Society for Immunotherapy of Cancer

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

Society for Immunotherapy of Cancer

Disclosures

Amgen, AstraZeneca, Bayer, Eisai & Merck

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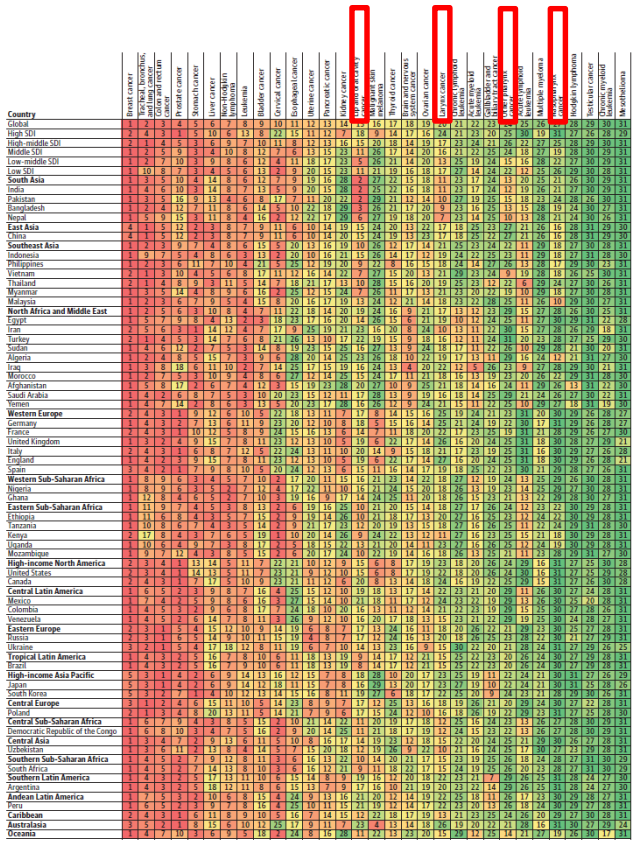


Country	Breast cancer	Tracheal, bronchus, and lung cancer	Colon and rectum cancer	Prostate cancer	Stomach cancer	Liver cancer	Non-Hodgkin lymphoma	Leukemia	Bladder cancer	Cervical cancer	Esophageal cancer	Uterine cancer	Pancreatic cancer	Kidney cancer	Lip and oral cavity cancer	Nasopharynx cancer	Malignant skin melanoma	Thyroid cancer	Brain and nervous system cancer	Ovarian cancer	Larynx cancer	Hodgkin lymphoma	Multiple myeloma	Gallbladder and biliary tract cancer	Other pharynx cancer	Acute lymphoid leukemia	Mesothelioma	Hodgkin lymphoma	Testicular cancer	Chronic myeloid leukemia	Uterine cancer
Global	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
High SDI	2	4	1	11	5	10	6	13	8	22	15	19	12	7	14	18	9	14	17	16	24	10	23	20	25	30	21	27	26	28	31
High-middle SDI	2	1	4	5	3	6	9	7	10	11	8	12	13	16	15	20	18	14	19	17	23	24	21	26	22	27	25	28	29	30	31
Middle SDI	1	2	5	9	3	4	10	8	12	7	6	13	15	23	11	26	17	14	20	16	21	22	25	24	18	27	19	28	30	29	31
Low-middle SDI	1	2	7	10	9	8	6	12	4	11	18	17	23	25	26	21	14	20	13	15	19	24	16	15	28	22	27	30	29	31	
Low SDI	1	10	8	7	3	4	5	6	13	2	9	20	15	23	11	21	19	16	18	17	27	14	24	22	12	25	26	29	30	28	31
South Asia	1	3	5	10	4	14	8	6	12	7	9	19	16	28	2	27	22	15	18	11	23	17	24	13	20	25	21	26	30	29	31
India	1	4	6	10	3	14	8	7	13	5	9	20	15	28	2	25	22	16	18	11	23	17	24	12	19	26	21	27	30	29	31
Pakistan	1	3	5	16	9	13	4	6	8	17	7	11	20	22	2	29	21	12	14	10	27	19	25	15	18	23	24	28	26	30	31
Bangladesh	1	2	4	12	7	11	8	6	14	5	10	22	18	29	3	26	21	17	20	9	23	16	25	13	15	28	19	24	30	27	31
Nepal	1	5	9	15	3	13	8	4	16	12	22	17	30	6	27	19	18	20	7	23	14	25	10	21	28	11	24	26	29	31	
East Asia	4	1	5	12	2	3	8	7	9	11	6	10	14	19	15	24	20	13	22	17	18	25	23	27	21	26	16	28	31	29	30
China	4	1	5	12	2	3	8	7	9	11	6	10	14	20	15	24	19	13	23	17	18	25	22	27	21	26	16	28	31	29	30
Southeast Asia	1	2	3	9	7	4	8	6	11	5	10	13	16	19	10	26	12	17	14	21	25	23	24	15	22	18	27	30	28	29	31
Indonesia	1	9	7	5	4	8	6	3	13	2	20	10	16	21	15	26	14	17	12	19	24	22	25	23	11	29	18	27	31	28	30
Philippines	1	2	3	6	11	7	10	4	21	5	25	12	19	20	9	22	8	16	15	18	24	14	27	26	13	28	17	29	30	23	31
Vietnam	2	1	3	10	4	5	6	9	11	12	16	14	22	27	27	15	20	13	21	30	23	24	9	19	18	26	25	30	31		
Thailand	2	1	4	8	9	3	11	5	14	7	18	21	17	13	10	28	15	16	20	19	25	23	12	22	6	29	24	27	30	26	31
Myanmar	1	3	5	14	4	8	9	6	16	2	25	12	15	24	7	26	11	17	13	21	23	20	22	19	10	29	18	27	30	28	31
Malaysia	1	3	6	7	9	5	4	15	8	20	16	17	19	13	24	12	21	14	18	23	22	28	25	11	26	10	29	30	27		
North Africa and Middle East	1	2	5	6	3	10	8	4	7	11	22	18	14	20	19	24	16	9	21	17	13	12	23	29	15	27	28	26	30	25	31
Egypt	1	5	7	9	8	4	13	2	3	18	23	17	16	20	14	26	15	6	21	19	10	12	24	25	11	27	30	29	31	22	28
Iran	2	5	6	3	1	14	13	4	7	9	25	19	21	28	16	20	8	24	26	15	12	11	22	30	17	29	27	26	18	31	
Turkey	2	1	4	5	3	14	7	6	8	21	26	13	10	17	22	19	15	9	18	16	12	11	24	31	20	23	28	27	25	29	30
Sudan	1	4	6	12	2	7	5	3	14	8	19	23	15	25	16	27	13	9	24	18	17	11	22	26	10	29	28	21	30	20	31
Algeria	2	4	8	5	15	7	3	9	6	28	20	14	29	23	26	18	10	22	19	17	13	11	29	16	24	12	21	30	27	31	
Iraq	1	3	8	18	6	11	10	2	7	14	25	17	15	19	16	24	13	4	20	22	12	5	26	23	9	27	28	29	30	21	31
Morocco	1	2	7	5	3	10	9	4	8	6	27	12	14	25	15	24	17	11	21	18	16	13	19	23	20	26	22	29	31	28	30
Afghanistan	1	5	6	17	2	6	7	4	12	3	15	19	23	26	20	27	10	9	25	21	18	14	16	24	11	30	26	13	22	29	
Saudi Arabia	1	4	2	6	8	7	5	3	10	20	23	15	12	11	17	28	13	9	19	16	18	14	25	29	21	24	26	27	30	22	31
Yemen	1	4	7	14	2	8	6	3	13	5	20	23	17	28	16	26	12	9	24	21	15	11	22	25	10	29	27	18	31	19	30
Western Europe	2	3	1	9	12	5	10	6	11	8	22	18	13	11	7	17	8	14	15	16	26	10	24	21	23	30	20	30	29	26	28
Germany	1	4	3	2	7	13	6	11	9	23	20	12	10	8	18	5	15	16	14	25	21	24	19	22	30	17	31	29	26	28	27
France	2	4	3	1	10	12	5	8	9	24	15	16	13	6	14	7	11	18	20	22	17	23	25	19	31	21	28	29	26	27	30
United Kingdom	1	3	2	4	9	15	8	11	14	13	10	5	6	22	17	14	26	16	20	24	25	31	18	30	28	27	29	21			
Italy	2	4	3	1	6	8	7	12	5	22	24	13	11	10	20	14	9	15	18	21	17	23	19	25	31	16	30	29	27	26	28
England	1	4	2	3	9	15	7	8	11	23	12	13	10	5	19	6	22	17	14	27	16	20	24	25	31	18	30	29	26	28	21
Spain	3	4	2	1	7	9	8	10	5	20	16	21	13	6	15	11	16	14	17	18	26	22	23	30	31	28	27	25			
Western Sub-Saharan Africa	1	8	9	6	3	4	5	7	10	2	17	20	11	15	16	21	23	14	22	18	27	12	19	24	13	25	29	26	30	28	31
Nigeria	1	8	9	6	3	5	2	7	12	4	17	22	11	10	16	21	24	15	20	18	26	13	19	23	14	25	29	27	30	28	31
Ghana	1	12	4	6	5	2	7	10	3	19	16	9	17	14	24	25	11	20	18	26	15	23	21	13	22	28	30	27	31		
Eastern Sub-Saharan Africa	1	11	9	7	4	5	3	8	13	2	6	19	16	25	10	21	20	15	14	18	27	17	26	24	12	23	22	30	29	28	31
Ethiopia	1	11	6	8	4	3	5	7	15	2	9	19	14	26	10	21	18	17	13	20	27	16	25	23	12	24	22	30	29	28	31
Tanzania	1	10	8	6	7	4	3	5	14	2	9	21	17	23	12	20	19	15	13	16	26	25	22	24	29	11	27	30	28	31	
Kenya	2	17	8	4	3	7	6	5	19	1	10	20	14	26	9	24	22	13	12	11	27	16	23	25	15	21	18	30	29	28	31
Uganda	1	10	6	8	9	7	3	8	17	2	5	18	15	22	13	21	20	14	11	23	27	16	26	25	12	24	19	30	29	28	31
Mozambique	1	9	7	12	10	3	8	5	15	2	6	20	17	24	18	22	19	14	16	26	13	25	21	23	27	28	29	31	27	30	
High-income North America	2	3	4	1	13	14	5	11	7	22	21	10	12	9	15	6	8	17	19	23	18	20	26	24	29	16	31	27	25	30	28
United States	2	3	4	1	14	13	5	11	7	23	21	9	12	10	15	6	8	17	19	22	18	20	26	24	30	16	31	27	25	29	28
Canada	2	4	3	1	7	17	5	10	9	21	11	12	6	20	8	13	14	15	24	16	19	22	25	29	15	31	27	26	30	28	
Central Latin America	1	6	5	2	3	9	8	7	16	4	25	15	12	10	19	18	13	17	14	22	23	21	20	29	11	26	30	27	24	28	31
Mexico	1	7	4	2	5	9	8	6	16	3	27	15	14	10	21	18	11	17	12	24	23	22	19	20	13	26	30	25	29	28	31
Colombia	1	4	3	2	5	9	6	8	17	7	24	18	10	20	16	13	12	14	21	22	23	19	29	15	30	27	28	26			
Venezuela	1	4	5	2	6	14	7	8	11	3	26	9	12	10	16	20	17	18	13	15	23	21	22	29	19	25	30	24	28	27	31
Eastern Europe	2	3	1	5	4	15	12	10	9	14	19	6	8	7	17	13	24	16	11	18	20	26	22	21	29	23	30	25	27	28	31
Russia	2	3	1	6	5	14	9	10	11	15	18	8	7	17	12	24	16	13	20	18	26	25	23	28	22	27	29	21	27	29	31
Ukraine	3	2	1	5	4	17	18	12	8	11	19	6	7	10	14	13	23	16	9	15	30	22	20	21	28	24	31	27	29	26	25
Tropical Latin America	1	4	3	2	5	16	7	8	10	6	11	18	13	19	9	14	17	12	21	15	25	22	23	20	26	24	30	27	29	28	31
Brazil	1	4	3	2	5	16	7	8	10	6	11	18	13	19	9	14	17	12	21	15	25	22	23	20	26	24	30	27	29	28	31
High-income Asia Pacific	5	3	1	4	2	6	9	14	13	16	12	15	7	8	18	28	10	20	17	23	25	19	11	22	24	21	30	31	27	26	29
Japan	5	3	1	4	2	6	9	14	12	18	11	15	7	8	16	29	13	20	17	23	27	19	10	22	24	21	30	31	25	28	26
South Korea	5	3	2	4	1	9	14	15	16	13	12	11	8	7	10	27	6	17	18	25	20	9	24	23	22	29	19	26	21	30	28
Central Europe	3	1	2	4	6	15	11	10	5	14	23	8	9	7	17	12	25	13	16	18	19	26	21	20	29	24	30	27	22	28	31
Poland	2	1	3	4	8	20	13	11	6	14	21	7	9	6	17	15	24	12	10	16	18	26	19	22	29	23	31	27	25	28	30
Central Sub-Saharan Africa	1	5	7	9	4	8	6	3	10	2	17	15	24	22	21	20	19	18	17	16	25	23	26	16	24	27	28	29	30	31	
Democratic Republic of the Congo	1	6	8	10	3	4	7	5	16	2	9	20	14	25	11	21	18	17	19	12	24	15	23	22	13	26	27	28	30	29	31
Central Asia	1	3	4	7	2	9	13	6	11	5	10	8	16	17	14	19	23	12	18	15	22	20	24	25	21	29	30	26	27	28	31
Uzbekistan	2	3	4	11	7	13	8	6	14	5	10	9	12	16	15	17	26	18	19	22	20	24	25	21	27	23	28	29	30	31	
Southern Sub-Saharan Africa	1	4	5	2	7	9	12	8	11	3	6	16	13	22	10	14	20	21	17	15	23	19	25	26	18	24	28	27	31	30	29
South Africa	1	4	5	2	7	14	13	8	10	3	6	16	12	21	9	11	18	22	17	15	24	19	25	26	20	23	28	27	31	30	29
Southern Latin America	1	4	3	2	5	13	14	6	11	8	9	10	15	12	20	18	22	17	16	19	21	27	24	7	28	26	23	25	29	30	
Argentina	1	4	3	2	5	18	12	11	8	6	15	13	7	9	17	16	10	21	19	20	23	22	14	29	26	25	31	28	24	27	30
Andean Latin America	1	7	5	3	2	10	6	8	15	4	24	9	13	16	21	20	12	14	19	22	25	18	11	26	17	23	30	29	28	27	31
Peru	1	6	5	3	2	9	7	8	16	4	25	10	11	15	21	19	12	14	18	22	20	17	13	26	24	23	30	29	27	28	31
Caribbean	2	4	3	1	6	11	8	9	10	5	16	7	14	15	12	22	18	17	19	13	21	23	25	24	26	20	29	27	30	28	31
Australasia	3	5	2	1	8	15	6	10	12	25	17	9	11	7	23	4	13	14	18	26	19	20	22	21	28	16	31	30	27	29	24
Oceania	1	4	7	10	3	6	9	5	18	8	24	8	16	28	11	22	13	23	20	15	28	12	25	14	21	27	19	26	30	17	31

Head and neck squamous cell carcinoma (HNSCC) encompasses a variety of tumours originating in the lip, oral cavity, hypopharynx, oropharynx, nasopharynx or larynx.

It is the sixth most common malignancy worldwide, accounting for approximately 6% of all cancer cases, responsible for an estimated 1%–2% of all cancer deaths.

Oral cavity and laryngeal cancers are the most common head and neck cancers globally (age-adjusted standardised incidence rate 3.9 and 2.3 per 100 000, respectively).

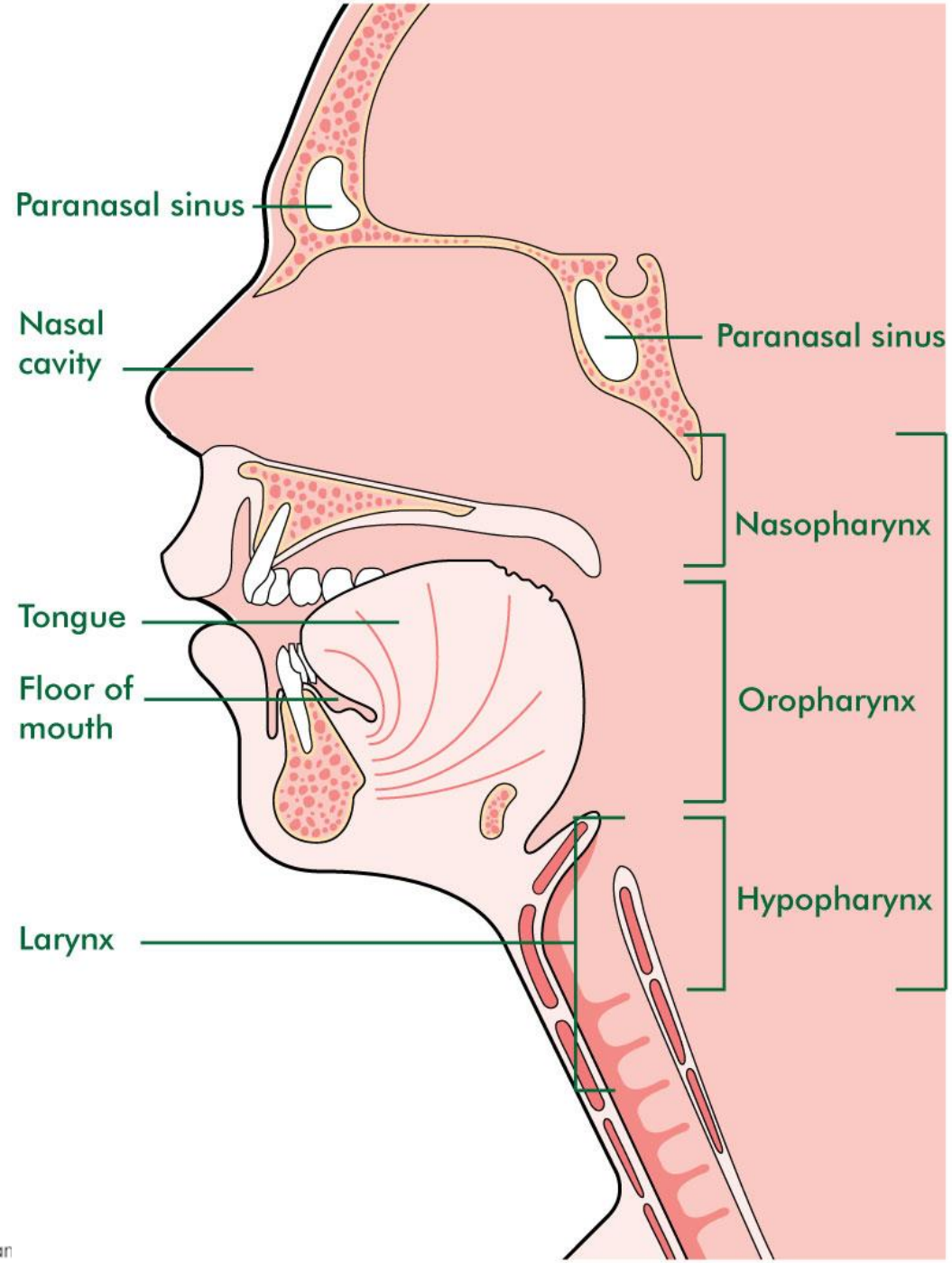
HNSCC is predicted to account for 742 270 new cases and 407 037 deaths worldwide, for the year 2015. It is the most common cancer in Central Asia.

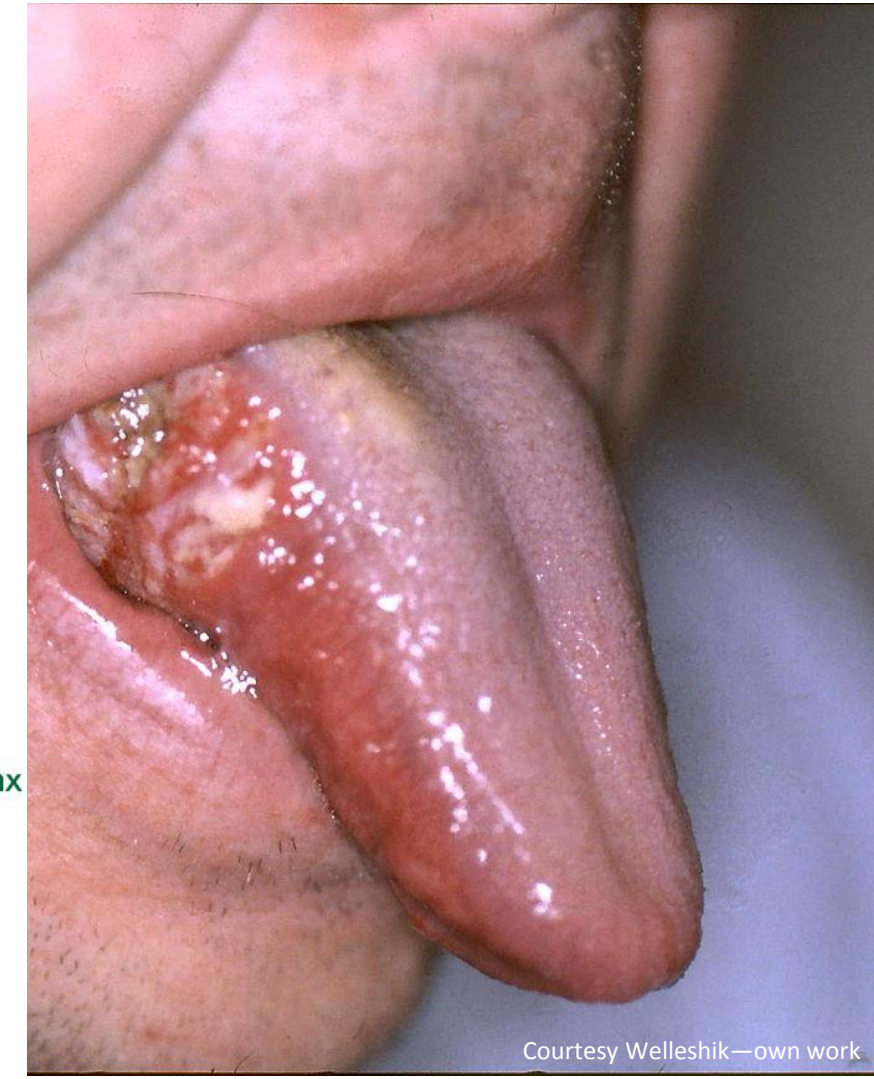
2017-ESMO-Essentials-for-Clinicians

AAEM American Academy of Emergency Medicine

ACCC Association of Community Cancer Centers

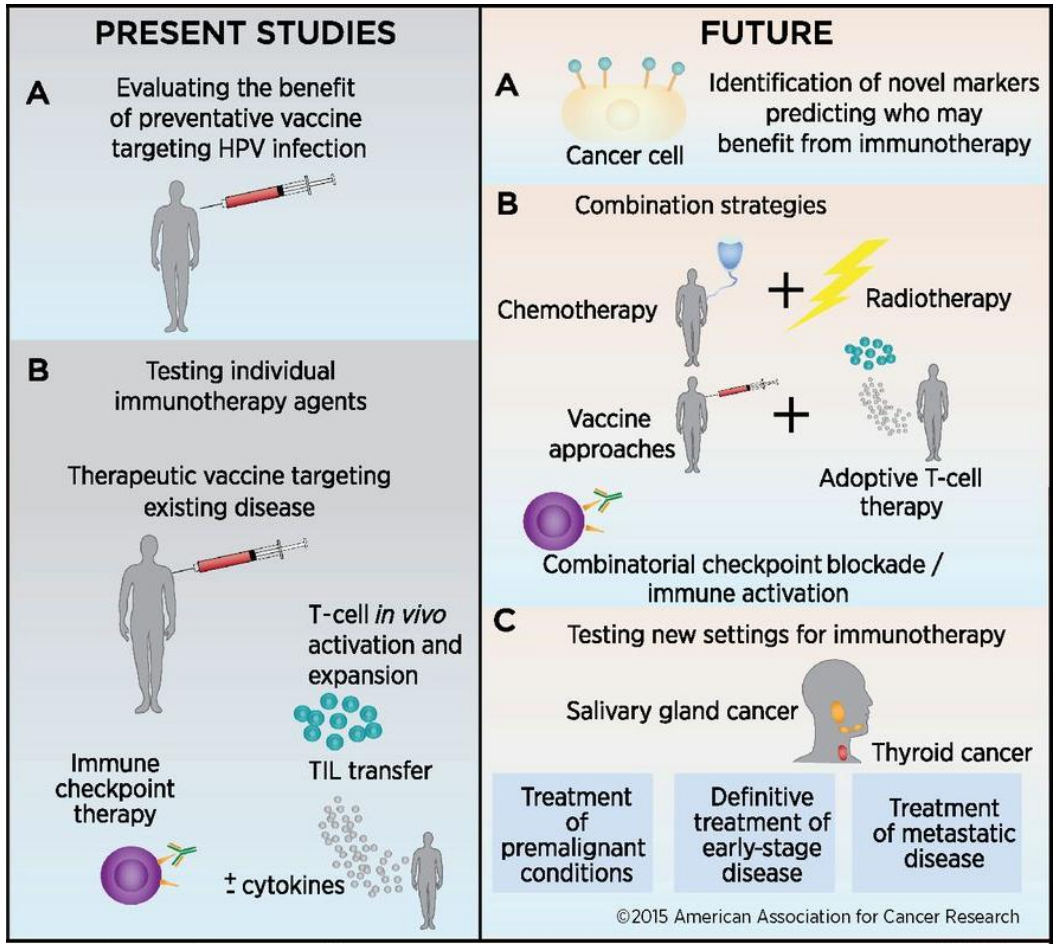
Society for Immunotherapy of Cancer




Courtesy Welleshik—own work

Immunotherapy for the Treatment of Head and Neck Cancers

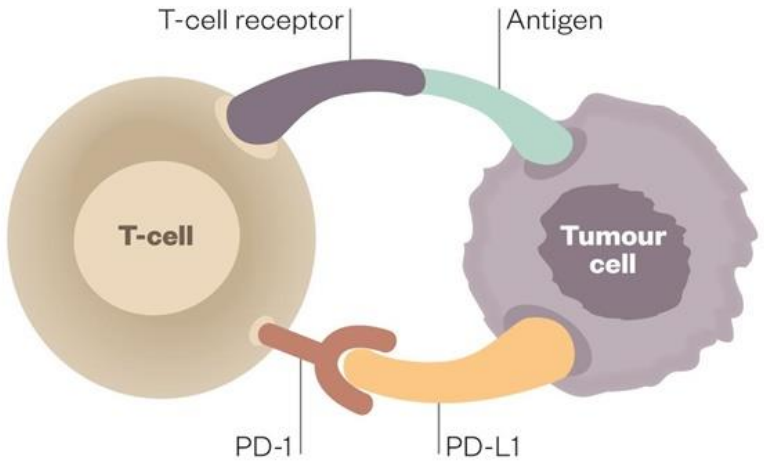
- Immuno-Oncology (I-O) developments in treatment of head and neck cancers
  - Preventive vaccination against virally mediated cancers
  - PD-1 checkpoint inhibitors for the treatment of metastatic disease
  - Testing new settings in non-squamous cancers and early stage squamous cell cancers



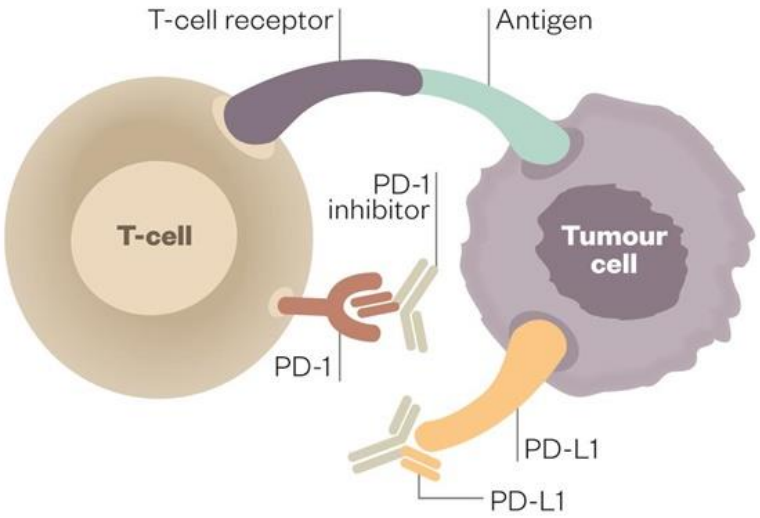
Schoenfeld JD, Cancer Immunol Res, 2015

Immunotherapy for the Treatment of Head and Neck Cancers

Immune Checkpoint Inhibitors (ICI)



PD-1 acts as “off-switch” for T cells, allowing cancer cells to evade immune attack



Antibodies against PD-1 and PD-L1 boost the immune response against cancer cells

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

Phase III Randomized, Safety and Efficacy Trial

Key Eligibility Criteria

- R/M SCCHN of the oral cavity, pharynx, or larynx
- Progression on or within 6 months of last dose of platinum-based therapy
- Irrespective of no. of prior lines of therapy
- Documentation of p16 to determine HPV status (oropharyngeal)
- Regardless of PD-L1 status[a]

Stratification factor

- Prior cetuximab treatment

R 2:1

Nivolumab
3 mg/kg IV Q2W

Vs.

Investigator's Choice

- Methotrexate 40 mg/m² IV weekly
- Docetaxel 30 mg/m² IV weekly
- Cetuximab 400 mg/m² IV once, then 250 mg/m² weekly

Primary endpoint

- OS

Other endpoints

- PFS
- ORR
- Safety
- DOR
- Biomarkers
- Quality of life

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

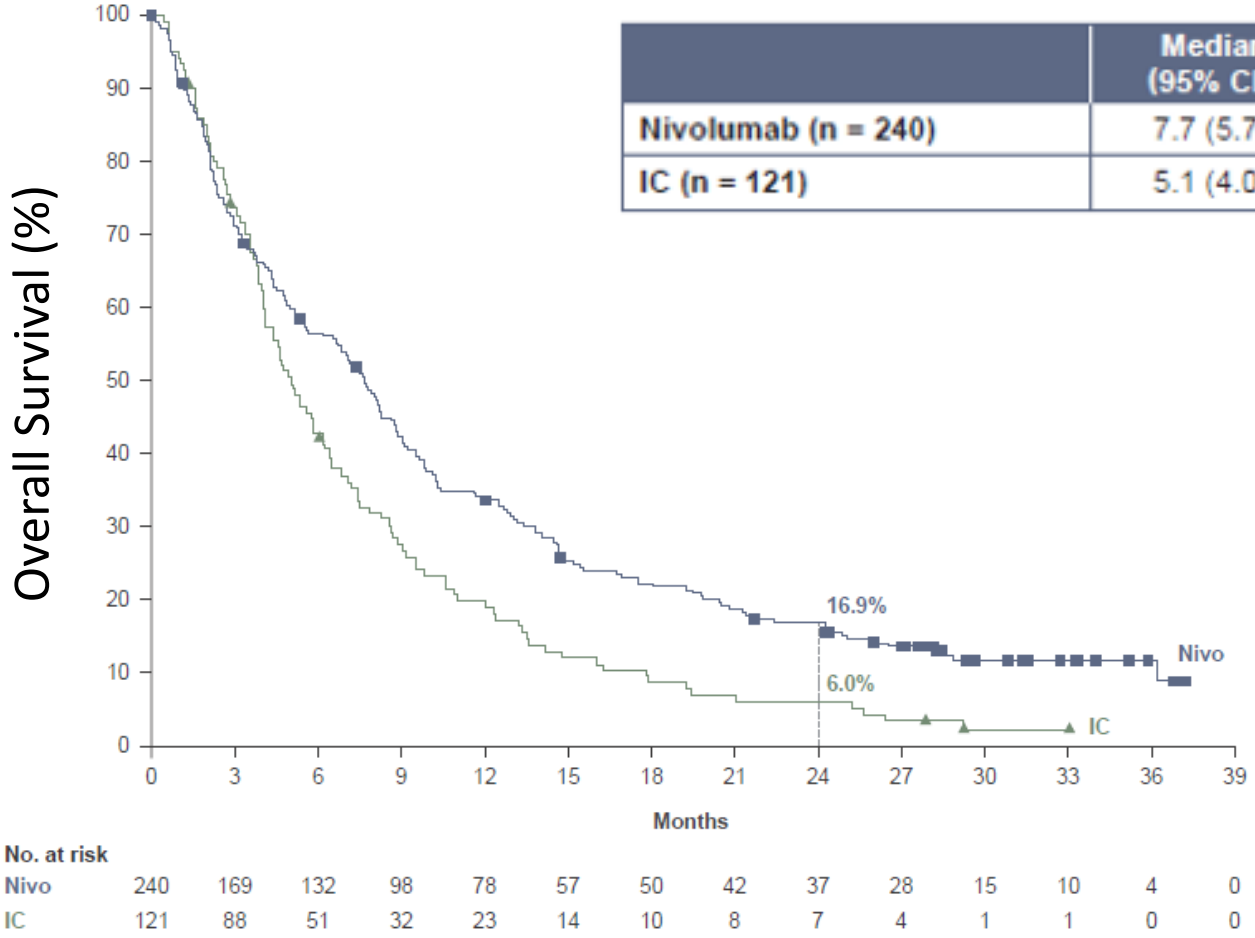
[a]Tissue required for testing

Ferris & Gillison, NEJM, 2016

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

Overall Survival: 2 year report

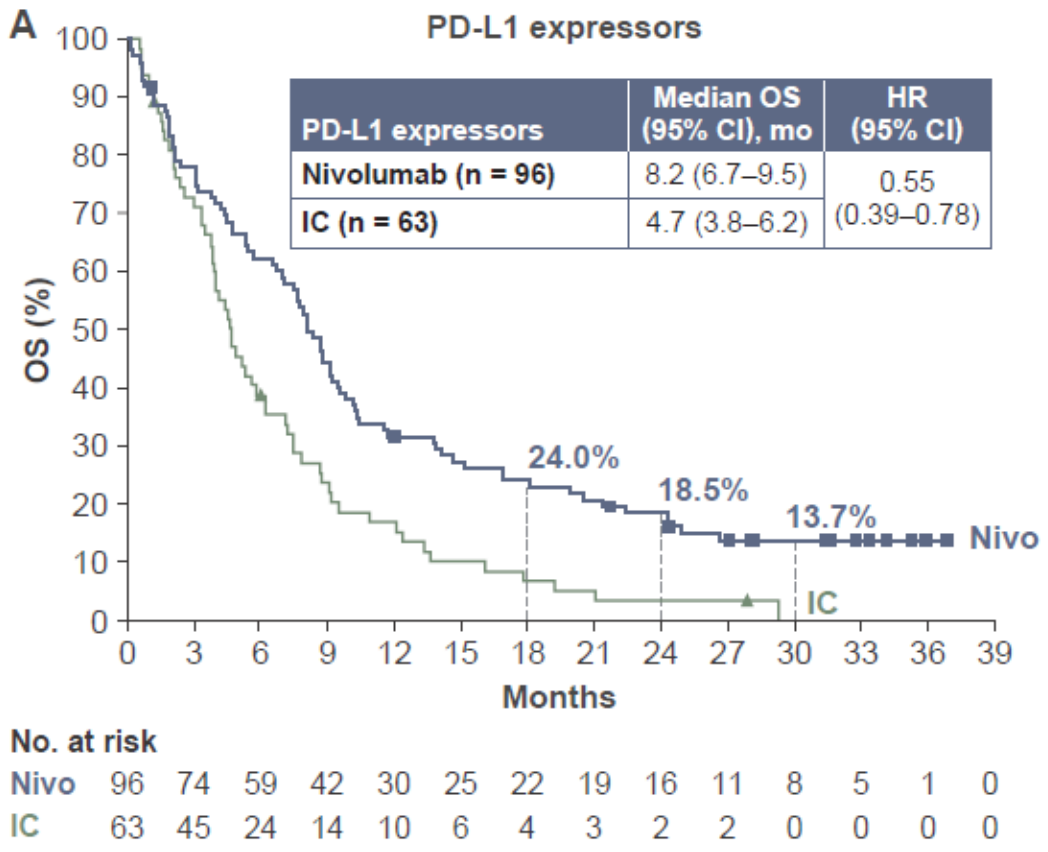
	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 240)	7.7 (5.7–8.8)	0.68 (0.54–0.86)
IC (n = 121)	5.1 (4.0–6.2)	

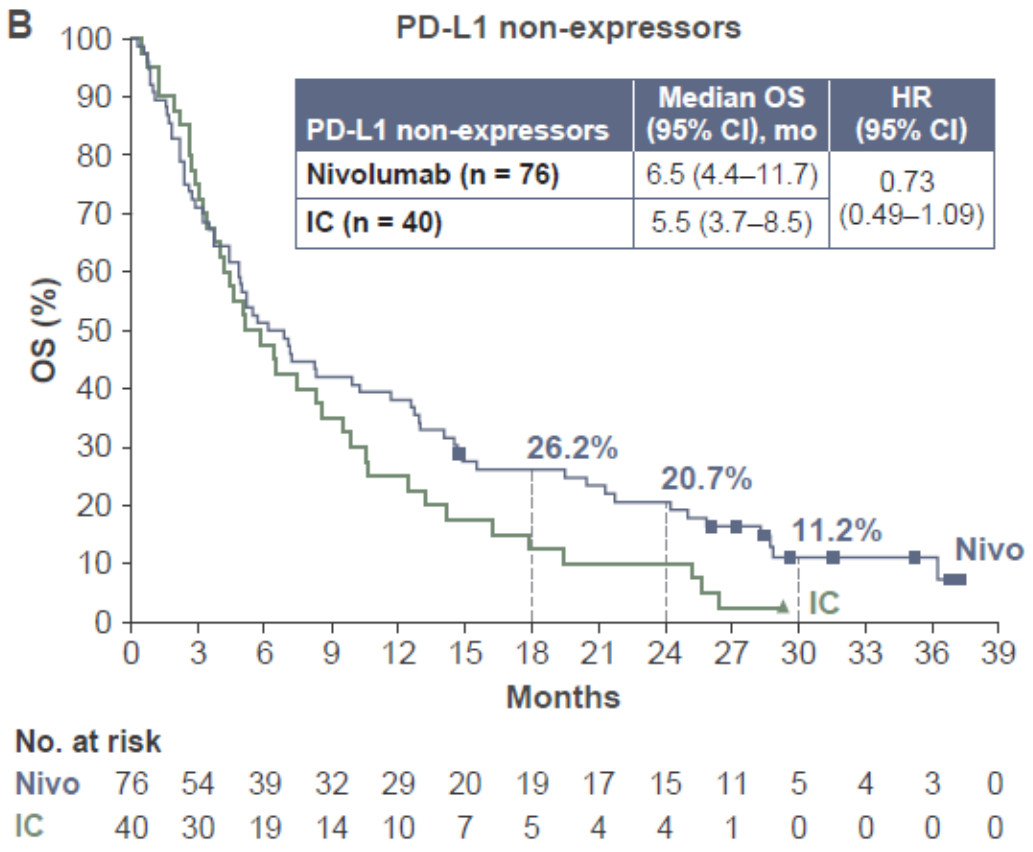


Ferris RL. Oral Oncology, 2018

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

Overall Survival by PD-L1 expression category





Ferris RL. Oral Oncology, 2018

Keynote-040: Pembrolizumab vs Investigator's Choice in R/M HNSCC after Platinum Therapy

Randomized open-label, phase 3 study

Key Eligibility Criteria

- R/M SCCHN of the oral cavity, pharynx, or larynx
- Progression within 3-6 months of last dose of platinum-based therapy
- Irrespective of no. of prior lines of therapy
- Documentation of p16 to determine HPV status (oropharyngeal)
- Regardless of PD-L1 status[a]

Stratification factors

- ECOG 0 or 1, p16 in OPC, PD-L1 TPS < or ≥50%

R 1:1

Pembrolizumab
200 mg IV Q3W

Vs.

Investigator's Choice

- Methotrexate 40 mg/m² IV weekly
- Docetaxel 75 mg/m² IV q3weekly
- Cetuximab 400 mg/m² IV once, then 250 mg/m² weekly

Primary endpoint

- OS

Other endpoints

- OS in CPS≥1
- PFS
- ORR
- Safety
- DOR
- DOR in CPS≥1

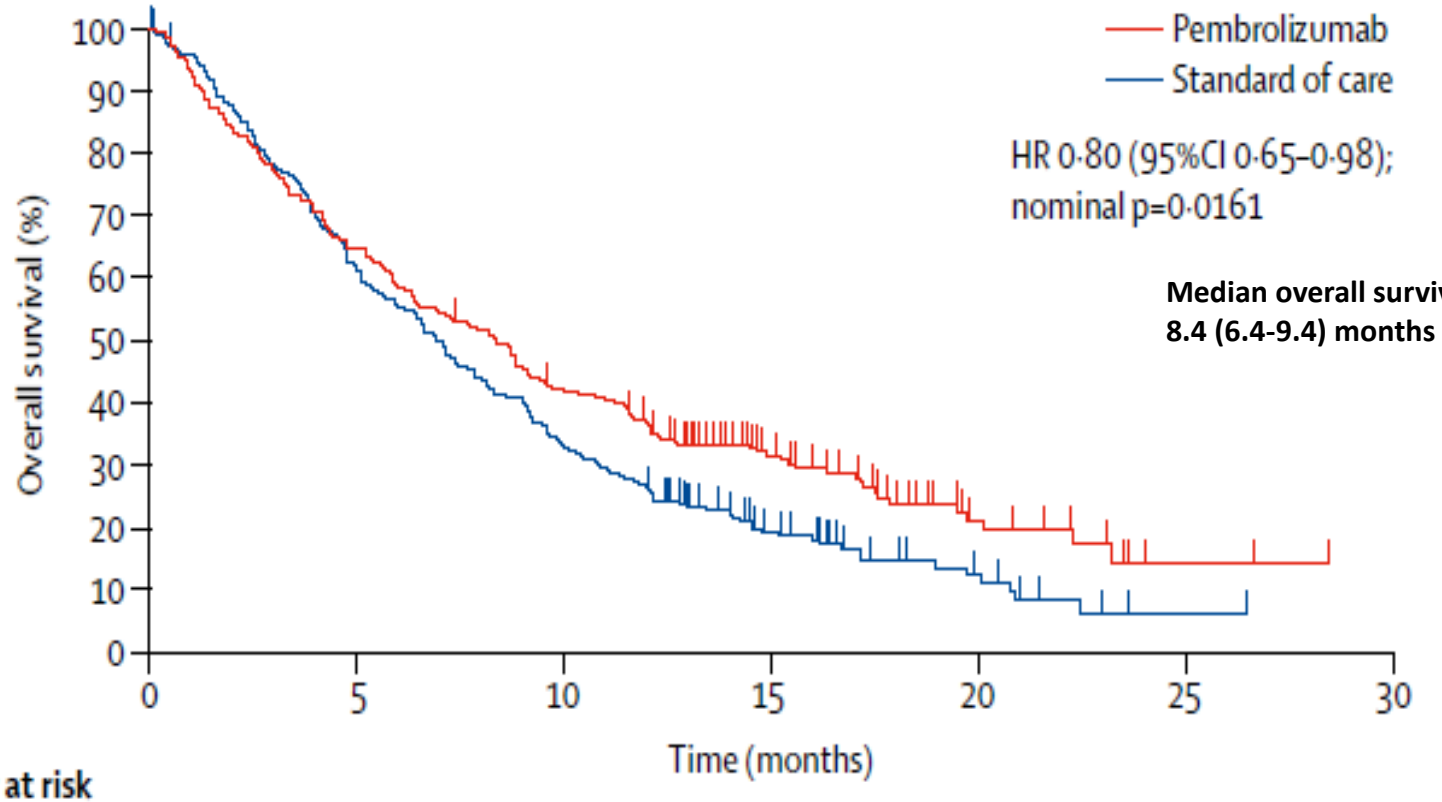
DOR = duration of response; IV = intravenous; ORR = objective response rate; PFS = progression-free survival; Q2W = once every 2 weeks; R = randomized. Clinicaltrials.gov NCT02105636.

[a]Tissue required for testing

Ferris & Gillison, NEJM, 2016

Keynote-040: Pembrolizumab vs Investigator's Choice in R/M HNSCC after Platinum Therapy

Overall survival *post hoc* update of final analysis



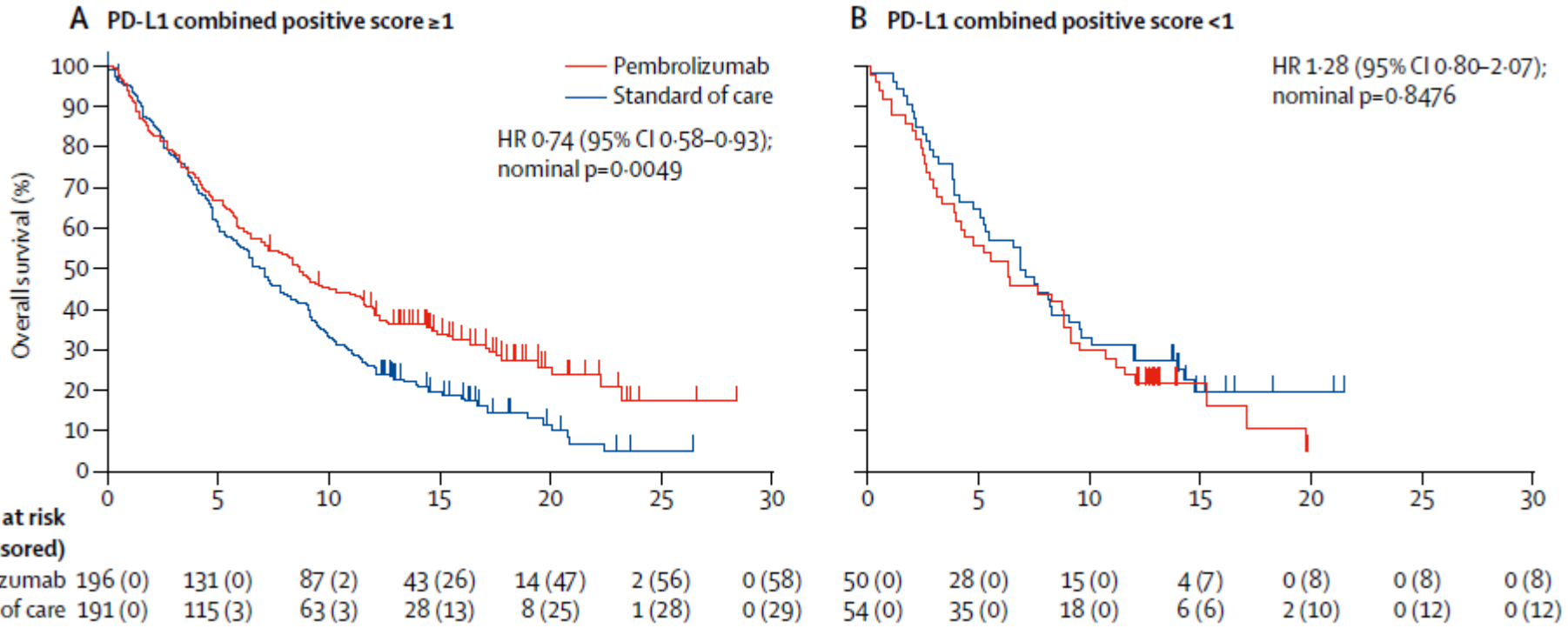
Median overall survival:
8.4 (6.4-9.4) months vs 6.9 (5.9-8.0) months

Number at risk (number censored)							
Pembrolizumab	247 (0)	160 (0)	103 (2)	48 (33)	14 (55)	2 (64)	0 (66)
Standard of care	248 (0)	151 (3)	82 (3)	34 (19)	10 (35)	1 (40)	0 (41)

Cohen Lancet 2019

Keynote-040: Pembrolizumab vs Investigator's Choice in R/M HNSCC after Platinum Therapy

Overall survival by PD-L1 expression category



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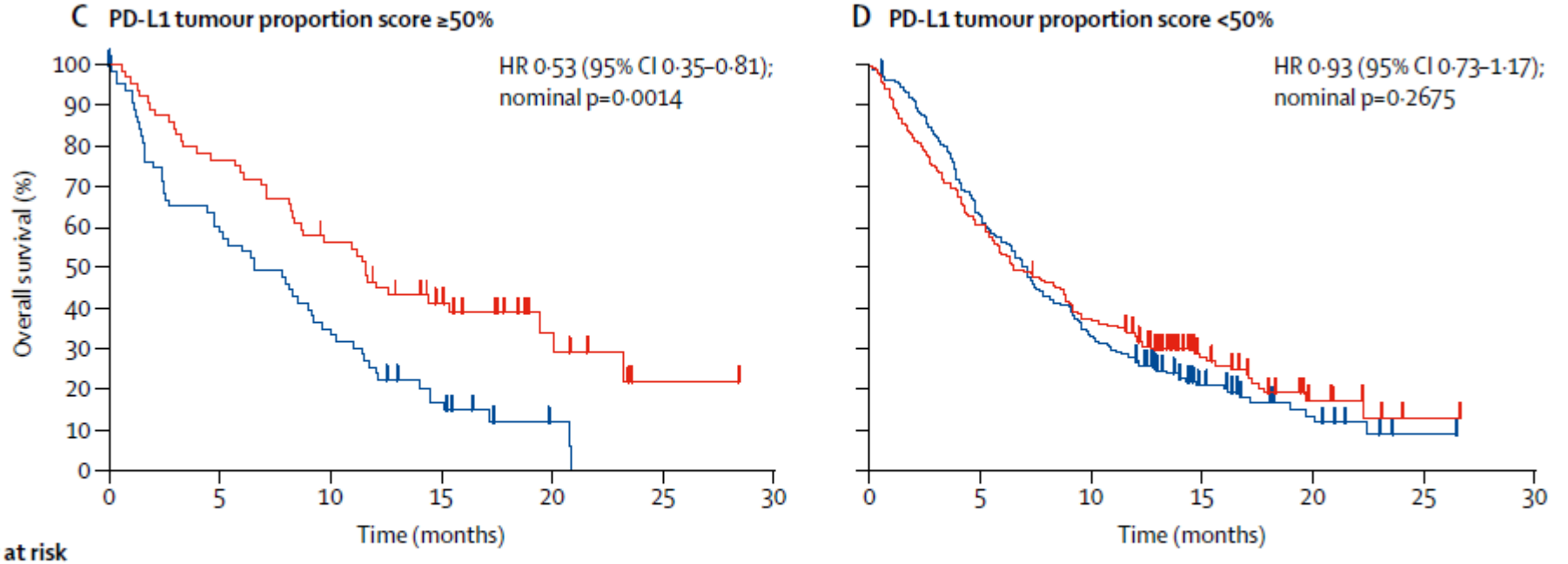
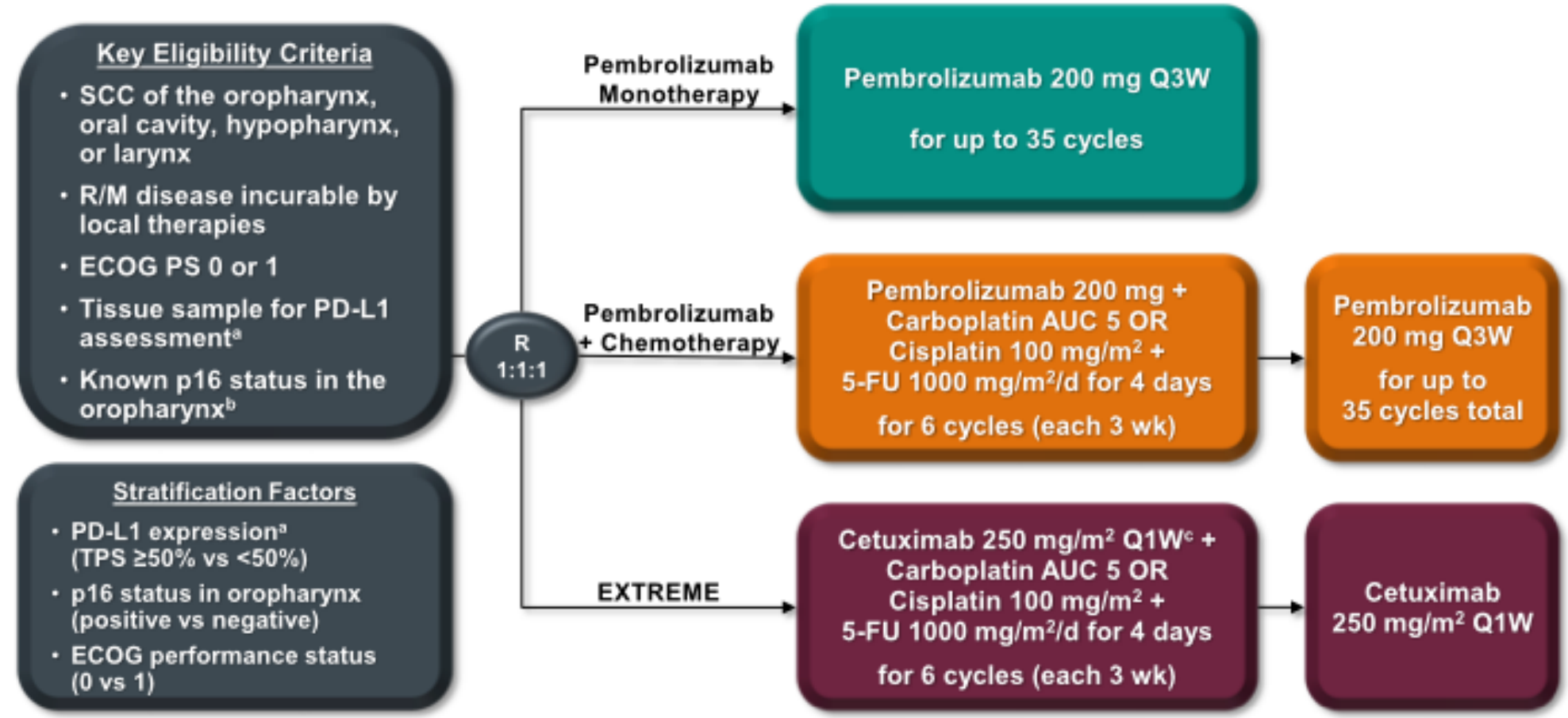


Number at risk (number censored)													
Pembrolizumab	64 (0)	49 (0)	35 (1)	19 (8)	7 (18)	1 (22)	0 (23)	182 (0)	110 (0)	67 (1)	28 (25)	7 (37)	1 (42)	0 (43)
Standard of care	65 (0)	38 (2)	22 (2)	9 (4)	2 (9)	0 (9)	0 (9)	180 (0)	112 (1)	59 (1)	25 (15)	8 (26)	1 (31)	0 (32)

Cohen Lancet 2019

KEYNOTE-048: Pembrolizumab +/- Chemotherapy in First-line R/M HNSCC



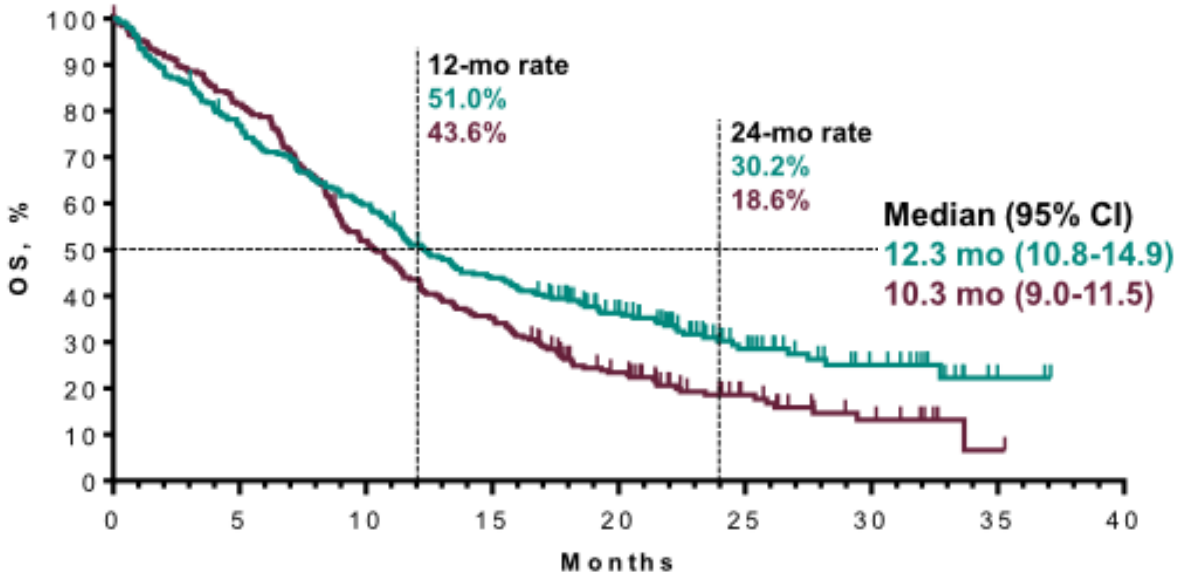
[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Burtness et al. ESMO 2018

KEYNOTE-048: Pembrolizumab +/- Chemotherapy in First-line R/M HNSCC

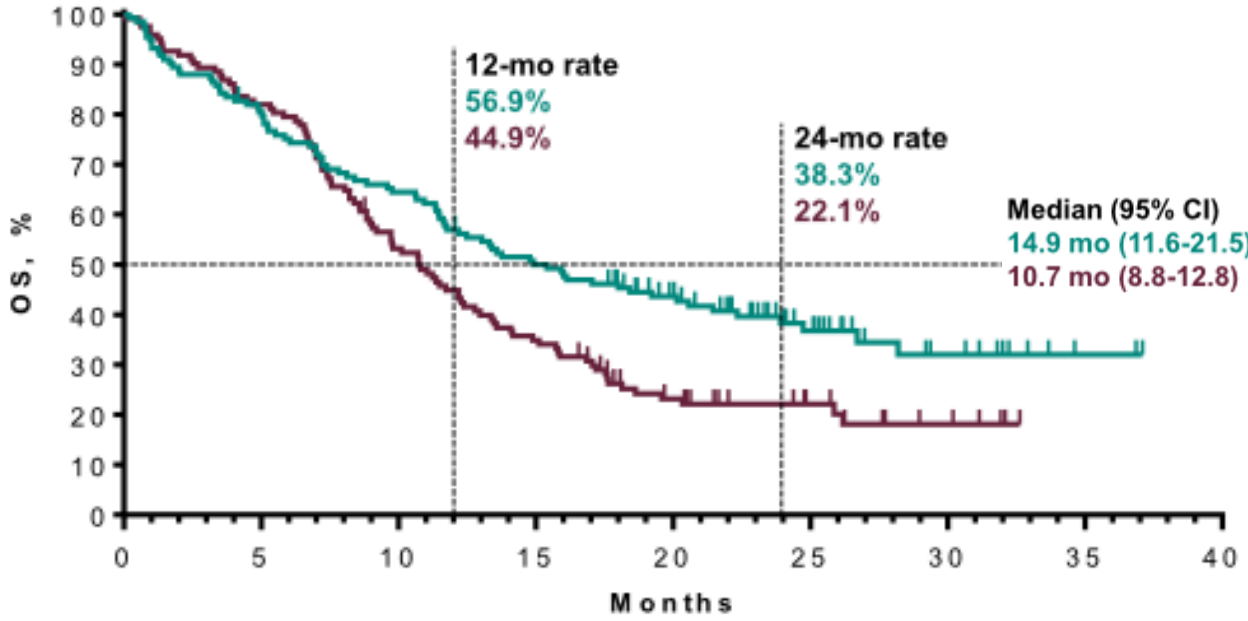
PD-L1 CPS ≥ 1%

	Events	HR (95% CI)	*P*
Pembro alone	69%	0.78 (0.64-0.96)	0.0086
EXTREME	81%		



PD-L1 CPS ≥ 20%

	Events	HR (95% CI)	*P*
Pembro alone	62%	0.61 (0.45-0.83)	0.0007
EXTREME	78%		

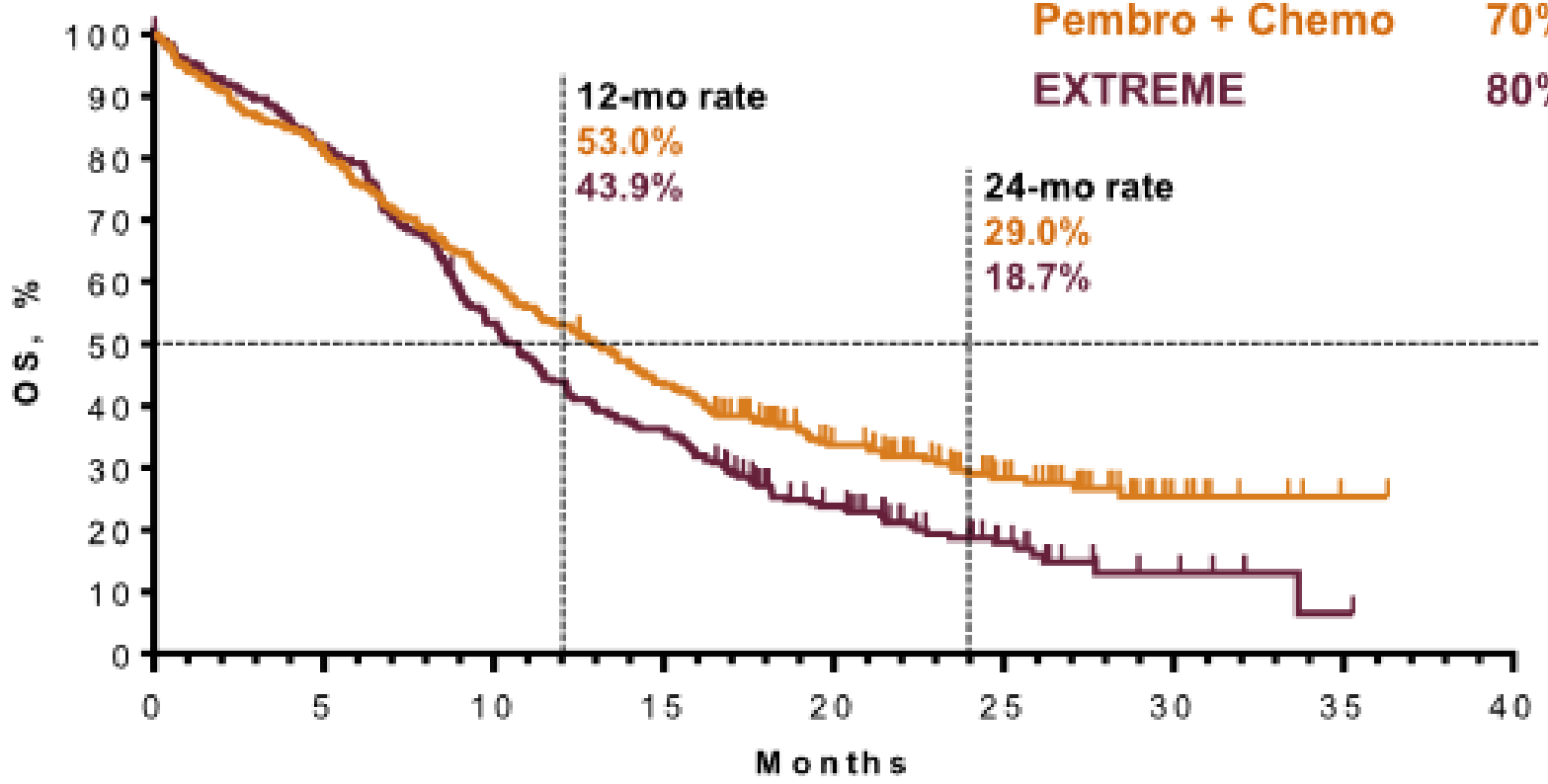


Burtness et al. ESMO 2018

KEYNOTE-048: Pembrolizumab +/- Chemotherapy in First-line R/M HNSCC

All Patients

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

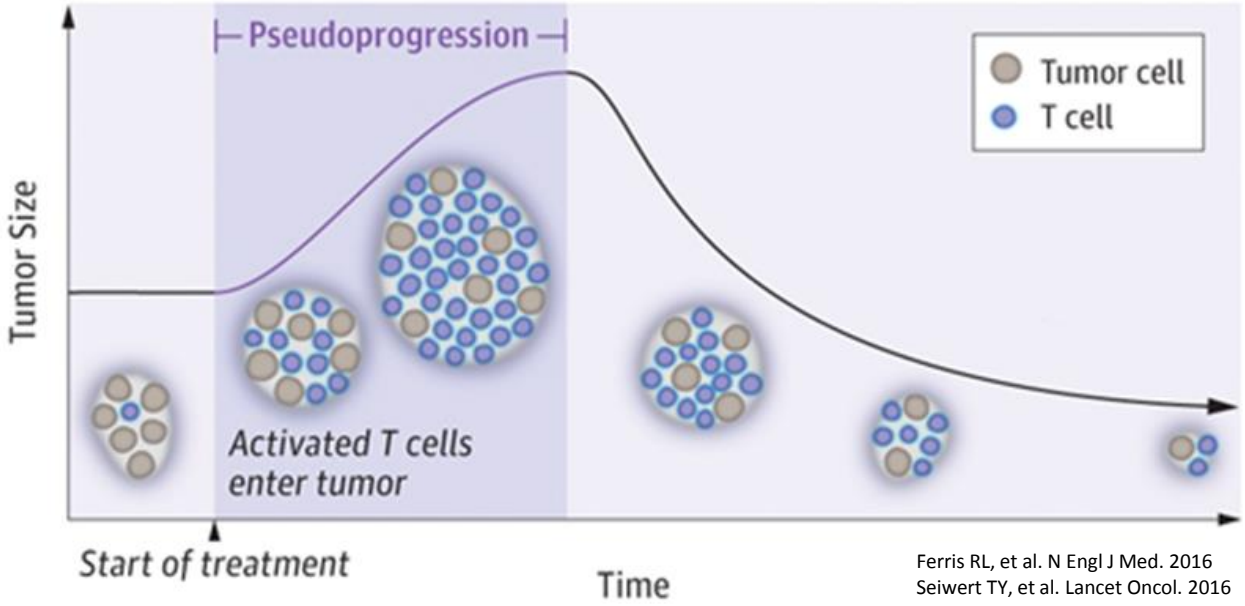


Burtness et al. ESMO 2018

Response to Immune Checkpoint Inhibitor Treatment with Brief Increase in Tumor Size

Pseudoprogression

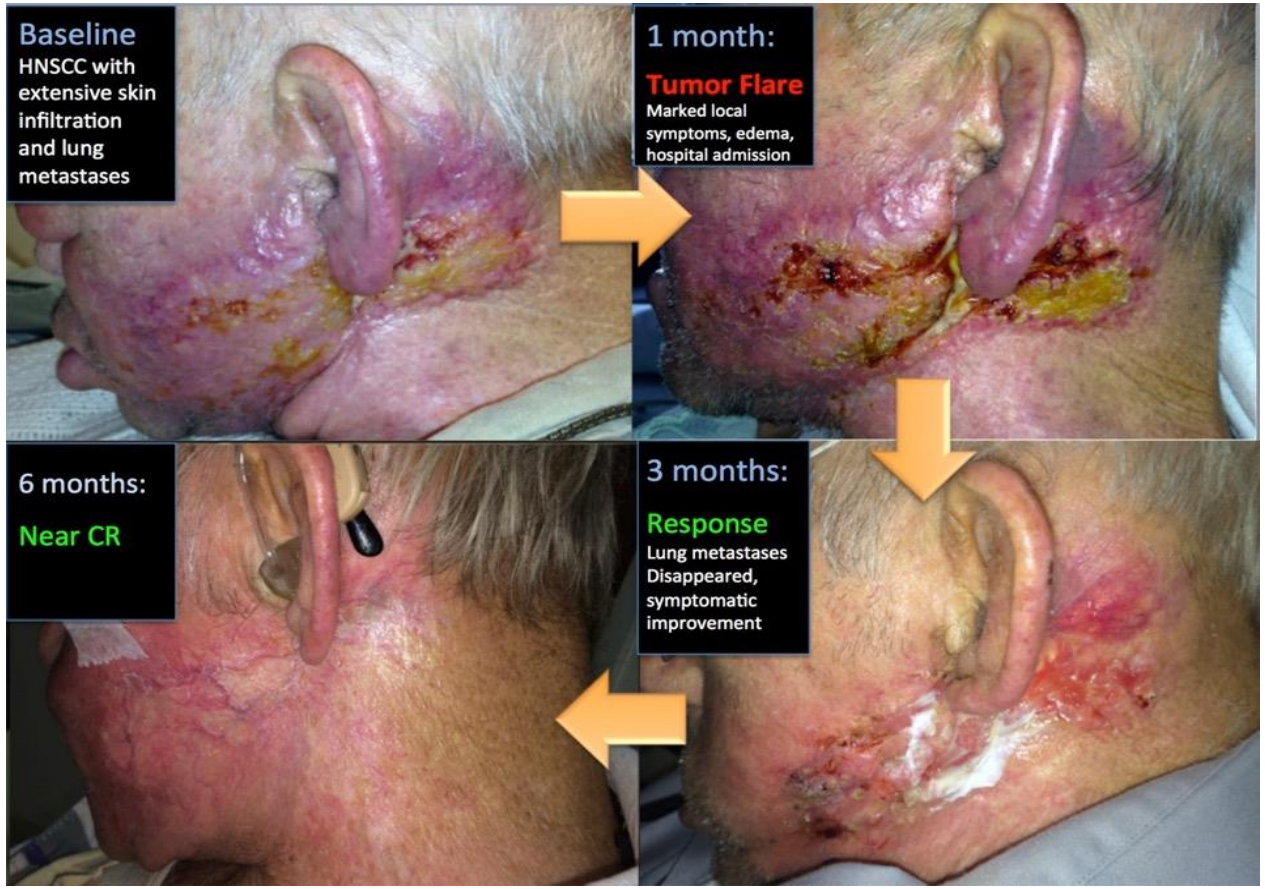
- Early appearance of an increase in tumor burden, subsequently followed by tumor regression
- Initially recognized in the melanoma trials, with incidence up to 10%



Ferris RL, et al. N Engl J Med. 2016
Seiwert TY, et al. Lancet Oncol. 2016

Response to Immune Checkpoint Inhibitor Treatment with Brief Increase in Tumor Size

Case Report – KEYNOTE-012



- KEYNOTE-012 and CheckMate 141 trials showed rare pseudoprogression with pembrolizumab and nivolumab.

Ferris RL, et al. N Engl J Med. 2016
Seiwert TY, et al. Lancet Oncol. 2016

Immune-related Adverse Events

KEYNOTE-012 and CheckMate 141

KEYNOTE 012

Table 2. Treatment-Related Adverse Events by Grade Severity (all-patients-as-treated population; N = 132)

Treatment-Related Adverse Event	Grade 1 or 2 (≥ 10% of patients), No. (%)	Grade 3 (any occurrence), No. (%)	Grade 4 (any occurrence), No. (%)
Patients with ≥ 1 event	70 (53)	8 (6)	4 (3)
Hypothyroidism	14 (11)	0	0
Immune thrombocytopenic purpura	0	0	1 (1)
Abdominal pain	1 (1)	1 (1)	0
Colitis	0	1 (1)	0
Dysphagia	1 (1)	1 (1)	0
Nausea	6 (5)	1 (1)	0
Stomatitis	1 (1)	1 (1)	0
Facial edema	0	1 (1)	0
Fatigue	28 (21)	0	0
Localized edema	0	1 (1)	0
Infection	0	1 (1)	0
Decreased appetite	9 (7)	2 (2)	0
Dehydration	0	1 (1)	0
Diabetic ketoacidosis	0	0	1 (1)
Hyperglycemia	1 (1)	0	1 (1)
Type I diabetes mellitus	0	1 (1)	0
Laryngeal edema	0	0	1 (1)
Pneumonitis	2 (2)	2 (2)	0
Respiratory distress	0	1 (1)	0
Facial swelling	3 (2)	1 (1)	1 (1)

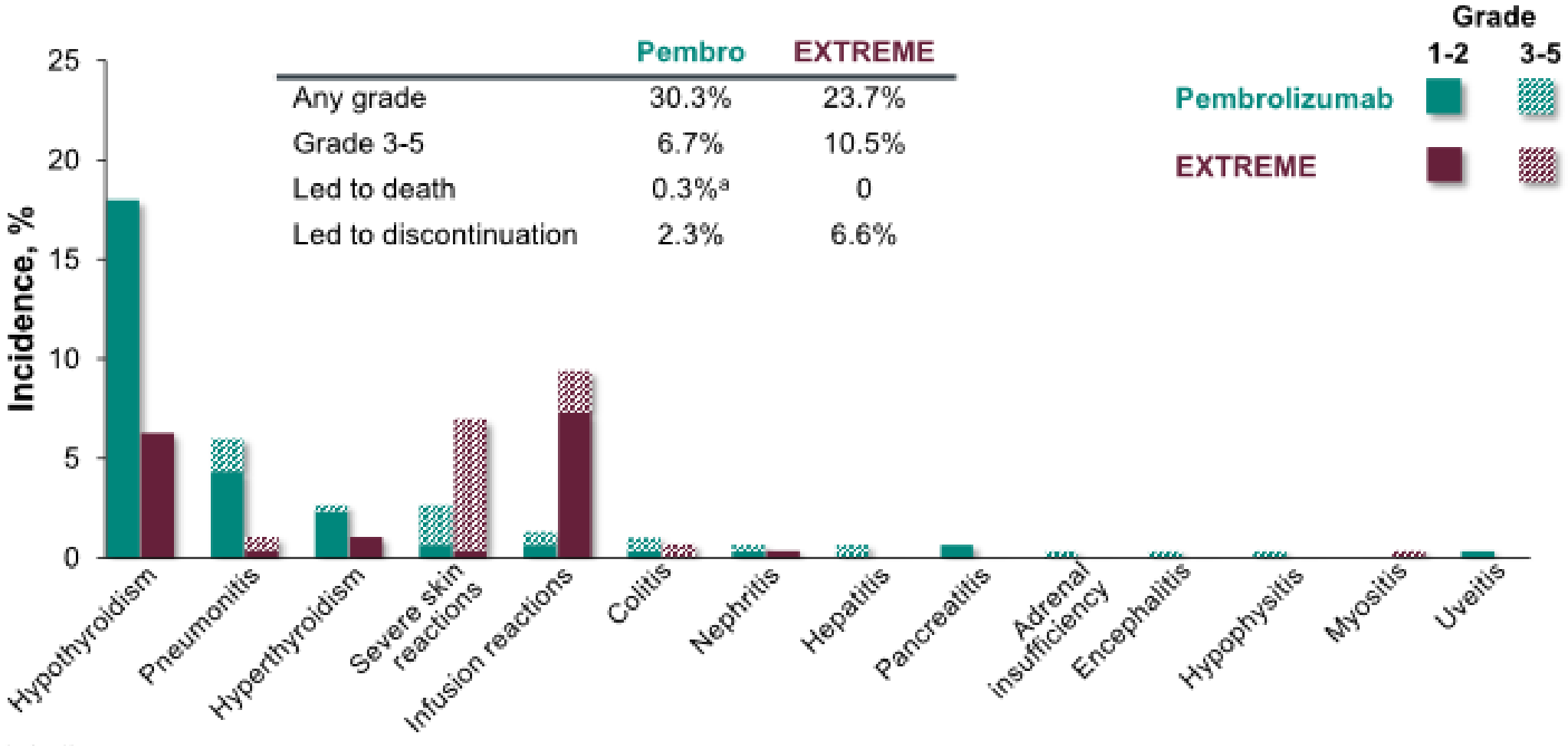
CheckMate 141

Event	Nivolumab (N=236)	
	Any Grade	Grade 3 or 4
Any event	139 (58.9)*	31 (13.1)
Fatigue	33 (14.0)	5 (2.1)
Nausea	20 (8.5)	0
Rash	18 (7.6)	0
Decreased appetite	17 (7.2)	0
Pruritus	17 (7.2)	0
Diarrhea	16 (6.8)	0
Anemia	12 (5.1)	3 (1.3)
Asthenia	10 (4.2)	1 (0.4)
Vomiting	8 (3.4)	0
Dry skin	7 (3.0)	0
Stomatitis	5 (2.1)	1 (0.4)
Weight loss	4 (1.7)	0
Mucosal inflammation	3 (1.3)	0
Peripheral neuropathy	1 (0.4)	0
Alopecia	0	0
Neutropenia	0	0

Immune-related Adverse Events

KEYNOTE-048 – Pembrolizumab monotherapy

	Pembro	EXTREME
Any grade	30.3%	23.7%
Grade 3-5	6.7%	10.5%
Led to death	0.3%[a]	0
Led to discontinuation	2.3%	6.6%

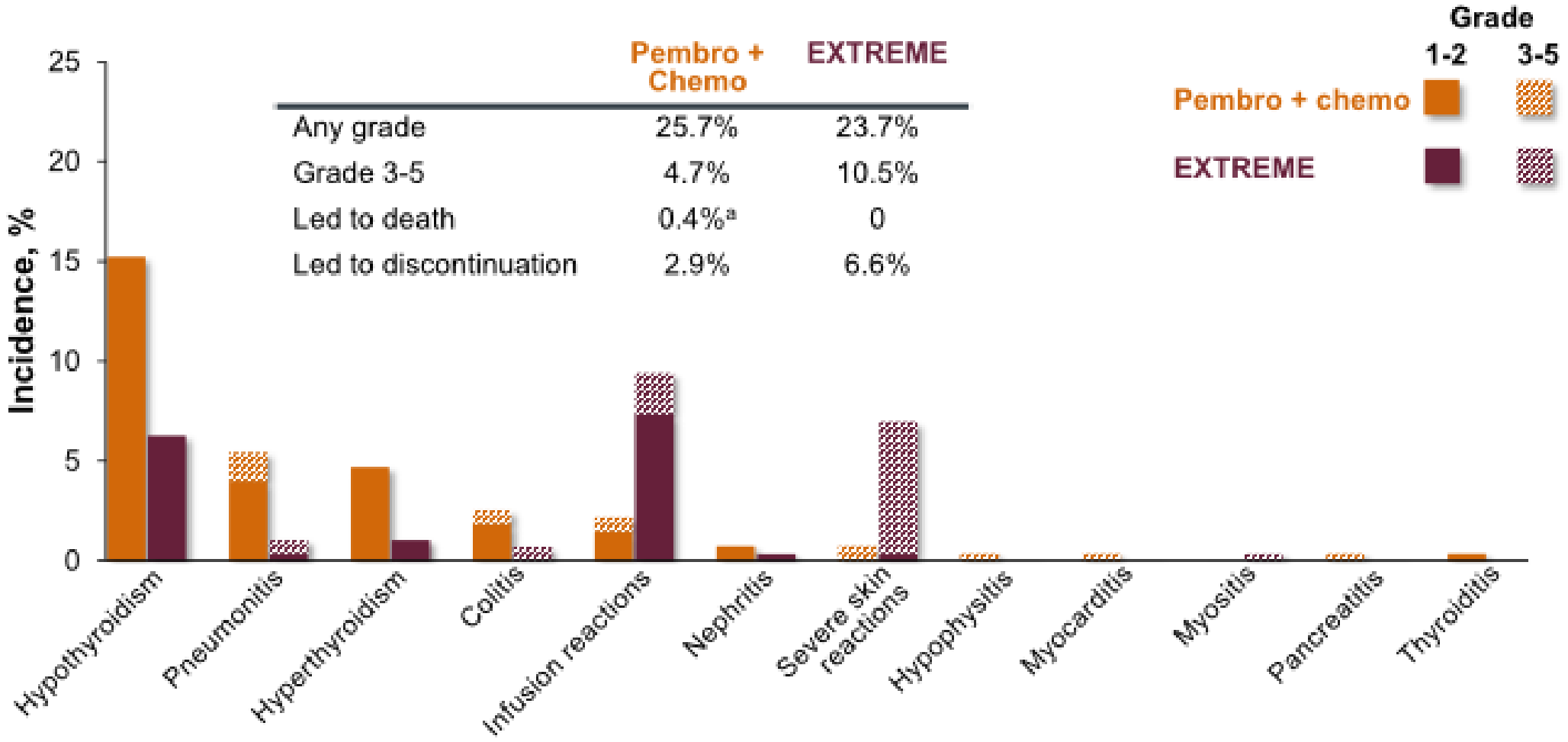


Burtness et al. ESMO 2018

Immune-related Adverse Events

KEYNOTE-048 – Pembrolizumab + Chemotherapy

	Pembro + Chemo	EXTREME
Any grade	25.7%	23.7%
Grade 3-5	4.7%	10.5%
Led to death	0.4%[a]	0
Led to discontinuation	2.9%	6.6%



Burtness et al. ESMO 2018

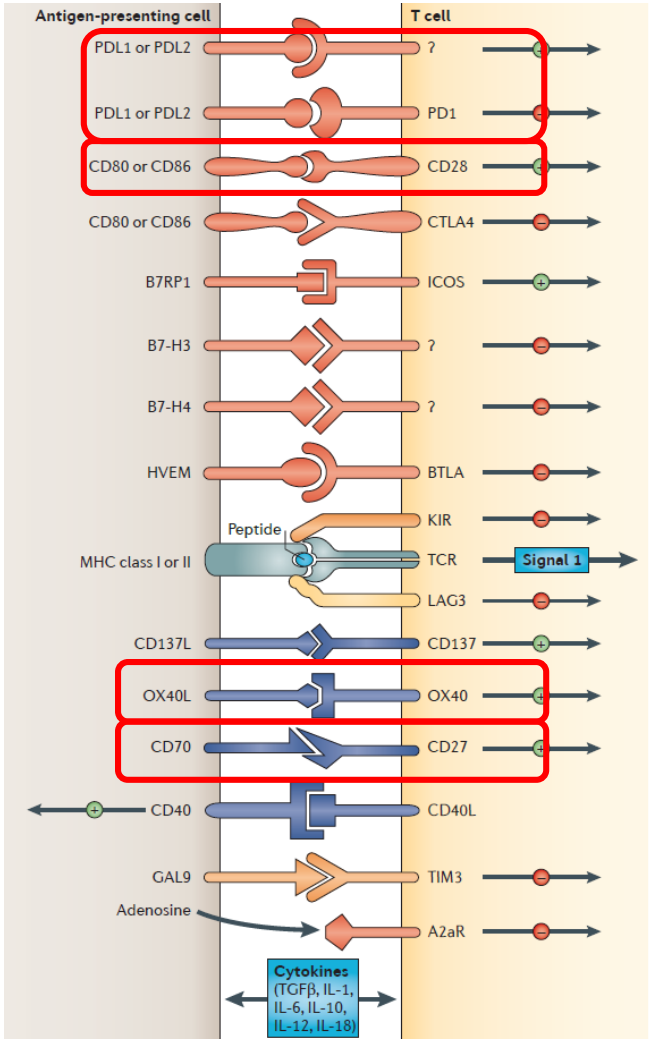
Immune-related Adverse Events

Table 2 General guidance for corticosteroid management of immune-related adverse events

Grade of immune-related AE (CTCAE/equivalent)	Corticosteroid management	Additional notes
1	• Corticosteroids not usually indicated	• Continue immunotherapy
2	• If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication. • If IV required, start methylprednisolone 0.5-1 mg/kg/day IV • If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day • Once improved to ≤grade 1 AE, start 4–6 week steroid taper	• Hold immunotherapy during corticosteroid use • Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids • Start proton pump inhibitor for GI prophylaxis
3	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant • Once improved to ≤ grade 1, start 4–6-week steroid taper • Provide supportive treatment as needed	• Hold immunotherapy; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy • Consider intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)
4	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant, e.g., infliximab • Provide supportive care as needed	• Discontinue immunotherapy • Continue intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)

Puzanov Journal for ImmunoTherapy of Cancer 2017

Developmental Immunotherapies for HNSCC



Pardoll DM Nature 2012

- Durvalumab, atezolizumab, avelumab, CK-301 (anti-PD-L1)
- Cemiplimab (anti-PD-1)
- Ipilimumab, tremelimumab (anti-CTLA-4)
- Varlilumab (anti-CD27)
- PF-04518600, tavolimab (anti-OX40)

Completed RCTs in R/M HNSCC

- KESTREL (n=823)
  - Durvalumab + tremelimumb versus durvalumab versus EXTREME regimen
- CheckMate 651 (n=930)
  - Nivolumab + ipilimumab versus EXTREME regimen

Pardoll DM Nature 2012

Developmental Immunotherapies for HNSCC

MASTERKEY 232/KEYNOTE-137

- Talimogene laherparepvec (T-Vec)
  - Genetically engineered herpes virus
- 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

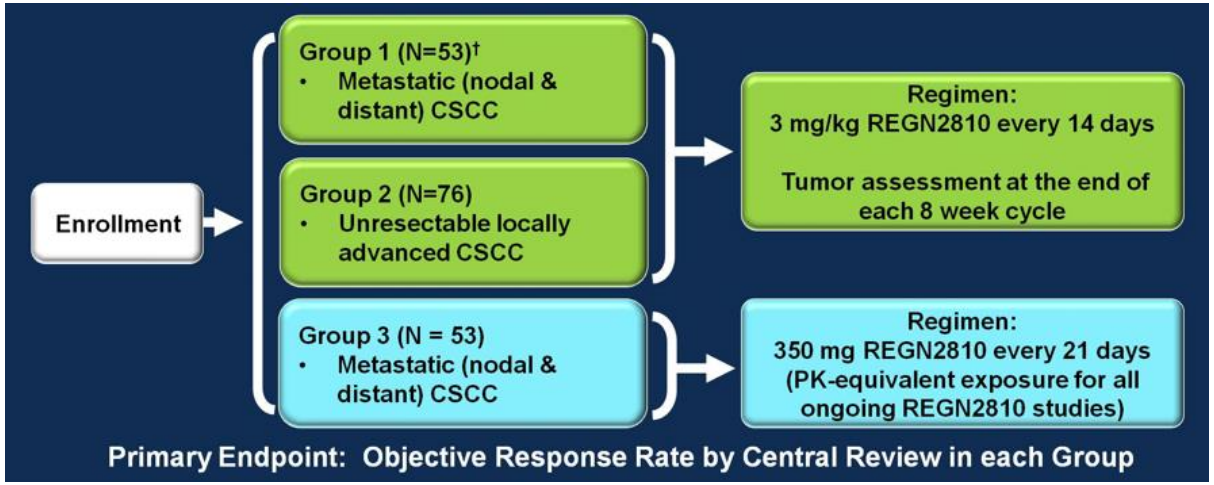
Developmental Immunotherapies for HNSCC

Cemiplimab (REGN2810) for treatment of patients with cutaneous squamous cell carcinoma (cSCC)

FDA approved – 09/28/2018

- Patients with metastatic cSCC
- Patients with locally advanced cSCC who are not candidates for radiation or surgery

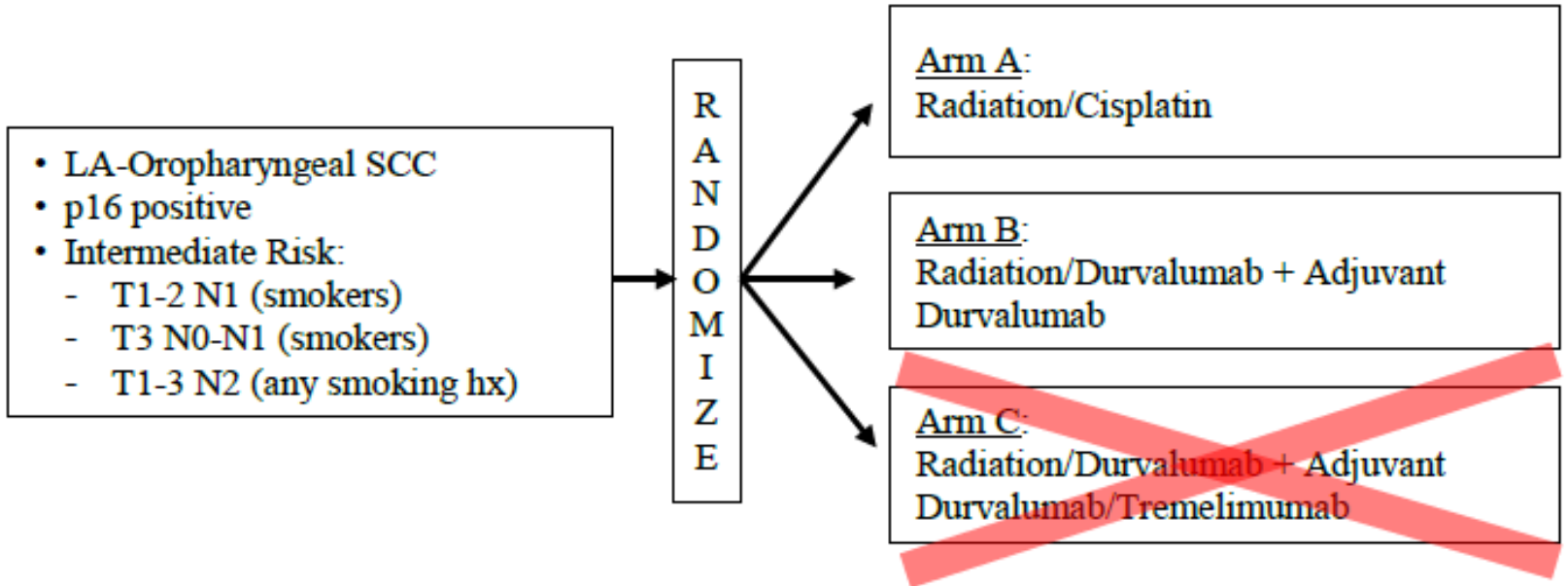
NCT02760498



- ORR 46% in 82 patients in study
- Responses durable, median DOR not reached

Developmental Immunotherapies for HNSCC

CCTG HN.9



Randomization 1:2 - Arm A:Arm B

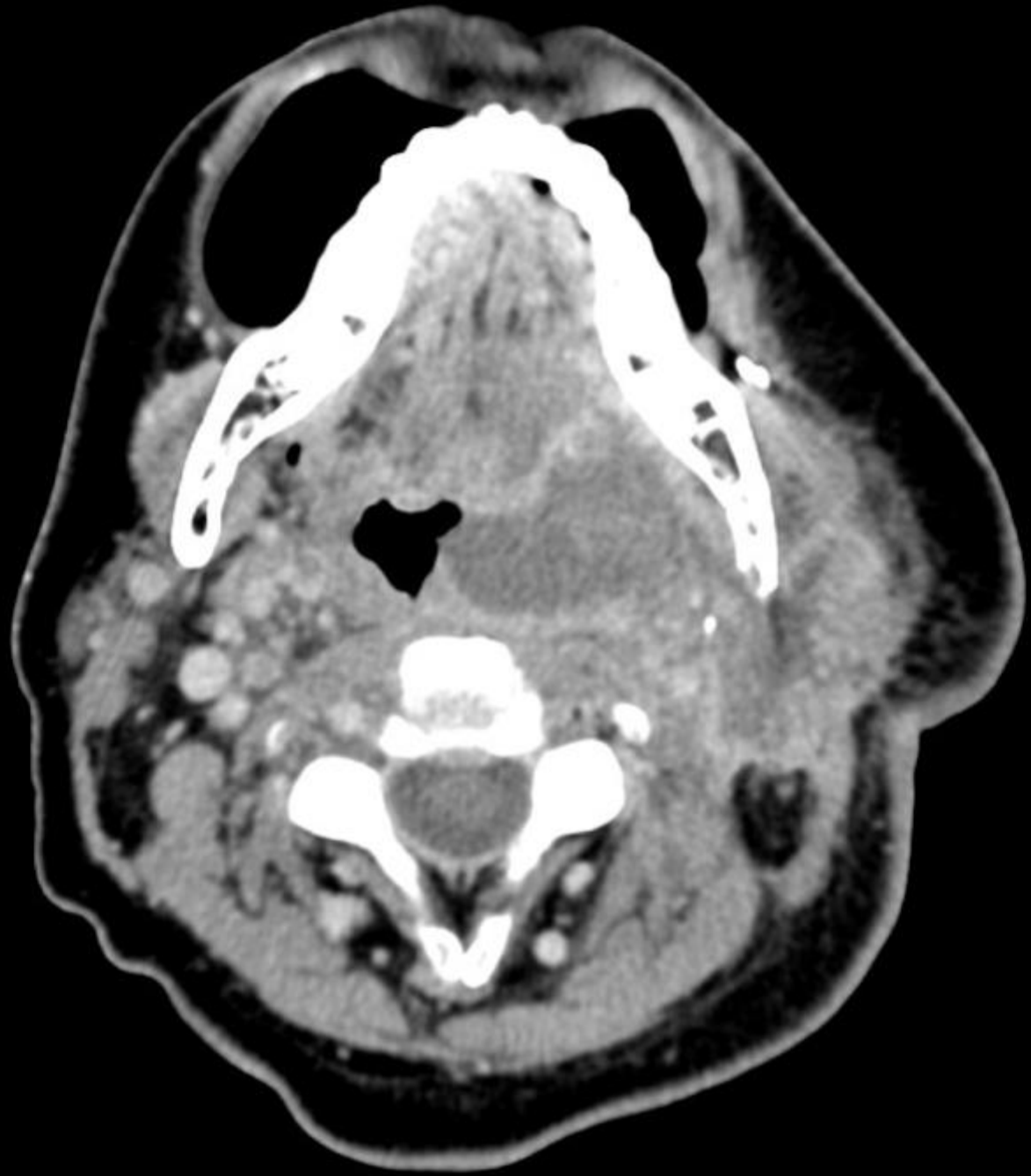
Sample Size: 180

Conclusions

1. Chemotherapy offers short survival with many side effects
2. PD-1 antibodies nivolumab and pembrolizumab are US FDA approved in *platinum-refractory* recurrent / metastatic HNSCC
3. Most patients have fewer side effects on PD-1 Abs than on chemotherapy
4. Clinical trials are underway to improve immunotherapy response rates and testing immunotherapy in other settings

Case Study 1

- 66 year old male
  - Seropositive rheumatoid arthritis x 30 years
  - Feb 2014: Left hemi-glossectomy, left selective neck dissection and buccal flap reconstruction
    - 2.0 cm well diff SCC margins negative, 1/39 LN +ve (no ENE), LVI indeterminate, PNI +ve
  - April 2014: completed postop RT
- July 2014: swelling left face
- November 2014: locoregional recurrence confirmed on CT and PET scans
- February 2015: minimal symptoms, left facial swelling & left neck mass

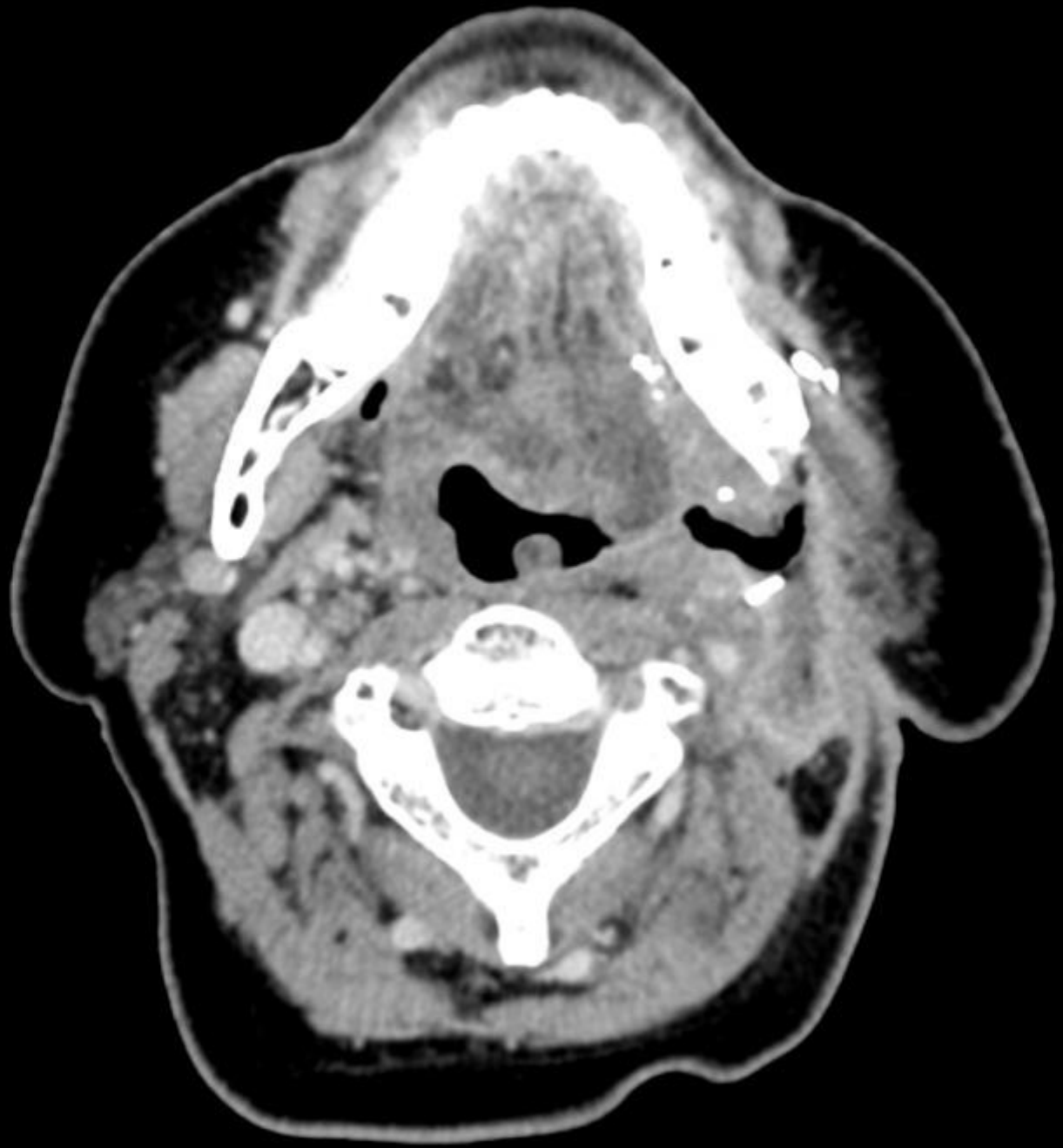


Case Study 1

- March-June 2015: cisplatin + 5-flourouracil
  - Objective partial response
  - Grade 3 mucositis, delayed N&V, neutropenic sepsis, G-CSF arthralgias, severe fatigue
- July 2015-October 2016: chronic infection/osteomyelitis, multiple antibiotic courses
  - RA requiring MTX, tracheostomy, development of chronic oro-cutaneous fistula
- July-August 2016: weekly paclitaxel
  - Minor objective and some symptomatic response, severe fatigue
- October 2016-May 2017: cetuximab
  - Stable disease, aspiration pneumonia, fatigue

Case Study 1

- September 2017-February 2018: cetuximab re-treatment
  - Evidence of radiological progression
  - On methotrexate + prednisone 5 mg for RA
- February 2018-present: nivolumab
  - Hydroxychloroquine and sulfasalazine added prior to initiation of niviolumab
  - RA minimally active



Case study 2

- 59 year old male with controlled HIV and HBsAg +ve on Genvoya and darunavir
  - Kaposi's sarcoma treated with liposomal doxorubicin 1999 and 2005
  - Oral cavity SCC resected 2005 and re-resected 2009
- Fall 2013: right neck adenopathy, biopsy = squamous cell carcinoma
  - Radical chemoradiation Feb-March 2014
- December 2014: resection of 1.5 cm mod differentiated SCC from left lung
- October 2015: 3 oligometastatic pulmonary recurrences treated with SBRT
- January 2018: Persistent cough, progressive mediastinal & pulmonary metastases

Case study 2

- Both you and patient agree it is time for treatment.
- What would you do?
  - Nivolumab
  - Chemotherapy
  - Clinical trial
  - Genomic testing

Case study 2

Tier I and II Variants *(variants of strong and potential clinical significance, therapeutic, prognostic & diagnostic)*
Results: No Pathogenic Variants Detected

Tier III (>10% allele frequency with 500X coverage)
ERBB4:c.1855C>T, p.(Pro619Ser) (14.6%)
EGFR:c.2625+1G>A (15.1%)
FGFR2:c.1156G>A, p.(Val386Ile) (10.3%)
EGFR:c.2602G>A, p.(Glu868Lys) (14.6%)
SMAD4:c.755G>A, p.(Gly252Glu) (13%)
APC:c.4541C>T, p.(Pro1514Leu) (13.6%)
APC:c.4282G>A, p.(Gly1428Arg) (26%)
KIT:c.122C>T, p.(Pro41Leu) (16.3%)
CDKN2A:c.203C>T, p.(Ala68Val) (13.7%)

Case study 2

- February-October 2018: afatinib
  - Minor response
  - Symptomatic progression with invasion right bronchus intermedius requiring hospitalization and palliative radiation
- Nivolumab is now available.
- What are your concerns about proceeding with this treatment?

Case study 2

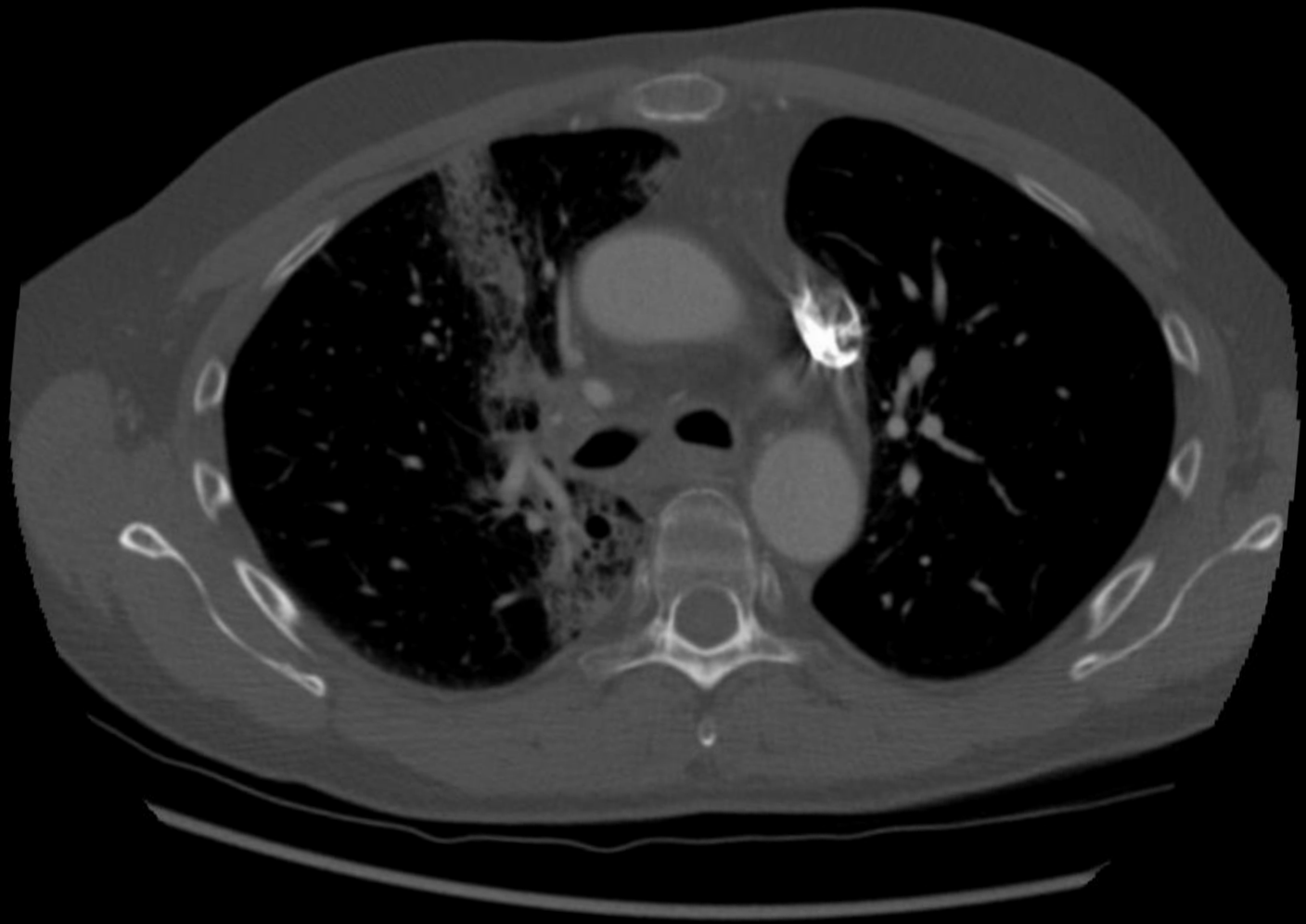
- February-October 2018: afatinib
  - Minor response
  - Symptomatic progression with invasion right bronchus intermedius requiring hospitalization and palliative radiation
- Nivolumab is now available.
- What are your concerns about proceeding with this treatment?
  - Safety in HIV
  - Safety in hepatitis B
  - Meets NDFP funding criteria

Case study 2

- November 2018-present: nivolumab
- January 2019: dry cough, dyspnea, atypical PND and chest “pressure”
- What are the possibilities?

Case study 2

- November 2018-present: nivolumab
- January 2019: dry cough, dyspnea, atypical PND and chest “pressure”
- What are the possibilities?
  - Immune pneumonitis
  - Infectious pneumonitis including opportunistic
  - Pulmonary embolism
  - Radiation pneumonitis



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Thank you!