IMMUNOTHERAPY IN HEAD AND NECK CANCER

SIMON ABI AAD, MD

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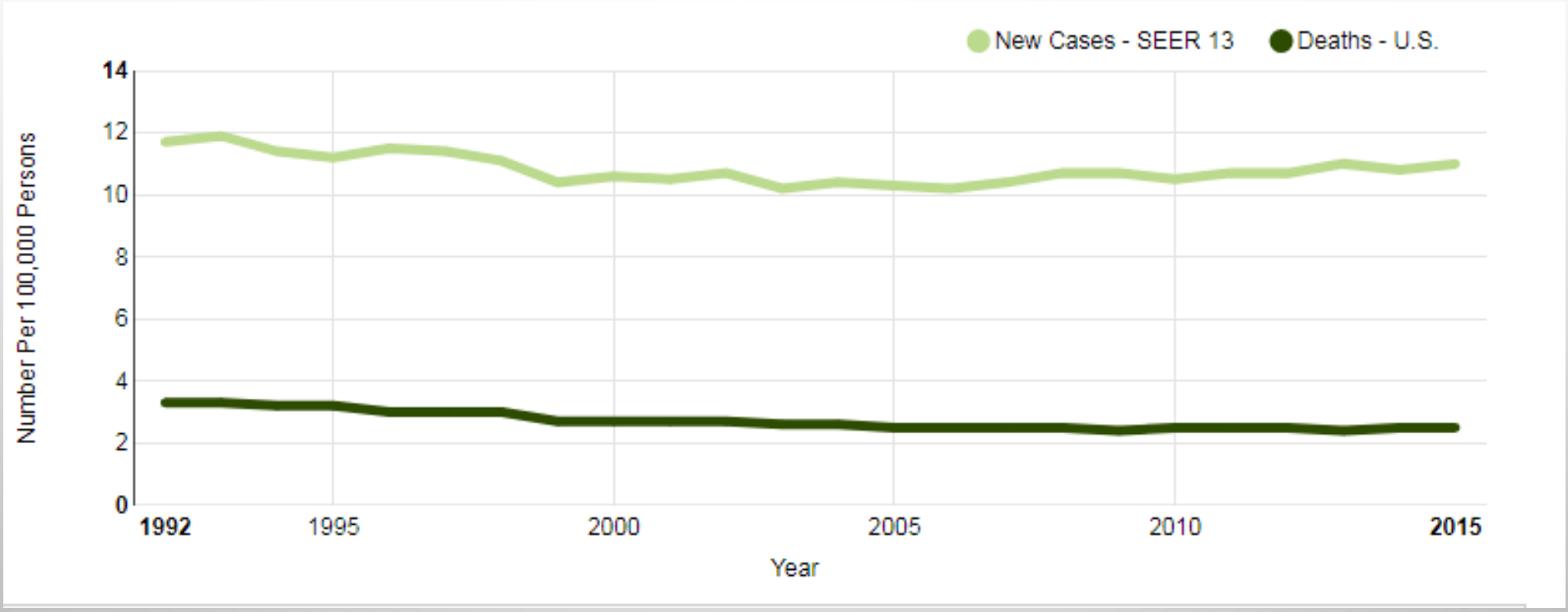
NO RELEVANT FINANCIAL RELATIONSHIPS IN THE PAST TWELVE MONTHS BY PRESENTER OR SPOUSE/PARTNER.

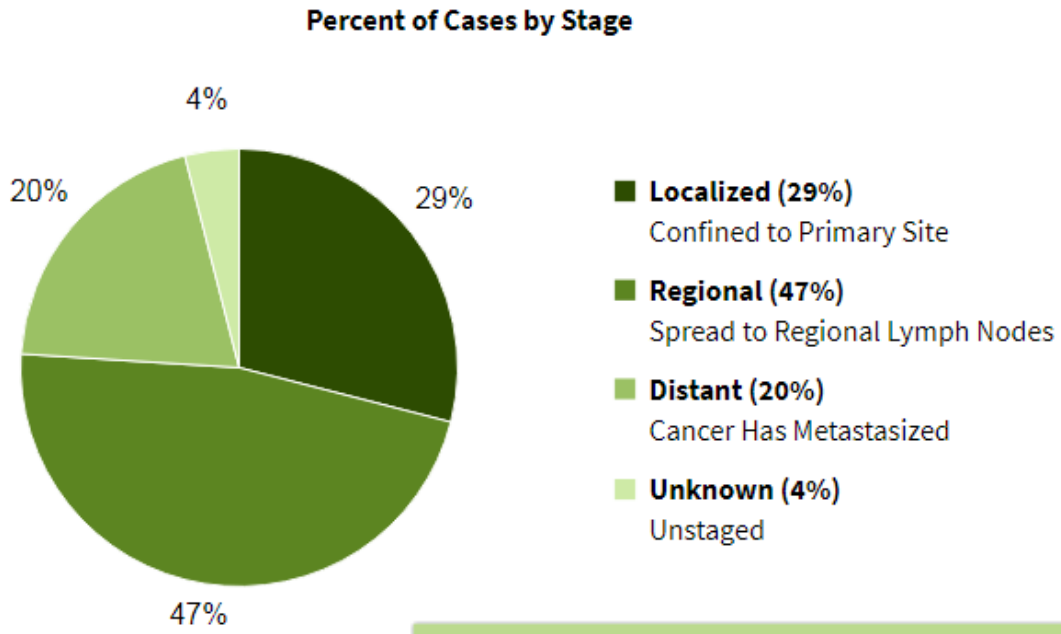
THE SPEAKER WILL DIRECTLY DISCLOSE THE USE OF PRODUCTS FOR WHICH ARE NOT LABELED (E.G., OFF LABEL USE) OR IF THE PRODUCT IS STILL INVESTIGATIONAL.

Some Statistics



SEER 2018

Some Statistics

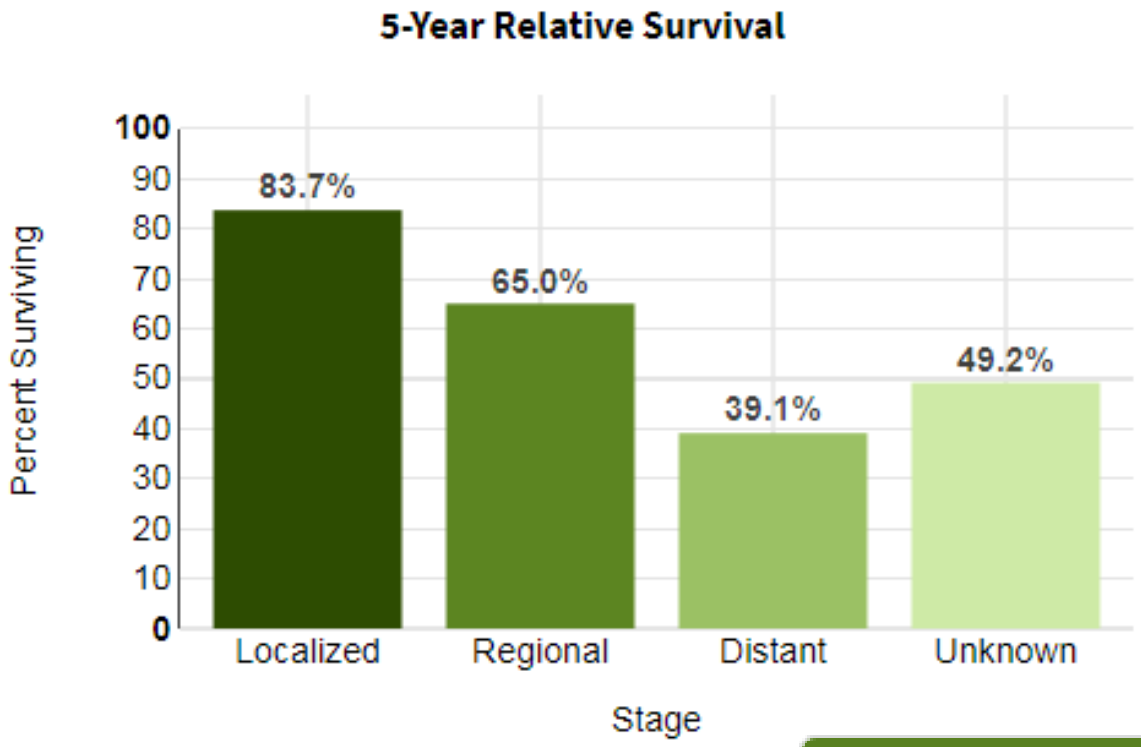


Estimated New Cases in 2018	51,540
% of All New Cancer Cases	3.0%

Estimated Deaths in 2018	10,030
% of All Cancer Deaths	1.6%

SEER 2018

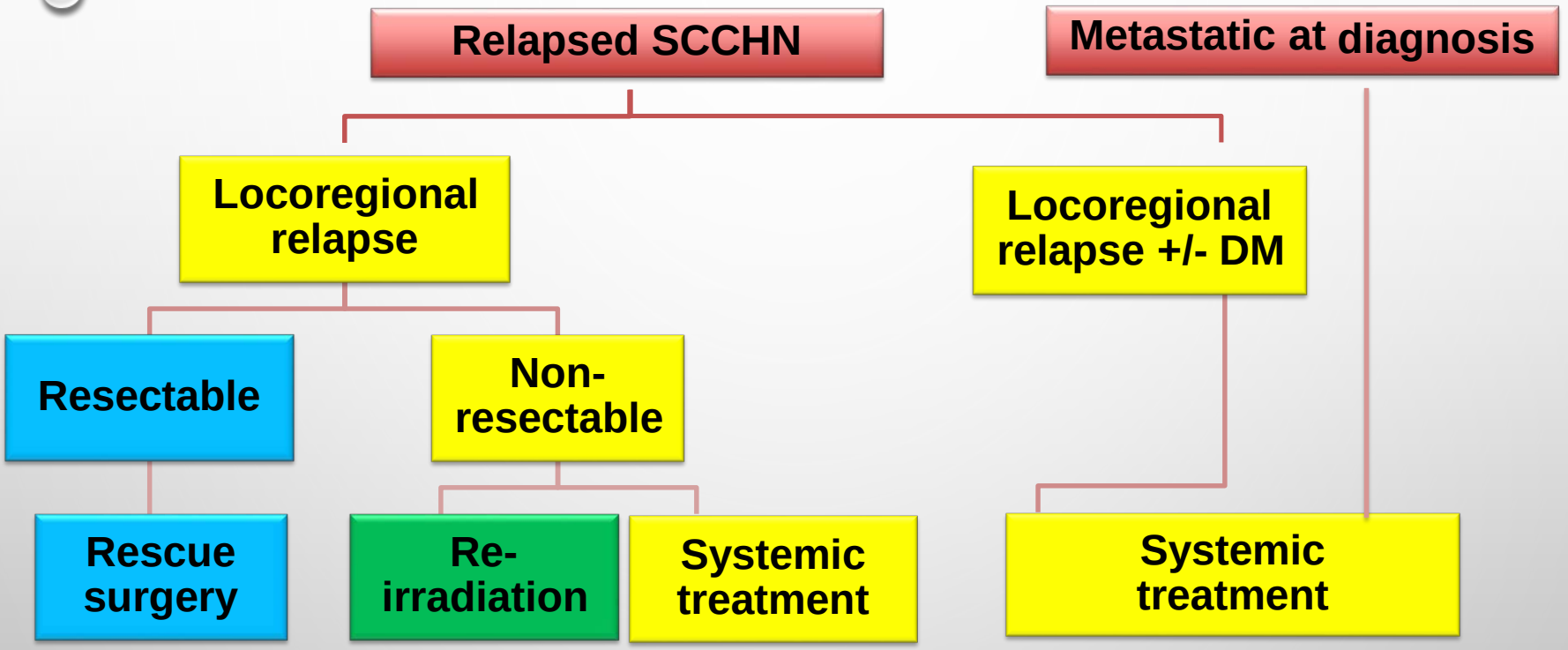
Some Statistics



Percent Surviving 5 Years
64.8%
2008-2014

SEER 2018

Treatment Options for R/M SCCHN



DM, distant mtastases; R/M, recurrent and/or metastatic

Factors Associated With Poor Outcome

Patient Related
Poor performance status
Comorbidities
Poor cognitive status
Persistent use of carcinogens (smoking, alcohol)
Disease Related
Tumor sites (primary and recurrences)
Advanced state
Great volume disease
History of aggressive disease
Paraneoplastic hypercalcemia
Treatment Related
Previous treatments
Time to tumor progression
Poor or null response to previous treatment

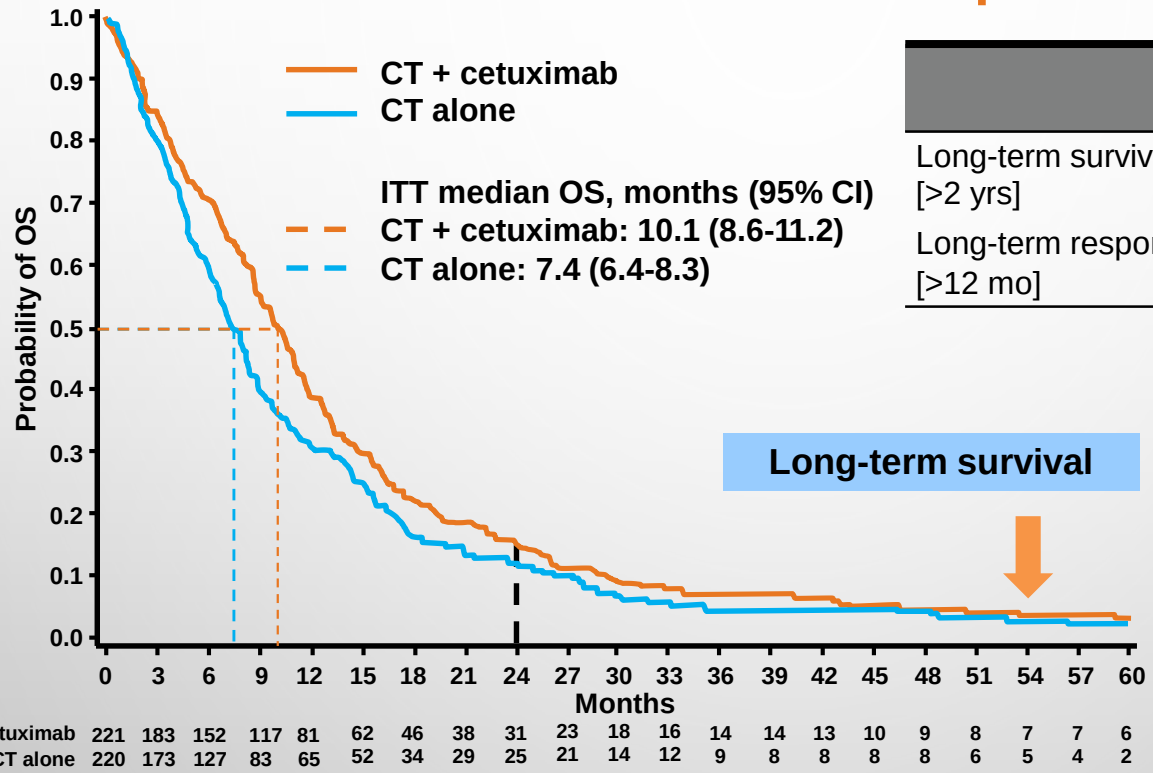
SCCHN R/M Not Suitable for Rescue Surgery or Re-Irradiation

- **Platinum-sensitive patients:**
  - **Recurrence after a combined treatment that included platinum with a PFS of more than 6 months**
  - **Platinum-naïve patients with R/M disease**
- **Platinum-refractory patients:**
  - **Recurrence after a combined treatment that included platinum with a PFS of less than 6 months**
  - **Patients with progressive disease during a platinum-containing treatment for R/M disease**

PFS, progression-free survival

EXTREME Trial: Overall Survival

5-Year Follow-Up



	CT* n = 220	Cetuximab + CT* n = 222
Long-term survivors [>2 yrs]	25 (11%)	31 (14%)
Long-term responders [>12 mo]	3 (1%)	12 (5%)

Vermorken JB, et al. *N Engl J Med.* 2008;359(11):1116–1127. Vermorken JB, et al. *J Clin Oncol.* 2014;32(Suppl): Abstract 6021.

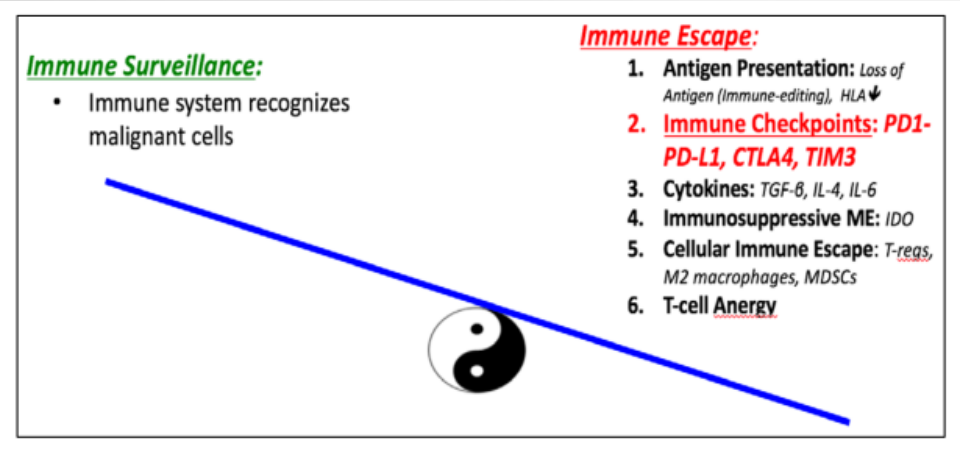
Cisplatin-Refractory R/M SCCHN

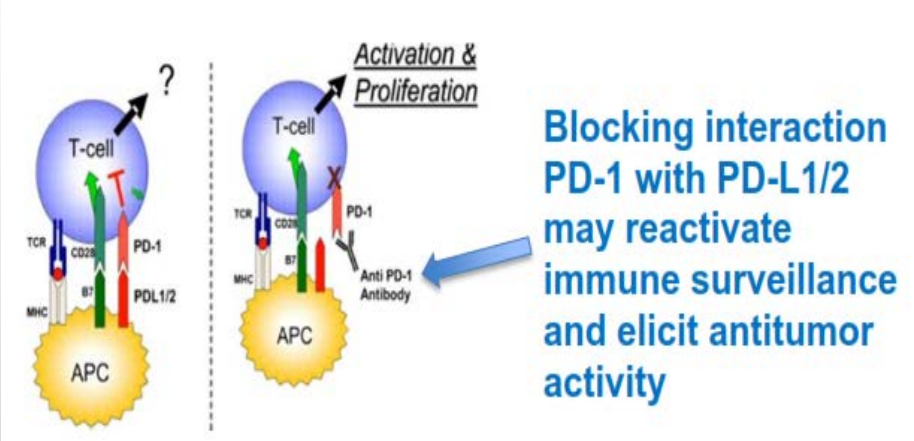
- **Survival is very poor (≤6 months)**
- **Conventional anticancer treatments have not been effective in increasing survival**
- **Immunotherapy arises as a new treatment option in this setting**

SCCHN May Benefit From Immune System–Targeted Treatments

- **High mutational burden due to tobacco usage, and expression of HPV-associated oncogenes, may contribute to immunogenicity in SCCHN tumors**
- **In HNSCC, tumors create a highly immunosuppressive microenvironment and can evade immune detection by exploiting inhibitory immune checkpoints such as PD-1/PD-L1**

Our goal is to:
Break Tolerance!

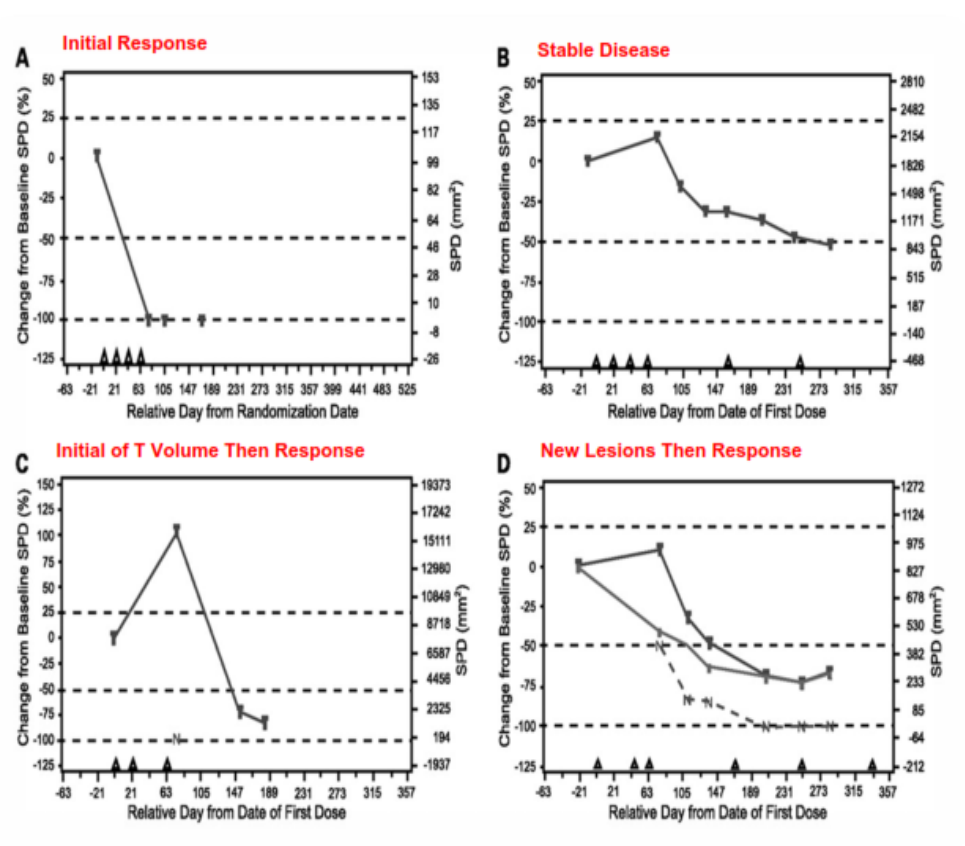




Keck MK, et al. *Clin Cancer Res*. 2015;21(4):870-881. Ferris RL. *J Clin Oncol*. 2015;33(29):3293-3304.

What Is Unique About Immunotherapy?

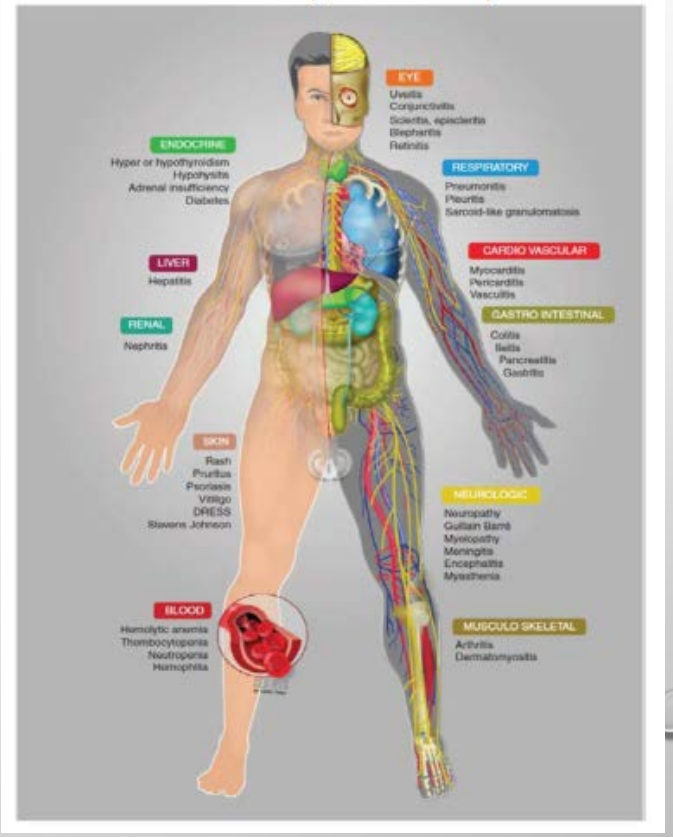
Atypical patterns of response



Wolchok JD, et al. *Clin Cancer Res.* 2009;15(23):7412-7420.

Immune-related toxicity

Autoimmune/inflammatory AEs may affect any organ



Champiat S, et al. *Annals of Oncol.* 2016;27(4):559-574.

Immune-Mediated Side Effects

- **Can arise every time**
- **Even after end of therapy!**
- **ALL organ systems might be involved**

Severe IO irAEs

	CTLA-4 Inhibitor	PD-1 Inhibitor		PD-L1 Inhibitor	
Severe irAE, %	Ipilimumab	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab
Dermatologic					
Pruritis	25-30	17	11-21	12-14	<1
Rash	33-34	15	10-21	15	<1
Vitiligo	3-4	10-11	9	NR	NR
Gastrointestinal					
Diarrhea	36-38	8-16	8-20	18-20	1-2
Colitis	8-10	1-3	1-2	<1	<1
Hepatic					
Increased ALT	<1	1-2	2-8	2-3	0
Increased AST	1-2	1-2	3-10	2-3	0
Hepatitis	<1	1-2	1-2	1-2	1
Endocrine					
Hypothyroidism	1-2	4-5	8-10	2-4	<1
Hyperthyroidism	0-2	0-3	3-4	1	<1
Hypophysitis	2-3	<1	<1	<1	<1
Renal failure	1	1-3	<1	0	NR
Pneumonitis	<1	1-5	4-6	2.6	<1
Neurologic	<1	<1	<1	0	NR

IO, immuno-oncology; irAE, immune-related adverse event; NR, not reported

Kumar V, et al. *Front Pharmacol.* 2017;8:49.

Guidelines For Specific Organ System–Based Toxicity Diagnosis and Management

Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & I
the ESMO Guidelines Committee*

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino, Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallmeyer, Jennifer Holter Chakrabarty, Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, Loretta J. Nastoupil, Tanyanika Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santomasso, Carole Seigel, Alexander Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wolchok, and John A. Thompson in collaboration with the National Comprehensive Cancer Network

Haanen JB, et al. *Ann Oncol*. 2017;28(Suppl_4):iv119-iv142. Brahmer JR, et al. *J Clin Oncol*. 2018 Feb 14. [Epub ahead of print].

Management of irAEs: General Principles

Early Recognition and Management is Essential

Severity—CTCAE grade	Ambulatory versus inpatient care	Corticosteroids	Other immunosuppressive drugs	Immunotherapy
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Topical steroids or Systemic steroids oral 0.5–1 mg/kg/day	Not recommended	Suspend temporarily[a]
3	Hospitalization	Systemic steroids Oral or i.v. 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	To be considered for patients with unresolved symptoms after 3–5 days of steroid course Organ Specialist referral advised	Suspend and discuss resumption based on risk/benefit ratio with patient
4	Hospitalization consider intensive care unit	Systemic steroids i.v. methylprednisolone 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	To be considered for patients with unresolved symptoms after 3–5 days of steroid course Organ specialist referral advised	Discontinue permanently

Some dysimmune toxicities may follow a specific management: this has to be discussed with the organ specialist.
[a]Outside skin or endocrine disorders where immunotherapy can be maintained.

Champiat S, et al. *Ann Oncol*. 2016;27(4):559-574.

Targeting the PD1/PDL1 Pathway in HNSCC

	IO agent	N	Design	Population
Anti-PD-1	**Nivolumab (Checkmate 141)[1]**	**240**	**Phase III**	**Unselected for PD-L1, platinum refractory based therapy)**
	Pembrolizumab (Keynote-012)[2,3]	192	Single arm (Phase Ib)	PD-L1 positive (initial cohort)[1] and unselected for PD-L1 (expansion cohort)[3]
	Pembrolizumab (Keynote-055)[4]	171	Single arm (Phase II)	Unselected for PD-L1, after progression on platinum and cetuximab therapy
	Pembrolizumab (Keynote-040)[5]	**247**	**Phase III**	**Unselected for PD-L1, PD after platinum-containing months of multimodal therapy using platinum regimen for R/M HNSCC or progression within 3-6**
Anti-PD-L1	Durvalumab (study 1108)[6]	62	Single arm	Unselected for PD-L1 (received median 3 prior systemic Tx)
	Durvalumab (HAWK)[7]	112	Phase II Single arm	PD-L1 high (TC ≥25%), failure after 1 platinum-based chemotherapy in R/M setting
	Atezolizumab[8]	32	Phase Ia	Unselected for PD-L1, 53% received ≥2L

1. Ferris RL, et al. *N Engl J Med.* 2016;375(19):1856-1867. 2. Seiwert TY, et al. *Lancet Oncol.* 2016;17(7):956-965. 3. Chow LQ, et al. *J Clin Oncol.* 2016;34(32):3838-3845. 4. Bauml J, et al. *J Clin Oncol.* 2017;35(14):1542-1549. 5. Cohen EE, et al. *Ann Oncol.* 2017;28(suppl_5): Abstract LBA45_PR. 6. Segal NH, et al. *Ann Oncol.* 2016;27(Suppl 6): Abstract 949O. 7. Zandberg D, *et al. Ann Oncol.* 2017;28(Suppl 5):Abstract 1042O. 8. Bahleda R, et al. *Ann Oncol.* 2017;28(Suppl 5):1044O.

NIVOLUMAB VS INVESTIGATOR'S CHOICE IN RECURRENT OR METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK: 2-YR OUTCOMES IN THE OVERALL POPULATION AND PD-L1 SUBGROUPS OF CHECKMATE 141

Robert L. Ferris,[1] George Blumenschein Jr,[2] Jerome Fayette,[3] Joel Guigay,[4] A. Dimitrios Colevas,[5] Lisa Licitra,[6] Kevin J. Harrington,[7] Stefan Kasper,[8] Everett E. Vokes,[9] Caroline Even,[10] Francis Worden,[11] Nabil F. Saba,[12] Lara Carmen Iglesias Docampo,[13] Robert Haddad,[14] Tamara Rordorf,[15] Naomi Kiyota,[16] Makoto Tahara,[17] Mark Lynch,[18] Vijayvel Jayaprakash,[18] Li Li,[18] Maura L. Gillison[2]

[1]University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, PA, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]Centre Leon Berard, Lyon, France; [4]Centre Antoine Lacassagne, FHU OncoAge, Université Côte d'Azur, Nice, France; [5]Stanford University, Stanford, CA, USA; [6]Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, Milan, Italy; [7]Royal Marsden NHS Foundation Trust/The Institute of Cancer Research, London, UK; [8]West German Cancer Center, University Hospital, Essen, Germany; [9]University of Chicago Medical Center, Chicago, IL, USA; [10]Gustave Roussy, Villejuif Cedex, France; [11]University of Michigan, Ann Arbor, MI, USA; [12]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [13]Hospital Universitario 12 de Octubre, Madrid, Spain; [14]Dana-Farber/Harvard Cancer Center, Boston, MA, USA; [15]Universitätsspital Zurich, Zurich, Switzerland; [16]Kobe University Hospital, Kobe, Japan; [17]National Cancer Center Hospital East, Kashiwa, Japan; [18]Bristol-Myers Squibb, Princeton, NJ, USA

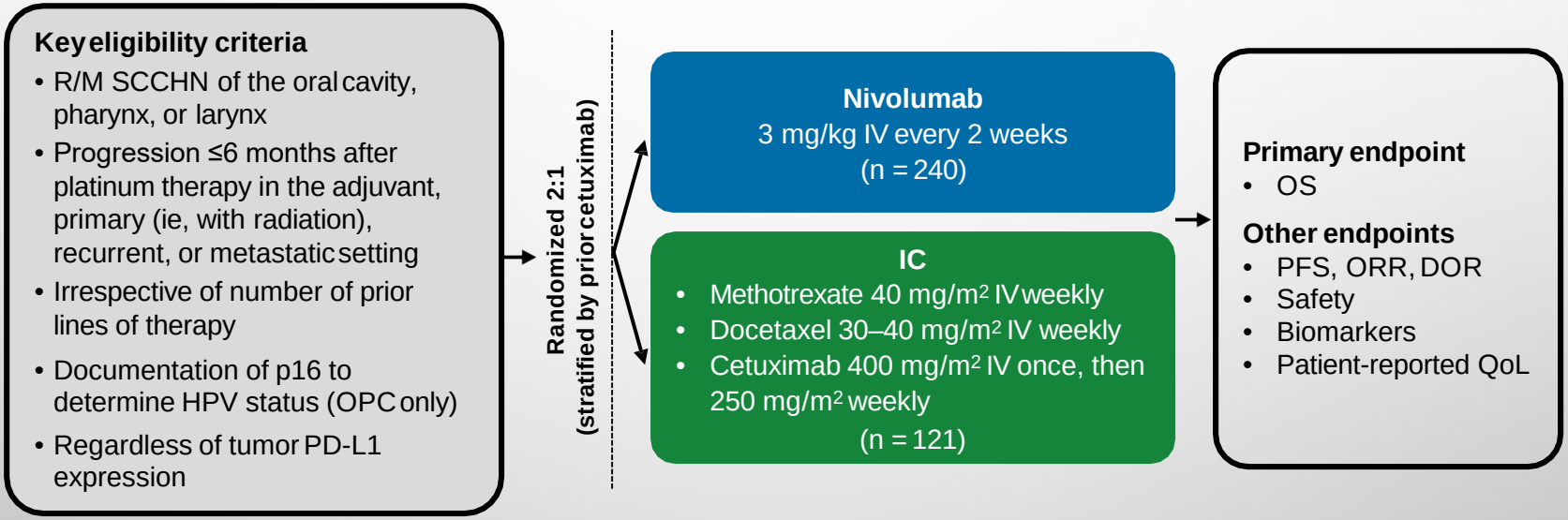
BACKGROUND

- Long-term prognosis for patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) post–platinum therapy has historically been poor, with a median overall survival (OS) of <6 months[1]
- Nivolumab demonstrated significant OS benefit and better tolerability vs investigator's choice (IC) in CheckMate 141, a randomized phase 3 trial:
  - Trial stopped early at the interim (primary) analysis due to statistically significant OS benefit
    - **Median OS: 7.5 vs 5.1 mo**; HR = 0.70 (97.73% CI: 0.51, 0.96); *P* = 0.01[2]
  - At minimum follow-up of 1-year, prolonged OS benefit was noted
    - **Median OS: 7.7 vs 5.1 mo**; HR = 0.71 (95% CI: 0.55, 0.90)[3]
  - Nivolumab was better tolerated, with stabilized quality of life, compared with IC (methotrexate, docetaxel, cetuximab)[2-4]
- At AACR 2018 (**2-year follow-up**) data in patients with R/M SCCHN post–platinum therapy from CheckMate 141

1. Saloura V, et al. *Cancer Chemother Pharmacol* 2014;73:1227–1239. 2. Ferris RL, et al. *N Engl J Med* 2016;375:1856–1867. 3. Gillison ML, et al. *The Oncologist* 2018; In Press. 4. Harrington KJ, et al. *Lancet Oncol* 2017;18:1104–1115.

CHECKMATE 141 STUDY DESIGN

- Randomized, open-label, phase 3 trial (NCT02105636)



- Data cutoff: September 2017 (minimum follow-up of 24.2 months)

DOR = duration of response; HPV = human papillomavirus; IV = intravenous; OPC = oropharyngeal cancer; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival; QoL = quality of life

BASELINE CHARACTERISTICS

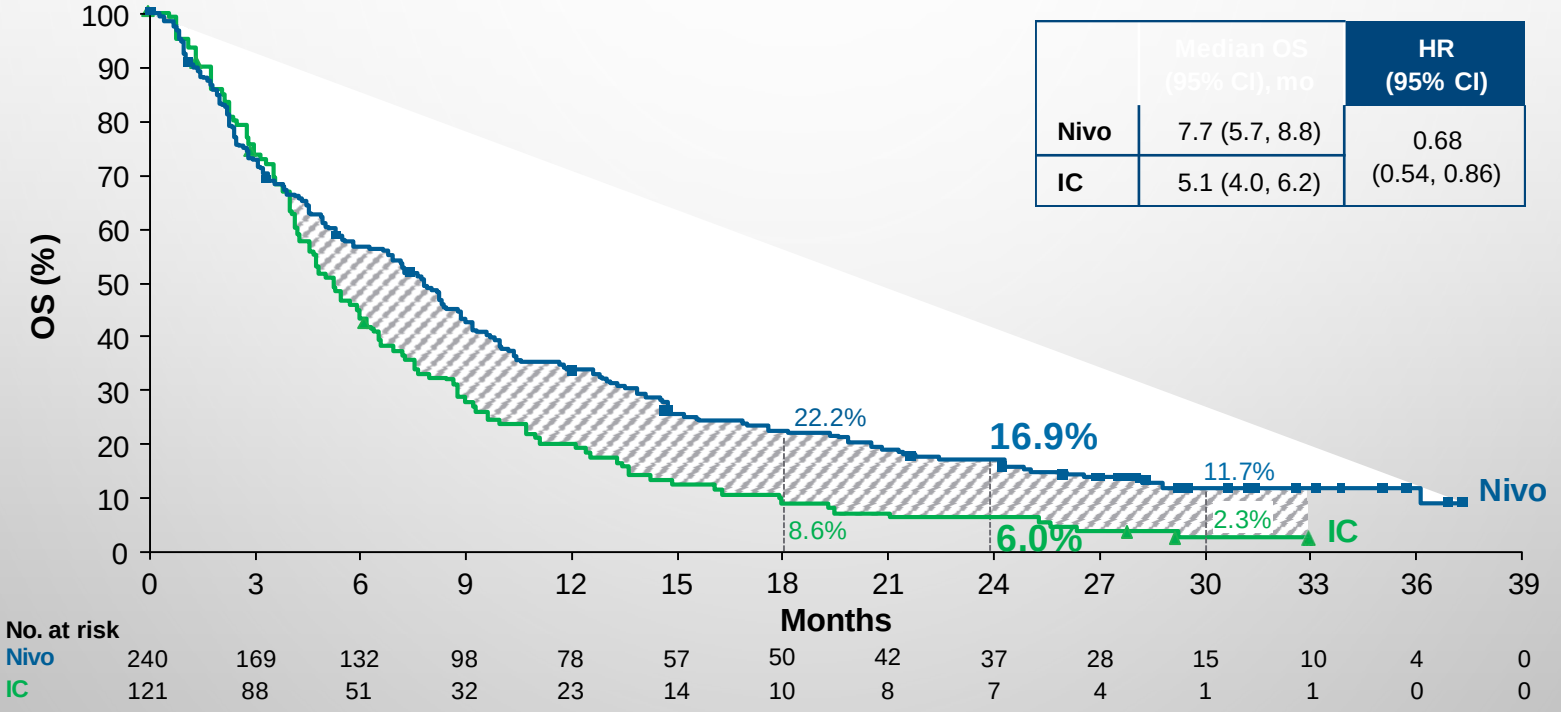
- Baseline characteristics were generally balanced between treatment arms, as previously reported

Patients, n (%)	Nivolumab (n = 240)	IC (n = 121)
Tumor PD-L1 expression[a]		
≥1% (PD-L1 expressors)	96 (40.0)	63 (52.1)
<1% (PD-L1 non-expressors)	76 (31.7)	40 (33.1)
Not quantifiable[b]	68 (28.3)	18 (14.9)
HPV status[c]		
Positive	64 (26.7)	29 (24.0)
Negative	56 (23.3)	37 (30.6)
Unknown/not reported	120 (50.0)	55 (45.5)

[a]PD-L1 status was determined using the Dako PD-L1 IHC 28-8 pharmDx test
[b]Tumor not present, sample not provided, or sample could not be processed
[c]HPV status was assessed using p16 immunohistochemical testing; required only for patients with OPC

SUSTAINED OS BENEFIT IN THE OVERALL (ITT) POPULATION

- Nivolumab reduced the risk of death by 32% vs IC
- The 24-month OS rate was nearly tripled with nivolumab compared with IC



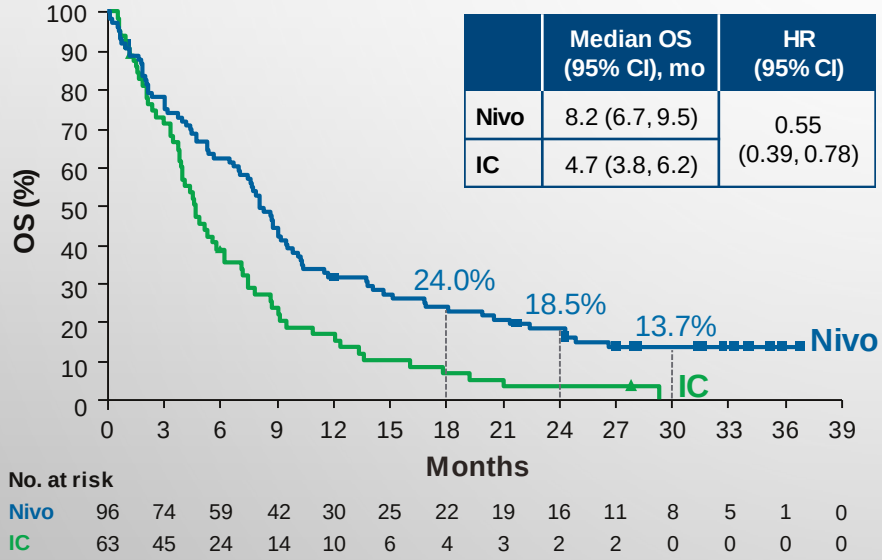
	Median OS (95% CI), mo	HR (95% CI)
Nivo	7.7 (5.7, 8.8)	0.68 (0.54, 0.86)
IC	5.1 (4.0, 6.2)	

Symbols represent censored observations. ITT = intent-to-treat; Nivo, nivolumab

OS BENEFIT ACROSS PD-L1 EXPRESSORS AND NON-EXPRESSORS

- OS rates at 18, 24, and 30 months were similar in both groups
  - PD-L1 expressors: nivolumab continued to provide OS benefit, with 45% reduction in risk of death vs IC
  - PD-L1 non-expressors: nivolumab resulted in 27% reduction in risk of death vs IC

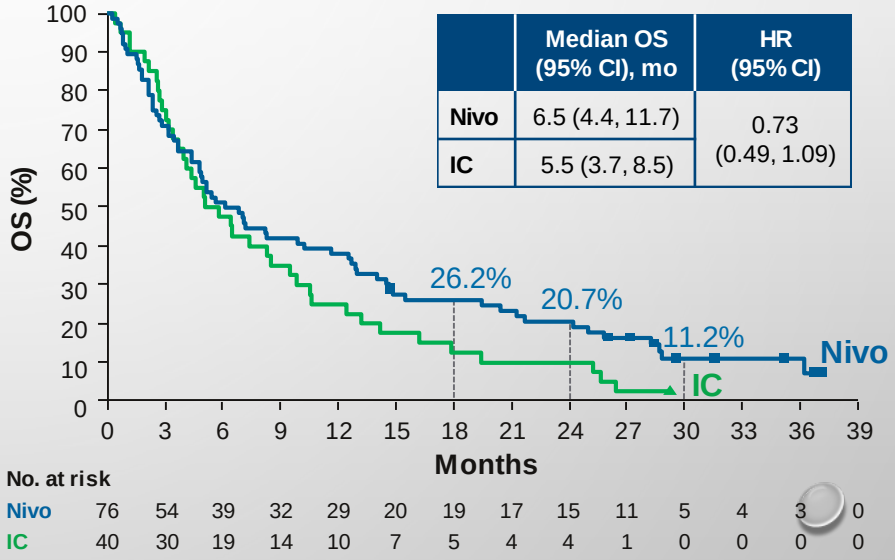
PD-L1 Expressors (≥1%)



	Median OS (95% CI), mo	HR (95% CI)
Nivo	8.2 (6.7, 9.5)	0.55 (0.39, 0.78)
IC	4.7 (3.8, 6.2)	

No. at risk														
Nivo	96	74	59	42	30	25	22	19	16	11	8	5	1	0
IC	63	45	24	14	10	6	4	3	2	2	0	0	0	0

PD-L1 Non-Expressors (<1%)



	Median OS (95% CI), mo	HR (95% CI)
Nivo	6.5 (4.4, 11.7)	0.73 (0.49, 1.09)
IC	5.5 (3.7, 8.5)	

No. at risk														
Nivo	76	54	39	32	29	20	19	17	15	11	5	4	3	0
IC	40	30	19	14	10	7	5	4	4	1	0	0	0	0

Symbols represent censored observations

OS IN PD-L1 NON-EXPRESSORS (<1%)

- In PD-L1 non-expressors, the HR for risk of death with nivolumab vs IC consistently trended lower with longer follow-up

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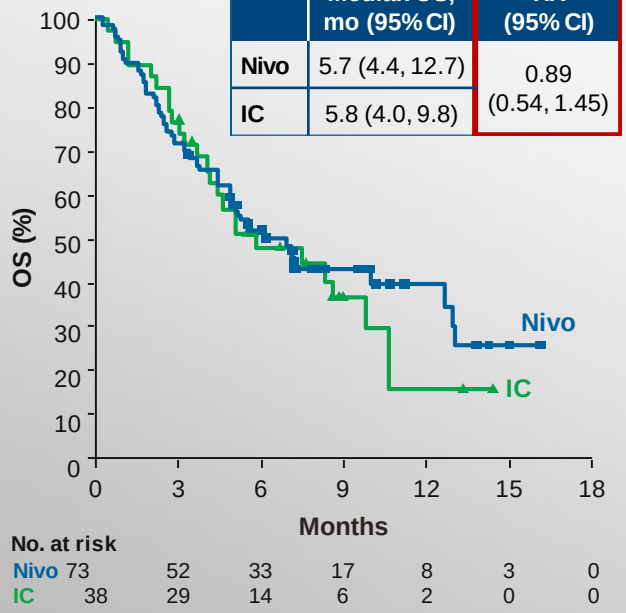
Primary Analysis[a] (Dec 2015 data cutoff)

	Median OS, mo (95% CI)	HR (95% CI)
Nivo	5.7 (4.4, 12.7)	0.89 (0.54, 1.45)
IC	5.8 (4.0, 9.8)	



Symbols represent censored observations; [a]FromNEJM, Ferris RL et al., Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck, 375, 1856-67, Copyright © 2016 Massachusetts Medical Society. Reprinted with permission fromMassachusetts Medical Society.

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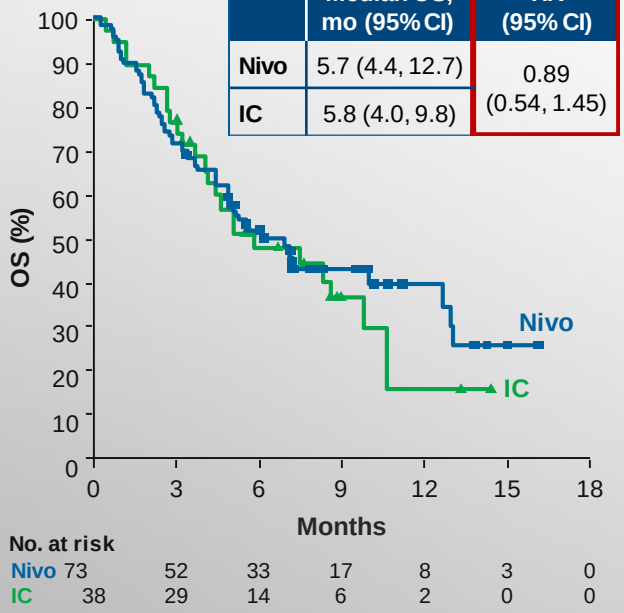
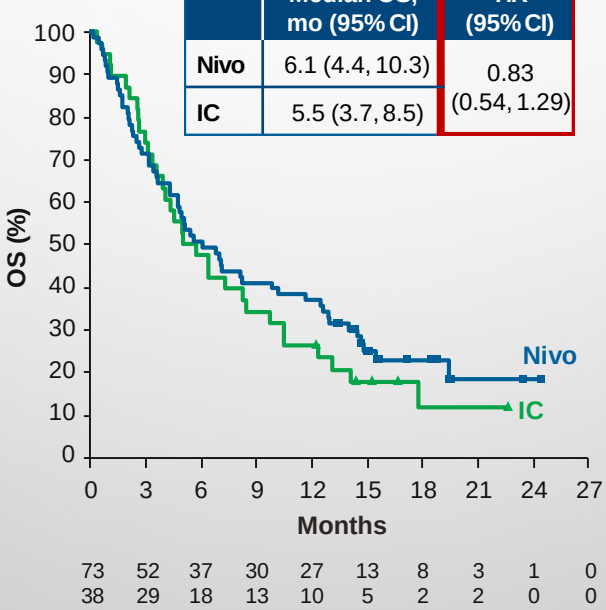


1-Year Follow-up (Sept 2016 data cutoff)

	Median OS, mo (95% CI)	HR (95% CI)
Nivo	6.1 (4.4, 10.3)	0.83 (0.54, 1.29)
IC	5.5 (3.7, 8.5)	



No. at risk							
Nivo	73	52	33	17	8	3	0
IC	38	29	14	6	2	0	0

73	52	37	30	27	13	8	3	1	0
38	29	18	13	10	5	2	2	0	0

Symbols represent censored observations; [a]FromNEJM, Ferris RL et al., Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck, 375, 1856-67, Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

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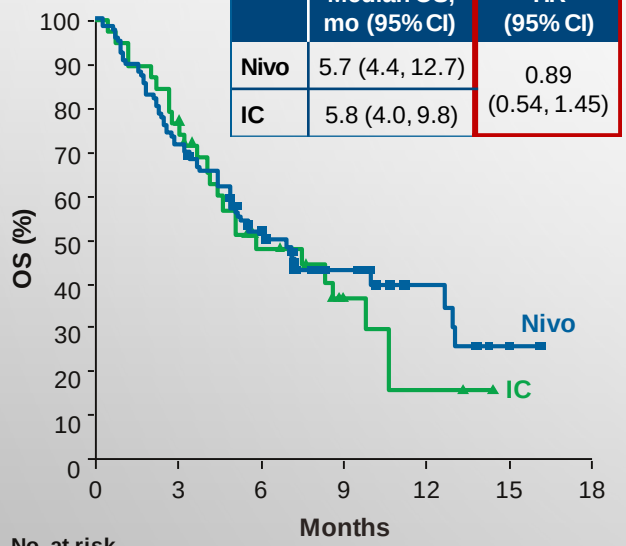

No. at risk

Nivo	73	52	33	17	8	3	0
IC	38	29	14	6	2	0	0

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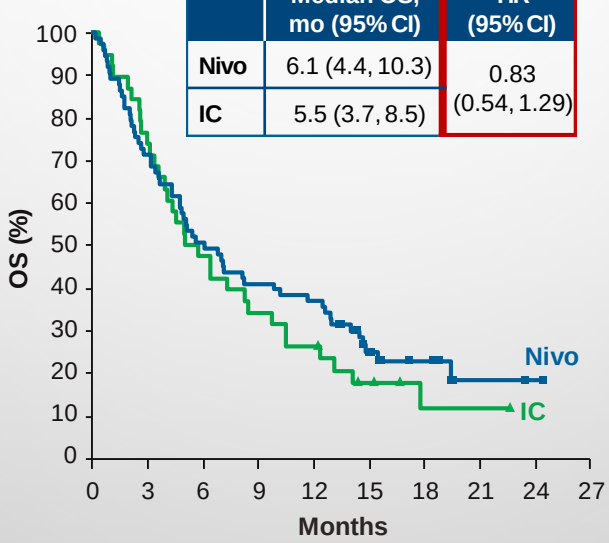
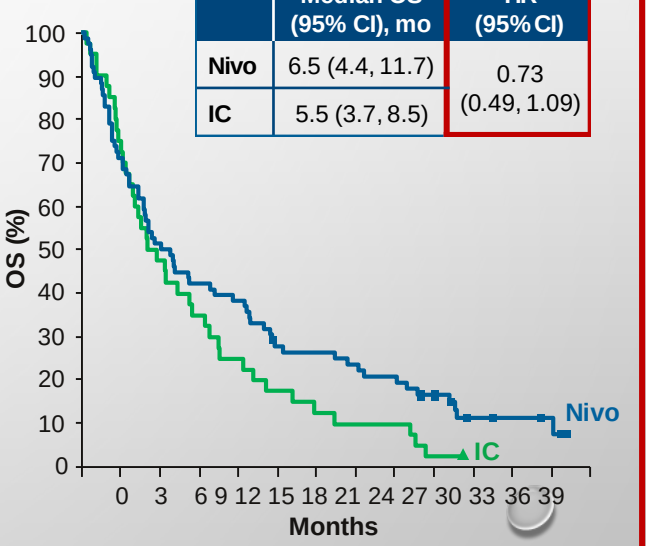


Nivo	73	52	37	30	27	13	8	3	1	0
IC	38	29	18	13	10	5	2	2	0	0

2-Year Follow-up (Sept 2017 data cutoff)

	Median OS (95% CI), mo	HR (95% CI)
Nivo	6.5 (4.4, 11.7)	0.73 (0.49, 1.09)
IC	5.5 (3.7, 8.5)	



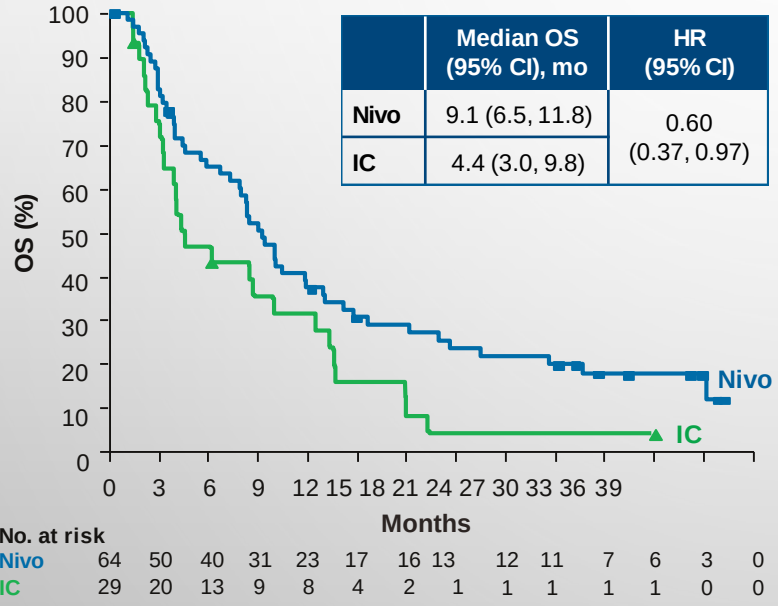
Nivo	76	54	39	32	29	20	19	17	15	11	5	4	3	0
IC	40	30	19	14	10	7	5	4	4	1	0	0	0	0

Symbols represent censored observations; [a]FromNEJM, Ferris RL et al., Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck, 375, 1856-67, Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

OS BY HPV STATUS

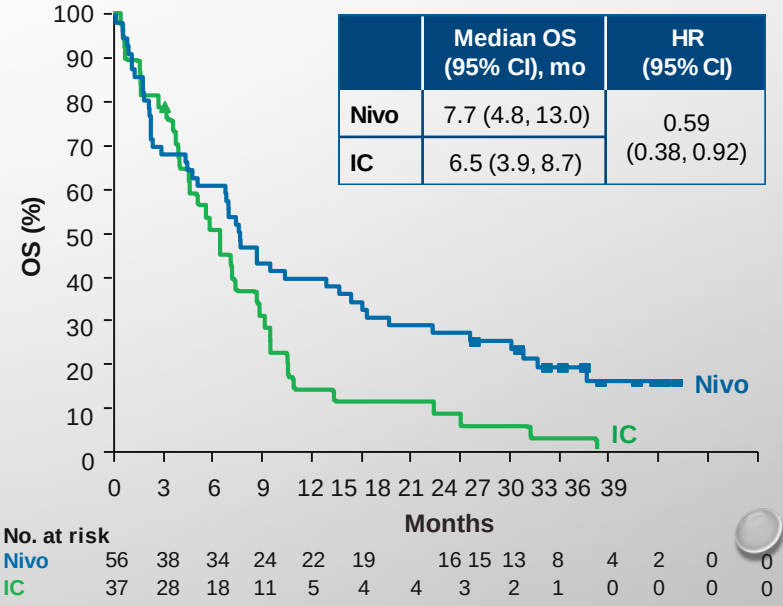
- Nivolumab demonstrated survival benefit in patients with HPV-positive and HPV-negative tumors, with comparable HRs for risk of death vs IC

HPV-Positive



	Median OS (95% CI), mo	HR (95% CI)
Nivo	9.1 (6.5, 11.8)	0.60 (0.37, 0.97)
IC	4.4 (3.0, 9.8)	

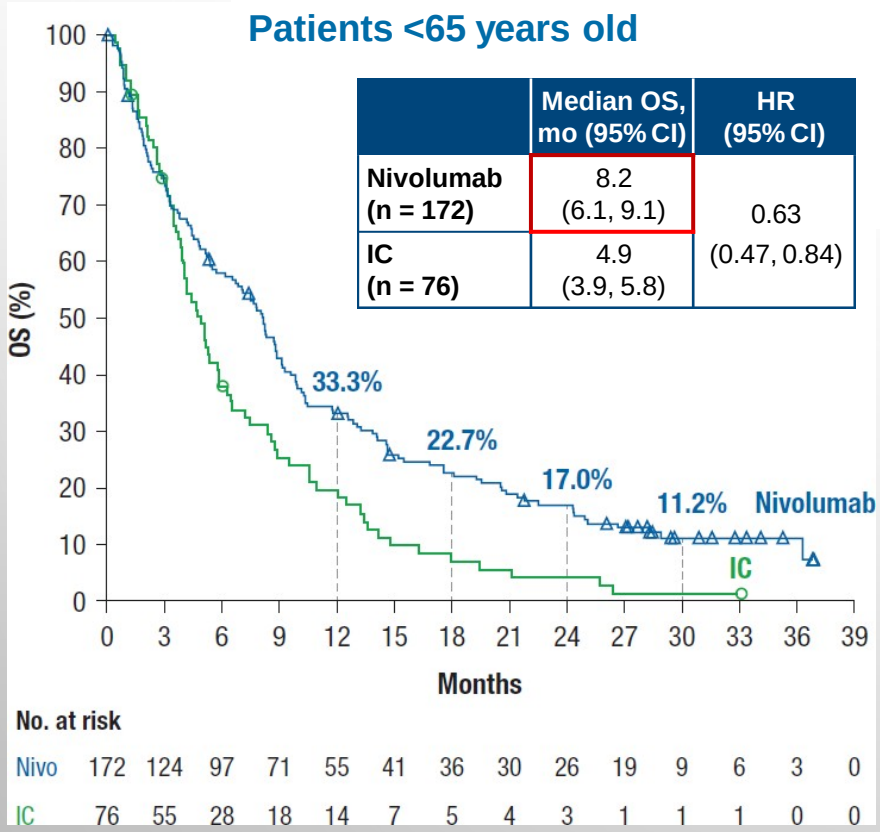
HPV-Negative

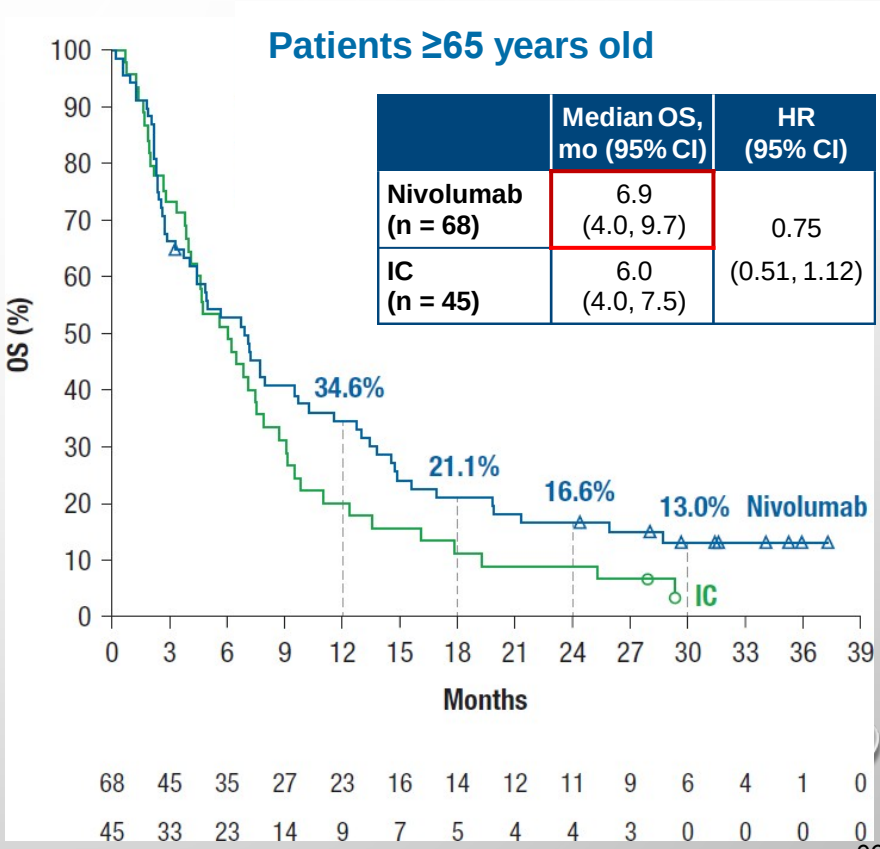


	Median OS (95% CI), mo	HR (95% CI)
Nivo	7.7 (4.8, 13.0)	0.59 (0.38, 0.92)
IC	6.5 (3.9, 8.7)	

[a]HPV testing was required only for patients with OPC; symbols represent censored observations

OVERALL SURVIVAL BY AGE





Saba et al. ASCO 2018

SUBSEQUENT THERAPIES AMONG PATIENTS WHO DISCONTINUED TREATMENT

- Nivolumab continued to improve in OS vs IC in spite of subsequent immunotherapy in 10.1% of patients in the IC arm

Patients, n (%)	Nivolumab (n = 228)	IC (n = 109)
Any therapy[a]	91 (39.9)	43 (39.4)
Radiotherapy	30 (13.2)	14 (12.8)
Surgery	2 (0.9)	3 (2.8)
Systemic therapy	82 (36.0)	36 (33.0)
Taxanes	35 (15.4)	11 (10.1)
Monoclonal antibodies (bevacizumab, cetuximab)	31 (13.6)	8 (7.3)
Other – approved agents	31 (13.6)	12 (11.0)
Folic acid analogue	22 (9.6)	7 (6.4)
Platinum-based chemotherapy	16 (7.0)	11 (10.1)
Other – experimental agents	15 (6.6)	3 (2.8)
Immunotherapy (nivolumab, pembrolizumab, durvalumab, urelumab)	12 (5.3)	11 (10.1)
PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab, durvalumab)	9 (3.9)	10 (9.2)
Unassigned	1 (0.4)	0

[a]Patients may have received more than 1 type of subsequent therapy, which was defined as non-study anticancer therapy started on or after first dosing date (or randomization date, if patient was not treated)

TUMOR RESPONSE

- In the nivolumab arm, complete responses were observed in both PD-L1 expressors and PD-L1 non-expressors
  - Seven complete responders (2 PD-L1 expressors, 2 PD-L1 non-expressors, and 3 with no data on tumor PD-L1 expression)
  - One patient had a partial response, which later converted to a complete response

	Nivolumab (n = 240)	IC (n = 121)
ORR, % (95% CI)	13.3 (9.3, 18.3)	5.8 (2.4, 11.6)
Time to response, median (range), months	2.1 (1.8 to 7.4)	2.0 (1.9 to 4.6)
Duration of response, median (range), months	9.7 (2.8 to 32.8+)	4.0 (1.5+ to 11.3)

TREATMENT-RELATED ADVERSE EVENTS

- The safety profile of nivolumab remained consistentwith previous analyses,[1,2] and manageable
  - Fewer grade 3–4 events in the nivolumab arm vs the IC arm
  - No new safety signals were reported
- The incidence of serious TRAEs was lower in the nivolumab arm (7.2%) vs the IC arm (15.3%)
- Rates of death due to drug toxicity remained unchanged from the primary analysis[1]

	Nivolumab (n = 236)		IC (n = 111)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE, n (%)	146 (61.9)	36 (15.3)	88 (79.3)	41 (36.9)
TRAEs in ≥15% of patients, n (%)				
Fatigue	37 (15.7)	5 (2.1)	20 (18.0)	3 (2.7)
Nausea	22 (9.3)	0	23 (20.7)	1 (0.9)
Anemia	12 (5.1)	3 (1.3)	19 (17.1)	6 (5.4)
Asthenia	10 (4.2)	1 (0.4)	17 (15.3)	2 (1.8)

1. Ferris RL, et al. *N Engl J Med* 2016;375:1856–1867. 2. Gillison ML, et al. *The Oncologist* 2018; In Press.
TRAE = treatment-related adverse event

CONCLUSIONS

- Nivolumab is the only immunotherapy to significantly improve OS vs IC in patients with R/M SCCHN post–platinum therapy, in the primary analysis of a randomized, phase 3 study (CheckMate 141)
  - Primary analysis: HR = 0.70 (97.73% CI: 0.51, 0.96); *P* = 0.01
  - 2-year follow-up: HR = 0.68 (95% CI: 0.54, 0.86)
- With long-term (2-year) follow-up, nivolumab demonstrated prolonged OS benefit compared with IC in the overall population with
  - Efficacy across PD-L1 expressors and non-expressors
  - Efficacy regardless of tumor HPV status
  - A favorable safety profile compared with IC maintained; no new safety signals observed
  - No observed differences in baseline characteristics or safety profile among long-term survivors in the nivolumab arm compared with the overall nivolumab population
- Nivolumab is an established therapeutic option in R/M SCCHN post–platinum therapy, with demonstrated long-term benefits in OS and safety compared with monotherapy options

UPDATED SURVIVAL RESULTS OF THE KEYNOTE-040 STUDY OF PEMBROLIZUMAB VS SOC CHEMOTHERAPY FOR RECURRENT OR METASTATIC HNSCC

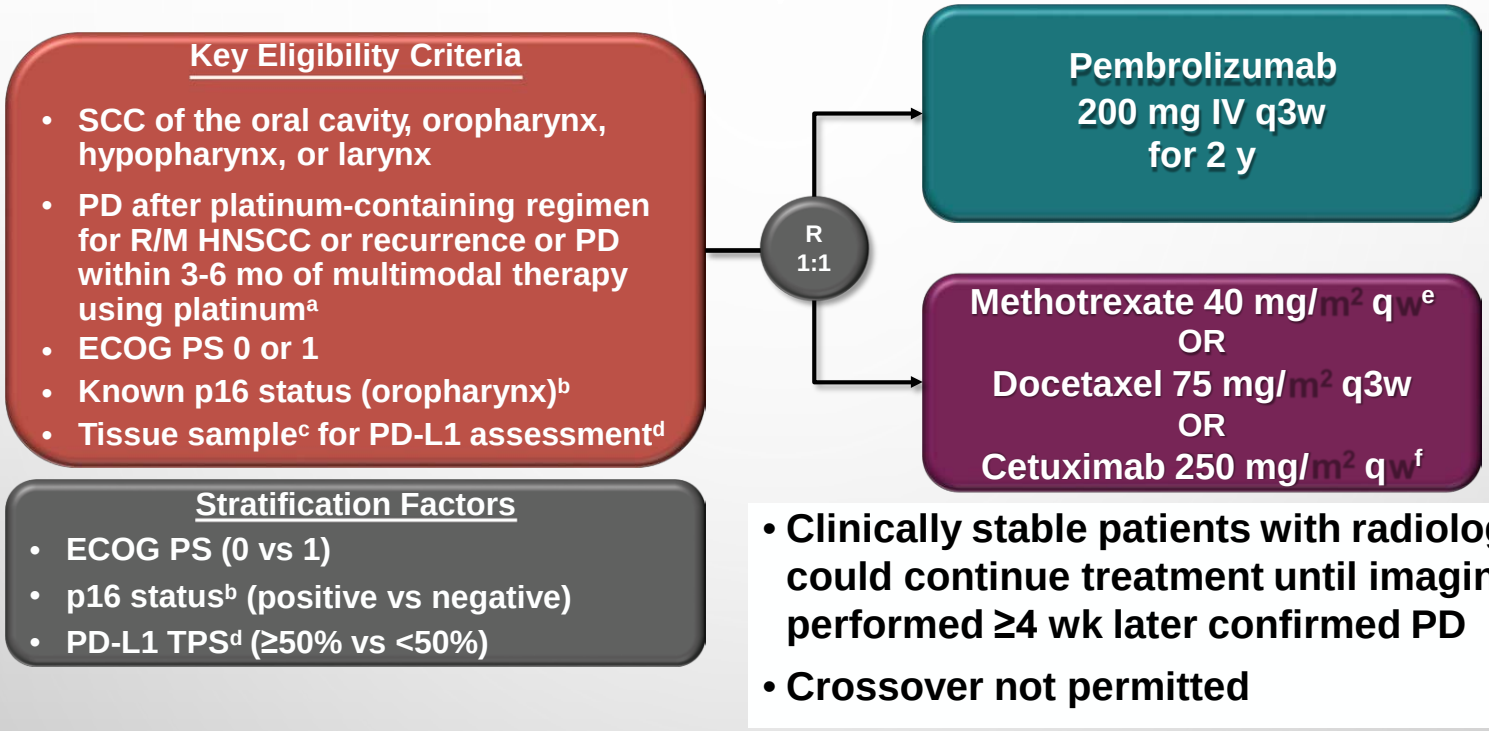
Denis Soulières et al. AACR 2018

PEMBROLIZUMAB AND HNSCC

Study	Population	ORR	Median DOR	Median PFS
KEYNOTE-012[1]	PD-L1–positive R/M HNSCC (N = 61)	18%	12.2 months	2 months
KEYNOTE-012 expansion cohort[2]	R/M HNSCC of any PD-L1 expression (N = 132)	Total: 18% PD-L1^{+}: 22% PD-L1^{-}: 4%	Not reached	2 months
KEYNOTE-055[3]	Platinum and cetuximab-refractory HNSCC of any PD-L1 expression (N = 171)	Total: 16% PD-L1^{+}: 18% PD-L1^{-}: 12%	8 months	2.1 months

1. Seiwert TY et al. *Lancet Oncol* 2016;17:956-965. 2. Chow LQM et al. *J Clin Oncol* 2016;34:3838-3845. 3. Bauml J et al. *J Clin Oncol* 2017;35:1542-1549.

Phase III KEYNOTE-040 Study



- **Clinically stable patients with radiologic PD could continue treatment until imaging performed ≥4 wk later confirmed PD**
- **Crossover not permitted**

[a]Limit of 2 prior therapies for R/M HNSCC. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Newly collected preferred. [d]Assessed using the PD-L1 IHC 22C3 pharmDx assay. TPS, tumor proportion score = % of tumor cells with membranous PD-L1 expression. [e]Could be increased to 60 mg/m² qw in the absence of toxicity. [f]Following a loading dose of 400 mg/m².

Cohen E, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract LBA45_PR.

KEYNOTE – 040: PRIMARY AND UPDATED ANALYSES

- Primary analysis presented at ESMO 2017
  - Prespecified significance boundary: P = 0.0175
  - Data cutoff date: May 15, 2017
  - No. of Death: 377 (data outstanding for 11 patients)
  - OS: HR 0.81 (95% Cl 0.66-0.99), P= 0.02024

- Updated analysis
  - Same data cutoff date: May 15, 2017 (i.e., update is without extending f/u duration)
  - Full acquisition of survival status, including the 11 pts previously outstanding
  - No. of death after acquisition of survival status: 388

Cohen E, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract LBA45_PR.

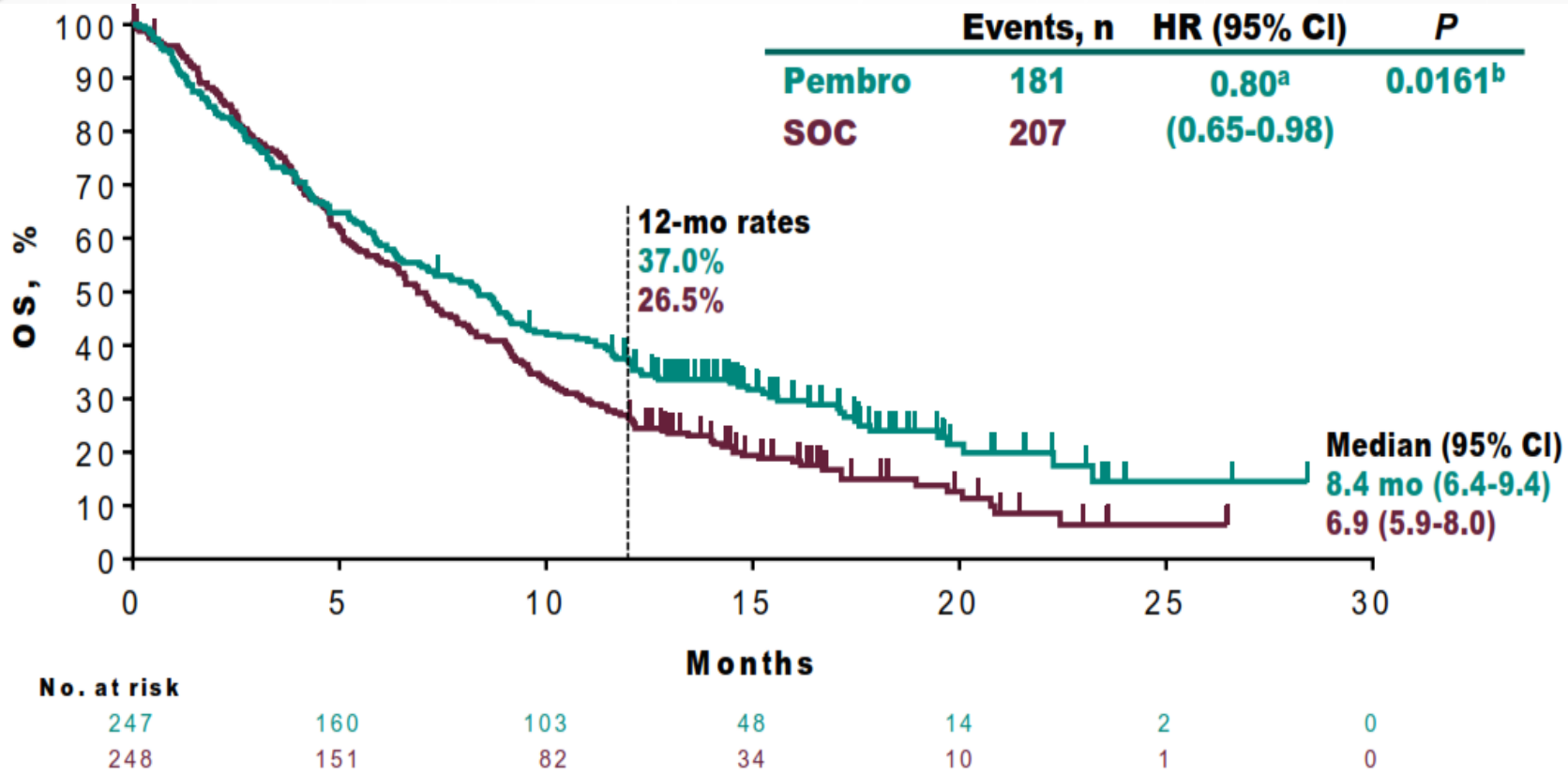
KEYNOTE – 040: BASELINE CHARACTERISTICS

Characteristic, n (%)	Pembro N = 247	SOC N = 248
Age, median (range)	60 (19-85)	60 (34-78)
Male	207 (83.8)	205 (82.7)
ECOG PS 1	176 (71.3)	180 (72.6)
Current/former smoker	179 (72.5)	182 (73.4)
Region of enrollment		
Europe	147 (59.5)	158 (63.7)
North America	73 (29.6)	60 (24.2)
Rest of world	27 (10.9)	30 (12.1)

Characteristic, n (%)	Pembro N = 247	SOC N = 248
p16 positive (oropharynx)	61 (24.7)	58 (23.4)
PD-L1 TPS ≥50%	64 (25.9)	65 (26.2)
PD-L1 CPS ≥1	196 (79.4)	191 (77.0)
Prior therapy		
(Neo)adjuvant or definitive	34 (13.8)	40 (16.1)
First line	141 (57.1)	141 (56.9)
Second line	69 (27.9)	64 (25.8)
Third line	3 (1.2)	3 (1.2)

Cohen E, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract LBA45_PR.

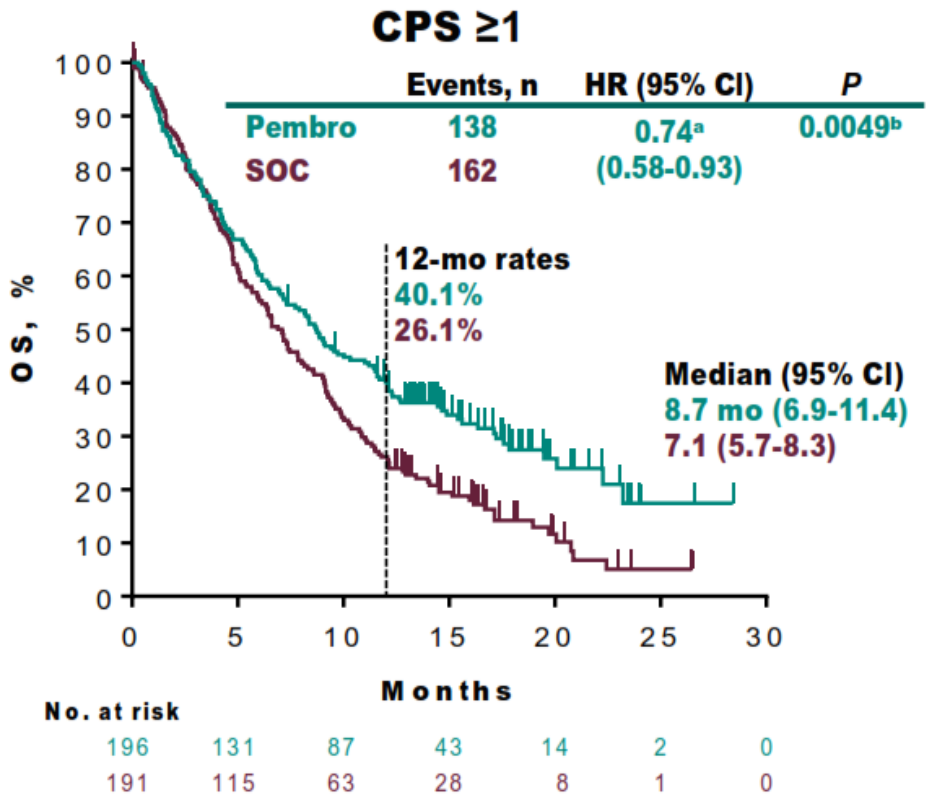
Updated Overall Survival in ITT Population

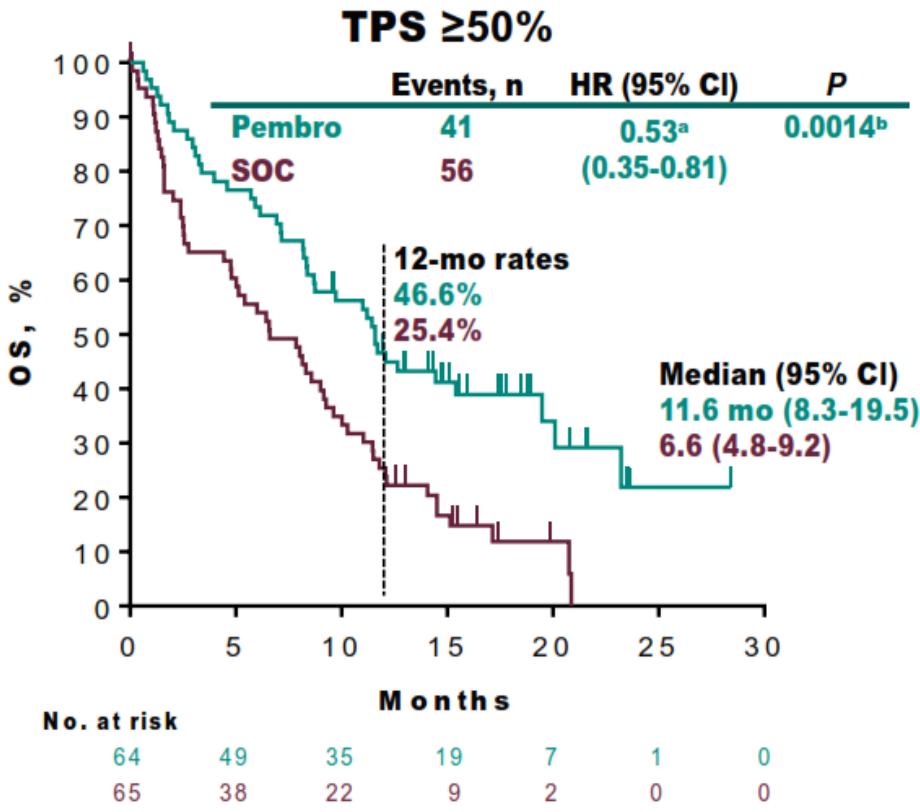


[a]Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors. [b]Nominal one-sided *P* value based on the log-rank test stratified by the randomization stratification factors. Data cutoff date: May 15, 2017.

Denis Soulières et al. AACR 2018

Updated Overall Survival by PD-L1 Expression

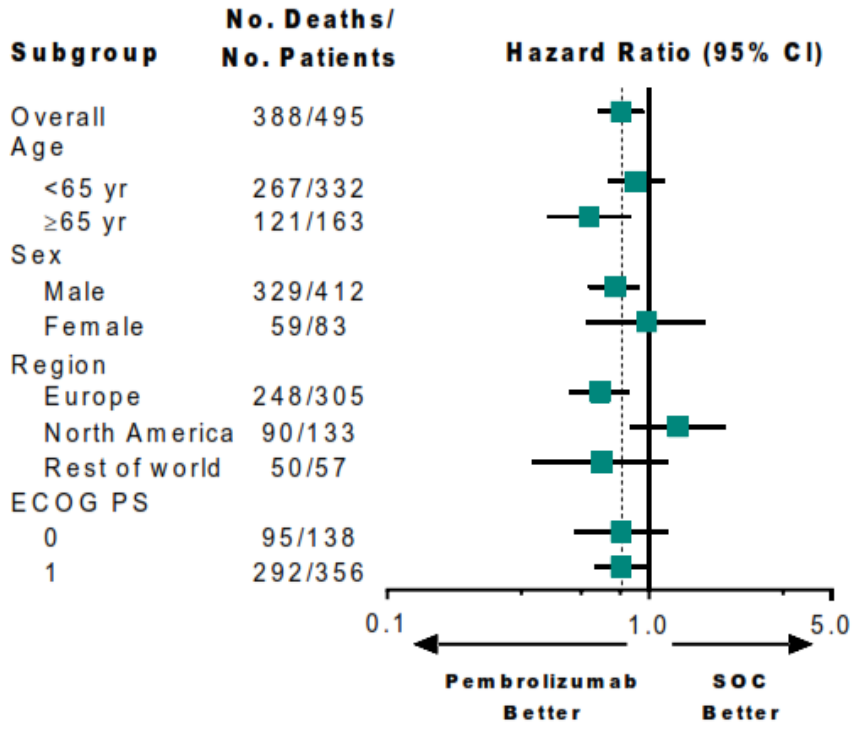


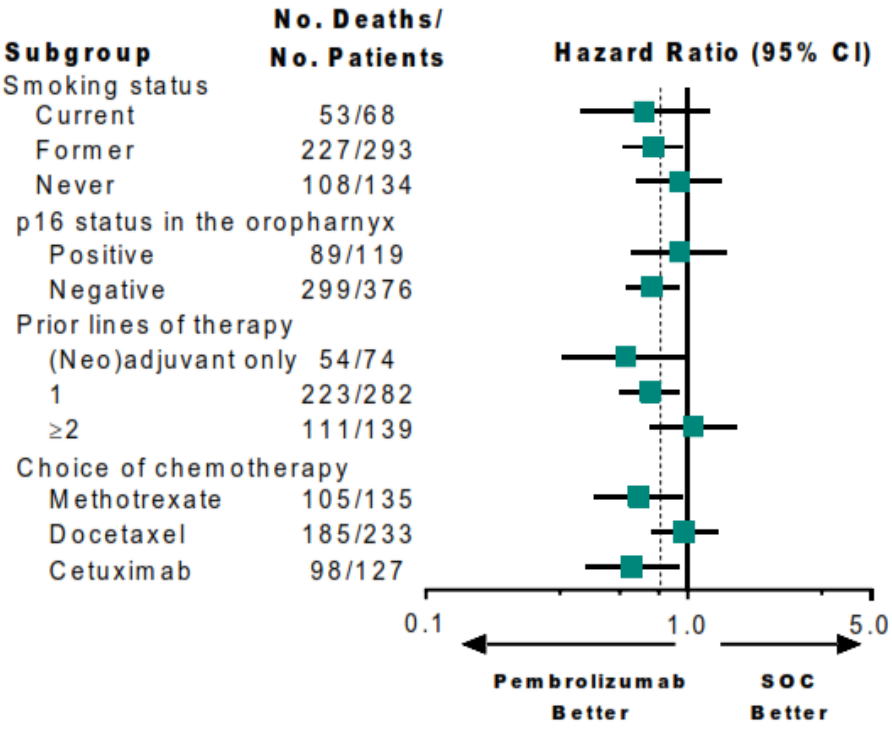


[a]Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors. [b]Nominal one-sided *P* value based on the log-rank test stratified by the randomization stratification factors. Data cutoff date: May 15, 2017.

Denis Soulières et al. AACR 2018

Updated Overall Survival by Subgroups



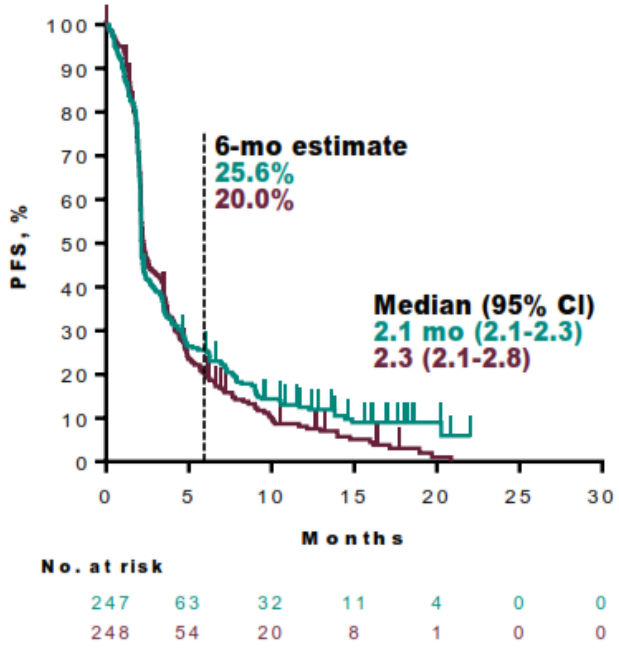


Unstratified Cox proportional hazards model with treatment as a covariate.
Data cutoff date: May 15, 2017.

UPDATED PROGRESSION-FREE SURVIVAL

ITT

	Events, n	HR[a] (95% CI)	P[b]
Pembro	218	0.96	0.3250
SOC	224	(0.79-1.16)	

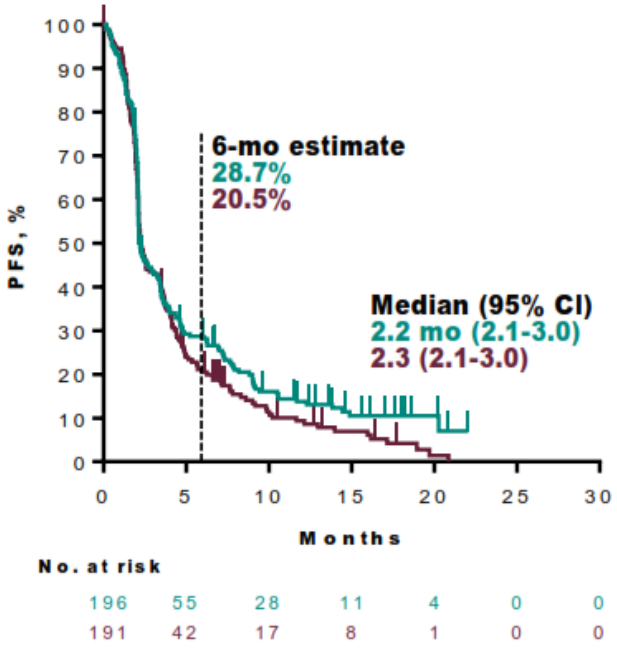


No. at risk

247	63	32	11	4	0	0
248	54	20	8	1	0	0

PD-L1 CPS ≥1

	Events, n	HR[a] (95% CI)	P[b]
Pembro	170	0.86	0.0774
SOC	170	(0.69-1.06)	

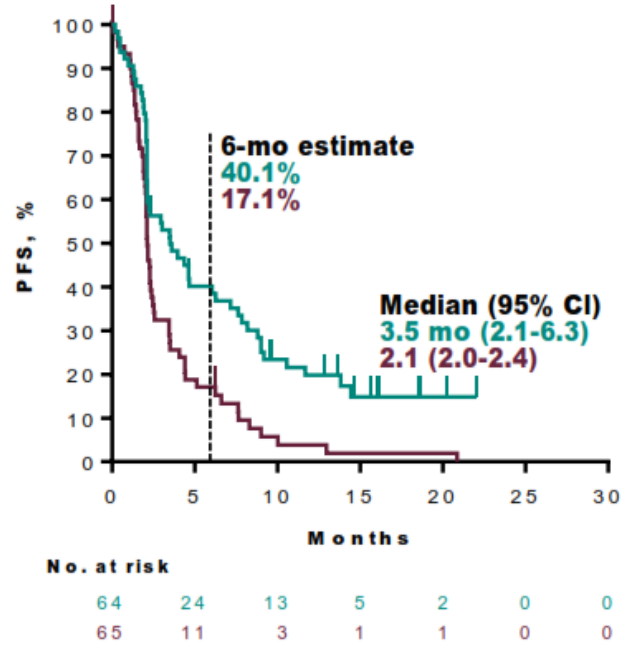


No. at risk

196	55	28	11	4	0	0
191	42	17	8	1	0	0

PD-L1 TPS ≥50%

	Events, n	HR[a] (95% CI)	P[b]
Pembro	52	0.58	0.0028
SOC	58	(0.39-0.86)	



No. at risk

64	24	13	5	2	0	0
65	11	3	1	1	0	0

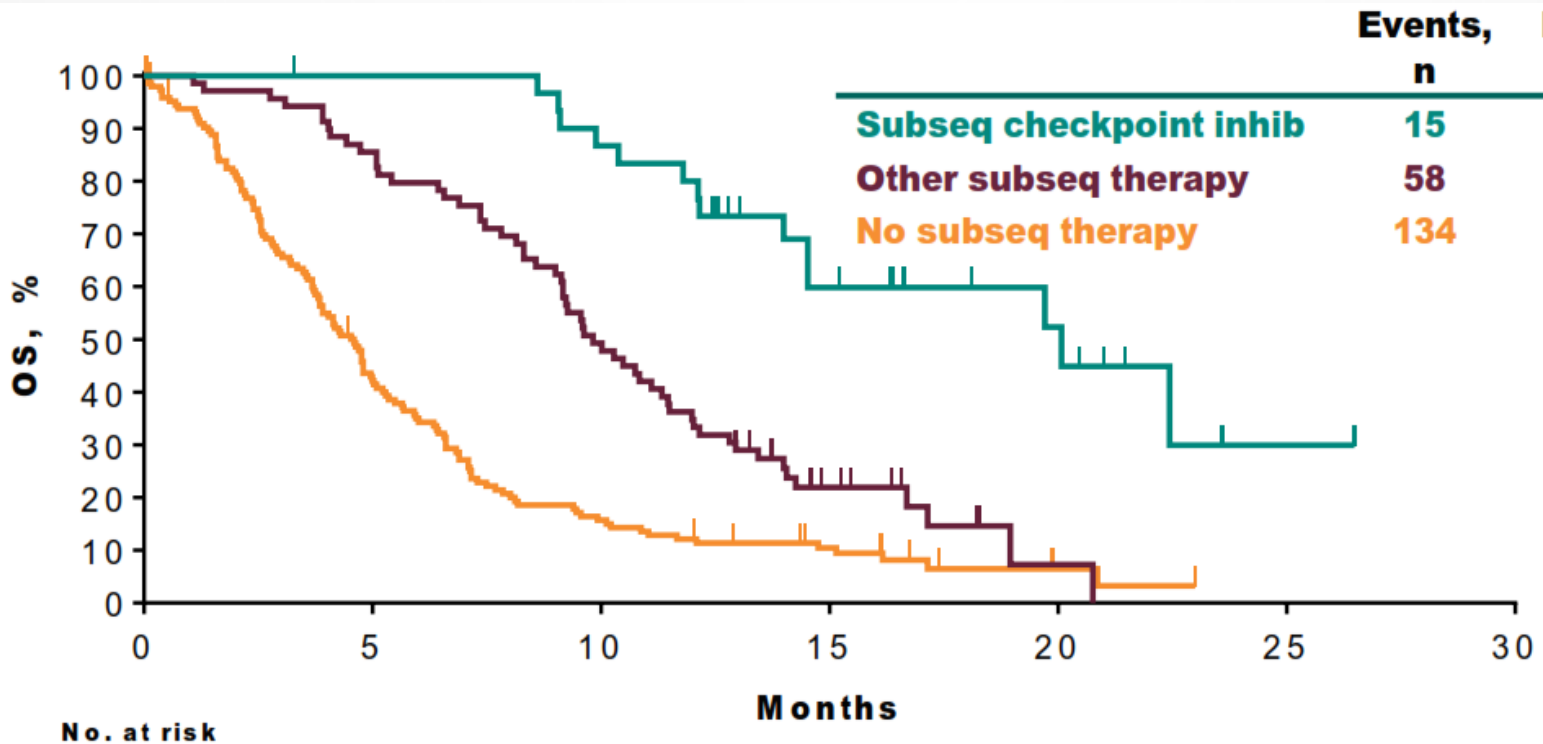
[a]Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors.
[b]Nominal one-sided *P* value based on the log-rank test stratified by the randomization stratification factors. Data cutoff date: May 15, 2017.

Updated Subsequent Therapy

Type, n (%)	Pembrolizumab N = 247	SOC N = 248
Any[a]	84 (34.0)	101 (40.7)
Chemotherapy	70 (28.3)	77 (31.0)
EGFR inhibitor	20 (8.1)	19 (7.7)
Kinase inhibitor	3 (1.2)	8 (3.2)
Immune checkpoint inhibitor	11 (4.5)	31 (12.5)
Other immunotherapy	5 (2.0)	1 (0.4)
Other	2 (0.8)	2 (0.8)

[a]Patients may have received ≥1 subsequent therapy.
Data cutoff date: May 15, 2017.

Updated OS: Effect of Subsequent Immune Checkpoint Inhibitors in the SOC Arm



Data cutoff date: May 15, 2017.

Treatment-Related Aes with Incidence of > 10%

	Pembrolizumab (N = 246)		SOC (N = 234)	
Event, n (%)	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Hypothyroidism	33 (13.4)	1 (0.4)	2 (0.9)	0
Fatigue	31 (12.6)	4 (1.6)	43 (18.4)	2 (0.9)
Diarrhea	20 (8.1)	4 (1.6)	24 (10.3)	1 (0.4)
Rash	19 (7.7)	1 (0.4)	34 (14.5)	1 (0.4)
Asthenia	18 (7.3)	1 (0.4)	28 (12.0)	4 (1.7)
Anemia	17 (6.9)	1 (0.4)	33 (14.1)	9 (3.8)
Nausea	12 (4.9)	0	29 (12.4)	1 (0.4)
Mucosal inflammation	9 (3.7)	1 (0.4)	30 (12.8)	5 (2.1)
Stomatitis	6 (2.4)	1 (0.4)	28 (12.0)	11 (4.7)
Neutrophil count decreased	3 (1.2)	1 ().4)	25 (10.7)	20 (8.5)
Alopecia	1 (0.4)	0	25 (10.7)	0

AEs did not change in updated analysis. Relationship to treatment was determined by the investigator.
Data cutoff date: May 15, 2017.

SUMMARY

- After all survival data analyzed using the same data cutoff date and comparing with the primary analysis:
  - HR for OS decreased from 0.81 to 0.80
  - P-value for OS decreased from 0.02024 to 0.0161
  - Better treatment effect in patients with PDL1 expressing tumors
  - Apparent effect of immune checkpoint inhibitors in SOC arm after failure of SOC

MADRID 2017 ESMO congress

TREATMENT BEYOND PROGRESSION WITH NIVOLUMAB IN PATIENTS WITH RECURRENT OR METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK IN THE PHASE 3 CHECKMATE 141 STUDY: A BIOMARKER ANALYSIS AND UPDATED CLINICAL OUTCOMES

Robert Haddad,[1] George Blumenschein, Jr.,[2] Jerome Fayette,[3] Joel Guigay,[4] A. Dimitrios Colevas,[5] Lisa Licitra,[6] Stefan Kasper,[7] Everett E. Vokes,[8] Francis Worden,[9] Nabil F. Saba,[10] Makoto Tahara,[11] Fernando Concha-Benavente,[12] Manish Monga,[13] Mark Lynch,[13] Li Li,[13] James W. Shaw,[13] Maura L. Gillison,[2] Kevin J. Harrington,[14] Robert L. Ferris[12]

[1]Dana-Farber/Harvard Cancer Center, Boston, MA, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]Centre Leon Berard, Lyon, France; [4]Centre Antoine Lacassagne, Université Côte d'Azur, Nice, France; [5]Stanford University, Stanford, CA, USA; [6]Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, Milan, Italy; [7]West German Cancer Center, University Hospital, Essen, Germany; [8]University of Chicago Medical Center, Chicago, IL, USA; [9]University of Michigan, Ann Arbor, MI, USA; [10]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [11]National Cancer Center Hospital East, Kashiwa, Japan; [12]University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, PA, USA; [13]Bristol-Myers Squibb, Princeton, NJ, USA; [14]Royal Marsden NHS Foundation Trust/The Institute of Cancer Research, London, UK

BACKGROUND

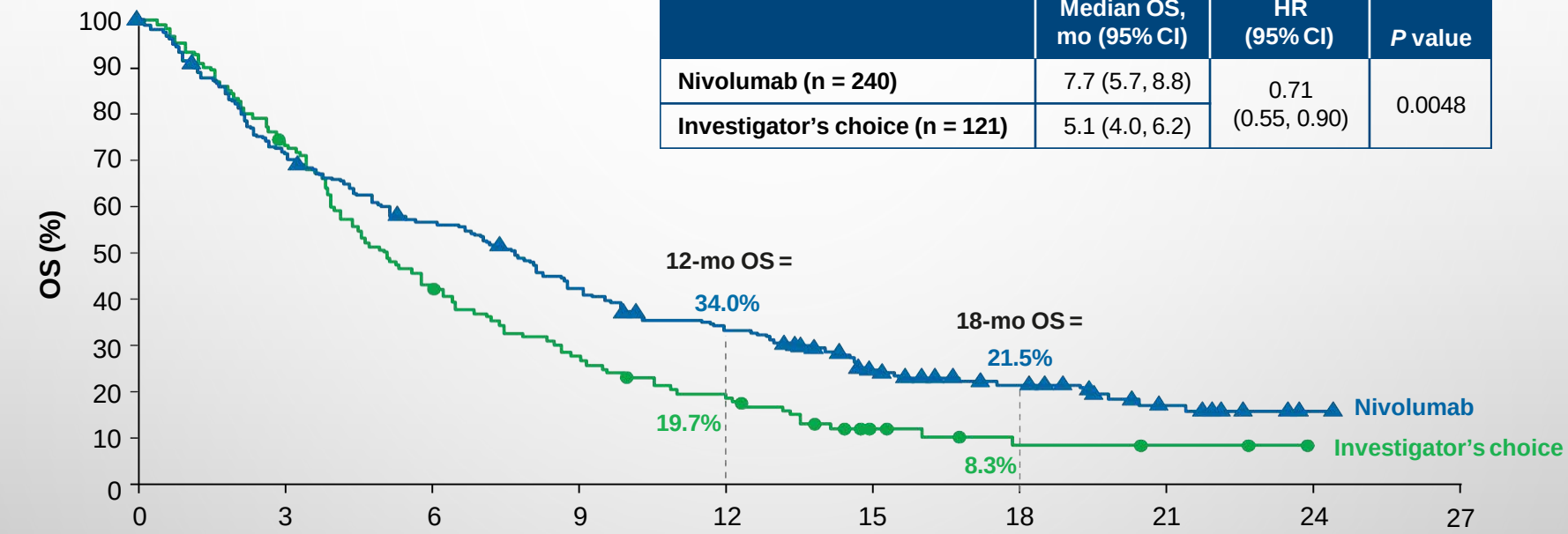
- RECIST 1.1 criteria assumed that early tumor growth indicated progressive disease and failure of cytotoxic agents
  - Novel response patterns observed with immunotherapeutic agents have indicated that clinical activity may not be properly interpreted using RECIST 1.1 criteria
  - Tumor lesions may appear to increase in size due to immune and inflammatory cell infiltration, with a delayed clinical response
  - Benefits with continued nivolumab treatment beyond RECIST-defined progression have been reported in some patients with melanoma, non-small cell lung cancer, and renal cell carcinoma
- This is an updated analysis of nivolumab treatment beyond first disease progression as well as correlative biomarkers in CheckMate 141

PD-1 = programmed death-1; RECIST = Response Evaluation Criteria in Solid Tumors

Wolchok JD, et al. *Clin Cancer Res* 2009;15:7412–7420. Ribas A, et al. *Clin Cancer Res* 2009;15:7116–7118. Oxnard GR, et al. *J Natl Cancer Inst* 2012;104:1534–1541. Chiou VL, et al. *J Clin Oncol* 2015;33:3541–3543. Robert C, et al. *N Engl J Med* 2015;372:320–330. 9. Topalian SL, et al. *N Engl J Med* 2012;366:2443–2454. Brahmer J, et al. *N Engl J Med* 2015;373:123–135. Escudier BJ, et al. *J Clin Oncol* 2016;34(suppl): abstract 4509. George S, et al. *JAMA Oncol* 2016;2:1179–1186.

OVERALL SURVIVAL, MINIMUM FOLLOW-UP: 11.4 MONTHS

	Median OS, mo (95% CI)	HR (95% CI)	*P* value
Nivolumab (n = 240)	7.7 (5.7, 8.8)	0.71 (0.55, 0.90)	0.0048
Investigator's choice (n = 121)	5.1 (4.0, 6.2)		



No. of patients at risk

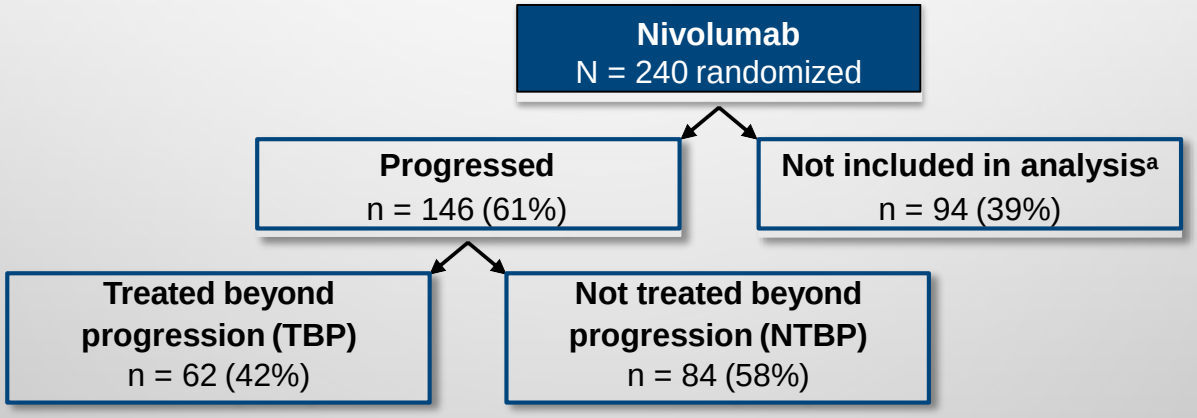
Nivo	240	169	132	98	76	45	27	12	3	0
IC	121	88	51	32	22	9	4	3	0	0

IC = investigator's choice

Gillison ML, et al. *J Clin Oncol* 2017;35(suppl): abstract 6019.

TREATMENT BEYOND PROGRESSION SUBGROUPS

- Treatment beyond first RECIST 1.1-defined progression was permitted in the nivolumab arm based on the following predefined, protocol-specified criteria:
  - Investigator-assessed clinical benefit
  - No rapid disease progression
  - Tolerance of nivolumab
  - Stable performance status
  - No delay of an imminent intervention to prevent serious complications of disease progression
  - Provided informed consent prior to receiving any additional nivolumab treatment

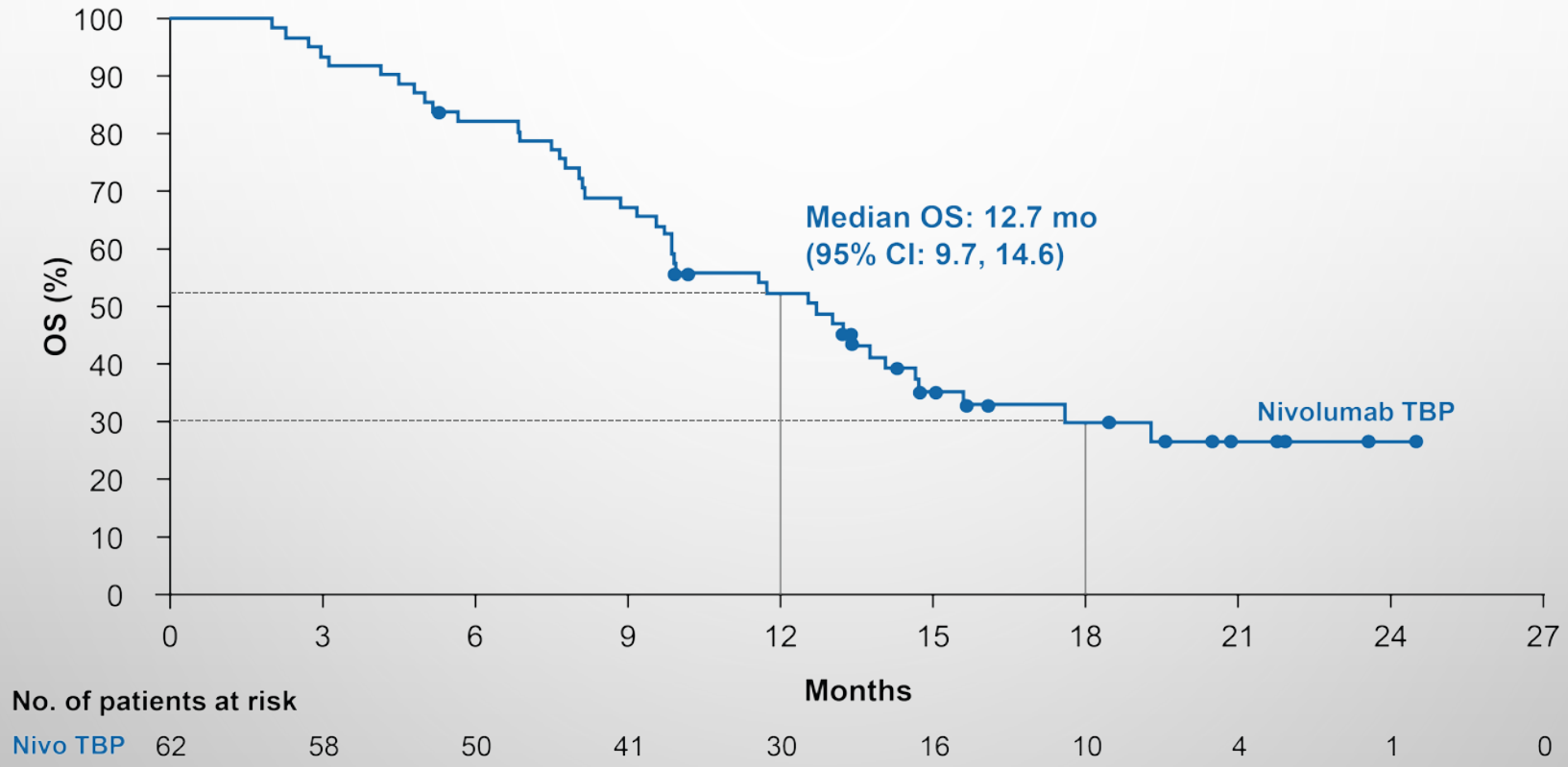


[a]Includes patients who were not treated, those without progression, and those who died or discontinued without a tumor assessment to determine progression

CHARACTERISTICS OF PATIENTS AT FIRST PROGRESSION

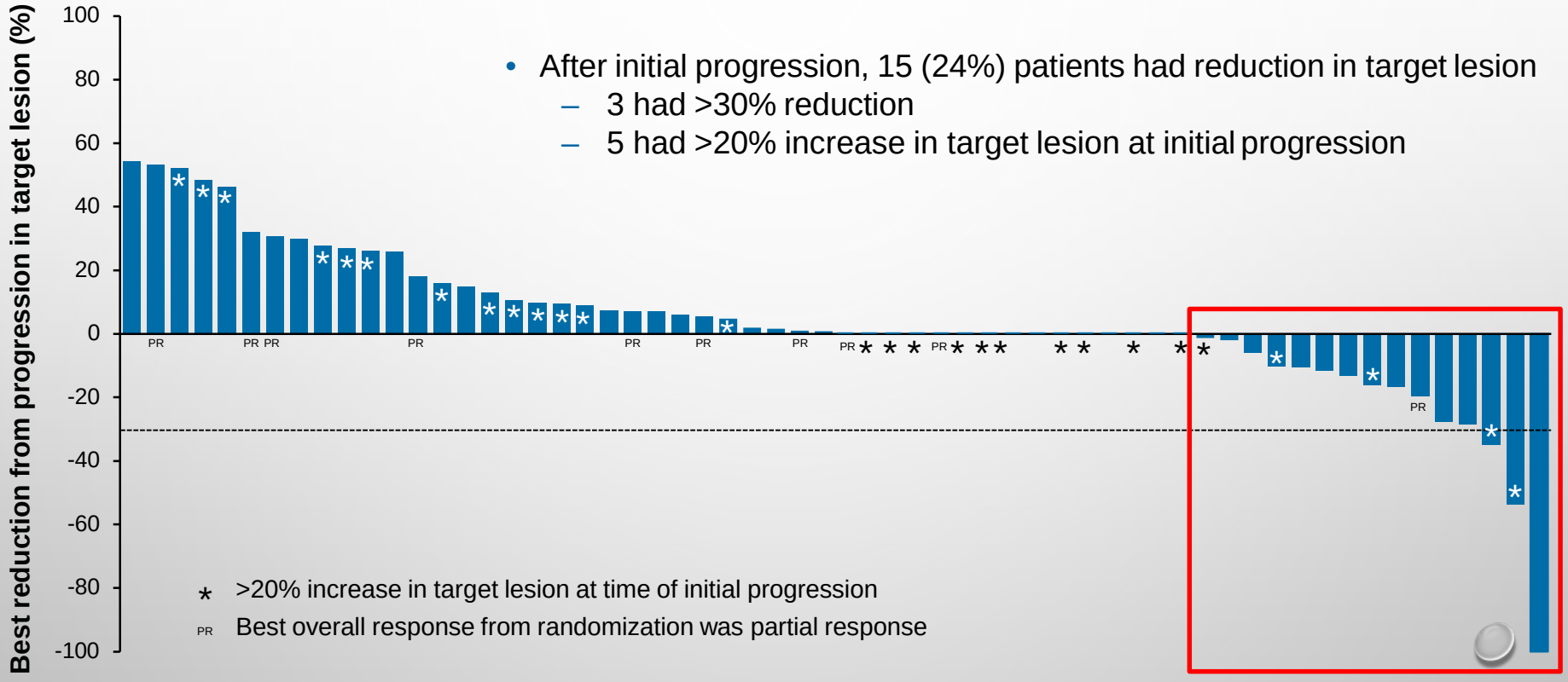
	Treated beyond progression (n = 62)	Not treated beyond progression (n = 84)
ECOG PS, n (%)		
0	22 (35.5)	11 (13.1)
1	40 (64.5)	32 (38.1)
2	0	7 (8.3)
Not recorded	0	34 (40.5)
Type of RECIST progression, n (%)		
Target lesion	38 (61.3)	47 (55.9)
New lesion	3 (4.8)	4 (4.8)
Both	21 (33.9)	33 (39.3)

OVERALL SURVIVAL, PATIENTS TREATED BEYOND PROGRESSION



TUMOR REDUCTION IN PATIENTS TREATED BEYOND PROGRESSION

- After initial progression, 15 (24%) patients had reduction in target lesion
  - 3 had >30% reduction
  - 5 had >20% increase in target lesion at initial progression



SAFETY

	Treated beyond progression (n = 62)		Not treated beyond progression (n = 84)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE, n (%)[a]	48 (77.4)	9 (14.5)	51 (60.7)	12 (14.3)
TRAEs in >10% of patients, n (%)				
Fatigue	10 (16.1)	1 (1.6)	17 (20.2)	2 (2.4)
Rash	10 (16.1)	0	6 (7.1)	0
Pruritus	9 (14.5)	0	3 (3.6)	0
Anemia	3 (4.8)	1 (1.6)	9 (10.7)	2 (2.4)
Decreased appetite	3 (4.8)	0	10 (11.9)	0
Select TRAEs, n (%)				
Skin	19 (30.6)	0	10 (11.9)	0
Endocrine	8 (12.9)	0	8 (9.5)	0
Gastrointestinal	6 (9.7)	0	8 (9.5)	1 (1.2)
Hepatic	3 (4.8)	0	2 (2.4)	1 (1.2)
Pulmonary	2 (3.2)	0	3 (3.6)	1 (1.2)
Hypersensitivity/infusion reaction	1 (1.6)	0	1 (1.2)	0
Renal	1 (1.6)	0	0	0

- Frequencies of grade 3–4 TRAEs were similar in both subgroups

[a]Events reported between first dose and 30 days after last dose of study therapy
TRAEs = treatment-related adverse events

CONCLUSIONS

- Nivolumab treatment beyond progression in patients with R/M SCCHN showed:
  - Evidence of subsequent tumor reduction in 24% of patients (15/62)
  - Median OS of 12.7 months
  - No increase in safety signals

- Treatment beyond progression with nivolumab can be considered in select patients with R/M SCCHN

Summary of IO Efficacy Data in R/M HNSCC

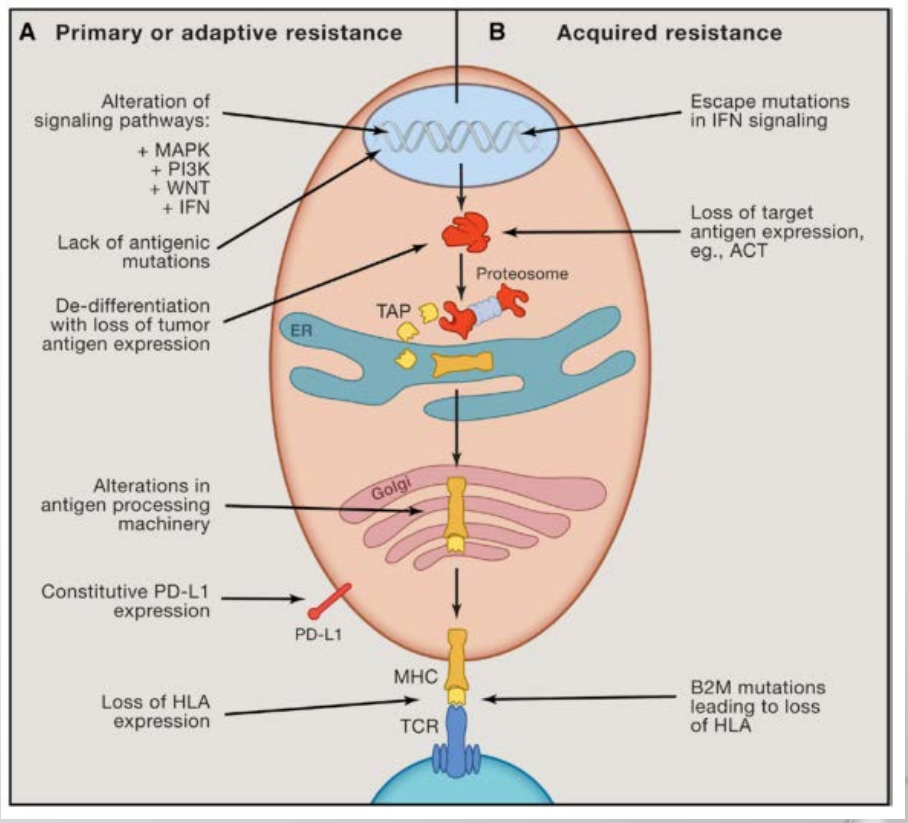
	CheckMate 141[1] all comers		KEYNOTE 040[2] all comers		Study 1108[3] all comers	HAWK[4] PD-L1 + only	NCT01375842[5] all comers
Treatment	**Nivo N = 240**	SOC N = 121	**Pembro N = 247**	SOC N = 248	**Durva N = 62**	**Durva N = 111**	**Atezo N = 32**
ORR, %	**13.3**	5.8	**14.6**	10.1	**11**	**16.2**	**22**
mPFS, mo	**1.0**	2.3	**2.1**	2.3		**2.1**	**2.6**
mOS, mo	**7.7**	5.1	**8.4**	7.1	**8.9**	**7.1**	**6.0**
12-mo OS rate, %	**34%**	19.7	**37.3**	27.2	**42%**	**33.6**	**36**

Nivo, nivolumab; pembro, pembrolizumab; durva, durvalumab; atezo, atezolizumab; SOC, standard of care

1. Ferris RL, et al. *N Engl J Med.* 2016;375(19):1856-1867. 2. Cohen EE, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract LBA45_PR. 3. Segal NH, et al. *Ann Oncol.* 2016;27(Suppl 6): Abstract 949O. 4. Zandberg D, *et al. Ann Oncol.* 2017;28(Suppl 5):Abstract 1042O. 5. Bahleda R, et al. *Ann Oncol.* 2017;28(Suppl 5):Abstract 1044O.

Resistance to Immunotherapy

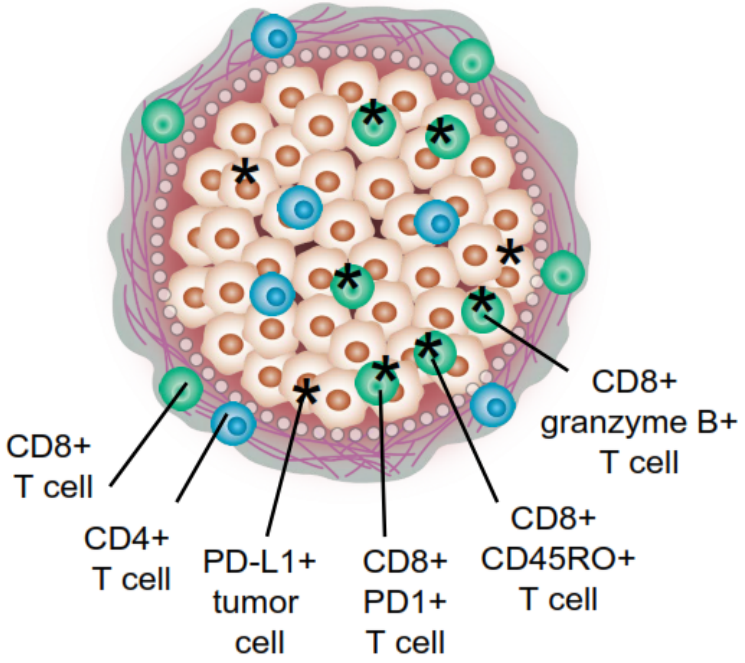
Resistance	Description
Primary	• **Lack of response to initial immunotherapy** • **Tumor not recognized by immune system** • **May include adaptive immune resistance**
Adaptive	• **Tumor recognized by the immune system but protects itself by adaptation** • **Due to evolving nature of the immune system/cancer cell interaction, this can manifest as primary resistance, mixed response, or acquired resistance**
Acquired	• **Tumor initially responds to immunotherapy, but loss of response occurs after a period of time, and tumor relapses/progresses**



Sharma P, et al. *Cell*. 2017;168(4):707-723.

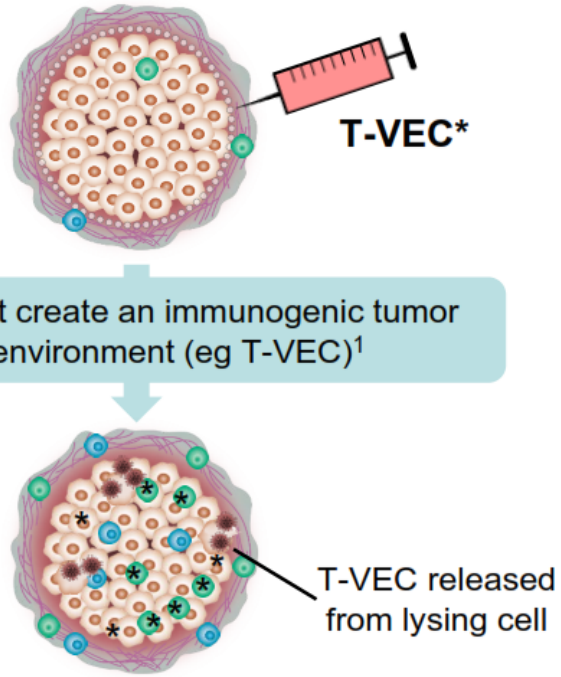
Oncolytic Viruses As Immunomodulators

Immunogenic tumor microenvironment – a 'hot' tumor[1,2]



- Immune-checkpoint inhibitors[1]
- T-VEC[3]

Nonimmunogenic tumor microenvironment – a 'cold' tumor[1,2]

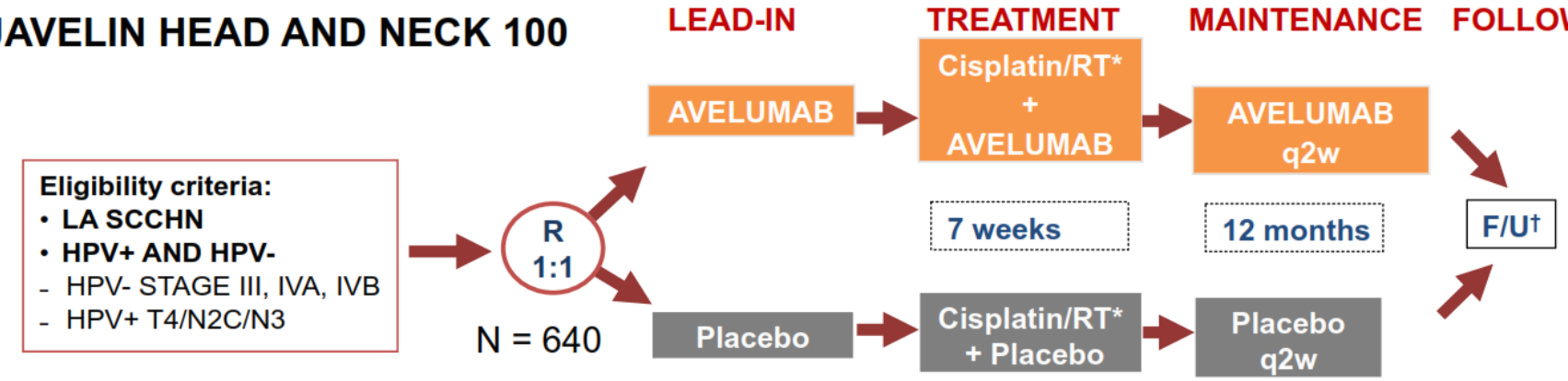


- Potential to combine T-VEC with immune-checkpoint inhibitors[1,3]

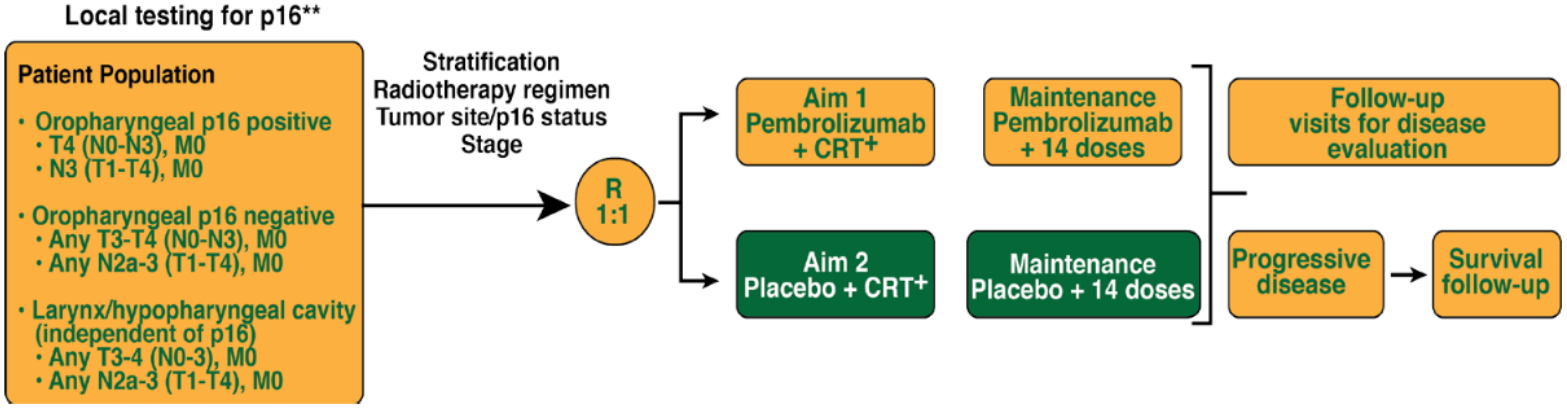
1. Sharma P, et al. *Science.* 2015;348(6230):56-61. 2. Wargo JA, et al. *Curr Opin Immunol.* 2016;41:23-31. 3. Lichty BD, et al. *Nat Rev Cancer.* 2014;14(8):559-567.

SCCHN: PD-L1/PD-1 Plus CRT

JAVELIN HEAD AND NECK 100



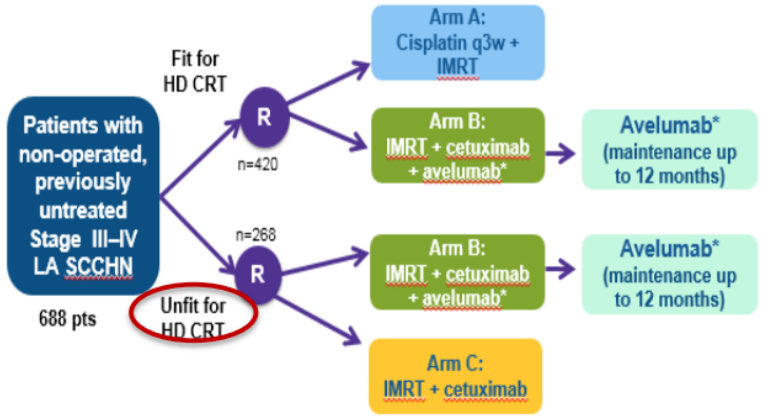
KEYNOTE-412



** Expression of P16 is highly correlated with HPV in oropharyngeal cancer. Tumors outside the oropharynx are considered HPV- regardless of results of p16 staining.
+ Chemotherapy: cisplatin 100 mg/m^2 x 3; RT: accelerated fractionation 200 cGY/6 per week, standard fractionation 200 cGy/5 per week

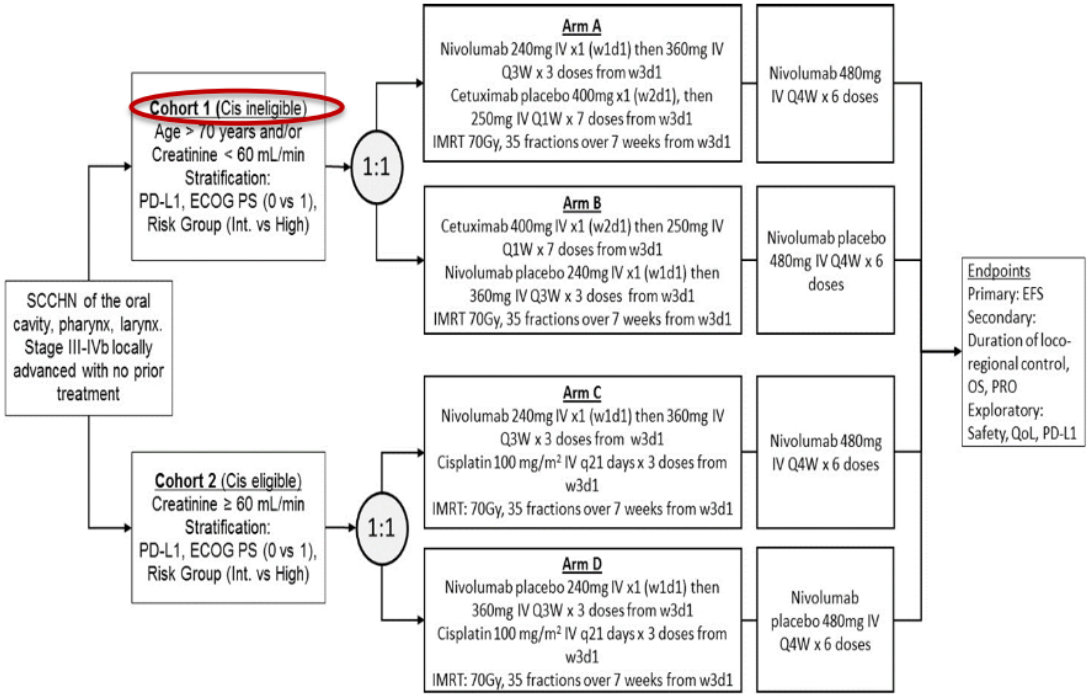
SCCHN: PD-L1/PD-1 Plus Cetuximab + RT

REACH (NCT02999087)



Primary endpoint: PFS

NCT03349710



Role of neoadjuvant/adjuvant immunotherapy remains to be seen

Ongoing Phase III Studies With Immune Checkpoint Inhibitors in First-Line R/M HNSCC vs Standard of Care

Trial Name (NCT #)	Immunotherapy Agent(s) in Study	Phase	Population	Treatment Arms
CheckMate 651 (NCT02741570)	**Nivolumab, Ipilimumab**	**III**	**Previously untreated R/M HNSCC, ≥6 months since last dose of platinum**	**Nivolumab + Ipilimumab vs EXTREME**
KEYNOTE-048 (NCT02358031) completed accrual	**Pembrolizumab**	**III**		**Pembrolizumab vs Pembrolizumab + Platinum/5FU vs EXTREME**
KESTREL (NCT02551159) completed accrual	**Durvalumab Tremelimumab**	**III**		**Durvalumab vs Durvalumab + tremelimumab vs EXTREME**

Key Take-Home Messages

- **EXTREME regimen (platinum/5FU/cetuximab → cetuximab) is standard first-line treatment for R/M HNSCC, recommended by international guidelines**
- **Nivolumab and pembrolizumab are new standard-of-care options for patients with R/M HNSCC after platinum-based therapy**

  In asymptomatic patients with no rapid progression, immune checkpoint can be continued until further radiographic assessment in 8 weeks
- **PD-L1 can not be used as a biomarker in SCCHN**
- **PD-1/PD-L1 inhibitors are in general well tolerated, but irAEs can develop; early recognition and management are important**
- **Several trials are ongoing investigating immunotherapy alone and in combinations in first-line therapy of R/M HNSCC**

QUESTIONS?