TAFINLAR® (dabrafenib) + MEKINIST® (trametinib): YOUR GUIDE TO MANAGING ADVERSE EVENTS

This guide has been developed to advise on adverse event management for patients with BRAF V600-positive unresectable or metastatic melanoma treated with TAFINLAR + MEKINIST combination therapy.[1]

This is only to be used as guidance and is not intended to replace individual medical judgement or experience with your patients

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Prescribing information can be found on the last slide

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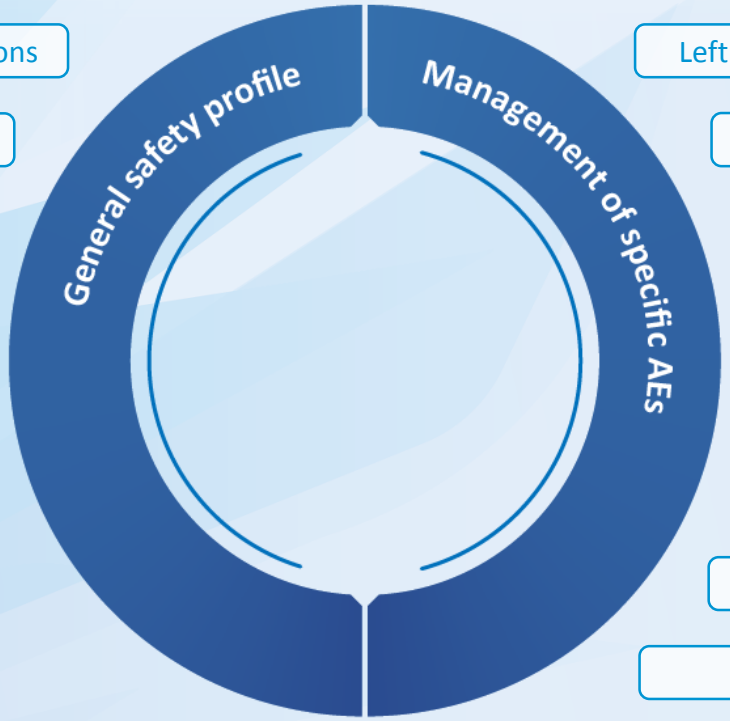

Your guide to managing adverse events

Dosing and administration

The recommended dose of TAFINLAR in combination with MEKINIST is 150 mg (two 75 mg capsules) twice daily. The recommended dose of MEKINIST is 2 mg once daily.[1]

If a dose of TAFINLAR is missed, it should not be taken if it is less than 6 hours until the next dose. If a dose of MEKINIST is missed, only take the dose of MEKINIST if it is more than 12 hours until the next scheduled dose.[1]

The management of adverse reactions may require treatment interruption, dose reduction or treatment discontinuation.[1]

Dose reductions of both TAFINLAR + MEKINIST (unless otherwise stated)[1,2]

Grade (CTCAE v4.0†)	Recommended dose modification
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

*Dose level reductions according to starting dose:
TAFINLAR: 150 mg twice daily to 100 mg twice daily; 100 mg twice daily to 75 mg twice daily; 75 mg twice daily to 50 mg twice daily.
MEKINIST: 2 mg once daily to 1.5 mg once daily; 1.5 mg once daily to 1 mg once daily (lowest dose).
†The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events (CTCAE) v4.0

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Contraindications and interactions

Contraindications

Any patients with contraindications to any active substance or excipient.

Drug interactions

Please refer to the Summary of Product Characteristics for TAFINLAR + MEKINIST for a full list of drug interactions before prescribing concomitant medicinal products.

TAFINLAR is an enzyme inducer and increases the synthesis of drug-metabolising enzymes (e.g. CYP3A4, CYP2Cs and CYP2B6). Due to this effect, interactions with many medicinal products metabolised by these enzymes or through active transport is expected. TAFINLAR may also be affected by the actions of other medicinal products, such as those affecting CYP2C8 and CYP3A4.[1]

MEKINIST may have drug-drug interactions via deacetylation mediated by hydrolytic enzymes (e.g. carboxyl-esterases). As MEKINIST is an in vitro substrate of P-gp, caution is advised when co-administering with strong P-gp inhibitors.[1]

Most common adverse events (≥10%) with TAFINLAR + MEKINIST combination therapy[1]

System Organ Class	Adverse Reaction
Infections and infestations	Urinary tract infection Nasopharyngitis
Blood and lymphatic system disorders	Neutropenia
Metabolism and nutrition disorders	Decreased appetite
Nervous system disorders	Headache Dizziness
Vascular disorders	Hypertension Haemorrhage*
Respiratory, thoracic and mediastinal disorders	Cough
Gastrointestinal disorders	Abdominal pain Constipation Diarrhoea Nausea Vomiting

System Organ Class	Adverse Reaction
Hepatobiliary disorder	Alanine aminotransferase increased Aspartate aminotransferase increased
Skin and subcutaneous disorders	Dry skin Pruritus Rash Dermatitis acneiform
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia Pain in extremity
General disorders and administration site conditions	Fatigue Chills Asthenia Peripheral oedema Pyrexia

* Bleeding from various sites, including intracranial bleeding and fatal bleeding

Monitoring recommendations[1,2]

Test	Frequency
Skin evaluation for new malignancies, including: cutaneous squamous cell carcinoma (cuSCC) and new primary melanoma	Prior to treatment initiation and monthly on treatment Continue for up to 6 months after stopping TAFINLAR + MEKINIST
Non-cutaneous malignancies: **head and neck examination with minimally visual inspection of oral mucosa and lymph node palpation**	Prior to initiation of therapy Every 3 months during treatment or as clinically appropriate
chest/abdomen computerised tomography (CT) scan	Prior to initiation of therapy Every 6 months during treatment or as clinically appropriate
anal and pelvic examination (women)	Before treatment At end of treatment or as clinically appropriate
complete blood counts	As clinically indicated
Left ventricular ejection fraction (LVEF)*	LVEF should be evaluated prior to treatment initiation, one month after initiation and every 3 months during treatment or as clinically appropriate
Visual impairment*	Routine monitoring while on therapy (e.g. monitor patients for changes in vision, eye pain, photophobia, loss of vision, blurred vision, decreased acuity etc)
Hypertension*	Blood pressure (BP) should be measured at baseline and monitored during treatment
Renal failure†	Serum creatinine should be routinely monitored while on therapy

* MEKINIST treatment related
† TAFINLAR treatment related

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Special warnings and precautions[1,2]

Test	Frequency
Haemorrhage	Haemorrhagic events, including major haemorrhagic and fatal haemorrhages, have occurred in patients taking TAFINLAR + MEKINIST If haemorrhage occurs, patients should be treated as clinically indicated
Pyrexia	Fever has been reported in clinical trials with TAFINLAR as monotherapy (1% of patients experienced serious non-infectious febrile events) and in combination with MEKINIST (see pages 10 and 11 for management)
Interstitial lung disease (ILD) /pneumonitis	Cases of pneumonitis or ILD have been reported in clinical trials with TAFINLAR + MEKINIST
Rash	Rash has been observed in about 25% of patients in clinical studies with TAFINLAR + MEKINIST (see pages 18 and 19 for management)
Rhabdomyolysis	Rhabdomyolysis has been reported in patients taking TAFINLAR + MEKINIST; severe cases may require hospitalisation, interruption or permanent discontinuation of treatment. Signs or symptoms of rhabdomyolysis warrant clinical evaluation and treatment as indicated
Pancreatitis	Pancreatitis has been reported in <1% of patients receiving TAFINLAR + MEKINIST Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase. Patients should be closely monitored when re-starting TAFINLAR after an episode of pancreatitis
Hepatic impairment	No dose adjustment is required for patients with mild hepatic impairment. There are no clinical data in subjects with moderate to severe hepatic impairment and the potential need for dose adjustment cannot be determined

Special warnings and precautions[1,2]

Test	Frequency
Deep vein thrombosis/ pulmonary embolism	Pulmonary embolism or deep vein thrombosis can occur with TAFINLAR + MEKINIST. Patients who develop shortness of breath, chest pain, or arm or leg swelling should immediately seek medical care Permanently discontinue TAFINLAR + MEKINIST for life-threatening pulmonary embolism
Colitis and gastrointestinal perforation	Colitis and gastrointestinal perforation, including fatal outcome, have been reported with TAFINLAR + MEKINIST; caution should be used in patients with risk factors for GI perforation and concomitant use of medications with a recognised risk of GI perforation
Renal impairment	No dosage adjustment is required for patients with mild or moderate renal impairment; due to lack of data, caution should be used in patients with severe renal impairment
Elderly	No adjustment of the initial dose of TAFINLAR is required in patients > 65 years of age Safety data in patients ≥ 75 years is limited for MEKINIST
Pregnancy	TAFINLAR should not be administered to pregnant women unless the potential benefit to the mother outweighs the possible risk to the foetus MEKINIST should not be administered to pregnant women or nursing mothers
Paediatric	The safety and efficacy of TAFINLAR + MEKINIST has not been established in children and adolescents (< 18 years)

Advice for counselling your patients at initiation of therapy

Do not take any new medications, including over the counter and herbal remedies, without asking your Hospital Team

Patients should be advised to keep a look out for these signs and symptoms and report to the Hospital Team:

- Feeling feverish, or experiencing chills; take your temperature and notify your healthcare professional immediately (see 'Pyrexia')
- Any rash, itching, skin soreness, or new lumps and bumps (see 'Rash', 'Other skin')
- Watery stools or motions, or going to the toilet more often than normal (see 'Rash', 'Other skin', 'Diarrhoea')
- Feeling joint pain or stiffness (see 'Arthralgia')
- Any visual disturbance (see 'Uveitis', 'RPED/RVO')
- Any difficulty breathing (see 'LVEF', 'Rash', 'ILD')

Pyrexia

In the 3-year update of COMBI-d, the incidence of pyrexia (defined as a body temperature of 38.5°C or more) was 59% (Grade 3, 7%) in patients treated with TAFINLAR + MEKINIST combination therapy, versus 33% (Grade 3, 2%) in patients treated with TAFINLAR alone.[3]

Approximately half of the first occurrences happened within the first month of therapy.[1] The median duration of the first event was 3 days and the majority were mild to moderate in severity.[4,5]

In patients receiving TAFINLAR in combination with MEKINIST, pyrexia may be accompanied by severe rigors, dehydration, and hypotension which in some cases can lead to acute renal insufficiency.[1]

Uncomplicated pyrexia can usually be managed with good patient education and symptomatic treatment or transient interruption of treatment.[4,6]

Practical advice

- Rule out infective cause. Check BP and carry out a full blood count to rule out neutropenia. If antifungal or antibiotic therapy is required, please refer to the Summary of Product Characteristics, as some products may interact with TAFINLAR.[1,6]
- Be aware that some patients with pyrexia may also have hypotension or general malaise and need to be hospitalised.[6]

Advice to patients[7]

- A lukewarm (tepid) bath and/or an ice pack or cool, moist flannel on the forehead or back of the neck can make you feel more comfortable.
- Drink plenty of (non-alcoholic and non-caffeinated) fluids, as fever can make you become dehydrated.
- Take appropriately prescribed antipyretic medication as recommended to control fever.

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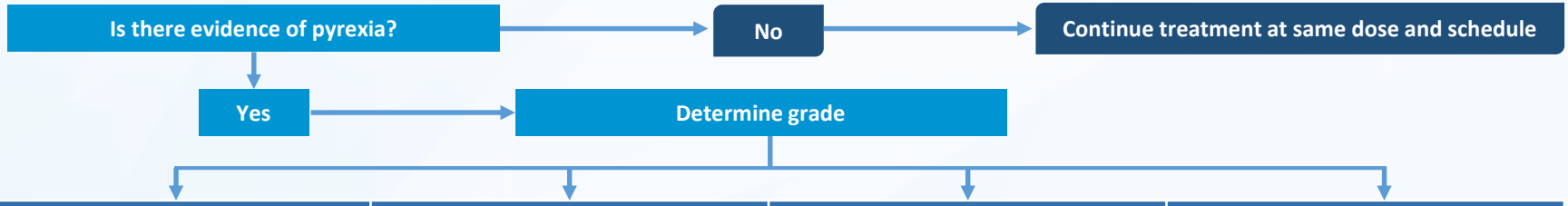
Managing pyrexia



Grade 1	Grade 2	Grade 3	Grade 4
38.0 - 39.0°C (100.4 -102.2°F).	>39.0 - 40.0°C (102.3 -104.0°F).	>40.0°C (>104.0°F) for ≤24 hrs.	>40.0°C (>104.0°F) for >24 hrs.

Evaluated for signs and symptoms of infection and if necessary treated in line with local practice.
If no infective source suspected, treatment with paracetamol and/or NSAIDs should be initiated.
The use of oral corticosteroids (e.g. prednisolone) should be considered in those instances in which anti-pyretics are insufficient.

No dose modification of MEKINIST is required

If temperature <38.5°C, continue TAFINLAR and monitor as clinically indicated.	If temperature ≥ 38.5°C, interrupt TAFINLAR until the fever resolves. The patient can continue taking their usual dose of MEKINIST. When the temperature resolves to <38.5ºC, within 3 days of dose interruption, the patient can re-start TAFINLAR.

Upon resolution of pyrexia, TAFINLAR should be restarted at the same dose level with appropriate anti-pyretic prophylaxis. If the pyrexia is recurrent and/or accompanied by other severe symptoms including dehydration, hypotension or renal failure, TAFINLAR dose should be reduced by one level when resuming TAFINLAR.* Consider admission to hospital if systemically unwell.	Upon resolution of pyrexia, TAFINLAR should be restarted at one dose level lower with appropriate anti-pyretic prophylaxis.* If Grade 4, reduce TAFINLAR by one dose level when resuming therapy, or consider discontinuation.* If no improvement, admit to hospital and consider intravenous fluids.

*TAFINLAR: 150 mg to 100 mg twice daily; 100 mg to 75 mg twice daily; 75 mg to 50 mg twice daily.

Adapted from references 1, 2, 6 and 8

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Left ventricular ejection fraction (LVEF)

In the integrated safety data from two Phase III clinical trials (n=559), decreased LVEF has been reported in 1% of patients treated with TAFINLAR as monotherapy, and 6 to 8% of patients treated with TAFINLAR in combination with MEKINIST, with most cases being asymptomatic and reversible.[1,2]

No dose reduction of TAFINLAR is necessary.[1]

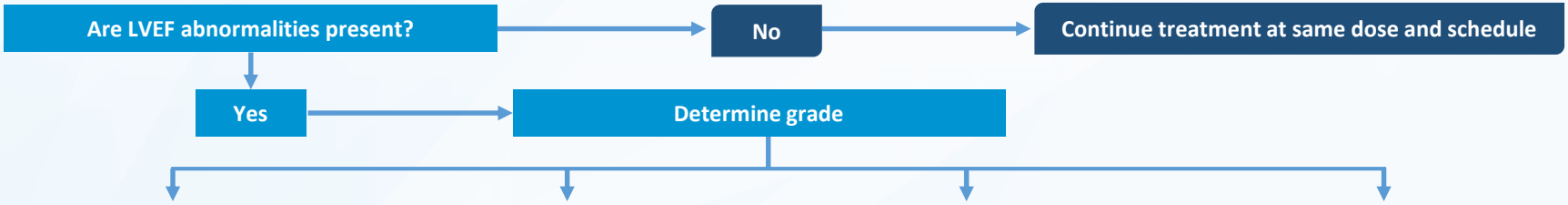
Practical advice[1,2,6]

- MEKINIST should be used with caution in patients with impaired LV function.

Advice to patients[9]

- Advise appropriate levels of exercise.
- Recommend relaxation techniques to alleviate anxiety.
- Suggest sleeping with head raised.

Managing left ventricular ejection fraction (LVEF)



Grade 1	Grade 2	Grade 3	Grade 4
LVEF ≥60%.	LVEF 40-59%.	Resting LVEF 39-20% or >20% absolute reduction from baseline.	Resting LVEF <20%.
Continue treatment.	Interrupt MEKINIST in patients with: • an asymptomatic decrease of >10% in LVEF • ejection fraction below 50% Reduce by one dose level when resuming therapy.†	If Grade 3/4 LVEF or intolerable Grade 2 LVEF occur, MEKINIST should be permanently discontinued.	

Adapted from references 2,6 and 10

†MEKINIST: 2 mg to 1.5 mg once daily; 1.5 mg to 1 mg once daily; 1 mg once daily (no reduction)

Retinal problems

Retinal pigment epithelial detachment (RPED) and retinal vein occlusion (RVO) may occur with TAFINLAR + MEKINIST.[2]

If RVO is diagnosed, treatment with MEKINIST should be permanently discontinued.[2]

RVO and RPED are likely to be class effects of MEK inhibition. In clinical trials with MEKINIST, the incidence of RVO and RPED across 1749 patients was 0.2% and 0.8%, respectively.[6]

The loss of visual acuity in patients developing RPED was resolved after a median of 11.5 days after stopping MEKINIST.[6]

Practical advice

- Prior to initiation of TAFINLAR + MEKINIST, carry out a risk assessment to exclude patients with ocular conditions that predispose to RVO such as glaucoma, ocular hypertension, uncontrolled hypertension and/or diabetes mellitus or a history of hyperviscosity or hypercoagulability syndromes. [2,6]
- If patients report new visual disturbances such as diminished central vision, blurry vision, or loss of vision at any time while on TAFINLAR + MEKINIST therapy, a prompt ophthalmological assessment is recommended.[2]

If RVO is diagnosed, treatment with MEKINIST should be permanently discontinued.

Advice to patients[11]

- Report any visual disturbance to your healthcare professional, especially:
  - the sudden appearance of floaters–black dots, specks or streaks that float across your field of vision (usually only one eye is affected)
  - if there are little floaters within the eye (cobweb effect). Patients also report a single large black floater, which resembles a housefly
  - if there are sudden short flashes of light in the affected eye lasting no more than a second
  - if there is blurring or distortion of vision.

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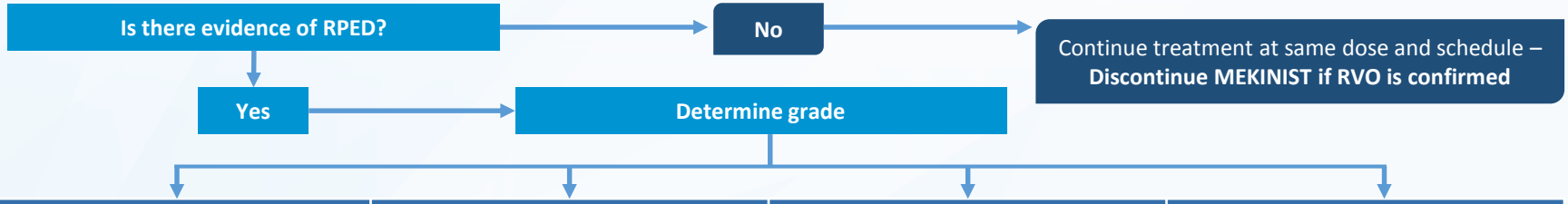
Managing retinal problems



Grade 1	Grade 2	Grade 3	Grade 4
Asymptomatic.	Exudative and visual acuity 20/40 or better.	Rhegmatogenous or exudative detachment; operative intervention indicated; decline in vision (worse than 20/40 but better than 20/200).	Blindness (20/200 or worse) in the affected eye.
No dose modification of TAFINLAR is required.			
Continue treatment with regular retinal evaluation until resolution. If RPED worsens follow instructions for higher grades and withhold MEKINIST for up to 3 weeks.	Withhold MEKINIST for up to 3 weeks. If improves to Grade 0-1 within 3 weeks, reduce MEKINIST by one dose level when resuming therapy.† If does not improve to Grade 0-1 in this time, discontinue MEKINIST permanently.	Refer to ophthalmology for urgent review. Withhold MEKINIST for up to 3 weeks. If improves to Grade 0-1 within 3 weeks, reduce MEKINIST dose by 0.5 mg when resuming therapy.† If does not improve to Grade 0-1 in this time, discontinue MEKINIST permanently.	Refer to ophthalmology for urgent review. Discontinue MEKINIST permanently.

Adapted from references 2 and 6

†MEKINIST: 2 mg to 1.5 mg once daily; 1.5 mg to 1 mg once daily; 1 mg once daily (no reduction)

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Uveitis

Inflammation of the uvea in the eyes (including iritis) is the most common ocular toxicity associated with TAFINLAR and has been reported in <1% of patients with TAFINLAR + MEKINIST.[12]

Uveitis tends to develop over weeks and months and is generally easily managed with temporary dose interruption/reduction and local control of inflammation.[6]

Practical advice

- Prior to initiating TAFINLAR + MEKINIST, a risk assessment should be undertaken to exclude from treatment patients with pre-existing ocular conditions, e.g. glaucoma.[6]
- Patients should be routinely monitored for visual signs and symptoms (such as, change in vision, photophobia, colour spots and eye pain) while on therapy.[1,2]

Advice to patients[13]

- Report any visual disturbance to your healthcare professional.
- Wear dark glasses when in bright sunshine.
- Place a warm flannel over the eye.
- Continue with any treatment prescribed for the full course.
- Try to avoid touching your eyes with the eye drop nozzle.
- Drops may cause blurriness, but this is temporary.

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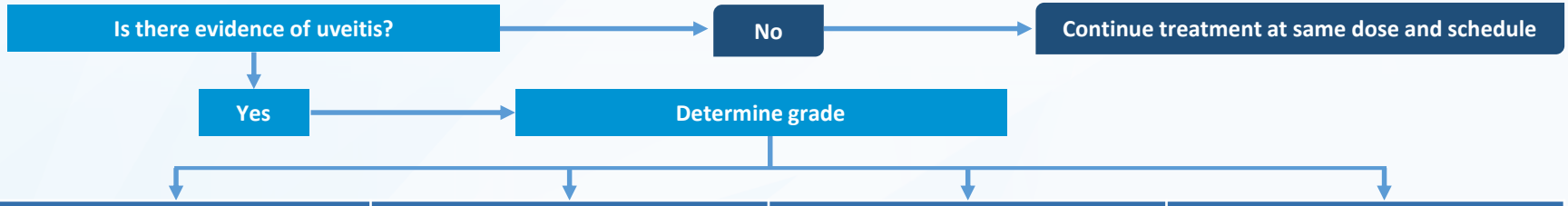
Managing uveitis



Grade 1	Grade 2	Grade 3	Grade 4
Asymptomatic; clinical or diagnostic observations only.	Anterior uveitis; medical intervention indicated.	Posterior or pan-uveitis.	Blindness (20/200 or worse) in the affected eye.
Treat with topical corticosteroids. **No dose modification of MEKINIST is required.**			
Continue treatment and monitor as clinically indicated. No dose modifications are required as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, withhold TAFINLAR until resolution of ocular inflammation and then restart reduced by one dose level.*	Medical intervention with local ocular therapy. Interrupt TAFINLAR and treat as above until toxicity is Grade 0-1, then restart reduced by one dose level.*		Discontinue TAFINLAR permanently, or interrupt therapy until Grade 0-1, then restart reduced by one dose level.*

Adapted from references 1, 6 and 8

*TAFINLAR: 150 mg to 100 mg twice daily; 100 mg to 75 mg twice daily; 75 mg to 50 mg twice daily

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Rash

In clinical studies with TAFINLAR + MEKINIST, rash was observed in about 25% of patients.[1,5,14] The incidence of rash was reduced with combination therapy versus vemurafenib monotherapy.[14]

Rashes associated with MEKINIST are usually papulopustular, which are often located on the face, scalp and chest. Maculopapular rashes are more common with TAFINLAR; these generally start on the trunk and often involve arms and legs but not usually the face.[15,16]

Milder rashes can be self-limiting and transient. In both Phase III trials, the incidence of Grade 3 rash was less than 5% in the TAFINLAR + MEKINIST arm.[6,11] Severe rashes can usually be avoided once an optimal dose has been identified within the first 2 months of therapy, and are generally reversible upon treatment discontinuation.[6, 17]

Majority of rashes require no dose interruption/reduction.[2]

Practical advice

- Eliminate allergic causes and exclude allergen if possible.
- Consider topical anti-pruritic medication, with or without corticosteroids.[15]
- Question patients about the presence of a rash during the first two weeks of therapy as this is when they are most likely to occur.[6,16]

Advice to patients[16]

- Notify your Hospital Team immediately if you have any difficulty breathing.
- Wear loose, non-irritating clothing.
- Use mild, unperfumed soaps when bathing.
- Dry your skin by gently patting the area rather than rubbing.
- Use sunscreen/protective clothing, even on cloudy days.
- Apply creams/ointments as recommended by your Hospital Team.

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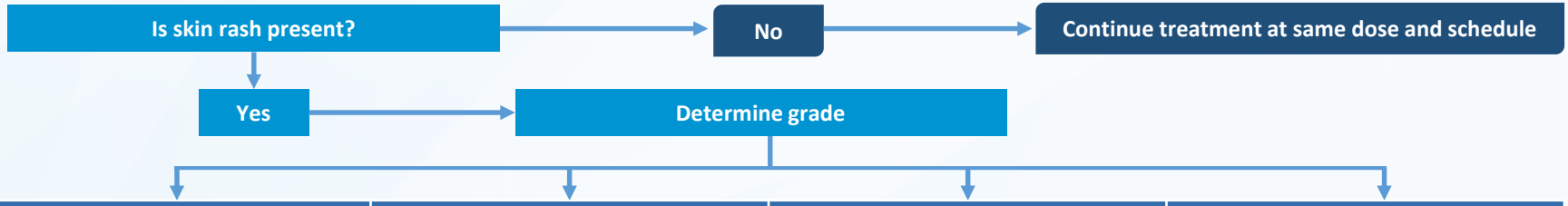
Managing rash



Grade 1	Grade 2	Grade 3	Grade 4
No symptoms.	Symptoms including itching or soreness. Affecting <50% of skin surface.	Symptoms including itching or soreness. Affecting ≥50% of skin surface.	Stevens-Johnson syndrome or toxic epidermal necrolysis. Widespread red skin, with peeling or blister formation + mucosal involvement.
Use emollients.	Treat with antihistamines and emollients. Consider topical corticosteroids.	Treat with emollients, antihistamines and topical corticosteroids. Consider oral prednisolone 0.5 mg/kg/day (up to 60 mg/day) for 5-7 days (or follow local policy).	
Continue treatment and monitor as clinically indicated.	If persistent, refer to dermatologist. If intolerable, interrupt therapy and treat as above until toxicity is Grade 0-1. Reduce by one dose level when resuming therapy.*†	Interrupt therapy until toxicity is Grade 0-1 and reduce by one dose level when resuming therapy.*† Refer to dermatologist.	Discontinue permanently. Hospitalise for intravenous hydration and electrolyte replacement. Request dermatological advice.

Adapted from references 1, 2 and 18

*TAFINLAR: 150 mg to 100 mg twice daily; 100 mg to 75 mg twice daily; 75 mg to 50 mg twice daily
†MEKINIST: 2 mg to 1.5 mg once daily; 1.5 mg to 1 mg once daily; 1 mg once daily (no reduction)

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Other skin problems

Patients treated with TAFINLAR + MEKINIST may experience a range of skin toxicities, including hyperkeratosis, skin papilloma and photosensitivity, squamous papillomas/warts, keratoacanthoma, dry skin, folliculitis or cysts, however they are rarely severe (Grade 3/4).[3,6]

Practical advice[1,2,6]

- Topical and oral steroids may be used for erythema nodosum-type rash.
- Some patients may need dermatological referral, in particular patients with SCC who should be referred urgently.
- Patients with cuSCC should not have their dose reduced as cases can be managed with excision.
- Sunburn should be treated as appropriate.

Advice to patients[6]

- For certain skin conditions (e.g. erythema nodosum-type rash and dry skin), patients should use emollients.
- Soap substitutes can be used to prevent skin drying.
- High SPF sunscreen can be used to protect against photosensitivity.

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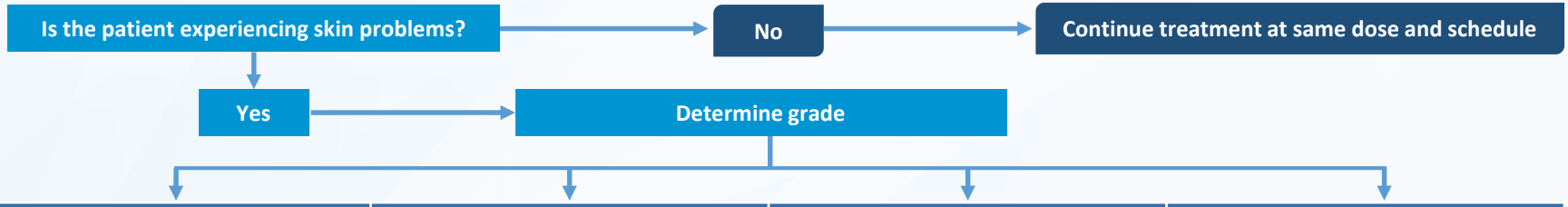
Managing other skin problems



Grade 1	Grade 2	Grade 3	Grade 4
No symptoms.	Symptoms including itching or soreness. Affecting <50% of skin surface.	Symptoms including itching or soreness. Affecting ≥50% of skin surface.	Stevens-Johnson syndrome or toxic epidermal necrolysis. Widespread red skin with peeling or blister formation and mucosal involvement.
Continue treatment. Observe. Use emollients.	Give antihistamines. Use emollients. If persistent and problematic, refer to dermatologist and consider topical steroids. Consider dose reduction of TAFINLAR + MEKINIST.*†	Interrupt TAFINLAR + MEKINIST. If toxicity returns to Grade 0 to 1 consider reducing by one dose level when resuming therapy.*† Topical treatments as before. Consider prednisolone 0.5 mg/kg/day (up to 60 mg/day) for 5-7 days.	Discontinue treatment. Hospitalise for IV hydration and electrolyte replacement. Refer to dermatologist.

Adapted from references 1, 2, 6 and 8

*TAFINLAR: 150 mg to 100 mg twice daily; 100 mg to 75 mg twice daily; 75 mg to 50 mg twice daily
†MEKINIST: 2 mg to 1.5 mg once daily; 1.5 mg to 1 mg once daily; 1 mg once daily (no reduction).

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Hypertension

In the 3-year update of COMBI-d, any grade hypertension occurred in 25% of 211 patients treated with TAFINLAR and MEKINIST, versus 16% of 212 TAFINLAR monotherapy patients. There were no Grade 3/4 events in the combination therapy arm.[3]

The incidence of hypertension in COMBI-d was similar to that seen in the Phase III METRIC study, where 15% (n=32) of TAFINLAR monotherapy-treated patients experienced any grade hypertension.[19]

Practical advice

- For prehypertension, monitor blood pressure every cycle while continuing treatment.
- For higher stages, hypertension should be treated according to local guidelines.

Advice to patients[20]

- Exercise as much as possible.
- Stop smoking.
- Try to reduce stress by following relaxation techniques.
- Eat a diet low in saturated fat and cholesterol, low in sodium, with lots of fresh fruits and vegetables.

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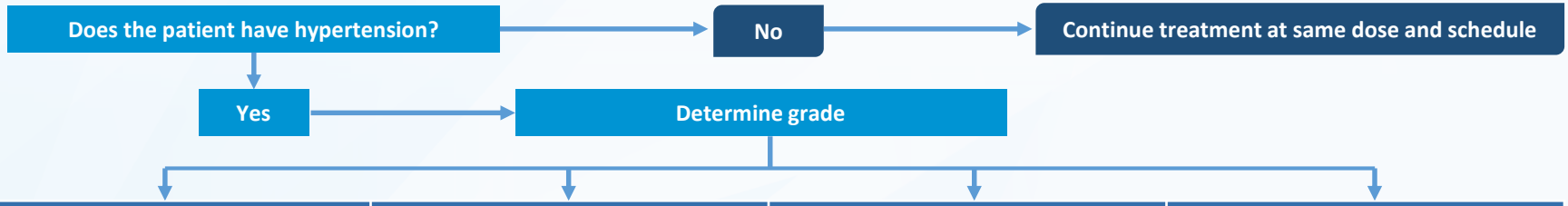
Managing hypertension



Grade 1	Grade 2	Grade 3	Grade 4
Prehypertension (BP 120 – 139 mm Hg or diastolic BP 80 - 89 mm Hg).	Stage 1 hypertension (Systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent (≥24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously within normal limits; monotherapy indicated.	Stage 2 hypertension (Systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated.	Life-threatening consequences; urgent intervention indicated.
Continue treatment. Monitor BP every cycle.	Continue treatment if tolerable. Treat hypertension according to local protocol. If intolerable, interrupt therapy until toxicity is Grade 0 to 1 and reduce by one dose level when resuming therapy.*†	Interrupt therapy. Treat hypertension according to local protocol. If intolerable, interrupt therapy until toxicity is Grade 0 to 1 and reduce by one dose level when resuming therapy.*†	Permanently discontinue therapy. Treat hypertension according to local protocol.

*TAFINLAR: 150 mg to 100 mg twice daily; 100 mg to 75 mg twice daily; 75 mg to 50 mg twice daily
†MEKINIST: 2 mg to 1.5 mg once daily; 1.5 mg to 1 mg once daily; 1 mg once daily (no reduction)

Adapted from references 1, 2, 6 and 8

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Pneumonitis and interstitial lung disease (ILD)

Pneumonitis is a known side effect of MEK inhibitors. In a Phase III trial, 2.4% (5/211) of patients treated with MEKINIST monotherapy developed ILD/pneumonitis, with a median time to presentation of 160 days.[2,6]

No dose reduction of TAFINLAR is necessary.[1]

Practical advice[1,2]

- Be alert for signs of pneumonitis with TAFINLAR + MEKINIST, it is rare, but can occur.
- MEKINIST should be withheld in patients with suspected ILD or pneumonitis, including patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnoea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations.

Advice to patients[21]

- Inform all healthcare providers of concomitant medications.
- Avoid smoking.
- Control secretions through coughing and deep breathing exercises.
- Take warm showers and baths to help control secretions.
- Try to avoid environmental allergens – e.g. smoke, pollution and seasonal allergens.

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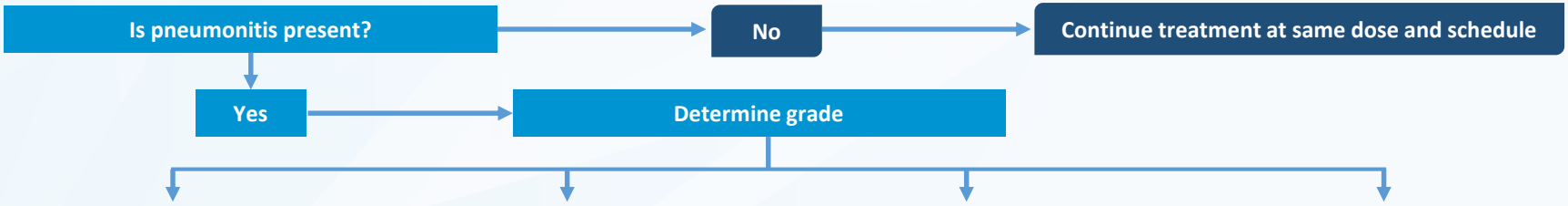
Managing pneumonitis and ILD



Grade 1	Grade 2	Grade 3	Grade 4
Asymptomatic; clinical or diagnostic observations only.	Symptomatic; medical intervention indicated; limiting instrumental activities of daily living (ADL).	Severe symptoms; limiting self-care ADL; oxygen indicated.	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation).
Reduce dose of MEKINIST and repeat chest X-ray.	Interrupt therapy; perform CT chest scan. Commence high-dose steroids. If toxicity returns to Grade 0 to 1 consider reducing MEKINIST by one dose level when resuming therapy. † Permanently discontinue MEKINIST if pneumonitis recurs.	Discontinue MEKINIST permanently. Perform CT chest scan and hospitalise. Refer to respiratory team. Prescribe high-dose steroids (according to local policy). No dose modification of TAFINLAR is needed for cases of pneumonitis/ILD when used in combination with MEKINIST.	

†MEKINIST: 2 mg to 1.5 mg once daily; 1.5 mg to 1 mg once daily; 1 mg once daily (no reduction)

Adapted from references 2, 6 and 8

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Arthralgia

Arthralgia was a very common adverse event in the COMBI-d trial, both in patients treated with TAFINLAR and MEKINIST (26%) and in patients treated with TAFINLAR monotherapy (32%). However, no Grade 4 events were seen and most cases were Grade 1 and 2 in severity, with only 6% Grade 3 in the combination therapy arm and 0% Grade 3 in the monotherapy arm.[3]

Arthralgia is not characteristic of MEKINIST-type therapy.[6]

Practical advice[23]

- Discuss the use of an incentive spirometer for 15 minutes per day, twice a day to promote oxygenation.

Advice to patients[23]

- Keep a diary of pain severity, location, intensity and duration to assess impact over time.
- Warm compresses may help if the source of pain can be found.
- If support groups are available locally, advise participation to help psychological impact.

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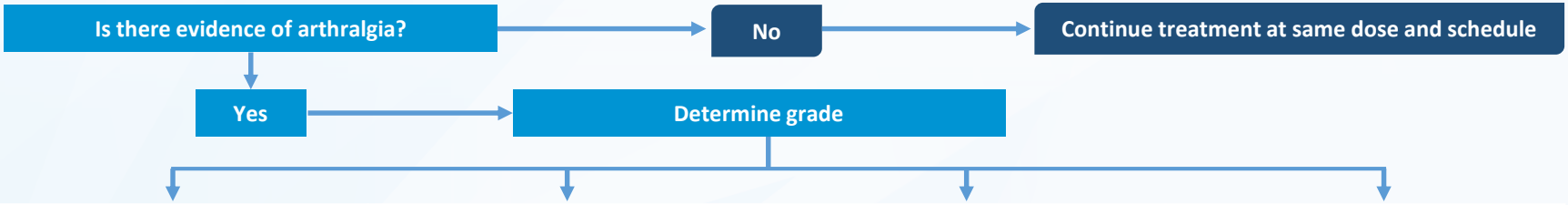
Managing arthralgia



Grade 1	Grade 2	Grade 3	Grade 4
Mild pain, not affecting ADL.	Moderate pain; limiting instrumental ADL.	Severe pain; limiting self-care activities of modern living.	
Prescribe paracetamol with or without an NSAID such as ibuprofen or aspirin.	Optimise analgesia; interrupt therapy until toxicity is Grade 0 to 1 and reduce TAFINLAR by one dose level when resuming therapy.* If symptoms recur repeat and consider adding low-dose corticosteroid (according to local policy) or reduce TAFINLAR dose further.* If symptoms persist after two TAFINLAR dose reductions, consider switching to another BRAFi.		

Adapted from references 1, 2, 6 and 8

*TAFINLAR: 150 mg to 100 mg twice daily; 100 mg to 75 mg twice daily; 75 mg to 50 mg twice daily

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Diarrhoea

In the 3-year COMBI-d update, 31% of patients treated with TAFINLAR + MEKINIST experienced any grade diarrhoea.[3]

Practical advice[1,2,6]

- Infectious causes should be ruled out.

Advice to patients

- Drink plenty of clear fluids (8-10 glasses per day).
- Patients with chronic but tolerable loose bowel motions should be advised of dietary modifications (e.g. the 'BRAT' diet – Bananas, Rice, Apples, Toast).[6]
- Avoid diarrhoea-inducing foods – e.g. greasy and fatty foods, strong spices, lactose containing products.[6,22]
- Clean skin around anus with warm water and soft cloth, then gently dry the complete area.[22]

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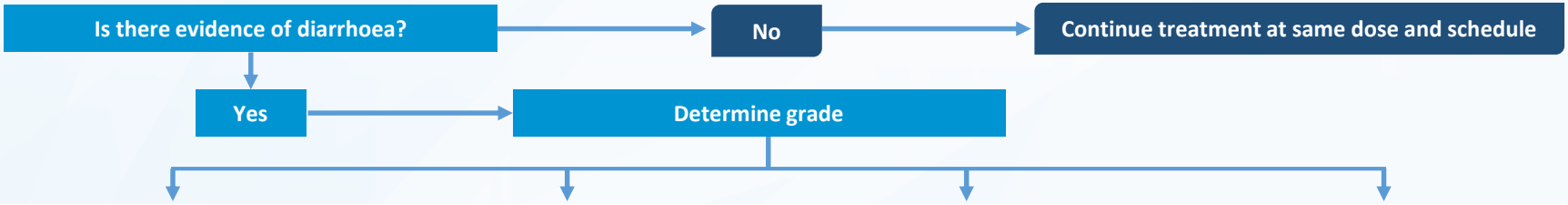
Managing diarrhoea



Grade 1	Grade 2	Grade 3	Grade 4
Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline.	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline.	Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL.	Life-threatening consequences; urgent intervention indicated.
Prescribe loperamide or codeine.	Continue loperamide or codeine. Interrupt therapy until toxicity is Grade 0 to 1 and reduce by one dose level when resuming therapy.*†	Discontinue therapy. Continue loperamide or codeine. Hospitalise for intravenous rehydration and electrolyte replacement. Give antibiotics if diarrhoea persists >24 hours, fever or Grade 3/4 neutropenia present. When toxicity returns to Grade 0 to 1, reduce by one dose level when resuming therapy.*†	Permanently discontinue treatment. Hospitalise for intravenous rehydration and electrolyte replacement. Consider colonoscopy to assess for colitis. Give antibiotics if diarrhoea persists >24 hours, fever or Grade 3/4 neutropenia present.

Adapted from references 1, 2, 6 and 8

*TAFINLAR: 150 mg to 100 mg twice daily; 100 mg to 75 mg twice daily; 75 mg to 50 mg twice daily
†MEKINIST: 2 mg to 1.5 mg once daily; 1.5 mg to 1 mg once daily; 1 mg once daily (no reduction)

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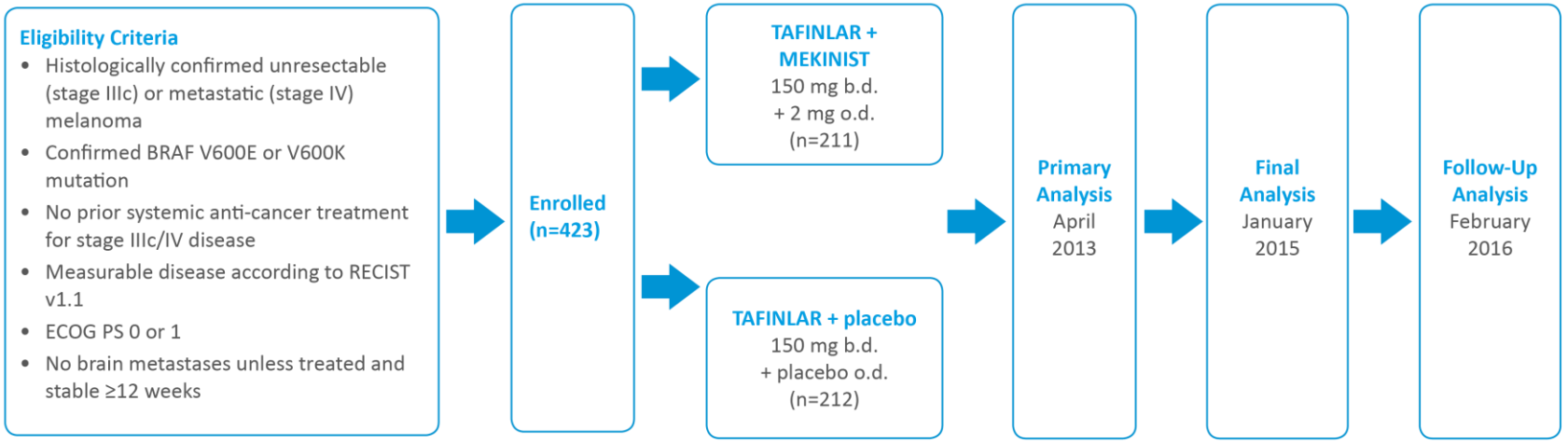
COMBI-d trial design

Phase III randomised trial of TAFINLAR + MEKINIST vs TAFINLAR monotherapy in BRAF mutation-positive metastatic melanoma[4]



RECIST=Response Evaluation Criteria In Solid Tumours; ECOG PS=Eastern Cooperative Oncology Group Performance Status.

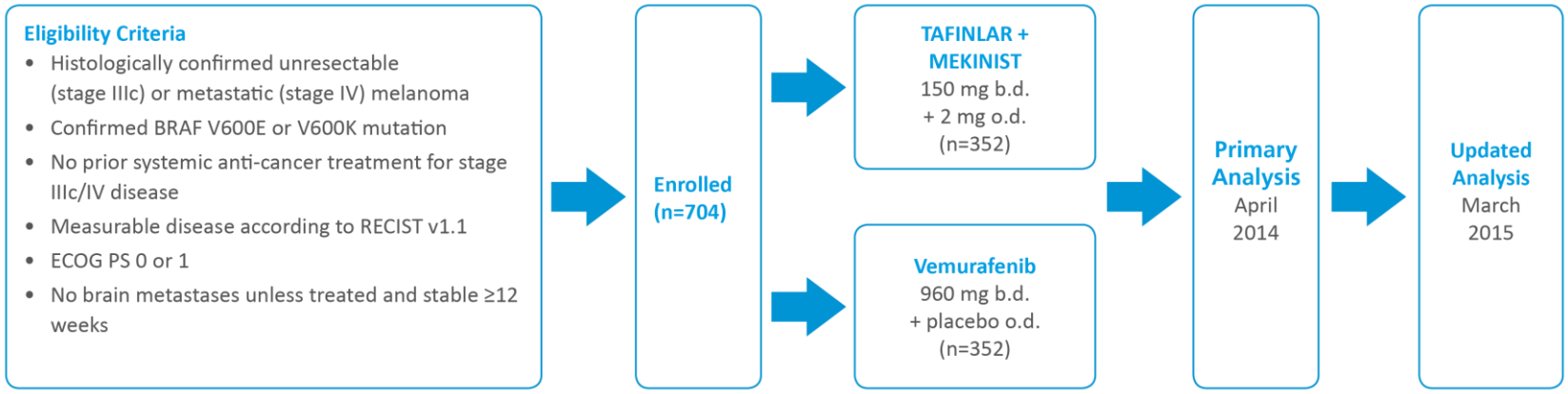
Adapted from reference 4

Study Endpoints

- Primary endpoint was investigator-assessed Progression-Free Survival (PFS)
- Secondary endpoints included: overall survival (OS), Overall Response Rate (ORR), durantion of response, safety and pharmacokintics
- No crossover was permited
- At 3-year time-point, patients were allowed to cross over prior to progression

COMBI-v trial design

Phase III randomised open-label trial of TAFINLAR + MEKINIST vs vemurafenib monotherapy in BRAF mutation positive metastatic melanoma[14]



Adapted from reference 14

RECIST=Response Evaluation Criteria In Solid Tumours; ECOG PS=Eastern Cooperative Oncology Group Performance Status.

Study Endpoints

- Primary endpoint Overall Survival (OS)
- Secondary endpoints included Progression-Free survival (PFS), Overall Response Rate (ORR), durantion of response, safety
- Crossover was only permitted after study was stopped for efficacy (July 2014) following review of results from the interim analysis (April 2014 data cut) by the Independent Data Monitoring Committee (IDMC)

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Prescribing Information

Prescribing Information
(Please refer to full Tafinlar and Mekinist SmPCs before prescribing)
Tafinlar®▼ (dabrafenib) 50mg and 75mg capsules. Each capsule contains dabrafenib mesilate, equivalent to 50mg and 75mg of dabrafenib, respectively. **Mekinist® ▼ (trametinib) 0.5mg and 2mg film-coated tablets**. Each tablet contains trametinib dimethyl sulphoxide, equivalent to 0.5mg and 2mg of trametinib, respectively. **Indication** Dabrafenib: As monotherapy and in combination with trametinib for adults with unresectable or metastatic melanoma with a BRAF V600 mutation. Trametinib: In combination with dabrafenib for adults with unresectable or metastatic melanoma with a BRAF V600 mutation. **Dosage and administration** Before taking dabrafenib or trametinib, patients must have confirmation of BRAF V600 mutation using a validated test. Dabrafenib: As monotherapy and in combination, 150mg twice daily (b.d.) with interval of ~12hrs between doses (max. total daily dose 300mg). Trametinib: In combination, 2mg once daily (o.d.), taken at same time each day with either morning or evening dose of dabrafenib. Treatment should continue until patient no longer derives benefit or develops unacceptable toxicity. Take both medicines whole with water, ≥1 hour before or ≥2 hours after a meal, at similar times every day; do not crush or chew. If dose of dabrafenib is missed, do not take if <6 hours until next dose. If trametinib dose is missed, do not take if <12 hours until next dose. *Dose modification:* Management of ADRs may require treatment interruption, dose reduction or discontinuation; this should occur simultaneously when both medicines used in combination with some exceptions (see Special Warnings & Precautions). Dabrafenib dose reduction is the same in monotherapy and in combination. 1st reduction: dabrafenib 100mg b.d., trametinib 1.5mg o.d; 2nd reduction: dabrafenib 75 mg b.d., trametinib 1mg o.d (min. dose); 3rd reduction: dabrafenib 50mg b.d. (min. dose), trametinib 1mg o.d. Consider dose re-escalation following same dosing steps as de-escalation when ADR under effective management. *Renal impairment:* Both medicines: no dose adjustment required in mild or moderate impairment; caution advised in severe renal impairment. *Hepatic impairment:* Both medicines: no dose adjustment required in mild impairment. Caution advised in moderate and severe hepatic impairment. *Elderly:* Both medicines; no initial dose adjustment required in patients >65 yrs. *Paediatrics:* Both medicines: safety & efficacy not established in patients <18 yrs. **Contraindications** Both medicines: hypersensitivity to active substance or excipients. **Special Warnings and Precautions** Not evaluated in wild-type BRAF melanoma; limited data for combination in patients who have progressed on prior BRAF inhibitor; not evaluated in patients with BRAF mutant melanoma metastatic to brain. *Cutaneous squamous cell carcinoma (CuSCC) and new primary melanoma:* Examine skin prior to treatment, monthly during treatment and for 6 months after discontinuation. Patients should inform their HCP immediately if a new lesion develops. Manage by excision; continue dabrafenib and trametinib without dose adjustment. *Deep vein thrombosis (DVT)/pulmonary embolism (PE):* Patients should seek immediate medical care if they develop symptoms of DVT or PE. Permanently discontinue both medicines if life-threatening PE. *Haemorrhage:* Risk increased with concomitant antiplatelet/anticoagulant therapy. Treat as clinically indicated. *Hepatic events:* Monitor liver function every 4 weeks for 6 months after starting combination treatment, then as clinically indicated. *Hypertension:* Monitor BP at baseline and during combination use and control hypertension with standard therapy as appropriate. *Interstitial lung disease (ILD):* Withhold trametinib in patients with suspected ILD or pneumonitis; discontinue trametinib permanently if treatment-related ILD or pneumonitis diagnosed and continue dabrafenib at same dose. *LVEF reduction/LV dysfunction:* Use trametinib with caution in patients with impaired LV function. Evaluate LVEF prior to treatment, after one month, then at 3 monthly intervals while on treatment. Interrupt trametinib if asymptomatic decrease >10% in LVEF vs. baseline and ejection fraction below LLN; continue dabrafenib at same dose. If LVEF recovers, restart trametinib at reduced dose with careful monitoring. Persistent LVEF reduction or Grade 3/4 LV dysfunction requires permanent discontinuation of trametinib. *Non-cutaneous secondary/recurrent malignancy:* Consider benefits and risks before administering dabrafenib to patients with a prior/concurrent cancer associated with RAS mutations. Undertake head and neck examination and chest/abdominal CT scan prior to treatment. Monitor as clinically appropriate during treatment and for up to 6 months after discontinuation. No dose modification of trametinib required. *Pancreatitis:* Investigate unexplained abdominal pain promptly, including serum amylase & lipase measurements. Monitor closely when re-starting dabrafenib. *Pyrexia:* Interrupt dabrafenib if temperature ≥38.5ºC and investigate for infection; continue trametinib at same dose. Initiate anti-pyretics (consider oral steroids if insufficient). Once fever resolves, restart dabrafenib, either at same dose, or at reduced dose if fever accompanied by other severe symptoms, along with anti-pyretic prophylaxis. *Rash:* Majority of cases in clinical studies have been Grade 1/2 and did not require dose interruptions/reductions. Follow dose modification schedule in SPCs if necessary. *Rhabdomyolysis:* Evaluate signs and symptoms and treat as indicated. Severe cases may require discontinuation of trametinib or both medicines. *Renal failure:* Monitor serum creatinine routinely, and interrupt dabrafenib as clinically appropriate if creatinine increases. *Visual impairment:* Monitor for signs/symptoms of ophthalmological reactions. Uveitis: If uveitis does not respond to local ocular therapy, interrupt dabrafenib until ocular inflammation resolves and restart at reduced dose. No dose modification of trametinib required. Retinal vein occlusion (RVO) and Retinal pigment epithelial detachment (RPED): Trametinib: not recommended in patients with history of RVO. Prompt ophthalmological examination recommended if patients report new visual disturbances. Permanently discontinue trametinib in patients diagnosed with RVO and follow trametinib dose modification schedule in SPC in patients diagnosed with RPED; continue dabrafenib at same dose. *Gastrointestinal disorders:* Treatment with trametinib monotherapy or in combination with dabrafenib should be used with caution in patients with risk factors for gastrointestinal perforation, including history of diverticulitis, metastases to the gastrointestinal tract and concomitant use of medications with a recognised risk of gastrointestinal perforation. **Undesirable effects** Please refer to full SmPCs before prescribing. Dabrafenib monotherapy: *Very common:* papilloma, decreased appetite, headache, cough, nausea, vomiting, diarrhoea, hyperkeratosis, alopecia, rash, PPE, arthralgia, myalgia, pain in extremity, pyrexia, fatigue, chills, asthenia. *Common:* cuSCC, seborrhoeic keratosis, skin tags, basal cell carcinoma, hypophosphataemia, hyperglycaemia, constipation, dry skin, pruritus, actinic keratosis, skin lesion, erythema, influenza-like illness, LVEF decrease. *Uncommon:* New primary melanoma; Hypersensitivity, panniculitis; Uveitis; Pancreatitis; Renal failure, nephritis. Dabrafenib and trametinib in combination: *Very common:* UTI, nasopharyngitis; neutropenia; decreased appetite; headache, dizziness; hypertension, haemorrhage; cough; abdominal pain, constipation, diarrhoea, nausea, vomiting; ALT/AST increased; dry skin, pruritus, rash, dermatitis acneiform; arthralgia, myalgia, pain in extremity; fatigue, chills, asthenia, peripheral oedema, pyrexia. *Common:* bradycardia, cellulitis, folliculitis, paronychia, rash pustular; cuSCC, papilloma, seborrhoeic keratosis, skin tags; anaemia, thrombocytopenia, leucopenia; dehydration, hyponatraemia, hypophosphataemia, hyperglycaemia; vision blurred, visual impairment; ejection fraction decreased; hypotension; dyspnoea; dry mouth, stomatitis; ALP/GGT increased; erythema, actinic keratosis, night sweats, hyperkeratosis, alopecia, PPE, skin lesion, hyperhidrosis, panniculitis, skin fissures; muscle spasm, blood CPK increased; mucosal inflammation, flu-like illness, face oedema. *Uncommon:* New primary melanoma; drug hypersensitivity; chorioretinopathy, uveitis, retinal detachment, periorbital oedema; pneumonitis; pancreatitis; renal failure, nephritis, colitis, gastrointestinal perforation. **Interactions** Dabrafenib (monotherapy/combination with trametinib): Drug utilisation review essential. Avoid co-administration with strong inducers or inhibitors of CYP2C8 and CYP3A4. Avoid agents that increase gastric pH. Exercise caution when co-administering with digoxin and with warfarin (consider additional INR monitoring). May reduce efficacy of hormonal contraceptives; use alternative effective contraception. Trametinib: Caution is advised when co-administering trametinib with medicinal products that are strong inhibitors of P-gp. **Pregnancy** Do not administer to pregnant women unless benefit to mother outweighs the risk to foetus. **Basic NHS Cost** Dabrafenib: 50mg x 28-capsule pack £933.33; 75mg x 28-capsule pack £1,400.00. Trametinib: 0.5mg x 30-tablet pack £1,200.00; 2mg x 30-tablet pack £4,800.00. 0.5mg x 7-tablet pack £280.00; 2mg x 7-tablet pack £1,120.00. **Marketing authorisation (MA) nos.** Dabrafenib: EU/1/13/865/001; EU/1/13/865/003. Trametinib: EU/1/14/931/02; EU/1/14/931/06. **MA holder** Novartis Europharm Ltd., Frimley Business Park, Camberley GU16 7SR. **Legal category** POM.

TMC16-C027 August 2016

Adverse events should be reported.
Reporting forms and information can be found at www.mhra.gov.UK/yellowcard. Adverse events should also be reported to Novartis on (01276) 698370, medinfo.uk@novartis.com or online through the Patient Safety Information tool at https://psi.novartis.com

Further information is available from Novartis Pharmaceuticals UK Ltd., Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR. Tel: 01276 692255.

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