Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

Squamous Cell Carcinoma of the Head and Neck (HNSCC) Webinar

Wednesday, July 24, 2019

3–4 p.m. EDT

Jointly provided by Postgraduate Institute for Medicine and the Society for Immunotherapy of Cancer

This webinar is supported, in part, by independent medical education grant funding from Amgen and AstraZeneca Pharmaceuticals LP

Webinar Agenda

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3:00–3:05 p.m. EDT	Welcome, Introductions and Overview
3:05–3:40 p.m. EDT	Review of SITC Cancer Immunotherapy Guideline – Squamous Cell Carcinoma of the Head and Neck (HNSCC)
3:40–3:55 p.m. EDT	Question and Answer Session
3:55–4:00 p.m. EDT	Closing Remarks

To Submit a Question

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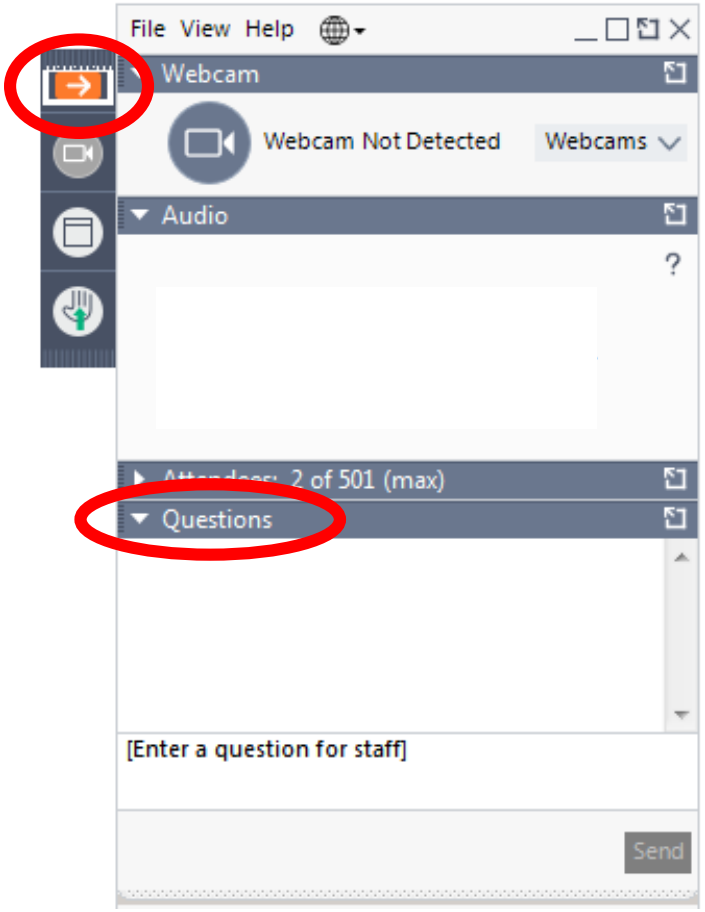
Computer



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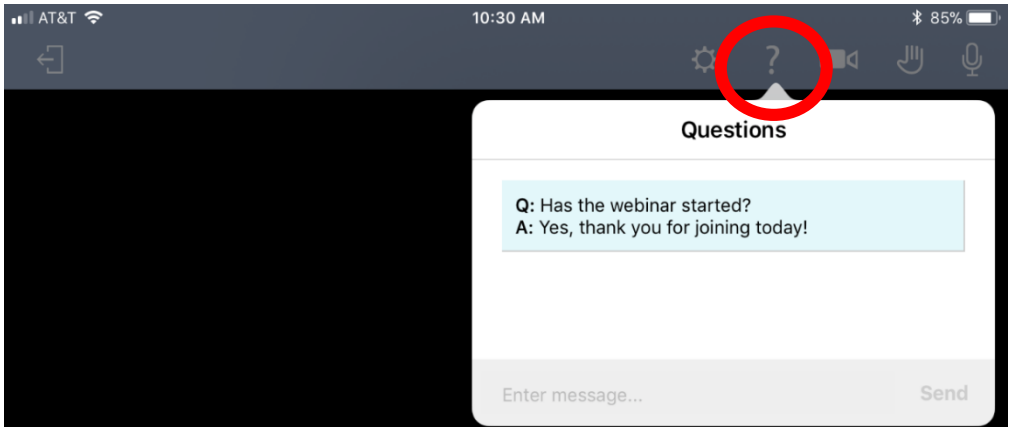

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Cohen *et al. Journal for ImmunoTherapy of Cancer* (2019) 7:184
https://doi.org/10.1186/s40425-019-0662-5

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*]

Webinar Faculty

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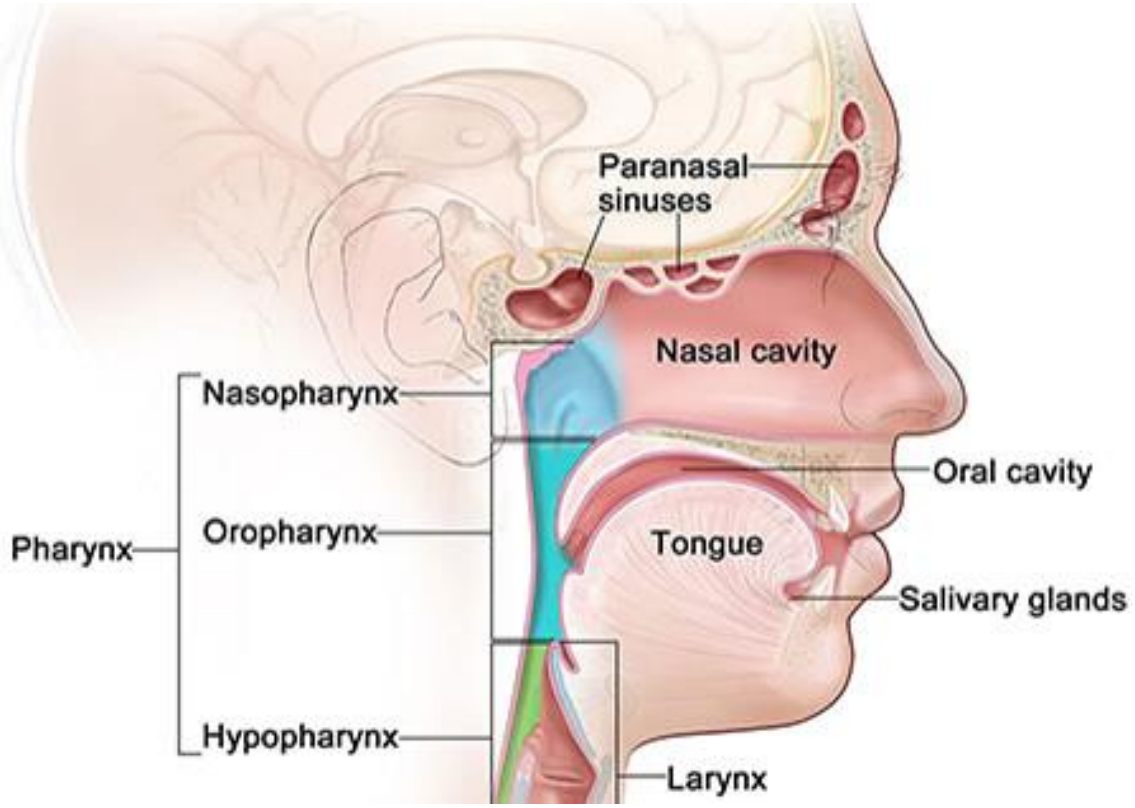
Squamous Cell Carcinoma of the Head and Neck (HNSCC)



FDA-approved Checkpoint Inhibitors in Head and Neck Cancer

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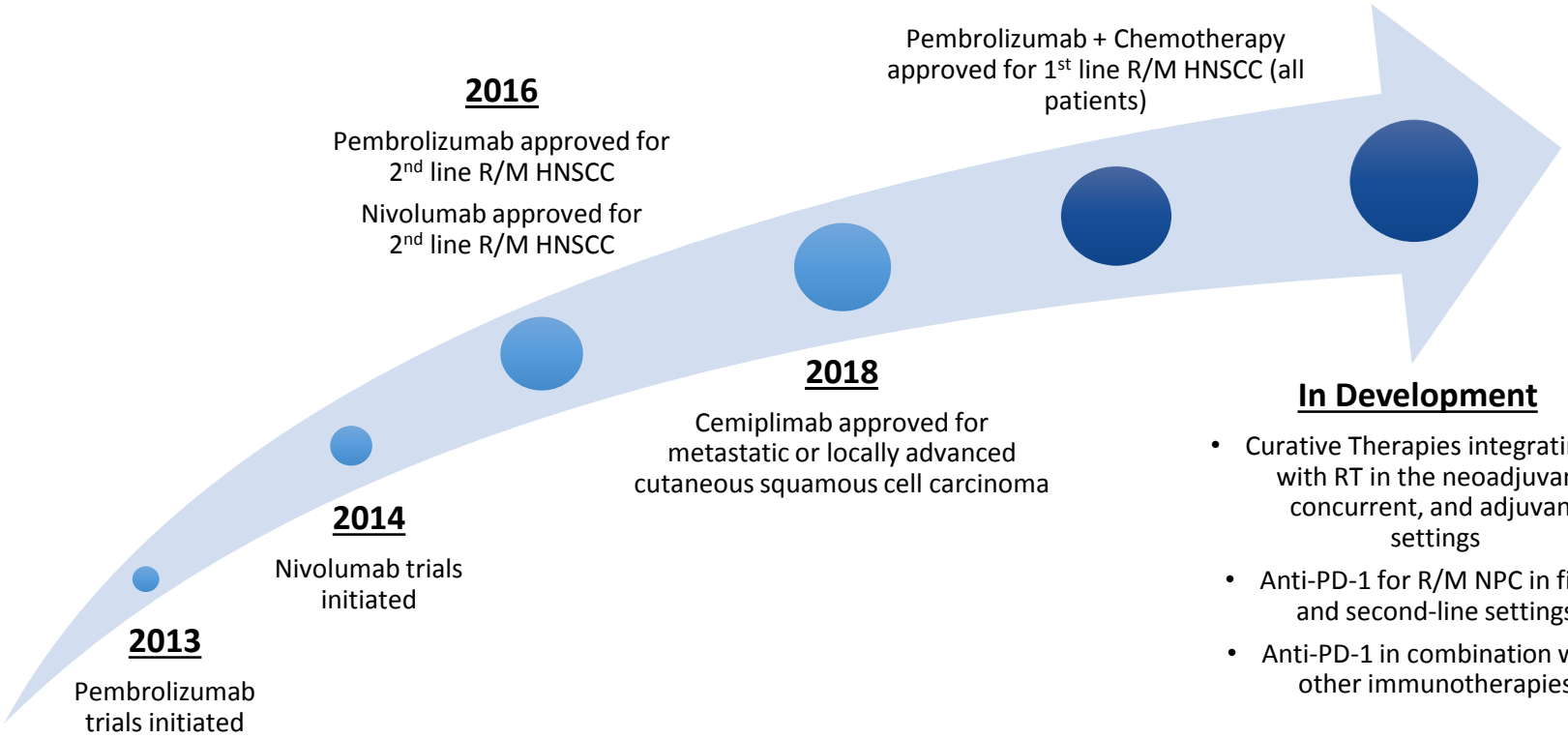

Immune Checkpoint Inhibitor (ICI)-based trials leading to FDA approvals

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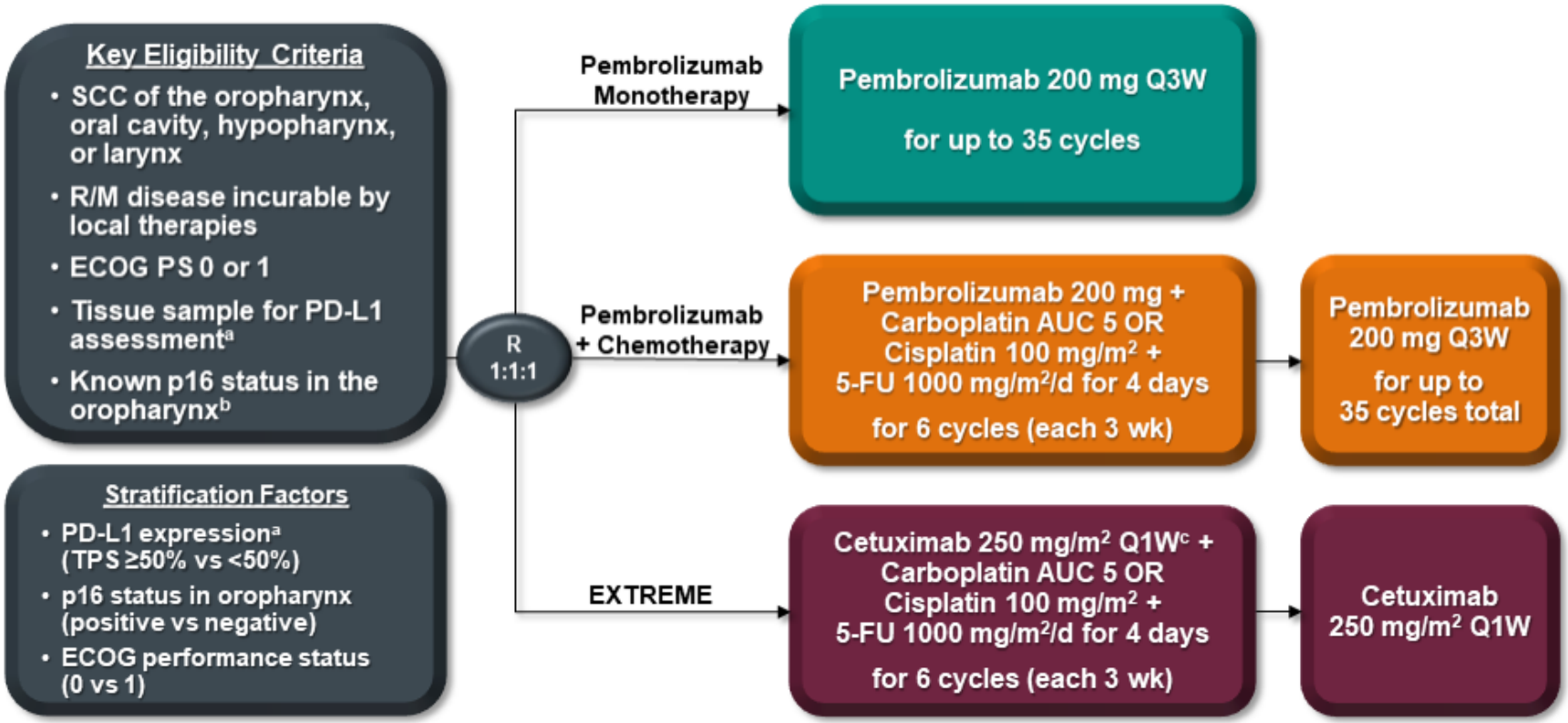
First-Line: Phase III KEYNOTE-048 Study Design

Pembrolizumab or Pembrolizumab + Chemotherapy (platinum/fluorouracil) vs. EXTREME in 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 B, et al. Presented at: ESMO 2018. Abstract LBA8_PR.

Immune Checkpoint Inhibitor (ICI)-based trials leading to FDA approvals

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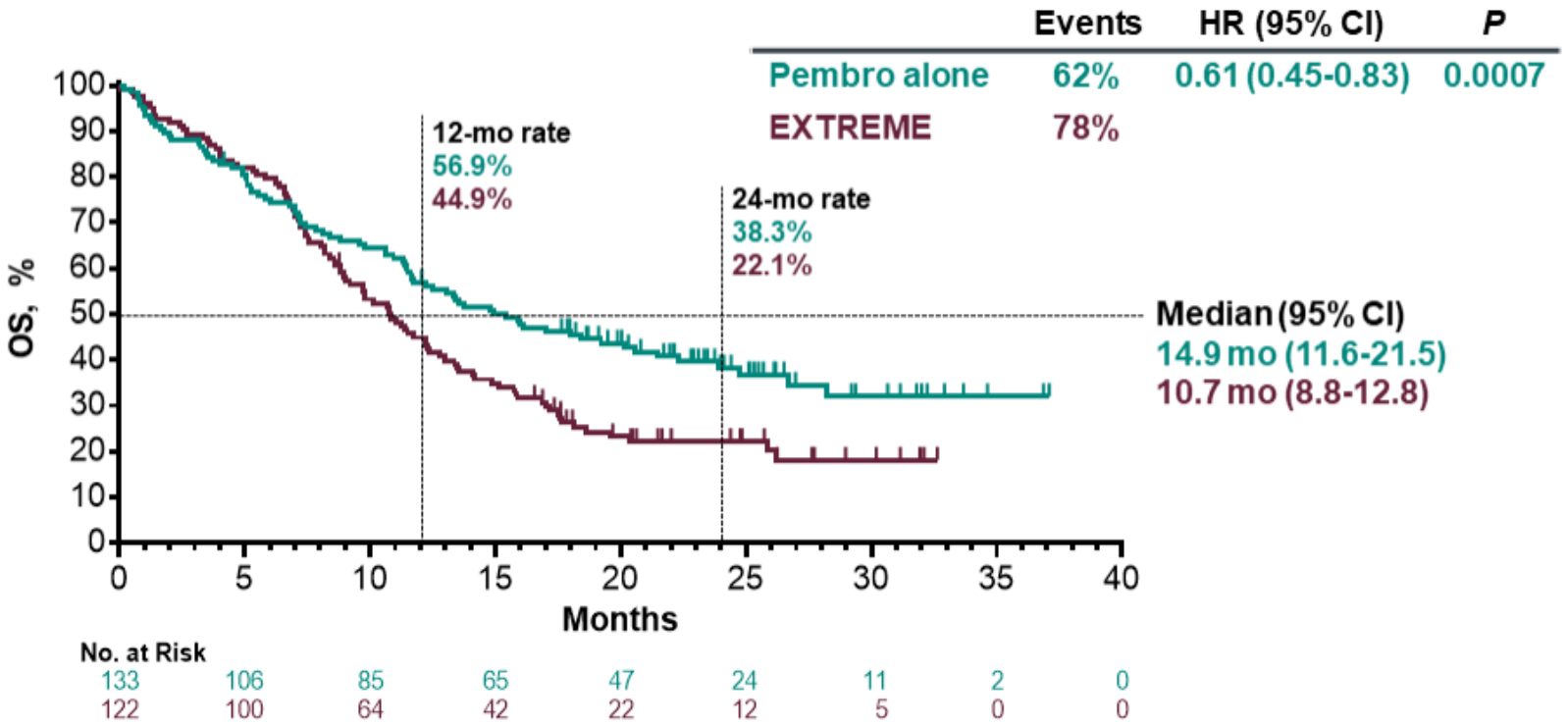
First-Line: Phase III KEYNOTE-048 Trial

Overall Survival: P vs E, CPS ≥20 Population



Data cutoff date: Jun 13, 2018.

Burtness B, et al. Presented at: ESMO 2018. Abstract LBA8_PR.

Immune Checkpoint Inhibitor (ICI)-based trials leading to FDA approvals

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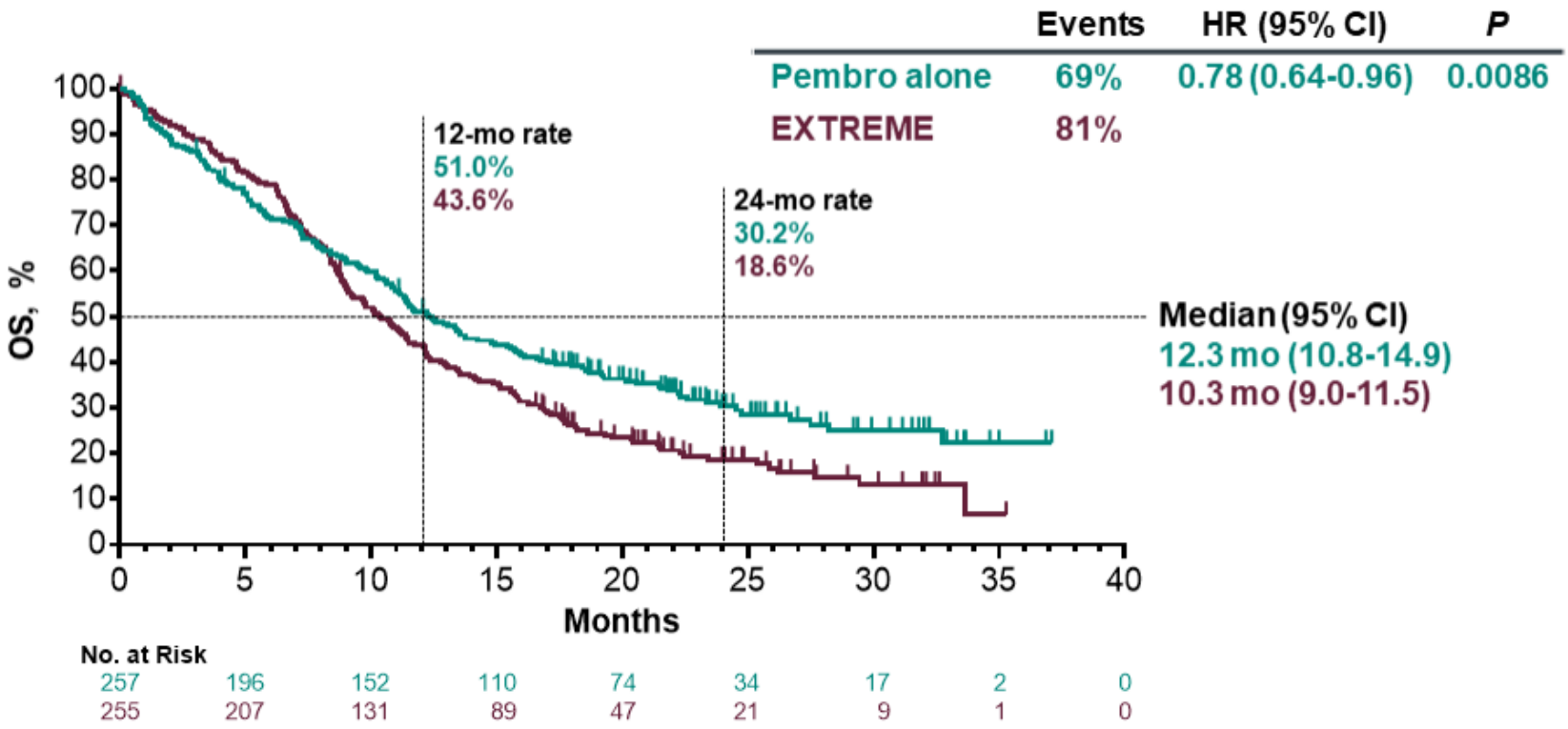
First-Line: Phase III KEYNOTE-048 Trial

Overall Survival: P vs E, CPS ≥1 Population



Data cutoff date: Jun 13, 2018.

Burtness B, et al. Presented at: ESMO 2018. Abstract LBA8_PR.

Immune Checkpoint Inhibitor (ICI)-based trials leading to FDA approvals

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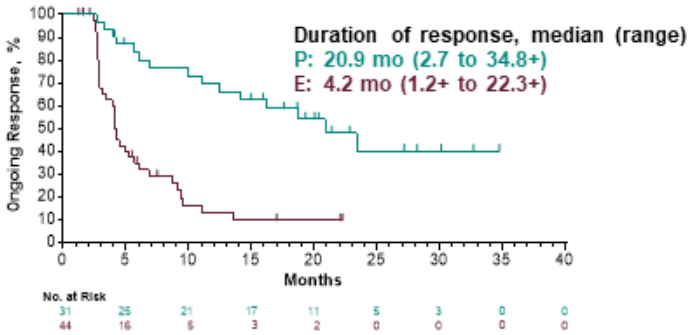
First-Line: Phase III KEYNOTE-048 Trial

Response Summary, P vs E

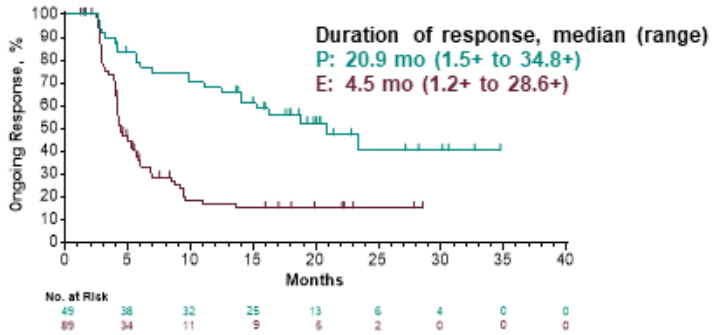
CPS ≥20

Confirmed Response, n (%)	Pembro N = 133	EXTREME N = 122
ORR	**31 (23.3)**	**44 (36.1)**
CR	10 (7.5)	4 (3.3)
PR	21 (15.8)	40 (32.8)
SD	40 (30.1)	42 (34.4)
PD	42 (31.6)	13 (10.7)
Non-CR/non-PD[a]	8 (6.0)	6 (4.9)
Not evaluable or assessed[b]	12 (9.0)	17 (13.9)



CPS ≥1

Confirmed Response, n (%)	Pembro N = 257	EXTREME N = 255
ORR	**49 (19.1)**	**89 (34.9)**
CR	14 (5.4)	7 (2.7)
PR	35 (13.6)	82 (32.2)
SD	72 (28.0)	83 (32.5)
PD	100 (38.9)	34 (13.3)
Non-CR/non-PD[a]	11 (4.3)	11 (4.3)
Not evaluable or assessed[b]	25 (9.7)	38 (14.9)



[a]Patients without measurable disease per central review at baseline who did not have CR or PD. [b]Patients who did not have a post-baseline imaging assessment evaluable for response or who did not have post-baseline imaging. Response assessed per RECIST v1.1 by blinded, independent central radiologic review. Data cutoff date: Jun 13, 2018.

Burtness B, et al. Presented at: ESMO 2018. Abstract LBA8_PR.

Immune Checkpoint Inhibitor (ICI)-based trials leading to FDA approvals

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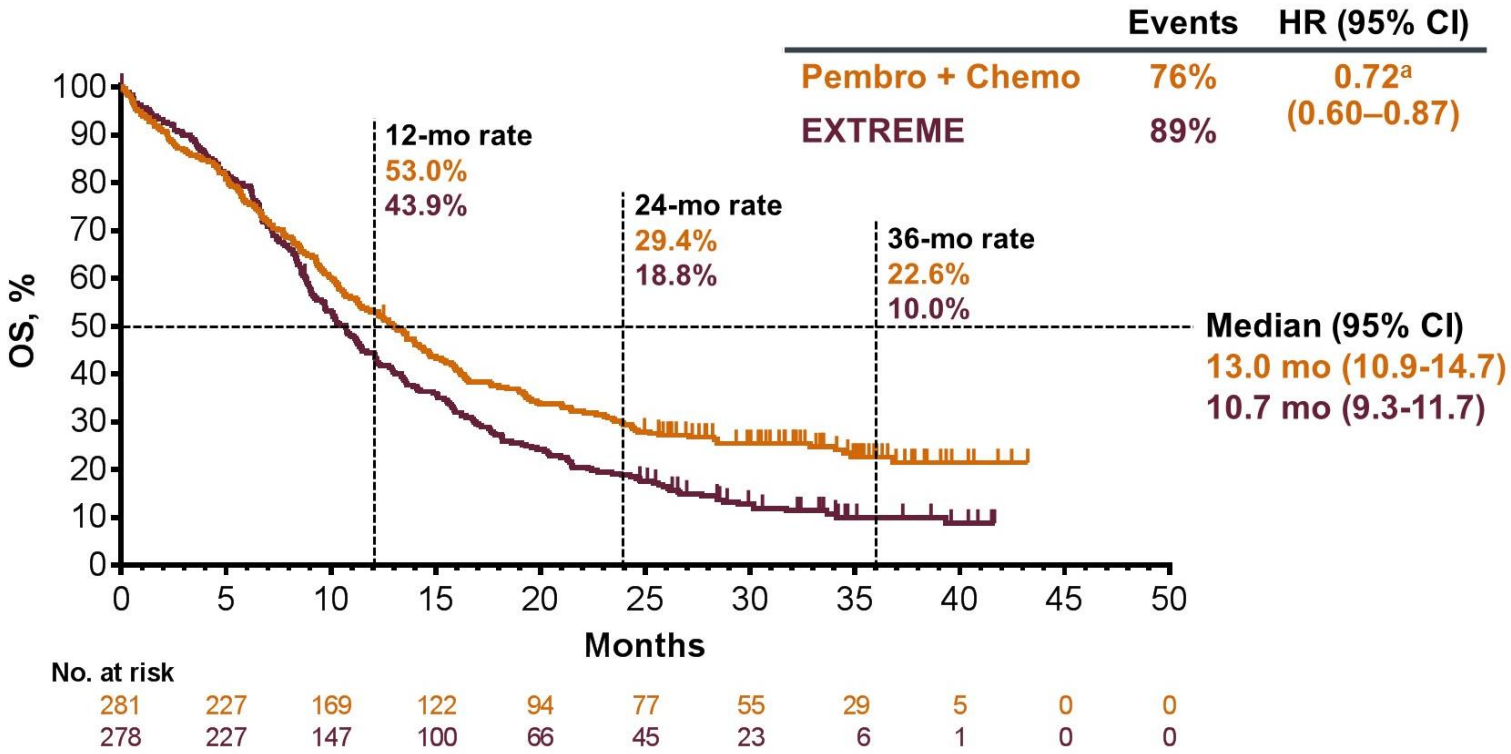
First-Line: Phase III KEYNOTE-048 Trial

Overall Survival, P+C vs. E, Total Population

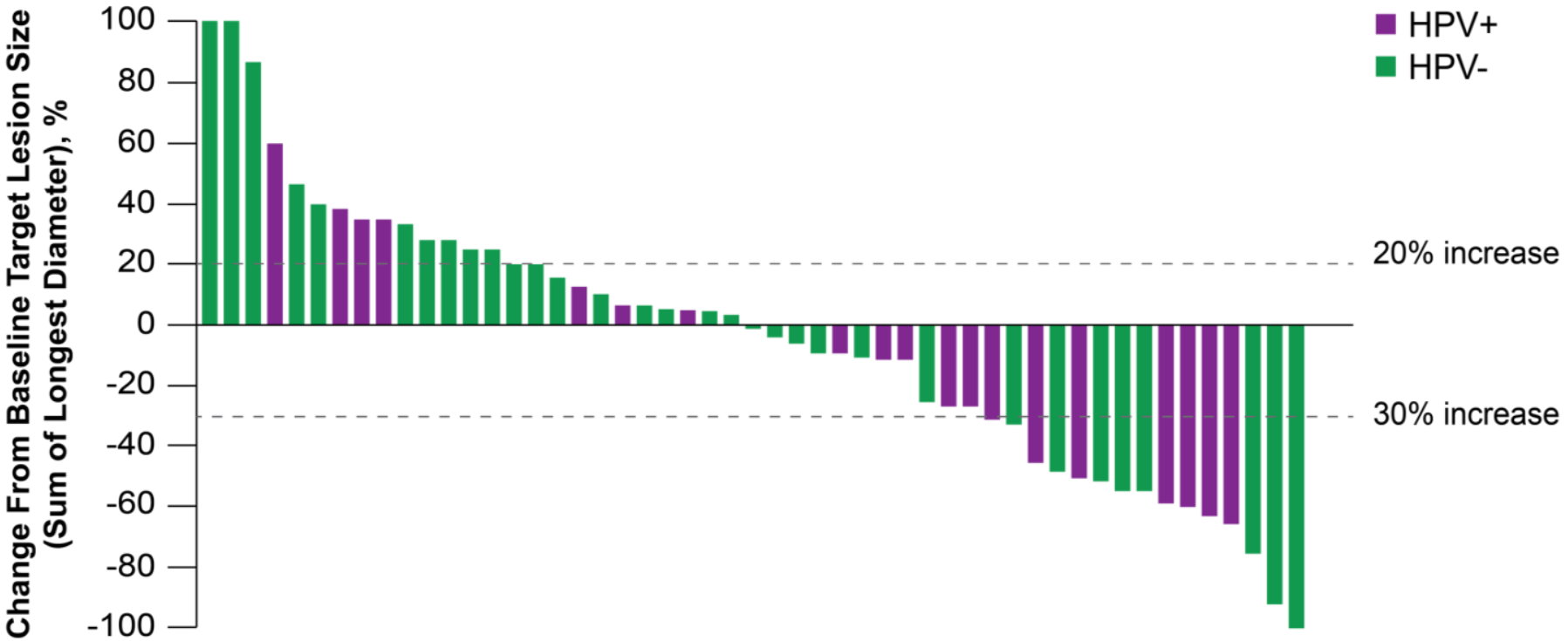


[a]At IA2 (data cutoff date: Jun 13, 2018): HR 0.77 (95% CI 0.53–0.93).
FA (data cutoff date: Feb 25, 2019).

ICI-based trials leading to FDA approvals

Second-Line: Phase I/II KEYNOTE-012 Trial

Single-Agent Pembrolizumab in R/M HNSCC

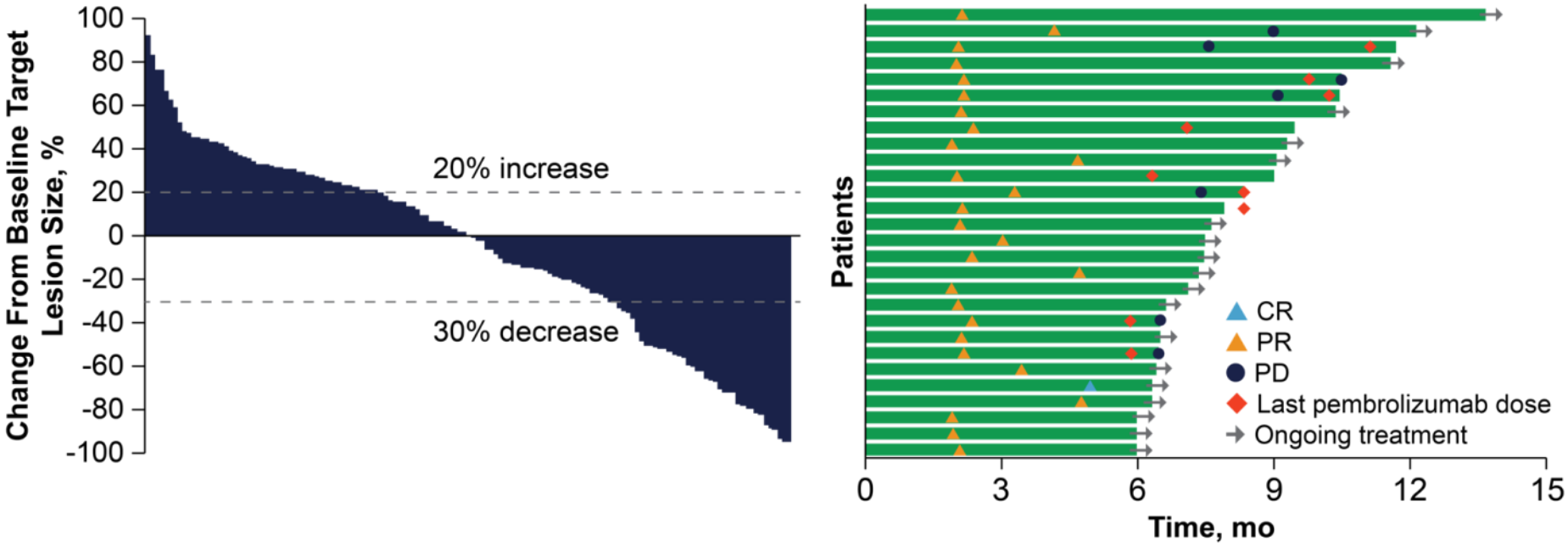


Seiwert TY et al. Lancet Oncology 2016

ICI-based trials leading to FDA approvals

Second-Line: Phase II KEYNOTE-055 Trial

Single-Agent Pembrolizumab in R/M HNSCC



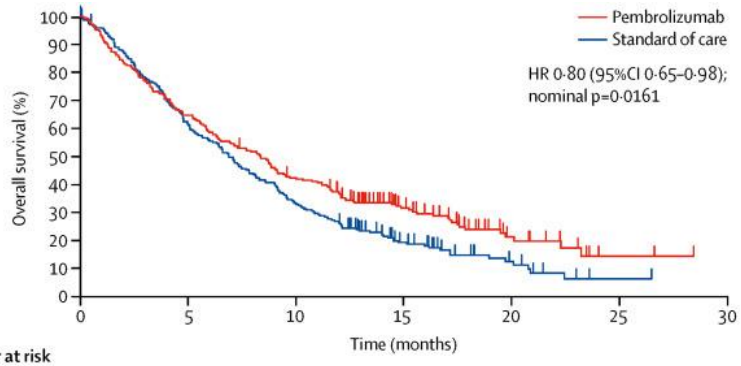
FDA-approved in 2016 for recurrent/metastatic HNSCC with disease progression on or after platinum-based tx

ICI-based trials leading to FDA approvals

Second-Line: Phase III KEYNOTE-040 Trial

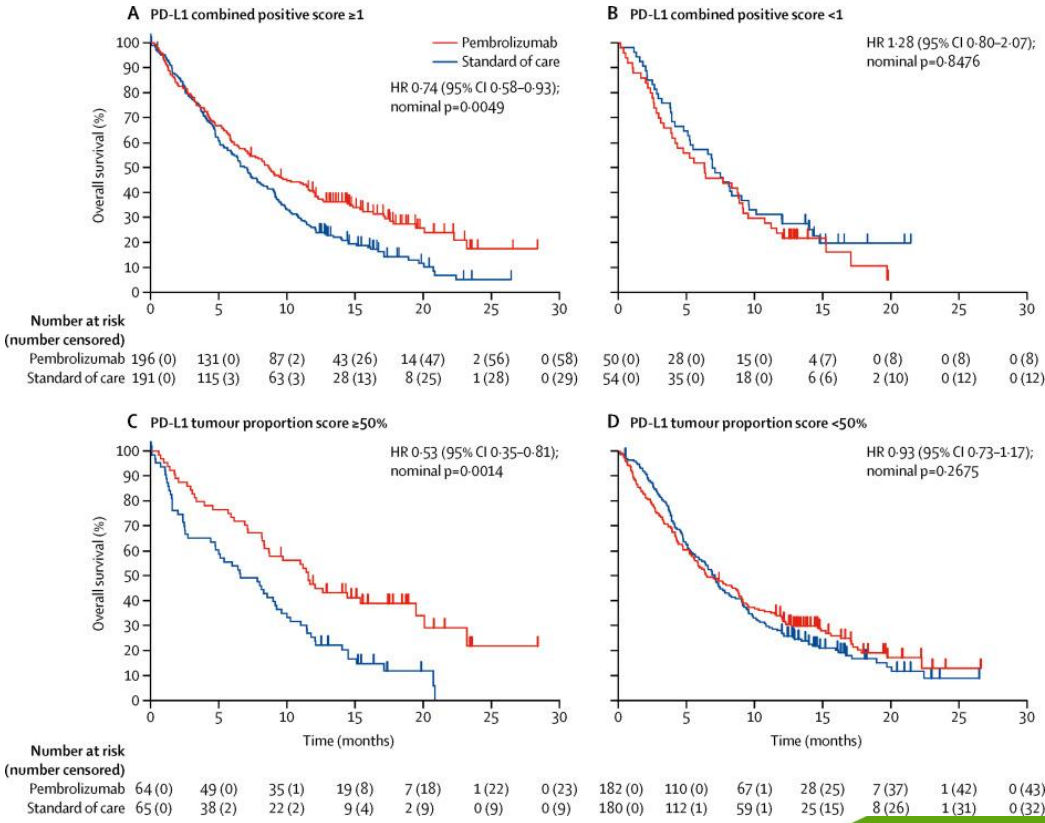
Pembrolizumab vs SOC (methotrexate, docetaxel or cetuximab) for R/M HNSCC with disease progression during or after platinum-based chemotherapy

Overall survival in the intention-to-treat population



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)

Overall survival by PD-L1 expression



Number at risk (number censored)														
Pembrolizumab	196 (0)	131 (0)	87 (2)	43 (26)	14 (47)	2 (56)	0 (58)	50 (0)	28 (0)	15 (0)	4 (7)	0 (8)	0 (8)	0 (8)
Standard of care	191 (0)	115 (3)	63 (3)	28 (13)	8 (25)	1 (28)	0 (29)	54 (0)	35 (0)	18 (0)	6 (6)	2 (10)	0 (12)	0 (12)
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)

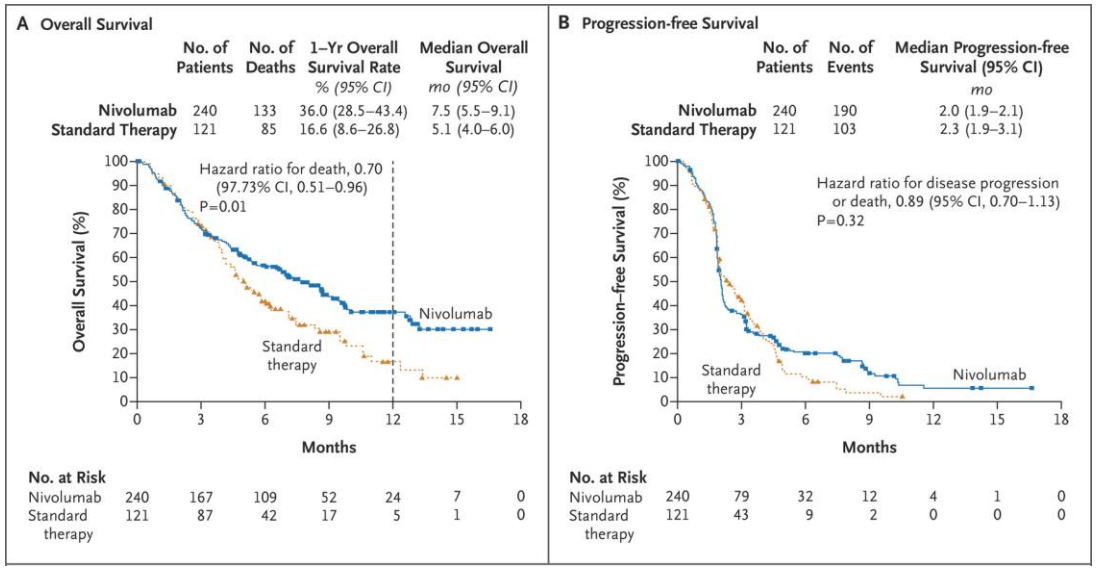
Lopes et al. ASCO 2018

ICI-based trials leading to FDA approvals

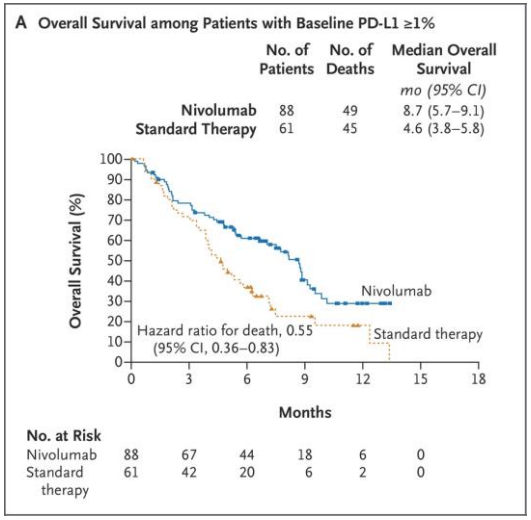
Second-Line: Phase III CheckMate141 Trial

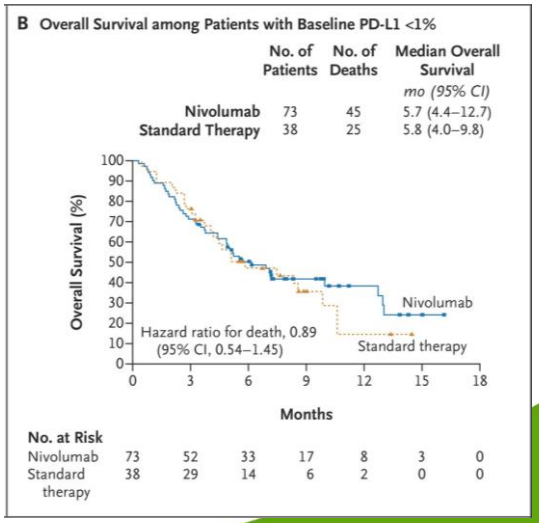
Nivolumab vs. SOC (methotrexate, docetaxel or cetuximab) for R/M HNSCC with disease progression within 6 months of platinum-based chemotherapy

Overall Survival, Progression-free Survival, and Treatment Effect on Overall Survival According to Subgroup



Nivolumab Standard Therapy





Ferris, et al. NEJM 375, 2016

ICI-based trials leading to FDA approvals

Phase I Study of Cemiplimab

Cemiplimab for patients with locally advanced or metastatic cutaneous squamous-cell carcinoma

Table 2. Tumor Response to Cemiplimab, as Assessed by Independent Central Review.*

Outcome	Expansion Cohorts of the Phase 1 Study (N=26)	Metastatic-Disease Cohort of the Phase 2 Study (N=59)
Best overall response — no. (%)†		
Complete response	0	4 (7)
Partial response	13 (50)	24 (41)
Stable disease	6 (23)	9 (15)
Progressive disease	3 (12)	11 (19)
Could not be evaluated‡	3 (12)	7 (12)
Nontarget lesions only§	1 (4)	4 (7)
Objective response — % (95% CI)	50 (30–70)	47 (34–61)
Durable disease control — % (95% CI)	65 (44–83)	61 (47–74)
Median observed time to response (range) — mo¶	2.3 (1.7–7.3)	1.9 (1.7–6.0)

* The expansion cohorts of the phase 1 study involved patients with metastatic or locally advanced cutaneous squamous-cell carcinoma. The metastatic-disease cohort of the phase 2 study involved patients with metastatic cutaneous squamous-cell carcinoma.

Migden, et al. NEJM, 2018

Consensus Treatment Recommendations for patients with R/M HNSCC

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Key clinical immunotherapy recommendations for treatment of patients with HNSCC	
Clinical Question	Summary recommendation

How should immunotherapy with PD-1 inhibitors be integrated into the treatment of recurrent/metastatic HNSCC?	First-line:
	• Pembrolizumab is indicated for treatment-naïve R/M HNSCC
	  ○ Pembrolizumab monotherapy may be used to treat patients with treatment naïve R/M HNSCC and PD-L1 CPS ≥1
	  ○ Pembrolizumab + Chemotherapy (platinum and fluorouracil (FU)) may be used to treat all patients with treatment naïve, biomarker-unspecified R/M HNSCC patients
	
	* Positivity for PD-L1 as ≥1 CPS by IHC staining

Cohen et al. JITC 2019

Consensus Treatment Recommendations for patients with R/M HNSCC

First-Line

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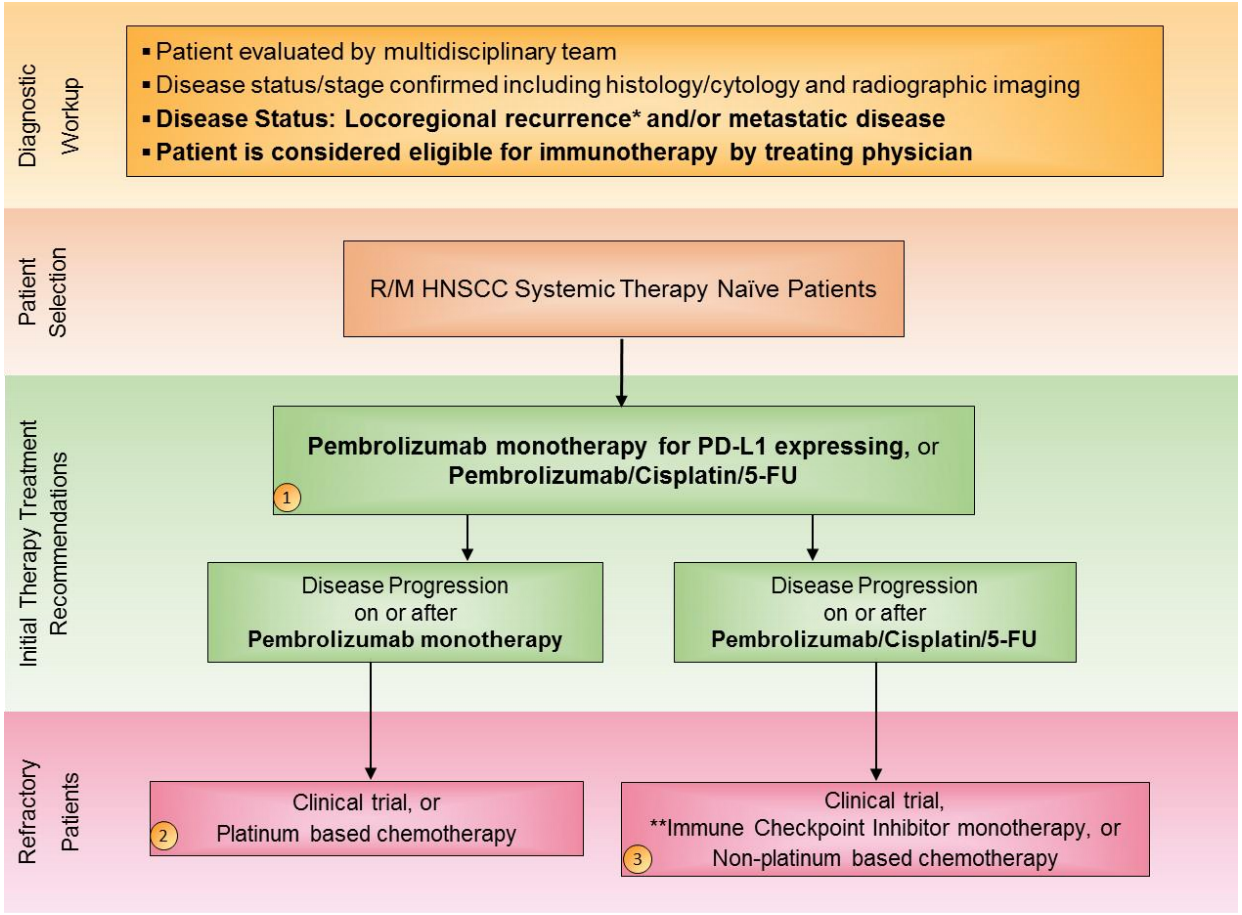

*Locoregional recurrence without salvage surgical or radiation option or declines local therapies
**Refer to Figure 2. Initial Therapy Treatment Recommendations: Immune Checkpoint Inhibitor monotherapy (nivolumab or pembrolizumab)

Cohen et al. JITC 2019

Consensus Treatment Recommendations for patients with R/M HNSCC

Second-Line

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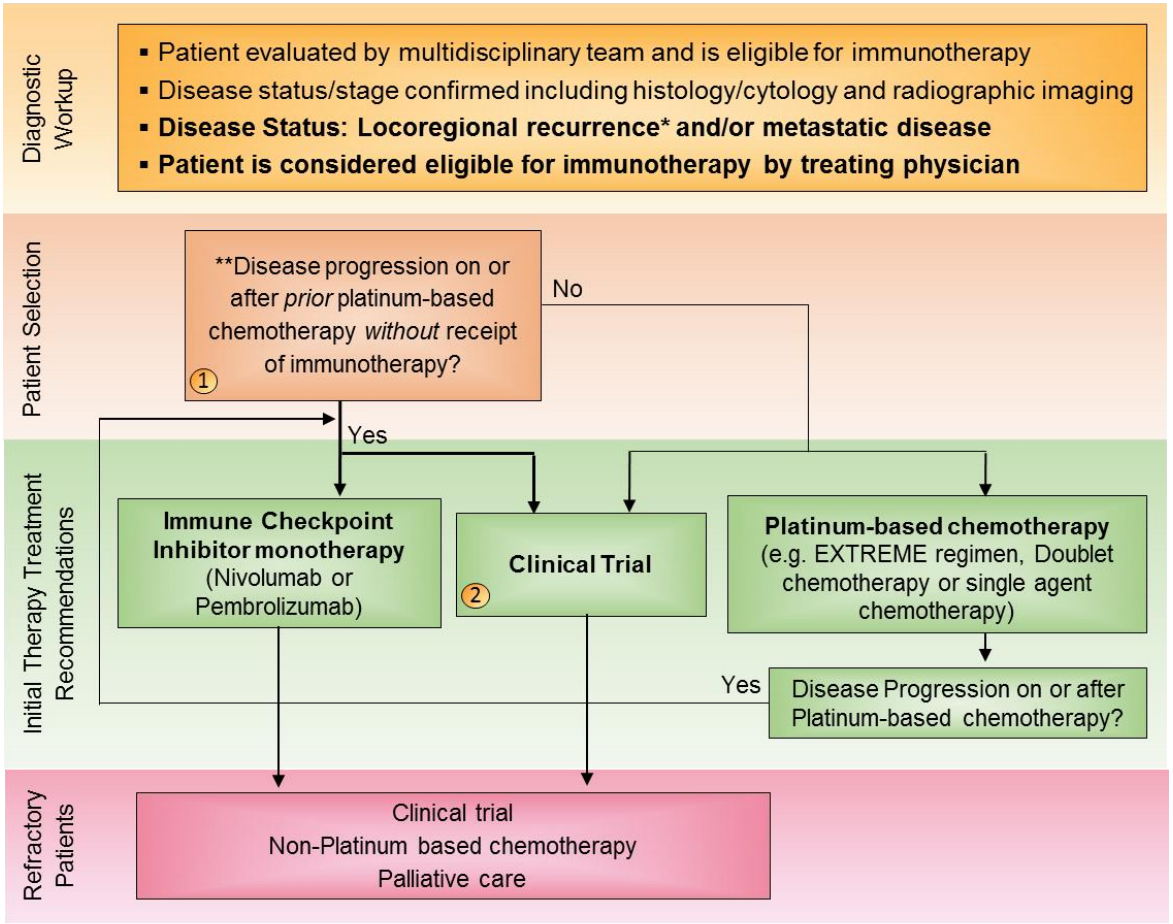

*Locoregional recurrence without salvage surgical or radiation option or declines local therapies

**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

Cohen et al. JITC 2019

Analysis of PD-L1 Expression and Efficacy from anti-PD-1 Trials

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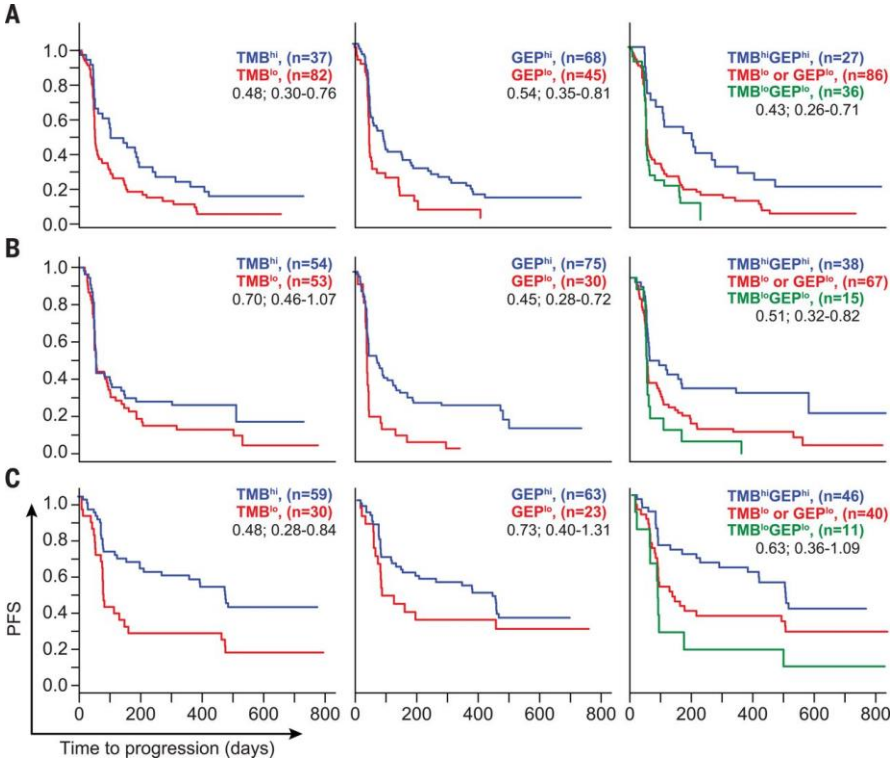
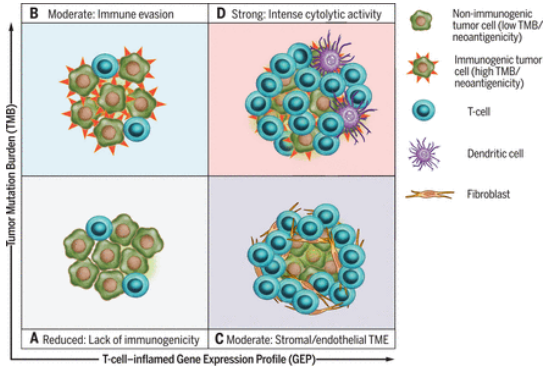
Pan-tumor genomic biomarkers for PD-1:

TMB and inflammatory biomarkers (T cell–inflamed GEP and PD-L1 expression) to jointly predict clinical response to pembrolizumab in patient samples

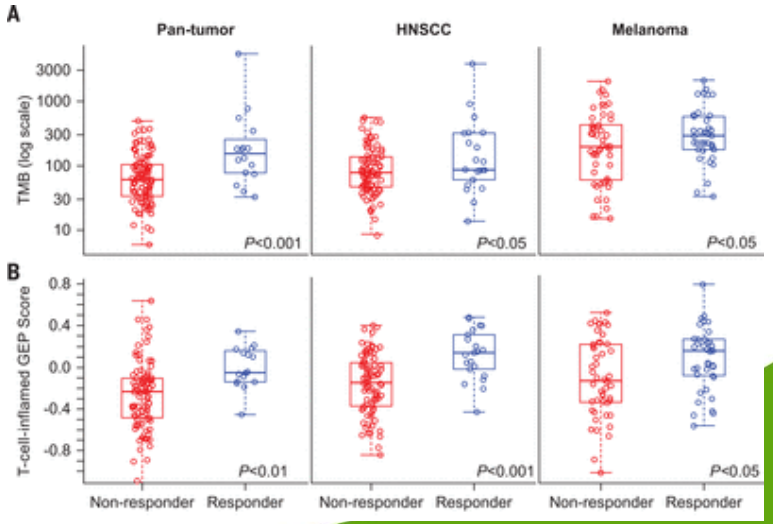
TMB and T cell–inflamed GEP signatures: PFS after anti–PD-1 treatment across multiple patient cohorts



Biomarker-defined responses to pembro monotherapy



Individual association of TMB or T cell–inflamed GEP with anti–PD-1 response across multiple patient cohorts



Cristescu et al. Science 2018 (DOI: 10.1126/science.aar3593)

Analysis of PD-L1 Expression and Efficacy from anti-PD-1 Trials

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Keynote-040: Pembrolizumab vs. SOC				
	CPS ≥1	CPS ≥20	TPS ≥50%	TPS <50%
OS HR (95% CI)	1.28 (0.8, 2.07)	0.74 (0.58, 0.93)	0.53 (0.35, 0.81)	0.93 (0.73, 1.17)
OS (mos) Median (95% CI)	6.3 vs. 7.0	8.7 vs. 7.1	11.6 vs. 6.6	6.5 vs 7.1

Cohen, et al. The Lancet 10167(393), 2018

CheckMate 141: Nivolumab vs. SOC			
	ITT	<1%	≥1%
OS HR (95% CI)	0.68 (0.54, 0.86)	0.73 (0.49, 1.09)	0.55 (0.36-0.83)
OS (mos) Median (95% CI)	7.7 (5.7, 8.8) vs. 5.1 (4.0, 6.2)	6.5 (4.4, 11.7) vs. 5.5 (3.7, 8.5)	8.2 (6.7, 9.5) vs. 4.7 (3.8, 6.2)
2-yr OS %	16.9% (12.4, 22.0) vs. 6.0% (2.7, 11.3)	20.7%	18.5%
PFS HR (95% CI)	0.89 (0.70-1.13)	1.13 (0.75, 1.71)	0.59 (0.41, 0.84)
PFS (mos) Median (95% CI)	2.0 (1.9, 2.1) vs. 2.3 (1.9, 3.1)	2.0 (1.9, 2.1) vs. 2.7 (2.0, 4.6)	2.1 (2.0, 3.5) vs. 2.0 (1.9, 3.1)

Ferris, et al. Oral Oncology 2018

Analysis of PD-L1 Expression and Efficacy from anti-PD-1 Trials

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	Keynote-048: Pembrolizumab vs. EXTREME			Keynote-048: Pembrolizumab + Chemotherapy vs. EXTREME		
	ITT	CPS ≥1	CPS ≥20	ITT	CPS ≥1	CPS ≥20
OS HR (95% CI)	0.83, 95% CI 0.70-0.99	0.77 [95% CI 0.61-0.90]	0.58 [95% CI 0.44-0.78]	0.77 [95% CI 0.63-0.93	0.65, 95% CI 0.53-0.80	0.60, 95% CI 0.45-0.82
Median OS (mos) (95% CI)	11.5 vs. 10.7	12.3 vs 10.3	14.8 vs 10.7	13.0 vs 10.7	13.6 vs 10.4	14.7 vs 11.0
ORR %	16.9% vs 36%	19% vs 35%	23% vs 36%	36% vs 36%	36.4% vs 35.7%	42.9% vs 38.2%
PFS HR (95% CI)	1.34 (1.13-1.59)	1.16 [95% CI 0.96-1.39]	0.99 [95% CI 0.75-1.29]	0.92 [95% CI 0.77-1.10]	0.82 (0.67-1.00)	0.73 (0.55-0.97)
Median PFS (mos) (95% CI)	2.3 vs. 5.2	3.2 vs. 5.0	3.4 vs. 5.0	4.9 vs. 5.1	5.0 vs. 5.0	5.8 vs. 5.2

Rischin, et al. J Clin Oncol 37, 2019 (suppl; abstr 6000)
Burtness, et al. Oncology Pro, ESMO 2018

Consensus Treatment Recommendations for patients with R/M HNSCC

The role of biomarker testing

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Key clinical immunotherapy recommendations for treatment of patients with HNSCC	
Clinical Question	Summary recommendation
What is the role of biomarker testing in patients with HNSCC?	The subcommittee recommends against standard MSI testing
	Positivity for PD-L1 is ≥1% TPS or ≥1 CPS by IHC staining
	The best use of biomarker testing when treating patients with HNSCC with immunotherapy is by combined positive score (CPS)

Cohen et al. JITC 2019

Does human papillomavirus (HPV) influence the use of immunotherapy in HNSCC?
HPV-related Data: Keynote-012, CheckMate 141, HAWK

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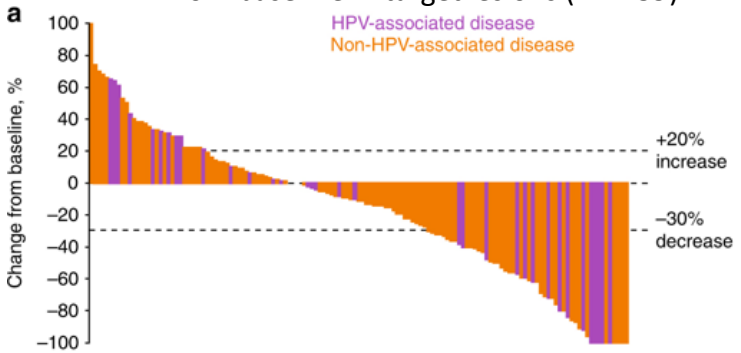
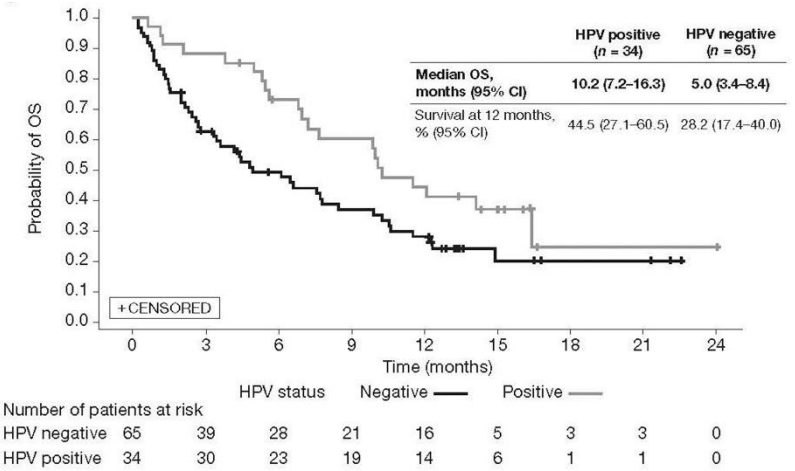
Keynote-012 Long-term follow-up: Best percentage change from baseline in target lesions (*n* = 139)



Keynote-012						
	All N = 192		HPV associated n = 45		Non-HPV associated n = 147	
	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)
Overall response rate	34	18 (13–24)	11	24 (13–40)	23	16 (10–23)
Complete response	8	4 (2–8)	4	9 (3–21)	4	3 (1–7)
Partial response	26	14 (9–19)	7	16 (7–30)	19	13 (8–19)
Stable disease	33	17 (12–23)	7	16 (7–30)	26	18 (12–25)
Progressive disease	93	48 (41–56)	19	42 (28–58)	74	50 (42–59)
Non-CR/Non-PD	7	4 (2–7)	1	2 (0.1–12)	6	4 (2–9)

Mehra, et al. British Journal of Cancer. 2018

HAWK Exploratory analysis of OS by HPV status



Zandberg, 2019. European Journal of Cancer; 107, 142-152

CheckMate 141: Outcomes by HPV status lesions (*n* = 139)

CheckMate 141		
OS HR (95% CI)	HPV+	0.60 (0.37, 0.97)
	HPV-	0.59 (0.38, 0.92)
OS (mos) Median (95% CI)	HPV+	9.1 (6.5, 11.8) vs. 4.4 (3.0, 9.8)
	HPV-	7.7 (4.8, 13.0) vs. 6.5 (3.9, 8.7)
PFS HR (95% CI)	HPV+	0.75 (0.46, 1.23)
	HPV-	1.01 (0.65, 1.56)
PFS (mos) Median (95% CI)	HPV+	2.0 (1.9, 3.3) vs. 2.0 (1.6, 2.8)
	HPV-	2.1 (1.9, 3.1) vs. 3.3 (1.9, 4.0)

Ferris, et al. Radiation Oncology. 2018

Consensus Treatment Recommendations for patients with R/M HNSCC

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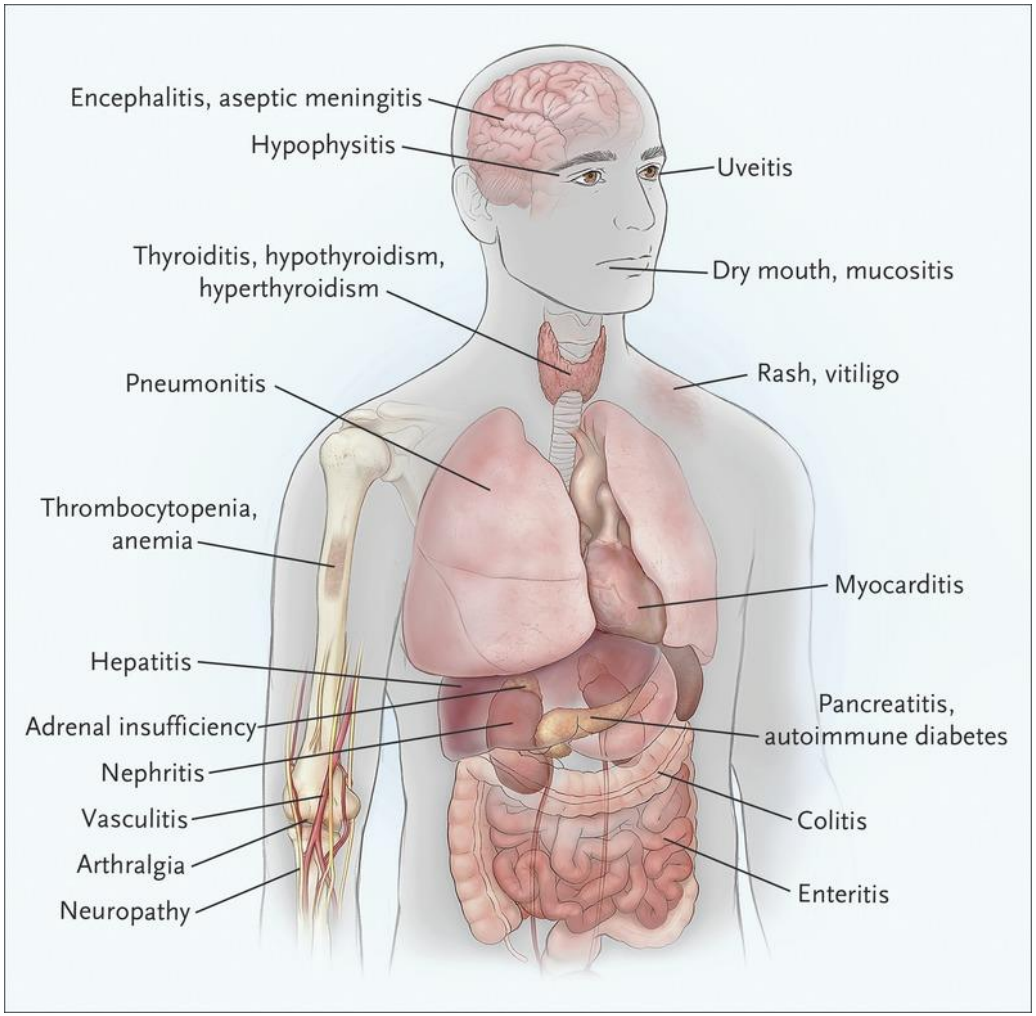
Does human papillomavirus (HPV) influence the use of immunotherapy in HNSCC?

Clinical Question	Summary Recommendation
How does HPV status influence the use of immunotherapy in HNSCC?	HPV status (based on p16 overexpression) should be included in treatment planning, but should not influence the decision to treat patients with R/M HNSCC with SOC immunotherapy

Immune-related Adverse Events (irAEs)



Postow, et al. 2018. NEJM

Immune-related Adverse Events

CheckMate 141, Keynote-012, Keynote-040, Keynote-048

Pembrolizumab or Nivolumab vs SOC (methotrexate, docetaxel or cetuximab) for R/M HNSCC with disease progression during or after platinum-based chemotherapy

	Nivolumab vs. SOC (CheckMate 141)	Pembrolizumab (Keynote-012)	Pembrolizumab vs. SOC (Keynote-040)	Pembrolizumab vs. SOC (Keynote-048)	Pembrolizumab or Pembrolizumab + Chemotherapy vs. SOC (Keynote-048)
Related Grade 3-5 AEs	15.3 vs. 36.9%	17%	13% vs 36%	54.7 vs. 83.3%	85.1 vs. 83.3%
Primary AEs	Hypothyroidism	Alanine aminotransferase, aspartate aminotransferase elevations, hyponatremia	Hypothyroidism	Fatigue, Anemia, Constipation, Nausea, Diarrhea	Anemia, Nausea, Constipation, Fatigue, Neutropenia, Diarrhea, Thromboctyopenia

*Of note, while most irAEs appear to occur during immunotherapy, there is growing evidence to suggest the existence of post-immunotherapy irAEs, which occur months or years after treatment discontinuation. With an increasing number of neoadjuvant/adjuvant IO trials currently being conducted in the definitive/curative setting, it will be necessary to recognize this emerging clinical entity and perhaps adjust follow-up and reporting times.

Consensus Treatment Recommendations for patients with R/M HNSCC

Treatment and Management of irAEs

Clinical Question	Summary recommendation
How should immune-related adverse events be recognized and managed in patients with HNSCC?	• *For further detail into toxicity management strategies please refer to the NCCN Clinical Practice Guidelines in Oncology: Management of Immunotherapy-Related Toxicities (2019)
	• For an irAE < grade 3, continue ICIs for grade 1 events with the exception of some neurologic, hematologic or cardiac toxicities. For grade 2 events, stop IO therapy and provide closely monitored outpatient treatment, including consideration of oral steroids.
	• For irAE development ≥ grade 3, halt treatment, admitting the patient to the hospital and administering steroids
	• Routine monitoring of thyroid function, neck and airway through imaging, and AST/ALT levels
	• In patients that develop hypothyroidism, continue immunotherapy, providing levothyroxine for management, and evaluating thyroid function in two-month intervals
	• In the event of bulky disease leading to functional or organ compromise: halt immunotherapy
	• Pneumonitis is not a greater concern in immunotherapy patients with HNSCC compared to other cancers

Cohen et al. JITC 2019

SITC Toxicity Management Guidelines

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GUIDELINES

Puzanov *et al. Journal for ImmunoTherapy of Cancer* (2017) 5:95
DOI 10.1186/s40425-017-0300-z

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES Open Access

CrossMark

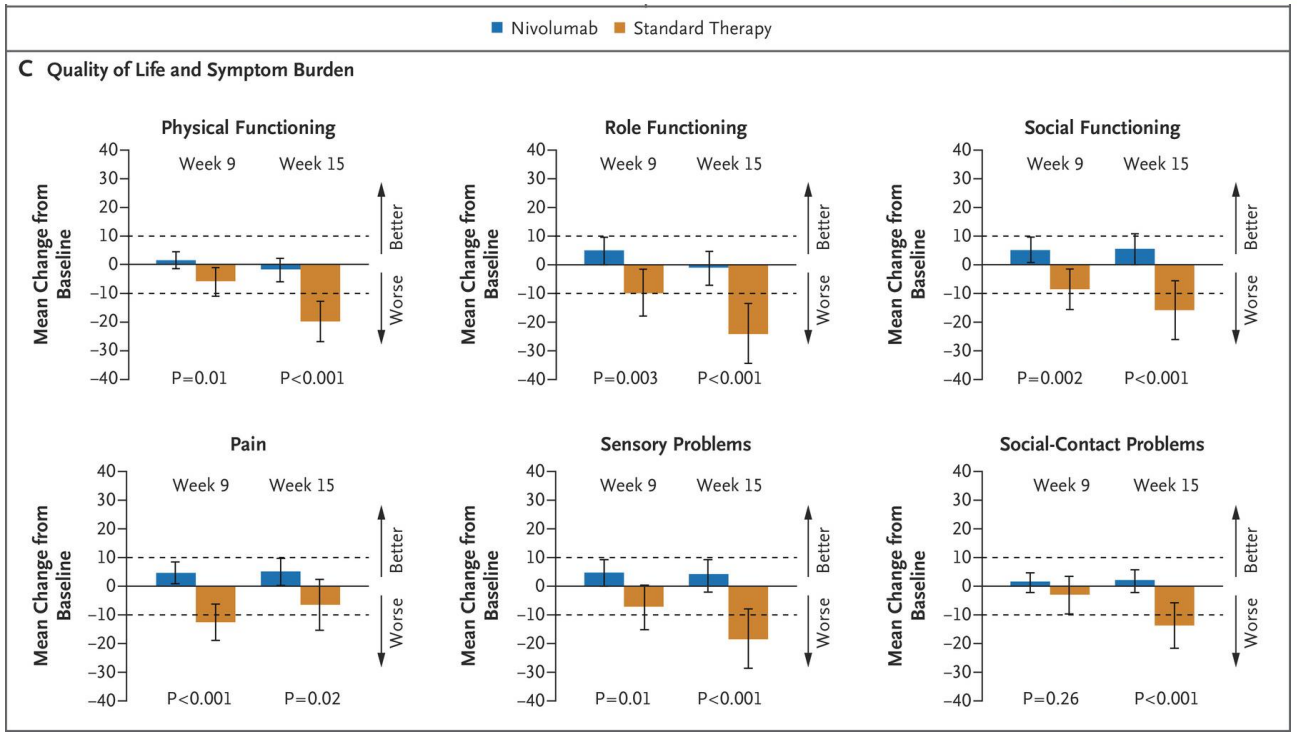
Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group

I. Puzanov[1†], A. Diab[2†], K. Abdallah[3], C. O. Bingham III[4], C. Brogdon[5], R. Dadu[2], L. Hamad[1], S. Kim[2], M. E. Lacouture[6], N. R. LeBoeuf[7], D. Lenihan[8], C. Onofrei[9], V. Shannon[2], R. Sharma[1], A. W. Silk[12], D. Skondra[10], M. E. Suarez-Almazor[2], Y. Wang[2], K. Wiley[11], H. L. Kaufman[12†], M. S. Ernstoff[1*†] and on behalf of the Society for Immunotherapy of Cancer Toxicity Management Working Group

Currently in development:

- Immune Checkpoint Inhibitor and Cytokine-related Adverse Events Guideline
- Immune Effector Cell-related Adverse Events Guideline

Quality of Life and Symptom Burden

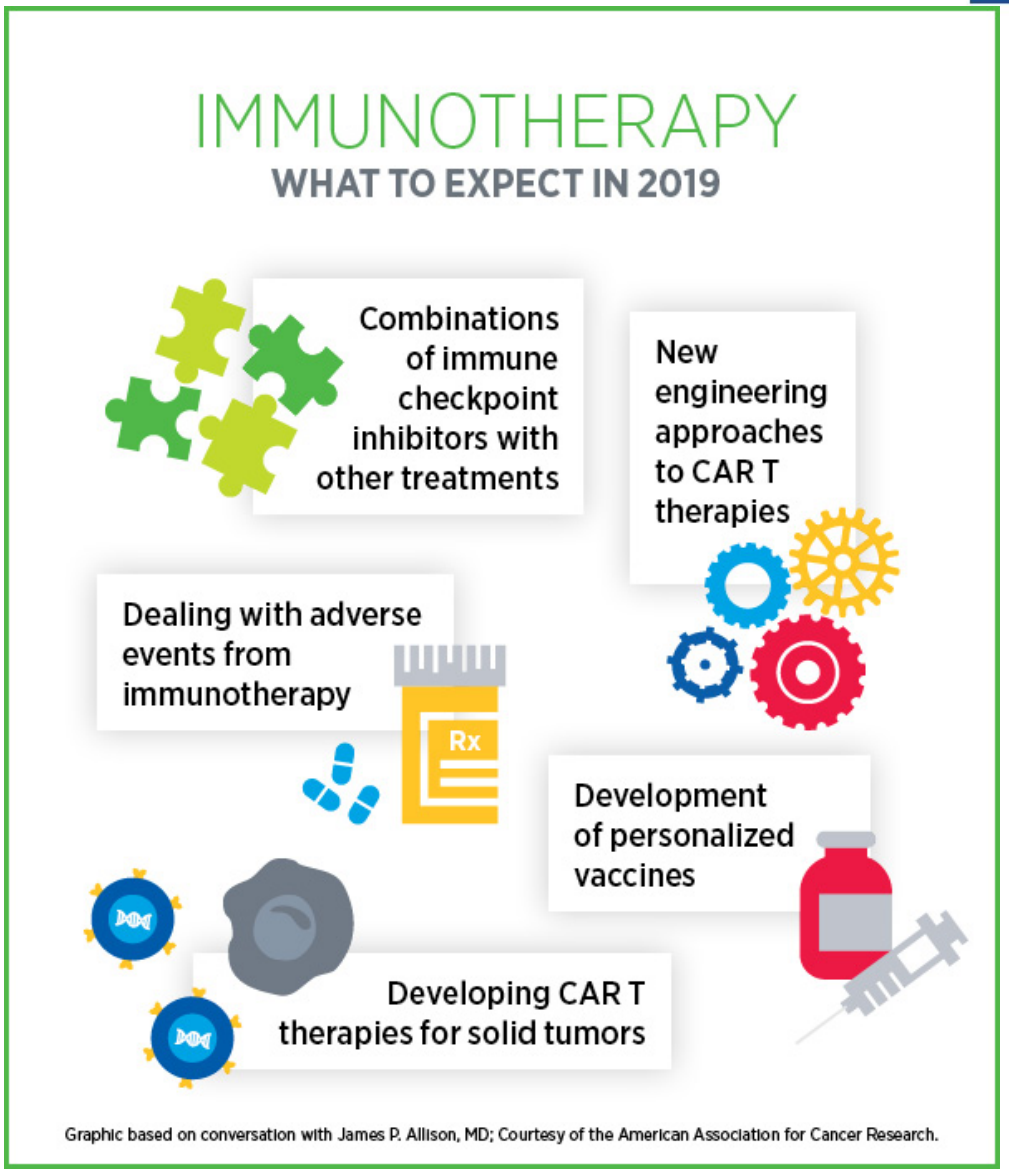


- Clinical benefit, as measured by validated PRO measures, indicates that pts experienced improved QoL in addition to prolonged survival, higher response rate, and fewer high-grade toxicities relative to investigator's choice
- Differences between groups were significant and clinically meaningful at weeks 9 and 15 in favor of nivolumab for role functioning, social functioning, fatigue, dyspnoea, and appetite loss on the EORTC QLQ-C30 and pain and sensory problems on the EORTC QLQ-H&N35
- Nivo delayed time to deterioration of patient-reported quality-of-life outcomes and stabilized symptoms and functioning from baseline to weeks 9 and 15, whereas investigator's choice led to clinically meaningful deterioration

*Scales range from 0 to 100 and were scored such that higher values indicated better functioning or lower symptom burden. A clinically meaningful score change was regarded as one of 10 points (dashed lines) or more

Harrington et al. Lancet Onc. 2017

Immunotherapies in Development



AACR, James P. Allison, October 2018

Ongoing Clinical Trials

Incorporation of immunotherapy within novel combination therapy strategies for HNSCC

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Treatment Setting				
Recurrent/Metastatic				
	Trial	Description	Objective	Results
IO-IO: checkpoint + vaccine	(NCT02426892)	Phase 2. Nivolumab + ISA101 in patients with incurable oropharyngeal cancer.	To determine if nivolumab efficacy is amplified through treatment with ISA 101, a synthetic long-peptide HPV-16 vaccine inducing HPV-specific T cells, in patients with incurable HPV-16-positive cancer.	mPFS: 2.7 months (95% CI, 2.5-9.4 months) and mOS: 17.5 months (95% CI, 17.5 months to inest). Response was positively correlated with tumor cell PD-L1 positivity (≥1%). 36% ORR in patients with oropharyngeal cancer compared to 16% by nivolumab alone.

Ongoing Clinical Trials

Incorporation of immunotherapy within novel combination therapy strategies for HNSCC

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Treatment Setting				
Definitive				
IO-Chemotherapy and/or radiotherapy	RTOG-3504 (NCT02764593)	Phase 2. Adding nivolumab to strd cetuximab-RT for pts with newly diagnosed interm/high-risk LA HNSCC.	Immunotherapy is added to enhance other conventional therapies such as surgery, CT and RT.	Nivo is safe and reasonable to administer in combination with a cetuximab-RT regimen for patients with newly diagnosed IR/HR HNSCC.
	GORTEC 2015-01 (NCT02707588)	Phase 2. Pembrolizumab or cetuximab + RT in LA HNSCC patients.	Determine synergistic effects when combining ICI with RT vs. SOC cetuximab + RT.	Decrease in serious AEs in pembrolizumab arm (78% pts) vs. cetuximab arm (94% pts).
	GORTEC 2017-01 (REACH) (NCT02999087)	Phase 3. Avelumab + cetuximab and RT vs. SOC in LA HNSCC.	Hypothesis: synergistic effect to occur upon combination of avelumab with cetuximab + RT.	Acceptable safety profile. Continuation approved by Data and Safety Monitoring Cmte.
	SH MISP203 (NCT02586207)	Phase I. Pembrolizumab + chemoradiation (CRT; cisplatin) in LA HNSCC	Defining a role for pembro in definitive therapy for LA-SCCHN; ccurrence of CRT or pembro dose-limiting AEs and irAEs; CR rate on imaging or with salvage surgery at 100 days post-CRT completion.	21/27 pts completed all planned doses of pembro; 3 discont due to irAEs (G2 peripheral motor neuropathy, G3 AST elevation, G1 Lhermitte-like syndrome); 3 discont due to protocol. All pts completed full RT dose (70 Gy) without significant delay (> 5 days). 23 pts received target dose of cisplatin (≥200 mg/m2).

Consensus Treatment Recommendations for patients with R/M HNSCC
Summary

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Clinical Question	Summary recommendation
How should immunotherapy with PD-1 inhibitors be integrated into the treatment of recurrent/metastatic HNSCC?	**First-line:** • Pembrolizumab is indicated for treatment-naïve R/M HNSCC ○ Pembrolizumab monotherapy may be used to treat patients with treatment naïve R/M HNSCC and PD-L1 CPS ≥1 ○ Pembrolizumab + Chemotherapy (platinum and fluorouracil (FU)) may be used to treat all patients with treatment naïve, biomarker-unspecified R/M HNSCC patients * Positivity for PD-L1 as ≥1 CPS by IHC staining
	Second-line: • Pembrolizumab or nivolumab monotherapy should be used to treat patients with R/M HNSCC who are platinum-refractory, including those that progressed within six months of platinum-based chemotherapy *Alternatively, if a clinical trial is available, this is the preferred option, especially if biomarker-based, hypothesis-driven
What is the role of biomarker testing in patients with HNSCC?	• The subcommittee recommends against standard MSI testing
	• Positivity for PD-L1 is ≥1% TPS or ≥1 CPS by IHC staining
	• The best use of biomarker testing when treating patients with HNSCC with immunotherapy is by combined positive score (CPS)

Cohen et al. JITC 2019

Consensus Treatment Recommendations for patients with R/M HNSCC
Summary

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Clinical Question	Summary recommendation
How should treatment response be evaluated and managed in patients with advanced HNSCC?	• If radiographic progression is observed early in treatment, and the patient is clinically stable, continue treatment until progression is confirmed on a second scan
	• If disease progression on or after treatment with a PD-1 inhibitor: enrollment in a clinical trial, treat with palliative radiotherapy and/or chemotherapy (a taxane)
	• Anatomical site of the tumor is an important consideration • *potential for airway obstruction, surgical resection or RT to the site may alter the course of treatment
	• The term “pseudoprogression” should be avoided in a setting of worsening symptoms
	• Hyperprogression defined as “a rapid increase in tumor growth rate (minimum two-fold) compared to expected or prior growth rate”

Cohen et al. JITC 2019

Consensus Treatment Recommendations for patients with R/M HNSCC
Summary

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Clinical Question	Summary recommendation
How should immune-related adverse events be recognized and managed in patients with HNSCC?	• *For further detail into toxicity management strategies please refer to the NCCN Clinical Practice Guidelines in Oncology: Management of Immunotherapy-Related Toxicities (2019)
	• For an irAE < grade 3, continue ICIs for grade 1 events with the exception of some neurologic, hematologic or cardiac toxicities. For grade 2 events, stop IO therapy and provide closely monitored outpatient treatment, including consideration of oral steroids.
	• For irAE development ≥grade 3, halt treatment, admit patient to the hospital and administer steroids
	• Routine monitoring of thyroid function, neck and airway through imaging, and AST/ALT levels
	• In patients that develop hypothyroidism, continue immunotherapy, providing levothyroxine for management, and evaluating thyroid function in two-month intervals
	• In the event of bulky disease leading to functional or organ compromise: halt immunotherapy
	• Pneumonitis is not a greater concern in immunotherapy patients with HNSCC compared to other cancers
Are there categories of patients with HNSCC who should not receive immunotherapy?	• Do NOT automatically disqualify patient for anti-PD-1 immunotherapy based on: age, lung metastases, co-morbidities, auto-immune disease
	• Patients with controlled diseases such as Hepatitis C or are HIV+ with normal CD4+ T cell counts and who are on antiretroviral therapy are generally suitable for ICI treatment

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Case Study 1: R/M HNSCC

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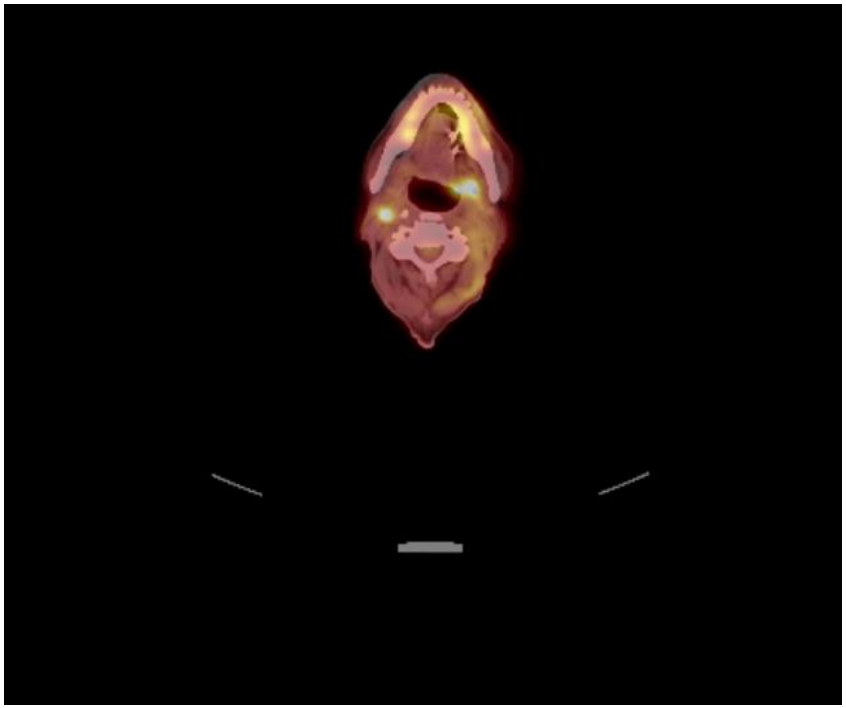
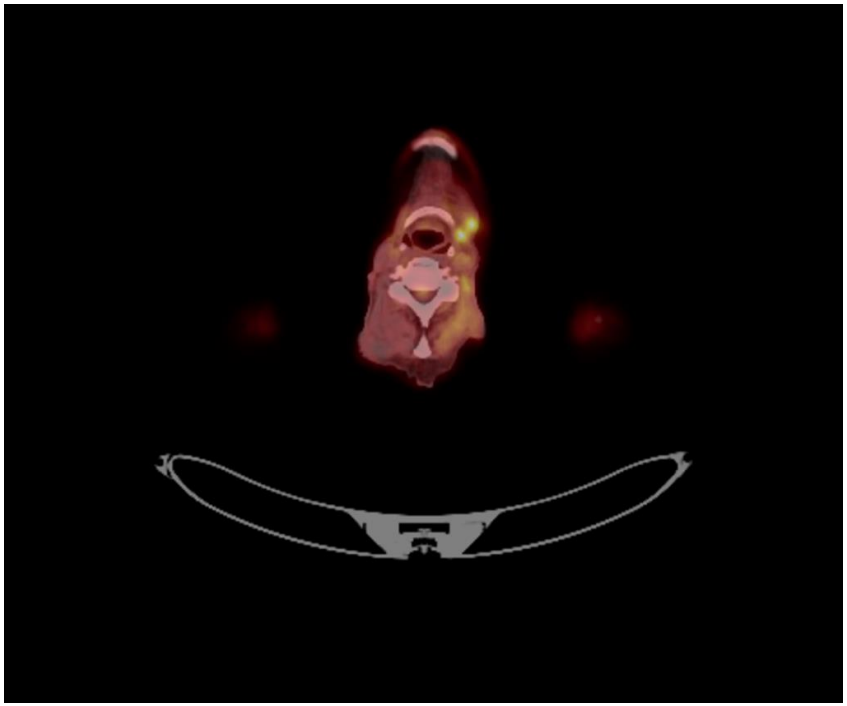
Background:

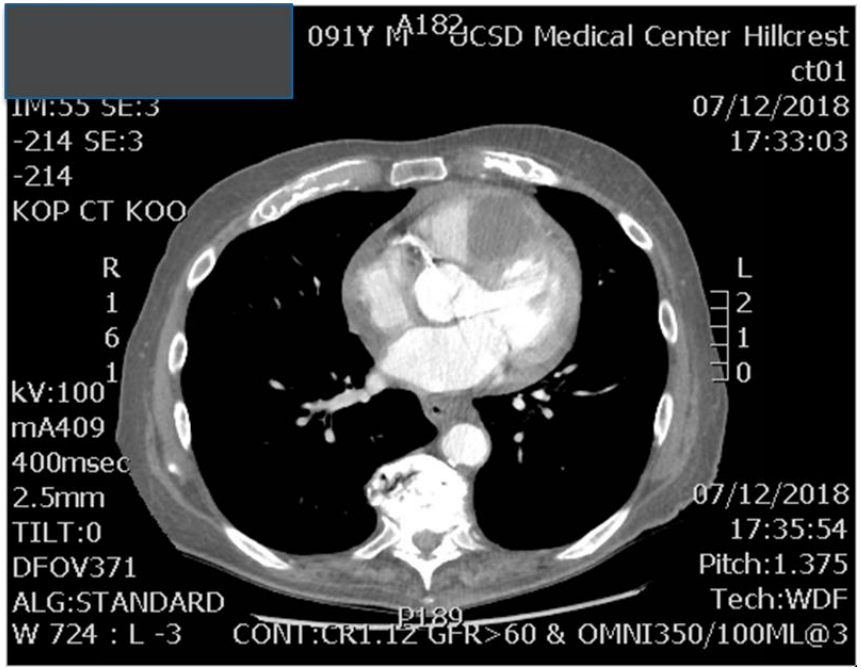
- 52 y/o man who initially presented to our clinic in January 2017 with recurrent oral tongue SCC
- Oncology history:
  - January 2010: Presented with T1, N2b, underwent surgery including neck dissection
  - February 20 – April 7 2010: Underwent adjuvant CDDP/RT
  - August 2016: Relapse - Left tongue SCC
  - August 2016: Hemiglossectomy, lymph node dissection
  - November 2016: New neck mass, FNA confirmed SCC
- Pain left head, neck, tongue; Mild dysphagia for liquids and some solids; Speech slurred
- CT chest demonstrates pulmonary nodules and intracardiac mass

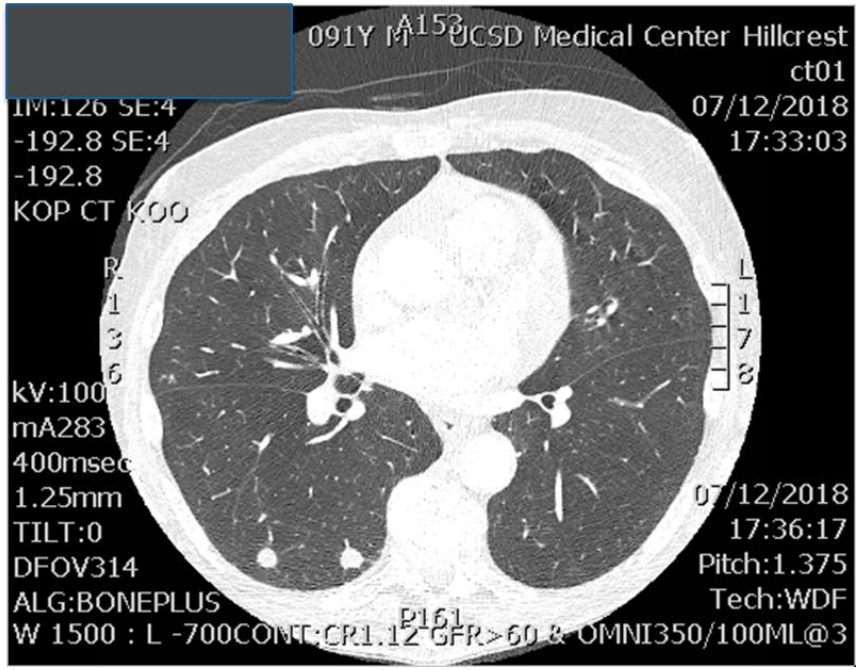
Case Study 1: R/M HNSCC





Case Study 1: R/M HNSCC





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How would you manage this patient?

Case Study 2: Toxicity

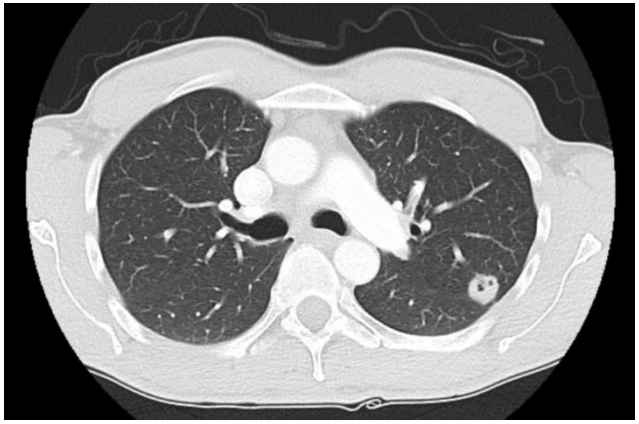
Background: 49-Year-Old Male with Recurrent HPV-Mediated (p16+) Tongue Cancer

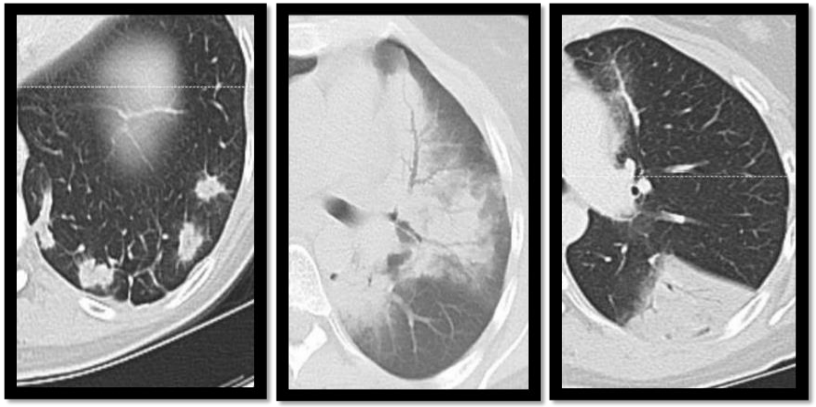
- 5 months post-treatment, chest x-ray and CT showed a suspicious lung nodule (images at right)

Biopsy: p16+ HPV+ SCC
His disease has recurred

- Received 4 doses of pembrolizumab at (200 mg q3 wk)

Developed dyspnea and cough





Case Study 2: Toxicity

What is the likely diagnosis?

A. pneumonia

B. pulmonary embolism

C. autoimmune pneumonitis

D. colitis

Case Study 2: Toxicity

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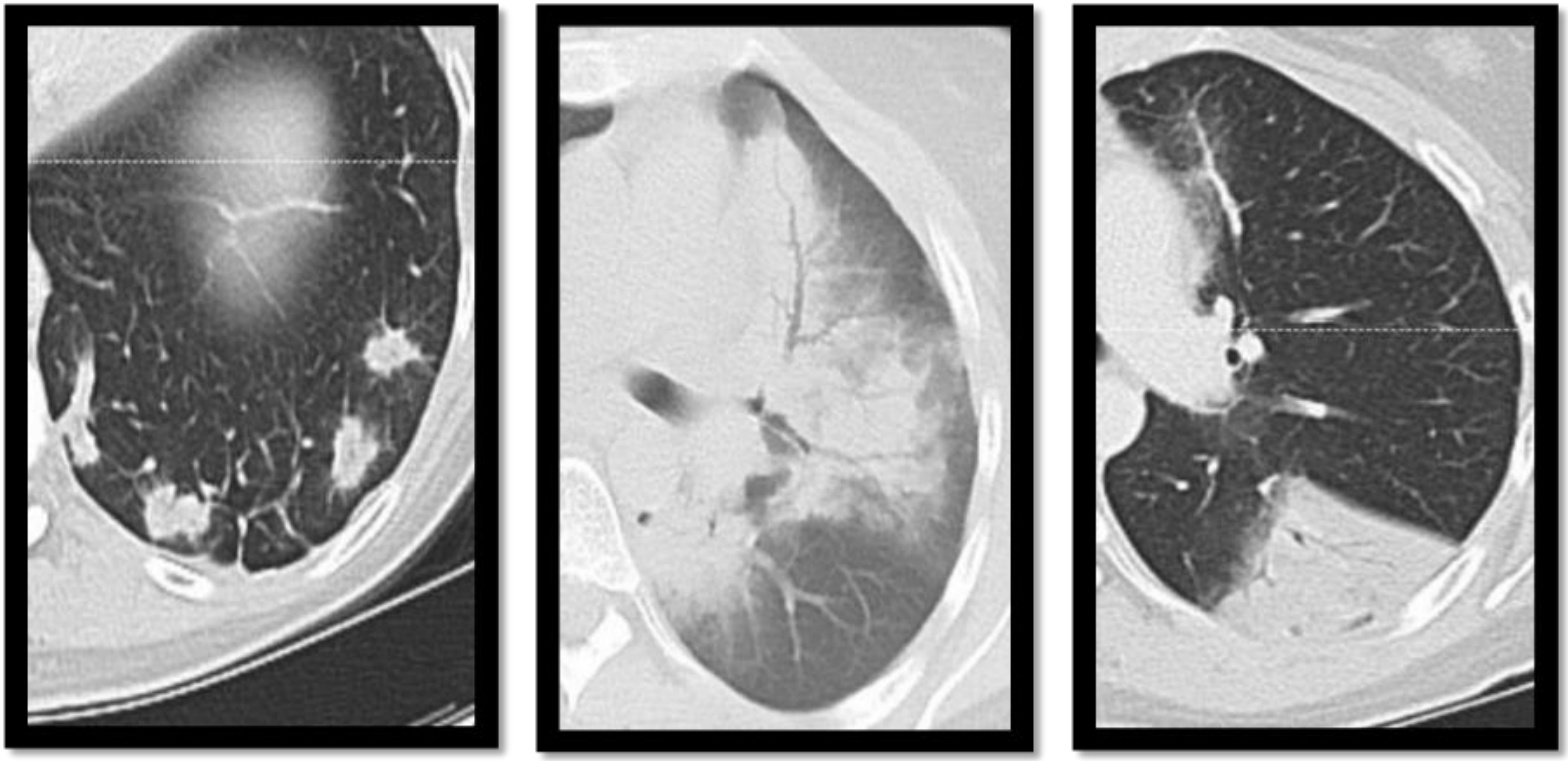
Conclusion/take-away:

- Autoimmune/inflammatory toxicities may occur at any point in IO therapy
- Early recognition and intervention, including stopping drug(s) and instituting anti-inflammatory agents is warranted
- Management of adverse events using steroids does not appear to decrease efficacy

Biopsy-Proven Pneumonitis is Highly Variable in Presentation



Management of Grade 3/4 Immune-Mediated Pneumonitis

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NCCN Guidelines® Recommendations

- Permanently discontinue immunotherapy
- Inpatient care
- Infectious workup:
  - Consider that patient may be immunocompromised
  - Nasal swab for potential viral pathogens
  - Sputum culture, blood culture, and urine culture
- Pulmonary and infectious disease consultation, consider PFTs
- Bronchoscopy with BAL to rule out infection and malignant lung infiltration
- Consider empiric antibiotics if infection has not yet been fully excluded
- Methylprednisolone* 1–2 mg/kg/day. Assess response within 48 hours and plan taper over ≥6 weeks
- Consider adding any of the following if no improvement after 48 hours:
  - Infliximab* 5 mg/kg IV, a second dose may be repeated 14 days later at the discretion of the treating provider
  - Mycophenolate mofetil* 1–1.5g BID then taper in consultation with pulmonary service
  - Intravenous immunoglobulin (IVIG*)--Total dosing should be 2 g/kg, administered in divided doses per PI.

*Please see IMMUNO-A for important guidance on administering this agent.

Management of Grade 3/4 Immune-Related Colitis

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NCCN Guidelines® Recommendations

- Grade 3: Discontinue anti-CTLA-4; consider resuming anti-PD-1/PD-L1 after resolution of toxicity
- Grade 4: Permanently discontinue immunotherapy agent responsible for toxicity
- Consider inpatient care for provision of supportive care
  -Intravenous (IV) methylprednisolone*§ (2 mg/kg/day)†
- No response in 2 days:
  -Continue steroids, consider adding infliximab‡§
  -If infliximab-refractory, consider vedolizumab§

*Convert to prednisone when appropriate.
†Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
‡Duration of therapy with tumor necrosis factor alpha (TNF-alpha) blockers is not clearly defined, but is usually a single dose. Repeat endoscopy may be helpful, but optional for the guidance of treatment. (See Principles of Immunosuppression regarding TB testing.)
§Please see IMMUNO-A for important guidance on administering this agent.

Immune-Related Colitis

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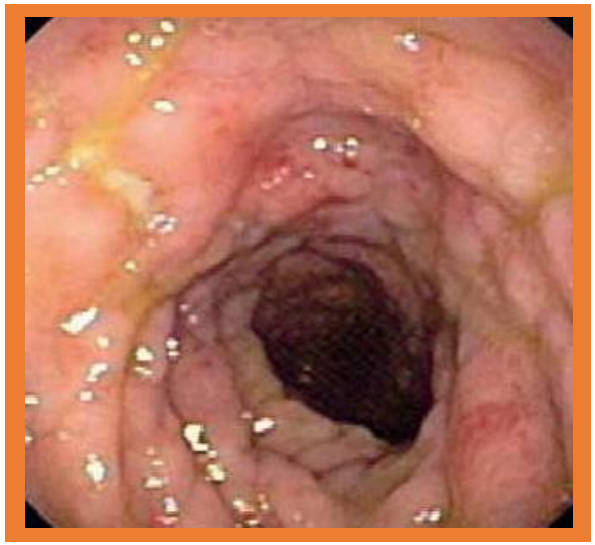
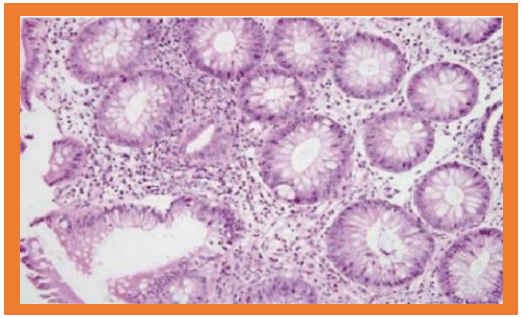
Ulceration in Descending Colon

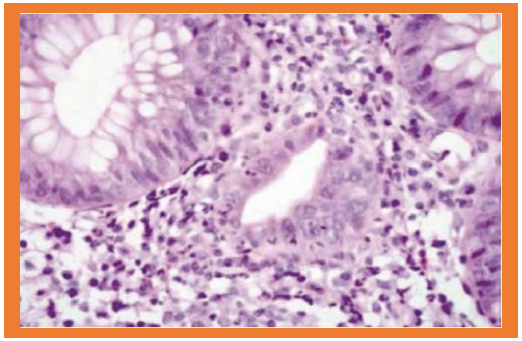


Maker. Ann Surg Oncol. 2005;12:1005.

Focal Active Colitis



Alterations in Crypt Epithelium



Question and Answer Session
Submit Your Questions

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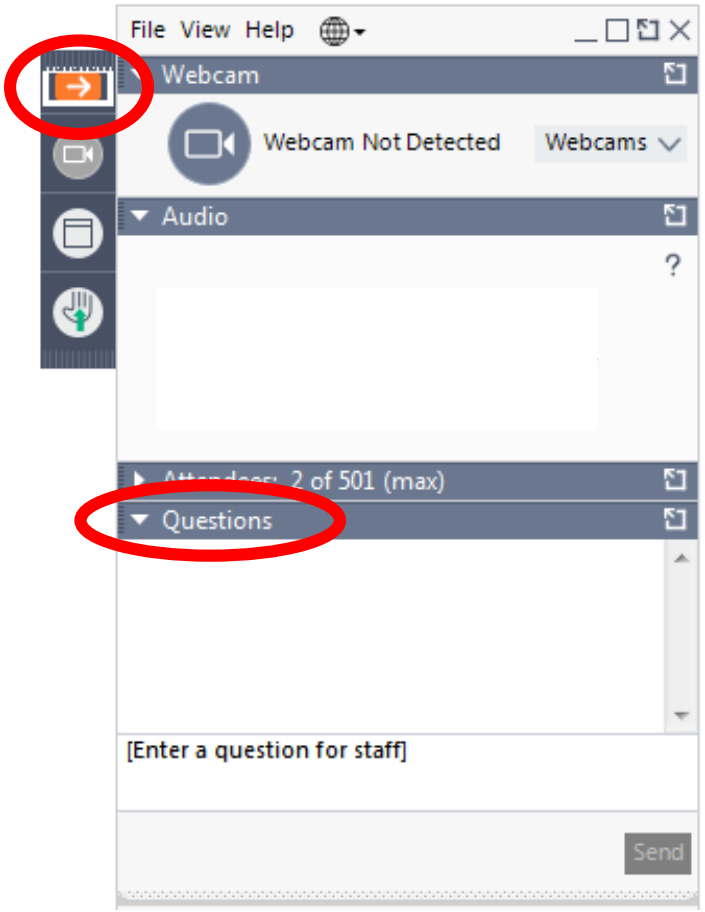
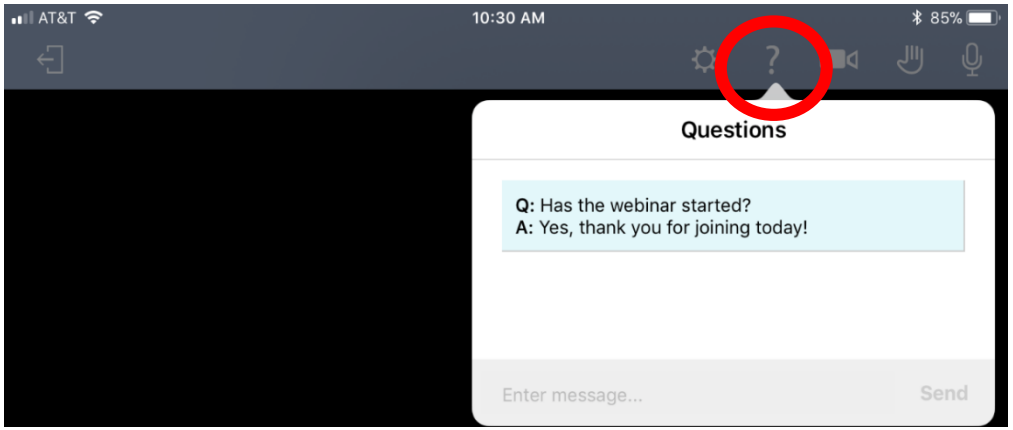
Computer



Mobile Phone



Additional Resources from SITC

Cancer Immunotherapy Guidelines:
www.sitcancer.org/cancer-immunotherapy-guidelines

Free Online Courses (CE) for Healthcare Providers:
www.sitcancer.org/clinician

Webinar Recording and Slides:
www.sitcancer.org/HeadNeckWebinar

SITC Cancer Immunotherapy Guidelines (CIG) are a collection of consensus statements developed by experts in the treatment of specific types of cancer. Each consensus statement provides key indicators to help practicing oncologists determine when and how to best use immunotherapy to treat their patients. These systematically developed recommendations promote enhanced clinical decisions concerning patient selection, toxicity management, clinical endpoints, and the sequencing or combination of therapies.

Current Guideline

Published July 15, 2019 in *Journal for ImmunoTherapy of Cancer* (JITC) as **"The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of squamous cell carcinoma of the head and neck (HNSCC)."**

VIEW GUIDELINE

Webinar

SITC CANCER IMMUNOTHERAPY GUIDELINES – SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (HNSCC) WEBINAR

July 24, 2019, from 3-4 p.m. EDT – **Register Now**

This **FREE** CME-, CNE-, CPE-certified webinar is a chance for healthcare providers who treat cancer patients, including oncologists, physicians, disease specialists, registered nurses, nurse practitioners, pharmacists and physician assistants to learn about the recommendations from the published guideline on immunotherapy for the treatment of head and neck cancers.

This free webinar will feature discussion of:

Society for Immunotherapy of Cancer
Cancer Immunotherapy GUIDELINES

Continuing Education Credits are offered for Physicians, PA's, NP's, RN's and Pharmacists.

You will receive an email following the webinar with instructions on how to claim credit.

Questions and comments: connectED@sitcancer.org

Thank you for attending the SITC Cancer Immunotherapy Guidelines- HNSCC Webinar!

Jointly provided by Postgraduate Institute for Medicine and the Society for Immunotherapy of Cancer

PIM Postgraduate Institute for Medicine
Professional Excellence in Medical Education

sitc Society for Immunotherapy of Cancer

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