IRE ISTITUTO NAZIONALE TUMORI REGINA ELENA ISG ISTITUTO DERMATOLOGICO SAN GALLICANO
ISTITUTI DI RICOVERO E CURA A CARATTERE SCIENTIFICO

UOC Acquisizione Beni e Servizi

Il dirigente della UOC Acquisizione Beni e Servizi

in virtù della delega conferita con deliberazione N°446/2024

HA ASSUNTO LA PRESENTE DETERMINAZIONE

N. 831 del 01/10/2024

OGGETTO: Autorizzazione alla liquidazione fatture per la pubblicazione di articoli scientifici alle Società Frontiers Media SA e Elsevier B.V .Fondo Ricerca Corrente ISG 2024 CUP H53C23001520001 responsabile Direttore Scientifico ISG f.f . Fondo Ricerca Corrente IRE 2024 CUP H83C24000170001 responsabile Direttore Scientifico IRE.

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Servizio Risorse Economiche: **Giovanna Evangelista**

UOC Acquisizione Beni e Servizi Proposta n° DT-837-2024

L'estensore

Daniela Kolziu

Il Responsabile del Procedimento

Andrea Scotti

Il Dirigente della UOC Acquisizione Beni e Servizi

Andrea Scotti

La presente determinazione si compone di n° 5 pagine e dei seguenti allegati che ne formano parte integrante e sostanziale:

allegati nr:9 ;note protocollo, copia fattura da pagare.

Il Dirigente della UOC Acquisizione Beni e Servizi

Visto il decreto legislativo 30 dicembre 1992 n. 502 e successive modificazioni ed integrazioni;
il decreto legislativo 16 ottobre 2003 n. 288 e il decreto legislativo 23 dicembre 2022 n. 200 di riordino della disciplina degli Istituti di ricovero e cura a carattere scientifico;

Vista la legge regionale 23 gennaio 2006, n. 2;

Visto l'Atto Aziendale adottato con deliberazione n. 153 del 19 febbraio 2019 e approvato dalla Regione Lazio con DCA n. U00248 del 2 luglio 2019, modificato e integrato con deliberazioni n. 1254 del 02 dicembre 2020, n. 46 del 2 gennaio 2021 e n. 380 del 25 marzo 2021, approvate dalla Direzione Salute e Integrazione Sociosanitaria della Regione Lazio, con Determinazione n. G03488 del 30 marzo 2021;

Vista la deliberazione della Giunta Regionale n. 256 del 17 aprile 2024, avente ad oggetto "*Commissariamento dell'IRCCS Istituti Fisioterapici Ospitalieri (Art. 8, comma 7 bis, della legge regionale 16 giugno 1994, n. 18 e s.m.i.)*";

Visto il Decreto del Presidente della Regione Lazio n. T00087 del 07 maggio 2024, avente ad oggetto: "*Nomina del Commissario straordinario dell'IRCCS Istituti Fisioterapici Ospitalieri (Art. 8, comma 7 bis, della legge regionale 16 giugno 1994, n. 18 e s.m.i.)*";

Visto il D.M. del Ministero della Salute del 20 giugno 2024 di conferma del riconoscimento del carattere scientifico dell'IRCCS di diritto pubblico a Istituti Fisioterapici Ospitalieri (IFO) relativamente alla disciplina di "oncologia" per

l'Istituto Nazionale Tumori Regina Elena (IRE) e alla disciplina di "dermatologia" per l'Istituto Santa Maria e San Gallicano (ISG);

Vista la deliberazione n. 446 del 27 maggio 2024 di attribuzione delle deleghe ai Dirigenti del Ruolo Professionale, Tecnico e Amministrativo degli IFO;

Tenuto Presente il concetto di infungibilità viene collegato agli obiettivi della ricerca individuati dal responsabile scientifico della stessa;

Premesso che con protocollo n. 16070 del 15 dicembre 2023 del Direttore Scientifico ff. ISG, munito di Nulla Osta del Direttore Generale f.f. IFO, è stato autorizzato l'appostamento della Ricerca Corrente 2024 ISG per un importo pari a € 966.909,34;

che con protocollo n. 16053 del 15 dicembre 2023 del Direttore Scientifico IRE, munito di Nulla Osta del Direttore Generale f.f. IFO, è stato autorizzato l'appostamento della Ricerca Corrente 2024 IRE per un importo pari a € 2.847.703,86;

Considerato che la Dr.ssa Vari Sabrina con nota protocollo n. 0012858 del 27-09-2024 e la Dr.ssa Fulvia Pimpinelli con nota protocollo 0012756 del 26/09/2024, hanno chiesto la liquidazione delle seguenti fatture:

- Fattura nr. 2024-1148692-2 del 02/07/2024 di € 3.328,50 Iva compresa della società Frontiers Media SA relativa alla pubblicazione del manoscritto dal titolo "Radiological evaluation of response in patients with lovally advanced/metastatic soft tissue sarcoma treated with trabectedin" nella Rivista scientifica Pharmacology.
- Fattura nr. OAD0000479638 del 19/09/2024 di € 3.294,00 Iva compresa della società Elsevier B.V relativa alla pubblicazione del manoscritto dal titolo" Staphylococcus aureus colonizing the skin microbiota of adult people with severe atopic dermatitis exhibits genomic diversity and convergence in biofilm traits" nella Rivista BioFilm.

Acquisito il parere favorevole del Direttore Scientifico dell'Istituto Regina Elena, apposto in calce alle richieste sopra citate;

Accertata la disponibilità sui Fondi citati in premessa;

Esperiti i controlli sulle richieste presentate dai responsabili dei progetti;

Attestato che il presente provvedimento, a seguito dell'istruttoria effettuata, nella forma e nella sostanza è totalmente legittimo e utile per il servizio pubblico, ai sensi dell'art.1 della legge 20/94 e successive modifiche, nonché alla stregua dei criteri di economicità e di efficacia di cui all'art.1, primo comma, della legge 241/90, come modificata dalla legge 15/2005;

DETERMINA

per i motivi di cui in narrativa che si intendono integralmente confermati di:

1-autorizzare il pagamento delle fatture:

- Fattura nr. 2024-1148692-2 del 02/07/2024 di € 3.328,50 Iva compresa della società Frontiers Media SA relativa alla pubblicazione del manoscritto dal titolo "Radiological evaluation of response in patients with lovally advanced/metastatic soft tissue sarcoma treated with trabectedin" nella Rivista scientifica Pharmacology.
- Fattura nr. OAD0000479638 del 19/09/2024 di € 3.294,00 Iva compresa della società Elsevier B.V relativa alla pubblicazione del manoscritto dal titolo" Staphylococcus aureus colonizing the skin microbiota of adult people with severe atopic dermatitis exhibits genomic diversity and convergence in biofilm traits" nella Rivista BioFilm.

2 - far gravare la spesa complessiva di € 6.622,50 Iva compresa sui Fondi: Fondo Ricerca corrente ISG 2024 per € 3.294,00 responsabile il Direttore Scientifico ISG f.f. Fondo Ricerca Corrente IRE 2024 per € 3.328,50 che presentano la necessaria disponibilità.

Ricerca Corrente IRE 2024			**Ricerca Corrente ISG 2024**		
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La UOC Acquisizione Beni e Servizi curerà tutti gli adempimenti per l'esecuzione della presente determinazione.

Il Dirigente della UOC Acquisizione Beni e Servizi

Andrea Scotti

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SISTEMA SANITARIO REGIONALE
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IRE ISTITUTO NAZIONALE TUMORI REGINA ELENA
ISG ISTITUTO DERMATOLOGICO SAN GALLICANO
ISTITUTI DI RICOVERO E CURA A CARATTERE SCIENTIFICO

Roma, 16/08/2023

Alla c.a. del Prof. Gennaro Ciliberto
Direzione Scientifica IRE

Oggetto: Richiesta pagamento fattura relativa a pubblicazione

Gentile Direttore,

si richiede cortesemente il pagamento della fattura relativa all'articolo "Radiological evaluation of response in patients with locally advanced/metastatic soft tissue sarcoma treated with trabectedin", di Serena Ceddia, Concetta Elisa Onesti, Sabrina Vari, Andrea Torchia, Antonella Cosimati, Federica Riva, Maria Teresa Maccallini, Marianna Cerro, Giovanni Benvenuti, Michelangelo Russillo, Vincenzo Anelli, Isabella Sperduti, Roberto Biagini e Virginia Ferraresi, accettato come pubblicazione in data 02/07/2024 da Frontiers in Pharmacology (IFG 4.4).

La richiesta era stata preventivamente autorizzata come da email del 28/03/24.

Cordiali saluti

I.F.O. ISTITUTO REGINA ELENA
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IL DIRETTORE SCIENTIFICO I.R.E.
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Radiological evaluation of response in patients with locally advanced/metastatic soft tissue sarcoma treated with trabectedin

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Background: Trabectedin is an antineoplastic drug approved for patients (pts) with advanced soft tissue sarcomas (STS). Interestingly, the radiological evaluation of response during trabectedin therapy is peculiar.

Methods: The aim of this single-center retrospective study is to analyze the concordance of response assessment according to RECIST compared with Choi criteria in patients with STS treated with trabectedin between 2009 and 2020 at Regina Elena National Cancer Institute in Rome.

Results: We present the preliminary data collected in the last 2 months (mos) on 37 pts who received the diagnosis between 2015 and 2020, with a median age of 52.5 years (range 32–78). The median number of trabectedin cycles administered was four (range 2–50) for a median follow up of 5.83 months (range 1–60). Histological subtypes of STS were five (13.5%) leiomyosarcoma, 14 (37.8%) liposarcoma, nine (24.3%) undifferentiated pleomorphic sarcoma, three (8.1%) synovial sarcoma, and six (16.2%) other rare histological subtypes. Eight pts (21.6%) received trabectedin in the first line setting, 21 (56.8%) in the second line, and seven (18.9%) received it in subsequent lines. One pt received trabectedin as neoadjuvant therapy in a clinical trial (ISG-STS 1001). Median progression-free survival was 3.6 months (CI95% 2.7–4.6); median overall survival was 34.3 months (CI95% 0–75.4). The radiological responses were evaluated with both RECIST and Choi criteria; responses matched in 33 pts (89.2%) but not in four (10.8%). The best responses obtained according to RECIST criteria were two (5.4%) partial response (PR), 13 (35.1%) stable disease (SD), and 22 (59.5%) progressive disease (PD). Instead, two (5.4%), 13 (35.1%), and 22 (59.5%) pts obtained PR, SD, and PD respectively, according to Choi criteria. Cohen's kappa coefficient of concordance was 0.792 (p-value <0.002). A specialized radiologist performed all imaging examinations using a dedicated workstation in the same center.

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2 Patients and methods

Eligible patients were adults (age ≥18 years) with various histotypes of STS undergoing treatment with trabectedin after a confirmed local relapse or metastatic disease. Other main inclusion criteria were: Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2; normal bone marrow, liver and kidney function; availability of CT for the assessments under study; availability of clinical follow-up. The study has been conducted under the principles of "Good Clinical Practice" required by the regulatory authorities and the main European and national regulations. The data, material and documentation related to the study were collected, stored, and processed following the provisions of the relevant legislation/regulations in a manner that guarantees its confidentiality. The study was conducted in accordance with the Declaration of Helsinki and current legislation in this regard and has been approved by the local ethics committee. Written informed consent from the participants was not required following national legislation and institutional requirements.

2.1 Study design and endpoints of the study

This is a single-center retrospective observational cohort study on patients with STS who are undergoing treatment with trabectedin at the Regina Elena National Cancer Institute in Rome (European Reference Network for Rare Adult Solid Cancers—EURACAN—referral center) over the reference time 2015–2020. The aim of this study was to evaluate radiological best response as assessed by CT scan in patients with unselected histotypes of STS treated with trabectedin, comparing the traditional morphological criteria of response (RECIST) with "functional" radiological evaluation criteria (Choi criteria). As per clinical practice, re-evaluation with CT was performed every three courses of treatment or at any time when disease progression was clinically suspected. Response assessment to decide continuation (disease response or stabilization) or discontinuation (disease progression) of trabectedin therapy was performed according to RECIST criteria.

2.2 Statistical analyses

From 2015 to 2020, the data relating to all the patients who meet the envisaged requirements were analyzed and processed. Descriptive statistics were calculated for all variables of interest. Categorical variables were reported through absolute frequencies and relative percentage values, while continuous variables will be reported through medians and ranges. All associations among the categorical variables considered were evaluated by Pearson's chi-square test or Fisher's exact test. DFS and OS curves were evaluated by the Kaplan–Meier method and the Mantel–Haenszel log-rank test, which were employed to compare survival between groups. Hazard ratio (HR) and odds ratio (OR) estimates, which allow quantification of the relative effect of each predictor on the outcome considered, and the corresponding 95% confidence intervals were calculated using the Cox regression model with proportional hazards and the logistic regression model. A p-value ≤0.05 was considered statistically significant.

TABLE 1 General demographic and clinical characteristics in treated patients.

Treated pts, n (%)	37	100%
Median age, years (range)	**52.5 (32–78)**	
Gender, M/F	**21/16**	
Histological subtypes, n (%)	**37**	**100%**
• Liposarcoma	14	38%
• Undifferentiated pleomorphic sarcoma	9	24%
• Leiomyosarcoma	5	14%
• Synovial sarcoma	3	8%
• Other	6	16%
Sarcoma primitive lesion, n (%)	**37**	**100%**
• Extremities	23	62%
• Retroperitoneal	8	22%
• Trunk	6	16%
Stage of disease at diagnosis, n (%)	**37**	**100%**
• Locally advanced	10	27%
• Metastatic	27	73%
Previous treatments, n (%)		
• Surgery	34	92%
• Radiotherapy	5	14%
• Chemotherapy	32	86%
Median number of previous metastatic systemic treatments, n (range)	**3 (1–5)**	
Starting dose of trabectedin, n (%)	**37**	**100%**
• 1.3 mg m2	12	32%
• 1.5 mg/mq	1	3%
• n.a.	24	65%
Median duration of treatment with trabectedin, months (range)	**5.8 (1–60)**	
Median number of trabectedin cycles, n (range)	**4 (1–60)**	
Line of therapy with trabectedin, n (%)	**37**	**100%**
• First line	8	22%
• Second line	22	59%
• Subsequent lines	7	19%

Abbreviation: n.a., not applicable. The bold value indicates the total number of patients for each main section.

TABLE 2 Best response according to physician evaluation RECIST, Choi N, %.

All treated pts, N = 37	RECIST criteria	Choi criteria
Partial response (PR)	2 (5.4%)	2 (5.4%)
Stable disease (SD)	13 (35.1%)	13 (35.1%)
Progressive disease (PD)	22 (59.5%)	22 (59.5%)

TABLE 3 Patients with RECIST and Choi criteria dissociated responses.

Patients, N = 4	Histological subtypes	RECIST criteria	Choi criteria
Patient 1	Pleomorphic liposarcoma	SD	PD
Patient 2	Leiomyosarcoma	PD	SD
Patient 3	Alveolar sarcoma	PD	SD
Patient 4	Myxoid liposarcoma	SD	PD

3 Results

We present data collected on 37 patients (pts) who received the diagnosis over 2015–2020, with a median age of 52.5 years (range 32–78) (Table 1).

Histological subtypes of STS were five (13.5%) leiomyosarcoma, 14 (37.8%) liposarcoma, nine (24.3%) undifferentiated pleomorphic sarcoma, three (8.1%) synovial sarcoma, and six (16.2%) other histological subtypes. Eight pts (21.6%) received trabectedin in the first-line setting (five had previously undergone treatment with anthracyclines in the adjuvant or neoadjuvant setting; three had contraindication to anthracyclines due to cardiac comorbidities), 22 pts (59.5%) in the second line (of whom 20 were treated with anthracyclines +/- ifosfamide in the neoadjuvant, adjuvant, or first-line setting, and two were treated with anthracyclines +/- ifosfamide in the neoadjuvant or adjuvant setting and subsequently received gemcitabine-docetaxel), and seven pts (18.9%) in subsequent lines. The median number of administered trabectedin cycles was four (range 2–50) with a median treatment duration of 5.8 months (range 1–60). Median progression-free survival was 3.6 months (CI95% 2.7–4.6) (Figure 1); median overall survival was 34.3 months (CI95% 0–75.4) (Figure 2).

A specialized radiologist performed all the imaging examinations using a dedicated workstation in the same center. The radiological responses were evaluated with both RECIST and, retrospectively, Choi criteria. The best responses obtained according to RECIST criteria were two (5.4%) partial response (PR) represented by a pleomorphic liposarcoma (PLPS) and an undifferentiated pleomorphic sarcoma (UPS), 13 (35.1%) stable disease (SD), and 22 (59.5%) progressive disease (PD). Two (5.4%), 13 (35.1%), and 22 (59.5%) pts obtained PR, SD and PD respectively according to CHOI criteria (Table 2).

In 33 pts (89.2%), the responses assessed according to RECIST and Choi criteria matched, whereas four pts (10.8%) did not match. Two pts were considered in SD according to RECIST 1.1 and PD with Choi criteria; two others with PD according to RECIST 1.1 were classified as SD with Choi criteria (Table 3). In pts 1 and 4, PD according to CHOI criteria was represented by an increase in the vascularized intralesional component, while dimensional stability was observed as per RECIST criteria. In pts 2 and 3, PD is attributed to an increase in the size of the target lesions, while SD was observed according to CHOI criteria due to intralesional remodeling and an increase in tissue density.

Cohen's kappa coefficient of concordance was 0.792 (p-value <0.002). The first pt affected by liposarcoma showed SD according to RECIST criteria and PD according to CHOI criteria. She discontinued trabectedin treatment and is reported as lost to follow-up. Pt 2, diagnosed with leiomyosarcoma, underwent trabectedin treatment in the second line and subsequently, following RECIST-defined disease progression, received three additional lines of therapy with modest benefit (gemcitabine-docetaxel, dacarbazine, and ifosfamide with PD after three, five and two cycles of treatment, respectively). Pt 3, with alveolar sarcoma, initiated trabectedin treatment in the sixth line and maintained disease stability for 21 months. Later, the pt underwent another and final line of treatment with off-label bevacizumab, with rapid disease progression after 3 months. Pt 4 underwent surgery after showing disease stability according to RECIST criteria, followed by a disease-free interval of 2 years. The treatment with trabectedin was overall well-tolerated. The most frequently reported toxicities were neutropenia and transient transaminase increase according to the literature. All pts received steroid pre- and post-medication as per recommended dosage.

4 Discussion

The RECIST 1.1 guidelines (Eisenhauer et al., 2009) represent the system mainly used for the assessment of disease status based on changes in tumor size. In selected cases, such as during treatment with tyrosine kinase inhibitors, different assessment methods could be useful because both changes in volume and density may better represent drug activity instead of classical two dimensional evaluation (Schuetze, 2005). Treatment-related changes in STS, especially assessment of trabectedin response, have been shown to be closely related to altered tumor composition and density; thus therapeutic benefit without tumor shrinkage appears to be relevant in STS (Schuetze, 2005). This novel response pattern was first described by Choi et al. (2007), defining it in the setting of patients with gastrointestinal stromal tumor (GIST) treated with imatinib. They described criteria based on both dimensional and density changes in GIST treated with the TKI imatinib, arguing that RECIST criteria significantly underestimate tumor response. Specifically, variations in tumor mass dimensions may not accurately reflect tumor activity; changes in tumor density represent an additional measure of treatment response, which can be objectively assessed and measured based on radiological images (Choi et al., 2007). In a retrospective study, Taieb et al. (2015) suggested that Choi's criteria can help identify cases of false progression (tumor progression according to RECIST but PR or SD according to CHOI criteria), demonstrating a longer OS in those patients compared to cases where progression is confirmed by both RECIST and Choi criteria. In this patient setting, the correct definition of disease progression is therefore crucial, considering the decisions in therapeutic strategies and

was financially supported through funding from the institutional *Ricerca Corrente* granted by the Italian Ministry of Health.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Staphylococcus aureus colonizing the skin microbiota of adults with severe atopic dermatitis exhibits genomic diversity and convergence in biofilm traits

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ABSTRACT

Atopic dermatitis (AD) is a chronic inflammatory skin disorder exacerbated by *Staphylococcus aureus* colonization. The specific factors that drive *S. aureus* overgrowth and persistence in AD remain poorly understood. This study analyzed skin barrier functions and microbiome diversity in lesional (LE) and non-lesional (NL) forearm sites of individuals with severe AD compared to healthy control subjects (HS). Notable differences were found in transepidermal water loss, stratum corneum hydration, and microbiome composition. *Cutibacterium* was more prevalent in HS, while *S. aureus* and *S. lugdunensis* were predominantly found in AD LE skin. The results highlighted that microbial balance depends on inter-species competition. Specifically, network analysis at the genus level demonstrated that overall bacterial correlations were higher in HS, indicating a more stable microbial community. Notably, network analysis at the species level revealed that *S. aureus* engaged in competitive interactions in NL and LE but not in HS. Whole-genome sequencing (WGS) showed considerable genetic diversity among *S. aureus* strains from AD. Despite this variability, the isolates exhibited convergence in key phenotypic traits such as adhesion and biofilm formation, which are crucial for microbial persistence. These common phenotypes suggest an adaptive evolution, driven by competition in the AD skin microenvironment, of *S. aureus* and underscoring the interplay between genetic diversity and phenotypic convergence in microbial adaptation.

1. Introduction

Atopic Dermatitis (AD), a common inflammatory skin disorder, poses significant challenges due to its chronic nature and symptom severity. AD is marked by severe pruritus, erythema, and skin barrier dysfunction, among other signs [1]. There is growing evidence that the skin microbiome plays an essential role in the pathophysiology of AD, with *Staphylococcus aureus* recognized as a critical species in this context [2–4].

Staphylococcus aureus is associated with skin health and various skin disorders [5]. In AD, it colonizes the skin and contributes significantly to disease exacerbation [6]. While the host's genetic risk factors are integral to the onset of AD, *S. aureus* colonization and its subsequent interactions with the host immune system often worsen the disease severity [7,8]. The overabundance of this bacterium contributes to immune dysfunction, reduced antimicrobial peptides, heightened allergic reactions, and skin barrier disruption [9]. In addition to dysbiosis, other ecological factors like humidity, temperature, pH, and lipid content influence the regulation of the skin microbiome. In people with AD, the skin exhibits several physiological changes, including increased transepidermal water loss (TEWL), alterations in the hydration of the stratum corneum (SC), and modifications in the lipidome com-

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