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Review

Fertility and reproductive concerns related to the new generation of cancer drugs and the clinical implication for young individuals undergoing treatments for solid tumors

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ABSTRACT

The treatment landscape of solid tumors has changed markedly in the last years. Molecularly targeted treatments and immunotherapies have been implemented and have, in many cancers, lowered the risk of relapse and prolonged survival. Patients with tumors harboring specific targetable molecular alterations or mutations are often of a younger age, and hence future fertility and family building can be important concerns in this group. However, there are great uncertainties regarding the effect of the new drugs on reproductive functions, including fertility, pregnancy and lactation and how young patients with cancers, both women and men should be advised. The goal with this review is to gather the current knowledge regarding oncofertility and the different novel therapies, including immune checkpoint inhibitors, antibody-drug conjugates, small molecules and monoclonal antibody targeted therapies. The specific circumstances and reproductive concerns in different patient groups where novel treatments have been broadly introduced are also discussed, including those with melanoma, lung, breast, colorectal and gynecological cancers. It is clear, that more awareness is needed regarding potential drug toxicity on reproductive tissues, and it is of essence that individuals are informed based on current expertise and on available fertility preservation methods.

1. Introduction

Increased knowledge on tumor and microenvironment biology has resulted in advancements in the treatment of many malignancies, with the development of effective targeted and immunological therapies. These new treatments significantly prolong survival and patients presenting with advanced disease may even be cured from their disease. This new situation endorses a different perspective when young patients with cancer are counselled regarding future family building. Several of these new agents have also been implemented in the adjuvant setting, and in such circumstances, it is particularly important to advise patients regarding the potential effects on fertility, as well as available fertility preservation measures. Many of the new drugs have also been approved across several different tumor forms, including the immune checkpoint inhibitors (ICI) and many of the targeted therapies, as molecular targets as present in different cancers. Importantly, some of the acquired "druggable" tumor mutations and rearrangements, such as in the *BRAF*, *EGFR*, *ALK, ROS1 or NRTK* genes are more common in younger patients [1–3]. There are also hereditary cancer syndromes with individuals affected at a young age, where carriers of specific germline genetic defects benefit from the specific drugs, as is the case for Lynch syndrome and *BRCA* mutation carriers [4,5]. Throughout the decades considerable knowledge has been gained on the effects of chemotherapy on fertility, pregnancy, and breast-feeding, while similar knowledge on the novel

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Table 1
Overview of anti-cancer drugs and known effect on fertility, pregnancy, and breast feeding.

Drug	Target	Drug type	Female fertility affected in animal studies*	Male fertility affected in animal studies*	Pregnancy	Breast feeding
Ipilimumab	CTLA-4	Monoclonal antibody	Not studied	Not studied	B:3	IVa
Pembrolizumab	PD-1	Monoclonal antibody	No	No	C	IVb
Nivolumab	PD-1	Monoclonal antibody	Not studied	Not studied	B:3	IVa
Cemiplimab	PD-1	Monoclonal antibody	No	No	D	IVa
Atezolizumab	PD-L1	Monoclonal antibody	Not studied	Not studied	D	IVa
Avelumab	PD-L1	Monoclonal antibody	Not studied	Not studied	D	IVb
Durvalumab	PD-L1	Monoclonal antibody	Not studied	Not studied	D	IVa
Vemurafenib	BRAF	Small molecule	No	No	B:2	IVa
Dabrafenib	BRAF	Small molecule	Yes	Yes	D	IVa
Encorafenib	BRAF	Small molecule	No	Yes	B:3	IVa
Trametinib	MEK	Small molecule	Yes	Yes	B:3	IVa
Binimetinib	MEK	Small molecule	Not studied	Not studied	B:3	IVa
Abemaciclib	CDK4/6	Small molecule	No	Yes	D	IVa
Ribociclib	CDK4/6	Small molecule	No	Yes	D	IVa
Palbociclib	CDK4/6	Small molecule	No	Yes	D	IVa
Olaparib	PARP	Small molecule	No	No	D	IVa
Niraparib	PARP	Small molecule	No	Yes	D	IVa
Osimertinib	EGFR	Small molecule	Yes	Yes	C	IVa
Afatinib	EGFR	Small molecule	Yes	Yes	D	IVa
Dacomitinib	EGFR	Small molecule	Yes	No	D	IVa
Erlotinib	EGFR	Small molecule	Yes	Yes	D	IVa
Gefitinib	EGFR	Small molecule	Not studied	Not studied	B:3	IVa
Cetuximab	EGFR	Monoclonal antibody	Not studied	Not studied	B:2	IVa
Panitumumab	EGFR	Monoclonal antibody	Yes	Yes	D	IVa
Trastuzumab	HER2	Monoclonal antibody	No	Not studied	C	IVa
Pertuzumab	HER2	Monoclonal antibody	No	Not studied	D	IVa
Trastuzumab deruxtekan	HER2	Antibody-drug conjugate	No	Yes	D	IVa
Trastuzumab emtansine	HER2	Antibody-drug conjugate	Not studied	Not studied	D	IVa
Crizotinib	ALK, ROS1, MET	Small molecule	Yes	Yes	D	IVa
Alectinib	ALK	Small molecule	No	Yes	D	IVa
Bevacizumab	VEGF	Monoclonal antibody	Yes	Yes	D	IVa
Ramucirumab	VEGF	Monoclonal antibody	Yes	Yes	D	IVa
Sotorasib	KRAS	Small molecule	Not studied	Not studied	C	IVa
Larotrectinib	TRK	Small molecule	No	Yes	B:1	IVa
Entrectinib	TRK	Small molecule	Not studied	Not studied	D	IVa

*Data only available from animal studies

Pregnancy category according to the Swedish Drug Authority:
Category A: Drugs that can be assumed to have been taken by a significant number of pregnant women and women of childbearing age without any type of confirmed disturbance in the reproductive process such as increased frequency of malformations or other adverse fetal effects being noted so far.
Category B: Drugs that can be assumed to have been taken by only a limited number of pregnant women and women of childbearing age without any type of confirmed disturbance in the reproductive process having been noted so far. See subgroups below.
Category B:1: Reproductive toxicology studies in animals have not indicated increased occurrence of birth defects or other harmful effects on the reproductive process.
Category B:2: Reproductive toxicology studies in animals are deficient or absent, but available data do not indicate an increased occurrence of birth defects or other harmful effects on the reproductive process.
Category B:3: Reproductive toxicology studies on animals have indicated an increased incidence of birth defects or other harmful effects on the reproductive process, the significance of which for humans has been judged to be unclear.
Category C: Medicinal products which, through their pharmacological effects, have given or on good grounds are presumed to be able to cause a risk to the fetus and/or the new-born child without being directly teratogenic.
Category D: Drugs which in humans have given or can be assumed to give rise to an increased frequency of fetal malformations or other forms of permanent men. Drugs with primarily teratogenic effects belong to this category. If, in addition, the medicine has negative pharmacological effects that can directly or indirectly cause adverse fetal effects, this is also stated.
Breast feeding group according to the Swedish Drug Authority:
Group I: Does not pass into breast milk.
Group II: Passes into breast milk but risk of impact on the child seems unlikely with therapeutic doses.
Group III: Passes into breast milk in such quantities that there is a risk of impact on the child even with therapeutic doses.
Group IVa: Data missing on passage into breast milk.
Group IVb: Data on passage into breast milk is insufficient to assess the risk to the child.

treatments is lacking [6–9]. There are no large studies on fertility with these new treatments and considering the ethical aspects, it is not to be expected that any high-grade evidence will be gained. Existing knowledge and recommendations are thus mostly based on animal studies, case reports or assumptions based on the drugs' known biological mechanisms and side effects. In parallel with the entrance introduction of new therapies, there have also been advancements in techniques and options for fertility preservation that need to be discussed and introduced in this group of patients [7]. Increased awareness has also been called upon from guideline-issuing societies, regarding the need for relevant data collection in prospective trials [10].

Worldwide, there are approximately 2.3 million individuals, diagnosed with a malignancy under the age of 45 years [11]. In this review we present current knowledge and concerns regarding reproduction, including fertility in both sexes, pregnancy and lactation, related to several novel oncological treatments (Table 1). We review the specific

situation in different solid tumors where new therapies have been broadly implemented, including melanoma, lung, colorectal, breast and gynecological cancers, that all can affect young individuals where family building is an important concern.

2. Specific fertility concerns in different patient groups

2.1. Malignant melanoma

The incidence of skin cancers has been consistently rising during the last decades, which is believed to be related to UV exposure habits. Tanning habits are also seen as a cause of an earlier onset of melanoma in females, compared to males. Currently, over 300,000 are diagnosed with melanoma per year globally, of which over 40,000 are diagnosed under the age of 45 years, with a certain overrepresentation in females [11]. Close to 60,000 die from the disease yearly [11]. Before 2010 there were essentially no oncologic treatments that significantly prolonged survival in metastatic melanoma. In recent years several new oncological treatments have emerged, in particular ICI and targeted therapies with BRAFi/MEKi [12–15]. BRAF/MEKi are only effective in tumors with acquired BRAF mutations that are present in approximately 50% of the patients, though a higher frequency is seen in younger patients. Both ICI and BRAF/MEKi have also been approved in the adjuvant setting in patients operated for high-risk melanomas, as they significantly lower the risk of disease recurrence [16–19]. Survival of patients with metastatic melanoma has improved significantly after the introduction of these agents in 2011 and onward, from a five-year survival under 5% to close to 50% [20,21]. A significant portion of patients with advanced disease are hence potentially cured from metastatic melanoma. Thus, fertility concerns have become increasingly important to address in this group of patients.

2.2. Lung cancer

Lung cancer is one of the most common cancer forms globally, with 2.5 million new cases each year and is also the deadliest with 1.8 million deaths annually worldwide. In many countries, the incidence has decreased in males, while it has increased in females, which is primarily related to smoking habits. Currently, over 60,000 are diagnosed under the age of 45, with approximately equal numbers in both sexes. The majority of patients are diagnosed with advanced disease showing a poorer prognosis with a median survival of 10–12 months and a 5-year survival of less than 10%. Several new effective treatments of lung cancer have emerged in the treatment of NSCLC, including targeted therapies, e.g., against genetic aberrations in EGFR, ALK, BRAF, KRAS, ROS1, RET, MET and NRTK genes [22]. ICI treatments, often in combination with chemotherapy, have also become standard-of-care. Moreover, ICI and EGFR inhibitors have been implemented in the adjuvant setting, and today the prognosis of lung cancer patients is markedly improved. Many of the genetic aberrations in lung cancer are also more common in younger patients which makes issues relating to fertility highly relevant [2,22].

2.3. Gynecological cancers

In many countries, the incidence and mortality from ovarian cancer has decreased which is probably related to the use of hormonal contraceptives that have a protective impact [23]. Currently, over 300,000 are diagnosed with ovarian cancer and over 200,000 die from the disease world-wide every year. [11,24]. Annually, over 60,000 are diagnosed under the age of 45 years [11]. Fertility preservation options are limited for patients with ovarian cancer since hysterectomy and bilateral salpingo-oophorectomy is part of staging and surgical treatment, however in early stages, fertility-sparing surgery is possible in some cases, and has been demonstrated as safe and effective [25,26]. Cytoreductive surgery followed by adjuvant platinum-based chemotherapy remains the cornerstone of treatment in most cases, and complete cytoreduction confers the best survival benefit, hence fertility-preserving surgery is typically not performed in advanced cases [27,28]. During the last years the use of PARPi has revolutionized the treatment of women with advanced ovarian cancer including not only *BRCA* associated cancers, but also homologous repair deficient (HRD), as well as HR proficient cancers [29–31]. A new standard of care was established when the first PARPi, olaparib was approved as maintenance in first line setting in patients with advanced BRCA-mutated high grade ovarian cancer, and shortly after two other PARPi strategies gained approval in HRD-positive and HR proficient patients [29–31]. With these advancements, more patients can access PARPi treatment and receive benefit, leading to increased number of long-term survivors and ultimately more patients being cured [5,32]. Less than 5% of all epithelial ovarian cancers constitutes of low-grade serous carcinoma. About 70% of these tumors have specific mutations, including *KRAS* and *BRAF* and such targeted drug therapies are therefor used in this patient group [33].

As a result of the HPV vaccination initiatives, cervical cancer incidence is projected to fall in the coming decades. Globally, approximately 650,000 are diagnosed with cervical cancer and 350,000 die from the disease [11]. Approximately 170,000 are under the age of 45 years at diagnosis [11]. As in ovarian cancer, fertility preservation options are limited since hysterectomy is part of standard surgical treatment for cervical cancer. In younger women with a small tumor and strong desire to preserve their fertility, a surgery to only remove a large part of the cervix is an option. Postoperative radiotherapy, external or brachytherapy further perturbs the ovarian function. Anti-PD-1, foremost in combination with chemotherapy are now a treatment widely used in metastatic cervical cancer [34,35].

2.4. Breast cancer

Breast cancer is the most common cancer diagnosis and cause of cancer-related death in women worldwide, with 2.2 million affected and close to 700.000 deceased yearly [11,24]. Approximately 430,000 are diagnosed under the age of 45 years[11]. Moreover, breast cancer is the most common pregnancy-associated malignancy and approximately 4% of all cases under the age of 50 are pregnancy-associated [36,37]. The treatment of early and locally advanced is multimodal and may include surgery, radiotherapy, cytotoxic chemotherapy, ICI, antibodies against HER2, endocrine therapy, PARPi and CDK4/6i. Patients presenting with estrogen positive cancers are recommended long-term adjuvant endocrine therapy which heavily impacts fertility considerations and decision making. On the other hand, therapeutic blockade of HER2 has transformed the management and prognosis of HER2-positive breast cancer. HER2-targeting antibodies such as trastuzumab and pertuzumab are commonly used in the pre- and postoperative settings, while the antibody drug conjugate (ADC) trastuzumab emtansine (T-DM1) is approved for the adjuvant treatment of residual invasive cancer following neoadjuvant therapy [38,39]. At the same time, multiple ongoing trials are currently evaluating trastuzumab deruxtecan (T-DXd) at the postneoadjuvant (NCT04622319) and neoadjuvant settings (NCT05113251, NCT05900206). These observations underscore the importance of the impact of HER2-targeting agents on fertility, in a patient population whose contemporary prognosis is otherwise excellent [40]. Importantly, the approval of T-DXd for the treatment of HER2-low breast cancer owing to its potent bystander effect greatly expands the eligible population for HER2-blockade and thus the relevance of oncofertility considerations [41]. CDK4/6i are a recent addition to our therapeutic armamentarium for non-metastatic breast cancer. The addition of adjuvant abemaciclib for two years to standard endocrine therapy led to statistically significant and clinically meaningful benefit in terms of disease-free and distant disease-free survival in high-risk patients with estrogen receptor positive, HER2-negative breast cancer [42,43]. Interestingly, the relative risk reduction with abemaciclib for premenopausal patients was numerically superior compared to

postmenopausal ones. Thus, abemaciclib was regulatory approved and is routinely used as adjuvant therapy, increasing our interest in its impact on fertility.

2.5. Colorectal cancer

Worldwide, 1,9 million are diagnosed with colorectal cancer and 900,000 succumb to the disease annually[11]. Over 100,000 are diagnosed under the age of 45 years, approximately equal numbers in both sexes. In colon cancer, surgery is standard of care and the procedure normally does not interfere with the sexual function. In rectal cancer the situation is quite different. The nerves can be affected by tumor and/or treatment procedures resulting in problems with lubrication, erection and ejaculation. In advanced tumors sexual organs i.e., ovary, uterus, vagina, seminal vesicles and prostate can be involved and thus, extirpated partly or complete. Preoperative radiotherapy plays an important role in curative treatment of rectal cancer [44]. The ovaries are always included with a high risk of permanent ovarian ablation [45]. In men, the testicular dose is generally low [46]. However, even this dose results in an acute negative effect on Leydig cell function and a dose-dependent 2.4 times increased risk hypogonadism at the time of surgery [47]. Drugs are given as neoadjuvant, adjuvant and palliative treatment, where chemotherapy has a central role. VEGF inhibitors can be added in most patients and different targeted therapies are a late-line option. Tumor analyses of mutations and alterations becomes increasingly important and guides the use of novel treatments. For patients with mismatch repair–deficient (dMMR) tumors, ICI is an option, e.g., as neoadjuvant treatment in colorectal cancer, including patients with the hereditary Lynch syndrome, that usually have a young age of onset [48,49]. EGFR inhibitors can be used if the tumor is *KRAS*, *NRAS* and *BRAF* wild type. BRAF inhibitors are used in *BRAF* mutated tumors and HER2 inhibitors when overexpression of HER2-neu is found. NTRK inhibitors are available in the case of TRK-fusion.

3. Potential mechanisms of reproductive drug toxicity

3.1. Immune checkpoint inhibitors

Women's fertility can be affected by ICI treatment, mainly due to endocrinological immune-related side effects that occur in approximately 15% of patients receiving programmed cell death protein 1 (PD-1) inhibitors monotherapy and approximately 30% receiving PD-1 and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitors in combination [15,50–52]. Endocrinological immune-related side effects are also significantly more common in premenopausal women compared to both postmenopausal women and men [53]. The resulting hormonal deficiency is usually non-reversible. Hypothyroidism is the most common endocrinological side effect and is seen in approximately 10% of those treated with anti-PD-1 and 15% of those treated with combination immunotherapy [15,50–52,54]. Hypothyroidism impairs female fertility as disturbances in the thyroid hormones affect the menstrual cycle, ovulation and increase the risk of miscarriage [55]. Adequate thyroid hormone replacement usually restores fertility [55]. Hypophysitis is a less common side effect occurring in 1–2% with anti-PD-1 monotherapy and approximately 5% with combination immunotherapy [15,50] but can have a significant impact on women's fertility [56,57]. The pituitary secretion of follicle-stimulating and luteinizing hormones (LH and FSH) necessary for a normal menstrual cycle and pregnancy, is often affected in hypophysitis resulting in infertility through hypogonadotropic hypogonadism [51,52,56,57]. In such circumstances fertility treatment using exogenous gonadotropins to induce follicle development and ovulation may be successful [56,57]. Endocrinological ICI-related side effects are less common in men compared to women, but since the use of ICI is increasing and the side effects are relatively common, potentially many men could be affected [58]. Hypothyroidism can also impair male fertility and e.g. cause reduced sperm quality [59]. Hypophysitis can also have a significant impact on male fertility if the pituitary's secretion of LH and FSH hormones is affected, resulting in reduced testosterone levels, erectile dysfunction and impaired spermatogenesis [58]. Hormonal substitution with testosterone injections can be offered, but it is not certain whether fertility function will be fully restored. Animal studies have also shown that the ICI antibodies can bind to tissues in the testicles, which can negatively impact gametes and fertility [58,60,61]. In different case reports and case series, impaired spermiograms and testicular histopathology have been found in men treated with ICI and there is evidence that the ICI may cause primary hypogonadism, or direct damage to the testes [62–65].

Animal studies have shown that ICI antibodies can bind to ovarian tissue, increase immune cell infiltration and tumor necrosis factor-alpha expression within the ovary, diminishing the ovarian follicular reserve and impairing the ability of oocytes to mature and ovulate [58,60,61,66]. Animal studies have also shown that the antibodies cross the placenta and that high doses of nivolumab and ipilimumab can cause miscarriage [58,61]. The immune system's increased capacity to recognize and attack foreign cells can thus increase the risk of fetal rejection [58,67]. In live-born offspring of ipilimumab-exposed animals, malformations were seen, while in nivolumab-exposed animals, no clinical abnormalities, such as malformations or underweight in the offspring, were noted[68]. In the few case reports published to date of children born to mothers treated with ICI during pregnancy, no malformations or serious disease were reported [69–73]. However, immune-related enteritis has been reported in a 4-month-old infant after in utero exposure to pembrolizumab [74]. In clinical trials for ICI, women of childbearing age had to use safe contraceptive methods during treatment and up to five months after treatment had ended. It is difficult to determine how long the recommendation should extend after the end of treatment, because even if the half-life of these antibodies is no longer than four weeks, side effects can appear several months after the end of treatment and effective binding to the receptors remains for several months or even years [58]. No studies have been done on whether any of the approved ICI are secreted in breast milk, but since it is known that other antibodies can be secreted in breast milk, a risk to the child cannot be excluded [68].

3.2. BRAF and MEK inhibitors

Animal studies have shown effects on ovaries and ovulation when exposed to B-Raf proto-oncogene (BRAF) and mitogen-activated protein kinase kinase (MEK) inhibitors dabrafenib, trametinib or cobimetinib [68]. Animal studies have further shown that the testicles shrank upon exposure to dabrafenib, trametinib and cobimetinib [68]. In the case reports published so far, there is one case of deterioration in sperm quality after treatment with dabrafenib and trametinib was initiated [75]. In another case who was treated with dabrafenib and trametinib, a marginal effect on sperm quality was seen, but despite this, this man was able to naturally father a healthy child born after a full-term pregnancy, during ongoing treatment [76]. There have also been reports of a man in whom no difference in sperm quality was seen during ongoing treatment with vemurafenib, and this man fathered a premature, but healthy child during ongoing treatment [75].

Toxic effects on fetuses have been observed where the female was exposed to dabrafenib, trametinib, encorafenib or binimetinib [68]. In the few case reports published of children born to mothers treated with BRAF/MEKi during pregnancy, malformations or serious diseases have not been seen [77,78]. In clinical trials for BRAF/MEKi, it was required that women of childbearing age agree to use safe contraceptive methods during treatment and up to four months after the end of treatment. No studies have been done on whether any of the approved BRAF/MEKi are excreted in breast milk, but it is likely that these small molecules can be excreted, thus risk to the child cannot be ruled out.

3.3. EGFR inhibitors

There are numerous Epidermal Growth Factor Receptor (EGFR) inhibitors, both tyrosine kinase inhibitors (TKIs) and antibodies, in routine clinical use. These TKIs include osimertinib, afatinib, dacomitinib, erlotinib and gefitinib. These TKIs target either only EGFR (erlotinib, gefitinib, and osimertinib), or are pan-HER TKIs (afatinib, dacomitinib and neratinib). Monoclonal antibodies are also used to target EGFR, including cetuximab and panitumumab. Many of the tyrosine kinases and their receptors have important roles in the ovary and the testis, and their inhibition may affect both ovarian and testicular function, in particular processes involving spermatogenesis, oogenesis, primordial follicle activation, folliculogenesis and corpus luteum formation and maturation [79,80]. EGFR activity is essential for oocyte maturation, cumulus expansion, and ovulation, where EGF signalling is responsible for communicating luteinising hormone and growth factor signals from the mural granulosa cells across the follicle to the oocyte [81]. Furthermore, preclinical studies have shown negative effects on ovary function. Despite these data, animal studies on lapatinib have not been able to show an adverse effect on ovary function [82] and although gefitinib was shown to reduce hormone levels, including testosterone, in women [83] there are no clinical studies describing the influence of EGFRi on fertility.

Regarding the use of EGFR TKIs during pregnancy, a study reported on six cases where some of the newborns were hypotrophic while no newborn malformations or developmental abnormalities were observed [84]. The study concluded relatively mild effects on the fetus and similar antitumoral efficacy in the affected mothers, as in the general population. In animal studies, it has been demonstrated that EGFRi are excreted in breast milk and growth retardation in suckling pups has further been observed [85].

3.4. HER2 inhibitors

Although the gonadotoxicity of Human Epidermal Growth Factor Receptor 2 (HER-2) targeting agents has not been rigorously evaluated, an analysis from the ALLTO trial did not report higher rates of post-treatment amenorrhea with dual (trastuzumab and lapatinib) compared with single HER2-blockade (trastuzumab or lapatinib), hinting thus towards a lack of gonadotoxic effect [86]. Similar reassuring findings were reported from the NeoALLTO trial, where levels of anti-müllerian hormone were less affected by HER2-blockade than by chemotherapy [87]. Data on ADCs are sparse. An intriguing implication of their increasing use at the early disease setting is the de-escalation of chemotherapy. For example, in the ATEMPT trial adjuvant T-DM1 compared with paclitaxel and trastuzumab for stage I HER2-positive breast cancer was associated with lower rates of amenorrhea at 18 months, 24% versus 50% ($p = 0.045$), while maintaining excellent efficacy with 3-year relapse free interval rates exceeding 99% [88,89]. In light of those findings, the results of ongoing studies that compare ADCs and traditional cytotoxic agents are eagerly awaited.

In utero exposure HER-2 inhibitor trastuzumab is associated with an increased risk for oligohydramnios, fetal abnormalities, pulmonary hypoplasia, and fetal death [90]. Consequently, the use of trastuzumab and trastuzumab-containing ADCs (T-DM1, T-DXd) is contraindicated during pregnancy, not least in the case of the two ADCs due to the potentially toxic effect on the fetus by the chemotherapy payloads [85]. Following discontinuation of trastuzumab and lapatinib, pregnancy appears to be safe and lapatinib does seem to have a negative impact on ovarian function in mice [82,91]. In animal studies, it has been demonstrated that HER2 inhibitors are excreted in breast milk and growth retardation in suckling pups has further been observed [85].

3.5. ALK inhibitors

Preclinical studies on mouse knock-out models have shown that homozygous Anaplastic lymphoma kinase (*ALK)* mutant animals are viable and fertile but have decreased levels of serum testosterone and display mild changes in testicular tissue organization, indicating a role of ALK in testis function [92]. A mechanism of hypogonadotropic hypogonadism was proposed with decreased levels of GnRH positive neurons in the hypothalamus. A clinical study in 19 men with metastatic ALK-positive non-small cell lung cancer (NSCLC) confirmed these results, demonstrating that crizotinib therapy caused a rapid decrease of testosterone levels suggested to occur via a central (hypothalamic or pituitary) effect [93]. The effect was shown to be reversible with discontinuation of crizotinib leading to increased testosterone back to normal levels. These observations of hypogonadism may have an impact on male fertility. In women the effect of ALK TKIs on fertility is more unclear. Preclinical studies demonstrated potential issues with ovarian follicle necrosis occurring in rats receiving significantly higher crizotinib doses than in humans.

One case report on a female patient treated with crizotinib reported a successful live birth of dizygotic twins via ovarian stimulation, in vitro fertilization and gestational surrogacy [94]. In addition, two cases of uneventful pregnancies and births without complications during treatment with alectinib have recently been reported [95,96]. No studies have been done on whether any of the approved ALKi are excreted in breast milk.

3.6. KRAS inhibitors

The Kirsten rat sarcoma viral oncogene homolog KRAS plays a vital role in a multitude of normal cellular events such as proliferation, survival, differentiation and migration. In its mutated and constitutively active form, *KRAS* has been shown to be an oncogene critical in carcinogenesis and is one of the most common oncogenes (~25% of all of human cancers) [97]. The role of KRAS in fertility and reproductive functions is not entirely clear. In mice expressing constitutively active KRAS G12D in gonadal theca and interstitial cells, females failed to ovulate and were thus infertile, indicating that normal KRAS activity in ovarian theca cells is crucial for ovulation and female fertility [98]. In a clinical setting, *KRAS* mutation status was found not to have an impact on outcome of fertility-preserving treatment in the patients with endometrioid endometrial cancer and endometrial atypical hyperplasia [99]. Recently, sotorasib was approved for the treatment of advanced non-small cell lung cancer harbouring a KRAS G12C mutation and progressing on at least previous line of therapy [100]. There are no clinical studies on the effect of sotorasib on fertility. However, there were no adverse effects on male or female reproductive organs in general toxicology studies conducted in dogs and rats [85]. Adagrasib, another KRAS G12C inhibitor approved by the US Food and Drug Administration (FDA), lacks fertility studies but animal studies indicate impairment of fertility in females and males of reproductive potential [68].

There are no reports of pregnancies while on treatment with KRASi. Out of precaution, women of childbearing potential are advised to avoid pregnancy while on sotorasib and use highly effective contraceptive methods. No studies have been done on whether KRASi are excreted in breast milk.

3.7. VEGF inhibitors

Given as monotherapy the effect of vascular endothelial growth factor (VEGF) monoclonal antibody inhibitors, including bevacizumab and ramucirumab, is low and rarely used. In combination with chemotherapy the VEGFi will enhance the anti-tumour effect, especially in combination with not full-dose regiments and is commonly used in advanced colorectal cancer, breast cancer and several other types of cancer. Repeated dose toxicity studies in animal have demonstrated a reduction in ovary maturity and a reduction/absence of corpora lutea followed by reduced weight of ovary and uterus and number of

menstruation cycles. Thus, a reduced female fertility can be anticipated. In a phase III colon cancer study, an increased incidence of ovary dysfunction compared to placebo control was observed in a subgroup of premenopausal women [101]. The ovary function recovered after end of treatment. However, the long-term effect on fertility is not known and since VEGFi are combined with chemotherapy it is exceedingly difficult to isolate the VEGF inhibitor effect. The impact on male fertility has not been studied.

It is known that immunoglobulin (IgG), i.e., bevacizumab, ramucirumab will pass the placenta and reduce angiogenesis of the fetus resulting in serious foetal damages, which has been observed in patients as well as in animal studies [85]. No studies have been done on whether VEGFi are secreted in breast milk, but since it is known that other IgG antibodies can be secreted in breast milk, a risk to the child cannot be excluded.

3.8. PARP inhibitors

Poly-ADP-ribose polymerase inhibitors (PARP) enzymes play an essential role in DNA damage detection and repair of single strand DNA breaks [102]. The rapid increase in the clinical use of PARPi (including Olaparib and niraparib) not only in ovarian cancer but also in other malignancies such as BRCA-mutated breast cancer, underscores the recognition and management of toxicity of PARPi, including issues of fertility preservation [29–31]. The potential effect of PARPi on ovarian function and female fertility remains poorly understood, but impairment of DNA repair by PARPi results in cell death, which may reduce ovarian reserves, ultimately leading to infertility. There is no clinical evidence regarding the potential impacts of PARPi on the ovary and female fertility, but animal studies have shown that olaparib treatment in mice significantly depleted the ovarian reserve of primordial follicles by 36% compared to the control [103]. The mice were pre-treated with different chemotherapeutic agents, each of which significantly reduced the number of primordial follicles compared to controls [30]. However, the administration of olaparib for 28 days did not enhance chemotherapy-mediated primordial follicle depletion compared to controls [103]. Another animal study showed similar results, indicating a depletion of primordial follicles when olaparib was administered, as well as induction of granulosa cell dysfunction, eventually resulting in impairment of ovarian reserve [104]. The effect of other PARPis on ovarian function and fertility has not been investigated and remains still unknown. Since further expansion of the use of PARPi is expected, pre-clinical and clinical research of potential impacts on fertility and ovarian function of PARPi are needed. In relation to this it is worth mentioning that there is research indicating that women carriers of germline mutations in *BRCA* genes (where PARPi can be indicated in those affected by cancers) have shorter reproductive life, higher risk for premature menopause and therefore they could be more sensitive to gonadotoxic effects of anti-cancer drugs [105–107].

In animal studies, embryonic toxicity related to olaparib has been observed and the use of PARPi is contraindicated during pregnancy. No studies have been done on whether any of the approved PARPi are excreted in breast milk.

3.9. CDK4/6 inhibitors

The approval of Cyclin-dependent kinases 4/6 inhibitors (CDK4/6i) abemaciclib in the adjuvant setting underscores the importance of additional gonadal toxicity caused by CDK4/6i, in light of the fact that high-risk patients for whom abemaciclib is indicated are routinely treated with cytotoxic chemotherapy which further impairs fertility [108]. In general, data from animal studies do not support a negative impact of CDK4/6i on female fertility [109]. In contrast, CDK4/6i may cause histologic changes on the male reproductive tract which however did not translate into impaired male fertility [85]. Relevant clinical data from the reported adjuvant studies are sparse. In an exploratory analysis from the PENELOPE-B trial, levels of estradiol, follicle-stimulating hormone and anti-Müllerian hormone at the end of one-year treatment with palbociclib were not significantly different than baseline [110]. Although this finding is reassuring, the trial was negative for its primary endpoint and palbociclib is not approved for the indication. As a result, similar analyses from the monarchE trial are eagerly awaited to better inform on fertility preservation strategies. The fact that temporary discontinuation of adjuvant endocrine therapy prior to pregnancy does not negatively impact short-term patient outcomes according to the POSITIVE trial further highlights the interest in the potential gonadotoxic effects of abemaciclib [111].

CDK4/6i are used in combination with endocrine therapy, which has known deleterious effects on the fetus. In addition, animal studies indicate that all three approved CDK4/6i (abemaciclib, ribociclib, palbociclib) cause fetal harm and have teratogenic potential at maternal exposures generally corresponding to, or higher than, patients' clinical exposure at the approved dosing [85]. Thus, the use of CDK4/6i is contraindicated during pregnancy. No studies have been done on whether CDK4/6i inhibitors are excreted in breast milk.

3.10. TRK inhibitors

The neurotrophic tropomyosin kinase receptors (*NTRK1–3* genes coding for TrkA-C proteins) have been found to act as oncogenic fusion genes in various cancer types, including e.g., lung, colorectal and breast cancer [112,113]. These gene fusions usually occur at a low frequency, below 1% in most cancers. The first generation of TRKi, larotrectinib and entrectinib are approved as tumor agnostic treatment of advanced or recurrent *NTRK* fusion-positive cancers in adult and pediatric patients. A new generation of TRKi, including repotrectinib and selitrectinib, is also in clinical use within or outside clinical studies. Preclinical studies in mice indicate that TrkB receptors are required for the early growth of ovarian follicles by supporting oocyte development and providing granulosa cells with proliferative signals [114]. Furthermore, in animal models of premature ovarian failure (POF), a leading cause of infertility in women, a TrkB agonistic antibody (Ab4B19) had the ability to rescue ovarian injury and restore the number and quality of oocytes [115]. The reported preclinical data on the role of Trk receptors in fertility may have an impact on the clinical situation in *NTRK*-fusion positive patients treated with TRKi, but data on the effect of fertility in humans is still pending.

Due to their mechanism of action, TRKi have a risk for fetal toxicity and the use of effective contraception is required while taking the drug and for a period after stopping the medication. No studies have been done on whether TRKi are excreted in breast milk.

4. Discussion

From this review, it is clear that there are several aspects related to fertility and reproduction in young patients that are currently diagnosed with cancer. According to international recommendations, patients of reproductive age facing treatments that can potentially lead to infertility should receive timely information on the risks, and also on options for fertility preservation. At present, there are several clinical options for fertility preservation, and these include the cryopreservation of sperms, oocytes, embryos and ovarian tissue [116,117]. In many European countries, fertility preservation measures are state funded if clinically indicated, and the use is regulated according to the general rules for assisted reproduction, including age restrictions. At Karolinska University Hospital in Stockholm, Sweden, where the authors of this review are practicing, more than 3000 patients with malignant diseases have undergone fertility preservation using cryopreservation methods. In 1988–2018, 1393 males and 852 females at median age of 31 and 28 years, respectively underwent such treatments [117]. The most common diagnoses in females were breast, gynecological and hematological malignancies and in males, testicular, hematological and CNS

Summary of recommendations regarding fertility and reproduction in patients receiving molecularly targeted systemic oncological treatments

• Knowledge on the impact of most of the new targeted therapies on fertility is scarce, individuals should be informed based on current knowledge and on available fertility preservation methods.

• In young cancer patients, possible effects on fertility should be discussed before starting treatment. If there is a desire for children, they should be referred to a reproductive medicine specialist for advice and a decision on fertility preservation measures, such as freezing eggs, sperm or embryos.

• In fertile patients, safe contraception is recommended during treatment and until six months after the last treatment was given. Six months is a general safety recommendation but should be considered depending on the situation of each patient (see related discussion in the main text).

• Breastfeeding is not recommended during treatment.

• If pregnancy does occur when either of parents are undergoing treatment or if women need to start treatment while pregnant, they should be counselled regarding potential risks and referred to specialist maternity care

Fig. 1. Recommendation summary.

malignancies. The majority underwent fertility preservation measure before initiating chemotherapy, and a lesser number before operation or radiotherapy. Still there are very few patients that undergo fertility preservation when initiating any of the novel immunotherapy or targeted drugs, although the numbers of patients with this indication have started to increase in the last years. As the examples in this review demonstrate, the novel molecularly targeted treatments have brought great advances in the field of oncology, but also pose new challenges in young patients when family building often is an essential part of their lives. Overall, the knowledge on potential toxic effects on reproduction are very scarce and will probably remain limited. Although there are noteworthy case reports of healthy births, they are too few to be able to draw any definite conclusions about the reproductive safety of any of the drugs. In Figure 1, a summary of recommendations is listed regarding young patients facing treatments with novel targeted therapies. In summary, due to the uncertainties regarding the reproductive effects from the drugs, a strictly precautionary approach is strongly advised. This includes routinely offering consultations on fertility preservation before treatment start and recommending safe contraceptive measures while on treatment and not to breastfeed. Regarding the recommended time from ending the treatment until attempting to conceive, we think that in many cases, six months is a reasonable period as there is so limited data on the effect from the new anti-cancer drugs on fertility and the conceptus and long-term follow-up data is entirely missing. It is however difficult to state a unison period, as the premises can differ widely depending on e.g., the patient sex, type and stage of cancer, other received treatments, side effects and physical and psychological recovery after cancer treatments. Further studies and reports are to be encouraged, including retrospective and prospective studies following young cancer patients and the gamete and reproductive status before and after the treatments.

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CRediT authorship contribution statement

HH: Conceptualization, Methodology, Funding acquisition, Visualization, Writing – original draft, Writing – review & editing, **AM:** Writing – original draft, Writing – review & editing, **JF:** Writing – original draft, Writing – review & editing, **JEF:** Writing – original draft, Writing – review & editing, **SE:** Writing – original draft, Writing – review & editing, **KARW,** Writing – original draft, Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

HH has received honoraria for lectures and consultancies from Novartis, MSD, Pierre Fabre, GSK and BMS. AM has had speaker/consultancy (no personal fees) to Roche, Seagen and Veracyte research funding paid to institution by MSD, AstraZeneca, Novartis and Veracyte. SE has received an unrestricted grant from Boehringer-Ingelheim and participated in non-remunerated expert meetings sponsored by MSD, BMS, Takeda, AstraZeneca, Amgen and Boehringer-Ingelheim. KARW has received honoraria for lectures from Roche, Pfizer, Organon, IBSA, and for consultancies from Merck and Ferring and travel support from Organon. JF and JEF report no conflict of interest.

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