BENCH TO BEDSIDE
URO-ONCOLOGY
GU CANCERS TRIAD

Proceedings from the SIU B2B Uro-Oncology: GU Cancers Triad Virtual Meeting

May 21–22, 2021

Kidney Cancer

SOCIÉTÉ INTERNATIONALE D'UROLOGIE SIU

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DOI: 10.48083/SCPM5983

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The Bench-to-Bedside Uro-Oncology GU Cancer Triad Meeting was organized by the Société Internationale d'Urologie and was held online on May 21st and 22nd, 2021. The session on kidney cancer took place on the morning of Friday, May 21st, and was chaired by Dr. Simon Tanguay (Canada). This session covered practice-changing advances on the horizon for renal cell carcinoma (RCC), optimal sequencing of systemic therapy, HIF-α inhibition as a novel therapy for RCC, the use of local therapy for metastatic disease, as well as the multimodal management of localized RCC.

The first presentation was led by Dr. Jason Abel (United States). He discussed five practice-changing advances on the horizon for differing RCC settings, including recent developments for small, sarcomatoid, and papillary tumours, as well as early-stage Von Hippel-Lindau syndrome (VHL) and high-risk, non-metastatic RCC. First, Dr. Abel focused on strategies for improving risk stratification for active surveillance of small RCC, which represents the majority of initially diagnosed kidney cancers[1]. Most patients diagnosed with small RCC will not progress to metastatic disease or die from kidney cancer, as pointed out by Dr. Abel. Active surveillance is an established management approach for small RCC, as indicated in several guidelines[2,3]. However, as more natural history data become available, improved risk stratification strategies may help to select patients and determine follow-up for active surveillance.

While active surveillance is usually recommended for elderly patients with limited life expectancy, new data are providing additional insights for managing younger patients with small RCC. In the DISSRM registry, which evaluated 224 patients aged 60 or younger, 30% of whom were managed with active surveillance, no patient developed metastatic disease or had disease recurrence following delayed intervention[4]. This study suggests that active surveillance is a safe initial strategy for selected younger patients and potentially avoiding some interventions. However, longer follow-up is necessary given the long natural history of the disease. Improved risk stratification based on genetic alterations may further help to select patients for active surveillance. In a study by the National Cancer Institute (NCI), patients with pathologic germline alterations and RCC were shown to have differing tumour growth rates[5]. While it may be difficult to extrapolate the results to the general RCC population, these findings are encouraging given the paucity of genetic characterization of kidney cancers in the context of active surveillance. Dr. Abel emphasized that, as the understanding of small RCC biology improves, active surveillance will become more personalized.

The presence of sarcomatoid features in RCC is associated with aggressive tumour biology and early mortality[6]. Although sarcomatoid dedifferentiation occurs in only ~5% of tumours overall, these patients have some of the worst outcomes: they frequently present with metastatic disease and have poor survival despite aggressive treatment[6]. While management of this patient population remains challenging, recent efforts have improved the molecular characterization of sarcomatoid tumours and identified the basis of response to immune checkpoint inhibitor (ICI) therapy[7]. In parallel, a post hoc subgroup analysis of

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139 patients with sarcomatoid RCC enrolled in the CheckMate 214 trial demonstrated positive outcomes in response to dual ICI therapy with nivolumab + ipilimumab[8]. Compared to treatment with sunitinib, treatment with nivolumab + ipilimumab resulted in significantly improved median overall survival (OS) (not reached vs. 14.2 months; HR=0.45 [95% CI 0.3–0.7]; P=0.0004) and higher confirmed objective response rate (ORR). Dr. Abel also highlighted the high proportion of patients achieving complete response (CR) with nivolumab + ipilimumab, which was almost double that observed in RCC without sarcomatoid dedifferentiation. These advances in tumour characterization and ICI combination therapy development may significantly improve outcomes for patients with sarcomatoid RCC.

Historically, most research in systemic therapies for metastatic RCC has targeted the most prevalent clear cell subtype. By contrast, very few clinical trial data are available for papillary RCC, the second most common subtype[9]. Papillary RCC is generally characterized by alterations in the MET pathway, which can be further classified into type 1 and type 2 tumours. However, the pathologic heterogeneity of this RCC subtype may be challenging. A recent trial with cabozantinib, a tyrosine kinase inhibitor (TKI) targeting vascular endothelial growth factor (VEGF) receptors and the MET pathway, has shown promising results for patients with papillary RCC. In this open-label, randomized, phase 2 trial, treatment with cabozantinib significantly improved median progression-free survival (PFS) compared to sunitinib in patients with metastatic papillary RCC (9.0 vs. 5.6 months; HR=0.60 [95% CI 0.37–0.97]; one-sided P=0.019)[10]. While data for systemic therapy in papillary RCC may be difficult to evaluate given the low frequency and complex pathology of this disease subtype, the promising results of combined MET and VEGFR2 inhibition with cabozantinib may lead to improved outcomes in this patient population in the future. Additionally, improved molecular characterization of the disease may help inform the selection of novel agents for treating papillary RCC.

Dr. Abel also discussed the recent potentially practice-changing use of HIF-2α inhibitors for the treatment of VHL disease, a syndrome caused by germline inactivation of the VHL gene[11]. Patients with VHL disease may develop clear cell RCC (ccRCC), as well as hemangioma, pheochromocytoma, and other tumours in the pancreas, retina, and other sites. The treatment of patients with VHL is challenging. Many of these patients undergo multiple partial nephrectomies for ccRCC over their lifetime and can progress to metastatic disease. In addition, repeated treatment can also lead to renal dysfunction. In an open-label, phase 2 trial, the efficacy of belzutifan (MK-6482) was evaluated in patients with VHL disease and nonmetastatic RCC[12]. Belzutifan is an inhibitor of HIF-2α, a transcription factor that becomes constitutively active and drives tumour growth due to VHL gene inactivation. In the trial, the ORR was 36% for VHL-associated ccRCC per RECIST v1.1 by independent review committee (IRC). Tumour response was also observed for non-RCC tumours, including ORR of 64% for pancreatic lesions, 30% for hemangioblastomas, and 69% for retinal lesions. Only one patient discontinued treatment due to a treatment-related adverse event (TRAE) and no grade 4 or 5 TRAEs were observed. These early results are encouraging and show the potentially practice-changing application of systemic therapy with HIF-2α inhibitors for treatment of RCC tumours associated with VHL disease.

Lastly, Dr. Abel presented recent advances for the treatment of high-risk nonmetastatic RCC. Generally, this patient population is treated with nephrectomy and surveillance. However, patients with pathologic T3 disease are more likely to develop metastasis after surgery compared to patients with T1 or T2 tumour stage. Two hypotheses may explain metastatic progression in this patient population: failure to detect micrometastasis by conventional imaging at the time of surgery or failure of the patient's immune system to prevent any tumour cells from implanting and growing at different sites. The latter could be improved with the use of ICIs as adjuvant therapy. Adjuvant therapy with pembrolizumab for high-risk nonmetastatic RCC is under investigation in the randomized phase 3 KEYNOTE-564 trial. In a recent press release, it was announced that the trial had met its primary endpoint of improved disease-free survival (DFS) compared to

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placebo[13]. These data are positive and have important future implications for managing patients with high-risk nonmetastatic RCC.

During the Q&A, Dr. Abel discussed whether early biopsy may help identify patients with a sarcomatoid subtype who could benefit from neoadjuvant therapy for locally advanced RCC. Although this is a rare subtype and biopsies are typically performed pre-operatively in patients with metastatic disease only, in the context of a clinical trial, Dr. Abel believes this is a logical approach that bears investigation in the future. Next, Dr. Abel addressed the utility of genetic profiling in patients with small RCC. He believes this will provide better insights on management options, particularly in patients who are neither very young or elderly and correspond to the majority of small RCC diagnoses. Lastly, Dr. Abel provided his perspective on the recently positive results of adjuvant ICI therapy in RCC. He believes that if ongoing clinical trials in this setting are able to demonstrate OS benefit, it will lead to important changes that would change clinical practice.

Next, Dr. Laurence Albigès (France) presented the optimal sequencing strategies in metastatic RCC. Over the past decades, advances in understanding the RCC pathophysiology have led to the identification of two major therapeutic targets: first, the role of the HIFα-VEGF axis in tumour angiogenesis[14] and, second, the development of ICIs as drivers of immune response to tumours[15]. In addition, management of metastatic RCC is also influenced by the IMDC risk assessment, not only to evaluate patient prognosis but also to guide treatment decisions[16].

The new guidelines of the European Society for Medical Oncology (ESMO) outline two main approaches for standard systemic first-line treatment of intermediate and poor risk ccRCC (adapted from [17]). The first approach uses dual ICI combination therapy with nivolumab + ipilimumab, which has demonstrated long-term benefits in OS and PFS[18]. The second approach combines VEGFR TKI with ICI. Multiple studies over the past 3 years have reported positive results for different TKI + ICI combinations in the treatment of metastatic RCC[19–21]. These studies have demonstrated that TKI + ICI combination may result in modulation of immune response by targeting VEGF inhibition, which may underlie the OS benefit with TKI + ICI versus standard of care observed in the trials. Most notably, TKI + ICI has been shown to result in high tumour response rate and sustained response over time, as well as clinical benefit across IMDC patient risk groups[19–21]. At the moment, both the dual ICI and TKI + ICI combination have demonstrated clinical benefits and there is no evidence to support one approach over the other. As highlighted by Dr. Albigès, clinical trials comparing dual ICI versus TKI + ICI would help guide treatment decisions between the two approaches.

In the second-line setting, there are well-defined treatment recommendations for patients who received single-agent first-line therapy[3]. However, the new combination therapy options available as first line may impact treatment decisions in the second-line setting. While ongoing clinical trials may help to identify the optimal second-line approach, several critical considerations are still unanswered. Dr. Albigès summarized those as the following questions: 1) Is there a role for salvage ipilimumab, if not used in the first line, for patients who progressed after programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy? 2) Is there a role for combination therapy as second-line or subsequent treatment? 3) Is there a role for sustained PD-1 inhibition in the second-line therapy? 4) Are there any new targets that should be considered in this setting? For salvage ipilimumab, several studies have shown only a small benefit of combining ipilimumab to nivolumab in patients who did not respond to anti-PD-1/PD-L1 as first-line monotherapy[22–24]. While dual ICI combination therapy following first-line ICI has shown ORR around ~10%–15% across studies[22,23], the VEGFR-ICI combination with lenvatinib + pembrolizumab reached 50%[25]. Dr. Albigès believes more data are necessary to elucidate the role of sustained PD-1 inhibition. This is currently under investigation in the phase 3 CONTACT-03 trial, which randomized patients to receive either atezolizumab + cabozantinib or cabozantinib following progression with ICI therapy[26].

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Among non-ccRCC subtypes, distinct response to ICI is observed depending on the tumour type. In papillary RCC, the encouraging results observed in the SWOG trial may result in the adoption of cabozantinib as the new standard to treat patients with this RCC subtype[10]. Ongoing studies are aiming to provide insights into molecular MET screening for papillary RCC, which may reveal new therapeutic targets. Other trials may also help to guide the choice of combination therapy in patients with non-ccRCC subtypes. Lastly, Dr. Albigès highlighted the critical implications of adjuvant ICI therapy on subsequent first-line metastatic treatment options, given the positive results of the KEYNOTE-564 trial, which may lead to important practice changes in advanced RCC.

In the Q&A period, Dr. Albigès was asked whether patients who progress while on treatment with nivolumab + ipilimumab could be rechallenged with ipilimumab. She indicated that there are no data supporting ipilimumab rechallenge and very limited information on ipilimumab activity at later stages. Instead of a rechallenge, she would recommend patient inclusion in a clinical trial with different agents. Next, Dr. Albigès detailed her approach for stopping treatment in patients who achieved CR or prolonged stable disease (SD). She emphasized that this is a discussion to be had with the tumour board as well as the patient. Generally, Dr. Albigès will only recommend discontinuation with at least 1 year of treatment if the patient has an overall good safety profile and has achieved CR. Otherwise, these discussions may occur between 1 to 2 years following the beginning of treatment. Lastly, Dr. Albigès discussed her perspective on new strategies for improving patient response to systemic therapy. She believes that a triple ICI-TKI combination may be a way to intensify treatment and potentially improve outcomes. She also emphasized that this approach may have an increased toxicity profile and that early identification of patients who could benefit from triple agent combination is critical.

The following presentation was made by Dr. Toni Choueiri (United States), who discussed the role of HIF-2α inhibitors as a novel therapeutic class for RCC treatment. HIF-α activity is intrinsically associated with oxygen concentration and VHL gene alterations. During hypoxia or when there are mutations in VHL, such as in VHL syndrome and ccRCC, HIF-α becomes intrinsically active, leading to downstream transcriptional effects[27]. HIF-2α is one of the three subunits of HIF-α and regulates multiple oncogenic pathways, making it an important therapeutic target for ccRCC[28].

PT2385 was the first generation of HIF-2α inhibitors. It was validated for the treatment of heavily pretreated patients with metastatic ccRCC in a phase 1 trial, resulting in an ORR of 13%[29]. Modifications of PT2385 led to the development of belzutifan a second generation of HIF-2α inhibitor with greater efficacy, increased bioavailability, and less protein binding[30]. In a recently published phase 1 trial of patients with metastatic ccRCC who had previously received systemic therapy, belzutifan resulted in an ORR of 25%, with a median PFS of 14.5 months[31]. This second-generation HIF-2α has also been investigated in VHL syndrome-associated RCC, which typically presents as localized ccRCC. In the preliminary analysis of a phase 2 trial, treatment with belzutifan resulted in an ORR of 28%, with ~87% of patients exhibiting tumour shrinkage[32]. In an updated analysis of this trial, discussed earlier by Dr. Abel, the ORR was improved to 36% for VHL-associated ccRCC[12].

In terms of safety profile, HIF-2α inhibitors have different toxicity compared to VEGF inhibitors. In a phase 1 trial, 15% of patients with metastatic ccRCC who received belzutifan developed grade 3 hypoxia[31]. This was seen without any concomitant cardiac or pulmonary complications. HIF-2α has an important role in the pulmonary vasculature and carotid body physiology. While the underlying mechanism is not fully understood, blocking HIF-2α might exacerbate ventilation-perfusion mismatch and ventilatory sensitivity to hypoxia. This is an important consideration for patients with chronic pulmonary diseases or those at high altitude, who may be relying on enhanced sensitivity to hypoxia to maintain adequate ventilation.

Combination therapy with HIF-2α inhibitor and ICI/TKI is also under investigation. In the phase 1 trial, patients with advanced RCC treated with PT2385 + nivolumab combination had an ORR of 22% and median PFS of 10 months, for those who were exposed

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to therapeutic doses of PT2385[33]. In a phase 2 trial, preliminary analysis of patients with up to two prior systemic therapies, including ICI (Cohort 2), demonstrated tumour shrinkage in 88% of patients and a median PFS of 16.8 months following treatment with belzutifan + cabozantinib[34]. Phase 3 studies are underway to evaluate the efficacy and safety of belzutifan either in combination with lenvatinib[35] or as monotherapy[36] for the treatment of advanced RCC.

Dr. Choueiri emphasized the importance of examining the potential mechanisms of resistance as part of the development of a new therapeutic agent. For HIF-2α inhibition, pre-clinical and translational models suggest that mutations in HIF-2α and HIF-1β may preclude binding of HIF-2α inhibitors and lead to increased affinity between the two subunits, resulting in activation of the HIF pathway (summarized in [28]). RNA interference (RNAi) may provide an alternative to small-molecule HIF-2α inhibition by targeting and silencing HIF-2α expression. This approach is under investigation in a phase 1 trial evaluating the efficacy of a proprietary targeted RNAi molecule delivery platform (ARO-HIF2) for the treatment of ccRCC[37] and has shown encouraging results in pre-clinical models[38]. With positive results from several trials and ongoing development, HIF-2α represents a novel therapeutic target whose implications may expand beyond VHL syndrome and RCC.

The presentation was followed by a Q&A session during which Dr. Choueiri discussed his perspective on how different VHL mutations may affect treatment response to HIF-2α inhibition in patients with RCC. He believes that most RCC patients likely have some form of VHL mutation that may be difficult to detect. He pointed out that, under these circumstances, downstream alterations may help identify other RCC syndromes that could be targeted with HIF-2α inhibitors. Next, Dr. Choueiri discussed the potential role of HIF-2α inhibitors in triple-agent combination therapy for RCC. He explained that the latest advances in HIF-2α inhibition are promising and may lead to the development of improved molecules that could be combined with other agents. However, he advised caution in regards to the cost and potentially increased toxicities of combination approaches.

Next, Dr. Axel Bex (United Kingdom) discussed why and when local therapy should be used to manage metastatic kidney cancer. First, Dr. Bex focused on the why. In general, patients who undergo resection of multiple metastases over time may have 5-year OS that are comparable to those who underwent single metastasectomy[39]. If achievable, complete resection of metastases may lead to cure, potential improvement of DFS, PFS, and OS (although not yet evaluated in a randomized clinical trial setting), as well as delay or discontinuation of targeted therapies. However, Dr. Bex questioned whether metastasectomy is indeed required to achieve these objectives. For instance, active surveillance may be a viable, safe option for patients with oligometastasis to manage the disease prior to starting systemic therapy[40]. In addition, cure is generally not achievable in high-risk patients treated for recurrence[41]. Finally, while a systematic review favours metastasectomy based on the hazard ratio for OS, this may be biased because of the distinct patient populations evaluated in retrospective studies[42].

RCC has different pathways of metastatic evolution and management approaches. In patients who present with the primary tumour and single metastasis, treatment involves nephrectomy and resection of the metastatic lesion, which may result in several years of survival without the disease. These patients generally present with a linear evolution driven by VHL mutation or an attenuated progression, as a result of PBRM1 mutations. On the other end of the spectrum, there are patients who present with multiple metastatic sites and follow a punctuated evolution with rapid progression, mainly driven by BAP1 alterations[43]. By contrast, translational data in prostate cancer suggest that metastasis-to-metastasis spread can occur[44]. The time to transformation into a more aggressive subtype may also be unpredictable and lead to a metastatic shower[45], which would further support the role of metastasectomy in patient management. Nevertheless, these treatment decisions remain challenging in the absence of prospective randomized studies to evaluate the true impact of metastasectomy on survival.

Dr. Bex then discussed the timing for performing metastasectomy. Although early presentation of

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recurrence is a strong indicator of poor prognosis[46], it is impossible to predict the momentum of metastatic progression. General predictors associated with positive outcomes after metastasectomy include: the presence of solitary or oligometastatic lesions, a complete resection, disease-free interval of over 2 years, single-organ site, no sarcomatoid features or high-grade tumour, absence of nodal metastases, good performance status, and a favourable-to-intermediate risk IMDC[47]. Dr. Bex emphasized the importance of keeping these factors in mind when deciding the management approach for metastases, given the high complication rates of metastasectomies[48].

There are ongoing phase 3 trials evaluating the role of adjuvant ICI therapy in RCC that have included patients who also underwent complete metastasectomy, namely KEYNOTE-564 (pembrolizumab vs. placebo) and IMmotion 010 (atezolizumab vs. placebo). If these trials demonstrate DFS or OS benefit, metastasectomy followed by ICI may become the new standard based on prospective randomized data.

During the Q&A, Dr. Bex discussed whether some sites should not undergo metastasectomy due to poor associated outcomes. He advised that the site as well as the complexity of the surgical procedure should be considered. In general, metastases in the liver, pancreas, and brain may require a different management approach. Next, Dr. Bex provided his insights on the advances of stereotactic body radiation therapy (SBRT) to manage multiple metastatic lesions. He believes that SBRT may provide an alternative, and even preferable, approach to metastasectomy, although data comparing both strategies are needed. Lastly, Dr. Bex discussed his management approach for patients who achieve partial response to ICI and have one or two metastatic sites. If the lesions are small and stable, he does not see a benefit for metastasectomy. By contrast, if the lesions grow during treatment, he recommends controlling the metastatic growth with a focal therapy (e.g., SBRT) rather than switching to a different line of systemic therapy.

The session concluded with a case-based panel on multimodal management of localized RCC. This was led by Dr. Umberto Capitanio (Italy), with the discussion based on the input of Drs. Simon Tanguay (Canada), Maxine Tran (United Kingdom), and Alessandro Volpe (Italy). The case was a 51-year-old male with a high body mass index (BMI) of 42 kg/m^2 who had a small renal mass incidentally detected during an abdominal ultrasound. Computed tomography (CT) revealed a 35-mm renal tumour, which was >50% endophytic and lay in close proximity to the renal calices and sinus, representing intermediate complexity for surgery.

The tumour was staged as cT1aN0M0, with a very low risk of metastasis, meaning that chest imaging and bone scan were not necessarily indicated according to published nomograms[49]. Other imaging options that may be considered for further evaluation include magnetic resonance imaging (MRI), if the patient had low estimated glomerular filtration rate (eGFR); sestamibi positron emission tomography (PET)/CT, to differentiate between RCC and oncocytoma; and contrast-enhanced ultrasound scan for equivocal lesions in patients with low eGFR.

Biopsies are not performed routinely in this patient population. However, they may provide additional insights given that small renal masses are heterogeneous and may have differing patterns of growth and spread that can be predicted through diagnostic biopsies[50]. In addition, renal biopsies have high sensitivity and specificity to detect malignancies[51], with minimal complications associated with the procedure. In the patient case, biopsy revealed a grade 2 ccRCC.

In this clinical case, the patient underwent robotic-assisted partial nephrectomy and final pathology indicated a grade 2 pT1a ccRCC with negative surgical margins. Surgery is the preferred management option for patients with small renal masses. Focal therapy and active surveillance may also be considered for some patients, such as the elderly and frail[2]. Focal therapies (such as cryoablation, radiofrequency ablation, and microwave ablation) generally have low morbidity and may be performed in the outpatient setting but should be reserved to tumours ≤3 cm[2]. In addition, while these focal approaches show generally good outcomes in clinical practice, evidence supporting the preferred use of either focal therapies or surgery in managing small renal masses is currently lacking. Active surveillance may also be considered for patients with low-grade small RCC, although the tumour size

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at diagnosis should also play a role in management selection[52]. Currently, the prospective EASE study is investigating the use of active surveillance in small RCC to determine standards for indication, follow-up, criteria for progression, and delayed intervention with this management approach[53].

Other approaches such as neoadjuvant treatment, systemic therapy, and radiotherapy are only recommended in this disease setting through clinical trial enrolment. Neoadjuvant therapy is usually implemented to reduce tumour size prior to surgery and would unlikely benefit the patient in the case. By contrast, the recent positive experience with HIF-2α inhibitors in patients with VHL and RCC[12] might lead to important developments in this setting. SBRT allows the delivery of precise radiation doses to the target tumour, with the additional benefit of being performed in the outpatient setting. While this may be a compelling option for morbid and inoperable patients, particularly with metastatic disease, SBRT may have limited applicability in the localized setting, in which other treatment options are available.

Abbreviations Used in the Text

BMI	body mass index
ccRCC	clear cell renal cell carcinoma
CI	confidence interval
CR	complete response
CT	computed tomography
DFS	disease-free survival
eGFR	estimated glomerular filtration rate
ESMO	European Society for Medical Oncology
HR	hazard ratio
ICI	immune checkpoint inhibitor
IMDC	International Metastatic RCC Database Consortium
IRC	independent review committee
MRI	magnetic resonance imaging
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
RNAi	RNA interference
SBRT	stereotactic body radiation therapy
SD	stable disease
TKI	tyrosine kinase inhibitor
TRAE	treatment-related adverse event
VEGF	vascular endothelial growth factor
VHL	Von Hippel-Lindau syndrome

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