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REVIEW

Fertility preservation and management of pregnancy in melanoma patients requiring systemic therapy

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Melanoma is one of the most common cancers in adolescents and adults at fertile age, especially in women. With novel and more effective systemic therapies that began to profoundly change the dismal outcome of melanoma by prolonging overall survival, the wish for fertility preservation or even parenthood has to be considered for a growing portion of melanoma patients—from the patients' as well as from the physicians' perspective. The dual blockade of the mitogen-activated protein kinase pathway by B-Raf proto-oncogene serine/threonine kinase and mitogen-activated protein kinase inhibitors and the immune checkpoint inhibition by anti-programmed cell death protein 1 and anti-cytotoxic T-lymphocyte-associated protein-4 monoclonal antibodies constitute the current standard systemic approaches to combat locally advanced or metastatic melanoma. Here, the preclinical data and clinical evidence of these systemic therapies are reviewed in terms of their potential gonadotoxicity, teratogenicity, embryotoxicity and fetotoxicity. Recommendations for routine fertility and contraception counseling of melanoma patients at fertile age are provided in line with interdisciplinary recommendations for the diagnostic work-up of these patients and for fertility-protective measures. Differentiated recommendations for the systemic therapy in both the adjuvant and the advanced, metastatic treatment situation are given. In addition, the challenges of pregnancy during systemic melanoma therapy are discussed.

Key words: fertility preservation, immunotherapy, melanoma, parenthood, pregnancy, targeted therapy

INTRODUCTION

Cutaneous melanoma, arising from oncogenic transformation of melanocytes, causes >60 000 deaths per year worldwide.[1] Melanoma is an aggressive skin cancer that tends to widespread metastasis. Once the primary tumor has spread, melanoma rapidly becomes a life-threatening disease.[2]

During the last decade, novel and more effective systemic therapies have profoundly changed the dismal outcome of melanoma by prolonging overall survival (OS) considerably.[2] Treatments targeting the B-Raf proto-oncogene serine/threonine kinase $(BRAF)^{V600}$ mutations and immune checkpoint-inhibiting monoclonal antibodies both have increased hope for long-term tumor control and potential cure, with 5-year OS rates of 30%-50%.[3] Immune checkpoint inhibition (ICI) of programmed cell death protein 1 (PD-1) (CD279) or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (CD152), or the dual blockade of the mitogen-activated protein kinase (MAPK) pathway by a BRAF inhibitor and mitogen-activated protein kinase kinase (MEK) inhibitor, is now routinely used not only in patients with unresectable or metastatic melanoma, but also as adjuvant therapy.[4-7] While the BRAF inhibitor dabrafenib in combination with the MEK inhibitor trametinib and the PD-1 inhibitor pembrolizumab have been approved as adjuvant treatment for stage III patients after surgery, nivolumab can

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also be used in resected stage IV patients without evidence of disease. The anti-CTLA-4-directed antibody ipilimumab has only been approved as adjuvant treatment for stage III after surgery by the US Food and Drug Administration but not by the European Medicines Agency.

Although the risk for melanoma increases with age—the average age of people at time of diagnosis is around 65 years[8]—disease manifestation is not uncommon even among those younger than 30 years. In fact, melanoma is one of the most common cancers in adolescents and young adults, especially in women.[9-11]

In the context of the improved outcomes for locally advanced and metastatic disease and an overall rise in melanoma prevalence, clinicians must consider that wishes for parenthood and fertility preservation affect a considerable and growing proportion of their female and male patients. Approximately one-third of women with an initial diagnosis of melanoma are of childbearing age, and melanoma is one of the most common malignancies diagnosed in pregnant women.[12]

In this narrative review, an interdisciplinary panel of dermato-oncologists, gynecologists, andrologists and endocrinologists reviews the preclinical and clinical evidence of current, widely used systemic therapies regarding gonadotoxicity, teratogenicity, embryotoxicity and fetotoxicity and provides advice for patient counseling. The aim is to give recommendations on diagnostics, patient management and monitoring for melanoma patients wishing to preserve their fertility or to realize parenthood after systemic melanoma therapy.

MATERIALS AND METHODS

Preclinical and clinical information on gonadotoxic or teratogenic effects of drugs used as systemic treatment for locally advanced or metastatic melanoma was derived by a review of the respective sections of the European Commission's Guideline on summary of product characteristics (SmPC) and a review of the clinical safety patterns observed in the clinical trials leading to drug approval. In addition, a database search was carried out in Medline/PubMed, Embase and BIOSIS in June 2018 using the search terms 'fertility', 'pregnancy' and the respective treatments ('immunotherapy', 'nivolumab', 'pembrolizumab', 'BRAF inhibitor', 'MEK inhibitor', 'dabrafenib', trametinib', 'vemurafenib', 'cobimetinib'). Relevant reviews, research papers and case reports on gonadotoxic, embryotoxic and fetotoxic effects in melanoma patients after ICI therapy or MAPK pathway inhibition were used for further discussion with the interdisciplinary expert panel.

Recommendations were developed by the interdisciplinary expert panel, who initially met in Frankfurt, Germany, in July 2018. In four meetings (November 2018; January, February and March 2019), recommendations were first developed by separate working groups. Each recommendation for the adjuvant therapy setting was then discussed and adopted with agreement of all experts. They were made publicly available in the form of a slide set via the Dermatologic Cooperative Oncology Group, which is affiliated with the German Cancer Society and the German Dermatologic Society. In May 2020, the experts agreed to

Table 1. Recommendations (tabulated) for fertility preservation and avoidance of on-treatment pregnancy

Chapter	Recommendation
1	Need for routine fertility and contraception counseling for patients at fertile age
1.1	Referral to a physician specialized in reproductive medicine should be offered to all patients of reproductive age who have not completed their family planning or who may develop such a wish.
1.2	Treatment decisions should be made with the patient after an individual discussion of the different options and risks.
2	Diagnostic 'work-up' of melanoma patients at fertile age: fertility-related issues
2.1	Any diagnostic fertility 'work-up' should always involve the melanoma patient and his/her partner.
2.2	Consider a comprehensive hormonal baseline assessment of both partners, complemented by clinical investigation by ultrasound and more invasive endoscopic techniques, if appropriate.
2.3	Anti-Müllerian hormone (AMH) represents the most appropriate serum parameter for assessing the ovarian reserve of the female partner.
3	Gonadotoxicity, teratogenicity, embryotoxicity and fetotoxicity: preclinical data
3.1	BRAF/MEK inhibitors may affect fertility.
3.2	Teratogenic effects of MAPK pathway inhibitors cannot be excluded.
3.3	The strong PD-L1 expression found in the placenta may pose a higher risk of abortion of PD-1/PD-L1 inhibitors.
4	Potential side-effects affecting fertility or pregnancy: clinical evidence
4.1	Severe side-effects of systemic melanoma therapy may potentially affect fertility and increase the risk of miscarriage and impaired embryonal development.
4.2	In immune checkpoint inhibitors (ICIs), potential endocrine autoimmune-related adverse events (hypophysitis, thyroiditis, adrenalitis and type 1 diabetes) should not be overlooked. They can be acutely life-threatening and can impair fertility. In general, they can be treated adequately (consultation of an endocrinologist is recommended; in case of suspected hypocortisolism immediate substitution with hydrocortisone).
4.3	During active hypophysitis, pregnancy should be avoided.
5	Fertility preservation in adults at fertile age with melanoma: recommendations
5.1	The use of GnRH agonists should be considered during gonadotoxic therapy; ovarian stimulation and cryopreservation of oocytes (unfertilized or fertilized) or of ovarian tissue should be discussed as options to preserve female fertility.
5.2	Cryopreservation of sperm should be considered to preserve male fertility.
6	Recommendations regarding pregnancy
6.1	Adjuvant melanoma therapy with pembrolizumab or nivolumab or with dabrafenib plus trametinib should not be commenced in a pregnant patient.
6.2	In advanced or metastatic melanoma, treatment with BRAF and MEK inhibitors should only be administered during pregnancy when the potential benefit for the pregnant patient outweighs the potential risk for the fetus.
7	Recommendations for contraception
7.1	The intervals of the duration of contraception after therapy vary between 4 and 5 months, as outlined in the respective EU SmPCs.
7.2	Dual contraceptive methods including one barrier method must be used.

BRAF, B-Raf proto-oncogene serine/threonine kinase; EU, European Union; GnRH, gonadotropin-releasing hormone; MAPK, mitogen-activated protein kinase; MET, mitogen-activated protein kinase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; SmPC, summary of product characteristics.

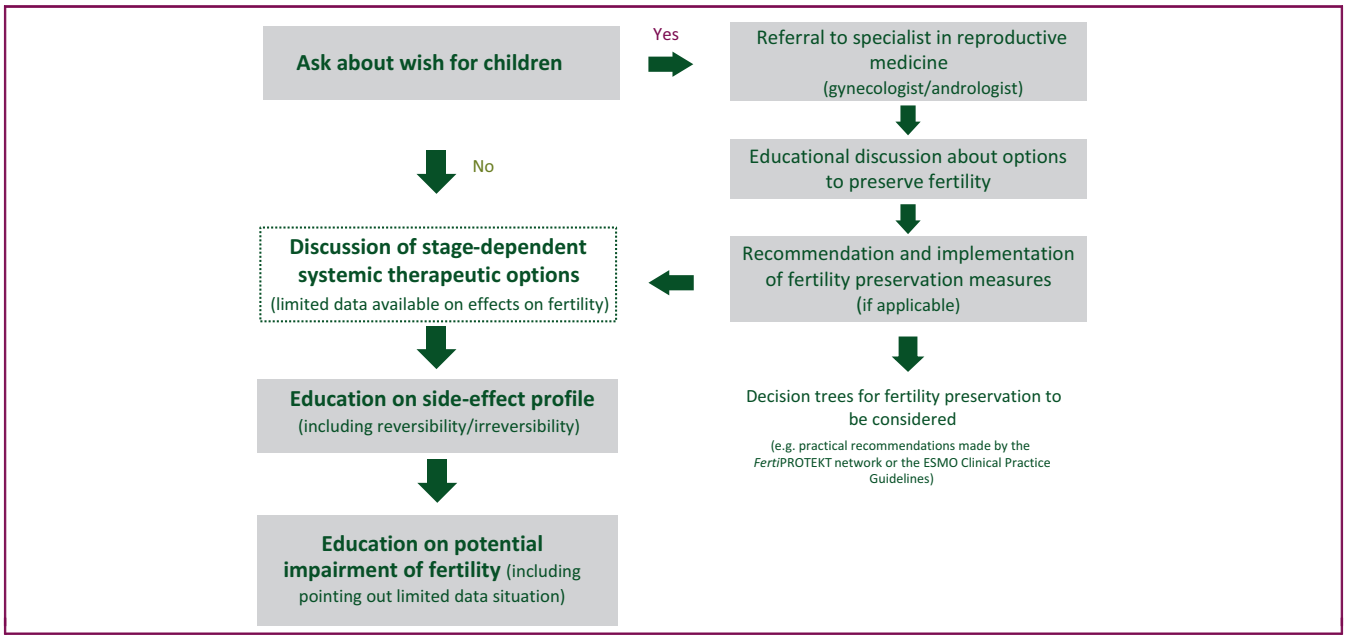

Figure 1. Flowchart outlining routine patient counseling of adults at fertile age diagnosed with melanoma.
Additional criteria to decide, e.g. for or against fertility preservation in women, are provided by the *Ferti*PROTEKT network,[15] or the recently published European Society for Medical Oncology (ESMO) Clinical Practice Guidelines.[16]

revise the recommendations in order to extend their applicability to patients with advanced unresectable or metastatic melanoma. At this stage, the PubMed database research was updated and extended for the terms 'fertility', 'pregnancy' and the treatments in the advanced setting ('immunotherapy', 'ipilimumab', 'nivolumab', 'pembrolizumab', 'BRAF inhibitor', 'MEK inhibitor', 'dabrafenib', 'trametinib', 'vemurafenib', 'cobimetinib', 'encorafenib', 'binimetinib'). Additionally, existing recommendations from guidelines and the most current clinical evidence were taken into account. Recommendations were discussed again in several rounds and only adopted when agreed by all experts. Standard recommendations to enhance the quality of evidence-based judgments were followed[13]; however, formal weighting of consensus recommendations (level of evidence, level of consensus, strength of recommendation) was not applied as recommendations were made on a level that all experts agreed. Medical terms like gonadotoxicity (i.e. toxicities to the ovaries or testicles), teratogenicity (i.e. patterns of, relating to, or causing developmental malformations of an embryo or fetus), embryotoxicity or fetotoxicity are used according to common medical terminology.[14]

RECOMMENDATIONS

A summary of the recommendations for fertility preservation and avoidance of on-treatment pregnancy consented by the expert panel is provided in Table 1.

Need for routine fertility and contraception counseling for patients at fertile age

Fertility preservation may be a crucial factor in the quality of life of melanoma patients, as of any other younger adults with cancer. Hence, fertility counseling and referral to a physician specialized in reproductive medicine (Figure 1) should be offered to all patients of reproductive age who have not completed their family planning or who may develop such a wish. Fertility preservation may affect adherence and therapy decision. For timely and competent counseling on fertility protection and implementation of fertility-protective measures, patients should be referred to an oncofertility unit. Networks are helpful to find experts who provide care for patients (both men and women) as comprehensively as possible.[17,18]

Treatment decisions should be made with the patient after an individual discussion of the different options and risks, as outlined in the next section. Reliable contraception should be used during and up to ~5 months after any melanoma therapy.

Diagnostic 'work-up' of melanoma patients at fertile age: fertility-related issues

In parallel to counseling and before therapeutic decision making, key influencing factors on female and male fertility should be assessed. It is important to note that male infertility is defined by the male's inability to induce pregnancy in a fertile female. The World Health Organization (WHO) defines infertility of a couple desiring to have children as 'pregnancy not occurring with regular sexual activity without use of contraceptive measures within one year'.[19] Male poor reproductive functions may be balanced by the optimal reproductive functions of the female partner, and vice versa.

Female age is the key factor affecting fertility and correlates negatively with the oocyte quantity and quality. The ovarian reserve, corresponding to the density of vital

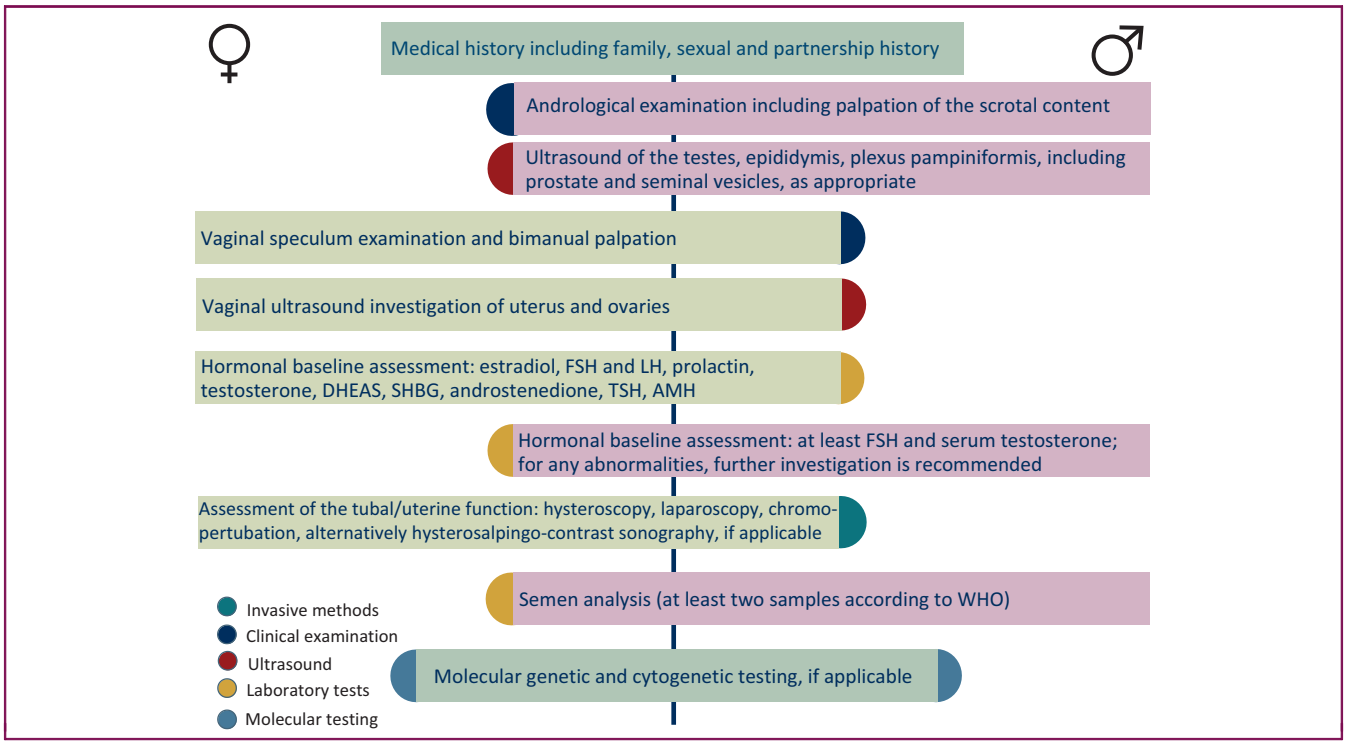

Figure 2. Fertility preservation-related diagnostic work-up in adults at fertile age diagnosed with melanoma.
AMH, anti-Müllerian hormone; DHEAS, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone-binding globulin; TSH, thyroid-stimulating hormone; WHO, World Health Organization.

follicles in the ovaries at a defined point in time, relates to the quantity of the eggs. The assessment of the ovarian reserve, which allows a prediction of the number of oocytes that can be obtained during ovarian stimulation, is a major objective during the diagnostic work-up of female fertility (Figure 2). Anti-Müllerian hormone (AMH), which negatively correlates with age and may be lowered up to 30% by combined hormonal contraception or decreases by gonadotoxic therapy, represents the most appropriate serum parameter for assessing the ovarian reserve.[20,21] However, especially in patients with low values, there might be some variability. AMH is produced by the primary to early antral follicles. A low AMH value suggests on the one hand an increased sensitivity to gonadotoxic therapy, but on the other hand also a reduced ovarian response to ovarian stimulation that is required for cryopreservation of oocytes. The antral follicle count (AFC) is a useful supplement to the assessment of ovarian reserve in addition to AMH. Although both usually correlate well, discordant values are found in about one in four patients.[22] In these cases, the marker that best corresponds to the clinical picture should be considered. AMH and AFC are superior to all other markers of ovarian reserve.[23] Cycle disorders or follicle-stimulating hormone (FSH) can provide additional information; however, they are of less informative value[20,24] as, for example, the early follicular FSH level varies greatly between cycles in the perimenopausal transition.[25] An elevated early follicular FSH deserves attention especially in combination with cycle disorders. In addition, reduced fertility of the partner (andrological factor) or reduced functioning or occlusion of the fallopian tubes (tubal factors) may also affect female fertility.

Key influencing factors of male fertility comprise the stimulation of spermatogenesis in the testes by secretion of FSH and luteinizing hormone (LH), the stimulation of testosterone production in the testes by LH as well as the spermatogenesis in the seminiferous tubules, with a duration of ~10 weeks. Male fertility can be assessed best by semen analysis and sperm function test (Figure 2). According to WHO, at least two semen samples collected on separate days by masturbation are recommended. In addition, andrological examination including palpation of the scrotal content and ultrasound of testis, epididymis, plexus pampiniformis, prostate and seminal vesicle should be carried out as appropriate.[26]

The extent to which the examinations shown in Figure 2 are carried out after a consultation or in preparation for a fertility-protective measure depends on the individual situation. For women, they are usually limited to gynecological/vaginal sonographic and endocrinological examinations, and for men to a semen analysis.

Gonadotoxicity, teratogenicity, embryotoxicity and fetotoxicity: preclinical data

The potential gonadotoxic impact of a drug depends on its dose and toxicological profile—both factors are investigated by reproductive toxicology studies during the preclinical development of a drug. However, the gonadotoxic effects of novel anticancer drugs are usually not

comprehensively known at the time of marketing authorization.[26-29]

Fertility. The available preclinical data of the three registered drug combinations of an anti-BRAF and anti-MEK inhibitor in melanoma therapy—dabrafenib and trametinib, vemurafenib and cobimetinib, encorafenib and binimetinib—indicate that, in line with the applicable guideline on non-clinical evaluation of anticancer drugs,[27,29] no specific fertility studies had been conducted before drug registration. As stated in the guideline, information from general toxicology studies on the drug's effect on reproductive organs constituted the basis for the assessment of fertility impairment before approval. Embryofetal toxicity studies, however, had to be conducted for the anti-BRAF and anti-MEK inhibitors before drug registration. In these studies, testicular degeneration was noted in male rats (e.g. for dabrafenib, encorafenib, cobimetinib) and a reduced number of ovarian corpora lutea in female rats (e.g. for dabrafenib, trametinib, cobimetinib). The respective quotes from Section 5.3 (Preclinical safety data) of the European Commission's Guideline SmPC are outlined in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2021.100248. The clinical relevance of the findings is unknown.

Compared to the small-molecule MAPK pathway inhibitors, the preclinical datasets for the ICIs pembrolizumab, nivolumab and ipilimumab differ in composition and tested species. The guidelines for biopharmaceuticals state that for embryofetal toxicology studies 'an assessment in one pharmacologically relevant species should usually be sufficient'.[27,29] Owing to the characteristics of immunologically acting monoclonal antibodies, cynomolgus monkeys were chosen for preclinical studies of the ICI. Additional preclinical evidence of effects on reproduction toxicology arose from studies in murine surrogate models.[30] As for the small-molecule tyrosine kinase inhibitors of the MAPK signaling pathway, dedicated fertility studies have not been conducted. The toxicity studies did not detect any notable effects in the male and female reproductive organs; however, as many animals used in the studies were sexually not mature, the clinical relevance of this observation is unknown.

Taking into account these scarce preclinical data, the following statements concerning gonadotoxicity can be made:

- Based on general toxicity studies and in the absence of dedicated animal studies on fertility, a fertility-lowering effect of the BRAF/MEK inhibitors cannot be excluded.
- PD-1 and programmed death-ligand 1 (PD-L1) are expressed at only very low levels in the ovary and the testes; however, because of missing preclinical data on fertility, a negative effect of ICI on fertility, e.g. spermiogenesis, cannot be excluded.

Pregnancy. Regarding pregnancy, the preclinical animal studies of the three BRAF inhibitors indicated potential teratogenicity. For the inhibitors of the MEK signaling pathway, the embryofetal developmental toxicity studies in rats and rabbits similarly indicated potentially teratogenic effects. Trametinib, for example, was embryotoxic and abortive in rabbits at doses below or slightly above the clinical exposures based on the area under the curve in humans. Cobimetinib showed malformations of the animal fetus on the great vessels and the skull in rats.

For immunotherapy with ICI, miscarriages were reported in mouse studies for pembrolizumab and nivolumab. Physiologically, the high PD-L1 expression on the placenta leads to materno-fetal tolerance. PD-1 blockage might therefore lead to fetal loss. For nivolumab, in pre- and postnatal studies in monkeys, a dose-dependent increase in fetal losses and neonatal mortality was observed beginning in the third trimester. However, development of surviving offspring mice was normal. Ipilimumab led to higher incidences of abortion, stillbirth and premature delivery in monkeys and some urogenital abnormalities with unclear causality.

Taking into account this divergent body of preclinical data, the following statements concerning teratogenicity, embryotoxicity and fetotoxicity can be made:

- Unfavorable effects on embryofetal development including teratogenic effects of the MAPK pathway inhibitors cannot be excluded.
- PD-L1 is highly expressed on the placenta, with miscarriage reported in mouse studies.

Potential side-effects affecting fertility or pregnancy: clinical evidence

In general, available clinical data on human fertility and pregnancy in conjunction with current melanoma therapies are scarce. Table 2 lists the relevant information as provided in the SmPC.

In the absence of studies in humans investigating the impact of the melanoma drugs or their adverse events (AEs) on fertility, an analysis of the AE patterns and their potential impact on fertility and embryo- and fetotoxicity was undertaken. The analysis was based on long-term safety data of the confirmatory phase III trials of the three BRAF—MEK inhibitor combinations in unresectable or metastatic melanoma,[40-42] as well as the corresponding datasets for the ICI.[43,44] For those melanoma drugs which are approved for adjuvant use, data from the respective adjuvant trials were additionally assessed.[4,5,7]

In general, severe side-effects, i.e. of National Cancer Institute Common Toxicity Criteria grade $\geq$3, may impact fertility during symptom period and increase the risk of miscarriage. Even common treatment-related disorders such as headache or fatigue can affect 'fertility' by reducing the desire and/or frequency of sexual intercourse.

Fertility. For the BRAF—MEK inhibitor combinations, the AE profile known from the multiple clinical studies of these medicines may be indicative of an indirect impact on fertility. The reported side-effects are usually reversible.[45] There are no dedicated clinical studies investigating the impact of MAPK inhibitor-related AE on fertility.

Table 2. Clinical evidence for gonadotoxic (male and female), embryo- and fetotoxic effects of current melanoma therapies used in (i) an adjuvant (AD) setting and/or (ii) in unresectable locally advanced or metastatic (LAM) melanoma

Therapy (drug)	Mechanism	Therapy setting	Effects on human female and/or male fertility (quotes from the EU summaries of product characteristics, i.e. Section 4.6)	Ref.
Dabrafenib (Dab)	BRAF inhibitor	Dab + Tra: AD and LAM	Fertility: There are no data in humans for dabrafenib as monotherapy or in combination with trametinib. (…) Male patients taking dabrafenib as monotherapy or in combination with trametinib should be informed of the potential risk for impaired spermatogenesis, which may be irreversible. Pregnancy: There are no data from the use of dabrafenib in pregnant women. (…) Dabrafenib should not be administered to pregnant women unless the potential benefit to the mother outweighs the possible risk to the fetus. If the patient becomes pregnant while taking dabrafenib, the patient should be informed of the potential hazard to the fetus.	31
Trametinib (Tra)	MEK inhibitor	Dab + Tra: AD and LAM	Fertility: There are no data in humans for trametinib as monotherapy or in combination with dabrafenib. (…) Trametinib may impair fertility in humans. Pregnancy: There are no adequate and well-controlled studies of trametinib in pregnant women. (…) If trametinib is used during pregnancy, or if the patient becomes pregnant while taking trametinib, the patient should be informed of the potential hazard to the fetus.	32
Vemurafenib (Vem)	BRAF inhibitor	Vem + Cob: LAM	Fertility: No specific studies with vemurafenib have been conducted in animals to evaluate the effect on fertility. Pregnancy: There are no data regarding the use of vemurafenib in pregnant women. Based on its mechanism of action, vemurafenib could cause fetal harm when administered to a pregnant woman; it should not be administered to pregnant women unless the possible benefit to the mother outweighs the possible risk to the fetus.	33
Cobimetinib (Cob)	MEK inhibitor	Vem + Cob: LAM	Fertility: There are no data in humans for cobimetinib. Pregnancy: There are no data from the use of cobimetinib in pregnant women. (…) Cobimetinib should not be used during pregnancy unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the fetus.	34
Encorafenib (Enc)	BRAF inhibitor	Enc + Bin: LAM	Fertility: There are no data on the effects of encorafenib on fertility in humans. (…) Male patients should be informed of the potential risk for impaired spermatogenesis. Pregnancy: There are no data on the use of encorafenib in pregnant women. (…) Encorafenib is not recommended during pregnancy and in women of childbearing potential not using contraception. If encorafenib is used during pregnancy or if the patient becomes pregnant while taking encorafenib, the patient should be informed of the potential hazard to the fetus.	35
Binimetinib (Bin)	MEK inhibitor	Enc + Bin: LAM	Fertility: There are no data on the effect on fertility in humans for binimetinib. Pregnancy: There are no data from the use of binimetinib in pregnant women. (…) Binimetinib is not recommended during pregnancy and in women of childbearing potential not using contraception. If binimetinib is used during pregnancy, or if the patient becomes pregnant while taking binimetinib, the patient should be informed of the potential hazard to the fetus.	36
Pembrolizumab (Pem)	Anti-PD-1	Pem: AD and LAM	Fertility: No clinical data are available on the possible effects of pembrolizumab on fertility. Pregnancy: There are no data on the use of pembrolizumab in pregnant women. Animal reproduction studies have not been conducted with pembrolizumab. (…) Human immunoglobulins G4 (IgG4) are known to cross the placental barrier; as pembrolizumab is an IgG4 antibody, it has the potential to be transmitted from the mother to the developing fetus. Pembrolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with pembrolizumab.	37
Nivolumab (Niv)	Anti-PD-1	Niv + Ipi: LAM; Niv: AD and LAM	Fertility: Studies to evaluate the effect of nivolumab on fertility have not been carried out. Thus, the effect of nivolumab on male and female fertility is unknown. Pregnancy: There are no data from the use of nivolumab in pregnant women. (…) Human IgG4 is known to cross the placental barrier; as nivolumab is an IgG4 antibody, it has the potential to be transmitted from the mother to the developing fetus. Nivolumab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk. Effective contraception should be used for at least 5 months following the last dose of nivolumab.	38
Ipilimumab (Ipi)	Anti-CTLA-4	Ipi: LAM (USA: AD and LAM)	Fertility: Studies to evaluate the effect of ipilimumab on fertility have not been carried out. Thus, the effect of ipilimumab on male and female fertility is unknown. Pregnancy: There are no data on the use of ipilimumab in pregnant women. (…) Human IgG1 crosses the placental barrier. The potential risk of treatment to the developing fetus is unknown. Ipilimumab is not recommended during pregnancy or in women of childbearing potential not using effective contraception, unless the clinical benefit outweighs the potential risk.	39

Section/reference to animal studies (and effects seen therein) is omitted. Please refer to Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2021.100248 for outcomes of preclinical studies.

BRAF, B-Raf proto-oncogene serine/threonine kinase; CTLA-4, cytotoxic T-lymphocyte-associated protein-4; EU, European Union; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Malfunctions of the blood—testes barrier with damage to the germ epithelium and impaired spermatogenesis might be a consequence of PD-1 inhibition leading to autoimmune orchitis. However, clinical reports on the impact of melanoma therapy on spermatogenesis are rare.[46-48] To date, there are two reports published on acute orchitis under ICI therapy with either pembrolizumab[49] or nivolumab plus ipilimumab.[50] Further evidence comes from a retrospective cadaver study.[48] Herein, the pathology and autopsy database from Johns Hopkins University was searched for testicular biopsies from patients who had been treated with ICI. In only one out of seven patients, a normal spermatogenesis was found histologically. This finding may indicate that PD-1 therapy may affect male fertility—an AE that has previously been overlooked. Of course, the limitations of such a retrospective analysis must be considered. Just recently, a small cross-sectional study on male patients under the age of 60 years previously or currently treated with ICI for cutaneous malignancies investigated male fertility including semen analysis. All patients reported a normal sexual function and most patients (18/22, 82%) had a normal semen analysis.[51] However, of four patients with pathological semen analysis, one case presented with an asymptomatic, inflammatory infiltrate in the ejaculate with subsequent azoospermia without any other likely cause than immunotherapy.

Regarding ICI therapy, endocrine autoimmune side-effects may adversely impact fertility. Endocrine side-effects of any grade are seen in up to 10% of patients receiving ICI monotherapy[52] or up to 30% in case of combined ICI therapy.[53] Endocrinological autoimmune AEs can be acutely life-threatening and often require immediate action. Moreover, hypophysitis, hyper- or hypothyroidism, adrenal insufficiency or type 1 diabetes can reduce fertility. Weighing the clinical evidence deduced from AE patterns, the following consensus statements are made:

- Endocrine side-effects of ICI therapy can impair fertility directly or indirectly.
- Hypophysitis can lead to an irreversible damage of the adrenocorticotropic, gonadotropic and/or thyrotropic function. The resulting reduction of fertility can usually be reversed by appropriate hormone replacement. During the acute phase, however, a pregnancy is not advisable.
- Both hyper- and hypothyroidism can lead to reduced fertility but can be treated.
- Adrenal insufficiency, which itself is a life-threatening condition, may impair fertility. This event is mostly irreversible but can be treated effectively by hormone replacement.

A recently published meta-analysis investigating fertility in female cancer survivors across various cancer types stated that reproductive chances in women surviving melanoma were rather unaffected.[54] However, the two studies including melanoma patients were from 2011 and 2013, before the era of routine clinical use of ICI and BRAF/MEK inhibition. Hence, to date, we cannot exclude an effect on female and/or male fertility by these treatments. Especially male patients should, independent of the therapeutic option (i.e. targeted therapy or ICI), be informed about the risk of impaired spermatogenesis.

Pregnancy. Regarding pregnancy, BRAF and/or MEK inhibitors could in theory affect fetal and embryonic growth and the infant's development through MAPK pathway signaling inhibition. The rat sarcoma protein (RAS)/MAPK signaling pathway is one of the main pathways to transduce intracellular signals in response to all kinds of mitogens (e.g. growth factors), thereby initiating proliferation, survival and antiapoptotic programs.[55] Germline mutations in the RAS/MAPK pathway can induce a wide range of syndromes that are summarized under the term RASopathies. They are associated with distinctive congenital defects (i.e. facial features, cardiopathies, growth and skeletal abnormalities), developmental delay, mental retardation and tumor predisposition.[55] RASopathies are generally thought to be caused by hyperactivation of the RAS/MAPK signaling pathway. There is no clinical evidence that BRAF and/or MEK inhibitors can have a teratogenic effect; however, it also cannot be ruled out. Vemurafenib is reported to cross the placenta[33] and was detected in the blood of a newborn whose mother had been treated with vemurafenib for metastatic melanoma.[56] In the few published case reports to date, no congenital malformations were described in newborns born to mothers treated with vemurafenib during pregnancy.[56-59]

The specific immune tolerance that both tumors and pregnancy require to partially circumvent their recognition by the pregnant women's own immune system shows some analogy.[60] Immune tolerance of the fetus by the maternal immune system is normally regulated via several mechanisms involving various immune cells, both in the periphery and locally at the feto-maternal interface. In the uterus, a state of dynamic T-cell homeostasis is maintained during gestation with antigen-specific regulatory T cells (T-regs) taking a major function in the maintenance of tolerance during gestation. An increase in circulating T-regs has been reported in humans during early pregnancy, with the increase reaching its peak in the second trimester and declining postpartum.[61,62] CTLA-4 and PD-1/PD-L1 play a relevant role in the regulation of effector T cells and in proliferation. They are thought to contribute to the immune tolerance of the fetus.[63-67] Although immunotherapy does not seem to induce teratogenic effects, the use of ICI nevertheless may present unique challenges for pregnancy as an activated immune response may cause miscarriages, restrict fetal growth or cause an immune-related AE in the fetus or mother.[68]

Fetal and embryonic growth and the infant's development may also be affected due to common side-effects of the drugs. Possible common side-effects of BRAF/MEK inhibition as well as of ICI include, but are not limited to, fever and gastrointestinal AEs. Only sporadic clinical evidence is available in the form of case reports, conveying favorable as well as unfavorable outcomes of ICI[62,69] or targeted

therapy[56,58,59] in pregnant melanoma patients, for whom individual therapeutic decisions to continue or initiate melanoma therapy had to be taken due to specific, sometimes woeful circumstances. Based on the review of the literature, safety data and SmPC information, we conclude that for BRAF and MEK inhibition as well as for ICI a risk for impaired embryonal development and miscarriage exists.

Fertility preservation in adults at fertile age with melanoma: recommendations

Fertility-protective measures are advised for melanoma patients at fertile age regardless of the type of melanoma therapy. In patients who are candidates for adjuvant melanoma therapy, measures should be initiated after individual risk/benefit evaluation, including counseling on the actually limited data on but potential risks for fertility and subsequent fertility preservation measures. In general, the start of an adjuvant systemic therapy is aimed to begin within a period of 12 weeks after surgery. In case of imminent wish for children, dependent on the patient's individual risk for recurrence of the melanoma, 'watch and wait' might be an option to consider. By contrast, in the metastatic stage, a delay of melanoma tumor therapy should be avoided.

For women, several options used individually or in combination may be considered to preserve fertility:

- Use of a gonadotropin-releasing hormone (GnRH) agonist during gonadotoxic therapy
- Ovarian stimulation and cryopreservation of unfertilized or fertilized oocytes
- Cryopreservation of ovarian tissue

Based on the currently available data,[70] the use of GnRH agonists is discussed critically. Even though randomized trials showed evidence for their benefit, there is a further need for high-quality studies. Cryopreservation of ovarian tissue is not considered experimental anymore[23,71] and there is increasing experience also with re-transplantation[72]; yet, further optimization of the method and clarification of open questions especially in cancer patients with an increased risk of ovarian metastasis are required. Therefore, ovarian stimulation and cryopreservation of unfertilized or fertilized oocytes is currently still the standard and first choice option. Detailed information on fertility preservation options, advantages, disadvantages as well as success rates can be found in several guideline and recommendation papers.[23,71,73-78] In hormone-dependent tumors, ovarian stimulation can theoretically promote tumor growth, which has led, for example, to the recommendation of aromatase inhibitors as part of the stimulation in hormone-sensitive breast carcinomas in order to mitigate the hormone increase.[23] Melanoma is considered a non-hormone-related cancer. During *in vitro* fertilization where women are exposed to 10 times greater estrogen levels than physiologically present, conflicting results are reported from different studies on melanoma risk. However, there is no clear evidence which would justify the use of aromatase inhibitors in melanoma patients.[79,80]

For men, the cryopreservation of sperm is an established and accepted standard procedure to preserve fertility. In case of azoospermia (or aspermia), testicular sperm extraction should be offered.

Recommendations regarding pregnancy

Adjuvant melanoma therapy with pembrolizumab or nivolumab, or with dabrafenib plus trametinib, should not be commenced in a pregnant patient. If a pregnancy is detected only after therapy was initiated but is ongoing—this situation is referred to as 'on-treatment pregnancy'—the adjuvant therapy should be stopped.

In the advanced stage of disease, treatment with BRAF and MEK inhibitors should only be administered during pregnancy when the potential benefit for the pregnant patient outweighs the potential risk for the fetus. An interdisciplinary tumor board should be consulted to aid decision making and therapeutic alternatives should be discussed. If treatment with targeted therapy with a BRAF plus MEK inhibitor is clinically mandated, e.g. in a situation of rapid and/or multi-organ progression, the time point to start therapy should be adapted individually, e.g. after completion of fetal organogenesis to reduce the risk of teratogenicity or after an early, planned cesarean section.

In general, the same recommendations also apply to ICI. Current data indicate no need for abortion, but miscarriage remains a potential risk for the embryo or fetus (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2021.100248). However, in line with their physicochemical, protein-like properties, the risk of teratogenicity is considered lower for ICI compared to targeted therapies. Narrow observation of the pregnancy, the development of the fetus as well as the newborn by a gynecologist and a pediatrician is required.

The management of pregnant patients with advanced melanoma sometimes mandates rapid systemic treatment causing an ethical dilemma. Upfront counseling on fertility preservation, contraceptive methods and options for pregnancy and parenthood after the therapy is completed is therefore strongly recommended to avoid such difficult situations in adults at fertile age with melanoma.

Recommendations for contraception

Recommendations for contraception methods are displayed in Figure 3. As BRAF inhibitors may reduce the efficacy of oral or systemic hormonal contraceptives, another effective contraceptive method should be used during BRAF/MEK inhibition. In addition, side-effects especially in the gastrointestinal system might influence resorption of the substances. We recommend the use of hormonal contraception or intrauterine device by the female patient plus an additional barrier method (condom) by the male partner. For male patients, no advice is given in the SmPC. Due to uncertain or missing data, we recommend the use of a barrier method by the male patient.[31-39]

Patient	Type of contraception	Duration of contraception according to type of melanoma therapy		
		Dabrafenib + trametinib	Vemurafenib + cobimetinib	Encorafenib + binimetinib
Female	Intrauterine device or hormonal contraception and	During melanoma therapy and up to at least **16 weeks** thereafter	During melanoma therapy and up to at least **5 months** thereafter	During melanoma therapy and up to at least **4 months** thereafter
Partner	Additional barrier method			
Male	Due to uncertain/lacking data, the use of a barrier method is recommended			
Patient	**Type of contraception**			
		Pembrolizumab	Nivolumab	Ipilimumab
Female	Intrauterine device or hormonal contraception and	During melanoma therapy and up to at least **4 months** thereafter	During melanoma therapy and up to at least **5 months** thereafter	No information in SmPC provided
Partner	Additional barrier method			
Male	Due to uncertain/lacking data, the use of a barrier method is recommended			

Instructions for contraception with oral hormonal contraceptives:

- Melanoma therapies can lead to diarrhea as a side-effect
  → In cases of diarrhea, the ingestion of oral contraceptives may be limited, and thus may impair efficacy.
- The efficacy of contraception may be reduced by degradation of the active substances via induction of CYP450 enzymes in the liver

Figure 3. Recommendations for contraceptive use in systemic melanoma therapy.
Recommended time intervals for contraception correspond to intervals mentioned by the respective summary of product characteristics (SmPC).[31-39] CYP450, cytochrome *P*-450.

A reliable contraception in female patients is required for ICI. We advise to use a dual contraceptive method in female patients who receive ICI. Again, gastrointestinal AEs like diarrhea frequently occur during and after ICI therapy and may reduce the resorption and thus the efficacy of oral hormonal contraception. In addition, the metabolic degradation of contraceptives in the liver may be impacted by drug—drug interactions. Contraception of the male patient is not mentioned in the European Union SmPC, but we advise to use a barrier method because of lacking data.

For the ICI as well as for the MAPK pathway inhibitors, contraception for 4-5 months after treatment discontinuation is recommended (Figure 3). This recommendation is most likely not based on scientific data but on safety interval considerations.

LIMITATIONS

While all recommendations are based on an extensive literature and database search, no systematic review process or formal consensus process was followed. However, all recommendations were developed by interdisciplinary working groups and then agreed upon by all involved experts. Especially because of the limited data available, all recommendations should be rated as expert opinions. At this stage, a patient advocate has not been involved yet. For future revisions, this should be considered to include a patients' view.

CONCLUSIONS—OVERALL RECOMMENDATIONS

Today, in view of effective melanoma therapies which lead to a reasonable chance of even melanoma cure, the counseling of melanoma patients at fertile age regarding family situation, desire for children and/or fertility preservation should be done routinely before the start of any systemic therapy.

As a significant step forward to long-term cancer survivorship has been achieved in not only melanoma but also other tumor entities, these issues are also relevant to other cancer patients at fertile age. General consensus guidelines have recently been published at the national[81] and the European level.[16] However, melanoma-specific recommendations are lacking, and literature reviews discussing single cancer indications are focusing predominantly on gynecological cancers[82-84] or dealing with the issue of ovarian function and protection.[85-87]

Our overall recommendations, as summarized in Figure 4, match the published German and European Society for Medical Oncology clinical practice guidelines on fertility preservation and post-treatment pregnancy in terms of patient counseling, diagnostic work-up and fertility preservation measures.[16,81] This paper adds, however, recommendations for the therapeutic management of these patients based on a detailed risk assessment of the currently used systemic therapies in use for melanoma.

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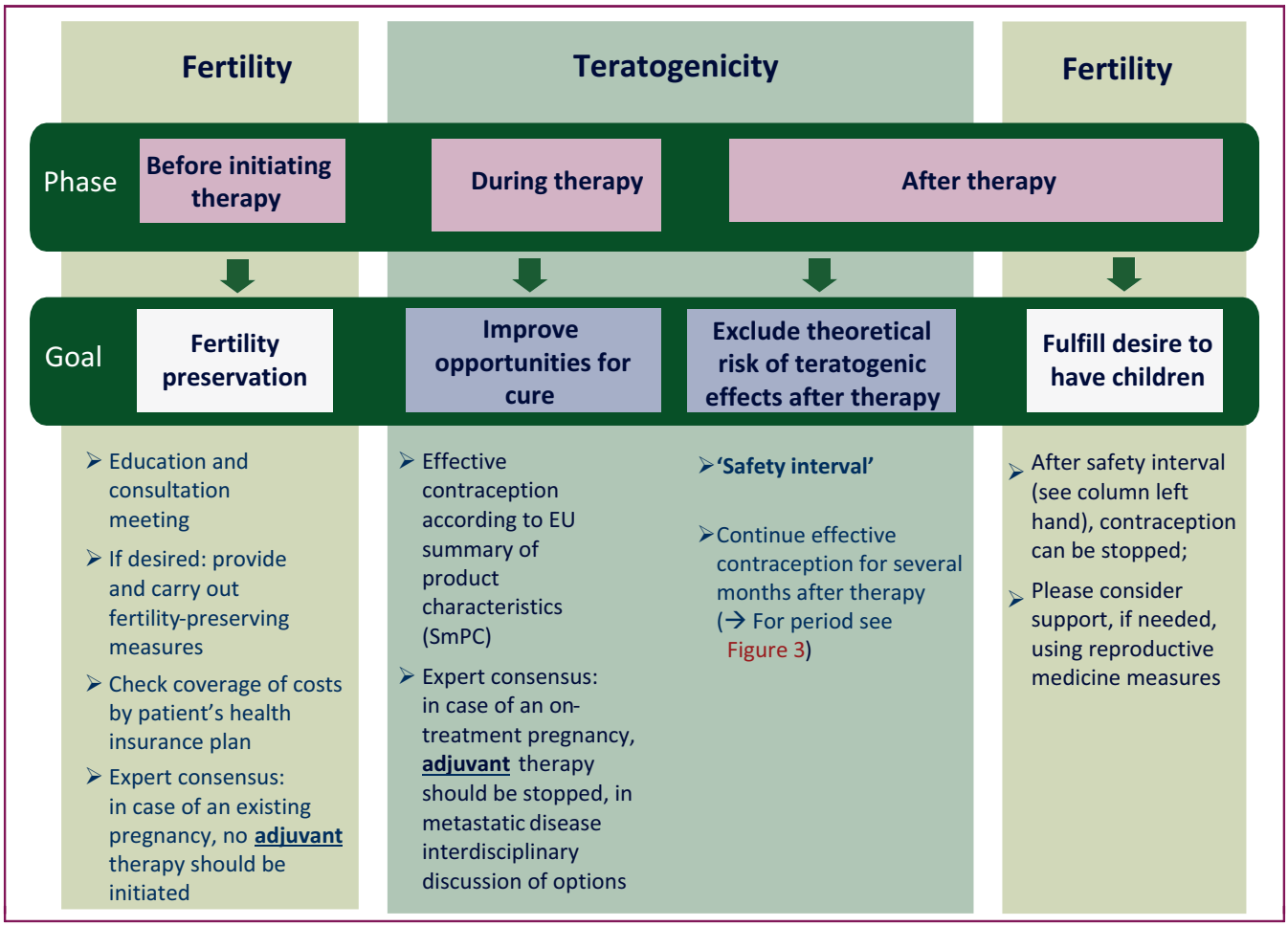

Figure 4. **Overall recommendations, by expert consensus, for fertility preservation and therapeutic management of melanoma patients in wish of parenthood.**

agreed on final approval of the version and agreed to be accountable for all aspects of the work.

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DISCLOSURE

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