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ORIGINAL ARTICLE

How to optimize the use of adjuvant pembrolizumab in renal cell carcinoma: which patients benefit the most?

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Abstract

Purpose The KEYNOTE-564 trial showed improved disease-free survival (DFS) for patients with high-risk renal cell carcinoma (RCC) receiving adjuvant pembrolizumab as compared to placebo. However, if systematically administered to all high-risk patients, it might lead to the overtreatment in a non-negligible proportion of patient. Therefore, we aimed to determine the optimal candidate for adjuvant pembrolizumab.

Methods Within a prospectively maintained database we selected patients who fulfilled the inclusion criteria of the KEYNOTE-564. We compared baseline characteristics and oncologic outcomes in this cohort with those of the placebo arm of the KEYNOTE-564. Regression tree analyses was used to generate a risk stratification tool to predict 1-year DFS after surgery.

Results In the off-trial setting, patients had worse tumor characteristics then in the KEYNOTE-564 placebo arm, i.e. there were more pT4 (5.4 vs. 2.7%, $p=0.046$) and pN1 (15 vs. 6.3%, $p<0.001$) cases. Median DFS was 29 (95% CI 21–35) months as compared to value not reached in KEYNOTE-564 and 1-year DFS was 64.2% (95% CI 59.6–69.2) as compared to 76.2% (95% CI 72.2–79.7), respectively. Patients with pN1 were at the highest risk of 1-year recurrence (1-year DFS 28.6% [95% CI 20.2–40.3]); patients without LNI, but necrosis were at intermediate risk (1-year DFS 62.5% [95% CI 56.9–68.8]); those without LNI and necrosis were at the lowest risk (1-year DFS 83.8% [95% CI 79.1–88.9]). LVI substratification furtherly improved the accuracy in the prediction of early recurrence.

Conclusions Patients potentially eligible for adjuvant pembrolizumab have worse characteristics and DFS in the off-trial setting as compared to the placebo arm of the KEYNOTE-564. Patients with either LNI or necrosis were at the highest risk of early-recurrence, which make them the ideal candidate to adjuvant pembrolizumab.

Keywords Renal cancer · Recurrence · Progression · Adjuvant · Pembrolizumab

Introduction

Recently, the KEYNOTE-564 randomized clinical trial reported for the first time improved disease-free survival (DFS) for patients with high-risk renal cell carcinoma (RCC) receiving adjuvant pembrolizumab when compared with placebo arm [1]. The study set a paradigm shift in clinical management of patients with RCC, re-defining the role of adjuvant systemic therapy. Consequently, adjuvant pembrolizumab received a category 2A recommendation in the National Comprehensive Cancer Network (NCCN) guidelines for kidney cancer v. 4.2022, a weak recommendation for its use in the European Association of Urology (EAU) guidelines, was included as an optional treatment

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by the European Society for Medical Oncology (ESMO) guidelines after careful patient counselling and has been recently approved by the Food and Drug administration (FDA) [2–4]. However, despite the enthusiasm elicited by these results, some questions remain unsolved. To what extent is it possible to generalize the findings of the KEYNOTE-564 trial to off-trial patients? Moreover, it is possible that some patients with RCC might not benefit from adjuvant therapy when disease progression is expected beyond the first year after surgery [5, 6]. To complicate the scenario and to further highlight the importance of this theme, the CheckMate-914 phase III trial, evaluating nivolumab plus ipilimumab, and the IMmotion010 phase III trial, evaluating atezolizumab, did not meet the primary endpoint of DFS, as recently announced [7, 8]. Based on these considerations, it is important to correctly identify among the potential candidates to adjuvant pembrolizumab those who will progress early and thus will benefit the most from an adjuvant approach, and those who will have late progression or no progression at all, and thus might not need any further treatment after surgery.

We aimed to answer these two critical questions relying on our prospectively maintained database, by comparing baseline characteristics and oncologic outcomes of patient potentially eligible for adjuvant pembrolizumab in the off-trial setting with those in the placebo arm of the KEYNOTE-564 and by identifying those patients who may benefit the most from adjuvant treatment according to the risk of disease progression at 1 year.

Materials and methods

Study design and population

This is a cohort study based on a prospectively maintained database of patients diagnosed and surgically treated for RCC at our tertiary referral center between 2000 and 2021. We retrospectively identified patients potentially eligible for enrollment in the KEYNOTE-564, according to its inclusion and exclusion criteria. Inclusion criteria were: histologically confirmed clear cell RCC, age $\geq$ 18 years, Eastern Cooperative Oncology Group (ECOG) performance status 0–1, no bone or brain metastases, no previous neoadjuvant therapies and one of the following (A) stage pT2 with grade 4 and/or sarcomatoid differentiation or (B) stage pT3-4 or (C) regional lymph-node metastasis (LNI) or D) stage M1 (pM1) with nonevidence of disease (NED) after surgical treatment of the metastasis. In addition, patients who underwent any neoadjuvant or adjuvant therapies were excluded from our analysis.

Variable definition

Baseline characteristics included age at surgery, gender and body mass index (BMI). Patient's comorbidities were assessed using the Charlson Comorbidity Index (CCI) [9]. Performance status at surgery was scored according to the ECOG definition. The data on each surgical procedure was also collected. Pathological staging (TNM) of surgically treated RCC was defined according to the American Joint Committee on Cancer manual [10]. The data from pathological reports, i.e. the presence of sarcomatoid features, necrosis, lymphovascular invasion (LVI), lymph nodes invasion (LNI) and nuclear grade, according to Fuhrman classification (G1 – G4) were included.

Outcome definition

The primary outcome of the study was disease-free survival. DFS was measured as the time between the date of surgery for RCC and the date of first disease recurrence, death or end of follow-up. The overall survival (OS) was also assessed and measured as the time between the date of surgery for RCC and the date of death from any cause or end of follow-up. The start of follow-up was the date of surgery for RCC, as a hypothetical and standardized date at which adjuvant treatment could have been considered. The end of follow-up was the date of the last time that each patient was reached by systematic online survey/phone call or in-presence visit, up to October 30th, 2021.

Statistical methods

First, descriptive statistics included frequencies and proportions for categorical variables and medians and interquartile ranges for continuously coded variables. Differences in baseline characteristics between our cohort and the placebo arm of the KEYNOTE-564 were tested by use of Chi-square test for categorical variables. Second, DFS and OS were estimated using the Kaplan – Meier method and compared with DFS and OS curves of the placebo arm of the KEYNOTE-564, respectively, which was digitalized and reconstructed for this purpose [11]. Specifically, we digitally scanned KM curves from included RCTs and reconstructed survival data using an algorithm that derives individual data from digitized published KM curves [11]. The algorithm reconstructs survival data by measuring curve drops relative to the number of patients at risk and number of events, when available [11]. Third, to identify risk categories for 1-year disease progression, a regression tree analysis for censored data was applied. To restrict the number of variables in the regression tree analysis

and given the paucity of data on what variables might be predictive of short-term DFS, only those variables that were univariably associated with DFS at Cox regression analysis were included. Using this method, patients were categorized according to risk of recurrence at 1-year from surgery into low, intermediate and high risk. The accuracy of this risk tool was evaluated with Harrel C-Index. For all statistical analyses, R-software environment for statistical computing and graphics (version 3.4.3) was used. All tests were two-sided with a level of significance set at $p < 0.05$.

The study has been conducted in accordance with the Declaration of Helsinki and each patient signed full informed consent before surgery allowing for retrieval, collection and use of data for research purpose. Data collection and use was approved by the IRCCS San Raffaele Hospital Ethical Committee (protocollo RENE-versione 29/08/2007-Ospedale San Raffaele di Milano).

Results

Of all, 408 patients fulfilled the KEYNOTE-564 inclusion criteria. Relative to the placebo arm of the trial, in the off-trial setting patients had worse ECOG (ECOG = 1 in 259 [63.5%] vs. 72 [14.5%]; $p < 0.001$), despite similar age at baseline (Table 1). Similarly, in the off-trial setting there were more pT4 (22 [5.4%] vs. 13 [2.7%]; $p = 0.046$), pN1 (62 [15.2%] vs 31 [6.2%]; $p < 0.001$) and M1 cases with NED (55 [13.5%] vs. 29 [5.8%]; $p < 0.001$). On the contrary, in the off-trial setting at pathology report there were slightly less frequently high nuclear grade cases (251 [61.5%] vs. 322

Table 1 Baseline characteristic of the cohort of study compared with the baseline characteristics of the KEYNOTE-564 placebo arm (intention to treat population)

	Overall ($n = 408$)	KYNOTE-564 ($n = 498$)	p value
Age (median, (IQR))	61.00 (54.0–70.0)	60.0 (25.0 – 84.0)	
Sex			
Male	295 (72.3)	359 (72.1)	0.999
Female	113 (27.7)	139 (27.9)	0.999
BMI (median, (IQR))	25.34 (23.2–27.7)	NA	–
CCI			–
0	227 (55.6)	NA	
1	101 (24.8)	NA	
≥ 2	80 (19.6)	NA	
ECOG			
0	149 (36.5)	426 (85.5)	< 0.001
1	259 (63.5)	72 (14.5)	< 0.001
pT (%)			
T1	15 (3.7)	15 (3.0)	0.711
T2	11 (2.7)	33 (6.6)	0.009
T3	360 (88.2)	437 (87.8)	0.901
T4	22 (5.4)	13 (2.6)	0.046
pN (%)			
pN0/x	346 (84.8)	467 (93.8)	< 0.001
pN1	62 (15.2)	31 (6.2)	< 0.001
pM (%)			
pM0	353 (86.5)	469 (94.2)	< 0.001
pM1 (NED)	55 (13.5)	29 (5.8)	< 0.001
Grade (%)			
G1	9 (2.2)	16 (3.2)	0.473
G2	148 (36.3)	150 (30.1)	0.058
G3	182 (44.6)	213 (42.8)	0.626
G4	69 (16.9)	119 (23.9)	0.012
Presence of necrosis	269 (65.9)	NA	
Presence of sarcomatoid features	29 (7.1)	59 (11.8)	0.022
Presence of lymphovascular invasion	140 (34.3)	NA	

IQR interquartile range, *BMI* Body Mass Index, *CCI* Charlson Comorbidity Index, *ECOG* Eastern Cooperative Oncology Group, *NED* nonevidence of disease, *NA* Non available

[66.7%]; $p = 0.012$) and sarcomatoid features (29 [7.1%] vs. 59 [11.8%]; $p = 0.022$).

In our cohort, median follow-up for survivors was 75 months (95% confidence interval [CI] 66–90). Overall, 229 patients had distant disease progression and 152 died. The median DFS was 29 months (95% CI 21–35) when compared with value not reached in the KEYNOTE-564. 1-year DFS was 64.2% (95% CI 59.6–69.2) when compared with a 1-year DFS of 76.2% (95% CI 72.2–79.7) in the placebo arm of the KEYNOTE-564 (Supplementary Fig. 1). At univariable Cox regression analysis, factors associated with DFS were high nuclear grade (for G4 Hazard Ratio [HR] 4.28; 95% CI 1.53–11.92; p value = 0.005), LNI (HR 3.64; 95% CI 2.69–4.94; p value < 0.001), presence of metastatic disease at the time of diagnosis (HR 3.57; 95% CI 2.60–4.89; p value < 0.001), necrosis in the specimen (HR 2.50; 95% CI 1.84–3.38; p value < 0.001), sarcomatoid feature (HR 2.63; 95% CI 1.75–3.97; p value < 0.001), and LVI (HR 1.98; 95% CI 1.52–2.57; p value < 0.001) (Supplementary Table 1).

According to the regression tree analysis, patients with pN1, who were 62 (15.2%) in our cohort, were at high risk of progression in the first year after surgery, with a 1-year DFS of 28.6% (95% CI 20.2–40.3); those with pN0/x and the presence of necrosis, who were 221 (54.2%) in our cohort, were at intermediate risk of progression in the first year after surgery, with 1-year DFS of 62.5% (95% CI 56.9–68.8); finally, those with pN0/x without necrosis, who were 125 (30.6%) in our cohort, were at low risk of recurrence in the

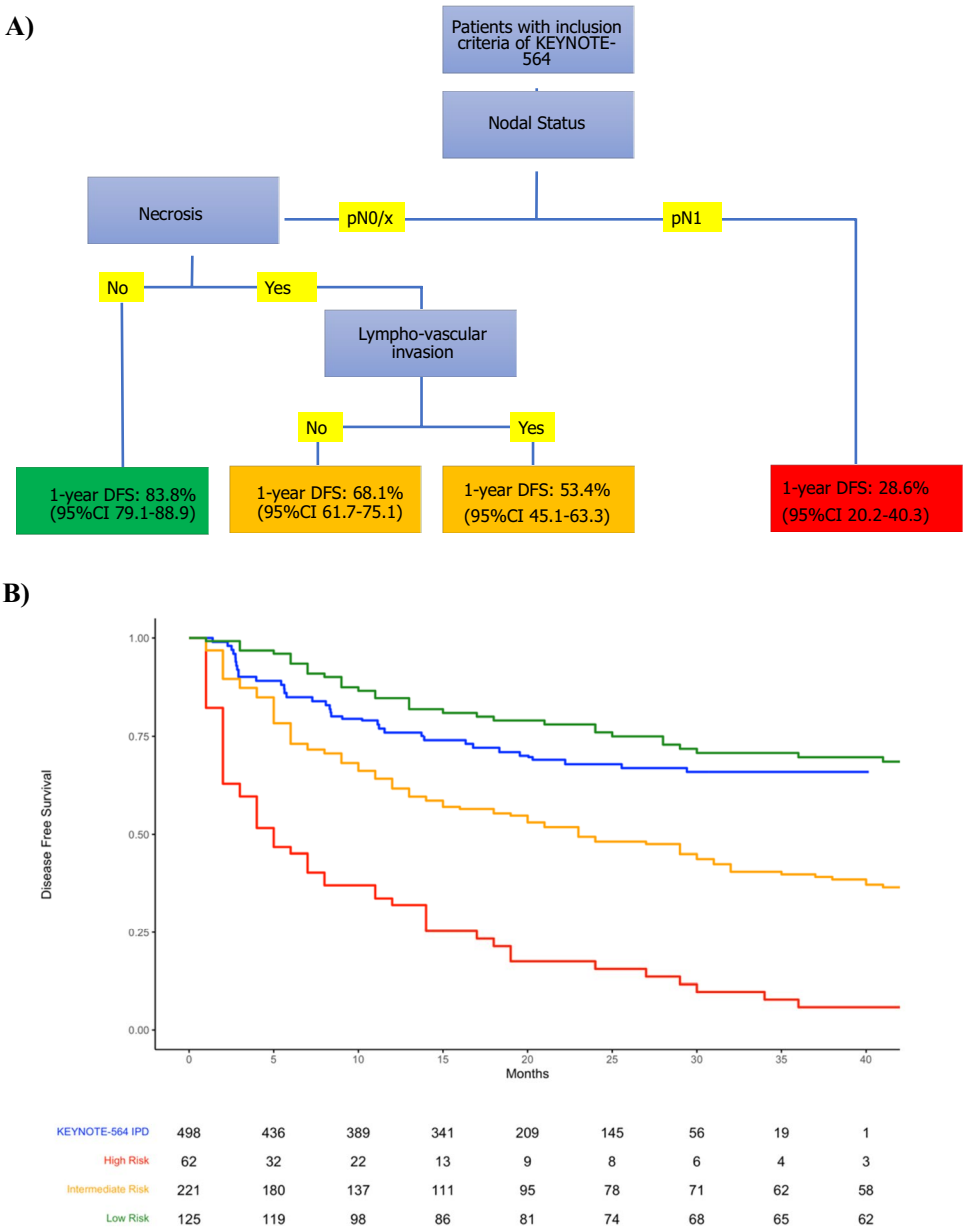

Fig. 1 **a** Risk stratification tree assessing 1-year recurrence for patients with renal cell cancer potentially eligible for adjuvant pembrolizumab according to the KEYNOTE-564 inclusion criteria. **b** Kaplan – Meier curves of the three risk categories and a digitalized and reconstructed Kaplan – Meier curve for DFS in the KEYNOTE-564 placebo arm (in blue)

first year after surgery, with a 1-year DFS of 83.8% (95% CI 79.1–88.9) (Fig. 1). Intermediate risk category can be further stratified according to the presence or absence of LVI, with a 1-year DFS of 53.4% (95% CI 45.1–63.3) and of 68.1 (95% CI 61.7–75.1), respectively. The 1-year DFS risk categories categorized well also OS (Supplementary Fig. 2). The C-Index of this model for DFS was 73.3% and for OS 77.0%.

Discussion

This study was aimed to answer two key clinical questions; one on the generalizability of the KEYNOTE-564 results, given the hypothesis that off-trial patients might have different baseline characteristics when compared with those included in randomized trials; and the other on the need for optimal selection of patients for adjuvant treatments, given the wide range of 1-year disease free survival of RCC patients.

The publication of the results of the KEYNOTE-564 is going to change our everyday clinical practice and we are likely going to elect more and more patients with high risk RCC for adjuvant treatment [12]. However, the treatment-related toxicities and costs should be taken into consideration, as well [13]. In addition, the use of immunotherapy in adjuvant setting might jeopardize indications and efficacy of salvage therapy in case of disease relapse. Therefore, it is mandatory to identify those patients who might benefit the most from adjuvant treatment.

In our study, we showed that off-trial patients with the same inclusion criteria of the KEYNOTE-564 trial had lower DFS when compared with those showed in the control arm of the trial. This is not a surprise, since it is well expected that off-trial patients have worse characteristics than those included in prospective trials, and as such, the introduction in every-day practice of adjuvant pembrolizumab is warranted at the earliest. In addition, we showed that patients with high risk RCC have a wide range of DFS and can be accurately classified into categories according to their risk of 1-year disease recurrence. Of note, those with high and intermediate risk were almost the 70% in our cohort and had a worse DFS than patients in the KEYNOTE-564. As such, we expected that results from off-trial adjuvant use of pembrolizumab on DFS and OS might be even more pronounced than those shown in the published trial.

A key point regards the limited inclusion of patients with LNI in published trials on adjuvant setting for RCC. The proportion of LNI in patients with cT3 nonmetastatic RCC might be up to 30% if retroperitoneal lymph node dissection is performed at the time of nephrectomy [14, 15]. The use of lymph node dissection at nephrectomy is decreasing both in the US and in Europe due to the lack of evidence of survival benefit and for cost – benefit reasons [16]. This might justify why only 6% of patients ($n = 31$ patients in each arm) included in the KEYNOTE-564 showed LNI at final pathology. On the other hand, a report including more than 10,000 nonmetastatic high-risk RCC patients demonstrated that LNI does represent the most informative predictor of early progression and mortality after surgery [17]. Our results confirmed this finding, since LNI represented the most important parameters to identify patients at high of early disease progression. On a speculative level, this might imply that an indefinite proportion of high-risk patients could not have been enrolled in the KEYNOTE-564 due to the lack of accurate lymph-node staging. Such hypothetical inclusion of more pN1 patients, which are at high risk of disease recurrence, might have further increased the survival advantage of the use of adjuvant pembrolizumab. In clinical practice, the lack of information on pN status might affect the decision on who should be referred to the oncologist for receiving adjuvant pembrolizumab [18]. We have already underlined this issue, calling for careful reconsideration of lymph-node dissection to better identify patients who might benefit from adjuvant immunotherapy [19].

In the current study, only those patients who fulfilled the KEYNOTE-564 criteria were included. Four other phase-III randomized control trials are ongoing for patients with intermediate or high-risk RCC (IMmotion-010[NCT03024996], CheckMate-914[NCT03138512], PROSPER [NCT03055013] and RAMPART [NCT03288532]), which differ from the KEYNOTE-564 in terms of inclusion criteria, with many of them including patients at intermediate or even low risk of early disease recurrence [20]. Despite all the results of these trials are not published yet, it is reasonable to expect that a more accurate selection of patients with more aggressive features might result in bigger survival benefit. Indeed, two press releases, one from Bristol – Meyers Squibb and one from Roche – Genentech, revealed that primary endpoint on DFS was not reached in the CheckMate-914 and in the IMmotion-010 trials, respectively [7, 8]. Marconi et al. by use of the RECUR database, a multicenter European retrospective database, tested DFS and OS according to the inclusion criteria of the KEYNOTE-564, IMmotion-010, CheckMate-914, PROSPER, and RAMPART trials [20]. They found a longer DFS when compared with ours for patients who fulfilled the KEYNOTE-564 criteria, but they did not collect data on M1 with NED patients (not included in the RECUR database) and a lower number of pN1 patients was included (almost 5%). This lower proportion of pN1 in the off-trial setting was also confirmed by the data from the Surveillance, Epidemiology, and End Results (SEER) where among patients who ideally fulfilled the KEYNOTE-564 criteria only almost 5% were pN1 [21]. Including too many

patients with low risk of 1-year disease progression may lead to a lower event rate, or worse, to a reduced power if the sample size calculation was based on a higher risk of disease recurrence.

Finally, the KEYNOTE-564 used DFS as primary outcome. The value of DFS as early surrogate for OS is still debated, particularly for RCC. A recent meta-analysis found a modest correlation between 5-year DFS and OS in RCC [22]. Our data suggest that the risk categories for 1-year DFS resulted from the regression tree analysis accurately predict long term OS. Interestingly only the RAMPART trial is using OS as primary endpoint, while all the other ongoing trials on adjuvant treatments for RCC are using DFS as primary endpoint. A positive finding regarding DFS as primary endpoint might not result in acceptance by regulatory authorities unless OS benefit as secondary endpoint is demonstrated. A similar scenario has happened with VEGF-TKIs inhibitors where the heterogeneity of inclusion criteria, the enrollment of patients with low-risk features and finally the use of DFS as primary endpoint have in some way impaired the approval of those drugs in the adjuvant setting [23]. FDA has just approved pembrolizumab use for the adjuvant treatment of patients with intermediate/high risk RCC and off-trial data on its efficacy are now warranted also for the validation of our classification.

Despite several strengths, our study is not devoid of limitations. First, despite the prospective collection of data, the retrospective design of the study might have determined the presence of unmeasured confounders, selection bias, and information bias. In addition, the fact that included patients came from a single tertiary referral center, where lymph nodes dissection might have been proposed more frequently than in nonacademic centers, might restrict the generalizability of our finding. In addition, the included patients ranged over a time span of 20 years, and this might represent a bias given the differences in patients' management over the years. Moreover, we were not able to assess if high risk patients are those who really benefit from adjuvant pembrolizumab or, on the contrary, the advantage of adjuvant pembrolizumab alone in this category is too small to be significant due to the aggressiveness of the disease. In this scenario the cost – benefit ratio of adjuvant therapy might not be adequate, and patients might have little survival advantage at the cost of unpleasant adverse events. At the same time, low risk category, despite quite good 1-year DFS, might still benefit from adjuvant pembrolizumab as compared to placebo, especially in long terms endpoint. Finally, when comparing randomized phase III trials with off-trial data, it should be considered that patients from a certain risk group may be disproportionally included in prospective trials when compared with their true distribution in the population, based on a multitude of factors such as patient and physician preference and trial awareness.

Conclusion

With no surprise, patients potentially eligible for adjuvant pembrolizumab have significantly worse baseline characteristics, pathological features, and early recurrence outcomes rates when compared with the placebo arm of KEYNOTE-564. With respect to the need for an accurate selection of patients who might benefit the most from the adjuvant treatment according to the risk of 1-year disease progression, those with LNI and necrosis appeared the best candidates.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00345-022-04153-6.

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Declarations

Conflict of interest Necchi reports honoraria from Roche, Merck Sharp & Dohme, AstraZeneca, Janssen Pharmaceuticals and Foundation Medicine; has served as a consultant or advisor for Merck Sharp & Dohme, Bristol-Myers Squibb, Rainier Therapeutics, Roche, Bayer, AstraZeneca, Clovis Oncology, Janssen Pharmaceuticals, Incyte, Seattle Genetics, Astellas Pharma and Rainier Therapeutics; has received research funding from Incyte, Merck Sharp & Dohme (institution), and AstraZeneca (institution); and has received travel funding from Roche, Merck Sharp & Dohme, Astra Zeneca, and Janssen Pharmaceuticals outside the submitted work.

Ethical approval and informed consent The study has been conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study. The study was approved by the IRCCS San Raffaele Hospital Ethical Committee (protocollo RENE-versione 29/08/2007-Ospedale San Raffaele di Milano).

References

1. Choueiri TK, Tomczak P, Park SH, Venugopal B, Ferguson T, Chang Y-H et al (2021) Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. New Engl J Med 385:683–694. https://doi.org/10.1056/nejmoa2106391
2. Network NCC (n.d.) Kidney Cancer Version 4.2022. https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf (accessed Decr 26, 2021).
3. Powles T, Albiges L, Bex A, Grünwald V, Porta C, Procopio G et al (2021) ESMO Clinical Practice Guideline update on the use of immunotherapy in early stage and advanced renal cell carcinoma. Ann Oncol 32:1511–1519. https://doi.org/10.1016/j.annonc.2021.09.014
4. Bedke J, Albiges L, Capitanio U, Giles RH, Hora M, Lam TB et al (2021) 2021 Updated European Association of Urology guidelines on the use of adjuvant pembrolizumab for renal cell carcinoma. Eur Urol 81:134–137. https://doi.org/10.1016/j.eururo.2021.11.022
5. Capitanio U, Montorsi F (2016) Renal cancer. Lancet 387:894–906. https://doi.org/10.1016/s0140-6736(15)00046-x
6. Martini A, Fallara G, Pellegrino F, Cirulli GO, Larcher A, Necchi A et al (2021) Neoadjuvant and adjuvant immunotherapy in renal cell carcinoma. World J Urol. https://doi.org/10.1007/s00345-020-03550-z
7. Bristol Myers Squibb Provides Update on CheckMate -914 Trial Evaluating Opdivo (nivolumab) Plus Yervoy (ipilimumab) as Adjuvant Treatment of Localized Renal Cell Carcinoma. Bristol Myers Squibb Provides Update on CheckMate -914 Trial Evaluating Opdivo (Nivolumab) Plus Yervoy (Ipilimumab) as Adjuvant Treatment of Localized Renal Cell Carcinoma 2022. https://news.bms.com/news/details/2022/Bristol-Myers-Squibb-Provides-Update-on-CheckMate--914-Trial-Evaluating-Opdivo-nivolumab-Plus-Yervoy-ipilimumab-as-Adjuvant-Treatment-of-Localized-Renal-Cell-Carcinoma/default.aspx (accessed Aug 16, 2022)
8. Roche's Tecentriq flunks in postsurgery kidney cancer as early-stage liver, lung cancer readouts draw near 2022. https://www.fiercepharma.com/pharma/roches-tecentriq-flunks-postsurgery-kidney-cancer-early-stage-liver-lung-cancer-readout-draw (accessed Aug 16, 2022)
9. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 40:373–383. https://doi.org/10.1016/0021-9681(87)90171-8
10. Paner GP, Stadler WM, Hansel DE, Montironi R, Lin DW, Amin MB (2018) Updates in the eighth edition of the Tumor-Node-Metastasis staging classification for urologic cancers. Eur Urol 73:560–569. https://doi.org/10.1016/j.eururo.2017.12.018
11. Guyot P, Ades A, Ouwens MJ, Welton NJ (2012) Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan−Meier survival curves. Bmc Med Res Methodol 12:9. https://doi.org/10.1186/1471-2288-12-9
12. Gul A, Rini BI (2019) Adjuvant therapy in renal cell carcinoma. Cancer 125:2935–2944. https://doi.org/10.1002/cncr.32144
13. Verma V, Sprave T, Haque W, Simone CB, Chang JY, Welsh JW et al (2018) A systematic review of the cost and cost-effectiveness studies of immune checkpoint inhibitors. J Immunother Cancer 6:128. https://doi.org/10.1186/s40425-018-0442-7
14. Marchioni M, Bandini M, Pompe RS, Martel T, Tian Z, Shariat SF et al (2018) The impact of lymph node dissection and positive lymph nodes on cancer-specific mortality in contemporary pT2-3 non-metastatic renal cell carcinoma treated with radical nephrectomy. Bju Int 121:383–392. https://doi.org/10.1111/bju.14024
15. Capitanio U, Becker F, Blute ML, Mulders P, Patard J-J, Russo P et al (2011) Lymph node dissection in renal cell carcinoma. Eur Urol 60:1212–1220. https://doi.org/10.1016/j.eururo.2011.09.003
16. Capitanio U, Stewart GD, Larcher A, Ouzaid I, Akdogan B, Roscigno M et al (2017) European temporal trends in the use of lymph node dissection in patients with renal cancer. Eur J Surg Oncol 43:2184–2192. https://doi.org/10.1016/j.ejso.2017.07.016
17. Bandini M, Smith A, Zaffuto E, Pompe RS, Marchioni M, Capitanio U et al (2017) Effect of pathological high-risk features on cancer-specific mortality in non-metastatic clear cell renal cell carcinoma: a tool for optimizing patient selection for adjuvant therapy. World J Urol 36:51–57. https://doi.org/10.1007/s00345-017-2093-6
18. Rosiello G, Larcher A, Fallara G, Giancristofaro C, Martini A, Re C et al (2022) Head-to-head comparison of all the prognostic models recommended by the European Association of Urology Guidelines to predict oncologic outcomes in patients with renal cell carcinoma. Urol Oncol Semin Orig Investig. https://doi.org/10.1016/j.urolonc.2021.12.010
19. Capitanio U, Larcher A, Montorsi F (2021) Re: Toni K. Choueiri, Piotr Tomczak, Se Hoon Park, et al. Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. N Engl J Med 2021;385:683–94 Adjuvant pembrolizumab after nephrectomy: a plea to reconsider the need for lymph node dissection. Eur Urol. https://doi.org/10.1016/j.eururo.2021.09.034
20. Marconi L, Sun M, Beisland C, Klatte T, Ljungberg B, Stewart GD et al (2021) Prevalence, disease-free, and overall survival of contemporary patients with renal cell carcinoma eligible for adjuvant checkpoint inhibitor trials. Clin Genitourin Cancer 19:e92–e99. https://doi.org/10.1016/j.clgc.2020.12.005
21. Palumbo C, Mazzone E, Mistretta FA, Knipper S, Perrotte P, Shariat SF et al (2020) A plea for optimizing selection in current adjuvant immunotherapy trials for high-risk nonmetastatic renal cell carcinoma according to expected cancer-specific mortality. Clin Genitourin Cancer 18:314-321.e1. https://doi.org/10.1016/j.clgc.2019.11.010
22. Harshman LC, Xie W, Moreira RB, Bossé D, Ares GJR, Sweeney CJ et al (2018) Evaluation of disease-free survival as an intermediate metric of overall survival in patients with localized renal cell carcinoma: a trial-level meta-analysis. Cancer 124:925–933. https://doi.org/10.1002/cncr.31154
23. Fallara G, Bandini M, Larcher A, Pederzoli F, Karakiewicz P, Tian Z et al (2021) High-risk surgically resected renal cell carcinoma: Is there a role for adjuvant VEGF-TKI inhibitors? Curr Prob Cancer. https://doi.org/10.1016/j.currproblcancer.2021.100759