SITC 2016

NATIONAL HARBOR, MD
NOVEMBER 9-13, 2016

sitc

Society for Immunotherapy of Cancer

SITC 2016
NATIONAL HARBOR, MD
NOVEMBER 9-13, 2016

Preliminary efficacy from a phase 1/2 study of the natural killer cell–targeted antibody, lirilumab in combination with nivolumab in squamous cell carcinoma of the head and neck

Rom Leidner,[1] Hyunseok Kang,[2] Robert Haddad,[3] Neil H. Segal,[4] Lori J. Wirth,[5] Robert L. Ferris,[6] F. Stephen Hodi,[3] Rachel E. Sanborn,[1] Thomas F. Gajewski,[7] William Sharfman,[2] Dan McDonald,[8] Shivani Srivastava,[8] Xuemin Gu,[8] Penny Phillips,[8] Chaitali Passey,[8] Tanguy Y. Seiwert[7]

[1]Earle A. Chiles Research Institute, Providence Cancer Center, Portland, OR, USA; [2]The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [5]Massachusetts General Hospital, Boston, MA, USA; [6]University of Pittsburgh, Pittsburgh, PA, USA; [7]University of Chicago Medical Center, Chicago, IL, USA; [8]Bristol-Myers Squibb, Princeton, NJ, USA

sitc
Society for Immunotherapy of Cancer

#SITC2016

Presenter Disclosure Information

Rom Leidner, MD

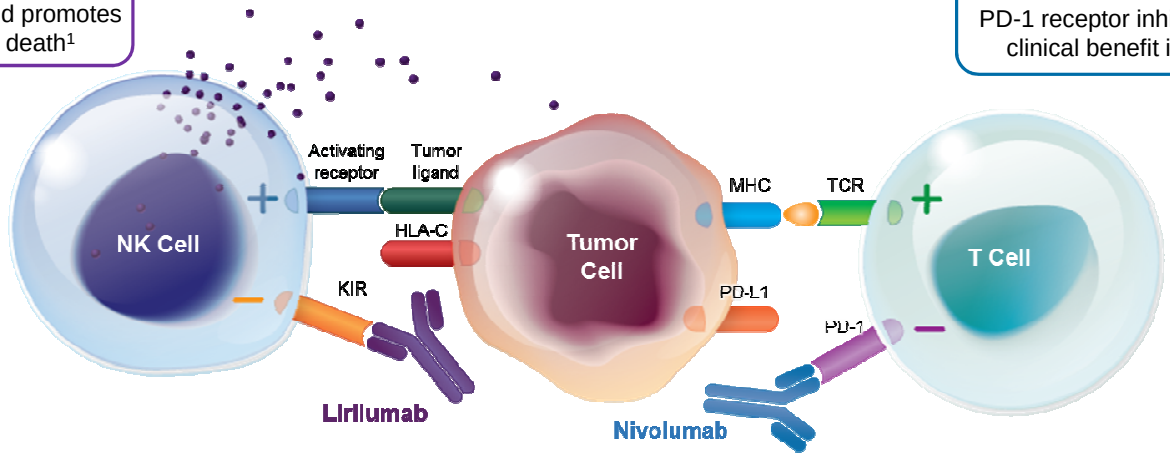
The following relationships exist related to this presentation:

No personal financial interest in products or processes involved in this research. Dr Leidner's research is supported by MedImmune/AZ and BMS

Rationale for Lirilumab + Nivolumab Combination Therapy

Lirilumab: a fully human IgG4 mAb that blocks inhibitory KIRs on NK cells and promotes NK-cell activation and tumor cell death[1]

Nivolumab: a fully human IgG4 mAb that blocks PD-1 receptor inhibition of T cells, with demonstrated clinical benefit in advanced/ metastatic cancers[2]



- Nivolumab improves survival compared with standard therapy in patients with advanced SCCHN[3]
- SCCHN tumors have high infiltration of NK cells and *KIR* gene expression,[4] suggesting that KIR blockade with lirilumab may enhance antitumor activity of nivolumab in patients with SCCHN
- In preclinical models, addition of an anti-KIR mAb potentiates the efficacy of an anti-PD-1 mAb[5]
- **Here we report preliminary efficacy of lirilumab plus nivolumab in patients with SCCHN**

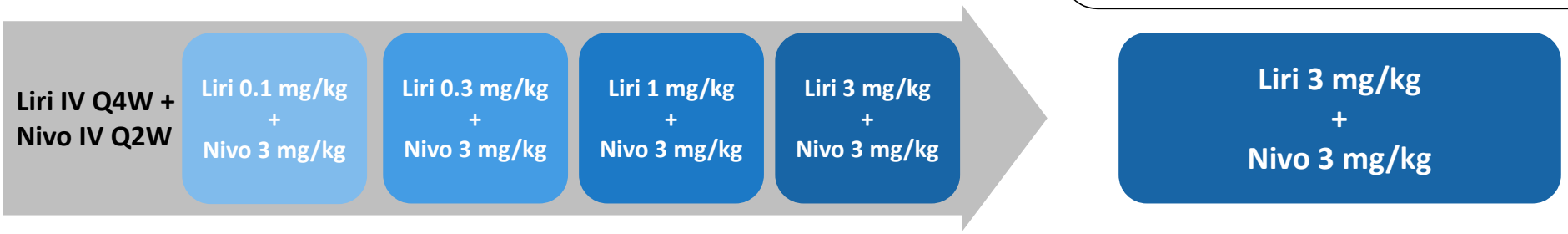
KIR, killer cell immunoglobulin-like receptor; mAb, monoclonal antibody; NK, natural killer; SCCHN, squamous cell carcinoma of the head and neck cancer.

1. Kohrt HE et al. *Blood*. 2014;123:678–86; 2. Opdivo [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2016; 3. Ferris RL, et al. *N Engl J Med.* 2016 Oct 8 [Epub ahead of print]; 4. Mandal R, et al. *JCI Insight*. 2016;1:e89829; 5. BMS data on file.

Phase 1/2 Study of Lirilumab + Nivolumab (NCT01714739)

Dose Escalation (3 + 3 + 3 design)
Advanced Solid Tumors
Progression/intolerance on ≥ 1 standard treatment in the advanced setting (except patients with Mel); primary CNS tumors excluded

Dose Expansion
SCCHN: Progression/recurrence ≤6 mo after platinum-based chemotherapy (adjuvant, primary, recurrent, or advanced setting)
CRC, HCC, MEL, NSCLC



Primary endpoints
- Safety/tolerability
  - DLTs/MTD
- Preliminary antitumor activity (RECIST 1.1)
  - ORR/DOR

Key secondary/exploratory endpoints
- Biomarkers
  - Response by PD-L1 expression
  - Gene expression
- Overall survival

Liri, lirilumab; MEL, melanoma; Nivo, nivolumab.

Patient Demographics and Disease Characteristics in All Patients Treated With Lirilumab + Nivolumab

	All Patients (N = 159)
Median age (range), years	60 (21–85)
Male, n (%)	98 (61.6)
ECOG performance status, n (%)	
0	57 (35.8)
1	101 (63.5)
2	1 (0.6)
Tumor type, n (%)	
Melanoma	55 (34.6)
SCCHN	41 (25.8)
NSCLC*	37 (23.3)
HCC	9 (5.7)
CRC	9 (5.7)
Other	8 (5.0)

*Open histology; 1 patient with squamous NSCLC was enrolled.

Treatment-Related Adverse Events (TRAEs) With Lirilumab + Nivolumab

Patients with TRAE, n (%)	All Patients N = 159	
	Any Grade	Grade 3/4
Any TRAE	114 (71.7)	24 (15.1)
TRAEs in >10% of all patients		
Fatigue	33 (20.8)	0
Pruritus	30 (18.9)	0
Infusion-related reaction	28 (17.6)	0
Rash	26 (16.4)	0
TRAEs leading to discontinuation	12 (7.5)	4 (2.5)*
TRAEs leading to discontinuation in >1 patient		
Pneumonitis	3 (1.9)	0
Diarrhea	2 (1.3)	0

*Grade 3/4 TRAEs leading to discontinuation were electrocardiogram QT prolonged (grade 3), hypopituitarism (grade 3), lipase increased (grade 3), and thrombocytopenia (grade 4).

- No DLTs were reported; rash and infusion-related reactions were clinically manageable
- No treatment-related deaths were reported
- Safety of lirilumab + nivolumab has been reported at ESMO 2016[1] and the SITC pre-meeting session on new I-O agents[2]

1. Segal NH, et al. *Ann Oncol*. 2016;27(Suppl 6): Abstract 1086P; 2. Segal NH, et al. Presented at: New Cancer Immunotherapy Agents in Development. Wed November 9, 2016.

Disease Characteristics and Prior Therapies in Patients with SCCHN Treated with Lirilumab + Nivolumab

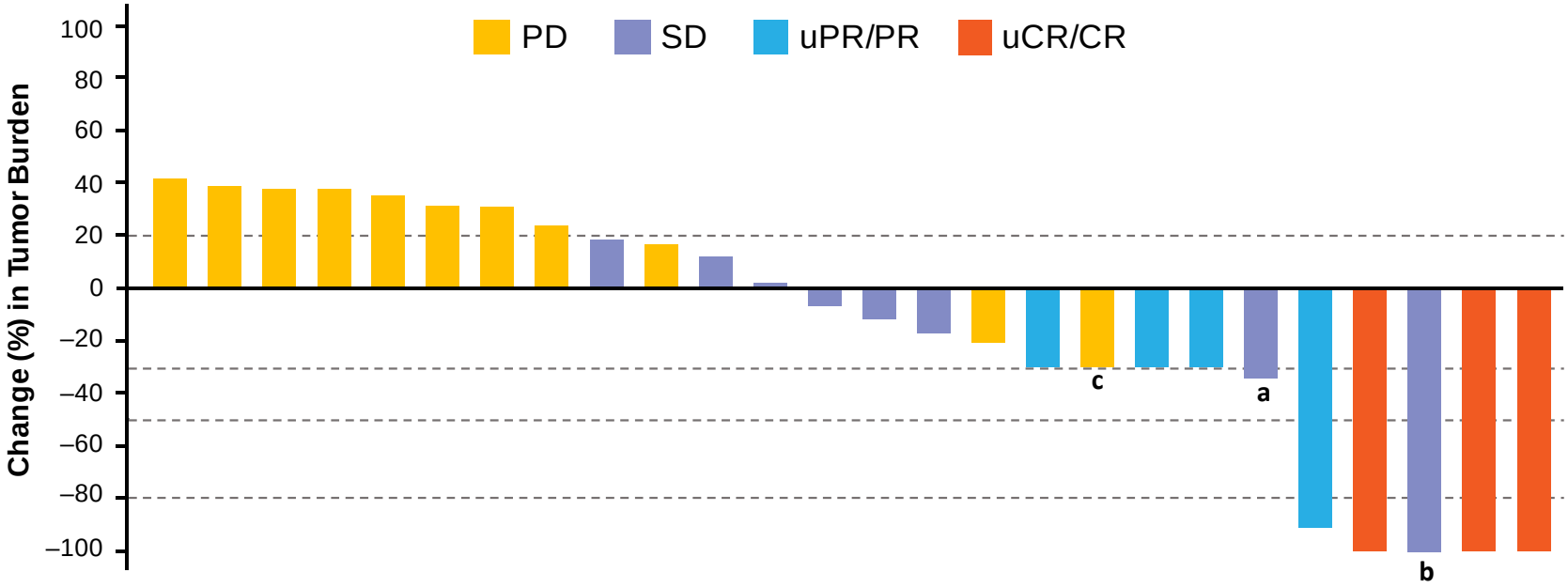
	Patients with SCCHN (n = 41)
ECOG performance status, n (%)	
0	9 (22.0)
1	32 (78.0)
≥2	0
Tumor location, n (%)	
Oral cavity	23 (56.1)
Pharynx and/or oropharynx	14 (34.1)
Larynx	3 (7.3)
Other	1 (2.4)
Prior therapies, n (%)	
1	13 (31.7)
2	17 (41.5)
≥3	11 (26.8)
HPV-positive oropharynx, n (%)*	8 (19.5)

Of the 41 patients with SCCHN, 29 were evaluable for response†:
26 patients had post-baseline scans; 3 progressed prior to first scans

*HPV positivity reported according to patient history.

†Majority of non-evaluable patients had not yet reached first on-study treatment assessment.

Preliminary Maximum Percent Reduction in Target Lesions in Evaluable Patients With SCCHN Treated With Lirilumab + Nivolumab (n = 26)*

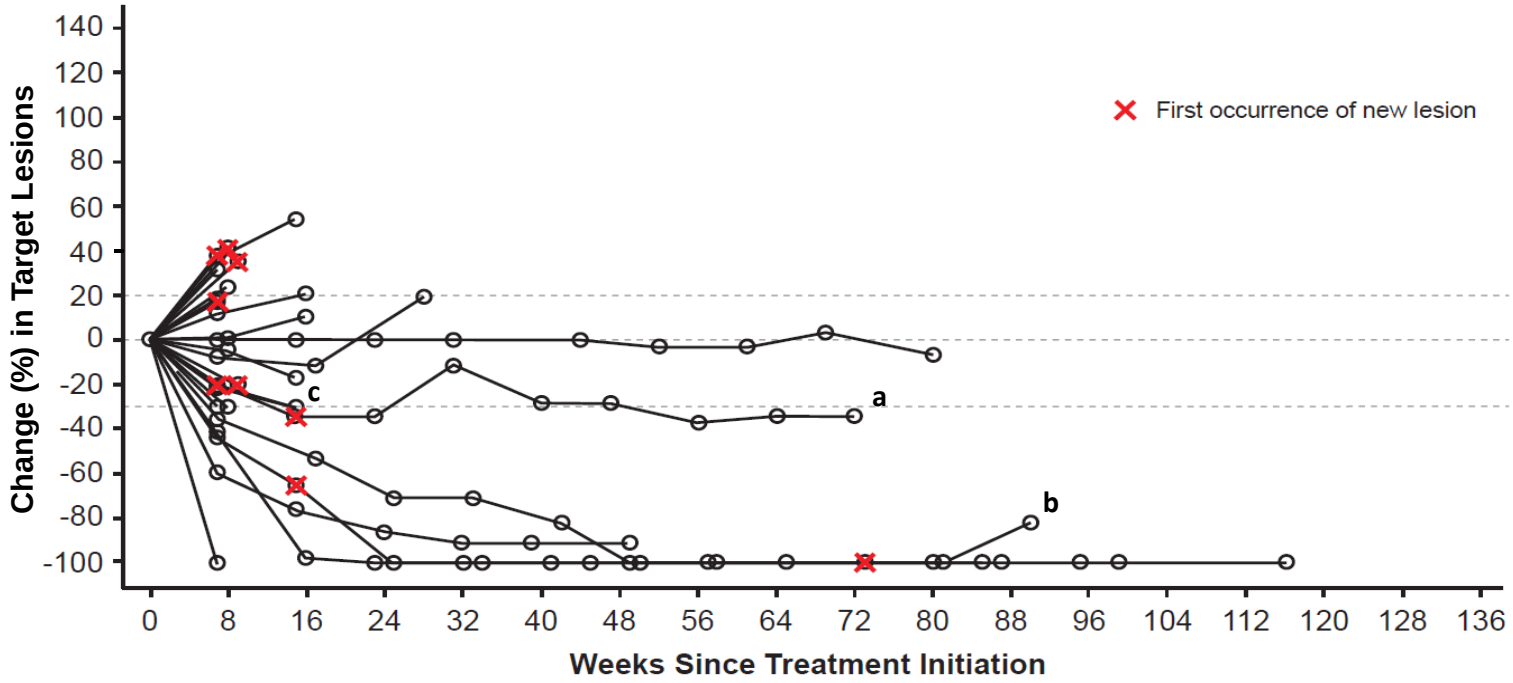


Of the seven patients with a response, none were HPV-positive oropharyngeal patients

*26 of 29 evaluable patients had a post-baseline assessment.

[a] Patient with a 37% reduction in target lesion classified as SD. [b] Patient with a 100% reduction in target lesion classified as SD. [c] Patient with a 30% reduction in target lesion classified as PD.

Preliminary Percent Change From Baseline in Target Lesions Over Time in Patients with SCCHN Treated with Lirilumab + Nivolumab (n = 26)*



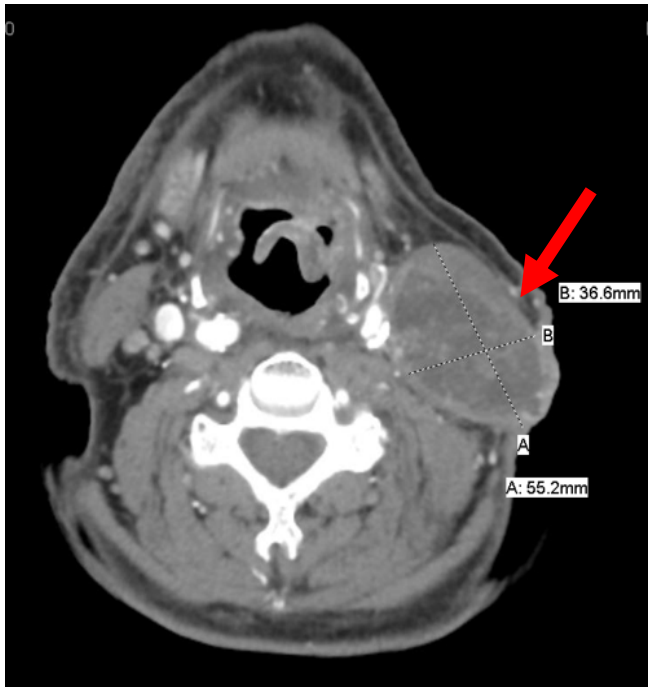
The median duration of response was not reached

*26 of 29 evaluable patients had a post-baseline assessment.

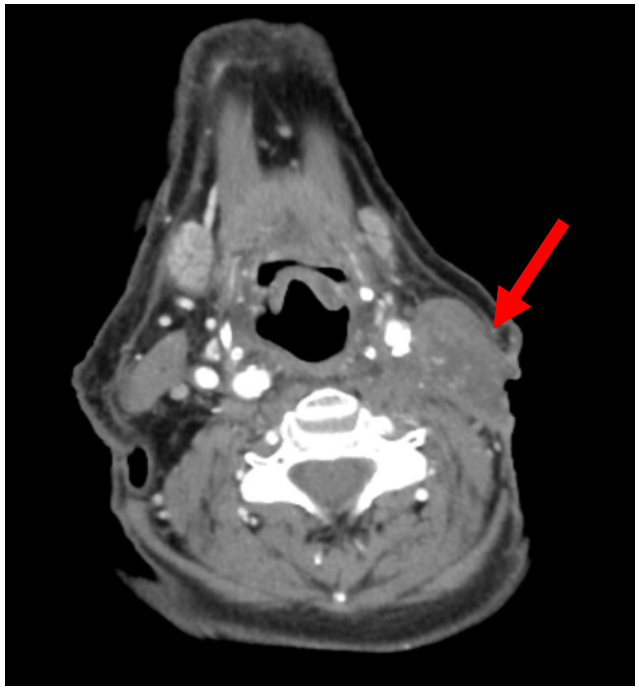
[a] Patient with a 37% reduction in target lesion classified as SD. [b] Patient with a 100% reduction in target lesion classified as SD. [c] Patient with a 30% reduction in target lesion classified as PD.

67-Year-Old Male Patient With HPV-Negative SCCHN of Larynx

19 JUN 2014: 36 mm

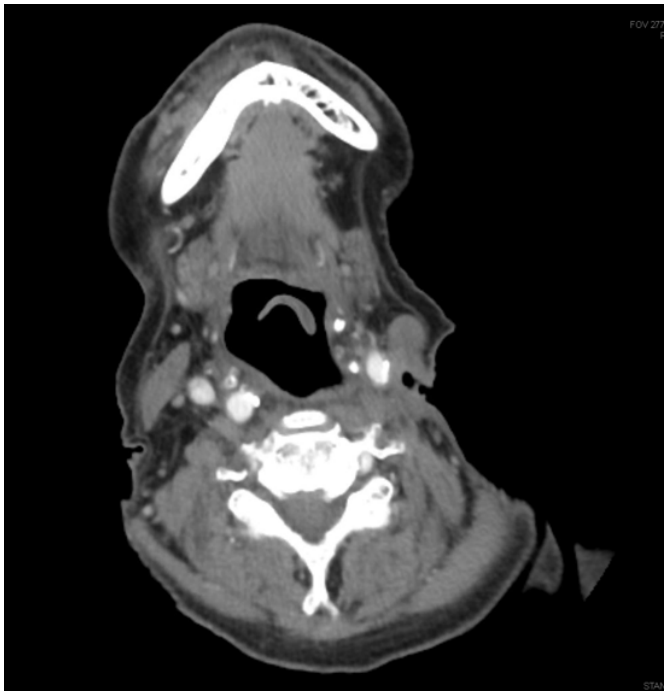


2 SEP 2014: 25 mm
(4 doses of nivolumab + 2 doses of lirilumab)



Overall tumor burden :
45% decrease by RECIST

6 JAN 2015: 0 mm
(12 doses of nivolumab + 6 doses of lirilumab)



Overall tumor burden :
100% decrease of target lesions*

*Patient developed new lesions after 2nd cycle but continued in trial with resolution of target lesions

Demographics of Patients With SCCHN Treated With Lirilumab + Nivolumab (NCT01714739) or Nivolumab Monotherapy (CheckMate 141)

	NCT01714739 (Phase 1/2) Lirilumab + Nivolumab (n = 41)	CheckMate 141 (Phase 3)[1] Nivolumab Monotherapy (N = 240)
ECOG performance status, n (%)*		
0	9 (22.0)	49 (20.4)
1	32 (78.0)	189 (78.8)
≥2	0	1 (0.4)
Tumor location, n (%)		
Oral cavity	23 (56.1)	108 (45.0)
Pharynx and/or oropharynx	14 (34.1)	92 (38.3)
Larynx	3 (7.3)	34 (14.2)
Other	1 (2.4)	6 (2.5)
Prior therapies, n (%)		
1	13 (31.7)	106 (44.2)
2	17 (41.5)	80 (33.3)
≥3	11 (26.8)	54 (22.5)
HPV-positive oropharynx, n (%)‡	8 (19.5)	63 (26.2)

*ECOG performance status was not reported in 1 patient in CheckMate 141. ‡For NCT01714739, HPV positivity reported according to patient history. In CheckMate 141, HPV status according to p16 positivity.

1. Ferris RL, et al. *N Engl J Med.* 2016 Oct 8 [Epub ahead of print].

ORR and BOR With Lirilumab + Nivolumab (NCT01714739) or Nivolumab Monotherapy (CheckMate 141) in Evaluable Patients With SCCHN

	NCT01714739 (Phase 1/2) Lirilumab + Nivolumab	
ORR, n/N (%)	**7/29 (24.1)***	
Complete response	3 (10.3)*	
Partial response	4 (13.8)*	
DCR, n/N (%)	15/29 (51.7)	

*Includes unconfirmed responses.

1. Ferris RL, et al. *N Engl J Med.* 2016 Oct 8 [Epub ahead of print]; 2. BMS data on file.

ORR and BOR With Lirilumab + Nivolumab (NCT01714739) or Nivolumab Monotherapy (CheckMate 141) in Evaluable Patients With SCCHN

	NCT01714739 (Phase 1/2) Lirilumab + Nivolumab	CheckMate 141 (Phase 3)[1,2] Nivolumab Monotherapy
ORR, n/N (%)	**7/29 (24.1)***	**32/240 (13.3)**
Complete response	3 (10.3)*	6 (2.5)
Partial response	4 (13.8)*	26 (10.8)
DCR, n/N (%)	15/29 (51.7)	NR

*Includes unconfirmed responses.

1. Ferris RL, et al. *N Engl J Med.* 2016 Oct 8 [Epub ahead of print]; 2. BMS data on file.

ORR and BOR With Lirilumab + Nivolumab (NCT01714739) or Nivolumab Monotherapy (CheckMate 141) in Evaluable Patients With SCCHN

	NCT01714739 (Phase 1/2) Lirilumab + Nivolumab	CheckMate 141 (Phase 3)[1,2] Nivolumab Monotherapy
ORR, n/N (%)	**7/29 (24.1)***	**32/240 (13.3)**
Complete response	3 (10.3)*	6 (2.5)
Partial response	4 (13.8)*	26 (10.8)
DCR, n/N (%)	15/29 (51.7)	NR
ORR by PD-L1 expression, n/N (%)†		
<1%	0/9 (0)	9/73 (12.3)
≥1%	7/17 (41.2)	15/88 (17.0)
≥5%	6/11 (54.5)	12/54 (22.2)
≥50%	4/7 (57.1)	7/19 (36.8)

*Includes unconfirmed responses. †PD-L1 expression was not determined in 3 patients; none of these patients were responders.

1. Ferris RL, et al. *N Engl J Med.* 2016 Oct 8 [Epub ahead of print]; 2. BMS data on file.

ORR and BOR With Lirilumab + Nivolumab (NCT01714739) or Nivolumab Monotherapy (CheckMate 141) in Evaluable Patients With SCCHN

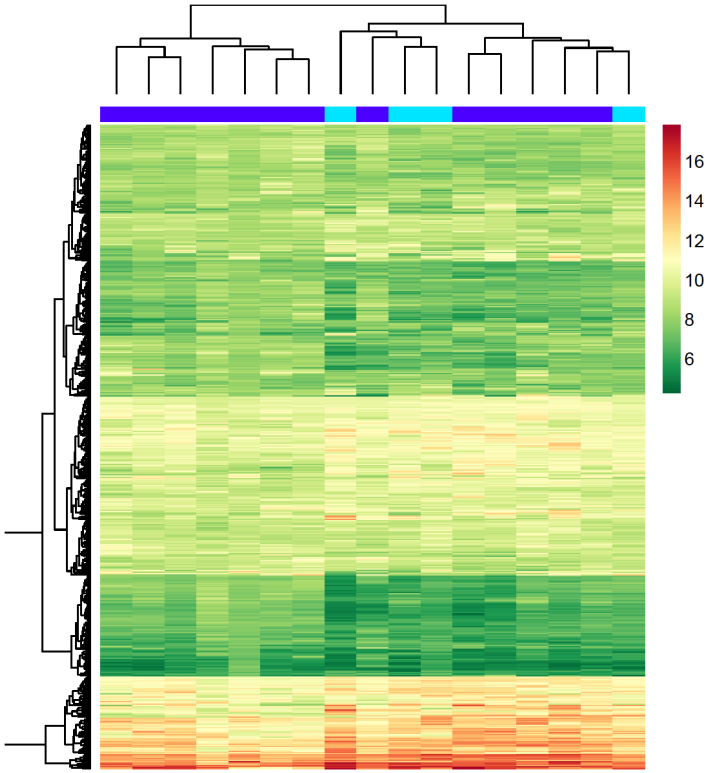
	NCT01714739 (Phase 1/2) Lirilumab + Nivolumab	CheckMate 141 (Phase 3)[1,2] Nivolumab Monotherapy
ORR, n/N (%)	**7/29 (24.1)***	**32/240 (13.3)**
Complete response	3 (10.3)*	6 (2.5)
Partial response	4 (13.8)*	26 (10.8)
DCR, n/N (%)	15/29 (51.7)	NR
ORR by PD-L1 expression, n/N (%)†		
<1%	0/9 (0)	9/73 (12.3)
≥1%	7/17 (41.2)	15/88 (17.0)
≥5%	6/11 (54.5)	12/54 (22.2)
≥50%	4/7 (57.1)	7/19 (36.8)
Overall survival in all patients, % (95% CI)		
At 6 months	90‡	55.6 (48.9, 61.8)
At 12 months	60§	36.0 (28.5, 43.4)

*Includes unconfirmed responses. †PD-L1 expression was not determined in 3 patients; none of these patients were responders. ‡Patients at risk, n = 15/41. §Patients at risk, n = 10/41.

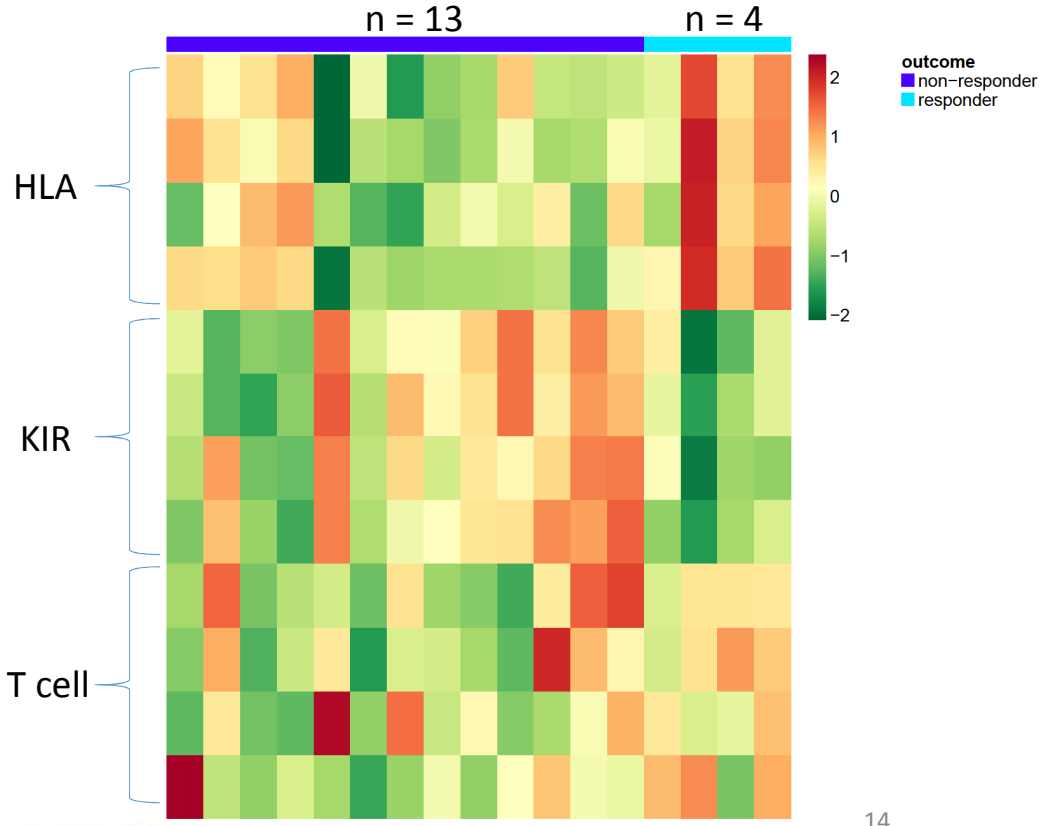
1. Ferris RL, et al. *N Engl J Med.* 2016 Oct 8 [Epub ahead of print]; 2. BMS data on file.

Preliminary Heat Map Analysis in Patients With SCCHN (n = 17): Lirilumab + Nivolumab Responders, Non-Responders Have Distinct Expression Patterns

Unsupervised Cluster Analysis
549 Gene panel Edgeseq from FFPE



KIR, HLA, T-Cell Genes Differentially Expressed



Conclusions

- This is the first report of efficacy with the anti-KIR agent lirilumab in combination with nivolumab in patients with SCCHN
- Lirilumab plus nivolumab demonstrated a potentially differentiated profile in patients with advanced, platinum-refractory SCCHN, with enhanced clinical activity, particularly in inflamed (PD-L1–positive) tumors and with deep and durable responses observed in some patients
- The combination of lirilumab plus nivolumab has a similar safety profile to that observed with nivolumab monotherapy[1-5]
- Further evaluation of the safety and efficacy of lirilumab plus nivolumab is ongoing in other tumor types

1. Brahmer JR, et al. *J Clin Oncol.* 2010;28;3167-75; 2. Brahmer JR, et al. *N Engl J Med*. 2012;366;2455-65; 3. Robert C, et al. *N Engl J Med.* 2015;372;320-30; 4. Borghaei H, et al. *N Engl J Med.* 2015;373:1627-39; 5. Ferris RL, et al. *N Engl J Med.* 2016 Oct 8 [Epub ahead of print].

Acknowledgements

- The patients and families that made this trial possible
- The clinical study teams that participated in this trial

- Dako for collaborative development of the PD-L1 IHC 28-8 pharmDx assay
- Bristol-Myers Squibb, Inc., Innate Pharma SA, Marseille, France, and Ono Pharmaceutical Company Limited, Osaka, Japan
- The study was funded by Bristol-Myers Squibb, Inc.
- All authors contributed to and approved the presentation; writing and editorial assistance was provided by Jonathan Morgan

Investigators

France
Joel Guigay, Caroline Even, Jerome Fayette, Christophe Le Tourneau

Italy
Lisa Licitra

United States of America
F. Stephen Hodi, Willian Sharfman, Neil Segal, Rachel Sanborn, Thomas Gajewski, Donald Lawrence, David McDermott, Robert Ferris, Maura Gillison, Moon Fenton