Immunotherapy for the Treatment of Head and Neck Cancer

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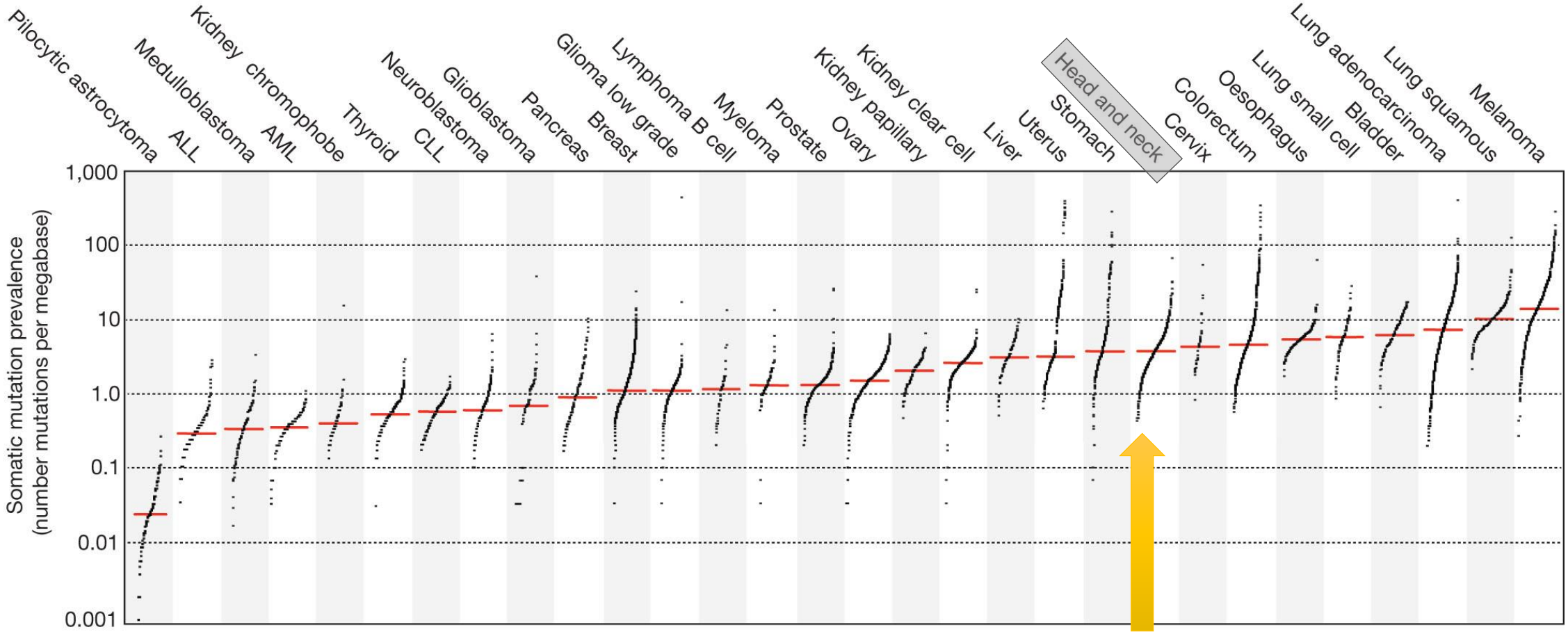
Disclosures

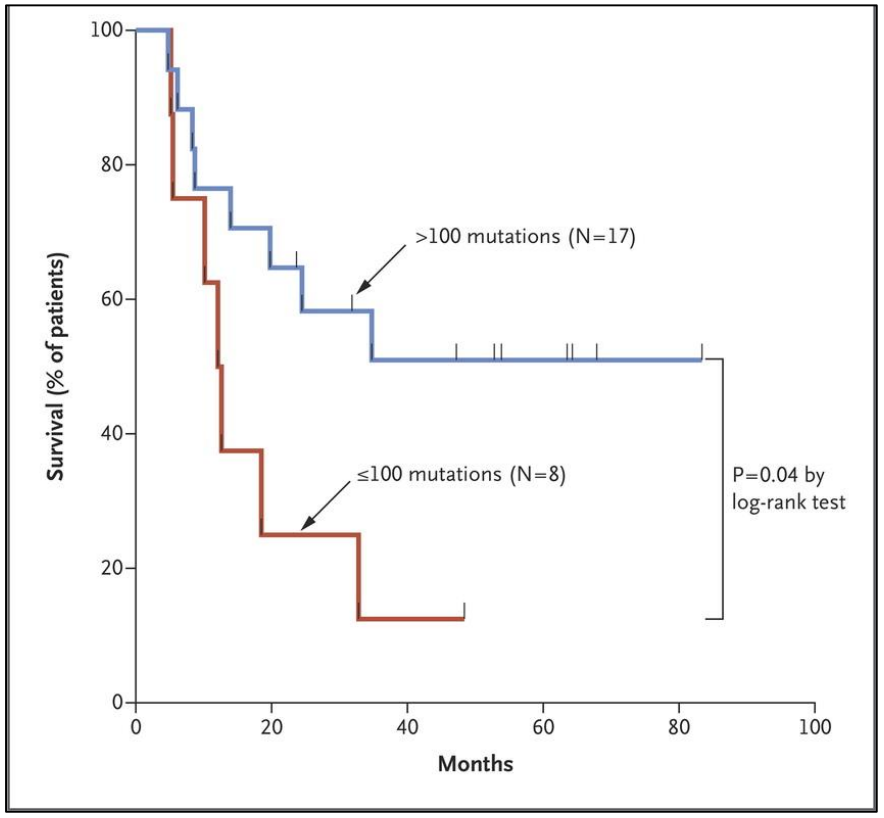
- Advisory Board Member: Merck, Roche, Celgene, Lilly, BMS, AZ
- Institutional Research Funding: Merck, Incyte, Macrogenics, AZ

Mutational load in carcinogen associated HNSCC is high

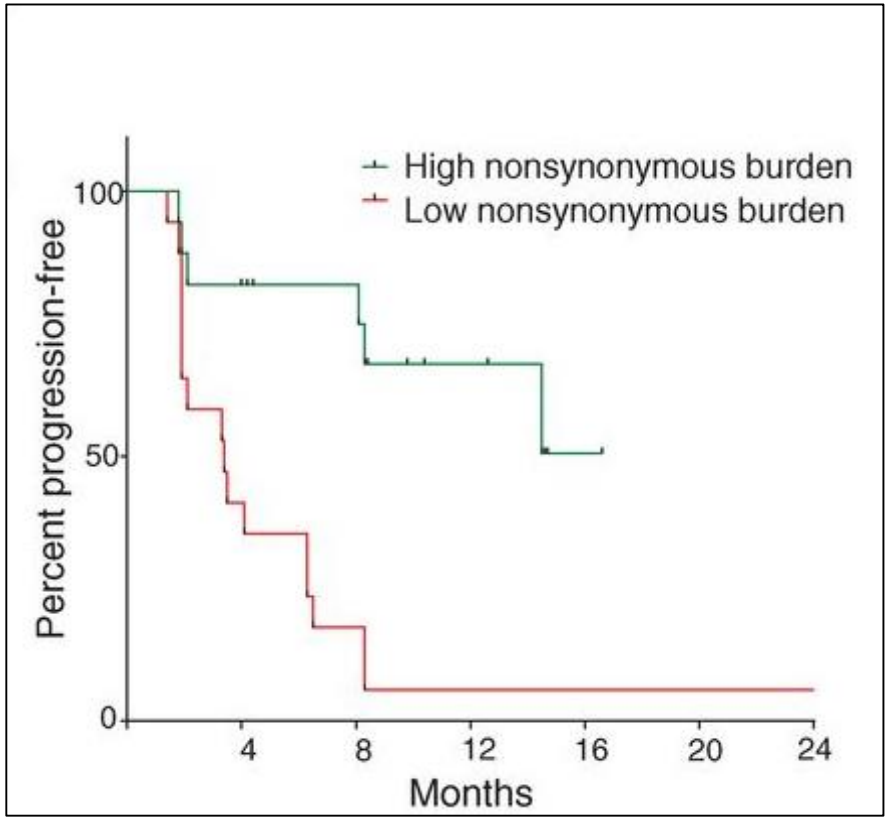


Presented by: Charu Aggarwal, MD, MPH

Response to immunotherapy correlates with mutational burden



Melanoma OS with CTLA-4



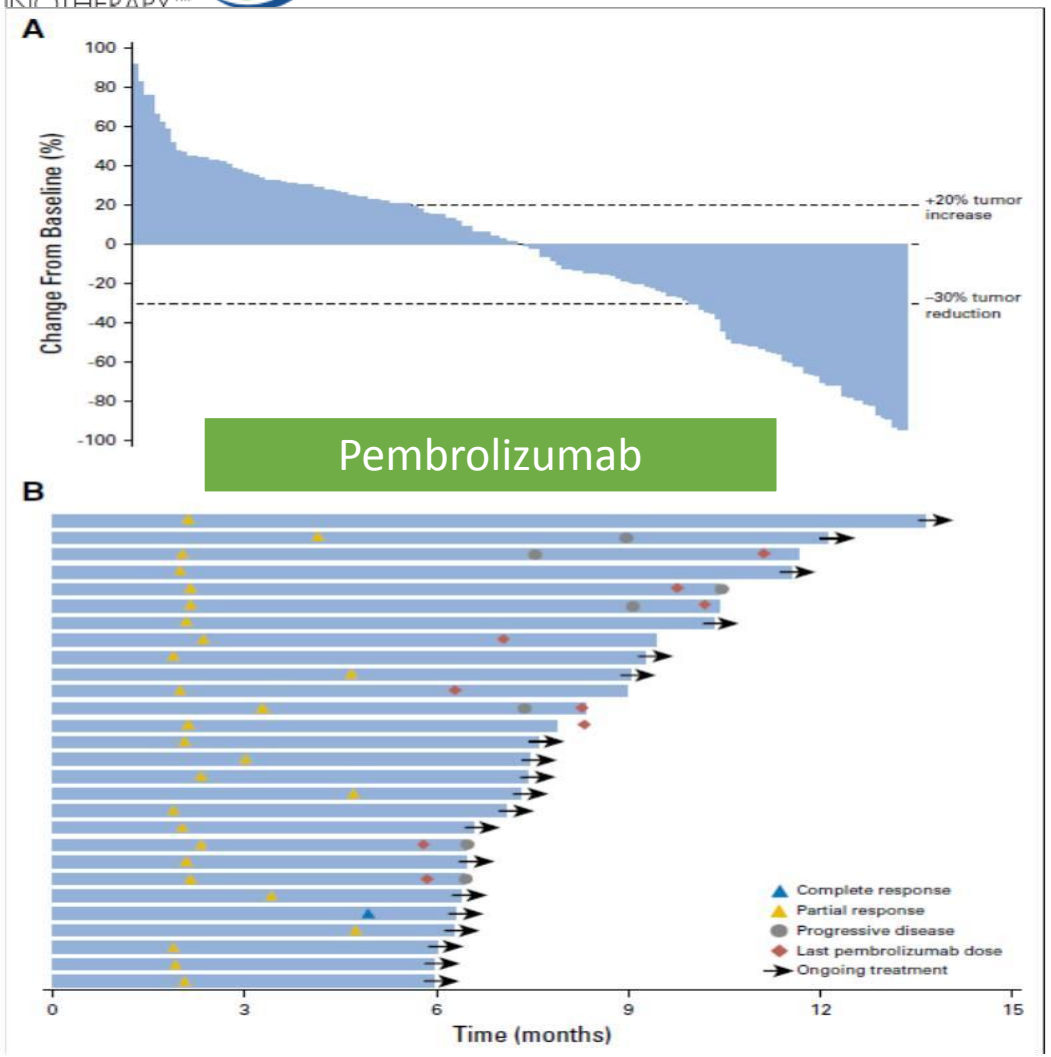
NSCLC PFS with anti PD-1

Presented by: Charu Aggarwal, MD, MPH

Approved checkpoint inhibitors in Head and Neck Cancers

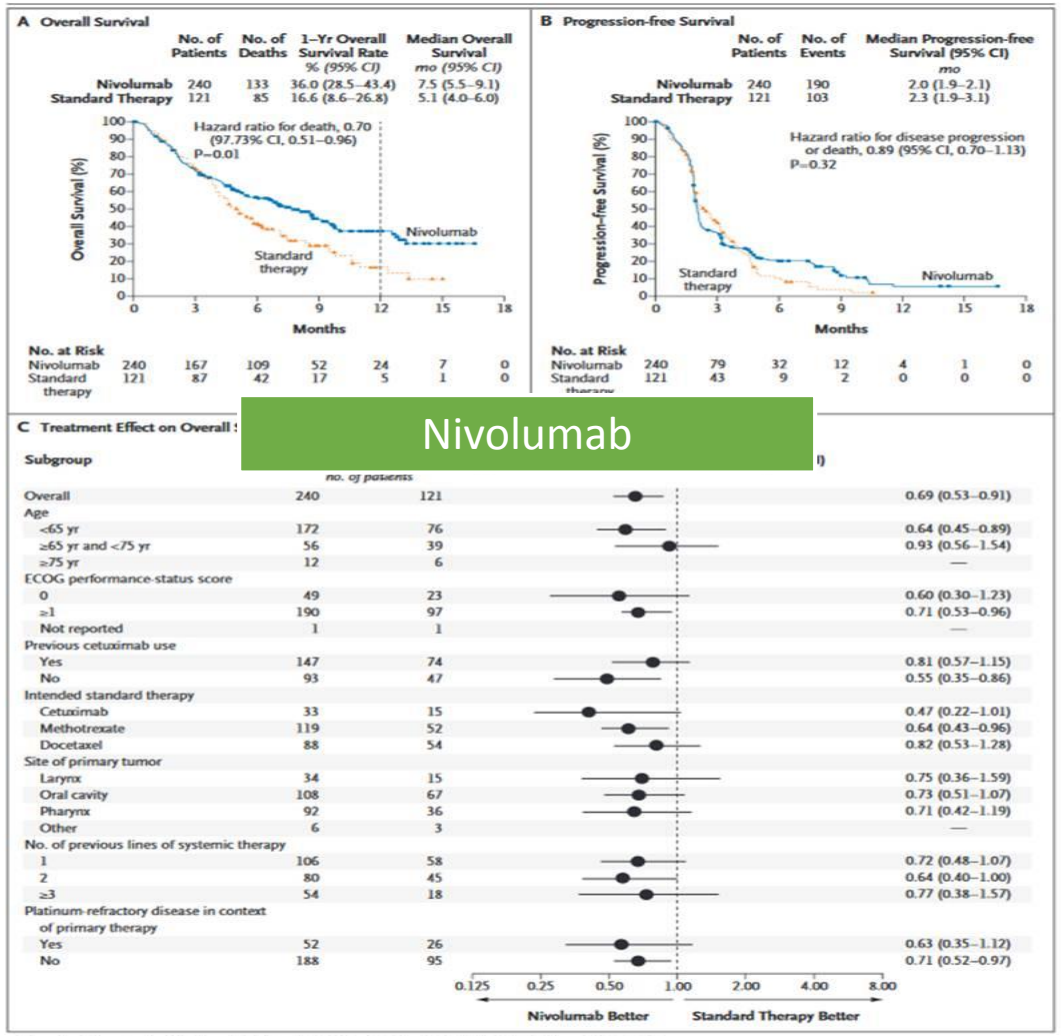
Drug	Approved	Indication	Dose
Pembrolizumab	2016	Recurrent/metastatic HNSCC, progression on/after chemotherapy	200 mg Q3W
Nivolumab	2016	Recurrent/metastatic HNSCC, progression on/after chemotherapy	240 mg Q2W or 480 mg Q4W
Cemiplimab-rwlc	2018	Metastatic cutaneous squamous cell carcinoma, not candidate for curative therapies (any site)	350 mg Q3W
Pembrolizumab + platinum + fluorouracil	2019	Recurrent/metastatic HNSCC 1st line – all patients	200 mg Q3W
Pembrolizumab	2019	Recurrent/metastatic HNSCC 1st line – PD-L1 CPS ≥ 1	200 mg Q3W

PD-1 inhibitors are associated with responses and survival benefit



Pembrolizumab

Bauml J et al. *Journal of Clinical Oncology* 35, no. 14 (May 2017) 1542-1549.



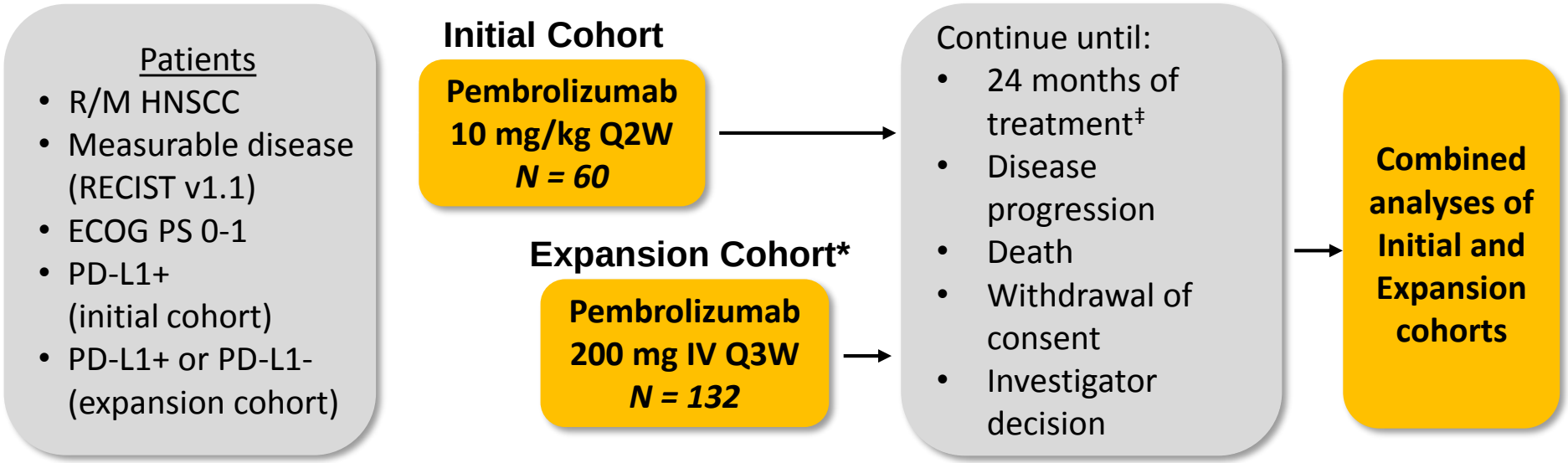
Nivolumab

Ferris RL et al. N Engl J Med 2016. DOI: 10.1056/NEJMoa1602252

Presented by: Charu Aggarwal, MD, MPH

KEYNOTE-012: Pembrolizumab in R/M HNSCC

Nonrandomized, Phase 1b Trial, Cohorts† B, B2



Response assessment: Every 8 weeks until disease progression

Primary end points: ORR (RECIST v1.1, central imaging vendor review), safety

Secondary end points: ORR (investigator), PFS, OS, duration of response (DOR), ORR in HPV+ patients §

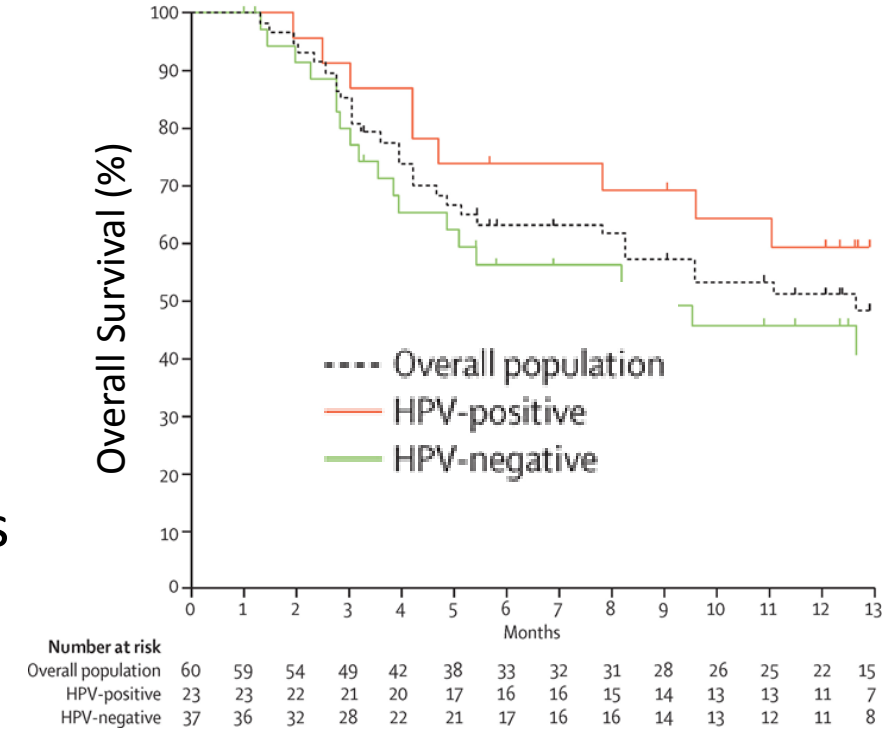
†Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
‡Treatment beyond progression was allowed.
§ Initial cohort only.
*Median duration of disease not reached.

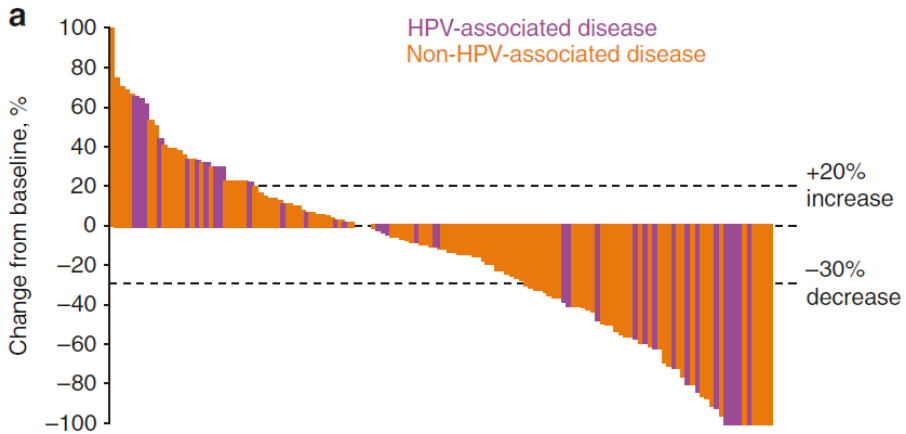
Seiwert, ASCO 2017.

KEYNOTE-012: Pembrolizumab in R/M HNSCC

Nonrandomized, Phase 1b Trial, Cohorts† B, B2

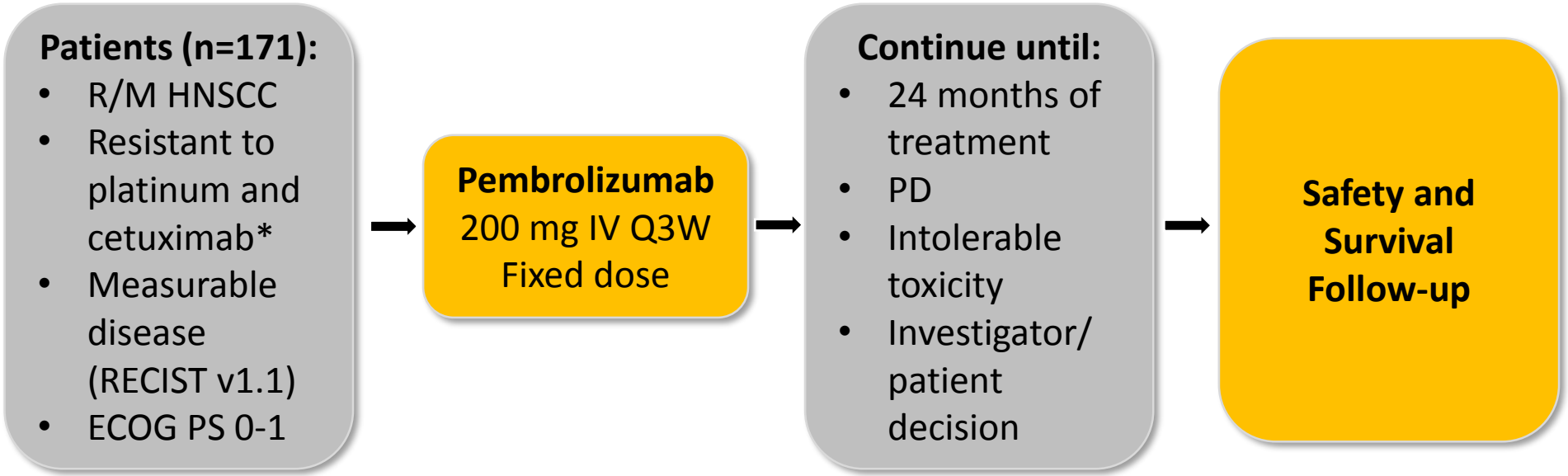
- ORR = 18%
  - CR = 4%
  - PR = 14%
- mOS = 8.0 months
- mPFS = 2.1 months





Seiwert, ASCO 2017.
Mehra, Br J Can 2018.

KEYNOTE-055: Pembrolizumab in R/M HNSCC
Phase II Trial, Single Arm



Response assessment: Imaging every 6 to 9 weeks (central radiology review)

Primary end points: ORR (RECIST v1.1) by Response Evaluation Criteria in Solid Tumors and safety

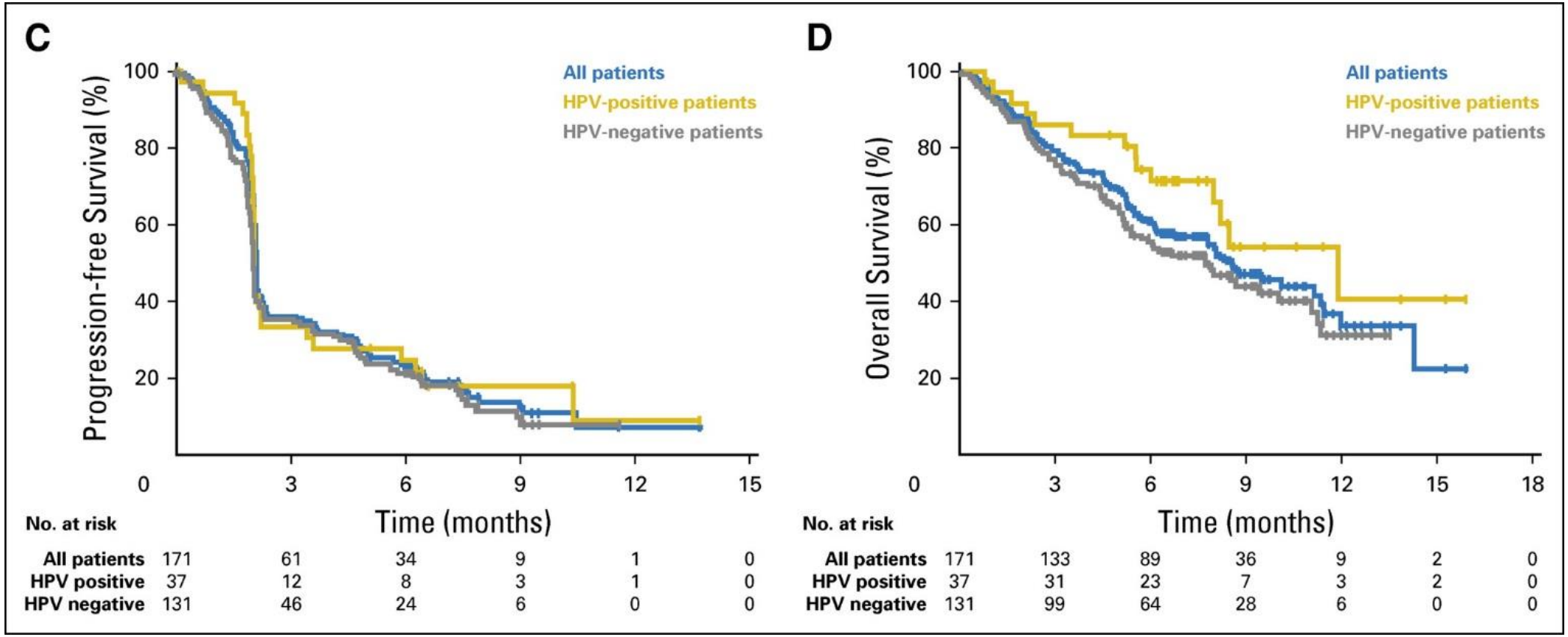
Secondary end points: ORR (RECIST v1.1) in all dosed patients, ORR for HPV+, PD-L1+, DOR, PFS, OS

*75% of patients had ≥ 2 prior lines of therapy for metastatic disease

Bauml, J Clin Oncol 2017.

KEYNOTE-055: Pembrolizumab in R/M HNSCC

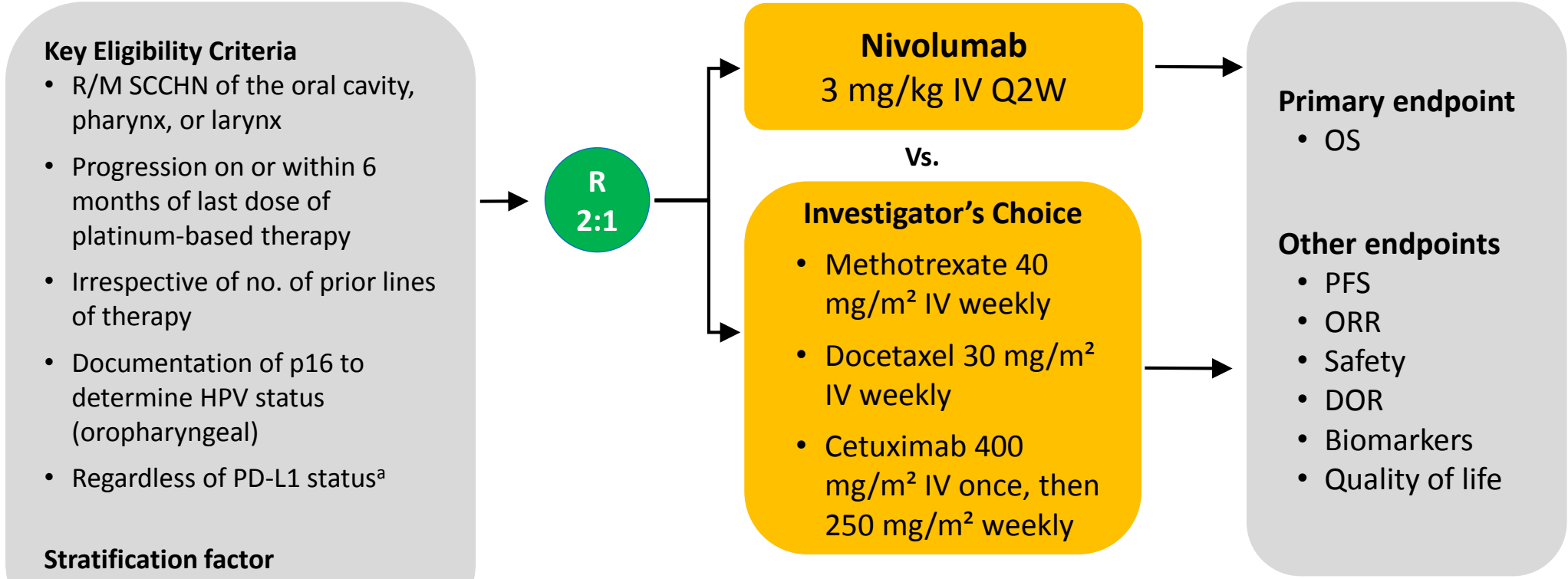
Phase II Trial, Single Arm



Bauml, J Clin Oncol 2017.

CheckMate 141: Nivolumab in R/M HNSCC

Phase III Randomized, Safety and Efficacy Trial



DOR = duration of response; IV = intravenous; ORR = objective response rate; PFS = progression-free survival; Q2W = once every 2 weeks; R = randomized. Clinicaltrials.gov NCT02105636.

[a]Tissue required for testing

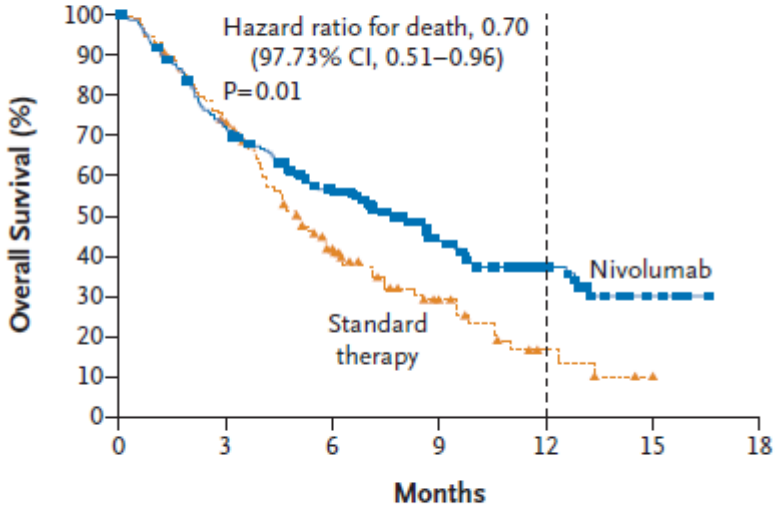
Ferris & Gillison, NEJM 2016.

CheckMate 141: Nivolumab in R/M HNSCC

Phase III Randomized, Safety and Efficacy Trial

A Overall Survival

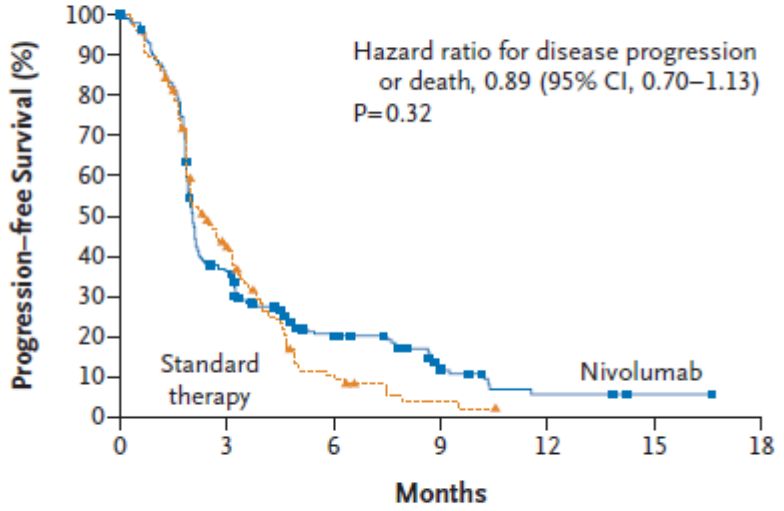
	No. of Patients	No. of Deaths	1–Yr Overall Survival Rate % (95% CI)	Median Overall Survival mo (95% CI)
Nivolumab	240	133	36.0 (28.5–43.4)	7.5 (5.5–9.1)
Standard Therapy	121	85	16.6 (8.6–26.8)	5.1 (4.0–6.0)



No. at Risk							
Nivolumab	240	167	109	52	24	7	0
Standard therapy	121	87	42	17	5	1	0

B Progression-free Survival

	No. of Patients	No. of Events	Median Progression-free Survival (95% CI) mo
Nivolumab	240	190	2.0 (1.9–2.1)
Standard Therapy	121	103	2.3 (1.9–3.1)

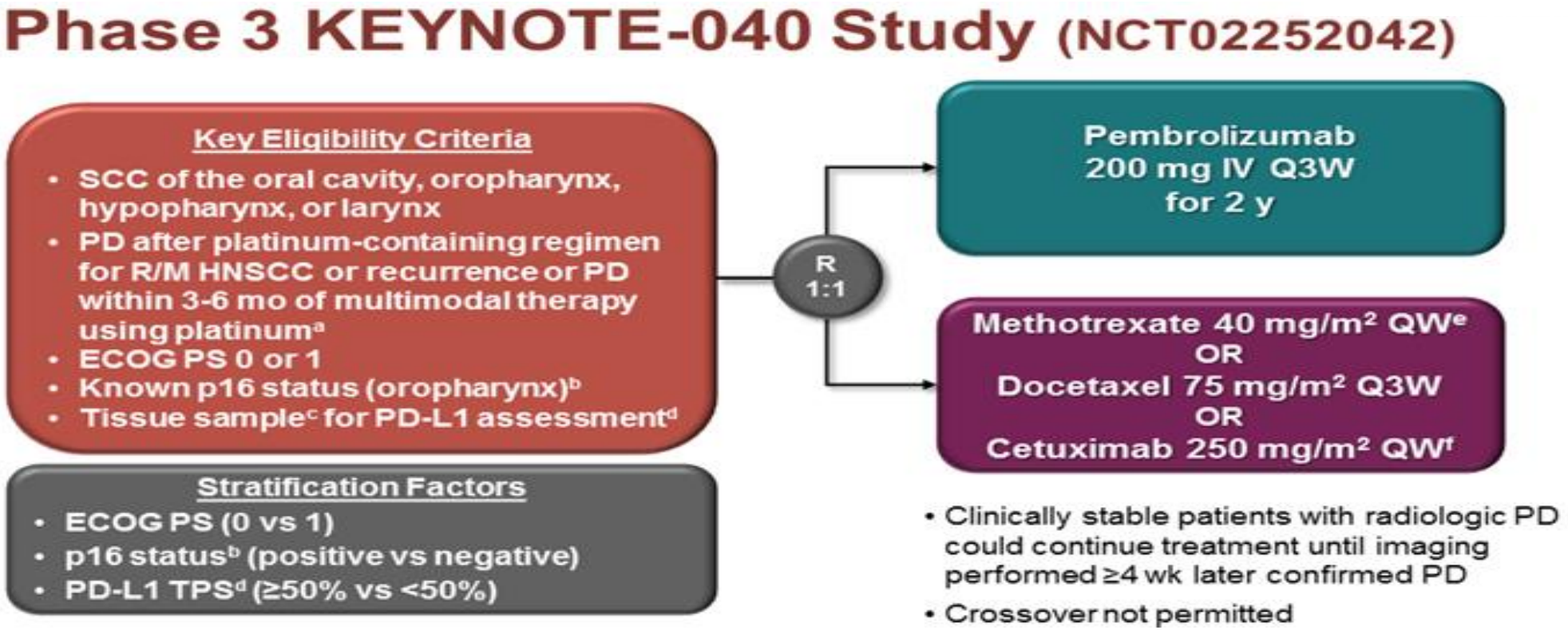


No. at Risk							
Nivolumab	240	79	32	12	4	1	0
Standard therapy	121	43	9	2	0	0	0

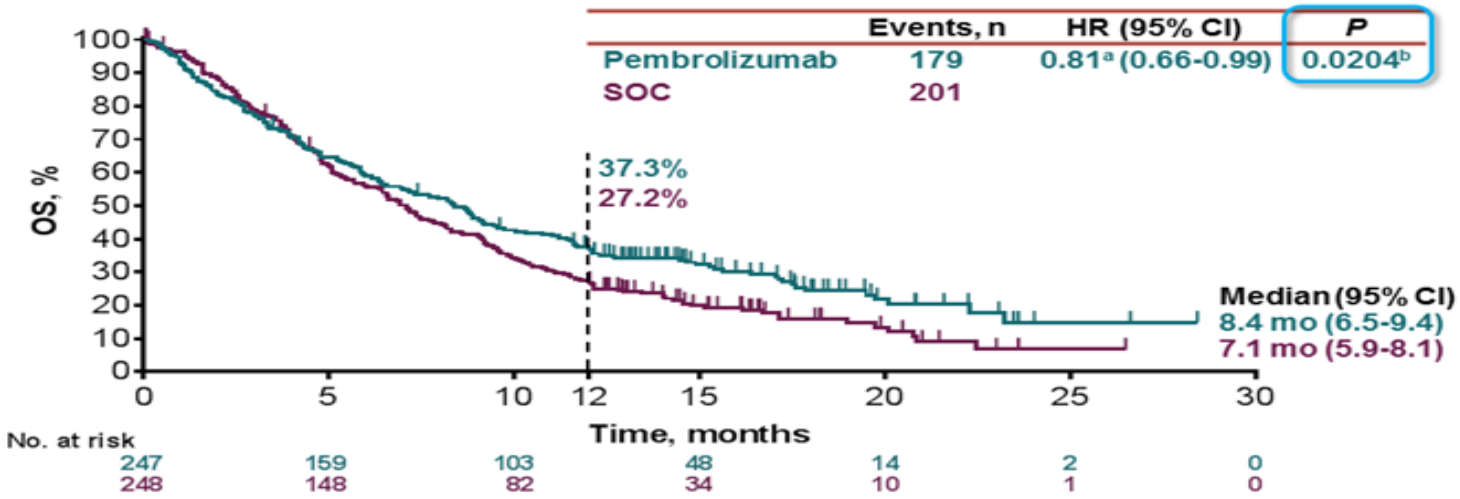
Ferris & Gillison, NEJM 2016.

Keynote 40: Pembrolizumab in R/M HNSCC

Phase III Randomized, Safety and Efficacy Trial

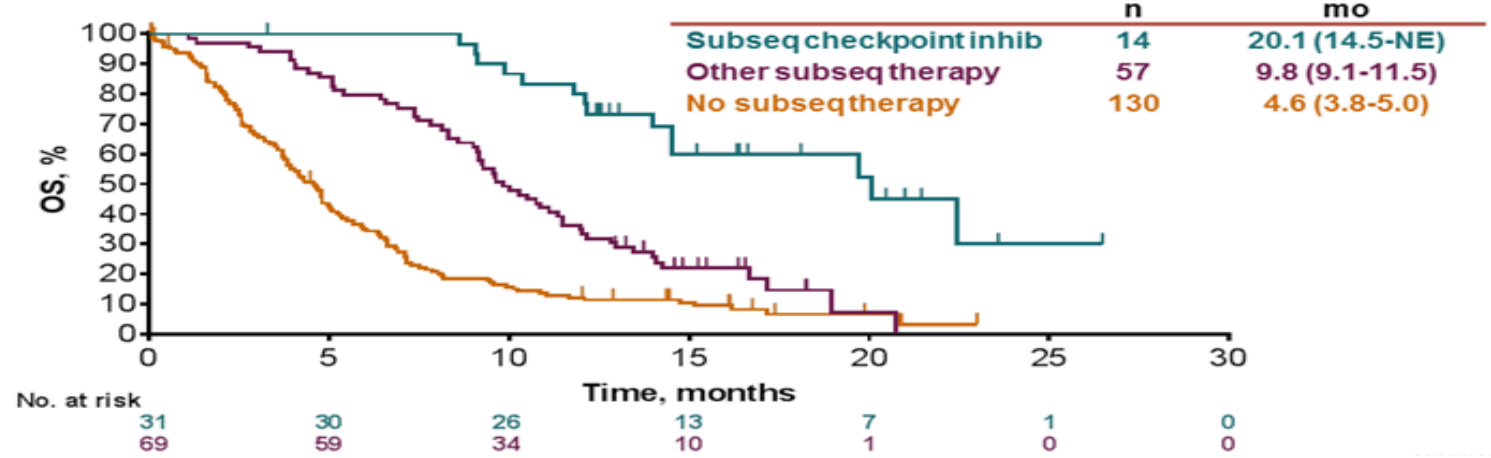


Overall Survival in ITT Population



E Cohen_ESMO 2017

Overall Survival: Effect of Subsequent Immune Checkpoint Inhibitors in the SOC Arm



Cemiplimab in advanced/metastatic cutaneous squamous cell carcinoma

Key Eligibility Criteria

- Advanced cutaneous squamous-cell carcinoma (any site)
- Not eligible for surgery
- ECOG 0-1
- ≥1 assessable lesion

→

Cemiplimab
3 mg/kg IV Q2W

→

Primary endpoint

- Response rate

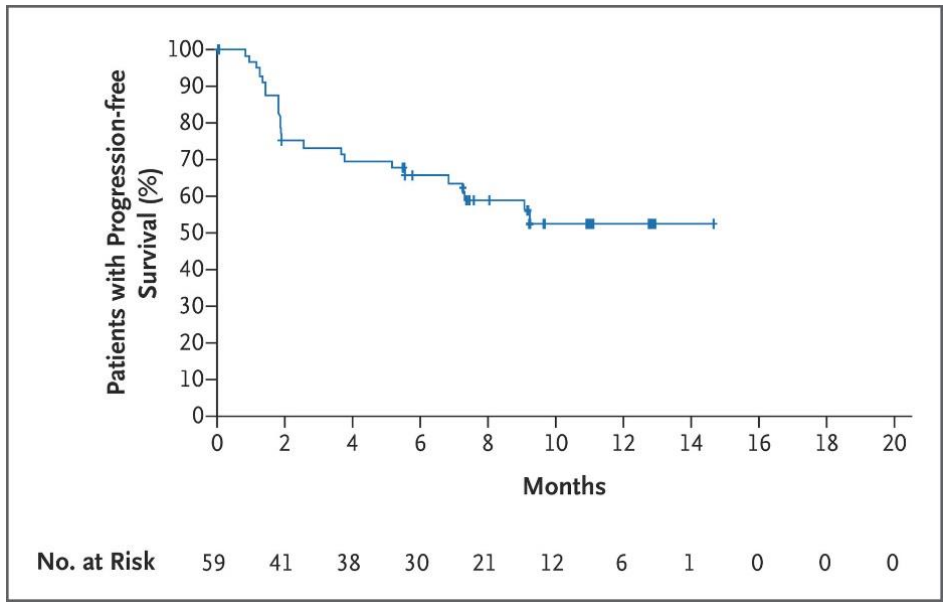
Other endpoints

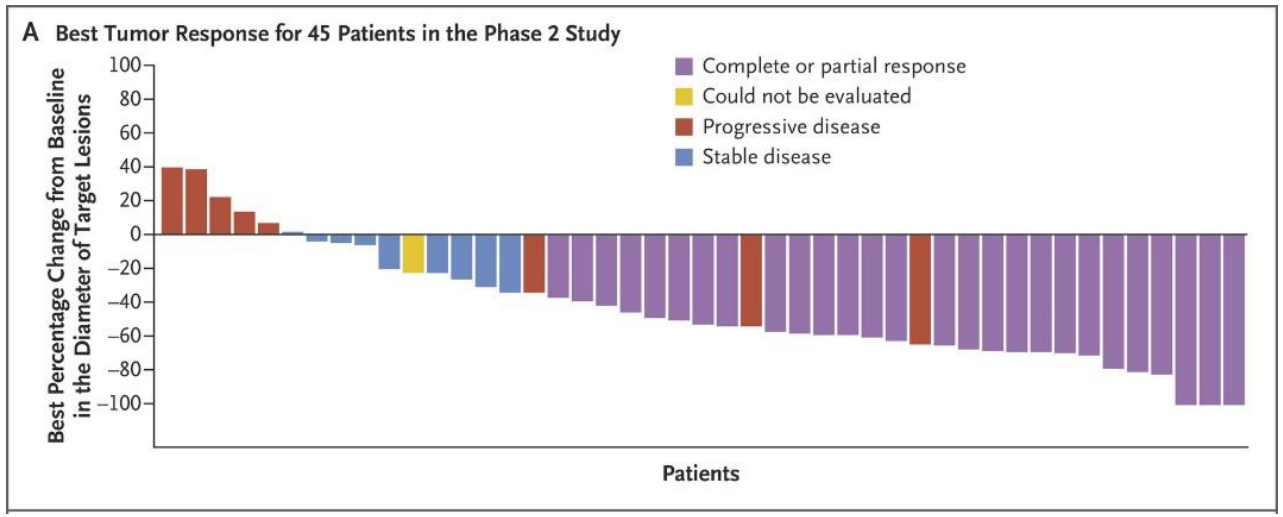
- Duration of response
- PFS
- OS
- Side effects
- Durable disease control

Migden, NEJM 2018.

Cemiplimab in advanced/metastatic cutaneous squamous cell carcinoma

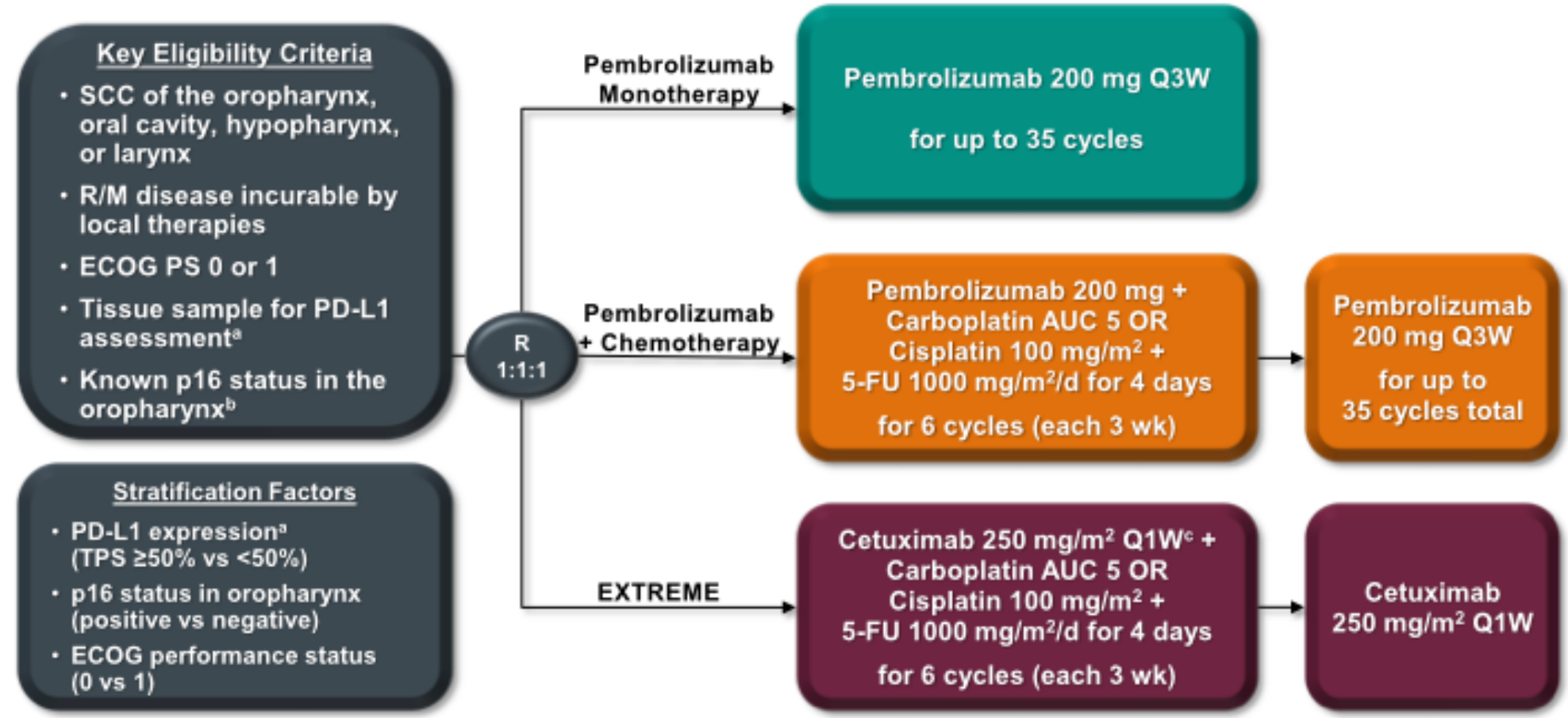
- Cemiplimab 3 mg/kg Q2W
- 47% response rate in metastatic patients
- 60% of locally advanced had objective response





Migden, NEJM 2018.

KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC

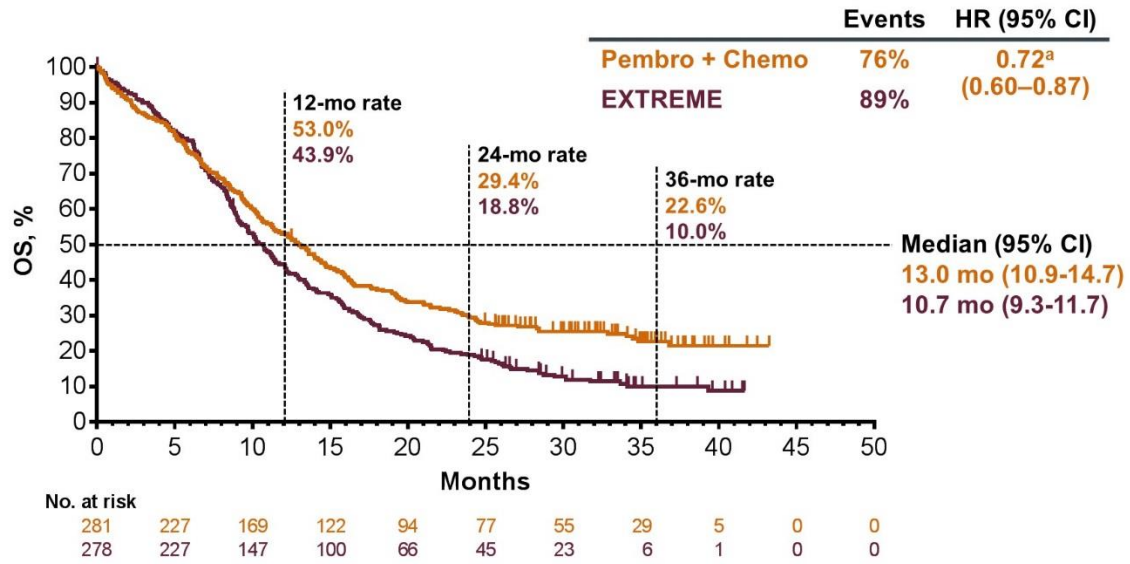


[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Rischin, ASCO 2019.

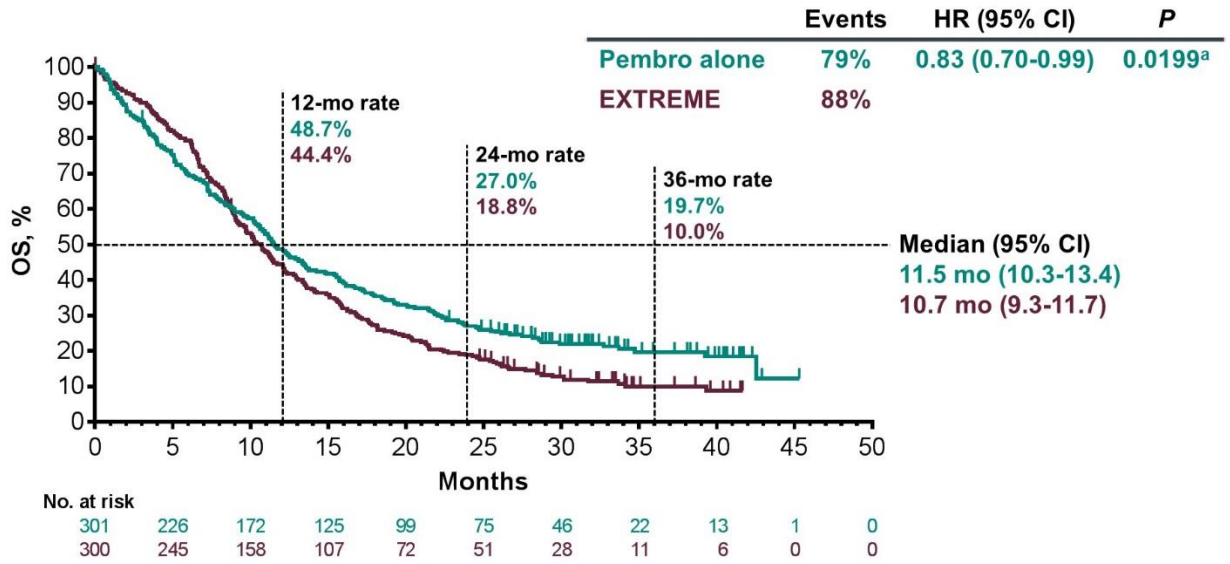
KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC

OS, P+C vs E, Total Population



[a]At IA2 (data cutoff date: Jun 13, 2018): HR 0.77 (95% CI 0.53–0.93).
FA (data cutoff date: Feb 25, 2019).

OS, P vs E, Total Population

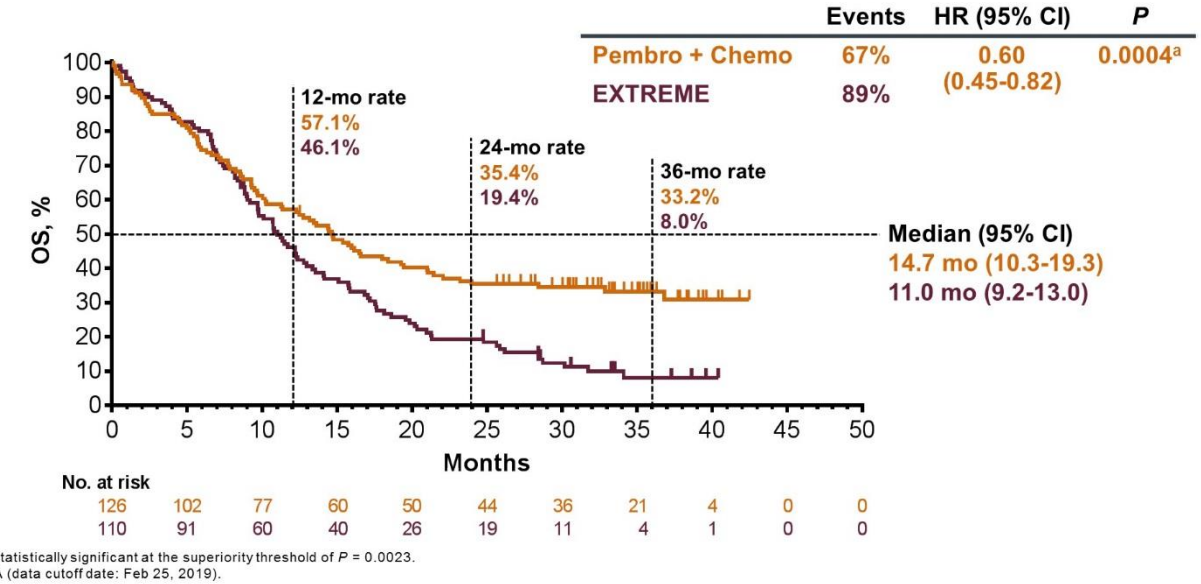


[a]Not statistically significant at the superiority threshold of $P = 0.0059$.
FA (data cutoff date: Feb 25, 2019).

Rischin, ASCO 2019.

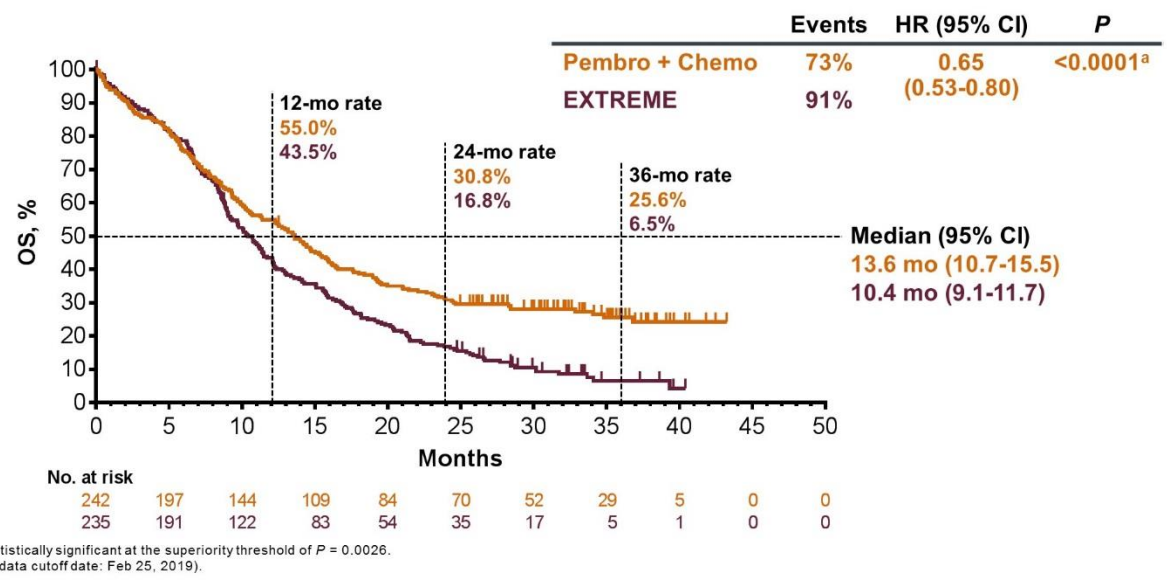
KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC

OS, P+C vs E, CPS ≥20 Population



[a]Statistically significant at the superiority threshold of $P = 0.0023$.
FA (data cutoff date: Feb 25, 2019).

OS, P+C vs E, CPS ≥1 Population

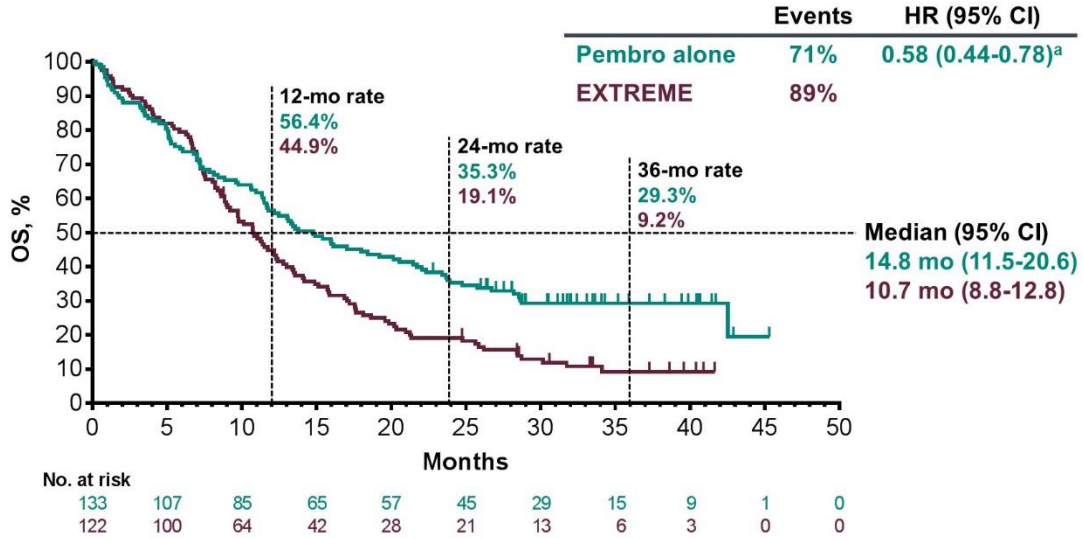


[a]Statistically significant at the superiority threshold of $P = 0.0026$.
FA (data cutoff date: Feb 25, 2019).

Rischin, ASCO 2019.

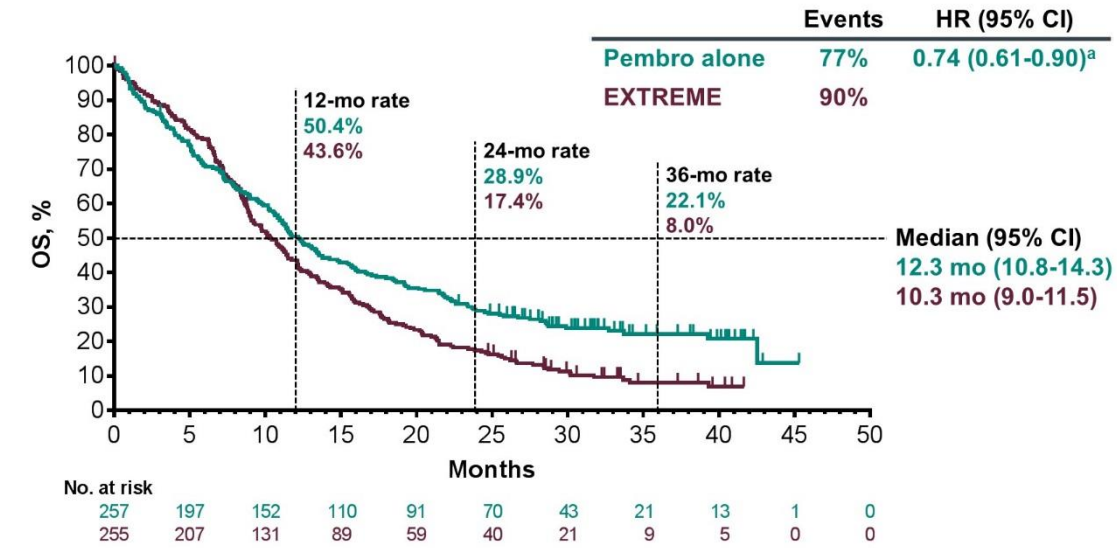
KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC

OS, P vs E, CPS ≥20 Population



[a]At IA2 (data cutoff date: Jun 13, 2018): HR 0.61 (95% CI 0.45–0.83).
FA (data cutoff date: Feb 25, 2019).

OS, P vs E, CPS ≥1 Population

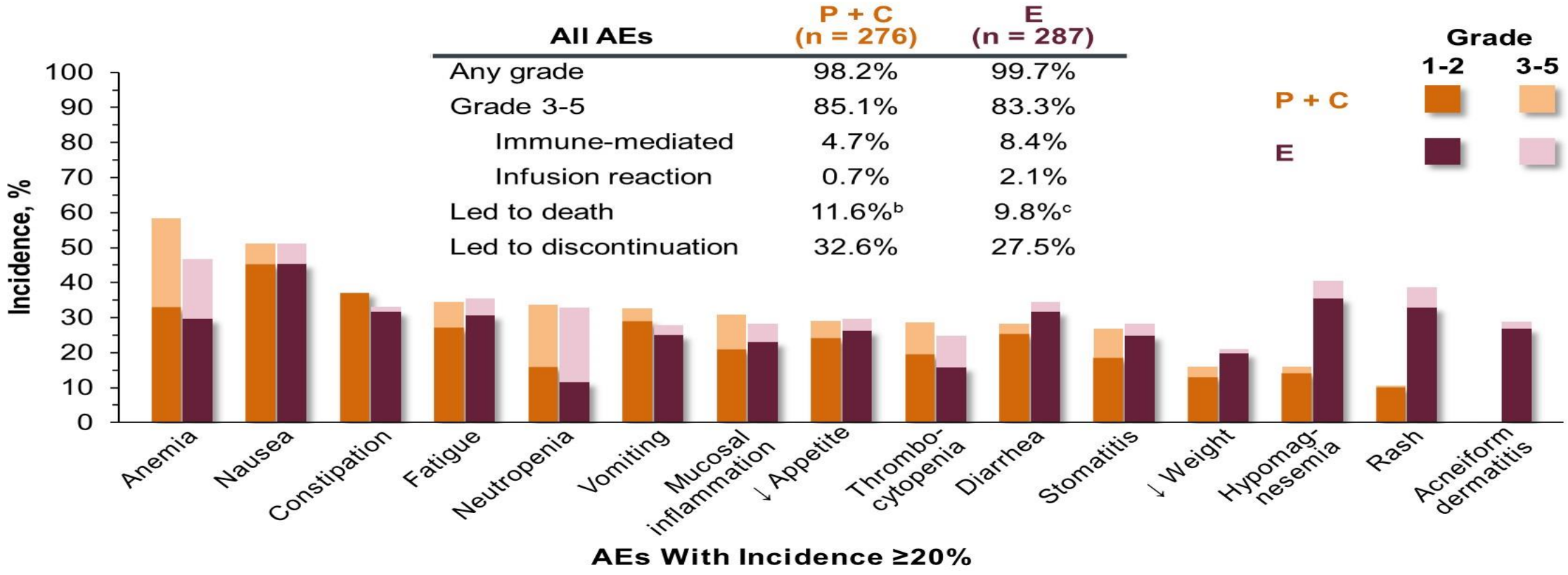


[a]At IA2 (data cutoff date: Jun 13, 2018): HR 0.78 (95% CI 0.64–0.96).
FA (data cutoff date: Feb 25, 2019).

Rischin, ASCO 2019.

All-Cause AEs,[a] P + C vs E, Total Population

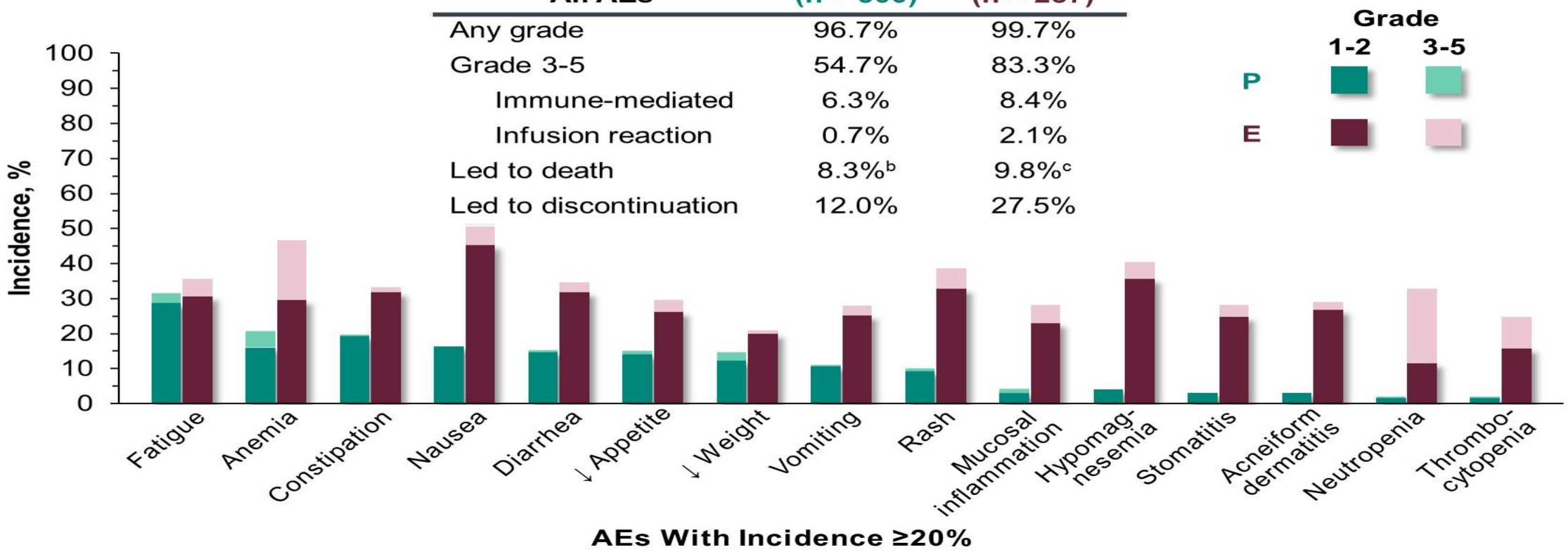
All AEs	P + C (n = 276)	E (n = 287)
Any grade	98.2%	99.7%
Grade 3-5	85.1%	83.3%
Immune-mediated	4.7%	8.4%
Infusion reaction	0.7%	2.1%
Led to death	11.6%[b]	9.8%[c]
Led to discontinuation	32.6%	27.5%



[a]Data for treatment-related AEs were presented at ESMO 2018. [b]Events were considered treatment related in 4.0%. [c]Events were considered treatment related in 2.8%. FA (data cutoff date: Feb 25, 2019).

All-Cause AEs,[a] P vs E, Total Population

All AEs	P (n = 300)	E (n = 287)
Any grade	96.7%	99.7%
Grade 3-5	54.7%	83.3%
Immune-mediated	6.3%	8.4%
Infusion reaction	0.7%	2.1%
Led to death	8.3%[b]	9.8%[c]
Led to discontinuation	12.0%	27.5%



AEs With Incidence ≥20%

[a]Data for treatment-related AEs were presented at ESMO 2018. [b]Events were considered treatment related in 1.0%. [c]Events were considered treatment related in 2.8%. FA (data cutoff date: Feb 25, 2019).

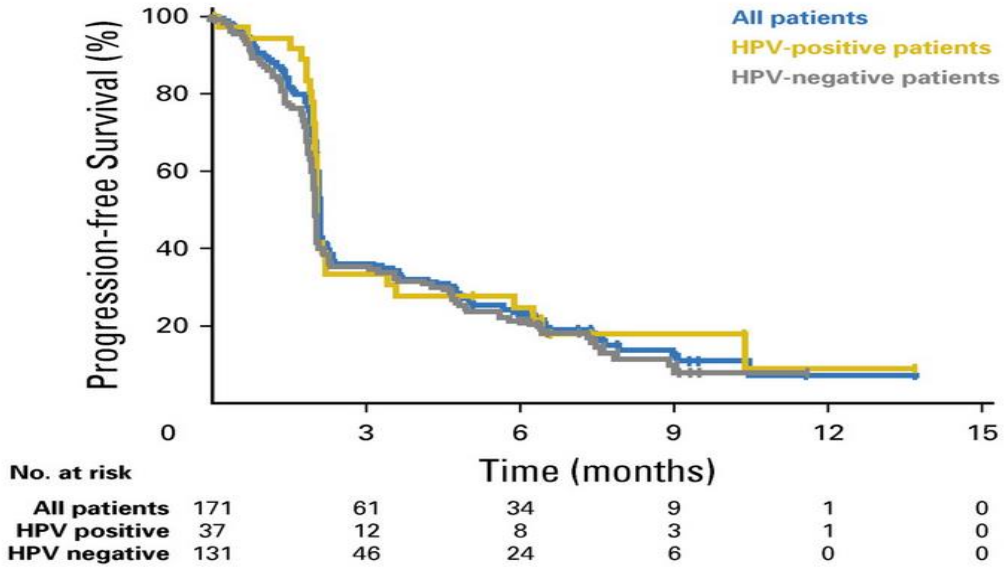
KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC

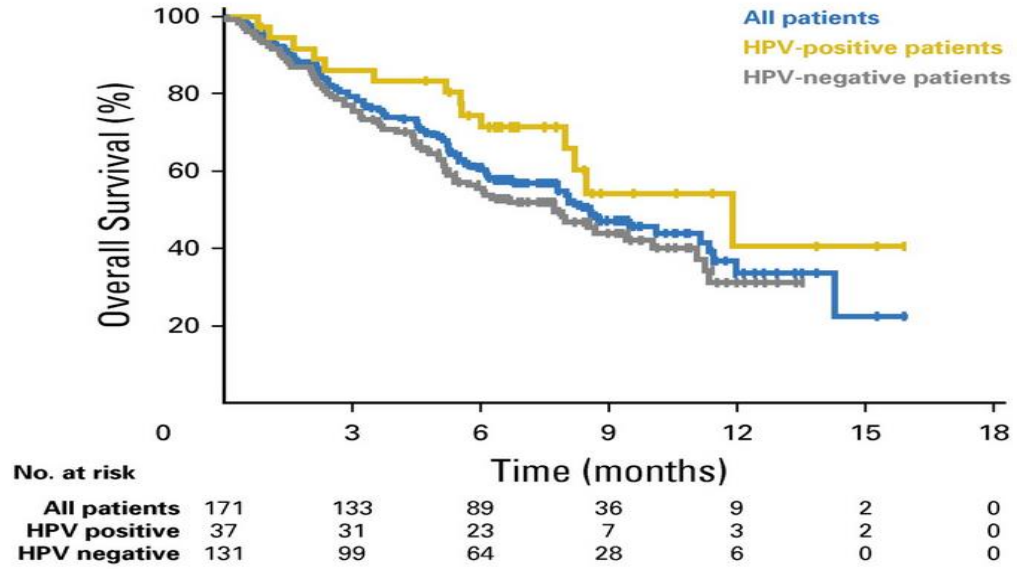
Population	IA2[1] HR (95% CI)	FA HR (95% CI)
Pembrolizumab monotherapy vs EXTREME		
PD-L1 CPS ≥20	0.61 (0.45–0.83); *P* = 0.0007[a]	0.58 (0.44–0.78)[c]
PD-L1 CPS ≥1	0.78 (0.64–0.96); *P* = 0.0086[a]	0.74 (0.61–0.90)[c]
Total	0.85 (0.71–1.03)[b]	0.83 (0.70–0.99); *P* = 0.0199[d]
Pembrolizumab + chemotherapy vs EXTREME		
PD-L1 CPS ≥20	—	0.60 (0.45–0.82); *P* = 0.0004[a]
PD-L1 CPS ≥1	—	0.65 (0.53–0.80); *P* < 0.0001[a]
Total	0.77 (0.63–0.93); *P* = 0.0034[a,b]	0.72 (0.60–0.87)[c]

Rischin, ASCO 2019.

Biomarkers

PD-1 inhibitors do not seem to have improved efficacy in HPV+ ds

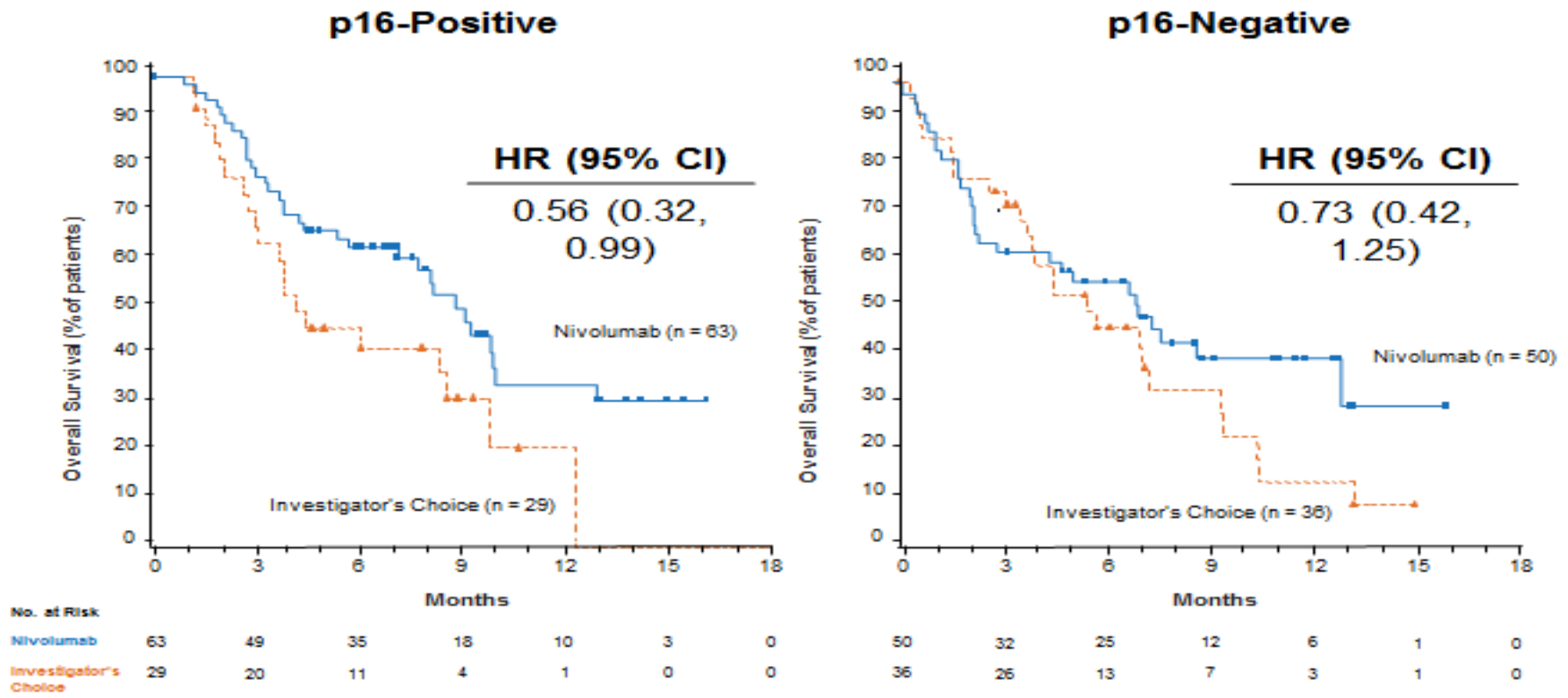




	HPV +	HPV -
N	100	71
RR	16%	15%
6 mo PFS %	25%	21%
6 mo OS %	72%	55%

Bauml et al, JCO 2017

PD-1 inhibitors do not seem to have improved efficacy in HPV+ ds



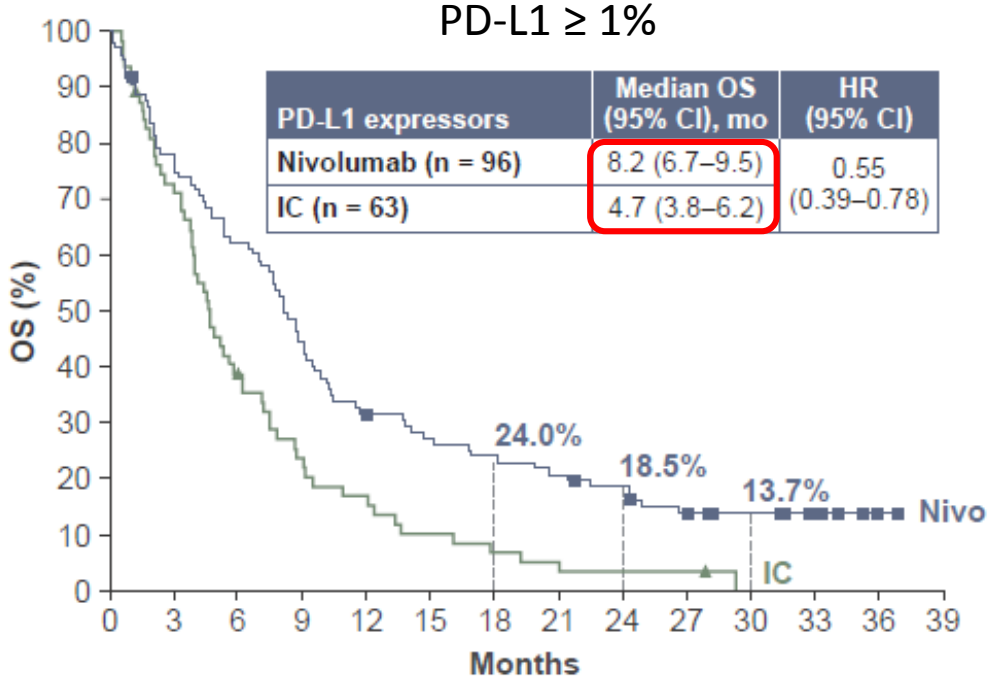
- HR seems to be improved for p16+ patients
- It is important to remember that these curves compare Nivo to chemotherapy
- There does not seem to be a dramatic difference between p16+ and p16 – patients that receive Nivolumab

Ferris RL et al, NEJM 2016

PD-1 inhibitor efficacy by PD-L1 status

CheckMate 141: 2 year update

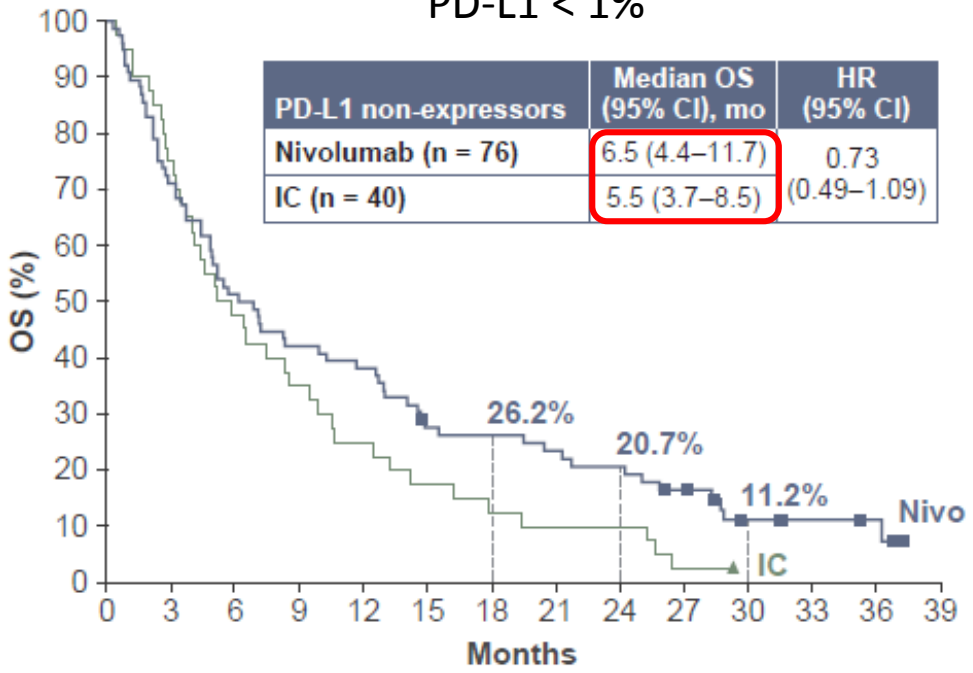
PD-L1 ≥ 1%



PD-L1 expressors	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 96)	8.2 (6.7–9.5)	0.55 (0.39–0.78)
IC (n = 63)	4.7 (3.8–6.2)	

No. at risk														
Nivo	96	74	59	42	30	25	22	19	16	11	8	5	1	0
IC	63	45	24	14	10	6	4	3	2	2	0	0	0	0

PD-L1 < 1%



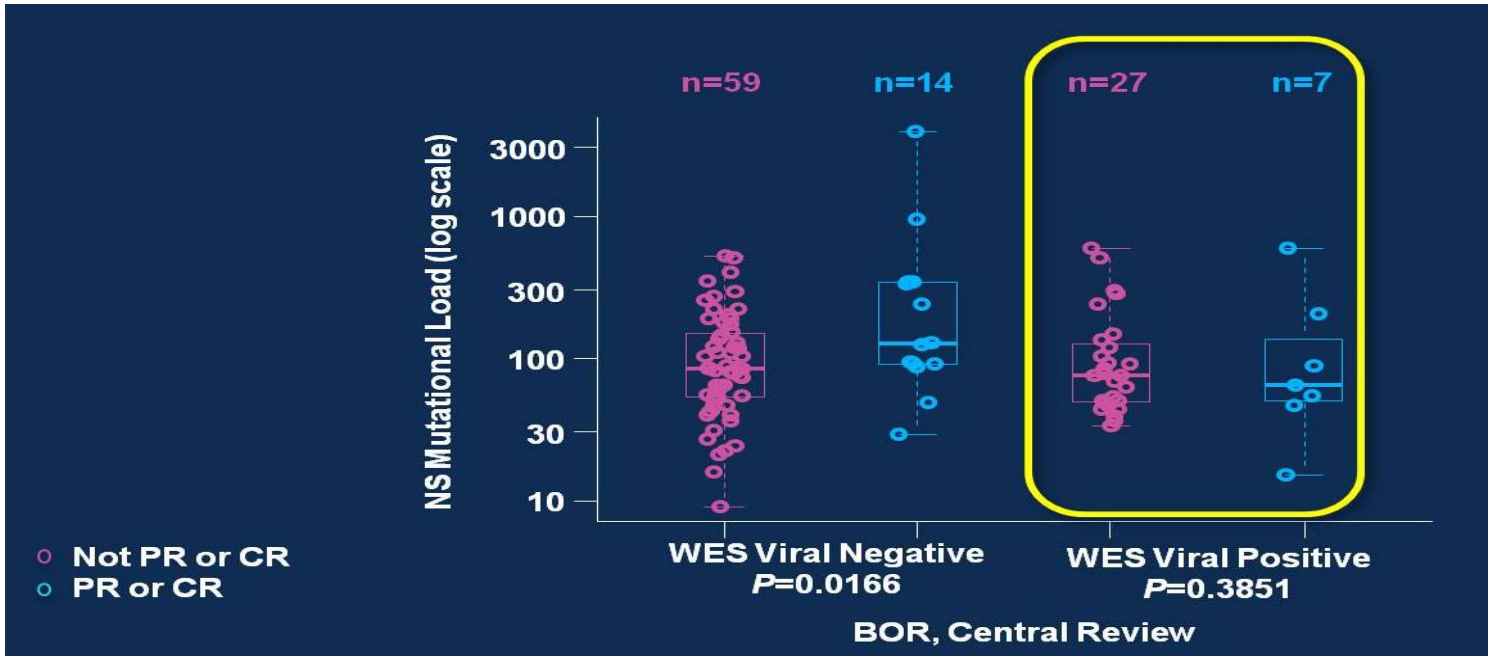
PD-L1 non-expressors	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 76)	6.5 (4.4–11.7)	0.73 (0.49–1.09)
IC (n = 40)	5.5 (3.7–8.5)	

No. at risk														
Nivo	76	54	39	32	29	20	19	17	15	11	5	4	3	0
IC	40	30	19	14	10	7	5	4	4	1	0	0	0	0

Ferris, Oral Oncol 2018.

Evaluating Other Biomarkers in HNSCC

- Patient samples from 2 HNSCC cohorts of KN-012 were analyzed
- 107 patients with WES data were analyzed
- B1=34 (PDL-1 positive) and B2=73 (PDL-1 unselected)
- Correlation with BOR (Central Review), PFS
- Other measures: GEP, NL, Clonality



ML does not correlate with response in HPV/EBV + patients

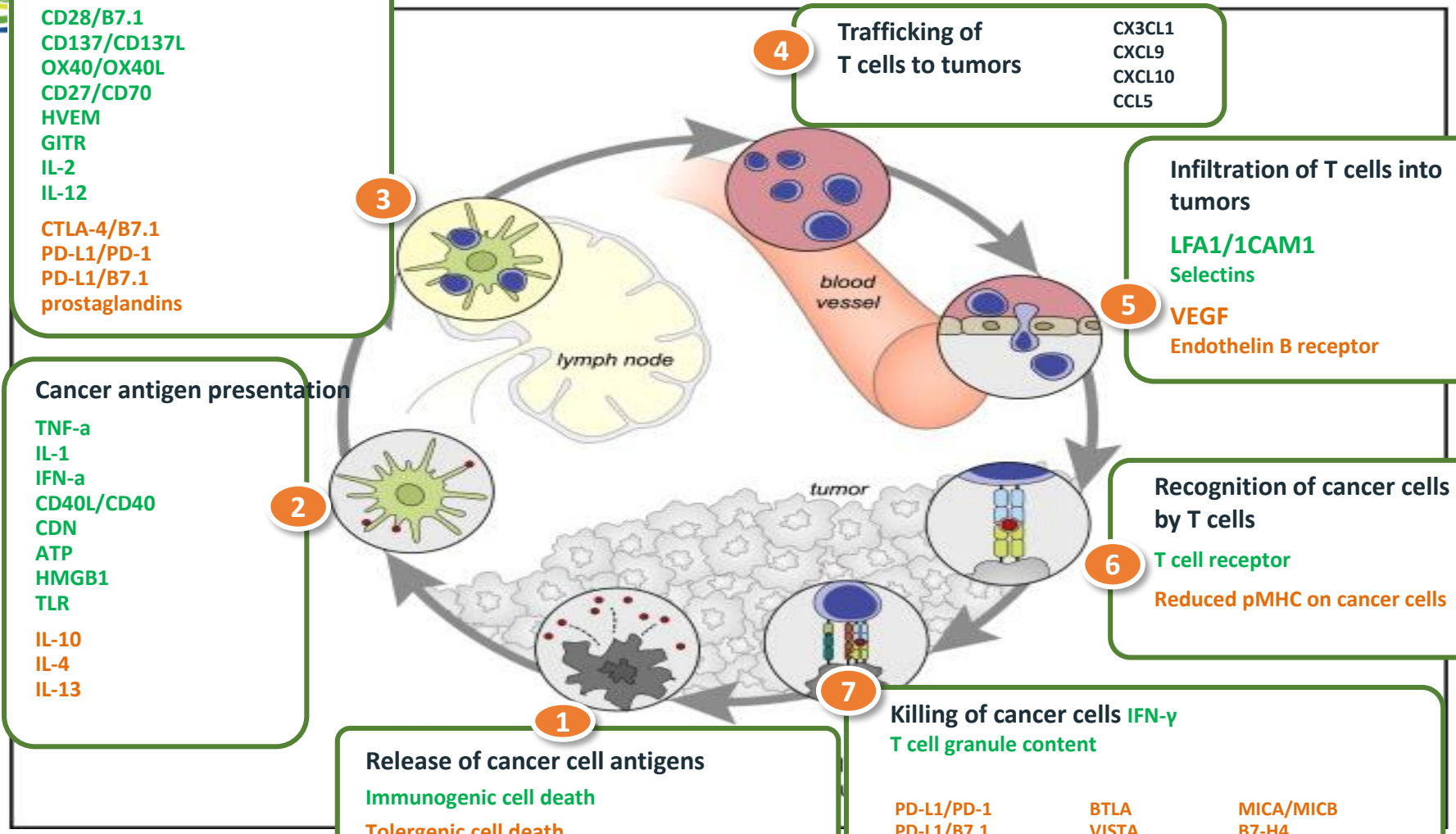
Presented By Robert Haddad at 2017 ASCO Annual Meeting

Biomarkers in HNSCC

- Only indication that relies on PD-L1 expression: pembrolizumab monotherapy in 1st line HNSCC – CPS ≥ 1 (KEYNOTE-048)

- All other approvals INdependent on PD-L1 expression
  - KEYNOTE-012/055: Response rates not significantly different on the basis of tumor PD-L1 staining
  - Checkmate 141: Higher benefit seen in PD-L1 positive tumors
  - KEYNOTE-040: pembrolizumab vs investigator's choice chemotherapy – did not meet survival endpoints in total population but improved outcomes in PD-L1-expressors

Cancer Immunity Cycle



Priming & activation

- CD28/B7.1
- CD137/CD137L
- OX40/OX40L
- CD27/CD70
- HVEM
- GITR
- IL-2
- IL-12
- CTLA-4/B7.1
- PD-L1/PD-1
- PD-L1/B7.1
- prostaglandins

Cancer antigen presentation

- TNF-a
- IL-1
- IFN-a
- CD40L/CD40
- CDN
- ATP
- HMGB1
- TLR
- IL-10
- IL-4
- IL-13

Release of cancer cell antigens

- Immunogenic cell death
- Tolergenic cell death

Trafficking of T cells to tumors

- CX3CL1
- CXCL9
- CXCL10
- CCL5

Infiltration of T cells into tumors

- LFA1/1CAM1
- Selectins
- VEGF
- Endothelin B receptor

Recognition of cancer cells by T cells

- T cell receptor
- Reduced pMHC on cancer cells

Killing of cancer cells IFN-γ

- T cell granule content
- PD-L1/PD-1
- PD-L1/B7.1
- IDO
- TGF-β
- BTLA
- VISTA
- LAG3
- Arginase
- MICA/MICB
- B7-H4
- TIM3/ phospholipids

■ Stimulatory factors
■ Inhibitors

Chen DS, Mellman I. *Immunity.* 2013;39:1-10.

Conclusions

- Checkpoint inhibitors that target the PD-1 axis, nivolumab and pembrolizumab, are approved in platinum-refractory/exposed recurrent/metastatic HNSCC.
- Nivolumab and pembrolizumab are in general better tolerated than cytotoxic chemotherapy, and lead to improved overall survival.
- Combination chemo + immunotherapy is a feasible approach for all comers with R/M disease.
- Ongoing areas of research include: combinations of immunotherapy with radiation and/or other drugs, development of predictive biomarkers and approaches to overcoming resistance.

Resources

Cohen *et al. Journal for ImmunoTherapy of Cancer* (2019) 7:184
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Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES Open Access

The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of squamous cell carcinoma of the head and neck (HNSCC)

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Case Studies

Case 1

67 year old male stage III (8th edition AJCC) HPV associated Squamous Cell Cancer of right base of tongue, is treated with definitive cisplatin based chemo-radiation therapy. Six months later, the patient presents with diffuse mediastinal lymphadenopathy and liver metastases. What is the next step?

1. Order PET Scan
2. Order biopsy, and p16 testing
3. Order PET, biopsy, p16 testing and CPS PD-L1 testing
4. Order PET, biopsy, p16 testing, CPD PD-L1 and NGS testing

Case 1

67 year old male stage III (8th edition AJCC) HPV associated Squamous Cell Cancer of right base of tongue, is treated with definitive cisplatin based chemoradiation therapy. Six months later, the patient presents with diffuse mediastinal lymphadenopathy and liver metastases.

PET CT confirms metastatic disease. Biopsy of the liver metastases show squamous cell cancer, p16+, PD-L1 CPS is 30%. Which of the following is not the correct step in management?

1. Immunotherapy with Pembrolizumab + carboplatin and 5FU
2. Immunotherapy with Pembrolizumab
3. Immunotherapy with Nivolumab
4. Chemotherapy with carboplatin, 5FU, cetuximab

Case 2

55 year old patient with Stage IVA Larynx Cancer undergoes surgery and adjuvant chemotherapy with radiation. He then presented with local recurrence 8 months after, and is seen in the clinic for next steps.

He does not have a significant burden of disease, and tissue biopsy of a neck node is consistent with recurrent SCCa.

PD-L1 CPS is 40%

What is your preferred therapeutic approach?

Case 2

55 year old patient with Stage IVA Larynx Cancer undergoes surgery and adjuvant chemotherapy with radiation. He then presented with local recurrence 8 months after, and is seen in the clinic for next steps.

He does not have a significant burden of disease, and tissue biopsy of a neck node is consistent with recurrent SCCa.

PD-L1 CPS is 0%

What is your preferred therapeutic approach?

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Thank you!