A Phase 1, Open-Label, Dose Escalation Study of Enoblituzumab in Combination with Pembrolizumab in Patients with Select Solid Tumors

Charu Aggarwal[1], Anthony Joshua[2], Robert Ferris[3], Scott Antonia[4], Osama Rahma[5], Anthony Tolcher[6], Roger B. Cohen[1], Yanyan Lou[7], Ralph Hauke[8], Nicholas Vogelzang[9], Dan Zandberg[10], Arash Kalebasty[11], Victoria Atkinson[12], Alex Adjei[13], Mahesh Seetharam[14], Ariel Birnbaum[15], Andrew Weickhardt[16], Vinod Ganju[17], Riva Bondarenko[18], Linda Peng[18], Tony Wu[18], Scott Currence[18], Jan Baughman[18], Ezio Bonvini[18], Stacie Goldberg[18], Jon Wigginton[18], Nehal Lakhani[19]

[1]University of Pennsylvania/Abramson Cancer Center, Philadelphia, PA; [2]St. Vincent's Hospital, Sydney, Australia; [3]University of Pittsburgh, Pittsburgh, PA; [4]Moffitt Cancer Center, Tampa, FL; [5]Dana Farber Cancer Institute, Boston, MA; [6]START, San Antonio, TX; [7]Mayo Clinic, Jacksonville, FL; [8]Nebraska Cancer Specialists, Omaha, NE; [9]Comprehensive Cancer Centers of Nevada, Las Vegas, NV; [10]University of Maryland, Baltimore, MD; [11]Norton Cancer Institute, Louisville, KY; [12]University of Queensland, Brisbane, Australia; [13]Mayo Clinic, Rochester, MN; [14]Mayo Clinic, Scottsdale, AZ; [15]Rhode Island Hospital, Providence, RI; [16]Olivia Newton-John Cancer Research Institute, Melbourne, Australia; [17]Peninsula and Southeast Oncology, Frankston, Australia; [18]MacroGenics, Inc., Rockville, MD; [19]START Midwest, Grand Rapids, MI

ClinicalTrials.gov #NCT02475213 Abstract #O24

Disclosures

Charu Aggarwal, M.D., M.P.H.:

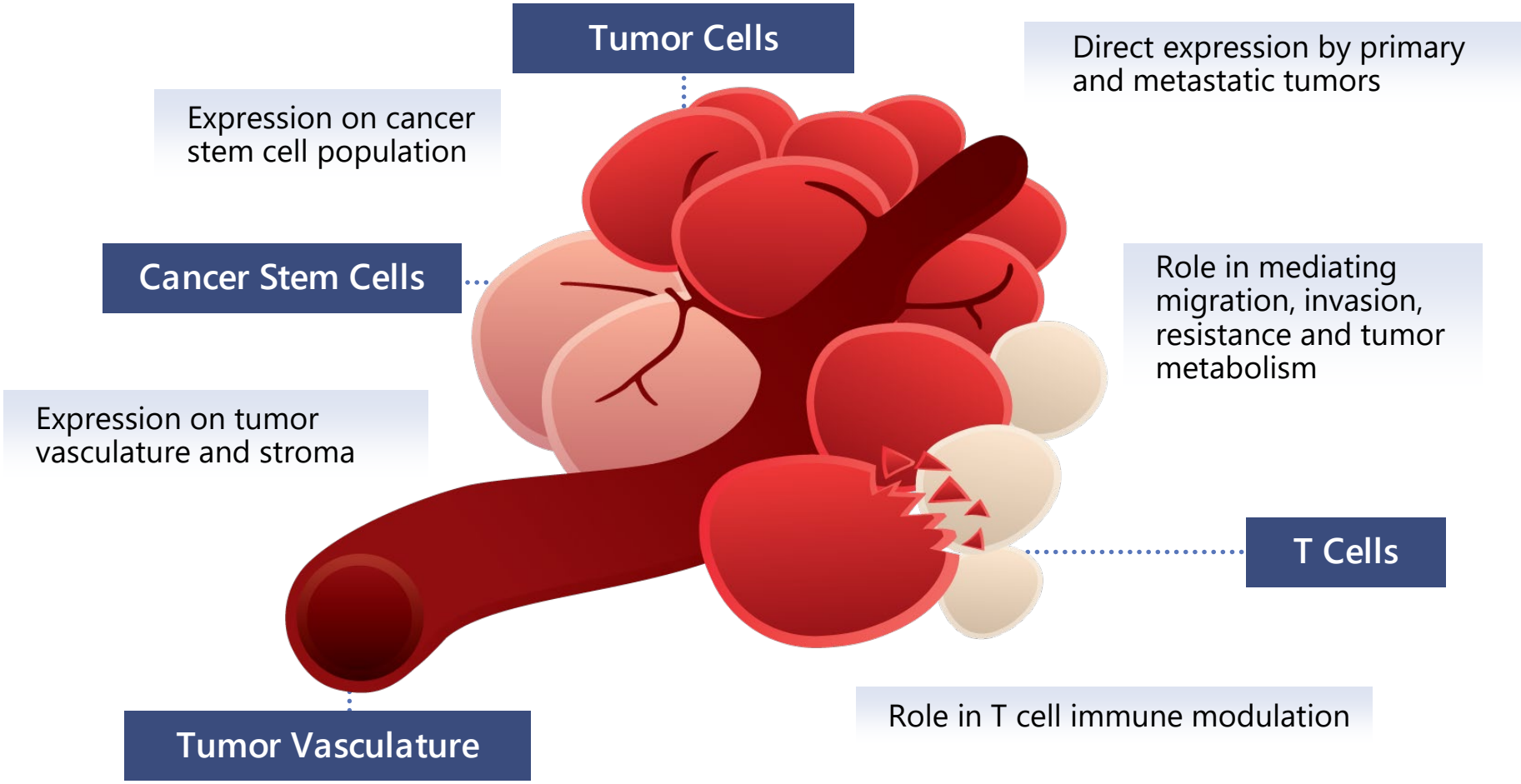
- Institutional Research Funding: Merck, Incyte, MacroGenics, MedImmune
- Advisory Board/ Consultant: BMS, Celgene, Genentech-Roche, Astra Zeneca
- Speakers Bureau: None

This study was sponsored by MacroGenics, Inc.

Enoblituzumab is not approved by the Food and Drug Administration

Rationale for Targeting B7-H3 in Cancer

- *B7-H3 expression associated w/adverse clinical features/outcome in various solid tumors*
- *B7-H3 expression may inversely correlate w/responsiveness to anti-PD-1 therapy**



** Yonesaka, et al., CCR, 2018*

High Rate of B7-H3 Positivity Across Broad Range of Solid Tumors

Majority of B7-H3-positive tumors express high levels of B7-H3 (2+ or above)

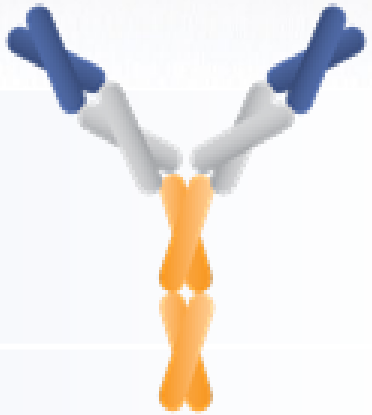
Enoblituzumab +Pembrolizumab Combination Study Indications Evaluated

Potential Indications:	IHC Summary of >1,400 Tumor Tissue Samples Screened			
	B7-H3 Positive*		2+ or Above	
Head and Neck	**19/19**	**100%**	**19/19**	**100%**
Kidney Cancer	77/78	**99%**	75/78	**96%**
Glioblastoma	65/66	**98%**	63/66	**95%**
Thyroid Cancer	34/35	**97%**	33/35	**94%**
Mesothelioma	41/44	**93%**	39/44	**89%**
Melanoma	**132/146**	**90%**	**94/146**	**64%**
Prostate Cancer	88/99	**89%**	51/99	**52%**
Pancreas Cancer	69/78	**88%**	45/78	**58%**
Bladder	**134/156**	**86%**	**123/156**	**79%**
Lung Cancer	**324/379**	**85%**	**300/379**	**79%**
Breast Cancer	189/249	**76%**	156/249	**63%**
Ovarian Cancer	59/79	**75%**	36/79	**46%**

Limited expression in normal tissue → favorable profile for targeting B7-H3 with CD3 bispecific (orlotamab, SITC #P305, #P366) and/or ADC (MGC018, SITC #P306)

** B7-H3 positivity reflects any grade staining via fixed tumor microarray; B7-H3 is expressed on tumor cells as well as tumor-associated vasculature.*

Enoblituzumab: Fc-optimized, Anti-B7-H3 Antibody



Candidate	• Humanized, Fc-optimized anti B7-H3 antibody
Function/MoA	• Enhances Fc-mediated activities, including ADCC – **Increases** binding to activating **FcγR, CD16A,** including low-affinity allele – **Decreases** binding to inhibitory **FcγR, CD32B** • Coordinate engagement of innate and adaptive immunity
Key Clinical Programs	• Phase 1b combination study (with pembrolizumab) enrolled • Investigator-sponsored study ongoing in neoadjuvant prostate cancer (SITC #P338) • Combination study with anti-PD-1 (MGA012*) planned

** Also known as INCMGA00012; see SITC #P669, P313, P336.*

Rationale for Enoblituzumab+Pembrolizumab Combination

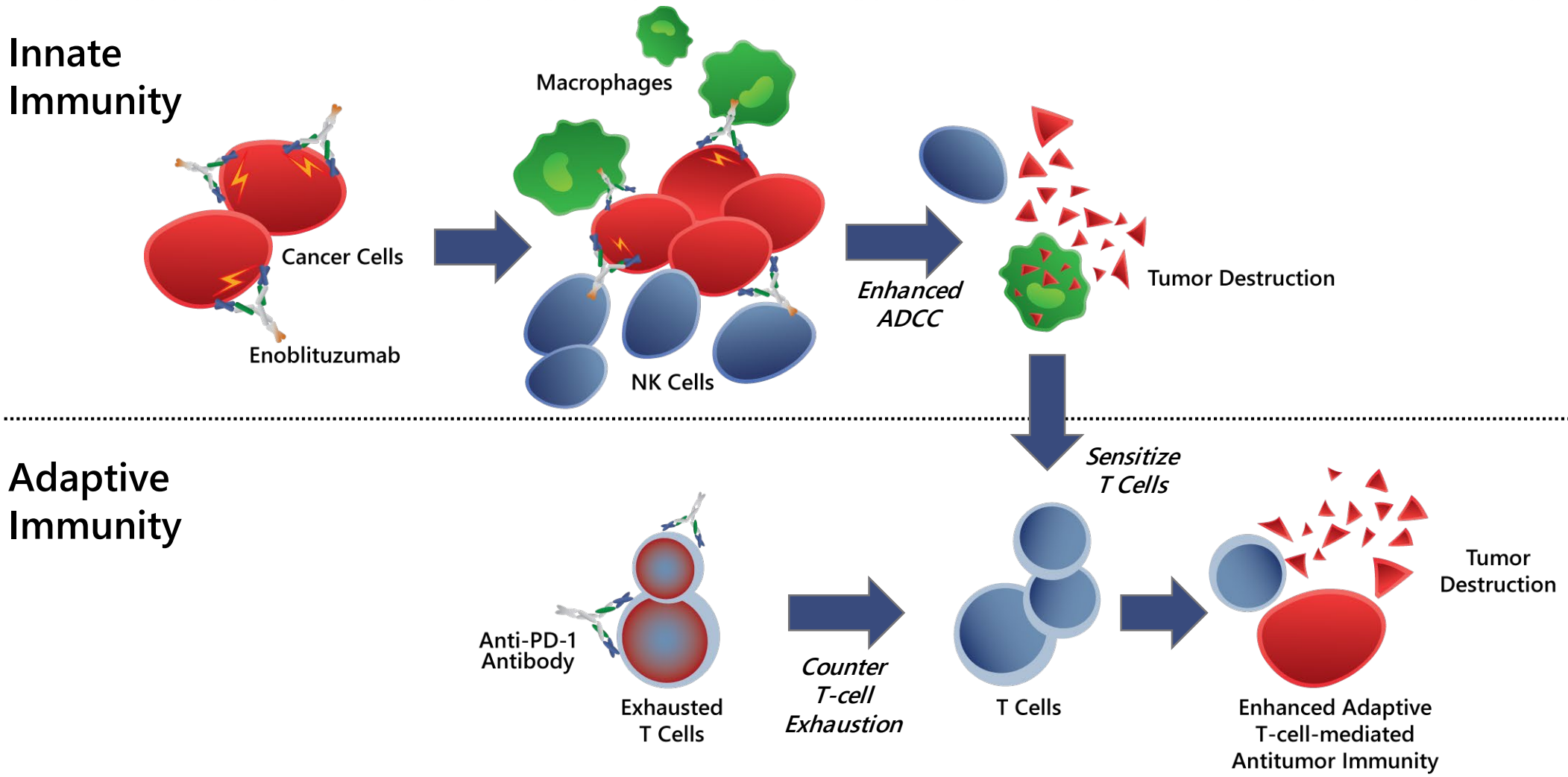
***Hypothesis**: Coordinate engagement of innate and adaptive immunity with enoblituzumab and anti-PD-1 may mediate greater antitumor activity than either single agent alone*

- Activity of Fc-optimized antibody (margetuximab, anti-HER2) combined with pembrolizumab benchmarked favorably vs. historical anti-PD-1 monotherapy experience in gastric carcinoma[(a)]
- Preliminary data indicates enoblituzumab can modulate T-cell repertoire in treated patients
  - Enhanced peripheral T-cell clonality and clone abundance[(b)]
  - Enhanced local T-cell infiltration in prostate cancer[(c)]
- Combined targeting of B7-H3 and PD-1/PD-L1 in preclinical tumor models can mediate greater antitumor activity than either single agent alone[(d)]
- NK cells may express PD-1, and PD-1/PD-L1 interaction can impair NK cell function
  - PD-1/PD-L1 blockade can enhance NK cell function and preclinical antitumor activity[(e)]

(a) Presented at ASCO 2018, #4030; (b) Unpublished; (c) Presented at SITC 2018, #P338; (d) Lee, et al., Cell Research, 2017; (e) Hsu, et al., J Clin Invest, 2018.

Rationale for Enoblituzumab+Pembrolizumab Combination

Coordinate engagement of innate and adaptive immunity to mediate tumor regression



Enoblituzumab+Pembrolizumab Study Design

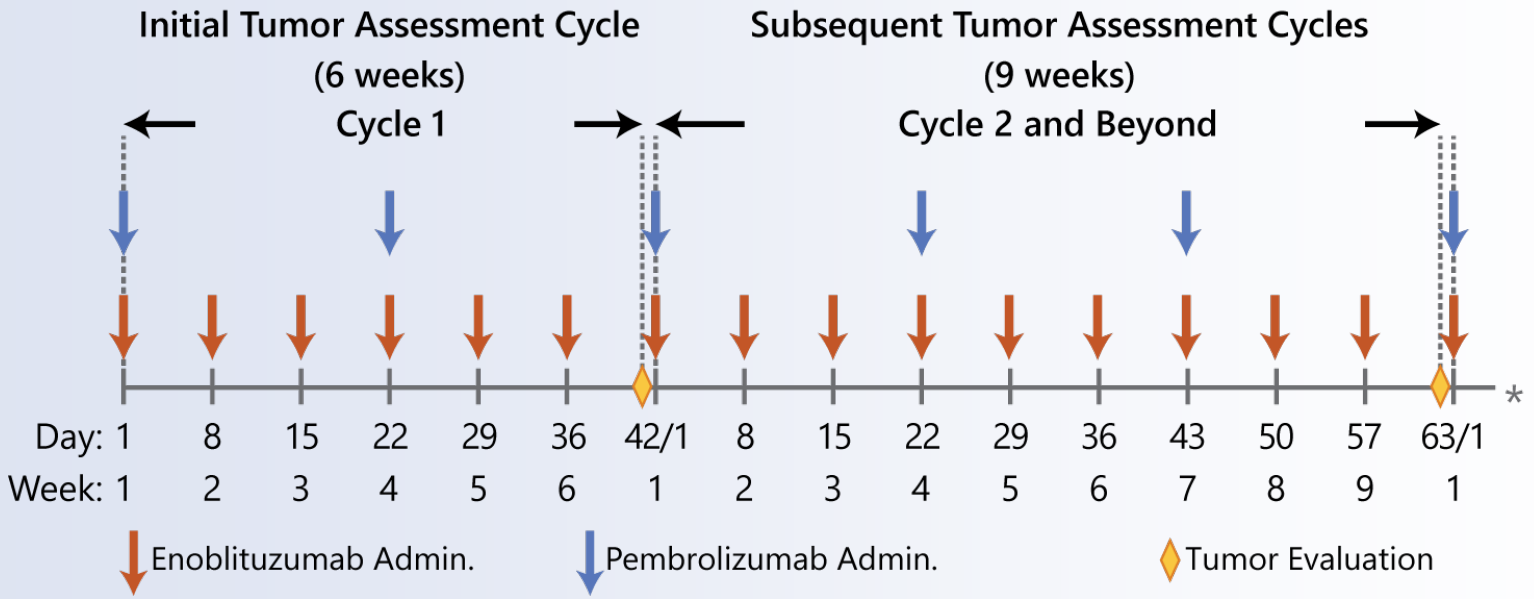
Dose Escalation + Expansion

Dose Escalation
(Dosing completed, No MTD defined)

Cohorts 1-3
3, 10, 15 mg/kg enoblituzumab +
2 mg/kg pembrolizumab
B7-H3 Positive Tumors
3+3+3 Design

Dose Expansion
- NSCLC (anti-PD-1/PD-L1 Naïve, PD-L1<1%)
- NSCLC (Post anti-PD-1/PD-L1)
- SCCHN (anti-PD-1/PD-L1 Naïve)
- SCCHN (Post anti-PD-1/PD-L1)
- Melanoma (Post anti-PD-1/PD-L1)
- Urothelial Cancer (Post anti-PD-1/PD-L1)

Dosing and Cycle Schedule



** Efficacy follow-up period: up to 96 weeks after last dose of either drug*

Safety Profile

Drug-Related Adverse Event (≥5% of Patients)	No. (%) of Patients	
	All Grades Total (N=133)	≥ Grade 3 (N=133)
Any adverse event	115 (86.5)	36 (27.1)
Infusion-related reaction	73 (54.9)	9 (6.8)
Fatigue	37 (27.8)	2 (1.5)
Rash	14 (10.5)	1 (0.8)
Nausea	12 (9.0)	0
Pyrexia	12 (9.0)	0
Lipase increased	11 (8.3)	8 (6.0)
Arthralgia	10 (7.5)	0
Decreased appetite	9 (6.8)	2 (1.5)
Diarrhea	9 (6.8)	1 (0.8)
Hypothyroidism	8 (6.0)	0
Anemia	7 (5.3)	1 (0.8)
Pneumonitis	7 (5.3)	2 (1.5)
Chills	7 (5.3)	0

Immune-Related Adverse Events of Special Interest (AESI)	No. (%) of Patients	
	All Grades Total (N=133)	≥ Grade 3 (N=133)
Pneumonitis	5 (3.8)	2 (1.5)
Myocarditis	2 (1.5)	1 (0.8)
Diarrhea	1 (0.8)	1 (0.8)
Adrenal insufficiency	1 (0.8)	1 (0.8)
Colitis	1 (0.8)	0

- Drug-related AE:
  - Leading to treatment discontinuation: 6.8%
  - Leading to death: 0.8% (1 patient with pneumonitis)
- Nature of events consistent with enoblituzumab or pembrolizumab alone

Data cut-off date: October 12, 2018.

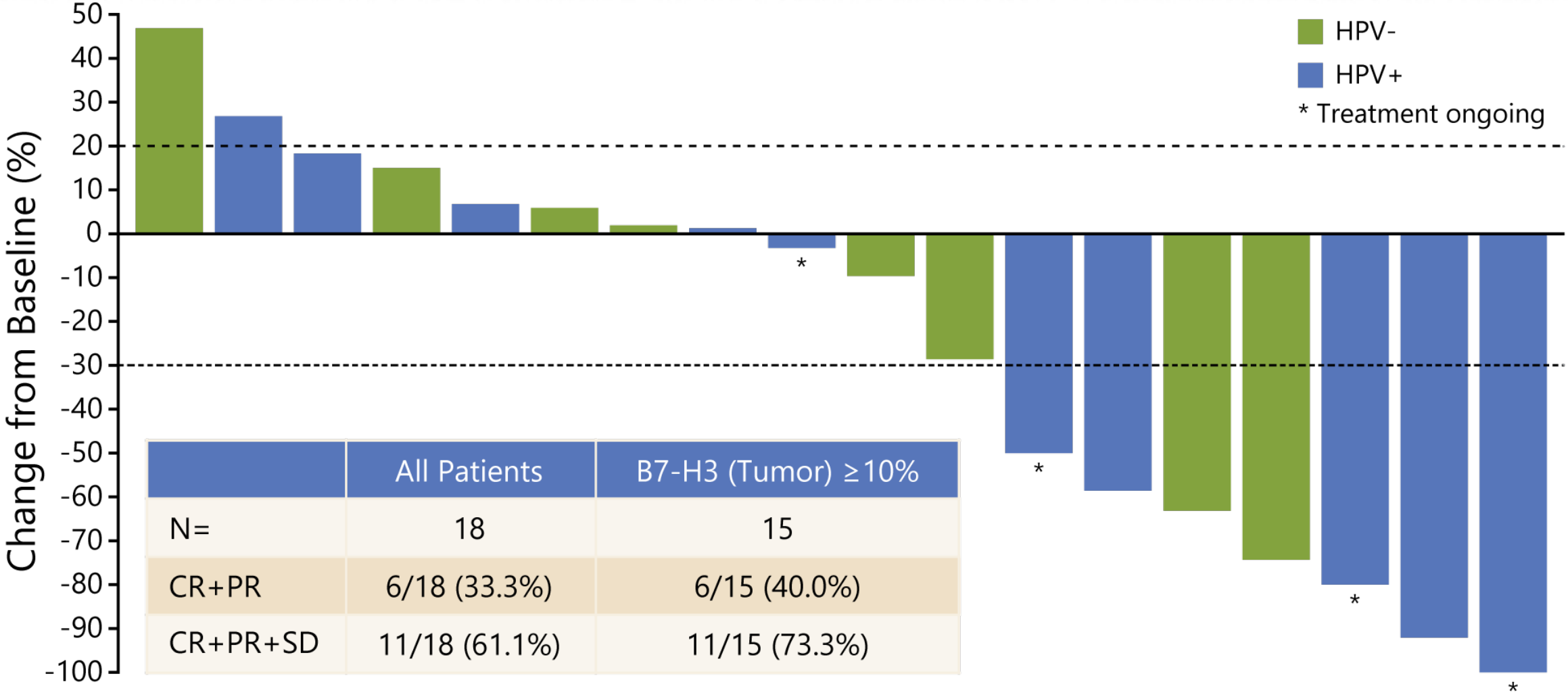
Summary of Overall Best Response Status (RECIST)

	Anti-PD-1/PD-L1 Naïve		Prior Anti-PD-1/PD-L1			
Indication	**SCCHN**	**NSCLC**	**SCCHN**	**NSCLC**	**Urothelial Cancer**	**Cutaneous Melanoma**
Total Treated Patients	21	16	24	25	21	14
Age (years) **Mean ± SD** **Median (Range)**	 62.8 ± 9.13 65.0 (44 - 74)	 65.7 ± 7.75 65.0 (50 - 79)	 62.7 ± 9.99 62.0 (34 - 76)	 64.2 ± 8.73 63.0 (50 - 83)	 67.1 ± 9.39 70.0 (40 - 79)	 60.5 ± 15.24 63.0 (25 - 79)
Gender **Female** **Male**	 3 (14.3) 18 (85.7)	 8 (50.0) 8 (50.0)	 2 (8.3) 22 (91.7)	 10 (40.0) 15 (60.0)	 6 (28.6) 15 (71.4)	 3 (21.4) 11 (78.6)
Response Evaluable	18	14	19	21	17	13
PR	6/18 (33.3%)	5/14 (35.7%)	0	1/21 (4.8%)	1/17 (5.9%)	1/13 (7.7%)
SD	5/18 (27.8%)	8/14 (57.1%)	9/19 (47.4%)	12/21 (57.1%)	8/17 (47.1%)	5/13 (38.5%)
PD	7/18 (38.9%)	1/14 (7.1%)	10/19 (52.6%)	7/21 (33.3%)	8/17 (47.1%)	6/13 (46.2%)
NE	0	0	0	1/21 (4.8%)	0	1/13 (7.7%)

PR=Confirmed Partial Response, SD=Stable Disease, PD=Progressive Disease, NE=Not Evaluable

Antitumor Activity in SCCHN Patients, Anti-PD-1/PD-L1 Naïve

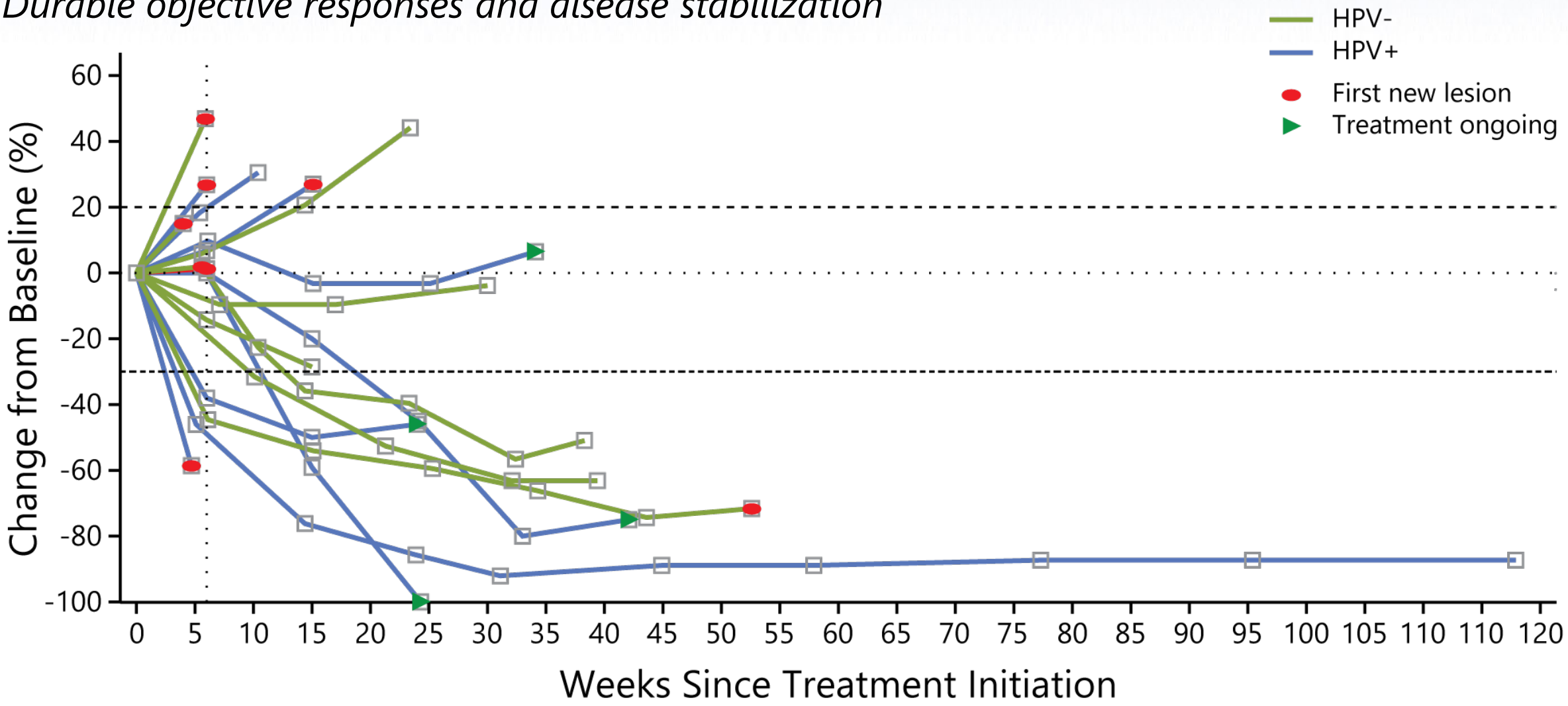
Tumor regression in patients with SCCHN, irrespective of HPV status



	All Patients	B7-H3 (Tumor) ≥10%
N=	18	15
CR+PR	6/18 (33.3%)	6/15 (40.0%)
CR+PR+SD	11/18 (61.1%)	11/15 (73.3%)

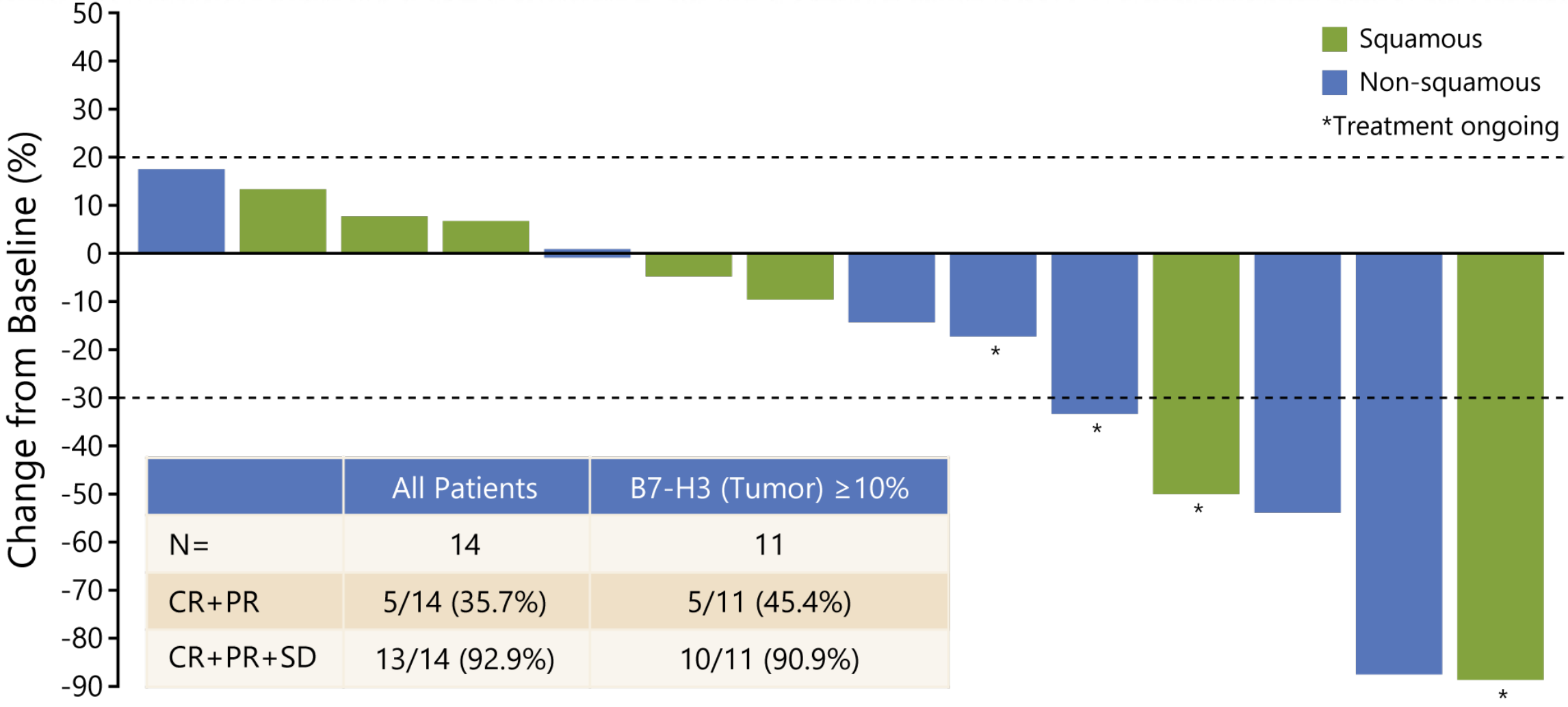
Antitumor Activity in SCCHN Patients, Anti-PD-1/PD-L1 Naïve

Durable objective responses and disease stabilization



Antitumor Activity in NSCLC Patients, Anti-PD-1/PD-L1 Naïve, PD-L1<1%

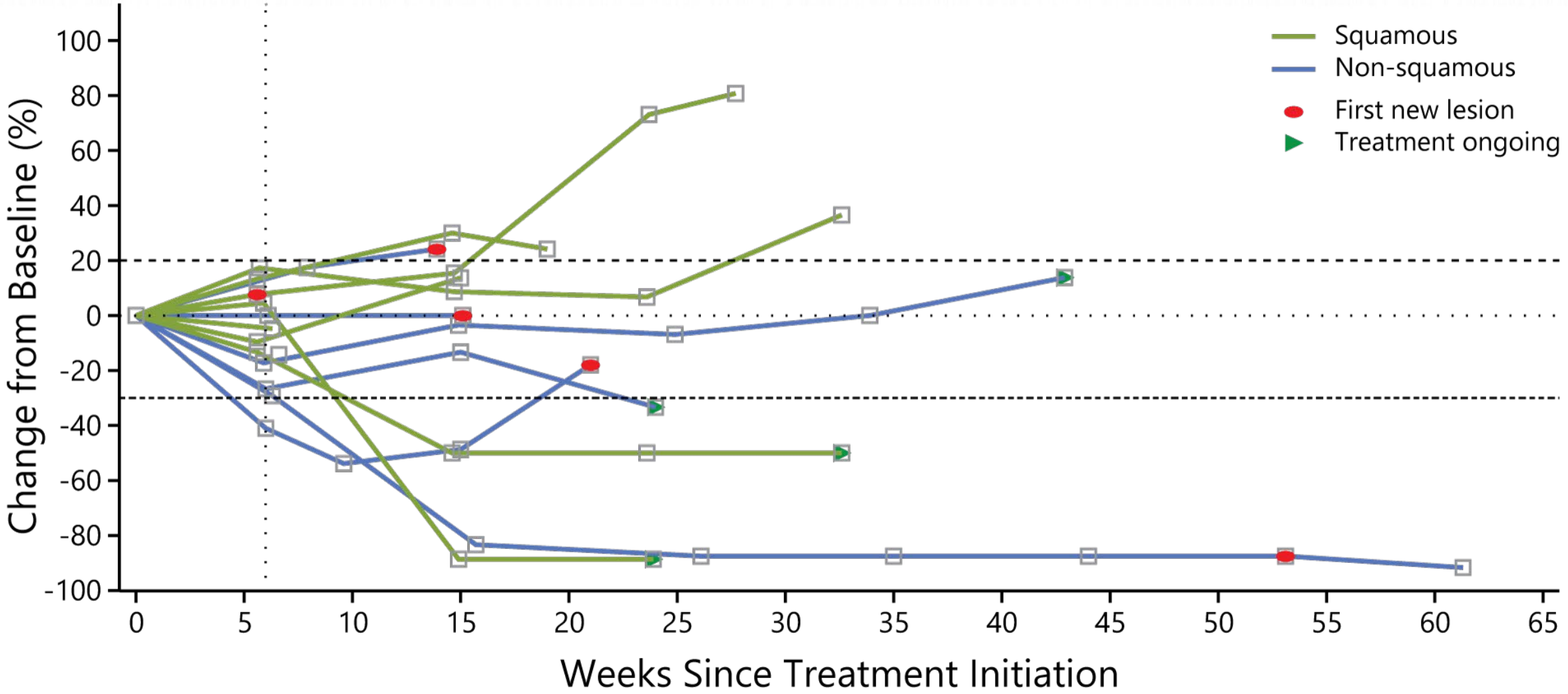
Tumor regression in NSCLC patients who are PD-L1 negative (i.e., <1%)



	All Patients	B7-H3 (Tumor) ≥10%
N=	14	11
CR+PR	5/14 (35.7%)	5/11 (45.4%)
CR+PR+SD	13/14 (92.9%)	10/11 (90.9%)

Antitumor Activity in NSCLC Patients, Anti-PD-1/PD-L1 Naïve, PD-L1<1%

Durable objective responses and disease stabilization



Enoblituzumab+Pembrolizumab Combination Benchmarks Favorably

SCCHN	Study Results			
Agent (Study)	Enoblituzumab +Pembrolizumab	Nivolumab (CM-141)[a]	Pembrolizumab (KN-012)[b]	Pembrolizumab (KN-040)[c]
N	18	240	174	247
ORR	33.3%	13%	16%	15%

NSCLC	Study Results			
Agent (Study)	Enoblituzumab +Pembrolizumab	Nivolumab (CM-057)[d]	Nivolumab (CM-017)[e]	Pembrolizumab (KN-001)[f]
Histology	Both	Non-Squamous	Squamous	Both
N	14	108	54	87
ORR	35.7%	9%	17%	8%

(a) Ferris, et al., 2016, N Eng J Med; (b) Keytruda® package insert; (c) Cohen, et al., 2017, ESMO LBA45; (d) Borghaei, et al., 2015, NEJM; (e) Brahmer, et al., 2015, NEJM; (f) Garon, et al., 2015, NEJM

Conclusions

- Enoblituzumab/pembrolizumab combination demonstrated acceptable safety profile
- Rate of immune-related adverse events comparable to experience w/anti-PD-1 monotherapy
- In anti-PD-1/PD-L1 naïve patients treated with enoblituzumab+pembrolizumab, objective response rates benchmark favorably with historical experience with anti-PD-1 monotherapy
  – SCCHN (post platinum chemotherapy): 33.3%
  – NSCLC (PD-L1 <1%): 35.7%
- Further investigation of enoblituzumab+anti-PD-1 combination is warranted in patients with SCCHN and NSCLC, including in combination with chemotherapy
- Given expression patterns of B7-H3, further investigation of combination of enoblituzumab and anti-PD-1 is warranted in other tumor types, including both checkpoint-naïve and experienced populations

Acknowledgements

Thank you to the patients and their families who participated in this study.