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1 ENSAT Registry-Based Randomized Clinical Trials for Adrenocortical Carcinoma

2

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51
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58 Study of Adrenal Tumours

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1 **Abstract** (204 words)

2 Adrenocortical carcinoma (ACC) is an orphan disease lacking effective systemic
3 treatment options. The low incidence of the disease and high cost of clinical trials are
4 major obstacles in the search for improved treatment strategies. As a novel approach,
5 registry-based clinical trials have been introduced in clinical research, so allowing for
6 significant cost reduction, but without compromising scientific benefit. Herein, we
7 describe how the European Network for the Study of Adrenal Tumours (ENSAT) could
8 transform its current registry into one fit for a clinical trial infrastructure. The rationale
9 to perform randomized registry-based trials in ACC is outlined including an analysis of
10 relevant limitations and challenges. We summarize a survey on this concept among
11 ENSAT members who expressed a strong interest of the concept and rated its
12 scientific potential as high. Legal aspects, including ethical approval of registry-based
13 randomization were identified as potential obstacles. Finally, we describe three
14 potential randomized registry-based clinical trials in an adjuvant setting and for
15 advanced disease with a high potential to be executed within the framework of an
16 advanced ENSAT registry. Thus we therefore provide the basis for future registry-
17 based trials for ACC patients. This could ultimately provide proof-of-principle of how to
18 perform more effective randomized trials for an orphan disease.

1 **Introduction**

2 Adrenocortical carcinoma (ACC) is a rare disease for which diagnostic approaches
3 and therapeutic strategies have only gradually changed over the past decades (1, 2).
4 Accordingly, the overall survival for patients diagnosed with ACC remains in the range
5 of 3–4 years (3, 4). Affected patients also experience severe morbidity due to
6 endocrine disturbances as well as tumour growth (1, 5, 6). In a recent review, we
7 identified topics including disease prevention and earlier detection, improved risk-
8 stratification, controlling tumour growth and invasiveness as well as suppressing
9 hormone production as unresolved problems that need to be addressed by research
10 with the overarching aim to reduce ACC-related morbidity and mortality (1).

11 While clinical trials have the potential to explore strategies to approach these problems,
12 the current research infrastructure fails in providing effective resources to perform such
13 projects on rare diseases. In this context, registry-based clinical trials have emerged
14 as a resource-efficient alternative solution to address clinical and translational
15 research questions (7-10). In this review, we aim to describe how registry-based trials
16 could be used to advance care of patients with ACC. Furthermore, we argue that the
17 European Network for the Study of Adrenal Tumours (ENSAT) is well positioned to
18 transform its current registry and advance its strong collaboration to implement
19 registry-based clinical trials. Finally, we propose potential research projects with
20 potential to be executed within this space.

21

22 **Randomized clinical trials**

23 A randomized controlled trial provides the experimental framework that aims to
24 evaluate the effectiveness and safety of a medical intervention. By randomly assigning
25 patients between experimental and control arms, it ensures the greatest reliability and
26 validity of the results, by reducing impact from both known and unrecognized bias.
27 Appropriately executed (11), it is considered as the gold standard for evaluating
28 healthcare interventions. In contrast, those medical practices that are based on

1 evidence from non-randomized controlled data are prone to bias and misinterpretation.
2 Clinical trials lacking a control arm and those using historical controls have repeatedly
3 been shown to exaggerate the efficacy of treatments (12). Similarly, early clinical trials
4 on small or diverse patient samples are prone to find higher response rates than those
5 in subsequent randomized studies (13). Overall, these shortcomings have well been
6 exemplified in a systematic review of >3000 randomized clinical studies demonstrating
7 that a total of 396 formerly established medical practices had been identified as lacking
8 clinical benefit (14).

9 While there are a few reported randomized controlled trials on ACC (Table 1), patient
10 scarcity and high resource demand has limited the use of this method. As a
11 consequence, among the 25 recommendations with evidence rating in the recent ACC
12 guidelines by *the European Society for Endocrinology* and ENSAT, none were
13 considered to have strong underlying evidence and only three were graded as having
14 moderate evidence (5). Currently, there is only one randomized clinical trial active
15 within the space of ACC: Mitotane With or Without Cisplatin and Etoposide After
16 Surgery in Treating Participants With Stage I-III ACC With High Risk of Recurrence
17 (ADIUVO-2, NCT03583710). This study has been designed to be executed within a
18 clinical environment but has yet to be directly integrated into an established patient
19 registry. This sets the stage for further optimization of the clinical trial method for the
20 study of ACC in order to further improve clinical evidence and refine patient care.

21

22 **Registry-based clinical trials**

23 A randomized registry-based clinical trial is a prospective study using a clinical registry
24 for patient identification, trial conduct and outcomes reporting. The registry-based
25 randomized clinical trial maintains the strengths of a prospective clinical study,
26 including high internal validity, stringent patient stratification, randomization to ensure
27 unbiased study of interventions and analysing patient outcomes to determine the effect
28 of the studied intervention (7, 9, 15). In variance to conventional trials, registry-based

1 studies provide the opportunity to lower costs and ensure more rapid patient inclusion
2 (7, 9, 15). This method is particularly suitable for evaluation of interventions that are
3 already established within the field, with documented data on adverse events and that
4 does not require additional evaluations than those already performed within standard
5 clinical practice.

6

7 A registry structure can be used to identify eligible patients, randomize between
8 different interventions, provide follow-up data and evaluate outcomes. To remain
9 resource-effective, addition of procedures beyond standard clinical practice should be
10 avoided. Experience from cardiovascular research has demonstrated that registry-
11 based clinical studies can be performed with more than 90% cost-saving compared to
12 conventional trials (7, 9). On-going developments of this method include refinements
13 of both biostatistical analysis and interpretation (16).

14

15 To our knowledge, there are no reported registry-based clinical trials and only a few
16 on-going within the field of medical oncology or endocrinology. In a review by Foroughi
17 and colleagues, on-going registry-based clinical trials were described (9) from which
18 we select two relevant examples:

19 ALT-TRACC (17) is a phase II clinical trial randomizing patients with treatment naïve
20 metastatic colorectal cancer between alternating oxaliplatin and irinotecan doublet
21 schedules (experimental arm) versus continuous doublet chemotherapy (control arm).
22 Primary objective is to evaluate the feasibility of conducting a multi-center, prospective,
23 registry-based randomized clinical trial. The primary endpoint is recruitment rate.
24 Secondary objectives focus on both efficacy and toxicity by collecting data from
25 medical records and other data collection tools. The aim is to estimate progression
26 free survival and radiological response rates. The study is based on the *Treatment of*
27 *Recurrent and Advanced Colorectal Cancer* registry (9).

1 EX-TEM (18) is a phase III trial randomizing patients with newly diagnosed
2 glioblastoma to six (control arm) versus twelve (experimental arm) cycles of post-
3 radiation temozolomide chemotherapy. The primary objective is to study treatment
4 efficacy and the primary endpoint is overall survival. Secondary endpoints include
5 adverse events and the necessity for temozolomide dose modification determined by
6 data recorded in the medical records. The study makes usage of *the Brain Registry*
7 *Australia: Innovation and Translation* registry (9).

8

9 **Current and previous randomized trials for ACC**

10 An overview of randomized clinical studies on ACC is provided in Table 1. FIRM-ACT
11 was the first randomized study performed on ACC and compared the efficacy of a
12 chemotherapy combination (etoposide, cisplatin and doxorubicin, EDP) plus mitotane
13 versus streptozocin plus mitotane in the advanced setting (19). It reported a hazard
14 ratio of 0.55 (95% Confidence Interval (CI) 0.43-0.69) in favour for EDP plus mitotane
15 for progression free survival. Survival was not significantly different, hazard ratio 0.79
16 (95% CI 0.61-1.02) in favour for EDP + mitotane. Quality of Life according the EORTC
17 QLQ-C30 questionnaire revealed no changes at follow-up compared to baseline for
18 the two treatment arms.

19 As recruitment within the FIRM-ACT protocol had been achieved, it was quickly
20 followed by GALACCTIC, a randomized phase III trial of linsitinib (inhibitor of IGF-1R
21 and the insulin receptor) versus placebo for locally advanced or metastatic ACC (20).
22 No difference in overall survival between linsitinib and placebo was noted, HR 0.94
23 (95% CI 0.61-1.44). This study did, however, provide valuable information on the
24 behaviour of untreated metastatic ACC progressive after mitotane therapy. In the
25 control arm, median survival was 356 days (95% CI 249–556) while the disease control
26 rate was 34.7% (95% CI 21.7–49.6) at 6 weeks and 8.2% at 12 weeks.

27 There are currently two on-going randomized trials on ACC, both in the adjuvant
28 setting (Table 1), mitotane versus follow-up in low to intermediate risk ACC (ADIUVO

1 study) and mitotane versus mitotane plus cisplatin and etoposide (ADIUVO-2 study) in
2 high risk ACC. These trials will be fundamental to evaluate current practices for
3 adjuvant therapy that are currently supported by retrospective data (21).

4

5 **The European Network for the Study of Adrenal Tumours**

6 The European Network for the Study of Adrenal Tumours was formally established in
7 2002 through a merger of three already existing national networks on adrenal
8 research: COMETE in France, GANIMED in Germany, and NISGAT in Italy with further
9 teams joining in from the United Kingdom. In 2009, ENSAT became a membership-
10 based society with statutes and by-laws. An increasing number of researchers and
11 health workers have joined in the efforts of the ENSAT with currently 479 members
12 from 35 different countries. The European Network for the Study of Adrenal Tumours
13 has structured its operation under four different working groups by disease subtype:
14 ACC, pheochromocytoma and paraganglioma, aldosterone-producing adenoma and
15 non-aldosterone producing cortical adrenal adenomas. Through its patient registry, the
16 largest body of clinical annotations and biospecimens from patients with adrenal
17 tumours has been aggregated (22). Currently (April 2020) it includes data from 17,680
18 patients of 107 institutions, representing 33 predominantly European countries. A long
19 list of disease specific clinical annotations has been collected. Current limitations of
20 the ENSAT registry include its non-consecutive patient enrolment and lack of quality
21 control.

22 Based on the information reviewed in previous sections, we hypothesized that registry-
23 based trials would be a potential new tool to allow for more efficient studies on adrenal
24 tumours. We hypothesized further that ENSAT would be ideally positioned to
25 implement this technology as it already forms a strong network with large patient
26 populations and operates a prospective registry. Finally, ACC was identified as the
27 most suitable patient population among adrenal tumours to be evaluated in a pilot
28 project due to large unmet needs in combination with up-to-date clinical practice

1 guidelines and potentially relevant study endpoint already available in the registry (5,
2 23).

3

4 **The ENSAT ACC registry**

5 Currently, the ACC database includes data from 3,835 patients from 63 institutions
6 (April 2020). It is structured under the following sections; diagnostic procedures (34
7 variables), tumour staging (16 variables), biomaterial (20 variables),
8 chemoembolization (four variables), chemotherapy (seven variables), follow-up (18
9 variables), metabolomics (two variables), mitotane (nine variables), pathology (20
10 variables), radiofrequency (five variables), radiotherapy (eight variables) and surgery
11 (six variables). In total, these comprehensive data can be used to study endpoints
12 relevant for patients with ACC; overall survival, recurrence free survival, progression
13 free survival (accordingly to local analysis, but no specific protocol for radiological
14 evaluation is requested, yet) and early discontinuation of medical therapy. Furthermore,
15 appropriate factors for disease characterization can be used as inclusion / exclusion
16 criteria as well as being incorporated into a future randomization module.

17

18 **Assessing the potential for registry-based clinical trials within ENSAT**

19 Two online surveys as well as discussions at scientific meetings had been conducted
20 to determine the potential of registry-based clinical trials to be performed within the
21 ENSAT community (Supplementary materials and methods). In a first survey
22 (Supplementary table 1) responses had been collected from eighty-six members,
23 including 66 full members and 20 associate members. The respondents represented
24 22 different countries; Italy ($n=22$), Germany ($n=10$), France ($n=8$), Greece ($n=7$),
25 United Kingdom ($n=7$), Netherlands ($n=6$) and Spain ($n=4$) being the most frequent.
26 The high interest for registry-based clinical trials in ACC was reflected not only in the
27 active participation in online surveys and real life meetings, but was also expressed
28 directly in the surveys through the rated scientific potential, mean score 4.5 (maximum

1 5), and the anticipation to collaborate and contribute, with a mean rating of 4.3
2 (maximum 5).

3 General topics for ENSAT registry-based trials were proposed with positive/negative
4 response options available (Figure 1A); evaluation of drugs or other medical
5 interventions (90% positive), evaluation of prognostic or predictive biomarkers for
6 therapeutic stratification (89% positive), prospective collection of clinical data and/or
7 bio samples (71% positive), and comparison of different follow-up strategies (69%
8 positive). Study participants were also asked, which ACC patient population should
9 primarily be addressed (positive/negative response options available); neo-adjuvant
10 setting (75% positive), adjuvant setting (87% positive) and advanced disease (61%
11 positive). Next, survey participants were asked if they would foresee legal or any other
12 administrative challenges related to registry-based clinical trials, which was answered
13 with yes in 56% of cases with eight free text comments provided. Among these
14 responses, reluctance from ethical review boards to provide ethical permissions were
15 specifically mentioned. Another example demonstrating the strong interest in registry-
16 based clinical trials could be noted in the active discussion of particular scientific
17 projects: There were a total of 48 different research projects being proposed. The
18 ENSAT ACC working group scientific board prioritized these projects based on
19 scientific quality and feasibility for further evaluation.

20 In the subsequent survey (Supplementary table 2) there were 62 respondents, 50 full
21 members and 12 associate members. These represented 19 different countries with
22 Italy ($n=19$), France ($n=6$), Germany ($n=6$), Greece ($n=5$) and the United Kingdom
23 ($n=5$) as the most frequent. A total of 87% of responders phrased the expectation that
24 a registry-based clinical trial would be accepted by the local ethical committee, with
25 eight additional comments in free text. In the next question, 43% assumed that
26 randomization of study sites to different interventions ("cluster randomization") would
27 be more likely to be acceptable to ethical review boards compared to randomization of

1 individual patients. Furthermore, concrete ideas for problems to be addressed within
2 an ENSAT registry-based platform were collected.

3

4 **Proposal for registry-based studies on ACC based on the ENSAT platform**

5 Of the 48 different research projects being proposed by the ENSAT ACC working
6 group, the scientific board and its members had previously selected and prioritized the
7 following projects that gained particularly high scoring based on scientific value and
8 feasibility (Figure 1B):

9

10 ***Adjuvant setting - Comparison of different durations of mitotane treatment for***
11 ***effectiveness and toxicity.*** Adjuvant treatment with mitotane is recommended in
12 patients without macroscopic residual tumour after surgery who have a perceived high
13 risk of recurrence (5, 21, 24). However, the optimal duration of mitotane treatment, to
14 balance efficacy and adverse effects of the compound is currently unknown. Therefore,
15 a randomized controlled study between a duration of e.g. 2 vs. 5 years of mitotane
16 treatment would be informative.

17 ***Advanced ACC I - Comparison of different first-line chemotherapy protocols for***
18 ***effectiveness and toxicity.*** The most validated first-line treatment option for
19 unresectable and advanced ACC is the combination of etoposide, doxorubicin,
20 cisplatin, and mitotane (EDP-M) (19). Treatment with EDP-M comes with a risk of
21 adverse events. Based on small trials (25, 26) and individual experience (5) it has been
22 hypothesized that omitting doxorubicin from the treatment protocol would increase
23 tolerability without a clinically relevant loss of efficacy. This hypothesis could be
24 evaluated through a randomized controlled study between EDP-M (standard arm)
25 versus etoposide, cisplatin and mitotane (experimental arm).

26 ***Advanced ACC II - Comparison of anti-tumour efficacy of mitotane at different***
27 ***concentrations.*** It is believed that mitotane toxicity and efficacy is strongly correlated
28 to plasma levels of the compound (27-29). It has been hypothesized that by lowering

1 the therapeutic concentration target for mitotane in advanced ACC, patients would
2 experience less treatment related toxicity. This could potentially result in improved
3 quality of life without clinically significant loss in efficacy. For this purpose, a
4 randomized controlled study between standard therapy aiming at a mitotane blood
5 level > 14 mg/L (standard arm) versus a mitotane regime aiming at lower concentration
6 (e.g. > 10 mg/L; experimental arm) would lead to clinically important information.

7 Potential objectives to be investigated in these three proposals include the evaluation
8 of recruitment feasibility, quality of data capture, patient benefit in terms of overall
9 survival and quality of life as well as drug tolerability. Furthermore, we propose that
10 quality of life could be measured through patient self-reporting through a web-based
11 application (currently not available in the ENSAT registry). In addition, safety could be
12 described from the documentations made in the patient records. We also argue that
13 both cluster and patient randomization could be used to address these three research
14 questions. The studies could also be designed as superiority and/or non-superiority
15 trials, all depending on what primary endpoint is finally selected.

16

17 In addition to studying different interventions, we envision the possibility to execute
18 prospective longitudinal observation studies to collect information and biomaterial on
19 predictive markers of treatment response as well as prognostic factors. The underlying
20 rationale comes from the rapid advances in our understanding of the biology of ACC
21 (1, 30-35), which translates into a need for efficient test beds to evaluate new
22 biomarkers for different clinical purposes.

23

24 **Challenges**

25 Examples in clinical cardiovascular research has provided a clear proof of concept of
26 how a strong network can be enhanced to perform registry-based clinical trials through
27 technical advances of the current infrastructure but only minor changes in clinical and
28 research practice (7). One potential factor limiting the dissemination of registry-based

1 trials could be legal and administrative restrictions. In our surveys, a high proportion of
2 participants (87%) anticipated acceptance of a registry-based trial by their local ethical
3 review boards. However, as the registry-based randomized trial is a concept currently
4 lacking a clear definition it is expected to be treated with the same level of scrutiny as
5 conventional clinical trials. This will impose rules and regulations not applicable to
6 registry based randomized trials. As such, the current legislative environment needs
7 to be adopted to fit randomized registry-based clinical trials in order to ensure a lower
8 complexity that will otherwise increase costs.

9 While the foundation for a future infrastructure for registry-based trails exist
10 within ENSAT, additional method development will be required including a
11 randomization module as well as the possibility for source data verification (Figure 2).
12 There is also a need for data monitoring to ensure high validity of the data within the
13 registry. Furthermore, our work also raised the potential to implement clinical decision
14 support, active suggestion of potential research studies and integration with patient
15 self-reporting into the ENSAT registry. While such infrastructure upgrades are all
16 technically feasible, additional resources will be necessary for its implementation. And
17 as this research direction is pursued in other medical settings, ENSAT could potentially
18 co-operate with other relevant registries for method development and to share
19 experiences.

20

21 **Summary**

22 The ENSAT ACC community has expressed a strong interest and support of in
23 registry-based trials as a new infrastructure with potential to significantly advance care
24 for patients with this rare disease. This review summarises the scientific foundation for
25 this research direction and outlines potential questions to be addressed within such a
26 new infrastructure and provides a roadmap for future pilot projects.

27

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- 41

1 Table 1. Randomized studies in ACC

Study	Design	Setting	Interventions	Primary Endpoint	Secondary endpoints	Patients enrolled, <i>n</i>	Recruitment period
FIRM-ACT (19)	Randomized, controlled, phase III study	Non resectable ACC	Mitotane + Cisplatin + Etoposide + Doxorubicin versus Mitotane + Streptozocin	OS	PFS, response rate and QoL	304	June 2004 – October 2009
GALACCTIC (20)	Randomized, controlled, phase III study	Locally advanced or metastatic ACC	Linsitinib versus placebo	OS	PFS, disease control rate, response rate and safety.	139	December 2009 - July 2011
ADIUVO	Randomized, controlled, phase III study	ACC after radical resection with low-intermediate risk of relapse	Mitotane versus follow-up	Disease free survival	OS, safety*	91	2011 - 2018
ADIUVO-2	Randomized, controlled, phase III study	ACC after radical resection with high risk of relapse	Mitotane versus mitotane + Cisplatin + Etoposide	Recurrence free survival	OS	240 (estimated)	July 2018 (on-going)

- 2 * Secondary endpoints also included, 1) Identification of clinical and pathological predictors of recurrence, and 2) Stratification of results by
3 mitotane levels.
4 ACC, Adrenocortical Carcinoma; ADIUVO, Efficacy of Adjuvant Mitotane Treatment; ADIUVO-2, Mitotane With or Without Cisplatin and Etoposide
5 After Surgery in Treating Participants With Stage I-III Adrenocortical Cancer With High Risk of Recurrence; FIRM-ACT, Trial in Locally Advanced

- 1 and Metastatic Adrenocortical Carcinoma Treatment; GALACCTIC, A Study of OSI-906 in Patients With Locally Advanced or Metastatic
- 2 Adrenocortical Carcinoma; OS, Overall survival; PFS, Progression Free Survival; QoL, Quality of Life.

Table 2. Comparison between conventional and registry-based clinical trials

	Conventional randomized clinical trials	Registry-based randomized clinical trials
Scientific aspects	Typically investigates new interventions	Typically investigates established interventions with documented safety profiles
	Capacity to include complex criteria and outcome measures including adverse events	Patient criteria and outcome factors less detailed and limited to existing registry
	Highly selected patient populations	Broad and representative patient populations
	Ensured high validity and data quality through monitoring	Validity and data quality depending on registry quality
Practical and organisational aspects	High cost	Low cost
	Executed within a dedicated environment separate to standard clinical care	Uses established clinical infrastructure. Integration with existing high quality registries mandatory.
	Individual identification of suitable candidates	Registry may facilitate integrated identification of suitable patients
	Demanding to achieve fast patient inclusion	More rapid patient inclusion rate due to broad eligibility and wide dissemination of centers
	Regulatory environment adopted to conventional trials	Regulatory environment not adopted to the registry-based clinical trial

Figure Legends

Figures 1A-B

Selected data from surveys 1 and 2 demonstrating different research topics where a registry-based trial infrastructure was proposed to provide value to patients with adrenocortical carcinoma. ACC, Adrenocortical carcinoma; EDP, Etoposide + doxorubicin + platinum based chemotherapy; EP, etoposide + platinum based chemotherapy.

Figure 2

Unmet needs of the European Network for the Study of Adrenal Tumours database in order to advance research and perform efficient randomized registry-based trials.