



Selecting first-line immunotherapy in advanced melanoma: Current evidence on efficacy across diverse patient populations

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ABSTRACT

Immunotherapy has dramatically changed the outcome for patients with advanced melanoma, with significant improvements in overall survival and potential cure for some. The recent approval of nivolumab in combination with relatlimab (nivolumab-relatlimab) added a third immunotherapy option for first-line treatment for advanced melanoma. Nivolumab-relatlimab has shown greater efficacy compared to single-agent nivolumab and has fewer unacceptable side effects compared to the combination of ipilimumab and nivolumab (ipilimumab-nivolumab). However, the lack of both long-term follow-up data and direct comparison with ipilimumab-nivolumab raises uncertainty about where to position nivolumab-relatlimab in clinical practice. Since most patients who respond to combination ipilimumab-nivolumab also respond to nivolumab-relatlimab, and many to single-agent anti-programmed death-1 (PD-1) monotherapy, the challenge is to identify the subgroup of patients who need ipilimumab-nivolumab and would not achieve similar benefits from less toxic alternatives. This review discusses the available data on efficacy of the three approved first-line immunotherapies (single-agent anti-PD-1, nivolumab-relatlimab or ipilimumab-nivolumab) and their value in distinct population groups to help guide clinical decisions.

1. Introduction

The combination of ipilimumab plus nivolumab (ipilimumab-nivolumab) has set the benchmark for overall survival in first-line therapy of advanced melanoma, based on results from Checkmate 067. In this study, 945 patients were randomly assigned to one of the three regimens: ipilimumab (3 mg/kg) plus nivolumab (1 mg/kg) every 3 weeks for four doses, followed by nivolumab (3 mg/kg) every 2 weeks; nivolumab (3 mg/kg) every 2 weeks plus ipilimumab matched placebo; or ipilimumab (3 mg/kg) every 3 weeks for four doses plus nivolumab-matched placebo. The trial lacked power for a formal statistical comparison between the ipilimumab-nivolumab and nivolumab treated patients. However, descriptive analyses revealed a consistent 8 % difference in overall survival (OS), melanoma-specific survival (MSS), and progression-free survival (PFS) between the groups from years 3–10 [1]. The OS at 10 years was 43 % (95 % CI, 38–49 %) and MSS 52 % (95 % CI, 46–58 %) for ipilimumab-nivolumab and 37 % (95 % CI, 32–43 %) and 44 % (95 % CI, 38–50 %) for nivolumab, respectively. The Keynote 006 study enrolled 834 patients, randomly assigning them to pembrolizumab (10 mg/kg every 2 or 3 weeks) or ipilimumab (3 mg/kg for

four doses). At 10 years, OS and MSS for pembrolizumab were 34 % and 45 %, highlighting durable control with PD-1 inhibition alone [2]. The 10-year PFS rate was 31 % for ipilimumab-nivolumab, 23 % for nivolumab (Checkmate 067) and 22 % for pembrolizumab (Keynote 006) [1, 2]. For patients alive and progression-free at 3 years, the 10-year MSS was 96 % for ipilimumab-nivolumab and 97 % for nivolumab, showing that relapses are rare beyond 3 years, regardless of regimen.

More recently, the phase 2/3 Relativity-047 trial (NCT03470922) randomised 714 patients to receive a fixed-dose of 160 mg relatlimab with 480 mg nivolumab or 480 mg nivolumab alone, administered every 4 weeks. Nivolumab-relatlimab showed a 3-year OS rate of 54.6 % (95 % CI, 49.2–59.6) compared to 48.0 % (95 % CI, 42.7–53.1) with nivolumab [3]. The 3-year PFS rate was 31.8 % (95 % CI, 26.6–37.1) and 26.9 % (95 % CI, 22.1–31.9), with an ORR of 43.7 % (95 % CI, 38.4–49.0) and 33.7 % (95 % CI, 28.8–38.9) in the combination and nivolumab arm, respectively [3]. Based on these results, nivolumab-relatlimab was approved by the Food and Drug Administration in March 2022 and subsequently received marketing authorization from the European Medicines Agency for patients with unresectable or metastatic melanoma with programmed cell death ligand 1 (PD-L1) expression < 1 % in September

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2022.

Cross trial comparisons are a challenge and need to be undertaken cautiously, particularly with differences in study design, times of the trials, baseline characteristics, staging system and response assessment (blinded independent central review in Relativity 047 vs investigator assessment in Checkmate 067). Checkmate 067 (2013–2014) used AJCC 7th staging with 57.6 % M1c patients including 3.5 % with brain metastasis in the combination arm whereas Relativity 047 (2018–2020) used AJCC 8th staging with 42.5 % M1c and 1.7 % M1d patients in the nivolumab-relatlimab arm [4,5]. Clinicians recruiting patients to Relativity 047 were potentially selecting those they judged did not require combination ipilimumab-nivolumab. An adjusted indirect treatment comparison of individual patient level data from Relativity 047 and Checkmate 067 showed similar efficacy in the overall cohorts and only minimal differences in subgroups. The 3-year OS was 57 % for both combinations, HR 0.94 (95 % CI, 0.75–1.19) and 3-year PFS 36 % for nivolumab-relatlimab vs 39 % for ipilimumab-nivolumab, HR 1.08 (95 % CI, 0.88–1.33) [6]. Here we discuss the efficacy of the three immunotherapy regimens based on tumour characteristics, to help guide treatment selection.

2. Lactate dehydrogenase

Lactate dehydrogenase (LDH) is a prognostic marker in metastatic melanoma. In Checkmate 067, 5-year OS was 60 % with ipilimumab-nivolumab and 53 % with nivolumab in patients with normal LDH. For elevated LDH, 5-year OS was 38 % vs 28 % and 5-year PFS was 28 % vs 18 %, respectively [4]. In Relativity 047, the 2-year PFS for nivolumab-relatlimab and nivolumab in patients with elevated LDH levels were 32.6 % and 18.0 %, respectively [7]. The indirect treatment comparison showed similar outcomes for both treatments in this group (HR for PFS 1.06 (95 % CI, 0.77–1.45); HR for OS 1.02 (95 % CI, 0.73–1.43); OR for ORR 1.14 (95 % CI, 0.76–1.73)) [6]. However, in patients with LDH > 2xULN, representing 9–11 % of each arm in Checkmate 067 and Relativity 047, the indirect comparison showed higher response rates for ipilimumab-nivolumab (10/33) vs nivolumab-relatlimab (4/33), with an OR of 3.54 (95 % CI, 1.2–10.4) [6].

3. BRAF status

Approximately 40 % of patients with advanced melanoma carry oncogenic BRAF V600 mutations, activating the mitogen-activated protein kinase pathway. Patients with BRAF-mutated melanoma benefit more from ipilimumab-nivolumab than patients with BRAF wildtype (WT) disease. The 5-year and 10-year OS in BRAF mutated melanoma were 60 % and 52 % for combination ipilimumab-nivolumab compared to 48 % and 39 % in BRAF WT disease. In BRAF WT disease, ipilimumab-nivolumab and nivolumab had similar outcomes (5-year PFS: 35 % vs 32 %, 5-year OS: 48 % vs 43 %, 10-year OS: 39 % vs 37 %). BRAF-mutated patients had worse outcome with nivolumab alone than patients with BRAF WT disease (5-year PFS 22 % vs 32 %) [1,4]. Nivolumab-relatlimab showed a benefit over nivolumab, regardless of BRAF mutation status. The median PFS with nivolumab-relatlimab was 10.15 months for BRAF mutated and 11.83 months for BRAF WT disease [7]. In Checkmate 067, the median PFS with ipilimumab-nivolumab was 16.8 months (95 % CI, 8.3–32.0) for BRAF mutant patients and 11.2 months (95 % CI, 7.0–18.1) for BRAF WT patients [4]. The indirect comparison showed more responses with ipilimumab-nivolumab than nivolumab-relatlimab in BRAF mutated disease, OR 1.54 (95 % CI, 1.04–2.27) [6].

4. Liver metastases

Liver metastases are associated with poorer outcomes with immunotherapy. The immune microenvironment of the liver is marked by a

relatively immunosuppressed state, promoting tolerance to harmless gut-derived antigens through immune cells that limit excessive immune responses [8,9]. In Checkmate 067, 5-year OS for liver metastases was 42 % with ipilimumab-nivolumab compared to 33 % with nivolumab alone [10]. A retrospective analysis showed a median PFS of 7.5 months (95 % CI, 5.3–11.8) vs 4.3 months (95 % CI, 3.2–6.8) and a median OS of 60.0 months (95 % CI, 27.3–not reached) vs 31.4 months (95 % CI, 22.6–44.6) for ipilimumab-nivolumab vs anti-PD-1 alone, with significant differences after multivariate adjustment [11]. The activity of nivolumab-relatlimab in patients with liver metastases has not been reported separately. Intriguingly, the indirect comparison found a trend favouring it over ipilimumab-nivolumab (PFS HR 0.82 (95 % CI, 0.56–1.20); OS HR 0.75 (95 % CI, 0.5–1.14)). Three-year PFS was 34 % vs 24 % for nivolumab-relatlimab vs ipilimumab-nivolumab [6]. Validation is needed to confirm this finding.

5. Brain metastases

Three trials evaluated ipilimumab-nivolumab in untreated brain metastases. In the ABC trial, patients with asymptomatic, treatment-naive brain metastases received ipilimumab 3 mg/kg + nivolumab 1 mg/kg every 3 weeks for four doses, followed by nivolumab 3 mg/kg every 2 weeks (n = 35) or nivolumab 3 mg/kg every 2 weeks (n = 25). Ipilimumab-nivolumab resulted in superior intracranial responses (59 % vs. 21 %), 5-year intracranial PFS (52 % vs. 14 %), and 5-year OS (55 % vs. 40 %) compared to nivolumab [12]. In Checkmate 204 (NCT02320058), ipilimumab-nivolumab achieved an intracranial response rate of 57 % with a 3-year intracranial PFS and 3-year OS rate of 54.1 % and 71.9 % in asymptomatic brain metastasis [13]. These studies established ipilimumab-nivolumab as a standard of care in patients with asymptomatic brain metastases. The NIBIT-M2 trial recently reported a 7-year OS rate of 42.8 % with ipilimumab-nivolumab in BRAF wildtype and mutated melanoma in untreated, asymptomatic brain metastases [14]. These findings of improved survival with durable responses have been validated by two real-world studies [15,16]. Mandalà et al. report an ORR of 52 % (including 17 % complete responses) on first-line ipilimumab-nivolumab in asymptomatic patients, with a 5-year OS rate of 52 % and 3-year PFS rate of 39.1 % [16]. Currently there are no data on the activity of nivolumab-relatlimab in patients with brain metastases; a phase 2 study is ongoing (NCT05704647).

6. Acral melanoma

Acral melanoma, a rare subtype of melanoma accounting for 2–3 % of cases, is associated with a lower response to immunotherapy. A retrospective study reported an ORR of 43 % for ipilimumab-nivolumab (25/58) vs 26 % (47/180) for anti-PD-1. The 5-year PFS was 18 % vs 7 %, respectively. Notably, among responders, the PFS was 53 % at 2 years, indicating a shorter duration of response and a high rate of acquired resistance [17]. In Relativity 047, acral melanoma patients achieved a higher ORR with nivolumab-relatlimab compared to nivolumab (27.5 % (11/40) vs 14.3 % (6/42)). Nivolumab-relatlimab showed a PFS benefit (HR 0.85 (95 % CI, 0.53–1.38) but no overall survival benefit (HR 1.06 (95 % CI, 0.63–1.78)) [3]. In the indirect comparison, acral melanoma constituted 7.7 % of nivolumab-relatlimab and 5.3 % of ipilimumab-nivolumab treated patients. Numerical differences were observed in PFS (HR, 1.42 (95 % CI, 0.69–2.93)), OS (HR, 1.72 (95 % CI, 0.76–3.91)), and ORR (OR, 1.71 (95 % CI, 0.62–4.69)), favouring ipilimumab-nivolumab [6].

7. Mucosal melanoma

Mucosal melanoma is a rare, aggressive subtype of melanoma with a poorer prognosis than cutaneous melanoma. D'Angelo et al. reported a median PFS of 5.9 months for ipilimumab-nivolumab and 3.0 months for nivolumab in a pooled analysis of clinical trials patients. Objective

responses were 37.1 % for ipilimumab-nivolumab (13/35) and 23.3 % (20/86) for nivolumab alone [18]. The 5-year PFS was 29 % vs 14 %, and the 5-year OS was 36 % vs 17 %, respectively [19]. In the Checkmate 401 trial, the 1- and 2-year OS rates for ipilimumab-nivolumab were 52 % and 38 % with an ORR of 44 % [20]. Within the Relativity 047 study, nivolumab-relatlimab showed a trend towards improved PFS over nivolumab (HR, 0.63 (95 % CI, 0.32–1.22)), but no benefit in OS (HR 1.05 (95 % CI, 0.55–2.00) or ORR (34.8 % vs 25.0 %) [3]. Small patient numbers (n = 23 for the combination and n = 28 for nivolumab), and short follow-up make comparison unreliable.

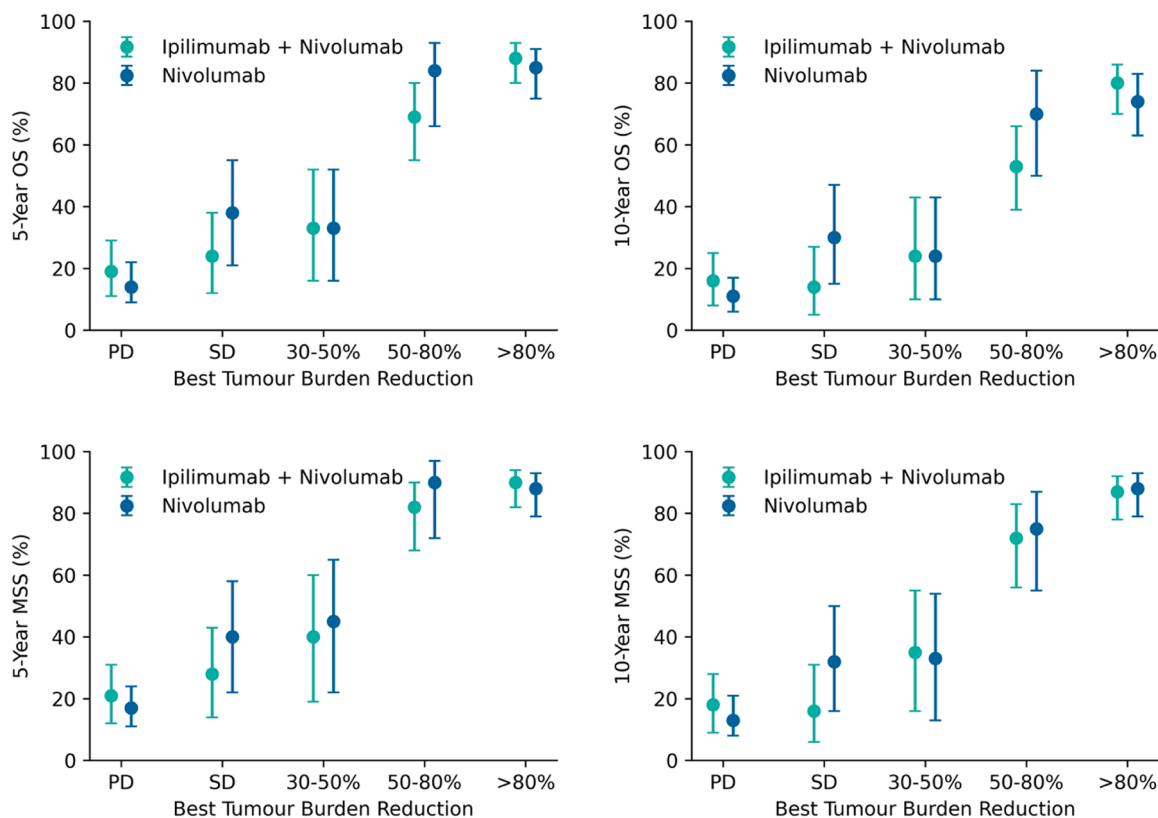
8. Depth of response

The depth of response to immunotherapy correlates with long-term benefit and risk of relapse. Patients achieving a CR or PR had improved OS compared to those with SD [10]. The 5-year OS for ipilimumab-nivolumab vs nivolumab was 88 % vs 87 % for CR, 79 % vs 75 % for PR, and 38 % vs 46 % for SD, after excluding patients who had an OS event in the first year [10]. While OS and MSS were similar for both treatments, ipilimumab-nivolumab showed a higher investigator-assessed ORR (58 % vs 45 %) and greater tumour reduction. The investigator-assessed CR for ipilimumab-nivolumab was 22 % in Checkmate 067 compared to 19.7 % for nivolumab-relatlimab in

Relativity 047, assessed per blinded independent central review [1,3]. The indirect comparison reported a CR of 20 % for ipilimumab-nivolumab and 15 % for nivolumab-relatlimab [6]. This is important to consider as achieving a CR is associated with a higher chance for cure. Fig. 1 shows the 5- and 10-year OS and MSS stratified by tumour reduction for ipilimumab-nivolumab and nivolumab [1].

9. Adjuvant treatment

Adjuvant therapy is now a standard of care for resected intermediate and high-risk melanoma. The impact of this in patients who relapse and the best treatment in this situation remains unclear. Data on management is limited as most landmark trials focused on treatment-naïve patients. Relativity 047 included < 2 % of patients who had received prior modern adjuvant therapy. Retrospective data show a 36 % response rate (13/36) for ipilimumab-nivolumab in patients progressing on single-agent PD(L)-1 inhibition in the adjuvant setting, and 30 % after progressing in the metastatic setting [21]. A phase II trial (NCT03033576) reported an ORR of 28 % vs 9 % for anti-PD-1 plus CTLA-4 blockade vs ipilimumab alone after progression on anti-PD(L)-1 [22]. The response rate to nivolumab-relatlimab in this situation was 12 % in the phase I/IIa Relativity 020 study, (half of the patients received two or more prior lines of treatment) [23]. A retrospective analysis of



	Best Tumour Burden Reduction				
	PD	SD	30-50%	50-80%	>80%
Ipilimumab + Nivolumab (n)	74	38	24	55	102
Nivolumab (n)	121	29	24	32	85

Fig. 1. Five- and ten-year overall survival and melanoma-specific survival, stratified by best tumour burden reduction (maximum reduction in the sum of diameters of evaluable target lesions). This analysis included patients with target lesions at baseline and at least one on-treatment tumour assessment up to progression or start of subsequent therapy. Data sourced from Fig. S8, Wolchok JD, Chiarion-Sileni V, Rutkowski P, et al# Final, 10-year outcomes with nivolumab plus ipilimumab in advanced melanoma. N Engl J Med. Published online September 15, 2024. DOI: 10.1056/NEJMoa2407417. Abbreviations: OS, overall survival; MSS, melanoma-specific survival; PD, progressive disease; SD, stable disease.

ipilimumab-nivolumab after relapse on adjuvant anti-PD-1 showed a 22 % ORR (5/23) for relapse during treatment, and 50 % (2/4) for relapse after treatment completion [24]. Rechallenge with single agent anti-PD-1 post relapse in the adjuvant setting resulted in 40 % responses [24]. In patients recurring after cessation of adjuvant targeted therapy, a small retrospective study (n = 13) reported an ORR of 62 % to ipilimumab-nivolumab and 46 % to anti-PD-1 [25].

10. PD-L1

PD-L1 expression has been widely studied as a biomarker for predicting response to immunotherapy and is often stratified in clinical trials. However, its use in clinical practice in melanoma is limited due to its low predictive value as a biomarker to inform treatment decision. The Checkmate 067 trial showed greater benefit of ipilimumab-nivolumab over anti-PD-1 alone for patients with PD-L1 expression < 1 %. Nivolumab-relatlimab showed improved outcomes compared to nivolumab particularly in melanoma expressing PD-L1 < 1 %. For patients with PD-L1 ≥ 1 %, efficacy was similar between the combination treatment and nivolumab in Checkmate 067 and Relativity 047. The European Medicines Agency (EMA) restricted nivolumab-relatlimab (Opdualag) to patients with PD-L1 expression < 1 %, while the U.S. Food and Drug Administration (FDA) and the UK's Medicines and Healthcare products Regulatory Agency (MHRA) approved nivolumab-relatlimab without such a restriction, allowing broader use based on clinical discretion. Despite the EMA's restriction, indirect comparison suggests that patients with PD-L1 < 1 % may benefit more from ipilimumab-nivolumab than from nivolumab-relatlimab. (Table 1)

11. Toxicity

Ipilimumab-nivolumab is associated with a significantly higher rate of severe toxicity than nivolumab-relatlimab. Grade 3–4 treatment-

related adverse events occurred in 63 % treated with ipilimumab-nivolumab on Checkmate 067 compared to 21 % treated with nivolumab-relatlimab on Relativity 047 [1,7]. The indirect comparison reported 41 % vs 17 % rates of adverse events leading to treatment discontinuation [6]. Gastrointestinal toxicities occurred in 47 % vs 19 % (grade 3–4: 16 % vs 3 %), hepatic toxicity in 31 % vs 14 % (grade 3–4: 20 % vs 4 %), and endocrine toxicity in 35 % vs 28 %. The lower toxicity seen for nivolumab-relatlimab may partly be attributed to improved toxicity management with immune checkpoint inhibitors. In Checkmate 067, the 35 % of patients (110/314) who discontinued ipilimumab-nivolumab during the induction due to adverse events had comparable survival outcomes to those completing the induction [1,27]. These findings suggest that treatment interruptions from toxicity do not affect survival, raising considerable debate over the required duration of treatment [27].

12. Other studies in similar patient population

The randomised phase 2 INITIUM trial (NCT04382664) investigated whether adding a peptide vaccine to TERT, (UV-1) to ipilimumab-nivolumab can improve outcomes compared to ipilimumab-nivolumab alone. Between July 2020 and June 2022, 156 patients were randomised 1:1 to ipilimumab-nivolumab +/- 12 doses of UV1 vaccine. This included 10 (12.8 %) patients in the ipilimumab+nivolumab+vaccine arm and 13 (15.4 %) in the ipilimumab+nivolumab arm who had received prior modern adjuvant treatment. Independently verified objective response rates were 59.8 % and 59.3 %, comparable to the ORR 58 % seen with ipilimumab-nivolumab in the Checkmate 067 study [1,28]. The 21 % CR rate for ipilimumab-nivolumab in the INITIUM trial aligns closely with the reported 22 % CR rate in the Checkmate 067 study. There was no benefit from adding the vaccine in terms of ORR, OS, PFS. The independently assessed 12-month PFS was 57 % in both arms, compared to 50 % for ipilimumab-nivolumab in Checkmate 067

Table 1

Comparison of efficacy data of immune checkpoint inhibitors stratified by PD-L1 expression [3–6,26].

	Checkmate 067 Assessment by investigator		Relativity 047 Assessment by BICR		Indirect Treatment comparison	
	Ipilimumab-Nivolumab	Nivolumab	Nivolumab-Relatlimab	Nivolumab	Favours Ipilimumab-Nivolumab	Favours Nivolumab-Relatlimab
PD-L1 < 1 %	Median PFS months (95 % CI)	11.2 (6.9–22.2) [26]	2.8 (2.8–5.6) [26]	6.4 (4.6–11.8)	2.9 (2.8–4.5)	
	HR (95 % CI)			0.68 (0.54–0.86)		1.16 (0.89–1.51)
	Median OS months (95 % CI)	61.4 (26.4–NR) [4]	23.5 (13.0–36.5) [4]		not reported	
	HR (95 % CI)			0.83 (0.64–1.07)		1.01 (0.74–1.37)
	ORR% (95 % CI)	54 % (44.4–62.7)	35 % (26.5–44.4)	37.3 %*	25.5 %	
OR					1.22 (0.89–1.68)	
PD-L1 > 1 %	Median PFS months (95 % CI)	16.1 (8.9–39.1) [26]	16.2 (8.1–27.7) [26]	15.7 (10.1–25.8)	14.7 (5.1–NR)	
	HR (95 % CI)			0.98 (0.73–1.32)		1.00 (0.73–1.37)
	Median OS months (95 % CI)	NR (39.1–NR) [4]	67.0 (39.0–NR) [4]		not reported	
	HR (95 % CI)			0.78 (0.56–1.08)		0.86 (0.60–1.23)
	ORR% (95 % CI)	65 % (56.4–72.0)	54 % (46.6–62.0)	52.7 %**	45.6 %	
OR					0.96 (0.68–1.35)	

BICR: blinded independent central review; ORR: overall response rate; PFS: progression-free survival; HR: hazard ratio; OS: overall survival; OR: Odds ratio; NR: not reached; CI: confidence interval; *unweighted ORR difference 11.8 (95 % CI, 3.0–20.5); **unweighted ORR difference 7.2 (95 % CI, –4.2–18.3); 26: Wolchok JD et al. NEJM 2017 (minimum follow-up time 36 months); 4: Larkin J et al. NEJM 2019 (minimum follow up time 60 months)

[6,28].

13. Discussion

Ipilimumab-nivolumab remains the immunotherapy combination with the highest response rate and greatest long-term survival. This comes at the expense of significant risk of major toxicity. Nivolumab-relatlimab provides a new, very effective option with a more acceptable toxicity profile. The dilemma is how to choose which treatment for which patient. The benefits of nivolumab-relatlimab over nivolumab seemed to be confined to patients with PD-L1 expression levels $< 1\%$ leading the EMA to limit approval to this group. Given that PD-L1 expression is not routinely tested in melanoma and there are discussions around the reliability of this as a marker to drive treatment decisions [29], it is likely many patients who would previously have received single-agent PD-1 inhibitors will now be offered nivolumab-relatlimab, where the marginal increase in toxicity is likely outweighed by improved efficacy.

Choosing the right combination therapy is challenging due to the lack of a randomised trial and the difference in toxicity between the two regimens. A recent study of US oncologists and patients suggested that both clinicians and patients prioritised minimising the risk of serious adverse events when differences in efficacy outcomes are minimal [30]. The indirect comparison helps with this decision, but the studies compared were very different, and despite the use of outcomes for nivolumab as an internal control, the findings need to be interpreted with caution. For specific clinical subgroups i.e. brain metastases, acral and mucosal melanoma, where evidence for nivolumab-relatlimab is limited, ipilimumab-nivolumab remains the default treatment. For patients not within these groups, the decision is more nuanced, requiring consideration of several factors. Ipilimumab-nivolumab provides greater benefits to some subgroups than others. For patients with a BRAF mutation, LDH $> 2x$ ULN, progression on adjuvant immunotherapy, multiple sites of disease or visceral disease, it is reasonable to consider ipilimumab-nivolumab the default option. For patients with normal or moderately raised LDH, BRAF WT, and PD-L1 expression $> 1\%$, nivolumab-relatlimab is a reasonable default option. For patients with liver metastases, the data from the indirect comparison suggest that

nivolumab-relatlimab may be superior. Fig. 2 highlights clinical and melanoma specific factors to consider for treatment selection.

Patients with autoimmune conditions are routinely excluded from clinical trials. However, real-world data report on the use of ipilimumab-nivolumab and single-agent anti-PD-1 inhibition in patients with inflammatory bowel disease, inflammatory arthritis, multiple sclerosis etc. Most clinical teams have now treated many of these patients [31–33]. The occurrence of flares varies by type of underlying autoimmune disease and treatment. Although there are no data on nivolumab-relatlimab in this situation, it may be a reasonable option for patients who would otherwise have been limited to single-agent anti-PD-1 inhibition due to significant autoimmune disease. The incidence of melanoma continues to rise, particularly among older individuals who often present with higher comorbidities, and many are not fit for ipilimumab-nivolumab. While there is no clear evidence that incidence of adverse effects increases with age, elderly patients may have reduced ability to tolerate these effects, and recovery can be prolonged [34]. Nivolumab-relatlimab is likely to be a better option for many of these patients.

The activity of ipilimumab after progression on nivolumab-relatlimab is unclear. A small retrospective study found that patients resistant to nivolumab-relatlimab rarely respond to CTLA-4 therapy, with an 11% response rate (4/36) and a median PFS of 2.6 months (range, 2.1–3.2) [35].

It is important to reflect on whether the Relativity 047 study was the correct design, given that it has not answered the key clinical question – is it equivalent to ipilimumab-nivolumab? Such a study would have required significantly more patients, especially if a non-inferiority design, and may have been negative, resulting in failure to approve a very effective treatment associated with significantly less toxicity. It is hoped that real-world data studies will help address many of the remaining unanswered and critically important questions.

14. Conclusion

Nivolumab-relatlimab is a better and safer option for many patients. In distinct patient populations with certain high-risk factors, ipilimumab-nivolumab remains the best chance of long-term survival.

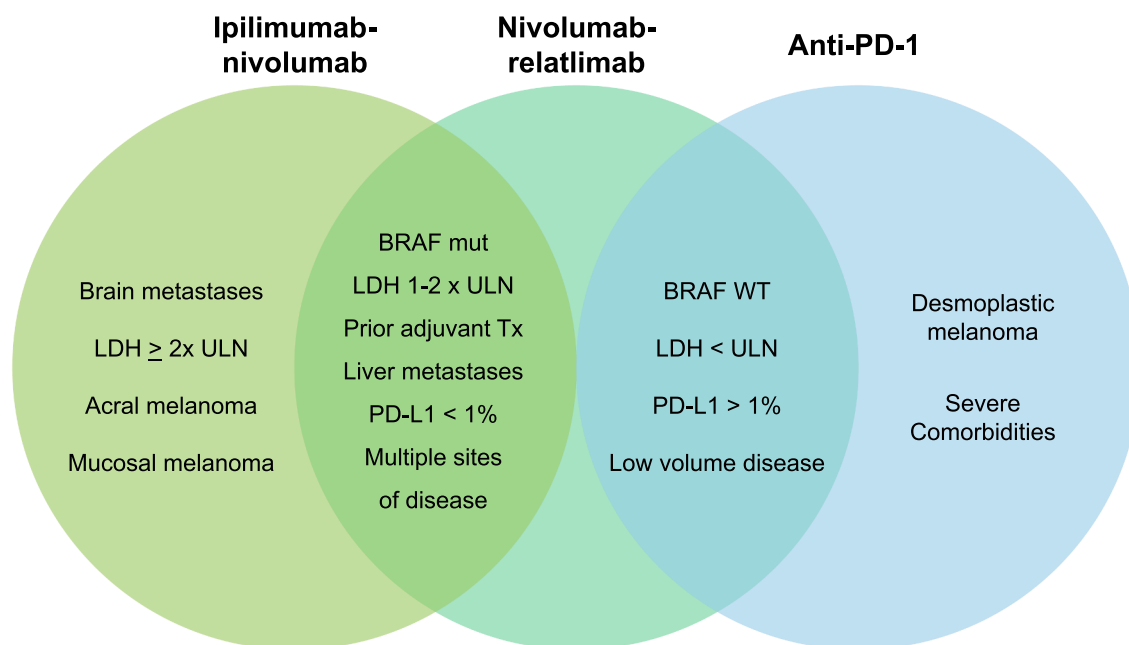


Fig. 2. Clinical factors and melanoma characteristics to consider when selecting firstline immune checkpoint blockade in patients with advanced melanoma. Abbreviations: LDH, lactate dehydrogenase; ULN, upper limit of normal; mut, mutation; WT, wild type; Tx, therapies.

As long-term data for nivolumab-relatlimab continues to mature, and evidence accumulates in common clinical scenarios, the optimum treatment selection will become clearer and more straightforward.

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Lorigan Paul: Writing – review & editing. **Lee Rebecca:** Writing – review & editing. **Bosetti Tommaso:** Writing – review & editing. **Kreft Sophia:** Writing – original draft, Visualization, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Sophia Kreft:** Honoraria/support for travel: Kyowa Kirin, Sanofi, Sun Pharma. **Rebecca Lee:** Institutional funding from Bristol Myers Squibb, Pierre Fabre, AstraZeneca, Chromitron. Speaker fees for Pierre Fabre. **Paul Lorigan:** Personal fees/advisory board/support for travel: MSD, Pierre Fabre, BMS, Iovance, MLA Diagnostics. Institutional support for research: BMS, Pierre Fabre. **Tommaso Bosetti** declared no conflict of interest.

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