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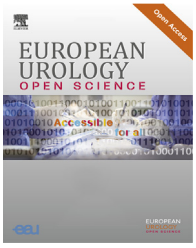

European Association of Urology

Open to Debate: Con

Cytoreductive Nephrectomy in 2021: Obsolete

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The role of cytoreductive nephrectomy (CN) in the treatment of patients with metastatic renal cell carcinoma (mRCC) is an area of continued controversy. Whereas nephrectomy can be performed in the metastatic setting for palliative indications to relieve gross hematuria, abdominal pain, or paraneoplastic syndromes, whether to pursue nephrectomy with therapeutic intent is a very different question. The treatment landscape for mRCC has gone through considerable changes in recent years. However, our collective understanding of CN has failed to evolve accordingly. Proponents of CN suggest that cytokines produced by a larger primary tumor potentially hinder the antitumor immune response elicited by immune checkpoint inhibitors. Others suggest that with the proven efficacy, safety, and—in some cases—quality-of-life improvements with newer combination therapies, subjecting patients to major surgery is of questionable benefit and may have higher potential for harm. As part of the *Open Debate Series*, we argue here that CN may pose undue harm and is largely unadvisable for patients with mRCC.

During the cytokine era, CN was positioned as a standard of care on the basis of its superior survival advantage when performed before treatment with interferon-α [1]. With the advent of targeted therapies such as sunitinib, the role of this procedure became uncertain. SURTIME and CARMENA are perhaps the most important clinical trials evaluating the relevance of CN in the targeted therapy era. The phase 3 SURTIME trial investigated differences in the timing of surgery in relation to treatment with sunitinib (upfront vs deferred). The study failed to meet its primary endpoint of progression-free survival (PFS) for deferred CN. SURTIME did show a modest survival advantage for the deferred approach, but these findings better answer the question of timing of surgery rather than whether it should be pursued at all [2]. By contrast, the phase 3 CARMENA trial was a randomized noninferiority trial that evaluated CN followed by sunitinib versus sunitinib alone in mRCC patients. Although the disproportionally high number of patients with poor risk may limit the applicability of the results, the study concluded that sunitinib was noninferior to CN followed by sunitinib in the intention-to-treat population. More recent results reinforce the notion that patients with two or more International Metastatic RCC Database Consortium risk factors experience inferior survival [3].

Since the conception of the aforementioned trials, and in the wake of the introduction of immune checkpoint inhibitors, the number of systemic therapy options has increased exponentially. Most recently, multimodal combination therapies have become the mainstay for first-line treatment of mRCC. This was in large part because of the impressive clinical efficacy benefit observed with this approach across three pivotal randomized clinical trials: Keynote-426, Checkmate 9ER, and Checkmate 214. Even though these combinations represent the current standard of care for mRCC, only a small percentage of patients with an intact primary tumor were included in these studies (17–30%)

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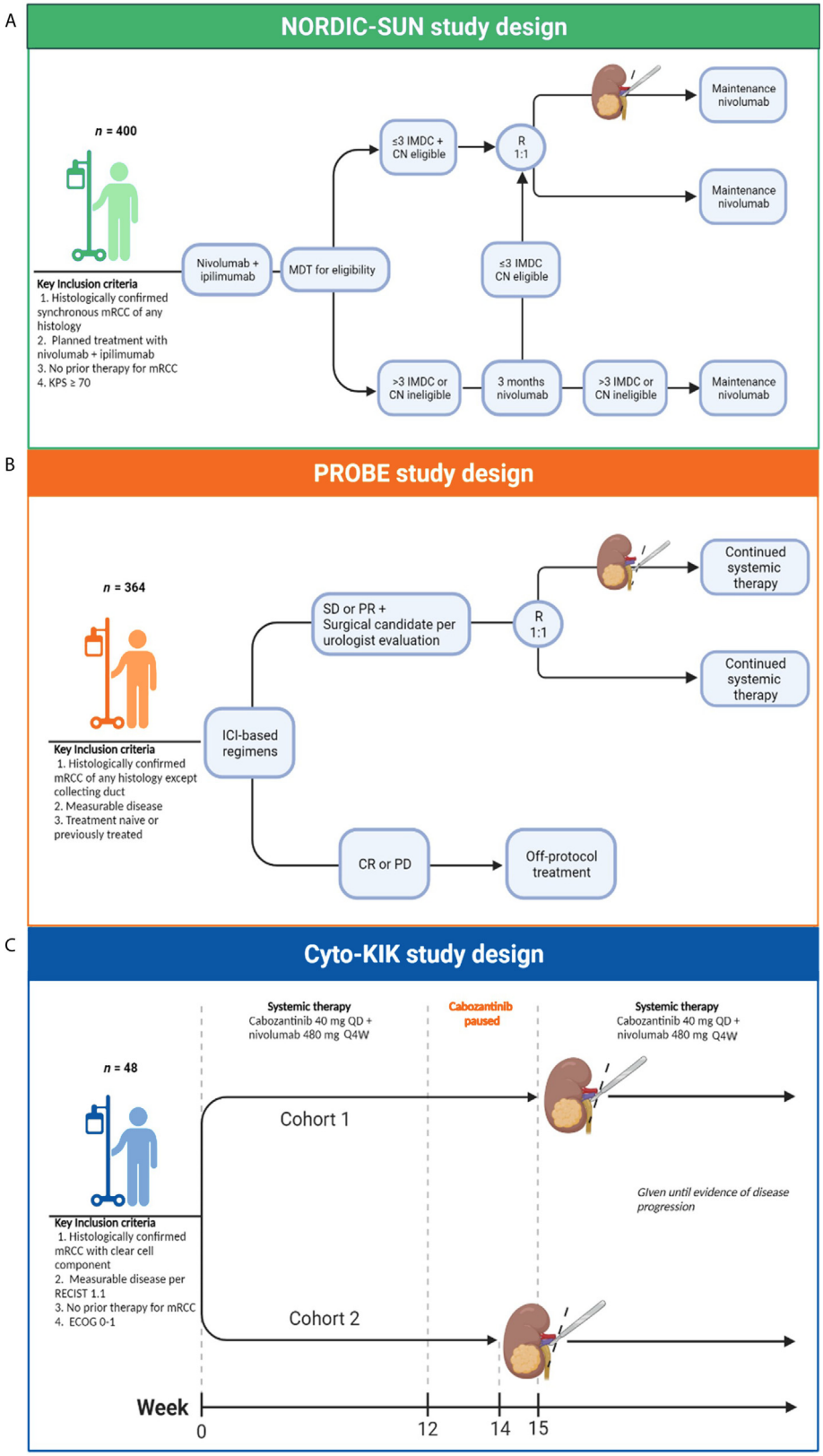

Fig. 1 – Study design for the phase 3 (A) NORDIC-SUN and (B) PROBE trials and (C) the phase 2 Cyto-KIK trial. mRCC = metastatic renal cell carcinoma; IMDC = International mRCC Database Consortium risk factors; KPS = Karnofsky performance status; R = randomization; PD = progressive disease; SD = stable disease; PR = partial response; CR = complete response; MDT = multidisciplinary tumor board; ICI = immune checkpoint inhibitor; QD = every day; Q4W = every 4 wk; RECIST = Response Evaluation Criteria in Solid Tumors; ECOG = Eastern Cooperative Oncology Group performance score. Kidney images denote cytoreductive nephrectomy (CN).

[4–6]. Hence, continued use of CN has been upheld primarily on the basis of retrospective data.

A recent post hoc analysis from the CLEAR trial showed an improvement in overall survival, PFS, and objective response rate for patients with an intact primary tumor receiving lenvantinib with pembrolizumab when compared to sunitinib [7]. While the results from this type of analysis are not conclusive, they suggest that the primary tumor can respond just as well as remaining systemic disease. Given the current lack of clinical equipoise for the role of CN in the current treatment paradigm, results from prospective clinical trials evaluating this intervention are eagerly awaited.

To help bridge this gap, two phase 3 clinical trials have been initiated. NORDIC-SUN (NCT03977571) will compare the standard of care of nivolumab/ipilimumab with or without CN. Similarly, the PROBE trial (NCT04510597) will compare standard-of-care first-line therapy with or without surgery (Fig. 1A,B). Both studies have overall survival as a primary endpoint. Cyto-KIK (NCT04322955) is a phase 2 clinical trial assessing the impact of this intervention in patients treated with cabozantinib plus nivolumab (Fig. 1C). The primary endpoint of the study is the percentage of participants with a complete response.

The lack of strong prospective data notwithstanding, it would be remiss to not address the potential harm a major surgical procedure such as nephrectomy can pose. A large study showed that the rate of postoperative complications after radical nephrectomy was approximately 22% for any complication and 4% for major complications [8]. Furthermore, there is growing concern about long-term outcomes such as chronic kidney disease (CKD). One study showed that rates of postoperative stage $\geq$3b CKD can range from 21% to as high as 69% in moderate- and high-risk groups, depending on age, diabetes, and preoperative kidney function [9]. These concerns become increasingly relevant as a growing number of patients become long-term survivors of mRCC.

In conclusion, despite the retrospective evidence supporting the use of CN in the immune checkpoint inhibitor era, prospective validation of these findings in randomized clinical trials remains an unmet need. Therefore, until such evidence is available, CN should only be considered in selected cases.

Conflicts of interest: The authors have nothing to disclose.

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