MODULE 4

MANAGEMENT AND FOLLOW UP OF MELANOMA PATIENTS ON SYSTEMIC TREATMENTS

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In partnership with Novartis

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*We would like to acknowledge the contributions of **Ms Sarah Lane** and **Ms Megan Trewhella** who contributed to the module development, but no longer work in their previous capacity as a melanoma nurse consultant*

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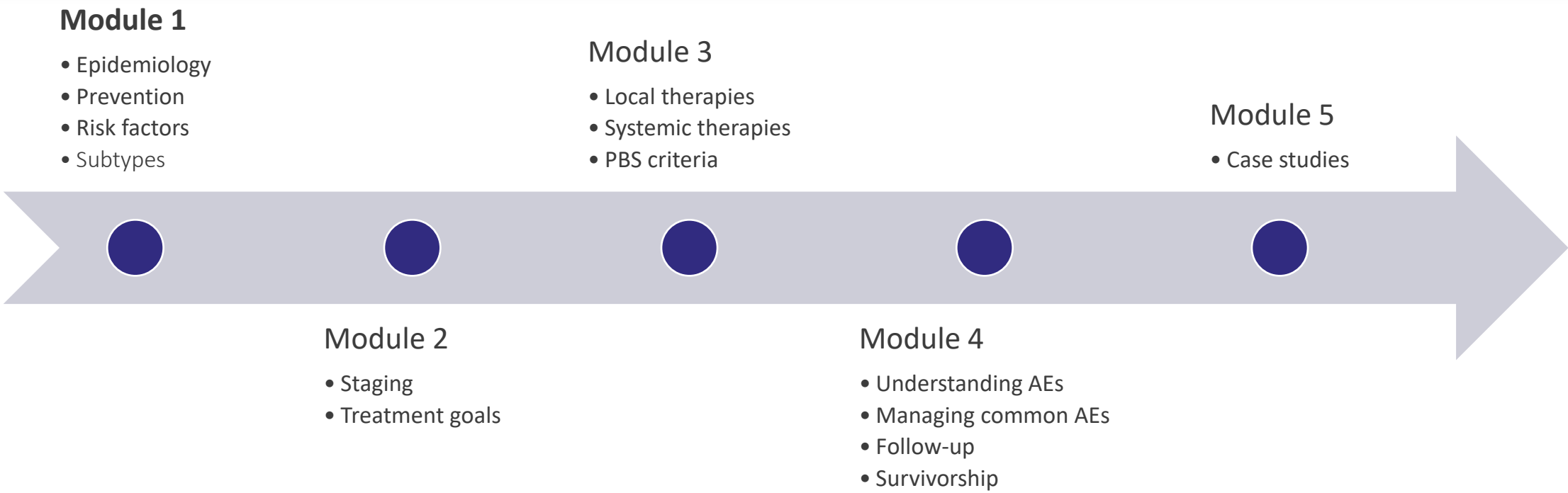
COURSE OVERVIEW



- To help you understand more about the practicality of treating melanoma patients, **Module 4** will look at understand the AEs of melanoma treatment options, the importance of patient education, understanding health literacy and informed decision making, and survivorship

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LEARNING OBJECTIVES

Having covered module 3 on melanoma treatment options, this module will focus primarily on how you can:

- Provide patient education on side effects management tailored to the patient's level of understanding (health literacy)
- Identify and manage side effects associated with targeted agents and immunotherapy
- Provide appropriate care following treatment with targeted agents and immunotherapy
- Understand the key aspects of survivorship

TARGETED THERAPIES AND IMMUNOTHERAPY FOR THE ADJUVANT TREATMENT OF RESECTABLE STAGE IIIB/C/D MELANOMA – A RECAP[1]

Patients with resected stage IIIB/C/D melanoma should be considered for adjuvant systemic therapy

Enrolment into clinical trials is encouraged where possible

For patients with a *BRAF V600* mutant melanoma, **targeted therapy** (combination BRAF and MEK inhibitors)

OR

Adjuvant **immunotherapy** (single agent anti-PD-1) can be administered

For patients without a *BRAF* mutation, adjuvant **immunotherapy** should be used

Adjuvant therapy is given for up to a year

Note: Adjuvant systemic therapy is not recommended for patients with stage IIIA melanoma.

1. Cancer Council Victoria and Department of Health Victoria 2021, Optimal care pathway for people with melanoma, 2nd edn, Cancer Council Victoria, Melbourne.

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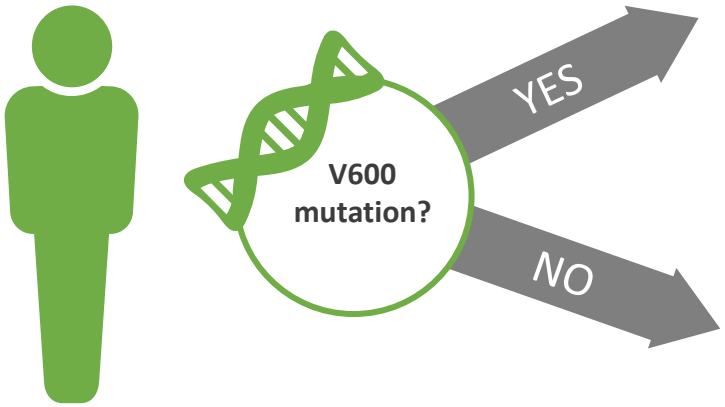
TARGETED THERAPIES AND IMMUNOTHERAPY FOR THE TREATMENT OF UNRESECTABLE STAGE III AND STAGE IV MELANOMA: A RECAP[1]

All patients with unresectable stage III or stage IV melanoma should be considered for systemic therapy



Enrolment into clinical trials is encouraged where possible

- Patients with BRAF V600 mutant metastatic melanoma are good candidates for **targeted therapy** i.e. combination therapy with a BRAF and a MEK inhibitor
- Treatment with targeted therapy should continue until the development of disease progression or unacceptable toxicity

- **Immunotherapy**, with either anti-PD-1 agents (pembrolizumab or nivolumab) alone or nivolumab in combination with the anti-CTLA-4 agent. Ipilimumab is also an option
- Immunotherapy should be continued until disease progression, unacceptable toxicity or completion of two years of treatment

1. Cancer Council Victoria and Department of Health Victoria 2021, Optimal care pathway for people with melanoma, 2nd edn, Cancer Council Victoria, Melbourne.

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IMPORTANT CONSIDERATIONS FOR PATIENTS WHEN DECIDING AND DISCUSSING CANCER TREATMENT

CANCER AND CANCER TREATMENT CAN HAVE A VERSATILE IMPACT ON A PATIENT'S LIFE, AND THE PEOPLE AROUND THEM

THE ROLE OF THE ONCOLOGY HEALTHCARE TEAM IS TO TREAT THE PATIENT'S DISEASE, AND MANAGE THE IMPACT THEIR DISEASE AND TREATMENT CAN HAVE ON THEIR LIFE GOALS

SEVERAL FACTORS IMPACT TREATMENT DECISIONS

- These can include[1]
  - Where the patient lives? Is there access to primary care, hospital, emergency department, allied health services?
  - Do they have a carer? What is the role of their carer in supporting the patient's health and condition?
  - Does the patient have any previous health conditions that may limit their treatment options (e.g. previous transplant, auto-immune conditions, allergies, co-morbidities, drug-drug interactions)?
  - What supportive care services can support them? What is the patient's level of health literacy and understanding on how to manage their disease?
- Many cancer treatments may cause fertility issues – this can be either reversible (fertility preserved after treatment is stopped) or life long[1]
  - Patients should be advised about and potentially referred for discussion about fertility preservation before starting treatment and about contraception before, during and after treatment
  - The potential for impaired fertility should be discussed and reinforced at different time points as appropriate throughout the diagnosis, treatment, surveillance and survivorship phases of care

Health literacy, patient education & survivorship will be discussed in detail in this module

1. Cancer Council Victoria and Department of Health Victoria 2021, Optimal care pathway for people with melanoma, 2nd edn, Cancer Council Victoria, Melbourne.

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HEALTH LITERACY DEFINED[1]

- Health literacy refers to how people understand information about health and health care, and how they apply that information to their lives, use it to make decisions and act on it
- Health literacy is important because it shapes people's health and the safety and quality of health care

Almost 60%

of adult Australians are estimated to have low individual health literacy. This means they may not be able to effectively exercise their choice or voice when making healthcare decisions.

1. Australian Commission on Safety and Quality in Health Care. Health literacy: Taking action to improve safety and quality. Sydney: ACSQHC, 2014.

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FACTORS THAT CAN INFLUENCE A PERSON'S INDIVIDUAL HEALTH LITERACY[1]

Factor	Impact
Age	Australians aged 20–44 years have been shown to have the highest level of individual health literacy; health literacy was lower for those aged 15–19 years and 45 years and older
Education	Education plays a strong role in shaping individual health literacy
Disability	People living with disabilities may be at particular risk of low individual health literacy for functional reasons such as poor vision or intellectual impairment
Culture and language	Language and culture affect the way that people make meaning out of their experiences, and influence their moral and emotional responses to physical and psychological conditions. This can lead to differing cultural expectations and understanding of health-related issues
Gender	Men and women have different focuses, motivations and roles when it comes to health; therefore, different strategies may be needed to address health literacy
Aboriginal and Torres Strait Islander peoples	While there is no national data on the individual health literacy of Aboriginal and Torres Strait Islander peoples, it is highly likely that Indigenous peoples may be at risk of lower individual health literacy

1. Australian Commission on Safety and Quality in Health Care. Health literacy: Taking action to improve safety and quality. Sydney: ACSQHC, 2014.

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CONSEQUENCES OF LOW HEALTH LITERACY[1]

- Low individual health literacy is associated with:
  - Higher use of health services
  - Knowledge of health and healthcare among consumers is low
  - Poorer health outcomes

People with low individual health literacy are estimated to be between 1.5 and 3 times more likely to experience an adverse outcome

1. Australian Commission on Safety and Quality in Health Care. Health literacy: Taking action to improve safety and quality. Sydney: ACSQHC, 2014.

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STRATEGIES TO ASSIST

- Plain language to communicate health information, instructions and choices

- Decision aids, which have been shown to lead to improvements in knowledge and understanding of screening, prevention and treatment options, and are often used to clarify the likelihood of risks and benefits of different care options

- Shared decision-making processes, which have been shown to be associated with favourable health outcomes

- Educative and recall strategies, including asking patients to recount the information given to them by their healthcare team to check understanding

1. Australian Commission on Safety and Quality in Health Care. Health literacy: Taking action to improve safety and quality. Sydney: ACSQHC, 2014.

HELPING PEOPLE MAKE DECISIONS ABOUT THEIR CARE WITH THE "ASK SHARE KNOW" PATIENT-COMMUNICATION MODEL[1]

This model is designed to encourage and empower people to engage with their healthcare team and make decisions about their health.

The model encourages people to communicate with their healthcare team by asking three questions:

- What are my options?
- What are the possible benefits and harms of those options?
- How likely are each of those benefits and harms to happen to me?

For more information, visit: **www.askshareknow.com.au**

1. Ask Share Know GP network. Available at: www.askshareknow.com.au. Accessed Decemeber 2021.

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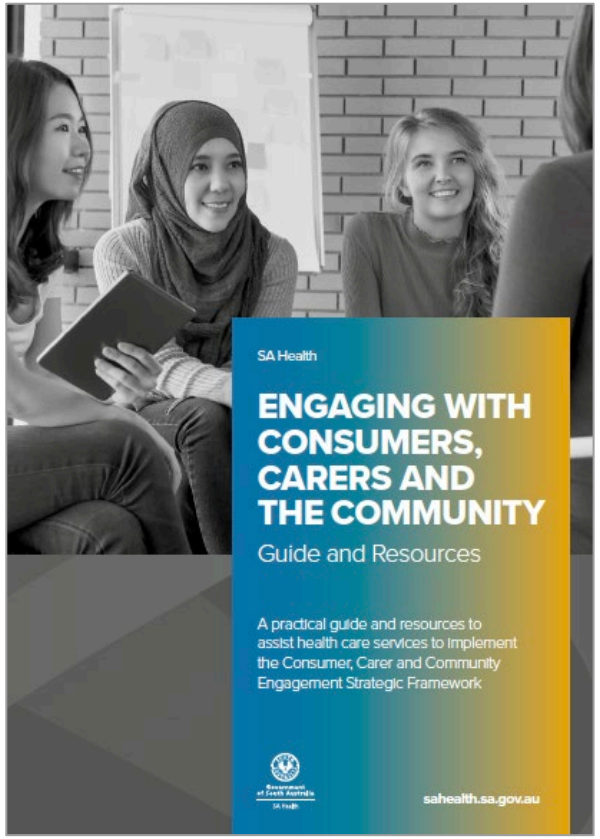
AN EXAMPLE OF AN AUSTRALIAN TOOLKIT FOR ENGAGING WITH PATIENTS[1]

South Australian Guide to Engaging with Consumers and the Community

Some of the tools included in the document that are relevant for addressing health literacy include:

- Tool 3: Tips for communicating clearly
- Tool 4: The teach-back method
- Tool 6: Encourage questions
- Tool 7: Assessing readability
- Tool 8: Writing health information.

https://www.sahealth.sa.gov.au/



1. SA Health. Engaging with consumers, carers and the community: guide and resources. Available at: https://www.sahealth.sa.gov.au/wps/wcm/connect/6dead9da-d1c2-4cbf-9568-74d2131df162/EngagingwithConsumersCarersandCommunityGuide%26Resources_Apr+2021+%281%29.pdf?MOD=AJPERES. Accessed December 2021.

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COMMUNICATION SKILLS TRAINING PROGRAMS AND RESOURCES CAN BE FOUND ON THE FOLLOWING WEBSITES:

- Australian Commission on Safety and Quality in Healthcare, Communicating for safety resource portal: www.c4sportal.safetyandquality.gov.au/home
- State and territory Cancer Councils: www.cancer.org.au/about-us/state-and-territory-councils/
- eviQ: https://education.eviq.org.au
- VITAL talk: www.vitaltalk.org

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MANAGING COMMON ADVERSE EVENTS

THE IMPORTANCE OF AE MANAGEMENT IN CANCER PATIENTS

The role of the oncology nurse can help extend the quality and quantity of time on treatment. This in turn may be linked to improved patient outcomes[1]

Irrespective of the therapy used, early identification and management of adverse events can lessen their severity, which has benefits for both the patient and health system.

This section will take you through the most common toxicities and their management and importantly key education points for patients so they can partner with you in their own treatment.

1. H Kerr *et al. Eur J Cancer Care* 2021;30:e13415

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AEs AND ADHERENCE TO ORAL TREATMENTS

ORAL TARGETED THERAPY: TOP 5 MOST COMMON AEs*

*Due to differences in study designs and populations, direct comparisons cannot be drawn.

Targeted therapy

MOST COMMON AEs PATIENTS TREATED WITH DABRAFENIB + TRAMETINIB (N = 559)[1]

AE	Any grade (%)	Grade 3 or 4 (%)
Pyrexia	58%	6%
Nausea	37%	1%
Diarrhoea	36%	1%
Fatigue	35%	2%
Chills	34%	1%

MOST COMMON AEs PATIENTS TREATED WITH ENCORAFENIB + BINIMETINIB (N = 192)[2]

AE	Any grade (%)	Grade 3 or 4 (%)
Nausea	43.8%	2.1%
Diarrhoea	38.5%	2.6%
Vomiting	31.8%	2.1%
Fatigue	29.7%	2.1%
Pyrexia	19.8%	3.6%

MOST COMMON AEs PATIENTS TREATED WITH VEMURAFENIB + COBIMETINIB (N = 248)[3]

AE	Any grade (%)	Grade 3 or 4 (%)
Diarrhoea	61%	7%
Nausea	44%	1%
Rash	42%	6%
Fatigue	38%	4%
Photosensitivity reaction	35%	3%

The combinations have different toxicity profiles, for example vemurafenib/cobimetinib is associated with a risk of photosensitivity and hepatotoxicity (most commonly a transaminitis), dabrafenib/trametinib commonly causes treatment related pyrexia syndrome, and encorafenib/binimetinib are associated with gastrointestinal toxicities[4]

Please see individual Product Information for additional safety information.

AE, adverse event.

1. Robert *et al. N Engl J Med* 2019;381:626-636 **2.** Ascierto *et al. Eur J Cancer* 2020;126:33-44 **3.** Ascierto *et al. Clin Cancer Res* 2021;27(19):5225-5235 **4.** Cancer Council Australia clinical guidelines. Targeted therapies for melanoma. Available at: https://wiki.cancer.org.au/australia/Guidelines:Targeted_therapies_NRAS_BRAF_mutant_melanoma. Accessed December 2021.

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SKIN AEs ASSOCIATED WITH TARGETED THERAPIES[1]

	Prevalence associated with drug (all grades)		
	Vemurafenib + cobimetinib	**Dabrafenib + trametinib**	**Encorafenib + binimetinib**
Rash	73%	23%	15%
Photosensitivity	48%	Not reported	5%
Plantar-palmar hyperkeratosis*	10%	5%	9%
Cutaneous SCC/ keratoacanthoma	6%	6%	2%
Basal cell carcinoma	Not reported	Not reported	1.1%

*Plantar-palmar hyperkeratosis and palmar-plantar erythrodysesthesia were both reported as "Hand-Foot Syndrome" in some of the studies.

- The prevalence of skin toxicities, including secondary cutaneous malignancies, is reduced with combined BRAF and MEK inhibition vs BRAF inhibition alone
- Skin toxicities may still be experienced with combination treatment; however, they are less frequent and less severe

1. eviQ. Skin toxicities associated with BRAF and MEK inhibitors. Available at: https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/hair-skin-and-nails/1426-skin-toxicities-associated-with-braf-and-mek. Accessed December 2021.

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IDENTIFYING AND MANAGING SKIN AEs ASSOCIATED WITH TARGETED THERAPY - RECOMMENDATIONS[1]

Assessment

Dermatological evaluation should be completed prior to initiation of therapy, monthly for the first 4-6 months of therapy, then every two months for the remainder of treatment.

It is recommended that patients continue to be monitored for 6 months following discontinuation of BRAF inhibitor.

Refer to your institutional guidelines to understand how skin AEs are managed in your clinic

Management

- Management of these skin toxicities involves pre-emptive education and advice, psychological support and appropriate symptomatic treatment
- If available, referral to a dermatologist throughout the duration of treatment is recommended
- Dose interruption and/or dose reduction of these drugs may be required
- Refer to the treatment protocol for specific guidance on dose modifications
- Any suspicious skin lesions should be excised, sent for pathology evaluation and treated as per standard of care.
- If severe hypersensitivity or dermatologic reaction develops, treatment should be permanently discontinued

1. eviQ. Skin toxicities associated with BRAF and MEK inhibitors. Available at: https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/hair-skin-and-nails/1426-skin-toxicities-associated-with-braf-and-mek. Accessed December 2021.

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PATIENT EDUCATION IS AN IMPORTANT PART OF MANAGING SKIN TOXICITIES ASSOCIATED WITH BRAF INHIBITORS[1]

Educate patient:

- On the likelihood of AEs and develop management plans
- On how to examine their skin for any changes
- To use soap free wash when bathing
- To gently pat the skin when washing and drying instead of rubbing
- To moisturise skin daily and if prescribed apply urea based creams to the feet regularly
- To keep nails short and avoid scratching
- To check their feet for the development of new calluses or worsening callus build-up
- To wear properly fitted shoes to alleviate plantar hyperkeratosis by reducing pressure on toes or soles of feet
- To report new skin abnormalities, including a new wart/mole, skin sore, non-healing lesions or changes to any moles.

Patients using vemurafenib require specific education on photosensitivity:

- to avoid or minimise exposure to sun, including through windows (e.g. when in the car or sitting by a window)
- to use sunscreen SPF30+ or greater (even on cloudy days)
- to wear protective clothing, such as long sleeves and wide-brimmed hats.

1. eviQ. Skin toxicities associated with BRAF and MEK inhibitors. Available at: https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/hair-skin-and-nails/1426-skin-toxicities-associated-with-braf-and-mek. Accessed December 2021.

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FEVER ASSOCIATED WITH TARGETED THERAPY (DABRAFENIB + TRAMETINIB)[1]

- Non-infectious febrile events are common with this treatment and can occur at any time
- The majority of events occur within the first 3 months and the median onset is 1 month
- Patient education about the prodrome of fever and drug cessation is an important step in managing fever

Educate patients:

- On how to recognise the early signs **and** symptoms of a fever
- To cease treatment upon symptom onset
- On symptom management
- To report symptoms to the treating team

When fever symptoms begin:

Pause your treatment

Contact your oncology team

Ask about what to do and when to **continue** treatment

1. eviQ. Fever and fever syndrome (BRAF MEK inhibitors only). Available at: https://www.eviq.org.au/side-effects-documents/1854-fever-and-fever-syndrome-braf-mek-inhibitors#history. Accessed December 2021.

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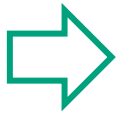
IDENTIFYING AND MANAGING FEVER ASSOCIATED WITH TARGETED THERAPY (DABRAFENIB + TRAMETINIB)[1,2]

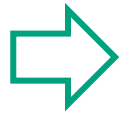
Symptoms and signs

- rigors
- dehydration
- hypotension
- dizziness
- weakness
- fatigue
- **OR** temperature ≥38°C.



Investigations/diagnosis

A septic work-up is **not** required for patients with uncomplicated pyrexia and without localising infective symptoms.



Management

Symptoms/Pyrexia

↓

Promptly interrupt both dabrafenib plus trametinib

↓

Symptom free ≥24 hours

↓

Resume dabrafenib plus trametinib at prior dose level

1. eviQ. Fever and fever syndrome (BRAF MEK inhibitors only). Available at: https://www.eviq.org.au/side-effects-documents/1854-fever-and-fever-syndrome-braf-mek-inhibitors#history. Accessed December 2021.
2. Atkinson V *et al.* Poster presented at the 2021 ASCO Annual Meeting, held virtually on 4–8 June 2021. Poster 9525.

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IDENTIFYING AND MANAGING FEVER ASSOCIATED WITH TARGETED THERAPY (DABRAFENIB + TRAMETINIB)[1,2]

Additional Management Tips

- Withhold treatment upon symptom onset. Early intervention results in prompt resolution of events, usually within 24 hours of dose interruption.
- Paracetamol and NSAIDs may alleviate symptoms during pyrexia.
- Recommencement of drug treatment can safely occur 24 hours after pyrexia resolution.
- In cases of recurrent or severe pyrexia, an intermittent dosing regimen, and/or corticosteroids (prednisolone 10 to 25 mg daily) may be useful.
- Unlike other toxicities such as fatigue, dose reduction does not appear to reduce the risk of pyrexia recurrence and is best avoided.

Evidence suggests the utilization of the pyrexia management algorithm leads to better outcomes for patients[2]

3.8% experienced a Grade 3/4 pyrexia event

4.3% required hospitalisation due to pyrexia

2.4% permanently discontinued treatment due to pyrexia

1. eviQ. Fever and fever syndrome (BRAF MEK inhibitors only). Available at: https://www.eviq.org.au/side-effects-documents/1854-fever-and-fever-syndrome-braf-mek-inhibitors#history. Accessed December 2021.
2. Atkinson V *et al.* Poster presented at the 2021 ASCO Annual Meeting, held virtually on 4–8 June 2021. Poster 9525.

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ADVERSE EVENTS AFFECT ADHERENCE[1]

- Prompt identification and management of adverse events are crucial for ensuring that patients are able to continue treatment
- However, patients may not report side effects out of fear that therapy could be discontinued. Furthermore, some may choose to skip doses because of the discomfort or pain of particular symptoms
- Patients should be reminded about when to call the clinic or healthcare professional regarding adverse events

Explaining that the clinical team shares the goals of continuing therapy and optimising outcomes as long as the treatment is working and the patient is tolerating it is important

1. Kottschade LA *et al. Clin J Oncol Nurs* 2017;21(4 Suppl):87-96.

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ENCOURAGING ADHERENCE IN YOUR PATIENTS

The number of pills, times per day and interruptions adds to the medication burden that patients' experience[1]

- Patients' knowledge, attitudes, beliefs, perceptions and expectations about the course of the disease and their ability to manage their illness and treatment regimen also affect adherence[2]
- Patients may perceive oral medication as less important or effective or as safer and more forgiving of dosage and administration errors as compared to IV therapy[2]
- Communicating key results from clinical trials, including risks, benefits and expected treatment outcomes, may motivate patients to make the dosing schedule, follow-up appointments and management of adverse events part of their everyday lives[2]

1. Given BA *et al. Asia Pac J Oncol Nurse* 2017;4:275–82. **2.** Kottschade LA *et al. Clin J Oncol Nurs* 2017;21(4 Suppl):87-96.

OPTIMISING ADHERENCE TO ORAL MEDICATIONS IN MELANOMA[1]

SCREENING PRIOR TO INITIATION OF BRAF/MEK THERAPY

General examination	Laboratory testing	Cardiac	Dermatological
• Patient medical history and current health status is critical in ongoing management • Check vitals and perform comprehensive history and physical examination to assess for pre-existing thromboembolic, cardiac, ocular, and other conditions per the manufacturer's instructions • Assess for previous toxicity (e.g., pulmonary, liver, ocular)	• Baseline measurements can help to identify and monitor abnormal test results (e.g. hepatitis) • Obtain complete blood count with differential and complete metabolic panel (with glucose for dabrafenib), as well as levels of alkaline phosphatase, ALT, AST, total and direct bilirubin, creatine kinase and gamma-glutamyltransferase	• MEK inhibitors may be associated with reduction in left ventricular ejection fraction • It is recommended to perform echocardiogram for any MEK-containing regimen and ECG for vemurafenib, especially for high-risk patients (e.g. history of cardiac failure)	• BRAF inhibitors may be associated with development of nonmelanoma skin cancers • Patient should under skin examination prior to treatment commencement • Refer to dermatology provider if patient has not had a comprehensive dermatological examination for 1 year or has a strong history of other non-melanoma skin cancer

1. Kottschade LA *et al. Clin J Oncol Nurs* 2017;21(4 Suppl):87-96.

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OPTIMISING ADHERENCE TO ORAL MEDICATIONS IN MELANOMA[1]

CONTINUED ASSESSMENT AND EVALUATION

Ongoing counselling	Laboratory testing	Cardiac	Dermatological
To ensure patient's understand their treatment dose, storage and identifying common side-effects, it is suggested nurses: • Query patients about how they are taking medications (e.g., storage, fasting, medication list changes). • Probe for side effects (checklist preferred) • Review when to call the clinic or healthcare professional, emphasising need for oncology team to be first contact for medical issues • Understand reasons for nonadherence, if any	• Repeat baseline laboratories at 1 month, and subsequent cycles (as clinically relevant) to monitor any abnormal laboratory changes	• Repeat echocardiography at 1 month and every 2–3 months while on treatment • If ECG is performed on vemurafenib, repeat at 14 days, monthly for 3 months, and then every 2–3 months while on treatment • Perform ECG more frequently if on medications affecting QTc or as needed if patient starts new agents that may have QTc prolongation	• Perform in-office skin examinations, as clinically relevant, to monitor for any skin-related adverse events common with BRAF/MEK inhibitors

1. Kottschade LA *et al. Clin J Oncol Nurs* 2017;21(4 Suppl):87-96.

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MANAGEMENT OF IMMUNOTHERAPY RELATED AEs

IMMUNOTHERAPY CAN CAUSE A UNIQUE SET OF SIDE EFFECTS, REFERRED TO AS IMMUNE-RELATED ADVERSE EVENTS (irAEs)[1]

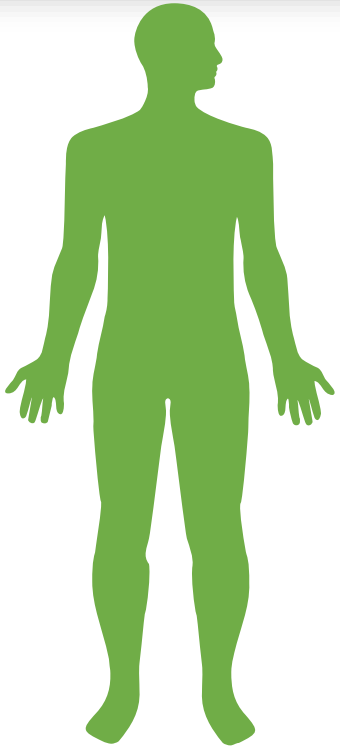
Cardiac toxicity

Endocrinopathies

Gastrointestinal toxicity

Haematological toxicity

Musculoskeletal toxicity



Neurological toxicity

Ocular toxicity

Pulmonary toxicity

Renal toxicity

Skin toxicity

These adverse events result in inflammation occurring in normal tissues and can affect any part of the body[2]

1. eviQ. Management of immune-related adverse events (irAEs). Available at: https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/immunological/1993-management-of-immune-related-adverse-events#cardiac-toxicity. Accessed December 2021. **2.** Cancer Council Victoria and Department of Health Victoria 2021, Optimal care pathway for people with melanoma, 2nd edn, Cancer Council Victoria, Melbourne.

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IMMUNOTHERAPY: TOP 5 MOST COMMON AES*

*Due to differences in study designs and populations, direct comparisons cannot be drawn.

Immunotherapy

MOST COMMON AEs PATIENTS TREATED WITH COMBINATION IPILIMUMAB/NIVOLUMAB (N = 313)[1]

AE	Any grade (%)	Grade ≥3 (%)
Diarrhoea	45%	10%
Fatigue	38%	4%
Pruritis	36%	2%
Rash	30%	3%
Nausea	28%	2%

MOST COMMON AEs PATIENTS TREATED WITH SINGLE AGENT ANTI-PD-1 (N = 509)

AE	Any grade (%)	Grade ≥3 (%)
Diarrhoea	34%	6%
Fatigue	28%	1%
Pruritis	36%	<1%
Rash	22%	2%
Nausea	16%	1%

Please see individual Product Information for additional safety information.

AE, adverse event.

1. Larkin *et al. N Engl J Med* 2019;381:1535-1546

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AEs ASSOCIATED WITH IMMUNOTHERAPIES IN PATIENTS WITH MELANOMA[1,2]

- Any patient on immunotherapy can develop an auto-immune toxicity directed of any organ – and this risk must be discussed with the patient
- Patients with preexisting autoimmune conditions are at risk of exacerbation of their autoimmune disease
- The common toxicities are fatigue, rash, itch, diarrhoea, thyroiditis and hepatitis. These can occur in 10-20% of patients

- The use of single agent anti-PD-1 and combination ipilimumab and nivolumab are associated with immune-related side effects
- Combination ipilimumab + nivolumab can induce grade 3/4 AEs in 59% of patients
- Although a rare toxicity, it is important to note hypophysitis (inflammation of the pituitary gland) with subsequent hypopituitarism may occur, especially in regimens containing anti-CTLA-4 (e.g. ipilimumab)
- Single agent anti-PD-1 (pembrolizumab or nivolumab monotherapy) can induce grade 3/4 AEs in 23% of patients

irAEs can escalate quickly – close monitoring of patients are required

AE, adverse event; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Please see individual Product Information for additional safety information.

1. Cancer Council Australia clinical guidelines. Summary of recommendations and practice points: Immunotherapy for melanoma. Available at: https://wiki.cancer.org.au/australia/Guidelines:Immunotherapy_for_melanoma_recommendations. Accessed December 2021. **2.** Larkin *et al. N Engl J Med* 2019;381:1535-1546

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MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS (irAEs)[1]

Skin toxicity

- May present as
  - Rash/Itch
  - Pruritis
  - Erythema/Blisters
  - Vitiligo
- Topical steroid and/or anti-histamine may be appropriate , in addition to referral for a complete physical examination of the skin
- In severe or unresolved cases, initiation of oral steroids may be needed

Hepatotoxicity

- May present as
  - Yellowing of skin/eye
  - Fatigue
  - Elevation in transaminases
- Generally asymptomatic and monitored through routine blood tests measuring serum transaminases and bilirubin
- Withholding treatment, followed by steroid initiation (if unresolved) may be appropriate

GI toxicity

- May present as
  - Diarrhea
  - Vomiting
  - Fatigue with weight loss
  - Abdominal pain
- Fluid and electrolyte supplementation may be given for symptom management, followed by withholding treatment steroid initiation (if unresolved)
- Referral to gastroenterology team for consideration of steroid-sparing agents

Refer to your institutional guidelines, and the eviQ immunotherapy assessment tool[2]

1. Haanen *et al. Ann Oncol* 2017;28(Suppl 4):i119–i142.

2. Immunotherapy patient assessment tool, 2021. Available at: https://www.eviq.org.au/clinical-resources/assessment-tools/3533-immunotherapy-patient-assessment-tool. Accessed December 2022

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MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS (irAEs)[1]

Endocrinopathy

Three common endocrinopathies include

1. Type 1 Diabetes Mellitus

- May present as
  - Frequent urination
  - Constant/extreme thirst
  - Numb or tingling hands or feet
  - Very hungry
- Blood glucose levels should be regularly monitored
- Referral to endocrinologist for life-long insulin substitution may be appropriate
- Steroids will likely negative influence diabetes control

2. Hypophysitis

- Presentation can be varied, and may include
  - Headaches
  - Unexplained fatigue
  - Hypothyroidism and/or hypocortolism
- Swollen or enlarged pituitary gland may be visible on brain MRI
- Referral to endocrinologist for life-long hormonal replacement treatment may be appropriate

3. Hyper/Hypothyriodism

- May present as
  - Hyper: High energy, weight loss, tachychardia
  - Hypo: Slowed metabolism, tiredness, weight gain, sensitive to cold
- Thyroid function tests should be conducted at baseline and every cycle
- Referral to endocrinologist for life-long hormonal replacement treatment may be appropriate

Refer to your institutional guidelines, and the eviQ immunotherapy assessment tool[2]

1. Haanen *et al. Ann Oncol* 2017;28(Suppl 4):i119–i142.

2. Immunotherapy patient assessment tool, 2021. Available at: https://www.eviq.org.au/clinical-resources/assessment-tools/3533-immunotherapy-patient-assessment-tool. Accessed December 2022

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MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS (irAEs)[1]

Optimal management of irAEs includes early recognition and appropriately-timed use of immunosuppressive agents based on the severity of the event

Why do patients get irAEs?

- As irAEs are induced by increased immune recognition and inflammation to other parts of the body, medicines to reduce immune activity are used to manage irAEs
- irAEs generally improves after introduction of immunosuppressive therapy – steroids are most commonly used

How does this impact treatment with immunotherapies?

- If multiple medium-grade irAEs occur concurrently on combination anti-CTLA-4 and anti-PD-1 therapy, permanent discontinuation of anti-CTLA-4 therapy may be considered
- For some toxicities that resolve quickly, re-commencement and/or re-challenge of immunotherapy may be considered, as per guidelines and after a multi-disciplinary decision

How are irAEs categorised[1,2]?

- irAEs are graded as per the CTCAE criteria, and refer to the severity of the AE from Grade 1-5. As a reminder, the general categories are defined below:
  - Grade 1 and 2: Mild or moderate; asymptomatic or mild symptoms; clinical or diagnostic observationally; may need local or minimally invasive intervention
  - Grade 3: Severe of medically significant, but not life-threatening; hospitalization may be required
  - Grade 4: Life-threatening consequences
  - Grade 5: Death related to AE

Click here for an example of grade 1-5 gastrointestinal irAE

CTCAE, Common Terminology Criteria for Adverse Events

1. Haanen *et al. Ann Oncol* 2017;28(Suppl 4):i119–i142.

2. Common Terminology Criteria for Adverse Events v5, 2017. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf. Accessed December 2022

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MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS (irAEs)[1]

Optimal management of irAEs includes early recognition and appropriately-timed use of immunosuppressive agents based on the severity of the event

- Steroid treatment (prednisolone and methylprednisolone) are common immunosuppressive agents to manage irAEs
  - Prednisolone and methylprednisolone dosing are not equivalent: 1 mg prednisolone = 0.8 mg methylprednisolone
- Patient education on steroid use is critical as steroids may cause unwanted side-effects, such as insomnia (sleep disturbance), weight gain (especially swelling in face), stomach irritation, increased blood sugar and an increased risk of infections
- Tips to manage these potential side-effects include taking the steroids in the morning (rather than at night), taking the steroids after food, and to be aware of hygiene practices to reduce the chance of infection
- Patients should be explained the concept of **weaning/tapering** steroid dose, and should NOT abruptly stop/interrupt treatment without consulting or discussing any concerns with their oncology healthcare team
- For patients who are receiving steroid treatment long-term and/or in high-doses, prophylactic trimethoprim/sulfamethoxazole may be appropriate to prevent the incidence of pneumocystis pneumonia

Patient education on steroid treatment is critical to avoid life-threatening side-effects
Patients should never abruptly stop steroid treatment

1. Haanen *et al. Ann Oncol* 2017;28(Suppl 4):i119–i142.

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ADDITIONAL INFORMATION ON MANAGING AES:

eviQ melanoma guidelines:

https://www.eviq.org.au/medical-oncology/melanoma

ESMO clinical practice guidelines: Management of toxicities from immunotherapy

https://www.esmo.org/guidelines/guidelines-by-topic/supportive-and-palliative-care/toxicities-from-immunotherapy

Individual Approved Product Information:

https://www.ebs.tga.gov.au

OPTIMISING CARE AFTER TREATMENT WITH TARGETED AGENTS AND IMMUNOTHERAPY

CARE AFTER INITIAL TREATMENT AND RECOVERY: CHECKLIST[1]

- ❑ Treatment and follow-up summary provided to the patient and/or carer and the patient's GP.
- ❑ Importance of skin self-examination and sun protection discussed with the patient and/or carer.
- ❑ Supportive care needs assessment completed and recorded, and referrals to allied health services actioned as required.
- ❑ Patient-reported outcome measures recorded.

1. Cancer Council Victoria and Department of Health Victoria 2021, Optimal care pathway for people with melanoma, 2nd edn, Cancer Council Victoria, Melbourne.

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CARE AFTER INITIAL TREATMENT AND RECOVERY[1]

Provide a treatment and follow-up summary to the patient, carer and GP outlining:

- the diagnosis, including tests performed and results
- melanoma characteristics, specifically the primary thickness and whether ulceration is present
- treatment received (types and date)
- current toxicities (severity, management and expected outcomes)
- interventions and treatment plans from other health professionals
- potential long-term and late effects of treatment and care of these
- supportive care services provided
- a follow-up schedule, including tests required and timing
- contact information for key healthcare providers who can offer support for lifestyle modification
- a process for rapid re-entry to medical services for suspected recurrence.

1. Cancer Council Victoria and Department of Health Victoria 2021, Optimal care pathway for people with melanoma, 2nd edn, Cancer Council Victoria, Melbourne.

FOLLOW UP AFTER INITIAL DEFINITIVE TREATMENT[1]

The majority of patients detect their own recurrence if they have received a thorough explanation of the signs and symptoms of recurrences and new primary melanomas

History and physical examination are the most effective methods for the detection of early, treatable melanoma recurrence

- Patients should have regular skin surveillance
- Ultrasound is most effective way to detect nodal recurrence
- FNA and core biopsy are accurate tests to confirm regional melanoma recurrence
- PET/CT is a useful test for the detection of melanoma recurrence during follow-up
- There are no data demonstrating superior survival outcomes as a result of routine imaging, even for patients at high risk of melanoma recurrence

CT, computed tomography; FNA, fine needle aspiration;; PET, positron emission tomography.

1. Cancer Council Australia clinical guidelines. Follow up after initial definitive treatment for each stage of melanoma. Available at: https://wiki.cancer.org.au/australia/Clinical_question:How_should_patients_at_each_stage_of_melanoma_be_followed_after_initial_definitive_treatment%3F. Accessed December 2021.

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SELF-EXAMINATION[1]

- Self-examination is essential for any new or changing skin lesion, cutaneous lump or persistent new symptom
- Metastatic disease will be detected most commonly by the patient presenting with symptoms and less commonly via routine follow-up

Highlight the importance of sun protection

Protect skin from the sun during sun protection times (when the ultraviolet levels are 3 or above) by using a combination of:

- long-sleeved clothing
- broad-brimmed hats
- broad-spectrum sunscreens with an SPF of 30 or higher
- sunglasses
- seeking out shade.

1. Cancer Council Victoria and Department of Health Victoria 2021, Optimal care pathway for people with melanoma, 2nd edn, Cancer Council Victoria, Melbourne.

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SURVEILLANCE AFTER CURATIVE TREATMENT FOR MELANOMA WILL VARY BUT MAY INCLUDE:[1]

Disease type	Suggested follow-up
Tumours <1 mm thick	Follow-up for 2 years unless the patient is at high risk for a second primary melanoma due to high naevus numbers, multiple dysplastic naevi or a history of melanoma in close relatives (patients should be seen 4–6 monthly for 2 years and then less frequently, according to risk factors, for an indefinite period)
Tumours >1 mm thick	Follow-up 3–4 monthly for the first 2 years, 6 monthly review to 5 years, and lifelong yearly review thereafter
Stage III disease	Follow-up 3–4 monthly for the first 2 years, 6 monthly for the next 2–3 years, and then as deemed clinically necessary

Intervals between routine visits are somewhat arbitrary. However, all studies stress that the more advanced the disease, the more frequent the visits need to be[2]

1. Cancer Council Victoria and Department of Health Victoria 2021, Optimal care pathway for people with melanoma, 2nd edn, Cancer Council Victoria, Melbourne. **2.** Cancer Council Australia clinical guidelines. Ideal settings, duration and frequency of follow-up for patients with melanoma. Available at: https://wiki.cancer.org.au/australia/Clinical_question:What_is_the_ideal_setting,_duration_and_frequency_of_follow-up_for_melanoma_patients%3F. Accessed December 2021.

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SURVIVORSHIP DEFINED[1]

The term ‘cancer survivor’ describes a person living with cancer, from the point of diagnosis until the end of life

Survivorship care in Australia has traditionally been provided to patients who have completed active treatment and are in the post-treatment phase

But there is now a shift to provide survivorship care and services from the point of diagnosis to improve cancer-related outcomes

1. Cancer Council Victoria and Department of Health Victoria 2021, Optimal care pathway for people with melanoma, 2nd edn, Cancer Council Victoria, Melbourne.

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SPECIFIC CHALLENGES AND NEEDS MAY ARISE FOR CANCER SURVIVORS[1]

- Upper and lower limb lymphoedema, which may require referral to a trained lymphoedema specialist
- Management of any ongoing toxicities after treatment cessation
- Financial and employment issues (such as loss of income and assistance with returning to work, and the cost of treatment, travel and accommodation)
- Appointing a substitute decision-maker and completing an advance care directive
- Legal issues such as completing a will

1. Cancer Council Victoria and Department of Health Victoria 2021, Optimal care pathway for people with melanoma, 2nd edn, Cancer Council Victoria, Melbourne.

SURVIVORSHIP CARE PLAN SHOULD COVER BUT IS NOT LIMITED TO:[1]

- What medical follow-up is required (surveillance for melanoma spread, recurrence or secondary and metachronous cancers, screening and assessment for medical and psychosocial effects)
- Model of post-treatment care, the health professional providing care and where it will be delivered
- Care plans from other health providers to manage the consequences of melanoma and melanoma treatment
- Wellbeing, primary and secondary prevention health recommendations that align with chronic disease management principles
- Rehabilitation recommendations
- Available support services
- A process for rapid re-entry to specialist medical services for suspected recurrence

Survivors generally need regular follow-up, often for 5 or more years after completion of melanoma treatment. Therefore, the survivorship care plan may need to be updated to reflect changes in the patient's clinical and psychosocial status and needs

1. Cancer Council Victoria and Department of Health Victoria 2021, Optimal care pathway for people with melanoma, 2nd edn, Cancer Council Victoria, Melbourne.

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TYPES OF SUPPORTIVE CARE THAT MAY BE REQUIRED[1]

Assistance for dealing with psychological and emotional distress while adjusting to the diagnosis; treatment phobias; existential concerns; stress; difficulties making treatment decisions; anxiety or depression or both; psychosexual issues such as potential loss of fertility and premature menopause; and interpersonal issues

Management of physical symptoms such as pain and fatigue

Malnutrition or undernutrition

Support for families or carers who are distressed with the patient's melanoma diagnosis

Support for families/relatives who may be distressed after learning of a genetically linked melanoma diagnosis

Specific spiritual needs that may benefit from the involvement of pastoral/spiritual care

1. Cancer Council Victoria and Department of Health Victoria 2021, Optimal care pathway for people with melanoma, 2nd edn, Cancer Council Victoria, Melbourne.

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TEMPLATES AND OTHER RESOURCES TO HELP WITH DEVELOPING TREATMENT SUMMARIES AND SURVIVORSHIP CARE PLANS[1]

- Australian Cancer Survivorship Centre
- Cancer Australia – Principles of Cancer Survivorship
- Cancer Council Australia and states and territories
- Clinical Oncology Society of Australia – Model of Survivorship Care
- eviQ – Cancer survivorship: introductory course
- MyCarePlan.org.au
- South Australian Cancer Service – Statewide Survivorship Framework resources
- American Society of Clinical Oncology – guidelines.
- Patient advocacy and support network: https://mscan.org.au/learning-hub/melanoma/recently-diagnosed-with-advanced-melanoma/

1. Cancer Council Victoria and Department of Health Victoria 2021, Optimal care pathway for people with melanoma, 2nd edn, Cancer Council Victoria, Melbourne.

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SURVIVORSHIP AND PALLIATIVE CARE[1]

"Survivorship and palliative care should be addressed for patients with recurrent melanoma or melanoma that has metastasised. Early referral to palliative care can improve quality of life and in some cases survival. Referral should be based on need, not prognosis."

Optimal care pathway for people with melanoma[1]

1. Cancer Council Victoria and Department of Health Victoria 2021, Optimal care pathway for people with melanoma, 2nd edn, Cancer Council Victoria, Melbourne.

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PALLIATIVE CARE RESOURCES

- Advance Care Planning Australia: www.advancecareplanning.org.au
- Care Search: www.caresearch.com.au/Caresearch/
- Dying to Talk: www.dyingtotalk.org.au
- The Palliative Care resource kit: www.health.gov.au/health-topics/palliative-care
- Palliative Care Australia (for patients and carers: www.palliativecare.org.au)

MODULE 4: SUMMARY

- Patients receiving targeted therapies or immunotherapy should be provided with education about possible side effects and what to do if they experience any of these[1]
- Almost 60% of Australian adults are estimated to have low individual health literacy highlighting the need to provide tailored patient education on side effects management based on the patient's own level of health literacy[2]
- Patient education and ongoing surveillance is important to maintain adherence to melanoma treatment, and to detect any recurrence/progression as early as possible[1]
- The majority of patients detect their own recurrence if they have received a thorough explanation of the signs and symptoms of recurrences and new primary melanomas[3]
- Survivorship care should start from diagnosis and continue throughout the post-treatment phase as needed[1]

1. Cancer Council Victoria and Department of Health Victoria 2021, Optimal care pathway for people with melanoma, 2nd edn, Cancer Council Victoria, Melbourne. **2.** Australian Commission on Safety and Quality in Health Care. Health literacy: Taking action to improve safety and quality. Sydney: ACSQHC, 2014. **3.** Cancer Council Australia clinical guidelines. Follow up after initial definitive treatment for each stage of melanoma. Available at: https://wiki.cancer.org.au/australia/Clinical_question:How_should_patients_at_each_stage_of_melanoma_be_followed_after_initial_definitive_treatment%3F. Accessed December 2021.

PRACTICE YOUR PRACTICE

- Observe treatment discussions (initiation, and/or ongoing counselling) between your colleagues and patients of varying backgrounds
  - What questions do patients commonly ask? Make a note of what are the motivating factors for each patient you observe
  - What supportive care needs are discussed? Think about what resources you might provide
- Ask your colleagues working in melanoma how patients are supported with adverse events in your institution
  - If able, attend a clinic consult with the patient
  - Who do patients they contact for advice? How do they get in touch?
  - What happens out of hours?
  - What are the most common adverse events that are seen in your institution in? How does this differ between immunotherapy and targeted therapies?
- Review your local institutional guidelines on managing adverse events for melanoma patients
  - Discuss with an oncologist how they determine when steroids, and how patients are counselled on this
  - Review and be familiar with the management of irAEs based on site (e.g. skin, gastrointestinal, hepatic etc.)

FOR **PRESCRIBING INFORMATION**, PLEASE CLICK:

Dabrafenib | Trametinib | Vemurafenib | Cobimetinib | Encorafenib
Binimetinib | Nivolumab | Ipilimumab | Pembrolizumab

FOR **PBS INFORMATION,** PLEASE CLICK:

Dabrafenib | Trametinib | Vemurafenib | Cobimetinib | Encorafenib
Binimetinib | Nivolumab | Ipilimumab | Pembrolizumab

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