Acta Biomed 2019; Vol. 90, N. 4: 468-474 DOI: 10.23750/abm.v90i4.7057

Original article

Correlations between tumor-infiltrating and circulating lymphocyte subpopulations in advanced renal cancer patients treated with nivolumab

Melissa Bersanelli[1], Letizia Gnetti[2], Augusto Vaglio[3], Nicola Sverzellati[4], Nicoletta Campanini[2], Monia Incerti[3], Maricla Galetti[3], Elena Varotti[2], Michele Corrado[4], Raffaele Parziale[4], Lorena Bottarelli[2], Cinzia Azzoni[2]; Enrico Maria Silini[2], Francesco Leonardi[1], Sebastiano Buti[1]

[1] University Hospital of Parma, Medical Oncology, Parma, Italy; [2] University Hospital of Parma, Pathologic Anatomy Unit, Parma, Italy; [3] University Hospital of Parma, Nephrology Unit, Parma, Italy; [4] University Hospital of Parma, Radiology Unit, Parma, Italy

Summary. *Background:* In clinical trials with immunotherapy, histological features such as tumor-infiltrating lymphocytes (TILs) are investigated as potential predictive biomarkers, with the limit of an outdated parameter for a typically dynamic element. *Methods:* This explorative study compared, in metastatic renal cell carcinoma (mRCC) patients, basal pathological data about TILs on diagnostic histological specimens with circulating lymphocyte subpopulations measured before and during therapy with nivolumab. *Results:* Of 11 mRCC patients, 5 had low presence of TILs (L-TILs), 3 moderate amount (M-TILs) and 3 high number (H-TILs). Overall, 8 patients had low intratumoral pathological CD4+/CD8+ ratio (LIPR) ≤1 and 3 cases high intratumoral pathological ratio (HIPR) ≥2. Of 8 patients with LIPR, only 2 matched with low circulating CD4+/CD8+ ratio (LCR) ≤1; 5 had high circulating ratio (HCR) ≥2. All 3 cases with HIPR (≥2) conversely had LCR (≤1). Circulating CD4+/CD8+ ratio remained unchanged during therapy (mean -0.12 in 8 weeks). The respective percentage values of CD4+ and CD8+ circulating T cells also remained stable (variation 0%); the absolute value of CD4+ was more likely to increase (mean +46.3/mm^3); the level of CD8+ tended to slightly decrease (mean -6.5/mm^3). No correlation of lymphocyte subpopulations with treatment outcome was found. Of note, we did not evidence correspondence between histopathological and circulating findings in terms of T-lymphocyte subpopulations, also suggesting the inconsistency of circulating data in terms of relative variations. *Conclusions:* Considering the likely high dynamism of TILs, rebiopsy before therapy might be proposed to assess the utility of TILs characterization for predictive purpose. (www.actabiomedica.it)

Key words: tumor infiltrating lymphocytes, renal cell carcinoma, circulating lymphocytes, immune checkpoint inhibitors, nivolumab

Background

The characterization of the tumor microenvironment is progressively acquiring the right crucial role for the strategy of harnessing the immune system to fight cancer. The mechanisms of immune escape are finally investigated, identified and described as strongly related to this complex and dynamic element (1).

One of the approaches attempted for the tumor microenvironment investigations is constituted by the characterization of tumor infiltrating lymphocytes (TILs), a possible manifestation of antitumor immunity. As a rule, the prognostic significance of abundant TILs has a positive connotation, representing the manifestation of antitumor immunity (particularly CD8+ T cells), as historically known and extensively

demonstrated for melanoma, breast and lung cancer (2-4).

Nevertheless, previous data in human renal cell carcinoma (RCC) suggest that infiltration of tumor tissue by T cells itself does not denote the efficacy of antitumor immunity, because it may be related to the the biological malignancy of tumor cells.

From a clinicopathological analysis of the biological significance of TILs in 221 cases of surgically resected RCC, Nakano et al demonstrated a correlation between abundant infiltration of tumor tissue, not only by CD8+ but also by CD4+ T cells, and a shorter survival of the patients. It was due to a positive correlation between the number of lymphocytes and representative tumor grade factors, thus suggesting that immune cell reactions are more pronounced as the tumor biological malignancy progresses, probably because of increased antigenicity of tumor cells (5).

Some features of TILs in terms of quality and quantity (immunohistochemistry with count and subpopulations) have been related to prognostic or predictive characteristics. For instance, in renal cell carcinoma (RCC) high density CD4+ T-cell infiltrate is associated with unfavorable tumor characteristics and poor prognosis (6-7). Moreover, also the relative ratios of the various TILs subpopulations deserve to be evaluated.

Only few studies correlated the basal features of TILs with the dynamic circulating T cells counterpart.

Such comparison was performed by Asma et al on CD4+ regulatory T cells (T-reg), which intratumoral and circulating subpopulations have been respectively investigated, with the further interesting comparison of circulating T-reg of healty donors (8). The investigators demonstrated that the proportion of T-reg in TILs was, in average, like that found in circulating CD4+ T cells of patients or healthy donors.

A similar but more detailed investigation was conducted in a very recent study by Giraldo et al, providing a multiparametric flow cytometric immunophenotypic analysis of TILs (defined as T cells isolated from tumor tissue), of T cells adjacent non-malignant renal tissue (defined as renal-infiltrating lymphocytes, RILs) and of peripheral blood lymphocytes (PBL), in a cohort of 40 patients with localized RCC (9). On the basis of TILs phenotypic characterization, they identified three dominant immune profiles in localized RCC, respectively called “immune-regulated” in inflamed tumors (22%), characterized by polyclonal/poorly cytotoxic CD8+/PD-1+/Tim-3+/Lag-3+ TILs and CD4+/ICOS+ cells with a T-reg phenotype (CD25+/CD127-/Foxp3+/Helios+/GITR+), highly PD-L1 positive; “immune activated” (22%) enriched in oligoclonal/cytotoxic CD8+/PD-1+/Tim-3+ TILs; and “immune silent” (56%), enriched in TILs exhibiting RIL-like phenotype. Only immune-regulated tumors resulted to have aggressive histologic features, high risk of disease progression after nephrectomy and a CD8+/PD-1+/Tim-3+ and CD4+/ICOS+ PBL phenotypic signature. According to the results of this study, in localized RCC, the infiltration with CD8+/PD-1+/Tim-3+/Lag-3+ exhausted TILs and ICOS+ T-reg identifies the patients with poor prognosis who could potentially benefit from adjuvant therapy with checkpoint blockade (9).

In clinical trials with immune-checkpoint inhibitors (CKI) in metastatic RCC (mRCC), histological features such as TILs in the primary tumor are investigated as potential predictive biomarkers, with the possible limit of an outdated parameter for a typically dynamic element.

Up today, no studies with the paired analysis of tumor infiltrating and circulating lymphocytes subpopulations in renal cancer patients in relation to the new immunotherapy with CKI have been published and any biomarker has been identified to predict response to nivolumab in such population.

Materials and methods

This explorative study compared, in consecutive mRCC patients treated with nivolumab, basal pathological data about TILs on diagnostic histological specimens from nephrectomies with circulating lymphocyte subpopulations, evaluated before and during therapy, considering both quantitative and qualitative features, with the primary aim to assess their concordance. Furthermore, a possible correlation of such features with treatment outcome was explored, assessing the treatment outcome in terms of objective responses through the complete, blinded radiologic revision of

basal computed tomography (CT) scans and of at least two subsequent CT scans assessment during treatment with nivolumab. The revision was performed by three radiologists, with at least two of them independently revising each exam, according both to the standard RECIST 1.1 and to the immune-related RECIST (iRECIST) (10-11).

For the pathologic analysis, we assessed at least 3 slides with well-preserved neoplastic tissue per each tumor sample. The slides were stained with hematoxylin and eosin for conventional evaluation, too. For the assessment of TILs, of CD8+ and CD4+ cells, we considered both qualitative and quantitative parameter. The presence of TILs was evaluated as "absent", "low", "moderate", or "high", with both intratumoral and peritumoral assessment. The presence of CD4+ and CD8+ cells and CD4+/CD8+ ratio was also evaluated in both sites. Immuno-histochemical staining of formalin fixed, paraffin-embedded, tissue sections was performed on all samples. After deparaffinization and rehydratation sections were treated with 3% hydrogen peroxidase for 5 mins. For antigen retrieval, sections were treated with pH9 Tris-EDTA buffer for 30 mins in water-bath at 98°C. Sections were stained with the following primary antibodies: CD4 (Roche; diluition ready to use), CD8 (Roche; diluition ready to use). The sections were immunostained with a polymeric system Ultraview DaB Detection Kit (Ventana-Roche) in accordance with the manufacture›s specifications. Diaminobenzidine (DAB) was used for staining development and the sections were counterstained with haematoxylin. Negative controls consisted of substituting normal serum for the primary antibody.

Results

Eleven mRCC patients consecutively treated with nivolumab in second or subsequent lines at our institution were included in this analysis. Table 1 shows patients' characteristics.

Our histopathological results demonstrated a heterogeneous expression of TILs, including CD4+ and CD8+ T cells. The heterogeneity was both inter-patient and intra-patient, with several cases of discordant CD4+/CD8+ ratio and different presence of immune infiltration among peritumoral and intratumoral tissue.

Of 11 patients included, the intratumoral analysis identified 5 cases with low presence of TILs, 2 with

Table 1

Sex	
male	7 (64%)
female	4 (36%)
Age	
mean	80
range	56 83
Histology	
clear-cell carcinoma	5 (45%)
mixed (clear/non-clear)	3 (27%)
chromophobe	2 (18%)
papillary	1 (10%)
ECOG PS	
0	9 (82%)
1	2 (18%)
≥2	0 (0%)
MSKCC risk group	
poor	0 (0%)
intermediate	7 (64%)
good	4 (36%)
IMDC risk group	
poor	0 (0%)
intermediate	6 (64%)
good	4 (36%)
Treatment line with Nivolumab	
second	7 (58%)
third2 (18%)	
further lines (4th or subsequent)	2 (17%)
Previous treatment received (immediately before Nivolumab)	
Pazopanib	3 (27%)
Sunitinib	5 (45%)
Everolimus	1 (9%)
Axitinib	1 (9%)
Sorafenib	1 (9%)
Nephrectomy	
yes	10 (91%)
no	1 (9%)

PS=performance status; MSKCC=Memorian Sloan Kettering Cancer Center; IMDC=International Metastatic Renal Cell Carinoma Database Consortium

moderate amount and 4 with high number of lymphocytes.

Overall, 9 patients had low intratumoral pathological CD4+/CD8+ ratio (≤1) and 2 cases had high intratumoral pathological CD4+/CD8+ ratio (≥2). Of 9 patients with the low pathological ratio, only 3 cases matched with low circulating CD4+/CD8+ ratio (≤1), whilst 5 cases had high circulating CD4+/CD8+ ratio (≥2). One case was undetermined (not evaluable). The 2 cases with high pathological ratio (≥2) conversely had low circulating ratio (≤1).

Unexpectedly, independently from the clinical outcome, circulating CD4+/CD8+ ratio remained unchanged during therapy with CKI in each patient, maintaining about the same value after 8 weeks (mean +0.18). The respective percentage values of CD4+ and CD8+ circulating T cells also remained stable during treatment (mean variation 0%); the absolute value of CD4+ was more likely to increase (mean gain +100.6/mm3); the level of CD8+ tended to decrease (mean loss -30.6/mm3).

Interestingly, several cases (3) of opposite findings among intratumoral and peritumoral lymphocytes presence and differences in terms of CD4+/CD8+ ratio were found (Table 2).

With the limit of a small sample size, no clear correlation of either tissue or circulating lymphocyte subpopulations with treatment outcome was found. In our group, only one patient had partial response; the disease control rate was 45%; 6 patients (the majority, 54.5%) were primary refractory to nivolumab, confirmed at the second radiologic assessment during therapy. Interestingly, a complete concordance of responses was found between RECIST 1.1. and iRECIST in these 11 cases, with the limit of having stopped such radiologic comparison at the second CT scan after the basal one.

Discussion

Before sinking into the exquisite scientific digressions on the T cell-mediated immune microenvironment emerged by our study, we should disclose that some particular features, mainly due to a selection bias from retrospective nature and small sample size, emerged in this population and should be considered to not misinterpret our findings.

First, the mean age of our population was of 80 years, with a range of 56-83. Despite not completely

Table 2

Case number	Intratumoral TILs	Intratumoral CD4+/CD8+ ratio	Peritumoral-infiltrating lymphocytes	Peritumoral CD4+/CD8+ ratio	Baseline circulating CD4+/CD8+ ratio	Circulating CD4+/CD8+ ratio after therapy	Treatment response according to irRECIST
Case N. 6954	Low	1:2	Low	1:3	2.5	3	PD (progression of disease)
Case N. 8205	High	1:3	High	3:1	3.5	4.9	PR (Partial response)
Case N. 10622	Low	2:1	High	1:2	1	0.9	SD (stable disease)
Case N. 15859	Moderate	1:2	Moderate	1:2	0.9	NE (not evaluated)	PD
Case N. 18659	Low	1:2	High	1:2	1.1	1.1	PD
Case N. 7985	Low	only CD8+	Moderate	1:2	2.7	2.2	SD
Case N. 2011	High	1:3	Moderate	1:2	NE	NE	PD
Case N. 274	Moderate	1:3	Moderate	1:2	2.8	2.4	PD
Case N. 5007	High	1:2	High	1:2	0.5	0.4	PD
Case N. 552	High	1:2	High	1:3	2.5	3.8	SD
Case N. 25620	Low	2:1	Low	1:2	0.3	0.4	SD

representing the elderly, this element should be taken in account because of the possible "exhausting effect" of the age on the immune system. Concerning the treatment outcome, a lesser degree of benefit in terms of overall survival was seen for the elderly in the pivotal trial CheckMate025, particularly among patients aged 75 years, with a trend that appeared to favor the comparator used in the control arm (12). This evidence could provide a justification for the scarce outcome achieved in our group (best responses according to immune-related RECIST are shown in Table 2).

Second, much of cases had non-clear cell histology (55%): it is still largely unknown if the microenvironment of clear-cell RCC differs from those of rarer histologies such as papillary, chromophobe or mixed tumors, all represented in our sample. Further, the same type of immune microenvironment might acquire different meaning and opposite prognostic value in cases with different histologic subtype. Up today, no data on non-clear cell histologies treated with CKI have been reported, confounding the interpretation of the present study also concerning the treatment outcome.

Third, 64% of patients were classified as intermediate risk both per MSKCC and IMDC criteria, increasing the "average risk level" of the entire population, with an unavoidable negative prognostic impact.

These unusual aspects should be considered, suggesting a reflection about the possibility that response to immunotherapy can mainly depend on age and clinical conditions.

The most unexpected but also the most interesting findings of our analysis are represented by three key concepts: the lack of correlation between tissue and circulating lymphocyte subpopulations; the opposite findings among intratumoral and peritumoral T cell infiltrate; the lack of variation of the circulating CD4+/CD8+ ratio during therapy. A further gold concept, here confirmed but already well known by the literature concerning this cancer type (13), is represented by the inter-patient and intra-patient heterogeneity.

Analyzing the cited issues, the first key element of the lack of correlation between tissue and circulating lymphocyte subpopulations may confirm that the treatment choice should not be based on the evaluation of the immune microenvironment of the primary tumor, as instead it was done in clinical trials with CKI, selecting or stratifying patients basing on the primary programmed-death ligand 1 (PD-L1) expression. Our experience once again suggests to carefully consider the risk of basing the patients' selection for immunotherapy trials on an outdated parameter (the primary tumor analysis) for the evaluation of a typically dynamic element (the immune microenvironment).

The specular results in some cases obtained when comparing intratumoral and peritumoral T cell subpopulations might cast the doubt that the same T cell population plays a different role in the two sites and that, conversely, the same role is played respectively in the two compartments by two different T cell types. Not surprisingly in the light of our current results, in the already cited study by Asma et al, despite a similar average proportion of T-reg in circulating and infiltrating component from a quantitative point of view, intratumoral T-reg exhibited a marked different phenotype when compared with the autologous circulating T-reg. Intratumoral T-reg showed a higher inhibitory function on autologous CD4+/CD25- T cells when compared with circulating T-reg. Despite comparing different districts, in this case the same T cell plays different roles based on the site where it is located.

Eventually, about the unexpected lack of variation of the circulating CD4+/CD8+ ratio during therapy, the reason in our case could be provided by the possible immunosenescence of our population. Immunosenescence is generally defined as age-related changes to the immune system that result in increased susceptibility to infectious diseases and a decreased response to vaccination. Several demonstrations of this issue have been reported, among others the evidence that the proliferative response of T cells from older adults after vaccination against hepatitis B is diminished, or the age-related decline in toll like receptor-induced expression of the CD80 costimulatory molecule that is associated with a decrease in humoral immunity to influenza vaccine; or moreover the decline in the frequency of influenza-specific CD4+ memory T-cells, and the decreased cytolytic properties CD8+ effector and effector memory cells in response to influenza vaccine in older subjects (14).

Despite the general expectancy of a better outcome in the case of CD8+ abundance and of a possible

negative prognostic impact of the CD4+ prevalence, in our population neither CD4+ nor CD8+ prevalence in any site did not seem to have a predictive role (the peritumoral/intratumoral pattern and the ratio were heterogeneous both in responders and refractory cases). The role of cytotoxic CD8+ TILs in the setting of RCC is still controversial, with conflicting results according to different studies (5, 9, 15-18), maybe due to technical factors, including antibodies and techniques used to detect CD8+ T-cells (immunohistochemistry versus flow cytometry) and tumor site examined (peritumoral versus intratumoral TILs). Of most relevance was the ability of previous studies to differentiate between the effector cytotoxic CD8+ T cells and their exhausted counterparts, expressing high levels of immune checkpoint molecules in a dysfunctional immune environment. When dichotomized in such a way, Giraldo et al clearly demonstrated good prognosis with the former CD8+ T-cell population, and poor prognosis with the latter (9). Similarly, Nakano et al showed that TILs with high CD8+ T-cell content that exhibited high proliferative activity were associated with improved survival among patients with mRCC (5). Unfortunately, we were unable to distinguish between these two T-cell subpopulations.

Concerning CD4+ component, despite the well-known prevalence of the role CD8+ effector T cells in the antitumor immunity, recent evidence also demonstrated the existence of CD4+ T-cell-mediated antitumor immunity, with signatures of heterogeneous T-cell expansion in CD4+ TILs repertoire (19). In our sample, the previously discussed negative prognostic impact of CD4+ TILs abundance did not emerge.

A further element to be considered is represented by previous treatments, which undoubtedly modulated the immune microenvironment, potentially becoming responsible of a different subsequent outcome of immunotherapy. For instance, considering the two standard tyrosine kinase inhibitors used in first line setting for mRCC treatment, it has been demonstrated that pazopanib appears to function as a potent activator of dendritic cells in vitro and in vivo associated with the neo-activation of a CD137+ T cell population (20), whilst sunitinib seems to promote TILs expansion by reducing intratumoral content of myeloid-derived suppressor cells (21).

In our population, previous drugs were collected (see Table 1) but no relationship of this element has been found with the T cell immune pattern or TILs presence, despite the trend of a more favorable clinical outcome for pazopanib-pretreated patients (the only partial response received prior pazopanib and any patient pretreated with this drug was primary refractory).

The main limit of our analysis is represented by the small sample size. Another limitation is represented by the missed identification of T-reg, maybe resulting in masking the real prognostic or predictive effect of the other respective subpopulations.

Considering these important limits, this study did not evidence significant correspondence between histopathological and circulating findings in terms of T-lymphocyte subpopulations in mRCC patients undergoing treatment with CKI, also suggesting the inconsistency of circulating data in terms of relative variations. Moreover, heterogeneity concerning immune infiltrate and the often opposite results for intratumoral and peritumoral subpopulations can invalidate the research of a clear relationship between pathological and circulating data.

Considering the likely high dynamism of TILs, rebiopsy before CKI therapy might be the most reliable way to assess the utility of TILs characterization for predictive purpose.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

References

1. Manson G, Norwood J, Marabelle A, et al. Biomarkers associated with checkpoint inhibitors. Annals of Oncology April, 27, 2016 [Epub ahead of print]
2. Schatton T, Scolyer RA, Thompson JF, et al. Tumor-infiltrating lymphocytes and their significance in melanoma prognosis. Methods Mol Biol 2014; 1102: 287-324.
3. Stanton SE, Disis ML. Clinical significance of tumor-infiltrating lymphocytes in breast cancer. J Immunother Cancer 2016; 4: 59.
4. Kilic A, Landreneau RJ, Luketich JD, et al. Density of tumor-infiltrating lymphocytes correlates with disease recurrence and survival in patients with large non-small-cell lung cancer tumors. J Surg Res 2011; 167(2): 207-10.

5. Nakano O, Sato M, Naito Y, et al. Proliferative activity of intratumoral CD8(+) T-lymphocytes as a prognostic factor in human renal cell carcinoma: clinicopathologic demonstration of antitumor immunity. Cancer Res 2001; 61(13): 5132-6.
6. Bromwich EJ, McArdle PA, Canna K, et al. The relationship between T-lymphocyte infiltration, stage, tumour grade and survival in patients undergoing curative surgery for renal cell cancer. British journal of cancer 2003; 89: 1906-1908.
7. Hotta K, Sho M, Fujimoto K, et al. Prognostic significance of CD45RO+ memory T cells in renal cell carcinoma. British journal of cancer 2011; 105: 1191-1196.
8. Asma G, Amal G, Raja M, et al. Comparison of circulating and intratumoral regulatory T cells in patients with renal cell carcinoma. Tumour Biol 2015; 36(5): 3727-34.
9. Giraldo NA, Becht E, Vano Y, et al. Tumor-Infiltrating and Peripheral Blood T-cell Immunophenotypes Predict Early Relapse in Localized Clear Cell Renal Cell Carcinoma. Clin Cancer Res 2017 Feb 17 [Epub ahead of print].
10. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45(2): S. 228-47.
11. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017; 18(3): e143-e152.
12. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015; 373: 1803-13.
13. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med 2012; 366(10): 883-92.
14. Poland GA, Ovsyannikova IG, Kennedy RB, et al. A systems biology approach to the effect of aging, immunosenescence and vaccine response. Curr Opin Immunol 2014; 0: 62-68.
15. McDermott DF, Sosman JA, Sznol M, et al. Atezolizumab, an Anti-Programmed Death-Ligand 1 Antibody, in Metastatic Renal Cell Carcinoma: Long-Term Safety, Clinical Activity, and Immune Correlates From a Phase Ia Study. J Clin Oncol 2016; 34(8): 833-42.
16. Choueiri TK, Figueroa DJ, Fay AP, et al. Correlation of PD-L1 Tumor Expression and Treatment Outcomes in Patients with Renal Cell Carcinoma Receiving Sunitinib or Pazopanib: Results from COMPARZ, a Randomized Controlled Trial. Clinical Cancer Research 2015; 21: 1071-1077.
17. Remark R, Alifano M, Cremer I, et al. Characteristics and clinical impacts of the immune environments in colorectal and renal cell carcinoma lung metastases: influence of tumor origin. Clinical Cancer Research 2013; 19: 4079-4091.
18. Weiss JM, Gregory Alvord W, Quinones OA, et al. CD40 expression in renal cell carcinoma is associated with tumor apoptosis, CD8(+) T cell frequency and patient survival. Human immunology 2014; 75: 614-620.
19. Zhang Q, Jia Q, Deng T, et al. Heterogeneous expansion of CD4+ tumor-infiltrating T-lymphocytes in clear cell renal cell carcinomas. Biochem Biophys Res Commun 2015; 458(1): 70-6.
20. Guislain A, Gadiot J, Kaiser A, et al. Sunitinib pretreatment improves tumor-infiltrating lymphocyte expansion by reduction in intratumoral content of myeloid-derived suppressor cells in human renal cell carcinoma. Cancer Immunol Immunother 2015; 64(10): 1241-50.
21. Nuti M, Zizzari I, Napoletano C, et al. Immunomodulatory effects of tyrosine kinase inhibitors (TKIs) in renal cell carcinoma (RCC) patients. Journal of Clinical Oncology 35, no. 15_suppl - published online before print.

Received: 31 January 2018
Accepted: 16 July 2018
Correspondence:
Dr. Melissa Bersanelli, MD,
University Hospital of Parma, Medical Oncology,
Via Gramsci 14, 43126, Parma (PR)
Tel. +390521702316
E-mail bersamel@libero.it