Application for the inclusion of the combination of BRAF/MEK inhibitors dabrafenib plus trametinib, vemurafenib plus cobimetinib, and encorafenib plus binimetinib in the WHO Model list of ESSENTIAL MEDICINES for the treatment of "adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation"

List of Contributors: George Pentheroudakis, ESMO Chief Medical Officer

Name of the organization(s) consulted and/or supporting the application:

European Society for Medical Oncology (ESMO)

General items

1. **Name of the focal point in WHO submitting or supporting the application**
   Andrè Ilbawi, WHO Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention (NVI).

2. **Name of the organization(s) consulted and/or supporting the application**
   European Society for Medical Oncology (ESMO), Via Ginevra 4,
   6900 Lugano, Switzerland

3. **International Nonproprietary Name (INN, generic name) and Anatomical Therapeutic Chemical (ATC) of the medicine**

   a) dabrafenib - ATC code: L01XE23
   b) trametinib - ATC code: L01XE25
   c) vemurafenib - ATC code: L01XE15
   d) cobimetinib - ATC code: L01XE38
   e) encorafenib - ATC code: L01XE46
   f) binimetinib - ATC code: L01XE41

The three combinations – dabrafenib plus trametinib; vemurafenib plus cobimetinib; encorafenib plus binimetinib - belong to the class of the mitogen-activated protein kinase (MAPK) pathway inhibitors, specifically they are BRAF/MEK inhibitors. All three combinations have been approved for the treatment of patients with irresectable or metastatic melanoma with a BRAFV600 mutation.

This application aims to address the priority indication for unresectable or metastatic melanoma where the role of the combination of BRAF/MEK inhibitors is definite and for which no controversies exist. In this submission, we will consider the indications for BRAF/MEK inhibitor combination treatment in unresectable or metastatic melanoma scored as European Society for Medical Oncology- Magnitude of Clinical Benefit Scale (ESMO-MCBS) grade 4 or 5 in Non-Curative settings. [1, 2].

4. Formulation proposed for inclusion; including adult and pediatric (if appropriate)

4.1. **Dabrafenib** - Trade name Tafinlar [3]

Dabrafenib is an inhibitor of RAF kinases. Oncogenic mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 50% of melanoma. The most commonly observed BRAF mutation is V600E which accounts for approximately 90% of the BRAF mutations that are seen in melanoma.

a) Therapeutic indications

1. Advanced Melanoma

Dabrafenib as monotherapy or in combination with trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

2. Adjuvant treatment of localised melanoma

Dabrafenib in combination with trametinib is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection. **This indication will not be considered in this application.**

3. Non-small cell lung cancer (NSCLC)

Dabrafenib in combination with trametinib is indicated for the treatment of adult patients with. advanced non-small cell lung cancer with a BRAF V600 mutation. **This indication will not be considered in this application.**

b) Pharmaceutical form:

1. Tafinlar 50 mg hard capsules
2. Tafinlar 75 mg hard capsules

The recommended dose of dabrafenib, either used as monotherapy or in combination with trametinib, is 150 mg (two 75 mg capsules) twice daily (corresponding to a total daily dose of 300 mg). The recommended dose of trametinib, when used in combination with dabrafenib, is 2 mg once daily. Dose reductions, treatment interruption or discontinuation may apply to manage adverse events.

The safety and efficacy of dabrafenib have not yet been established in children and adolescents (<18 years).

4.2. **Trametinib** – Trade name Mekinist [4]

Trametinib is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and kinase activity. MEK proteins are components of the extracellular signal-related kinase (ERK) pathway. In melanoma and other cancers, this pathway is often activated by mutated forms of BRAF which activates MEK. Trametinib inhibits activation of MEK by BRAF and inhibits MEK kinase activity.

a) Therapeutic indications

1. Advanced Melanoma

Trametinib as monotherapy or in combination with dabrafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAFV600 mutation. Trametinib monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy.

2. Adjuvant treatment of localised melanoma

Trametinib in combination with dabrafenib is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection. **This indication will not be considered in this application.**

3. Non-small cell lung cancer (NSCLC)

Trametinib in combination with dabrafenib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation. **This indication will not be considered in this application.**

Trametinib **is not indicated** for treatment of patients with melanoma who have progressed on prior BRAF inhibitor therapy. [5]

a) Pharmaceutical form

1. Mekinist 0.5 mg film-coated tablets
2. Mekinist 2 mg film-coated tablets

The recommended dose of trametinib, either used as monotherapy or in combination with dabrafenib, is 2 mg once daily. The recommended dose of dabrafenib, when used in combination with trametinib, is 150 mg twice daily. Dose reductions, treatment interruption or discontinuation may apply to manage adverse events.

The safety and efficacy of trametinib have not been established in children and adolescents (<18 years).

4.3. **Vemurafenib** – Trade name Zelboraf [6]

Vemurafenib is an inhibitor of BRAF serine-threonine kinase.

a) Therapeutic indications

Vemurafenib is indicated as monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma .

b) Pharmaceutical form

Film-coated tablet

The recommended dose of vemurafenib is 960 mg (4 tablets of 240 mg) twice daily (equivalent to a total daily dose of 1,920 mg). Vemurafenib may be taken with or without food, but consistent intake of both daily doses on an empty stomach should be avoided. Dose reductions, treatment interruption or discontinuation may apply to manage adverse events.

The safety and efficacy of vemurafenib have not been established in children and adolescents (<18 years).

4.4. **Cobimetinib** – Trade name Cotellic[7]

Cobimetinib is a reversible, selective, allosteric, oral inhibitor that blocks the mitogen-activated protein kinase (MAPK) pathway by targeting the mitogen-activated extracellular signal-regulated kinase (MEK) 1 and MEK 2 which results in inhibition of phosphorylation of the extracellular signal regulated kinase (ERK) 1 and ERK 2. Therefore, cobimetinib blocks the cell proliferation induced by the MAPK pathway through inhibition of the MEK1/2 signaling node. In the preclinical models, the combination of cobimetinib and vemurafenib showed that by simultaneously targeting mutated BRAFV600 proteins and MEK proteins in melanoma cells, the combination of the two products inhibits MAPK pathway reactivation through MEK1/2, resulting in a stronger inhibition of intracellular signaling and decreased tumor cell proliferation.

a) Therapeutic indications

Cobimetinib is indicated for use in combination with vemurafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

b) Pharmaceutical form

Film-coated tablet

The recommended dose of cobimetinib is 60 mg (3 tablets of 20 mg) once daily. Cobimetinib is taken on a 28-day cycle. Each dose consists of three 20 mg tablets (60 mg) and should be taken once daily for 21 consecutive days (days 1 to 21-treatment period); followed by a 7-day break (days 22 to 28-treatment break). Each subsequent cobimetinib treatment cycle should start after the 7-day treatment break has elapsed. In the combination regimen, the recommended dose of vemurafenib is 960 mg (4 tablets of 240 mg) twice daily for 28 days.

The safety and efficacy of cobimetinib in children and adolescents below <18 years of age have not been established.

4.5. **Encorafenib** – Trade name Braftovi [8]

Encorafenib is a potent and highly selective ATP-competitive small molecule RAF kinase inhibitor that suppresses the RAF/MEK/ERK pathway in tumor cells expressing several mutated forms of BRAF kinase (**V600E, D and K**). Specifically, encorafenib inhibits in vitro and in vivo **BRAF V600E, D and K** mutant melanoma cell growth and BRAF V600E mutant colorectal cancer cell growth. Encorafenib does not inhibit RAF/MEK/ERK signaling in cells expressing wild-type BRAF.

a) Therapeutic indications

1. Melanoma

Encorafenib is indicated in combination with binimetinib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

2. Colorectal cancer

Encorafenib is indicated in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy. **This indication will not be considered in this application.**

b) Pharmaceutical form

1. Encorafenib 50 mg hard capsules
2. Encorafenib 75 mg hard capsules

The recommended dose of encorafenib for melanoma is 450 mg (six 75 mg capsules) once daily, when used in combination with binimetinib. The recommended dose of encorafenib for colorectal cancer is 300 mg (four 75 mg capsules) once daily, when used in combination with cetuximab. Dose reductions, treatment interruption or discontinuation may apply to manage adverse events.

The safety and efficacy of encorafenib have not yet been established in children and adolescents.

4.6. **Binimetinib** – Trade name Mektovi [9]

Binimetinib is an ATP-uncompetitive, reversible inhibitor of the kinase activity of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. Binimetinib inhibits activation of MEK by BRAF and inhibits MEK kinase activity. Binimetinib inhibits growth of BRAF V600 mutant melanoma cell lines and demonstrates anti-tumor effects in BRAF V600 mutant melanoma animal models.

a) Therapeutic indications

Binimetinib in combination with encorafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

b) Pharmaceutical form

Film-coated tablet

The recommended dose of binimetinib is 45 mg (three 15 mg tablets) twice daily, corresponding to a total daily dose of 90 mg approximately 12 hours apart. Dose reductions, treatment interruption or discontinuation may apply to manage adverse events.

The safety and efficacy of binimetinib in children and adolescents have not yet been established.

5. International availability - sources, if possible, manufacturers and trade names

The trade names for each of the substances have been provided in section 4, and will be used next for the purpose of identification of the manufactures, considering the information provided in the respective SmPC. [3, 4, 6-9]

Name and address of the manufacturers responsible for batch release for:

a) Tafinlar
   1. GLAXO WELLCOME, S.A. Avda. Extremadura, 3, Pol. Ind. Allendeduero 09400, Aranda de Duero (Burgos) Spain
   2. Novartis Pharmaceuticals UK Limite Frimley Business Park Frimley Camberley, Surrey GU16 7SR United Kingdom
   3. Novartis Pharma GmbH Roonstraße 25 D-90429 Nuremberg Germany

b) Mekinist
   1. Lek Pharmaceuticals d.d. Verovskova ulica 57 1526, Ljubljana Slovenia
   2. Novartis Pharma GmbH Roonstraße 25 D-90429 Nuremberg Germany
   3. Glaxo Wellcome, S.A. Avda. Extremadura, 3 09400, Aranda de Duero Burgos Spain

c) Zelboraf
   1. Roche Pharma AG Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany

d) Cotellic
   1. Roche Pharma AG Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany

e) Braftovi
   1. Pierre Fabre Médicament Production Aquitaine Pharm International 1 Avenue du Béarn 64320 Idron France
   2. PIERRE FABRE MEDICAMENT PRODUCTION Site Progipharm, rue du Lycée 45500 GIEN France

f) Mektovi
   1. Pierre Fabre Médicament Production Aquitaine Pharm International 1 Avenue du Béarn 64320 Idron France
   2. PIERRE FABRE MEDICAMENT PRODUCTION Site Progipharm, rue du Lycée 45500 GIEN France

6. Whether listing is requested as an individual medicine or as an example of a therapeutic group?

Therapeutic group: "*Combined BRAF/MEK inhibitors dabrafenib plus trametinib; vemurafenib plus cobimetinib; and encorafenib plus binimetinib*", **square-boxed** as dabrafenib plus trametinib (vemurafenib plus cobimetinib; encorafenib plus binimetinib).

Treatment details, public health relevance and evidence appraisal and synthesis

7. Treatment details (requirements for diagnosis, treatment and monitoring)

7.1. **Approved diagnostic tests for determination of BRAF status, i.e., presence or absence of BRAFV600 mutation**

Mutational analysis is normally performed on Formalin-Fixed Paraffin-Embedded (FFPE) samples, using standardised protocols to remove paraffin and extract DNA.

The determination of the BRAF status is decisive for providing targeted and personalised therapy for patients with melanoma, particularly for cutaneous melanoma.

The ESMO Clinical Practice Guidelines describe that testing for actionable mutations is mandatory in patients with resectable or unresectable stage III or stage IV melanoma and is highly recommended patients with high-risk resected disease stage IIC, but not for stage I/IIA/B. (Level of evidence – I; Grade of recommendation A). BRAF testing is mandatory (I; A).[10]

The NCCN guidelines do not recommend to perform BRAF status evaluation in resected stage I-II cutaneous melanoma, unless to inform the inclusion in a clinical trial. BRAF testing is recommended for patients with stage III at high risk for recurrence, for whom targeted therapy with BRAF inhibitors might be an option. [11] The NCNN also recommends testing for patients newly diagnosed or with disease recurrence in stage IV. Here testing in a metastatic sample is preferred, as it is the most recent lesion. [11] If not possible, testing in the primary tumour or lymph node metastasis can be considered, as there seems to exist a high concordance between primary and metastatic tissue in terms of BRAF mutation status. [12-14]

In the pivotal trials, the assays used to identify the presence of BRAF mutation were the following:

a) Dabrafenib plus trametinib

In the COMBI-d study, which investigated the combination of dabrafenib plus trametinib versus dabrafenib, patients were included if they had histologically confirmed, unresectable stage IIIC or stage IV metastatic melanoma with BRAF Val600Glu or Val600Lys mutations, as determined by PCR (ThxID BRAF Assay, bioMérieux) done at a central reference laboratory. [15] The previously referred assay is an CE market assay, which means that the product meets all the legal (safety, health, and environmental protection) requirements for CE marking, and can be sold throughout the European Economic Area.

For the COMBI-v study, which investigated the combination of dabrafenib plus trametinib versus vemurafenib, the same test was used to determine the presence of the BRAFV600E/K mutations. [16]

b) Vemurafenib plus cobimetinib

In the co-BRIM study, which investigated the combination of cobimetinib plus vemurafenib compared with vemurafenib, patients were included if they had unresectable stage IIIC or stage IV melanoma harbouring a BRAFV600, detected with the use of a real-time PCR assay (cobas 4800 BRAFV600 Mutation Test []). [17]

c) Encorafenib plus Binimetinib

The COLUMBUS study, which investigated encorafenib plus binimetinib, encorafenib or vemurafenib, included patients with histologically confirmed locally advanced (stage IIIB, IIIC, or IV), unresectable or metastatic cutaneous melanoma, or unknown primary melanoma with BRAFV600E/K mutation determined with the bioMérieux THxID BRAF diagnostic test (bioMérieux, Marcy l'Etoile, France).[18]

In Europe, all BRAF/MEK combinations are approved by the European Medicine Agency (EMA) to be used in patients with unresectable or metastatic melanoma harbouring a BRAFV600 mutation identified with a validated test. [3, 4, 6-9] In the United States of America (USA), the combinations can be prescribed for the treatment of unresectable or metastatic melanoma, after confirmation of the presence of BRAFV600E/K mutation using a Food and Drug Administration (FDA)-approved test. [5, 19-24]

According to the FDA prescribing information, dabrafenib can be prescribed in combination with trametinib, after confirmation of the presence of BRAFV600E/K mutation using one of the FDA-approved tests for the detection of BRAF V600 mutations in melanoma. [21] These tests are: (1) FoundationOne CDx from Foundation Medicine, Inc., and (2) THXID BRAF Kit, bioMérieux Inc. [20] Cobimetinib can be prescribed in combination with vemurafenib, after confirmation of the presence of BRAFV600E/K mutation using one of the FDA-approved tests for the detection of BRAF V600 mutations in melanoma. These tests are: (1) Cobas 4800 BRAF V600 Mutation Test from Roche Molecular Systems, Inc. (only for BRAFV600E), and (2) FoundationOne CDx from Foundation Medicine, Inc. [19, 20] Finally, encorafenib can be prescribed in combination with binimetinib, after confirmation of the presence of BRAFV600E/K mutation using one of the FDA-approved tests for the detection of BRAF V600 mutations in melanoma. For encorafenib and binimetinib the approved test is (1) THXID BRAF Kit, bioMérieux Inc. [20]

THXID BRAF Kit, bioMérieux Inc. and cobas 4800 BRAF V600 Mutation Test from Roche Molecular Systems, Inc., are both real-time PCR-based assays. FoundationOne CDx from Foundation Medicine, Inc. is a next generation sequencing (NGS) panel assay.

7.2. **Currently available diagnostic tests for BRAFV600 in melanoma**

In the clinical practice, the assays used to confirm the presence of a BRAFV600 mutation can be, and often are, different from the ones used in pivotal clinical trials. Table 1 provides and overview on the different sensitivity and specificity of the various assays available for the detection of BRAF mutations.

The use of NGS has been broadly implemented and has some advantages compared to traditional quantitative polymerase chain reaction (qPCR) and Sanger Sequencing. Both provide highly sensitive

and reliable variant detection, but qPCR can only detect known sequences. NGS allows a diagnostic approach that does not require prior knowledge of sequence information. While qPCR is effective for low number of samples and targets, NGS is preferable for evaluations in many targets or samples.

An Italian study recently compared BRAF mutation screening strategies in a large real-life series of patients with advanced melanoma (n=319). [25] The authors compared BRAF mutational testing performed by conventional nucleotide sequencing approaches (Sanger-based sequencing and pyrosequencing) with either real-time polymerase chain reaction (rtPCR) or next-generation sequencing (NGS). Their results showed that rtPCR and NGS were able to detect additional BRAF mutant cases in comparison with conventional sequencing methods.

Other assays are also available for the detection of BRAF mutations: immunohistochemistry (IHC), digital PCR (dPCR), High-Resolution Melting curve analysis (HRM) and Matrix Assisted Laser Desorption Ionization-Time Of Flight Mass Spectrometry (MALDI-TOF MS; Sequenom). [26] Particularly for droplet digital PCR (ddPCR), results comparing this technique with others, namely Cobas 4800 system, Sanger sequencing, allele-specific PCR, pyrosequencing, IHC using the anti-BRAF-V600E (VE1) mouse monoclonal antibody (BRAF-VE1 IHC) and Idylla BRAF- Mutation Test, seem to result in good concordance among the different technics. [27-30]

Based on the previously results, Vanni et al [26] proposed the use of ddPCR as the primary method for detecting and monitoring BRAFV600E mutated cutaneous melanomas due to the higher sensitivity and lower LOD of mutant allele. The ddPCR higher sensitivity could also allow investigating mutation heterogeneity and its changes during tumour progression. Currently, only the ThxID BRAF Assay, bioMérieux is CE certified. There is an ongoing proposal for all the assays to be IVD certified - Europe's new In Vitro Diagnostic Regulation (IVDR 2017/746), starting 2022. [31]

Table 1: Overview of the different technics available to detect the presence of BRAFV600 in melanoma and the respective sensitivity and specificity

Diagnostic technic for BRAFV600 mutation	Sensitivity (%)	Specificity (%)	Limit of detection of mutant alleles (%)
IHQ	93-97	92-98	-
Sanger Sequencing	80-93	100	20-25
Pyrosequencing	95-100	90-10	5-10
Real-time PCR based technics	93-99.56	98-100	0.5-5
dPCR	100	95	0.001
HRM	87-99	96-99	5.0
MALDI-TOF MS	97.6	100	1.5
NGS	98	100	5

IHQ: immunohistochemistry; PCR: protein chain reaction; dPCR: digital PCR; HRM: High-Resolution Melting curve analysis; MALDI-TOF MS: Matrix Assisted Laser Desorption Ionization-Time Of Flight Mass Spectrometry; NG: Next generation sequencing. (*Adapted from Vanni et al. [26]*)

7.3. **Treatment details**

All combinations can be used for the treatment of adult patients with unresectable or metastatic melanoma, harbouring a BRAFV600 mutation in 1st line or after progression on immunotherapy with immune checkpoint inhibitors according to the ESMO Clinical Practice Guidelines. [10] The studies evaluating the combination therapy in 1st line were the ones evaluated by the ESMO-MCBS – see Table 3. Monotherapy with BRAF inhibitors is no longer the standard of care in advanced melanoma, since the combination BRAF/MEK inhibitors improved both PFS and OS compared to monotherapy. [15, 16, 32] Monotherapy with BRAF inhibitors should be used only in case of an absolute contraindication for MEK inhibitors. [10] For more details on the results from the pivotal clinical trials see section 9.

There is no defined treatment duration for targeted therapy in the advanced setting, also for patients deriving benefit, i.e., with stable disease, partial response or complete response, optimal therapy duration is not known. [11] Some studies showed that patients who discontinue therapy, even after a complete response, relapse later. [33, 34] Based on the ESMO consensus conference recommendations on the management of metastatic melanoma, permanent discontinuation of targeted therapy, particularly outside clinical trials and if no other therapeutic options are available, should be avoided if possible (IV;E). [35] Patients should be treated for as long as they benefit (until disease progression) or as long as the therapy is well tolerated, i.e., without unacceptable toxicity. Treatment beyond confirmed progression can be considered in the absence of appropriate alternative treatment (IV;B).

A particularity that is important for patients who have other co-morbidities and already need to take other oral therapies, is the number of tablets/capsules that are necessary , daily, in each combination.

The posology for each combination is as follow:

a) 150 mg dabrafenib twice daily (2+2 capsules) + 2mg trametinib once daily (1 tablet) = **5 tablets/capsules/day**
b) 960 mg vemurafenib twice daily (4+4 tablets) + 60 mg cobimetinib once daily (3 tablets for 21 days) = **11 tablets/capsules/day**
c) 450 mg encorafenib once daily (6 capsules) + 45 mg binimetinib twice daily (3 tablets) = **9 tablets/capsules/day**

7.4. **Treatment monitoring**

BRAF/MEK treatment can only be offered to patients with advanced melanoma with the presence of a BRAFV600 mutation confirmed with a validated assay, in Europe, or with an FDA approved assay in the USA.

Since all BRAF/MEK inhibitors are orally administered, there is no need for specialised treatment facilities, and there are no particular administration requirements. The physicians prescribing these therapies need to be familiar with the toxicity profile and the dose reduction schemas available in the prescribing information. Some clinical, laboratory and complementary diagnostic examinations may be recommended before treatment start, based on the personal medical history of the patient and the

combination prescribed. For more details on this aspect, please refer to the information provide on toxicity and toxicity management on section 11.

8. Information supporting the public health relevance

8.1. Epidemiological information on disease burden

In recent years, there was a worldwide increase of melanoma incidence. [36] By 2020, the number of newly diagnosed melanomas worldwide is expected to reach 279,938, and it is estimated that about 67,809 people will die from this disease. The numbers are from the International Agency for Research on Cancer (IARC). [37] Differences between countries can be seen in this report. As an example, in 2018 in Portugal, the age-standardised incidence rate (World) per 100,000 for both sexes, all ages, was 6.4 compared to 21.6 in Germany.

National reports provided similar data, showing that the increased incidence rate of melanoma is a global issue. [38-40] The incidence rate of cutaneous melanoma is higher in white populations compared to Spanish, Afro-American, Indian and Asian. [41] The mean annually age-adjusted incidence of melanoma in whites per 100 000 persons is 18.4 and in Spanish, Afro-Americans, Indians and Asians it is 2.3, 0.8, 1.6 and 1.0, respectively.

In most European countries, the melanoma incidence rate almost doubled between 1990 and 2005, increasing between + 2% and + 10% annually. [42] The highest incidence rates were observed in Scandinavian and North-Western countries such as the United Kingdom (UK). [43-47] Southern and Eastern Europe have lower incidence rates but have shown an increase in the last two decades. [48, 49] With incidence rates of around 1 per 100 000 in 1950, [50] the current age-standardised incidence rate exceeds 20/100 000/year in Belgium, the Netherlands, Denmark and the UK. [44, 47, 51, 52]

In 2012, melanoma was the fifth most frequent solid tumour entity in Germany. The incidence rate according to the age-standardisation rose from 12.4/100,000 to 19.2/100,000 between 1999 and 2012, representing an increase of approximately 55%. [38] In this publication the authors reported an increase in incidence of melanoma from 12.7/100,000 to 19.2/100,000 in men and from 12.1/100,000 to 19.2/100,000 in women, which represents an average annual increase of +3.1% and +3.5%, respectively. An extrapolation of the data until 2030 shows that the age-standardised incidence rates will continue to increase with expected incidence rates of 31/100,000 and 30/100,000 for men and women, corresponding to a relative increase of about 60% for both sexes. [38]

8.1.1. Cutaneous melanoma

The two most common subtypes of cutaneous melanoma are the 1) superficial spreading melanoma (SSM) in about 57% of cases, and the 2) nodular melanoma (NM) in about 21% of cases. Other less frequent melanoma subtypes are 3) the lentigo maligna melanoma (LMM) in about 9% of cases, occurring mainly in chronically sun-exposed skin of older patients, and the 4) acral-lentiginous melanoma (ALM) in about 4% of cases, which can be located in fingers, toes, palms and soles, and is associated with a poorer prognosis. [53-56]

There is robust evidence that cutaneous melanoma is associated with the intermittent exposure to ultraviolet (UV) radiation and history of sunburns early in life, namely throughout childhood and adolescence; however, the risk appears to be present regardless the age group. [57-59] The change

in leisure and holiday patterns in the later decades, and the change on the type of protective clothes used while sunbathing resulted in a significant increase in UV exposure. It is assumed that this is the main reason for the global increase of this tumour entity. [60, 61]

Approximately 6% of all diagnosed melanomas occur in body regions that have little exposure to UV radiation. Contrary, the majority of melanomas (94%) are located in body regions frequently or intermittently exposed to UV radiation, such as the face, chest, back, arms and legs. [53, 62]

The development of melanomas as its correlation with UV exposure has been shown previously by several groups. In 2010 the whole spectrum of somatic mutations in the entire genome of a melanoma metastasis was catalogued for the first time. [63] Aout 70% of the detected single base substitutions were of the type C-T and also around 70% of the dinucleotide substitutions were of the type CC-TT. It is largely known that these are "signature mutations" for exposure to UV radiation, and therefore, this finding represents an important proof of the connection between the development of melanoma and UV radiation exposure.

Due to this relation between UV radiation exposure and cutaneous melanoma, this subtype of melanoma belongs to the human malignancies with the highest tumour mutational burden. [64] The high tumour mutational burden has been associated with response to immunotherapy in melanoma and other solid tumours. [65, 66]

8.2. **Assessment of current use and targeted populations**

As previously mentioned, BRAF/MEK inhibitors are approved to treat adult patients with advanced melanoma harbouring a BRAFV600 mutation. Actionable BRAFV600 mutations are present in approximately 40%-60% of the patients with cutaneous melanoma, a relatively high incidence. Melanoma patients with BRAFV600 mutated melanoma can also be treated with PD-1 based immunotherapy, as this therapy is approved for both BRAFV600 mutated and BRAF wild-type melanoma. The best sequence of therapies – i.e. targeted therapy 1st line and immunotherapy 2nd line or the other way around - in patients with BRAFV600 mutation is not established and treatment decisions need to be individualised. [10] According to the ESMO consensus recommendation's, 1st line immunotherapy should be considered in patients with BRAFV600 mutated melanoma, if this therapy can be safely delivered upfront, i.e., if the patients have slowly progressive lesions, and if there is no immediate threat to an important organ or function (IV;C). [35] For both targeted and immunotherapy, known negative prognostic and predictive markers such as elevated LDH, number of organs with metastases and Eastern Cooperative Oncology Group (ECOG) performance status have been identified. [67, 68] This seems to be true also for 2nd line therapies in BRAFV600 mutated melanoma. [69] ESMO consensus recommendations describe that for patients with BRAF-mutated metastatic melanoma and elevated LDH, 1st line therapy with ipilimumab plus nivolumab is generally preferred over BRAF/MEK inhibitors, depending on the presence of other adverse prognostic factors. For patients with LDH >1x and ≤ 2x ULN, anti-PD-1 monotherapy is an additional option (V;C). [35]

Although without direct randomised comparison, meta-analyses suggest that, despite better outcome within the first 12 months for BRAF/MEK inhibitors and when evaluating PFS, patients receiving immunotherapy first may have a better overall survival. [70-72] This trend seems to be inverted, when comparing 2nd line therapies. However, these are again, indirect comparisons. [71] Re-challenge with targeted therapy can be considered for patients who have progressed after 1st line targeted therapy and 2nd line immunotherapy (IV;C). [35]

8.3. **Likely impact of treatment on the disease**

The favourable impact of targeted therapy in the survival (PFS and OS) of patients with unresectable or metastatic melanoma harbouring a BRAFV600 mutation has been shown in randomised phase III trials. Combination therapy with BRAF/MEK inhibitors have been rated with a score of 4 or 5 by the ESMO-MCBS v1.1. ESMO-MCBS scores ≥4 are considered substantial. For more details, refer to section 9 and Table 3.

9. Review of benefits: summary of evidence of comparative effectiveness

9.1. **Pivotal trials, treatment setting, population included and main outcomes**

In this submission for the inclusion of BRAF/MEK inhibitors for the treatment of unresectable or metastatic melanoma, we will consider the indications scored as ESMO-MCBS scores 4 or 5, and for which no controversies exist in the indications, namely the use in the 1st line unresectable or metastatic melanoma with the BRAF V600E mutation (see Table 3).

Approximately 40 to 60% of cutaneous melanomas harbour mutations in BRAF that lead to constitutive activation of downstream signalling through the MAPK pathway. [73] Roughly 90% of these mutations result in the substitution of glutamic acid for valine at codon 600 (BRAFV600E), although other activating mutations are known (e.g., BRAFV600K and BRAFV600R).

Vemurafenib, was the first selective BRAFV600 inhibitor to be investigated in the treatment of advanced melanoma. [74] The BRIM-3 trial was a phase III randomised clinical trial that compared vemurafenib with the SOC dacarbazine in patients with previously untreated, metastatic melanoma with the BRAFV600E mutation. The results showed that vemurafenib was superior to dacarbazine in terms of prolonging PFS and OS.

Dabrafenib is another BRAF inhibitor investigated at the same time as vemurafenib with similar results in terms of efficacy. [75] The difference between the both BRAF inhibitors is mainly related with the toxicity profile. Dabrafenib induces almost no photosensitivity compared to vemurafenib (41%), fewer keratoacanthomas and squamous cell carcinomas (7% versus 20-30%). Arthralgia (56%), fatigue (46%) and rash (41%) were commonly reported with vemurafenib treatment. [74] On the other hand, pyrexia is the most common adverse event associated with dabrafenib treatment - almost 50% of the patients reported pyrexia that led to treatment interruption.

Treatment with BRAF inhibitors monotherapy induces high response rates but resistance supersedes shortly after. [74, 76, 77] Combination with another MAPK inhibitor, in this case a MEK inhibitor, is one of the ways to overcome the resistance and short duration of response of monotherapy with BRAF inhibitors. [78]

Three different BRAF/MEK combinations are currently available for patients with advanced melanoma. These combinations were investigated in randomised phase III trials and compared with BRAF inhibitors monotherapy showing improved survival outcomes in BRAFV600 mutated melanoma. Table 2 provides an overview of the population included in the pivotal trials, the main outcomes and the most frequent adverse events.

The combination of vemurafenib plus cobimetinib was investigated in the coBRIM trial, dabrafenib plus trametinib was investigated in the COMBI-d and COMBI-v study, and encorafenib plus binimetinib was investigated in the COLUMBUS study. [18, 79-81]

Recently, a pooled analysis evaluating the survival of patients with BRAFV600 mutated melanoma treated with BRAF/MEK inhibitors in the COMBI-d and COMBI-v trials showed that, with a median follow-up of 5-years, the OS rate was 34%. A complete response was observed in 19% of the patients, and in this subgroup the 5-year OS rate was 71% (95% CI, 62 to 79). [82] These results show that if targeted therapy is chosen to treat patients with BRAFV600 mutated melanoma, combined targeted therapy instead of monotherapy should be used.

Since the efficacy and survival outcomes are very similar with the three combinations of BRAF/MEK inhibitors, the combination chosen is mostly related with the safety profile that differs between them. There are no clinical trials evaluating the three combinations head-to-head. Recently an indirect analysis comparing all three combinations showed a non-significant risk reduction for progression and death in the subgroup of patients with elevated baseline LDH receiving vemurafenib plus cobimetinib, compared with dabrafenib plus trametinib and encorafenib plus binimetinib. Therefore, in this subgroup of patients, combination of vemurafenib plus cobimetinib might be considered. [83]

Table 2: Summary of results from the trials investigating targeted therapy in advanced melanoma

Study	**Combination targeted therapy**				
	COMBI-d	COMBI-v	CoBRIM	COLUMBUS	
Agent(s)	D + T	D + T	V + C	E + B	
Patients, n (study arm)	211	352	247	577 (Part1)	258 (Part2)
ECOG ≥ 1, %	27	29	24	29	27
M1c, %	67	63	59	64	67
LDH > ULN, %	36	34	46	29	31
Follow up, months	≥ 36.0	23	21.2	36.8	
Median OS, months	25.1	26.1	22.5	33.6	
1-yr OS, %	74	73	74.5	76	
2-yr OS, %	52	53	49.0	58	
3-yr OS, %	44	45	38.5	47	
4-yr OS, %	37		34.7	39	
5-yr OS, %	34		---	---	
Median PFS, months	11.0	12.1	12.3	14.9	12.9
1-yr PFS, %	---	---	---	56	
2-yr PFS, %	30	30	---	37	
3-yr PFS, %	22	24	---	29	
4-yr PFS, %	21		---	25	
5-yr PFS, %	19		---	---	
ORR, %	69	67	70	64	66
CR/PR, %	16/53	19/48	16/54	13/51	8/58

Median DOR, months	12	13.8	13.0	18.6	12.7
Related AEs, %	97	99	99	98	98
Discontinuation due to AE %	14	16	13	15	12
CTCAE grade 3/4 AEs, %	48	57	77	64	47

D+T= Dabrafenib plus Trametinib; V+C= Vemurafenib plus Cobimetinib; E+B= Encorafenib plus Binimetinib

9.2. **Targeted therapy in patients with melanoma brain metastases (MBM)**

Patients with MBM pose a particular therapeutic challenge, and have a worse prognosis compared to stage other IV patients. This has been acknowledged in the new AJCC classification, that included patients with MBM in a particular subgroup – M1d. [84] The studies evaluating systemic therapy in patients with advanced melanoma have systematically excluded patients with brain metastases. In fact, active MBM is an exclusion criterion for the great majority of phase III clinical trials, regardless ofthe tumour entity. Trials specifically investigating immunotherapy and targeted therapy in patients with MBM have shown that these therapies are also effective intracranially, and that the intracranial response rate is similar to the extracranial response. [85-88] Currently, there is evidence that PD-1-based immunotherapy, and particularly combined immunotherapy with nivolumab and ipilimumab might be more effective than BRAF/MEK inhibitors. [72, 89]

Two trials have evaluated targeted therapy in MBM: the BREAK-MB trial and the COMBI-MB trial. [87, 88] However, only the COMBI-MB trial evaluated the combination therapy of BRAF/MEK dabrafenib plus trametinib. This trial included 4 cohorts: (A) patients with BRAFV600E, asymptomatic MBM, with no previous local brain therapy, and an ECOG performance status of 0 or 1; (B) patients with BRAFV600E, asymptomatic MBM, with previous local brain therapy, and an ECOG performance status of 0 or 1; (C) patients with BRAFV600D/K/R, asymptomatic MBM, with or without previous local brain therapy, and an ECOG performance status of 0 or 1; and (D) patients with BRAFV600D/E/K/R, symptomatic MBM, with or without previous local brain therapy, and an ECOG performance status of 0, 1, or 2. The primary endpoint and secondary endpoints were investigator assessed intracranial response. The interim median PFS (months) for each sub-group of patients was: (A) 5·6 (5·3–7·4); (B) 7·2 (4·7–14·6); (C) 4·2 (1·7–6·5) and (D) 5·5 (2·8–7·3). The interim median OS (months) for each sub-group of patients was: (A) 10·8 (8·7–19·6); (B) 24·3 (7·9–NE); (C) 10·1 (4·6–17·6); and (D) 11·5 (6·8–22·4). Although preliminary, these data seem to suggest that patients with BRAFV600 mutated melanoma, with asymptomatic MBM and who received previous local therapy seem to do better than the other sub-groups.

No new safety issues were observed.

According to the ESMO recommendations, targeted therapy is preferred to immunotherapy in patients with MBM in case of continuous dependency on corticosteroids (>10 mg prednisolone or equivalent) at initiation of systemic treatment (III;B). [35]

9.3. Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

The majority of the data referred in this application, particularly for the clinical trials evaluating the three BRAF/MEK combinations proposed, has been referred in the ESMO and NCCN guidelines [10, 11] for the management of advanced melanoma. The ESMO Clinical Practice Guidelines and the ESMO consensus conference recommendations were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development. [90] The relevant literature has been selected by the expert authors, reporting the levels of evidence (I-V) and the grades of recommendations (A-E), adapting the Infectious Diseases Society of America-United States Public Health Service Grading System.

A manual research of other databases (Medline, Scopus, Ovid, Google Scholar) was also performed, namely for information regarding incidence and prevalence of melanoma and comparative cost and cost-effectiveness. The prescribing information available on the EMA and FDA websites was also used, particularly to accurately define the approved therapeutic indications.

The ESMO-MCBS v1.1 calculated score for the three BRAF/MEK combinations are also presented. Scores of 4 or 5 are considered valuable scores to suggest priority medicines in advanced setting. [2]

10. Summary of available data on comparative cost and cost-effectiveness of the medicine

A recently published economic evaluation of the systemic treatments for advanced melanoma that included vemurafenib plus cobimetinib, dabrafenib plus trametinib, ipilimumab, pembrolizumab, nivolumab and nivolumab plus ipilimumab has shown that the targeted combinations where not cost-effective, at current prices, in any jurisdiction. [91] PD-1 inhibitors nivolumab and pembrolizumab seem to be more cost-effective compared to ipilimumab, but this has not been established in comparison to chemotherapy. The combination of nivolumab plus ipilimumab doesn't seem to be cost effective in the settings where PD-1 monotherapy is approved. Data from the following countries were included USA, UK, Norway, Italy, Portugal, Australia, Canada and Switzerland. This study evaluated the estimates of relative treatment effects from randomised controlled trials. However, as the authors point out, a high number of patients treated in the real-life setting do not meet the criteria for inclusion in clinical trials. [92, 93] So, the exact cost-effectiveness in a real-world setting is not established. Moreover, the access to effective systemic therapies for unresectable or metastatic melanoma remains highly asymmetric even in Europe. [94]

The exact costs for each therapy are difficult to evaluate and characterise as they differ across countries and centres, due to different national legislation and local reimbursement negotiations. The availability of other effective systemic therapies such as PD-1 based immunotherapies might be another factor that weights when establishing the final price of the BRAF/MEK therapies.

One aspect that needs to be taken into consideration is the management of the potential toxicities for both targeted and immunotherapy. While severe and chronic adverse events that require other supportive therapies and hospitalisation are rare in patients receiving BRAF/MEK inhibitors, the same is not true for patients treated with immune checkpoint inhibitors. Also, the expertise and facilities necessary to manage oral and intravenous therapies needs to be considered, particularly in middle- and low-income countries, where the more differentiated facilities needed for treating patients with

immunotherapy might not be accessible. Finally, targeted therapy is restricted to patients harbouring a BRAFV600 mutation, while PD-1 based immunotherapy can be provided to all patients with unresectable or metastatic melanoma, and therefore, to a higher number of patients. However, the costs associated with testing for the presence of BRAFV600 mutation should also be considered.

11. Review of harms and toxicity: summary of evidence of safety

The frequency of AE between the three combinations available is similar. [95] However, the type of AE is different, and this aspect is the one that frequently leads to choosing one or the other combination. Dabrafenib induces almost no photosensitivity compared to vemurafenib (41%). This might represent and advantage for patients living in countries with high solar exposure. Patients should be informed of the need to protect skin from UVA exposure prior to treatment initiation. Broad-spectrum sunscreens, lip balm and protective clothing are effective in reducing photosensitivity. Patients need to be aware that UVA intensity is relatively constant. Moreover, UVA radiation can also penetrate glass and therefore, sunburns can appear even when the patient is indoors or driving.

Dabrafenib induces fewer keratoacanthomas and squamous cell carcinomas when compared to vemurafenib (7% versus 20-30%). Since the cutaneous toxicities might be difficult to manage or to correctly identify by medical oncologists, access to an experienced dermatologist might be of benefit.

Arthralgia (56%), fatigue (46%) and rash (41%) were commonly reported with vemurafenib treatment. [74] On the other hand, pyrexia is the most common problem associated with dabrafenib treatment, with almost 50% of the patients reporting pyrexia that leads to treatment interruption (see more details below). [95]

As for encorafenib plus binimetinib, the most frequent AE were gastro-intestinal (28% to 40%). The cutaneous AE were manageable, and in a percentage between 3% to 13%, similar to dabrafenib plus trametinib and lower than for vemurafenib plus cobimetinib. [18]

a) Ophthalmological toxicity

Treatment with MEK inhibitors is associated with ophthalmological toxicity, which is a class effect, and normally requires treatment delay and/or suspension. The frequency of surveillance for ocular events is not uniform and depends on the type of MEK inhibitor used. [4, 5, 7, 9, 19, 23] Regular ophthalmologic evaluations might be useful for asymptomatic patients to ensure that treatment is offered earlier. If visual disturbances are newly reported, an ophthalmologic evaluation is mandatory in order to identify potential complications of retinal vein occlusion (RVO) such as macular oedema, decreased visual function, neovascularisation, and glaucoma. Patients with previous history of ophthalmological issues should be evaluated before treatment start. [96] Generally, patients with RVO events should discontinue treatment with MEK inhibitors.

b) Cardiovascular toxicity

The mechanism responsible for cardiotoxicities associated with treatment with MAPK inhibitors is not completely understood. Treatment with MEK inhibitors is associated with cardiomyopathy either alone or in combination with BRAF inhibitors. Decreased left ventricular ejection fraction (LVEF) was present in 4-9% of the patients in trails evaluating treatment with targeted therapy. [15, 16, 32, 97, 98]

Based on the prescribing information, patients should have a cardiological assessment, particularly an LVEF assessed by echocardiogram or multigated acquisition scan before therapy initiation, after 1 month, and at 2- to 3-month intervals while on treatment. Decrease in LVEF is usually managed with treatment interruption, reduction, or discontinuation. Additional monitoring is required in patients who restart therapy following dose reduction or interruption for decreased LVEF. Permanent discontinuation of cobimetinib is recommended if the symptoms persist, if LVEF is less than the lower limits of normal (LLN) or absolute decrease from baseline LVEF is more than 10%. For binimetinib and trametinib, permanent discontinuation is recommended in case of symptomatic congestive heart failure or if absolute decrease in LVEF of greater than 20% from baseline that is also below the LLN. Rarely, QTc prolongation is observed with vemurafenib therapy, but not with MEK inhibitors monotherapy. In patients with QTc >500 ms, long QT syndrome, and/or being treated with medications known to prolong the QT interval, treatment with vemurafenib is not recommended. From our clinical experience, significant and symptomatic cardiovascular toxicity is not frequent.

a) Pyrexia

Pyrexia can be seen in patients treated with BRAF inhibitors but is characteristically associated with the combination of dabrafenib plus trametinib. [99] Almost 60% of patients developed pyrexia during treatment, and 24% of which had pyrexia symptoms without an elevation in body temperature. Pyrexia was grade ≥2 in 60% of pyrexia patients. Median time to onset of first pyrexia was 19 days, and the median duration was 9 days.

Treatment guidelines and prescribing information recommend dose reduction and/or intermittent administration. Corticotherapy might be considered in recurrent or severe pyrexia. Acetaminophen or nonsteroidal anti-inflammatory drugs are also helpful in improving symptoms. Our clinical experience shows that prompt interruption of dabrafenib plus trametinib at the time of the first episode might result in better control of pyrexia.

In summary, cutaneous toxicity was reduced with the combination BRAF/MEK. Compared to BRAF monotherapy. However, treatment with MEK inhibitors is associated with other toxicities (e.g. cardiovascular and ophthalmological).

12. Overview

The treatment of unresectable or metastatic melanoma has significantly changed in the last decade with the introduction of immune checkpoint inhibitors, and targeted therapy with mitogen-activated protein kinase inhibitors. Both therapies were able to provide sustainable survival benefits. For 40-60% of the patients diagnosed with melanoma, an actionable BRAFV600 mutation can be detected and, in these cases, targeted therapy with BRAF/MEK inhibitors can be offered. In order to guide the therapeutical options in this population of patients, determination of the mutation BRAF status in patients with advanced melanoma (III/IV) is mandatory according to the ESMO and the NCCN guidelines. In earlier stages it can be recommended only if considering inclusion is clinical trials, as no approved systemic therapy for these patients. An exception might be considered for stage IIC patients (AJCC 8th edition [84]), in case the patient can be offered systemic therapy.

BRAFV600 mutated melanoma patients can receive treatment with both targeted and immunotherapy. The best sequence of therapy is not defined, as there are no randomised controlled trials with head-to-head comparisons. In the 1st line setting, patients treated with targeted therapy seem to do better during the first 12 months and when PFS is evaluated, with immunotherapy showing a survival benefit after that. When looking into 2nd line setting, the data seems to be inverse, with targeted therapy providing more benefit. These are however indirect comparisons and need to be interpreted cautiously. Ongoing trials evaluating the best therapeutic sequence are ongoing, that might provide information to answer this question. [100]

Targeted therapy, provides a better initial outcome in patients with BRAFV600 mutated melanoma. Therefore those patients who need a fast response, such as those with a higher tumor volume, symptomatic disease, a high risk of organ or function deterioration due to the metastates, and with elevated, tend to be offered 1st line targeted therapy instead of immunotherapy in the clinical practice. There are no direct comparisons available between the three BRAF/MEK inhibitor combinations. The choice between one or the other normally takes into consideration the experience of the treating physician and the toxicity profile (Table 2).

Table 3 shows in more detail the ESMO-MCBS evaluation of the combinations of BRAF/MEK inhibitors used in the treatment of unresectable or metastatic melanoma.

Table 3: The ESMO-MCBS scores for targeted therapy with BRAF/MEK inhibitors for unresectable or metastatic melanoma harbouring a BRAFV600 mutation. Scores ≥4 are substantial

Tested Agent	Comb-ined agents	Control arm	Treatment setting	Primary outcome / evaluated outcome	PFS control (months)	PFS gain (months)	PFS HR	OS control	OS gain	OS HR	QoL	Toxicity	ESMO-MCBS v1.1	Ref
T	D	D	1st line unresectable or metastatic melanoma with the BRAF V600E mutation	PFS/ PFS	5.8	3.6	0.39 (0.25-0.62)	-	-	-	-	12% reduction skin cancer	**4**	[97]
T	D	V	1st line unresectable or metastatic	OS/OS	7.3	4.1	0.56 (0.46 - 0.69)	18.0 months* 3-years survival	8.0 months* 3-years survival	0.69 (0.53 - 0.89) Interim OS (p=0.	Improved QoL (exploratory outcome) **	17% reduction skin cancer	**5**	[16, 80, 82]

			melanoma with the BRAF V600E mutation					31%	13%	005< 0.02)			
C	V	V + placebo	1st line unresectable or metastatic melanoma with the BRAF V600E mutation	PFS/ OS	7.2	5.1	0.58 (0.46 - 0.72)	17.4 months	4.9 months	0.70 (0.55 - 0.90)	-	9% reduction skin cancer Annotation: 2.8% increase Grade3+ retinopathy	**4**	[101-103]
B	E	V	Advanced unresectable or metastatic melanoma	PFS &OS/ OS	7.3	7.6	0.51 (0.39 - 0.67)	16.9 months	16.7 months	0.61 (0.47 - 0.79)	-	-	**4**	[18, 104]

			with BRAF V600											

D= Dabrafenib; T= Trametinib; V= Vemurafenib; C= Cobimetinib; E= Encorafenib; B= Binimetinib

*Estimated from Kaplan-Meier plot

**QoL evaluated as an exploratory endpoint (as distinct from primary or secondary endpoint) is not eligible for ESMO-MCBS grading.

References

1. Cherny NI, Sullivan R, Dafni U et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol 2015; 26: 1547-1573.
2. Cherny NI, Dafni U, Bogaerts J et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Ann Oncol 2017; 28: 2340-2366.
3. EMA. SUMMARY OF PRODUCT CHARACTERISTICS - TAFINLAR In Edition https://www.ema.europa.eu/en/documents/product-information/tafinlar-epar-product-information_en.pdf: 2020.
4. EMA. SUMMARY OF PRODUCT CHARACTERISTICS - MEKINIST In Edition https://www.ema.europa.eu/en/documents/product-information/mekinist-epar-product-information_en.pdf: 2020.
5. FDA. MEKINIST prescribing information In Edition https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204114s007lbl.pdf: 2020.
6. EMA. SUMMARY OF PRODUCT CHARACTERISTICS - ZELBORAF. In Edition https://www.ema.europa.eu/en/documents/product-information/zelboraf-epar-product-information_en.pdf: 2020.
7. EMA. SUMMARY OF PRODUCT CHARACTERISTICS - COTELLIC In Edition https://www.ema.europa.eu/en/documents/product-information/cotellic-epar-product-information_en.pdf: 2020.
8. EMA. SUMMARY OF PRODUCT CHARACTERISTICS - BRAFTOVI. In Edition https://www.ema.europa.eu/en/documents/product-information/braftovi-epar-product-information_en.pdf: 2020.
9. EMA. SUMMARY OF PRODUCT CHARACTERISTICS - MEKTOVI. In Edition https://www.ema.europa.eu/en/documents/product-information/braftovi-epar-product-information_en.pdf: 2020.
10. Michielin O, van Akkooi ACJ, Ascierto PA et al. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up††Approved by the ESMO Guidelines Committee: February 2002, last update September 2019. Annals of Oncology 2019; 30: 1884-1901.
11. NCCN. NCCN guidelines - Cutaneous melanoma - https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. In Edition.
12. Cormican D, Kennedy C, Murphy S et al. High concordance of BRAF mutational status in matched primary and metastatic melanoma. Journal of Cutaneous Pathology 2019; 46: 117-122.
13. Colombino M, Capone M, Lissia A et al. BRAF/NRAS Mutation Frequencies Among Primary Tumors and Metastases in Patients With Melanoma. Journal of Clinical Oncology 2012; 30: 2522-2529.
14. Casula M, Colombino M, Manca A et al. Low Levels of Genetic Heterogeneity in Matched Lymph Node Metastases from Patients with Melanoma. Journal of Investigative Dermatology 2016; 136: 1917-1920.
15. Long GV, Stroyakovskiy D, Gogas H et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet 2015; 386: 444-451.
16. Robert C, Karaszewska B, Schachter J et al. Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib. New England Journal of Medicine 2014; 372: 30-39.
17. Ascierto PA, McArthur GA, Dréno B et al. Cobimetinib combined with vemurafenib in advanced BRAF/V600-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. The Lancet Oncology 2016; 17: 1248-1260.
18. Dummer R, Ascierto PA, Gogas HJ et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. The Lancet Oncology 2018; 19: 603-615.
19. FDA. COTELLIC prescribing information In Edition https://www.gene.com/download/pdf/cotellic_prescribing.pdf: 2020.
20. FDA. https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools. In Edition 2020.
21. FDA. TAFINLAR prescribing information In Edition https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202806s008lbl.pdf: 2020.
22. FDA. BRAFTOVI prescribing information. In Edition https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210496s006lbl.pdf: 2020.
23. FDA. MEKTOVI prescribing information In Edition https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210498lbl.pdf: 2020.
24. FDA. ZELBORAF prescribing information In Edition https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/202429s012lbl.pdf: 2020.
25. Colombino M, Rozzo C, Paliogiannis P et al. Comparison of BRAF Mutation Screening Strategies in a Large Real-Life Series of Advanced Melanoma Patients. J Clin Med 2020; 9.
26. Vanni I, Tanda ET, Spagnolo F et al. The Current State of Molecular Testing in the BRAF-Mutated Melanoma Landscape. Frontiers in Molecular Biosciences 2020; 7.
27. Malicherova B, Burjanivova T, Grendar M et al. Droplet digital PCR for detection of BRAF V600E mutation in formalin-fixed, paraffin-embedded melanoma tissues: a comparison with Cobas(®) 4800, Sanger sequencing, and allele-specific PCR. American journal of translational research 2018; 10: 3773-3781.
28. McEvoy AC, Wood BA, Ardakani NM et al. Droplet Digital PCR for Mutation Detection in Formalin-Fixed, Paraffin-Embedded Melanoma Tissues: A Comparison with Sanger Sequencing and Pyrosequencing. The Journal of Molecular Diagnostics 2018; 20: 240-252.
29. Lamy P-J, Castan F, Lozano N et al. Next-Generation Genotyping by Digital PCR to Detect and Quantify the BRAF V600E Mutation in Melanoma Biopsies. The Journal of Molecular Diagnostics 2015; 17: 366-373.
30. Bisschop C, ter Elst A, Bosman LJ et al. Rapid BRAF mutation tests in patients with advanced melanoma: comparison of immunohistochemistry, Droplet Digital PCR, and the Idylla Mutation Platform. Melanoma Research 2018; 28.

31. Parliament E. Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU. In Edition https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.L_.2017.117.01.0176.01.ENG&toc=OJ%3AL%3A2017%3A117%3ATOC: 2020.
32. Larkin J, Ascierto PA, Dreno B et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014; 371: 1867-1876.
33. Tolk H, Satzger I, Mohr P et al. Complete remission of metastatic melanoma upon BRAF inhibitor treatment - what happens after discontinuation? Melanoma Res 2015; 25: 362-366.
34. Carlino MS, Vanella V, Girgis C et al. Cessation of targeted therapy after a complete response in BRAF-mutant advanced melanoma: a case series. Br J Cancer 2016; 115: 1280-1284.
35. Keilholz U, Ascierto PA, Dummer R et al. ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO Guidelines Committee. Annals of Oncology 2020; 31: 1435-1448.
36. Apalla Z, Nashan D, Weller RB, Castellsague X. Skin Cancer: Epidemiology, Disease Burden, Pathophysiology, Diagnosis, and Therapeutic Approaches. Dermatol Ther (Heidelb) 2017; 7: 5-19.
37. Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.
38. Garbe C, Keim U, Eigentler TK et al. Time trends in incidence and mortality of cutaneous melanoma in Germany. J Eur Acad Dermatol Venereol 2019; 33: 1272-1280.
39. Coory M, Baade P, Aitken J et al. Trends for in situ and Invasive Melanoma in Queensland, Australia, 1982–2002. Cancer Causes & Control 2006; 17: 21-27.
40. Australia AG-C. Melanoma of the skin statistics. In Edition https://melanoma.canceraustralia.gov.au/statistics: 2020.
41. Cormier JN, Xing Y, Ding M et al. Ethnic differences among patients with cutaneous melanoma. Arch Intern Med 2006; 166: 1907-1914.
42. Arnold M, Holterhues C, Hollestein LM et al. Trends in incidence and predictions of cutaneous melanoma across Europe up to 2015. J Eur Acad Dermatol Venereol 2014; 28: 1170-1178.
43. Moan J, Baturaite Z, Grigalavicius M, Juzeniene A. Cutaneous malignant melanoma incidence rates in Norway. Scand J Public Health 2013; 41: 336-339.
44. Liu-Smith F, Farhat AM, Arce A et al. Sex differences in the association of cutaneous melanoma incidence rates and geographic ultraviolet light exposure. J Am Acad Dermatol 2017; 76: 499-505.e493.
45. Whiteman DC, Green AC, Olsen CM. The Growing Burden of Invasive Melanoma: Projections of Incidence Rates and Numbers of New Cases in Six Susceptible Populations through 2031. J Invest Dermatol 2016; 136: 1161-1171.
46. Helvind NM, Hölmich LR, Smith S et al. Incidence of In Situ and Invasive Melanoma in Denmark From 1985 Through 2012: A National Database Study of 24,059 Melanoma Cases. JAMA Dermatol 2015; 151: 1087-1095.
47. Bay C, Kejs AM, Storm HH, Engholm G. Incidence and survival in patients with cutaneous melanoma by morphology, anatomical site and TNM stage: a Danish Population-based Register Study 1989-2011. Cancer Epidemiol 2015; 39: 1-7.
48. Barbaric J, Sekerija M, Agius D et al. Disparities in melanoma incidence and mortality in South-Eastern Europe: Increasing incidence and divergent mortality patterns. Is progress around the corner? Eur J Cancer 2016; 55: 47-55.
49. Forsea AM, Del Marmol V, de Vries E et al. Melanoma incidence and mortality in Europe: new estimates, persistent disparities. Br J Dermatol 2012; 167: 1124-1130.
50. Osterlind A, Møller Jensen O. Trends in incidence of malignant melanoma of the skin in Denmark 1943-1982. Recent Results Cancer Res 1986; 102: 8-17.
51. Holterhues C, Hollestein LM, Nijsten T et al. Burden of disease due to cutaneous melanoma has increased in the Netherlands since 1991. British Journal of Dermatology 2013; 169: 389-397.
52. Karimkhani C, Green AC, Nijsten T et al. The global burden of melanoma: results from the Global Burden of Disease Study 2015. Br J Dermatol 2017; 177: 134-140.
53. Blum A, Garbe C. Epidemiologie, Prävention und Nachsorge maligner Melanome. Der Onkologe 2001; 7: 18-35.
54. Minini R, Rohrmann S, Braun R et al. Incidence trends and clinical-pathological characteristics of invasive cutaneous melanoma from 1980 to 2010 in the Canton of Zurich, Switzerland. Melanoma Res 2017; 27: 145-151.
55. Sacchetto L, Zanetti R, Comber H et al. Trends in incidence of thick, thin and in situ melanoma in Europe. Eur J Cancer 2018; 92: 108-118.
56. Teramoto Y, Keim U, Gesierich A et al. Acral lentiginous melanoma: a skin cancer with unfavourable prognostic features. A study of the German central malignant melanoma registry (CMMR) in 2050 patients. Br J Dermatol 2018; 178: 443-451.
57. Dennis LK, Vanbeek MJ, Beane Freeman LE et al. Sunburns and risk of cutaneous melanoma: does age matter? A comprehensive meta-analysis. Annals of epidemiology 2008; 18: 614-627.
58. Gandini S, Sera F, Cattaruzza MS et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer 2005; 41: 45-60.
59. Oliveria SA, Saraiya M, Geller AC et al. Sun exposure and risk of melanoma. Archives of disease in childhood 2006; 91: 131-138.
60. Leiter U, Garbe C. Epidemiology of melanoma and nonmelanoma skin cancer--the role of sunlight. Adv Exp Med Biol 2008; 624: 89-103.
61. Arnold M, de Vries E, Whiteman DC et al. Global burden of cutaneous melanoma attributable to ultraviolet radiation in 2012. Int J Cancer 2018; 143: 1305-1314.

62. Blum A, Garbe C, Bauer J. Epidemiologie und Risikofaktoren des malignen Melanoms. Der Onkologe 2004; 10: 688-700.
63. Pleasance ED, Cheetham RK, Stephens PJ et al. A comprehensive catalogue of somatic mutations from a human cancer genome. Nature 2010; 463: 191-196.
64. Alexandrov LB, Nik-Zainal S, Wedge DC et al. Signatures of mutational processes in human cancer. Nature 2013; 500: 415-421.
65. Forschner A, Battke F, Hadaschik D et al. Tumor mutation burden and circulating tumor DNA in combined CTLA-4 and PD-1 antibody therapy in metastatic melanoma – results of a prospective biomarker study. Journal for ImmunoTherapy of Cancer 2019; 7: 180.
66. Chan TA, Yarchoan M, Jaffee E et al. Development of tumor mutation burden as an immunotherapy biomarker: utility for the oncology clinic. Annals of Oncology 2019; 30: 44-56.
67. Weide B, Martens A, Hassel JC et al. Baseline Biomarkers for Outcome of Melanoma Patients Treated with Pembrolizumab. Clinical Cancer Research 2016; 22: 5487.
68. Schadendorf D, Long GV, Stroiakovski D et al. Three-year pooled analysis of factors associated with clinical outcomes across dabrafenib and trametinib combination therapy phase 3 randomised trials. Eur J Cancer 2017; 82: 45-55.
69. Ascierto PA, Ribas A, Larkin J et al. Impact of initial treatment and prognostic factors on postprogression survival in BRAF-mutated metastatic melanoma treated with dacarbazine or vemurafenib ± cobimetinib: a pooled analysis of four clinical trials. Journal of Translational Medicine 2020; 18: 294.
70. Ugurel S, Röhmel J, Ascierto PA et al. Survival of patients with advanced metastatic melanoma: the impact of novel therapies-update 2017. Eur J Cancer 2017; 83: 247-257.
71. Ugurel S, Rohmel J, Ascierto PA et al. Survival of patients with advanced metastatic melanoma: The impact of MAP kinase pathway inhibition and immune checkpoint inhibition - Update 2019. Eur J Cancer 2020; 130: 126-138.
72. Franken MG, Leeneman B, Gheorghe M et al. A systematic literature review and network meta-analysis of effectiveness and safety outcomes in advanced melanoma. Eur J Cancer 2019; 123: 58-71.
73. Davies H, Bignell GR, Cox C et al. Mutations of the BRAF gene in human cancer. Nature 2002; 417: 949-954.
74. Chapman PB, Hauschild A, Robert C et al. Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation. New England Journal of Medicine 2011; 364: 2507-2516.
75. Hauschild A, Grob JJ, Demidov LV et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012; 380: 358-365.
76. Amaral T, Sinnberg T, Meier F et al. The mitogen-activated protein kinase pathway in melanoma part I - Activation and primary resistance mechanisms to BRAF inhibition. Eur J Cancer 2017; 73: 85-92.
77. Amaral T, Sinnberg T, Meier F et al. MAPK pathway in melanoma part II-secondary and adaptive resistance mechanisms to BRAF inhibition. Eur J Cancer 2017; 73: 93-101.
78. Villanueva J, Vultur A, Lee JT et al. Acquired resistance to BRAF inhibitors mediated by a RAF kinase switch in melanoma can be overcome by cotargeting MEK and IGF-1R/PI3K. Cancer Cell 2010; 18: 683-695.
79. Ascierto PA, McArthur GA, Dréno B et al. Cobimetinib combined with vemurafenib in advanced BRAFV600mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. The Lancet Oncology 2016; 17: 1248-1260.
80. Grob JJ, Amonkar MM, Karaszewska B et al. Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial. The Lancet Oncology 2015; 16: 1389-1398.
81. Long GV, Flaherty KT, Stroyakovskiy D et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAFV600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Annals of Oncology 2017; 28: 1631-1639.
82. Robert C, Grob JJ, Stroyakovskiy D et al. Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma. New England Journal of Medicine 2019; 381: 626-636.
83. Glutsch V, Amaral T, Garbe C et al. Indirect Comparison of Combined BRAF and MEK Inhibition in Melanoma Patients with Elevated Baseline Lactate Dehydrogenase. Acta dermato-venereologica 2020.
84. Gershenwald JE, Scolyer RA, Hess KR et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA: a cancer journal for clinicians 2017; 67: 472-492.
85. Long GV, Atkinson V, Lo S et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol 2018; 19: 672-681.
86. Tawbi HA, Forsyth PA, Algazi A et al. Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain. New England Journal of Medicine 2018; 379: 722-730.
87. Davies MA, Saiag P, Robert C et al. Dabrafenib plus trametinib in patients with BRAF(V600)-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol 2017; 18: 863-873.
88. Long GV, Trefzer U, Davies MA et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol 2012; 13: 1087-1095.
89. Rulli E, Legramandi L, Salvati L, Mandala M. The impact of targeted therapies and immunotherapy in melanoma brain metastases: A systematic review and meta-analysis. Cancer 2019; 125: 3776-3789.
90. ESMO. Standard Operating Procedures (SOPs) for Authors and templates for ESMO Clinical Practice Guidelines (CPGs) and ESMO-MCBS Scores In Edition https://www.esmo.org/content/download/77789/1426712/1/ESMO-Clinical-Practice-Guidelines-Standard-Operating-Procedures.pdf: 2020.

91. Gorry C, McCullagh L, Barry M. Economic Evaluation of Systemic Treatments for Advanced Melanoma: A Systematic Review. Value in Health 2020; 23: 52-60.
92. Donia M, Kimper-Karl ML, Høyer KL et al. The majority of patients with metastatic melanoma are not represented in pivotal phase III immunotherapy trials. Eur J Cancer 2017; 74: 89-95.
93. Sam D, Gresham G, Abdel-Rahman O, Cheung WY. Generalizability of clinical trials of advanced melanoma in the real-world, population-based setting. Med Oncol 2018; 35: 110.
94. Kandolf Sekulovic L, Guo J, Agarwala S et al. Access to innovative medicines for metastatic melanoma worldwide: Melanoma World Society and European Association of Dermato-oncology survey in 34 countries. Eur J Cancer 2018; 104: 201-209.
95. Heinzerling L, Eigentler TK, Fluck M et al. Tolerability of BRAF/MEK inhibitor combinations: adverse event evaluation and management. ESMO open 2019; 4: e000491-e000491.
96. Stjepanovic N, Velazquez-Martin JP, Bedard PL. Ocular toxicities of MEK inhibitors and other targeted therapies. Annals of Oncology 2016; 27: 998-1005.
97. Flaherty KT, Infante JR, Daud A et al. Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations. New England Journal of Medicine 2012; 367: 1694-1703.
98. Flaherty KT, Robert C, Hersey P et al. Improved Survival with MEK Inhibition in BRAF-Mutated Melanoma. New England Journal of Medicine 2012; 367: 107-114.
99. Menzies AM, Ashworth MT, Swann S et al. Characteristics of pyrexia in BRAFV600E/K metastatic melanoma patients treated with combined dabrafenib and trametinib in a phase I/II clinical trial. Ann Oncol 2015; 26: 415-421.
100. P.A. Ascierto MM, P.F. Ferrucci, P. Rutkowski, M. Guidoboni, A.M. Arance Fernandez, V. Ferraresi, E. Maiello, M. Guida, M. Del Vecchio, M.T. Fierro, P. Queirolo, C. Lebbé, H. Helgadottir, I. Melero, G. Palmieri, D. Giannarelli A.M. Grimaldi, R. Dummer, V. Chiarion Sileni. LBA45 - First report of efficacy and safety from the phase II study SECOMBIT (SEquential COMBo Immuno and Targeted therapy study). Annals of Oncology (2020) 31 (suppl_4): S1142-S1215. 10.1016/annonc/annonc325 2020.
101. Ascierto PA, McArthur GA, Dréno B et al. Cobimetinib combined with vemurafenib in advanced BRAFV600-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. The Lancet Oncology 2016; 17: 1248-1260.
102. de la Cruz-Merino L, Di Guardo L, Grob J-J et al. Clinical features of serous retinopathy observed with cobimetinib in patients with BRAF-mutated melanoma treated in the randomized coBRIM study. Journal of Translational Medicine 2017; 15: 146.
103. Dréno B, Ribas A, Larkin J et al. Incidence, course, and management of toxicities associated with cobimetinib in combination with vemurafenib in the coBRIM study. Annals of Oncology 2017; 28: 1137-1144.
104. Dummer R, Ascierto PA, Gogas HJ et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. The Lancet Oncology 2018; 19: 1315-1327.