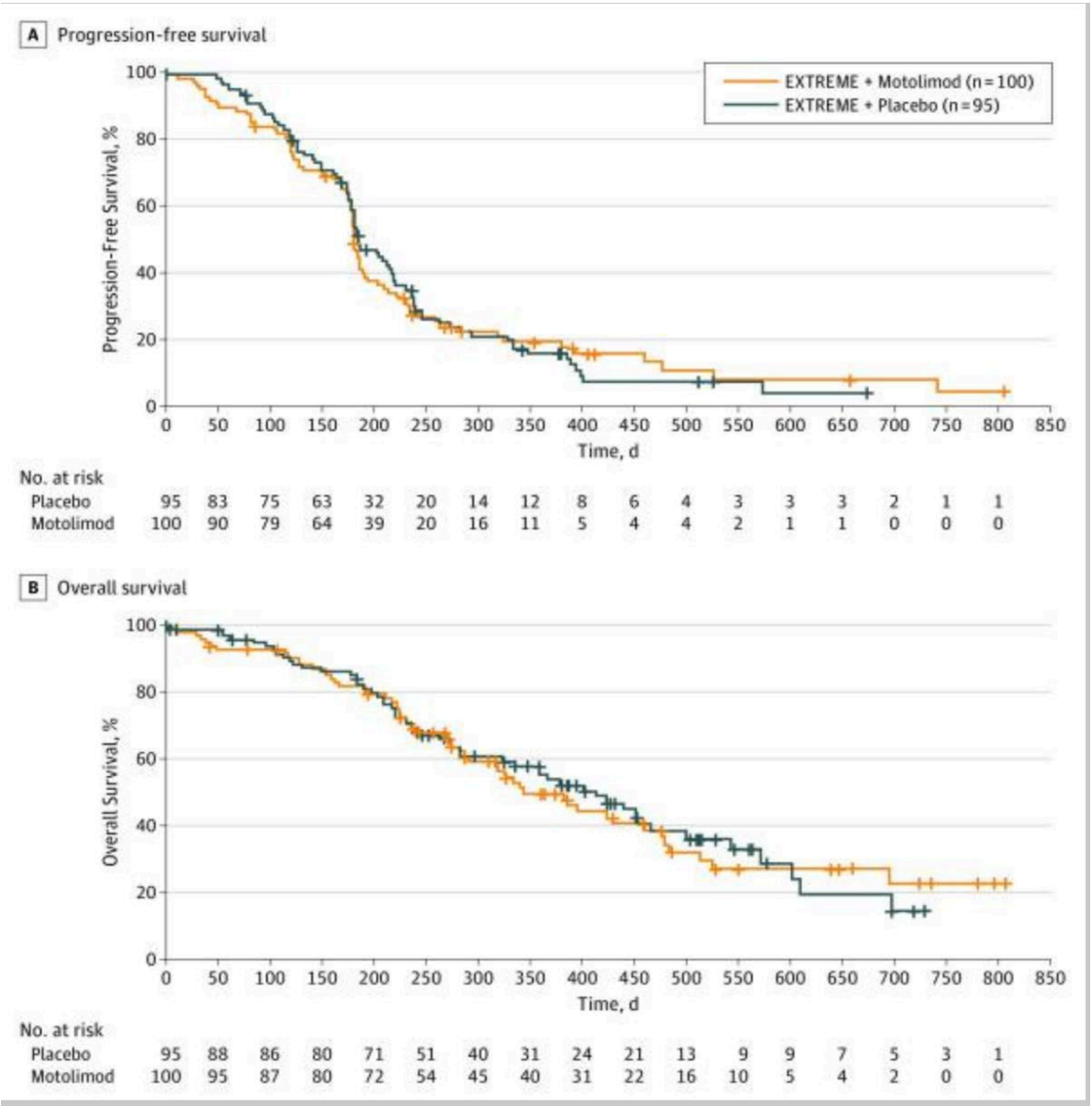
Effect of Adding Motolimod to Standard Combination Chemotherapy and Cetuximab Treatment of Patients With Squamous Cell Carcinoma of the Head and Neck

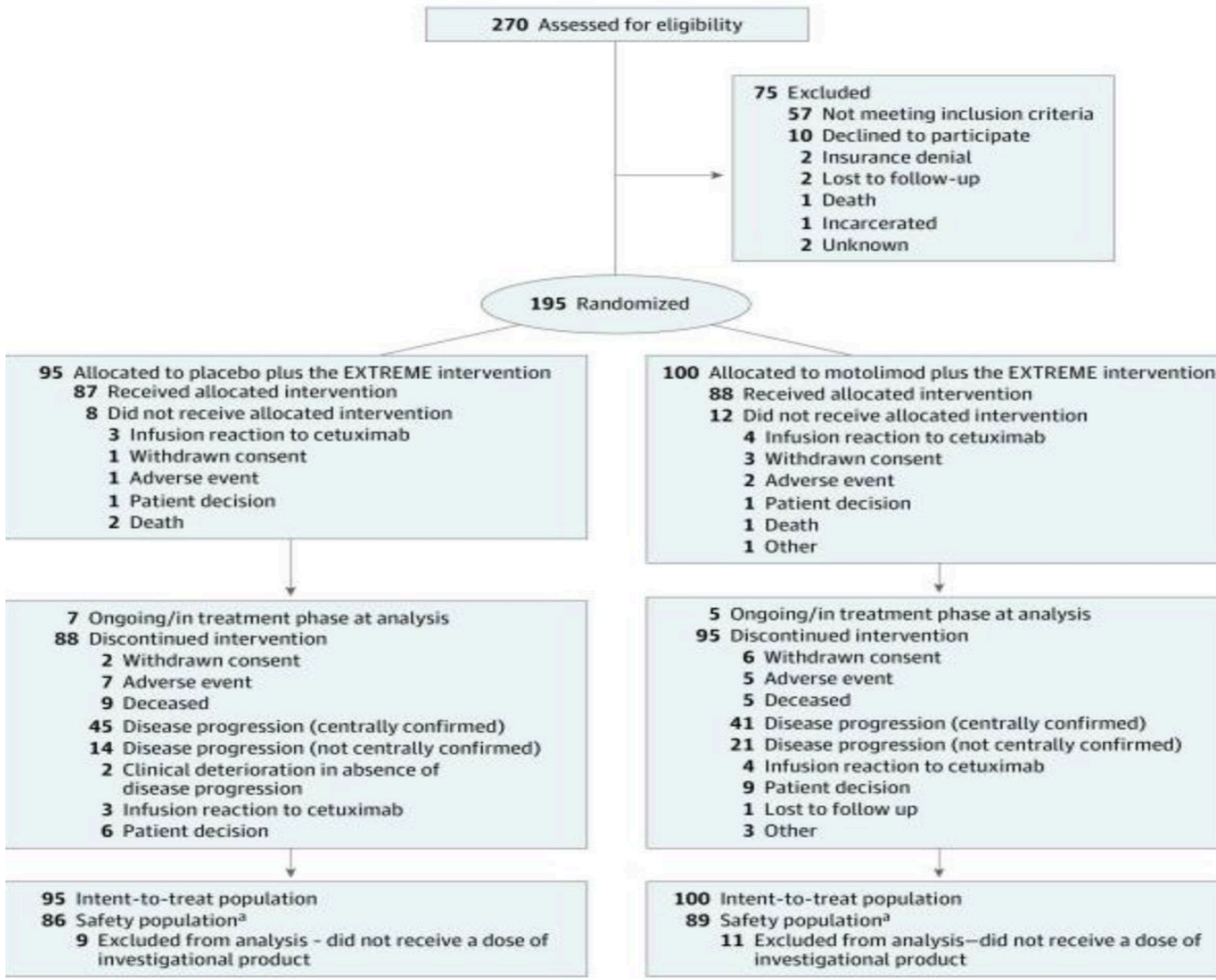
The Active8 Randomized Clinical Trial

Robert L. Ferris, MD, PhD[1]; Nabil F. Saba, MD[2]; Barbara J. Gitlitz, MD[3]; Robert Haddad, MD[4]; Ammar Sukari, MD[5]; Prakash Neupane, MD[6]; John C. Morris, MD[7]; Krzysztof Misiukiewicz, MD[8]; Julie E. Bauman, MD, MPH[1]; Moon Fenton, MD, PhD[9]; Antonio Jimeno, MD[10]; Douglas R. Adkins, MD[11]; Charles J. Schneider, MD[12]; Assuntina G. Sacco, MD[13]; Keisuke Shirai, MD[14]; Daniel W. Bowles, MD[15]; Michael Gibson, MD, PhD[16]; Tobenna Nwizu, MD[17]; Raphael Gottardo, PhD[18]; Kristi L. Manjarrez, BS[13]; Gregory N. Dietsch, PhD[13]; James Kyle Bryan, MD[13]; Robert M. Hershberg, MD, PhD[13]; Ezra E. W. Cohen, MD[19]

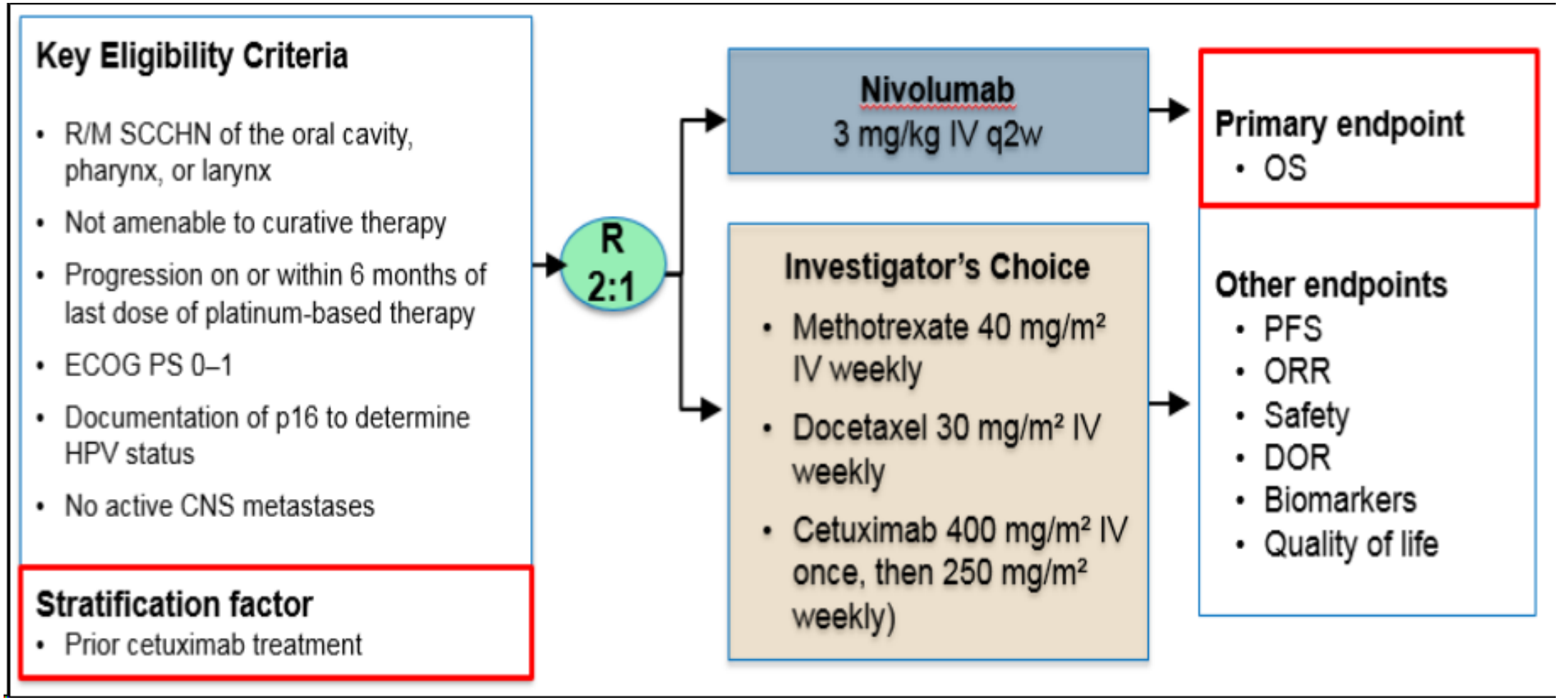
JAMA Oncol. 2018;4(11):1583–1588. doi:10.1001/jamaoncol.2018.1888

The Active 8 Randomized trial



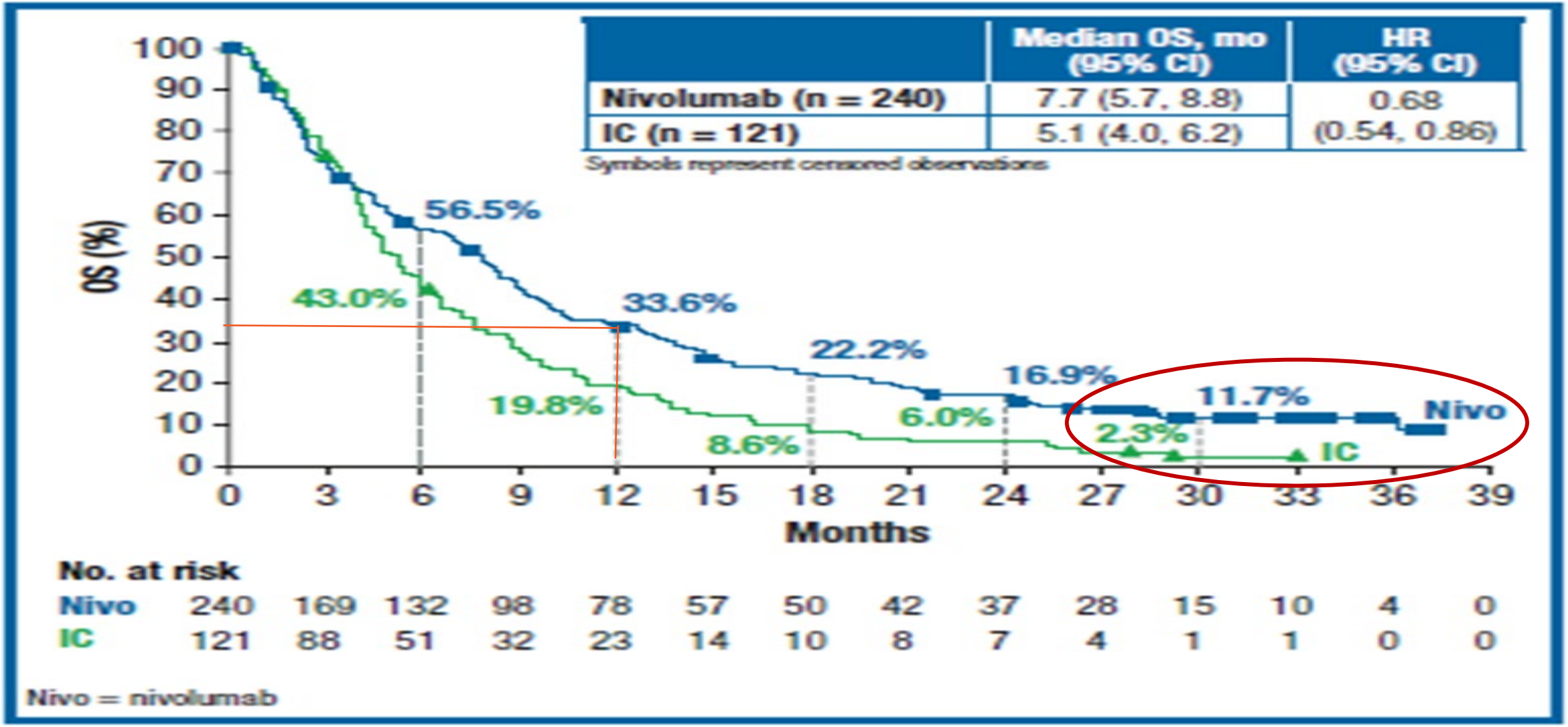


Checkmate- 141- New Standard for RMD



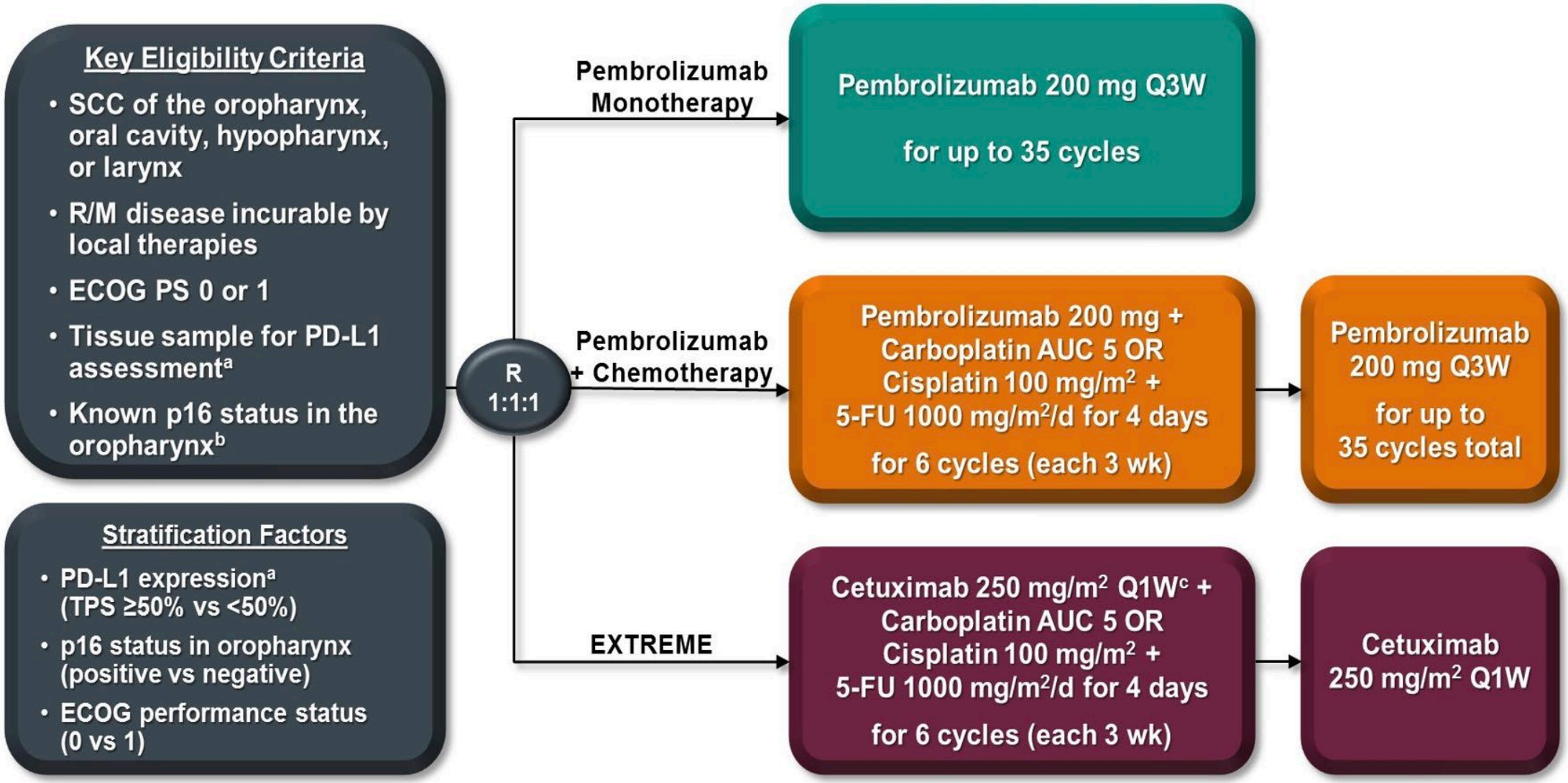
Ferris et al, NEJM 2016

Checkmate 141- *Pretreated incurable*



Ferris et al, NEJM, 2016

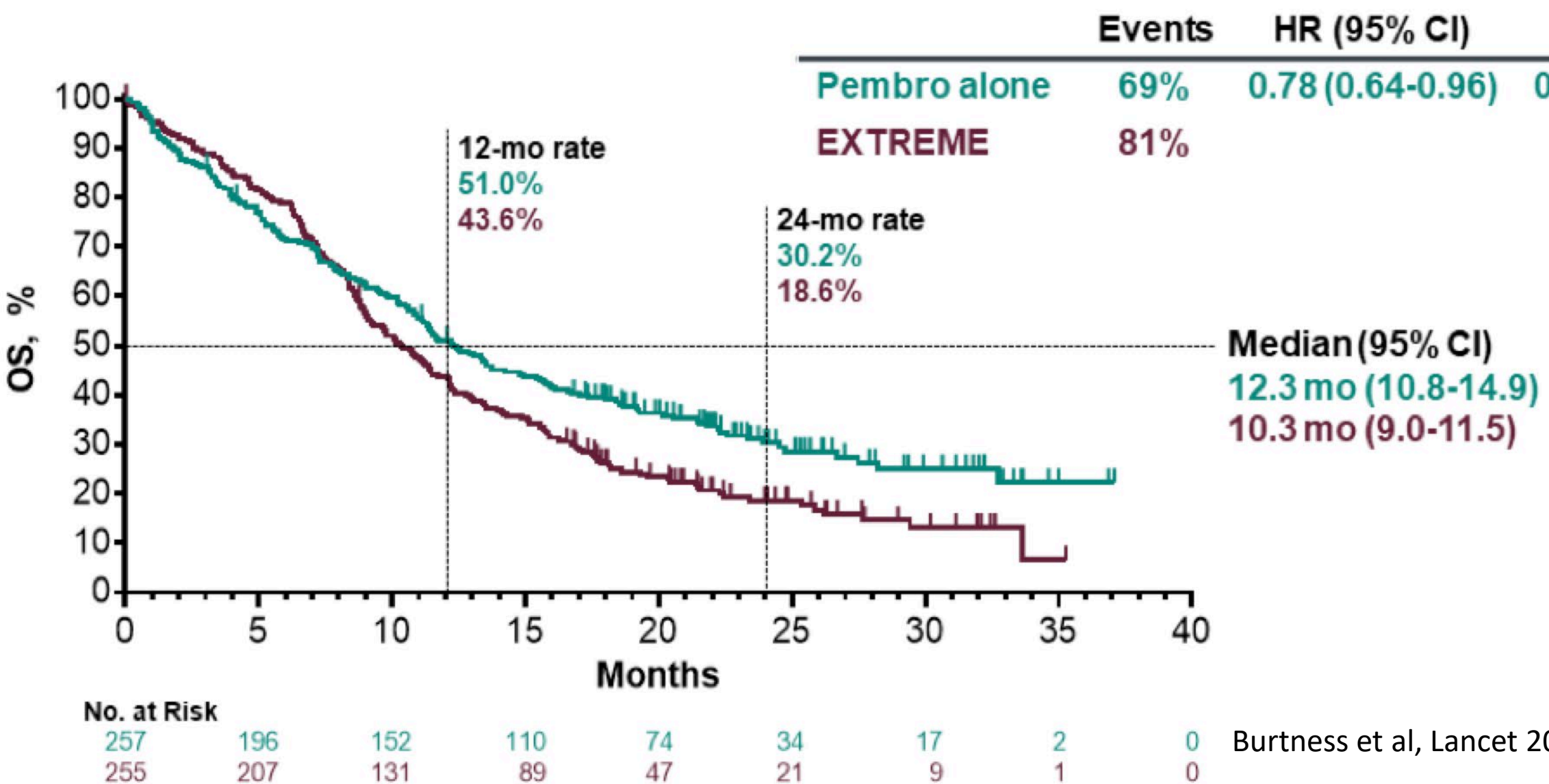
KEYNOTE-048 Study Design (NCT02358031)



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression.
[b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Burtness B et al, Lancet 2019

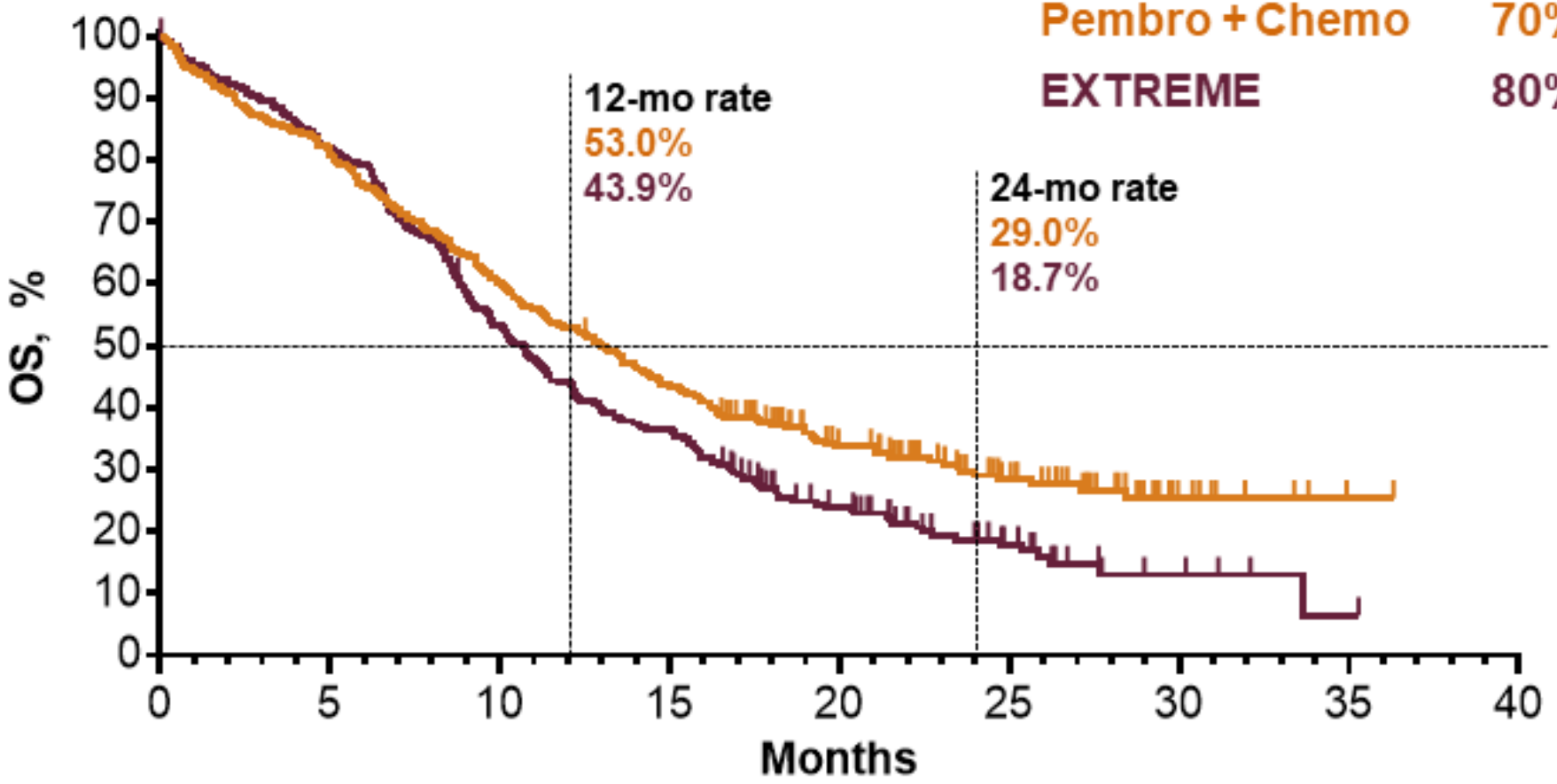
Overall Survival: P vs E, CPS ≥1 Population



Burtness et al, Lancet 2019

Overall Survival: P+C vs E, Total Population

	Events	HR (95% CI)	*P*
Pembro + Chemo	70%	0.77 (0.63-0.93)	0.0034
EXTREME	80%		



Median (95% CI)
13.0 mo (10.9-14.7)
10.7 mo (9.3-11.7)

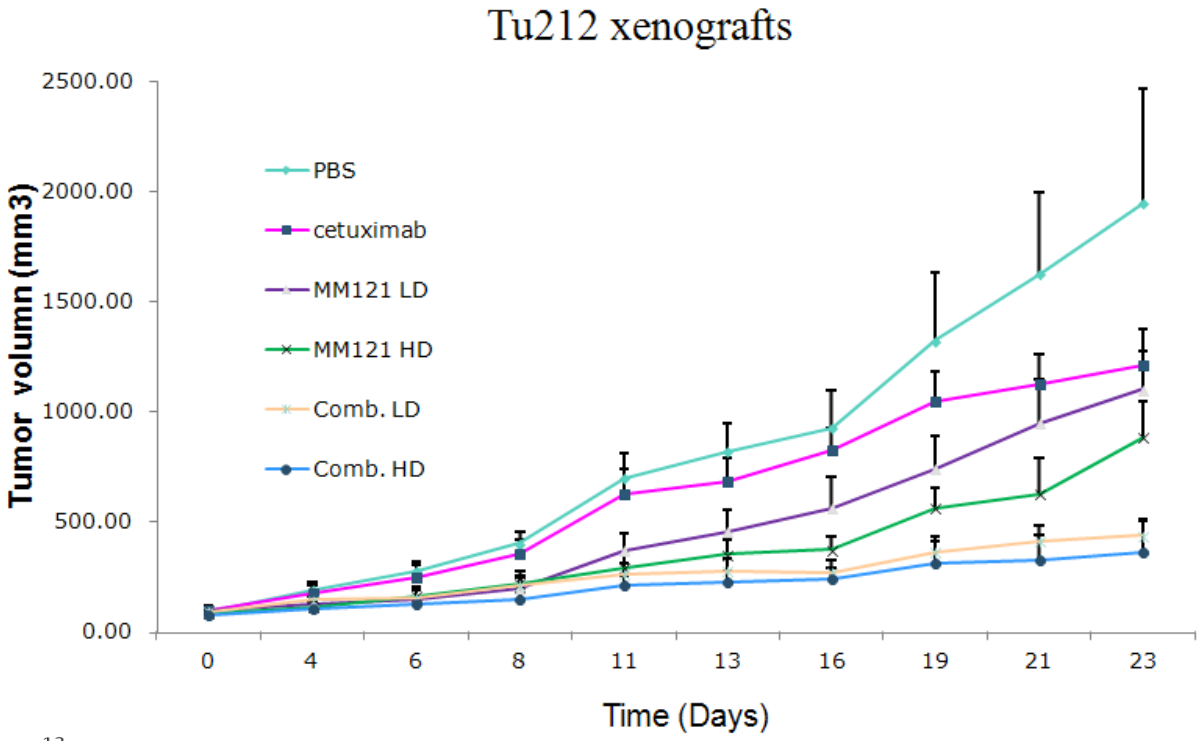
No. at Risk

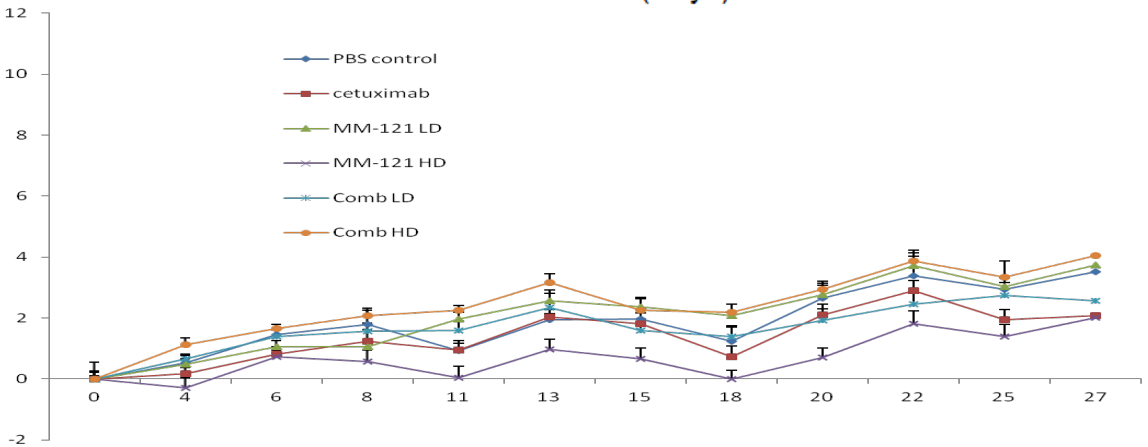
281	227	169	122	75	40	10	1	0
278	227	147	100	51	20	5	1	0

Data cutoff date: Jun 13, 2018.

Burtness et al, Lancet 2019

Cetuximab and anti HER3 (MM121)combination inhibited TU212 tumor growth in vivo

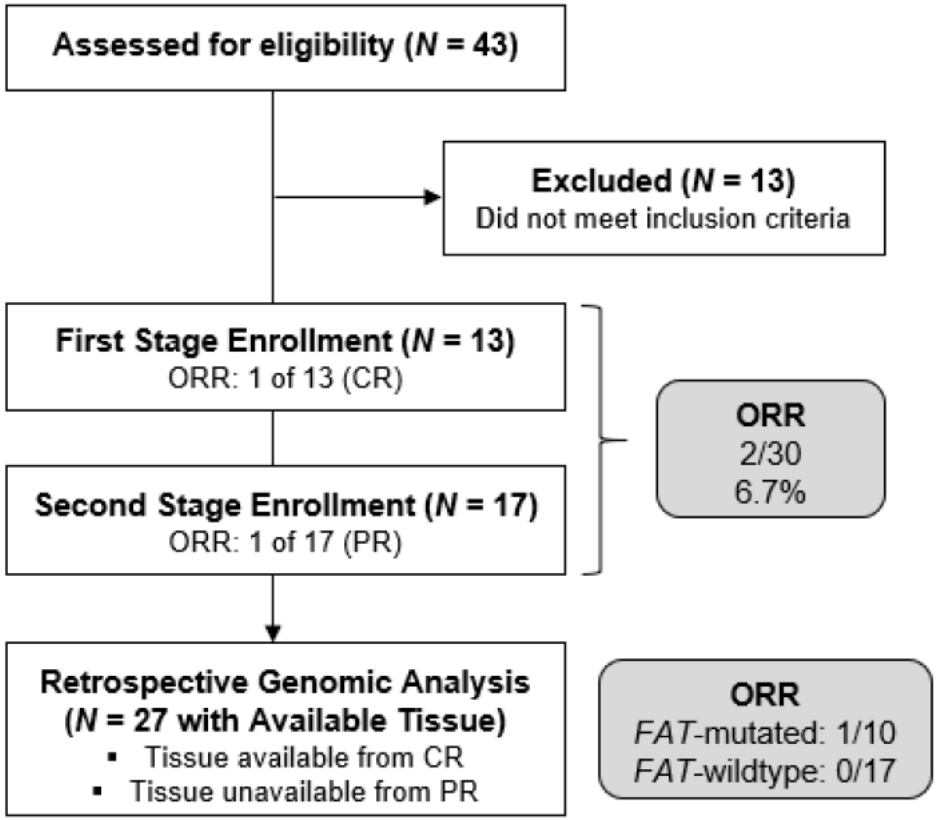




Comparison	P-value
Cetuximab vs.Control	0.0063
MM-121 LD vs.Control	<.0001
MM-121 HD vs.Control	<.0001
Comb. LD vs. Control	<.0001
Comb. HD vs.Control	<.0001
MM-121 LD vs.Cetuximab	0.0132
MM-121 HD vs.Cetuximab	0.0005
Comb. LD vs. Cetuximab	<.0001
Comb. HD vs.Cetuximab	<.0001
MM-121 HD vs.MM-121 LD	0.2841
Comb. LD vs.MM-121 LD	0.0046
Comb. HD vs.MM-121 LD	0.0008
Comb. LD vs.MM-121 HD	0.0765
Comb. HD vs.MM-121 HD	0.0218
Comb. HD vs.Comb. LD	0.5994

Jiang N, Mol Cancer Ther, 2014

CDX-3379 and Cetuximab in Recurrent/Metastatic, HPV-Negative, Cetuximab Resistant HNCA



Bauman J, et al, Cancers, 2022

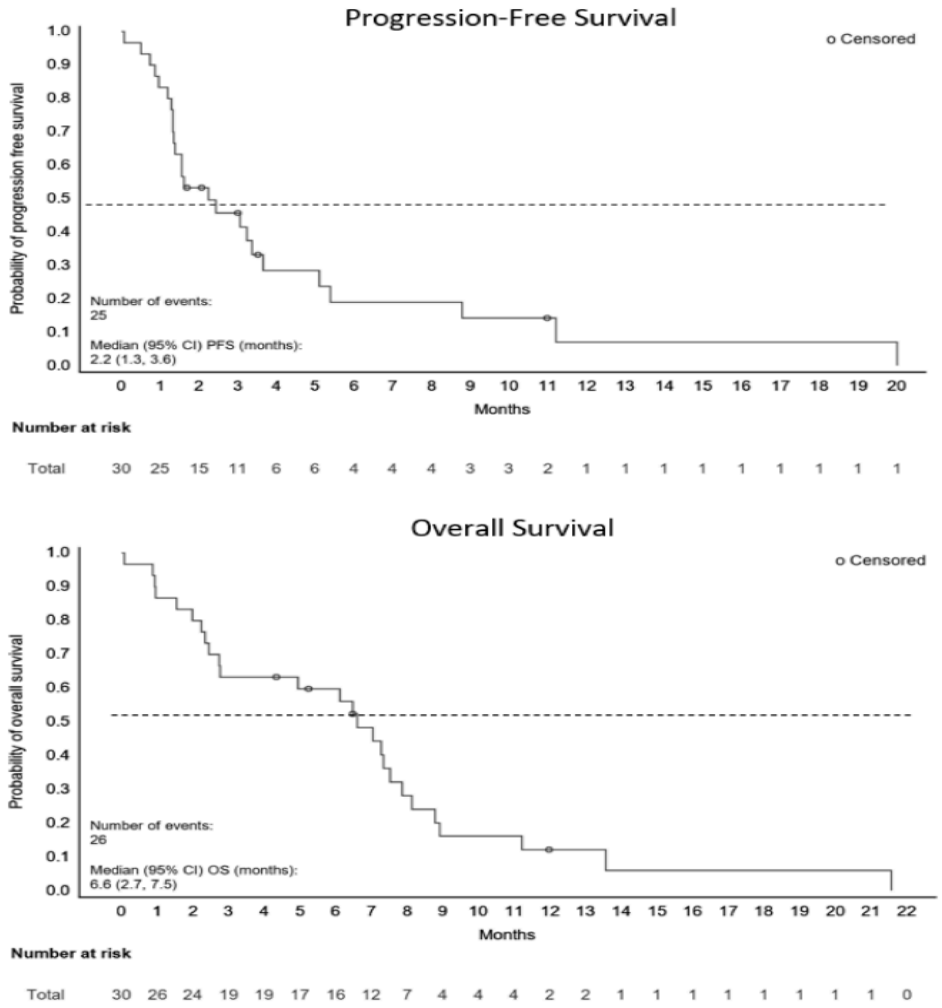


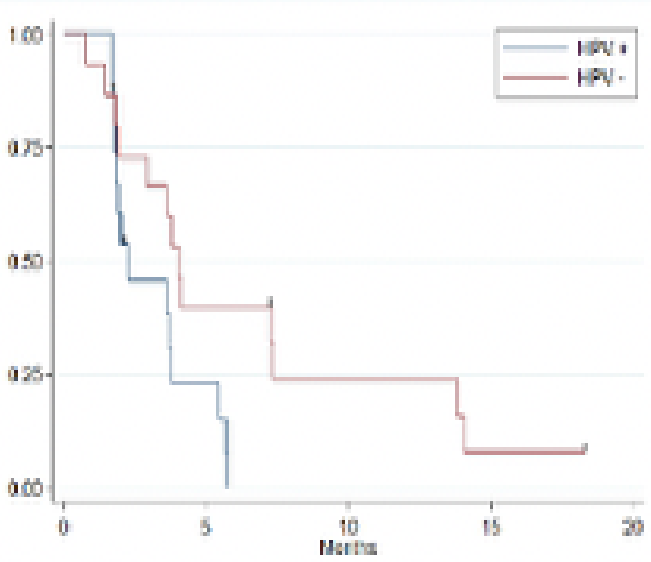
Figure 2. Progression-Free and Overall Survival.

Ficlatuzumab (HGF antibody) with and without Cetuximab in RMD

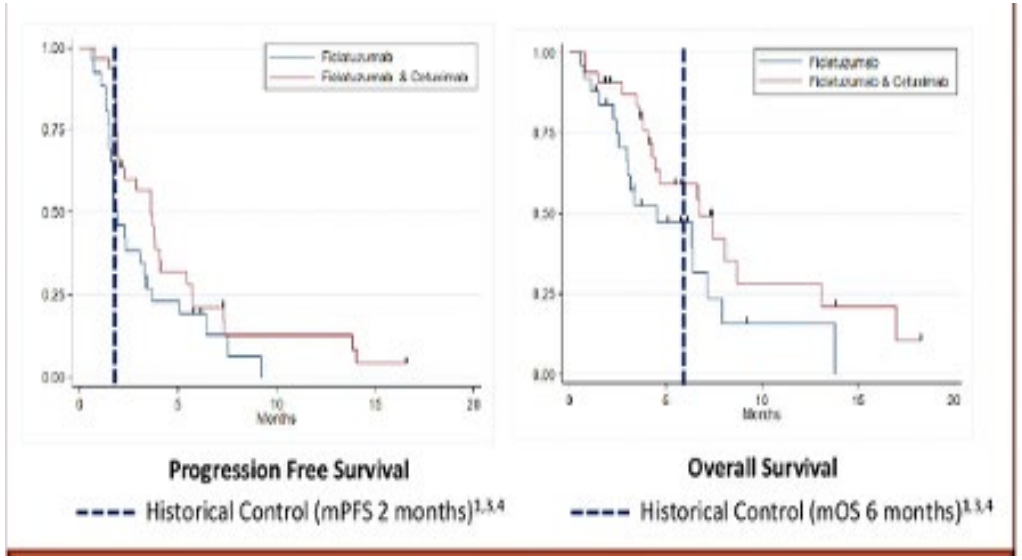
- An exploratory comparison of ORR and mPFS in the HPV+ and HPV- subgroups was performed in the combination arm. HPV- subjects had superior ORR (p=0.02) and mPFS (p=0.03).

	Ficlatuzumab + Cetuximab (N=32)	p-value
ORR[a]		0.02
HPV+	0/16 (0%)	
HPV-	2CR + 4PR/16 (38%)	
mPFS		0.03
HPV+	2.3 (1.9)	
HPV-	4.1 (2.9)	

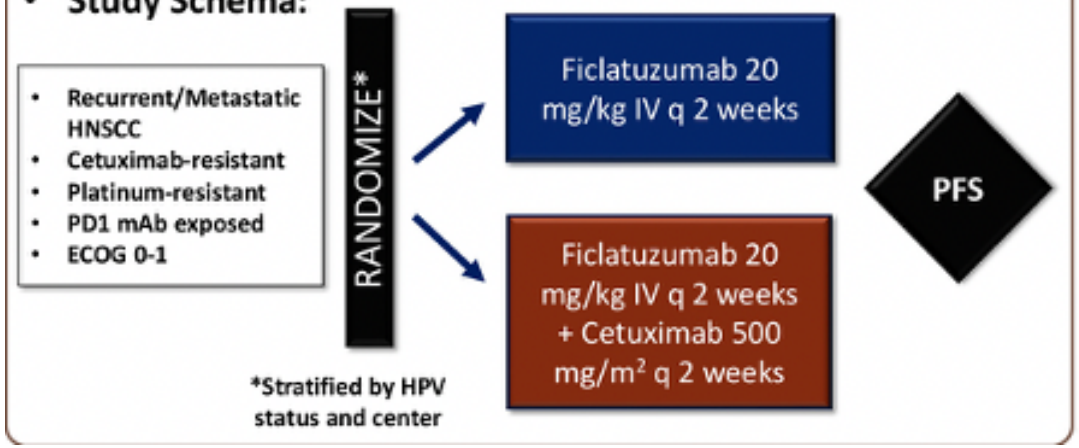
a. ORR: CR+PR/n
b. mPFS: Months (lower bound of 90% 1-sided CI)



Progression Free Survival by HPV Status
Ficlatuzumab + Cetuximab Arm

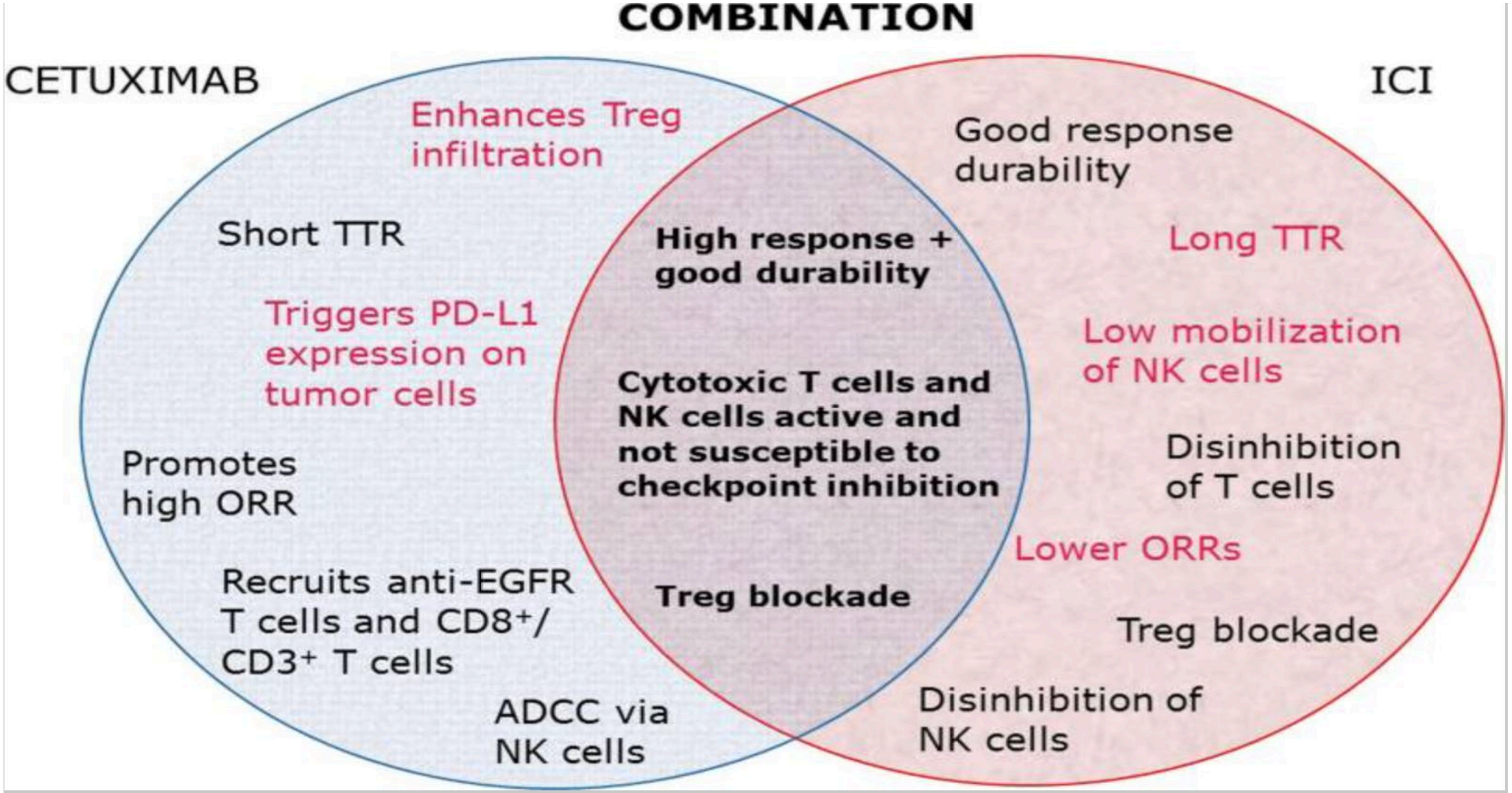


- **Study Schema:**



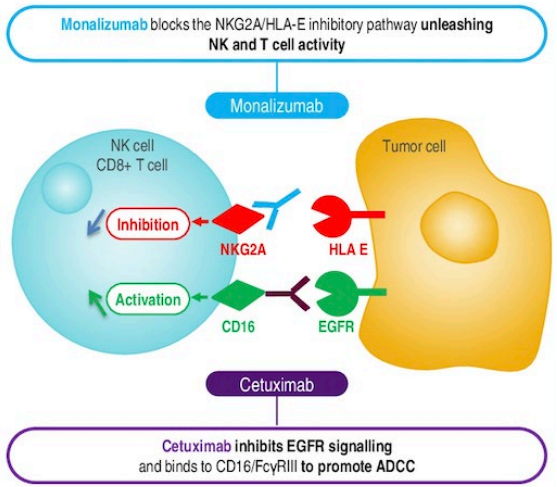
Bauman et al, ASCO 2021

Rationale For Combining EGFR MoAb with ICI

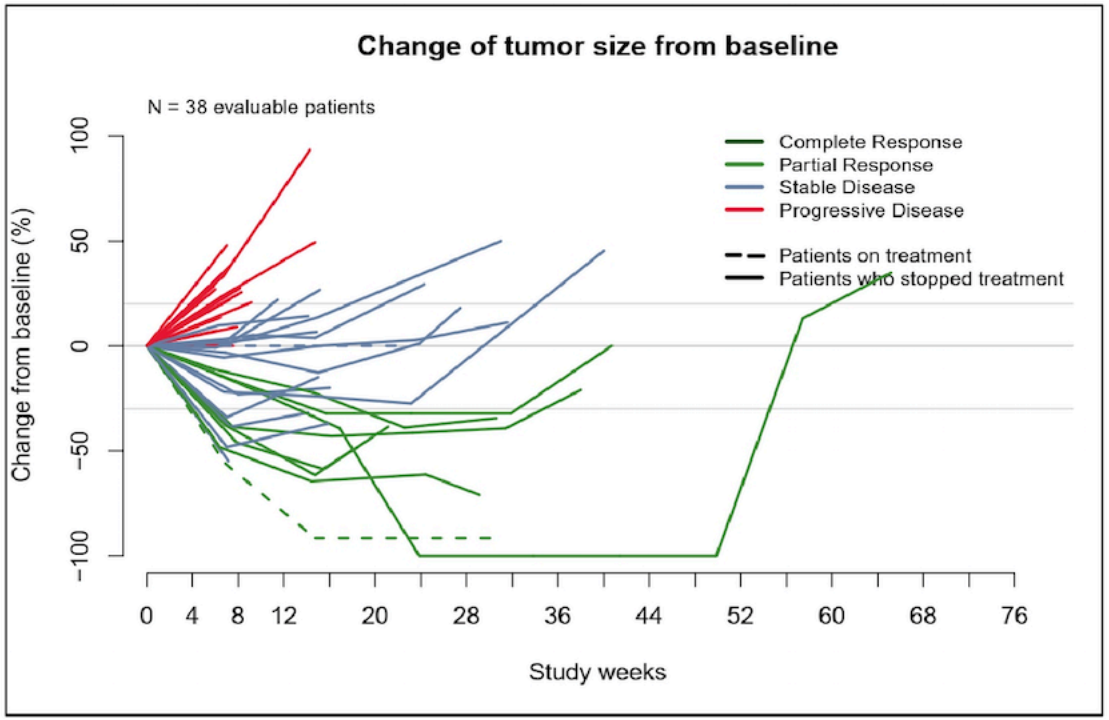


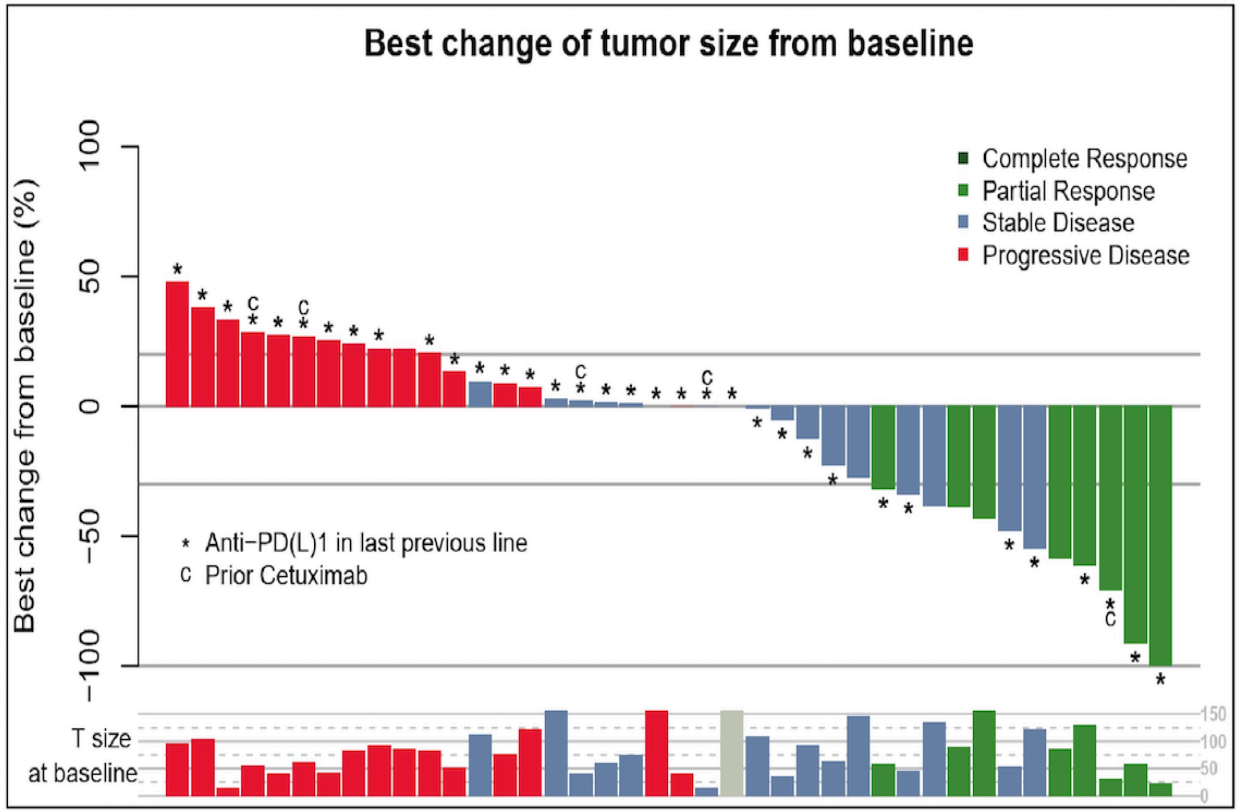
Ferris, *et al.* Cancer Treatment Reviews, 2018

Monalizumab and Cetuximab in RMHNSCC following ICI and cisplatin therapy



IgG4 Inhibitor of NKG2A receptor expressed on NK cells and CD8+ T cells

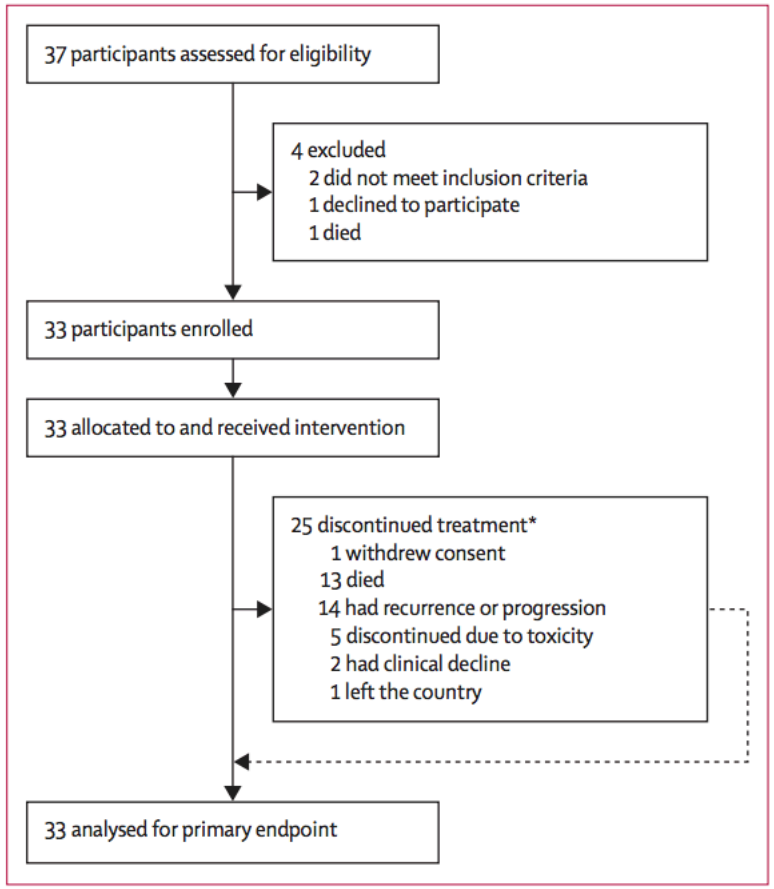




	Cohort 2, n=40
PR n (%)	8 (20%)
SD n (%)	15 (37.5%)
PD n (%)	15 (37.5%)
NE n (%)	2* (5%)
ORR %, [95% CI]	**20% [10.5-34.8]**
Time to Response median, [95% CI]	1.6 mo [1.6-5.3]
Duration of Response median, [95% CI]	5.2 mo [3.9-NR]

Cohen RB, ASCO 2020

Pembrolizumab and Cetuximab in patients with RMHNSCC



Sacco AG, Lancet Oncology 2021

	All participants in cohort 1 (n=33)
Median age, years (IQR, range)	60 (54–65; 30–86)
Sex	
Female	11 (33%)
Male	22 (67%)
Ethnic origin	
White, non-Hispanic	22 (67%)
White, Hispanic	3 (9%)
Asian	4 (12%)
More than one race	2 (6%)
Not reported	2 (6%)
ECOG performance status score	
0	12 (36%)
1	21 (64%)
Smoking history	
Never	12 (36%)
Former	18 (55%)
Passive	1 (3%)
Current	2 (6%)
Alcohol use	
Never	15 (45%)
Former	8 (24%)
Current	10 (30%)
Primary tumour site	
Oral cavity	15 (45%)
Oropharynx, HPV-related	11 (33%)
Oropharynx, non-HPV-related	2 (6%)
Nasopharynx	2 (6%)
Larynx	3 (9%)
Recurrence pattern	
Local or regional recurrence only	12 (36%)
Local or regional and distant	8 (24%)
Distant metastases only	13 (39%)

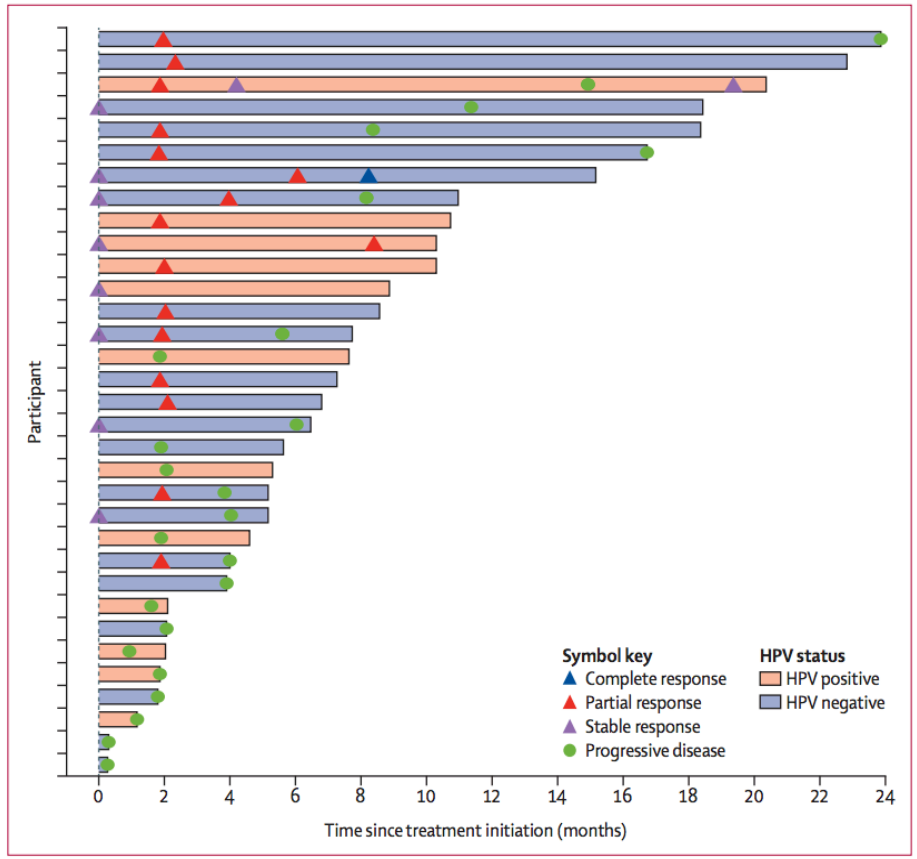
(Table 1 continues in next column)

	All participants in cohort 1 (n=33)
(Continued from previous column)	
Previous lines of systemic therapy for recurrent or metastatic disease	
None	29 (88%)
One	4 (12%)
Platinum ineligible	12 (36%)
Hearing loss or severe tinnitus	9 (27%)
Peripheral neuropathy	1 (3%)
Other*	2 (6%)
Platinum resistant	21 (64%)
Relapse within 6 months of curative intent treatment	17 (52%)
Progression after platinum for recurrent or metastatic disease	4 (12%)
PD-L1 combined positive score	
<1	16 (48%)
≥1 and <20	1 (3%)
≥20	10 (30%)
Inadequate tissue sample	6 (18%)

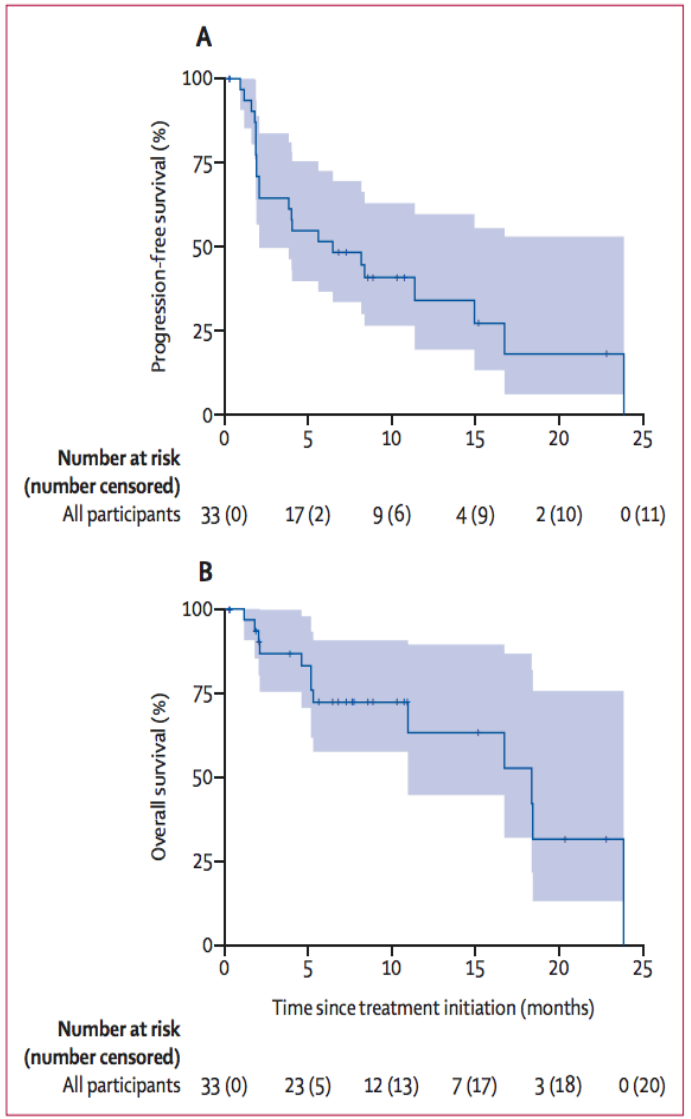
ECOG=Eastern Cooperative Oncology Group. HPV=human papillomavirus. Overall percentages might not add up to 100 due to rounding. *One participant had advanced age (86 years) and cardiac disease; one participant had chronic obstructive pulmonary disease and other health factors not considered suitable for platinum-based therapy by the treating physician.

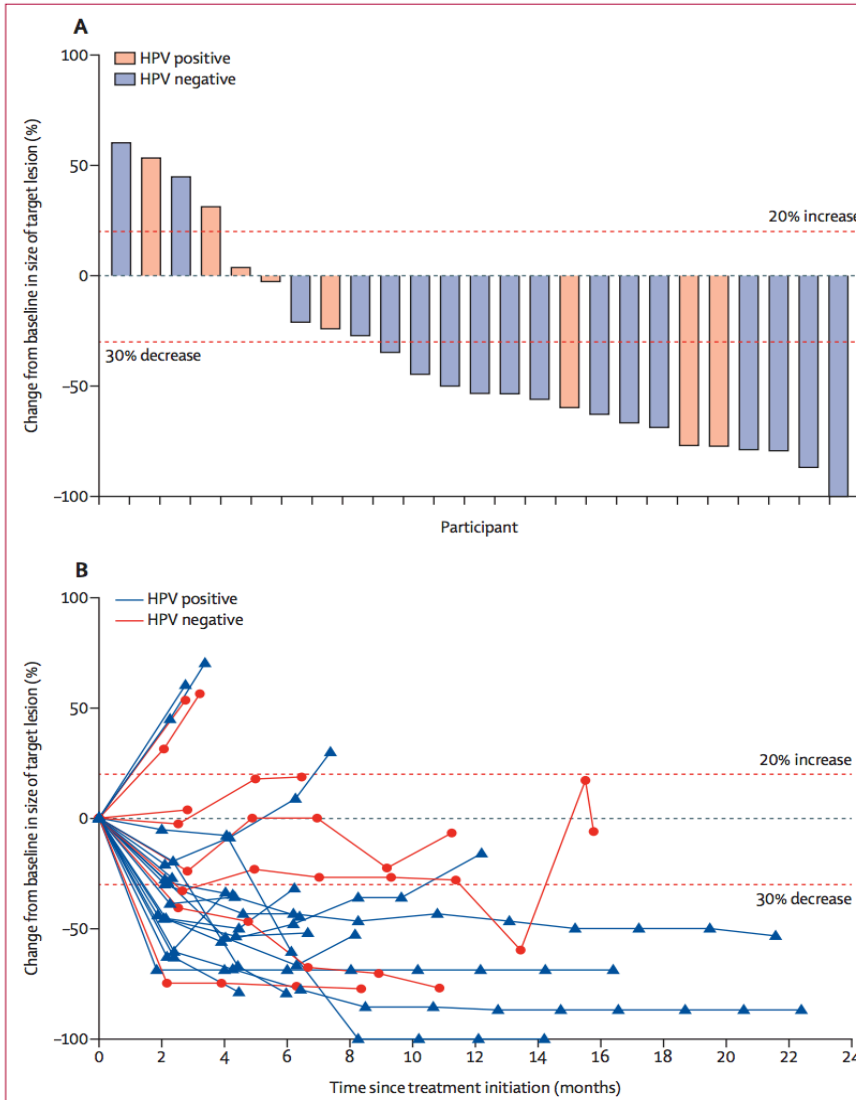
Table 1: **Baseline characteristics**

Pembrolizumab + Cetuximab



Sacco AG, Lancet Oncology 2021





NCCN Guidelines ; Pembrolizumab + Cetuximab

Recurrent, Unresectable, or Metastatic (with no surgery or RT option)

Preferred Regimens

First-Line[c]
- Pembrolizumab/platinum (cisplatin or carboplatin)/5-FU (category 1)[c,30]
- Pembrolizumab (for tumors that express PD-L1 with CPS ≥1) (category 1 if CPS ≥ 20)[c,30]

Subsequent-Line (if not previously used)
- Nivolumab[31] (if disease progression on or after platinum therapy) (category 1)
- Pembrolizumab[32-34] (if disease progression on or after platinum therapy) (category 1)

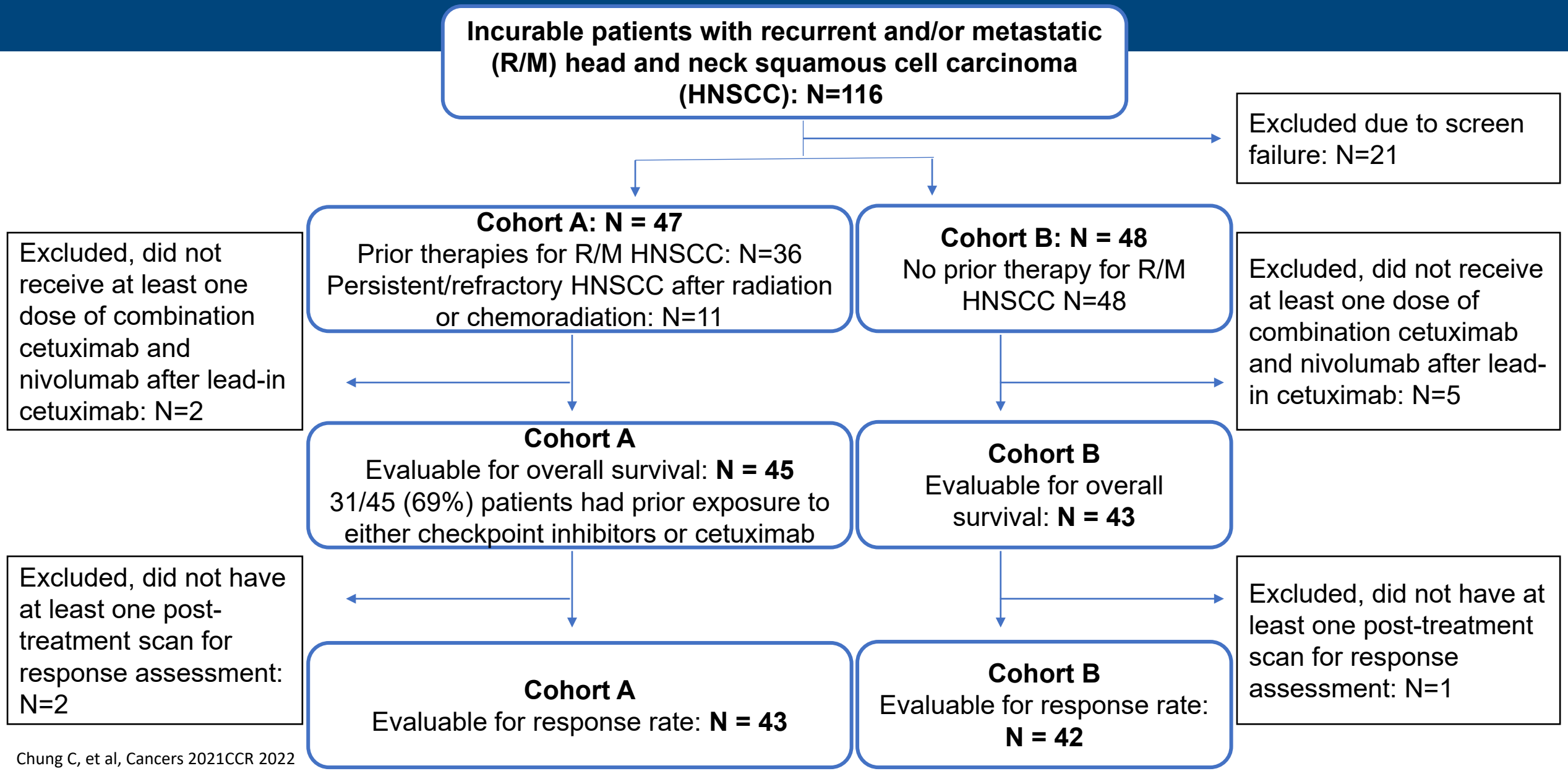
Other Recommended Regimens
(First- and Subsequent-Line)

Combination Regimens
- Cetuximab/platinum (cisplatin or carboplatin)/5-FU[35] (category 1)
- Cisplatin/cetuximab[36]
- Cisplatin or carboplatin/docetaxel[37] or paclitaxel[38]
- Cisplatin/5-FU[38,39]
- Cisplatin or carboplatin/docetaxel/cetuximab[40]
- Cisplatin or carboplatin/paclitaxel/cetuximab[41]
- Pembrolizumab/platinum (cisplatin or carboplatin)/docetaxel[30,37]
- Pembrolizumab/platinum (cisplatin or carboplatin)/paclitaxel (category 2B) [30,38]

Single Agents
- Cisplatin[36,42]
- Carboplatin[43]
- Paclitaxel[44]
- Docetaxel[45,46]
- 5-FU[42]
- Methotrexate[39,47]
- Cetuximab[48]
- Capecitabine[49]
- Afatinib[50] (subsequent-line only, if disease progression on or after platinum therapy) (category 2B)

Useful in Certain Circumstances
(First- and Subsequent-Line)
- Cetuximab/pembrolizumab (category 2B)[51]
- For select ethmoid/maxillary sinus cancers (small cell, SNEC, high-grade olfactory esthesioneuroblastoma, SNUC with neuroendocrine features):
  - Cisplatin/etoposide or carboplatin/etoposide[14]
  - Cyclophosphamide/doxorubicin/vincristine (category 2B)[15]
- Pembrolizumab (for MSI-H tumors)[52]

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



Chung C, et al, Cancers 2021CCR 2022

Overall Response Rate

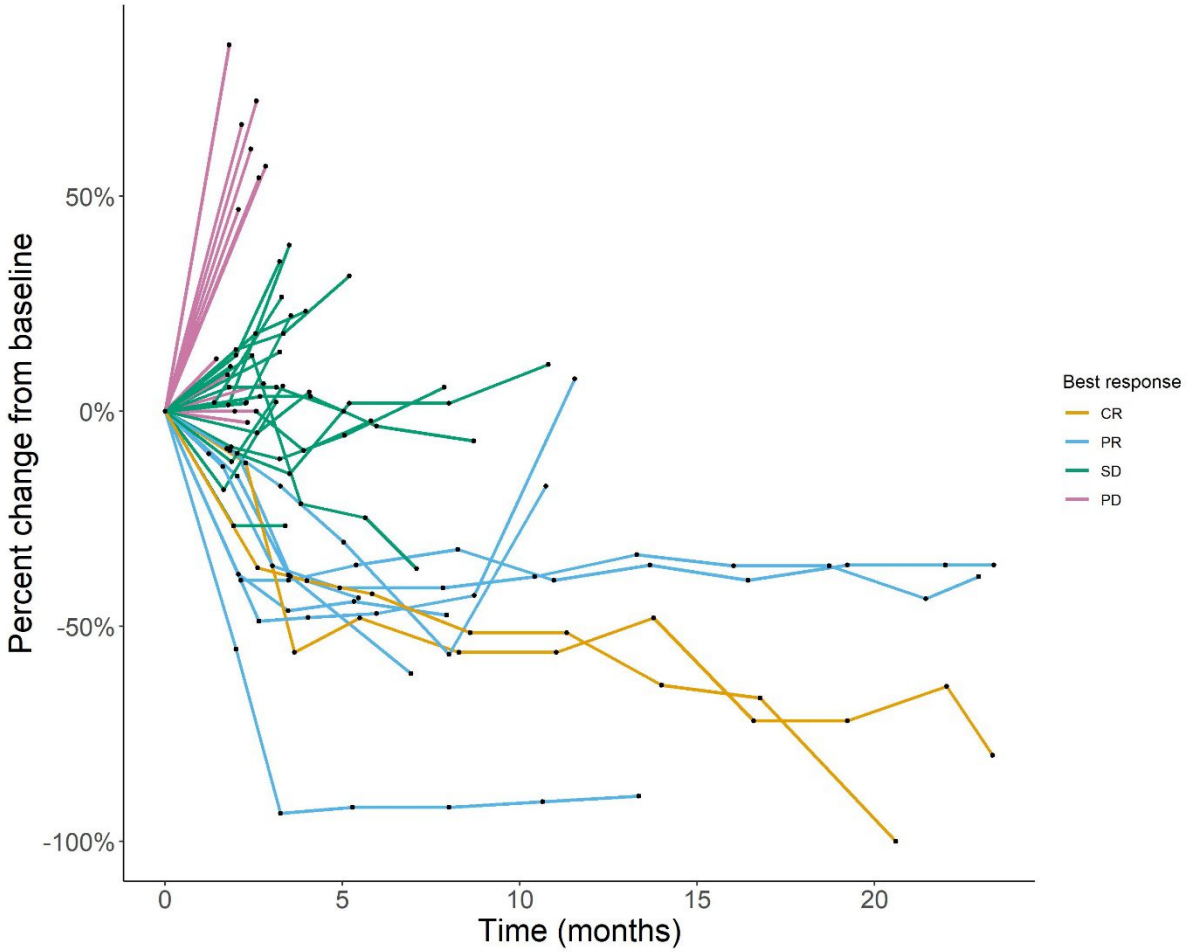
Cohort			CR/PR	SD/PD	p-value#
Cohort B	p16 IHC N=42 (%)	Positive	5 (12)	13 (31)	0.192
		Negative	11 (26)	13 (31)	
	PD-L1 IHC N=39 (%)	CPS < 1	1 (3)	6 (15)	0.153
		CPS >= 1	14 (36)	18 (46)	
Cohort A + B	p16 IHC N=85 (%)	Positive	7 (8)	32 (38)	0.017
		Negative	19 (22)	27 (32)	
	PD-L1 IHC N=76 (%)	CPS < 1	1 (1)	13 (17)	0.025
		CPS >= 1	23 (30)	39 (51)	
	Prior cetuximab or immunotherapy exposure* N=85 (%)	Yes	6 (7)	23 (27)	0.119
		No	20 (24)	36 (42)	
	Platinum resistant disease+ N=85 (%)	Yes	5 (6)	7 (8)	0.281
		No	21 (25)	52 (61)	
	TTMV DNA in plasma N=35 (%)	> median (high)	0 (0)	17 (49)	0.019
		< median (low)	6 (17)	12 (34)	

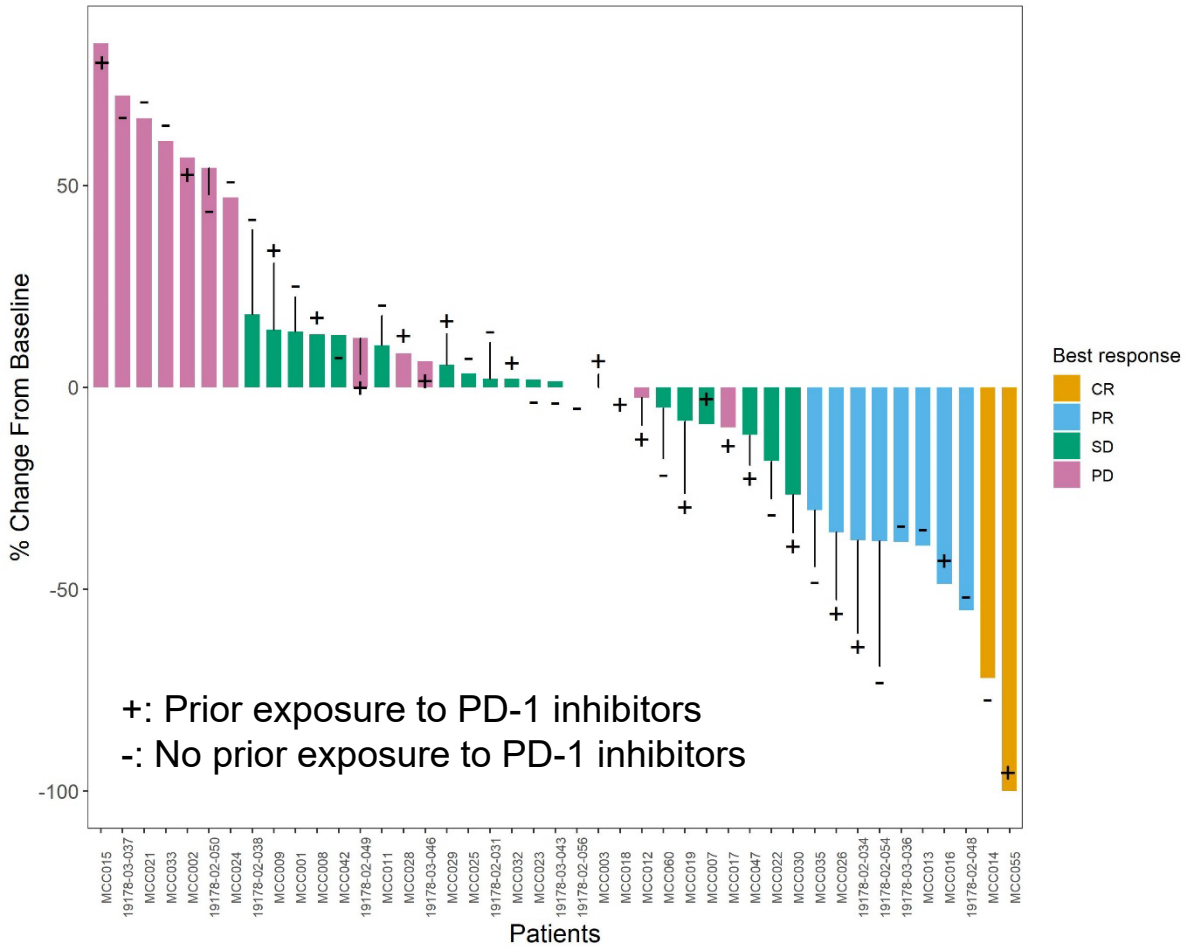
*Exclude cetuximab given with radiation
+Relapse within 6 months of platinum containing curative therapy
#p value is derived from one-side Fisher's exact test.

Chung C, et al, Cancers 2021CCR 2022

Cohort A: Second line and beyond therapy for R/M HNSCC

Overall response rate: 22.2%
CR: 2 (4.4%), PR: 9 (17.8%), SD:19 (42.2%), PD: 16 (35.6%)





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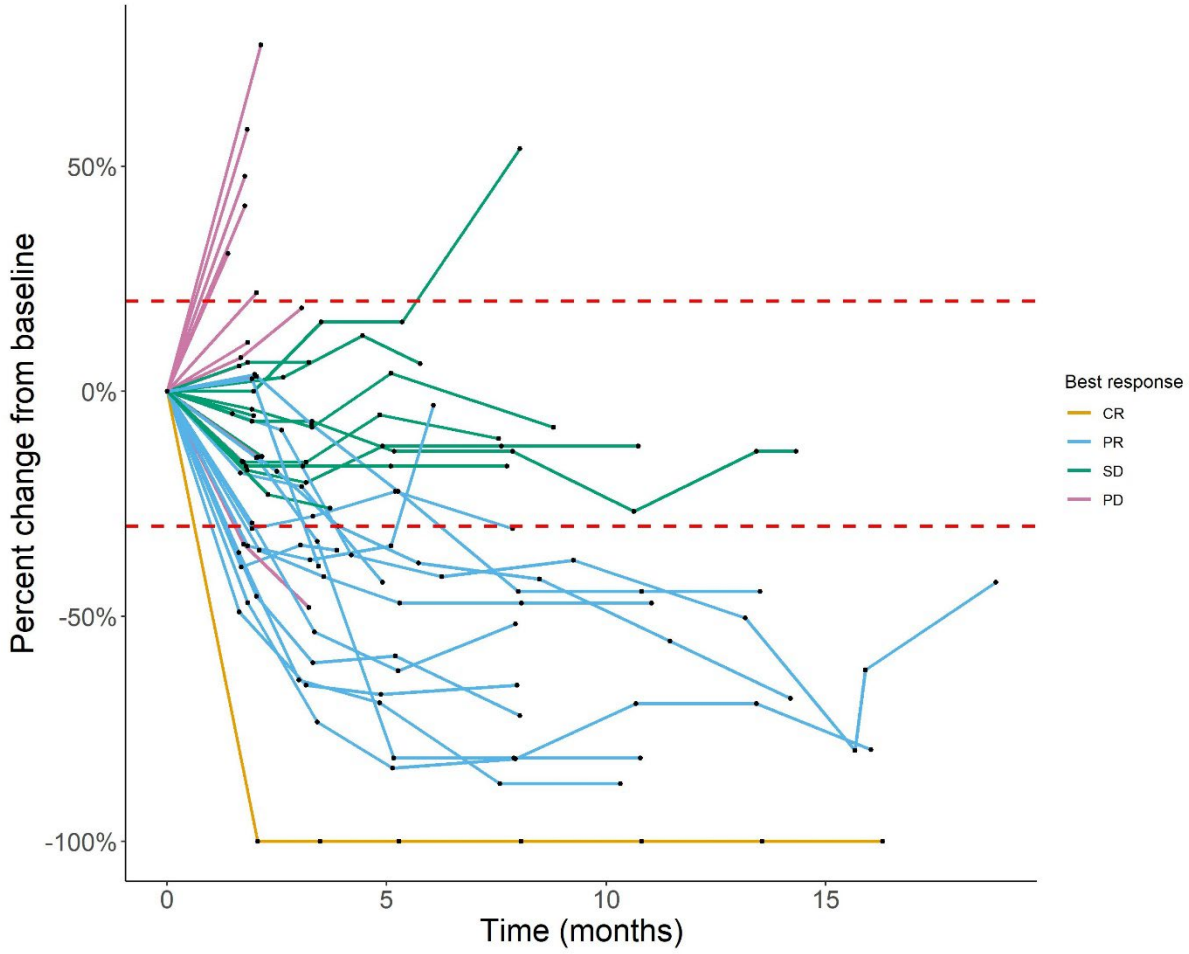
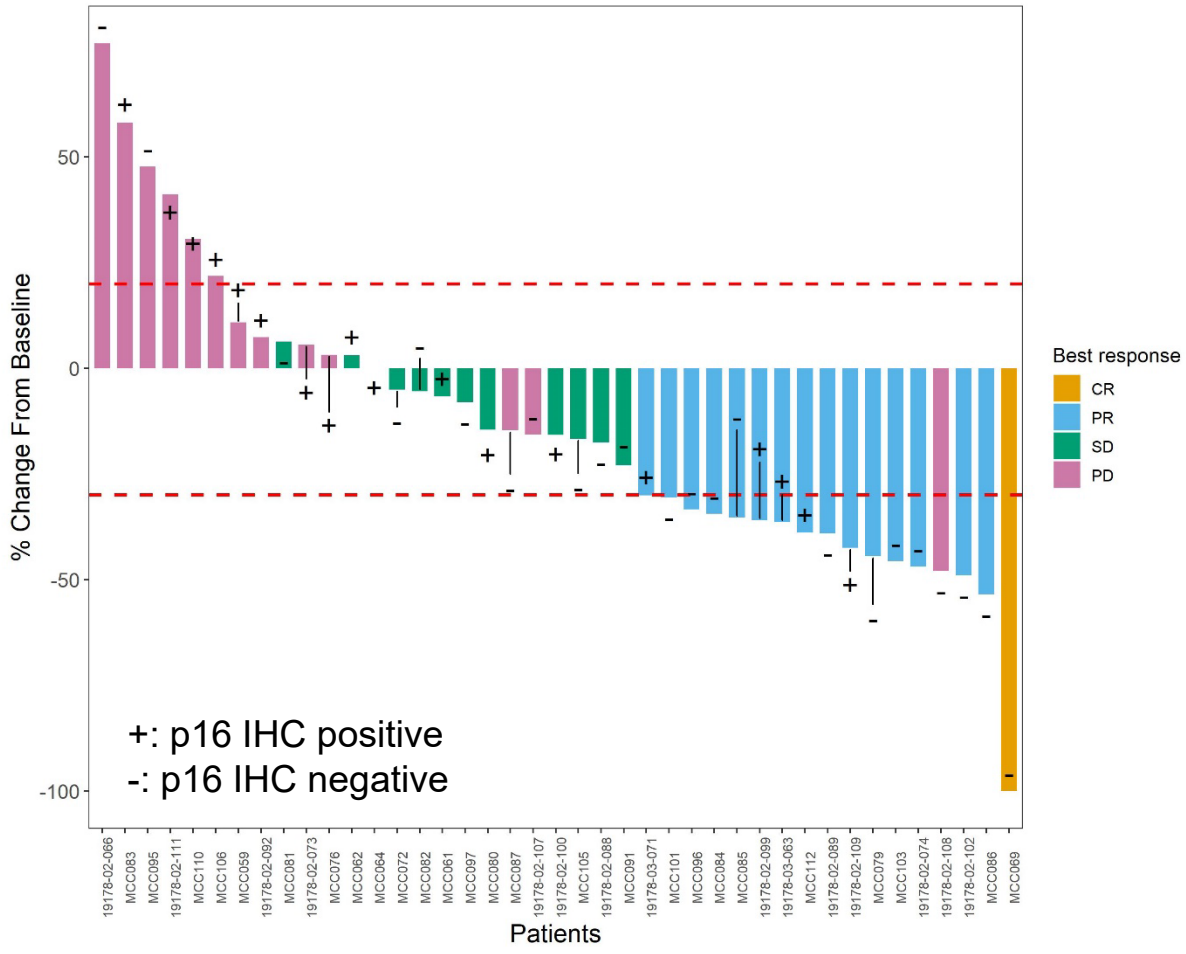
Cohort B: First line therapy for R/M HNSCC

Overall response rate: 37% (16/43)





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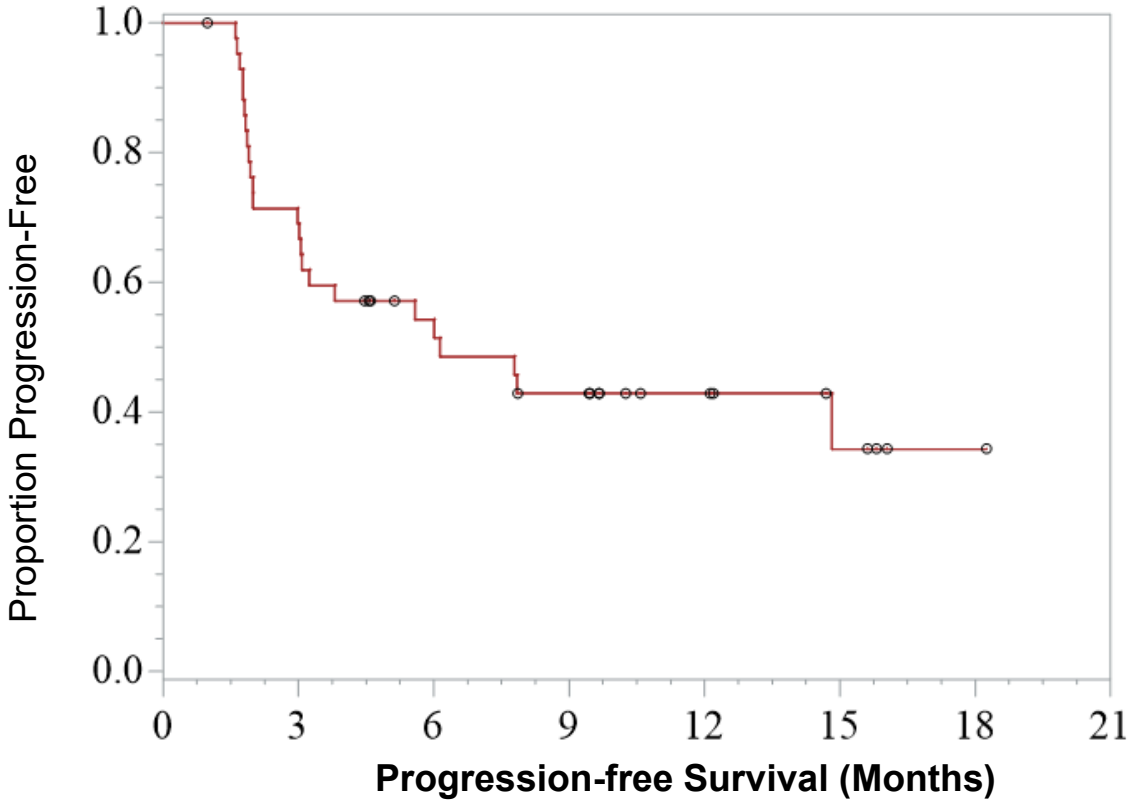
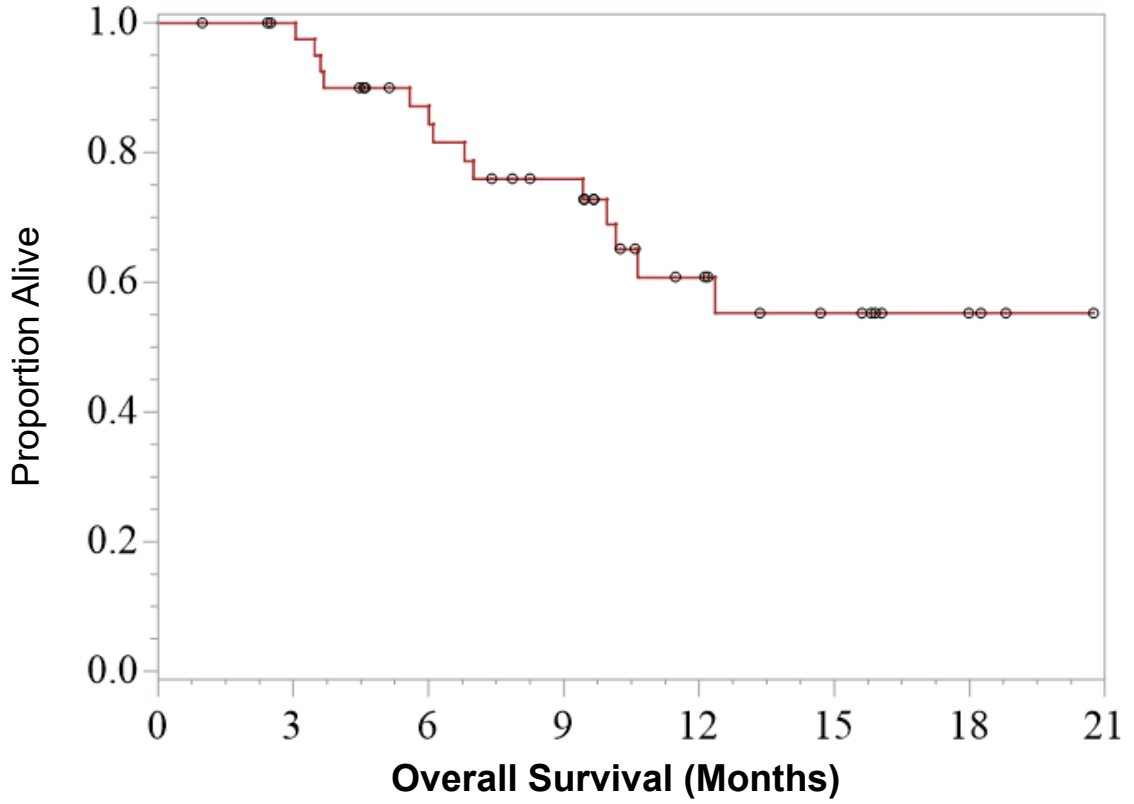
Cohort B: First line therapy for R/M HNSCC
Survival analyses by Kaplan-Meier method



N	Event	Censored	Median PFS (95% CI)	1-Year PFS (90% CI)
43	24 (56%)	19 (44%)	6.15 (3.06, NA)	0.43 (0.30, 0.55)



N	Event	Censored	Median OS (95% CI)	1-Year OS (90% CI)
43	14 (33%)	29 (67%)	NA (10.16, NA)	0.61 (0.45, 0.74)

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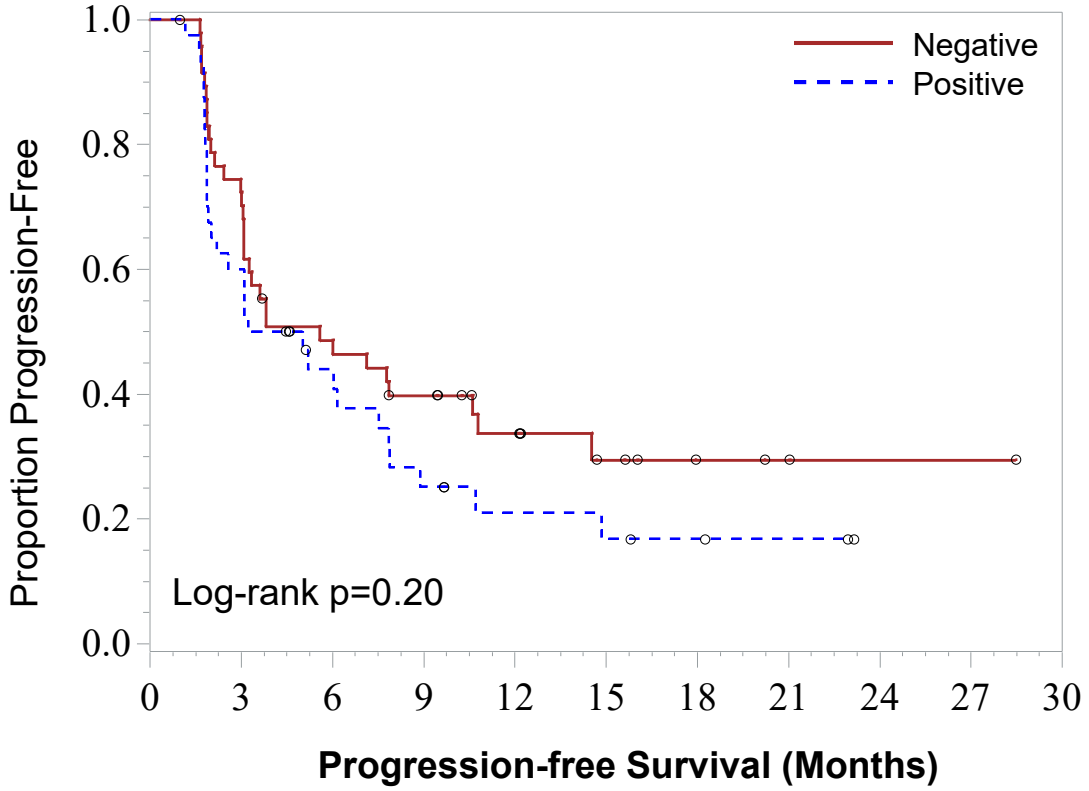
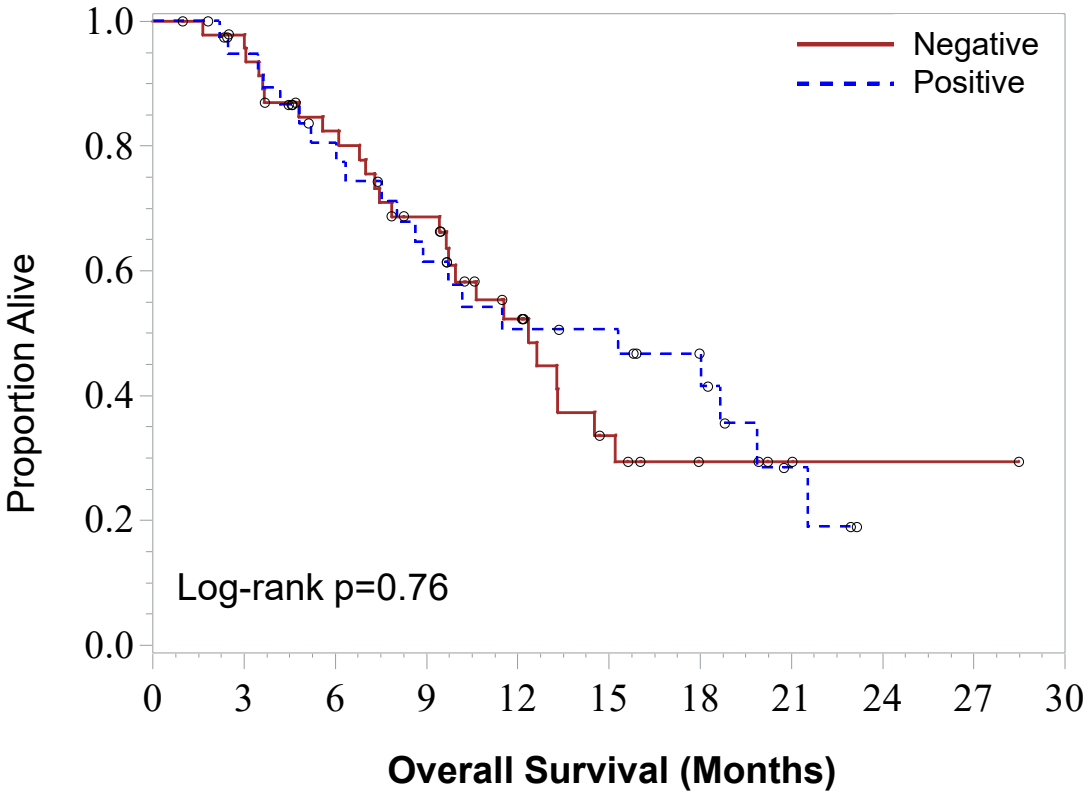
Cohort A and B: Survival based on p16 Status



p16 status	N	Event	Censored	Median PFS (95% CI)
Negative	48	31 (65%)	17 (35%)	5.6 (3.1, 10.8)
Positive	40	30 (75%)	10 (25%)	4.1 (2.0, 7.5)



p16 status	N	Event	Censored	Median OS (95% CI)
Negative	48	26 (54%)	22 (46%)	12.4 (9.7, 14.5)
Positive	40	21 (53%)	19 (48%)	15.3 (8.0, 19.9)

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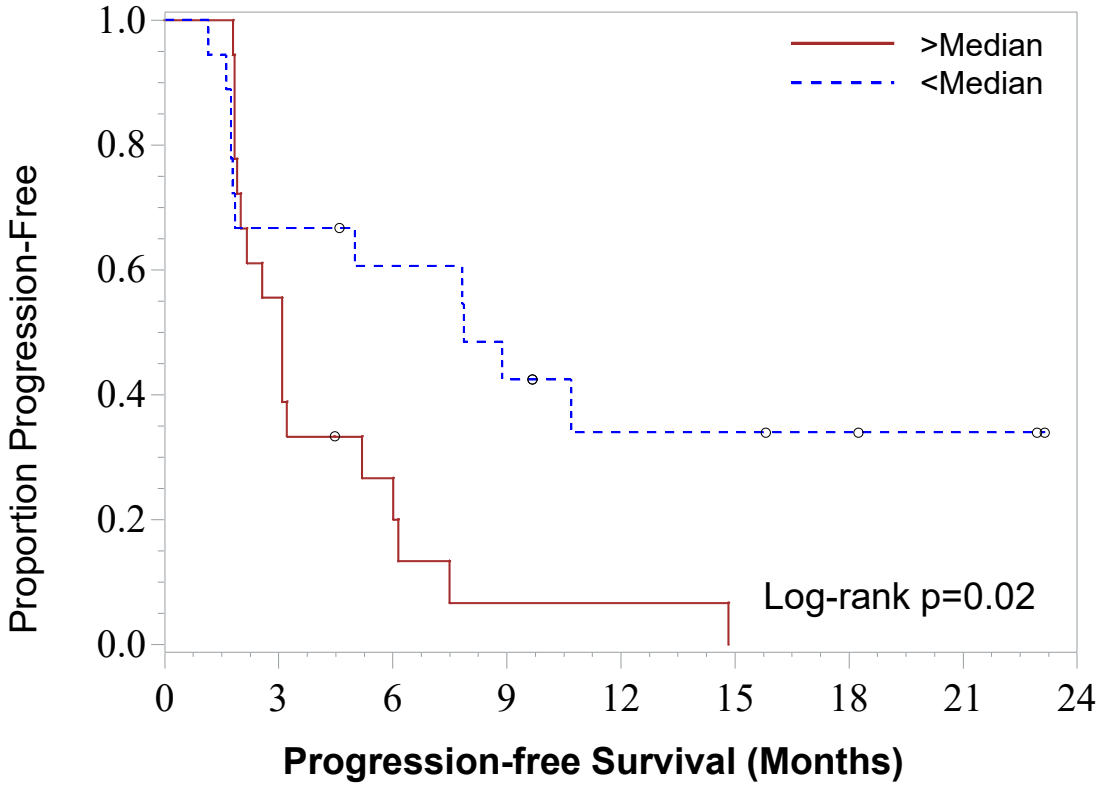
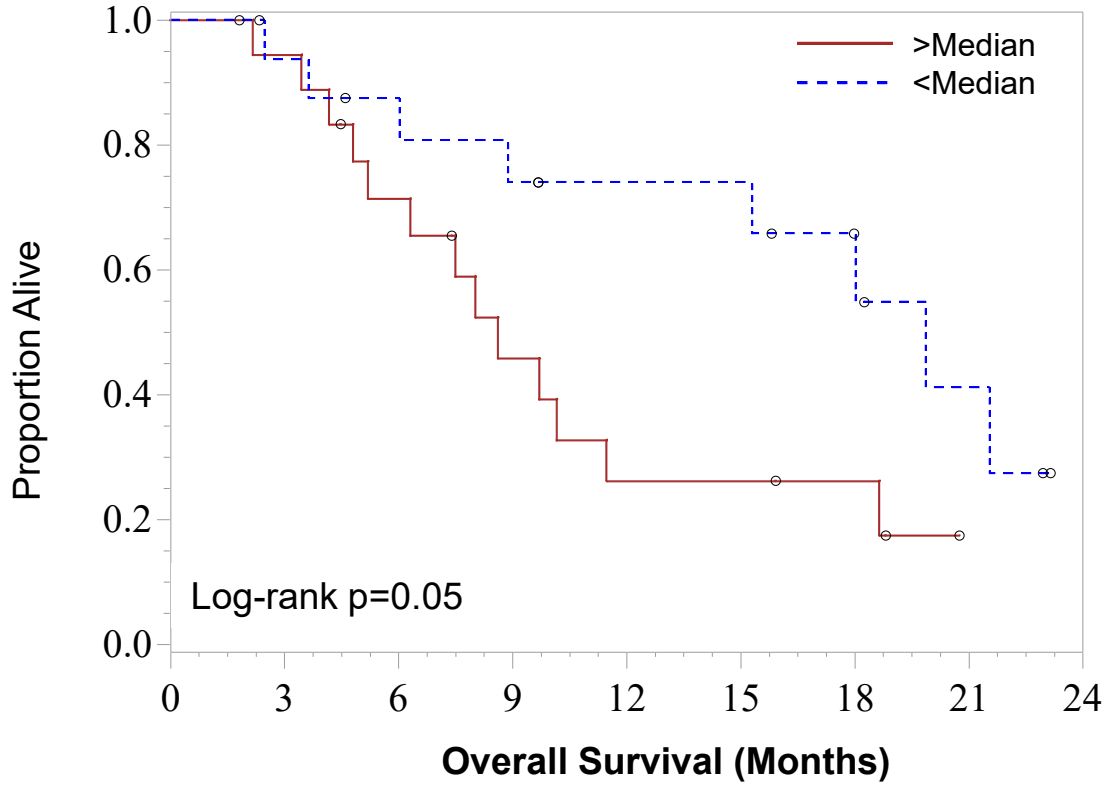
Cohort A and B: Survival based on TTMV DNA in p16 positive HNSCC (median 1,230 copies/mL)



TTMV-HPV DNA	N	Event	Censored	Median PFS (95% CI)
>Median	18	17 (94%)	1 (6%)	3.1 (1.9, 5.2)
<Median	18	11 (61%)	7 (39%)	7.9 (1.8, NA)



TTMV-HPV DNA	N	Event	Censored	Median OS (95% CI)
>Median	18	13 (72%)	5 (28%)	8.6 (5.2, 11.5)
<Median	18	8 (44%)	10 (56%)	19.9 (8.9, NA)

Chung C, et al, Cancers 2021CCR 2022

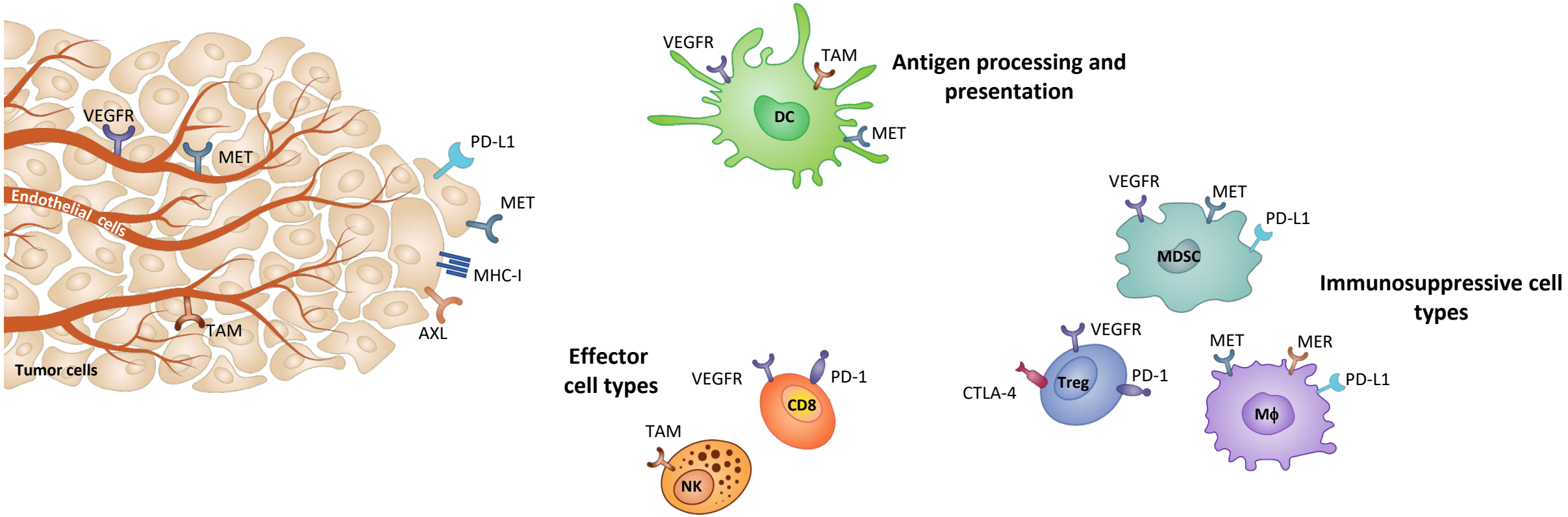
2022 ASCO® ANNUAL MEETING

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

Nabil F. Saba, Asari Ekpenyong, Ashley McCook-Veal, Mihir Patel, Nikki Schmitt, Bill Stokes, James Bates, Soumon Rudra, Marin Abousaud, Jameel Muzaffar, Kedar Kirtane, Yong Teng, Conor Steuer, Dong M. Shin, Liu Yuan, Christine H. Chung

Abstract 6008

VEGFR, MET, and TAM Family Receptor Tyrosine Kinases Are Expressed on Different Cell Types



CTLA-4 = cytotoxic-T-lymphocyte associated protein 4; DC = dendritic cell; Mϕ = macrophages; MDSC = myeloid-derived suppressor cells; MHC-I = major histocompatibility complex I; NK = natural killer cells; TAM = Tyro3, AXL, MER receptor family; Treg = T regulatory cells.

1. Li Y, et al. Cancer Biol Med. 2015;13:206-214. 2. Benkoucha M, et al. J Immunol. 2014;193:2743-2752. 3. Peeters MJW, et al. Canc Immunol Immunother. 2020;69:237-244. 4. Qin W, et al. Front Immunol. 2019: Epub. 5. Walker L, et al. Trends Immunol. 2015;36:63-70. Lu C, et al. Oncoimmunology. 2016;5:e1247135; Bergerot et al. Mol Cancer Ther. 2019;18:2185-93.

Study Design

Phase II, open label, multi-center, single arm trial

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

Patient Characteristics

Patient Characteristic		N=36 n (%)
Age, median (range), years		62 (54-67)
Gender	Male Female	30 (83) 6 (17)
ECOG performance status, %	0 1	18 (50) 18 (50)
Primary site	Oropharynx Oral cavity Hypopharynx Larynx Nasopharynx	22 (61) 2 (6) 2 (6) 4 (11) 6 (16)
HPV (p16)	Positive Negative Unknown	17 (47) 12 (33) 7 (20)
Prior therapy	Radiation Cisplatin Cetuximab	31 (89) 36 (100) 3 (8)
PD-L1 CPS score (total of 34)	CPS <1 CPS 1-19 CPS ≥20	2 (6) 15 (44) 17 (50)

Most Common Grade ≥3 Treatment-Related Adverse Events

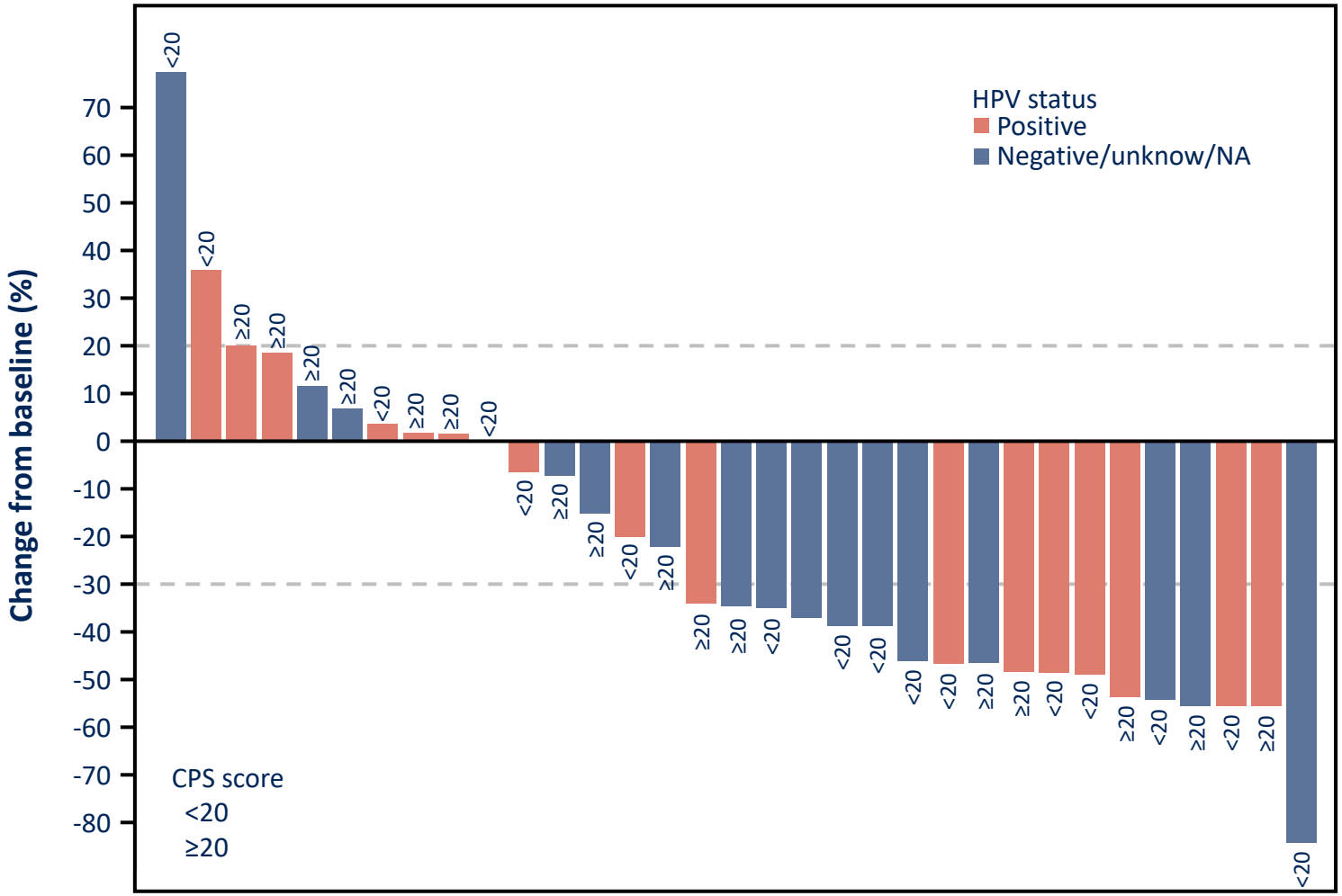
Treatment-Related Adverse Event (Grade ≥3)	N=36 n (%)
AST increase	3 (8.3)
Hyponatremia	3 (8.3)
GGT increase	2 (5.6)
Lipase increase	2 (5.6)
Oral mucositis	2 (5.6)
ALT/AST increase	1 (2.8)
Bilirubin increase	1 (2.8)
Hypertension	1 (2.8)

There were no grade 5 treatment-related AEs

ALT = alanine aminotransferase; GGT = gamma-glutamyl transferase

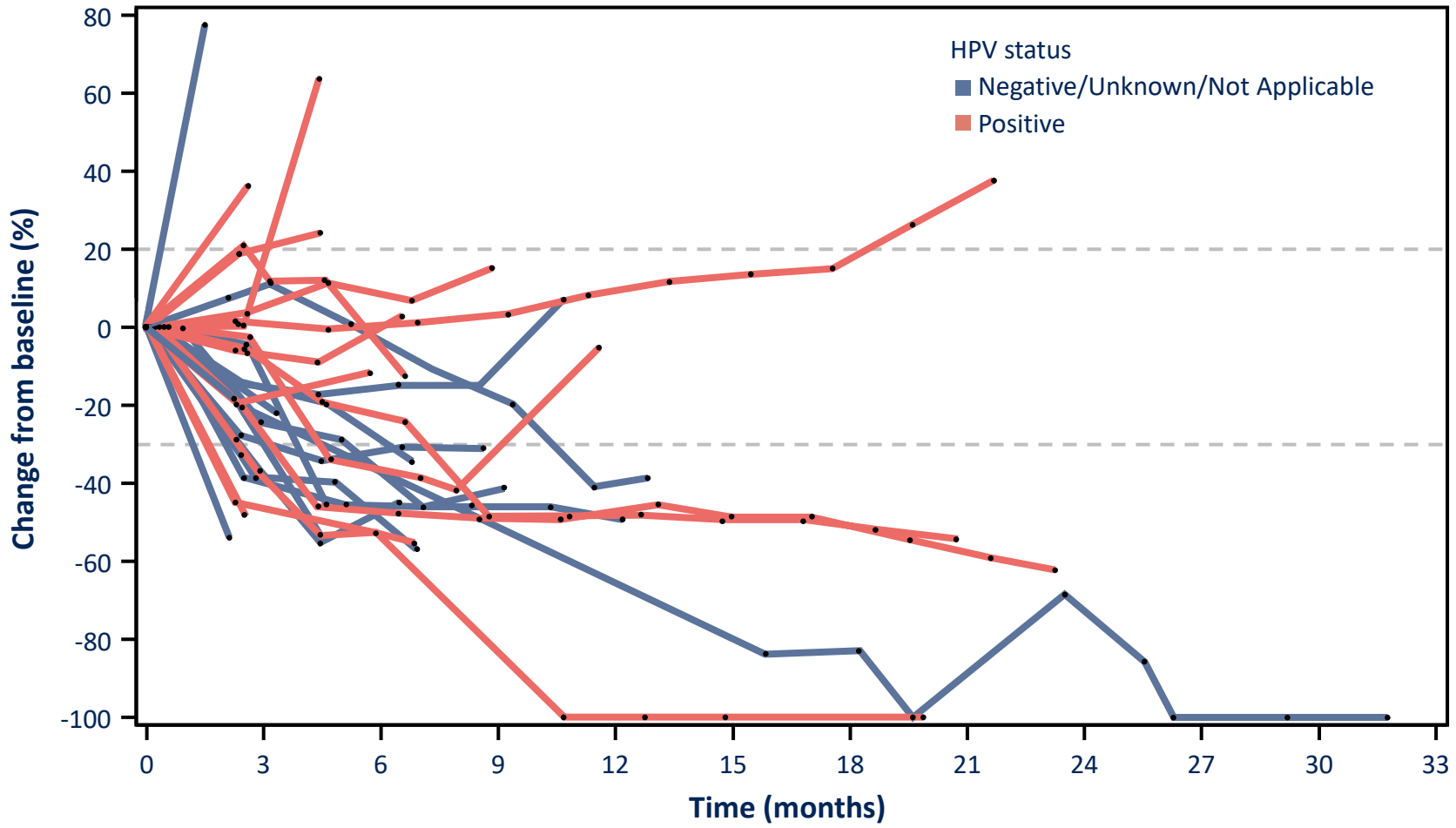
Best Overall Response in Evaluable Patients

	N=33 n (%)
ORR	17 (52)
CR	0 (0)
PR	18(54)
SD	13(39)
PD	3(9)
Clinical benefit	30(91)

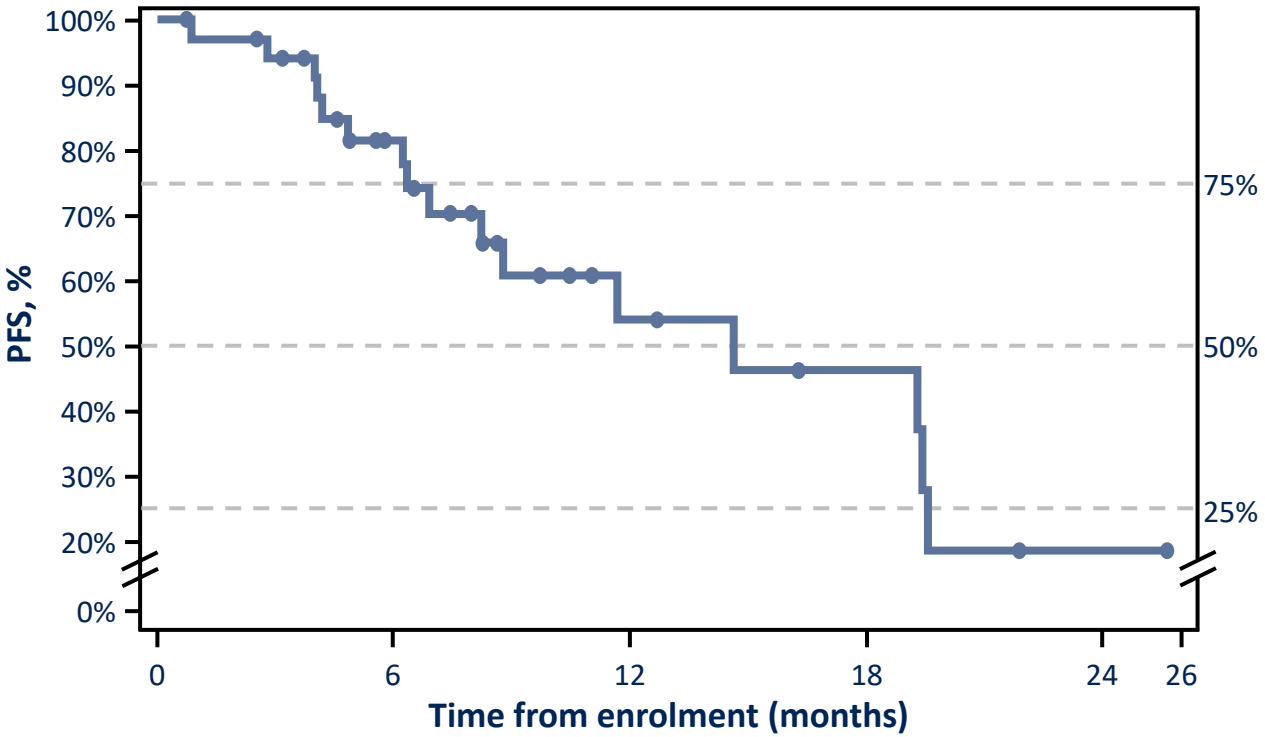


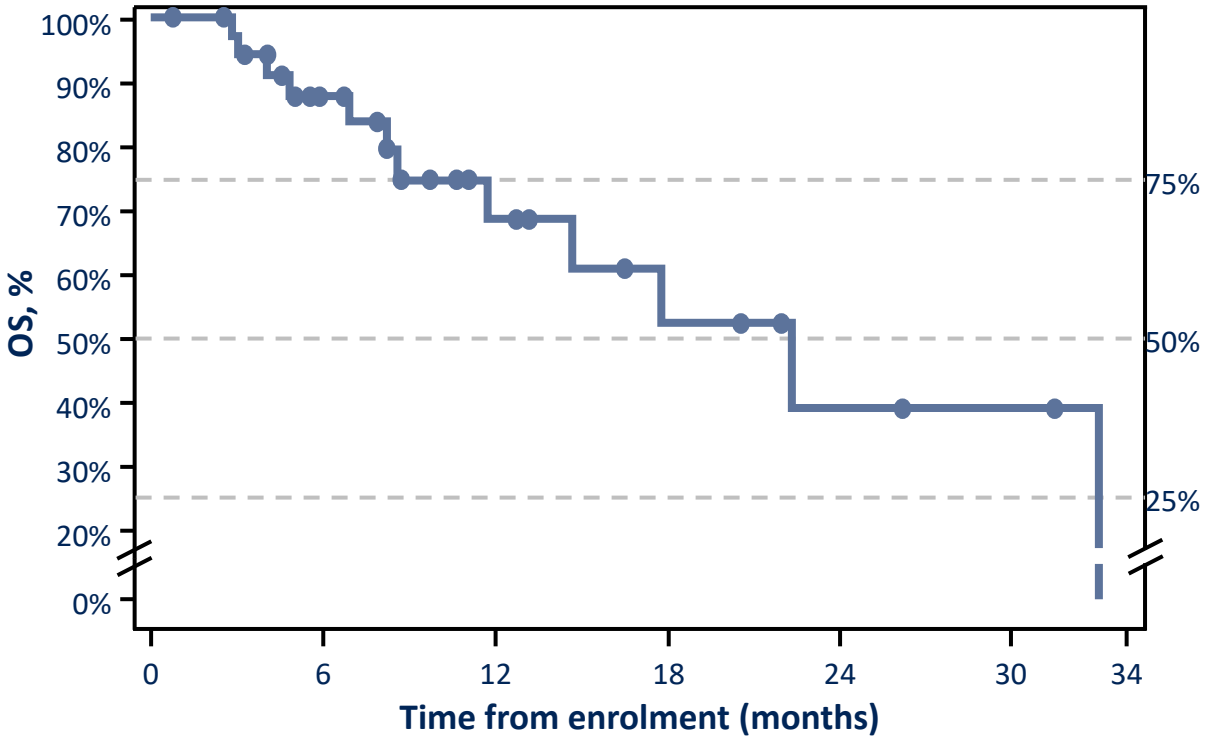
CR = complete response; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease

Efficacy in Patients Evaluable for Response



Progression-Free Survival and Overall survival

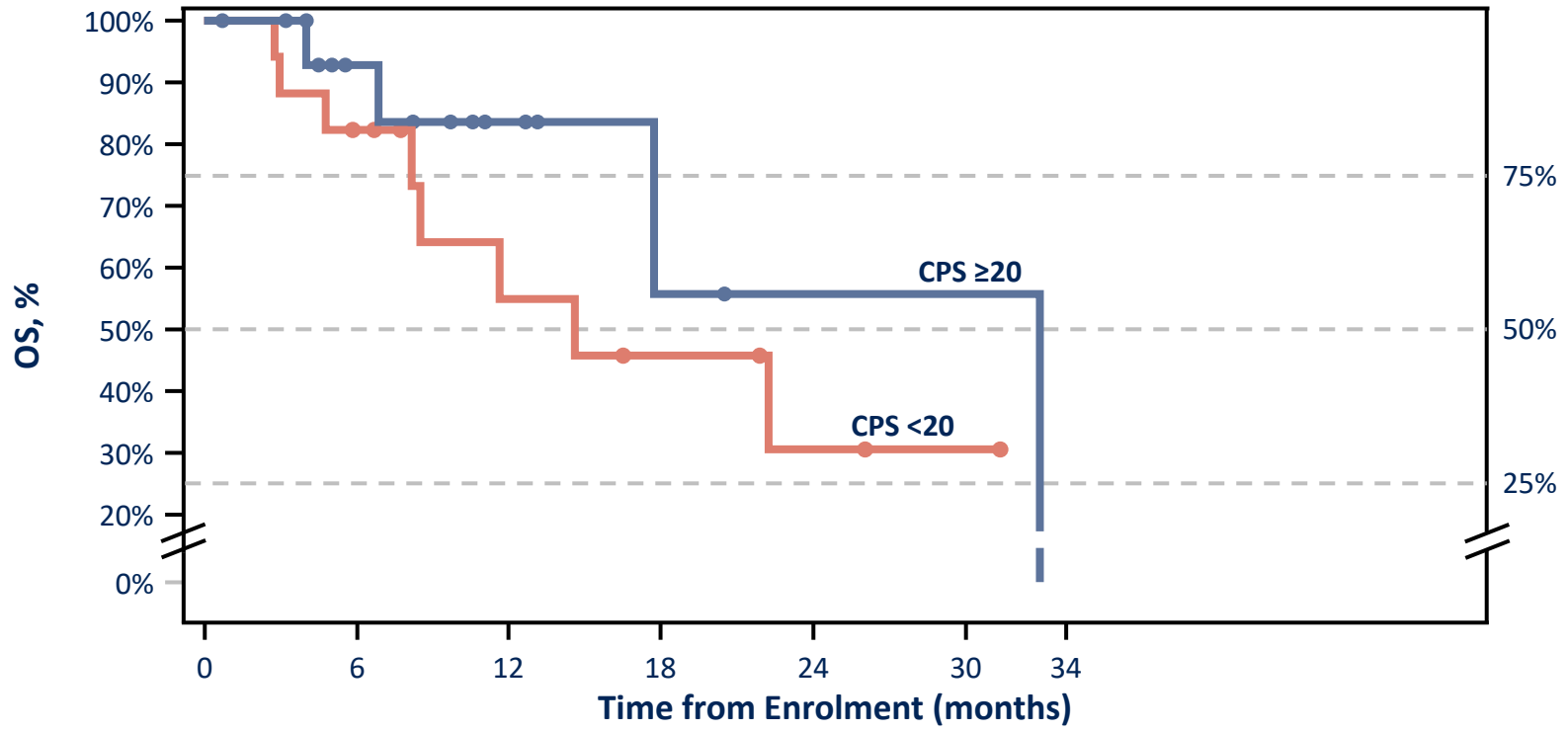




N	Event	Censored	mPFS (95% CI), mo	1-yr PFS (95%CI), %	Median follow-up (95% CI), mo
36	16 (44%)	20 (56%)	14.6 (8.2–19.6)	54.0 (31.5–72.0)	10.6 (7.8–16.5)

N	Event	Censored	mOS (95% CI), mo	1-yr OS (95%CI), %	Median follow-up (95% CI), mo
36	12 (33%)	24 (67%)	22.3 (11.7–32.9)	68.4 (45.1–83.5)	10.6 (7.8–16.5)

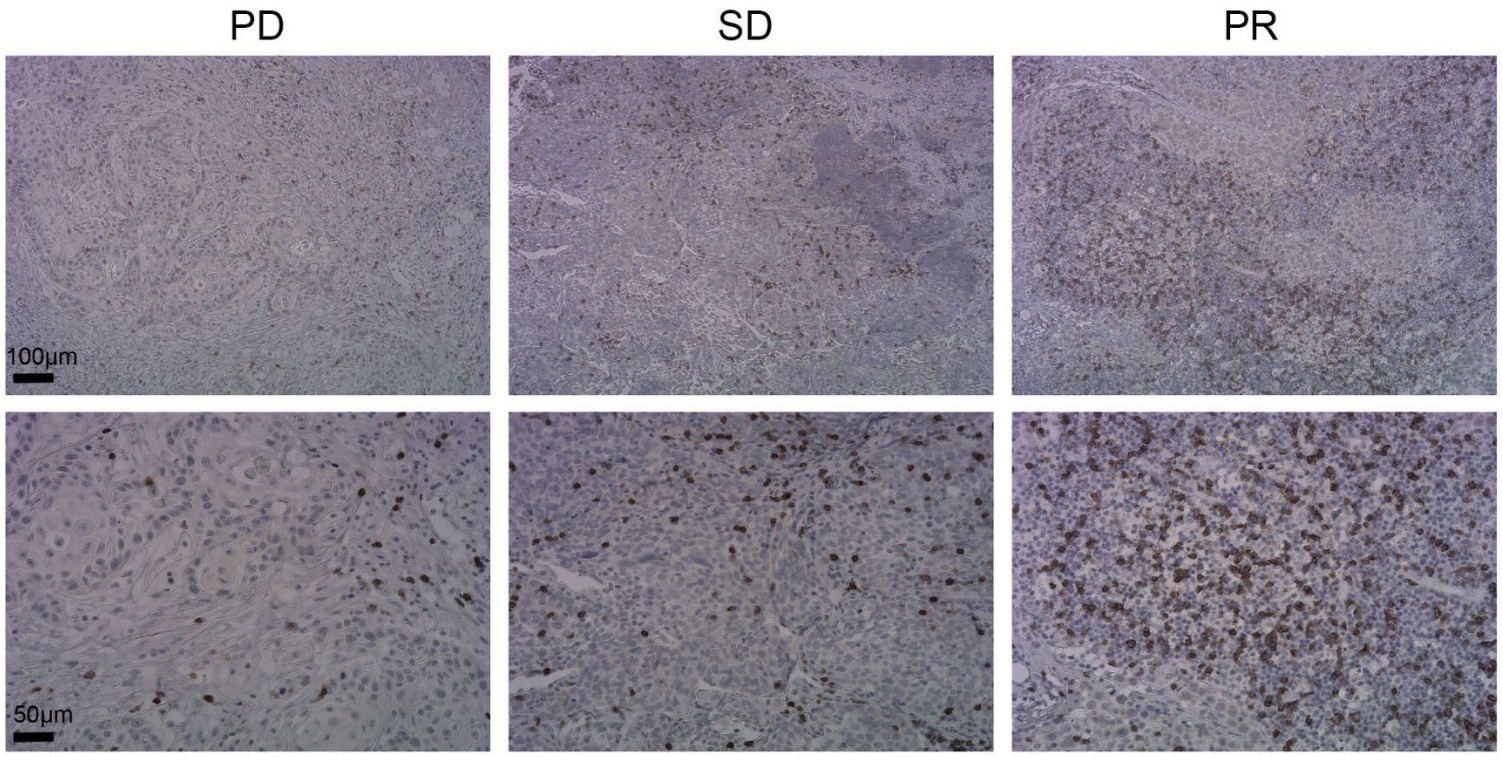
Overall Survival by CPS Score

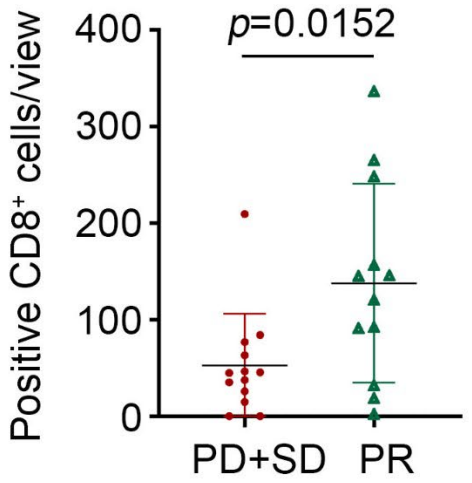


CPS category	N	Event	Censored	mOS (95% CI), mo	1-yr OS (95%CI), %	Median follow-up (95% CI), mo	P value
<20	17	8 (47%)	9 (53%)	14.6 (8.2–NE)	54.9 (24.5–77.5)	21.9 (6.7–31.4)	0.2638
≥20	17	4 (24%)	13 (76%)	32.9 (6.9–32.9)	83.6 (48.0–95.7)	9.7 (4.5–13.1)	

NE = not estimable

Pre-existing CD8+ T-cell Tumor infiltration (26 patients)





Updates in Immunotherapy and EGFR inhibition

- There has been no recent changes in the SOC for the use of either EGFR inhibitors or ICI in HNCA
- Cetuximab in combination with ICI appears to have promising activity
- Cetuximab based therapy appears to be most effective in HPV unrelated disease (phase II data)
- Encouraging phase II of ICI with TKI (Pembrolizumab+ Cabozantinib) deserves further evaluation
- The post ICI or Chemo-ICI failure is an opened space for novel new standards

HPV Vaccination is Probably One of the Most Effective Cancer Prevention Tools

The identification of a single necessary cause for any cancer provides a rare and perhaps extraordinary opportunity for cancer prevention

Winship Cancer Institute joins national effort urging HPV vaccination

Woodruff Health Sciences Center | Jan. 27, 2016

Contact

Judy Fortin
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Vaccination rates remain low across the U.S., with under 40 percent of girls and just over 21 percent of boys receiving the recommended three doses.

Print Share

Winship Cancer Institute of Emory University has joined all 69 of the nation's top cancer centers in issuing a statement urging increased human papillomavirus (HPV) vaccination for the prevention of cancer. The statement is in response to low national vaccination rates for HPV. These institutions collectively recognize insufficient vaccination as a public health threat and call upon the nation's physicians, parents and young adults to take advantage of this rare opportunity to prevent many types of cancer.

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Adolescent vaccine study highlights need for education of parents and

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