Stage IIA Skin Melanoma Treatment With ECHO-7 Oncolytic Virus Rigvir

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Ingrīda Čēma, MD, and Simona Doniņa, MD, are the attending doctors of the patient and made substantial contributions to acquisition of data. Regīna Kleina, MD; Sergejs Isajevs, MD; and Tatjana Zablocka, MD, carried out the histopathology analysis and made substantial contributions to acquisition of data. Agnija Rasa, MSc, and Pēteris Alberts, PhD, made substantial contributions to the acquisition and interpretation of data and drafted the manuscript. All authors have read and approved the final version of the manuscript.

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Abstract

Melanoma is a global problem due to the rising numbers of skin melanoma cases. Current treatment guidelines for patients with stage IIA melanoma recommend only observation after surgery. In this report, the authors describe a patient with stage IIA skin melanoma treated with surgery and Rigvir virotherapy. Two years after the patient discovered a brown spot on the right cheek, surgery was indicated because the mass had started to ulcerate. Rigvir virotherapy was applied both before and after surgery. Observations made more than 7 years after surgery indicated no signs of disease progression. This case report illustrates an early treatment approach. Neoadjuvant treatment for early-stage melanoma is gaining more interest in both scientific and medical communities; therefore, the authors believe it is relevant to share their observations.

Introduction

In 2020, there were 324,635 new skin melanoma cases globally according to the World Cancer Research Fund,[1] and 106,369 cases were diagnosed in the European Union.[2] The incidence of skin melanoma has been growing for the past few decades.[3]

Melanoma is considered a complicated disease because of its heterogenic and aggressive nature. If not detected early, cutaneous melanoma is increasingly difficult to manage when it progresses because of a shortage of effective treatments for advanced-stage disease.[3] Therefore, melanoma of the skin contributes to relatively high death rates compared to other skin cancers.[4]

Rigvir is an oncolytic, nonpathogenic, and genetically unmodified ECHO-7 virus that has been selected and adapted for melanoma.[5] In addition, oncolytic viruses are also immunomodulators and can be genetically engineered to increase the immunomodulatory effect.[6] For example, Rigvir has been shown to cause the formation of clusters of lymphocytes at the tumor. During the selection process, about 60 different enteroviruses were screened in heterotransplants to observe tumor tropism, after which studies of adsorption were performed. After these studies, ECHO-7 was selected. Virus adaptation was achieved by repeated

passages on human melanoma, thus increasing the oncolytic and oncotropic properties. Rigvir was registered for cutaneous and subcutaneous metastasis of melanoma after surgery in Latvia, Georgia, Armenia, and Uzbekistan.[5] In a previous retrospective study, patients with stage IB and stage II melanoma receiving Rigvir after surgery had 4.39- to 6.57-fold lower mortality, respectively, compared with the control group.[7] Here, the authors report a patient with stage IIA skin melanoma treated with the oncolytic virus Rigvir both before and after surgery. Rigvir is usually administered intramuscularly after surgery.[5] In this case, however, the patient also received peritumoral Rigvir injections before surgery.

This case report was prepared following the CARE guidelines.[8]

Case Presentation

In 2012, a 66-year-old woman discovered a 3–4 mm brown spot on her right cheek that became darker with time. In 2013, the patient went on an excursion to the Alps, after which continued growth was observed. Although she intended to visit a doctor in January 2014, an appointment at a dermatology clinic was scheduled only in the autumn. By that time, peripheral pigmentation had appeared, along with horizontal growth. The patient was then referred to an oncologist. Before the visit, she unintentionally tore off a scab; an exophytic red mass formed in its place. On October 15, 2014, a visual examination was performed by an oncologist (Figure 1A). The mass had started to ulcerate, and surgery was indicated.

By then, the oncolytic virus Rigvir had been in use for quite some time, and no severe side effects had been registered.[5] Because the patient had become extremely worried, she was offered both neoadjuvant and adjuvant therapy with Rigvir. One week before the surgery, the patient received subcutaneous peritumoral injections of Rigvir. Four administrations (0.25–0.3 mL each) around the primary tumor in healthy tissue at a distance 5–7 mm from the tumor were made (Figure 1E). For each administration, a new 27-gauge 2 mL syringe was used. In addition, about 1 mL was administered intramuscularly in the right shoulder. Tumor excision was performed on October 30, 2014 (Figure 1B).

The histopathological examination of tumor tissue showed that the tumor was composed of epithelioid and nevoid cells with large, round, and elongated nuclei with prominent vesicular nuclei and large nucleoli and abundant eosinophilic cytoplasm, surrounded by mature collagen bundles with focal epidermis ulceration. The tumor cells demonstrated moderate nuclear pleomorphism, with variation in cell size, shape, and staining.

Melanin pigment, however, was not observed by hematoxylin–eosin staining. The mitotic activity was up to 4 mitotic figures per square millimeter. The solar elastosis was mild. The tumor Clark invasion level was II, and the Breslow thickness was 1.5 mm. The findings were consistent with a diagnosis of superficial spreading melanoma, low chronic sun-induced damage type. The pathological stage was $pT_{2b}N_xM_0$L-V-R0 (Figure 2A–C). Immunohistochemistry demonstrated that the tumor cells were positive for HMB-45, Melan A, S-100, SOX-10, and the Ki-67 index was 12% (Figure 2D–G).

The melanoma diagnosis was confirmed according to the World Health Organization diagnostic criteria. The tumor staging was assessed according to the American Joint Committee on Cancer guidelines.[9]

During surgery, clear resection lines were achieved, and no complications were observed. Considering the presence of ulceration and mitoses and the location of the tumor, adjuvant Rigvir therapy was prescribed. The therapy was started on December 22, 2014, with 3 intramuscular administrations for 3 consecutive days at 3- to 4-week intervals. Subsequently, the administrations were once per month. The administration schedule was changed to once every 6 weeks in December 2015, to once every 2 months in June 2016, and to once every 3 months in December 2016. The adjuvant therapy was ceased in December 2017.

Serum clinical chemistry parameters were recorded and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events.[10] Except for elevated hemoglobin levels on 2 occasions (rated as grade 1), no other values above grade 1 were observed during Rigvir therapy. No side effects were recorded after the administrations.

The patient is being checked by ultrasound imaging every few months and has regular doctor appointments (Figure 1C and D). There are no signs of disease progression or lymph node growth.

The patient is retired and enjoys spending time outdoors and working in her garden. She was

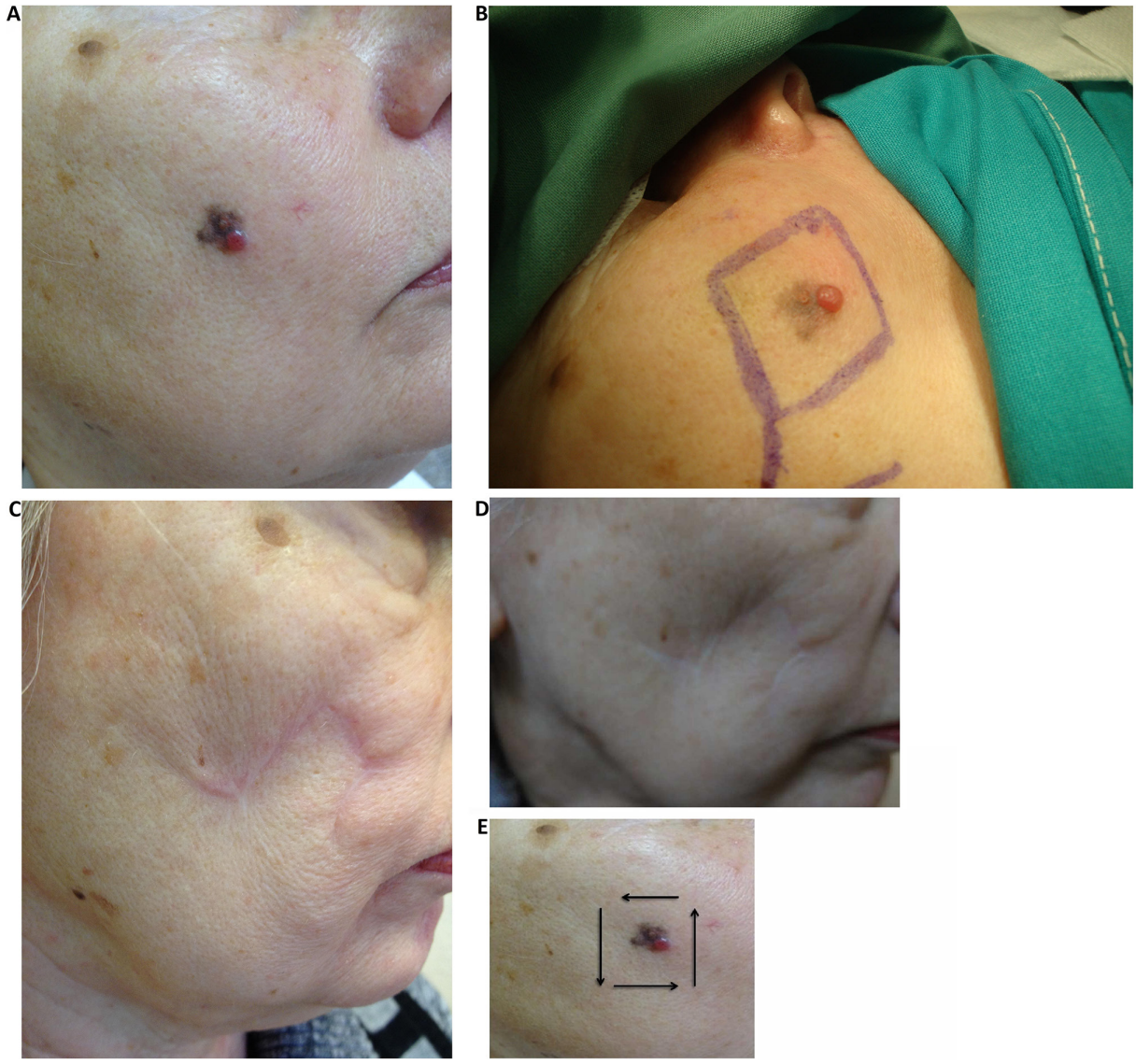

Figure 1: (A) Primary melanoma on the skin of the right patient's cheek on October 15, 2014. (B) The purple-colored line indicates the cutting line during the surgery, the distance of the derogation from the primary focus of the melanoma, and the flap formation from the local tissues (October 30, 2014). (C,D) The surgery locus (C) 1.2 and (D) 5.2 years after surgery (C, January 21, 2016; D, January 9, 2020). Visual and palpable scar without specific changes. (E) Arrows indicate the direction of Rigvir administrations around the primary focus of melanoma on October 22, 2014.

reported to have had gastritis and erysipelas disease in the lumbar region (winter 2019). There is a family history of cancer. Therefore, the patient has experienced anxiety while suffering from an oncological disease. At present, however, the patient is happy and maintains a good quality of life.

Discussion

The decision in favor of adjuvant therapy in this case was based on several factors. Melanoma of the head and neck is known to have worse outcomes than melanomas of other sites.[11] Ulceration and presence of mitoses are known to be prognostic indicators for early recurrence in cases of cutaneous melanoma.[12] Sentinel lymph nodes were examined with ultrasound imaging before surgery because the biopsy of cervical lymph nodes was not standard practice in Latvia in 2014. Even when positive sentinel lymph nodes have been found, lymph node dissection is controversial, as several studies have failed to show substantial benefit in progression-free and overall survival after lymph node dissection.[13,14] Furthermore, National Comprehensive Cancer Network guidelines do not recommend lymph node dissection in patients at risk for regional metastases with clinically negative lymph nodes and without a performed sentinel node

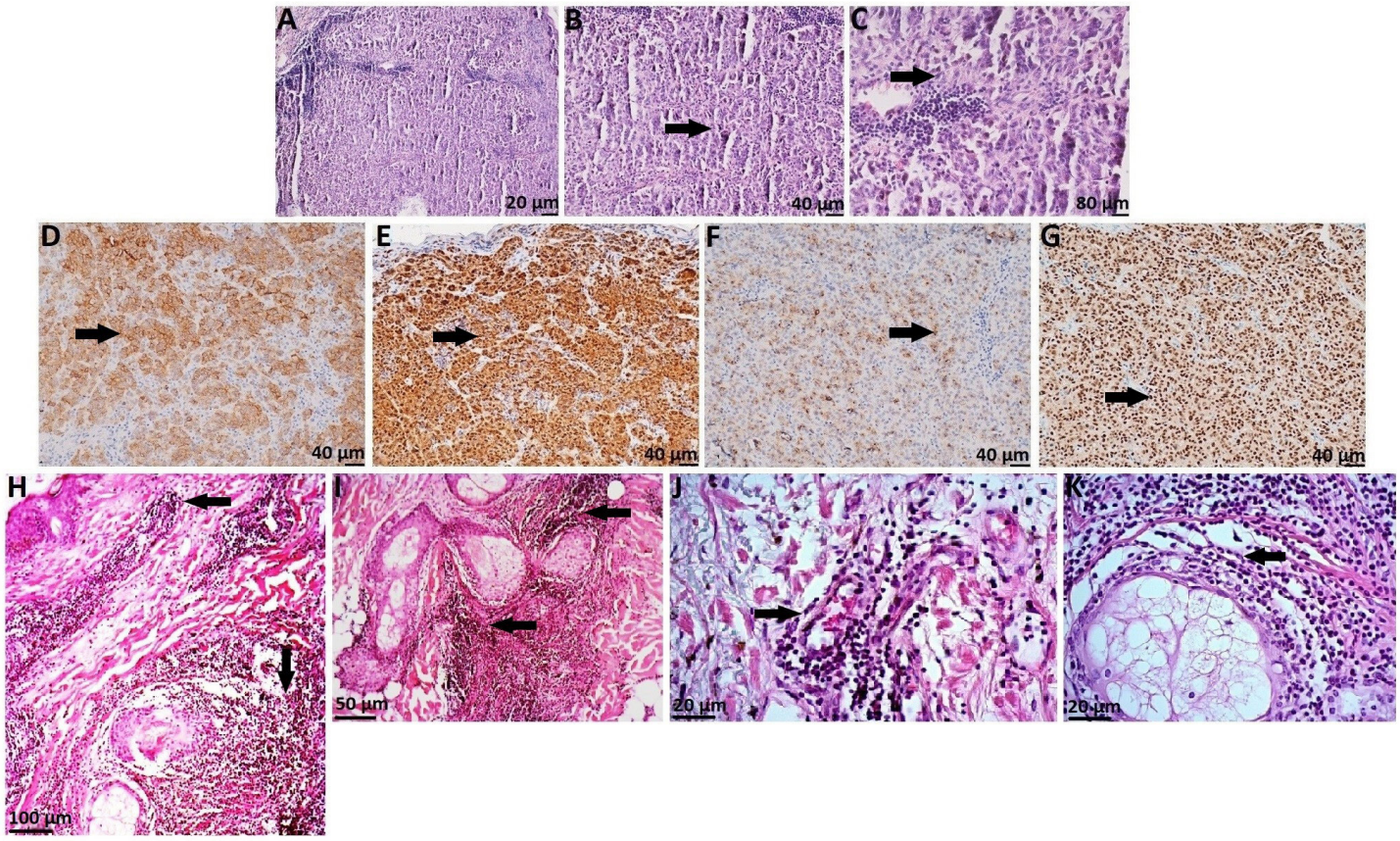

Figure 2: Representative photomicrographs of superficial spreading melanoma, low chronic sun-induced damage type. Breslow 1.5 mm, Clark II. Pathological mitosis of 4 per field of vision, without invasion into vessels and lymphatic vessels. (A–C, H–K) Hematoxylin–eosin staining and (D–G) immunohistochemical staining method. (A) Magnification × 10, scale bar = 20 μm. (B) Magnification = × 20, scale bar = 40 μm. Arrow indicates tumor cells. (C) Magnification = × 40, scale bar = 80 μm. Arrow indicates tumor cells. (D) Melan A. Magnification = × 20, scale bar = 40 μm. Arrow indicates immunopositive cells. (E) SOX-10. Magnification = × 20, scale bar = 40 μm. Arrow indicates immunopositive cells. (F) HMB45. Magnification = × 20, scale bar = 40 μm. Arrow indicates immunopositive cells. (G) S100. Magnification = × 20, scale bar = 40 μm. Arrow indicates immunopositive cells. (H) The resection line of epithelioid pigmentated melanoma is free from malignant cells, but expressed infiltration of mononuclear cells in superficial and deep areas of skin are present (arrows). Magnification = × 10, scale bar = 100 μm. (I) Dense lymphocytic infiltration around skin appendages (arrows) after Rigvir administration. Magnification = × 20, scale bar = 50 μm. (J) Immune cell reaction around capillaries of derma (arrows) after Rigvir administration. Magnification = × 40, scale bar = 20 μm. (K) Diffuse lymphocytic infiltrate around sebaceous gland in derma (arrow) after Rigvir administration. Magnification = × 40, scale bar = 20 μm.

biopsy.[15,16] Therefore, in the absence of suspicious lesions during ultrasound examination, lymph node dissection was not performed. Melanoma is considered to be a tumor that is responsive to immune modulation.[4] At the time, the only standard treatment option for localized melanoma was interferon α-2b, but only for stages IIB, IIC, and III melanoma. Therefore, according to international treatment guidelines, no treatment option other than surgery was available for stage IIA melanoma. In Latvia, Rigvir was approved in 2004 for the treatment of melanoma, the local treatment of skin and subcutaneous metastases of melanoma, and the prevention of relapse and metastasis after radical surgery, enabling the patient to be offered this treatment. Currently, neoadjuvant therapy for localized, early-stage melanoma is being tested in clinical trials, including one with the oncolytic virus talimogene laherparepvec in a neoadjuvant setting in high-risk early melanoma.[17–19]

During preclinical and clinical studies with Rigvir, the formation of large clusters of lymphocytes around the edges of tumors and within the tumors has been observed (cf. Figure 2H–K).[5,20–22] Other oncolytic viruses have also been shown to attract T lymphocytes to the tumor, thus contributing to the anticancer effect.[23–26] Therefore, peritumoral Rigvir was administered prior to tumor excision to promote lymphocyte emergence and surround the melanoma cells, creating a barrier between the tumor and healthy tissues.

The presence of tumor-infiltrating lymphocytes in the tumor microenvironment is considered to be a favorable prognostic feature.[27,28] In a phase Ib study

involving patients with 21 metastatic melanoma, intralesional talimogene laherparepvec used in combination with pembrolizumab shown to result in enhanced T cell infiltration.[29]

Conclusions

The present case report describes a patient with stage IIA skin melanoma treated with peritumoral Rigvir virotherapy administrations prior to surgery and a 3-year Rigvir therapy course after surgery. For 7.3 years after diagnosis, the patient has been stable without signs of disease progression. Based on the literature regarding the role of tumor-infiltrating lymphocytes in disease prognosis, preclinical studies of lymphocytes surrounding the tumor after administration of Rigvir, and observations in the present study, the authors believe that, in addition to adjuvant Rigvir treatment, neoadjuvant administrations could also be made for better prognosis in patients with early-stage melanoma. Further studies in this field are required.

REFERENCES

1. World Cancer Research Fund International. Worldwide cancer data. Accessed February 23, 2022. https://www.wcrf.org/dietandcancer/worldwide-cancer-data
2. European Cancer Information System. Skin melanoma burden in EU-27. Accessed February 23, 2022. https://ecis.jrc.ec.europa.eu/pdf/factsheets/Melanoma_cancer_en.pdf
3. Coricovac D, Dehelean C, Moaca E-A, et al. Cutaneous melanoma—A long road from experimental models to clinical outcome: A review. Int J Mol Sci. 2018;19(6):1566. DOI: https://doi.org/10.3390/ijms19061566
4. Leonardi GC, Candido S, Falzone L, Spandidos DA, Libra M. Cutaneous melanoma and the immunotherapy revolution (Review). Int J Oncol. 2020;57(3):609–618. DOI: https://doi.org/10.3892/ijo.2020.5088
5. Alberts P, Tilgase A, Rasa A, Bandere K, Venskus D. The advent of oncolytic virotherapy in oncology: The Rigvir® story. Eur J Pharmacol. 2018;837:117–126. DOI: https://doi.org/10.1016/j.ejphar.2018.08.042
6. Russell L, Peng KW, Russell SJ, Diaz RM. Oncolytic viruses: Priming time for cancer immunotherapy. BioDrugs. 2019;33(5):485–501. DOI: https://doi.org/10.1007/s40259-019-00367-0
7. Doniņa S, Strēle I, Proboka G, et al. Adapted ECHO-7 virus Rigvir immunotherapy (oncolytic virotherapy) prolongs survival in melanoma patients after surgical excision of the tumour in a retrospective study. Melanoma Res. 2015;25(5):421–426. DOI: https://doi.org/10.1097/CMR.0000000000000180
8. Riley DS, Barber MS, Kienle GS, et al. CARE guidelines for case reports: Explanation and elaboration document. J Clin Epidemiol. 2017;89:218–235. DOI: https://doi.org/10.1016/j.jclinepi.2017.04.026
9. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. *American Joint Committee on Cancer (AJCC) Cancer Staging Manual*. 7th ed. New York: Springer; 2010.
10. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events (CTCAE) v4.03. June 14, 2010. Accessed April 1, 2018. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40
11. Tseng WH, Martinez SR. Tumor location predicts survival in cutaneous head and neck melanoma. J Surg Res. 2011;167(2):192–198. DOI: https://doi.org/10.1016/j.jss.2010.10.008
12. Matheson JAH, Te Marvelde L, Mailer S, et al. Prospective evaluation of prognostic indicators for early recurrence of cutaneous melanoma. Melanoma Res. 2017;27(1):43–49. DOI: https://doi.org/10.1097/CMR.0000000000000302
13. Stenger M. No Survival Benefit With Complete Lymph Node Dissection vs Observation in Sentinel Node-Positive Melanoma. 2019. Accessed October 21, 2021. https://ascopost.com/news/october-2019/complete-lymph-node-dissection-vs-observation-in-sentinel-node-positive-melanoma
14. Faries MB, Thompson JF, Cochran AJ, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. N Engl J Med. 2017;376(23):2211–2222. DOI: https://doi.org/10.1056/NEJMoa1613210
15. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Melanoma. 2014 (Version 4). Accessed July 8, 2014. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1492
16. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Melanoma: Cutaneous. 2021 (Version 2). Accessed August 10, 2021. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1492
17. Neoadjuvant T-VEC in High Risk Early Melanoma. ClinicalTrials.gov identifier: NCT04427306. Updated June 21, 2022. Accessed September 23, 2021. https://clinicaltrials.gov/ct2/show/NCT04427306
18. Neoadjuvant PD-1 Blockade in Patients With Stage IIB/C Melanoma. ClinicalTrials.gov identifier: NCT03757689. Updated May 23, 2022. Accessed September 23, 2021. https://clinicaltrials.gov/ct2/show/NCT03757689?term=NCT03757689&draw=2&rank=1
19. Neoadjuvant Atezolizumab in Cutaneous Melanoma. ClinicalTrials.gov identifier: NCT04020809. Updated January 14, 2022. Accessed September 23, 2021. https://clinicaltrials.gov/ct2/show/NCT04020809?term=NCT04020809&draw=2&rank=1
20. Garklāva R, Brūvere R, Vītoliņa L. Morphological and clinical parallels of changing rectal cancer during combined treatment (in Russian). In: Muceniece A, ed. *Immunological Aspects of Viral Oncotropism*. Riga, Latvia: Zinātne; 1979:114–120.
21. Brūvere R, Vītoliņa L, Garklāva R. Influence of a viral immunomodulator (Rigvir®) on cellular composition and topographic characteristics of the infiltration of the stroma of primary tumours of colorectal cancer (in Russian). Proc Latv Acad Sci. 1980;396:137–142.
22. Muceniece A, Venskus D. *How to Assess Immunity - the Melanoma Model [Kā Vērtēt Imunitāti - Melanomas Modelis (in Latvian)]*. Riga, Latvia: Ainas Mucenieces biedrība vēža imūnterapijas izstrādei sabiedriskā organizācija; 2007:117–121.
23. Liu TC, Galanis E, Kirn D. Clinical trial results with oncolytic virotherapy: A century of promise, a decade of progress. Nat Clin Pract Oncol. 2007;4(2):101–117. DOI: https://doi.org/10.1038/ncponc0736

24. Ribas A, Dummer R, Puzanov I, et al. Oncolytic virotherapy promotes intratumoral T cell infiltration and improves anti-PD-1 immunotherapy. Cell. 2017;170(6):1109–1119. DOI: https://doi.org/10.1016/j.cell.2017.08.027
25. Berkey SE, Thorne SH, Bartlett DL. Oncolytic virotherapy and the tumor microenvironment. Adv Exp Med Biol. 2017;1036:157–172. DOI: https://doi.org/10.1007/978-3-319-67577-0_11
26. Harrington K, Freeman DJ, Kelly B, Harper J, Soria JC. Optimizing oncolytic virotherapy in cancer treatment. Nat Rev Drug Discov. 2019;18(9):689–706. DOI: https://doi.org/10.1038/s41573-019-0029-0
27. Fu Q, Chen N, Ge C, et al. Prognostic value of tumor-infiltrating lymphocytes in melanoma: A systematic review and meta-analysis. Oncoimmunology. 2019;8(7):e1593806. DOI: https://doi.org/10.1080/2162402X.2019.1593806
28. Mihm MC, Mulé JJ. Reflections on the histopathology of tumor-infiltrating lymphocytes in melanoma and the host immune response. Cancer Immunol Res. 2015;3(8):827–835. DOI: https://doi.org/10.1158/2326-6066.CIR-15-0143
29. Haanen J. Converting cold into hot tumors by combining immunotherapies. Cell. 2017;170(6):1055–1056. DOI: https://doi.org/10.1016/j.cell.2017.08.031