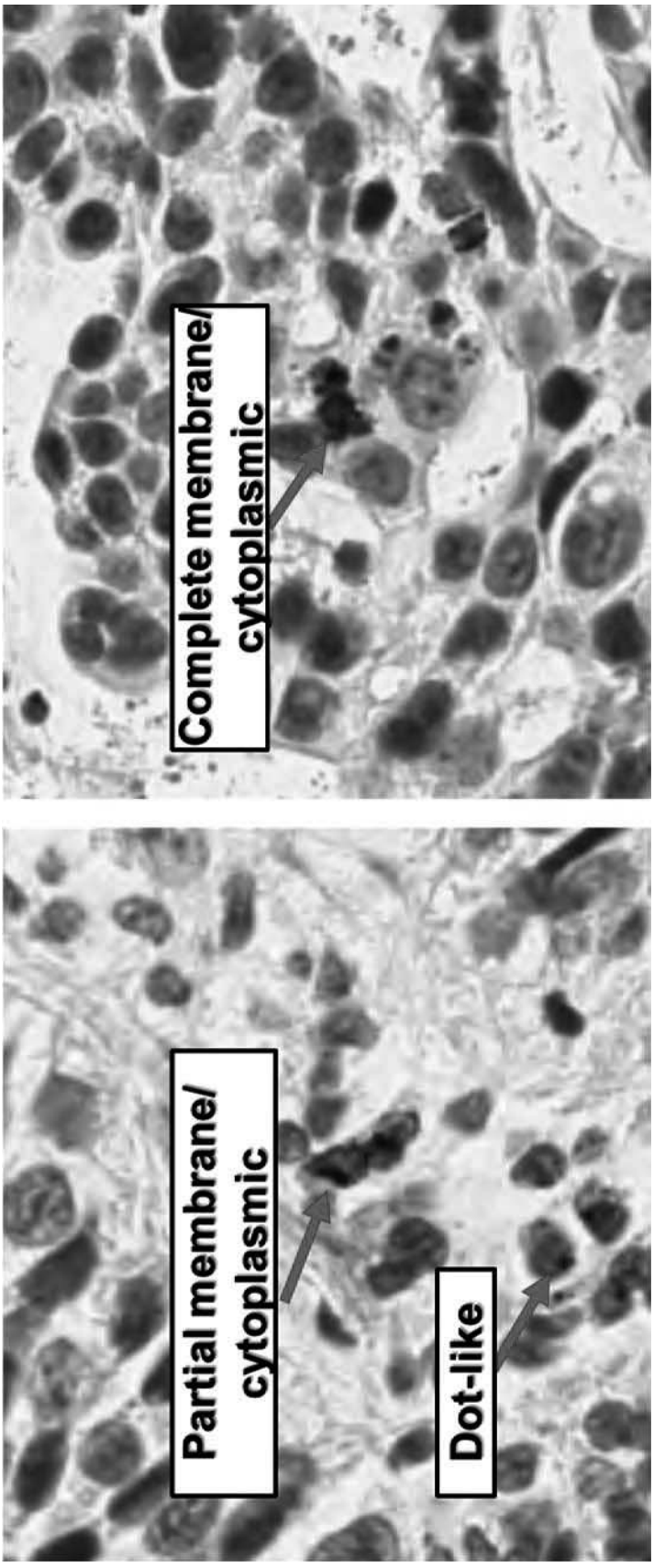

Complete membrane/
cytoplasmic
Partial membrane/
cytoplasmic
Dot-like

Figure 1

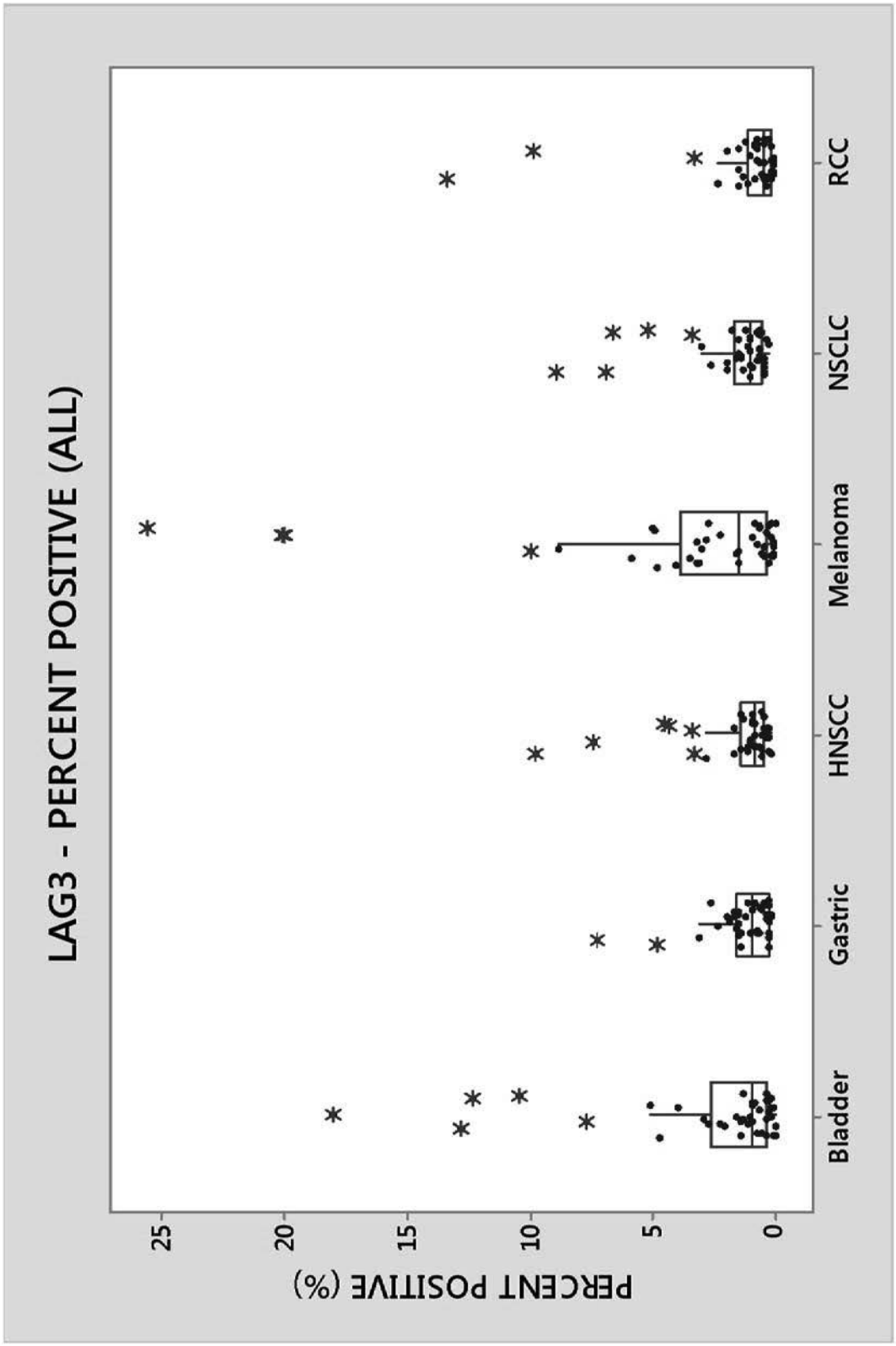
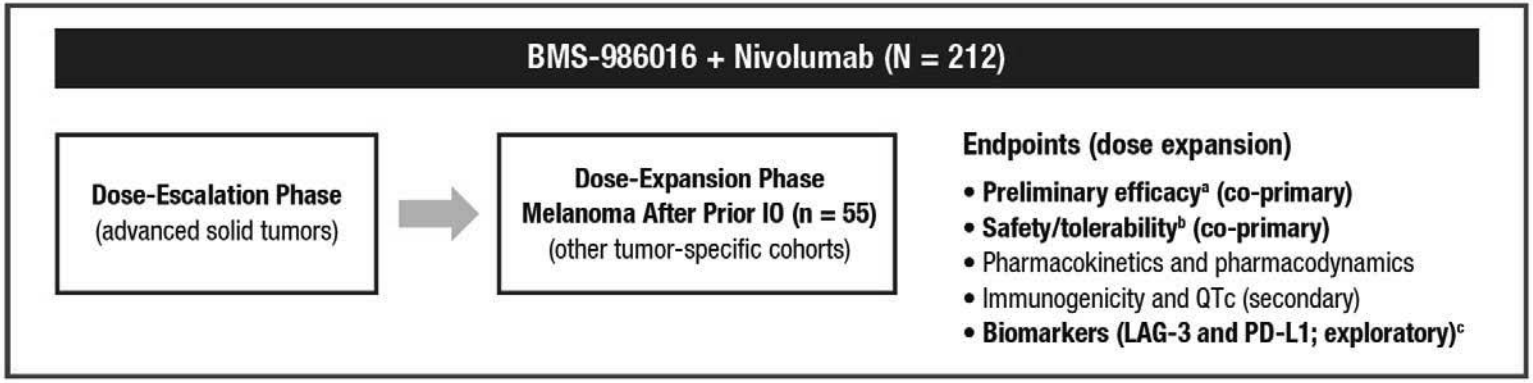

LAG3 - PERCENT POSITIVE (ALL)
PERCENT POSITIVE (%)
0
5
10
15
20
25
Bladder
Gastric
HNSCC
Melanoma
NSCLC
RCC

Figure 2

Figure 3A



[a]Tumor response evaluated per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1[10] (investigator assessment). [b]Safety evaluated per Common Terminology Criteria for Adverse Events v4.0[11] during treatment and up to 135 days after discontinuation. [c]LAG-3 and PD-L1 expression (percent of positive cells within invasive margin, tumor, and stroma) evaluated using immunohistochemistry (IHC) assays on formalin-fixed, paraffin-embedded tumor sections. Immune cell LAG-3 expression (≥ 1% or < 1%) determined using mouse antibody clone 17B4; tumor cell PD-L1 expression (≥ 1% or < 1%) determined using Dako 28-8 PD-L1 IHC 28-8 kit.

Figure 3B

Key Eligibility Criteria for Patients in the Melanoma Prior-IO Expansion Cohort

Inclusion	Exclusion
At least 18 years of age and ECOG PS ≤ 1	Prior exposure to IOs other than anti–CTLA-4 and/or anti–PD-1/PD-L1 antibody therapy (eg, anti–PD-L2, anti–KIR, anti–CD137, and anti–OX40)
Advanced (metastatic and/or unresectable) melanoma	Uveal melanoma
Progression on/intolerance of ≥ 1 and ≤ 3 prior standard regimens	Uncontrolled brain metastases
Prior treatment with anti–PD-1/PD-L1 (± anti–CTLA-4 ± BRAF ± MEK inhibitors) required	Active autoimmune disease
Prior adjuvant or neoadjuvant therapy with cytokines (IL-2 or IFN) or anti–CTLA-4 antibodies allowed	
At least 1 measurable lesion per RECIST v1.1[10]	

CD137, cluster of differentiation 137; CTLA-4, cytotoxic T lymphocyte antigen-4; ECOG PS, Eastern Cooperative Oncology Group performance status; IFN, interferon; IL-2, interleukin-2; KIR, anti–killer-cell immunoglobulin-like receptor.

Figure 4

Table 1. Baseline Demographics and Disease Characteristics

	Mel Prior IO (n = 55)
Median age (range), years	59 (25–80)
< 65 years, n (%)	36 (65)
Male, n (%)	39 (71)
Race, n (%)	
White	52 (95)
Black	1 (1.8)
Asian	1 (1.8)
Other	1 (1.8)
ECOG PS, n (%)	
0	38 (69)
1	17 (31)
M stage at study entry, n (%)	
M0	7 (13)
M1A	6 (11)
M1B	4 (7.3)
M1C with brain metastasis	1 (1.8)
M1C without brain metastasis	37 (67)
LDH, n (%)	
Normal	25 (45)
Normal to < 2 × ULN	13 (24)
≥ 2 × ULN	8 (15)
Unknown	9 (16)
Liver metastases, n (%)	
Yes	11 (20)
No	44 (80)
BRAF status, n (%)	
Mutation	21 (38)
No mutation	31 (56)
Unknown	3 (5.5)

M, metastasis.

Figure 5

Table 2. Prior Therapy

Patients, n (%)	Mel Prior IO (n = 55)
Prior radiotherapy	16 (29)
Prior systemic therapy	54 (98)
Immunotherapy	54 (98)
Anti–CTLA-4[a]	32 (58)
Anti–PD-1/PD-L1[b]	52 (95)
Best response to prior anti–PD-1/PD-L1[c]	
CR	1 (1.8)
PR	12 (22)
SD	16 (29)
PD	22 (40)
BRAF inhibitors	16 (29)
MEK inhibitors	11 (20)
Number of systemic regimens	
1	12 (22)
2	17 (31)
≥ 3	25 (45)
Median (range)	2 (1–5)

CR, complete response; PR, partial response; SD, stable disease. [a]Two patients received anti–PD-1/PD-L1+ anti–CTLA-4, 5 patients received anti–CTLA-4 after anti–PD-1/PD-L1, and 29 patients received anti–CTLA-4 before anti–PD-1/PD-L1; prior anti–CTLA-4 therapy was not reported in 4 patients. [b]Twenty-five patients received nivolumab, 25 patients received pembrolizumab, and 2 patients received other therapies; 2 patients did not receive prior anti–PD-1/PD-L1; prior anti–PD-1/PD-L1 was unknown in 1 patient. [c]Response in 1 patient was reported as not applicable.

Figure 6

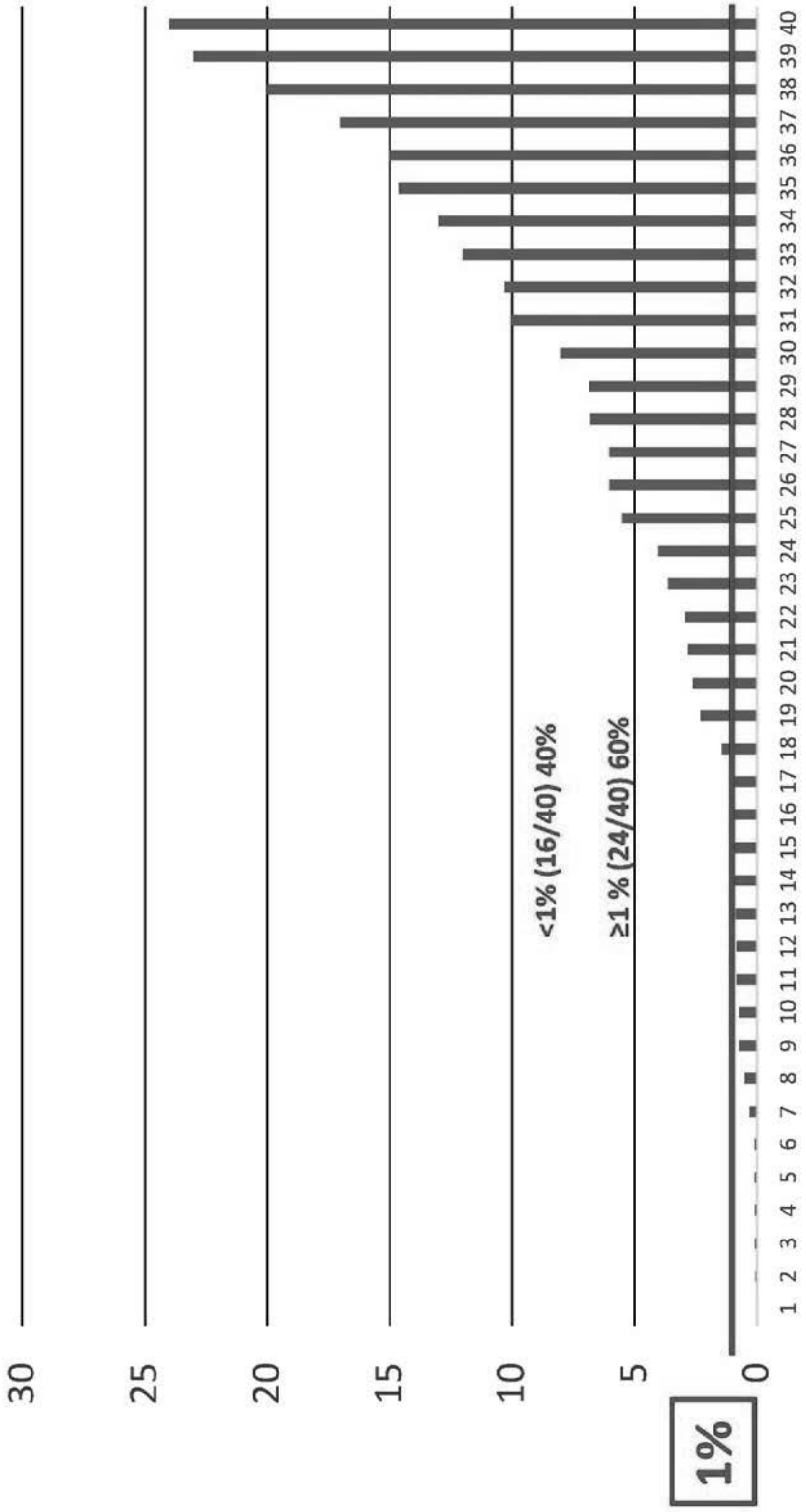

LAG-3 Monoplex % Positive: First 40 IO Experienced
Melanoma
30
25
20
15
10
5
0
1%
<1% (16/40) 40%
≥1 % (24/40) 60%
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40

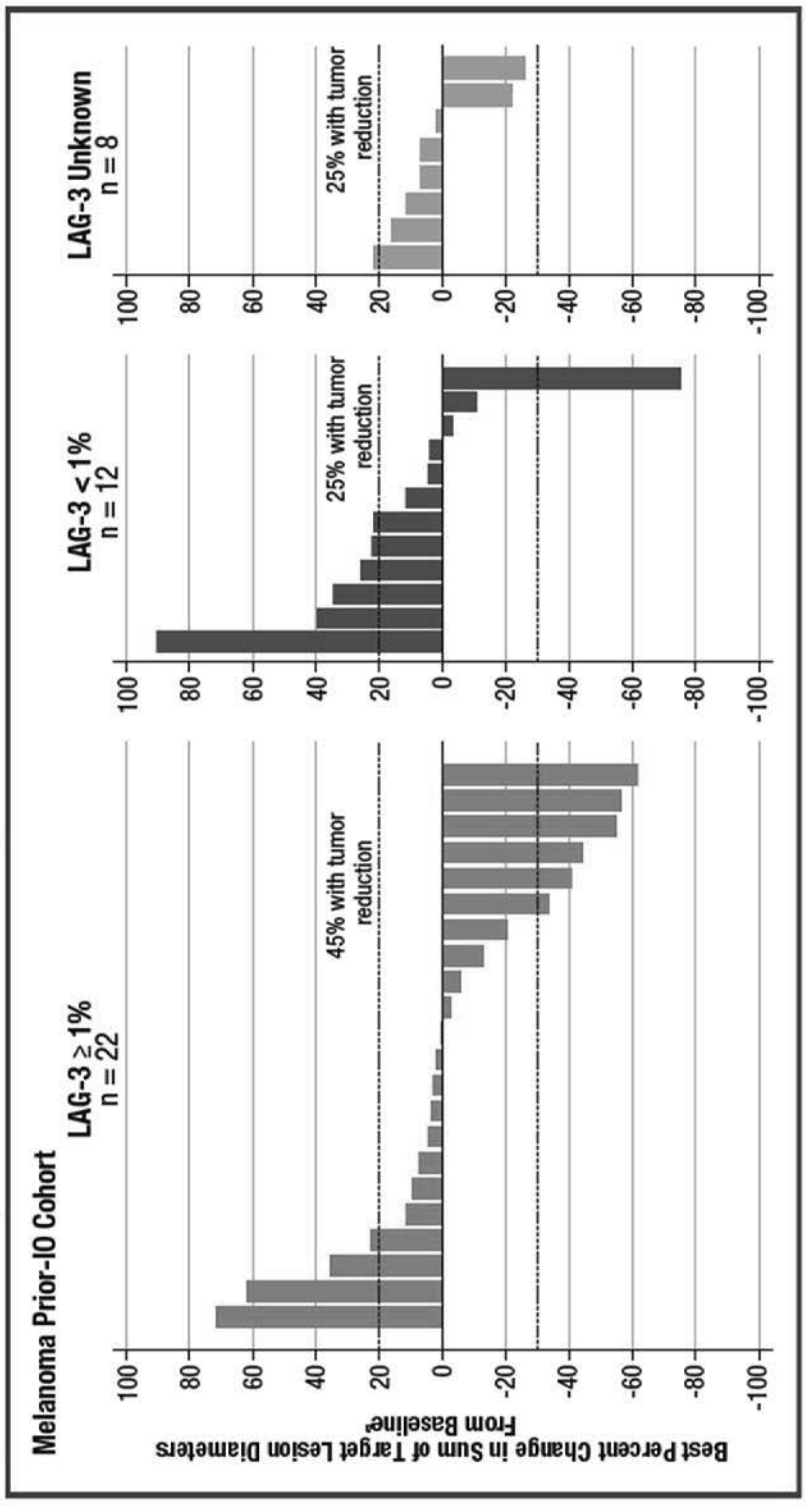
Figure 7

Table 3. Preliminary Evidence of Antitumor Activity

Patients, n (%)	Mel Prior IO (n = 48[a])
BOR	
CR	0
PR[b]	6 (13)
SD	20 (42)
PD	16 (33)
Clinical progressions[c]	6 (13)
ORR, 95% CI[b]	6 (13), 4.7, 25
LAG-3 ≥ 1% (n = 25)	5 (20), 6.8, 41
LAG-3 < 1% (n = 14)	1 (7.1), 0.2, 34
DCR (CR + PR + SD)[b]	26 (54)
LAG-3 ≥ 1% (n = 25)	16 (64)
LAG-3 < 1% (n = 14)	5 (36)

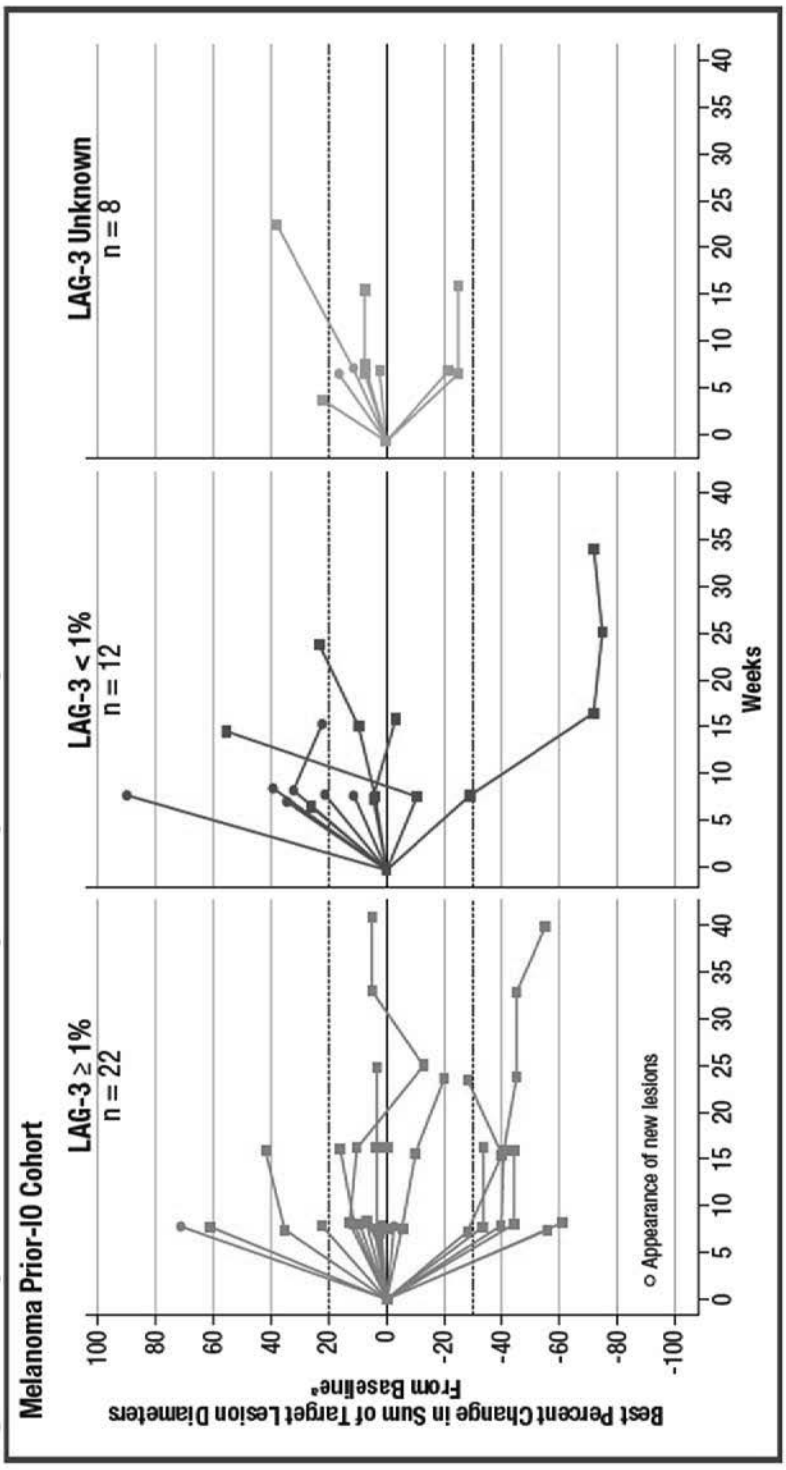
BOR, best overall response; DCR, disease control rate. [a]All response-evaluable patients; all progressed on prior anti–PD-1/PD-L1 therapy. [b]Two responses were unconfirmed. [c]Occurred prior to first radiographic scan.

Figure 8



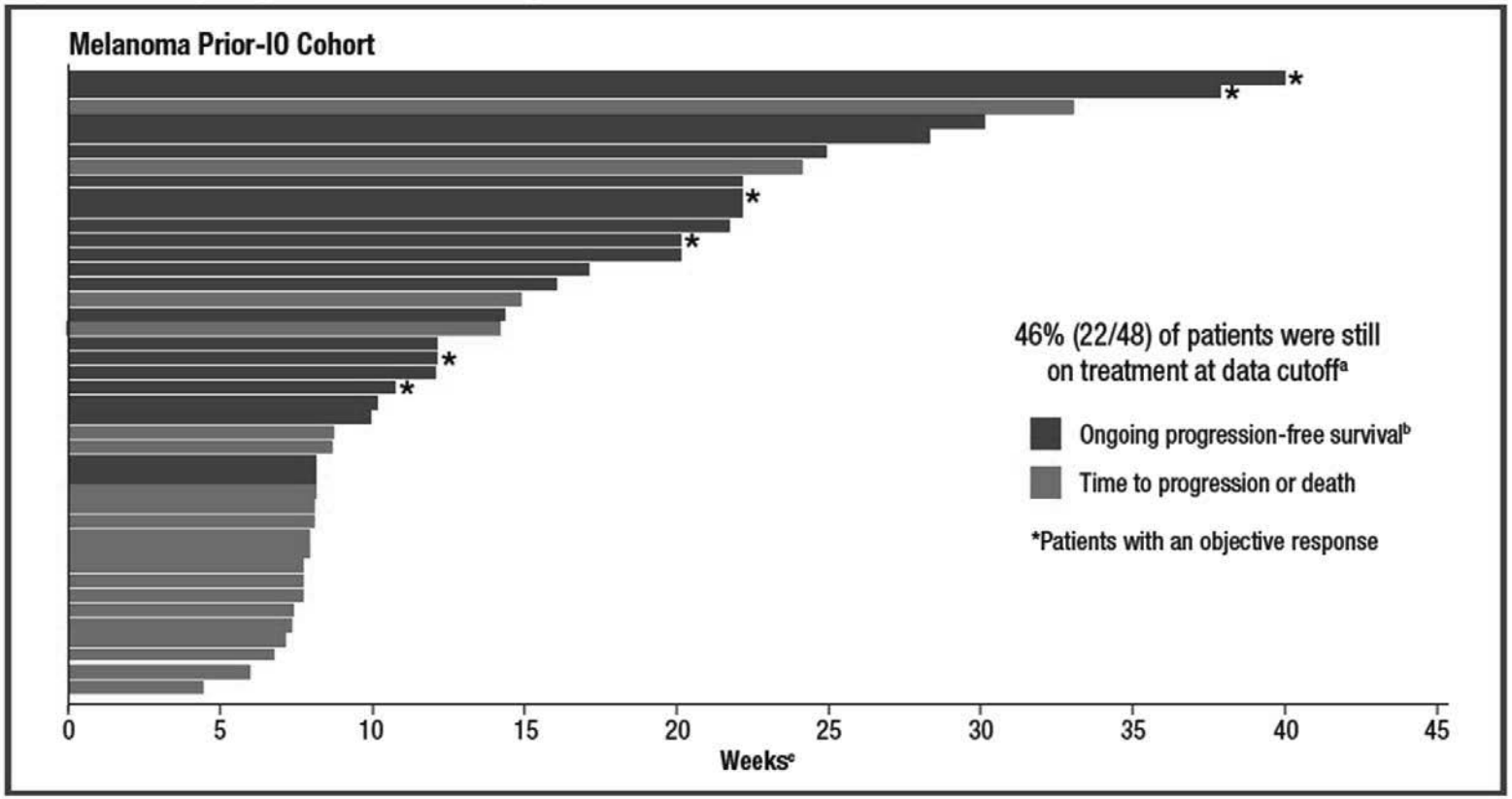
*Six patients had clinical progression prior to their first scan and are not included in the plot. One patient with best change from baseline > 30% had an unconfirmed best response of SD.

Figure 9



*Six patients had clinical progression prior to their first scan and are not included in the plot.

Figure 10



[a]Six patients had clinical progression prior to their first scan and are not included in the plot. [b]Censored on last visit. [c]Evaluations are planned for every 8 weeks.

Figure 11

Table 4. Response by Baseline Characteristics (investigator assessed)

	Mel Prior IO (n = 48[a])		
		ORR	
	n	n (%)	95% CI
LAG-3 expression			
≥ 1%	25	5 (20)	6.8, 41
< 1%	14	1 (1.7)	0.2, 34
PD-L1 expression			
≥ 1%	16	2 (13)	1.6, 38
< 1%	19	4 (21)	6.1, 46
Response based upon prior BOR to anti–PD-1/PD-L1 only			
CR	1	0	–
PR	12	2 (17)	–
SD	14	1 (7.1)	–
CR + PR + SD	27	3 (11)	2.4, 29
PD	20	2 (10)	1.2, 32
M stage at study entry			
M1A	6	1 (17)	0.4, 64
M1B	3	0	0, 71
M1C with brain metastasis	1	0	0, 97.5
M1C without brain metastasis	32	4 (13)	3.5, 29
Liver metastases			
Yes	11	1 (9.1)	0.2, 41
No	37	5 (14)	4.5, 29
BRAF status			
Mutation	19	0	0, 18
No mutation	28	6 (21)	8.3, 41

[a]All response-evaluable patients; all progressed on prior anti–PD-1/PD-L1 therapy.

Figure 12

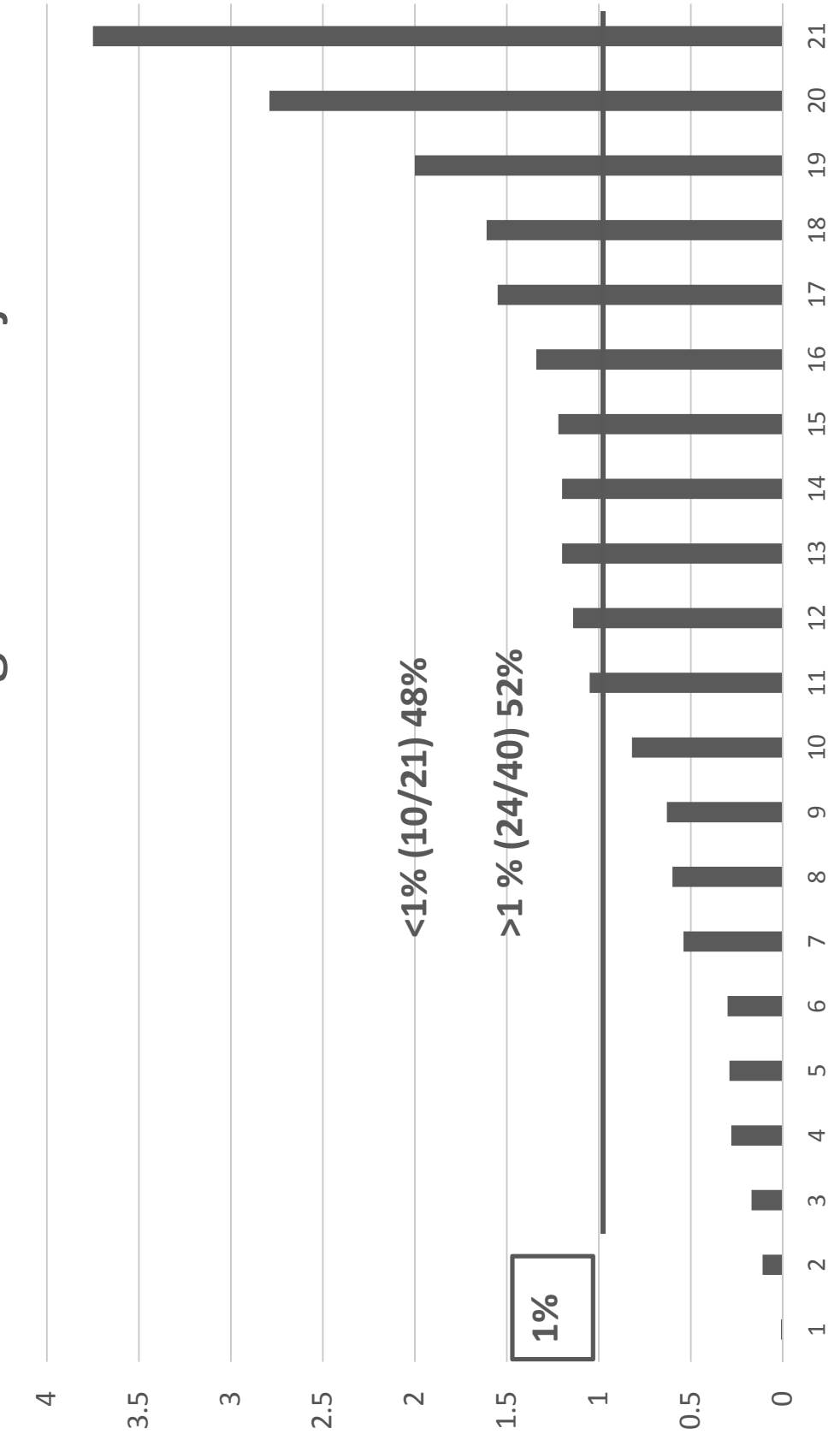

Gastric LAG3 Staining First 21 Subjects
4
3.5
3
2.5
2
1.5
1
0.5
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
<1% (10/21) 48%
>1 % (24/40) 52%
1%

Figure 13

Preliminary Clinical Activity of LAG-3 + nivo in IO Naïve Gastric Patients Enriched in LAG+ Patients

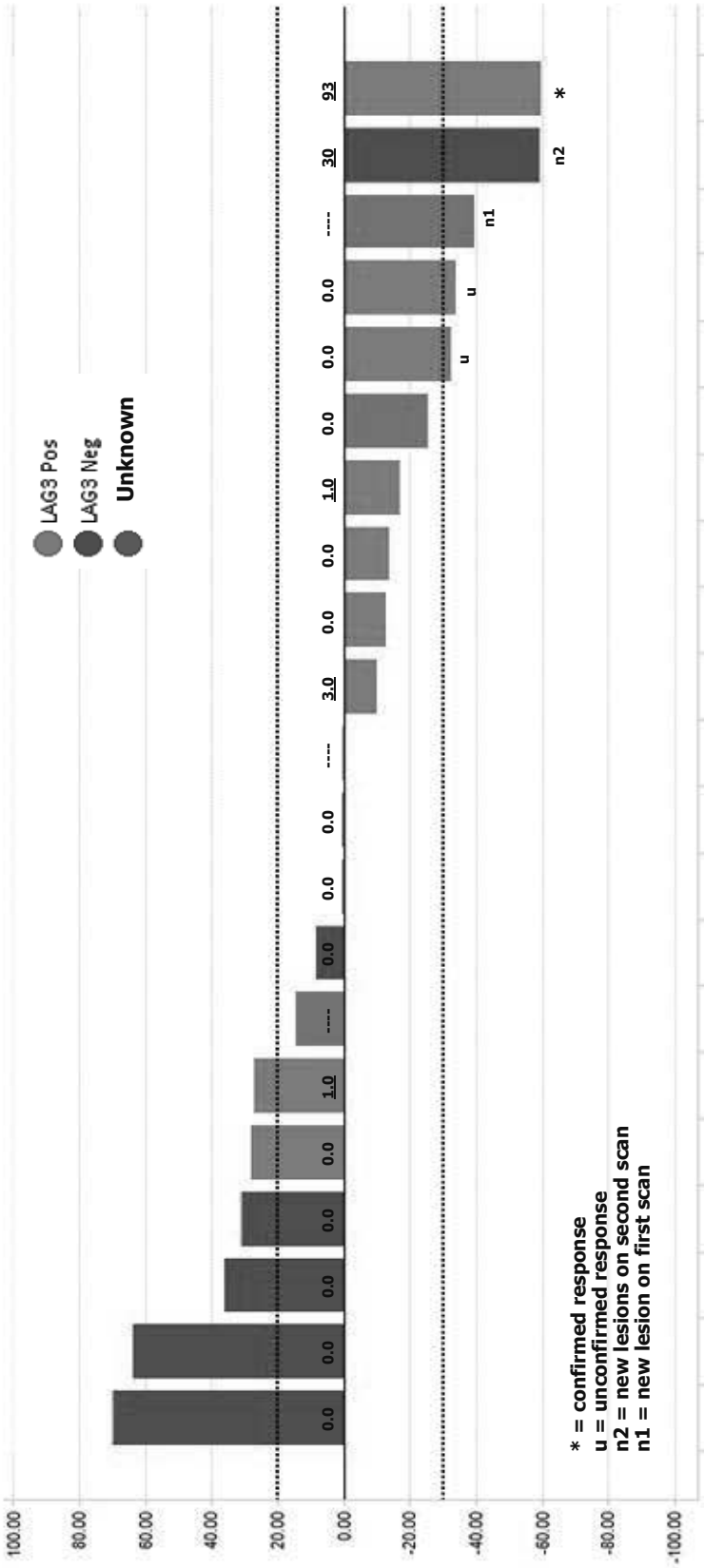


Figure 14

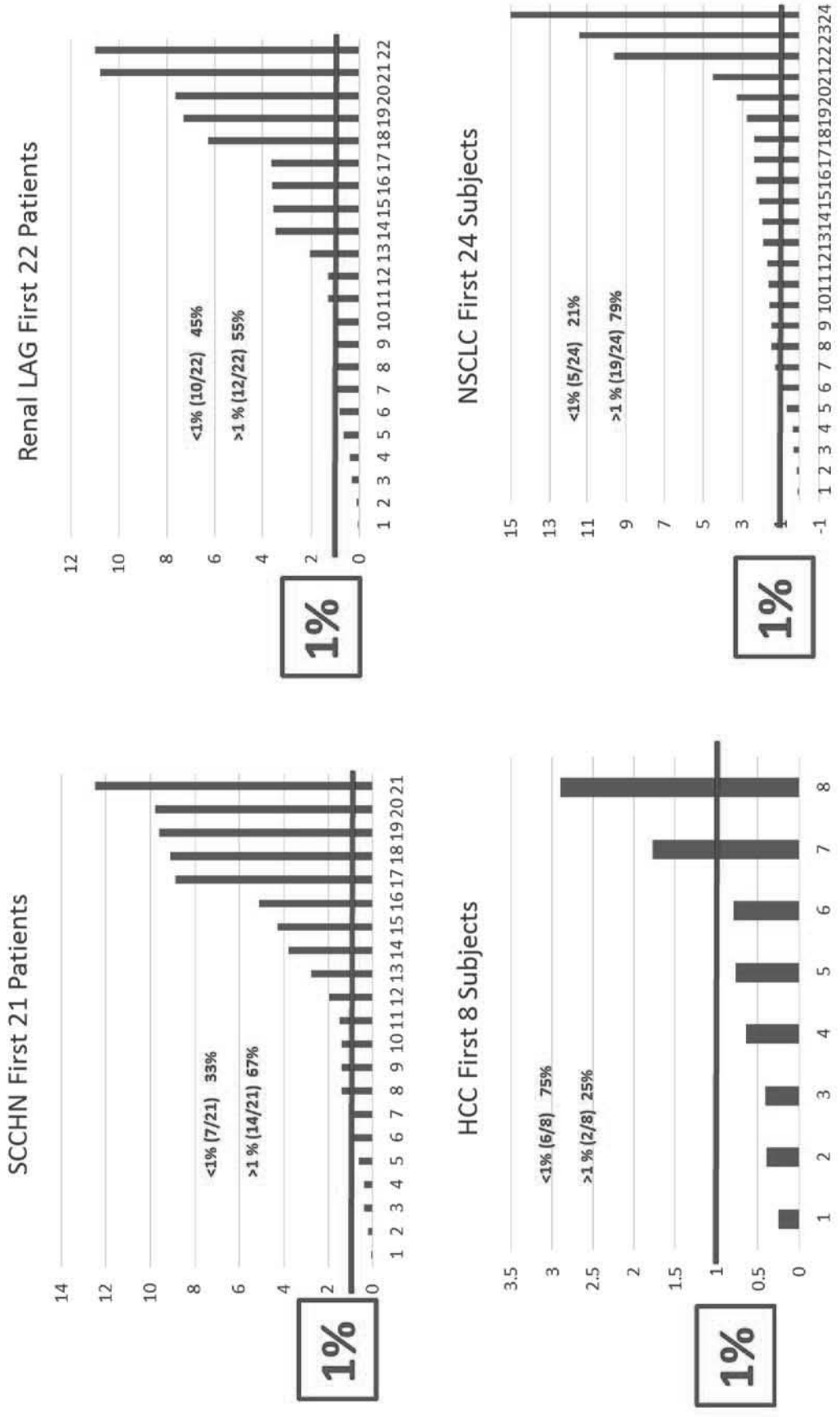
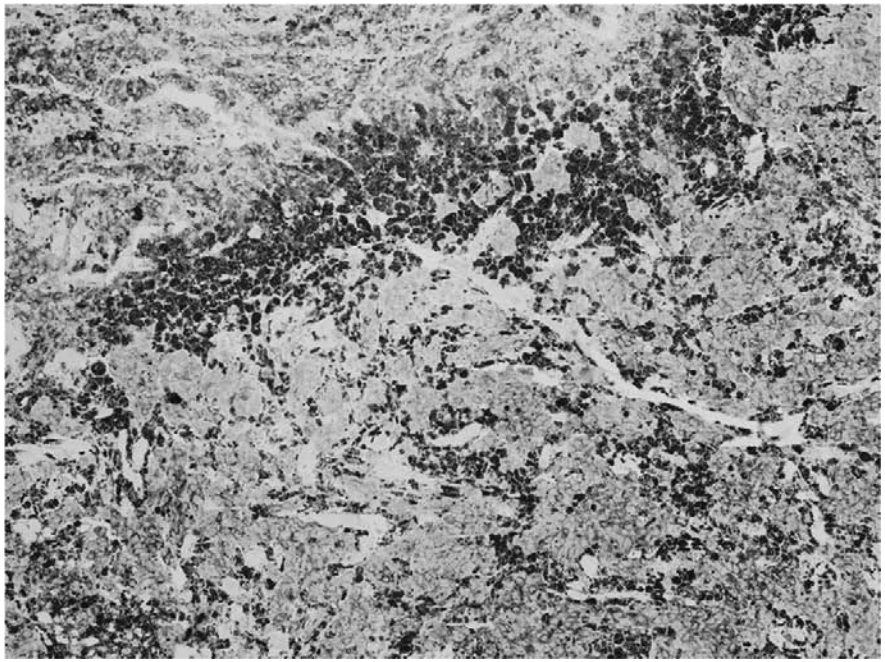
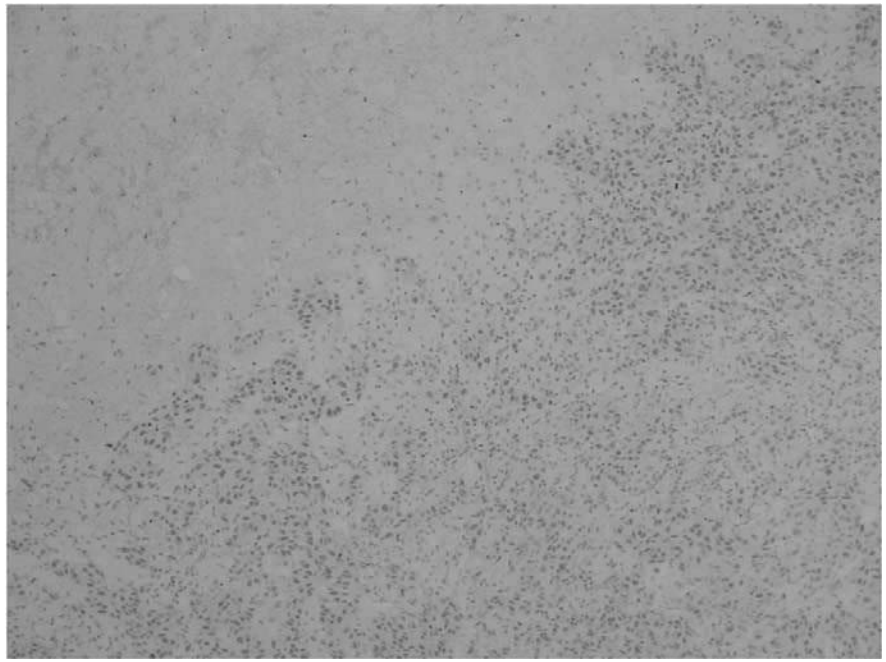

SCCHN First 21 Patients
<1% (7/21) 33%
>1 % (14/21) 67%
1%
Renal LAG First 22 Patients
<1% (10/22) 45%
>1 % (12/22) 55%
1%
HCC First 8 Subjects
<1% (6/8) 75%
>1 % (2/8) 25%
1%
NSCLC First 24 Subjects
<1% (5/24) 21%
>1 % (19/24) 79%
1%

Figure 15A

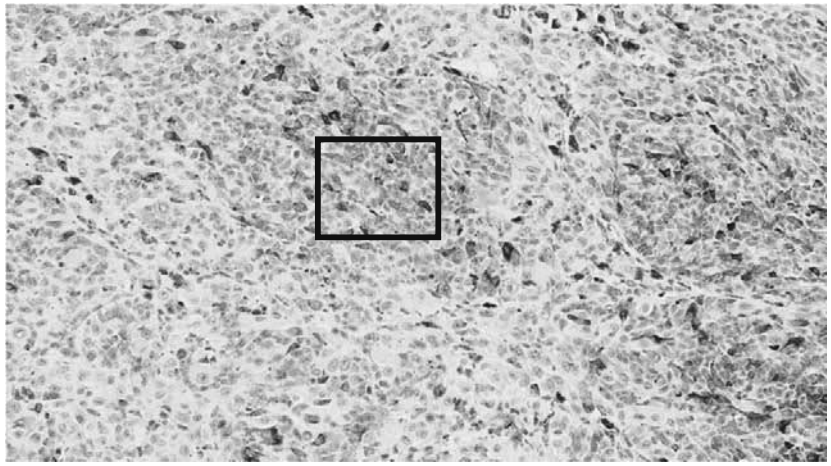


Pigmented melanoma without bleaching
(nuclei counterstained with hematoxylin)

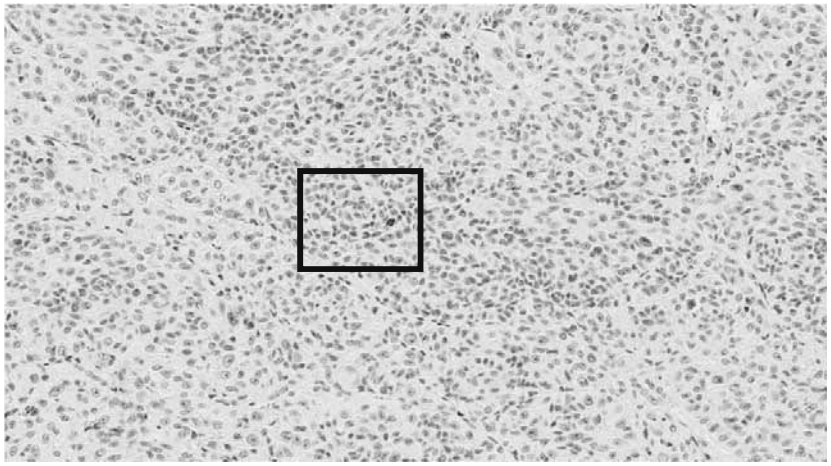


Pigmented melanoma following bleaching
(nuclei counterstained with hematoxylin)

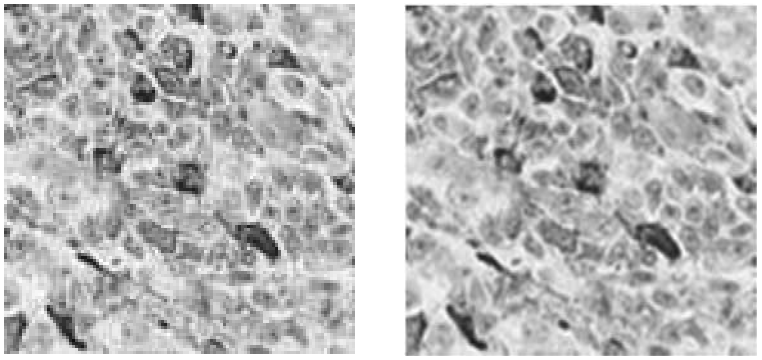
Figure 15B



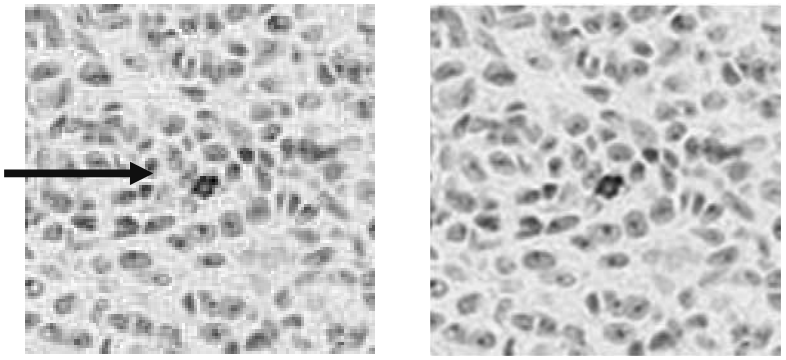
Pigmented melanoma - LAG-3 by IHC
without bleaching
(nuclei counterstained with hematoxylin)



Pigmented melanoma - LAG3 by IHC following
bleaching
(nuclei counterstained with hematoxylin)



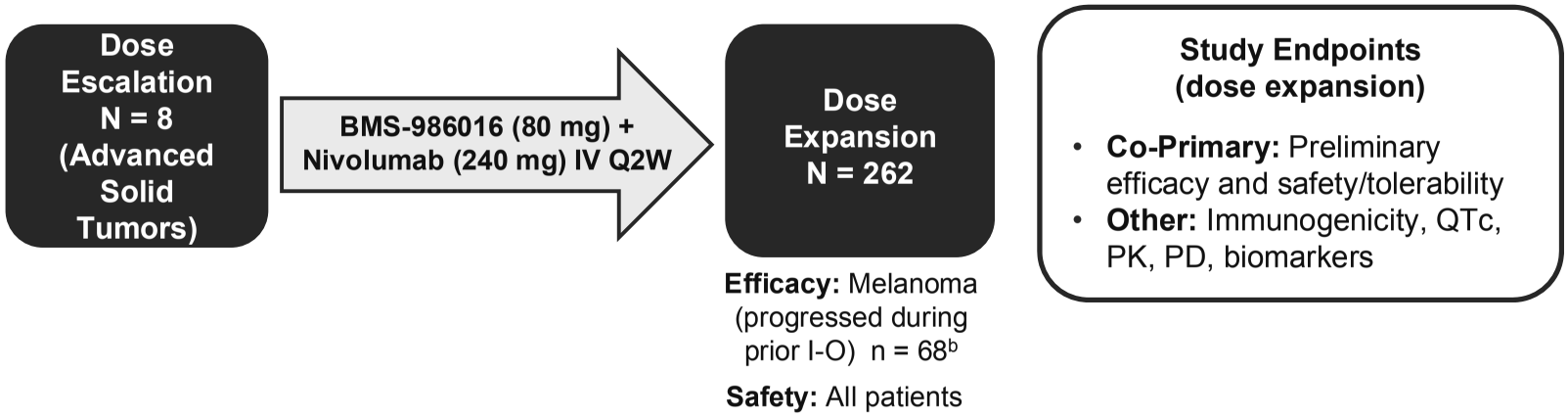
LAG-3 IHC indistinguishable from melanin



LAG-3 IHC following bleaching

Figure 16

Study Rationale and Design



[b]Sixty-one patients were response-evaluable.

Figure 17

Baseline Demographics and Disease Characteristics

	Mel Prior PD-(L)1 n = 68
Median age (range), years	60 (25–81)
< 65 years, n (%)	44 (65)
Male, n (%)	46 (68)
Race, n (%)	
White	65 (96)
Other	3 (4.4)
ECOG PS, n (%)	
0	44 (65)
1	24 (35)
M stage at study entry, n (%)	
M0	6 (8.8)
M1A	7 (10)
M1B	8 (12)
M1C with brain metastasis	1 (1.5)
M1C without brain metastasis	46 (68)

	Mel Prior PD-(L)1 n = 68
LDH, n (%)	
Normal	35 (51)
Normal to < 2 × ULN	15 (22)
≥ 2 × ULN	9 (13)
Unknown	9 (13)
Liver metastases, n (%)	
No	51 (75)
Yes	17 (25)
***BRAF* status, n (%)**	
No mutation	43 (63)
Mutation	23 (34)
Unknown	2 (2.9)

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; M, metastasis; Mel Prior PD-(L)1, patients with melanoma who progressed during prior anti–PD-1/PD-L1 therapy; ULN, upper limit of normal.

Figure 18

Prior Therapies

	Mel Prior PD-(L)1 n = 68
Prior radiotherapy, n (%)	19 (28)
Prior systemic therapy, n (%)	68 (100)
Immunotherapy	68 (100)
Anti–CTLA-4[a]	39 (57)
Anti–PD-1/PD-L1[b]	68 (100)
Best response to prior anti–PD-1/PD-L1[c]	
CR	1 (1.5)
PR	12 (18)
SD	20 (29)
PD	31 (46)
BRAF inhibitors	19 (28)
MEK inhibitors	13 (19)
Number of systemic regimens	
1	16 (24)
2	21 (31)
≥ 3	31 (46)
Median (range)	2 (1–5)

CR, complete response; CTLA-4, cytotoxic T lymphocyte antigen-4;
PD, progressive disease; PR, partial response; SD, stable disease.
[a]Four patients received anti–PD-1/PD-L1 + anti–CTLA-4, 8 patients received anti–CTLA-4 after anti–PD-1/PD-L1, and 33 patients received anti–CTLA-4 before anti–PD-1/PD-L1; prior anti–CTLA-4 therapy was not reported in 2 patients [b]Thirty-three patients received nivolumab, 33 patients received pembrolizumab, and 2 patients received other therapies. [c]Response in 1 patient was reported as not applicable.

Figure 19

Antitumor Activity of BMS-986016 + Nivolumab

	Mel Prior PD-(L)1[a]	
	All n = 61	LAG-3 ≥ 1%[b] n = 33
ORR,[c] n (%) 95% CI	7 (11.5)[d] 4.7, 22	6 (18)[d] 7, 36
BOR,[c] n (%)		
CR	1 (1.6)	1 (3.0)
PR	6 (9.8)[d]	5 (15)[d]
SD	23 (38)	15 (45)
PD	25 (41)	8 (24)
Clinical progression[e]	6 (9.8)	4 (12)
DCR (CR + PR + SD),[c] n (%) 95% CI	30 (49) 36, 62	21 (64) 45, 80

BOR, best overall response.

[a]Response-evaluable patients; all progressed during prior anti–PD-1/PD-L1 therapy. [b]Immune-cell LAG-3 expression (percent of positive cells within invasive margin, tumor, and stroma) evaluated by IHC in tumor sections with antibody clone 17B4. [c]Tumor response evaluated by investigator per Response Evaluation Criteria in Solid Tumors v1.1. [d]One response was unconfirmed. [e]Occurred prior to first radiographic scan.

Figure 20

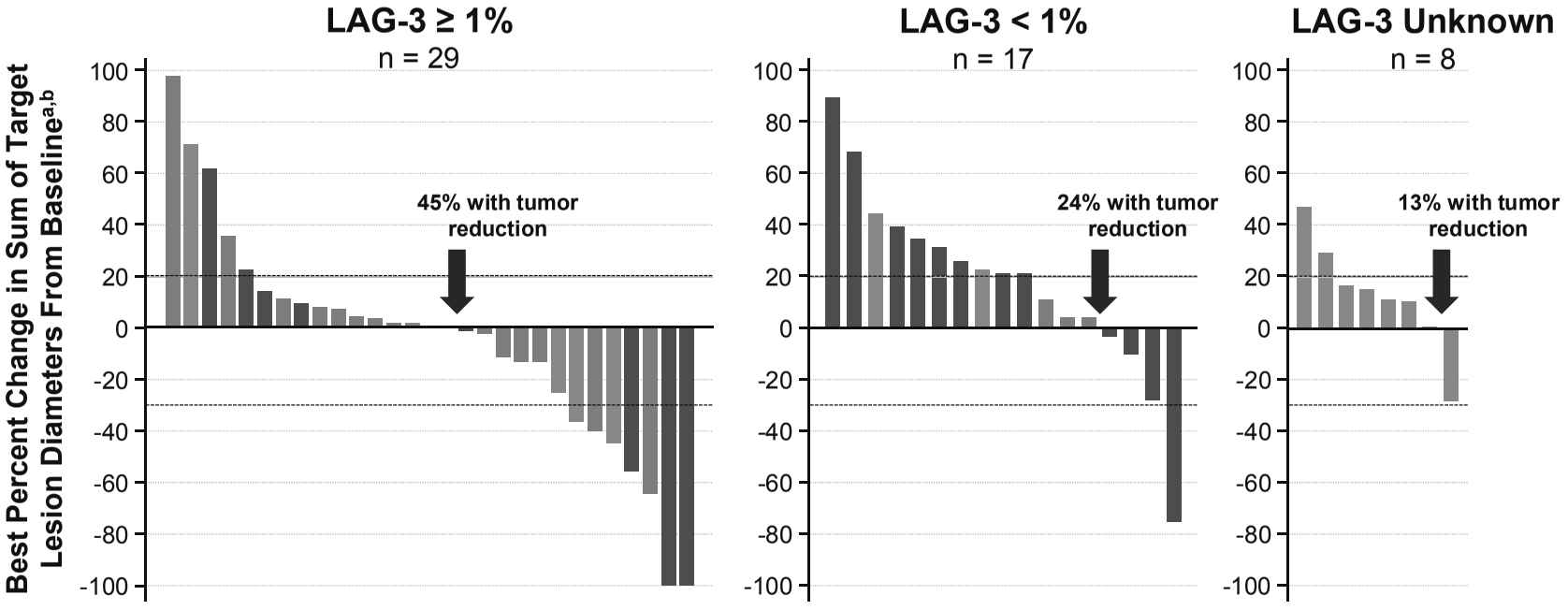
Response by Baseline Characteristics and LAG-3 Expression

	Mel Prior PD-(L)1[a]			
	LAG-3 Expression (N = 53)			
	LAG-3 ≥ 1%		LAG-3 < 1%	
	N	ORR, n (%)	N	ORR, n (%)
PD-L1 expression[b] (N = 44)				
≥ 1%	16	1 (6.3)	4	0
< 1%	11	3 (27)	13	1 (7.7)
BRAF status (N = 52)				
No mutation	21	5 (24)	11	1 (9.1)
Mutation	11	1 (9.1)	9	0
Prior anti–CTLA-4 (N = 53)				
No	12	1 (8.3)	7	1 (14)
Yes	21	5 (24)	13	0

[a]Response-evaluable patients; all progressed during prior anti–PD-1/PD-L1 therapy. [b]Tumor-cell PD-L1 expression (percent of positive cells within invasive margin, tumor, and stroma) evaluated by IHC in tumor sections with the Dako PD-L1 IHC 28-8 kit.

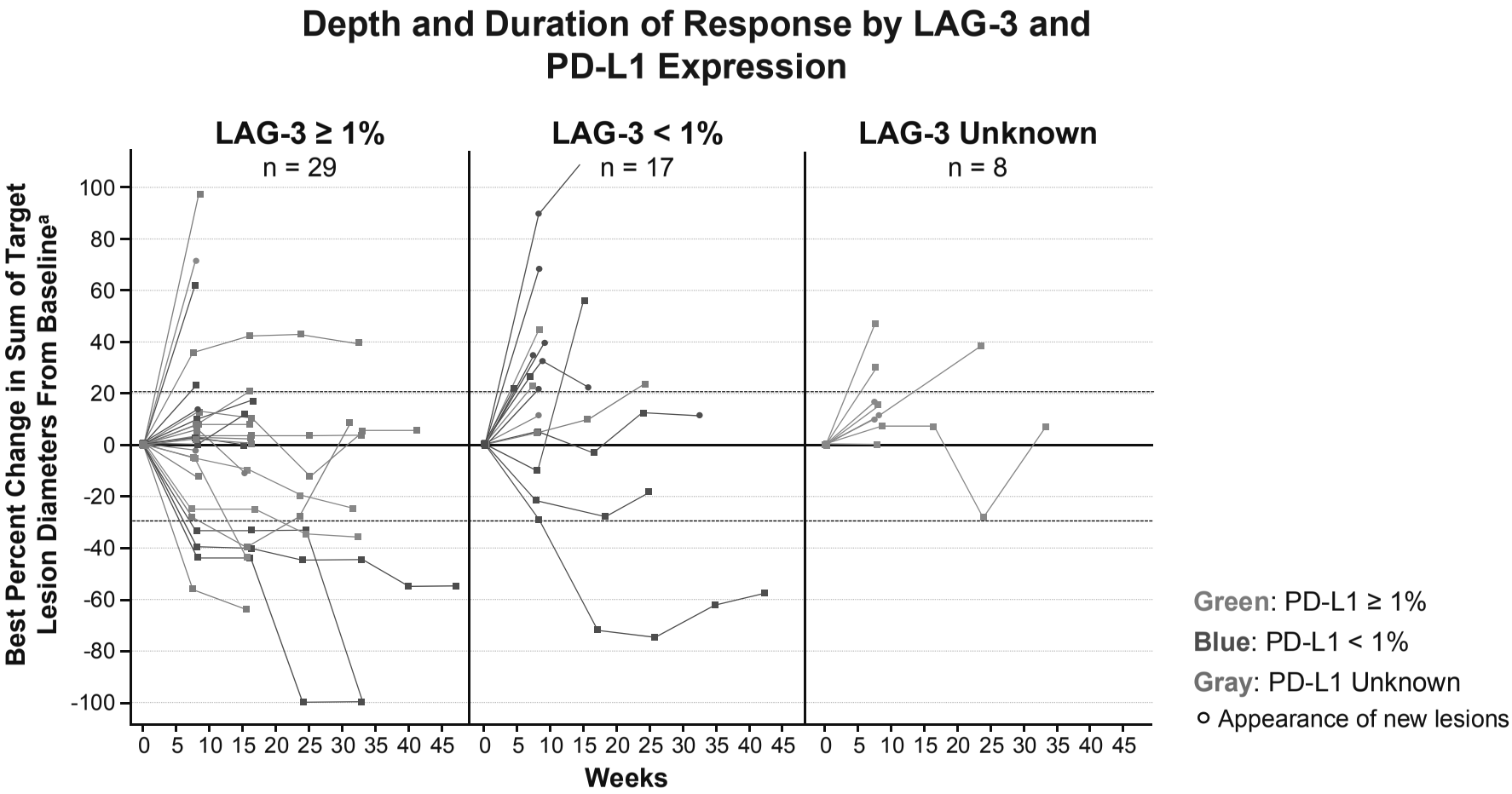
Figure 21

Best Change in Target Lesion Size by LAG-3 and PD-L1 Expression



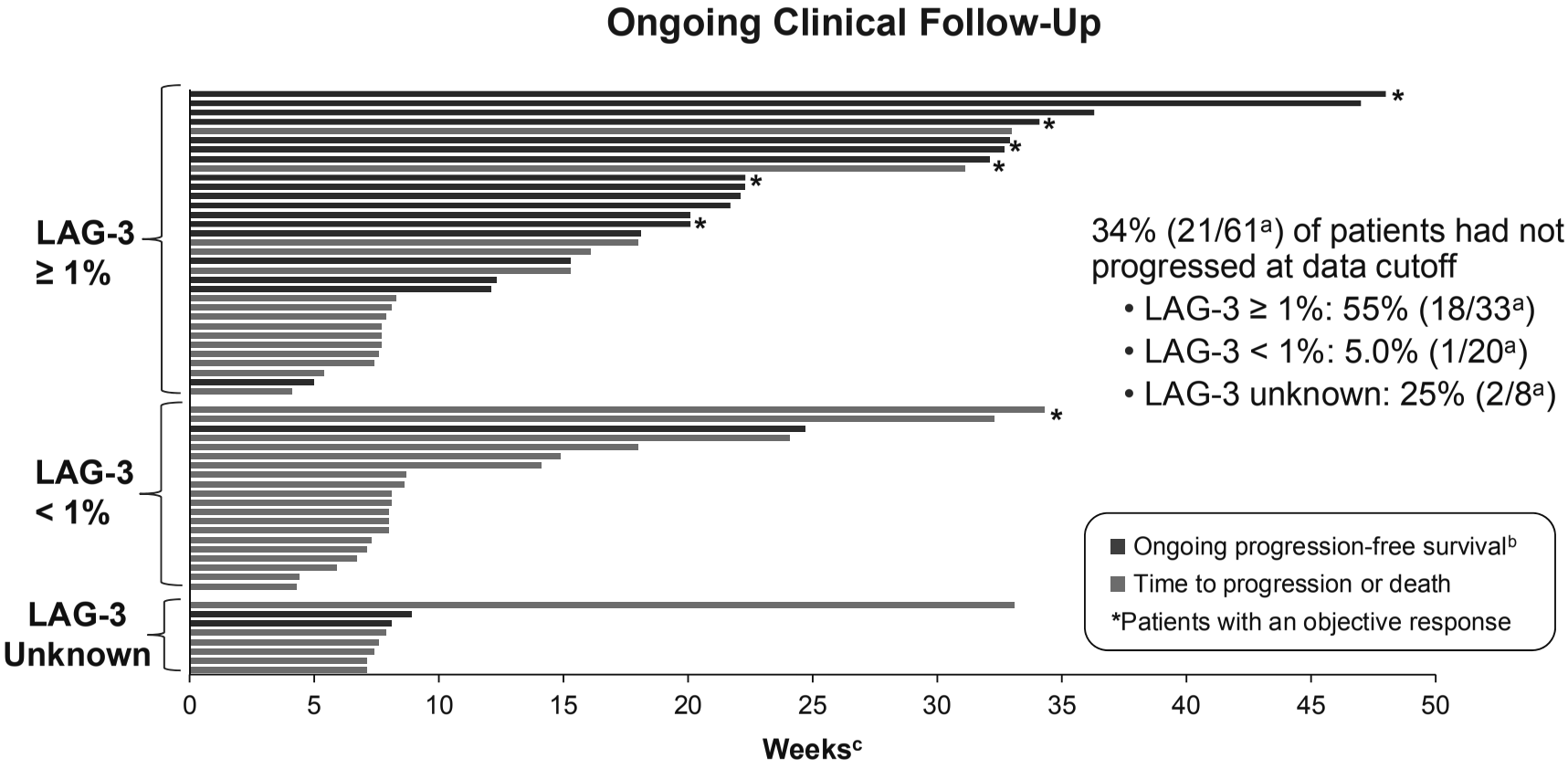
[a]Six patients with clinical progression prior to their first scan and one with PD due to an imaged new symptomatic brain metastasis prior to getting full scans were not included.
[b]One patient with best change from baseline > 30% had a best response of SD.

Figure 22



[a]Six patients with clinical progression prior to their first scan and one patient with PD due to a new symptomatic brain metastasis prior to getting full scans were not included.

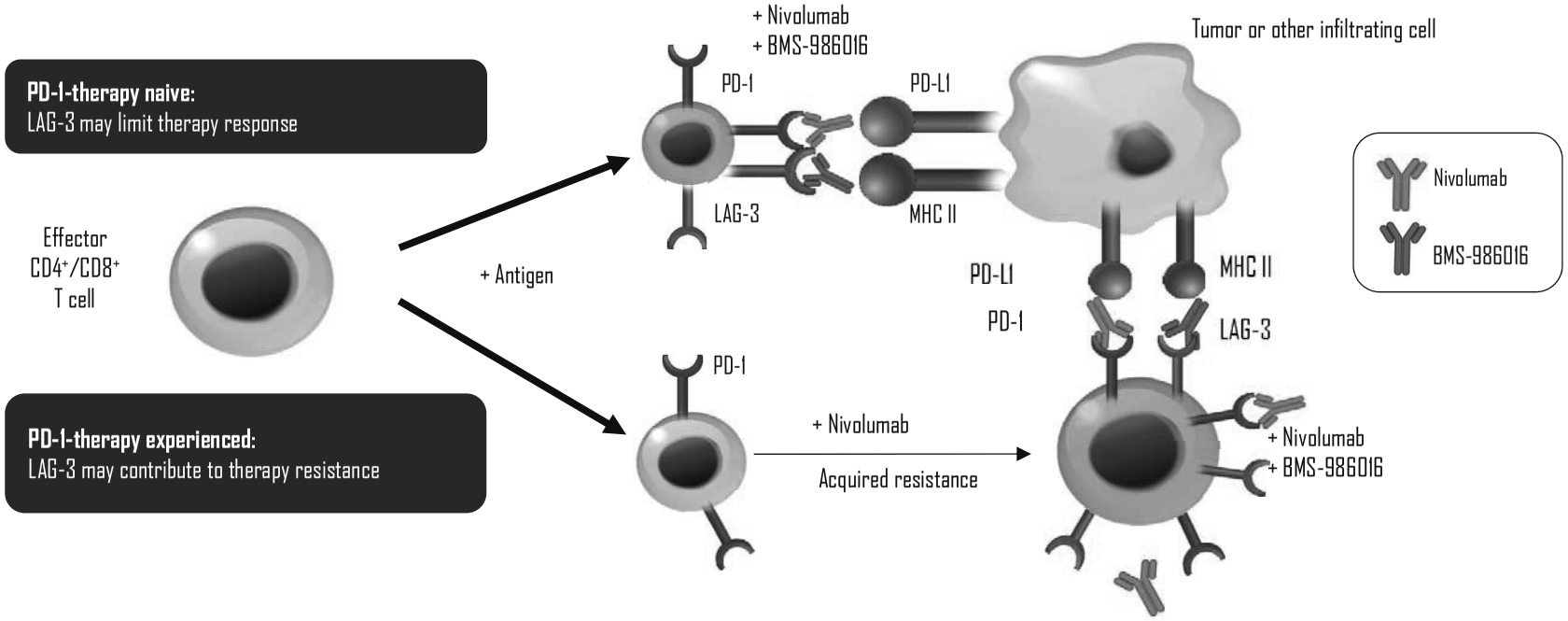
Figure 23



[a]Response-evaluable patients; all progressed during prior anti–PD-1/PD-L1 therapy. [b]Censored on last visit.
[c]Evaluations are planned for every 8 weeks.

Figure 24

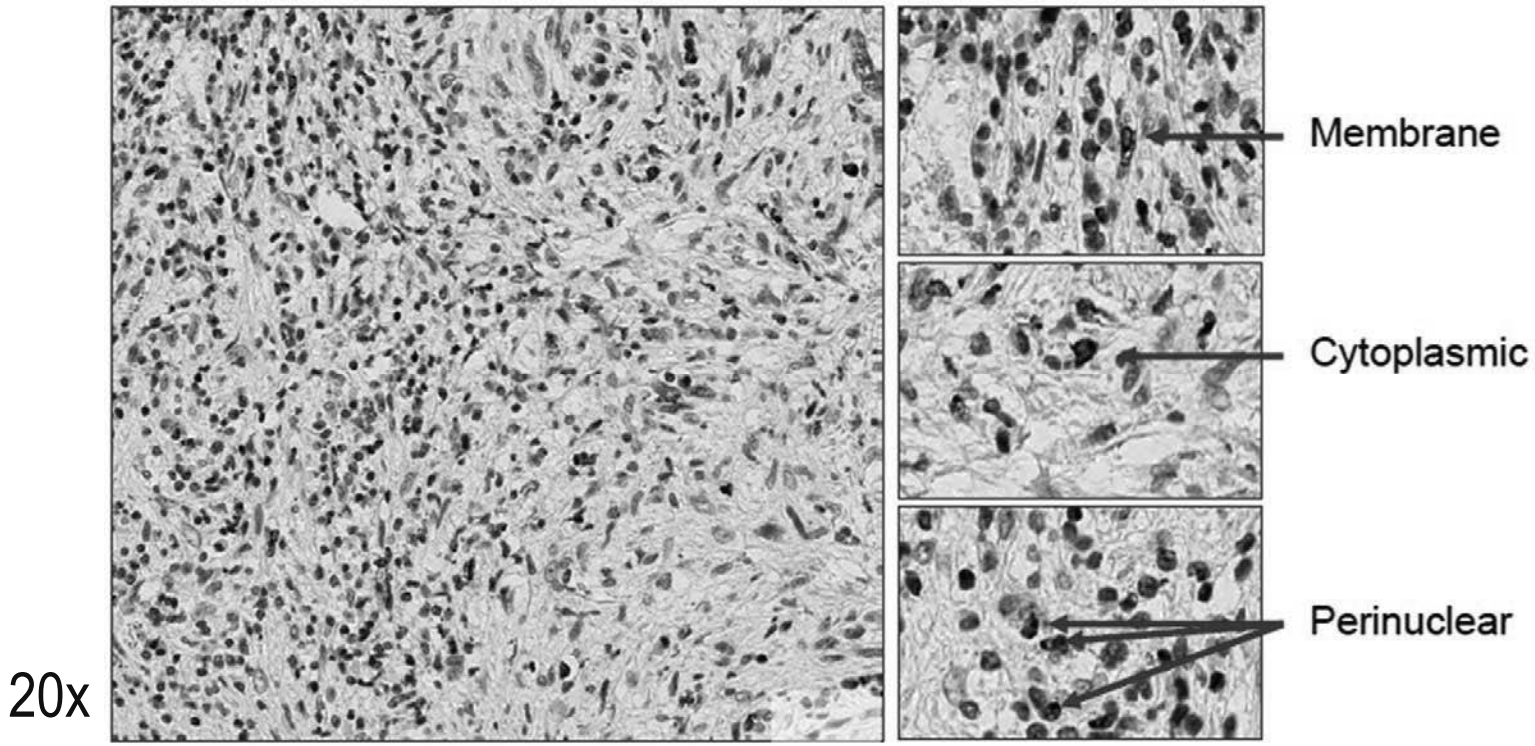
Role of LAG-3 and PD-1 in T-cell exhaustion and proposed clinical utility of BMS-986016 combined with nivolumab



CD = cluster of differentiation; LAG-3 = lymphocyte-activation gene 3; MHC II = major histocompatibility complex class II; PD-1 = programmed death-1; PD-L1 = programmed death-1 ligand 1.

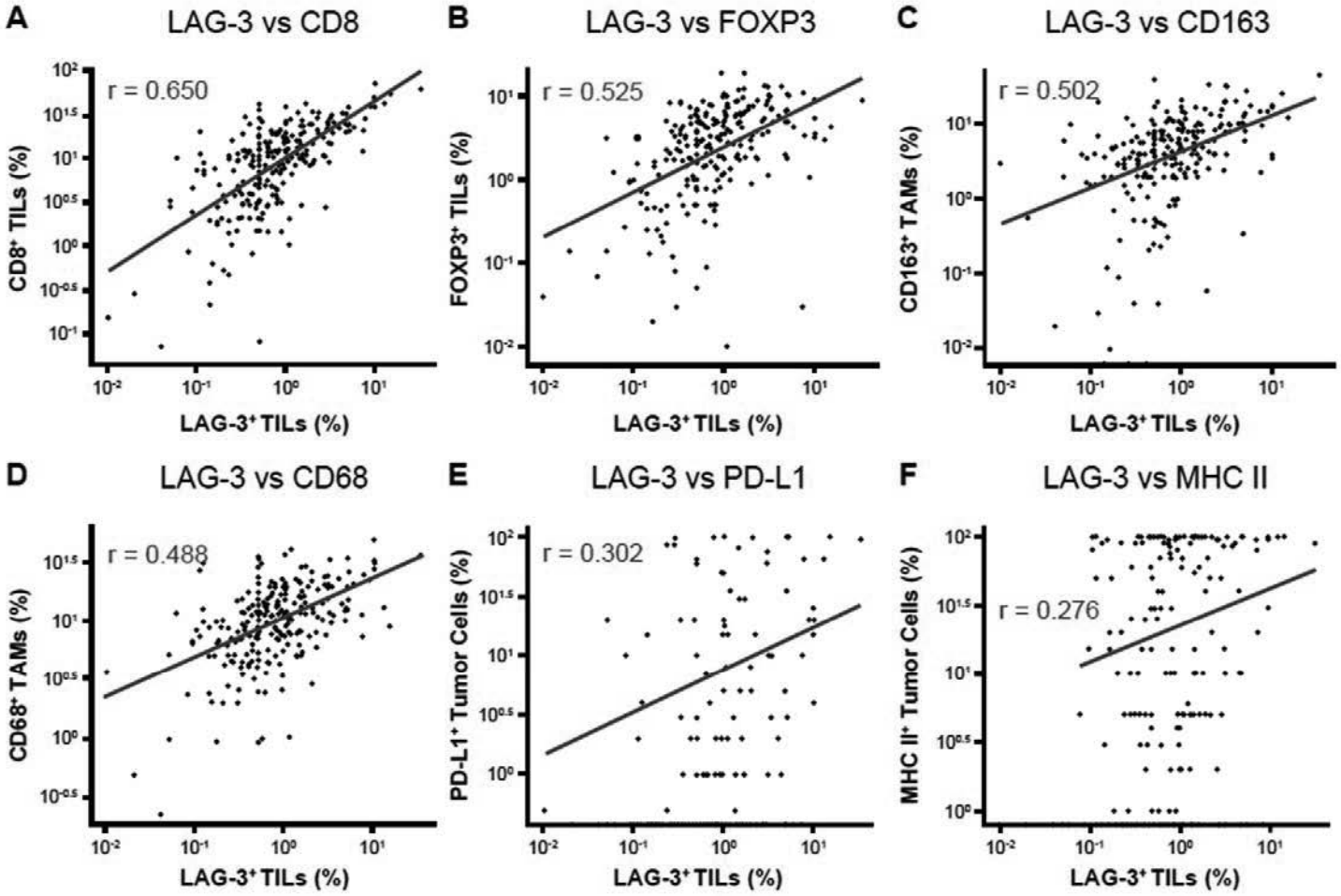
Figure 25

LAG-3 patterns of expression by IHC staining of total nucleated cells in a melanoma tumor specimen



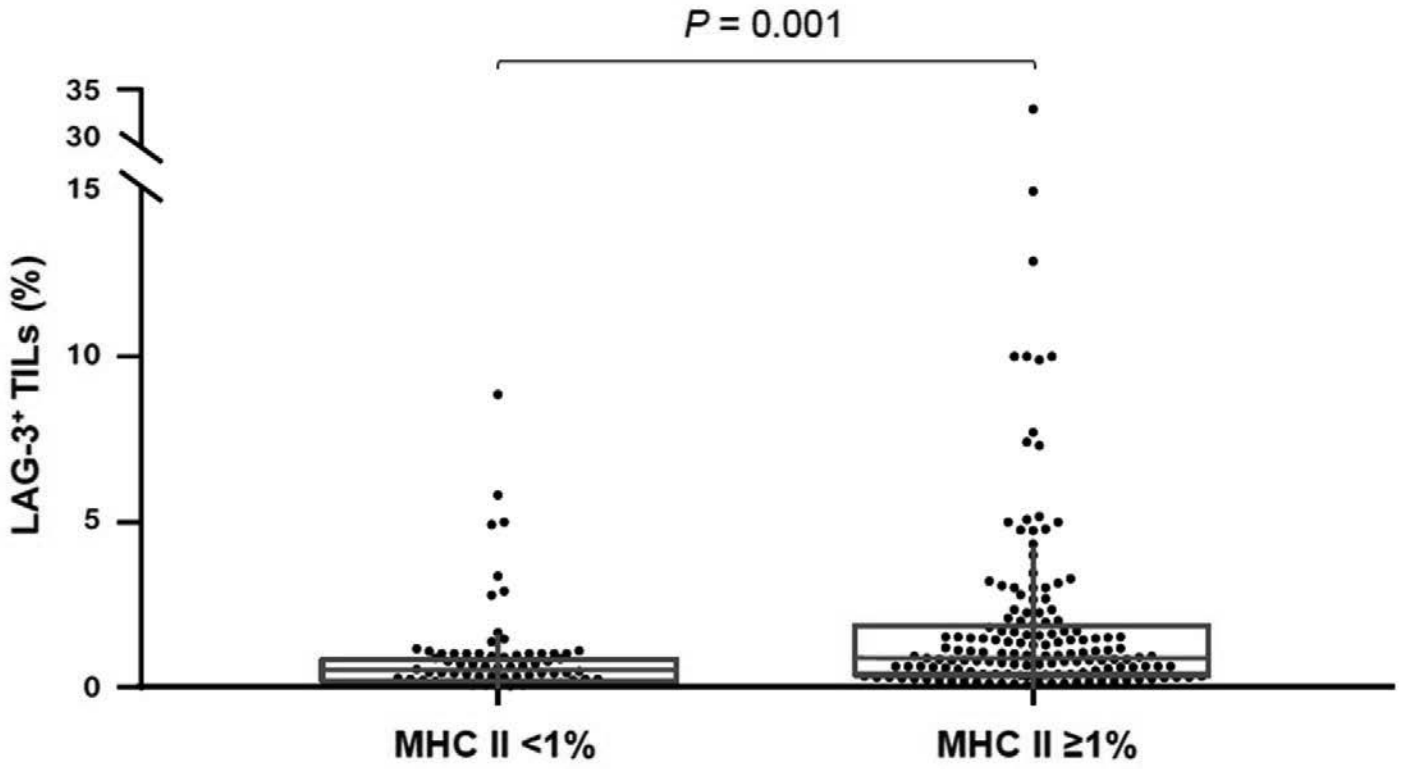
IHC = immunohistochemistry; LAG-3 = lymphocyte-activation gene 3.

Figures 26A-F. Association of LAG-3 with immune and inflammatory biomarkers



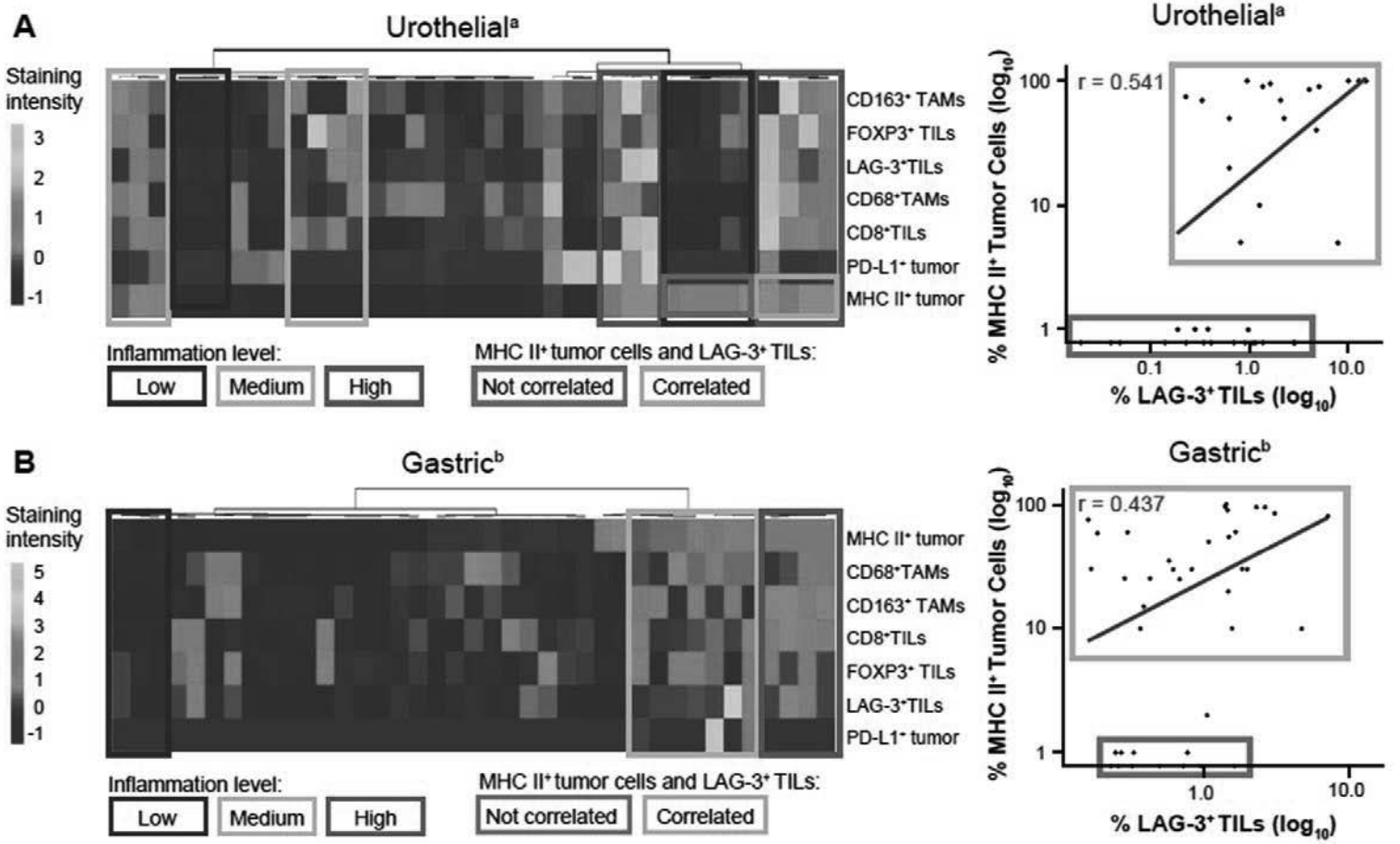
n = 237. LAG-3, CD8, FOXP3, CD163, CD68 quantified on immune cells; PD-L1 and MHC II quantified on tumor cells. CD = cluster of differentiation; FOXP3 = forkhead box P3; LAG-3 = lymphocyte-activation gene 3; MHC II = major histocompatibility complex class II; PD-L1 = programmed death-1 ligand 1; TAMs = tumor-associated macrophages; TILs = tumor-infiltrating lymphocytes.

Figure 27. LAG-3+ TILs by MHC II tumor cell expression



n = 241. Vertical bars represent the interquartile range. LAG-3 = lymphocyte-activation gene 3; MHC II = major histocompatibility complex class II; TILs = tumor-infiltrating lymphocytes.

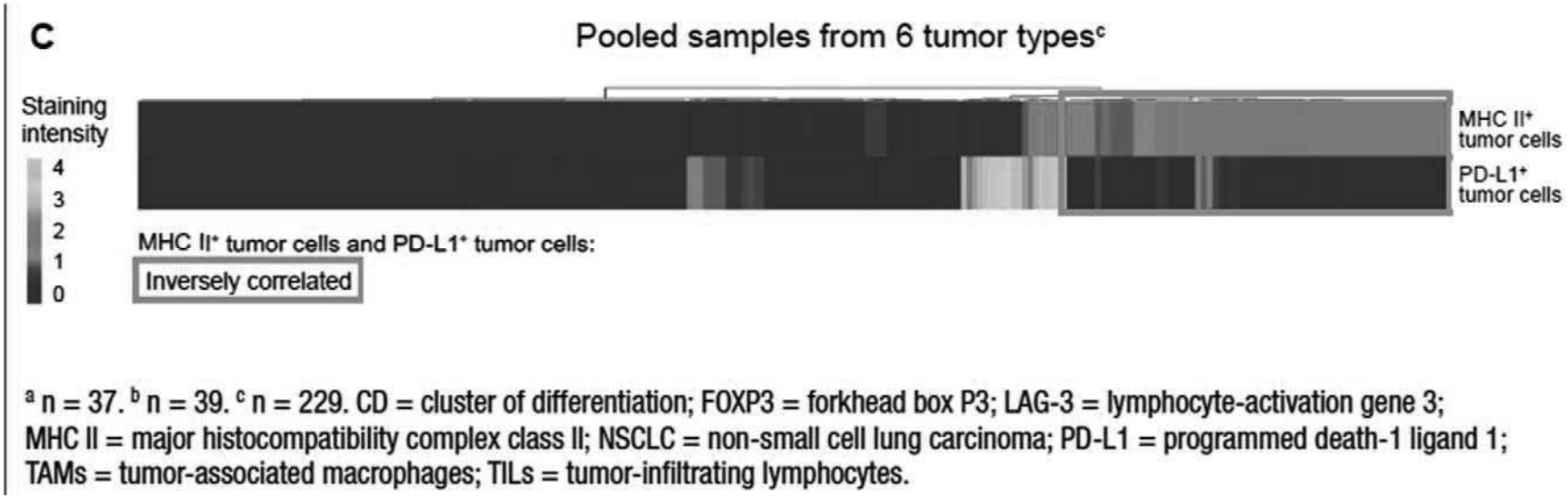
Figures 28A-B. Relationship between inflammation clusters and biomarker expression



[a] n = 37. [b] n = 39. [c] n = 229. CD = cluster of differentiation; FOXP3 = forkhead box P3; LAG-3 = lymphocyte-activation gene 3; MHC II = major histocompatibility complex class II; NSCLC = non-small cell lung carcinoma; PD-L1 = programmed death-1 ligand 1; TAMs = tumor-associated macrophages; TILs = tumor-infiltrating lymphocytes.

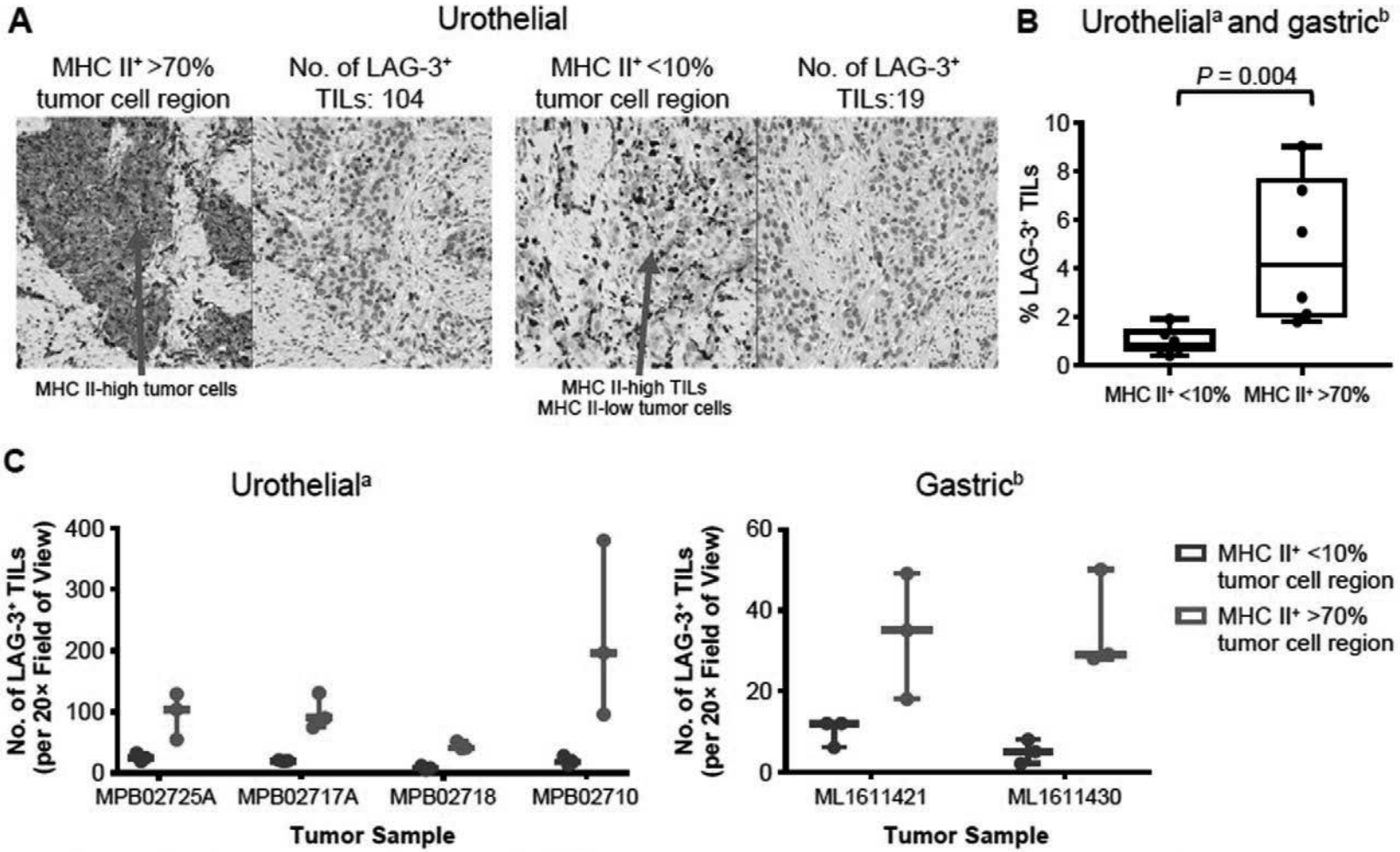
Figures 28C.

Relationship between inflammation clusters and biomarker expression



[a] n = 37. [b] n = 39. [c] n = 229. CD = cluster of differentiation; FOXP3 = forkhead box P3; LAG-3 = lymphocyte-activation gene 3; MHC II = major histocompatibility complex class II; NSCLC = non-small cell lung carcinoma; PD-L1 = programmed death-1 ligand 1; TAMs = tumor-associated macrophages; TILs = tumor-infiltrating lymphocytes.

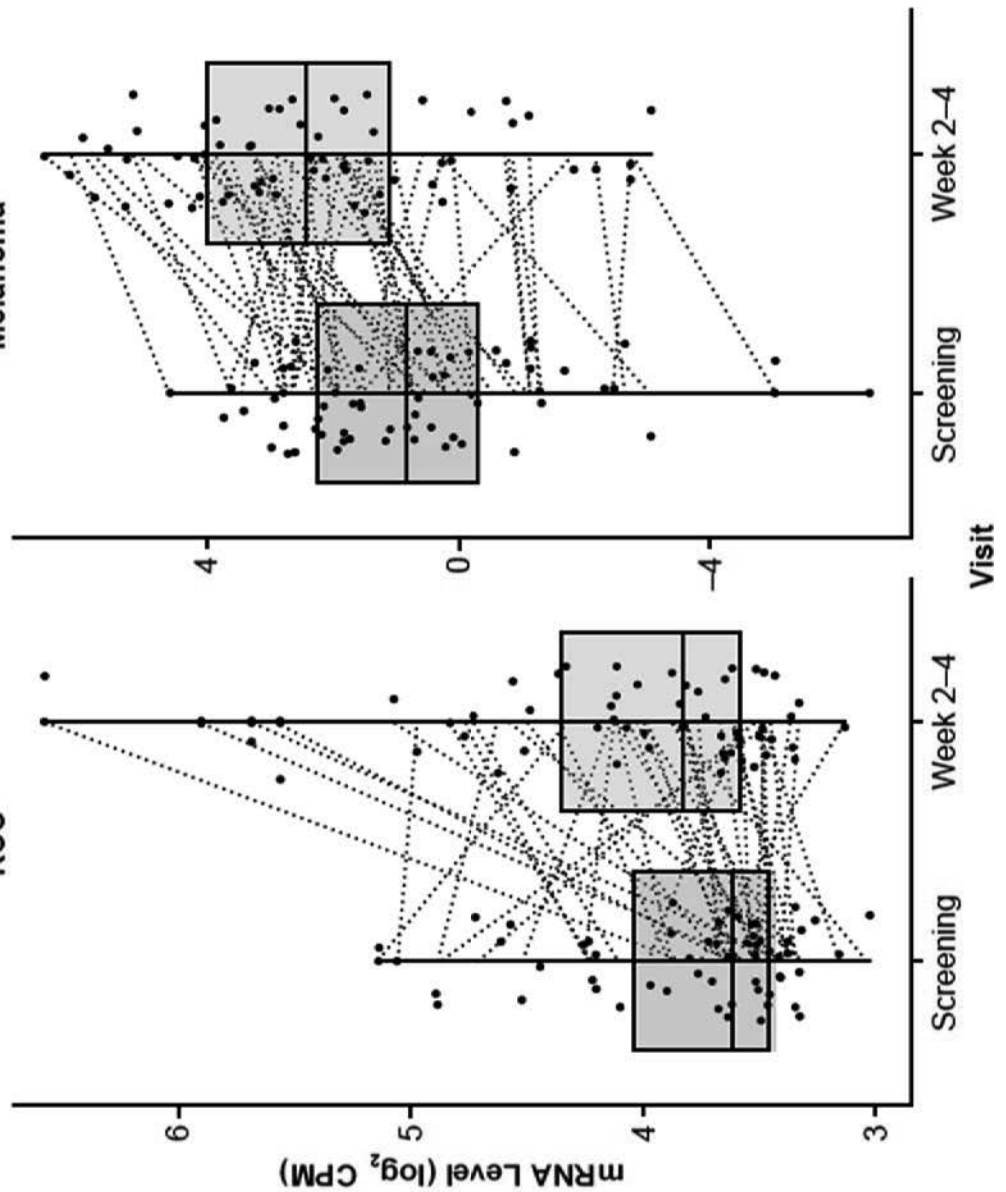
Figures 29A-C. Heterogeneous MHC II tumor cell expression and LAG-3+ TILs



[a] n = 4. [b] n = 2. LAG-3 = lymphocyte-activation gene 3; MHC II = major histocompatibility complex class II; TILs = tumor-infiltrating lymphocytes.

Figures 30A.

LAG-3 mRNA levels at screening and at week 2–4 of nivolumab monotherapy



Figures 30B.

LAG-3 mRNA levels at screening and at week 2–4 of nivolumab monotherapy

Changes in LAG-3 mRNA levels	RCC	Melanoma
n: pretreatment, posttreatment	59, 55	61, 62
P value	0.0479	0.00002
Mean fold increase from pretreatment baseline	1.2	3.1

Dashed lines represent samples from the same patient. CPM = counts per million; LAG-3 = lymphocyte-activation gene 3; RCC = renal cell carcinoma.