Nivolumab and Relatlimab-rmbw (Opdualag™) is recommended as a Category 1 preferred first-line treatment option for unresectable or metastatic melanoma in the NCCN Clinical Practice Guideline in Oncology (NCCN Guidelines®)[2]

RELATIVITY-047: Opdualag™ (nivolumab and relatlimab-rmbw) for the treatment of patients with unresectable or metastatic melanoma[1]

Opdualag is indicated for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma.[1]

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Please see updated NCCN Guidelines for a complete listing of all NCCN-recommended agents, including preferred options. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Category 1=based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate[2]; NCCN=National Comprehensive Cancer Network® (NCCN®).[2] Preferred=interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.[2]

Please see Important Safety Information for Opdualag throughout and US Full Prescribing Information for Opdualag.

1425-US-2300102 06/23

Select Important Safety Information

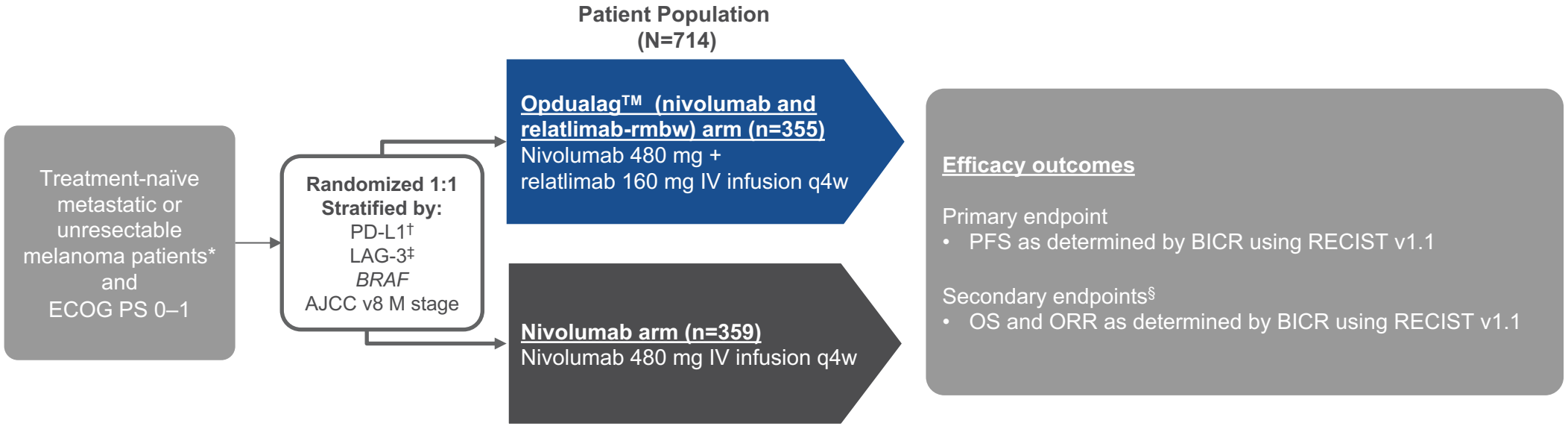
Summary of Warnings and Precautions

Opdualag™ (nivolumab and relatlimab-rmbw) is associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions (IMARs); infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); and embryo-fetal toxicity.

- Immune-Mediated Adverse Reactions (IMARs): Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune mediated pneumonitis, immune-mediated colitis, immune mediated hepatitis, immune-mediated endocrinopathies, immune-mediated dermatologic adverse reactions, immune-mediated nephritis with renal dysfunction, and immune-mediated myocarditis. Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. Withhold or permanently discontinue Opdualag based on severity and type of reaction
- Infusion-Related Reactions: Interrupt, slow the rate of infusion, or permanently discontinue Opdualag based on severity of reaction.
- Complications of Allogeneic HSCT: Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody.
- Embryo-fetal toxicity: Opdualag can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus and to use effective contraception.

Study Design

RELATIVITY-047: First phase 3 trial showing the benefits of an anti–LAG-3 therapy in combination with the PD-L1 inhibitor, nivolumab[1]



Median duration of treatment for Opdualag at the 25.3-month median follow-up was 8.3 months.[3] Treat until disease progression or unacceptable toxicity.[1]

Inclusion criteria[1,4]:

- Histologically confirmed unresectable stage III or stage IV melanoma
- Expression of LAG-3 and PD-L1 that could be evaluated in tumor tissue

Exclusion criteria[1]:

- Patients with active autoimmune disease
- Medical conditions requiring systemic treatment with moderate- or high-dose corticosteroids or immunosuppressive medications
- Patients with uveal melanoma
- Patients with active or untreated brain or leptomeningeal metastases

*Patients were allowed to receive prior adjuvant and neoadjuvant melanoma therapy. Anti–PD-1, anti–CTLA-4, or *BRAF*-MEK therapy was allowed as long as there was at least 6 months between the last dose of therapy and date of recurrence; interferon therapy was allowed as long as the last dose was at least 6 weeks prior to randomization.[1] †PD-L1 expression (≥1% vs <1%) using PD-L1 IHC 28-8 pharmDx test.[1] ‡LAG-3 expression (≥1% vs <1%) using a clinical trial assay.[1] §The final analysis of OS was not statistically significant.[1]

AJCC=American Joint Committee on Cancer; BICR=blinded independent central review; *BRAF*=B-Raf proto-oncogene; CTLA-4=cytotoxic T-lymphocyte antigen 4; ECOG PS=Eastern Cooperative Oncology Group Performance Status; IHC=immunohistochemistry; IV=intravenous; LAG-3=lymphocyte-activation gene 3; M=metastases; *MEK*=mitogen-activated protein kinase; ORR=overall response rate; OS=overall survival; PD-1=programmed death receptor-1; PD-L1=programmed death-ligand 1; PFS=progression-free survival; q4w=every 4 weeks; RECIST=Response Evaluation Criteria In Solid Tumors.

Baseline characteristics across pre-specified subgroups[1,4]

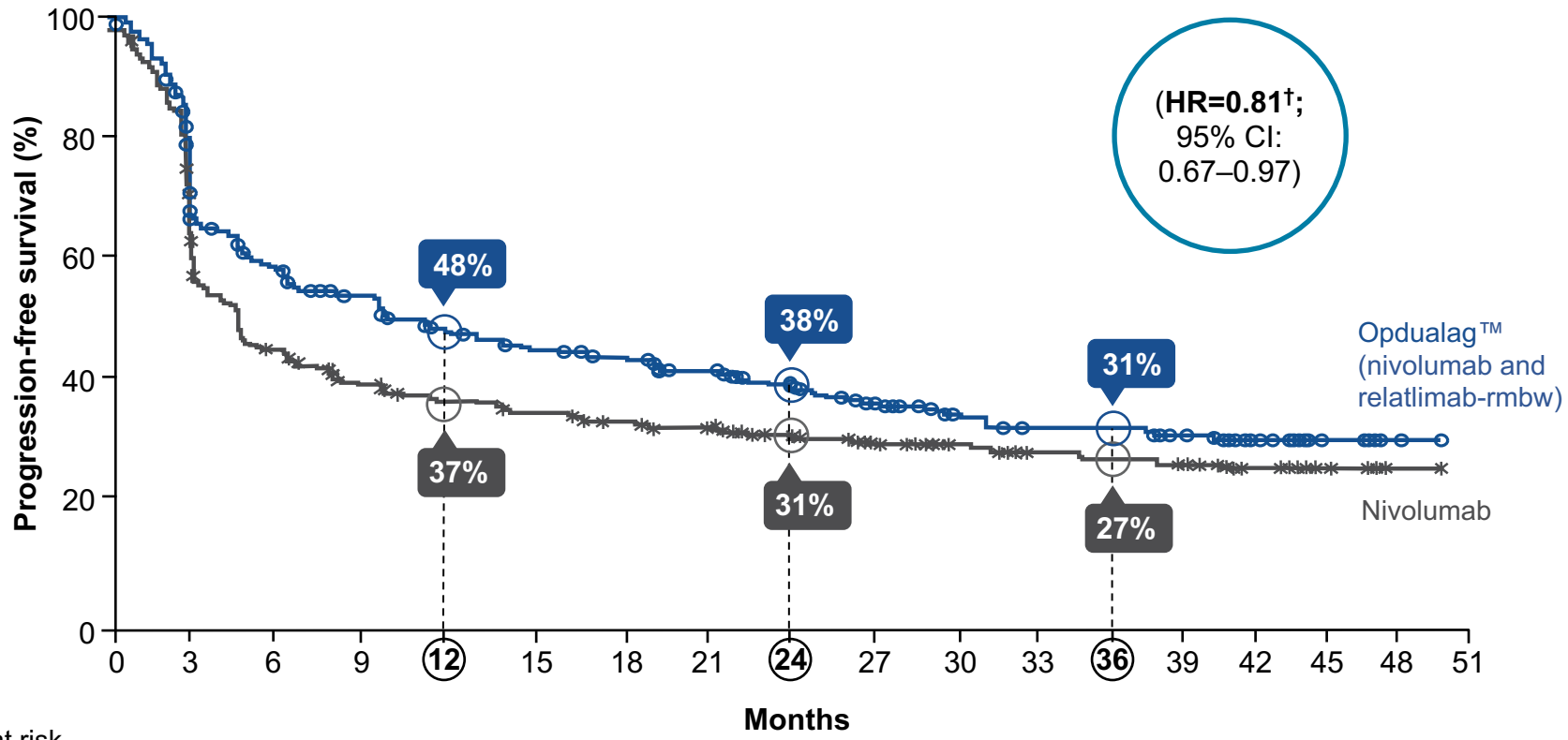
Characteristic		Opdualag™ (nivolumab and relatlimab-rmbw) (n=355)	Nivolumab (n=359)
Median age, years		63	62
Female, n (%)		145 (40.8)	153 (42.6)
AJCC v8 M stage, n (%)	M0 M1A or B M1C M1D	35 (9.9) 162 (45.6) 151 (42.5) 6 (1.7)	23 (6.4) 195 (54.3) 127 (35.4) 11 (3.1)
ECOG PS, n (%)	0 1	236 (66.5) 119 (33.5)	242 (67.4) 117 (32.6)
Serum LDH level, n (%)	>ULN >2× ULN	130 (36.6) 32 (9.0)	128 (35.7) 31 (8.6)
Prior systemic therapy,* n (%)	Adjuvant Neoadjuvant Unknown or other	31 (8.7) 2 (0.6) 0	26 (7.2) 1 (0.3) 2 (0.6)
Tumor burden, median (min–max), mm		59.0 (10–317)	54.5 (10–548)
Melanoma subtype classification, n (%)	Cutaneous acral Cutaneous non-acral Mucosal Other	41 (11.5) 249 (70.1) 23 (6.5) 42 (11.8)	41 (11.4) 254 (70.8) 28 (7.8) 36 (10.0)
Stratification factor, n (%)			
***BRAF* mutation status**	Mutant Wild type	136 (38.3) 219 (61.7)	139 (38.7) 220 (61.3)
AJCC v8 M stage (metastasis stage with LDH level)	M0, M1, and normal LDH level M1 and elevated LDH level	232 (65.4) 123 (34.6)	237 (66.0) 122 (34.0)
PD-L1 expression	≥1% <1%	146 (41.1) 209 (58.9)	147 (40.9) 212 (59.1)
LAG-3 expression	≥1% <1%	268 (75.5) 87 (24.5)	269 (74.9) 90 (25.1)

*Most common therapy was interferon.[1,4]

LDH=lactate dehydrogenase; ULN=upper limit of normal.

PFS* per BICR in the ITT population[1,4,5]

PFS at the 25.3-month median follow-up



No. at risk

Opdualag	355	221	188	165	144	130	123	108	92	82	70	53	49	49	43	23	3	0
Nivolumab	359	194	152	128	116	109	101	89	76	68	56	44	41	39	35	17	3	0

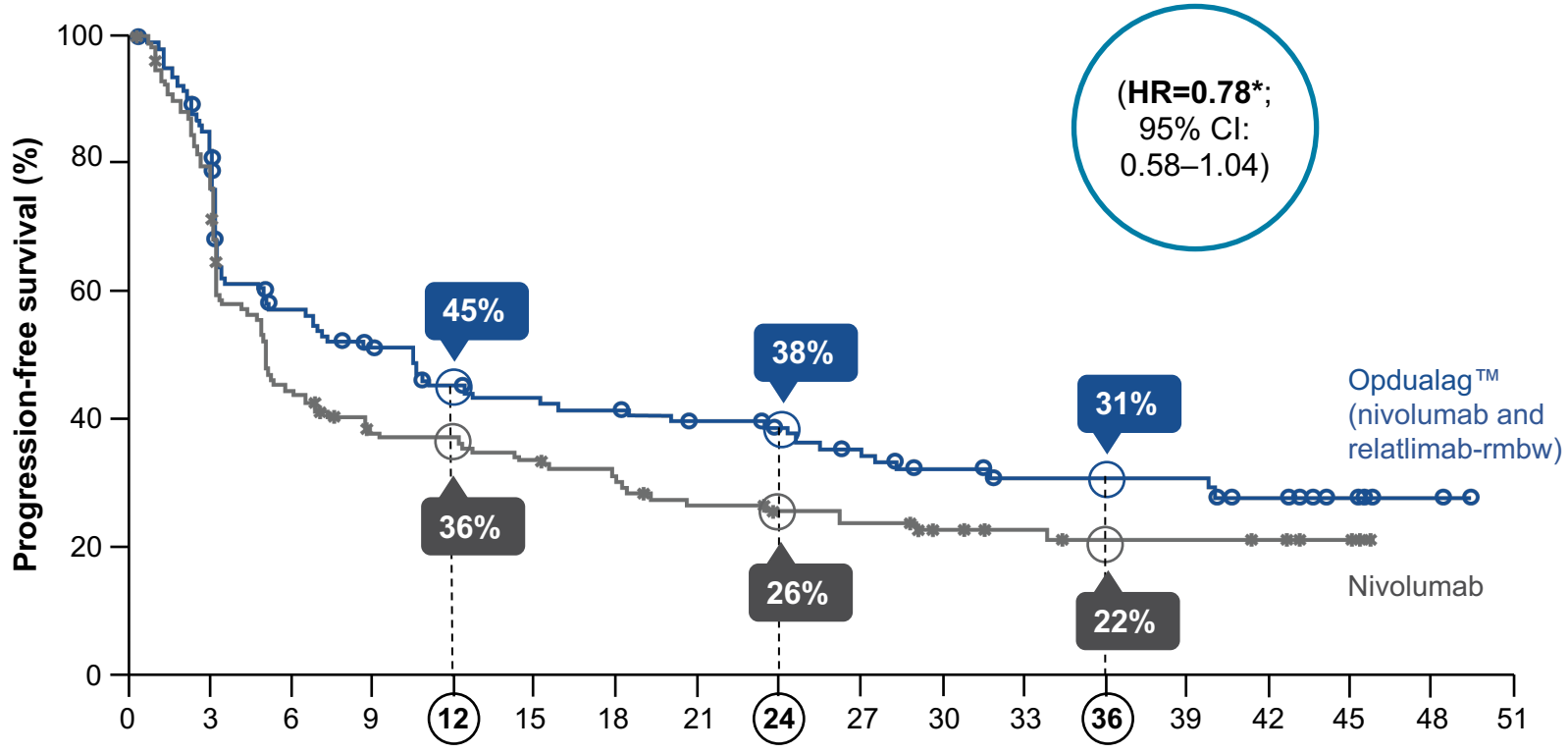
Symbols represent censored observations.[1]

- At the 13.2-month median primary analysis[1,4]: HR vs nivolumab: 0.75†; (95% CI: 0.62–0.92); *P*=0.0055‡

*Kaplan-Meier estimate.[1] † Based on stratified Cox proportional hazard model.[1] ‡Based on stratified log-rank test.[1] CI=confidence interval; HR=hazard ratio.

BRAF mutant PFS per BICR at the 25.3-month median follow-up[3]*

BRAF status: Mutant



No. at risk																		
Opdualag	136	78	69	59	49	47	45	41	36	31	27	21	21	21	17	7	1	0
Nivolumab	139	74	56	44	42	38	33	30	27	25	19	17	15	15	13	5	0	0

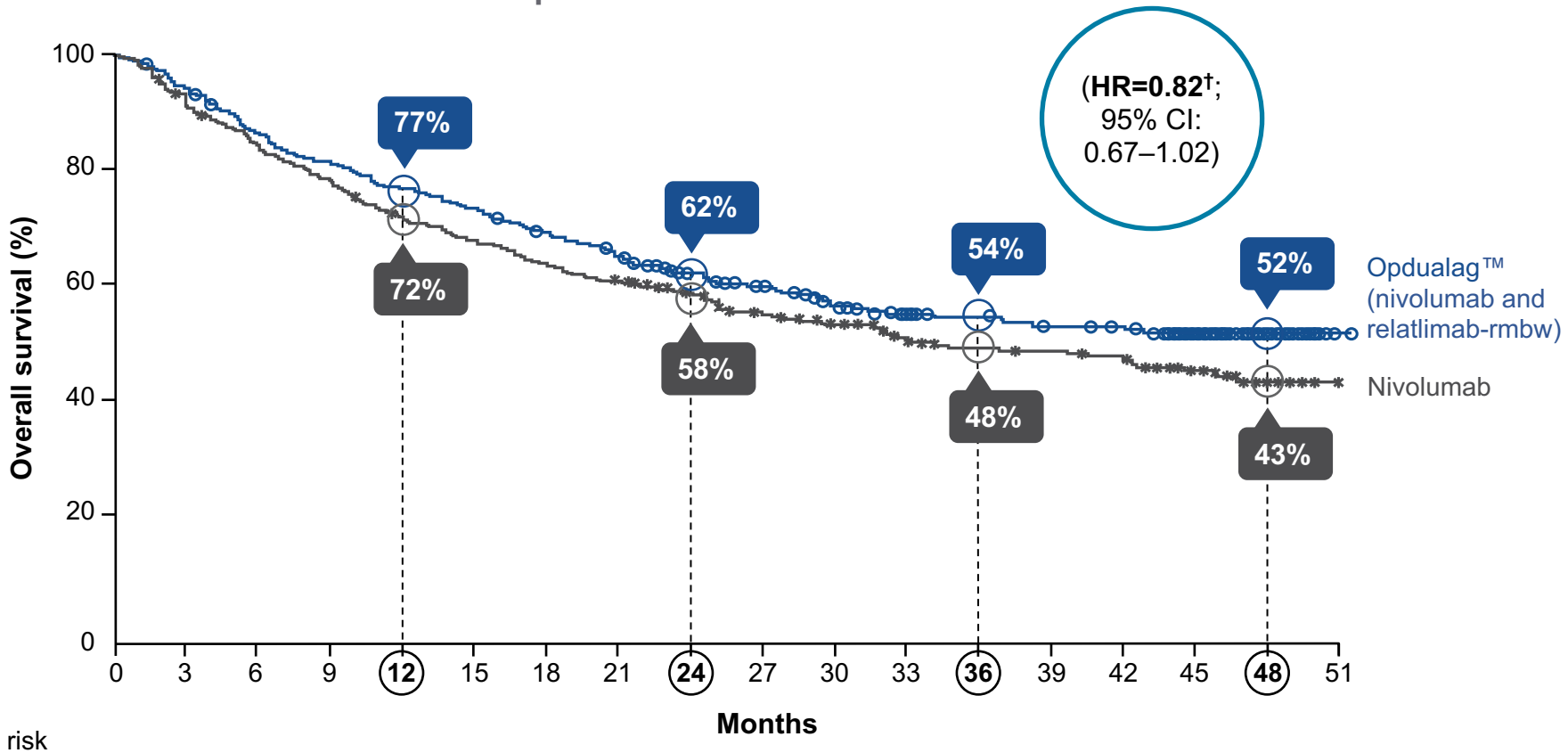
Symbols represent censored observations.
Based on an exploratory analysis.

- *BRAF* wild-type PFS at the 25.3-month median follow-up[3]: HR vs nivolumab (95% CI): 0.82* (0.65–1.04)

*Based on unstratified Cox proportional hazard model.[3]

Median OS has not yet been reached vs 33.2 months for nivolumab monotherapy[1,5*]

Overall survival at the 25.3-month median follow-up



No. at risk																		
Opdualag	355	334	305	287	270	258	241	226	197	179	160	136	128	122	120	78	26	2
Nivolumab	359	329	301	278	253	238	224	211	185	162	144	118	106	104	100	64	17	0

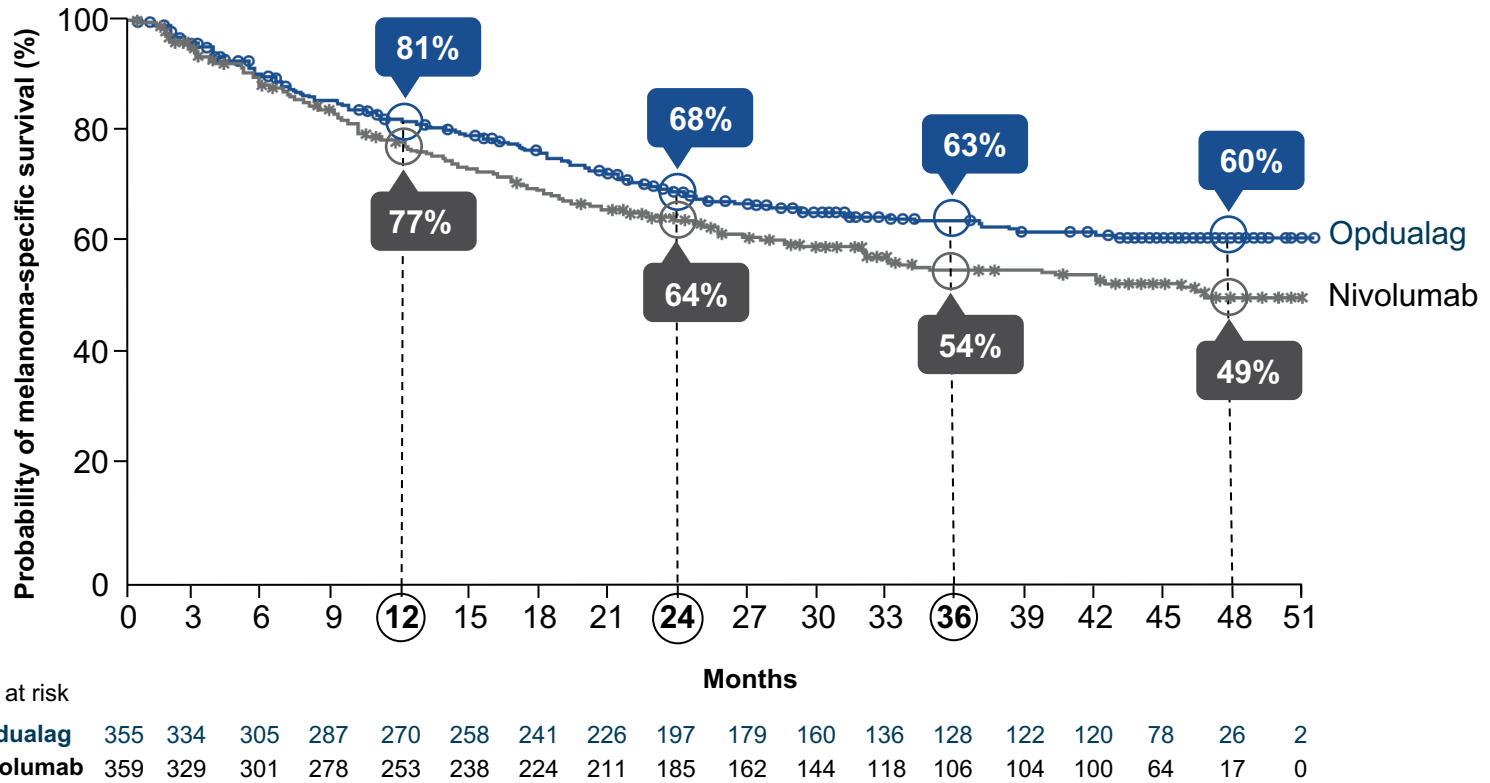
Symbols represent censored observations.[1] OS did not meet statistical significance.[1]

- Median OS at the 25.3-month median follow-up (95% CI): NR (31.5–NR) with Opdualag vs 33.2 months (25.2–45.8) with nivolumab[5]
- At the 19.3-month median primary analysis: HR vs nivolumab: 0.80† (95% CI: 0.64–1.01); *P*=0.0593[1,6‡]

*At the 19.3-month median primary analysis, OS was not statistically significant.[1] †Based on stratified Cox proportional hazard model.[1] ‡Based on stratified log-rank test.

Melanoma-specific survival[5]

Investigator-assessed MSS at the 25.3-month median follow-up



	Opdualag™ (n=355)	Nivolumab (n=359)
Median MSS, months (95% CI)	**NR** (NR–NR)	**46.7** (33.2–NR)
HR (95% CI)	**0.77 (0.61–0.97)**	
Melanoma deaths, n (%)	126 (36)	154 (43)
Censored patients, n (%)	229 (64)	205 (57)
Non-melanoma deaths, n (%)	**36 (10)**	**31 (9)**
Study drug toxicity*	4 (1)	2 (1)
Unknown	7 (2)	10 (3)
Other†	25 (7)	19 (5)

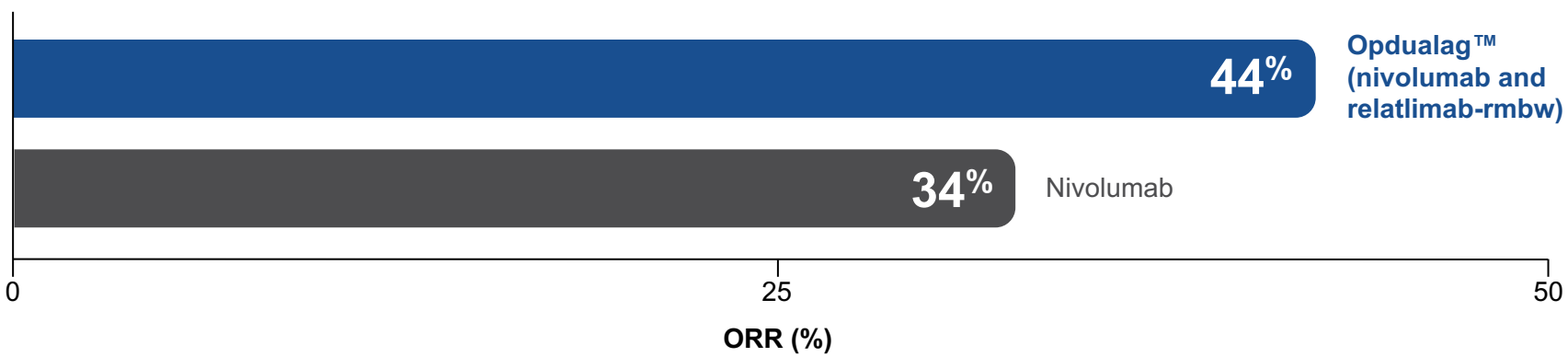
Symbols represent censored observations.[1]

- At the time of the 19.3-month median primary analysis, which was event-driven and occurred after the final PFS analysis, OS did not meet statistical significance
- This analysis was exploratory and not pre-specified within study protocol
- Melanoma-specific survival (MSS) is defined as the time from randomization to death due to melanoma; deaths for any other reason were censored. Patients who were alive were censored at their last known alive date. Reasons for death were determined by the investigator

*Death due to toxicity was considered non-melanoma death. †Most common reasons for other included septic shock, myocardial infarction, stroke, pneumonia, and respiratory insufficiency.
MMS=melanoma-specific survival; NR=not reached.

Higher overall response rates were observed vs nivolumab monotherapy[1,5]

Overall response rate per BICR at the 25.3-month median follow-up



10%
increase in ORR for Opdualag

At the 25.3-month median follow-up:

- Median DOR was not yet reached for both Opdualag and nivolumab[5]
- Overall response rate at the 25.3-month median follow-up for Opdualag was 44% (n=155/355; 95% CI: 38–49) vs 34% (n=121/359; 95% CI: 29–39) for nivolumab[5]
  - CR was 18% (64/355) for Opdualag vs 18% (63/359) for nivolumab
  - PR was 26% (91/355) for Opdualag vs 16% (58/359) for nivolumab
- Median time to response for Opdualag was 2.79 months (1.2–20.1) and for nivolumab was 2.79 months (1.7–42.3)[3]

At the 19.3-month median primary analysis:

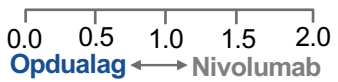
- ORR*† for Opdualag was 43% (n=153/355; 95% CI: 38–48) vs 33% (n=117/359; 95% CI: 28–38) for nivolumab[1]
  - CR was 16% (58/355) for Opdualag vs 14% (51/359) for nivolumab[1]
  - PR was 27% (95/355) for Opdualag vs 18% (66/359) for nivolumab[1]

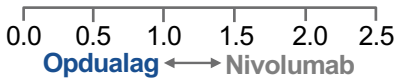
*At the time of the final OS analysis, which was event-driven and occurred after the final PFS analysis.[1] †Not formally tested based on the testing hierarchy.[1]
CR=complete response; DOR=duration of response; PR=partial response.

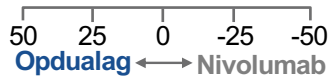
PFS, OS, and ORR across pre-specified subgroups and stratification factors[3,5]

Opdualag showed a numerical increase in PFS, OS, and ORR over nivolumab across the majority of key subgroups and prognostic factors

Subgroup		NIVO+ RELA No. of patients	NIVO No. of patients	PFS by BICR Unstratified HR (95%CI)	OS Unstratified HR (95%CI)	NIVO+ RELA ORR %	NIVO ORR %	ORR by BICR Unweighted ORR difference (95%CI)
Overall		355	359	0.81 (0.67–0.97)	0.83 (0.67–1.02)	43.7	33.7	10.0 (2.8–17.0)
Age categorization, years	≥18 and <65	187	196	0.83 (0.65–1.07)	0.79 (0.59–1.06)	48.0	40.8	10.0 (0.5–19.3)
	≥65	168	163	0.80 (0.61–1.04)	0.87 (0.65–1.18)	48.2	38.7	9.6 (-1.1 to 19.9)
	≥75	66	60	0.71 (0.45–1.10)	0.89 (0.56–1.42)	48.5	35.0	13.5 (-3.7 to 29.5)
Sex	Male	210	206	0.71 (0.56–0.90)	0.87 (0.66–1.16)	43.1	35.0	13.1 (3.7–22.3)
	Female	145	153	0.97 (0.73–1.29)	0.78 (0.56–1.07)	37.2	32.0	5.2 (-5.5 to 15.8)
Baseline LDH	≤ULN	225	231	0.80 (0.63–1.01)	0.82 (0.61–1.10)	51.1	35.9	15.2 (6.1–23.9)
	>ULN	129	128	0.78 (0.58–1.04)	0.80 (0.59–1.09)	31.0	29.7	1.3 (-9.8 to 12.4)
	≤2 × ULN	322	328	0.81 (0.66–0.98)	0.79 (0.63–0.99)	47.2	36.0	11.2 (3.7–18.6)
	>2 × ULN	32	31	0.73 (0.41–1.29)	0.96 (0.56–1.66)	9.4	9.7	-0.3 (-16.7 to 15.9)
Baseline ECOG PS	0	235	242	0.77 (0.62–0.98)	0.71 (0.54–0.94)	48.9	37.6	11.3 (2.4–20.0)
	1	120	117	0.87 (0.64-1.18)	1.02 (0.73–1.43)	33.3	25.6	7.7 (-3.9 to 19.0)
Tumor burden at baseline	<Q1 (31mm)	73	83	0.81 (0.52–1.27)	0.63 (0.34–1.16)	60.3	47.0	13.3 (-2.4 to 28.0)
	Q1 to <Q3	163	158	0.87 (0.67–1.14)	0.86 (0.62–1.18)	47.9	38.6	9.2 (-1.6 to 19.8)
	≥Q3 (96mm)	85	75	0.66 (0.46–0.95)	0.73 (0.51–1.07)	31.8	21.3	10.4 (-3.4 to 23.5)
***BRAF* mutation status**	Mutant	136	139	0.78 (0.58–1.04)	0.77 (0.54–1.11)	43.4	30.9	12.4 (1.0–23.4)
	Wild-type	219	220	0.82 (0.65–1.04)	0.86 (0.66–1.11)	43.8	35.5	8.4 (-0.8 to 17.3)
LAG-3 expression	≥1%	268	269	0.85 (0.69–1.05)	0.82 (0.64–1.05)	47.4	36.8	10.6 (2.2–18.7)
	<1%	87	90	0.71 (0.50–1.00)	0.86 (0.58–1.28)	32.2	24.4	7.7 (-5.5 to 20.7)
PD-L1 expression	≥1%	146	147	1.04 (0.77–1.41)	0.82 (0.58–1.16)	52.7	46.3	6.5 (-4.9 to 17.6)
	<1%	209	212	0.68 (0.54–0.86)	0.83 (0.63–1.08)	37.3	25.0	12.3 (3.5–20.9)
Baseline metastasis stage	M0	36	23	0.86 (0.45–1.66)	0.83 (0.38–1.81)	33.3	43.5	-10.1 (-33.8 to 14.0)
	M1	1	3	Not calculated	Not calculated	100.0	0	Not calculated
	M1a	74	107	0.71 (0.48–1.07)	1.07 (0.68–1.68)	55.4	39.3	16.2 (1.4–30.0)
	M1b	87	88	0.70 (0.49–1.01)	0.66 (0.42–1.04)	51.7	30.7	21.0 (6.5–34.4)
	M1c	150	127	0.83 (0.62–1.10)	0.78 (0.57–1.07)	37.3	29.1	8.2 (-3.0 to 18.9)
	M1d	7	11	Not calculated	Not calculated	0	45.5	Not calculated
Histology disease subtype	Cutaneous Acral	40	42	0.86 (0.53–1.40)	1.07 (0.63–1.82)	27.5	14.3	13.2 (-4.5 to 30.3)
	Cutaneous non-acral	250	253	0.82 (0.66–1.03)	0.87 (0.66–1.13)	48.0	39.5	8.5 (-0.2 to 17.0)
	Mucosal	23	28	0.64 (0.33–1.26)	1.09 (0.56–2.14)	34.8	25.0	9.8 (-14.5 to 33.6)







OS at the 19.3-month median primary analysis did not meet statistical significance. Exploratory/descriptive analyses. DBL date: October 27, 2022. Median follow-up: 25.3 months.

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Adverse reactions occurring in ≥15% of patients in RELATIVITY-047[1,4]

	Opdualag™ (nivolumab and relatlimab-rmbw) (n=355)	Nivolumab (n=359)	Opdualag (n=355)	Nivolumab (n=359)
Adverse reaction*	**All Grades (%)**	**All Grades (%)**	**Grades 3/4 (%)**	**Grades 3/4 (%)**
Musculoskeletal and connective tissue				
Musculoskeletal pain†	45	31	4.2	1.7
General				
Fatigue†	39	29	2	0.6
Skin and subcutaneous tissue				
Rash†	28	21	1.4	1.9
Pruritus	25	17	0	0.6
Gastrointestinal				
Diarrhea†	24	17	2	1.4
Nausea	17	14	0.6	0
Nervous system				
Headache†	18	12	0.3	0.3
Endocrine				
Hypothyroidism†	17	14	0	0
Metabolism and nutrition disorders				
Decreased appetite	15	7	0.6	0.3
Respiratory, thoracic, and mediastinal disorders				
Cough†	15	11	0.3	0

- Grade 3/4 increases greater than 1% vs nivolumab monotherapy were fatigue (1.4%) and musculoskeletal pain (2.5%)[1]
- Treatment-related discontinuation rates were 14.6% with Opdualag vs 6.7% with nivolumab[7]
  - Grade 1/2 discontinuation rate was 5.8% with Opdualag vs 3.6% with nivolumab
  - Grade 3/4 discontinuation rate was 8.5% with Opdualag vs 3.1% with nivolumab
- With 19.3 months median follow-up, there were no new or unexpected safety events observed with the combination of nivolumab plus relatlimab. The safety profile of nivolumab plus relatlimab remains consistent and in line with the analyses previously presented and included within the Opdualag PI[6]

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.[1]
*Clinically relevant adverse reactions in <15% of patients who received Opdualag included vitiligo, adrenal insufficiency, myocarditis, and hepatitis.[1] †Includes multiple terms.[1]

Laboratory abnormalities[1]

Laboratory values worsening from baseline* occurring in ≥15% of patients

	Opdualag™ (nivolumab and relatlimab-rmbw)* (n=355)	Nivolumab* (n=359)	Opdualag* (n=355)	Nivolumab* (n=359)
Laboratory Abnormality	**Grades 1–4 (%)**	**Grades 1–4 (%)**	**Grades 3/4 (%)**	**Grades 3/4 (%)**
Chemistry				
Increased AST	30	22	2.3	1.4
Increased ALT	26	25	3.2	2
Decreased sodium	24	21	1.2	0.6
Increased alkaline phosphatase	19	17	0.6	0.9
Increased creatinine	19	16	0	0
Hematology				
Decreased hemoglobin	37	31	2.7	3.5
Decreased lymphocytes	32	24	2.5	2.9

*Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Opdualag group (range: 280–342 patients) and nivolumab group (range: 276–345 patients).
ALT=alanine aminotransferase; AST=aspartate aminotransferase.

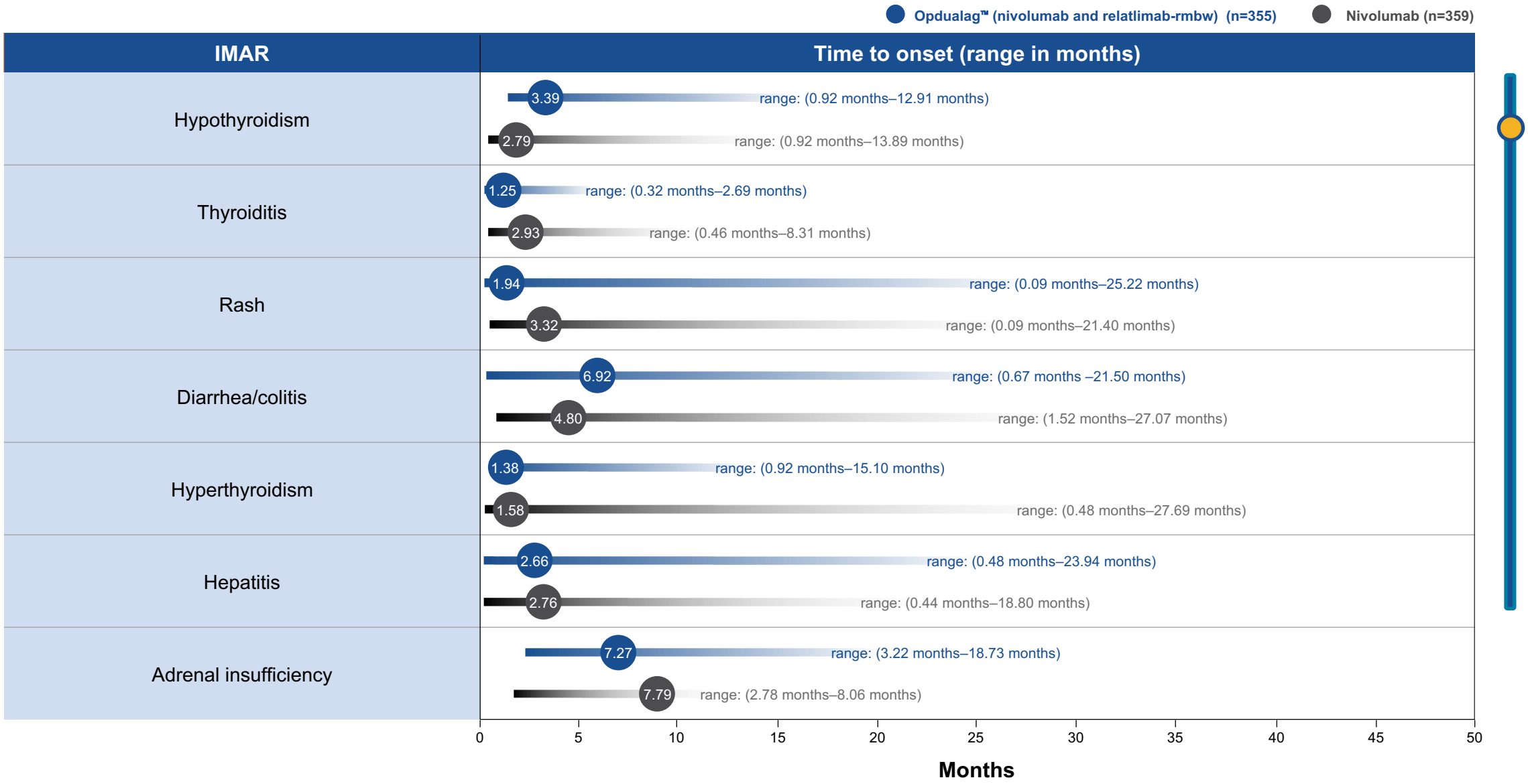
IMARs in RELATIVITY-047[1,7]

Increases seen in Grade 3/4 IMARs with Opdualag™ (nivolumab and relatlimab-rmbw) vs nivolumab were hepatitis (2.8%), adrenal insufficiency (1.4%) and myocarditis (0.6%)[1,7]

IMAR	Opdualag (n=355) All Grades, n (%)	Nivolumab (n=359) All Grades, n (%)	Opdualag (n=355) Grades 3/4, n (%)	Nivolumab (n=359) Grades 3/4, n (%)
Hypothyroidism	59 (16.6)	47 (13.1)	0	0
Thyroiditis	10 (2.8)	5 (1.4)	0	0
Rash	33 (9.3)	24 (6.7)	2 (0.6)	5 (1.4)
Diarrhea/colitis	24 (6.8)	11 (3.1)	4 (1.1)	5 (1.4)
Hyperthyroidism	22 (6.2)	24 (6.7)	0	0
Hepatitis	20 (5.6)	9 (2.5)	14 (3.9)	4 (1.1)
Adrenal insufficiency	15 (4.2)	3 (0.8)	5 (1.4)	0
Pneumonitis	13 (3.7)	6 (1.7)	2 (0.6)	2 (0.6)
Hypophysitis	9 (2.5)	3 (0.8)	1 (0.3)	1 (0.3)
Nephritis and renal dysfunction	7 (2)	5 (1.4)	4 (1.1)	4 (1.1)
Infusion-related reactions	4 (1)	4 (1.1)	0	0
Type 1 diabetes, which can present with diabetic ketoacidosis	1 (0.3)	2 (0.6)	1 (0.3)	1 (0.3)
Myocarditis	6 (1.7)	2 (0.6)	2 (0.6)	0

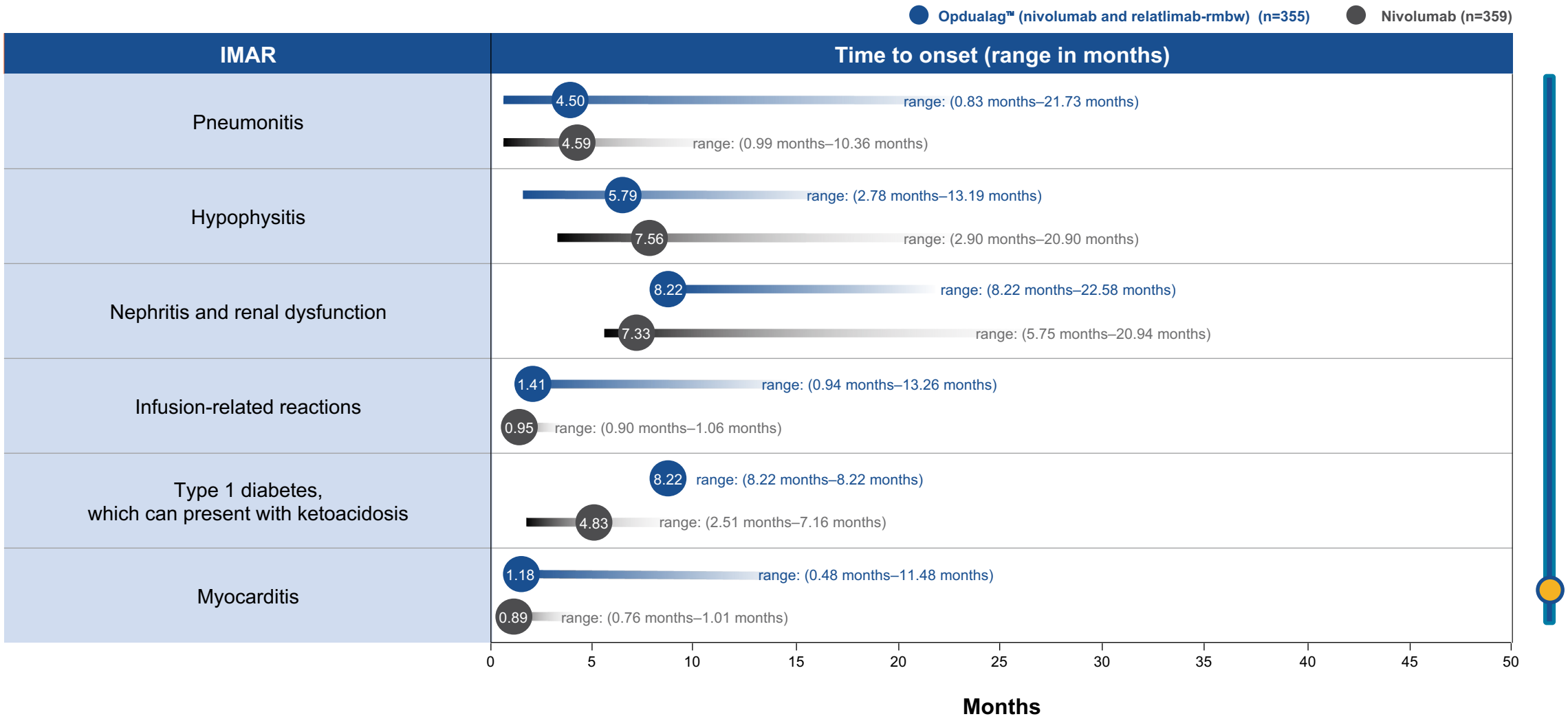
IMAR=immune-mediated adverse reaction.

Similar median time to onset of IMARs across treatment arms[1,7,8]



Please see Important Safety Information for Opdualag throughout and US Full Prescribing Information for Opdualag.

Similar median time to onset of IMARs across treatment arms (cont'd)[1,7,8]



Standard management of IMARs[1,7]

Adverse reaction	Opdualag™ (nivolumab and relatlimab-rmbw) (n=355)	Nivolumab (n=359)	Opdualag (n=355)	Nivolumab (n=359)	Opdualag (n=355)	Nivolumab (n=359)	Opdualag (n=355)	Nivolumab (n=359)
	Permanent discontinuation (%)		Dose delay or interruption (%)		Systemic corticosteroids required, % (n/n)		Resolution rate (%)	
Pneumonitis	0.8	0.6	2.5	1.1	100 (13/13)	100 (6/6)	85% of 13	50% of 6
Diarrhea/colitis	2	0.8	4.2	1.9	100 (24/24)	100 (11/11)	83% of 24	64% of 11
Hepatitis	1.7	1.1	3.9	1.7	100 (20/20)	100 (9/9)	70% of 20	100% of 9
Nephritis with renal dysfunction	0.8	0.8	1.1	0.6	100 (7/7)	100 (5/5)	71% of 7	80% of 5
Rash	0	0.3	1.4	1.7	100 (33/33)	100 (24/24)	70% of 33	63% of 24
Hypersensitivity/ infusion-related reaction	0	0.3	0	0	100 (4/4)	100 (4/4)	100% of 4	100% of 4
Adrenal insufficiency	1.1	0	1.1	0.3	87 (13/15)	100 (3/3)	33% of 15	33% of 3
Hypophysitis	0.3	0	0.8	0	100 (9/9)	100 (3/3)	22% of 9	67% of 3
Hypothyroidism	0.3	0	2.5	1.7	0	0	12% of 59	13% of 47
Thyroiditis	0	0	0.3	0	20 (2/10)	20 (1/5)	90% of 10	100% of 5
Hyperthyroidism	0	0	0.6	1.4	23 (5/22)	8 (2/24)	82% of 22	79% of 24
Type 1 diabetes, which can present with diabetic ketoacidosis	0	0	0.3	0.3	100 (1/1)	0	0	0
Myocarditis	1.7	0.3	0	0.6	100 (6/6)	100 (2/2)	100% of 6	50% of 2

Treatment modifications[1]

Adverse Reactions	Severity*	Dose Modification
IMAR		
Pneumonitis	Grade 2	Withhold†
	Grade 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold†
	Grade 4	Permanently discontinue
Hepatitis	AST/ALT increases to more than 3 and up to 8 times ULN **– or –** Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold†
	AST or ALT increases to more than 8 times ULN regardless of baseline **– or –** Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies‡	Grade 3 or 4	Withhold until clinically stable or permanently discontinue, depending on severity
Nephritis with renal dysfunction	Grade 2 or 3 increased blood creatinine	Withhold†
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative dermatologic conditions	Suspected SJS, TEN, or DRESS	Withhold
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological toxicities	Grade 2	Withhold†
	Grade 3 or 4	Permanently discontinue
Other Adverse Reactions		
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

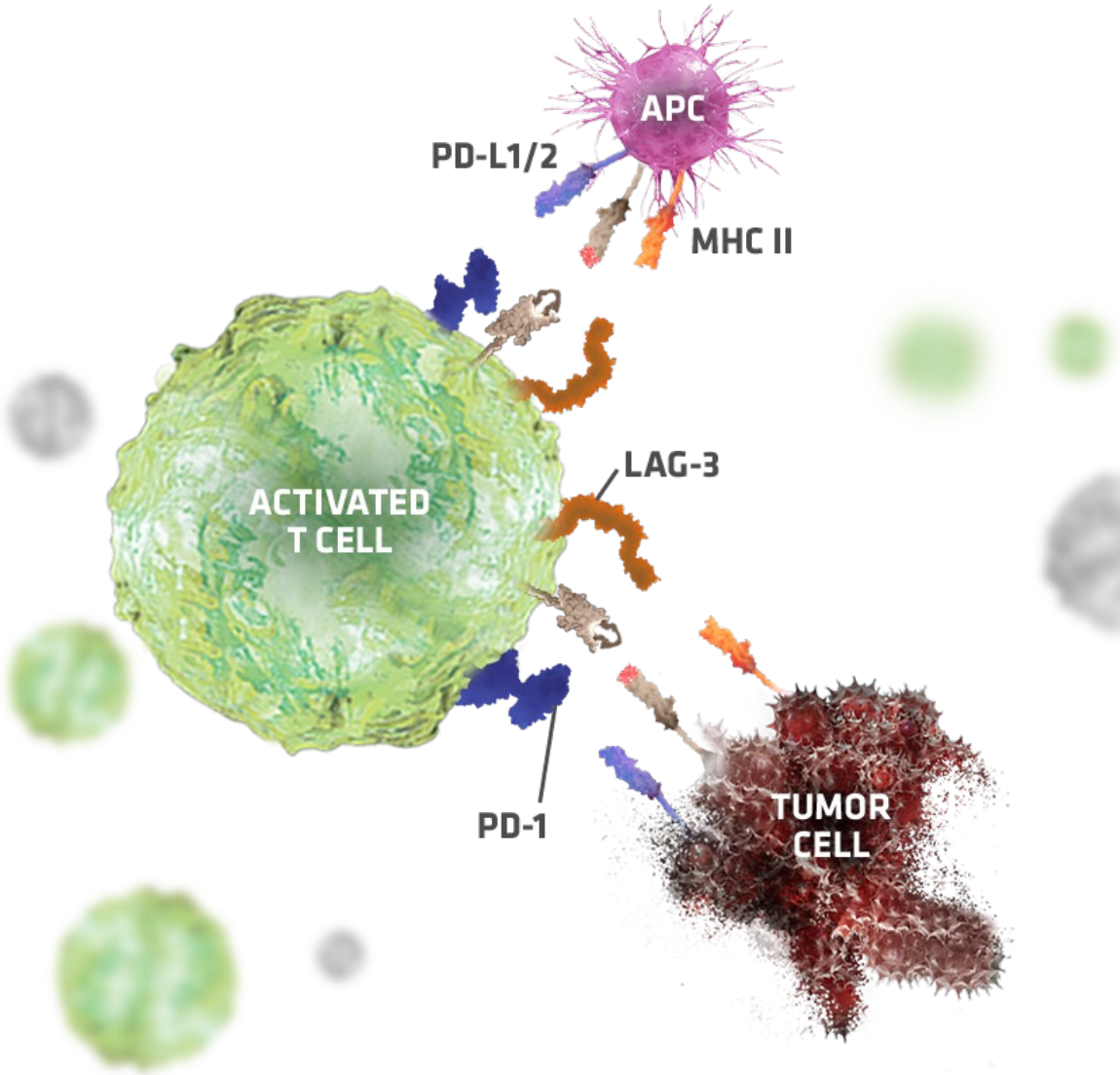
- No recommended dose reductions for Opdualag™ (nivolumab and relatlimab-rmbw)[1]
- In general, withhold Opdualag for severe (Grade 3) IMARs[1]
- Permanently discontinue Opdualag for life-threatening (Grade 4) IMARs, recurrent severe (Grade 3) IMARs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids[1]

*Based on National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.[1] †Resume in patients with complete or partial resolution (Grade 0 or 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.[1] ‡Depending on clinical severity, consider withholding for Grade 2 endocrinopathy until symptom improvement with hormone replacement. Resume once acute symptoms have resolved.[1]

DRESS=drug reaction with eosinophilia and systemic symptoms; SJS=Stevens-Johnson syndrome; TEN=toxic epidermal necrolysis.

Mechanism of action[1,9]

- LAG-3 is a cell-surface molecule, which is expressed on T cells and other immune cells that has diverse inhibitory biologic effects on the function of T cells[10,11]
  - In addition to activated CD4+ and CD8+ T cells, LAG-3 is expressed on several immune cell types, including memory T cells, Tregs, and natural killer cells[12,13]
- LAG-3 reduces T-cell activation and proliferation, and may attenuate pro-inflammatory responses[10,11,14]
- Activation of the LAG-3 pathway occurs when LAG-3 interacts with its ligands. Ligands for LAG-3 are distinct from the ligands of other inhibitory immune checkpoints, such as PD-1 or CTLA-4[10]



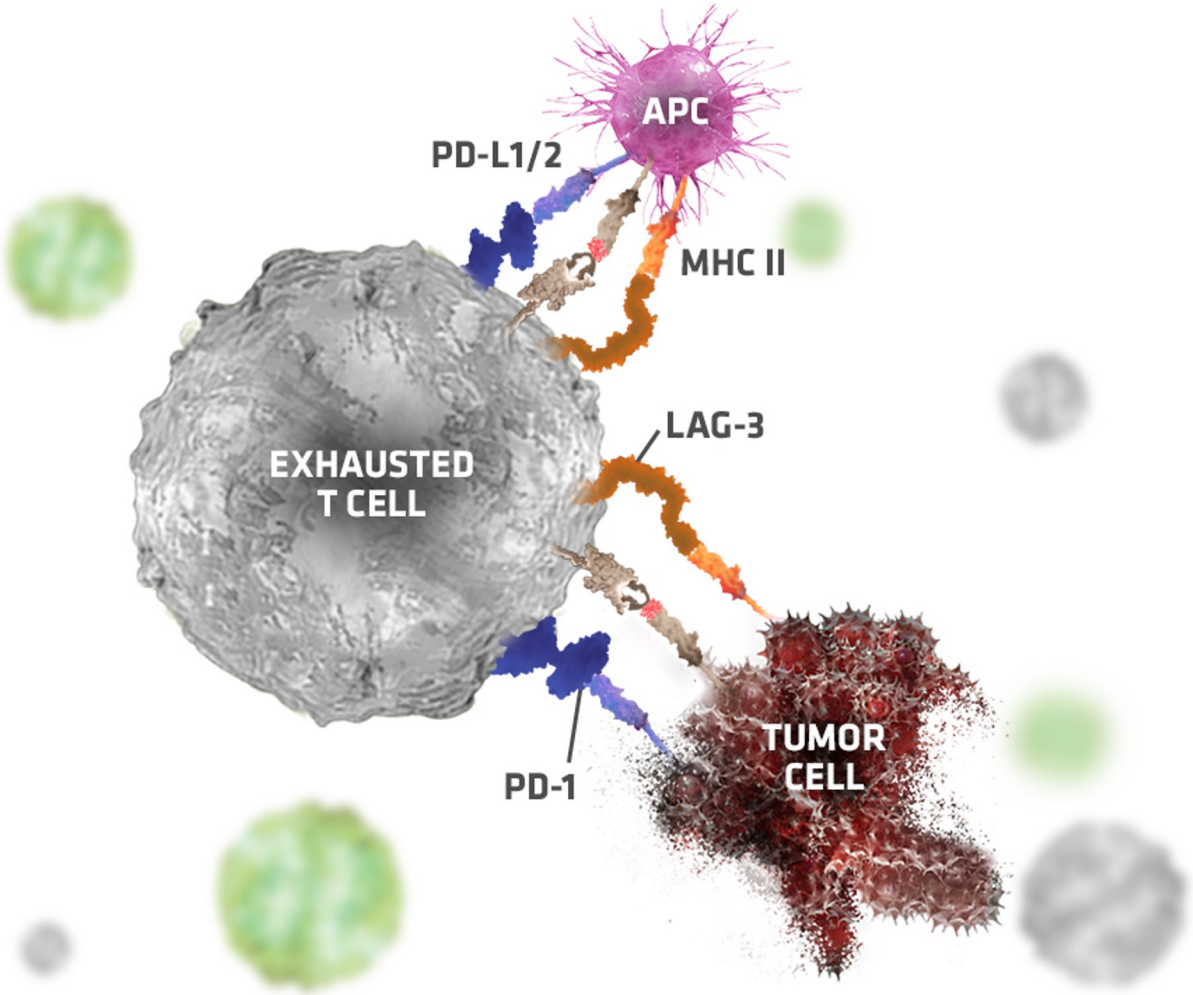
Targeting of normal cells can occur.

The illustrated mechanism of action may vary for each patient and may not directly correlate with clinical significance.

APC=antigen-presenting cell; CD=cluster of differentiation; MHC ||=major histocompatibility complex class II; PD-L2=programmed death-ligand 2; Treg=regulatory T cell.

Mechanism of action (cont'd)[1,9]

- Activation of the LAG-3 pathway triggers inhibitory activity that reduces the function of effector T cells, leading to an impaired ability to attack tumor cells and an increased potential for tumor growth[4,10]
- LAG-3 and PD-1 are 2 distinct inhibitory immune checkpoint pathways that act synergistically on effector T cells, leading to the inhibition of T cell proliferation and impaired cytokine production[1,4,9]

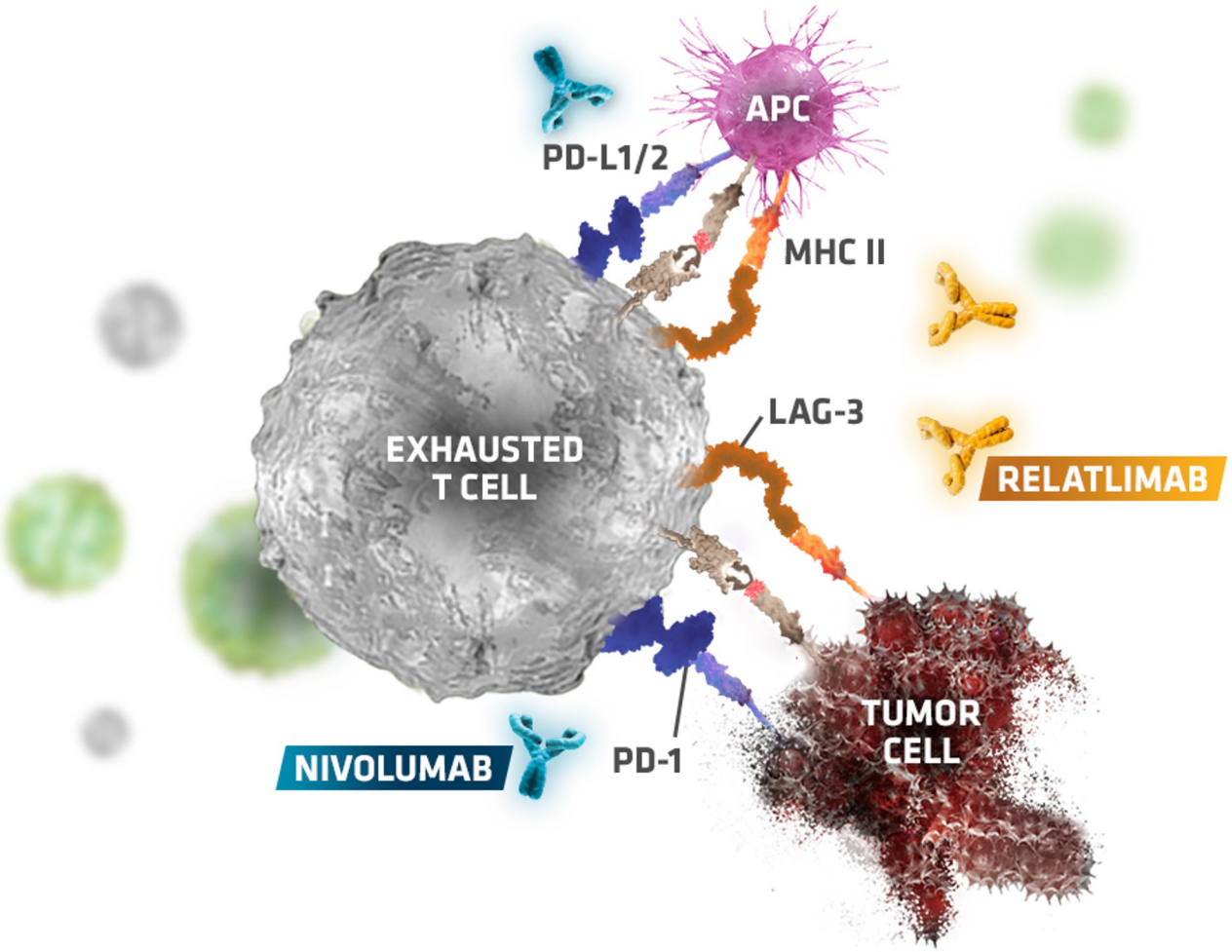


Targeting of normal cells can occur.

The illustrated mechanism of action may vary for each patient and may not directly correlate with clinical significance.

Mechanism of action (cont'd)[1,9]

- Combined nivolumab (anti–PD-1) and relatlimab (anti–LAG-3) inhibition results in increased T cell activation compared to the activity of either antibody alone. This initiates an improved anti-tumor immune response[1]



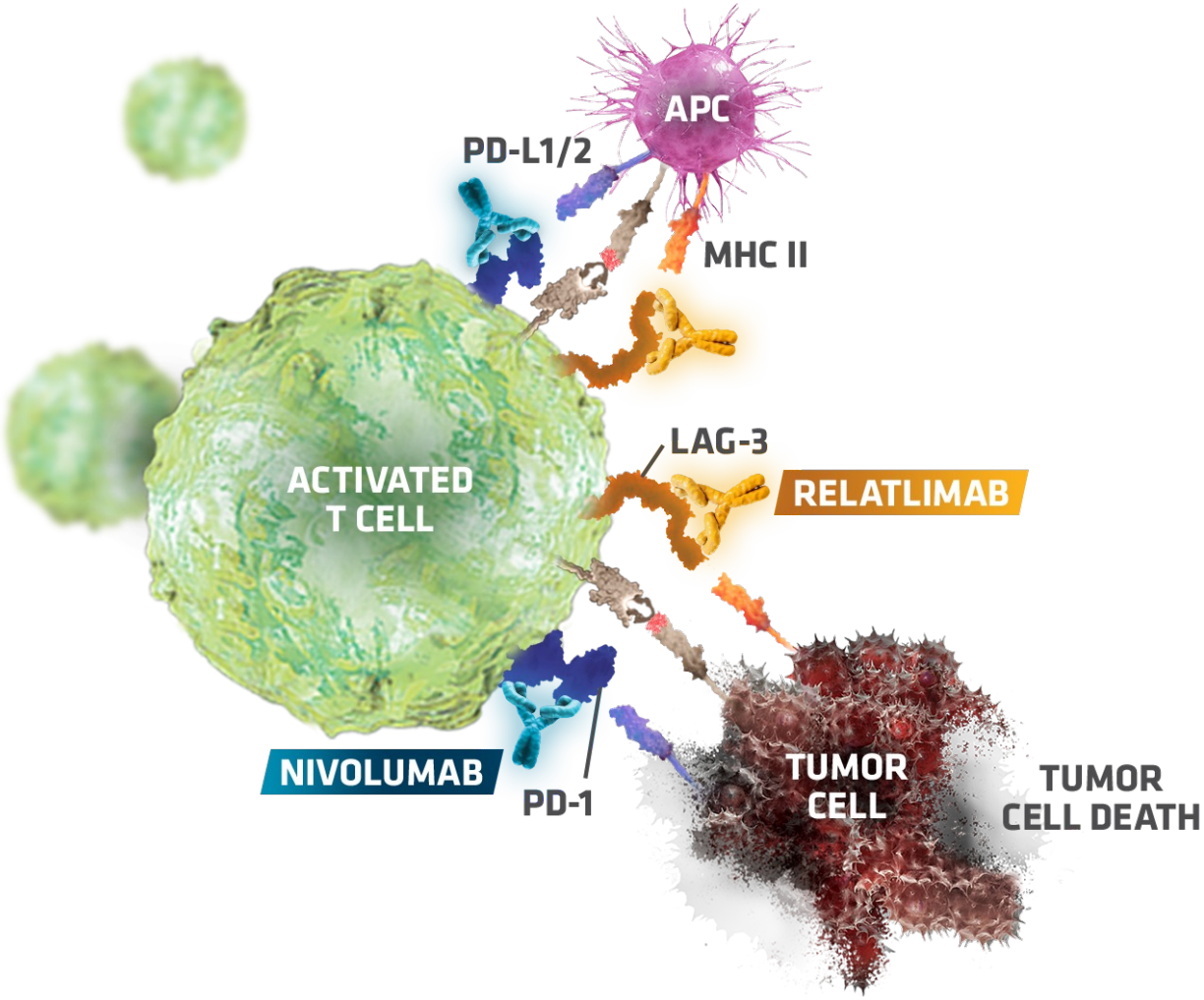
Targeting of normal cells can occur.

The illustrated mechanism of action may vary for each patient and may not directly correlate with clinical significance.

Mechanism of action (cont'd)[1,9]

LAG-3 and PD-1 are 2 distinct immune checkpoints[1,4]

- Relatlimab binds to the LAG-3 receptor and blocks its interaction with the ligands, including MHC II, reducing LAG-3 pathway–mediated inhibition of the immune response, thereby promoting T cell proliferation and cytokine secretion[1]
- Nivolumab binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thereby relieving T cell dysfunction and improving cytotoxic function[1]
- The combination of nivolumab- and relatlimab-mediated inhibition increases T cell activity compared to the activity of either antibody alone[1]



Targeting of normal cells can occur.

The illustrated mechanism of action may vary for each patient and may not directly correlate with clinical significance.

Fixed-dose combination administered as a 30-minute intravenous infusion every 4 weeks[1]

30 minutes

Fixed-dose combination of nivolumab and relatlimab[1]

Adult patients and pediatric patients*
Single 30-minute infusion of nivolumab 480 mg and relatlimab 160 mg every 4 weeks[1]

Treat until disease progression or unacceptable toxicity[1]

*12 years of age or older who weigh at least 40 kg. A recommended dosage for pediatric patients 12 years of age or older who weigh less than 40 kg, and pediatric patients younger than 12 years of age has not been established.[1]

A single, fixed-dose infusion may help reduce preparation and infusion times and could help minimize potential risk of administration errors[4†]

†Two vials are required for the nivolumab 480 mg + relatlimab 160 mg indication dose.[1]

- Opdualag™ (nivolumab and relatlimab-rmbw) is a fixed-dose combination: a co-formulation of 2 active ingredients in a single vial administered as a single infusion[1,15]
- A single-dose vial contains 240 mg of nivolumab and 80 mg of relatlimab per 20 mL[1]

SELECT IMPORTANT SAFETY INFORMATION

Infusion-related reactions

- Opdualag™ (nivolumab and relatlimab-rmbw) can cause severe infusion-related reactions. Discontinue Opdualag in patients with severe or life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild to moderate infusion-related reactions. In patients who received Opdualag as a 60-minute intravenous infusion, infusion-related reactions occurred in 7% (23/355) of patients.

Important Safety Information

Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions (IMARs) listed herein may not include all possible severe and fatal immune-mediated adverse reactions.

IMARs which may be severe or fatal, can occur in any organ system or tissue. IMARs can occur at any time after starting treatment with a LAG-3 and PD-1/PD-L1 blocking antibodies. While IMARs usually manifest during treatment, they can also occur after discontinuation of Opdualag™ (nivolumab and relatlimab-rmbw). Early identification and management of IMARs are essential to ensure safe use. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying IMARs. Evaluate clinical chemistries including liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected IMARs, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue Opdualag depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if Opdualag requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose IMARs are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

Opdualag can cause immune-mediated pneumonitis, which may be fatal. In patients treated with other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.7% (13/355) of patients receiving Opdualag, including Grade 3 (0.6%), and Grade 2 (2.3%) adverse reactions. Pneumonitis led to permanent discontinuation of Opdualag in 0.8% and withholding of Opdualag in 1.4% of patients.

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Important Safety Information (cont'd)

Severe and Fatal Immune-Mediated Adverse Reactions (cont'd)

Immune-Mediated Colitis

Opdualag™ (nivolumab and relatlimab-rmbw) can cause immune-mediated colitis, defined as requiring use of corticosteroids and no clear alternate etiology. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-mediated diarrhea or colitis occurred in 7% (24/355) of patients receiving Opdualag, including Grade 3 (1.1%) and Grade 2 (4.5%) adverse reactions. Colitis led to permanent discontinuation of Opdualag in 2% and withholding of Opdualag in 2.8% of patients.

Immune-Mediated Hepatitis

Opdualag can cause immune-mediated hepatitis, defined as requiring the use of corticosteroids and no clear alternate etiology.

Immune-mediated hepatitis occurred in 6% (20/355) of patients receiving Opdualag, including Grade 4 (0.6%), Grade 3 (3.4%), and Grade 2 (1.4%) adverse reactions. Hepatitis led to permanent discontinuation of Opdualag in 1.7% and withholding of Opdualag in 2.3% of patients.

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Important Safety Information (cont'd)

Severe and Fatal Immune-Mediated Adverse Reactions (cont'd)

Immune-Mediated Endocrinopathies

Opdualag™ (nivolumab and relatlimab-rmbw) can cause primary or secondary adrenal insufficiency, hypophysitis, thyroid disorders, and Type 1 diabetes mellitus, which can be present with diabetic ketoacidosis. Withhold or permanently discontinue Opdualag depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. In patients receiving Opdualag, adrenal insufficiency occurred in 4.2% (15/355) of patients receiving Opdualag, including Grade 3 (1.4%) and Grade 2 (2.5%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of Opdualag in 1.1% and withholding of Opdualag in 0.8% of patients.

Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Hypophysitis occurred in 2.5% (9/355) of patients receiving Opdualag, including Grade 3 (0.3%) and Grade 2 (1.4%) adverse reactions. Hypophysitis led to permanent discontinuation of Opdualag in 0.3% and withholding of Opdualag in 0.6% of patients.

Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Thyroiditis occurred in 2.8% (10/355) of patients receiving Opdualag, including Grade 2 (1.1%) adverse reactions. Thyroiditis did not lead to permanent discontinuation of Opdualag. Thyroiditis led to withholding of Opdualag in 0.3% of patients. Hyperthyroidism occurred in 6% (22/355) of patients receiving Opdualag, including Grade 2 (1.4%) adverse reactions. Hyperthyroidism did not lead to permanent discontinuation of Opdualag. Hyperthyroidism led to withholding of Opdualag in 0.3% of patients. Hypothyroidism occurred in 17% (59/355) of patients receiving Opdualag, including Grade 2 (11%) adverse reactions. Hypothyroidism led to the permanent discontinuation of Opdualag in 0.3% and withholding of Opdualag in 2.5% of patients.

Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated. Diabetes occurred in 0.3% (1/355) of patients receiving Opdualag, a Grade 3 (0.3%) adverse reaction, and no cases of diabetic ketoacidosis. Diabetes did not lead to the permanent discontinuation or withholding of Opdualag in any patient.

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Important Safety Information (cont'd)

Severe and Fatal Immune-Mediated Adverse Reactions (cont'd)

Immune-Mediated Nephritis with Renal Dysfunction

Opdualag™ (nivolumab and relatlimab-rmbw) can cause immune-mediated nephritis, which is defined as requiring use of steroids and no clear etiology. In patients receiving Opdualag, immune-mediated nephritis and renal dysfunction occurred in 2% (7/355) of patients, including Grade 3 (1.1%) and Grade 2 (0.8%) adverse reactions. Immune-mediated nephritis and renal dysfunction led to permanent discontinuation of Opdualag in 0.8% and withholding of Opdualag in 0.6% of patients.

Withhold or permanently discontinue Opdualag depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

Immune-Mediated Dermatologic Adverse Reactions

Opdualag can cause immune-mediated rash or dermatitis, defined as requiring use of steroids and no clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, and Drug Rash with eosinophilia and systemic symptoms has occurred with PD-1/L-1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes.

Withhold or permanently discontinue Opdualag depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

Immune-mediated rash occurred in 9% (33/355) of patients, including Grade 3 (0.6%) and Grade 2 (3.4%) adverse reactions. Immune-mediated rash did not lead to permanent discontinuation of Opdualag. Immune-mediated rash led to withholding of Opdualag in 1.4% of patients.

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Important Safety Information (cont'd)

Severe and Fatal Immune-Mediated Adverse Reactions (cont'd)

Immune-Mediated Myocarditis

Opdualag™ (nivolumab and relatlimab-rmbw) can cause immune-mediated myocarditis, which is defined as requiring use of steroids and no clear alternate etiology. The diagnosis of immune-mediated myocarditis requires a high index of suspicion. Patients with cardiac or cardio-pulmonary symptoms should be assessed for potential myocarditis. If myocarditis is suspected, withhold dose, promptly initiate high dose steroids (prednisone or methylprednisolone 1 to 2 mg/kg/day) and promptly arrange cardiology consultation with diagnostic workup. If clinically confirmed, permanently discontinue Opdualag for Grade 2-4 myocarditis.

Myocarditis occurred in 1.7% (6/355) of patients receiving Opdualag, including Grade 3 (0.6%), and Grade 2 (1.1%) adverse reactions. Myocarditis led to permanent discontinuation of Opdualag in 1.7% of patients.

Other Immune-Mediated Adverse Reactions

The following clinically significant IMARs occurred at an incidence of <1% (unless otherwise noted) in patients who received Opdualag or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *Cardiac/Vascular:* pericarditis, vasculitis; *Nervous System:* meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *Ocular:* uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other IMARs, consider a Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss; *Gastrointestinal:* pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis; *Musculoskeletal and Connective Tissue:* Myositis/polymyositis, rhabdomyolysis (and associated sequelae including renal failure), arthritis, polymyalgia rheumatica; *Endocrine:* hypoparathyroidism; *Other (Hematologic/Immune):* hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.

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Important Safety Information (cont'd)

Infusion-Related Reactions

Opdualag™ (nivolumab and relatlimab-rmbw) can cause severe infusion-related reactions. Discontinue Opdualag in patients with severe or life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild to moderate infusion-related reactions. In patients who received Opdualag as a 60-minute intravenous infusion, infusion-related reactions occurred in 7% (23/355) of patients.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 receptor blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 receptor blocking antibody prior to or after an allogeneic HSCT.

Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, Opdualag can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Opdualag and for at least 5 months after the last dose of Opdualag.

Lactation

There are no data on the presence of Opdualag in human milk, the effects on the breastfed child, or the effect on milk production. Because nivolumab and relatlimab may be excreted in human milk and because of the potential for serious adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with Opdualag and for at least 5 months after the last dose.

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Important Safety Information (cont'd)

Serious Adverse Reactions

In Relativity-047, fatal adverse reaction occurred in 3 (0.8%) patients who were treated with Opdualag™ (nivolumab and relatlimab-rmbw); these included hemophagocytic lymphohistiocytosis, acute edema of the lung, and pneumonitis. Serious adverse reactions occurred in 36% of patients treated with Opdualag. The most frequent serious adverse reactions reported in ≥1% of patients treated with Opdualag were adrenal insufficiency (1.4%), anemia (1.4%), colitis (1.4%), pneumonia (1.4%), acute myocardial infarction (1.1%), back pain (1.1%), diarrhea (1.1%), myocarditis (1.1%), and pneumonitis (1.1%).

Common Adverse Reactions and Laboratory Abnormalities

The most common adverse reactions reported in ≥20% of the patients treated with Opdualag were musculoskeletal pain (45%), fatigue (39%), rash (28%), pruritus (25%), and diarrhea (24%).

The most common laboratory abnormalities that occurred in ≥20% of patients treated with Opdualag were decreased hemoglobin (37%), decreased lymphocytes (32%), increased AST (30%), increased ALT (26%), and decreased sodium (24%).

Please see U.S. Full Prescribing Information for Opdualag.

References

1. Opdualag [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2022.
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