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First-line treatment for unresectable stage III or IV melanoma

Making Education Easy 2024

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He has a clinical interest in the treatment of melanoma and non-melanoma skin cancer and is an investigator on multiple Phase 1, 2, and 3 clinical trials in this area.

In recent years, the median overall survival of patients with advanced melanoma has increased from the order of a few months to potentially many years due to the availability of immune checkpoint inhibitors (ICIs) and BRAF/MEK-inhibiting targeted therapy. For patients with unresectable stage III and stage IV malignant melanoma, until recently, first-line treatment with ICIs involved either monotherapy with a PD-1 inhibitor or combined therapy with nivolumab+ipilimumab. The inhibitor for the checkpoint LAG-3, relatlimab, is the latest to be added to the armamentarium for advanced melanoma, with the combination of nivolumab+relatlimab increasing the available treatment options.

This article will review the currently available first-line options for patients with advanced melanoma, with a focus on the recent evidence for use of ICIs in this patient population.

Introduction

Australia has the highest incidence of melanoma in the world.[1] In 2022, melanoma was the third most commonly diagnosed cancer in Australia, with an age-standardised incidence rate of 56.9 cases per 100,000 persons.[2] The high incidence of melanoma in Australia has a large economic impact on the Australian healthcare system, with the mean cost of melanoma per patient (all stages) in 2021 estimated to be AU$11,787, ranging from AU$644 for melanoma *in situ* to AU$100,725 for unresectable stage III/IV disease.[3]

Since peaking in 2013, the life-time melanoma mortality risk has sharply decreased, indicative of improving survival outcomes for those diagnosed with melanoma.[4] This decrease in mortality has coincided with the introduction and approval of targeted therapy and immunotherapy for patients with advanced melanoma.[5]

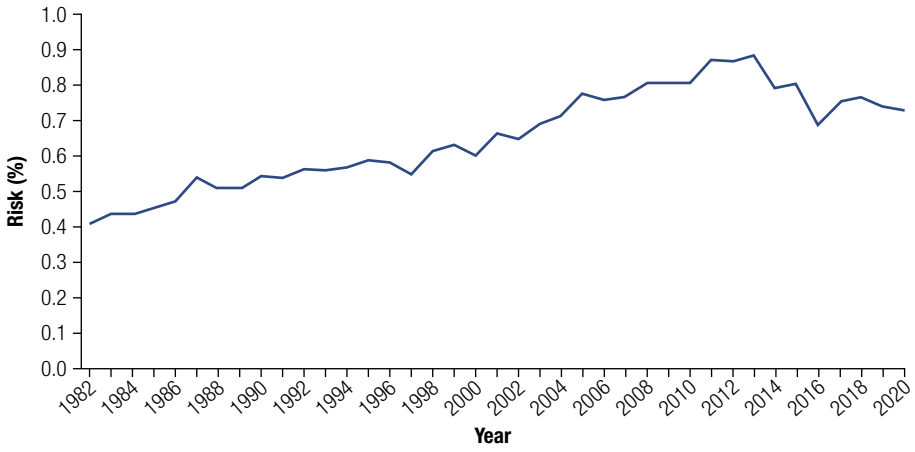

Figure 1. Australian lifetime mortality risk due to melanoma of the skin[4]

Treatment of unresectable melanoma

The management of unresectable stage III and stage IV melanoma (metastatic or advanced melanoma) has significantly improved over the past decade with the advent of novel systemic therapies, including immune checkpoint inhibitors (ICIs) and BRAF/MEK-inhibiting targeted therapy, increasing patient survival from the order of months to potentially many years.[5-7]

Current Cancer Council Australia Clinical Practice Guidelines note that immunotherapy is standard treatment for most patients with unresectable stage III and stage IV melanoma, with a BRAF inhibitor combined with a MEK inhibitor also to be considered as first-line/upfront drug treatment for patients with *BRAF* V600 mutation positive melanoma (**Table 1**).[8]

Table 1. Therapeutic Goods Administration-approved treatment options for first-line treatment of unresectable stage III and stage IV melanoma in Australia[9-18]

	Brand name	Phase 3 trial(s)	PBS listed
Anti–PD-1 monotherapy			
Nivolumab	Opdivo®[9]	CheckMate 066[19] CheckMate 067[20-24]	✓
Pembrolizumab	Keytruda[10]	KEYNOTE-006[25-29]	✓
Combination checkpoint inhibition			
Nivolumab+ipilimumab	Opdivo® plus Yervoy®[9, 11]	CheckMate 067[20-24]	✓
Nivolumab+relatlimab	Opdualag™[12]	RELATIVITY-047[30, 31]	✓
Combination targeted therapy for *BRAF* V600–mutant disease			
Dabrafenib/trametinib	Tafinlar® plus Mekinist®[13, 14]	COMBI-d and COMBI-v[32-34]	✓
Encorafenib/binimetinib	Braftovi® plus Mektovi®[15, 16]	COLUMBUS[35-37]	✓
Vemurafenib/cobimetinib	Zelboraf® plus Cotellic[17, 18]	coBRIM[38-40]	✓

Immune checkpoint inhibitors (ICIs) in melanoma

Immunotherapies seek to augment the immune response and overcome or circumvent the immune evasion mechanisms employed by cancer cells and tumours.[5, 41, 42] Some of the most effective immunotherapies target immune checkpoints — often exploited by cancers to decrease immune activity.[5, 41, 42] Cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1), and lymphocyte-activation gene 3 (LAG-3) are examples of the immune checkpoint receptors on T cells, which upon ligand binding trigger a signalling cascade that inhibits T-cell activation and function, limiting the immune response.[41-43] ICIs (e.g., ipilimumab, nivolumab, pembrolizumab, and relatlimab) are monoclonal antibodies that target these receptors and prevent receptor-ligand interaction, and thus reduce the inhibition of T-cell activation.[5, 41, 42]

- **Nivolumab** and **pembrolizumab** are PD-1 ICIs that bind to the PD-1 receptor and block its interaction with the ligands PD-L1 and PD-L2 and result in T-cell proliferation and cytokine secretion (**Figure 2**).[9, 10]
- **Ipilimumab** is a CTLA-4 ICI that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of tumour reactive T-effector cells which mobilise to mount a direct T-cell immune attack against tumour cells.[7]
- **Relatlimab** is a first-in-class human IgG4 antibody that binds to the LAG-3 T-cell receptor, blocks interaction with its ligands (including major histocompatibility complex [MHC] Class II) and reduces LAG-3 pathway-mediated inhibition of the immune response (**Figure 2**).[12, 43, 44] Antagonism of this pathway promotes T-cell proliferation and cytokine secretion.[12, 43]

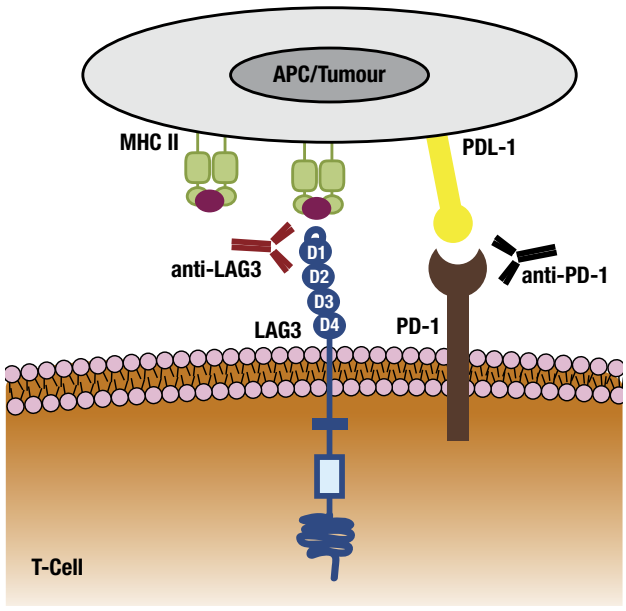

Figure 2. Mechanism of action of PDL-1 and LAG-3 checkpoint inhibitors[43]
APC = antigen-presenting cell; **LAG-3** = lymphocyte-associated gene 3; **MHC II** = major histocompatibility complex II; **PD-1** = programmed cell death protein 1; **PDL-1** = programmed cell death protein ligand 1.
Adapted from Wong et al. Clin Transl Med. 2021.

Until recently, the decision for first-line treatment with these ICIs was between monotherapy with a PD-1 inhibitor (nivolumab or pembrolizumab) or combined nivolumab+ipilimumab.[8] The inhibitor for the checkpoint LAG-3, relatlimab, is the latest to be added to the armamentarium for advanced melanoma, with a fixed-dose combination of nivolumab+relatlimab (Opdualag™) increasing the available treatment options.[12, 44] The following sections will review the available ICIs when used as monotherapy or in combination.

Monotherapy with PD-1 checkpoint inhibitors

Positive outcomes from the clinical studies that investigated the efficacy and safety of the PD-1 checkpoint inhibitors pembrolizumab and nivolumab led to the approval of these two agents for use as monotherapy in patients with unresectable or metastatic melanoma.[9, 10]

Nivolumab

Phase 3 trials have evaluated nivolumab against standard of care chemotherapy, first in previously treated patients[45, 46] and then as a first-line treatment.[19]

In the phase 3 CheckMate 066 trial (NCT01721772), nivolumab (3 mg/kg every 2 weeks) was evaluated in treatment-naïve metastatic melanoma patients with wild-type *BRAF*.[19] Outcomes from Checkmate 066 indicated that nivolumab, compared with chemotherapy, improved response rate, progression-free survival (PFS), and overall survival (OS); 1-year OS rates were 72.9% versus 42.1% (hazard ratio [HR] for death 0.42; p<0.001), median PFS was 5.1 months versus 2.2 months (p<0.001), and objective response rates were 40.0% versus 13.9% (p<0.001).[19]

The efficacy of nivolumab, compared with ipilimumab, in previously untreated patients was also further demonstrated in the CheckMate 067 trial (NCT01844505) (see below).[20-24]

Pembrolizumab

The use of pembrolizumab monotherapy in patients with unresectable or metastatic melanoma in the front-line setting was based on the open-label, randomised phase 3 KEYNOTE-006 study (NCT01866319), which compared pembrolizumab (n=556) with ipilimumab (n=278) in participants with advanced melanoma.[25-29] Of the patients, 65.9% were treatment naïve.*

The estimated 6-month PFS rates were 47.3% for pembrolizumab every 2 weeks, 46.4% for pembrolizumab every 3 weeks versus 26.5% for ipilimumab (p<0.001).[25] Estimated 12-month survival rates were 74.1%, 68.4%, and 58.2%, respectively.[25] After 5 years of follow-up, pembrolizumab continued to improve OS and PFS compared with ipilimumab, with 5-year survival rates of 38.7% for pembrolizumab (combined data) versus 31.0% with ipilimumab; 48-month PFS rates were 23.0% and 7.3%, respectively.[27]

After the KEYNOTE-006 trial concluded, participants were eligible to transition to KEYNOTE-587 (NCT03486873) for extended follow-up. 210 former participants of KEYNOTE-006 (158 patients treated with pembrolizumab and 52 patients treated with ipilimumab) were assessed for 7-year follow-up.[28]

At the 7-year follow-up, median OS was 32.7 months for patients treated with pembrolizumab and 15.9 months for ipilimumab (HR 0.70; 95% CI 0.58, 0.83). The 7-year OS rates were 37.8% for pembrolizumab and 25.3% for ipilimumab (**Figure 3**).[28]

*In the KEYNOTE-006 trial, the dosage of pembrolizumab was 10 mg/kg every 2 or 3 weeks. The approved dosage of pembrolizumab is a flat dose of 200 mg every 3 weeks or a flat dose of 400 mg every 6 weeks.[10]
The dose of ipilimumab (3 mg/kg every 2 weeks for 4 doses) used in this trial is the same as the approved dose for ipilimumab.[11]

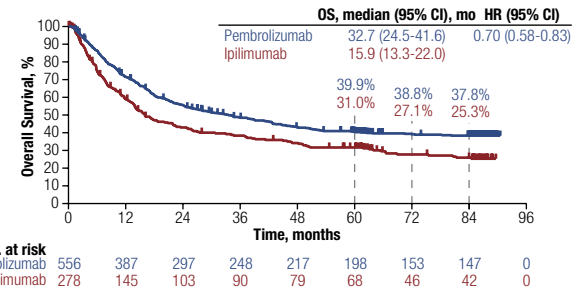

Figure 3. Overall survival (OS) in patients with advanced melanoma treated with pembrolizumab or ipilimumab[28]

The dosage of pembrolizumab was 10 mg/kg every 2 or 3 weeks. The approved dosage of pembrolizumab is a flat dose of 200 mg every 3 weeks or a flat dose of 400 mg every 6 weeks.[10]

The dose of ipilimumab (3 mg/kg every 2 weeks for 4 doses) used in the trial is the same as the approved dose for ipilimumab.[11]

Combination checkpoint inhibitor therapy

Nivolumab+ipilimumab

The efficacy and tolerability of the combination of a PD-1 inhibitor (nivolumab) with a CLTA-4 inhibitor (ipilimumab) was investigated in the three-arm CheckMate 067 trial that randomly assigned patients with previously untreated advanced melanoma to either nivolumab+ipilimumab (n=314), nivolumab (n=316), or ipilimumab (n=315; **Figure 4**).[20-24] The co-primary endpoints were PFS and OS in the nivolumab-containing arms versus ipilimumab alone.

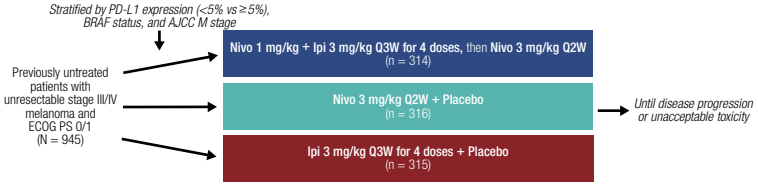

Figure 4. Trial design of CheckMate 067[20-24]

The study was not powered to compare nivolumab+ipilimumab with nivolumab

AJCC = American Joint Committee on Cancer;
ECOG PS = Eastern Cooperative Oncology Group performance status; **Ipi** = ipilimumab; **Nivo** = nivolumab; **PD-L1** = programmed cell death protein ligand 1; **Q2/3W** = every 2/3 weeks.

In the first report of this trial (minimum follow-up of 9 months), the median PFS was 11.5 months for nivolumab+ipilimumab compared with 2.9 months for ipilimumab alone (HR 0.42; 95% CI 0.31, 0.57; p<0.00001), and was 6.9 months for nivolumab alone (HR in the comparison with ipilimumab alone 0.57; 95% CI 0.43, 0.76; p<0.00001).[20] The benefits of combination therapy with nivolumab+ipilimumab persisted with long-term follow-up (**Table 2**) in this population with aggressive disease (58.0% with M1c disease and 3.6% with brain metastases).[20-24] The median OS with nivolumab+ipilimumab after 7.5 years of follow-up was 72.1 months (95% CI 38.2, not reached; **Figure 5**).[24]

Table 2. Long-term efficacy outcomes in the CheckMate 067 trial[20-24]*

	Nivolumab+ipilimumab (n=314)	Nivolumab (n=316)	Ipilimumab (n=315)
Overall survival, % patients			
3 years	58	52	34
5 years	52	44	26
6 years	50	43	23
7.5 years	48	42	22
Progression-free survival, % patients			
3 years	39	32	10
5 years	37	29	7
6 years	36	29	7
7.5 years	33	27	7
Overall response rate, % patients			
3 years	58	44	19
5 years	58	45	19
6.5 years	58	45	19
7.5 years	58	45	19

*Landmark analyses are descriptive, p-values not evaluated.

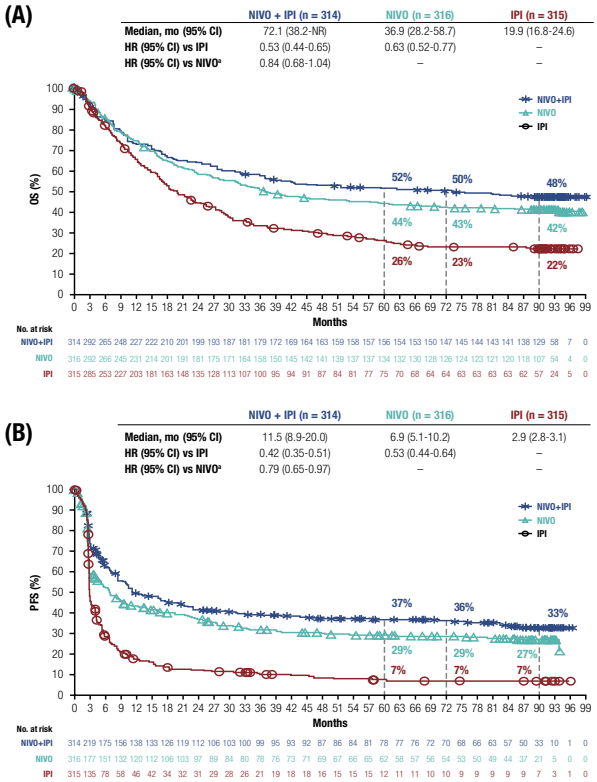

Figure 5. Overall survival (A) and progression-free survival (B) in patients with previously untreated advanced melanoma in the CheckMate 067 trial[24]

[a] Descriptive analysis.

Ipi = ipilimumab; **Nivo** = nivolumab; **OS** = overall survival; **PFS** = progression-free survival.

Adapted from Hodi et al. 2022

Patients treated with nivolumab+ipilimumab were less likely to receive subsequent systemic therapy than those treated with nivolumab or ipilimumab (36%, 49%, and 66%, respectively, descriptive analysis).[24] The median time to subsequent therapy was not reached for patients treated with nivolumab+ipilimumab, and was 24.7 months for those treated with nivolumab monotherapy and 8.0 months for those treated with ipilimumab monotherapy.[24]

In the updated 7.5 year analysis, melanoma-specific survival (MSS; which excludes deaths unrelated to melanoma) was not reached, 49.4 months, and 21.9 months in patients treated with nivolumab+ipilimumab, nivolumab, and ipilimumab, respectively.[24] The 6.5-year data from the CheckMate 067 trial showed that the numerically highest response rates for patients with liver metastases were in the combined immunotherapy group.[23]

The enhanced efficacy of combined immunotherapy was accompanied by increased toxicity (**Table 3**).[23] In the Checkmate 067 trial, after all patients had been followed for a minimum of 6.5 years, treatment-related adverse events of any grade, treatment-related grade 3 or 4 adverse events, and the percentage of patients discontinuing treatment due to any grade treatment-related adverse events are shown in **Table 3**.[23] One death in the nivolumab group and one death in the ipilimumab group were considered to be drug-related;[20] one death was due to neutropenia (nivolumab group) and one due to colon perforation (ipilimumab group). Two deaths considered to be related to the study drug (>100 days after the last dose) were reported in the combination therapy group: one due to autoimmune myocarditis (approximately 2 months after receiving a single dose of the PD-1 inhibitor outside the context of the trial) and one due to liver necrosis.[21]

Over the 6.5 years, the most frequent grade 3 or 4 treatment-related select adverse events with a potential immunologic aetiology were diarrhoea (8%, 3%, and 8% of patients in the nivolumab+ipilimumab, nivolumab, and ipilimumab groups, respectively), colitis (7%, 1%, and 9%, respectively), increased alanine aminotransferase (6%, 1%, and 1%, respectively), and increased aspartate aminotransferase (4%, 1%, and <1%, respectively).[23]

No previously unreported long-term adverse events were noted at the 5-,[22] 6.5-,[23] or 7.5-year[24] analyses.

Table 3. Summary of adverse events in the CheckMate 067 trial[23]

Patients Reporting Event	Nivolumab+ipilimumab (n = 313)		Nivolumab (n = 313)		Ipilimumab (n = 311)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AE, % pts	96	59	87	24	86	28
Treatment-related AE leading to discontinuation, % pts	42	31	14	8	15	14
Treatment-related death, n (% pts)	2 (1)		1 (<1)		1 (<1)	

pts = patients.

Patients with asymptomatic brain metastases

Open-label phase 2 trials (CheckMate 204; NCT2320058) [47-49] and the Anti-PD1 Brain Collaboration [ABC] trial (NCT02374242)[50, 51] in patients with advanced melanoma with untreated asymptomatic brain metastasis have shown significant and durable activity of nivolumab+ipilimumab in this patient group.

In the CheckMate 204 trial, 101 patients with asymptomatic brain metastases treated with first-line nivolumab+ipilimumab showed durable efficacy; the 36-month intracranial PFS was 54.1% (95% CI 42.7, 64.1) and OS was 71.9% (95% CI 61.8, 79.8) after a median follow-up of 34.3 months.[49] The intracranial clinical benefit rate (complete response, partial response, or stable disease ≥6 months) was 57.4%.[49]

The randomised, open-label, phase 2 ABC study in Australia also treated patients with asymptomatic melanoma brain metastases who were naïve to ICI therapy.[50, 51] Treatment-naïve patients with asymptomatic brain metastases were randomised to nivolumab+ipilimumab (n=27) or nivolumab monotherapy (n=19).[51] The 5-year intracranial PFS was 52% versus 14% in patients treated with nivolumab+ipilimumab versus nivolumab monotherapy. The 5-year OS were 55% and 40%, respectively.[51] Grade 3/4 treatment-related adverse events were reported in 63% of patients in the combination treatment group and 20% of those in the monotherapy group. [51]

Nivolumab+relatlimab

Following the beneficial outcomes of nivolumab in combination with ipilimumab, other combinations of ICIs have been investigated. One such combination involves relatlimab, a LAG-3 inhibitor, and nivolumab.[30, 31]

The efficacy and tolerability of nivolumab+relatlimab (n=355), compared with nivolumab monotherapy (n=359), was investigated in the global, randomised, double-blind phase 2/3 RELATIVITY-047 trial (NCT03470922) in patients with previously untreated advanced melanoma (**Figure 6**).[30, 31] The primary end point was PFS as assessed by blinded independent central review (BICR).

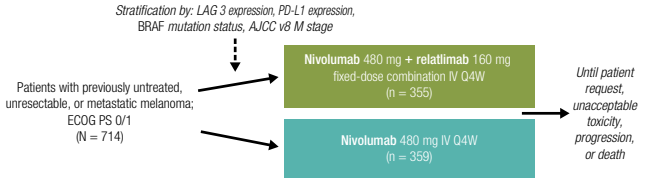

Figure 6. Trial design of RELATIVITY-047[30, 31]
AJCC = American Joint Committee on Cancer; **ECOG PS** = Eastern Cooperative Oncology Group performance status; **IV** = intravenous; **PD-L1** = programmed cell death protein ligand 1; **Q4W** = every 4 weeks.

At a median follow-up of 25.3 months, median PFS was 10.2 months (95% CI 6.5, 14.8) with nivolumab+relatlimab compared with 4.6 months (95% CI 3.5, 6.5) with nivolumab (HR 0.81; 95% CI 0.67, 0.97; **Figure 7**).[31] The PFS benefit observed in patients treated with nivolumab+relatlimab versus nivolumab alone was largely consistent across key prespecified patient subgroups, including those with varying levels of PDL-1 and LAG-3 expression, LDH levels, *BRAF* status, and across other key clinical characteristics, including baseline patient age and tumour burden.[31]

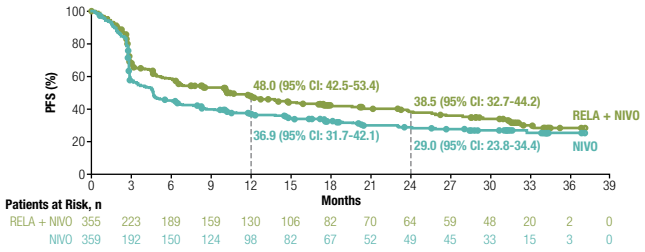

Figure 7. Progression-free survival in RELATIVITY-047 assessed by blinded independent central review[31]
CI = confidence interval; **HR** = hazard ratio; **NIVO** = nivolumab; **OS** = overall survival; **PFS** = progression-free survival; **RELA** = relatlimab.

At a median follow-up of 25.3 months, treatment with nivolumab+relatlimab versus nivolumab alone was associated with a numerical, although not statistically significant, improvement in median OS (not reached vs 33.2 months; HR 0.82; 95% CI 0.67, 1.02).[31]

The confirmed objective response rates (ORR) by BICR for nivolumab+relatlimab were 43.7% (95% CI 38.4, 49.0) versus 33.7% (95% CI 28.8, 38.9) with nivolumab alone (descriptive analysis).[31] Due to the hierarchy of statistical analysis of secondary endpoints, ORR could not be formally tested as the OS was not significant.

The nivolumab+relatlimab combination had a higher rate of grade 3/4 treatment-related adverse events compared with nivolumab alone (22% vs 12%), and more patients discontinued treatment due to adverse events (10% vs 4%). There were no new or unexpected safety signals with longer follow-up (25.3 months) compared with the original report (**Table 4**).[31] In the nivolumab+relatlimab group, the most common grade 3/4 treatment-related adverse effects were fatigue, diarrhoea, rash, and arthralgia.[31]

Table 4. Summary of adverse events in the RELATIVITY-047 trial[31]

	Nivolumab+relatlimab (n = 355)		Nivolumab (n = 359)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AE, % pts	85	22	73	12
Treatment-related AE leading to discontinuation, % pts	17	10	9	4
Treatment-related deaths, n (% pts)*	4 (1.1)		2 (<1)	

*Treatment-related deaths: nivolumab+relatlimab (n=4): hemophagocytic lymphohistiocytosis, acute oedema of the lung, pneumonitis, and multiorgan failure; nivolumab (n=2): sepsis and myocarditis and worsening pneumonia.
pts = patients.

Treatment considerations

Given the difference in efficacy and tolerability profiles between the currently approved monotherapies and combination therapies of ICIs, treatment decisions are also required.[41, 52] Given the differences in efficacy and safety profiles of single anti-PD-1 immunotherapy versus nivolumab-based combination therapies, critical questions to be answered are: which patients would benefit from combined immunotherapy and which patients would benefit from PD-1 monotherapy.[52]

Current data suggests that nivolumab+ipilimumab combination therapy provides intracranial responses in patients with asymptomatic brain metastases,[47-51] with guidelines recommending nivolumab+ipilimumab in this patient group.[53-55]

The spectrum of adverse events associated with immunotherapy is different from those associated with cytotoxic or targeted therapies.[5, 56, 57] The adverse events associated with ICIs are mostly related to activation of the immune system and may result in immune-mediated inflammation of diverse organs or tissues.[5, 56] Adverse effects of CTLA-4 and/or PD-1 inhibition are most commonly observed in the skin, gastrointestinal tract, liver, and endocrine systems and include pruritus, rash, nausea, diarrhoea, and thyroid disorders. Although a rare toxicity, hypophysitis (inflammation of the pituitary gland) with subsequent hypopituitarism may occur, especially in regimens containing anti-CTLA-4 (e.g., ipilimumab).[8] Treatment-related adverse events are more common when anti-CTLA and anti-PD-1 agents are used in combination, with high-grade events reported in 55% to 60% of individuals receiving combination therapy versus 10% to 20% of individuals receiving anti-PD-1 monotherapy (see above).[57] Severe immune-mediated adverse events (irAEs) have resulted in death in up to 1% of patients (see above). In regards to these irAEs, relative indications for combination nivolumab+ipilimumab in comparison to PD-1 inhibitor monotherapy include the patient's willingness to take on the high risk of irAEs, the absence of comorbidities or auto-immune processes that would elevate the risk of irAEs, and the patient's social support and anticipated compliance with the medical team to handle toxicities.[41] Optimal management of irAEs requires the recognition and grading of toxicity, immunosuppression, and individualised modification of the ICI(s), as well as the ability to recognise and treat these events early to avoid adverse outcomes.[57] Guidance for the management of the immune-related adverse events is available in recent NCCN Clinical Practice Guidelines.[57]

Although comparisons between trials should be made with caution, it appears that the newer combination of nivolumab+relatlimab is associated with an improved safety profile compared with nivolumab+ipilimumab (see above).[44]

Expert comment

Prior to the availability of combination nivolumab+relatlimab, clinicians and patients decided on immunotherapy treatment with either single-agent anti-PD-1 or nivolumab+ipilimumab, balancing the greater efficacy of nivolumab+ipilimumab against the toxicity 'cost' of the combination. This choice was typically made based on identifying patient populations who were felt likely to gain a higher incremental benefit of the combination (*BRAF* mutant, those with brain or liver metastases, and/or an elevated LDH), while also factoring in patient factors (comorbidities/physiological reserve and patient choice).

With the availability of nivolumab+relatlimab, patients now have a third immunotherapy choice.

In my opinion, a significant proportion of patients who historically were treated with single-agent PD-1 inhibitor would likely now be treated with combination nivolumab+relatlimab. The exceptions to this are those patients where minimising toxicity risk is a priority (e.g., those with severe auto-immune disease) and/or in those where response to single-agent PD-1 inhibitor is felt to be highly likely (e.g., desmoplastic primary melanoma/M1b disease).

For those patients historically treated with nivolumab+ipilimumab, the decision between nivolumab+ipilimumab and nivolumab+relatlimab will depend on clinical features. In my opinion, there are a number of clinical scenarios where nivolumab+ipilimumab will remain the preferred option, these include patients with brain metastasis or *BRAF* V600E mutant disease, particularly in younger patients.

For all patients, the choice of first-line ICI therapy will be an individualised choice.

Combination targeted therapy

Approximately half of the patients with metastatic melanoma harbour an activating mutation of *BRAF,* which codes for an intracellular signalling kinase in the MAPK pathway.[58] Most *BRAF*-activating mutations occurring in melanomas are at residue V600.[58] BRAF inhibitors (e.g., dabrafenib,[13] vemurafenib,[17] and encorafenib[16]) have clinical activity as first-line therapy in unresectable metastatic melanomas with *BRAF* V600 mutations, with co-administration of inhibitors of MEK, a signalling molecule downstream of BRAF, potentiating these effects.[8, 32-40] Examples of MEK inhibitors include trametinib,[14] cobimetinib,[18] and binimetinib.[15] In patients with previously untreated advanced melanoma, combination therapy leads to 5-year OS rates of 31-35% and 5-year PFS rates of 14-23% (**Table 5**). Current combinations available in Australia include dabrafenib/trametinib, encorafenib/binimetinib, and vemurafenib/cobimetinib.

Dabrafenib+trametinib: COMBI-d and COMBI-v

The first BRAF-MEK inhibitor combination approved for metastatic or unresectable melanoma was the result of outcomes from the two randomised phase 3 clinical trials, COMBI-d (NCT01584648) and COMBI-v (NCT01597908), which evaluated the combination of dabrafenib+trametinib compared with dabrafenib or vemurafenib (as the control arm).[32, 33] Both trials demonstrated a significant improvement in PFS and OS with the combination of dabrafenib+trametinib compared with the controls.[32, 33] A pooled long-term analysis of both trials suggested PFS and OS rates of 19% and 34% at 5 years (**Table 5**).[34]

Over the 5-year period, dabrafenib+trametinib was associated with grade 3 or 4 adverse events in approximately 59% of patients.[34] Pyrexia (any grade) was the most common adverse event occurring in 58% of all patients.[34] Adverse events leading to permanent discontinuation of dabrafenib+trametinib occurred in 18% of the patients, with pyrexia (4%), decreased ejection fraction (4%), and an increased alanine aminotransferase level (1%) being the most common reasons for discontinuation. However, the incidence of hyperproliferative skin adverse events was lower with the combination.[32, 33]

Encorafenib+binimetinib

The multicentre, open-label COLUMBUS trial (NCT01909453) represents the basis for the approval of the combination of encorafenib+binimetinib (**Table 5**).[35-37] In this phase 3 trial, patients with metastatic or unresectable melanoma who harboured *BRAF* V600E or V600K mutations were randomised to receive the encorafenib+binimetinib combination, encorafenib monotherapy, or vemurafenib monotherapy. In the 5-year analysis, encorafenib+binimetinib demonstrated long-term PFS and OS benefits (**Table 5**).[36] The safety profile of encorafenib+binimetinib in the 5-year updated analysis was generally manageable and consistent with previous observations; no new safety signals were reported.[36]

Grade 3/4 adverse events occurred in 70%, 66%, and 70% of patients treated with encorafenib+binimetinib, vemurafenib, and encorafenib, respectively. Adverse events led to dose adjustment or interruption in 56%, 62%, and 72% of patients in the encorafenib+binimetinib, vemurafenib, and encorafenib groups, respectively.[36]

Data from the 7-year analysis also confirmed the long-term, sustained efficacy and known safety profile of encorafenib+binimetinib, with no new safety signals emerging.[37]

Vemurafenib+cobimetinib

The combination of vemurafenib+cobimetinib, compared with vemurafenib, was evaluated in the phase 3, multicentre, randomised coBRIM trial (NCT01689519).[38-40] Patients in the vemurafenib+cobimetinib arm, compared with patients treated with vemurafenib, had greater PFS and OS at the 5-year analysis (**Table 5**).[39] OS and PFS were longest in patients with normal baseline lactate dehydrogenase levels and low tumour burden, and in those achieving complete response.[39] At the 5-year follow-up, complete response was achieved in 21% of patients treated with vemurafenib+cobimetinib and 13% of those treated with vemurafenib.[39] The safety profile at 5 years was consistent with previously published reports, with no new safety signals detected over extended follow-up.[39] Grade 3/4 adverse events occurred in 78% and 63% of patients treated with vemurafenib+cobimetinib and vemurafenib, respectively. Adverse events leading to discontinuation of any study drug occurred in 27% and 12% of patients in the vemurafenib+cobimetinib and vemurafenib groups, respectively.[39]

The toxicity profile of vemurafenib/cobimetinib is different from that of dabrafenib+trametinib, which may guide the treatment choices for individual patients/circumstances.[6]

Table 5. Long-term outcomes in trials involving combination targeted therapy

Study	Study design	Treatment arms	Pts	Progression-free survival (% pts)			Overall survival (% pts)		
				3 years	4 years	5 years	3 years	4 years	5 years
COMBI-d/v (pooled analysis)[34]	COMBI-d: r, db COMBI-v: r, ol	Dabrafenib+trametinib	536	24	21	19	44	37	34
COLUMBUS[37]	r, ol	Encorafenib+binimetinib	192	29	25	23	47	39	35
		Vemurafenib	191	14	12	10	31	26	21
		Encorafenib	194	25	22	19	41	37	35
coBRIM[39]	r, db	Vemurafenib+cobimetinib	247	23	17	14	38	34	31
		Vemurafenib	248	13	12	10	31	29	26

db = double-blind; **ol** = open label; **pts** = patients; **r** = randomised.

Expert comment

While not directly compared in a clinical trial, the three available BRAF/MEK inhibitor combinations have comparable efficacy but different toxicity profiles. As such, once a decision has been made to treat a patient with targeted therapy, be that in the first-line setting (see below) or in the ICI-refractory setting, the differing toxicity profiles will guide treatment selection.

As an example, the photosensitivity associated with vemurafenib may result in some patients preferring an alternative combination. Similarly, dabrafenib and trametinib are more likely to cause treatment-related pyrexia and encorafenib+binimetinib is more likely to cause elevated liver function tests.

Other factors which may influence treatment choice are pill burden (encorafenib+binimetinib involves 12 pills a day, dabrafenib+trametinib involves 5 pills a day) or the need to take treatment on an empty stomach (required for dabrafenib+trametinib but not encorafenib+binimetinib).

Sequencing BRAF/MEK inhibitors and checkpoint inhibitors

For patients with advanced melanoma with targetable *BRAF* mutations, treatment with BRAF/MEK inhibitors and checkpoint inhibitor immunotherapy are both potential front-line treatment options.[8, 59] However, the optimal sequence of targeted molecular therapy versus checkpoint inhibitor immunotherapy as first-line treatment presents a major therapeutic challenge.

The DREAMseq study sought to determine the optimal treatment sequence between combination nivolumab+ipilimumab checkpoint inhibitor immunotherapy and combination dabrafenib/trametinib targeted therapy in this patient population (**Figure 8**),[60] with patients initiated on either combination nivolumab+ipilimumab (arm A) or dabrafenib+trametinib (arm B).

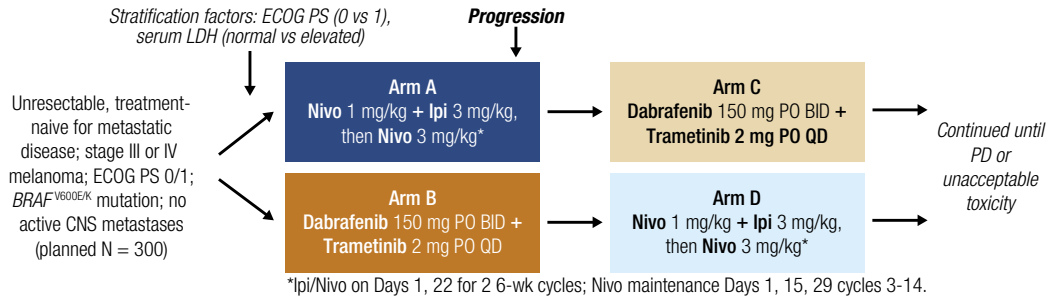

Figure 8. Study design of the DREAMseq study[60]
BID = twice daily; **CNS** = central nervous system; **ECOG PS** = Eastern Cooperative Oncology Group performance status; **Ipi** = ipilimumab; **LDH** = lactate dehydrogenase; **Nivo** = nivolumab; **PD** = progressive disease; **PO** = orally; **QD** = once daily.

Of the 265 patients enrolled, 73 progressed and proceeded to the second phase of the trial. The study was stopped early by the Data Safety Monitoring Committee because a clinically significant OS benefit was seen in patients treated with the combination of nivolumab+ipilimumab first compared with initiation with dabrafenib+trametinib (2-year OS 71.8% vs 51.5%, p=0.01 respectively; **Figure 9**).[60] The objective response rates were similar with either combination treatment when used in the front-line setting (46% vs 43%, respectively). When used in the second-line setting, dabrafenib+trametinib demonstrated a similar objective response rate of 47.8%.[60] However, the combination nivolumab+ipilimumab revealed a lower objective response rate of 29.6% after progression on initial therapy with dabrafenib+trametinib.[60]

Grade 3/4 adverse events occurred with similar frequencies across the treatment groups (50-60%).[60]

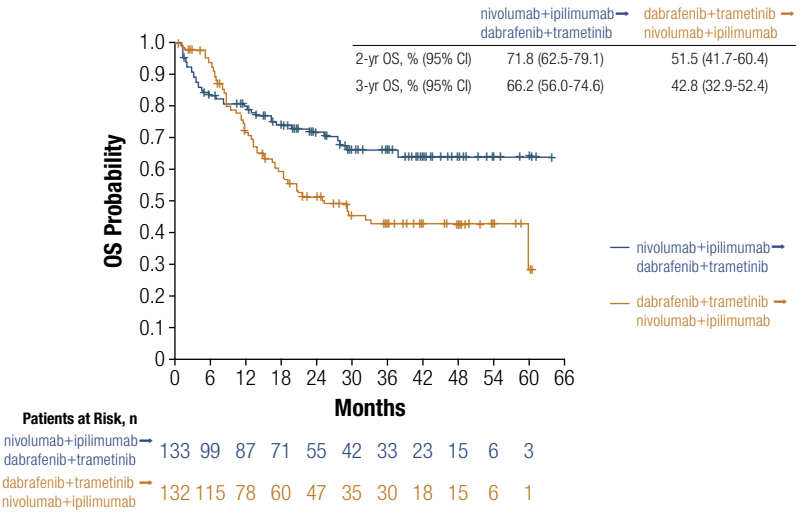

Figure 9. Kaplan-Meier curve of overall survival (OS) for the two treatment sequences[60]

Expert comment

The results of the DREAMseq study supports the upfront use of ICIs in the majority of patients with *BRAF*-mutant melanoma. There is, however, a group of patients, who are not represented in clinical trials, who require first-line treatment with BRAF/MEK inhibitor therapy. These include patients with multiple poor prognostic features such as an Eastern Cooperative Oncology Group performance status >2 and/or symptomatic brain metastasis requiring corticosteroids and not amenable to local therapy or those with an absolute or relative contraindication to immune checkpoint inhibition (e.g., patients with a solid organ transplant or severe autoimmune disease).

Take-home messages

- In recent years, the availability of ICIs and BRAF/MEK inhibiting targeted therapies has increased the median OS of patients with advanced melanoma from the order of a few months to potentially many years
- In the case of immunotherapy, until recently, the decision for first-line treatment of patients with advanced melanoma was between anti–PD-1 monotherapies (nivolumab or pembrolizumab) and combined nivolumab+ipilimumab
- The inhibitor for the checkpoint LAG-3, relatlimab, is the latest agent to be added to the armamentarium for advanced melanoma, with the combination of nivolumab+relatlimab increasing the available treatment options
  - In patients with previously untreated unresectable stage III/IV melanoma, nivolumab+relatlimab improved PFS compared with nivolumab (10.2 vs 4.6 months; HR 0.81; 95% CI 0.67, 0.97 after 25.3 months of follow-up); the safety profile of nivolumab+relatlimab appears to be more favorable than that of nivolumab+ipilimumab
- The safety profile of nivolumab+relatlimab is typical of that of other immunotherapy agents, with patients experiencing a grade 3/4 treatment-related adverse event rate of 22%
- Data from the DREAMseq trial indicated that upfront nivolimumab+ipilimumab should precede targeted therapy as the first-line treatment for patients with *BRAF* V600 metastatic disease

Expert's concluding comments

The availability of nivolumab+relatlimab gives patients with advanced melanoma another first-line treatment option. Treatment options will need to be individualised. A number of questions remain, including the role of nivolumab+relatlimab versus nivolumab+ipilimumab in patients treated with prior adjuvant PD-1 inhibitor, and the role of sequencing nivolumab+ipilimumab and nivolumab+relatlimab. Randomised trials are unlikely to inform every clinical scenario, and prospective data sets may help clinicians and patients select therapy.

References

1. World Cancer Research Fund International. Skin cancer statistics. 2020. Available from: 'https://www.wcrf.org/cancer-trends/skin-cancer-statistics/'.
2. Australian Institute of Health and Welfare. Cancer data in Australia. 2022. Available from: 'https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-rankings-data-visualisation'.
3. Gordon LG, Leung W, Johns R, et al. Estimated healthcare costs of melanoma and keratinocyte skin cancers in Australia and Aotearoa New Zealand in 2021. Int J Environ Res Public Health. 2022;19(6).
4. Australian Institute of Health and Welfare. Risk of melanoma of the skin by age and over time. 2022. Available from: 'https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-data-commentaries/risk-of-melanoma-of-the-skin-by-age-and-over-time'.
5. Lazaroff J, Bolotin D. Targeted therapy and immunotherapy in melanoma. Dermatol Clin. 2023;41(1):65-77.
6. Jenkins RW, Fisher DE. Treatment of advanced melanoma in 2020 and beyond. J Invest Dermatol. 2021;141(1):23-31.
7. Bhave P, Wong J, McInerney-Leo A, et al. Management of cutaneous melanoma in Australia: a narrative review. Med J Aust. 2023;218(9):426-31.
8. Cancer Council Australia. Summary of recommendations and practice points: Immunotherapy for melanoma. 2020. Available from: 'https://wiki.cancer.org.au/australia/Guidelines:Immunotherapy_for_melanoma_recommendations'.
9. Bristol-Myers Squibb Australia Pty Ltd. Australian product information OPDIVO® (nivolumab) 2023. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2016-PI-01052-1'.
10. Merck Sharp & Dohme (Australia) Pty Limited Australian product information – KEYTRUDA® (pembrolizumab (rch)) 2023. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2023-PI-01512-1'.
11. Bristol-Myers Squibb Australia Pty Ltd. Australian product information - Yervoy® (ipilimumab) 2023. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2011-PI-02907-3&d=20230529172310101'.
12. Bristol-Myers Squibb Australia Pty Ltd. Australian product information OPDUALAG™ (nivolumab/relatlimab) 2023. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2022-PI-02090-1'.
13. NOVARTIS Pharmaceuticals Australia Pty Limited. Australian product information - TAFINLAR (dabrafenib) capsules 2023. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-02126-1&d=20230530172310101'.
14. NOVARTIS Pharmaceuticals Australia Pty Limited. Australian product information – MEKINIST (trametinib) tablets 2023. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2014-PI-01394-1'.
15. Pierre Fabre Australia Pty Limited. Australian product information MEKTOVI (binimetinib) film-coated tablets 2021. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2019-PI-01021-1'.

16. Pierre Fabre Australia Pty Limited. Australian product information BRAFTOVI® (encorafenib) capsules 2022. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2019-PI-01022-1&d=202004201016933'.
17. Roche Products Pty Limited. Australian product information Zelboraf® (vemurafenib) 2020. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2012-PI-01949-3&d=20230611172310101'.
18. Roche Products Pty Limited. Australian product information Cotellic® (cobimetinib fumarate) 2023.
19. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372(4):320-30.
20. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015;373(1):23-34.
21. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2017;377(14):1345-56.
22. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2019;381(16):1535-46.
23. Wolchok JD, Chiarion-Sileni V, Gonzalez R, 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; plus supplement.
24. Hodi FS, Chiarion-Sileni V, Lewis KD, et al. Long-term survival in advanced melanoma for patients treated with nivolumab plus ipilimumab in CheckMate 067. J Clin Oncol. 2022;40 (16 Suppl): 9522.
25. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015;372(26):2521-32.
26. Schachter J, Ribas A, Long GV, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet. 2017;390(10105):1853-62.
27. Robert C, Ribas A, Schachter J, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol. 2019;20(9):1239-51.
28. Robert C, Carlino MS, McNeil C, et al. 7-year follow-up of KEYNOTE-006: Pembrolizumab versus ipilimumab in advanced melanoma. 18th International Congress of the Society for Melanoma Research; 2021; Virtual.
29. Carlino MS, Long GV, Schadendorf D, et al. Outcomes by line of therapy and programmed death ligand 1 expression in patients with advanced melanoma treated with pembrolizumab or ipilimumab in KEYNOTE-006: A randomised clinical trial. Eur J Cancer. 2018;101:236-43.
30. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. N Engl J Med. 2022;386(1):24-34.
31. Tawbi HA, Hodi FS, Lipson EJ, et al. Nivolumab (NIVO) plus relatlimab (RELA) vs NIVO in previously untreated metastatic or unresectable melanoma: 2-year results from RELATIVITY-047. J Clin Oncol. 2023;41 (16_Suppl):9502.
32. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014;371(20):1877-88.
33. Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet. 2015;386(9992):444-51.
34. Robert C, Grob JJ, Stroyakovskiy D, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. N Engl J Med. 2019;381(7):626-36.
35. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2018;19(5):603-15.
36. Dummer R, Flaherty KT, Robert C, et al. COLUMBUS 5-Year update: A randomized, open-label, phase iii trial of encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF V600–mutant melanoma. J Clin Oncol. 2022;40(36):4178-88.
37. Schadendorf D, Dummer R, Flaherty KT, et al. COLUMBUS 7-year update: A randomized, open-label, phase III trial of encorafenib (enco) + binimetinib (bini) vs vemurafenib (vemu) or enco in patients (pts) with BRAF V600–mutant melanoma. Ann Oncol, 34 (Suppl. 2) S670-1.
38. Ascierto PA, McArthur GA, Dréno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol. 2016;17(9):1248-60.
39. Ascierto PA, Dréno B, Larkin J, et al. 5-year outcomes with cobimetinib plus vemurafenib in BRAFV600 mutation-positive advanced melanoma: extended follow-up of the coBRIM Study. Clin Cancer Res. 2021;27(19):5225-35.
40. Larkin J, Ascierto PA, Dréno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med. 2014;371(20):1867-76.
41. National Comprehensive Cancer Network. NCCN Guidelines Version 2.2023 Melanoma: Cutaneous. 2023.
42. Mutz-Rabl CG, Koelblinger P, Koch L. Immunotherapy for metastatic melanoma—from little benefit to first-line treatment. memo. 2023:1-5.
43. Wang M, Du Q, Jin J, et al. LAG3 and its emerging role in cancer immunotherapy. Clin Transl Med. 2021;11(3):e365.
44. Albrecht LJ, Livingstone E, Zimmer L, et al. The latest option: Nivolumab and relatlimab in advanced melanoma. Curr Oncol Rep. 2023;25(6):647-57.
45. Weber J, D'Angelo S, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015;16(4):375-84.
46. Larkin J, Minor D, D'Angelo S, et al. Overall survival in patients with advanced melanoma who received nivolumab versus investigator's choice chemotherapy in CheckMate 037: A randomized, controlled, open-label phase III trial. J Clin Oncol. 2018;36(4):383-90.
47. Long GV, Atkinson V, Lo S, 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.
48. Tawbi HA, Forsyth PA, Hodi FS, et al. Safety and efficacy of the combination of nivolumab plus ipilimumab in patients with melanoma and asymptomatic or symptomatic brain metastases (CheckMate 204). Neuro Oncol. 2021;23(11):1961-73.
49. Tawbi HA, Forsyth PA, Hodi FS, et al. Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): final results of an open-label, multicentre, phase 2 study. Lancet Oncol. 2021;22(12):1692-704.
50. Long G, Atkinson V, Lo S, et al. Long-term outcomes from the randomized phase II study of nivolumab (nivo) or nivo+ ipilimumab (ipi) in patients (pts) with melanoma brain metastases (mets): Anti-PD1 brain collaboration (ABC); abstract 1311O. Ann Oncol. 2019;30:v534.
51. Long GV, Atkinson V, Lo S, et al. Five-year overall survival from the anti-PD1 brain collaboration (ABC Study): Randomized phase 2 study of nivolumab (nivo) or nivo+ipilimumab (ipi) in patients (pts) with melanoma brain metastases (mets). J Clin Oncol. 2021;39(15_suppl):9508-.
52. Dimitriou F, Hauschild A, Mehnert JM, et al. Double trouble: Immunotherapy doublets in melanoma-approved and novel combinations to optimize treatment in advanced melanoma. Am Soc Clin Oncol Educ Book. 2022;42:1-22.
53. Keilholz U, Ascierto PA, Dummer R, et al. ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO Guidelines Committee. Ann Oncol. 2020;31(11):1435-1448.
54. Tan XL, Le A, Lam FC, et al. Current Treatment Approaches and Global Consensus Guidelines for Brain Metastases in Melanoma. Front Oncol. 2022;12:885472.
55. Vogelbaum MA, Brown PD, Messersmith H, et al. Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline. J Clin Oncol. 2022;40(5):492-516.
56. Champiat S, Lambotte O, Barreau E, et al. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. Ann Oncol. 2016;27(4):559-74.
57. National Comprehensive Cancer Network. Management of immunotherapy-related toxicities: NCCN Guidelines Version 2.2023. 2023.
58. Long GV, Menzies AM, Nagrial AM, et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. J Clin Oncol. 2011;29(10):1239-46.
59. Cancer Council Australia. Clinical Guidelines - Does systemic drug therapy improve progression-free, overall survival in unresectable stage III and stage IV melanoma? 2019. Available from: 'https://wiki.cancer.org.au/australia/Clinical_question:Does_systemic_drug_therapy_improve_progression_free,_overall_survival_in_Stage_3C_unresectable_and_stage_4_melanoma%3F'.
60. Atkins MB, Lee SJ, Chmielowski B, et al. Combination dabrafenib and trametinib versus combination nivolumab and ipilimumab for patients with advanced BRAF-mutant melanoma: The DREAMseq trial-ECOG-ACRIN EA6134. J Clin Oncol. 2023;41(2):186-97.

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