A. Cover Page

1. Title

Training in Checkpoint Inhibitors and Generation of a Network with the Establishment of Reference Centers for Immuno-Oncology in European Countries with Limited Financial Resources from Central and Southeastern Europe (CSEE) – an Educational Initiative of the Central European Cooperative Group (CECOG)

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2. Abstract

Countries of Central and Southeastern Europe (CSEE) have an impressive economic growth ranging well above the Western part of the EU, yet are considered to be financially restricted regarding the reimbursement of EMA-registered compounds. The deficit in access to high-quality cancer care results in an increase in mortality in CSEE. The introduction of immune-checkpoint-inhibitors (ICPI) has resulted in a change in treatment paradigm involving many malignant diseases, but has largely bypassed countries from CSEE Therefore, it is the aim of the present project to

- Familiarize physicians from CSEE with immuno-oncology (IO)
- Establish cross-border tumor boards on immuno-oncology (TB- IO) under the participation of 13 “Centers of Excellence” identified by CECOG with an interdisciplinary participation in TB-IOs thus generating future “Centers of Reference in IO” in the respective country and CSEE
- 26 “Associated Centers” in turn identified by Centers of Excellence in the respective country. Members of Associated Centers will also participate in IO-TBs involving medical oncologists thus generating future “Centers of High Medical Expertise” in the respective country
    - Update physicians from CSEE regarding the registration of ICPIs
    - Monitor the access to IPCIs treatment and its impediments in CSEE countries
    - Generate two publications in peer-review journals about first, the described cross-border educational activities and second, access to ICPIs and its obstacles in CSEE

The program follows the ***vision*** of the establishment of Centers of High Medical Expertise in IO in CSEE thus establishing the important concept of IO as therapeutic modality in this largely underserved region.

3. Keywords

Immuno-Oncology, Immune Checkpoint Inhibitors (ICPI), Education, European Countries with Restricted Financial Resources, Paradigm Change in Education for Financially Restricted Areas, Prescription Practices, Telemedicine, Tumor Boards

B. Table of Contents

C. Main Section of the proposal

1.) Overall Goal & Objectives:

GOAL A

Provide oncologists from countries with limited financial resources from Central and Southeastern Europe (CSEE) all – except Serbia - being members of the EU with:

1. The thorough understanding of the immune system and its role in cancer
2. Information on outcomes of immune checkpoint inhibitor (ICPI) treatments in various indications
3. Information on options of combination therapies to ameliorate treatment outcomes with currently available clinical examples and an outlook on upcoming options
4. Use of immune checkpoint inhibitors in special clinical situations
5. Management of side effects

GOAL B

To assist physicians from CSEE in the direct handling of ICPIs via regular cross-border interdisciplinary immuno-oncology tumor boards (IO-TB) discussing indications for treatment of patients with ICPIs. IO-TBs will be held under the participation of predefined Centers of Excellence (to become after the program Centers of Reference) and Associated Centers (to become after the program Centers of High Medical Expertise) from each country of the CSEE region. IO-TBs will focus on the selection, treatment, treatment duration and side effects of ICPIs. Tumor boards will be based upon an electronic exchange concept corresponding to the "Project Echo" which has been successfully replicated in various clinical areas and geographic regions (http://echo.unm.edu/about-echo/model/) and is being currently established in the CECOG headquarters for this particular project, but also for future forms of cooperation.

GOAL C

Assess whether an increase in education and information results in increased prescription practices of ICPIs in the region of CSEE and possible impediments. A resulting registry of the use and its impediments would be used for publication purposes in order to generate awareness of the issue.

These goals align with the focus of the RFP by implementing training modules and training maintenance and its expansion via regular cross-border patient-centered tumor boards in a geographically vast area of env. 120 million inhabitants. The challenge of the size of the region would be met by the predefinition of centers of excellence within each participating country. These centers of excellence would then recruit other institutions in the area, which would further function as "associated" centers. Regular electronic tumor boards discussing patients eligible for treatment with ICPIs would include the CECOG headquarters, centers of excellence defined by their interdisciplinarity in attendance and monodisciplinary associated centers with oncologic gravitation.

Moreover, regular newsletters will inform about new registrations by the European Medicines Agency regarding an expansion of indications of ICPIs.

These goals also align with the goals of the applicant organization, which is the Central European Cooperative Oncology Group (CECOG; www.cecog.org). CECOG is strongly engaged in continuing medical education in CSEE by having organized preceptorship Programs, Academies and topic-centered Meetings, which have attracted env. 2500 participants, and has recently focused on the topic of immuno-oncology. Within this context, seven Preceptorship Programs (with env. 250 participants from CSEE) have been organized, which have been rated excellently by attendees. All these activities have resulted in the recent establishment of the CECOG Academy (www.cecog.org), which is exclusively dedicated to continuous medical education in the area of CSEE. As a logical step, It is now the vision of CECOG to expand on the topic of immuno-oncology by the help of the current RFP in order to not only enforce state-of-the art ICPI treatment in the geographic region, but also establish cross-border internet-based tumors boards stretching across the entire region of CSEE via the "Project ECHO" (http://echo.unm.edu/about-echo/) in order to assist oncologists in their day-to-day decisions in patient management using ICPIs. Finally, in this geographic area of persisting financial restrictions, CECOG intends to widen its endeavors to assist physicians and patients to obtain state-of-the-art ICPI treatment in registered indications and to record possible impediments followed by a publication in a peer-review scientific journal corresponding to the publications by E. Vrdoljak et al. and R. Luengo-Fernandez et al.

KEY OBJECTIVES related to the established needs for the project

Identification of Participants in the Program: Establish Centers of Excellence (to become after the program Centers of Reference for Immuno-Oncology) in each country (in large countries these are two according to geographic distribution) which act as "hubs" for the identification and involvement of "associated" centers (to become after the program Centers of High Medical Expertise in Immuno-Oncology) in each country to nominate and identify coworkers. These individuals will participate in the initial education program, participate in interdisciplinary cross-border IO-TBs and will be recipients of periodic newsletters sent out by the CECOG headquarters informing about EMA's decisions on registrations of ICPIs in new indications as well as about relevant scientific developments in the field

Initial Education: Organized by the CECOG headquarters, participants consisting of coworkers of established "Excellence Centers" and " Associated Centers" we will be trained to

- Understand the basics of tumor immunology
- Learn about the essentials of immunotherapies and their applications in cancer medicine
- Learn about the status of development and clinical experience of immunotherapies alone or in various combinations in different tumor types
- Learn about biomarker development
- Learn to manage side effects of immune checkpoint inhibitor treatments

Establishment of Cross-Border Tumor Boards for Immuno-Oncology:

Participants in the initial training module will be involved in electronic cross-border interdisciplinary tumor boards based upon the "Project ECHO" concept and will

- Knowledge related to ICPI treatment will be maintained and further expanded under the guidance of the CECOG headquarters and at least three members of the teaching faculty of the initial education program all being experts in immuno-oncology as well as by experts coming from Centers of Excellence consisting of medical oncologists, pathologists and radiologists. The expansion of knowledge will be achieved through the establishment and participation of physicians who were all participating in the initial training program coming from Centers of Excellence and Associated Centers in cross-border electronic immuno-oncology tumor boards (IO-TBs) covering the vast geographic area of CSEE. This design will generate points of gravitation in expertise in immuno-oncology in the region of CSEE.
  Thus, IO-TBs will not only serve the region, but also create a paradigm for high-quality handling of ICPIs regarding indications, treatment durations and complications for physicians dispersed across large geographic areas characterized by mixed expertise in the field ranging from excellent to limited. Moreover, the program will create points of specialized gravitation ranging from Centers of Reference to Centers of High Medical Expertise in Immuno-Oncology in the field in a relatively large and dispersed area.

Continuing information on Immuno-Oncology: Learn about new indications registered by EMA or relevant scientific news regarding ICPI treatment through monthly newsletters.

Analysis of Impediments to Access: Report on access and regulatory impediments leading to an assessment of the situation in a vital part of Europe with a subsequent report for the generation of public awareness

2.) Current Assessment of need in target area

The area of CSEE is characterized by a mixed, yet generally viable access to ICPI treatment, as shown in Table 1.

Table 1: Reimbursement of ICPI Treatment according to Indication in Various Countries of CSEE (*NSCLC: non-small cell lung cancer; **RCC: renal cell cancer)

Country	Nivolumab	Pembrolizumab
Bulgaria	-	• Met. melanoma • 1st and 2nd line monotherapy for relapsed/metastatic NSCLC*
Czech Republic	1st line met. melanoma	-
Greece	• NSCLC: after approval of national health insurance agency (mean time needed 7 days) • Met. melanoma: after approval of national health insurance agency • Urothelial carcinoma: after approval of national health insurance agency • RCC**: after approval of national health insurance agency • Classical Hodgkin Lymphoma: after	• NSCLC: after approval of national health insurance agency in 1st (PD-L1>50%) or 2nd line (PD-L1 >1%) • Melanoma: after approval of national health insurance agency • Classical Hodgkin Lymphoma: after approval of national health insurance agency • Granted for off-label indications after approval of the National Agency for

	approval of national health insurance agency • Granted for off-label indications after approval of the National Agency for Medicines (mean time needed 45 days)	Medicines (mean time needed 45 days)
Hungary	Available for RCC in the second line setting - with special permission	Urothelial cancer
Romania	1st line met. melanoma	-
Serbia	-	1st line advanced melanoma
Slovenia	• met. melanoma • NSCLC • 2nd line RCC	met. melanoma

In contrast to the somewhat limited, yet present access to ICPIs in CSEE, a survey performed in 2017 showed that knowledge about immuno-oncology was considered to be acceptable in only 33% of oncologists from CSEE vs. 100% of oncologists from Western Europe (1). Our own data originating from questionnaires regarding the self-assessment of skills given by env. 250 participants from CSEE of CECOG-based programs on immuno-oncology corroborate these findings by showing that only 24% of all participating oncologists considered themselves to have appropriate knowledge about immuno-oncology.

These data originating from oncologists from CSEE are in remarkable discrepancy to the pronounced wish of oncologists to be trained in immuno-oncology (2). Thus, it would be the aim of the current project to increase the percentage of oncologists from CSEE informed about immuno-oncology and the appropriate use of ICPIs from currently 24-33% to 60%.

According to a recently published analysis, only 10% of patients from CSEE have actual access to ICPI treatment (3). This is obviously the result of restrictions to access by restrictive reimbursement policies in the various countries of CSEE, but also to a deficit in the knowledge on immuno-oncology by oncologists from the area, as assessed by questionnaires generated by CECOG which have analyzed the self-assessment of oncologists in the field. In addition to larger analyses (1), our own analyses have corroborated the results of such surveys by the use of pre-training questionnaires asking for the self-assessment of oncologists from CSEE in the field of immuno-oncology (see above). An example of such results originating from a pre-course questionnaire filled out by 32 oncologists from CSEE in May 2017 is shown in Table 2.

Table 2: Knowledge on ICPIs by 32 selected oncologists from CSEE reflected in a questionnaire filled out before a CECOG-initiated Immuno-Oncology Preceptorship in May 2017

How would you rate your knowledge on Immuno Oncology? (0=worst, 5=best)	**0**	**1**	**2**	**3**	**4**	**5**
Basics		3	5	13	9	2
Clinical Usability		1	4	11	13	3
Indications			2	10	16	4
Biomarkers		2	9	11	9	1
Treatment Combinations with Other Drugs	1	1	7	15	8	0
Side Effects and Their Management			2	14	15	1

3.) Target Audience

CECOG targets an audience in its geographic area of activity in CSEE where CECOG has viable interactions with 150 academic centers in 23 countries from where participating centers and their employed physicians will be recruited. These physicians are dealing with a total population of approx. 120 million inhabitants in CSEE countries. In order to reach the appropriate, tightly knit audience, the following concept will be followed:

- Centers of Excellence already established in each country (see "main collaborators" on the cover page of the current proposal) representing centers of gravitation in the respective geographic region of CSEE (in large countries of the region two such excellence centers will be involved) will act as scientific "hubs" in each country, which is part of the vast geographic region of CSEE
- Excellence centers will in turn identify, contact and recommend physicians (medical oncologists, pathologists and radiologists) from their own institutions as well as medical oncologists from important "associated" institutions in their country to nominate participants for an onsite training module in immuno-oncology at the CECOG headquarters in Vienna, Austria. These individuals will then participate in electronic cross-border "immuno-oncologic tumor boards" (IO-TB) and be recipients of regular newsletters on updates in immuno-oncology.

Levels of commitment:

- Highest level of commitment of CECOG as organizer and facilitator of the program
- High level of commitment of each "Center of Excellence" in each country by becoming a "hub" for the distribution of knowledge and access to expertise and later a "Center of Reference" in an emerging scientific area of utmost importance

- Good level of commitment among the "Associated Centers" which will be provided with information from which they might have been excluded, so far, with hands-on expertise via a cross-border tumor board experience and by becoming "Centers of High Medical Expertise" after the training program and thus part of a regional network of expertise in a rapidly emerging field of highest medical and scientific importance and relevance

Benefits from the project:

Patients from the region who - through the extensive training of physicians in immuno-oncology and by the discussion of patients' cases in IO-TBs – will receive optimized treatment by ICPIs.

- Physicians who through the training, involvement in IO-TBs, their inter-disciplinarity and a constant flow of information on the topic will gain expertise and confidence in such treatments, but also generate a network of expertise in the hitherto underserved region of CSEE
- Centers of Excellence where a multidisciplinary expertise regarding immuno-oncologists will be created thus generating Centers of Reference in the field in each country
- Associated Centers who through the participation of physicians in the educational program will become Centers of High Medical Expertise
- Pharmaceutical industry which via the planned training of physicians and by raised awareness regarding the topic of immuno-oncology as such and physicians' considerations of ICPI treatment in EMA-registered indications will benefit directly through optimization of access to the huge market of CSEE consisting of env. 120 million inhabitants, but also indirectly by strengthening its image as driver of innovation in the region

4.) Project Design and Methods

The current program will stretch over a period of up to two years during which it will include

- Centers of Excellence designed to become future Reference Centers for immuno-oncology in each country of CSEE
- Centers of Excellence will identify, contact and recommend physicians (medical oncologists, pathologists and radiologists) from their own institutions as well as medical oncologists from important downstream "associated" institutions in their country to nominate participants for an onsite training module in immuno-oncology at the CECOG headquarters in Vienna, Austria. These individuals will then participate in electronic cross-border "immuno-oncologic tumor boards" (IO-TB) as well as to be recipients of regular newsletters on updates in immuno-oncology.
- Physicians who through the training, involvement in IO-TBs, their interdisciplinarity and a constant flow of information on the topic will gain expertise and confidence in such treatments, but also generate a network of expertise in the hitherto underserved region of CSEE
- Associated centers which will become centers of expertise in immuno-oncology

- This network will be created and further organized as follows:

  Initially, participants of the program will be invited by CECOG after their recommendation by the leaders of "Centers of Excellence" from the region, as described above. Such "Centers of Excellence" and their leaders (listed as main collaborators, cover page) have been identified by CECOG due to their years-long cooperation with and their achievements within CECOG regarding trial performance and educational initiatives. These "Centers of Excellence" will represent "hubs" in each region and will be supported to become reference centers for immuno-oncology by the inclusion of medical oncologists, radiologists and pathologists into further decision-making processes after the end of the program. These Centers of Excellence will further identify important "associate centers" from their countries, which again will recommend participants consisting of medical oncologists in an initial training program leading to the assignment of a "Center of High Medical Expertise in Immuno-Oncology" after the end of the program. In total, 13 Centers of Excellence with 26 subordinated "Associated Centers" will be generated in this project thus representing a network of high expertise in immuno-oncology in CSEE. A total of 330 patients with malignant diseases qualifying for treatment with IPCIs will be evaluated within IO-TBs. This project working-plan is based on the inclusion of 2 cases/center/month. During the active project phase, a total of 40 IO-TBs will be held in 13 countries with 39 TB-centers.

- The physicians identified in the above manner will attend an initial two-day teaching seminar, which will include basics, clinical indications, possible future expansions and management of side effects of immuno- oncologic compounds taught by specialists in the field as faculty who were involved in previous quality-controlled CECOG-driven perceptorship programs on immuno-oncology
- Participants will have to adhere to strict and predefined rules, which will consist in the testing of their pre- and post-seminar as well as post-program knowledge on immuno-oncology.
- After the end of the seminar, an internet-based cross-border, interdisciplinary IO-TB consisting of at least three members of the CECOG faculty involved in the initial training program, medical oncologists, pathologists and radiologists coming from Centers of Excellence (to become Reference Centers after the program) and Medical Oncologists from Associated Centers (to become Centers of High Medical Expertise in Immuno-Oncology after the program) will be established. IO-TBs will originate from the CECOG Head office and will be coordinated, organized and monitored regarding participants' attendance, number of patients included, number of patients receiving ICPI treatment, number of patients refused EMA-registered ICPI treatment due to reimbursement issues in individual countries etc. by CECOG. Thus, the resulting interdisciplinary IO-TBs (which will be held in English) will include physicians with various levels of expertise in immuno-oncology ranging from very high to limited. Technically, IO-TBs will be technically based upon well-established models like the "Project ECHO" (http://echo.unm.edu/about-echo/) under the strict observation of data safety rules regarding patients' identities.

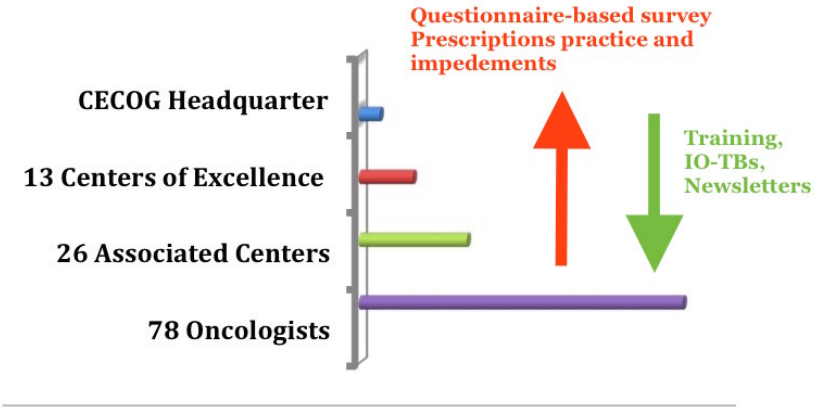
- Periodic newsletters will be sent out to all participants of the initial training course by email informing them about registrational issues of ICPIs and important scientific developments.

Assessments and Evaluations of Engagement

Participants will be *tested for their knowledge* in immuno-oncology

- Before and after the initial introduction by a two-day seminar,
- At predefined intervals (see below) regarding information and knowledge on immuno-oncology as well as their innovations informing participants in the program by periodical newsletters (see Figure 1)

Figure 1: Flow of assessments on information regarding Immuno-Oncology during the educational program.



Participants' *engagement* in the project will be monitored by

- Their attendance of cross-border IO-TBs
- Their participation in answering periodic questionnaires regarding the contents of newsletters

Development of ICIP prescriptions will be followed by

- The frequency of prescriptions and the use of immuno- oncologic compounds in various indications will primarily be analyzed retrospectively followed by a prospective and structured questionnaire recording EMA-registered disease indications, but also by obstacles in obtaining ICPIs in various countries of CSEE This will be followed by a publication submitted to a peer-review journal reporting on outcomes.

➢ This is an original and hitherto never attempted or performed model in CSEE and - to the best of our knowledge – or on a global scale when considering countries of financially limited resources according to World Bank criteria

(http://maps.worldbank.org/p2e/mcmap/map.html?org=ibrd&level=region&code=ECA&title=Europe%20And%20Central%20Asia) and their access to innovative, paradigm changing drugs in oncology.

- The model foresees that the concept of immuno-oncology and of the clinical use of ICPIs in various indications will be spread among important centers and their employees in CSEE and will increase the access of patients qualified for ICIP treatment to appropriate treatment in a structured manner thus fulfilling the criteria of the RFP.
- The model builds upon and expands importantly previous experience of CECOG in the organization, performance and handling of seminars, perceptorship programs, consensus conferences and educational academies including the publication of their outcomes (T. Rordorf et al.: Breast 2014; 23: 511-525). Recent educational activities have centered around immuno-oncology and have been published as educational endeavors (M. Preusser et al.: ESMO Open 2016; 1: e000056)

5.) Evaluation Design

According to the above set-up, the project will

- Assess prospectively the development of knowledge and command of the subject by physicians from important centers in CSEE
- The use of immuno-oncologic compounds in association with the increase in knowledge as well study prescriptions and their dynamics in dependence of the acquired knowledge
- Analyze administrative obstacles in various countries of immuno-oncologic compounds in EMA-registered indications and, finally, result in
- A publication of results in a peer-review journal

The project will be conducted over a period of 24 months. The following parameters will be analyzed.

1. Evaluation of knowledge and skills of participating oncologist of the centers of excellence as well of the associated centers in the field of immuno-oncology (participating oncologist n= env.. 78 (2 oncologists/center)

   ➔ Method:

   A questionnaire-based survey will be conducted. 4 questionnaires will be send out during the project phase:

   - 1st questionnaire - before the two-day seminar
   - 2nd questionnaire - end of the two-day seminar
   - 3rd questionnaire - after 20 held IO-TBs (middle of the active project phase)
   - 4th questionnaire - at the end of the project phase
2. Evaluation of the use of immuno-oncologic compounds as well as prescriptions practice and faced obstacles.

   ➔ Method:

   a.) A questionnaire-based survey will be conducted. 4 questionnaires will be send out during the project phase:

- 1st questionnaire - before the two-day seminar
- 2nd questionnaire - end of the two-day seminar
- 3rd questionnaire - after 20 held IO-TBs (middle of the active project phase)
- 4th questionnaire - at the end of the project phase

b.) Data of prescriptions and treatment recommendations of the IO TBs will be collected and analyzed. Adherence to international treatment guidelines will be evaluated.

c.) Participating oncologist will be invited to state (free text form) the faced obstacle during the project phase and und rate the value of implemented tumor boards in their countries.

6.) Detailed Work plan and Deliverables Schedule:

Regarding a general work plan, please see point 4 above where this has been put into context with the strategy, the methodology and the assessment of success.

A detailed work plan would have the following flow (see also Appendix 1):

1. Invitation sent out of „excellence centers“ from each country to
    a. Identify participants in the program consisting of medical oncologists, radiologists and pathologists in order to enable them to become national reference centers in the field, and
    b. “Associated centers“ to nominate medical oncologists as participants in the educational initiative
2. CECOG headquarters sets up an infrastructure regarding cross-border immuno-oncology tumor boards
3. CECOG headquarters hires and trains an assistant for the performance, organization, administration and quality control of IO-TBs
4. Preparation of a declaration of dedication and adherence to the project including a short outline of its contents and goals to be sent out to potential participants. Participants have to confirm their willingness and ability to participate in weekly cross-border IO-TB, include patients for discussion and to guide patients through the resulting process
5. Identified participants are being invited by the CECOG headquarters to the program requesting to fill out a form of dedication and adherence to the project and its goals (see point 4)
6. Participants who are eligible by the virtue of a declaration of dedication to the program are invited for a two-day educational seminar held at the CECOG headquarters in Vienna, Austria including a pre- and a post-course questionnaire relating to and testing their knowledge in Immuno-oncology and their prescription practices of ICPIs
7. CECOG headquarters expands the established infrastructure regarding cross-border tumor boards to centers of excellence and associated centers
8. CECOG headquarters prepares the first newsletter sent out by email announcing the initiation and start of cross-border IO-TBs

9. The first cross-border IO-TB is held followed by weekly sessions. These are being continued until 30 patients from each country will have been included in the discussion resulting in a total of 330 patients
10. CECOG headquarters prepares a template for newsletters regarding EMA registrations of new indications or new compounds in the field of immuno-oncology and sends out every two months.
11. After the termination of the project (i.e. the inclusion of 330 patients in IO-TBs), a final questionnaire is sent out by CECOG headquarters testing for the knowledge on immuno-oncology acquired by participants through the program
12. Two manuscripts are being prepared and submitted by the CECOG headquarters and the leaders of excellence centers:
    a. Outcomes of a structured education program in immuno-oncology
    b. Access and impediments to access to immune checkpoint inhibitor treatment in European countries of restricted financial resources
13. End of program with the delivery of certificates of participation to individual participants in the program and certificates to institutions to have qualifications of a Center of Reference in Immuno-Oncology or a Center of High Medical Expertise in Immuno-Oncology, respectively, naming the grantor and thus the facilitator of the educational program.

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