MODULE 3

SYSTEMIC AND LOCAL TREATMENTS FOR MELANOMA

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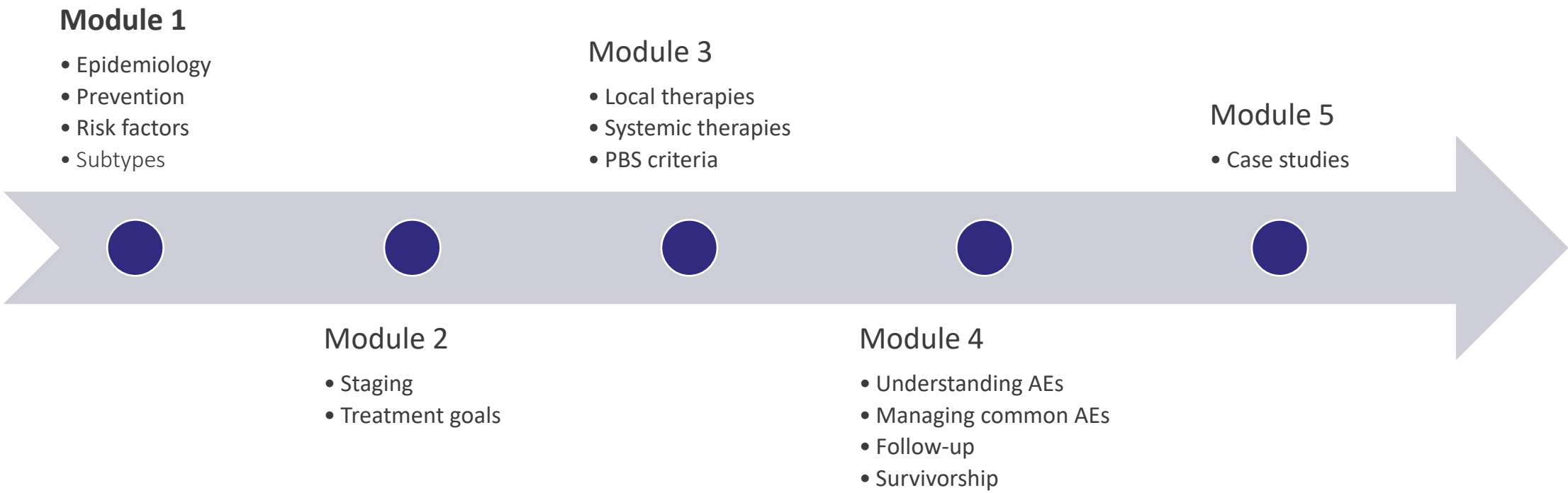
*We would like to acknowledge the contributions of **Ms Sarah Lane** and **Ms Megan Trewhella** who contributed to the module development, but no longer work in their previous capacity as a melanoma nurse consultant*

COURSE OVERVIEW



- To help you understand more about the treatment options for melanoma patients, **Module 3** will look local and systemic therapy options approved for melanoma patients, as well as Pharmaceutical Benefits Scheme (PBS) restrictions

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LEARNING OBJECTIVES

Having covered epidemiology and pathophysiology of melanoma in modules 1&2, this module will help you:

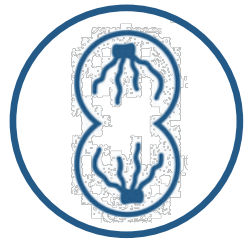
- To understand the role of local therapies in melanoma
- To understand the different systemic treatments available for melanoma, their current indications and PBS reimbursement criteria
- To appreciate the differing treatment considerations across melanoma stages of disease
- To articulate clearly the mode of action of each treatment class

PBS, Pharmaceutical Benefits Scheme.

INTRODUCTION TO TYPES OF TREATMENT FOR MELANOMA[1]







Surgery	Radiotherapy	Targeted therapy	Immunotherapy	Chemotherapy
Local therapy		Systemic therapy		
Stage I-IV	Stage III-IV	Stage III-IV		Seldom used

1. National Institutes of Health. Melanoma Treatment (PDQ®)-Patient Version. Available at: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq. Accessed December 2021.

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LOCAL TREATMENT

Type of treatment	Description
Surgery 	• Surgery to remove the tumour is the **primary treatment** of all stages of melanoma • Patients diagnosed with stage I/II/IIIa melanoma can usually be cured with surgical resection • Surgery to resect cancer that has spread to the lymph nodes, lung, GI tract or brain may occasionally be performed to improve QOL by controlling symptoms (palliative resection)
Radiation therapy 	• Radiation therapy uses high-energy x-rays or other types of radiation to kill cancer cells or stop them from growing • External radiation therapy is used to treat melanoma and may also be used as palliative therapy to relieve symptoms and improve QOL

National Institutes of Health. Melanoma Treatment (PDQ®)-Patient Version. Available at: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq. Accessed December 2021.

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SURGERY – CURATIVE

- Surgery is the only treatment most patients with melanoma will ever need
- Patients confirmed to have a melanoma should undergo a wide local excision (WLE) to take additional tissue from around the site of the tumour to reduce the risk of local recurrence.
  - WLE should be done even if the tumour was previously completely excised with an excisional biopsy
- The tissue taken beyond the site of the primary tumour must be found to be clear of melanoma cells. This tissue is called the surgical margin.
  - The recommended margin is usually between 5mm and 10mm, depending on the type, thickness and site of the melanoma. For thicker tumours, a wider margin of up to 20mm may be advised

Cancer Council Australia. Surgery for melanoma. Available at https://www.cancercouncil.com.au/melanoma/treatment/surgery/. Accessed on September 2022

SURGERY – PALLIATIVE

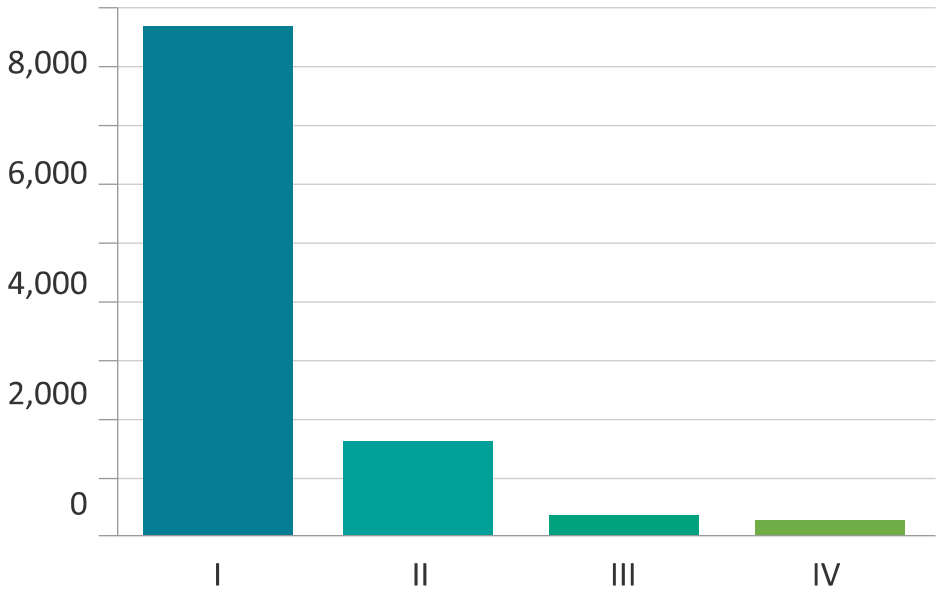
- Patients with metastatic disease may develop complications related to the tumour putting pressure on adjacent organs e.g. chronic cough/shortness of breath related to a metastasis in or near the lung
- Surgery can be useful in this setting for local control of advanced soft tissue malignancy where there is a limited number of lesions with the aim of durable symptom relief and improved quality of life
- These procedures may positively impact patients regardless of primary tumour type or tumour extent, but careful patient selection is important to ensure the benefits outweigh the risks

Blakely, A., McPhillips, J., & Miner, T. Annals Of Palliative Medicine, 2015;4(2):48-53

THE EVOLVING MELANOMA TREATMENT LANDSCAPE

- As discussed in module 1, fortunately most patients are diagnosed with Stage I/II melanoma (78%/14.1%)[1]
  - Patients diagnosed with stage I/II/IIIa melanoma can usually be cured with local treatments, such as surgery
- Those diagnosed with stage IIIB, C, D and IV melanoma should be offered **systemic treatment**[1,2]
- Clinical trials should be considered for those with Stages ll to IV

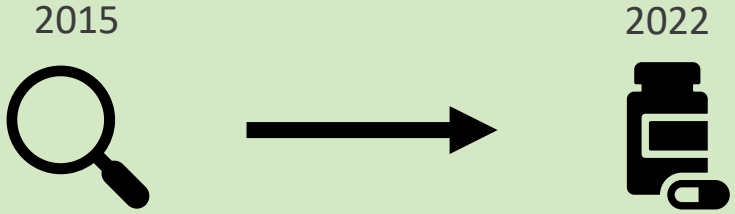
Number of cases, by stage at diagnosis[1]



Adapted from AIHW 2021.[1]

- Systemic treatment options for patients with advanced Stage III/IV melanoma have increased over the past ~8 years to include targeted therapies and immunotherapy.
- These have significantly extended survival[2]

Resected advanced Stage III/IV melanoma



1. Australian Institute of Health and Welfare 2021. updated 7/06/2021 v5.0 Canberra: AIHW Available from: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-incidence-and-survival-by-stage-data-visualisation. Accessed October 2021 **2.** Kwak M *et al. J Surg Oncol* 2019;119:222–31.

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SYSTEMIC TREATMENT FOR MELANOMA[1]

Targeted therapy:

- Works by interfering with specific proteins in the cell involved in growth, progression and spread of cancer
- These are mainly small molecule drugs
- Usually administered orally

Immunotherapy:

- Works by enabling the immune system to attack cancer cells
- These include monoclonal antibodies, such as checkpoint inhibitors
- Usually administered by IV infusion

Melanoma therapies have complex mechanisms of action. It can be challenging to explain these to patients in terms that they understand

1. National Institutes of Health. Melanoma Treatment (PDQ®) Available at: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq. Accessed October 2021.

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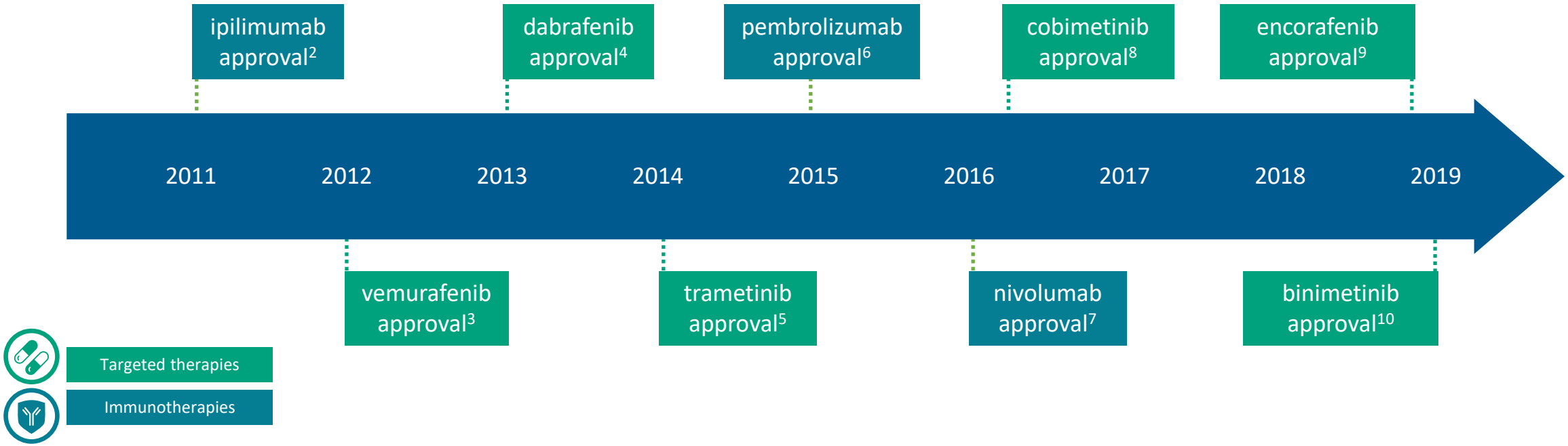
TARGETED THERAPIES AND IMMUNOTHERAPIES HAVE BEEN DEVELOPED TO ADDRESS THE LIMITATIONS OF CONVENTIONAL CHEMOTHERAPY[1]

- The advanced melanoma treatment landscape has been rapidly evolving with several new drug approvals
- Since 2011, nine new agents have been approved for the treatment of melanoma:



1. Vanneman M, Dranoff G. *Nat Rev Cancer* 2014;12:237–51. **2.** YERVOY® (IPILIMUMAB) Product Information, 2021. **3.** Zelboraf® (vemurafenib) Product Information, 2020. **4.** TAFINLAR® (dabrafenib) Product Information, 2021. **5.** MEKINIST® (trametinib) Product Information. **6.** KEYTRUDA® (pembrolizumab (rch)) Product Information, 2021. **7.** OPDIVO® (NIVOLUMAB) Product Information, 2021. **8.** Cotellic® (cobimetinib fumarate) Product Information, 2021. **9.** BRAFTOVI® (encorafenib) Product Information, 2019. **10.** MEKTOVI (binimetinib) Product Information, 2019.

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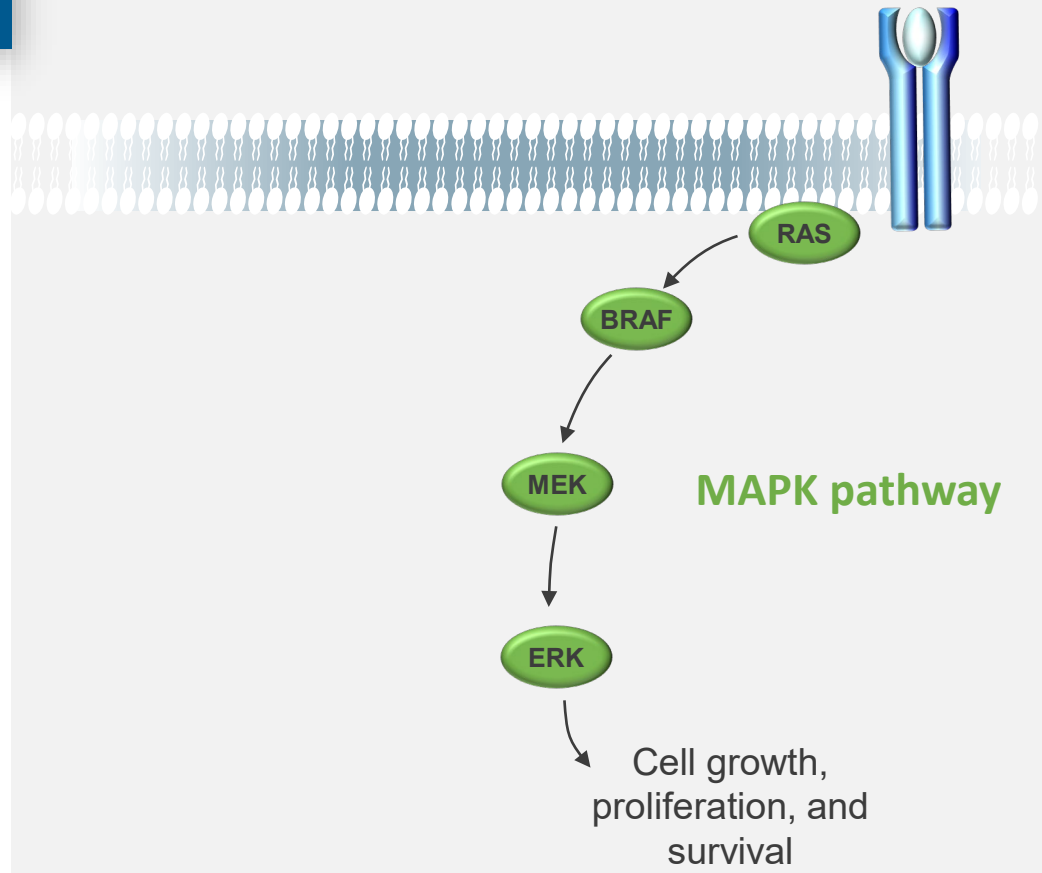
TARGETED THERAPY IS HIGHLY SPECIFIC[1]

- Targeted therapy uses small molecules to disrupt protein signaling pathways that specific cancer cells are dependent on[1]
- As a result, they usually cause less harm to non-cancerous cells than chemotherapy or radiation therapy[1]
- Mutations in the BRAF gene occur in nearly half of all melanoma cases. This has led to the development of highly selective small-molecule inhibitors targeting BRAF and other stages in the MAPK cell signaling pathway[2]



Adapted from The Cancer Genome Atlas Network, 2015.[2]

1. National Institutes of Health. Melanoma Treatment (PDQ®) Available at: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq. Accessed December 2021. **2.** The Cancer Genome Atlas Network. *Cell.* 2015;161(7):1681-1696

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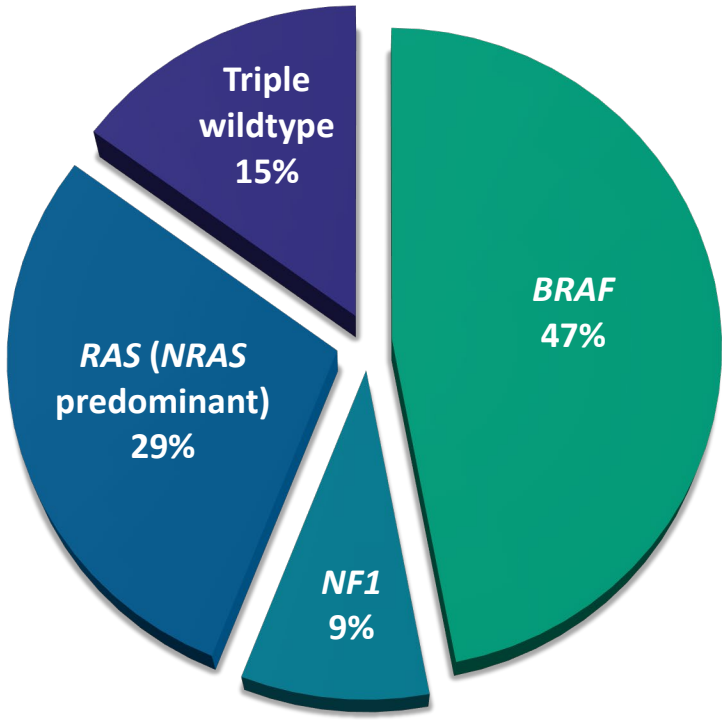
BRAF SUBSTITUTIONS ARE THE MOST COMMON DRIVER MUTATIONS IN METASTATIC MELANOMA[1]



Adapted from The Cancer Genome Atlas Network, 2015.[1]

- *As* the most commonly mutated gene in cutaneous melanoma, about one in two patients will have a mutation in *BRAF*
- *BRAF* mutations are more common in:[2]
  - Tumours from patients who are younger at diagnosis
  - Tumours with a truncal location
  - Superficial spreading and nodular histopathological subtypes
  - Tumours containing mitoses
  - Patients with a single or occult primary melanoma
- *BRAF* mutation is rare in melanomas arising from the mucosa or acral surfaces (i.e. palms of the hands, soles of the feet, or under the fingernails or toenails), or chronic sun-damaged skin, such as that typically seen in the head and neck[2]
- *BRAF* mutations are not found in ocular melanoma[3]

Patients with Stage IV melanoma (or Stage III melanoma if clinically appropriate) must have documentation of the presence or absence of activating *V600 E or K BRAF* mutations prior to commencing systemic treatment due to the availability of targeted treatments for patients with these mutations[4,5]

1. The Cancer Genome Atlas Network. *Cell.* 2015;161(7):1681-1696. **2.** Jang S, Atkins MB. *Lancet Oncol.* 2013;14(2):e60-e69. **3.** National Cancer Institute. Skin cancer treatment (PDQ®)- health professional version. Available at: https://www.cancer.gov/types/skin/hp/skin-treatment-pdq. Accessed December 2021. **4.** Cancer Council Australia. Cancer Guidelines Wiki. What investigations should be performed when in-transit and/or regional node disease (stage III melanoma) is diagnosed? Available from: https://wiki.cancer.org.au/australia/Clinical_question:What_investigations_should_be_performed_when_in_transit_and/or_regional_node_disease_(Stage_III_melanoma)_is_diagnosed%3F. Accessed March 2022. **5.** Cancer Council Australia. Cancer Guidelines Wiki. What investigations should be performed when stage IV melanoma is diagnosed? Available from: https://wiki.cancer.org.au/australia/Clinical_question:What_investigations_should_be_performed_when_Stage_IV_melanoma_is_diagno sed%3F. Accessed March 2022.

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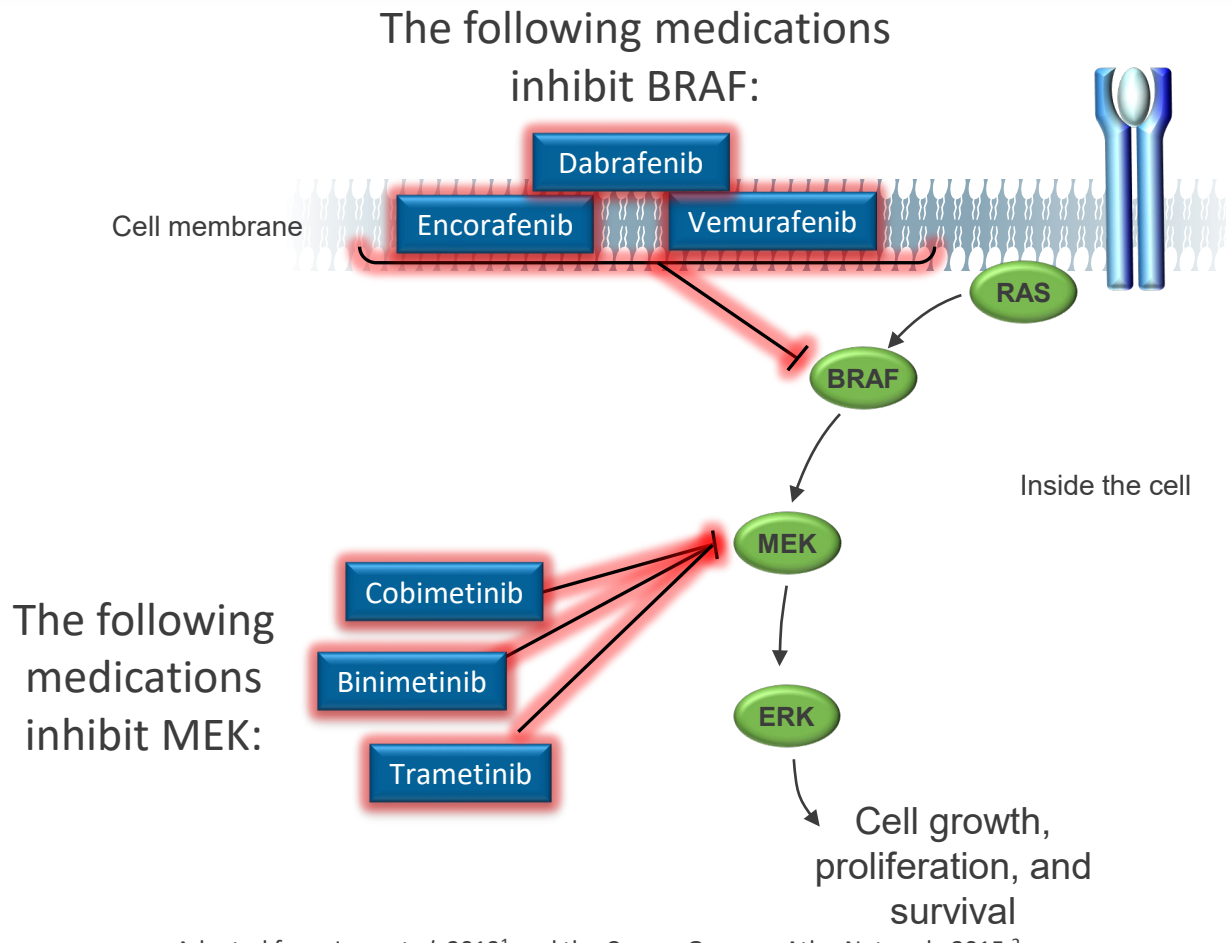
MELANOMA THERAPIES TARGET *BRAF* AND *MEK* TO INHIBIT THE EFFECTS OF MUTATED *BRAF*[1]

- Driver mutations in BRAF cause increased activation of BRAF and the downstream signaling of the MAPK pathway, leading to cancer cell growth, proliferation, and survival[1]
- Numerous medications inhibiting BRAF (BRAFi) are approved for melanoma treatment: dabrafenib, encorafenib and vemurafenib[2]
- These are used in combination with medications inhibiting MEK (MEKi): trametinib, binimetinib and cobimetinib[2]



Adapted from Jang *et al,* 2013[1] and the Cancer Genome Atlas Network, 2015.[2]

1. Jang S, Atkins MB. *Lancet Oncol.* 2013;14(2):e60-e69. **2.** National Institutes of Health. Melanoma Treatment (PDQ®). Available at: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq. Accessed October 2021.

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COMBINATION BRAF AND MEK INHIBITOR THERAPY

- Simultaneous targeting of **both** BRAF + MEK, combination therapy has led to greater magnitude and duration of response in these patients and may reduce the incidence of some side effects[3-5]

Combinations of BRAF inhibitors and MEK inhibitors used to treat melanoma include:

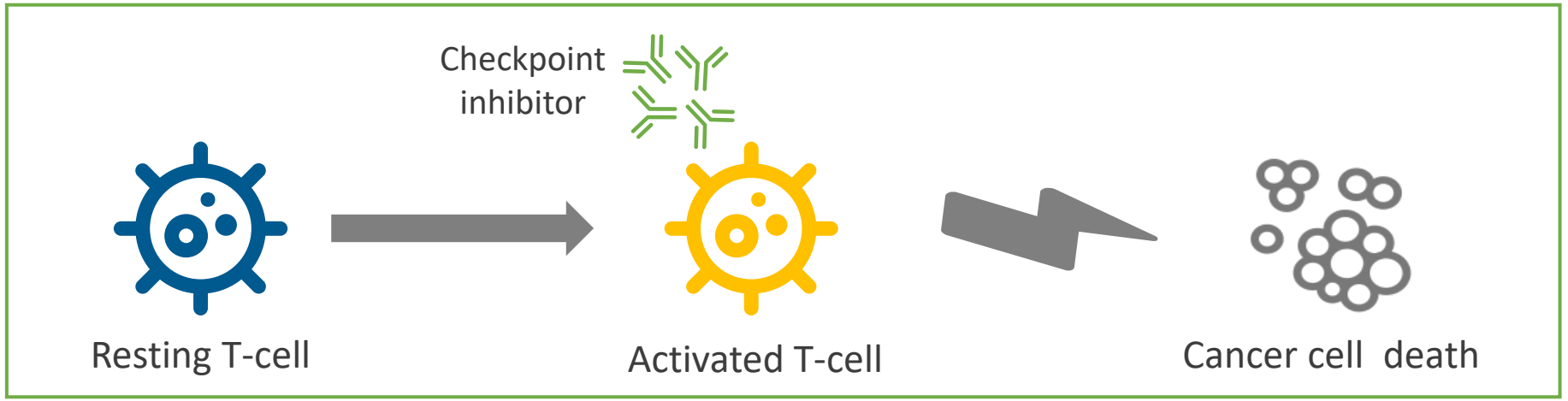
BRAF inhibitor		MEK inhibitor
Dabrafenib	+	Trametinib
Encorafenib	+	Binimetinib
Vemurafenib	+	Cobimetinib

Next up...
Immunotherapies

1. McArthur GA *et al. Lancet Oncol.* 2014;15(3):323-332. **2.** Hauschild A *et al. Lancet.* 2012;380(9839):358-365. **3.** Flaherty KT *et al. N Engl J Med.* 2012;367(18):1694-1703.
4. Robert C *et al. N Engl J Med.* 2015;372(1):30-39. **5.** Ascierto PA *et al. Lancet Oncol.* 2016;17(9):1248-1260. **6.** TAFINLAR® (dabrafenib) Product Information, 2021

IMMUNOTHERAPY USES THE PATIENT'S OWN IMMUNE SYSTEM TO FIGHT CANCER[1]

- Immune checkpoints act as brakes on the immune system, controlling the strength and duration of immune responses so that healthy tissues are not harmed in the presence of an infection etc.
- Some tumours produce these same molecules and thereby "putting the brakes on", preventing the immune system attacking the tumour
- Immune checkpoint inhibitors have been developed to release these brakes on the immune system, unleashing it to attack cancer cells



1. National Institutes of Health. Melanoma Treatment (PDQ®) Available at: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq. Accessed October 2021.

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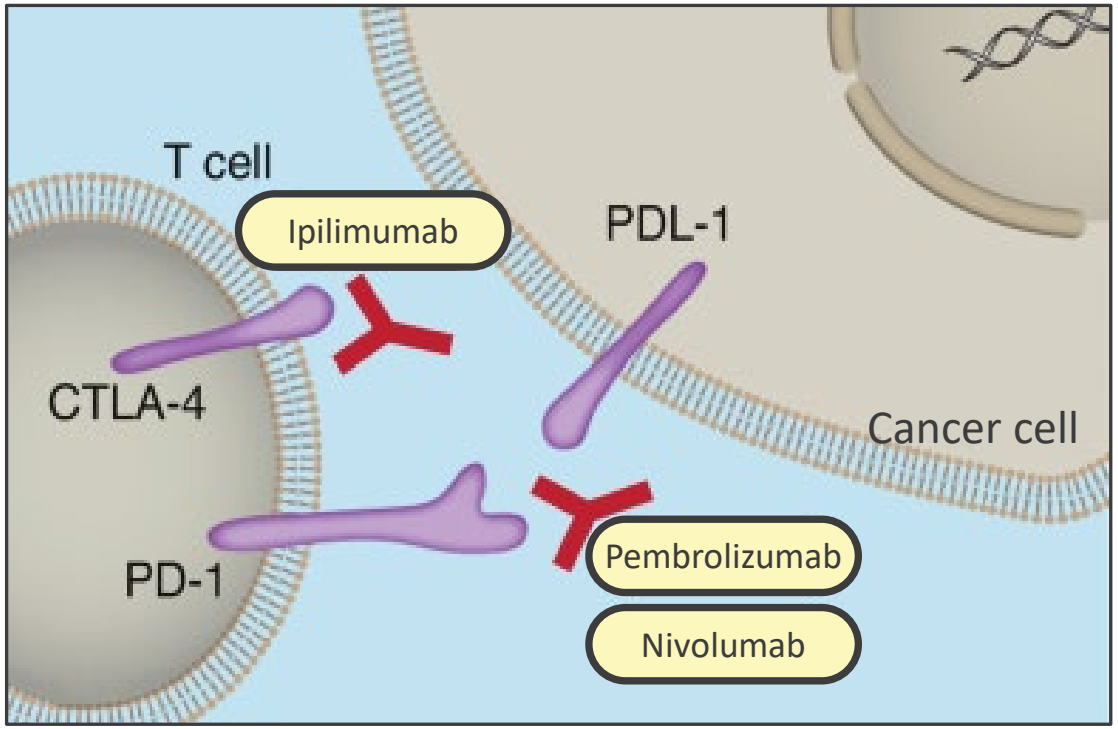
CHECKPOINT INHIBITORS TO TREAT MELANOMA[1]

- By binding and inhibiting immune checkpoints PD-1 and/or CTLA-4, monoclonal antibodies activate T-cells to enhance the body's own immune response against cancer cells



Adapted from Marrocco et al, 2019.[1]

- Combining CTLA-4 and PD-1 inhibition has been shown to increase response rates and duration of response and survival in metastatic melanoma[2]
- This combination has increased efficacy but may come at a cost of higher rates and grades of immune-mediated adverse events[2]

1. Marrocco I. *et al.* (2019) Methods in Molecular Biology, vol 1904. Humana Press, New York, NY.
2. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al.. J Clin Oncol. 2022;40(2):127-137

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WHEN ARE THESE MEDICINES CONSIDERED?

Treatment setting

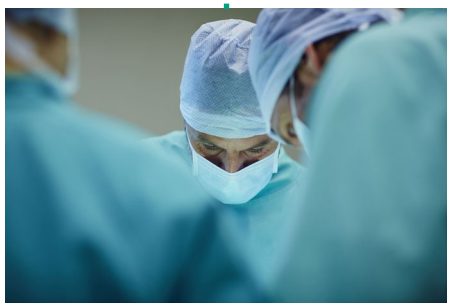
High risk resectable disease

Unresectable/ distal disease

Neoadjuvant
Before surgical resection
(Clinical trials)

Adjuvant
After surgical resection

Metastatic
+/- palliative surgical/radio therapy



Next up...

More information on the treatment settings

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NEOADJUVANT TREATMENT

Is there a role for systemic neoadjuvant therapy for patients with locally advanced or metastatic melanoma?[1,2]

- Neoadjuvant therapy involves giving systemic therapy before surgical resection
- With the introduction of targeted therapies and immunotherapy as adjuvant therapy following surgery, this approach is currently being assessed in clinical trials
- Patients presenting with resectable disease should be considered for these studies **prior** to wide local excision (WLE)

1. Sosman JA *et al.* UpToDate. Adjuvant therapy for cutaneous melanoma, April 2019 [Internet]. Available from: https://www.uptodate.com/contents/adjuvant-therapy-for-cutaneous-melanoma. Accessed December 2021. **2.** Kwak M *et al. J Surg Oncol* 2019;119:222–31.

ADJUVANT TREATMENT

When is adjuvant therapy recommended?

- For patients with melanoma who are at high risk of the cancer recurring after it has been surgically removed, there is a growing number of adjuvant therapy options which may be given to lower the risk of the melanoma coming back[1]
- Patients with resected stage IIIB/C/D melanoma should be considered for adjuvant systemic therapy[2]
  - Adjuvant systemic therapy for stage IIIA patients is not recommended as the risk of the recurrence is low and was not meaningfully improved by drug treatment[2]
- For patients with a *BRAF V600* mutant melanoma, targeted therapy (combination BRAF and MEK inhibitors) or adjuvant immunotherapy (single agent anti PD-1) may be a suitable option[2]
- For patients without a *BRAF* mutation, adjuvant immunotherapy should be considered[2]
- Therapy is given for up to a year[2]

1. National Institutes of Health. Melanoma Treatment (PDQ®) Available at: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq. 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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WHY IS ADJUVANT THERAPY RECOMMENDED?

Several phase III randomized-controlled trials (RCTs) have established the benefit of adjuvant treatment in patients with resected stage IIIB-D melanoma. The primary endpoint of these studies was RFS (relapse/recurrence-free survival) and statistically significant results have led to both the TGA approval and PBS reimbursement of these medications. Overall survival results continue to be collected and at this point have not shown statistical significance.

Study	Therapy (12 months)	Comparator arm	Patient population*	Relapse free survival (RFS, %)	Overall survival (OS, %)
COMBI-AD[1,2]	Dabrafenib + Trametinib	Placebo	Resected stage IIIA-C **BRAFV600 E/K mutation positive only**	3 years: 59 vs. 37 4 years: 55 vs. 38 5 years: 52 vs. 36	3 years: 86 vs. 77 4 years: NA 5 years: NA
CHECKMATE-238[3]	Nivolumab	Ipilimumab (4 cycles, then placebo)	Resected stage IIIB & C, IV	3 years: 58 vs. 44 4 years: 52 vs. 41 5 years: NA	3 years: 82 vs. 82 4 years: 77.9 vs. 76.6 5 years: NA
KEYNOTE-054[4]	Pembrolizumab	Placebo	Resected stage IIIA-C	3 years: 63.7 vs. 44.1 4 years: NA 5 years: NA	3 years: NA 4 years: NA 5 years: NA

***The three adjuvant studies described in this slide included patients based on the AJCC v7 staging criteria. Following the initiation of the studies, AJCC v8 staging criteria was introduced, which included stage IIID patients. Accordingly, both TGA and PBAC restrictions include stage IIIB-D patients, as per AJCC v8 staging criteria. NA; not available**

1. Dummer *et al. N Engl J Med* 2020;381:1139-48. **2.** Long *et al. N Engl J Med* 2017;377:1813-23. **3.** Ascierto *et al. Lancet Oncol.* 2019;21:11;1465-77. **4.** Eggermont *et al.* American Society of Clinical Oncology Presentation 2020 KN054

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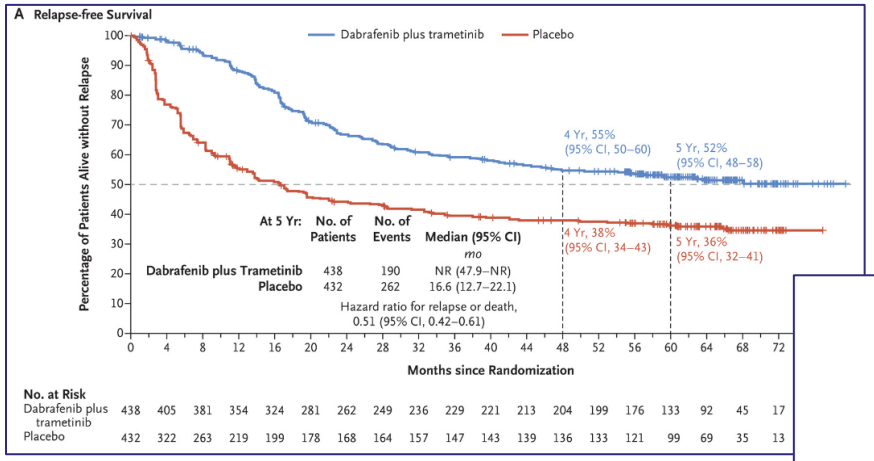
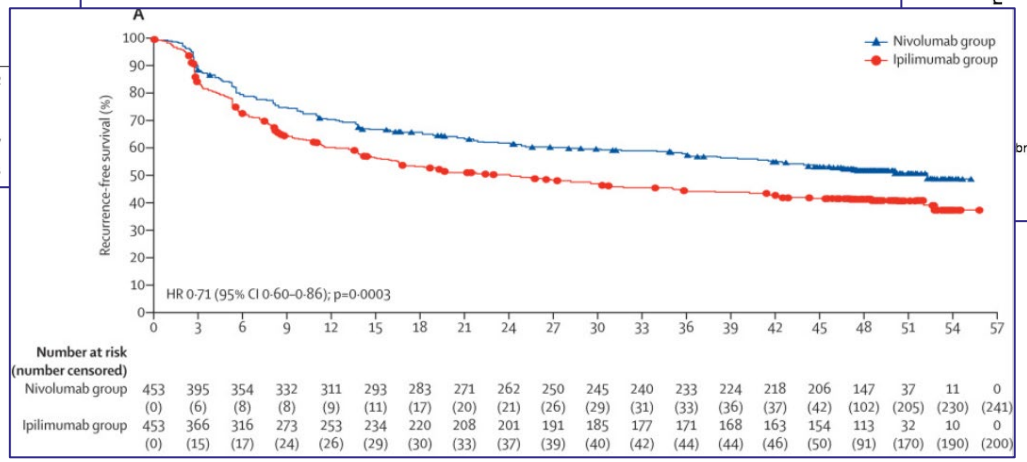
WHY IS ADJUVANT THERAPY RECOMMENDED? RFS SHOWED SIGNIFICANT BENEFIT VS. CONTROL ARM

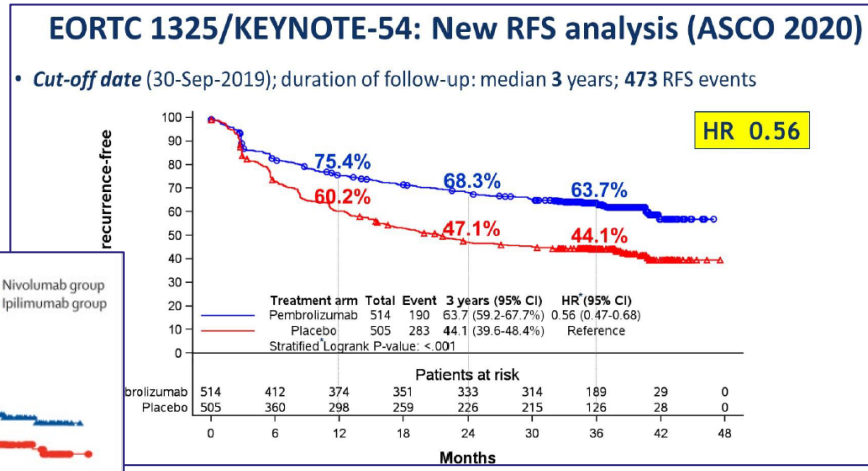
COMBI-AD[1,2]



CHECKMATE-238[3]



KEYNOTE-054[4]



*The three adjuvant studies described in this slide included patients based on the AJCC v7 staging criteria. Following the initiation of the studies, AJCC v8 staging criteria was introduced, which included stage IIID patients. Accordingly, both TGA and PBAC restrictions include stage IIIB-D patients, as per AJCC v8 staging criteria
Results are shown for illustrative purposes. Cross trial comparison should not be made

1. Dummer *et al. N Engl J Med* 2020;381:1139-48. **2.** Long *et al. N Engl J Med* 2017;377:1813-23. **3.** Ascierto *et al. Lancet Oncol.* 2019;21:11;1465-77. **4.** Eggermont *et al.* American Society of Clinical Oncology Presentation 2020 KN054

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SUMMARY – ADJUVANT TREATMENT[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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ADJUVANT TREATMENT- PBS CRITERIA[1,2]

Therapy	Route of administration	Mechanism of Action	PBS Restriction
Targeted therapies			
Dabrafenib + Trametinib[1] 150mg BD + 2mg QD	Oral	BRAFi + MEKi	• Adjuvant resected + lymph node involvement (Stage IIIB, C, D)
Immunotherapies			
Nivolumab[2] 240mg Q2W OR 480mg Q4W	IV infusion	Anti-PD-1	• Adjuvant resected + lymph node involvement (Stage IIIB, C, D, stage IV)
Pembrolizumab[3] 400mg Q6W OR 200mg Q3W	IV infusion	Anti-PD-1	• Adjuvant resected + lymph node involvement (Stage IIIB, C ,D)

Always view the approved product information found at www.tga.com.au.

1. Dabrafenib and Trametinib (adjuvant) PBS criteria. Available at www.pbs.gov.au. Accessed December 2021. **2**. Nivolumab (adjuvant) PBS criteria. Available at www.pbs.gov.au. Accessed December 2021. **3.** Pembrolizumab (adjuvant) PBS criteria. Available at www.pbs.gov.au. Accessed December 2021

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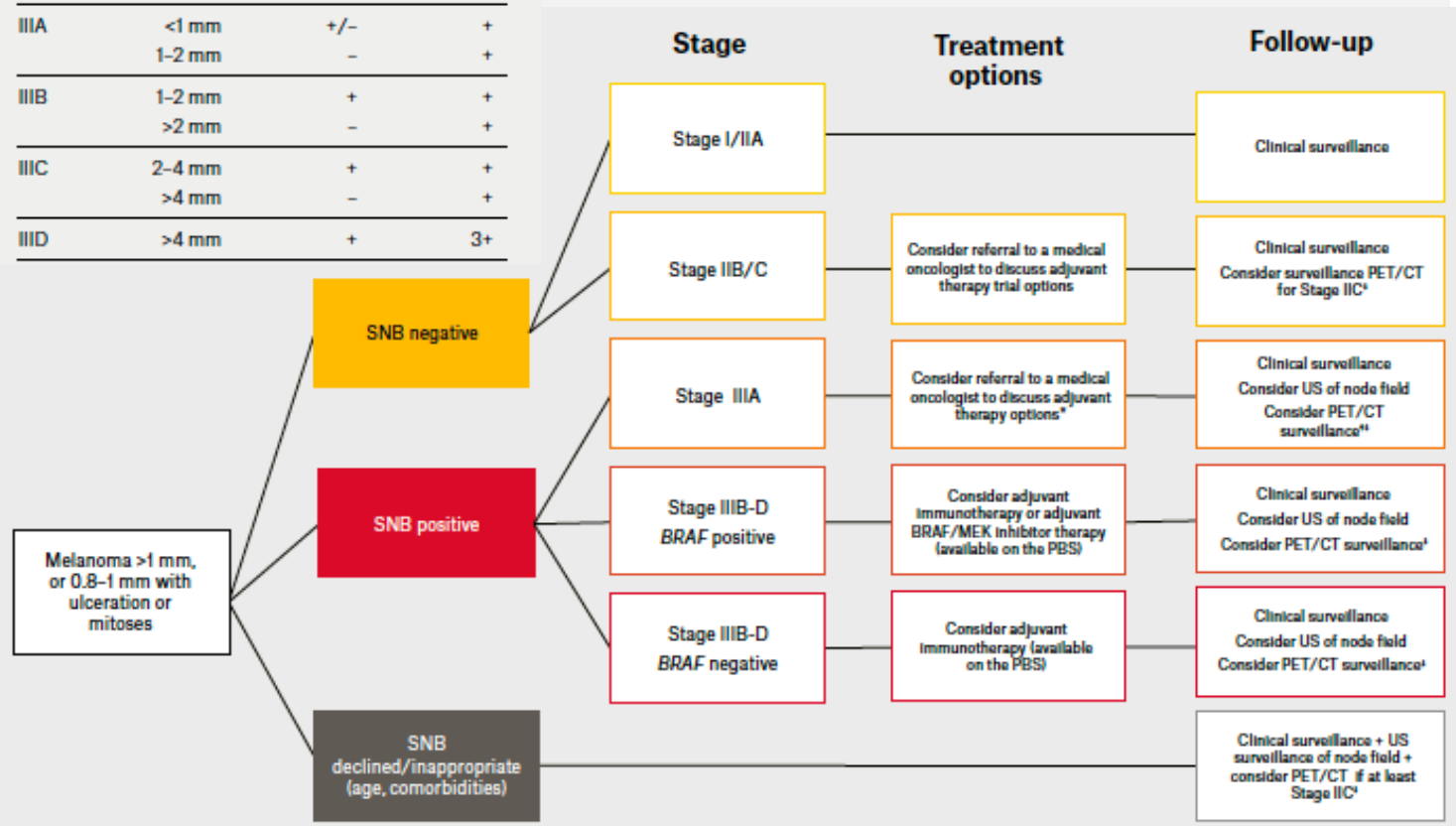
MELANOMA MANAGEMENT DECISION TREE IN STAGE I-III[1]

Stage	Thickness	Ulceration	SLN status
IIB	2–4 mm	2–4 mm	–
	>4 mm	>4 mm	–
IIC	>4 mm	>4 mm	–
IIIA	<1 mm	+/–	+
	1–2 mm	–	+
IIIB	1–2 mm	+	+
	>2 mm	–	+
IIIC	2–4 mm	+	+
	>4 mm	–	+
IIID	>4 mm	+	3+



The AJCC Cancer Staging Manual, Eighth Edition, takes primary tumour thickness, ulceration and SLN status into account. Patients with Stage IIIB (>1 mm thick ulcerated or >2 mm thick non-ulcerated and SLN-positive) and more advanced stages are eligible for adjuvant targeted therapy or immunotherapy, both of which are now available on the PBS.

Note: patients presenting with a clinically-detected node will be at least Stage IIIB.

*Adjuvant therapy is currently not funded on the Australian PBS for Stage IIIA patients; however, referral should be considered to discuss therapeutic options and clinical trials.

†The yield of baseline imaging of patients with Stage IIIA disease is extremely low, and the Australian guidelines recommendation is to 'consider NOT performing PET/CT or CT in newly diagnosed sentinel node positive patients', based on evidence that the yield of PET/CT and CT in detecting occult metastases is only 0.5–3.7%.

‡There is no evidence that routine surveillance imaging improves survival; however, PET/CT should be considered by the treating team if the finding of early metastatic disease would alter management. Patients should be counselled about the risks of radiation, false-positive results and possible anxiety.

Adapted from Mar *et al,* 2020.[1]

CT, computed tomography; PET, positron emission tomography; SLN, sentinel lymph node; SNB, sentinel node biopsy; US, ultrasonography.

1. Mar VJ *et al. Aust J General Practice* 2020;49:733–9.

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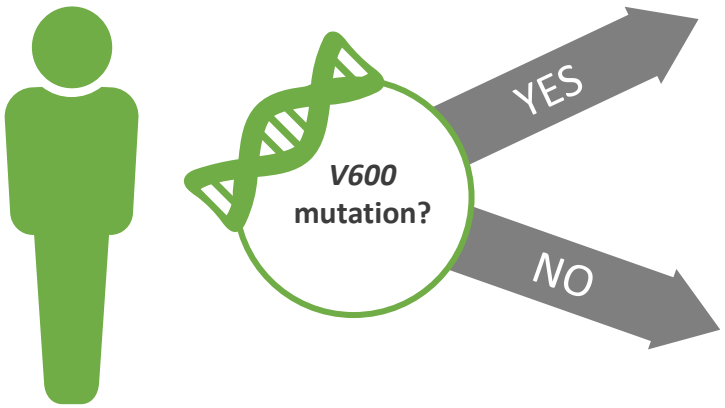
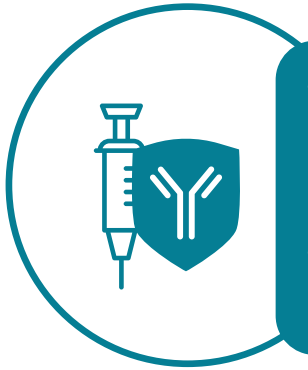
UNRESECTABLE MELANOMA: TREATMENT OPTIONS[1]

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 eligible 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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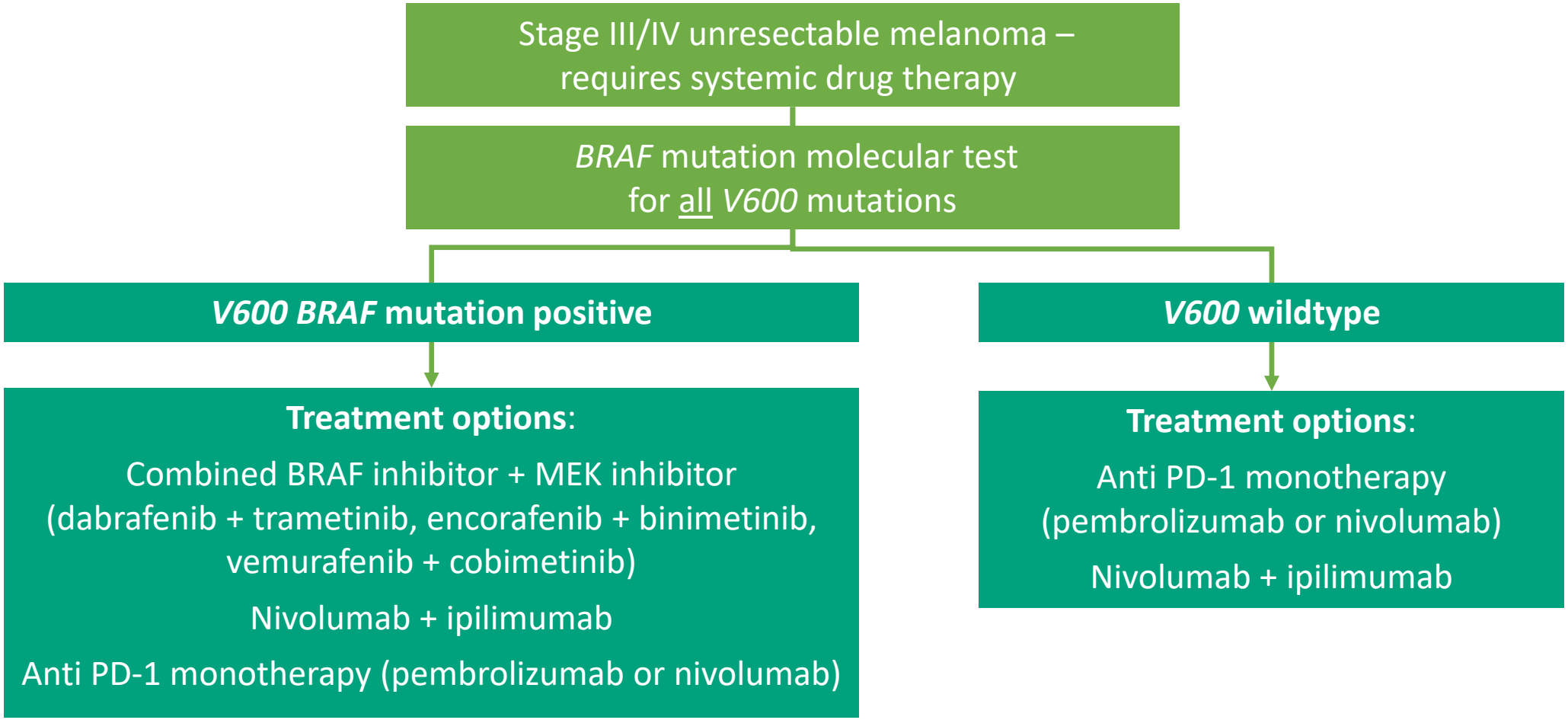
MELANOMA MANAGEMENT DECISION TREE IN UNRESECTABLE STAGE III/IV:[1]



Note: the options in the flowchart are not listed in order of preference.

1. Cancer Council Australia clinical guidelines. Does systemic drug therapy improve progression-free, overall survival in unresectable stage III and stage IV melanoma? Available at: 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. Accessed December 2021.

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CANCER COUNCIL AUSTRALIA CLINICAL GUIDELINES: CHOICE OF FIRST-LINE THERAPY[1]

Immunotherapy

- While not formally compared, there is no suggestion that there is a difference in efficacy or toxicity between pembrolizumab and nivolumab
- Combination of nivolumab + ipilimumab has demonstrated improved efficacy compared to anti-PD-1 alone, including increase in toxicity

Targeted therapies

- While not formally compared, there is no suggestion that there is a difference in efficacy between dabrafenib/trametinib, vemurafenib/cobimetinib or encorafenib/binimetinib combinations, but toxicity profiles are distinct

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.

MELANOMA MANAGEMENT IN UNRESECTABLE STAGE III/IV – CHOICE OF 1L TREATMENT IN BRAF+ PATIENTS

- For patients with a BRAF V600E/K mutation, both immunotherapy and targeted therapy agents are indicated.
- Sequencing studies have suggested that combination immunotherapy (ipilimumab + nivolumab) followed by a BRAF + MEK inhibitor upon progression may provide superior overall survival outcomes, compared to if a BRAF + MEK inhibitor is used first[1,2].
- Whilst not formally compared, clinical experience suggests immunotherapy provides a more durable clinical response compared to BRAF + MEK inhibitor.
- As BRAF + MEK inhibitors provide BRAF+ patients an almost certain quick and deep response, there are some circumstances where they may be preferred to be used first e.g. for patients with[2]:
  - Symptomatic brain metastasis;
  - High-burden disease with multiple sites of metastasis;
  - High LDH and/or ECOG 2-3;
  - Other contraindications to immunotherapy

1. Atkins *et al.* American Society of Clinical Oncology Plenary Series 2022 Abstract 356154. **2.** Keilholz *et al. Ann. Oncol.* 2020;31:11; 1435-48.

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PBS REIMBURSED TARGETED THERAPY – UNRESECTABLE STAGE III/STAGE IV MELANOMA[1-3]

Combination Therapy	Route	Daily capsule/ tablets	Mechanism of action	PBS indications
Dabrafenib + Trametinib 150mg BD + 2mg OD	Oral	5	BRAFi + MEKi	• Unresectable/met (stage III or IV)
Encorafenib + Binimetinib 450mg OD + 45mg BD	Oral	12	BRAFi + MEKi	• Unresectable/met (stage III or IV)
Vemurafenib + Cobimetinib 960mg BD + 60mg OD 21/28	Oral	11	BRAFi + MEKi	• Unresectable/met (stage III or IV)

Use of single agent BRAF inhibitors may be used in rare situations where significant contraindications or intolerance occurs[1,5]

Always view the approved product information found at www.tga.com.au.

1. Dabrafenib and Trametinib (metastatic) PBS criteria. Available at www.pbs.gov.au. Accessed December 2021. **2.** Vemurafenib and Cobimetinib (metastatic) PBS criteria. Available at www.pbs.gov.au. Accessed December 2021. **3.** Encorafenib and Binimetinib (metastatic) PBS criteria. Available at www.pbs.gov.au. Accessed December 2021

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THE SAFETY PROFILE OF TARGETED THERAPIES ARE DIFFERENT[1,2]

- Combination dabrafenib/trametinib, vemurafenib/cobimetinib and encorafenib/binimetinib have different toxicity profiles
  - Dabrafenib/trametinib is commonly associated with treatment-related pyrexia syndrome
  - Vemurafenib/cobimetinib is commonly associated with a risk of photosensitivity and hepatotoxicity (most commonly a transaminitis)
  - Encorafenib/binimetinib is commonly associated with a risk of rash and gastrointestinal complications

Adverse event management will be discussed in more detail in Module 4

Please see individual Product Information for additional safety information.

1. 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. **2.** 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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TARGETED THERAPIES- SAFETY[1]

While this varies by choice of combination, common side effects of any targeted therapy in melanoma include:

Common side effects can include:

- Skin thickening
- Rash
- Itching
- Sensitivity to the sun
- Headache
- Fever
- Joint pain
- Fatigue
- Hair loss
- Nausea

Less common but serious side effects can include:

- Arrythmias
- Liver problems
- Kidney failure
- Severe allergic reactions
- Severe skin or eye problems
- Bleeding
- Hyperglycaemia (increased blood sugar levels)

Please see individual Product Information for additional safety information.

1. American Cancer Society. Targeted Therapy Drugs for Melanoma Skin Cancer. Available at: https://www.cancer.org/cancer/melanoma-skin-cancer/treating/targeted-therapy.html. Accessed October 2021.

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PBS REIMBURSED IMMUNOTHERAPIES – UNRESECTABLE STAGE III AND STAGE IV MELANOMA[1-3]

Immunotherapy	Route of administration	Mechanism of Action	Combination treatment?	PBS restriction[4]
Pembrolizumab[3] 400mg Q6W OR 200mg Q3W	IV infusion	Anti-PD-1	Single agent therapy	• Unresectable/met (stage III or IV)
Nivolumab[1] Single-agent and maintenance: 240mg Q2W OR 480mg Q4W Induction phase in combination: 1mg/kg Q3W maximum 4 doses	IV infusion	Anti-PD-1	Can be combined with ipilimumab	• Unresectable/met (stage III or IV)
Ipilimumab[2] 3mg/kg Q3W maximum 4 doses	IV infusion	Anti-CTLA-4	Can be combined with nivolumab	• Unresectable/met (stage III or IV)

Always view the approved product information found at www.tga.com.au.

1. Ipilimumab (metastatic) PBS criteria. Available at www.pbs.gov.au. Accessed December 2021. **2.** Nivolumab (metastatic) PBS criteria. Available at www.pbs.gov.au. Accessed December 2021
3. Pembrolizumab (metastatic) PBS criteria. Available at www.pbs.gov.au. Accessed December 2021

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ADVERSE REACTIONS ASSOCIATED WITH IMMUNOTHERAPIES USED TO TREAT MELANOMA[1]

- Immunotherapy side-effects, or immune-related adverse events (irAEs) can occur with immunotherapy
- These result in immune system activation and can affect any part of the body
- Patients with pre-existing autoimmune conditions may be at a risk of their autoimmune disease getting worse
- irAEs may require interruption of the immunotherapy and, immunosuppressive doses of corticosteroids
- It is important to differentiate e.g. *c.diff* diarrhea and collitis

Most common irAEs
Rash
Itch
Thyroid dysfunction
Hypophysitis (inflammation of the pituitary gland)
Hepatitis
Colitis
Arthritis
Pneumonitis

Please see individual Product Information for additional safety information.

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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CANCER COUNCIL AUSTRALIA CLINICAL GUIDELINES: SAFETY PROFILE OF IMMUNOTHERAPIES[1,2]

- Any patient on immunotherapy can develop an auto-immune toxicity directed at any organ. This can be a lifelong toxicity, extending beyond the cessation of treatment. Symptoms can start even 6-12months after treatment has ended. This risk must be discussed with the patient
  - The common toxicities are fatigue, rash, itch, diarrhoea, thyroiditis and hepatitis
  - 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)
- The use of single agent anti-PD-1 is associated with a grade 3/4 AE rate of 23%
  - Majority of all-grade toxicities include skin-related AEs (rash, pruritis, dry skin), fatigue, diarrhea and nausea
- The combination of ipilimumab and nivolumab causes immune-related side effects, inducing grade 3/4 AEs in 59% of patients, including asymptomatic laboratory abnormalities
  - Disease factors that may be considered in the selection of patients for this combination regimen include: rapidly progressive melanoma, baseline serum LDH > ULN, mucosal melanoma, active brain metastases, BRAF mutation-positive melanoma
  - The presence of auto-immune disease, other co-morbidities and age should also be taken into consideration

Adverse event management will be discussed in more detail in Module 4

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;381:1535-46. (Suppl Appendix)

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MODULE 3: SUMMARY

- Patients diagnosed with stage I/II/IIIa melanoma can usually be cured with local treatments, such as surgery, whereas those patients diagnosed with stage IIIB,C,D and IV melanoma are often managed with systemic treatment[1,2]
- Systemic treatments include:[3,4]
  - Targeted therapy – works by interfering with specific proteins involved in the growth, progression and spread of cancer
  - Immunotherapy – unlocks the immune system to attack cancer cells
- Over the last decade, many innovative targeted therapies and immunotherapies have been approved for both unresectable metastatic melanoma and as adjuvant therapy in resectable stage IIIB,C,D melanoma[2-4]
  - Targeted therapies (BRAF inhibitors and MEK inhibitors) are usually given orally as combination therapy in patients with BRAF mutation positive melanoma
  - Immunotherapies targeting PDL-1 and CTLA-4 can be given alone or in combination

1. Australian Institute of Health and Welfare 2021. updated 7/06/2021 v5.0 Canberra: AIHW Available from: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-incidence-and-survival-by-stage-data-visualisation. Accessed October 2021 **2.** Cancer Council Victoria and Department of Health Victoria 2021, Optimal care pathway for people with melanoma, 2nd edn, Cancer Council Victoria, Melbourne. **3.** National Institutes of Health. Melanoma Treatment. Available at: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq. Accessed October 2021. **4.** Vanneman M, Dranoff G. *Nat Rev Cancer* 2014;12:237–51.

PRACTICE YOUR PRACTICE

- Shadow your fellow oncology melanoma nurse and/or medical oncologist on how patients receiving systemic treatments are educated on the mechanism of action
  - What key questions do they ask?
  - What concerns them the most?
- Speak to your medical oncologist about the role of sequencing treatments (immunotherapy and targeted therapy)
  - Do any specific clinical features make a difference?
  - What does the role of BRAF status mean when considering treatment options?
- Find any active/enrolling clinical trials in melanoma by using the Clinical Trials Australia website https://www.australianclinicaltrials.gov.au/clinical-trial-sites
  - Are there any trials available nearby that a patient in your clinic may be eligible for?
- Read one of the pivotal phase III trial results of the adjuvant melanoma studies (by searching for COMBI-AD, CHECKMATE-238 or KEYNOTE-054) and discuss with your colleague/s

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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