Published in final edited form as:

J Am Acad Dermatol. 2016 September ; 75(3): 528–534. doi:10.1016/j.jaad.2016.04.031.

Oncofertility considerations in adolescents and young adults given a diagnosis of melanoma: Fertility risk of Food and Drug Administration—approved systemic therapies

Jessica R. Walter, MD^{#a}, Shuai Xu, MD, MSc^{#b}, Amy S. Paller, MD^b, Jennifer N. Choi, MD^b, and Teresa K. Woodruff, PhD^{a,c}

^aDepartment of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

^bDepartment of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

^cWomen's Health Research Institute, Northwestern University, Chicago, Illinois

[#] These authors contributed equally to this work.

Abstract

Background—Melanoma is the most common cancer diagnosed for patients ages 25 to 29 years, the group with the highest birth rates in the United States. Oncofertility is a new field addressing the reproductive needs of patients with cancer facing fertility-threatening treatments.

Objective—We sought to assess gender-specific fertility risk for Food and Drug Administration (FDA)-approved melanoma therapies with a new risk category system.

Methods—We conducted a retrospective review of FDA, European Union, and Health Canada regulatory filings, along with previously published reports to grade fertility risk of systemic melanoma therapies. The proposed fertility risk category system is analogous to the FDA's A/B/C/D/X/N pregnancy-risk categories.

Results—For female patients, 58% of treatments represent a fertility risk (Category C and D), 33% have unknown risk (Category N), and 1 therapy (vemurafenib) did not show animal ovarian toxicity (Category B). For male patients, 33% represented a fertility risk (Category C and D), 50% of treatments had unknown risk (Category N), and 17% did not show animal testicular toxicity (Category B).

Limitations—Data on fertility risk for melanoma therapies approved after 2009 are limited to preclinical animal studies.

Conclusion—Dermatologists have an opportunity to discuss fertility preservation, make appropriate referrals, and steward registries on reproductive outcomes for patients with melanoma.

Reprint requests: Jessica R. Walter, MD, Prentice Women's Hospital, 250 E Superior, Suite 03-2303, Chicago, IL 60611. jessica.walter@northwestern.edu.

Conflicts of interest: None declared.

Keywords

cancer survivorship; melanoma; oncofertility

Melanoma disproportionately affects the young. It is the most common cancer diagnosed in patients ages 25 to 29 years,¹ the age group with the highest birth rates in the United States.² Of those patients given a diagnosis of melanoma from 20-49 years of age, 10% present with regional or distant disease.³ Furthermore, there are more than 200,000 melanoma survivors with reproductive potential,⁴ each of whom carries a 9-fold increased risk of developing a secondary melanoma,⁵ with the highest risk of developing a second melanoma within the first 2 years.⁶

These demographics underscore how melanoma care is complicated by an understanding of the disease and its treatment within the context of varying reproductive goals. Given a potential hormonal component of melanoma pathogenesis,⁷ 2 recent studies examined the progression and mortality of melanoma during pregnancy yielding conflicting results.^{8,9} Understanding the effect of pregnancy on melanoma is only one aspect of reproductively conscious and comprehensive cancer care. As new cancer treatments improve survival, particularly in melanoma, and society trends toward delayed childbearing, there is an increasing proportion of melanoma survivors who have yet to complete family building.¹⁰

Oncofertility is a new interdisciplinary field anticipating the reproductive needs for patients with cancer facing potentially fertility-threatening treatment and surgery.¹¹⁻¹³ As both therapeutic options for the treatment of melanoma and technologies for reproductive preservation grow, consideration of future fertility is increasingly becoming a critical component of comprehensive cancer care.¹⁴ Estimates suggest that 75% of patients with cancer who were childless at the time of diagnosis anticipate desiring children.¹⁵ Dermatologists are frequently the first providers who diagnose and discuss treatment options for patients with melanoma and maintain lifelong relationships to monitor disease progression and screen for additional cancer, highlighting both an opportunity and responsibility to participate in survivorship issues, including reproductive health.

METHODS

Fertility risk of all Food and Drug Administration (FDA)-approved systemic treatments of melanoma were based on an assessment of the FDA package insert, the European public assessment reports, the product monograph required by the Health Products and Food Branch of Health Canada, and previously published reports identified through a MEDLINE literature search. We propose a new system analogous to the FDA's A/B/C/D/X/N pregnancy-risk category designation for prescription medications to rate fertility risk. Although there has been recent policy change in pregnancy and lactation risk labeling of prescription drugs, including a new requirement to provide information on infertility as it relates to the drug, this new labeling is a gradual process with the previous pregnancy category system likely to remain clinically relevant for the foreseeable future.¹⁶ See Table I for a detailed definition of fertility risk grading. Briefly, a fertility risk of A is applied to treatments that have not shown a risk to future male or female fertility in high-quality human

studies. A rating of B is assigned to treatments that have animal studies without evidence of gonadal toxicity and no available human data. A rating of C is given to treatments in which there is evidence of gonadal toxicity in animal studies and no available human data. A rating of D is given to treatments with evidence of fertility risk in human studies. Category X ratings are given to treatments with irreversible fertility risk. Finally, an N category designation implies no available human or animal data. All ratings are specific to male and female gender. We use the National Comprehensive Cancer Network guidelines on melanoma to determine the first-line and second-line treatments.¹⁷

RESULTS

For female fertility risk, 33% of the systemic treatments had unknown risk (Category N). For male fertility risk, half of the FDA-approved therapies had unknown fertility risk (Category N). For female patients, 58% of the systemic treatments represented a fertility risk in animal or human studies (Category C and D), whereas for male patients 33% of the systemic treatments represented a fertility risk (Category C and D). For female and male patients, vemurafenib received a Category B fertility rating. For male patients, trametinib was also given a Category B fertility rating. No melanoma treatments were assigned a Category X rating (Table II).

First-line therapies

Regarding first-line therapies, dabrafenib (BRAF inhibitor) has been shown to reduce corpora lutea in female rats and testicular degeneration in both male rats and dogs. Although vemurafenib (BRAF inhibitor) was given a fertility category B for male and female patients, preclinical drug testing of male and female rats and dogs were performed at doses up to 450 mg/kg/d, which is significantly below the anticipated clinical exposure (10%) based on an area under the curve comparison.

Both MEK inhibitors, cobimetinib and trametinib, have shown fertility toxicity in animal studies for female patients. In female rats, preclinical studies demonstrated that cobimetinib exposure increased apoptosis and necrosis of corpora lutea and vaginal epithelial cells whereas trametinib showed similar adverse effects to ovarian tissue as dabrafenib. Trametinib use was not associated with testicular damage in animal studies at 13 weeks whereas cobimetinib caused testicular degeneration.

Immunotherapies such as ipilimumab and the PD-1 inhibitors have an unclear impact on fertility. For ipilimumab, preclinical studies in monkeys showed antibody binding specifically to ovary connective tissue, but no histopathological changes in ovum morphology; in addition, monkey testicular weights decreased, but sperm showed no histopathological changes. A significant proportion of patients treated with ipilimumab exhibited persistent anterior hypophysitis (11%), the portion of the pituitary responsible for gonadotropin production.^{18,19} There is no available evidence for the PD-1 inhibitors.

Second-line, adjuvant, and in-transit therapies

For second-line, adjuvant, and in-transit therapies, fertility data also remained limited. Data for fertility risk of dacarbazine, a DNA alkylating agent approved in the 1970s, were derived

from retrospective studies of reproductive-age patients treated for lymphoma. It is associated with a 4-fold increase of human premature ovarian failure, and temporary azoospermia and oligospermia in 54% of patients.^{20,21} Interferon- α 2b altered serum estradiol and progesterone levels in women with an unknown risk to long-term fertility, however this study was performed in only 5 healthy patients.²²

DISCUSSION

With the approval of 7 new melanoma drugs in the past 5 years and a better understanding of the molecular underpinnings of the disease, dermatologists and oncologists have a growing armamentarium. Our results reveal limitations in knowledge of the fertility risk for most of the newer systemic agents. The only relevant available human data on fertility risk pertain to older agents such as dacarbazine and interferon. For the newer agents approved after 2009, all of the available evidence is derived only from preclinical animal studies. The International Conference on Harmonization (a collaboration between the European, Japanese, and US regulatory agencies) provides guidance on preclinical testing of reproductive toxicity, including fertility risk assessment, for new small molecules and biotherapeutics.²³ Typically, fertility studies are conducted on rats and last for at least 2 weeks. The reproductive organs of male and female animals are sampled for histopathology allowing for assessments such as the number of corpora lutea to estimate preimplantation loss.²⁴ Because of high target specificity, humanized monoclonal antibody therapeutics may require reproductive toxicity testing in nonhuman primates as in the case of ipilimumab. Even though primates have more comparable reproductive physiologies such as menstrual cycle timing and duration of spermatogenesis,²⁴ it is difficult to translate fertility risk from preclinical animal testing alone, particularly in rodents, to humans. Although longitudinal data on ipilimumab-induced hypophysitis is limited to individuals ages 40 or greater^{18,19} making generalization to younger patients more challenging, the majority of patients presenting with hypophysitis demonstrated gonadotroph deficiency, which persisted in 23% of cases at 33 months follow-up.¹⁹ The approvals of combination therapies such as trametinib/dabrafenib, ipilimumab/nivolumab, and vemurafenib/cobimetinib with several more in late-stage clinical trials will only further complicate the assessment of fertility risk. There is even less known about the additive or cumulative risks to fertility with drugs used in combination or in serial.

With an increase in therapeutic options, there is greater uncertainty on how these therapies affect long-term survivorship. Comprehensive cancer care to address future quality-of-life concerns, including fertility preservation, has become paramount, particularly in the context of malignancies such as melanoma that disproportionately afflict the young. Infertility resulting from cancer itself or subsequent treatment leads to significant loss of quality of life for patients, at times causing more distress than the diagnosis of cancer itself.^{12,25} Endocrine disturbances, such as premature ovarian failure and estrogen deficiency, have significant implications such as early osteoporosis. In men, persistent azoospermia rather than hypogonadism is more common in cancer survivors, given the fact that the germinal epithelium is more sensitive to cytotoxic agents because of a higher mitotic rate compared with testosterone-producing Leydig cells.²⁶

The American Society of Clinical Oncology and the American Society for Reproductive Medicine recommend that patients of reproductive age with cancer be counseled regarding the effects of cancer treatment on future reproduction and options for fertility preservation as early in their care as possible and ideally before therapy initiation.²⁷ Despite these recommendations, there are several clinical provider-based and economic challenges to fertility preservation for patients with cancer.^{28,29} Examples include the lack of physician awareness of fertility preservation options, clinician presumption of a patient's lack of interest in future fertility, lack of overall awareness of the reproductive-related toxicities of treatment, and the balance of timeliness and optimization of cancer therapy with fertility preservation.¹³ Thus, there remains a significant gap in provider counseling for both young male and female patients facing fertility-threatening treatments, contributing to a small proportion of eligible patients who ultimately pursue fertility preservation.^{28,30} Formalized oncofertility programs have increased sperm cryopreservation for men with cancer.³¹ Several institutions have successfully implemented programs to support female fertility preservation as well.^{32,33}

Dermatologists frequently have a long-term, sustained relationship with their patients, which would facilitate discussions about the significant uncertainty surrounding fertility preservation and long-term endocrine health. A survey of young women with a diagnosis of breast cancer demonstrated that 57% of participants were concerned about infertility after treatment, and 29% stated that fears of fertility loss influenced treatment decisions.¹⁰ To address these concerns, evidence suggests that simply providing patients with pretreatment counseling regarding risks of infertility and options for fertility preservation demonstrated improvements in quality-of-life and statistically significant reduction in rates of regret.³⁴ Even greater benefit was seen from referring patients to reproductive endocrinologists.³⁰ Men facing fertility-threatening treatment have the more straightforward option of sperm banking. Recent technological advances have made oocyte retrieval followed by egg or embryo freezing a viable alternative and the current standard of care for women.³⁵ We direct the interested reader to a detailed discussion on available fertility preservation options for men³⁶ and women.³⁷

It is reasonable for dermatologists to provide the initial referrals to reproductive endocrinologists for concerned patients and provide first-line counseling on cancer survivorship concerns regarding fertility at the time of diagnosis. The lack of available data underscores the need to extend the use of existing registries^{38,39} to track reproductive outcomes for young melanoma survivors. A diagnosis of advanced melanoma is traumatic, particularly for young patients. Given their unique clinical position, dermatologists have an opportunity to introduce the potential fertility risks of treatment, provide timely referrals to specialists for interested patients, and most importantly, steward registries to develop prospective data on reproductive outcomes for patients with melanoma.

Acknowledgments

Funding sources: None.

REFERENCES

1. Bleyer, A.; O'Leary, M.; Barr, R. Cancer epidemiology in older adolescents and young adults 15 to 29 years of age, including SEER incidence and survival: 1975-2000. National Cancer Institute; Bethesda (MD): 2006.
2. Martin J, Hamilton B, Osterman MJ, Curtin S, Matthews T. Births: final data for 2013. NCHS Data Brief. 2015; (216):1-8.
3. Surveillance, Epidemiology, and End Results (SEER) Program. Stage Distribution (SEER Summary Stage 2000) By Age At Diagnosis/Death Melanoma of the Skin, All Races, Both Sexes. Centers for Disease Control and Prevention and the National Cancer Institute; Atlanta, GA: 2004-2013.
4. DeSantis CE, Lin CC, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin. 2014; 64(4):252-271. [PubMed: 24890451]
5. Goggins WB, Tsao H. A population-based analysis of risk factors for a second primary cutaneous melanoma among melanoma survivors. Cancer. 2003; 97(3):639-643. [PubMed: 12548605]
6. Bradford PT, Freedman DM, Goldstein AM, Tucker MA. Increased risk of second primary cancers after a diagnosis of melanoma. Arch Dermatol. 2010; 146(3):265-272. [PubMed: 20231496]
7. Enninga EA, Holtan SG, Creedon DJ, et al. Immunomodulatory effects of sex hormones: requirements for pregnancy and relevance in melanoma. Mayo Clin Proc. 2014; 89(4):520-535. [PubMed: 24684874]
8. Merkel EA, Martini MC, Amin SM, et al. A comparative study of proliferative activity and tumor stage of pregnancy-associated melanoma (PAM) and non-PAM in gestational age women. J Am Acad Dermatol. 2016; 74(1):88-93. [PubMed: 26545488]
9. Tellez A, Rueda S, Conic RZ, et al. Risk factors and outcomes of cutaneous melanoma in women less than 50 years of age. J Am Acad Dermatol. 2016; 74(4):731-738. [PubMed: 26803345]
10. Partridge AH, Gelber S, Peppercorn J, et al. Web-based survey of fertility issues in young women with breast cancer. J Clin Oncol. 2004; 22(20):4174-4183. [PubMed: 15483028]
11. De Vos M, Smitz J, Woodruff TK. Fertility preservation in women with cancer. Lancet. 2014; 384(9950):1302-1310. [PubMed: 25283571]
12. Jeruss JS, Woodruff TK. Preservation of fertility in patients with cancer. N Engl J Med. 2009; 360(9):902-911. [PubMed: 19246362]
13. Woodruff TK. The Oncofertility Consortium—addressing fertility in young people with cancer. Nat Rev Clin Oncol. 2010; 7(8):466-475. [PubMed: 20498666]
14. Grunewald S, Jank A. New systemic agents in dermatology with respect to fertility, pregnancy, and lactation. J Dtsch Dermatol Ges. 2015; 13(4):277-289. quiz 290. [PubMed: 25819232]
15. Schover LR. Patient attitudes toward fertility preservation. Pediatr Blood Cancer. 2009; 53(2):281-284. [PubMed: 19301387]
16. Department of Health and Human Services; Food and Drug Administration. Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. Federal Register. 2014; 79 FR 72063:72063-72103. [PubMed: 25509060]
17. National Comprehensive Cancer Network. [Accessed November 25, 2015] Melanoma. version 2.2016. Available from: https://www.nccn.org/professionals/physician_gls/PDF/melanoma.pdf
18. Faje AT, Sullivan R, Lawrence D, et al. Ipilimumab-induced hypophysitis: A detailed longitudinal analysis in a large cohort of patients with metastatic melanoma. J Clin Endocrinol Metab. 2014; 99(11):4078-4085. [PubMed: 25078147]
19. Albarel F, Gaudy C, Carré T, et al. Long-term follow-up of ipilimumab-induced hypophysitis, a common adverse event of the anti-CTLA-4 antibody in melanoma. Eur J Endocrinol. 2015; 172(2):195-204.
20. Meirow D. Reproduction post-chemotherapy in young cancer patients. Mol Cell Endocrinol. 2000; 169(1-2):123-131. [PubMed: 11155944]
21. Viviani S, Santoro A, Ragni G, Bonfante V, Bestetti O, Bonadonna G. Gonadal toxicity after combination chemotherapy for Hodgkin's disease. Comparative results of MOPP vs ABVD. Eur J Cancer Clin Oncol. 1985; 21(5):601-605. [PubMed: 2408897]

22. Kauppila A, Cantell K, Janne O, Kokko E, Vihko R. Serum sex steroid and peptide hormone concentrations, and endometrial estrogen and progesterone receptor levels during administration of human leukocyte interferon. *Int J Cancer*. 1982; 29(3):291–294. [PubMed: 6175589]
23. Barrow PC. Reproductive toxicity testing for pharmaceuticals under ICH. *Reprod Toxicol*. 2009; 28(2):172–179. [PubMed: 19631153]
24. Chellman GJ, Bussiére JL, Makori N, Martin PL, Ooshima Y, Weinbauer GF. Developmental and reproductive toxicology studies in nonhuman primates. *Birth Defects Res B Dev Reprod Toxicol*. 2009; 86(6):446–462. [PubMed: 20025046]
25. Tschudin S, Bitzer J. Psychological aspects of fertility preservation in men and women affected by cancer and other life-threatening diseases. *Hum Reprod Update*. 2009; 15(5):587–597. [PubMed: 19433413]
26. Vassilakopoulou M, Boostandoost E, Papaxoinis G, de La Motte Rouge T, Khayat D, Psyrri A. Anticancer treatment and fertility: effect of therapeutic modalities on reproductive system and functions. *Crit Rev Oncol Hematol*. 2015; 97:328–334. [PubMed: 26481950]
27. Loren AW, Mangu PB, Beck LN, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2013; 31(19):2500–2510. [PubMed: 23715580]
28. Schover LR, Brey K, Lichtin A, Lipshultz LI, Jeha S. Knowledge and experience regarding cancer, infertility, and sperm banking in younger male survivors. *J Clin Oncol*. 2002; 20(7):1880–1889. [PubMed: 11919248]
29. Tschudin S, Bunting L, Abraham J, Gallop-Evans E, Fiander A, Boivin J. Correlates of fertility issues in an Internet survey of cancer survivors. *J Psychosom Obstet Gynaecol*. 2010; 31(3):150–157. [PubMed: 20718586]
30. Letourneau JM, Ebbel EE, Katz PP, et al. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. *Cancer*. 2012; 118(6):1710–1717. [PubMed: 21887678]
31. Sheth KR, Sharma V, Helfand BT, et al. Improved fertility preservation care for male patients with cancer after establishment of formalized oncofertility program. *J Urol*. 2012; 187(3):979–986. [PubMed: 22264454]
32. Ali A, Warner E. Pynk: breast cancer program for young women. *Curr Oncol*. 2013; 20(1):e34–e39. [PubMed: 23443036]
33. Gracia CR, Chang J, Kondapalli L, et al. Ovarian tissue cryopreservation for fertility preservation in cancer patients: successful establishment and feasibility of a multidisciplinary collaboration. *J Assist Reprod Genet*. 2012; 29(6):495–502. [PubMed: 22466745]
34. Deshpande NA, Braun IM, Meyer FL. Impact of fertility preservation counseling and treatment on psychological outcomes among women with cancer: a systematic review. *Cancer*. 2015; 121(22):3938–3947. [PubMed: 26264701]
35. Roberston J. Egg freezing and egg banking: empowerment and alienation in assisted reproduction. *J Law Biosci*. 2015; 1(2):113–136.
36. Katz DJ, Kolon TF, Feldman DR, Mulhall JP. Fertility preservation strategies for male patients with cancer. *Nat Rev Urol*. 2013; 10(8):463–472. [PubMed: 23835578]
37. Donnez J, Dolmans MM. Fertility preservation in women. *Nat Rev Endocrinol*. 2013; 9(12):735–749. [PubMed: 24166000]
38. The Oncofertility Consortium. [Accessed December 3, 2015] Fertility Information Research Study: FIRST in young cancer survivors. Available at: <http://oncofertility.northwestern.edu/first-registry>
39. Food and Drug Administration. [Accessed February 1, 2016] List of pregnancy exposure registries. Available at: <http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm>

CAPSULE SUMMARY

- Oncofertility is a new field focused on patients with cancer facing fertility-threatening treatment.
- For Food and Drug Administration—approved melanoma therapies, 92% represent an unknown/potential risk to female fertility and 83% represent an unknown/potential risk to male fertility.
- Dermatologists can counsel patients on fertility risk, provide appropriate referrals, and steward registries tracking reproductive outcomes.

Table I

Fertility risk category system

Fertility risk category	Definition
A	No risk in controlled human studies: adequate and well-controlled studies have failed to demonstrate a risk to male or female fertility
B	No risk in other studies: animal studies have failed to demonstrate a risk to the male or female reproductive organs AND there are no adequate and well-controlled studies in humans of reproductive potential OR animal studies have shown an adverse effect to animal male or female reproductive organs, but adequate and well-controlled studies in humans of reproductive potential have failed to demonstrate fertility risk
C	Risk not ruled out: animal studies have shown an adverse effect on male or female reproductive organs AND there are no adequate and well-controlled studies in humans of reproductive potential
D	Positive evidence of risk: there is positive evidence of human fertility risk based on data from investigational or marketing experience OR studies in humans of reproductive potential
X	Irreversible risk: studies in animals or humans have demonstrated clear, irreversible infertility
N	No available evidence in preclinical animal or human data

The fertility risk category system is defined to be analogous to the former FDA pregnancy prescription medication labeling scheme. A few important distinctions must be noted. Regarding category X, no cancer therapy should be considered contraindicated based on fertility risk. However, patients should be counseled that interventions such as bilateral oophorectomy, orchiectomy, or high-dose radiation to the gonads lead to irreversible infertility. Category N for the original Food and Drug Administration pregnancy categories relate to prescription medication not yet given a designation. For fertility risk, we assign Category N to drugs without any available evidence on fertility risk in either animal or human studies.

Table II
Evidence of male and female fertility risk for Food and Drug Administration—approved melanoma treatments

FDA-approved therapy	Mechanism	Approved	Female		Male	
			Available fertility data	Risk rating	Available fertility data	Risk rating
First-line for metastatic and unresectable disease						
Pembrolizumab	Anti-PD1	2014	None available	N	None available	N
Nivolumab *	Anti-PD1	2014	None available	N	None available	N
Ipilimumab *	Anti-CTLA 4	2011	(1) Preclinical animal studies in monkeys: bound specifically to connective tissue of the ovary although no histopathology changes in ovum morphology; (2) humans: 11% of patients exhibited immune-mediated hypophysitis ^{18,19}	D	(1) Preclinical animal studies in monkeys: decreased testicular weight but no sperm histopathology changes; (2) humans: 11% of patients exhibited immune-mediated hypophysitis ³⁸	D
Dabrafenib †	BRAF inhibitor	2013	Preclinical animal studies in rats: reduced ovarian corpora lutea	C	Preclinical animal studies in rats and dogs: testicular degeneration and depletion seen in both animal species	C
Vemurafenib ‡	BRAF inhibitor	2011	Preclinical animal studies in rats and dogs: no histopathology findings noted on reproductive organs ⁸	B	Preclinical animal studies in rats and dogs: no histopathology findings noted in reproductive organs ⁸	B
Cobimetinib ‡	MEK inhibitor	2015	Preclinical animal studies in rats: increased apoptosis/necrosis of corpora lutea and vaginal epithelial cells	C	Preclinical animal studies in dogs: testicular degeneration	C
Trametinib †	MEK inhibitor	2013	Preclinical animal studies in rats: increased follicular cysts and reduced ovarian corpora lutea	C	Preclinical animal studies in rats and dogs: no observed effect in male reproductive tissues at 13 wk	B
Second-line for metastatic and unresectable disease						
High-dose interleukin-2	Recombinant protein	1998	None available	N	None available	N
Dacarbazine	DNA alkylating agent	1975	Humans: 4-fold increase in premature ovarian failure ¹⁰	D	Humans: temporary azoospermia and oligospermia in 54% ¹¹	D
Stage III in-transit disease						
Talimogene laherparepvec	Oncolytic virus	2015	None available	N	Unknown	N
Stage II disease—adjuvant therapy						
Pegylated interferon alfa-2b	Recombinant protein	2009	Preclinical animal studies in	C	None available	N

FDA-approved therapy	Mechanism	Approved	Female		Male		Risk rating
			Available fertility data	Risk rating	Available fertility data	Risk rating	
Interferon alfa-2b	Recombinant protein	1995	monkeys: prolongation of menstrual cycle				
			(1) Preclinical animal studies in monkeys: menstrual cycle abnormalities; (2) humans: decrease in serum estradiol and progesterone ¹²	C	None available	N	

All data are derived from the approval summaries of drug safety from the European Union, Canada, and the FDA unless specified by a specific citation. *FDA*, Food and Drug Administration.

^{*}Ipilimumab and nivolumab were approved as combination therapy as of 2015.

[†]Dabrafenib and trametinib, previously approved as single agents in 2013, are also approved as a combination therapy.

[‡]Cobimetinib is approved as a combination therapy with vemurafenib.

For female fertility risk, 33% of the systemic treatments have unknown risk (Category N). For men, half of the FDA-approved therapies have unknown fertility risk (Category N). For female patients, 58% of the systemic treatments represent a fertility risk (Category C and D) whereas for male patients 33% of the systemic treatments represent a fertility risk (Category C and D). For female patients, only vemurafenib received a Category B fertility rating. However, vemurafenib is also approved as a combination therapy with cobimetinib (Category C fertility rating). The additive effect of these medications on fertility is unknown. For male patients, vemurafenib and trametinib were given Category B fertility ratings.

[§]In regards to vemurafenib, preclinical testing of male and female rats and dogs were performed at doses up to 450 mg/kg/d, which is below the anticipated clinical exposure based on area under the curve comparison.