Leading Opinions

Hämatologie & Onkologie

März 2021

Sonderpublikation

Meet the Experts:

Successful Treatment of Melanoma & Renal Cell Carcinoma

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Nivolumab & ipilimumab

Successful treatment of melanoma and renal cell carcinoma

As immunotherapy is advancing based on the development of new agents and refined ways of administration, nivolumab (Opdivo®) and ipilimumab (Yervoy®) have remained first-line treatment pillars for melanoma and renal cell cancer. Patient cases demonstrate the efficacy and manageability of these drugs that offer long-term survival in many patients.

On January 19, 2021, the interactive workshop on Swiss patient cases in the field of immunotherapies "Meet the experts" took place as a virtual event. This workshop is conducted at least once annually and provides a platform for exchange between physicians, particularly regarding treatment challenges and side effect management.

This publication summarizes three cases presented at the workshop and two independent cases exemplifying the management of patients with advanced melanoma or renal cell carcinoma (RCC). All of them received combination immunotherapy with the PD-1 inhibitor nivolumab (Opdivo®) and the CTLA-4 inhibitor ipilimumab (Yervoy®).

Synergy within the cancer-immunity cycle

Dual checkpoint inhibition with nivolumab and ipilimumab is based on a sound scientific rationale as it gives rise to potentially synergistic effects. The CTLA-4 and PD-1 immune checkpoints are negative regulators of T-cell immune function, with distinct roles in inhibiting immune responses including antitumor responses.[1] Correspondingly, agents blocking different steps in the cancer-immunity cycle[2] can heighten the benefits of checkpoint inhibition. While ipilimumab supports the activation and proliferation of effector T cells, nivolumab restores their function in the periphery.[1]

CheckMate 067: Over 50 % survival rate at 5 years

In the setting of metastatic melanoma, the pivotal phase III CheckMate 067 study has demonstrated the efficacy of first-line checkpoint inhibition. Patients with untreated advanced melanoma were randomized to either nivolumab plus ipilimumab, nivolumab monotherapy, or ipilimumab monotherapy. Initial and follow-up analyses showed significantly higher response rates as well as longer progression-free survival and overall survival (OS) with nivolumab plus ipilimumab or with nivolumab monotherapy compared to ipilimumab alone.[3–5]

According to the 5-year update of CheckMate 067, median OS exceeded 60.0 months in the combination arm while it was 36,9 months for nivolumab and 19,9 months for ipilimumab.[6] More than half of patients receiving nivolumab plus ipilimumab were alive at 5 years; at that time, the OS rates amounted to 52 %, 44 % and 26 % for the combination, nivolumab and ipilimumab, respectively. Notably, long-term survival was obtained regardless of the BRAF mutation status. The 5-year rate was even 60 % for the subgroup with a BRAF mutation who received dual checkpoint inhibition. Late treatment-related adverse events were consistent with the known safety profiles of nivolumab and ipilimumab.

Four-year update of CheckMate 214

The approval of nivolumab plus ipilimumab for the first-line treatment of patients with advanced RCC and IMDC (International Metastatic Renal-Cell Carcinoma Database Consortium) intermediate/poor (I/P) risk was based on the randomized, phase III CheckMate 214 trial. Compared to sunitinib, nivolumab plus ipilimumab showed superiority with respect to OS (HR, 0,63; p <0,001) and objective response rates (42 % vs. 27 %; p<0,001) in the I/P population.[7] These benefits persisted over time. The 4-year analysis, which represents the longest follow-up for any first-line IO in the setting of advanced RCC, revealed that 50 % of immunotherapy-treated patients with I/P risk were alive at 48 months (vs. 35,8 % with sunitinib).[8] Median duration of response had not been reached yet in the experimental arm and was 19,7 months in the control arm.

Importantly, nivolumab plus ipilimumab also continued to show improved health-related quality of life compared to

KEYPOINTS

- *In the patient cases presented here, nivolumab plus ipilimumab induced potent tumor regression including long-term disease stabilization and complete remission*
- *Responses occurred at different paces, with complete remission being achieved within two cycles in some patients and after extended periods in others*
- *Mixed responses or slight increases in tumor size on treatment are not unusual and do not necessarily indicate treatment failure*
- *Stereotactic body radiotherapy can be added to control oligometastatic disease*
- *Immune-related side effects including hepatitis and pneumonitis proved manageable. The patient susceptibility with respect to the emergence of these adverse events varies considerably and needs to be accounted for in the long-term management*

sunitinib with significant differences using the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-19) total score to asses patient-reported outcomes.[9] ■

Medical writer of the publication:
Judith Moser, MD

Literature:

1 Buchbinder EI, Desai A: CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. Am J Clin Oncol 2016; 39(1): 98-106 **2** Chen DS, Mellman I: Oncology meets immunology: the cancer-immunity cycle. Immunity 2013; 39(1): 1-10 **3** Larkin J et al.: Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015; 373(1): 23-34 **4** Wolchok JD et al.: Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2017; 377(14): 1345-56 **5** Hodi FS et al.: Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol 2018; 19(11): 1480-92 **6** Larkin J et al.: Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2019; 381(16): 1535-4 **7** Motzer RJ et al.: Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018; 378(14): 1277-90 **8** Albiges L et al.: Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. ESMO Open 2020; 5(6): e001079 **9** Cella D et al.: Time to deterioration in quality of life in previously untreated patients with advanced renal cell carcinoma in CheckMate 214. Ann Oncol 2020; 31(Suppl 4): S562

Melanoma case report 1

Long-term remission in a young patient

C. Lamos, Bern

Rapidly progressing relapse

A woman in her late thirties was diagnosed with low-risk, non-ulcerated melanoma of her right thigh in May 2016 (pT1a cN0 cM0). The tumor depth was 0,76 mm according to Breslow, and the mitosis index was < 1/mm^2. Almost three years after resection, in February 2019, an induration of the right inguinal region prompted PET/CT assessment that revealed subcutaneous melanoma recurrence of the thigh sized approximately 16 mm, as well as lymph node metastases in the right inguinal region with a diameter of up to 33 mm. Fine needle aspiration confirmed the relapse.

The tumor board recommended completion lymph-node dissection (CLND) followed by adjuvant immunotherapy with a PD-1 inhibitor. CLND performed in March 2016 demonstrated that 4 out of 6 lymph nodes contained tumor tissue. Mutation testing showed BRAFV600E positivity. However, adjuvant therapy was forestalled by progression as multiple subcutaneous nodules erupted on the trunk and extremities in April. In addition, PET/CT yielded bone lesions in both femurs and tibiae as well as intra-pancreatic lesions and metastases located in the mammary parenchyma.

VGPR after mixed response

On May 3rd, 2019, combined immunotherapy with ipilimumab and nivolumab was initiated. The planned schedule included 4 cycles followed by nivolumab monotherapy every 2 weeks according to the CheckMate 067 trial regimen. In the beginning of June, the patient reported pain in her left eye without any other symptoms. Cranial MRI revealed an intraorbital lesion in the lower antero-lateral corner of the socket (Fig. 1). During the same month, the subcutaneous nodules clearly responded to the therapy, which was continued according to the schedule.

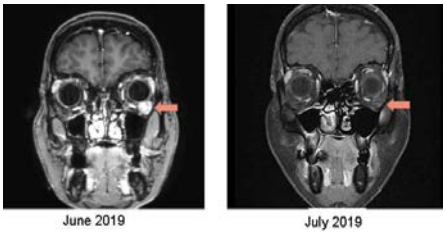


Fig. 1: Almost complete resolution of the intraorbital metastasis within two months after treatment initiation with nivolumab plus ipilimumab

In July 2019, the patient developed immune-mediated hepatitis grade 3 with increased liver enzymes (ASAT: 399 U/L; ALAT: 464 U/L; total bilirubin: 5µmol/L; LDH: 872 U/L) that necessitated discontinuation of the combination regimen after 3 cycles. High-dose corticosteroid treatment was started with prednisolone 1 mg/kg, and the patient responded quickly.

The first staging assessment after the initiation of immunotherapy conducted at the end of July yielded predominantly regressive findings with infrequent and low metabolic activity of the known metastases. Only one new subcutaneous lesion had erupted on the right thigh. According to cranial MRI, the size of the intraorbital metastasis had decreased considerably (Fig. 1). Overall, the patient response was classified as very good partial remission.

Management of pneumonitis

Switching to BRAF inhibitor therapy was discussed at this point, but it was decided to start single-agent nivolumab after three cycles of combination therapy. In September 2019, the patient developed symptoms indicative of immune-mediated pneumonitis; these included cough without discharge and exercise-induced dyspnea in the absence of fever. The chest CT demonstrated nodular ground glass opacities with subpleural fibrotic parts in both lungs, which was consistent with pneumonitis. Nivolumab was discontinued after four cycles, and the patient was transferred to the pulmonology department. Lung function testing in October showed reduced dynamic lung volumes with slightly decreased diffusion capacity. Forced expiratory volume in the first second (FEV1) was 2.17 L (78 % predicted), forced vital capacity (FVC) 2.66 L (76 % predicted), and diffusion capacity of carbon monoxide (DLCO) 64 %. The patient received steroid therapy with prednisone at an initial dose of 40 mg/d. From the end of October, Pneu-

mocystis carinii pneumonia (PCP) prophylaxis was administered together with prednisone 1 mg/kg that was tapered off over the course of 3 months.

In January 2020, the lung volumes had been restored to normal and the patient reported no symptoms, although slightly reduced diffusion capacity remained. Lung function testing in February 2020 showed FEV1 of 2.41 L (86 % predicted), FVC of 3.22 L (94 % predicted), and DLCO of 73 %.

Sustained complete tumor regression

When the PET/CT staging in October 2019 demonstrated complete remission for the first time, the tumor board suggested discontinuation of immunotherapy considering its pronounced efficacy in this patient and her increased risk of immune-mediated adverse events. Indeed, the treatment was stopped, and no relapses have occurred to date. The PET/CT follow-up until January 2021 has shown continued complete morphological and metabolic regression of the previously metabolically active metastases.

Overall, checkpoint inhibition has undoubtedly revolutionized oncology. However, a number of immune-related adverse events can occur, especially with combination therapies. Toxicities also emerge earlier with combined treatment than with monotherapy regimens, although a wide range has been observed here.[1] Side effects require appropriate attention and should be detected early on. Nevertheless, the field of immunotherapy is incessantly evolving as novel regimens are being explored, as well as different settings and combinations with various other treatments. ■

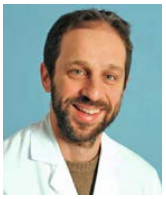
Case presented by:
Cristina Lamos, MD
Department of Dermatology
University Hospital of Bern, Switzerland

Literature:

1 Haanen JBAG et al.: Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28(suppl_4): iv119-42

Melanoma case report 2

Repeated excellent responses



Y. Metaxas, Chur

First-line consideration: targeted treatment vs. immunotherapy

In September 2016, a patient aged above 60 in good condition presented with acute dyspnea and a large mediastinal mass according to chest x-ray. She had a history of malignant melanoma that had been treated 6 years earlier (pT1a, stage IA). Computed tomography now showed a large tumor suggestive of lung cancer (Fig. 2), although the analysis of tissue obtained via bronchoscopy revealed malignant melanoma which was BRAFV600E-positive and PD-L1–negative.

This case presentation included questions to the audience who had the possibility to vote. Regarding the choice of initial treatment, it was obvious that each of the options discussed had its pros and cons. Combined BRAF and MEK inhibition conveys the advantage of rapid treatment response,[1,2] which might be particularly helpful in this case considering that the patient was symptomatic. Immunotherapy, on the other hand, appears to work better when administered prior to targeted treatment with BRAK and MEK inhibitors.[3] The patient's willingness to accept the risk of increased toxicity in favor of expected higher efficacy was mentioned as a major factor influencing the decision between single-agent and combination immunotherapy. If immunotherapy represents the treatment of choice, lack of PD-L1 expression, from the presenter's point of view, is an argument for the combination rather than for checkpoint inhibition monotherapy.

Two efficacious immunotherapy treatment cycles

BRAF plus MEK inhibition was started in October 2016 with the objective of reducing the patient's symptom burden. The treatment induced partial remission, which was followed by disease stabilization. However, progression occurred in May 2017, and the patient was switched to nivolumab plus ipilimumab. At that time, the large thoracic lesion was still present according to imaging. Three months and two cycles of nivolumab plus ipilimumab later, computed tomography showed complete remission (Fig. 2).

However, grade 2 skin toxicity emerging after each of these two cycles necessitated treatment breaks. Moreover, the patient developed grade 2 pneumonitis after cycle 2. The adverse events did not pose major medical challenges as they proved to be manageable. Cortisone treatment was initiated in addition to temporary immunotherapy discontinuation, and complete recovery ensued.

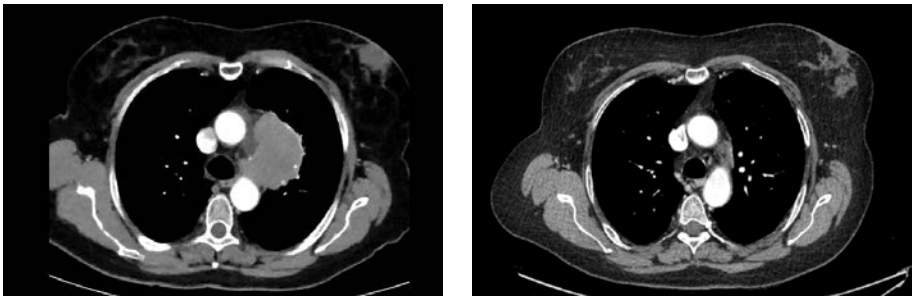


Fig. 2: Large mediastinal mass in September 2016 (left) and complete remission after two cycles of nivolumab plus ipilimumab in August 2017 (right)

After that, the treatment was stopped altogether based on the consideration that further side effects might outweigh the benefits of resumed immunotherapy. However, the discussion at the workshop showed that continued administration of either nivolumab plus ipilimumab or nivolumab alone was also regarded as a valuable option by the experts.

Reinduction of complete remission

In December 2017, imaging yielded progressive disease in the pleura, mediastinum, and lymph nodes. Immunotherapy with single-agent nivolumab was restarted because of the anticipated excellent patient response and the prospect of long-term disease control provided by checkpoint inhibitors in general. Still, ipilimumab rechallenge was avoided to decrease the risk of toxicity.

Nivolumab monotherapy reinduced complete remission that has been ongoing ever since. The patient is still on treatment and has not experienced any side effects. When asked about their opinion on whether to stop immunotherapy or to continue nivolumab until progression, the audience favored treatment continuation. ■

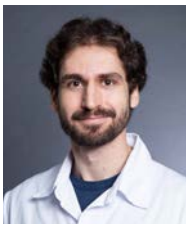
Case presented by:
Yannis Metaxas, MD
Kantonsspital Graubünden
Chur, Switzerland

Literature:

1 Long GV et al.: COMBI-d: A randomized, double-blinded, Phase III study comparing the combination of dabrafenib and trametinib to dabrafenib and trametinib placebo as first-line therapy in patients (pts) with unresectable or metastatic BRAFV600E/K mutation-positive cutaneous melanoma. BMC Cancer 2017; 17(1): 649 **2** Grob JJ et al.: Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial. Lancet Oncol 2015; 16(13): 1389-9 **3** Tétu P et al.: Benefit of the nivolumab and ipilimumab combination in pretreated advanced melanoma. Eur J Cancer 2018; 93: 147-149

RCC case report 1

Immunotherapy in conjunction with stereotactic irradiation



A. Friedlaender, Geneva

Local treatment for isolated lesions

When a man who was in his sixties was assessed for an anal abscess in January 2017, imaging showed a large tumor of his left kidney. The patient underwent nephrectomy and was diagnosed with clear-cell RCC, pT3a (6,5 cm), G2. No other evidence of disease was found.

Two years later, in March 2019, CT was performed because the patient reported pain. This assessment revealed multiple bone lesions of the vertebrae and ribs, as well as bilateral lung metastases. The patient's IMDC risk was classified as intermediate (2 points) based on slightly elevated calcium levels and platelet counts. In April 2019, combined immunotherapy with ipilimumab and nivolumab according to the CheckMate 214 schedule was started. Four cycles of induction were followed by nivolumab maintenance. After the completed induction phase, imaging demonstrated partial response of all bone lesions including a large costal lesion (Fig. 3). The pulmonary lesions had completely disappeared.

In November 2019, the patient became symptomatic again while he was on nivolumab maintenance. CT showed that the size of the costal lesion had almost doubled. Stereotactic body radiotherapy (SBRT) at a dose of 35 Gy was administered in five fractions, leading to local control with significant shrinkage. No new metastases had appeared according to CT in February 2020, although progression of a single sacral lesion became apparent at that time. Therefore, SBRT at a dose of 30 Gy in five fractions was administered in March 2020, while biweekly nivolumab treatment was maintained. The latest CT performed in December 2020 showed stable bone disease in the absence of any other metastases. Nivolumab treatment every 2 weeks is ongoing.

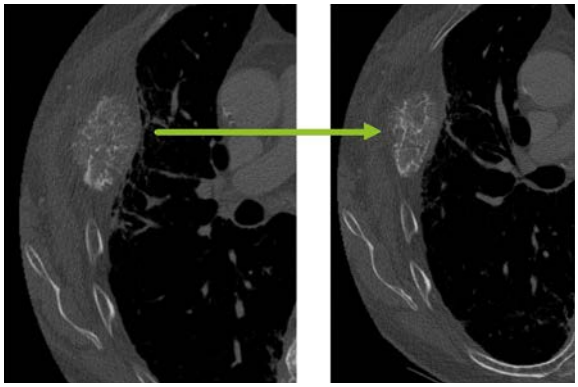


Fig. 3: Partial remission of a large costal lesion after four cycles of combined immunotherapy

Expert opinion: data on SBRT in oligoprogression

The patient described here experienced oligoprogression, which has been defined by Hellman et al. as progression of up to 3–5 lesions after an initial response.[1] It is assumed that these "rogue" lesions have a different biology based on the acquisition of mutations that differ from those found in metastases that are under control.[2] This provides the rationale for local ablative therapy such as radiotherapy or surgery with the goal of preventing the wider spread of these treatment-resistant clones, thus prolonging time to treatment failure.[3]

Data on the role of irradiation in oligoprogressive RCC are scant. Several retrospective trials have been published, such as the study by Santini et al. that showed an OS benefit due to local ablative therapy (i.e., radiotherapy, surgery) in patients treated with tyrosine kinase inhibitors.[4] Among prospective studies, a Canadian multicenter phase II trial assessing the safety and impact of SBRT on patients with metastatic RCC treated with sunitinib or pazopanib who had up to five progressing metastases was recently completed (NCT02019576). This demonstrated that median time to treatment failure was extended by approximately 1 year, while no patient experienced grade 3–5 toxicity.[5] The randomized, phase II GETUG-StORM-01 study is currently evaluating SBRT compared to continuing active therapy alone in patients with up to 3 lesions in up to 2 organs (NCT04299646). GETUG-StORM-01 will also provide data on the use of SBRT in patients treated with immunotherapy.

Overall, SBRT appears to be an advantageous approach for the treatment of oligoprogressive metastatic RCC. Although evidence from trials is currently limited, irradiation offers a good additional option with low toxicity.[6] ■

Case presented by:
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Geneva, Switzerland

Literature:

1 Hellman S et al.: Oligometastases. J Clin Oncol 1995; 13(1): 8-10 **2** Gerlinger M et al.: Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med 2012; 366(10): 883-92 **3** Weickhardt AJ et al.: Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. J Thorac Oncol 2017; 7(12): 1807-14 **4** Santini D et al.: Outcome of oligoprogressing metastatic renal cell carcinoma patients treated with locoregional therapy: a multicenter retrospective analysis. Oncotarget 2017; 8(59): 100708-16 **5** Cheung P et al.: A phase II multicenter study of stereotactic radiotherapy (SRT) for oligoprogression in metastatic renal cell cancer (mRCC) patients receiving tyrosine kinase inhibitor (TKI) therapy, J Clin Oncol 2020; 38(15_suppl): 5065 **6** Meyer et al., Stereotactic radiation therapy in the strategy of treatment of metastatic renal cell carcinoma: A study of the Getug group. Eur J Cancer 201; 98: 38-47

RCC case report 2

Long-term stable disease and manageable adverse events

P. von Burg, Solothurn

Stabilization of disease burden with immunotherapy

A female patient in her late sixties was admitted to the hospital due to rapidly increasing left-sided back pain in December 2018. Computed tomography showed a tumor of her left kidney sized 7 x 8 x 8 cm that was infiltrating the adjacent tissue and had already caused grade 1 urine retention. Additional findings included local lymphadenopathy and lesions of both lungs that indicated metastatic spread. In January 2019, transabdominal nephrectomy was performed. Histology showed clear-cell RCC with a maximum diameter of 9 cm, as well as nodular infiltration of the peritoneum. The tumor stage was classified as pT3a cN+ pM1 (PER) L0 V1 Pn0. According to the IMDC score, the patient had intermediate risk.

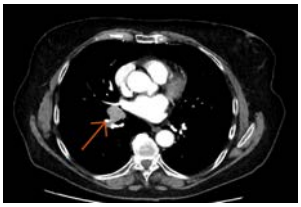

Fig. 4: Stable disease according to chest CT in February 2020: the arrow indicates the largest lesion (approximately 3 x 2 cm)

IO treatment with ipilimumab plus nivolumab was commenced in February 2019. In mid-April, after three cycles of combined checkpoint inhibition, computed tomography showed slight increases in the number and size of some of the pulmonary lesions, as well as progressive lymphadenopathy of possible inflammatory origin in the mediastinum and the hilum of the lung. Metastatic affliction of these lymph nodes was deemed unlikely. The tumor board recommended continuation of treatment, and all of the four planned cycles of nivolumab and ipilimumab were administered. This treatment did not elicit any adverse events. From April 2019, the patient received single-agent nivolumab.

Reactivation of psoriatic arthritis

Two months later, in June 2019, the patient underwent CT after four cycles of nivolumab monotherapy. At that time, one lymph node showed slightly increased size, while no other evidence of localized or distant disease was observed. According to Response Evaluation Criteria In Solid Tumors (RECIST), these findings were classified as stable disease, and the treatment with nivolumab was continued as recommended by the tumor board.

In October 2019, the patient experienced reactivation of her psoriatic arthritis that had initially been diagnosed in 2008 and had been in remission for years after successful treatment with methotrexate. Now she reported swelling and severe pain of both wrists as well as pain at the back of her neck radiating to the shoulder girdle. A rheumatologist was consulted, and the patient received topical steroid injections. The use of systemic immunosuppressants was avoided.

Long-term stability on nivolumab therapy

Imaging of the chest and abdomen performed at the end of November 2019 continued to show no evidence of local recurrence or incident metastases. Stable disease was present despite slight progression of the lymph nodes at the right hilum. The tumor board recommended continua-

tion of IO and follow-up imaging after 3 months. By the end of February 2020, the patient had received 23 cycles of nivolumab monotherapy. Again, CT was devoid of any signs of progression, while a lymph node at the hilum of the lung had slightly decreased in size and the lesions in the right lung showed stable diameters of 2,5–3 mm (Fig. 4). These findings were unchanged according to computed tomography conducted in June 2020.

The patient was seen again by the rheumatologist in July 2020 due to intermittent, multifocal psoriatic arthritis. Topical steroid injections were applied. In January 2021, the patient received her 47nd cycle of nivolumab monotherapy. Imaging again revealed stable disease. The follow-up is ongoing. ■

Case presented by:
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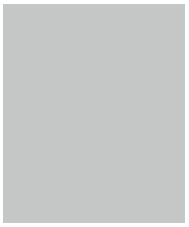
Solothurn, Switzerland

RCC case report 3

Pain relief and complete responses within 10 months



Y. Buccella, Zürich

Unusual location of distant metastases

Clear-cell RCC of the right kidney that had spread to the pancreas was diagnosed in September 2013 in a woman who was in her mid-forties. The disease was classified as pT2a, pN0 (0/11), pM1, Fuhrmann grade III. In October 2013, laparoscopic nephrectomy was performed. In the following month, multiple pancreatic lesions made pancreatectomy and splenectomy necessary, which gave rise to type 1 diabetes mellitus.

Four years later, in January 2018, the patient underwent resection of 7 pulmonary metastases located across both lungs. A tumor of her left kidney was identified in spring 2018, in addition to lesions affecting the soft tissue of the left gluteal region. In June, thermoablation of the kidney tumor and ultrasound-guided tumor resection of the gluteal subcutaneous lesions were performed.

Stable disease ensued as demonstrated by CT in September 2018. This slowly began to change early in 2019, when imaging showed slight progression of the soft tissue lesion located in the right-sided gluteal region and emergence of a 3 mm-sized metastasis of the left lung. By September 2019, progression was obvious with respect to the pulmonary lesions and soft tissue metastasis of the right gluteal region that had eroded the iliac bone and was infiltrating the iliacus muscle (Fig. 5). The patient reported severe pain. Also, a new lesion had erupted in the left gluteal region.

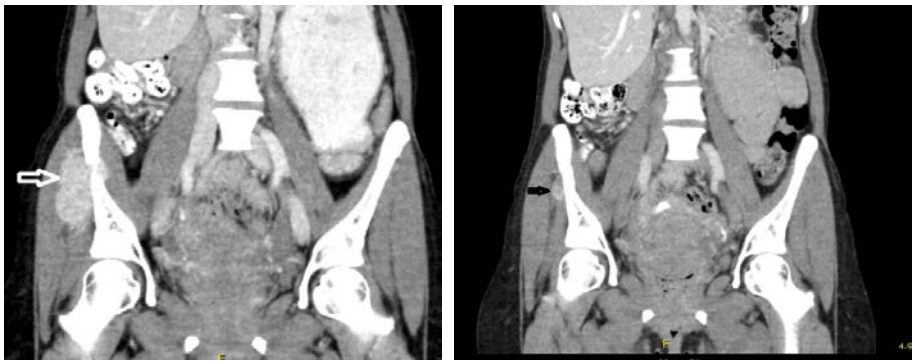


Fig. 5: Destruction of the right iliac bone due to a soft tissue lesion in September 2019 (left); remission in August 2020 (right)

Effective and well-tolerated systemic therapy

Because the patient's IMDC risk profile was classified as intermediate due to the presence of thrombocytosis, treatment with nivolumab plus ipilimumab was initiated in October 2019. The patient received all four cycles until December and continued with nivolumab monotherapy in January 2020. In February, CT yielded partial regression of the pulmonary lesions. Also, the right-sided gluteal soft tissue metastasis was shrinking, with diminished infiltration of the bone and muscle. No change had occurred concerning the left-sided gluteal region. The patient reported resolution of all her symptoms in June 2020. Imaging conducted in August demonstrated partial or complete remissions of the soft tissue tumors (Fig. 5). The pulmonary lesions had decreased in size or assumed a stable appearance.

No adverse events related to immunotherapy occurred throughout the treatment, neither during induction with dual checkpoint inhibition nor during the monotherapy phase. In January 2020, the patient still continues to receive single-agent nivolumab. ■

Case presented by:
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Clinic of Medical Oncology and Hematology
Stadtspital Waid und Triemli
Zürich, Switzerland

OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

BUILT TO LAST

OPDIVO® + YERVOY®, the only dual immunotherapy helping more patients experience what matters most: time[1,2]

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1. Larkin J, Chiarion-Sileni V, Gonzalez R et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. NEJM 2019;381:1535 – 1546.
2. Albiges L, Tannir NM et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. ESMO Open 2020;5:e001079.

OPDIVO® (Nivolumab). I: Treatment of locally advanced or metastatic non-small cell lung carcinoma (NSCLC) after previous chemotherapy. Treatment of advanced (unresectable or metastatic) melanoma in adults for monotherapy or combination with ipilimumab. Adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. Treatment of advanced (unresectable or metastatic) renal cell carcinoma (RCC) in previously untreated adult patients with intermediate/poor-risk profile in combination with ipilimumab. Treatment of advanced renal cell carcinoma (RCC) in adults after previous anti-angiogenic therapy. Treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin. Treatment of recurrent or metastatic squamous cell cancer of the head and neck after platinum-based therapy in adults. Treatment of adults with mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal carcinoma for monotherapy or combination with ipilimumab after prior fluoropyrimidine-based therapy in combination with irinotecan or oxaliplatin. Treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after prior platinum-containing chemotherapy. Treatment of advanced or recurrent gastric or gastroesophageal junction adenocarcinoma after two or more prior systemic therapies in adults. **P:** The recommended dose of OPDIVO® monotherapy is 240 mg administered as intravenous (IV) infusion over 30 minutes every 2 weeks. Melanoma – in combination with ipilimumab: The recommended dose of OPDIVO® is 1 mg/kg administered as an intravenous infusion over 30 minutes in combination with intravenous ipilimumab 3 mg/kg over 90 minutes every 3 weeks for the first 4 doses, followed by the single-agent phase with OPDIVO®. RCC, dMMR/MSI-H mCRC – combination with ipilimumab: The recommended dose is 3 mg/kg nivolumab administered as an intravenous infusion over 30 minutes in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes every 3 weeks for the first 4 doses, followed by the single-agent phase with OPDIVO®. Dose increase or reduction is not recommended. The maximum treatment duration with OPDIVO® as monotherapy for adjuvant melanoma is 12 months. For all other approved indications, treatment with OPDIVO® monotherapy or in combination with ipilimumab should be continued as long as clinical benefit is observed or until the patient no longer tolerates the treatment. For more details see the product information. **CI:** Hypersensitivity to the active substance or to any of the excipients. **W&P:** OPDIVO® is associated with inflammatory adverse reactions resulting from increased or excessive immune activity (immune-related adverse reactions), likely to be related to its mechanism of action and to occur more frequent in combination therapy with ipilimumab. Immune-related adverse reactions, which can be severe or life-threatening, may involve the lung, heart, gastrointestinal, liver, skin, muscular system, renal, endocrine, brain or other organ systems. Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions. OPDIVO®-specific management guidelines for immune-related adverse reactions are described in the product information. For additional warnings, see the product information. **UAE:** upper respiratory tract infection, pneumonia, bronchitis, aseptic meningitis, decreased hemoglobin, decreased platelet count, eosinophilia, decreased lymphocyte count, decreased neutrophil count, infusion related reaction, hypersensitivity, anaphylactic reaction, sarcoidosis, solid organ transplant rejection, graft-versus-host-disease (GVHD), haemophagocytic lymphohistiocytosis, hypothyroidism, hyperthyroidism, hyperglycaemia, adrenal insufficiency, hypopituitarism, hypophysitis, thyroiditis, diabetes mellitus, hypoglycaemia, diabetic ketoacidosis, decreased appetite, hyponatremia, hyperkalemia, hypokalemia, hypercalcemia, weight decreased, dehydration, hypocalcemia, hypermagnesemia, metabolic acidosis, peripheral neuropathy, headache, dizziness, encephalitis, Guillain-Barré Syndrom, myasthenia gravis, uveitis, vision blurred, tachycardia, myocarditis, hypertension, pneumonitis, dyspnea, cough, pleural effusion, diarrhoea, nausea, colitis, stomatitis, vomiting, abdominal pain, constipation, dry mouth, gastrointestinal perforation, duodenitis, increased lipase, increased amylase, pancreatitis, increased AST, increased ALT, increased alkaline phosphatase, increased total bilirubin, hepatitis, cholestasis, rash, pruritus, vitiligo, dry skin, erythema, alopecia, urticaria, toxic epidermal necrolysis, arthralgia, musculoskeletal pain, arthritis, rhabdomyolysis, myositis (including polymyositis), increased creatinine, renal failure, tubulointerstitial nephritis, fatigue, pyrexia, oedema (including peripheral oedema), autoimmune hemolytic anemia. **PF:** 10 mg/ml concentrate for solution for infusion, vial of 40 mg/4 ml, 100 mg/10 ml and 240 mg/24 ml (A). **Prep:** see product information. **AH:** Bristol Myers Squibb SA, CH-Steinhausen. **Date of revision of the text:** January 2021. www.swissmedicinfo.ch

YERVOY® (ipilimumab). I: Treatment of advanced (unresectable or metastatic) melanoma in adults. Treatment of previously untreated adult patients with intermediate/poor risk advanced (unresectable or metastatic) renal cell carcinoma in combination with nivolumab. Treatment of adults with mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal carcinoma in combination with nivolumab after prior fluoropyrimidine-based therapy in combination with irinotecan or oxaliplatin. **P:** Melanoma monotherapy: The recommended induction regimen of YERVOY® is 3 mg/kg administered intravenously (IV) over a 90-minute period every 3 weeks for a total of 4 doses. Melanoma – combination with nivolumab: The recommended dose is 1 mg/kg nivolumab administered as an intravenous infusion over 30 minutes in combination with 3 mg/kg YERVOY® administered intravenously over 90 minutes every 3 weeks for the first 4 doses. This is then followed by a single-agent phase in which 240 mg nivolumab is administered as an intravenous infusion over 30 minutes every 2 weeks. RCC, dMMR/MSI-H mCRC – combination with nivolumab: The recommended dose is 3 mg/kg nivolumab administered as an intravenous infusion over 30 minutes in combination with 1 mg/kg YERVOY® administered intravenously over 30 minutes every 3 weeks for the first 4 doses. This is then followed by a second phase in which 240 mg nivolumab is administered as an intravenous infusion over 30 minutes every 2 weeks. Dose reduction is not recommended. For more details see the product information. **CI:** Hypersensitivity to the active substance or to any of the excipients. **W&P:** YERVOY® is associated with inflammatory adverse reactions resulting from increased or excessive immune activity (immune-related adverse reactions), likely to be related to its mechanism of action. Immune-related adverse reactions, which can be severe or life-threatening, may involve the gastrointestinal, liver, skin, nervous, endocrine, or other organ systems. While most immune-related adverse reactions occurred during the induction period, onset months after the last dose of YERVOY® has also been reported. Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions. YERVOY®-specific management guidelines for immune-related adverse reactions are described in the product information. For additional warnings, see the product information. **UAE:** sepsis, septic shock, pneumonia, upper respiratory tract infection, bronchitis, aseptic meningitis, infusion-related reaction, graft-versus-host disease (GVHD), haemophagocytic lymphohistiocytosis, hypersensitivity, anaphylactic reaction (shock), tumour pain, anaemia, lymphopenia, decreased lymphocyte count, decreased hemoglobin, decreased neutrophil count, hypopituitarism (including hypophysitis), hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, thyroiditis, diabetes mellitus,hyperglycaemia, hypoglycaemia, diabetic ketoacidosis, decreased appetite, dehydration, hyponatraemia, hyperkalaemia, hypokalaemia, hypercalcaemia, hypermagnesaemia, weight decreased, metabolic acidosis, confusional state, peripheral sensory neuropathy, dizziness, headache, lethargy, Guillain-Barré syndrome, autoimmune central neuropathy (encephalitis), myasthenia gravis, blurred vision, eye pain, arrhythmia, atrial fibrillation, myocarditis, tachycardia, hypertension, hypotension, flushing, hot flush, angiopathy, pneumonitis, dyspnea, pleural effusion, cough, acute respiratory distress syndrome, diarrhoea, vomiting, nausea, increased lipase, increased amylase, gastrointestinal haemorrhage, colitis, constipation, dry mouth, gastroesophageal reflux disease, abdominal pain, stomatitis, pancreatitis, gastrointestinal perforation, large intestine perforation, intestinal perforation, peritonitis, abnormal hepatic function, increased ALT, increased AST, increased total bilirubin, hepatitis, increased blood alkaline phosphatase, hepatic failure, rash, pruritus, dermatitis, erythema, vitiligo, urticaria, alopecia, night sweats, dry skin, toxic epidermal necrolysis (including Stevens Johnson syndrome), arthralgia, myalgia, musculoskeletal pain, muscle spasms, arthritis, myositis, rhabdomyolysis, renal failure, increased creatinine, fatigue, injection site reaction, pyrexia, chills, asthenia, oedema, pain, influenza-like illness (symptoms), chest pain. **PF:** 5 mg/ml concentrate for solution for infusion, vial of 50 mg/10 ml and 200 mg/40 ml (A). **Prep:** see product information. **AH:** Bristol Myers Squibb SA, CH-Steinhausen. **Date of revision of the text:** November 2019. www.swissmedicinfo.ch

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