

Immunotherapy for the Treatment of Head and Neck Cancer

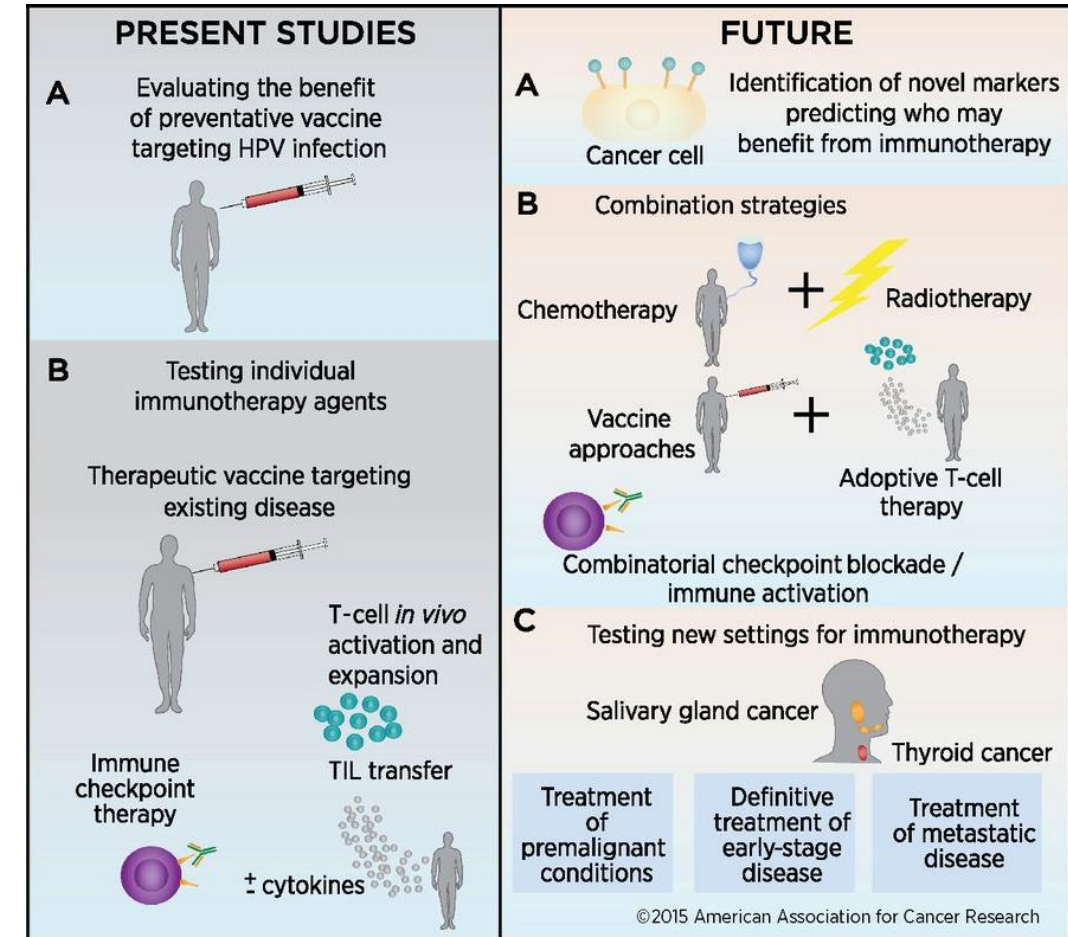
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Disclosures

- I served for scientific advisory board for Genentech, Bayer and GSK
- I will be discussing non-FDA approved indications during my presentation.

Immunotherapy for the Treatment of Head and Neck Cancers

- Immuno-Oncology (I-O) developments in treatment of head and neck cancers
 - Expression of immunologic markers to guide treatment
 - Preventive vaccination against virally mediated cancers
 - Therapeutic vaccines for established cancers
 - CAR-T and cell-mediated therapies
 - Combinations with immunotherapies

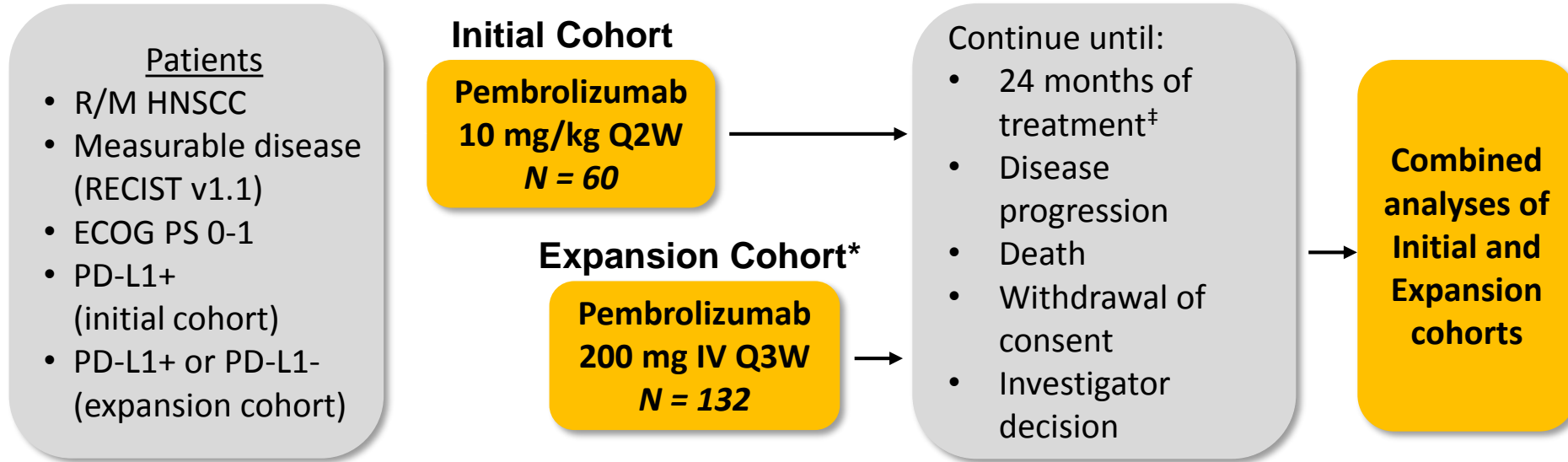


Approved checkpoint inhibitors in Head and Neck Cancers

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 1 st line – all patients	200 mg Q3W
Pembrolizumab	2019	Recurrent/metastatic HNSCC 1 st line – PD-L1 CPS ≥ 1	200 mg Q3W
Pembrolizumab	2019	Recurrent locally advanced/metastatic squamous cell carcinoma of esophagus (PD-L1 CPS ≥ 10)	200 mg Q3W

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.

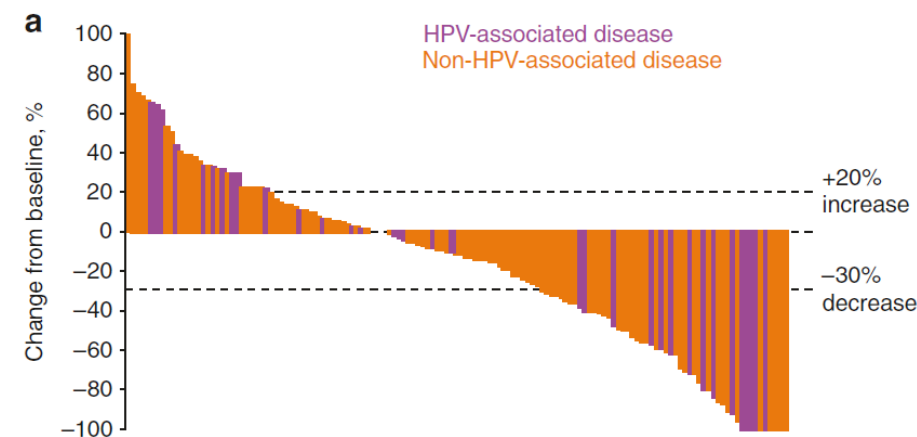
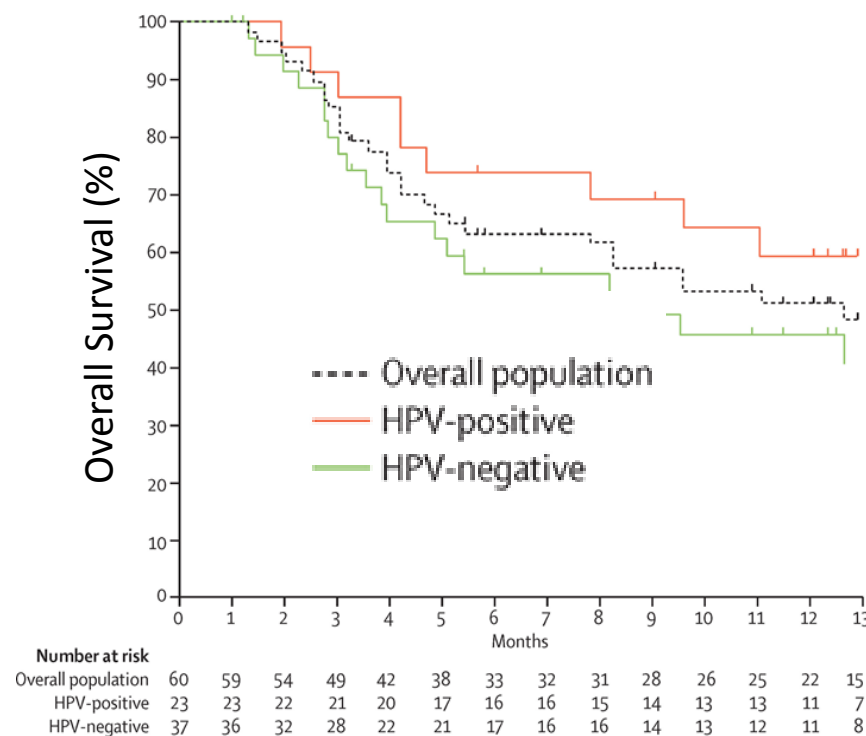
[§] Initial cohort only.

*Median duration of disease not reached.

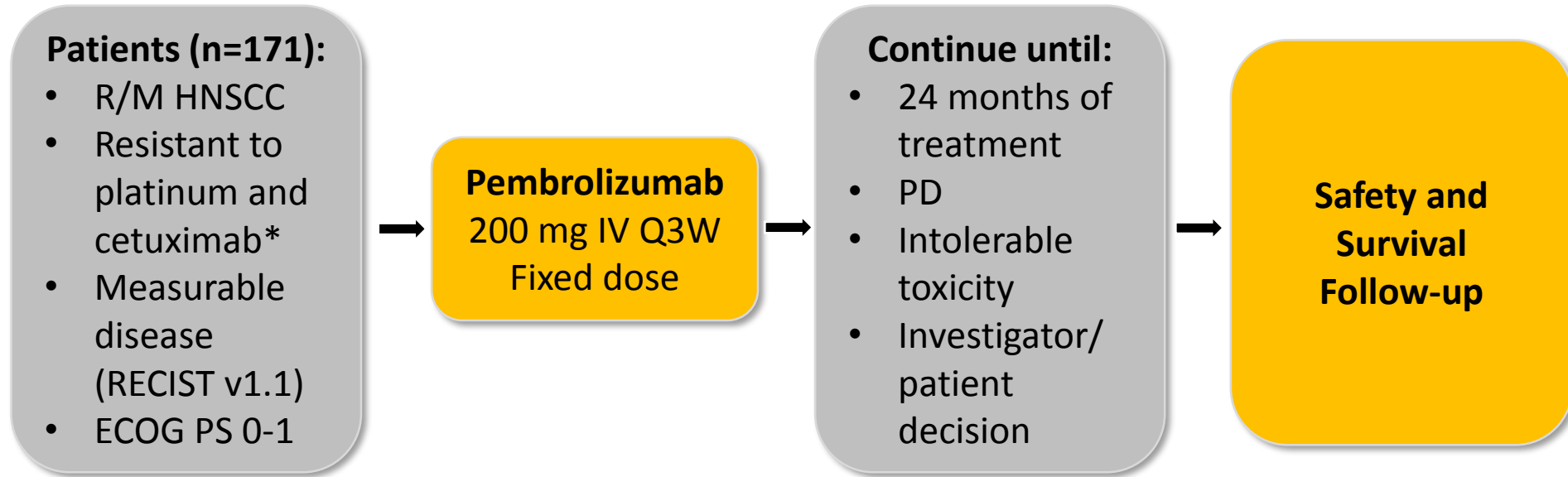
KEYNOTE-012: Pembrolizumab in R/M HNSCC

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

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



KEYNOTE-055: Pembrolizumab in R/M HNSCC after Progression on Platinum/Cetuximab Phase II Trial, Single Arm



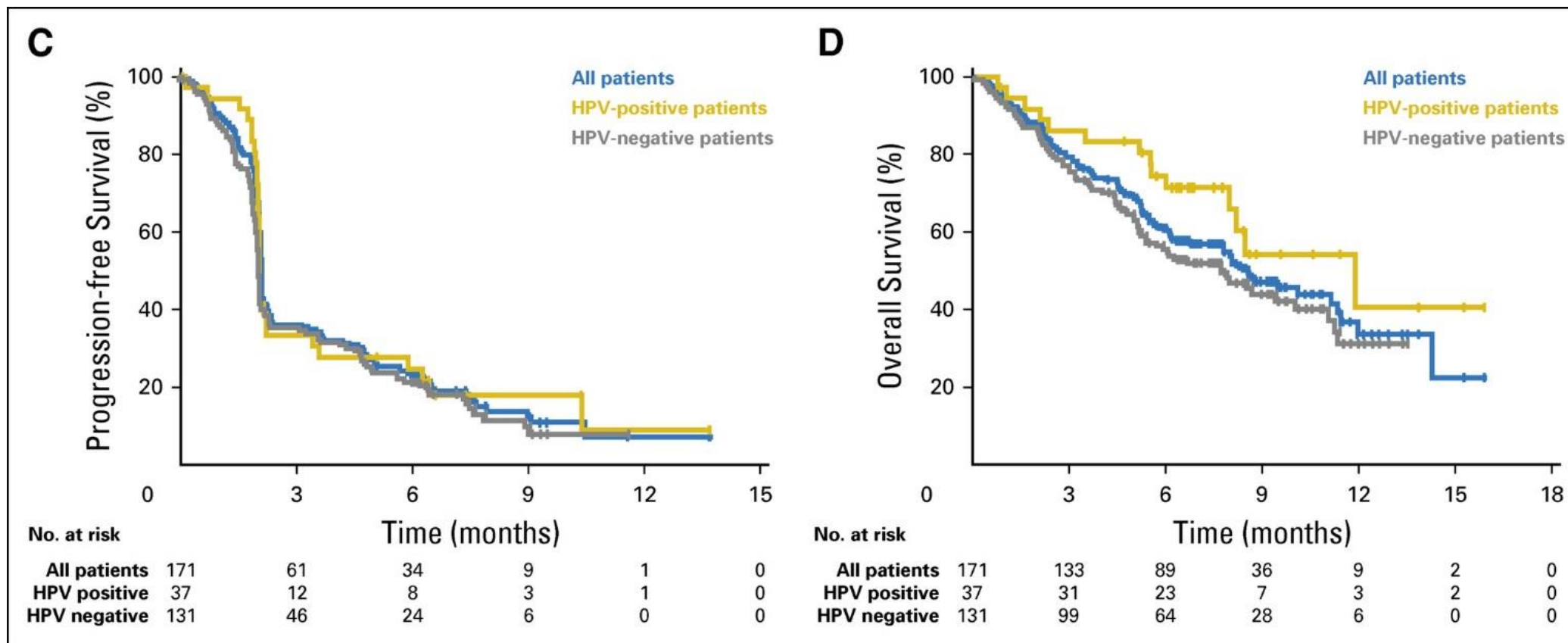
Response assessment: Imaging every 6 to 9 weeks (central radiology review)

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

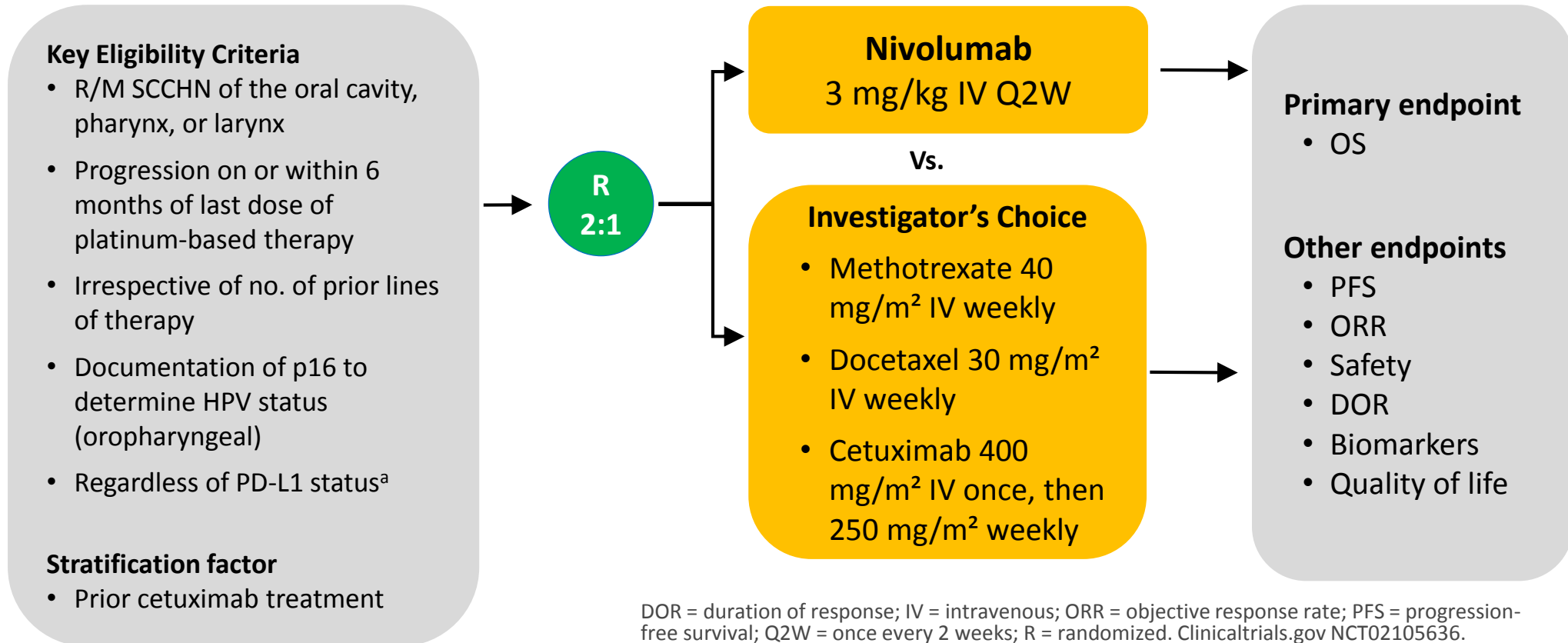
Secondary end points: ORR (RECIST v1.1) in all dosed patients, ORR for HPV+, PD-L1+, DOR, PFS, OS

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

KEYNOTE-055: Pembrolizumab in R/M HNSCC after Progression on Platinum/Cetuximab Phase II Trial, Single Arm



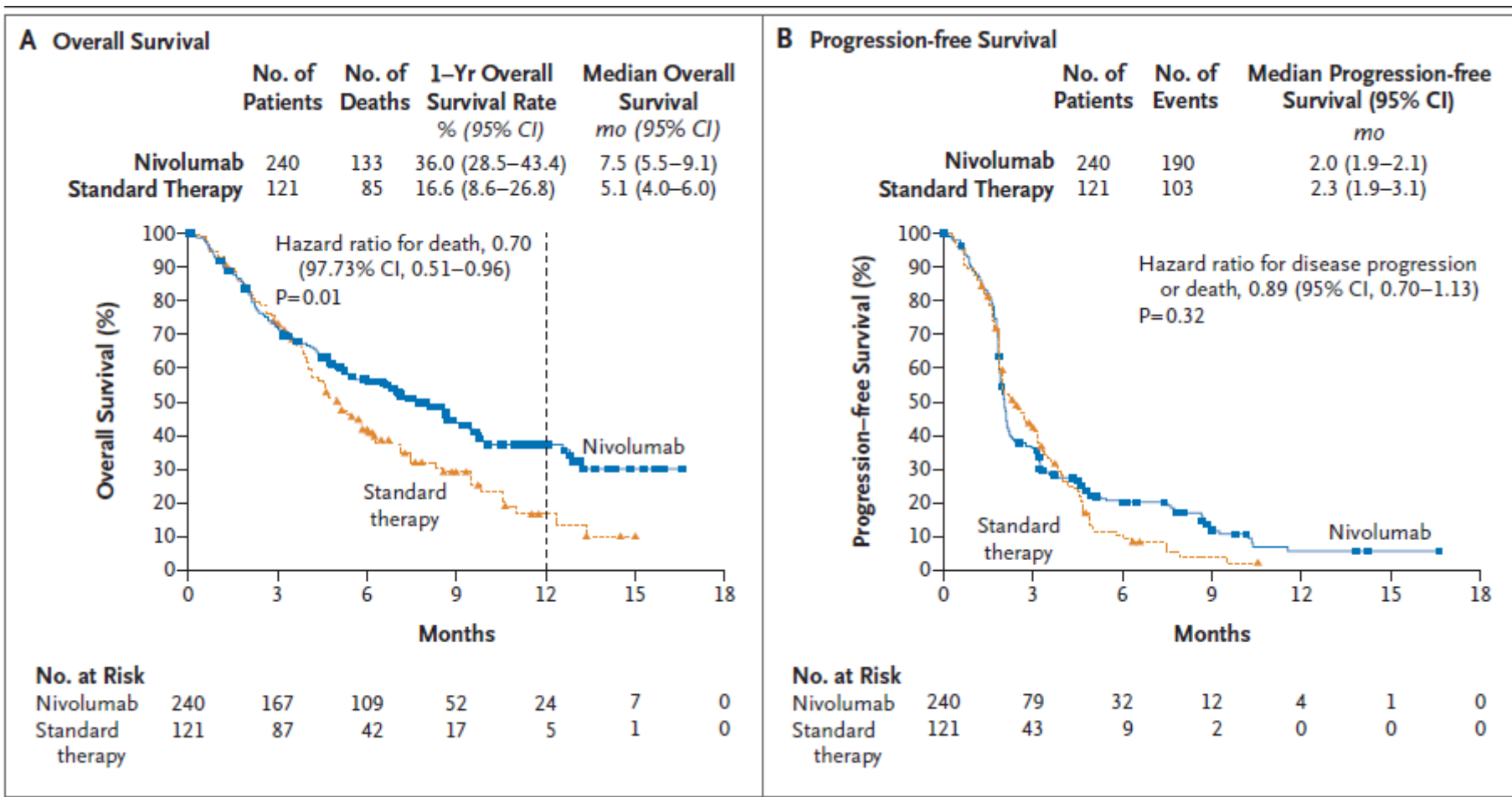
CheckMate 141: Nivolumab vs Investigator's Choice in R/M HNSCC after Platinum Therapy Phase III Randomized, Safety and Efficacy Trial



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

^aTissue required for testing

Checkmate 141: Nivolumab vs Investigator's Choice in R/M HNSCC after Platinum Therapy



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

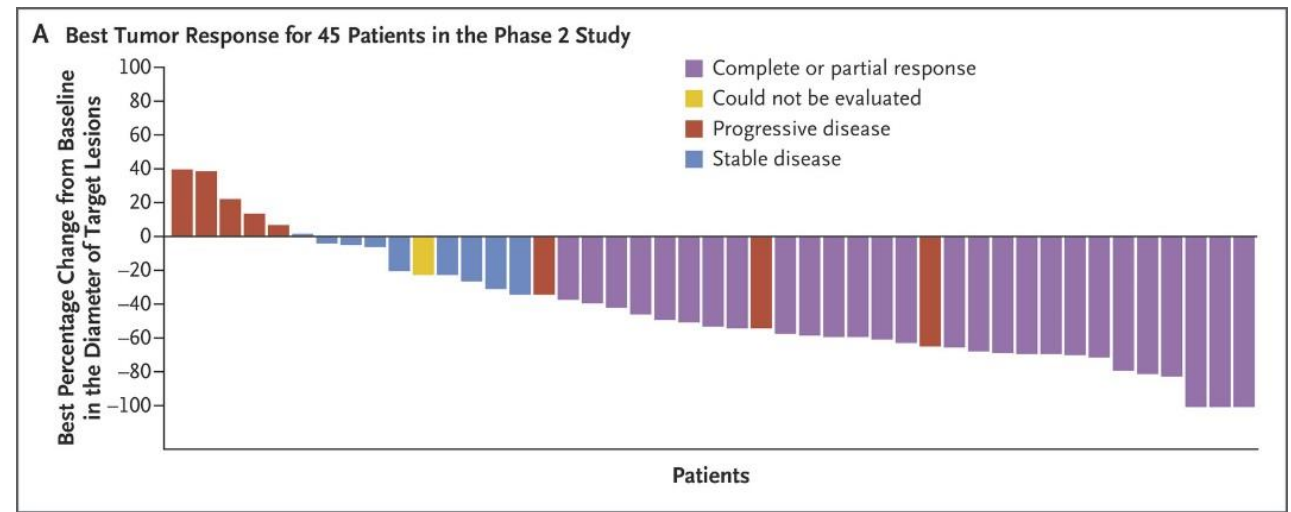
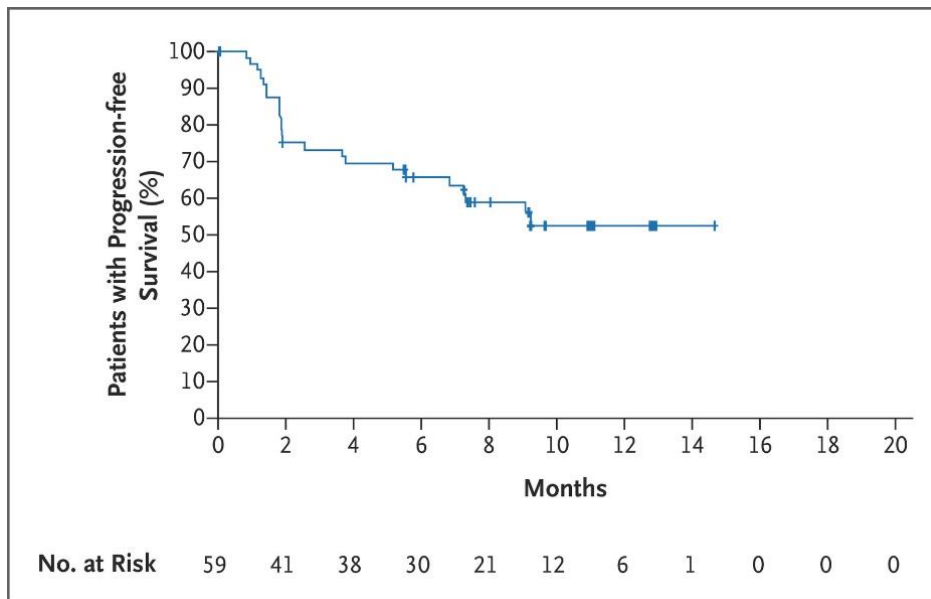
- Response rate

Other endpoints

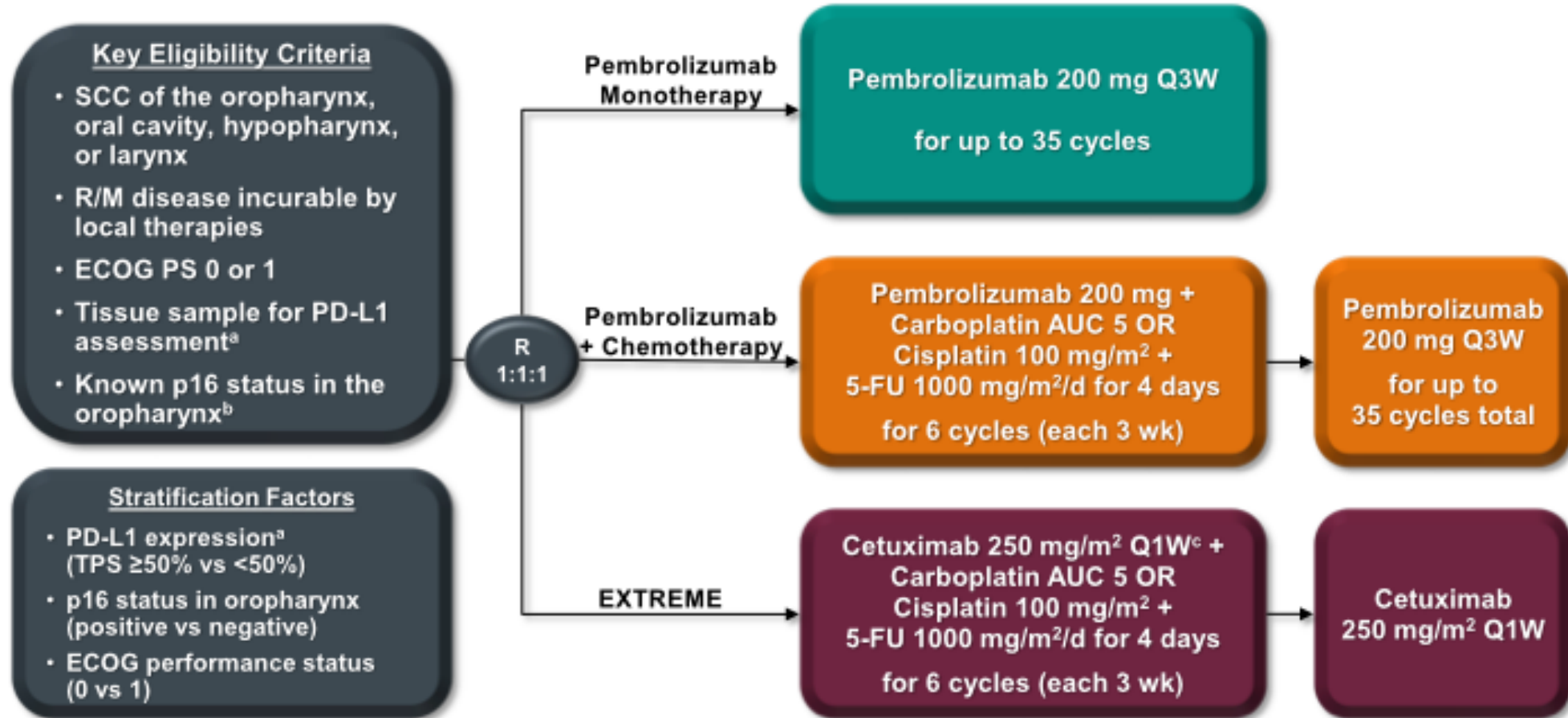
- Duration of response
- PFS
- OS
- Side effects
- Durable disease control

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



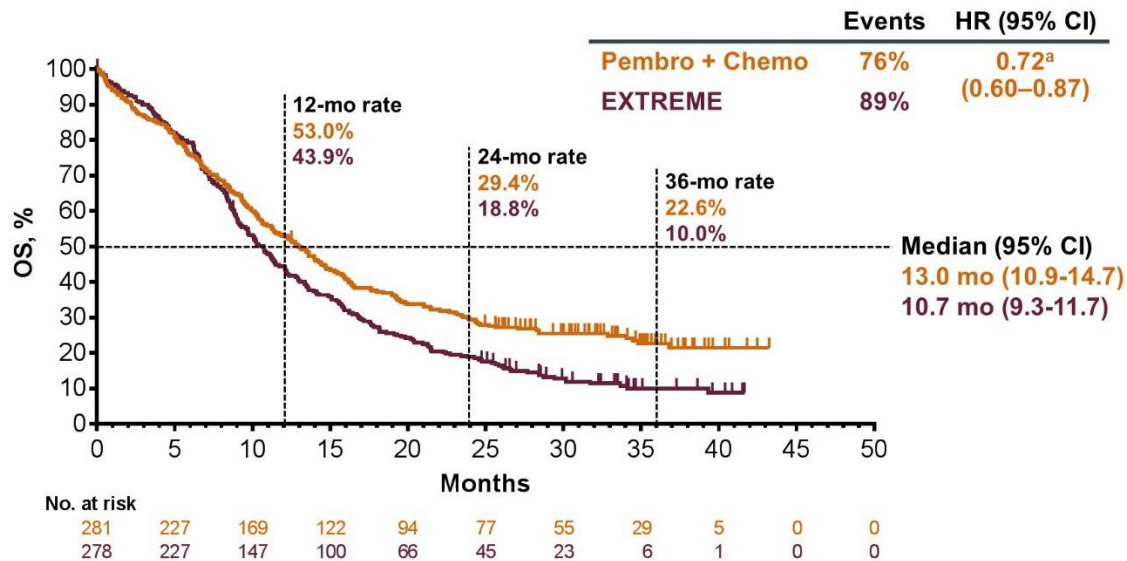
KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC



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

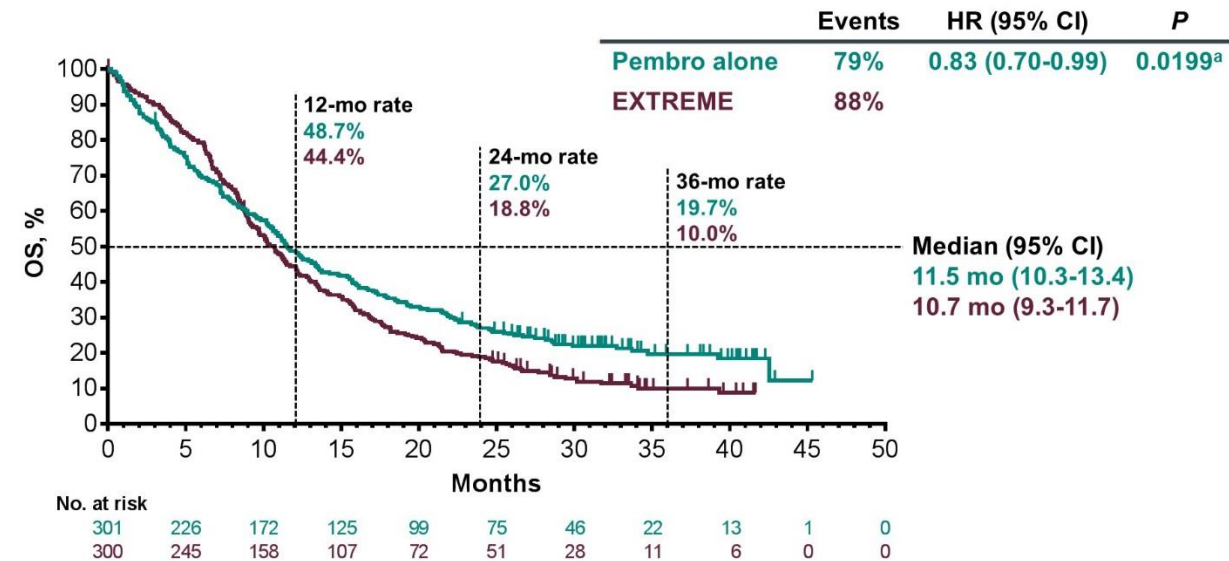
KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC

OS, P+C vs E, Total Population



^aAt 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



^aNot statistically significant at the superiority threshold of $P = 0.0059$.
FA (data cutoff date: Feb 25, 2019).

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

Summary of Overall Survival

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

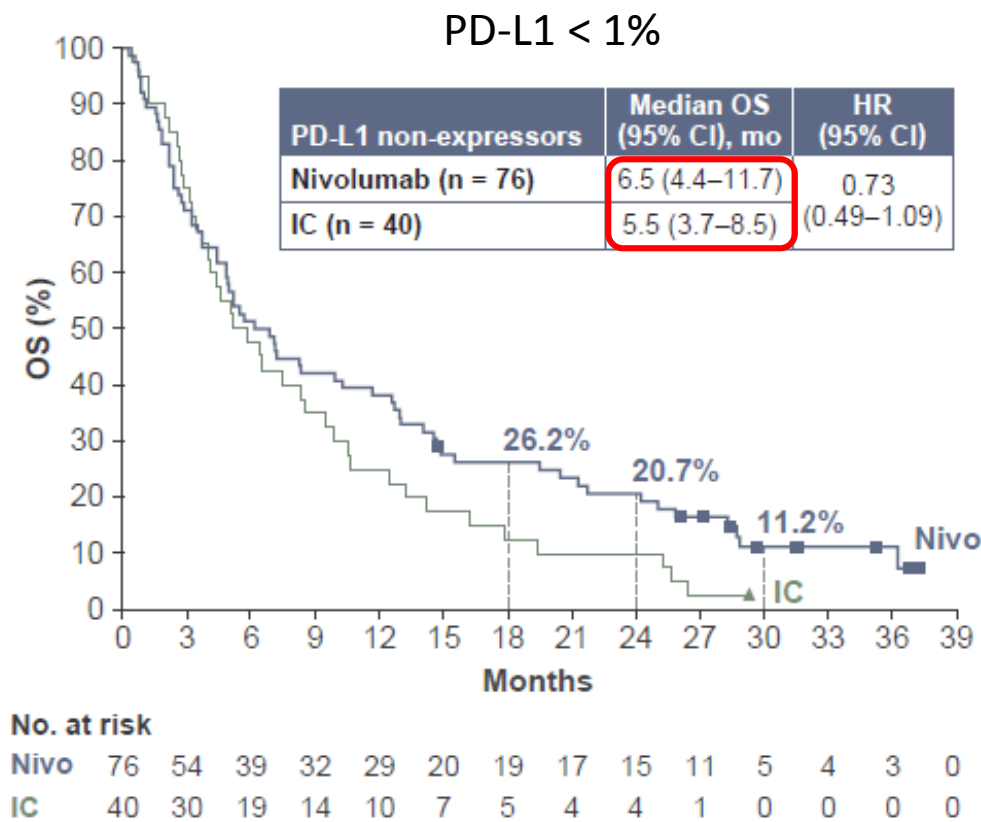
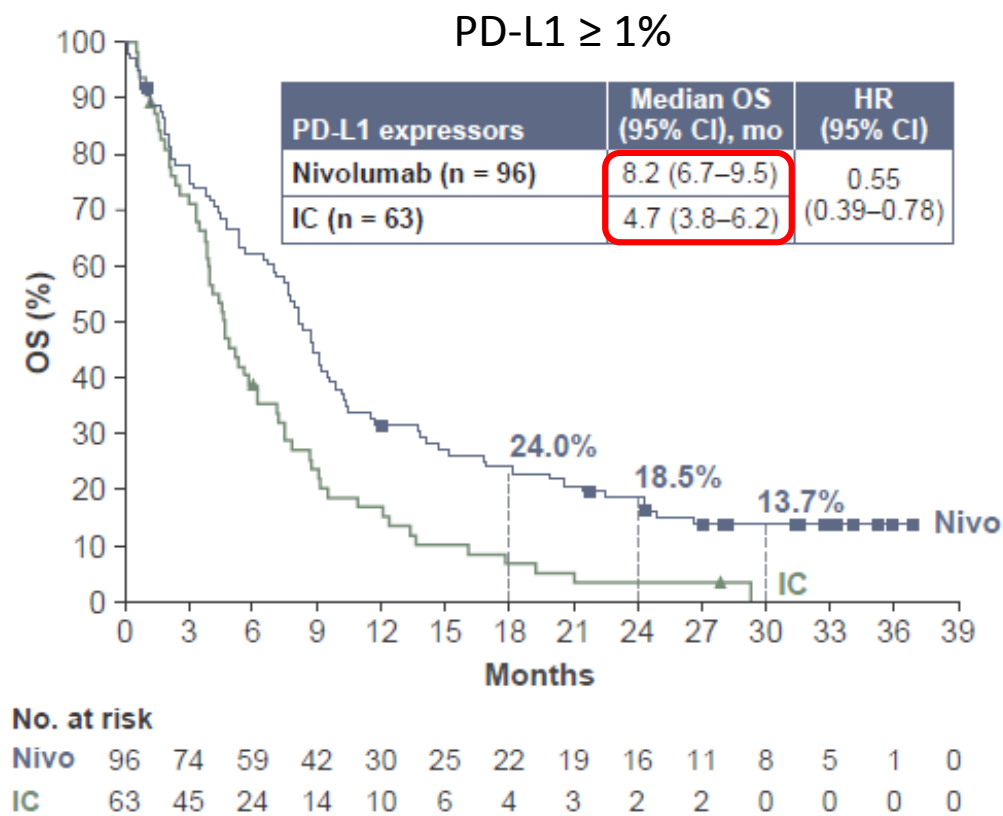
^aSuperiority demonstrated. ^bNoninferiority demonstrated (boundary of 1.2). ^cNo statistical testing performed. ^dSuperiority not demonstrated.
 1. Burtness B et al. *Ann Oncol* 2018;29(suppl 8):LBA8_PR.

Evaluating Biomarkers in HNSCC

- Only indication that relies on PD-L1 expression: pembrolizumab monotherapy in 1st line HNSCC – CPS \geq 1 (KEYNOTE-048)
- All other approvals not dependent on PD-L1 expression
 - KEYNOTE-012/055: Response rates not significantly different on the basis of tumor PD-L1 staining
 - Checkmate 141: Most 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

Evaluating Biomarkers in HNSCC

CheckMate 141: 2 year update



In development:

T-VEC + pembrolizumab

KEYNOTE-137

- T-Vec 10^6 PFU/mL intratumoral injection followed by 10^8 PFU/mL Q3W
- Pembrolizumab 200 mg IV Q3W
- Eligibility:
 - R/M HNSCC not suitable for curative therapy
 - Progressed after platinum treatment
 - At least 1 injectable cutaneous, subcutaneous, or nodal tumor ≥ 10 mm in longest diameter
- ORR: 16.7%

In development: Checkpoint inhibitors + radiotherapy

- NCT03247712: neoadjuvant nivolumab + SBRT
 - Decreased tumor size prior to surgery; high pathologic CR rate
- KEYNOTE-412: pembrolizumab + chemoradiation
 - Safety confirmed
- REACH: avelumab + cetuximab + radiation
 - Safety confirmed

Conclusions

- Cytotoxic chemotherapy achieves limited survival with unfavorable side effects.
- 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.
- Ongoing areas of research include: combinations of immunotherapy with radiation and/or other drugs, development of predictive biomarkers and approaches to overcoming resistance.

Cohen et al. *Journal for Immunotherapy of Cancer* (2019) 7:184
<https://doi.org/10.1186/s40425-019-0662-5>

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)

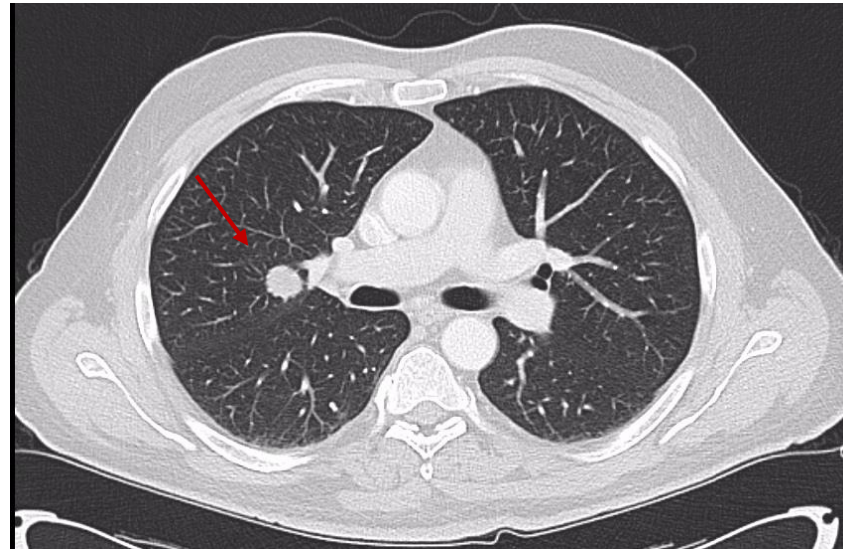


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Case Studies

Case Study 1

59 year old male with 15 PY smoking history, presented with 3 months history of left sided neck mass. FNA confirms p16 positive squamous cell carcinoma. Staging CT chest revealed the following finding.



Case Study 1

What should be the next step?

Raise your hand to indicate you would select option A or B:

Option A: Obtain PD-L1 IHC (22C3 pharmDx by CPS)

Option B: Immediately start cisplatin, 5-FU and cetuximab (EXTREME regimen)

Case Study 1

Option A would be more appropriate to determine what would be the best therapeutic option.

Keynote-048 study demonstrated OS benefit with pembrolizumab alone for patients with PD-L1 positive (>1% by CPS) patients.

Case Study 2

76 year old female with no past smoking history presented with 18 month history of ulcerating neck mass. She has history of multiple resections of skin squamous carcinoma in forehead. On exam, she was found to have a 3 cm parotid mass. FNA of the neck mass revealed squamous cell carcinoma.

She does not have any systemic metastasis. CT scan of the neck showed a large mass encasing the carotid artery. Her case was discussed at the tumor board and deemed to be unresectable.

Case Study 2

What would be the next best step?

Raise your hand to indicate you would select option A or B:

Option A: Obtain PD-L1 IHC (22C3 pharmDx by CPS)

Option B: Immediately start cemiplimab

Case Study 2

Option B would be more appropriate for patients with cutaneous squamous carcinoma, not amenable for surgical resection.

Cemiplimab demonstrated overall survival benefit in patients with advanced cutaneous squamous cell carcinoma, including patients with localized disease not amenable for curative surgical resection.