# A phase II study of neoadjuvant axitinib for reducing extent of venous tumour thrombus in clear cell renal cell cancer with venous invasion (NAXIVA)

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**Abstract**

**Background:** Surgery for renal cell carcinoma (RCC) with venous tumour thrombus (VTT) extension into renal vein (RV) and/or inferior vena cava (IVC) has high peri-surgical morbidity/mortality. NAXIVA assessed response of VTT to axitinib, a potent tyrosine kinase inhibitor.

**Methods:** NAXIVA was a single-arm, multi-centre, phase 2 study. 20 patients with resectable clear cell RCC and VTT received upto 8 weeks of pre-surgical axitinib. Primary endpoint was percentage of evaluable patients with VTT improvement by Mayo level on MRI. Secondary endpoints were percentage change in surgical approach and VTT length, response rate (RECISTv1.1) and surgical morbidity.

**Results:** 35% (7/20) patients with VTT had a reduction in Mayo level with axitinib: 37.5% (6/16) with IVC VTT and 25% (1/4) with RV only VTT. No patients had an increase in Mayo level. 75% (15/20) of patients had a reduction in VTT length. 41.2% (7/17) of patients who underwent surgery had less invasive surgery than originally planned. Non-responders exhibited lower baseline microvessel density (CD31), higher Ki67 and exhausted or regulatory T cell phenotype.

**Conclusions:** NAXIVA provides the first level II evidence that axitinib downstages VTT in a significant proportion of patients leading to reduction in the extent of surgery.

**Clinical Trial Registration:** NCT03494816

## Introduction

Venous tumour thrombus (VTT) extension into the renal vein (RV) and/or inferior vena cava (IVC) occurs in 4-15% cases of renal cell cancer (RCC) (1). Peri-surgical mortality is high (5-15%) and increases with the height of the VTT (1,2). Following this extensive surgery, cure is possible with 5 year survival rates of ~40-65% for patients with non-metastatic RCC (3,4). The concept of using targeted therapies, to downstage VTT prior to surgery is appealing. It is hypothesised that by reducing the level of the VTT and the extent of surgery, morbidity and mortality would be reduced.

There is no level I or II evidence of pre-surgical targeted therapy in non-metastatic or metastatic RCC VTT. Four retrospective studies focused on mixed groups of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKI) (5–8): sunitinib (9,10), axitinib (11) and pazopanib (12). VTT level decreased in a median of 22.6% patients (range 14.9%-32.9%), remained stable in 73.6% (64.1%-81.4%) and increased in 7.2% (3.4%-14.3%). Results were most favourable for sunitinib and axitinib (5,7,11). There are several prospective studies on VEGFR TKIs in the pre-nephrectomy setting (13–15), but none specifically addresses the question of surgical downstaging of vein-involved local extension. Wood *et al* reported on four patients with IVC VTT but reported no change in surgical management, and did not report specifically about change in the extent of venous involvement (13). In a phase II trial of 12 weeks neoadjuvant axitinib in clear cell RCC (ccRCC; all patients were cT3a), the median reduction in primary tumour diameter was 28% (15). Most of the reduction in tumour size had occurred within 7 weeks of axitinib treatment. The results of these small studies in non-metastatic RCC patients suggest that neoadjuvant VEGFR TKI treatment of RCC patients is safe and reduces tumour size. However, the effect of these drugs on the extent of the VTT and effect on surgical approach has not been confirmed.

The objective of NAXIVA was to determine safety, efficacy and effect of neoadjuvant axitinib on VTT.

## Patients and methods

### *Study design*

NAXIVA was a single arm, single agent, open label, multi-site, UK-based, phase II feasibility study of 8 weeks axitinib treatment in M0 and M1 patients with resectable ccRCC primary tumours with VTT. NAXIVA was prospectively, publicly registered (ISCRTN96273644; EudraCT Number 2017-000619-17; NCT03494816) and approved by an independent ethics committee (REC reference: 17/EE/0240). See appendix for full study protocol.

### *Endpoints*

The primary endpoint was the percentage of evaluable patients with a reduction in extent of VTT by Mayo level after 8 weeks of axitinib therapy. Definitions of the Mayo level (levels are ordered by increasing extensiveness; figure 1a) as previously described (2):

- Level 0: thrombus limited to the renal vein (RV);
- Level 1: into IVC <2cm from RV ostium level;
- Level 2: IVC extension >2cm from RV ostium but below hepatic veins;
- Level 3: thrombus at the level of or above the hepatic veins but below the diaphragm;
- Level 4: thrombus extending above the diaphragm.

Secondary endpoints were percentage change in surgical approach, percentage change in VTT length, response rate by RECIST version 1.1, and evaluation of surgical morbidity assessed by Clavien-Dindo classification (16). Exploratory endpoints were translational studies correlating changes in molecular markers with the response to axitinib in the VTT and primary tumour.

### *Participants/Eligibility criteria*

Key inclusion criteria were RV (cT3a) or IVC VTT (cT3b/c), N0/1, M0/1, biopsy proven ccRCC, over 18 years of age, suitable for immediate surgical resection of the primary tumour. Participants had to be Eastern Cooperative Oncology Group (ECOG) performance status <2; have urinalysis <2+ protein, urinary protein <2g/24 hours or protein:creatinine ration (PCR) <200mg/mmol; and serum creatinine ≤1.5xULN or estimated creatinine clearance ≥30mL/min calculated using the Cockcroft-Gault

equation. Key exclusion criteria were Memorial Sloan Kettering Cancer Center (MSKCC) poor-risk disease (M1 participants) and recent history of cardiac or vascular events.

***Drug treatment***

The starting dose of axitinib was 5mg BD, escalated to 7mg BD and then 10mg BD every 2 weeks, as tolerated. Dose reductions were allowed. Patients stopped axitinib a minimum of 36 hours and a maximum of 7 days prior to surgery in week 9.

***Assessments***

Patients had clinical and safety assessments according to the Schedule of Assessments (see Protocol in Appendix). Axitinib-related toxicity was assessed using Common Terminology Criteria for Adverse Events version 4 (CTCAEv4) criteria. MRI scans were performed before treatment, during week 3 and before surgery (see Supplementary methods for MRI protocol). CT scans were performed before treatment, week 3 (M0 patients only to assess for development of chest metastases), week 9- and 3-months post-surgery.

***Surgery***

Surgeons were asked to report their *planned* approach to the VTT after reviewing the baseline MRI scan and record the *performed* approach after axitinib therapy, plus *planned* and *performed* adjuvant venous procedures. RV/IVC level of control planned/performed intraoperatively was recorded:

- Thrombus milked into RV and side clamped;
- Infra-hepatic IVC clamping with no liver mobilisation;
- Retro-hepatic IVC clamping below hepatic veins, with liver mobilisation;
- Retro-hepatic IVC clamping above hepatic veins, with liver mobilisation;
- Supra-hepatic, infradiaphragmatic clamping;
- Supra-hepatic, supradiaphragmatic clamping.

***Outcome measures***

Mayo level and VTT length was assessed using the baseline and week 9 MRI scans, if no week 9 scan was undertaken, the week 3 scan (if available) was used; calculation

details are provided in Supplementary Methods. In order to minimise reporter bias due to the inability to blind, the primary and relevant secondary endpoint data was based on a consensus by two central uro-radiologists' (SU and FAG) review of the MRI images.

Response rate was determined at local sites using RECIST version 1.1 comparing the screening (baseline) and pre-surgical CT scans. Primary tumour measurements were included in RECISTv1.1 measurements in all patients. Surgical morbidity was assessed by Clavien-Dindo classification (16).

***Method of calculating primary endpoints***

The definition of an improvement varied according to the patient's Mayo level as captured at screening. For patients presenting at screening with a Mayo level 1 or above, an improvement in disease was represented by a reduction in their Mayo level at week 9. For patients presenting at screening with Mayo level 0, an improvement in disease was represented by either: a change of VTT from main renal vein to branches of the renal vein (on the right); or a change of VTT from main renal vein to the renal vein lateral to the gonadal vein (on the left), or if the VTT was lateral to the gonadal vein at screening, a change from the main renal vein lateral to the gonadal vein to the branches of the renal vein. This response designation for RV only patients was developed as such changes would enable minimally invasive surgery to be undertaken. The number and percentage of patients with no change in VTT status or extension of the VTT into the inferior vena cava between screening and week 9 was recorded.

***Method of calculating secondary endpoint of percentage change in VTT length***

Percentage change in VTT length was calculated using the following methodology for each timepoint as follows:

1. Calculate the sum of (i) length of RV thrombus; (ii) the length of IVC tumour thrombus ABOVE RV (measured from mid-point of the ostium of RV+IVC to tip of tumour thrombus); (iii) the length of IVC tumour thrombus BELOW RV (measured from mid-point of the ostium of RV+IVC to tip of tumour thrombus) at timepoint T. Note that in RV only patients only distance (i) is measurable;

2. Calculate the % reduction at each timepoint T as follows: 1-($Sum_T/Sum_0$), where $Sum_T$ is the sum calculated as in Step 1 for timepoint T, and $Sum_0$ is the sum calculated as in Step 1 at baseline.

***Method of calculating secondary endpoint of percentage change in surgical approach***

Percentage change in surgical approach was determined by comparing the surgeon-reported *planned* vs *performed* surgical approaches using three pieces of data:

1. Change from "Open Surgery" to "Minimally invasive surgery";
2. Change from a more invasive open to a less invasive open surgical approach (between that *planned* by surgeons based on the baseline MRI scan and that actually *performed*);
3. Less extensive surgical incision used.

***Statistical Plan***

A Simon two-stage minimax design (17) was used to distinguish a ≤5% from a ≥25% cohort improvement in the Mayo level this required 20 evaluable patients (90% power, 10% 1-sided). For the clinical trial to be considered a success, at least three evaluable patients would demonstrate an improvement in disease on treatment between screening and week 9.

In the two-stage design, thirteen patients were to be recruited in the first stage. If no patients demonstrated an improvement in their Mayo level between screening and week 9, accrual to the clinical trial would stop. If one or more patients demonstrated an improvement in the Mayo level between screening and week 9, the final seven patients would be recruited.

The intention-to-treat (ITT) population included all patients registered onto the study. The evaluable and safety populations included all patients in the ITT population who received at least one dose of the study drug (including any patients who were enrolled in error, received study drug and/or were subsequently found to be ineligible).

80% two-sided confidence intervals (to correspond to the 10% 1-sided sample size calculation) for the proportions relevant to the efficacy endpoints were calculated using the approach of Koyama and Chen(18).

All analyses were carried out using R v3.5.1 and reporting was heavily supported by the CTutils package (https://github.com/LisaHopcroft/CTutils). The trial data upload to

EudraCT was enabled, in part, by the EudraCT package (https://eudract-tool.medschl.cam.ac.uk/).

***Biosampling***

Blood, urine and tissue (fresh frozen and formalin-fixed paraffin embedded (FFPE)) samples for translational studies were taken prior to, during and after therapy to evaluate biomarkers of treatment response according to the Schedule of Assessments in the Protocol; see appendix). Samples were processed and stored according to the NAXIVA Laboratory Manual (see appendix).

***Immunofluorescence***

Formalin-fixed paraffin-embedded sections were dewaxed in xylene and rehydrated in graded alcohols prior to antigen retrieval in Tris-EDTA pH9. Slides were blocked and incubated with primary antibodies at 4 °C overnight (CD31 (JC/70A, Abcam), Ki67 (EPR3610, Abcam), CD8 (SP16, Invitrogen), Granzyme B (NCL-L-GRAN-B, Leica), PD-1 (AF1086, RnD Systems), CD4 (EPR6855, Abcam), FOXP3 (236A/E7, Abcam), SMA (ab5694, Abcam), CD68 (KP1, Invitrogen)). Samples were washed and incubated in fluorescently conjugated secondary antibodies; nuclei were counterstained with DAPI. Whole slides were scanned at 40x magnification on the Zeiss Axio Scan Z1 system. Image analysis was performed using HALO Software (Indica Labs, analysis algorithms: HighPlex FL v3.1.0, Object Colocalization FL v1.0, Area Quantification FL v2.1.5).

***ctDNA analysis***

ctDNA analysis was carried out as published previously (19). Briefly, cell-free DNA was extracted from blood and urine using the QIASymphony platform (QIAGEN). Libraries were prepared from DNA using the Thruplex Tag-Seq protocol (Takara) and sequenced on the Illumina HIseq4000 platform. Sequence data was analysed using an “in-house” pipeline that consists of the following: paired-end sequence reads were aligned to the human reference genome (GRCh37) after removing any contaminant adapter sequences. Duplicate reads or reads of with low mapping quality/secondary alignments, were excluded from downstream analysis. Data were analysed with the ichorCNA algorithm, version 0.2.0, using default parameters (20). Samples were deemed to have ‘detected ctDNA’ if the predicted tumour fraction score was >0.025,

and visual inspection of copy number plots confirmed somatic copy number aberrations.

## Results

### *Patient characteristics*

Figure 1b and Table 1 detail patients recruited between December 2017 and January 2020. 21 participants at five centres made up the evaluable population. On central review of imaging one of the 21 patients was found not to have a VTT, making 20 patients who were both eligible and evaluable and in whom the study endpoints are reported.

### *Primary endpoint-Reduction in Mayo level*

Of the 20 eligible and evaluable patients, 37.5% (6/16) IVC VTT patients had a reduction in Mayo level and 25% (1/4) patients with RV-only VTT responded (Figure 2). Hence, the overall response rate in evaluable and eligible patients with VTT was 35.0% (7/20). The remaining 13 patients had a stable Mayo level (65%), none had an increase in Mayo level. By the inference procedures for Simon two-stage minimax design there was a response rate of 32.8% [80% CI 20.7%,46.7%]. This was a statistically significant result ($p=3.395x10^{-5}$), where the null hypothesis that the true response rate is <5% can be rejected in favour of the alternative hypothesis of a "good" (>25%) response.

### *Secondary Endpoint-Percentage change in venous tumour thrombus length*

Although 65% (13/20) patients had a stable Mayo level (Figure 2; classed as 'non-responders'), seven of these 13 patients had a percentage reduction in the VTT length after 8 weeks of axitinib, therefore 15 of 20 patients (75%) had any degree of reduction in VTT length (range 2% to 51%) (Figure 3). One patient (5%) had no change in VTT length. At week 3 four patients (20%) had an increase in VTT length, two had surgery expedited as detailed below. For all patients the direction of change in VTT on the week 3 safety MRI was predictive of the response at 9 weeks (Figures 2&3).

There was a 15.2% (range -41% to 41%; negative numbers indicating an increase in length) and 27.2% (range -20% to 51%) median reduction in VTT length at weeks 3 and 9, respectively.

### *Absolute changes in VTT length*

The percentage change in VTT length, equated to an absolute median reduction in VTT length at weeks 3 and 9 of 10mm (range -12mm to 56mm) and 20mm (range -

34mm to 68mm) respectively. In four patients who had an increase in length of VTT at 3 weeks, increases were 1mm, 9mm, 11mm and 12mm and at 9 weeks for the two patients with increase in VTT these were 8mm and 34mm. IVC VTT was identified and measured both above and below the ostium with the RV in 14 of 16 patients with IVC VTT (figure S2). Changes in IVC VTT length on axitinib below the RV ostium trended with the changes of VTT above the RV ostium.

***Secondary Endpoint-RECIST response***

At week 3, one patient (5% of those having scan) had a RECIST-defined partial response (PR), 19 patients (95%) had stable disease (SD) and data was missing for one patient (N0601) who failed to attend the MRI (Table S1). By week 9, three patients (16.7%) had a PR, 13 (72.2%) had SD, two (11.1%) had PD, and data was missing for three patients as they had exited the trial. None of the M0 patients became M1 during the trial.

At week 9, seven of 17 patients (41.2%) had a PR in their VTT (i.e. >30% reduction in length) (Figure 3b&c).

***Secondary Endpoint-Surgical approach***

17 patients underwent surgery. Despite an inclusion criterion for NAXIVA being suitability for surgery, four patients did not have surgery (19.0%; three M1 and one M0). Of the M1 patients, reasons for not having surgery were progression of metastatic disease despite axitinib (n=2) and partial response but a general performance status decline resulting in becoming unfit for surgery (n=1). One M0 patient had stable disease at week 9 but declined surgery. Surgery was brought forward in two patients from the planned surgery date of week 9. One patient stopped drug after 16 days and another after 33 days.

Improvement in the ‘level of control’ of IVC/renal vein was observed in five out of 17 (29.4%) patients (Table S2). No patients had deterioration in ‘level of control’ of IVC/renal vein performed relative to that planned. Two patients had change of approach from planned open to performed minimally invasive surgery (one also had an improved, lower venous ‘level of control’). One additional patient had a substantially smaller incision (planned thoraco-abdominal & midline laparotomy to performed subcostal & midline laparotomy). Therefore, 7/17 (41.1%) patients had a less extensive surgery performed than was planned prior to axitinib treatment. Four Mayo

‘responders’ also had a reduction in extent of surgery. In 16 patients the VTT tissue was macroscopically cleared.

***Planned and performed surgery***

Table S2 and S3 detail the planned and performed surgery in terms of correlation between Mayo change and change in surgery. Four Mayo ‘responders’ also had a reduction in extent of surgery (N0205, N0101, N0105, N0201). Two Mayo responders did not have change in surgery (N0905, N0606); these were both reduction from level 2 to level 1 and for both the surgeon predicted and performed ‘Infra-hepatic (IVC clamping with no liver mobilisation)’. Cardiac surgery and performing a Pringle manoeuvre are both morbid and in NAXIVA two patients (N0101, N0205) had supradiaphragmatic surgery and/or hypothermic cardiac arrest predicted and both had reduction to infradiaphragmatic surgery performed (N0205 to Retro-hepatic (liver mobilisation and clamping below hepatic veins; N0101 to Supra-hepatic (infradiaphragmatic)). There were no suprahepatic/infradiaphragmatic cases predicted at baseline. One patient was planned to have veno-venous bypass and one to have hypothermic cardiac arrest but following treatment neither of these manoeuvrers was needed. In terms of patients with infra-hepatic (IVC clamping with no liver mobilisation) planned at baseline, two (N0201 and N0904) actually had thrombus milked back into renal vein and side clamping performed. A further three patients had improvement in surgery but no change in Mayo level (N0103, N0904, N0901). One patient with a Mayo response did not have surgery as described above (N0801).

***Intra- and post-operative details and complications***

Median operation time was 240 minutes (range 120-720 minutes). Median estimated blood loss was 1000ml (range 50-7000ml). Six patients had an intraoperative complication, five related to bleeding with two patients requiring a transfusion and one patient had an intraoperative cerebrovascular accident (CVA; identified post-operatively). Six patients had a post-operative complication of any grade (35.3%). Four complications were Clavien-Dindo 1/2 (expected CPAP post-operation, persistent wound pain, one chest and one wound infection) and two were grade 3 or above (11.8%). Poor wound healing is a concern during VEGFR TKI use, but all patients had discontinued axitinib prior to surgery and no issues of wound healing

were reported. One patient had a cardiorespiratory arrest requiring one round of CPR to resuscitate (IVa), another had a CVA intra-operatively and died (V) (1/17=5.9% mortality rate). None of these events was considered to have been caused by axitinib. Seven patients had planned or unplanned ITU admissions post-operatively (41.2%). No patients had a delayed surgical complication at 6 or 12-weeks post-surgery follow-up.

***Axitinib dose delivered and duration of therapy***

Figure S3a illustrates the axitinib dose received per patient. Axitinib dose was escalated in 12 of 21 patients (57%), two patients (9.5%) required dose reduction from the 5mg b.d. starting dose. The median daily dose received (excluding breaks) was 5.8mg b.d. (range 3.1-8.0mg b.d.). Total dose of axitinib was not significantly different between patients with or without a Mayo level response (p=0.405). However, patients who did not have an improvement in Mayo level or a RECIST response received a significantly lower total dose of axitinib (p=0.030) (Figure S3b) and had a shorter duration of axitinib treatment (excluding breaks) compared to patients who had a Mayo level improvement (p=0.026) (Figure S3c) or had either a Mayo or a RECIST response (p=0.007) (Figure S3d). There was no correlation between total dose of axitinib and VTT reduction at week 9 (Pearson's r(16)=0.07, p=0.78).

***Adverse events (AEs)***

Serious AEs whilst on axitinib were myasthenia gravis (recovered following nephrectomy, not after stopping axitinib), pathological fracture, hyperglycaemia, left cerebellar mass development, wound pain, confusion, and hyperkalaemia. None were judged by local investigators to be related to axitinib. Table 2 and Figure S4 details AEs related to axitinib by CTCAEv4 grade. AEs were consistent with previous data and did not delay surgery. No grade 4 or 5 AEs were observed. Correlations with clinical features are details in supplementary results.

Patients with either a Mayo level response (p=0.0034) and/or those with a RECIST response (p=0.0003) had significantly lower maximum levels of proteinuria during treatment than non-responders (range 0-1 in responders vs 0-3 in non-responders). Baseline proteinuria was not significantly different between responders and non-responders (p=>0.05). Neither mean baseline systolic or diastolic blood pressure (BP),

406 change in systolic or diastolic BP during treatment, nor maximum systolic or diastolic
407 BP reached during treatment correlated with Mayo response (p=>0.05).
408
409 ***Translational analyses***
410 Baseline biopsies, available from 17 patients, were assessed for the presence of
411 markers associated with treatment outcome in ccRCC (21–23). There was a trend for
412 higher CD31 microvessel density in responders (Figures 4a&c) and higher Ki67 index
413 in non-responders (Figures 4b&d).
414 Non-responders exhibited trends toward higher T cell infiltration but populations
415 shifted towards exhausted (PD1+) or regulatory (FOXP3+) phenotypes compared to
416 an activated (PD1- granzyme B+) phenotype in responders (CD8+ cells: Figures 4e-
417 h; CD4+ cells: Figure S5a-c). No differences were observed in other stromal markers
418 (Figure S5d&e).
419 Consistent with previous studies showing low detection of ctDNA in RCC, only 25%
420 (5/20) patients (2 in plasma, 3 in urine) had detectable ctDNA at baseline. There was
421 no concordance in the levels or composition of ctDNA between the plasma and urine.
422 Only 20% (1/5) patients with detectable ctDNA at baseline showed an improvement in
423 Mayo level or RECIST response.

## Discussion

NAXIVA is the first prospective study to evaluate drug treatment in managing RCC VTT, a frequently discussed question in clinical practice. The trial met its primary and secondary endpoints demonstrating that it is feasible to use systemic therapy to downstage VTT of all Mayo levels and reduce the extent of surgery in patients with resectable M0 and M1 ccRCC. Importantly, axitinib and surgical toxicity, morbidity and mortality were as expected (2) and no patient had clinically relevant VTT progression. Ordinarily, surgery for patients with VTT would be expedited because of concern about disease progression and metastasis. In NAXIVA no participants progressed from non-metastatic to metastatic disease. Two patients did not proceed to surgery due to progression of their known metastatic disease, suggesting that, consistent with results from the SURTIME trial (24), pre-surgical systemic therapy in M1 ccRCC may allow time for very aggressive disease to declare itself and ultimately enable patients to avoid inappropriate surgery. Reassuringly, the patterns of eventual VTT response at week 9 were mirrored on the 3-week safety MRI scan (originally included to ensure that any patient with clinically relevant progression could undergo surgery immediately); indeed, two patients had surgery expedited following a 3-week scan showing extension of VTT. If confirmed in future studies, this suggests that scans performed early during treatment could be a useful strategy as both a response prediction and reassuring safety feature for neoadjuvant systemic therapy (25,26). A shorter duration of neoadjuvant treatment may also be possible for adequate response.

Patients with M0 and M1 disease and all levels of VTT, from those within the RV-only to those with VTT extending to the right atrium were included in NAXIVA because all were hypothesised to benefit from a reduction in VTT extent if axitinib treatment reduced the extent of surgery and the associated surgical morbidity. The broad inclusion criteria in a small feasibility study limits firm conclusions on each subgroup, but conversely allowed signal seeking from each stage of the disease which informs future trials. The positive results showing significant reductions in VTT length (regardless of M0 or M1 status) are clinically relevant as they are linked to subsequent changes in surgical approach in 7/17 patients (41.1%). Importantly, axitinib treatment resulted in less extensive surgery such as avoidance of open nephrectomy in favour of laparoscopic/robotic procedures, and reduced requirement for intrathoracic approaches, cardiac bypass or Pringle manoeuvre which are associated with

significant morbidity (2). Conversely, reduction from level 2 to level 1 VTT appear less significant in changing the surgery undertaken, while the patient is still exposed to drug toxicity. The Mayo levels at which downstaging of VTT make most clinical difference are levels 0, 1, 3 and 4, although further investigation would be prudent given the relatively small numbers of such patients investigated within NAXIVA. Although no unexpected peri-operative complications were reported, future studies should specifically measure this using the EAU Intraoperative Adverse Incident Classification (EAUiaiC) (27).

In NAXIVA axitinib was used, a potent TKI, with an established aggressive dose escalation regime which has previously been demonstrated to have proven effect in non-metastatic and metastatic ccRCC (15). After 8 weeks of axitinib 16.7% patients had a partial response (10% in M0 patients). This compares with 45.8% in the phase 2 trial of Karam et al where axitinib treatment was given for 12 weeks . This suggests that a longer period of treatment is needed for deeper response, although by 9 weeks 41.1% of patients had >30% response in the VTT, downstaging of which was the aim of NAXIVA, suggesting this was an adequate treatment duration to assess the endpoints of this trial. Interestingly, results from NAXIVA are superior to previous retrospective studies, 37.5% vs 14.9-32.9% reduction in Mayo levels 1-4 (5–12). Despite permissive product labels in advanced disease, VEGFR TKIs do appear less active in non-ccRCC (28), and we caution against extrapolation of the findings of NAXIVA to patients in whom there is not pre-treatment histological proof of ccRCC.

An important question is whether baseline information or that obtained early during treatment, can be used to select patients that may benefit, or not, from a period of neoadjuvant treatment. Previous studies have identified a number of molecular, genetic and other factors correlating with response to TKI (29). We saw similar trends in predictive markers of angiogenesis, immune infiltrate, and proliferation to those seen in large scale published datasets (21,23). We reconfirmed ctDNA is challenging to detect in RCC (19) and our finding that detectable ctDNA at baseline generally predicts poor response to axitinib may be clinically relevant and warrants investigation in larger cohorts. Additionally, although previous studies have shown TKI-related AEs may correlate with response (30), we showed that non-responders received a significantly lower total dose of axitinib and had a shorter duration of treatment, with responders having significantly lower maximum levels of proteinuria during treatment than non-responders. This highlights the importance of active management of TKI-

related AEs during neoadjuvant treatment to ensure patients remain on drug to enable effective tumour control.

A limitation of NAXIVA is that axitinib is now used in combination with immunotherapy in the first line metastatic setting, and only used as single agent in subsequent lines of treatment. Coupled with our finding that the immune profile in non-responders is consistent with an exhausted and regulatory T cell phenotype suggests future trials should evaluate combinations such as IO-TKI where there is potential to improve the response rate in patients unlikely to respond to TKI alone, and enable both rapid downstaging with the TKI component and immune priming which could have longer-term survival implications (31–33). However, we hypothesize that the downstaging effect may not be significantly greater with an IO-TKI combination compared with TKI alone. The Neoavax neoadjuvant study of 12 weeks of axitinib/avelumab there was a 30% PR, compared with 43% in the 12 week axitinib neoadjuvant protocol of Karam *et al* (15,34). Additionally, none of 17 patients treated with three every-2-week doses of neoadjuvant nivolumab had a PR (35). Future randomised studies should explore the impact on overall survival, differences in the extent of surgery and optimisation of treatment schedule and duration.

In conclusion, the results from NAXIVA showed feasibility that systemic therapy, such as axitinib, can be used to downstage RCC VTT in 35% of patients and reduce the extent of surgery to a less morbid option in 41%. As newer combination therapies are associated with higher response rates in advanced ccRCC, the study of these combinations in patients with operable locally advanced disease should now be prioritised.

## Additional information

## Consortium authorship list

*NAXIVA Trial Group*

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## Authors' contributions

Conception and design: Stewart, R Jones. Acquisition of data: Stewart, Welsh, Ursprung, Gallagher, J Jones, Shields, Smith, Mitchell, Warren, Bex, Boleti, Eisen, Fife, Hamid, Laird, Leung, Malik, Mendichovszky, Mumtaz, Oades, Riddick, Venugopal, R Jones. Analysis and interpretation of data: Stewart, Welsh, Ursprung, Gallagher, Jones, Shields, Smith, Mitchell, Warren, Bex, Boleti, Eisen, Fife, Hamid, Laird, Leung, Malik, Mendichovszky, Mumtaz, Oades, Riddick, Venugopal, Welsh, Riddle, Hopcroft, Jones. Drafting of manuscript: Stewart, Welsh, J Jones. Review and revision of manuscript: Stewart, Welsh, Ursprung, Gallagher, J Jones, Shields, Smith, Mitchell, Warren, Bex, Boleti, Eisen, Fife, Hamid, Laird, Leung, Malik, Mendichovszky, Mumtaz, Oades, Riddick, Venugopal, Welsh, Riddle, Hopcroft, R Jones. Statistical analysis: Hopcroft, Carruthers. Funding: Stewart. Administrative support: Stewart. Supervision: Stewart.

## Ethics approval and consent to participate

Ethics approval was granted by East of England - Cambridgeshire and Hertfordshire Research Ethics Committee (REC reference: 17/EE/0240). All patients were consented following GCP principals. The study was performed in accordance with the Declaration of Helsinki.

## Consent to publication

Consent for publication of imaging (figure S1) provided via trial consent form.

## Data availability

The datasets generated and analysed during NAXIVA are available from the corresponding author following assessment of a brief research proposal which will form the basis of a data sharing agreement. All reasonable requests will be granted.

## Competing interests

GDS - educational grants from Pfizer, AstraZeneca and Intuitive Surgical; consultancy fees from Pfizer, Merck, EUSA Pharma and CMR Surgical; Travel expenses from Pfizer and Speaker fees from Pfizer. TE - employment: Roche (current), AstraZeneca (to March 2020); stock: AstraZeneca, Roche; research support: AstraZeneca, Bayer, Pfizer. FAG - Research support from GE Healthcare; Grants from GSK; Consulting for AZ on behalf of the University of Cambridge. KF has received advisory, consultancy or speaker fees from ESAI, Ipsen, Roche, Novartis, Merck, Pfizer, EUSA Pharma, BMS, MSD and Sanofi and conference support from Novartis, Ipsen, MSD and EUSA Pharma and Institutional research funding from Roche, Merck and Exelixis. AB - received honoraria for participation in advisory boards for Pfizer, Novartis, and Ipsen, and an educational grant from Pfizer. RJ has received educational grants from Astellas, Bayer, Clovis and Exelixis; consultany fees from Roche, AstraZeneca, Bristol Myers Squibb, Bayer, Novartis/AAA, Astellas, Janssen, MSD, Pfizer, Merck Serono; honoraria from Roche, AstraZeneca, Bristol Myers Squibb, Bayer, Astellas, Janssen, MSD, Pfizer, Merck Serono; conference support from MSD and Bayer; advisory board payment from Roche. None of the other authors had conflicts of interest.

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## References


1. Kirkali Z, Van Poppel H. A critical analysis of surgery for kidney cancer with vena cava invasion. Eur Urol. 2007 Sep;52(3):658–62.

2. Blute ML, Leibovich BC, Lohse CM, Cheville JC, Zincke H. The Mayo Clinic experience with surgical management, complications and outcome for patients with renal cell carcinoma and venous tumour thrombus. BJU Int. 2004 Jul;94(1):33–41.

3. Parra J, Drouin SJ, Hupertan V, Comperat E, Bitker MO, Rouprêt M. Oncological outcomes in patients undergoing radical nephrectomy and vena cava thrombectomy for renal cell carcinoma with venous extension: a single-centre experience. Eur J Surg Oncol. 2011 May;37(5):422–8.

4. Lambert EH, Pierorazio PM, Shabsigh A, Olsson CA, Benson MC, McKiernan JM. Prognostic risk stratification and clinical outcomes in patients undergoing surgical treatment for renal cell carcinoma with vascular tumor thrombus. Urology. 2007 Jun;69(6):1054–8.

5. Cost NG, Delacroix SE, Sleeper JP, Smith PJ, Youssef RF, Chapin BF, et al. The impact of targeted molecular therapies on the level of renal cell carcinoma vena caval tumor thrombus. Eur Urol. 2011 Jun;59(6):912–8.

6. Bigot P, Fardoun T, Bernhard JC, Xylinas E, Berger J, Rouprêt M, et al. Neoadjuvant targeted molecular therapies in patients undergoing nephrectomy and inferior vena cava thrombectomy: is it useful? World J Urol. 2014 Feb;32(1):109–14.

7. Peng C, Gu L, Wang L, Huang Q, Wang B, Guo G, et al. Role of presurgical targeted molecular therapy in renal cell carcinoma with an inferior vena cava tumor thrombus. Onco Targets Ther. 2018;11:1997–2005.

8. Fukuda H, Kondo T, Takagi T, Iizuka J, Nagashima Y, Tanabe K. Limited benefit of targeted molecular therapy for inferior vena cava thrombus associated with renal cell carcinoma. Int J Clin Oncol. 2017 Aug;22(4):767–73.

9. Ujike T, Uemura M, Kawashima A, Nagahara A, Fujita K, Miyagawa Y, et al. Clinical and histopathological effects of presurgical treatment with sunitinib for renal cell carcinoma with inferior vena cava tumor thrombus at a single institution. Anticancer Drugs. 2016;27(10):1038–43.

10. Horn T, Thalgott MK, Maurer T, Hauner K, Schulz S, Fingerle A, et al. Presurgical treatment with sunitinib for renal cell carcinoma with a level III/IV vena cava tumour thrombus. Anticancer Res. 2012 May;32(5):1729–35.

11. Tanaka Y, Hatakeyama S, Hosogoe S, Tanaka T, Hamano I, Kusaka A, et al. Presurgical axitinib therapy increases fibrotic reactions within tumor thrombus in renal cell carcinoma with thrombus extending to the inferior vena cava. Int J Clin Oncol. 2018 Feb;23(1):134–41.

12. Terakawa T, Hussein AA, Bando Y, Guru KA, Furukawa J, Shigemura K, et al. Presurgical pazopanib for renal cell carcinoma with inferior vena caval thrombus: a single-institution study. Anticancer Drugs. 2018 Jul;29(6):565–71.

13. Wood CG, Ferguson JE, Parker JS, Moore DT, Whisenant JG, Maygarden SJ, et al. Neoadjuvant pazopanib and molecular analysis of tissue response in renal cell carcinoma. JCI Insight. 2020 Nov 19;5(22):132852.

14. Rini BI, Plimack ER, Takagi T, Elson P, Wood LS, Dreicer R, et al. A Phase II Study of Pazopanib in Patients with Localized Renal Cell Carcinoma to Optimize Preservation of Renal Parenchyma. J Urol. 2015 Aug;194(2):297–303.

15. Karam JA, Devine CE, Urbauer DL, Lozano M, Maity T, Ahrar K, et al. Phase 2 Trial of Neoadjuvant Axitinib in Patients with Locally Advanced Nonmetastatic Clear Cell Renal Cell Carcinoma. Eur Urol. 2014 Feb 7;

16. Dindo D, Demartines N, Clavien P-A. Classification of Surgical Complications. Ann Surg. 2004 Aug;240(2):205–13.

17. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989 Mar;10(1):1–10.

18. Koyama T, Chen H. Proper inference from Simon's two-stage designs. Stat Med. 2008 Jul 20;27(16):3145–54.

19. Smith CG, Moser T, Mouliere F, Field-Rayner J, Eldridge M, Riediger AL, et al. Comprehensive characterization of cell-free tumor DNA in plasma and urine of patients with renal tumors. Genome Med. 2020 Feb 28;12(1):23.

20. Adalsteinsson VA, Ha G, Freeman SS, Choudhury AD, Stover DG, Parsons HA, et al. Scalable whole-exome sequencing of cell-free DNA reveals high concordance with metastatic tumors. Nat Commun. 2017 Nov 6;8(1):1324.

21. Motzer RJ, Banchereau R, Hamidi H, Powles T, McDermott D, Atkins MB, et al. Molecular Subsets in Renal Cancer Determine Outcome to Checkpoint and Angiogenesis Blockade. Cancer Cell. 2020 Dec 14;38(6):803-817.e4.

22. McDermott DF, Huseni MA, Atkins MB, Motzer RJ, Rini BI, Escudier B, et al. Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. Nat Med. 2018 Jun;24(6):749–57.

23. Motzer RJ, Robbins PB, Powles T, Albiges L, Haanen JB, Larkin J, et al. Avelumab plus axitinib versus sunitinib in advanced renal cell carcinoma: biomarker analysis of the phase 3 JAVELIN Renal 101 trial. Nat Med. 2020 Nov;26(11):1733–41.

24. Bex A, Mulders P, Jewett M, Wagstaff J, van Thienen JV, Blank CU, et al. Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients With Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib: The SURTIME Randomized Clinical Trial. JAMA Oncol. 2019 01;5(2):164–70.

25. Welsh SJ, Thompson N, Warren A, Priest AN, Barrett T, Ursprung S, et al. Dynamic biomarker and imaging changes from a phase II study of pre- and post-surgical sunitinib. BJU Int. 2021 Sep 22;

26. Ursprung S, Priest AN, Zaccagna F, Qian W, Machin A, Stewart GD, et al. Multiparametric MRI for assessment of early response to neoadjuvant sunitinib in renal cell carcinoma. PLoS One. 2021;16(10):e0258988.

27. Biyani CS, Pecanka J, Rouprêt M, Jensen JB, Mitropoulos D. Intraoperative Adverse Incident Classification (EAUiaiC) by the European Association of Urology ad hoc Complications Guidelines Panel. European Urology. 2020 May 1;77(5):601–10.

28. Gore ME, Szczylik C, Porta C, Bracarda S, Bjarnason GA, Oudard S, et al. Final results from the large sunitinib global expanded-access trial in metastatic renal cell carcinoma. Br J Cancer. 2015 Jun 30;113(1):12–9.

29. Sharma R, Kadife E, Myers M, Kannourakis G, Prithviraj P, Ahmed N. Determinants of resistance to VEGF-TKI and immune checkpoint inhibitors in metastatic renal cell carcinoma. J Exp Clin Cancer Res. 2021 Jun 7;40(1):186.

30. Association between tyrosine-kinase inhibitor induced hypertension and treatment outcomes in metastatic renal cancer - Gadd - 2020 - Cancer Reports - Wiley Online Library [Internet]. [cited 2021 Sep 10]. Available from: https://onlinelibrary.wiley.com/doi/ftr/10.1002/cnr2.1275

31. Choueiri TK, Powles T, Burotto M, Escudier B, Bourlon MT, Zurawski B, et al. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. New England Journal of Medicine. 2021 Mar 4;384(9):829–41.

32. Motzer R, Alekseev B, Rha S-Y, Porta C, Eto M, Powles T, et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. New England Journal of Medicine. 2021 Apr 8;384(14):1289–300.

33. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019 Mar 21;380(12):1116–27.

34. Dynamic changes of the immune infiltrate after neoadjuvant avelumab/axitinib in patients (pts) with localized renal cell carcinoma (RCC) who are at high risk of relapse after nephrectomy (NeoAvAx). | Journal of Clinical Oncology [Internet]. [cited 2022 Mar 6]. Available from: https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.4573

35. Gorin MA, Patel HD, Rowe SP, Hahn NM, Hammers HJ, Pons A, et al. Neoadjuvant Nivolumab in Patients with High-risk Nonmetastatic Renal Cell Carcinoma. European Urology Oncology [Internet]. 2021 May 26 [cited 2021 Sep 10]; Available from: https://www.sciencedirect.com/science/article/pii/S2588931121000766

36. Stewart GD, Welsh SJ, Ursprung S, Gallagher F, Mendichovszky I, Riddick A, et al. NAXIVA: A phase II neoadjuvant study of axitinib for reducing extent of venous tumor thrombus in clear cell renal cell cancer (RCC) with venous invasion. JCO. 2021 Feb 20;39(6_suppl):275–275.

37. Neves RJ, Zincke H. Surgical treatment of renal cancer with vena cava extension. Br J Urol. 1987 May;59(5):390–5.

738 **Table 1.** Baseline characteristics of evaluable population

| **Characteristic** | **n** | % |
|---|---|---|
| Number of patients | 21 | 100 |
| Median age, yr (range) | 69 (49-78) | |
| Sex | | |
| Male | 15 | 71 |
| Female | 6 | 29 |
| Median BMI, kg/m$^2$ (range) | 27.7 (19.4-44.6) | |
| ECOG grade | | |
| 0 | 13 | 61.9 |
| 1 | 8 | 38.1 |
| Clinical T-stage | | |
| T3a | 6 | 28.6 |
| T3b | 13 | 61.9 |
| T3c | 2 | 9.5 |
| M-stage | | |
| M0 | 11 | 52.4 |
| M1 | 10 | 47.6 |
| Median number of metastases (range) | 1 (1-4) | |
| Site of metastases | | |
| Lymph nodes | 2 | 18.2 |
| Adrenal | 1 | 9.1 |
| Lung | 7 | 63.6 |
| Bone | 1 | 9.1 |
| MSKCC classification (M1 patients only) | | |
| Intermediate | 9 | 90 |
| Poor* | 1 | 10 |

| | | |
|---|---|---|
| Histological subtype on baseline biopsy | | |
| ccRCC | 21 | 100 |
| ISUP grade on baseline biopsy | | |
| 1 | 2 | 9.5 |
| 2 | 10 | 47.6 |
| 3 | 2 | 9.5 |
| 4 | 4 | 19.0 |
| No data | 3 | 14.3 |
| Mayo Level of VTT on baseline imaging[+] | | |
| RV-only (Level 0) | 4 | 20 |
| Level 1 | 3 | 15 |
| Level 2 | 9 | 45 |
| Level 3 | 2 | 10 |
| Level 4 | 2 | 10 |

*For eligibility M1 participants had to be intermediate risk by MSKCC criteria. This patient was entered into the trial when they were thought to have M0 disease. Central imaging review following completion of the trial, identified M1 disease at baseline and retrospectively the patient was found to have MSKCC poor risk disease (newly diagnosed RCC, haemoglobin, LDH). However, as they received study drug and had a VTT they were in the evaluable population and remain in the study analysis.

[+]One evaluable patient was found on central imaging review to be ineligible for NAXIVA as they did not have a VTT; thus the baseline VTT level is only available for the 20 eligible and evaluable patients.

748 **Table 2.** Drug toxicity by CTCAEv4 grade

| **Event, %** | **Any grade** | **Grade 3*** |
|---|---|---|
| Treatment-related adverse events in ≥10% of patients | 100 | 52 |
| Hypertension | 86 | 24 |
| Fatigue | 67 | 10 |
| Proteinuria | 48 | 5 |
| Voice alteration | 48 | 0 |
| Mucositis | 43 | 10 |
| Diarrhoea | 38 | 0 |
| Constipation | 33 | 0 |
| Back pain | 29 | 0 |
| Cough | 29 | 0 |
| Weight loss | 29 | 0 |
| Insomnia | 24 | 0 |
| Muscular weakness | 24 | 5 |
| Abdominal pain | 19 | 0 |
| Dry skin | 19 | 0 |
| Dysgeusia | 14 | 0 |
| Epistaxis | 14 | 0 |
| Headache | 14 | 0 |
| Hypothyroidism | 14 | 0 |
| PPE syndrome | 14 | 0 |
| Stomatitis | 14 | 0 |
| Vomiting | 14 | 0 |

749 *No grade 4 or 5 AEs were observed.

750

751

752

## Figure legends

**Figure 1.** (a) Summary of Mayo level, figure adapted from (37). (b) Consort diagram. *Participants who had at least one dose of the study drug were included in the evaluable population, irrespective of whether surgery was performed.

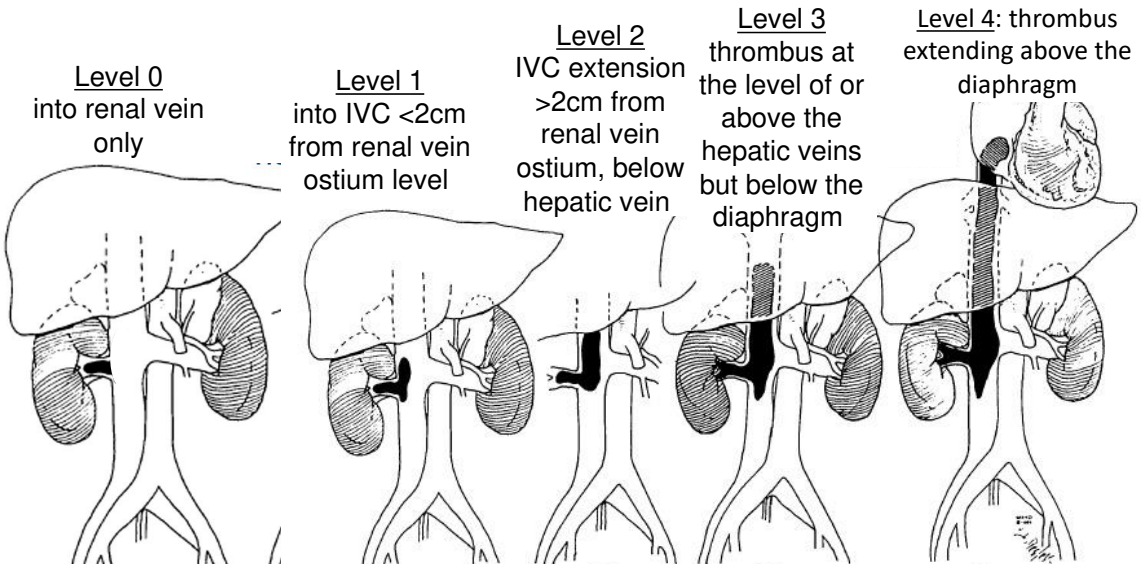
**Figure 2.** Mayo level at baseline, week 3 and week 9 for eligible and evaluable patients. Note that N105 had a RV-only VTT response receding from medial to the insertion of the gonadal vein to lateral to it. Figure S1 shows examples of two IVC responder patients.

**Figure 3.** Percentage change in VTT length over axitinib treatment period. (a) Line chart showing percentage change in VTT length for IVC responders, RV responders and non-responders. Waterfall plot of VTT response against tumour response at (**b**) 3 and (**c**) 9 weeks of treatment. N0601 (surgery expedited), N0605 (surgery expedited) and N0903 (exited trial due to new brain metastasis) did not have scans at week 9. Bar colour indicates patient's overall RECIST status distinct from VTT assessment.

**Figure 4.** Representative images of baseline biopsies stained for (a) blood vessels (CD31), (b) proliferating cells (Ki67) and (e) CD8+ T cell activation status (Granzyme B and PD-1). Whole slides were scanned and quantified using automated computer image analysis on HALO (c, d, f-h, two tailed student t-test).

# Figure 1

a


Level 0
into renal vein only
Level 1
into IVC <2cm from renal vein ostium level
Level 2
IVC extension >2cm from renal vein ostium, below hepatic vein
Level 3
thrombus at the level of or above the hepatic veins but below the diaphragm
Level 4: thrombus extending above the diaphragm

b

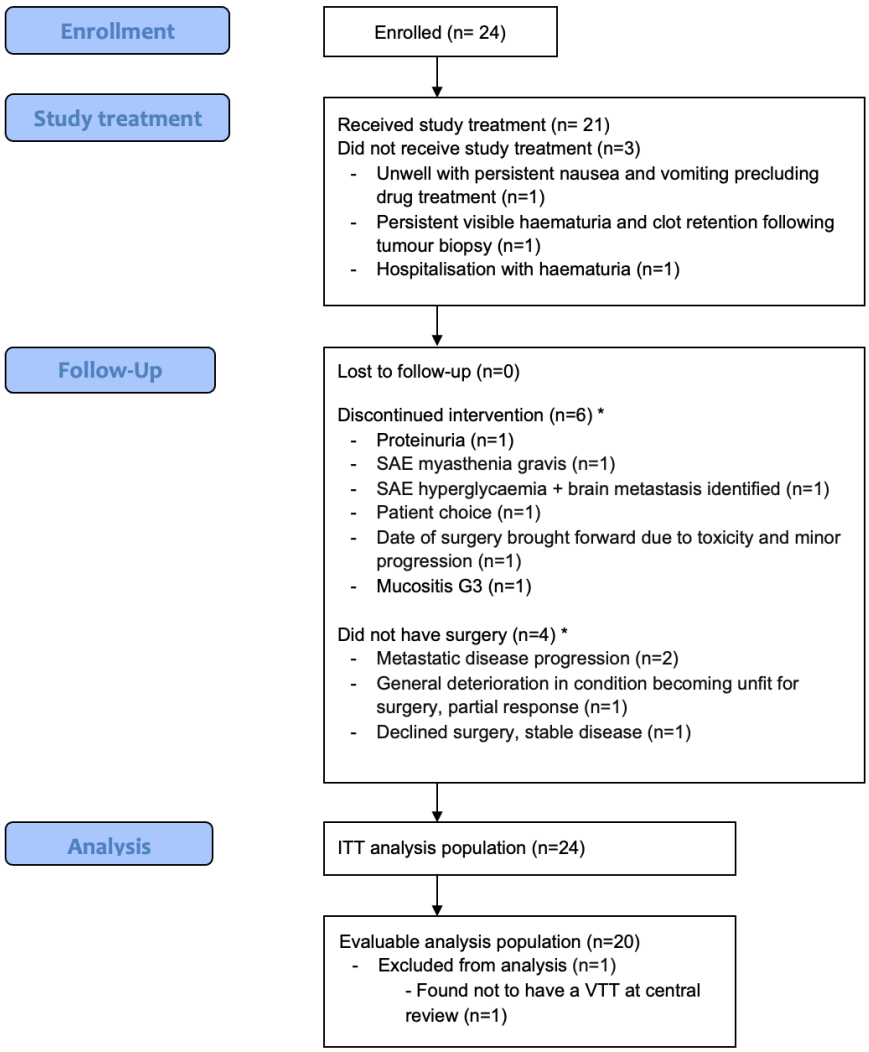

Enrollment
Enrolled (n= 24)
Study treatment
Received study treatment (n= 21)
Did not receive study treatment (n=3)
- Unwell with persistent nausea and vomiting precluding drug treatment (n=1)
- Persistent visible haematuria and clot retention following tumour biopsy (n=1)
- Hospitalisation with haematuria (n=1)
Follow-Up
Lost to follow-up (n=0)
Discontinued intervention (n=6) *
- Proteinuria (n=1)
- SAE myasthenia gravis (n=1)
- SAE hyperglycaemia + brain metastasis identified (n=1)
- Patient choice (n=1)
- Date of surgery brought forward due to toxicity and minor progression (n=1)
- Mucositis G3 (n=1)
Did not have surgery (n=4) *
- Metastatic disease progression (n=2)
- General deterioration in condition becoming unfit for surgery, partial response (n=1)
- Declined surgery, stable disease (n=1)
Analysis
ITT analysis population (n=24)
Evaluable analysis population (n=20)
- Excluded from analysis (n=1)
- Found not to have a VTT at central review (n=1)

Figure 2

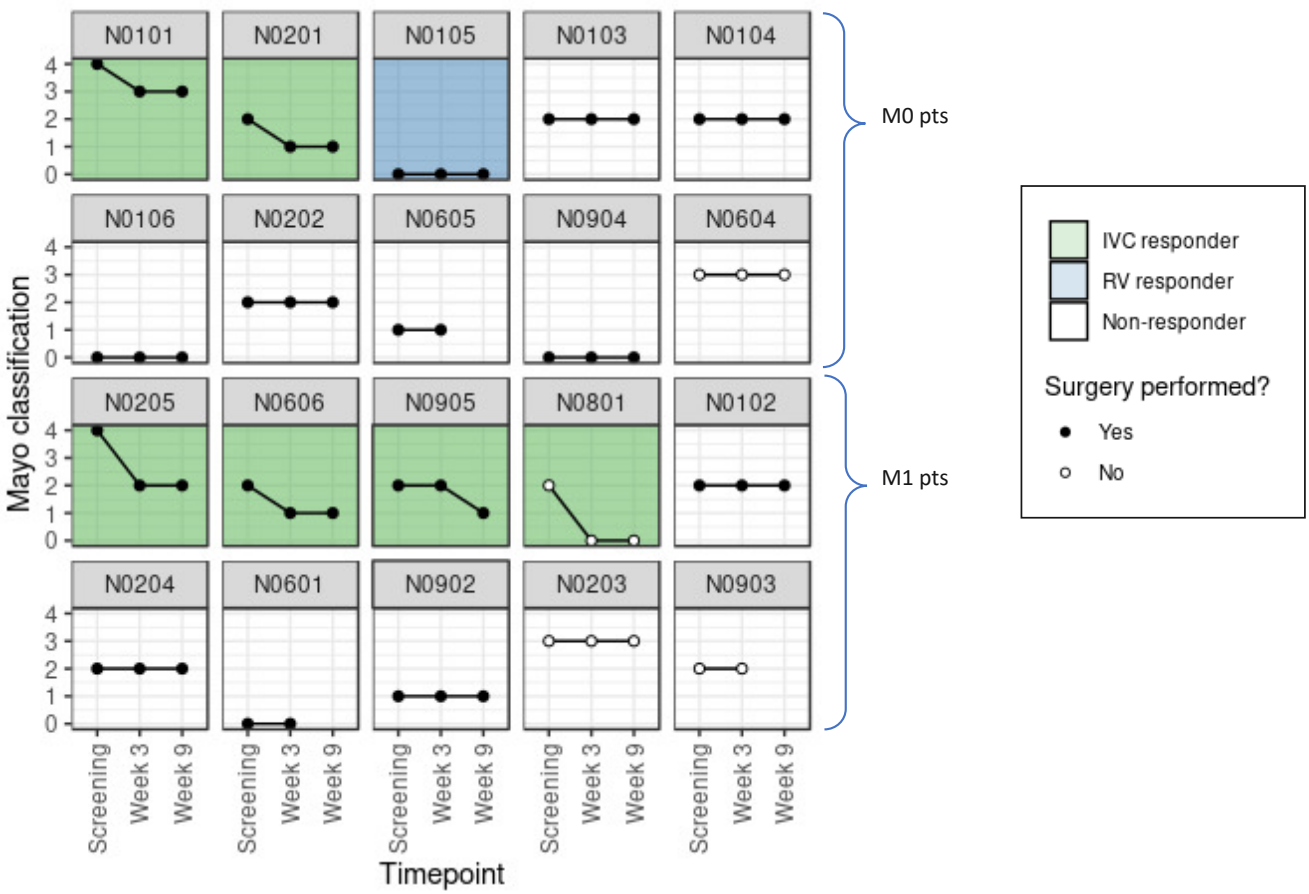

N0101
N0201
N0105
N0103
N0104
N0106
N0202
N0605
N0904
N0604
N0205
N0606
N0905
N0801
N0102
N0204
N0601
N0902
N0203
N0903
Mayo classification
0
1
2
3
4
Screening
Week 3
Week 9
Timepoint
M0 pts
M1 pts
IVC responder
RV responder
Non-responder
Surgery performed?
Yes
No

Figure 3

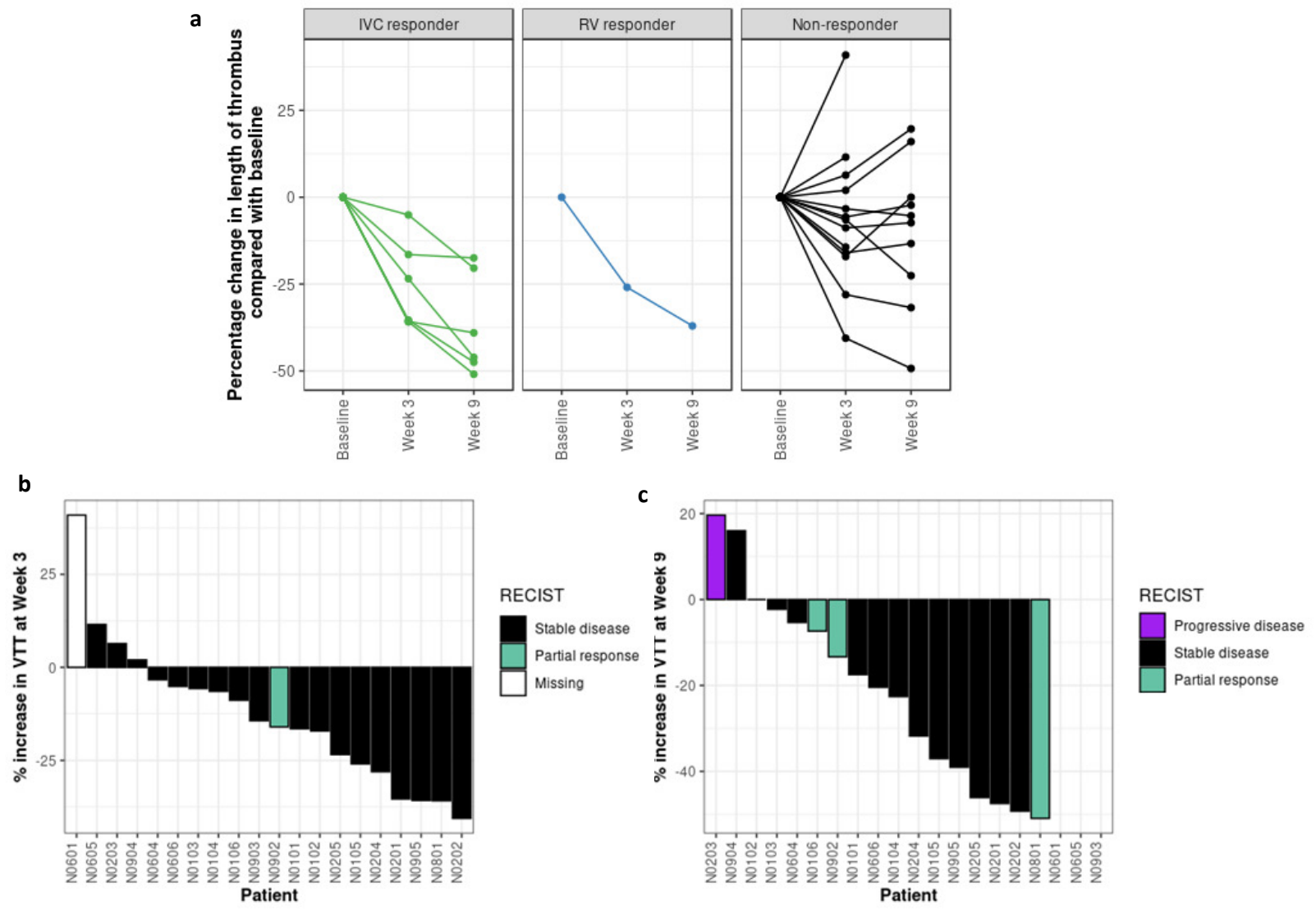
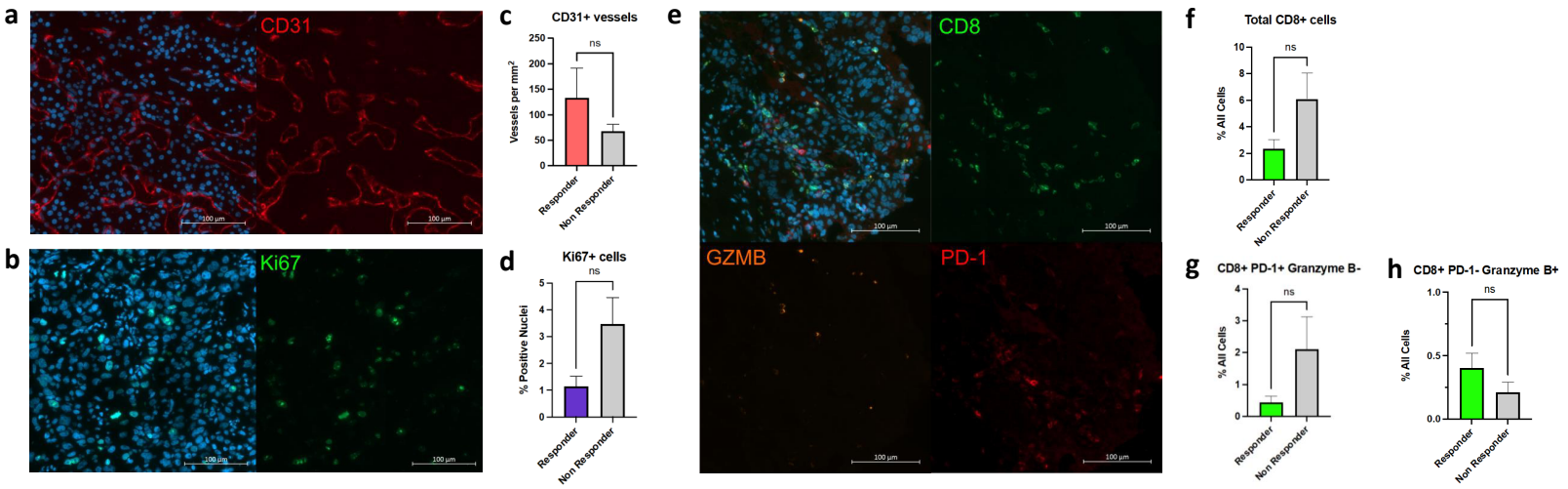

a
IVC responder
RV responder
Non-responder
Percentage change in length of thrombus compared with baseline
25
0
-25
-50
Baseline
Week 3
Week 9
b
% increase in VTT at Week 3
25
0
-25
N0601
N0605
N0203
N0904
N0604
N0606
N0103
N0104
N0106
N0903
N0902
N0101
N0102
N0205
N0105
N0204
N0201
N0905
N0801
N0202
Patient
RECIST
Stable disease
Partial response
Missing
c
% increase in VTT at Week 9
20
0
-20
-40
N0203
N0904
N0102
N0103
N0604
N0106
N0902
N0101
N0606
N0104
N0204
N0105
N0905
N0205
N0201
N0202
N0801
N0601
N0605
N0903
Patient
RECIST
Progressive disease
Stable disease
Partial response

Figure 4


a
CD31
100 µm
b
Ki67
100 µm
c
CD31+ vessels
Vessels per mm²
250
200
150
100
50
0
ns
Responder
Non Responder
d
Ki67+ cells
% Positive Nuclei
5
4
3
2
1
0
ns
Responder
Non Responder
e
CD8
GZMB
PD-1
100 µm
f
Total CD8+ cells
% All Cells
10
8
6
4
2
0
ns
Responder
Non Responder
g
CD8+ PD-1+ Granzyme B-
% All Cells
4
3
2
1
0
ns
Responder
Non Responder
h
CD8+ PD-1- Granzyme B+
% All Cells
1.0
0.5
0.0
ns
Responder
Non Responder