The ARON PROJECT

Global experiences, perspectives and access to cure in patients with genitourinary tumors

ARON-3 Study Protocol

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Summary

List of Abbreviations

ADT = Androgen deprivation therapy

AR = Androgen Receptor

ARTA = Androgen receptor Targeted Angets

CI = Confidence Interval

CR = Complete Response

FDA = Food and Drug Administration

GCP = Good Clinical Practice

mCRPC = metastatic Castration resistant Prostace Cancer

mHSPC metastatic Hormone Sensitive Prostate Cancer

ORR = Overall Response Rate

OS = Overall Survival

PARP = Poly (ADP-ribose) polymerase

PCa = Prostate Cancer

PD = Progressive Disease

PFS = Progression-Free Survival

PR = Partial Response

SD = Stable Disease

1. The ARON-3 study

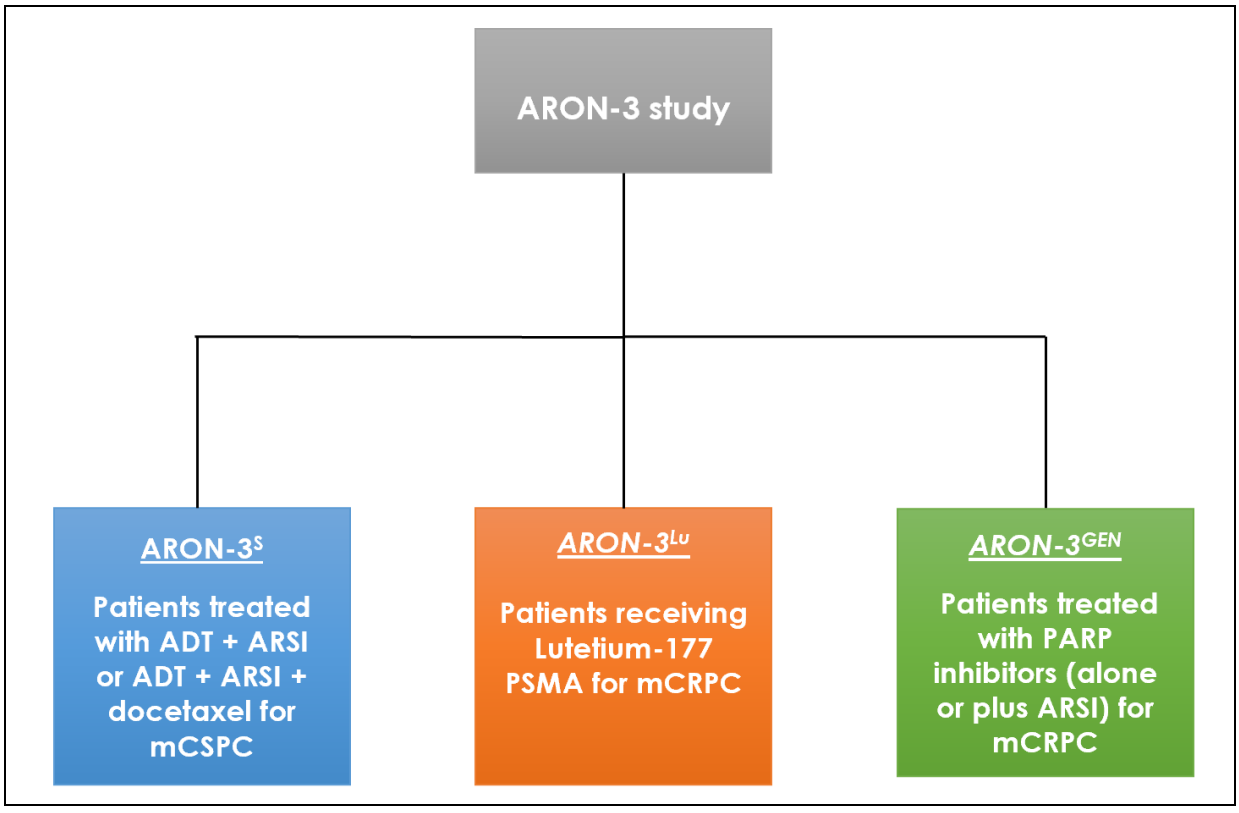
In the last two decades, the introduction of targeted agents and immune checkpoint inhibitors has dramatically improved the outcome and quality of life of patients with solid tumors. The rapidity with which our therapeutic armamentarium has been changed parallels with the overall lack of expanded access programs and phase IV trials aimed to assess the real-world efficacy and tolerability of these emerging strategies and answer clinicians' daily questions on the management of these drugs: the potential drug-drug interactions, how and when to integrate surgery and radiotherapy, the comparison in terms of efficacy of these emerging agents, which are usually compared with historical standard of care in the context of phase III trials.

The treatment scenario of metastatic Prostate Cancer (PC) has undergone a revolution through the introduction of Androgen Receptor Targeted Agents (ARTA) and, successively, by the development of radioligand therapies that delivers alfa or beta-particle radiations and of Poly (ADP-ribose) polymerase (PARP) inhibitors for patients harboring defects in the DNA repair pathways.

In the last two years, the Covid emergency and other challenges have increased the difficulties in attending Congresses and collaborating with Collegues from other Countries. The ARON project has been designed to create a global network of uro-oncologists, aimed to easily share our global experiences in the use of emerging agents in genitourinary tumors.

The ARON-3 Study has been designed as an International Multicentric Retrospective Study to collect global experiences in the treatment of patients with metastatic PCa. In the ARON-3 Study we focused on three different settings:

- *ARON-3^{S}*: Patients with de novo or metachronous metastatic hormone/castration-sensitive PCa treated with ADT + ARSI or ADT + ARSI + docetaxel
- *ARON-3^{Lu}*: Patients receiving Lutetium-177 PSMA for castration resistant PC (CRPC)
- *ARON-3^{GEN}*: Patients treated with PARP inhibitors (alone or plus ARSI) for CRPC



2. ARON-3^{S}

2.1 Background and Rational of the ARON-3^{SENS} study

The androgen receptor (AR) signaling pathway, which regulates the expression of genes involved in cellular proliferation, differentiation, and PC cell survival, is the main axis of PC growth. The standard treatment for metastatic prostate cancer was androgen deprivation therapy (ADT), which reduces circulating testosterone to castration levels while controlling the illness. Despite ADT, castration resistance grows over time. (1)

Beyond non-metastatic or mCRPC, the usefulness of these ARTA has been broadened to include metastatic hormone sensitive PC (mHSPC) and, even more, high risk non-metastatic prostate cancer. In general, blocking the AR axis is essential in several contexts. This can be done by inhibiting androgen production (abiraterone) or by inhibiting AR using second-generation AR antagonists (enzalutamide, darolutamide, apalutamide). (2)

Abiraterone is a cytochrome P450 (CYP)17 (selective) inhibitor (CYP17A1) that prevents the production of androgen in tumor cells, testicles, and adrenal tissue. Abiraterone's role in mHSPC has been studied. The LATITUDE trial comprised de novo high risk mHSPC patients with at least two aggressive features, such as a Gleason score more than 8, at least three bone metastatic lesions, and/or visceral metastases. With the addition of abiraterone to ADT, PFS and OS both experienced significant improvements. To evaluate the effects of abiraterone in combination to ADT and docetaxel, the PEACE-1 trial, which was focused on the de novo mHSPC

condition, randomized 710 patients in a 2 2 factorial design. Patients who received triplet therapy and had a large volume disease presented improvements in their OS and rPFS of 19 months and 30 months, respectively. (3,4)

Enzalutamide is a second-generation, nonsteroidal AR inhibitor that binds to the AR with higher affinity than bicalutamide, hinders AR nuclear translocation, and limits the recruitment of AR cofactors. In the mHSPC setting, the role of enzalutamide has been evaluated in two different clinical trials: the ARCHES and ENZAMET studies, showing a benefit from the addition of enzalutamide to ADT over ADT alone or in combination with standard nonsteroidal antiandrogen therapy, respectively. (5,6)

Darolutamide is a new generation AR inhibitor that prevents nuclear translocation of the AR receptor by having a greater AR affinity than enzalutamide or apalutamide. Its primary trait is that it has a distinct structure from AR antagonists like enzalutamide or apalutamide, which results in a different profile of AE since it cannot cross the blood-brain barrier. In the ARASENS study, the addition of darolutamide to ADT and docetaxel significantly improved the patient survival in those with de novo mHSPC. (7,8)

Apalutamide, an oral nonsteroidal antiandrogen, binds directly to the ligand-binding domain of the AR and prevents it from translocating, attaching to DNA, or regulating transcription. In the mHSPC setting, apalutamide was studied in the phase III TITAN trial with a significant improvement in the co-primary endpoints of radiographic PFS and OS. (9,10)

As a result of these data, triplet therapy or doublet therapy (ADT plus abiraterone, enzalutamide, or apalutamide) are a reasonable alternative, for treating patients in this setting. ARON-3^{S} study aims to understand the patterns of use of the different combinations depending on the disease, comorbidities and characteristics of the patients. This information will provide real life data to understand how these patients behave and how they can be adequately treated in each scenario.

2.2 Primary End-Point of the ARON-3^{S} study

- To assess and compare real-world data on the outcome of patients treated with ADT + ARSI or ADT + ARSI + docetaxel in patients with hormone/ castration-sensitive PC in terms of Progression-Free Survival (PFS), Overall Survival (OS) and Overall Response Rate (ORR).

2.3 Secondary End-Points of the ARON-3^{S} study

- To apply artificial intelligence technology to the study of real-world data for cluster and Artificial Neural Network analyses
- To explore the outcome of the elderly population
- To observe the efficacy of the distinct combinations in patients with different metastatic sites (i.e. bone or visceral metastases)
- To assess the influence of lifestyle and concomitant medications in PC patients treated with ADT + ARSI or ADT + ARSI + docetaxel
- To observe real-world data on the role of prostatectomy and radioterapy in

PC patients treated with ADT + ARSI or ADT + ARSI + docetaxel

- To compare different therapeutic sequences

2.4 Evaluation of the Endpoints (*ARON-3^S study)*

- Overall Survival (OS) was defined as the time from the start of immuno-combination to death from any cause
- Progression-Free Survival (PFS) was defined as the time from the start of treatment to progression or death from any cause. Patients without a tumor progression to following line of treatment or death or lost at follow-up at the time of analysis were censored at their last follow-up date
- Progression-Free Survival 2 (PFS2) was defined as the time from the start of treatment to objective tumour progression on next-line treatment or death from any cause
- Duration of Response was calculated as the time between the initial response to therapy and subsequent disease progression or death from any cause
- Tumor radiological assessment was led according to the RECIST 1.1 (11) and data on tumor response (complete (CR) or partial responses (PR), stable (SD) or progressive disease (PD)) were collected and analyzed
- The Overall Response Rate (ORR) was defined as the rate of CR + PR according to the RECIST 1.1 (11)

2.5 Study Population (ARON-3^S study)

The ARON-3 study retrospectively analyze patients treated with ADT + ARSI or ADT + ARSI + docetaxel according the standard clinical practice in the different Countries involved in this project.

Inclusion Criteria of the ARON-3^S study:

- Patients aged >18y
- Cytological or Histologically confirmed diagnosis of PC
- Histologically or radiologically confirmed diagnosis of metastatic disease
- Treatment with ADT + Apalutamide or ADT + enzalutamide or ADT + Abiraterone or ADT + Abiraterone + Docetaxel or ADT + Darolutamide + Docetaxel (patients treated with previous docetaxel in the hormone-sensitive setting – CHAARTED - resulted eligible)

Exclusion Criteria of the ARON-3^S study:

- Patients without histologically confirmed diagnosis of PC
- Patients without histologically or radiologically confirmed metastatic disease
- Patients treated with doublets or triplets not included in the list reported in the Inclusion Criteria Section

2.6 Estimated Enrollment

In order to determine the minimum sample size for the purpose of the ARON-3^{S} study, we identified the smallest population, which was represented by ADT + ARTA + docetaxel. In the study that led to the FDA approval of Darolutamide in PC patients (7), the OS rate at 4 years was 62.7% (95% CI, 58.7 to 66.7) in the darolutamide group and 50.4% (95% CI, 46.3 to 54.6) in the placebo group, with a delta of 20 among the two groups. In this study, we tested the hypothesis that, using the ADT+ARSI or ADT+ARSI+docetaxel in clinical practice, OS would reach at least 70% at 4 years from the start of therapy. Study plan will include at least 240 patients with an estimated drop out of 10–15%. It was calculated that a minimum of 198 evaluable patients should be enrolled with an α of 0.05 and a β of 0.80 (STATASOFt).

3. ARON-3^{LU}

3.1 Background and Rational

A cell membrane protein called PSMA, sometimes referred to as folate hydrolase I and glutamate carboxypeptidase II, is extensively expressed on the surface of prostate cancer cells. PSMA is expressed in a lower degree on other cells, including the kidney and salivary glands. There are other radioisotope-related PSMA ligands that have been created, including lutetium-177 (177-Lu), a beta particle emitter. (12)

Where accessible, lutetium Lu 177 vipivotide tetraxetan is a treatment option for patients with metastatic CRPC that is taxane- and ARTA-refractory and PSMA-positive. Multiple retrospective and prospective studies have been conducted with lutetium Lu 177 vipivotide tetraxetan:

- 200 males with PSMA-positive metastatic CRPC who had previously received androgen receptor-directed therapy and docetaxel were enrolled in the Australian randomized phase II ANZUP 1603 trial, in which lutetium Lu 177 vipivotide tetraxetan (every six weeks for up to six cycles) was directly compared with cabazitaxel. Males who received radioligand therapy had a greater chance of a 50% decrease in PSA (the main objective, 66 versus 37 percent) and experienced fewer grade 3 or 4 adverse events (33 versus 53 percent). Compared to the cabazitaxel group, there were also clinically significant gains in health-related quality of life. After a median follow-up of 36 months in the most recent research presented at the 2022 ASCO conference, overall survival was comparable to that in the cabazitaxel group, however post-protocol crossover restricts this comparison. (13,14)
- 831 patients with PSMA-positive metastatic CRPC who had previously received one to two taxane-containing regimens and an androgen receptor signaling inhibitor were enrolled in the phase III VISION trial, which compared standard of care alone to standard of care plus lutetium Lu 177 vipivotide tetraxetan (four cycles every six weeks; responding patients could receive an additional two cycles). Although 60% of patients had already

received an androgen receptor-targeted medication, the standard of care was chosen by the investigator and did not include taxane-based chemotherapy or radium-223. At a median follow-up of 20.9 months, lutetium Lu 177 vipivotide tetraxetan significantly increased median radiographic PFS (8.7 versus 3.4 months, hazard ratio [HR] for progression 0.40, 95% CI 0.29-0.57) and median OS (15.3 versus 11.3 months, HR for death 0.62, 95% CI 0.52-0.74), as well as the median time to first skeletal event and objective response rate (11.5 versus 6.8 months, HR 0.50). The therapy was generally well tolerated, although the radioligand group experienced a larger percentage of significant (grade 3 or 4) treatment emergent side events (53 vs 38%). (15)

A second phase III trial with Luthetium-177-PSMA in mCRPC (PSMAfore) met the primary endpoint of radiographic progression-free survival (rPFS) in a recent press release. (16)

The ARON-3^{Lu} study aims to understand the patterns of use of Luthetium-177-PSMA depending on the disease, comorbidities and characteristics of the patients. This information will provide real life data to understand how these patients behave and how Luthetium-177-PSMA therapy should be used in the clinical scenario.

3.2 Primary End-Point of the ARON-3^{Lu} study

- To assess the real-world efficacy of Luthetium-177-PSMA therapy in patients

with castration resistant PC in terms of Progression-Free Survival (PFS), Overall Survival (OS) and Overall Response Rate (ORR).

3.3 Secondary End-Points of the ARON-3^{Lu} study

- To apply artificial intelligence technology to the study of real-world data for cluster and Artificial Neural Network analyses
- To explore the role of Luthetium-177-PSMA therapy in the elderly populaton
- To observe the efficacy of Luthetium-177-PSMA therapy in patients with different metastatic sites (i.e. bone and liver metastases)
- To assess the prognostic role of lifestyle and concomitant medications in PC patients treated with Luthetium-177-PSMA therapy
- To observe real-world data on the role of prostatectomy and radioterapy in PC patients treated with Luthetium-177-PSMA therapy
- To compare different therapeutic sequences

3.4 Evaluation of the Endpoints *(ARON-3^{Lu} study)*

- OS was defined as the time from the start of immuno-combination to death from any cause
- PFS was defined as the time from the start of treatment to progression or death from any cause. Patients without a tumor progression to following line of treatment or death or lost at follow-up at the time of analysis were censored at their last follow-up date

- PFS2 was defined as the time from the start of treatment to objective tumour progression on next-line treatment or death from any cause
- DoR was calculated as the time between the initial response to therapy and subsequent disease progression or death from any cause
- Tumor radiological assessment was led according to the RECIST 1.1 (11) and data on tumor response (CR or PR, SD or PD) were collected and analyzed
- The ORR was defined as the rate of CR + PR according to the RECIST 1.1 (11)

3.5 Study Population (ARON-3^{Lu} study)

The ARON-3^{Lu} study retrospectively analyze patients treated with Luthetium-177-PSMA therapy according the standard clinical practice in the different Countries involved in this project.

Inclusion Criteria of the ARON-3^{Lu} study

- Patients aged >18y
- Cytological or Histologically confirmed diagnosis of PC
- Histologically or radiologically confirmed diagnosis of metastatic disease
- Treatment with Luthetium-177-PSMA therapy for castration resistant PC

Exclusion Criteria of the ARON-3^{Lu} study

- Patients without histologically confirmed diagnosis of PC

- Patients without histologically or radiologically confirmed metastatic disease
- Patients treated with Luthetium-177-PSMA therapy for hormone/castration sensitive PC

3.6 Estimated Enrollment

In the study that led to the FDA approval of Luthetium-177-PSMA in PC patients (15), the estimated percentage of patients alive at 12 months was about 50% in the control group and about 70% in the Luthetium-177-PSMA group with a delta of 20 among the two groups. In this study, we tested the hypothesis that, using the Luthetium-177-PSMA in clinical practice, OS would reach at least 75% after 12 months from the start of therapy. Study plan will include at least 154 patients with an estimated drop out of 10–15%. It was calculated that a minimum of 134 evaluable patients should be enrolled with an α of 0.05 and a β of 0.80 (STATASOFt).

4. ARON-3^{GEN}

4.1 Background and Rational of the ARON-3^{GEN} study

PARP inhibitors limit the repair of DNA single-strand breaks, resulting in cell death in cancers linked with HRR deficiency due to inefficiencies in cell repair pathways. After the failure of an androgen receptor pathway inhibitor (ARPI) with or without a taxane, many PARP inhibitors have been examined in males with metastatic CRPC

with DNA repair mutations. Two of them (olaparib and rucaparib) are currently licensed for use in CRPC with HRR deficiency. (17,18)

A growing body of evidence suggests that men with mCRPC with a pathogenic mutation in the HRR gene may benefit from therapy with a PARP inhibitor. BRCA2 mutations seem to be connected to the largest benefit from PARP inhibitors among the HRR genes involved DNA damage response pathways. Olaparib and rucaparib, two PARP inhibitors, are licensed by FDA for the treatment of males with CRPC and changes linked to HRR deficiency. However, the approval for olaparib covers multiple genes that have not separately been proved to predict for response to PARP inhibition, but the authorisation for rucaparib is restricted to patients with pathogenic mutations in BRCA1 or BRCA2. (19-21)

- Olaparib: the most important study in this setting was the randomized phase III PROfound trial. 387 males with metastatic CRPC who had alterations in any of 15 predefined genes with direct or indirect roles in HRR (245 males with pathogenic variants in BRCA1, BRCA2, or ATM [cohort A; the primary cohort] and 142 males with alterations in other genes [cohort B]) were compared to olaparib (300 mg twice daily) versus second-generation hormonal therapy (physician's choice). The median radiographic progression-free survival was considerably longer in the olaparib-treated males in cohort A (7.4 versus 3.6 months, hazard ratio [HR] 0.34, 95% CI 0.25-0.47), and they also had a higher objective response rate (33 versus 2 percent). In a later analysis, survival was significantly improved for both cohorts despite significant crossover from control therapy to olaparib (cohort A: median

19.1 versus 14.7 months; cohort B: median 14.1 versus 11.5 months). In comparison to second-generation hormonal treatment, olaparib also prevented the decline in health-related quality of life (HRQoL). (19,20)

- Rucaparib: In the single arm phase II TRITIN 2 trial; 157 males with CRPC and HRR deficiency (identified by germline testing, next-generation sequencing of tumor tissue, or assay of ctDNA) were treated with rucaparib at a dosage of 600 mg twice daily. According to a blinded independent review of 115 males with BRCA1/2-mutated CRPC, 62 of whom had detectable disease, the confirmed objective response rate was 44 percent, and the median duration of response (within the range of 1.7 to 24 or more months) was not reached at the time of data review. In soft tissue disease, eight out of the 27 responders showed a confirmed complete response. The phase III TRITON3 trial is evaluating the efficacy of rucaparib in comparison to abiraterone, enzalutamide, or docetaxel in men with metastatic CRPC with HRR mutations. (21)

4.2 Primary End-Point of the ARON-3^{GEN} study

- To assess and compare real-world data on the use of PARP inhibitors alone or in combined regimens in patients with castration resistant PC in terms of Overall Survival (OS), Progression-Free Survival (PFS), and Overall Response Rate (ORR).

4.3 Secondary End-Points of the ARON-3^{GEN} study

- To apply artificial intelligence technology to the study of real-world data for

cluster and Artificial Neural Network analyses

- To explore the role of PARP inhibitors in the elderly population
- To observe the efficacy of PARP inhibitors in patients with different metastatic sites (i.e. bone and brain metastases)
- To assess the influence of lifestyle and concomitant medications in PC patients treated with PARP inhibitors
- To observe real-world data on the role of prostatectomy and radioterapy in PC patients treated with PARP inhibitors
- To compare different therapeutic sequences

4.4 Evaluation of the Endpoints of the *ARON-3^{GEN} study*

- OS was defined as the time from the start of immuno-combination to death from any cause
- PFS was defined as the time from the start of treatment to progression or death from any cause. Patients without a tumor progression to following line of treatment or death or lost at follow-up at the time of analysis were censored at their last follow-up date
- PFS2 was defined as the time from the start of treatment to objective tumour progression on next-line treatment or death from any cause
- DoR was calculated as the time between the initial response to therapy and subsequent disease progression or death from any cause
- Tumor radiological assessment was led according to the RECIST 1.1 (11) and

data on tumor response (CR or PR, SD or PD) were collected and analyzed

- The ORR was defined as the rate of CR + PR according to the RECIST 1.1 (11)

4.5 Study Population

The ARON-3^{GEN} study retrospectively analyze patients treated with PARP inhibitors for metastatic castration-resistant PC according the standard clinical practice in the different Countries involved in this project.

Inclusion Criteria of the ARON-3^{GEN} study

- Patients aged >18y
- Cytological or Histologically confirmed diagnosis of PC
- Histologically or radiologically confirmed diagnosis of metastatic disease
- **Homologous Recombination (HR) DEFICIENT PATIENTS (HRD)**
- Treatment with PARP inhibitors for castration resistant PC. Treatment included: olaparib (as 1st, 2nd or 3rd line therapy), olaparib + abiraterone (as 1st line therapy) or niraparib + abiraterone (as 1st line therapy) or talazoparib + enzalutamide

Exclusion Criteria of the ARON-3^{GEN} study

- Patients without histologically confirmed diagnosis of PC
- Patients without histologically or radiologically confirmed metastatic disease

- **PATIENTS WITHOUT HR DEFICIENCY (no HRD)**
- Patients treated with PARP inhibitors alone or in combination regimens not included in the ARON-3GEN study

4.6 Estimated Enrollment

In the study that led to the FDA approval of Olaparib in PC patients (19), the estimated percentage of patients alive at 12 months was 57% in the control group and 73% in the olaparib group with a delta of 16 among the two groups. In this study, we tested the hypothesis that, using the Olaparib in clinical practice, OS would reach at least 80% after 12 months from the start of therapy. Study plan will include at least 160 patients with an estimated drop out of 10–15%. It was calculated that a minimum of 143 evaluable patients should be enrolled with an α of 0.05 and a β of 0.80 (STATASOFt).

5. Statistical Analysis and Data Collection

PFS and OS were estimated by Kaplan-Meier method with Rothman's 95% confidence intervals (CI) and compared by using the log-rank test. Univariate and multivariate analyses were performed by using Cox proportional hazards models. The chi-square test was used to compare categorical end-points. Significance levels were set at a 0.05 value and all *p* values were two-sided. The statistical analysis was led by using MedCalc version 19.6.4 (MedCalc Software, Broekstraat

52, 9030 Mariakerke, Belgium).

Data will be retrospectively extracted from paper and electronic charts. For each patient, the following data will be collected by the database of each Institution and analyzed: histology, time and type of surgery, time and type of ADT, sites of metastases, Body Mass Index (BMI), laboratory tests and treatments. Patients without sufficient data on tumor assessment and response to therapy will be excluded from this study. Data will be collected in Excel datasets. A code will be used to identify each patient included in this analysis.

6. End-dates for Data Collection and Authorship

Due to the large number of Centers involved from different Countries, we have scheduled a series of deadlines in order to complete step-by-step the planned analyses and prepare the manuscripts for publication:

- The first deadline is January 31h, 2024 - Second analysis of data collection and preparation of four of our planned manuscripts within 31st March, 2024
- The second deadline is March 31th, 2024 - Third data analysis of data collection and preparation of the other planned manuscripts within May 31st, 2024
- The third deadline is May 31th, 2024 - Third data analysis of data collection and preparation of the other planned manuscripts within July 31st, 2024

For each manuscript, one author's name for each Institution involved in this project will be considered. We will consider, according to Journal policies, two names for each Oncological Center that has enrolled at least 50 patients in the dataset or which has sustantially participated to the different phases of the manuscripts.

Before the submission, a draft of each manuscript will be sent to all the authors from the Institutions involved in order to revise potential errors and propose additional comments and suggestions.

Potential publication fees with be sustained by the Center of the Principal Investigator (Macerata Hospital).

7. Data Confidentiality and Management

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training. The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents.

The Principal Investigator is responsible for assuring that the data entered are

complete and accurate. Essential documents (written and electronic) should be retained for a period of seven (7) years from the completion of the Study. Biological samples will be stored till they will maintain their integrity

8. Ethical Considerations

The ARON-3 Study will be conducted according to Good Clinical Practice (GCP) and has been designed with the ethical principles laid down in the Declaration of Helsinki on human experimentation. The Study will be approved by the Ethical Committees of the participating Institutions according to local guidelines.

9. Informed Consent Procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), informed consent form. Informed consent must be obtained before conducting any study-specific procedures (i.e., any of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

10. Fundings and Fees

No fees are required from or provided to the Centers that participate to the ARON-

3 projects. The costs for sending tissue samples for the Centers participating also to one or both of the Supplementary studies ARON-3a and ARON-3β will be sustained by the PI, as well as the potential publication fees.

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