J Gynecol Oncol. 2019 Nov;30(6):e94
https://doi.org/10.3802/jgo.2019.30.e94
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Investigating the role of immunotherapy in advanced/recurrent female genital tract melanoma: a preliminary experience

Alice Indini,[1] **Lorenza Di Guardo**,[1] **Carolina Cimminiello**,[1] **Domenica Lorusso**,[2] **Francesco Raspagliesi**,[2] **Michele Del Vecchio**[1]

[1]Melanoma Medical Oncology Unit, Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy
[2]Gynecologic Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy

Received: Aug 9, 2018
Revised: Sep 17, 2018
Accepted: May 7, 2019

Correspondence to
Alice Indini
Melanoma Medical Oncology Unit, Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Via Venezian 1, 20133 Milan, Italy.
E-mail: alice.indini@gmail.com

ORCID iDs
Alice Indini
https://orcid.org/0000-0001-8686-4106
Lorenza Di Guardo
https://orcid.org/0000-0002-7297-319X
Carolina Cimminiello
https://orcid.org/0000-0002-7637-9681
Domenica Lorusso
https://orcid.org/0000-0003-0981-0598
Francesco Raspagliesi
https://orcid.org/0000-0002-4740-7794
Michele Del Vecchio
https://orcid.org/0000-0001-9060-2512

ABSTRACT

Objective: immunotherapy with immune checkpoint inhibitors has become one of the standard therapeutic modalities for patients with advanced melanoma. Melanoma of the female lower genital tract is a rare and aggressive disease, with poor long-term clinical outcomes. To date, no study evaluated the role of immunotherapy in metastatic melanoma of the lower genital tract.
Methods: Data of women with metastatic melanoma of the lower genital tract were prospectively collected. Survival outcomes over time was assessed using Kaplan-Meier model.
Results: Seven cases of metastatic melanoma of the lower genital tract (vulva [n=2], vagina [n=4], and uterine cervix [n=1]) treated with immune checkpoint inhibitors are reviewed. Two patients had metastatic disease at diagnosis, while 5 patients developed metastatic disease at a mean (standard deviation) time of 9.9 (±3.0) months from primary diagnosis. Four patients received an anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA4) (ipilimumab) and 3 received an anti-programmed cell death 1 (PD-1) (pembrolizumab [n=2], nivolumab [n=1]) therapy. The response rate to immunotherapy was 28.5%. Patients receiving an anti-PD-1 experienced a better progression-free survival than patients treated with anti-CTLA4 (p=0.01, log-rank test). Although not reaching statistical significance, overall survival was better in patients having an anti-PD-1 therapy in comparison to anti-CTLA4 (p=0.15, log-rank test).
Conclusion: Results from our series confirm the poor prognosis of women with metastatic melanoma of the lower genital tract, thus supporting the need of exploring new treatment modalities. Further studies are warranted to improve knowledge on the role of immunotherapy in metastatic melanoma of the lower genital tract.

Keywords: Melanoma; Immunotherapy; Genital; Gynecological; PD-1; CTLA-4

INTRODUCTION

Mucosal melanomas primarily occur in the head and neck region (e.g. nasal and oral cavities), followed by the gastrointestinal tract (anorectum) and the female genital tract (vulva and vagina). Melanoma of the female genital tract is an uncommon malignancy that

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: I.A.; Data curation: I.A.; Investigation: I.A., R.F.; Methodology: I.A.; Supervision: D.G.L., C.C., L.D., R.F., D.V.M.; Validation: C.C., L.D.; Visualization: L.D., D.V.M.; Writing - original draft: I.A.; Writing - review & editing: I.A., D.G.L., C.C., L.D., D.V.M.

is associated with a high-risk of recurrence and distant metastases. Prognosis is generally poor, with a 5-year overall survival (OS) of about 8%–60% across different series [1-3], due to lacking well-established protocols for staging and treatment, late diagnosis at disease presentation and anatomic location, often precluding complete surgical resection [4]. Survival of women affected by genital melanoma has not significantly changed during the last decades, especially for patients with advanced stage and recurrent/metastatic disease. In fact, despite recent therapeutic developments, patients' outcomes remain poor and difficult to predict.

Traditional cytotoxic agents (such as platinum compounds, dacarbazine and temozolomide, either alone or in combination) have shown limited or no benefit in the treatment of metastatic disease, like those observed in cutaneous melanoma [5]. Oncologic outcomes of patients with cutaneous melanoma have dramatically improved over the last 5 years with the introduction of 2 distinct class of drugs, the monoclonal antibodies targeting the cytotoxic T lymphocyte-associated antigen 4 (CTLA4), and the programmed cell death 1 (PD-1), and the small molecule inhibitors of MAPK signaling pathway (serine/threonine-protein kinase B-Raf [BRAF] and mitogen-activated protein kinase kinase) [6-10]. However, mucosal melanoma only in less than 10% of the cases shows activating BRAF mutations, thus making these latter drugs not effective usable for treatment. Mucosal melanoma shows different molecular features compared to its cutaneous counterpart [11,12]: aberrations in KIT, a receptor tyrosine kinase, are found in nearly 30%–40% of patients but phase II study investigating the efficacy of KIT inhibitors have shown only suboptimal results [13-15].

Therefore, immunotherapy remains the only promising therapeutic option for advanced genital melanoma. A limited evidence on the safety and efficacy of immunotherapy in advanced/recurrent female genital melanoma is currently available, with data coming from few case reports [16,17] and subpopulation analysis in the context of large clinical trials [18,19]. In the present series we aimed to describe our preliminary experience of advanced/recurrent genital melanoma treated with immunotherapeutic agents.

MATERIALS AND METHODS

This is a retrospective study on patients with advanced/recurrent female lower genital tract melanoma who received immunotherapy at IRCCS National Cancer Institute—Milan (Italy) between January 2011 and December 2016. Institutional Review Board (IRB) was obtained from the Ethical Committee of the IRCCS National Cancer Institute of Milan (Italy) (IRB06812). All patients gave written consent for data collection for health research and data publication.

Inclusion criteria were: 1) histological diagnosis of genital melanoma; 2) advanced or recurrent disease; and 3) treatment with immunotherapeutic agents (anti-CTLA4, and/or anti-PD-1). Exclusion criteria were: 1) age less than 18 years; 2) autoimmune diseases; 3) poor performance status (PS) not allowing systemic treatments; and 4) necessity of chronic corticosteroid treatment.

The IRB-approved database contained data of consecutive women undergoing systemic treatment for genital melanoma. Data regarding baseline demographical characteristics, therapeutic schedules, and treatment-related toxicity were recorded. Moreover, data concerning details of follow-up visits were recorded prospectively in our computerized

database, with a research-quality database maintained by trained residents or fellows and updated on regular basis. Rigorous efforts were made to collect details of patients experiencing disease progression.

Primary treatment of women affected by genital melanoma included radical surgery. Details on surgical treatments have been presented elsewhere [20]. Over the study period, adjuvant treatments were not considered for patients who had complete resection of the disease. Patients with metastatic disease were treated with chemotherapy or immunotherapy, in some cases in association with local radiotherapy, if clinically indicated.

Demographic and baseline patients' characteristics were collected for the present study, together with data regarding previous systemic treatment. Genital melanoma was staged according to the 2017 classification of the American Joint Committee on Cancer (AJCC) 8th edition [21]. BRAF mutation status was determined on tumor tissue with polymerase chain reaction amplification and direct sequencing (3500 DX Genetic Analyzer; Thermo Fisher Scientific, Life Technologies, Carlsbad, CA, USA). PS at the beginning of treatment was assessed according to the Eastern Cooperative Oncology Group scale.

Treatment with immune-checkpoint inhibitors included: ipilimumab 3 mg/kg once every 21 days (4 total courses); pembrolizumab 2 mg/kg once every 21 days; nivolumab 3 mg/kg once every 14 days. Immunotherapy was administered until disease progression, a report of unacceptable toxicity, or patients' decision. Clinical assessments were performed according to the standard of care criteria at the treating Institution. Radiological disease assessment was made with whole body computed tomography scans performed at baseline every 3 months. Radiological response was evaluated using the response evaluation criteria in solid tumors guideline version 1.1 [22].

Safety profile of immunotherapy was assessed recording the onset of immune-related adverse events (irAEs). Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 4.0 (National Cancer Institute 2009). Progression-free survival (PFS) was defined as the time from treatment start until the date of the first recurrence (local, regional, or distant metastasis) or new primary melanoma. OS was defined as the time from treatment start until the date of death from any cause.

1. Statistical analysis

Statistical analysis was performed with GraphPad Prism version 6 for Mac (GraphPad Software, San Diego, CA, USA). Disease-free and OSs within 5 years were estimated using the Kaplan-Meier method and compared between groups using the log-rank test. The p values less than 0.05 were considered statistically significant.

RESULTS

1. Study population

Overall, 7 patients affected by metastatic melanoma of the lower genital tract received immunotherapy for metastatic disease. Primary disease site included: vulva (n=2), vagina (n=4) and uterine cervix (n=1). Mean (standard deviation [SD]) age at diagnosis was 63.7 (±8.9) years. Disease stage at presentation were: AJCC stage IIc (n=4), IIIa (n=1), and stage IV M1c (n=2). **Table 1** shows patients' characteristics. For patients with localized disease at

https://doi.org/10.3802/jgo.2019.30.e94

Table 1. Patients' characteristics

Patient	Age	Histology	Site	BRAF	NRAS	c-kit	Disease stage at diagnosis	LDH	PS (ECOG)
1	62	Mucosal melanoma	Vulva	N.E.	N.E.	Del W557 ex11	IIIA	<ULN	0
2	73	Superficial spreading melanoma	Vulva	WT	N.E.	WT	IIC	<ULN	0
3	79	Mucosal melanoma	Vagina	WT	WT	WT	M1c	>ULN	0
4	57	Epithelioid cell melanoma	Vagina	WT	N.E.	WT	IIC	<ULN	0
5	53	Submucosal melanoma	Vagina	WT	WT	WT	M1C	N.E.	0
6	61	Melanoma NOS	Uterine Cervix	WT	N.E.	N.E.	IIC	>ULN	1
7	62	Epithelioid cell melanoma	Vagina	WT	Q61R	WT	IIC	N.E.	1

Del, deletion; ECOG, Eastern Cooperative Oncology Group; ex, exon; LDH, lactate dehydrogenase; N.E., not evaluated; NOS, not otherly specified; PS, performance status; ULN, upper limit of normal; WT, wild type.

diagnosis, the mean (SD) time interval between primary diagnosis and the occurrence of metastatic disease was 9.9 (±3.0) months.

2. Treatment and oncologic outcomes

All patients recurred as stage M1c: 2 patients developed pelvis recurrence (both visceral and nodal), while 5 patients developed distant visceral metastases. Details on patients' local and systemic treatment are listed in **Table 2**. Two patients received adjuvant chemotherapy (dacarbazine [n=1]; combination of cisplatin, vinblastine and dacarbazine [n=1]). Six patients received immunotherapy as first line systemic treatment; 1 patient received immunotherapy as third line treatment, after being treated with first line tyrosine kinase inhibitor (TKI) nilotinib within a phase II study (clinical trial details are available elsewhere [15]) and second line chemotherapy with fotemustine. Four patients received ipilimumab, 2 patients pembrolizumab and 1 patient nivolumab. Response rate to immunotherapy was 28.5%. PFS and OS were influenced by the type of immunotherapy the patients received: patients treated with anti-PD-1 experienced a better PFS than patients receiving anti-CTLA4 (p=0.01, log-rank test). Although not reaching a statistical significance, OS was better in patients treated with anti-PD-1 in comparison to those treated with an anti-CTLA4 (p=0.15, log-rank test). **Fig. 1** shows survival curves according to type of immunotherapy received.

Five patients developed progressive disease after a mean (SD) time interval of 2.63 (±1.1) months after starting immunotherapy, and subsequently discontinued treatment. One patient received 2 more lines of systemic therapy for disease progression after 1st line ipilimumab (chemotherapy, pembrolizumab), and eventually died of disease; 4 patients

Table 2. Details of local and systemic treatments

Patient	Type of surgery	RFS (mo)	Adjuvant chemotherapy	Site of metastases	Radiotherapy (site)	Immunotherapy	BOR	PFS (mo)	OS (mo)	irAEs (grading)	Follow-up status
1	R0	12	CVD	Lung, groin nodes	None	Ipilimumab	PD	4	7	None	Died of disease
2	R1	9	None	Lung, lymph-nodes, bone	None	Pembrolizumab	PR	10	10	Arthralgia G2, hypothyroidism G2	Alive, on treatment
3	Diagnostic biopsy	0	None	Liver, lymph-nodes	None	Pembrolizumab	PD	2	4	None	Alive
4	R1	4	None	Vagina, urethra	Vagina	Nivolumab	SD	4	4	Cutaneous rash G1	Alive, on treatment
5	R0	1	None	Liver, pancreas, soft tissues, bone	None	Ipilimumab	PD	3	7	None	Died of disease
6	R0	7	None	Lung, liver	None	Ipilimumab	PD	2	2	None	Died of disease
7	R0	5	DTIC	Lung	None	Ipilimumab	PD	3	18	None	Died of disease

BOR, best overall response; CVD, cisplatin-vinblastine-dacarbazine; DTIC, dacarbazine; irAEs, immune-related adverse events; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; R0, resection for cure or complete remission; R1, resection with microscopic residual tumor; RFS, recurrence-free survival; SD, stable disease.

https://doi.org/10.3802/jgo.2019.30.e94

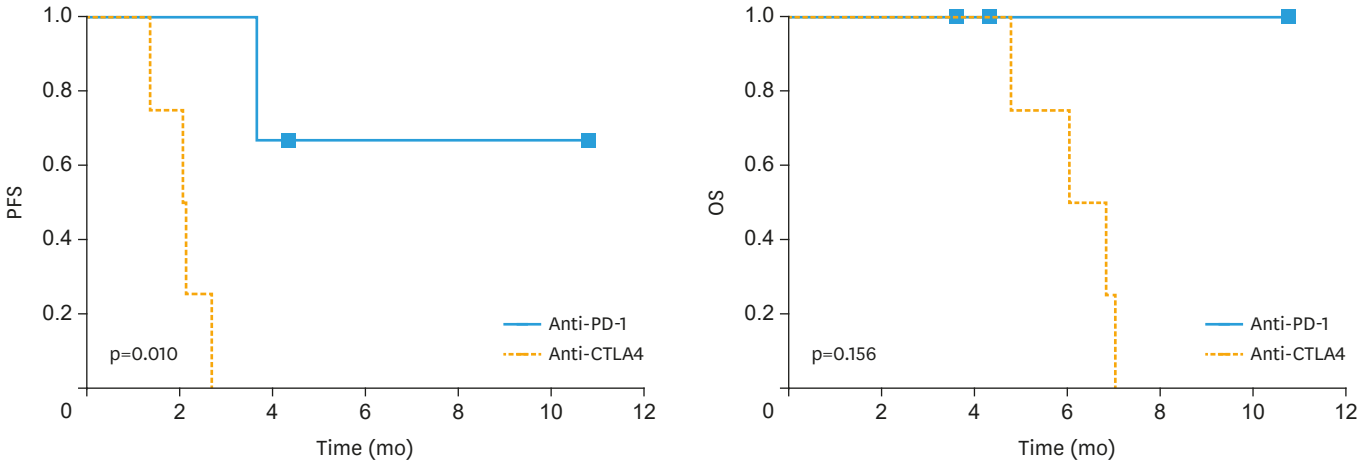

Fig. 1. Survival curves according to type of immunotherapy.

received only best supportive care due to poor clinical conditions (**Table 2**). At the time of the present report, 2 patients are still on treatment: one patient has experienced partial response during treatment with pembrolizumab, the other patient showed stable disease during treatment with nivolumab. After a mean follow-up of 6.1 (±2.2) months 4 patients died of disease while 3 patients are still alive. **Fig. 2** shows survival outcomes of patients.

3. Safety

Regarding safety, the observed irAEs were mild (i.e. G1-2) and transient. One patient developed G2 arthralgia and G2 hypothyroidism during treatment with pembrolizumab, and 1 patient developed G1 cutaneous rash during treatment with nivolumab. The first patient was managed with temporary immunotherapy withdrawal: treatment for irAEs consisted in non-steroidal anti-inflammatory drugs for arthralgia and hormone replacement therapy for hypothyroidism. The second patient was treated with topic steroids application without treatment withdrawal. There was no permanent treatment discontinuation due to irAEs onset.

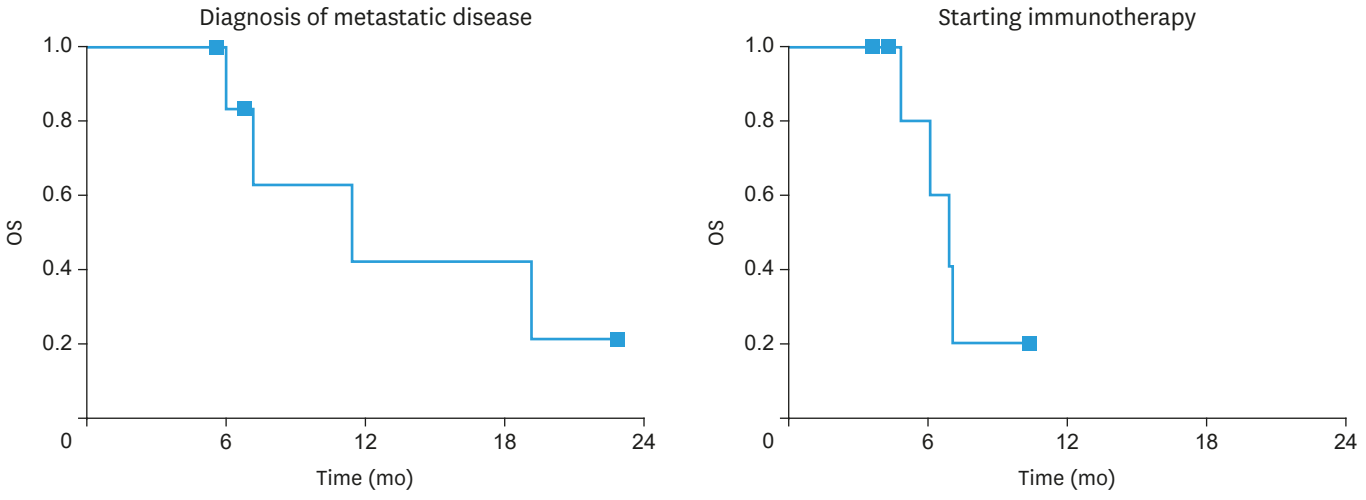

Fig. 2. Survival outcomes.

https://doi.org/10.3802/jgo.2019.30.e94

DISCUSSION

The present paper reports 7 cases of metastatic melanoma of the female genital tract treated with immune-checkpoint inhibitors, thus reporting a number of noteworthy findings. The response rate to immunotherapy of patients in our series is nearly 28% and mean (SD) survival is about 6.1 (± 2.2) months. Therefore, we observed that even when using innovative therapeutic strategies, the prognosis of this subset of patients remains poor. Furthermore, although the limitations of the small sample size and the short-term follow-up do not allow us to draw any definitive conclusion, we observed that anti-PD-1 treatment is related to improved outcomes in comparison to our and literature data referring to anti-CTLA4 therapy. Finally, we found that treatment was well tolerated, with a relatively low reported incidence of irAEs and an overall manageable toxicity profile.

Evidence regarding outcomes of patients with melanoma of the female genital tract is limited. Only a few papers reported outcomes of early stage disease with discordant results [20,23]. Surgery represents the mainstay of treatment for early stage genital melanoma [20,24]. In fact, there is still no consensus on the use of adjuvant therapy and only a single case series and few case reports on this topic are available [16,17,25]. Schiavone et al., [16] reviewed data of 4 patients receiving combined radiation therapy and immunotherapy (ipilimumab) in the adjuvant setting of melanoma of the lower genital tract (vagina [n=3] and cervix [n=1]). The reported OS rates were good (2 patients recurred and 1 died of disease), considering that this population did not include metastatic patients.

Chanal et al., [17] reported a case report of a woman with locally advanced/unresectable melanoma arising into the vagina. The patient was treated with the combination of the TKI imatinib and ipilimumab, with no objective response. After disease progression, the patient received a second line treatment with pembrolizumab, experiencing partial response with an important reduction in target lesions.

Accumulating evidence supports the role of immunotherapy in improving survival of patients with metastatic melanoma [7-9,19,20,26,27]. Due to the rarity of mucosal melanoma, there are no randomized clinical trials evaluating the role of systemic therapies in this subset of patients. Thus, data on the efficacy of innovative treatments are mostly based on anecdotal evidence and small retrospective analyses [19,28-30]. The recent paper by D'angelo et al. [18] provides a pooled analysis of 6 clinical studies reporting a clinically meaningful improvement in PFS and response-rate for nivolumab combined with ipilimumab compared with either agent alone, with evidence of durable tumor responses. Safety profiles were consistent with those observed in cutaneous melanoma. However, to date there are no studies specifically evaluating the role of immunotherapy in metastatic melanoma of the female genital tract. Thus, our study is the first investigating the safety and effectiveness of immunotherapy in metastatic female genital tract melanoma. In agreement with the literature background, we reported that the response rate is quite poor, as observed in other primary sites mucosal melanoma. The inherent biases of the single center study design represent the weakness of the present investigation. Moreover, the relatively small sample size of our report and the length of follow-up might influence the interpretation of our results. Notwithstanding, this is the largest case series to date describing outcomes of metastatic melanoma of the female lower genital tract.

In conclusion, metastatic melanoma of the lower genital tract represents an aggressive disease. Owing to its rarity, an international register should be created in order to evaluate

the real efficacy of different treatment modalities. Moreover, further studies are warranted to test safety and long-term efficacy of immunotherapy in this cluster of patients. A better knowledge of molecular, genetic and epigenetic factors influencing tumor progression is needed to better understand factors improving outcomes of these patients.

REFERENCES

1. Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer 1998;83:1664-78.
PUBMED | CROSSREF
2. Vaysse C, Pautier P, Filleron T, Maisongrosse V, Rodier JF, Lavoue V, et al. A large retrospective multicenter study of vaginal melanomas: implications for new management. Melanoma Res 2013;23:138-46.
PUBMED | CROSSREF
3. Mert I, Semaan A, Winer I, Morris RT, Ali-Fehmi R. Vulvar/vaginal melanoma: an updated surveillance epidemiology and end results database review, comparison with cutaneous melanoma and significance of racial disparities. Int J Gynecol Cancer 2013;23:1118-25.
PUBMED | CROSSREF
4. Mihajlovic M, Vlajkovic S, Jovanovic P, Stefanovic V. Primary mucosal melanomas: a comprehensive review. Int J Clin Exp Pathol 2012;5:739-53.
PUBMED
5. Yi JH, Yi SY, Lee HR, Lee SI, Lim DH, Kim JH, et al. Dacarbazine-based chemotherapy as first-line treatment in noncutaneous metastatic melanoma: multicenter, retrospective analysis in Asia. Melanoma Res 2011;21:223-7.
PUBMED | CROSSREF
6. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-23.
PUBMED | CROSSREF
7. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320-30.
PUBMED | CROSSREF
8. Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015;16:375-84.
PUBMED | CROSSREF
9. Larkin J, Ascierto PA, Dréno B, Atkinson V, Liszkay G, Maio M, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014;371:1867-76.
PUBMED | CROSSREF
10. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet 2015;386:444-51.
PUBMED | CROSSREF
11. Udager AM, Frisch NK, Hong LJ, Stasenko M, Johnston CM, Liu JR, et al. Gynecologic melanomas: a clinicopathologic and molecular analysis. Gynecol Oncol 2017;147:351-7.
PUBMED | CROSSREF
12. Rouzbahman M, Kamel-Reid S, Al Habeeb A, Butler M, Dodge J, Laframboise S, et al. Malignant melanoma of vulva and vagina: a histomorphological review and mutation analysis--a single-center study. J Low Genit Tract Dis 2015;19:350-3.
PUBMED | CROSSREF
13. Kalinsky K, Lee S, Rubin KM, Lawrence DP, Iafrarte AJ, Borger DR, et al. A phase 2 trial of dasatinib in patients with locally advanced or stage IV mucosal, acral, or vulvovaginal melanoma: a trial of the ECOG-ACRIN Cancer Research Group (E2607). Cancer 2017;123:2688-97.
PUBMED | CROSSREF
14. Hodi FS, Corless CL, Giobbie-Hurder A, Fletcher JA, Zhu M, Marino-Enriquez A, et al. Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. J Clin Oncol 2013;31:3182-90.
PUBMED | CROSSREF

15. Guo J, Carvajal RD, Dummer R, Hauschild A, Daud A, Bastian BC, et al. Efficacy and safety of nilotinib in patients with KIT-mutated metastatic or inoperable melanoma: final results from the global, single-arm, phase II TEAM trial. Ann Oncol 2017;28:1380-7.
PUBMED | CROSSREF
16. Schiavone MB, Broach V, Shoushtari AN, Carvajal RD, Alektiar K, Kollmeier MA, et al. Combined immunotherapy and radiation for treatment of mucosal melanomas of the lower genital tract. Gynecol Oncol Rep 2016;16:42-6.
PUBMED | CROSSREF
17. Chanal J, Kramkimel N, Guegan S, Moguelet P, Fourchotte V, Avril MF. Locally advanced unresectable vaginal melanoma: response with anti-programmed death receptor 1. J Low Genit Tract Dis 2016;20:e4-5.
PUBMED | CROSSREF
18. D'Angelo SP, Larkin J, Sosman JA, Lebbé C, Brady B, Neyns B, et al. Efficacy and safety of nivolumab alone or in combination with ipilimumab in patients with mucosal melanoma: a pooled analysis. J Clin Oncol 2017;35:226-35.
PUBMED | CROSSREF
19. Del Vecchio M, Di Guardo L, Ascierto PA, Grimaldi AM, Sileni VC, Pigozzo J, et al. Efficacy and safety of ipilimumab 3mg/kg in patients with pretreated, metastatic, mucosal melanoma. Eur J Cancer 2014;50:121-7.
PUBMED | CROSSREF
20. Ditto A, Bogani G, Martinelli F, Di Donato V, Laufer J, Scasso S, et al. Surgical management and prognostic factors of vulvovaginal melanoma. J Low Genit Tract Dis 2016;20:e24-9.
PUBMED | CROSSREF
21. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67:472-92.
PUBMED | CROSSREF
22. Massard C, Borget I, Farace F, Aspeslagh S, Le Deley MC, Le Tourneau C, et al. RECIST response and variation of circulating tumour cells in phase 1 trials: a prospective multicentric study. Eur J Cancer 2017;83:185-93.
PUBMED | CROSSREF
23. Nagarajan P, Curry JL, Ning J, Piao J, Torres-Cabala CA, Aung PP, et al. Tumor thickness and mitotic rate robustly predict melanoma-specific survival in patients with primary vulvar melanoma: a retrospective review of 100 Cases. Clin Cancer Res 2017;23:2093-104.
PUBMED | CROSSREF
24. Ditto A, Bogani G, Martinelli F, Raspagliesi F. Treatment of genital melanoma: are we ready for innovative therapies? Int J Gynecol Cancer 2017;27:1063.
CROSSREF
25. McGuire SE, Frank SJ, Eifel PJ. Treatment of recurrent vaginal melanoma with external beam radiation therapy and palladium-103 brachytherapy. Brachytherapy 2008;7:359-63.
PUBMED | CROSSREF
26. Del Vecchio M. AACR update on 5-year survival rates, efficacy and long-term safety in previously treated advanced/metastatic melanoma patients receiving mono-immunotherapy with nivolumab. Recenti Prog Med 2016;107:414-7.
PUBMED
27. Ascierto PA, Del Vecchio M, Robert C, Mackiewicz A, Chiarion-Sileni V, Arance A, et al. Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol 2017;18:611-22.
PUBMED | CROSSREF
28. Postow MA, Luke JJ, Bluth MJ, Ramaiya N, Panageas KS, Lawrence DP, et al. Ipilimumab for patients with advanced mucosal melanoma. Oncologist 2013;18:726-32.
PUBMED | CROSSREF
29. Alexander M, Mellor JD, McArthur G, Kee D. Ipilimumab in pretreated patients with unresectable or metastatic cutaneous, uveal and mucosal melanoma. Med J Aust 2014;201:49-53.
PUBMED | CROSSREF
30. Zimmer L, Eigentler TK, Kiecker F, Simon J, Utikal J, Mohr P, et al. Open-label, multicenter, single-arm phase II DeCOG-study of ipilimumab in pretreated patients with different subtypes of metastatic melanoma. J Transl Med 2015;13:351.
PUBMED | CROSSREF