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# CHAPTER 6

## Indications and Outcomes for Deferred Cytoreductive Nephrectomy Following Immune Checkpoint Inhibitor Combination Therapy: Can Systemic Therapy be Withdrawn in Patients with No Evidence of Disease?

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## Abstract

### Background

Upfront cytoreductive nephrectomy (CN) is no longer standard of care for metastatic renal cell carcinoma (mRCC) patients with intermediate or poor International mRCC Database Consortium prognosis.

### Objective

To investigate indications for CN following first-line ipilimumab-nivolumab and focus on management and outcome of patients who were resected to no evidence of disease (NED).

### Design, setting, and participants

A retrospective cohort study among patients with synchronous mRCC who received treatment with ipilimumab-nivolumab (n=125) between March 2019 and June 2022 at four European medical centres.

### Interventions

Deferred CN. At one of the four centres, nivolumab was stopped following NED.

### Outcome measurements and statistical analysis

Complete response of metastases (mCR) according to RECIST 1.1, near mCR was defined as >80% reduction of cumulative metastatic volume. Treatment-free survival (TFS), disease-free survival (DFS), progression-free survival (PFS) and cancer-specific survival (CSS) were determined.

### Results and limitations

At a median follow-up of 25 months, 23 of 125 patients (18%) underwent deferred CN. Of 26 patients (21%) with a (near) mCR, 19 (73%) underwent CN to achieve NED, of whom 11 (58%) discontinued nivolumab with a median TFS of 21 months. For patients who continued (n=8(42%)) versus discontinued nivolumab following NED, 2-year DFS was 83% versus 60% (p=0.675) and 3-year CSS was 100% versus 70% (p=0.325), respectively. Four patients received CN because of a dissociated response of the primary tumour and were still alive at a median follow-up of 5 months.

**Conclusion**

CN can result in NED, durable DFS and substantial time off systemic therapy. More collaborative data are required to ascertain the benefits of treatment discontinuation versus oncological safety.

**Patient summary**

In this real-world data study 18% of patients who received immunotherapy underwent a deferred nephrectomy. The majority was disease-free at 3 years follow-up. Half of the patients who stopped immunotherapy after nephrectomy are off therapy for 21 months or longer. Larger studies are needed to investigate the effect of nephrectomy and treatment discontinuation on survival.

## 1. Introduction

According to recent epidemiological data, between 10-20% of patients diagnosed annually with renal cell carcinoma present with metastatic disease and the primary tumour in place (1).

Two randomised controlled trials (RCT) in the era of VEGFR-targeted therapy showed that upfront cytoreductive nephrectomy (CN) should no longer be standard of care among patients with clear-cell primary metastatic renal cell carcinoma (mRCC) that require systemic therapy (2,3). Instead, based on the results of CARMENA and SURTIME, guidelines recommend that deferred CN can be offered to patients with a sustained response to systemic therapy (4,5). Meanwhile, systemic therapy for treatment-naive clear-cell mRCC has changed to immune checkpoint inhibitor (ICI) combination therapies (4,5,6). RCTs investigating the role of deferred CN in the era of ICI are ongoing (7). In the interim, major guidelines recommend upfront systemic therapy for patients with synchronous mRCC based on the inclusion of up to 30% of patients without prior nephrectomy in the pivotal ICI trials (4,5,6).

With ICI treatment options expanding, an increasing number of patients are being offered deferred CN for various indications (8-13). While severe desmoplastic tissue planes following ICI can be of concern during deferred CN (10), surgery is generally considered safe. Complete pathological responses of the primary tumour have been described in 11-13% of patients previously treated with ICI (10). Anecdotally, withdrawal of systemic therapy has been reported in patients who had a complete response of metastatic sites (mCR) to first-line ICI and were rendered disease-free by deferred CN (10, 11). Promising results have been described in a series of 5 patients who remained off treatment for a median of 531 days (10). However, the lack of information regarding indication and frequency of deferred CN in comparison to the unselected patient population with synchronous mRCC receiving first-line ICI, as well as variations in ICI/ICI or ICI/TKI combinations or single-agent nivolumab impact on the interpretation of the reported series (8-13).

Here we retrospectively reviewed a multi-centre series of patients with mRCC and the primary tumour in place, treated with first-line nivolumab plus ipilimumab. We investigated response to systemic treatment, indications for CN and focus on

further management and outcome of patients who had mCR and were resected to no evidence of disease (NED) following deferred CN.

## 2. Patients and Methods

We reviewed clinicopathological data of consecutive biopsy confirmed synchronous mRCC patients who received first-line ipilimumab-nivolumab at four European medical centres: Netherlands Cancer Institute (NKI, n= 73) and the Amsterdam University Medical Centers (n= 26) in Amsterdam, the Royal Free Hospital and St. Bartholomew's Hospital in London (n= 26). Treatment consisted of four cycles of ipilimumab (1 mg/kg) and nivolumab (3 mg/kg), followed by maintenance nivolumab monotherapy (480 mg monthly). Information on gender, age, number and site of metastases, treatment duration, response of the primary tumour and metastatic sites, International Metastatic Database Consortium (IMDC) risk groups, and CN were collected.

All patients were discussed at a multidisciplinary tumour board prior to treatment. Deferred CN was considered if patients had an ongoing mCR or near mCR with the intention to resect to NED. Near mCR was defined as a residual lesion at a single organ site following a major partial response, defined as >80% reduction of cumulative metastatic volume, as previously described by Pignot et al. (11). Another indication for deferred CN was to achieve local control in case of symptoms or progression of the primary tumour despite ongoing response of metastases. Treatment response was monitored with cross-sectional imaging of the chest, abdomen, and pelvis every three months and analysed according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 (14).

At the NKI, nivolumab was discontinued in all patients with NED following CN. At the other three centres, nivolumab was continued unless drug-related adverse events required discontinuation. Treatment-free survival (TFS) was defined as the time between nivolumab discontinuation until restarting nivolumab upon disease recurrence. Disease free survival (DFS) was defined as the time between resection to NED and disease recurrence, progression-free survival (PFS) was defined as time from CN to disease progression, cancer specific survival (CSS) was recorded as time between first start of ICI and death of disease.

### 2.2 Statistics

DFS, PFS and CSS Kaplan Meier were compared between IMDC risk groups and between modalities using log rank tests. Analyses were conducted with IBM SPSS software (version 27, SPSS Inc., Chicago, III.USA). On two-sided analysis, P-values of <0.05 were considered significant.

## 3. Results

Between March 2019 and June 2022, 125 patients with a median age of 64 years (range 40-90 years) started ICI for synchronous mRCC. Baseline characteristics are displayed in **Table 1.** Of these patients, 70 (65%) were intermediate IMDC risk and 53 (42%) IMDC poor risk. Data were missing in 2 patients. A consort diagram of management following response at metastatic sites is shown in **Figure S1.** Median follow up was 25.1 (95%CI 18.6-31.5) months since start of ICI. Cancer specific survival and PFS for the entire cohort and for both IMD risk groups are shown in **Figure S2**. Median PFS was 12.6 (95%CI 9.6-15.7) months, Median CSS was not reached.

### 3.1 Deferred CN

Twenty-three of 125 patients underwent deferred CN (18.4%). Median ICI duration prior to CN was 13.6 (95%CI 11.7-15.5) months. Nineteen patients underwent CN to achieve NED following (near) mCR and 4 patients received CN because of increase (n=3) or symptoms (n=1) of the primary tumour. Median follow-up following CN was 18.6 (95%CI 13.7-23.6) months. Sixteen CNs were performed with a robot-assisted approach, 7 with an open transabdominal approach. At CN, median time of surgery was 144 (IQR 495)) minutes, median estimated blood loss was 50 (IQR 495) millilitres and median length of hospital stay was 4 (IQR 2) days. One patient required transfusion post CN. Additionally, 4 complications occurred within 30 days post CN (urinary tract infection, grade II; atrial fibrillation, grade II; arrhythmia with spontaneous resolution, grade 1; and coprostasis, grade I). Three of the 23 patients (13%) with deferred CN had a complete pathological response in the primary tumour.

### 3.2 CN versus no CN following (near) complete response of metastases

In total, 26 patients had an ongoing complete (n=16, 13%) or near complete (n=10, 8%) response of metastatic sites, of whom 19 underwent CN to achieve

NED. Their patient and tumour characteristics are shown in **Table 2**. Median ICI duration prior to CN to achieve NED was 14.0 (95%CI 12.6-15.4) months. Median time to best response to ICI was 5.5 (95%CI 4.0-8.4) months and median time from best response to CN was 5.9 (95%CI 5.4-11.0) months.

**Table 1:** Baseline characteristics of the entire cohort; patients who received cytoreductive nephrectomy (CN); patients with a (near) complete response of metastatic sites (mCR) who did not receive CN; and patients with partial response (PR), stable disease (SD) or progressive disease (PD) who did not receive CN.

| | | **Entire cohort N = 125** | **CN patients N = 23** | **Non-CN patients with (near) mCR N =7** | **Non-CN patients Without (near) mCR N = 90** | **p** |
|---|---|---|---|---|---|---|
| Age (yrs), mean (SD) | | 64 (10) | 62 (10)[1] | 71 (12)[2] | 64 (10)[3] | 1 vs 2 p=0.044<br>1 vs 3 p=0.387 |
| Sex, n (%) | Male | 90 (72) | 13 (56) | 4 (57) | 70 (78) | 0.81 |
| | Female | 35 (28) | 10 (43) | 3 (42) | 20 (22) | |
| ECOG performance status, N (%) | 0 | 46 (37) | 12 (52) | 2 (29) | 29 (32) | 0.316 |
| | 1 | 57 (46) | 9 (39) | 5 (71) | 41 (46) | |
| | ≥2 | 18 (15) | 1 (4) | 0 | 17 (19) | |
| | unknown | 4 (3) | 1 (4) | 0 | 3 (3) | |
| IMDC prognostic group, N (%) | Intermediate | 70 (56) | 12 (52) | 3 (42) | 52 (58) | 0.744 |
| | Poor | 53 (42) | 9 (39) | 4 (57) | 38 (42) | |
| | unknown | 2 (2) | 2 (9) | 0 | 0 | |
| Number of metastatic sites, N (%) | 1 | 31 (25) | 7 (30) | 1 (14) | 20 (22) | 0.259 |
| | 2 | 51 (41) | 12 (52) | 5 (71) | 33 (37) | |
| | ≥3 | 42 (34) | 3 (13) | 1 (14) | 37 (41) | |
| | Unknown | 1 (1) | 1 (4) | 0 | 0 | |
| Histology of biopsy specimens, N (%) | Clear cell RCC | 105 (88) | 21 (92) | 4 (57) | 80 (89) | 0.007 |
| | Papillary Type 2 | 1 (1) | 0 | 1 (14) | 0 | |
| | Clear cell RCC with sarcomatoid variant | 4 (3) | 1 (4) | 1 (14) | 2 (2) | |
| | Clear cell RCC with other variant | 2 (2) | 0 | 0 | 2 (2) | |
| | Sarcomatoid | 2 (2) | 1 (4) | 0 | 1 (1) | |
| | Poorly differentiated | 6 (5) | 0 | 1 (14) | 5 (6) | |
| Radiologic response of the primary tumour | CR | 0 | 0 | 0 | 0 | 0.368 |
| | PR | 50 (40) | 13 (57) | 5 (71) | 31 (34) | |
| | SD | 63 (50) | 10 (43) | 2 (29) | 48 (53) | |
| | PD | 3 (2) | 0 | 0 | 3 (3) | |
| | Unknown | 9 (7) | 0 | 0 | 9 (10) | |

ECOG = Eastern Cooperative Oncology Group; IMDC = International mRCC Database Consortium, RCC = renal cell carcinoma

**Table 2:** Characteristics of patients who received CN to achieve no evidence of disease

| Nr | Sex | age | ECOG | IMDC | Nr mets | Metastatic sites | Biopsy histology | ICI duration prior to CN (months) | Response Metastatic Sites | ypT | Histology CN | ISUP Grade CN | ICI stopped | ICI restarted | Recurrence | Site of recurrence | DFS (mo) | CSS (mo) | status |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | male | 71 | 1 | 3 | 2 | Lung, lymph nodes | CC RCC | 15 | nCR | 3a | CC RCC | 3 | yes | Yes | Yes | Lung, lymph nodes | 4 | 32 | DOD |
| 2 | male | 62 | 1 | 3 | 2 | Lung, pleura | CC RCC | 15 | nCR | 3a | CC RCC | 4 | yes | no | no | - | 20 | 31 | NED |
| 3 | female | 68 | 0 | 2 | 2 | Lung, liver | CC RCC | 14 | nCR | 2a | CC RCC | 2 | yes | yes | yes | Lung, lymph nodes | 5 | 32 | AWD |
| 4 | male | 57 | 1 | 2 | 2 | Lung, lymph nodes | CC RCC | 18 | CR | 2a | CC RCC | - | yes | no | no | - | 16 | 27 | NED |
| 5 | female | 45 | 0 | 2 | 2 | Lung, skin | CC RCC | 14 | CR | 0 | - | - | yes | no | no | - | 21 | 30 | NED |
| 6 | male | 64 | 0 | 2 | 2 | Pleura, adrenal | CC RCC | 8 | CR | 1b | CC RCC | 2 | yes | no | yes | brain | 2 | 29 | DOD |
| 7 | male | 74 | 0 | 2 | 1 | lung | CC RCC | 10 | CR | 1b | CC RCC | 2 | yes | no | no | - | 21 | 24 | NED |
| 8 | male | 62 | 0 | 3 | 1 | lymph nodes | CC RCC | 10 | CR | 2b | CC RCC | 2 | yes | no | no | - | 19 | 21 | NED |
| 9 | female | 74 | 0 | 2 | 2 | lymph nodes, lung | CC RCC | 10 | CR | 2b | CC RCC | 2 | yes | yes | yes | lung | 13 | 23 | AWD |
| 10 | male | 50 | 0 | 1 | 1 | liver | CC RCC | 25 | CR | 3a | CC RCC | 3 | yes | no | no | - | 1 | 26 | NED |
| 11 | male | 71 | 2 | 4 | 1 | lung | CC RCC | 19 | CR | 0 | - |  | No | n.a. | no | - | 1 | 20 | NED |
| 12 | female | 75 | 1 | 2 | 2 | Lung, lymph nodes | CC RCC | 10 | nCR | 2a | CC RCC | 3 | No | n.a. | no | - | 10 | 20 | NED |
| 13 | female | 66 | 1 | 3 | 2 | Lung, bone | CC RCC | 9 | nCR | 4 | CC RCC | 3 | no | n.a. | no | - | 1 | 9 | NED |
| 14 | male | 60 | 0 | 3 | 2 | lung, lymph nodes | CC RCC | 13 | CR | 3a | CC RCC,sarcomatoid variant | 4 | No | n.a. | yes | Lung, renal bed | 6 | 34 | AWD |
| 15 | male | 62 | 0 | 1 | 2 | Bone, lymph nodes | CC RCC | 12 | nCR | 3 | CC RCC | 2 | No | n.a. | no | - | 26 | 39 | NED |
| 16 | female | 75 | 1 | 2 | 2 | lung, lymph nodes | CC RCC | 19 | CR | 1b | CC RCC | 1 | No | n.a. | yes | Lymph nodes | 15 | 38 | AWD |
| 17 | male | 40 | 1 | 2 | 1 | lung | CC RCC | 15 | nCR | 3a | CC RCC | 4 | No | n.a. | no | - | 3 | 18 | NED |
| 18 | female | 62 | - | - | - | - | CC RCC | 22 | CR | - | - | - | No | n.a. | no | - | 3 | 25 | NED |
| 19 | male | 52 | 0 | - | 1 | peritoneal | CC RCC, sarcomatoid variant | - | CR | 0 | - | - | yes | no | no | - | 3 | 34 | NED |

ECOG = Eastern Cooperative Oncology Group performance status; IMDC = International mRCC Database Consortium, nr mets = number of metastatic sites; CC RCC = clear cell renal cell carcinoma; ICI pre CN = duration of immune checkpoint inhibitor treatment until cytoreductive nephrectomy; ypT = pathological T stage of the primary tumour following systemic treatment; ISUP = International Society of Urological pathology ; ICI = immune checkpoint inhibitors; DFS = disease; free survival; CSS = cancer specific survival; CR = complete response; nCR = near complete response; mo = months DOD = dead of disease, NED = no evidence of disease; AWD = alive with disease; - = unknown

**Figure 1** shows PFS and CSS for patients with (near) mCR who received CN (n=19) and for (near) mCR patients who did not receive CN (n= 7). 3-year CSS was 80% (SE 13%) for CN patients versus 100% for non-CN patients (p=0.511). Four of the seven non-CN patients had stopped nivolumab maintenance after a median duration of 17,4 (95%CI 8,9-25,8) months because of toxicity.

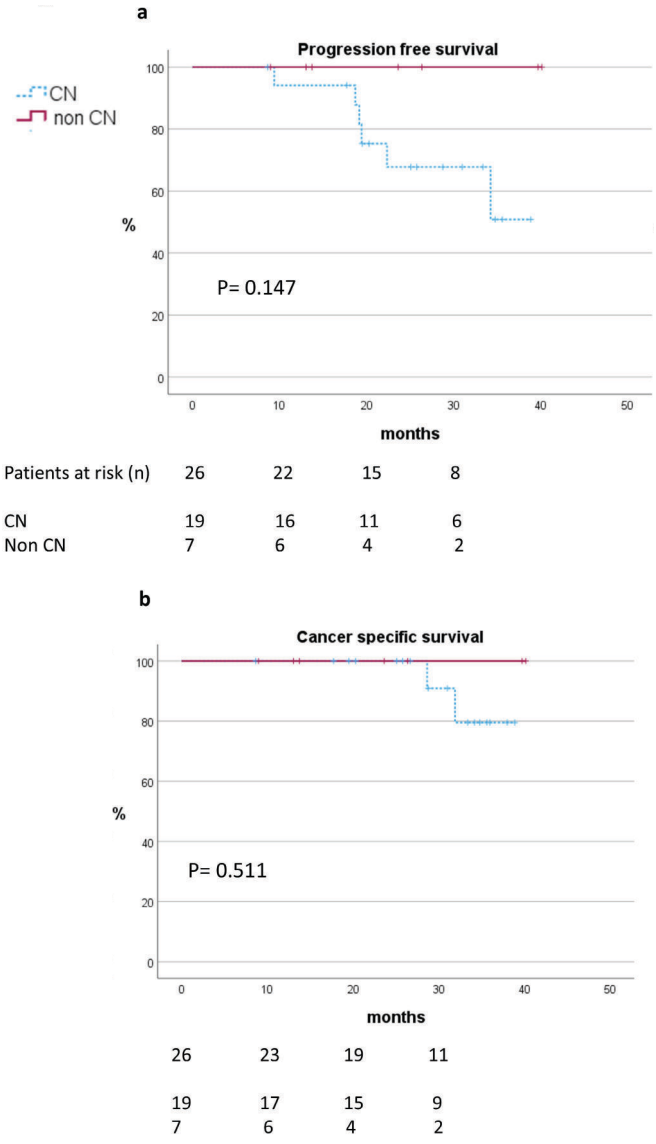



**Figure 1:** (A) Progression-free survival and (B) cancer-specific survival for patients with a complete or near-complete response of metastases stratified by receipt of cytoreductive nephrectomy (CN).

### 3.3 NED after CN with nivolumab discontinuation

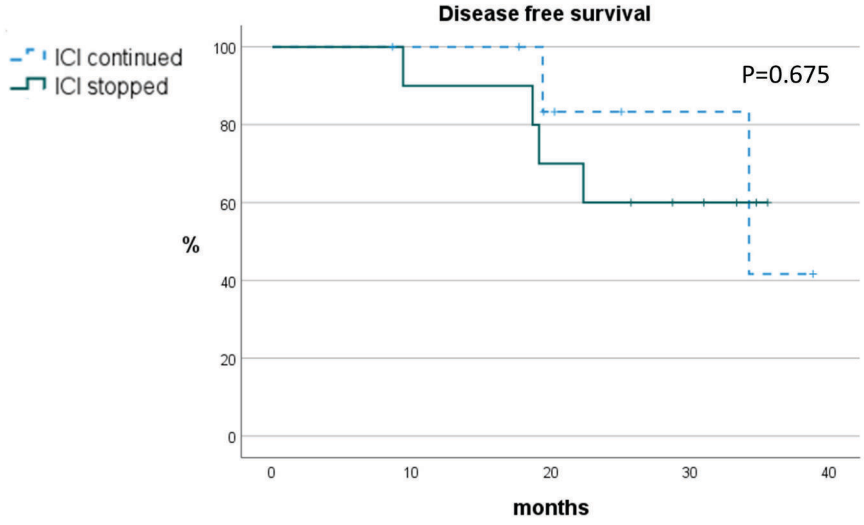
Eleven of 19 patients resected to NED discontinued nivolumab. One patient stopped nivolumab because of toxicity, 10 patients stopped nivolumab because this was considered appropriate after achieving NED at their institute of treatment. After a median systemic TFS of 21 (95%CI 13-30) months, four of the 11 patients had recurrent disease (36%, 95%CI 15-64%) **(Table 2)**. Two patients restarted nivolumab and had a partial response, one patient died of disease despite restarting nivolumab, and one patient received radiotherapy for brain metastases and died of RCC. Two of the four patients with a recurrence initially had mCR, and two patients had had (near) mCR. The patient who stopped nivolumab because of toxicity still had NED at three months FU (**Table 2**, patient 19).

### 3.4 NED after CN with nivolumab continuation

Eight of the 19 patients resected to NED continued nivolumab post-surgery. Of these patients, two had recurrent disease. One patient started second-line systemic therapy. The other patient received radiotherapy for paraaortic lymph node metastases and continued nivolumab monotherapy. Both were alive at last FU (**Table 2**). **Figure 2** shows DFS and CSS of patients who continued and who discontinued nivolumab following CN to NED. 2-year DFS rates were 83% (SE 22%) versus 60% (SE 16%, p=0.675) and 3-year CSS rates were 100% versus 70% (SE 18%, p=0.325), for patients who continued versus discontinued nivolumab, respectively.

### 3.5 CN for primary tumour control

Four patients received CN because of growing/symptomatic tumours after a median ICI duration of 8.0 (95%CI 0-17.1) months. All four patients were still alive at a median FU of 5.3 (95%CI 3.1-7.5) months.



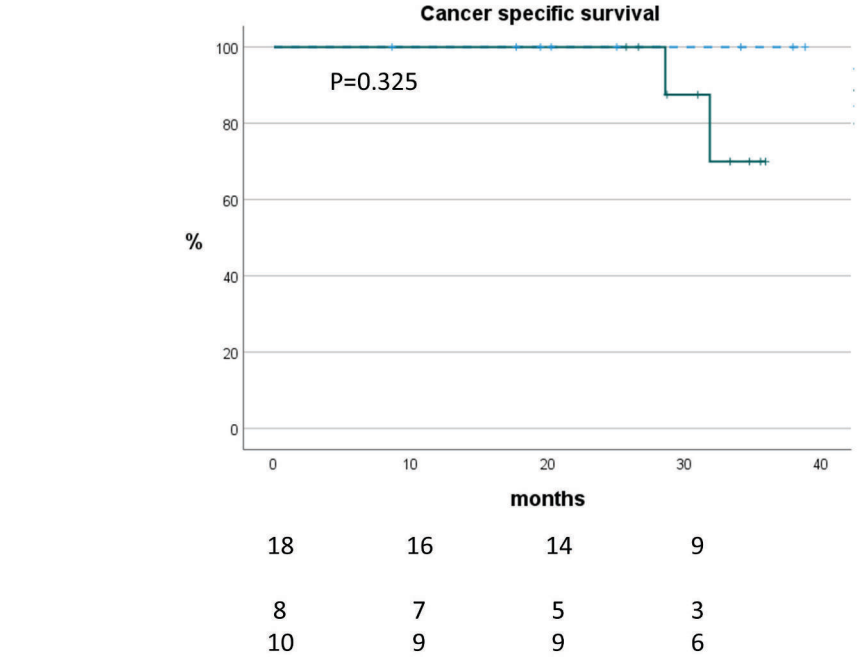




**Figure 2**: (A) Disease-free survival and (B) cancer-specific survival for patients resected to no evidence of disease who stopped (n = 11) or continued (n = 8) nivolumab immune checkpoint inhibitor (ICI) treatment

## 4. Discussion

With follow-up of over 5 years for ipilimumab-nivolumab therapy and median overall survival (OS) of 48 months being reported for this combination in the pivotal study (15, 16), the recent literature reflects an increasing number of patients being offered deferred CN in the synchronous metastatic setting following front-line ICI therapies (8-13). To our knowledge, this is the largest series describing indications for and outcome of CN following- ipilimumab plus nivolumab treatment for synchronous mRCC in an unselected, real-world population.

In our series, 13% of patients had mCR with an additional 8% of patients achieving near mCR (total 21%) . The 13% mCR rate is comparable to the described 10% CR by both the Checkmate 214 subgroup analysis of patients treated with the primary tumour in place and also concur with previously described real world data (9, 13, 17, 18).

Patients are offered deferred CN either because of progression of primary tumours in the setting of otherwise controlled disease or because resection of the primary tumour renders them NED. It is currently uncertain whether patients who have radiographically NED need to continue systemic therapy. The CheckMate 214 results must be interpreted in the context of the design to continue treatment until disease progression, but recent post-hoc analyses from the trial at 42 months follow-up revealed that patients experience a substantial time (mean 6.9 months) off treatment (19). Of the 847 patients with IMDC intermediate or poor prognostic risk, 52% of those receiving ipilimumab/ nivolumab were still alive of whom 31% were free of subsequent therapy with a mean duration of 6.9 months. While the authors acknowledged that different reasons may apply for coming off treatment and for not receiving subsequent therapy, these data are evidence that treatment discontinuation is frequent in combination with durable responses (19). These were however predominantly patients who developed metachronous mRCC after a nephrectomy with curative intent. In our series of synchronous mRCC, 58% of patients with NED achieved by deferred CN following (near) mCR stopped maintenance nivolumab, which resulted in a median TFS of 21 months. Apart from cost reduction (20), ICI discontinuation could reduce treatment-related toxicity. In the CheckMate 214 trial grade ≥3 ICI related toxicity has been reported for 46% of patients, while serious adverse events occurred within a median duration of 0.6 months after

ICI withdrawal (6, 19).

However, the possible negative effect of ICI discontinuation on oncologic outcome is unknown. The largest other series thus far to describe CN outcome following ICI is by Pignot et al. and includes a total of 30 CN patients, of whom 19 discontinued ICI following surgery (11). Although the authors do not compare oncologic outcomes between patients who stopped or continued ICI, they describe a promising 2-year DFS of 69% among these 30 patients. In our series DFS was comparable (2-year DFS 70%, SE 13%), despite a larger proportion of IMDC poor risk patients (39% in our series versus 20% (11)). Unfortunately, Pignot et al. describe only patients who underwent CN and do not give insight into the unselected population and the indications for CN of those with an intervention, which hinders further data comparison. Additionally, 60% of their patients had received immunotherapy combined with a TKI or nivolumab monotherapy. In our series, patients who stopped ICI following CN tended to have a poorer CSS than patients who continued ICI, although the numbers are too low to reach statistical significance. As only a minority achieves (near) mCR, prospective randomised studies of treatment discontinuation after deferred CN and NED will be difficult to perform without multi-institutional collaboration. Data from larger collaborative registries are needed to investigate the oncological safety of nivolumab discontinuation and prognostic factors to enhance patient selection.



The potential therapeutic value of CN following ICI has been investigated by Singla et al. in a recent national population-based study. They found a significantly improved survival for 221 patients treated with ICI and CN compared to 170 patients treated with ICI alone (12). This retrospective study is limited by two major selection biases: 197 (89%) patients received CN prior to ICI and represented younger patients with relatively limited disease and better performance status. The remaining 24 patients who underwent CN following ICI lacked information on the population they were selected from. In addition, response to systemic treatment was not registered, nor was IMDC risk or type of immunotherapy. In our series, 19 of 26 patients (73%) with (near) mCR were offered CN, while 7 patients were not, potentially because of comorbidities. Both DFS and CSS tended to be better for patients with (near) mCR who did not receive CN, although again no conclusions can be drawn due to our small sample size. One could hypothesize that an ongoing response of micrometastases to ICI determines prognosis, rather than resection of residual

disease. On the other hand, molecular analyses of driver mutations suggest that evolution of subclones in the primary tumour following systemic therapy may cause fatal systemic progression (21). The awaited randomized PROBE (SWOG, NCT04510597) and NORDIC-SUN (NCT03977571) studies will ultimately have to demonstrate additional value of deferred CN combined with ICI over ICI alone.

Noteworthy, in our series 3 CN patients (13%) had pathological complete response (pCR) of the primary tumour following ipilimumab and nivolumab. Previous series report absence of viable tumour in CN specimens ranging from 10-30% (8, 9, 11, 12). The wide range of pCR rates could be explained by a difference in patient selection and systemic treatment modalities and the low number of patients in each series. A pCR of the primary tumour in conjunction with mCR could be of prognostic value. Given the inability to confirm a pCR with the currently available diagnostic imaging modalities and limitations of biopsies, a CN would be required to rule out vital tumour. Also, as reported in previous series (8-13), our results confirm that CN following ICI is safe in high-volume centres with experienced surgeons, as only 2 (both Clavien Dindo grade$\leq$2) complications occurred.

Limitations of this study are its retrospective nature and a small sample size of patients with deferred CN. Numbers are too limited to investigate prognostic factors for DFS and CSS following CN to achieve NED. Strengths are a homogeneous series of synchronous mRCC, treated with first-line ipilimumab/nivolumab, the insight into the baseline cohort, description of reasons for CN, and the relatively long follow-up in a real world population.

## 5. Conclusions

Approximately 20% of patients with synchronous mRCC develop a (near) CR at metastatic sites following first line treatment with ipilimumab-nivolumab. Durable DFS can be achieved for patients who undergo deferred CN to achieve NED in this setting which, in the absence of data from randomised trials, may be an appropriate indication for deferred CN. When ICI was discontinued, patients attained a median treatment-free interval of 21 months. As resection to NED is a rare event, further collaborative data are required to ascertain the benefits of treatment discontinuation versus oncological safety.

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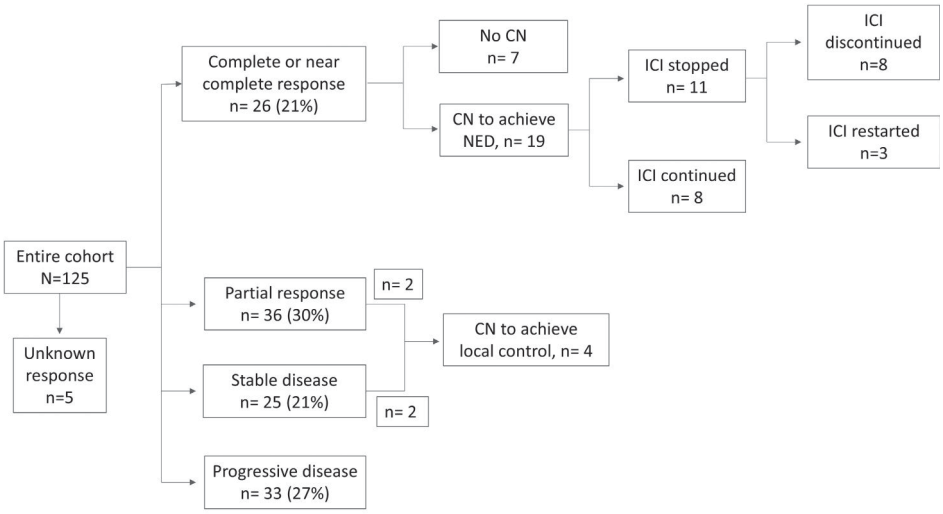
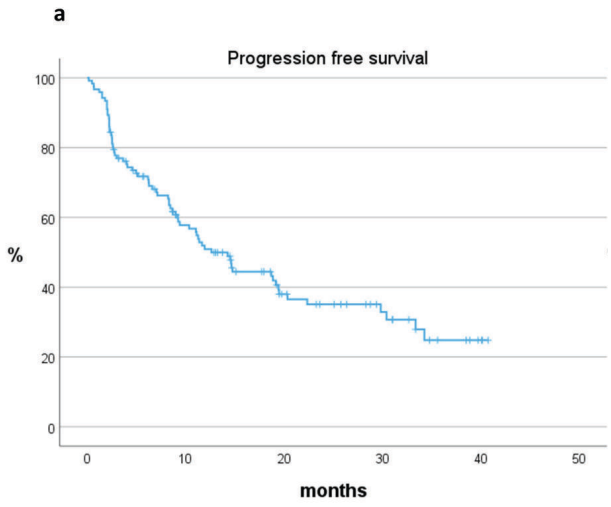
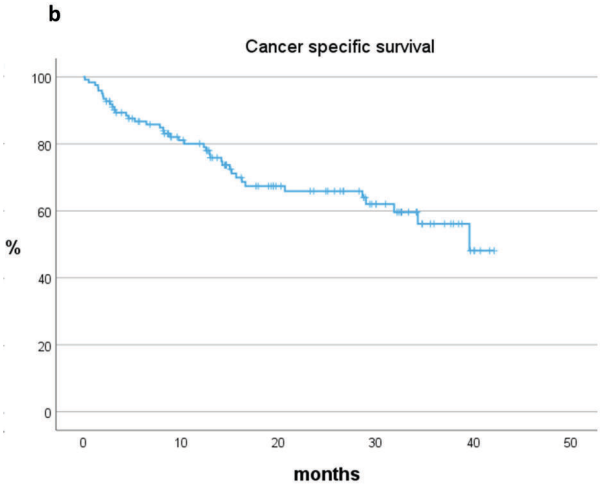



**Supplementary figure 1:** CONSORT Diagram

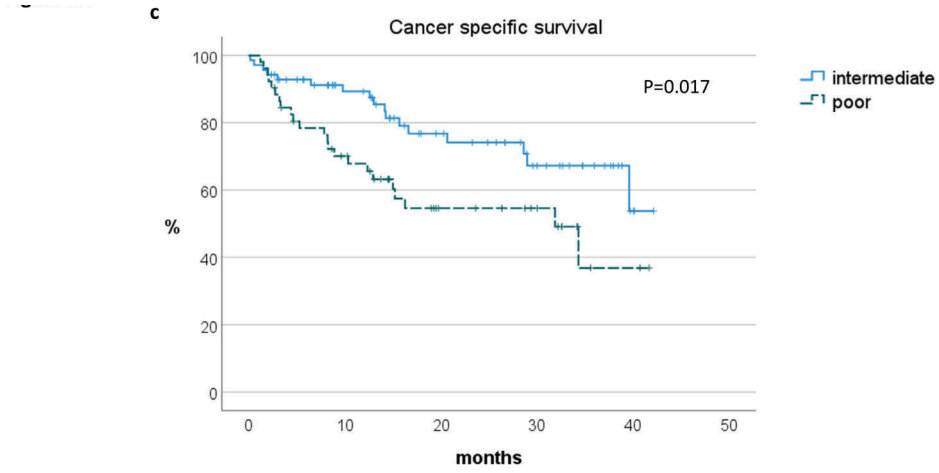



| Patients at risk (n) | 125 | 59 | 27 | 15 | 3 |
|---|---|---|---|---|---|




| | | | | | |
|---|---|---|---|---|---|
| | 125 | 81 | 46 | 28 | 5 |

**Supplementary Fig. 2:** (A) Progression-free survival and (B) cancer-specific survival for the entire cohort.




| | | | | | |
|---|---|---|---|---|---|
| Patients at risk (n) | 125 | 80 | 45 | 28 | 5 |
| Intermediate prognosis | 70 | 48 | 30 | 17 | 3 |
| Poor prognosis | 53 | 32 | 15 | 11 | 2 |

**Supplementary Fig. 2:** (C) Cancer-specific survival for patients with IMDC intermediate (n= 70) versus poor (n= 53) prognosis

IMDC = International Metastatic RCC Database Consortium.