Immunotherapy in Head and Neck Cancer

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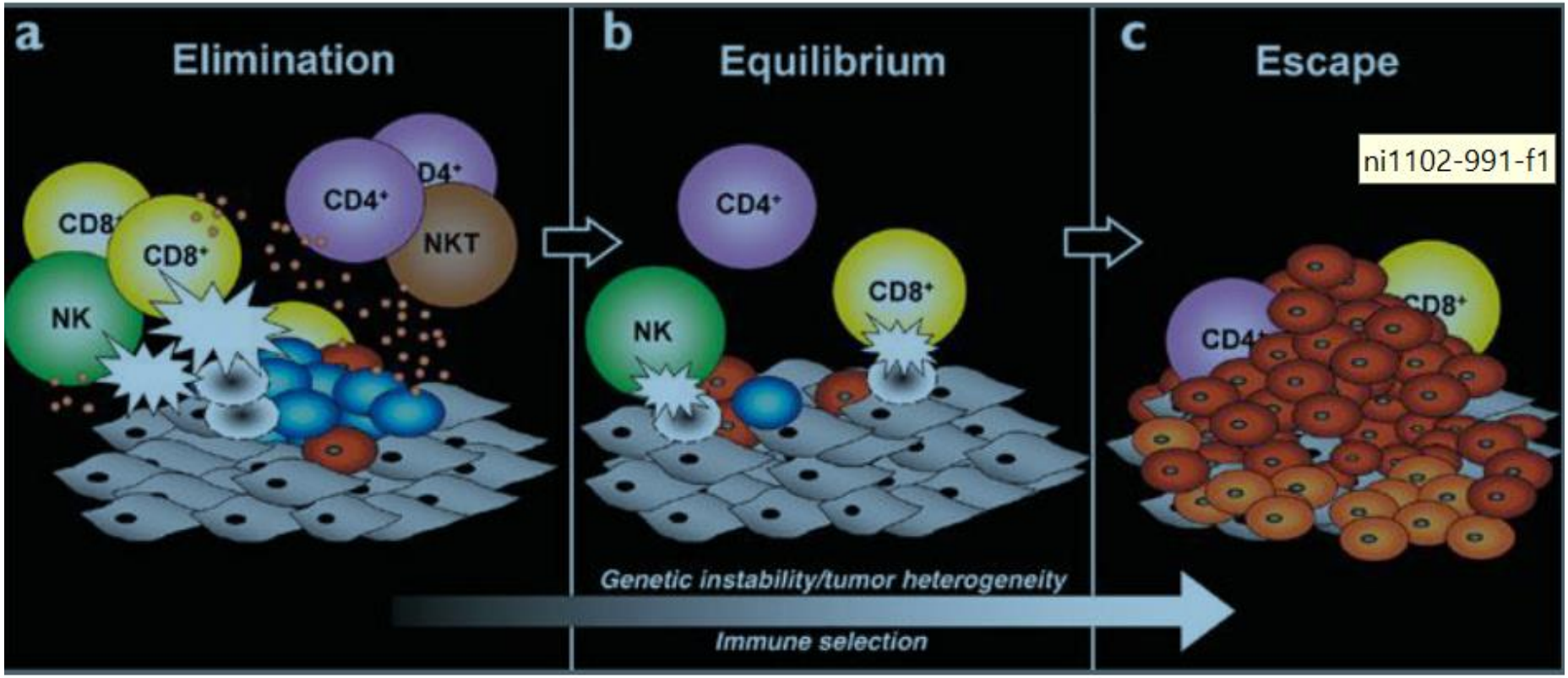
Nobel Prize in Medicine

***James P. Allison** (USA)* **and** ***Tasuku Honjo** (JPN)* **have won the 2018 Nobel Prize in Medicine for their discovery that the body's immune system can be harnessed to attack cancer cells**

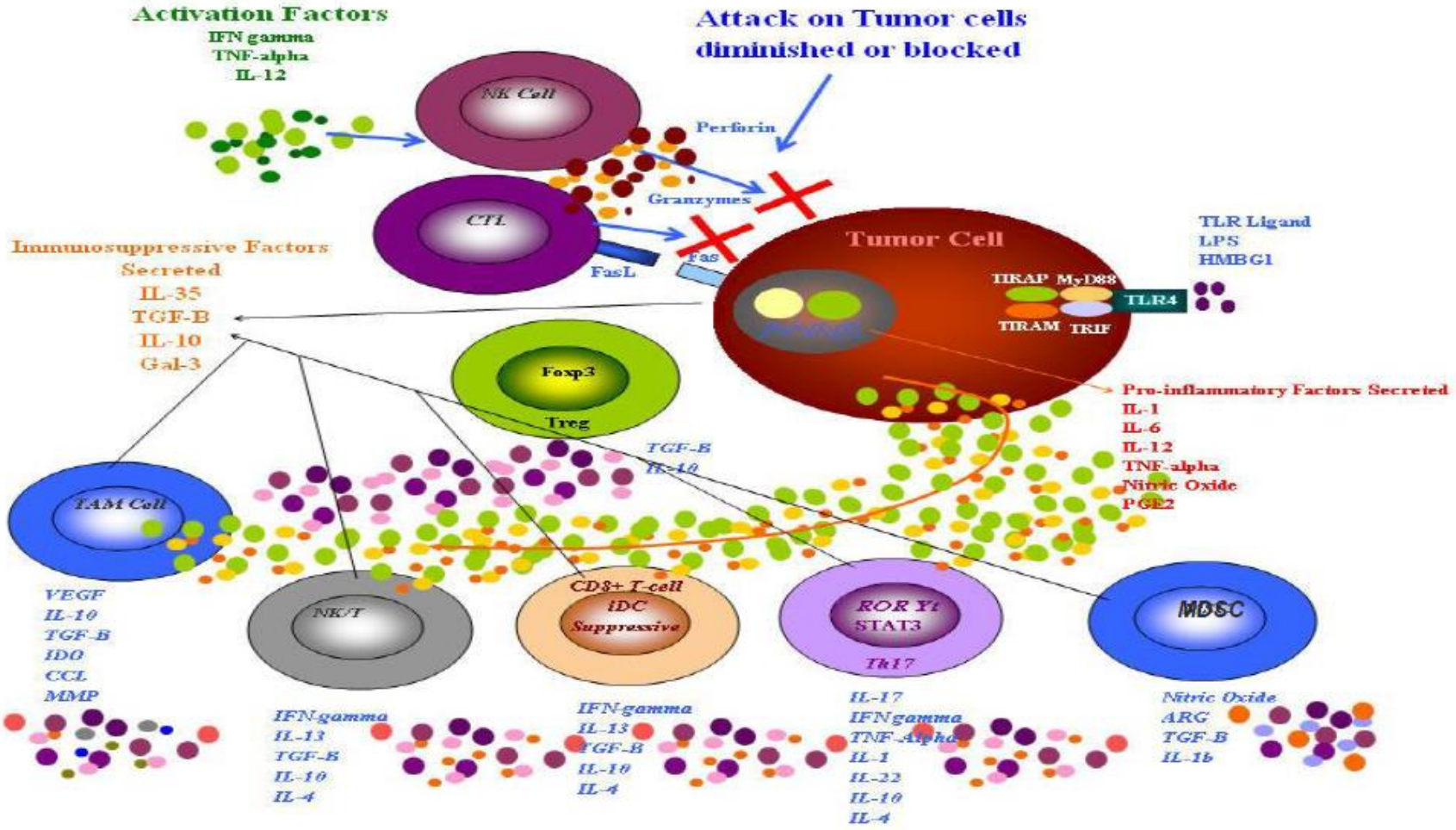
Overview

- MOA
- Indications
- Predictive Biomarkers
- Side Effects
- Future Trends
- Conclusion

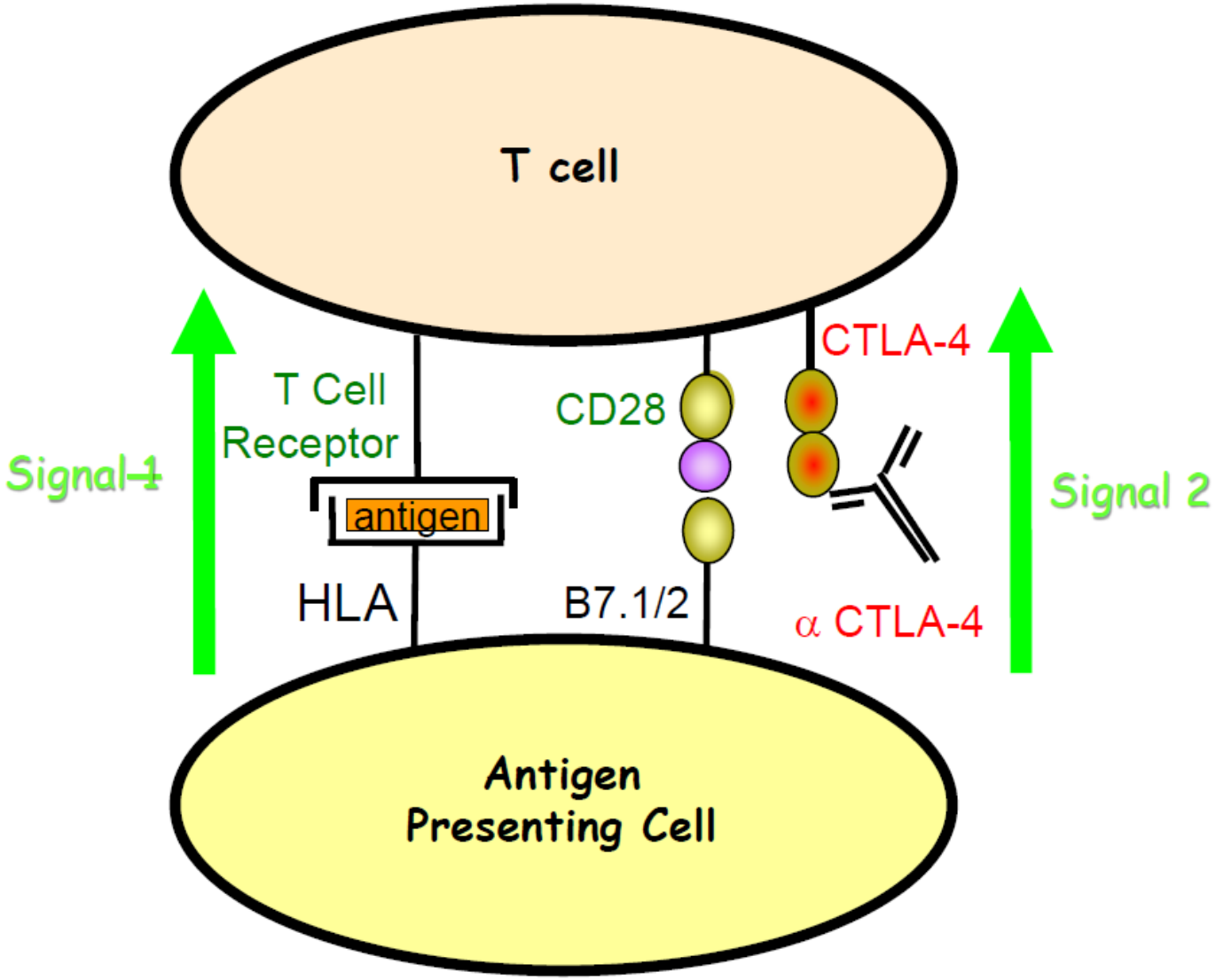
The Immune Editing Hypothesis (3E's)



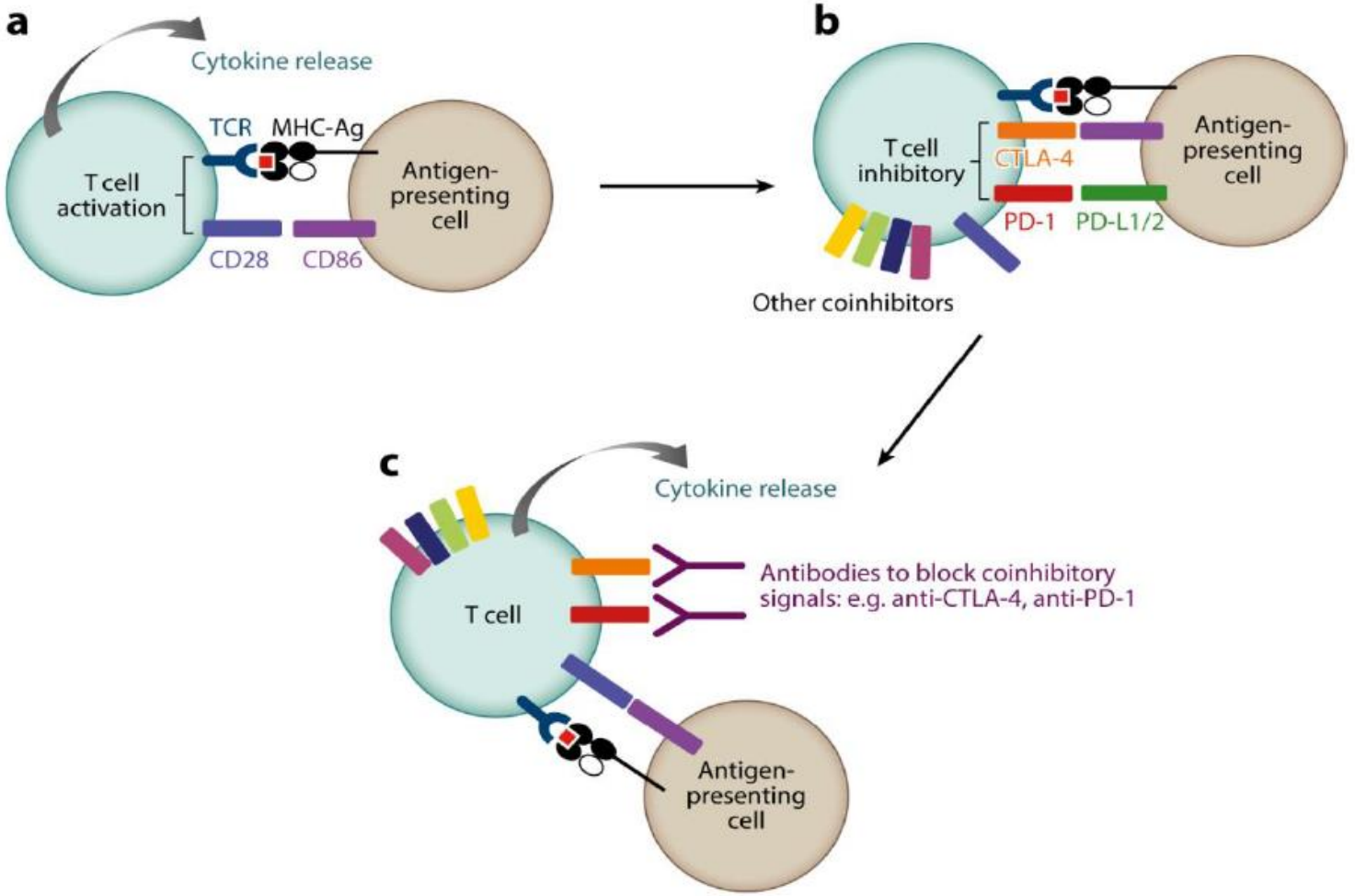
Mechanisms of Tumor-induced Immune Tolerance



Ipilimumab (Anti-CTLA-4) Blocks the CTLA-4 Checkpoint, RestoringT Cell Activation



Role of Checkpoint Inhibitors



Lizée G, et al. 2013.
Annu. Rev. Med. 64:71–90

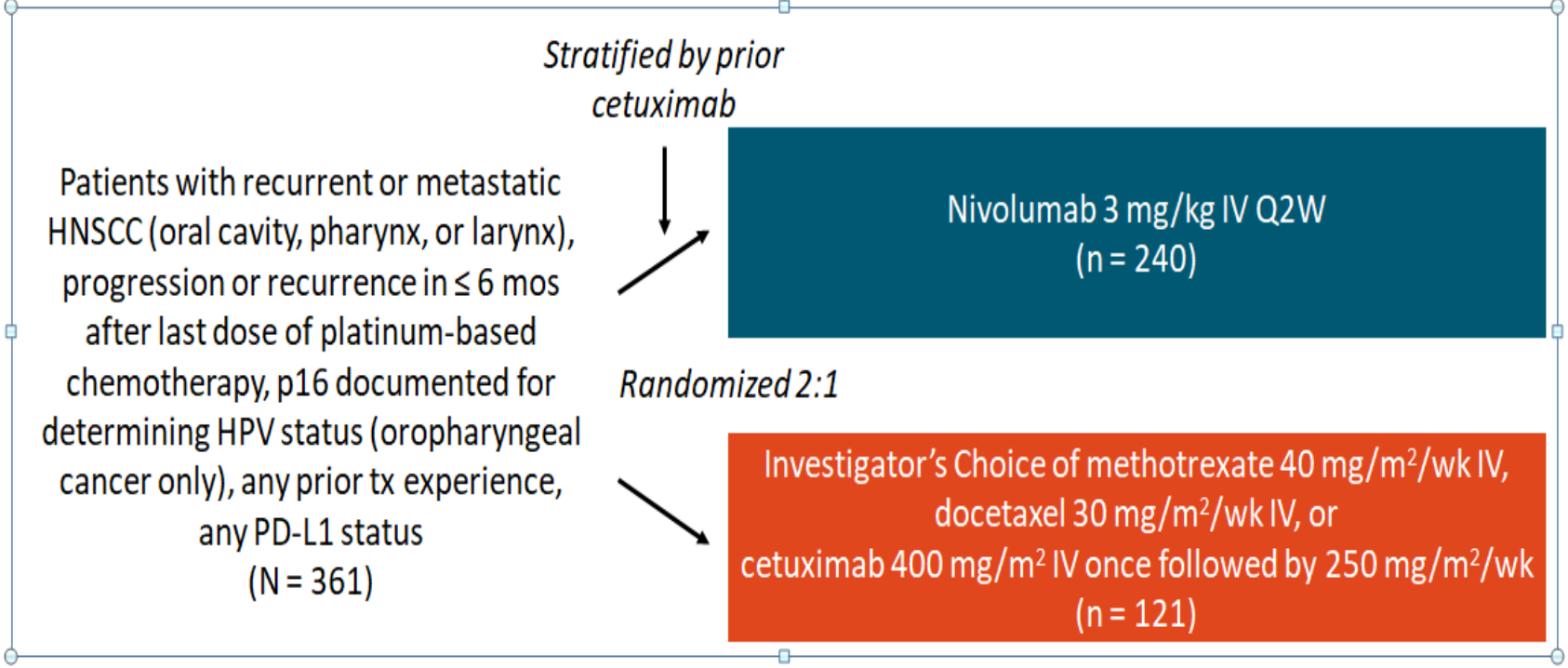
Indications

Immune Checkpoint Inhibitors in Head and Neck Cancer

Drug	Approved Indication	Target
Nivolumab[1]	Second line in R/M HNSCC with progression on/after platinum-based chemotherapy	PD-1
Pembrolizumab[2]	Second line in R/M HNSCC with progression on/after platinum-containing chemotherapy First line in R/M HNSCC as a single agent in patients with PD-L1–expressing tumors (CPS ≥ 1) and in combination with platinum + 5-FU for all patients	PD-1
Atezolizumab[3]	Not approved in HNSCC	PD-L1
Durvalumab[4]	Not approved in HNSCC	PD-L1
Avelumab[5]	Not approved in HNSCC	PD-L1

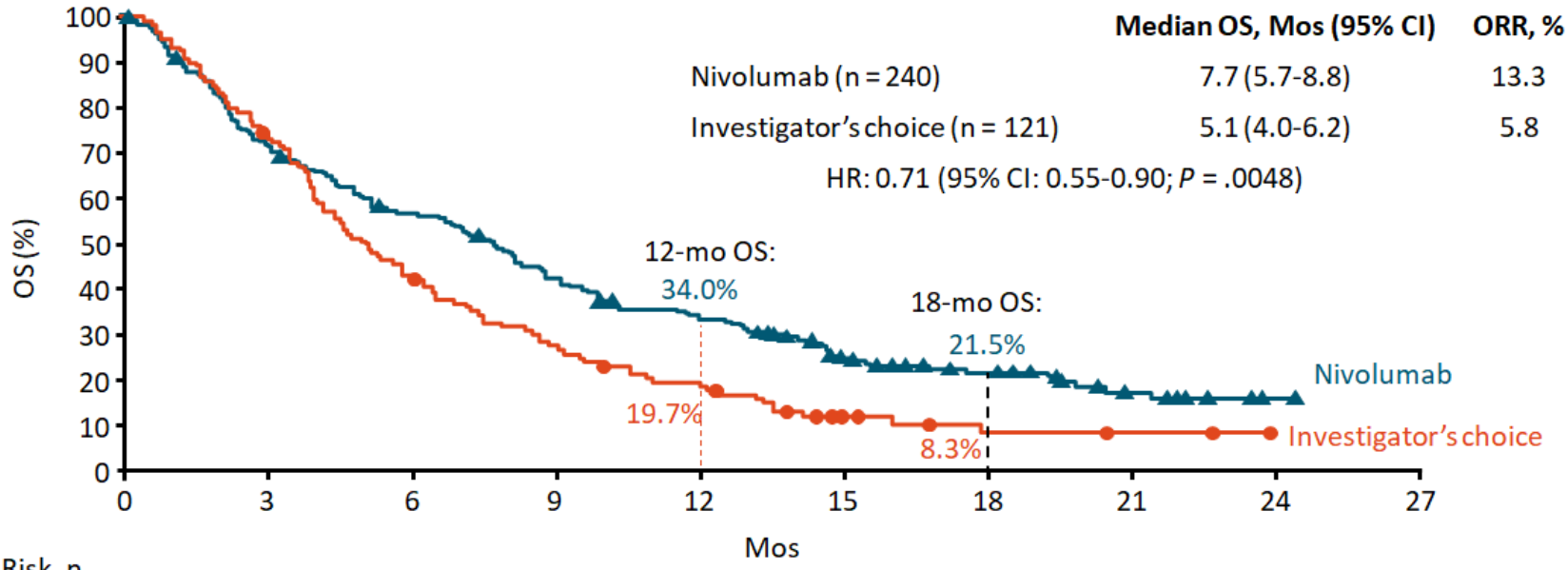
1.. Nivolumab PI. 2. Pembrolizumab PI. 3. Atezolizumab PI. 4. Durvalumab PI. 5. Avelumab PI.

Phase III CheckMate 141: Nivolumab in Recurrent/Metastatic HNSCC After Platinum Therapy



- Primary endpoint: OS
- Other endpoints: PFS, ORR, DoR, safety, biomarkers, QoL

CheckMate 141: OS for Nivolumab vs Investigator's Choice in Recurrent/Metastatic HNSCC



Patients at Risk, n

Nivo	240	169	132	98	76	45	27	12	3	0
IC	121	88	51	32	22	9	4	3	0	0

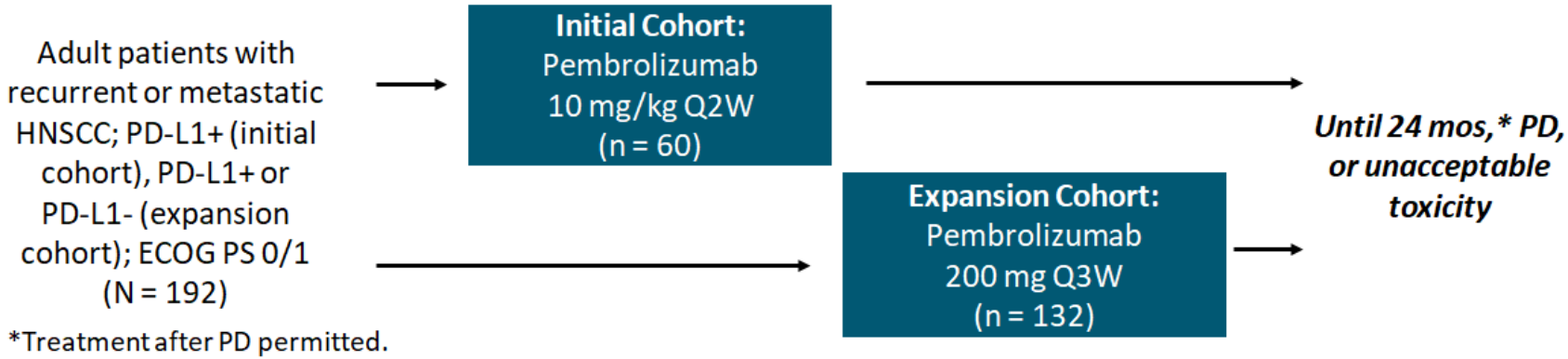
Median follow-up: 11.4 mos

Ferris. Oral Oncol. 2018;81:45.

Slide credit: clinicaloptions.com

KEYNOTE-012: HNSCC Cohorts

- Nonrandomized, open-label, multicohort phase Ib trial
  - Analysis of combined Initial and Expansion Cohorts (N = 192)



*Treatment after PD permitted.

- Primary endpoints: ORR per RECIST v1.1 by BICR, safety
- Secondary endpoints: investigator-assessed ORR, PFS, OS, DoR, ORR in HPV-positive patients (initial cohort only)

Mehra. Br J Cancer. 2018;119:153.

Slide credit: clinicaloptions.com

KEYNOTE-012: ORR by PD-L1 Status

PD-L1 Expression Sites Analyzed	PD-L1 Status	Nonresponders, n	Responders, n	ORR, % (95% CI)	*P* Value
TPS (tumor cells)	Positive	101	22	17.9 (11.6-25.8)	.461
	Negative	53	12	18.5 (9.9-30)	
CPS (tumor and inflammatory cells)	Positive	120	32	21.1 (14.9-28.4)	.023
	Negative	34	2	5.6 (0.7-18.7)	

- Incorporating inflammatory cells into PD-L1 expression analysis enhances ability to detect responders

Chow. J Clin Oncol. 2016;34:3838.

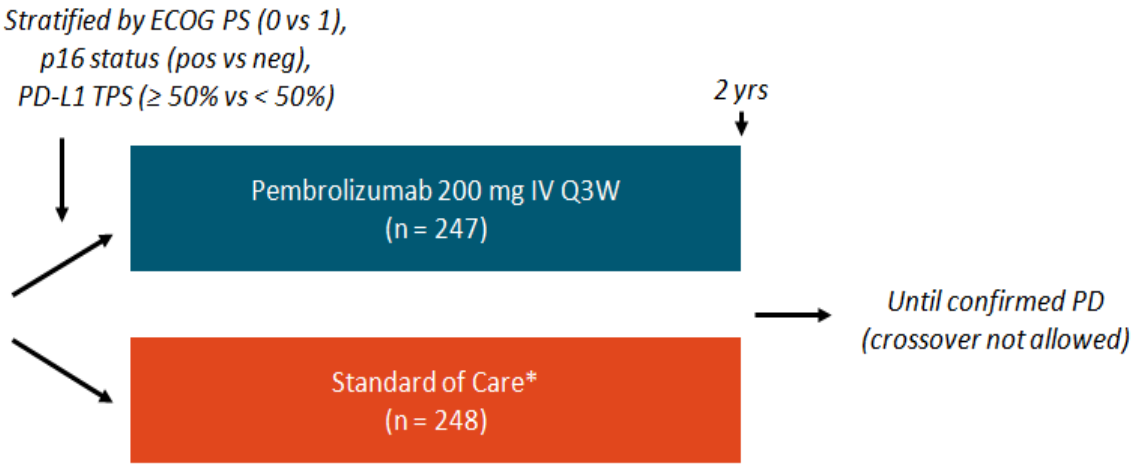
Slide credit: clinicaloptions.com

KEYNOTE-040: Pembrolizumab vs Standard of Care in Recurrent/Metastatic HNSCC

Patients with SCC of oral cavity, oropharynx, hypopharynx, or larynx, and:

- recurrent disease or PD 3-6 mos after multimodal tx with platinum or PD after platinum-based tx for RM HNSCC
- ≤ 2 prior tx for RM HNSCC
- known p16 status with oropharynx disease
- ECOG PS 0/1

(N = 495)



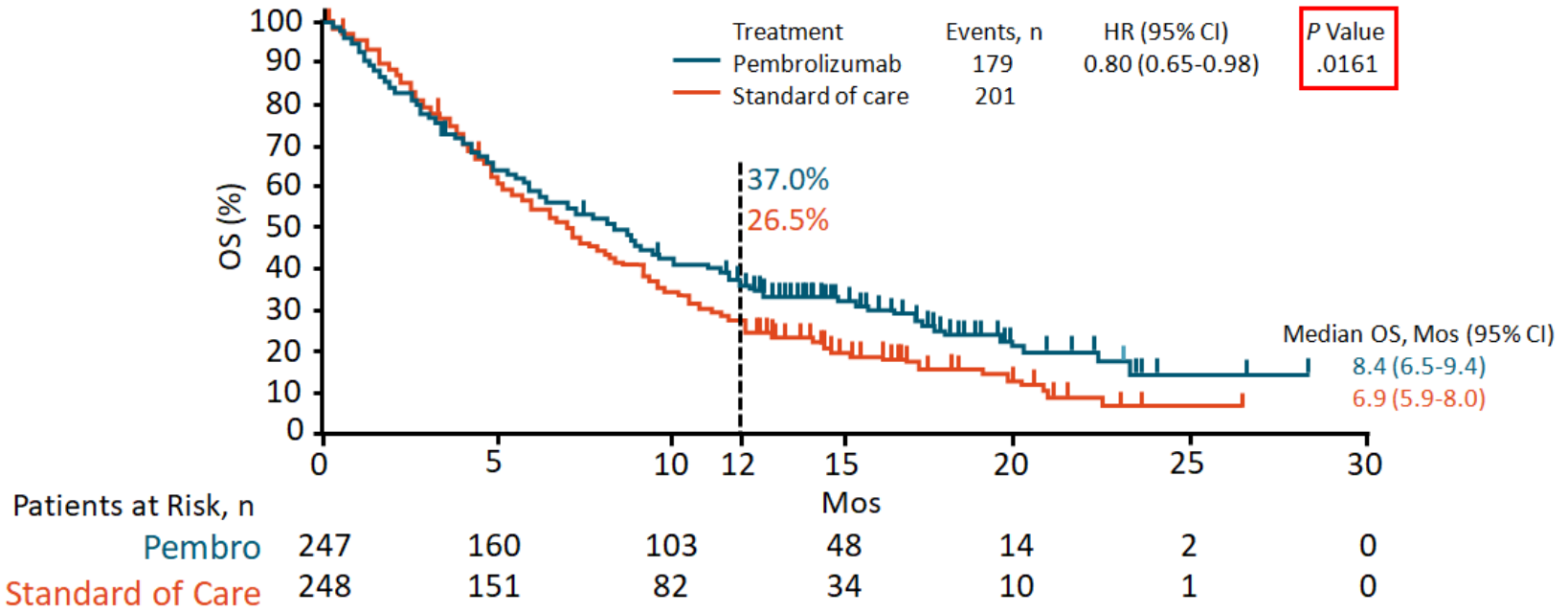
*Investigator's choice of methotrexate 40 mg/m^2/wk (in absence of toxicity could increase to 60 mg/m^2), docetaxel 75 mg/m^2 Q3W, or cetuximab loading dose of 400 mg/m^2 followed by 250 mg/m^2/wk.

- Primary endpoint: OS in ITT population
- Secondary endpoints: OS in PD-L1–positive subgroups, PFS, ORR, DoR, safety, tolerability

Cohen. Lancet. 2019;393:156.

Slide credit: clinicaloptions.com

KEYNOTE-040: OS in ITT Population



Cohen. Lancet. 2019;393:156.

Slide credit: clinicaloptions.com

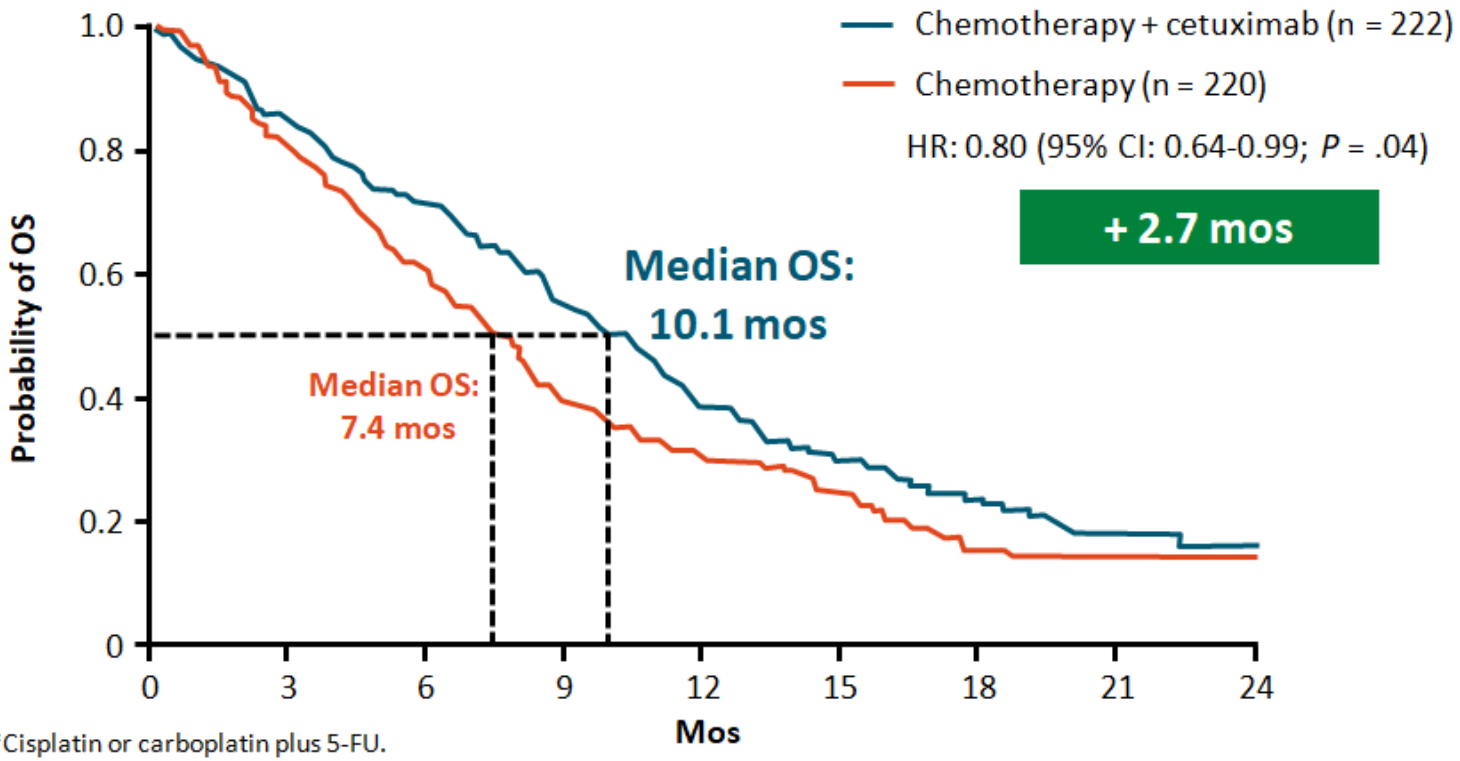
KEYNOTE-040: TRAEs for Pembrolizumab vs Standard of Care in Recurrent/Metastatic HNSCC

TRAEs, n (%) (≥ 15% Either Arm)	Pembrolizumab (n = 246)		SoC (n = 234)	
	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Any TRAE	155 (63)	33 (13)	196 (84)	85 (36)
TRAE leading to tx discontinuation	15 (6)	12 (5)	12 (5)	9 (4)
TRAE mortality	4 (2)	4 (2)	2 (1)	2 (1)

Cohen. Lancet. 2019;393:156.

Slide credit: clinicaloptions.c

EXTREME Chemotherapy* + Cetuximab: OS



*Cisplatin or carboplatin plus 5-FU.

Vermorken. NEJM. 2008;359:1116.

Slide credit: clinicaloptions.com

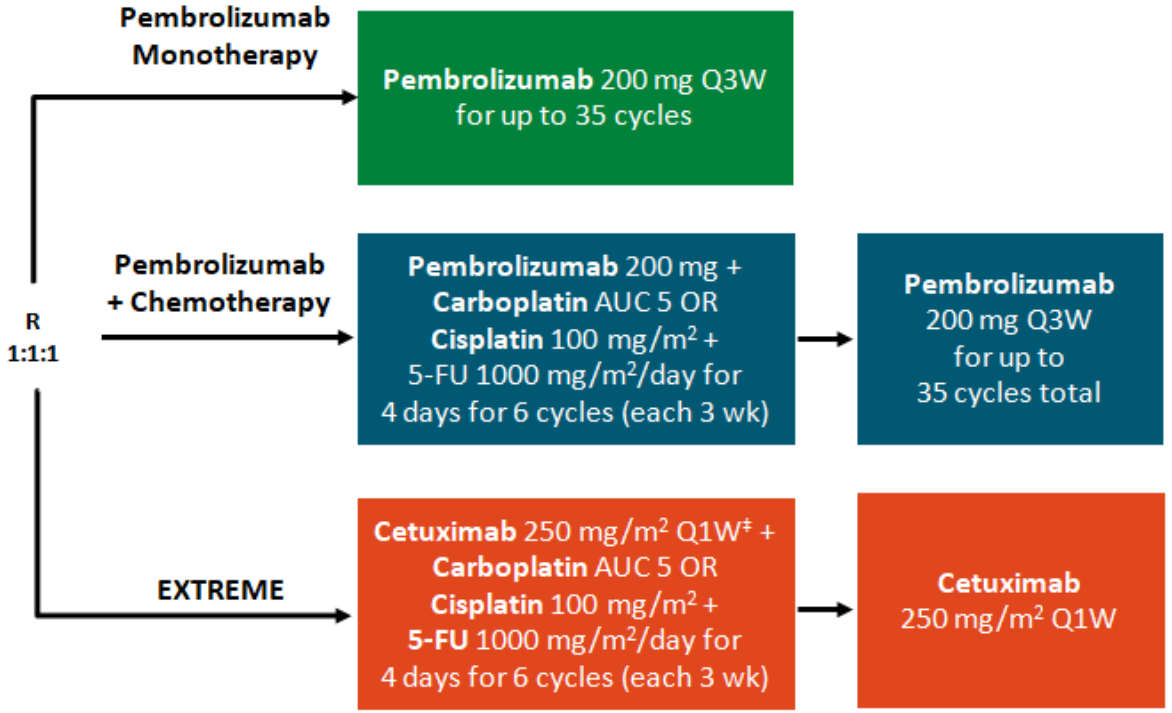
KEYNOTE-048: Study Design

Key Eligibility Criteria

- SCC of the oropharynx, oral cavity, hypopharynx, or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment*
- Known p16 status in the oropharynx†

Stratification Factors

- PD-L1 expression* (TPS ≥ 50% vs < 50%)
- p16 status in oropharynx (positive vs negative)
- ECOG PS (0 vs 1)



*Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent) †Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity: 70%. ‡Following a loading dose of 400 mg/m².

Burtness. Lancet. 2019;394:1915.

Slide credit: clinicaloptions.com

KEYNOTE-048: Baseline Characteristics, ITT Population

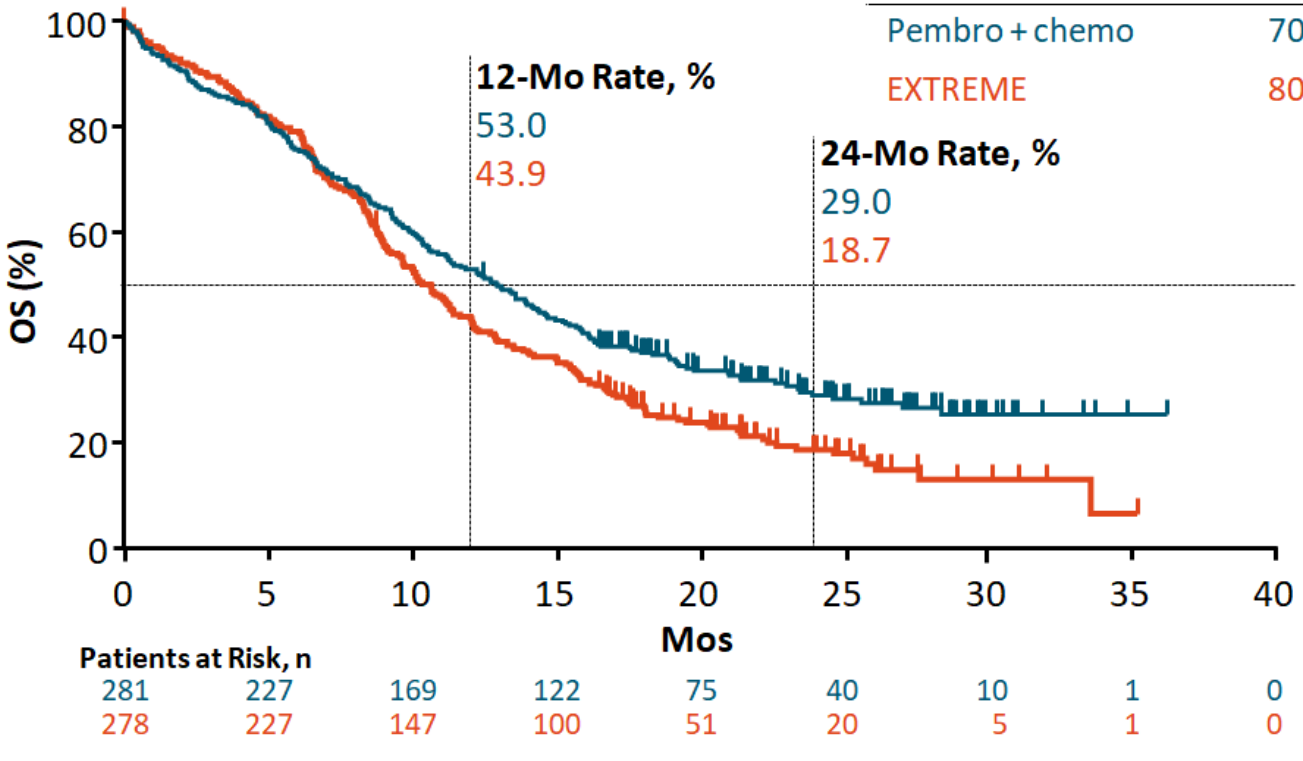
Characteristic	Pembrolizumab Alone vs EXTREME		Pembrolizumab + Chemo vs EXTREME	
	Pembrolizumab (n = 301)	EXTREME (n = 300)	Pembro + Chemo (n = 281)	EXTREME (n = 278*)
Age, median, yrs (range)	62 (22-94)	61 (24-84)	61 (20-85)	61 (24-84)
Male, n (%)	250 (83.1)	261 (87.0)	224 (79.7)	242 (87.1)
ECOG PS 1, n (%)	183 (60.8)	183 (61.0)	171 (60.9)	170 (61.2)
Current/former smoker, n (%)	239 (79.4)	234 (78.0)	224 (79.7)	215 (77.3)
p16 positive (oropharynx) , n (%)	63 (20.9)	67 (22.3)	60 (21.4)	61 (21.9)
PD-L1 status, n (%)				
▪ TPS ≥ 50%	67 (22.3)	66 (22.0)	66 (23.5)	62 (22.3)
▪ CPS ≥ 20	133 (44.2)	122 (40.7)	126 (44.8)	110 (39.6)
▪ CPS ≥ 1	257 (85.4)	255 (85.0)	242 (86.1)	235 (84.5)
Disease status,† n (%)				
▪ Metastatic	216 (71.8)	203 (67.7)	201 (71.5)	187 (67.3)
▪ Recurrent only‡	82 (27.2)	94 (31.3)	76 (27.0)	88 (31.7)

*Patients randomized to EXTREME during pembro + chemo enrollment hold excluded from pembro + chemo vs EXTREME efficacy comparisons.
†3 patients in pembro arm, 3 patients in EXTREME arm, and 4 patients in pembro + chemo arm had neither metastatic nor recurrent disease.
‡Includes locally recurrent disease and disease that spread to cervical lymph nodes. Data cutoff date: June 13, 2018.

Burtness. Lancet. 2019;394:1915.

Slide credit: clinicaloptions.com

KEYNOTE-048: OS for Pembrolizumab + Chemotherapy vs EXTREME



	Events	HR (95% CI)	*P* Value
Pembro + chemo	70%	0.77 (0.63-0.93)	.0034
EXTREME	80%		

Median OS, Mos (95% CI)

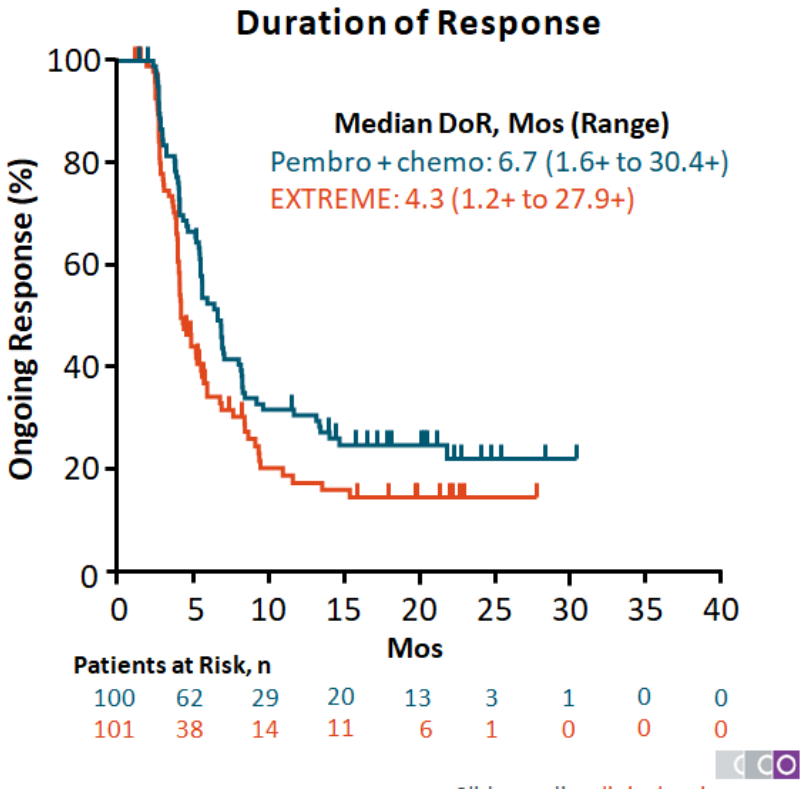
13.0 (10.9-14.7)

10.7 (9.3-11.7)

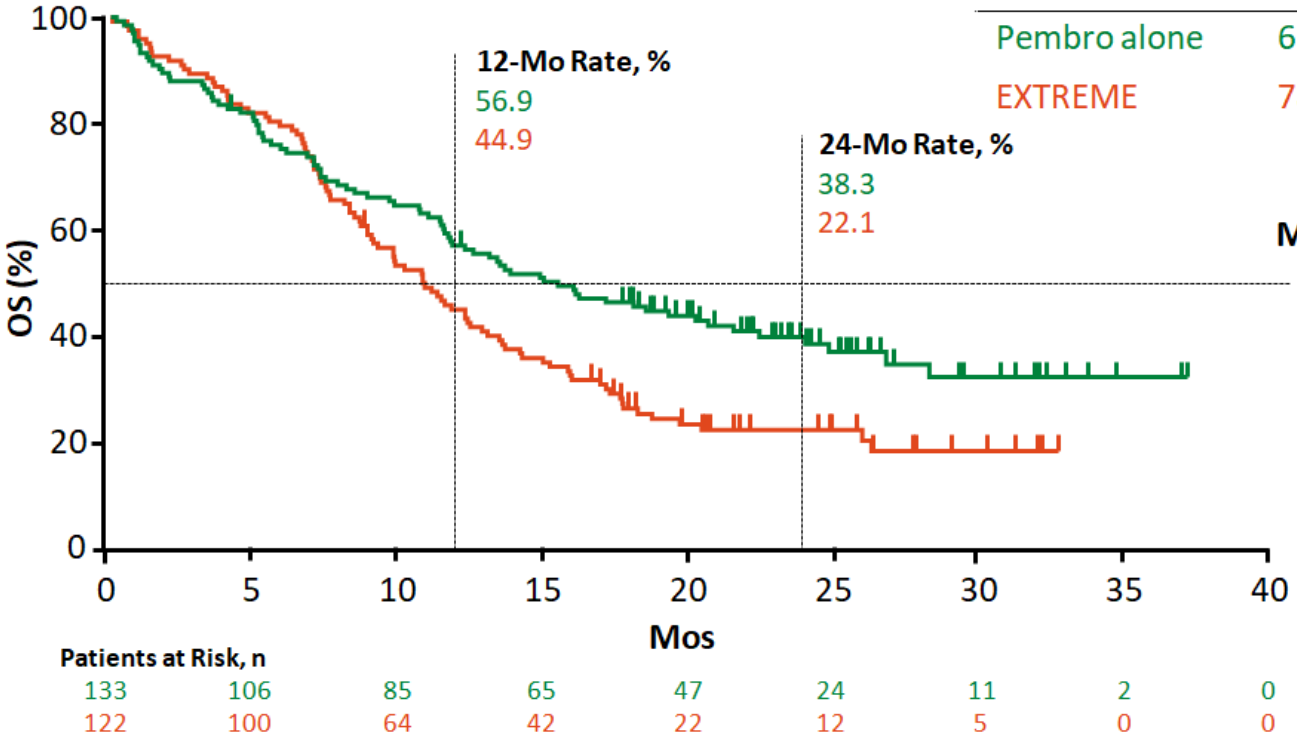
KEYNOTE-048: Response for Pembrolizumab + Chemotherapy vs EXTREME

Confirmed Response, n (%)	Pembro + Chemo (n = 281)	EXTREME (n = 278)
ORR	**100 (35.6)**	**101 (36.3)**
CR	17 (6.0)	8 (2.9)
PR	83 (29.5)	93 (33.5)
SD	78 (27.8)	94 (33.8)
PD	48 (17.1)	34 (12.2)
Non-CR/non-PD*	13 (4.6)	9 (3.2)
Not evaluable or assessed†	42 (14.9)	40 (14.4)

*No measurable disease per central review at baseline and no CR or PD.
†No postbaseline imaging assessment evaluable for response or who did not have postbaseline imaging. Response assessed per RECIST v1.1 by BICR. Data cutoff date: June 13, 2018.



KEYNOTE-048: OS (CPS ≥ 20) for Pembrolizumab vs EXTREME



	Events	HR (95% CI)	*P* Value
Pembro alone	62%	0.61 (0.45-0.83)	.0007
EXTREME	78%		

Median OS, Mos (95% CI)

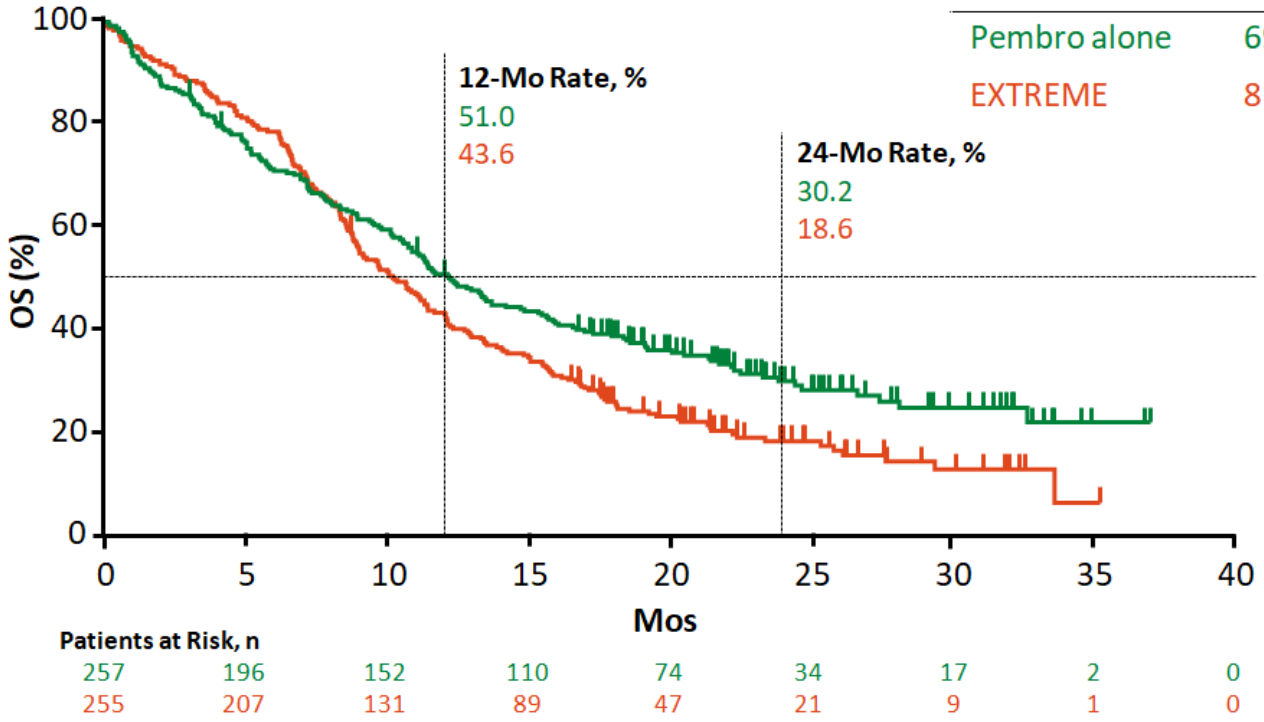
14.9 (11.6-21.5)

10.7 (8.8-12.8)

Burtness. Lancet. 2019;394:1915.

Slide credit: clinicaloptions.com

KEYNOTE-048: OS (CPS ≥ 1) for Pembrolizumab vs EXTREME



	Events	HR (95% CI)	*P* Value
Pembro alone	69%	0.78 (0.64-0.96)	.0086
EXTREME	81%		

Median OS, Mos (95% CI)

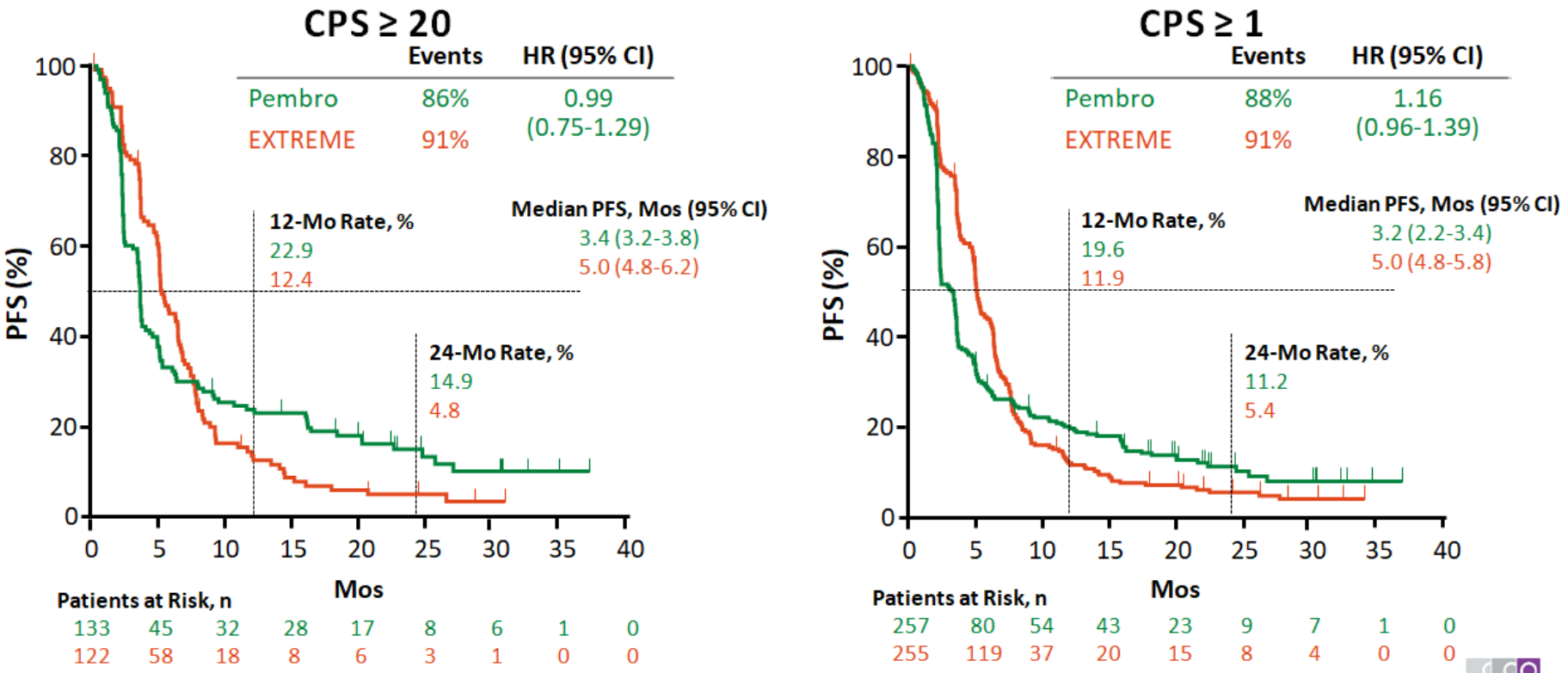
12.3 (10.8-14.9)

10.3 (9.0-11.5)

Burtness. Lancet. 2019;394:1915.

Slide credit: clinicaloptions.com

KEYNOTE-048: PFS for Pembrolizumab vs EXTREME

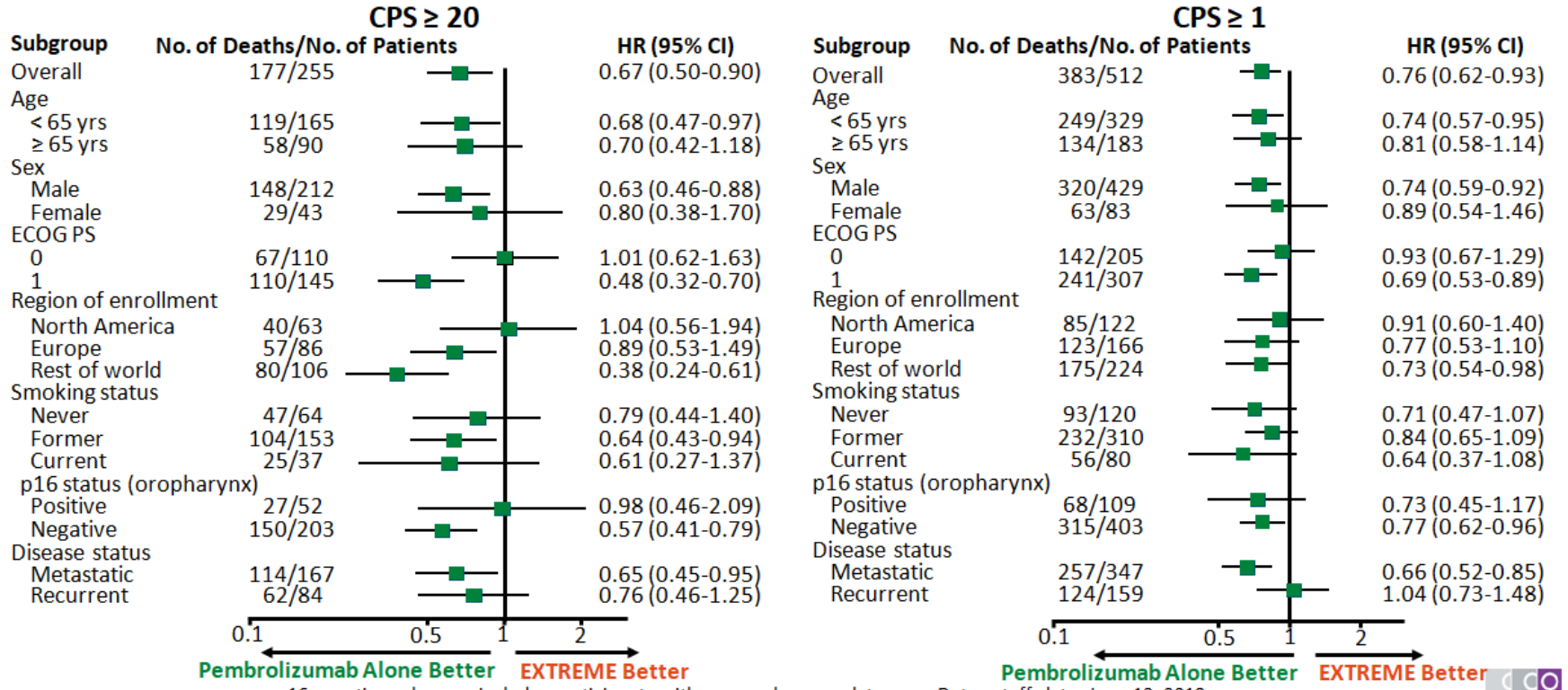


Burtness. Lancet. 2019;394:1915.

PFS assessed per RECIST v1.1 by blinded, independent central radiologic review.

Slide credit: clinicaloptions.com

KEYNOTE-048: OS in Subgroups for Pembrolizumab vs EXTREME



p16-negative subgroup includes participants with nonoropharyngeal tumors. Data cutoff date: June 13, 2018.

Burtness. Lancet. 2019;394:1915.

Slide credit: clinicaloptions.com

Biomarkers

Current and Potential Biomarkers of Response to Immunotherapy in HNSCC

- Immune cell infiltration
- PD-L1 expression (85% CPS ≥ 1, 45% CPS ≥ 20)
- Interferon gene expression signature profiles
- High mutation burden/neoantigens
- T-cell clonality
- Gut microbiome

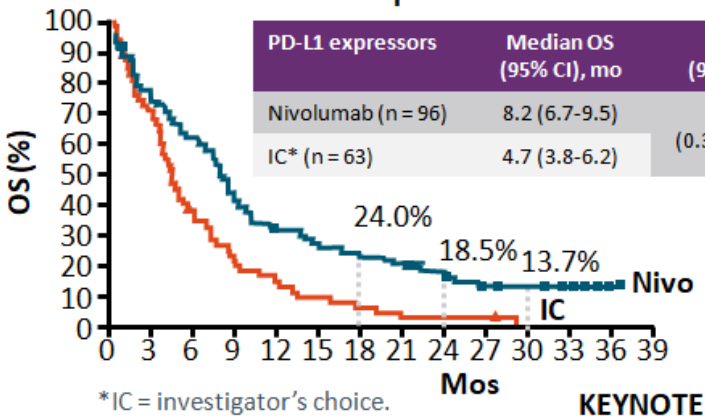
Maleki Vareki. Crit Rev Oncol Hematol. 2017;116:116.

PD-L1 Expression in HNSCC

Checkmate 141: Platinum Failure[1]

PD-L1 expressors

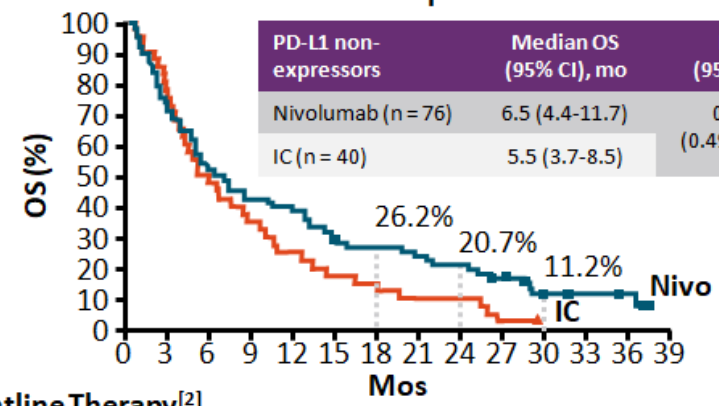
PD-L1 expressors	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 96)	8.2 (6.7-9.5)	0.55 (0.39-0.78)
IC* (n = 63)	4.7 (3.8-6.2)	



*IC = investigator's choice.

PD-L1 non-expressors

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)	

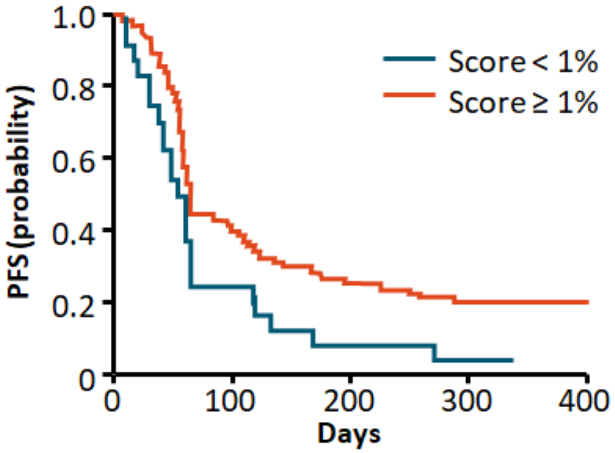


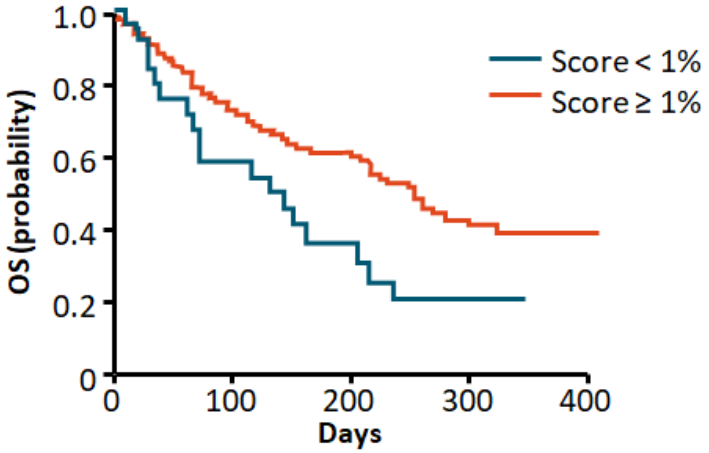
KEYNOTE 048: Frontline Therapy[2]

Agent	Population	ORR	Median OS	Significant OS
Pembrolizumab	Total	17%	11.6	No
	CPS ≥ 1	19%	12.3	Yes
	CPS ≥ 20	21%	14.9	Yes
Chemo + Pembro	Total	36%	13	Yes
	CPS ≥ 1	36%	13.6	Yes
	CPS ≥ 20	43%	14.7	Yes

1. Ferris. Oral Oncol. 2018;81:45. 2. Burtness. Lancet. 2019;394:1915.

PD-L1 Expression on Tumor and Tumor-infiltrating Lymphocytes



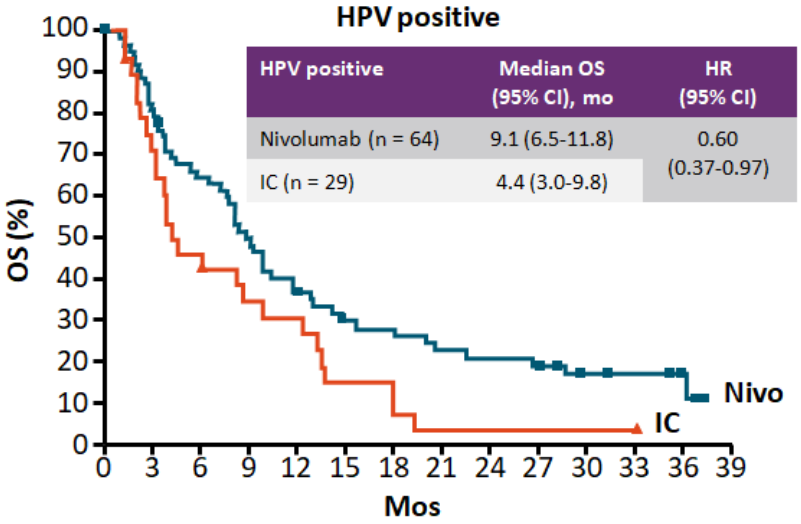


PD-L1 Status	Tumor and Immune Cells			Tumor Cells Only		
	Nonresponders, n	Responders, n	Response, % (95% CI)	Nonresponders, n	Responders, n	Response, % (95% CI)
Negative (< 1%)	24	1	4 (0.1 to 20)	36	7	16 (7 to 31)
Positive (≥ 1%)	84	23	22 (14 to 31)	72	17	19 (12 to 29)

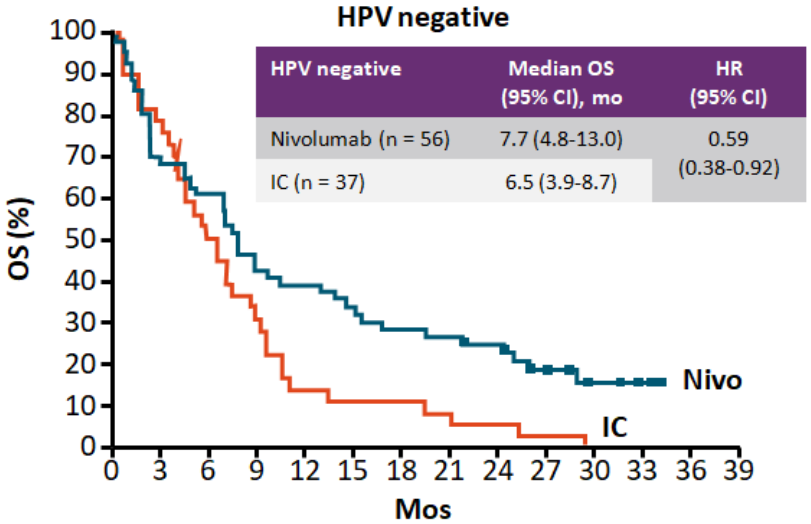
Chow. J Clin Oncol. 2016;34:3838.

Slide credit: clinicaloptions.com

Nivolumab in HPV Positive vs HPV Negative Patients



HPV positive	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 64)	9.1 (6.5-11.8)	0.60 (0.37-0.97)
IC (n = 29)	4.4 (3.0-9.8)	

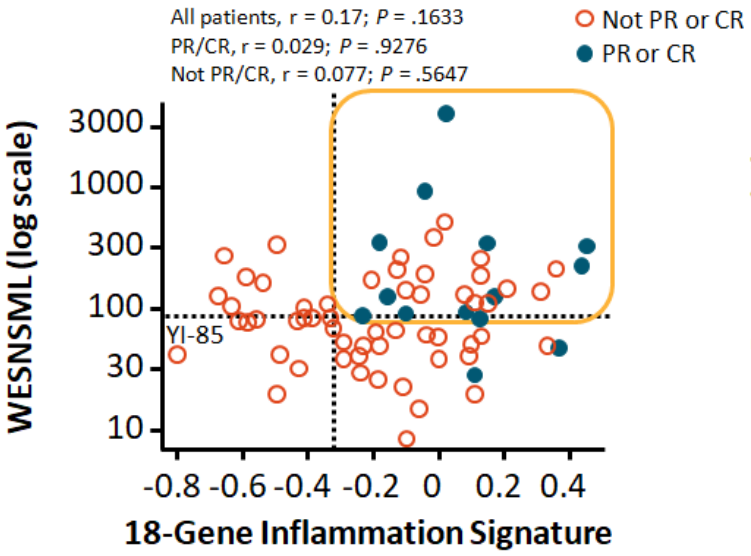


HPV negative	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 56)	7.7 (4.8-13.0)	0.59 (0.38-0.92)
IC (n = 37)	6.5 (3.9-8.7)	

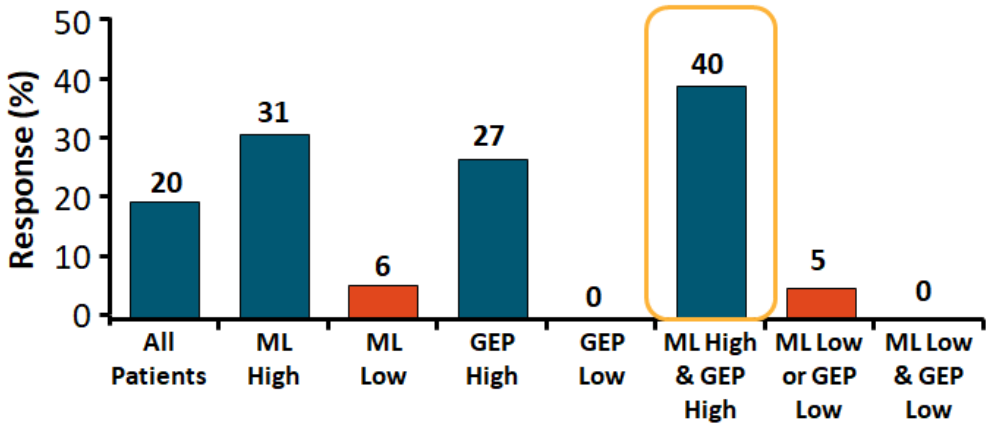
Ferris. Oral Oncol. 2018;81:45.

Slide credit: clinicaloptions.com

Mutational Load and GEP-Associated Best Overall Response: HPV/EBV—Whole Exome Sequencing



- ML high and low: ≥ and < 86
- GEP high and low: ≥ and < -0.318



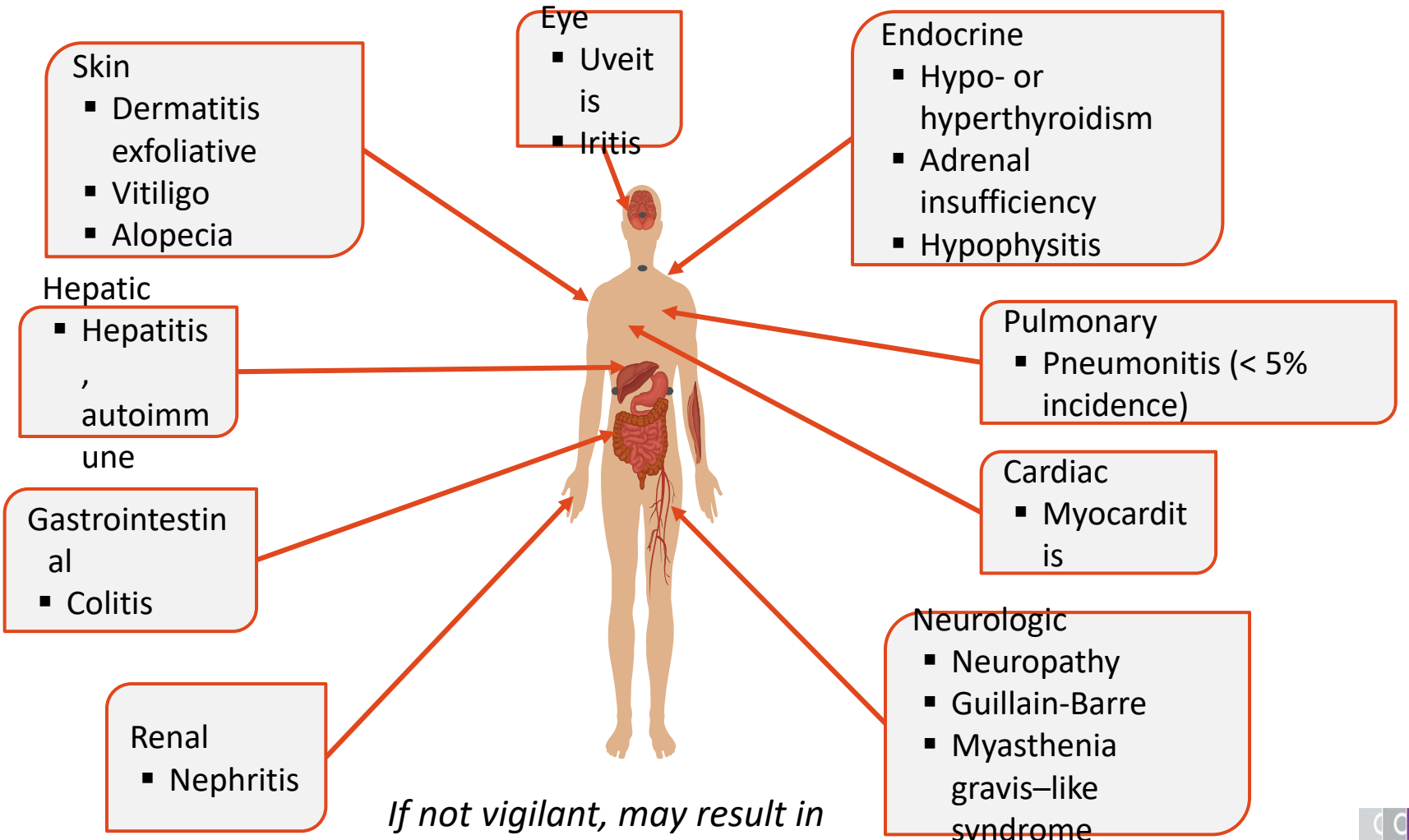
- ML and GEP weakly correlated, remained significant predictors in adjusted multivariate model
  - (ML, *P* = .0349; GEP, *P* = .0056)
- Strongest response with high ML or GEP, particularly with both

Haddad. ASCO 2017. Abstract 6009.

Slide credit: clinicaloptions.com

Adverse Events

Immune-Related Adverse Events Can Affect Any Organ System



If not vigilant, may result in more serious immune-related AEs

Brigden. Oncology Exchange. 2016;15(1):14

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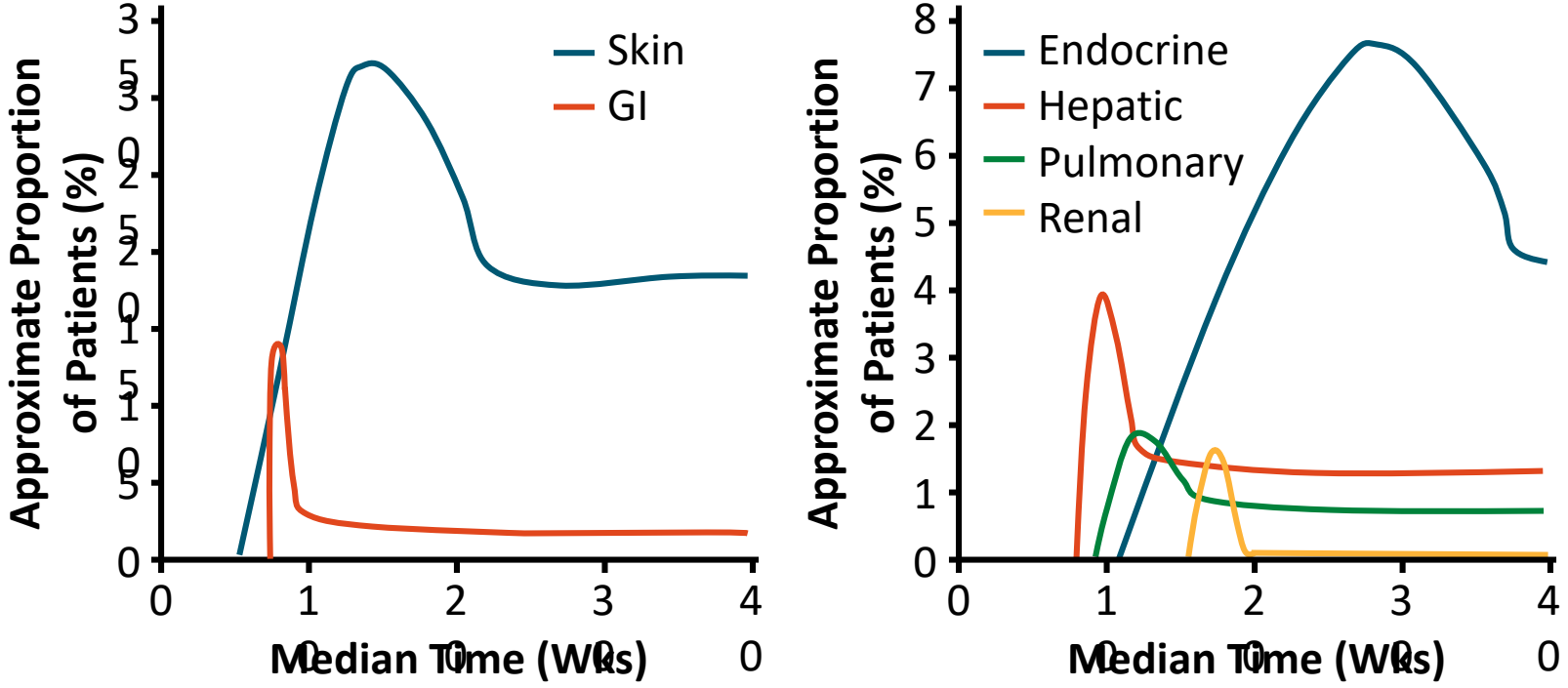
PD-1 Inhibitor Time to Onset and Time to Resolution Based on Melanoma Data



- Pooled data from largest and most comprehensive analysis to date of the safety profile of anti–PD-1 monotherapy
- Understanding typical onset of immune-related select AEs may help in recognition, management, and resolution in clinical practice

Weber. J Clin Oncol. 2016;35:785.

General Guidelines for Management of Immune-Related AEs

- **Grade 1: asymptomatic to mild symptoms**
  - Observation
  - Intervention not needed
- **Grade 2: moderate symptoms**
  - Local or noninvasive intervention indicated
  - Withhold drug, consider re-dose if toxicity resolves to grade ≤ 1
  - Low-dose corticosteroids likely needed
  - May be able to continue treatment
- **Grade 3: medically significant but not immediately life-threatening**
  - Stop immunotherapy immediately
  - Hospitalization indicated
  - High-dose steroids indicated
  - Slow steroid taper over ≥ 1 mo once toxicity resolves to grade ≤ 1
- **Grade 4: life-threatening consequences**
  - Urgent intervention
  - Permanently discontinue treatment

CTCAE v4.03. June 2010. Atezolizumab adverse reaction management brochure. Nivolumab adverse reaction management guide. Pembrolizumab adverse reaction management guide.

Immunotherapy-Related AEs in Head and Neck Cancer: Special Considerations

- Early progression of HNC with immune checkpoint inhibition
- Pseudoprogression in HNC < 1%
- Patients with prior definitive or postoperative therapy may have earlier radiation-induced apical lung injury with increased risk of pneumonitis[1]
- Patients with bulky tumors are often highly symptomatic
  - Early progression or pseudoprogression may increase risk pain, dysphagia, tumor bleeding, or airway compromise
- There exists anecdotal evidence of increased carotid bleeding
  - Vascular endothelium expresses PD-L1[2]
  - Patients must be warned to alert physician to any herald bleeding and they should be referred immediately to interventional neurovascular radiology

1. Shibaki. Ann Oncol. 2017;28:1404. 2. Rodig. Eur J Immunol. 2003;33:3117.

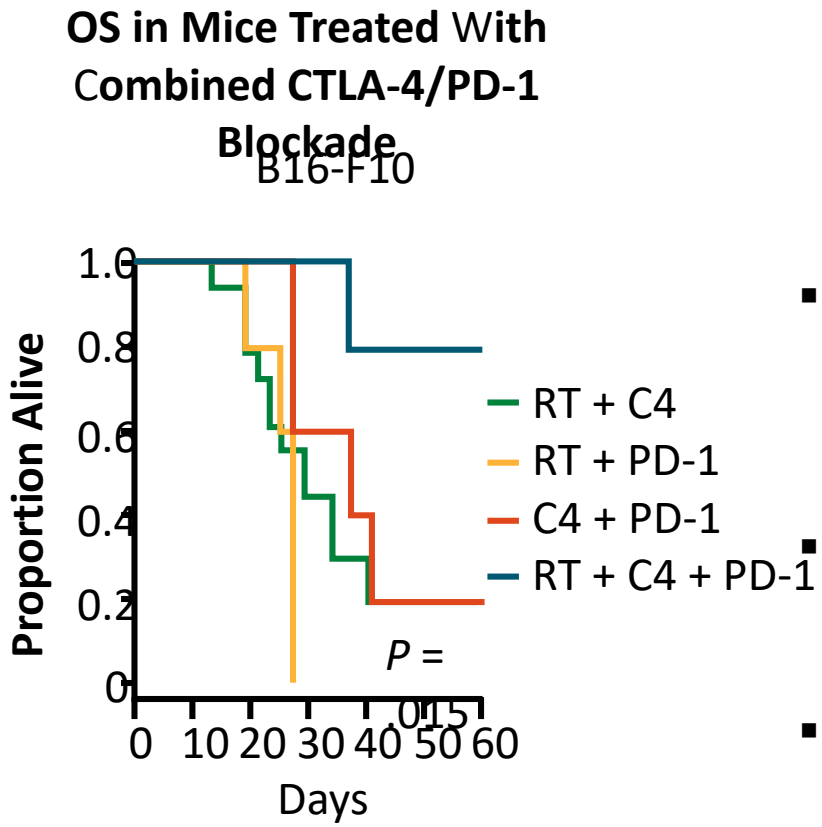
Future Directions

Contemporary Trial Design in the Immunotherapy Era

- Rapid proliferation of studies in HNSCC
- 2 main themes:

1. Use of PD-1 inhibitors in previously untreated locally advanced HNSCC
   - Neoadjuvant, concurrent, and adjuvant administration
2. Optimizing activity in recurrent/metastatic HNSCC
   - Combinations in first-line therapy and after prior checkpoint inhibitors
   - Salvage therapy or reirradiation
   - Cellular therapeutics

Combined Radiation, Anti–CTLA-4, and Anti–PD-1 Therapies: Prolonged Survival, Decreased Resistance



- Major tumor regressions in melanoma patients with CTLA-4 antibody and radiation therapy, tumor responses outside XRT field
  - Effect reproduced in mouse models
- Combined treatment improved responses, but resistance was common
  - Resistance due to PD-L1 upregulation and associated with T-cell exhaustion
- Addition of PD-L1 blockade improved responses in resistant tumors after radiation therapy plus a CTLA-4 antibody
- Responses stronger in treatment-naive tumors when PD-L1/PD-1 antibodies added to radiation therapy plus CTLA-4 blockade

Twyman-Saint Victor. Nature. 2015;520:373.

Slide credit: clinicaloptions.c

Neoadjuvant Single-Agent Checkpoint Inhibition in HNSCC: Human Safety Data

Trial	Phase	N	Treatment	Outcomes
NCT02296684[1]	II	24	Pembrolizumab x 1 prior to surgery	42% with pathologic evidence of tumor regression
CheckMate 358[2]	I/II	29	Nivolumab x 2 doses prior to surgery	28.5% experienced TEAEs; no surgical delays
NCT02274155[3]	Ib	17	MEDI6469 (OX40 antibody) x 3 doses prior to surgery	No grade ≥ 3 AEs, no surgical delays
NCT03247712[4]	I	10	Nivolumab x 3 doses + SBRT prior to surgery	No surgical delays Grade 1/2 mucositis dermatitis 5 patients with adrenal insufficiency Delayed healing

1. Uppaluri. ASCO 2017. Abstr 6012. 2. Ferris. ESMO 2017. Abstr LBA46. 3. Bell. ASCO 2018. Abstr 6011. 4. Leidner. AACR 2019.

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Slide credit: clinicaloptions.c

Prospectively Reported Combination Therapies in Recurrent/Metastatic HNSCC

- Anti–PD-1 and PD-L1 mAbs and
  - Cytotoxic chemotherapy
  - Hypofractionated radiation therapy
  - CTLA-4 blockade
  - T-cell agonists/NK cell agonists
  - Therapeutic vaccines
  - Small molecule inhibitors

Summary

- Immunotherapy is active in head and neck cancer and proper selection of patient is needed.
- Need more specific biomarkers to know who will benefit the most.
- More appropriate combination strategies are needed for improving outcomes.
- Potentially practice-changing trials are anticipated in locally advanced HNSCC approached with curative intent
- Various combination strategies being explored in the recurrent/ metastatic setting
- Cellular therapeutics gaining momentum in HNSCC

THANK YOU