NHS
Thames Valley

Thames Valley SACT Regimens

Skin

NHS
Thames Valley

Notes from the editor

These regimens are available on the Network website **www.tvscn.nhs.uk**.

Any correspondence about the regimens should be addressed to:
Sally Coutts, Cancer Pharmacist, Thames Valley
email: sally.coutts@nhs.net

Acknowledgements
These regimens have been compiled by the Network Pharmacy Group in collaboration with the Skin CAG with key contribution from
Mark Middleton, *Consultant Oncologist, OUH*
Alice Freebairn, *Consultant Oncologist, RBFT*
Karen Carter, *Pharmacist, RBFT*
Madhumita Bhattacharyya, *Consultant Oncologist, RBFT*
Miranda Payne, *Consultant Oncologist, OUH*

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Thames Valley SACT Regimens

Skin

The regimens listed below are in use across the Thames Valley for the treatment of skin cancer
Date published: October 2019
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SACT Regimens

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List of amendments in this version

Protocol type: Skin Tumours
Date due for review: October 2021
Previous Version number: 3.0
This version number: 3.1

Clinicians may use their discretion when following regimens.

Table 1 Amendments

Page	Action Type	Amendment	Made/ asked by
23&25		Pembrolizumab 6 weekly dosing added	SPC

Table 2 New regimens to be approved and checked by CAG included in this version

Name of protocol	Indication	Reason / Proposer
Encorafenib Binimetinib	Melanoma	CDF www.england.nhs.uk/publication/national-cancer-drugs-fund-list/
Cemiplimab	Squamous cell	CDF

For anti-emetic guidelines: http://tvscn.nhs.uk/networks/cancer/cancer-topics/chemotherapy/
For dose banded chemotherapy standardized product specifications: www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b02/dose-banded-chemotherapy-standardised-product-specifications/

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DACARBAZINE

Indication: Malignant melanoma

DRUG REGIMEN

Day 1 **DACARBAZINE** 1000mg/m^2 in 1000ml sodium chloride 0.9% infusion over 1 hour

Cycle Frequency: Every 21 days for 6 cycles

DOSE MODIFICATIONS

Dacarbazine

CrCl 46-60ml/min give 80% dose
CrCl 30-45ml/min give 75% dose
CrCl <30ml/min give 70% dose
Can be hepatotoxic, consider dose reduction
Increases in AST, ALT, alk phos, LDH. Levels usually return to normal within two weeks

INVESTIGATIONS

Routine Blood test

1) Blood results required before SACT administration

	Give	*Discuss*
Hb x g/dL	≥10	< 10
Plt x 10^9/L	≥100	< 100
Neutrophils x 10^9/L	≥1.5	< 1.5
Serum creatinine		

2) Non urgent blood tests - Tests relating to disease response/progression

CONCURRENT MEDICATION

Anaphylaxis treatment should be prescribed if the patient has had an anaphylactic episode previously.
Dexamethasone 20mg IV bolus
Chlorphenamine 10mg IV bolus
Ranitidine 50mg IV bolus

ANTIEMETIC POLICY

Highly emetogenic

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Patients have experienced an influenza type syndrome of fever, myalgias and malaise usually occurring after large single doses and approximately seven days after treatment lasting 7-21 days.
Anaphylaxis can occur very rarely following administration of Dacarbazine.
Photosensitivity reactions may occur rarely.

DABRAFENIB (Tafinlar)

***Indication:* The treatment of advanced unresectable or metastatic melanoma (PS 0 or 1) with a BRAF V600 mutation and intolerance to vemurafenib (severe intolerance necessitating discontinuation, without disease progression whilst on full dose, within 2 months of initiating vemurafenib) No other previous systemic treatment other than vemurafenib.**

NICE TA321 Dabrafenib is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic BRAF V600 mutation-positive melanoma only if the company provides dabrafenib with the discount agreed in the patient access scheme.

DRUG REGIMEN

Day 1 **DABRAFENIB** 150mg orally twice daily

Cycle Frequency: Every 28 days until disease progression

DOSE MODIFICATIONS

Dabrafenib

Dose level	**Resulting dose/schedule**
Full dose	150 mg twice daily
First reduction	100 mg twice daily
Second reduction	75 mg twice daily
Third reduction	50 mg twice daily

Dabrafenib dose modification schedule based on the grade of any Adverse Events (AE)

Grade (CTC-AE)*	**Recommended dabrafenib dose modifications**
Grade 1 or Grade 2 (Tolerable)	Continue treatment and monitor as clinically indicated.
Grade 2 (Intolerable) or Grade 3	Interrupt therapy until toxicity is grade 0-1 and reduce by one dose level when resuming therapy.
Grade 4	Discontinue permanently, or interrupt therapy until grade 0-1 and reduce by one dose level when resuming therapy.

Renal:
No dose adjustment for patients with mild or moderate renal impairment. Use in caution with severe impairment.

Hepatic:
No dose adjustment for patients with mild hepatic impairment. Use with caution in moderate or severe impairment.

INVESTIGATIONS

Routine Blood test

1) Blood results required before SACT administration

	Give	*Discuss*
Hb x g/dL	≥10	< 10
Plt x 10^9/L	≥100	< 100
Neutrophils x 10^9/L	≥1.5	< 1.5

Serum creatinine
Electrolytes including Magnesium
ECG

2) Non urgent blood tests - Tests relating to disease response/progression

CONCURRENT MEDICATION

None required.

ANTIEMETIC POLICY

Low emetogenic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Cutaneous squamous cell carcinoma
New primary melanoma
Non-cutaneous secondary / recurrent malignancy
Renal failure
Uveitis
Pancreatitis
QT prolongation
Pyrexia

DABRAFENIB TRAMETINIB (Tafinlar and Mekinist)

Indications: As per Blueteq criteria (check website for most up to date criteria www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)
The treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation where all the following criteria are met:
Histologically confirmed stage III (unresectable) or stage IV melanoma, BRAF V600 mutation positive, No progression on treatment with a tyrosine kinase inhibitor targeting BRAF (ie already on either dabrafenib or vemurafenib and wishing to switch to combination ofdabrafenib and trametinib).
No active brain metastases or leptomeningeal metastases ie brain secondaries previously treated with surgery or stereotactic radiotherapy and considered to be stable
NICE TA397

Dabrafenib in combination with trametinib for the adjuvant treatment of completely resected stage III BRAF V600 positive malignant melanoma where confirmed histological diagnosis of malignant melanoma which is BRAF V600 mutation positive with disease that has been staged as stage III disease. This stage III disease has been completely resected either via sentinel lymph node biopsy ('sentinel lymphadenectomy') or when indicated via completion lymph node dissection
Treatment naïve to systemic therapy for malignant melanoma and in particular has not previously received any BRAF V600 inhibitors or MEK inhibitors or immunotherapy with any check point inhibitors.
ECOG performance status of either 0 or 1. Treatment with dabrafenib in combination with trametinib will be continued for a maximum of 12 months from the start of treatment in the absence of disease recurrence, unacceptable toxicity or withdrawal of patient consent
A formal medical review as to whether treatment with dabrafenib in combination with trametinib should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment
No treatment breaks of more than 6 weeks beyond the expected 4-weekly cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve)**Requests for continuation of treatment after unplanned treatment breaks over this duration should be made via the treatment break approval process.
Dabrafenib in combination with trametinib is to be otherwise used as set out in their respective SPC

Blueteq registration required for all patients

DRUG REGIMEN

Day 1 **DABRAFENIB** 150mg orally twice daily
TRAMETINIB 2mg orally daily

Cycle Frequency: Every 28 days maximum 12 months in the absence of disease progression for adjuvant patients or (CDF) until disease progression metastatic (TA397)

DOSE MODIFICATIONS

Dose level	Dabrafenib dose/schedule	Trametinib dose/schedule
Full dose	150 mg twice daily	2mg od
First reduction	100 mg twice daily	1.5mg od
Second reduction	75 mg twice daily	1mg od
Third reduction	50 mg twice daily	1mg od

Dabrafenib dose modification schedule based on the grade of any Adverse Events (AE)

Grade (CTC-AE)*	Recommended dabrafenib dose modifications
Grade 1 or Grade 2 (Tolerable)	Continue treatment and monitor as clinically indicated.
Grade 2 (Intolerable) or Grade 3	Interrupt therapy until toxicity is grade 0-1 and reduce by one dose level when resuming therapy.
Grade 4	Discontinue permanently, or interrupt therapy until grade 0-1 and reduce by one dose level when resuming therapy.

Renal:
No dose adjustment for patients with mild or moderate renal impairment. Use in caution with severe impairment.

Hepatic:
No dose adjustment for patients with mild hepatic impairment. Use with caution in moderate or severe impairment.

INVESTIGATIONS

Routine Blood test

1) Blood results required before SACT administration

	Give	*Discuss*
Hb x g/dL	≥10	< 10
Plt x 10^9/L	≥100	< 100
Neutrophils x 10^9/L	≥1.5	< 1.5

Serum creatinine
Electrolytes including Magnesium
ECG

2) Non urgent blood tests - Tests relating to disease response/progression

CONCURRENT MEDICATION

None required.

ANTIEMETIC POLICY

Low emetogenic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Cutaneous squamous cell carcinoma
New primary melanoma
Non-cutaneous secondary / recurrent malignancy
Renal failure
Uveitis
Pancreatitis
QT prolongation
Pyrexia

NHS
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ENCORAFENIB BINIMETINIB (Braftovi and Mektovi)

Indications: As per Blueteq criteria (check website for most up to date criteria www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)
The treatment of unresectable stage III or stage IV BRAF V600 mutation positive malignant melanoma where the following criteria are met:
2. Confirmed histological diagnosis of BRAF V600 mutation positive malignant melanoma
3. Uresectable stage III or stage IV disease AJCC 8th edition
4. Treatment naïve to BRAF V600 and MEK inhibitors for malignant melanoma unless either the patient has previously received adjuvant dabrafenib and trametinib and did not progress during such therapy or has received a sufficient trial of dabrafenib plus trametinib for advanced disease and this has had to be stopped solely as a consequence of persistent dose-limiting toxicity and in the documented absence of disease progression. Note: sequential treatment is not commissioned with dabrafenib plus trametinib and then on disease progression with encorafenib plus binimetinib.
5. Sufficient ECOG PS to tolerate treatment with the combination of encorafenib plus binimetinib
6. Treatment with encorafenib in combination with binimetinib will be continued until loss of clinical benefit or unacceptable toxicity or withdrawal of patient consent.
7. A formal medical review as to whether treatment with encorafenib in combination with binimetinib should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment
8. No treatment breaks of more than 6 weeks beyond the expected 4-weekly cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve)**Requests for continuation of treatment after unplanned treatment breaks over this duration should be made via the treatment break approval process.
9. Encorafenib in combination with binimetinib is to be otherwise used as in their SPC

DRUG REGIMEN

Day 1 **Encorafenib** 450mg od PO
Binimetinib 45mg bd PO

Cycle Frequency: ***every 28 days until loss of benefit***

DOSE MODIFICATIONS

See Encorafenib and binimetinib SPCs for dose reduction criteria for Cutaneous reactions, Palmar-plantar erythrodysaesthesia syndrome (PPES), Uveitis including iritis and iridocyclitis, QTc Prolongation, other adverse reactions:

Dose level	Encorafenib dose when used in combination with binimetinib
Starting dose	450 mg once daily
1st dose reduction	300 mg once daily
2nd dose reduction	200 mg once daily
Subsequent modification	There are limited data for dose reduction to 100mg once daily. Encorafenib should be permanently discontinued if patient is unable to tolerate 100mg once daily.

Administration of encorafenib at a dose of 450 mg once daily as a single agent is not recommended. If binimetinib is temporarily interrupted, encorafenib should be reduced at 300 mg once daily during the time of binimetinib dose interruption as encorafenib is not well-tolerated at the dose of 450 mg as a single agent. If binimetinib is permanently discontinued, encorafenib should be discontinued.

If encorafenib is temporarily interrupted, binimetinib should be interrupted. If encorafenib is permanently discontinued, then binimetinib should be discontinued.
gical exam - Every 4 weeks and after 6 months every 8 weeks

Hepatic impairment
Patients with mild to severe hepatic impairment may have increased encorafenib exposure

Administration of encorafenib should be undertaken with caution at a reduced dose of 300 mg once daily in patients with mild hepatic impairment (Child-Pugh Class A).
No dosing recommendation can be made in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

Renal impairment
No dose adjustment is required for patients with mild or moderate renal impairment based on a population pharmacokinetics (PK) analysis. There are no clinical data with encorafenib in patients with severe renal impairment. Therefore, the potential need for dose adjustment cannot be determined. Encorafenib should be used with caution in patients with severe renal impairment

The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation.
For patients receiving 45 mg binimetinib twice daily, the recommended reduced dose of binimetinib is 30 mg twice daily. Dose reduction below 30 mg twice daily is not recommended. Therapy should be discontinued if the patient is not able to tolerate 30 mg orally twice daily.
If the adverse reaction that resulted in a dose reduction is under effective management, dose re-escalation to 45 mg twice daily may be considered. Dose re-escalation to 45 mg twice daily is not recommended if the dose reduction is due to left ventricular dysfunction (LVD) or any Grade 4 toxicity.
Dose modifications recommendations in case of adverse reactions see above and in SPC
If treatment-related toxicities occur when binimetinib is used in combination with encorafenib, then both treatments should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose reductions are necessary for encorafenib only (adverse reactions primarily related to encorafenib) are: palmar-plantar erythrodysaesthesia syndrome (PPES), uveitis including iritis and iridocyclitis and QTc prolongation.
If one of these toxicities occurs, see encorafenib SPC for dose modification instructions for encorafenib.
If binimetinib is temporarily interrupted, encorafenib should be reduced to 300 mg once daily during the time of binimetinib dose interruption as encorafenib is not well-tolerated at the dose of

450 mg as a single agent. If binimetinib is permanently discontinued, encorafenib should be discontinued.
If encorafenib is temporarily interrupted (see encorafenib SmPC), binimetinib should be interrupted.
If encorafenib is permanently discontinued, then binimetinib should be discontinued.

Hepatic impairment
No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh A).
As encorafenib is not recommended in patients with moderate (Child Pugh B) or severe hepatic impairment (Child-Pugh C), administration of binimetinib is not recommended in these patients.

Renal impairment
No dose adjustment is recommended for patients with renal impairment

INVESTIGATIONS
FBC, LFTs

ANTI-EMETIC POLICY
Low emetic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Left ventricular dysfunction
Haemorhage
Ocular toxicities
CK elevation and rhabdomyolosis
QT prolongation
Hypertension
VTE
Pneumonitis/interstitial lung disease
Liver abnormalities
Renal and hepatic toxicities

REFERENCES
CDF 21/1/19
SPC 3/10/18

IPILIMUMAB (Yervoy)

Indication: Malignant melanoma

NICE recommends ipilimumab as a possible treatment for people with previously untreated or treated advanced (unresectable or metastatic) melanoma.

DRUG REGIMEN

Day 1 **IPILIMUMAB** 3mg/kg in 100ml sodium chloride 0.9% infusion over 90 minutes

Cycle Frequency: every 21 days for 4 doses
Treatment breaks of up to 12 weeks beyond the expected cycle length of ipilumumab are allowed but solely to allow immune toxicities to settle *(treatment break form to be completed).*

DOSE MODIFICATIONS

Ipilimumab
See Immuno-oncology adverse event management guidelines

INVESTIGATIONS

Routine Blood test
1) Blood results required before SACT administration

	Give	*Discuss*
AST	<5xULN	≥5xULN
ALT	<5xULN	≥5xULN
T Bililrubin	<3xULN	≥3xULN
Thyroid function tests	normal	abnormal
Endocrine profile including cortisol and glucose		

2) Non urgent blood tests - Tests relating to disease response/progression

CONCURRENT MEDICATION

ANTIEMETIC POLICY

Low emetogenic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

See Immuno-oncology adverse event management guidelines
Involve consultant in all grade 2 or higher toxicities.
CMV related colitis

REFERENCES

1. European guidelines for the expanded access programme of Ipilimumab. 6 August 2010
2. SPC Ipilimumab July 2011

IPILIMUMAB NIVOLUMAB (Yervoy and Opdivo)

Indication: As per Blueteq criteria (check website for most up to date criteria www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)
The treatment of advanced (unresectable ot metastatic) melanoma in adults where all the following criteria are met:
Histologically confirmed stage III (unresectable) or stage IV melanoma, PS 0 or 1
No previous treatment with any of anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, or anticytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibody.
Only prior systemic therapy allowed is either prior adjuvant therapy with immune checkpoint inhibitors when given as part of a clinical trial either as monotherapy or in combination with ipilimumab and/or BRAF/MEK inhibitor targeted therapies when given for advanced disease; prior adjuvant therapy with ipilimumab + nivolumab is not allowed.
No active brain metastases or leptomeningeal metastases ie brain secondaries previously treated with surgery or stereotactic radiotherapy and considered to be stable.
Treatment breaks are allowed as long as these are solely for toxicity and each cycle commences within 12 weeks of the start date of the previous cycle of treatment.
NICE TA400
Blueteq registration required for all patients

DRUG REGIMEN

Day 1 **NIVOLUMAB** 1mg/kg in 50ml* sodium chloride 0.9% infusion over 60 minutes
IPILIMUMAB 3mg/kg in 100ml sodium chloride 0.9% infusion over 90 minutes

*doses 120mg to 440mg in 100ml sodium chloride 0.9%

Cycle Frequency: every 21 days for 4 doses
Then nivolumab maintenance (see Nivolumab monotherapy regimen for doses)
Treatment breaks of up to 12 weeks beyond the expected cycle length of ipilumumab are allowed but solely to allow immune toxicities to settle *(treatment break form to be completed).*

DOSE MODIFICATIONS

Ipilimumab and Nivolumab
See Immuno-oncology adverse event management guidelines

INVESTIGATIONS

Routine Blood test
1) Blood results required before SACT administration
AST, ALT, Bilirubin
Thyroid function tests
Endocrine profile including cortisol and glucose

CONCURRENT MEDICATION

ANTIEMETIC POLICY

Low emetogenic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

See Immuno-oncology adverse event management guidelines
Involve consultant in all grade 2 or higher toxicities.
CMV related colitis

REFERENCES

1. European guidelines for the expanded access programme of Ipilimumab. 6 August 2010
2. SPC Ipilimumab July 2011
3. SPC Nivolumab 12.5.16

NIVOLUMAB (Opdivo) (adjuvant)

Indication: As per Blueteq criteria (check website for most up to date criteria www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)
Nivolumab for the adjuvant treatment of newly diagnosed and completely resected stage III or completely resected stage IV malignant melanoma where histological diagnosis of malignant melanoma, stage III disease or completely resected stage IV disease. (If stage III melanoma, the disease has been completely resected via sentinel node biopsy ('sentinel lymphadenectomy') or when indicated via completion lymph node dissection and/or there has been complete resection of intransit metastases; if stage IV melanoma, the distant metastatic disease has been completely resected)
Treatment naïve to systemic therapy for malignant melanoma and in particular has not previously received any BRAF V600 inhibitors or MEK inhibitors, has not previously received immunotherapy with any check point inhibitor. The patient has an ECOG performance status of either 0 or 1
Formal medical review to assess tolerability and whether treatment with nivolumab should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment
Nivolumab is to be otherwise used as set out in its Summary of Product Characteristics

DRUG REGIMEN

Day 1 **NIVOLUMAB** 3mg/kg in 100ml* sodium chloride 0.9% infusion over 60 minutes
***** doses 58mg to 110mg in 50ml, 120mg to 440mg in 100ml sodium chloride 0.9%

Cycle Frequency: every 14 days until maximum of 12 months (maximum of 26 cycles) from the start of treatment in the absence of disease recurrence, unacceptable toxicity, formal medical review to assess tolerability and whether treatment with nivolumab should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment. Treatment breaks of up to 12 weeks beyond the expected 2-weekly cycle length are allowed but solely to allow any immune toxicities to settle

DOSE MODIFICATIONS

Nivolumab
See Immuno-oncology adverse event management guidelines

INVESTIGATIONS

Blood results required before SACT administration
AST, ALT, Bilirubin
Thyroid function tests
Endocrine profile including cortisol and glucose
Thyroid function tests normal abnormal
Endocrine profile including cortisol and glucose

CONCURRENT MEDICATION

ANTIEMETIC POLICY

Low emetogenic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

See Immuno-oncology adverse event management guidelines
Involve consultant in all grade 2 or higher toxicities.

REFERENCES

1. SPC Nivolumab April 2018

NIVOLUMAB (Opdivo) (metastatic)

Indication: As per Blueteq criteria (check website for most up to date criteria www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)
Monotherapy for treating advanced (unresectable or metastatic) melanoma in adults *NICE TA384*

DRUG REGIMEN

Day 1 **NIVOLUMAB** 480mg in 100ml sodium chloride 0.9% infusion over 60 minutes

Cycle Frequency: every 28 days until progression or intolerance

Or
Day 1 **NIVOLUMAB** 240mg in 100ml sodium chloride 0.9% infusion over 30 minutes

Cycle Frequency: every 14 days until progression or intolerance

DOSE MODIFICATIONS

Nivolumab
See Immuno-oncology adverse event management guidelines

INVESTIGATIONS

Blood results required before SACT administration
AST, ALT, Bilirubin
Thyroid function tests
Endocrine profile including cortisol and glucose
Thyroid function tests normal abnormal
Endocrine profile including cortisol and glucose

CONCURRENT MEDICATION

ANTIEMETIC POLICY

Low emetogenic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

See Immuno-oncology adverse event management guidelines
Involve consultant in all grade 2 or higher toxicities.

REFERENCES

1. SPC Nivolumab April 2018

VEMURAFENIB (Zelboraf)

Indication: BRAF V600 mutation-positive unresectable or metastatic malignant melanoma

NICE recommends vemurafenib as a possible treatment for unresectable or metastatic melanoma with the BRAF V600 mutation. NICE TA269

DRUG REGIMEN

Day 1 **VEMURAFENIB** 960mg orally twice daily

Cycle Frequency: Every 28 days until disease progression

DOSE MODIFICATIONS

Vemurafenib

Patients with moderate to severe hepatic impairment should be closely monitored.
Patients with severe renal impairment should be closely monitored.

Dose modification schedule based on the grade of any AEs

Grade (CTC-AE)	Details	Recommended dose modification
Grade 1 or Grade 2 (tolerable)		Maintain vemurafenib at a dose of 960 mg twice daily.
Grade 2 (intolerable) or Grade 3	1st occurrence of any grade 2 or 3 AE	Interrupt treatment until grade 0 – 1. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).
	2nd occurrence of any grade 2 or 3 AE or persistence after treatment interruption	Interrupt treatment until grade 0 – 1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily) or continue with intermittent therapy (1 week on / 1 week off.
	3rd occurrence of any grade 2 or 3 AE or persistence after 2nd dose reduction	Discontinue permanently.
Grade 4	1st occurrence of any grade 4 AE	Discontinue permanently or interrupt vemurafenib treatment until grade 0 – 1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
	2nd occurrence of any grade 4 AE or persistence of any grade 4 AE after 1st dose reduction	Discontinue permanently.

Dose modification schedule based on prolongation of the QT interval

QTc value	Recommended dose modification
QTc >500 ms at baseline	Treatment not recommended.
QTc increase meets values of both > 500 ms and >60 ms change from pre-treatment values	Discontinue permanently.
1st occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60 ms	Temporarily interrupt treatment until QTc decreases below 500 ms. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).
2nd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60ms	Temporarily interrupt treatment until QTc decreases below 500 ms. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
3rd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60ms	Discontinue permanently.

INVESTIGATIONS

Routine Blood test

1) Blood results required before SACT administration

	Give	*Discuss*
Hb x g/dL	≥10	< 10
Plt x 10^9/L	≥100	< 100
Neutrophils x 10^9/L	≥1.5	< 1.5

Serum creatinine
Electrolytes including Magnesium
ECG

2) Non urgent blood tests - Tests relating to disease response/progression

CONCURRENT MEDICATION

None required.

ANTIEMETIC POLICY

Low emetogenic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

See SPC for Vemurafenib pregnancy prevention programme
Mild to moderate photosensitivity.
Diarrhoea and vomiting.
Arthralgia and musculoskeletal pain.
Hypersensitivity reactions, including anaphylaxis.
QT prolongation and ventricular arrhythmias.
Cutaneous squamous cell carcinoma (keratoacanthoma).

REFERENCES

1. An open-label, multicenter expanded access study of RO5185426 in patients with metastatic melanoma
2. SPC February 2012

PEMBROLIZUMAB (Keytruda) (adjuvant)

Indication: As per Blueteq criteria (check website for most up to date criteria www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)
Pembrolizumab for adjuvant treatment of melanoma with high risk of recurrence, confirmed histological diagnosis of malignant melanoma, staged as stage III disease . If stage III melanoma, the disease has been completely resected via sentinel node biopsy ('sentinel lymphadenectomy') or when indicated via completion lymph node dissection and/or there has been complete resection of intransit metastases
Patient is treatment naïve to systemic therapy for malignant melanoma and in particular has not previously received any BRAF V600 inhibitors or MEK inhibitors or immunotherapy with any check point inhibitors. ECOG PS 0 or 1. Otherwise used as set out in its SPC

DRUG REGIMEN

Day 1 **PEMBROLIZUMAB** 200mg in sodium chloride 0.9% infusion over 30 minutes

Cycle Frequency: Every 21 days until disease progression maximum of 12 months (maximum of 18 cycles) from the start of treatment in the absence of disease recurrence, unacceptable toxicity. A formal medical review to assess the tolerability of treatment and whether treatment with pembrolizumab should continue or not will be scheduled to occur at least by the end of the first 9 weeks of treatment

May switch to 6 weekly dosing after 4 doses of 200mg 3 weekly dosing
Day 1 **PEMBROLIZUMAB** 400mg in sodium chloride 0.9% infusion over 30 minutes

Cycle Frequency: Every 42 days until disease progression up to total maximum of 12 months ie 4 doses of 200mg 3 weekly then 7 cycles of 400mg 6 weekly dosing

Treatment breaks of up to 12 weeks beyond the expected cycle length of pembrolizumab are allowed but solely to allow immune toxicities to settle *(treatment break form to be completed).*

DOSE MODIFICATIONS

Pembrolizumab
See Immuno-oncology adverse event management guidelines

INVESTIGATIONS

Routine Blood test
1) Blood results required before SACT administration
FBC,U&Es including magnesium, ,Cr, LFTs Every cycle
TFT Every other cycle
ECG
Non urgent blood tests - Tests relating to disease response/progression

CONCURRENT MEDICATION

None required.

ANTIEMETIC POLICY

Low emetogenic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

See Immuno-oncology adverse event management guidelines
Involve consultant in all grade 2 or higher toxicities.

REFERENCES

CDF December 2018

PEMBROLIZUMAB (Keytruda) (metastatic)

Indication: As per Blueteq criteria (check website for most up to date criteria www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)
For the treatment of unresectable (can't be completely removed by surgery or has spread to other parts of the body and has been treated with ipilimumab (melanoma that is BRAF V600 mutation-positive must also have had treatment with vemurafenib, dabrafenib or trametinib) (NICE TA357) or not previously treated with ipilimumab (*NICE TA366****).***

DRUG REGIMEN

Day 1 **PEMBROLIZUMAB** 200mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes

Cycle Frequency: Every 21 days until disease progression

May switch to 6 weekly dosing after 4 doses of 200mg 3 weekly dosing
Day 1 **PEMBROLIZUMAB** 400mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes

Cycle Frequency: Every 42 days until disease progression ie 4 doses of 200mg 3 weekly then 400mg 6 weekly dosing until disease progression

Treatment breaks of up to 12 weeks beyond the expected cycle length of avelumab are allowed but solely to allow immune toxicities to settle *(treatment break form to be completed).*

DOSE MODIFICATIONS

Pembrolizumab
See Immuno-oncology adverse event management guidelines

INVESTIGATIONS

Routine Blood test
2) Blood results required before SACT administration

	Give	*Discuss*
Hb x g/dL	≥10	< 10
Plt x 10^9/L	≥100	< 100
Neutrophils x 10^9/L	≥1.5	< 1.5

FBC,U&Es including magnesium, ,Cr, LFTs Every cycle
TFT Every other cycle
ECG
Non urgent blood tests - Tests relating to disease response/progression

CONCURRENT MEDICATION

None required.

ANTIEMETIC POLICY

Low emetogenic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

See Immuno-oncology adverse event management guidelines
Involve consultant in all grade 2 or higher toxicities.

REFERENCES

EAMS March 2015
NICE TA357 October 2015
SPC July 2015

TALIMOGENE LAHERPAREPVEC (Imlygic) (gene therapy)

Indication: As per Blueteq criteria (check website for most up to date criteria www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)
Talimogene laherparepvec for treating unresectable metastatic melanoma
For cutaneous, subcutaneous or nodal deposit(s) of melanoma which is/are suitable for direct injection but is/are not surgically resectable. When systemically administered immunotherapies or approved targeted therapies are not considered the best option by the specialist melanoma MDT.
Stage IIIb, stage IIIc or stage IVM1a disease and if stage IVM1a disease (ie metastases to the skin, subcutaneous tissues or distant lymph nodes) has a normal serum LDH.
The patient has no bone, brain, lung or any other visceral secondaries and if stage IVM1a disease, the serum LDH is not elevated.
Only be administered as a single agent and not in combination with systemic therapies eg chemotherapy, targeted agents or immunotherapy unless this is within the context of a HRA clinical trial. *NICE TA410*
This is a gene therapy product and as such should not be prescribed, clinically screened, administered or handled by those who are not trained to do so.
Blueteq registration required for all patients

DRUG REGIMEN

TALIMOGENE LAHERPAREPVEC intralesional injection

Talimogene laherparepvec is provided in single use vials of 1 mL each in two different concentrations:
• 10^6 (1 million) PFU/mL - For initial dose only.
• 10^8 (100 million) PFU/mL - For all subsequent doses.
The total injection volume for each treatment visit should be up to a maximum of 4 mL. The initial recommended dose is up to a maximum of 4 mL of Talimogene laherparepvec at a concentration of 10^6 (1 million) PFU/mL. Subsequent doses should be administered up to 4 mL of Talimogene laherparepvec at a concentration of 10^8 (100 million) PFU/mL.

Treatment visit	Treatment interval	Maximum total injection volume	Dose concentrations	Prioritisation of lesions to be injected
Initial	-	Up to 4 mL	10^6 (1 million) PFU/mL	• Inject largest lesion(s) first. • Prioritise injection of remaining lesions based on lesion size until maximum injection volume is reached.
Second	3 weeks after initial treatment	Up to 4 mL	10^8 (100 million) PFU/mL	• First inject any new lesions (lesions that may have developed since initial treatment). • Prioritise injection of remaining lesions based on lesion size until maximum injection volume is reached.
All subsequent treatment visits (including re-initiation)	2 weeks after previous treatment	Up to 4 mL	10^8 (100 million) PFU/mL	• First inject any new lesions (lesions that may have developed since previous treatment). • Prioritise injection of remaining lesions based on lesion size until maximum injection volume is reached.

Lesion size (longest dimension)	Talimogene laherparepvec injection volume
> 5 cm	up to 4 mL
> 2.5 cm to 5 cm	up to 2 mL
> 1.5 cm to 2.5 cm	up to 1 mL
> 0.5 cm to 1.5 cm	up to 0.5 mL
≤ 0.5 cm	up to 0.1 mL

DOSE MODIFICATIONS
None

INVESTIGATIONS
Routine blood tests

CONCURRENT MEDICATION
None

ANTIEMETIC POLICY
None

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Cellulitis and impaired healing at injection site
Plasmacytoma
Influenza like symptoms

REFERENCES
NICE TA410

IMIQUIMOD

Indication: Superficial basal cell carcinoma, Bowen's disease, Lentigo Maligna

DRUG REGIMEN
Apply imiquimod 5% cream 5 times per week for 6 weeks leaving on the skin for 8 hours overnight

DOSE MODIFICATIONS
None

INVESTIGATIONS
None

CONCURRENT MEDICATION
None

ANTIEMETIC POLICY
None

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

REFERENCES
1. Geisse J, Caro I, Lindholm J, Golitz L, Stampone P, Owens M. J Am Acad Dermatol. 2004 May;50(5):722-33.

CEMIPLIMAB (Libtayo)

***Indication:* Cemiplimab monotherapy for the treatment of patients with locally advanced or metastatic cutaneous squamous cell carcinoma where all the treatment criteria met:**
3. Histologically- or cytologically-confirmed diagnosis of cutaneous squamous cell carcinoma.
4. Either locally advanced disease or metastatic disease and is not a candidate for curative surgery or curative radiotherapy.
5. The patient does not have a contra-indication to being treated with cemiplimab and that I am aware that immunocompromised patients were not included in the main cemiplimab clinical study: exclusion criteria in this study excluded any patient with a previous solid organ transplant or autoimmune disease which required systemic therapy with immunosuppressive agents within the previous 5 years or a history of pneumonitis within the last 5 years.
6. Cemiplimab is to be given solely as monotherapy
7. Treatment with cemiplimab will continue until loss of clinical benefit or unacceptable toxicity or withdrawal of patient consent or for a maximum treatment duration of 2 years (or 35 3-weekly cycles of cemiplimab), whichever occurs first. In those patients transferring from the Sanofi early access scheme (see below in criterion 10), a maximum total treatment duration of 2 years of treatment applies.
8. Fit for treatment with cemiplimab and has an ECOG performance status score of 0 or 1. NB a patient with an ECOG PS of 2 or more is not eligible for funding.
9. No symptomatically active brain metastases or leptomeningeal metastases.
10. The patient has not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody unless the patient has been entered into the Sanofi cemiplimab early access scheme and all other treatment criteria on this form are fulfilled (eg ECOG performance status).
11. A formal medical review as to whether treatment with cemiplimab should continue or not will be scheduled to occur at least by the end of the first 6 weeks of treatment.
12. Treatment breaks of up to 12 weeks beyond the expected cycle length are allowed but solely to allow any immune toxicities to settle.
13. Cemiplimab will be otherwise used as set out in its Summary of Product Characteristics

DRUG REGIMEN

Day 1 CEMIPLIMAB 350mg IV infusion in 100ml sodium chloride 0.9% over 30 minutes via 0.2/0.22micron in-line filter.

***Cycle Frequency:* every 3 weeks until progression up to a maximum of 2 years**

DOSE MODIFICATIONS

Pneumonitis
Grade 2 -Withhold cemiplimab. Initial dose of 1 to 2mg/kg/day prednisone or equivalent followed by a taper.
Resume cemiplimab if pneumonitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10mg/day prednisone or equivalent
Grade 3 or 4 or recurrent Grade 2 - Permanently discontinue. Initial dose of 2 to 4mg/kg/day prednisone or equivalent followed by a taper.

Colitis
Grade 2 or 3 - Withhold cemiplimab. Initial dose of 1 to 2mg/kg/day prednisone or equivalent followed by a taper.
Resume cemiplimab if colitis or diarrhoea improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10mg/day prednisone or equivalent.
Grade 4 or recurrent Grade 3 - Permanently discontinue. Initial dose of 1 to 2mg/kg/day prednisone or equivalent followed by a taper.

Hepatitis
Grade 2 with AST or ALT >3 and ≤5×ULN or total bilirubin >1.5 and ≤3×ULN - Withhold cemiplimab Initial dose of 1 to 2mg/kg/day prednisone or equivalent followed by a taper.
Resume cemiplimab if hepatitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10mg/day prednisone or equivalent or returns to baseline AST or ALT after completion of corticosteroid taper.
Grade ≥3 with AST or ALT >5×ULN or total bilirubin >3×ULN - Permanently discontinue. Initial dose of 1 to 2mg/kg/day prednisone or equivalent followed by a taper

Hypothyroidism
Grade 3 or 4 - Withhold cemiplimab Initiate thyroid hormone replacement as clinically indicated
Resume cemiplimab when hypothyroidism returns to Grade 0 to 1 or is otherwise clinically stable

Hyperthyroidism
Grade 3 or 4 - Withhold cemiplimab Initiate symptomatic management
Resume cemiplimab when hyperthyroidism returns to Grade 0 to 1 or is otherwise clinically stable

Hypophysitis
Grade 2 to 4 - Withhold cemiplimab Initial dose of 1 to 2mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated.
Resume cemiplimab if hypophysitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or is otherwise clinically stable.

Adrenal insufficiency
Grade 2 to 4 - Withhold cemiplimab. Initial dose of 1 to 2mg/kg/day prednisone or equivalent followed by a taper.
Resume cemiplimab if adrenal insufficiency improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10mg/day prednisone or equivalent or is otherwise clinically stable.

Type 1 diabetes mellitus
Grade 3 or 4 (hyperglycaemia) - Withhold cemiplimab Initiate treatment with anti-hyperglycaemics as clinically indicated.
Resume cemiplimab when diabetes mellitus returns to Grade 0 to 1 or is otherwise clinically stable

Skin adverse reactions
Grade 2 lasting longer than 1 week, Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) - Withhold cemiplimab, Initial dose of 1 to 2mg/kg/day prednisone or equivalent followed by a taper
Resume cemiplimab if skin reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10mg/day prednisone or equivalent.
Grade 4 or confirmed SJS or TEN - Permanently discontinue. Initial dose of 1 to 2mg/kg/day prednisone or equivalent followed by a taper.

Immune-related skin reaction or other immune-related adverse reactions in patients with prior treatment with idelalisib
Grade 2 - Withhold cemiplimab. Initiate symptomatic management immediately, including initial dose of 1 to 2mg/kg/day prednisone or equivalent followed by a taper.
Resume cemiplimab if skin reaction or other immune-related adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent.
Grade 3 or 4 (excluding endocrinopathies) or recurrent Grade 2 - Permanently discontinue
Initiate symptomatic management immediately, including initial dose of 1 to 2mg/kg/day prednisone or equivalent followed by a taper Nephritis.
Grade 2 - Withhold cemiplimab. Initial dose of 1 to 2mg/kg/day prednisone or equivalent followed by a taper.
Resume cemiplimab if nephritis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10mg/day prednisone or equivalent.
Grade 3 or 4 - Permanently discontinue. Initial dose of 1 to 2mg/kg/day prednisone or equivalent followed by a taper.

Other immune-related adverse reactions (including but not limited to meningitis, paraneoplastic encephalomyelitis, arthritis, Guillain-Barre syndrome, encephalitis, chronic inflammatory demyelinating polyradiculoneuropathy, central nervous system inflammation, autoimmune myocarditis, and immune thrombocytopenic purpura, myalgia, Sjogren's syndrome, vasculitis, myasthenia gravis)
Grade 3 clinical signs or symptoms of an immune-related adverse reaction not described above - Withhold cemiplimab Initiate symptomatic management
Resume cemiplimab if other immune-related adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent
– Grade 4 adverse reaction (excluding endocrinopathies)
– Recurrent severe Grade 3 immune-related adverse reaction
– Persistent Grade 2 or 3 immune-related adverse reactions lasting 12 weeks or longer (excluding endocrinopathies)
– Inability to reduce corticosteroid dose to 10mg or less of prednisone or equivalent per day within 12 weeks
Permanently discontinue. Initial dose of 1 to 2mg/kg/day prednisone or equivalent followed by a taper

Infusion-related reaction
Grade 1 or 2 - Interrupt or slow rate of infusion Initiate symptomatic management.
Grade 3 or 4 - Permanently discontinue Initiate symptomatic management

INVESTIGATIONS
U&Es, LFTs, FBC
Endocrine profile including cortisol and glucose

CONCURRENT MEDICATION

ANTI-EMETIC POLICY
Low emetic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Immune related pneumonitis
Immune related colitis
Immune related hepatitis
Immune related endocrionapthies
Thyroid disorders
Hypophysitis
Type 1 diabetes mellitus
Immune related skin reactions
Immune related nephritis

REFERENCES
SPC

CISPLATIN and FLUOROURACIL (CF) infusor

Indication: Metastatic SCC (performance status 0-1 with no significant co-morbidities)

DRUG REGIMEN

Day 1 Pre-hydration
CISPLATIN 100mg/m^2 in 1000ml sodium chloride 0.9% infusion over 2 hours
FLUOROURACIL 4000mg/m^2 in an infusor over 96 hours
Post-hydration

N.B. For patients with performance status >2 reduce dose of cisplatin to 80mg/m^2 and fluorouracil to 3200mg/m^2.
NB The fluorouracil may be given via an inpatient daily infusion instead.

Cycle Frequency: Every 21 days for 6 cycles

DOSE MODIFICATIONS

Cisplatin
GFR >60ml/min give 100% dose
GFR 45-60ml/min give 75% dose
GFR <45ml/min consider carboplatin
If patient complains of tinnitus, tingling of fingers and/or toes discuss with SpR or Consultant before administration

Fluorouracil
Consider dose reduction in severe renal impairment only.
Bilirubin >85micromol/L or AST >180 omit

Treatment delays
If neutrophils <1.5x10^9/L and/or the platelet count < 100x10^9/L delay chemotherapy by one week, recheck blood count.
If satisfactory (>1.5 x 10^9/L and >100x10^9/L) give 75% dose of Cisplatin and fluorouracil.
If not satisfactory delay by a further week and recheck blood count,
if satisfactory (>1.5 x 10^9/L and >100 x 10^9/L) then give 50% dose of Cisplatin and fluorouracil.
If still unsatisfactory after 2 week delay chemotherapy should be discontinued.

INVESTIGATIONS

Routine Blood test

1. Blood results required before SACT administration

	Give	*Discuss*
Hb x g/dL	≥10	< 10
Plt x 10^9/L	≥100	< 100
Neutrophils x 10^9/L	≥1.5	< 1.5

Creatinine clearance (GFR) calculated or EDTA at the Consultant discretion. (Cisplatin)

Liver function tests

2. Non urgent blood tests

Tests relating to disease response/progression

CONCURRENT MEDICATION

Ensure adequate pre and post hydration prescribed as per day case schedule at the end of the TVCN protocols. If urine output is < 100 ml/hour or patient gains > 2kg in weight during IV administration post Cisplatin give 20-40 mg Furosemide PO/IV or 200 ml Mannitol 10% IV

ANTIEMETIC POLICY

Highly emetogenic day 1
Low emetogenic risk days 2, 3, 4

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Nephrotoxicity – ensure adequate pre and post hydration is prescribed.
Ototoxicity – assess patient for tinnitus or hearing abnormalities.
Palmar plantar (hand foot syndrome) causing red palms and soles – treat with pyridoxine 50mg tds
Mucositis – use routine mouthcare
Diarrhoea –treat with codeine or loperamide
Cardiotoxicity - special attention is advisable in treating patients with a history of heart disease, arrhythmias or angina pectoris or those who develop chest pain during treatment with fluorouracil.

REFERENCES

CISPLATIN and FLUOROURACIL (CF PS>2) infusor

Indication: Metastatic SCC (performance status 0-1 with co-morbidities or older patients)

DRUG REGIMEN

Day 1 Pre-hydration
CISPLATIN 80mg/m^2 in 1000ml sodium chloride 0.9% infusion over 2 hours
FLUOROURACIL 3200mg/m^2 in an infusor over 96 hours
Post-hydration

N.B. For patients with performance status <2 increase dose of cisplatin to 100mg/m^2 and fluorouracil to 4000mg/m^2.
NB The fluorouracil may be given via an inpatient daily infusion instead.

Cycle Frequency: Every 21 days for 6 cycles

DOSE MODIFICATIONS

Cisplatin
GFR >60ml/min give 100% dose
GFR 45-60ml/min give 75% dose
GFR <45ml/min consider carboplatin
If patient complains of tinnitus, tingling of fingers and/or toes discuss with SpR or Consultant before administration

Fluorouracil
Consider dose reduction in severe renal impairment only.
Bilirubin >85micromol/L or AST >180 omit

Treatment delays
If neutrophils <1.5x10^9/L and/or the platelet count < 100x10^9/L delay chemotherapy by one week, recheck blood count.
If satisfactory (>1.5 x 10^9/L and >100x10^9/L) give 75% dose of Cisplatin and fluorouracil.
If not satisfactory delay by a further week and recheck blood count, if satisfactory (>1.5 x 10^9/L and >100 x 10^9/L) then give 50% dose of Cisplatin and fluorouracil.
If still unsatisfactory after 2 week delay chemotherapy should be discontinued.

INVESTIGATIONS

Routine Blood test

1. Blood results required before SACT administration

	Give	*Discuss*
Hb x g/dL	≥10	< 10
Plt x 10^9/L	≥100	< 100
Neutrophils x 10^9/L	≥1.5	< 1.5

Creatinine clearance (GFR) calculated or EDTA at the Consultant discretion. (Cisplatin)
Liver function tests

2. Non urgent blood tests

Tests relating to disease response/progression

CONCURRENT MEDICATION

Ensure adequate pre and post hydration prescribed as per day case schedule at the end of the TVCN protocols. If urine output is < 100 ml/hour or patient gains > 2kg in weight during IV administration post Cisplatin give 20-40 mg Furosemide PO/IV or 200 ml Mannitol 10% IV

ANTIEMETIC POLICY

Highly emetogenic day 1
Low emetogenic risk days 2, 3, 4

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Nephrotoxicity – ensure adequate pre and post hydration is prescribed.
Ototoxicity – assess patient for tinnitus or hearing abnormalities.
Palmar plantar (hand foot syndrome) causing red palms and soles – treat with pyridoxine 50mg tds
Mucositis – use routine mouthcare
Diarrhoea –treat with codeine or loperamide
Cardiotoxicity - special attention is advisable in treating patients with a history of heart disease, arrhythmias or angina pectoris or those who develop chest pain during treatment with fluorouracil.

REFERENCES

VISMODEGIB (Erivedge)

Indication: Locally advanced or metastatic basal cell carcinoma, inappropriate for surgery or radiotherapy

Ensure individual funding has been obtained for patient prior to prescribing

DRUG REGIMEN

Day 1 **VISMODEGIB** 150mg orally once daily

Cycle Frequency: Every 28 days until disease progression or unacceptable toxicity

DOSE MODIFICATIONS

Vismodegib

No specific dose recommendations for these patient populations are available. Patients with severe renal impairment or moderate to severe hepatic impairment should be carefully monitored for adverse reactions

INVESTIGATIONS

Routine Blood test
Blood results required before SACT administration
FBC, Biochemistry, ECG
FBC and U&Es including magnesium
Serum creatinine
Non urgent blood tests - Tests relating to disease response/progression
Pregnancy prevention portal

CONCURRENT MEDICATION

ANTIEMETIC POLICY

Moderate to high emetogenic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Nausea, diarrhoea, constipation
Pruritis
Muscle spasms

REFERENCES

1. SPC August 2013

NHS
Thames Valley

AVELUMAB (Bavencio)

Indications: As per Blueteq criteria (check website for most up to date criteria www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)
The treatment of previously untreated (with systemic therapy) metastatic Merkel cell carcinoma where the patient has a confirmed histological or cytological diagnosis of metastatic Merkel cell carcinoma. *NICE TA517*
Avelumab is to be used as monotherapy only
Treatment naïve to any systemic anti-cancer therapy for Merkel cell carcinoma and in particular has not received any prior treatment with any anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti-cytotoxic T-lymphocyte-associated antigen-4 [CTLA-4] antibody
ECOG PS of either 0 or 1. Note: a patient with a PS ≥ 2 is not eligible for avelumab
Any brain metastases have been treated and are stable

The treatment of previously treated (with systemic cytotoxic chemotherapy) metastatic Merkel cell carcinoma where the patient has a confirmed histological or cytological diagnosis of metastatic Merkel cell carcinoma.
Avelumab is to be used as monotherapy only
Patient has previously been treated with cytotoxic chemotherapy for metastatic Merkel cell carcinoma and has not received any prior treatment with any anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti-cytotoxic T-lymphocyte-associated antigen-4 [CTLA-4] antibody
ECOG PS of either 0 or 1. Note: a patient with a PS ≥ 2 is not eligible for avelumab
Any brain metastases have been treated and are stable
Blueteq registration required for all patients

DRUG REGIMEN

Pre medication (30 minutes prior to Avelumab infusion for first 4 cycles, then if the fourth infusion is completed without an infusion-related reaction, premedication for subsequent doses should be administered at the discretion of the physician.):

Chlorphenamine 10 mg iv bolus
Paracetamol 1 g po

AVELUMAB 10mg/kg iv infusion in 250 ml sodium chloride 0.9% over 60 minutes

Cycle Frequency: Every 14 days
A medical review as to whether treatment with avelumab should continue or not will need to occur at least by the end of the first 8 weeks of treatment
Avelumab is to be continued until loss of clinical benefit or unacceptable toxicity or patient choice to stop treatment. Patients with radiological disease progression not associated with significant clinical deterioration (defined as no new or worsening symptoms and no change in performance status for greater than 2 weeks and no need for salvage therapy: all 3 conditions must apply) can continue treatment.
Treatment breaks of up to 12 weeks beyond the expected cycle length of avelumab are allowed but solely to allow immune toxicities to settle *(treatment break form to be completed).*

DOSE MODIFICATIONS

See Immuno-oncology adverse event management guidelines

Guidelines for withholding or discontinuation of Avelumab:
Infusion-related reactions
Grade 1 infusion-related reaction
Reduce infusion rate by 50%

Grade 2 infusion-related reaction
Withhold until adverse reactions recover to Grade 0-1; restart infusion with a 50% slower rate

Grade 3 or Grade 4 infusion-related reaction
Permanently discontinue

Pneumonitis
Grade 2 pneumonitis
Withhold until adverse reactions recover to Grade 0-1

Grade 3 or Grade 4 pneumonitis or recurrent Grade 2 pneumonitis
Permanently discontinue

Hepatitis
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN
Withhold until adverse reactions recover to Grade 0-1

AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN
Permanently discontinue

Colitis
Grade 2 or Grade 3 colitis or diarrhoea
Withhold until adverse reactions recover to Grade 0-1

Grade 4 colitis or diarrhoea or recurrent Grade 3 colitis
Permanently discontinue

Endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, hyperglycaemia)
Grade 3 or Grade 4 endocrinopathies
Withhold until adverse reactions recover to Grade 0-1

Nephritis and renal dysfunction
Serum creatinine more than 1.5 and up to 6 times ULN - Withhold until adverse reactions recover to Grade 0-1
Serum creatinine more than 6 times ULN - Permanently discontinue

Other immune-related adverse reactions (including myocarditis myositis, hypopituitarism, uveitis, Guillain-Barré syndrome)
For any of the following:
• Grade 2 or Grade 3 clinical signs or symptoms of an immune-related adverse reaction not described above - Withhold until adverse reactions recover to Grade 0-1

For any of the following:
• Life threatening or Grade 4 adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy)
• Recurrent Grade 3 immune-related adverse reaction
• Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks
• Persistent Grade 2 or Grade 3 immune-mediate adverse reactions lasting 12 weeks or longer
Permanently discontinue

Renal impairment
No dose adjustment is needed for patients with mild or moderate renal impairment. There are insufficient data in patients with severe renal impairment for dosing recommendations.

Hepatic impairment
No dose adjustment is needed for patients with mild hepatic impairment. There are insufficient data in patients with moderate or severe hepatic impairment for dosing recommendations.

Infusion-related reactions
Infusion-related reactions, which might be severe, have been reported in patients receiving avelumab. Patients should be monitored for signs and symptoms of infusion-related reactions including pyrexia, chills, flushing, hypotension, dyspnoea, wheezing, back pain, abdominal pain, and urticaria.
For Grade 3 or Grade 4 infusion-related reactions, the infusion should be stopped and avelumab should be permanently discontinued.
For Grade 1 infusion-related reactions, the infusion rate should be slowed by 50% for the current infusion. For patients with Grade 2 infusion-related reactions, the infusion should be temporary discontinued until Grade 1 or resolved, then the infusion will restart with a 50% slower infusion rate.
In case of recurrence of Grade 1 or Grade 2 infusion-related reaction, the patient may continue to receive avelumab under close monitoring, after appropriate infusion rate modification and premedication with paracetamol and antihistamine.
In clinical trials, 98.6% (433/439) of patients with infusion-related reactions had a first infusion-related reaction during the first 4 infusions of which 2.7% (12/439) were Grade ≥ 3. In the remaining 1.4% (6/439) of patients, infusion-related reactions occurred after the first 4 infusions and all were of Grade 1 or Grade 2.

INVESTIGATIONS
FBC, renal and liver profiles

CONCURRENT MEDICATION FOR PREVENTION
Nil specific.

ANTIEMETIC POLICY
Minimal.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Immune related reactions
Immune related pneumonitis
Immune related hepatitis
Immune related colitis
Immune related nephritis and renal insufficency

REFERENCES
SPC September 2017

CARBOPLATIN ETOPOSIDE

Indication: Merkel cell cancer

DRUG REGIMEN

Day 1 **CARBOPLATIN** AUC 5 infusion in 500ml glucose 5% infusion over 30 minutes
Dose (mg) = AUC x (GFR+25)
ETOPOSIDE 100mg/m^2 infusion in 1000ml* sodium chloride 0.9% over 60 minutes
Day 2 **ETOPOSIDE** 100mg/m^2 infusion in 1000ml* sodium chloride 0.9% over 60 minutes
Day 3 **ETOPOSIDE** 100mg/m^2 infusion in 1000ml* sodium chloride 0.9% over 60 minutes

*doses 48mg to 88mg in 250ml, doses 96mg to 180mg in 500ml sodium chloride 0.9%

NB Day 2 and 3 can be given orally ETOPOSIDE 100mg/m^2 bd PO but is not recommended as oral absorption is variable (it may cause reduced efficacy or severe toxicity in patients), the intravenous route is preferred, however for logistical reasons the oral route may be necessary. Etoposide doses <200mg may be administered in 500ml sodium chloride 0.9%

Ideally EDTA GFR should be used,

Cycle Frequency: Every 21 days
Number of cycles: Usually 6 (subject to tolerance and response)

DOSE MODIFICATIONS

Carboplatin:
Discuss if patient has a serum creatinine > 150 micromol/L
If GFR / calculated CrCl = or < 20ml/min contraindicated.
Dose capped at GFR 125mls/min

Etoposide:
CrCl >50ml/min give 100% dose
CrCl 15-50ml/min give 75% dose
CrCl <15ml/min give 50% dose
Bilirubin 26-51micromol/L or AST 60-180u/L give 50% dose
Bilirubin >51micromol/L or AST >180u/L Clinical decision

INVESTIGATIONS

Routine Blood test 1) Blood results required before SACT administration

	Give	*Discuss*
Hb x g/dL	≥10	< 10
Plt x 10^9/L	≥100	< 100
Neutrophils x 10^9/L	≥1.5	< 1.5

Ideally EDTA GFR should be used (Carboplatin) Creatinine clearance (GFR) calculated, at the Consultants discretion
Liver function tests (LFT)

2) Non urgent blood tests. Tests relating to disease response/progression

CONCURRENT MEDICATION FOR PREVENTION

Anaphylaxis treatment should be prescribed if the patient has had an anaphylactic episode previously.
DEXAMETHASONE 20mg IV bolus
CHLORPHENAMINE 10mg IV bolus
RANITIDINE 50mg IV bolus
Carboplatin should be given at a slower rate e.g. 2-4 hours.

ANTIEMETIC POLICY

Moderate emetic risk day 1
Low emetic risk days 2 and 3

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Ototoxicity - monitor
Neurotoxicity – monitor.

REFERENCES

1. Skarlos DV *et al.* Ann Oncol 1994; 5: 601 607
2. Daniels, S. and S. Gabriel, Dosage adjustment for cytotoxics in renal impairment and hepatic impairment. 2009, The North London Cancer Network.
3. Study 12/14

LIPOSOMAL DOXORUBICIN (KS) (Caelyx)

Indication: treatment of AIDS-related Kaposi's sarcoma

Liposomal doxorubicin (Caelyx) may be used as first-line systemic chemotherapy, or as second line chemotherapy in AIDS-KS patients with disease that has progressed with, or in patients intolerant to, prior combination systemic chemotherapy comprising at least two of the following agents: a vinca alkaloid, bleomycin and standard doxorubicin (or other anthracycline).

DRUG REGIMEN

Day 1 PEGYLATED LIPOSOMAL DOXORUBICIN *2*0mg/m^2 in 250ml glucose 5% infusion over 30 minutes

Cycle Frequency: Every 14 days (maybe given every 21 days)

NB Continue treatment as needed to maintain a therapeutic response.

DOSE MODIFICATIONS

Previous neutropenic sepsis, discuss with Consultant or Registrar.

Dose reduce in severe liver impairment.
Bilirubin 20-50micromol/L give 75% dose
Bilirubin > 51micromol/L give 50% dose
Use with caution – do not exceed 100mg/m2

Palmar plantar erythema or stomatitis:
Delay for 1 week if grade 2 -4. Use steroids (e.g. prednisolone 30mg daily or Dexamethasone 8mg daily) for treatment. Anecdotally, pyridoxine 50mg tds can be used.
Give 75% dose if > 2 week delay at grade II.
Withdraw patient if >2 week delay grade 3 of above

Maximum cumulative dose = 450-550 mg/m^2 (in normal cardiac function)
= 400 mg/m^2 (in patients with cardiac dysfunction or exposed to mediastinal irradiation)

.

INVESTIGATIONS

Routine Blood test

1. Blood results required before SACT administration

	Give	*Discuss*
Hb x g/dL	≥10	< 10
Plt x 10^9/L	≥100	< 100
Neutrophils x 10^9/L	≥1.5	< 1.5

2. ECG monitoring (possibly ECHO), particularly if patient has pre-existing cardiac disease

3. Non-urgent blood tests

Tests relating to disease response/progression

ANTI-EMETIC POLICY

Low emetogenic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Cardiotoxicity – use with caution in cardiac dysfunction. Doxorubicin may be stopped in future cycles if signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue.
Infusion related reactions – allergic or anaphylactic like reactions consider prophylaxis
Palmar-plantar erythema treat with steroids prednisolone 30mg od or dexamethasone 8mg od. Consider pyridoxine.

REFERENCES

1. Caelyx Summary of Product Characteristics eMC
2. Daniels, S. and S. Gabriel, *Dosage adjustment for cytotoxics in renal impairment*. 2003, The North London Cancer Network.
3. Daniels, S. and S. Gabriel, *Dosage adjustment for cytotoxics in hepatic impairment*. 2003, The North London Cancer Network.

LIPOSOMAL DAUNORUBICIN (KS) (DAUNOXOME)

Indication: AIDS-related Kaposi's Sarcoma in patients with low CD4 cell counts (<200cells/mm^3) and extensive mucocutaneous or visceral disease.

DRUG REGIMEN

Day 1 PEGYLATED LIPOSOMAL DAUNORUBICIN 40mg/m^2 in 250ml glucose 5% infusion over 30-60 minutes

Cycle Frequency: Every 14 days

NB Continue treatment as needed to maintain a therapeutic response.
NB The recommended concentration after dilution is between 0.2 mg and 1 mg daunorubicin /mL of solution

DOSE MODIFICATIONS

Previous neutropenic sepsis, discuss with Consultant or Registrar.

Renal impairment
Cr >265micromol/L give 50% dose.

Hepatic impairment
Bilirubin 20-50micromol/L give 75% dose
Bilirubin >51micromol/L give 50% dose

LVEF must be determined when a cumulative dose of 320mg/m^2 has been reached, then every 160mg/m^2 thereafter, in order to identify at an early stage any changes in LVEF that may be a precursor to cardiomyopathy if liposomal daunorubicin (DaunoXome) therapy is continued

INVESTIGATIONS

Routine Blood test

1. Blood results required before SACT administration

	Give	*Discuss*
Hb x g/dL	≥10	< 10
Plt x 10^9/L	≥100	< 100
Neutrophils x 10^9/L	≥1.5	< 1.5

ECG monitoring (possibly ECHO), particularly if patient has pre-existing cardiac disease.

2. Non-urgent blood tests

Tests relating to disease response/progression

ANTI-EMETIC POLICY

Moderate emetogenic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Cardiotoxicity – monitor cardiac function. Daunorubicin may be stopped in future cycles if signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue.
Daunorubicin has been associated with local tissue necrosis at the site of drug infiltration, care should be taken to ensure that there is no extravasation of drug when DaunoXome is administered

REFERENCES

1. SUMMARY OF THE PRODUCT CHARACTERISTICS (Ireland) DaunoXome 2 mg/mL, concentrate for solution for infusion Gilead Sciences International Ltd, 09 August 2006

Pre-hydration and post-hydration regimens

Ensure adequate diuresis is obtained prior to administration and maintained during and after administration.

1. Inpatient

Pre 1L sodium chloride 0.9% + 20mmol KCl + 8mmol $MgSO_4$ infusion over 4 hours
Give cisplatin in 1000ml volume over 4 hours
Post 1L sodium chloride 0.9% + 20mmol KCl + 8mmol $MgSO_4$ infusion over 4 hours
1L sodium chloride 0.9% + 20mmol KCl + 8mmol $MgSO_4$ infusion over 4 hours

NB 1L sodium chloride 0.9% + 20mmol KCl + 8mmol $MgSO_4$ infusion over 6 hours if oral intake is inadequate

2. Day case

Pre 1L sodium chloride 0.9% + 20 mmol KCl + 8mmol $MgSO_4$ infusion over 2 hours
200ml mannitol 10% infusion over 30 minutes
Give cisplatin in 1000ml volume over 2 hours
Post 1L sodium chloride 0.9% + 20 mmol KCl + 8mmol $MgSO_4$ infusion over 2 hours

NB Furosemide 40mg may be added if required