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# European multidisciplinary tumor boards support cross-border networking and increase treatment options for patients with rare gynecological tumors

Ulrika Joneborg <sup>1,2</sup>, Alice Bergamini,<sup>3,4</sup> Emelie Wallin,<sup>1,5</sup> Giorgia Mangili,<sup>3</sup> Olesya Solheim <sup>6</sup>, Gloria Marquina <sup>7,8</sup>, Antonio Casado,<sup>8,9</sup> Erik Rokkones,<sup>6</sup> John Coulter,<sup>10</sup> Christianne A R Lok <sup>11</sup>, Nienke van Trommel,<sup>11</sup> Frédéric Amant <sup>12,13</sup>, Pierre-Adrien Bolze,<sup>14,15</sup> Jalid Sehoul <sup>16</sup>, Sileny Han <sup>12</sup>, Frédéric Kridelka,<sup>17</sup> Frederic Goffin,<sup>18</sup> Patricia Pautier,<sup>19,20</sup> Isabelle Ray-Coquard <sup>21,22</sup>, Michael Seckl <sup>23</sup>

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For numbered affiliations see end of article.

## Correspondence to

Dr Ulrika Joneborg, Department of Pelvic Cancer, Karolinska University Hospital, Stockholm, 171 64, Sweden; [ulrika.joneborg@regionstockholm.se](mailto:ulrika.joneborg@regionstockholm.se)

IR-C and MS contributed equally.

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## ABSTRACT

**Objective** To evaluate outcomes of European cross-border multidisciplinary tumor boards in terms of participation, adherence to treatment recommendations, and access to novel treatment strategies.

**Methods** The European reference network for rare gynecological tumors (EURACAN G2 domain) aims to improve the diagnosis, management, and treatment of patients with these cancers. Cross-border multidisciplinary tumor boards were initiated to facilitate intercollegiate clinical discussions across Europe and increase patients' access to specialist treatment recommendations and clinical trials. All G2 healthcare providers were invited to participate in monthly multidisciplinary meetings. Patient data were collected using a standardized form and case summaries were distributed before each meeting. After each tumor board, a meeting summary with treatment recommendations was sent to all participants and the project manager at the coordinating center. The multidisciplinary tumor board format and outcomes were regularly discussed at G2 domain meetings. Anonymized clinical data and treatment recommendations were registered in a prospective database. For this report, clinical data were collected between November 2017 and December 2020 and follow-up data retrieved until May 2021.

**Results** During the 3-year period, 31 multidisciplinary tumor boards were held with participants from 10 countries and 20 centers. 91 individual patients were discussed between one and six times for a total of 109 case discussions. Follow-up data were retrieved from 64 patients and 80 case discussions. Adherence to treatment recommendations was 99%. Multidisciplinary tumor board recommendations resulted in 11 patients getting access to off-label treatment and one patient being enrolled in a clinical trial in another European country. 14/91 patients were recommended for surveillance only when additional treatment had been considered locally.

**Conclusion** Cross-border multidisciplinary tumor boards enable networking and clinical collaboration between healthcare professionals in different countries. Surveillance strategies, off-label drug use, and increased participation in clinical trials are possible benefits to patients with rare gynecological tumors.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Multidisciplinary tumor board discussions have been shown to improve patient management.

## WHAT THIS STUDY ADDS

⇒ This analysis demonstrates the feasibility of virtual cross-border multidisciplinary tumor boards for rare gynecological tumors in increasing networking and clinical collaboration between healthcare professionals across Europe. Potential benefits to patients include surveillance strategies, off-label drug use, and inclusion in clinical trials.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Data aggregation of rare cancers increases our common understanding of these diseases and facilitates joint clinical trials and development of new treatment options.

## INTRODUCTION

Rare cancers, defined as an annual incidence of less than six per 100 000, make up approximately 20–25% of all new cancer cases.<sup>1,2</sup> More than half of all gynecological cancers can be classified as rare.<sup>3,4</sup> Given the low prevalence and lack of consensus and guidelines, poor availability of clinical trials, and challenges in timely and accurate diagnosis, 5-year survival rates are lower for rare compared with common cancers, with rates of 47% and 67%, respectively.<sup>5</sup> Large differences in frequency of correct diagnosis and clinical outcomes have been reported among European countries, reflecting disparities in patient care.<sup>6</sup> Regional and national centers of expertise are often limited by a low number of patients and lack of specialized multidisciplinary teams. Cross-border collaborative networks enable gathering of the best available expertise within different disciplinary fields to ensure a rapid and accurate diagnosis and clinical decision.<sup>7</sup> These multinational networks could overcome the



**Figure 1** EURACAN: European network for rare adult solid cancer. Endocr., endocrinology; GI, gastrointestinal; GU, genito-urinary; GYN, gynecology; H&N, head and neck; NET, neuroendocrine tumors.

inequalities in patient care by diagnostic and clinical support. Given the low prevalence, rare cancers also suffer from a lack of clinical trials with difficulties in study designs, patient accrual, and funding. International research collaboration has proven effective to define issues unique to rare cancers, to define appropriate study designs, and to promote data collection in international registries.<sup>8,9</sup> In order to improve knowledge and management of rare cancers, national and European efforts have been made to set up dedicated networks and reference groups.<sup>9–12</sup>

European reference networks are virtual networks of healthcare providers specialized in rare diseases which were implemented by the European Commission in 2017 to concentrate knowledge and optimize patient care.<sup>13</sup> EURACAN is the reference network for rare adult solid tumors coordinated by the French Comprehensive Cancer Center Léon Bérard in Lyon, France.<sup>14</sup> It consists of 10 domains, of which rare gynecological tumors make up the G2 domain (Figure 1).<sup>1,13</sup> The first two groups of diseases included in this domain were gestational trophoblastic disease and rare ovarian tumors, including non-epithelial ovarian tumors and non-high grade serous epithelial ovarian cancers. A third group of rare uterine and cervical cancer is being formed.

In cancer care, multidisciplinary tumor boards are essential for patient management. Studies have demonstrated clinical benefits for patients discussed in a multidisciplinary tumor board, including more accurate assessment and oncological management.<sup>15,16</sup> Within the G2 domain, virtual multidisciplinary tumor boards were created to overcome the challenges of rare cancers, concentrate knowledge, and find support in clinical management. The cross-border tumor boards were initiated in November 2017 and organized by the Department of Gynecologic Cancer at Karolinska University Hospital in Stockholm, Sweden and from April 2021 by the Department of Obstetrics and Gynecology at San Raffaele Hospital in Milan, Italy. All EURACAN G2 healthcare providers were invited to participate in these multidisciplinary tumor boards.

The aim of this report is to evaluate the outcome of the first 3 years of EURACAN G2 multidisciplinary tumor boards in terms of

participation, adherence to recommendations, and access to novel treatment strategies.

## METHODS

This was an observational and descriptive cohort study of all patients discussed at the cross-border multidisciplinary tumor boards within the EURACAN G2 subdomain. In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study if requested.

## Organization

The cross-border meetings were held monthly using a Cisco video and telephone conference system for the first 2 years, and thereafter replaced by Webex meetings with digital links supplied by the European Commission Directorate-General for Health and Food Safety (DG Santé). The common language used for all communication was English.

Meeting invitations were sent by email to all healthcare representatives of the EURACAN G2 domain. A standardized form for patient data collection was used. The form included information on medical background, histopathological diagnosis and molecular characterization, radiological findings, previous and planned treatments, and current clinical questions (online supplemental appendix 1). The patient cases were summarized and anonymized and shared among the participants before the meetings. The meeting chair led the discussion and summarized the individual treatment recommendations, which were distributed to the healthcare representatives and the project manager at the EURACAN coordinating center after each meeting. The tumor board format and outcomes were discussed at the EURACAN G2 domain meetings held every 3 to 6 months.

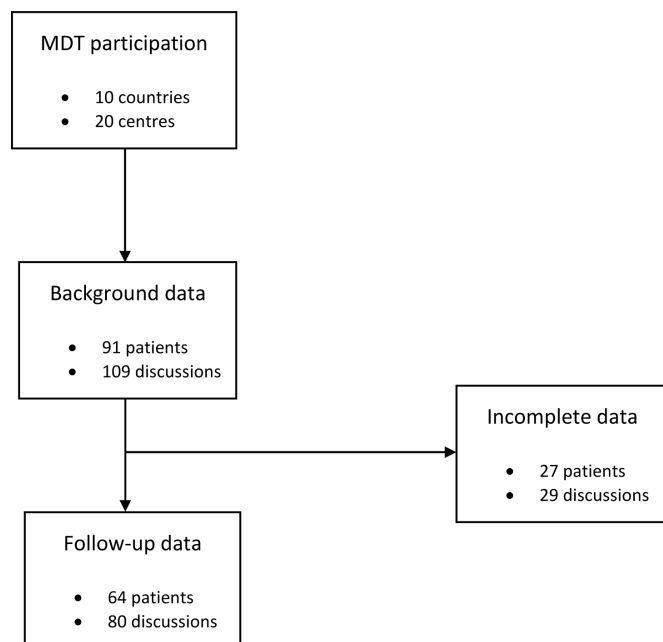
Anonymized patient data were registered in a prospective database. Follow-up data on adherence to treatment recommendations and outcomes were included retrospectively by collecting individual patient data from the respective healthcare providers.

## Inclusion and Exclusion

Background data from all patients discussed at the cross-border multidisciplinary tumor boards from November 2017 until December 2020 were included. Data included patient age, diagnosis (gestational trophoblastic disease; malignant ovarian germ cell tumor; sex cord stromal tumor of the ovary; other rare ovarian tumor; rare cervical cancer; rare uterine cancer; other), center of referral, number of times discussed at a multidisciplinary tumor board, indication for discussion (primary treatment; disease progression; relapse; other), and treatment recommendation (no treatment; surgery; chemotherapy; radiotherapy; targeted therapy; immunotherapy; hormonal treatment; combined treatment; other).

Follow-up data were retrieved until May 2021. Recorded outcomes included adherence to treatment recommendations, disease status at 1 year of follow-up, access to treatment not otherwise available, and inclusion in clinical trials not available in referring country. Patients who lacked follow-up data were excluded from the analysis of outcomes.

Data were presented using descriptive statistics.



**Figure 2** Patient and data inclusion flow chart. MDT, multidisciplinary tumor boards.

## RESULTS

During the first 3 years of EURACAN G2 cross-border multidisciplinary tumor boards, 31 virtual meetings were held. Physicians, including gynecologic oncologists, medical oncologists, radiologists, and pathologists, from 10 different countries and 20 different centers presented cases for discussion. Participating countries included Sweden, Italy, Norway, UK, France, Ireland, the Netherlands, Spain, Belgium, and Germany.

Ninety-one individual patients were discussed between one and six times for a total of 109 case discussions. Follow-up data were retrieved from 64/91 patients (70%) and 80/109 (73%) case discussions. Patients' flow diagram is shown in [Figure 2](#).

The most common diagnosis discussed was rare non-high grade serous epithelial ovarian cancer, followed by gestational trophoblastic disease, and malignant ovarian germ cell tumors. In more than 50% of cases the indication for discussion was primary treatment. More detailed background data are summarized in [Table 1](#). In almost all patient cases (79/80, 99%) where follow-up data were available, treatment suggestions of the multidisciplinary tumor boards were followed, except in one case due to the patient's treatment refusal. Surveillance was recommended for 14 patients (22%) where other treatment interventions had been considered. Almost one fifth (12/64, 19%) of discussed patients were able to receive a treatment not otherwise available in their center or country. The majority of patients were alive without disease after 1 year. Follow-up data are presented in [Table 2](#). The recommendations enabled local teams to obtain off-label treatments in 11 patients (17%) and aided in getting drugs not yet approved in the respective countries. The most common off-label drug and treatment indication was pembrolizumab for chemotherapy-resistant or relapsed gestational trophoblastic neoplasia. The complete treatment list is specified in [Table 3](#). One patient was recruited to a clinical trial in another European country.

**Table 1** Background data

EURACAN MDT 2017–2020	
n=91 patients	
Age, years, median (IQR)	37 (27–52)
Diagnosis n (%)	
GTD	19 (21)
mOGCT	19 (21)
SCST	13 (14)
Rare ovarian	25 (27)
Rare uterine	9 (10)
Rare cervical	2 (2)
Other	4 (4)
Previous lines of treatment	
Median (IQR)	1 (0–2)
Indication for discussion* n (%)	
Primary treatment	59 (54)
Disease progression	7 (6)
Relapse	42 (39)
Other	1 (1)

\*n=109 individual case discussions.  
 .GTD, gestational trophoblastic disease; MDT, multidisciplinary tumor boards; mOGCT, malignant ovarian germ cell tumor; SCST, sex cord stromal tumor.

An example case of recommendation for diagnosis and management is a young woman who had undergone extensive work-up due to low persisting levels of human chorionic gonadotropin. Radiological and sonographic investigation found no abnormalities and she was going to start chemotherapy on the suspicion of gestational trophoblastic neoplasia. The multidisciplinary tumor board recommended investigation with positron emission tomography, and an ovarian lesion was detected. After oophorectomy, ovarian dysgerminoma was diagnosed, with no further treatment needed.

An example case of getting access to off-label treatment is a young woman with relapsed gestational trophoblastic neoplasia who had undergone hysterectomy and four lines of chemotherapy. She was discussed at the multidisciplinary tumor board after a thoracic wedge resection of a new relapse and was recommended pembrolizumab for the remaining pulmonary metastases. Thanks to this recommendation, she was granted access to the treatment and 1 year after the end of treatment she was in complete remission.

## DISCUSSION

### Summary of Main Results

During the first 3 years of European collaboration within the EURACAN G2 domain, 31 cross-border multidisciplinary tumor boards were held with participants from 10 countries and 20 centers. Expert consensus recommendations were made 109 times for 91 individual patients, mainly for primary treatment, giving patients access to expertise not possible within each center or regional hospital. Follow-up information was received in 70% of all patients, and in all but one case the treatment recommendations

**Table 2** Follow-up data

<b>EURACAN MDT 2017–2020</b>	
<b>n=64 patients</b>	
Adherence to treatment recommendations* n (%)	
Yes	79 (99)
No	1 (1)
Treatment not otherwise available n (%)	
Off-label treatment	11 (17)
Clinical trial abroad	1 (2)
Surveillance only n (%)	
14 (22)	
1-year follow-up n (%)	
Alive without disease	28 (44)
Alive with disease	16 (25)
Dead of disease	5 (8)
1 year not reached	15 (23)
*n=80 individual case discussions. MDT, multidisciplinary tumor boards.	

were followed. The multidisciplinary recommendations included surveillance only in 22% of cases sparing these patients unnecessary toxicity. Based on the treatment recommendations, 11 patients

**Table 3** Indication for and type of off-label treatment

<b>Diagnosis</b>	<b>Indication for MDT</b>	<b>Previous lines of treatment</b>	<b>Off-label drug use</b>
mOGCT	Relapse	4	ICI
GTD	Relapse	1	ICI
GTD	Relapse	0	ICI
Other rare ovarian cancer	Relapse	3	MEK inhibitor
GTD	Relapse	4	ICI
SCST	Relapse	1	PI3K inhibitor, CDK 4/6 inhibitor
GTD	Relapse	4	ICI
GTD	Primary treatment	1	ICI
mOGCT	Progressive disease	1	ICI
GTD	Progressive disease	2	ICI
GTD	Primary treatment	1	ICI
GTD, gestational trophoblastic disease; ICI, immune checkpoint inhibitor; CDK 4/6 inhibitor, cyclin-dependent kinase 4/6 inhibitor; PI3K inhibitor, phosphoinositide 3-kinase inhibitor; MDT, multidisciplinary tumor boards; MEK inhibitor, mitogen-activated protein kinase inhibitor; mOGCT, malignant ovarian germ cell tumor; SCST, ovarian sex cord stromal tumor.			

(17%) were able to access a treatment not otherwise available in their center or country, and one patient was enrolled in a clinical trial in another European country.

### Results in the Context of Published Literature

The development of precision medicine and patient tailored treatment in cancer care is dependent on access to expert centers, new molecular analyses, and availability of targeted treatments.<sup>17–18</sup> Modern cancer treatment is becoming increasingly complex, and multidisciplinary and cross-border collaborations are essential parts of individualized cancer treatment.<sup>19</sup> This is particularly true for rare tumors, where standardized treatment and harmonized patient care among centers in different countries are common challenges.<sup>20</sup> Given the lack of consensus and guidelines for rare tumor management, the possibility of discussing cases within multidisciplinary tumor boards gathering international experts from different fields is of unique value.<sup>7–21</sup>

One of the tasks when establishing the G2 domain in EURACAN was to establish cross-border multidisciplinary tumor boards to facilitate and optimize clinical decisions and treatment of complex cases for which local or national experience was not sufficient. Participation in multidisciplinary tumor boards has been demonstrated to increase the number of complete diagnostic investigations, the proportion of patients followed according to established guidelines, and participation in clinical trials.<sup>16–22</sup> The influence on clinical management is illustrated in a prospective study of 85 consecutive gynecological cancer cases in Korea where 27% had a change of treatment plan based on tumor board discussions,<sup>23</sup> while a retrospective study of 741 cases of gynecological cancer in the USA found a 20% change in clinical management based on tumor board review.<sup>15</sup> Patients discussed at the EURACAN G2 domain tumor boards were mainly complicated cases with rare diagnoses or extensive tumor dissemination, or patients who had undergone several treatment regimens with subsequent relapse. All patients were given recommendations for treatment or follow-up. In our study, we have not been able to demonstrate the actual benefit of the multidisciplinary tumor boards to the individual patient in terms of oncological outcome. However, concurrent with the literature, outcomes in terms of clinical management supported by the network of experts from different countries has increased treatment alternatives for patients with rare gynecological cancers.

Adherence to the multidisciplinary treatment recommendations was 99%. The only case where the recommendation was not followed was due to patient refusal. This is in accordance with data from several studies demonstrating a high compliance to multidisciplinary tumor board recommendations. The reasons for discordance between recommendations and clinical management are usually due to the patients' wishes or changes in their clinical condition, such as deterioration in the patients' status or comorbidities unknown at the time of treatment decision.<sup>24–26</sup>

Worldwide telemedicine and technology-based healthcare forms are increasing.<sup>27</sup> The advantages are various and can help overcome the growing physician and nursing shortage and the lack of specialty expertise in rare diseases.<sup>28</sup> The initiation of European reference networks is an effort to ensure optimal clinical care for a larger number of patients, and the use of telemedicine is necessary for cross-border collaboration.<sup>20</sup> In most networks, virtual case consultations are made in a secure clinical patient management

system platform. The active usage is, however, still insufficient despite adaptations, mainly due to technical difficulties and lack of time.<sup>29 30</sup> The EURACAN G2 domain actively chose a different virtual meeting format with easily accessible meetings and has seen an increasing number of participants over time. This concurs with previous reports on virtual meeting platforms which demonstrate an increased attendance at multidisciplinary tumor boards by overcoming barriers of distance and lack of time and resources.<sup>31 32</sup> The ECHO project, a telemedicine and internet-based educational program from the USA, is an example of a successful method to manage the shortage of healthcare providers with expertise in chronic diseases, leading to significant improvements in disease management.<sup>27 33</sup>

### Strengths and Weaknesses

The main strength of this study is that it demonstrates the feasibility of cross-border European multidisciplinary tumor boards and that the intercollegiate discussions benefit patients by increasing treatment options. We also demonstrate that virtual networks work well in achieving the missions of EURACAN, such as the concentration of knowledge and optimization of care of patients with rare cancers. One of the weaknesses with this report is the descriptive study design with lack of a control group, precluding us to demonstrate a true benefit in terms of oncological outcomes. Another weakness is the lack of complete follow-up data.

### Implications for Practice and Future Research

The aim of creating the cross-border multidisciplinary tumor boards was to overcome the challenges of rare cancers such as incorrect diagnosis and treatment, lower survival rates, and unequal patient care across centers. After the first 3 years we have access to 109 discussions as reference cases. This knowledge bank of patient cases gives information of both diagnostic pathways and treatment recommendations for rare gynecological cancers which can be used when new similar cases present. As a result of the tumor board recommendations, 14 patients were recommended surveillance only. In rare diseases, an option is sometimes to refrain from a toxic treatment with low evidence of a survival benefit. Additionally, 11 patients gained access to off-label treatments, emphasizing the significance of expert knowledge in tailoring individualized cancer treatment.

The multidisciplinary discussion summaries delivered to all participating centers were needed to get the approval of off-label drugs. In addition to difficulties in clinical decision making, rare cancers also pose a challenge in timely and correct diagnosis. For some cases, international collaboration is crucial to ensure a correct pathological diagnosis and to interpret the molecular profiling, which could lead to access to targeted therapies. Notably, the possibility of virtually discussing complex cases allows patients to avoid multiple consultations, exposing them to increased risk of delayed treatment and higher costs. Continuing the practice of cross-border multidisciplinary tumor boards is a way to keep increasing common knowledge and experience in treating rare gynecological cancers.

Another challenge with rare cancers is the possible lack of interest in developing new therapies and scarcity of available registries and tissue banks. Randomized trials are seldom feasible in rare tumors. Alternative options are real life studies, observational

prospective trials, and broad registers for which the international cross-border tumor boards provide a unique possibility to pool data. One of the missions of EURACAN is that patients should be able to take part in clinical trials across country borders. In this report only one patient gained access to a clinical trial, demonstrating that there is still room for improvement within this collaboration. It is crucial to facilitate transfer of patients and also biobank tissue between countries to set up international multicenter trials. Legal aspects of sharing data in common registries and harmonization of ethical approvals between countries need to be addressed in order to optimize research and ultimately to improve patient care.

### CONCLUSION

Cross-border multidisciplinary tumor boards can overcome some of the challenges of low prevalence disease and enable networking and clinical collaboration between healthcare professionals in different countries. Surveillance strategies, off-label drug use, innovative approaches to treatment, and participation in clinical trials are possible benefits improving overall care and management of patients with rare gynecological tumors. Adherence to treatment recommendations is high.

#### Author affiliations

<sup>1</sup>Department of Pelvic Cancer, Karolinska University Hospital, Stockholm, Sweden

<sup>2</sup>Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

<sup>3</sup>San Raffaele Hospital Department of Obstetrics and Gynaecology, Milano, Italy

<sup>4</sup>Faculty of Medicine and Surgery, Vita-Salute San Raffaele University, Milano, Italy

<sup>5</sup>Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden

<sup>6</sup>Department of Gynecological Oncology, Oslo University Hospital, Oslo, Norway

<sup>7</sup>Department of Medical Oncology, Hospital Clinico San Carlos, Madrid, Spain

<sup>8</sup>Department of Medicine, Complutense University of Madrid, Madrid, Spain

<sup>9</sup>Department of Medical Oncology, Hospital Clínico San Carlos, Madrid, Spain

<sup>10</sup>Department of Gynaecological Oncology, Cork University Hospital, Cork, Ireland

<sup>11</sup>Department of Gynecologic Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands

<sup>12</sup>Division of Gynecologic Oncology, KU Leuven University Hospitals Leuven, Leuven, Belgium

<sup>13</sup>Division of Surgery, Netherlands Cancer Institute, Amsterdam, The Netherlands

<sup>14</sup>Hospices Civils de Lyon, Université Lyon 1 Faculté de Médecine et de Maïeutique Lyon-Sud Charles Merieux, Lyon, France

<sup>15</sup>Department of Gynecological and Oncological Surgery and Obstetrics, Hospital Lyon-South, Lyon, France

<sup>16</sup>Department of Gynecology with Center of Oncological Surgery, Charité Medical Faculty Berlin, Berlin, Germany

<sup>17</sup>Department of Obstetrics & Gynecology, Division of Gynecologic Oncology, Central University Hospital of Liege, Liege, Belgium

<sup>18</sup>Department of Obstetrics and gynecology, Central University Hospital of Liege, Liege, Belgium

<sup>19</sup>Gustave Roussy Institute, Villejuif, France

<sup>20</sup>Paris-Saclay University, Villejuif, France

<sup>21</sup>Centre Leon Berard, Lyon, France

<sup>22</sup>Université Claude Bernard Lyon 1, Villeurbanne, France

<sup>23</sup>Department of Medical Oncology, Imperial College London - Charing Cross Campus, London, UK

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## Original research

IR-C, MS. Final approval: UJ, AB, EW, GM, OS, ER, GM, AC, JC, CAL, NVT, FA, PAB, JS, SH, FK, FG, PP, IR-C, MS. IR-C and MS are joint last authors.

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**Ethics approval** This study involves human participants. This paper is a summary of the results of the first three years of cross-border multidisciplinary tumor boards. All patients included in this report had consented to their data being presented at the cross-border multidisciplinary tumor boards. The type of patients' informed consent adopted by each referring center was that required by local regulations. The first author has an ethical approval from the regional ethics committee at Karolinska Institutet, Stockholm, Sweden (Dnr 2020-01357). Participants gave informed consent to participate in the study before taking part.

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### ORCID iDs

Ulrika Joneborg <http://orcid.org/0000-0002-1922-0738>

Olesya Solheim <http://orcid.org/0000-0003-1936-3453>

Gloria Marquina <http://orcid.org/0000-0002-8961-9787>

Christianne A R Lok <http://orcid.org/0000-0001-8693-7299>

Frédéric Amant <http://orcid.org/0000-0002-5452-4905>

Jalid Sehouli <http://orcid.org/0000-0002-5963-6623>

Sileny Han <http://orcid.org/0000-0002-7476-3372>

Isabelle Ray-Coquard <http://orcid.org/0000-0003-2472-8306>

Michael Seckl <http://orcid.org/0000-0003-4078-2599>

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