SUMMARY OF RESULTS OF THE CLINICAL TRIAL – SYNOPSIS

A phase III study testing the role of PRoactivE coaching on PAtient REported outcome in advanced or metastatic renal cell carcinoma treated with sunitinib or a combination of pembrolizumab + axitinib or avelumab + axitinib in first line therapy

Short handle: PREPARE 2.0

Protocol Number: AIO-NZK-0115/ass

EudraCT Number: 2016-000399-28

Investigational Medicinal Products:	Sunitinib, Axitinib, Avelumab, Pembrolizumab
Intervention:	Concomitant coaching
Phase of Development:	Phase III
Date of First Patient In:	17-Jan-2017
Date of Last Patient Out:	16-Jan-2024
Indication:	Advanced or metastatic renal cell carcinoma
Design:	Open-label, randomized, phase III study
Sponsor:	AIO-Studien-gGmbH Kuno-Fischer-Straße 8 14057 Berlin, Germany
Coordinating Investigator:	Prof. Dr. med. Viktor Grünwald University Hospital Essen (AöR) West-German Cancer Center Hufelandstraße 55 45147 Essen, Germany
Date of Report (Synopsis, FINAL 3.0):	23-Apr-2026

This study was performed in accordance with Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki and other applicable regulatory.

Name of Company: AIO-Studien-gGmbH Name of Finished Product: Sutent®, Inlyta®, Bavencio®, Keytruda® Name of Active Ingredient: Sunitinib, Axitinib, Avelumab, Pembrolizumab	Individual Study Table Referring to Part of the Dossier Volume: N/A Page: N/A	(For National Authority Use Only)
Title of Study: A phase III study testing the role of PRoactivE coaching on PAtient REported outcome in advanced or metastatic renal cell carcinoma treated with sunitinib or a combination of pembrolizumab + axitinib or avelumab + axitinib in first line therapy		
Deutscher Studientitel: Eine Phase III Studie zum Stellenwert einer pro-aktiven Therapiebegleitung (Coaching) in Bezug auf die Patienteneinschätzung der Lebensqualität bei Behandlung mit Sunitinib, einer Kombination von Pembrolizumab + Axitinib oder Avelumab + Axitinib bei fortgeschrittenen oder metastasierten Nierenzellkarzinom		
Principal Investigator: Prof Dr. med. Viktor Grünwald		
Study Sites: 28 study sites in Germany		
Publications: Eine Phase-III-Studie zur pro-aktiven Therapiebegleitung unter Behandlung mit Sunitinib oder Pembrolizumab in Kombination mit Axitinib bzw. Avelumab in Kombination mit Axitinib eines fortgeschrittenen oder metastasierten Nierenzellkarzinoms (PREPARE) – AUO-Nr. AN 49/18. Urol 2020; 59:1157–1159. Grünwald V, Ivanyi P, Jakobasch L, Zahn M-O, Eberhardt B, Detzner M. PREPARE: Phase-III-Studie zur proaktiven Therapiebegleitung (Coaching) in Bezug auf die Patienteneinschätzung der Lebensqualität unter Behandlung eines fortgeschrittenen oder metastasierten Nierenzellkarzinoms mit Checkpoint-Inhibitoren plus Axitinib oder Sunitinib-Monotherapie. Forum (Genova) 2020; 35:152–154. Rexer H, Grünwald V, Doehn C. PREPARE – Phase-III-Studie zur Erstlinientherapie des unbehandelten fortgeschrittenen oder metastasierten Nierenzellkarzinoms: Proaktive Begleitung der Therapie mit Sunitinib, Pembrolizumab plus Axitinib oder Avelumab plus Axitinib. Forum (Genova) 2021; 36:253–255. PREPARE: Eine Phase-III-Studie zur pro-aktiven Therapiebegleitung bei Behandlung eines fortgeschrittenen oder metastasierten Nierenzellkarzinoms mit Checkpoint-Inhibitoren plus Axitinib oder Sunitinib Monotherapie. 34. Deutscher Krebskongress, Berlin, Poster Nr. 958 (2020) A phase III study testing the role of proactive coaching on patient reported outcome in advanced or metastatic renal cell carcinoma treated with sunitinib or a combination of axitinib + pembrolizumab or avelumab in first line therapy (PREPARE; AIO-NZK-011). ASCO GU 2025, Abstract 523		
Study Dates: First Patient Informed Consent: 17- Jan-2017 First Patient Randomized: 18-Jan-2017 Last Patient Completed: 16-Jan-2024	Phase of Development: Phase III	

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Objectives:

Primary objective

- To determine the impact of a 24 weeks concomitant coaching on patient reported outcomes of patients receiving standard first-line treatment for mRCC with sunitinib or a combination of checkpoint inhibitor (CPI) + axitinib.

Secondary objective

- Assessment of the impact of a 24 weeks concomitant coaching on additional QoL measures, patient compliance, efficacy and safety.

Exploratory objectives

- Assessment of inflammatory markers in tumor samples and serum.

Note: The exploratory endpoint could not be examined since samples were not collected in the study and thus could not be analyzed.

Methodology:

Open label, randomized, phase III study

Number of Patients:

Planned: 430

Actual: 121 screened, 113 randomized, 110 received study drug, 55 received study intervention (coaching)

A pooled, blinded interim analysis of the primary endpoint after the randomization of N=100 subjects in order to verify the statistical assumptions and, if required, to recalculate and adapt the sample size was planned in the CSP. This interim analysis was not conducted because of the premature study end.

Main Criteria for Inclusion:

1. Written informed consent and any locally-required authorization (EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations
2. Age ≥ 18 years at time of study entry
3. Advanced or metastatic renal cell carcinoma, not amenable to surgery with curative intent, rendering the patient eligible for 1st line systemic treatment
4. Intended first-line treatment with sunitinib, with pembrolizumab plus axitinib or with avelumab plus axitinib
5. Documented progressive disease within 6 months prior to study inclusion
6. Patients with measurable disease (at least one unidimensionally measurable target lesion by CT-scan or MRI) according to modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and non-measurable disease are eligible.
7. Prior radiotherapy and surgery were allowed if completed 4 weeks (for minor surgery and palliative radiotherapy for bone pain: 2 weeks) prior to start of treatment and patient recovered from toxic effects.

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Main Criteria for Exclusion:

1. Any other anti-cancer treatment aside of sunitinib or axitinib with CPI for mRCC (except palliative radiotherapy)
2. Previous malignancy (other than mRCC) which either progresses or requires active treatment. Exceptions were basal cell cancer of the skin, pre-invasive cancer of the cervix, T1a or T1b prostate carcinoma, and superficial bladder tumor [Ta, Tis and T1].
3. CNS metastases, unless local therapy had been completed for at least 3 months and patient did not require the use of steroids.
4. Chronic liver disease with Child-Pugh B or C score

Intervention:

The intervention group (Arm A) received proactive coaching in addition to 1st-line treatment according to Standard of Care.

The cornerstones of the pro-active coaching were as follows:

- Patient education
  - Information on nature and severity of treatment emergent AEs
  - Information about remedies for TEAEs
  - Propagation and explanation of tests and treatment decisions
  - Patient instruction on self-care and preventive measures
  - Patient education was to be provided a) as an educational video and b) continuously at personal interactions of coach and patient. Face-to-face meetings were to be performed before initiation of cancer therapy and during regular medical visits (at Baseline, at Visit 1 (Day 28±3), at Visit 2 (Day 42±7), Visit 3 (week 10), Visit 5 (week 16), Visit 7 (week 22) and at Visit 8/EOT (week 24))
  - Therapy surveillance by phone with a structured interview (week 1, 2, 3, 5 during first 2 cycles; thereafter at least every 2 weeks unless a face-to-face meeting had been scheduled)
  - Availability of coach for unscheduled contacts by phone (during normal business hours)
- Preemptive AE treatment strategies:
  - Installation of preemptive measures for skin reactions and stomatitis at start of treatment
  - Proactive assessment of treatment emergent AEs with emphasis on predefined ADRs of special interest (fatigue, diarrhea, stomatitis, skin toxicities, hypertension)
  - Follow-up of availability of remedies for TEAEs
- Supervision of reported ADR severity, ADR mitigation strategies according to recommendations of the PREPARE protocol and cancer treatment modification by treating physician in close collaboration with the coach

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Investigational Medicinal Products – Dose and Mode of Administration, Batch Numbers:

All IMPs were to be dosed according to marketing authorization.

Sunitinib: recommended dosage was 50 mg sunitinib once daily for 4 weeks followed by 2 weeks off treatment [4/2 schedule; total cycle length = 6 weeks].

Axitinib: The recommended dose of axitinib was 5 mg twice daily. Patients who tolerated treatment well could have their dose increased to 7 mg twice daily and subsequently to 10 mg twice daily.

Avelumab: recommended dose of avelumab in combination with axitinib is 800 mg administered intravenously over 60 minutes every 2 weeks.

Pembrolizumab: recommended dose of pembrolizumab as part of combination therapy was either 200 mg every 3 weeks, or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes.

Only commercial products were used, and batch numbers were not recorded within the study.

Substantial Amendment to Study Intervention and IMPs:

At the beginning of the study, sunitinib was the only study drug as per study protocol. When the alternative treatment regimens axitinib plus avelumab and axitinib plus pembrolizumab gained marketing authorization, the study protocol was amended to use these treatments as standard-of-care agents within the study. The coaching instructions were also slightly modified to reflect requirements of CPI side effect management.

Duration of Study Intervention (Coaching, Arm A only): 24 weeks per patient

Duration of Assessment for Primary Endpoint (QoL questionnaires): 24 weeks per patient

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Criteria for Evaluation:

Due to premature study end, the amount of statistical analysis was reduced and it was decided to not analyze the following secondary endpoints described in the CSP:

- Dose density of SOC 1st-line treatment: was not analyzed, since the dose values were reported inconsistently in the eCRF.
- Treatment beyond progression
- Patient adherence/ treatment discontinuation due to protocol-specific AESIs: instead, the rate of protocol-specific AESIs was analyzed.

Thus, we are reporting the following endpoints:

Quality of Life:

- Rate of responders to concomitant coaching assessed by the FKSI-15 questionnaire (primary endpoint)
- Health related Quality of Life (FACT-G, EQ-5D)
- Time to (definitive) improvement/deterioration with regards to increase/decrease of FKSI-15 score
- Duration of coaching

Efficacy:

- Objective response rate (ORR) according to RECIST 1.1 criteria
- Duration of response (DOR)
- Overall survival (OS)
- Progression-free survival (PFS)
- Progression-free survival of 2nd-line treatment (PFS2)
- Further cancer treatment and time to first subsequent therapy (TFST)

Safety:

- Duration of treatment
- Median follow-up time
- Adverse events (AEs) according to Common Terminology Criteria for AEs (CTCAE), version 4.03:
    - Summary of AEs and SAEs by severity and maximum severity, treatment emergent AEs, drug-related AEs, drug-related SAEs, drug-related AESIs, alternative AESIs
- Time to onset of an adverse drug reaction (ADR)

Additional analyses were conducted and are documented in the statistical analysis results and the full clinical study report.

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Statistical Methods:

Quality of Life:

The health related Quality of Life (QoL) of patients was measured using the three QoL questionnaires FKSI-15, FACT-G and EQ-5D. Scores were calculated as outlined in the Statistical Analysis Plan (SAP) and were tabulated by visit.

The primary endpoint was analyzed based on the FKSI-15 score. A QoL responder was defined as a patient achieving an increase of ≥3 points (minimally important difference (MID)) at any individual time point during the study treatment compared to baseline. Further, a confirmed QoL responder was defined as a QoL responder with at least one subsequent time point to confirm response. The response rates were calculated by dividing the number of (confirmed) responders by the number of all QoL evaluable patients. The rates were accompanied by corresponding two-sided 95% Clopper-Pearson confidence intervals.

In order to test the hypothesis that the QoL response rate in the experimental (coaching) arm exceeds the response rate in the control arm, a two-sided Cochran–Mantel–Haenszel (CMH) test stratified for 1st-line treatment was applied. The test used a significance level of 0.05, which is corresponding to a one-sided test with significance level 0.025. As sensitivity analysis, similar tests stratifying for bone metastatic status, co-morbidity, histology and sex were applied.

Further, the QoL deterioration and the confirmed QoL deterioration rates were calculated analogously to the response rates, i.e. deterioration was defined as a decrease of ≥3 points at any individual time point during study compared to baseline. Definitions of response and deterioration were used to calculate also time to improvement (TTI) and deterioration (TTD), which were defined as the time from randomization until the first improvement/deterioration. In addition, time to definitive improvement (TTDI)/deterioration (TTDD) was defined as time from randomization until the date of first confirmed improvement/deterioration, i.e. two subsequent FKSI assessments with improvement/deterioration. Patients without event were censored at the time of last FKSI assessment. These time-to-event endpoints were analyzed by means of the Kaplan Meier method. Median time-to-event endpoints at certain time points (3, 6, 9 and 12 months) were analyzed and presented together with 95% confidence intervals. Log-rank tests were performed to compare study arms.

Further, TTI, TTDI, TTD, and TTDD were analyzed using a Cox regression model which treated baseline QoL-scores and the type of 1st line treatment as a covariates to obtain the hazard ratio and the respective two-sided 80% confidence interval.

Efficacy:

Time-to-event endpoints (DOR, OS, PFS, PFS2 and TFST) were analyzed by means of the Kaplan Meier method. Median survival and survival at pre-defined time points (6, 12, 24, 36, 48 and 60 months) were analyzed and presented together with 95% confidence intervals. Log-rank tests were performed to compare study arms. Time-to-event measures were performed for the overall populations as well as stratified by treatment arm, metastatic status, co-morbidity, 1st-line treatment, histology and MSKCC risk category.

DOR was defined as the time in days from onset of the first CR or PR to the date of the first PD or death. Patients were censored at last available tumor assessment date, in case no PD or death occurred or if they still had CR or PR at the time of the analysis.

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OS was defined as the time in months between the date of randomization and the date of death from any cause. If no event was observed, the patient was censored at the day of last contact.

PFS was defined as the time in months between the date of randomization and the date of confirmed PD (based on investigator assessments) or the date of death from any cause. The patients without event were censored at the time of last tumor assessment.

PFS2 was defined as the time in months between the date of randomization and the date of PD or death of subsequent line of therapy (second PD). Patients without event were censored at the time of last tumor assessment.

TFST was defined as the interval from the start date of any therapy until the first date of subsequent medical anti-cancer therapy. Patients without event were censored at the time of last tumor assessment.

ORR was the rate of patients having CR or PR as best overall response during treatment among patients in the analysis set of interest. Patients without any response assessment or NE as response were considered non-responders. The ORR was analyzed descriptively using binomial response rates and corresponding two-sided 95% exact confidence intervals using the Clopper-Pearson method.

<u>Safety:</u>

AEs were summarized for different types of events (all AEs, treatment emergent AEs, drug-related AEs, serious AEs, severe AEs, drug-related AESIs, alternative AESIs, drug-related alternative AESIs) and are also presented by CTC system organ class (CTC SOC) and AE term. AEs were generally coded automatically via eCRF according to CTCAE v4.03, except AEs entered in the eCRF field 'Other, specify'. Those AEs were coded manually using MedDRA version 26.1. Further, AEs were presented by severity. In AE summary tables, 90% confidence intervals according to Altman were provided for all AE rates.

In this study, two types of AESIs were investigated. The following five events were defined in the CSP as protocol-specific AESIs: hand-foot syndrome, diarrhea, stomatitis, fatigue and hypertension. During study conduct another AESI definition with regard to pharmacovigilance became important. So called 'alternative AESIs' were defined in the SAP via a list of pre-defined Preferred Terms.

Further, time to onset of an ADR was defined as time between first drug administration and the start date of the respective drug-related AE. It was not calculated in case of missing or incomplete dates. Time to ADR was analyzed using the Kaplan Meier method. Median time to ADR and rate of patients with ADR at certain time points (20, 40, 60, 100, 140 and 180 days) was analyzed and presented together with 95% confidence intervals. Log-rank tests were performed to compare study arms.

Treatment duration in months was analyzed descriptively for sunitinib and for axitinib combined with avelumab and pembrolizumab. Median follow-up time was analyzed using reverse Kaplan Meier statistics. It was defined as the time in months between the date of randomization and the date of lost to follow up. Patients without date of lost to follow up available were censored at the date of last contact.

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Summary of Results:

Disposition:

In total, 121 patients were screened, of which 113 were randomized, 56 patients into the intervention group that received coaching (Arm A) and 57 into the control group (Arm B). For randomization, the following stratification factors were considered: ECOG performance status, bone metastatic status, co-morbidities and type of 1st-line treatment. At screening, the majority of patients had an ECOG performance status of 0 or 1 (92.9% of patients in Arm A and 91.2% of patients in Arm B). For most patients no bone metastasis were present (67.9% of patients in Arm A and 73.7% of patients in Arm B). Concerning comorbidities, 22 patients (39.3%) in Arm A had a Charlson Comorbidity Index >=2, compared to 28 patients (49.1%) in Arm B. With regard to type of 1st-line treatment, patients were assigned to either receive sunitinib or a combination of axitinib and checkpoint inhibitor (avelumab or pembrolizumab). At screening, 51.8% of patients in Arm A and 50.9% of patients in Arm B were assigned to the pembrolizumab plus axitinib cohort, 37.5% of Arm A and 42.1% of Arm B to the sunitinib cohort and 10.7% of Arm A and 7.0% of Arm B to the avelumab plus axitinib cohort.

Of the randomized patients, 110 were treated (55 of Arm A and 55 of Arm B) and hence are part of the safety population. Patients with a baseline and at least one post-baseline QoL evaluable assessment were included in the QoL evaluable population. This was true for 89 patients (46 of Arm A and 43 of Arm B).

Baseline Characteristics:

The safety population was the primary population for evaluating baseline endpoints. Age in this population was similar between groups, the average age being 70.5 years in Arm A vs. 69.0 years in Arm B. Equally, the distribution of sex was comparable between arms (67.3% of the patients in Arm A vs 70.9% of the patients in Arm B were male) and all patients were white. Living arrangements also appeared to be similar between groups: 78.2% of Arm A and 76.4% of Arm B were living with their spouse or partner. Body Mass Index was comparable too, the average being 26.8 kg/m² in Arm A and 28.3 kg/m² in Arm B.

The majority of patients in both arms had renal cell carcinoma of clear cell histology (87.3% in Arm A vs. 83.6% in Arm B). In Arm A 61.8% of patients and in Arm B 47.3% of patients had received (neo) adjuvant surgery.

MSKCC average scores were 1.2 in Arm A vs. 1.5 in Arm B. Regarding MSKCC risk categories, the majority of Arm A was in the intermediate category (64.8%), another 22.2% were in the favorable category and 13.0% in the poor category. In Arm B rates were comparable, with 68.0% of patients in the intermediate category, 18.0% in the favorable and 14.0% in the poor category.

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Quality of Life Results:

The primary analysis was the QoL response rate in the QoL evaluable population assessed by the FKSI-15 questionnaire. The response rates in both arms were similar, being 39.1% in Arm A with a 95% confidence interval (CI) of [25.1, 54.6] and 39.5% in Arm B (95% CI [25.0, 55.6]). Further, also the confirmed response rate was comparable with 10 confirmed responders per arm (21.7% in Arm A vs. 23.3% in Arm B). The CMH-test stratifying for 1st-line treatment did not show any statistically significant differences (p-value: 0.8722). The same was true for the CMH-test applied to the strata bone metastatic status, co-morbidity, histology and sex.

The QoL deterioration rate showed only slight differences between both arms, the rate being 76.1% in Arm A vs. 74.4% in Arm B. Also, the confirmed response rate was higher in Arm A (58.7% vs. 51.2% in Arm B).

Similar response rates and deterioration rates were observed in the randomized and the safety population.

Regarding completion of QoL questionnaires in the QoL evaluable population, both FKSI-15 and FACT-G, were completed at baseline by 89.1% of patients in Arm A and 95.3% in Arm B. At the last cycle (Cycle 4/ V8), the completion rate was 60.9% in Arm A vs. 53.5% in Arm B. Differences between arms only reached statistical significance for the FACT-G at Cycle 3/ V5 (p-value: 0.0478).

FKSI-15 and FACT-G scores as well as EQ-VAS did not show a pattern (no stable increase nor decrease over time). Also, the number of patients reporting problems among the EQ-5D dimensions did not show a clear pattern.

Median TTI was not calculable in Arm A and 6.2 months in Arm B. Median TTDI was again not calculable for Arm A and 9.4 months in Arm B. Median TTD was 1.8 months in Arm A vs. 2.1 months in Arm B. TTDD was 5.1 months in Arm A vs. 3.7 months in Arm B. None of these differences reached statistical significance. Results of the Cox regression model which included baseline QoL-scores and the type of 1st line treatment as covariates, obtained a hazard ratio of 0.87 with corresponding two-sided 80% Wald confidence interval of [0.55, 1.39] for TTI. The hazard ratio for TTDI was 1.09 (80% Wald CI [0.60, 1.97]). For TTD and TTDD similar hazard ratios of 1.05 (80% Wald CI [0.76, 1.45]) and 0.99 (80% Wald CI [0.68, 1.44]) were obtained. No statistically significant p-values for comparison of arms were observed.

Coaching:

Of the 55 treated patients in Arm A, 53 received a baseline coaching as per protocol, and all patients received the first post-baseline coaching after initiation of treatment. The maximum number of on-treatment coaching visits attended was 19; the median was 13. In the set of 46 QoL-evaluable patients, 44 received a baseline coaching. The median number of attended on-treatment coaching visits was 13 in the QoL set as well. For the baseline coaching visit, coaches reported that the aims of the coaching were discussed with all participants of the baseline coaching, and all individual AEs targeted by the coaching (hypertension, fatigue, hand-foot-syndrome, stomatitis, diarrhea) were discussed with 35 of 44 participating patients (79.5%). For 7 patients (15.9%), some of the events were discussed, and none for 2 patients (4.5%). During the baseline coaching visit, level 1 coaching measures (as defined in the coaching manual) were initiated for 31 patients (72.1%) for hypertension, for 29 patients (67.4%) for fatigue, for 21 patients (48.8%) for diarrhea, for 27 patients (62.8%) for stomatitis, and for 28 patients (65.1%) for hand-foot-syndrome. 43 patients (93.5%) attended 7 coaching visits or more. Up to their 7th coaching visit, 39 patients (84.8%) had received intervention for management of hypertension, 39 patients (84.4%) for fatigue, 38 patients (82.6%) for diarrhea, 38 patients (82.6%) for stomatitis, and 31 patients (67.4%) for hand-foot-syndrome.

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Efficacy Results:

All described results are based on the safety population.

Median OS was 49.6 months with a 95% confidence interval of [30.6, 61.6] months in Arm A, and 25.4 months (95% CI [17.8, NC]) in Arm B. The log-rank test shows a p-value of 0.1066 and was not able to demonstrate a significant difference.

Median PFS was 11.1 months (95% CI [8.3, 18.9]) in Arm A and 9.2 months (95% CI [5.6, 14.6]) in Arm B. The log-rank test shows a p-value of 0.2067 and was not able to demonstrate a significant difference. For PFS of 2nd-line treatment the median survival was 23.9 months (95% CI [16.7, 49.6]) in Arm A and 14.8 months (95% CI [7.7, 27.1]) in Arm B, also with no significant difference observed (p-value: 0.1184).

TFST was comparable between arms with a median of 13.7 months (95% CI [9.0, 19.8]) for Arm A and 11.6 months (95% CI [9.3, 23.2]) for Arm B.

The objective response rate (ORR) was similar in both arms, with 21 of 55 patients (38.2%, 95% CI [25.4, 52.3]) with response assessment according to RECIST 1.1 experiencing a partial response in Arm A, and 19 of 55 patients (34.5%, 95% CI [22.2, 48.6]) in Arm B.

Median duration of response was 8.4 months (95% CI [2.7, NC]) in Arm A and 9.7 months (95% CI [3.8, 28.5]) in Arm B.

Comparing the results from the safety population to the QoL evaluable population, we see similar patterns of results across all time-to-event parameters.

Safety Results:

Of the 110 treated patients, 43 received sunitinib (20 in Arm A vs. 23 in Arm B), 57 a combination of axitinib and pembrolizumab (29 in Arm A vs. 28 in Arm B) and 10 a combination of axitinib and avelumab (6 in Arm A vs. 4 in Arm B) as cancer therapy according to Standard of Care. Mean duration of treatment was comparable between arms for each drug cohort. The mean duration of treatment for the sunitinib cohort was 10.0 months in Arm A and 10.6 months in Arm B. For the combination of axitinib plus pembrolizumab the mean duration was 7.2 months in Arm A and 5.5 months in Arm B. The mean duration for axitinib plus avelumab was 5.8 months in Arm A and 5.9 months in Arm B. Treatment durations that exceed the duration of study intervention arise from the fact that also the follow-up visits were considered for the calculation of treatment duration. Further, for combination of axitinib plus CPI the calculation might also consider phases of monotherapy, i.e. phases where a patient received only one component.

The median follow-up time was 21.3 months (95% CI [15.7, 23.4]) in Arm A and 24.2 months (95% CI [20.3, 38.0]) in Arm B. The p-value of 0.4153 obtained by the log-rank test was not able to demonstrate a statistically significant difference between median follow-up times of the two arms.

Overall, 108 of the 110 patients included in the safety population experienced 1039 AEs with slightly higher AE rates in Arm A. Out of 563 AEs reported by 55 patients of Arm A (100%), 537 were treatment emergent. In Arm B, 53 patients (96.4%) experienced 476 AEs, including 463 treatment emergent AEs. There were 363 drug-related AEs in 53 patients of Arm A (96.4%) and 312 drug-related AEs in 47 patients of Arm B (85.5%).

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Name of Finished Product: Sutent®, Inlyta®, Bavencio®, Keytruda®		
Name of Active Ingredient: Sunitinib, Axitinib, Avelumab, Pembrolizumab		

In total, 34 SAEs were reported in 25 patients of Arm A (45.5%), of which 8 were drug-related. One SAE was related to pembrolizumab and axitinib (hepatitis), 4 SAEs were related to pembrolizumab only (diarrhea, hyperthyroidism, syndrome of inappropriate antidiuretic hormone secretion, alanine aminotransferase increased), one to axitinib only (hepatitis) and 2 to sunitinib (chills, perianal abscess). In Arm B, 33 SAEs were reported in 18 patients (32.7%), including 9 drug-related SAEs. One SAE was related to avelumab and axitinib (hypertensive crisis), another one was related to pembrolizumab and axitinib (platelet count decreased), 4 SAEs were related to axitinib only (two events of diarrhea, paresis of nervus laryngeus right, acute kidney injury), 2 to pembrolizumab only (myocarditis, immune related hepatitis) and one to sunitinib (pleural effusion).

In Arm A, 49 (89.1%) patients reported 143 protocol-specific AESIs; in Arm B, 39 (70.9%) patients reported 102 of such events. Alternative AESIs were experienced by 35 (63. 6%) patients of Arm A (66 events) and 28 (50.9%) patients of Arm B (54 events).

Regarding severity grading, most AEs were reported as mild or moderate (469 AEs in Arm A and 410 AEs in Arm B). The number of severe AEs reported in Arm A was 85, affecting 42 patients (76.4%), and 51 events affecting 28 patients (50.9%) in Arm B. Life-threatening events were reported for 5 patients in Arm A (9.1%, one event per patient), while 11 such events were reported for Arm B, which affected 6 patients (10.9%). Fatal AEs were reported for 3 patients (5.5%) in Arm A and 4 patients (7.3%) in Arm B.

Most common drug-related AEs in Arm A were diarrhea and fatigue (both reported by 27 (49.1%) patients) and hypertension (reported by 16 (29.1%) patients). In Arm B, the most frequently observed AEs with relation to study drug were also diarrhea (reported by 20 (36.4%) patients), fatigue (reported by 18 (32.7%) patients), hypertension and dysgeusia (both reported by 14 (25.5%) patients).

The above-mentioned most common drug-related AEs reflect most of the 5 study-specific AESIs, which were defined as hand-foot syndrome, diarrhea, stomatitis, fatigue and hypertension. Drug-related hand-foot syndrome was reported by 11 patients of Arm A and 5 patients of Arm B when summarizing the reported AE terms ‘Palmar-plantar erythrodysesthesia syndrome’ and ‘Hand and foot syndrome’. Analogously, drug-related stomatitis was reported under the synonymous AE terms ‘Stomatitis’ and ‘Mucositis oral’, leading to 14 patients in Arm A and 11 patients in Arm B with event.

The median time to onset of an ADR was 13.5 days among all treated patients. The log-rank test showed significant differences between arms (p-value <0.0001), median time to ADR being 8 days in Arm A and 20 days in Arm B.

Conclusions:

Target patient accrual was not reached. In this limited patient sample, proactive coaching did not improve the rate of QoL responders or the treatment efficacy. However, there was a trend towards a considerable extension of OS in the coaching group, tentatively suggesting an overall beneficial impact of proactive coaching compared to standard reactive therapy management.

No significant safety signals were detected. Rates of reported AEs were slightly higher in the coaching arm than in the control arm, which can be due to heightened awareness to AEs and thus a reporting bias due to the coaching.

This report is based on protocol version Final 5.1, dated 18-Sep-2023.

Date of Report (Synopsis): 31-Jan-2025