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Immunotherapy in head and neck cancer and MSI in solid tumors

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»No disclosures

Objectives

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- Discuss the role of immunology in head and neck cancer
- Overview of FDA-approved current immunotherapeutic agents for head and neck cancer – ESMO & AACR updates
- Future immunotherapeutic options for patients with head & neck cancer

Background

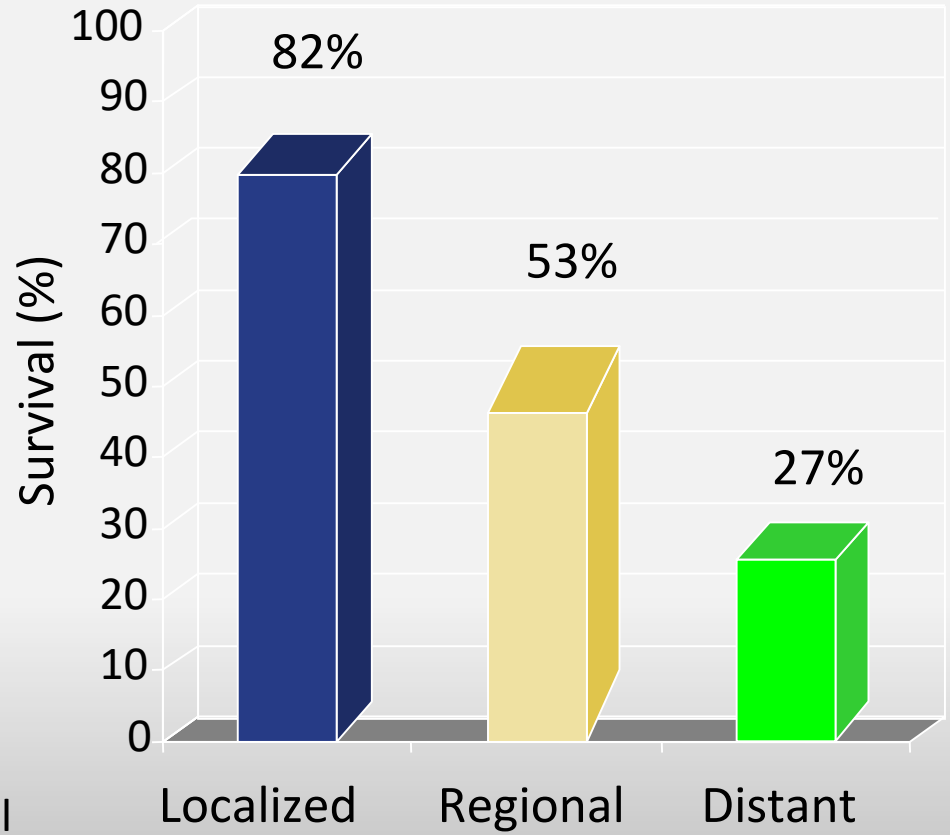
- Head and neck cancer (HNC) is 6th most common cancer worldwide
  - 60,000 new cases per year in the United States
- Human Papilloma Virus (HPV) is involved in the etiology of Oropharyngeal HNC – but typically NOT other sites
  - ~70% of OP HNC are HPV(+)
- Predominant loco-regional presentation ➔ curative intent therapy
  - Goal 1: Improve Survival / cure rates
  - Goal 2: Organ preservation
- Distant metastasis (at presentation) are uncommon
  - 10-15% present with distant metastasis
  - Goal: improve survival / palliative intent

HNC: Prognosis

- High cures rates are achieved for localized and loco-regional disease using combined modality approaches
  - Chemoradiation (CRT)
  - Surgery + Chemoradiation
    - +/- induction chemotherapy (+immunotherapy?)
- Survival rates for recurrent/metastatic disease remain poor
  - Little progress over past 20 years – until recently
  - Addition of Cetuximab improves survival by 2-3 months
  - New agents – Immunotherapy

"EXTREME" standard of care

5-year relative survival rate by stage at diagnosis



ACS, 2010a, 2009.

The fourth modality

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- »Surgery
- »Radiation therapy
- »Chemotherapy
- »Immunotherapy

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FDA Approves Pembrolizumab for Head and Neck Cancer

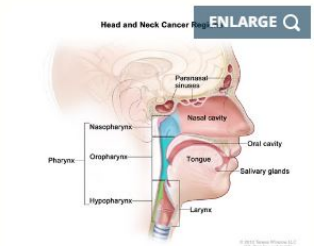
Subscribe

August 24, 2016, by NCI Staff

The Food and Drug Administration (FDA) approved pembrolizumab (Keytruda®) on August 5 for the treatment of some patients with an advanced form of head and neck cancer. The approval is for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) that has continued to progress despite standard-of-care treatment with chemotherapy.

This is the third indication for which the drug has been approved. Pembrolizumab, part of a class of drugs known as immune checkpoint inhibitors, has also been approved to treat some patients with advanced melanoma and lung cancer.

The FDA granted accelerated approval based on early data from 174 patients with HNSCC enrolled in the nonrandomized KEYNOTE-012 trial. These patients had HNSCC that continued to grow and spread despite treatment with a platinum-containing chemotherapy; the majority of patients in the trial previously had received at least two different courses of treatment.



On August 5, the FDA approved the immunotherapy drug pembrolizumab for some patients with head and neck cancer.
Credit: Terese Winslow

Pembrolizumab (Anti-PD-1 mab)- August 5th, 2016
Patients with Recurrent or Metastatic HNSCC with Disease Progression on or after Platinum-Containing Chemotherapy (KEYNOTE-012)

FDA Approves Nivolumab for Head and Neck Cancer

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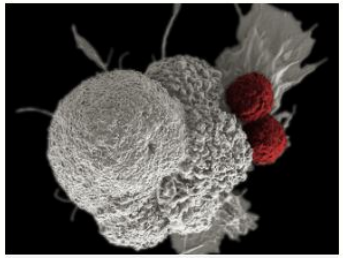
December 1, 2016, by NCI Staff

The Food and Drug Administration (FDA) approved nivolumab (Opdivo®) on November 10 for the treatment of squamous cell cancer of the head and neck (SCCHN).

Nivolumab is already approved for the treatment of several other cancers. This new approval is for the use of nivolumab in patients with SCCHN that has progressed during chemotherapy with a platinum-based drug or that has recurred or metastasized after platinum-based chemotherapy.

Nivolumab is the second immunotherapy drug approved to treat SCCHN. In August of this year, the FDA approved pembrolizumab (Keytruda®) for patients with SCCHN whose disease has progressed during or after platinum-containing chemotherapy. Both nivolumab and pembrolizumab are immune checkpoint inhibitors, drugs that prevent tumor cells from blocking attack by the immune system.



Cytotoxic T cells (red) attacking an oral squamous cancer cell (white). Immune checkpoint inhibitors like nivolumab prevent tumors from turning off T cells, allowing them to attack and kill the tumor cells.
Credit: National Cancer Institute

Nivolumab (Anti-PD1 mab)- November 10, 2016
Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck with Disease Progression on or after a Platinum-Based Therapy (CheckMate 141)

Pembrolizumab
KEYNOTE-012

KEYNOTE-012

Mehra, R. ASCO 2016. Clinical Science Symposium

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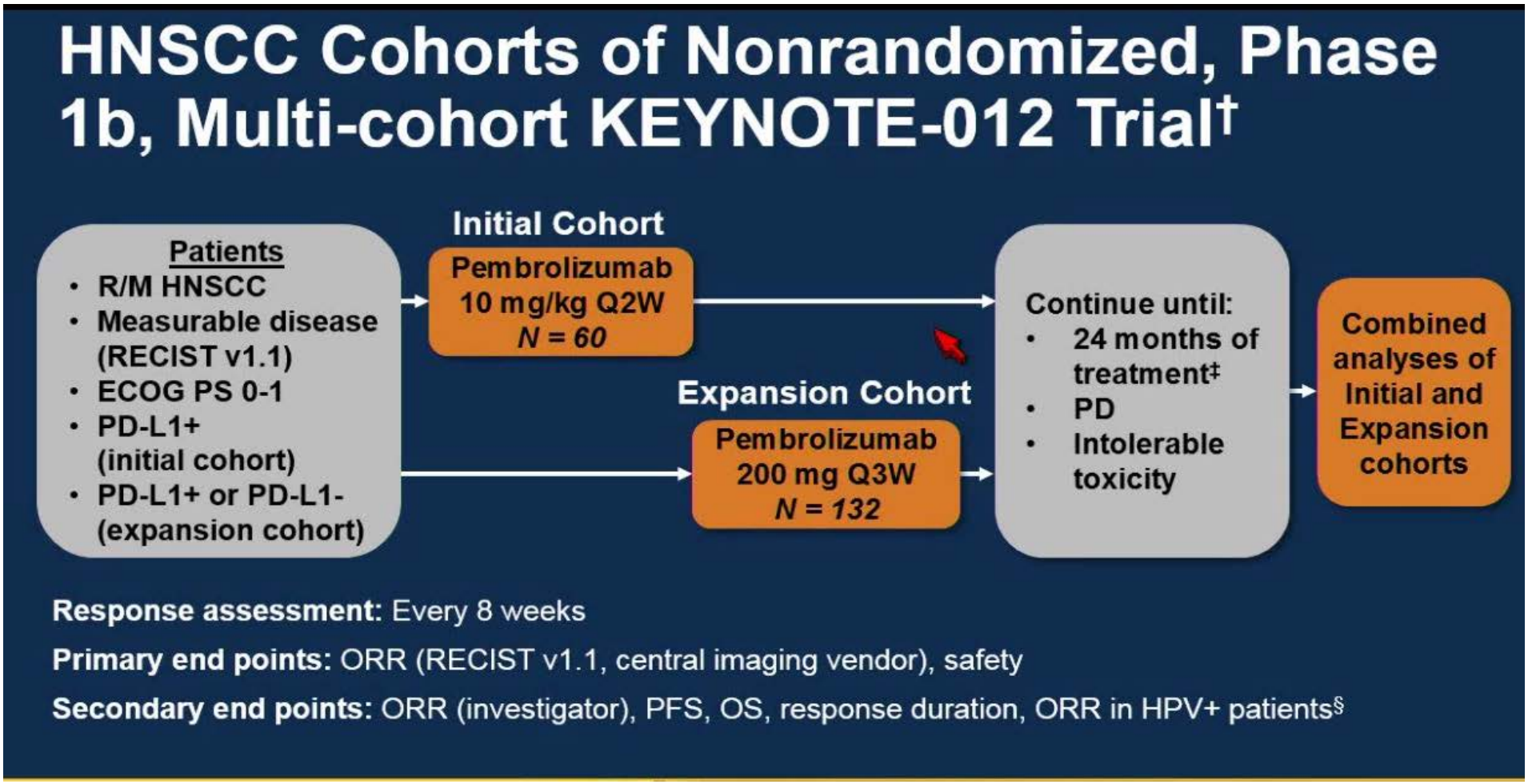

KEYNOTE-012 ORR

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Overall Response Rate

Best Overall Response	Total N = 192†			HPV+ n = 45‡			HPV– n = 147‡		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
ORR	**34**	**18**	**13–24**	**11**	**24**	**13–40**	**23**	**16**	**10–23**
CR	8	4	–	4	9	–	4	3	–
PR	26	14	–	7	16	–	19	13	–
SD	33	17	–	7	16	–	26	18	–
PD	93	48	–	19	42	–	74	50	–
NA§	32	17	–	8	18	–	24	16	–

Data cutoff date: Apr 26, 2016. Response assessed per RECIST v1.1 (central imaging vendor review, all patients as treated). Only confirmed responses are included.
†Includes patients who received ≥1 dose of pembrolizumab in the initial or expansion cohort.
‡HPV status was determined by the local institution. Cancers outside the oropharynx, identified from primary diagnosis/prior radiation/prior surgery, were considered HPV negative.
§No assessment because patient did not have central imaging review data or images were not evaluable.

KEYNOTE 012
PFS & OS

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KEYNOTE 012
Best Change from Baseline in Tumor size

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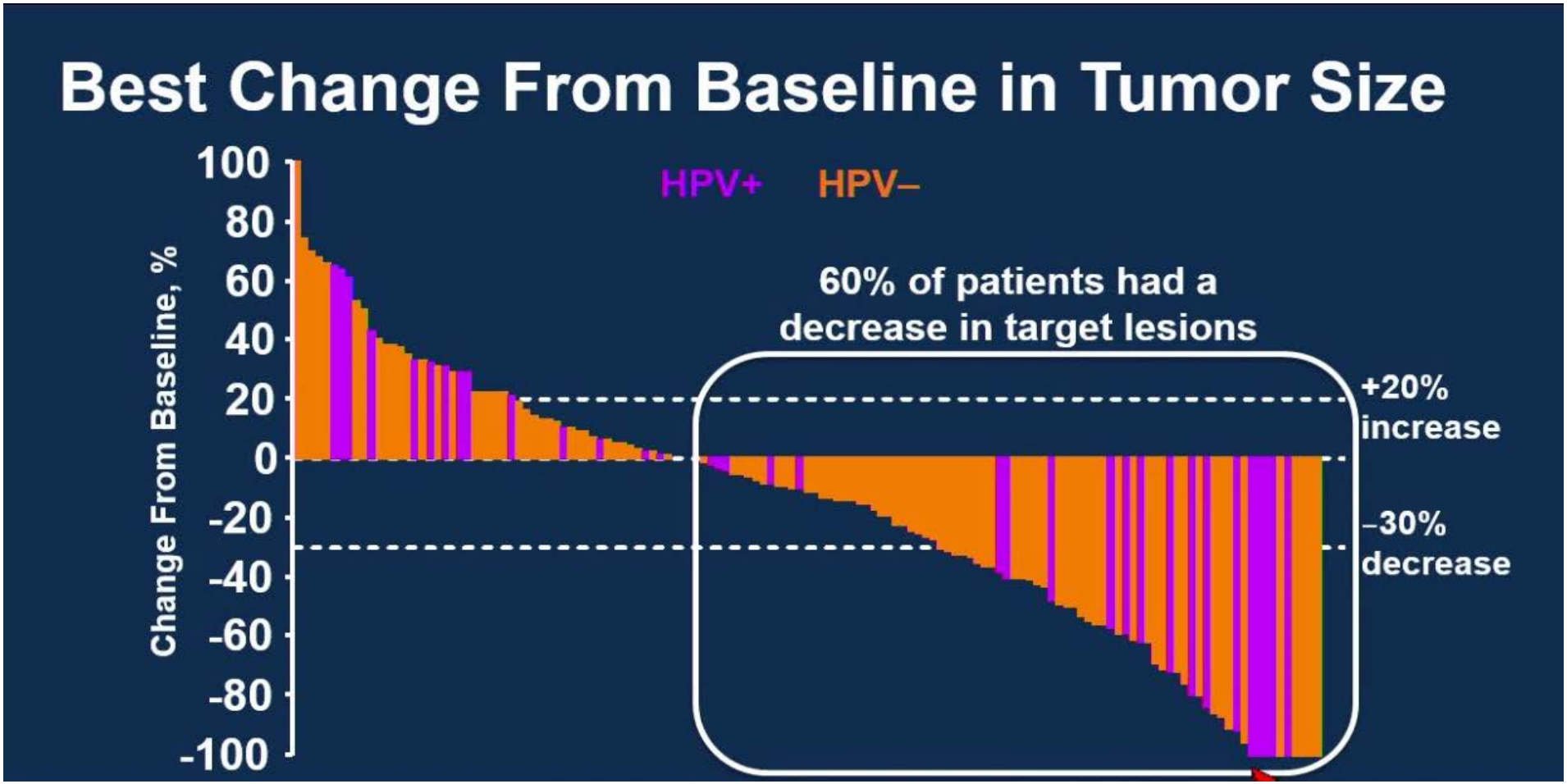

Duration of Response in Responders
Swimmer plot

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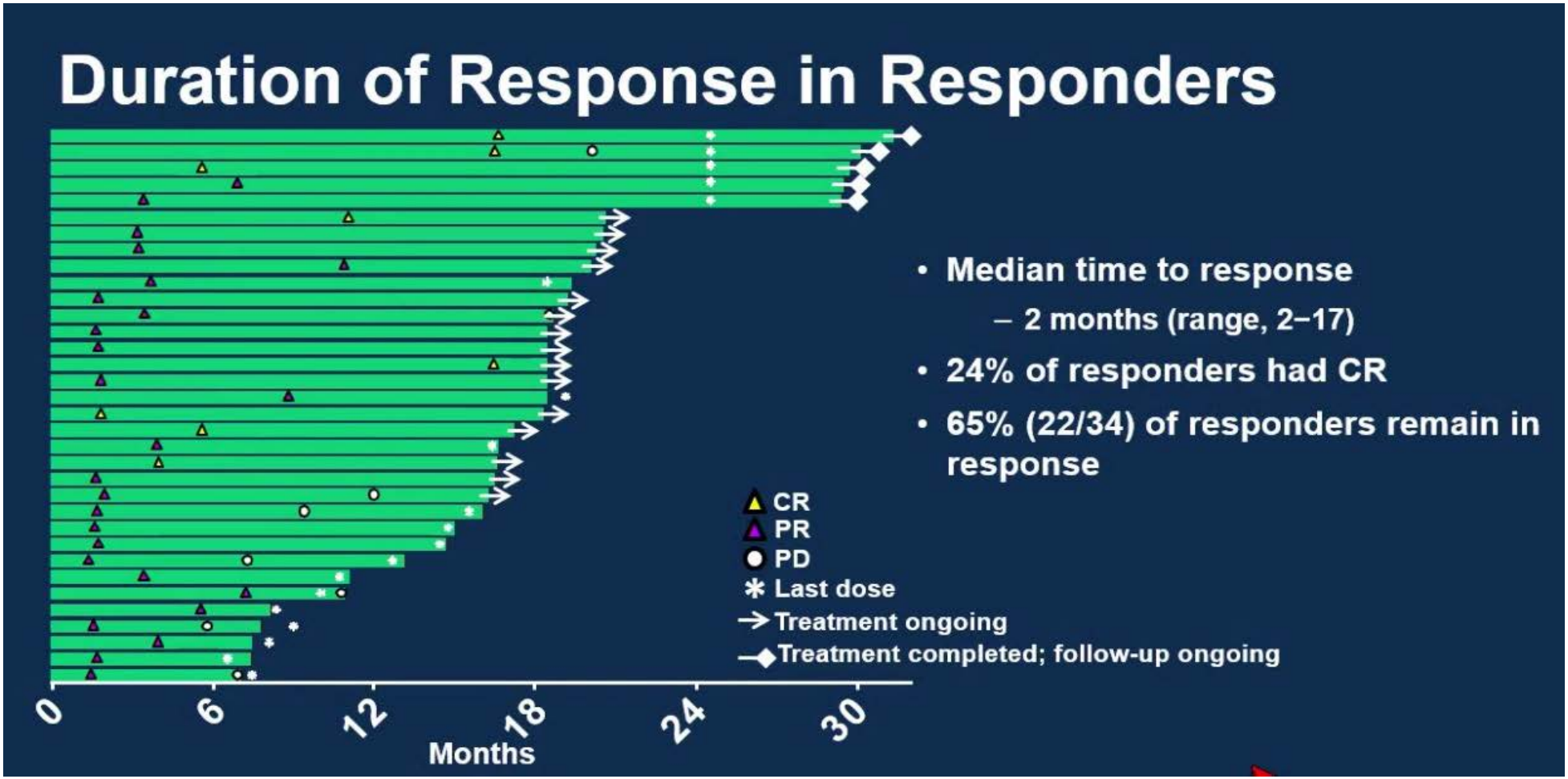

KEYNOTE-012
Duration of Response

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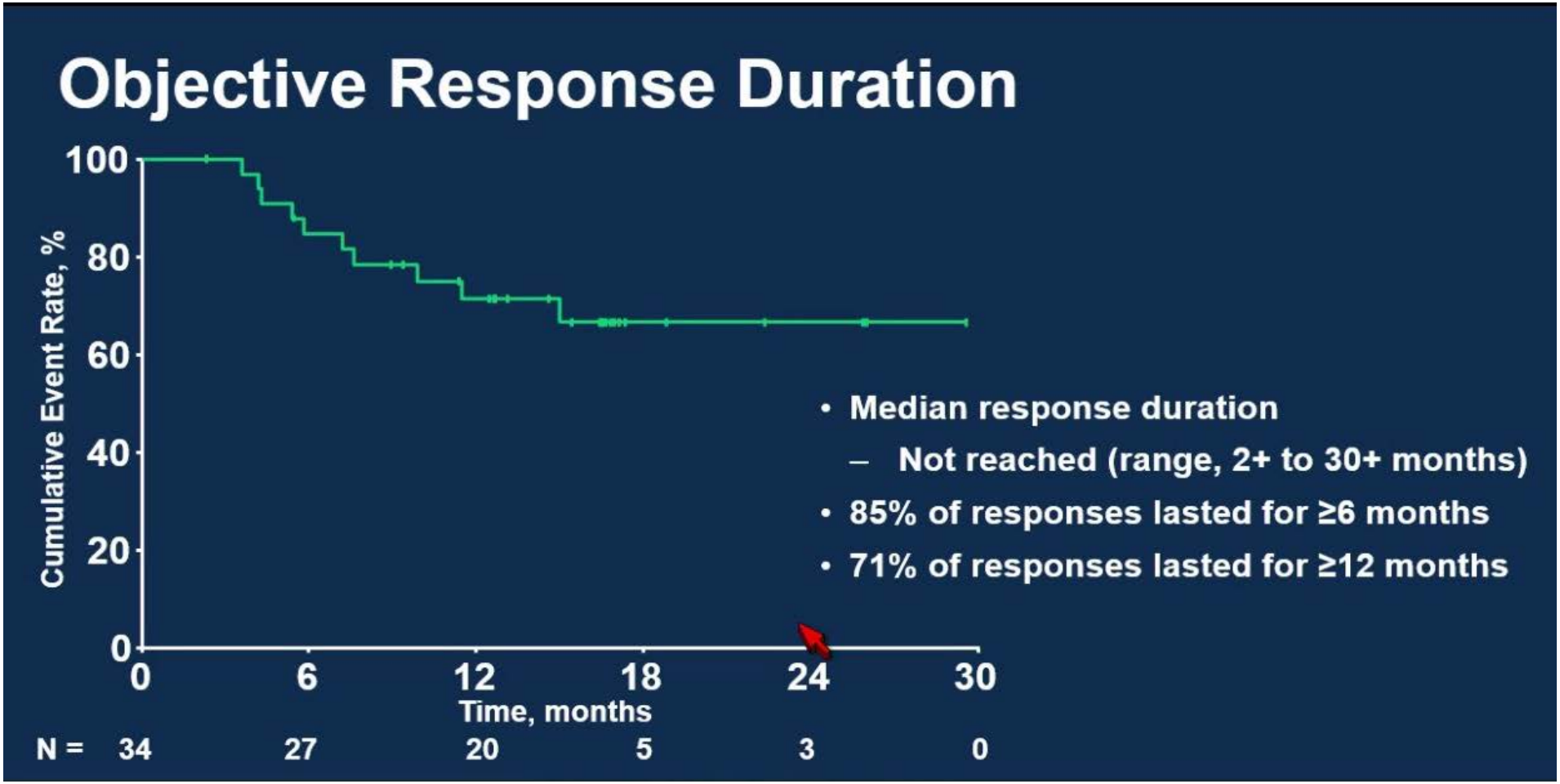

KEYNOTE-012 AE

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Treatment-Related Adverse Events

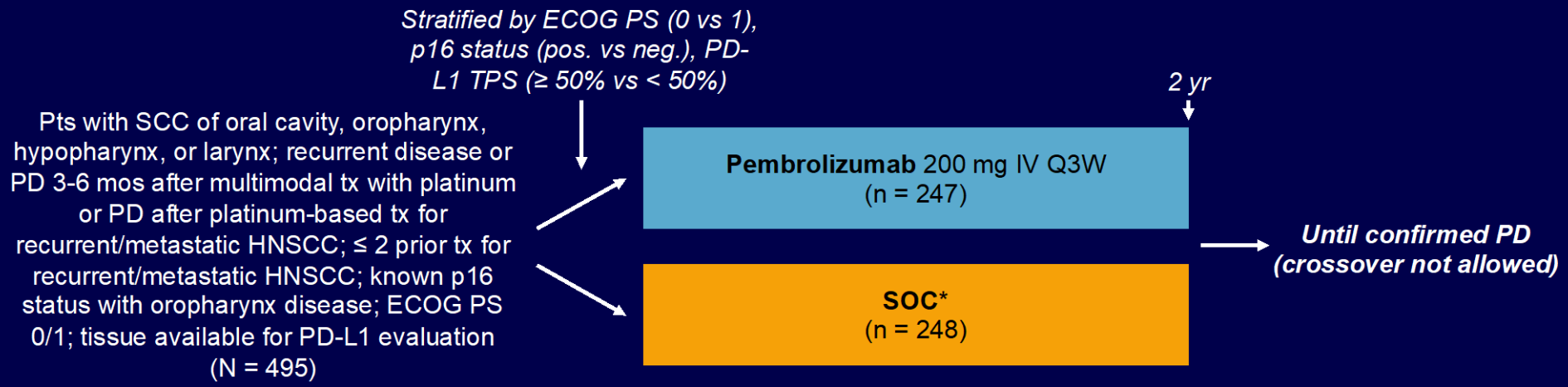
Any Grade With Incidence ≥5%	N = 192† n (%)
Any	123 (64)
Fatigue	42 (22)
Hypothyroidism	19 (10)
Rash	18 (9)
Pruritus	16 (8)
Decreased appetite	16 (8)
Pyrexia	12 (6)
Nausea	11 (6)

- Median (range) time on pembrolizumab
  - 9 months (<1-32 months)

Grade 3-4 in ≥2 Patients	N = 192† n (%)
Any	24 (13)
ALT increase	3 (2)
AST increase	3 (2)
Fatigue	2 (1)
Decreased appetite	2 (1)
Hyponatremia	2 (1)
Pneumonitis	2 (1)
Facial swelling	2 (1)
Hypothyroidism	2 (1)

- No deaths due to treatment-related AEs
- 12 (6%) patients discontinued due to a treatment-related AE

Pembrolizumab vs SoC in Recurrent or Metastatic HNSCC (KEYNOTE-040)



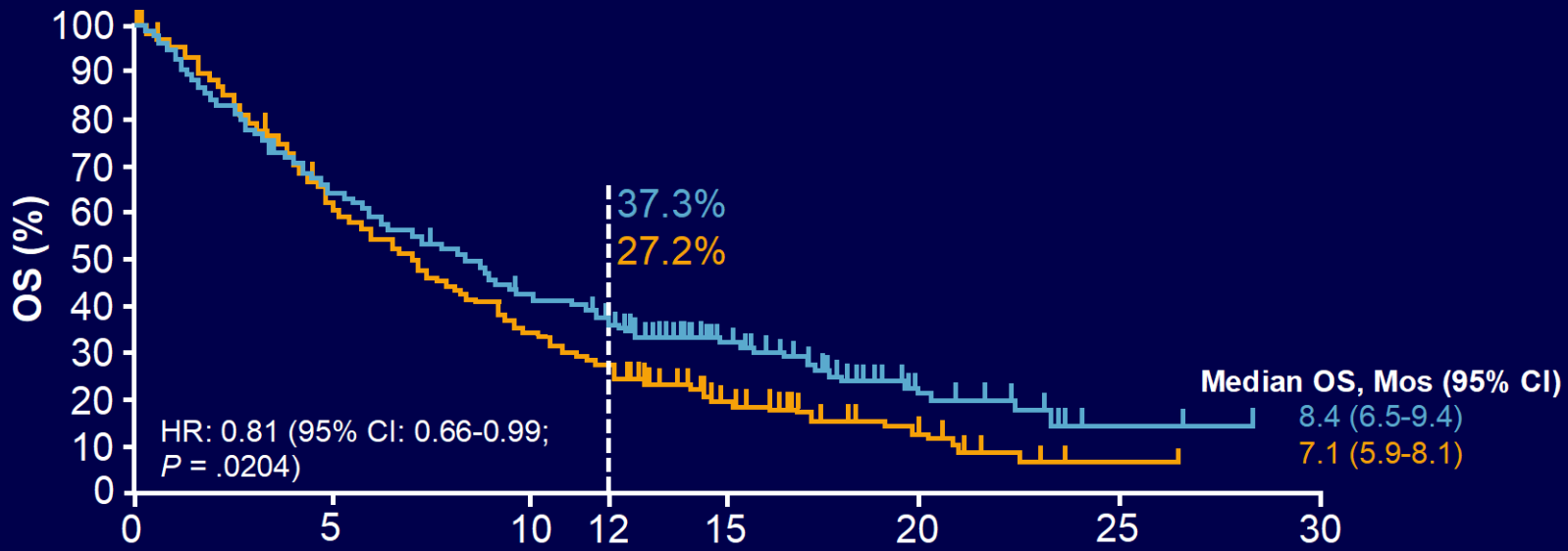
*Investigator's choice of methotrexate 40 mg/m^2 weekly (in absence of toxicity could increase to 60 mg/m^2), docetaxel 75 mg/m^2 Q3W, or cetuximab loading dose of 400 mg/m^2 followed by 250 mg/m^2 weekly.

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

Cohen EE, et al. ESMO 2017. Abstract LBA45_PR.

Slide credit: clinicaloptions.com

KEYNOTE-040: OS in ITT Population



Pts at Risk, n							
Pembro	247	159	103	48	14	2	0
SoC	248	148	82	34	10	1	0

- Prespecified significance boundary not reached (*P* = .0175)

Cohen EE, et al. ESMO 2017. Abstract LBA45_PR. Reproduced with permission.

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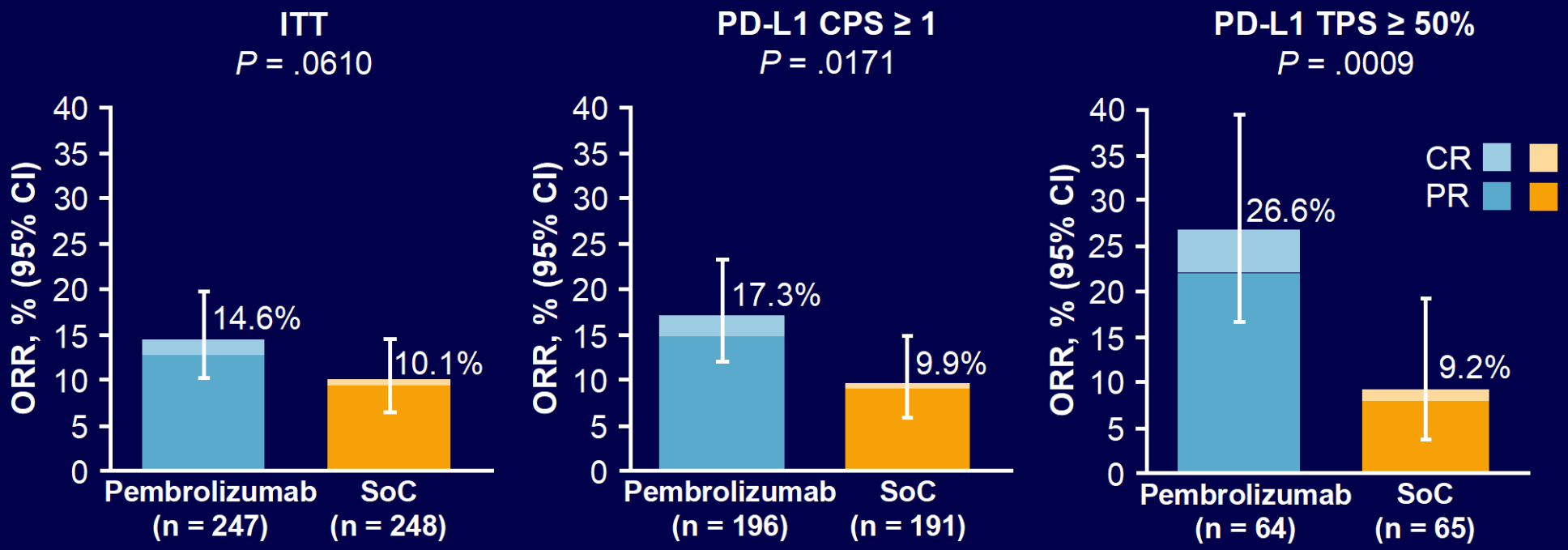
KEYNOTE-040: Response



- Median DoR longer with pembrolizumab vs SoC (18.4 vs 5.0 mos)

Cohen EE, et al. ESMO 2017. Abstract LBA45_PR. Reproduced with permission.

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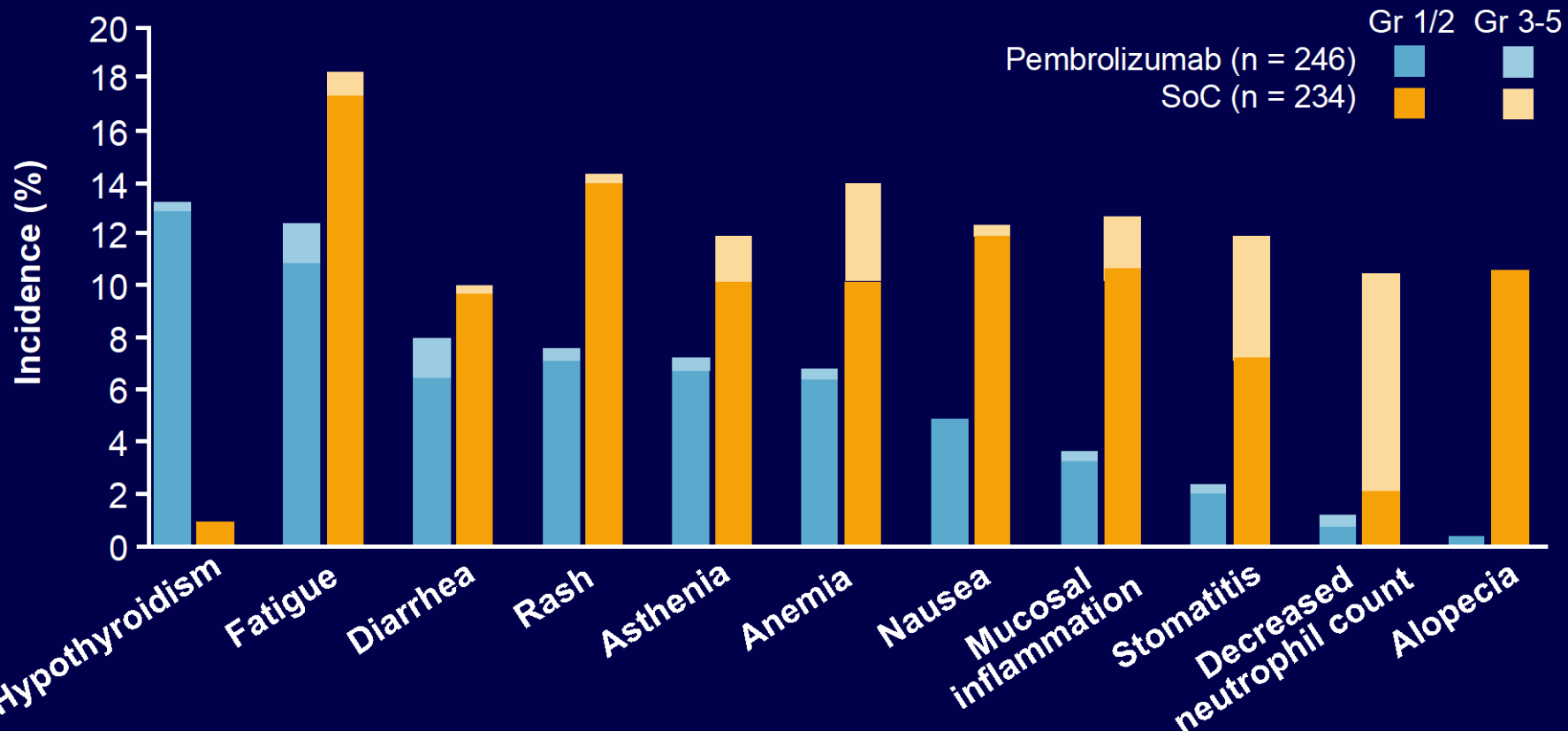
KEYNOTE-040: Treatment-Related AEs (≥ 10% Incidence)



Cohen EE, et al. ESMO 2017. Abstract LBA45_PR. Reproduced with permission.

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AACR 2018

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- »Mature OS data benefit (median, 8.4 months vs. 6.9 months; HR = 0.8; 95% CI, 0.65-0.98)
- »PFS benefit was not statistically significant (median, 2.1 months vs. 2.3 months; HR = 0.96; 95% CI, 0.79-1.16)
- »Pts with PDL >1, statistically significant OS advantage (median, 8.7 months vs. 7.1 months; HR = 0.58-0.93).
- »PDL 1 > 50%, statistically significant benefits in median PFS (3.5 months vs. 2.1 months; HR = -.58; 95% CI, 0.39-0.86) and median OS (**11.6 months vs. 6.6 months**; HR = 0.53; 95% Ci, 0.35-0.81).

Nivolumab
CheckMate 141

CheckMate 141

Ferris et al. NEJM 2016: 375:1856-1867|Nov, 10, 2016

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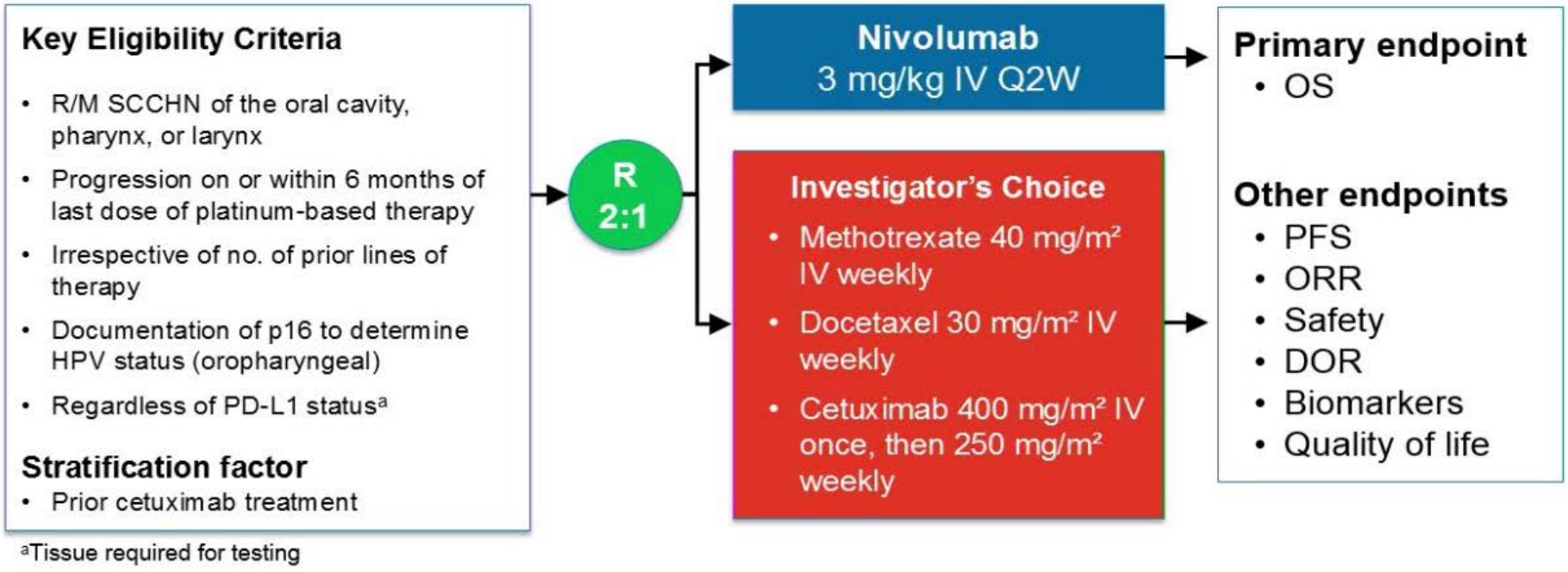
Phase 3 CheckMate 141 Study Design
Nivolumab in R/M SCCHN After Platinum Therapy

Randomized, global, phase 3 trial of the efficacy and safety of nivolumab vs investigator's choice in patients with R/M SCCHN



[a]Tissue required for testing

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

CheckMate 141
OS

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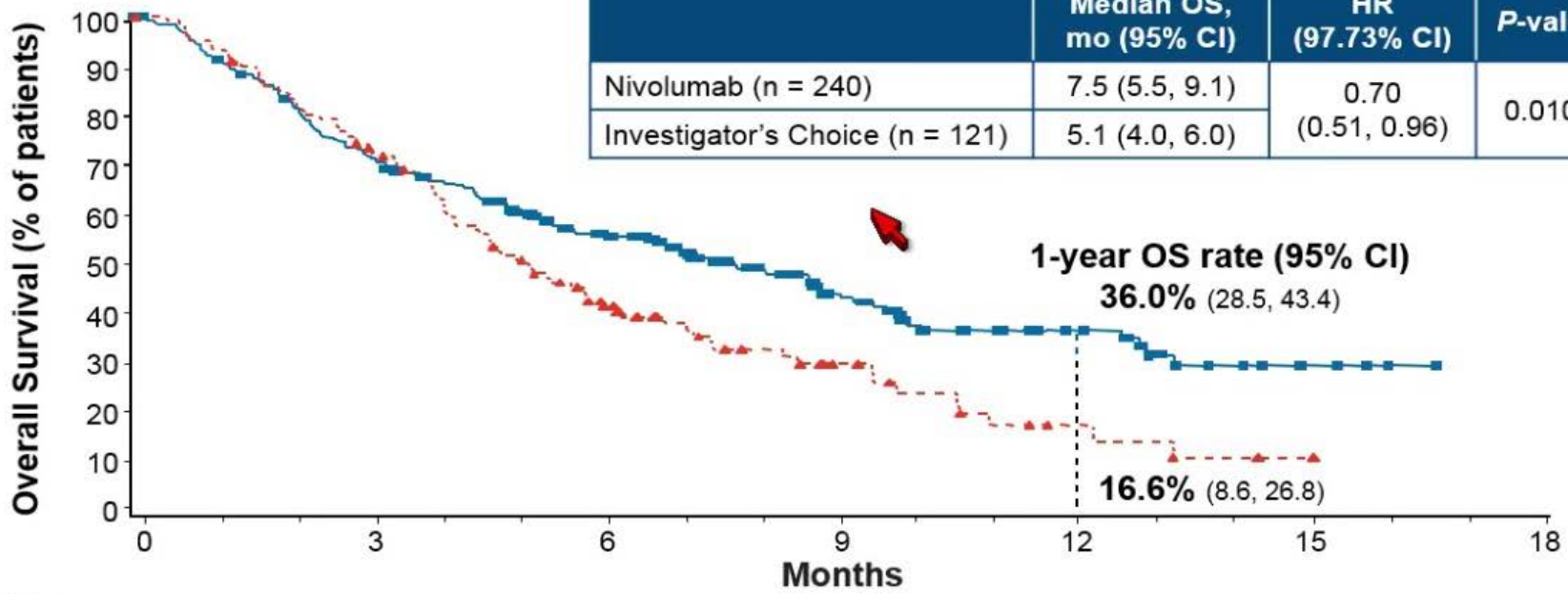
Overall Survival
Nivolumab in R/M SCCHN After Platinum Therapy

	Median OS, mo (95% CI)	HR (97.73% CI)	*P*-value
Nivolumab (n = 240)	7.5 (5.5, 9.1)	0.70 (0.51, 0.96)	0.0101
Investigator's Choice (n = 121)	5.1 (4.0, 6.0)		



No. at Risk							
Nivolumab	240	167	109	52	24	7	0
Investigator's Choice	121	87	42	17	5	1	0

The response rate was 13.3% in the nivolumab group versus 5.8% in the standard-therapy group

CheckMate 141
PFS

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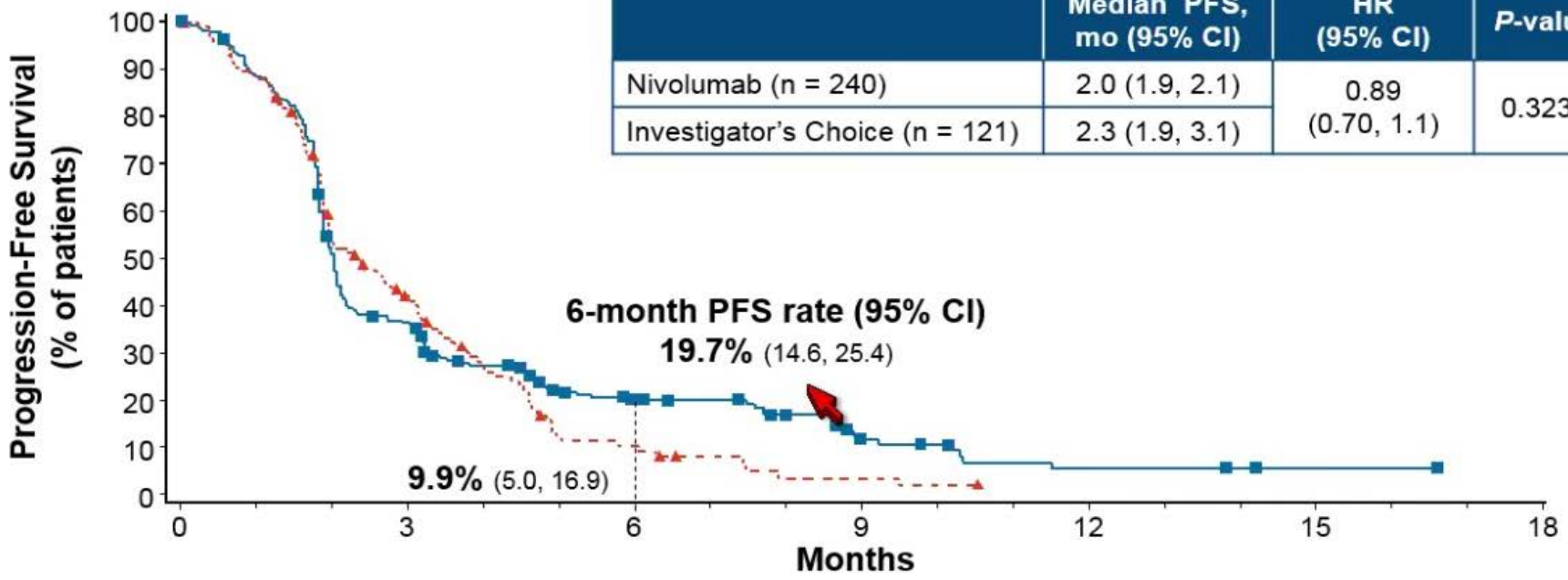
Progression-Free Survival
Nivolumab in R/M SCCHN After Platinum Therapy

	Median PFS, mo (95% CI)	HR (95% CI)	*P*-value
Nivolumab (n = 240)	2.0 (1.9, 2.1)	0.89 (0.70, 1.1)	0.3236
Investigator's Choice (n = 121)	2.3 (1.9, 3.1)		



No. at Risk							
Nivolumab	240	79	32	12	4	1	0
Investigator's Choice	121	43	9	2	0	0	0

CheckMate 141 AES

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Treatment-Related Adverse Events

Nivolumab in R/M SCCHN After Platinum Therapy

Event	Nivolumab (n = 236)		Investigator's Choice (n = 111)	
	Any grade n (%)	Grade 3–4 n (%)	Any grade n (%)	Grade 3–4 n (%)
Any treatment-related AE in ≥ 10% of patients[a]	139 (58.9)	31 (13.1)	86 (77.5)	39 (35.1)
Fatigue	33 (14.0)	5 (2.1)	19 (17.1)	3 (2.7)
Nausea	20 (8.5)	0	23 (20.7)	1 (0.9)
Diarrhea	16 (6.8)	0	15 (13.5)	2 (1.8)
Anemia	12 (5.1)	3 (1.3)	18 (16.2)	5 (4.5)
Asthenia	10 (4.2)	1 (0.4)	16 (14.4)	2 (1.8)
Mucosal inflammation	3 (1.3)	0	14 (12.6)	2 (1.8)
Alopecia	0	0	14 (12.6)	3 (2.7)
Treatment-related select AEs				
Skin	37 (15.7)	0	14 (12.6)	2 (1.8)
Endocrine	18 (7.6)	1 (0.4)	1 (0.9)	0
Gastrointestinal	16 (6.8)	0	16 (14.4)	2 (1.8)
Hepatic	5 (2.1)	2 (0.8)	4 (3.6)	1 (0.9)
Pulmonary	5 (2.1)	2 (0.8)	1 (0.9)	0
Hypersensitivity/infusion reaction	3 (1.3)	0	2 (1.8)	1 (0.9)
Renal	1 (0.4)	0	2 (1.8)	1 (0.9)

[a]One Grade 5 event (hypercalcemia) in the nivolumab arm and one Grade 5 event (lung infection) in the investigator's choice arm were reported. A second death occurred in the nivolumab arm subsequent to pneumonitis.

AACR 2018

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»Data with a minimum 2 year f/u

»Median overall survival (OS) was 7.7 months (95% CI, 5.7-8.8) with nivolumab compared with 5.1 months (95% CI, 4.0-6.2) for investigator's choice of therapy (HR, 0.68; 95% CI, 0.54-0.86).

»2-year OS rate was 16.9% with nivolumab (95% CI, 12.4-22.0) versus 6% in the control arm (95% CI, 2.7-11.3).

»Safety data for the two arms remained consistent with longer follow-up.

AACR 2018

- In patients with SCCHN with PD-L1 expression ≥1% there was a 45% reduction in the risk of death with nivolumab over investigator's choice (HR, 0.55; 95% CI, 0.39-0.78).
- For those with PD-L1 expression on <1% of cells, the OS benefit was less pronounced, with a 27% reduction in the risk of death (HR, 0.73; 95% CI, 0.49-1.09).

ASCO 2017 (Selected abstracts)

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- »Epacadostat plus pembrolizumab in patients with SCCHN: Preliminary phase 1/2 results from ECHO-202/KEYNOTE-037
- »Safety of pembrolizumab with chemoradiation (CRT) in locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN).

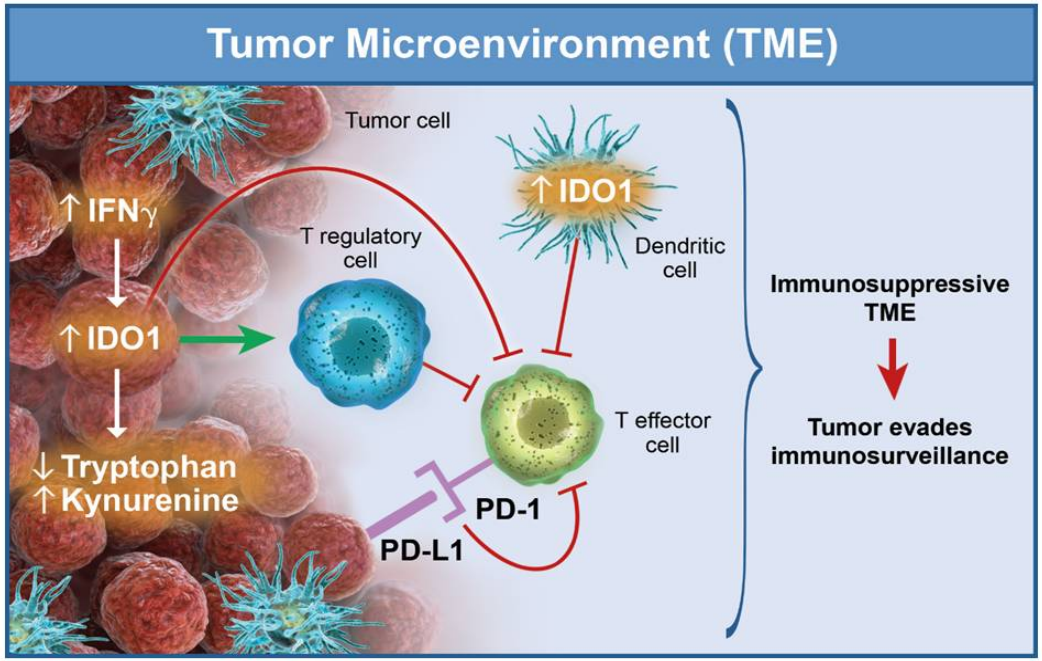
Epacadostat Plus Pembrolizumab in Patients With SCCHN: Preliminary Phase 1/2 Results From ECHO-202/KEYNOTE-037

Omid Hamid,[1] Todd M. Bauer,[2] Alexander I. Spira,[3] Anthony J. Olszanski,[4] Sandip P. Patel,[5] Jeffrey S. Wasser,[6] David C. Smith,[7] Ani S. Balmanoukian,[1] Charu Aggarwal,[8] Emmett V. Schmidt,[9] Yufan Zhao,[10] Hema Gowda,[10] Tara C. Gangadhar[8]

[1]The Angeles Clinic and Research Institute, Los Angeles, CA; [2]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [3]Virginia Cancer Specialists Research Institute, Fairfax, VA; [4]Fox Chase Cancer Center, Philadelphia, PA; [5]University of California San Diego Moores Cancer Center, La Jolla, CA; [6]University of Connecticut Health Center, Farmington, CT; [7]University of Michigan, Ann Arbor, MI; [8]Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; [9]Merck & Co., Inc., Kenilworth, NJ, USA; [10]Incyte Corporation, Wilmington, DE

Abstract #6010
Session: Clinical Science Symposium: What's Next in Immunotherapy for Head and Neck Cancer?
Presented at the ASCO Annual Meeting 2017
Chicago, IL
June 2–6, 2017

IDO1 Enzyme and Epacadostat

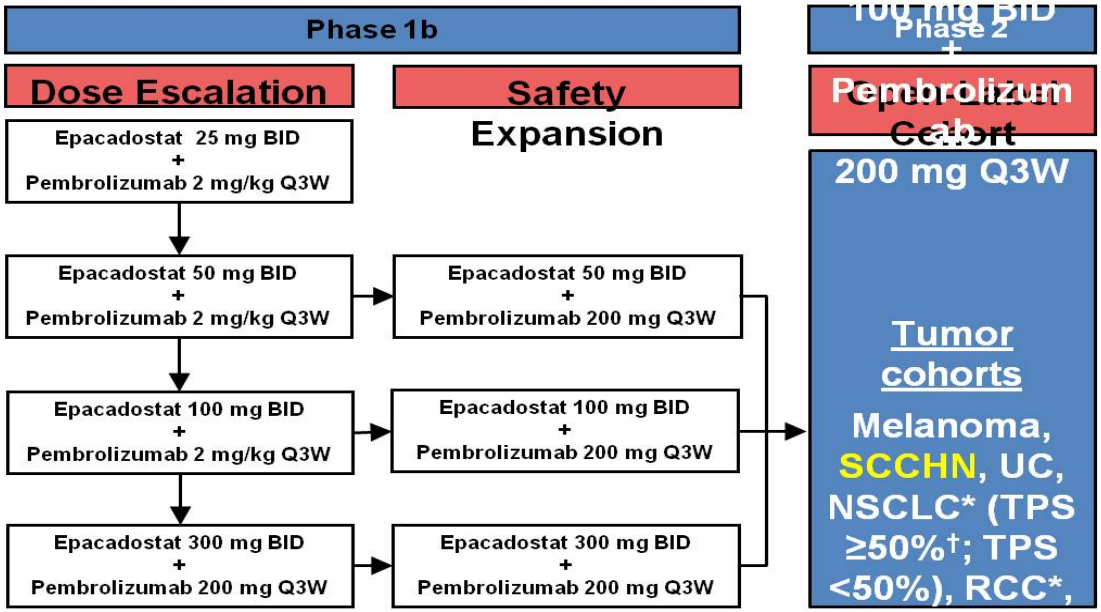


- Tumors can evade immunosurveillance through a number of mechanisms including immune checkpoint inhibition of T-cell activation and upregulation of the IDO1 enzyme
- IDO1 is an IFNγ-induced, intracellular enzyme that catalyzes the first and rate-limiting step of tryptophan degradation in the kynurenine pathway[1]
- Depletion of tryptophan and production of kynurenine and other metabolites shifts the local immune microenvironment to an immunosuppressive state[1]
- Epacadostat is a potent and specific oral inhibitor of IDO1, inhibiting tryptophan metabolism and augmenting immunosurveillance in the tumor microenvironment[2]
- Combining epacadostat with a checkpoint inhibitor may improve patient outcomes

IDO1, indoleamine 2,3 dioxygenase 1; IFNγ, interferon gamma.

1. Moon YW, et al. *J Immunother Cancer*. 2015;3:51. **2.** Liu X, et al. *Blood*. 2010;115(17):3520-3530.

ECHO-202/KEYNOTE-037: Study Design



BID, twice daily; CRC, colorectal cancer; DLBCL, diffuse large B-cell lymphoma; GC, gastric cancer; HCC, hepatocellular carcinoma; MSI, microsatellite instability; NSCLC, non-small cell lung cancer; OC, ovarian cancer; Q3W, every 3 weeks; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; TNBC, triple-negative breast cancer; TPS, tumor proportion score; UC, urothelial carcinoma.
Note: GC and HCC cohorts were not yet open for patient enrollment at data cutoff (February 27, 2017).
* Ongoing patient enrollment at data cutoff (February 27, 2017). † Ongoing patient enrollment at time of ASCO presentation (June 6, 2017).

Best Objective Response by RECIST v1.1

Epacadostat Plus Pembrolizumab
Phase 1/2 Metastatic or Recurrent SCCHN

Patients, n (%)	Total (N=38)	Number of Prior Lines of Treatment		PD-L1 Expression (CPS)*		HPV Status†	
		1–2 (n=31)	≥3 (n=7)	Positive (CPS ≥1%) (n=22)	Negative (CPS <1%) (n=7)	HPV Associated (n=13)	Non-HPV Associated (n=24)
ORR (CR+PR)	**13 (34)**	**12 (39)**	**1 (14)**	**6 (27)**	**3 (43)**	**6 (46)**	**7 (29)**
CR	3 (8)	3 (10)	0	2 (9)	0	1 (8)	2 (8)
PR	10 (26)	9 (29)	1 (14)	4 (18)	3 (43)	5 (38)	5 (21)
SD	10 (26)	8 (26)	2 (29)	7 (32)	1 (14)	1 (8)	9 (38)
DCR (CR+PR+SD)	**23 (61)**	**20 (65)**	**3 (43)**	**13 (59)**	**4 (57)**	**7 (54)**	**16 (67)**
PD	11 (29)	8 (26)	3 (43)	7 (32)	1 (14)	6 (46)	5 (21)
Not evaluable	4 (11)	3 (10)	1 (14)	2 (9)	2 (29)	0	3 (13)

- Same response results by irRECIST criteria

CPS, combined positive score; CR, complete response; DCR, disease control rate; HPV, human papillomavirus; irRECIST, immune-related RECIST; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease.
* Of 9 patients with unknown PD-L1 expression, there were 1 CR, 3 PR, 2 SD, and 3 PD by RECIST v1.1. † 1 patient had unknown HPV status and was not evaluable for response by RECIST v1.1.

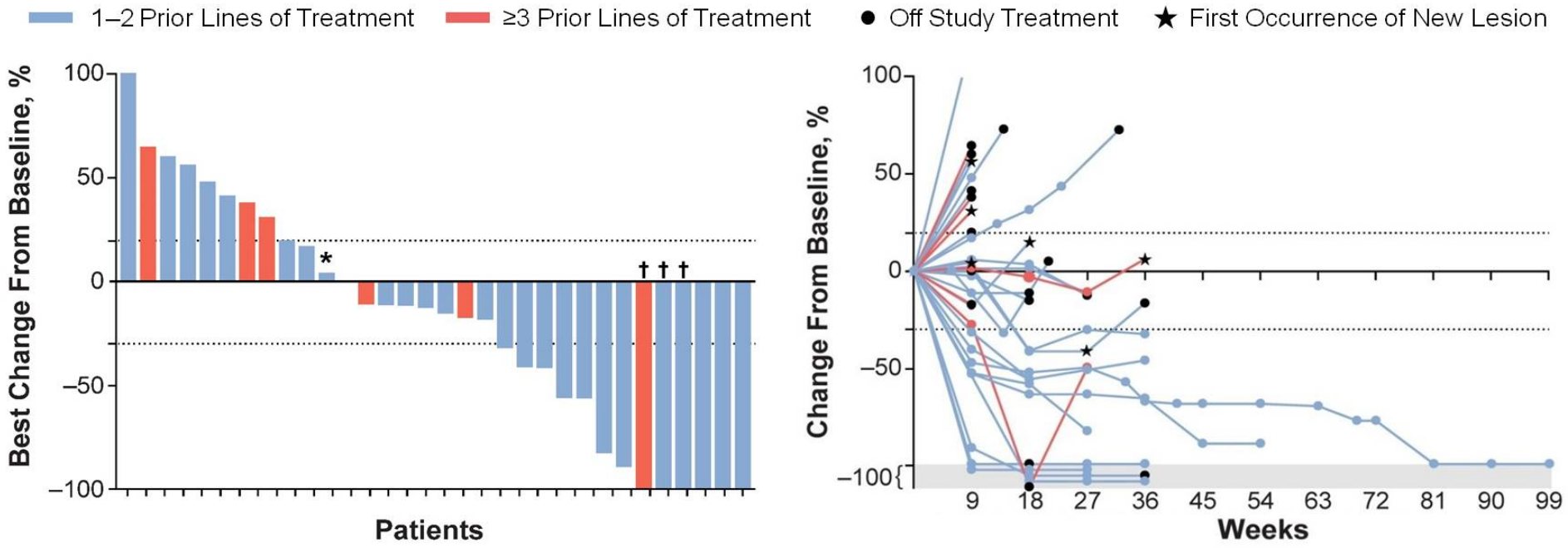
Remember the 15-20% ORR in the Nivo/Pembro trials?

Percentage Change From Baseline in Target Lesions

Epacadostat Plus Pembrolizumab

Phase 1/2 Metastatic or Recurrent SCCHN by Prior Lines of Treatment

Patients With 1–2 Prior Lines of Treatment: ORR=39%, DCR=65% by RECIST v1.1



CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease.

Of 38 efficacy-evaluable patients, data are shown for the 32 with ≥1 postbaseline scan that included assessment of target lesions. Six patients are not included in this figure: 2 patients were PD per new lesions (target lesions were not assessed); 2 patients had clinical progression and discontinued treatment prior to the first postbaseline scan; and 2 patients died before the first postbaseline scan.

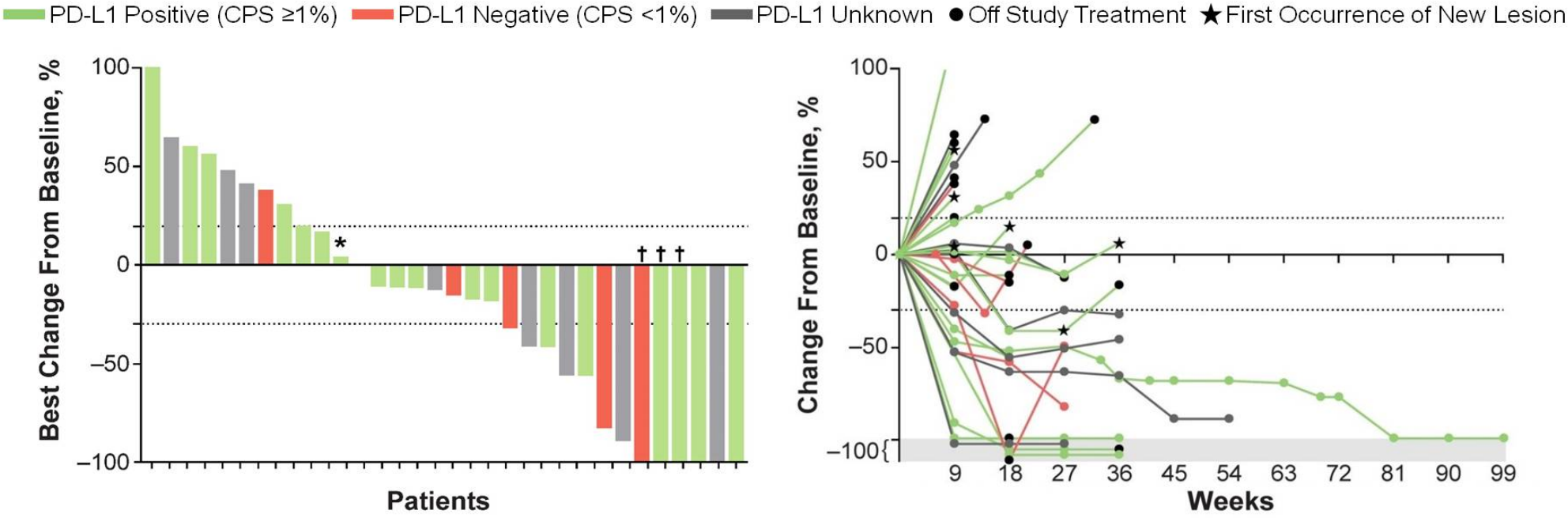
* Overall response is PD (SD per target lesions, PD per new lesions). † Overall response is PR (CR per target lesions, non-CR/non-PD per nontarget lesions).

Percentage Change From Baseline in Target Lesions

Epacadostat Plus Pembrolizumab

Phase 1/2 Metastatic or Recurrent SCCHN by PD-L1 Expression

Responses Were Observed Regardless of PD-L1 Expression



CPS, combined positive score; CR, complete response; PD, progressive disease; PD-L1, programmed death ligand 1; PR, partial response; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease.

Of 38 efficacy-evaluable patients, data are shown for the 32 with ≥1 postbaseline scan that included assessment of target lesions. Six patients are not included in this figure: 2 patients were PD per new lesions (target lesions were not assessed); 2 patients had clinical progression and discontinued treatment prior to the first postbaseline scan; and 2 patients died before the first postbaseline scan.

* Overall response is PD (SD per target lesions, PD per new lesions). † Overall response is PR (CR per target lesions, non-CR/non-PD per nontarget lesions).

Treatment-Related AEs (≥5%)

Epacadostat Plus Pembrolizumab
Phase 1/2 Metastatic or Recurrent SCCHN

AE, n (%)	All Grade (N=38)	Grade 3/4* (N=38)
Total	**24 (63)**	**7 (18)**
Fatigue	12 (32)	1 (3)
Rash†	5 (13)	0
Diarrhea	4 (11)	2 (5)
Nausea	4 (11)	0
Blood iron decreased	3 (8)	0
Dizziness	3 (8)	0
Pruritus‡	3 (8)	0
Vomiting	3 (8)	0
Weight decreased	3 (8)	1 (3)
Amylase increased	2 (5)	2 (5)
Asthenia	2 (5)	0
Decreased appetite	2 (5)	1 (3)
Dehydration	2 (5)	1 (3)
Erythema	2 (5)	0
Hypothyroidism	2 (5)	0
Lipase increased	2 (5)	2 (5)
Pyrexia	2 (5)	0

- Treatment-related AEs led to dose interruptions in 7 patients (18%)
  - The most common were fatigue and dizziness (n=2 [5%] each)
- One patient had a dose reduction due to a treatment-related AE (pneumonitis)
- One patient discontinued treatment due to treatment-related AEs (asymptomatic grade 3 amylase increased and grade 3 lipase increased); these were manageable with supportive care
- There was 1 treatment-related death due to respiratory failure (secondary to aspiration pneumonia; pneumonitis could not be ruled out)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SCCHN, squamous cell carcinoma of the head and neck.
* Other grade 3/4 treatment-related AEs not included in the table: liver function test abnormal, facial pain, and respiratory failure (n=1 each). † Rash includes the following MedDRA preferred terms: rash, rash macular, and rash maculopapular. ‡ Pruritus includes the following MedDRA preferred term: pruritus generalized.

AEs of Special Interest

Epacadostat Plus Pembrolizumab
Phase 1/2 Metastatic or Recurrent SCCHN

AE, n (%)	All Grade (N=38)	Grade 3/4 (N=38)
Total	**5 (13)**	**0**
Hypothyroidism	3 (8)	0
Adrenal insufficiency	1 (3)	0
Pneumonitis	1 (3)	0

- AEs of special interest include AEs with an immune-related cause, regardless of attribution to study treatment by the investigator

AE, adverse event; SCCHN, squamous cell carcinoma of the head and neck.

Conclusions

Epacadostat Plus Pembrolizumab

- These phase 1/2 study results show that epacadostat plus pembrolizumab is active in patients with metastatic or recurrent SCCHN
  - In patients with 1–2 prior lines of treatment, the ORR was 39% (CR, 10%) and the DCR was 65% by RECIST v1.1
  - Responses were observed regardless of PD-L1 expression and HPV association
  - 10/13 responses were ongoing; median (range) duration of response was 18.4+ (7.1 to 90.3+) weeks
- Epacadostat plus pembrolizumab was generally well tolerated in patients with metastatic or recurrent SCCHN
  - The safety profile was consistent with the previously reported phase 1 findings,[1] as well as the phase 1/2 safety data in other tumor types and pooled phase 2 safety data from this study (presented at ASCO 2017)
  - In general, the frequency of grade 3/4 treatment-related AEs, treatment discontinuation due to treatment-related AEs, and AEs of special interest observed with this combination were similar to pembrolizumab monotherapy; the frequency of grade 3/4 rash was higher with this combination[2,3]
- The efficacy of epacadostat plus pembrolizumab in SCCHN patients was consistent with findings in patients with other tumor types (melanoma, NSCLC, RCC, and UC), supporting phase 3 investigation of this combination in SCCHN

CR, complete response; DCR, disease control rate; HPV, human papillomavirus; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-L1, programmed death ligand 1; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; SCCHN, squamous cell carcinoma of the head and neck; UC, urothelial carcinoma.

1. Gangadhar TC, et al. Epacadostat plus pembrolizumab in patients with advanced melanoma and select solid tumors: updated phase 1 results from ECHO-202/KEYNOTE-037. Presented at: European Society for Medical Oncology Congress 2016; October 7–11, 2016; Copenhagen, Denmark. **2.** Bauml J, et al. *J Clin Oncol.* 2017;35(14):1542-1549. **3.** Chow LQM, et al. *J Clin Oncol.* 2016;34(32):3838-3845.

AACR update “hot of the press”

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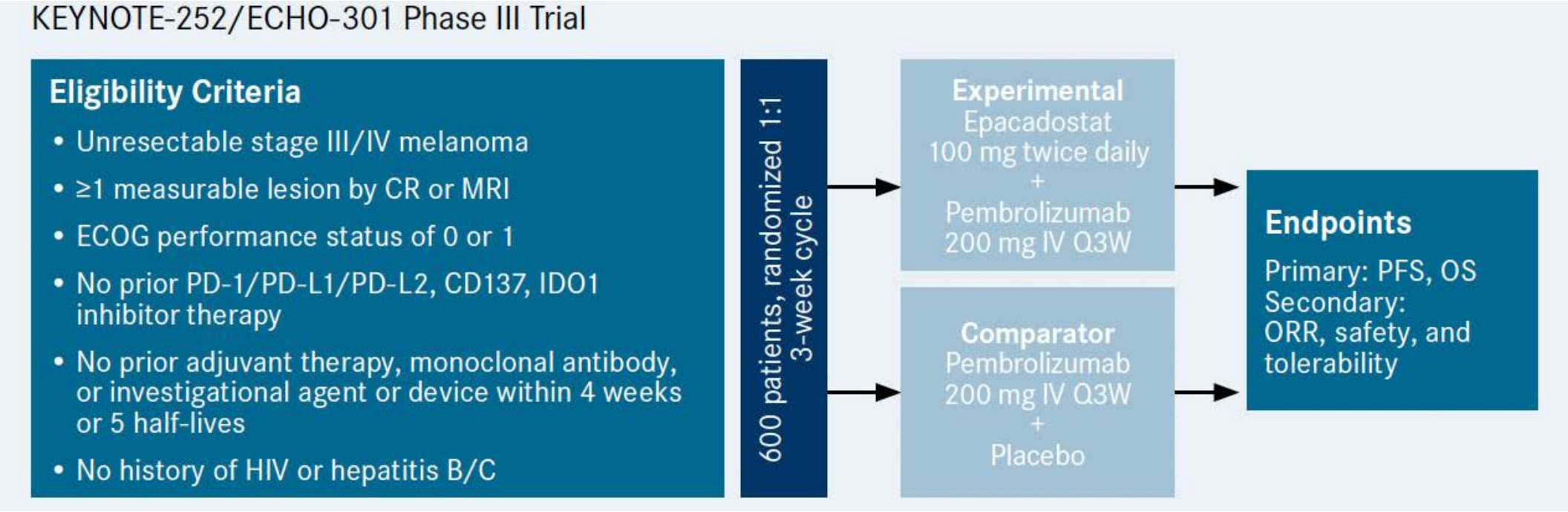

The combination of the PD-1 inhibitor pembrolizumab and the IDO1 inhibitor epacadostat failed to improve progression-free survival (PFS) versus single-agent pembrolizumab in patients with unresectable or metastatic melanoma, according to findings from the phase III ECHO-301/KEYNOTE-252 trial.

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Safety of Pembrolizumab with Chemoradiation (CRT) in Locally Advanced Squamous Cell Carcinoma of the Head and Neck (LA-SCCHN).

Steven F. Powell[1], Mark M. Gitau[2], Christopher J. Sumey[1], John T. Reynolds[3], Andrew M. Terrell[2], Michele M. Lohr[1], Steven C. McGraw[1], Ryan K. Nowak[1], Ashley W. Jensen[2], Miran J. Blanchard[2], Christie A. Ellison[1], Lora J. Black[1], Paul A. Thompson, PhD[1], Kathryn A. Gold[4], Ezra E.W. Cohen[4], John H. Lee[1,5], William C. Spanos[1]

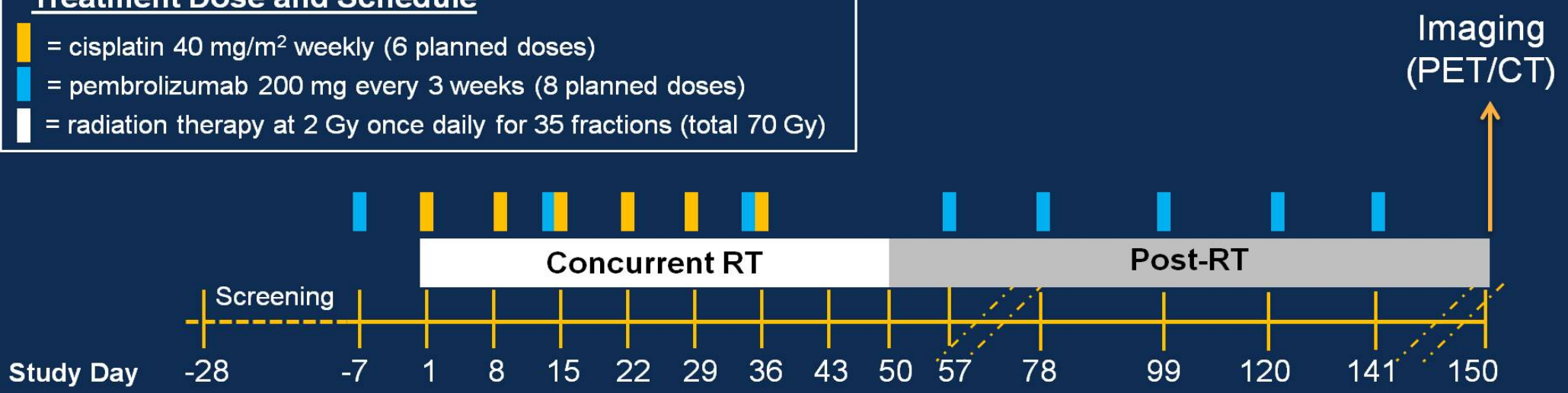
[1]Sanford Health, Sanford Cancer Center, Sioux Falls, SD; [2]Sanford Health, Roger Maris Cancer Center, Fargo, ND; [3]Sanford Health, Sanford Cancer Center, Bismarck, ND, [4]University of California, San Diego, Moores Cancer Center, La Jolla, CA, [5]NantKwest, Inc., Culver City, CA

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

Study Design

Treatment Dose and Schedule

- = cisplatin 40 mg/m^2 weekly (6 planned doses)
- = pembrolizumab 200 mg every 3 weeks (8 planned doses)
- = radiation therapy at 2 Gy once daily for 35 fractions (total 70 Gy)



Primary end points:

- Safety - dose-limiting adverse events (AEs) and immune-related AEs (irAEs)
- Efficacy - complete response (CR) rate on imaging or salvage surgery at day 150

Secondary end points: PFS, OS, locoregional control, distant metastasis rate, quality-of-life (FACT H&N)

Patient Population

INCLUSION	EXCLUSION
Squamous cell carcinoma of the oral cavity (excluding lip), oropharynx, hypopharynx, or larynx	Prior chemotherapy, radiotherapy, or immunotherapy for SCCHN
Stage III, IVA, or IVB	Stage IVC (distant metastases)
HPV + or HPV - (by p16 IHC)	Concurrent active malignancy (excluding skin basal cell and squamous cell carcinomas)
Age ≥18	Active infections
ECOG PS 0-1	Active autoimmune disease
RECIST 1.1 measurable disease	History of HIV or active Hepatitis B or C
cisplatin eligible	

Patient Characteristics

All Patients n = 27	
Age (median, range)	61.7 yrs (36-80 yrs)
Sex (% male)	23 (85%)
Primary site:	
Oropharynx	22 (81.5%)
Larynx	4 (14.8%)
Hypopharynx	1 (3.7%)
Stage	
III	1 (3.7%)
IVA	25 (92.6%)
IVB	1 (3.7%)
T stage	
T1-3	19 (70%)
T4	8 (30%)
N Stage	
N0-1	2 (7%)
N2	24 (89%)
N3	1 (4%)
Tobacco use (>10 PYH)	21 (78%)
Prophylactic feeding tube	22 (82%)

Disease Characteristics by HPV status	HPV + (n = 20)	HPV – (n = 7)
Primary site:		
Oropharynx	20 (100%)	2 (29%)
Larynx	0	4 (57%)
Hypopharynx	0	1 (14%)
Stage		
III	0	1 (14%)
IVA	20 (100%)	5 (71%)
IVB	0	1 (14%)
T stage		
T1-3	14 (70%)	5 (71%)
T4	6 (30%)	2 (29%)
N Stage		
N0-1	1 (5%)	1 (14%)
N2	19 (95%)	5 (71%)
N3	0	1 (14%)
Tobacco use (>10 PYH)	15 (75%)	6 (85%)

Pembrolizumab – Discontinuations and irAEs

Pembrolizumab (8 planned doses)	N (%)
<3 doses (CRT)	2 (7.4%)
>3 but <8 doses (post-CRT)	4 (15%)
All 8 doses	21 (78%)

- 3 discontinuations due to irAEs (11%)
  - Grade 3 AST increase
    - Resolved with corticosteroids
  - Grade 2 peripheral motor neuropathy
  - Grade 1 Lhermitte-like syndrome
- No other irAEs requiring discontinuation or treatment
- 3 discontinuations due to protocol reasons
  - Early neck dissection (N = 2)
  - Prolonged hospitalization

Treatment Compliance - CRT

Cisplatin (40 mg/m² x 6 weekly doses)

Dose reduction (N,%)	4 (15%)
Dose omission (N,%)	7 (26%)
Completed ≥ 200 mg/m² (N,%)	23 (85%)
Median Cumulative Dose (SD)	225 mg/m² (25)

- Reasons for discontinuation
  - neutropenia (n = 4)
  - thrombocytopenia (n = 1)
  - elevated creatinine (n = 2)

Radiation Therapy (70 Gy planned)

Treatment Delay > 5 days (N,%)	0 (0%)
Treatment Delay ≤ 5 days (N,%)	2 (7.4%)
Mean Days Duration (SD)	49.5 (2.4)
70 Gy RT Completed (N,%)	27 (100%)

- Reasons for delay (<5 days)
  - Hospitalization (n =1)
  - Equipment Malfunction (n =1)

Selected Adverse Events - CRT

AE	All Grades	Grade 3	Grade 4
Dysphagia	26 (96%)	12 (44%)	None
Mucositis (oral/pharyngeal)	26 (96%)	8 (30%)	
Dermatitis radiation	22 (81%)	4 (15%)	
Weight loss	22 (81%)	4 (15%)	
Neutropenia	17 (63%)	9 (33%)	1(4%)
Anemia	25 (93%)	4 (15%)	None
Thrombocytopenia	11 9(41%)	2 (7%)	
Hyponatremia	20 (74%)	5 (19%)	None
Hypomagnesemia	17 (63%)	1 (4%)	
Hypophosphatemia	12 (44%)	4 (15%)	1 (4%)

Overall Response Rate – Day 150

Response	All Patients (n = 27)	95% CI	HPV+ (n = 20)	95% CI	HPV- (n = 7)	95% CI
CR*	21 (78%)	58-91	17 (85%)	62-97	4 (57%)	18-90
PR	4 (15%)	-	2 (10%)	-	2 (29%)	-
SD	-	-	-	-	-	-
PD	1 (3.5%)	-	1 (5%)‡	-	-	-
Death (not evaluable)	1 (3.5%)	-	-	-	1 (14%)	-

*All Based on Imaging (PET/CT)

‡Distant Metastatic Disease

Summary

- Pembrolizumab can be safely delivered with weekly cisplatin and radiation in LA-SCCHN
- No new toxicity signals seen
  - **Pembrolizumab –** Discontinuations due to irAEs in a small proportion (N=3, 11%)
  - **Radiation –**Definitive dose delivered without significant delays
  - **Cisplatin –** 85% of participants received ≥200 mg/m^2
- Early efficacy data supports ongoing investigation of this approach
  - Expansion cohorts will explore efficacy in HPV+ and HPV- disease
  - Phase II/III trials currently enrolling participants
- Correlative research will explore biomarkers, timing, and potential combinations

Conclusions

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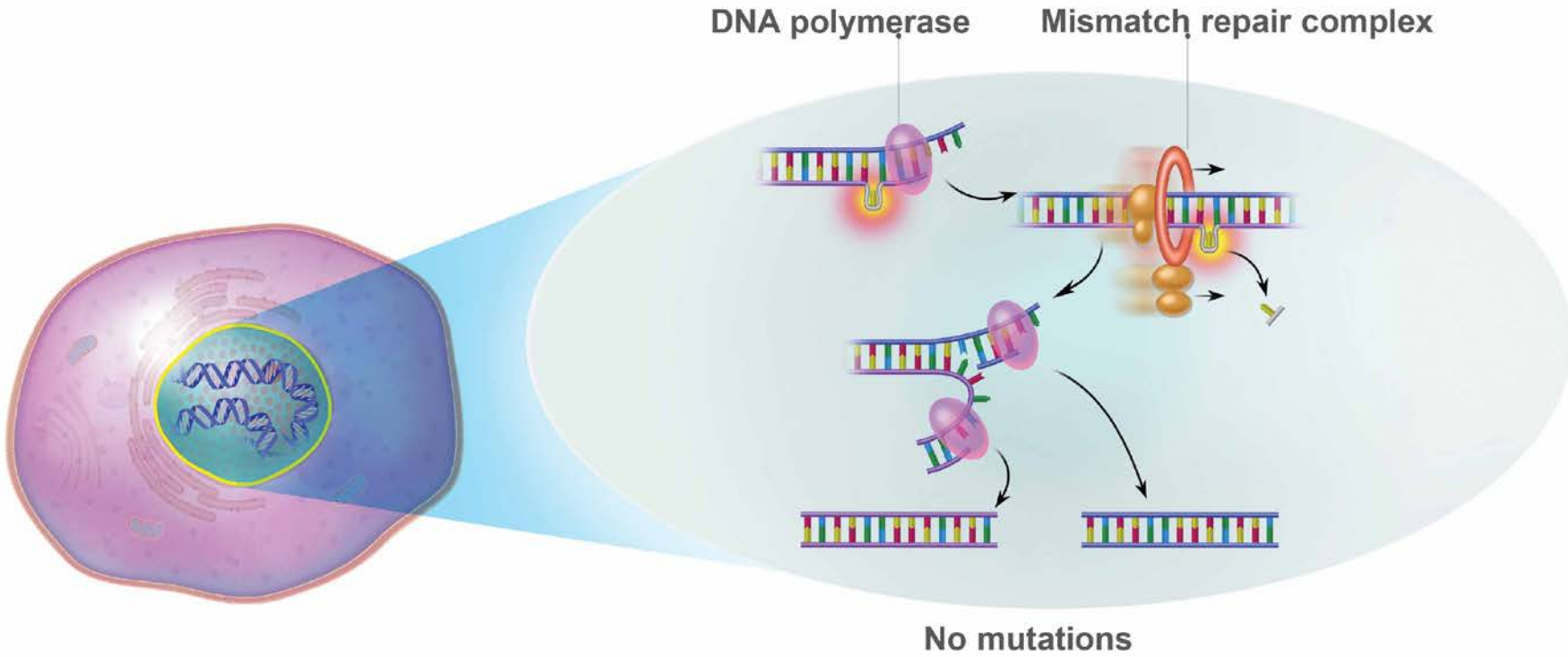
- PD-1 inhibitors Nivolumab and Pembrolizumab are FDA-Approved therapies for R/M platinum-refractory head and neck cancer
- Use of immunotherapy in first line therapy for R/M and in combination with RT for localized disease is under investigation
- Immunotherapy 2.0 – combination with chemo, upfront therapy, neoadjuvant. “Just the beginning”
- Side note: Cisplatin 100mg/M2 superior to Weekly Cisplatin. ASCO 2017 Noronha et al.
- The 2-year locoregional relapse rate was 38.67% with weekly cisplatin, and 24.67% with 3-weekly cisplatin, yielding a hazard ratio (HR) of 1.76 (95% CI, 1.11–2.79; *P* = .014).
- Disease-free survival (DFS) differences did not reach significance, but favored the 3-weekly group. The median DFS was 20.8 months with weekly cisplatin, and 37.7 months in the 3-weekly group, for an HR of 1.38 (*P* = .069). Progression-free survival was similar, at 17.7 months with weekly cisplatin and 28.6 months with 3-weekly cisplatin, for an HR of 1.24 (*P* = .21). The median overall survival was 39.5 months in the weekly patients, and it was not yet reached in the 3-weekly patients (*P* = .48).

Proficient MMR (pMMR) Cell



Successful repair of mismatched base pair by pMMR system

Adapted from Li et al.

in normal cells, the DNA mismatch repair (MMR) system recognizes and repairs genetic mismatches generated during DNA replication

Deficient MMR (dMMR) Cell

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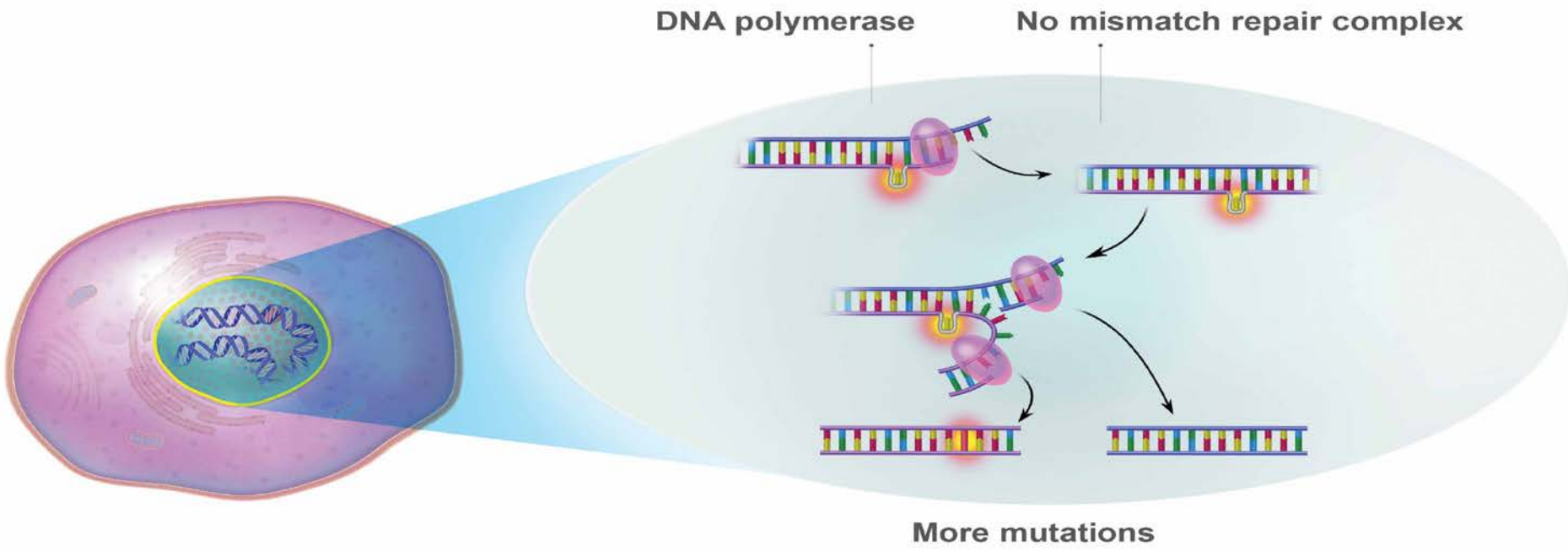
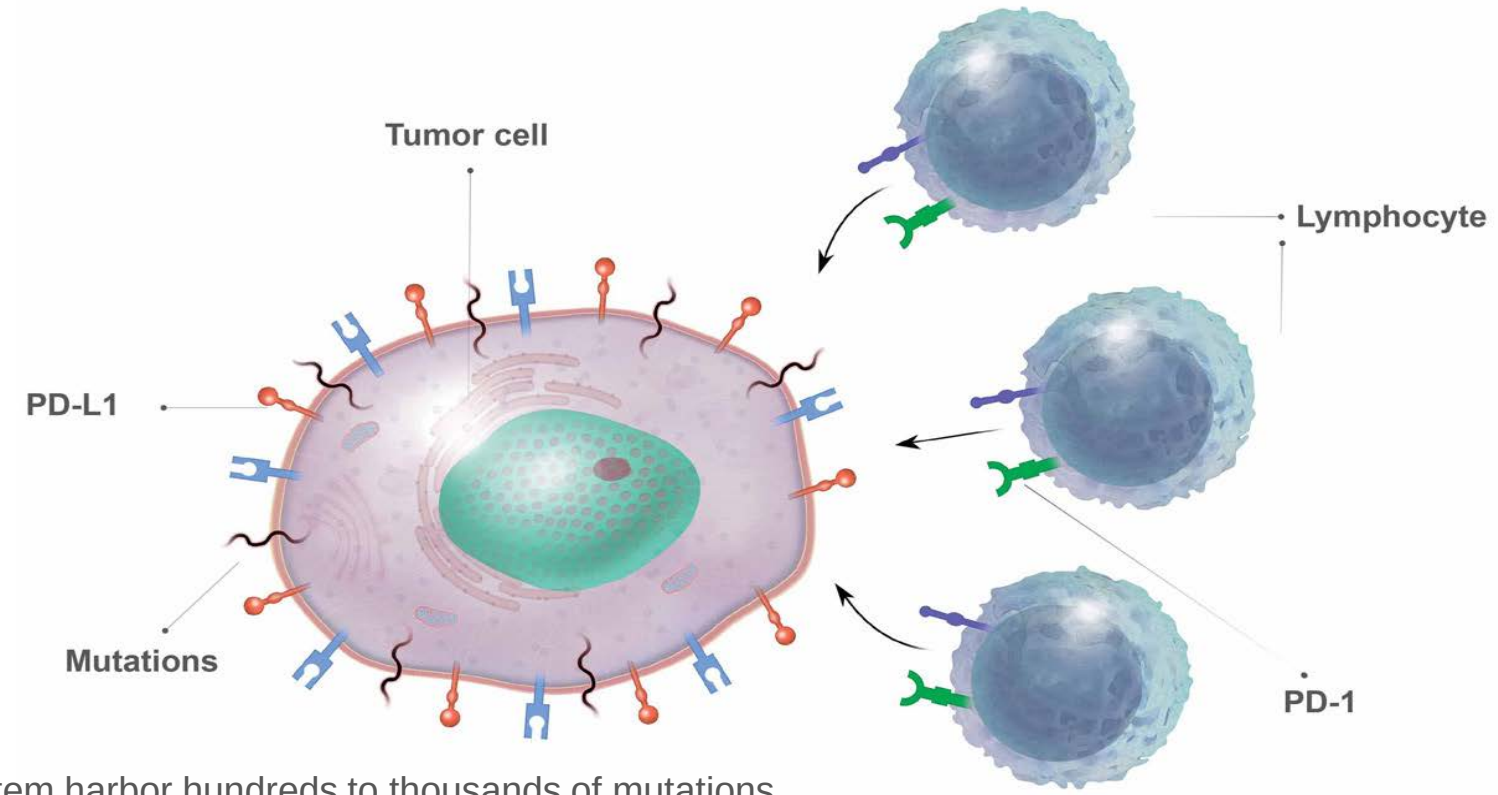


Failure to repair mismatched base pair due to dMMR system

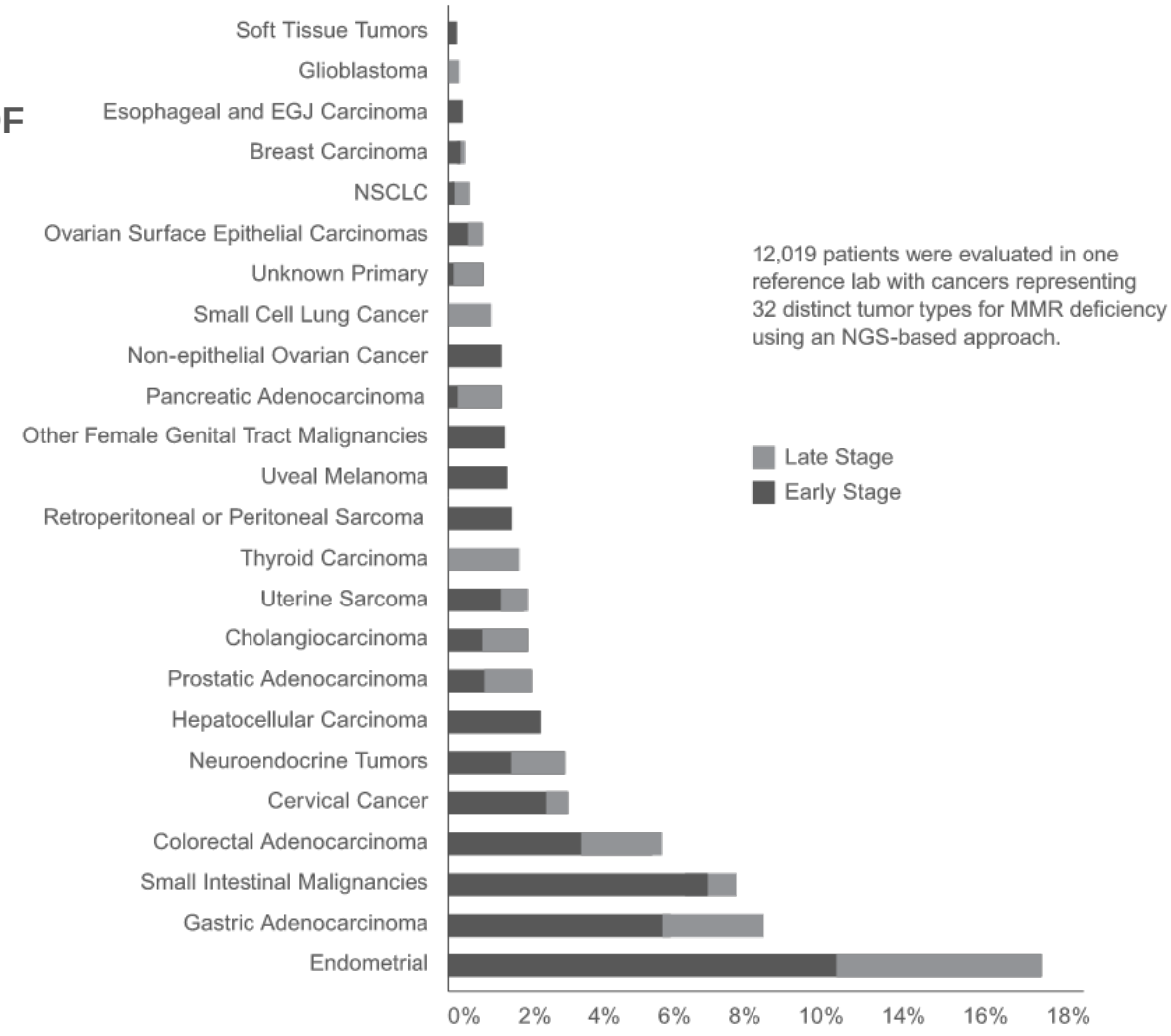
Adapted from Li et al.

- A deficient MMR (dMMR) system results in the persistence of DNA mismatches in microsatellites that may then be incorporated into the genetic code as mutations.
- A dMMR system can be hereditary or sporadic in nature.
- Tumors that have a dMMR system can develop MSI, which is the expansion or reduction in the length of repetitive sequences in tumor DNA compared with normal DNA.
- Tumors that have MSI due to a dMMR system can exhibit the MSI-high (MSI-H) phenotype.



•Tumors with a dMMR/MSI-H system harbor hundreds to thousands of mutations, which stimulates the immune system.
•MSI-H tumors contain high levels of lymphocyte infiltrates and strong expression of immune checkpoints, including PD-1 and PD-L1.
•In colorectal MSI-H cancers, the dominant source of PD-L1 may be macrophages or other tumor-infiltrating lymphocytes and myeloid cells, rather than tumor cells.

MSI-H/dMMR OCCURS IN A VARIETY OF CANCERS



The NEW ENGLAND JOURNAL of MEDICINE

Perspective

OCTOBER 12, 2017

First FDA Approval Agnostic of Cancer Site — When a Biomarker Defines the Indication

Steven Lemery, M.D., M.H.S., Patricia Keegan, M.D., and Richard Pazdur, M.D.

Trial	Description
KEYNOTE-016	Six-site prospective, investigator-initiated trial included patients with CRC (n=28) and non-CRC (n=30) who received KEYTRUDA 10 mg/kg Q2W following ≥2 prior regimens for CRC or ≥1 for non-CRC; tested with local PCR or IHC.
KEYNOTE-164	Prospective, international, multicenter trial of patients with CRC (n=61) who received KEYTRUDA 200 mg Q3W following fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR monoclonal antibody; tested with local PCR or IHC.
KEYNOTE-012	Retrospectively identified patients (n=6) with PD-L1–positive gastric, bladder, or triple-negative breast cancer who received KEYTRUDA 10 mg/kg Q2W following ≥1 prior regimen; tested with central PCR.
KEYNOTE-028	Retrospectively identified patients (n=5) with PD-L1–positive esophageal, biliary, breast, endometrial, or CRC who received KEYTRUDA 10 mg/kg Q2W following ≥1 prior regimen; tested with central PCR.
KEYNOTE-158	Prospective, international, multicenter enrollment of patients with MSI-H/dMMR non-CRC and retrospectively identified patients who were enrolled in specific rare-tumor non-CRC cohorts (n=19) who received KEYTRUDA 200 mg Q3W following ≥1 prior regimen; tested with local PCR or IHC (central PCR for patients in rare-tumor non-CRC cohorts).

Efficacy studied in 15 different MSI-H/dMMR cancers in 149 patients

KEYTRUDA: Objective Response Rate and Duration of Response

Objective Response Rate n=149 **39.6%** (95% CI, 31.7–47.9)	**7.4%**	**Complete response**
	32.2%	**Partial response**

% With Duration ≥6 Months **78%**	**Median duration of response had not been reached** (range: 1.6+ to 22.7+ months)

Efficacy in a subset of patients across a range of *other solid tumors*

Response by Tumor Type: Non-CRC

Objective Response Rate
n=27/59
46%
(95% CI, 33–59)

Ongoing duration of response
(range: 1.9+ to 22.1+ months)

Efficacy in a subset of patients with advanced MSI-H/dMMR *colorectal cancer*

Response by Tumor Type: **CRC**

Objective Response Rate
n=32/90
36%
(95% CI, 26–46)

Ongoing duration of response
(range: 1.6+ to 22.7+ months)