ANTICANCER RESEARCH *40*: 7095-7100 (2020)
doi:10.21873/anticanres.14738

Nivolumab for the Treatment of Advanced Pediatric Malignancies

AGATA MARJAŃSKA[1*], MONIKA DROGOSIEWICZ[2*], BOŻENNA DEMBOWSKA-BAGIŃSKA[2], KATARZYNA PAWIŃSKA-WĄSIKOWSKA[3], WALENTYNA BALWIERZ[3], KATARZYNA BOBEFF[4], WOJCIECH MŁYNARSKI[4], AGNIESZKA MIZIA-MALARZ[5], ANNA RACIBORSKA[6], MARIUSZ WYSOCKI[1] and JAN STYCZYŃSKI[1]

[1]*Department of Pediatric, Hematology and Oncology, Nicolaus Copernicus University Torun, Jurasz University Hospital, Collegium Medicum, Bydgoszcz, Poland;*
[2]*Department of Oncology, The Children's Memorial Health Institute, Warsaw, Poland;*
[3]*Department of Pediatric, Oncology and Hematology, Faculty of Medicine, Jagiellonian University Medical College, Cracow, Poland;*
[4]*Department of Pediatrics, Oncology, Hematology and Diabetology, Medical University of Lodz, Lodz, Poland;*
[5]*Department of Pediatric, Oncology, Hematology and Chemotherapy, Upper Silesia Children's Care Health Centre, Medical University of Silesia, Katowice, Poland;*
[6]*Department of Oncology and Surgical Oncology for Children and Youth, Institute of Mother and Child, Warsaw, Poland*

Abstract. *Background/Aim: Nivolumab is an immune checkpoint inhibitor with high antitumor activity in selected neoplasms. The aim of the study was to evaluate the efficacy and safety of nivolumab in pediatric patients with various types of highly malignant advanced tumors. Patients and Methods: Ten patients with a median age of 15.1 years were included in the study. The indications for treatment were: malignant skin melanoma (n=5), brain tumor (n=2), malignant melanoma of the brain (n=1), Hodgkin lymphoma (n=1) and soft tissue sarcoma (n=1). Results: Complete disease remission was observed in 4 patients. Overall survival at 24 months from diagnosis for the entire group was 0.36. Two patients receiving combination therapy of nivolumab and ipilimumab did not achieve a remission. Adverse events of immunotherapy were observed in 4/10 patients. Conclusion: Nivolumab is a promising option in pediatric advanced malignancies. Treatment with immunotherapy was relatively well tolerated, and emerging side-effects were manageable.*

Immune checkpoint inhibitors are one of the major advances of modern oncology, leading to improvement of overall survival (OS) of patients with advanced and refractory malignancies (1). Still, current experience with these drugs is limited in the pediatric setting.

Nivolumab is a human IgG4 monoclonal antibody that binds to programmed death 1 (PD-1) receptor, and as a result it blocks the interaction between PD-1 and its ligands PD-L1 and PD-L2. Binding of the PD-1 ligands to the PD-1 receptor located on T lymphocytes surface, inhibits the proliferation of T cells and the production of cytokines (2). Immunotherapy with nivolumab is based on blockade of immune checkpoints, *i.e.* a group of costimulatory molecules negatively regulating the immune system. This blockade overcomes immune tolerance in the tumor microenvironment and amplifies antitumor immunity (3). About 50% of oncological patients with indications for treatment with nivolumab, may not benefit from monotherapy with this drug. To overcome this, a combination of nivolumab and cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitors is investigated as an approach to improve treatment outcomes (4). Ipilimumab is a humanized IgG1 monoclonal antibody that inhibits CTLA-4. Anti-CTLA-4 antibody blocks CD80 and CD86 on antigen-presenting cells (APCs) forms binding to CTLA-4 on T lymphocytes. The resulting blockade of

*These Authors contributed equally to the study.

Correspondence to: Agata Marjańska, MD, Department of Pediatric Hematology and Oncology, Collegium Medicum, Nicolaus Copernicus University, Antoni Jurasz University Hospital No. 1, ul. Sklodowskiej-Curie 9, 85-094 Bydgoszcz, Poland. Tel: +48 525854860, Fax: +48 525854087, e-mail: agata.marjanska@wp.pl

Key Words: Nivolumab, ipilimumab, anti-PD-1, pediatric cancer, malignant melanoma, brain tumor.

CTLA-4 signaling prolongs T-cell activation, restores T-cell proliferation, and thus amplifies T-cell-mediated immunity, which enhances the patient's capacity to mount an antitumor immune response (1, 5).

Current indications for nivolumab +/– ipilimumab treatment include advanced forms of malignancies such as melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), classical Hodgkin lymphoma (cHL), squamous cell cancer of the head and neck (SCCHN) and urothelial cancer (6). The drug is licensed for adult patients only, however, research is ongoing focused on its effectiveness in the treatment of pediatric cancers. In addition, numerous clinical trials are currently underway to assess the safety and efficacy of PD-1 and CTLA-4 inhibitors in brain cancer, breast cancer, colon cancer and many other types of tumors (7).

The aim of the study was to evaluate the safety and efficacy of nivolumab used as monotherapy or in combination with ipilimumab in a series of pediatric patients with various types of highly advanced malignancies given on compassionate-use basis.

Patients and Methods

Patients. Ten patients with a median age of 15.1 years (range=3.1-17.9 years) were included in the study. The indications for treatment with nivolumab alone or in combination with ipilimumab were as follows: malignant skin melanoma in 5 patients, brain tumor in 2, primary malignant melanoma of the brain in 1, Hodgkin lymphoma in 1 and soft tissue sarcoma in 1. Patient characteristics are presented in Table I. No evaluation of PD-L1 expression in tumor cells was performed.

Therapy. All participants got immunotherapy as a life-saving therapy. Two patients additionally received ipilimumab. Details of treatment with nivolumab are presented in Table I. The applied doses of drugs were based on the recommendations for dosing in patients >18 years of age and were adjusted to body weight. All patients were treated between 15.12.2015-15.08.2020. Informed consent was obtained from the patients and/or their parents. The study was performed according to the institutional guidelines and was approved by the Institutional Review Boards.

Assessment of therapeutic response. The follow-up imaging examinations were performed every three months or when progression was suspected. Pseudoprogression, a response to immune therapy was defined as a reaction to treatment after first increase in size of tumors, caused by the infiltration of cancer tissue by immune cells. The rate of this phenomenon does not exceed 10% in individuals treated with immune checkpoint inhibitors. Due to the fact that classic response evaluation criteria for solid tumors (RECIST) should not apply for immunotherapy, separate criteria for treatment response have been established, based on immune related response criteria (irRC) and immunotherapy RECIST (iRECIST) (8). Follow-up of patients was based on irRC and iRECIST criteria.

Adverse events. All adverse events observed in patients were reported using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical analysis. The primary endpoint was the probability of overall survival (OS), calculated with the Kaplan-Meier method, and compared by the log-rank test. Event was defined as death from progression. Mean survival was determined by Kaplan-Meier method. The Cox regression model was used to calculate treatment outcomes for available risk factors [age, sex, primary diagnosis (skin melanoma *vs*. others), Eastern Cooperative Oncology Group (ECOG) performance status scale, and number of lines of previous therapy] in uni- and multivariate analysis. Hazard ratios (HR) were calculated with 95% confidence interval (95%CI). All the tests were two-sided. Statistical significance was defined as $p<0.05$. SPSS 25 (IBM, Armonk, NY, USA) statistical package was used.

Results

Clinical course. Median follow-up of all patients included into the study was 9.6 (range=1.1-22.7) months. At the end of follow-up, complete remission (CR) was observed in 4 children, with a mean survival 11.1 (95%CI=5.2-16.9) months. Patients who survived received immunotherapy as a median 1 (range=1-3) line of therapy. Patients with Hodgkin lymphoma completed the treatment, and in three patients with malignant skin melanoma immunotherapy was still ongoing. All these patients received nivolumab monotherapy. A rapid progression of tumors was observed in 4 patients with poor general condition (ECOG ≥2) before the initiation of immunotherapy, largely impaired by numerous lines of prior treatment. The median number of nivolumab doses for children with observed progression was 4 (range=2-14).

Survival. Data on individual patient outcomes are shown in Table I. Probability of overall survival for the entire group at 24 months was 0.36 (Figure 1). Patients with ECOG ≤1 had OS=0.63 while all patients with ECOG≥2 died ($p=0.006$). Patients without previous lines of therapy presented a trend for better survival than those with ≥1 line of therapy (OS=0.67 *vs*. 0.17; $p=0.056$). Patients with skin melanoma had OS=0.53, while others 0.20 ($p=0.135$). Two factors (ECOG score and number of lines of previous therapy) were included in multivariate analysis. The only significant adverse risk factor was ECOG score ≥2 (HR=12.6; 95%CI=1.4-117; $p=0.026$).

Safety. Adverse events were observed in 4 out of 10 patients, presenting as hypothyroidism (2), pneumonia (2), diarrhea (1), blood hypotension (1), hepatotoxicity (1) and skin rash (1). Pseudoprogression was observed in one patient. One of the two patients on combination therapy with ipilimumab presented hypothyroidism, diarrhea and hepatotoxicity. All reported adverse events were manageable by delaying treatment for several weeks and/or steroid administration and did not lead to termination of immunotherapy.

Table I. *Patient characteristics, dosage of drugs, and effects of treatment.*

No	Age (years), gender	ECOG status	Diagnosis	Staging (staging system)	BRAF mutation	Treatment	Previous lines of therapy (number of courses)	Number of cycles of nivolumab	Effect of treatment	Adverse events (CTCAE grade)
1	17.8/F	0	Cutaneous malignant melanoma	III (TNM)	Negative	NIVO 3 mg/kg/2 weeks (as adjuvant treatment)	None	31 (aim: 52)	CR (OS=18.7 months)	None
2	8.4/M	0	Cutaneous malignant melanoma	III (TNM)	Negative	NIVO 3 mg/kg + IPI 1 mg/kg/3 weeks (4 doses) followed by NIVO 3 mg/kg/2 weeks (as adjuvant treatment)	None	14	Progression and death	None
3	3.1/F	1	Cutaneous malignant melanoma	IV (TNM)	Negative	NIVO 3 mg/kg/ 2 weeks	1) VP-16+DTIC (3); as adjuvant treatment 2) IVADo (3)	4	Progression and death	Pneumonia (3)
4	8.8/F	0	Cutaneous malignant melanoma	III (TNM)	Negative	NIVO 3 mg/kg/ 4 weeks (as adjuvant treatment)	None	8 (aim: 12)	CR (OS=6.76 months)	None
5	15.5/F	0	Cutaneous malignant melanoma	III (TNM)	Negative	NIVO 3 mg/kg/ 2 weeks (as adjuvant treatment)	None	41 (aim: 52)	CR (OS=21.96 months)	Hypothyroidism (4), blood hypotension (3), diarrhea (2), tumor pseudo-progression
6	14.5/F	2	Localized brain malignant melanoma	No classification	Negative	NIVO 3 mg/kg + IPI 1 mg/kg/3 weeks (4 doses) followed by NIVO 3 mg/kg/2 weeks (as adjuvant treatment)	1) Stereotactic RTH	4	Progression and death	Hypothyroidism (1), diarrhea (1), hepatotoxicity (3), skin rash (2)
7	5.3/M	2	Diffuse intrinsic pontine glioma	No classification	Unknown	NIVO 3 mg/kg/ 2 weeks	1) Temozolo-mide+CPPD (1) followed by RTH	2	Progression and death	Pneumonia (3)
8	17.9/M	3	Cerebellar medullo-blastoma	No classification	Unknown	NIVO 3 mg/kg/ 2 weeks	1) CBDCA+ VP-16+VCR+ CTX (4), RTH, VCR+CPPD+ CCNU (8)	4	Progression and death	None
9	15.9/M	1	Nodular sclerosis classical Hodgkin lymphoma	IV (Ann Arbor)	Unknown	NIVO 3 mg/kg/ 2 weeks	1) OEPA (2), COPDAC (2) 2) BV+IEP (4), BV+IGEV (1), BV+ABVD (2)	8	CR (OS=22.7 months)	None
10	17.9/F	2	Localized extrasceletal chondro-sarcoma myxoidale	No classification	Unknown	NIVO 3 mg/kg/ 2 weeks	1) Treatment based on EURO-EWING 2012 protocol 2) Treatment based on CWS-EFS program 3) Irinotecan+ Temozolomide	2	Progression and death	None

F: Female, M: male, NIVO: Nivolumab, IPI: Ipilimumab, VP-16: Etoposide, DTIC: Dacarbazine, IVADo: Ifosfamide, Vincristine, Doxorubicin, Dactinomycin, RTH: radiotherapy, CPPD: Cisplatin, CBDCA: Carboplatin, VCR: Vincristine, CTX: Cyclophosphamide, CCNU: Lomustine, OEPA: Vincristine (Oncovin), Etoposide, Prednisone, Doxorubicin (Adriamycin), COPDAC: Cyclophosphamide, Vincristine (Oncovin), Dacarbazine, Prednisone, BV: Brentuximab vedotin, IEP: Ifosfamide, Epirubicin, Cisplatin, IGEV: Ifosfamide, Gemcitabine, Vinorelbine, ABVD: Doxorubicin (Adriamycin), Bleomycin, Vinblastine, Darcarbazine, CR: complete remission.

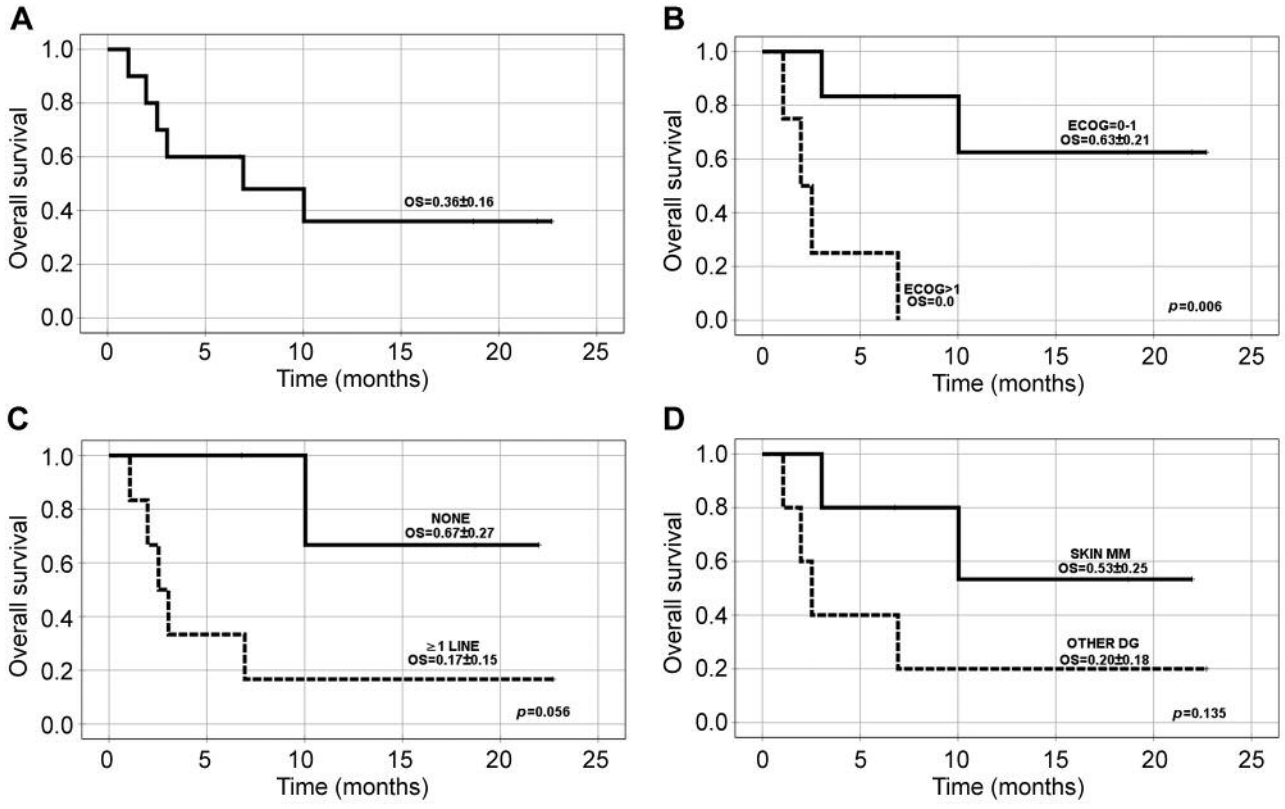

Figure 1. *Overall survival: (A) for the entire group; (B) depending on ECOG score; (C) depending on number of previous lines of therapy; (D) depending on primary diagnosis.*

Discussion

This study adds information to real-world data on the use of nivolumab for treatment of advanced pediatric malignancies. So far, such data are sparse. Davis *et al*. reported the results of a pediatric phase 1-2 trial on nivolumab monotherapy in 85 children and young adults with recurrent or refractory lymphoma and non-CNS solid tumors. The most common overall toxicities observed in the study were anemia (47%) and fatigue (37%). Responses were observed in patients with lymphoma (3/10 with Hodgkin lymphoma and 1/10 with non-Hodgkin lymphoma), but not in other cancer types (9). Besides, only several case reports of nivolumab and other anti-PD1 drugs use in children are available (10-15). More data exist on the treatment of adult patients.

In the study of 945 adult patients with stage III or IV of malignant melanomas, treated with nivolumab and/or ipilimumab, sustained 5-year OS was observed in 52% patients on nivolumab+ipilimumab, 44% on nivolumab alone, and 26% on ipilimumab alone (16). It seems that in our study group, immunotherapy was beneficial mainly for patients with advanced malignant melanomas of the skin. Complete remission rate of 60% in our melanoma patients was within the range of best outcomes in adults.

Momotow *et al*. analyzed the existing favorable efficacy and safety profile of PD1-blockade in the study of 30 relapsed/refractory classical Hodgkin lymphoma (r/r cHL) patients treated with nivolumab. They showed that a durable response after treatment with nivolumab might be achieved by consolidating stem cell transplantation (SCT) (17). Lepik *et al*. reported the results of experience with nivolumab in 99 adult r/r cHL patients. Complete response was achieved in 67.7% cases, and the response rate was comparable across two treatment groups: after autologous SCT (ASCT) and in ASCT-naïve patients (18). The results of the meta-analysis of 7 studies revealed that nivolumab increases the survival rate of patients with r/r cHL and its various histopathologic subtypes (19). In our study, one patient was treated for r/r cHL. Successful immunotherapy with nivolumab was preceded by treatment with brentuximab vedotin, and ASCT was performed in this patient after eight cycles of nivolumab. He is in complete remission 18-month from completing treatment.

Gorsi *et al*. analyzed 10 children (age 2-17 years) with refractory/recurrent brain tumors treated with nivolumab.

Three patients (2 with high-grade glioma and 1 with CNS embryonal tumor) had a partial radiographic response to immunotherapy. PD-L1 expression status was assessed, and the median time to progression on nivolumab for PD-L1 positive individuals was 13.7 weeks, when compared with 4.2 weeks for PD-L1 negative patients (14).

Our study has obvious limitations. Even with this pediatric cases series, the number of patients was relatively low and heterogenous. We did not evaluate PD-L1 expression in tumor cells. Still emerging is the identification of a reliable biomarker or panel of targeting the PD-1 pathway in pediatric brain tumors and other solid tumors that can allow appropriate patient selection. Available data suggest that PD-L1 expression on tumor cells, an increased mutational burden and a strong lymphocytic presence in the tumor microenvironment, are significant but not yet definitive markers that predict its efficacy. These properties are variably present in some high-risk pediatric tumors, and support further research of PD-1-targeted therapy. Data from adult studies show that the presence or absence of these biomarkers does not guarantee the success or failure of this therapeutic strategy (20, 21). Although off-label use is tempting for individuals with recurrent or refractory cancers, caution should be taken in light of the still unproven benefit of these drugs for pediatric tumors, and the potential for organ toxicity related to immune effects. Trials are underway, which will better define the role these agents in pediatric cancers, either as single inhibitors or in combination with chemotherapy, radiation, or other molecularly targeted therapies (22).

The drugs were well tolerated, however there are some pitfalls of using nivolumab +/– ipilimumab immunotherapy, related to possible adverse events of immunological background, as well as infectious complications. In spite of relatively good efficacy, these drugs are not yet adopted as standard practice in pediatric oncology due to lack of clinical data and lack of clinical trials, related to rarity of pediatric cases. Still, the knowledge on the pharmacokinetics of new oncological medications in children is limited.

In conclusion, the treatment with nivolumab +/– ipilimumab is a promising approach in advanced pediatric malignancies. This immunotherapy is well tolerated and safe for pediatric patients, and side-effects are manageable. In our series best results were observed for patients with good performance status, no previous therapy, and skin melanoma. Since some clinical trials indicate a correlation between the PD-L1 expression on cancer cells and response to the PD-1 inhibitors, possibly limiting anti-PD-1 agent administration to the patients expressing PD-L1 may result in better therapeutic effect in pediatric tumors. Further studies are needed to evaluate the efficacy of checkpoint blockade in pediatric setting.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Design of the study: AM, JS. Data collection and analysis: all authors. Manuscript writing: AM, MD, BDB, JS. Critical revision and final approval: all authors.

References

1 Tarhini A, Lo E and Minor DR: Releasing the brake on the immune system: Ipilimumab in melanoma and other tumors. Cancer Biother Radiopharm *25(6)*: 601-613, 2010. PMID: 21204754. DOI: 10.1089/cbr.2010.0865

2 Czarnecka AM and Rutkowski P: An update on the safety of nivolumab for the treatment of advanced melanoma. Expert Opin Drug Saf *19(4)*: 409-421, 2020. PMID: 32293935. DOI: 10.1080/14740338.2020.1757068

3 Malesa A, Nowak J, Skórka K, Karp M and Giannopoulos K: Monoclonal antibodies against PD-1/PD-L1 pathway. Acta Haemat Pol *49(4)*: 207-227, 2018. DOI: 10.2478/ahp-2018-0025

4 Rotte A: Combination of CTLA-4 and PD-1 blockers for treatment of cancer. J Exp Clin Cancer Res *38(1)*: 255, 2019. PMID: 31196207. DOI: 10.1186/s13046-019-1259-z

5 Savoia P, Astrua C and Fava P: Ipilimumab (anti-CTLA-4 Mab) in the treatment of metastatic melanoma: Effectiveness and toxicity management. Hum Vaccin Immunother *12(5)*: 1092-1101, 2016. PMID: 26889818. DOI: 10.1080/21645515.2015.1129478

6 OPDIVO. Available at: https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf [Last accessed on 29th October 2020]

7 Clinical trials. Available at: https://clinicaltrials.gov/ct2/results?cond=&term=nivolumab&cntry=&state=&city=&dist= [Last accessed on 29th October 2020]

8 Onesti CE, Freres P and Jerusalem G: Atypical patterns of response to immune checkpoint inhibitors: Interpreting pseudoprogression and hyperprogression in decision making for patients' treatment. J Thorac Dis *11(1)*: 35-38, 2019. PMID: 30863564. DOI: 10.21037/jtd.2018.12.47

9 Davis KL, Fox E, Merchant MS, Reid JM, Kudgus RA, Liu X, Minard CG, Voss S, Berg SL, Weigel BJ and Mackall CL: Nivolumab in children and young adults with relapsed or refractory solid tumours or lymphoma (advl1412): A multicentre, open-label, single-arm, phase 1-2 trial. Lancet Oncol *21(4)*: 541-550, 2020. PMID: 32192573. DOI: 10.1016/S1470-2045(20)30023-1

10 Marjanska A, Galazka P, Marjanski M, Wysocki M and Styczynski J: Efficacy and toxicity of pembrolizumab in pediatric metastatic recurrent melanoma. Anticancer Res *39(7)*: 3945-3947, 2019. PMID: 31262925. DOI: 10.21873/anticanres.13547

11 Bose S, Robles J, McCall CM, Lagoo AS, Wechsler DS, Schooler GR and Van Mater D: Favorable response to nivolumab in a young adult patient with metastatic histiocytic sarcoma. Pediatr Blood Cancer *66(1)*: e27491, 2019. PMID: 30270506. DOI: 10.1002/pbc.27491

12 Samoa RA, Lee HS, Kil SH and Roep BO: Anti-PD-1 therapy associated type 1 diabetes in a pediatric patient with relapsed classical Hodgkin lymphoma. Diabetes Care, 2020. PMID: 32616607. DOI: 10.2337/dc20-0740

13 Foran AE, Nadel HR, Lee AF, Savage KJ and Deyell RJ: Nivolumab in the treatment of refractory pediatric Hodgkin lymphoma. J Pediatr Hematol Oncol *39(5)*: e263-e266, 2017. PMID: 27841828. DOI: 10.1097/MPH.0000000000000703

14 Gorsi HS, Malicki DM, Barsan V, Tumblin M, Yeh-Nayre L, Milburn M, Elster JD and Crawford JR: Nivolumab in the treatment of recurrent or refractory pediatric brain tumors: A single institutional experience. J Pediatr Hematol Oncol *41(4)*: e235-e241, 2019. PMID: 30681550. DOI: 10.1097/MPH.0000000000001339

15 Ehlert K, Hansjuergens I, Zinke A, Otto O, Siebert N, Henze G and Lode H: Nivolumab and dinutuximab beta in two patients with refractory neuroblastoma. J Immunother Cancer *8:* e000540, 2020. PMID: 32414861. DOI: 10.1136/jitc-2020-000540.

16 Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, Cowey CL, Schadendorf D, Wagstaff J, Dummer R, Ferrucci PF, Smylie M, Hogg D, Hill A, Marquez-Rodas I, Haanen J, Guidoboni M, Maio M, Schoffski P, Carlino MS, Lebbe C, McArthur G, Ascierto PA, Daniels GA, Long GV, Bastholt L, Rizzo JI, Balogh A, Moshyk A, Hodi FS and Wolchok JD: Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med *381(16)*: 1535-1546, 2019. PMID: 31562797. DOI: 10.1056/NEJMoa1910836

17 Momotow J, Goergen H, Behringer K, Brockelmann PJ, Borchmann S, Tresckow BV, Kobe C, Engert A and Sasse S: Nivolumab in relapsed/refractory classical Hodgkin lymphoma - extended follow-up of 30 patients treated within the checkmate 205 trial in a single-center. Hemasphere *3(5)*: e293, 2019. PMID: 31942546. DOI: 10.1097/HS9.0000000000000293

18 Lepik KV, Mikhailova NB, Moiseev IS, Kondakova EV, Tsvetkova LA, Zalyalov YR, Borzenkova ES, Babenko EV, Baykov VV, Markova IV and Afanasyev BV: Nivolumab for the treatment of relapsed and refractory classical Hodgkin lymphoma after asct and in asct-naive patients. Leuk Lymphoma *60(9)*: 2316-2319, 2019. PMID: 30712423. DOI: 10.1080/10428194.2019.1573368

19 Amraee A, Evazi MR, Shakeri M, Roozbeh N, Ghazanfarpour M, Ghorbani M, Ansari J and Darvish L: Efficacy of nivolumab as checkpoint inhibitor drug on survival rate of patients with relapsed/refractory classical Hodgkin lymphoma: a meta-analysis of prospective clinical study. Clin Transl Oncol *21(8)*: 1093-1103, 2019. PMID: 30739242. DOI: 10.1007/s12094-018-02032-4

20 Ando K, Hamada K, Watanabe M, Ohkuma R, Shida M, Onoue R, Kubota Y, Matsui H, Ishiguro T, Hirasawa Y, Ariizumi H, Tsurutani J, Yoshimura K, Tsunoda T, Kobayashi S and Wada S: Plasma levels of soluble pd-l1 correlate with tumor regression in patients with lung and gastric cancer treated with immune checkpoint inhibitors. Anticancer Res *39(9)*: 5195-5201, 2019. PMID: 31519633. DOI: 10.21873/anticanres.13716

21 Inomata M, Kado T, Okazawa S, Imanishi S, Taka C, Kambara K, Hirai T, Tanaka H, Tokui K, Hayashi K, Miwa T, Hayashi R, Matsui S and Tobe K: Peripheral PD1-positive CD4 T-lymphocyte count can predict progression-free survival in patients with non-small cell lung cancer receiving immune checkpoint inhibitor. Anticancer Res *39(12)*: 6887-6893, 2019. PMID: 31810958. DOI: 10.21873/anticanres.13908

22 Wagner LM and Adams VR: Targeting the pd-1 pathway in pediatric solid tumors and brain tumors. Onco Targets Ther *10:* 2097-2106, 2017. PMID: 28442918. DOI: 10.2147/OTT.S124008

Received October 7, 2020
Revised October 26, 2020
Accepted October 30, 2020