The Latest Option: Nivolumab and Relatlimab in Advanced Melanoma

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Abstract

Purpose of Review Dual immune checkpoint inhibition with ipilimumab plus nivolumab is currently the most effective, but also by far the most toxic treatment for advanced melanoma. Therefore, other combination partners that also lead to high and long-lasting responses but cause fewer adverse events were explored.

Recent Findings Relatlimab, a LAG-3 blocking antibody, was investigated in combination with nivolumab in a phase 2/3 randomized double-blind trial (RELATIVITY-047) and could demonstrate significantly improved progression-free survival in treatment-naive advanced melanoma patients compared with nivolumab monotherapy. While the safety profile is more favorable than that of ipilimumab plus nivolumab, no significant survival benefit has yet been demonstrated with the new combination over nivolumab monotherapy.

Summary The approval of relatlimab plus nivolumab by both the Food and Drug Administration and the European Medicines Agency expands the arsenal of treatment options for melanoma but raises new questions in clinical practice and a re-evaluation of currently established treatment standards and sequences.

Keywords Dual checkpoint inhibition · Relatlimab plus nivolumab · LAG-3 blocking antibody · Melanoma · T-cell exhaustion · Overcoming anti-PD-1 resistance

Introduction

The development of immune checkpoint inhibitors has fundamentally revolutionized the therapeutic landscape and has led to a marked improvement in survival outcomes in patients with advanced melanoma by enabling profound and durable responses [1]. Based on the results of two randomized, double-blind trials (CheckMate 069, CheckMate 067) combined immunotherapy with anti-cytotoxic T lymphocyte antigen-4 antibody (anti-CTLA-4) ipilimumab plus anti-programmed cell death protein 1 antibody (anti-PD-1) nivolumab was the first dual checkpoint blockade approved by the Food and Drug

Administration (FDA) for the treatment of metastatic melanoma [2, 3]. Since dual immunotherapy has demonstrated its clear superiority over anti-CTLA-4 monotherapy in both progression-free survival (PFS) and overall survival (OS), it is nowadays the standard of care for first-line treatment [3]. However, ipilimumab plus nivolumab is associated with a high risk of toxicity inducing a range of immune-related adverse events, and approximately 40% of patients discontinue treatment prematurely [4]. Moreover, a relevant subset of patients shows primary non-response or develops disease progression after a period of response [5, 6], thus many studies focus on overcoming resistance. The molecular mechanisms of resistance have not been fully elucidated to date. Since the expression of distinct immune checkpoint receptors could be a possible explanation, the identification of new checkpoint targets represents an appealing approach. Lymphocyte-activation gene 3 (LAG-3), a cell surface molecule on immune cells, which negatively regulates immune responses and is often co-expressed with PD-1 [7], represents one of the latest immune checkpoint receptors. In the phase 2/3 randomized double-blind study (RELATIVITY-047), relatlimab, the first-in-class LAG-3 inhibiting antibody (anti-LAG-3), demonstrated its efficacy, safety, and superiority over nivolumab monotherapy

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in a fixed-dose combination with nivolumab and represents the first dual checkpoint blockade to be approved along with ipilimumab and nivolumab [8••, 9]. Herein, we provide an overview of the latest therapeutic option of dual checkpoint blockade with relatlimab and nivolumab in melanoma and highlight its antitumor activity in different stages and patient populations. Moreover, we summarize the current state of clinical investigation of LAG-3 targeting molecules in melanoma and discuss the position of dual checkpoint inhibition with anti-LAG-3 plus anti-PD-1 antibodies in the arsenal of current melanoma therapies.

Molecular Insights of LAG-3 Function

Immune checkpoints are membrane-bound receptors expressed by immune or tumor cells that lead to positive or negative regulation of the immune response [10]. Inhibitory receptors, such as CTLA-4 and PD-1, are physiologically upregulated during activation, expansion, and differentiation of naive T cells, especially during permanent antigen presentation, to maintain self-tolerance, i.e., suppress autoimmunity and prevent tissue damage, and thus contribute to immune escape and T cell exhaustion in carcinogenesis [11, 12]. Immune checkpoint inhibitors exert their effects by antagonizing the interaction between receptors and their ligands, thus counteracting immune exhaustion by activating a tumor-specific immune response [10, 13]. The LAG-3 gene (also known as CD223), first identified in 1990 [14] is located on chromosome 12 (12p13.32), like the coreceptor CD4, and encodes a 70 KDa single-pass transmembrane glycoprotein consisting of 498 amino acids [15]. It belongs to the Ig superfamily and contains an extracellular, a transmembrane and an intracellular region with four extracellular immunoglobulin-like superfamily regions (D1-D4) with one variable (type V) and three constant (type C) Ig-like domains [15–17]. LAG-3 is expressed on the surface of CD4$^+$ and CD8$^+$ T lymphocytes and inhibits the tumor immunological microenvironment by negatively affecting T cell proliferation and inducing T cell exhaustion [18–20]. It has been shown to be frequently co-expressed with PD-1, whereby high LAG-3 expression is found primarily in tumor-infiltrating T cells [7, 21]. Additionally, LAG-3 can be detected on other cell populations such as natural killer cells, NK T cells, regulatory T cells, dendritic cells, and activated B cells, although it is not clear whether expression on these cell populations contributes to antitumor immunity [18, 22–24]. Major histocompatibility complex class II (MHC II) molecules, which are highly expressed in cutaneous melanomas [25], represent the canonical ligands of LAG-3, as they do for CD4, however, the proline-rich D1 domain allows LAG-3 to bind with higher affinity to MHC II than to CD4 [26–28]. In addition to MHC II molecules, other ligands of LAG-3 have been described previously [29]. Based on its molecular function, constitutive LAG-3 expression may

limit the antitumor effect of PD-1 blockade in treatment-naive patients, and combined checkpoint inhibition might improve response and increase its durability. Moreover, adaptive upregulation of LAG-3 expression may result in treatment resistance and tumor progression in patients receiving anti-PD-1 therapy, and anti-LAG-3 in combination with nivolumab could potentially restore T cell activation and tumor response.

New Combined Checkpoint Inhibition with Anti-LAG-3 Antibody Relatlimab Plus Anti-PD-1 Antibody Nivolumab in Advanced Melanoma

Relatlimab is a first-in-class human IgG4-LAG-3 blocking antibody that, in combination with nivolumab, is the third immune checkpoint inhibitor to receive approval for the treatment of patients with advanced melanoma. Relatlimab plus nivolumab is a fixed-dose combination immunotherapy for the treatment of various advanced-stage cancer entities and received FDA approval in March 2022 for the treatment of advanced melanoma in adult patients and children ≥ 12 years of age weighing at least 40 kg [30]. On 09/15/2022, the European Medicines Agency (EMA) issued marketing authorization for relatlimab plus nivolumab throughout the European Union for patients 12 years of age and older with unresectable or metastatic melanoma with programmed cell death ligand 1 (PD-L1) expression less than 1% [31]. The approval based on the results of a global, double-blind, randomized phase 2/3 study (RELATIVITY-047), demonstrating the superiority in PFS of combined PD-1/LAG-3 inhibition with relatlimab plus nivolumab compared to nivolumab alone in patients with untreated metastatic or unresectable melanoma [8••]. Previously, the phase 1/2 dose escalation and cohort expansion study (RELATIVITY-020; NCT01968109) which also included patients with advanced melanoma who had failed or exhibited disease progression to anti-PD-1 therapy was able to prove favorable tolerability and long-term response to relatlimab plus nivolumab with an overall response rate (ORR) of 16% and disease control rate (DCR) of 45% [32].

First-line treatment with relatlimab plus nivolumab resulted in improved and more than doubled PFS (10.1 vs 4.6 months) compared with nivolumab monotherapy after a median follow-up of 13.2 months, with a nearly 12% difference in PFS at 12-month follow-up and an overall risk reduction of disease progression of 25% compared to nivolumab monotherapy (hazard ratio (HR) 0.75; 95% confidence interval (CI), 0.62 to 0.92; P = 0.006). In an updated report at a median follow-up time of 19.3 months, no major change in PFS between the two treatment groups (10.2 vs 4.6 months; HR 0.78; 95% CI 0.64–0.94) has been observed. Moreover, treatment with nivolumab plus relatlimab resulted in numerically improved

ORR (ORR: complete response (CR) + partial response (PR)) (43.1 vs 32.6%) and DCR (DCR: CR + PR + stable disease (SD)) (62.8 vs 50.7%) compared to nivolumab monotherapy. Median OS has not yet been reached in patients treated with relatlimab plus nivolumab, as opposed to nivolumab monotherapy (34.1 months, 95%CI 25.2 - not reached (NR)), yielding a 20% risk reduction of death to date (HR 0.8; 95%CI 0.64–1.01; $P = 0.0593$) [33••]. Although cross-trial comparisons should be made with caution, and survival data from the Checkmate 067 trial were investigator-assessed and not by a blinded independent central review (BICR) as in the RELATIVITY047 trial, ipilimumab plus nivolumab and relatlimab plus nivolumab show comparable efficacy data with similar PFS rates (2-year PFS; 38.5 vs 43%) and OS rate (2-year OS; 63.7 vs 64.0%) (Table 1) 2, 4, 8••, 34.

Furthermore, treatment with relatlimab plus nivolumab showed superiority to monotherapy across all key subgroups. Dual checkpoint inhibition with relatlimab plus nivolumab resulted in prolonged PFS regardless of LAG-3 status, LAG-3 expression ≥ 1% was associated with superior PFS in both treatment arms. In contrast, patients with PD-L1 expression ≥ 1% did not benefit more from combination therapy (median PFS 15.7 vs 14.7 months). PFS was higher in both treatment groups when PD-L1 expression was ≥ 1%. However, in patients with low PD-L1 expression (< 1%), dual checkpoint inhibition resulted in longer PFS compared with nivolumab monotherapy (6.4 vs 2.9 months). Moreover, the benefit of relatlimab plus nivolumab was shown to be independent of v-raf murine sarcoma viral oncogene homolog B1 (BRAF) mutational status (median PFS in BRAF V600 and BRAF wild-type: 10.1 vs 4.6 months). Even with prognostically unfavorable factors such as increased LDH levels, increased tumor burden, or increasing American Joint Committee on Cancer (AJCC) M-stage, which are generally associated with shorter PFS, combined immunotherapy resulted in a better outcome independent of key prognostic factors and demographic data such as age and gender. The analysis of an early on-treatment biopsy in the phase 2 study showed an association between the immune-related pathological response and the radiological response at four weeks follow-up, whereby the highest major pathological response (≤ 10% residual viable tumor) rate was recorded under treatment with relatlimab plus nivolumab, thus validating the clinical benefit of combined immunotherapy at the pathological level. Thus, early-on treatment biopsy may serve as a biomarker of treatment response in advanced melanoma [35].

Dual therapy with relatlimab plus nivolumab showed manageable tolerability with an acceptable safety profile without new or unexpected safety signals (Table 2). The frequency of grade 3/4 treatment-related adverse events was higher with combination therapy (21.1 vs 11.1%), and more patients discontinued treatment due to adverse events (9.0 vs 3.6%) [33••]. The most common grade 3 or 4 treatment-related adverse events in the relatlimab-nivolumab group included elevated lipase, alanine aminotransferase, aspartate aminotransferase, and fatigue. Hypothyroidism, thyroiditis,

Table 1 Comparison of efficacy data of dual checkpoint inhibition [2, 4, 8••, 34]

		RELATIVITY-047[1] (Assessment by BICR)		Checkmate 067[2] (Assessment by investigator)	
		Relatlimab /Nivolumab	Nivolumab	Ipilimumab /Nivolumab	Nivolumab
ORR %		43	33	58	44
Median PFS months (95% CI)		10.2 (6.5–14.8)	4.6 (3.48–6.44)	11.5 (8.7–19.3)	6.9 (5.1–9.7)
HR (95% CI)*		0.78 (0.64–0.94)		0.78 (0.64–0.96)	
Median OS months (95% CI)		NR (34.2-NR)	34.10 (25.23-NR)	72.1[3] (38.2-NR)	37.6 (29.1-NR)
HR (95% CI)*		0.80 (0.64–1.01)		0.85 (0.68–1.07)**	
1-year	**PFS %** **(95% CI)**	48.0 (42.5–53.4)	36.9 (31.7–42.1)	50.0[4] (44.0–55.0)	43.0[4] 37.0–49.0)
	OS % **(95% CI)**	77.0 (72.2–81.1)	71.6 (66.6–76.0)	73.0[4] (68.0–78.0)	74.0[4] (69.0–79.0)
2-years	**PFS %** **(95% CI)**	38.5 (32.7–44.2)	29.0 (23.8–34.4)	43.0[4] (37.0–48.0)	37.0[4] (31.0–43.0)
	OS % **(95% CI)**	63.7 (58.1–68.7)	58.3 (52.7–63.4)	64.0[5] (59.0–69.0)	59.0[5] (53.0–64.0)

BICR: blinded independent central review; ORR: overall response rate; PFS: progression-free survival, HR: hazard ratio; OS: overall survival; NR: not reached; CI: confidence interval; *in comparison with nivolumab mono; **descriptive analysis; 1: median follow-up time: 19.3 months; 2: median follow-up time: 36 months; 3: minimum follow-up time 77 months; 4: minimum follow-up time 12.2–12.5 months; 5: minimum follow-up 28 months

Table 2 Summary of adverse events of RELATIVITY-047 [8••]. *Adapted from Tawbi et al., N Engl J Med. 2022*

Adverse Event	Relatlimab-Nivolumab (N=359)		Nivolumab (N=355)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
number of events (%)				
Any adverse event	345 (97.2)	143 (40.3)	339 (94.4)	120 (33.4)
Treatment-related adverse event	288 (81.1)	67 (18.9)	251 (69.9)	35 (9.7)
Led to discontinuation of treatment	52 (14.6)	30 (8.5)	24 (6.7)	11 (3.1)
Treatment-related adverse event in ≥ 10% of patients in the relatlimab–nivolumab group				
Pruritus	83 (23.4)	0	57 (15.9)	2 (0.6)
Fatigue	82 (23.1)	4 (1.1)	46 (12.8)	1 (0.3)
Rash	55 (15.5)	3 (0.8)	43 (12.0)	2 (0.6)
Arthralgia	51 (14.4)	3 (0.8)	26 (7.2)	1 (0.3)
Hypothyroidism	51 (14.4)	0	43 (12.0)	0
Diarrhea	48 (13.5)	3 (0.8)	33 (9.2)	2 (0.6)
Vitiligo	37 (10.4)	0	35 (9.7)	0
Immune-mediated adverse events				
Hypothyroidism or thyroiditis	64 (18.0)	0	50 (13.9)	0
Rash	33 (9.3)	2 (0.6)	24 (6.7)	5 (1.4)
Diarrhea or colitis	24 (6.8)	4 (1.1)	11 (3.1)	5 (1.4)
Hyperthyroidism	22 (6.2)	0	24 (6.7)	0
Hepatitis	20 (5.6)	14 (3.9)	9 (2.5)	4 (1.1)
Adrenal insufficiency	15 (4.2)	5 (1.4)	3 (0.8)	0
Pneumonitis	13 (3.7)	2 (0.6)	6 (1.7)	2 (0.6)
Hypophysitis	9 (2.5)	1 (0.3)	3 (0.8)	1 (0.3)
Nephritis and renal dysfunction	7 (2.0)	4 (1.1)	5 (1.4)	4 (1.1)

rash, and diarrhea or colitis were the most common immune-mediated adverse events. Myocarditis was slightly more frequent under combination therapy compared to monotherapy. Overall, there was a more than half reduced risk of treatment-related adverse events grade 3/4 adverse events with the new combination compared with ipilimumab plus nivolumab (21 vs 59%) [2, 8••].

Although the clinical benefit of LAG-3 inhibition with relatlimab and its establishment as a third immune checkpoint inhibitor has been clearly demonstrated, further investigation and studies are needed to understand the efficacy of relatlimab plus nivolumab in patient populations that are often excluded from clinical trials, such as patients with active or untreated brain metastases or with rare melanoma subtypes.

Targeting LAG-3 in Uveal Melanoma

Uveal melanoma represents a rare subtype of melanoma but is the most common intraocular malignancy [36]. Although the diagnosis is usually made at an early stage and enucleation or brachytherapy provides effective local therapeutic control, approximately 50% of patients develop metastases, primarily to the liver [37, 38]. In contrast to cutaneous melanomas, uveal melanomas show unsatisfactory response rates to

immune checkpoint inhibitors [39–41]. Only 3.6% of patients responded to anti-PD-1-based monotherapy with a median PFS of 2.6 months and OS of 7.6 months. Slightly better response rates of 15 to 18% were achieved with dual immune checkpoint blockade with ipilimumab and nivolumab, however, these rates are far below those achieved in cutaneous melanomas [42, 43]. As previously discussed, the expression of additional immune checkpoint receptors such as LAG-3 or distinct expression levels of these immune checkpoints could also explain the unfavorable response rates to anti-CTLA-4 and anti-PD-1 therapies in uveal melanoma. Analysis of The Cancer Genome Atlas (TCGA) datasets proved the presence of LAG-3 in uveal melanoma and its association with an increased rate of metastasis [44]. Increased LAG-3 expression correlated positively with high-risk factors such as epithelioid/mixed cell type and BAP1 loss, and high expression of both LAG-3 and its ligands was associated with unfavorable survival rates. Further analyses identified that the expression levels of checkpoint inhibitors of CD8⁺ T cells of the tumor microenvironment varied, showing high expression of LAG-3 and low expression of CTLA-4 and PD-1, thus identifying LAG-3 as the predominant checkpoint inhibitor [45], suggesting that dual immune checkpoint blockade with anti-LAG-3 may be the preferred treatment option in uveal melanoma [39]. In order to test this hypothesis, enrollment

is currently in progress in an open-label, single arm, single site, investigator-initiated phase 2 study (CA224-094) evaluating the efficacy and safety of nivolumab in combination with relatlimab in patients with therapy-naive advanced uveal melanoma (NCT04552223) [46].

(Neo-) Adjuvant Approaches with Relatlimab Plus Nivolumab

Anti-PD-1 antibodies have demonstrated their clinical benefit also as adjuvant treatment and have become part of the clinical routine in the management of fully resectable high-risk stage IIB-IV melanoma patients. Given the positive data of relatlimab plus nivolumab compared to anti-PD-1 monotherapy in metastatic and non-resectable stages, the question arises whether dual checkpoint inhibition will also outperform anti-PD-1 monotherapy in the adjuvant setting. Currently, a phase 3 study investigates the efficacy and tolerability of adjuvant therapy with relatlimab plus nivolumab compared to nivolumab monotherapy in patients with fully resected stage III/IV cutaneous melanoma (NCT05002569). Recruitment is expected to be reached by February 28th, 2023.

Neoadjuvant therapy approaches have been able to achieve significantly more robust immune responses to immune checkpoint inhibitors due to the intact tumor microenvironment compared to adjuvant therapy regimens [47], thus bringing them into the focus of current research. Early initiation of therapy potentially leads to eradication of micrometastases [48], reduction of tumor burden lowers surgical morbidity, and the ability to personalize adjuvant therapy based on pathologic response are further advantages in favor of neoadjuvant approaches. Patients who achieve a pathologic complete response with neoadjuvant therapy show significantly improved relapse-free survival with both targeted and immunotherapy-based therapeutic approaches [49]. In contrast to targeted therapy, the clinical benefit of neoadjuvant immunotherapy appears to be warranted with any pathologic response (pathological complete response (pCR), near pCR, pathological partial response (pPR)) [49]. Neoadjuvant therapeutic approaches based on dual immune checkpoint inhibition with ipilimumab and nivolumab result in more favorable response rates compared with anti-PD-1 monotherapy, however, they are associated with increased toxicity [50–52]. Based on the superiority of relatlimab plus nivolumab over monotherapy in advanced-stage melanoma and the improved outcome of neoadjuvant therapy approaches with dual checkpoint inhibition with ipilimumab plus nivolumab, it is hypothesized that combined immunotherapy with relatlimab plus nivolumab may also show its clinical benefit in the neoadjuvant setting. In a small phase 2 trial, patients with resectable stage IIIB/C or IV melanoma received two doses of relatlimab plus nivolumab 160/480 mg neoadjuvantly at 4-week intervals followed by adjuvant relatlimab plus nivolumab to complete one year [53]. Surgical resection was performed at week 9 followed by adjuvant therapy continuation. An overall radiographic response rate of 57% was recorded in a total of 30 included patients. In 29 patients who received surgical resection, a pCR rate of 59% and a near pathological response rate of 7% were observed. A major pathological response (pCR + near pCR: 66%) was associated with improved relapse-free survival, and radiologic evaluation of treatment response seems to underestimate the pathological response rate as has also been seen in other neoadjuvant trials. Moreover, neoadjuvant treatment did not show any treatment-related grade 3/4 adverse events or surgery delay. The adverse event rate of grade 3 side effects amounted to 26% in the adjuvant setting comparable to the adverse event rate in patients treated with relatlimab plus nivolumab in the advanced stage [53]. With a median follow-up time of 16.2 months, neoadjuvant treatment with relatlimab plus nivolumab was able to demonstrate high response rates and showed improved relapse-free survival without new safety signals. Notably, the efficacy appears to be comparable to that of neoadjuvant ipilimumab plus nivolumab but with significantly reduced toxicity and more favorable tolerability, though the number of treated patients was low [53]. Currently, many clinical trials are ongoing worldwide to evaluate the clinical benefit of relatlimab in different stages and conditions of melanoma (Table 3A).

New Anti-LAG-3/PD-1 Combinations

Apart from relatlimab, many molecules targeting LAG-3 are in clinical development (e.g., fianlimab (REGN3767) [NCT05352672], LAG525 [NCT03484923], MK4280 [NCT02720068], and RG6139 [NCT04140500]). In a phase 3 trial the efficacy and tolerability of fianlimab (REGN3767) in combination with cemiplimab compared to pembrolizumab in patients with previously untreated unresectable locally advanced or metastatic melanoma will be evaluated [NCT05352672]. Fianlimab is a newly developed fully human anti-LAG-3 antibody with high affinity, blocking LAG-3/MHC II driven T cell inhibition. Together with cemiplimab, a high affinity, human, hinge-stabilized IgG4 antibody to PD-1 receptor, fianlimab showed promising antitumor effects in preclinical studies. In a phase 1 dose escalation study [NCT03005782], combined therapy with fianlimab and cemiplimab demonstrated an acceptable safety profile and already indicated clinical activity in patients with advanced malignancies [54]. Preliminary data from two expansion cohorts of the phase 1 trial, in which anti-PD-1/PD-L1-naive and experienced patients with advanced melanoma were treated with fianlimab in combination with

Table 3 Ongoing clinical trials investigating anti-LAG3 molecules in melanoma

A Clinical trials investigating relatlimab in melanoma

Condition	Title	Trail ID	Status on ClinicalTrials.gov (Accessed on 27 August 2022)
Metastatic uveal melanoma	A phase 2 study of nivolumab + BMS-986016 (relatlimab) in patients with metastatic uveal melanoma	NCT04552223	Recruiting
Unresectable or metastatic melanoma	A phase 2 study of anti-PD1 monoclonal antibody (nivolumab, BMS-936558) administered in combination with anti-LAG3 monoclonal antibody (relatlimab, BMS-986016) in patients with metastatic melanoma naive to prior immunotherapy in the metastatic setting	NCT03743766	Recruiting
Unresectable or metastatic melanoma	A phase 1/2a study to evaluate the safety, tolerability, and efficacy of relatlimab administered in combination with ipilimumab or ipilimumab alone in participants with unresectable or metastatic melanoma who have progressed on anti-PD-1 therapy	NCT03978611	Recruiting
Completely resected stage III/IV melanoma	A phase 3, randomized, double-blind study of adjuvant immunotherapy wit relatlimab and nivolumab fixed-dose combination versus nivolumab monotherapy after complete resection of stage III-IV melanoma	NCT05002569	Recruiting
Stage II melanoma	A phase 2, open label, single arm, clinical trial of neoadjuvant relatlimab and nivolumab in high risk, clinical stage II cutaneous melanoma	NCT05418972	Not yet recruiting

B Clinical trials investigating new anti-LAG3 molecules in advanced malignancies including melanoma

Agent	Class	Condition	Phase	Trail ID	Status on ClinicalTrials.gov (Accessed on 27 August 2022)
REGN3767 Cemiplimab	Anti-LAG-3 monoclonal antibody Anti-PD-1 monoclonal antibody	Advanced malignancies	1	NCT03005782	Recruiting
RO7247669 (RG6139)	Anti-PD1-LAG-3 bispecific antibody	Solid tumors Metastatic melanoma Non-small cell lung cancer Esophageal squamous cell carcinoma	1	NCT04140500	Recruiting
IMP321 Avelumab	LAG-3 Ig Fusion Protein Anti-PD-L1 monoclonal antibody	Solid Tumors Peritoneal Carcinomatosis	1	NCT03252938	Recruiting
ABL501	Anti-PD1-LAG-3 bispecific antibody	Advanced solid tumors	1	NCT05101109	Recruiting
HLX26 HLX10	Anti-LAG-3 monoclonal antibody Anti-PD-1 monoclonal antibody	Adult solid tumor	1	NCT05400265	Not yet recruiting
HLX26	Anti-LAG-3 monoclonal antibody	Solid tumor Adult Lymphoma	1	NCT05078593	Recruiting
LBL-007 Toripalimab Axitinib	Anti-LAG-3 monoclonal antibody Anti-PD-1 monoclonal antibody Tyrosine kinase inhibitor	Advanced melanoma	1	NCT04640545	Recruiting
EMB-02	Anti-PD1-LAG-3 bispecific antibody	Advanced solid tumors	1/2	NCT04618393	Recruiting
FS118	Anti-PD1-LAG-3 bispecific antibody	Advanced cancer Metastatic cancer Squamous cell carcinoma of head and neck	1/2	NCT03440437	Recruiting
INCAGN02385 INCAGN02390 INCMGA00012	Anti-LAG-3 monoclonal antibody Anti-TIM-3 monoclonal antibody Anti-PD-1 monoclonal antibody	Melanoma	1/2	NCT04370704	Recruiting
Fianlimab (REGN3767) Cemiplimab Pembrolizumab Placebo	Anti-LAG-3 monoclonal antibody Anti-PD-1 monoclonal antibody Anti-PD-1 monoclonal antibody	Melanoma	3	NCT05352672	Recruiting

LAG-3: lymphocyte-activation gene 3; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; TIM-3: T-cell immunoglobulin and mucin domain 3

cemiplimab showed encouraging antitumor activity with an ORR of 63.8% for anti-PD-1/PD-L1-naive and 13.3% for anti-PD-1/PD-L1-experienced patients. DCR was 75.8% for anti–PD-1/PD-L1-naive patients and 40% for anti-PD-1/PD-L1 experienced patients and estimated PFS at 12 months follow-up was 60.6% for anti–PD-1/PD-L1-naive patients and 9.5% for anti–PD-1/PD-L1 experienced patients, whereas median PFS and median duration of response have not been reached for both cohorts. No correlation between LAG-3 or MHC II expression in immunohistochemistry and therapy response was found in either cohort and antitumor activity seemed to be independent of PD-L1 expression. LAG-3 inhibition was beneficial even in subgroups of poor prognosis e.g., elevated LDH levels or presence of liver metastasis [55•]. Notably, both patients with a complete response to dual therapy with fianlimab plus cemiplimab of the cohort of anti-PD-1/PD-L1 experienced patients had shown progressive disease as their best response to prior immunotherapy [56]. The combination of fianlimab and cemiplimab showed a similar safety profile to anti-PD-1 monotherapy except for adrenal insufficiency, which was slightly increased by 10.4%, and in turn, is comparable to the observed rate under dual checkpoint inhibition with anti-PD-1 and anti-CTLA-4. Treatment-related adverse events grade ≥ 3 occurred in 39.6% of patients, whereby 16.3% of patients discontinued therapy prematurely due to adverse events. Furthermore, numerous clinical trials are underway to investigate new anti-LAG-3 molecules in advanced solid tumors including melanoma (Table 3B).

What Place Will the New Anti-LAG-3/anti-PD-1 Combo have in the Arsenal of Checkpoint Inhibitors?

The approval of the new combination therapy with relatlimab plus nivolumab for patients with advanced melanoma expands the arsenal of immune checkpoint inhibitors, raising new questions in clinical practice and requiring re-evaluation of currently established therapeutic standards and sequences. A key role is played by understanding factors that determine treatment response, resistance, and toxicity, in order to identify the appropriate combination and sequence of treatments for each patient and define an individually tailored therapy. Both, anti-PD-1 monotherapy or in combination with ipilimumab represent the current standard of care for patients with advanced melanoma. Although the Checkmate-067 trial was not powered enough to compare ipilimumab plus nivolumab with nivolumab alone, it demonstrated a numerical efficacy benefit [57•] establishing the combination as first-line therapy with a median PFS of 11.5 months after a minimum 60-month follow-up and a staggering median OS of 72.1 months [3]. Even though

cross-trial comparisons should be made with caution, ipilimumab plus nivolumab and relatlimab plus nivolumab show comparable efficacy data with similar PFS rates (2-year PFS; 38.5 vs 43%) (Table 1) and OS rate (3-year OS; 55.8 vs 58%) [2, 8••, 34]. However, the high toxicity rate of ipilimumab and nivolumab with immune-mediated adverse events grade 3/4 in up to 59% of patients [2], requires its use to be carefully considered and the benefit-risk ratio to be weighed. First-line treatment may be moving towards the new anti-LAG-3/PD-1 combination due to its better safety profile. Yet, long-time survival data are lacking and data from the RELATIVITY-047 trial are still growing. It remains to be seen whether the new combination with relatlimab plus nivolumab will catch up to dual checkpoint inhibition with ipilimumab and nivolumab. It is unlikely that a large randomized head-to-head comparison of both combination treatments will be done as the differences in the safety profile are clearly in favor of the new combination and no significant difference in PFS or OS can be expected. More importantly, longer follow-up data are needed to clarify the difference in response between melanomas with high and low PD-L1 expression, especially since the EMA has approved combination therapy with relatlimab and nivolumab only for the treatment of melanomas with PD-L1 expression of less than 1%. The benefit of both ipilimumab plus nivolumab and relatlimab plus nivolumab was shown to be independent of key factors such as PD-L1 status, although both combinations showed their benefit, particularly in melanoma with PD-L1 expression of less than 1% (relatlimab/nivolumab vs Nivolumab: HR 0. 66 (95% CI, 0.51–0.84); ipilimumab/nivolumab vs nivolumab: HR 0.67 (95% CI, 0.51–0.84) [4, 8••]. However, it could have been demonstrated that the tumor-derived PD-L1 expression was not predictive of response to ipilimumab and nivolumab therapy [3]. Longer follow-up data are needed to shed light on the difference in response between melanomas with high and low PD-L1 expression under therapy with relatlimab plus nivolumab.

Although the new dual checkpoint inhibition shows positive antitumor activity and appears to be effective by prolonging PFS, a large proportion of patients will not respond to therapy or will experience disease progression after a period of response, requiring follow-up therapy. To date, we do not know whether the same patients who do not respond to relatlimab plus nivolumab also do not respond to ipilimumab plus nivolumab or vice versa and whether they differ. In a small, pooled, retrospective, multicenter analysis, anti-CTLA-4-based therapy was shown to be less effective after treatment failure on relatlimab plus nivolumab with an overall response rate of 11%, although the cohort was too small to allow robust analysis between ipilimumab mono and combined therapy with ipilimumab plus nivolumab [58•]. In the updated results of Part D of the RELATIVITY-020, an open-label Phase I/II study, the combination of relatlimab plus nivolumab demonstrated

similar clinical activity, albeit lower than the first-line setting, in patients with advanced melanoma who had previously failed to respond to one or more anti-PD-1 or anti-PD-L1-containing therapies, with ORRs of 12.0% and 9.2%, respectively *(unpublished data)* [59••]. Within the C-144–01 study, which evaluates the efficacy and safety of Lifileucel, an investigational autologous tumor-infiltrating lymphocyte (TIL) cell therapy in patients with advanced melanoma previously treated with anti-LAG3 antibody a small proportion of patients who failed prior therapy with nivolumab plus relatlimab achieved durable responses with an ORR of 38.5% [60].

Furthermore, it remains to be seen what value the new dual checkpoint combination will have in distinct patient groups such as brain metastases, elevated LDH and liver metastases. Therapy with ipilimumab and nivolumab shows superior efficacy with long-lasting effects compared with anti-PD-1 monotherapy while inducing both extracranial and intracranial responses. Based on the results of two phase 2 trials the combination therapy with ipilimumab and nivolumab lead to an ORR of up to 56% intracranially in patients with active brain metastases. Thus, it has become established as first-line treatment in melanoma patients with brain metastases [61, 62]. Since the RELATIVITY-047 study included only 2% of patients with treated and asymptomatic brain metastasis, it is still unclear whether dual checkpoint inhibition with nivolumab plus relatlimab will have similar effects intracranially [8••].

Conclusions

The need for oncological treatment options with an improved benefit-to-risk ratio has increased with new treatment options for patients that can significantly prolong survival and, in some cases, lead to cure. Dual immune checkpoint inhibition has become the focus of research by both prolonging duration of response and improving therapy response rates [63]. Relatlimab is the third immune checkpoint inhibitor to receive approval for advanced melanoma therapy, along with ipilimumab and nivolumab/pembrolizumab, and has shown significant improvement in PFS survival in therapy-naive advanced melanoma compared with anti-PD-1 monotherapy when used in combination with nivolumab [8••]. PFS and 3-year OS for both combination immunotherapies are similar, the safety profile of relatlimab plus nivolumab appears to be more favorable than that of ipilimumab plus nivolumab. Neither relatlimab plus nivolumab nor ipilimumab plus nivolumab could demonstrate a significant OS benefit versus nivolumab monotherapy [8••, 19]. Ultimately, apart from long-term data for relatlimab plus nivolumab, predictive, and prognostic biomarkers and risk prediction tools that include patient- and tumor-related clinical factors are needed to determine the appropriate treatment combination and sequence for each patient.

Declarations

References

Papers of particular interest, published recently, have been highlighted as:
● Of importance
●● Of major importance

1. Curti BD, Faries MB. Recent Advances in the Treatment of Melanoma. N Engl J Med. 2021;384(23):2229–40. https://doi.org/10.1056/NEJMra2034861.
2. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab

or Monotherapy in Untreated Melanoma. N Engl J Med. 2015;373(1):23–34. https://doi.org/10.1056/NEJMoa1504030.

3. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2019;381(16):1535–46. https://doi.org/10.1056/NEJMoa1910836.

4. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2017;377(14):1345–56. https://doi.org/10.1056/NEJMoa1709684.

5. Gide TN, Wilmott JS, Scolyer RA, Long GV. Primary and Acquired Resistance to Immune Checkpoint Inhibitors in Metastatic Melanoma. Clin Cancer Res. 2018;24(6):1260–70. https://doi.org/10.1158/1078-0432.Ccr-17-2267.

6. Kluger HM, Tawbi HA, Ascierto ML, Bowden M, Callahan MK, Cha E, et al. Defining tumor resistance to PD-1 pathway blockade: recommendations from the first meeting of the SITC immunotherapy resistance taskforce. J Immunother Cancer. 2020;8(1):e000398. https://doi.org/10.1136/jitc-2019-000398.

7. Woo SR, Turnis ME, Goldberg MV, Bankoti J, Selby M, Nirschl CJ, et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. Cancer Res. 2012;72(4):917–27. https://doi.org/10.1158/0008-5472.Can-11-1620.

8.•• Tawbi HA, Schadendorf D, Lipson EJ, Ascierto PA, Matamala L, Castillo Gutiérrez E, et al. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. N Engl J Med. 2022;386(1):24–34. https://doi.org/10.1056/NEJMoa2109970. (**This study proved the efficacy of relatlimab plus nivolumab and its superiority to nivolumab mono in untreated patients with advanced melanoma.**)

9. FDA approves Opdualag for unresectable or metastatic melanoma. US Food & Drug Administration; 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-opdualag-unresectable-or-metastatic-melanoma. Accessed 24 July 2022

10. Tang XY, Shi AP, Xiong YL, Zheng KF, Liu YJ, Shi XG, et al. Clinical Research on the Mechanisms Underlying Immune Checkpoints and Tumor Metastasis. Front Oncol. 2021;11:693321. https://doi.org/10.3389/fonc.2021.693321.

11. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev. 2010;236:219–42. https://doi.org/10.1111/j.1600-065X.2010.00923.x.

12. Romo-Tena J, Gómez-Martín D, Alcocer-Varela J. CTLA-4 and autoimmunity: new insights into the dual regulator of tolerance. Autoimmun Rev. 2013;12(12):1171–6. https://doi.org/10.1016/j.autrev.2013.07.002.

13. Carlino MS, Larkin J, Long GV. Immune checkpoint inhibitors in melanoma. Lancet. 2021;398(10304):1002–14. https://doi.org/10.1016/s0140-6736(21)01206-x.

14. Triebel F, Jitsukawa S, Baixeras E, Roman-Roman S, Genevee C, Viegas-Pequignot E, et al. LAG-3, a novel lymphocyte activation gene closely related to CD4. J Exp Med. 1990;171(5):1393–405. https://doi.org/10.1084/jem.171.5.1393.

15. Wang M, Du Q, Jin J, Wei Y, Lu Y, Li Q. LAG3 and its emerging role in cancer immunotherapy. Clin Transl Med. 2021;11(3):e365. https://doi.org/10.1002/ctm2.365.

16. Huard B, Mastrangeli R, Prigent P, Bruniquel D, Donini S, El-Tayar N, et al. Characterization of the major histocompatibility complex class II binding site on LAG-3 protein. Proc Natl Acad Sci U S A. 1997;94(11):5744–9. https://doi.org/10.1073/pnas.94.11.5744.

17. Burnell SEA, Capitani L, MacLachlan BJ, Mason GH, Gallimore AM, Godkin A. Seven mysteries of LAG-3: a multi-faceted immune receptor of increasing complexity. Immunother Adv. 2022;2(1):ltab025. https://doi.org/10.1093/immadv/ltab025.

18. Ruffo E, Wu RC, Bruno TC, Workman CJ, Vignali DAA. Lymphocyte-activation gene 3 (LAG3): The next immune checkpoint receptor. Semin Immunol. 2019;42:101305. https://doi.org/10.1016/j.smim.2019.101305.

19. Lythgoe MP, Liu DSK, Annels NE, Krell J, Frampton AE. Gene of the month: lymphocyte-activation gene 3 (LAG-3). J Clin Pathol. 2021;74(9):543–7. https://doi.org/10.1136/jclinpath-2021-207517.

20. Wei SC, Duffy CR, Allison JP. Fundamental Mechanisms of Immune Checkpoint Blockade Therapy. Cancer Discov. 2018;8(9):1069–86. https://doi.org/10.1158/2159-8290.Cd-18-0367.

21. Lecocq Q, Keyaerts M, Devoogdt N, Breckpot K. The next-generation immune checkpoint LAG-3 and its therapeutic potential in oncology: third time's a charm. Int J Mol Sci. 2020;22(1):75. https://doi.org/10.3390/ijms22010075.

22. Workman CJ, Wang Y, El Kasmi KC, Pardoll DM, Murray PJ, Drake CG, et al. LAG-3 regulates plasmacytoid dendritic cell homeostasis. J Immunol. 2009;182(4):1885–91. https://doi.org/10.4049/jimmunol.0800185.

23. Kisielow M, Kisielow J, Capoferri-Sollami G, Karjalainen K. Expression of lymphocyte activation gene 3 (LAG-3) on B cells is induced by T cells. Eur J Immunol. 2005;35(7):2081–8. https://doi.org/10.1002/eji.200526090.

24. Andrews LP, Cillo AR, Karapetyan L, Kirkwood JM, Workman CJ, Vignali DAA. Molecular Pathways and Mechanisms of LAG-3 in Cancer Therapy. Clin Cancer Res. 2022. https://doi.org/10.1158/1078-0432.Ccr-21-2390.

25. Hemon P, Jean-Louis F, Ramgolam K, Brignone C, Viguier M, Bachelez H, et al. MHC class II engagement by its ligand LAG-3 (CD223) contributes to melanoma resistance to apoptosis. J Immunol. 2011;186(9):5173–83. https://doi.org/10.4049/jimmunol.1002050.

26. Workman CJ, Rice DS, Dugger KJ, Kurschner C, Vignali DA. Phenotypic analysis of the murine CD4-related glycoprotein, CD223 (LAG-3). Eur J Immunol. 2002;32(8):2255–63. https://doi.org/10.1002/1521-4141(200208)32:8%3c2255::Aid-immu2255%3e3.0.Co;2-a.

27. Huard B, Tournier M, Hercend T, Triebel F, Faure F. Lymphocyte-activation gene 3/major histocompatibility complex class II interaction modulates the antigenic response of CD4+ T lymphocytes. Eur J Immunol. 1994;24(12):3216–21. https://doi.org/10.1002/eji.1830241246.

28. Workman CJ, Dugger KJ, Vignali DA. Cutting edge: molecular analysis of the negative regulatory function of lymphocyte activation gene-3. J Immunol. 2002;169(10):5392–5. https://doi.org/10.4049/jimmunol.169.10.5392.

29. Shi AP, Tang XY, Xiong YL, Zheng KF, Liu YJ, Shi XG, et al. Immune Checkpoint LAG3 and Its Ligand FGL1 in Cancer. Front Immunol. 2021;12:785091. https://doi.org/10.3389/fimmu.2021.785091.

30. Paik J. Nivolumab Plus Relatlimab: First Approval. Drugs. 2022;82(8):925–31. https://doi.org/10.1007/s40265-022-01723-1.

31. European Medicines Agency: Opdualag. https://www.ema.europa.eu/en/medicines/human/EPAR/opdualag (2022). Accessed 28 Sept 2022.

32. Ascierto PA, Melero I, Bhatia S, Bono P, Sanborn RE, Lipson EJ, et al. Initial efficacy of anti-lymphocyte activation gene-3 (anti–LAG-3; BMS-986016) in combination with nivolumab (nivo) in pts with melanoma (MEL) previously treated with anti–PD-1/PD-L1 therapy. J Clin Oncol. 2017;35(15_suppl):9520. https://doi.org/10.1200/JCO.2017.35.15_suppl.9520.

33.•• Long GV, Hodi FS, Lipson EJ, Schadendorf D, Ascierto PA, Matamala L, et al. Relatlimab and nivolumab versus nivolumab in previously untreated metastatic or unresectable melanoma:

Overall survival and response rates from RELATIVITY-047 (CA224–047). J Clin Oncol. 2022; 40(36_suppl):360385. https://doi.org/10.1200/JCO.2022.40.36_suppl.360385. **This article reports the updated survival data of the combination of relatlimab plus nivolumab in untreated patients with advanced melanoma.**

34. Grob JJ, Schadendorf D, Wagstaff J, Márquez-Rodas I, Lebbé C, Ascierto PA, et al. Regional differences in overall survival (OS) in patients with advanced melanoma (MEL) who received nivolumab (NIVO) combined with ipilimumab (IPI) or NIVO alone in a phase 3 trial (CheckMate 067). Ann Oncol. 2017;28:v432–3. https://doi.org/10.1093/annonc/mdx377.009.

35. Karapetyan L, Karunamurthy A, Cillo A, Rohatgi A, Massa RC, Gooding WE, et al. Phase II study of nivolumab (nivo) with relatlimab (rela) in patients (pts) with first-line advanced melanoma: Early on-treatment major pathologic response on biopsy. J Clin Oncol. 2022;40(16_suppl):9514. https://doi.org/10.1200/JCO.2022.40.16_suppl.9514.

36. Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. Ophthalmology. 2011;118(9):1881–5. https://doi.org/10.1016/j.ophtha.2011.01.040.

37. Rantala ES, Hernberg M, Kivelä TT. Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis. Melanoma Res. 2019;29(6):561–8. https://doi.org/10.1097/cmr.0000000000000575.

38. Yang J, Manson DK, Marr BP, Carvajal RD. Treatment of uveal melanoma: where are we now? Ther Adv Med Oncol. 2018;10:1758834018757175. https://doi.org/10.1177/1758834018757175.

39. Heppt MV, Steeb T, Schlager JG, Rosumeck S, Dressler C, Ruzicka T, et al. Immune checkpoint blockade for unresectable or metastatic uveal melanoma: A systematic review. Cancer Treat Rev. 2017;60:44–52. https://doi.org/10.1016/j.ctrv.2017.08.009.

40. Luke JJ, Callahan MK, Postow MA, Romano E, Ramaiya N, Bluth M, et al. Clinical activity of ipilimumab for metastatic uveal melanoma: a retrospective review of the Dana-Farber Cancer Institute, Massachusetts General Hospital, Memorial Sloan-Kettering Cancer Center, and University Hospital of Lausanne experience. Cancer. 2013;119(20):3687–95. https://doi.org/10.1002/cncr.28282.

41. Khoja L, Atenafu EG, Suciu S, Leyvraz S, Sato T, Marshall E, et al. Meta-analysis in metastatic uveal melanoma to determine progression free and overall survival benchmarks: an international rare cancers initiative (IRCI) ocular melanoma study. Ann Oncol. 2019;30(8):1370–80. https://doi.org/10.1093/annonc/mdz176.

42. Algazi AP, Tsai KK, Shoushtari AN, Munhoz RR, Eroglu Z, Piulats JM, et al. Clinical outcomes in metastatic uveal melanoma treated with PD-1 and PD-L1 antibodies. Cancer. 2016;122(21):3344–53. https://doi.org/10.1002/cncr.30258.

43. Pelster MS, Gruschkus SK, Bassett R, Gombos DS, Shephard M, Posada L, et al. Nivolumab and Ipilimumab in Metastatic Uveal Melanoma: Results From a Single-Arm Phase II Study. J Clin Oncol. 2021;39(6):599–607. https://doi.org/10.1200/jco.20.00605.

44. Figueiredo CR, Kalirai H, Sacco JJ, Azevedo RA, Duckworth A, Slupsky JR, et al. Loss of BAP1 expression is associated with an immunosuppressive microenvironment in uveal melanoma, with implications for immunotherapy development. J Pathol. 2020;250(4):420–39. https://doi.org/10.1002/path.5384.

45. Durante MA, Rodriguez DA, Kurtenbach S, Kuznetsov JN, Sanchez MI, Decatur CL, et al. Single-cell analysis reveals new evolutionary complexity in uveal melanoma. Nat Commun. 2020. https://doi.org/10.1038/s41467-019-14256-1.

46. Lutzky J, Feun LG, Magallanes N, Kwon D, Harbour JW. NCT04552223: a phase II study of nivolumab plus BMS-986016 (relatlimab) in patients with metastatic uveal melanoma (UM) (CA224-094). J Clin Oncol. 2021;39(15_suppl):TPS9590-TPS.

47. Liu J, Blake SJ, Yong MCR, Harjunpää H, Ngiow SF, Takeda K, et al. Improved Efficacy of Neoadjuvant Compared to Adjuvant Immunotherapy to Eradicate Metastatic Disease. Cancer Discov. 2016;6(12):1382–99. https://doi.org/10.1158/2159-8290.Cd-16-0577.

48. Topalian SL, Taube JM, Pardoll DM. Neoadjuvant checkpoint blockade for cancer immunotherapy. Science. 2020;367(6477):eaax0182. https://doi.org/10.1126/science.aax0182.

49. Menzies AM, Amaria RN, Rozeman EA, Huang AC, Tetzlaff MT, van de Wiel BA, et al. Pathological response and survival with neoadjuvant therapy in melanoma: a pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC). Nat Med. 2021;27(2):301–9. https://doi.org/10.1038/s41591-020-01188-3.

50. Amaria RN, Reddy SM, Tawbi HA, Davies MA, Ross MI, Glitza IC, et al. Neoadjuvant immune checkpoint blockade in high-risk resectable melanoma. Nat Med. 2018;24(11):1649–54. https://doi.org/10.1038/s41591-018-0197-1.

51. Blank CU, Rozeman EA, Fanchi LF, Sikorska K, van de Wiel B, Kvistborg P, et al. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. Nat Med. 2018;24(11):1655–61. https://doi.org/10.1038/s41591-018-0198-0.

52. Rozeman EA, Menzies AM, van Akkooi ACJ, Adhikari C, Bierman C, van de Wiel BA, et al. Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): a multicentre, phase 2, randomised, controlled trial. Lancet Oncol. 2019;20(7):948–60. https://doi.org/10.1016/s1470-2045(19)30151-2.

53. Amaria RN, Postow MA, Tetzlaff MT, Ross MI, Glitza IC, McQuade JL, et al. Neoadjuvant and adjuvant nivolumab (nivo) with anti-LAG3 antibody relatlimab (rela) for patients (pts) with resectable clinical stage III melanoma. J Clin Oncol. 2021;39(15_suppl):9502. https://doi.org/10.1200/JCO.2021.39.15_suppl.9502.

54. Papadopoulos KP, Lakhani NJ, Johnson ML, Park H, Wang D, Yap TA, et al. First-in-human study of REGN3767 (R3767), a human LAG-3 monoclonal antibody (mAb), ± cemiplimab in patients (pts) with advanced malignancies. J Clin Oncol. 2019;37(15_suppl):2508. https://doi.org/10.1200/JCO.2019.37.15_suppl.2508.

55.● Hamid O, Weise A, Kim TM, Mckean MA, Lakhani5 NJ, Kaczmar J, et al. Phase I study of fianlimab, a human lymphocyte activation gene-3 (LAG-3) monoclonal antibody, in combination with cemiplimab in advanced melanoma. Ann Oncol. 2022;33(suppl_7):S356-S409. https://doi.org/10.1016/annonc/annonc1059. **This study highlights the data of the combination of fianlimab plus cemiplimab in anti-PD-1/PD-L1-naive and experienced patients with advanced melanoma showing encouraging antitumor activity.**

56. Hamid O, Wang D, Kim TM, Kim S-W, Lakhani NJ, Johnson ML, et al. Clinical activity of fianlimab (REGN3767), a human anti-LAG-3 monoclonal antibody, combined with cemiplimab (anti-PD-1) in patients (pts) with advanced melanoma. J Clin Oncol. 2021;39(15_suppl):9515. https://doi.org/10.1200/JCO.2021.39.15_suppl.9515.

57.● Wolchok JD, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. J Clin Oncol. 2022;40(2):127–37. https://doi.org/10.1200/jco.21.02229. (**This article provides an update on the long-term survival data of dual checkpoint blockade with ipilimumab plus nivolumab, showing**

the longest median OS in a phase 3 melanoma study with durable response.)

58.● Menzies AM, Pires da Silva I, Trojaniello C, Vieu E, Amaria RN, Zimmer L, et al. CTLA-4 Blockade Resistance after Relatlimab and Nivolumab. N Engl J Med. 2022;386(17):1668–9. https://doi.org/10.1056/NEJMc2119768. **This article describes the reduced efficacy of dual checkpoint blockade with ipilimumab plus nivolumab after treatment failure on relatlimab plus NIvolumab.**

59●● Ascierto PA, Lipson EJ, Dummer R, Larkin J, Long GV, Sanborn RE, et al. Title. 2022. [Manuscript submitted for publication; in revision]. **This study shows the definitive efficacy data of relatlimab plus nivolumab in PD-1/PD-L1-pretreated melanoma patients and demonstrates its, albeit lower clinical efficacy in the second-line setting.**

60. Larkin J, Dalle S, Sanmamed MF, Wilson M, Hassel JC, Kluger H, Orloff M, Weber JS, Graf Finckenstein F, Hari P, et al. 844P Efficacy and safety of lifileucel, an investigational autologous tumor-infiltrating lymphocyte (TIL) cell therapy, in patients with advanced melanoma previously treated with anti-LAG3 antibody. Ann Oncol. 2022;33:S935–S6. https://doi.org/10.1016/j.annonc.2022.07.970

61. Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol. 2018;19(5):672–81. https://doi.org/10.1016/s1470-2045(18)30139-6.

62. Tawbi HA, Forsyth PA, Algazi A, Hamid O, Hodi FS, Moschos SJ, et al. Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain. N Engl J Med. 2018;379(8):722–30. https://doi.org/10.1056/NEJMoa1805453.

63. LaFleur MW, Muroyama Y, Drake CG, Sharpe AH. Inhibitors of the PD-1 Pathway in Tumor Therapy. J Immunol. 2018;200(2):375–83. https://doi.org/10.4049/jimmunol.1701044.