NOVARTIS

TAF MEK melanoma - Pooled COMBI-v and COMBI-d safety data - HCP

Prescribing information

Image

Image

Pooled COMBI-v and COMBI-d safety data

TAFINLAR® (dabrafenib) in combination with MEKINIST® (trametinib) is indicated in adult patients with unresectable or metastatic melanoma with a *BRAF* V600 mutation.[1,2]

TAFINLAR in combination with MEKINIST is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a *BRAF* V600 mutation, following complete resection.[1,2]

Common adverse events include:

- TAFINLAR + MEKINIST: The most common adverse reactions (incidence ≥20%) for dabrafenib in combination with trametinib were pyrexia, fatigue, nausea, chills, headache, diarrhoea, vomiting, arthralgia and rash[1,2]

- TAFINLAR: The most common adverse reactions (incidence >15%) reported with dabrafenib were hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, papilloma, alopecia, rash and vomiting[1]

- MEKINIST: The most common adverse reactions (incidence ≥20%) for trametinib were rash, diarrhoea, fatigue, oedema peripheral, nausea and dermatitis acneiform[2]

For more safety information on TAFINLAR and MEKINIST, click here.

For the full safety profile, please refer to the Summary of Product Characteristics (SmPC) for TAFINLAR and MEKINIST.

Adverse event reporting: Details of how to report adverse events are available at the bottom of the page. Please refer to the respective SmPC for all licensed indications.

Important safety profile information – Pyrexia

- Therapy (TAFINLAR when used as monotherapy, and both MEKINIST + TAFINLAR when used in combination) should be interrupted if the patient's temperature is ≥38°C

- In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia

- Treatment with antipyretics such as ibuprofen or acetaminophen/paracetamol should be initiated

- The use of oral corticosteroids should be considered in instances where antipyretics are insufficient

- Patients should be evaluated for signs and symptoms of infection

- Therapy can be restarted once the fever resolves

- If fever is associated with other severe signs or symptoms, therapy should be restarted at a reduced dose once fever resolves and as clinically appropriate

The safety profile of TAFINLAR + MEKINIST is well established[1–3]

Key safety profile insights from COMBI-v and COMBI-d trials in metastatic melanoma

No unexpected adverse events (AEs) were reported with extended follow-up.[3]

The most common AEs observed with TAFINLAR + MEKINIST in the pooled 5-year analysis included: pyrexia, nausea, diarrhoea, fatigue, headache, chills and vomiting.[3]

Please visit the **pooled efficacy** page for further information on the landmark 5-year pooled analysis.

Adverse event profile at 5 years

TAFINLAR + MEKINIST has a generally well-established AE profile, and there were no unexpected AEs after extended follow-up with TAFINLAR + MEKINIST[1–3]

- In the pooled analysis, AEs led to permanent discontinuation of TAFINLAR + MEKINIST in 18% of patients[1]

- No treatment-related deaths were reported in the 5-year pooled analysis[3]

All-causality AEs occurring in ≥20% of patients treated with TAFINLAR + MEKINIST (5-year pooled analysis)[3]

Adverse event, n (%)	COMBI-d (n=209)		COMBI-v (n=350)		COMBI-v/COMBI-d (n=559)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	203 (97)	113 (54)	345 (99)	218 (62)	548 (98)	331 (59)
Pyrexia	123 (59)	16 (8)	202 (58)	18 (5)	325 (58)	34 (6)
Nausea	79 (38)	1 (<1)	128 (37)	2 (1)	207 (37)	3 (1)
Diarrhoea	68 (33)	3 (1)	131 (37)	5 (1)	199 (36)	8 (1)
Fatigue	81 (39)	5 (2)	117 (33)	4 (1)	198 (35)	9 (2)
Headache	71 (34)	1 (<1)	122 (35)	5 (1)	193 (35)	6 (1)
Chills	68 (33)	1 (<1)	122 (35)	4 (1)	190 (34)	5 (1)
Vomiting	58 (28)	2 (1)	115 (33)	5 (1)	173 (31)	7 (1)
Arthralgia	57 (27)	2 (1)	104 (30)	3 (1)	161 (29)	5 (1)
Hypertension	52 (25)	12 (6)	109 (31)	55 (16)	161 (29)	67 (12)
Rash	62 (30)	0	96 (27)	5 (1)	158 (28)	5 (1)
Cough	51 (24)	0	87 (25)	0	138 (25)	0
Peripheral oedema	47 (22)	2 (1)	61 (17)	2 (1)	108 (19)	4 (1)
Myalgia	27 (13)	1 (<1)	76 (22)	0	103 (18)	1 (<1)

Adapted from Robert C, et al. 2019.[3]

Pyrexia was the most common AE associated with TAFINLAR + MEKINIST treatment in the adjuvant setting of patients with Stage III . The majority of pyrexia events were Grade 1 or 2.[4]

TAFINLAR/MEKINIST when used as monotherapy, and both TAFINLAR and MEKINIST when used in combination, should be interrupted if the patient's temperature is ≥38°C. In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Treatment with antipyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. The use of oral corticosteroids should be considered in those instances in which antipyretics are insufficient. Patients should be evaluated for signs and symptoms of infection. Therapy can be restarted once the fever resolves. If fever is associated with other severe signs or symptoms, therapy should be restarted at a reduced dose once fever resolves and as clinically appropriate.[1,2]

Adverse event profile over time

Incidence of AEs was observed to decrease over a 3-year period in patients who received TAFINLAR + MEKINIST[5]

- In a separate pooled analysis of the 3-year data from the COMBI-v and COMBI-d trials, the incidence of AEs was highest at 6 months, and was observed to decrease over time in patients completing at least 36 months of treatment (n=50)[5]

- The incidence of pyrexia more than halved from 60% at 0–6 months to 12% at 30–36 months of treatment[5]

Incidence of AEs (≥15% for 0–6 months) over time in patients treated with TAFINLAR + MEKINIST for ≥36 months (pooled analysis at 3 years)[5]

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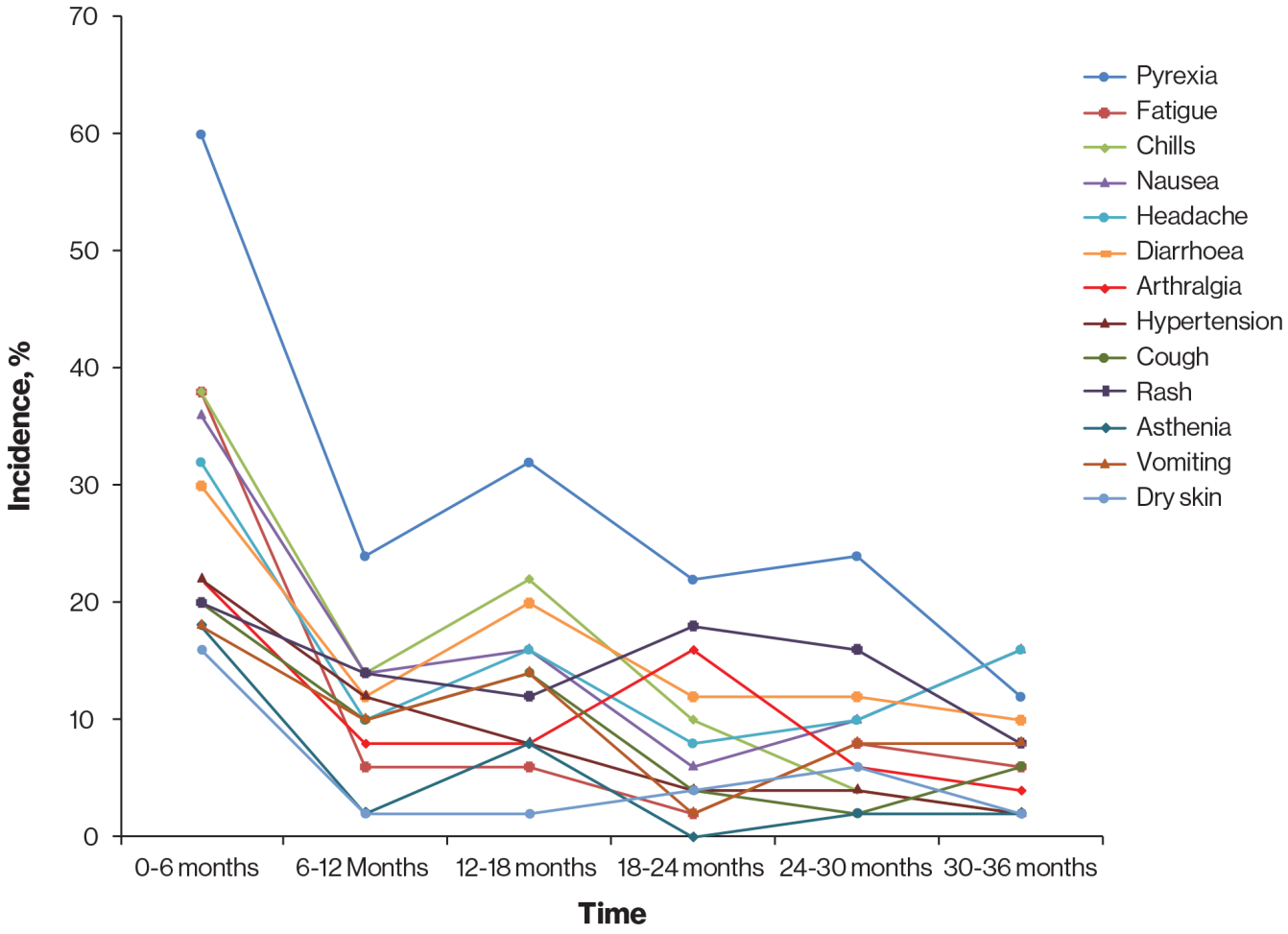


Adapted from Grob GG, et al. 2016.[5]

A pooled analysis of pyrexia from patients treated with TAFINLAR + MEKINIST

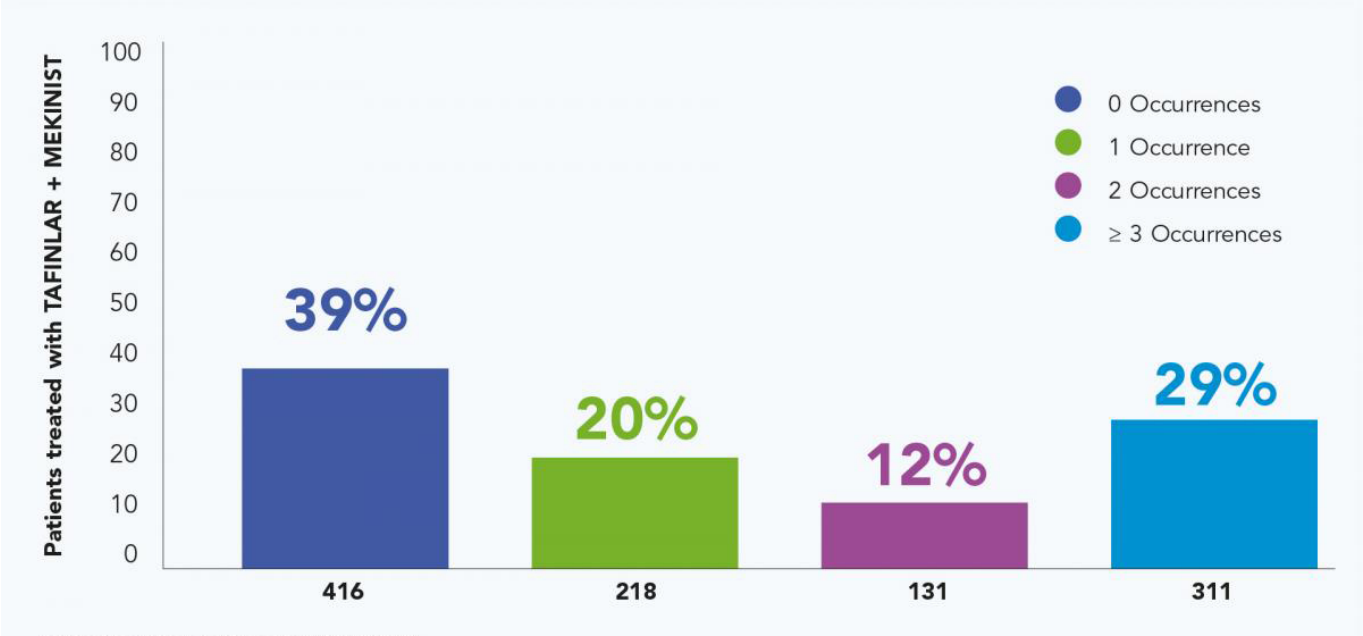
- Across four TAFINLAR + MEKINIST clinical trials (n=1076), 39% of patients treated with TAFINLAR + MEKINIST did not experience a pyrexia event, while 32% of patients experienced only one or two events[6,7]
- The majority of pyrexia events were mild or moderate (Grade 1/2). Only 9% of patients treated with TAFINLAR + MEKINIST experienced Grade 3 events and <1% of patients experienced Grade 4 events[6,7]
- Most pyrexia events were completely resolved with either temporary dose interruption or no dose change[6,7]

- Only 6% of patients discontinued treatment with TAFINLAR or MEKINIST due to pyrexia[6,7]

Pooled analysis of pyrexia: Single vs multiple occurrences*[5]

The data are based on a pooled analysis of pyrexia occurrence across four clinical trials* representing the largest analysis of a *BRAF* inhibitor + MEK inhibitor-induced pyrexia to date.[6,7]

Image



Adapted from Robert C, et al. 2019.[6]

*Pyrexia was analysed from the following clinical trials in melanoma and in metastatic non-small cell lung cancer (NSCLC): Registrational Phase II trial (NCT01336634) in metastatic NSCLC (n=82); COMBI-AD in resected Stage III melanoma (n=435); COMBI-d in unresectable or metastatic melanoma (n=209); COMBI-v in unresectable or metastatic melanoma (n=350).[3,6–8]

Please visit the **management of patients with *BRAF* V600-positive melanoma page** for further information on monitoring for, and managing, pyrexia in patients receiving TAFINLAR + MEKINIST.

AE, adverse event; *BRAF* V600, mutation of the *BRAF* gene at valine (V) 600; NSCLC, non-small cell lung cancer; SmPC, summary of product characteristics.

References

1. TAFINLAR (dabrafenib) Summary of Product Characteristics.

2. MEKINIST (trametinib) Summary of Product Characteristics.

3. Robert C, et al. *N Engl J Med* 2019;381:626–636.

4. Long GV, et al. *N Engl J Med* 2017;377:1813–1823.

5. Grob JJ, et al. Presented at SMR 2016; 6–9 November, Boston, MA, USA.

6. Robert C, et al. Presented at ESMO 2019; 27 September – 1 October, Barcelona, Spain.

7. Schadendorf D, et al. *Eur J Cancer* 2021;153:234–241.

8. Planchard D, et al. *J Thorac Oncol* 2022;17:103–115.

UK | April 2025 | FA-11218913

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