National Cancer Control Programme

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Systemic anti-cancer therapy of patients with metastatic melanoma

Evidence into Practice – a rapid review
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1.0 Background

Melanoma represents 4.7% of all diagnosed invasive cancers, with 968 new cases diagnosed annually during 2012-2014. The annual incidence rate of melanoma is higher in Irish males (20.2 per 100,000) than females (20.0 per 100,000). The total number of deaths attributable to melanoma between 2011-2013 was 159, with a mortality rate of 4.0 (deaths per 100,000 per year) for males and 2.6 for females (NCRI, 2017).

There are a number of Systemic Anti-Cancer Therapy (SACT) treatments which have already been approved for reimbursement by the HSE for the treatment of advanced (unresectable or metastatic) melanoma in adults.

In June 2016, the HSE Drugs Group recommended reimbursement for pembrolizumab monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults in both first and second line treatments (second line only following ipilimumab). Ipilimumab is currently reimbursed for the first and second line treatment of advanced (unresectable or metastatic) melanoma in adults. Ipilimumab can only be given following pembrolizumab in patients unable to tolerate pembrolizumab.

As there are a number of other SACTs expected to be available for the treatment of advanced (unresectable or metastatic) melanoma in adults in the near to medium term the HSE Drugs Group requested that the NCCP convene a Melanoma Systemic Anti-Cancer Therapy (SACT) Clinical Advisory Group which would provide advice and agree recommendations with regard to the use and sequencing of SACT for the treatment of advanced (unresectable or metastatic) melanoma in adults.

1.1 Methodology and literature review

The methodology for the development of the 'Evidence into practice – a rapid review' was designed by a research methodologist and is based on the principles of evidence-based practice (EBP) (Sackett et al., 2000). The methodology is described in detail in the NCCP Methodology Manual for guideline development.

1.1.1 Step 1: Develop clinical questions

The questions were developed by the rapid review team, based on the scope of the rapid review. These questions then formed the basis for the types of evidence being gathered, the search strategy, and the inclusion and exclusion criteria.

To formulate the clinical questions they were broken down into their component parts using the PICO(T) framework:

- Participant/Population
- Intervention/Exposure
- Control/Comparison
- Outcome
- Time

1.1.2 Step 2: Search for the evidence

Clinical questions formulated in step one were used to conduct literature searches of the primary literature. The systematic literature review protocol was developed for the guideline development process by the HSE librarians in conjunction with the NCCP. The following bibliographic databases were searched in the order specified below using keywords implicit in the PICO(T) question and any identified subject headings:

- Cochrane Library
- Point-of-Care Reference Tools
- Medline
- Embase (where available)
- Other bibliographic databases such as PsycINFO, CINAHL, as appropriate.

The literature was searched based on the hierarchy of evidence. This is a live document; updates and reviews are carried out as new evidence emerges. The methodology for this piece of work is documented in our methodology manual (Available on request).

1.1.3 Step 3: Appraise the literature for validity and applicability

Primary papers were appraised using validated checklists developed by the Scottish Intercollegiate Guideline Network (SIGN).

There were three main points considered when appraising all the research evidence:

- Are the results valid? (internal validity)
- What are the results? (statistical and clinical significance)
- Are the results applicable/generalisable to the patient/population of this guideline? (external validity)

2.0 Evidence into practice – a rapid review: recommendations

2.1 Summary of recommendations

For adult patients with metastatic melanoma and who are BRAF wild-type (BRAF mutation negative), what systemic anticancer therapy (SACT) improves overall survival?	
Recommendation	**Grade**
Recommendation 2.2.1.1 In patients with metastatic or unresectable melanoma who are BRAF wild-type and treatment naive, monotherapy with nivolumab* or pembrolizumab is recommended.	**A**
Recommendation 2.2.1.2 In patients with metastatic or unresectable melanoma who are BRAF wild-type and treatment naive, chemotherapy should only be considered in patients who are deemed unsuitable for immunotherapy, following discussion at an MDT.	**A**

For adult patients with metastatic melanoma and who are BRAF mutated (BRAF mutation positive), what systemic anticancer therapy (SACT) improves overall survival?	
Recommendation	**Grade**
Recommendation 2.2.2.1 In patients with metastatic or unresectable melanoma who are BRAF mutated and treatment naive, combination treatment with BRAF and MEK* inhibitors is the recommended treatment over single agent BRAF inhibitor.	**A**
Recommendation 2.2.2.2 In patients with metastatic or unresectable melanoma who are BRAF mutated and treatment naive, if the combination of BRAF and MEK* inhibitors is not available, BRAF monotherapy is preferred over chemotherapy.	**A**
Recommendation 2.2.2.3 In patients with metastatic or unresectable melanoma who are BRAF mutated and treatment naive, monotherapy with nivolumab* or pembrolizumab is also a therapeutic option.	**A**

For adult patients with metastatic melanoma and who are BRAF wild-type (BRAF mutation negative) and who have relapsed following first line therapy, what is the best second line therapy?	
Recommendation	**Grade**
Recommendation 2.2.3.1 In patients with metastatic or unresectable melanoma who are BRAF wild-type and have been previously treated with ipilimumab, IL-2 or chemotherapy, second line treatment with an anti-PD-1 monoclonal antibody (pembrolizumab or nivolumab*) is recommended.	**A**
Recommendation 2.2.3.2 In patients with metastatic or unresectable melanoma who are BRAF wild-type and have been previously treated with an anti-PD-1 monoclonal antibody (pembrolizumab or nivolumab*), there is currently no accepted evidence based standard of care. Treatment options such as chemotherapy should be considered following discussion at an MDT.	**D**

For adult patients with metastatic melanoma and who are BRAF mutated (BRAF mutation positive) and who have relapsed following first line therapy, what is the best second line therapy?

Recommendation	Grade
Recommendation 2.2.4.1 In patients with metastatic or unresectable melanoma who are BRAF mutation positive and who have received BRAF or BRAF/MEK* inhibitors as first line therapy, treatment with an anti PD-1 monoclonal antibody (pembrolizumab or nivolumab*) is the recommended second line treatment.	**A**
Recommendation 2.2.4.2 In patients with metastatic or unresectable melanoma who are BRAF mutation positive and have not received BRAF or BRAF/MEK* inhibitors as first line therapy, treatment with BRAF/MEK* inhibitors is the recommended second line treatment.	**C**
Recommendation 2.2.4.3 In patients with metastatic or unresectable melanoma who are BRAF mutation positive and have not received BRAF or BRAF/MEK* inhibitors as first line therapy, if the combination of BRAF and MEK* inhibitors is not available, BRAF monotherapy is the recommended second line treatment.	**D**

***Explanatory note:** Nivolumab and a number of MEK inhibitors are licensed for these indications in the ROI and are currently being reviewed by the HSE under the pricing and reimbursement framework agreed by the DOH with the pharmaceutical industry.

Good practice points

These reflect current best practice based on the clinical experience of the guideline development group (GDG).

2.2 Evidence statement and recommendations

Clinical question 2.2.1

For adult patients with metastatic melanoma and who are BRAF wild-type (BRAF mutation negative), what systemic anticancer therapy (SACT) improves overall survival?

Evidence statement

There are a number of high quality randomised controlled trials (RCTs) to address this clinical question (Robert et al., 2015c - CheckMate 066, Robert et al., 2015d - KEYNOTE-006, Schachter, 2016 - KEYNOTE-006, Larkin et al., 2015a - CheckMate 067, Wolchok et al., 2016 - CheckMate 067).

Nivolumab

One RCT has demonstrated an overall survival advantage of nivolumab compared to dacarbazine in BRAF wild-type treatment naive patients (Robert et al., 2015c - CheckMate 066) (Table X).

Pembrolizumab

A phase III RCT demostrated a survival advantage of giving first-line pembrolizumab compared to ipilimumab in treatment naive patients (Robert et al., 2015d - KEYNOTE-006). Sixty-six percent of patients in this trial were treatment naive of mixed BRAF status (35-38% had a BRAF mutation). Estimated two year overall survival (OS) and progression free survival (PFS) figures from a recent abstract of the KEYNOTE-006 also show an advantage for treatment with pembrolizumab compared to Ipilimumab (Schachter, 2016) (Table 1).

Table 1: Studies of systemic anticancer therapy (SACT) in patient with metastatic melanoma and who are BRAF wild-type.

CheckMate 066 (Robert et al., 2015c)	**Nivolumab**	**Dacarbazine**	
Overall survival (OS) @ 1 year	72.9% (95% CI, 65.5 to 78.9)	42.1% (95% CI, 33.0 to 50.9)	p<0.001
Median progression-free survival (PFS)	5.1 mths (95% CI, 3.5 to 10.8)	2.2 mths (95% CI, 2.1 to 2.4)	p<0.001
KEYNOTE-006 (Robert et al., 2015d)	**Pembrolizumab**	**Ipilimumab**	**(PEM vs IPI)**
	2 wk / 3 wk		
Median OS	NR / NR	NR	
est. OS @ 12 mths	74.1% / 68.4%	58.2%	p<0.001
Median PFS	5.5 mths (95% CI, 3.4 to 6.9) / 4.1 mths (95% CI, 2.9 to 6.9)	2.8 mths (95% CI, 2.8 to 2.9)	
est. PFS @ 6 mths	47.3% / 46.4%	26.5%	p<0.001
KEYNOTE-006 ((Schachter, 2016)– ASCO abstract)	**Pembrolizumab**	**Ipilimumab**	**(PEM vs IPI)**
	2 wk / 3 wk		
Median OS	NR / NR	16 mths	
est. OS @ 2 years	55.1% / 55.3%	43%	p=0.0008
HR (versus ipilimumab)	0.68 (95% CI, 0.53-0.87) / 0.68 (95% CI, 0.53-0.86)		
Median PFS	5.6 mths / 4.1 mths	2.8	
est. PFS @ 2 years	31.2% / 27.8%	13.5%	p<0.0001
HR (versus ipilimumab)	0.61 (95% CI, 0.50-0.75) / 0.61 (95% CI, 0.50-0.75)	-	

Combination therapy
A phase III RCT investigated the combination of Nivolumab plus Ipilimumab vs. Ipilimumab vs. Nivolumab monotherapy (Larkin et al., 2015a - CheckMate 067) and recent follow-up data (18 mths) has been released demonstrating that in patients with wild-type BRAF, the median PFS for the Nivo+Ipi, Nivo, and Ipi groups, was 11.3, 7.1, and 2.8 months, respectively. The frequency of drug-related grade 3/4 adverse events were 56.5%, 19.8% and 27%, respectively (Wolchok et al., 2016 - CheckMate 067).

Evidence to support combination in patients with metastatic or unresectable melanoma who are BRAF wild-type and treatment naive is evolving. Longer follow-up and OS data from the phase III trial will be required to determine if combination therapy should replace monotherapy as the preferred approach in treatment naive patients.

The guideline development group (GDG) recommend the evidence on combination therapy will be re-evaluated when new evidence emerges.

Recommendation 2.2.1.1	Grade
In patients with metastatic or unresectable melanoma who are BRAF wild-type and treatment naive, monotherapy with nivolumab* or pembrolizumab is recommended.	**A**

Recommendation 2.2.1.2	Grade
In patients with metastatic or unresectable melanoma who are BRAF wild-type and treatment naive, chemotherapy should only be considered in patients who are deemed unsuitable for immunotherapy, following discussion at an MDT.	**A**

*__Explanatory note:__ Nivolumab is licensed for this indication in the ROI and is currently being reviewed by the HSE under the pricing and reimbursement framework agreed by the DOH with the pharmaceutical industry.

Clinical question 2.2.2

For adult patients with metastatic melanoma and who are BRAF mutated (BRAF mutation positive), what systemic anticancer therapy (SACT) improves overall survival?

Evidence statement

A number of randomised trials addressed the use of BRAF and MEK inhibitors in patients with metastatic or unresectable melanoma who are BRAF mutated and treatment naive (Larkin et al., 2014 - coBRIM , Ascierto et al., 2016 - coBRIM, Long et al., 2015 - COMBI-d, Long et al., 2014 - COMBI-d, Robert et al., 2015a - COMBI-v, Grob et al., 2015 - COMBI-v)

There are three randomised studies supporting the use of combination BRAF and MEK inhibitor therapy in BRAF mutation positive patients (Table 2). All studies concluded that combination is superior to BRAF therapy alone.

A follow-up analysis of COMBI-V (Grob et al., 2015) compared effects of combination therapy and monotherapy on health-related quality of life (HRQoL) as self-assessed by patients. The study found differences in mean scores between treatment groups were significant and clinically meaningful in favour of the combination compared with vemurafenib monotherapy for most domains across all three questionnaires during study treatment and at disease progression, including EORTC QLQ-C30 global health.

Table 2: Studies of combination BRAF and MEK inhibitor therapy in BRAF mutation positive patients

CoBRIM (Ascierto et al., 2016)	**Vemurafenib + cobimetinib**	**Vemurafenib + placebo**	
Median OS	22.3 months (95% CI 20.3–not estimable)	17.4 months (95% CI 15.0–19.8)	P=0.005
Median PFS	12.3 months (95% CI 9.5–13.4)	7.2 months (95% CI, (5.6–7.5))	P<0.0001
COMBI-d (Long et al., 2015)	**Dabrafenib + trametinib**	**Dabrafenib**	
Median OS	25.1 months (95% CI 19.2–not reached)	18.7 months (95% CI, 15.2–23.7)	P=0.0107
Median PFS	11.0 months (95% CI, 8.0–13.9)	8.8 months (95% CI, 5.9–9.3)	P=0.0004
COMBI-V (Robert et al., 2015a)	**Dabrafenib + trametinib**	**Vemurafenib**	
OS – 12 months	72% (95% CI, 67 to 77)	65% (95% CI, 59 to 70)	P=0.005
Median PFS	11.4 months	7.3 months	P<0.001
COMBI-V (update) (Robert et al., 2015b) - Abstract	**Dabrafenib + trametinib**	**Vemurafenib**	
Median OS	25.6 months	18.0 months	P<0.001
Median PFS	12.6 months	7.3 months	P<0.001

Immunotherapy

A number of randomised trials addressed the use of immunotherapy in patients with metastatic or unresectable melanoma who are treatment naive (Robert et al., 2015c - CheckMate 066, Robert et al., 2015d - KEYNOTE-006, Schachter, 2016 - KEYNOTE-006, Larkin et al., 2015a - CheckMate 067, Wolchok et al., 2016 - CheckMate 067).

As the randomised studies mentioned above included patients with BRAF mutations (20-30%), the guideline development group decided that immunotherapies as discussed previously are relevant to this question.

Nivolumab
One RCT has shown median progression-free survival advantage of combined treatment with nivolumab and ipilimumab compared to nivolumab or ipilimumab alone (Larkin et al., 2015a - CheckMate 067) (Table 3).

Pembrolizumab
A phase III RCT demostrated a survival advantage of giving first-line pembrolizumab compared to ipilimumab in treatment naive patients (Robert et al., 2015d - KEYNOTE-006). Sixty-six percent of patients in this trial were treatment naive of mixed BRAF status (35-38% had a BRAF mutation). Estimated two year overall survival (OS) and progression free survival (PFS) figures from a recent abstract update of the KEYNOTE-006 also show an advantage for treatment with pembrolizumab compared with Ipilimumab (Schachter, 2016) (Table 3).

Table 3: Studies of systemic immunotherapy in patient with metastatic melanoma

CheckMate 067 (Larkin et al., 2015a)	**Nivolumab + Ipilimumab**	**Nivolumab**	**Ipilimumab**	
Median PFS	11.5 mths (95% CI, 8.9 to 16.7)	6.9 mths (95% CI, 4.3 to 9.5)	2.9 mths (95% CI, 2.8 to 3.4)	p<0.001 (NIV+IPI) vs NIV (NIV+IPI) vs IPI
KEYNOTE-006 (Robert et al., 2015d)	**Pembrolizumab**		**Ipilimumab**	**(PEM vs IPI)**
	2 wk	3 wk		
Median OS	NR	NR	NR	
est. OS @ 12 mths	74.1%	68.4%	58.2%	p<0.001
Median PFS	5.5 mths (95% CI, 3.4 to 6.9)	4.1 mths (95% CI, 2.9 to 6.9)	2.8 mths (95% CI, 2.8 to 2.9)	
est. PFS @ 6 mths	47.3%	46.4%	26.5%	p<0.001
KEYNOTE-006 ((Schachter, 2016)– ASCO abstract)	**Pembrolizumab**		**Ipilimumab**	**(PEM vs IPI)**
	2 wk	3 wk		
Median OS	NR	NR	16 mths	
est. OS @ 2 years	55.1%	55.3%	43%	p=0.0008
HR (versus ipilimumab)	0.68 (95% CI, 0.53-0.87)	0.68 (95% CI, 0.53-0.86)		
Median PFS	5.6 mths	4.1 mths	2.8	
est. PFS @ 2 years	31.2%	27.8%	13.5%	p<0.0001
HR (versus ipilimumab)	0.61 (95% CI, 0.50-0.75)	0.61 (95% CI, 0.50-0.75)	-	

Combination therapy
A phase III RCT investigated the combination of Nivolumab plus Ipilimumab vs. Ipilimumab vs. Nivolumab monotherapy (Larkin et al., 2015a - CheckMate 067) and recent follow-up data (18 mths) has been released demonstrating that in patients with BRAF mutation positive, the median PFS for the Nivo+Ipi, Nivo, and Ipi groups, was 15.5, 5.6, and 4.0 months, respectively. The frequency of drug-related grade 3/4 adverse events were 56.5%, 19.8% and 27%, respectively (Wolchok et al., 2016 - CheckMate 067).

Evidence to support combination in patients with metastatic or unresectable melanoma who are BRAF mutation positive and treatment naive is evolving. Longer follow-up and OS data from the phase III trial will be required to determine if combination therapy should replace monotherapy as the preferred approach in treatment naive patients.

The guideline development group (GDG) recommend the evidence on combination therapy will be re-evaluated when new evidence emerges.

Recommendation 2.2.2.1	Grade
In patients with metastatic or unresectable melanoma who are BRAF mutated and treatment naive, combination treatment with BRAF and MEK* inhibitors is the recommended treatment over single agent BRAF inhibitor.	**A**

Recommendation 2.2.2.2	Grade
In patients with metastatic or unresectable melanoma who are BRAF mutated and treatment naive, if the combination of BRAF and MEK* inhibitors is not available, BRAF monotherapy is preferred over chemotherapy.	**A**

Recommendation 2.2.2.3	Grade
In patients with metastatic or unresectable melanoma who are BRAF mutated and treatment naive, monotherapy with nivolumab* or pembrolizumab is also a therapeutic option.	**A**

Good Practice Point
The preferred first line approach should be based on patient characteristics taking into account the toxicity profile, following discussion at an MDT.

***Explanatory note:** Nivolumab and a number of MEK inhibitors are licensed for these indications in the ROI and are currently being reviewed by the HSE under the pricing and reimbursement framework agreed by the DOH with the pharmaceutical industry.

Clinical question 2.2.3

For adult patients with metastatic melanoma and who are BRAF wild-type (BRAF mutation negative) and who have relapsed following first line therapy, what is the best second line therapy?

Evidence statement

A number of randomised trials have addressed second line therapy in adult patient with metastatic melanoma who are BRAF wild -type (BRAF mutation negative) and who have relapsed following first line therapy (Robert et al., 2015d - KEYNOTE-006, Schachter, 2016- KEYNOTE-006, Weber et al., 2015 - CheckMate-037, Larkin et al., 2015b).

Patients previously treated with ipilimumab

There is consistent evidence that patients previously treated with ipilimumab benefit from second line treatment with anti-PD-1 antibodies (Weber et al., 2015 - CheckMate-037, Larkin et al., 2015b). Weber et al., conducted a phase III randomised controlled trial (RCT) to assess the efficacy and safety of nivolumab compared with investigator's choice of chemotherapy (ICC) as a second-line or later-line treatment in patients with advanced melanoma. The results of this study are outlined in Table 4 below.

Larkin et al., (2015) carried a retrospective pooled analysis to evaluate the efficacy and safety of nivolumab in patients with wild-type BRAF (n=334) and mutant BRAF (n=106) metastatic melanoma. The study included a phase III study (Weber et al., 2015 - CheckMate-037) and three phase I studies (Topalian et al., (2014), NCT01621490, Wolchok et al., (2013). The study population was heavily pre-treated, with about 75% of the patients having received more than 2 prior therapies for advanced melanoma, of these the most common prior treatment regimen was ipilimumab in 76.6% of patients. The objective response rate was 34.6% (95% CI, 28.3-41.3) for the 217 patients with wild-type BRAF status. A subgroup analysis of treatment effect on objective response rate (ORR) across patient subgroups showed that in patients previously treated with ipilimumab ORR was 36.0 (95% CI 27.6-45.1) in BRAF wild-type patients. However, the number of patients evaluated in the subgroup analysis was very small (BRAF wild-type n=45).

Patients previously treated with alternate systemic anti-cancer therapies.

Two studies addressed the question of second-line therapy in patients previously treated with systemic anti-cancer therapies (Weber et al., 2015 - CheckMate-037, Robert et al., 2015d - KEYNOTE-006, Schachter, 2016- KEYNOTE-006).

As mentioned previously, Weber (2015) conducted a phase III RCT to assess the efficacy and safety of nivolumab compared with investigator's choice of chemotherapy (ICC) as a second-line or later-line treatment in patients with advanced melanoma. The study included patients that were previously treated, with 21% and 23% of the nivolumab and ICC patients receiving >2 previous systemic therapies, respectively. Of these 53% (Nivolumab arm, n=145) and 54% (ICC arm, n=72) received chemotherapy. The results of this study are outline in Table 4 below.

The phase III RCT conducted by Robert (2015d - KEYNOTE-006), included patients that had received one previous systemic therapy, which included (34.4%) in the pembrolizumab every 2 weeks arm (n=96), 32.9% in the pembrolizumab every 3 weeks arm (n=91) and 34.9% in the Ipilimumab arm (n=97). Of those that had received previous systemic therapy, 12.9% in the pembrolizumab every 2 weeks arm (n=36), 14.8% in the pembrolizumab every 3 weeks arm (n=41), and 10.4% in the Ipilimumab arm (n=97), received chemotherapy. The results of this study are outlined in Table 4 below.

Table 4: Studies on second line therapy in adult patient with metastatic melanoma

CheckMate-037 (Weber et al., 2015)	Nivolumab	Investigators choice of chemotherapy	
Objective response	31.7% (95% CI 23.5-40.8)	10.6% (95% CI 3.5-23.1)	
Median PFS	4.7 months (95% CI 2.3-6.5)	4.2 months (95% CI 2.1-6.3)	HR 0.85 (99.9% CI 0.32-2.05)
6 month PFS	48% (95% CI 38-65)	34% (95% CI 18-51)	

KEYNOTE-006 (Robert et al., 2015d)	Pembrolizumab		Ipilimumab	(PEM vs IPI)
	2 wk	3 wk		
Median OS	NR	NR	NR	
est. OS @ 12 mths	74.1%	68.4%	58.2%	p<0.001
Median PFS	5.5 mths (95% CI, 3.4 to 6.9)	4.1 mths (95% CI, 2.9 to 6.9)	2.8 mths (95% CI, 2.8 to 2.9)	
est. PFS @ 6 mths	47.3%	46.4%	26.5%	p<0.001

KEYNOTE-006 ((Schachter, 2016)– ASCO abstract)	Pembrolizumab		Ipilimumab	(PEM vs IPI)
	2 wk	3 wk		
Median OS	NR	NR	16 mths	
est. OS @ 2 years	55.1%	55.3%	43%	p=0.0008
HR (versus ipilimumab)	0.68 (95% CI, 0.53-0.87)	0.68 (95% CI, 0.53-0.86)		
Median PFS	5.6 mths	4.1 mths	2.8	
est. PFS @ 2 years	31.2%	27.8%	13.5%	p<0.0001
HR (versus ipilimumab)	0.61 (95% CI, 0.50-0.75)	0.61 (95% CI, 0.50-0.75)	-	

Patients previously treated with a PD-1 inhibitor

There is no evidence to support the use of ipilimumab in patients previously treated with a PD-1 inhibitor. The two classes of agents have mechanisms of action which are not entirely overlapping. In theory, there may be a rationale for following anti- PD-1 therapy with anti-CTLA4 therapy. However, there is no data to assess the benefit of CTLA-4 following relapse from treatment with anti-PD-1.

The use of chemotherapy following anti-PD-1 has also not been investigated in prospective, randomised trials.

The guideline development group (GDG) recommend the evidence on second-line therapy will be re-evaluated when new evidence emerges.

Final recommendation 2.2.3.1	Grade
In patients with metastatic or unresectable melanoma who are BRAF wild-type and have been previously treated with ipilimumab, IL-2 or chemotherapy second line treatment with an anti-PD-1 monoclonal antibody is recommended.	**A**

Final recommendation 2.2.3.2	Grade
In patients with metastatic or unresectable melanoma who are BRAF wild-type and have been previously treated with an anti-PD-1 monoclonal antibody, there is currently no accepted evidence based standard of care. Treatment options such as chemotherapy should be considered following discussion at an MDT.	**D**

Good Practice Point
Given the lack of prospective data, enrollment in clinical trials is recommended for patients in this setting.

Clinical question 2.2.4

For adult patients with metastatic melanoma and who are BRAF mutated (BRAF mutation positive) and who have relapsed following first line therapy, what is the best second line therapy?

Evidence statement

A number of trials have addressed second line therapy in adult patients with metastatic melanoma who are BRAF mutation positive and who have relapsed following first line therapy (Robert et al., 2015d - KEYNOTE-006, Weber et al., 2015 - CheckMate-037, Larkin et al., 2015b, Flaherty et al., 2012a, Flaherty et al., 2012b, Kim et al., 2013).

The quality of the included evidence is inferior compared with the evidence for first line studies due to the heterogenous patient population and study designs.

Patients treated with BRAF MEK inhibitors

In patients that are BRAF mutation positive and who have received BRAF/MEK inhibitors in the first line setting, a number of phase III studies (Robert et al., 2015d - KEYNOTE-006, Weber et al., 2015 - CheckMate-037) and a pooled anaylsis (Larkin et al.,2015) support the treatment of these patients with an anti PD-1 monoclonal antibody.

The phase III RCT conducted by Robert (2015 - KEYNOTE-006) randomised patients with advanced melanoma to receive pembrolizumab (at a dose of 10 mg per kilogram of body weight) every 2 weeks or every 3 weeks or four doses of ipilimumab (at 3 mg per kilogram) every 3 weeks. The study included patients that had received one previous systemic therapy. Of those that had received previous systemic therapy, 17.9% in the pembrolizumab every 2 weeks arm (n=50), 16.2% in the pembrolizumab every 3 weeks arm (n=45), and 20.1% in the Ipilimumab arm (n=56), received a BRAF or MEK inhibitor or both. The results of this study are outlined in Table 5 below.

Weber et al., conducted a phase III RCT to assess the efficacy and safety of nivolumab compared with investigator's choice of chemotherapy (ICC) as a second-line or later-line treatment in patients with advanced melanoma. The study included patients with metastatic melanoma who were $BRAFV^{600}$ mutation-positive and previously treated with ipilimumab and a BRAF inhibitor (Weber et al., 2015 - CheckMate-037). The results of this study are outlined in Table 5 below.

Larkin et al., (2015b) carried a retrospective pooled analysis to evaluate the efficacy and safety of nivolumab in patients with wild-type BRAF (n=334) and mutant BRAF (n=106) metastatic melanoma. The study included a phase III study (Weber et al., 2015 - CheckMate-037)and three phase I studies (Topalian et al., 2014, NCT01621490, Wolchok et al., 2013). The study population was heavily pre-treated, with about 75% of the patients having received more than 2 prior therapies for advanced melanoma, of these the most common prior treatment regimen was ipilimumab in 76.6% of patients. The objective response rates were 29.7% (95% CI, 19.7-41.5) for the 74 patients with BRAF mutations. A subgroup analysis of treatment effect on objective response rate (ORR) across patient subgroups showed that the ORR in patients previously treated with ipilimumab was 25.0 (95% CI 12.1-42.22) in BRAF mutation positive patients. However, the number of patients evaluated in the subgroup analysis was very small (mutant BRAF, n=9).

Kim et al., (2013) conducted a phase II trial which suggests that if a patient has been treated with a BRAF or BRAF/MEK inhibitor they should not be treated with a BRAF or BRAF/MEK inhibitor in the second line setting.

The guideline development group (GDG) recommends that the evidence on combination therapy with nivolumab and ipilimumab will be re-evaluated when new evidence emerges.

Table 5: Studies on second line therapy in adult patient with metastatic melanoma

CheckMate-037 (Weber et al., 2015)	Nivolumab	ICC	
Objective response	31.7% (95% CI 23.5-40.8)	10.6% (95% CI 3.5-23.1)	
Median PFS	4.7 months (95% CI 2.3-6.5)	4.2 months (95% CI 2.1-6.3)	HR 0.85 (99.9% CI 0.32-2.05)
6 month PFS	48% (95% CI 38-65)	34% (95% CI 18-51)	

KEYNOTE-006 (Robert et al., 2015d)	Pembrolizumab		Ipilimumab	(PEM vs IPI)
	2 wk	3 wk		
Median OS	NR	NR	NR	
est. OS @ 12 mths	74.1%	68.4%	58.2%	p<0.001
Median PFS	5.5 mths (95% CI, 3.4 to 6.9)	4.1 mths (95% CI, 2.9 to 6.9)	2.8 mths (95% CI, 2.8 to 2.9)	
est. PFS @ 6 mths	47.3%	46.4%	26.5%	p<0.001

KEYNOTE-006 ((Schachter, 2016)– ASCO abstract)	Pembrolizumab		Ipilimumab	(PEM vs IPI)
	2 wk	3 wk		
Median OS	NR	NR	16 mths	
est. OS @ 2 years	55.1%	55.3%	43%	p=0.0008
HR (versus ipilimumab)	0.68 (95% CI, 0.53-0.87)	0.68 (95% CI, 0.53-0.86)		
Median PFS	5.6 mths	4.1 mths	2.8	
est. PFS @ 2 years	31.2%	27.8%	13.5%	p<0.0001
HR (versus ipilimumab)	0.61 (95% CI, 0.50-0.75)	0.61 (95% CI, 0.50-0.75)	-	

BRAF/ MEK naive patients

A phase II study (Flaherty et al., 2012a)supports the use of BRAF/MEK inhibitor as second line treatment in patients who are BRAF mutation positive and who have received therapy other than BRAF or BRAF/MEK inhibitiors in the first line setting. The GDG support the use of BRAF/MEK inhibitors in this setting.

The GDG support the use of BRAF inhibitor monotherapy when the combination of BRAF and MEK inhibitors is not available.

Final recommendation 2.2.4.1	Grade
In patients with metastatic or unresectable melanoma who are BRAF mutation positive and who have received BRAF or BRAF/MEK* inhibitors as first line therapy, treatment with an anti PD-1 (pembrolizumab or nivolumab*) is the recommended second line treatment.	**A**

Final recommendation 2.2.4.2	Grade
In patients with metastatic or unresectable melanoma who are BRAF mutation positive and have not received BRAF or BRAF/MEK* inhibitors as first line therapy, treatment with BRAF/MEK* inhibitors is the recommended second line treatment.	**C**

Final recommendation 2.2.4.3	Grade
In patients with metastatic or unresectable melanoma who are BRAF mutation positive and have not received BRAF or BRAF/MEK* inhibitors as first line therapy, if the combination of BRAF and MEK* inhibitors is not available, BRAF monotherapy is the recommended second line treatment.	**D**

Good Practice Point
Given the lack of prospective data, enrollment in clinical trials is recommended for patients with BRAF mutation positive melanoma who have had prior therapy with a BRAF/MEK* inhibitor and immunotherapy.

***Explanatory note:** Nivolumab and a number of MEK inhibitors are licensed for these indications in the ROI and are currently being reviewed by the HSE under the pricing and reimbursement framework agreed by the DOH with the pharmaceutical industry**.**

Appendix I Members of the Rapid Review Group

Medical Oncologists

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Appendix II Clinical questions in PICO format

Clinical question 2.1.1 For adult patients with metastatic melanoma and who are BRAF wild-type (BRAF mutation negative), what systemic anticancer therapy (SACT) improves overall survival?	
Population:	Adult patients with advanced (unresectable or metastatic) melanoma that is BRAF wild-type (BRAF mutation negative)
Intervention:	Treatment with systemic anticancer therapy such as monoclonal antibody targeting CTLA-4 e.g. ipilimumab, checkpoint inhibitors e.g. nivolumab or humanised, anti-programmed cell death 1 (PD-1) monoclonal IgG4 antibody e.g. pembrolizumab, cytotoxic chemotherapy, interleukin or any combination of the above.
Comparison:	None
Outcome:	PFS or Overall survival, (1month, 3 month, 6 month, 1year)
Clinical question 2.1.2 For adult patients with metastatic melanoma and who are BRAF mutated (BRAF mutation positive), what systemic anticancer therapy (SACT) improves overall survival?	
Population:	Adult patients with advanced (unresectable or metastatic) melanoma that is BRAF mutated (BRAF mutation positive)
Intervention:	Treatment with systemic anticancer therapy such as BRAF inhibitors e.g. vemurafenib, dabrafenib, trametinib, monoclonal antibody targeting CTLA-4 e.g. ipilimumab, checkpoint inhibitors e.g. nivolumab or humanised, anti-programmed cell death 1 (PD-1) monoclonal IgG4 antibody e.g. pembrolizumab, cytotoxic chemotherapy, interleukin or any combination of the above.
Comparison:	None
Outcome:	PFS or Overall survival, (1month, 3 month, 6 month, 1year)
Clinical question 2.1.3 For adult patients with metastatic melanoma and who are BRAF wild-type (BRAF mutation negative) and who have relapsed following first line therapy, what is the best second line therapy?	
Population:	Adult patients with advanced (unresectable or metastatic) melanoma that is BRAF wild-type (BRAF mutation negative) who have had previous therapy
Intervention:	Treatment with systemic anticancer therapy such as monoclonal antibody targeting CTLA-4 e.g. ipilimumab, checkpoint inhibitors e.g. nivolumab or humanised, anti-programmed cell death 1 (PD-1) monoclonal IgG4 antibody e.g. pembrolizumab, cytotoxic chemotherapy, interleukin or any combination of the above.
Comparison:	None
Outcome:	PFS or Overall survival, (1month, 3 month, 6 month, 1year)

Clinical question 2.1.4 For adult patients with metastatic melanoma and who are BRAF mutated (BRAF mutation positive) and who have relapsed following first line therapy, what is the best second line therapy?	
Population:	Adult patients with advanced (unresectable or metastatic) melanoma that is BRAF mutated (BRAF mutation positive) who have had previous therapy
Intervention:	Treatment with systemic anticancer therapy such as second line BRAF inhibitors or immnotherapy e.g. vemurafenib, dabrafenib, trametinib, monoclonal antibody targeting CTLA-4 e.g. ipilimumab,
Comparison:	Checkpoint inhibitors e.g. nivolumab or humanised, anti-programmed cell death 1 (PD-1) monoclonal IgG4 antibody e.g. pembrolizumab, cytotoxic chemotherapy, interleukin or any combination of the above.
Outcome:	PFS or Overall survival, (1month, 3 month, 6 month, 1year)

Appendix III Levels of Evidence & Grading Systems

Table 6 Levels of Evidence for interventional studies (SIGN grading system 1999-2012)

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias.
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
3	Non-analytic studies (e.g. case reports, case series).
4	Expert opinion.

Table 7 Grades of recommendations for interventional studies (SIGN grading system 1999-2012)

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+.
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Note: the grade of recommendation does not necessarily reflect the clinical importance of the recommendation.

Good practice points

Recommended best practice based on the clinical experience of the GDG.

Appendix IV Abbreviations

AGREE	Appraisal of Guidelines for Research and Evaluation II
CUH	Cork University Hospital
DOH	Department of Health
EBP	Evidence Based Practice
GDG	Guideline Development Group
HR	Hazard Ratio
HSE	Health Service Executive
HRQoL	Health related Quality of Life
ICC	Investigator's choice of chemotherapy
MDT	Multidisciplinary Team
NCCP	National Cancer Control Programme
NCRI	National Cancer Registry Ireland
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression Free Survival
PICO	Population/patient; intervention; comparison/control; outcome
ROI	Republic of Ireland
RCT	Randomised Controlled Trial
SACT	Systemic Anticancer Therapy
SIGN	Scottish Intercollegiate Guideline Network
SVUH	St. Vincent's University Hospital
WUH	Waterford University Hospital

Appendix V Systematic Literature Review Protocol

The systematic literature review protocol used in the development of this evidence into practice rapid review are available upon request.

Appendix VI Literature search protocol

The search strategies used in the development of this evidence into practice rapid review are available upon request.

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