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ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Head and Neck Cancer

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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Disclosures

- Consulting Fees: Merck, GSK, Pfizer, Biontech, CUE
- I will be discussing non-FDA approved indications during my presentation.

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Outline

- Approved immunotherapies in head and neck cancers
- Biomarkers and immunotherapy responsiveness
- Unique considerations for head and neck cancers
- Future directions

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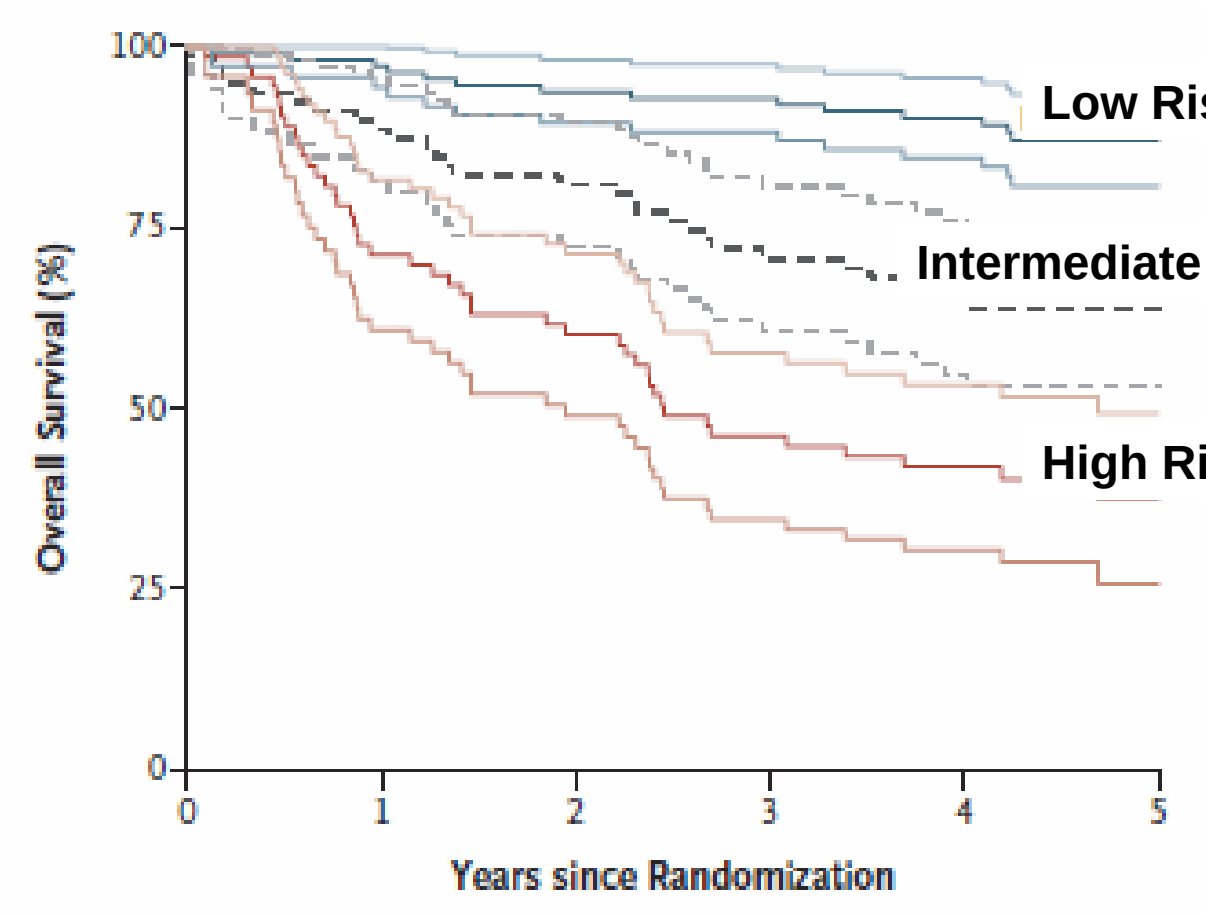
HPV(+) & HPV(-) tumors have different prognoses



Ang, et al. NEJM 2010

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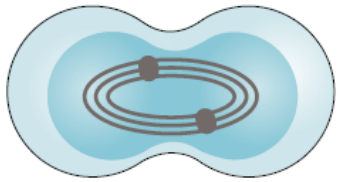
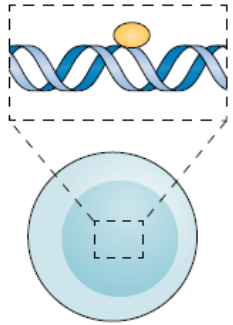
Immunotherapy Advances
Treatment Paradigm for HNSCC

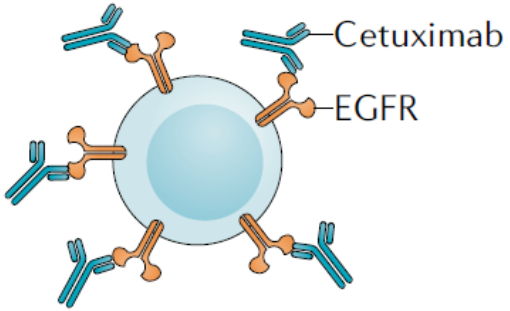
Paclitaxel inhibits microtubule disaggregation



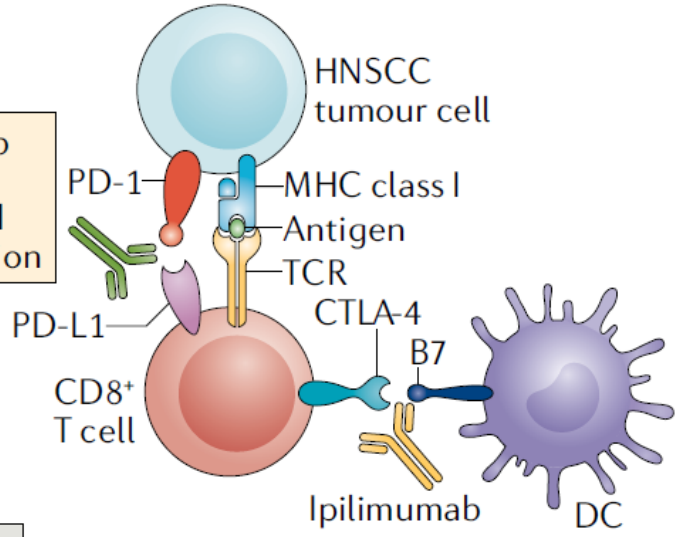
Cisplatin inhibits DNA replication and mRNA transcription



HNSCC tumour cell overexpressing EGFR



Pembrolizumab and nivolumab block PD-1 and PD-L1 interaction



2006 — Cetuximab and radiotherapy approved in LRA HNSCC and as monotherapy in platinum-refractory R/M HNSCC

2009 — da Vinci robotic system approved for transoral resection of oropharyngeal cancer

2011 — EXTREME regimen (cetuximab, 5-FU and cisplatin or carboplatin) approved for first-line R/M HNSCC

2016 — Pembrolizumab and nivolumab are approved in platinum-refractory R/M HNSCC

2018 — Data presented showing superiority of pembrolizumab in first-line R/M HNSCC

Cramer et al, 2019 Nature reviews clinical oncology

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How does immunotherapy fit into the treatment of SCCHN?

R/M SCHHN
Locally recurrent not candidates for salvage radiation or surgery
Or
distant metastases

Primary metastatic chemo-naive –6 Mo post Definitive therapy (first line RMD)	Post platinum failure Or- within 6 months of platinum In definitive setting	failing PD-1 inhibitors
KN 048 results CPS>1, Pembro Biomarker unselected Pembro + Chemotherapy	(based on Checkmate -141, Keynote 040) Pembrolizumab Nivolumab Or Clinical trial	Clinical Trial Or Single agent therapy Cetuximab Methotrexate Docetaxel

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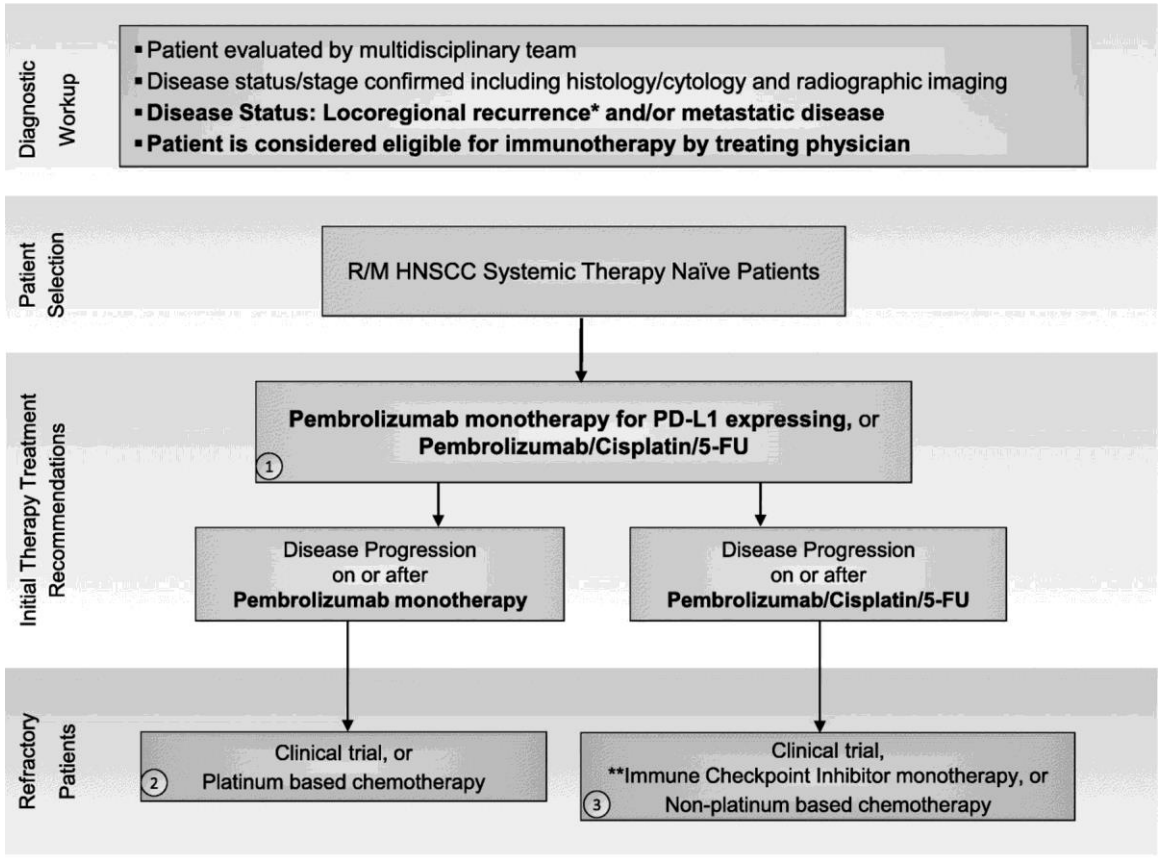
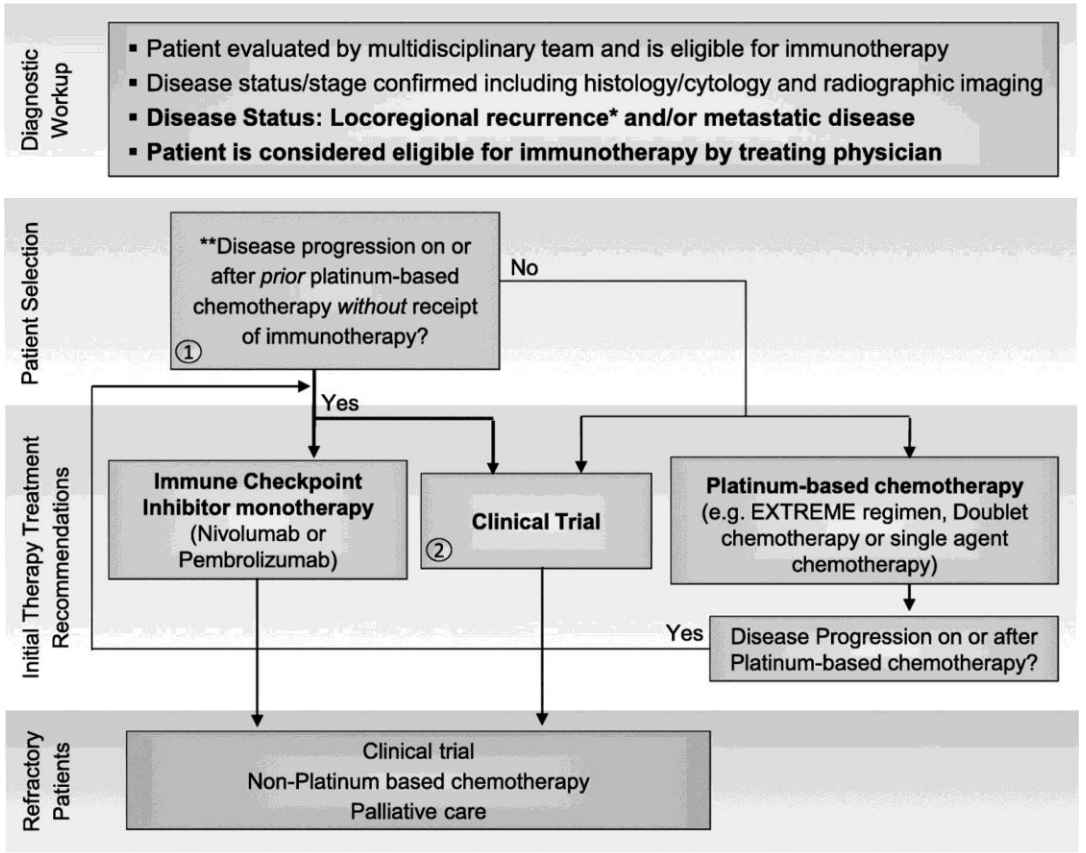
Immunotherapy in head and neck cancer treatment



*Locoregional recurrence without salvage surgical or radiation option or declines local therapies
**Refer to Figure 2. Initial Therapy Treatment Recommendations: Immune Checkpoint Inhibitor monotherapy (nivolumab or pembrolizumab)



*Locoregional recurrence without salvage surgical or radiation option or declines local therapies
**Disease Progression on or after Platinum-Based Therapy: Disease progression on or after platinum-based therapy including within 6 months of platinum-based CRT given in the locally advanced setting. Patients that receive but cannot tolerate platinum-based chemotherapy would also be included in this category.
HNSCC: head and neck squamous cell carcinoma

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Approved checkpoint inhibitors in head and neck cancers

Drug	Approved	Indication	Dose
Pembrolizumab	2016	Recurrent/metastatic HNSCC, progression on/after chemotherapy	200 mg Q3W or 400 mg Q6W
Nivolumab	2016	Recurrent/metastatic HNSCC, progression on/after chemotherapy	240 mg Q2W or 480 mg Q4W
Pembrolizumab + platinum + fluorouracil	2019	Recurrent/metastatic HNSCC 1st line – all patients	200 mg Q3W or 400 mg Q6W
Pembrolizumab	2019	Recurrent/metastatic HNSCC 1st line – PD-L1 CPS ≥ 1	200 mg Q3W or 400 mg Q6W

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Clinical trials in HNSCC

Trial	Patient selection criteria	Treatment arm(s)	N	ORR	Median PFS (months)	Median OS (months)
KEYNOTE-048	**Untreated** R/M HNSCC (total population)	Pembrolizumab	301	16.9%	2.3	11.5
		Pembrolizumab + chemo	281			13.0
		Cetuximab + chemo	300	36.0%	5.2	10.7
KEYNOTE-012	R/M HNSCC	Pembrolizumab	192	18% (PD-L1+: 21%, PD-L1-: 6%)	2.1	8
CheckMate 141	R/M HNSCC with **progression on platinum**	Nivolumab	240	13.1% (PD-L1+: 17.7%, PD-L1-: 11.8%)	2.0	7.7
		Investigator's choice	121	5.8%	2.3	5.1
KEYNOTE-040	R/M HNSCC with **progression on platinum**	Pembrolizumab	247	14.6%	2.1	8.4
		Investigator's choice	248	10.1%	2.3	6.9

Mehra, Br J Cancer 2018; Ferris, Oral Oncol 2018; Cohen, Lancet 2018; Burtness, Lancet 2019.

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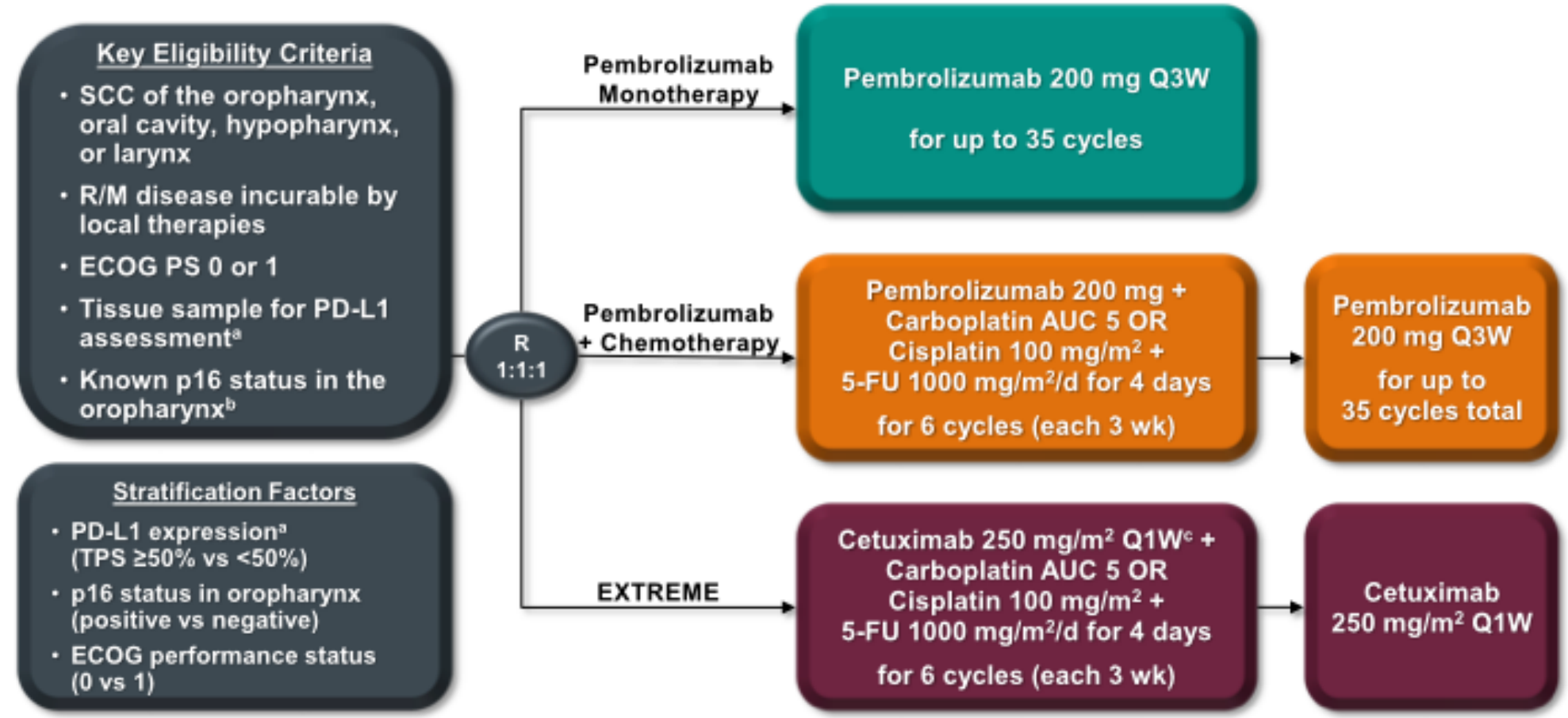
KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC



[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.

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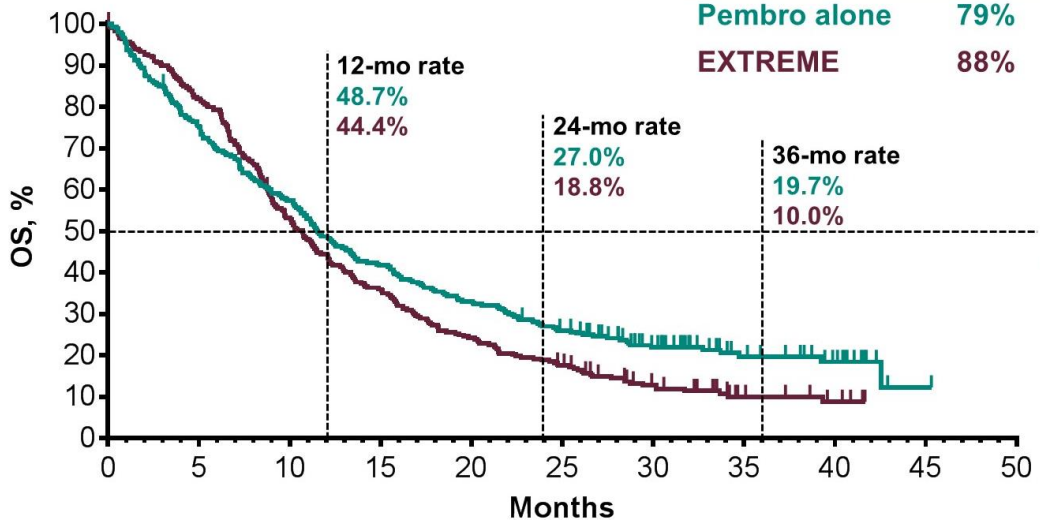
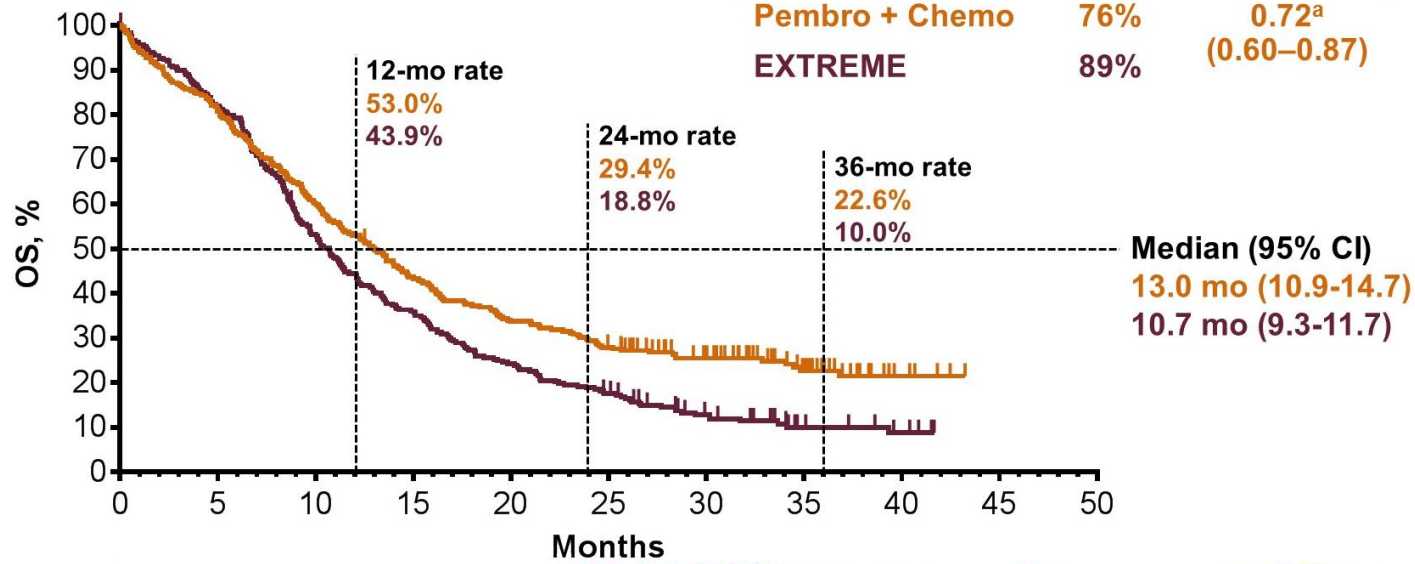
KEYNOTE-048: Overall survival in the total population

	Events	HR (95% CI)	*P*
Pembro alone	79%	0.83 (0.70-0.99)	0.0199[a]
EXTREME	88%		



	Events	HR (95% CI)
Pembro + Chemo	76%	0.72[a] (0.60–0.87)
EXTREME	89%	



Rischin, ASCO 2019

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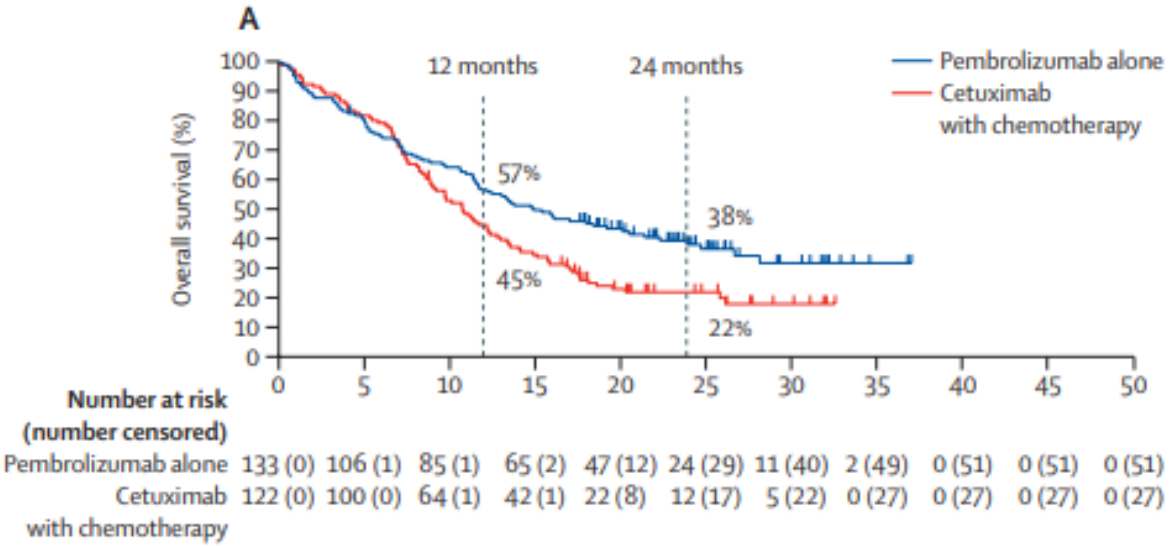
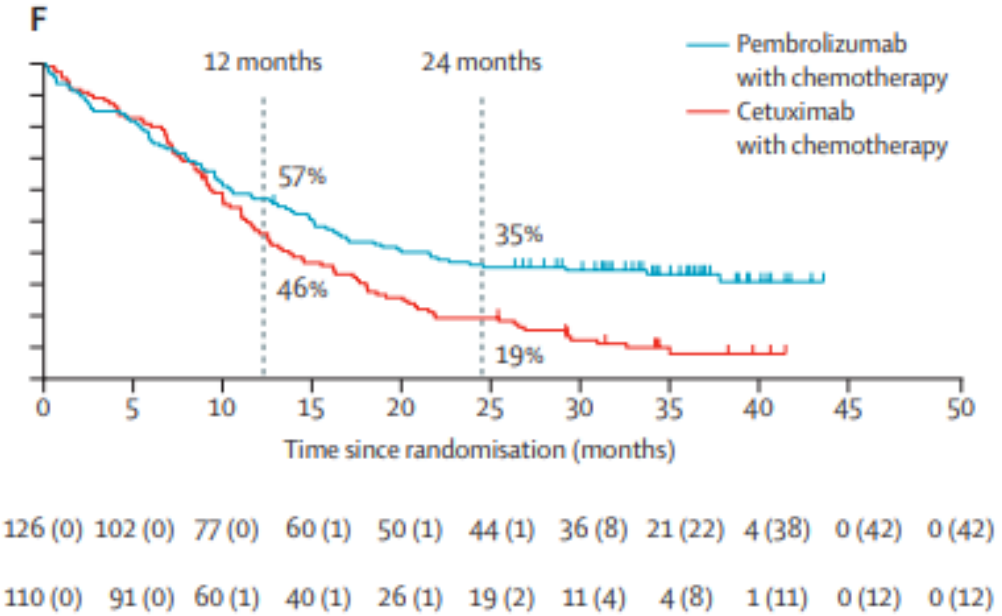
KEYNOTE-048: Overall survival in the PD-L1 positive population

PD-L1 CPS ≥1



PD-L1 CPS ≥1



Burtness, Lancet 2019

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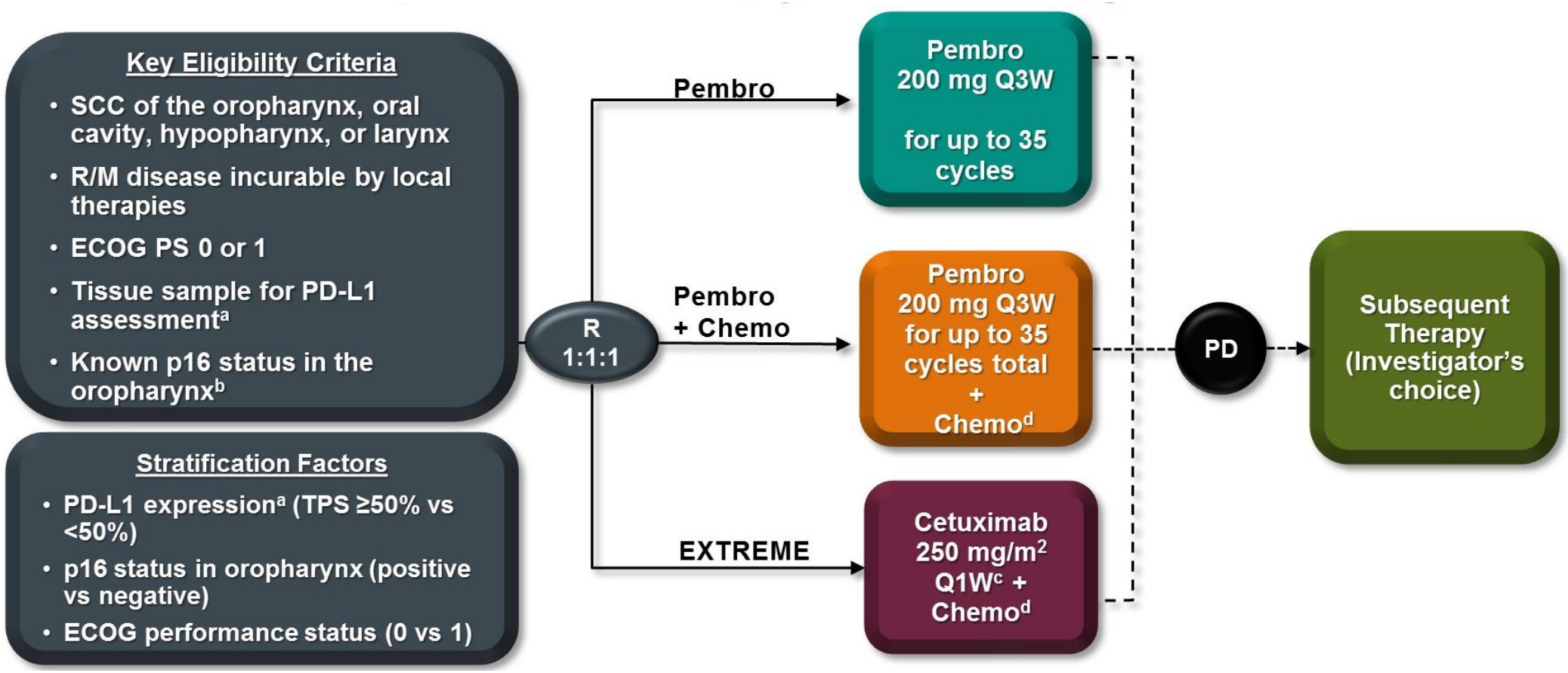
KEYNOTE-048: Outcomes on subsequent therapy



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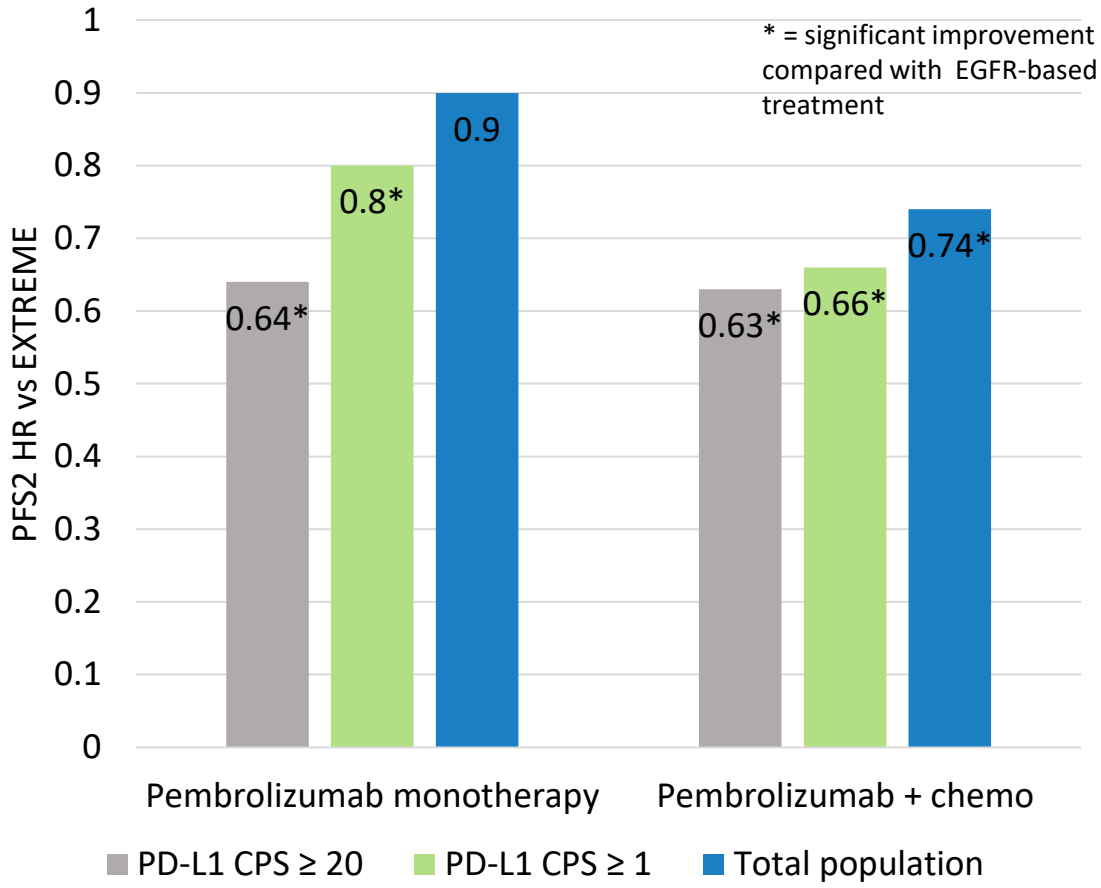
KEYNOTE-048: Outcomes on subsequent therapy

- After progression, most common next treatment was a chemotherapy regimen
- PFS2: Progression-free survival on second treatment (after progression on KEYNOTE-048 treatment)
- Benefits seen for patients who received pembrolizumab regimens up-front
- Provides support to use of immunotherapy in front-line setting



Harrington, ASCO 2020.

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Outline

- Approved immunotherapies in head and neck cancers
- Biomarkers and immunotherapy responsiveness
- Unique considerations for head and neck cancers
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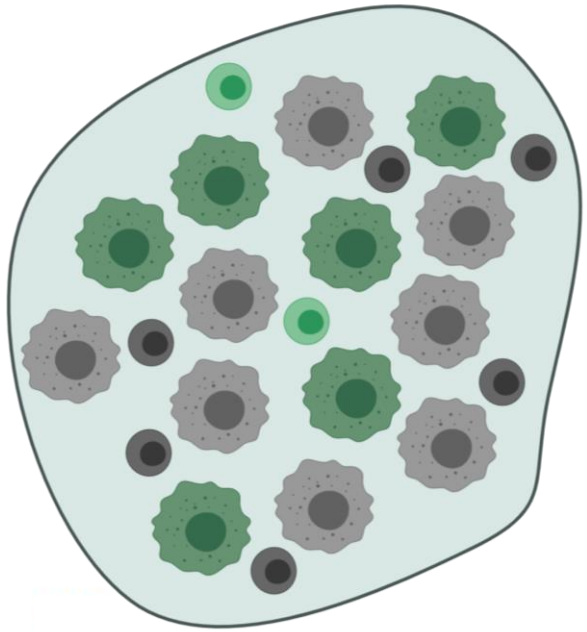
PD-L1: TPS vs CPS

$$TPS = \frac{\#\ of\ \mathrm{PD{-}L1}\ positive\ tumor\ cells}{number\ of\ viable\ tumor\ cells} \times 100$$

$$CPS = \frac{\#\ of\ \mathrm{PD{-}L1}\ positive\ cells\ (tumor\ cells, lymphocytes, macrophages)}{total\ number\ of\ tumor\ and\ immune\ cells} \times 100$$



PD-L1-positive immune cell

PD-L1-negative immune cell

PD-L1-positive tumor cell

PD-L1-negative tumor cell

$$TPS = \frac{6\ positive\ tumor\ cells}{14\ total\ tumor\ cells} \times 100 = 43$$

$$CPS = \frac{6\ positive\ tumor\ cells + 2\ positive\ immune\ cells}{22\ total\ cells} \times 100 = 36$$

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Impact of PD-L1 in HNSCC

PD-L1 CPS

- KEYNOTE-048
  - First-line treatment
  - Approval of pembrolizumab monotherapy: CPS ≥ 1
- KEYNOTE-040
  - After platinum
  - Improved outcomes in PD-L1-positive patients (by CPS ≥ 1), no significance in total population

PD-L1 TPS

- CheckMate 141
  - After platinum
  - Greatest benefit seen for PD-L1-positive tumors (TPS ≥ 1%), but benefit regardless
- KEYNOTE-012
  - Second-line treatment
  - Higher response rate with PD-L1 CPS-positive tumors
  - No difference for PD-L1-positive tumors by TPS

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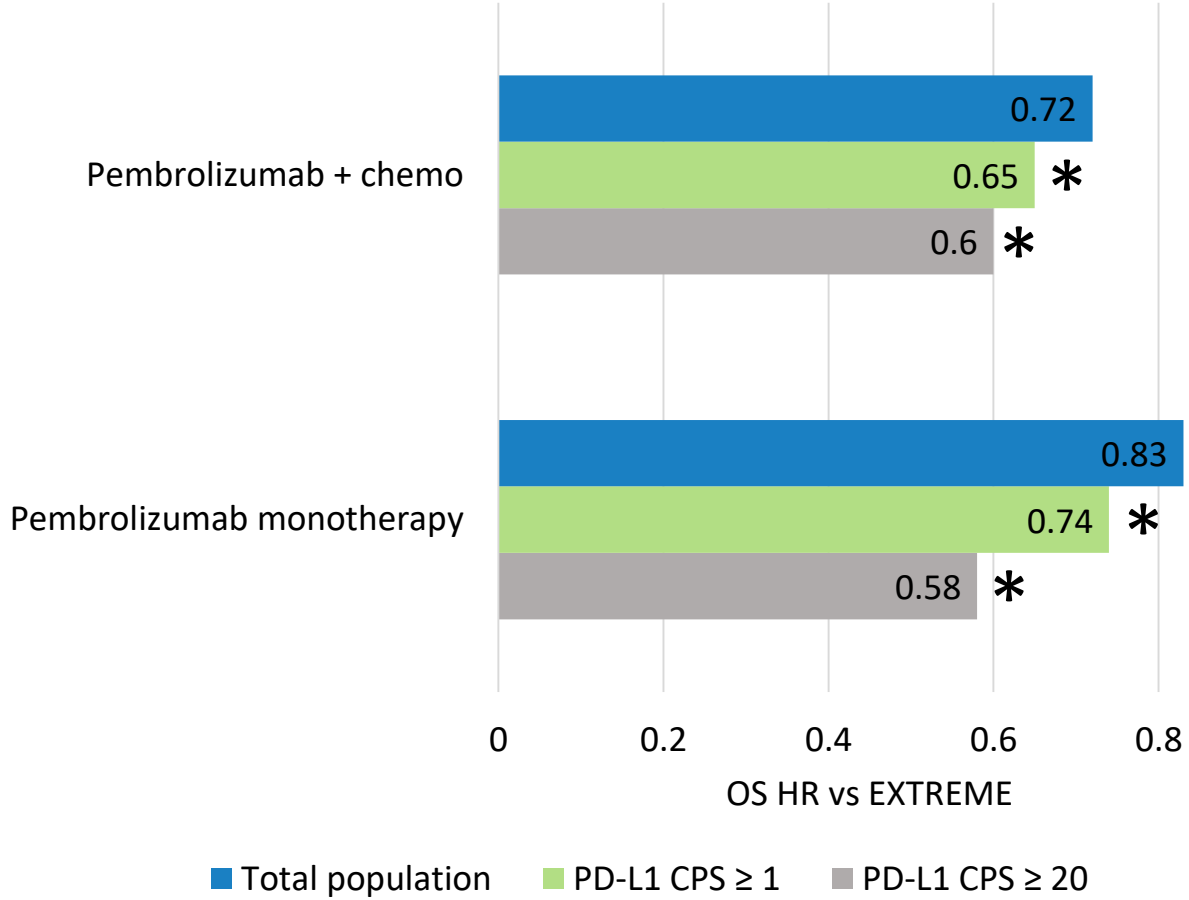
KEYNOTE-048: Outcomes by PD-L1 status

- Greatest benefits seen in tumors with highest PD-L1 expression
- Approval requires PD-L1 expression (CPS) only for monotherapy
- For total population, only pembrolizumab + chemotherapy should be considered, not monotherapy



*superiority statistically demonstrated at interim or final analysis

Rischin, ASCO 2019.

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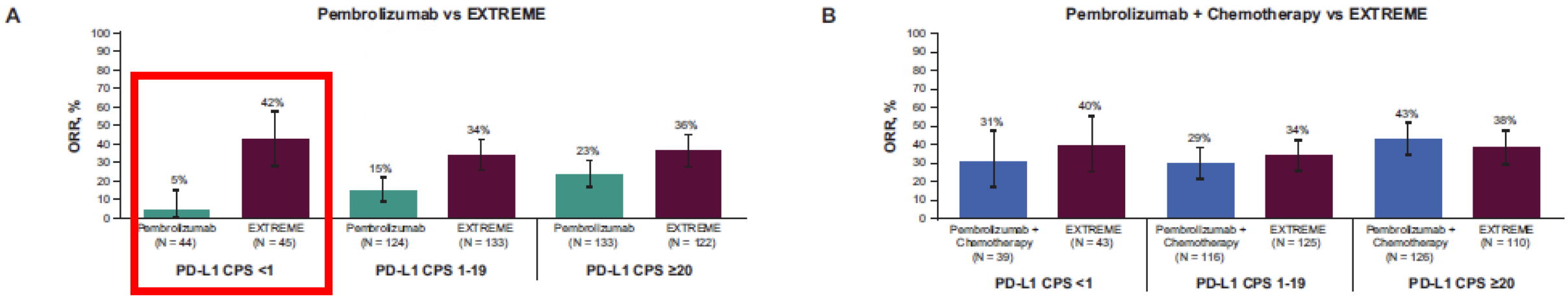
Figure 3. ORR[a] in PD-L1 CPS <1, CPS 1-19, and CPS ≥20 Subgroups



[a]Assessed per RECIST v1.1 by blinded independent central review.

Burtness et al, AACR 2020

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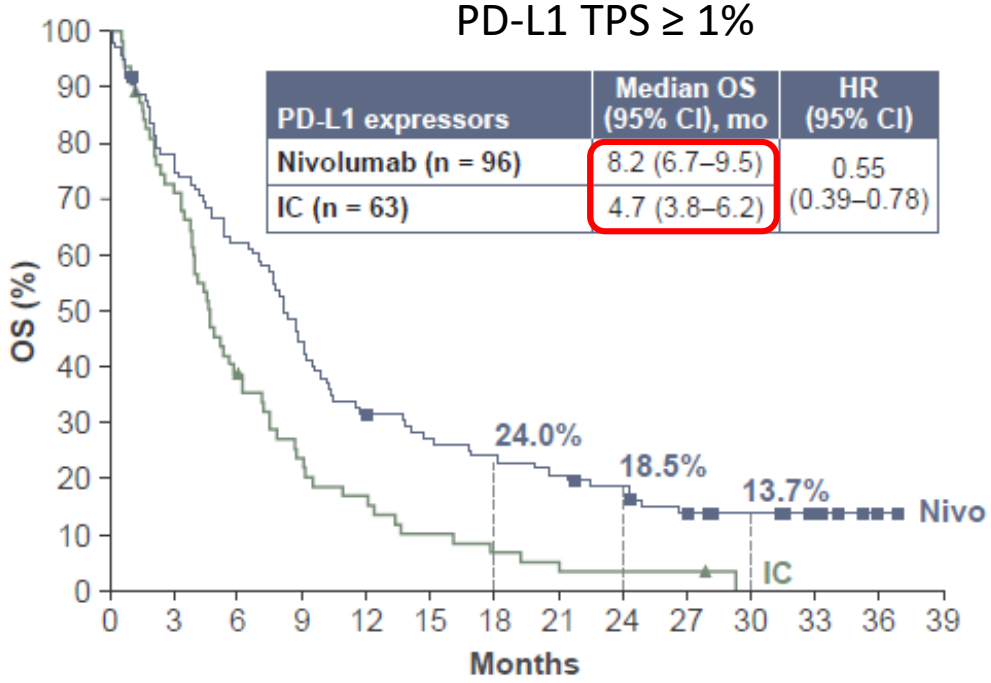
CheckMate 141: Outcomes by PD-L1 status

CheckMate 141: 2 year update

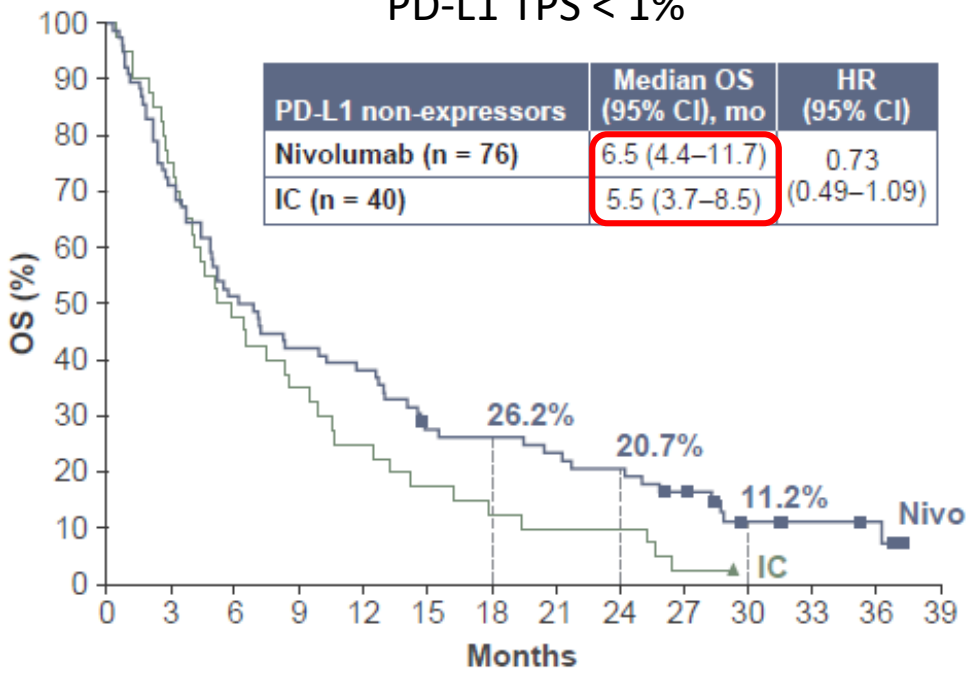
PD-L1 TPS ≥ 1%



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 TPS < 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.

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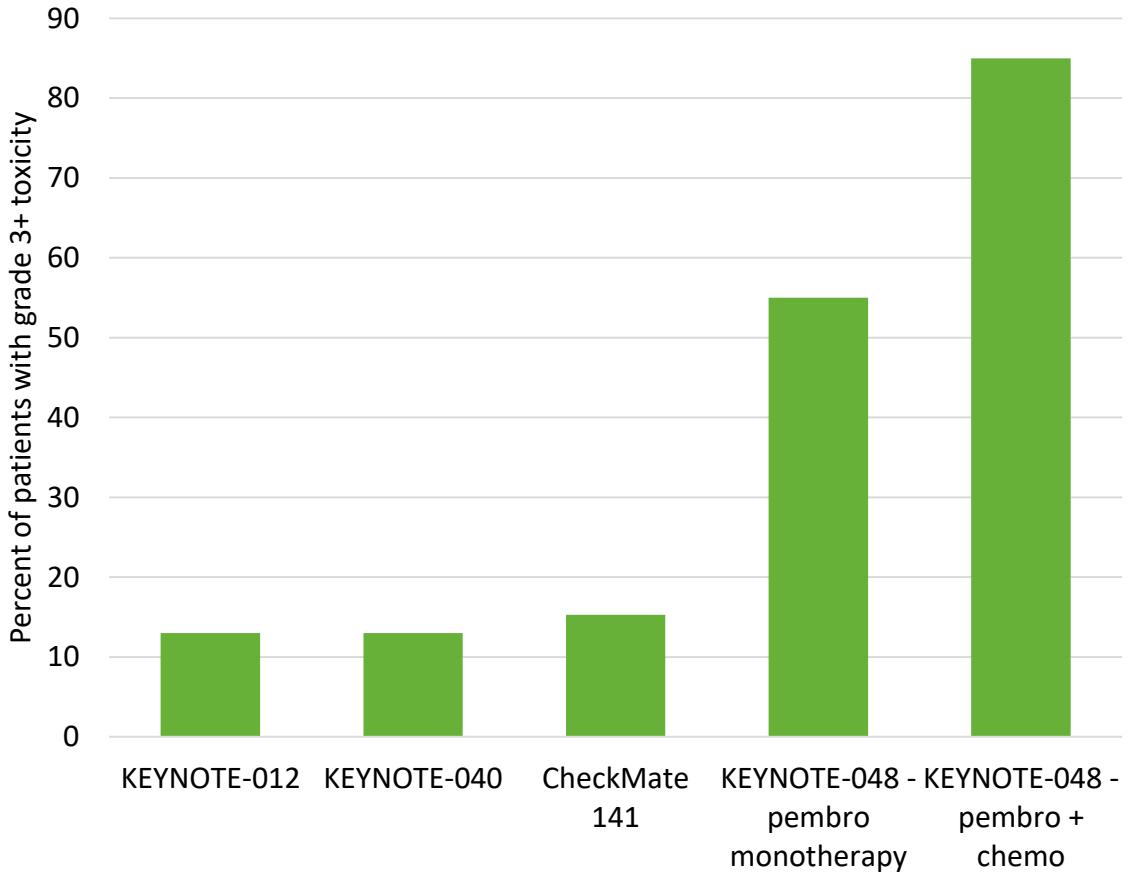
Toxicities in head and neck cancer patients

- Patients typically receive aggressive radiation treatment, with accompanying side effects
- Radiation in combination with chemotherapy, immunotherapy and/or surgery can further complicate toxicity profiles
- While combinations may have higher response rates, also have higher toxicity rates



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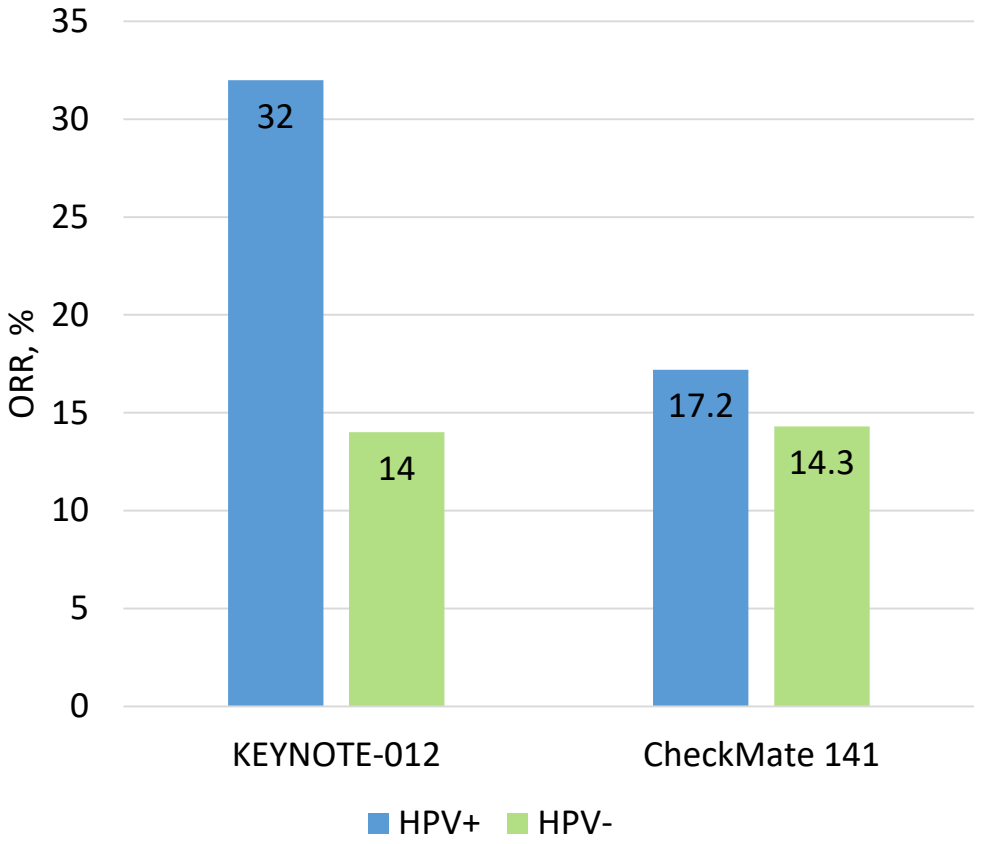
Viral infections in HNSCC

- Virally-associated cancers are biologically and clinically distinct
  - Human papillomavirus associated with oropharynx cancer
  - Epstein Barr virus associated with nasopharyngeal cancer
- Evidence that HPV+ tumors may perform better, but there is benefit with immunotherapy regardless of HPV status



Cohen, J Immunother Cancer 2019.

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Combination immune checkpoint inhibition in HNSCC – *limited success to date*

Trial	Patient population	Treatment arms	ORR	Median OS (months)	Landmark OS
EAGLE	R/M HNSCC after platinum	Durvalumab	17.9%	7.6	24-months: 18.4%
		Durvalumab + tremelimumab	18.2%	6.5	24-months: 13.3%
		SoC	17.3%	8.3	24-months: 10.3%

Trial	Patient population	Treatment arms	Expected study completion
KESTREL	Untreated HNSCC	Durvalumab	February 2021
		Durvalumab + tremelimumab	
		SoC	
CheckMate 714	Platinum-refractory HNSCC	Nivolumab + ipilimumab	January 2024
		Nivolumab	
CheckMate 651	Untreated HNSCC	Nivolumab + ipiliumumab	February 2026
		EXTREME regimen	

Ferris, Ann Oncol 2020

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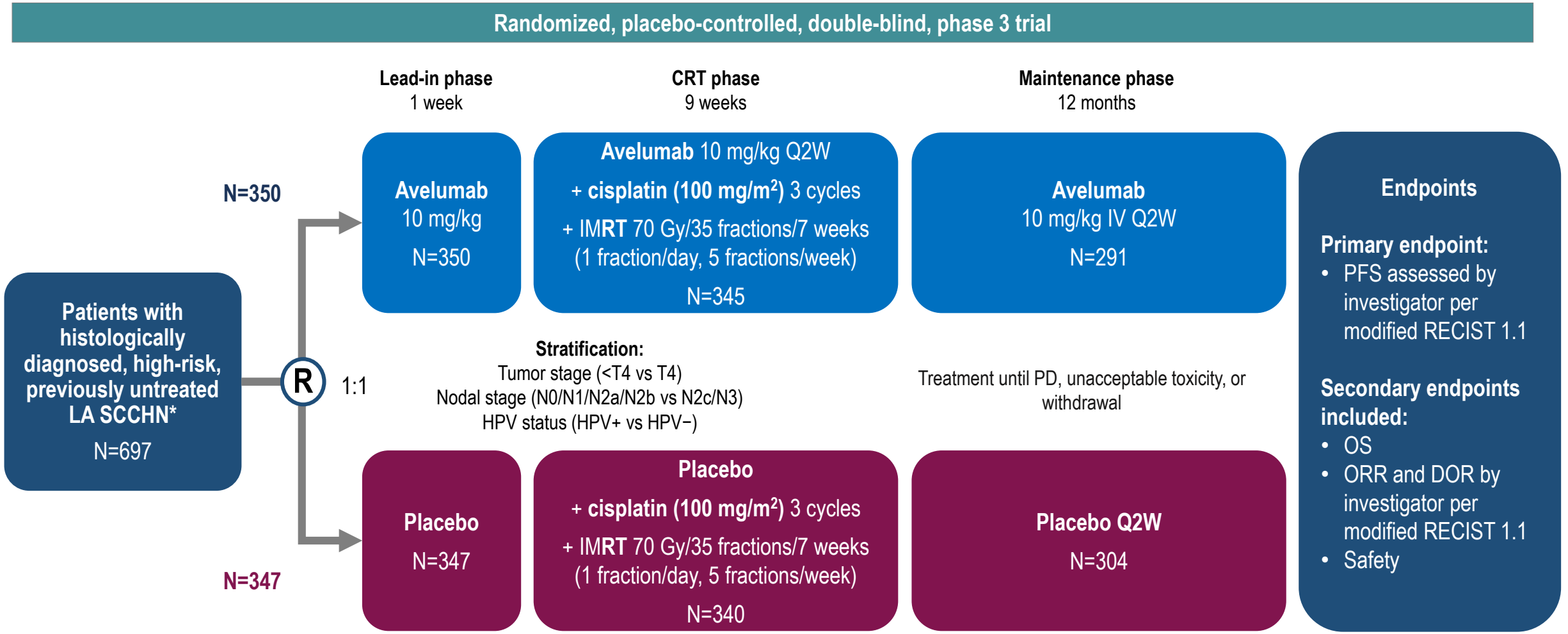

DOR, duration of response; **HPV**, human papillomavirus; **IMRT**, intensity-modulated radiation therapy; **IV**, intravenously; **ORR**, objective response rate; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **Q2W**, every 2 weeks; **R**, randomized; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumors version 1.1.

* High-risk LA SCCHN (oral cavity, oropharynx, larynx, or hypopharynx): HPV-negative disease stage III, IVa, IVb; nonoropharyngeal HPV-positive disease stage III, IVa, IVb; HPV-positive oropharyngeal disease T4 or N2c or N3 (TNM staging per AJCC, 7th edition).

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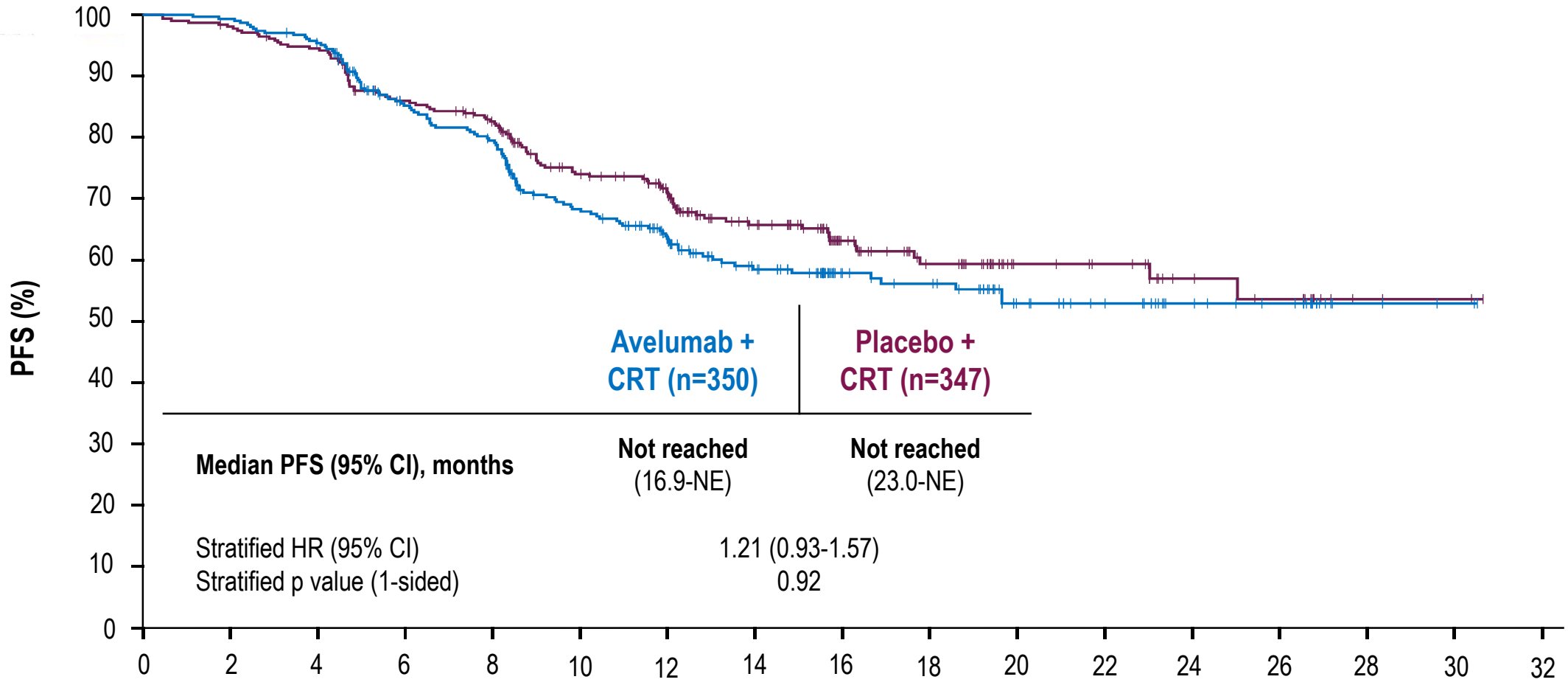

At risk																	
Avelumab + CRT	350	303	289	239	222	176	143	107	69	63	41	33	22	18	4	2	0
Placebo + CRT	347	303	291	257	241	200	172	121	75	56	31	28	18	15	3	2	0

NE, not estimable.

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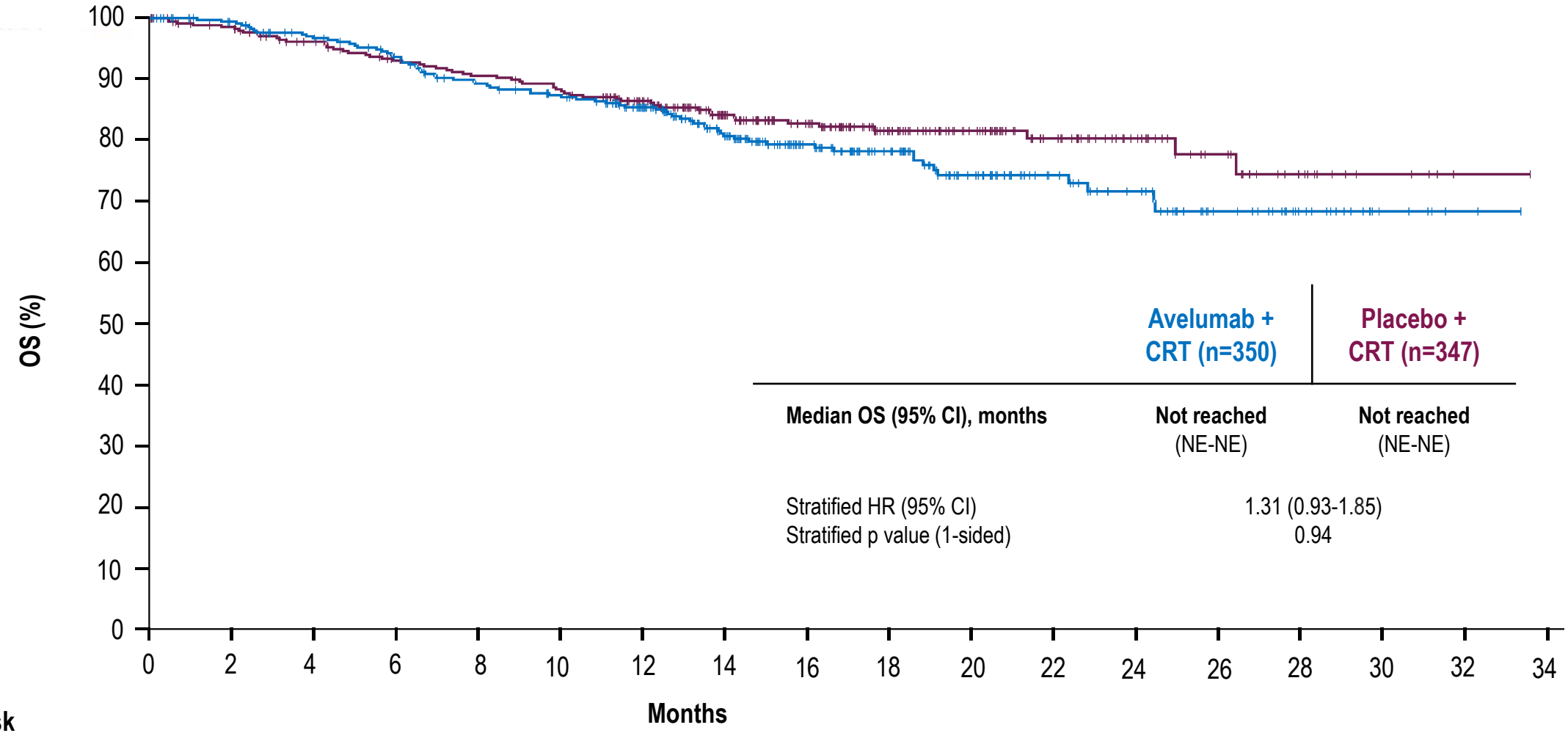

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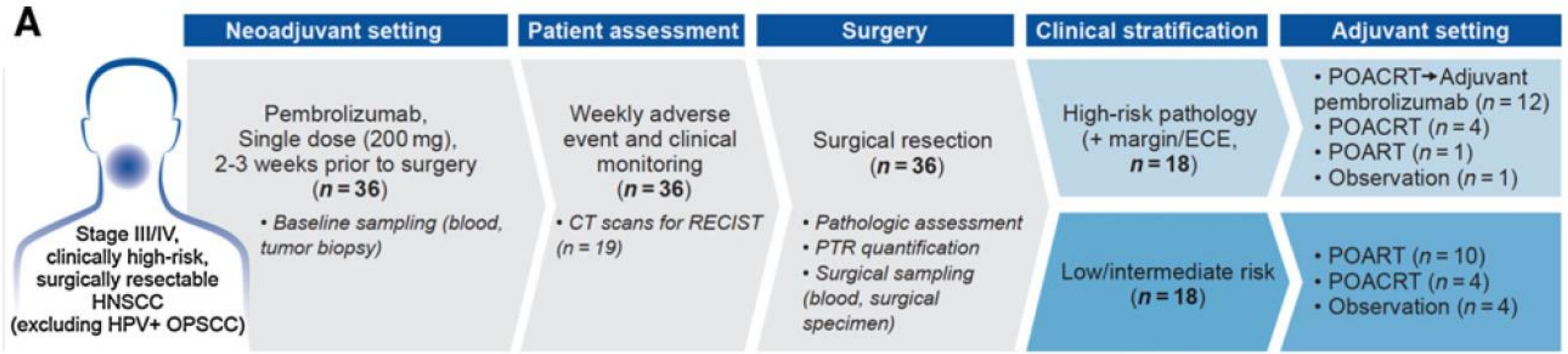
In development: Oral cavity cancer



Uppaluri, Clin Cancer Res 2020

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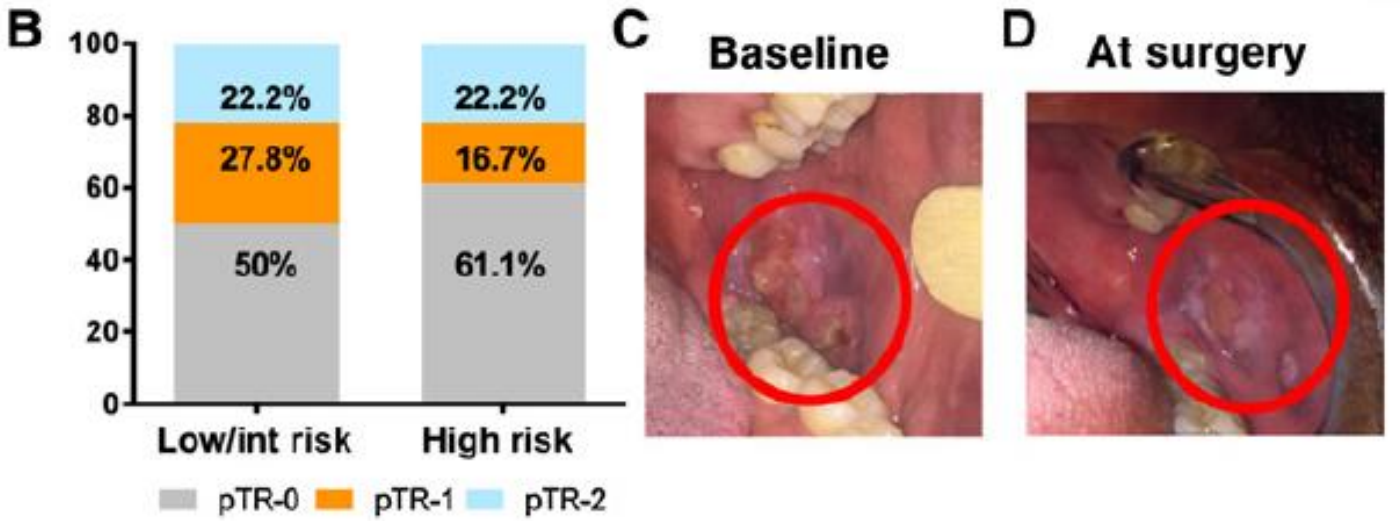
In development: Oral cavity cancer

- No serious AEs or unexpected surgical complications/delays
- pTR-2: 22%
- pTR-1: 22%
- 1-year relapse rate: 16.7%



Uppaluri, Clin Cancer Res 2020

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Trials in Progress using ICI in PULA for Cisplatin eligible patients

KN 412 Cisplat-RT + pembro versus + placebo

Avelumab + cetuximab RT instead of cisplatin RT

REACH (GORTEC) closed ; > 430 pts

Adjuvant atezolizumab after Chemo-RT

IMVOKe 10

***Adjuvant Nivolumab after Chemo-RT*;**

EA3161 (Intermediate Risk HPV related)

Concurrent Nivolumab with RT

HN005 (Low risk HPV related- compared to Cis RT)

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In development: Checkpoint inhibitors + radiotherapy as primary therapy

- NCT03247712: neoadjuvant nivolumab + SBRT
  - Phase I
  - Decreased tumor size prior to surgery; high pathologic CR rate
- KEYNOTE-412: pembrolizumab + chemoradiation
  - Phase III
  - Safety confirmed, estimated completion 2021
- JAVELIN Head and Neck 100: avelumab + chemoradiation
  - Phase III trial terminated in early 2020, due to likelihood of limited efficacy
- REACH: avelumab + cetuximab + radiotherapy
  - Phase III
  - Safety confirmed, estimated completion 2027

Leidner, AACR 2019.

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In development: cetuximab + pembrolizumab for recurrent metastatic disease

- Cetuximab and pembrolizumab are both approved as monotherapies for HNSCC
- Phase II trial testing cetuximab + pembrolizumab:
  - Platinum refractory or ineligible disease
  - ORR: 45%
  - Median OS: 18.4 months
  - Safety profile consistent with individual drugs

Sacco, H&N Cancers Symposium 2020.

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study of concurrent cetuximab and nivolumab in rec/met HNSCC

All patients will have baseline MRI or CT scans.
Archival tumor tissue (or fresh biopsy if archived tumor is not available) will be required at baseline.
Blood samples (20 ml) will be obtained before treatment.

↓

LEAD-IN PERIOD: Cetuximab 500 mg/m^2 IV x 1 (Day -14)

Cetuximab 500 mg/m^2 IV Q 2 weeks, Nivolumab 240 mg IV Q 2 weeks (Each Cycle = 4 weeks)

↓

Treat until disease progression, intolerable toxicity, withdrawal of consent, or up to 24 cycles

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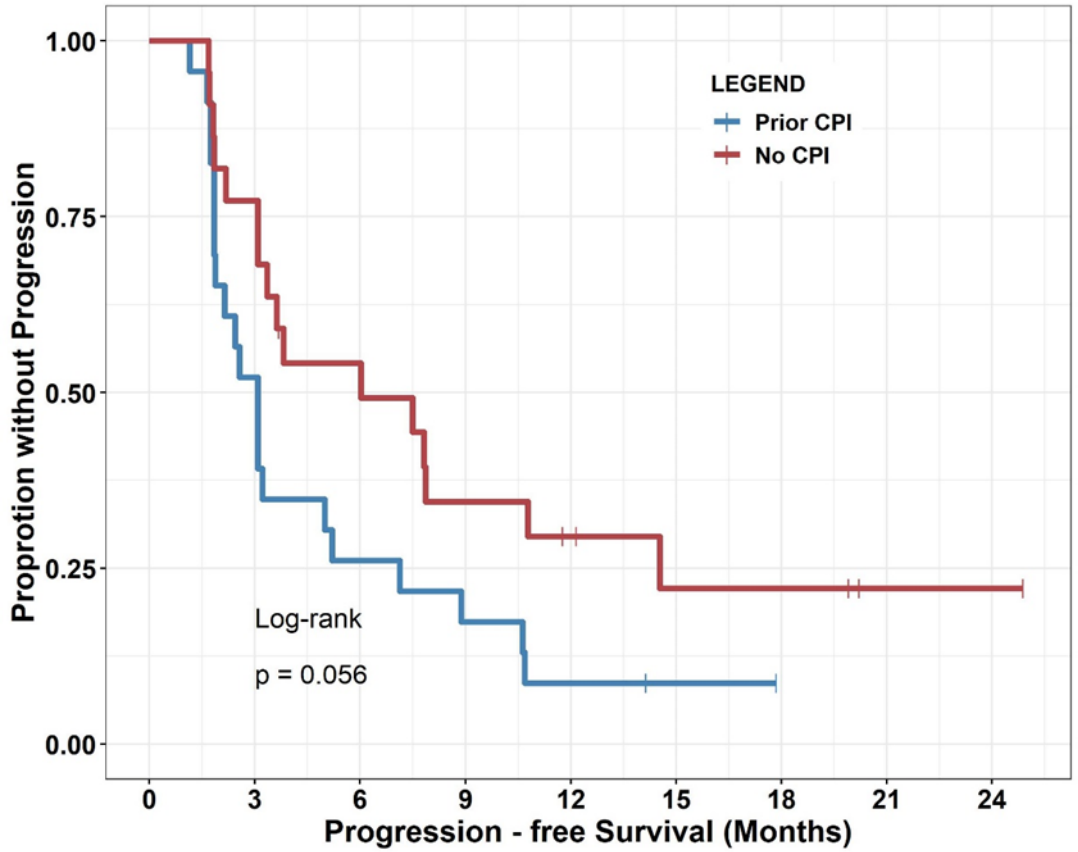
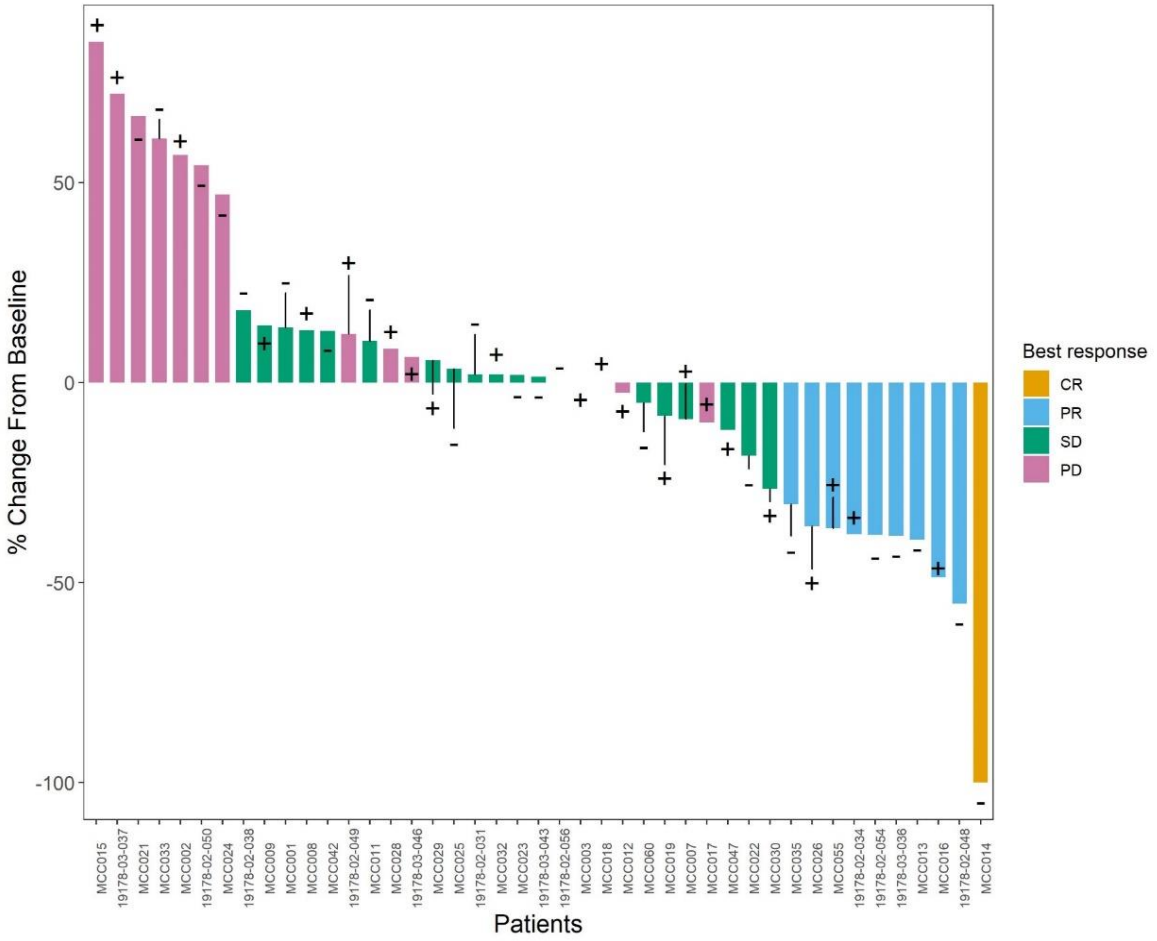
Response Assessments





Chung C et al, ASCO 2020

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In development: Selected ongoing combination trials

Trial	Patient population	Treatment arms	Targets	Expected study completion
LEAP-010	Untreated recurrent/ metastatic PD-L1+ HNSCC (CPS ≥ 1)	Pembrolizumab + lenvatinib	PD-1 + multikinase inhibitor	April 2024
		Pembrolizumab	PD-1	
INDUCE-3	Untreated recurrent/ metastatic PD-L1+ HNSCC (CPS ≥ 1)	Pembrolizumab + GSK609	PD-1 + ICOS	July 2023
		Pembrolizumab	PD-1	
NCT02643550	HNSCC after 1-2 therapies, including progression on Pt	Monalizumab + cetuximab	NKG2A + EGFR	Phase 1/2: 2021 Phase 3: planned

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Conclusions

- Cytotoxic chemotherapy achieves limited survival in HNSCC 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 and development of predictive biomarkers.

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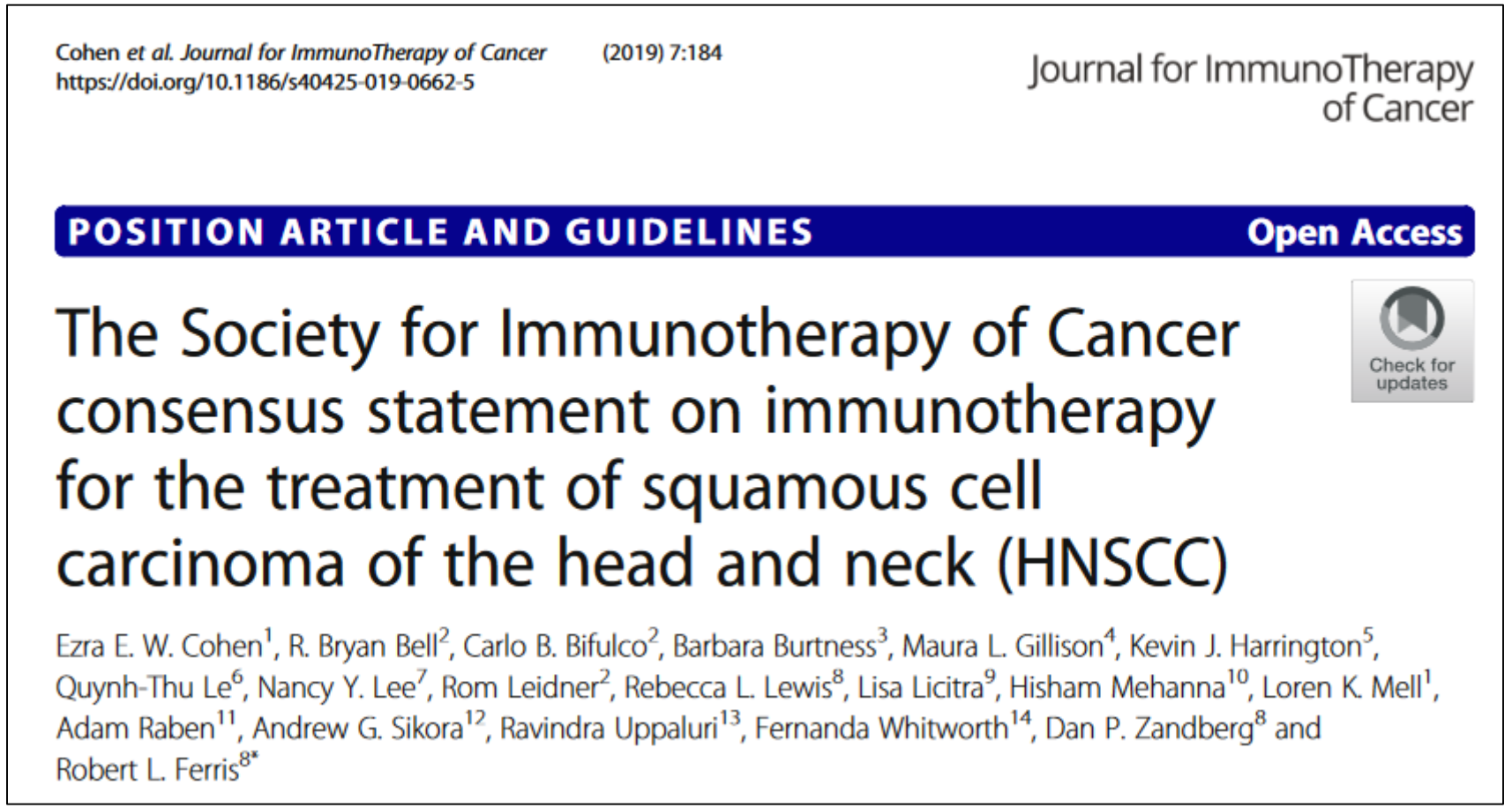
Resources



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)

Ezra E. W. Cohen[1], R. Bryan Bell[2], Carlo B. Bifulco[2], Barbara Burtness[3], Maura L. Gillison[4], Kevin J. Harrington[5], Quynh-Thu Le[6], Nancy Y. Lee[7], Rom Leidner[2], Rebecca L. Lewis[8], Lisa Licitra[9], Hisham Mehanna[10], Loren K. Mell[1], Adam Raben[11], Andrew G. Sikora[12], Ravindra Uppaluri[13], Fernanda Whitworth[14], Dan P. Zandberg[8] and Robert L. Ferris[8*]

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Society for Immunotherapy of Cancer

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Case Studies

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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Knowledge base assessment question

- A patient with known HPV related OPSCC presents with evidence of lung metastases 9 months after completion of concurrent therapy for a T4N3 (AJCC8) disease; his disease is PD-L1 negative (CPS <1) what would be your systemic therapy of choice (based on currently approved recommendations)?

- 1- Pembrolizumab
- 2- Nivolumab
- 3- EXTREME regimen
- 4- Pembro with Taxol and Carboplatin

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Knowledge base assessment question

- A patient with known HPV unrelated LC presents with T4aN1 disease; his disease is PD-L1 positive (CPS =20); He is deemed to have a functioning larynx and you are planning a larynx preservation approach; what would your best choice of treatment be;

- 1- Cisplatin with radiotherapy
- 2- Avelumab + Cisplatin + radiotherapy based on the Javelin results
- 3- Concurrent therapy followed by maintenance immunotherapy
- 4-Refer for a clinical trial of chemo-immunotherapy

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Instructions - Case Study 1

Please use the format below to present a case study with which you are familiar. Case studies that are written, should follow this format so that the case studies can be used as inquiry-based practice for clinicians both at the live ACI programs, as well as in the ACI online interactive courses.

Case Study Format

1. A brief summary of the patient, age, gender, cancer and stage, prior treatment, what is happening now – why she is in your office at this point.
2. Question 1 about the case (What would you do?)
   A. Option 1 (include written feedback about this option- correct/incorrect and why)
   B. Option 2 (“)
   C. Option 3 (“)
   D. Option 4 (“)
3. Summary of the results of that decision.
4. Question 2 about the case (What is the next step?)
   A. Option 1 (include written feedback about this option- correct/incorrect and why)
   B. Option 2 (“)
   C. Option 3 (“)
   D. Option 4 (“)
5. Summary of the results of that decision and the final outcome for that patient.

* If there are more treatment decisions that were made in the case, please just add subsequent steps to account for them, using the same format.

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